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Application of cyclic sulfates in the synthesis of enantiomers of 1-[3-(4-aryl-piperazin-1-yl)-2-hydroxy-propyl]-pyrrolidin-2-one

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ABSTRACT

The synthesis of enantiomers of 1-[3-(4-aryl-piperazin-1-yl)-2-hydroxy-propyl]-pyrrolidin-2-one derivatives is described. These enantiomers were synthesized starting from (*R*)- or (*S*)-1-chloro-2,3-dihydroxypropane using relevant cyclic sulfates as chiral intermediates. The enantiomeric purities of the final compounds were in the range of 99.3–100.0%, as determined by high performance liquid chromatography. The final compounds were found to display moderate potency as ligands for α_1-adrenoreceptors.

1. Introduction

Chiral aminoalcohols and their derivatives are widely used in pharmaceuticals, for example, as adrenomimetics or β-adrenoreceptor antagonists, and as chiral auxiliaries in asymmetric synthesis. They can be obtained in several ways,[1] either by the reduction of homochiral amino acids whose products are restricted to chiral secondary amines with a primary hydroxyl group, or by the stereospecific reduction of nitrogen functionalized ketones employing either a chemical route, using a chiral auxiliary, or an enzymatic process, with baker's yeast methods.[2]

The main industrial process leading to aminoalcohols **I** consists of the preparation of a methyloxirane derivative (**II**) followed by its opening by the relevant amine (Fig. 1). It is a simple and economic process when the target product is a racemic mixture, but this method loses its advantages in the synthesis of pure enantiomers. Firstly, enantiopure 2-chloromethyl-oxirane is a compound that is neither inexpensive nor easy to be obtained. Secondly, the reaction of C^1-activated 2,3-epoxypropanes with nucleophiles can proceed by two pathways. Instead of the normal attack on the C^1 carbon atom, the nucleophile can also attack the C^3 carbon atom (Fig. 2). Due to these different substitution pathways, partial racemization of the product is observed.[3–5] Thirdly, the reaction of nucleophiles with 1-chloro-2,3-epoxypropane could also lead to disubstituted products (Fig. 3).[6]

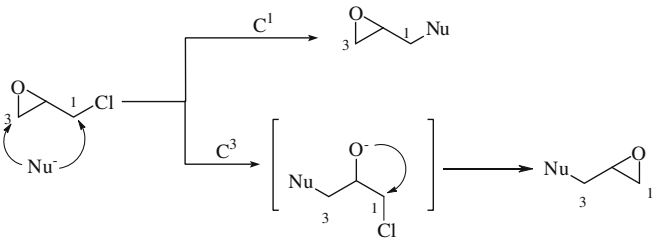

Figure 2. Mechanism of reaction 1-chloromethyl-oxirane with nucleophiles.

In order to limit the amount of product obtained by the nucleophilic attack on the C^3 carbon atom of 1-chloro-2,3-epoxypropane, the substitution of the chlorine atom in this molecule by tosylate, triflate, or *m*-nitrobenzenosulfonate groups has been carried out.[3,4] The enantiomeric purity of the products synthesized varied, although generally it was higher than when 1-chloro-2,3-epoxypropane was used. However, the high price of the reagents limits the application of these approaches.

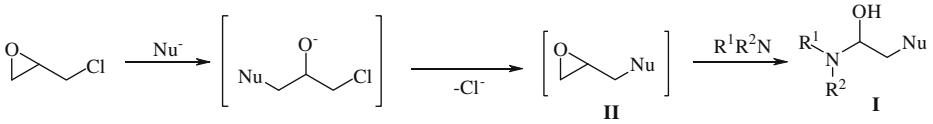

Figure 1. Synthesis of racemic mixture of aminoalcohols.

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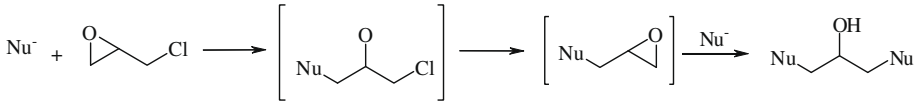


Figure 3. Synthesis of double substituted side product.

