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A convenient synthesis of *R*-(−)-carnitine from *R*-(−)-epichlorohydrin

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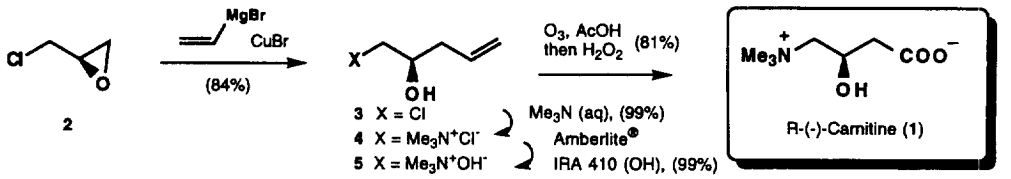
Abstract: A convenient four-step synthesis of *R*-(−)-carnitine (**1**) is described from the reaction of *R*-(−)-epichlorohydrin (**2**) with vinylmagnesium bromide followed by formation of the ammonium salt **4** with trimethylamine and finally ozonolysis of the corresponding ammonium hydroxide **5**. © 1997 Elsevier Science Ltd

R-(−)-Carnitine (**1**, vitamin B_T) plays an important role in human energy metabolism by facilitating the entry of long-chain fatty acids, the substrate for oxidation and subsequent energy production, into cellular mitochondria,[1] and has been used in therapy as a stimulator of fatty acid degradation. In addition, this compound has found significant medical application as a hypolipidemic agent in hemodialysis patients,[2] in the treatment of myocardial ischaemia,[3] seizure,[4] and other disorders. The (*S*)-enantiomer of **1** acts as competitive inhibitor of carnitine acetyltransferase[5] causing depletion of carnitine.

In recent years, there have been a number of reports and patents on the preparation of *R*-(−)-carnitine (**1**) involving asymmetric synthesis,[6] resolution through diastereomeric derivatives,[7] fermentation techniques,[8] or the use of chiral starting materials;[9] however, only a few of these procedures are of practical use. In this paper we report a convenient four-step synthesis of *R*-(−)-carnitine (**1**) from commercially available *R*-(−)-epichlorohydrin (**2**)[10] that proceeds in 67% overall yield.



Coupling of *R*-(−)-epichlorohydrin (**2**) with vinyl magnesium bromide in the presence of CuBr afforded the homoallylic alcohol **3** in 84% yield.[11] Reaction of compound **3** with an excess of aqueous trimethylamine at 40°C for 16 hours produced quantitatively the quaternary ammonium chloride **4**. Crude **4** was converted into the quaternary ammonium hydroxide **5** using an ion exchange resin (OH^- form). The key step of the synthesis, the oxidative removal of the terminal carbon atom with formation of carboxyl functionality, was carried out by ozonolysis of **5** in acetic acid at room temperature followed by treatment with an excess of hydrogen peroxide, then heating at 70°C for 24 hours. After evaporation of the solvents, the crude oil was purified by passing through an ion exchange resin to afford crude (single spot by tlc) *R*-(−)-carnitine (**1**)[12,13] in 98% yield. Upon crystallization from 2-propanol/acetone pure carnitine (**1**) was obtained in 81% yield. No epimerization or dehydration was observed during the preparation of intermediates **3**, **4**, and **5**, as well as the final product **1**.

In comparison with the other syntheses,[6–9] the present synthesis of carnitine (**1**) is efficient, and is characterized by experimental simplicity, especially the work-up and purification procedures, that makes it attractive for scale-up.

