Stereoselective synthesis of 3-azabicyclo[3,3,1]nonan-9α-yl α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetate hydrochloride

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The isomers of α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetic acid esters derived from 3-azabicyclo[3,3,1]nonan-9α-ol ((*R*)-1 and (*S*)-1) were obtained in high enantiomeric excess by effective stereoselective synthesis from the chiral starting material, (*S*) or (*R*)-mandelic acid using pivaldehyde as a sterically hindered reagent

Keywords: stereoselective synthesis, tertiary α-hydroxy acid, mandelic acid

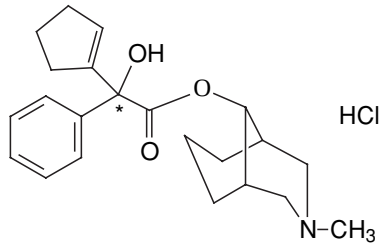
The development, of new chiral drugs are now important, owing to their better pharmacokinetics and, safety.[1,2] Anticholinergic drugs have been widely used for the treatment of certain diseases, such as chronic obstructive pulmonary diseases, Alzheimer's disease and urinary incontinence. However, their therapeutic applicability was limited, due to side effects on both the peripheral and central nervous system. Most of the muscarinic receptor antagonists contain a chiral tertiary α-hydroxy acid as a key component.[3] We have been engaged in the synthesis and biological activity study of anticholinergic drugs for many years.[4] Our recent drug candidate 3-azabicyclo[3,3,1]nonan-9α-yl α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetate hydrochloride (**1**·HCl) is a potent selective M_1 antagonist for the treatment and prevention of motion sickness. It exhibits classical antimuscarine side effects, such as dry mouth. Tertiary α-hydroxy acids have one stereogenic centre. The biological results suggest that the (-)-configuration of **1** displays an improved therapeutic profile compared to its racemic counterpart.

In addition to studies on the stereoselective pharmacodynamics and pharmacokinetics, which are important in chiral drug bioanalysis and the relative contribution of the enantiomers to overall drug action,[5] we have investigated the synthesis of the isomers of **1** in order to study their individual activity. We now describe an efficient and scalable asymmetric synthesis of the target molecule **1** by the stereoselective α-alkylation of α-hetereosubstituted acids from the chiral starting material, (*S*) or (*R*)-mandelic acid.

Recently various asymmetric synthetic protocols for the preparation of pure enantiomers of tertiary α-hydroxy phenylacetic acid have been reported in[6] Chrial mandelic acid is inexpensive and available on a commercial scale. The final target compound **1** can be dissected at the ester bond to give two segments, the cabocyclic mandelic acid derivative **6** and the 3-azabicyclo[3,3,1]nonan-9α-ol. Diastereoselective synthesis of **1** was performed as outlined in Scheme 1 using (*S*)-mandelic acid as an example. The preparation of high yielding and highly diastereoselective acetal **2** from mandelic acid was readily accomplished by a method which was amenable to scale-up. Deprotonation of pure **2** with lithium bis(trimethylsilyl) amide(LHMDS) and followed by the addition of cyclopentanone affords the aldol **3**. The hydroxy group of **3** can be easily eliminated using simple reagents ($SOCl_2$/pyridine) to give the lactone **4**, which was then hydrolysed to produce α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetic acid **5.**

Experimental

All the reagents were commercially available. Melting points were determined using a RY-1 apparatus and are uncorrected. IR spectra (KBr) were recorded on a Nicolet 550 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on JNM-ECA-400 400 MHz instrument in the solvent indicated below. Chemical shift values are reported in parts per million (ppm) relative to that for tetramethylsilane used as an internal reference standard. Mass spectra were obtained from Micromass ZabSpec and API3000 instruments. Elemental analysis was carried at the CarloErba-1106. 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 moll^{-1}): H_2O=25:2:60:18 as elute. All reactions were monitored by TLC on 25 × 75mm glass sheets precoated with silica gel (GF254) to a thickness of 0.25mm and viewed at 254nm UV-light. 3-azabicyclo[3,3,1]nonan-9α-ol was synthesised by reduction 3-azabicyclo[3,3,1]nonan-9-one of using PtO_2 as catalyser as a sole product.[4d,7] The key intermediates of (*S*) and (*R*)- α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetic acid were synthesised by a modified method as described in the literature.[8]



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(2S,5S)-2-(tert-Butyl)-5-phenyl-1,3-dioxolan-4-one (**2**): (*S*)-Mandelic acid (15.2 g, 100 mmol) and pivaldehyde (13 ml, 120mmol) 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 5.5 h, then allowed to cool to room temperature, Aqueous $NaHCO_3$ (5%) was added. The mixture was concentrated *in vacuo* to remove pentane. (*2*S,*5*S)-2-(*tert*-Butyl)-5-phenyl-1,3-dioxolan-4-one **2** 20.1 g (91%) was obtained by filtration of the slurry. $[\alpha]^{20}_D$= +87.3°(*c*=0.5, $CHCl_3$), m.p. 141–143 °C. IR(KBr)ν_{max}(cm^{-1})2982m, 1805s, 1204m, 1095m, 970s. 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).

