Enzymatic Preparation of Optically Pure *trans*-1,2-Cycloalkanediols

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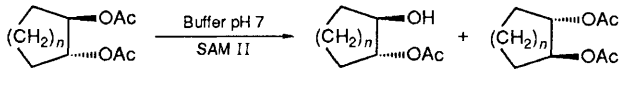
trans-1,2-Cycloalkanediols (*R,R*)-**1–4** and (*S,S*)-**1–3** of high optical purities are prepared by enzymatic hydrolysis and esterification catalysed by a lipase from *Pseudomonas sp.* (SAM II).

Enantiomerically pure (*R,R*)- and (*S,S*)-1,2-cycloalkanediols such as **1–4** are of considerable interest for many applications, *e.g.* the synthesis of optically active crown ethers[1] or as auxiliaries for the preparation of bidentate ligands. Organometallic catalysts using chiral ligands of that type have previously been successfully applied in asymmetric synthesis.[2,3]

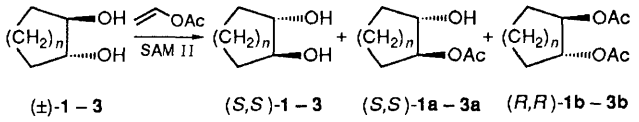
Esterhydrolases (esterases, lipases) are well known for their ability to differentiate between enantiomeric alcohols and esters. We recently described the use of a lipase from *Pseudomonas sp.*,[4] which proved to be suitable for the preparation of secondary alcohols,[5] including cyclohexanols[6a,b] and tetrahydrofuranols.[7] We expected this enzyme to be the reagent of choice for the preparation of the enantiomeric title compounds both by enzymatic hydrolysis (Scheme 1) or synthesis of their esters (Scheme 2).

It has been reported previously[8] that the racemic diacetates (±)-**1b–3b** can be partially resolved by incubation in the presence of a different *Pseudomonas* lipase leading to the optically pure monoacetates (*R,R*)-**1a–3a**. However, all experiments were terminated prior to 50% completion resulting in the formation of only one enantiomer of high optical purity. Moreover, using incubation techniques, only small quantities (*e.g.* 100 mg) of the desired compounds can be obtained this way. We have, therefore, studied the enzymatic resolution of these compounds on a preparative scale, both by enzymatic hydrolysis and esterification under systematic variation of the ring size.



(±)-**1b – 4b** $n = 1 - 4$ (*R,R*)-**1a – 4a** (*S,S*)-**1b – 4b**

Scheme 1



(±)-**1 – 3** $n = 1 - 3$ (*S,S*)-**1 – 3** (*S,S*)-**1a – 3a** (*R,R*)-**1b – 3b**

Scheme 2

Table 1 Enzymatic hydrolysis of (±)-**1b–4b**[a]

Substrate	*n*	*t*/h	Conversion (%)	Products	Yield(%)	E.e.(%)	*E*[c]
(±)-**1b**[d]	1	3.8	23.8	(1*R*,2*R*)-**1a**	41	97	
				(1*S*,2*S*)-**1b**	50	88	≥100
		5.4	27.8	(1*R*,2*R*)-**1a**	41	92	
				(1*S*,2*S*)-**1b**	47	≥98	
(±)-**2b**[e]	2	22	25	(1*R*,2*R*)-**2a**	36	96	≥100
				(1*S*,2*S*)-**2b**	32	97	
(±)-**3b**	3	49	21	(1*R*,2*R*)-**3a**	39	≥95	82
				(1*S*,2*S*)-**3b**	57	70	
(±)-**4b**	4	60	12	(1*R*,2*R*)-**4a**	16	≥95	53
				(1*S*,2*S*)-**4b**	57	31	

[a] Conditions: see text. [b] Absolute configurations were assigned after conversion into the known diols, optical purities were determined by: monoacetates **1a–4a**: ^{1}H NMR (250 MHz) of their 'Mosher' esters; diacetates **1b–4b**: ^{1}H NMR (250 MHz) in the presence of Eu(tfc)$_3$ as a chiral shift reagent. [c] For definition of *E* see Ref. 9. [d] See Ref. 6*c*. [e] See Ref. 6*a*.

