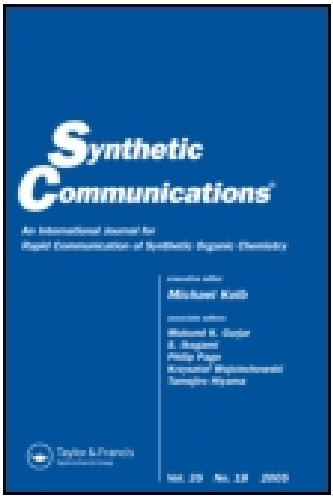

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Preparation of Ethyl (*R*)-3-hydroxy-4-chlorobutyrate by Selective Reduction of (*R*)-4-(Trichloromethyl)-oxetan-2-one: Key Intermediate to (*R*)-Carnitine and (*R*)-4-Amino-3-hydroxybutyric Acid

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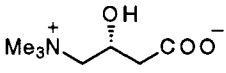
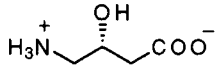
Abstract: Selective reduction of (*R*)-4-(trichloromethyl)-oxetan-2-one in ethanol by catalytic hydrogenation on Pd-C in the presence of KOAc gave directly ethyl (*R*)-3-hydroxy-4-chlorobutyrate, which can be used as a key intermediate for the synthesis of some biologically active γ-amino-β-hydroxy amino acids, (*R*)-carnitine and γ-amino-β-hydroxy amino acid ((*R*)-GABOB).

The ready availability of (*R*)-4-(trichloromethyl)-oxetan-2-one **1** via enantioselective [2+2]-cycloaddition of chloral and ketene in the presence of catalytic amounts of quinidine[1a-b] or polymer-bound quinidine[1c] initiated a search for selective and efficient conversion routes of **1** into ethyl (*R*)-3-hydroxy-4-

chlorobutyrate, which can be used as a key intermediate for the synthesis of some biologically active γ-amino-β-hydroxy amino acids, (*R*)-carnitine (vitamin B_T)[2] and γ-amino-β-hydroxy amino acid (*R*)-GABOB.[3]

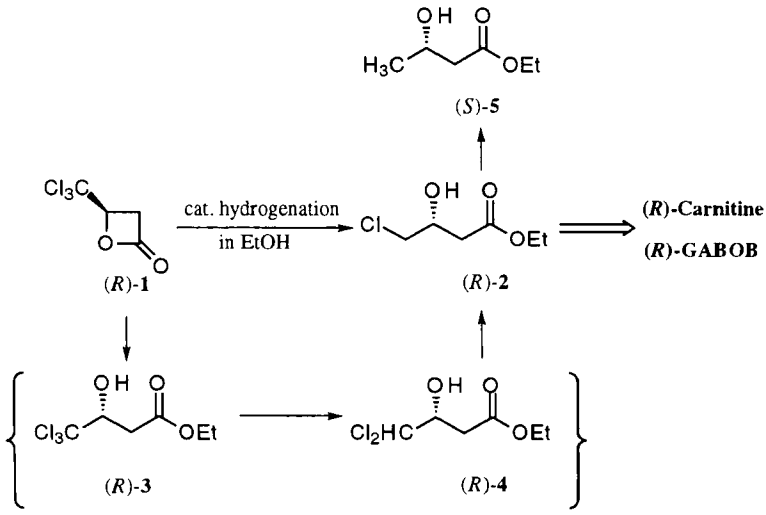


(*R*)-Carnitine



(*R*)-GABOB

Recently, we reported[4] a new method for the preparation of (*R*)-carnitine and (*R*)-GABOB from (*R*)-4-(trichloromethyl)oxetan-2-one [(*R*)-**1**], in which the key intermediate, ethyl (*R*)-3-hydroxy-4-chlorobutyrate [(*R*)-**2**], was prepared by ethanolysis of oxetanone **1** followed by selective bis-dechlorination of the resulting ethyl (*R*)-3-hydroxy-4,4,4-trichlorobutyrate [(*R*)-**3**] using tri-*n*-butyltin hydride. However, the use of tin compounds as reducing agents could be provide a limitation for the large-scale synthesis. To find more convenient and economical reduction conditions, the catalytic hydrogenation of **1** was carefully examined under various conditions and here we wish to report the results.



