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## Supporting Data

**3 $\alpha$ -(4-Fluorophenyl)-2 $\beta$ -(3'-methyl-1',2',4'-oxadiazol-5'-yl)tropane (5a):** A 250 mL r.b. flask was equipped with a stirbar, thermometer with adapter and an addition funnel with nitrogen inlet. The assembly was flame-dried and allowed to cool under nitrogen. The flask was charged with a solution of bromofluorobenzene (4.2 g, 24 mmol) in 45 mL of dry THF and cooled to -78 °C in an dry ice/acetone bath. t-Butyllithium (1.7M in pentane, 48 mmol, 28.3 mL) was added dropwise, maintaining the temperature below -55 °C. After 20 min at -78 °C, a solution of anhydroecgonine oxadiazole (**4**, 2.1 g, 10 mmol) in 10 mL of anhydrous THF was added dropwise. The reaction was stirred at -78 °C for 2 h, then quenched at -78 °C by dropwise addition of a 20% solution of trifluoroacetic acid in ethyl ether (5 mL). The reaction was allowed to warm to room temperature and concentrated. The residual oil was purified by flash column chromatography (3:1 ethyl acetate/petroleum ether + 5% saturated ammonia in methanol) to give compound **5a** as a colorless oil which solidified on standing. Yield: 2.55 g (85%); mp 71-72 °C; [ $\alpha$ ]<sub>D</sub> = -78.4° (c 0.32, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.12 (m, 2 H), 6.91 (m, 2 H), 3.32-3.48 (m, 3 H), 3.65 (m, 1 H), 3.01 (dd, 1 H), 2.51 (m, 1 H), 2.32 (s, 3 H), 2.26 (s, 3 H), 2.14-2.28 (m, 1 H), 1.54-1.70 (m, 2 H), 1.37 (m, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  181.77, 166.98, 161.46 (d), 138.60, 129.16, 129.04, 115.43, 115.09, 64.26, 59.36, 50.00, 41.05, 39.61, 37.54, 29.11, 11.60; Analysis calculated for C<sub>17</sub>H<sub>20</sub>N<sub>3</sub>OF: C, 67.74; H, 6.70; N, 13.94. Found: C, 67.76; H, 6.71; N, 13.86.

**3 $\alpha$ -(4-Fluorophenyl)tropane-2 $\beta$ -carboxylic acid methyl ester (2a):** A 250 mL r.b. flask equipped with a stirbar and a condenser was charged with nickel(II) acetate (5.3 g, 21.4 mmol) and methanol (50 mL). A solution of sodium borohydride (0.8 g, 21.4 mmol) in methanol (25 mL) was added dropwise (caution: reaction is vigorously exothermic). A black colloidal suspension formed immediately. A solution of **5a** (1.3 g, 4.3 mmol) in 50 mL of methanol and 1.8 mL of concentrated HCl was slowly added and the resulting mixture stirred for 2 h at room temperature then heated at reflux for 3 h. The reaction was allowed to cool to room temperature then ethyl ether (100 mL) and saturated bicarbonate were added. The pH of the solution was adjusted to 10-11 by careful addition of concentrated ammonium hydroxide. Following

extraction with ethyl ether (4 x 20 mL), the organic phase was washed with water (3 x 20 mL), dried over sodium sulfate, filtered and concentrated under vacuum. Compound **2a** was isolated as a colorless oil which was converted to the D-tartrate salt. Yield: 1.0 g (86%). mp 65 °C (dec);  $[\alpha]^{25}_{546} = -34.4^\circ$  (c 0.54, methanol);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.42 (m, 2 H), 7.07 (m, 2 H), 4.12 (m, 1 H), 3.93 (m, 1 H), 3.66 (s, 3 H), 3.40-3.23 (m, 2 H), 2.80 (s, 3 H), 2.68-2.55 (m, 1 H), 2.39 (m, 2 H), 2.16-1.98 (m, 3 H); Analysis calculated for  $\text{C}_{20}\text{H}_{26}\text{FNO}_8 \cdot 0.5 \text{H}_2\text{O}$ : C, 55.04; H, 6.24; N, 3.21. Found: C, 55.09; H, 6.28; N, 3.16.

