Enzymic Preparation of Tetrahydrofuran Derivatives of High Optical Purity

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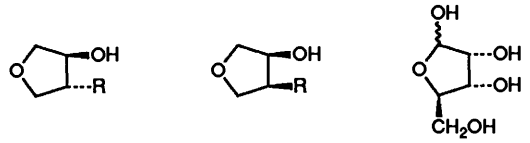
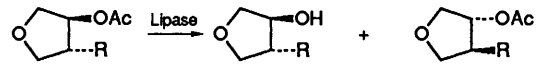
3,4-Disubstituted tetrahydrofurans (**1**)–(**4**) and (**7**) of high optical purities have been prepared by enantioselective enzymic hydrolysis of their acetates (±)-(**1a**)–(**4a**) and (**7a**) using a lipase from *Pseudomonas* sp. (SAM-II).

In view of their close structural relationship to furanoses (*e.g.* D-ribose) and their potential usefulness as chiral auxiliaries[1] or ligands,[2] enantiomerically pure tetrahydrofurans such as (**1**)–(**7**) are attractive synthetic targets.



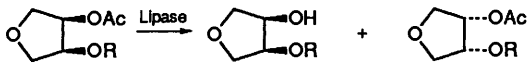
R	R	
(±)-(**1**) Ph	(**6**) OAc	D-Ribose
(±)-(**2**) $PhCH_2$	(±)-(**7**) $PhCH_2O$	
(±)-(**3**) PhO		
(±)-(**4**) $PhCH_2O$		
(±)-(**5**) OAc		

The capability of esterhydrolases (esterases, lipases) to differentiate between enantiomeric esters has been well documented. In our hands a lipase from *Pseudomonas* sp. (SAM-II)[3] had been particularly successful for the preparation of numerous acyclic[4] and alicyclic[5] secondary alcohols. It seemed reasonable, therefore, to try this biocatalyst for the resolution of heterocyclic molecules with a tetrahydrofuran substructure.[6]



(±)-(**1a**)–(**5a**) (**1**)–(**5**) (**1a**)–(**5a**)

In typical experiments, the acetates (±)(**1a**)–(**7a**) (10 mmol) were suspended in pH 7.0 phosphate buffer (20 ml). After addition of crude lipase SAM-II (1600 U, standard; tributyrin; 200 mg) the initial hydrolysis was indicated by a decrease in the pH value which was kept constant by continuous addition of 1 M aqueous NaOH using an autotitrator (pH-stat method). The reactions were conveniently monitored by the consumption of NaOH and terminated after the desired conversions. Continuous extraction of the reaction mixtures with ether and separation by column chromatography on silica gel led to the products summarized in the Table.



(±)-(**7a**) R = $PhCH_2O$ (**7**) (**7a**)

The enantiomeric purities of the alcohols (**1**)–(**7**) were determined by ^1H NMR (250 MHz) analysis of the diastereoisomeric 'Mosher'-esters; the acetates (**1a**)–(**7a**) were analysed by ^1H NMR (400 MHz) in the presence of $Pr(tfc)_3$ as a chiral shift reagent.

The absolute configurations of compounds (**3**)–(**5**) and (**3a**)–(**5a**) were secured by their conversion into the known (*R,R*)- and (*S,S*)-anhydrothreitols,[8] respectively. Those of (**1**), (**1a**), (**2**), and (**2a**) were determined using the methods of Horeau[9] and Mosher.[10] From the results in the Table it is clear that only derivatives of (**1**)–(**4**) and (**7**) can be obtained in high optical purity. This is because only in these cases are the selectivity factors *E* sufficiently high to allow optimisation of the conversion to the desired enantiomers. In the listed experiments, conversions of slightly above 50% are thus sufficient to obtain the acetates (3*R*,4*S*)-(**1a**)–(**2a**), (3*S*,4*S*)-(**3a**)–(**4a**), and (3*S*,4*R*)-(**7a**) enantiomerically pure. It can be calculated that conversions of slightly under 50% result in optical purities for the corresponding alcohols of 90–98% e.e.

Table. Enzymatic hydrolysis of 4-substituted tetrahydrofuran-3-yl acetates.[a]

Substrate	Conversion (%)	*t*/h	Products	Yield (%)	% e.e.	E[b]
(±)-(**1a**)	51	120	(3*S*,4*R*)-(**1**)	45	93	
			(3*R*,4*S*)-(**1a**)	42	≥98	≥100
(±)-(**2a**)	51	15	(3*S*,4*R*)-(**2**)	43	90	
			(3*R*,4*S*)-(**2a**)	45	93	65
(±)-(**3a**)	54	63	(3*R*,4*R*)-(**3**)	45	84	
			(3*S*,4*S*)-(**3a**)	45	≥98	52
(±)-(**4a**)	55	64	(3*R*,4*R*)-(**4**)	43	80	
			(3*S*,4*S*)-(**4a**)	40	≥98	40
(±)-(**5a**)	25	50	(3*R*,4*R*)-(**5**)	38	51	
			(3*S*,4*S*)-(**5a**)	45	46	4.4
(**6a**)	50	80	(±)-(**6**)	92	/	
(±)-(**7a**)	52	8	(3*R*,4*S*)-(**7**)	42	92	
			(3*S*,4*R*)-(**7a**)	47	≥98	87

[a] For conditions see text. [b] For definition see ref. 7.

In contrast to experiments published with *trans*-1,2-diacetoxycyclopentane,[6b] the enantioselectivity observed during the hydrolysis of (±)-(**5a**) was very low (*E* 4.4) leading to rather low enantiomeric purities for (3*R*,4*R*)-(**5**) and (3*S*,4*S*)-(**5a**). Again, and in strong contrast to results reported with *cis*-1,2-diacetoxycyclopentane,[6b] the enzymic hydrolysis of (**6a**) showed no selectivity at all. In agreement with our earlier observations[11] the isolated monoacetate (**6**) was racemic. In view of the similarity of (**6**) with furanoses one might assume that acyl group migrations occur more rapidly than in the corresponding carbocyclic system. In this connection, it was rewarding to find that (3*R*,4*S*)-(**7**) and (3*S*,4*R*)-(**7a**) [equivalents of the elusive (3*R*,4*S*)- and (3*S*,4*R*)-(**6**) and nicely protected against acyl group migrations], can be obtained with very high optical purities.

In summary, a whole class of tetrahydrofurans, including anhydrothreitol and optically active derivatives of anhydroerythritol have been made available in the described way by a simple enzymatic approach. This now enables us to study the synthetic usefulness of these compounds.

Acknowledgements

We are grateful to Prof. Dr. J. Buddrus (Dortmund) for his assistance in the use of NMR techniques for the determination of enantiomeric purities and the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support.

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Paper 0/01955K
Received 27*th February* 1990
Accepted 2*nd May* 1990