Supporting information

Concise total synthesis of (±)-Maritidine

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(2-iodo-4,5-dimethoxy-benzyl)-[2-(4-methoxycyclohexa-1,4-dienyl)-ethyl]-amine **6**

A stirred solution of **4** (1.42 g; 4.88 mmol) and amine **5** (726.5 mg; 4.75 mmol) in dry MeOH (70 mL) was refluxed for 1 hr. The solution was cooled at room temperature, then NaBH₄ (369 mg; 9.75 mmol) was added and the pH was adjusted to 4-5 using acetic acid. The reaction mixture was stirred at room temperature for 30 min. The solvent was removed *in vacuo*. The residue was diluted with EtOAc and washed with aqueous saturated Na₂CO₃. The combined organic layers were washed with water, brine, dried (Na₂SO₄) and evaporated. Flash chromatography (elution with CH₂Cl₂/MeOH 99/1 (+ NH₃), 98/2 (+ NH₃)) of the residue afforded **6** (1.63 g; 78%) as a yellow oil.

H.R.M.S. (FAB, m/z) calcd for C₁₈H₂₅O₃NI (MH⁺) 430.0879, found : 430.0874.

I.R. (CHCl₃) ν (cm⁻¹) : 3021, 2933, 1696 (C=C), 1664 (C=C), 1598, 1502, 1257, 798, 723.

M. S. (FAB, m/z) : 430 (MH), 428 (M-H), 277.

¹H RMN (CDCl₃, 300 MHz) δ (ppm) : 7.21 (1H, s, H_{3''}), 6.93 (1H, s, H_{6''}), 5.46 (1H, s, H_{2'}), 4.60 (1H, s, H_{5'}), 3.86 (3H, s, OMe), 3.84 (3H, s, OMe), 3.74 (2H, s, H_{bz}), 3.54 (3H, s, OMe), 2.72 (6H, m, H_{6'}, H₂, H_{3'}), 2.24 (2H, t, J=6.6 Hz, H₃).

¹³C RMN (CDCl₃, 75 MHz) δ (ppm) : 153.0 (C_{4'}), 149.4 (C_{5''}), 148.6 (C_{4''}), 134.8 (C_{1''}), 133.1 (C_{1'}), 121.7 (C_{3''}), 119.4 (C_{2'}), 112.8 (C_{6''}), 90.4 (C_{5'}), 87.4 (C_{2''}), 57.9 (C_{Bz}), 56.3 (OMe), 56.0 (OMe), 54.0 (OMe), 46.7 (C₂), 37.0 (C₃), 29.3 (C_{6'}, C_{3'}).

[2-(1,4-dioxo-spiro[4.5]dec-7-en-8-yl)-ethyl]-(2-iodo-4,5-dimethoxy-benzyl)-amine **7**

To a solution of **6** (287.9 mg; 0.67 mmol) in THF (15 mL) were successively added at 0°C ethylene glycol (15 µl; 1.34 mmol) and BF₃.OEt₂ (85 µl; 0.67 mmol). After being stirred 1.5 hr at room temperature, the reaction mixture was quenched with aqueous saturated NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were washed with water, brine, dried (Na₂SO₄), filtered and evaporated. Flash chromatography (elution with CH₂Cl₂/MeOH 99.5/0.5 (+NH₃), 99/1 (+NH₃)) of the residue afforded **7** (257.5 mg; 84%) as a pale yellow oil.

H.R.M.S. (I.C., m/z) calcd for C₁₉H₂₇O₄NI (MH⁺) 460.09849; found : 460.0988.

I.R. (CHCl₃) ν (cm⁻¹) : 3020, 2927, 2854, 1600 (C=C), 1501, 1256, 795, 736.

M. S. (I.E., m/z) : 459 (M⁺·), 277, 151.

¹H RMN (CDCl₃, 300 MHz) δ (ppm) : 7.20 (1H, s, H_{3''}), 6.95 (1H, s, H_{6''}), 5.40 (1H, s, H_{7'}), 3.96 (4H, s, H_{2'}, H_{3'}), 3.88 (3H, s, OMe), 3.85 (3H, s, OMe), 3.75 (2H, s, H_{Bz}), 2.73 (2H, t, J = 6.6 Hz, H₂), 2.26-2.22 (4H, m, H_{6'}, H₃), 2.17 (2H, t, J = 6.6 Hz, H_{9'}), 1.75 (2H, t, J = 6.6 Hz, H_{10'}), 1.25 (1H, m, H₁).