This study is part of a project aimed at finding new 1-[3-(4-aryl-piperazin-1-yl)-2-hydroxy-propyl]-pyrrolidin-2-one derivatives to function as α-adrenoreceptor antagonists with antiarrhythmic and hypotensive activity.[7,8]

Previously, we have reported that the enantiomers of 1-[3-(4-phenyl-piperazin-1-yl)-2-hydroxy-propyl]-pyrrolidyn-2-one and 1-{2-hydroxy-[4-(2-hydroxy-phenyl)-piperazin-1-yl]-propyl}-pyrrolidin-2-one could be obtained by two synthetic pathways, via either asymmetric hydrolytic kinetic resolution using water soluble[9] or immobilized Jacobsen salen Co(III)OAc catalyst,[10] which gave high enantiomeric purity (about 95%).

Herein, we report the synthesis of the enantiomers of 1-[3-(4-aryl-piperazin-1-yl)-2-hydroxy-propyl]-pyrrolidyn-2-one derivatives using cyclic sulfates.

2. Results and discussion

Cyclic sulfates are at least as reactive as epoxides, if not more so, toward various nucleophiles.[11–16] Their reactivity is the result of their ring strain which may be due to angle strain, the partial double bond character between the ring oxygen and sulfur atom due to 2p(O)–3d(S) orbital interaction, and the 1,3 non-bonding interactions between the ring oxygen and the exocyclic oxygen atoms. The X-ray analysis of parent ethylene sulfate indicated that this molecule exists in a puckered conformation, with an angle 20.6° between the C4 and C5 bond and a O–S–O bond angle of 98.4° which is substantially smaller than the strained tetrahedral angle of 109.5°.[17] In addition, application of cyclic sulfate in the synthesis produced only the single substituted products (Fig. 4).[6,18]

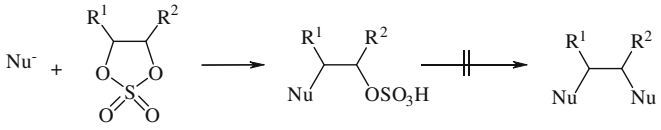
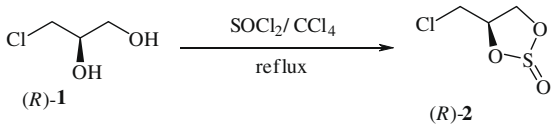


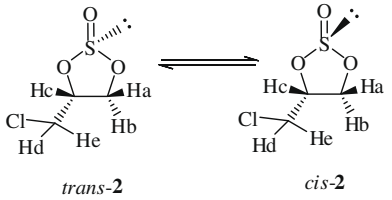
Figure 4. Reaction of nucleophile with cyclic sulfates.

As a starting material for the synthesis of the enantiomers of the title compounds, (*R*)-1-chloro-2,3-dihydroxypropane (*R*)-**1** was used; its reaction with an equimolar quantity of thionyl chloride afforded a cyclic sulfite (*R*)-**2** in 96% yield (Scheme 1). According to the ^{1}H nuclear magnetic resonance (NMR) spectra and literature data, compounds (*R*)-**2** are a mixture of *cis*- and *trans*-isomers (2:3) (Table 1).[19]



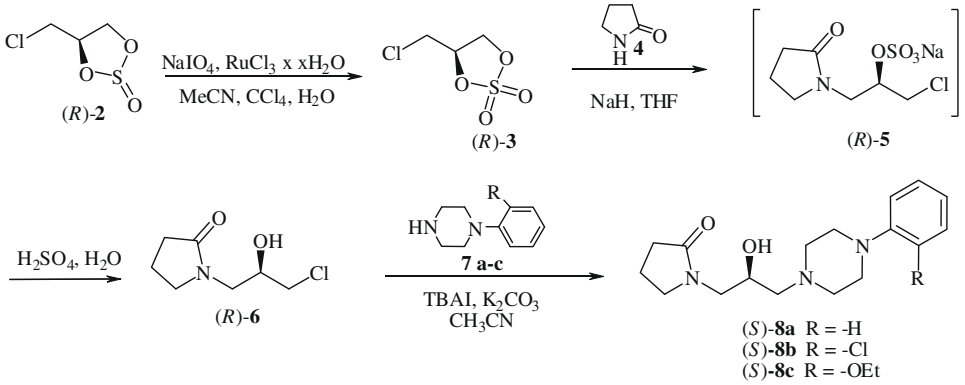
Scheme 1. Synthesis of (*R*)-4-chloromethyl-[1,3,2]dioxathiolane 2-oxide (*R*)-**2**.

