Supplementary Information for:

Opioid ligands with mixed properties from substituted enantiomeric *N*-phenethyl-5-phenylmorphans. Synthesis of a μ-agonist δ–antagonist and δ-inverse agonists‡

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Experimental Section:

The following are the experimental details for compounds **3**, (±)-**6** (and the resolution to (+)- and (-)-**6**), **7**, **7a** through **7l**, (+)- and (-)-**8** and (+)- and (-)-**9**).

1-Benzyl-4-(3-methoxyphenyl)-1,2,3,6-tetrahydropyridine (3)

1.6M *n*-BuLi in hexanes (130 mL, 208 mmol) was added to a solution of 3-bromoanisole (37.0 g, 198 mmol) in THF (200 mL) at -60 °C and stirred for 2 h. A solution of 1-benzyl-4-piperidinone (37.4 g, 197 mmol) in THF (160 mL) was added to the mixture, which was slowly allowed to warm to room temperature over 2 h with stirring. After being cooled to 0 °C, the reaction was quenched by addition of H_2O (10 mL). After evaporation, 1N-HCl (400 mL) was added to the mixture, which was extracted with Et_2O (3 x 200 mL). The aqueous layer was basified with NH_4OH (pH ~ 10) and extracted with ethyl acetate : Et_2O (1 : 1.3 x 200 mL). The combined organic solution was washed with H_2O an brine, dried over Na_2SO_4, filtered, and concentrated to give the crude amino alcohol (58.5 g), which was used for the next step reaction without further purification. A mixture of crude amino alcohol (58.5 g, 197 mmol) and p-toluenesulfonic acid monohydrate (49.6 g, 261 mmol) in toluene (850 mL) was refluxed for 6 h with a Dean-Stark trap to remove H_2O formed in the reaction. After the removal of toluene, the mixture was diluted with ethyl acetate and basified with NH_4OH. The aqueous layer was extracted with ethyl acetate (3 x 200 mL), washed with H_2O and brine, dried over Na_2SO_4, and concentrated to dryness. Column chromatography of the crude material with 1.5% MeOH in CH_2Cl_2 gave 3 (51.4 g, 93% over 2 steps) as a colorless oil; ^{1}H NMR ($CDCl_3$): 7.39-7.19 (m, 6H), 6.99-6.92 (m, 2H), 6.77 (dd, 1H, J = 8 and 2 Hz), 6.06 (br-s, 1H), 3.79 (s, 3H), 3.63 (s, 2H), 3.16 (br-s, 2H), 2.72-2.68 (m, 2H), 2.54 (m, 2H); m/z: HRMS (ESI) calculated for $C_{19}H_{22}NO$ $(M+H)^+$: 280.1697. Found, 280.1695.

2-Benzyl-5-(3-methoxyphenyl)-2-aza-bicyclo[3.3.1]nonane ((±)-6)

1.3 M *sec*-BuLi in cyclohexane (176 mL, 229 mmol) was added dropwise to a solution of **3** (51.0 g, 183 mmol) in THF (1 L) at -50 °C and allowed to warm to -40 °C over 1 h. The temperature was again lowered to -50 °C, allyl bromide (15.8 mL, 187 mmol) was added and the mixture was allowed to slowly warm to 0 °C over 2 h. The reaction was quenched by addition of water, and the mixture was extracted with Et_2O (2 x 100 mL). The organic solution was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated to give crude enamine 4, which was used directly for the next step reaction. The crude 4 was diluted with HCO_2H : H_3PO_4 (450 mL : 450 mL) and stirred at room temperature for 72 h. The reaction mixture was poured into ice water, treated with sufficient 40% NaOH solution to bring the pH to ~8, and extracted with ethyl acetate (3 x 500 mL). The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated to give the crude enamine 5. $NaBH_4$ (14.0 g, 370 mmol) was added to a solution of 5 in MeOH (750 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. After removal of MeOH, the residue was diluted with H_2O, treated with 2N-HCl solution (to pH ~8), extracted with ethyl acetate (3 x 300 mL), washed with H_2O and brine, dried over Na_2SO_4 and concentrated to dryness. Column chromatography of the crude material with 0.5% MeOH in CH_2Cl_2 afforded (±)-6 (35.2 g, 60% over 3 steps) as a yellow oil; ^{1}H NMR ($CDCl_3$): 7.51-7.33 (m, 6H), 7.08-7.02 (m, 2H), 6.85 (dd, 1H, J = 8 and 2 Hz), 3.93 (s, 3H), 3.73 (q, 2H, J = 14 Hz), 3.11-3.02 (m, 2H), 2.84-2.79 (m, 1H), 2.22-2.02 (m, 5H), 1.98-1.85 (m, 2H), 1.42-1.32 (m, 3H); *m/z*: HRMS (ESI) calculated for $C_{22}H_{28}NO$ $(M+H)^+$: 322.2177. Found, 322.2180.

