Synthesis of (*R*)-(-)-phenylpiperidin-1-yl-acetic acid and its utilization for the synthesis of (*R*)-(-)-Bietamiverine and (*R*)-(-)-Dipiproverine

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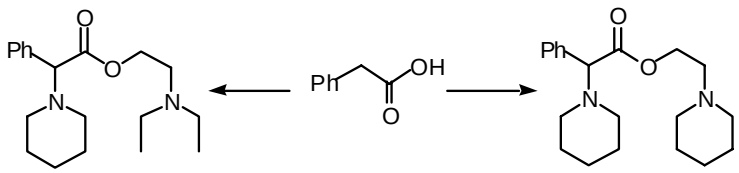
Abstract

A synthesis of (*R*)-(-)-phenylpiperidin-1-yl-acetic acid **2** starting from (*R)*-(-)-α-phenylglycine **1** is described. Additionally, an enantiopure synthesis of bietamiverine **6** and dipiproverine **7** using as starting material **2** is reported.

Keywords: Asymmetry synthesis, (*R*)-(-)-phenylpiperidin-1-yl-acetic acid, (*R*)-(-)-bietamiverine and (*R*)-(-)-dipiproverine

Introduction

Chirality is a major concern in the modern pharmaceutical industry. This interest can be attributed largely to a heightened awareness that enantiomers of a racemic drug may have different pharmacological activities, as well as different pharmacokinetic and pharmacodynamic effects. Thus, one isomer may produce the desired therapeutic activities while the other may be inactive or, in worst cases, produce unwanted effects.[1] However, bietamiverine and dipiproverine have been only synthesized as racemic mixtures by transformation of phenylacetic and these are used as antispasmodic and anticholinergic respectively.[2-4] (Scheme 1).

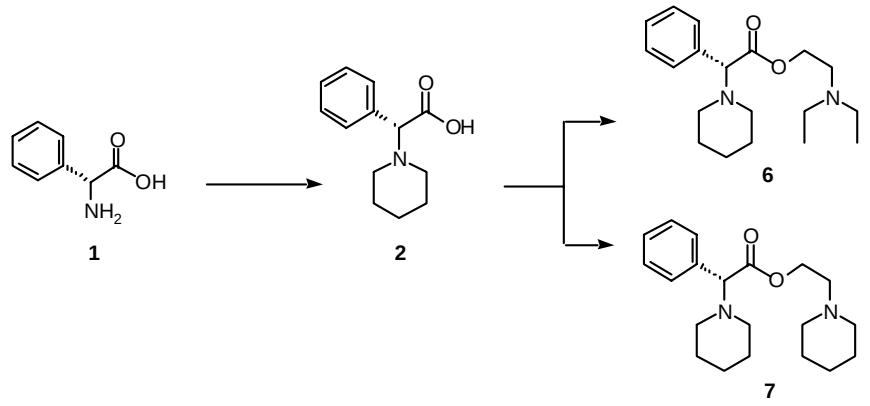


(±)-Bietamiverine Phenyl-acetic acid (±)-Dipiproverine

Scheme 1

Results and Discussion

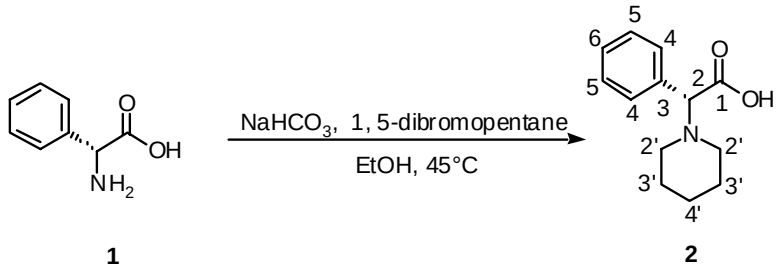
In this work, we described an enantiopure synthesis of (*R*)-(-)-phenylpiperidin-1-yl-acetic acid **2** starting from (*R)*-(-)-α-phenylglycine **1**. Additionally, we reported an enantiopure synthesis of bietamiverine **6** and dipiproverine **7** using as starting material compound **2**. (Scheme 2).



