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Synthesis of (*S*)-Mappicine and Mappicine Ketone via Radical Cascade Reaction of Isonitriles

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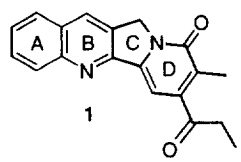
Abstract: (*S*)-Mappicine (**2**) and mappicine ketone (**1**) have been prepared from methylacetoacetate (**4**) by a strategy featuring a radical cascade reaction of an isonitrile as the key step. The introduction of the hydroxy group of (*S*)-mappicine occurred with moderate selectivity through asymmetric hydroxylation.

In the race toward the design of new selective anti viral molecules, mappicine ketone (MPK) (**1**) has recently been identified as a lead against several herpes viruses (HSV) and human cytomegalovirus.[1] MPK is an oxidized form of the natural alkaloid mappicine (**2**)[2] and an E-ring decarboxylated analog of (20*S*)-camptothecin (CPT) (**3**), which is the parent member of an important family of anti-cancer agents.[3]



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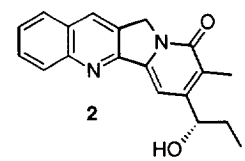

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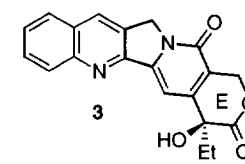

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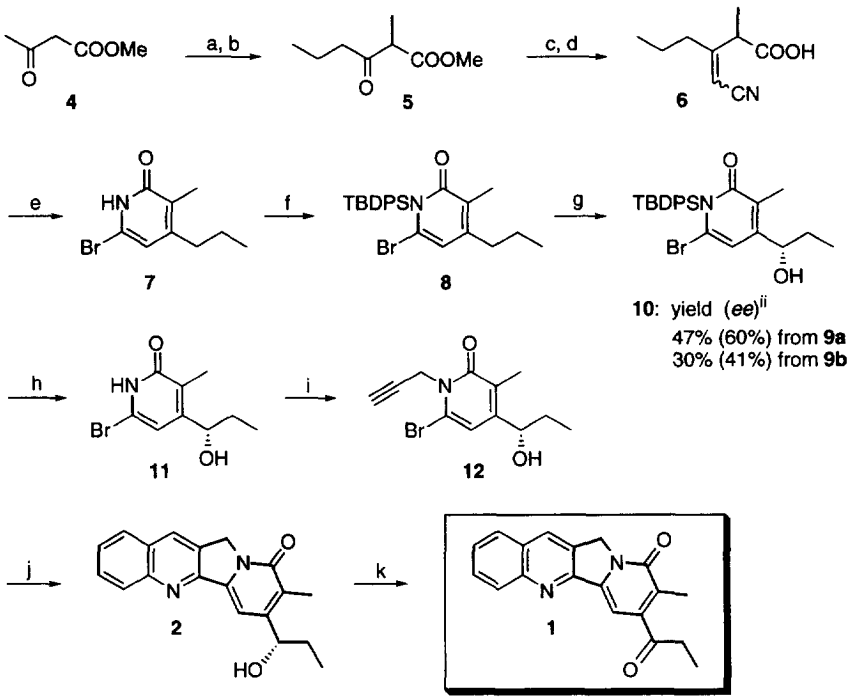
MPK was originally synthesized by thermolysis of CPT.[4] However this method has limited prospect for the preparation of ring-substituted MPK derivatives needed for structure-activity relationship (SAR) studies. Pendrak and co-workers have recently reported two more practical syntheses of MPK derivatives,[1] based on an inverse-demand intramolecular Diels-Alder reaction[1a] and Friedlander condensation.[1b] Since general synthetic methods for this class of compounds are still needed for SAR studies, we decided to embark upon the preparation of (*S*)-mappicine and MPK and the result of our efforts is summarized in Scheme 1.

