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# "Alternative Method for the Resolution of 1-Benzoyl-2-*tert*-butyl-3-methyl-1,3-imidazolidin-4-one"

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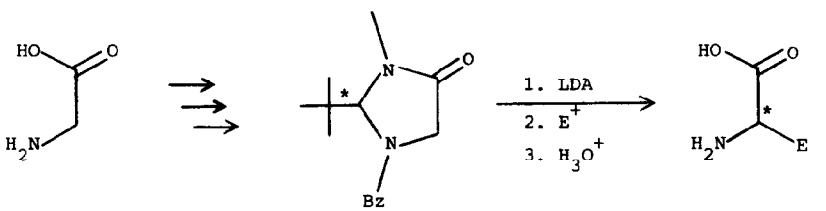
Abstract. The title heterocycles, which are useful chiral precursors for the asymmetric synthesis of α-amino acids, can be prepared in enantiomerically pure form via the separation of diastereomeric derivatives incorporating (*S*)-α-methyl-benzylamine.

## Introduction.

α-Amino acids are finding increasing use in pharmaceutical and agricultural chemistry, in the food industry, in molecular biology, etc. Among the available methods to synthesize α-amino acids in *optically active* form,[2] methodologies based on the homologation of glycine derivatives offer the greatest versatility.[3] In particular, the successful development of the imidazolidinones (*R*)- and (*S*)-1 as precursors of (*R*)- or (*S*)-α-amino acids[4] (Scheme I) has prompted the elaboration of several synthetic approaches to enantiomerically pure 1.

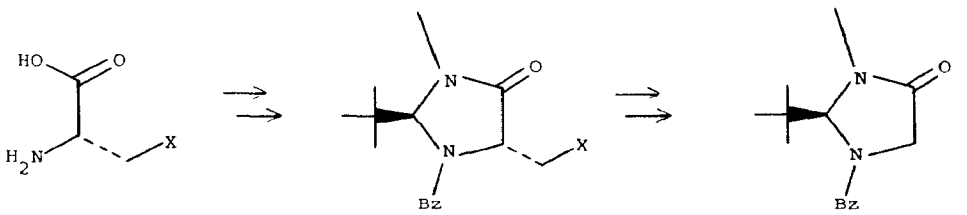
Scheme I




glycine (R)- or (S)-1 (R)- or (S)-α-amino acid

First, a multistep degradation of imidazolidinones derived from serine[5] or methionine[6] afforded small amounts of (S)-1 (Scheme II).

**Scheme II**



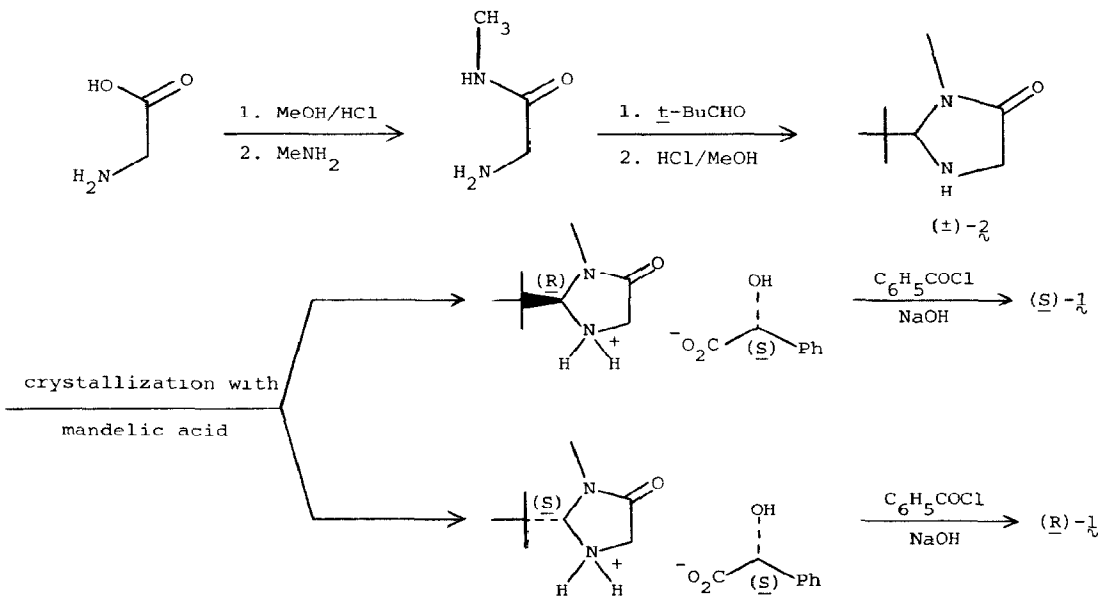
X = OH, serine

X = $CH_2SMe$, methionine

(S)-1

**Much better results were obtained by the resolution of the imidazolidinone 2 with mandelic acid,[7] followed by acylation under Schotten-Baumann conditions. (Scheme III).**

