Stereoselective actions of methylenedioxypyrovalerone (MDPV) to inhibit dopamine and norepinephrine transporters and facilitate intracranial self-stimulation in rats

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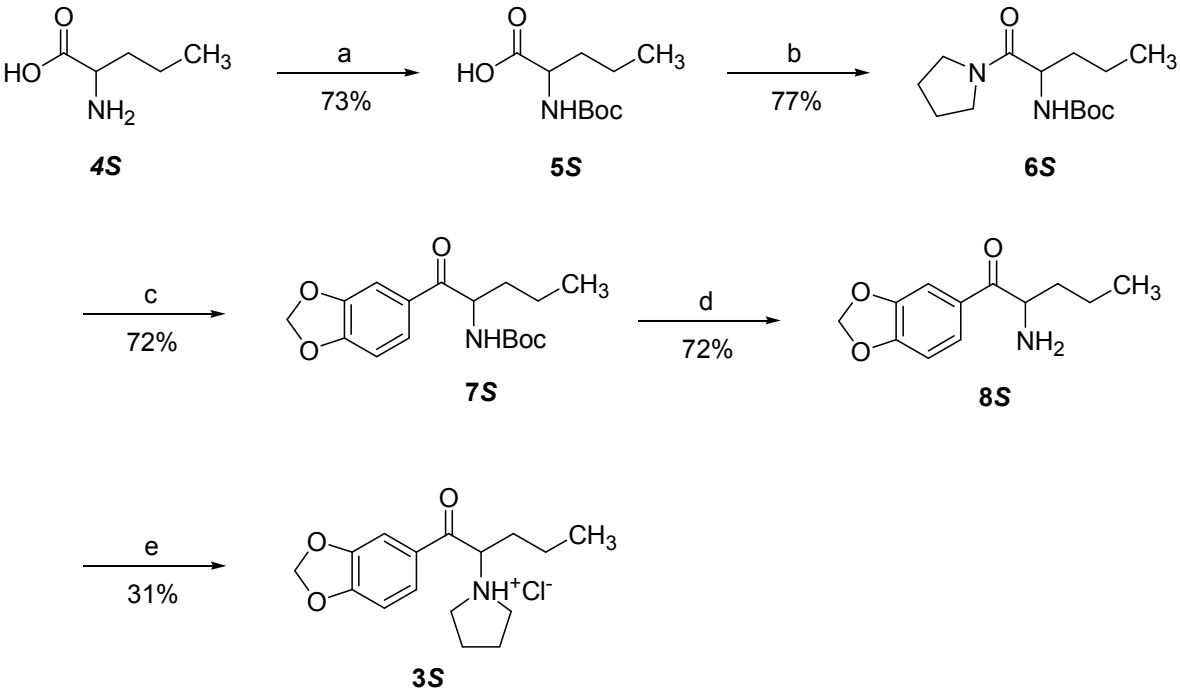
SUPPORTING INFORMATION

Enantio-enriched MDPV. Two different approaches were initially explored to synthesize the isomers of MDPV (**3**) in a stereoselective manner. Both procedures resulted in enhanced optical activity, but it was (subsequently) evident that partial racemization occurred in both cases. These approaches (described here because some of the intermediates might be of interest to others) were subsequently followed by the successful synthesis shown in the main body of the manuscript.

Method 1

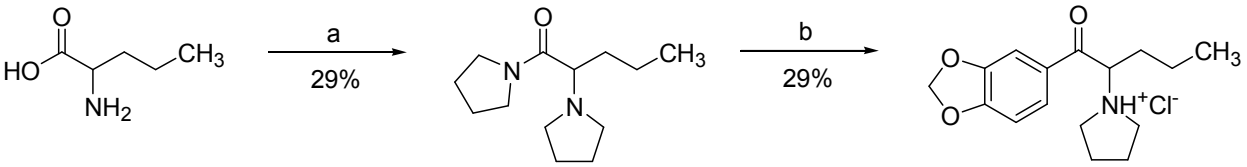


a. $(Boc)_2O$, $NaHCO_3$, dioxane, H_2O, reflux, 18 h, b. i) pivaloyl chloride, Et_3N, THF, 0 °C, 1 h, ii) pyrrolidine, rt, 7 h, c. 3,4-methylenedioxyphenylmagnesium bromide, THF, rt, 18 h, d. HCl/dioxane, rt, 30 min, e. i) 1,4-dibromobutane, $KHCO_3$, NaI, CH_3CN, reflux, 7 h, ii) HCl/Et_2O.

