Stereoselective synthesis of the optical isomers of a new muscarinic receptor antagonist, quinuclidin-3-yl 2-(cyclopent-1-enyl)-2-hydroxy-2-phenylacetate

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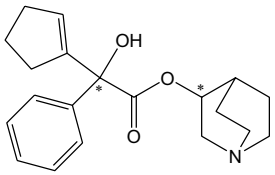
The enantiopure isomers of a new muscarinic receptor antagonist, quinuclidin-3-yl 2- (cyclopent-1-enyl)-2-hydroxy-2-phenylacetate were synthesised by a practical stereoselective synthetic method, using pivaldehyde as steric hindrance agent from the chiral starting material, (*S*) or (*R*)-mandelic acid. The isomers were obtained with 72–78 % yields in 98–99 % e.e.

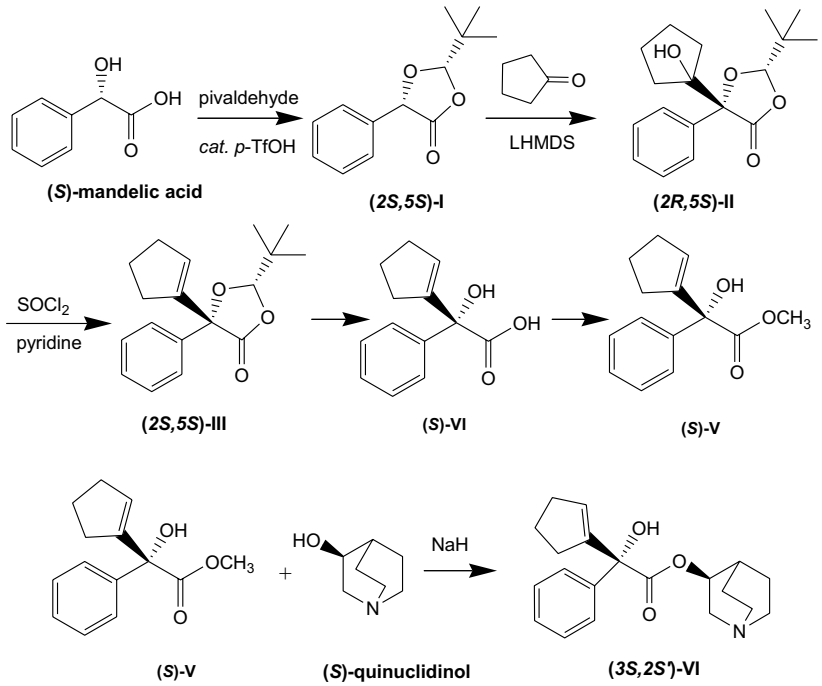
Keywords: stereoselective synthesis, optical isomer, muscarinic receptor antagonist

Design, development, and marketing of new chiral active substances are a major theme in the drugs research and industry.[1] The awareness and interest in the stereochemistry of drug action have increased, and the worldwide sales of chiral drugs in single-enantiomer form continued to grow. Over the past century, classical anticholinergic drugs have been widely used for the treatment of certain diseases, such as chronic obstructive pulmonary diseases, Alzheimer's disease and urinary incontinence. Most of the muscarinic receptor antagonists comprise of a chiral tertiary α-hydroxy acid as a key component.[2] However, their therapeutic applicability was limited, due to side effects in both the peripheral and central nervous system.

We have engaged in the synthesis and biological activity study of anticholinergic drugs for many years.[3] A novel muscarinic receptor antagonist, quinuclidin-3-yl 2-(cyclopent-1-enyl)-2-hydroxy-2-phenylacetate (in Scheme 1.) was synthesised. It is composed of an ester bond as a linkage that connected the two parts, that is, tertiary a hydroxyl structure and the azepine base substituent. There are two chiral carbon atoms in the title compound that should have four optical isomers. The receptor binding assay showed that this compound had far greater selectivity for M_3 over M_1 receptor subtype, which makes it has potentially use in the treatment of respiratory disorders such as COPD. Preliminary biological results suggest that the (3*S*,2'*S*)-isomer display an improved therapeutic profile compared to its racemic counterpart.



