Single Step Conversion of Chiral Carnitine and Derivatives into (*S*)- and (*R*)-β-Substituted-γ-Butyrolactones

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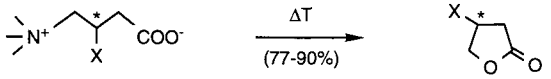
Abstract: This paper describes an efficient single step transformation of chiral carnitine and carnitine derivatives into stereoisomerically pure (*S*)- and (*R*)-β-substituted-γ-butyrolactones, obtained by intramolecular nucleophilic displacement. (*S*)- Or (*R*)-carnitine and (*R*)-aminocarnitine inner salts give β-hydroxy-γ-butyrolactone and β-amino-γ-butyrolactone respectively (82% and 77%) with the same configuration as the starting material. (*R*)-Acetylaminocarnitine inner salt gives (*R*)-β-acetylamino-γ-butyrolactone (90%), while (*R*)-acetylcarnitine gives 2(5*H*)-furanone under the same reaction conditions (77%, *via* cyclization and subsequent elimination reaction). (*R*)-N-Benzyloxycarnitineamide gives a mixture of pyrrolidinone (11%) and furanoyl imidate (50%) derivatives. The direct transformation of waste (*S*)-carnitine into the valuable (*S*)-β-hydroxy-γ-butyrolactone or (after acetylation) into the precious 2(5*H*)-furanone is of particular interest.

(*S*)-β-Hydroxy-γ-butyrolactone **1** has been reported to be an endogenous factor able to modulate food intake by conveying signals of satiety to neurons in the hypothalamus.[1] It is also a useful synthon for the preparation of a variety of chiral compounds like the nootropic drug (*S*)-oxiracetam,[2a] precursors of HMG reductase inhibitors,[2b] and natural products like multistriatine;[2c] it is also a constituent of the Puerto Rican *Lingbya majuscula*[2d] and *Rosa laevigata*,[2e] and it is described as a substrate for alkylation and aldol reactions leading to *trans*-2-alkyl-3-hydroxy lactones.[2f] In the (*R*)-form it is a useful intermediate for the synthesis of β-lactam antibiotics[3a-c] and it has also been employed in the syntheses of (-)-Aplysistatin[3d] and (*S*)-(+)-Ipsdienol.[3e] Syntheses of **1** have been reported which make use of D-isoascorbic acid as the starting material (7 steps, 40% yield; L-ascorbic acid gives **3** in 7 steps, 29% yield),[4a] of dimethyl (*S*)-(-)-malate (2 steps, 80% yield ; a reduction step with borane-methyl sulfide complex and $NaBH_4$ is involved)[4b] or of D-erythrono-1,4-lactone (direct α-deoxygenation with SmI_2, 45% yield);[4c] less common starting materials and more complicated reaction strategies have also been employed.[4d-f]

In this paper we report a simple one-step synthesis of chiral β-hydroxy-γ-butyrolactones **1** and **3** starting from easily available carnitine inner salts (γ-trimethylammonium-β-hydroxybutyrate) of the same configuration, *via* intramolecular nucleophilic displacement of the γ-trimethylammonium ion by the carboxylate ion under thermal conditions.[5] It is worth mentioning that (*R*)-carnitine **4** is a natural product, available in bulk quantities by industrial synthesis;[6] (*S*)-carnitine **2** is a competitive inhibitor of the (*R*)-isomer,[7] which is formed in equimolar amount with (*R*)-carnitine during its industrial production.[6b] Related reactions leading to differently β-substituted γ-butyrolactones, to 2(5*H*)-furanone and in one case to a β-substituted γ-butyrolactam, are also reported.



2 : X = OH (*S*)-form
4 : X = OH (*R*)-form
5 : X = NH_2 (*R*)-form
7 : X = NHAc (*R*)-form

1 : X = OH (*S*)-form
3 : X = OH (*R*)-form
6 : X = NH_2.HCl(*R*)-form
8 : X = NHAc (*R*)-form

SCHEME 1

The reactions with (*S*)-carnitine **2** and (*R*)-carnitine **4** (Scheme 1, Table 1) were simply performed by heating at 150 °C a solution of their inner salts in a high-boiling, aprotic dipolar solvent: DMF and DMSO (500 mL for 50 g) were used and the reaction times were 2h and 1h respectively. After evaporation of the solvent and purification by flash chromatography (SiO_2/EtOAc) the corresponding products **1** and **3**[8] were obtained as clear oils in 82% yield (the use of DMSO as the reaction medium made chromatography compulsory, due to the presence in the reaction mixture of unvolatile compounds, possibly arising from solvent degradation). In CH_3CN the reaction did not take place, because of the non-solubility of the starting material. When, under dilute conditions, a small amount of water was added, just sufficient to have a clear solution, a much longer period of time (two weeks) under vigorous reflux was necessary in order to completely convert the substrate. In all cases the

