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Resolution of Diols with C_2-Symmetry by Lipase Catalysed Transesterification

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Abstract: S-Ethyl thiooctanoate was used as acyl donor in the transesterification of 2,3-butanediol (**1**), 2,4-pentanediol (**2**), and 2,5-hexanediol (**3**), catalysed by a lipase from *Candida antarctica*. Mixtures of all stereoisomers were used as substrates in each case. 2,5-Hexanediol was transesterified with high stereoselectivity and the (2*S*,5*S*)-2,5-hexanediol was isolated in good yield with >99 % ee. The diester of (2*R*,5*R*)-2,5-hexanediol was formed in good yield and was hydrolysed to yield the (2*R*,5*R*)-2,5-hexanediol of high enantiomeric excess (>99% ee). Similar results were obtained for 2,4-pentanediol with >99% ee for both enantiomers. The stereoselectivity for 2,3-butanediol was lower than for **2** and **3**, giving 89% ee for the *R*,*R*-enantiomer and 34% ee for the *S*,*S*-enantiomer.

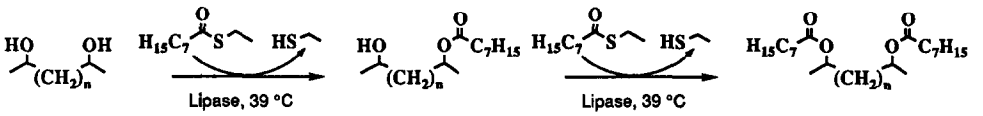
INTRODUCTION

Compounds with C_2-symmetry have been widely used in asymmetric synthesis as chiral auxiliaries and ligands.[1] They provide a high degree of stereochemical control, because of the reduction of the number of possible stereoisomers in the transition state. Ligands with C_2-symmetry have proven to be very useful in metal catalysed reactions. An excellent example is the Sharpless epoxidation,[2] which uses the C_2-symmetry of tartaric acid. Diols with C_2-symmetry are useful as chiral starting materials in asymmetric synthesis, as ligands and as chiral auxiliaries. Enzymatic resolution should be a promising approach for the preparation of diols with C_2-symmetry and such a proposal is supported by recent investigations.[3,6] We have recently developed a convenient method for the displacement of the equilibrium in lipase catalysed resolution of secondary alcohols.[4,5] In this communication we present a successful use of this method for the resolution of diols with C_2-symmetry.

RESULTS AND DISCUSSION

The transesterification of the diols was catalysed by lipase from *Candida antarctica* (component B), using 2 equivalents of S-ethyl thiooctanoate as acyl donor. No solvent was used. The general reaction pathway

is presented in Scheme 1. The diol is first converted into a monoester, which is then transformed into a diester in a second step.



1 n=0
2 n=1
3 n=2

Scheme 1.

With the use of two consecutive lipase-catalysed steps, the optical purity of the remaining diol as well as that of the produced diester might be enhanced. If there are large differences in the reaction rates between the *R*- and *S*-type alcohol moieties, the enantiomer with two highly reactive hydroxyl groups will be transesterified to the diester. The *R,S*-isomer with one fast- and one slow-reacting hydroxyl group will be transesterified to the monoester, and the enantiomer with two slow-reacting hydroxyl groups will remain unesterified. Starting with 2 mol of the acyl donor and 1 mol of the diol with the proportions 1:1:2 of the *R,R*-, *S,S*-, and *R,S*-isomers, respectively, the reaction will stop at 50% conversion of the acyl donor and 75% conversion of the diol, under optimal conditions.

We have investigated the transesterification of three homologous diols: 2,3-butanediol (**1**), 2,4-pentanediol (**2**) and 2,5-hexanediol (**3**). Mixtures of the *R,R*-, *S,S*-, and *R,S*-isomers were used in each case. After the transesterification reactions, the products were separated by column chromatography and the esters were hydrolysed to the corresponding diols. In all cases the *R,R*-enantiomers reacted faster in the transesterification than the *S,S*-enantiomers, in accordance with the transesterification of related secondary alcohols[4,5]. The results are given in Table 1.

Table 1. Compositions of Substrates and Hydrolysed Products.