Diastereoselective synthesis of the enantiomers of the title compound was performed as outlined in Scheme 1 ((3*S*,2'*S*)-isomer as an example). The preparation of high yielding and highly diastereoselective acetal (2*S*,5*S*)-**I** from mandelic acid was readily accomplished in practical and amenable to scale-up. Deprotonation of pure **I** with lituium bis(trimethylsilyl) amide(LHMDS) and followed by the



Scheme 1

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Table 1 Synthetic results of the four isomers of VI

Entry	Methyl-2-(cyclopent-1-enyl)-2-hydroxy-2-phenylacetate	Quinuclidin-3-ol	e.e.(%)[a]	Yield/%[b]
(3*R*,2′*R*)-**VI**	(*R*)-**V**	(*R*)-quinuclidinol	98.5	76
(3*S*,2′*R*)-**VI**		(*S*)-quinuclidinol	98.2	78
(3*R*,2′*S*)-**VI**	(*S*)-**V**	(*R*)-quinuclidinol	99.1	75
(3*S*,2′*S*)-**VI**		(*S*)-quinuclidinol	99.0	72

[a]The ee is determined by HPLC (Chiradex Cartridge, mobile phase 40 % acetonitrile/60 % 0.05M KH_2PO_4/0.1 % Et_3N at pH 6.5. [b]Yield of the reaction between ester **V** and 3-quinuclidinol.

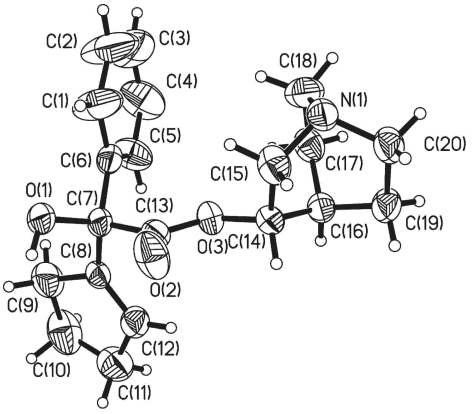

Fig. 1 Crystal structure of the (3*S*,2′*S*)-VI

addition of cyclo-pentanone affords the aldolate (2*R*,5*S*)-**II**. The hydroxy group of **II** can easily eliminate using simple reagents $SOCl_2$/pyridine to give lactone (2*S*,5*S*)-**III**. (*S*)-2-(cyclopent-1-enyl)-2-hydroxy-2-phenylacetic acid **IV** was produced by hydrolysis of **III**. Then **IV** reacted with CH_2N_2 to obtain methyl (*S*)-2-(cyclopent-1-enyl)-2-hydroxy-2-phenylacetate **V**. (3*S*,2'*S*)-**VI** was synthesised by (*S*)-**V** with (*S*) quinuclidin-3-ol. Other isomers were synthesised in the same method as described for (3*S*,2'*S*)-**VI** from the starting material, (*S*) or (*R*)-mandelic acid and (*S*) or (*R*) quinuclidin-3-ol. The final step involved the ring opening of chiral ester with alcohol, which could readily be performed by simple nucleophile substitution with NaH in *n*-heptane, and the results are shown in Table 1.The data in Table 1 show that the enantiopure isomers of **VI** were obtained in moderate yields with high e.e. values by using this synthetic method. Crystals of the (3*S*,2'*S*)-**VI** suitable for X-ray structure determination were obtained by slow evaporation of its CH_2Cl_2 solution. The crystal structure of the (3*S*,2'*S*)-**VI** with atomic labelling is shown in Fig. 1.[4] X-ray structure analytical data showed that the title compound is composed of a quinuclidin-3-ol structure and a tertiary hydroxy acid moiety. In the cyclopentene ring, the bond length of C(8)–C(12) is 1.337(3) Å indicated that the double bond formed in 1-position.

The isomers of quinuclidin-3-ol were resoluted according to the method.[5] The acetate product of racemic quinuclidin-3-ol was obtained by reacting with $(CH_3CO)_2O$ at 160 °C for 3 h, which reacted with (2*R*,3*R*)-tartaric acid to form tartaric acid salt. After recrystallisation in 80 % EtOH for four times, the salt was treated with 2N NaOH at 75 °C for 2 h, then the solution was saturated with anhydrous K_2CO_3 and extracted with benzene at 75 °C give (*S*) quinuclidin-3-ol in 63 % yield. Similarly, (*R*) quinuclidin-3-ol could be obtained with (2*S*,3*S*)-tartaric acid as resolution agent.

