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AN EASY ENTRY TO (1S, 2S) AND (1R, 2R)-*THREO*-IFENPRODIL

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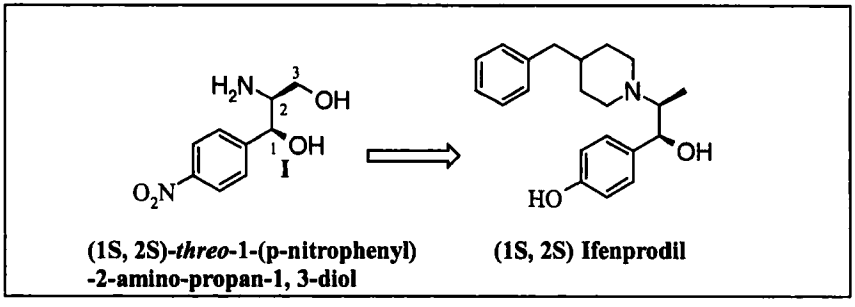
Abstract: A facile and practical synthesis of enantiomerically pure (L) or (D)-*threo*-Ifenprodil was accomplished from (1S, 2S)- and (1R, 2R)-*threo*-1-(p-nitrophenyl)-2-amino-propan-1, 3-diol *via* 3-phenylthio derivatives followed by Raney nickel reduction and conversion of the aromatic amine into phenol.

Glutamate-induced hyperexcitation of N-methyl-D-aspartate (NMDA) receptors results in neuronal death in a variety of acute and chronic neurodegenerative diseases. As a consequence, NMDA receptor antagonists may find clinical use in the treatment of neurological disorders. [1, 2] Studies at the molecular level suggest that native NMDA receptors are heterooligomeric assemblies of two different types of subunits. Subtype-selective NMDA antagonists may have a better pharmacological profile compared to broad spectrum antagonists. The α-1 adrenergic antagonist Ifenprodil, originally designed as an antihypertensive agent, was found to display NMDA subtype-selectivity. More interestingly, NMDA and α-1 adrenergic receptor activities can be dissociated by selection of the *threo* relative stereochemistry.[3] In connection

with our studies on neuroprotectant agents acting on NMDA receptor complex, large quantities of enantiomerically pure (1S, 2S)- and (1R, 2R)-*threo*-Ifenprodil were required. Several methods have been previously reported in the literature for the preparation of these enantiomers, e.g. *via* fractional crystallization of diastereomeric salts or derivatives. However, these approaches have a number of disadvantages such as low yield or tedious crystallisations. Therefore, an enantioselective synthetic approach was considered attractive. Structural and stereochemical resemblances and retrosynthesis analysis suggested that conversion of easily accessible optically pure (1S, 2S)- and (1R, 2R)-*threo*-1-(p-nitrophenyl)-2-amino-propan-1, 3-diol into (1S, 2S)- and (1R, 2R)-*threo* Ifenprodil could be a convenient entry (Scheme **1**). These compounds are key intermediate in the synthesis of amphenicol-type antibiotics. There is ample literature precedent on the successful exploitation as homochiral starting materials as well as chiral auxilaries and ligands in asymmetric transformation.[4]

Scheme 1

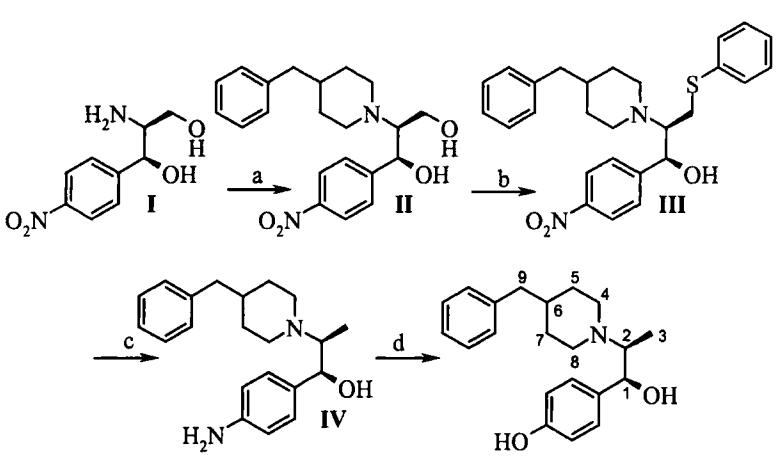


(1S, 2S)-*threo*-1-(p-nitrophenyl) -2-amino-propan-1, 3-diol **(1S, 2S) Ifenprodil**

