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Synthesis of some tolperisone metabolites in racemic and optically active form

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Abstract—1-(4′-Carboxyphenyl)-2-methyl-3-(piperidine-1-yl)-propan-1-one **M3**, *erythro*-1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)-propan-1-ol **M4** and *threo*-1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)-propan-1-ol **M5**, metabolites of the muscle relaxant tolperisone were synthesized in racemic and optically active forms.

1. Introduction

This paper is the third part of a series of papers presenting our work on the tolperisone metabolites. As known, tolperisone is a widely used muscle relaxant. The D-enantiomer is mainly responsible for the muscle relaxing effect, while L-tolperisone has bronchodilatory and peripheral vasodilatory activity.[1] Following the metabolic pathway described by Japanese researchers[2] we aimed to produce all of the major human metabolites on preparative scale for pharmacological purposes. Following on from the synthesis of 3′-hydroxy-4′-methylphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-one, **M1**[3] and 1-(4′-hydroxymethylphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-one **M2**[4] the preparation of racemic and optically active 1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-one **M3**, *erythro*-1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-ol **M4** and *threo*-1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-ol **M5** is presented herein.

2. Results and discussion

It was assumed that racemic **M3** could be synthesized from 4-propionyl-benzoic acid via the Mannich reaction. However, known methods for producing 4-propionylbenzoic acid **2** are complicated reactions, often with low yield.[5] We obtained the acid **2** in a workable yield from (4′-hydroxymethylphenyl)propan-1-one[4] by $KMnO_4$ oxidation of the benzyl alcohol **1** (Fig. 1).

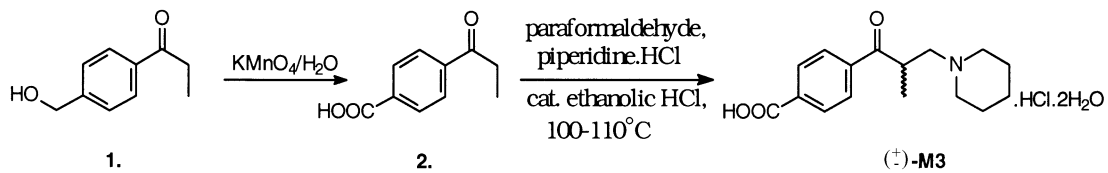

Figure 1. Preparation of (±)-**M3**.

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Normal Mannich reaction (ethanol/paraformaldehyde or water/formaldehyde systems) failed to yield **M3**, but the previously reported solvent-free method[3,4] proved to be efficient: thus, compound **2** was heated with paraformaldehyde and a catalytic amount of ethanolic hydrogen chloride without solvent, and (±)-**M3** was produced in a few hours (Fig. 1).

The carbonyl group of **M3** can be reduced with sodium borohydride (Fig. 2). As 1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-ol (**M4** and **M5**) has two asymmetric centers, the reaction mixture will contain all of the four possible stereoisomers: the (1*S*,2*R*)- and (1*R*,2*S*)-isomers are of *erythro*-configuration, while the (1*S*,2*S*)- and (1*R*,2*R*)-isomers are of *threo*-configuration (**M4** and **M5**, respectively). The **M4**/**M5** ratio is about 65:35, as determined by HPLC (see Section 3). **M4** and **M5** can be separated by fractional crystallization and preparative HPLC.

Attempts at the resolution of **M3** using several resolving agents failed. To eliminate difficulties due to the amphotherism of the molecule, the **M3** ethyl ester was also subjected to resolution experiments, but these were also unsuccessful. Finally, (*S*)-**M3** and (*R*)-**M3** were synthesized from the corresponding enantiomers of the previous metabolite **M2** by oxidation (for the (*S*)-enantiomer see Fig. 3; (*R*)-**M3** was obtained from (*R*)-**M2** the same way).

As reduction of **M3** with sodium borohydride resulted in almost complete racemization, another method was sought. We found that catalytic hydrogenation did not affect the enantiomeric purity. Hydrogenation of (*S*)- and (*R*)-**M3** resulted in an 80:20 mixture of **M4** and **M5** (For (1*S*,2*S*)-**M5** and (1*R*,2*S*)-**M4** see Fig. 4) (*R*)-**M3** yields (1*S*,2*R*)-**M4**) and (1*R*,2*R*)-**M5**. As in this case the starting **M3** was homochiral, the reaction mixture contained only two stereoisomers from the four possible. As the two products have a diastereoisomeric relationship (*erythro*- and *threo*-), they should be separated without further chiral effect. In fact, **M4** could be obtained in an enantiopure form by fractional crystallization from methanol, but we could obtain pure **M5** only by chromatographic separation.

