Synthesis of (+/-) Mappicine and Mappicine Ketone

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Mappicine and mappicine ketone are camptothecin analogs of interest as antiviral agents. A novel synthesis of these compounds is described using a Friedlander condensation. The requisite ketone is prepared *via* a regioselective *ortho*-directed metallation/alkylation of a trisubstituted pyridine. This is condensed with *N*-*t*-butyloxycarbonyl-*o*-aminobenzaldehyde as a convenient, stable *o*-aminobenzaldehyde equivalent in the Friedlander condensation.

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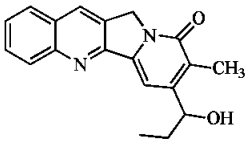
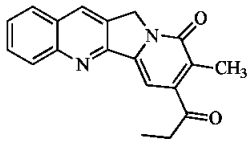
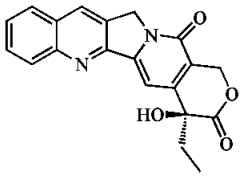
Mappicine is an analog of camptothecin originally isolated from Mapia Foetida [1]. The closely related mappicine ketone (nothapodyne A) was isolated from Nothapodytes foetida, and is of interest due the antiviral properties of it and some of its analogs [2,3]. A number of syntheses of mappicine and mappicine ketone have been reported [4] and these two compounds are readily interconverted through oxidation and reduction. Both mappicine ketone and mappicine have been prepared by degradation of camptothecin [5,6].



