A Three-Step Synthesis of Cerpegin

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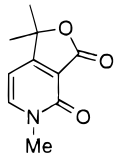
The pyridone natural product cerpegin (**1**) was isolated from *Ceropegia juncea*, a plant used in traditional Indian medicine for its tranquilizer, anti-inflammatory, analgesic, and antiulcer properties.[1,2] Three syntheses of cerpegin have been reported, employing five to six synthetic steps.[3] Because of our interest in the directed lithiation of pyridines[4] and its utility in the synthesis of natural products,[5] we have developed a concise route to cerpegin from commercially available 2-methoxypyridine (**2**).



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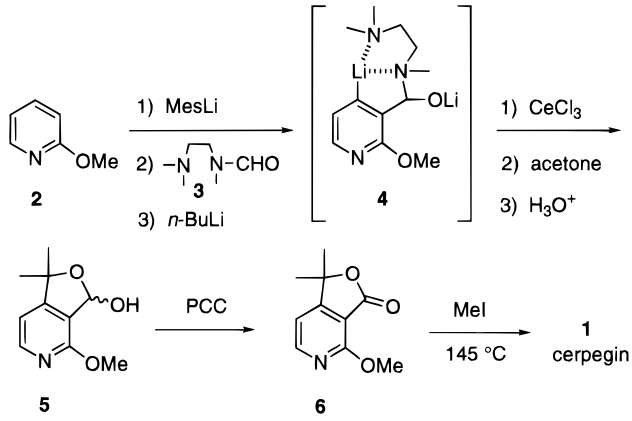
Lithiation of **2** at C-3 was effected using mesityllithium as the metalating agent[4a] (Scheme 1). Addition of *N*-formyl-*N*,*N*′,*N*′-trimethylethylenediamine[6] (**3**) gave an α-amino alkoxide *in situ*, which was treated with *n*-butyllithium to effect a directed lithiation[5,7] giving dianion **4**. The dianion **4** proved to be too basic to add to an enolizable ketone in acceptable yield. When acetone was added to **4**, 2-methoxy-3-pyridinecarboxaldehyde was isolated as the major product. Previous work from our laboratories[5b] has demonstrated that dianions of the type **4** will add to enolizable ketones if first treated with $CeCl_3$.[8] Addition of **4** to a slurry of anhydrous $CeCl_3$ in THF resulted in a homogeneous solution, which on treatment with acetone provided lactol **5** as a low-melting solid in 46% yield. Oxidation of **5** to lactone **6** was effected in an 83% yield using PCC. The final step of the synthesis was carried out by heating **6** in methyl

Scheme 1



iodide at 140 °C as reported by Kelly[3b] to give cerpegin (**1**) in 90% yield. The mp and spectral data for **1** were in agreement with reported data for naturally derived[1] and synthetic cerpegin.[3] The overall yield of this three-step synthesis was 34%.

Experimental Section

1,1-Dimethyl-4-methoxy-3-hydroxy-1,3-dihydrofuro[3,4-*c*]pyridine (5). Cerium chloride heptahydrate (5.0 g, 13.4 mmol) was placed in a dry 100-mL round-bottomed flask and heated at 145−150 °C under vacuum (0.25 mmHg) for 24 h. Under a N_2 atmosphere, the dry $CeCl_3$ powder was cooled to room temperature and suspended in THF (35 mL). The resulting slurry was vigorously stirred under N_2 overnight. Immediately prior to use, the $CeCl_3$ slurry was titrated with *tert*-butyllithium until a light orange coloration was achieved.[9]

To a solution of *tert*-butyllithium (2.5 M/pentane, 6 mL, 15 mmol) in 35 mL of THF at −78 °C was added 0.91 mL (5.9 mmol) of 2-bromomesitylene. After stirring at −78 °C for 1 h, a white heterogeneous mixture resulted. To this mixture was added 2-methoxypyridine (0.56 mL, 5.35 mmol), and stirring was continued at −78 °C for 1 h, at −23 °C for 1 h, and at room temperature for 1 h. The mixture was cooled to −78 °C, and *N*-formyl-*N*,*N*′,*N*′-trimethylethylenediamine[6] (0.75 mL, 7 mmol) was added dropwise. After stirring at −78 °C for 1 h, the mixture was warmed to −23 °C, and *n*-butyllithium (2.5 M/hexane, 3.2 mL, 8 mmol) was added. The mixture was stirred at −23 °C for 2 h to give a dark solution, which was transferred via a double-tipped needle to the $CeCl_3$ slurry in THF at −23 °C. After stirring at −23 °C for 2 h, the homogeneous solution was cooled to −78 °C, and anhydrous acetone (1.2 mL, 16 mmol) was added in one portion. The mixture was stirred at −78 °C for 1 h and at −23 °C for 30 min. Glacial acetic acid (0.8 mL) was added at −23 °C, and stirring was continued for 10 min. After addition of 30 mL of saturated aqueous $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water and brine and then dried over $MgSO_4$. Concentration under reduced pressure gave 2.08 g of crude product, which was purified by radial PLC (silica gel, 15−50% EtOAc/hexanes) to give 482 mg (46%) of 1,1-dimethyl-4-methoxy-3-hydroxy-1,3-dihydrofuro[3,4-c]pyridine (**5**) as a semisolid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 1 H, J = 5.25 Hz), 6.74 (d, 1 H, J = 5.25 Hz), 6.25 (s, 1 H), 4.36 (br s, 1 H), 4.02 (s, 3 H), 1.63 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 148.2, 120.1, 98.1, 86.1, 53.6, 30.1, 28.1; IR (KBr) 3387, 1613, 1591, 1453 cm^{-1}; HRMS calcd 195.0895, found 195.0899.

1,1-Dimethyl-4-methoxyfuro[3,4-c]pyridin-3(1H)-one (6). To a stirred solution of **5** (118 mg, 0.5 mmol) in CH_2Cl_2 (6 mL) was added PCC (118 mg, 0.55 mmol) at room temperature. After stirring for 6 h, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with 5-mL portions of cold 10% aqueous HCl, water, and brine. The aqueous layers were combined and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were

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dried over $MgSO_4$. The residue obtained from concentration under reduced pressure was purified by radial PLC (silica gel, 15−50% EtOAc/hexanes) to give 97 mg (83%) of 1,1-dimethyl-4-methoxyfuro[3,4-*c*]pyridin-3(1*H*)-one (**6**) as a white crystalline solid: mp 112−113 °C (lit.[3b] mp 111−113 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, 1 H, J = 5.15 Hz), 6.94 (d, 1 H, J = 5.15 Hz), 4.14 (s, 3 H), 1.63 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.8, 167.9, 152.7, 109.3, 99.1, 84.0, 72.2, 54.4, 26.7; IR (KBr) 1746, 1613, 1592, 1475 cm^{-1}.

Cerpegin (1). Following a literature procedure,[3b] a solution of **6** (103 mg) in iodomethane (1 mL) was heated at 140 °C in a sealed tube for 24 h. The resulting red mixture was diluted with CH_2Cl_2, washed successively with 10% HCl and brine, dried over $MgSO_4$, and concentrated to yield 93 mg (90%) of **1** as a light yellow solid, which was pure as judged by ^{1}H NMR: mp 267−269 °C (lit.[1b] mp 268−270 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 1 H, J = 7.02 Hz), 6.22 (d, 1 H, J = 7.02 Hz), 3.63 (s, 3 H), 1.59 (s, 6 H). These NMR data are in agreement with the corrected spectral data.[3b]

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