Supplementary Material for Organic & Biomolecular Chemistry

A Short Synthesis of (±)-Cytisine

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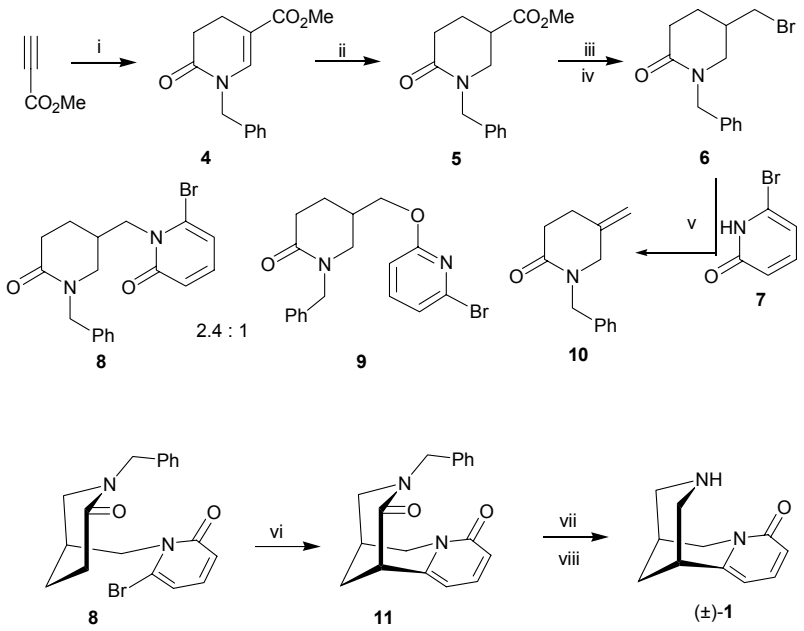
Supplementary data

Characterization Data



***N*-Benzyl-5-(hydroxymethyl)piperidin-2-one**

Colourless oil**.**

IR (neat) : 3373 (w), 2926 (w), 1614 (s), 1495 (m), 1239 (m); ^{1}H NMR (400 MHz, $CDCl_3$) : 1.56 (m, 1 H), 1.89 (m, 1 H), 2.04 (m, 1 H), 2.45 (d d d, *J* = 18.1, 11.2, 6.4, 1H), 2.58 (d d d, *J* = 18.1, 6.4, 3.4, 1 H), 3.02 (d d, *J* = 12.2, 9.7, 1H), 3.30 (d d d, *J* = 12.2, 5.3, 1.6, 1 H), 3.45 (m, 1 H), 3.58 (m, 1 H), 4.60 (s, 2 H), 7.23-7.35 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) : 23.8 (CH_2), 31.2 (CH_2), 36.5 (CH), 49.7 (CH_2), 50.4 (CH_2), 64.5 (CH_2), 127.5 (CH), 128.1 (2xCH), 128.6 (2xCH), 137.1 (C), 170.0 (C);

MS (m/z): 219 (M^+), 201, 184, 170, 158, 144 , 132, 118, 106 , 91; HRMS calcd for $C_{13}H_{17}NO_2$ 219.1259, obsd 219.1259.

1-Benzyl-5-(bromomethyl)piperidin-2one 6

Yellow oil which was used without any further purification.

IR (neat): 3029 (w), 2929 (w), 1636 (s), 1493 (m), 1258 (m). ^{1}H NMR (400 MHz, $CDCl_3$) : 1.67 (m, 1 H), 2.00 (m, 1 H), 2.08 (m, 1 H), 2.55 (d d d, *J* = 17.5, 10.7, 6.3, 1 H), 2.70 (m, 1 H), 3.05 (d d, *J* = 12.2, 11.7, 1 H), 3.27 (d d, *J* = 12.4, 12.2, 1 H), 3.33 (m, 2 H), 4.61 (q, *J* = 14.6, 2 H), 7.26-7.38 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) : 26.2 (CH_2), 30.9 (CH_2), 34.7 (CH), 36.0 (CH_2), 50.3 (CH_2), 51.0 (CH_2), 127.6 (CH), 128.17 (2xCH), 128.7 (2xCH), 136.8 (C), 169.3 (C); MS (m/z) 283 (M^+), 281, 120, 106, 91; HRMS calcd for $C_{13}H_{16}NO^{79}Br$ 281.0415, obsd 281.0426.