¹³C RMN (CDCl₃, 75 MHz) δ (ppm) : 149.5 (C_{5''}), 148.7 (C_{4''}), 135.2 (C_{8'}), 134.9 (C_{1''}), 121.8 (C_{3''}), 120.2 (C_{7'}), 112.9 (C_{6''}), 108.1 (C_{5'}), 87.4 (C_{2''}), 64.5 (C_{2'}, C_{3'}), 58.0 (C_{Bz}), 56.3 (OMe), 56.1 (OMe), 46.9 (C₂), 37.4 (C₃), 35.8 (C_{6'}), 31.3 (C_{10'}), 27.5 (C_{9'}).

[2-(1,4-dioxa-spiro[4.5]dec-7-en-8-yl)-ethyl]-(2-iodo-4,5-dimethoxybenzyl)-carbamic acid tert-butylester **8**

To a solution of **7** (350 mg; 0.76 mmol) in a 1/1 mixture of tBuOH/H₂O (50 mL) were added Boc₂O (200 mg; 0.92 mmol) and 1N aqueous NaOH (0.8 mL; 0.8 mmol). After being stirred at room temperature for 4.5 hrs, the solvents were evaporated. The residue was extracted with AcOEt. The combined organic layers were washed with water, brine, dried (MgSO₄) and evaporated. The residue was purified by flash chromatography (elution with Heptane/AcOEt 90/10, 80/20) to give **8** (397 mg; 93%) as a pale yellow oil.

H.R.M.S. (E.S.I., m/z) calcd for C₂₄H₃₄O₆NINa (MNa⁺) 582.1329; found : 582.1326.

I.R. (CHCl₃) ν (cm⁻¹) : 3013, 2962, 2933, 1683 (C=O), 1599 (C=C), 1503, 1494, 1254, 1157.

M. S. (E.S.I. ; m/z) : 582 (MNa⁺), 560 (MH⁺), 504 (MH⁺- C₄H₉), 460 (MH⁺- Boc).

¹H RMN (CDCl₃, 300 MHz) δ (ppm) : 7.18 (1H, s, H_{3''}), 6.82 and 6.70 (1H, s, H_{6''}), 5.32 (1H, s, H_{7'}), 4.41 and 4.32 (2H, s, H_{BZ}), 3.94 (4H, s, dioxolane), 3.83 (3H, s, OMe), 3.79 (3H, s, OMe), 3.29 and 3.17 (2H, m, H_{1'}), 2.22-2.16 (6H, m, H_{6'}, H_{2'}, H_{3'}), 1.73 (2H, m, H_{4'}), 1.49 and 1.42 (9H, s, Boc).

¹³C RMN (CDCl₃, 75 MHz) δ (ppm) : 155.0 and 154.3 (C=O), 148.7 (C_{5''}), 147.7 (C_{4''}), 133.5 (C_{8'}), 132.1 (C_{1''}), 120.4 (C_{3''}), 119.6 and 119.4 (C_{7'}), 110.3 and 109.4 (C_{6''}),

106.9 (C_{5'}), 85.5 and 84.8 (C_{2''}), 78.8 (Boc), 63.4 (dioxolane), 55.2 (OMe), 54.8 (OMe), 54.0 and 53.2 (C_{BZ}), 45.0 and 44.5 (C_{1'}), 34.7 (C_{6'}), 35.0 and 34.4 (C_{2'}), 30.2 (C_{4'}), 27.4 (Boc), 26.5 (C_{3'}).

tert-Butyl-7,8-dimethoxy-(1,4-dioxaspiro[4.5])-2, 3, 4, 5-tetrahydro-1H-[2]-benzazepine-5-spiro-8-cyclohexa-6-ene-2-carboxylate **9**

9

A mixture of Pd₂(dba)₃ (309.8 mg; 0.034 mmol) and dppe (269.6 mg; 0.68 mmol) in CH₃CN (30 mL) was stirred at room temperature. Then TIOAc (1.1 g; 4.06 mmol) and **6** (1.9 mg; 3.38 mmol) in CH₃CN (75 mL) were added. After being stirred at 90°C for 72 hrs, the reaction mixture was filtered through celite (elution with AcOEt) and evaporated. Flash chromatography of the residue (elution with Heptane/AcOEt 90/10, 80/20, 70/30) afforded **9** (859.5 mg; 59 %) as a pale yellow oil.

