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Preparation of Optically Pure Pyridyl-1-ethanols

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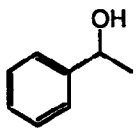
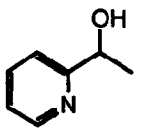
Abstract: Using a highly enantioselective lipase from *Pseudomonas sp.* (SAM II) all enantiomers of the isomeric pyridyl-1-ethanols (*R*)- and (*S*)- **1** - **3** were prepared in optically pure form both by enzymatic hydrolysis and esterification.

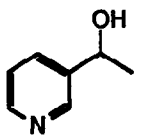
(*R*)- and (*S*)-2-, 3- and 4-pyridyl-1-ethanols are attractive chiral auxiliaries especially for the resolution of carboxylic acids sensitive to racemisation. This is mainly due to the fact, that the resulting diasteromeric esters - obtained e.g. by reaction of arylpropionic anhydrides with equimolar amounts of (*R*)-1-(4-pyridyl)-ethanol[1-3] can be cleaved under acidic conditions allowing the convenient recovery of both the chiral auxiliary and the corresponding carboxylic acid without detectable loss of optical activity.
Enantiomerically pure pyridyl-1-ethanols like (*R*)- and (*S*)- **1** - **3** were so far accessible *via* classical resolution techniques. These methods however, suffer from either low chemical yields or poor enantioselectivities[4-10]. (*S*)-(4-pyridyl)-1-ethanol was obtained in 79% yield and 96% ee by bakers' yeast reduction of the corresponding ketone[11].



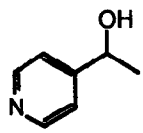
(±)-**1**



(±)-**2**

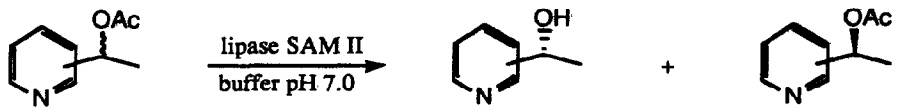


(±)-**3**



a: acetates

In view of our previous experience in the enzymatic resolution of structurally closely related aryl-1-ethanols[12,13] we felt that the above target molecules could be made accessible both by enzymatic hydrolysis and esterification provided they would be accepted as substrates by the highly selective lipase from *Pseudomonas sp.* (SAM II)[14].



2-pyridyl: (±)-**1a**
3-pyridyl: (±)-**2a**
4-pyridyl: (±)-**3a**

(*R*)-**1** - **3**

(*S*)-**1a** - **3a**

In typical experiments 10 mmol of the racemic acetates (±)-**1a** - **3a** were hydrolysed in 20 ml phosphate buffer pH 7.0 in presence of 200 mg lipase SAM II. The pH value was kept constant during the reaction by continuous addition of 1M sodium hydroxide solution. The progress of the reactions can be easily followed *via* the consumption of sodium hydroxide. After the desired conversions were achieved, the products were isolated by continuous extraction of the aqueous phase with ethylacetate and separation of the obtained products by column chromatography (silica gel, diethylether).
The results are summarized in table 1.

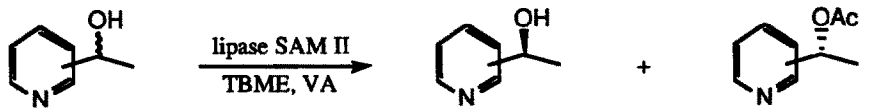
Table 1: Enzymatic hydrolyses of (±)-**1a** - **3a**[a]

substrate	time	conversion[b]	products	yield[c]	% ee[d]	E[e]
(±)-**1a**	40 h	50 %	(*R*)-**1**	37 %	≥ 95	
			(*S*)-**1a**	45 %	≥ 95	≥ 100
(±)-**2a**	120 h	50 %	(*R*)-**2**	41 %	≥ 95	
			(*S*)-**2a**	37 %	≥ 95	≥ 100
(±)-**3a**[15]	75 h	50 %	(*R*)-**3**	44 %	≥ 95	
			(*S*)-**3a**	40 %	≥ 95	≥ 100

a: for conditions see text; b: determined *via* the consumption of 1M sodium hydroxide solution; c: isolated yield after column chromatography and bulb to bulb destillation; d: determined after conversion into the corresponding (*R*)-MTPA-ester using ^{1}H-NMR, acetates were previously converted into the alcohols (K_2CO_3, methanol); e: for definition of E see reference 16.

All experiments were leading to conversions very close to 50%. The obtained alcohols (*R*)-**1** - **3** and acetates (*S*)-**1a** - **3a** showed high optical purities as confirmed by the ^{1}H-NMR of their "Mosher" esters[17] (250 MHz). The acetates (*S*)-**1a** - **3a** were previously converted into the corresponding alcohols (*S*)-**1** - **3** (K_2CO_3/MeOH, 30 Min.; roomtemperature). All absolute configurations were determined *via* the optical rotation of the products and correlated with literature data[5,6,9]. The hydrolyses of all three acetates (±)-**1a** - **3a** proceeded with very high selectivities in the presence of the lipase SAM II. This is clearly reflected in the large selectivity factors E (E ≥ 100).

Next to their capability of catalyzing enzymatic hydrolyses under aqueous or biphasic conditions, esterhydrolases have become equally well known for their ability to catalyze the corresponding ester syntheses both by direct esterification and reversible as well as irreversible acyl transfer. Due to the identical selectivities displayed by the enzyme towards the absolute configuration of the parent molecule, complementary stereochemistry is usually resulting from these alternative processes.



