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N-(2-Carboxyphenyl)glycine (12). To the solution of KOH (25.0 g, 446 mmol) and K_2CO_3 (25.0 g, 180 mmol) in water (400 mL) at rt was added 2-bromobenzoic acid, (38.2 g, 190 mmol), followed by glycine (25 g, 330 mmol) and CuBr (540 mg, 3.76 mmol). This mixture was refluxed for 4 h. After cooling to rt, the mixture was filtered over a fritted funnel and then the filtrate was acidified to pH 3 with concentrated HCl. The precipitate was collected and dried to obtain 32.4 g (88%) of **12**, mp 225.9-226.2 °C (dec., white foam) (lit.[63] ~215 °C; lit.[64] 220 °C): ^{1}H NMR (DMSO-d_6) δ 12.4 (br, 1H), 8.06 (br, 1H), 7.80 (m, 1H), 7.35 (m, 1H), 6.60 (m, 2H), 3.99 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 171.8, 169.7, 150.0, 134.4, 131.7, 114.7, 111.5, 110.6, 44.4; MS (EI, *m/z*) 195 (M^+). The dimethylester of **12** was obtained by reaction with diazomethane: ^{1}H NMR ($CDCl_3$) δ 8.4 (bs, 1H), 7.94 (dd, J = 8.0, J = 1.6, 1H), 7.35 (ddd, J = 7.2, J = 7.2, J = 1.6, 1H), 6.67 (ddd, J = 7.6, J = 7.2, J = 1.2, 1H), 6.53 (dd, J = 8.4, J = 0.8, 1H), 4.03 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.82, 168.76, 149.86, 134.57, 131.75, 115.64, 111.09, 52.23, 51.56, 44.88; HRMS (EI) calcd for $C_{11}H_{13}NO_4$ 223.0845, found 223.0858.

1-Acetyl-3-acetoxyindole (13). To a mixture of **12** (2.30 g, 11.8 mmol) and sodium acetate (3.75 g, 47.1 mmol) in DMF (29 mL) was added slowly acetic anhydride (11.7 mL, 118 mmol) and the mixture was refluxed for 2 h. After cooling, the mixture was concentrated to about 10 mL, partitioned between water (60 mL) and chloroform (120 mL), and the aqueous layer was extracted with chloroform (3 times). The combined organic layer was washed sequentially with 1M Na_2CO_3, water and brine, and then dried ($MgSO_4$). Purification of the crude oil by LPLC, eluting with ethyl acetate-hexane (1:2) gave 1.89 g (74%) of **13** as a light yellow powder, R_f 0.34 (ethyl acetate-hexane 1:2), mp 79.6-80.5 °C (lit.[65] 82 °C; lit.[66] 81 °C): ^{1}H NMR ($CDCl_3$) δ 8.47 (d, J = 8.0, 1H), 7.72 (s, 1H), 7.55 (d, J = 8.0, 1H), 7.40 (dd, J = 8.0, J = 8.0, 1H), 7.31 (dd, J = 8.0, J = 8.0, 1H), 2.62

(s, 3H), 2.40 (s, 3H), ^{13}C NMR ($CDCl_3$) δ 168.7, 167.8, 134.6, 132.8, 126.2, 123.7, 123.6, 117.4, 116.7, 113.3, 23.9, 21.0; MS (EI, *m/z*) 217 (M^+).

1-Acetyl-3-oxoindole (14). By analogy, the procedure of Galen was used.[67] To a refluxing solution of **13** (1.88 g, 8.66 mmol) in ethanol (46 mL) was added a hot solution (ca 90 °C) of sodium sulfite (1.24 g, 9.87 mmol) in water (46 mL). This mixture was refluxed for 10 min. The mixture was cooled to rt, the ethanol was removed *in vacuo*, and the aqueous layer extracted with chloroform (3 times). The combined chloroform layer was washed with water and brine, dried ($MgSO_4$), and then concentrated to give 1.46 g (96%) of **14** as a slightly greenish powder, R_f 0.11 (ethyl acetate-hexane 1:2), mp 137.6-138.1 °C (dec.) (lit.[65] 136 °C; lit.[64] 138 °C): ^{1}H NMR ($CDCl_3$) δ 8.57 (d, J = 8.8, 1H), 7.76 (d, J = 7.6, 1H), 7.68 (dd, J = 7.6, J = 7.6, 1H), 7.24 (m, 1H), 4.31 (s, 2H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 194.7, 168.1, 153.8, 137.4, 124.8, 124.2, 123.7, 118.6, 56.1, 24.3; MS (EI, *m/z*) 175 (M^+).

