Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 8, pp. 2411-2416, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00299-6

An Efficient Synthesis of (3*R*)-4-Amino-3-Hydroxy Butyric Acid (GABOB) *via* Cyclic Sulfite Methodology

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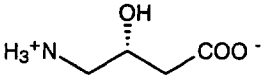
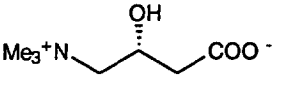
Abstract: The cyclic sulfite **6** prepared from enantiomerically pure N-[(2*S*)-2,3-dihydroxypropan-1-yl]phthalimide **2** derived from *D*-mannitol upon treatment with KCN in DMF afforded N-[(2*S*)-3-cyano-2-hydroxy propan-1-yl]phthalimide which was hydrolysed to furnish good yield of GABOB.

The (3*R*)-(-)-4-amino-3–hydroxybutyric acid (GABOB) is a well known neuromodulator in the mammalian central nervous system and is used as an antiepileptic and hypotensive drug.[1] Trimethylamino analogue of GABOB *i.e.* (*R*)-(-)-Carnitine, also known as vitamin B_T, plays a significant role in the human energy metabolism *via* the transport of long chain fatty acids into mitochondria.[2] (*R*)-Carnitine is also effective in certain cardiac disorders[3] and myopathic deficiencies [2ii, iv] and acts as a hypolipidemic agent.[4]

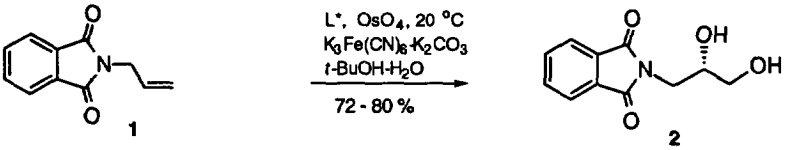


(*R*) - GABOB



(*R*) - Carnitine

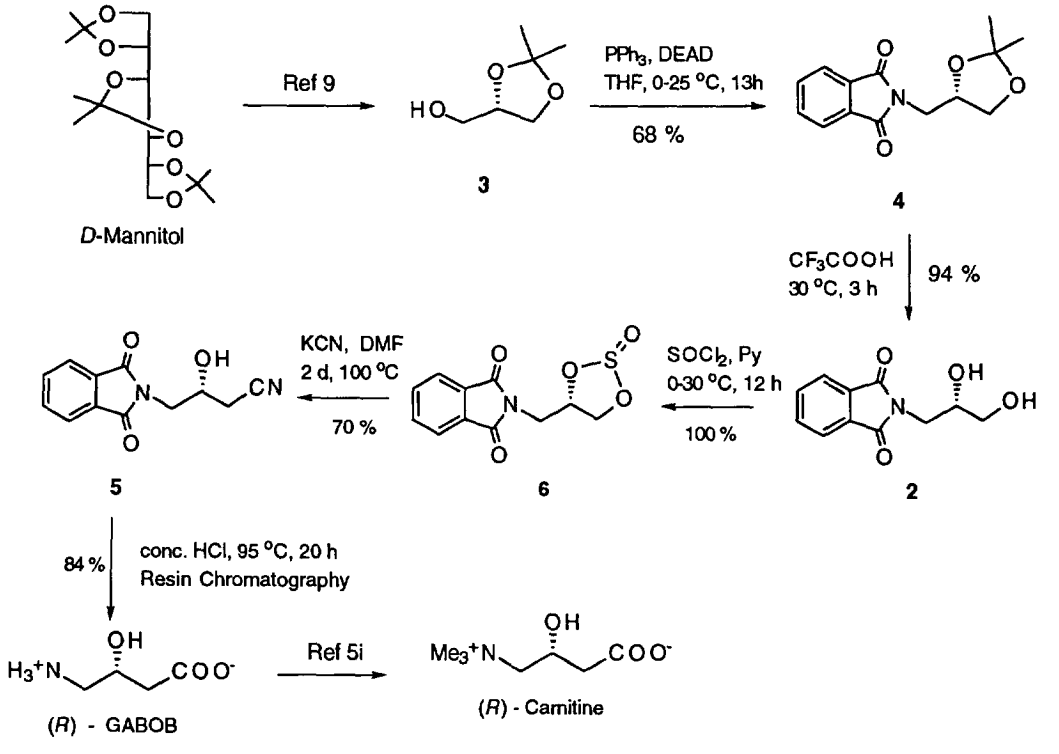
The interest in this class of compounds is exemplified by numerous reports and patents.[5] In continuation with our interest in the stereoselective transformation of diols *via* cyclic sulfites,[6] we report here a short synthesis of GABOB and carnitine in good yield and high enantiomeric purity, *via* cyclic sulfite methodology. Initially we attempted to prepare 1-phthalimido-(*R*)-propan-2,3-diol **2** by asymmetric dihydroxylation of the N-allylphthalimide **1** using various chiral auxiliaries as shown in Scheme 1.[7] However, the enantiomeric purity of the diol was unsatisfactory (25-37 % ee).[8] Therefore, we decided to prepare the enantiomerically pure diol **2** from *D*-mannitol as an alternative source. The (*S*)-glycerol 1,2-acetonide **3** was prepared from *D*-mannitol by known method (Scheme 2).[9] Attempts to convert (*S*)-glycerol acetonide **3** to N-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-methy]phthalimide **4** *via* bromination of **3** followed by treatment with sodium salt of phthalimide lead to a mixture of products with very poor yield of the desired product **4**. Similarly, reactions of the corresponding mesylate or tosylate of **3** with phthalimide under various conditions were not satisfactory.



