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TETRAHEDRON: *ASYMMETRY*

Chemoenzymatic synthesis of (4*S*,5*R*)-5-hydroxy-ɣ-decalactone †

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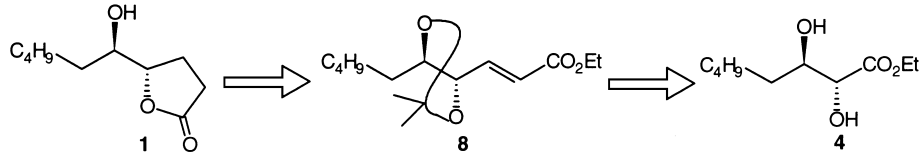
Abstract

Reduction of ethyl 2-hydroxy-3-oxooctanoate with immobilised baker's yeast at pH 4.0 yields *anti*-2*R*,3*R*-dihydroxy ester with high diastereoselectivity and enantioselectivity (de 70%, ee 80%) which is conveniently converted to (4*S*,5*R*)-5-hydroxy-ɣ-decalactone.

1. Introduction

Functionalised ɣ-lactones such as (4*S*,5*R*)-5-hydroxy-ɣ-decalactone, the so-called L-factor, **1** isolated from the cultures of *Streptomyces griseus*[1] and 5-hydroxy-ɣ-heptanolactone (muricatcin) isolated from the seeds of *Annona muricata*[2] have attracted synthetic chemists to develop new strategies for their synthesis[3] since they have been found to be of considerable biological importance.[4] Although several methods of synthesis of **1** are available in the literature, many of them are tedious and involve several steps, particularly the methods based on the chiron approach.[5–7] It is obvious that the 2,3-dihydroxy ester **4** would be an appropriate intermediate for the synthesis of **1** (Scheme 1).



Scheme 1.

However, the direct synthesis of such enantiomerically pure vicinal diols is not easy. An important method available in the literature is Sharpless asymmetric dihydroxylation of *cis* or *trans* olefins which give enantiomerically pure *anti* or *syn* diols, respectively, but the protocol is more suitable for *trans* olefins. The *cis* olefins usually lead to products with a low enantioselectivity,[8] while the enzymatic

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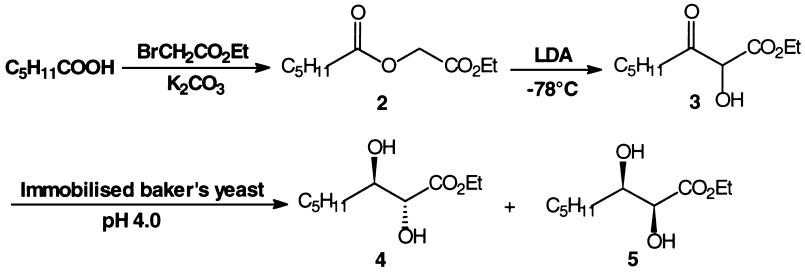
method based on selective oxidation of unwanted enantiomer in the racemic diol is quite tedious and expensive.[9,10] Here we present a simple methodology for the preparation of optically active *anti*-(4*S*,5*R*)-5-hydroxy-γ-decalactone **1** based on the enantiospecific reduction of α-hydroxy-β-ketoester **3** with baker's yeast immobilised in calcium alginate at low pH (pH 4.0).