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References

1. (a) Bremer, J. *Physiol. Rev.* **1983**, *63*, 1420. (b) Borum, P. R. *Annu. Rev. Nutr.* **1983**, *3*, 233. (c) Combrisson, H. *Recl. Med. Vet.* **1983**, *159*, 693. (d) Engel, A. G. in *Carnitine Biosynthesis, Metabolism, and Function*, Frenkel, R. A.; McGarry, J. D. Eds. Academic Press: New York, 1980; pp 271–285.
2. Guarnieri, G.; Ranieri, F.; Toigo, G.; Vasile, A.; Cinam, M.; Rizzoli, V.; Morachiello, M.; Campanacci, L. *Am. J. Clin. Nutr.* **1980**, *33*, 1489.
3. Woster, P. M.; Murray, W. J. *J. Med. Chem.* **1986**, *29*, 865.
4. Cavazza, C. (Sigma Tau) Eur. Pat. Appl., EP 637449, **1995**; *Chem. Abstr.* **1995**, *122*: 205212.
5. (a) Vary, T. C.; Neely, J. R. *Am. J. Physiol.* **1982**, *242*, H585. (b) Bresser, R.; Brendel, K. *J. Biol. Chem.* **1966**, *241*, 4092.
6. (a) Kolb, H. C.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron: Asymmetry* **1993**, *4*, 133. (b) Kitamura, M.; Ohkuma, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555.
7. (a) Cavazza, C. (Sigma Tau), BE-B 877609, **1979**, *Chem. Abstr.* **1980**, *93*: 114973v. (b) Voeffray, R.; Pelberger, J.-C.; Tenud, L.; Gosteli, J. *Helv. Chim. Acta* **1987**, *70*, 2058.
8. (a) Kasai, N.; Sakaguchi, K. *Tetrahedron Lett.* **1992**, *33*, 1211. (b) Hashiguchi, S.; Kawada, A.; Natsugari, H. *Synthesis* **1992**, 403. (c) Lu, Y.; Miet, C.; Kunesh, N.; Poisson, J. *Tetrahedron: Asymmetry* **1990**, *1*, 707. (d) Bianchi, D.; Cabri, W.; Cesti, P.; Francalanci, F.; Ricci, M. *J. Org. Chem.* **1988**, *53*, 104. (e) Fuganti, C.; Grasselli, P.; Seneci, P. F.; Servi, S. *Tetrahedron Lett.* **1986**, *27*, 2061. (f) Gopalan, A. S.; Sih, C. J. *Tetrahedron Lett.* **1984**, *25*, 5235.
9. (a) Bols, M.; Lundt, I.; Pedersen, C. *Tetrahedron* **1992**, *48*, 319. (b) Takano, S.; Yanase, M.; Sekiguchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1987**, *28*, 1784. (c) Pellegata, R.; Dosi, I.; Villa, M.; Lesma, G.; Palmisano, G. *Tetrahedron* **1985**, *41*, 5607. (d) Bock, K.; Lundt, I.; Pedersen, C. *Acta Chem. Scand.* **1983**, *B 37*, 341. (e) Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304.
10. Bulk quantities of *R*-(−)-epichlorohydrin are available from Daiso Co. Ltd. (Japan).
11. De Camp Schuda, A.; Mazzocchi, P. H.; Fritz, G.; Morgan, T. *Synthesis* **1986**, 309.
12. *Experimental procedures.* (a) Synthesis of **3** was accomplished according to Ref. 11, by using *R*-(−)-epichlorohydrin (9.84 g, 0.11 mol), vinylmagnesium bromide (0.24 mol), and CuBr (3.26 g, 0.023 mol), which gave **3** (10.77 g, 84%), bp 90°C/30 mmHg, *ee* 98.9% by GC on permethylated γ-cyclodextrin, 25 m×0.32 mm, $[\alpha]_D^{25} = -7.0$ (c=0.47, CH_2Cl_2). ^{13}C NMR ($CDCl_3$): 38.7, 49.4, 70.7, 118.6, 133.3. (b) Synthesis of **4**. Compound **3** (10.77 g, 89.3 mmol) and Me_3N (60 ml of 25% solution in water) was stirred at 40°C for 24 hours. Then, the mixture was concentrated to dryness to yield a slightly yellow syrup, which solidified during drying under high vacuum (15.89 g, 99%), $[\alpha]_D^{25} = -30.0$ (c=1.0, H_2O). ^1H NMR (D_2O, 400 MHz): 2.33 (m, 2H), 3.23 (s, 9H), 3.28–3.36 (m, 2H), 4.36 (m, 1H), 5.22 (m, 2H), 5.86 (m, 1H), 4.81 (HDO ref.). ^{13}C NMR (D_2O): 42.5, 56.9, 68.1, 72.9, 122.1, 135.6. IR: 3416, 3285 (OH), 1645 (C=C). MS: 144 (M-Cl, 100%), 102 (6). HRMS for $C_8H_{18}NO$ (M-Cl) calcd 144.1388, observed 144.1390. (c) Synthesis of **5**. Compound **4** (15.89 g, 88.4 mmol) was dissolved in water (40 ml) and passed through Amberlite® IRA-410 ion exchange resin (350 g, OH form) eluting with water. The basic elutes containing the product were combined. The aqueous solution was evaporated *in vacuo* to give compound **5** (14.12 g, 99%) as a yellow oil, $[\alpha]_D^{25} = -25.0$ (c=1, H_2O). IR (nujol): 3279 (OH), 1643 (C=C). ^1H NMR (D_2O, 400 MHz): 2.32 (m, 2H), 3.21 (s, 9H), 3.35–3.45 (m, 2H), 4.32 (m, 1H), 5.21 (m, 2H), 5.85 (m, 1H), 4.86 (HDO, ref.). ^{13}C: 42.8, 56.9, 68.2, 73.1, 121.9, 135.8. MS: 144 (M-OH, 100%), 136 (24), 107 (12). HRMS: for $C_8H_{18}NO$ (M-OH) calcd 144.1388, observed 144.1391. (d) Synthesis of *R*-(−)-carnitine (**1**). A solution of compound **5** (14.12 g, 87.6 mmol) in AcOH (200 ml) was ozonized at rt for 1 h. Then, hydrogen peroxide (80 ml of 30% solution in water) was added and the reaction mixture was stirred at 70°C for 24 hours. The solvents were evaporated *in vacuo* and the residue was dissolved in water (40 ml) and passed through Amberlite® IRA-410 ion exchange resin (350 g, OH form) eluting with water. Elutes containing product were combined and

evaporated *in vacuo* to give carnitine (**1**) (13.8 g, 98%), $[\alpha]_D^{26} = -26.2$ (c=1.0, H_2O), which was crystallized from 2-propanol/acetone (1:1) to give **1** (10.0 g, 71%), $[\alpha]_D^{25} = -30.9$ (c=1.3, H_2O); lit[13] $[\alpha]_D^{25} = -31.3$ (c=10, H_2O); ^1H NMR (D_2O, 400 MHz): 2.44 (m, 2H), 3.23 (s, 9H), 3.41 (d, 2H), 4.57 (m, 1H), 4.81 (HDO, ref.). ^{13}C (D_2O): 45.8, 56.9, 66.9, 73.0, 180.9. After concentration of the mother liquors, a second crop of **1** (1.3 g, 10%), $[\alpha]_D^{25} = -30.5$ (c=1.2, H_2O), was obtained from 2-propane/acetone (1:1).

13. The optical rotation of carnitine (**1**) as function of its concentration and temperature has previously been reported; *cf.* Ref. 7b.

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