Mappicine



Mappicine ketone

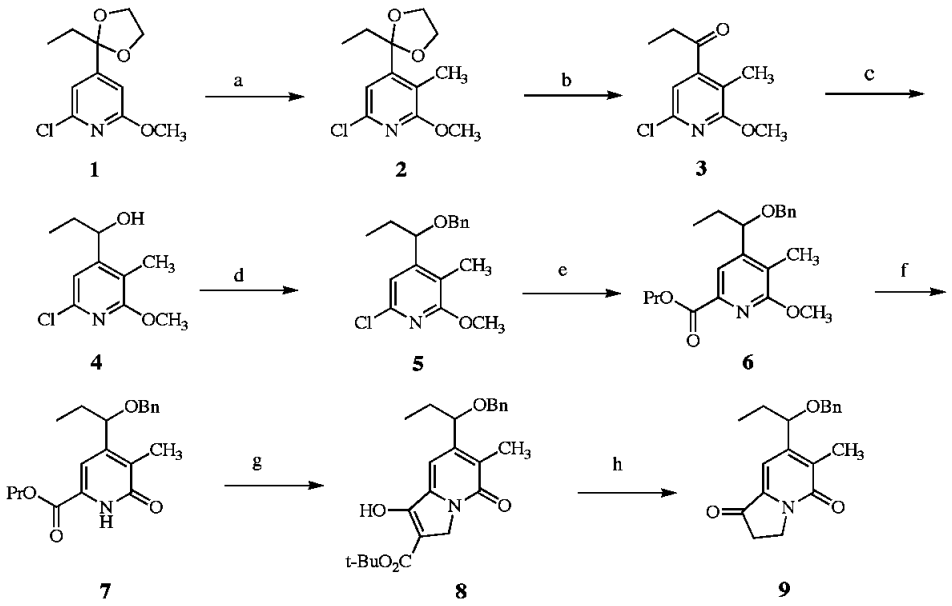


Camptothecin

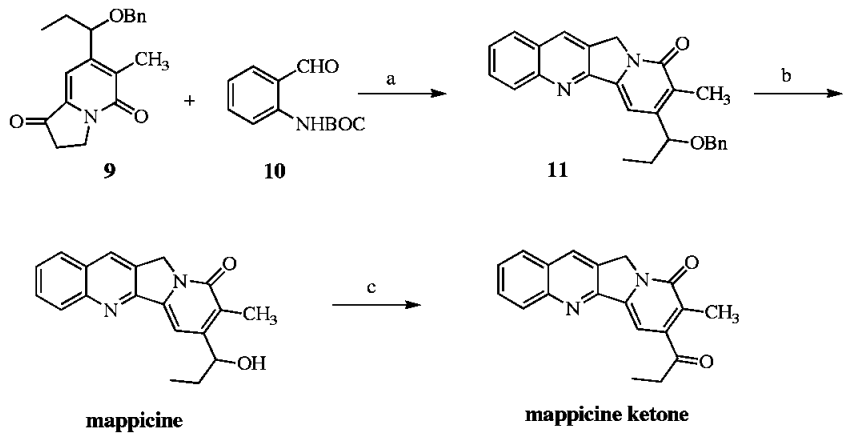
We report a total synthesis of mappicine and mappicine ketone which was developed in conjunction with our work on the synthesis of the camptothecin analog irinotecan [7]. The starting material for the synthesis is **1** (Scheme 1), which is readily available and has been prepared on a ton scale [7]. Deprotonation of **1** with *n*-BuLi in heptane followed by reaction of the resultant anion with methyl iodide proceeded poorly, presumably due to competitive transmetallation between the alkyl iodide and the aryl anion. However, reaction of the anion with dimethyl sulfate proceeded smoothly to give the methylated product **2** in 66 % yield after chromatography to remove unreacted starting material and the small amount of the regioisomer formed. Deketalization with trifluoroacetic acid cleanly yielded the ketone **3**, which was then reduced with sodium borohydride to give the racemic alcohol **4**. Due to time constraints, enantioselective reduction of the ketone was not examined but this compound should be a good substrate for this type of reduction. To avoid the formation of intermolecular esters in the subsequent palladium catalyzed carbonylation, the alcohol **4** was then converted to the benzyl ether **5** by reaction with sodium hydride and benzyl bromide. The carbonylation reaction of the chloropyridine **5** proceeded readily at 90 °C in a mixture of DMF and *n*-propanol with atmospheric pressure CO in the presence of $Pd(OAc)_2$ and 1,3-bis(diphenylphosphino)propane (DPPP) to give the ester **6**. The methoxypyridine was then converted to the pyridone **7** by demethylation with *in situ* generated trimethylsilyl iodide (TMS-I) [8]. Reaction of the pyridone **7** with Cs_2CO_3 in DMSO under carefully defined conditions yielded the cyclized keto ester **8**, which according to spectral data exists entirely in the enol form. Deesterification-decarboxylation of **8** under acidic conditions yielded the tricyclic ketone **9** as a relatively unstable gum or amorphous foam.

Friedlander condensations to give A-ring unsubsituted quinolines have been reported with *o*-aminobenzaldehyde or the Borsche imine [9]. *o*-Aminobenzaldehyde itself is unstable and difficult to prepare and store [10], and the preparation of the Borsche imine is troublesome [11]. We found that N-BOC-*o*-aminobenzaldehyde **10** is an excellent reactant in the Friedlander condensation. This material is prepared without difficulty from N-BOC-aniline *via* an orthometallation procedure [12] and is isolated as a stable crystalline solid that can be stored for extended periods without decomposition. Reaction of the ketone **9** with N-BOC-*o*-aminobenzaldehyde **10** (Scheme 2) smoothly gave *O*-benzyl mappicine **11** in 80% yield. The condensation can also be done directly with the ketoester **8** but this reaction is not nearly as clean as with the ketone **9**. Debenzylation of **11** by catalytic hydrogenation over palladium catalysts was sluggish. However, reaction of **11** with BBr_3 in the presence of tetra-*n*-butylammonium iodide as a soluble iodide source proceeded rapidly to give mappicine

Scheme 1



Scheme 2



a) acetic acid 80%; b) BBr_3, $(n\text{-}Bu)_4NI$, 88%; c) PCC, 62%.

in 88 % yield [13]. Isolation of mappicine was complicated by the poor solubility properties of this material. Oxidation of mappicine to the ketone proceeded cleanly with Jones reagent but the isolated yield was low. Oxidation with PCC [4d] gave mappicine ketone in 62% yield.

EXPERIMENTAL

Materials were used as received from commercial suppliers. Melting points were determined on a Buchi automatic melting point determination instrument. Infrared spectra were recorded, as noted, in potassium bromide for solid samples (2 mg sample/200 mg potassium bromide) or as thin films for oils. Microanalyses and high resolution mass spectra were performed by Structural and Medicinal Chemistry (Pfizer). All silica used was 230-400 mesh Merck silica 60.

