# Practical and efficient utilisation of (*R*)-3-chloro-1,2-propanediol in synthesis of *L*-carnitine

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As a by-product originating from Salen Co(III) catalysed hydrolytic kinetic resolution (HKR) of (±)-epichlorohydrin in the manufacturing procedure of *L*-Carnitine, (*R*)-3-chloro-1,2-propanediol was utilised as a starting chiral material to prepare via key nitrile intermediates and by a final hydrolysis *L*-Carnitine. The new synthetic approach demonstrated an efficient utilisation of the by-product.

**Keywords:** *L*-carnitine, (*R*)-3-chloro-1,2-propanediol, (±)-epichlorohydrin

*L*-Carnitine (Vitamine $B_T$) (**1**) is an essential bioactive compound in the transportation of fatty acids from cytosol into mitochondria for the generation of metabolic energy.[1] A need for *L*-carnitine led us to develop a practical and efficient synthesis. A number of synthetic methods including asymmetric catalytic synthesis,[2–8] optical resolution of enantiopure intermediates[9–20] and use of synthetic chiral units in synthesis[21–30] have been developed for the synthesis of *L*-carnitine. However the development of a new practical synthesis route to *L*-carnitine is still desirable.

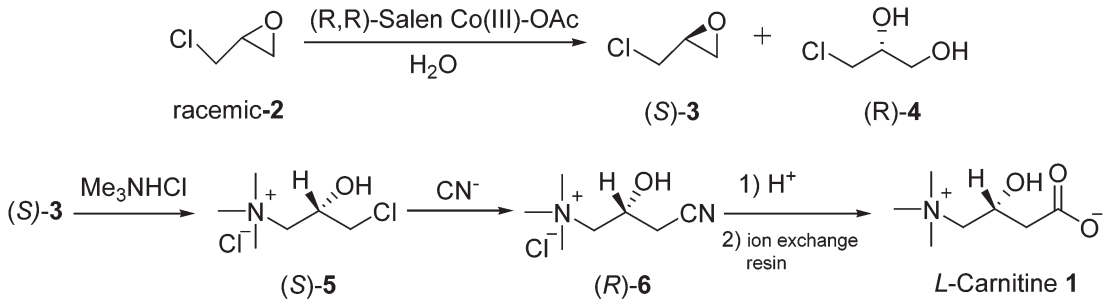
## Results and discussion

Jacobsen and coworkers developed a Chiral Salen Co(III) catalysed hydrolytic kinetic resolution (HKR) strategy to produce enantiopure terminal epoxides as important intermediates for the synthesis of numerous chiral chemicals and bioactive compounds[31–35]. Up to now, *L*-carnitine has been synthesised[36,37] by a multi-step reaction originating from a large scale by HKR of (±)-epichlorohydrin (**2**) to give the starting material (*S*)-epichlorohydrin (**3**) (Scheme 1).

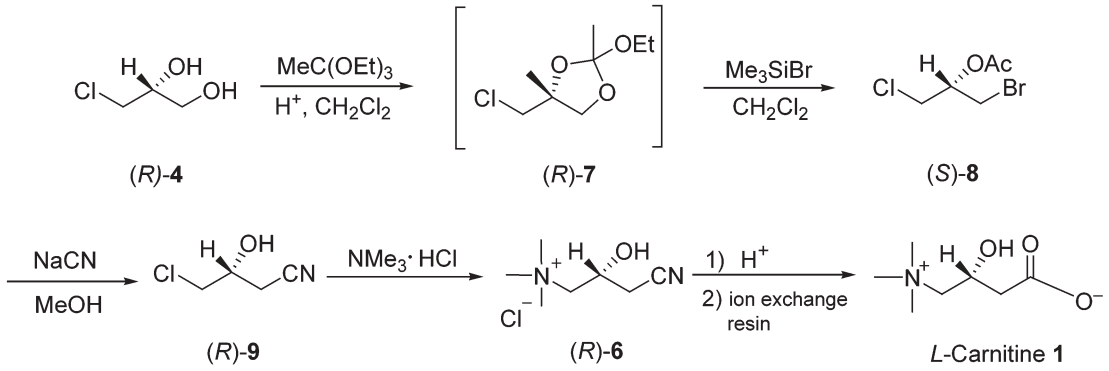
However, in the HKR process giving the enantiopure (*S*)-**3**, chirally enriched (*R*)-3-chloro-1,2-propanediol ((*R*)-**4**) was produced as a by-product in 50–52% yield, in an overall low atom-economy process. On the other hand, toxicological evaluation revealed that (*R*)-**4** was genotoxic in humans and has anti-fertility effects in male rats.[38,39] The discharge of (*R*)-**4** in waste water might cause serious environmental hazards. In the interest of green chemistry, a rational utilisation of (*R*)-**4** is required, and that prompted us to develop a practical method to convert (*R*)-**4** to *L*-carnitine.