1-[(1-Benzyl-6-oxopiperidin-3-yl)methyl]-6-bromopyridin-2(1H)-one 8

IR (neat) : 3447 (w), 2924 (w), 1633 (s), 1583 (s), 1507 (s), 1259 (w); ^{1}H NMR (400 MHz, $CDCl_3$) : 1.70 (m, 1 H), 1.90 (bs, 1 H), 2.43 (m, 2 H), 2.62 (d d d, *J* = 18.1, 5.9, 3.4, 1 H), 3.12 (d d, *J* = 12.2, 10.2, 1 H), 3.21 (d d, *J* = 12.2, 3.9, 1 H), 4.20 (d, *J* = 6.8, 2 H), 4.61 (q, *J* = 14.6, 2 H), 6.47 (d, *J* = 9.3, 1 H), 6.50 (d, *J* = 7.4, 1 H), 7.15 (d d, *J* = 9.3, 7.4, 1 H), 7.30 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) : 25.2 (CH_2), 31.2 (CH_2), 34.1 (CH), 50.3 (CH_2), 50.5 (CH_2), 51.3 (CH_2), 111.6 (CH), 119.3 (CH), 126.9 (C), 127.4 (CH), 128.1 (2xCH), 128.6 (2xCH), 136.8 (C), 139.3 (CH), 163.0 (C), 169.3 (C); MS (m/z): 375 (M^+, 3), 295 (93), 267 (10), 235 (10), 201 (8), 188 (15), 173 (12), 146 (14), 118 (10), 91 (100); HRMS calcd for $C_{18}H_{19}N_2O_2{}^{81}Br$ 374.0630, obsd 374.0665.

1-Benzyl-5-{[(6-bromopyridin-2-yl)oxy]methylpiperidin-2-one 9

IR (neat) : 3050 (w), 2929 (w), 1635 (s), 1585 (s), 1437 (s), 1292 (m); ^{1}H NMR (400 MHz, $CDCl_3$) : 1.66 (m, 1 H), 2.02 (m, 1 H), 2.35 (m, 1 H), 2.49 (m, 1 H), 2.62 (d d d, *J* = 17.6, 5.9, 3.5, 1 H), 3.12 (d d, *J* = 11.7, 10.3, 1 H), 3.36 (d d d, *J* = 11.7, 5.9, 1.5, 1 H), 4.15 (d d, *J* = 10.7, 7.3, 1 H), 4.21 (d d, *J* = 10.7, 7.3, 1 H), 4.62 (q, *J* = 14.6, 2 H), 6.62 (d, *J* = 7.8, 1 H), 7.05 (d, *J* = 7.3, 1 H), 7.29 (m, 5 H), 7.40 (dd, *J* = 7.8, 7.3, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) : 24.2 (CH_2), 31.2 (CH_2), 33.8 (CH), 49.7 (CH_2), 50.3 (CH_2), 67.9 (CH_2), 109.4 (CH), 120.6 (CH), 127.4 (CH), 128.1 (2xCH), 128.6 (2xCH), 137.0 (C), 138.5 (C), 140.5 (CH), 163.0 (C), 169.5 (C); MS (m/z): 375 (M^+, 10), 281 (10), 201 (70), 186 (10), 173 (40), 158 (10), 146 (15), 132 (8), 118 (12), 110 (16), 91 (100); HRMS calcd for $C_{18}H_{19}N_2O_2{}^{81}Br$ 376.0609, obsd 376.0620.