1-Acetyl-2-(2-nitrophenylmethylene)-3-oxo-2,3-dihydroindole (16). A mixture of **14** (2.0 g, 11.43 mmol), 2-nitrobenzaldehyde (3.47 g, 22.86 mmol), 4Å molecular sieves (40 g), and 10 drops of piperidine in toluene (100 mL) was stirred at rt for 3 days, during which time a yellow precipitate formed. Dichloromethane was added to dissolve the precipitate. The mixture was filtered through a funnel and the molecular sieves were washed with dichloromethane. The organic solution was concentrated and the crude mixture was purified by LPLC (dichloromethane to dichloromethane-ethyl acetate, 4:1) to afford unreacted **14** (180 mg) and product **16** (2.14 g, 61% yield, 67% corrected yield), mp 199.2-200.2 °C (lit.[68] 200 °C): ^{1}H NMR ($CDCl_3$) δ 8.24 (d, J = 8.4, 1H), 8.02-8.10 (m, 2H), 7.64-7.73 (m, 3H), 7.55-7.61 (m, 2H), 7.25 (ddd, J = 7.6, J = 7.6, J = 0.4, 1H), 2.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 183.6, 169.1, 148.6, 136.5, 133.9, 133.1, 132.2, 130.0, 129.3, 124.8, 124.7, 124.5, 124.4, 124.0, 117.2, 26.9; MS (EI, *m/z*) 266 (M^+-$COCH_3$), 119 (100%).

10-Acetylquindoline (17). A mixture of **16** (660 mg, 2.14 mmol) and Pd/C (10%, 100 mg) in 75 mL ethanol was shaken in a Parr bomb under an atmosphere of hydrogen (50 psi) for 3 h. The mixture was filtered through celite and the filtrate was concentrated to give the crude product, which was purified by LPLC (dichloromethane-ethyl acetate 40:1) to afford **17** (230 mg, 41% yield), mp 177.5-178.5 °C (lit.[20] 177-178 °C): ^{1}H NMR ($CDCl_3$) δ 9.01 (s, 1H), 8.54 (d, J = 7.5, 1H), 8.30 (d, J = 8.5, 1H), 8.13 (d, J = 8.3, 1H), 8.00 (dd, J = 8.1, J = 1.4, 1H), 7.77 (ddd, J = 8.3, J = 6.9, J = 1.4, 1H), 7.67 (ddd, J = 8.5, J = 7.5, J = 1.4, 1H), 7.60 (ddd, J = 8.1, J = 6.9, J = 1.2, 1H), 7.53 (dd, J = 7.2, J = 7.2, 1H), 2.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.6, 147.2, 145.8, 141.3, 131.2, 130.5, 128.8, 128.5, 128.4, 127.2, 126.0, 125.5, 124.3, 121.9, 121.3, 115.7, 27.6; MS (EI, *m/z*) 260 (M^+), 218 (100%).

10-Acetyl-5-methylquindolinium hydroiodide (18). A mixture of compound **17** (160 mg, 0.62 mmol) and methyl iodide (5 mL) was sealed in a Parr bomb and heated at 150 °C for 24 h. The bomb was cooled to rt and the unreacted methyl iodide was removed. The yellow solid was washed with dichloromethane, filtered, and washed again with dichloromethane. The sample was dried under vacuum to afford **18** (200 mg, 81% yield), mp 218.5 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 9.99 (s, 1H), 8.95 (d, J = 8.4, 1H), 8.84 (d, J = 8.8, 1H), 8.73 (dd, J = 8.4, J=1.6, 1H), 8.56 (d, J = 8.8, 1H), 8.29 (ddd, J = 8.8, J = 7.2, J = 1.6, 1H), 8.11 (ddd, J = 8.4, J = 7.2, J = 1.2, 1H), 8.05 (ddd, J = 7.6, J = 6.8, J = 0.8, 1H), 7.79 (ddd, J = 8.4, J = 7.2, J = 0.8, 1H), 5.05 (s, 3H), 3.10 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 170.5, 142.9, 141.6, 136.6, 135.1, 134.2, 132.1, 130.9, 130.2, 128.4, 127.3, 126.8, 125.1, 118.2, 117.3, 116.8, 41.0, 27.8; MS (EI, *m/z*) 275 (100%, M^+-I). HRMS (FAB) calcd for $C_{18}H_{15}N_2O^+$ 275.1184, found 275.1200.