S(+)-Enriched methylendioxypyrovalerone Hydrochloride (3S-enriched). 1,4-Dibromobutane (0.097 g, 0.45 mmol) was added to a mixture of a free base of **8*S*** (0.100 g, 0.45 mmol), potassium bicarbonate (0.135 g, 1.35 mmol) and sodium iodide (0.135 g, 0.90 mmol) in anhydrous CH_3CN (15 mL). The reaction mixture was heated at reflux for 7 h. After cooling to room temperature it was filtered and the solid was washed with CH_3CN. Solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel; hexanes/EtOAc; 4:1) to afford a yellow oil. The oil was dissolved in anhydrous Et_2O and converted to the hydrochloride salt by adding a saturated solution of gaseous HCl in Et_2O. The precipitate was collected by filtration and recrystallized twice from a mixture of absolute EtOH and anhydrous Et_2O to afford the product (0.043 g, 31%) as white crystals: mp 235–237 °C, dec.; ^{1}H NMR (DMSO-d_6) δ 0.61 (t, J = 7.2 Hz, 3H, CH_3), 0.71–0.81 (m, 1H, CH_2), 1.04–1.13 (m, 1H, CH_2), 1.31–1.35 (m, 1H, CH_2), 1.63–1.72 (m, 1H, CH_2), 1.89–2.10 (m, 4H, CH_2), 3.05–3.16 (m, 1H, CH_2), 3.27–3.37 (m, 1H, CH_2), 3.50–3.58 (m, 1H, CH_2), 3.62–3.68 (m, 1H, CH_2), 5.18 ms, 1H, CH), 6.01 (s, 2H, CH_2), 6.21 (d, J = 4.2 Hz, 1H, CH), 6.92 (m, 2H, ArH), 6.99 (s, 1H, ArH), 9.92 (br s, 1H, NH^+ ex with D_2O); $[\alpha]_D^{27}$ +8.1°, c 0.545, MeOH.

Because **8*S*** is the same intermediate employed in Scheme 1, it is likely that partial racemization occurred in the last step of the synthesis.

Method 2



4R **11*R*** **3*R***

a. i)1,4-dibromobutane, Na_2CO_3, EtOH, reflux, 24 h, ii) HCl, iii) pivaloyl chloride, Et_3N, THF, 0 °C, 3 h, iiii) pyrrolidine, rt, 20 h, b. i) 3,4-methylenedioxyphenylmagnesium bromide, THF, rt, 21 h, 45 °C, 18 h, ii) HCl/Et_2O

R*(–)-1,2-Di(pyrrolidin-1-yl)pentan-1-one (11*R*).**1,4-Dibromobutane (2.38 g, 11 mmol) was added to a mixture of D-norvaline (**4*R) (1.17 g, 10 mmol) and sodium carbonate (3.18 g, 30 mmol) in absolute EtOH (60 mL). The reaction mixture was heated at reflux for 24 h. After cooling to room temperature the reaction mixture was filtered. Solvent was removed under reduced pressure. The residue was taken into EtOAc and insolubilities were removed by filtration. The filtrate was treated with 1 N HCl, stirred for 10 min and solvent was removed under reduced pressure to afford 1-(1-carboxybutyl)pyrrolidin-1-ium chloride as a sticky solid that was used for the next step without further purification.