H.R.M.S. (E.S.I., m/z) calcd for C₂₄H₃₃O₆NNa (MNa⁺) 454.2206 : found : 454.2198.

I.R. (CHCl₃) ν (cm⁻¹) : 3009, 2959, 2933, 1683 (C=O), 1605 (C=C), 1516, 1256, 1168, 750, 734.

M. S. (E.S.I. ; m/z) : 454 (MNa⁺), 432 (MH⁺), 376 (MH⁺-tBu), 332 (MH⁺-Boc).

¹H RMN (CDCl₃, 300 MHz) δ (ppm) : 6.87 (1H, s, H₆), 6.74 and 6.63 (1H, s, H₉), 5.82 (2H, d, J = 10.1 Hz, H_{7'}), 5.71 (2H, d, J = 10.1 Hz, H_{6'}), 4.43 and 4.40 (2H, s, H₁), 3.99 (4H, m, H_{2'}, H_{3'}), 3.85 (3H, s, OMe), 3.82 (3H, s, OMe), 3.69 (2H, m, H₃), 2.11-1.97 (3H, m, H_{9'}, H₄), 1.82-1.77 (3H, m, H_{10'}, H₄), 1.42 and 1.35 (9H, s, Boc).

¹³C RMN (CDCl₃, 75 MHz) δ (ppm) : 154.0 and 153.7 (C=O), 146.1 (C₇), 145.4 (C₈), 140.1 (C_{7'}), 135.5 and 135.2 (C_{5a}), 129.4 and 129.1 (C_{9a}), 124.8 and 124.7 (C_{6'}),

113.1 (C₆), 112.6 (C₉), 104.3 (C_{5'}), 78.5 (Boc), 63.6 and 63.5 (C_{2'}, C_{3'}), 54.9 (OMe), 54.8 (OMe), 49.9 and 48.8 (C₁), 42.7 (C₅), 42.5 (C₃), 36.9 and 36.6 (C₄), 30.6 and 30.4 (C_{9'}), 28.8 (C_{10'}), 27.5 and 27.4 (Boc).

tert-Butyl-7,8-dimethoxy-4'-oxo-2,3,4,5-tetrahydro-1H-[2]-benzazepine-5-spiro-1'-cyclohexa-2'-ene-2-carboxylate **10**

10

To a solution of **9** (221.9 mg; 0.52 mmol) in THF (20 mL) was added aqueous HCl (1N, 10 mL). After being stirred at room temperature for 18 hrs, the reaction mixture was extracted with AcOEt. The combined organic layers were washed with water, brine, dried (MgSO₄) and evaporated. **10** (165.8 mg; 83 %) was isolated as a pale yellow oil.

H.R.M.S. (E.S.I., m/z) calcd for C₂₂H₂₉O₅NNa (MNa⁺) 410.1943 ; found : 410.1940.

I.R. (CHCl₃) ν (cm⁻¹) : 3024, 2928, 2856, 1681 (C=O), 1606 (C=C), 1464, 1258, 1165, 803, 770.

M. S. (E.S.I. ; m/z): 410 (MNa⁺), 388 (MH⁺), 332 (MH⁺-tBu), 288 (MH⁺-Boc).

¹H RMN (CDCl₃, 300 MHz) δ (ppm) : 6.82 (1H, d, J= 10.2 Hz, H_{2'}), 6.76 and 6.65 (1H, s, H₆), 6.68 (1H, s, H₉), 6.09 (1H, d, J= 10.2 Hz, H_{3'}), 4.53 and 4.44 (2H, s, H₁), 3.85 (3H, s, OMe), 3.78 (3H, s, OMe), 3.74 (2H; m, H₃), 2.47 -2.14 (5H, m, H₄, H_{5'}, H_{6'}), 1.94 and 1.89 (1H, m, H₄), 1.42 and 1.35 (9H, s, Boc).