6-Chloro-4-(2-ethyl-1,3-dioxolan-2-yl)-2-methoxy-3-methylpyridine (**2**).

Compound **1** (10.0 g, 41.0 mmol) was dissolved in 500 mL of heptane. The solution was cooled to 0 °C and 24.4 mL of a solution of *n*-BuLi in hexanes (51.2 mmol) was added while maintaining reaction temperature at 0 °C. The bright-orange slurry was stirred at 0 °C for 1.75 hours. Dimethyl sulfate (4.8 mL, 51.2 mmol) was added keeping the temperature below 10 °C. The reaction was stirred at 0 °C for 2 hours, and then 1.5 mL of conc. ammonium hydroxide was added and the mixture stirred for 1 hour. Water (40 mL) and EtOAc (75 mL) were added. After 15 minutes, the phases were partitioned and the aqueous extracted with EtOAc (3 x 50 mL). The organic extracts were combined, dried over sodium sulfate, filtered, and concentrated to a red oil. Chromatography on silica (methylene chloride) gave **2** (6.97 g, 66%) as a clear, colorless oil, IR (film)

1580, 1550, 1405, 1040 cm^{-1}; ^1H NMR (300.14 MHz, deuteriochloroform): δ 7.08 (s, 1H), 4.05-4.01 (m, 2H), 3.97 (s, 3H), 3.80-3.75 (m, 2H), 2.28 (s, 3H), 1.93 (dd, J = 7.4, 14.9 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75.47 MHz, deuteriochloroform): δ 162.9, 153.3, 144.9, 116.9, 114.4, 110.1, 64.5, 54.2, 31.5, 12.0, 7.4;MS (EI) *m/z* 257, 259; MS (CI) *m/z* ($-NH_3^+$) 258, 260; HRMS calcd for $C_{12}H_{16}ClNO_3$; *m/z* 257.0818; Found *m/z* 257.0815.

Anal. Calcd. for $C_{12}H_{16}ClNO_3$: C, 55.93; H, 6.26; N, 5.43. Found: C, 55.77; H, 6.30; N, 5.45.

6-Chloro-2-methoxy-3-methyl-4-(1-oxopropyl)pyridine (**3**).

Compound **2** (12.0 g, 46 mmol) was dissolved in 25 mL of aqueous TFA (64% v/v) and heated to 40 °C. After 4 hours, the mixture was cooled and quenched with water (50 mL) and 2:1 EtOAc/heptane (75 mL). The phases were separated and the aqueous phase extracted with 2:1 EtOAc/heptane (3 x 40 mL). The organic extracts were combined and neutralized with 200 mL of saturated aqueous sodium bicarbonate solution. The phases were partitioned and the aqueous phase was extracted with EtOAc (3 x 50 mL). The organic phases were combined, dried (sodium sulfate), filtered, and concentrated under vacuum to give 9.9 g of **3** as a slightly yellow oil (99%), IR (film) 1706 cm^{-1}; ^1H NMR (300.14 MHz, deuteriochloroform): δ 6.88 (s, 1H), 3.99 (s, 3H), 2.82 (dd, J = 7.2, 14.5 Hz, 2H), 2.16 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.47 MHz, deuteriochloroform): δ 204.2, 162.6, 150.5, 145.5, 116.3, 113.0, 54.4, 35.9, 11.8, 7.6; MS (EI) *m/z* 213, 215; MS (CI) *m/z* ($-NH_3^+$) 214, 216; HRMS calcd for $C_{10}H_{12}ClNO_2$; *m/z* 213.0556; Found *m/z* 213.0547.

Anal. Calcd. for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.30; H, 5.67; N, 6.43.

6-Chloro-4-[1-hydroxypropyl]-2-methoxy-5-methylpyridine (**4**).

