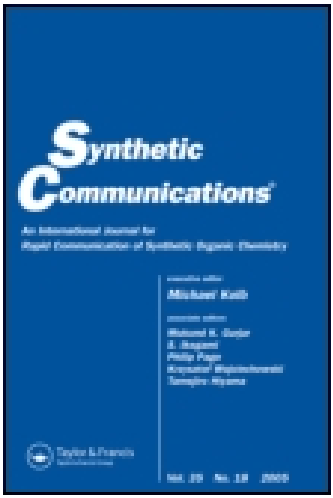

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Optical Resolution, Stereoselective Synthesis, and Crystal Structure of 9α-(3-Azabicyclo[3,3,1]nonanyl)-2

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Optical Resolution, Stereoselective Synthesis, and Crystal Structure of 9α-(3-Azabicyclo[3,3,1]nonanyl)-2′-cyclopentyl-2′-hydroxy-2′-phenylacetate

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Abstract: 9α-(3-Azabicyclo[3,3,1]nonanyl)-2′-cyclopentyl-2′-hydroxy-2′-phenylacetate (**1**) was synthesized and its enantiomers were obtained by the optical resolution of racemates with the chiral host N-*p*-toluenesulfonylglutamic acid. Optical pure **1** was also effective diastereoselective synthesized using benzaldehye as steric hindrance agent from the chiral starting material, (*S*) or (*R*)-mandelic acid. The structure of the title compound was first elucidated by X-ray analysis.

Keywords: Crystal structure, optical resolution, stereoselective synthesis

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Design, development, and marketing of new chiral drugs are now major themes in drug chirality research and industry.[1] The FDA announced it would consider further incentives for developing single-isomer drugs for their better pharmacokinetics prosperity, safety, and tolerability.[2] Our recent drug candidate, 9α-(3-azabicyclo[3,3,1]nonanyl)-2′-cyclopentyl-2′-hydroxy-2′-phenylacetate (**1**), is a potent muscarinic antagonist shown to be more effective treating centric and peripheral choline dysfunctions.[3,4] It is composed of a tertiary hydroxy acid as a key component as in many of the muscarinic receptor antagonists.[5] It exhibits classical antimuscarine side effects, such as dry mouth. Tertiary α-hydroxy acid esters have a stereogenic center and the biology results suggest that the (−)-configuration of **1** displays an improved therapeutic profile compared with its racemic counterpart. The optical resolution of racemates via diastereoisomeric salt formation is a common way for the preparation of optical isomers.[6,7] In our efforts to produce the enantiopure **1**, we found that inclusion crystallization with N-*p*-toluenesulfonylglutamic acid (TSGA) as a chiral host is an effective method for the resolution of the title compound with high enantiomeric excess. In this article we also describe an efficient and scalable asymmetric synthesis of the target molecule **1** by stereoselective α-alkylation of α-hetereosubstituted acids from the chiral starting material, (*S*) or (*R*)-mandelic acid. See Chart 1.

Racemate **1** can be conveniently synthesized by demethylate reaction of 9α-(*N*-methyl-3-azabicyclo[3,3,1]nonanyl)-2′-cyclopentyl-2′-hydroxy-2′-phenylacetate **2**.[4] Optical resolution of **1** was performed as outlined in Scheme 1. To demethylate **2**, carbamate would be desirable. 2,2,2-Trichloroethyl carbamate can be removed with zinc dust in glacial HAc at room temperature.[8] A 1:1 ratio of *rac*-**1** and *L*-(−)-*N*-(*p*-toluenesulfonylglutamic) glutamic acid (*L*-TSGA) were mixed in the anhydrous ethanol at 50°C, then cooled, and an inclusion complex of (−)-**1**·*L*-TSGA was separated out. The precipitated inclusion complex was recrystalized three times in the anhydrous ethanol. (−)-**1** was obtained through alkaline hydrolysis of the resolved acid. The mother liquor was concentrated and alkaline. The residue was added to a solution of *D*-TSGA and then (+)-**1** was obtained through alkaline hydrolysis of (+)-**1**·*D*-TSGA salts.

