Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2533–2536

TETRAHEDRON: *ASYMMETRY*

Stereocontrolled synthesis of the enantiomers of 1-[2-hydroxy-3-(4-phenyl-1-piperazinyl)-propyl]-pyrrolidin-2-one

Katarzyna Kulig,[a] Ulrike Holzgrabe[b] and Barbara Malawska[a,*]

[a]*Department of Pharmaceutical Chemistry, Collegium Medicum Jagiellonian University, ul. Medyczna 9, 30-688 Kraków, Poland*
[b]*Institut für Pharmazie und Lebensmittelchemie, Universität Würzburg, Am Hubland, 97074 Würzburg, Germany*

Received 6 August 2001; accepted 4 September 2001

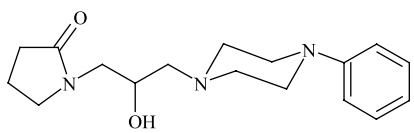
Abstract—The asymmetric synthesis of 1-[2-hydroxy-3-(4-phenyl-1-piperazinyl)-propyl]-pyrrolidin-2-one **1** is described. Enantiomers of compound **1** were obtained using the Sharpless asymmetric dihydroxylation (AD) or hydrolytic kinetic resolution (HKR) methods. The enantiomers of compound **1**, which were obtained by HKR had higher enantiomeric excesses than those which were synthesized by AD and epoxidation. The enantiomeric purity of the synthesized compounds was determinated by capillary electrophoresis.

1. Introduction

Chiral drugs have long been used as therapeutic agents, but in most cases only in racemic form. Over the last 20 years, however, great advances in production technology and quality control techniques have made chirality an important issue. In the development process of a new drug, differentiation due to chirality is now an integral part of preclinical and clinical investigations. The choice of racemate must be justified and the criteria for this will become more demanding in the future.[1,2]

For example, it has been demonstrated in the case of β-blocker of type $ArOCH_2CH(OH)CH_2NHR$ that only the (*S*)-enantiomer is sufficiently active. Thus β-blockers, such as timolol, penbutolol and levobunolol are used in therapy only as (*S*)-enantiomers.[3]

In the context of our studies on new therapeutic agents for arrhythmia and hypertension a series of pyrrolidin-2-one was synthesized. One of the most active compounds was 1-[2-hydroxy-3-(4-phenyl-1-piperazinyl)-propyl]-pyrrolidin-2-one **1**.[4]



1

Preliminary biological studies showed that compound **1** prevented or ameliorated the adrenaline-, barium chloride induced arrhythmia and statistically diminished arrhythmias associated with coronary artery occlusion and reperfusion in the isolated rat heart. Compound **1** demonstrates potent local anesthetic properties and depressed the depolarization phase of the action potential of cardiac cells. According to Williams classification compound **1** is in class Ia of antiarrhythmic drugs.[5] Compound **1** also showed hypotensive effects and displayed α_1 and α_2 adrenergic blocking activities.[4,6,7]

Knowing that the interactions between compound and receptor site are stereoselective, efforts to synthesize enantiomers of compound **1** were undertaken. In our earlier studies racemic 1-[2-hydroxy-3-(4-phenyl-1-piperazinyl)-propyl]-pyrrolidin-2-one **1** was obtained from the reaction between phenylpiperazine and 1-(2,3-epoxypropyl)-pyrrolidin-2-one **4**. Based on this as a starting material for the stereoselective synthesis of compound **1**, enantiomers of 1-(2,3-epoxypropyl)-pyrrolidin-2-one **4** were selected. Herein we report a comparison between the two methods of synthesis of the enantiomers of **1**.

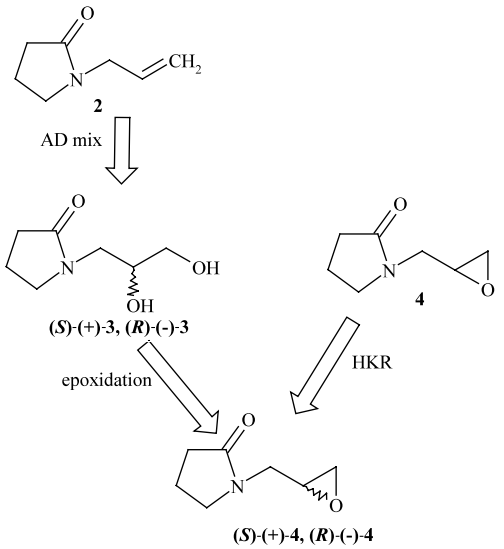
2. Results and discussion

As shown in Scheme 1, we considered that the stereogenic center in compound **4** could be installed by catalytic asymmetric dihydroxylation (AD)[8,9] of olefin **2**

