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A Concise Synthesis of (R)-GABOB from L-Malic Acid

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A CONCISE SYNTHESIS OF (*R*)-GABOB FROM L-MALIC ACID

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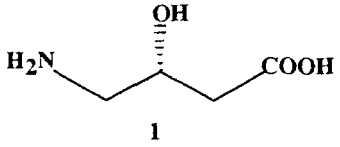
ABSTRACT: A concise synthesis of (*R*)-4-amino-3-hydroxybutanoic acid, starting from L-malic acid, is reported. The approach is based on the conversion of the oxazolidin-2-one **9** into a full protected form of (*R*)-GABOB by an Arndt-Eistert reaction.

4-Amino-3-hydroxybutanoic acid (GABOB) is a compound of great pharmacological importance, due to its biological function as a neuromodulator in the mammalian central nervous system.[1,2] The (*R*)(+)-isomer **1** showed an hypotensive and antiepileptic activity[3] and was found to have greater biological activity[4] than that of the (*S*)(-)-isomer.

GABOB has also been used as a synthetic precursor for some heterocyclic GABA-receptor agonists.[5] Moreover, the related (*R*)-carnitine **2**, readily available by methylation of **1**,[6] plays an important role in the transportation of fatty acids through the membranes of mitochondria.[7]



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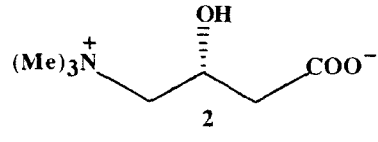

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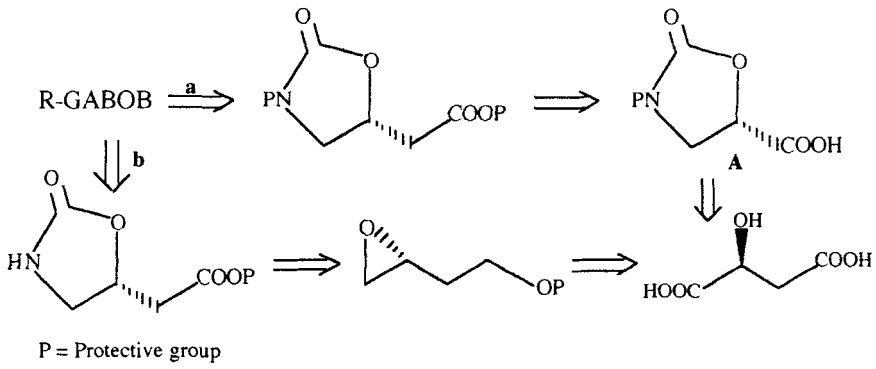
Whilst (*S*)-carnitine is a competitive inhibitor of carnitine acyltransferase (CAT),[8] (*R*)-carnitine was proved to be beneficial to heart patients[9] and its effectiveness in systemic and myopathic deficiencies is now recognized.[10]

Enantiomerically pure GABOB and carnitine have been prepared by several syntheses which involve separation of diastereoisomeric salts,[11] homogeneous hydrogenation,[12] yeast reduction[13] and enzymatically catalyzed hydrolysis.[14] The chiral center has been introduced either by means of enantioselective reactions[15] or employing selected starting materials from the chiral pool.[16]

For instance, malic acid was used by two different research groups to prepare (*R*)-GABOB[17] and (*R*)-carnitine;[18] these approaches have shortcomings, due to the use of expensive and unnatural D-malic acid. Surprisingly, no report appeared in the literature concerning the use of the less expensive L-malic acid as starting material. This prompted us to study synthetic approaches to the title compound from L-malic acid; two plausible retrosynthetic analyses are shown in Scheme I.