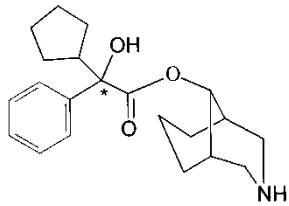
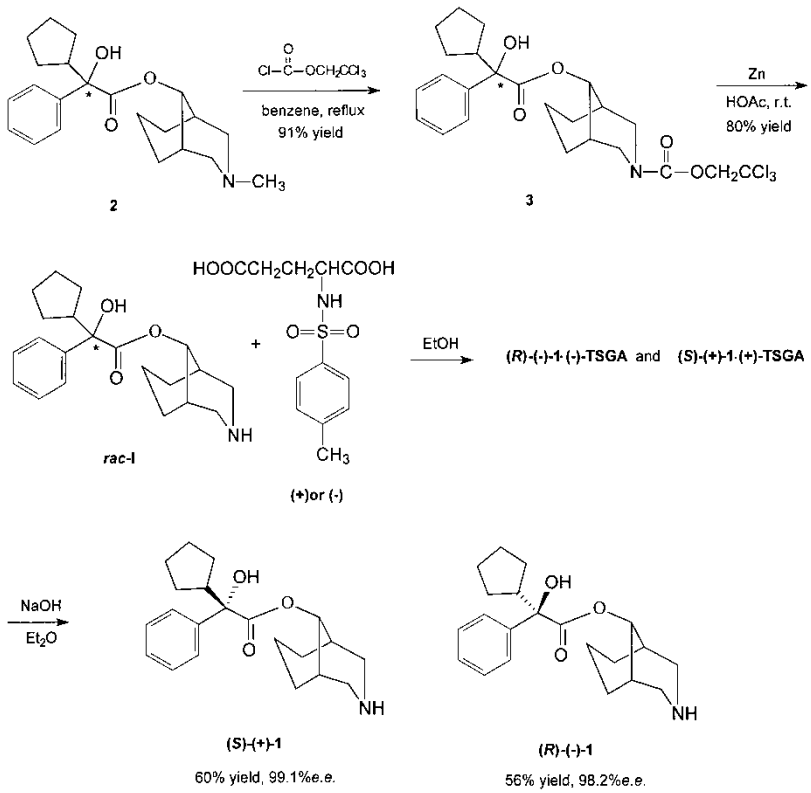
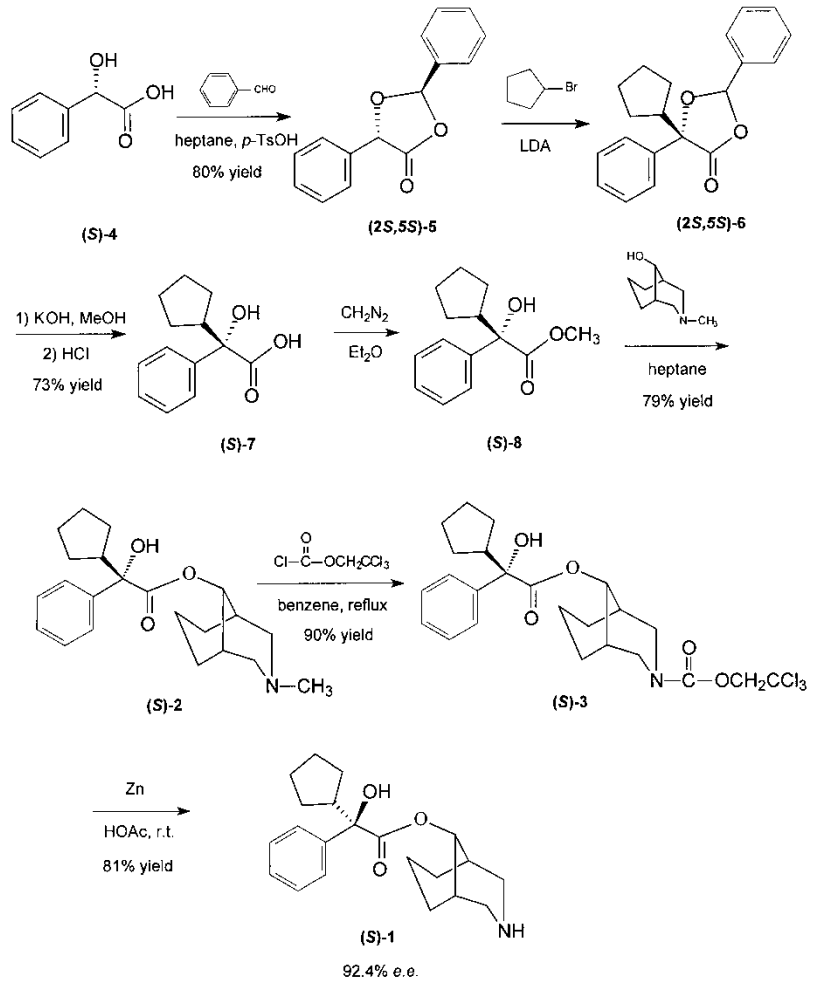