The synthetic sequence is outlined in Scheme **2** (only one enantiomer is depicted for clarity). In this present instance, **I** was straightforward converted into

piperidine derivative **II** in 85% yield by action of 1,5-dibromo-3-benzyl-pentane in DMF in presence of Hünig's base. The bis-alkylating agent was conveniently prepared by von Braun degradation of easily available 4-benzyl-piperidine. Benzoylation and nitrogen abstraction, using PBr_3/Br_2, to provide 1,5-dibromo-3-benzyl-pentane was accomplished in 60% overall yield.[5]

Scheme **2**

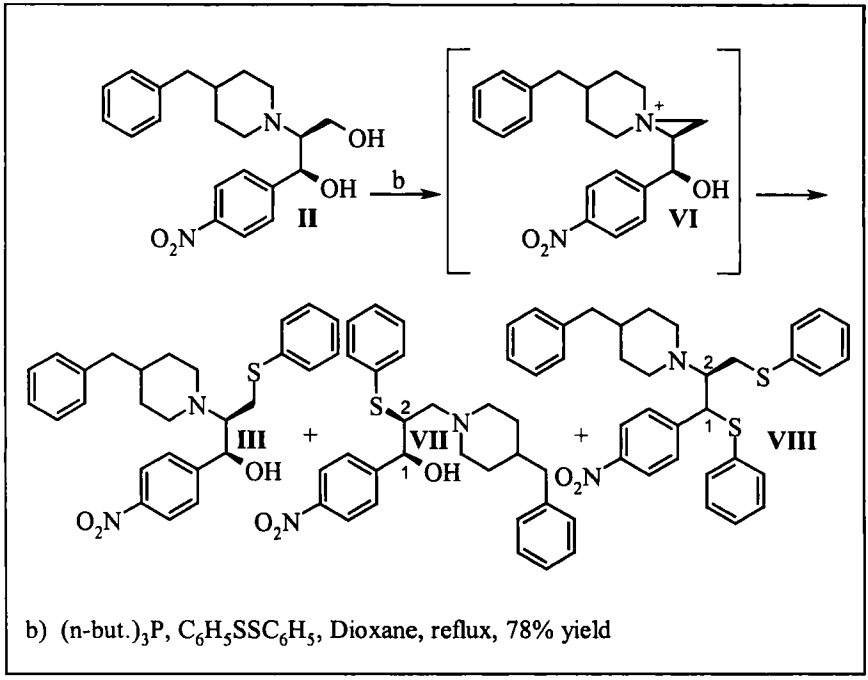


a) 1,5-dibromo-3-benzyl-pentane, DIPEA, DMF, 70°C, 85% yield
b) (n-but.)$_3$P, $C_6H_5SSC_6H_5$, Dioxane, reflux, 78% yield
c) 3 atm. H_2, Raney nickel, Ethanol, 88% yield
d) $NaNO_2$, 35% H_2SO_4, Cu_2O, $Cu(NO_3)_2 \cdot 3\ H_2O$, 0°C, 89% yield

The following conversion of **II** into **III** took place in good yield employing the reagent combination diphenyl disulfide and tri-n-butylphosphine according to Hata methodology.[6] Under this condition, activation *via* an alkoxyphosphorane, mostly of the primary, rather then the more encumbered secondary hydroxy group of **II** and subsequent internal nucleophilic attack of the neighbouring nitrogen atom, gave rise to the aziridinium salt **VI** as depicted in Scheme **3**. This labile

intermediate underwent ring opening by nucleophile (PhSH) providing in such a way, **III** in 78% yield, the rearranged product **VII** in 12% yield and small amount of disulfide **VIII** stemming from further thiophenylation at C-1. An indirect evidence of the involvement of the aziridinium salt **VI**, as a transient intermediate in the reaction outcome, accounts for the formation of **VII**.