Compound **3** (9.9 g, 46 mmol) was dissolved in 100 mL of MeOH and cooled to 0°C. A freshly-prepared solution of 2.18 g of sodium borohydride (58 mmol) in 20 mL of 50% aqueous MeOH was added all at once. After 20 minutes, the reaction was quenched with 50 mL of 1 *M* hydrochloric acid and then diluted with 100 mL of methylene chloride and 10 mL of water. The phases were separated and the aqueous phase was extracted with methylene chloride (3 x 50 mL). The organic extracts were concentrated to a white solid. The solid material was recrystallized from hexane to give **4** (8.54 g, 85%) as long needles, mp 97.0-97.5 °C; IR (film) 3127, 3224 cm^{-1}; ^1H NMR (300.14 MHz, deuteriochloroform): δ 7.05 (s, 1H), 4.85 - 4.81 (m, 1H), 3.95 (s, 3H), 2.08 (s, 3H), 1.76-1.63 (m, 2H), 0.98 (t, J = 7.4 Hz. 3H); ^{13}C NMR (75.47 MHz, deuteriochloroform): δ 161.8, 155.6, 145.4, 115.0, 113.1, 71.0, 54.1, 30.4, 10.5, 9.8; MS (EI) *m/z* 215, 217; MS (CI) *m/z* ($-NH_3^+$) 216, 218;

Anal. Calcd. for $C_{10}H_{14}NO_2Cl$: C, 55.69; H, 6.49; N, 6.49. Found: C, 55.61; H, 6.55; N, 6.56.

6-Chloro-2-methoxy-3-methyl-4-[1-(phenylmethoxy)propyl]-pyridine.(**5**).

A solution of **4** (4.00 g, 18.5 mmol) in 40 mL of THF was stirred with sodium hydride (1.55 g, 64.6 mmol) for 30 minutes at room temperature. Benzyl bromide (2.3 mL, 18.9 mmol) was added and the mixture was stirred for 8 hours at room temperature. Saturated aqueous ammonium chloride solution (10 mL), water (10 mL), and methylene chloride (20 mL) were added. The phases were separated and the aqueous phase was adjusted to pH 7 with 1 *M* hydrochloric acid, then extracted with methylene chloride (3 x 20 mL). The organic phases were combined, dried (sodium sulfate), filtered, and concentrated to a yellow oil. Chromatography on silica (4:1 hexane/EtOAc) gave **5** (5.09 g, 90%) as a clear oil: IR (film) 1738, 1717, 1454, 1369, 1227 cm^{-1}; ^1H NMR (300.14 MHz, deuteriochloroform): δ 7.38-7.32 (m, 5H), 7.07 (s, 1H), 4.53-4.46 (m, 2H), 4.26 (d, J = 11.7 Hz, 1H), 4.00 (s, 3H), 2.09 (s, 3H), 1.83-1.62 (m, 2H), 0.98 (t, J=7.3 Hz, 3H); ^{13}C NMR (75.47 MHz, deuteriochloroform): δ 162.0, 154.0, 145.6, 137.9, 128.4, 127.8, 127.7, 116.3, 113.8, 78.0, 71.0, 54.2, 29.5, 10.5, 10.1;MS (EI) *m/z* 305, 307; MS (CI) *m/z* ($-NH_3^+$) 306, 308; HRMS calcd for $C_{17}H_{20}NO_2Cl$; *m/z* 305.1183; Found *m/z* 305.1166.

Anal. Calcd. for $C_{17}H_{20}ClNO_2$: C, 66.77; H, 6.59; N, 4.58;Cl, 11.59. Found: C, 66.76; H, 6.58; N, 5.03; Cl, 11.56.

6-Methoxy-5-methyl-4-[1-(phenylmethoxy)propyl)pyridine-2-carboxylic Acid, Propyl Ester (**6**).

