Concise Synthesis of Mappicine Ketone and (±)-Mappicine

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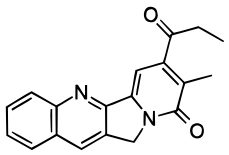
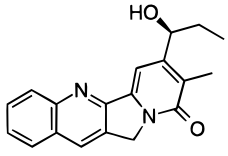
Mappicine ketone (**1**) is a derivative of a natural alkaloid mappicine (**2**), isolated from *Mapia foetida* Miers.[1] It has been reported that **1** possesses potent activity against the herpes viruses HSV-1 and HSV-2 and human cytomegalovirus (HCMV).[2] Mappicine ketone has been prepared by partial synthesis (three steps) from natural camptothecin,[1c] by reaction of camptothecin with sodium azide in hot DMF,[3] and by total synthesis (13 steps).[4] Recognizing that these preparations are not well-suited for general analog preparation, Pendrak and co-workers[2] developed synthetic routes to mappicine ketone derivatives for antiviral evaluation. Their approaches were based on the Friedlander condensation strategy used by Wall and co-workers[5] for the synthesis of camptothecin alkaloids and on Sugasawa's[6] methods for the total synthesis of camptothecin. Their syntheses of analogs required 12−15 steps.



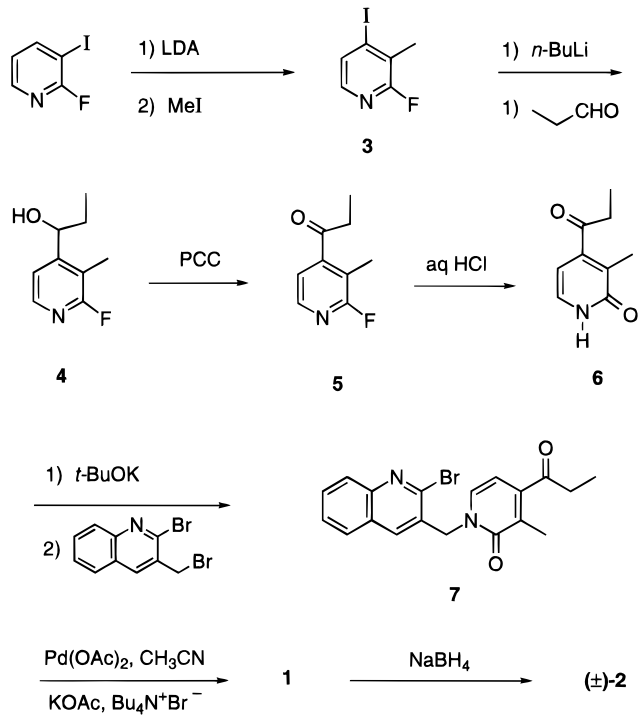
1
mappicine ketone



2
mappicine

On the basis of our own work in the camptothecin area,[7] we have developed a short, convergent route to mappicine ketone and (±)-mappicine as shown in Scheme 1. Treatment of 2-fluoro-3-iodopyridine with LDA and methyl iodide provided 2-fluoro-4-iodo-3-methylpyridine (**3**) via a halogen-dance reaction.[8] Lithium−iodine exchange and addition of propionaldehyde gave alcohol **4** in 84% yield, which was oxidized to ketone **5** with pyridinium chlorochromate (84%). Hydrolysis of **5** with aqueous hydrochloric acid provided ketopyridone **6** in 92% yield. *N*-Alkylation of **6** with potassium *tert*-butoxide and 2-bromo-3-(bromomethyl)quinoline[7a] gave an 81% yield of intermediate **7** as a light yellow solid. The Heck reaction was used to convert **7** to mappicine ketone (**1**) in 57% yield.[7,9] As reported,[4] reduction of **1** with sodium borohydride provided (±)-mappicine in 77% yield.

Scheme 1



In summary, mappicine ketone and mappicine have been prepared from readily available 2-fluoro-4-iodo-3-methylpyridine using five and six steps in yields of 30 and 23%, respectively.

