

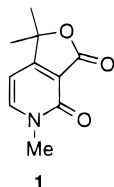
A Three-Step Synthesis of Cerpegin

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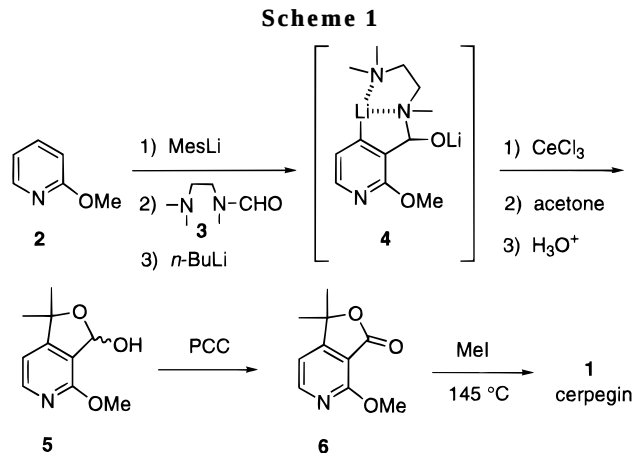
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The pyridone natural product cerpegin (**1**) was isolated from *Ceropegia juncea*, a plant used in traditional Indian medicine for its tranquilizer, anti-inflammatory, analgesic, and antiulcer properties.^{1,2} Three syntheses of cerpegin have been reported, employing five to six synthetic steps.³ Because of our interest in the directed lithiation of pyridines⁴ and its utility in the synthesis of natural products,⁵ we have developed a concise route to cerpegin from commercially available 2-methoxypyridine (**2**).



Lithiation of **2** at C-3 was effected using mesityllithium as the metalating agent^{4a} (Scheme 1). Addition of *N*-formyl-*N,N,N'*-trimethylethylenediamine⁶ (**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



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 derived¹ 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'*-trimethylethylenediamine⁶ (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 $\times$ 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: ^1H 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 $\times$ 10 mL). The combined organic extracts were

(1) (a) Sivakumar, K.; Eswaramurthy, S.; Subramanian, K.; Narayanan, S. *Acta. Crystallogr.* **1990**, C46, 839. (b) Adibatti, N. A.; Thirugnanasambantham, P.; Kulothungan, C.; Viswanathan, S.; Kameswaran, L.; Balakrishna, K.; Sukumar, E. *Phytochemistry* **1991**, 30, 2449.

(2) (a) Usman, A. S.; Narayanaswamy, V. *J. Res. Indian Med.* **1970**, 5, 10. (b) Adibatti, N. A. Ph.D. Thesis, University of Madras, 1985.

(3) (a) Guiller, F.; Nivoliors, F.; Bourguignon, J.; Dupas, G.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron Lett.* **1992**, 33, 7355. (b) Kelly, T. R.; Walsh, J. J. *J. Org. Chem.* **1992**, 57, 6657. (c) Matsuo, K.; Arase, T. *Chem. Pharm. Bull.* **1994**, 42, 715.

(4) (a) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1988**, 29, 773. (b) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1990**, 55, 69. (c) For a recent review on the directed metalation of pyridines and π -deficient aza aromatics, see: Queguiner, G.; Marsais, F.; Sneickus, V.; Epszajn, J. *Adv. Heterocycl. Chem.* **1991**, 52, 187.

(5) (a) Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, 114, 10971. (b) Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, 59, 5120. (c) Comins, D. L.; Hong, H.; Jianhua, G. *Tetrahedron Lett.* **1994**, 35, 5331.

(6) Einhorn, J.; Luche, J. L. *Tetrahedron Lett.* **1986**, 27, 1791.

(7) For a review of α -amino alkoxide directed lithiations, see: Comins, D. L. *Synlett* **1992**, 615.

(8) Organocerium reagents are known to undergo addition to a wide range of enolizable carbonyl compounds; see: (a) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, 49, 3904. (b) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, 111, 4392. (c) Imamoto, T. *Pure Appl. Chem.* **1990**, 62, 747. (d) Bunnelle, W. H.; Narayanan, B. A. *Org. Synth.* **1990**, 69, 89.

(9) Paquette, L. A.; Thompson, R. C. *J. Org. Chem.* **1993**, 58, 4952.

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); ^1H 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 ^1H NMR: mp 267–

269 °C (lit.^{1b} mp 268–270 °C); ^1H 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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