2. Results and discussion

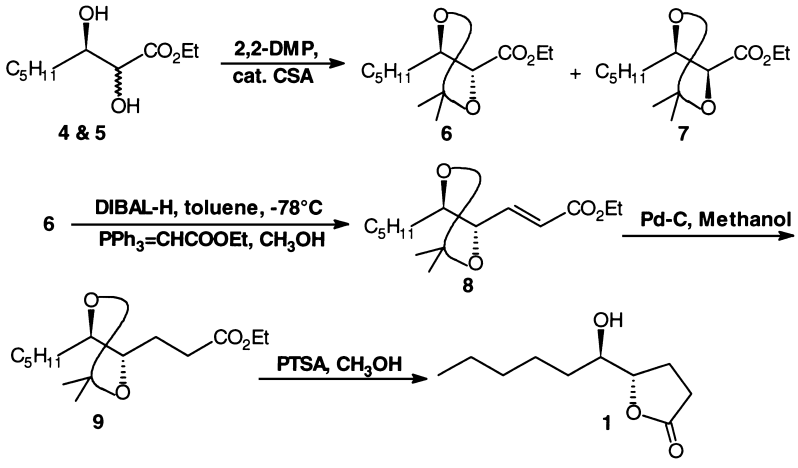
Sato et al. have reported the reduction of ethyl 2-hydroxy-3-oxoalkanoates by baker's yeast to obtain predominantly *anti* dihydroxyalkanoates with high enantiomeric excesses (>95%).[11] The diastereoselectivity of the reaction and the enantiomeric excess of the *syn* product was, however, reported to vary with the substrate, and also the ees of the *anti* and *syn* products were reported to be different. In our studies, we have consistently observed that the stereochemical outcome of the reduction of prochiral β-ketoesters and α-substituted-β-ketoesters by baker's yeast is strongly dependent on the pH of the medium.[12–14] Thus, for consistent results the α-hydroxy-β-ketoester **3** was reduced by baker's yeast immobilised in calcium alginate at pH 4.0, and the resulting dihydroxyester was converted to optically active *anti*-(4*S*,5*R*)-5-hydroxy-γ-decalactone **1** (Schemes 2 and 3). Treatment of hexanoic acid with ethyl α-bromoacetate and anhydrous potassium carbonate in refluxing acetone provided ethyloxycarbonyl methyl hexanoate **2** which was treated with 2 equivalents of LDA in THF at −78°C to obtain the required ethyl 2-hydroxy-3-oxooctanoate **3** in 55% yield. Reduction of **3** with baker's yeast immobilised in calcium alginate at pH 4.0 in a phosphate–borate–citrate mixed buffer (0.05 M) at room temperature (72 h) provided a mixture of diastereomers *anti*-**4** and *syn*-**5** (70%) (Scheme 2).



Scheme 2.

The crude diastereomeric mixture was treated with 2,2-dimethoxypropane and a catalytic amount of camphorsulfonic acid to furnish the acetonides **6** (major) and **7** (minor) which were separated by column chromatography using hexane as the eluent (isolated ratio 11:2) (Scheme 3). The *anti* and *syn* configurations of **6** and **7** were evident from their ^{1}H NMR spectra.

The H-2 proton of the *anti* acetonide **6** resonates at 4.49 ppm as a doublet (J=7.5 Hz) and the H-3 proton resonates along with -OC*H*$_2$CH$_3$ at 4.2 ppm, while both the H-2 and H-3 proton of the *syn* diastereomer **7** resonate as a multiplet at 4.12 ppm. The enantiomeric excess of the dihydroxy ester **4** (obtained from the acetonide of the major fraction, ee 80%) was determined by analysis of its corresponding phenylacetyl derivative 2,3-di(benzylcarbonyloxy)octanoic acid on a chiral HPLC column (Chiralcel OJ, Daicel, Japan)[15] and its configuration was assigned as 2*R*,3*R* based on its conversion to the title compound **1** according to Scheme 3. The acetonide of the minor fraction **7** was converted to the corresponding diol. Comparison of its specific rotation with the literature[16] indicated that the minor diol had the configuration 2*S*,3*R*.



Scheme 3.

The acetonide **6** was reduced with DIBAL-H in toluene at −78°C to provide the unstable aldehyde which was converted to the olefin **8** by Wittig reaction with carboethoxymethylene triphenylphosphorane in the same pot without isolation. The olefin **8** was hydrogenated and treated with PTSA in methanol to effect both the deprotection of the acetonide and formation of the lactone **1** with 80% ee. The compound **1** obtained in the above manner showed identical spectral and physical data to those reported in the literature.[7]

In conclusion, our results show that, similar to simple β-ketoesters,[12] stereoselectivity during baker's yeast reduction of α-substituted β-ketoesters with an aliphatic side chain is comparatively less than that observed for the aromatic counterparts,[13,14] and the diastereomeric excess can be improved by carrying out the reaction at low pH. Our route to *anti*-(4*S*,5*R*)-5-hydroxy-γ-decalactone **1** as shown in Scheme 1 is a simple approach which can be extended to the synthesis of several other natural products.

3. Experimental

Baker's yeast was obtained from Sigma, USA. All other reagents were A.R. grade obtained from SD Fine-Chem Ltd, India. NMR spectra were recorded on a Varian FT-200 MHz (Gemini) instrument using tetramethylsilane (TMS) as the internal standard. Infrared spectra were scanned on a Perkin–Elmer 683 or 1310 spectrophotometer with sodium chloride optics. Elemental analyses were carried out on Vario EL, Elementar, Germany. HPLC analyses were carried out on a Hewlett Packard HP1090 unit with diode array detector and HP ChemStation.