The reductions were carried out in ethanol solvent under hydrogen atmosphere using catalysts such as Pd-C, PtO_2 and Rany-Ni in the presence of base at 25 °C and 1 atm. As shown in table 1, the selectivities were largely dependent on the catalyst and base. The hydrogenation of **1** on the Pd-C in the presence of NEt_3 gave only dichloromethyl compound **4** as a major product (entry 1-2). However, when the base was changed to KOAc, the chloromethyl compound **2** was formed in high yield (entry 4). The reaction proceeded stepwise: i.e. when the reaction was carried out for 20 hr, only dichloromethyl compound **4** was formed selectively (entry 3). This compound **4** was then converted to chloromethyl compound **2** as prolonged the reaction time to 80 hr (entry 4). Moreover, the activity of the catalyst seems to be not dependent upon the quantity of the base (compare entry 4 and 5). The catalytic hydrogenation was also examined using other metals such as PtO_2 and Raney-Ni in the presence of KOAc base. In contrast, the PtO_2 catalyst afforded only dichloromethyl compound **4** quantitatively even the reaction was carried out for 80 hr (entry 6 and 7). The hydrogenation of **1** on Raney-Ni gave also the monodechlorinated compound **4** as a major product along with bisdechlorinated compound **2** (entry 8 and 9). Moreover, specific rotations and ^1H NMR analysis of the (*R*)-MTPA esters of chloroalcohol (*R*)-**2** revealed no racemization under reduction conditions. Thus, the chloroalcohol (*R*)-**2** can be converted to (*R*)-carnitine and (*R*)-GABOB using known methods.[2,3]

The observed results provide the following conclusion : the selectivities are largely dependent on the catalyst and base, thus, Pd-C/KOAc system afforded bisdechlorinated product (*R*)-**2** selectively. However, hydrogenation of **1** under PtO_2/KOAc and Rany-Ni/KOAc conditions produced monodechlorinated compound **4** in high yields.

Table 1. Catalytic reduction of (*R*)-**1**

Entry	conditions (in EtOH)		Product ratio[b] (%)			
	cat / base (time)	ratio ((*R*)-**1**: C: B)[a]	(*R*)-**2**	(*R*)-**3**	(*R*)-**4**	(*R*)-**5**
1	Pd-C/ NEt_3 (20 h)	1: 1: 4	-	-	100	-
2	Pd-C/ NEt_3 (80 h)	1: 1: 4	14	-	86	-
3	Pd-C/ KOAc (20 h)	1: 1: 3	-	-	100	-
4	Pd-C/ KOAc (80 h)	1: 1: 3	88	-	-	12
5	Pd-C/ KOAc (80 h)	1: 1: 10	87	-	6	7
6	PtO_2/ KOAc (20 h)	1: 1: 3	-	-	100	-
7	PtO_2/ KOAc (80 h)	1: 1: 3	-	-	100	-
8	Raney-Ni/ KOAc (20 h)	1: 1: 3	13	-	87	-
9	Raney-Ni/ KOAc (80 h)	1: 1: 3	22	-	74	-

[a] Weight proportions of (*R*)-**1**, catalysts (C) and added base (B).

[b] Determined by GC.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded with a Gemini 300 (300 MHz) varian spectrometer using TMS as an internal standard. Optical rotations were measured on a AUTOPOL III Rudolph Research Polarimeter. The advance of all reactions were monitored by GC. GC analyses were performed on a Varian 3300 Gas Chromatograph with FID using 30 m x 0.3 mm capillary column packed with DB-1701. (*R*)-4-(Trichloromethyl)-oxetan-2-one [(*R*)-**1**] was synthesized by known method.[1]

1. **Preparation of ethyl (*R*)-3-hydroxy-4-chlorobutyrate** [(*R*)-**2**]: A mixture of (*R*)-**1** (1 g, 15.8 mmol), 10% Pd-C (1 g) and KOAc (3 g, 91.7 mmol) in EtOH (30 mL) was stirred in a standard hydrogenation apparatus at 25 °C and atmospheric

pressure of hydrogen for 80 hours. After removal of the catalyst by filtration, EtOH was removed in vacuo. Ethyl acetate was added to the residue and washed with brine, dried over magnesium sulfate and concentrated in vacuo to afford 2.7 g of the crude product (*R*)-**2** (89 % purity based on GC-analysis), which was purified by bulb-to-bulb distillation to give 2.32 g (88.0 %, >99 % purity based on GC-analysis) (*R*)-**2** : bp 57 °C/0.5 mmHg; $[\alpha]_D^{23}$ +22.3 (*c* 4.12, $CHCl_3$).

2. **Preparation of ethyl (*R*)-3-hydroxy-4,4'-dichlorobutyrate** [(*R*)-**4**]: A mixture of (*R*)-**2** (3 g, 15.8 mmol), 10% Pd-C (3 g) and NEt_3 (12 g, 118.6 mmol) in EtOH (90 mL) was stirred in a standard hydrogenation apparatus at 25 °C and atmospheric pressure of hydrogen for 80 hours. After removal of the catalyst by filtration, EtOH was removed in vacuo. Ethyl acetate was added to the residue and washed with brine, dried over magnesium sulfate and concentrated in vacuo to afford 2.9 g (91.5 %, >99 % purity based on GC-analysis) of (*R*)-**4**: bp 75 °C/0.5 mmHg; $[\alpha]_D^{23}$ +27.0 (*c* 3.65, $CHCl_3$).

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