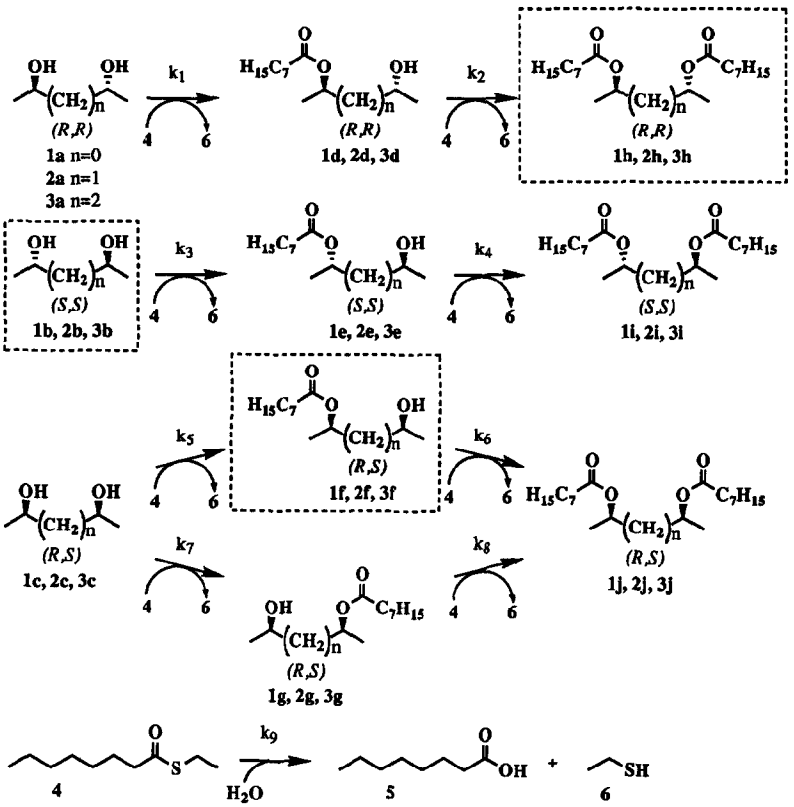
	Substrate Composition			Con-version[a]	Products														
					Remaining Alcohol					Monoester					Diester				
	SS	*RS*	*RR*		*SS*	*RS*	*RR*	ee[b]	yield[c]	*SS*	*RS*	*RR*	de[d]	yield[e]	*SS*	*RS*	*RR*	ee[b]	yield[f]
1[g]	17	61	22	70	36	46	18	~34	91	20	71	9	~41	88	5	19	76	~89	73
2	23	53	24	47	96.7	2.9	<0.1	>99	92	1.0	75.5	23.5	51	80	~0	23.5	76.5	>99	69
3	22	57	21	50	98.7	1.3	~0	>99	86	0.8	98.5	0.7	97	71	~0	1.1	98.9	>99	78

All numbers given in percent (%). a: *conversion* of the acyl donor. b: The enantiomeric excess was calculated as *ee*=abs[(*RR*-*SS*)/(*RR*+*SS*)]. c: *yield* of *S,S*-diol in relation to the *S,S*-diol present in the starting material. d: The diastereomeric excess was calculated as *de*=abs[(*RS*-(*RR*+*SS*))/(*RS*+*RR*+*SS*)]. e: *yield* of *R,S*-monoester in relation to the *R,S*-diol present in the starting material. The *yield* was calculated after hydrolysis to the corresponding diol. f: *yield* of *R,R*-diester in relation to the *R,R*-diol present in the starting material. The *yield* was calculated after hydrolysis to the corresponding diol. g: The gas chromatographic resolution was unsatisfactory for an exact determination of the proportions of the three isomers of 2,3-butanediol.

In the transesterification of **3**, both the *S,S*-enantiomer of the diol and the *R,R*-enantiomer of the

diester were obtained in high enantiomeric excess. Moreover, only small amounts of the *R*,*S*-meso isomer were present in the diester and the remaining diol fractions. The *S*,*S*- and *R*,*R*-enantiomers of **2** were obtained in high enantiomeric excess, although the *R*,*R*-enantiomer was contaminated with the *R*,*S*-meso isomer in a ratio of 3:1. The stereoselectivity of the lipase in the reaction of **1** was lower than that in the reactions of **2** and **3**, but the *R*,*R*-enantiomer was obtained in acceptable enantiomeric excess with contamination by the *R*,*S*-meso isomer in a ratio of 4:1.

Scheme 2 shows the reaction pathways for the transesterifications of the three isomers of **1**, **2**, and **3** and the competing hydrolysis of the acyl donor. The transesterifications were considered to be irreversible due to the effective displacement of the equilibrium at each reaction step through the removal of ethanethiol.[5] Guo *et al.*[6] have described a lipase catalysed resolution of the enantiomeric pair of 2,4-pentanediol. They found that the step from monoester to diester of the fast-reacting isomer had a reaction rate of the same magnitude as the step from diol to monoester for the slow-reacting isomer. Thus the optical purity was enhanced only to a small extent in their experiment. We found that with the lipase from *Candida antarctica* the slow-reacting isomer of 2,4-pentanediol, **2b**, was almost totally unreactive (see Table 1).