We now report a new practical synthetic route of *L*-carnitine by the use of (*R*)-**4** as a chiral starting material. After four reaction steps from (*R*)-**4**, via the salt (**5**), the key nitrile intermediate (*R*)-**6** could be easily obtained. Then *L*-carnitine (**1**) was synthesised according to the known procedures[30,36,37] (the synthetic route is shown in Scheme 2).

The by-product (*R*)-**4** resolved by (*R,R*)-Salen Co (III) from the HKR of (±)-epichlorohydrin (**2**) was purified by distillation under reduced pressure[30] with a yield of 52% (purity 96.0% by gas chromatography, $[\alpha]^{20}_D$ = –5.6 (c=1.0, $H_2O$))




**Scheme 1** Preparation of *L*-carnitine from (*S*)-**3** by (*R,R*)-Salen Co(III) catalysed HKR.




**Scheme 2** Synthesis of *L*-carnitine from the by-product (*R*)-**4** of (*R,R*)-Salen Co(III) catalysed HKR.

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and then purified. (*R*)-**4** was used as starting material for the synthesis of *L*-carnitine.

A one-pot synthetic approach[40–43] was employed to convert (*R*)-**4** to (*S*)-**8.** In the presence of a catalytic amount of *p*-TsOH, (*R*)-**4** reacted with triethyl orthoacetate at room temperature which was followed by subsequent removal of the volatiles to give the crude cyclic orthoester (*R*)-**7**. Subsequent treatment of (*R*)-**7** with $Me_3SiBr$ at room temperature for 2h afforded acetoxy bromides (*S*)-**8** in a high yield of 90%.

We performed a selective nucleophilic substitution reaction of the $C_3$-bromide with NaCN at 30 °C for 6 h to afford chloronitrile (*R*)-**9** in 90% yield. (*R*)-**9** was treated with aqueous trimethylamine according to the reported method[30,36,37] to generate the nitrile (*R*)-**6**, which was further recrystallised from ethanol to obtain pure (*R*)-**6** in 75.6% yield. This key intermediate (*R*)-**6** was pure enough chemically and optically, and could be hydrolysed directly in the presence of concentrated hydrochloride acid to obtain *L*-carnitine as the hydrochloride salt. After purification by chromatography on an ion exchange resin[30,36,37], *L*-carnitine was obtained (m.p. 196–197 °C; $[\alpha]_D^{23}$ =-30.9 (c 1.0, $H_2O$)).

## Experimental

IR spectra were recorded on a BIO–RADFTS 165 spectrometer (KBr disk or liquid film). Mass spectra were recorded on a Finnegan 4021C MS-spectrometer and Biflex III MALDI-TOF MS-spectrometer. The polarimeter apparatus used to measure optical rotations was a WZZ-3. $^1$H NMR spectra were recorded on a 400 MHz Varian Gemini instrument. (*R*)-3-Chloro-1,2-propanediol was obtained from an authentic sample from HKR. The other solvents and reagents were purchased from the Beijing Chemical Company Ltd.

*(S)-l-Bromo-3-chloro-2-propyl acetate ((S)-***8***)*: Triethyl orthoacetate (25.27 g. 0.156 mol) was added to a solution of (*R*)-**4** (15.68 g. 0.142 mol) and a catalytic amount of *p*-TsOH in $CH_2Cl_2$ (70 mL) at room temperature. After 30 min, the solvent was evaporated and residual methanol was removed under vacuum. The residue was dissolved in $CH_2Cl_2$ (25 mL) and $Me_3SiBr$ (223.87 g, 0.156 mol) was added. After 2 h, the reaction stopped. Purification of the residue by vacuum distillation gave (*R*)-**4** as a colourless liquid (27.54 g, 90 %), $[\alpha]_D^{23}$ = −2.20° (c 3.24, $CHCl_3$), (lit.[30], b.p. 76°C /6.8 mmHg, 96 %, $[\alpha]_D^{23}$ = −2.20° (c 3.23, $CHC1_3$)). IR (KBr, film) ν: 3029, 2968, 1747, 1431, 1373, 1232, 1035, 931, 864, 759, 601cm$^{-1}$; $^1$H NMR (400M, $CDCl_3$) δ: 4.12–4.15 (t, *J* = 5.20 Hz, 1H, –C*H*(OAc)–), 3.76–3.73 (t, *J* = 4.80 Hz, 2H, –C$H_2$–), 3.59–3.56 (t, *J* = 4.80 Hz, 2H, –C$H_2$-), 2.11 (s, 3H, -C$H_3$-); MS (EI) *m/z*, (%): 43 (100), 165 (84), 217 ($M^+$, 38), 219 ($M^+$, 3).