2.1. Absolute configurations

The configuration of **M2** has already been established[4] and as the oxidation (**M2** to **M3**) does not influence the stereogenic center, the configuration of **M3** can be deduced. As for **M4** and **M5**, when starting from homochiral **M3**, the absolute configuration at the 2-position remains the same and the two stereoisomers

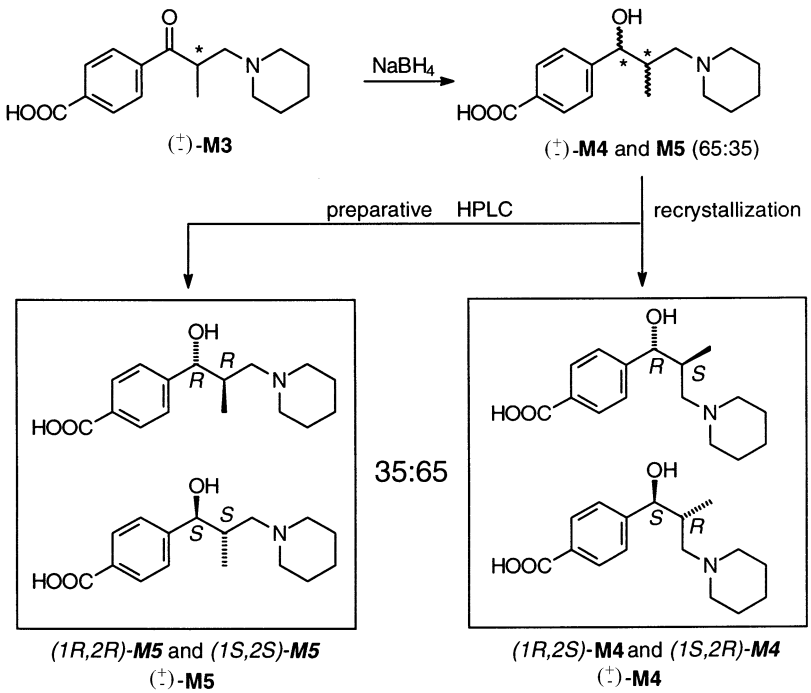

Figure 2. Synthesis of racemic 1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-ol (±)-**M4** and (±)-**M5**.

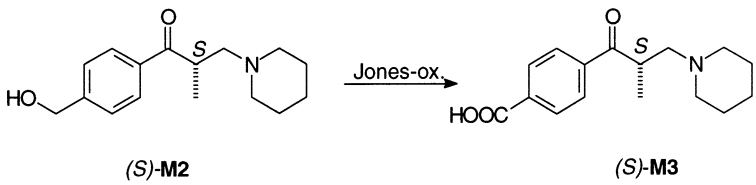

Figure 3. Synthesis of (*S*)-**M3**.

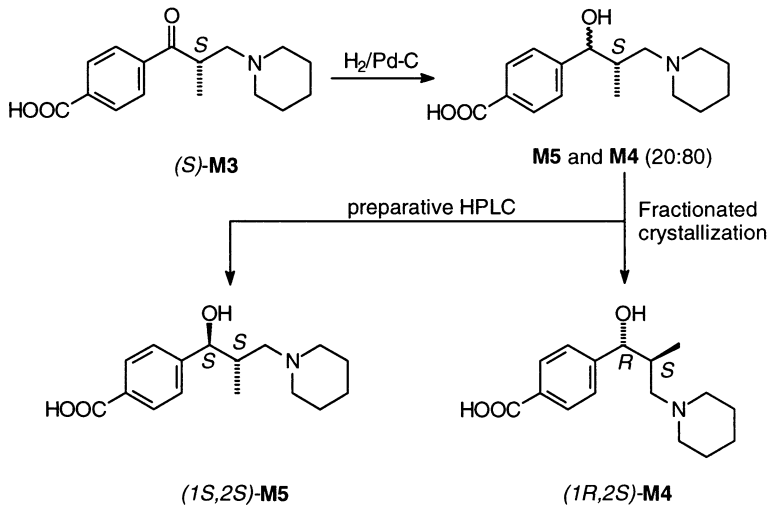

Figure 4. Synthesis of enantiopure **M4** and **M5**.