¹³C RMN (CDCl₃, 75 MHz) δ (ppm) : 198.3 (C=O), 156.8 (C_{2'}), 154.0 and 153.6 (C=O, Boc), 146.5 (C₇), 146.3 and 145.9 (C₈), 133.6 and 133.0 (C_{5a}), 129.9 and 129.6 (C_{9a}), 126.3 (C_{3'}), 112.7 (C₉), 112.3 (C₆), 79.0 (Cq, Boc), 55.0 (OMe), 54.9 (OMe), 49.4

and 48.4 (C₁), 43.5 and 43.3 (C₅), 35.2 and 34.8 (C₄), 33.2 (C_{5'}), 32.4 and 32.1 (C_{6'}), 27.5 and 27.4 (Boc).

tert-Butyl 7,8-dimethoxy- 4'-oxo-2,3,4,5-tetrahydro-1H-[2]-benzazepine 5 spiro-1'-cyclohexa-2',5'-diene-2-carboxylate **11**

A mixture of α,β -unsaturated ketone **10** (862 mg; 2.23 mmol), selenium dioxide (989 mg; 8.9 mmol), acetic acid (4 mL) in tBuOH (140 mL) was heated at reflux for 48 hrs. The reaction mixture was filtered through celite (elution with AcOEt) and extracted with AcOEt. The combined organic layers were washed with water, brine, dried (MgSO₄) and evaporated. Flash chromatography of the residue (elution with Heptane/AcOEt 80/20, 70/30) yielded **11** (623 mg; 73 %) as a pale yellow oil.

H.R.M.S. (E.S.I., m/z) calcd for C₂₂H₂₇O₅NNa (MNa⁺) 408.1787; found : 408.1787.

I.R. (CHCl₃) ν (cm⁻¹) : 3010, 2934, 1686 (C=O), 1666 (C=O), 1622 (C=C), 1606(C=C), 1519, 1414, 1256, 1166, 716.

M. S. (E.S.I. ; m/z): 408 (MNa⁺), 386 (MH⁺), 330 (MH⁺- tBu), 286 (MH⁺-Boc).

¹H RMN (CDCl₃, 300 MHz) δ (ppm) : 6.99 (2H, d, J = 10.2 Hz, H_{2'}, H_{6'}), 6.73 and 6.62 (1H, s, H₉), 6.50 (1H, s, H₆), 6.28 (2H, d, J= 10.2 Hz, H_{3'}, H_{5'}), 4.60 and 4.49 (2H, s, H₁), 3.86 (3H, s, OMe), 3.76 (2H, m, H₃), 3.72 (3H, s, OMe), 2.26 (2H, m, H₄), 1.46 and 1.35 (9H, s, Boc).

¹³C RMN (CDCl₃, 75 MHz) δ (ppm) : 185.8 (C_{4'}), 155.1 and 154.7 (C=O, Boc), 154.0 (C_{2'}, C_{6'}), 147.9, 147.5 (C₇, C₈), 131.6 and 131.2 (C_{9a}), 127.9 and 127.8 (C_{5a}),

126.8 (C_{3'}, C_{5'}), 113.2 and 112.9 (C₉), 112.7 (C₆), 80.3 and 80.1 (C_q, Boc), 55.9 (OMe, OMe), 48.8 (C₅), 48.6 and 47.7 (C₁), 44.5 and 43.7 (C₃), 35.9 and 35.7 (C₄), 28.5 and 28.3 (Boc).

(±)-Oxomaritidine **2**

To a solution of **11** (386.8 mg; 1.00 mmol) in CH₂Cl₂ (28 mL) was added trifluoroacetic acid (12 mL). After 30 min at room temperature, the mixture was basified with solid NaOH and dissolved in water (pH 10). After 1h, the solution was extracted with CH₂Cl₂. The combined organic layers were washed with water, brine, dried (MgSO₄) and evaporated. Flash chromatography (elution with CH₂Cl₂/MeOH 95/5) yielded oxomaritidine **2** (193.4 mg; 68 %) as white powder.

