Anticholinergic Agents 3.* Synthesis and Configurational Assignment of the Four Stereoisomers of 1-Cyclohexyl-1,2-epoxy-1-phenyl-3-piperidylpropane

Peter Sjö and Arne Jørgen Aasen

Department of Pharmacy, University of Oslo, P.O. Box 1068, Blindern, N-0316 Oslo 3, Norway


The four stereoisomers of 1-cyclohexyl-1,2-epoxy-1-phenyl-3-piperidylpropane which are putative muscarinic antagonists, have been synthesised employing (S)- and (R)-1-cyclohexyl-1-phenyl-1,3-propanediol as chiral synths. The relative configuration of the second chiral centre of the four isomers was deduced from NOE results and by finding identical 1H NMR spectra for one of the optically active intermediates and its corresponding racemate of known relative stereochemistry.

At least four subtypes of muscarinic receptors (M1, M2, M3, and M4) can now be discriminated on the basis of radioligand binding experiments1-3 and pharmacological studies employing a number of selective antagonists.4-5 Data obtained during recent years suggest that the muscarinic receptor subtypes can also be differentiated on the basis of their stereoselectivity.6-12

As part of an on-going programme on structure–activity relationships of muscarinic antagonists, we have prepared a new series of optically active epoxides which are unable to form the hydrogen bond required for the interaction with one of the four subtypes of the muscarinic M1, M2, M3 and M4 receptor model advanced by Waelbroeck et al.8,13

Results and discussion

Synthesis. Initially, the synthesis of the optically active epoxides 10 were attempted by subjecting the readily available allylic alcohol (Z)-14 to the Sharpless asymmetric epoxidation15 furnishing the epoxy alcohol 8 which was assumed to be an appropriate precursor for the amine 10 (Scheme 1). However, the optical purity of the epoxy alcohol 8 was unacceptable; furthermore, recrystallization did not effect enantiomeric enrichment. The moderate enantiomeric excess is attributed to the steric hindrance exerted by the cyclohexyl and phenyl substituents. We then turned to a more arduous route in which the isomeric epoxides 7 were isomerised to the epoxides 8 employing the Payne rearrangement.16 The chirality was introduced through the known optically active diols 417 (Scheme 2).

The epoxides 7 were synthesised in seven steps as outlined in Scheme 2. Optically pure (R)-(−)- and (S)-(−)-1-cyclohexyl-1-phenyl-1,3-propanediols 4 were prepared essentially as previously described by Schjelderup et al.17 The action of an ultrasonic bath during the Reformatsky reaction18 provided (±)-ethyl 3-cyclohexyl-3-hydroxy-3-phenylpropanoate devoid of by-products. Hydrolysis of the racemic ester followed by enantiomeric resolution of the resulting acids and subsequent borane reduction gave the diols (R)-(−)-4 and (S)-(−)-4 of high optical purity (>97 % ee), as judged from 19F NMR spectroscopy of their (R)-MPTA-esters.19

The diols 4 were converted into the allylic alcohols 6 in fair overall yields employing the elegant selenoxide

![Scheme 1. Sharpless epoxidation of (Z)-1. (±)-Disopropyl tartrate, Ti(OPr)4, BuOOH, CH2Cl2, molecular sieves, −20°C.](image)

Fig. 1. Observed nuclear Overhauser effects on irradiation of the cyclohexyl protons at 1.6 ppm.
route for transforming primary and secondary alcohols into the corresponding alkenes.\textsuperscript{36} The diols 4 were monosylated (4-nitrobenzenesulfonyl esters) providing an excellent leaving group for the subsequent nucleophilic attack of sodium 2-nitrophenyl selenide.\textsuperscript{21} Less reactive sulfonates such as the mesylate or the tosylate did not react satisfactorily. The selenides were oxidized with aqueous hydrogen peroxide to the corresponding selenoxides which readily fragmented to the alkenols 6.

The allylic alcohols 6 were epoxidized with 3-chloroperbenzoic acid in the presence of sodium hydrogen carbonate. The diastereomeric epoxy alcohols 7 were readily separated by flash chromatography on silica gel. Base-induced Payne rearrangement of the epoxides 7 afforded the isomeric epoxides 8. The corresponding nosylates 9 of the epoxy alcohols 8 reacted with piperidine furnishing the four target compounds 10.

