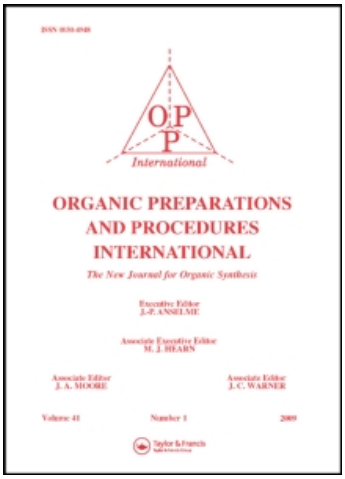


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN EFFICIENT SYNTHESIS OF (R)-GABOB AND OF (+)-GABOB

Engin Sahin[a]; Nurhan Kishali[a]; Latif Kelebekli[a]; Ebru Mete[a]; Hasan Secen[a]; Ramazan Altundas[a]; Yunus Kara[a]
[a] Department of Chemistry, Faculty of Arts and Sciences Atatürk University, Erzurum, TURKEY

To cite this Article Sahin, Engin , Kishali, Nurhan , Kelebekli, Latif , Mete, Ebru , Secen, Hasan , Altundas, Ramazan and Kara, Yunus(2007) 'AN EFFICIENT SYNTHESIS OF (R)-GABOB AND OF (+)-GABOB', Organic Preparations and Procedures International, 39: 5, 509 — 513
To link to this Article: DOI: 10.1080/00304940709458603
URL: http://dx.doi.org/10.1080/00304940709458603

ORGANIC PREPARATIONS AND PROCEDURES INT., 39 (5), 509-522 (2007)

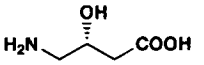
OPPI BRIEFS

AN EFFICIENT SYNTHESIS OF (R)-GABOB AND OF (±)-GABOB

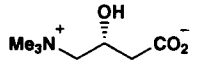
Submitted by Engin Sahin, Nurhan Kishali, Latif Kelebekli, Ebru Mete
(04/26/07) Hasan Secen, Ramazan Altundas* and Yunus Kara*

Department of Chemistry, Faculty of Arts and Sciences
Atatürk University, 25240 Erzurum, TURKEY
e-mail: yukara@atauni.edu.tr

(R/S)-4-Amino-3-hydroxybutanoic acid (GABOB) is a drug with known neuromodulator,[1] anti-epileptic[2] and hypotensive[3] activity. (R)-GABOB (**4**) is a compound of great pharmacological importance because of its biological action as a neuromediator in the mammalian central nervous system and has been shown to have a greater biological activity than its (S)-isomer.[4] Its N-trimethyl derivative, (R)-carnitine[5] (**4a**), plays a central role in the transportation of fatty acids through mitochondrial membranes. To date, several synthetic procedures have been described for the preparation of racemic GABOB.[6] In addition, over 40 methods for (R)-GABOB[6,7] and 20 for (S)-GABOB[6] have been developed. This paper reports an efficient synthesis of (R)-GABOB from **1** and (±)-GABOB from **5**.