Table 1
^{1}H NMR data for *cis*- and *trans*-isomers of compound (*R*)-**2**



Config.	Ha (dd)	Hb (dd)	Hc (m)	Hd (dd)	He (dd)
cis	4.80 J_{ab} = 8.7 Hz, J_{ac} = 7.5 Hz	4.77 J_{ab} = 8.7 Hz, J_{bc} = 6.4 Hz	4.71–4.75	3.90 J_{cd} = 4.8 Hz, J_{de} = 11.2 Hz	3.77 J_{ce} = 4.5 Hz, J_{de} = 11.2 Hz
trans	4.62 J_{ab} = 9.0 Hz, J_{ac} = 5.6 Hz	4.44 J_{ab} = 9.0 Hz, J_{bc} = 6.4 Hz	5.08–5.16	3.65 J_{cd} = 4.4 Hz, J_{de} = 11.6 Hz	3.53 J_{ce} = 4.6 Hz, J_{de} = 11.6 Hz

Cyclic sulfite (*R*)-**2** was then oxidized further using $NaIO_4$ and a catalytic amount of ruthenium trichloride to furnish the corresponding cyclic sulfate (*R*)-**3** in 80% yield. The ring opening of cyclic sulfate (*R*)-**3** with pyrrolidin-2-one **4** was performed in tetrahydrofuran (THF) using NaH as base. The obtained 2-sulfate ester (*R*)-**5** (not isolated) was subsequently hydrolyzed to the 2-hydroxy compound (*R*)-**6** by treatment with concentrated sulfuric acid and water, at a 60% yield. Finally, the alcohol (*R*)-**6** with relevant substi-



Scheme 2. Synthesis of (*S*)-1-[3-(4-aryl-piperazin-1-yl)-2-hydroxypropyl]-pyrrolidin-2-one derivatives (*S*)-**8a–c**.

tuted *N*-aryl-piperazines **7a–c** in the reaction of phased transfer catalysis catalyzed by tetrabutylammonium iodide (TBAI) and carried out in a mixture of acetonitrile/K_2CO_3 gave enantiomers of 1-[3-(4-aryl-piperazin-1-yl)-2-hydroxy-propyl]-pyrrolidyn-2-one (*S*)-**8a–c** in 80–85% yield (Scheme 2). The (*R*)-enantiomers of 1-[3-(4-aryl-piperazin-1-yl)-2-hydroxy-propyl]-pyrrolidyn-2-one (*R*)-**8a–c** were obtained analogously using (*S*)-1-chloro-2,3-dihydroxypropane as the starting material.

The enantiomeric excess (ee) % of the final enantiomers **8a–c** was determined by high performance liquid chromatography (HPLC) using Chiralpak IA (enantiomer **8a**) or Chiralcel OD (enantiomers **8b** and **8c**) columns and a mixture of *n*-hexane/ethanol (85:15) as the mobile phase. It was shown that all the synthesized enantiomers **8a–c** were characterized by an ee % of over 99% (Table 2).

Table 2
Retention times and ee % of enantiomers of compounds **8a–c**

Compound	Retention time (min)	ee %
(*R*)-**8a**	28.4	99.6
(*S*)-**8a**	56.7	99.8
(*R*)-**8b**	34.5	99.6
(*S*)-**8b**	26.3	99.0
(*R*)-**8c**	23.3	100.0
(*S*)-**8c**	25.2	99.3

Enantiomers **8a–c** were evaluated for their in vitro activity on the α_1-adrenoreceptor by a radioreceptor assay.[20,21] The binding affinities were determined on rat cerebral cortex with [^{3}H]prazosin as a specific ligand. As depicted in Table 3, the (*S*)-enantiomers of compounds **8a–c** appeared to be more potent for α_1AR than their racemic mixtures or (*R*)-enantiomers. Moreover, the potencies of enantiomers **8a–c** were only weakly influenced by their stereochemistry.