The optical purities of the epoxy alcohols 8 were measured to be, as expected, better than 97% ee as judged from gas chromatographic analysis of their (R)-MPTA esters.\textsuperscript{19,22}

Absolute configuration. Configurational assignment of all stereoisomers of 10 follows from (a) the known\textsuperscript{17} absolute configurations of the diols 4, and (b) the significant nuclear Overhauser effects due to interaction, probably, between the C-1 axial proton and/or one of the C-2/6 equatorial protons of the cyclohexyl moiety with the methine proton of the oxirane ring of the nosylate (2S,3R)-9 observed on irradiation of the cyclohexyl protons at ca. 1.6 ppm (Fig. 1). Corresponding connectivity through space was not observed for the diastereomer (2R,3R)-9. The results from the Overhauser experiments were confirmed by finding identical \textsuperscript{1}H NMR spectra for the epoxide (2S,3R)-9 and the racemic product obtained by epoxidation of the Z-isomer of the alkenol 1 with 3-chloroperbenzoic acid.

The potency of the individual isomers of the amino alcohol 10 at muscarinic receptor subtypes will be reported elsewhere.

Experimental

General methods. Optical rotations were recorded with a Perkin-Elmer 241 polarimeter. Measurements were carried out in chloroform, concentration 1.0 g/100 ml, unless otherwise stated. Melting points were determined on a Büchi melting point apparatus and are uncorrected. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on Varian Gemini-200 or XL-300 instruments. All NMR measurements were carried out in CDCl\textsubscript{3} solutions. The solvent peak of chloroform (\(\delta\) 7.26 ppm) and the central solvent peak of chloroform-d (\(\delta\) 7.70 ppm) were used as internal references. All couplings are given in Hz. Approximate
values for shifts and couplings of ABC- and ABX-spin systems were obtained using the LAOCOON spin-simulation program included in the software of the Varian Gemini 200 instrument. Dioxane and THF distilled from sodium–benzophenone, DMF distilled from calcium hydrate and dichloromethane dried over 4A molecular sieves were used when anhydrous conditions were required. The reagents were used as received. All reactions were run in a nitrogen atmosphere.

\[±\cdot3\text{-Cyclohexyl-3-hydroxy-3-phenylpropanoic acid (3).}\]

Cyclohexyl phenyl ketone (5.00 g, 26.6 mmol), ethyl bromoacetate (5.32 g, 31.9 mmol), zinc dust (3.12 g, 47.8 mmol) and iodine (0.67 g, 2.66 mmol) were added to dry dioxane (50 ml) in a round-bottomed flask. The reaction mixture was cooled on ice in the sonication vessel and the sonication started. After an induction period of 0.25 h the slurry turned green, indicating the start of the reaction. Sonication was continued for 3 h at room temperature. Water (50 ml) and diethyl ether (50 ml) were added and the resulting suspension was filtered. The phases were separated and the aqueous phase extracted with diethyl ether (3 × 25 ml). The combined organic phases were dried over Na₂SO₄ and evaporated to dryness and the residue was recrystallised from heptane–ethyl acetate. Yield: 6.18 g (85%) of the ethyl ester of 3.

The ethyl ester was hydrolysed in refluxing 15% aqueous KOH (50 ml) for 2.5 h. Acidification, extraction and recrystallisation from heptane–ethyl acetate yielded 5.28 g (80% from cyclohexyl phenyl ketone) of the acid 3. M.p. 174°C. 1H NMR (200 MHz): δ 0.85–1.30 (5 H, m), 1.48–1.85 (6 H, m), 2.90 (1 H, d, J 16.2), 3.07 (1 H, d, J 16.1), 7.20–7.45 (5 H, m). Anal. C₁₅H₂₀O₃: C, H.