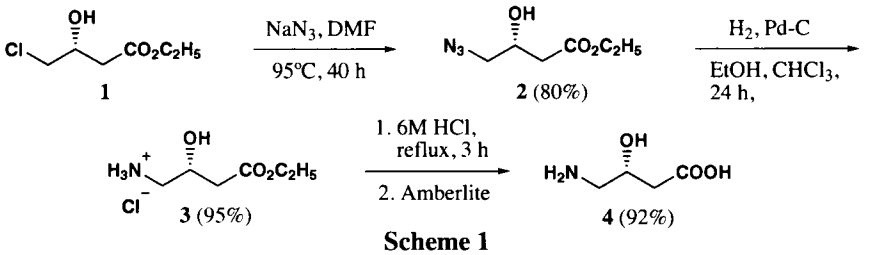


4 (R)-(–)-GABOB



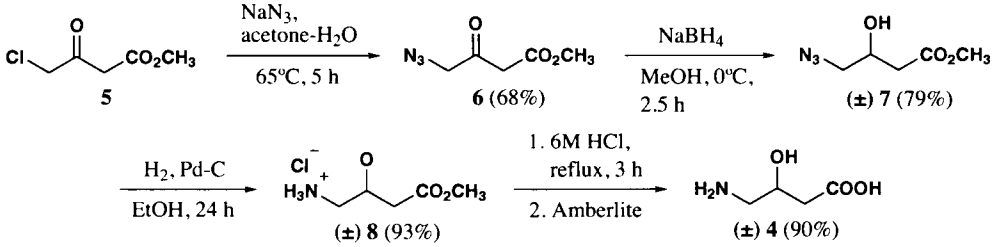
4a (R)-(–)-Carnitine

Our synthetic strategy for (R)-GABOB shown in *Scheme I* is based on commercially available (R)-ethyl 4-chloro-3-hydroxybutanoate (**1**). (R)-4-Chloro-3-hydroxybutyronitrile, a compound with similar structure, was previously used to prepare (R)-carnitine by substituting the chlorine with trimethylamine.[8] Tiecco *et al.*[7] used **1** in the preparation of (R)-GABOB in 50% overall yield through organoselenium intermediates in five steps. On the other hand, in previous studies methyl 4-chloroacetoacetate (**5**), a less expensive starting material, has been used for the preparations of racemic[9] or asymmetric[10] carnitine. Substitution of chlorine in **1** with NaN_3 gave azide **2** in 80% yields. Direct Pd-C catalyzed reduction of the azido group gave side products due to the further reaction of the free amine group. In the literature, this problem is overcome by performing the reduction in the presence of a small amount of $CHCl_3$. Thus, the HCl formed from the reduction of $CHCl_3$ stops further reaction of the NH_2 group. This method



Scheme 1

was successfully applied to reductions of azide or carbamate esters to give the corresponding amine hydrochlorides.[11] By this procedure, Pd-C catalyzed hydrogenation of **2** gave amine hydrochloride **3** in excellent yield (95%). Acidic hydrolysis of ester **3** in 6M HCl proceeded smoothly, and chromatography performed after hydrolysis on Amberlite, eluted with aqueous ammonia, gave (R)-GABOB (**4**) in a yield of 92%. Specific optical rotation of (R)-GABOB yielded data identical to those of the literature.[8] The result shows that no racemization occurred at the asymmetric carbon (C-3). Conversion of ester **3** to the corresponding carboxylic acid (GABOB) under the basic conditions proceeded with cyclization to give the (S)-isomer[12] of 4-hydroxypyrrolidin-2-one as the main product, identified by NMR. Under basic conditions, similar cyclization of (S)-ethyl 4-amino-3-hydroxybutanoate to give (S)-4-hydroxypyrrolidin-2-one was previously described in the literature.[13] Our synthetic approach to (±)-GABOB is shown in *Scheme 2*. Compound **5** was subjected to substitution with NaN_3 to give azide **6**. Chemoselective reduction of the carbonyl group at C-3 with $NaBH_4$ at 0°C gave azido alcohol **7**. As with the synthesis of (R)-GABOB above, Pd-C catalyzed hydrogenation of **7** with $CHCl_3$ gave the corresponding amine hydrochloride **8.** Subsequent hydrolysis of **8** afforded (±)-GABOB (**4**).



Scheme 2

In conclusion, (R)-GABOB was synthesized from readily available (R) ethyl 4-chloro-3-hydroxybutanoate (**1**) in three steps, in 70% overall yield, and (±)-GABOB was obtained from methyl 4-chloroacetoacetate (**5**) in four steps, in 45% overall yield.

EXPERIMENTAL SECTIONS

Melting points were determined on a Büchi 539 capillary melting apparatus and are uncorrected. Infrared spectra were obtained from KBr or film on a Mattson 1000 FT-IR spectrophotometer.

The ^1H and ^{13}C NMR spectra were recorded on 400 (100) and 200 (50) MHz Varian spectrometers and are reported in δ units with $SiMe_4$ as internal standard.