Table 3
Affinity of compounds **8a–c** toward different α_1-AR subtypes in rat cerebral cortex

Compound	pK_i α_1
rac-**8a**	5.72
(*S*)-**8a**	6.27
(*R*)-**8a**	5.88
rac-**8b**	6.57
(*S*)-**8b**	6.64
(*R*)-**8b**	5.60
rac-**8c**	6.15
(*S*)-**8c**	6.29
(*R*)-**8c**	5.82

Inhibition constants (K_i) were calculated according to the equation of Cheng and Prusoff.[21]

3. Conclusion

In conclusion, the enantiomers of compounds **8a–c** were synthesized by using cyclic sulfates. The above described method could be used in the synthesis of analogues of compounds **8** and other 2-hydroxy-amino-propyl derivatives. The final compounds **8a–c** were found to be ligands for α_1-adrenoreceptor, but their potencies were only weakly influenced by their configuration.

4. Experimental

4.1. General methods

Unless otherwise noted, the starting materials were obtained from commercial suppliers and used without further purification. All experiments were carried out in oven-dried glassware under a dry nitrogen atmosphere. Standard vacuum techniques were used for handling air-sensitive materials. Tetrahydrofuran (THF) was dried, kept under nitrogen, and freshly distilled over sodium/benzophenone before use. Uncorrected melting points were determined in an open capillary on a Büchi 535 melting point apparatus (Flawil, Switzerland). Elemental analyses (C, H, and N) were carried out on Elementar Vario EL III (Elementar Analysensystem, Hanau, Germany), giving values within 0.4% of the theoretical values. ^{1}H NMR and ^{13}C-spectra were recorded on a Varian Mercury VX 300 MHz (Hansen Way, USA) instrument in DMSO-d_6 or $CDCl_3$ at ambient temperature using the solvent signal as an internal standard. Thin layer chromatography was carried out on Merck silica gel pre-coated F_{254} plates (0.2 mm) (Darmstadt, Germany) using chloroform/acetone (1:1), ethyl acetate and dichloromethane/methanol (9:1), as developing systems. The plates were visualized with ultraviolet (UV) light (λ = 254 nm) or a mixture of 5% $(NH_4)_xMo_7O_{24}$ and 0.2% $Ce(SO_4)_2$ in 5% H_2SO_4. Column chromatography was performed using a Merck Kieselgel 60 (0.063–0.200 mm) and the following solvents: chloroform/acetone (1:1), ethyl acetate, and dichloromethane/methanol (9:1). Optical rotations were determined at the sodium D line with a DIP 1000 Jusco polarimeter (Essex, UK). HPLC analyses were performed using a Waters (Vienna, Austria) pump Model 590, UV–vis detector Model 490, a 5 μl loop Rheodyne type injector and the following columns: Chiralpak IA—amylose tris (3,5-dimethylphenylcarbamate) immobilized on 5 μm silica gel and Chiralcel OD—cellulose tris (3,5-dimethylphenylcarbamate) coated on 10 μm silica gel (all columns 25 cm × 0.46 cm I.D. Daicel) (Chiral Technologies Europe, Illkirch, France). Samples of compounds were dissolved in EtOH, the concentration of the sample being about 1 mg/ml. The mobile phase was *n*-hexane/EtOH (85/15, v/v).

4.1.1. (*R*)- or (*S*)-4-Chloromethyl-[1,3,2]dioxathiolane 2-oxide (*R*)-2 or (*S*)-2

An equimolar amount of thionyl chloride was added dropwise via syringe to the 1 M suspension of 3-chloro-1,2-dihydroxypropane (*R*)-**1** or (*S*)-**1** in CCl_4 and the resulting mixture was refluxed for 2 h. Then the solvent was evaporated and the resulting oil was purified by column chromatography using ethyl acetate as solvent.

(*R*)-3-Chloro-1,2-dihydroxypropane (*R*)-**1** gave 15.1 g of (*R*)-4-chloromethyl-[1,3,2]dioxathiolane 2-oxide (*R*)-**2** (yield 95%). Anal. Calcd for $C_3H_5O_3SCl$: C, 23.01; H, 3.22; S, 20.48. Found: C, 22.78; H, 3.06; S, 20.45. R_f (EtOAc) 0.77; $[\alpha]_D^{20} = -44.65$ (*c* 1, CH_2Cl_2).