Compound **5** (4.00 g, 13.1 mmol), potassium acetate (1.92 g, 19.6 mmol), palladium acetate (0.147 g, 0.65 mmol), and DPPP (0.268 g, 0.65 mmol), were stirred with 80 mL of DMF and 40 mL of *n*-PrOH. The flask was purged with carbon monoxide and then heated to 85 °C under carbon monoxide (15 PSI). After 25 hours the mixture was cooled to room temperature and purged with nitrogen. The solution was filtered over celite and the filtrate was concentrated and then partitioned between 80 mL of water and 160 mL methyl *t*-butyl ether. The aqueous phase was extracted with methyl *t*-butyl ether (3 x 50 mL). The organic extracts were combined, washed with water (4 x 25 mL), dried (sodium sulfate), filtered, and concentrated to a brown oil. The oil was chromatographed on silica (methylene chloride) to give **6** (4.14 g, 89%) as a colorless oil, IR (film) 1717, 1739 cm^{-1}; ^1H NMR (300.14 MHz, deuteriochloroform): δ 7.88 (s, 1H), 7.38-7.28 (m, 5H), 4.57-4.53 (m, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.36-4.32 (m, 2H), 4.25 (d, J = 11.6 Hz, 1H), 4.09 (s, 3H), 2.18 (s, 3H), 1.90-1.80 (m, 3H), 1.78-1.64 (m, 1H), 1.06 (t, J = 7.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75.47 MHz, deuteriochloroform): δ 165.5, 162.3, 151.5, 142.8, 138.0, 128.3, 127.8, 127.7, 122.9, 116.5, 78.1, 70.9, 66.8, 53.8, 29.5, 22.0, 11.3, 10.4, 10.2; MS (EI) *m/z* 358; MS (CI) *m/z* ($-NH_3^+$) 358, 360; HRMS calcd for $C_{21}H_{27}NO_4$; *m/z* 357.1940; Found *m/z* 357.1932.

Anal. Calcd. for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.40; H, 7.62; N, 4.40.

1,6-Dihydro-5-methyl-6-oxo-4-[1-(phenylmethoxy)propyl]-2-pyridinecarboxylic Acid, Propyl Ester (**7**).

A solution of sodium iodide (1.89 g, 12.6 mmol) and **6** (3.00 g, 8.4 mmol) in 30 mL of acetonitrile was cooled to 0° C and trimethylsilyl chloride (1.6 mL, 12.6 mmol) was added. After 15 minutes the reaction mixture was allowed to warm to room temperature. After 24 hours the reaction was quenched by adding sequentially 4.2 mL of 6 *M* hydrochloric acid, 5.3 mL of saturated aqueous sodium chloride solution, 10.6 mL of water, 0.4 mL of 38% aqueous sodium bisulfite solution, and 20 mL of EtOAc. After stirring at room temperature for 30 minutes, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The organic solutions were combined and washed with 7 mL of saturated aqueous sodium bicarbonate solution containing 0.25 mL of 38% aqueous sodium bisulfite solution. After stirring for 15 minutes, the phases were separated and the organic solution was washed with saturated aqueous sodium chloride solution (2 x 10 mL). The solution was dried over

sodium sulfate, then filtered and concentrated to give 2.80 g (97%) of **7** as a waxy yellow-white solid, mp 91.0-92.0 °C; IR (potassium bromide) 1721 cm^{-1}; ^1H NMR (300.14 MHz, deuteriochloroform): δ 9.82 (br s), 7.39-7.29 (m, 6H), 4.51-4.46 (m, 1H), 4.35-4.26 (m, 2H), 2.14 (s, 3H), 1.87-1.75 (m, 3H), 1.71-1.57 (m, 1H), 1.05-0.95 (m, 6H); ^{13}C NMR (75.47 MHz, deuteriochloroform): δ 162.42, 161.28, 150.41, 137.63, 133.04, 130.54, 128.40, 127.87, 108.01, 77.76, 71.13, 67.95, 28.80, 21.84, 12.04, 10.29, 10.06; MS (EI) *m/z* 343, 344; MS (CI) *m/z* ($-NH_3^+$) 344, 345; HRMS calcd for $C_{20}H_{25}NO_4$; *m/z* 343.1783; Found *m/z* 343.1781.

Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.94; H, 7.30; N, 4.08.

2,3-Dihydro-6-methyl-7-[1-(phenylmethoxy)-propyl]-1,5-indolizinedione-2-carboxylic Acid 1,1-Dimethylethyl Ester (**8**).

