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New Method for the Preparation of (*R*)-Carnitine

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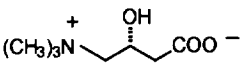
Abstract: A new method for the preparation of (*R*)-carnitine (**1**) has been developed from enantiomerically pure (*R*)-4-(trichloromethyl)-oxetan-2-one [(*R*)-**2**] which was easily obtained from the [2+2]-cycloaddition of ketene and chloral in the presence of catalytic amounts of poly(acryloyl quinidine). The key intermediate, ethyl (*R*)-3-hydroxy-4-chlorobutyrate [(*R*)-**5**], was prepared by ethanolysis of (*R*)-**2** followed by selective bis-dechlorination of ethyl (*R*)-3-hydroxy-4,4,4-trichlorobutyrate [(*R*)-**3**].

(*R*)-Carnitine (vitamin B_T) plays an essential role for the metabolism of long-chain fatty acids by regulating their transportation through mitochondrial membranes.[1] (*R*)-Carnitine has also been applied in therapy as a stimulator of fatty acid degradation and in the treatment of heart disease and other disorders.[2] Because of the competitive inhibitor property of (*S*)-carnitine to (*R*)-carnitine acyltransferase,[3] enantiomerically pure (*R*)-carnitine has received a great deal of interest from synthetic and industrial chemists. A wide variety of methods have been reported for the synthesis of (*R*)-carnitine employing the resolution of intermediates,[4] biological processes,[5] asymmetric synthesis from chiral pool materials,[6] and catalytic asymmetric synthesis.[7]



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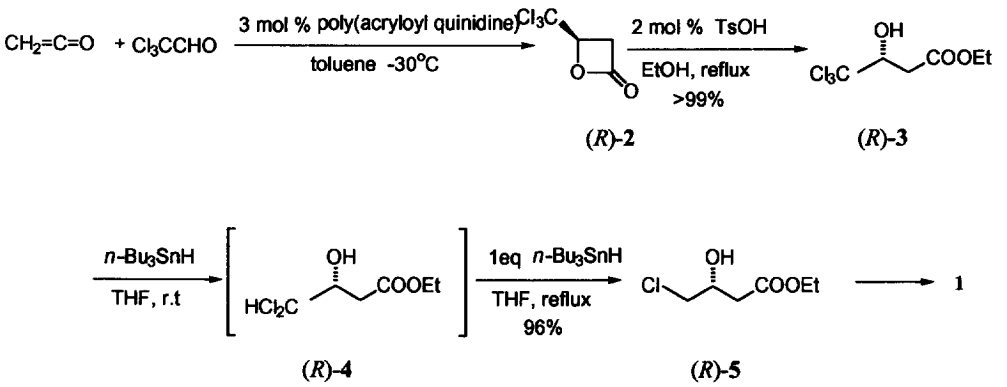
We report here a new method for the preparation of (*R*)-carnitine as shown in scheme 1. The starting material, (*R*)-4-(trichloromethyl)oxetan-2-one [(*R*)-**2**], can be easily prepared by enantioselective [2+2]-cycloaddition of chloral and ketene in the presence of catalytic amounts of quinidine[8a-b] or polymer-bound quinidine[8c] with nearly quantitative chemical and optical yields. Enantiomerically pure (*R*)-**2** was easily obtained by simple recrystallization from methylcyclohexane.[8a] Recently, (*R*)-**2** has been used for the production of (*S*)-malic acid in commercial scale by Lonza.[9] However, to our best knowledge, the oxetanone (*R*)-**2** has not been used for the preparation of (*R*)-carnitine. Thus, we report an efficient synthetic route to (*R*)-carnitine using (*R*)-**2** as a chiral synthon. Ethanolysis of (*R*)-**2** in the presence of catalytic amounts of *p*-toluenesulfonic acid afforded ethyl (*R*)-3-hydroxy-4,4,4-trichlorobutyrate (*R*)-**3**[10] in nearly quantitative yield without any difficulty. In order to obtain the key intermediate, ethyl (*R*)-3-hydroxy-4-chlorobutyrate [(*R*)-**5**], from (*R*)-**3**, a mild method for the selective dechlorination was

