Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 3, pp. 907-910, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00088-2

Preparation of Homochiral (S)- and (R)-1-(2-Furyl)ethanols by Lipase-Catalyzed Transesterification

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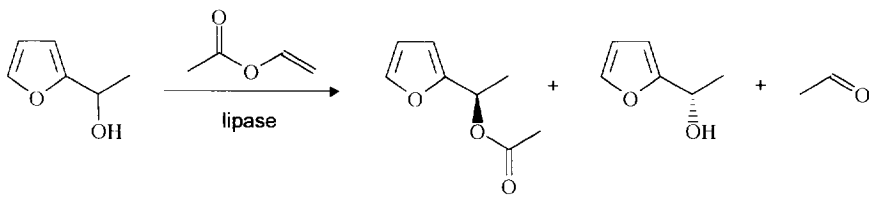
Abstract: 1-(2-Furyl)ethanol **1** was resolved by irreversible transesterification with vinyl acetate using Lipozyme IM or Porcine Pancreas Lipase (PPL) in an organic solvent. (S)-alcohol (99% e.e.) was obtained in 80-85% yield using Lipozyme IM in carbon tetrachloride while (R)-1-(2-furyl)ethyl acetate (96% e.e.) in 75-80% yield resulted from transesterification using Lipozyme IM in hexane or PPL in tetrahydrofuran.

1-(2-Furyl)ethanol **1** and its derivatives are versatile starting materials for the construction of numerous natural products such as carbohydrates, macrolides, pheromones and alkaloids[1,2]. The availability of both enantiomers is essential in the synthesis of chiral compounds for determination of structure-activity relationship. Various preparations of optically active **1** could be found in the literature, based on the kinetic resolution of **1** using titanium(IV)-tartrate complex[3], asymmetric reduction of 2-acetylfuran[4,8], microbial[5] or enzymatic[6,7] reductions of this ketone, microbial oxidation[9] of **1**, and enzymatic hydrolysis and/or esterification[10-12]. The best results from the point of view enantiomeric purity (ca.95% ee for S-, and ca. 88% ee for R-enantiomer) were achieved by acylation of racemic alcohol with vinyl acetate in the presence of Lipase P[11]. It is known that in enzymatic resolutions enantioselectivity depends strongly on enzyme specifity and solvent used[13,14]. Taking this into account we decided to search for effective preparative method yielding both enantiomers of high enantiomeric purity in multigram scale. These compounds are starting materials for synthesis of amino sugar - (L)- and (D)-daunosamine.

Scheme 1



1 **2-R** **1-S**

For preliminary screening we chose six different lipases: Porcine Pancreas Lipase, *Candida cylindracea* lipase (CCL), Lipozyme IM (immobilized lipase from *Mucor miehei*), Lipase A (from *Aspergillus* sp.), AY (from *Candida rugosa*), and PS (from *Pseudomonas* sp). Transesterification was carried out at room temperature in carbon tetrachloride at molar ratio vinyl acetate to racemic **1** - 5:1.

Table 1.

Lipase	% conversion	[%]ee **1-S**	[%]ee **2-R**	E[a)]
PPL	12	14	>99	227
CCL	22	10	34	2
Lipozyme IM	53	>99	87	64
Lipase A	4	1	22	6
Lipase AY	12	5	36	4
Lipase PS	28	37	96	70

200 mg of enzyme, 2 mM of **1**, 10 mM of vinyl acetate, 5 ml CCl_4, , room temp., 24 h
a) calculated according to ref. 15

The best enantioselectivity for S-1-(2-furyl)ethanol (**1-S**, 100% e.e.) was obtained with Lipozyme IM, while enantiomerically pure **R**-1-(2-furyl)ethyl acetate **2-R** was formed when PPL was used. These two enzymes were chosen for further investigation in order to determine the effect of solvent on enantioselectivity and rate of transesterification.

Table 2.

