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Efficient large scale stereoinversion of (*R*)-ethyl 3-hydroxybutyrate

Andrew J. Carnell,[a,*] Robert Head,[b] Derek Bassett[b] and Michael Schneider[b]

[a]*Department of Chemistry, Robert Robinson Laboratories, University of Liverpool, Liverpool L69 7ZD, UK*
[b]*The Associated Octel Company Ltd., Oil Sites Road, Ellesmere Port, South Wirral L65 4HF, UK*

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Abstract—A three step method for the large scale preparation of enantiomerically pure ethyl (*S*)-3-hydroxybutyrate is reported starting from the commercial biopolymer poly[(*R*)-hydroxybutyrate]. The key step depends on the ability to cleanly invert the stereochemistry of (*R*)-ethyl 3-hydroxybutyrate via its mesylate ester under neutral conditions, avoiding the competing elimination process. This has been achieved in good (75%) yield on >100 g scale by controlled addition of the mesylate to a stirred slurry of calcium carbonate in water at 80 °C.

1. Introduction

Homochiral 3-hydroxybutyrate esters have been widely employed as synthetic intermediates. Both enantiomers have found use in patented syntheses of β-lactam antibiotics and β-lactamse inhibitors.[1,2] Seebach et al. has demonstrated that a wide range of useful chiral intermediates[3] such as (*R*)-butan-1,3-diol and (*R*)-3-hydroxybutyrolactone[4] are available from chiral 3-hydroxybutyrates. DuPont have used homochiral 3-hydroxybutyric acid to synthesise phosphorus ligands using the Kolbe electrochemical coupling to generate (*R*,*R*) or (*S*,*S*)-hexan-2,5-diol as a pivotal intermediate.[5] The use of biotransformations to access 3-hydroxyesters in reasonably high enantiomeric purity is well established. However, whole cell bioreduction with, most commonly, Baker's yeast suffers from limited throughput (ca 10 g/l).[6] Use of isolated dehydrogenase enzymes with requisite cofactor recycling holds greater promise for the production of kilogram quantities. The use of lipase resolutions is limited by the lack of efficient methods for recycling the unwanted enantiomer. The biopolymer poly[(*R*)-3-hydroxybutyrate] **1** is produced in volumes of tonnes/annum by fermentation of *Alcaligenes eutrophus* spp.[7,8] The polymer is synthesised by the organism as an intracelluler storage product. *Pseudomonas acidovorans* produces terpolyesters of 3-hydroxybutyrate (3-HB) and 3-hydroxyvalerate (3HV) when grown on 1,4-butanediol and pentanol.[9] Biopolymers containing various ratios of 3-HB and 3-HV are produced commercially and are used in production of biodegradable plastics. The polymer can be degraded by alcoholysis to give the monomer alkyl (*R*)-3-hydroxybutyrate **2** (Scheme 1).[3b] (*R*)-Methyl 3-hydroxybutyrate is used for the manufacture of the anti-glaucoma drug Trusopt.[10] Either enantiomer of 3-hydroxybutyrate can be obtained by catalytic asymmetric hydrogenation using the chiral ruthenium (COD)(BINAP)-catalyst although the enantiomeric purity is lower than that obtained from the biopolymer. This technology was developed by Noyori and co-workers and used commercially by Takasago Co.[11] We became interested in the possibility of converting (*R*)-3-hydroxybutyrate derived from the polymer into its enantiomer by stereoinversion of the hydroxy group. Seebach reacted (*R*)-3-hydroxybutyric acid **3** with triethyl orthoacetate in benzene to afford the dioxanone **4**. Upon heating, this dioxanone breaks down to form 3-acetoxybutanoate **5** (42%) and the β-lactone **6** (33–40%), which upon hydrolysis gives (*S*)-3-hydroxybutyrate **2**.[12] The yields of this reaction limit its usefulness, unless the acetoxybutanoate **5** is recycled, however the resulting acid (*R*)-**3** is difficult to extract efficiently.