H.R.M.S. (F.A.B., m/z) calcd for C₁₇H₂₀O₃N (MH⁺) 286.14432; found : 286.14400.

I.R. (CHCl₃) ν (cm⁻¹) : 2960, 2932, 1680 (C=O), 1607 (C=C), 1514, 1260, 1133, 1038.

M.S. (ESI. ; m/z) : 308 (MNa⁺), 286 (MH⁺).

¹H RMN (CDCl₃, 300 MHz) δ (ppm) : 7.67 (1H, d, J = 10 Hz, H₁), 6.89 (1H, s, H₁₀), 6.54 (1H, s, H₇), 6.07 (1H, dd, J = 10, 1 Hz, H₂), 4.39 (1H, d, J = 16 Hz, H₆), 3.89 (3H, s, OMe), 3.82 (3H, s, OMe), 3.78 (1H, d, J = 16 Hz, H₆), 3.65 (1H, dd, J = 13, 5.5 Hz, H_{4a}), 3.54 (1H, ddd, J = 13, 10.5, 3.5 Hz, H₁₂), 3.01 (1H, ddd, J = 13, 9, 6.5 Hz, H₁₂), 2.68 (1H, ddd, J = 17.1, 5.5, 1.1 Hz, H₄), 2.46 (1H, dd, J = 17, 13.1 Hz, H₄), 2.39 (1H, ddd, J = 12.5, 9.1, 3.5 Hz, H₁₁), 2.17 (1H, ddd, J = 12.5, 10.5, 6.5 Hz, H₁₁)

¹³C RMN (CDCl₃, 75 MHz) δ (ppm) : 198.2 (C₃), 149.6 (C₁), 148.0 (C₈), 147.7 (C₉), 134.8 (C_{10a}), 128.8 (C₂), 125.2 (C_{6a}), 110.2 (C₇), 105.5 (C₁₀), 69.0 (C_{4a}), 61.6 (C₆), 56.2 (OMe), 55.9 (OMe), 54.2 (C₁₂), 44.9 (C₁₁), 44.4 (C_{10b}), 40.2 (C₄).

(±)-Epi-Maritidine **12**

To a solution of **2** (14.1 mg; 0.052 mmol) in dry MeOH (1.5 mL) was added NaBH₄ (3.9 mg; 0.104 mmol) and CeCl₃·7H₂O (38.7 mg; 0.104 mmol). After 45 min at room temperature, the reaction mixture was filtered through celite (elution with MeOH) and evaporated. The residue was extracted with CHCl₃. The combined organic layers were washed with aqueous saturated NaHCO₃, dried (MgSO₄) and evaporated. **12** (13.2 mg; 93%) was isolated as a white powder.

H.R.M.S. (F.A.B., m/z) calcd for C₁₇H₂₂O₃N (MH⁺) 288.115997; found : 288.15960.

I.R. (CHCl₃) ν (cm⁻¹) : 2961, 2934, 1507, 1464, 1261, 1231, 1099, 1024.

M.S. (ESI. ; m/z) : 288 (MH⁺).

¹H RMN (CDCl₃, 300 MHz) δ (ppm) : 6.81 (1H, s, H₁₀), 6.52 (1H, s, H₇), 6.50 (1H, dd, J=10.2, 2.1 Hz, H₁), 5.80 (1H, d, J = 10.2 Hz, H₂), 4.44 (1H, d, J = 16.8 Hz, H₆), 4.46 (1H, m, H₃), 3.88 (3H, s, OMe), 3.82 (3H, s, OMe), 3.81 (1H, d, J = 16.8 Hz, H₆), 3.45 (1H, ddd, J = 14.3, 10.5, 4.6 Hz, H₁₂), 3.27 (1H, dd, J = 13.2, 3.2, H_{4a}), 2.94 (1H, ddd, J = 14.3, 8.9, 5.8 Hz, H₁₂), 2.26-2.05 (3H, m, H₄, H₁₁, H₁₁), 1.63 (1H, ddd, J=12, 12, 12 Hz, H₄)

