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A practical synthesis of ethyl (*R*)- and (*S*)-2-hydroxy-4-phenylbutanoate and D-homophenylalanine ethyl ester hydrochloride from L-malic acid

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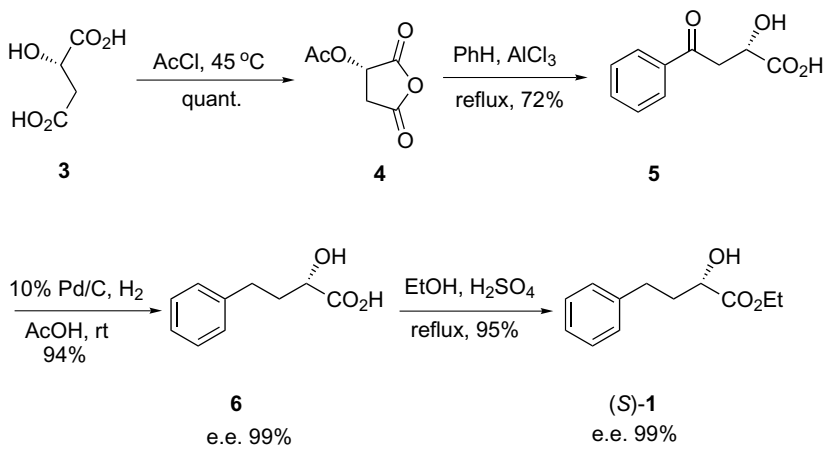
Abstract—With the readily available L-malic acid as starting material, both enantiomers of ethyl 2-hydroxyl-4-phenylbutanoates and D-homophenylalanine ethyl ester hydrochloride were prepared conveniently in excellent optical purity and 64, 53 and 49% overall yield, respectively. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Ethyl (*R*)-2-hydroxyl-4-phenylbutanoate (*R*)-**1** and ethyl (*S*)-2-hydroxyl-4-phenylbutanoate (*S*)-**1** are unnaturally occurring α-hydroxy esters, which have attracted great attention from synthetic chemists because they can be employed as key building blocks for the synthesis of biologically active compounds, such as angiotensin converting enzyme inhibitors,[1] which are widely used as antihypertensive drugs and the therapy of CHF. In addition, they are also valuable synthetic intermediates.[2] For this reason, many methods for the preparation of **1** have been developed, such as chemical[3] and enzymatic resolution[4] and asymmetric[1e,5] and microbiological syntheses.[6] However, there is no practical method with the potential for large scale processing. Herein, we present a convenient procedure for the synthesis of (*S*)-**1** and its conversion to (*R*)-**1** and D-homophenylalanine ethyl ester hydrochloride **2**[7] starting from the readily available L-malic acid **3** (Scheme 1).



Scheme 1.

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2. Results and discussion

2.1. Preparation of ethyl (*S*)-2-hydroxy-4-phenylbutanoate (*S*)-1

The key step of our procedure is the Friedel–Crafts reaction of (*S*)-α-acetoxybutanedioic anhydride **4** with anhydrous benzene in the presence of anhydrous aluminum chloride.[8] The synthesis of **4** was completed using the literature procedure[9] by acetylation–dehydration with acetyl chloride at 45°C over 4 hours. Using this procedure **4** was obtained in quantitative yield. Friedel–Crafts acylation of benzene with **4** in the presence of anhydrous aluminum chloride afforded (*S*)-2-hydroxy-4-oxo-4-phenylbutanoic acid **5** in 72% yield.[10] Hydrogenolysis of **5** over 10% palladium on charcoal in acetic acid at room temperature (under 1 atmosphere pressure of hydrogen) then afforded (*S*)-2-hydroxyl-4-phenylbutanoic acid **6** in 94% yield with e.e. of 99% as determined by GC analysis (Varian 3380, CP-Chirasil-Dex, $T_c = 140$°C). Treatment of **6** with ethanol in the presence of catalytic concentrated sulfuric acid yielded (*S*)-**1** with 99% e.e. by GC in 95% yield.