A mixture of **7** (3.22 g, 9.4 mmol), cesium carbonate (6.12 g, 18.8 mmol), *t*-butyl acrylate (13.5 mL, 92.3 mmol), and 50 mL of DMSO was heated to 65 °C. After 3 hours the reaction mixture was cooled to 0 °C and 60 mL of 0.5 *M* hydrochloric acid was added, maintaining the internal reaction temperature < 15°C. The mixture was diluted with 30 mL of 4:1 toluene/EtOAc and partitioned. The aqueous phase was extracted with 4:1 toluene/EtOAc (2 x 30 mL). The organic extracts were combined and washed with water (3 x 30 mL), dried over sodium sulfate, filtered, and concentrated to 4.57 g of yellow oil. Chromatography on silica (5% MeOH in methylene chloride) yielded 3.28 g of **8** as an off-white solid (85%), IR (potassium bromide) 1690, 1720 cm^{-1}; ^1H NMR (300.14 MHz, deuteriochloroform): δ 9.91 (br s), 7.39-7.29 (m, 5H), 6.91 (s, 1H), 4.67 (s, 2H), 4.52-4.48 (m, 2H), 4.26 (d, J = 11.8 Hz, 1H), 2.18 (s, 3H), 1.87-1.78 (m, 1H), 1.70-1.53 (m, 1 H), 1.59 (s, 9H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75.47 MHz, deuteriochloroform): δ 166.61, 160.77, 160.28, 150.69, 140.25, 137.89, 128.35, 127.77, 127.69, 126.63, 103.99, 99.13, 82.95, 78.02, 70.88, 49.08, 29.01, 28.25, 27.87, 11.84, 10.07; MS (EI) *m/z* 411, 412; MS (CI) *m/z* ($-NH_3^+$) 412, 413.

Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 69.69; H, 7.04; N, 3.47.

2,3-Dihydro-6-methyl-7-[1-(phenylmethoxy)-propyl]-1,5-indolizinedione (**9**).

A solution of **8** (0.25 g, 0.61 mmol), trifluoroacetic acid (0.45 mL), and toluene (18 mL) was heated to 75 °C. After 24 hours, the solution was concentrated to an oil. The oil was diluted with 20 mL of toluene and again concentrated to an oil. The oil was chromatographed on silica (5% MeOH in methylene chloride) to yield 0.138 g (73%) of **9** as a yellow foam, IR (potassium bromide) 1737, 1650, 1606, 1198 cm^{-1}; ^1H NMR (300.14 MHz, deuteriochloroform): δ 7.27-7.18 (m, 5H), 7.04 (s, 1H), 4.43- 4.38 (m, 2H), 4.23-4.13 (m, 3H), 2.80 (t, J = 6.9 Hz, 2H), 2.09 (s, 3H), 1.75-1.47 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75.47 MHz, deuteriochloroform): δ 196.91, 161.48, 150.48, 137.67, 136.95, 132.94, 128.36, 127.71, 102.40, 77.77, 70.97, 41.92, 33.69, 28.90, 12.41, 9.98; MS (EI) *m/z* 311, 205; HRMS calcd for $C_{19}H_{22}NO_3$ (m+H^+); *m/z* 312.1599; Found *m/z* 312.1597.

(+/-) *O*-Benzylmappicine (**11**).

A solution of **9** (0.50 g, 1.6 mmol), N-Boc-*o*-aminobenzaldehyde (0.47 g, 2.0 mmol), and AcOH (20 mL) was heated to 100 °C. After 4 hours the black solution was concentrated under vacuum to dryness. The residue was chromatographed on silica (EtOAc) to give 0.51 g (80%) of **11** as a light tan solid, mp 175.0 °C; IR (potassium bromide) 1658, 1605 cm^{-1}; ^1H NMR (300.14 MHz, deuteriochloroform): δ 8.33 (s, 1H), 8.22 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.80 (t, J = 7 Hz, 1H), 7.64-7.57 (m, 2H), 7.38 - 7.29 (m, 5H), 5.28 (s, 2H), 4.64-4.54 (m, 2H), 4.32 (d, J = 12 Hz, 1H), 2.25 (s, 3H), 1.94-1.65 (m, 2H), 1.02 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75.47 MHz, deuteriochloroform): δ 161.51, 153.51, 151.30, 148.78, 142.67, 138.12, 130.67, 130.12, 129.56, 128.64, 128.33, 127.98, 127.76, 127.60, 127.29, 126.87, 99.51, 78.18, 70.81, 49.91, 29.08, 11.99, 10.19; MS (CI) *m/z* 397; HRMS calcd for $C_{26}H_{24}N_2O_2$ (M+H^+); *m/z* 397.1917; Found *m/z* 397.1919.