L* = DHQD$_2$- PYR (37 %) DHQD$_2$- PHAL
DHQD$_2$- DPP DHQD$_2$- TP
DHQD$_2$-ITP DHQD$_2$- PY

Scheme 1

Alternative attempts to prepare **4** *via* DCC coupling of **3** with phthalimide also did not give encouraging results. Finally, the (*S*)-glycerol acetonide **3** was treated with phthalimide under Mitsunobu condition using Ph3P-DEAD in THF to furnish 68 % yield of N-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-methy]phthalimide **4**. The compound **4** upon subsequent hydrolysis with 50-70 % aqueous acetic acid gave moderate to poor yield (34 - 20 %) of N-[(2*S*)-2,3-dihydroxypropan-1-yl]phthalimide **2** under various conditions. However, the reaction proceeded cleanly using aqueous trifluoroacetic acid at *ca.*



Scheme 2

30 °C to furnish diol **2** in 94 % yield. The enantiomeric purity of the diol was determined by ^{1}H NMR by shift experiment on the corresponding bisacetate derivative using Eu(hfc)$_3$ as shift reagent. The specific rotation of **2** , $[\alpha]_D^{25}$ = -17.47 (c, 0.79, $CHCl_3$) also suggests the enantiomeric purity of **2** to be ≥ 98 %. The diol **2** was treated with thionyl chloride in pyridine at *ca.* 0 °C to afford a diastereomeric mixture of cyclic sulfite **6** in quantitative yield. The mixture of diastereomers of cyclic sulfite **6** has been separated by recrystallization. However, the diastereomeric mixture of cyclic sulfite was used for further transformation. The cyclic sulfite **6** was then reacted with potassium cyanide in DMF at 100 °C for 2 d under nitrogen atmosphere to afford hydroxynitrile **5** in 70 % yield. The hydroxynitrile **5** was hydrolysed with conc. HCl at *ca* 95 °C for 20 h to give a mixture of GABOB and phthalic acid. Phthalic acid was removed by repeated extraction with $CHCl_3$ and the aqueous layer was then evaporated to give a residue which was purified by chromatography on a cation exchange resin, Dowex 50 Wx2-100 using 25 % ammonium hydroxide as eluent to afford pure (3*R*)-(-)-4-amino-3-hydroxybutyric acid (3*R*-GABOB) in 84% yield. The (3*R*)-GABOB prepared from the diol **2** (37 % ee) obtained *via* AD reaction was enantiomerically enriched (76 % ee) by recrystallisation from ethanol-water mixture. The enantiomerically pure (3*R*-GABOB) obtained from 2(*S*)-glycerol was converted into (3*R*)-(-)-Carnitine by a reported procedure.[5i]