Scheme 2

Racemization studies of enantiopure phenylglycine and its derivatives have been of interest to divers specialists. Analytical chemists find it a challenge to measure the rate of racemization using small quantities while synthetic peptide chemists take precautions to avoid the process.[5]

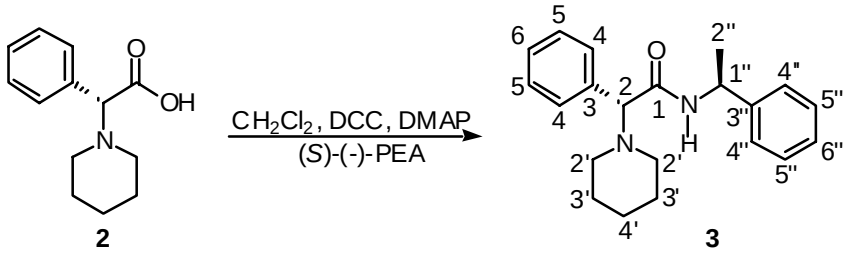
In this context, we investigated firstly the conditions to convert the (*R*)-(-)-α-phenylglycine **1** into compound **2** and evaluated its enantiomeric purity. We found that if a suspension of **1** in ethanol in presence of sodium bicarbonate is added 1,5-dibromopentane and stirred during 8 h gave **2** in 95% yield. In this process, we can establish that between 40°C and 50°C was possible to avoid the racemization of **1** to furnish **2** in its enantiopure form. (Scheme 3).



Scheme 3

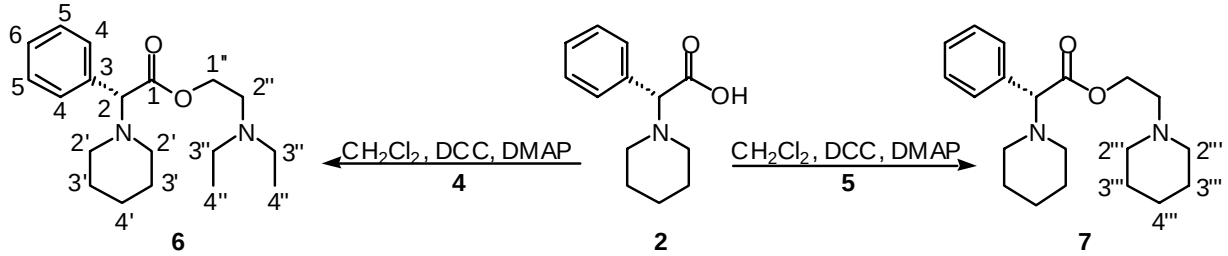
To determinate the enantiomeric purity of **2**, this compound was converted to the corresponding (2*R*,1"*S*)-(-)-phenyl-*N*-(1"-phenylethyl)-2-piperidin-1'-yl-acetamide **3** using (*S*)-(-)-1-phenylethylamine. Treatment of **2**

with 1,3-dicyclohexylcarbodiimide (DCC) in presence of 4-dimethylaminopyridine (DMAP) at 0°C, followed by reaction with (*S*)-(-)-1-phenylethylamine [(S)-(-)-PEA)] delivered the desired compound **3** in 90% yield. The ^{1}H and ^{13}C NMR spectral data of the crude reaction not showed diasteromeric contributions, these results demonstrated that no racemization occurs in the preparation of **2** and **3**. Assignments of the ^{1}H NMR of **3** were confirmed by ^{1}H-^{13}C correlation techniques (Scheme 4).



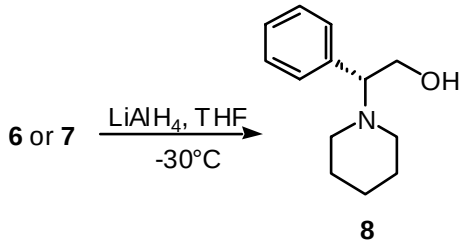
Scheme 4

Following the same procedure to prepare the amide **3**, we carried out the esterification of **2** with 2-diethylamino-ethanol **4** and 2-piperidin-1-yl-ethanol **5** in 90% yield respectively. Assignments of the ^{1}H NMR of **6** and **7** were confirmed by ^{1}H-^{13}C correlation techniques. (Scheme 5).



Scheme 5

Finally, to confirm the optical purity of **6** and **7**, these compounds were converted into **8** with $LiAlH_4$, in 90% yield. All spectral properties of this compound were in complete agreement with those reported in our previous publication. (Scheme 6).[6]



Scheme 6

Conclusions

We have described an efficient enantiopure synthesis of (*R*)-(-)-phenylpiperidin-1-yl-acetic acid **2** starting from (*R*)-(-)-α-phenylglycine **1**. According to our knowledge, this is the first report that describes the conditions to prepare the enantiopure compounds **2**, **6** and **7**.