Lipozyme IM				PPL		
E	[%]ee **1-S**	[%]ee **2-R**	Solvent	[%]ee **1-S**	[%]ee **2-R**	E
83	46	96	THF	30	>99	266
82	59	96	hexane	8	70	86
57	79	92	cyclohexane	6	66	5
50	71	92	toluene	18	94	39
94	22	97	CH_2Cl_2	8	>99	214
106	48	97	$CHCl_3$	12	>99	225
64	>99	87	CCl_4	14	>99	227
70	92	90	benzene	n.t	n.t.	
83	35	97	dioxane	26	>99	258
69	71	94	isooctane	n.t	n.t	

n. t.- not tested

Porcine Pancreas Lipase shows high enantioselectivity in THF, chloromethanes and toluene, and moderate in aliphatic hydrocarbons (hexane, cyclohexane). The reaction rate was the highest in tetrahydrofuran. Lipozyme IM is highly enantioselective in any of solvents tested, differences can be seen in reaction rate only.

Preparative transesterifications (up to 0.6 mole of **1**) were performed on Lipozyme IM in carbon tetrachloride for obtaining pure S-alcohol, and in hexane for getting high purity R-acetate. **R-2** (96% e.e.) was also obtained from transesterification in tetrahydrofuran using PPL. We have found that in any case enzymes can be used several times, although deactivation is observed after each run. In the case of PPL after every run lower conversion is achieved at the same time but enantioselectivity remains almost the same. On the other hand using Lipozyme IM it is possible to obtain 100% e.e. of S-alcohol in the first use only. The second and third transformation on reused enzyme provide high purity R-acetate (ca. 93% e.e.) and enantiomerically enriched S-alcohol (70-80% e.e.) depending on the extent of conversion.

Further investigations directed to getting more insight into spatial demands of active site of Lipozyme IM are continued and will be published in the near future.

EXPERIMENTAL

General. Lipase from *Candida cylindracea* and Porcine Pancreas Lipase were purchased from Aldrich, Lipases A, AY, and PS from Amano Pharmaceuticals, and Lipozyme IM from Novo Nordisk. 2-Acetylfuran and vinyl acetate, were obtained from Aldrich, all solvents reagent grade from POCH. All reagents were used as received. Racemic 1-(2-furyl)ethanol was prepared by $NaBH_4$ reduction of 2-acetylfuran (0° C, MeOH) in 98% yield. Enantiomeric excesses were determined by GC using Chiraldex G-TA column. Optical rotations were measured using Horiba or SR-6 PolyScience polarimeters. All transesterifications were performed at room temperature with magnetic stirring.

(S)-1-(2-furyl)ethanol. 1-S. To the solution of 0.5 M of **1**, and 2.5 M vinyl acetate in 200 ml CCl_4, 20 g of Lipozyme IM was added with stirring. Progress of the reaction was monitored by GC. After 48 h enzyme was filtered, and solvent together with excess of vinyl acetate were distilled off. The residue was distilled under reduced pressure, and then chromatographed on silica gel with hexane: acetone. Usually 80-85% yield of **1-S** (98-99% e.e.) was achieved, $[\alpha]_D^{20}$-24.4 (neat). We have noticed that during column chromatography racemization of **1-S** as well as **2-R** takes place to some extent. In our opinion the reason is acidity of silica gel. Racemization was totally eliminated after addition of ca. 1% of sodium acetate. to the chromatographed sample[16].

(R)-1-(2-furyl)ethyl acetate. 2-R. To the solution of 0.25 M of **1**, and 1.25 M of vinyl acetate in 200 ml hexane, 20 g of Lipozyme-IM was added. After 24 h (ca. 40-45% conversion) enzyme was filtered. The filtrate was worked up as above. Average yield 75-80% of **2-R** (94-96% e.e.) was achieved. Specific rotation for 96% optical purity sample was $[\alpha]_D^{20}$-3.4 (neat), d_4^{20} 1.054 g/ml.

(R)-1-(2-furyl)ethanol 1-R . This enantiomer (96% e.e.) was obtained in 96% yield by methanolysis of **2-R** with 0.01 M MeONa in methanol solution at 0-5° C overnight. Specific rotation for **1-R** was $[\alpha]_D^{20}$ 24.3 (neat).

Acknowledgements: This work was financially supported by Instytut Farmaceutyczny in Warsaw, grant 1/94(1017). Authors thank to Novo Nordisk and Amano Pharmaceuticals for generous gift of enzymes.

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(*Received in UK* 23 *January* 1996)