3.1. Ethyloxycarbonyl methyl hexanoate ***2***[17]

To a solution of hexanoic acid (1.1 g, 0.01 mol) in dry acetone (15 ml) was added anhydrous K_2CO_3 (3.8 g, 0.023 mol) followed by ethyl α-bromoacetate (1.1 ml, 0.01 mol) under N_2 atmosphere. After refluxing overnight, the mixture was cooled to room temperature and evaporated in vacuo. The residue was partitioned between ether (25 ml) and 10% aq. K_2CO_3 solution (10 ml). The organic layer was washed with water until neutral pH and finally with brine. It was then dried over anhydrous sodium sulfate and concentrated to obtain **2** (1.8 g, 89%) as a colourless liquid. Anal. calcd for $C_{10}H_{18}O_4$: C,

59.39; H, 8.97; found: C, 59.28; H, 8.87. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.95 (t, 3H), 1.35 (m, 7H), 1.7 (m, 2H), 2.45 (t, 2H), 4.35 (q, 2H), 4.6 (s, 2H).

3.2. *Ethyl 2-hydroxy-3-oxooctanoate* ***3***[17]

To a stirred solution of diisopropylamine (3.4 ml, 0.025 mol) in dry THF (20 ml) was added *n*-BuLi (15 ml of 1.6 M in hexane) followed by **2** (2.02 g, 0.010 mol) in THF (20 ml) under nitrogen at 0°C. After 30 min the reaction mixture was cooled to −78°C and quenched with 0.1N HCl. The mixture was allowed to warm to room temperature and concentrated. It was diluted with ether (30 ml). The ethereal solution was washed with water (2×15 ml) and brine (1×15 ml), dried with Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography (hexane:ethyl acetate, 21:1) to give a colourless oil (1.1 g, 55%). Anal. calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97; found: C, 59.31; H, 8.82. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.95 (t, 3H), 1.35 (m, 7H), 1.7 (m, 2H), 2.45 (t, 2H), 4.35 (q, 2H), 5.5 (s, 1H); IR (neat): ν_{max} 3600–3150, 1735, 1700 cm^{-1}.

3.3. *Ethyl 2,3-dihydroxy-3-octanoates* ***4*** *and* ***5***

Baker's yeast (10 g), immobilised in calcium alginate,[12] was suspended in a phosphate–borate–citrate mixed buffer (500 ml, 0.05 M, pH 4) containing glucose (20 g) and stirred with magnetic bead at room temperature. After activation of the yeast for 2 h, the pH of the medium was adjusted with 10% ammonia and **3** (1 g in 10 ml ethanol) was added slowly over 10 h with stirring. The reactants were stirred for another 48 h with addition of glucose (4 g) every 6 h. The pH of the solution was measured every 15 min and readjusted. The reaction was followed by TLC and, after complete reduction, the beads were filtered and washed with chloroform. The reaction mixture was extracted with chloroform and the combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography (hexane:diethyl ether, 10:1) to obtain a mixture of diastereomers (700 mg, 70%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.9 (t, 3H), 1.2–1.6 (m, 11H), 2.6 (br s, 1H), 3.4 (br s, 1H), 3.8 (m, 1H), 4.15 (d, *J*=4.2 Hz, 1H), 4.3 (dq, 2H); IR (neat): ν_{max} 3340, 1715 cm^{-1}.

3.4. *Ethyl (2*R,*3*R*)-2,3-isopropylidenyloxyoctanoate* ***6***

To a stirred solution of **4** and **5** (0.4 g, 2 mmol) and camphorsulfonic acid (1 mg) in dichloromethane (10 ml) was added 2,2-dimethoxypropane (0.99 ml, 6 mmol). After stirring for 12 h at room temperature, aqueous sodium bicarbonate solution (5 ml) was added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2×20 ml). The combined organic layers were washed with brine (10 ml), dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography using hexane as an eluent to afford *anti*-**6** (0.364 g, 76%) and *syn*-**7** (0.062 g, 13%). Compound **6**: $[\alpha]_D^{25}$ +10.8 (*c* 1.0, $CHCl_3$). Anal. calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90; found: C, 63.48; H, 9.81. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.9 (t, 3H), 1.2–1.5 (m, 14H), 1.6 (s, 3H), 4.2 (m, 3H), 4.49 (d, *J*=7.5 Hz, 1H); IR (neat): ν_{max} 1745 cm^{-1}.

3.5. *Ethyl (2*S,*3*R*)-2,3-isopropylidenyloxyoctanoate* ***7***

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.9 (t, 3H), 1.28–1.49 (m, 14H), 1.75 (m, 3H), 4.12 (m, 2H), 4.26 (q, *J*=7.16 Hz, 2H); IR (neat): ν_{max} 1745 cm^{-1}.

