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Synthesis of Cribrostatin 6

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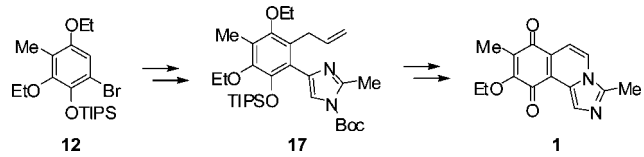
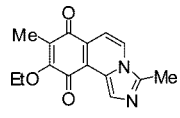


The synthesis of cribrostatin 6 (**1**) is described. A regioselective bromination, a biaryl coupling, and an intramolecular cyclization are the key steps in the synthesis.

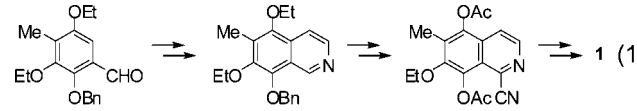
Introduction

In 2003, Pettit and colleagues reported the isolation and structure determination of cribrostatin 6 (**1**) based on spectral and X-ray crystallographic data.[1] Cribrostatin 6, a constituent of the Republic of Maldives' marine sponge *Cribrochalina* sp., was found to be a cancer cell growth inhibitor (P388 ED_{50} 0.3 μg/mL) and to inhibit the growth of a number of pathogenic bacteria and fungi.[2] Cribrostatin 6 is also the first known naturally occurring example of the imidazo[5,1-*a*]isoquinoline ring system. On the basis of its unique polycyclic framework and biological activity, the synthesis of cribrostatin 6 was undertaken.[3]

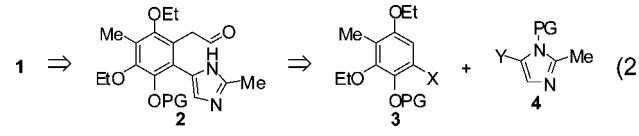


Results and Discussion

Shortly after our efforts had commenced, Nakahara et al. confirmed[4] the structure of **1** through total synthesis. Their synthesis is summarized in eq 1. Herein, we report our synthesis of cribrostatin 6 using an entirely different strategy.



Retrosynthetic analysis (eq 2) suggested to us that **1** might be derived from biaryl **2** through an intramolecular dehydrative cyclization of the imidazole ring onto the neighboring aldehyde followed by an oxidation. Biaryl **2** was envisioned to originate from an appropriate cross-coupling reaction between monocycles **3** and **4**, followed by functional group manipulation. Both **3** and **4** should be derivable from commerically available starting materials.



(1) Pettit, G. R.; Collins, J. C.; Knight, J. C.; Herald, D. L.; Nieman, R. A.; Williams, M. D.; Pettit, R. K. *J. Nat. Prod.* **2003**, *66*, 544–547.

(2) Pettit, R. K.; Fakoury, B. R.; Knight, J. C.; Weber, C. A.; Pettit, G. R.; Cage, G. D.; Pon, S. *J. Med. Microbiol.* **2004**, *53*, 61–65.

(3) For a leading reference to some previous syntheses of the imidazo[5,1-*a*]isoquinoline ring system, see: Hajos, G.; Riedl, Z. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Neier, R., Bellus, D., Eds.; Category 2: Hetarenes and related ring systems; Georg Thieme Verlag: Stuttgart, Germany, 2002; Vol. 12, pp 643−648.

(4) (a) Nakahara, S.; Kubo, A. *Heterocycles* **2004**, *63*, 2355–2362. (b) Nakahara, S.; Kubo, A.; Mikami, Y.; Ito, J. *Heterocycles* **2006**, *68*, 515–520.