Quindoline 8 from 17: Solid **17** (30 mg, 0.115 mmol) was added to a solution of KOH (64.5 mg, 1.15 mmol) in methanol (1 mL) in one portion. After stirring at rt for 30 min, the mixture was quenched with aqueous NH_4Cl, causing a heavy precipitate to form. This mixture was extracted twice with dichloromethane and the combined dichloromethane

solution was washed with aqueous NH_4Cl and then dried ($MgSO_4$). This solution was passed through a short silica gel column to remove a very polar impurity. The solvent was evaporated and **8** (21 mg, 84% yield) was obtained as a yellow solid, mp 249-251 °C (lit.[57] 251-252 °C).

Preparation of Cryptolepine Hydroiodide (2) from 1. To a solution of cryptolepine (**1**) in chloroform was added a solution of HI in ether (prepared from ether extraction of commercially available 57% HI water solution). The yellow precipitate which formed was filtered, washed with ether, and dried over P_2O_5 under vacuum: MS (FAB, *m/z*) ($M+H^+$); HRMS (FAB) calcd for $C_{16}H_{13}N_2^+$ 233.1079, found 233.1089. Anal. ($C_{16}H_{13}N_2I \cdot H_2O$) C, N; H: calcd, 3.99; found, 3.36.

Preparation of Cryptolepine Hydrotrifluoromethanesulfonate (3) from 1. To a solution of cryptolepine (**1**) in chloroform was added triflic acid in ether (1M, prepared from 3 g of triflic acid and 20 mL of ether). The yellow precipitate which formed was filtered, washed with ether, and dried over P_2O_5 under vacuum, mp 241-243 °C: MS (FAB, *m/z*) 233 ($M+H^+$); MS (-FAB, *m/z*) [M^-] 148.9 (OTf^-); IR (KBr) 3188, 1617, 1215, 1157, 1034, 746 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{13}N_2^+$ 233.1079, found 233.1072.

Preparation of Cryptolepine Hydrochloride (4) from 18. Compound **18** (60 mg, 0.149 mmol) was suspended in 40 mL at chloroform in a separatory funnel. Saturated aqueous Na_2CO_3 solution (40 mL) was added and the mixture was shaked until two layers became clear solutions and the bottom chloroform layer had a fresh purple color. The two phases were separated and the aqueous phase was extracted further with chloroform. The chloroform layers were combined, washed with aqueous Na_2CO_3 solution and brine, dried, filtered and then concentrated to afford the free base. The free base was redissolved in chloroform (3 mL) and a solution of 1M HCl in ether was added. A yellow solid formed immediately. The solid was filtered, washed thoroughly with diethyl ether, and then dried under vacuum to afford **4** (30.9 mg, 77%) as a bright yellow solid, mp 268 °C.

Preparation of Cryptolepine Hydroiodide (4) from 2. Cryptolepine hydroiodide

(1.6 g, 4.4 mmol) was dissolved in chloroform, Na_2CO_3 (~5 g) was added, and then the mixture was evaporated to dryness. The solid adsorbate was loaded onto a short column of basic alumina and the column was eluted with chloroform to remove the quindoline impurity. Further elution with 1-2% methanol in chloroform, collection of the purple fractions, concentration to a small volume, and then acidification with a 1M solution of HCl in ether gave a yellow-orange precipitate. The precipitate was filtered, washed with ether, and then dried to yield 0.72 g (60.8%) of **4** as a bright yellow solid, mp 268 °C: see Tables 6 and 7 for NMR data.

Elemental Analyses:

5-Methylquindoline (1) (Cryptolepine). Anal. Calcd for $C_{16}H_{12}N_2 \cdot 1.5\ H_2O$: C, 74.11; H, 5.83; N, 10.80. Found: C, 73.91; H, 5.61; N, 10.61.

Cryptolepine Hydroiodide (2). Anal. Calcd for $C_{16}H_{13}N_2I$: C, 53.35; H, 3.63; N, 7.77. Found: C, 53.55; H, 3.81; N, 7.61.

Cryptolepine Hydrotrifluoromethanesulfonate (3). Anal. Calcd. for $C_{17}H_{13}N_2F_3O_3S$: C, 53.32; H, 3.42; N, 7.32. Found: C, 53.10; H, 3.35; N, 7.20.

Cryptolepine Hydrochloride (4). Anal. Calcd for $C_{16}H_{13}N_2Cl \cdot 1.5\ H_2O$: C, 64.97; H, 5.45; N, 9.47. Found: C, 64.98; H, 4.89; N, 9.22.

Quindoline-11-carboxylic Acid (7). Anal. Calcd for $C_{16}H_{10}N_2O_2 \cdot 0.5\ H_2O$: C, 70.84; H, 4.08; N, 10.32. Found: C, 70.83; H, 3.86; N, 10.32.