Anal. Calcd. for $C_{26}H_{24}N_2O$: C, 78.76; H, 6.10; N, 7.07. Found: C, 79.08; H, 5.95; N, 7.06.

(+/-)-Mappicine.

To a dry, argon-purged flask equipped with magnetic stirring and an internal temperature probe was charged 0.148 g of **11** (0.37 mmol), 0.54 g of tetra-*n*-butylammonium iodide (1.5 mmol), and 20 mL of methylene chloride. The mixture was stirred to dissolve the solids and then cooled to -40 °C. Boron tribromide (0.4 mL, 4.4 mmol) was added and the mixture was stirred for 30 minutes at -40 °C. Twenty mL of saturated sodium bicarbonate solution was added. The mixture was filtered to isolate crude mappicine as a light orange solid. This was dissolved off the filter with methanol. The methanol solution was evaporated to yield an off-white solid (0.34 g) that was chromatographed on silica (95:5:1 methylene chloride-methanol-acetic acid) to give 0.074 g of the product as a slightly yellow solid. The two-phase filtrate from the isolation of crude mappicine was separated and the organic phase was evaporated. The residue was chromatographed on silica to give 0.026 g of (+/-)-mappicine (total yield, 0.100 g, 88 %) as a slightly yellow solid, mp 267.4 °C (lit. [4a] mp 271-273 °C, lit. [4b] mp 283-286 °C); ^1H NMR (500 MHz, deuteriochloroform/methanol-d_4): δ 8.20 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.70 (m, 2H), 7.54 (s, 1H), 7.50 (t, J = 7.5 Hz, 1H), 5.22 (d, J = 18.5, 1H), 5.14 (d, J = 18.5, 1H), 4.88 (t, J = 5.5 Hz, 1H), 2.21 (s, 3H), 1.8-1.70 (m, 2H), 1.02 (t, J = 7 Hz, 3H); ^{13}C NMR (125.77 MHz, deuteriochloroform/methanol-d_4): δ 161.63, 154.80, 152.60, 148.01, 141.81, 131.05, 130.25, 128.56, 128.37, 127.94, 127.59, 127.37, 125.01, 100.19, 70.98, 49.99, 29.91, 11.84, 9.90; MS (EI) *m/z* 306, 307; MS (CI) *m/z* ($-NH_3^+$) 307, 308.

Mappicine Ketone.

(+/-)-Mappicine (0.050 g, 0.165 mmole) and 0.2 g of celite were suspended in 5 mL of methylene chloride. Pyridinium chlorochromate (PCC) (0.14 g, 0.66 mmole) was added and the mixture stirred overnight at room temperature. Isopropyl alcohol (1 mL) was added and the mixture was stirred at room temperature for 1 hour. The solids were filtered over celite and washed with 10 mL of methylene chloride. The filtrates were evaporated to a dark residue. This was dissolved in chloroform and chromatographed on silica, eluting with 97.5:2.5 methylene chloride-methanol. Yield of product was 0.031 g (62%) as a light yellow solid, mp 235 °C, (lit. [4a] mp 237-238 °C, lit. [4b] mp 238-239 °C); ^1H NMR (500 MHz, deuteriochloroform): δ 1.25 (t, J=9.0 Hz, 3H), 2.29 (s, 3H), 2.91 (q, J=9Hz, 2H), 5.27 (s, 2H), 7.27 (s, 1H) 7.65 (t, J=9Hz, 1H), 7.80 (t, J=9 Hz, 1H), 7.90 (d,

J=10 Hz, 1H), 8.19 (d, J=10 Hz, 1H), 8.34, s, 1H); ^{13}C NMR (125.77 MHz, deuteriochloroform): δ 7.74, 13.61, 35.96, 50.32, 97.80, 126.99, 127.65, 127.97, 128.10, 128.54, 129.52, 130.40, 130.96, 143.31, 148.08, 148.77, 152.84, 161.70, 205.42. MS (electrospray) *m/z* 305.

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