In summary, we have demonstrated a very simple method for the synthesis of enantiomerically pure (*R*)-GABOB and (*R*)-Carnitine *via* cyclic sulfite chemistry. The present methodology could be easily extended to other analogs of 4-amino-3-hydroxyacids such as 3-Amino-2-hydroxypropanyl phosphonic acid or 3-amino-2-hydroxypropanyl sulfonic acid using suitable nucleophiles for stereoselective ring opening of cyclic sulfite **6** which is being currently under investigation in our laboratory.

Experimental Section

All melting points were determined on a Melt-Temp. apparatus and are uncorrected. Phthalimide, triphenyl phosphine, thionyl chloride, potassium cyanide were obtained from LOBA fine chemicals. Allyl bromide, diethyl azodicarboxylate, trifluoroacetic acid were obtained from Alrich and was used after distillation. Flash chromatography was performed using silica gel, EM Science (230-400 mesh). Gas chromatography was carried out on a Shimadzu 17 AFW using a DB-1 (0.25 mm x 30 M) column. Elemental analysis were performed on a Perkin Elmer automatic CHN analyser-2400 series II. NMR spectra were recorded on a Varian Gemini 200 MHz (^{1}H) and 50 MHz (^{13}C) NMR spectrophotometer. All chemical shifts have been recorded using TMS as an internal standard. Stereochemical assignments are based on the stereochemistry of the starting sugar derivatives. Enantiomeric purity was determined by ^{1}H NMR using shift reagent on a Varian Gemini 200 MHz NMR spectrophotometer. IR was recorded on a Perkin Elmer 1620-FT spectrophotometer. Optical rotation was measured on a JASCO DIP - 370 polarimeter. Mass spectrometer used was Hewlett-Packard-5989A. (*S*)-1,2-Isopropylidene glycerol was prepared from *D*- mannitol by a known procedure.[9] Solvents used were purified by standard procedure.

Preparation of N-allylphthalimide 1 In a flame dried flask was placed phthalimide (4.41 g, 33 mmol), K_2CO_3 (4.14 g, 33 mmol), KOH (0.17 g, 3 mmol) and 18-crown-6 (0.1 g) in dry dioxane (100 mL) under argon atmosphere. The reaction mixture was stirred at room temperature for 10 min followed by addition

of allyl bromide (4.2 g, 35 mmol) over a period of 0.25 h. The reaction mixture was refluxed for 18 h at *ca* 100 °C. The reaction mixture was cooled under argon and filtered. The filtrate was evaporated and the product was purified by flash chromatography on silica gel to afford 4.7 g (76 %) of **1**.

General procedure for Asymmetric dihydroxylation of N-Allyl phthalimide In a double jacketed reaction flask attached to a cooling system was placed a mixture of potassium ferricyanide (0.987 g / mmol, 3 equiv.) and potassium carbonate (0.414 g / mmol, 3 equiv.) in t-BuOH : H_2O (1 : 1, 10 mL / mmol) and stirred at *ca* 20 °C for 10 min. Chiral auxiliary (2 mol %) and osmium tetroxide (20 µL, 0.5 M in toluene, 1 mol %) were added and stirred vigorously for 5 min. N-Allyl phthalimide (1 mmol) was added in one portion and the reaction mixture was stirred vigorously at *ca* 20 °C. The reaction was followed by TLC and finally was quenched with sodium metabisulfite (1.5 g / mmol) cautiously and stirred at room temprature for 30 min. $CHCl_3$ (10 mL / mmol) was added and the organic layer was separated. The aqueous layer was further extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and then concentrated under reduced pressure. The crude product was flash chromatographed on silica gel to furnish N-[(2*S*)-2,3-dihydroxypropane-1-yl]phthalimide **2** mp. 122 - 124 °C. The diol **2** was converted into the bis acetate derivative using acetic anhydride-DMAP-pyridine in order to determine the % ee using Eu(hfc)3 as chiral shift reagent.

