Optical Resolution of Ethyl 2-(Benzylamino)-4-oxo-4-phenylbutanoate with Tartaric Acid A Practical Synthesis of D-Homophenylalanine

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The resolution of ethyl (±)-2-(benzylamino)-4-oxo-4-phenylbutanoate with L-tartaric acid, followed by catalytic hydrogenation represents a practical and convenient three-step synthesis of D-homophenylalanine starting from commercial ethyl benzoylacrylate. Capillary zone electrophoresis in the presence of cyclodextrins was used to determine the ee of the L-tartrate.

The synthesis of modified peptides based on the substitution of natural amino acids by nonstandard residues in order to change the bioavailability and/or the inhibiting activity of the peptides has attracted significant attention over the last decade. Homophenylalanine (Hfe) is the unnatural amino acid of high biological importance. Its L-enantiomer forms a vital substructure unit of about twenty commercial ACE inhibitors and has been used as a key building block for some other metalloproteinase inhibitors [1—4]. D-Enantiomer has attracted the medicinal chemists' attention in the last few years only. The incorporation of D-Hfe into the di- resp. oligopeptides having cysteine protease inhibiting activity [5] resp. efflux pump inhibiting activity [6, 7] is in progress nowadays.

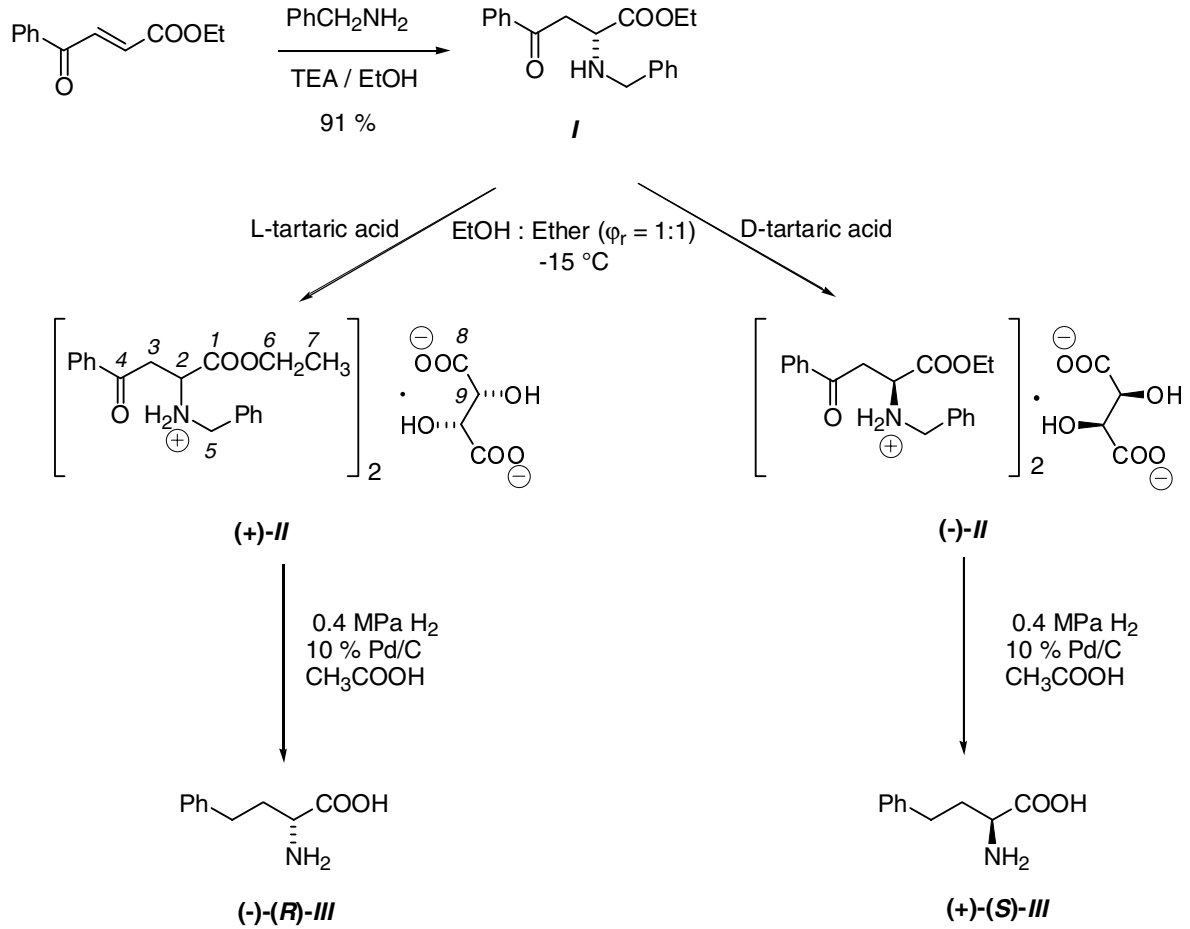
For the reason mentioned above, the majority of synthetic methods has been developed for the synthesis of enantiomerically pure L-Hfe [8—12]. Recent literature uses derivatives of benzoylalanine as key intermediates for the synthesis of L-Hfe, mostly starting from the available derivatives of L-aspartic acid [11, 13]. The practical syntheses of D-Hfe from alkenylboronic acids [14] or D-Hfe ethyl ester chloride starting from L-malic acid [15] have been published only recently.

