Enzymatic Preparation of Enantiomerically Pure and Selectively Protected 1,2- and 1,3-Diols

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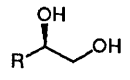
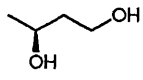
The optically pure, selectively protected 1,2- and 1,3-diol derivatives (*R*)- and (*S*)-**1–8** have been prepared by enzymatic hydrolysis of their racemic acetates and chloroacetates in the presence of ester hydrolase from *Pseudomonas fluorescens* (SAM-1).

Enantiomerically pure C_3- and C_4-building blocks with the 1,2- or 1,3-diol substructure, *e.g.* compounds *A* and *B* are valuable intermediates for the synthesis of various biologically active compounds and natural products.[1] They are usually prepared with considerable effort *via* (*a*) classical resolution or (*b*) chiral pool synthesis. Their application in organic synthesis is frequently complicated by the fact that these molecules contain structurally heterotopic functionalities, *i.e.* secondary and primary hydroxy groups. In an attempt to solve problems of both preparation and practicability simultaneously, we looked for facile routes to these molecules in enantiomerically pure and synthetically useful form.

Ester hydrolases are well known for their enantiomer differentiation capability and enantioselective ester hydrolysis or synthesis could, in principle, provide alternative routes to the above target molecules. However, owing to the small



1,2-Diol
(*A*)



1,3-Diol
(*B*)

R = Me, Et, CH_2Cl
$CH{=}CH_2$, $CH_2OCH{=}CH_2$

differences in steric bulk enzymatic resolutions of small molecules of this kind with aliphatic C_3-or C_4-skeletons have been largely unsuccessful in the past.[2]

In an earlier study, leading to a working model for the active site of a lipase from *Pseudomonas sp.*, we found that sterically demanding aromatic substituents were required in order to induce the desired high degree of stereodifferentiation.[3] If steric factors alone were responsible for that we would predict that sterically demanding protecting groups would serve equally well for that purpose. From a synthetic point of view trialkylsilyl ethers such as *tert*-butyldimethylsilyl or thexyldimethylsilyl (thexyl = 1,1,2-trimethylpropyl) groups are extremely useful because molecules protected with these groups display high stabilities towards hydrolysis and during chromatographic separations.

On this basis enantioselective ester hydrolysis or synthesis of selectively protected 1,2- and 1,3-diol derivatives like (±)-**1–8** would provide an excellent route to these target molecules in enantiomerically pure and synthetically useful form. Compounds (±)-**1–8** were prepared conveniently by silylation of the corresponding, racemic diols. Minor amounts of disilyl derivatives and traces of undesired regioisomers were easily removed by flash chromatography. Esterification of (±)-**1–8** with C_3H_7COCl or $(ClCH_2CO)_2O$ and pyridine led in excellent yields to the corresponding butyrates (±)-**1a–3a** and chloroacetates (±)-**4b–8b**, respectively. The enzymatic hydrolysis of the racemic esters (±)-**1a–3a** and (±)-**4b–8b** was carried out under controlled pH conditions in phosphate buffer (pH 7) in the presence of a lipase from *Pseudomonas fluorescens* (SAM 1) as described earlier[4] (eqn. 1). All

$$(\pm)\text{-ROAcyl} \longrightarrow (R)\text{-ROH} + (S)\text{-ROAcyl} \quad (1)$$

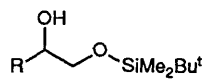
(±)-**1a–3a** (*R*)-**1–8** (*S*)-**1a–3a**
(±)-**4b–8b** (*S*)-**4b–8b**

a; Acyl = C_3H_7CO
b; Acyl = $ClCH_2CO$

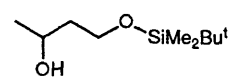
Conditions: Lipase, phosphate buffer, pH 7

reactions were terminated after the desired or possible conversions had been reached and the products isolated by extraction with CH_2Cl_2, followed by distillation or chromatography on silica gel. The absolute configurations of the products were determined after their transformation (MeOH–HCl) into the corresponding, known diols by comparison of optical rotations. The enantiomeric purities of (*R*)-**1–8** were determined by 400 MHz ^1H NMR spectroscopy of the corresponding 'Mosher' methoxy(trifluoromethyl)phenylacetyl (MTPA) esters.[5] (*S*)-**1a–3a** and (*S*)-**4b–8b** were first converted into the diols; their enantiomeric purities were determined *via* HPLC analysis of the corresponding di-MTPA esters.