Pathway "**a**" is based on the conversion of the oxazolidin-2-one **A** to a full protected form of (*R*)-GABOB by an Arndt-Eistert reaction and utilizes a cyclic carbamate as protecting group for the 1,2-amino alcohol function. The alternative approach shown in pathway "**b**", that requires an inversion of configuration at the



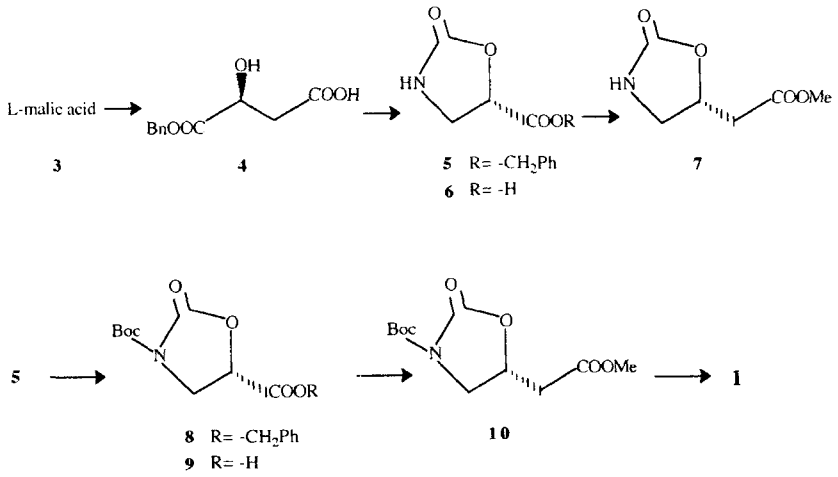
Scheme I

chiral center, has been extensively studied but it needs a major number of steps. Moreover, two of these steps were not completely regioselective,[19] so it was not competitive with the approach "**a**".

In details, the readily available 1-monobenzyl L-malic acid **4**, prepared from L-malic acid **3** according to the procedure of Miller,[20] was smoothly converted into the oxazolidin-2-one **5**[21] by treatment with diphenylphosphoryl azide in refluxing toluene. Removal of the benzyl group by catalytic hydrogenolysis gave the acid **6**, which was subjected to the Arndt-Eistert reaction.

All the attempts to convert in good yield **6** to **7** were unsuccessful, due to the low solubility of the acid in the solvents commonly required by this reaction. For instance, when the reaction was carried out in THF, the oxazolidin-2-one **7** was obtained in only 20% yield. Therefore, we chose to convert the benzyl ester **5** into the corresponding N-Boc-derivative **8**, which by hydrogenolysis gave acid **9** (Scheme II).

The methyl ester **10** was then prepared by conversion of the above acid into the corresponding diazoketone followed by rearrangement in MeOH in the presence of silver benzoate. Finally, acid hydrolysis of **10** gave the (*R*)-GABOB in 30% overall yield from the monobenzyl L-malic acid **4**.



Scheme II

In conclusion, a synthesis of (*R*)-GABOB has been achieved, starting from the readily available L-malic acid. The use of an unexpensive starting material, the short number of steps and the mild reactions involved make this approach quite attractive.

EXPERIMENTAL

Melting points were determined in open capillaries using a Büchi apparatus and are uncorrected. IR spectra were recorded on a Nicolet 5DX FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were run on a Varian GEMINI spectrometer at 300 and 75 MHz, respectively, in $CDCl_3$, unless otherwise reported. Optical rotations were determined on a Perkin-Elmer 243 polarimeter at 25°C. All solvents were dried[22] prior to use. Thin layer chromatography were performed on Merck silica gel 60 F_{254} glass plates.