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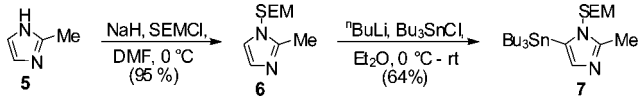
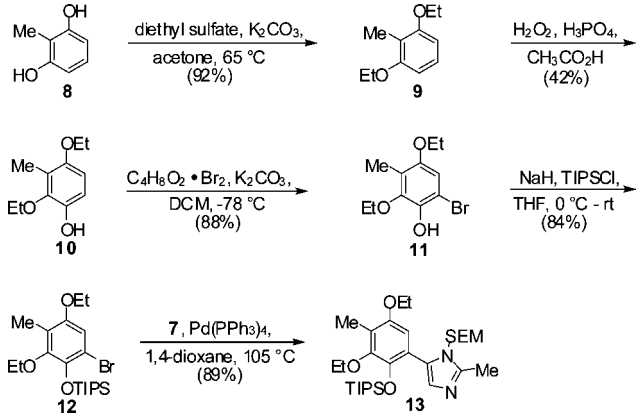
SCHEME 1. Synthesis of Imidazole 7



SCHEME 2. Synthesis of Biaryl 13

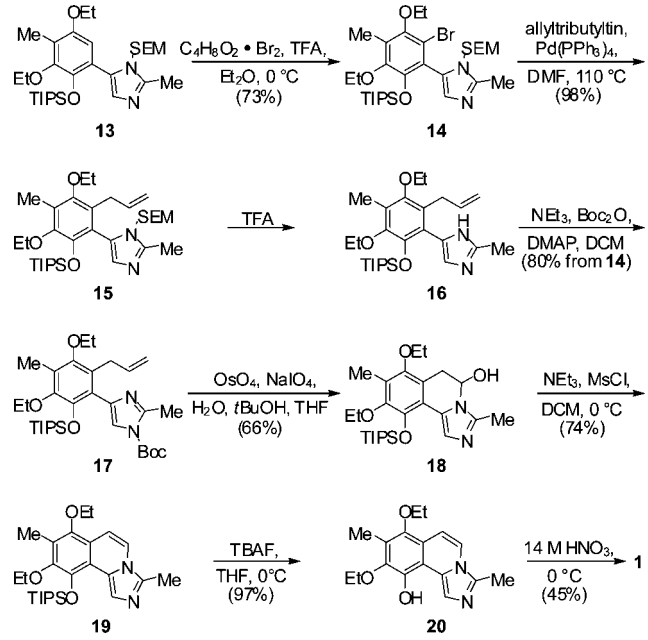


The synthesis began (Scheme 1) with the known protected imidazole **6**, available[5] in one step from 2-methylimidazole (**5**) and 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl). Directed *ortho*-metalation of **6** with *n*-butyllithium and subsequent quenching with tributyltin chloride gave the desired specific embodiment (**7**) of **4**.[6]

Preparation of the unit (**12**) corresponding to **3** commenced (Scheme 2) with the known[7] diethyl ether **9** of commercially available 2-methylresorcinol (**8**). Hydroxylation[8] of **9** with hydrogen peroxide in acetic acid gave phenol **10** directly.[9] Monobromination of phenol **10** with bromine-1,4-dioxane[10,11] followed by protection of the hydroxyl group[12] as its triisopropylsilyl (TIPS) ether afforded bromide **12**. Palladium-catalyzed cross-coupling[13] between bromide **12** and stannane **7** forged the biaryl bond to give intermediate **13**.

Introduction of the final two carbons began (Scheme 3) with a regioselective bromination of intermediate **13** with bromine-

SCHEME 3. Completion of the Synthesis of Cribrostatin 6



1,4-dioxane in a 1:1 (v:v) solvent mixture of diethyl ether (Et_2O) and trifluoroacetic acid (TFA) to give bromide **14**. We speculate that the TFA deactivates the imidazole ring toward electrophilic bromination by protonation. If the bromination of **13** is carried out in the absence of TFA, only bromination of the imidazole ring is observed.

