Inversion of Configuration of (*S*)-*β*-Hydroxy-*γ*-butyrolactone with Total Retention of the Enantiomeric Purity

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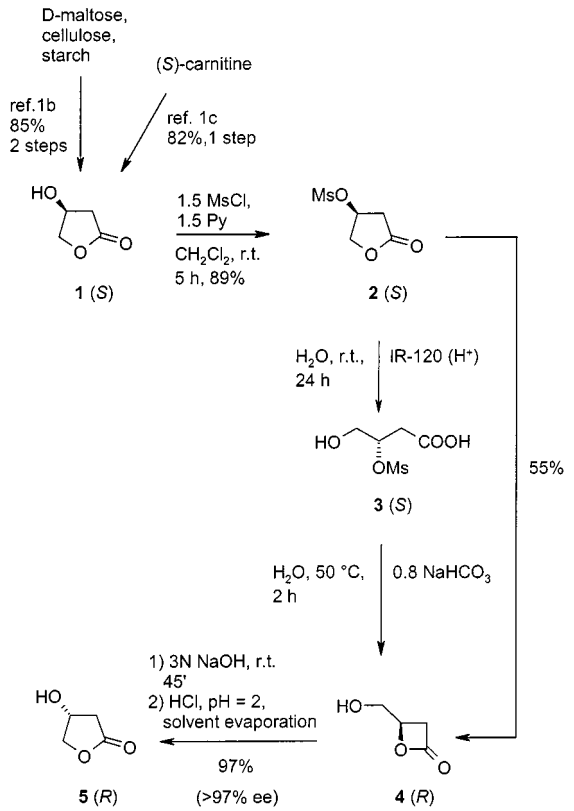
In this paper we report the inversion of configuration of (*S*)-β-hydroxy-γ-butyrolactone [(*S*)-**1**] to its (*R*) enantiomer (*R*)-**1**, with total retention of the enantiomeric purity, by a four-step procedure. The (*R*)-β-hydroxy-γ-butyrolactone [(*R*)-**1**] was thus synthetized with an overall chemical yield of 47% and > 97% *ee*. This transformation opens an economic route to the production of (*R*)-GABOB and (*R*)-carnitine, among other biologically active compounds, from a D-hexose source, or, alternatively, from the industrial waste compound (*S*)-carnitine. During the reaction sequence, the intermediate β-lactone **4** is also prepared, which is now under investigation as a chiral synthon for new synthetic applications.

(*S*)-*β*-Hydroxy-*γ*-butyrolactone (*S*)-**1** is a natural product[1a] and a known chiral synthon that can be obtained by several synthetic methods.[1b−1e] Two of them, which make use of a D-hexose source[1b] or (*S*)-carnitine,[1c] the waste product of the industrial production of (*R*)-carnitine, as starting materials, appear particularly economical and convenient for large scale syntheses. Moreover, (*S*)-**1** has also been recently introduced to the market both in bulk and on a laboratory scale. (*R*)-**1** is also a valuable synthon which has been used for the preparation of (*R*)-GABOB and (*R*)-carnitine,[2] for the synthesis of *β*-lactam antibiotics,[3] and also natural products like (−)-aplysistatin[4a] and (*S*)-(+)-ipsdienol.[4b] The absence from the literature of a convenient synthesis of (*R*)-**1**,[5] as compared with those reported for the (*S*)-enantiomer, prompted us to investigate the possibility of converting, with simple reactions, the (*S*)-enantiomer into the (*R*)-enantiomer, in order to exploit the same cheap sources. In addition, the inversion of configuration of chiral, biologically active compounds or their synthetic precursors is a chemical challenge of great importance in the pharmaceutical business.[6] In this paper we report the inversion of configuration of (*S*)-*β*-hydroxy-*γ*-butyrolactone {(*S*)-**1**} to its (*R*)-enantiomer {(*R*)-**1**}, with total retention of the enantiomeric purity, according to a four-step procedure (two steps are performed in sequence with no need for isolation of the intermediate compound).[7] The (*R*)-*β*-hydroxy-*γ*-butyrolactone {(*R*)-**1**} was thus synthesized with an overall chemical yield of 47% and >97% *ee*. The overall process is straightforward and does not employ sophisticated reagents. Along the reaction sequence, the intermediate *β*-lactone **4** is also prepared, which is now under investigation as a chiral synthon for new synthetic applications.