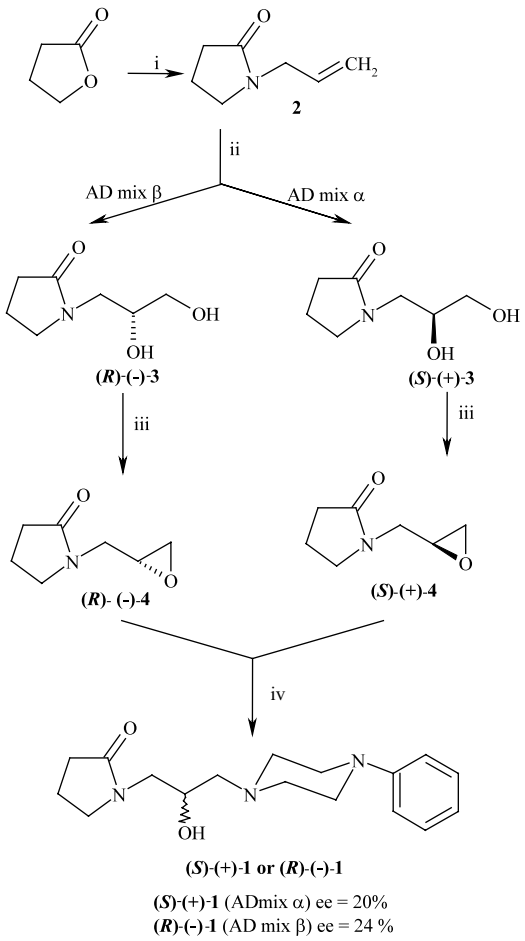
* Corresponding author. E-mail: mfmalaws@cyf-kr.edu.pl

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00390-1

and stereospecific conversion of diols **3** into epoxides **4**,[10] or by hydrolytic kinetic resolution (HKR) of the terminal epoxide **4** catalyzed by a (Salen)Co complex.[11,12]



Scheme 1.



Scheme 2. *Conditions*: (i) 1-allylamine; (ii) *t*-BuOH/H_2O, 0°C; (iii) $MeC(OMe)_3$, $MeSiCl/CH_2Cl_2$, K_2CO_3, MeOH, rt; (iv) phenylpiperazine, MeOH, rt. The relative configurations are tentatively assigned by comparison of closely related diols.[9]

According to this procedure, the required non-racemic epoxides were obtained via the Sharpless AD and epoxidation. As the starting material for our synthesis, 1-allylpyrrolidin-2-one **2** was used. Compound **2** was obtained by reaction between tetrahydrofuran-2-one and allylamine. Oxidation of **2** by standard procedures with commercially available AD-mix α or β provided the diols (*S*)-(+)-**3** or (*R*)-(−)-**3** in 70–80% yield. AD mix α or β is a mixture of potassium osmate, $K_3[Fe(CN)_6]$, K_2CO_3 and $(DHQ)_2$-PHAL (AD mix α) and $(DHQD)_2$-PHAL (AD mix β), respectively. The diols (*S*)-(+)-**3** and (*R*)-(−)-**3** were easily converted to the epoxides (*S*)-(+)-**4** and (*R*)-(−)-**4** using the process based on the acetoxonium ion-mediated formation of acetate esters of halohydrins. Subsequently, base-mediated ester saponification and cyclization give the enantiomeric epoxides (*S*)-(+)-**4** and (*R*)-(−)-**4** (Scheme 2).

Design of low-molecular-weight catalysts for reaching enantioselectivities similar to those obtained in enzymatic reactions has become an important goal of asymmetric synthesis. HKR processes introduced by Jacobsen are recent examples of achievements in this area. In the presence of (*R*,*R*)- or (*S*,*S*)-SalenCo(III)Ac and water racemic, 1-(2,3-epoxypropyl)-pyrrolidin-2-one **4** was transformed into enantiomers of (*S*)-(+)-**4** or (*R*)-(−)-**4** and enantiomers of 1-(2,3-dihydroxypropyl)-pyrrolidin-2-one (not isolated) (Scheme 3).

