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Synthesis of the optical isomers of a new anticholinergic drug, penehyclidine hydrochloride (8018)

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Abstract—A practical diastereoselective synthetic method for **8018** enantiopure isomers is described. The intramolecular asymmetric epoxidation of mono-sulfonate **4** was applied for the execution of the synthesis of the key chiral building block for the first time. The isomers were obtained with 70–76% yields in 99–100% ee.

1. Introduction

The design, development, and marketing of new chiral drugs are now a major theme in the drug chirality 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. In January 1996, the FDA announced it would consider further incentives for developing single isomer drugs, owing to their better pharmacokinetics prosperity, safety, and tolerability.[2] Over the past century classical anticholinergic drugs have been widely used for the treatment of certain diseases, such as chronic obstructive pulmonary diseases (COPD), Alzheimer's disease (AD), and urinary incontinence (UI). However, their therapeutic applicability was limited, due to side effects in both the peripheral and central nervous system. For example, oxybutynin (Ditropan),[3] a widely prescribed muscarinic receptor antagonist for the treatment of urinary incontinence, exhibit classical antimuscarine side effects, such as dry mouth. However, another chiral drug candidate, J-104129,[4] a highly potent, orally active, long acting, M_1/M_3 selective antagonist with lower side effects and as such is being investigated for the treatment of COPD. Furthermore, many other muscarinic receptor antagonists were reported in recent years.[5] So there are still many developing rooms in searching for better chiral selective muscarinic receptor antagonists with new molecular structures.

Our groups have engaged in the synthesis and biological activity studies of anticholinergic drugs for many years.[6] And in this process, we found that penehyclidine hydrochloride (**8018**), a new anticholinergic drug, had both antimuscarinic and antinicotinic activities and retained potent central and peripheral anticholinergic activities.[7] Recently, the clinic results demonstrated that **8018** had good curative effect for the pesticides poison of organic phosphorus and soman. Other than the anticholinergic effects to soman, **8018** could accelerate the elimination of P(−)soman in the rabbits blood and reduced the distribution of P(−)soman in the mice diaphragm. Moreover, it could significantly increase bound [^{3}H]soman distribution in small intestine as well as in plasma.[8] 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. Similarly, this kind of racemic compound has also exhibited side effects as classical antimuscarinic drugs in clinical.

Differing from the majority of muscarinic receptor antagonists[9] composed of a tertiary α-hydroxy acid ester bond, **8018** is composed of an ether bond as a linkage that connected the two parts, that is, tertiary α-hydroxyl structure and the azepine base substituent (Fig. 1).

Keywords: Asymmetric; Epoxidation; Isomers; Penehyclidine hydrochloride.
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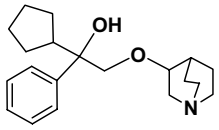
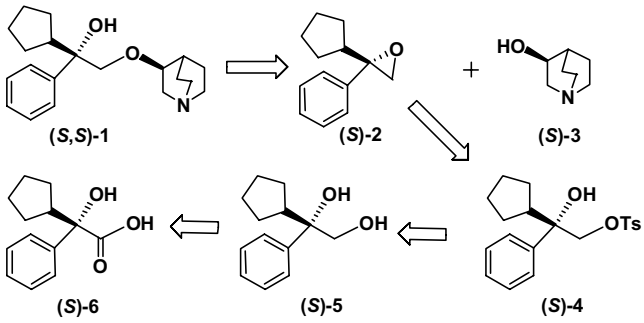


Figure 1. The structure of **8018**.

There are two chiral carbon atoms in **8018** that should have four optical isomers. Preliminary biological results suggested that the four enantiomers have significant difference in cell toxicity on HepG2 and HK-2 cells, and the pharmacology study performed recently showed that the *R*-**1a** isomer in which the two chiral carbon atoms have *R*-configuration displayed an improved therapeutic profile compared to its racemic counterpart (pre-investigated in our institute, unpublished data). Therefore, the synthesis of enantioisomer pure compounds is very important to study the different pharmacological behavior of each optical isomer, to explore new suitable symptoms of these compounds and to reduce side effects that its racemic counterparts have.