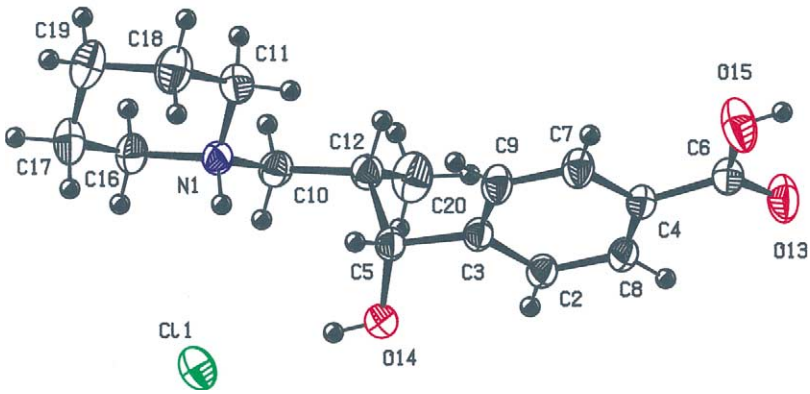

Figure 5. X-Ray structure model of (+)-(1*R*,2*S*)-**M4** hydrochloride.

are formed around C(1). The *erythro* and *threo* relationships were determined by the ^{1}H NMR coupling constants (see Section 3), allowing us to assign the absolute configuration, which was confirmed by single crystal X-ray crystallography of (+)-**M4** (Fig. 5).

The crystal structure of (+)-(1*R*,2*S*)-**M4** hydrochloride has been determined by single crystal X-ray diffraction. Its absolute configuration has been established based on the absolute structure parameter of 0.00(3).[6] Fig. 5[7] shows the configuration and the conformation (1*R*,2*S*)-**M4** cation adopts in the crystal lattice. Two cations related by a two-fold screw axis are hydrogen bond donors to the same chloride ion. The same two cations are hydrogen bonded with an N–H···O(=C) hydrogen bond as well, giving rise to a 12-membered ring motif with three donor and two acceptor atoms ($R_3^2(12)$). The cation chains run parallel to the **b** axis and are linked by weaker C–H···O hydrogen bonds.

3. Experimental

3.1. Materials and methods

^{1}H NMR spectra were recorded at 250 MHz on a Bruker WM250 spectrometer as well as on a Varian $^{\text{UNITY}}$*INOVA* spectrometer at 300 and 500 MHz. Chemical shifts are given relative to $\delta_{\text{TMS}}=0.00$ ppm. Chemical shift values are expressed in ppm values on the δ scale. IR spectra of KBr samples were taken on a Perkin–Elmer 1600 Series FT-IR spectrophotometer. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. Chemicals were purchased from Aldrich Chemical Company. All solvents used were freshly distilled.

Analytical HPLC conditions for **M4**/**M5** ratios were as follows: column: Macherey–Nagel nucleosil 100–5 C18 5 μm 125×4 mm; eluent: acetonitrile:McIlvain buffer 38:62, containing 0.01 M sodium lauryl sulfate (McIlvain buffer: 98 mL of 0.1 M citric acid, 2 mL of 0.2 M Na_2HPO_4, 900 mL of HPLC grade water, pH adjusted to 2.2 by H_3PO_4); flow rate 0.5 mL/min; detector: UV, $\lambda 1=254$ nm and $\lambda 2=235$ nm; injected volume: 20 μL; temperature: rt.

The enantiomeric purity of **M2** was determined by ^{1}H NMR using (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol as described in our previous paper.[4] For assessing the enantiomeric purity of **M4** and **M5** we developed the following NMR method.

