Simple Three-Step Synthesis of (*R*)- and (*S*)-4-Amino-3-hydroxybutanoic Acid (GABOB) by Stereoselective Aldol Addition

Manfred Braun,* Delia Waldmüller

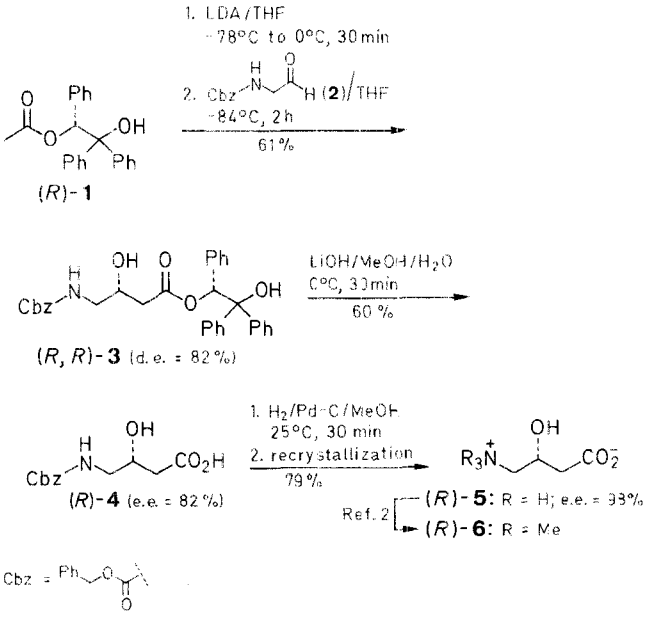
Institut für Organische Chemie und Makromolekulare Chemie der Universität Düsseldorf, Universitätsstraße 1, D-4000 Düsseldorf 1, Federal Republic of Germany

A simple synthesis of both (*R*)- and (*S*)-GABOB **(5)** is reported. In the key step, doubly deprotonated (*R*)- or (*S*)-2-Hydroxy-1,2,2-triphenylethyl acetate (HYTRA) **(1)** is added to Cbz-protected glycinal **(2)**.

(*R*)-4-Amino-3-hydroxybutanoic acid (GABOB, **5**) has been found to have remarkable hypotensive and antiepileptic activity.[1] (*R*)-Carnitine **(6)**, available by methylation of (*R*)-**5**,[2] plays a key role in the transportation of fatty acids through the membranes of mitochondria.[3] The enantiomer (*S*)-carnitine, however, has proven to be a competitive inhibitor of carnitine acyltransferase.[4] On the other hand, (*R*)-carnitine **(6)** has turned out to be an effective drug for the treatment of systemic and myopathic deficiencies.[5]

Several syntheses of enantiomerically pure GABOB **(5)** and carnitine **(6)** have been described. Besides by the resolution of racemic mixtures,[2,6] the target compounds **5** and **6** are available by the "chiron approach",[7] starting from carbohydrate precursors[8]; or more recently, from malic acid[9] and 4-hydroxyproline,[10] as well as by stereoselective conversions, including the Sharpless oxidation,[11] homogeneous hydrogenation,[12] yeast reductions,[13] and enzymatically catalyzed hydrolyses.[14]

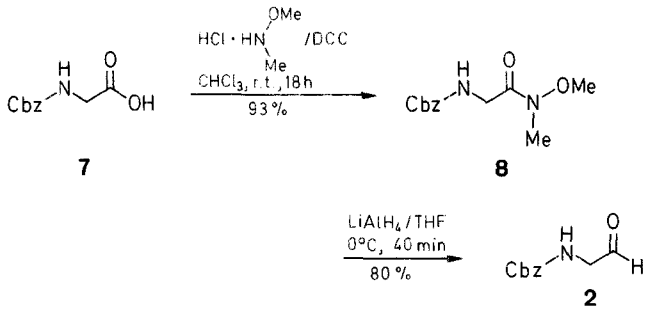
In this communication, we report a simple three-step synthesis of either (*R*)- or (*S*)-GABOB, depending on whether the (*R*)- or the (*S*)-enantiomer of the chiral auxiliary reagent 2-hydroxy-1,2,2-triphenylethyl acetate (HYTRA, **1**)[15] is used in the key step. Thus, (*R*)-**1** is deprotonated with two equivalents of lithium diisopropylamide in tetrahydrofuran, and the lithium enolate thus generated is treated with *N*-Cbz-glycinal **(2)** at −84 °C to give the ester **3** in 82% de (as shown by ^{1}H-NMR spectrometry). The crude product is purified by column chromatography, whereby no enrichment of one of the diastereoisomers (total yield: 61%) occurs. Mild alkaline hydrolysis not only