2-pyridyl: (±)-**1**
3-pyridyl: (±)-**2**
4-pyridyl: (±)-**3**

(*S*)-**1** - **3**

(*R*)-**1a** - **3a**

10 mmol of the racemic alcohols (±)-**1** - **3** were dissolved in a mixture of 20 ml tert.butylmethylether (TBME) and 30 mmol vinylacetate (VA) to which 200 mg lipase SAM II was added. The mixtures were stirred at room temperature while the reaction progress was monitored conveniently by glc (OV 17 capillary column). After the desired conversions were achieved, the enzyme was filtered off and the solvent was removed *in vacuo*. The products were separated by column chromatography on silica gel (diethylether). The results are given in table 2.

Table 2: Enzymatic esterification of (±)-**1** - **3**[a]

substrate	time	conversion[b]	products	yield[c]	% ee[d]	E[e]
(±)-**1**	40 h	50 %	(*S*)-**1**	33 %	≥ 95	
			(*R*)-**1a**	41 %	≥ 95	≥ 100
(±)-**2**	40 h	50 %	(*S*)-**2**	38 %	≥ 95	
			(*R*)-**2a**	43 %	≥ 95	≥ 100
(±)-**3**	55 h	50 %	(*S*)-**3**	33 %	≥ 95	
			(*R*)-**3a**	50 %	≥ 95	≥ 100

a,c,d,e: see footnotes in table 1; b: determined by glc on OV 17 capillary column.

From table 2 it is obvious that all reactions were highly selective, leading to optically pure (*S*)-alcohols **1** - **3** and (*R*)-acetates **1a** - **3a**. As previously reported[13,18] the absolute configurations of the obtained products were opposite to those obtained by enzymatic hydrolyses.

Again the lipase from *Pseudomonas sp.* (SAM II) has proven to be the biocatalyst of choice for the desired resolution of the racemic alcohols (±)-**1** - **3**. Both reaction modes, enzymatic hydrolysis and esterification, are resulting in optically pure products. The reactions can be scaled up easily into the 100 mmol range thereby

providing an excellent access to both enantiomers of the title compounds. Table 3 is summarizing the chiroptical properties of the thus prepared molecules.

Table 3: Chiroptical properties of the obtained products[a]

products obtained by enzymatic hydrolysis				products obtained by enzymatic esterification			
compound	$[\alpha]_D^{20}$	conc.	solvent	compound	$[\alpha]_D^{20}$	conc.	solvent
(*R*)-**1**	+ 25.6	1.27	$CHCl_3$	(*S*)-**1**	- 26.4	1.34	$CHCl_3$
(*S*)-**1a**	- 102.3	1.09	$CHCl_3$	(*R*)-**1a**	+ 100.3	0.92	$CHCl_3$
(*R*)-**2**	+ 52.4	1.40	$CHCl_3$	(*S*)-**2**	- 53.5	1.09	$CHCl_3$
(*S*)-**2a**	- 101.9	1.21	$CHCl_3$	(*R*)-**2a**	+ 99.6	0.96	$CHCl_3$
(*R*)-**3**	+ 42.5	1.04	MeOH	(*S*)-**3**	- 43.0	1.24	MeOH
(*S*)-**3a**	- 80.0	1.10	$CHCl_3$	(*R*)-**3a**	+ 81.0	1.01	$CHCl_3$
a: measured on Perkin Elmer 241 Polarimeter							

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References and Notes

1) U. Salz and C. Rüchardt, *Chem. Ber.* **1984**, *117*, 3457.
2) H. Gärtner, U. Salz and C. Rüchardt, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 172.
3) A.Franck and C. Rüchardt, *Chem. Lett.* **1984**, 1431.
4) O. Cervinka, O. Belovsky, P. Rejmanova, *Coll. Czech. Chem. Commun.* **1973**, *38*, 1358.
5) M. Imuta and H. Ziffer, *J. Org. Chem.* **1978**, *43*, 3530.
6) H. Ziffer, K. Kawai, M. Imuta and C. Froussious, *J. Org. Chem.* **1983**, *48*, 3017.
7) M. Bucciarelli, A. Forni, I. Moretti and G. Torre, *Synthesis* **1983**, 879.
8) K. Soai, S. Niva and T. Kobayashi, *J. Chem. Soc., Chem. Commun.* **1987**, 801.
9) M. Takeshita, K. Terada, N. Akutsu, S. Yoshida and T. Sato, *Heterocyles* **1987**, *26*, 3051.
10) J.P. Rasor, Ph.D. thesis, Universität Freiburg, Germany, 1988.
11) J.P. Rasor and C. Rüchardt, *Chem. Ber.* **1989**, *122*, 1375.
12) K. Laumen and M.P. Schneider, *J. Chem. Soc., Chem. Commun.* **1988**, 598.
13) K. Laumen, D. Breitgoff and M.P. Schneider, *J. Chem. Soc., Chem. Commun.* **1988**, 1459.
14) Lipase SAM II from *Pseudomonas sp.* (8000 U/g, standard: tributyrine) was obtained from AMANO Pharmaceutical Co., supplied by FLUKA AG, CH-9470 Buchs, Switzerland and Mitsubishi Int. GmbH, D-4000 Düsseldorf, Germany.
15) K. Laumen, Ph.D. thesis, Bergische Universität - GH - Wuppertal, Germany, 1987.
16) C.S. Chen, Y. Fijimoto, G. Girdaukas and C.J. Sih, *J. Am. Chem. Soc.* **1982**, *104*, 7294.
17) J.A. Dale, D.L. Dule and H.S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543.
18) R. Seemayer and M.P. Schneider, *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 171.