There are only few articles on synthetic methods, which permit construction of both (*R*)- and (*S*)-antipodes [16]. The recent pathways use the enantioselective hydrogenation [17] of unsaturated amino acids, catalytic asymmetric Strecker synthesis using chiral Zr-catalysts [18] or a tandem of crystallization-induced asymmetric transformation (CIAT [19]) and conjugate addition of chiral amines [20] or amino alcohols [21] on aroylacrylic acids with subsequent catalytic hydrogenation. Despite the accessibility of used amines in both enantiomeric forms, the economical and easy-to-perform procedure for the manufacture of D-Hfe with the capability of a scale-up is yet to be discovered.

Herein we now describe a facile three-step preparation of D-Hfe using the resolution of racemic adducts of benzyl amine on ethyl benzoylacrylate with cheap L-tartaric acid as a key step. The diastereomeric salt can easily be converted to the desired product by hydrogenolysis. The outline of this idea is shown in Scheme 1.

The ester of benzoylalanine (*I*) can be obtained readily in an excellent yield from the commercially available ethyl benzoylacrylate (an intermediate in ACE inhibitors production) and benzylamine. The reaction is completely regiospecific and the desired adduct precipitates in excellent yield. We have attempted to resolve this ester by a relatively conventional technique, using optically active acids. Among the chiral resolving agents the tartaric acid has been selected because of its cheapness and availability.

In the optimized conditions a selective crystallization of diastereomeric tartrate in the form of a hydrate has been achieved. The resolution gives reproducible yields and purity of crystalline dextrorotatory salt *II*. Moreover, the unwanted enantiomer of ethyl 2-(benzylamino)-4-oxo-4-phenylbutanoate (*I*) decomposes under the reaction conditions at the slightly elevated temperature and the benzylammonium salt of tartaric acid precipitates from the solution. After its filtration the unreacted ethyl benzoylacrylate can be easily recovered [22].



Scheme 1

The absolute configuration of (-)-(*R*)-Hfe (*III*) has been assigned by converting it to the homophenylalanine and comparing the sign of the specific rotation with the reported data. Hydrogenolysis of the salt (0.4 MPa H_2) in the presence of 10 % Pd/C at room temperature provided (*R*)-Hfe in high yield with > 98 % ee (determined by HPLC).

A capillary zone electrophoresis in the presence of cyclodextrins was used to analyze the process of separation of enantiomers of ethyl 2-(benzylamino)-4-oxo-4-phenylbutanoate (*I*). The resolution of (*R*)-*I* and (*S*)-*I* was observed only in the presence of G-CD and D-CD. The complex of D-CD/(*I*) was more stable than G-CD/(*I*) (migration time of (*R*)-*I* was 9.16 min and 6.21 min, respectively, at concentration of the particular cyclodextrin 20 mmol dm^{-3}) but the enantioselectivity was higher with the latter one (resolution of peaks of (*R,S*)-*I* was 1.13 and 2.59, respectively). Resolution of peaks as well as migration times of the studied enantiomers were dependent on concentration of the added cyclodextrin (Figs. 1 and 2). The $R_s = 1.5$ was achieved in background electrolyte completed with 7.5 mmol dm^{-3} of G-CD. The electrophoreogram of a model mixture of the (*R*)-*I* (ee = 91.5 %) prepared from the racemate by rapid crystal-