Scheme 3



The stereochemistry at C-2 for **VII** and at C-1 for **VIII** has not been clearly defined by ^{1}H-NMR spectroscopy. For the former, the stereochemistry at C-2 should be dictated by the attack of the nucleophile at the transient **VI** leading to inversion of configuration. Conversely, for the latter, the participation of an

aziridinium salt formed by internal nucleophilic attack of the nitrogen atom on activated C-1, could likely bring to retention of configuration at the stereogenic center *via* two consecutive inversions in a SN-2 fashion. Subsequently, by catalytic hydrogenation in presence of Raney nickel in ethanol, desulfuration and nitro group reduction took readily place, converting **III** into **IV** in 88% yield besides a small amount of 1-deoxy derivative formed by hydrogenolysis of the C-1 hydroxy group. The aromatic amine **IV** was afterwards transformed into **V** by oxidation with cupric ion of the aryl radical generated from the diazonium salt. Addition of cuprous oxide to a dilute solution of the diazonium salt dissolved in a solution containing a large excess of cupric nitrate provided **V** in 89% yield without the variety of competing reactions that generally plague the conversion of aromatic amines into phenols (e.g. coupling, reduction).[7]

In conclusion, a concise enantioselective synthesis of enantiomers of *threo*-Ifenprodil (4 steps) has been accomplished using readily available starting material, offering in this manner a viable pathway for the synthesis of analogues.

Experimental section

^{1}H-NMR spectra were recorded on Varian VXR 400 S MHx spectrometer using TMS as an internal standard. Optical rotation was measured at 589 nm using a JASCO DIP-140 polarimeter. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. Electron mass spectra were

recorded in form of m/z (intensity to base = 100) on a Finnigan MAT SSQ 7000 mass spectrometer. Microanalyses were performed on a Carlo Erba autoanalyser and were within 0.4% of the calculated values.

(1S, 2S)-*Threo*-1-(4-nitrophenyl)-2-(4-benzylpiperidino)-propan-1, 3-diol II

A slurry of (1S, 2S)-*threo*-1-(4-nitrophenyl)-2-amino-propan-1, 3-diol **I** (35 g, 165 mmol) and DIPEA (63 ml, 363 mmol) in dimethylformamide (300 ml) was heated to solution before the addition of 1, 5-dibromo-3-benzyl-pentane (58 g, 181 mmol). The yellow solution was heated overnight at 80°C. The solvent was removed *in vacuum* and the residue taken up in ethylacetate was thoroughly washed with 0.1 M Na_2CO_3 solution, then with brine and dried over Na_2SO_4. After removal of the solvent, the crude reaction mixture was crystallised twice from boiling acetone to afford **II** as shining yellow crystals (52 g, 85% yield), mp 119-122°C. $[\alpha]_D^{20}$ –27.2° (c= 0.3, methanol). MS (m/z) 339 (2, $[M\text{-}CH_2OH]^+$), 218 (100, $[M\text{-}HOCHC_6H_4NO_2]^+$), 91 (28, $[CH_2C_6H_5]^+$). NMR (DMSO-d_6) δ (ppm) 1.10 (m, 2 H, 7ax+5ax), 1.43 (m, 1 H, H-6), 1.50 (m, 2 H, 7eq+5eq), 2.41 (m, 1 H, 4ax), 2.47 (m, 2 H, CH_2-9), 2.53 (m, 1 H, H-2), 2.69 (m, 2 H, CH_2-8), 2.93 (m, 1 H, 4eq), 3.29 (dd, J= 4.4, 10.9 Hz, 1 H, C<u>H</u>(H)-3), 3.42 (dd, J= 7.6, 10.9 Hz, 1 H, C<u>H</u>(H)-3), 4.35 (b.s., 1 H, OH-3), 4.61 (d, J= 7.9 Hz, 1 H, H-1), 5.25 (b.s., 1 H, OH-1), 7.1-7.3 (m, 5 H, aromatic H (C_6H_5)), 7.61 (d, J= 8.7 Hz, 2 H, meta-NO_2), 8.16 (d, J= 8.7 Hz, 2 H, ortho-NO_2). Anal. Calcd. For $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.82; H, 6.85; N, 7.38.