N-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-methyl]phthalimide 4 Pthalimide (10g, 68 mmol) was dissolved in THF (20 ml), triphenylphosphine (21.2 g, 81 mmol), diethylazodicarboxylate (17.7 g, 102 mmol) and 1,2(*S*)-*O*-isopropylidene glycerol (13.4 g, 101.5 mmol) are added subsequently. After being stirred at room temperature for 13 h, the mixture was diluted with ethyl acetate (50 ml). The organic layer was washed with water, dried over Na_2SO_4 and concentrated in vaccum to give a syrupy liquid that was crystallized from petroleum ether to give **4** (12.0 g, 68 %), mp. 76 - 78 °C. Analysis calcd. for $C_{14}H_{15}NO_4$: C, 64.37 ; H, 5.75 ; N, 5.36. Found C, 64.07 ; H, 5.80 ; N, 5.40.; $[\alpha]_D^{26}$ = - 41.24 (c, 0.37, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.33 (S, 3H), 1.46 (S, 3H), 3.65 - 4.15 (m, 4H), 4.45 (m, 1H), 7.75 (m, 2H), 7.9 (m, 2H). IR υ_{max} (KBr) 1772, 1715 cm^{-1}; Mass m/z (relative intensity) 246 (M^+-CH_3, 45), 204 (100).

N-[(2*S*)-2,3-dihydroxypropan-1-yl]phthalimide 2 The compound **4** (10 g, 38.3 mmol) was dissolved in trifluoroacetic acid (10 ml) and water (0.1 ml) and stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue was purified by crystallization (PhH, MeOH, Hexane = 5:1:4) to give the title compound **2** (7.9 g, 94 %). mp. 122 - 124 °C, Analysis calcd. for $C_{11}H_{11}NO_4$: C, 59.73 ; H, 4.98 ; N, 6.33. Found C, 59.80; H, 5.00 ; N, 6.01. $[\alpha]_D^{27}$= -17.47 (c, 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.22 (bs, 2H, D_2O exchangeable), 3.6 (m, 2H), 3.9 (m, 3H), 7.75 (m, 2H), 7.9 (m, 2H); IR υ_{max} (KBr) 3449, 3290, 1768, 1714 cm^{-1}; Mass m/z (relative intensity) 222 (M^++ 1, 55).

N-[(4*S*)-2-Oxo-1,3,2-dioxothiolan-4-methyl]phthalimide 6 The diol **2** (5g, 22.6 mmol) was stirred with dry pyridine (7.5 ml) and thionylchloride (3 ml) at room temperature for 12 h under argon and the reaction mixture was diluted with ethyl acetate(25 mL) and then washed with 6 N HCl (5 mL). The reaction mixture was washed with aqueous saturated $NaHCO_3$ solution (2 x 5 mL) followed by brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure (6.0 g, 100 %). The crude product was purified by crystallization (C_6H_6 and hexane 1 : 1) to give the title compound **6** (3.4 g, 56 %). mp. 88-90 °C; Analysis calcd. for $C_{11}H_9NO_5S$: C, 49.44 ; H, 3.37 ; N, 5.24. Found C, 50.08 ; H, 3.7 ; N, 5.51; $[\alpha]_D^{28}$ = - 57.3 (c, 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 3.75 - 4.05 (m, 2H), 4.4

(dd, J = 9.0 and 4.4 Hz, 1H), 4.77 (dd, J = 9.0 and 6.4 Hz, 1H), 5.2 (m, 1H), 7.75 (m, 2H), 7.9 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.0, 69.2, 77.6, 80.0, 123.5, 131.5, 134.3, 167.8; IR υ_{max} (KBr) 1717, 1206 cm $^{-1}$; Mass m/z (relative intensity) 268 (M^++ 1, 1), 160 (100).