(R)+(+)- and (S)-(−)-3-Cyclohexyl-3-hydroxy-3-phenylpropanoic acid [(R)+(+)- and (S)-(−)-3]. Racemic 3 (18.00 g, 72.49 mmol) was dissolved in hot ethanol (200 ml). (R)+(+)-1-Phenyldimethane (8.61 g, 71.04 mmol) was added. The (R)+(+)-1-phenylethylammonium salt of (R)+(+)-3 crystallised immediately. Recrystallisation from ethanol and acidic work-up yielded 7.69 g (43%) of (R)+(+)-3, m.p. 170°C, lit. 17 170–172°C; [α]D⁰ +27.3° (c 1.8, EtOH), lit. 17 [α]D⁰ +26.2° (c 1.6, EtOH). Anal. C₁₅H₂₀O₃: C, H. (S)-(−)-3 was obtained from the mother liquor following the same procedure above, but using (S)-(−)-1-phenylethylamine as the resolving agent. Yield: 7.62 g (42%). M.p. 170°C, [α]D⁰ +27.9° (c 1.6, EtOH), lit. 17 [α]D⁰ +25.6° (c 1.92, EtOH). Anal. C₁₅H₂₀O₃: C, H.

(S)+(+)-1-Cyclohexyl-1-phenyl-1,3-propanediol [(S)+(+)-4]. The diol was synthesised from (S)+(+)-3 as described by Schjelderup et al. 17 (S)+(+)-4 was obtained as a white solid. M.p. 99°C, lit. 17 100–102°C; [α]D² +22.9° (c 2.7, EtOH), lit. 17 [α]D² +22.5° (c 3.6, EtOH). 1H NMR (200 MHz): δ 0.90–1.40 (5 H, m), 1.50–2.05 (7 H, m), 2.25–2.42 (1 H, m), 3.40–3.55 (1 H, m), 3.60–3.80 (1 H, m), 7.20–7.45 (5 H, m). Anal. C₁₅H₂₀O₃: C, H. The optical purity was determined to be >97% ee using 19F NMR (300 MHz, CDCl₃) analysis of the corresponding (R)-a-methoxy-a-trifluoromethylphenylacetate [(R)-MPTA] whose trifluoromethyl group resonated 71.95 ppm upfield from CFCI₃.

(R)-(−)-1-Cyclohexyl-1-phenyl-1,3-propanediol [(R)-(−)-4]. The diol was prepared from (R)+(−)-3 in a similar way as described by Schjelderup et al. 17 M.p. 100°C, [α]D⁰ −21.8° (c 1.5, EtOAc). Anal. C₁₅H₂₀O₃: C, H. The optical purity was determined to be >97% ee using 19F NMR (300 MHz, CDCl₃) analysis of the corresponding (R)-a-methoxy-a-trifluoromethylphenylacetate [(R)-MPTA] whose trifluoromethyl group resonated 72.03 ppm upfield from CFCI₃.

(S)-(−)-3-Cyclohexyl-3-hydroxy-3-phenylpropyl 4-nitrobenzenesulfonate [(S)+(−)-5]. 4-Nitrobenzenesulfonyl chloride (NsCl) (4.18 g, 18.86 mmol) was dissolved in dry dichloromethane (25 ml) and cooled to 0°C. Triethylamine (2.60 g, 25.71 mmol) and 4-dimethylaminopyridine (DMAP) (0.11 g, 0.86 mmol) were added. A solution of (S)-(−)-4 (4.00 g, 17.14 mmol) in dichloromethane (50 ml) was added slowly. The reaction was complete within 4 h. Saturated NaHCO₃ (aq.) (50 ml) and diethyl ether (150 ml) were added. The organic phase was washed with brine (2 × 25 ml) and dried over Na₂SO₄. Evaporation followed by filtration through a short silica gel column gave (S)-(−)-5 as a white solid. Recrystallisation from heptane–ethyl acetate yielded 5.91 g (82%), M.p. 79°C (decomp.), [α]D⁰ +25.9°. 1H NMR (200 MHz): δ 0.80–1.36 (5 H, m), 1.45–1.95 (6 H, m), 2.15–2.47 (2 H, m), 3.83–3.95 (1 H, m), 4.04–4.13 (1 H, m), 7.19–7.37 (5 H, m), 7.94 (2 H, m, J 2.1, 9.1), 8.32 (2 H, m, J 2.1, 9.0). 13C NMR (50 MHz): δ 26.8, 27.0, 27.1, 27.4, 38.7, 49.2, 69.4, 77.8, 123.7, 124.7, 126.1, 127.5, 128.5, 140.8, 142.6, 149.7. Anal. C₂₁H₂₃NO₄S: C, H.

(R)-(−)-3-Cyclohexyl-3-hydroxy-3-phenylpropyl 4-nitrobenzenesulfonate [(R)-(−)-5]. (R)+(−)-5 was prepared from (R)-(−)-4 as described above. M.p. 76°C (decomp.). [α]D⁰ −25.7°. Anal. C₂₁H₂₃NO₄S: C, H.