The yields reported for the multi-tonne scale depolymerisation of PHB are good and we now report a high yielding, scalable method for inversion of the

* Corresponding author. Tel.: +44-151-794-3531; fax: +44-151-794-3588; e-mail: acarnell@liv.ac.uk

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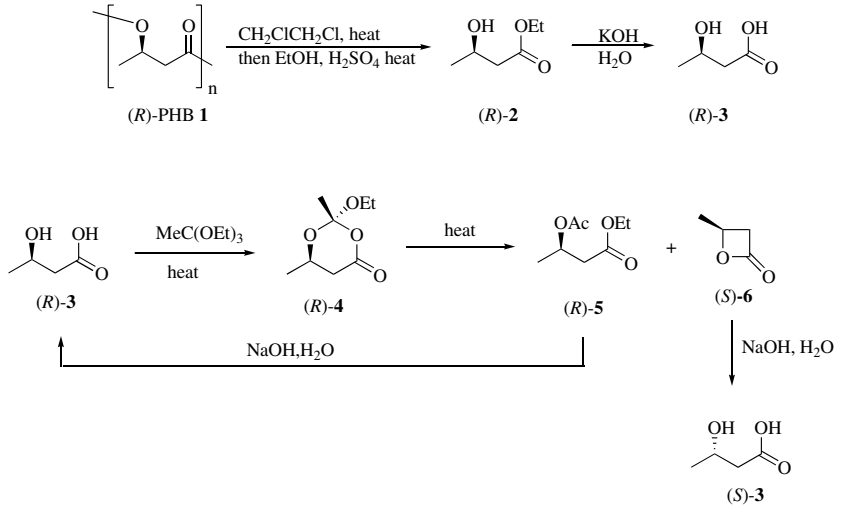


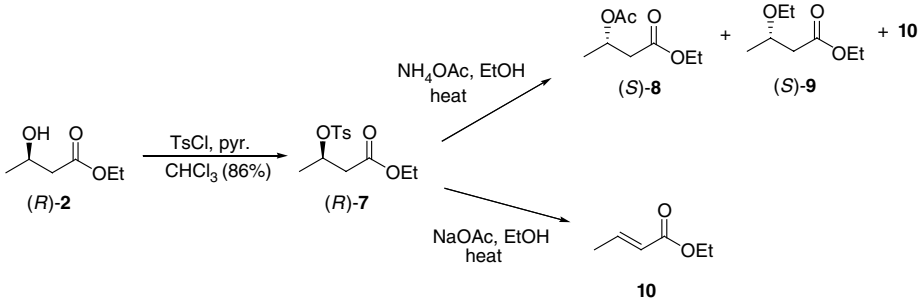
Scheme 1.

stereocentre of (*R*)-ethyl 3-hydroxybutyrate under neutral conditions.

