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A NEW, SHORT AND EFFICIENT SYNTHESIS OF BOTH ENANTIOMERS OF CARNITINE

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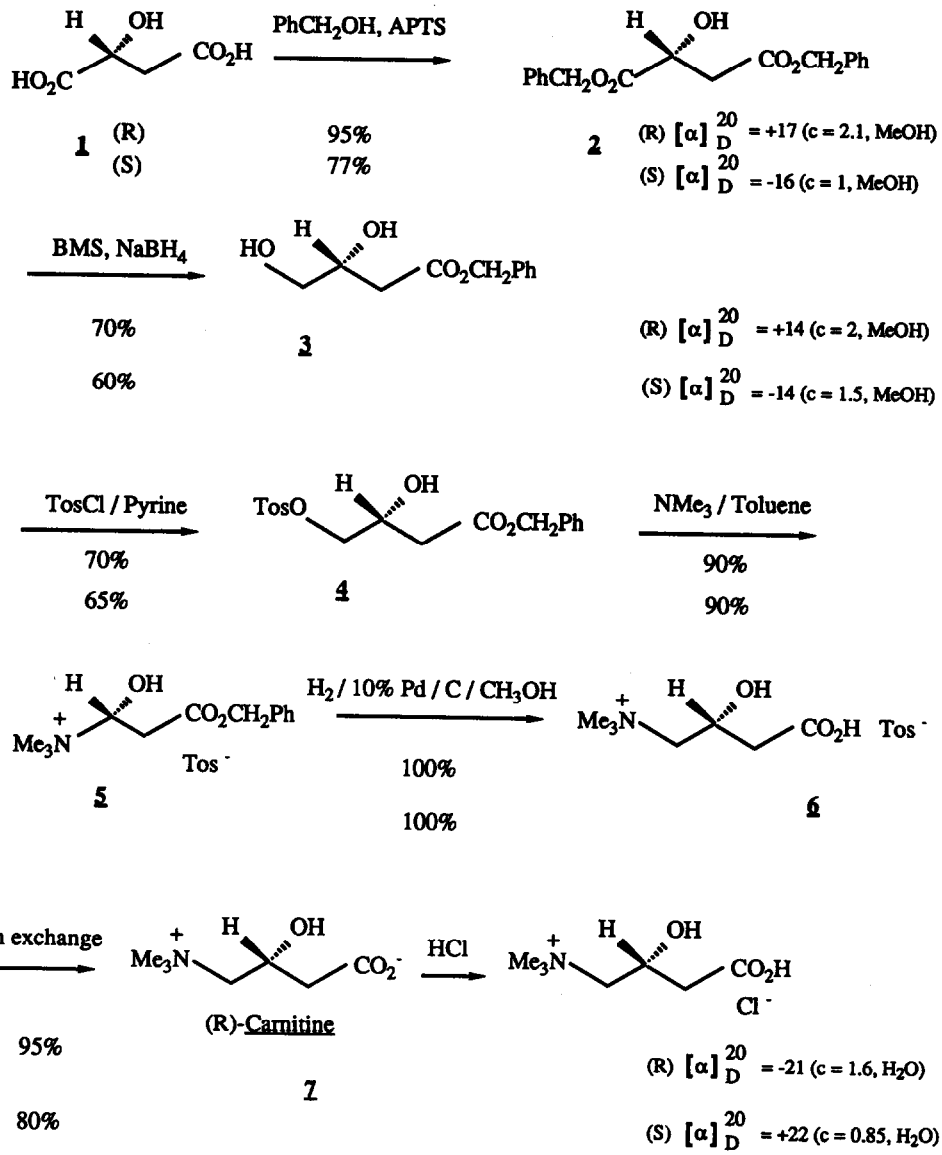
Summary : A short, efficient and enantioselective synthesis of both (R) and (S) enantiomers of carnitine is reported starting with (R) or (S) malic acid and involving a chemoselective reduction step.

(R)-Carnitine, a vitamin-like substance, plays an important role in converting stored body fat into energy. Its primary role is to transport large fat molecules into cellular compartiments where the fats can be converted into energy. In the absence of (R)-Carnitine, many fats cannot be "burned" and accumulate within the cell and the bloodstream as fats and triglycerides (1). Supplemental (R)-Carnitine has proved to be beneficial to heart patients (2) and its effectiveness in systemic and myopathic deficiencies is now well recognized (3). Moreover, this compound has been successfully used as a hypolipidemic agent in hemodialysis patients (4).

Over the past decade, numerous preparations of both enantiomers of carnitine appeared in the literature (5). Many of them are based on the resolution of the racemic product or some of its precursors (6). Recently, W.J. Brouillette described the resolution of (R)- and (S)-Carnitine via the chromatographic resolution of diastereoisomeric esters (7). Microorganisms have also been often utilized for the enantioselective hydrolysis of racemic esters (8) as well as for the formation of the chiral center of (R)-Carnitine (9).

It is surprising to see how few enantioselective syntheses of this simple but very important molecule have been developed. In some of the procedures available, the chiral center is introduced by means of an enantioselective reaction (10) but more often the synthesis utilizes, as starting material, a molecule of the chiral pool (11). This last approach usually affords a single enantiomer.

In this letter, we describe a 6 step enantioselective synthesis of either (R)- or (S)-Carnitine starting with malic acid **1** which is commercially available in both (R) and (S) configurations. If the (S) form is rather inexpensive, the (R) enantiomer appears to be quite expensive but is easily available either from aspartic acid (12) or from (R,R)-dimethyltartrate (13). The key step of this synthetic scheme is based on the chemoselective reduction of the α-hydroxyester group of a diester derivative of malic acid, according to Moriwake's procedure (14). Our early studies utilized the dimethylester as substrate of this


PhCH2OH, APTS
95%
77%
(R) [α] D 20 = +17 (c = 2.1, MeOH)
(S) [α] D 20 = -16 (c = 1, MeOH)
BMS, NaBH4
70%
60%
(R) [α] D 20 = +14 (c = 2, MeOH)
(S) [α] D 20 = -14 (c = 1.5, MeOH)
TosCl / Pyrine
70%
65%
NMe3 / Toluene
90%
90%
H2 / 10% Pd / C / CH3OH
100%
100%
ion exchange
95%
80%
HCl
(R)-Carnitine
(R) [α] D 20 = -21 (c = 1.6, H2O)
(S) [α] D 20 = +22 (c = 0.85, H2O)

reduction. However, the penultimate step, i.e. the saponification of the remaining methylester group proved to be sluggish. No similar complications of this nature were expected when using the dibenzylester since the deprotection step is usually a clean reaction.

The synthesis of (R)-Carnitine was performed as follows : (R)-Malic acid (15) was diesterified by benzylalcohol in 95% yield following the procedure described for the racemic compound (15). The resulting diester **2** was then submitted to a chemoselective reduction by BMS, $NaBH_4$ (14) affording the diol **3** in 70% yield. Monotosylation of this diol led to compound **4** (70%) which, upon substitution by trimethylamine gave the carnitine derivative **5** (90%). Debenzylation with palladium on charcoal in methanol afforded, after an easy work-up, the expected compound **6** in quantitative yield. (R)-Carnitine was obtained as an inner salt by ion exchange chromatography. All the reactions described could be carried out on a large scale and the (S)-isomer of carnitine is accessible by the same procedure but by using (S)-malic acid as starting material.

We have thus developed an efficient synthesis of (R)- and (S)-carnitine, the optical purity of which [assessed by the rotational measurements of their respective hydrochloride salts **7** (17)] depends only on the enantiomeric purity of the starting malic acids (6a, 12).

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