(S)+(−)-1-Cyclohexyl-1-phenyl-1,2-propanediol [(S)+(−)-6]. NaN₃ (0.65 g, 17.2 mmol) was added to an ice-cooled solution of 2-nitrophenyl selenocyanate 35a,b 3.25 g, 14.3 mmol) in absolute ethanol (100 ml). Gas evolution and the solution assumed a deep red colour. When the gas production had ceased the temperature was allowed to rise to room temperature and the solution was left undisturbed overnight. The deep red solution was collected by filtration and exchanged for acetonitrile, was complete within 5 h (TLC). THF (175 ml) was added and the solution cooled on ice whereupon 30% aqueous H₂O₂ (27 ml) was added dropwise. The temperature was allowed to rise to ambient temperature and the reaction mixture was
stirred for 18 h. Water (175 ml) was added and the mixture extracted with heptane (175 ml + 3 × 50 ml). The combined organic phases were washed with brine (2 × 50 ml), dried over Na₂SO₄ and evaporated. The crude product was flash chromatographed on silica gel to furnish 1.92 g of (S)-(−)-6 (75%) as a pale yellow oil. [x]₂⁰ D + 42.2°. ¹H NMR (200 MHz): δ 0.95–1.35 (5 H, m), 1.40–1.85 (6 H, m), 5.18 (1 H, B part of an ABX system, J_AB 1.3, J_BX 10.7), 5.31 (1 H, A part of an ABX system, J_AX 17.2), 6.31 (1 H, X part of an ABX system), 7.23–7.46 (5 H, m). ¹³C NMR (50 MHz): δ 27.1, 27.2, 27.3, 27.4, 27.8, 48.1, 79.1, 112.1, 124.9, 125.9, 127.4, 142.5, 144.8. Anal. C₁₅H₂₀O₂: C, H.

(R)-(−)-1-Cyclohexyl-1-phenyl-2-propen-1-ol [(R)-(−)-6], (R)-(−)-6 was prepared from (R)-(−)-5 as described above. [x]₂⁰ D = −42.3°. Anal. C₁₅H₂₀O₂: C, H.

(1S,2R)-(+)-7 and (1S,2S)-(+)-1-Cyclohexyl-2,3-epoxy-1-phenyl-1-propen-1-ol [(1S,2S)-(+)-7], 3-Chloroperbenzoic acid (1.80 g, 10.40 mmol) was added to a solution of (S)-(−)-6 (1.50 g, 6.93 mmol) and NaHCO₃ (2.91 g, 34.67 mmol) in dichloromethane (35 ml). The reaction was terminated after 3 h by the addition of water (25 ml) and diethyl ether (50 ml). The organic phase was extracted with sat. aq. NaHCO₃ (25 ml) followed by brine (2 × 25 ml) and dried over Na₂SO₄ and evaporated to furnish a solid product. The diastereomeric mixture was flash chromatographed on silica gel whereupon (1S,2R)-(+)-7 and (1S,2S)-(+)-7 were obtained as white crystals. Yields: 0.53 g (33%) and 0.82 g (51%) of (1S,2R)-(+)-7 and (1S,2S)-(+)-7, respectively.

(1S,2R)-(+)-7: m.p. 123°C. [x]₂⁰ D + 13.6°. ¹H NMR (200 MHz): δ 0.95–1.35 (5 H, m), 1.45–1.90 (6 H, m), 2.53 (1 H, B part of an AB system, J_AB 5.0, J_BX 3.9), 2.55 (1 H, A part of an AB system, J_AX 3.2), 3.56 (1 H, X part of an AB system), 7.20–7.55 (5 H, m). ¹³C NMR (50 MHz): δ 27.0, 27.2, 27.5, 43.2, 48.9, 57.1, 74.1, 124.2, 126.2, 127.5, 142.4. Found: C 76.96; H 8.44. Calc. for C₁₃H₁₅C₄O₂: C 77.55; H 8.68.