**3 $\alpha$ -(4-Iodophenyl)-2 $\beta$ -(3'-methyl-1',2',4'-oxadiazol-5'-yl)tropane tosylate (5b):** A 1 L two-neck flask was equipped with a stirbar, thermometer with adapter and an addition funnel with nitrogen inlet. The assembly was flame-dried and allowed to cool under nitrogen. The flask was charged with a solution of 1,4-diiodobenzene (20.70 g, 63 mmol) in 350 mL of anhydrous THF and cooled to -65 °C in an dry ice/acetone bath. Diiodobenzene precipitated out of solution. t-Butyllithium (1.7M in pentane, 126 mmol, 74 mL) was added dropwise over 30 min, maintaining the temperature below -55 °C. The resulting dark green solution was cooled to -78 °C. The addition funnel was rinsed with 10 mL of anhydrous THF, then charged with a solution of anhydroecgonine oxadiazole (**4**, 6.15 g, 30.0 mmol) in 25 mL of anhydrous THF. This solution was added to the reaction dropwise, maintaining the temperature below -70 °C. The resulting brown solution was stirred at -78 °C for 2.5 h, then quenched at -78 °C by dropwise addition of a 20% solution of trifluoroacetic acid in ethyl ether (50 mL). The reaction was allowed to warm to room temperature, then successively washed with saturated sodium bicarbonate (25 mL) and 1N HCl (4 x 25 mL). The aqueous phase was washed with ethyl ether (1 x 50 mL) and the ethereal layers discarded. The aqueous layer was neutralized to pH 10 by addition of concentrated ammonium hydroxide then extracted with dichloromethane (4 x 50 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under vacuum. The residual oil was purified by flash column chromatography (3:1 ethyl acetate/petroleum ether + 5% saturated ammonia in methanol) to give **5b** as a colorless oil which solidified on standing. Also recovered from the crude product was 2.06 g (20%) of the 2 $\alpha$ , 3 $\beta$ -isomer. Compound **5b**

was converted to the tosylate salt for characterization. Yield: 2.61 g (23%); mp 208.2-109.8 °C;  $[\alpha]_D^{25} = -60.52^\circ$  (c 0.760, methanol);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  11.18 (br s, 1 H), 7.76 (d, 2 H,  $J = 8.2$  Hz), 7.59 (d, 2 H,  $J = 8.4$  Hz), 7.17 (d, 2 H,  $J = 8.1$  Hz), 6.91 (d, 2 H,  $J = 8.5$  Hz), 4.28 (d, 1 H,  $J = 6.6$  Hz), 4.18 (t, 1 H,  $J = 6.2$  Hz), 3.87-3.79 (m, 1 H), 3.53 (d, 1 H,  $J = 8.0$  Hz), 3.12-3.01 (m, 1 H), 2.94 (s, 3 H), 2.58-2.50 (m, 1 H), 2.37 (s, 3 H), 2.30 (s, 3 H), 2.26-2.14 (m, 1 H), 2.12-2.00 (m, 1 H), 1.91-1.81 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  177.36, 167.16, 142.51, 139.87, 139.80, 137.71, 129.25, 128.71, 125.86, 92.78, 64.00, 61.59, 46.29, 39.68, 35.83, 34.81, 27.02, 26.32, 21.29, 11.42; Analysis calculated for  $\text{C}_{24}\text{H}_{28}\text{IN}_3\text{O}_4\text{S}$ : C, 49.57; H, 4.85; N, 7.23. Found: C, 49.50; H, 4.84; N, 7.13.