Transesterification of 2,3-butanediol (**1**), 2,4-pentanediol (**2**) and 2,5-hexanediol (**3**) with S-ethyl thiooctanoate. Dashed boxes indicate the main isolated compounds of the (2*R*,5*R*)- and (2*S*,5*S*)-2,5-hexanediol types and the suggested main isolated product of (2*R*,5*S*)-2,5-hexanediol.

Scheme 2.

The result of the transesterification of 2,5-hexanediol (3) (Table 1) shows for the rate constants, that $k_1 >> k_3$ and $k_2 >> k_3$. In other terms, the *R*-moiety of 2,5-hexanediol (3) reacted much faster than the *S*-moiety both in the first and in the second acylation step. The ratio between the yields of the monoesters **3f** and **3g** was not explicitly investigated, but since **3b** did not react and **3a** was converted into the diester **3h**, it could be assumed that **3c** reacted to form more or less exclusively the monoester **3f**. Only small amounts of the *R,S*-diester **3j** were found.

2,4-Pentanediol (2) reacted almost like 2,5-hexanediol (3) but with one important difference. A significant formation of the *R,S*-diester **2j** took place and the diastereomeric excess (53%) of the *R,R*-diester **2h** was low. Still, there was almost no formation of the *S,S*-monoester **2e** or the *S,S*-diester **2i**. A possible explanation of the formation of the *R,S*-diester **2j** could be a change in stereoselectivity caused by an additional interaction between the enzyme and the second functional group of the substrate. Alternatively, an intramolecular acyl migration might occur in the monoesters. As regards the *R,S*-monoester, the more reactive hydroxyl group would be regenerated if the acyl group would migrate from the *R*- to the *S*-moiety and the fast-reacting *R*-moiety would be transesterified again to yield the diester **2j**. A similar acyl migration in the *R,R*- and *S,S*-monoesters would, on the other hand, provide the identical compounds.

The result of the reaction of 2,3-butanediol (1) is difficult to discuss due to poor resolution of the isomers in the determination of their proportions. However, the results indicate that the enantiomeric excess was acceptable for the *R,R*-enantiomer and poor for the *S,S*-enantiomer.

In the transesterifications of **2** and **3** the hydrolysis of the acyl donor (k_9), which was easily monitored, was predominant in the end of the incubations. The reactions were stopped at this point by removing the enzyme. The fact that water present in the system was a better nucleophile than the hydroxyl group attached to a carbon atom with *S* configuration, was a useful indication that an optimal conversion had been reached. In the transesterification of **1**, the hydrolysis of the acyl donor never became the predominant reaction.

The results presented in this communication show that the *Candida antarctica* lipase catalysed transesterification with S-ethyl thiooctanoate is a promising method for the resolution of diols with C_2-symmetry.

EXPERIMENTAL

Enzyme. The lipase (component B) derived from *Candida antarctica* is a product from Novo-Nordisk A/S. The enzyme was used as an immobilized preparation on a macroporous polypropylic resin, containing approximately 1% enzyme w/w. The catalytic activity was approximately 20000 LU/g.

Gas Chromatography. Capillary GC was performed on Carlo Erba Fractovap 2150 and Perkin Elmer 8500 instruments. The conversion of the acyl donor and the diol was measured on a Chrompack CP-SIL™ 19CB column. Enantiomeric excesses were determined either on an Astec Chiraldex™ G-TA column, after derivatisation with trifluoroacetic anhydride, or direct on a J & W Cyclodex™ B column.

Absolute configuration. The absolute configurations were determined by comparisons of the optical rotations of the diols with data given in the literature.

Product ester hydrolysis, general procedure. The ester was dissolved in MeOH (20 ml) and after addition of KOH (0.5 g) the reaction mixture was stirred overnight. Formic acid (1 ml) was then added, the solvent was evaporated, EtOAc (50 ml) was added, and the solid material was collected on a filter and

washed with EtOAc. The product was purified by column chromatography.