Chart 1.



Scheme 1.

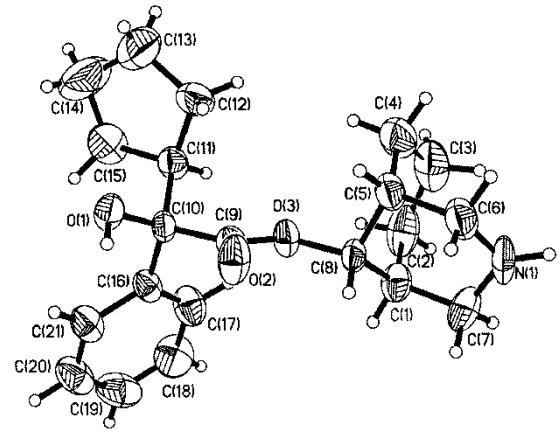
The final target, compound **1**, can be dissected at the ester bond to give two segments, the cabocyclic mandelic acid derivative **7** and the heterobicyclic amine. Recently various asymmetric synthetic protocols for preparation of pure enantiomers of tertiary α-hydroxy phenylacetic acid were reported in the literature.[9] In 1999, Mitsuya reported a diastereoselective synthetic route in which the *(R)*-α-cyclohexyl-α-hydroxy-α-phenylacetic acid with only 86% ee could be obtained.[10] Recently, a new enantioselective synthesis of α-cyclohexyl-α-hydroxy-α-phenylacetic acid employing the Sharpless asymmetric dihydroxylation of α-cyclohexylstyrene as the key step was reported.[11] Herein we present our diastereoselective synthesis results of acid **1** by using benzaldehyde and S-mandelic acid as starting materials. Chrial mandelic acid is inexpensive and available on a commercial scale. Diastereoselective synthesis of the enantiomers of **1** was performed as outlined in Scheme 2 (*S*-mandelic acid **4** is an example). The preparation of high-yielding and highly diastereoselective acetal **5** from mandelic acid was readily accomplished and is amenable to scaling. Deprotonation of pure **5** with lituium



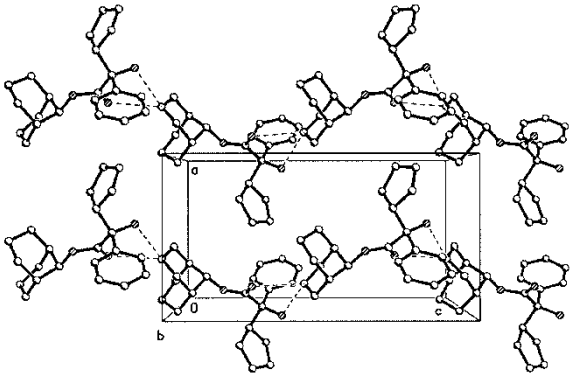
Scheme 2.