Experimental

All the reagents were commercially available or used without further purification or purified by standard methods prior to use. Melting points were determined using a RY-1 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on JNM-ECA-400 400 MHz instrument in the solvent indicated below. Mass spectra were obtained from Micromass ZabSpec and API3000 instruments. Elemental analysis was carried at the CarloErba-1106. Four isomers were synthesised in the same method as described below for (3*S*,2'*S*)-**VI** as an example from the starting material, (*S*) or (*R*)-mandelic acid.

(2S,5S)-2-tert-Butyl-5-phenyl-1,3-dioxolan-4-one **(I):** (*S*)-mandelic acid (15.2 g, 100 mmol) and pivaldehyde (13 ml, 120 mmol) were dissolved in 200 ml pentane, followed by addition of trifluoromethanesulfonic acid (0.3 ml, 3.6 mmol) at 20 °C. The mixture was warmed to 36 °C and allowed to reflux for 5 h, then allowed to cool to room temperature, aqueous $NaHCO_3$ (5 %) was added. The mixture was concentrated *in vacuo* to remove pentane. **I** was obtained by filter the slurry, 20.1 g (90 %). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.81; H, 7.40. ^{1}H NMR ($CDCl_3$): δ 7.45 (m, 5H), 5.31 (s, 1H), 5.25 (s, 1H), 1.10 (s, 9H).

(2R,5S)-2-tert-Butyl-5-(1-hydroxycyclopentyl)-5-phenyl 1,3-dioxolan-4-one **(II):** A homogenised mixture of lithiumbis(trimethylsilyl) amide(50 ml, 50 mmol, 1.0 M in hexanes) and **I** (10.0 g, 45 mmol) in 250 ml THF at –70 °C. The reaction mixture was stirred for 1 h followed by the addition of cyclopentanone (5.5 ml, 60 mmol). After stirring for 3 h, a saturated $NaHPO_4$ solution (25 ml) was added. The reaction mixture was poured into the saturated NH_4Cl solution (150 ml). The aqueous layer was separated and extracted with ethyl acetate. After being concentrated in a vacuum, **II** was obtained as a white solid, 10.8 g (68 %). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.91; H, 7.90. ^{1}H NMR ($CDCl_3$): δ 7.78 (m, 2H), 7.31 (m, 3H), 5.52 (s, 1H), 1.52-2.06 (s, 8H), 0.88 (s, 9H).

(2S,5S)-2-tert-Butyl-5-(cyclopent-1-enyl)-5-phenyl-1,3-dioxolan-4-one **(III): II** (7.6 g, 25 mmol) was dissolved in THF (150 ml), was charged with, followed by adding thionyl chloride (5 ml, 65 mmol) and pyridine (4.5 ml, 5.5 mmol) at 0°C. The reaction mixture was allowed to stir for 3 h at 0 °C, followed by the addition of saturated NH_4Cl solution (150 ml). The aqueous layer was separated and washed with ethyl acetate (50 ml ↔ 3). The combined organic layers were dried (anhydrous Na_2SO_4), filtered, and concentrated *in vacuo* to give **III**, 6.1 g (85 %). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.61; H, 7.85. ^{1}H NMR ($CDCl_3$): δ 7.59 (m, 1H), 7.25 (m, 4H), 6.02 (m, 1H), 5.21 (s, 1H), 1.92-2.50 (m, 6H), 1.07 (s, 9H).