Ethyl (R)-4-Azido-3-hydroxybutanoate (2).- To ethyl (R)-(+)-4-chloro-3-hydroxybutanoate (**1**) (300 mg, 1.8 mmol) in DMF (5 mL) was added sodium azide (235 mg, 3.6 mmol). The solution was stirred at 90°C for 40 h. The mixture was extracted with ethyl acetate (3 x 50 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave ethyl (R)-4-azido-3-hydroxybutanoate (**2**) (250 mg, yield 80%, a pale yellow oil). IR (CH_2Cl_2): 3463 (OH), 2110 (N_3), 1738 (CO) cm^{-1}. ^1H-NMR (200 MHz, $CDCl_3$): δ 1.24 (t, 3H, J = 7.1 Hz, CH_3 of OEt), 2.50 (quasi d, 2H, J = 6.6 Hz, 2x H-2), 3.31 (quasi d, 2H, J = 4.8 Hz, 2x H-4), 4.14 (q, 2H, J = 7.1 Hz, CH_2 of OEt), 4.15 (m, 1H, H-3). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 14.0 (CH_3), 38.5 (C-2), 55.5 (C-4), 60.9 (CH_2O), 67.2 (C-3),171.8 (C-1). The ^1H-NMR is agreement with the data given in the literature.[4]

Ethyl (R)-4-Amino-3-hydroxybutanoate HCl (3).- To ethyl (R)-4-azido-3-hydroxybutanoate (**2**) (350 mg, 2.0 mmol) in ethyl alcohol (5 mL) and chloroform (0.5 mL) was added palladium on charcoal (10%) (50 mg). The suspension was stirred under hydrogen atmosphere for 24 h. After filtration, evaporation of the solvent afforded (R)-4-amino-3-hydroxybutanoate hydrochloride (**3**) as a thick yellow oil (350 mg, 95%). ^1H-NMR (400 MHz, $CDCl_3$): δ 1.22 (t, 3H, J = 7.0 Hz, CH_3), 2.62 (m, 2H, 2x H-2), 3.16 (m, 1H, one of H-4), 3.29 (m, 1H, one of H-4), 4.11 (q, 2H, J = 7.0 Hz, CH_2 of OEt), 4.47 (m, 1H, H-3), 5.15 (bs, 1H, OH), 7.89 (bs, 3H, NH_3^+). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.3 (CH_3), 39.7 (C-2), 44.9 (C-4), 61.1 (-CH_2 of OEt), 64.8 (C-3), 171.6 (C-1).

(R)-4-Amino-3-hydroxybutyric Acid (4, R-GABOB).- (R)-4-Amino-3-hydroxybutanoate•HCl (**3**) (400 mg, 2.2 mmol) was dissolved in 6M HCl (5 mL) and heated to reflux for 3 h. After cooling, the solution was made basic with solid $BaCO_3$ (3.94 g, 20 mmol) and heated for 1 h. Then it was filtered with suction and the filtrate neutralized exactly to pH = 7 with 6M HCl. The water was evaporated and the resulting mixture was filtered through Amberlite IR- 120 (H^+), eluted with a 10% ammonium hydroxide (250 mL). The eluate was concentrated to give (R)-4-amino-3-hydroxybutyric acid [(R)-(-) GABOB (**4**)] (240 mg, 92%) as a white solid, m.p. 210-212°C (*Lit*:[8] 211-212°C) (recrystallized from H_2O:ethanol (1:1). $[\alpha]_D^{22}$ = -15 (c 0.30, H_2O), [*lit*:[7] $[\alpha]_D^{21}$ = -17.51 (c 0.96, H_2O). ^1H-NMR (400 MHz, D_2O): δ 2.28 (d, 2H, J = 6.6 Hz, 2x H-2), 2.80 (B part of AB system, dd, 1H, ^2J = 13.2, ^3J = 9.5 Hz, H-4), 3.01 (A part of AB system, dd, 1H, ^2J = 13.2, ^3J = 2.9 Hz, H-4), 4.05 (dddd, 1H, J = 9.5; 6.6; 6.6; 2.9 Hz, H-3). ^{13}C-NMR (100 MHz, D_2O): δ 42.6 (C-2), 44.4 (C-4), 65.8 (C-3), 178.8 (C-1). The ^1H-NMR and ^{13}C-NMR are agreement with data given in the literature.[7,8]