diisopropylamide (LDA), followed by the addition of bromocyclopentane, affords the aldolate **6**. (*S*)-α-Hydroxy-α-cyclopentyl-α-phenylacetic acid **7** was produced by hydrolysis of **6**. Then, **7** reacted with CH_2N_2 to obtain methyl (*S*)-α-hydroxy-α-cyclopentyl-α-phenylacetate **8**. Reaction of **8** with 9α-(*N*-methyl-3-azabicyclo[3,3,1]nonane afforded (*S*)-9α-(*N*-methyl-3-azabicyclo[3,3,1]nonanyl)-2′-cyclopentyl-2′-hydroxy-2′-phenylacetate (*S*)-**2**. (*S*)-**1** could be obtained from demethylate reaction. The optical rotation of (*S*)-**1** agreed with the value of (+)-**1** from the optical-resolution method. The absolute structure of (+)-**1** adopted an (*S*)-configuration by two comparison methods. The enantiomers of (*R*)-**1** could be obtained from (*R*)-mandelic acid in a similar way.

(*R*)-(−)-9α-(3-Azabicyclo[3,3,1]nonanyl)-2′-cyclopentyl-2′-hydroxy-2′-phenylacetate [(*R*)-(−)-**1**] was recrystallized from CH_2Cl_2 to give colorless crystal. Its structure was elucidated by X-ray analysis. The X-ray ORTEP structure of (*R*)-(−)-**1** with atomic labeling is shown in Fig. 1a. X-ray structure analytical data showed that the title compound is composed of a 3-azabicyclo[3,3,1]nonane structure and a tertiary hydroxy acid that adopted *R* configuration. The bicyclic structure adopts a twin-chair conformation; this is the most favored conformation for the bicyclo[3,3,1]nonane ring system. In the cyclohexane ring, atoms C(3) and C(8) deviate from the C(1)-C(2)-C(4)-C(5) plane by −0.5642 and 0.7077 Å. In the piperidine



(a)



(b)

Figure 1. (a) The ORTEP structure of (*R*)-**1** with atom labeling; (b) packing diagram showing the quasi-one-dimensional structure with hydrogen bonding.

ring, atoms C(8) and N(1) deviate from the C(1)-C(5)-C(6)-C(7) plane by 0.7661 and −0.4832 Å. So, the cyclohexane and piperidine rings are departures from the ideal chair conformation.[12]

As shown in Fig. 1b, a zigzag quasi-one-dimensional liner structure was formed through N-H···O and N···H-O hydrogen bonds in which two O atoms of the carbonyl and hydroxy groups link the N atom of 3-azabicyclo[3,3,1]nonane in the adjacent molecule. The N···O separations are in the range of 2.837–2.892 Å with the H···O and H···N separations are in the range of 2.029–2.285 Å; the bond angles are 122.15–168.36°, falling into the normal range of the N···O separation for hydrogen bonding.[13]

EXPERIMENTAL

All the reagents for syntheses were commercially available and used without further purification or purified by standard methods prior to use. Melting points were determined using a RY-1 apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240C analyzer. ^{1}H NMR spectra were measured in $CDCl_3$ using a multinuclear FT-NMR spectrometer ARX300 (Bruker). Mass spectra were obtained from Micromass ZabSpec and API3000 instruments. Optical rotations were measured with POLAX-2L polarmeter. The enantiomeric excess of the title compound was determined by HPLC. Condition of HPLC: Hypersil BDS column and β-cyclodextrin as chiral mobile phase additive, methanol–acetonitrile–KH_2PO_4 ($0.075\ mol \cdot L^{-1}$)–H_2O = 25:2:60:18 as eluent. 9α-(*N*-methyl-3-azabicyclo[3,3,1]nonanyl)-2′-cyclopentyl-2′-hydroxy-2′-phenylacetate was synthesized as described in the literature.[4]

9α-(N-trichloroethylformyl-3-azabicyclo[3,3,1]nonanyl)-2′-cyclopentyl-2′-hydroxy-2′-phenylacetate **3**: A mixture of **2** (3.6 g, 10 mmol) and 2,2,2-trichloroethylchloroformate (2.5 g, 12 mmol) in 50 mL of anhydrous benzene was heated under reflux for 20 h. After evaporation of the solvent and excessive 2,2,2-trichloroethylchloroformate, the residual oil was added to a solution of 50 mL of 25–28% $NH_3 \cdot H_2O$ and 50 mL of ether. The organic solution was washed with two 10 mL portions of saturated brine and dried over anhydrous magnesium sulfate. The solution evaporated under reduced pressure to give **3** 4.7 g (91% yield) as a yellow oil. MS (ESI): 519.2$(M+1)^+$.