3.6. Ethyl (2S,3R)-dihydroxy-3-octanoate **5**

$[\alpha]_D^{25}$ +10.0 (*c* 1.0, ethanol) {lit.[16] $[\alpha]_D^{23}$ +12.5 (*c* 1.01, ethanol, ee 99%)}. Anal. calcd for $C_{10}H_{20}O_4$: C, 58.8; H, 9.87; found: C, 58.41; H, 9.79. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.9 (t, 3H), 1.25–1.45 (m, 9H), 1.65 (m, 2H), 1.9 (br s, 2H), 3.8 (m, 1H), 4.15 (d, *J*=4.2 Hz, 1H), 4.3 (q, 2H); IR (neat): ν_{max} 3340, 1720 cm^{-1}.

3.7. Ethyl (4S,5R)-4,5-isopropylidenyloxy-2-decenoate **8**

To a solution of **6** (244 mg, 1 mmol) in dry toluene (5 ml) DIBAL-H (0.67 ml of 1.5 M solution in hexane, 1 mmol) was added under an N_2 atmosphere at −78°C with stirring. The reaction was followed by TLC. When the starting material had disappeared, carboethoxymethylene triphenylphosphorane (0.525 g, 1.5 mmol) in methanol (2 ml) was added carefully at −78°C. The reaction mixture was slowly brought to room temperature and refluxed for 6 h. The solvent was evaporated and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:20) to afford **8** as a colourless liquid (190 mg, 70%). $[\alpha]_D^{25}$ +17.2 (*c* 1.5, $CHCl_3$). Anal. calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69; found: C, 66.18; H, 9.61. IR (neat): ν_{max} 1695, 1630, 1200 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.9 (t, 3H), 1.25–1.4 (m, 14H), 1.5 (s, 3H), 4.2 (m, 3H), 4.6 (dt, 1H), 6.0 (dd, *J*=15.0, 1.0 Hz), 6.8 (dd, *J*=15.0, 4.0 Hz, 1H).

3.8. Ethyl (4S,5R)-4,5-isopropylidenyloxy-2-decanoate **9**

To a stirred solution of **8** (135 mg, 0.5 mmol) in ethanol (2.5 ml) was added 10% Pd–C (10 mg) under an H_2 atmosphere. The reaction mixture was stirred for 3 h at room temperature and the solvent was evaporated. The crude residue was purified by column chromatography (hexane:ethyl acetate, 25:1) to furnish **9** as a colourless liquid (122 mg, 90%). $[\alpha]_D^{25}$ +4.1 (*c* 1.0, $CHCl_3$). Anal. calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36; found: C, 66.10; H, 10.23. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.9 (t, 3H), 1.25–1.4 (m, 17H), 1.7 (m, 2H), 2.25–2.55 (m, 2H), 4.0 (m, 2H), 4.15 (q, 2H).

3.9. (4S,5R)-5-Hydroxy-γ-decalactone **1**

To a stirred solution of **9** (110 mg, 0.4 mmol) in methanol (10 ml) was added *p*-toluenesulfonic acid (5 mg). After stirring for 3 h at room temperature, aqueous sodium bicarbonate solution (5 ml) was added. The reaction mixture was extracted with ethyl acetate, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2×20 ml). The combined organic layers were washed with brine (10 ml), dried over Na_2SO_4 and dried under reduced pressure. The residue was purified by column chromatography (ethyl acetate:hexane, 1:20) as an eluent to afford **1** as a colourless oil (62 mg, 82%). $[\alpha]_D^{25}$ +9.5 (*c* 1.0, CCl_4) {lit.[7] $[\alpha]_D^{25}$ +11.0 (*c* 1.37, CCl_4)}. Anal. calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74; found: C, 64.29; H, 9.71. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.9 (t, 3H), 1.2–1.7 (m, 8H), 2.0–2.4 (m, 2H), 2.55 (m, 2H), 3.9 (m, 1H), 4.45 (m, 1H); IR (neat): ν_{max} 3440, 2980, 1770, 1465 cm^{-1}.

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15. Chiral HPLC conditions: Chiralcel OJ™, Daicel, Japan; 5×250 mm, λ=254 nm; 20% isopropanol in hexane; flow rate 0.3 ml/min; retention times: 2*R*,3*S*=15.1, 2*R*,3*R*=17.1; ee 80% {$[\alpha]_D^{25}$ 18.7 (*c* 1.0, CH_3OH)}.
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