required. Since it has been known that tri-*n*-butyltin hydride shows substantial selectivity toward polyhalogenated compounds,[11] we carefully examined this reagent for the bis-dechlorination of (*R*)-**3**. It was found the dechlorination of (*R*)-**3** with tri-*n*-butyltin hydride was largely dependent on the temperature. When the (*R*)-**3** was treated with tri-*n*-butyltin hydride in THF under reflux for 28 hrs, the desired ethyl (*R*)-3-hydroxy-4-chlorobutyrate [(*R*)-**5**] (e.e.> 99%; $[\alpha]_D^{23}$ +22.4 (*c* 4.57, $CHCl_3$); lit.:[7a] $[\alpha]_D^{21}$ +20.9 (*c* 7.71, $CHCl_3$)) was obtained in 96 % yield. However, when the same reaction was carried out at room temperature, only mono dechlorination occurred within 1 hr to give dichloride (*R*)-**4** ($[\alpha]_D^{23}$ +26.8 (*c* 3.79, $CHCl_3$)) in 89 % yield. The (*R*)-**4** was further reduced to (*R*)-**5** at elevated temperature in the presence of equivalent amount of tri-*n*-butyltin hydride. In practice, the tri-*n*-butyltin hydride was generated in situ using tri-*n*-butyltin chloride and sodium borohydride or sodium cyanoborohydride in ethanol. The dechlorination was conducted by addition of the (*R*)-**3** to tri-*n*-butyltin hydride generated in situ in the presence of AIBN as an initiator to give (*R*)-**5** in 90% yield. Specific rotations and ^1H NMR analysis of the (*R*)-MTPA esters of (*R*)-**4** and (*R*)-**5** revealed no racemization under any dechlorination reaction conditions and there was no sign of overreduction to ethyl (*S*)-3-hydroxybutyrate [(*S*)-**6**], while the dechlorination of (*R*)-**3** over Pd-C provided only the totally reduced product (*S*)-**6**. The key intermediate (*R*)-**5** and tri-*n*-butyltin chloride were easily separated by simple extraction. Thus, after completion of bis-dechlorination, the solvent was removed in vacuo and the residue was dissolved in acetonitrile. Tri-*n*-butyltin chloride was separated by extraction with hexane and can reuse for the further reactions. Evaporation of the acetonitrile provided (*R*)-**5**.

The chloroalcohol (*R*)-**5** can be easily converted to (*R*)-carnitine (**1**) using known procedures.[5b,12] Enantiomerically pure (*R*)-**5** can also serve as an important key intermediate for the synyhesis of 4-amino-3-hydroxybutyric acid (GABOB)[6a-c,13] used as an antiepileptic and hypotensive agent.



Scheme 1

In conclusion, the present method, using the bis-dechlorination of (*R*)-**3** as the key step, provides quick access to the biologically active γ-amino-β-hydroxy amino acids, (*R*)-carnitine and (*R*)-GABOB. Especially, compared to other methods, the configuration of the product was controlled very easily in the first step which could be an advantage of this route. Furthermore, all intermediates and products can be easily purified by simple recrystallization or distillation which makes scale-up feasible.

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. Melting points were determined on a Thomas Hoover capillary melting point apparatus. (*R*)-4-(Trichloromethyl)-oxetan-2-one [(*R*)-**2**] was synthesized by our method.[8c)]

1. **Preparation of ethyl (*R*)-3-hydroxy-4,4,4-trichlorobutyrate [(*R*)-3]:** The solution of (*R*)-**2** (25 g, 132 mmol) and *p*-TsOH (0.5 g, 2.6 mmol) in 100 ml EtOH was refluxed for 25 hrs. After completion of the ethanolysis, EtOH was removed in vacuo. Ethyl acetate was added to the residue and washed with brine (3 x 100 ml), dried over magnesium sulfate and concentrated in vacuo to afford 30.9 g (99.6 %; >99 % purity based on GC-analysis) of (*R*)-**3**: bp 87 °C/0.5 mmHg; $[\alpha]_D^{23}$ +26.9 (*c* 5.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, *J*=7.1Hz, 3H), 2.76 (dd, J_{gem}=16.1Hz, J_{vic}=9.4Hz, 1H), 3.07 (dd, J_{gem}=16.1Hz, J_{vic}=2.2Hz, 1H), 4.07 (d, *J*=5.2Hz, 1H), 4.20 (q, *J*=7.2Hz, 2H), 4.62 (sym.m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.06, 37.42, 61.45, 79.30, 102.40, 170.79; Anal Cacld: C, 30.60; H, 3.85. Found: C, 30.6; H, 3.78.