Pivaloyl chloride (1.21 g, 10 mmol) was added in a dropwise manner to a stirred suspension of 1-(1-carboxybutyl)pyrrolidin-1-ium chloride and Et_3N (2.02 g, 20 mmol) in anhydrous THF (30 mL) at 0 °C (ice-bath) under an N_2 atmosphere. The resulting

suspension was allowed to stir at 0 °C for 3 h. Pyrrolidine (1.42 g, 20 mmol) was added in a dropwise manner and the reaction mixture was allowed to stir at room temperature for 20 h. Solvent was removed under reduced pressure. The residue was taken into H_2O, basified with an aqueous solution of NaOH (5%, to pH 10-11) and extracted with EtOAc (3 × 20 mL), The combined organic layer was washed with brine (20 mL), dried (Na_2SO_4) and solvent was removed under reduced pressure. The resulting yellow oil was purified by flash chromatography (silica gel; CH_2Cl_2/MeOH; 9:1) to afford the product (0.64 g, 29%) as a light-yellow oil: ^{1}H NMR ($CDCl_3$) *δ* 0.83 (t, *J* = 7.3 Hz, 3H, CH_3), 1.15–1.25 (m, 2H, CH_2), 1.46–1.54 (m, 1H, CH_2), 1.56–1.68 (m, 5H, CH_2), 1.71–1.78 (m, 2H, CH_2), 1.81–1.88 (m, 2H, CH_2), 2.42–2.50 (m, 2H, CH_2), 2.60–2.67 (m, 2H, CH_2), 3.25–3.36 (m, 3H, CH_2), 3.50 (td, *J* = 6.7, 2.9 Hz, 2H, CH_2); $[\alpha]_D^{27}$ –8.7°, *c* 1.255, MeOH.

R*(–)-Enriched methylendioxypyrovalerone Hydrochloride (3*R*-*enriched*).** 3,4-(Methylenedioxy)phenylmagnesium bromide (0.5 M in THF; 2.7 mL, 1.35 mmol) was added in a dropwise manner to a stirred solution of **11*R (0.1 g, 0.45 mmol) in anhydrous THF (2 mL) at 0 °C (ice-bath) under an N_2 atmosphere. The reaction solution was allowed to stir at room temperature for 16 h. After this time additional amount (0.9 mL, 0.45 mmol) of Grignard reagent was added at 0 °C (ice-bath) and the reaction mixture was allowed to stir at room temperature for 5 more hours, and then heated at 45 °C for 18 h. A saturated solution of NH_4Cl (10 mL) was added in a dropwise manner at 0 °C (ice-bath) followed by EtOAc (10 mL). The organic layer was separated and the aqueous portion was extracted with EtOAc (2 × 10 mL). The combined organic portion

was washed with brine (10 mL), dried (Na_2SO_4) and solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel; hexanes/EtOAc; 9:1 to 7:3) to afford a yellow oil. The oil was dissolved in anhydrous Et_2O and converted to the hydrochloride salt by adding a saturated solution of gaseous HCl in Et_2O. The precipitate was collected by filtration and recrystallized twice from a mixture of absolute EtOH and anhydrous Et_2O to afford the product (0.04 g, 29%) as white crystals: mp 231–235 °C, dec.; ^{1}H NMR (DMSO-d_6) δ 0.61 (t, J = 7.2 Hz, 3H, CH_3), 0.71–0.81 (m, 1H, CH_2), 1.04–1.13 (m, 1H, CH_2), 1.31–1.35 (m, 1H, CH_2), 1.63–1.72 (m, 1H, CH_2), 1.89–2.10 (m, 4H, CH_2), 3.05–3.16 (m, 1H, CH_2), 3.27–3.37 (m, 1H, CH_2), 3.50–3.58 (m, 1H, CH_2), 3.62–3.68 (m, 1H, CH_2), 5.18 ms, 1H, CH), 6.01 (s, 2H, CH_2), 6.21 (d, J = 4.2 Hz, 1H, CH), 6.92 (m, 2H, ArH), 6.99 (s, 1H, ArH), 9.92 (br s, 1H, NH^+ ex with D_2O); $[\alpha]_D^{28}$ –9.7°, c 0.55, MeOH.