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LIPASE-CATALYZED KINETIC RESOLUTION OF (±)-2-HYDROXYMETHYL-1,4-BENZODIOXANE

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In memory of G.Snatzke.

Who hath his life from rumours freed,
Whose conscience is his strong retreat;
Whose state can neither flatterers feed,
Nor ruin make accusers great;

Who God doth late and early pray
More of His grace than gifts to lend;
And entertains the harmless day
With a well chosen book or friend;

This man is freed from servile bands
Of hope to rise, or fear to fall;
Lord of himself, though not of lands;
And have nothing, yet hath all.

(Sir Henry Wotton, 1568-1639)

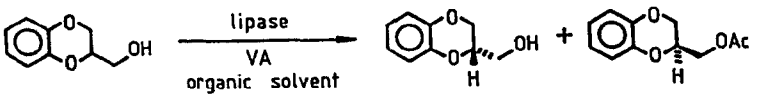
Abstract: The title compound has been kinetically resolved in a lipase-catalyzed transesterification with vinyl acetate in organic solvents. The influence of the enzyme source as well as the character of the solvent on the enantioselectivity has been studied.

The 1,4-benzodioxane moiety has been widely used in the design of therapeutic agents with α-adrenergic blocking[1-6], antigastric[7], spasmolytic[8], antipsychotic[9] and anxiolytic[10] properties. For the syntheses of the different compounds possessing the mentioned biological activity, 2-hydroxymethyl-1,4-benzodioxane (1) has usually been applied as the appropriate synthon. The biological activity of these compounds is, however, considerably influenced by the chirality of the 1,4-benzodioxane unit.

Bovet[11] and later others[10,12] have namely recognized that the compounds synthesized from (-)-*S*-1 have, as a rule, significantly higher activities, than their enantiomers.

The first synthesis of the optically pure enantiomers of 1 starting from *D*-mannitol[13] requires a great number of steps. Although (-)-1 and (+)-1 could be obtained by direct condensation of catechol with enantiomerically enriched glycidol prepared by Sharpless epoxidation[14] or with enantiomerically pure epichlorohydrin derivatives synthesized from *L*-ascorbic acid or *D*-mannitol[15], the preparation of these synthons also requires multistep sequences. Although a simple synthesis of (-)-1 via the resolution of racemic 1,4-benzodioxane 2-carboxylic acid with (+)-dehydroabiethylamine and subsequent reduction with LAH has been published[6], not only the yield of the resolution is very poor (ca. 1%), but also the chiral base was not readily available.

In this paper we report that (±)-2-hydroxymethyl-1,4-benzodioxane [(±)-1] can be efficiently resolved in a lipase-catalyzed transesterification using vinyl acetate (VA) as an irreversible acyl donor (Scheme 1). To optimize this process we carried out the reaction using lipases of different origins and in different solvents. The results are summarized in Table 1.



(±)-1 (-)-1 (+)-2

Seven enzymes and five organic solvents have been tested to examine the enantioselective acylation of (±)-1 with vinyl acetate. Except the lipase from *Candida lypolytica* (ClL) (entry 12) all enzymes catalyzed the acetylation of (±)-1, but with two of them the enantioselectivity was rather poor (entries 9 and 10), moreover, the use of one of them resulted in a mixture of racemates (entry 11). While lipases from porcine pancreas (PPL), *Mucor javanicus* (MjL), *Pseudomonas fluorescens* (PsfL), and *Aspergilus niger* (AnL) acetylated selectively the *R*-enantiomer affording (+)-2 (entries 1-10), the lipase of *Candida cylindracea* (CcL) preferred the *S*-enantiomer as the substrate (entry 13). The highest enantioselectivity was achieved in the reaction carried out by PsfL in dioxane (entry 8). The enantioselectivity as well as the activity of the enzymes were significantly influenced by the solvent, giving the best results in dioxane. Although no unambiguous correlation could be detected between the dielectric constant/dipole moment of the solvents and the enantioselectivity/activity of the enzymes, reactions carried out in dioxane - possessing the lowest dielectric constant/dipole moment among the solvents used - have shown the highest enantioselectivity. More hydrophobic solvents