The four optical isomers of **8018** were usually synthesized by combining the racemic epoxide **2** and (*R*)- or (*S*)-quinuclidinol **3** to produce a mixture of diastereomers (*R*-**1a**) and (*R*-**1b**) or (*S*-**1a**) and (*S*-**1b**), then each pair of diastereomers were usually prepared by TLC method,[10] which was a tedious work and the yields were often relatively low. Therefore, a practical and direct asymmetric synthetic method for the optical isomers should be developed.

Herein, we report a new and enantioselective synthetic method for the four isomers of **8018** through optical epoxide **2** by employing the asymmetric intramolecular S_N2 process of mono-sulfonate **4** as the key step.



Scheme 1. Retrosynthetic route to (*S*,*S*)-**1**.

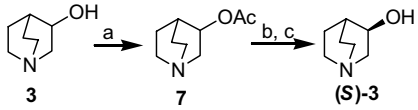
2. Results and discussion

The retrosynthetic route for the synthesis of **8018** optical isomers is shown in Scheme 1 ((*S*,*S*)-**1** as an illustration, other isomers could be obtained in the similar way). Chiral epoxide **2**, the important intermediate for the synthesis of target molecules, could be obtained by the intramolecular Williamson ether synthesis from the mono-sulfonated product of (*S*)-diol **5**. The component (*S*)-**3** required for the (*S*,*S*)-**1** synthesis could be easily obtained through chemical resolution from racemic quinuclidinol **3**.

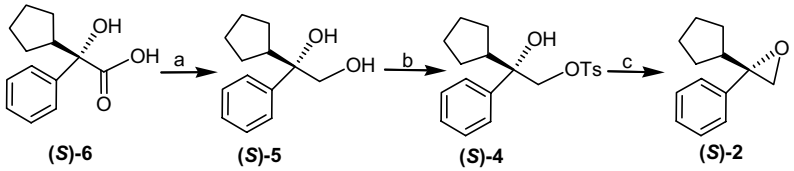
The synthesis of epoxide **2** started from chiral cyclopentyl phenyl hydroxyl acetic acid **6**[11] as illustrated in Scheme 2.

Compound **6** was treated with $LiAlH_4$ in THF to give the reductive product diol **5** in quantitative yield. The absolute configuration of diol **5** should be in accordance with **6** because the reduction did not involve the stereocenter, and this suggestion was confirmed from %ee of the target isomers of **8018** in this paper. Recently, Gupta et al. described the Sharpless asymmetric dihydroxylation of α-cyclohexylstyrene, of which the (*S*)-cyclohexylphenyl-1,2-diol could be obtained with only 92% ee.[12] Therefore, in this paper, we did not adopt this dihydroxylated method but adopted the method shown in Scheme 2. The mono-sulfonation of compound **5** with *p*-TsCl in CH_2Cl_2 under ice-bath condition to give the crude product, which recrystallized from petroleum ether afforded the pure mono-sulfonated product **4** in 79% yield.[13] The subsequent intramolecular Williamson ether synthetic method from **4** in order to obtain the optical pure epoxide **2** was unsuccessful with NaH and catalytic amount of DMSO in THF,[14] of which the ee value of the epoxide **2** only reached 20–30%, while the mono-sulfonate **4** proceeded intramolecular ring closing reaction with K_2CO_3 in MeOH[15] could give epoxide *S*-**2** in quantitative yield.

The compound *S*-**3** was resoluted according to the method[10,16] shown in Scheme 3. The racemic 3-quinuclidinol was reacted with $(CH_3CO)_2O$ at 160 °C for 3 h to give acetate **7**, which reacted with D-(−)-tartaric acid to form

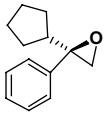
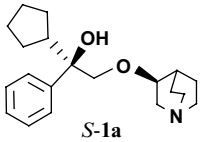
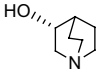
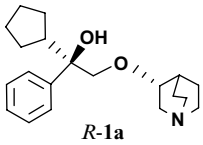
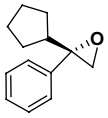
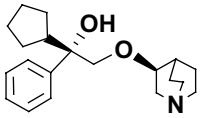
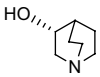
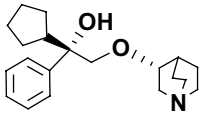


Scheme 3. Reagents and conditions: (a) $(CH_3CO)_2O$, reflux, 3 h, 81%; (b) D-(−)-tartaric acid and 80% EtOH; (c) 2 N NaOH, 70 °C, 1 h, K_2CO_3, extracted with benzene at 70 °C, 63%.