Methyl 4-Azido-3-oxobutanoate (6).- A mixture of sodium azide (1.00 g, 15.4 mmol), methyl 4-chloro-3-oxobutanoate (**5**) (2.00 g, 13.2 mmol), acetone (18 mL) and water (6 mL) was stirred under reflux for 5 h. The solvent was removed and the residue was extracted with ethyl acetate (2 x 100 mL). After the solvent was removed, the residue was purified by column chromatography on silica gel, eluting with hexane-chloroform (7:3) to give oily methyl 4-azido-3-oxobutanoate (**6**)

(1.40 g, 68%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.46 (s, 2H, 2x H-2), 3.67 (s, 3H, OCH_3), 4.07 (s, 2H, 2x H-4). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 46.1 (C-2), 52.3 (C-4), 57.5 (OCH_3), 166.6 (C-1), 197.0 (C-3). IR (CH_2Cl_2, cm^{-1}): 2124 (N_3), 1738 (CO). Its ^{1}H-NMR is in agreement with data given in the literature.[14]

(±)-Methyl 4-Azido-3-hydroxybutanoate (7).- To a solution of $NaBH_4$ (115 mg, 3 mmol) in MeOH (10 mL) cooled to 0°C by means of an ice-salt bath was added dropwise a solution of methyl 4-azido-3-oxobutanoate (**6**) (314 mg, 2 mmol) in MeOH (10 mL). The mixture was stirred at 0°C for 2.5 h. The solvent was removed and the residue was dissolved in water (5 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried (Na_2SO_4) and filtered, and the solvent was removed to give (±)-methyl 4-azido-3-hydroxybutanoate (**7**) as a thick yellow oil (250 mg, 79%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.47-2.43 (AB system, m, 2H, 2x H-2), 3.26-3.23 (AB system, m, 2H, 2x H-4), 3.61 (s, 3H, OCH_3), 3.62 (bs, 1H, OH), 4.17-4.06 (m, 1H, H-3). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 38.3 (C-2), 51.6 (C-4), 55.4 (OCH_3), 67.0 (C-3), 172.0 (C-1). IR (CH_2Cl_2, cm^{-1}) 3489 (OH), 2124 (N_3), 1738 (CO). Its ^{1}H-NMR is in agreement with data given in the literature.[15]

(±)-Methyl 4-Amino-3-hydroxybutanoate. HCl (8).- The procedure described for the synthesis of **3** was applied to **(±)-7** to give yellow oil **(±)-8** (93%). ^{1}H-NMR (200 MHz, D_2O): δ 2.76-2.67 (AB system, m, 2H, 2x H-2), 3.31-3.23 (AB system, m, 2H, 2x H-4), 3.75 (s, 3H, OCH_3), 4.40 (m, 1H, H-3), 4.70 (bs, 3H, NH_3^+). ^{13}C-NMR (50 MHz, D_2O): δ 43.7 (C-2), 48.4 (C-4), 57.0 (OCH_3), 68.9 (C-3), 177.5 (C-1). The ^{13}C-NMR spectrum is agreement with data given in the literature.[16]

(±)-4-amino-3-hydroxybutyric acid (4) ((±)-GABOB).- The procedure described for the synthesis of **4** was applied to **(±)-8** to give (±)- GABOB (**4**) as a white solid (90%), mp. 210-212°C. The ^{1}H-NMR and ^{13}C-NMR spectra are agreement with data given in the literature.[6-8]

Acknowledgments.- The authors thank Ataturk University for its financial support (BAP-2006/50) of this work and Dr. Cavit Kazaz for the NMR spectra.