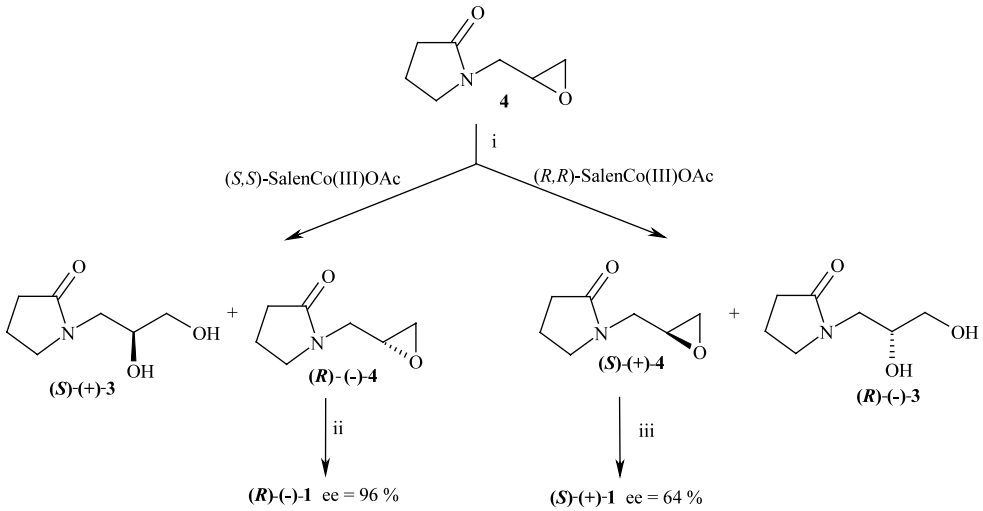
The aminolysis of compounds (+)-**4** and (−)-**4** with 1-phenylpiperazine gave the enantiomers of compound (*S*)-(+)-**1** and (*R*)-(−)-**1** in about 65% yield. The enantiomeric excess of the enantiomer of compound **1** was established by capillary electrophoresis using sulfated β-cyclodextrin as a chiral pseudostationary phase. The ees for compounds (+)-**1** and (−)-**1**, which were synthesized by asymmetric dihydroxylation using AD-mix α or AD-mix β, were in range 20–24%. The highest ees were determined for (*S*)-(+)-**1** enantiomer (64%) and (*R*)-(−)-**1** enantiomer (96%), which were synthesized via hydrolytic kinetic resolution of **4** using (*R*,*R*)- and (*S*,*S*)-SalenCo(III)OAc as the catalyst. The yields in the HKR reactions are essentially identical (44 and 42%) for the two enantiomers. It is possible that the conversions were not the same or a racemization of (*S*)-(+)-**4** took place during aminolysis.

In summary, the enantiomers of compounds **1** were synthesized via two synthetic pathways. The enantiomers of **1**, which were obtained by HKR characterized higher enantiomeric excess than those which were synthesized by AD and epoxidation. The above described method of HKR could be used in the synthesis of pharmacologically active analogues of compounds **1**.

3. Experimental

3.1. General

Uncorrected melting points were determined in open capillary on a Büchi melting point apparatus. Elemen-



Scheme 3. *Conditions*: (i) H_2O, rt; (ii) phenylpiperazine, MeOH, rt, 48 h; (iii) phenylpiperazine, MeOH, 40°C, 12 h. The relative configurations are tentatively assigned according to the literature.[12]

tal analyses (C, H, N) were determined within 0.4% of theoretical values. Optical rotations were determined at the sodium D line with a Krüss P-3002 polarimeter. TLC was performed on Merck aluminium precoated plates of silica gel 60 F-254 (detection by UV and by spraying with 0.05 mol J_2 solution in 10% HCl. Column chromatography was carried out on a Merck Kieselgel 60 (0.063–0.200 mm). Solvent for chromatography: S_1 – chloroform:acetone (1:1), S_2 – methanol:25% ammonium (98:2), S_3 – chloroform:methanol:25% ammonium (90:10:3), S_4 – *n*-butanol:*i*-propanol:25% ammonium (11:6:2).