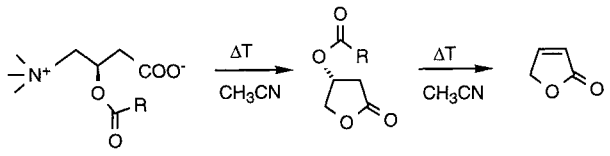
TABLE 1

starting material	product	solvent	temperature	time	purification	yield
2 or **4**	**1** or **3**	DMSO (500 mL for 50 g)	150 °C	1 h	flash chromatography SiO_2/EtOAc	82 %
5	**6**	DMSO (500 mL for 5 g)	150 °C	1.5 h	HPLC C_{18}/H_2O	77%
7	**8**	CH_3CN (50 mL for 0.5 g)	150 °C (bath temperature)	24 h	filtration	90%

stereogenic center was not involved during the reaction and the products were obtained with optical rotation values comparable with those reported in the literature (**1**: $[\alpha]_D^{20}$ = -88.2 (c = 0.8 in MeOH); Lit.[1]: $[\alpha]_D^{20}$ = -75.7 (c = 0.806 in MeOH); Lit.[4a]: $[\alpha]_D^{21}$ = -86.1 (c = 3.1, EtOH)).

The same cyclization reaction has been performed successfully (Scheme 1, Table 1) with enantiomerically pure (*R*)-aminocarnitine inner salt **5**,[9] in DMSO (500 mL for 5 g), to give the corresponding (*R*)-β-amino-γ-butyrolactone **6**,[10] isolated as hydrochloride in 77% yield after addition of stoichiometric HCl 1N and preparative HPLC separation (optical rotation consistent with the one reported in Lit.[10a], see purification and data for **6** in note 10). (*R*)-Acetylamminocarnitine inner salt **7**[11] reacted in CH_3CN (50 mL for 0.5 g), under vigorous reflux (bath temperature 150°C) for 24 h, to afford after filtration and solvent evaporation the corresponding (*R*)-β-acetylamino-γ-butyrolactone **8**[12] in 90% yield (as to its optical purity, we were not able to detect traces of its enantiomer either by ^{1}H NMR (chiral NMR shift reagents have been used) or by chiral phase HPLC).

With regard to other related substrates more complicated results were obtained. In the case of (*R*)-acetylcarnitine inner salt **9** (Scheme 2), the substrate was vigorously refluxed in CH_3CN for four hours : the ^{1}H NMR spectrum of the raw material revealed, besides the starting acetylcarnitine, a mixture of β-acetoxy-γ-butyrolactone **10** and 2(5*H*)-furanone **11**.[13] This latter was actually formed in 77% yield after longer reaction times (24 h). This was also the reaction fate when we treated (*R*)-pivaloylcarnitine **12**; probably, owing to the better ability of the pivaloyloxy moiety to behave as a leaving group, we were not able to detect the expected β-pivaloyloxy-γ-butyrolactone intermediate during the reaction course.



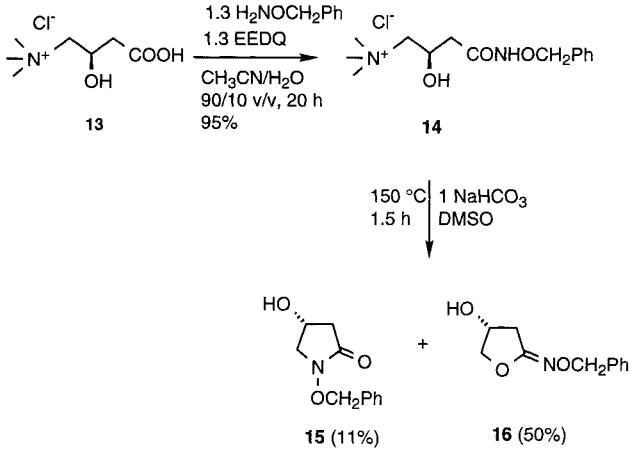
9 : R = CH_3
12 : R = $C(CH_3)_3$

10 : R = CH_3

11
(overall: 77%)