The synthesis features in its key step a BC-ring assembly starting with bromopyridone **12** and phenylisonitrile (**13**) *via* a [4 + 1] radical cascade reaction. This strategy was originally used by our group for the synthesis of racemic camptothecin[5a,b] and it has recently been extended to prepare (20*S*)-camptothecin and a number of important analogs.[5c] By analogy with this work, we envisioned a synthesis of bromopyridone **12** starting from methylacetoacetate (**4**). Successive alkylations of **4** with ethyl iodide and methyl iodide provided the ketoester **5** in good yield.[6] A standard Doebner condensation with cyanoacetic acid[7] followed by hydrolysis with potassium hydroxide in ethanol gave the acid **6** in a moderate yield. This acid **6** was then reacted with phosphorous pentachloride[7] at −78 °C and the reaction mixture was saturated with hydrobromic acid[5b] to provide, after workup, the

bromopyridone **7** in 40% yield. At this stage of the synthesis, we envisioned the introduction of the ketone of MPK by using classical oxidation methods.[8] The *N*-Boc-protected derivative of **7** (not shown) was thus subjected to reaction with *t*-BuOOH-PDC,[8a] *t*-BuOOH-CrO_3,[8b] or SeO_2.[8c] However, none of these conditions produced any desired product and the starting material was recovered quantitatively. These failures prompted us to investigate electrophilic hydroxylation on derivatives of **7**.[9] Davis *N*-sulfonyl oxaziridines **9a** and **9b**[10,11] have been extensively used in literature,[11] and we attempted their reaction with the TBDPS-protected **8a**. The results are summarized in Table 1.

Scheme 1 [i]



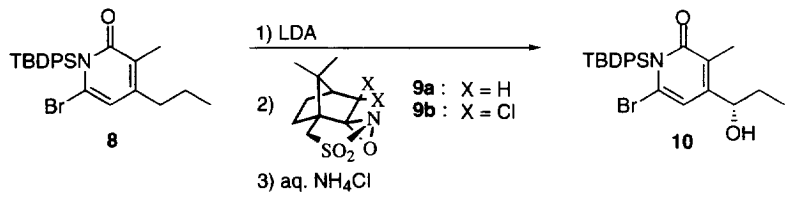
[i] *Steps*: (a) NaH, *n*-BuLi, EtI, THF (76%); (b) NaH, MeI, DME (86%); (c) $NCCH_2COOH$, $AcONH_4$, AcOH, PhH (44%); (d) KOH, EtOH (100%); (e) PCl_5, CH_2Cl_2; HBr (40%);[5a] (f) TBDPS-Cl, Et_3N, CH_2Cl_2 (100%); (g) LDA, THF/HMPA; **9a,b** (see Table 1); aq. NH_4Cl; (h) TBAF, THF (72%); (i) NaH, LiBr, $HC{\equiv}C\text{-}CH_2Br$, DME/DMF (95%);[13] (j) PhNC (**13**), Me_6Sn_2, PhH, hv (38%);[5a] (k) PCC, CH_2Cl_2 (85%).

[ii] *ee* determined from the Mosher's ester with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetylchloride.

As shown in Table 1, the reaction was highly dependent on the conditions used for the deprotonation.[10] At –10 to –15 °C, only trace amounts of the carbanion were generated as evidenced by the near-absence of product **10** in NMR (< 10%) after quenching with **9a** (entry 1). By contrast, when the temperature was raised to 0 °C, carbanion product **10** was isolated in low yield together with starting material (entry 2). Warming to room temperature resulted only in decomposition of **8** (data not shown). Addition of HMPA proved to be beneficial to the reaction and, under the same conditions as entry 1, led to a 1:1 mixture of product and starting material (entry 3). Since the

temperature could not be raised much further without degradation of the starting material, an excess of base was then used, and this provided a good **10**:**8** ratio (4:1, entry 4). Finally, adding more HMPA proved satisfactory for the preparation of **10** in reasonable isolated yield (47%, entry 5). The enantiomeric excess was 60%, as determined from the Mosher's ester with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetylchloride (Scheme 1). By contrast, the same conditions gave **10** in much lower yield and *ee* when **9b**[11] was used as the hydroxylating agent (Scheme 1).

