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AN EFFICIENT SYNTHESIS OF (R)-CARNITINE

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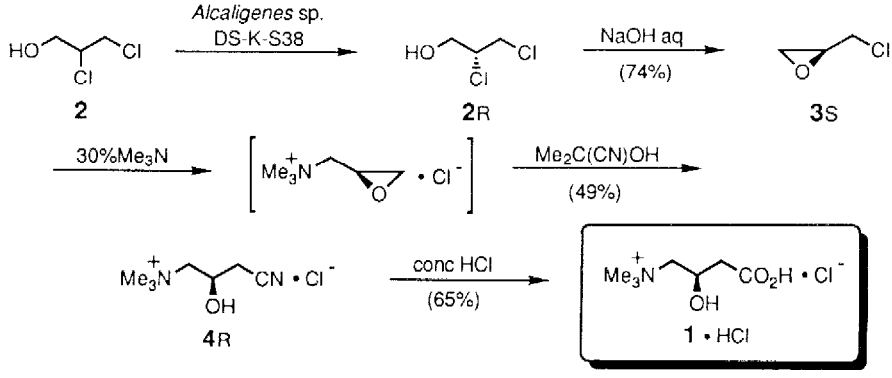
Summary: An efficient synthesis of (R)-carnitine hydrochloride is described. The starting material is obtained by microbial resolution of (RS)-2,3-dichloro-1-propanol.

(R)-Carnitine (vitamin B_T, **1**) is a very important and essential substance in fatty acid metabolism in mammals,[1] and therefore, it is also useful as a pharmaceutical for hemodialysis,[2] heart disease,[3] and myopathic deficiency.[4] A number of reports on the preparation of **1** have been described, including enantioselective reduction or hydrolysis by microorganisms,[5,6] resolution through diastereomer derivatives,[7] and asymmetric synthesis.[8] However, there are few practical preparations, and further efficient method is desired.

In this letter, we would like to report that highly optically active (R)-2,3-dichloro-1-propanol (**2R**) and (S)-epichlorohydrin (**3S**) were obtained by microbial resolution using a (S)-2,3-dichloro-1-propanol assimilating bacterium newly isolated from soil, and also a short-step synthesis of (R)-carnitine hydrochloride (**1**•HCl) from **3S** was established.



When Alcaligenes sp. DS-K-S38[9] was applied to **2**, its (S)-form was dehalogenated and assimilated via glycerol, and **2R** that resided in the culture broth was recovered (41%, bp 76 °C/20 mmHg, $[\alpha]_D^{22}$ +10.7 (c=1.36, CH_2Cl_2)). This was converted into **3S** by alkaline treatment (74 %, $[\alpha]_D^{22}$ + 34.5 (c=1.20, MeOH), 99.5 % ee[10,11]).

Since the previously reported procedure from 3S to (R)-carnitine nitrile chloride (4R) was a stepwise conversion,[12] a novel and efficient one pot procedure was developed. The enantiomer 3S was allowed to react with acetone cyanohydrin and 30 % trimethylamine aq. at 40°C for 2 hours whereby 4R was formed in 49 % yield, achieving two stepwise reactions in one pot. Its specific rotation ($[\alpha]_D^{22}$ -25.8 (c=2.10, H_2O)) was in good accord with the reported value (lit.,[13] $[\alpha]_D^{22}$ -26.1 (c=1.99, H_2O)). Finally, hydrolysis of the cyano group of 4R using conc. HCl under reflux for 4 hours gave (R)-carnitine hydrochloride (1•HCl, 65 %, $[\alpha]_D^{22}$ -22.4 (c=0.86, H_2O), lit.,[8] $[\alpha]_D^{20}$ -22 (c=0.86, H_2O)).

Thus, we developed an efficient and practical synthesis of (R)-carnitine hydrochloride (1•HCl) consisting of the novel microbial resolution and the one pot convenient conversion. (RS)-2,3-dichloro-1-propanol 2 has been economically produced, and therefore, it should be possible to use highly pure optically active (S)-epichlorohydrin 3S for easily accessible C3 chiral building block using our method.

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9. This strain was deposited with Fermentation Research Institute, Agency of Industrial Science and Technology, Japan (FERM BP-3101).
10. The analysis was carried out with a complexation gas chromatography. Analysis conditions: column, 0.25 mm X 30 m (coated with Co (II) Bis[(1R)-3-(heptafluorobutyryl) camphorate] in SE-54 as chiral stationary phase by dynamic method); sample 0.6 μL of 5 % (v/v) hexane solution, column temp., 40 °C; injection temp. and detector temp. (FID), 150 °C; carrier gas (nitrogen), 1 mL/min; split ratio, 1/50.
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