11-Benzyl-7, 11-diazatricyclo[7.3.1.]trideca-2,4-diene-6,12-dione 11

Colourless oil.

IR (neat) : 2922 (m), 2853 (w), 1655 (s), 1575 (w), 1543 (s), 1260 (w). ^{1}H NMR (400 MHz, $CDCl_3$) : 2.12 (d, *J* = 13.1, 1 H), 2.23 (d, *J* = 13.1, 1 H), 2.78 (s, 1 H), 3.19 (d, *J* = 12.8, 1 H), 3.52 (d d, *J* = 12.8, 5.8, 1 H), 3.74 (s, 1 H), 3.95 (d d, *J* = 15.7, 6.6, 1 H), 4.05 (d, *J* = 15.7, 1 H), 4.42 (d, *J* = 14.6, 1 H), 4.63 (d, *J* = 14.6, 1 H), 6.33 (d, *J* = 6.6, 1 H), 6.49 (d, *J* = 9.1, 1 H), 7.08 (d, *J* = 7.3, 2 H), 7.27 (m, 3 H), 7.31 (d d, *J* = 9.1, 6.6, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) : 23.2 (CH_2), 25.8 (CH), 43.3 (CH), 49.7 (CH_2), 50.1 (CH_2), 53.0 (CH_2), 106.5 (CH), 118.4 (CH), 127.8 (CH), 127.9 (2xCH), 128.9 (2xCH), 136.2 (C), 139.2 (CH), 144.0 (C), 163.4 (C), 167.4 (C);

MS (m/z): 294 (M^+, 62), 203 (32), 160 (6), 146 (25), 118 (12), 91 (100); HRMS calcd for $C_{18}H_{18}N_2O_2$ 294.1368, obsd 294.1367.

N-Benzyl cytisine

Colourless solid.

IR (neat) : 2934 (w), 2792 (w), 1647 (s), 1567 (m), 1544 (s), 1452 (w), 1138 (m); ^{1}H NMR (400 MHz, MeOD) 1.93 (q, *J* = 13, 2 H), 2.38 (t, *J* = 11, 1 H), 2.45 (bs, 2 H), 2.83 (d, *J* = 10, 1 H), 2.93 (d, *J* = 10, 1 H), 3.42 (q, *J* = 13, 2 H), 3.87 (d d, *J* = 15, 6.9, 1 H), 4.04 (d, *J* = 15, 2 H), 6.20 (d, *J* = 7.3, 1 H), 6.46 (d, *J* = 8.7, 1 H), 6.97 (m, 2 H), 7.14 (m, 3 H), 7.46 (d d, *J* = 8.7, 7.3, 1 H); ^{13}C NMR (67 MHz, MeOD) : 26.0 (CH_2), 28.2 (CH), 35.6 (CH), 50.0 (CH_2), 60.0 (CH_2), 60.1 (CH_2), 62.1 (CH_2), 104.7 (CH), 116.6 (CH), 126.9 (2xCH), 128.2 (2xCH), 133.2 (C), 138.1 (CH), 138.6 (CH), 151.0 (C), 161.9 (C); MS (m/z): 280 (M^+, 45), 187 (14), 172 (6), 160 (10), 146 (28), 134 (66), 91 (92), 84 (100); HRMS calcd for $C_{18}H_{20}N_2O$ 280.1575, obsd 280.1572.

(±)-Cytisine HCl salt 1.HCl

A pale yellow solid, which was directly compared (TLC, IR, and ^{1}H and ^{13}C NMR to an authentic (commercially available) sample of (-)-cytisine hydrochloride. Data for cytisine.HCl: ^{1}H NMR (270 MHz, MeOD) : 2.20 (bs, 2 H), 2.84 (bs, 1 H), 3.58 (m, 5 H), 4.30 (m, 2 H), 6.84 (m, 2 H), 7.86 (m, 1 H).