The side chain was introduced with another palladium-catalyzed cross-coupling reaction between **14** and allyltributyltin to give allyl biaryl **15**. A two-step deprotection/reprotection of **15** was necessary to set the stage for the intramolecular cyclization. Thus, **15** was first deprotected with TFA and then regioisomerically reprotected with di-*tert*-butyl dicarbonate (Boc_2O) to afford carbamate **17**. Thanks to the protecting group shuffle, biaryl **17** underwent intramolecular cyclization upon exposure to catalytic osmium tetroxide and excess sodium periodate to generate aminal **18**. Dehydration of **18** was performed with methanesulfonyl chloride (MsCl) and triethylamine to give imidazo[5,1-*a*]isoquinoline **19**. Finally, removal of the TIPS group from **19** with tetrabutylammonium fluoride (TBAF) followed by the known[4b] oxidation of phenol **20** with HNO_3 delivered cribrostatin 6 (**1**). The spectra of synthetic **1** are in excellent agreement with those reported for the natural product.[1]

In summary, we report a convergent synthesis of cribrostatin 6. The synthesis provides a new approach to both the imidazo[5,1-*a*]isoquinoline ring system and cribrostatin 6.

Experimental Section

2,4-Diethoxy-3-methylphenol (10). To a 250 mL round-bottomed flask, open to the air, were added **9** (5.00 g, 27.8 mmol), acetic acid (125 mL, glacial), phosphoric acid (7.9 mL, ≥85 wt % solution in water), hydrogen peroxide (5.8 mL, ca. 56 mmol, 30−32 wt % solution in water), and a stir bar. The resulting solution was stirred open to the air at room temperature for 15 h and then quenched with saturated $NaHSO_3$ (75 mL). The homogeneous solution was transferred to a 500 mL Erlenmeyer flask and stirred until the peroxides (**CAUTION: Explosion Hazard**) were quenched (ca. 15 min, checked with peroxide test paper, EM Science catalog # 10011-1). The solution was transferred to a separatory funnel

(5) Clader, J. W.; Berger, J. G.; Burrier, R. E.; Davis, H. R.; Domalski, M.; Dugar, S.; Kogan, T. P.; Salisbury, B.; Vaccaro, W. *J. Med. Chem.* **1995**, *38*, 1600–1607.

(6) Compare: (a) Keenan, R. M.; Weinstock, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulos, D. E.; Girard, G. R.; Hill, D. T.; Morgan, T. M.; Samanen, J. M.; Hempel, J.; Eggleston, D. S.; Aiyar, N.; Griffin, E.; Ohlstein, E. H.; Stack, E. J.; Weidley, E. F.; Edwards, R. *J. Med. Chem.* **1992**, *35*, 3858–3872. For a recent review of directed metalations, see: (b) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206–2225.

(7) Doyle, F. P.; Hardy, K.; Nayler, J. H. C.; Soulal, M. J.; Stove, E. R.; Waddington, H. R. J. *J. Chem. Soc.* **1962**, 1453–1458.

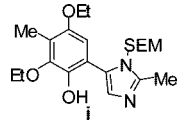
(8) González, R. R.; Gambarotti, C.; Liguori, L.; Bjorsvik, H.-R. *J. Org. Chem.* **2006**, *71*, 1703–1706.

(9) For a three-step conversion of **9** to **10**, see ref 4.

(10) Finkelstein, B. L. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley: Chichester, UK, 1995; Vol. 1, p 686.

(11) The structure of **11** was confirmed by X-ray crystallography (see the Supporting Information).

(12) Cursory attempts to achieve a palladium-catalyzed cross-coupling reaction between **11** and **7** failed to give any of the desired biaryl product **i**. Compounds **11** and **6** (protodestannylated **7**) were recovered from the reaction mixture.