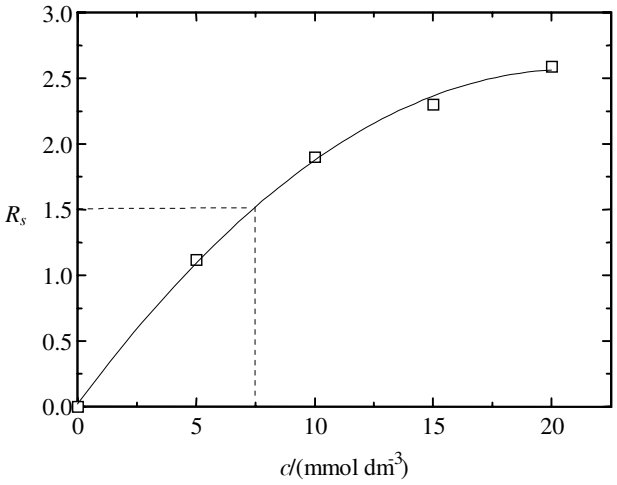


Fig. 1. Dependence of resolution (R_s) of peaks of ethyl (*R*)- and (*S*)-2-(benzylamino)-4-oxo-4-phenylbutanoate on the concentration of G-CD.

lization of the diastereomeric salt with L-tartaric acid is shown in Fig. 3. Following the procedure precised in Experimental, the purity of the salt can be enhanced (ee > 95 %) and the crystals can be used directly into

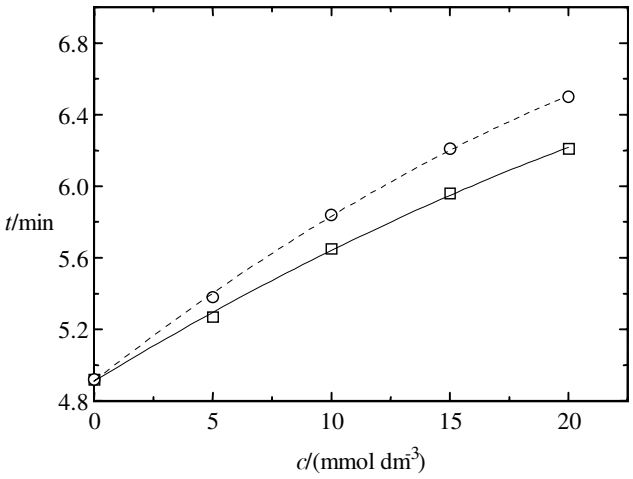


Fig. 2. Dependence of migration time of ethyl (*R*)-(——) and (*S*)-2-(benzylamino)-4-oxo-4-phenylbutanoate (– – –) on the concentration of G-CD.

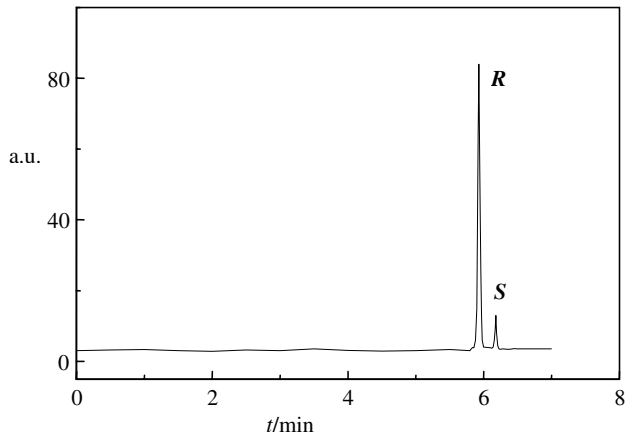


Fig. 3. Electrophoreogram of ethyl (*R*)-2-(benzylamino)-4-oxo-4-phenylbutanoate in the presence of its (*S*)-enantiomer. Capillary 48.5 cm × 0.05 mm, 50 mmol dm^{-3} TRIS/phosphate buffer of pH 2.37, 15 mmol dm^{-3} G-CD.

the hydrogenation step. The described sequence represents an easy three-step synthesis of (*R*)-Hfe in good yields and high enantiomeric purity.

EXPERIMENTAL

Melting points were obtained using a Kofler hot plate. Optical rotations were measured with a POLAR L-μP polarimeter (IBZ Messtechnik) with a water-jacketed 10.000 cm cell at a wavelength of sodium line D (λ = 589 nm). Specific rotations are given in units of 10^{-1} ° cm^{-1} g^{-1} and concentrations are given in 0.01 g cm^{-3}. Elemental analyses were performed by the Microanalytical service of the Slovak University of Technology. Infrared spectra were recorded on a Philips Analytical PU9800 FTIR spectrometer as KBr discs. ^{1}H NMR spectra were recorded on a Varian VXR 300 (299.94 MHz) spectrometer; ^{13}C NMR spectra were recorded on a Varian VXR 300 (75.43 MHz) spectrometer.