9α-(3-azabicyclo[3,3,1]nonanyl)-2′-cyclopentyl-2′-hydroxy-2′-phenylacetate **rac-1**: A solution of the yellow oil product in 50 ml of glacial HAc and 3.5 g of zinc dust was stirred for 5 h at room temperature. After removal of the zinc by filtration, the filtrate was basified with concentrated NaOH and extracted with three 50-ml portions of ether. The solution evaporated under reduced pressure to give 2.8 g (80% yield) of colorless solid. MS (ESI): 344.2$(M+1)^+$. Mp 131–133°C. Anal. calcd. for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.51; H, 8.71; N, 4.18. ^{1}H NMR ($CDCl_3$): 7.69

(m, 2H), 7.33 (m, 2H), 7.26 (m, 1H), 4.93 (m, 1H), 3.86 (br, 1H), 3.18 (m, 1H), 3.08 (m, 2H), 3.00 (m, 2H), 2.18 (m, 1H), 2.00 (m, 1H), 1.90 (s, 2H), 1.30–1.70 (m, 12H).

Optical resolution of rac-1: A solution of *rac*-**1** (3.5 g, 10 mmol) and *L-N*-toluenesulfonylglutamic acid (TSGA) (3.0 g, 10 mmol) in anhydrous ethanol (150 mL) was kept at 50°C for 12 h. After being cooled to room temperature, a 1:1 inclusion complex (*R*)-(−)-**1** · *L*-TSGA was obtained as colorless crystals. Recrystallization of the salts from ethanol three times gave pure inclusion crystals. The inclusion complex was basified with $2\,mol \cdot L^{-1}$ NaOH and extracted with ether (50 mL × 3) and dried over anhydrous magnesium sulfate. The solution evaporated under reduced pressure to give optical pure (*R*)-(−)-**1** 0.99 g (56% yield). $[\alpha]_D^{20} = -32.1^\circ$ (c = 2, ethanol), 98.2% ee. Mp 132–133°C. Anal. calcd. for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.41; H, 8.61; N, 4.10.

The mother liquor was concentrated in vacuo and the residue was make alkaline with $2\,mol \cdot L^{-1}$ NaOH. The ester was extract with ether (50 mL × 3) and dried over anhydrous magnesium sulfate. After evaporation of the solvent, a solution of *D-N*-toluenesulfonylglutamic acid (4.0 g, 13 mmol) in anhydrous ethanol (100 mL) was added and the salt (*S*)-(+)-**1** · *D*-TSGA formed was purified in same process as described previously. (*S*)-(+)-**1** was obtained by basified the salt 1.05 g (60% yield). $[\alpha]_D^{20} = +32.5^\circ$ (c = 2, ethanol), 99.1% ee. Mp 132–133°C. Anal. calcd. for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.48; H, 8.48; N, 4.04.

cis-(2S,5S)-2,5-diphenyl-1,3-dioxolan-4-one ((*S*, *S*)-**5**): To a suspension of (*S*)-mandelic acid (25.0 g, 164 mmol) in pentane (250 mL) was added benzaldehyde (20.9 g, 200 mmol), followed by addition of trifluoromethanesulfonic acid (1.23 mL, 14 mmol) at 25°C. To the reaction flask was added a Dean-Stark trap. The mixture was warmed to 36°C and allowed to reflux for 24 h. The reaction mixture was allowed to cool to room temperature and 10 wt % aqueous $NaHCO_3$ was added. The organic layer was separated and the aqueous layer was extracted with ether (50 mL × 3). The combined organic layer was washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was crystallized twice with diethyl ether-pentane to give pure (*S, S*)-**5**, 31.5 g (80%). Mp 83–84°C, $[\alpha]_D^{25} = +66.6^\circ$. ^1H NMR ($CDCl_3$) δ 5.41 (s, 1H), 6.55 (d, $J = 1$ Hz, 1H), 7.30–7.65 (m, 10H). Anal. calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.95; H, 4.99.