2. **Preparation of ethyl (*R*)-3-hydroxy-4,4-dichlorobutyrate [(*R*)-4]:** Tri-*n*-butyltin hydride (20.39 g, 70 mmol) was added to a solution of (*R*)-**3** (15.0 g, 63.7 mmol) in THF (100 ml). After stirring for 1 hr at room temperature, the solvent was evaporated under reduced pressure. The residue was dissolved in acetonitrile and washed with hexane. Evaporation of acetonitrile gave almost pure 11.2 g (89 %; 97 % purity based on GC-analysis) of (*R*)-**4**: bp 75 °C/0.5 mmHg; mp 31-32 °C; $[\alpha]_D^{23}$ +26.8 (*c* 3.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, *J*=7.0Hz, 3H), 2.73 (dd, J_{gem}=16.5Hz, J_{vic}=8.6Hz, 1H), 2.86 (dd, J_{gem}=16.5Hz, J_{vic}=3.7Hz, 1H), 3.86 (d, *J*=5.4Hz, 1H), 4.21 (q, *J*=7.1Hz, 2H), 4.42 (sym.m, 1H), 5.87 (d, *J*=4.0Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.06, 36.67, 61.22, 72.78, 74.92, 171.28; Anal Cacld: C, 35.84; H, 5.01. Found: C, 35.9; H, 5.10.

3. **Preparation of ethyl (*R*)-3-hydroxy-4-chlorobutyrate [(*R*)-5]:**

Method A: Tri-*n*-butyltin hydride (57.6 g, 198 mmol) was added to a solution of (*R*)-**3** (22.0 g, 93.4 mmol) in THF (120 ml). The solution was refluxed under nitrogen atmosphere for 28 hrs. After evaporation of the solvent, the residue was dissolved in acetonitrile and washed with hexane to extract tri-*n*-butyltin chloride. Evaporation of acetonitrile gave almost pure 15.0 g (96 %; >99 % purity based on GC-analysis) of (*R*)-**5**.

Method B: To tri-*n*-butyltin chloride (14.51 g, 44.6 mmol) in absolute ethanol (40 ml, degassed) was added sodium borohydride (1.69 g, 44.6 mmol) under N_2 at 0 °C. After stirring at 20 °C for 1 hr, AIBN (0.14 g, 0.85 mmol) and (*R*)-**3** (5.0 g, 21.2 mmol) were added successively and the solution was refluxed for 8 hrs. The reaction was then allowed to cool room temperature and filtered. After evaporation of the solvent, the residue was dissolved in acetonitrile and washed with hexane to extract tri-*n*-butyltin chloride. Evaporation of acetonitrile gave 3.1 g (90 %; >99 % purity based on GC-analysis) of (*R*)-**5**: bp 57 °C/0.5 mmHg; $[\alpha]_D^{23}$ +22.4 (*c* 4.57, $CHCl_3$); >99% ee by ^{1}H NMR analysis of the MTPA ester; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, *J*=7.2Hz, 3H), 2.61 (dd, J_{gem}=16.2Hz, J_{vic}=7.6Hz, 1H), 2.68 (dd, J_{gem}=16.1Hz, J_{vic}=4.6Hz, 1H), 3.52 (d, *J*=5.0Hz, 1H), 3.62 (d, *J*=6.0Hz, 2H), 4.19 (q, *J*=7.1Hz, 2H), 4.27 (sym.m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.08, 38.66, 48.19, 60.93, 67.98, 171.67; Anal Cacld: C, 43.25; H, 6.65. Found: C, 42.7; H, 6.70.

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