affords hydroxycarboxylic acid (*R*)-**4**[16] (60% yield), but also liberates (*R*)-1,1,2-triphenyl-1,2-ethanediol, which may be used again in the preparation of (*R*)-HYTRA (**1**).[17] Finally, catalytic hydrogenation of the crude *N*-Cbz-protected acid **4** leads to (*R*)-GABOB (**5**). The enantiomeric excess of crude (*R*)-**5**, which amounts 80–82% e.e., can be enhanced to 98% e.e. by a single recrystallization [yield of (*R*)-**5**: 79%, based on (*R*)-**4**].

In an analogous way, (*S*)-GABOB [(*S*)-**5**] of the same optical purity is available from (*S*)-HYTRA [(*S*)-**1**]. Since the conversion of GABOB (**5**) into carnitine (**6**) is known,[2] both enantiomers of the two amino acids should be accessible by our method in 25–27% overall yield.

Two reliable methods have been used for the preparation of *N*-Cbz-aminoacetaldehyde (**2**). The first one, elaborated by us, starts from *N*-(benzyloxycarbonyl)glycine (**7**), which is converted into the *N*-methoxy-*N*-methylamide[18] **8**. Subsequent reduction with lithium aluminum hydride affords aldehyde **2** in 74% overall yield. Alternatively, *N*-(benzyloxycarbonyl)allylamine can be cleaved by ozonolysis to give **2** in 85% yield.[19]



7 **8** **2**

Melting points (uncorrected) were determined with a Büchi/Tottoli melting point apparatus. Specific rotations were determined with a Perkin-Elmer 141 polarimeter. Mass spectra: Varian MAT CH-5. IR spectra: Perkin-Elmer 710 B. ^{1}H-NMR spectra: Varian EM 360 A, Varian VXR 300, and Bruker WP 80. TLC: Polygram-Sil-G/UV$_{254}$-Fertigfolien (Macherey-Nagel). Preparative TLC: Kieselgel-Fertigplatten Sil G-200/UV$_{254}$ (Merck). Column chromatography: Kieselgel 60, mesh size 0.2–0.5 mm (Merck). Ozonolyses: Ozongenerator 502 (Fischer). General remarks concerning the handling of lithium enolates are given in Lit.[17]

(1′*R*,3*R*)-4-[(Benzyloxycarbonyl)amino]-3-hydroxybutanoic Acid 2′-Hydroxy-1′,2′,2′-triphenylethyl Ester [(*R*,*R*)-3]:

A 250-mL two-neck flask, connected with a combined nitrogen-vacuum line, is equipped with a magnetic stirrer and closed with a septum. During the following manipulations, an N_2 atmosphere (about 70 Torr excess pressure) is maintained in all flasks. Dry THF (80 mL) and *i*-Pr_2NH (9.0 mL, 63.5 mmol) are injected through the septum by syringe. The mixture is cooled to −78 °C and stirred, and a 1.6 M solution in hexane of BuLi (40.0 mL, 64.0 mmol) is added dropwise. Stirring is continued for 30 min at 0 °C. In a 500 mL flask, a magnetically stirred suspension of ester (*R*)-**1** (10.0 g, 30.1 mmol) in dry THF (200 mL) is cooled to −78 °C under N_2. The solution of LDA (0 °C), prepared as described above, is added by cannula, whereby the 500 mL flask is slightly evacuated. The mixture is stirred at 0 °C for 30 min to complete the double deprotonation, and the solution is then cooled to −80° to −84 °C. A solution of aldehyde **2** (4.6 g, 23.9 mmol) in THF (30 mL) is added within 5 min by means of a cannula and stirring at −80° to −84 °C is continued for 2 h. Then, sat. aq. NH_4Cl (50 mL) is added, the mixture is allowed to reach r.t., H_2O (100 mL) is added, and the organic layer is separated. The aqueous phase is extracted with CH_2Cl_2 (4 × 300 mL). The combined organic layers are dried ($MgSO_4$) and evaporated under reduced pressure. The solid residue is purified by column chromatography on silica gel (300 g). Elution with $CHCl_3$/EtOAc (9:1) affords recovered (*R*)-**1** (R_F = 0.80) and a mixture of **3** and the (1′*R*,3*S*) isomer as a colorless solid material (R_F = 0.16); yield: 7.61 g (61%); mp 123 °C $[\alpha]_D^{25}$ +124.2° (*c* = 1, EtOH). The ratio (*R*,*R*)-**3**: (1′*R*,3*S*)-**3** is 91:9 according to ^{1}H-NMR analysis.