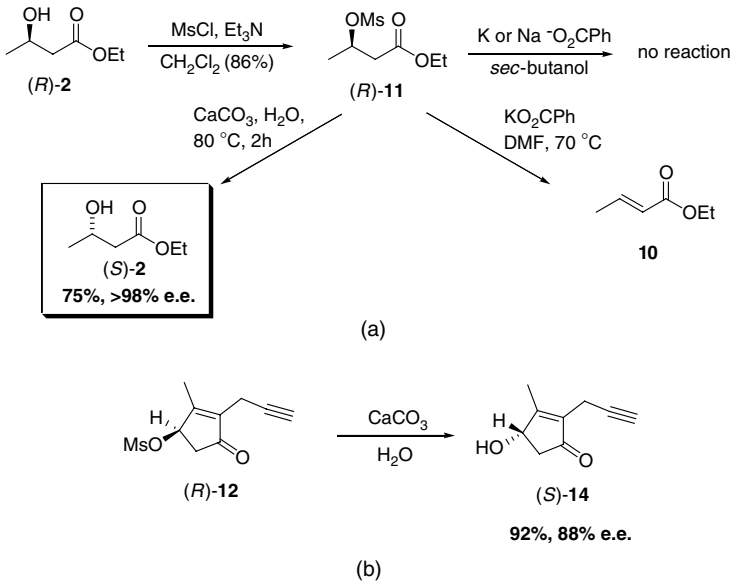
2. Results and discussion

We obtained ethyl (*R*)-3-hydroxybutyrate in 78% yield, >98% ee by ethanolysis depolymerisation using the published procedure for the methyl ester.[3b] The yield for this step was variable and on the large scale (200 g of polymer) we obtained 53%. We then assessed conditions for the formation of a 3-sulfonate ester leaving group. Initially the (*R*)-tosylate **7**[13] was made in 86% yield using the reactants in the ratio alcohol–TsCl–pyridine (1:1.5:2). Use of 2.5 molar equivalents each of tosyl chloride and pyridine resulted in a lower yield (46%). In selecting suitable conditions for the desired S_N2 displacement reaction, we were cognizant of the competing E1cb elimination process, which would be particularly favoured by the presence of the adjacent ester group. Indeed, in almost all successful examples of this type of displacement reported in the literature, the α-carbon centre is fully substituted. Cainelli et al. have reported displacement of the (*R*)-toslyate **7** with nitrate using $(n\text{-}Bu_4)N^+NO_3^-$ in pentane under pressure.[14] The reported yield of inverted nitroester product was good (94%), however a further reduction step was required to remove the nitroester. We were unable to repeat this displacement reaction. Treatment of the (*R*)-tosylate **7** with sodium acetate/ethanol gave only the elimination product ethyl crotonate **10**. Changing the counterion to ammonium gave S_N2 displacement by acetate and the solvent to give a mixture of compounds **8** and **9** in a low (20%) overall yield, in addition to ethyl crotonate (Scheme 2).

No improvement could be made by changing to the non-nucleophilic solvents acetone, acetonitrile or dimethylformamide. Although various other oxygen nucleophiles (KO_2 and RCO_2Cs) have been used for displacement of normal activated secondary alcohols, we wished to explore cheaper and simpler alternatives since the intention was to develop a large scale process. We therefore examined the possibility of displacing the smaller mesylate group with simple benzoate salts, in which the carboxylate is softer than the acetate previously used. A similar approach was reported to displace the triflate in (*R*)-diethyl 2-(trifluoromethylsulfonyloxy) succinate, although the reaction needed to be carried out at −45 °C in acetonitrile in order to avoid elimination.[15] The mesylate derivative **11** was made using triethylamine (1.1 equiv) as the base and mesyl chloride (1.11 equiv), keeping the internal reaction temperature below 13 °C to avoid elimination. This reaction was



Scheme 2.



Scheme 3.

done on an 80 g scale reproducibly to give an 86% isolated yield of the mesylate **11** (Scheme 3a).

Reaction with either the sodium or potassium salt of benzoic acid in *sec*-butanol at 70 °C gave no reaction. Changing the solvent to dimethylformamide resulted in predominantly elimination. We noted a report by Danda et al. on the efficient S_N2 inversion of the mesylate **12** using water as the nucleophile and $CaCO_3$ to neutralise the methanesulfonic acid produced (Scheme 3b).[16] The lack of elimination in this case could be explained by the quasi-antiaromatic nature of the cyclopentadienone that would result. Fortunately, our mesylate **11** underwent clean S_N2 inversion to give (*S*)-ethyl 3-hydroxybutyrate **2** in good yield (75%), with no loss of enantiomeric purity (>98% ee). On a large scale (120 g of mesylate) we were able to isolate 57 g of (*S*)-ethyl 3-hydroxybutyrate **2** after distillation. We were unable to detect any of the (*R*)-enantiomer, which might result from an S_N1 reaction or hydrolysis. The temperature (80 °C) and the way in which the reaction is performed appear to be critical for the success of this reaction. On a large scale, the best yields (75%) were obtained by heating the water/$CaCO_3$ mixture to 80 °C prior to addition of 40 g of the (*R*)-mesylate **2**. This was reacted for 1 h followed by portionwise (10 g) addition of a further 80 g of mesylate over 160 min. Heating was then continued for 100 min prior to cooling, extraction and distillation. The ee of the product was determined by Chiral HPLC (Chiracel OB-H)[17] and the absolute configuration by comparison of the retention times of the racemic starting material and the starting (*R*)-enantiomer.