Table 1. Optimization of the Asymmetric Hydroxylation of 8 with 9a.[a]



Entry	LDA (equiv.)	**9a** (equiv.)	Cosolvent (%)	Deprotonation conditions	**10**:**8** (yield **10**)
1	1.2	1.25	-	-10 °C, 2 h, -5 °C, 30 min	trace **10**
2	1.2	1.25	-	0 °C, 1 h 30	1.2:1 (23)[b]
3	1.2	1.25	HMPA (5)	-10 °C, 2 h, -5 °C, 30 min	0.9:1
4	3.0	3.0	HMPA (5)	-10 °C, 2 h, -5 °C, 30 min	4:1 (41)[c]
5	3.0	1.25	HMPA (12)	-10 °C, 2 h, -5 °C, 30 min	4:1 (47)

[a] In all reactions **8** was deprotonated with LDA following the above mentioned conditions then reacted with **9a** at -78 °C for 1 h before aqueous workup. [b] **8** was recovered in 35% yield. [c] An identical result was obtained with 1.25 equiv. of **9a**.

By analogy to the work of Davis *et al.*, the (*S*)-configuration was predicted for the enantiomerically enriched isomer of **10**. This was confirmed later by comparison with the optical properties of natural mappicine (see below).

In the last part of the synthesis, **10** was deprotected and selectively *N*-propargylated under optimized conditions[12] to afford the radical precursor **12**.[13] The key radical cascade reaction was then performed by irradiating a benzene solution of **12**, phenylisonitrile (6 equiv) and hexamethylditin (3 equiv) at 80 °C for 48 h. Enantiomerically enriched (*S*)-mappicine (**2**) directly formed in the reaction and was isolated in 38% yield and 60% *ee* after purification by flash chromatography. The (*S*)-configuration was confirmed from the circular dichroism of this compound, which showed a negative Cotton effect in the region 300-400 nm as observed with natural (*S*)-mappicine.[2] In the final step of the synthesis, oxidation of **2** with PCC provided (achiral) MPK (**1**) in good yield. In comparison, the same radical cascade when carried out on the ketone analog of **2** gave only trace amount of MPK.

This synthesis of MPK provides yet another example of the power of the [4 + 1] radical transannulation, one of the very few radical cascades to proceed first through intermolecular bond formation. Because the radical cascade reaction is tolerant of a variety of functionalities[5] the strategy should be applicable to the preparation of a wide assortment of MPK derivatives substituted on B

and/or A ring(s) by starting from the key late intermediate **11** and varying the propargyl halide and isonitrile components in the next two reactions.

Experimental Section

General: All reactions were run under argon atmosphere unless otherwise noted. Tetrahydrofuran (THF) and benzene (PhH) were freshly distilled from sodium/benzophenone. Toluene, methylene chloride (CH_2Cl_2), *N,N*-dimethylformamide (DMF), dimethoxyethane (DME), hexamethylphosphoramide (HMPA), pyridine, and triethylamine (Et_3N) were distilled from CaH_2. All other reagents were used as received.

