Electrochemical Decarboxylation of Hydroxyproline: A Simple Three-Step Conversion of (2*S*,4*R*)-4-Hydroxyproline to (*R*)-γ-Amino-β-hydroxybutanoic Acid (GABOB)

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A high yield conversion on preparative scale of (2*S*,4*R*)-*N*-acetyl-4-hydroxyproline (**1**) to (*R*)-GABOB (**4**) is reported. The key step of the synthesis is the electrochemical oxidative decarboxylation of **1**.

The anodic oxidation of carboxylic acids leads to radicals which couple [*Kolbe*-elektrolysis[2], Reaction *(1)*] or which are further oxidized to carbenium ions, and these in turn are trapped by the solvent[3] [e.g. alcohols, Reaction *(2)*].

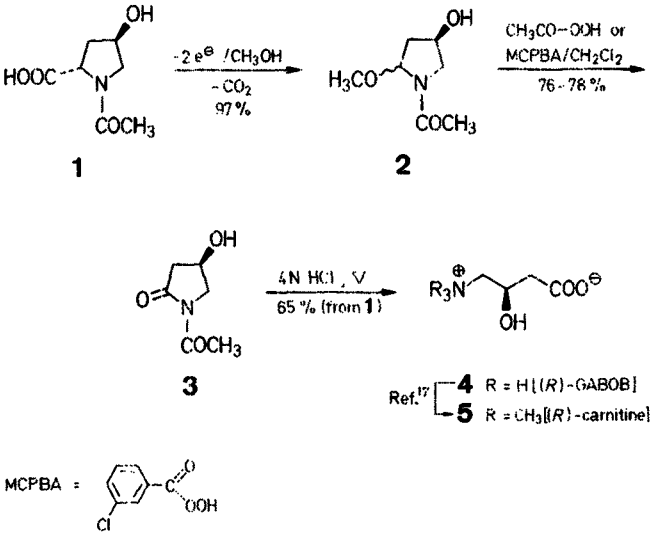
(1) $R^1\text{-}COOH \quad HOOC\text{-}R^2 \longrightarrow R^1\text{-}R^2$

(2) $R^1\text{-}COOH \quad H\text{-}OR^2 \longrightarrow R^1\text{-}OR^2$

Kolbe-electrolysis[4] has been applied to the synthesis of enantiomerically pure compounds (EPC syntheses[5]) such as pheromones[6], hydroxy acids[7], alcohols[8] and amino acids[9].

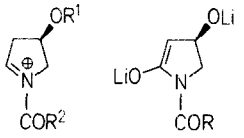
The two-electron oxidation in Reaction *(2)* is especially favored with α-heterosubstituted carboxylic acids[10,11]. So far, it has hardly been used for EPC syntheses[12]. In the course of our work on transformations of amino acids without racemization[13], we became interested in this process, and employed it as the key step of a conversion of hydroxyproline to GABOB[14] and carnitine[15].

The electrochemical oxidation of (2*S*,4*R*)-*N*-acetyl-4-hydroxyproline[16] (**1**) in methanol gives the 2-methoxypyrrolidine derivative **2** in 97% yield (mixtures of diastereomers). The *N*,*O*-acetal derivative **2** is oxidized to the γ-lactam **3** with peracetic acid or 3-chloroperbenzoic acid in dichloromethane. The lactam is opened in refluxing 4 normal hydrochloric acid to give, after purification over an ion-exchange resin, optically pure (*R*)-4-amino-3-hydroxybutanoic acid (**4**) in about 65% overall yield from the acetylproline **1**. Methylation of GABOB under basic conditions is known to produce carnitine (**5**; vitamine B_T)[17].



Previous EPC syntheses of GABOB and carnitine involve chemical resolutions of racemic mixtures[17,18]. (*R*)-GABOB has also been prepared from ascorbic acid[19,20], from L-arabinose[20], and by using a *Sharpless* oxidation[21], a microbial hydrolysis[22] or a yeast reduction[23] as enantioselective steps. (*R*)-Carnitine has been obtained by enzymatic or microbial asymmetric reduction of suitable β-ketoesters[24] or by cholinesterase-catalyzed resolution[25].

