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Synthesis of (*S,S*)-2-Amino-3-phenylbutyric Acid

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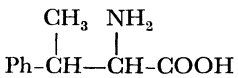
Synopsis. (*S,S*)-2-Amino-3-phenylbutyric acid was synthesized starting from diethyl (*R*)-(1-phenylethyl)malonate which was obtained by desulfurization of the adduct in the stereoselective Michael reaction of (*R*)-styryl *p*-tolyl sulfoxide with diethyl malonate. This synthetic amino acid was identical with the 2-amino-3-phenylbutyric acid obtained by degradation of bottromycin and thus the absolute configuration of the naturally occurring amino acid was proved to be (*S,S*).

In 1957, (−)-2-amino-3-phenylbutyric acid [(−)-**1**] was reported to be a component of bottromycin which was isolated from a culture of *Streptomyces bottropensis*.[1]



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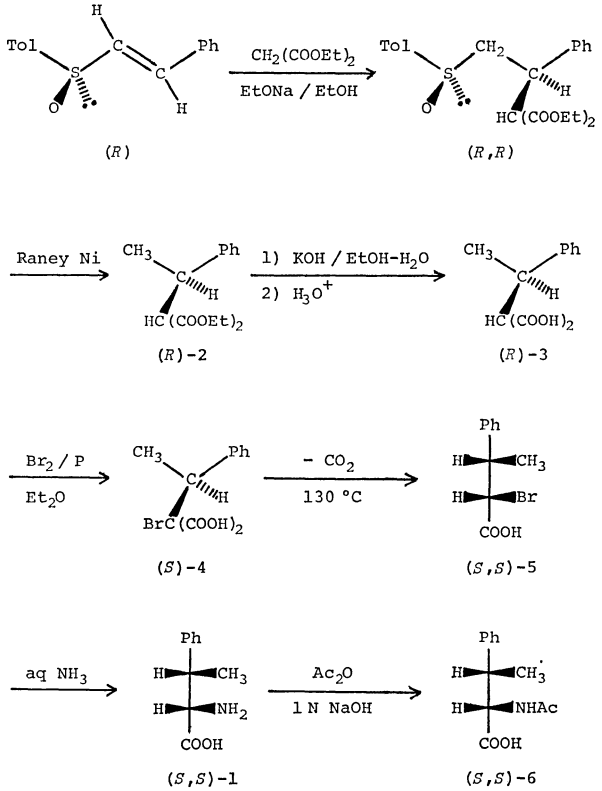
Since this amino acid contains two chiral centers, four isomers [(2*R*,3*R*), (2*R*,3*S*), (2*S*,3*R*), and (2*S*,3*S*)] are possible. As to the absolute configuration at the 2-position, (*S*) was suggested, based on the positive Cotton effect in the ORD of its *N*-ethylthiothiocarbonyl derivative, the resistance against a D-amino acid oxidase,[2] and the application of the Clough, Lutz, and Jirgensons rule to the optical rotatory powers of the amino acid and its derivatives.[3] Later, the diastereomeric relationship between the 2- and 3-positions was determined to be erythro by the chemical transformation[3] and the NMR study.[4]

We previously synthesized diethyl (*R*)-(1-phenylethyl)malonate [(*R*)-**2**] by desulfurization of diethyl (*R,R*)-[1-phenyl-2-(*p*-tolylsulfinyl)ethyl]malonate, which was obtained by the stereoselective Michael reaction of (*R*)-styryl *p*-tolyl sulfoxide with diethyl malonate.[5,6] Now, we have synthesized (*S,S*)-**1** starting from this (*R*)-**2** according to the Fischer's method[7-9] as shown in Scheme 1 and have found that the naturally occurring **1** is identical with this (*S,S*)-**1**.