2.2. Inversion of the configuration of ethyl (*S*)-2-hydroxy-4-phenylbutanoate (*S*)-1

Inversion of the configuration of (*S*)-**1** was thought to be a more practical procedure for the preparation of (*R*)-**1**. However, few methods for the inversion of configuration of α-hydroxy esters are known[11] thus, the inversion of (*S*)-**1** to (*R*)-**1** was investigated. Firstly, inversion using the Mitsunobu method ($EtO_2CN{=}NCO_2Et/Ph_3P/ClCH_2CO_2H$) followed by chemoselective hydrolysis with potassium carbonate gave the acid (*R*)-**1** in only 31% yield after column chromatography.[12] Nucleophilic substitution of ethyl (*S*)-2-methanesulfonyloxyl-4-phenylbutanoate **7** with potassium acetate in DMF in the presence of 18-crown-6 provided, after hydrolysis, (*R*)-**1** in 47% yield and 74% e.e.[13] In the absence of 18-crown-6, the yield increased to 63% and the e.e. improved to 81%. Reaction of **7** with caesium propionate in DMF gave (*R*)-1 in 55% yield with 92% e.e.[11c] and reaction with potassium propionate in DMF, afforded (*R*)-1 with e.e. of 85% in 58% yield. The equivalent reaction with sodium propionate in DMF afforded product with 42% e.e. in 60% yield. The best result was obtained on reaction of **7** with potassium propionate in ethanol, which gave (*R*)-**1** with 97% e.e. in 83% yield for the two-step displacement–hydrolysis sequence.

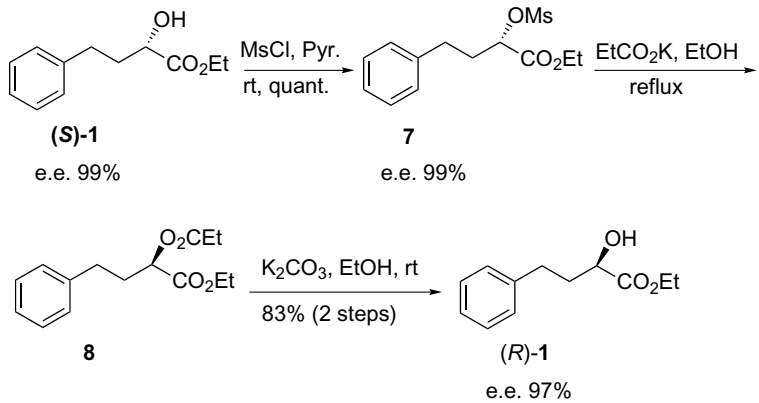
Thus, ethyl (*S*)-2-hydroxyl-4-phenylbutanoate (*S*)-**1** was converted to ethyl (*R*)-2-hydroxyl-4-phenylbutanoate (*R*)-**1** by mesylation with methanesulfonyl chloride in the presence of pyridine to give **7** with e.e. of 99% in quantitative yield (HPLC, AD column, 2.5% *iso*-propanol-hexane, 1.0 mL/min, UV 220 nm). **7** reacted cleanly with potassium propionate in refluxing ethanol to give ethyl (*R*)-2-propionyloxyl-4-phenylbutanoate **8**, which, without purification, was selectively hydrolyzed with potassium carbonate in ethanol at room temperature to afford (*R*)-**1** in 97% e.e. with 83% yield. The route is illustrated in Scheme 2.

2.3. Preparation of D-homophenylalanine ethyl ester hydrochloride 2 from (*S*)-1

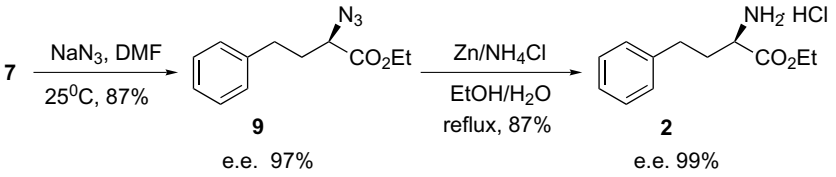
In our previous work, we have successfully synthesized L-homophenylalanine,[14] but not D-homophenylalanine. Azidation of **7** was effected by treatment with sodium azide in DMF at 25°C to give ethyl (*R*)-2-azido-4-phenylbutanoate **9** in 87% yield and 97% e.e. (HPLC, OB column, 5% *iso*-propanol-hexane, 1.0 mL/min, UV 220 nm),[15] which was reduced to D-homophenylalanine ethyl ester hydrochloride **2** with zinc and ammonium chloride[16] in 87% yield and 99% e.e. determined by HPLC (CR column, $HClO_4$(aq., pH 2), 0.8 mL/min, $T = 18$°C, UV 215 nm) as shown in Scheme 3.

3. Conclusion

In conclusion, we have presented a convenient method for the preparation of ethyl (*S*)-2-hydroxyl-4-phenylbutanoate (99% e.e., 64% overall yield), ethyl (*R*)-2-hydroxyl-4-phenylbutanoate (97% e.e., 53% overall yield) and D-homophenylalanine ethyl ester hydrochloride (99% e.e., 49% overall yield) starting from the readily available L-malic acid.



