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Synthesis of Porritoxin

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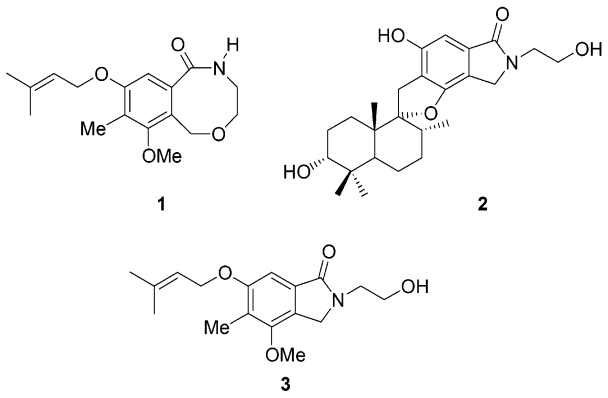
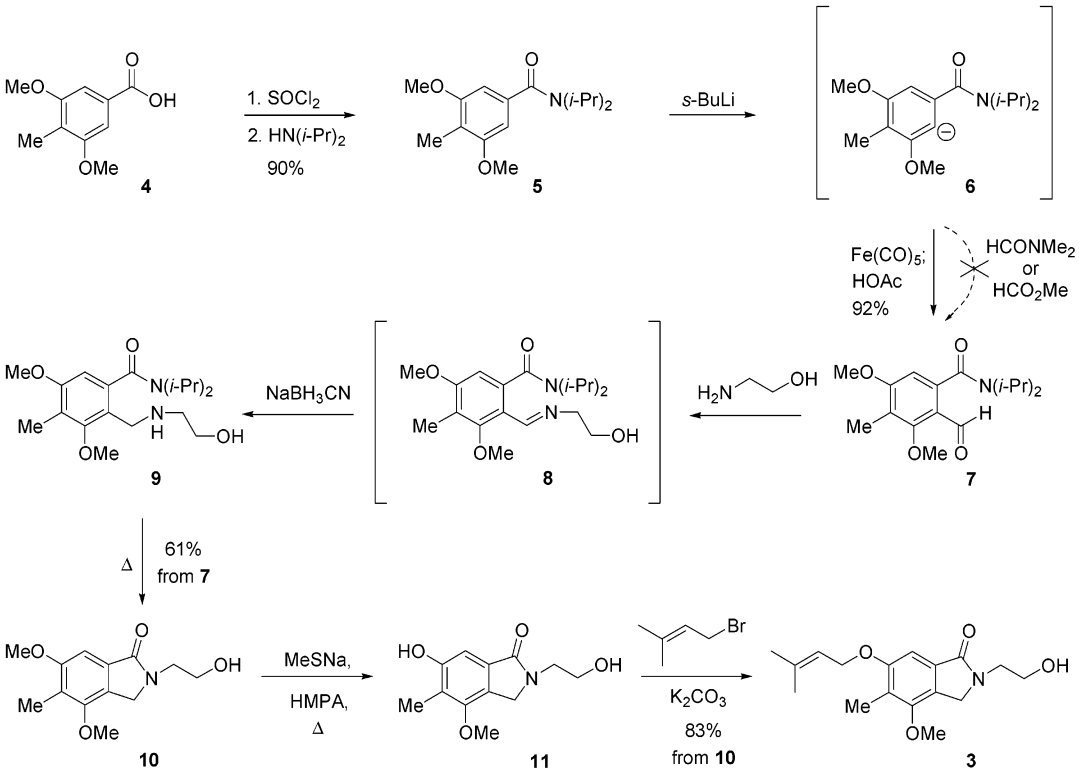
Abstract: A total synthesis following the sequence in Scheme 1 confirms that porritoxin possesses revised structure **3**, not the originally assigned **1**. A key reaction was the use of iron pentacarbonyl to formylate an aryllithium when DMF and methyl formate proved insufficiently reactive.

The isolation of the phytoxin porritoxin was recorded in 1992.[1] Porritoxin was assigned structure **1**, based largely on spectroscopic—especially NMR—measurements. A reinvestigation[2] of the structure of porritoxin was stimulated by the similarity of its spectra with corresponding parts of spectra subsequently recorded[3] for stachybotramide (**2**). The reinvestigation (reported in 2002), which relied primarily on detailed 2D NMR analysis, led to the revision of the structure of porritoxin from **1** to **3**. The data supporting the structure reassignment of **1** to **3** are persuasive, but an independent corroboration is desirable and neither **1** nor **3** has previously been prepared by total synthesis. We now report the total synthesis of **3** and the identity of synthetic **3** with natural porritoxin, thereby confirming **3** as the structure of the natural product.



