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A direct synthesis of denbinobin

George A. Kraus* and Ning Zhang

Department of Chemistry, Iowa State University, Ames, IA 50011, USA

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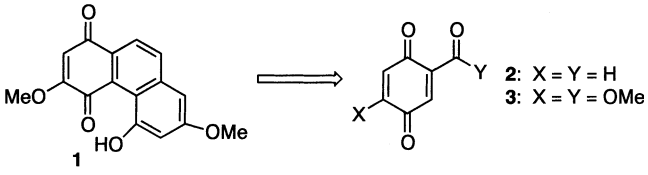
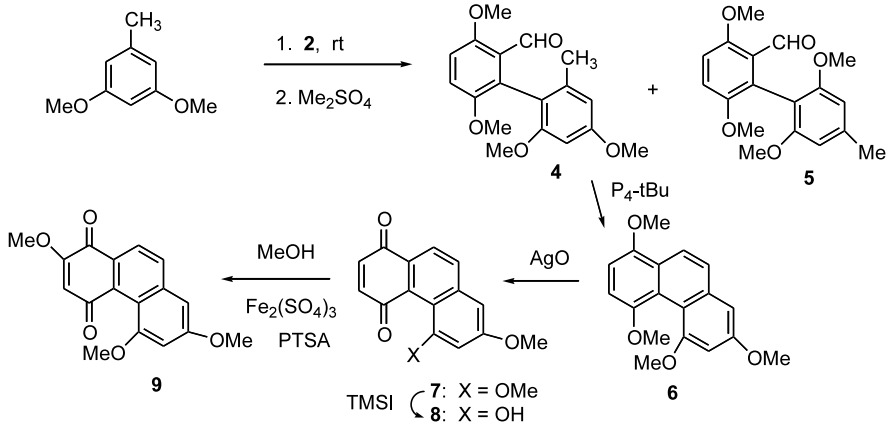
Abstract—Denbinobin was made in seven steps from quinone **3**. The cyclization of aldehyde **12** using P_4-*t*Bu and the oxidation of a hindered alcohol with MnO_2 were key steps.

Denbinobin (**1**) is a phenanthrene quinone from *Dendrobium moniliforme*.[1] It exhibits antitumor activity in vitro and in vivo[2] and potent anti-inflammatory[3] activity. A synthesis of denbinobin has been reported by Krohn and co-workers.[4] As part of a study of the applications of phosphazine bases to organic synthesis, we report the total synthesis of **1** by a strategy distinctly different from that of Krohn.[5]



We viewed quinones **2**[6] or **3**[7] as starting materials for the synthesis of **1**. Although we have studied additions of electron rich aromatic rings to quinones,[8,9] the installation of the methoxyl group at C-3 later in the synthesis was a concern. The reaction of orcinol dimethyl ether with **2** followed by methylation afforded adducts **4** and **5** in a ratio of 6:1 in 62% yield (Scheme 1). Cyclization of **4** using P_4-*t*Bu (benzene, 100°C) gave **6** in 90% yield. This cyclization did not occur with strong bases such as LDA or lithium tetramethylpiperidide. Oxidation with silver oxide[10] furnished quinone **7** in 50% yield. Deprotection of **7** (TMSI, −78°C, 1 h) afforded **8** in only 20% yield. Unfortunately, the addition of methanol to **7** catalyzed by ferric sulfate[11] gave a product whose NMR was different from that of the methyl ether of **1**. It's structure was tentatively assigned as **9**.

Since quinone **3** contains the methoxyl group with the correct regiochemistry, we prepared it from commer-



Scheme 1.

* Corresponding author.