Scheme 2.



Scheme 3.

4. Experimental

4.1. General methods

All melting points were determined on an electrothermal digital melting point apparatus and were uncorrected. Infrared spectra were recorded on a Nicolet MX-1 spectrometer. Mass spectra were recorded on a VG7070E GC/MS/DS (England) instrument. ^{1}H NMR and ^{13}C NMR were measured on Bruker-300 spectrometers. The enantiomeric excesses were determined by means of GC (Varian 3380, CP-Chirasil-Dex, T_c = 140°C) and HPLC with a CR column on Shimadzu chromatography with UV–vis detector. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Benzene was dried over 3 Å molecular sieves. Methylene chloride was distilled from CaH_2. Pyridine was dried using potassium hydroxide and distilled.

4.2. (*S*)-2-Hydroxy-4-oxo-4-phenylbutanoic acid 5

To a solution of **4** (9.5 g, 0.05 mol)[9] in anhydrous benzene (80 mL), anhydrous aluminum chloride (30.0 g, 0.15 mol) was added in one portion at 0°C. The mixture was stirred vigorously under reflux for 4 h, and then poured onto a mixture of crushed ice (100 g) and concentrated aqueous HCl (100 mL). The mixture was stirred for 2 h, extracted with ethyl acetate (150, 100 and 50 mL). The combined organic solution was washed with brine and dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford crude **5**. The crude product was recrystallized from ethyl acetate and petroleum ether to give **5** as a white powder (8.4 g, 72%). Mp 142–144°C, $[\alpha]_D^{22} = -2.0$ (*c* 2, acetone). IR (Nujol mull) cm^{-1}: 3476, 3062, 1734 (COOH), 1678 (C=O), 1596, 1451; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.60 (1H, d, J=6.6 Hz, C**H**HCO), 3.63 (1H, d, J=4.5 Hz, C**H**HCO), 4.75 (1H, dd, J=4.5, 6.3, HOC**H**CO), 7.53 (2H, dd, J=7.8, 7.2 Hz, Ar-**H**), 7.65 (1H, dd, J=6.3, 1.2 Hz, Ar-**H**), 8.00 (2H, dd, J=7.2, 1.2 Hz, Ar-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 42.3, 66.5, 127.8, 128.3, 133.0, 136.7, 175.7, 197.4.

4.3. (*S*)-2-Hydroxyl-4-phenylbutanoic acid 6

A solution of **5** (5.0 g, 0.026 mol) in acetic acid (80 mL), was hydrogenolyzed with 10% palladium on carbon (0.5 g) at room temperature under 1 atmosphere pressure of hydrogen. When the reaction was over as indicated by TLC, the solution was filtered and evaporated under reduced pressure to provide crude **6**, which was recrystallized from toluene to give **6** as a white powder (4.4 g, 94%). Mp 119–121°C, e.e. = 99% (GC Varian 3380, CP-Chirasil-Dex, T_c = 140°C). IR (KBr) cm^{-1}: 3455, 2915, 1717 (COOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.74–2.10 (1H, m, $ArCH_2C$**H**H), 2.16–2.25 (1H, m, $ArCH_2C$**H**H), 2.80–2.85 (2H, m, $ArCH_2$), 4.29–4.30 (1H, m, -CH), 7.20–7.34 (5H, m, Ar-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 30.9, 35.6, 69.4, 126.1, 128.4, 128.5, 140.6, 179.8); MS (*m*/*z*): 180 (M^+), 91(100%).

4.4. Ethyl (*S*)-2-hydroxyl-4-phenylbutanoate (*S*)-1

To a solution of **6** (8 g, 0.044 mol) in anhydrous ethanol (200 mL) was added concentrated sulfuric acid (3 mL). The mixture was stirred under reflux for 2 h and evaporated under reduced pressure to remove the excess ethanol. The residue was partitioned between water (50 mL) and ethyl acetate (200 mL). The organic layer was washed with saturated sodium bicarbonate, brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give (*S*)-**1** as a light yellow oil (8.9 g, 95%) e.e. = 99% (GC Varian 3380, CP-Chirasil-Dex, T_c = 140°C). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.31 (3H, t, J=7.2 Hz, OCH_2C**H**$_3$), 2.02–2.07 (1H, m, $ArCH_2C$**H**H), 2.15–2.21 (1H, m, $ArCH_2C$**H**H), 2.84 (2H, m, OC**H**$_2CH_3$), 3.61 (1H), 4.20–4.28 (3H, m, ArC**H**$_2$, C**H**), 7.21–7.36 (5H, m, Ar-**H**); MS (*m*/*z*): 208 (M^+), 91 (100%).