(1S, 2S)-*Threo*-1-(4-nitrophenyl)-2-(4-benzylpiperidino)-3-phenythiomethyl-propan-1-ol III

A stirred solution of **II** (45 g, 166 mmol) in dioxane (450 ml) was treated with diphenyl disulfide (52 g, 250 mmol) and tri-*n*-butylphosphine (62.3 ml, 250 mmol) and heated at reflux overnight. The cooled reaction mixture was concentrate to leave a viscous residue, that was crystallised three times from boiling ethanol to provide **III** as whitish crystals (60 g, 78% yield), mp 131-134°C. $[\alpha]_D^{20}$ +12.2° (c= 0.3, methanol). MS (m/z) 339 (9, $[M\text{-}CH_2SC_6H_5]^+$), 310 (100, $[M\text{-}HOCHC_6H_4NO_2]^+$), 200 (7, $[CH_2{=}C{=}NC_5H_9C_7H_7]^+$), 152 (11, $[HOHCC_6H_4NO_2]^+$), 123 (7, $[CH_2SC_6H_5]^+$), 109 (11, $[SC_6H_5]^+$), 91 (34, $[CH_2C_6H_5]^+$). NMR (DMSO-d_6) δ (ppm) 0.98, 1.06 (m, 2 H, 5ax+7ax), 1.41 (m, 3 H, H-6+5eq+7eq), 2.40 (m, 3 H, CH_2-9+4ax), 2.55 (m, 2 H, CH_2-8), 2.78 (m, 1 H, H-2), 2.84 (dd, J= 6.2, 12.8 Hz, 1 H, C<u>H</u>(H)-3), 2.97 (m, 1 H, 4eq), 3.20 (dd, J= 7.6, 12.8 Hz, 1 H, C<u>H</u>(H)-3), 4.85 (dd, J= 5.8, 2.9 Hz, 1 H, H-1), 5.51 (d, J= 2.9 Hz, 1 H, OH-1), 7.1-7.3 (m, 10 H, aromatic H (2 x C_6H_5)), 7.59 (d, J= 9.0 Hz, 2 H, meta-NO_2), 8.15 (d, J= 9.0 Hz, 2 H, ortho-NO_2). Anal. Calcd. For $C_{27}H_{30}N_2O_3S$: C, 70.10; H, 6.54; N, 6.06. Found: C, 70.21; H, 6.32; N, 5.87. The mother liquor was evaporated to dryness and the residue was chromatographed [silica gel, h cyclohexane/ethylacetate (5/2)], to provide **VIII** (1.3 g) as yellow oil. MS (m/z) 271 (10, $[CH_2CHCH(SC_6H_5)C_6H_4NO_2]^{+\cdot}$), 218 (91, $[M\text{-}NO_2C_6H_4CH_2SC_6H_5\text{-}CH_2C_6H_5]^+$), 109 (100, $[SC_6H_5]^+$), 91 (21, $[CH_2C_6H_5]^+$). NMR (DMSO-d_6) δ (ppm) 1.18 (m, 2 H, 7ax+5ax), 1.48 (m, 3 H, H-6+7eq+5eq), 2.46 (m, 3 H, CH_2-9+4ax), 2.6-2.8 (m, 3 H, C<u>H</u>(H)-3+CH_2-8), 3.02 (m, 1 H, 4eq),