Experimental Section

1-(2′-Fluoro-3′-methyl-4′-pyridyl)propan-1-ol (4). To a stirred solution of 2-fluoro-4-iodo-3-methylpyridine[8] (100 mg, 0.422 mmol) in 3 mL of THF at −78 °C under argon was added *n*-BuLi in hexane (2.13 M, 0.21 mL, 0.443 mmol). After 1 min, propionaldehyde (40 μL, 0.554 mmol) was added, and the mixture was stirred for 15 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ at −78 °C and then extracted with ether. The combined ether extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residual yellow oil (434 mg) was purified by radial PLC (silica gel, 20−30% ethyl acetate/hexanes) to give 60 mg (84%) of alcohol **4** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, l H, J = 5 Hz), 7.31 (d, l H, J = 5 Hz), 4.89 (m, l H), 2.21 (s, 3 H), 1.72 (m, 2 H), 0.99 (t, 3 H, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (d, J_{CF} = 236 Hz), 157.8, (d, J_{CF} = 4 Hz), 143.5 (d, J_{CF} = 15 Hz), 118.5, 115.8 (d, J_{CF} = 30 Hz), 70.4, 30.2, 9.8, 9.7; IR ($CHCl_3$) 3688, 3606, 1602 cm^{-1}; HRMS calcd for ($C_9H_{12}FNO$ + H) 170.0981 [(M + H)$^+$], found 170.0978.

1-(2′-Fluoro-3′-methyl-4′-pyridyl)propan-1-one (5). To a stirred solution of alcohol **4** (358 mg, 2.12 mmol) in 20 mL of dichloromethane at 0 °C under nitrogen was added Celite, pyridinium chlorochromate (481 mg, 2.23 mmol), and 4 Å molecular sieves. The reaction mixture was warmed to rt and stirred for 29 h. The mixture was filtered through Celite, and the solid was washed with CH_2Cl_2. The filtrate was concentrated *in vacuo*, and the residual brown gum (560 mg) was purified by radial PLC (silica gel, 10−30% ethyl acetate/hexanes) to give 297 mg (84%) of ketone **5** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, 1 H, J = 5 Hz), 7.21 (d, l H, J = 5 Hz), 2.87 (q, 2 H, J = 7 Hz), 2.32 (s, 3 H), 1.21 (t, 3 H, J = 7 Hz);

(1) (a) Govindachari, T. R.; Viswranathan, N. *Indian J. Chem.* **1972**, *10*, 453. (b) Govindachari, T. R.; Viswanathan, N. *Phytochemistry* **1972**, *11*, 3529. (c) Govindachari, T. R.; Ravindranath, K. R.; Viswanathan, N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1215.

(2) (a) Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem.* **1994**, *59*, 2623. (b) Pendrak, I.; Wittrock, R.; Kingsbury, W. D. *J. Org. Chem.* **1995**, *60*, 2912.

(3) Kingsbury, W. D. *Tetrahedron Lett.* **1988**, *29*, 6847.

(4) (a) Kametani, T.; Takeda, H.; Nemoto, H.; Fukumoto, K. *Heterocycles* **1975**, *3*, 167. (b) Kametani, T.; Takeda, H.; Nemoto, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans 1* **1975**, 1825.

(5) Wani, M. C.; Ronman, P. E.; Lindley, J. T.; Wall, M. E. *J. Med. Chem.* **1980**, *23*, 554.

(6) Sugasawa, T.; Toyoda, T.; Sasukura, K. *Tetrahedron Lett.* **1972**, 5109.

(7) (a) Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971. (b) Comins, D. L.; Hong, H.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 5331. (c) Comins, D. L.; Hong, H.; Saha, J.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120. (d) Comins, D. L.; Saha, J. K. *Tetrahedron Lett.* **1995**, *36*, 7995.

(8) Rocca, P.; Cochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Quequiner, G. *J. Org. Chem.* **1993**, *58*, 7832 and references cited therein.

(9) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003.

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^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 162.9 (d, J_{CF} = 238 Hz), 150.5 (d, J_{CF} = 4 Hz), 144.9 (d, J_{CF} = 15 Hz), 118.6 (d, J_{CF} = 4 Hz), 117.6 (d, J_{CF} = 33 Hz), 35.7, 11.4, 7.7; IR ($CHCl_3$) 2940, 1702, 1600, cm^{-1}. Anal. Calcd for $C_9H_{10}FNO$: C, 64.66; H, 6.03; N, 8.38. Found: C, 64.70; H, 6.01; N, 8.31.

1-(3′-Methyl-2′-oxo-4′-pyridyl)propan-1-one (6). A mixture of ketone **5** (45 mg, 0.269 mmol) and 3 N HCl (2 mL) was heated at reflux in air for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by radial PLC (silica gel, CH_2Cl_2−5% MeOH/CH_2Cl_2) to give 41 mg (92%) of pyridone **6** as a white solid: mp 128−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, l H, J = 7 Hz), 6.21 (d, 1 H, J = 7 Hz), 2.77 (q, 2 H, J = 7 Hz), 2.14 (s, 3 H), 1.19 (t, 3 H, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 165.6, 149.6, 132.0, 125.8, 103.9, 35.9, 13.0, 7.6; IR ($CHCl_3$) 3690, 1706, 1646 cm^{-1}; HRMS calcd for $C_9H_{11}NO_2$ 165.0790 (M^+), found 165.0797.