The synthesis of **3** was accomplished according to Scheme 1. Thus, commercially available acid **4** was converted to diisopropylamide **5** by acid chloride formation ($SOCl_2$) followed by reaction with diisopropylamine. Ortho-lithiation/formylation of **5** to give **7** was anticipated to be routine, given the known, high-yielding ortho-lithiation/formylation conversions of **12** to **14**[4] and **13** to

SCHEME 1. Synthesis of Porritoxin



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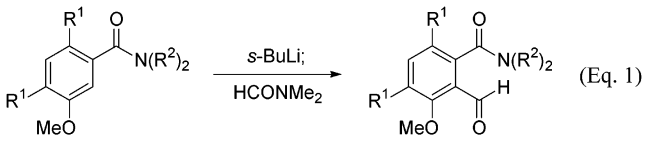
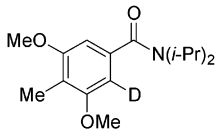
15[5] (eq 1).



12, R^1=H, R^2=*i*-Pr
13, R^1=OMe, R^2=Et

14, R^1=H, R^2=*i*-Pr
15, R^1=OMe, R^2=Et



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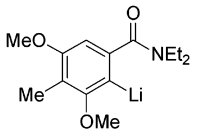

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To our surprise, ortho-lithiation of **5** with *s*-BuLi followed by attempted formylation with dimethylformamide or methyl formate led either to formation of only traces of **7** and recovery of **5** or, under forcing conditions (e.g., reaction of **6** with DMF or methyl formate at 60 °C), nonproductive consumption of **5**. Inclusion of additives (HMPA or tetramethylethylenediamine) or use of solvents other than THF failed to circumvent the impasse. D_2O-quench studies gave **16** (assayed by integration of the resonance for the aromatic proton(s) in **5**/**16**), establishing that formation of **6** was occurring cleanly. Given the positive precedents (eq 1), we attribute the failure of **6** to react with $HCONMe_2$/HCOOMe to a buttressing effect in which the C-4 methyl in **6** forces the C-3 methoxy into a conformation that inhibits reaction with $HCONMe_2$/HCOOMe. Use of the less sterically encumbered diethylamide analogue **17** did not improve the outcome. Since **6** does react with D_2O (to give **16**), **6** is clearly capable of reaction. Thus, a formylating agent more reactive than $HCONMe_2$/HCOOMe but compatible with the aprotic environment necessitated by an organolithio species was required. Examination of Larock's[6] three-page list of anion-compatible formylating agents did not lead to an obvious sure cure, but the list included iron pentacarbonyl. The relative reactivity of $Fe(CO)_5$ vis-à-vis HCOOMe was not clear, but $Fe(CO)_5$ was listed as a reagent that formylates Grignard reagents.[7] A particularly compelling argument in favor of trying $Fe(CO)_5$ is that—unlike many of the formylating agents listed by Larock—$Fe(CO)_5$ is commercially available.

In the event, ortho-lithiation of **5** to **6** followed by reaction with $Fe(CO)_5$ and treatment with acetic acid (presumably[7] for protonolysis of the carbonyl/iron bond) gave **7** in excellent yield.

The remainder of the synthesis proceeded uneventfully. Condensation of **7** with ethanolamine gave imine **8**, which was ordinarily not isolated but reduced in situ to **9** with $NaBH_3CN$. Heating of **9** neat at 180 °C resulted in cyclization, affording **10**. We have previously described the utility of MeSLi in hot hexamethylphosphoramide (HMPA) for the nucleophilic cleavage of aryl methyl ethers.[8] Use of the commercially available sodium analogue MeSNa[9] in HMPA at 160 °C led to selective monodeprotection of the less hindered ether in **10** to give phenol **11**. Finally, the prenylation of **11** afforded **3**. The melting point and spectra of synthetic **3** are in excellent agreement with those reported[1] for natural porritoxin.

In conclusion, we have accomplished the first total synthesis of porritoxin and confirmed that the revised structure **3** is that of the natural product.