The success of this inversion process for such a potentially base sensitive substrate presumably results from the insolubility of calcium carbonate in water and therefore the neutral conditions under which the nucleophilic substitution takes place. Only when the mesylate is released does the calcium carbonate come into play in neutralising the methanesulfonic acid formed upon protonation of the leaving group by water. It is obviously important for the mesylation step to proceed to completion otherwise any residual (*R*)-hydroxyester would reduce the enantiomeric purity of the (*S*)-enantiomer after the inversion process.

3. Conclusions

It is clear from this study that it is possible to obtain enantiomerically pure (*S*)-ethyl 3-hydroxybutyrate in ca 100 g quantities starting from poly[(*R*)-3-hydroxybutyrate] in three successive steps: (1) depolymerisation, (2) mesylation of the C-3 hydroxyl group and (3) displacement of the mesylate with water under neutral conditions. The yields for the three steps are 53%, 86% and 75%, respectively, and could be further optimised. This inversion methodology yields the inverted alcohol directly with no requirement for further functional group interconversion and should be applicable to other sensitive mesylates of 3-hydroxyesters, particularly where only one enantiomer is available at a reasonable cost. Given the respectable reactant concentrations for each step (300 g mesylate/l for the inversion), the process described could easily be scaled up to provide large quantities of (*S*)-ethyl 3-hydroxybutyrate and may provide a competitive route to this chiral intermediate.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker 400 MHz spectrometer. Chemical shifts are described in parts per million downfield shift from $SiMe_4$ and are reported

consecutively as position (δ_H or δ_C), relative integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double of doublets, sep = septet, m = multiplet and br = broad), coupling constant (J, Hz) and assignment (numbering according to the IUPAC nomenclature for the compound). Mass spectra and accurate mass measurements were recorded on a VG 70-070E, or a TRIO 1000. Optical rotations were measured at room temperature on a Optical Activity AA-1000 polarimeter using 10 or 20 cm path length cells and specific rotations are given in 10^{-1} deg cm^2 g^{-1}. Analytical thin layer chromatography (TLC) was carried out on 0.25 mm precoated silica gel plates (Macherey-Nagel SIL g/UV$_{254}$) and compounds were visualised using potassium permanganate dip. The solvents (Analar grade) were used as supplied. THF and diethyl ether were dried over sodium-benzophenone ketyl and distilled under nitrogen.

4.2. (*R*)-Ethyl 3-hydroxybutyrate 2

A 2 l SVL reactor was fitted with an overhead stirrer, reflux condenser, thermometer and 250 ml dropping funnel. To this was added poly[(3-hydroxybutyrate)] (BIOPOL D300G) (200 g) and dichloromethane (800 ml) and the suspension was stirred at reflux (83 °C) for 2 h whereupon a thick creamy suspension was obtained. At this stage half a solution of concentrated sulfuric acid (2.5 ml, 2 mol%) in ethanol (136 ml, 2.32 mol, 1 equiv) was added quickly through the dropping funnel and the mixture returned to reflux for 2 h. The remaining acidic ethanol was added and the mixture refluxed for 21 h. after which a further 1 equiv of ethanol (136 ml) was added and refluxing continued for 48 h. The reaction was allowed to cool to 45 °C and solid sodium bicarbonate (7.9 g) was added and stirred for 10 min. After allowing the reaction to cool to room temperature the mixture was filtered through a bed of Celite (with suction) and the solvent removed in vacuo to give a dark orange oil as the crude product. Vacuum distillation 50 °C/1.5 mmHg or 59 °C/3.5 mmHg gave the product ester as a colourless liquid 162 g (53%). GC–MS analysis showed: ethyl (*R*)-3-hydroxybutyrate (96.2%), ethyl (*R*)-3-hydroxypentanoate (3.8%). $[\alpha]_D = -44.5$ (*c* 1, $CHCl_3$) on a sample of 99.2% pure ethyl (*R*)-3-hydroxybutyrate. Chiral HPLC (Chiracel OB-H), 96:4 hexane–isopropanol, UV 230 nm, (*R*)-enantiomer t_R 20.0 min, (*S*)-enantiomer t_R 18.4 min.[17]

