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Kinetic Resolution of Aliphatic 1,2-Diols by a Lipase-Catalyzed Sequential Acetylation[1]

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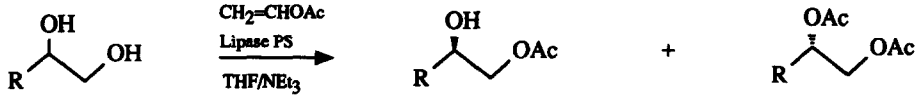
Abstract: The kinetic resolution of 13 racemic aliphatic 1,2-diols (*rac*-**1a-m**) by means of a lipase-catalyzed sequential acetylation was investigated. The enantioselectivity of the 3-aryloxy-propane-1,2-diols *rac*-**1a-k** depends on the substitution pattern at the aryl ring.

Homochiral 1,2-diols are of increasing interest as synthetic intermediates for different classes of substances.[2] Thus, these compounds play an important role as target molecules in asymmetric synthesis with enzymes as chiral catalysts. It is known that lipases catalyze the regioselective acylation of aliphatic 1,2-diols at the primary hydroxy group[3] with low enantioselectivity.[4] To overcome this problem it is necessary to protect the primary hydroxy group with a bulky group.[5]

3-Aryloxy-propane-1,2-diols are building blocks for ß-blockers.[6] Derived[7] and related[8] compounds are used as substrates in bioconversions. The increasing number of papers in this field prompted us to publish our recent results in a preliminary manner.

It was our aim to use diols, which do not require a manipulation at the primary hydroxy group, as substrates in a lipase-catalyzed sequential acetylation.[9] We could demonstrate the amplification of the enantioselectivity by application of this concept in the case of racemic *Mephenesin*^{R} (*rac*-**1b**) as substrate.[4b] This reaction showed a moderate enantioselectivity (E = 27).[10] In order to obtain information about the influence of the side chain of these diols on the enantioselectivity of the lipase-catalyzed sequential acetylation, the 2-methylphenoxy residue was replaced by other substituted aryloxy groups and by one alkyl, as well as one aryl substituent in the 2-position of the diol (Scheme 1).



***rac*-1a - m** **(R)-2a - m** **(S)-3a - m**

Scheme 1

These lipase-catalyzed transesterifications were carried out as previously described.[4b] The results of the kinetic resolutions are summarized in Table 1. In the presence of lipase *Amano PS*, the (S)-enantiomers of **1a-k** are converted at a lower rate into the primary (R)-monoacetates **2a-k**. The corresponding (R)-enantiomers of **1a-k** are converted at a higher rate into the (S)-diacetates **3a-k**. In general, the derivatives with substituents in the 4-position of the aromatic ring show significantly higher enantioselectivities than those with substituents in the 2-position. Such a clear relationship could not be observed for the compounds substituted in the 3-position of the aromatic ring. Furthermore, a substituent in the 4-position seems to be a

prerequisite for a high enantioselectivity of the resolution procedure (Table 1). The observed selectivities correspond with Kazlauskas' rule.[11]

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Table 1: Kinetic Resolution of the Diols *rac*-**1a - m**

Substrate	R	e.e. of (R)-2 (%)	e.e. of (S)-3 (%)	Conv.	E
1a	Ph-OCH_2	85	79	0.52	23
1b	2-Me-C_6H_4-OCH_2	93	80	0.54	27
1c	3-Me-C_6H_4-OCH_2	66	87	0.43	28
1d	4-Me-C_6H_4-OCH_2	66	93	0.42	55
1e	2-OMe-C_6H_4-OCH_2	63	87	0.42	27
1f	3-OMe-C_6H_4-OCH_2	91	95	0.49	>100
1g	4-OMe-C_6H_4-OCH_2	96	94	0.51	>100
1h	2-Cl-C_6H_4-OCH_2	55	88	0.38	27
1i	3-Cl-C_6H_4-OCH_2	86	92	0.48	67
1j	4-Cl-C_6H_4-OCH_2	94	92	0.50	85
1k	1-naphthyl-OCH_2	42	78	0.35	12
1l	Ph	66	93	0.42	55
1m[a]	Et	49[b]	94[c]	0.34	53

[a] Pancreatin was used as lipase. [b] It corresponds to (S)-2. [c] It corresponds to (R)-3.

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