(13) For a recent review, see: Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704–4734.

containing saturated NaCl solution (230 mL). The resulting mixture was extracted with CH_2Cl_2 (4 × 175 mL). The extracts were pooled, washed with saturated NaCl solution (1 × 200 mL), dried with $MgSO_4$, and filtered. Removal of the solvent in vacuo gave a brown oil. This oil was purified by flash column chromatography (24 cm × 4 cm; silica gel) with 15% Et_2O in hexanes (1 L) to afford 1.00 g of **9** and 2.30 g (42%, or 53% based on unrecovered **9**) of **10**[14] as a white solid (R_f = 0.3; 20% Et_2O in hexanes; silica). An analytically pure sample of **10** could be obtained by recrystallization from cold (−25 °C) pentane to give a white solid: mp 42−43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 5.25 (s, 1H), 3.98−3.91 (m, 4H), 2.17 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 144.8, 143.1, 120.4, 111.4, 108.0, 69.2, 64.5, 15.7, 15.0, 9.7; IR (neat) ν 3375, 2977, 1488 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{17}O_3$ (MH^+) 197.1178, found 197.1177. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.03; H, 8.15.

5-[2-Bromo-3,5-diethoxy-4-methyl-6-(triisopropylsiloxy)phenyl]-2-methyl-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-imidazole (14). To a 250 mL round-bottomed flask were added **13** (950 mg, 1.69 mmol), anhydrous Et_2O (40 mL), and a stir bar. The flask was stirred, placed in an ice bath (0 °C), and to it was added trifluoroacetic acid (40 mL) over a period of 15 min. The resulting solution was stirred at 0 °C for 10 min and then bromine-1,4-dioxane (see preparation of **11** in Supporting Information, 831 mg, 3.35 mmol) was added in one portion. The orange solution was stirred at 0 °C for 15 min and then slowly (ca. 15 min) quenched with 6 M NaOH (100 mL). The flask was removed from the ice bath and neutralized (ca. pH = 7) with solid NaOH (ca. 2 g). The mixture was transferred to a separatory funnel, the ether layer was separated, and the aqueous layer was extracted with Et_2O (3 × 40 mL). The ether layer and extracts were pooled, washed with 1 M NaOH (1 × 50 mL), H_2O (1 × 50 mL) and saturated NaCl solution (1 × 50 mL), dried with $MgSO_4$, and filtered. Removal of the solvent in vacuo gave an orange oil. The oil was purified by flash column chromatography (18 cm × 4 cm; silica) with 45% Et_2O in hexanes (1 L) to afford 788 mg (73%) of **14** (R_f = 0.3; 50% Et_2O in hexanes; silica) as a white solid: mp 96−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H), 5.18 (d, J = 11.6 Hz, 1H), 4.82 (d, J = 11.6 Hz, 1H), 4.08−3.83 (m, 3H), 3.72−3.64 (m, 1H), 3.34−3.28 (m, 1H), 3.06−2.99 (m, 1H), 2.47 (s, 3H), 2.26 (s, 3H), 1.41 (t, J = 6.8 Hz, 3H), 1.35 (t, J = 6.8 Hz, 3H), 0.94−0.84 (m, 21 H), 0.71−0.66 (m, 2H), −0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 148.3, 145.3, 145.2, 128.3, 127.9, 127.8, 121.8, 115.7, 72.6, 68.3, 68.2, 65.2, 17.6, 17.4, 17.3, 15.1, 14.9, 13.3, 13.2, 10.7, −1.7; IR (neat) ν 2942, 2865, 1415, 1381 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{54}BrN_2O_4Si_2$ (MH^+) 641.2806, found 641.2810. Anal. Calcd for $C_{30}H_{53}BrN_2O_4Si_2$: C, 56.14; H, 8.32; N, 4.36. Found: C, 56.28; H, 8.31; N, 4.30.