4.3. (*R*)-Ethyl 3-mesyloxybutryrate 11

A 1 l SVL reactor was fitted with an overhead stirrer, thermometer, dropping funnel (100 ml) and drying tubes. To this was added dichloromethane (600 ml), (*R*)-ethyl 3-hydroxybutyrate (80 g, 0.57 mol) and mesyl chloride (47 ml, 0.61 mol, 1.06 equiv) and the mixture was cooled to 0 °C. Triethylamine (87.4 ml, 0.61 mol, 1.06 equiv) was added dropwise over 1 h 10 min maintaining the internal temperature below 13 °C. A further 2.8 ml (0.05 equiv) of mesyl chloride and 4 ml of triethylamine were added and the reaction stirred for 10 min at 7 °C. The reaction mixture was filtered cold by suction to remove the triethylamine hydrochloride and the filtrate was evaporated to give a white slurry. Diethyl ether (100 ml) was added and the solution filtered by suction, washing with diethyl ether. The filtrate was evaporated to give a colourless oil/solid (121 g), which was not further purified and used immediately for the next step. GC–MS analysis showed this crude product to contain (*R*)-ethyl 3-mesyloxybutyrate (92.6%), (*R*)-ethyl 3-mesyloxypentanoate (5.3%) and ethyl mesylate (1.3%). ^{1}H NMR ($CDCl_3$) δ 5.12 (1H, m, H-3), 3.70 (2H, d, *J* 7.1 Hz, CH_2CH_3), 3.02 (3H, s, SO_3CH_3), 2.80 (1H, dd, *J* 16.6, 8.3 Hz, H-2), 2.60 (1H, dd, *J* 16.6, 4.6 Hz, H-2), 1.49 (3H, d, *J* 6.3 Hz, $CHCH_3$), 1.35 (3H, d, *J* 7.1 Hz, CH_3CH_2).[18]

4.4. (*S*)-Ethyl 3-hydroxybutyrate 2

A 1 l SVL reactor was fitted with a reflux condenser, an overhead stirrer and a thermometer. To this was added deionised water (400 ml) and calcium carbonate (32 g, 0.317 mol, 0.55 equiv) and the suspension heated with stirring to 80 °C. (*R*)-Ethyl 3-hydroxybutyrate (40 g, 0.19 mol) was added (the mesylate required gentle heating to render it fully liquid) and the reaction mixture stirred for 1 h at 80 °C. A further 81 g (0.386 mol) of the mesylate was then added over 2 h 40 min in 10 g portions. Reflux was continued for 1 h 40 min and then the reaction was allowed to cool to room temperature before suction filtration. The filtrate was extracted to give 76 g of a crude oil. Distillation under reduced pressure gave the our product (*S*)-ethyl 3-hydroxybutyrate **2** (57.1 g, 75%) as a colourless liquid. GC–MS analysis showed (*S*)-ethyl 3-hydroxybutyrate (93.7%), (*S*)-ethyl 3-hydroxypentanoate (4.9%), ethyl but-2-enoate (1.4%), $[\alpha]_D = +40 \pm 2.5$ (*c* 1, $CHCl_3$). Chiral HPLC (Chiracel OB-H) showed >98% ee.

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