Synthesis of 6,7-Dihydroxyoxindole (A Subunit of Paraherquamide A)

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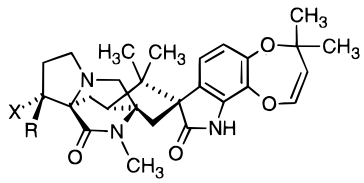
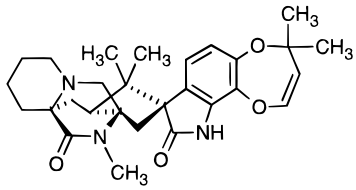
Paraherquamide A (**1**) and marcfortine A (**2**) are alkaloids isolated from *Penicillium paraherquei*[1] and *Penicillium roqueforti*,[2] respectively. Both of these natural products have potent anthelmintic activity,[3] and they are structurally very similar. In particular, they both contain the 4,4-dimethyldioxepinooxindole ring system that was first prepared by Williams and Cushing.[4] The Williams research group used this methodology in a total synthesis of paraherquamide B.[5]



Paraherquamide A, R = CH_3, X = OH, **1**
Paraherquamide B, R = H, X = H

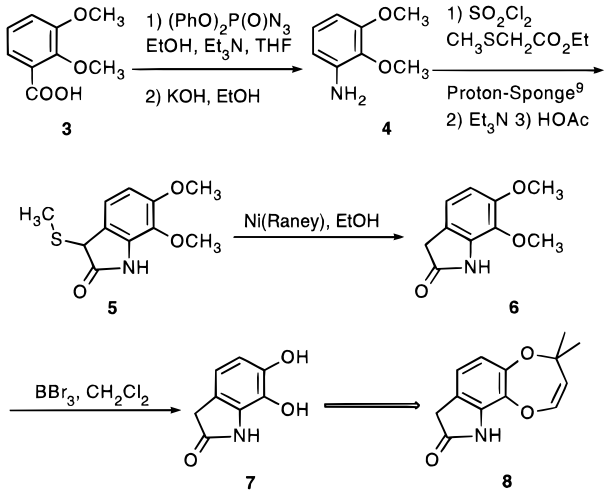


Marcfortine A, **2**

We report a short and efficient synthesis of 6,7-dihydroxyoxindole (**7**). We use the methodology of Gassman and co-workers[6] to form 6,7-dihydroxyoxindole (**7**) in four steps with an overall yield of 35% from a commercially available starting material as opposed to the seven steps and 23% overall yield in the synthesis of Williams and Cushing.[4] 6,7-Dihydroxyoxindole can be converted to 4,4-dimethyldioxepinooxindole (**8**) by the route developed by these researchers.[4] 4,4-Dimethyldioxepinooxindole (**8**) or its precursors are envisoned to be intermediates in a total synthesis of paraherquamide A or marcfortine A.

Commercially available 2,3-dimethoxybenzoic acid (**3**) was converted to 2,3-dimethoxyaniline (**4**) by the Yamada modification of the Curtius rearrangement[7] followed by hydrolysis of the resulting urethane (Scheme 1). 2,3-Dimethoxyaniline (**4**) was converted to 3-(methylthio)-6,7-dimethoxyoxindole (**5**) by means of a modified Gassman oxindole synthesis.[6,8] Ethyl methylthioacetate was chlorinated with sulfuryl chloride and reacted with 2,3-dimethoxyaniline (**4**) in the presence of 1,8-bis(dimethylamino)naphthylene[9] to produce an azasulfonium salt, which was in turn treated with triethylamine to bring about the rearrangement of the azasulfonium ylide to afford the ethyl ester of 2-amino-3,4-dimethoxy-α-(methylthio)benzeneacetic acid. This carboxylic acid was treated with glacial acetic acid to yield 3-(methylthio)-6,7-dimethoxyoxindole (**5**) in 80% overall yield. The presence of electron-donating substituents on the aniline ring necessitate chlorination of the thioether rather than the aniline.[6b] This oxindole **5** was desulfurized with Raney nickel to give 6,7-dimethoxyoxindole (**6**) in 62% yield. 6,7-Dimethoxyoxindole (**6**) was demethylated with BBr_3 in CH_2Cl_2 to produce 6,7-dihydroxyoxindole (**7**) in 86% yield.

Scheme 1



3 **4** **5** **6** **7** **8**

In summary, we prepared 6,7-dihydroxyoxindole (**7**) in four steps with an overall yield of 35% from 2,3-dimethoxybenzoic acid (**3**). Oxindole (**7**) can be converted to 4,4-dimethyldioxepinooxindole (**8**) by the method of Williams and Cushing.[4]

Experimental Section

General Information. 2,3-Dimethoxybenzoic acid was purchased from Aldrich. All moisture-sensitive reactions were conducted under N_2. Unless specified, all commercially available solvents and reagents were used without further purification. Brine refers to a saturated aqueous sodium chloride solution. Solvent removal was accomplished by a rotary evaporator operating at house vacuum (40−50 Torr). Column chromatography was performed with silica gel 60 (EM Science, 230−400 mesh ASTM). *J* values are given in Hz.