(S)-α-Cyclopentyl-α-hydroxy-α-phenylacetic acid ((S)-7): To a −78°C solution of lithium diisopropylamide (60 g, 55 mmol, 10% in hexane solution) in Et_2O (50 mL) was added **5** (12.0 g, 62 mmol, dissolved in 50 mL of Et_2O). The reaction mixture was allowed to stir for 30 min at −60°C, followed by the addition of neat bromocyclopentane (14.9 g, 100 mmol). After stirring for 2 h at −60°C, saturated NaH_2PO_4 solution (50 mL) was added. The reaction mixture was poured into a separatory funnel containing saturated NH_4Cl solution (100 mL). The aqueous layer was separated and extracted with Et_2O (200 mL × 3). The combined organic layers were dried

(Na_2SO_4), filtered, and concentrated in vacuo to provide 11.0 g of crude aldol product **6**, which was used in the next step without purification.

To a solution of 11.0 g crude **6** in 50 mL MeOH and 100 mL water was added solid KOH (25.0 g). The reaction was allowed to reflux for 3 h. After cooling to room temperature, the reaction mixture was poured into 50 mL water and extracted with Et_2O (50 mL × 3) and discarded. The aqueous layer was acidified to pH 1 with 2 N HCl, and the resulting mixtures were extracted with ethyl acetate (100 mL × 3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide 15 g of colorless needle crystals of (S)-α-cyclopentyl-α-hydroxy-α-phenylacetic acid **7**, 9.8 g (73%). ^{1}H NMR ($CDCl_3$) δ 1.84 (s, 3H), 7.30–7.65 (m, 5H, Ar-H). ^{13}C NMR δ 26.0, 75.5, 76.6, 125.1, 128.2, 141.7, 180.4. Anal. calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.81; H, 7.35.

*(S)-9α-(N-Methyl-3-azabicyclo[3,3,1]nonanyl)-2′-cyclopentyl-2′-hydroxy-2′-phenylacetate (S)-**2***: To a solution of 2.2 g **7** (10 mmol) in 50 mL Et_2O was added a solution of CH_2N_2 in Et_2O (about 30 mmol); the mixture was stirred at room temperature for 30 min and concentrated in vacuo to provide crude (*S*)-methyl α-cyclopentyl-α-hydroxy-α-phenylacetate **8**, which was used in the next step without purification. **8** (2.6 g, 11 mmol) and 3-azabicyclo[3,3,1]-nonan-9α-ol (1.5 g, 10 mmol) were dissolved in anhydrous n-heptane (100 mL); NaH (0.5 g assay 80%) was added. The solution was refluxed for 3 h. The solvent was removed under reduced pressure; the residue was dissolved in ether (150 mL), washed with water and brine, dried over anhydrous sodium sulfate, and concentrated to dryness. (*S*)-**2** was purified by flash chromatography (chloroform/methanol, 9:1) and isolated as oil (2.8 g, 79%). Anal. calcd. for $C_{22}H_{31}NO_3$: C, 73.92; H, 8.74; N, 3.92. Found: C, 73.84; H, 8.89; N, 3.90. ^{1}H NMR ($CDCl_3$): 7.63 (m, 2H), 7.35 (m, 3H), 5.00 (s, 1H), 3.76 (m, 2H), 3.15 (m, 2H), 3.00 (m, 2H), 2.89 (s, 3H), 2.287 (s, 1H), 2.07 (s, 1H), 1.94 (m, 2H), 1.30–1.75 (m, 12H). MS (ESI): 364.2 $(M+1)^+$.

(*S*)-**1** could be obtained from demethylate reaction by 2,2,2-trichloroethyl carbamate in a similar way as described in optical resolution process. 92.4% ee. Mp 132–133°C. Anal. calcd. for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.38; H, 8.45; N, 4.01.

