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Kinetic Resolution of (1RS,2SR)-2-(Hydroxymethyl)cyclopentanol by a Biocatalytic Transesterification Using Lipase PS

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Abstract: The kinetic resolution of *(1RS,2SR)*-2-(hydroxymethyl)cyclopentanol [*(1RS,2SR)*-**1**] by a sequential lipase-catalyzed transesterification with vinyl acetate in organic solvents in the presence of lipase from *Pseudomonas cepacia* (lipase PS) is described. The results are compared with data for the resolution of two structurally related 1,3-diols.

Introduction

Enantiomerically pure diols are of current interest as targets in organic synthesis. E.g., the title compound **1** can be used in enantiomerically pure form as a chiral auxiliary in asymmetric 1,4-additions[1] or as a precursor in the synthesis of bisphosphine ligands for chiral rhodium catalysts.[2] Optically active **1** has been prepared either by a lipase-catalyzed hydrolysis of racemic ethyl *trans*-2-acetoxycyclopentanecarboxylate[1] or by asymmetric reduction of prochiral ethyl 2-oxocyclopentanecarboxylate.[2] In both cases the asymmetric step was followed by a reduction with $LiAlH_4$ to give the corresponding diols.

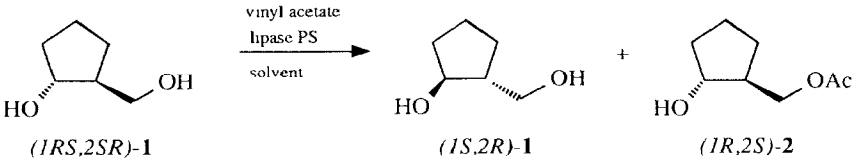
In this paper we wish to report on an alternative access to both enantiomers of **1**. In continuation of our work on asymmetrizations and resolutions of diols[3] we have chosen *(1RS,2SR)*-**1** as a substrate for a sequential lipase-catalyzed transesterification. The *trans*-diol *(1RS,2SR)*-**1** is available by reduction of ethyl 2-oxocyclopentanecarboxylate.[4,5] The sequential lipase-catalyzed transesterification has already been used for the resolution of a couple of 1,2-diols[3c,d] avoiding additional protection-deprotection steps.

Results and Discusssion

As expected, a first attempt to resolve *(1RS,2SR)*-**1** by monoacylation at the primary hydroxy group with vinyl acetate in the presence of lipase PS in THF/triethylamine (Scheme 1) gave only poor results (E = 2).[6]

Therefore, the sequential resolution procedure was applied to the diol *(1RS,2SR)*-**1**. In the first step of this sequence of two acylations *(1RS,2SR)*-**1** is converted regioselectively into the primary monoacetate *(1RS,2SR)*-**2** as an intermediate. At this stage an effective enantioselection is realized to

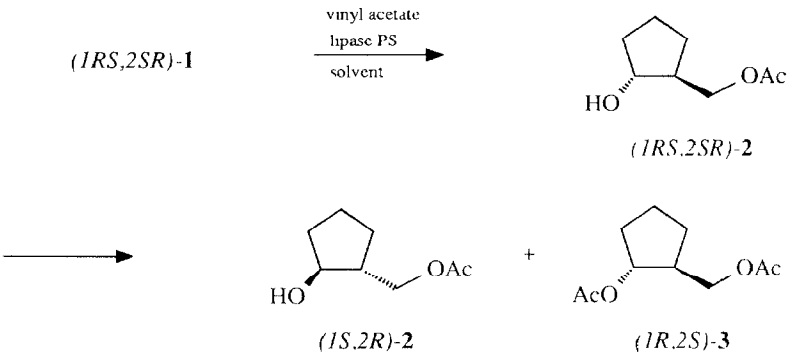
give the almost unaffected monoacetate *(1S,2R)*-**2** and the diacetate *(1R,2S)*-**3** (Scheme 2).



(1RS,2SR)-**1** *(1S,2R)*-**1** *(1R,2S)*-**2**

Scheme 1

The results using various organic solvents are summarized in Table 1. High E values have been calculated in most cases. The diols *(1R,2S)*-**1** and *(1S,2R)*-**1** were obtained by transesterification of *(1R,2S)*-**3** and *(1S,2R)*-**2**, respectively, with a basic ion exchange resin in methanol.



(1RS,2SR)-**1** *(1RS,2SR)*-**2**

(1S,2R)-**2** *(1R,2S)*-**3**

Scheme 2

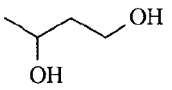
Table 1: Resolution of *(1RS,2SR)*-**1** by Sequential Transesterification

solvent	time (h)	monoacetate *(1S,2R)*-**2** yield (%)	ee (%)	diacetate *(1R,2S)*-**3** yield (%)	ee (%)	conversion	E
THF/NEt_3	100	47	82	49	83	0.50	27
THF	100	51	92	46	96	0.49	>100 (162)
Et_2O	72	48	>99	50	90	0.53	>100 (312)
t-BuOMe	72	41	>99	51	90	0.53	>100 (312)

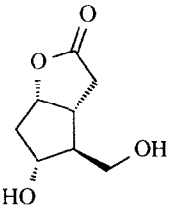
Compared with *(1RS,2SR)*-**1**, butane-1,3-diol [*(RS)*-**4**], as the simplest representative of the 1,3-diols, is an extremely poor substrate. With lipase PS no enantioselection at all was observed. In the

case of pancreatin as the biocatalyst, poor selectivity was observed in the monoacylation step (E = 3).[7] This result could be slightly improved (E = 5) by application of the sequential resolution procedure.