Table 1. Results of the lipase catalyzed acetylation of (±)-1

Entry	Lipase[a] amount[b]	Solvent[c] (Dk; μ)[d]	Time (h)	Conv.[e] %	Alcohol[f] %ee, conf.		E[g]
1	PPL (209)	dichloromethane (8.9; 1.5)	8	32	23	*S*	3.62
2	PPL (1830)	dichloromethane	0.5	33	23	*S*	3.42
			1.0	58	53		3.67
			1.5	76	72		3.05
			2.5	88	83		3.27
3	PPL (1740)	chloroform (4.7; 1.1)	0.2	26	14	*S*	2.66
4	PPL (1740)	THF (7.4; 1.7)	0.2	61	56	*S*	3.55
5	PPL (1740)	vinylacetate (-; -)	0.2	86	83	*S*	2.75
6	PPL (1740)	dioxane (2.2; 0.4)	0.2	41	37	*S*	4.65
			0.4	57	59		4.43
			0.8	83	94		4.13
7	PsfL (523)	dichloromethane	4	56	68	*S*	6.49
8	PsfL (523)	dioxane	3	19	21	*S*	22.21
			8	53	87		21.65
			13.5	62	99.5		22.63
9	MjL (0.84)	dichloromethane	3.5	11	3	*S*	1.69
10	AnL (0.66)	dichloromethane	24	18	6	*S*	1.86
11	PrL (0.30)	dichloromethane	24	3	-	*R,S*	-
12	ClL (0.15)	dichloromethane	24	-	-	-	-
13	CcL* 4 ($2x10^5$)	dichloromethane	1	61	35	*R*	2.1

a) All the enzymes were commercially available (FLUKA or SIGMA, the latter marked with asterisk); PPL denotes porcine pancreas lipase (spec. act. 2.4 U/mg), PsfL denotes Pseudomonas flourescens lipase (spec. act. 31.5U/mg), MjL denotes lipase from Mucor javanicus (spec. act. 5U/g), AnL denotes lipase from Aspergillus niger (spec. act 4U/g), PrL denotes lipase from Penicillium roquerforti (spec. act. 1.8U/g), ClL denotes lipase from Candida lipolytica (spec. act. 0.94U/g), CcL denotes lipase from Candida cylindracea (spec. act. 30U/mg); b) In units of enzyme per mmol of (±)-1; c) All the solvents were anhydrous and contained 8 mmol vinyl acetate/mmol(±)-1; d) Dielectric constant and dipole moment (Debye) values were taken from Ref. 16; e) Conversion degrees were calculated from the yields of the isolated products obtained by flash-chromatography. The reactions were carried out at room temperature; f) The enantiomeric excess was determined by measuring the optical rotation in ethanol (c=0.71-1) at the sodium D-line and at r.t. $[\alpha]_D$=-34.3 (c=0.7, EtOH) for optically pure S-1[13,14]; g) Calculated according to Ref. 17.

were not tried as they did not dissolve the substrate. To investigate the influence of the conformation of the substrate on the enantioselectivity the CD of (−)-1 was measured in dichloromethane and dioxane (Fig. 1). Relying upon the negative sign of the ^1L_b-band at 279 nm, the *M*-helicity of the heteroring, carrying the hydroxymethyl group in *equatorial* position, was established applying the helicity rule published by two of us[18]. The solvent dependence of the conformation was clearly demonstrated by the different Δε-values. In dioxane the enantiomer of *S*-configuration [(−)-1] is present in a higher concentration in the conformation with *M*-helicity [(−)-1_{eq} >>> (−)-1_{ax}] than in dichloromethane (Scheme 2). This conformational change (ca 22%) resulted in a comparable increase of the enantioselectivity (26–35%) using PsfL and PPL.