Benzyl-(*S*)-2-oxo-oxazolidine Carboxylate (5)

To a well stirred solution of (*S*)-malic acid 1-monobenzyl ester[20] **4** (3.3 g, 14.7 mmol) in dry toluene (30 ml) and Et_3N (2.36 ml, 16.9 mmol) at room temperature under argon, diphenylphosphoryl azide (3.64 ml, 16.9 mmol) was added. After stirring for 15 min, a reflux condenser was attached and the solution was heated in a bath oil up to 80°C, when a vigorous gas evolution ensued. The mixture was stirred for additional 3 h, then was evaporated to dryness, taken up in EtOAc (150 ml), washed with saturated aqueous $NaHCO_3$ (2 x 100 ml), brine, dried (Na_2SO_4) and evaporated under reduced pressure. Purification by silica gel flash chromatography with $CHCl_3$/MeOH (98:2) as eluent gave **5** (2.28 g, 75%).
Mp: 129-30°C (EtOAc/*i*-Pr_2O). $[\alpha]_D$ = +3.81 (c = 1.7, DMF) [Lit[21]: $[\alpha]_D$ = +3.6° (c = 1, DMF)]. IR ν_{max}/cm^{-1} (nujol): 3353, 1790, 1760, 1458, 1376, 1154, 1081. ^1H NMR δ: 7.36 (5H, s, $-C_6H_5$), 6.46 (1H, brs, -NH), 5.25, 5.23 (1H each, d, J = 12.0 Hz, $-OC\underline{H}_2Ph$), 5.03 (1H, dd, J = 9.5 and 5.5 Hz, -CHO), 3.85 (1H, t, J = 2 x 9.5 Hz, $-C\underline{H}_AH_BN$), 3.64 (1H, dd, J = 9.5 and 5.5 Hz, $-CH_A\underline{H}_BN$). ^{13}C NMR δ: 168.62 (s, -COO), 158.89 (s, -CONH), 134.58 (s, C-1'), 128.71 (d, C-4'), 128.67, 128.43 (2 x d each, C-2', C-3', C-5', C-6'), 72.58 (d, -CHO), 67.73 (t, $-OCH_2$), 43.49 (t, $-CH_2N$).

(*S*)-2-Oxo-5-oxazolidine Carboxylic Acid (6)

Compound **5** (2 g, 9.05 mmol) was dissolved in absolute ethanol (30 ml) and hydrogenated over 10% Pd/C at 1 atm for 6 h. The mixture was filtered over celite and concentrated under reduced pressure to give **6** (1.127 g, 95%).
Mp: 59-60°C. $[\alpha]_D$ = – 6.1 (c = 0.6, MeOH). Anal. Calcd. for $C_4H_{15}NO_4$: C, 36.65; H, 3.84; N, 10.69. Found: C, 36.80, H, 3.91; N, 10.78. IR ν_{max}/cm^{-1}: 3246, 1745, 1690, 1450, 1376, 1244, 1203, 1097. ^1H NMR (CD_3OD) δ: 5.06 (1H, dd, J = 9.5 and 5.5 Hz, -CHO), 4.81 (1H, brs, NH), 3.88 (1H, t, J = 2 x 9.5 Hz,

-C$\underline{H}_A$H$_B$N), 3.61 (1H, dd, J = 9.5 and 5.5 Hz, -CH$_A\underline{H}_B$N). ^{13}C NMR δ: 172.55 (s, -COOH), 161.31 (s, -CONH), 73.99 (d, -CHO), 44.83 (t, -CH$_2$N).

Methyl-(*R*)-2-oxo-5-oxazolidine Acetate (7)

To a well stirred and cooled (0°C) solution of **6** (205 mg, 1.57 mmol) in THF (10 ml), dry Et$_3$N (0.218 ml, 1.57 mmol) was added, followed by ethyl chloroformate (0.150, 1.57 mmol). The reaction mixture was stirred at 0°C for 40 min, filtered through a pad of celite and an excess of an ethereal solution of diazomethane was added and stirring was continued for 2h. The solution was then concentrated under reduced pressure, dissolved in methanol (8 ml) and treated with silver benzoate (80 mg), Et$_3$N (0.8 ml) under a positive pressure of nitrogen. After 3 h of stirring at room temperature, the mixture was concentrated under reduced pressure, dissolved in EtOAc (100 ml), washed with a satd. solution of NaHCO$_3$ (2 x 50 ml), water (100 ml), 1N aq. KHSO$_4$ (2 x 50 ml), brine and dried with Na$_2$SO$_4$. The solution was filtered, concentrated and purified by flash chromatography (EtOAc/hexane 4:6) to give **7** (50 mg, 20%).