1*S*,5*R*-(+)-2-Benzyl-5-(3-methoxyphenyl)-2-aza-bicyclo[3.3.1] nonane ((+)-6) and 1*R*,5*S*-(-)-2-benzyl-5-(3-methoxyphenyl)-2-aza-bicyclo[3.3.1] nonane ((-)-6) from resolution of 2-benzyl-5-(3-methoxyphenyl)-2-aza-bicyclo[3.3.1] nonane ((±)-6)

A solution of (+)-di-*O,O'-p*-toluyl-*D*-tartaric acid (68.9 g, 178 mmol) in acetone (125 mL) was added to a solution of **(±)-6** (57.2 g, 178 mmol) in acetone (125 mL), and the mixture was stirred for 20 min. Then, Et_2O (250 mL) was added to the solution and the crystals that formed on standing at 4 °C overnight were filtered and washed with Et_2O. The solid was recrystallized twice from EtOH, filtered and dried under reduced pressure to give 31.5 g of the (+)-di-*O,O'-p*-toluyl-*D*-tartrate salt, mp 155-158.5 °C; $[\alpha]_D^{20}$ +63.1° (c 0.55, EtOH). The tartrate salt was basified with NH_4OH, extracted with 5% isopropyl alcohol in CH_2Cl_2, washed with H_2O and brine, dried over Na_2SO_4 and concentrated to give 6 as a free base, $[\alpha]_D^{20}$ +0.5° (c 0.82, EtOH). The enantiomeric excess of **(+)-6** was >99.8% (mobile phase: 5% isopropyl alcohol in hexane with 0.25% diethylamine, flow rate: 0.6 mL/min; retention time: 22.38 min). The filtrates from the crystallization and recrystallization of the (+)-di-*O,O'-p*-toluyl-*D*-tartrate salt were combined, evaporated, and converted to the free base (NH_4OH, 5% isopropyl alcohol in CH_2Cl_2) to give 37.1 g of material enriched in (-)-6. The (-)-di-*O,O'-p*-toluyl-*D*-tartrate salt of (-)-6 was obtained from (-)-di-*O,O'-p*-toluyl-*D*-tartaric acid, as noted above for the (+)-salt, mp 177.5-179 °C; $[\alpha]_D^{20}$ -65° (c 0.56, EtOH). The enantiomeric excess of **(-)-6** was >99.8% (mobile phase: 5% isopropyl alcohol in hexane with 0.25% diethylamine, flow rate: 0.6 mL/min; retention time: 19.85 min).

General procedure for synthesis of O-arylethyltosylate (7)

The corresponding tosylates were prepared according to the procedure described in the literature. Triethylamine (~6.6 mmol) in CH_2Cl_2 (4 mL) was added dropwise to a solution of arylethanol (~6 mmol) and p-toluenesulfonyl chloride (~6.6 mmol) in CH_2Cl_2 (20 mL) at 10 °C. The reaction was allowed to warm to room temperature and stirred overnight. After addition of 1N-HCl solution (2 mL), the organic layer was separated, and the organic layer was washed with aqueous $NaHCO_3$ solution and brine, dried and concentrated to give a crude product, which was purified by column chromatography using hexanes-ethyl acetate to give 7a-7n (80-91%). The physical constants and

analytical data of compounds 7b,[29] 7c,[29] 7d,[30] 7e,[31] 7f,[29] 7h,[29] 7i,[29] 7m[29] and 7n[28] were identical with published data.

2-Methylphenethyl 4-methylbenzenesulfonate (7a)

Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.69 (d, 2H, *J* = 8 Hz), 7.7.28 (d, 2H, *J* = 8 Hz), 7.13-7.05 (m, 4H), 4.17 (t, 2H, *J* = 7 Hz), 2.97 3.93 (s, 3H), 3.73 (q, 2H, *J* = 14 Hz), 3.11-3.02 (m, 2H), 2.84-2.79 (t, 2H, *J* = 7 Hz), 2.43 (s, 3H), 2.22 (s, 3H); ^{13}C NMR: δ 144.83, 136.50, 134.33, 133.07, 130.56, 129.92, 129.70, 127.92, 127.20, 126.31, 68.80, 32.80, 21.74, 19.34; HRMS (ESI): calculated for $C_{16}H_{19}O_3S$ $(M+H)^+$ 291.1055, Found 291.1050.