$C_{32}H_{31}NO_6$	calc.	C 73.12	H 5.95	N 2.67
(525.6)	found	73.11	5.95	2.56

MS (70 eV): *m*/*z* = 343 ($M^+ - [C_6H_5]_2COH$, 12%); 273 (10), 183 (46), 165 (31); 145 (62); 107 (30); 105 (70); 91 (100); 77 (22).

IR (KBr): ν = 3340, 1710, 1680 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$/TMS) of (*R*,*R*)-**3**: δ = 2.37 (m_c, 2 H, 2-H); 2.92 (m_c, 1 H, 4-H); 2.95 [d, 1 H, *J* = 3.3 Hz, $CH_2CH(OH)CH_2$]; 3.17 (m_c, 1 H, 4-H); 3.47 (s, 1 H, Ph_2COH); 3.87 (m_c, 1 H, 3-H); 5.08 (s, 2 H, $PhCH_2OCONH$); 5.16 (t, 1 H, *J* = 5.7 Hz, NH); 6.70 (s, 1 H, 1′-H); 7.00–7.60 (m, 20 H_{arom}). The ^{1}H-NMR spectrum of (1′*R*,3*S*)-**3** differs significantly from that of (*R*,*R*)-**3** in: δ = 3.02 (d, *J* = 3.3 Hz); 3.52 (s).

(*R*)-4-[(Benzyloxycarbonyl)amino]-3-hydroxybutanoic Acid [(*R*)-4]:

A 0.4 M aq. solution of LiOH (100 mL, 40 mmol) is added dropwise to a stirred solution of **3** (7.60 g, 14.6 mmol) in MeOH (175 mL) + dioxane (175 mL) at 0 °C. Stirring is continued for 30 min at 0 °C and thereafter the pH of the mixture is adjusted to 6 by addition of 10% aq. $KHSO_4$ solution. The solvent is removed in a rotary evaporator, the bath temperature not being allowed to exceed 30 °C. Water (100 mL) is added to the residue, and the pH is adjusted to 11 by addition of 1 M aq. NaOH solution. The mixture is extracted with CH_2Cl_2 (2 × 100 mL) to remove triphenylglycol and the aqueous layer is acidified (pH = 3) with $KHSO_4$ solution and extracted several times with EtOAc (total amount 500 mL). The organic extract is dried ($MgSO_4$) and the solvent is removed under reduced pressure to give (*R*)-**4** as an oil which crystallizes overnight; yield: 2.1 g (60%). For further transformations, the product (which can be recrystallized from CH_2Cl_2/hexane) is used without further purification; mp 62 °C; $[\alpha]_D^{25}$ −8° (*c* = 1, $CHCl_3$).

$C_{12}H_{15}NO_5$	calc.	C 56.91	H 5.97	N 5.53
(253.3)	found	56.48	5.87	5.74

MS (70 eV): *m*/*z* = 253 (M^+, 3); 146 (6); 108 (99); 107 (31); 91 (100).

IR (KBr): ν = 3600, 3350, 1700 (broad) cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$/TMS): δ = 2.47 (m_c, 2 H, 2-H); 3.17 (m_c, 1 H, 4-H); 3.31 (m_c, 1 H, 4-H); 4.11 (m_c, 1 H, 3-H); 5.06 (s, 2 H, $PhCH_2OCONH$); 5.66 (t, 1 H, *J* = 5.7 Hz, NH); 7.30 (s, 5 H_{arom}).