The present high-yield three- and four-step conversions of *N*-acetylhydroxyproline to (*R*)-GABOB and (*R*)-carnitine, respectively, compare favorably with the syntheses described in the literature[17–25]. Moreover, the two intermediates **2** and **3** are precursors to iminium ions[26] of type **6** and to enolates[27] of type **7**, respectively, and thus useful starting materials for EPC syntheses of a variety of other products[1].



6 **7**

Melting points (uncorrected) were determinated by using a Büchi 510 apparatus. I.R. spectra were recorded on a Perkin-Elmer 297 spectrometer (film, $CHCl_3$) and a Perkin-Elmer 287 spectrometer (KBr) (s = strong, m = middle, w = weak, br. = broad). ^{1}H-N.M.R. spectra were recorded on a Varian EM-390 spectrometer (90 MHz), with TMS signal at 0 ppm or in water with HDO signal at 4.70 ppm (s = singlet, d = doublet, m = multiplet, br. = broad). ^{13}C-N.M.R. spectra were recorded on a Varian CFT-20 spectrometer (20 MHz), with TMS signal at 0 ppm. M.S. spectra were recorded on a Hitachi-Perkin-Elmer RMU-6M (M^+ = molecular peak, intensity in %). For flash column chromatography, Merk silica gel 60 (230–400 mesh) was used. Commercially available peracetic acid (40% in acetic acid, Elfa oxychemie) was used. Solvents and other reagents were purchased from Fluka (puriss. quality) and used without further purification. Electrolyses[28] are performed in a cooled, undivided cell using an Amel Model 552 Potentiostat/Galvanostat connected with an Hengstler 794.4 integrator under galvanostatic conditions. A rotating (1000 rpm) disk electrode of platinium (3.0 cm^2) was used as anode and a wire grating of platinium (6.2 cm^2) as cathode[29]. No additional stirring was required. The temperature of the reaction mixture was maintained at about 15°C.

***l*- and *u*-(4*R*)-*N*-Acetyl-2-methoxypyrrolidin-4-ol (2):**

A solution of (2*R*,4*S*)-*N*-acetyl-4-hydroxyproline[16] (**1**; 17.3 g, 100 mmol) and triethylamine (2.8 ml, 20 mmol) in methanol (120 ml) is electrolyzed with a current density of i = 260 mA/cm^2 (2.5 F/mol). Evaporation of the methanol under reduced pressure (T < 25°C) and filtration of the residue through silica gel (diethyl ether/ethanol, 7:3) gives **2**; (yield: 15.5 g (97%) as an oil (7:3 mixture of diastereomers). Separation of the diastereomers is possible by flash-chromatography diethyl ether/ethanol, 9:1).

$C_7H_{13}NO_3$	calc.	C 52.82	H 8.23	N 8.80
(159.2)	found	52.67	8.23	8.64

M.S. (mixture of diastereomers): *m/e* = 159 (M^+, 0.4); 144 (15); 129 (85); 128 (60); 86 (94); 73 (47); 43 (100).

I.R. (KBr, mixture of diastereomers): ν = 3360 (br.); 2920 (m); 1630 (s), 1440 cm^{-1} (m).

^{1}H-N.M.R. ($CDCl_3$): major diastereomer, R_f = 0.38 (ether/methanol, 7:3); two rotamers: δ = 2.07, 2.17 (2 S, 3 H, CH_3CO); 1.83–2.33 (m, 2 H, H—C-3); 3.40, 3.47 (2 S, 3 H, CH_3O); 3.23–3.57 (br., 1 H, OH); 3.57–3.73 (m, 2 H, H—C-5); 4.30–4.60 (m, 1 H, H—C-4); 5.07, 5.57 ppm (2 d, J = 4.5 Hz, H—C-2).