(1S,2S)-(+)-7: m.p. 129°C. [x]₂⁰ D + 1.0°. ¹H NMR (200 MHz): δ 1.00–1.50 (5 H, m), 1.55–2.10 (6 H, m), 2.88 (1 H, B part of an AB system, J_AB 5.1, J_BX 4.0), 3.01 (1 H, A part of an AB system, J_AX 2.8), 3.56 (1 H, X part of an AB system), 7.15–7.55 (5 H, m). ¹³C NMR (50 MHz): δ 27.0, 27.2, 27.5, 28.1, 45.6, 46.9, 56.4, 75.2, 125.1, 126.4, 127.5, 143.8. Anal. C₁₃H₁₅C₄O₂: C, H.

(1R,2S)-(+)-7 and (1R,2R)-(+)-1-Cyclohexyl-2,3-epoxy-1-phenyl-1-propen-1-ol [(1R,2R)-(+)-7], (1R,2R)-(+)-7 and (1R,2S)-(+)-7 were prepared from (R)-(−)-6 as described above.

(1R,2S)-(+)-7: m.p. 124°C. [x]₂⁰ D = −15.5°. Found: C 76.80; H 8.55. Calc. for C₁₃H₁₅C₄O₂: C 77.55; H 8.68.

an ABX system, $J_{AB}$ 11.2, 4.57 (1 H, A part of an ABX system), 7.15–7.45 (5 H, m), 8.18 (2 H, d, $J$ 9.1), 8.44 (2 H, d, $J$ 9.0). $^1$H NMR (50 MHz): $\delta$ 2.63, 26.3, 26.6, 28.9, 30.4, 42.3, 60.2, 69.1 (2 $\times$ C), 124.0, 127.0, 127.1, 127.2, 128.7, 136.6, 140.7, 149.9. Found: C 61.70; H 5.84. Calc. for C$_2$H$_2$NO$_3$S: C 60.41; H 5.55.

(2R,3S)-(-)-3-Cyclohexyl-2,3-epoxy-3-phenylpropyl 4-nitrobenzensulfonate [(2R,3S)-(+)-9]. (2R,3S)-(+)-9 was prepared as above from (2R,3S)-(+)–8; yield 90%. M.p. 70°C (decomp.). $\delta$ 7.05–7.35 (5 H, m), 7.98 (2 H, d, $J$ 9.1). $^1$C NMR (50 MHz); $\delta$ 4.94, 4.96. 1H NMR (200 MHz); $\delta$ 0.75–1.35 (5 H, m), 1.50–1.85 (6 H, m), 3.40 (1 H, C part of an ABX system, $J_{AC}$ 4.4, $J_{BC}$ 6.6), 3.64 (1 H, B part of an ABX system, $J_{AB}$ 11.0), 3.90 (1 H, A part of an ABX system), 7.05–7.35 (5 H, m), 7.98 (2 H, d, $J$ 9.1), 8.34 (2 H, d, $J$ 9.1). $^1$C NMR (50 MHz); $\delta$ 26.4, 26.5, 26.8, 28.2, 29.8, 44.6, 57.9, 69.1, 70.6, 123.8, 126.7, 127.4, 127.5, 128.6, 135.0, 140.6, 143.6. Found: C 61.09; H 5.79. Calc. for C$_2$H$_2$NO$_3$S: C 60.41; H 5.55.

Acknowledgments. The authors are indebted to the Norwegian Research Council for Science and the Humanities (NAVF) for grants. We also thank Dr. T. Skjetne and Dr. J. Krane at the MR centre in Trondheim for carrying out some of the NOE difference experiments.

References
14. (Z)-1 can easily be prepared from cyclohexyl phenyl ketone by treating it with sodium triethyl phosphonoacetate in refluxing DME followed by separation of the $E$ and $Z$ isomers. Reduction with DIBALH in n-hexane afforded the allylic alcohol (Z)-1. $^1$H NMR (200 MHz, CDC1$_3$): $\delta$ 1.00–1.40 (5 H, m), 1.55–1.90 (5 H, m), 2.05–2.30 (1 H, m), 3.93 (2 H, d, $J$ 7.6 Hz), 5.60 (1 H, t, $J$ 6.9 Hz), 7.00–7.40 (5 H, m).
22. A 50 m × 0.32 mm ID Permabond®-L-Chirasil-val capillary column from Macherey-Nagel was used in the analysis.
>97% ee implies that the other enantiomer could not be detected.
24. Erratic values are probably due to partial decomposition during transportation. On storage at room temperature this substance assumes a deep purple colour.

Received July 10, 1992.