Enzymic Preparation of Enantiomerically Pure Cyclohexanols: Ester Synthesis by Irreversible Acyl Transfer

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Enantiomerically pure cyclohexanols are prepared enzymically *via* irreversible acyl transfer; they are valuable substitutes for 8-phenylmenthols and are potentially useful as chiral auxiliaries.

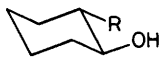
2-Substituted cyclohexanols like (1*R*)-[(**1**)—(**5**)] and (1*S*)-[(**1**)—(**5**)] have been either shown[1] [(1*R*,2*S*)- and (1*S*,2*R*)-(**1**)] to be suitable substitutes for (+)- and (−)-8-phenylmenthol[2] or are expected to be useful as chiral auxiliaries in asymmetric syntheses and for analytical purposes.

In contrast to previous enzymatic approaches to these molecules *via* ester hydrolase (PLE[3] or *Pseudomonas sp.*[4]) catalysed hydrolysis of their acetates in aqueous or biphasic systems, it would be highly advantageous to use the racemic alcohols directly without derivatisation for enzyme catalysed

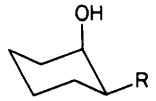
Table 1. Enzymic esterification of the alcohols (±)-[(**1**)—(**5**)] by irreversible acyl transfer.[a]

Substrate	Method	*t*/days	Conversion/%[b]	Product	Yield/%	% E.e.[c]	*E*[d]
(±)-(**1**)	A	21	47.6	(1*S*,2*R*)-(**1**)	41	89	≥100
				(1*R*,2*S*)-(**1a**)	40	≥98	
	B	4	50	(1*S*,2*R*)-(**1**)	40	≥95	
				(1*R*,2*S*)-(**1a**)	42	≥98	
(±)-(**2**)	A	7	50	(1*S*,2*R*)-(**2**)	38	≥95	≥100
				(1*R*,2*S*)-(**2a**)	41	96	
	B	2	50	(1*S*,2*R*)-(**2**)	39	≥95	
				(1*R*,2*S*)-(**2a**)	42	96	
(±)-(**3**)	A	8	50	(1*S*,2*S*)-(**3**)	45	≥95	≥100
				(1*R*,2*R*)-(**3a**)	41	≥98	
	B	2	50	(1*S*,2*S*)-(**3**)	40	≥95	
				(1*R*,2*R*)-(**3a**)	43	≥98	
(±)-(**4**)	A	3	33.8	(1*S*,2*S*)-(**4**)	35	50	≥100
				(1*R*,2*R*)-(**4a**)	33	≥98	
	B	1	50	(1*S*,2*S*)-(**4**)	38	≥95	
				(1*R*,2*R*)-(**4a**)	41	≥98	
(±)-(**5**)	A	7	42.0	(1*S*,2*R*)-(**5**)	33	71	≥100
				(1*R*,2*S*)-(**5a**)	36	≥98	
	B	2	50	(1*S*,2*R*)-(**5**)	39	≥95	
				(1*R*,2*S*)-(**5a**)	42	≥98	

[a] Reaction conditions: see text. [b] Determined by GLC. [c] Determined: alcohols (**1**)—(**5**): 250 MHz ^{1}H NMR of the corresponding α-methoxy-(trifluoromethyl)phenylacetyl (MTPA) esters, acetates (**1a**)—(**5a**): 400 MHz ^{1}H NMR using tris-[3-(trifluoromethylhydroxymethylene)-D-camphorato]europium(III) [Eu(tfc)$_3$] as chiral shift reagent. [d] For definition of *E* see ref. 5b.



(±)-(**1**) R = Ph
(±)-(**2**) R = $PhCH_2$
(±)-(**3**) R = PhO
(±)-(**4**) R = $PhCH_2O$



(±)-(**5**) R = $PhCH_2O$

enantioselective esterification. We have found that cyclohexanols of that kind can indeed be prepared easily by irreversible acyl transfer [equation (1)], using vinyl acetate as acyl donor and a lipase from *Pseudomonas sp.*[5] as a highly selective biocatalyst.

$$CH_2{=}CHCO_2Me + \text{enzyme} \rightarrow [\text{acyl-enzyme}]$$

$$[\text{acyl-enzyme}] \xrightarrow{(\pm)\text{-}[(\mathbf{1})\text{—}(\mathbf{5})]} (1S)\text{-}[(\mathbf{1})\text{—}(\mathbf{5})] + (1R)\text{-}[(\mathbf{1a})\text{—}(\mathbf{5a})] \quad (1)$$

In typical experiments (method A) (±)-[(**1**)—(**5**)] (10 mmol) was dissolved in Bu^{t}OMe (20 ml) containing vinyl acetate (30 mmol). After addition of lipase (200 mg) (SAM-II, *Pseudomonas sp.*, 1600 U, standard: tributyrine) the mixture was stirred at room temperature and the reaction was monitored by TLC (qualitative) and GLC (quantitative).

After the achieved or desired conversions, the enzyme, crude protein without immobilisation, was simply filtered off (paper filter) and stored for reuse. After removal of the solvent the product mixtures, consisting of the alcohols (1*S*)-[(**1**)—(**5**)] and the acetates (1*R*)-[(**1a**)—(**5a**)] were separated by flash chromatography on SiO_2 (Et_2O/n-hexane, 1 : 2). The enantiomeric purities were easily determined by comparison of the optical rotations with samples of known optical purity (determined independently by ^{1}H NMR using chiral shift reagents[4]). The absolute configurations of (**1**)—(**4**) were known,[4] those of (**5**) and (**5a**) were assigned tentatively using the methods of Mosher[6] and Horeau.[7] It should be noted that opposite pairs of enantiomers are being obtained in these esterification reactions as compared to enzymatic hydrolyses [*e.g.* (1*S*)-(**1**) and (1*R*)-(**1a**) *vs.* (1*R*)-(**1**) and (1*S*)-(**1a**)]. As summarized in Table 1, all esters (**1a**)—(**5a**) were produced with very high optical purities [≥95% enantiomeric excess (e.e.)]. Since for simple kinetic reasons,[8] the optical purities depend on the achievable conversion, it was not surprising to isolate (**4**) and (**5**) (method A) with lower (50 and 71% e.e., respectively) enantiomeric purities. The desired 50% conversion can only be achieved within reasonable reaction times by strongly increasing the amount of employed enzyme.

Clearly, the most convenient way to that effect would be the use of a continuous column reactor. Consequently, (method B) with the same lipase (*Pseudomonas sp.*,[4] immobilised on kieselguhr, 5.0 g equal to 900 mg native enzyme) a solution of the reactants [racemic alcohol (30 mmol), Bu^{t}OMe (80 ml), and vinyl acetate (90 mmol)] was continuously circulated over the column (loop reactor).

As is obvious from Table 1, greatly enhanced rates of transformations are achievable in this way (method B). The desired 50% conversions are reached 3 to 5 times faster as compared to the batch procedure (method A), all products are obtained with very high enantiomeric purities (≥95% e.e.). This approach is clearly highly attractive from a synthetic point of view and we are presently engaged in scaling up method B into the molar range.

From our own experiments[9] and published work,[10] it is known that optically active monoesters of cyclic *cis*-1,2-diols can be prepared in some cases. They are, however, notoriously unstable due to the ease of acyl group migrations frequently encountered in these molecules. As a highly attractive alternative, the benzyl-protected equivalents such as (**5**) and (**5a**) can be obtained easily, using the method described here, in a stable and enantiomerically pure (≥ 95% e.e.) form.

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