Concise synthesis of 22-Hydroxyacuminatine, cytotoxic camptothecinoid from *Camptotheca acuminata*, by pyridone benzannulation

Matej Babjak, Alice Kanazawa*, Regan J. Anderson and Andrew E. Greene
Université Joseph Fourier de Grenoble, Chimie Recherche (LEDSS)
38041, Grenoble, France

Electronic Supplementary Information

Methyl (2*E*,4*E*)-5-(5-Oxo-1,2,3,5-tetrahydroindolizin-6-yl)penta-2,4-dienoate (6). Yellow–orange crystals, mp 171-173 °C (ethyl acetate–pentane); R_f 0.43 (ethyl acetate); IR (Nujol) 1716, 1636, 1615, 1540, 1377; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (tt, *J* = 7.5, 7.5 Hz, 2 H), 3.12 (t, *J* = 7.5 Hz, 2 H), 3.75 (s, 3 H), 4.19 (t, *J* = 7.5 Hz, 2 H), 5.96 (d, *J* = 14.7 Hz, 1 H), 6.17 (d, *J* = 6.8 Hz, 1 H), 6.87 (d, *J* = 14.7 Hz, 1 H), 7.40 (dd, *J* = 14.7, 14.7 Hz, 1 H), 7.43 (d, *J* = 6.8 Hz, 1 H), 7.51 (dd, *J* = 14.7, 14.7 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1 (CH_2), 31.9 (CH_2), 48.9 (CH_3), 51.3 (CH_2), 101.4 (CH), 120.0 (CH), 123.4 (C), 127.7 (CH), 136.4 (CH), 139.2 (CH), 146.1 (CH), 150.7 (C), 160.4 (C), 167.6 (C); MS (DCI, NH_3+isobutane) *m/z* 246 (MH^+); Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.54; H, 6.25; N, 5.72.

Methyl 5-Oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline-9-carboxylate (7). Pale yellow crystals, mp 151-152 °C (ethyl acetate–ether); R_f 0.60 (ethyl acetate); IR (Nujol) 1718, 1652, 1625, 1590, 1429, 1399, 1377; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.22 (tt, *J* = 7.2, 7.2 Hz, 2 H), 3.15 (t, *J* = 7.2 Hz, 2 H), 3.95 (s, 1 H), 4.19 (t, *J* = 7.2 Hz, 2 H), 7.42 (t, *J* = 7.9 Hz, 1 H), 7.60 (s, 1 H), 8.28 (d, *J* = 7.9 Hz, 1 H), 8.62 (d, *J* = 7.9 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.8 (CH_2), 31.7 (CH_2), 48.1 (CH_2), 52.1 (CH_3), 98.1 (CH), 124.4 (CH), 124.9 (C), 125.9 (C), 132.5 (CH), 135.1 (CH), 137.8 (C), 145.8 (C), 161.1 (C), 167.4 (C); MS (DCI, NH_3+isobutane) *m/z* 244 (MH^+); HRMS calcd for $C_{14}H_{14}NO_3$: 244.0973. Found: 244.0985 (MH^+).

Methyl 1-Hydroxy-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline-9-carboxylate (8). Pink–violet needles, mp 214-216 °C (ethyl acetate–CH_2Cl_2); R_f 0.32 (ethyl acetate); IR (Nujol) 1717, 1652, 1609, 1585, 1558, 1377, 1256; ^{1}H NMR (300 MHz, CD_3OD–$CDCl_3$ 1:1) δ 2.08 (m, 1 H), 2.43 (m, 1 H), 3.89 (s, 3 H), 3.98 (m, 1 H), 4.22 (m, 1 H), 5.16 (dd, *J* = 5.9, 6.9 Hz, 1 H), 7.43 (dd, *J* = 7.4, 7.4 Hz, 1 H), 7.74 (m, 1 H), 8.24 (pseudo d, *J* = 7.4 Hz, 1 H), 8.49 (pseudo d, *J* = 7.4 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_3OD–$CDCl_3$ 1:1) δ 31.3 (CH_2), 45.1 (CH_2), 51.7 (CH_3), 72.1 (CH), 99.2 (CH), 124.9 (CH), 125.5 (C), 125.7 (C), 131.6 (CH), 135.1 (CH), 137.2 (C), 146.9 (C), 160.7 (C), 167.0 (C); MS (DCI, NH_3+isobutane) *m/z* 260 (MH^+), 241; HRMS calcd for $C_{14}H_{14}NO_4$: 260.0923. Found: 260.0933 (MH^+).