Mp: 54-5°C (Et$_2$O/hexane). [α]$_D$ = +26.1 (c = 1.0, CHCl$_3$). Anal. Calcd. for C$_6$H$_9$NO$_4$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.30, H, 5.79; N, 8.72. IR ν_{max}/cm^{-1} (nujol): 3279, 1728, 1432, 1256, 1176, 1096. ^{1}H NMR δ: 6.62 (1H, brs, -NH), 4.94 (1H, dq, J = 9.0 and 3 x 6.5 Hz, -CHO), 3.75 (1H, t, J = 2 x 9.0 Hz, -C$\underline{H}_A$H$_B$N), 3.66 (3H, s, -OCH$_3$), 3.29 (1H, dd, J = 9.0 and 6.5 Hz, -CH$_A\underline{H}_B$N), 2.83 (1H, dd, J = 16.5 and 6.5 Hz, -C$\underline{H}_C$H$_D$CO), 2.67 (1H, dd, J = 16.5 and 7.0 Hz, -CH$_C\underline{H}_D$CO). ^{13}C NMR δ: 169.66 (s, -COO), 159.60 (s, -CONH), 72.46 (d, -CHO), 51.90 (q, -OCH$_3$), 45.59 (t, -CH$_2$N), 38.92 (t, -CH$_2$).

Benzyl-(*S*)-N-*tert*-butoxycarbonyl-2-oxo-5-oxazolidine Carboxylate (8)

To a well stirred solution of **5** (915 mg, 4.14 mmol) and Et$_3$N (0.693 ml, 4.97 mmol) in THF (50 ml) was added Boc$_2$O (1.174 g, 5.38 mmol) followed by

DMAP (54 mg). The mixture was stirred overnight at room temperature, then concentrated under reduced pressure. The oily residue was dissolved in CH_2Cl_2 (50 ml), washed with 1N HCl (20 ml), 5% $NaHCO_3$ (20 ml) and brine. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure to give crude **8**. Recrystallization from EtOAc/hexane (1:3) afforded pure **8** (1.196 g, 90%).

Mp: 135-6°C. $[\alpha]_D$ = +21.7 (c = 0.02, $CHCl_3$). Anal. Calcd. for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.70, H, 6.19; N, 4.50. IR ν_{max}/cm^{-1}: 1810, 1769, 1712, 1458, 1368, 1302, 1081. ^1H NMR δ: 7.38 (5H, s, $-C_6H_5$), 5.26 (2H, s, J = 12.0 Hz, $-OC\underline{H}_2Ph$), 4.93 (1H, dd, J = 9.5 and 5.5 Hz, -CHO), 4.16 (1H, t, J = 2 x 9.5 Hz, $-C\underline{H}_AH_BN$), 4.00 (1H, dd, J = 9.5 and 5.5 Hz, $-CH_A\underline{H}_BN$). ^{13}C NMR δ: 167.77 (s, -COO), 150.42, 148.80 (s each, 2 x -CON), 134.29 (s, C-1'), 128.84 (d, C-4'), 128.72 (2 x d, C-3', C-5'), 128.49 (2 x d, C-2', C-6'), 84.46 (s, >C<), 68.90 (d, -CHO), 68.07 (t, $-OCH_2$), 45.96 (t, $-CH_2N$), 27.86 (q, $-CH_3$).