(R)-**1** could be obtained from (*R*)-mandelic acid as the start materials in the same process. 91.1 % ee. Mp 132–133°C. Anal. calcd. for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.36; H, 8.53; N, 4.14.

Crystal data: $C_{21}H_{29}NO_3$, $Mr = 343.45$, orthorhombic, $P2_12_12_1$, $a = 8.097(3)$ Å, $b = 14.856(5)$ Å, $c = 15.418(5)$ Å, $V = 1854.6(11)$ Å^3, $D_x = 1.230\,g\,cm^{-3}$, $Z = 4$, $\mu = 0.081\,mm^{-1}$, $T = 293(2)$ K. A colorless crystal with dimensions of 0.26 mm × 0.24 mm × 0.20 mm was mounted on a BRUKER SMART 1000 CCD diffractometer equipped with a graphite monochromator for data collection. The determination of unit cell parameters and data collections were performed with Mo$K\alpha$ radiation ($\lambda = 0.71073$ Å). A total of 8571 reflections with 3776 independent ones with $R_{int} = 0.0129$ and

1600 observed reflections with $I > 2\sigma(I)$ were collected in the range of $1.90 < \theta < 26.41^\circ$ by an $\omega - \theta$ scan mode. All data were corrected by using SADABS method. The structure was solved by direct methods with SHELXL-97 program.[14] The final refinement was performed by full-matrix least-squares method with anisotropic thermal parameters for nonhydrogen atoms on F^2. The hydrogen atoms were added theoretically, riding on the parent atoms, with fixed thermal factors also riding. The weighting scheme was $w = 1/[\sigma^2(F_o^2) + (0.0300P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$. The refinement converged to the final $R = 0.0682$ and $wR = 0.1090$. $S = 0.932$. Molecular graphics were drawn with the program package XP. Full crystallographic details have been deposited with the Cambridge Crystallographic Data Center and allocated the deposition number CCDC-212449.

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REFERENCES

1. (a) Caner, H.; Groner, E.; Lery, L.; Agranat, I. Trends in the development of chiral drugs. *Drug Discovery Today* **2004**, *9*, 105; (b) Rouhi, A. M. Chiral business. *Chem. Eng. News* **2003**, *81*, 45.
2. Food and Drug Administration, FDA's policy statement for the development of new stereoisomeric drugs. Fed. Reg. 22 249, **1992**, *57*.
3. (a) Liu, H.; Liu, C. H.; Han, X. Y.; Zhong, B. H.; Liu, K. L. Studies on crystal structure of inclusion chiral crystal of (S)-α-cyclopentyl-α-hydroxy-α-thienylacetic acid with (R)-α-methyl benylamine. *J. Chem. Res.* **2004**, 482; (b) Liu, H.; Han, X. Y.; Liu, C. H.; Zhong, B. H.; Liu, K. L. Crystal structure of (2S,5R)-2-(tert-butyl)5-phenyl-5-(cyclopentyl-ol)-1,3-dioxolan-4-one. *Anal. Sci.* **2004**, *20*, x121; (c) Wu, P. J.; Yun, L. H. Synthesis of anticholinergics of 2-(1-naphtyl)-2-cyclopentyl-2-hydroxy ethoxy cyclic amine compounds. *Chin. J. Med. Chem.* **1999**, *9*, 102.
4. Wang, L.; Yun, L. H.; Zhang, Q. K. Synthesis of optical isomers of 2α-(2′,2′-disubstitiuted-2′-hydroxyethoxy)tropane as potential M-receptor antagonists. *Acta. Pharmaceutica Sin.* **1996**, *31*, 790.
5. (a) Mitsuya, M.; Ogino, Y.; Ohtake, N.; Mase, T. Diastereoselective synthesis of the acid part of a new muscarinic M_3 receptor antagonist. *Tetrahedron* **2000**, *56*, 9901; (b) McPherson, D. W.; Knapp, F. F. Structure elucidation via stereoselective synthesis of the acetate center of 1-azabicyclo[2.2.2]oct-3-yl α-hydroxy-α-(1-iodo-1-propen-3-yl)-α-phenylacetate (IQNP). A high affinity muscarinic imaging agent for SPECT. *J. Org. Chem.* **1996**, *61*, 8335; (c) Carter, J. P.; Noronha-Blob, L.; Audia, V. H.; Dupout, A. C.; McPherson, D. W.; Natalie, K. J.; Rzeszotarski, J.; Spagnuolo, C. J.; Wald, P. P.; Kaiser, C. Analogues of oxybutynin. Synthesis and antimuscarinic and bladder activity of some substituted7-amino-1-hydroxy-5-heptyn-2-ones and related compounds. *J. Med. Chem.* **1993**, *4*, 2183.