(*S*)-3-Chloro-1,2-dihydroxypropane (*S*)-**1** gave 6.9 g of (*S*)-4-chloromethyl-[1,3,2]dioxathiolane 2-oxide ((*S*)-**2**) (yield 89%). Anal. Calcd for $C_3H_5O_3SCl$: C, 23.01; H, 3.22; S, 20.48. Found: C, 22.85; H, 3.12; S, 20.40. R_f (EtOAc) 0.77; $[\alpha]_D^{20} = +44.6$ (*c* 1, CH_2Cl_2).

4.1.2. (*R*)- or (*S*)-4-Chloromethyl-[1,3,2]dioxathiolane 2,2-dioxide (*R*)-3 or (*S*)-3

To an ice-cold solution of (*R*)- or (*S*)-4-(2-chloromethyl)-[1,3,2]dioxathiolane-2-oxide (*R*)-**2** or (*S*)-**2** (3.13 g, 20 mmol) in a mixture of acetonitrile (20 mL) and chloroform (20 mL) was added $NaIO_4$ (6.4167 g, 30 mmol), followed by $RuCl_3{\cdot}H_2O$ (0.0025 g, 0.012 mmol) and water (30 mL). The resulting mixture was stirred for 1 h, and then diluted with diethyl ether (160 mL). The organic layer was washed with water (2 × 10 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (40 mL), dried over anhydrous $MgSO_4$, and evaporated in a vacuum. The crude product (oil) was purified by flash chromatography using ethyl acetate.

(*R*)-4-Chloromethyl-[1,3,2]dioxathiolane 2-oxide (*R*)-**2** to give 2.75 g of (*R*)-4-chloromethyl-[1,3,2]dioxathiolane 2,2-dioxide (*R*)-**3** (yield 81%). Anal. Calcd for $C_3H_5O_4SCl$: C, 20.88; H, 2.92; S, 18.58. Found: C, 20.92; H, 2.99; S, 18.65. R_f (EtOAc) 0.69; $[\alpha]_D^{20} = +4.2$ (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ [ppm]: 3.75–3.90

(m, 2H, CH_2Cl), 4.63 (dd, 1H, J = 6 Hz, J = 9 Hz, CH_2), 4.83 (dd, 1H, J = 6 Hz, J = 6 Hz, CH_2), 5.05–5.13 (m, 1H, CH).

(*S*)-4-Chloromethyl-[1,3,2]dioxathiolane 2-oxide (*S*)-**2** gave 2.71 g (*S*)-4-chloromethyl-[1,3,2]dioxathiolane 2,2-dioxide (*S*)-**3** (yield 79%), R_f (EtOAc) 0.69. Anal. Calcd for $C_3H_5O_4SCl$: C, 20.88; H, 2.92; S, 18.58. Found: C, 20.95; H, 3.03; S, 18.68; $[\alpha]_D^{20} = -4.2$ (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ [ppm]: 3.75–3.90 (m, 2H, CH_2Cl), 4.63 (dd, 1H, J = 6 Hz, J = 9 Hz, CH_2), 4.83 (dd, 1H, J = 6 Hz, J = Hz, CH_2), 5.05–5.13 (m, 1H, CH).

4.1.3. (*S*)- or (*R*)-1-(3-Chloro-2-hydroxy-propyl)-pyrrolidin-2-one (*S*)-6 or (*R*)-6

To an ice-cold suspension of 60% NaH (2.6 g, 65 mmol) in 130 mL THF, pyrrolidin-2-on **4** (5.5 g, 65 mmol) was added dropwise. The reaction mixture was stirred for 1 h then (*S*)- or (*R*)-4-chloromethyl-[1,3,2]dioxathiolane 2,2-dioxide (*S*)-**3** or (*R*)-**3** (13.5 g, 75 mmol) was added and the reaction mixture was stirred overnight. Cleavage was carried out by the addition of 3.6 mL of H_2SO_4 (concd) and water (1.3 mL). After stirring for 1 h at room temperature, the reaction mixture was acidified by adding saturated $NaHCO_3$, and washed with $CHCl_3$ (2 × 20 mL). The organic layers were collected, dried with anhydrous Na_2SO_4, and evaporated. The oil obtained was purified by column chromatography using a mixture of acetone and chloroform (1:1).