(2S,5R)-2-(tert-Butyl)-5-phenyl-5-(cyclopentyl-1-ol)-1,3-dioxolan-4-one (**3**): A homogenised mixture of lithiumbis(trimethylsilyl)amide (20 ml, 20mmol, 1.0 M in hexanes) and **2** (4.0 g, 18.2 mmol) in 100 ml THF at –78 °C. The reaction mixture was stirred for 0.5 h followed by the addition of cyclopentanone (2.2 ml, 24 mmol). After stirring the mixture for 2 h, a saturated $NaHPO_4$ solution (5 ml)was added. The reaction mixture was poured into the saturated NH_4Cl solution (30 ml). The aqueous layer was separated and extracted with ethyl acetate. After being concentrated *in vacuo*, (*2*S,*5R*)-2-(*tert*-butyl)-5-phenyl-5-(cyclopentyl-1-ol)-1,3-dioxolan- 4-one **3** 4.1 g (67%) was obtained as a white solid. $[\alpha]^{20}_D$ = –57.8°(*c*=0.75, $CHCl_3$), m.p. 112–114 °C. 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 7.76 (dd, *J*=1.4, 8.1Hz, 2H), 7.35 (m, 3H), 5.54 (s, 1H), 1.55–2.10 (m, 8H), 0.92 (s, 9H). ^{13}C NMR ($CDCl_3$), δ 172.80, 136.10, 128.30, 127.82, 126.82, 111.19, 87.15, 85.60, 35.81, 35.28, 35.16, 23.70, 23.40, 23.01.

(2S,5S)-2-(tert-butyl)-5-phenyl-5-(cyclopentyl-1-ene)-1,3-dioxolan-4-one (**4**): Compound **3** (3.0 g, 10 mmol) was dissolved in THF (50ml), was treated with thionyl chloride (2 ml, 27 mmol) and pyridine (1.76 ml, 21.73 mmol) at 0°C. The reaction mixture was allowed to stir for 2 h at 0 °C, followed by the addition of saturated NH_4Cl solution (60 ml). The aqueous layer was separated and washed

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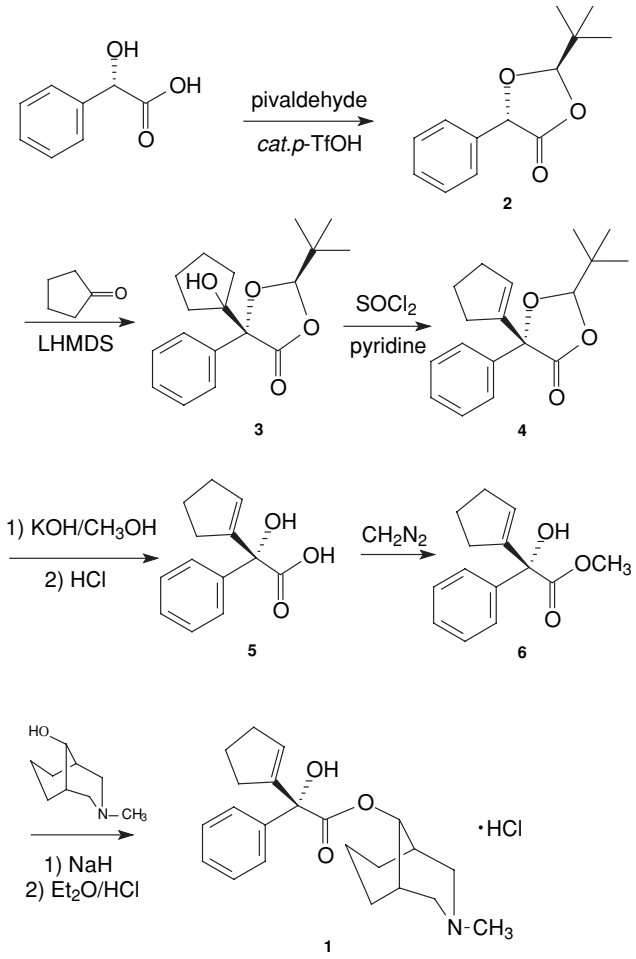

Scheme 1

with ethyl acetate (100 ml × 3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give (2*S*,5*S*)-2-(tert-butyl)-5-phenyl-5-(cyclopentyl-1-ene)-1,3-dioxolan-4-one **4** 2.8 g (98%). $[\alpha]^{20}_D$ = –24.6°(c=0.5, $CHCl_3$), m.p. 89–90 °C. 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 7.56 (m, 1H), 7.30 (m, 4H), 6.02 (m, 1H), 5.24 (s, 1H), 1.91-2.50 (m, 6H), 1.05 (s, 9H).