The transformation was realized as described in Scheme 1. The key step is the formation of the (*R*)-*β*-lactone **4** with clean inversion of configuration at the stereogenic center, starting from the (*S*)-*β*-hydroxy-*γ*-lactone derivative **2**, via intramolecular nucleophilic displacement of the activated



Scheme 1. Inversion of configuration of (*S*)-*β*-hydroxy-*γ*-butyrolactone {(*S*)-**1**} to give the (*R*)-**1** enantiomer

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  1434−193X/99/1111−2705 $ 17.50+.50/0

hydroxyl group of compound **3** operated by the carboxylate anion. Basic hydrolysis of **4**, followed by acid catalyzed recyclization, gave the desired product (*R*)-**1** without racemization, with the expected (*R*)-configuration at carbon 3. The stereochemical course of the reaction allows the assignement of the *R* configuration for the *β*-lactone **4**, which has been previously described in the literature only as a racemate.[8]

We devised this synthetic strategy after the failure of other inversion of configuration strategies; in particular the Mitsunobu reaction led only to elimination products, owing to the high tendency of the triphenylphosphonium intermediate to convert into the stable 2-furanone, while treatment with dicyclohexylcarbodiimide and carboxylic acids[9] led only to degradation products.

Following the "*β*-lactone" strategy described in Scheme 1, (*S*)-*β*-hydroxy-*γ*-butyrolactone {(*S*)-**1**} was thus treated with methanesulfonyl chloride to afford the (*S*)-*β*-methanesulfonyloxy-*γ*-butyrolactone **2** in 89% yield.[10] Compound **2** was then treated with Amberlite IR-120 to catalyze ring hydrolysis, in a modification of a literature procedure.[11] A ^{1}H NMR spectrum (D_2O) of the reaction mixture showed the presence of the intermediate (*S*)-*γ*-hydroxy-*β*-methanesulfonyloxy-butyric acid **(3)** which was not isolated due to its high tendency, under acidic or neutral conditions, to undergo back-cyclization to **2**. Sodium hydrogencarbonate was then added. After water evaporation and column chromatography (*R*)-*β*-hydroxymethyl-*β*-propiolactone **(4)** was obtained as an oil, in 55% yield starting from **2**. Compound **4** was then hydrolyzed with base; after acidification and solvent evaporation the residue was taken up with EtOAc and the insoluble material was filtered off to give pure (*R*)-*β*-hydroxy-*γ*-butyrolactone {(*R*)-**1**} {$[\alpha]_D^{20} = +86$, c = 0.8 in MeOH; $[\alpha]_D^{20} = +88$, c = 0.8 in MeOH[1c]} with an optical purity of ca. 98% (97.8% *ee*) checked by gas chromatography on a chiral stationary phase [2,6-*O*-dimethyl-3-trifluroacetyl-*β*-cyclodextrin column].[12]

All attempts to perform the direct conversion of the *β*-lactone **4** into (*R*)-**1** under acidic conditions, i.e. hydrolysis followed by cyclization, under different reaction conditions, always ended up in the partial racemization. For example, addition of 1N HCl to an aqueous solution of **4** down to pH = 1 and stirring for 1 h at 50°C, gave, after water evaporation, **5** in only 80% *ee*. Even more surprisingly, treatment of **4** with a stoichiometric amount of $NaHCO_3$ in water at room temp., led slowly (4 days) to the expected sodium dihydroxybutyrate; after acidification and water evaporation, an almost racemic mixture of the final hydroxy-*γ*-butyrolactone was obtained.

In conclusion this simple and relatively high yielding transformation opens an economic route to the production of (*R*)-GABOB and (*R*)-carnitine,[2] among other biologically active compounds,[3,4] from a D-hexose source or, alternatively, from the industrial waste compound (*S*)-carnitine. We anticipate that the intermediate compound *β*-lactone **4** could also be a versatile chiral synthon offering, for example, new opportunities for the synthesis of chiral *β*-functionalized-*γ*-hydroxybutyric acids.

Experimental Section

Melting points were determined by the capillary method on an electrothermal apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz; chemical shifts are expressed in δ values downfield from TMS. Chiral GC analyses were performed using a 2,6-*O*-dimethyl-3-trifluroacetyl-*β*-cyclodextrin column supplied from ASTEC {length = 30 m; injector temperature = 200°C; column temperature = 100°C (5 min), 100 → 160°C (rate 10°C/min), 160°C (15 min), detector temperature (FID) = 250°C}. Methanesulfonyl chloride, Amberlite IR 120, dry pyridine and dry dichloromethane, sodium bicarbonate and dry sodium sulfate were purchased from Aldrich. (*S*)-*β*-Hydroxy-*γ*-butyrolactone (*S*)-**1** was prepared as described in ref.[1c] from (*S*)-Carnitine (Biosint, Sigmatau group).