(*R*)-4-Amino-3-hydroxybutanoic Acid [(*R*)-5, (*R*)-GABOB]:

A mixture of Pd-C (10%, 75 mg), MeOH (80 mL), and H_2O (20 mL) is stirred in a two-neck flask equipped with a septum and a magnetic stirrer and connected with an ambient-pressure hydrogenation apparatus. When the solution has been saturated with H_2, a mixture of acid (*R*)-**4** (1.26 g, 5.0 mmol) and MeOH (20 mL) is injected through the septum by syringe. Hydrogenation is continued for 30 min at r.t. The mixture is filtered, the solvent is removed in a rotary evaporator, and the residue is dissolved in H_2O (20 mL). This solution is filtered and the filtrate is concentrated under reduced pressure. On addition of EtOH to the remaining aqueous solution (2–3 mL), product (*R*)-**5** is precipitated; yield: 0.565 g (95%); $[\alpha]_D^{25}$ −16.7° (*c* = 1, H_2O), corresponding to 81% ee {Lit.[10] $[\alpha]_D^{25}$ −20.5° (*c* = 1.75, H_2O)}. Recrystallization from aq. EtOH affords sufficiently pure (*R*)-**5**; yield: 0.468 g (79%); mp 210 °C (dec) (Lit.[10] mp 213–214 °C); $[\alpha]_D^{25}$ −20.1° (*c* = 1.97, H_2O); 98% ee.

^{1}H-NMR (60 MHz; D_2O/TMS_{ext}): δ = 2.3 (d, 2 H, *J* = 6 Hz, 2-H); 2.6–3.3 (m, 2 H, 4-H); 4.1 (m_c, 1 H, 3-H). (Lit.[10] δ = 2.33; 2.60–3.23; 3.91–4.30).

N^{α}-(Benzyloxycarbonylglycine *N*-Methoxy-*N*-methylamide (8):

A mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (3.21 g, 33.0 mmol), *N*-(benzyloxycarbonyl)glycine (**7**; 6.63 g, 31.8 mmol) and $CHCl_3$ (480 ml) is stirred under N_2 at r.t., a solution of DCC (7.44 g, 36.0 mmol) in $CHCl_3$ (15 ml) is added, followed by the addition of Et_3N (3.63 g, 5.1 mL, 36.0 mmol). Stirring is continued for 18 h, excess DCC is destroyed by the dropwise addition of AcOH and the solvent is removed in a rotary evaporator. The residue vigorously shaken with EtOAc (400 mL) and the mixture then kept in a refrigerator for 5 h. The precipitated dicyclohexylurea is filtered off, and washed with EtOAc (2 × 100 ml). The combined filtrates are concentrated to a volume of about 300 mL, washed with 2N aqueous HCl (3 × 100 mL) and with brine (3 × 100 ml), and dried ($MgSO_4$). Evaporation of the solvent affords a yellowish residue, which is dissolved in the minimum amount of hot $CHCl_3$. The fourfold volume of hexane is added, the solution is concentrated in a rotary evaporator, and kept in a refrigerator overnight to give colorless needles of **8**; yield: 7.41 g (93%); mp 77–78 °C.

$C_{12}H_{16}N_2O_4$	calc.	C 57.13	H 6.39	
(252.3)	found	57.09	6.35	

MS (70 eV): m/z = 251 ($M^+ - 1$, 12); 191 (52); 107 (9); 91 (100); 65 (30).

IR (KBr): ν = 3275, 1680 cm^{-1}.

^{1}H-NMR (80 MHz; $CDCl_3$/TMS): δ = 3.17 (s, 3H, NCH_3); 3.70 (s, 3H, $NOCH_3$); 4.15 (d, 2H, J = 5 Hz, $NHCH_2CON$); 5.16 (s, 2H, $PhCH_2OCONH$); 5.51 (m_c, 1H, NH); 7.31 (m_c, 5H_{arom}).

N-(Benzyloxycarbonyl)aminoacetaldehyde (2), prepared from 8:

A mixture of compound **8** (7.41 g, 29.6 mmol), THF (250 mL), and $LiAlH_4$ (1.15 g, 30.4 mmol) is stirred under N_2 for 40 min in an ice bath. A solution of $KHSO_4$ (5.66 g, 41.8 mmol) in H_2O (130 mL) is added, and THF is removed under reduced pressure. The residue is extracted with $CHCl_3$ (4 × 100 mL). The combined organic layers are washed with aqueous HCl (3 × 100 mL), sat. aq. $NaHCO_3$ (100 mL), and brine (100 ml) and are dried ($MgSO_4$). Evaporation of the solvent in a rotary evaporator gives **2** as a colorless oil; yield: 4.6 g (80%). The product is used in further reactions without purification. It is strongly recommended, to use only freshly prepared aldehyde **2**. The analytical and spectrometric data are in accord with those of a sample of **2** prepared according to Lit.[19].