On the other hand, we recently found that the bicyclic 1,3-diol *(1SR,5RS,6SR,7RS)*-**5**, a prostaglandin intermediate, could be resolved efficiently (E = 69) by monoacylation at the primary hydroxy group with vinyl acetate in THF/triethylamine by lipase PS.[3a] Under the reaction conditions diacylation has not been observed.



(RS)-**4**



(1SR,5RS,6SR,7RS)-**5**

These results demonstrate, the bulkier the hydrophobic residue connected with the 1,3-diol system the higher the enantioselectivity of the transesterification in the presence of lipase PS either in the second or already in the first acylation step. According to the existing active site model for the lipase PS[8] a bulky hydrophobic residue fits with the hydrophobic pocket as one of the three interacting domains with the substrate. As a result an effective enantioselection is realized

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Experimental

General. The solvents were dried over sodium wire. All reactions were monitored by thin-layer chromatography on glass plates coated with a 0.25 mm layer of silica gel. Compounds were visualized with a 3.5% solution of molybdatophosphoric acid in ethanol. Flash chromatography was performed with silica gel 60 (0.063-0.040 mm). ^{1}H NMR spectra were recorded on a Bruker WP 200 SY spectrometer. ^{13}C NMR spectra were obtained on a Varian Gemini 300 spectrometer. The enantiomeric excess (ee) of the diols *(1R,2S)*-**1** and *(1S,2R)*-**1** was determined by GLC on Lipodex E (10 m) with hydrogen as carrier gas. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Resolution of *(1RS,2SR)*-1. A solution of *(1RS,2SR)*-**1** (1.32 g, 11.4 mmol) in diethyl ether (25 ml) was treated with vinyl acetate (6.10 g, 70 mmol) and lipase PS (0.50 g). This suspension was stirred at room temperature for 72 h and monitored by TLC. After filtration through Celite the filter cake was washed with diethyl ether (3 x 10 ml). The solvent was distilled off under reduced pressure, and the residue was separated by flash chromatography with hexane - ethyl acetate (3 1 → 1 : 1) yielding *(1S,2R)*-**2** (0 86 g, 48%) and *(1R,2S)*-**3** (1 14 g, 50%)

(1S,2R)-2-(Acetoxymethyl)cyclopentanol [*(1S,2R)*-**2**]: Colorless oil; b.p. 135°C (30 Pa, Kugelrohr); ee >99% (determined on the diol stage); ^{1}H NMR (200 MHz, $CDCl_3$): 1.26 (m, 1H, CH), 1.47-1.97 (m, 6H, cycl. CH_2), 2.00 (s, 3H, OAc), 2.40 (br s, 1H, OH), 3.90-4.07 (superimposed signals, 3H, CH_2OAc, CH-O); ^{13}C NMR (75 MHz, $CDCl_3$): 20.95, 21.82, 26.92, 34.41, 47.02, 66.43, 76.10, 171.38; calcd.: C 59.01, H 8.91 for $C_8H_{14}O_3 \times 0.25\ H_2O$, found: C 58.71, H 8.68.

(1R,2S)-1-Acetoxy-2-(acetoxymethyl)cyclopentane [*(1R,2S)*-**3**]: Colorless oil; b.p. 110°C (20 Pa, Kugelrohr); ee 90% (determined on the diol stage); ^{1}H NMR (200 MHz, $CDCl_3$): 1.29 (m, 1H, CH), 1.58-1.95 (m, 6H, cycl. CH_2), 1.96 (s, 3H, OAc), 1.99 (s, 3H, OAc), 3.97 (d, *J* 7 Hz, 2H, CH_2OAc), 4.88 (m, 1H, CH-O); ^{13}C NMR (75 MHz, $CDCl_3$): 20.89, 21.25, 22.89, 27.31, 32.14, 44.58, 65.49, 78.07, 170.74, 171.10; calcd.: C 59.98, H 8.05 for $C_{10}H_{16}O_4$, found: C 59.57, H 8.02.

A solution of *(1S,2R)*-**2** (0.86 g) in methanol (50 ml) was treated with the ion exchange resin *Wofatit SBW* (OH^-, 10 g) and stirred at room temperature for 24 h. The ion exchange resin was filtered off and the solvent was removed under reduced pressure yielding *(1S,2R)*-**1** (0.63 g). The same procedure with *(1R,2S)*-**3** (1.14 g) yielded *(1R,2S)*-**1** (0.65 g).

(1R,2S)-2-(Hydroxymethyl)cyclopentanol [*(1R,2S)*-**1**]: ee 90%; $[\alpha]_D^{20}$ −11.1 (*c* 1, $CHCl_3$), {ref. 1, $[\alpha]_D^{20}$ −13.7 (*c* 1, $CHCl_3$)}.

(1S,2R)-2-(Hydroxymethyl)cyclopentanol [*(1S,2R)*-**1**]: ee >99%; $[\alpha]_D^{20}$ + 13.4 (*c* 1, $CHCl_3$).

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5. The one-pot reduction according to ref. 4a was preferred to give a 4 : 1 mixture of the *trans*- and *cis*-2-(hydroxymethyl)cyclopentanol which could be separated by flash chromatography.
6. The *E* values were calculated according to: Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294-7299.
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