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 1 h, quant; (b) TsCl, anhydrous CH_2Cl_2, Et_3N, 0–5 °C, 79%; (c) K_2CO_3, MeOH, rt, 30 min, quant.

Table 1. Synthetic results of the four isomers[17] of **8018**

Entry	2	3	1	%Ee[a]	Yield[b] (%)
1			 *S*-**1a**	100	75
2			 *R*-**1a**	100	72
3			 *S*-**1b**	99	76
4			 *R*-**1b**	99	70

[a] The ee is determined by HPLC (Chiradex Cartridge, mobile phase 30% acetonitrile/70% 0.05 M KH_2PO_4/0.3% Et_3N at pH 6.0, and the $t_{S\text{-}\mathbf{1a}}$ = 42.8 min, $t_{R\text{-}\mathbf{1b}}$ = 47.9 min).

[b] Yield of the reaction between epoxide **2** and **3**.

tartaric acid salt. After recrystallized in 80% EtOH for three times, the *S*-quinuclidinol tartaric acid salt was obtained in 60% yield. The salt reacted with 2 N NaOH at 70 °C for 1 h, then the solution was saturated with anhydrous K_2CO_3 and extracted with benzene at 70 °C to give *S*-quinuclidinol **3** in 63% yield. Similarly, the compound *R*-**3** could be obtained with D-(+)-tartaric acid as resolution agent.

The final step involved the ring opening of chiral epoxide **2** with alcohol **3**, which could readily be performed by simple nucleophile substitution with NaH[10] in DMSO, and the results are shown in Table 1. The data in Table 1 show that the enantiopure isomers of **8018** were obtained in moderate yields with high ee values by using our synthetic method.

In summary, we developed a facile and efficient procedure to prepare the isomers of **8018** by employing the asymmetric epoxidation of mono-sulfonate **4** for the first time as the key step. The synthetic strategy can be further extended to the asymmetric synthesis of other related C–S and C–N bonds analogs. Currently studies are in progress in these directions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2005.02.071.

References and notes

1. (a) Caner, H.; Groner, E.; Lery, L.; Agranat, I. *Drug Discovery Today* **2004**, *9*, 105; (b) Rouhi, A. M. *Chem. Eng. News* **2003**, *81*, 45; (c) Agranat, I.; Caner, H.; Caldwell, J. *Nat. Rev. Drug Discovery* **2002**, *1*, 753; (d) Eichelbaum, M.; Gross, A. S. *Adv. Drug Res.* **1996**, *28*, 1.
2. Richards, A.; McCague, R. *Chem. Ind.* **1997**, 422.
3. (a) Gupa, P.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 4231; (b) Yarker, Y. E.; Goa, K. L.; Fitton, A. *Drug Aging* **1995**, *6*, 243.
4. (a) Mitsuga, M.; Kobayashi, K.; Kawakami, K.; Satoh, A.; Ogino, Y.; Kawakawa, T.; Ohtake, N.; Kimura, T.; Hirose, H.; Sato, A.; Numazawa, T.; Hasegawa, T.; Noguchi, K.; Mase, T. *J. Med. Chem.* **2000**, *43*, 5017; (b) Mitsuya, M.; Mase, T.; Tsuchiya, Y.; Kawakami, K.; Hattori, H.; Kobayashi, K.; Ogino, Y.; Fujikawa, T.; Satoh, A.; Kimura, T.; Noguchi, K.; Ohtake, N.; Tomimoto, K. *Bioorg. Med. Chem.* **1999**, *2*, 2555.
5. (a) Angeli, P. *IL Farmaco* **1998**, *53*, 1–21; (b) Mckittrick, B. A.; Guo, G. H.; Zhu, Z. N.; Ye, Y. Z. WO Patent 02/051808; (c) Wang, Y. G.; Chang, W. K.; Dugar, S.; Chackalamannil, S. WO Patent 98/051808; (d) Bakale, R. P.; Lopez, J. L.; McConville, F. X.; Vandenbossche, C. P.; Senanayake, C. H. U.S. Patent 6,14,529; (e) Banholzer, R.; Bauer, R.; Reichl, R. U.S. Patent 5,610,163; (f) Beecham, S. *Curr. Opin. Chem. Biol.* **2000**, *4*, 412–419.
6. (a) Liu, H.; Liu, C. H.; Han, X. Y.; Zhong, B. H.; Liu, K. L. *J. Chem. Res.* **2004**, 482; (b) Liu, H.; Han, X. Y.; Liu, C. H.; Zhong, B. H.; Liu, K. L. *Anal. Sci.* **2004**, *20*, 121–122; (c) Wu, P. J.; Yun, L. H. *Chin. J. Med. Chem.* **1999**, *9*, 102; (d) Wang, L.; Yun, L. H.; Zhang, Q. K. *Acta Pharm. Sin. (Chin.)* **1996**, *31*, 790; (e) Wang, X. M.; Yun, L. H.; Wen, G. L.; Zhang, Q. K. *Acta Pharm. Sin. (Chin.)* **1984**, *19*, 748.
7. (a) Niu, W. Z.; Zhao, D. L.; Liu, C. G. *Arch. Int. Pharmacod. Ther.* **1990**, *304*, 64–74; (b) Xue, M.; Ruan, J. X.; Yuan, S. L.; Zhang, Z. Q.; Qiao, J. Z.; Wu, B.; Li, Y. H. *Chin. Pharmacol. Bull.* **2002**, *18*, 447–451.

