Pergamon

Tetrahedron Letters 40 (1999) 1791–1792

TETRAHEDRON LETTERS

Synthesis of Phosphocarnitine[1, 2]

Elżbieta Tadeusiak, Bożena Krawiecka,* and Jan Michalski *

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90-363 Łódź, Sienkiewicza 112, Poland

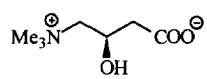
Received 30 October 1998; revised 22 December 1998; accepted 23 December 1998

Abstract: Stereoselective synthesis of phosphocarnitine has been achieved for the first time starting from R(-)-epichlorohydrin.

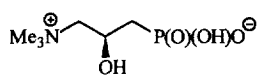
Keywords: Aminoacids and derivatives, Phosphonic acids and derivatives.

R(-)-Carnitine, γ-trimethylammonio-β-hydroxybutanoate **1** [1] is an essential cofactor for the transport of acyl groups across the mitochondrial membrane and is therefore involved primarily in fatty acid metabolism. (R)-Carnitine is ubiquitous in mammalian tissues; it is an endogenous metabolite that is also obtained by dietary uptake and is present in biological materials as free carnitine and as acylcarnitines; the latter are metabolic products of reactions that utilize acyl CoA, catalyzed by carnitine acyltransferases [1]. It is well known [2] that phosphonic analogues of naturally occuring aminoacids are produced by certain organisms and are of great interest in bioorganic and medicinal chemistry.

In spite of wide interest in the chemistry of carnitines and their derivatives, the phosphonic analogue of carnitine, phosphocarnitine, γ-trimethylammonio-β-hydroxypropylphosphonate **2** has not been described.



1

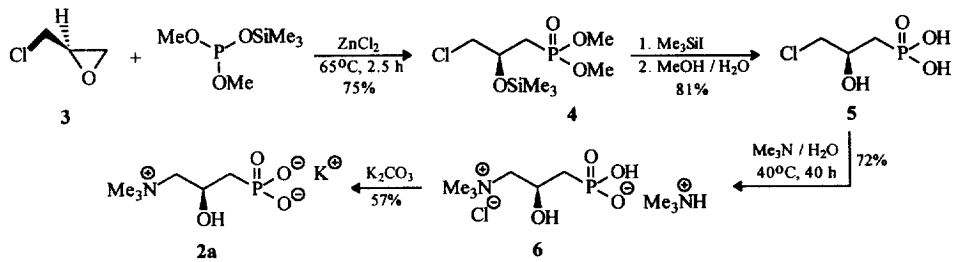


2

As a part of our studies on polyfunctional phosphorus acids we report herein the first synthesis of phosphocarnitine **2**. The starting material was the phosphonic ester **4** obtained from epichlorohydrin **3** and dimethyl (trimethylsilyl)phosphite [3].

[1] Dedicated to Professor A.Zamojski on the occasion of his 70th birthday.
[2] This work was presented at the XIV International Conference on Phosphorus Chemistry, Cincinnati, July 12-17, 1998.
* E-mail addresses: jmich@bilbo.cbmm.lodz.pl; bokraw@bilbo.cbmm.lodz.pl.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00010-6



The compound **4** underwent dealkylation leading to 3-chloro-2-hydroxypropylophosphonic acid **5**. The final step was the replacement of chloride by a trimethylammonium group by treating with a large excess of trimethylamine in aqueous medium at 40° for 40 h. The salt **6** [4] was treated with an equimolar amount of potassium carbonate to yield the potassium salt of racemic phosphocarnitine **2a**.

The racemic phosphocarnitine monopotassium salt **2a** crystallized as an undecahydrate and its structure was confirmed by elemental analysis and MS, ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectroscopy [5]. The total yield of **2a** was 33% based on the phosphonate **4** and was not optimized.

Starting from R (-) epichlorohydrin [$[\alpha]_D^{20}$ -44.5 neat] optically active phosphocarnitine potassium salt **2a** [$[\alpha]_D^{20}$ -11.7 (c 0.75 in MeOH/H_2O, 1:1] was obtained. In the above transformation no bond formation or bond breaking is expected at the chiral center, therefore the R configuration is anticipated. Further synthetic and stereochemical studies on phosphocarnitine and related compounds are in progress.

Acknowledgement

The work has been supported by the Polish State Committee for Scientific Research grant Nr 3T09A 038 09.

References

1. Fritz I.B. in *Current Concepts in Carnitine Research* (Ed.: Karter A.L.), CRC, **1992**, pp. 107-119; Di Donato S., Garavaglia B., Rimoldi M., Carrara F. in *L-Carnitine and its Role in Medicine: from Function to Therapy* (Eds.: Ferrari R., DiMauro S., Sherwood G.), Academic Press, **1992**, pp. 5-19 and 69-74.
2. Kafarski P., Lejczak B., *Phosphorus Sulfur Silicon Relat. Elem.*, **1991**, 63, 193; Engel R. in *Handbook of Organophosphorus Chemistry* (Ed. Engel R.) Marcel Dekker, New York, **1992**, Chapter 11.
3. Azuhata J., Okamoto Y., *Synthesis* **1983**, 916.
4. **6** δ_P (81 MHz, D_2O): 19.26 ppm; δ_H (200 MHz, D_2O): 1.77-1.82 [m, 1H, C<u>H</u>$_2$-P(O)], 1.86-1.91 [m, 1H, CH$_2$-P(O)], 2.8 (s, 9H, HN-C<u>H</u>$_3$), 3.14 (s, 9H, N-C<u>H</u>$_3$), 3.25-3.56 (m, 2H, C<u>H</u>$_2$-N), 4.41-4.60 (m, 1H, C<u>H</u>OH). MS FAB (M+1) 293.5.
5. **2a** δ_P (81 MHz, D_2O): 16.90 ppm; δ_H (200 MHz, D_2O): 1.59 [d, 1H $^{2}J_{H\text{-}P}$ 6.7 Hz, C<u>H</u>$_2$P(O)], 1.67 [d, 1H $^{2}J_{H\text{-}P}$ 6.7 Hz, C<u>H</u>$_2$-P(O)], 3.15 (s, 9H, N-C<u>H</u>$_3$); 3.21 - 3.58 (m, 2H, C<u>H</u>$_2$-N), 4.60 - 4.63 [m, 1H, C<u>H</u>(OH)].
δ_C (50 MHz, D_2O): 38.80 and 36.33 [P(O)-<u>C</u>H$_2$], 56.94 (N-<u>C</u>H$_2$), 66.37 (N-<u>C</u>H$_3$), 73.97 [<u>C</u>H(OH)]; MS FAB (M+1) 236.3, $C_6H_{15}O_4NPK$. 11 H_2O (433.434) requires: C, 16.62%; N, 3.22%; P, 7.14%. Found: C, 16.22%; N, 3.10%, P, 7.01%.