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A Simple Enantioselective Synthesis of γ-Valerolactone

John A. O'Neill,[a] Stephen D. Lindell,[b] Thomas J. Simpson,[a] and Christine L. Willis*,[a]

[a] School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK.

[b] Schering Agrochemicals Ltd., Chesterford Park, Saffron Walden, Essex CB10 1XL.

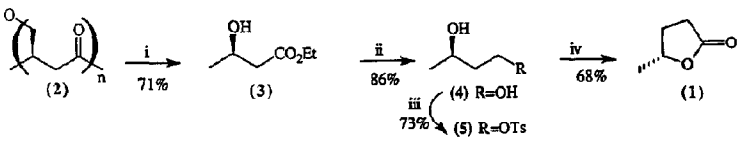
Abstract: The readily available biopolymer, poly-(*R*)-3-hydroxybutyrate was converted to (*R*)-(+)-γ-valerolactone in 32% overall yield in a simple 4 stage procedure.

For ongoing biosynthetic and synthetic studies on the macrodiolide metabolites in *Cytospora* sp ATCC 20502,[1] we required gram quantities of (*R*)-(+)-γ-valerolactone **1**. Several methods have been described for the enantioselective synthesis of γ-valerolactone including the resolution of (±) γ-hydroxy esters with porcine pancreatic lipase[2], the use of a baker's yeast reduction to give (*S*)-(-)-γ-valerolactone in 12% overall yield[3] and a high pressure BINAP catalysed reduction of ethyl 4-oxopentanoate[4]. Although each of these approaches has obvious merits, we ideally required a route which would not only yield gram quantities of **1** using inexpensive reagents, but which could be simply adapted for the efficient incorporation of an isotopic label for biosynthetic studies. A simple 4 stage synthesis of (*R*)-(+)-γ-valerolactone is now described.

Results and Discussion

Treatment of the readily available biopolymer poly-(*R*)-3-hydroxybutyrate **2** with concentrated sulphuric acid in ethanol gave the ethyl ester **3** which, on reduction with lithium aluminium hydride, gave the diol **4**. Selective tosylation of **4** with 1.1 equivalents of p-toluenesulphonyl chloride followed by nucleophilic displacement of the primary tosylate of **5** with potassium cyanide and *in situ* hydrolysis of the resultant nitrile with hydrochloric acid, cleanly gave the target compound **1** in 32% overall yield from the biopolymer.

A carbon-13 label may be efficiently introduced at the final stage of the synthesis by use of potassium [^{13}C] cyanide. In addition, ethyl (*S*)-3-hydroxybutyrate is available from the yeast reduction of ethyl acetoacetate[5], hence this route may be simply adapted for the preparation of (*S*)-(-)-γ-valerolactone.



Reagents: i) EtOH, H^+; ii) $LiAlH_4$, Et_2O; iii) TsCl, Et_3N, DMAP; iv) KCN, EtOH then H^+

Experimental: Poly-(*R*)-3-hydroxybutyrate was obtained from Aldrich Chemical Co.

Ethyl 3(*R*)-hydroxybutyrate (3). Poly-3(*R*)-hydroxybutyrate (50g) in EtOH (360ml), 1,2-dichloroethane (300ml) and conc. H_2SO_4 (20ml) was heated to reflux with vigorous stirring for 96 h. The cooled mixture was filtered through celite, and the celite then washed with CH_2Cl_2 (500ml). The filtrate was washed with aq $NaHCO_3$ (500ml) and then with brine (500ml), dried ($MgSO_4$) and concentrated *in vacuo*. The hydroxy ester **3** was purified by distillation (51°C at 2mm Hg); yield: 54.5g (71%); $[\alpha]_D^{21}$ -48 (c 7.2, CH_2Cl_2), lit.[6] $[\alpha]_D$ -46 (c 1.0 , $CHCl_3$) ; IR (nujol): 3440, 1739 cm^{-1}; ^{1}H NMR: δ 1.23 (3H, d, J=6.3 Hz), 1.28 (3H, t, J=7 Hz), 2.41 (1H, dd, J=16.3, 8.6 Hz), 2.49 (1H, dd, J=16.3, 3.4 Hz), 4.17 (2H, q, J=7 Hz), 4.2 (1H, ddq, J=8.6, 6.3, 3.4 Hz); m/z 131 (M^+-1, 2%), 43 (100).