A HP ^{3D}Capillary Electrophoresis System (HP ^{3D}CE, Waldbronn, Germany) was used. The electrophoreograms were collected at fixed UV wavelengths of 215 nm with data processed on a HP ChemStation. A 48.5 cm (effective length 40 cm) with 0.05 mm i.d. untreated fused silica capillary tube (Hewlett—Packard) was used for analyses. The background electrolyte consisted of 50 mmol dm^{-3} TRIS/phosphate buffer of pH 2.37. The sample solutions were prepared by dissolving 10 mg of the selected compound in 2 cm^3 of 0.1 mol dm^{-3} phosphoric acid and filling up to 10 cm^3 with water; before pressure injection (7500 Pa s) it was filtered through a 0.20 μm nylon membrane filter. The resolution of peaks was calculated according to the equation $R_s = 2(t_2 - t_1)/(w_1 + w_2)$, where t = migration time, w = baseline peak width (in time). The migration time reproducibility varied in the range ± 5%. γ-Cyclodextrin (G-CD) and heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (D-CD) were from Sigma Chemical Co., St. Louis, USA. Chiral column for HPLC ee determination of the free amino acid was purchased from Daicel Industries (CROWNPAK CR(+), 5 μm, 150 mm × 4 mm, $HClO_4/H_2O$, pH 2.0, 1 cm^3 min^{-1}, 25 °C): t_R 14.9 min (*R*)-Hfe; t_R 21.9 min (*S*)-Hfe.

The commercial ethyl benzoylacrylate was used freshly distilled under diminished pressure.

Ethyl (±)-2-(Benzylamino)-4-oxo-4-phenylbutanoate (*I*)

To a cooled (0—5 °C) solution of benzylamine (6.6 cm^3; 0.06 mol) and triethylamine (4.2 cm^3; 0.03 mol) in 99.8 % ethanol (30 cm^3) the ethyl (*E*)-4-oxo-4-phenylbutenoate (12.2 g; 0.06 mol) was added dropwise within 15 min. The stirring was continued at the same temperature for additional 2—3 h. The slurry of the product was filtered off and washed with small quantity of cold ethanol. Yield: 17 g (91 %), m.p. = 57—58.5 °C (ethanol). For $C_{19}H_{21}NO_3$ (M_r = 311.4) w_i(calc.): 73.29 % C, 6.80 % H, 4.50 % N; w_i(found): 73.51 % C, 6.85 % H, 4.59 % N. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1595, 1682 ν(C═O), 1728 ν(C═O), 3312 ν(NH). ^{1}H NMR spectrum ($CDCl_3$), δ: 7.22—7.94 (m, 10H, 2 × Ph), 4.20 (q, 2H, J = 7.1 Hz, C-6—H), 3.95 (d, 1H, J = 13.0 Hz, C-5—H), 3.86 (t, 1H, J = 6.0 Hz, C-2—H), 3.80 (d, 1H, J = 13.0 Hz, C-5—H), 3.44 (dd, J = 17.3 Hz, J = 6.0 Hz, C-3—H), 3.40 (dd, J = 17.3 Hz, J = 6.0 Hz, C-3—H), 2.7 (bs, 1H, NH), 1.26 (t, 3H, J = 7.1 Hz, C-7—H). ^{13}C NMR spectrum ($CDCl_3$), δ: 197.5 (C-4), 173.9 (C-1), 139.3, 136.6, 133.3, 128.6, 128.4, 128.4, 128.1, 127.2, 61.1 (C-6), 56.7 (C-2), 52.2 (C-5), 42.0 (C-3), 14.2 (C-7). Tosylate: m.p. = 146—148 °C (dichloromethane), IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1743 ν(C═O), 1689 ν(C═O), 1221, 1167.