Methyl 2-Methyl-3-oxohexanoate (5). To a suspension of NaH (60% in mineral oil, 8.80 g, 0.22 mol) in THF (300 mL) were slowly added methylacetoacetate (21.6 mL, 0.2 mol) at room temperature, then 1.6 N *n*-BuLi in hexanes (130 mL, 0.2 mol) at 0 °C. After 15 min at 0 °C, the solution was cooled to –78 °C and ethyl iodide (16 mL, 0.2 mol) was added all at once. The reaction mixture was allowed to warm to room temperature, stirred 3 h, and poured into a mixture of saturated NH_4Cl (600 mL) and Et_2O (600 mL). The organic layer was washed with saturated NH_4Cl (3 x 150 mL), dried (Na_2SO_4) and evaporated. The residue was distilled (bp 60 °C/0.2 mm Hg) to provide 22.0 g (76%) of a colorless oil. This compound (21.6 g, 150 mmol) was slowly added to a suspension of NaH (60% in mineral oil, 6.60 g, 165 mmol) in DME (250 mL). The mixture was stirred 15 minute at room temperature, then cooled in a water bath and methyl iodide (11.0 mL, 170 mmol) was added. After 3 h at room temperature, the same workup as above provided, upon distillation (bp 85-90 °C/0.2 mm Hg), 20.3 g (86%) of a colorless oil: IR (neat, cm^{-1}) 1745, 1718; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.3 Hz, 3 H), 1.24 (d, *J* = 7.2 Hz, 3 H), 1.54 (m, 2 H), 2.45 (m, 2 H), 3.47 (q, *J* = 7.2 Hz, 1 H), 3.68 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 13.4, 16.9, 43.1, 52.3, 52.5, 171.0, 205.8; HRMS (EI) *m/z* calcd for $C_8H_{14}O_3$ (M^+) 158.0943, found 158.0950; LRMS (EI) *m/z* 158 (M^+), 131, 127, 115.

4-Cyano-2-methyl-3-propyl-3-butenoic acid (6). A mixture of **5** (19.8 g, 0.125 mol), cyanoacetic acid (11.7 g, 0.14 mol), acetic acid (3.2 mL, 56 mmol), and ammonium acetate (1.95 g, 25 mmol) in benzene (50 mL) was refluxed in a flask equipped with a Dean-Stark apparatus, until no more water was collected (48 h, about 2.3 mL). The final solution was then cooled to room temperature, diluted with water (100 mL) and extracted with Et_2O (4 x 50 mL). The combined organic layers were washed with water (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL), then dried (Na_2SO_4). The residue obtained after evaporation of the solvents was distillated (bp 90-95 °C/0.3 mm Hg) to provide 9.95 g (44%) of a colorless oil. A solution of this oil (9.75 g, 53.8 mmol) and KOH (6.10 g, 0.11 mol) in absolute ethanol (125 mL) was stirred 5 h at room temperature. After concentration of the solvent, the residue was taken up in ice water (100 mL), slowly acidified with 6N HCl (20 mL) and extracted with AcOEt (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford 9.00 g (100%) of a slightly yellow oil as a 63: 37 mixture of *trans* and *cis* isomers: IR (neat, cm^{-1}) 3192, 2221, 1713, 1624, 1460, 1405, 1194; ^1H NMR (300 MHz, $CDCl_3$) *trans* isomer δ 0.97 (t, *J* = 7.2 Hz, 3 H), 1.35 (d, *J* = 7.0 Hz, 3 H), 1.57 (m, 2 H), 2.46 (t, *J* = 7.8 Hz, 2 H), 3.31 (q, *J* = 7.0 Hz, 1 H), 5.35 (s, 1 H); *cis* isomer δ 0.94 (t, *J* = 7.2 Hz, 3 H), 1.37 (d, *J* = 7.2 Hz, 3 H), 1.51 (m, 2 H), 2.17 (td, *J* = 7.5, 1.0 Hz, 2 H), 3.96 (q, *J* = 7.2 Hz, 1 H), 5.26 (t, *J* = 1.0 Hz, 1 H); HRMS (EI) *m/z* calcd for $C_9H_{11}NO$ ($M - H_2O^+$) 149.0841, found 149.0832; LRMS (EI) *m/z* 149 (M^+), 121, 106, 94.