Minor diastereomer, R_f = 0.56 (ether/methanol, 7:3), two rotamers: δ = 2.05, 2.10 (2 S, 3 H, CH_3CO); 1.88–2.32 (m, 2 H, H—C 3); 3.25, 3.33 (2 S, 3 H, CH_3O); 3.20–4.00 (m, 3 H, H—C 5, OH); 4.40–4.80 (m, 1 H, H—C 4); 5.07–5.20 and 5.40–5.55 ppm (2 m, 1 H, H—C 2).

^{13}C-N.M.R. ($CDCl_3$), methoxy signal, two rotamers, major diastereomer: δ = 54.29, 54.82 ppm; minor diastereomer: δ = 52.92, 53.41 ppm.

(*R*)-*N*-Acetyl-4-hydroxy-2-pyrrolidone (3):

Method A: Oxidation with peracetic acid: To a solution of **2** (0.80 g, 5 mmol) in dichloromethane (20 ml) are added 40% peracetic acid in acetic acid (1.33 ml, 7 mmol) and ion exchanger Amberlyst 15, strongly acidic (100 mg, $H^{\oplus}$-form). The reaction mixture is stirred for 9 days at room temperature and gives, after flash-chromatography (ether/methanol, 9:1), pure **3**; yield: 0.56 g (78%) as a colorless oil.

Method B: Oxidation with 3-chloroperbenzoic acid (MCPBA)[30]: 3-Chloroperbenzoic acid (16.0 g, 79 mmol) and boron trifluoride etherate (0.35 ml, 2.8 mmol) are added to a solution of **2** (11.0 g, 69.2 mmol) in dichloromethane (200 ml) at 0°C. After 12 h stirring at room temperature, pentane (200 ml) is added to the reaction mixture, the white precipitate is filtered off and washed with a 1:1 mixture of dichloromethane/pentane. Evaporation of the filtrate and flash-chromatography of the residue gives **3**; yield: 7.60 g (76%); $[\alpha]_{436}^{25}$: −22.8° (*c* 1.2, $CHCl_3$).

$C_6H_9NO_3$	calc.	C 50.35	H 6.34	N 9.79
(143.1)	found	50.29	6.41	9.72

M.S.: *m/e* = 143 (M^+, 36); 125 (4); 115 (35); 101 (11); 83 (12); 72 (18); 43 (100).

I.R. (film): ν = 3450 (br.); 2940 (w); 1745 (s); 1690 (s); 1380 (s); 1300 cm^{-1} (s).

^{1}H-N.M.R. ($CDCl_3$): δ = 2.50 (s, 3 H, CH_3CO); 2.60–2.87 (m, 2 H, H—C-3); 3.03 (d, J = 4 Hz, 1 H, OH); 3.87 (d, J = 4, 2 H, H—C-5); 4.40–4.67 ppm (m, 1 H, H—C-4).

(*R*)-4-Amino-3-hydroxybutanoic acid (4):

A sample of **3** (0.50 g, 3.5 mmol) is heated at reflux with 4 normal hydrochloric acid (7 ml). After 4 h, water is evaporated and the residue dried under high vacuum to give the crude hydrochloride of **4**. The salt is dissolved in water (20 ml) and adsorbed on acidic Dowex 50 W × 8 (30 g). The resin is washed with distilled water until neutral, and then the free amino acid is eluted with 1.3 normal aqueous ammonia. Evaporation in vacuo gives crude **4** (0.45 g) which is recrystallized from water/ethanol; m.p. 213.0–214.0°C (Lit.[18], m.p. 212°C); $[\alpha]_D^{25}$: −20.5° (*c* 1.75, H_2O) (Lit.[18], $[\alpha]_D^{25}$: −21.06° (*c* 2.2, H_2O).

^{1}H-N.M.R. (D_2O): δ = 2.33 (d, J = 6 Hz, 2 H, H—C-2); 2.60–3.23 (m, 2 H, H—C-4; 3.93-4.30 ppm (m, 1 H, H—C-3).

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