Table 2 Enzymatic esterification of *trans*-cycloalkandiols (±)-**1–3**[a]

Substrate	*n*	*t*/days	Products	Yield(%)	E.e.(%)[b]
			traces-**1**	not isolated	
(±)-**1**	1	7	(1*S*,2*S*)-**1a**	42	≥95
			(1*R*,2*R*)-**1b**	44	≥98
			(1*S*,2*S*)-**2**	31	83
(±)-**2**	2	10	(1*S*,2*S*)-**2a**	16	66
			(1*R*,2*R*)-**2b**	39	≥98
			(1*S*,2*S*)-**3**	24	≥95
(±)-**3**	3	14	(1*S*,2*S*)-**3a**	20	70
			(1*R*,2*R*)-**3b**	42	≥98

[a] For conditions see text. [b] Optical purities of the alcohol **2**, **3**: ^{1}H NMR (250 MHz) of their 'Mosher' esters; for mono- and di-acetates see footnote *b* in Table 1.

In a series of experiments the racemic diacetates (10 mmol) (±)-**1b–4b** were hydrolysed in the previously described way (pH stat. method[5]) using phosphate buffer pH 7.0 (20 ml) and the lipase[4] (200 mg, 6600 U, standard tributyrin). All reactions slowed down considerably after *ca.* 25% conversion (*i.e.* hydrolysis of one ester group of one enantiomer); this is to be expected for a highly selective enantiomeric differentiation ($E \geq 50$) and supported by the high enantiomeric purities of the products.

Table 1 shows that with increasing ring size both the rates of transformation and the selectivities decrease. Also, the achievable enantiomeric purities are strongly conversion dependent; exact termination of the reactions is required for optimized optical purities of a particular enantiomer. A good example of this effect is the resolution of (±)-**1b** (Table 1). With only a small variation in the conversion both (*R,R*)-**1a** or (*S,S*)-**1b** can be obtained in near enantiomeric purity. In all cases the selectivity factors *E* are high enough to allow in principle the preparation of both enantiomers with high optical purities. However, in view of the low reaction rates the preparation of (*S,S*)-**3b**, **4b** in optically pure form seems impractical by this method because of the required long reaction times.

As pointed out earlier[10] enzymatic esterifications are stereochemically complementary to enzymatic hydrolyses and should result in opposite pairs of enantiomers. In view of the experimental simplicity, enantioselective enzymatic esterifaction by irreversible acyl transfer using vinylacetate as the acyl donor[11] has proved to be the most convenient route to enantiomerically pure alcohols and esters of that kind.

In typical experiments the racemic diols (±)-**1–4** (10 mmol) were dissolved in a mixture of t-butyl methyl ether (20 ml) and vinyl acetate (20 mmol). After addition of the lipase[4] (200 mg) the mixtures were stirred at room temperature until *ca.* 50% of diacetates were produced as determinated by GC. Under the conditions employed the esterification of *trans*-1,2-cyclooctanediol (±)-**4** was too slow to be of synthetic value and no attempt was, therefore, made to isolate the small quantities of products. In all other cases the enzyme was simply filtered off and the crude products were separated by column chromatography on silica gel.

Table 2 shows that all diacetates (*R,R*)-**1b–3b** were obtained enantiomerically pure (≥ 98% e.e.). High enantiomeric purities could also be achieved for the monoacetate (*S,S*)-**1a** and the diol (*S,S*)-**3** (≥ 95% e.e.) while (*S,S*)-**2**, **2a** and **3a** were isolated with only moderate enantiomeric purities. In analogy to the enzymatic hydrolyses the reactions rates decrease with increasing ring size. This is to a certain degree true for all esterifications. As recently reported,[6b] we have found a way to overcome this deficiency by carrying out these reactions in a continuous column reactor (loop reactor) using the lipase immobilized on Kieselguhr. Thus, in an optimized preparation 10 g quantities of enantiomerically pure (*R,R*)-**1b** were conveniently prepared in 24 h.

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