Racemic **M4** (1 mg) and β-cyclodextrin (7 mg) were dissolved in D_2O (1 mL) and the pH was adjusted to pH 13.1 by adding NaOD (30 μL of 40 m/m%) to the solution. In the presence of β-cyclodextrin, applied as a chiral additive, the aromatic protons and the methyl group of the respective enantiomers showed distinct sets of signals in the ^{1}H NMR spectrum. From a quantitative analysis point of view the aromatic doublets resonating at 7.35 ppm [(1*R*,2*S*)-(+)-**M4**] and 7.39 ppm [(1*S*,2*R*)-(−)-**M4**] proved to be the most feasible as they exhibited the largest enantiomeric separation ($\Delta\delta_{(1S,2R)\text{-}(1R,2S)}=26.6$ Hz at 500 MHz). In the case of optically pure **M4** samples only one signal set corresponding to the respective enantiomer could be detected. Based on the NMR results, (1*R*,2*S*)-(+)-**M4** and (1*S*,2*R*)-(−)-**M4** are assumed to be enantiopure (e.e. >99%).

The enantiomeric purity of **M5** was assessed from a mixture of **M4** and **M5** using the β-cyclodextrin method as described above. However, due to a substantial signal overlap of the aromatic protons of **M4**/**M5**, the enantiomeric purity of **M5** was determined using the CH–CH_3 methyl signal resonating at 0.62 ppm [(1*S*,2*S*)-(−)-**M5**] and 0.66 ppm [(1*R*,2*R*)-(+)-**M5**] ($\Delta\delta_{(1R,2R)\text{-}(1S,2S)}=18.6$ Hz at 500 MHz). Note that the methyl signals of **M4** appear at 0.82 ppm [(1*R*,2*S*)-(+)-**M4**] and 0.85 ppm [(1*S*,2*R*)-(−)-**M4**], respectively. The observed separation ($\Delta\delta_{(1S,2R)\text{-}(1R,2S)}=11.4$ Hz at 500 MHz) is still sufficient for the e.e. measurement of **M4** in the **M4**/**M5** mixture. In the ^{1}H NMR spectrum of the **M4**/**M5** mixture, only one methyl signal corresponding to a single enantiomer was observed for both **M4** and **M5** when the reaction was carried out from enantiomerically pure **M3**. Therefore **M5** is assumed to be enantiomerically pure (e.e. >99%)

Due to the fact that at basic pH **M3** underwent rapid racemization, the developed β-cyclodextrin method could not be applied for assessing the enantiomeric purity of **M3**. At neutral pH the observed slight enantiomeric separation of the signals was insufficient for quantitative e.e. determination. However, since the reaction mixture of **M4**/**M5** was neither recrystallized nor treated in other ways that would affect e.e., the enantiomeric purity of **M3** follows indirectly from the results obtained in the **M4**/**M5** mixture.

3.2. 4-Carboxypropiophenone 2

To a suspension of (4′-hydroxymethyl-phenyl)-propiophenone (**1**, 4.1 g, 0.025 mol) in water (20 mL) containing phase-transfer catalyst TEBA (0.1 g), was added $KMnO_4$ (4.0 g, 0.025 mol) slowly at 10–15°C. After the color of $KMnO_4$ disappeared, the MnO_2 precipitate was filtered off. The filtrate was acidified with cc. HCl to pH 3. During this addition white crystals precipitated. The mixture was filtered, and the filter cake washed with water and dried to afford 4-carboxypropiophenone **2** (3.29 g, 18.5 mmol, 74%), mp: 153–154°C (lit.:[8] 157–158°C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23 (t, 3H, CH_3, $^3J=7.3$ Hz), 3.03 (q, 2H, CH_2, $^3J=7.3$ Hz), 8.05 (d, 2H, Ar-H, $^3J=7.7$ Hz), 8.19 (d, 2H, Ar-H, $^3J=8.2$ Hz); FT-IR (KBr, cm^{-1}): 3430, 3069, 2979, 2940, 2674, 2553, 1686, 1570, 1504, 1427, 1413, 1321, 1294, 1127, 1114, 954, 760. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66; found C, 67.36; H, 5.68%.