As is obvious from Table 1 high enantioselectivities were observed in all transformations. While in most cases optically pure products of both enantiomeric series were obtained, for two different reasons only one pure enantiomer resulted from the transformation of (±)-**5b** and (±)-**6b**. The enantioselective hydrolysis of (±)-**5b** was too slow for all practical purposes and a conversion of only 35% could be achieved in a reasonable time. Thus, for kinetic reasons and in spite of the



1 R = Me
2 R = Et
3 R = CH_2Cl
4 R = $CH{=}CH_2$
5 R = $CH_2OCH{=}CH_2$



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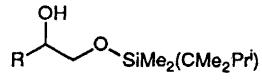

7 R = CH=CH

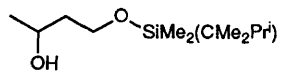

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Table 1 Enzymatic hydrolysis of (±)-**1a–3a** and (±)-**4b–8b** with a lipase from *P. fluorescens* (SAM-1)[6]

	t(25%)/h[a]	Conversion (%)	Product	E.e. (%)[b]	E[c]
(±)-**1a**	9	50	(*R*)-**1**	>95	>100
			(*S*)-**1a**	>95	
(±)-**2a**	10	50	(*R*)-**2**	>95	>100
			(*S*)-**2a**	>95	
(±)-**3a**	10	50	(*R*)-**3**	>95	>100
			(*S*)-**3a**	>95	
(±)-**4b**	1	49	(*R*)-**4**	>95	>100
			(*S*)-**4b**	91	
(±)-**5b**	14	35	(*R*)-**5**	>95	99
			(*S*)-**5b**	51	
(±)-**6b**	2	52	(*R*)-**6**	89	72
			(*S*)-**6b**	>95	
(±)-**7b**	2	50	(*R*)-**7**	>95	>100
			(*S*)-**7b**	>95	
(±)-**8b**	3	50	(*R*)-**8**	>95	>100
			(*S*)-**8b**	>95	

[a] Time required for 25% conversion under standard conditions (10 mmol substrate, 200 mg enzyme, 20 ml 0.1 mol dm^{-3} phosphate buffer, pH 7). [b] Enantiomeric excess. [c] For definition of E see ref. 7.

Table 2 Enzymatic esterification of (±)-**6** and (±)-**8** with a lipase from *P. fluorescens* (SAM-1) as biocatalyst

	t(25%)/h	Conversion (%)	Product	E.e. (%)	E
(±)-**6**	58	50	(*S*)-**6**	93	94
			(*R*)-**6a**	93	
(±)-**8**	31	50	(*S*)-**8**	>95	>100
			(*R*)-**8a**	>95	

relatively high selectivity factor (E 99) only (*R*)-**5** was obtained optically pure. The selectivity factor (E 72) determined in the hydrolysis of (±)-**6b** does not allow the isolation of both enantiomers in optically pure form, and only by increasing the conversion to 52% could (*S*)-**6b** be obtained optically pure at the expense of a lower enantiomeric purity for (*R*)-**6**. Obviously the steric bulk in (±)-**6b** is not large enough in order to achieve a higher degree of selectivity. In a nice demonstration of the importance of this effect we were able to show that the increase in steric bulk in going from (±)-**6b** to (±)-**8b** resulted in a considerable increase of enantioselectivity allowing both enantiomeric products (*R*)-**8** and (*S*)-**8b** to be obtained in optically pure form. In order to study

the validity of this effect under different conditions we also looked at the enantioselective esterification of (±)-**6** and (±)-**8** under the conditions of irreversible acyl transfer (eqn. 2). Clearly, as also obvious from Table 2 the increase in steric bulk in (±)-**8** leads to high enantioselectivities both in enzymatic hydrolysis and synthesis as compared to (±)-**6**.

$$(\pm)\text{-ROH} \longrightarrow (S)\text{-ROH} + (R)\text{-ROAc} \qquad (2)$$

(±)-**6,8** (*S*)-**6,8** (*R*)-**6a**, **8a**

a = acetate

Conditions: Lipase, vinyl acetate, Bu^{t}OMe

By application of simple steric arguments compounds unsuitable for selective enzymatic transformations can be transformed into excellent substrates for these reactions allowing their transformation into valuable and synthetically useful enantiomers. It is our feeling therefore that the results presented in this paper further enhance the synthetic usefulness of ester hydrolases. The enantiomerically pure compounds resulting from the above transformations are useful building blocks for numerous synthetic applications. Thus the silyl ether moiety in (*R*)-**1**–**8** can be converted easily into other acyl derivatives: alkyl bromides, carboxylic acids[8] and chiral epoxides.[9]

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