S-Ethyl thiooctanoate (4). Ethanethiol (49.7 g, 0.80 mol) and pyridine (77.6 ml, 0.96 mol) were dissolved in dry diethyl ether (295 ml) and the solution was cooled to 0 °C. Octanoyl chloride (65.1 g, 0.40 mol) was dissolved in dry diethyl ether (95 ml) and added drop-wise to the ethanethiol solution. The temperature was allowed to rise to room temperature. After 24 hours the reaction was completed. The reaction mixture was washed twice with water and dried over $MgSO_4$, followed by distillation, bp 65 °C, yield 75 g. After flash chromatography on silica gel 60 (Merck; hexane/EtOAc, 90:10, v/v) 74.4 g of pure product (4) (GC 99.5 %) was isolated (99 %). ^{1}H-NMR ($CDCL_3$): 0.88 (t, 3H), 1.21-1.4 (m, 8H), 1.25 (t, 3H), 1.59-1.68 (m, 2H), 2.49-2.55 (t, 2H), 2.72-2.91 (m, 2H).

2,3-Butanediol (1). 2,3-Butanedione (2.00 g, 23 mmol) was dissolved in 50 ml methanol. $NaBH_4$ (2.00 g, 52 mmol) was slowly added to the solution at a temperature not exceeding 50 °C. After the addition, the temperature was kept at 40-50 °C for 2 hours. The excess of $NaBH_4$ was then destroyed by adding NH_4Cl (1g). After evaporation of the solvent 50 ml of EtOAc was added. The mixture was filtered and purified using column chromatography, yielding 1.8 g (86 %) of **1**. ^{1}H-NMR ($CDCL_3$): 1.1-1.2 (m, 6H), 2.0-2.8 (b, 2H), 3.5 (m, 0.86H, dl), 3.8 (m, 1.14H, meso).

(2*R*,3*R*)-2,3-Butanediol (1a), (2*S*,3*S*)-2,3-butanediol (1b) and (2*R*,3*S*)-2,3-butanediol (1c). 2,3-Butanediol (363 mg, 4.03 mmol; 22% *RR*, 17% *SS*, 61% *RS*) and S-ethyl thiooctanoate (1515 mg, 8.05 mmol) were mixed. The reaction was started by addition of 50 mg of the lipase preparation. The reaction was carried out at 39 °C with magnetic stirring in an open flask to allow the evaporation of ethanethiol. After 22 h the enzyme was removed by filtration and the reaction products were separated using column chromatography. The remaining diol was isolated yielding 55 mg (91%) of **1b** (34% ee, 8% de). The monoester was hydrolysed and purified using column chromatography, yielding 197 mg (88%) of **1c** (41% de), and the diester was also hydrolysed and purified by column chromatography, yielding 58 mg (73%) of **1a** (89% ee, 61% de).

(2*R*,4*R*)-2,4-Pentanediol (2a), (2*S*,4*S*)-2,4-pentanediol (2b) and (2*R*,4*S*)-2,4-pentanediol (2c). 2,4-Pentanediol (426 mg, 4.09 mmol; 24% *RR*, 23% *SS*, 53% *RS*) and S-ethyl thiooctanoate (1537 mg, 8.16 mmol) were mixed. The reaction was started by addition of 50 mg of the lipase preparation. The reaction was carried out at 39 °C with magnetic stirring in an open flask, allowing the ethanethiol to evaporate. After 3.5 h the hydrolysis of the S-ethyl thiooctanoate became the predominant reaction and the enzyme was removed by filtration. The products were separated using column chromatography. The remaining diol was isolated yielding 92 mg (92%) of **2b** (>99% ee, 94% de). The monoester was hydrolysed and purified using column chromatography, yielding 180 mg (80%) of **2c** (51% de). The diester was also hydrolysed and purified through column chromatography, yielding 71 mg (69%) of **2a** (>99% ee, 53% de).

(2*R*,5*R*)-2,5-Hexanediol (3a), (2*S*,5*S*)-2,5-hexanediol (3b) and (2*R*,5*S*)-2,5-hexanediol (3c). 2,5-Hexanediol (475 mg, 4.02 mmol; 21% *RR*, 22% *SS*, 57% *RS*) and S-ethyl thiooctanoate (1514 mg, 8.04 mmol) were mixed. The reaction was started by addition of 50 mg of the lipase preparation and carried out at 39 °C with magnetic stirring in an open flask, allowing evaporation of the ethanethiol. After 4.5 h the hydrolysis of the S-ethyl thiooctanoate became the predominant reaction and the enzyme was removed by filtration. The products were separated using column chromatography. The remaining diol was isolated, yielding 91 mg (86%) of **3b** (>99% ee, 97% de), the monoester was hydrolysed and

purified by means of column chromatography, yielding 192 mg (71%) of **3c** (97% de) and the diester was hydrolysed and purified using column chromatography, yielding 76 mg (78%) of **3a** (>99% ee, 98% de).

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