1-[1′-[(2″-Bromo-3″-quinolyl)methyl]-3′-methyl-2′-oxo-4′-pyridyl]propan-1-one (7). To a stirred solution of the pyridone **6** (80 mg, 0.485 mmol) in DME (10 mL) was added potassium *tert*-butoxide in THF (1M, 0.53 mL, 0.53 mmol) at rt under argon. The yellow solution was stirred at rt for 30 min. Solid 2-bromo-3-(bromomethyl)quinoline[7a] (190 mg, 0.631 mmol) was added, and the heterogeneous reaction mixture was heated at reflux for 4 d. The mixture was cooled to rt and then concentrated on a rotary evaporator. The residue was purified by radial PLC (silica gel, CH_2Cl_2−2% MeOH/CH_2Cl_2) to give 151 mg (81%) of **7** as a yellow solid: mp 242−244 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (m, 2 H), 7.80 (d, 1 H, J = 8 Hz), 7.73 (t, 1 H, J = 8 Hz), 7.57 (t, 1 H, J = 8 Hz), 7.46 (d, 1 H, J = 7 Hz), 6.16 (d, 1 H, J = 7 Hz), 5.37 (s, 2 H), 2.78 (q, 2 H, J = 7 Hz), 2.18 (s, 3 H), 1.2 (t, 3 H, J = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 163.0, 147.9, 147.6, 142.3, 138.2, 135.1, 130.8, 129.3, 128.3, 127.8, 127.5, 127.2, 127.0, 103.2, 52.4, 35.9, 13.9, 7.6; IR ($CHCl_3$) 2993, 1701, 1646, 1600 cm^{-1}; HRMS calcd for $C_{19}H_{17}BrN_2O_2$ (M^+) 385.0552, found 385.0551.

Mappicine Ketone (1). A mixture of **7** (49 mg, 0.127 mmol), potassium acetate (41 mg, 0.42 mmol), tetrabutylammonium bromide (66 mg, 0.205 mmol), and palladium acetate (5 mg, 0.022 mmol) in acetonitrile (5 mL) was heated at reflux under argon for 3 h. The hot reaction mixture was filtered through Celite, and the residue was washed with hot 40% MeOH/CH_2Cl_2. The filtrate was concentrated *in vacuo*, and the residue was purified by radial PLC (silica gel, CH_2Cl_2−2% MeOH/CH_2Cl_2) to give 22 mg (57%) of mappicine ketone (**1**): mp 238−239 °C (lit.[4a] mp 237−238 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1 H), 8.19 (d, 1 H, J = 8 Hz), 7.92 (d, 1 H, J = 8 Hz), 7.81 (t, 1 H, J = 7 Hz), 7.64 (t, 1 H, J = 7 Hz), 7.25 (s, 1 H), 5.29 (s, 2 H), 2.91 (q, 2 H, J = 7 Hz), 2.30 (s, 3 H), 1.25 (t, 3 H, J = 7 Hz).

(±)-Mappicine (2). To a stirred solution of mappicine ketone **7** (9 mg, 0.03 mmol) in 2 mL of 1:1 MeOH/CH_2Cl_2 was added sodium borohydride (5 mg, 0.132 mmol) at rt, and the reaction mixture was stirred for 3.5 h in air. The mixture was diluted with 1 mL of water and then concentrated in vacuo. The residue was purified by radial PLC (silica gel, CH_2Cl_2−5% MeOH/CH_2Cl_2) to give 7 mg (77%) of (±)-mappicine as a yellow solid: mp 283−286 °C (lit.[4a] mp 271−273 °C); ^{1}H NMR (300 MHz, $CDCl_3$−CD_3OD) δ 8.25 (s, 1 H), 8.06 (d, 1 H, J = 8 Hz), 7.74 (m, 2 H), 7.53 (m, 2 H), 5.22 (m, 2 H), 4.89 (t, 1 H, J = 6 Hz), 2.22 (s, 3 H), 1.78 (m, 2 H), 1.03 (t, 3 H, J = 7 Hz).

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Supporting Information Available: Comparison tables of spectroscopic data for **1** and **2** and ^{1}H and ^{13}C NMR spectra of **4**, **6**, and **7** (8 pages). 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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