3-(Methylthio)-6,7-dimethoxyoxindole (5). CH_2Cl_2 (200 mL, dried over 4 Å sieves) was cooled to −78 °C under N_2. Ethyl (methylthio)acetate (3.95 mL, 30.7 mmol) was added by syringe,

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(7) (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) White, J. D.; Yager, K. M.; Yakura, T. *J. Am. Chem. Soc.* **1994**, *116*, 1831−1838. (c) 2,3-Dimethoxyaniline is commercially available from TCI-US.
(8) (a) Wierenga, W. *J. Am. Chem. Soc.* **1981**, *103*, 5621−5623. (b) Warpehoski, M. A. *Tetrahedron Lett.* **1986**, *27*, 4103−4106. (c) Warpehoski, M. A.; Gebhard, I.; Kelly, R. C.; Krueger, W. C.; Li, L. H.; McGovern, J. P.; Praire, M. D.; Wicnienski, N.; Wierenga, W. *J. Med. Chem.* **1988**, *31*, 590−603. (d) Johnson, P. D.; Aristoff, P. A. *J. Org. Chem.* **1990**, *55*, 1374−1375.
(9) 1,8-bis(dimethylamino)naphthalene is sold by Aldrich under the name Proton-Sponge.

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followed by sulfuryl chloride (2.47 mL, 30.7 mmol), and the resulting mixture was stirred for 15 min. A solution of **4** (4.7 g, 31 mmol) and 1,8-bis(dimethylamino)naphthalene (6.58 g, 30.7 mmol) in CH_2Cl_2 (100 mL) was added over 1 h. After the mixture was stirred for 2 h, a solution of triethylamine (4.28 mL, 30.7 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the reaction was allowed to warm to rt. This mixture was washed with water (3 × 100 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to yield ethyl 2-amino-3,4-dimethoxy-α-(methylthio)benzeneacetic acid as a brown oil. The crude material was taken up in glacial acetic acid (200 mL) and stirred under N_2 for 3 h. The acetic acid was removed by azeotropic rotary evaporation using toluene to yield a brown tacky solid that was suspended in Et_2O (100 mL), stirred for 30 min, filtered, and washed with cold Et_2O. The crude product (5.6 g) was obtained in 80% yield. An analytically pure sample was obtained by recrystallization from toluene to yield orange crystals: mp 168−170 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (3H, s), 3.88 (3H, s), 3.88 (3H, s), 4.26 (1H, s), 6.60 (1H, d, J = 8), 7.04 (1H, d, J = 8), 7.69 (1H, br s); MS (EI, 70eV) m/z (relative intensity) 241 (M^+ + 2H, 1), 240 (M^+ + H, 3), 239 (M^+, 26). Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.18; H, 5.19; N, 5.49.

6,7-Dimethoxyoxindole (6). Under N_2, **5** (4.05 g, 16.9 mmol) was dissolved in ethanol (100 mL) and treated with a large excess of Raney nickel. The suspension was refluxed for 2 h. Analysis (TLC, 1:1 EtOAc:Hex) showed the reaction to be complete. The reaction was filtered through Celite and concentrated to give crude **6** (2.96 g) as an orange solid. The crude product was recrystallized from EtOAc/hexane to give pure **6** (2.04 g, mp 188−191 °C dec) in 62% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (2H, s), 3.87 (3H, s), 3.89 (3H, s), 6.55 (1H, d, J = 8), 6.89 (1H, d, J = 8), 7.52 (1H, br s); MS (EI, 70eV) m/z (relative intensity) 194 (M^+ + H, 11), 193 (M^+, 100); HRMS (EI) m/z calcd for $C_{10}H_{11}NO_3$ (M^+) 193.0739, found 193.0740.

6,7-Dihydroxyoxindole (7). Under N_2, **6** (2.00 g, 10.4 mmol) was dissolved in dry CH_2Cl_2 (175 mL). The mixture was cooled to −78 °C to give an orange suspension. Boron tribromide (52 mL, 52 mmol, 1.0 M in CH_2Cl_2) was added dropwise over 30 min. The reaction was warmed to rt over 90 min and was maintained at rt for 1 h. The reaction mixture was poured over ice/water (500 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 100 mL). The aqueous layer was combined with the original organic layer and again separated. The aqueous layer was again extracted with EtOAc. The combined EtOAc extracts were dried over $MgSO_4$ and concentrated to yield **7** (1.04 g, 61% yield) as a tan solid: mp 237−245 °C dec. The aqueous layer was saturated with NaCl and reextracted with EtOAc (4 × 50 mL). Additional **7** (0.43 g, 25% yield) was isolated from these extracts: ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD) δ 3.46 (2H, d, J = 1), 6.52 (1H, d, J = 8), 6.62 (1H, d, J = 8); MS (EI, 70eV) m/z (relative intensity) 167 (M^+ + 2H, 1), 166 (M^+ + H, 9), 165 (M^+, 100); HRMS (EI) m/z calcd for $C_8H_7NO_3$ (M^+) 165.0426, found 165.0423. Anal. Calcd for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 57.98; H, 4.46; N, 8.35.

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Supporting Information Available: Copies of IR and UV data for compounds **5**−**7** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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