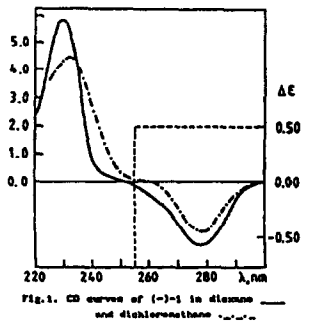
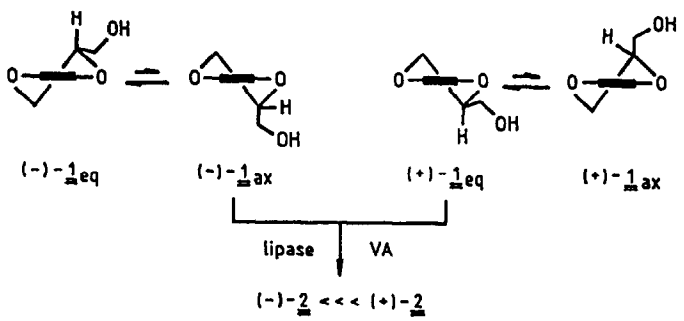


Fig. 1. CD curves of (−)-1 in dioxane ___ and dichloromethane -.-.-.-

Scheme 2.



Taking into account the higher reactivity of (+)-*R*-1 in the lipase-catalyzed transesterification (excepting lipase from *Candida cylindracea*), the binding of the substrate [(±)-1] to the active site of the enzyme should take place with the conformation of *P*-helicity, in which the *equatorial* position of the hydroxymethyl group leads to the preferable ES-complex. The alternative orientation of the hydroxymethyl function (*axial*) is energetically much less preferred and does not lead to a favourable ES-complex, thus the acetylation of (−)-1 takes place very slowly.

Summing up, we have shown that the proper selection of the solvent in the *Pseudomonas fluorescens* lipase-catalyzed acetylation of (±)-1 using vinyl acetate as acylating agent, provides (−)-1 in an acceptable chemical yield (47%) and enantiomeric purity (ee = 87%). This purity could be increased to ca. 98% by crystallization from n-hexane. The same optical purity has been achieved when the acetylation was allowed to proceed upto 62% conversion.

This method is a contribution to the reported chemical syntheses of (-)-**1** hitherto starting from *D*-mannitol[13,15] or from 1,4-benzodioxane-2-carboxylic acid[6].

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Experimental:

All reactions were carried out in dry solvents in the presence of activated molecular sieves of type 4Å and monitored by TLC. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. CD-spectra were recorded on a Jobin-Yvon dichrograph-VI.

General procedure for the lipase-catalyzed resolution of (±)-1

a) A solution of *rac*-**1** (1 g, 6.02 mmol) in dry dichloromethane (7 ml) was treated with vinylacetate (4 ml, 49.9 mmol) and lipase from porcine pancreas (4.59 g = 11016 U) in the presence of molecular sieves type 4Å. The suspension was stirred at room temperature for 1.5 h. After filtration of the lipase[19] the filter cake was washed with dry dichloromethane (3x5 ml). The filtrate was evaporated and separated by flash-chromatography on silica gel 60 (0.063 - 0.2 mm) (column size 10x2.5 cm) with toluene-acetone (30:1) yielding *S*-(-)-**1** as crystals {240 mg, $[\alpha]_D^{24}$= -24.69 (c = 1, EtOH), ee = 72%} and *S*-(+)-**2** as a colourless oil {948 mg, $[\alpha]_D^{24}$= +5.98 (c = 1, EtOH), ee = 16%[20]}. Crystallization of (-)-**1** (240 mg) from n-hexane (36 ml) gave enantiomerically pure *S*-(-)-**1** (76 mg, m.p.: 74-75°C with an ee. > 99.8%, lit.[12,14] m.p.: 73-74°C)

b) Using lipase from *Pseudomonas fluorescens* (100 mg, 3.15 U) in the same procedure *S*-(-)-**1** [370 mg (37%), ee > 99.5%] and *S*-(+)-**2** (750 mg, ee.= 26%) were obtained.

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19) Although a loss of the activity of the enzyme filtered off was detected, it did not prevent its repeated application, furnishing *S*-(-)-**1** of the same enantioselectivity in a somewhat longer procedure.

20) The optically pure *R*-(-)-**2** was prepared by acetylation of (-)-**1** (ee. > 99.8 with acetic anhydride in pyridine at room temperature. Colourless oil, $[\alpha]_D$= -38.9 (c = 1, EtOH) R_f = 0.47 in toluene - acetone (20:1).