4.5. Ethyl (*S*)-2-methanesulfonyloxyl-4-phenylbutanoate 7

To a solution of (*S*)-**1** (8.0 g, 0.038 mol) in anhydrous methylene chloride (25 mL) and dried pyridine (30 mL) was added methanesulfonyl chloride (7.5 mL) dropwise at 0°C. The resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (200 mL), and the resultant organic solution was washed sequentially with water, aqueous HCl (2 M), saturated sodium bicarbonate and brine, dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give **7** as a light yellow oil (11.0 g, 100%) e.e. = 99% (HPLC, AD column, 2.5% *iso*-propanol-hexane, 1.0 mL/min, UV 220 nm). IR (neat) cm^{-1} 3028 2937, 1750, 1603, 1497 (C=O), 1361 (SO_2), 1175 (SO_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.27–1.32 (3H, t, J=7.4 Hz, OCH_2C**H**$_3$), 2.20–2.27 (2H, m, $ArCH_2C$**H**$_2$), 2.77–2.83 (2H, m, OC**H**$_2CH_3$), 3.15 (3H, s, C**H**$_3SO_2$), 4.19–4.27 (2H, m, ArC**H**$_2$), 5.00–5.05 (1H, m, C**H**CO), 7.21–7.34 (5H, m, Ar-**H**).

4.6. Ethyl (*R*)-2-hydroxyl-4-phenylbutanoate (*R*)-1

Potassium propionate (7.0 g, 0.063 mol) was added to a solution of **7** (6.0 g, 0.021 mol) in ethanol (200 mL). The resulting mixture was stirred under reflux for 48 h, then cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL). The resulting solution was washed twice with brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to give **8**, which was directly used for the next hydrolysis without purification.

To the solution of **8** in ethanol (400 mL) was added potassium carbonate (9 g, 0.064 mol). The resulting mixture was stirred at room temperature overnight and filtered. The filtrate was neutralized with aqueous HCl (6 M) and evaporated under reduced pressure. The residue was partitioned between ethyl acetate (150 mL) and water (50 mL). The organic layer was washed with brine, and dried (anhydrous Na_2SO_4). The solvent was evaporated to give (*R*)-**1** as an oil (3.6 g, 83% from **7**) e.e. = 97% (GC Varian 3380, CP-Chirasil-Dex, T_c = 140°C).

4.7. Ethyl (*R*)-2-azido-4-phenylbutanoate (*R*)-9

A solution of **7** (1.8 g, 6.3 mmol) in DMF (10 mL) was treated with sodium azide (0.5 g, 7.7 mmol) at room temperature for 6 h. To the reaction mixture, ethyl acetate (80 mL) and water (40 mL) were added. The organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated to give **9** as a pale yellow oil (1.37 g, 87%) e.e. = 97% (HPLC, OB column, 5% *iso*-propanol–hexane, 1.0 mL/min, UV 220 nm). IR (neat) cm^{-1}: 2105 (N=N=N), 1738 (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.32–1.37 (3H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.10–2.21 (2H, m, $ArCH_2C\underline{H}_2$), 2.75–2.84 (2H, m, $ArC\underline{H}_2$), 3.85 (1H, dd, J = 5.08, 8.72 Hz, $N_3C\underline{H}CO$), 4.26 (2H, q, J = 7.1 Hz, $OC\underline{H}_2CH_3$), 7.24–7.37 (5H, m, Ar-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 14.1, 31.7, 32.9, 61.1, 61.8, 126.3, 128.5, 140.1, 170.4.

4.8. D-Homophenylalanine ethyl ester hydrochloride 2

To a stirred solution of **9** (1.3 g, 5.2 mmol) in ethanol (15 mL) and water (5 mL), ammonium chloride (0.6 g, 11 mmol) and zinc powder (0.4 g, 11 mmol) were added. The reaction mixture was stirred under reflux for 10 min and cooled to room temperature, filtered and evaporated. The residue was dissolved in a mixture of ethyl acetate (100 mL) and 10% aqueous ammonia (30 mL). The organic layer was dried (anhydrous Na_2SO_4) and filtered. Anhydrous hydrogen chloride was bubbled into the filtrate. The solution was evaporated to give a white solid, which was recrystallized from ethanol and ether to afford **2** as a white crystalline solid (1.17 g, 87%). $[\alpha]_D^{25} = -38.6$ (c 1 H_2O), e.e.: 99% (HPLC, CR column, $HClO_4$ (aq., pH 2), 0.8 mL/min, T = 18°C, UV 215 nm).

Acknowledgements

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