3.3. Racemic 1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-one (±)-M3

To a mixture of 4-carboxypropiophenone **2** (8.0 g, 0.045 mol), piperidine hydrochloride (8.8 g, 0.072 mol) and paraformaldehyde (2.7 g), was added ethanolic hydrogen chloride (1.5 mL). The mixture was stirred at 100–110°C for 2.5 h. After cooling, ethyl acetate (20 mL) was added to the solid mass. The resulting crystals were filtered, washed with acetone, dried and recrystallized from hot water: white crystalline 1-(4′-carboxyphenyl) - 2 - methyl - 3 - (piperidine - 1 - yl)propan - 1-one·HCl·$2H_2O$ (**M3**·HCl·$2H_2O$, 6.76 g, 19.4 mmol, 43%), mp: 166–168°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.20 (d, 3H, CH_3, 7.3 Hz), 1.30–2.00 (br, 6H, piperidine-CH_2), 3.13 (dd, 1H, H_x-CH_2, $^2J=13.2$ Hz and $^3J=4.2$ Hz), 3.60 (dd, 1H, H_y-CH_2, $^2J=13.2$ Hz and $^3J=7.3$ Hz), 2.70–3.70 (br, 4H, piperidine-CH_2+ exchangeable protons), 4.26–4.41 (m, 1H, CH), 8.06–8.21 (m, 4H, Ar-H), 10.4 (br s, 1H, exchangeable proton); FT-IR (KBr, cm^{-1}): 3401, 3180, 1941, 2754, 1679, 1571, 1410, 1276, 1081, 967, 719, 549. Calcd for $C_{16}H_{26}ClNO_5$: C, 55.25; H, 7.53, N, 4.03; found C, 55.32; H, 7.93; N, 4.02%.

3.4. Racemic *erythro*-1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-ol (±)-M4

To a solution of racemic 1-(4′-carboxyphenyl)-2-methyl - 3 - (piperidine - 1 - yl)propan - 1 - one·HCl·$2H_2O$ (**M3**·HCl·$2H_2O$, 10.0 g, 28.75 mmol) in methanol (50 mL) was added NaOH solution (2.3 g, 57 mmol in 5 mL of water). The resulting crystalline suspension was treated by slow addition of sodium borohydride (1.2 g, 31.7 mmol). The clear solution was stirred for 10 min at room temperature and then stirred under reflux for 5 min. After cooling, aqueous 37% HCl solution (14 mL) was added and the solvent was evaporated in vacuo. After adding methanol (50 mL) and bringing the mixture to boil, inorganic impurities were removed by filtration. To the solution diethyl ether (100 mL) was added and the crystals were filtered to give a mixture of **M4** and **M5** (ca. 65:35) as a white crystalline solid (5.75 g), which was recrystallized from methanol (11.5 mL) to yield *erythro*-1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-ol·HCl (**M4**·HCl, 2.62 g, 8.35 mmol, 29%), mp: 236–238°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.70 (d, 3H, CH_3, $^3J=6.8$ Hz), 1.30–2.10 (br m, 6H, piperidine-CH_2), 2.30–2.41 (m, 1H, CH), 2.80–3.05 (m, 2H, piperidine-CH_2), 2.89 (dd, 1H, H_x-CH_2, $^2J=13.0$ Hz and $^3J=6.0$ Hz), 3.23 (dd, 1H, H_y-CH_2, $^2J=13.0$ Hz and $^3J=7.0$ Hz), 3.30–3.60 (br, 2H, piperidine-CH_2), 5.07 (d, 1H, CH, $^3J=2.7$ Hz), 5.69 (br s, 1H, OH), 7.56 (d, 2H, Ar-H, $^3J=8.5$ Hz), 7.92 (d, 2H, Ar-H, $^3J=8.5$ Hz), 10.42 (br s, 1H, exchangeable proton), 12.80 (br s, 1H, exchangeable proton); FT-IR (KBr, cm^{-1}): 3441, 3100–2400, 1704, 1611, 1476, 1397, 1237, 1100, 1053, 961, 880, 841, 748, 675, 559. Calcd for $C_{16}H_{24}ClNO_3$: C, 61.24; H, 7.71; N, 4.46; found C, 61.35; H, 7.73; N, 4.47%.

3.5. (*S*)-1-(4′-Carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-one (*S*)-M3