6. Kozma, D.; Ács, M.; Fogassy, E. Predictions of which diastereoisomeric salt precipitates during an optical resolution via diastereoisomeric salt formation. *Tetrahedron* **1994**, *50*, 6907.
7. Vries, T.; Wynberg, H.; van Echtenm, E.; Koek, J.; ten Hoeve, W.; Kellogg, R. M.; Broxterman, Q. B.; Minnaard, A.; Kaptein, B.; van der Sluis, S.; Hulshof, L.; Kooistra, J. The family approach to the resolution of racemates. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2349.
8. Gilbert, A. M.; Coleman, T.; Kodah, J.; Mewshaw, R. E.; Scerni, R.; Schechter, L. E.; Smith, D. L.; Andree, T. H. Novel aryloxy-8-azabicyclo [3.2.1]oct-3-enes with 5-HT transporter and 5-HT_{1A} affinity. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5281.
9. (a) Grover, P. T.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. Chiral mandelic acid template provides a highly practical solution for (*S*)-oxybutynin synthesis. *J. Org. Chem.* **2000**, *65*, 6283; (b) Ortholand, J. Y.; Vicart, N.; Greiner, A. Transacetalization reaction of acetals by lactic acid. Diastereoselective synthesis of 2-substituted 5-methyl-1,3-dioxolan-4-ones. *J. Org. Chem.* **1995**, *60*, 1880; (c) Seebach, D.; Naef, R.; Calderari, G. α-Alkylation of α-heterosubstituted carboxylic acids with racemization. *Tetrahedron* **1984**, *40*, 1313; (d) Seebach, D.; Naef, R. 274. Enantioselective generation and diastereoselective reactions of chiral enolates derived from α-heterosubstituted carboxylic acids. *Helv. Chim. Acta* **1981**, *64*, 2704.
10. Mitsuya, M.; Kawakami, K.; Ogino, Y. Stereoselective synthesis of a new muscarinic M_3 receptor antagonist, J-104129. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2037.
11. Gupta, P.; Fernandes, R. A.; Kumar, P. An asymmetric dihydroxylation route to (*S*)-oxybutynin. *Tetrahedron Lett.* **2003**, *44*, 4231.
12. (a) Kunaran, D.; Ponnuswamy, M. N.; Shanmugam, G.; Ponnuswamy, S.; Jevaraman, R.; Shivakuman, K.; Fun, H.-K. Molecular structure and conformation of three 3-azabicyclonane. *Acta. Cryst.* **1999**, *B55*, 793L; (b) Vijayalakshmi, L.; Parthasarathi, V.; Venkatraj, M.; Jeyaraman, R. 2,4-Bis(O-tolyl)-3-azabicyclo[3.3.1]nonan-9-one. *Acta. Cryst.* **2000**, *C56*, 1240.
13. (a) Desiraju, G. R. The C-H$\cdots$O hydrogen bond in crystals: What is it? *Acc. Chem. Res.* **1991**, *24*, 290; (b) Jeffrey, G. A.; Saenger, W. Eds.; *Hydrogen Bonding in Biological Structure*rey; Springer: Berlin, 1991; pp. 29–32.
14. Sheldrick, G. M. *SHELXS-97, Program for X-ray Crystal Structure Solution*; Göttingen University: Germany, 1997.