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Enantioselective preparation of (*R*) and (*S*)-3-hydroxycyclopentanone by kinetic resolution

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ABSTRACT

A straightforward approach to enantiomerically enriched (*R*) and (*S*)-3-hydroxycyclopentanone is described. The key step involves a kinetic resolution of racemic 3-hydroxycyclopentanone using commercial *Pseudomonas cepacia* lipase immobilized on diatomite (Amano lipase PS-DI). The absolute stereochemistry of the product was determined by derivatization into (*R*)-3-(benzyloxy)-cyclopentanone.

1. Introduction

Cyclic and acyclic β-hydroxy ketones are important structural motifs in various biologically active organic compounds, as they provide two different functionalities in the same molecule ready for manipulation [1–3]. However, most β-hydroxy ketones are not commercially available. Indeed, many seemingly simple molecules have to be prepared via multi-step syntheses, in particular so if they are optically active. One such molecule is 3-hydroxycyclopentanone. At first glance it seems a quite straightforward molecule to chemists. However, in its simplicity it also lacks any handles for stereo- and regio-control during its synthesis and side reactions such as the intermolecular aldol reactions, and follow-up reactions (e.g. dehydration) [4,5] of the desired product can easily occur. In this reactivity the power of this building block is hidden, which can readily be converted into chiral diols [6,7], and amino alcohols [2,3,8]. Here a straightforward approach to this valuable building block for amongst others the Prostaglandins' is described [9,10]. Moreover 3-hydroxycyclopentanone is a valuable compound for the study of enantioselective Michael addition reactions of water [11–13].

To date, there are only two methods describing the preparation of enantiomerically enriched 3-hydroxycyclopentanone. In the chemical kinetic resolution of racemic 4-hydroxycyclopent-2-enone by BINAP-Ruthenium (II)-catalyzed hydrogenation *R*-enriched 3-hydroxycyclopentanone was obtained as a side product [14]. Due to the sensitivity of the desired product, the unconverted enantiomer of the starting material, (*R*)-3-hydroxycyclopentanone was not purified. In an enzymatic biohydroxylation it was first attempted to convert cyclopentanone into the 3-hydroxycyclopentanone but no reaction occurred. However, when the ketone was protected the hydroxylation proceeded. Nonetheless, enantioselectivity (40% *ee*) and yields after deprotection were modest [15].

Enzymatic kinetic resolutions are today recognized as a key tool for obtaining optically active compounds [16,17]. For secondary alcohols the outcome of the kinetic resolution is normally highly predictable and it follows Kazlauskas' rule [17–19]. It is however not straightforward to apply this rule to cyclic compounds [20] like the target molecule (Fig. 1). Therefore a full screening of a range of commercially available lipases and a subsequent characterization of absolute configuration and enantiomeric excess were performed.

It is interesting to note that a large number of substituted cyclopentanol derivatives have been subjected to kinetic resolutions. A general trend observed is that derivatives with large substituents are readily resolved [21–33], while simple compounds similar to our target molecule tend to give low *E* values [34–38].

2. Experimental

2.1. General information

Cyclopentane-1,3-diol, benzyl bromide, silver oxide, sodium dichromate, sulfuric acid, diethyl ether, acetone, ethanol, MTBE,

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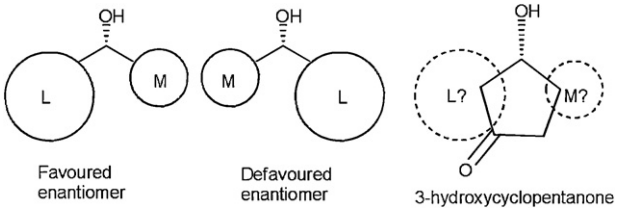

Fig. 1. Kazlauskas' rule for kinetic resolution of secondary alcohols.

and vinyl acetate were purchased from Sigma–Aldrich and Acros Organics. Various lipases namely, *Candida antarctica* B (CAL-B, Novozyme 435, Novo Nordisk A/S LC200015), *Candida antarctica* A (CAL-A, Chirazyme L5, Roche Diagnostics), *Candida rugosa* (CRL, Sigma L1754), *Pseudomonas fluorescens* (PFL, Fluka 62312), *Pseudomonas stutzeri* (Meito Sangyo Co. Ltd., Lot No. TH8901), *Alcaligenes* sp. (Meito Sangyo Co. Ltd., Lot No. B3102), *Pseudomonas cepacia* (PCL, Sigma 62309), Amano lipase PS-DI (*P. cepacia* immobilized on diatomite, Aldrich 534870), and *Porcine pancreatic* lipase (PPL, Sigma L3126) were purchased or obtained as a gift. Enzyme activity was determined according to the reported procedure [39]. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 400 (400 MHz and 100 MHz, respectively) instrument and were internally referenced to residual solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. Optical rotations were obtained with a Perkin-Elmer 241 polarimeter (sodium D line at 20 °C). Column chromatography was carried out with siliga gel (0.060–0.200 mm, pore diameter ca. 6 nm) and with mixtures of petroleum ether (PE) and ethyl acetate (EtOAc) as solvent. Thin-layer chromatography (TLC) was performed on 0.20 mm silica gel 60-F plates. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

2.2. Analytical methods

GC analysis of the conversion (%) of 3-hydroxycyclopentanone **2** were followed with a Shimadzu type GC 2014 equipped with a CP WAX 52 CB column (50 m × 0.53 mm × 2 μm) using N_2 as the carrier gas. The following conditions were used for the nonchiral separation: injector 250 °C, detector (FID) 270 °C, FID hydrogen 30 oxygen 300, column flow 20 mL/min, maximum temp: 255 °C, temperature program: start 165 °C, hold time 11 min, rate 30 °C/min to 250 °C hold time 1 min. The quantification of 3-oxocyclopentyl acetate and 3-hydroxycyclopentanone was done by using calibration curves with decane as an internal standard (7 standard samples marked 1, 2, 3, 4, 5, 6, 7; each sample contained 0.125 mmol/mL decane and 1 mmol/mL, 0.5 mmol/mL, 0.25 mmol/mL, 0.125 mmol/mL, 0.0625 mmol/mL, 0.03125 mmol/mL, 0.015625 mmol/mL 3-hydroxycyclopentanone in ethyl acetate, respectively). The retention times of 3-oxocyclopentyl acetate and 3-hydroxycyclopentanone were 6.63 and 8.78 min, respectively.