Resolution of (±)-*I*

To the solution of (±)-*I* (15.6 g; 0.05 mol) in 99 % ethanol (100 cm^3) the solid L-tartaric acid (7.5 g; 0.05 mol) was added in one portion at room temperature. The mixture was intensively stirred until clear solution was formed. Then the dry diethyl ether (100 cm^3) was added. On standing at −15 °C for 24—30 h the formed fine crystals were filtered off and washed with a small quantity of ether. Drying at 25 °C under the diminished pressure (50 Pa) for 3—5 h gives colourless crystals of ethyl (*R*)-2-(benzylamino)-4-oxo-4-phenylbutanoate tartrate hydrate (+)-*II*. Yield: 8.7 g (44 %), m.p. = 79—81 °C (ethanol—diethyl ether, volume ratio 1:1), $[\alpha]$ (D, 26 °C, ρ = 0.41 g dm^{-3}, methanol) = + 4.4°. For $(C_{19}H_{21}NO_3)_2 \cdot C_4H_6O_6 \cdot H_2O$ (M_r = 790.85) w_i(calc.): 63.79 % C, 6.37 % H, 3.54 % N; w_i(found): 63.97 % C, 6.36 % H, 3.46 % N. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1597, 1582, 1688 ν(C═O), 1739 ν(C═O), 1742 ν(C═O), 3322, 3407.

^{1}H NMR spectrum (acetone-d_6), δ: 7.2—8.2 (m, 10H, 2 × Ph), 4.7 (bs, 2H, C—OH, H_2O), 4.49 (s, 1H, C-9—H), 4.18 (q, 2H, J = 7.1 Hz, C-6—H), 4.01 (d, 1H, J = 13.2 Hz, C-5—H), 3.90 (t, 1H, J = 5.0 Hz, C-2—H), 3.85 (d, 1H, J = 13.2 Hz, C-5—H), 2.1 (C-3—H overlapped with solvent signal), 1.24 (t, 3H, J = 7.1 Hz, C-7—H). ^{13}C NMR spectrum (acetone-d_6), δ: 198.0 (C-4), 173.90 and 173.85 (C-1 and C-8), 140.5, 137.8, 134.0, 129.5, 129.1, 129.0, 128.9, 127.8 (2 × Ph), 72.8 (C-9), 61.3 (C-6), 57.3 (C-2), 52.2 (C-5), 41.2 (C-3), 14.7 (C-7).

The same experiment with D-tartaric acid gives opposite enantiomer of the diastereomeric salt ((-)-*II*). Yield 8.7 g (44 %), m.p. = 79—80 °C (ethanol—diethyl ether, volume ratio 1:1), $[\alpha]$ (D, 26 °C, ρ = 0.41 g dm^{-3}, methanol) = −4.1°.

(-)-(*R*)-2-Amino-4-phenylbutanoic Acid ((*R*)-*III*)

The freshly prepared dextrorotatory salt (+)-*II* (9 g) was dissolved in glacial acetic acid (200 cm^3) and stirred with 10 % Pd/C (1 g) under hydrogen (0.4 MPa) at room temperature for 3 days. Acetic acid was evaporated under the reduced pressure, the residue was triturated with 4 M-HCl (100 cm^3) and stirred at 50 °C for 1 h. The catalyst was filtered off and the filtrate basified with concentrated aqueous ammonia to pH 4.8. The filtered product was dried at 50 °C under the pressure of 50 Pa for 5 h. Yield: 2.6—2.9 g (65—71 %), m.p. = 290—292 °C, $[\alpha]$ (D, 20 °C, ρ = 1 g dm^{-3}, 1 M-HCl) = −48.2° ($[\alpha]$ (D, 19 °C, ρ = 1 g dm^{-3}, 1 M-HCl) = −48° [23]) ; ee > 98 % (HPLC). ^{1}H NMR spectrum (NaOD/D_2O), δ: 7.10—7.30 (m, 10H, Ph), 3.15 (t, 1H, J = 6.3 Hz, C-2—H), 2.53 (t, 2H, J = 8.3 Hz, C-4—H), 1.60—1.85 (m, 2H, C-3—H). ^{13}C NMR spectrum (NaOD/D_2O), δ: 186.1 (C-1), 145.2 (C-1′), 131.5, 131.3, 128.9 (C-4′), 58.6 (C-2), 39.7 (C-4), 34.3 (C-3).

(+)-(*S*)-2-Amino-4-phenylbutanoic Acid ((*S*)-*III*)

In the same conditions the laevorotatory salt (-)-*II* (3.5 g) afforded the (+)-(*S*)-homophenylalanine. Yield: 1.2 g (75 %), m.p. = 286—290 °C, $[\alpha]$ (D, 20 °C, ρ = 1 g dm^{-3}, 1 M-HCl) = + 46.5° ($[\alpha]$ (D, 20 °C, ρ = 1 g dm^{-3}, 1 M-HCl) = 47.2° [10] resp. 45.5° [13]); ee > 98 % (HPLC).

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