Experimental Section[10]

***N*,*N*-Diisopropyl-3,5-dimethoxy-4-methylbenzamide (5).** A suspension of 3,5-dimethoxy-4-methylbenzoic acid (**4**) (10.2 g, 51.0 mmol) in $SOCl_2$ (15.0 mL, 206 mmol) was stirred under N_2 at 80 °C until gas evolution ceased (ca. 0.5 h). Excess $SOCl_2$ was then removed by repeated azeotropic distillation with dry toluene (3 × 100 mL) in vacuo (rotary evaporator at 40 °C, ca. 6 Torr), and the resulting brownish solid was dissolved in dry CH_2Cl_2 (20 mL). *i*-Pr_2NH (15.0 mL, 107 mmol) was then added via syringe dropwise over 15 min; the reaction was exothermic, and a precipitate formed. The resulting mixture was stirred overnight (14 h) at room temperature to ensure complete reaction and then diluted with more CH_2Cl_2 (80 mL) and washed with 1 N NaOH (200 mL). The aqueous wash was extracted with more CH_2Cl_2 (100 mL), and the combined organic phases were successively washed with water and brine and dried over magnesium sulfate. The solvent was evaporated in vacuo to give a crystalline brownish solid which was purified by flash column chromatography on silica gel (8 × 7 cm) with 2% then 5% (v/v) MeOH in CH_2Cl_2 as eluent to yield a slightly yellow crystalline solid (12.9 g, 90%): mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 2 H), 3.81 (s, 6 H), 3.69 (bs, 2 H), 2.08 (s, 3 H), 1.46 (bs, 6 H), 1.24 (bs, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 157.9, 136.9, 114.9, 101.0, 55.8, 20.9, 8.3 (due to coincidence or broadening into the baseline, one peak appears missing); IR (film) ν 2967, 2935, 1630, 1606 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{25}NO_3Na$ [M + Na] 302.1732, found 302.1725. Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.84; H, 9.10; N, 5.01.

2-Formyl-*N*,*N*-diisopropyl-3,5-dimethoxy-4-methylbenzamide (7). A 1.40 M solution of *s*-butyllithium in hexanes (0.80 mL, 1.1 mmol) was added dropwise to a solution of *N*,*N*-diisopropyl-3,5-dimethoxy-4-methylbenzamide (**5**) (313 mg, 1.12 mmol) in dry THF (10 mL) stirred under Ar at −78 °C in a dry ice/acetone bath. After 1 h at the same temperature, D_2O-quench of a 0.1 mL aliquot showed correct deuterium incorporation by ^{1}H NMR. Iron pentacarbonyl (0.16 mL, 1.2 mmol; **CAUTION: pyrophoric and highly toxic**) was added dropwise over 1 min, and the reaction mixture was allowed to warm to room temperature overnight (ca. 11 h). Glacial acetic acid (0.10 mL, 1.7 mmol) was added in one portion to the dark green solution, and the resulting deep red mixture was stirred for 15 min. Dilution with

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(4) Chen, C.-W.; Beak, P. *J. Org. Chem.* **1986**, *51*, 3325−3334. The conversion of **12** to **14** had already been reproduced in good yield in our laboratories (Scopton, A.; Kelly, T. R., unpublished results).
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(8) Kelly, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977**, 3859−3860.
(9) For an early use of CH_3SNa, see: Kornblum, N.; Scott, A. *J. Am. Chem. Soc.* **1974**, *96*, 590−591. For an overview of aryl methyl ether cleavage with thiolates, see: Merriman, G. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 5, pp 3161−3163.
(10) For general experimental procedures see the Supporting Information in: Kelly, T. R.; Silva, R. A.; De Silva, H.; Jasmin, S.; Zhao, Y. *J. Am. Chem. Soc.* **2000**, *122*, 6935−6949.

diethyl ether (100 mL) was followed by washing the organic layer with aqueous 1 N HCl (50 mL), 0.1 N NaOH (50 mL), a saturated solution of $NaHCO_3$ (40 mL), water, and brine. The organic phase was dried over magnesium sulfate, and the solvent was evaporated in vacuo to give a yellow solid which was purified by flash column chromatography on silica gel (2 × 15 cm) with 2% then 5% (v/v) MeOH in CH_2Cl_2 as eluent to yield a slightly yellow solid (311 mg, 92%): mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1 H), 6.44 (s, 1 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 3.48 (m, 2 H), 2.13 (s, 3 H), 1.63 (bs, 3 H), 1.55 (bs, 3 H), 1.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.0, 168.8, 163.1, 162.5, 139.7, 119.9, 118.7, 104.1, 63.0, 56.0, 51.0, 45.7, 21.0, 20.8, 20.0, 19.7, 8.6; IR (film) ν 2971, 2936, 1684, 1636 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{25}NO_4Na$ [M + Na] 330.1681, found 330.1685. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.45; H, 8.28; N, 4.59.