(S)-2-(Cyclopent-1-enyl)-2-hydroxyl-2-phenylacetic acid (IV) and methyl (S)-(cyclopent-1-enyl)-2-hydroxy-2-phenylacetate **(V):** To a solution of **III** (5.7 g, 20 mmol) in methanol (50 ml) was added water (20 ml) and solid KOH (8.0 g, 200 mmol) was added. The reaction was allowed to reflux for 3 h. After cooling to room temperature, the reaction mixture was washed with heptane (100 ml ↔3). The aqueous layer was acidified to pH = 1 with 1 N HCl, and the resulting mixture was extracted with ethyl acetate (100 ml ↔3). The combined organic layers were dried (anhydrous Na_2SO_4), filtered, and concentrated *in vacuo* to give (*S*)-2-(cyclopent-1-enyl)-2-hydroxyl-2-phenylacetic acid **IV**. The crude product **IV** was not separate and further purification and treated with a solution of CH_2N_2 in Et_2O (about 300 mmol), the mixture was stirred at room temperature for 30 minutes, and concentrated *in vacuo* to provide **V** 4.4 g (95 %). MS (ESI): 233.2(M + 1); ^{1}H NMR ($CDCl_3$): δ 7.53 (m, 2H), 7.32 (m, 3H), 5.62 (s, 1H), 3.80 (m, 3H), 2.40 (m, 2H), 1.90 (m, 2H). ^{13}C NMR (CD_3Cl): δ 176.07, 141.65, 127.98, 127.32, 125.82, 79.15, 53.11, 47.16, 26.85, 26.26, 26.20, 25.85.

(3S,2'S)-Quinuclidin-3-yl 2-cyclopentyl-2-hydroxy-2-phenylacetate ((3S,2'S)-VI) **V:** (4.6 g, 20 mmol) and (*S*)-3-quinuclidinol (2.2 g, 18 mmol) were dissolved in anhydrous *n*-heptane (200 ml), NaH (1 g assay 80 %) was added. The solution was reflux for 4 hours. The solvent was removed under reduced pressure; the residue was dissolved in ether (200 ml), washed with water and brine, dried over anhydrous sodium sulfate, and concentrated to dryness. The product was purified by flash-chromatography and (3*S*,2'*S*)-**VI** was isolated

as an white solid (4.7 g, 72 %). m.p. 89–91 °C. ^{1}H NMR ($CDCl_3$): 7.56(2H, m), 7.34 (3H, m), 5.69(1H, s), 4.90 (1H, s), 3.99(s, 1H), 3.14 (m, 1H), 2.75(m, 4H), 2.05(s, 1H), 1.91(m, 2H),1.70(m, 2H), 1.55(m, 1H), 1.39(m, 1H). ^{13}C NMR δ($CDCl_3$), 173.92, 144.47, 140.06, 127.94, 127.81, 126.46, 77.31, 55.10, 47.11, 46.24, 32.53, 32.05, 25.25, 24.29, 23.48, 19.49. ESI-MS: 330.2 (M + 1). Anal. calc. For $C_{20}H_{25}NO_3$: C 73.37, H 7.70, N 4.28; found: C 73.48, H 7.61, N4.22.

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References

1 (a) H. Caner, E. Groner, L. Lery and I. Agranat, 2004, **9**, 105; (b) J. Caldwell, *Modern Drug Discov.* 1999, **2**, 51.
2 (a) M. Mitsuya, Y. Ogino, N. Ohtake and T. Mase, *Tetrahedron* 2000, **56,** 9901; (b) J. P. Carter, L. Noronha-Blob, V.H. Audia, A.C. Dupont, D.W. McPherson, Jr. K.J. Natalie, W.J. Rzeszotarski, C.J. Spagnuolo, P.P. Waid and C. Kaiser, *J. Med. Chem.* 1991, **34**, 3065.
3 (a) X.Y. Han. H. Liu, C.H. Liu, B. Wu, L.F. Chen, B.H. Zhong and K.L. Liu, *Bioorg. Med. Chem. Lett.* 2005, **15**, 1979; (b) H. Liu, C.H. Liu, X.Y. Han, B.H. Zhong and K.L. Liu, *J. Chem. Res.* 2004, 482; (c) P.J. Wu and L.H. Yun, *Chin. J. Med. Chem.* 1999, **9**, 102; (d) L. Wang, L.H. Yun and Q.K. Zhang, *Acta. Pharmaceutica. Sin.* 1996, **31**, 790.
4 H. Liu, X.Y. Han, Y.M. Liu and B.H. Zhong, *Chinese J. Struct. Chem*, In press.
5 B. Ringdahl, B. Resul and R. Dahlbom, *Acta Pharm. Suee.* 1979, **16**, 281.