**3 $\alpha$ -(4-Iodophenyl)tropane-2 $\beta$ -carboxylic acid methyl ester tosylate (2b):** A 250 mL r.b. flask equipped with a stirbar and a condenser was charged with nickel(II) acetate (9.0 g, 36.0 mmol) and methanol (50 mL). A solution of sodium borohydride (1.4 g, 36.0 mmol) in methanol (15 mL) was added dropwise (caution: reaction is vigorously exothermic). A black colloidal suspension formed immediately. A solution of **5b** (4.9 g, 12.0 mmol) in 25 mL of methanol and 3.0 mL of concentrated HCl was added and the resulting mixture heated at reflux for 4 h. The reaction was allowed to cool to room temperature then filtered through celite. The pale green filtrate was concentrated to approximately 15 mL and diluted with water (50 mL). The pH of the solution was adjusted to 10-11 by careful addition of concentrated ammonium hydroxide. Following extraction with ethyl ether (4 x 20 mL), the organic phase was washed with water (3 x 20 mL), dried over sodium sulfate, filtered and concentrated under vacuum. The residual oil was purified by flash column chromatography (5:3 petroleum ether/ethyl acetate + 2% methanolic ammonia) gave pure **2b** as a colorless oil. Yield: 2.1 g (45%). This material was converted to the tosylate salt for characterization. mp 204.6°-205.3 °C;  $[\alpha]_D^{25} = -38.91^\circ$  (c 1.30, methanol);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.74-7.65 (m, 4 H), 7.27-7.15 (m, 4 H), 4.15 (d, 1 H,  $J = 6.8$  Hz), 3.76 (t, 1 H,  $J = 6.4$  Hz), 3.68 (s, 3 H), 3.38-3.25 (m, 2 H), 2.82 (s, 3 H), 2.62-2.47 (m, 1 H), 2.43-2.20 (m, 6 H), 2.06-1.92 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  174.70, 142.43, 142.36, 141.75, 138.99, 130.44, 129.89, 127.0, 91.24, 64.87, 63.43, 53.25, 52.83, 39.69, 35.53, 35.14, 26.01, 25.98, 21.36;

Analysis calculated for  $C_{23}H_{28}INO_5S$ : C, 49.55; H, 5.03; N, 2.51. Found: C, 49.47, H, 5.05; N, 2.53.

**3 $\alpha$ -(4-Chlorophenyl)-2 $\beta$ -(3'-methyl-1',2',4'-oxadiazol-5'-yl)tropane tosylate (5c):** A 250 mL three-neck flask was equipped with a stirbar, septum, thermometer with adapter and an addition funnel with nitrogen inlet. The assembly was flame-dried and allowed to cool under nitrogen. The flask was charged with a solution of 1-chloro-4-iodobenzene (6.55 g, 27.5 mmol) in 50 mL of anhydrous ethyl ether and cooled to 0 °C. t-Butyllithium (1.7M in pentane, 55 mmol, 32.3 mL) was added dropwise over 15 min. The resulting yellow solution stirred for 20 min, then cooled to -78 °C in an dry ice/acetone bath. The addition funnel was rinsed with 5 mL of anhydrous ether, then charged with a solution of anhydroecgonine oxadiazole (**4**, 2.56 g, 12.5 mmol) in 20 mL of anhydrous ethyl ether. This solution was added to the reaction dropwise, maintaining the temperature below -70 °C. A mild exotherm was observed during the addition. The resulting brown solution was stirred at -78 °C for 2.5 h then quenched at -78 °C by dropwise addition of a 20% solution of trifluoroacetic acid in ethyl ether (25 mL). The reaction was allowed to warm to room temperature, then successively washed with saturated sodium bicarbonate (15 mL) and 1N HCl (2 x 25 mL). The aqueous phase was washed with ethyl ether (1 x 25 mL) and the ethereal layers discarded. The aqueous layer was neutralized to pH 10 by addition of concentrated ammonium hydroxide then extracted with dichloromethane (3 x 50 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under vacuum. The residual oil was purified by flash column chromatography (3:1 ethyl acetate/petroleum ether + 5% saturated ammonia in methanol) to give 3.20 g (81%) of **5c** as a colorless oil. This compound was converted to the tosylate salt for characterization: mp 174.9-178.2 °C;  $[\alpha]^{25}_{546} = -74.56^\circ$  (c 0.515, methanol);  $^1H$  NMR ( $CD_3OD$ )  $\delta$  7.70 (d, 2 H,  $J = 8.2$  Hz), 7.39 (d, 2 H,  $J = 8.7$  Hz), 7.34 (d, 2 H,  $J = 8.9$  Hz), 7.22 (d, 2 H,  $J = 8.0$  Hz), 4.31 (d, 1 H,  $J = 6.5$  Hz), 4.10-3.98 (m, 2 H), 3.45 (q, 1 H,  $J = 8.13$  Hz), 2.87 (s, 3 H), 2.72-2.54 (m, 2 H), 2.51-2.45 (m, 2 H), 2.36 (s, 3 H), 2.25 (s, 3 H), 2.23-2.05 (m, 2 H); Analysis calculated for  $C_{23}H_{28}ClN_3O_4S$ : C, 57.78; H, 5.90; N, 8.79. Found: C, 58.22, H, 5.76; N, 8.42.