10-Methylquindoline (9). Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.64; H, 5.06; N, 11.91.

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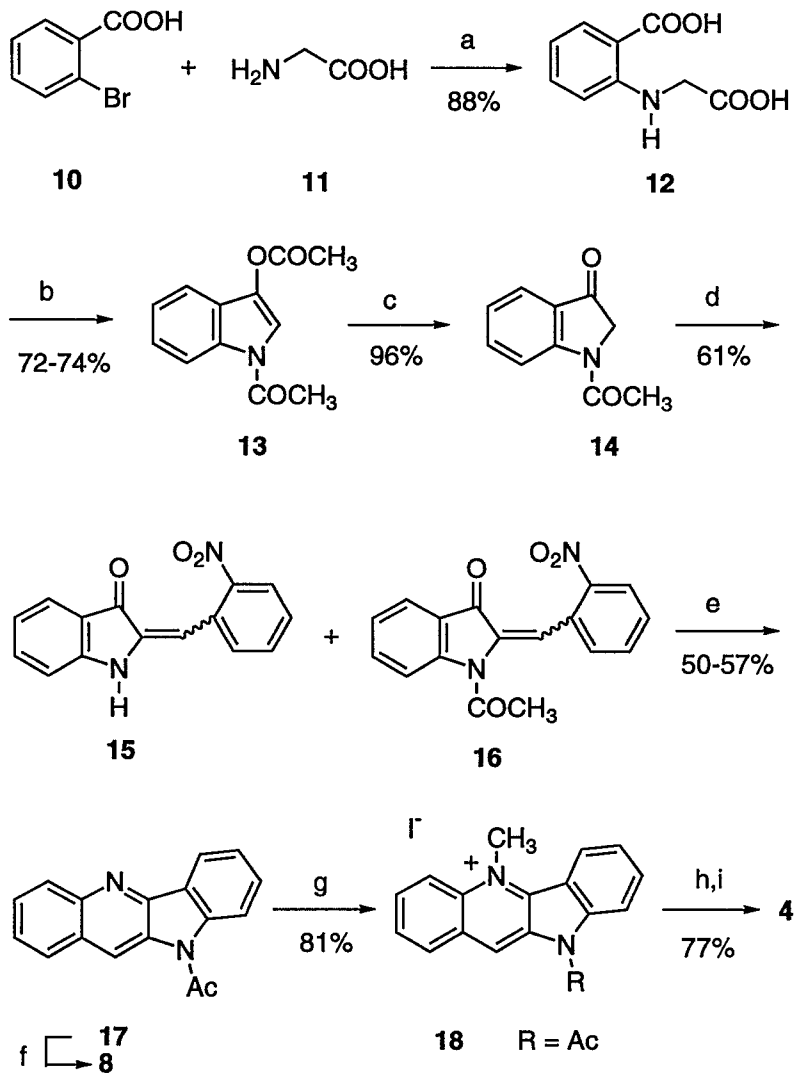
Scheme 2[a]



[a] (a) KOH (aq), K_2CO_3, CuBr, reflux; (b) Ac_2O, NaOAc, DMF; (c) Na_2SO_3, H_2O/EtOH; (d) 2-nitrobenzaldehyde, piperidine (cat.), toluene, molecular sieves, rt; (e) H_2, Pd/C, MeOH; (f) KOH, MeOH rt, 84%; (g) MeI, MeOH, bomb; (h) aq. Na_2CO_3; (i) HCl

Table 6. 'H NMR Assignments for Cryptolepine (1), its Salt Forms, and Regioisomer (9) in DMSO-d_6[a,b]