2,3-Dihydro-2-(2-hydroxyethyl)-4,6-dimethoxy-5-methyl-1*H*-isoindol-1-one (10). A mixture of 2-formyl-*N*,*N*-diisopropyl-3,5-dimethoxy-4-methylbenzamide (**7**) (1.00 g, 3.25 mmol), ethanolamine (0.39 mL, 6.5 mmol), and $NaBH_3CN$ (0.41 g, 6.5 mmol) in dry methanol (10 mL) was stirred under Ar in the presence of activated 3 Å molecular sieves (ca. 1 g) for 1 h. Bromocresol green (ca. 5 mg) was then added;[11] a change in color from yellow to blue was observed. Then, concentrated HCl was added until (ca. 0.5 mL) the blue coloration changed to yellow (pH ∼4). The reaction mixture was stirred at room temperature (ca. 2 h) until formation of **9** was complete as indicated by TLC (5:95 MeOH/CH_2Cl_2). A saturated aqueous solution of $NaHCO_3$ was added until (ca. 20 mL) the pH was ∼9; the reaction mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with water and brine and dried over magnesium sulfate. The solvent was evaporated in vacuo to give an off-white solid (975 mg); 200 mg of that crude material was heated at 180 °C until (ca. 3 h) gas evolution (presumably diisopropylamine) ceased. Once at room temperature, the resulting pale yellow solid was purified by preparative TLC (5:95 MeOH/CH_2Cl_2) to yield **10** as an off-white solid (105 mg, 61% from **7**): mp 125−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1 H), 4.52 (s, 2 H), 3.90 (t, J = 4.8 Hz, 2 H), 3.85 (s, 3 H), 3.85 (s, 3 H), 3.74 (t, J = 4.8 Hz, 2 H), 3.45 (bs, 1 H), 2.16 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 159.1, 153.1, 131.5, 123.9, 122.7, 99.9, 61.7, 59.7, 56.0, 50.0, 46.4, 9.5; IR (film) ν 3378, 2936, 1668, 1621 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{17}NO_4Na$ [M + Na] 274.1055, found 274.1054. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.28; H, 6.90; N, 5.68.

2,3-Dihydro-2-(2-hydroxyethyl)-4-methoxy-5-methyl-6-[(3-methyl-2-butenyl)oxy]-1*H*-isoindol-1-one (Porritoxin, 3). A suspension of 2,3-dihydro-2-(2-hydroxyethyl)-4,6-dimethoxy-5-methyl-1*H*-isoindol-1-one (**10**) (29 mg, 0.11 mmol), sodium thiomethoxide (29 mg, 0.41 mmol), and dry HMPA (0.20 mL) was stirred at 160 °C. After 2 h at the same temperature, TLC (1:9 MeOH/CH_2Cl_2) of an aliquot partitioned between water and dichloromethane showed disappearance of starting material (R_f ∼0.4) and a new spot at R_f ∼ 0.2. Once at room temperature, water (10 mL) was added to the mixture and the HMPA was washed out of the aqueous phase by extracting with CH_2Cl_2 (6 × 10 mL). The water was evaporated in vacuo, and the crude, water-soluble phenol **10** (or the corresponding phenoxide) was dissolved in dry acetone (3 mL). K_2CO_3 (18 mg, 0.13 mmol) was added, and the mixture was stirred under Ar. Dimethylallyl bromide (25 μL, 0.21 mmol) was added via syringe, and the resulting suspension was refluxed overnight (ca. 11 h). TLC (1:9 MeOH/CH_2Cl_2) showed consumption of starting material and a new spot at R_f ∼0.3. Filtration and evaporation of the filtrate afforded a pale yellow oil which was purified by preparative TLC (1:9 MeOH/CH_2Cl_2) to yield **3** as an off-white solid (28 mg, 83% from **10**): mp 114−116 °C (lit.[1] mp 115−116 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.95 (s, 1 H), 5.47 (t, J = 6.8 Hz, 1 H), 4.84 (bs, 1 H), 4.57 (s, 2 H), 4.51 (d, J = 6.8 Hz, 2 H), 3.84 (s, 3 H), 3.60 (m, 2 H), 3.55 (t, J = 5.2 Hz, 2 H), 2.10 (s, 3 H), 1.74 (s, 3 H), 1.65 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5, 158.7, 152.4, 138.0, 132.2, 125.1, 121.8, 120.5, 99.7, 68.7, 59.7, 56.4, 49.2, 45.1, 26.0, 18.5, 10.2; IR (film) ν 3344, 2960, 1667 (broad) cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}NO_4Na$ [M + Na] 328.1511, found 328.1525.

Acknowledgment. We thank Dr. M. Horiuchi[1] for providing a copy of the ^{1}H NMR spectrum of natural porritoxin and Mr. Alex Scopton for helpful discussions.

Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra of synthetic **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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