SCHEME 2

Concerning (*R*)-*N*-benzyloxycarnitineamide **14**,[14] obtained by reaction of (*R*)-carnitine hydrochloride **13** (4.8 g) with *O*-benzylhydroxylamine and EEDQ (Scheme 3) in CH_3CN/H_2O (90/10 v/v, 140 mL), heating in DMSO (350 mL for 3.5 g) at 150 °C for 1.5 h, in the presence of 1 eq. of $NaHCO_3$, afforded after flash chromatography (SiO_2/Hexane-EtOAc 2:8) two isomers in 11% and 50% yield (CAUTION! Heating DMSO, especially when halogens are present, is reported to involve risk of explosion!). The minor isomer corresponds to the expected (*R*)-N-benzyloxy-4-hydroxy-2-pyrrolidinone **15**,[15] while to the most abundant compound the structure **16**[16] was attributed. The structure assignments were made on the grounds of their ^{1}H NMR spectra. In particular the C-5 hydrogens appear as a multiplet centered at δ 4.30 for **16**, and as two double doublets centered at δ 3.55 and 3.25 for **15**. Any attempt to change the ratio of the two isomers in favor of **15** by using different reaction conditions failed. We can tentatively assume that the benzyloxy group, introduced in order to have an activated amidic hydrogen, due to its steric hindrance may interfere with the bulky trimethylammonium moiety when the nitrogen atom is the nucleophile, thus favoring the formation of a less hindered transition state leading to **16**. It is worth noting that possible oxidation products[17] were not revealed in the reaction mixture.



SCHEME 3

In conclusion, we consider these intramolecular nucleophilic substitution reactions, operated by the carboxylate anion on the γ-trimethylammonium ion under thermal conditions, a useful straightforward way to obtain chiral γ-butyrolactones substituted at C-3, starting from carnitine or carnitine analogues of the same configuration. The direct transformation of a waste product, *i.e.* (*S*)-carnitine inner salt **2**, into the valuable (*S*)-β-hydroxy-γ-butyrolactone **1**, or, after acetylation, into the costly 2(5*H*)-furanone **11**, is of particular interest especially from an industrial point of view.

References and Notes

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(8) Data for **3**: oily; TLC: eluant = EtOAc, R_f = 0.63; $[\alpha]_D^{20}$ = + 88,2 (*c* = 0.8 in MeOH); ^{1}NMR ($CDCl_3$) δ 4.62 (m, 1H), 4.40 (dd, ^2J = 10.5 Hz, ^3J = 4.2 Hz, 1H), 4.28 (dm, ^2J = 10.50 Hz, 1H), 3.50 (brs, 1H), 2.73 (dd, ^2J = 18.4 Hz, ^3J = 5.9 Hz, 1H), 2.45 (dm, 1H, ^2J = 18.4 Hz); Anal. Calcd. for $C_4H_6O_3$: C, 47.06; H, 5.92. Found C, 46.88; H, 5.83.

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Purification was performed by preparative reverse-phase HPLC (eluant = H_2O, flow rate = 15 mL/min, retention time = 6.3 min, column = Lichrosorb RP18 (7 µm), dimensions = 4x250 mm).

Data for **6**: mp 175-177 °C; TLC: eluant = ETOAc-MeOH 6:4, R_f = 0.20; $[\alpha]_D^{20}$ = + 56.7 (*c* = 1 in H_2O); ^{1}H NMR (DMSO-d_6) δ 8.30 (br, 3H), 4.50 (dd, ^2J = 10.5 Hz, ^3J = 6.6 Hz, 1H), 4.34 (dd, ^2J = 10.5 Hz, ^3J = 2.9 Hz, 1H), 4.10 (m, 1H), 2.90 (dd, ^2J = 18.6 Hz, ^3J = 8.7 Hz, 1H), 2.56 (dd, ^2J = 18.6 Hz, ^3J = 2.9 Hz, 1H); Anal. Calcd. for $C_4H_8ClNO_2$: C, 34.92; H, 5.86; N, 10.18; Cl, 25.77. Found C, 34.76; H, 5.95; N, 9.96; Cl, 25.97. An analytical sample was transformed into the hydrobromide form in order to compare the value of optical rotation with that reported (Lit.[10a]: $[\alpha]_D^{20}$ = -42.6, *c* = 1.08 in H_2O, (*S*) form). Thus, after elution with water on Amberlite IRA 402 (Br^- form) and evaporation under vacuum, a residue was obtained with $[\alpha]_D^{20}$ = + 47.8 (*c* = 1.08 in H_2O, (*R*) form).

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(12) Data for **8**: mp 123-125 °C (decomp); TLC: eluant = ETOAC, R_f = 0.18; $[\alpha]_D^{20}$ = + 87.96 (*c* = 1 in H_2O); ^{1}H NMR ($CDCl_3$) δ 6.30 (brs, 1H), 4.7 (m, 1H), 4.50 (dd, ^2J = 10.2 Hz, ^3J = 5.4 Hz, 1H), 4.22 (dd, ^2J = 10.2 Hz, ^3J = 2.3 Hz), 2.84 (dd, ^2J = 17.6 Hz, ^3J = 7.4 Hz, 1H), 2.42 (dd, ^2J = 17.6 Hz, ^3J = 2.3 Hz, 1H), 2.00 (s, 3H); Anal. Calcd. for $C_6H_9NO_3$: C, 50.34; H, 6.33; N, 9.78; Found C, 50.15; H, 6.17; N, 9.47.