Position	(1) lit[c]	(1)	(2)	(3)	(4)	(9)[d]
1	8.40 (dd, 8.4, 1.4)	8.39 (dd, 8.4, 1.2)	8.58 (dd, 8.4, 1.2)	8.58 (dd, 8.4, 1.2)	8.58 (dd, 8.0, 0.8)	7.87 (d, 8.0)
2	7.69 (ddd, 7.9, 6.6, 0.8)	7.69 (dd, 7.6, 7.2)	7.95 (dd, 8.2, 8.2)	7.95 (ddd, 8.4, 8.4, 0.8)	7.92 (dd, 7.2, 6.8)	7.51 (ddd, 8.0, 7.2, 0.8)
3	7.90 (ddd, 9.1, 6.8, 1.4)	7.89 (ddd, 8.4, 6.8, 1.2)	8.17 (ddd, 7.6, 7.6, 1.2)	8.17 (ddd, 8.0, 8.0, 1.6)	8.16 (dd, 7.6, 7.6)	7.66 (ddd, 8.4, 7.2, 0.8)
4	8.53 (dd, 9.2, 0.8)	8.52 (d, 9.2)	8.77 (d, 9.2)	8.77 (d, 9.2)	8.76 (d, 9.6)	8.33 (d, 8.4)
6	8.51 (ddd, 7.6, 0.8, 0.8)	8.50 (d, 8.0)	8.81 (d, 8.4)	8.81 (d, 8.4)	8.79 (d, 8.4)	8.55 (d, 7.6)
7	7.05 (ddd, 8.6, 6.8, 1.2)	7.04 (ddd, 8.4, 6.4, 0.8)	7.50 (dd, 7.2, 7.2)	7.52 (ddd, 7.2, 7.2, 0.8)	7.50 (dd, 7.6, 7.6)	7.33 (dd, 7.6, 7.6)
8	7.53 (ddd, 8.6, 6.6, 1.2)	7.53 (ddd, 8.0, 6.8, 1.2)	7.92 (dd, 8.2, 8.2)	7.94 (ddd, 8.4, 8.4, 0.8)	7.91 (dd, 7.2, 6.8)	7.61 (ddd, 8.4, 7.6, 0.8)
9	7.66 (ddd, 8.6, 1.0, 1.0)	7.66 (dd, 8.0, 0.8)	7.86 (d, 8.4)	7.85 (d, 8.4)	7.85 (d, 8.4)	7.30 (d, 8.4)
11	8.95 (s)	8.94 (s)	9.30 (s)	9.29 (s)	9.31 (s)	7.74 (s)
5-NCH_3	4.92 (s)	4.92 (s)	5.04	5.04 (s)	5.04 (s)	-
10-NH	-	-	12.88	12.88 (s)	13.35 (s)	3.72 (s, 10-CH_3)

[a] *at 400 MHz*
[b] *data reported as δ (multiplicity, coupling constants in Hz)*
[c] *literature data recorded at 500 MHz; see reference 55*
[d] *in $CDCl_3$*

Table 7. ^{13}C NMR Assignments for Cryptolepine, its Salt Forms, and Regioisomer (9) in DMSO-d_6[a,b]

Position	(1) lit [c]	(1)	(2)	(3)	(4)	(9)[d]
1	129.6	129.5	129.8	129.5	129.8	127.1
2	123.9	123.6	127.0	126.7	127.0	125.1
3	128.9	128.6	132.4	132.1	132.3	126.2
4	116.6	116.3	117.8	117.4	117.8	129.1
4a	132.8	132.6	135.3	135.2	135.3	143.9
5a	139.0	138.9	138.1	138.1	138.0	145.9
5b	113.8	113.6	113.2	113.6	113.7	121.5
6	125.1	124.9	126.3	125.9	126.2	122.0
7	116.6	116.2	121.4	121.1	121.2	119.6
8	130.4	130.1	133.9	133.6	133.8	129.6
9	119.5	119.3	113.1	112.9	113.2	108.3
9a	160.0	160.5	133.2	133.1	133.3	144.8
10a	144.4	144.8	145.7	145.6	145.8	134.0
11	126.2	126.2	124.8	124.6	124.8	110.6
11a	124.4	124.2	126.2	125.8	126.2	126.7
N-CH_3	38.9	38.7	40.2	39.8	40.1	29.0

[a] *at 100 MHz*
[b] *refer to Table I for structures*
[c] *literature data reported at 75 MHz; see reference 55*
[d] *in $CDCl_3$*

Table 8. Melting Point and UV Data for Cryptolepine (1), its Salt Forms (2-4), and Regioisomer 9

Compound	mp (°C)	λ max (ε)	λ max (ε)	λ max (ε)	λ max (ε)	λ max (ε)	λ max (ε)	λ max (ε)
1	178-180	434 (3,170)	369 (32,500)	354 (17,200)	282 (42,500)	264 (41,600)	244 (16,900)	223 (31,500)
2	283.5-284	433 (3,180)	369 (32,800)	355 (sh) (17,600)	282 (42,900)	274 (41,700)	242 (17,800)	222 (45,200)
3	241-243	434 (3,380)	369 (27,700)	354 (sh) (16,800)	281 (31,800)	274 (31,600)	245 (16,200)	223 (25,400)
4	268	436 (3,350)	369 (34,300)	355 (sh) (18,300)	282 (44,600)	274 (43,300)	245 (17,800)	223 (33,000)
9	115-116	409 (4,720) 392 (5,020)	344 (26,200)	339 (18,500) 329 (14,900)	280 (63,900)	277 (63,200)	267 (57,000)	226 (44,600)