2-Chlorophenethyl 4-methylbenzenesulfonate (7g)

White solid, mp 43-44 °C (recrystallized from hexanes-ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 7.63 (d, 2H, *J* = 8 Hz), 7.28-7.25 (m, 3H), 7.12-7.11 (m, 2H), 4.24 (t, 2H, *J* = 7 Hz), 3.03 (t, 2H, *J* = 7 Hz), 2.44 (s, 3H); ^{13}C NMR: δ 144.83, 134.14, 133.94, 132.92, 131.61, 129.92, 129.68, 128.61, 127.91, 127.09, 68.82, 33.37, 21.74; HRMS (ESI): calculated for $C_{15}H_{16}ClO_3S$ $(M+H)^+$: 311.0509, Found, 311.0561.

2,4-Dichlorophenethyl 4-methylbenzenesulfonate (7j)

White solid, mp 54-55 °C (recrystallized from hexanes-ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 7.68 (d, 2H, *J* = 8 Hz), 7.9-7.26 (m, 4H), 7.19-7.16 (m, 2H), 4.25 (t, 2H, *J* = 7 Hz), 3.08 (t, 2H, *J* = 14 Hz), 2.43 (s, 3H); ^{13}C NMR: δ 144.97, 134.70, 133.70, 132.78, 132.71, 132.50, 129.91, 129.45, 127.91, 127.31, 68.51, 32.88, 21.80; HRMS (ESI): calculated for $C_{15}H_{15}Cl_2O_3S$ $(M+H)^+$: 345.0119, Found, 345.0116.

2-Nitrophenethyl 4-methylbenzenesulfonate (7k)

White solid, mp 49-50 °C (recrystallized from hexanes-ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 7.95 (dd, 1H, *J* = 8 and 1 Hz), 7.67 (dd, 2H, *J* = 8 and 2 Hz), 7.55 (dd, 1H, *J* = 8 and 1 Hz), 7.44-7.37 (m, 2H), 7.27 (dd, 2H, *J* = 6 and 4 Hz), 4.35 (t, 2H, *J* = 6 Hz), 3.26 (t, 2H, *J* = 6 Hz), 2.43 (s, 3H); ^{13}C NMR: δ 145.01, 133.56, 133.51, 132.76, 131.81, 130.00, 128.49, 127.93, 125.25, 69.50, 33.27, 21.78; HRMS (ESI): calculated for $C_{15}H_{16}NO_5S$ $(M+H)^+$: 322.0749, Found, 322.0756.

3-Nitrophenethyl 4-methylbenzenesulfonate (7l)

White solid, mp 93-94 °C (recrystallized from hexanes-ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 7.65 (dd, 2H, *J* = 7 and 2 Hz), 7.63-7.41 (m, 2H), 7.28-7.25 (m, 4H), 4.28 (t, 2H, *J* = 6 Hz), 3.06 (t, 2H, *J* = 6 Hz), 2.42 (s, 3H); ^{13}C NMR: δ 145.19, 138.72, 135.49, 132.63, 129.98, 129.64, 127.86, 123.69, 122.08, 69.74, 34.92, 21.69; HRMS (ESI): calculated for $C_{15}H_{16}NO_5S$ $(M+H)^+$: 322.0749, Found, 322.0756.

1*S*,5*R*-(+)-5-(3-Methoxyphenyl)-2-aza-bicyclo-[3.3.1]nonane ((-)-8) and 1*R*,5*S*-(-)-5-(3-methoxyphenyl)-2-aza-bicyclo-[3.3.1]nonane ((+)-8)

A mixture of (+)-6 (1.0g, 2.83 mmol), 10% Pd-C (100 mg) and MeOH (15 mL) was stirred under hydrogen (60 psi) at room temperature for 6 h. After filtration, the organic layer was evaporated in vacuo to give a crude product. Column chromatography of crude material with 5% MeOH in CH_2Cl_2 gave the desired 1*S*,5*R*-secondary amine (-)-8 (0.61g, 93%) ($[\alpha]_D^{20}$ -2.8° (c 0.82, EtOH, $[\alpha]_{365}^{20}$ -14.0° (*c* 0.82, EtOH)) as a pale yellow oil that was converted to its hydrochloride salt: mp 179-180 °C; $[\alpha]_D^{20}$ +5.1° (*c* 0.59, MeOH); ^{1}H NMR ($CDCl_3$, free base): δ 7.27-7.22 (m, 1H), 6.94 (br-d, 1H, *J* = 8 Hz), 6.89 (d, 1H, *J* = 2 Hz), 6.74 (br-d, 1H, *J* = 8 Hz), 3.82 (s, 3H), 3.55 (dt, 1H, *J* = 12 and 5 Hz), 3.40 (br-s, 1H), 3.02 (dt, 1H, *J* = 12 and 7 Hz), 2.21-2.15 (m, 1H), 2.11-1.99 (m, 3H), 1.94-1.68 (m, 3H), 1.77-1.69 (m, 2H), 1.64-1.56 (m, 1H); ^{13}C NMR (free base): *δ* 159.62, 154.22, 129.22, 117.23, 111.41, 110.29, 55.22, 47.70, 42.38, 38.39, 38.16, 35.35, 31.90, 25.55, 22.59; HRMS (ESI):