Chiral NMR shift reagents: Tris-[3-(heptafluoropropylhydroxymethylen)-*d*-camphorato]-europium (III) and Tris-[3-(heptafluoropropylhydroxymethylen)-*d*-camphorato]-praseodymium (III).

Chiral phase HPLC: column = Crownpak-CR (+) (5µm), dimensions = 4x150 mm, eluant = $HClO_4$ 0.02 M, flow rate = 0.5 mL/min, temperature = 0 °C, retention time = 3.15 min.

(13) (*R*)-Acetylcarnitine inner salt **9** (1 g, 4.92 mmol) in CH_3CN (250 mL) was refluxed for 4 h under stirring (bath temperature 125 °C). After solvent evaporation of a control sample, a mixture containing **9, 10** and **11** (in ratio approximately corresponding to 0.6 : 0.4 : 1 by ^{1}H NMR) together with small amounts of elimination and hydrolysis products was obtained. **10** ^{1}H NMR (D_2O) δ 5.50 (m, 1H), 4.67 (dd, ^2J = 11 Hz, ^3J = 4.4 Hz, 1H), 4.58 (dm, ^2J = 11 Hz, 1H), 3.1 (dd, ^2J = 17.6 Hz, ^3J = 6.6 Hz, 1H), 2.76 (dm, ^2J = 17.6 Hz, 1H), 2.17 (s, 3H); **11** ^{1}H NMR (D_2O) δ 7.85 (m, 1H), 6.22 (m, 1H), 5.05 (m, 2H) (identical to that reported in Aldrich FT-NMR library). After additional 20 h of reflux the solvent was evaporated, the oily residue taken up in Et_2O and filtered. Careful evaporation of the filtrate gave **11** (320 mg, 77 %) as an oil: TLC: eluent = ETOAc, R_f = 0.73; Anal. Calcd. for $C_4H_4O_2$: C, 57.15; H, 4.79; Found C, 57.06; H, 4.64.

(14) Data for **14**: mp 180 °C (decomp); TLC: eluant = $CHCl_3$-*i*-PrOH-MeOH-H_2O-AcOH 420:70:280:105:105, R_f = 0.33; $[\alpha]_D^{20}$ = -22.3 (*c* = 1 in H_2O); ^{1}H NMR (D_2O) δ 7.50 (s, 5H), 4.90 (m, 2H), 4.60 (m, 1H), 3.42 (dd, ^2J = 14.35 Hz, ^3J = 9.8 Hz, 1H), 3.32 (dd, ^2J = 14.35 Hz, ^3J = 2.3 Hz, 1H), 3.20 (s, 9H), 2.35 (m, 2H); Anal. Calcd. for $C_{14}H_{23}N_2ClO_3$: C, 55.53; H, 7.65; N, 9.29; Cl, 11.71. Found C, 55.31; H, 7.93; N, 9.20; Cl, 11.53.

(15) Data for **15**: mp 91-92 °C; TLC: eluant = Hexane-EtOAc 2:8, R_f = 0.16; $[\alpha]_D^{25}$ = +15.2 (*c* = 0.5 in MeOH); ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 5H) 5.00 (s, 2H), 4.40 (m, 1H), 3.55 (dd, ^2J = 9.8 Hz, ^3J = 5.8 Hz, 1H) 3.25 (dd, ^2J = 9.8 Hz, ^3J = 2.7 Hz, 1H), 2.80 (brs, 1H) , 2.65 (dd, ^2J = 17.45 Hz, ^3J = 6.9 Hz, 1H), 2.35 (dd, ^2J = 17.45 Hz, ^3J = 3.2 Hz, 1H). Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.75. Found C, 63.75; H, 6.60; N, 6.71.

(16) Data for **16**: mp 93-94 °C; TLC: eluant = Hexane-EtOAc 2:8, R_f = 0.35; $[\alpha]_D^{25}$ = +27.0 (*c* = 0.5 in MeOH); ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 5H), 5.00 (s, 2H), 4.50 (m, 1H), 4.30 (m, 2H), 2.80 (dd, ^2J = 16 Hz, ^3J = 5.4 Hz, 1H), 2.60 (dm, ^2J = 16 Hz, 1H); Anal.

Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; 6.75. Found: C, 63.63; H, 6.61; N, 6.78.

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