N-[(2*S*)-3-Cyano-2-hydroxy propan-1-yl]phthalimide 5 Potassium cyanide (0.61 g, 9.2 mmol) was added to a stirred solution of **6** (2 g, 7.5 mmol) in DMF (20 mL) and the solution is stirred at 100 °C for 48 h under argon atmosphere. The reaction mixture was carefully neutralized with conc. HCl (0.95 mL), extracted with ethyl acetate (2 x 20 mL), dried over Na_2SO_4 and evaporated under vacuum to furnish a residue (1.2 g, 70 %) which was purified by crystallization (benzene-hexane (2 : 1) mixture) to give the title compound **5**. mp. 104-106 °C Analysis calcd. for $C_{12}H_{10}N_2O_3$: C, 62.61 ; H, 4.35 ; N, 12.17. Found C, 62.01; H, 4.55; N, 12.48 $[\alpha]_D^{25}$ = - 13.2 (c, 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.6 (m, 2H), 3.24 (d, J = 5.4 Hz, 1H, D_2O exchangeable), 3.92 (d, J = 5.2 Hz, 2H), 4.3 (m, 1H), 7.75 (m, 2H), 7.9 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.0, 43.0, 66.23, 75.0, 116.9, 123.6, 131.6, 134.4, 168.7; IR υ_{max} (KBr) 3390, 2253, 1705 cm $^{-1}$; Mass m/z (relative intensity) 231 (M^++ 1, 20), 160 (100).

(3*R*)-4-Amino-3-hydroxybutyric acid (GABOB) The hydroxynitrile **5** (0.75 g, 3.26 mmol) was heated at 95 °C with conc. HCl (7 ml) for 20 h. The aqueous layer was washed with $CHCl_3$ (3 x 20 ml) and evaporated. The resulting crystalline product was dried under vacuum to give (3*R*-GABOB) hydrochloride (0.32 g, 84 %). The above hydrochloride was dissolved in distilled water (1 ml) and passed through a column containing Dowex 50 W x 2 - 100 resin (4 g) followed by distilled water (60 ml). The column was eluted with 25 % aqueous ammonia (20 ml) and the ammoniacal eluent was evaporated to dryness under vacuum to provide (3*R*-GABOB). mp 206 - 208 °C (Lit [10] mp. 213-214 °C). Analysis calcd. for $C_4H_9NO_3$: C, 40.34 ; H, 7.56; N, 11.76. Found C, 40.32, H, 7.57 ; N 11.79 $[\alpha]_D$25 = - 18.6 (c, 0.5, H_2O) (Lit [10] $[\alpha]_D$25 = - 20.5 (c, 1.75, H_2O). Recrystallization from aqueous ethanol afforded nearly enantiomerically pure (3*R*-GABOB); $[\alpha]_D$25 = - 20.2 (c, 1.9, H_2O) ; ^{1}H NMR (D_2O, 200 MHz) δ : 2.4 (d, J = 6.6 Hz, 2H), 2.91 (dd, J = 12.8 and 9.6 Hz, 1H), 3.14 (dd, J = 13.4 and 3.0 Hz, 1H), 4.15 (m, 1H).

(3*R*)-4-Trimethylamino-3-hydroxybutyric acid (*R*-Carnitine) Methylation of (3*R*-GABOB) (0.12 g, 1 mmol) was carried out by reported method[5i] to furnish (*R*)-carnitine (0.1 g; 62 % yield), mp 192-195 °C; $[\alpha]_D$25 = - 22.5 (c, 0.80, H_2O)(lit [5i], mp 197-198 °C; $[\alpha]_D^{25}$ = - 23.9 (c, 0.86, H_2O).

Acknowledgements: We are thankful to Dr. Reddy's Research Foundation, Hyderabad for providing financial support, Mr. E. Nandanan for a few preliminary experiments, Dr. K. Anji Reddy and Dr. A Venkateswarlu for encouragement.

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(*Received in UK* 29 *May* 1996)