(S)-methyl- α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetate (**6**): Water (10 ml) was added to a solution of **4** (2.8 g, 10 mmol) in methanol (10 ml) followed by solid KOH (4.0 g, 100 mmol). The reaction was allowed to reflux for 3 h. After cooling to room temperature, the reaction mixture was washed with heptane (50 ml × 2). The aqueous layer was acidified to pH1 with 1 N HCl, and the resulting mixture was extracted with ethyl acetate (50 ml × 3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give (*S*)-α-(cyclopentyl-1-ene)-α-hydroxyl-α-phenylacetic acid **5**. The crude product **5** was not separated and further purified but treated with a solution of CH_2N_2 in Et_2O (about 300 mmol). The mixture was stirred at room temperature for 30 min, and concentrated *in vacuo* to provide (*S*)-methyl α-(cyclopentyl-1-ene)-α-hydroxyl-α-phenylacetate **6** (2.5 g (95%)). $[\alpha]^{20}_D$ = +12.5°(*c*=0.5, $CHCl_3$). IR(KBr)ν_{max}(cm^{-1}) 3350s, 3075m, 2930m, 1715s, 1581m, 1425m, 1295m, 930s, 700m. MS (ESI): 255.2(M+Na^+); ^{1}H NMR ($CDCl_3$): δ 7.53 (m, 2H), 7.32 (m, 3H), 5.62 (d, *J*=1.7Hz, 1H), 3.80 (s, 3H), 2.40 (m, 4H), 1.90 (q, *J*=7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$), δ 174.65, 144.59, 139.87, 129.54, 127.99, 127.83, 126.54, 78.61, 53.26, 32.49, 31.92, 23.40.

(S)-3-azabicyclo[3,3,1]nonan-9α-yl α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetate hydrochloride ((*S*)-**1**·HCl): Compound **6** (2.3g, 10mmol) and 3-azabicyclo[3,3,1]nonan-9α-ol (1.5g, 10mmol) were dissolved in anhydrous *n*-heptane (100 ml), and NaH (0.5g assay 80%) was added. The solution was refluxed for 3 hours. 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. The solution was treatment with a solution of anhydrous HCl in Et_2O (1.0 mol l^{-1}, 20ml), the precipitation was filtered and washed with cooled Et_2O, dried under vacuum. (*S*)-**1**·HCl (3.2g, 81%). $[\alpha]^{20}_D$ = +24.3°(*c*=0.5, $CHCl_3$), 98 % e.e.. m.p. 215–216 °C. IR(KBr)ν_{max}(cm^{-1}) 3492s, 3076m, 2923m, 1708s, 1571m, 1448m, 1251m, 1062m, 966s, 700m. Anal. Calcd for $C_{22}H_{30}ClNO_3$: C, 67.42; H, 7.72; N, 3.57. Found: C, 67.34; H, 7.70; N, 3.61%. ^{1}H NMR δ($CDCl_3$) δ 7.58(m, 2H), 7.31(m, 3H), 5.71(d, *J*=2.00 Hz, 1H), 4.87 (d, *J*=3.4 Hz, 1H), 3.86(s, 1H), 2.84(m, dd, *J*=17.1, 11.5 Hz, 2H), 2.39(m, 5H), 2.28(*t*, *J*=13.7 Hz, 2H), 2.11(s, 3H), 1.93(m, 3H), 1.80(brs, 2H), 1.56(m, 1H), ^{13}C NMR (CD_3Cl) δ 173.80, 144.65, 140.15, 129.22, 127.85, 127.73, 126.65, 78.47, 60.92, 60.80, 45.84, 33.16, 32.67, 32.58, 32.07, 25.17, 24.73, 23.52, 20.70.

(*R*)-*3-azabicyclo[3,3,1]nonan-9α-yl α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetate hydrochloride* ((*R*)-**1**·HCl): Compound (*R*)-**1**·HCl was synthesised in the same method as described for (*S*)-**1** from (*R*)-mandelic acid as the starting material. (*R*)-**1**·HCl: $[\alpha]^{20}_D$ = -24.4°(*c*=0.5, $CHCl_3$), 96 % e.e.. m.p. 215–216 °C. IR(KBr)ν(cm^{-1}) 3490s, 3078m, 2925m, 1709s, 1575m, 1450m, 1250m, 1065m, 966s, 701m. Anal. Calcd for $C_{22}H_{30}ClNO_3$: C, 67.42; H, 7.72; N, 3.57. Found: C, 67.31; H, 7.83; N, 3.51%. ^{1}H NMR δ($CDCl_3$) δ 7.58(m, 2H), 7.31(m, 3H), 5.71(d, *J*=1.96 Hz, 1H), 4.87(d, *J*=3.4 Hz, 1H), 3.86(s, 1H), 2.84(m, dd, *J*=17.1, 11.5 Hz, 2H), 2.38(m, 5H), 2.26(t, *J*=13.7 Hz, 2H), 2.11(s, 3H), 1.93(m, 3H), 1.81(brs, 2H), 1.56(m, 1H), 1.38(m, 3H). ^{13}C NMR ($CDCl_3$) δ 173.80, 144.65, 140.15, 129.22, 127.87, 127.73, 126.65, 78.46, 62.75, 60.91, 60.79, 45.84, 33.14, 32.67, 32.58, 32.08, 25.15, 24.72, 23.53, 20.71.

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