Experimental Section

General Procedures. ^{1}H NMR spectra of $CDCl_3$ solutions were recorded with a Varian Unity instrument at 300 and 400 MHz (internal tetramethylsilane as reference). IR spectra were obtained with a Nicolet FT-IR Magna 750 spectrometer. Chromatography was carried out using Al_2O_3. Mass spectra were recorded with a JEOL JEM-AX505HA instrument at a voltage of 70 eV. Optical rotations were determined at room temperature with a Perkin-Elmer 341 polarimeter, using a 1dm cell with a total volume of 1mL and are referenced to the D-line of sodium.

(*R)*-(-)-Phenylpiperidin-1-yl-acetic acid (2). To a suspension of **1** (0.529 g, 3.50 mmol) in ethanol (40 mL) at 0^{o}C was stirred and then added sodium bicarbonate (1.029 g, 12.25 mmol), after 1,5-dibromopentane (0.805 g, 3.85 mmol) was added dropwise over 10 min. The reaction was heated and vigorously stirred during 8 h in such a way that the reaction temperature did not exceed 45 ^{o}C. The reaction mixture was cooled to 0°C and poured into HCl solution (10% aqueous to pH=7), extracted with dichloromethane (3x20 mL), and the extract was washed with water (2x10 mL), dried over sodium sulfate and evaporated in vacuo to give compound **2** as a white solid in 95% yield. Mp. 145-147°C; $[\alpha]_D^{20}$ -54.6 (c 1.0, CH_2Cl_2); IR (film, cm^{-1}): 1633; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm, *J* Hz): 7.52 (2H-5, m); 7.34 (2H-4, 1H-6, m); 4.57 (1H-2, s), 3.12 (2H-2'$_{ax}$, m); 2.80 (2H-2'$_{eq}$, m); 1.66 (4H-3', m); 1.41 (2H-4' m). ^{13}C NMR ($CDCl_3$): C-1, 162.21; C-3, 133.97; 2C-4, 2C-5, C-6 129.83-128.90; C-2, 74.03; 2C-2', 51.76; 2C-3', 22.82; C-4', 22.25. EI-MS: m/z (%) 220 (10, M^++1), (174, 100). HRMS (FAB+): Calcd for $C_{13}H_{17}NO_2$: 220.1259; found: 220.1250.

(2*R*,1''*S*)-(-)-Phenyl-*N*-(1''-phenylethyl)-2-piperidin-1'-yl-acetamide (**3**)**.** To a solution of **2** (0.219 g, 1.0 mmol) in anhydrous dichloromethane (20 mL) at 0 ^{o}C, under nitrogen atmosphere, was added DCC (0,227 g, 1.1 mmol), DMAP (0.012 g, 0.1 mmol) and (S)-(-)-PEA (0.137 g, 1.0 mmol). The reaction mixture was vigorously stirred for 4 h and then poured into NH_4Cl solution (5 mL), extracted with dichloromethane (3x20 mL), and the extract was washed with water (2x10 mL), dried over sodium sulfate and evaporated in vacuo. Compound **3** was obtained in 95% yield as oil colorless after purification by column chromatography on Al_2O_3 (petroleum ether/dichloromethane); $[\alpha]_D^{20}$ –81.5 (c 1.0, CH_2Cl_2); IR (film, cm^{-1}): 1652; ^{1}H NMR (400 MHz, $CDCl_3$,): δ (ppm, *J* Hz): 7.55 (1H, d, 8.07, N-H); 7.38-7.13 (10H, m, 2H-4, 2H-5, 1H-6, 2H-4'', 2H-5'', 1H-6''); 5.15 (1H-1'', m, 6.97, 7.33); 3.86 (1H-2, s); 2.34 (4H-2', m); 1.55 (4H-3', m, 5.50); 1.53 (3H-2'', d, 6.60); 1.41 (2H-4', m). ^{13}C NMR ($CDCl_3$): C-1, 171.01; C-3, 143.39; C-3'', 135.96; 2C-4, 2C-5, C-6, 2C-4'', 2C-5'', C-6'', 129.11-126.12; C-2, 76.39; 2C-2', 52.80; C-1'', 47.91; 2C-3', 26.34; C-4', 24.31; C-2'', 21.76. EI-MS: m/z (%) 323 (15, M^++1), (174, 60), (120, 100). HRMS (FAB+): Calcd for $C_{21}H_{26}N_2O$: 322.2045; found: 322.2039.