3.19 (m, 2 H, CH(H)-3+H-2), 4.96 (d, J= 8.6 Hz, 1 H, H-1), 7.0-7.4 (m, 15 H, aromatic H (3 x C_6H_5)), 7.54 (d, J= 8.9 Hz, 2 H, meta-NO_2), 7.98 (d, J= 8.9 Hz, 2 H, ortho-NO_2). Anal. Calcd. For $C_{33}H_{34}N_2O_2S_2$: C, 71.45; H, 6.18; N, 5.05. Found: C, 71.31; H, 5.98; N, 4.83. Continuing the elution [cyclohexane/ethylacetate (5/3)], **VII** (9.2 g, yield 12%) was obtained as white foam. MS (m/z) 310 (6, $[M\text{-}NO_2C_6H_4CHOH]^{+\cdot}$), 218 (7, $[M\text{-}NO_2C_6H_4CH_2OH\text{-}CH_2C_6H_5]^+$), 188 (87, $[NC_5H_9CH_2C_6H_5]^+$), 152 (14, $[NO_2C_6H_4CHOH]^+$), 109 (50, $[SC_6H_5]^+$), 91(100, $[CH_2C_6H_5]^+$). NMR (DMSO-d_6) δ (ppm) 1.00 (m, 2 H, 7ax+5ax), 1.37 (m, 1 H, H-6), 1.43 (m, 2 H, 5eq+7eq), 1,70, 1.78 (2 m, 2 H, 4ax+8ax), 2.40 (d, J= 6.9 Hz, 2 H, CH_2-9), 2.42 (dd, J= 13.3, 5.8 Hz, 1 H, CH(H)-3), 2.50 (dd, J= 13.3, 9.0 Hz, 1 H, CH(H)-3), 2.69 (m, 1 H, H8eq), 2.87 (m, 1 H, 4eq), 3.72 (ddd, J= 9.0, 5.8, 5.1 Hz, 1 H, H-2), 5.00 (d, J= 5.1 Hz, H-1), 7.1-7.4 (m, 10 H, aromatic H (2 x C_6H_5)), 7.63 (d, J= 8.8 Hz, 2 H, meta-NO_2), 8.13 (d, J= 8.8 Hz, 2 H, ortho-NO_2). Anal. Calcd. For $C_{27}H_{30}N_2O_3S$: C, 70.10; H, 6.54; N, 6.06. Found: C, 69.93; H, 6.37; N, 5.85.

(1S, 2S)-*Threo*-1-(4-aminophenyl)-2-(4-benzylpiperidino)-propan-1-ol IV

A solution of **III** (15 g, 32.5 mmol) in ethanol (350 ml) was hydrogenated at 3 atmosphere pressure over Raney nickel W-2 (25 g) previously washed with ethanol. The calculated amount of H_2 was taken up in 3 h. The catalyst was removed by filtration and thoroughly washed with ethanol. Concentration of the solution yielded **IV** (9.3 g, 88% yield), mp 154-156°C. $[\alpha]_D^{20}$ –43.3° (c= 0.3, methanol). MS (m/z) 325 (1, $[M]^{+\cdot}$), 307 (7, $[M\text{-}H_2O]^{+\cdot}$), 202 (100, [M-