(*R*)-(1-Phenylethyl)malonic acid [(*R*)-**3**], which was obtained by hydrolysis of (*R*)-**2** in 88% yield, was subjected to bromination with bromine–red phosphorus to give (*S*)-bromo(1-phenylethyl)malonic acid [(*S*)-**4**]. Thermal decarboxylation of (*S*)-**4** afforded a crystalline product which was recrystallized from benzene to give pure (*S,S*)-2-bromo-3-phenylbutyric acid [(*S,S*)-**5**; 40% overall yield from (*R*)-**3**]:[9] mp 167—168 °C; $[\alpha]_D^{30}$ −31.4° (*c* 0.327, benzene). Treatment of (*S,S*)-**5** with aqueous ammonia gave a mixture of (*S,S*)-2-amino-3-phenylbutyric acid [(*S,S*)-**1**] and ammonium bromide. This mixture was subjected to the reaction with acetic anhydride–1 M aqueous sodium hydroxide[1b] to afford (*S,S*)-2-acetylamino-3-phenylbutyric acid [(*S,S*)-**6**; 95% yield from (*S,S*)-**5**]: mp 188—190 °C (from 20% ethanol); $[\alpha]_D^{29}$ +34.8° (*c* 0.810, 96% ethanol). These values agree well with those reported for the *N*-acetyl derivative of the naturally occurring **1** [mp 177—185 °C (from 20% ethanol) and $[\alpha]_D^{25}$ +35.0° (*c* 2%, 96% ethanol)].[1b]



Scheme 1.

The starting material of the present synthesis, (*R*)-**2**, was already connected to (−)-3-phenylbutyric acid,[5] whose absolute configuration was determined as (*R*) by the comparison with the authentic specimen synthesized from (*S*)-hydratropic acid.[10] Based on these relations, the present synthesis clearly established that the absolute configuration of the 2-amino-3-phenylbutyric acid from bottromycin is (*S,S*).

Experimental

All melting points were measured by a Yanagimoto micro melting point apparatus and uncorrected. Infrared spectra were taken on a Hitachi EPI-G3 spectrophotometer. NMR spectra were recorded on Varian T-60 and Varian HA-100 spectrometers. Optical rotations were measured on a Yanagimoto polarimeter OR 50.

Hydrolysis of (R)-*2*. To a solution of 472 mg (1.79 mmol) of (*R*)-**2** having $[\alpha]_D^{26}$ −21.0° (*c* 2.365, $CHCl_3$)[11] in 6 ml of ethanol, were added 3 ml of water and 550 mg of potassium hydroxide and the reaction mixture was stirred at 100 °C for 3 h. After cooling, 20 ml of water was added and the mixture was washed with dichloromethane (10 ml). The aqueous layer was acidified by adding concd hydrochloric

acid and extracted with diethyl ether (20 ml×4). The extract was washed with water (10 ml) and dried (Na_2SO_4). After evaporation *in vacuo*, the crystalline residue was recrystallized from benzene to afford 328 mg (88% yield) of (*R*)-**3** as colorless crystals: mp 94—96 °C; $[\alpha]_D^{21}$ −30.1° (*c* 0.866, methanol); IR (KBr): 3500—2800, 1740, 1695, 1220, 1200, 1155, 760, and 700 cm^{-1}; NMR ($CDCl_3$): δ=1.34 (3H, d, J=6 Hz), 3.2—3.8 (2H, m), 7.27 (5H, s), and 12.70 (2H, s). The NMR spectrum was identical with that of the racemic compound.[5,7]

Transformation of (R)-**3** *into* (S,S)-**5** via (S)-**4**. To a solution of 237 mg (1.14 mmol) of (*R*)-**3** in 5 ml of diethyl ether, were added a solution of 184 mg of bromine in 0.8 ml of dichloromethane and 1 mg of red phosphorus and the mixture was stirred for 45 min at room temperature. After reduction of remaining bromine by adding aqueous sodium thiosulfate, the mixture was extracted with diethyl ether (15 ml×4). The extract was dried ($MgSO_4$) and evaporated *in vacuo* to give crude (*S*)-**4** as an oil: NMR ($CDCl_3$): δ= 1.62 (3H, d, J=7 Hz), 3.77 (1H, q, J=7 Hz), 7.32 (5H, m), and 10.50 (2H, broad s). This oil was heated at 130 °C for 15 min under reduced pressure (*ca.* 20 Torr). The resulting crystalline product was recrystallized from benzene to give 105 mg (40% yield[9] from (*R*)-**3**) of (*S,S*)-**5** as colorless crystals: mp 167—168 °C; $[\alpha]_D^{30}$ −31.4° (*c* 0.327, benzene); NMR (acetone-d_6): δ=1.43 (3H, d, J=7 Hz), 3.41 (1H, dq, J=10 and 7 Hz), 4.57 (1H, d, J=10 Hz), and 7.2—7.5 (5H, m). The NMR spectrum was identical with that of the racemic specimen.[7]