*(R)-4-Chloro-3-hydroxybutyronitrile ((R)-***9***)*: Bromide (*R*)-**4** (20.36 g, 0.094 mol) was added to a stirred solution of KCN (7.44 g, 0.15 mol) in methanol (70 mL). After 6 h, the mixture was diluted with 2M HCl (40 mL), filtered and the solid residue washed thoroughly with methanol. After evaporation of the filtrate, the residue was distilled *in vacuo* to give (*R*)-**9** (10.12 g, 90 %) as a colourless oil. $[\alpha]_D^{23}$ = + 7.0 (c 3.0, $CHCl_3$), (lit.[30], b.p. 111–113 °C/6.8 mmHg, 70 %, $[\alpha]_D^{23}$ = + 6.9 (c 3.0, $CHCl_3$)); IR (KBr, film) ν: 3444, 3419, 2960, 2933, 2256, 1641, 1568, 1417, 1355, 1161, 945, 858cm$^{-1}$; $^1$H NMR (400M, $CDCl_3$) δ: 4.17–4.23 (m, 1H, –$CH_2$C*H*(OH)$CH_2$–), 3.64–3.66 (d, *J* = 5.32 Hz, 2H, –C$H_2$–), 3.22 (bs, 1H, O*H*), 2.71–2.74 (t, *J* = 6.43 Hz, 2H, –C$H_2$–); MS (EI) *m/z*, (%): 42 (100), 79 (91), 120 ($M^+$, 48), 122 ($M^+$ + 2H, 13).

*(R)-3-Cyano-2-hydroxypropyltrimethylammonium chloride (R)-***6***:* (*R*)-**9** (10.12 g, 0.084mol) was added to trimethylamine (11.23g, 0.12mol) and the reaction was reacted at 63 °C for 3 h. The solution was evaporated *in vacuo* to obtain a crude product, which was recrystallised and afforded (*R*)-**6** (12.14g, 75.6 %) as long needles. M.p. 247–249 °C (dec.), $[\alpha]_D^{25}$ = –26.7 (c 1.0, $H_2O$), (lit.[30], $[\alpha]_D^{22}$ = – 25.7 (c 2.1, $H_2O$), m.p. 247–249 °C, dec); IR (KBr, film) ν: 3276, 3244, 3018, 2977, 2921, 2244, 1479, 1409, 1367, 1307, 1232, 1135, 1089, 842, 626 cm$^{-1}$; $^1$H NMR (400M, $D_2O$) δ: 4.78–4.76 (t, *J* = 6.4 Hz, 1H, –C*H*(OH)), 3.68–3.58 (m, 2H, –C$H_2$–), 3.34 (s, 9H, –(C$H_3$)$_3$), 3.00–2.85 (m, 2H, –C$H_2$–); MS (ESI) *m/z*, (%): 143.2 ($M^+$, –$Cl^-$).

## Conclusion

We developed a new method for efficient conversion of the by-product of (*R*)-3-chloro-1,2-propanediol to *L*-carnitine through a four step synthesis. It should be noticed that *L*-carnitine and the intermediates in the above synthetic route are obtained in good yields and in high chemical and enantiomeric purity. The new synthetic route demonstrates a potential utilisation of the by-product (*R*)-**4** in the synthesis of bioactive compounds.

We thank the Science and Technology Innovation Foundation for the College Students of Beijing (no. B091000814); the National Natural Science Foundation of China (NSFC no. 20972015) and the Natural Science Foundation of Beijing (no. 2082016) for financial support.

*Received 4 March 2011; accepted 7 May 2011*
*Paper 1100607 doi: 10.3184/174751911X13090786031880*
*Published online: 11 July 2011*

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