**3 $\alpha$ -(4-Chlorophenyl)tropane-2 $\beta$ -carboxylic acid methyl ester tosylate (2c):** A 50 mL r.b. flask equipped with a stirbar and a condenser was charged with nickel(II) acetate (0.89 g, 3.6 mmol) and methanol (10 mL). A solution of sodium borohydride (0.14 g, 3.6 mmol) in methanol (3 mL) was added dropwise (caution: reaction is vigorously exothermic). A black colloidal suspension formed immediately. A solution of **5c** (0.57 g, 1.80 mmol) in 5 mL of methanol and 0.33 mL of concentrated HCl was added and the resulting mixture heated at reflux for 4 h. The reaction was allowed to cool to room temperature then filtered through celite. The celite was washed with methanol (50 mL) and the filtrate concentrated under vacuum. The residue was diluted with water (10 mL) and poured into ethyl ether (50 mL). The aqueous layer was basified to pH 10 by addition of concentrated ammonium hydroxide then washed with ethyl ether (3 x 25 mL). The combined organic layers were concentrated under vacuum and the residue dissolved in dichloromethane (25 mL). The remaining water was removed in a separatory funnel and the dichloromethane solution dried over sodium sulfate, filtered and concentrated under vacuum. The residual oil was purified by flash column chromatography (5:3 petroleum ether/ethyl acetate + 2% saturated methanolic ammonia) to give **2c** as a waxy solid. mp 115.8-116.9 °C. Yield: 0.29 g (54.0%) This compound was converted to the tosylate salt for characterization. mp 182.4-183.8 °C;  $[\alpha]_D^{25} = -39.91^\circ$  (c 0.451, methanol);  $^1\text{H NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  7.71 (d, 2 H,  $J = 8.3$  Hz), 7.40 (d, 2 H,  $J = 8.9$  Hz), 7.34 (d, 2 H,  $J = 9.0$  Hz), 7.22 (d, 2 H,  $J = 8.5$  Hz), 4.17 (d, 1 H,  $J = 6.7$  Hz), 3.94 (t, 1 H,  $J = 6.3$  Hz), 3.67 (s, 3 H), 3.34-3.29 (m, 2 H), 2.82 (s, 3 H), 2.68-2.57 (m, 1 H), 2.49-2.38 (m, 4 H), 2.30-2.18 (m, 2 H), 2.04-1.92 (m, 2 H);  $^{13}\text{C NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  174.66, 143.65, 141.78, 141.28, 133.99, 130.01, 129.91, 129.85, 127.01, 84.88, 83.39, 53.23, 53.08, 39.71, 35.44, 35.41, 26.36, 26.30, 21.36; Analysis calculated for  $\text{C}_{23}\text{H}_{28}\text{ClNO}_5\text{S}$ : C, 59.28; H, 6.06; N, 3.01. Found: C, 59.34, H, 6.03; N, 2.96.

**3 $\alpha$ -(4-Methylphenyl)-2 $\beta$ -(3'-methyl-1',2',4'-oxadiazol-5'-yl)tropane tosylate (5d):** A 100 mL two-neck flask was equipped with a stirbar, thermometer with adapter and an addition funnel with nitrogen inlet. The assembly was flame-dried and allowed to cool under nitrogen. The flask was charged with a solution of 4-bromotoluene (3.76 g, 22 mmol) in 20 mL of