(*R*)-4-(2-Chloromethyl)-[1,3,2]dioxathiolane-2,2-dioxide (*R*)-**3** gave 6.7 g (*S*)-1-(3-chloro-2-hydroxypropyl)-pyrrolidin-2-one (*R*)-**6** (yield 58%). Anal. Calcd for $C_7H_{12}O_2N$: C, 47.33; H, 6.81; N, 7.89. Found: C, 47.54; H, 6.93; N, 7.90. R_f (acetone/$CHCl_3$ (1:1)) 0.50; $[\alpha]_D^{20} = +30.9$ (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ [ppm]: 2.05–2.13 (m, 2H, $CH_2CH_2CH_2$), 2.42 (t, 2H, CH_2CO, J = 9 Hz), 3.45–3.57 (m, 6H, CH_2CH, CH_2Cl, CH_2CH_2), 3.95–4.05 (m, 1H, CH), 4.30 (s (broad), 1H, OH).

(*S*)-4-(2-Chloro-methyl)-[1,3,2]dioxathiolane-2,2-dioxide (*S*)-**3** gave 6.7 g (*R*)-1-(3-chloro-2-hydroxy-propyl)-pyrrolidin-2-one (*S*)-**6** (yield 58%). Anal. Calcd for $C_7H_{12}O_2N$: C, 47.33; H, 6.81; N, 7.89. Found: C, 47.45; H, 6.89, N, 7.91. R_f (acetone/$CHCl_3$ (1:1)) 0.50; $[\alpha]_D^{20} = -31.0$ (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ [ppm]: 2.05–2.13 (m, 2H, $CH_2CH_2CH_2$), 2.42 (t, 2H, CH_2CO, J = 9 Hz), 3.45–3.57 (m, 6H, CH_2CH, CH_2Cl, CH_2CH_2), 3.95–4.05 (m, 1H, CH), 4.30 (s (broad), 1H, OH).

4.1.4. (*S*)- or (*R*)-1-[2-Hydroxy-3-(4-phenyl-piperazin-1-yl)-propyl]-pyrrolidin-2-one (*S*)-8a or (*R*)-8a

(*R*)- or (*S*)-1-(3-Chloro-2-hydroxy-propyl)-pyrrolidin-2-one (0.89 g, 5 mmol) (*R*)-**6** or (*S*)-**6** and 1-phenylpiperazine (0.81 g, 5 mmol) were dissolved in 5 mL acetonitrile. Then anhydrous K_2CO_3 (0.69 g, 5 mmol) and TBAI (0.02 g, 0.05 mmol) were added. The reaction mixture was stirred at room temperature for 24 h. The inorganic salt was filtered and washed with 5 mL MeOH. The filtrate was evaporated and the oil obtained was purified by column chromatography using an acetone/chloroform (1:1) mixture.

(*R*)-1-(3-Chloro-2-hydroxypropyl)-pyrrolidin-2-one (*R*)-**6** gave 1.21 g of 1-[(*S*)-2-hydroxy-3-(4-phenyl-piperazin-1-yl)-propyl]-pyrrolidin-2-one (*S*)-**8a** (yield 80%) R_f (acetone/$CHCl_3$ (1:1)) 0.42; $[\alpha]_D^{20} = -10.3$ (*c* 1, EtOH); mp 98–99 °C. Anal. Calcd for $C_{17}H_{25}N_3O_2$: C, 67.26; H, 8.29; N, 13.65. Found: C, 67.30; H, 8.31; N, 13.85. ^{1}H NMR ($CDCl_3$) δ [ppm]: 1.94–2.09 (m, 2H, $CH_2CH_2CH_2$ (pyrrol)), 2.31–2.48 (m, 4H, CH_2CO (pirol), NCH_2CH), 2.50–2.62 (m, 2H, piper), 2.78–2.83 (m, 2H, piper), 3.11–3.20 (m, 4H, piper), 3.29 (s, 1H, OH), 3.52 (d, 2H, CHCH_2N), 3.55–3.67 (m, 2H, CH_2CH_2N (pirol)), 3.87–3.96 (m, 1H, CHOH), 7.22–7.30 (m, 5H, phenyl).