Methyl 1,5-Dioxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline-9-carboxylate (9). Yellow–pale orange solid, mp 158-159 °C (ethyl acetate); R_f 0.52 (ethyl acetate); IR (Nujol) 1738, 1726, 1709, 1644, 1617, 1599, 1396, 1377; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.95 (t, *J* = 7.2 Hz, 2 H), 4.07 (s, 3 H), 4.39 (t, *J* = 7.2 Hz, 2 H), 7.68 (t, *J* = 7.5 Hz, 1 H), 8.35 (s, 1 H), 8.40 (d, *J* = 7.5 Hz, 1 H), 8.74 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 33.9 (CH_2), 41.4 (CH_2), 52.5 (CH_3), 102.5 (CH), 128.2 (CH), 128.4 (C), 129.2 (C), 132.2 (CH), 135.3 (C), 135.6 (C), 135.7 (CH), 160.7 (C), 166.5 (C), 197.4 (C); MS (DCI, NH_3+isobutane) *m/z* 258 (MH^+), 223, 194; HRMS calcd for $C_{14}H_{12}NO_4$: 258.0766. Found: 258.0772 (MH^+).

11-Oxo-11,12-dihydro-5,11a-diaza-dibenzo[*b*,*h*]fluorene-7-carboxylic Acid Methyl Ester (10). Pale yellow solid, mp 264-266 °C (ethyl acetate); R_f 0.68 (6% acetone–CH_2Cl_2); IR (Nujol) 1708, 1655, 1631, 1592, 1377; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (s, 3 H), 5.30 (s, 2 H), 7.54 (m, 2 H), 7.77 (m, 1 H), 8.19 (d, *J* = 8.4 Hz, 1 H), 8.23 (s, 1 H), 8.34 (d, *J* = 7.9 Hz, 1 H), 8.64 (s, 1 H), 8.70 (d, *J* = 7.9 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 49.4 (CH_2), 52.4 (CH_3), 98.8 (CH), 125.9 (CH), 126.8 (C), 127.1 (C), 127.4 (CH), 127.9 (CH), 128.0 (C), 128.7 (C), 129.7 (CH), 129.8 (C), 130.1 (CH), 130.5 (CH), 132.2 (CH), 135.5 (CH), 137.1 (C), 141.4 (C), 148.9 (C), 160.5 (C), 167.1 (C); MS (DCI, NH_3+isobutane) *m/z* 343 (MH^+), 299, 285, 244, 223; HRMS calcd for $C_{21}H_{15}N_2O_3$: 343.1083. Found: 343.1081 (MH^+).

7-Hydroxymethyl-12H-5,11a-diaza-dibenzo[*b*,*h*]fluoren-11-one (22-Hydroxyacuminatine) (3). Pale yellow solid, mp 290-295 °C (CH_3OH–CH_2Cl_2, dec); R_f 0.37 (4% CH_3OH–48% ethyl acetate–48% CH_2Cl_2); UV λ_{max} nm (log ε) 222 (4.45), 251 (4.46), 285 (3.99), 366 (4.13), 378 (4.14); IR (Nujol) 3361, 1653, 1613, 1595, 1505, 1377; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.92 (d, *J* = 5.5 Hz, 1 H), 5.30 (s, 2 H), 5.46 (t, *J* = 5.5 Hz, 2 H), 7.53 (t, *J* = 7.7 Hz, 1 H), 7.64 (m, *J* = 7.7 Hz, 1 H), 7.66 (s, 1 H), 7.80 (m, 2 H), 8.04 (d, *J* = 7.2 Hz, 1 H), 8.16 (d, *J* = 8.4 Hz, 1 H), 8.25 (d, *J* = 8.2 Hz, 1 H), 8.58 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 49.3 (CH_2), 61.1 (CH_2), 96.0 (CH), 125.7 (CH), 125.8 (C), 126.5 (CH), 127.1 (CH), 127.7 (C), 128.3 (CH), 128.7 (CH), 129.5 (C), 130.0 (CH), 130.9 (CH), 131.1 (CH), 135.1 (C), 138.3 (C), 139.9 (C), 147.7 (C), 153.1 (C), 159.7 (C); MS (DCI, NH_3+isobutane) *m/z* 315 (MH^+), 260, 244; MS (EI, 70eV) *m/z* 314 (M^+), 297, 285, 268, 255; HRMS calcd for $C_{20}H_{15}N_2O_2$: 315.1134. Found: 315.1138 (MH^+).