3.2. Capillary electrophoresis

All experiments were performed on a Beckman P/ACE MDQ system (Beckman Instruments, Fullerton, CA, USA) using a fused-silica capillary with a total length of 60 cm, a detection length of 50 cm, and an internal diameter of 50 μm. Samples were loaded by 5 s of pressure injection and separated at 25°C using a constant voltage of 20 KV. Phosphate buffer (100 mM) pH 6.0 was prepared by mixing appropriate concentrations of H_3PO_4 and KH_2PO_4 solution. The sulfated cyclodextrin (Aldrich, Steinheim, FRG) was dissolved in buffer, the samples subjected to the CE were dissolved in deionized water (conc. $\approx$1 mg/ml). All solutions were filtered through a 0.45 μm syringe (Schleicher and Schüll, Dassel, FRG). The drug solution had a concentration of 25 μg/ml and was detected using a diode array detector at 194 nm. The capillary was conditioned for 20 min with 0.1 M NaOH, and 10 min with water. Additionally, the capillary was washed for 2 min with 0.1 M NaOH, 1 min with water, and 2 min with the running buffer before each run.

3.3. 1-Allylpyrrolidin-2-one (2)

Tetrahydrofuran-2-one [0.2 mol (9.1 cm^3)] and allylamine [0.4 mol (16.0 cm^3)] were heated in an autoclave for 21 h at 200°C. The obtained oil was distilled under reduced pressure. Yield: 77.9% (19.5 g), bp 110°C/20 mbar, anal: $C_7H_{11}NO$, M_r=125.17, R_f (S_2)=0.78, R_f (S_3)=0.63, R_f (S_4)=0.60.

3.4. 1-(2,3-Dihydroxypropyl)-pyrrolidin-2-one (*S*)-(+)-3 or (*R*)-(−)-3

To a mixture of 50 ml of *tert*-butyl alcohol and 50 ml of water, 14 g of AD-mix α or β was added. Stirring at room temperature produced two clear phases. The mixture was cooled to 0°C then 0.001 mol (1.25 g) of **2** was added at once and the heterogeneous slurry was stirred at 0°C for 21 h (progress monitored by TLC). While the mixture was stirred solid sodium sulfite (15 g) was added and the mixture was allowed to warm to room temperature and stirred for 30 min. Methylene chloride was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with methylene chloride. The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography using S_2 as an eluent.

AD-mix α gave 1.28 g of (*S*)-(+)-**3** (yield 81%). Anal. 159.00, $C_7H_{13}O_3N$ R_f (S_2)=0.66, $[\alpha]_D^{20}$=+14.3 (*c*=1, MeOH).

AD-mix β gave 1.15 g of (*R*)-(−)-**3** (yield 72%). Anal. 159.00, $C_7H_{13}O_3N$ R_f (S_2)=0.66, $[\alpha]_D^{20}$=−16.3 (*c*=1, MeOH).

3.5. 1-(2,3-Epoxypropyl)-pyrrolidin-2-one (*S*)-(+)-4 or (*R*)-(−)-4

3.5.1. Epoxidation of 1-(2,3-dihydroxypropyl)-pyrrolidin-2-one (*S*)-(+)-3 or (*R*)-(−)-3. Trimethylsilyl chloride (0.01 mol, 1.4 cm^3) was added to a solution of (*S*)-(+)-**3** or (*R*)-(−)-**3** and trimethyl orthoacetate (0.01 mol, 1.3 cm^3) in methylene chloride at 0°C. The solution was stirred for 1 h, then evaporated. The crude product was dissolved in dry methanol and K_2CO_3 (0.02 mol, 2.91 g) was added. The suspension was stirred for 2 h, then

filtered and the residue was washed with methylene chloride. The filtrate was evaporated under vacuum and the residue was purified by column chromatography using S_1 as a solvent.

From (*S*)-(+)-**3** was obtained 0.77 g of (*S*)-(+)-**4** (yield 68%). Anal. 141.17, $C_7H_{11}O_2N$ R_f (S_1) = 0.59, $[\alpha]_D^{20}$ = 10.3 (*c* = 1, MeOH).

From (*R*)-(−)-**3** was obtained 0.69 g of (*R*)-(−) **4** (yield 68.3%). Anal. 141.17, $C_7H_{11}O_2N$ R_f (S_1) = 0.59, $[\alpha]_D^{20}$ = −11.65 (*c* = 1, MeOH).

3.5.2. Hydrolytic kinetic resolution of racemic 1-(2,3-epoxypropyl)-pyrrolidin-2-one 4. A mixture of (*R*,*R*)- or (*S*,*S*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (SalenCo(II)) (0.2 mmol, 0.12 g) and acetic acid (0.4 mmol, 0.02 cm^3) was stirred for 1 h at room temperature. The solvent was removed by rotary evaporation and the brown residue was dried under vacuum. 1-(2,3-Epoxypropyl)-pyrrolidin-2-one **4** (0.1 mol, 14.1 g) was added in one portion, and the stirred mixture was cooled in an ice-water bath. Water (0.05 mol, 0.1 cm^3) was slowly added. The reaction was stirred at room temperature for 11 h. The obtained oil was distilled under reduced pressure.