**Scheme III**

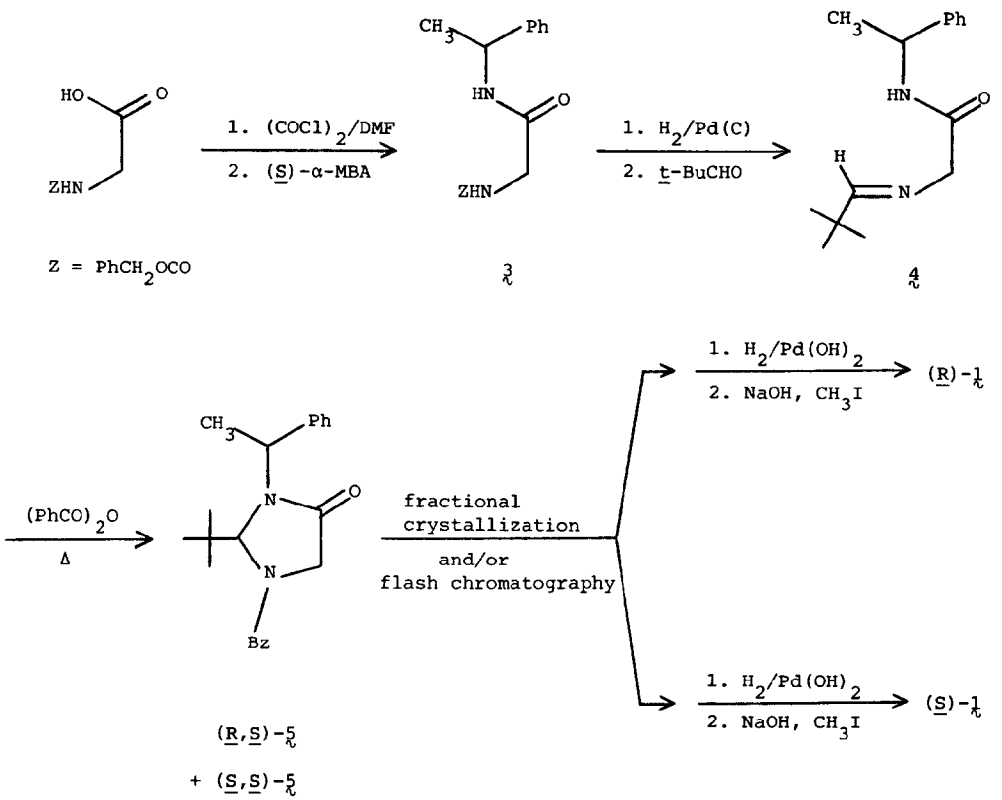



**We would like to describe now an alternative route for the preparation of enantiomerically pure (*R*)- and (*S*)-1, which makes use of (*S*)-α-methyl-benzylamine[8] [(*S*)-α-MBA] as the chiral adjuvant for the resolution step.**

**Results and Discussion.**

**As shown in Scheme IV, carbobenzyloxyglycine[9] was converted to its acid chloride with oxalyl chloride/DMF,[10] and then treated with (S)-α-methyl-benzylamine to afford the crystalline chiral amide 3 in 65% yield. Hydrogenolysis of 3 permitted the quantitative removal of the Z-protecting group, and condensation with pivalaldehyde (azeotropic separation of water) afforded imine 4 in 85% yield. Cyclization was then achieved upon treatment with benzoic anhydride[11] to furnish a 57:43 diastereomeric mixture of (*R,S*)- and (*S,S*)-5, in 66% yield.**

**Scheme IV**




**Separation of (*R*,*S*)- and (*S*,*S*)-5 was best carried out by initial crystallization (from methanol) of the (*R*,*S*) isomer, mp 185-186°C, followed by flash chromatography of the mother liquor to obtain the (*S*,*S*) isomer, mp 126-127°C, as well as an additional amount of the (*R*,*S*) diastereomer. The efficiency of this process was ca. 62%.**