Methyl-(*R*)-N-*tert*-butoxycarbonyl-2-oxo-5-oxazolidine Acetate (10)

A solution of **8** (1 g, 3.12 mmol) in absolute EtOH (15 ml) was hydrogenated over 10% Pd/C (100 mg) at 1 atm for 6 h. The mixture was then filtered over celite and concentrated under reduced pressure to give the crude acid **9**. To a cold solution of **9** in THF (20 ml), dry NMM (0.312 ml, 3.12 mmol) was added followed by ethyl chloroformate (0.297 ml, 3.12 mmol). The reaction mixture was stirred at 0°C for 30 min, then filtered off through a pad of celite and an excess of an ethereal solution of diazomethane was added with stirring at 0°C for 20 min. The mixture was stirred for 4 h at the same temperature and concentrated under reduced pressure; the residue was dissolved in methanol (16 ml) and treated with silver benzoate (156 mg) and Et_3N (1.56 ml) under a positive pressure of nitrogen. After 2 h stirring at room temperature, the mixture was concentrated under

reduced pressure, dissolved in EtOAc (100 ml), washed with a satd. solution of $NaHCO_3$ (2 x 50 ml), water (100 ml), 1N aq. $KHSO_4$ (2 x 50 ml), brine and dried with Na_2SO_4. The solution was filtered and concentrated under reduced pressure to give an amber oil. Flash chromatography (EtOAc/hexane 3:2) afforded pure **10** (383 mg, 53%).

Mp: 79-80°C (Et_2O/hexane). $[\alpha]_D$ = +28.0 (c = 16, $CHCl_3$). Anal. Calcd. for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40. Found: C, 50.82, H, 6.80; N, 5.52. IR ν_{max}/cm^{-1}(nujol): 1797, 1751, 1702, 1450, 1379, 1302. ^1H NMR δ: 4.89 (1H, ddt, J = 8.5, 2 x 7.0 and 6.0 Hz, -CHO), 4.16 (1H, dd, J = 10.5 and 8.5 Hz, -C$\underline{H}_A$H$_B$N), 3.74 (3H, s, -OCH_3), 3.68 (1H, dd, J = 10.5 and 7.0 Hz, -CH$_A$$\underline{H}_B$N), 2.92 (1H, dd, J = 17 and 6.0 Hz, -C$\underline{H}_C$H$_D$N), 2.74 (1H, dd, J = 17.0 and 7.0 Hz, -CH$_C$$\underline{H}_D$N). ^{13}C NMR δ: 169.28 (s, -COO), 151.29, 149.20 (s each, 2 x -CON), 83.99 (s, >C<), 68.80 (d, -CHO), 52.16 (q, -OCH_3), 49.45 (t, -CH_2N), 38.74 (t, -CH_2CO), 27.88 (q, -CH_3).

(*R*)-4-Amino-3-hydroxybutanoic Acid (1)

To a solution of **10** (260 mg, 1 mmol), 6N HCl (10 ml) was added and refluxed under stirring for 6 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by ion-exchange chromatography on Dowex 50W-X8 (200-400 mesh, H^+ form), eluting first with water and then with 2N NH_4OH to yield **1** (98 mg, 85%).

Mp: 210-3°C (H_2O/EtOH). $[\alpha]_D$ = –20.1 (c = 1.6, H_2O) [Lit[14d]: $[\alpha]_D$ = -20.9 (c = 1.6, H_2O)]. IR ν_{max}/cm^{-1} (KBr): 3450, 3069, 2530, 2148, 1663. ^1H NMR (D_2O/dioxane) δ: 4.25 (1H, m, $\sum J$ = 25.5, -CHO), 3.16 (1H, dd, J = 13.0 and 2.0 Hz, -C$\underline{H}_A$H$_B$N), 2.95 (1H, dd, J = 13.0 and 10.0 Hz, -CH$_A$$\underline{H}_B$N), 2.65 (1H, dd, J = 16.0 and 5.0 Hz, -C$\underline{H}_C$H$_D$CO), 2.53 (1H, dd, J = 16.0 and 8.5 Hz, -CH$_C$$\underline{H}_D$CO). ^{13}C NMR (D_2O/dioxane) δ: 177.34 (s, -CO), 67.19 (d, -CHO), 46.67 (t, -CH_2N), 41.98 (t, -CH_2CO).