^{13}C RMN (CDCl_3 , 75 MHz) δ (ppm) : 147.4 (C_8 , C_9), 137.5 ($\text{C}_{10\text{a}}$), 131.5 (C_2), 128.9 (C_1), 124.7 ($\text{C}_{6\text{a}}$), 107.9 (C_7), 105.6 (C_{10}), 67.7 (C_3), 66.8 ($\text{C}_{4\text{a}}$), 61.9 (C_6), 56.1 (OMe), 55.9 (OMe), 53.3 (C_{12}), 45.1 (C_{11}), 44.1 ($\text{C}_{10\text{b}}$), 35.0 (C_4).

($\pm$)-Maritidine **1**

To a solution of **12** (39.0 mg; 0.13 mmol) in dry CH_2Cl_2 (3 mL) was added at room temperature MsCl (53 μl ; 0.68 mmol) and Et_3N (95 μl ; 0.68 mmol). After 1 h at room temperature, the solvent was removed *in vacuo*, the residue was dissolved in DMF (3 ml) and transferred via syringe to a flask containing CsOAc (391.3 mg; 2.04 mmol). The resulting suspension was stirred at room temperature for 40 hrs. The reaction mixture was filtered (elution with EtOAc). The combined filtrates were dissolved in 1 N HCl , and the aqueous solution was washed with Et_2O . The aqueous phase was basified with aqueous saturated K_2CO_3 (pH 12) and then extracted with CH_2Cl_2 . The combined organic layers were washed with water, brine, dried (MgSO_4) and evaporated. The crude allylic acetate was immediately dissolved in dry MeOH containing powdered K_2CO_3 (169.0 mg). After being stirred at room temperature for 2 hrs, the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with saturated NaHCO_3 . The combined organic layers were washed with water, brine, dried (MgSO_4) and evaporated. Preparative thin-layer chromatography (elution with $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{Et}_3\text{N}$: 9/1/1) yielded **1** (20.4 mg; 52%) as a white powder.

H.R.M.S. (F.A.B., m/z) calcd for $C_{17}H_{22}O_3N$ (MH^+) 288.15997; found : 288.16003.

I.R. ($CHCl_3$) ν (cm^{-1}) : 1961, 2935, 1609, 1508, 1465, 1315, 1261, 11232, 1096, 1042, 1028.

M.S. (ESI. ; m/z) : 288 (MH^+).

1H RMN ($CDCl_3$, 300 MHz) δ (ppm) : 6.85 (1H, s, H_{10}), 6.65 (1H, d, $J = 10$ Hz, H_1), 6.51 (1H, s, H_7), 5.99 (1H, dd, $J = 10, 5$ Hz, H_2), 4.45 (1H, d, $J = 16.6$ Hz, H_6), 4.37 (1H, m, H_3), 3.88 (3H, s, OMe), 3.82 (3H, s, OMe), 3.83 (1H, d, $J = 16.6$ Hz, H_6), 3.5-3.38 (2H, m, H_{4a} , H_{12}), 2.92 (1H, ddd, $J = 15.1, 8.9, 6.1$ Hz, H_{12}), 2.21 (1H, ddd, $J = 16.2, 8.9, 3.95$ Hz, H_{11}), 2.06 (1H, ddd, $J = 13.9, 3.95, 2.8$ Hz, H_4), 1.95 (1H, ddd, $J = 18.1, 11.5, 6.1$ Hz, H_{11}), 1.76 (1H, ddd, $J = 17.7, 13.9, 4.15$ Hz, H_4).

^{13}C RMN ($CDCl_3$, 75 MHz) δ (ppm) : 147.6, 147.4 (C_8 , C_9), 136.9 (C_{10a}), 131.9 (C_1), 127.7 (C_2), 124.6 (C_{6a}), 109.9 (C_7), 105.8 (C_{10}), 63.9 (C_3), 63.0 (C_{4a}), 61.7 (C_6), 56.1 (OMe), 55.9 (OMe), 53.4 (C_{12}), 44.0 (C_{10b}), 43.9 (C_{11}), 32.5 (C_4).