calculated for $C_{15}H_{22}NO$ $(M+H)^+$ 232.1701, Found 232.1708. The enantiomeric 1*R*,5*S*-(+)-8 (4.32 g, 93%), isolated as an oil ($[\alpha]_D^{20}$ +2.9° (c 0.82, EtOH, $[\alpha]_{365}^{20}$ +15.3° (*c* 0.805, EtOH)), was obtained from (-)-6 (6.44 g) according to the method described above. It was converted to its hydrochloride salt: mp 179-180.5 °C, $[\alpha]_D^{20}$ -5.7° (*c* 0.875, MeOH), $[\alpha]_{365}^{20}$ –17.0° (*c* 0.88, MeOH)

(1*S*,5*R*)-(+)-5-(3-(Cyclopropylmethoxy)phenyl)-2-aza-bicyclo[3.3.1]nonane ((+)-9) and 1R,5S-(-)-5-(3-(cyclopropylmethoxy)phenyl)-2-aza-bicyclo[3.3.1]nonane ((-)-9)

1.0M $BBr_3 \bullet SMe_2$ in CH_2Cl_2 (31 mL, 31 mmol) was added to a solution of (+)-6 (3.3g, 10.28 mmol) in 1,2-dichloroethane (30mL) and heated at 50 °C for 6 h. After cooling, the reaction was diluted with $CHCl_3$ and washed with saturated Na_2CO_3 solution and brine, dried over Na_2SO_4 and concentrated to dryness. The residue was passed through a pad of silica gel using 2% MeOH in CH_2Cl_2 as the eluting solvent, and concentrated to give a phenolic compound (~75% yield). This phenolic compound was also obtained by refluxing (+)-6 with 48% HBr for 1h. *t*-BuOK (0.96g, 8.56mmol) in dry DMF (12 mL) was added to a solution of phenolic compound in dry THF (20 mL) over a period of 10 min at 0 °C, and the mixture was stirred for 15 min. (Bromomethyl) cyclopropane (0.82 mL, 8.56 mmol) in dry THF (10 mL) was added, and the mixture was stirred at room temperature for 20 min and heated at 50°C for 3 h. After filtration and removal of DMF, the residue was passed through a pad of silica gel and washed with 1% MeOH in CH_2Cl_2. The solvents were removed in vacuo to provide a protected phenol, which was directly subjected to catalytic debenzylation (see the preparation of (-)-8). Column chromatography of the crude product with 5% MeOH in CH_2Cl_2 gave (-)-9 (1.501g, 54% over 3 steps) as a pale yellow oil ($[\alpha]_D^{20}$ -3.7° (c 1.18, EtOH, $[\alpha]_D^{365}$ –15.5° (*c* 1.175, EtOH)) that was converted to its HBr salt, mp 148-150 °C; $[\alpha]_D^{20}$ +3.5°, $[\alpha]_D^{365}$ +12.5° (*c* 0.96, MeOH); ^{1}H NMR ($CDCl_3$, free base): δ 7.23 (m, 1H), 6.94-6.89 (m, 2H), 6.71 (m, 1H), 3.79 (d, *J* = 7 Hz, 2H), 3.53 (dt, *J* = 13 and 5 Hz, 1H), 3.38 (m, 1H), 2.98 (ddd, J = 13, 7, and 2 Hz, 1H), 2.23-1.85 (m, 5H), 1.81-1.58 (m, 4H), 1.34-1.20 (m, 1H), 0.68-0.61 (m, 2H), 0.38-0.32 (m, 2H); ^{13}C NMR ($CDCl_3$, free base): δ

159.14, 154.40, 129.24, 117.27, 112.20, 111.00, 72.84, 47.84, 42.59, 38.89, 38.52, 38.43, 35.52, 32.28, 22.72, 10.52, 3.34; HRMS (ESI) calculated for $C_{18}H_{26}NO$ $(M+H)^+$ 272.2014, Found 272.2021. (+)-9 (1.25g, 57% over 3 steps, $[\alpha]_D^{20}$ +3.8° (*c* 1.17, EtOH), $[\alpha]_D^{365}$ +17.5° (*c* 1.17, EtOH)) was obtained from (-)-6 (2.58 g) according to the method described above. Treatment of (+)-9 with HBr gave the HBr salt, mp 151-153 °C; $[\alpha]_D^{20}$ –3.6° (*c* 0.53, MeOH), $[\alpha]_D^{365}$ –11.3° (*c* 0.81, MeOH).