$H_2NC_6H_4CHOH]^+$), 122 (11, $[H_2NC_6H_4CHOH]^+$), 91(92, $[CH_2C_6H_5]^+$). NMR ($CDCl_3$) δ (ppm) 0.70 (d, J= 6.7 Hz, 3 H, C<u>H</u>$_3$CH), 1.28, 1.41 (m, 2 H, 5ax+7ax), 1.56 (m, 1 H, H-6), 1.70 (m, 2 H, 5eq+7eq), 2.07 (m, 1 H, 4ax), 2.55 (m, 4 H, CH_2-9+H-2+8ax), 2.66, 2.82 (m, 2 H, 4eq+8eq), 3.62 (b.s., 2 H, NH_2), 4.11 (d, J= 10.1 Hz, 1 H, H-1), 5.21 (b.s., 1 H, OH), 6.64 (d, J= 8.4 Hz, 2 H, ortho-NH_2), 7.1-7.3 (m, 7 H, meta-NH_2+aromatic H (C_6H_5)). Anal. Calcd. For $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.63. Found: C, 77.53; H, 8.48; N, 8.47. The mother liquor was evaporated to dryness and the residue was chromatographed [silica gel, cyclohexane/ethylacetate (3/2)], affording after crystallisation from diethylether, **(2S)-1-(4-aminophenyl)-2-(4-benzylpiperidino)-propane** (0.7 g), mp 43-45°C. $[\alpha]_D^{20}$ +6.3° (c= 0.3, methanol). MS (m/z) 309 (51, $[MH]^+$), 308 (100, $[M]^{+\cdot}$), 202 (41, $[M\text{-}H_2NC_6H_4CH_2]^+$), 106 (3, $[H_2NC_6H_4CH_2]^+$), NMR ($CDCl_3$) δ (ppm) 0.91 (d, J= 6.6 Hz, 3 H, C<u>H</u>$_3$CH), 1.33 (m, 2 H, 5ax+7ax), 1.51 (m, 1 H, H-6), 1.66 (m, 2 H, 5eq+7eq), 1.82 (m, 1 H, 4ax), 2.26 (m, 2 H, C<u>H</u>(H)-1+8ax), 2.54 (d, J= 7.3 Hz, 2 H, CH_2-9), 2.74 (m, 1 H, H-2), 2.86 (m, 2 H, 4eq+8eq), 2.90 (m, 1 H, C<u>H</u>(H)-1), 3.50 (b.s., 2 H; NH_2), 6.61 (d, J= 8.3 Hz, 2 H, ortho-NH_2), 6.95 (d, J= 8.3 Hz, 2 H, meta-NH_2), 7.1-7.3 (m, 5 H, aromatic H(C_6H_5)). Anal. Calcd. For $C_{21}H_{28}N_2$: C, 81.77; H, 9.15; N, 9.08. Found: C, 81.45; H, 9.03; N, 8.89.

(1S, 2S)-*Threo*-1-(4-hydroxyphenyl)-2-(4-benzylpiperidino)-propan-1-ol <u>V</u>

To a stirred ice cooled solution of **V** (25 g, 77 mmol) dissolved in 35% sulfuric acid (225 ml) was added dropwise a solution of sodium nitrite (7 g, 102 mmol) in ice water (35 ml) such a rate as to maintain the temperature at 0-5°C. After the

solution has been stirred for additional 15 min., urea was added to decompose any excess of sodium nitrite. To the resulting cold solution of the diazonium salt was added a solution of cupric nitrate trihydrate (48 g, 199 mmol) in water (300 ml). Under vigorous stirring, cuprous oxide (10.5 g, 73 mmol) was added to the solution. After the evolution of nitrogen has ceased, the resulting green solution was set aside at room temperature for 15 min then alkalinized with dilute ammonia solution and thoroughly partitioned with ethylacetate. The organic phase was washed with brine and dried. After removal of the solvent, the residue was filtered on a small pad of [silica gel, cyclohexane/acetone (3/2)] to provide, after crystallisation from ethylacetate, **V** (22.3 g, 89% yield), mp 187-189°C. $[\alpha]_D^{20}$ –39.7° (c= 0.3, methanol), (lit. $[\alpha]_D^{20}$ –38.3° (c= 1, methanol)) [3]. MS (m/z) 326 (100, $[MH]^{+\cdot}$), 202 (53, $[CH_3CHNC_5H_9CH_2C_6H_4]^+$), 123 (8, $[OHC_6H_4CHOH]^+$), 122 (11, $[OHCH_2C_6H_5CHO]^{+\cdot}$). NMR ($CDCl_3$) δ (ppm) 0.71 (d, J= 6.9 Hz, 3 H, $C\underline{H}_3CH$), 1.29, 1.40 (m, 2 H, 7ax+5ax), 1.55 (m, 1 H, H-6), 1.72 (m, 2 H, 7eq+5eq), 2.08 (m, 1 H, 4ax), 2.54 (m, 4 H, CH-2+CH_2-9+8ax), 2.67, 2.81 (m, 2 H, 4eq+8eq), 4.16 (d, J= 9.7 Hz, 1 H, H-1), 5.11 (b.s., 1 H, OH), 6.70 (d, J= 8.6 Hz, 2 H, ortho-OH), 7.1-7.4 (m, 7 H, meta-OH+aromatic H (C_6H_5)). Anal. Calcd. For $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.32; H, 8.18; N, 4.23.

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