References

1. Otsuka, M.; Obata, K.; Miyata, Y.; Yaneka, Y. *J. Neurochem.* **1971**, *18*, 287.
2. Otsuka, M.; Miyata, Y., *Advances in Biochemical Psychopharmacology*; Raven, New York, 1972, Vol.6, p. 61.
3. De Maio, D.; Madeddu, A.; Faggioli, L. *Acta Neurol.* **1961**, *16*, 748.; Buscaino, G.A.; Ferrar, E. *Acta Neurol.* **1961**, *16*, 748.
4. Kurano, M.; Miyarnoto, S.; Shigeoka, S.; Mori, A.; *Japan Kokai,* **1976**, 76.100.026; *Chem. Abstr.* **1977**, *86*, 89207n.
5. Brehm, L.; Jacobsen, P.; Johansen, J. S.; Krogsgaardt-Larsen, P. *J. Chem. Soc. Perkin Trans.* **1983**, *1*, 1459.
6. Kaneko, T.; R.Yoshida T. *Bull. Chem. Soc. Japan.* **1962**, *35*, 1153.
7. Mc Garry, J. D.; Foster, D. W. *Ann. Rev. Biochem.* **1980**, *49*, 395.
8. Fritz, I. B.; Shultz, S. K. *J. Biol. Chem.* **1965**, *240*, 2188.
9. Thomsen, J. H.; Sug, A. L.; Yap, V. O.; Patel, A. K.; De Felice, S. L. *Amer. J. Cardiol.* **1979**, *33*, 300.
10. Borum, P. *Nutrition Revs.* **1981**, *39*, 385.
11. Voeffray, R.; Perlberger, J. C.; Tenud, L. *Helv. Chim. Acta* **1987**, *70*, 2058.
12. Kitamora M.; Ohkuma, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555.
13. Zhou, B.; Gopalan, A. S.; Van Middlesworth, F.; Shieh, W.; Sih, C. J. *J. Amer. Chem. Soc.* **1983**, *105*, 5925; Seebach, D.; Zuger, M. F.; Giovannini, F.; Sonnleitner, B.; Feichter, A. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 151; Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1985**, *26*, 101.
14. a) Gopalan, A.S.; Sih, C. J. *Tetrahedron Lett.* **1984**, *25*, 5235; b) Dropsy, E. P.; Klibanov, A. M. *Biotechn. Bioeng.* **1984,** *26*, 911; c) Bianchi, D.; Cabri, W.; Cesti, P.; Francalanci, F.; Ricci, M. *J. Org. Chem.* **1988,** *53*, 104; d) Lu, Y.; Miet, C.; Kunesch, N.; Poisson, J. *Tetrahedron: Asym.* **1990,** *1*, 707.
15. Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707; Braun, M.; Waldmuller, D. *Synthesis* **1989**, 856.

16. Jung, M. E.; Shaw, T. J. *J. Amer. Chem. Soc.* **1980**, *102*, 6304; Bock, R.; Lundt, I.; Pedersen, C. *Acta Chem. Scand.* **1983**, *B37*, 341; Bols, M.; Lundt I.; Pedersen, C. *Tetrahedron* **1992**, *48*, 319.
17. Rajashekhar, B.; Kaiser, E. T. *J. Org. Chem.* **1985**, *50*, 5480.
18. Bellamy, F. D.; Boudoux M.; Dodey P. *Tetrahedron Lett.* **1990**, *31*, 7323.
19. Misiti, D.; Zappia, G.; Delle Monache, G. Unpublished results.
20. Miller, M. J.; Bajwa, J. S.; Mattingly, P. G.; Peterson, K. *J. Org. Chem.* **1982**, *47*, 4928.
21. Maeda, H.; Suzuki, M.; Sugano, H.; Matsumoto, K. *Synthesis* **1988**, 401.
22. Perrin, D. D.; Armarego, W. L. *Purification of Laboratory Chemicals*, Pergamon Press, 1988.

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