**Conversion of (*R*,*S*)- and (*S*,*S*)-5 to (*R*)- and (*S*)-1 was completed by hydrogenolytic cleavage of the benzylic amine moiety,[12] followed by methylation under basic conditions. The combined yield of these two steps was a low 31%, largely due to the difficulties encountered during removal of the benzyl group from an amide. It should be pointed out, however, that enantiomerically pure (*R*,*S*)- and (*S*,*S*)-5, which are obtained in good yields (Scheme IV), may be used directly for the asymmetric synthesis of α-amino acids.[13]**

**Summary.**

**A new method for the preparation of enantiomerically pure imidazolidinones (*R*)- and (*S*)-1 is now available. Attractive features of this method are the use of inexpensive (*S*)-α-methyl-benzylamine as chiral adjuvant in the separation step, and the potential of the precursor (*R*,*S*)- and (*S*,*S*)-5 heterocycles as chiral glycine templates.**

**Experimental Part.**

General. TLC: Merck-DC-$F_{254}$ plates; detection by UV light. Flash column chromatography:[14] Merck silica gel (0.040-0.063 mm). M.p.: Mel-Temp apparatus; not corrected. Optical rotations were determined in a Perkin-Elmer 241 polarimeter, at the sodium D-line. $^1$H NMR spectra: Varian EM-360 (60 MHz), Varian EM-390 (90 MHz), and Jeol GSX-270 (270 MHz) spectrometers. $^{13}$C NMR spectra: Jeol FX-90Q (22.49 MHz) spectrometer. Chemical shifts ($\delta$) in ppm downfield from the internal TMS reference; the coupling constants (J) in Hz. Elemental analysis were obtained at the microanalytical laboratory, ETH-Zürich.

2-(*N*-Carbobenzyloxy)amino-*N'*-(α-methyl-benzyl)acetamide (3). In a 500-mL round-bottom flask, provided with stirring bar and two addition funnels, was placed under nitrogen 10.33 g (42 mmol) of 1 in 150 mL of $CH_2Cl_2$. The flask was submerged in a ice-water bath at 0°C, and then 0.3 mL dimethylformamide and 4.04 (5.88 g, 46 mmol) of oxalyl chloride was added. The ice-water bath was removed and stirring continued at ambient temperature for 90 minutes. The solution was cooled to -15°C and treated with 9.75 mL (9.17 g, 76 mmol) of (*S*)-(-)-phenylethylamine diluted in 150 mL of $CH_2Cl_2$. The reaction mixture was stirred at -15°C for 9 h. under nitrogen atmosphere, and then treated with 100 mL 1 N HCl (cold) and 100 mL of cold water. The organic phase was separated and shaken with saturated aqueous $NaHCO_3$ (2 x 150 mL), dried over anh. $Na_2SO_4$ and concentrated to afford 10.33 g (70% yield) of 3 as a white solid; mp 91-92°C. $[\alpha]_D^{29°C}$ = -75.2 (c = 1, ethanol). $^1$H NMR (90 MHz, $CDCl_3$) $\delta$ 1.4 (d, J = 7.2 Hz, 3 H), 3.78 (d, J = 6 Hz, 2 H), 5.05 (q, J = 7.2 Hz, 1 H), 5.05 (s, 2 H), 5.88 (t, J = 6 Hz, 1 H), 7.0 (b, 1 H), 7.3 (s, 5 H), 7.4 (s, 5 H). $^{13}$C NMR (22.49 MHz, $CDCl_3$) $\delta$ 21.69, 44.33, 48.67, 66.82, 125.92, 127.11, 127.76, 127.98, 128.36, 128.36, 136.0, 142.88, 156.53, 168.12.

2-Amino-*N'*-(α-phenylethyl)acetamide. In a hydrogenation flask was placed 8 g (25.6 mmol) of 3, 30 mL of methanol and 0.8 g of 10% Pd/C. The flask was pressurized to 10 atm $H_2$ and shaken at ambient temperature for 90 min. The reaction mixture was filtered over celite and concentrated to afford 4.5 g (quantitative yield) of the desired product as a yellow liquid; $[\alpha]_D^{29°C}$ = -84.5 (c = 1, ethanol). $^1$H NMR (90 MHz, $CDCl_3$) $\delta$ 1.5 (d, J = 7.2 Hz, 3 H), 1.85 (s, 2 H), 3.4 (s, 2 H), 5.2 (dq, J ∝ 6 Hz, $J^1$ = 7.2 Hz, 1 H), 7.4 (s, 5 H), 7.6 (b, 1 H). $^{13}$C NMR (22.49 MHz, $CDCl_3$) $\delta$ 22.01, 44.55, 48.12, 126.03, 127.17, 128.52, 143.26, 171.70.