REFERENCES

1. (a) D. S. Bose and M. K. Gurjar, *Synth. Commun.*, **19**, 3313 (1989). (b) Y. N. Bubnov, L. I. Lavrinovich, A. Y. Zykov and A. V. Ignatenko, *Mendeleev Commun.*, 86 (**1992**).

2. (a) E. García-Flores and R. Farías, *Stereotact. Funct. Neurosurg.*, **69**, 243 (1997). (b) R. Chemello, D. Giaretta, A. Pellegrini and G. Testa, *Riv. Neurol.*, **50**, 253 (1980). (c) A. Tartara, A. Arrigo, C. Scamoni and A. Presazzi, *Minerva Med.*, **64**, 1943 (1973). (d) S. Banfi, W. Fonio, E. Allievi and S. Raimondo, *Pharmacol. Res. Commun.*, **15**, 553 (1983).

3. (a) M. A. Enero, D. Solignac and J. A. Apud, *Clin. Exp. Hypertens A.*, **10**, Suppl 1, 331 (1988). (b) K. Kamei, *Toho Igakkai Zasshi*, **25**, 64 (1978); *Chem. Abstr.*, **89**, 140626 (1978).

4. M. Larcheveque and S. Henrot, *Tetrahedron*, **46**, 4277 (1990).

5. F. M. Vaz and R. J. A. Wanders, *Biochem. J.*, **361**, 417 (2002).

6. E. Mete, A. Maras and H. Secen, *Russ. Chem. Bull.*, **52**, 1879 (2003) and references therein.

7. M. Tiecco, L. Testaferri, A. Temperini, R. Terlizzi, L. Bagnoli, F. Marini and C. Santi, *Synthesis*, 579 (**2005**) and references therein.

8. H. C. Kolb, Y. L. Bennani and K. B. Sharpless, *Tetrahedron Asymmetry*, **4**, 133 (1993).

9. L. Tenud, DE Pat. 2542227 (1976); *Chem. Abstr.*, **85**, 6052 (1976).

10. (a) B. N. Zhou, A. S. Gopalan, F. van Middlesworth, W. R. Shieh and C. J. Sih, *J. Am. Chem Soc.*, **105**, 5925 (1983). (b) R. Noyori, M. Kitamura, T. Okuma and H. Kumobayashi, *JP Pat. 01211551* (1989). *Chem. Abstr.*, ***112, 157695 (1989).***

11. (a) M. E. Jung and T. J. Shaw, *J. Am. Chem. Soc.*, **102**, 6304 (1980). (b) S. Göksu, H. Secen and Y. Sütbeyaz, *Helv. Chim Acta*, **89**, 270 (2006). (c) S. Göksu and H. Secen, *Tetrahedron*, **61**, 6801 (2005). (d) S. Göksu, H. Secen, Y. Sütbeyaz and C. Kazaz, *Helv. Chim. Acta*, **86**, 3310 (2003).

12. (a) P. Q. Huang, X. Zheng, S. L. Wang, J. L. Ye, L. R. Jin and Z. Chen, *Tetrahedron Asymmetry*, **10**, 3309 (1999).

13. N. Masahiro, *EP Pat. 0844242* (**1998**); *Chem. Abstr.*, **129**, 27885, (1998).

14. M. Shigeru, S. Kenzo, M. Takashi and S. Tsukasa, *EP Pat. 0947505* (**2002**); *Chem. Abstr.*, **131**, 271805 (2002)

15. S. Nakatani, M. Ikura, S. Yamamoto, Y. Nishita, S. Itadani, H. Habashita, T. Sugiura, K. Ogawa, H. Ohno, K. Takahashi, H. Nakai and M. Toda, *Bioorg. Med. Chem.*, **14**, 5402 (2006).

16. J. Wityak, C. B. Xue, T. M. Sielecki-Dzurdz, R. E. Olson, W. F. Degrado, G. A. Cain, D. G. Batt and D. Pinto, *EP Pat. 0730590* (**1996**); *Chem. Abstr.*, **130**, 66484.

****