8. Li, J. T.; Ruan, J. X.; Zhang, Z. Q.; Yuan, S. L.; Yu, W. D.; Song, Z. Y. *Life Sci.* **2003**, *73*, 1053–1062.
9. (a) Mitsuya, M.; Ogino, Y.; Ohtake, N.; Mase, T. *Tetrahedron* **2000**, *56*, 9901; (b) Mitsuya, M.; Kawakami, K.; Ogino, Y.; Miura, K.; Mase, T. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2037; (c) McPherson, D. W.; Knapp, F. F. *J. Org. Chem.* **1996**, *61*, 8335; (d) Kiesewetter, D. O. *Tetrahedron: Asymmetry* **1993**, *4*, 2183.
10. Gao, J. H.; Wen, G. L.; Zhang, Q. K. *Acta Pharm. Sin. (Chin.)* **1987**, *22*, 708–710.
11. Grover, P. T.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *J. Org. Chem.* **2000**, *65*, 6283–6287.
12. Gupta, P.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 4231–4232.
13. Luo, Y. F.; Li, Y. C. *You Ji Hua Xue. (Chin.)* **2002**, *4*, 262–264.
14. Behrens, C. H.; Soo, Y. K.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687.
15. Gurjar, M. K.; Murugaiah, A. M. S.; Radhakrishna, P.; Ramana, C. V.; Chorghadeb, M. S. *Tetrahedron: Asymmetry* **2003**, *14*, 1363–1370.
16. Ringdahl, B.; Resul, B.; Dahlbom, R. *Acta Pharm. Suee.* **1979**, *16*, 281–283.
17. Analytical data of **8018** isomers: *S*-**1a** and *R*-**1b**: Colorless liquid. IR (KBr): 3575, 1450, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20–7.44 (m, 5H), 3.71 (d, 1H, J = 9 Hz), 3.59 (d, 1H, J = 9 Hz), 3.38–3.40 (m, 1H), 2.93–2.96 (m, 1H), 2.85 (s, –OH, 1H), 2.52–2.77 (m, 5H), 2.26–2.32 (m, 1H), 1.98–1.99 (m, 1H), 1.20–1.73 (m, 13H); EIMS (*m*/*z*): 315 (M^+). Compounds *S*-**1b** and *R*-**1a**: Colorless liquid. IR (KBr): 575, 1450, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.42 (m, 5H), 3.71 (d, J = 9 Hz, 1H), 3.58 (d, J = 9 Hz, 1H), 3.35–3.38 (m, 1H), 2.89–2.95 (m, 1H), 2.84 (s, –OH, 1H), 2.52–2.77 (m, 5H), 2.26–2.32 (m, 1H), 1.96–1.99 (m, 1H), 1.23–1.75 (m, 13H); EIMS (*m*/*z*): 315 (M^+).