1,3(*R*)-Dihydroxybutane (4). A slurry of $LiAlH_4$ (12g, 324 mmol) in dry Et_2O(1L) was added dropwise to a stirred solution of ethyl 3(*R*)-hydroxybutyrate (**3**) (35.64g, 270 mmol) in Et_2O (150ml) at 0°C under N_2. After the addition of $LiAlH_4$ was complete, the mixture was stirred for a further 0.5h. Water (90ml) was cautiously added with stirring and the mixture was filtered through celite and the celite then washed with Et_2O (500ml). The filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to give the diol **4**; yield: 20.8g (85.6%); $[\alpha]_D^{21}$ -28.7 (c 3.2, EtOH), lit.[7] -29 (c 1.0, EtOH); IR (nujol) 3444 cm^{-1} ; ^{1}H NMR: δ 1.24(3H, d, J=6.4 Hz), 1.7 (2H, m), 2.4 (2H, br.s), 3.84 (1H, m), 4.08 (1H, m); m/z 75 (M^+-15, 10%), 45 (100).

3(*R*)-Hydroxy-1-(p-toluenesulphonyl)-butane (5). *p*-Toluenesulphonyl chloride (27.91g, 146.4 mmol) was added to a solution of the diol **4** and 4-dimethylaminopyridine (122mg, 1 mmol) in Et_3N (40.8ml, 293 mmol) and CH_2Cl_2 (250ml) and stirred at room temperature for 16 h. at ambient temperature. HCl (0.5M, 1L) was added and the mixture extracted with CH_2Cl_2 (2 x 1L). The organic phase was dried ($MgSO_4$), concentrated *in vacuo* and the resultant oil purified by chromatography (silica gel, EtOAc/ light petroleum 3:7) to give **5** as a colourless oil, yield 21.75g (73%); $[\alpha]_D^{21}$ -14.8 (c 5.1 in CH_2Cl_2); IR (nujol): 3411, 1598, 1351 cm^{-1}; ^{1}H NMR: δ 1.19 (3H, d, J=6.4 Hz), 1.7 (1H, m), 2.45 (3H, s), 3.95 (1H, m), 4.14 (1H, m), 4.25 (1H, m), 7.35 (2H, d, J=8.1 Hz), 7.8 (2H, d, J=8.1 Hz); m/z 229 (M^+-15, 1%), 91 (100)

(*R*)-(+)-γ-valerolactone (1). The tosylate **5** (21.75g, 89 mmol) in EtOH (270ml) and H_2O (90ml) was heated to reflux with KCN (6.94g, 106.8 mmol) for 16 h. The mixture was cooled to ambient temperature prior to the addition of conc. HCl (360ml) and then heated to reflux for 24h. After cooling, H_2O (900ml) was added and the reaction mixture extracted with $CHCl_3$ (3 x 1.4L). The organic phase was dried ($MgSO_4$), concentrated *in vacuo* and then purified by distillation (106°C at 20mm Hg) to give **1**; yield: 6.07g (68%); $[\alpha]_D^{21}$ +29.4 (c 9.2, CH_2Cl_2), lit.[8] +30.1 (c 0.85, CH_2Cl_2); IR (nujol): 1777 cm^{-1}; ^{1}H NMR: 1.42 (3H, d, J=6.3 Hz); 1.84 (1H, m), 2.36 (1H, m), 2.56 (2H, m), 4.66 (1H, m); m/z 100 (M^+, 8%), 56 (100).

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