(*R*,*R*)-SalenCo(III)OAc gave 6.13 g of (*S*)-(+)-**4** (yield 44%). Anal. 141.17, $C_7H_{11}O_2N$ R_f (S_1) = 0.59, bp 135°C/12 mbar, $[\alpha]_D^{20}$ = 11.8 (*c* = 1, MeOH).

(*S*,*S*)-SalenCo(III)OAc gave 5.89 g of (*R*)-(−)-**4** (yield 42%). Anal. 141.17, $C_7H_{11}O_2N$ R_f (S_1) = 0.59, bp 135°C/12 mbar, $[\alpha]_D^{20}$ = −11.9 (*c* = 1, MeOH).

3.6. 1-[2-Hydroxy-3-(4-phenyl-1-piperazinyl)-propyl-pyrrolidin-2-one (*S*)-(+)-1 and (*R*)-(−)-1

An equimolar quantity of (*S*)-(+)-**4** or (R)-(−)-**4** and 1-phenylpiperazine in methanol was stirred at room temperature for 48 h or heated at 40°C for 12 h. Then the solvent was evaporated, and the crude product was cooled down. The residue thus obtained was crystallized from a mixture of *n*-hexane and ethyl acetate (1:4).

The asymmetric dihydroxylation method using AD-mix α gave 0.73 g of (*S*)-(+)-**1** (yield 47.0%). The condition of reaction: rt, 48 h. Anal. 302.42, $C_{16}H_{26}O_3N_3$, $[\alpha]_D^{20}$ = 19.6 (*c* = 1, MeOH), mp 91.3–92.7°C, ee = 20%.

The asymmetric dihydroxylation method using AD-mix β gave 0.83 g of (*R*)-(−)-**1** (yield 53%). The condition of reaction: rt, 48 h. Anal. 302.42, $C_{16}H_{26}O_3N_3$, $[\alpha]_D^{20}$ = −18.6 (*c* = 1, MeOH), mp 91.3–92.7°C, ee = 24%.

Hydrolytic kinetic resolution method using (*R*,*R*)-SalenCo(III)OAc gave 1.84 g of (*S*)-(+)-**1** (yield 62%). The condition of reaction: 40°C, 12 h. Anal. 302.42, $C_{16}H_{26}O_3N_3$, $[\alpha]_D^{20}$ = 24.5 (*c* = 1, MeOH), mp 91.3–92.7°C, ee = 64%.

Hydrolytic kinetic resolution method using (*S*,*S*)-SalenCo(III)OAc gave 2.06 g of (*R*)-(−)-**1** (yield 68%). The condition of reaction: rt, 48 h. Anal. 302.42, $C_{16}H_{26}O_3N_3$, $[\alpha]_D^{20}$ = −30.0 (*c* = 1, MeOH), mp 91.3–92.7°C, ee = 96%.

Acknowledgements

The study was supported by the project KBN 4 P 05 F 03919.

References

1. Seri-Levy, A.; West, S.; Richards, W. *J. Med. Chem.* **1994**, *37*, 1727–1732.
2. Agranat, I.; Caner, H. *Drug Discovery Today* **1999**, *7*, 313–321.
3. Roth, H. J.; Müller, Ch. E.; Folkers, G. *Stereochemie & Arzneistoffe*; WUG: Stuttgart, 1998; pp. 268–269.
4. Malawska, B.; Gorczyca, M.; Filipek, B. *Pol. J. Pharmacol. Pharm.* **1992**, *44*, 561–574.
5. Vaughan Williams, M. In *Pharmacology Antiarrhythmic Agents*; Szekeres, L., Ed.; Pergamon Press: Oxford, 1981.
6. Filipek, B.; Sapa, J.; Malawska, B.; Kulig, K.; Antkiewicz-Michaluk, L. *Arch. Pharm. Pharm. Med. Chem.* **1997**, *330*, 225–231.
7. Filipek, B.; Malawska, B.; Kulig, K.; Sapa, J. Polish Patent Application, P-319983, 1997.
8. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
9. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771.
10. Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515–10530.
11. Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776–6777.
12. Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938.