2-*N*-(2,2'-Dimethylpropyliden)amino-*N'*-(α-phenylethyl)acetamide (4). In a 100 mL round-bottom flask, provided with stirring bar, and inverted Dean-Stark trap, was placed 5.83 g (33 mmol) of 2-amino-*N'*-(α-phenylethyl)acetamide, 40 mL of $CH_2Cl_2$, 6.88 mL (3.33 g, 33 mmol) of triethylamine and 7.15 mL (5.67 g, 66 mmol) of pivalaldehyde. The resulting mixture was heated to reflux for 5 h, and then allowed to cool to room temperature to be washed with two 30-mL portions of distilled water. The organic phase was dried over anh. $Na_2SO_4$ and concentrated to afford 6.89 g (85% yield) of 4 as a yellowish viscous oil; $[\alpha]_D^{29°C}$ = -73.8 (c = 1, ethanol). $^1$H NMR (90 MHz, $CDCl_3$) $\delta$ 1.1 (s, 9 H), 1.5 (d, J = 7.2 Hz, 3 H), 4.05 (s, 2 H), 5.25 (dq, J ∿ 6 Hz, $J^1$ = 7.2 Hz, 1 H), 7.3 (b, 1 H), 7.4 (s, 5 H). $^{13}$C NMR (22.49 MHz, $CDCl_3$) $\delta$ 22.07, 26.35, 36.26, 47.91, 125.54, 126.89, 128.30, 143.09, 169.15, 174.68.

(*R,S*)- and (*S,S*)-1-Benzoyl-2-*t*-butyl-3-(α-phenylethyl)-1,3-imidazolidin-4-one [(*R,S*)- and (*S,S*)-5]. In a 250-mL round-bottom flask, provided with stirring bar and condenser, was placed 2 g (8.13 mmol) of imine 4, 2.02 g (8.93 mmol) of benzoic anhydride and 10 mL of freshly distilled benzene. The resulting solution was heated under reflux for 7 h, and then concentrated to afford a yellow semisolid, which was dissolved in $CH_2Cl_2$, washed with aqueous saturated $NaHCO_3$ (2 x 25 mL), dried over anh. $Na_2SO_4$ and concentrated to afford 2.1 g (66% yield) of the crude product as a 57:43 mixture of the expected diastereomers.

Separation of (*R,S*)-5- and (*S,S*)-5. A chromatographic column (40 cm length, 4 cm diameter) was packed with 230-400 mesh silica gel before the separation of 408 mg of the mixture of (*R,S*)- and (*S,S*)-5. Elution with hexane-ethyl acetate-methylene chloride, 8:1:1 afforded first the less polar diastereomer, later identified as (*S,S*)-5, 108 mg (61.7% recovery); mp 126- 127°C; $[\alpha]_D^{29\,°C}$ = +60.5 (c = 1, $CH_2Cl_2$). Further elution afforded then the more polar (*R,S*)-5; 150 mg (64.5% recovery); mp 185-186°C; $[\alpha]_D^{29°C}$ = +45.5 (c = 1, $CH_2Cl_2$).

(*R,S*)-5: $^1$H NMR (270 MHz, $CDCl_3$) δ 0.98 (s, 9 H), 1.77 (d, J = 7.3 Hz, 3 H), 3.95 (*AB*, $J_{gem}$ = 15.8 Hz, 1 H), 4.23 (*AB*, $J_{gem}$ = 15.8 Hz, 1 H), 4.65 (q, J = 7.3 Hz, 1 H), 5.74 (s, 1 H), 7.26-7.61 (m, 10 H). $^{13}$C NMR (22.49 MHz, $CDCl_3$) δ 20.33, 25.75, 39.51, 54.14, 58.96, 81.88, 126.89, 128.09, 128.47, 131.45, 134.10, 141.14, 170.34, 171.16.

Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.48; H, 7.48; N, 7.99. Found: C, 75.24; H, 7.63; N, 7.90.

(*S,S*)-5: $^1$H NMR (270 MHz, $CDCl_3$) δ 1.10 (s, 9 H), 1.98 (d, J = 7.3 Hz, 3 H), 3.77 (*AB*, $J_{gem}$ = 15.8 Hz, 1 H), 4.14 (*AB*, $J_{gem}$ = 15.8 Hz, 1 H), 4.82 (q, J = 7.3 Hz, 1 H) 5.85 (s, 1 H), 7.26-7.56 (m, 10 H). $^{13}$C NMR (22.49 MHz, $CDCl_3$) δ 17.14, 25.91, 39.68, 53.71, 55.60, 79.93, 126.73, 127.44, 127.87, 128.30, 128.30, 131.23, 133.99, 140.55, 170.13, 170.88.

Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.33; H, 7.49; N, 7.87.

Procedure for the hydrogenolysis of (*R,S*)- or (*S,S*)-5. The appropriate diastereomer (0.8 g, 2.3 mmol), 25 mL of ethanol, 0.16 g of 20% Pd(C) and 0.1 mL of acetic acid were placed in a hydrogenation flask and exposed to hydrogen (24-30 atm) with stirring and heating (50-60°C) during 72 h. The catalyst was then removed by filtration (celite), and the filtrate was concentrated at reduced pressure to afford 0.23 g (41% yield) of the desired product, (*R*)- or (*S*)-1-benzoyl-2-*tert*-butyl-3(H)-1,3-imidazolidin-4-one, which was recrystallized from methanol-water (8:2). Melting point 217-219°C; $^1$H NMR (60 MHz, $CDCl_3$) δ 1.05 (s, 9 H), 4.05 (dd, $J_{gem}$ = 15 Hz, 2 H), 5.79 (s, 1 H), 6.7 (b, 1 H), 7.64 (m, 5 H).

(*R*)- and (*S*)-1-Benzoyl-2-*tert*-butyl-3-methyl-1,3-imidazolidin-4-one. (*R*)- and (*S*)-1. The N-H precursor obtained from the hydrogenolysis (0.072 g, 0.3 mmol), 15 mL of $CH_3CN$, 0.036 g (0.027 mL, 0.3 mmol) of $(CH_3)_2SO_4$ and 0.012 g (0.3 mmol) of NaOH were mixed and heated to 55°C for 2 h and then concentrated at reduced pressure. The solid residue was dissolved in ethyl acetate and washed with water. The usual workup procedure afforded the

crude product, which was recrystallized from hexane-methylene chloride (8:2) to afford 0.059 g (77% yield) of the desired product.

(*R*)-1: mp 142-144°C (lit.[3a] mp 143-144°C. $[\alpha]_D$ = -123 (c = 1, $CH_2Cl_2$) [lit.[3a] $[\alpha]_D$ = -128° (c = 1, $CH_2Cl_2$)].

(*S*)-1: $[\alpha]_D$ = +122° [lit.[3a] $[\alpha]_D$ = +127 (c = 1, $CH_2Cl_2$)].

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References and Notes.

(1) (a) Instituto Politécnico Nacional. (b) Universidad Nacional Autónoma de México.

(2) (a) Williams, R.M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989. (b) See also: O'Donnell, M.J., Ed. *α-Amino Acid Synthesis. Tetrahedron Symposia-In-Print Number 33*; Pergamon Press: Oxford, 1988.

(3) (a) Seebach, D.; Imwinkelried, R.; Weber, Th. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4. (b) Schöllkopf, U. *Top. Curr. Chem.* 1983, 109, 65-130. (c) Evans, D.A.; Weber, A.E. *J. Am. Chem. Soc.* 1986, 108, 6757-6761. (d) Williams, R.M.; Sinclair, P.J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* 1988, 110, 1547-1557, and references therein.

(4) (a) Seebach, D.; Juaristi, E.; Miller, D.D.; Schickli, C.; Weber, Th. *Helv. Chim. Acta* 1987, 70, 237-261. (b) Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* 1989, 1215-1232.

(5) Seebach, D.; Miller, D.D.; Müller, S.; Weber, Th. *Helv. Chim. Acta* 1985, 68, 949-952.

(6) Weber, Th.; Aeschimann, R.; Maetzke, Th.; Seebach, D. *Helv. Chim. Acta* 1986, 69, 1365-1377.

(7) (a) Fitzi, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* 1986, 25, 345-346. (b) Fitzi, R.; Seebach, D. *Tetrahedron* 1988, 44, 5277-5292.

(8) Both enantiomers of α-methyl-benzylamine are available at ca. $85 US dls from commercial laboratory suppliers.[9]

(9) Cf. Aldrich Chemical Company.

(10) Cf. Buckley, T.F.; Rapoport, H. *J. Am. Chem. Soc.* 1981, 103, 6157-6163.

(11) Cf. Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* 1991, 56, 2553-2557.

(12) Yoshida, K.; Nakajima, S.; Wakamatsu, T.; Ban, Y.; Shibasaki, M. *Heterocycles* 1988, 27, 1167-1168.

(13) Seebach, D.; Pfammatter, E.; Juaristi, E.; García-Barradas, O.; Anzorena, J.L. unpublished results. See, also: Amoroso, R.; Cardillo, G.; Tomasini, C. *Tetrahedron Lett.* 1991, 32, 1971-1974

(14) Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, 43, 2923-2925.