(*S*)-1-(3-Chloro-2-hydroxypropyl)-pyrrolidin-2-one (*S*)-**6** gave 1.21 g of 1-[(*R*)-2-hydroxy-3-(4-phenyl-piperazin-1-yl)-propyl]-pyrrolidin-2-one (*R*)-**8a** (yield 80%) TLC: R_f (CH_2Cl_2/MeOH (9:1)) 0.42; $[\alpha]_D^{20} = +10.3$ (*c* 1, EtOH); mp 98–99 °C, Anal. Calcd for $C_{17}H_{25}N_3O_2$: C, 67.26; H, 8.29; N, 13.65. Found: C, 67.28; H, 8.30; N, 13.76. ^{1}H NMR ($CDCl_3$) δ [ppm]: 1.94–2.09 (m, 2H, $CH_2CH_2CH_2$ (pirol)), 2.31–2.48 (m, 4H, CH_2CO (pirol), NCH_2CH), 2.50–2.62 (m, 2H, piper), 2.78–2.83 (m, 2H, piper), 3.11–3.20 (m, 4H, piper), 3.29 (s, 1H, OH), 3.52 (d, 2H, CHCH_2N), 3.55–3.67 (m, 2H, CH_2CH_2N (pirol)), 3.87–3.96 (m, 1H, CHOH), 7.22–7.30 (m, 5H, phenyl).

4.1.5. (*S*)- or (*R*)-1-[3-[4-(2-Chlorophenyl)piperazin-1-yl]-2-hydroxypropyl]pyrrolidin-2 -one (*S*)-8b or (*R*)-8b

(*R*)- or (*S*)-1-(3-Chloro-2-hydroxypropyl)-pyrrolidin-2-one (0.89 g, 5 mmol) (*R*)-**6** or (*S*)-**6** and 1-(2-chloro-phenyl)-piperazine (0.98 g, 5 mmol) were dissolved in 5 mL acetonitrile. Then anhydrous K_2CO_3 (0.69 g, 5 mmol) and TBAI (0.02 g, 0.05 mmol) were added. The reaction mixture was stirred at room temperature for 24 h. The inorganic salt was filtered and washed with 5 mL MeOH. The filtrate was evaporated and the oil obtained was purified by column chromatography using an acetone/chloroform (1:1) mixture.

(*R*)-1-(3-Chloro-2-hydroxypropyl)-pyrrolidin-2-one (*R*)-**6** gave 1.3 g of (*S*)-1-[3-[4-(2-chlorophenyl)piperazin-1-yl]-2-hydroxy-propyl]pyrrolidin-2-one (*S*)-**8b**. Colorless oil (yield: 80%). Anal. Calcd for $C_{17}H_{24}N_3O_2Cl$: C, 67.26; H, 8.29; N, 13.65. Found: C, 67.39; H, 8.38; N, 13.79. R_f (CH_2Cl_2/MeOH (9:1)) 0.46; $[\alpha]_D^{20} = -19.0$ (*c* 1, EtOH); ^{1}H NMR ($CDCl_3$) δ [ppm]: 1.89–2.19 (m, 2H, $CH_2CH_2CH_2$(pirol)), 2.23–2.50 (m, 4H, CH_2CO (pirol), NCH_2CH,), 2.51 (m, 4H, CH_2 (piper)), 3.07–3.47 (m, 7H, CH_2, (piper), CHCH_2N, OH), 3.57–3.70 (m, 3H, CH_2N, CH), 7.00–7.40 (m, 4H, phenyl).

(*S*)-1-(3-Chloro-2-hydroxy-propyl)-pyrrolidin-2-one (*S*)-**6** gave 1.28 g of (*R*)-1-[3-[4-(2-chlorophenyl)piperazin-1-yl]-2-hydroxy-propyl]pyrrolidin-2-one (*R*)-**8b**. Colorless oil (yield: 76%). Anal. Calcd for $C_{17}H_{24}N_3O_2Cl$: C, 60.44; H, 7.16; N, 12.44. Found: C, 60.32; H, 7.09; N, 12.29. R_f (CH_2Cl_2/MeOH (9:1)) 0.46; $[\alpha]_D^{20} = +19.9$ (*c* 1, EtOH); ^{1}H NMR ($CDCl_3$) δ [ppm]: 1.89–2.19 (m, 2H, $CH_2CH_2CH_2$(pirol)), 2.23–2.50 (m, 4H, CH_2CO (pirol), NCH_2CH,), 2.51 (m, 4H, CH_2 (piper)), 3.07–3.47 (m, 7H, CH_2, (piper), CHCH_2N, OH), 3.57–3.70 (m, 3H, CH_2N, CH), 7.00–7.40 (m, 4H, phenyl).