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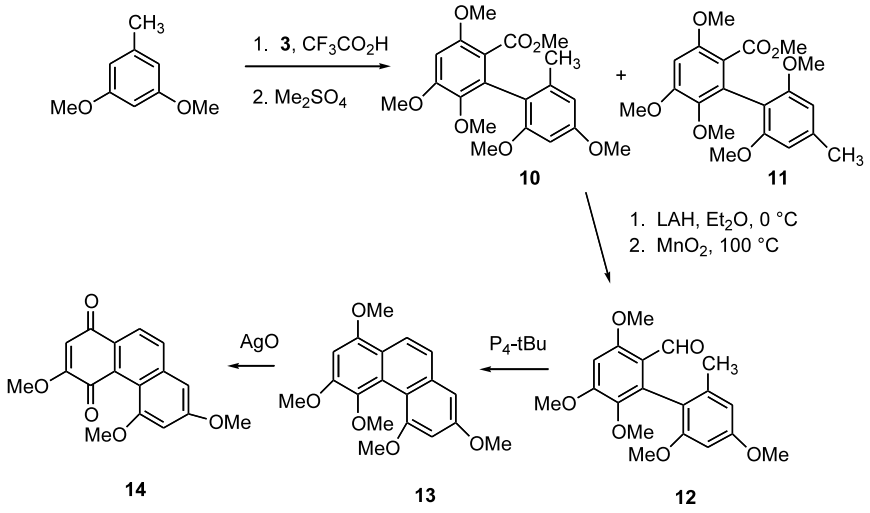

Scheme 2.

cially available 2,4,5-trimethoxybenzoic acid. The reaction of **3** with orcinol dimethyl ether required 1 equiv. of trifluoroacetic acid and generated two inseparable isomers (Scheme 2). The mixture of isomers was methylated (Me_2SO_4, K_2CO_3, acetone, 60°C) to give biphenyls **10** and **11** as an 8:1 ratio of separable isomers. Initially, we attempted to reduce **10** to aldehyde **12** using DIBAL. Despite modifications of temperature (−78 to 25°C) and stoichiometry (1–3 equiv. DIBAL/**10**), we recovered mostly unreacted starting material. Fortunately, the ester could be reduced in 92% yield using LAH in ether at 0°C. Attempted oxidation (Swern, DDQ[12]) led to recovered starting material. This is consistent with molecular modeling experiments, which show that the benzylic alcohol is not very accessible. However, reaction of the alcohol with MnO_2 in boiling toluene at 110°C afforded aldehyde **12** in 65% yield from **10**. The reaction of **12** with P_4-*t*Bu (benzene, 100°C, 8 h) followed by oxidation gave quinone **14** (in 60% yield from **12**) whose NMR was identical to that reported by Krohn.[13] Selective demethylation using the conditions of Krohn (TMSI, CH_2Cl_2, rt) provided denbinobin in 52% yield.

Denbinobin has been synthesized in seven steps from quinone **3**. This route is direct enough to permit the synthesis of quantities of **1** sufficient for extensive biological evaluation. The testing of intermediates **7**, **8** and **14** will be reported in due course.

Acknowledgements

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13. Compound **12**: ^{1}H NMR ($CDCl_3$): δ 1.98 (s, 3H), 3.46 (s, 3H), 3.67 (s, 3H), 3.84 (s, 3H), 3.96 (s, 3H), 3.98 (s, 3H), 6.36–6.37 (d, 1H, $J=2.1$ Hz), 6.43–6.44 (d, 1H, $J=2.1$ Hz), 6.54 (s, 1H), 9.70 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.6, 55.5, 55.8, 56.1, 56.3, 60.6, 95.7, 96.0, 106.5, 115.6, 116.8, 137.0, 138.9, 140.6, 157.9, 158.3, 158.9, 160.4, 190.5. HRMS: found 346.1422, calcd 346.1416. Mp = 141–142°C.

Compound **14**: ^{1}H NMR ($CDCl_3$): δ 3.93 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 6.01 (s, 1H), 6.70–6.71 (d, 1H, $J=2.1$ Hz), 6.77–6.78 (d, 1H, $J=2.1$ Hz), 7.87–7.90 (d, 1H, $J=8.4$ Hz), 8.04–8.07 (d, 1H, $J=8.4$ Hz). ^{13}C NMR ($CDCl_3$): δ 55.8, 56.2, 56.8, 99.3, 102.2, 106.4, 117.1, 122.8, 131.0, 132.5, 133.0, 139.2, 158.3, 161.0, 163.1, 182.0, 184.9. HRMS: found 298.0848, calcd 298.0841. Mp = 181–182°C.