6-Bromo-3-methyl-4-propyl-1*H*-pyridin-2-one (7). To a solution of **6** (9.00 g, 53.8 mmol) in CH_2Cl_2 (400 mL) was added phosphorous pentachloride (13.6 g, 65 mmol) portionwise at 0 °C, then the mixture was stirred 12 h at room temperature. The reaction was cooled to –78 °C and evacuated with an aspirator, and then gaseous anhydrous hydrobromic acid (about 10 L, 400 mmol) was adsorbed in the solution. The flask was then refilled with argon, fitted with a drying tube connected to a gas trap, and allowed to warm to room temperature overnight. The final solution was diluted with ice water (150 mL), and the aqueous layer extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated and the residue was subjected to flash chromatography ($CHCl_3$ then $CHCl_3$/MeOH 95:5) and recrystallization (hexanes/Et_2O) to provide 4.90 g (40%) of a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.3 Hz, 3 H), 1.56 (m, 2 H), 2.10 (s, 3 H), 2.48 (t, *J* = 7.7 Hz, 2 H), 6.58 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 13.9, 22.7, 35.2, 118.4, 120.2, 127.2, 154.8, 164.0; HRMS (EI) *m/z* calcd for $C_9H_{12}BrNO$ (M^+) 229.0102, found 229.0112; LRMS (EI) *m/z* 231, 229 (M^+), 216, 214, 150, 95.

6-Bromo-1-(*tert*-butyldiphenylsilyl)-3-methyl-4-propyl-1*H*-pyridin-2-one (8). To a solution of **7** (1.82 g, 7.85 mmol) in CH_2Cl_2 (40 mL) were successively added Et_3N (2.40 mL, 17.3 mmol) and *t*-

butylchlorodiphenylsilane (4.40 mL, 17.3 mmol). The resulting mixture was stirred 24 h at room temperature and poured into water (100 mL). The organic layer was washed with water, brine, and dried (Na_2SO_4). After evaporation of the solvent, the residue was subjected to flash chromatography (hexanes/AcOEt 95:5) to afford 3.68 g (100%) of a colorless oil: IR (neat, cm^{-1}) 1570, 1418, 1377, 1101, 791; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3 H), 1.17 (s, 9 H), 1.57 (m, 2 H), 2.23 (s, 3 H), 2.50 (t, J = 7.8 Hz, 2 H), 6.80 (s, 1 H), 7.32-7.45 (m, 6 H), 7.75-7.80 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 14.3, 20.0, 22.9, 27.9, 35.0, 118.6, 121.8, 127.6, 129.8, 133.5, 134.7, 136.2, 154.8, 159.8; HRMS (EI) m/z calcd for $C_{21}H_{21}BrNOSi$ (M – t-Bu$^+$) 410.0576, found 410.0581; LRMS (EI) m/z 412, 410 (M – t-Bu$^+$), 274, 217.

(*S*)-6-Bromo-1-(*tert*-butyldiphenylsilyl)-4-(1-hydroxypropyl)-3-methyl-1*H*-pyridin-2-one (10). To a solution of **8** (235 mg, 0.5 mmol) in THF (2 mL) at –78 °C were successively added added 2 N LDA in heptane/THF/ethylbenzene (1.0 mL, 2.0 mmol) and HMPA (0.30 mL). The reaction mixture was stirred 2 h at –10 °C, 30 min at –5 °C, and then cooled to –78 °C. A solution of **9a** (148 mg, 0.63 mmol) in THF (0.5 mL) was injected, and the resulting mixture was stirred 1 h at this temperature then quenched at –78 °C with saturated NH_4Cl (15 mL) and Et_2O (20 mL). After separation of the layers, the organic phase was further washed with saturated NH_4Cl (5 x 10 mL) and dried (Na_2SO_4). After concentration of the solvents, the residue was subjected to flash chromatography (hexanes/AcOEt 9:1 to 8:2) to provide, in order of elution, **8** (29 mg, 12% recovery), and **10** (114 mg, 47%) as a white solid: $[\alpha]_D^{20}$ –105.5 (c 1, $CHCl_3$); IR (neat, cm^{-1}) 3445, 1579, 1426, 1391, 1111, 700; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7.4 Hz, 3 H), 1.18 (s, 9 H), 1.66 (m, 2 H), 2.21 (s, 3 H), 4.80 (dd, J = 7.4, 5.3 Hz, 1 H), 7.13 (s, 1 H), 7.30-7.45 (m, 6 H), 7.70-7.80 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.3, 11.8, 19.8, 27.7, 30.7, 71.5, 116.8, 118.0, 127.5, 129.8, 133.0, 135.1, 136.0, 156.2, 159.7; HRMS (EI) m/z calcd for $C_{21}H_{21}BrNO_2Si$ (M – t-Bu$^+$) 426.0525, found 426.0521; LRMS (EI) m/z 428, 426 (M – t-Bu$^+$), 239, 199.