This work was supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie. Generous gifts of chemicals were provided by BASF AG. We thank Dr. A. Steigel, Dr. H. Haddad, Mr. M. Ackermann, and Mr. J. Keul for recording the spectra.

Received: 8 June 1989; revised: 10 July 1989

(1) See for example:
The Merck Index, M. Windholz (ed.), 10th ed., Merck & Co, Inc., Rahway, 1983.
Pharmazeutische Stoffliste, Arzneibüro der Bundesvereinigung deutscher Apothekerverbände (ed.), 7th extended edition, Frankfurt/Main, 1988.
(2) Kaneko, T., Yoshida, R. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1153.
(3) See textbooks on biochemistry, e.g. Lehninger, A.L. *Prinzipien der Biochemie*, de Gruyter, Berlin 1987, p. 566.
(4) Fritz, I.B., Schultz, S.K. *J. Biol. Chem.* **1965**, *240*, 2188.
(5) Borum, P.R. *Nutr. Rev.* **1981**, *39*, 385; see also Ref. 1.
(6) Tomita, M., Sendju, Y. *Z. Physiol. Chem.* **1927**, *169*, 263.
(7) Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*, Pergamon Press, Oxford, 1983.
(8) Jung, M.E., Shaw, T.J. *J. Am. Chem. Soc.* **1980**, *102*, 6304.
Bock, K., Ludt, I., Pedersen, C. *Acta Chem. Scand. B.* **1983**, *37*, 341.
(9) Rajaskhar, B., Kaiser, E.T. *J. Org. Chem.* **1985**, *50*, 5480.
(10) Renaud, P., Seebach, D. *Synthesis* **1986**, 424.
(11) Rossiter, B.E., Sharpless, K.B. *J. Org. Chem.* **1984**, *49*, 3707.
(12) Kitamura, M., Ohkuma, T., Takaya, H., Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555.
(13) Zhou, B., Gopalan, A.S., Van Middlesworth, F., Shieh, W.R., Sih, C.J. *J. Am. Chem. Soc.* **1983**, *105*, 5925.
Seebach, D., Züger, M.F., Giovannini, F., Sonnleitner, B., Fiechter, A. *Angew. Chem.* **1984**, *96*, 155; *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 151.
Fuganti, C., Grasselli, P. *Tetrahedron Lett.* **1985**, *26*, 101.
(14) Gopalan, A.S., Sih, C.J. *Tetrahedron Lett.* **1984**, *25*, 5235.
Dropsy, E.P., Klibanov *Biotechn. Bioeng.* **1984**, *26*, 911.
Bianchi, D., Cabri, W., Cesti, P., Francalanci, F., Ricci, M. *J. Org. Chem.* **1988**, *53*, 104.
(15) Braun, M. *Angew. Chem.* **1987**, *99*, 24; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 24.
Mahler, U., Devant, R.M., Braun, M. *Chem. Ber.* **1988**, *121*, 2035.
(*R*)- and (*S*)-HYTRA are commercially available from Merck-Schuchardt; see: *MS INFO* **1988**, 88-4.
(16) The enantiomeric excess of (*R*)- **4** was found to be 80% ± 2 ee by conversion of the methyl ester of **4** [prepared from the mixture of (*R,R*)- **3** and (1′*R*,3*S*)- **3** by saponification and treatment with diazomethane] into the MTPA esters, which were analyzed by ^{19}F-NMR spectrometry (cf. Dale, J.A., Dull, D.L., Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543). Thus, (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(+)-2-methoxy-2-phenyl-3-trifluorpropanoic acid] was allowed to react with the methyl ester of **4** in the presence of DCC (cf. Schreiber, S.L., Kelly, S.E., Porco, Jr., J.A. Sammakia, T., Suh, E.M. *J. Am. Chem. Soc.* **1988**, *110*, 6210).
(17) Devant, R., Mahler, U., Braun, M. *Chem. Ber.* **1988**, *121*, 397.
(18) cf. Fehrentz, J.-A., Castro, B. *Synthesis* **1983**, 676.
(19) Bischofberger, N., Waldmann, H., Saito, T., Simon, E.S., Lees, W., Bednarski, M.D., Whitesides, G.M. *J. Org. Chem.* **1988**, *53*, 3457.