anhydrous THF and cooled to 0 °C. *t*-Butyllithium (1.7M in pentane, 44 mmol, 26 mL) was added dropwise over 15 min. The resulting yellow solution stirred for 20 min, then cooled to -78 °C in an dry ice/acetone bath. The addition funnel was rinsed with 5 mL of anhydrous THF, then charged with a solution of anhydroecgonine oxadiazole (**4**, 2.05 g, 10.0 mmol) in 10 mL of anhydrous THF. This solution was added to the reaction dropwise, maintaining the temperature below -70 °C. A mild exotherm was observed during the addition. The resulting brown solution was stirred at -78 °C for 3.5 h, then quenched at -78 °C by dropwise addition of a 20% solution of trifluoroacetic acid in ethyl ether (25 mL). The reaction was allowed to warm to room temperature, then successively washed with saturated sodium bicarbonate (15 mL) and 1N HCl (2 x 25 mL). The aqueous phase was washed with ethyl ether (1 x 25 mL) and the ethereal layers discarded. The aqueous layer was neutralized to pH 10 by addition of concentrated ammonium hydroxide then extracted with dichloromethane (3 x 50 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under vacuum. The residual oil was purified by flash column chromatography (5:8 ethyl acetate/petroleum ether + 2% saturated ammonia in methanol) to give 1.97 g (66%) of **5d** as a white solid mp 105.6-107.4 °C. Also recovered from the crude product was 0.45 g (15%) of the 2 $\alpha$ , 3 $\beta$ -isomer. Compound **5d** was converted to the tosylate salt for characterization: mp 199.3-200.0 °C;  $[\alpha]^{25}_{546} = -53.50^\circ$  (c 0.415, methanol);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  10.5 (br s, 1 H), 7.74 (d, 2 H,  $J = 8.1$  Hz), 7.15 (d, 2 H,  $J = 7.9$  Hz), 7.10-6.99 (m, 4 H), 4.22 (d, 1 H,  $J = 6.6$  Hz), 4.19-4.11 (m, 1 H), 3.74 (t, 1 H,  $J = 7.3$  Hz), 3.64 (d, 1 H,  $J = 8.1$  Hz), 2.91 (s, 3 H), 2.61-2.42 (m, 1 H), 2.34 (s, 3 H), 2.29 (s, 3 H), 2.27-2.19 (m, 5 H), 2.10-1.84 (m, 3 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  177.62, 167.08, 142.62, 139.64, 136.85, 129.39, 128.60, 126.72, 125.81, 63.98, 62.12, 46.08, 39.62, 35.02, 34.52, 26.49, 25.75, 21.20, 20.81, 11.35; Analysis calculated for  $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_4\text{S}$ : C, 63.94; H, 6.65; N, 8.95.

**3 $\alpha$ -(4-Methylphenyl)tropane-2 $\beta$ -carboxylic acid methyl ester tosylate (2d):** A 100 mL r.b. flask equipped with a stirbar and a condenser was charged with nickel(II) acetate (2.66 g, 10.7 mmol) and methanol (20 mL). A solution of sodium borohydride (0.40 g, 10.7 mmol) in methanol (10 mL) was added dropwise (caution: reaction is vigorously exothermic). A black

colloidal suspension formed immediately. A solution of **5d** (0.80 g, 2.7 mmol) in 10 mL of methanol and 0.9 mL of concentrated HCl was added and the resulting mixture heated at reflux for 4 h. The reaction was allowed to cool to room temperature then filtered through celite. The celite was washed with methanol (50 mL) and the filtrate concentrated under vacuum. The residue was diluted with water (10 mL) and poured into ethyl ether (50 mL). The aqueous layer was basified to pH 10 by addition of concentrated ammonium hydroxide then washed with ethyl ether (3 x 25 mL). The combined organic layers were concentrated under vacuum and the residue dissolved in dichloromethane (25 mL). The remaining water was removed in a separatory funnel and the dichloromethane solution dried over sodium sulfate, filtered and concentrated under vacuum. Flash column chromatography (5:3 petroleum ether/ethyl acetate + 2% methanolic ammonia) gave **2d** as a waxy solid. mp 74.6-76.8 °C. Yield: 0.375 g (51%). This compound was characterized as the tosylate salt. mp 174.8-175.4 °C;  $[\alpha]_{546}^{25} = -43.14^{\circ}$  (c 0.554, methanol);  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.71 (d, 2 H,  $J = 8.2$  Hz), 7.27 (d, 2 H,  $J = 8.2$  Hz), 7.22 (d, 2 H,  $J = 8.0$  Hz), 7.15 (d, 2 H,  $J = 8.1$  Hz), 4.13 (d, 1 H,  $J = 6.9$  Hz), 3.92 (t, 1 H,  $J = 6.8$  Hz), 3.67 (s, 3 H), 3.38-3.32 (m, 2 H), 2.80 (s, 3 H), 2.59-2.51 (m, 1 H), 2.35 (s, 3 H), 2.25 (s, 3 H), 2.25-2.12 (m, 3 H), 2.01-1.92 (m, 2 H); Analysis calculated for  $\text{C}_{24}\text{H}_{31}\text{NO}_5\text{S}$ : C, 64.69; H, 7.01; N, 3.14. Found: C, 64.55, H, 7.04, N, 3.15.