Mosher ester of 10 with (*S*)-(+)-α-methoxy-α-(trifluromethyl)phenylacetylchloride. To a solution of **10** (25 mg, 0.052 mmol) in pyridine (250 µL) were successively added (*S*)-(+)-α-methoxy-α-(trifluromethyl)phenylacetylchloride (12 µL, 0.062 mmol) and DMAP (1 mg, 0.008 mmol). The reaction was stirred 2 d at room temperature and poured into water (3 mL) and Et_2O (5 mL). The separated organic layer was washed with water (3 x 2 mL) and brine, and dried (Na_2SO_4) to give, after evaporation of the solvents 26 mg (72%) of a colorless oil: d.e. = 60%; ^1H NMR (300 MHz, $CDCl_3$) major isomer (main signals) δ 2.30 (s, 3 H), 3.60 (s, 3 H), 5.87 (dd, J = 7.2, 5.3 Hz, 1 H), 6.49 (s, 1 H); minor isomer (main signals) δ 2.31 (s, 3 H), 3.45 (s, 3 H), 5.96 (dd, J = 7.2, 5.4 Hz, 1 H), 6.79 (s, 1 H).

(*S*)-6-Bromo-4-(1-hydroxypropyl)-3-methyl-1*H*-pyridin-2-one (11). To a solution of **10** (395 mg, 0.815 mmol) in THF (2 mL) at 0 °C was added 1 N TBAF in THF (1 mL, 1.0 mmol) then the reaction was stirred 30 min at room temperature. The final solution was poured into brine (20 mL), extracted with AcOEt (6 x 15 mL) and dried (Na_2SO_4). After evaporation of the solvents the residue was purified by flash chromatography ($CHCl_3$/AcOEt 7:3) to provide 145 mg (72%) of a white solid: $[\alpha]_D^{20}$ –22.3 (c 1, MeOH); ^1H NMR (300 MHz, CD_3OD) δ 0.96 (t, J = 7.4 Hz, 3 H), 1.62 (m, 2 H), 2.03 (s, 3 H), 4.74 (t, J = 6.8 Hz, 1 H), 6.86 (s, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 9.4, 10.6, 29.6, 70.1, 110.5, 120.2, 122.2, 156.0, 163.0; HRMS (EI) m/z calcd for $C_9H_{12}BrNO_2$ (M$^+$) 245.0051, found 245.0041; LRMS (EI) m/z 247, 245 (M$^+$), 229, 227, 218, 216, 128, 137.

(*S*)-6-Bromo-4-(1-hydroxypropyl)-3-methyl-1-propargyl-1*H*-pyridin-2-one (12). To a solution of **11** (92 mg, 0.37 mmol) in DME (1.3 mL) and DMF (0.3 mL) were added portionwise 60% NaH (17 mg, 0.41 mmol) at 0 °C. LiBr (65 mg, 0.75 mmol) was added 10 min later. The mixture was stirred 15 min at room temperature, 80% propargyl bromide in toluene (87 µL, 0.74 mmol) was added and the reaction was heated 24 h at 75 °C. The final solution was poured into brine (15 mL), extracted with AcOEt (6 x 20 mL), and dried over Na_2SO_4. The residue obtained after concentration of the solvents was subjected to flash chromatography ($CHCl_3$ then $CHCl_3$/AcOEt 7:3) to afford 101 mg (95%) of a white solid: $[\alpha]_D^{20}$ -19.5 (c 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7.4 Hz, 3 H), 1.64 (m, 2 H), 2.02 (s, 3 H), 2.27 (t, J = 2.5 Hz, 1 H), 4.74 (dd, J = 7.3, 5.4 Hz, 1 H), 5.03 (d, J = 2.5 Hz, 2 H), 6.74 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.1, 12.2, 29.9, 39.0, 70.7, 72.5, 110.1, 122.2, 123.0, 153.5, 162.9; HRMS (EI) m/z calcd for $C_{12}H_{14}BrNO_2$ (M$^+$) 283.0208, found 283.0203; LRMS (EI) m/z 285, 283 (M$^+$), 268, 256, 254.