(*S*)-β-Methanesulfonyloxy-γ-butyrolactone (2): To a solution of (*S*)-**1** (8 g, 78.36 mmol) and dry pyridine (9.3 g, 117.54 mmol) in dry CH_2Cl_2 (400 mL), refrigerated in an ice bath, was added methanesulfonyl chloride (13.464 g, 117.54 mmol) dropwise under stirring. The solution was stirred for an additional 5 h at room temp., washed with 5% aqueous HCl, H_2O, a saturated solution of NaCl, and dried over anhydrous Na_2SO_4. Diisopropyl ether was added to the residue; precipitation of the product occurred, and the mixture was left overnight at 4°C. Solvent was then decanted off and the solid collected and dried under vacuum to give (**2**) in 89% yield (12.6 g). – M.p. 81–82°C (decomp.). – $[\alpha]_D^{20} = -62$ (*c* = 0.6, $CHCl_3$). – R_f (TLC, silica gel) = 0.69 (EtOAc). – ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): δ = 5.45 (m, 1 H), 4.55 (dd, ^2J = 11.5 Hz, ^3J = 1.5 Hz, 1 H), 4.45 (dd, ^2J = 11.5 Hz, ^3J = 5.0 Hz, 1 H), 3.08 (s, 3 H), 2.90 (dd, ^2J = 17.5 Hz, ^3J = 6.0 Hz, 1 H), 2.80 (dd, ^2J = 17.5 Hz, ^3J = 3.5 Hz, 1 H). – $C_5H_8O_5S$ (180.18): calcd. C 33.33, H 4.47, S 17.79; found C 33.32, H 4.48, S 17.53.

(*R*)-β-Hydroxymethyl-β-propiolactone (4): Amberlite IR 120 in acidic form (230 mL) was added to a mixture of (**2**) (10.6 g, 58.83 mmol) in water (115 mL). After 24 h at room temp. under flask shaking the resin was filtered off and washed with additional water (550 mL). The ^{1}H NMR spectrum of a sample evidenced the presence of the intermediate (*S*)-*γ*-hydroxy-*β*-methanesulfonyloxy-butyric acid (**3**) (^{1}H NMR (200 MHz, D_2O, 25°C): δ = 5.12 (m, 1 H), 3.88 (dd, ^2J = 12.5 Hz, ^3J = 3.5 Hz, 1 H), 3.75 (dd, ^2J = 12.5 Hz, ^3J = 5.5 Hz, 1 H), 3.20 (s, 3 H), 2.82 (d, ^3J = 6.0 Hz, 2 H)). $NaHCO_3$ (3.953 g; 47.06 mmol, in order to avoid excess alkalinity) was added, the solution heated at 50°C under stirring for 2 h and evaporated under vacuum. The residue was taken up with EtOAc, the solid was filtered off and the solvent evaporated. Flash chromatography (silica gel, *n*-hexane/EtOAc 6:4) of the residue gave (**4**) (3.31 g, 55%) as a colorless oil. – $[\alpha]_D^{20} = -29$ (*c* = 0.95, $CHCl_3$). – R_f (TLC, silica gel) = 0.21 (*n*-hexane/EtOAc 6:4). – ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): δ = 4.65 (m, 1 H), 4.10 (dd, ^2J = 13.5 Hz, ^3J = 2.5 Hz, 1 H), 3.80 (dd, ^2J = 13.5 Hz, ^3J = 4 Hz, 1 H), 3.45 (d, ^3J = 5 Hz, 2 H), 2.15 (br. s, 1 H). – $C_4H_6O_3$ (102.09): calcd. C 47.06, H 5.92; found C 46.75, H, 5.97.

(*R*)-β-Hydroxy-γ-butyrolactone {(*R*)-1}: Compound **4** (3.5 g, 34.28 mmol) was dissolved in 3N NaOH (100 mL) and the solution stirred at room temp. for 45 min. 3N HCl was added whilst cooling the solution with an ice bath and the pH was adjusted to 2. Solvent was then evaporated under vacuum and the residue taken up with EtOAc. Solid NaCl was eliminated by filtration, the solution dried over anhydrous Na_2SO_4, and the solvent evaporated under vacuum to give {(*R*)-**1**} as a colorless oil (3.4 g, 97%). – $[\alpha]_D^{20} = +86$ (*c* = 0.8, MeOH). – R_f (TLC, silica gel) = 0.63 (EtOAc). – ^{1}H NMR (200 MHz, $CDCl_3$, 25°C,TMS): δ = 4.62 (m, 1 H), 4.40 (dd, ^2J = 10.5 Hz, ^3J = 4.0 Hz, 1 H), 4.28 (dm, ^2J = 10.5 Hz, 1 H),

3.00−2.30 (br, 1 H), 2.73 (dd, ^2J = 18.5 Hz, ^3J = 6.0 Hz, 1 H), 2.45 (dm, ^2J = 18.5 Hz, 1 H). − $C_4H_6O_3$ (102.09): calcd. C 47.06, H, 5.92; found C 46.75, H 5.97.

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[12] Details of the *ee* determination by GC will be published in a subsequent paper.

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