Esterification of 2. General procedure. To a solution of **2** (0.219 g, 1.0 mmol) in anhydrous dichloromethane (30 mL) at 0 ^{o}C under nitrogen atmosphere, was added DCC (0.227 g, 1.1 mmol), DMAP (0.012 g, 0.10 mmol) and aminoalcohol **(4)** or **(5)** (1.0 mmol). The reaction mixture at 10 ^{o}C

was vigorously stirred for 4 h, then poured into NH_4Cl solution (5 mL), extracted with dichloromethane (3x10 mL) and the extract was washed with water (2x10 mL), dried over sodium sulfate and evaporated in vacuo. Compound **6** and **7** were obtained as colorless oil in 90% yield respectively after purification by column chromatography on Al_2O_3 (dichloromethane/*n*-hexane).

(*R*)-(-)-Phenylpiperidin-1'-yl-acetic acid 2''-diethylaminoethyl ester (6). For **6** (2HCl, white solid); $[\alpha]_D^{20}$ -57.4 (c 1.0, CH_2Cl_2); Mp. 142-144°C; (lit[2]: 194-195°C racemic). IR (film, cm^{-1}): 1738. ^{1}H NMR (free base); (400 MHz, $CDCl_3$): δ (ppm, *J* Hz): 7.44 (2H-4, m); 7.30 (3H, m, 2H-5, 1H-6); 4.17 (2H-1", m, 5.13, 5.87, 6.23); 3.96 (1H, s, H-2), 2.63 (2H-2", t, 6.23); 2.49 (4H-3", q, 6.97, 7.33); 2.38 (4H-2' m); 1.59 (4H-3', m, 5.13, 5.50, 5.87); 1.43 (2H-4', m, 5.13, 5.87, 6.60); 0.97 (6H-4", t, 6.97, 7.33). ^{13}C NMR ($CDCl_3$): C-1, 171.82; C-3, 136.24; 2C-4, 128.84; 2C-5, 128.37; C-6, 128.07; C-2, 75.05; C-1", 62.85; 2C-2', 52.42; C-2", 50.92; 2C-3", 47.34; 2C-3', 25.75; C-4', 24.34; 2C-4", 11.83. EI-MS: m/z (%) 319 (28, M^++1), (247, 17) (174, 50), (100, 100). HRMS (FAB+): Calcd for $C_{19}H_{30}N_2O_2$: 318.2307; found: 318.2298.

(*R*)-(-)-Phenylpiperidin-1'-yl-acetic acid 2''-piperidin-1'''-yl-ethyl ester (7). For **7** (2HCl, white solid); $[\alpha]_D^{20}$ -48.8 (c 1.0, CH_2Cl_2). Mp. 148-150°C; (lit[2]: 212-214°C racemic). IR (film, cm^{-1}): 1752. ^{1}H NMR (free base); (400 MHz, $CDCl_3$,): δ (ppm, *J* Hz): 7.42 (2H-4, m); 7.28 (3H, m, 2H-5, 1H-6); 4.19 (2H-1", t, 5.86); 3.93 (1H-2, s); 2.51 (2H-2", t, 5.86); 2.34 (8H, m, 4H-2', 4H-2'"); 1.53 (8H, m, 5.49, 5.86, 6.22, 4H-3', 4H-3'"); 1.39 (4H, m, 5.49, 5.86, 6.22, 2H-4', 2H-4'"). ^{13}C NMR ($CDCl_3$): C-1, 171.78; C-3, 136.33; 2C-4, 128.95; 2C-5, 128.46; C-6, 128.16; C-2, 75.33; C-1", 62.14; C-2", 57.19; 2C-2', 54.59; 2C-2'", 52.54; 2C-3', 25.91; 2C-3'", 25.81; C-4', 24.43; C-4'", 24.23. EI-MS: m/z (%) 331 (25, M^++1), (247, 19) (174, 52), (112, 100). HRMS (FAB+): Calcd for $C_{20}H_{30}N_2O_2$: 330.2307; found: 330.2300.

Acknowledgments

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