Synthesis of (S,S)-**6**. A mixture of 105 mg (0.43 mmol) of (*S,S*)-**5** and 4 ml of 28% aqueous ammonia was heated in a sealed tube at 90 °C for 2.5 h and then concentrated *in vacuo* to yield a mixture of (*S,S*)-**1** and ammonium bromide. After addition of 2.5 ml of 1 M aqueous sodium hydroxide to the above mixture, 0.15 ml of acetic anhydride and 1.3 ml of 1 M aqueous sodium hydroxide were simultaneously added over 5 min and the mixture was stirred for 1 h under ice-cooling. After simultaneous addition of 0.15 ml of acetic anhydride and 3 ml of 1 M aqueous sodium hydroxide, the resulting mixture was further stirred for 30 min under ice-cooling, acidified to pH 1 with concd hydrochloric acid, and extracted with ethyl acetate (15 ml×4). The extract was dried ($MgSO_4$) and evaporated *in vacuo* to afford 91 mg (95% yield) of (*S,S*)-**6** as colorless crystals: mp 188—190 °C (from 20% ethanol), $[\alpha]_D^{29}$ +34.8° (*c* 0.810, 96% ethanol) [lit,[1b] mp 177—185 °C (from 20% ethanol), $[\alpha]_D^{25}$ +35.0° (*c* 2%, 96% ethanol)]; IR (KBr): 3330, 1710, 1610, 1550, 1265, 765, 705, and 695 cm^{-1}; NMR (DMSO-d_6): δ=1.19 (3H, d, J=7 Hz), 1.68 (3H, s), 2.9—3.3 (1H, m), 4.42 (1H, t, J=8 Hz, 7.19 (5H, s), and 7.85 (1H, diffused d, J=8 Hz, NH). The NMR spectrum was identical with that of the racemic compound.[1c]

References

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8) The identification of the synthetic **1** obtained by Fischer and Schmitz[7] with the naturally occurring **1** was unequivocally established.[1,3]

9) Fischer and Schmitz reported that the decarboxylation of racemic **4** resulted in the formation of a single compound (75% yield) which melted at 188—190 °C.[7] This compound was determined to have erythro, *i.e.* (*S,S*/*R,R*), configuration.[3] We traced Fischer's experiment and obtained the following results. When racemic **4** was heated at 130 °C under reduced pressure (*ca.* 20 Torr), carbon dioxide gas evolved, giving a crystalline material which was recrystallized from benzene to afford (*S,S*/*R,R*)-**5** (53% yield): mp 187—189 °C. Its NMR spectrum was in complete agreement with that of (*S,S*)-**5**. The mother liquor was concentrated *in vacuo* to give an oily residue (44% yield), which was shown by an NMR analysis to consist of (*S,S*/*R,R*)-**5** and (*S,R*/*R,S*)-**5** in a ratio of 1:2 [NMR of (*S,R*/*R,S*)-**5** (acetone-d_6): δ=1.53 (3H, d, J=7 Hz), 3.41 (1H, dq, J=10 and 7 Hz), 4.61 (1H, d, J=10 Hz), and 7.2—7.5 (5H, m)]. Thus, the ratio of (*S,S*/*R,R*)-**5**: (*S,R*/*R,S*)-**5** in the crude product can be calculated to be *ca.* 7:3.

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11) This material was synthesized according to the previously reported method.[5]