7,9-Diethoxy-5,6-dihydro-3,8-dimethyl-10-(triisopropylsilyloxy)imidazo[5,1-*a*]isoquinolin-5-ol (18). To a 25 mL round-bottomed flask were added **17** (226 mg, 0.395 mmol), THF (7 mL), *tert*-butanol (3.5 mL), H_2O (3.5 mL), OsO_4 (155 μL, ca. 0.024 mmol, 4 wt % in H_2O), $NaIO_4$ (279 mg, 1.30 mmol), and a stir bar. The solution was stirred open to the air at room temperature, and the progress of the reaction was monitored by TLC (desired product R_f = 0.2; 100% EtOAc; silica). Once the reaction was complete (ca. 18 h), the solution was transferred to a separatory funnel, diluted with H_2O (20 mL), and extracted with Et_2O (3 × 20 mL). The organic extracts were pooled, washed with H_2O (1 × 25 mL) and saturated NaCl solution (1 × 25 mL), dried with $MgSO_4$, and filtered. Removal of the solvent in vacuo gave a crude solid. The solid was purified by flash column chromatography (15 cm × 2 cm; silica) with 100% EtOAc (300 mL) to afford 121 mg (66%) of **18** as a white solid: mp 190−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 5.81 (br s, 1H), 4.63 (br s, 1H), 4.10−4.03 (m, 1H), 3.84−3.70 (m, 3H), 3.55 (dd, J = 16.0, 2.2 Hz, 1H), 2.88 (dd, J = 16.0, 3.8 Hz, 1H), 2.35 (s, 3H), 2.20 (s, 3H), 1.43−1.34 (m, 9H), 1.05−0.99 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 148.5, 142.4, 142.3, 126.1, 124.5, 124.2, 118.0, 116.3, 72.6, 68.9, 68.8, 31.5, 18.1, 18.0, 15.6, 15.4, 14.1, 12.4, 10.3; IR (neat) ν 3089, 2931, 2702, 2865, 1460, 1386, 1083 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{43}N_2O_4Si$ (MH^+) 475.2992, found 475.3001.

7,9-Diethoxy-3,8-dimethyl-10-(triisopropylsilyloxy)imidazo[5,1-*a*]isoquinoline (19). To a 25 mL round-bottomed flask were added **18** (52 mg, 0.11 mmol), anhydrous CH_2Cl_2 (5 mL), triethylamine (77 μL), and a stir bar. The solution was stirred, placed in an ice bath (0 °C), and to it was added distilled (see general procedures) methanesulfonyl chloride (9 μL, 0.1 mmol). The solution was stirred at 0 °C, and the progress of the reaction was monitored by TLC (desired product R_f = 0.4; 75% EtOAc in hexanes; silica). Once the reaction was complete (ca. 2.5 h), the solution was transferred to a separatory funnel. To the separatory funnel was added H_2O (20 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer and extracts were pooled, washed with H_2O (1 × 25 mL) and saturated NaCl solution (1 × 25 mL), dried with $MgSO_4$, and filtered. Removal of the solvent in vacuo gave a crude solid. The solid was purified by flash column chromatography (10 cm × 2 cm; silica) with 75% EtOAc in hexanes (300 mL) to afford 37 mg (74%) of **19** as a beige solid: mp 134−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 3.96−3.88 (m, 4H), 2.63 (s, 3H), 2.28 (s, 3H), 1.54−1.43 (m, 6H), 1.36 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 7.2 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 147.7, 141.7, 136.6, 125.6, 123.6, 122.9, 118.4, 117.7, 117.6, 107.8, 69.8, 69.1, 18.1, 15.6, 15.4, 14.1, 12.8, 10.4; IR (neat) ν 2865, 1459, 1367, 1255, 1015 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{41}N_2O_3Si$ (MH^+) 457.2886, found 457.2888. Anal. Calcd for $C_{26}H_{40}N_2O_3Si$: C, 68.38; H, 8.83; N, 6.13. Found: C, 68.40; H, 8.98; N, 5.89.

Acknowledgment. We thank the NSF for financial support of the BC Mass Spectrometry Center (Grant # DBI-0619576). We are also grateful to Dr. Bo Li (Boston College) for X-ray crystallographic studies, and Dr. Alex Scopton for helpful discussions.

Supporting Information Available: General experimental procedures, experimental procedures for compounds **1**, **6**, **7**, **9**, **11**−**13**, **15**−**17**, and **20**, copies of the ^{1}H and ^{13}C NMR spectra for compounds **1**, **6**, **7**, **9**−**15**, and **17**−**20**, and a CIF file giving X-ray data for structure **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Phenol **10** is somewhat unstable to the reaction conditions. A better yield of **10** is obtained if the reaction is not run to completion.