4.1.6. (*S*)- or (*R*)-1-{3-[4-(2-Ethoxyphenyl)piperazin-1-yl]-2-hydroxypropyl}-pyrrolidin-2-one (*S*)-8c or (*R*)-8c

(*R*)- or (*S*)-1-(3-Chloro-2-hydroxypropyl)-pyrrolidin-2-one (0.89 g, 5 mmol) (*R*)-**6** or (*S*)-**6** and 1-(2-ethoxy-phenyl)-piperazine (1.03 g, 5 mmol) were dissolved in 5 mL acetonitrile. Then anhydrous K_2CO_3 (0.69 g, 5 mmol) and TBAI (0.02 g, 0.05 mmol) were added. The reaction mixture was stirred at room temperature for 24 h. The inorganic salt was filtered and washed with 5 mL MeOH. The filtrate was evaporated and the oil obtained was purified by column chromatography using an acetone: chloroform (1:1) mixture.

(*R*)-1-(3-Chloro-2-hydroxy-propyl)-pyrrolidin-2-one (*R*)-**6** gave 1.38 g of (*S*)-1-{3-[4-(2-ethoxyphenyl)piperazin-1-yl]-2-hydroxy-propyl}-pyrrolidin-2-one ((*S*)-**8c**). Colorless oil (yield: 80%). Anal. Calcd for $C_{19}H_{29}N_3O_3$: C, 65.68; H, 8.41; N, 12.09. Found: C, 65.25; H, 8.19; N, 12.21. TLC (CH_2Cl_2/MeOH (9:1)) 0.57; $[\alpha]_D^{20} = -18.4$ (*c* 1, EtOH); ^{1}H NMR $CDCl_3$): δ [ppm]: 1.33 (t, 3H, CH_3, J = 3.5 Hz), 1.96 (m, 2H, $CH_2CH_2CH_2$ (pirol)), 2.18–2.25 (m, 4H, CH_2CO, NCH_2CH_2), 2.61–2.72 (m, 4H, CH_2 (piper)), 2.80–2.93 (m, 4H, CH_2 (piper)), 3.19 (dd, 2H, CH_2CH_2N), 3.32 (s, 1H, OH), 3.53–3.63 (m, 3H, CH_2CH_2N, CH), 3.98 (qw, 2H, J = 3.5 Hz, CH_2), 6.34–6.71 (m, 4H, phenyl).

(*S*)-1-(3-Chloro-2-hydroxy-propyl)-pyrrolidin-2-one (*S*)-**6** gave 1.39 g of (*R*)-1-{3-[4-(2-ethoxyphenyl)piperazin-1-yl]-2-hydroxy-propyl}-pyrrolidin-2-one (*R*)-**8c**. Colorless oil (yield: 81%). Anal. Calcd for $C_{19}H_{29}N_3O_3$: C, 65.68; H, 8.41; N, 12.09. Found: C, 65.75; H, 8.49; N, 12.01. TLC (CH_2Cl_2/MeOH (9:1)) 0.57; $[\alpha]_D^{20} = +18.6$ (*c* 1, EtOH); ^{1}H NMR $CDCl_3$): δ [ppm]: 1.33 (t, 3H, CH_3, J = 3.5 Hz), 1.96 (m, 2H, $CH_2CH_2CH_2$ (pirol)), 2.18–2.25 (m,

4H, CH_2CO, NCH_2CH_2), 2.61–2.72 (m, 4H, CH_2 (piper)), 2.80–2.93 (m, 4H, CH_2 (piper)), 3.19 (dd, 2H, CH_2CH_2N), 3.32 (s, 1H, O*H*), 3.53–3.63 (m, 3H, CH_2CH_2N, C*H*), 3.98 (qw, 2H, $J = 3.5$ Hz, CH_2), 6.34–6.71(m, 4H, phenyl).

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