The enantiomeric excess (*ee*) of 3-oxocyclopentyl acetate **5** was determined with a Shimadzu type GC 2012 equipped with a chiradex GTA column (50 m × 0.25 mm × 0.12 μm) using Helium as the carrier gas. The following conditions were used for the chiral separation: injector 200 °C, detector 220 °C, split 60, FID hydrogen 30 oxygen 300, column flow: 0.49 mL/min, maximum temp: 175 °C, temperature program: start 150 °C, hold time 10 min, rate 25 °C/min to 170 °C hold time 1.20 min. The retention times of (*R*) and (*S*)-3-oxocyclopentyl acetate were 4.70 and 4.89 min, respectively.

The enantiomeric excess (*ee*) 3-hydroxycyclopentanone **7** was determined with a Shimadzu type GC 2012 equipped with a chiradex GTA column (50 m × 0.25 mm × 0.12 μm) using Helium as the carrier gas. The following conditions were used for the chiral separation: injector 200 °C, detector 220 °C, split 60, FID hydrogen 30 oxygen 300, column flow: 0.49 mL/min, maximum temp: 175 °C, temperature program: start 100 °C, hold time 40 min, rate 5 °C/min to 170 °C hold time 1.20 min. The retention times of (*R*) and (*S*)-3-oxocyclopentyl acetate were 45.19 and 45.52 min, respectively.

2.3. General procedures

2.3.1. Racemic 3-hydroxycyclopentanone (*2*)

In a round-bottom flask (100 mL) fitted with a mechanical stirrer, cyclopentane-1,3-diol **1** (3.52 g, 34.44 mmol) was dissolved in 40 mL of acetone. The solution was cooled in an ice bath, and a solution of $Na_2Cr_2O_7{\cdot}2H_2O$ (3.49 g, 11.72 mmol), concentrated H_2SO_4 (2 mL), and H_2O (14 mL) was added over 25 min. The green-blue solution was allowed to warm to room temperature over 15 min. The reaction mixture was filtered through Celite and the solid was washed with acetone, then the solvent was evaporated. The residue was purified by flash column chromatography (eluent: PE/EtOAc 1:2) to give **2** (2.36 g, 67%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.98–2.08 (m, 1H), 2.08–2.32 (m, 3H), 2.32–2.54 (m, 2H), 2.78 (s, 1H), 4.38–4.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.38, 35.40, 47.91, 69.72, 217.80.

2.3.2. Racemic 3-oxocyclopentyl acetate (*3*)

Acetic anhydride (2.0 mL, 60.00 mmol) was added to a solution of 3-hydroxycyclopentanone **2** (700 mg, 6.99 mmol) in pyridine (0.5 mL). The reaction mixture was stirred at room temperature for 12 h. Then the solvent was evaporated, and the residue was purified by chromatography on silica gel (eluent: EtOAc/PE 2:1) to give compound **3** (914 mg, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.99 (s, 3H), 2.28–2.42 (m, 5H), 2.54 (dd, J = 19.0, 6.0 Hz, 1H), 5.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.70, 28.73, 34.30, 44.12, 71.74, 169.85, 215.98.

2.3.3. Kinetic resolution of 3-hydroxycyclopentanone using different lipases

The screening of lipases for kinetic resolution was performed at 25 °C in 2 mL of freshly distilled vinyl acetate **4** containing 0.5 mmol of *rac*-3-hydroxycyclopentanone **2** and 450 (or 112.5) U lipase activity. After 4 h, 100 μL sample was taken from the reaction mixture and added 100 μL of internal standard solution (0.25 mmol/mL decane in ethyl acetate). Then the mixture was centrifuged to separate the lipase. All of the obtained samples were analyzed by GC to determine the conversion of substrate **2** and the *ee* of 3-oxocyclopentyl acetate **5**.

2.3.4. Kinetic resolution of 3-hydroxycyclopentanone using Amano lipase PS-DI

To a round-bottom flask (100 mL) was added *rac*-3-hydroxycyclopentanone **2** (700 mg, 7.00 mmol), freshly distilled vinyl acetate **4** (26 mL) and Amano lipase PS-DI (1568 U, 412 mg). The reaction mixture was stirred at 25 °C for 4 h. Then the lipase was filtered off and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 2:1) to give the enantiomerically enriched (*S*)-3-hydroxycyclopentanone **6** $[\alpha]_D^{20}$ −18.3 (*c* 0.50, CH_2Cl_2) and (*R*)-3-oxocyclopentyl acetate **5** $[\alpha]_D^{20}$ +46.4 (*c* 0.57, CH_2Cl_2) in 47% and 21% yield, respectively.

2.3.5. Ethanolysis of (R)-3-oxocyclopentyl acetate *5* using Candida antarctica lipase

To a round-bottom flask was added (*R*)-3-oxocyclopentyl acetate **5** (160 mg, 1.13 mmol), ethanol (1 mL), MTBE (1 mL) and