(*S*)-7-(1-Hydroxypropyl)-8-methyl-11*H*-indolizino[1,2-b]quinolin-9-one (Mappicine, 2). A solution of **12** (134 mg, 0.47 mmol), phenyl isonitrile (146 mg, 1.42 mmol) and hexamethylditin (240 mg, 0.72 mmol) in benzene (15 mL) was irradiated at 80 °C with a 275W GE sunlamp for 24 h. The same amount of phenyl isonitrile and hexamethylditin were then added and the mixture was irradiated another 24 h. The final solution was concentrated and the residue was subjected to flash chromatography ($CHCl_3$/acetone 95:5 to 1:1 then $CHCl_3$/MeOH 95:5) to give, in order of elution, **12** (25.7 mg, 19% recovery), then **2** (43.9 mg, 30%, 38%

including recovered **12**) as a white solid: c.d. $[\theta]_{375}$ −1332° (c 0.040, dioxane); $[\alpha]_D^{20}$ −7.4 (c 0.1, $CHCl_3$/MeOH 4:1); ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.4 Hz, 3 H), 1.63 (m, 2 H), 2.11 (s, 3 H), 4.52 (br s, 1 H), 4.94 (t, *J* = 6.5 Hz, 1 H), 4.94 (d, *J* = 18.8 Hz, 1 H), 5.20 (d, *J* = 18.8 Hz, 1 H), 7.21 (br t, *J* = 7.6 Hz, 1 H), 7.30 (br d, *J* = 8.0 Hz, 1 H), 7.39 (s, 1 H), 7.50 (br t, *J* = 7.6 Hz, 1 H), 7.75 (br d, *J* = 8.0 Hz, 1 H), 7.81 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ 5:1) δ 9.5, 11.5, 28.5, 29.6, 70.6, 100.2, 124.6, 127.2, 127.5, 128.1, 130.2, 131.1, 141.7, 147.7, 152.2, 154.9, 161.4; HRMS (EI) *m/z* calcd for $C_{19}H_{18}N_2O_2$ (M^+) 306.1368, found 306.1373; LRMS (EI) *m/z* 306 (M^+), 291, 289, 273, 247, 219.

8-Methyl-7-propionyl-11*H*-indolizino[1,2-b]quinolin-9-one (Mappicine ketone, 1). A solution of **2** (22.0 mg, 0.072 mmol) in CH_2Cl_2 (0.5 mL) was added to a mixture of PCC (31 mg, 0.14 mmol) and Celite (40 mg) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred overnight at room temperature then filtered over a short pad of Florisil rinsed with $CHCl_3$/acetone 1:1 to provide 18.4 mg (85%) of a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.1 Hz, 3 H), 2.27 (s, 3 H), 2.89 (q, *J* = 7.2 Hz, 2 H), 5.25 (br s, 2 H), 7.21 (s, 1 H), 7.61 (br t, *J* = 7.6 Hz, 1 H), 7.78 (br t, *J* = 7.8 Hz, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H), 8.15 (d, *J* = 8.4 Hz, 1 H), 8.33 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.7, 13.6, 35.9, 50.2, 97.8, 127.0, 127.7, 128.0, 128.5, 129.5, 130.4, 131.0, 143.3, 148.0, 148.7, 152.8, 161.7, 205.5; HRMS (EI) *m/z* calcd for $C_{19}H_{16}N_2O_2$ (M^+) 304.1212, found 304.1214; LRMS (EI) *m/z* 304 (M^+), 289, 275, 248, 218.

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References and Notes

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