(*S*)-1-(4′-Hydroxymethylphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-one (**M2**, 4.7 g, 18.0 mmol, $[\alpha]_D^{25}=+28.8$ [$c=1$, methanol]) was suspended in acetone (47 mL) and modified Jones' reagent[†] (7 mL) was added dropwise. The mixture was stirred at 40–45°C for 0.5 h, then further Jones reagent (2.4 mL) was added. After an additional stirring of 20 min, more Jones reagent (1.3 mL) was added and the mixture was stirred for a further 10 min. The solvent was decanted from the thick, green, slurry and the solid was washed with acetone (2×5 mL). To the supernatant liquid, diethyl ether (75 mL) and isopropanolic hydrogen chloride (4 mL, 17 g HCl/100 mL) was added. The crystallizing mixture was allowed to stand at room temperature for 1 h then at −78°C for a further hour. The crystals were collected by filtration, washed with acetone:water (1:1) and then washed with acetone and dried to afford (*S*)-1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-one·HCl·H_2O (*S*)-HCl·H_2O, (3.57 g, 10.8 mmol, 60%), $[\alpha]_D^{25}=+42.8$ ($c=1$, methanol), mp: 120–123°C. NMR, IR and EA data were identical within experimental error to those of the racemate.

3.6. (*R*)-1-(4′-Carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-one (*R*)-M3

Starting from (*R*)-1-(4′-hydroxymethylphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-one **M2** (2.5 g, 9.57 mmol), $[\alpha]_D^{25}=-28.1$ ($c=1$, methanol), proceeding as described above, (*R*)-1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-one·HCl·H_2O (*R*)-HCl·H_2O, 1.64 g, 4.97 mmol, 52%), $[\alpha]_D^{25}=-43.3°$ ($c=1$, methanol), mp: 120–123°C was obtained. NMR, IR and EA data were identical within experimental error to those of the racemate.

3.7. (1*R*,2*S*)-1-(4′-Carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-ol (1*R*,2*S*)-M4

To a solution of (*S*)-1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-one·HCl·H_2O (*S*)-**M3**·HCl·H_2O, 7.0 g, 21.22 mmol, $[\alpha]_D^{25}=+42.8$ ($c=1$, methanol) 10% Pd–C catalyst (SQ-6,[9] 0.7 g) and the mixture was hydrogenated for 45 min at room temperature and atmospheric pressure. Hydrogen uptake was 465 cm^3. After filtering off the catalyst and removing the methanol 6.77 g of an amorphous foam was obtained: about 80:20 mixture of **M4** and **M5**. It was recrystallized twice from methanol (7 and 4 mL, respectively) to yield a white crystalline solid of (1*R*,2*S*)-1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)-propan-1-ol·HCl (1*R*,2*S*)-**M4**·HCl, 2.12 g, 6.76 mmol, 32%), $[\alpha]_D^{25}=+16.2$ ($c=1$, methanol), mp: 218–221°C. NMR, IR and EA data were identical within experimental error to those of the racemate.

[†] Modified Jones' reagent: CrO_3 (6.75 g) and 96% H_2SO_4 (5.75 mL) made up with distilled water to a total volume of 25.0 mL.

3.8. (1*S*,2*R*)-1-(4′-Carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-ol (1*S*,2*R*)-M4

Starting from (*R*)-1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-one·HCl·H_2O (*R*)-HCl·H_2O (5.56 g, 16.86 mmol), $[\alpha]_D^{25}=-43.2$ ($c=1$, methanol), and proceeding as described above, crystalline (1*S*,2*R*)-1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-ol·HCl (1*S*,2*R*)-**M4**·HCl, 1.88 g, 5.99 mmol, 36%), $[\alpha]_D^{25}=-16.2$ ($c=1$, methanol), mp: 218–221°C was obtained. NMR, IR and EA data were identical within experimental error to those of the racemate.

3.9. Threo-1-(4′-carboxyphenyl)-2-methyl-3-(piperidine-1-yl)propan-1-ol M5: racemic and optically active

M5 can be obtained by preparative HPLC from the mother liquor of the recrystallization of the **M4**–**M5** mixtures. Preparative HPLC conditions were as follows: Column: Waters Preppack Cartridge C18 125 Å 55–105 μm, 300×47 mm (WAT 025876); eluent: methanol:water 15:85 and 0.5 mL 37% aqueous HCl solution added to each litre of eluent; detector: UV, $\lambda=254$ nm; flow rate: 40 mL/min; sample preparation: dissolving in eluent (1–2 g of sample, dissolved in 100 mL); three subsequent separation steps were carried out to result in a final purity of ≥95%.

(±)-**M5** mp: 233–236°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.87 (d, 3H, CH_3, $^3J=6.8$ Hz), 1.30–2.05 (br m, 6H, piperidine-CH_2), 2.25–2.33 (m, 1H, CH), 2.67–3.00 (br m, 2H, piperidine-CH_2), 2.92 (dd, 1H, H_x-CH_2, $^2J=13.2$ Hz and $^3J=7.7$ Hz), 3.18 (dd, 1H, H_y-CH_2, $^2J=13.2$ Hz and $^3J=4.4$ Hz), 3.21–3.50 (br m, 2H, piperidine-CH_2), 4.46 (d, 1H, CH, $^3J=7.5$ Hz), 5.97 (br s, 1H, OH), 7.50 (d, 2H, Ar-H, $^3J=8.5$ Hz), 7.92 (d, 2H, Ar-H, $^3J=8.5$ Hz), 9.99 (br s, 1H, exchangeable proton), 12.87 (br s, 1H, exchangeable proton); FT-IR (KBr, cm^{-1}): 3700–2200, 2952, 1710, 1612, 1578, 1458, 1421, 1108, 1016, 972, 778, 708, 655. Anal. calcd for $C_{16}H_{24}ClNO_3$: C, 61.24; H, 7.71; N, 4.46. Found C, 61.14; H, 7.70; N, 4.47%.

(1*R*,2*R*)-**M5**: Oily amorphous solid, $[\alpha]_D^{25}=+24.6$ ($c=1$, methanol); NMR, IR and EA data were identical within experimental error to those of the racemate.

(1*S*,2*S*)-**M5**: Oily amorphous solid, $[\alpha]_D^{25}=-24.4$ ($c=1$, methanol); NMR, IR and EA data were identical within experimental error to those of the racemate.

3.10. X-Ray crystallography

(+)-**M4** (50 mg) was dissolved in warm methanol (0.2 mL) and acetone (2 mL) was added. After seeding and standing for 48 h suitable crystals formed. A crystal of (+)-(1*R*,2*S*)-**M4** hydrochloride was mounted on a glass fiber. Cell parameters were determined by least-squares of the setting angles of 25 ($19.07\leq\theta\leq19.93°$) reflections.

Crystal data, experimental and refinement details. Empirical formula: $C_{16}H_{24}ClNO_3$, formula weight: 313.81, colorless, block crystals, size: 0.55×0.45×0.40 mm, crystal system: monoclinic, space group $P2_1$, unit cell dimensions: $a=7.201(1)$, $b=14.958(1)$, $c=7.792(1)$ Å, $\beta=90.43(1)°$, $V=839.27(17)$ Å^3, $T=295(2)$ K, $Z=2$, $F(000)=336$, $D_x=1.242$ Mg/m^3, $\mu=0.237$ mm^{-1}.

Intensity data were collected on a Enraf–Nonius CAD4 diffractometer (graphite monochromator; Mo Kα radiation, $\lambda=0.710730$ Å) at 295(2) K in the range $2.72\leq\theta\leq34.95°$ using $\omega/2\theta$ scans. Backgrounds were measured one half the total time of the peak scans. The intensities of three standard reflections were monitored regularly (every 60 min). The intensities of the standard reflections indicated a crystal decay of 4% (the data were corrected for decay).

A total of 7876 reflections were collected of which 6915 were unique [$R_{(int)}=0.0092$, $R(\sigma)=0.0127$]; intensities of 6140 reflections were greater than 2σ (I). Completeness to $\theta=0.938$.

A psi-scan absorption correction was applied to the data (the minimum and maximum transmission factors were 0.489 and 1.00).

The initial structure model was obtained by direct methods.[10]

Anisotropic full-matrix least-squares refinement[11] on F^2 for all non-hydrogen atoms yielded $R_1=0.0305$ and $wR_2=0.0805$ for 6140 [$I>2\sigma(I)$] and $R_1=0.0369$ and $wR_2=0.0832$ for all (6915) intensity data, (number of parameters = 194, goodness-of-fit = 1.023, absolute structure parameter $x=0.00(3)$, the maximum and mean shift/esd is 0.007 and 0.001).

The maximum and minimum residual electron density in the final difference map was 0.362 and −0.182 e Å^{-3}. (The applied weighting scheme was $w=1/[\sigma^2(F_o^2)+(0.0630P)^2+0.0000P]$ where $P=(F_o^2+2F_c^2)/3$.)

Hydrogen atomic positions were calculated from assumed geometries except those of the OH group and salt proton, which were located in difference maps. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the U(eq) value of the atom they were bonded to.

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