Synthesis and Lipase-Catalyzed Enantiotope Selective Acetylation of 2-Benzoyloxy-1,3-propanediol

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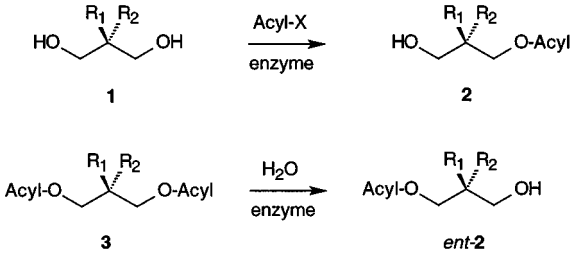
Abstract: Preparation and porcine pancreatic lipase (PPL)-catalyzed enantiotope selective acetylation of the prochiral 2-benzoyloxy-1,3-propanediol (**1a**) is described. The reaction with PPL and vinyl acetate gave monoacetate (**2a**) of 96 % e.e.

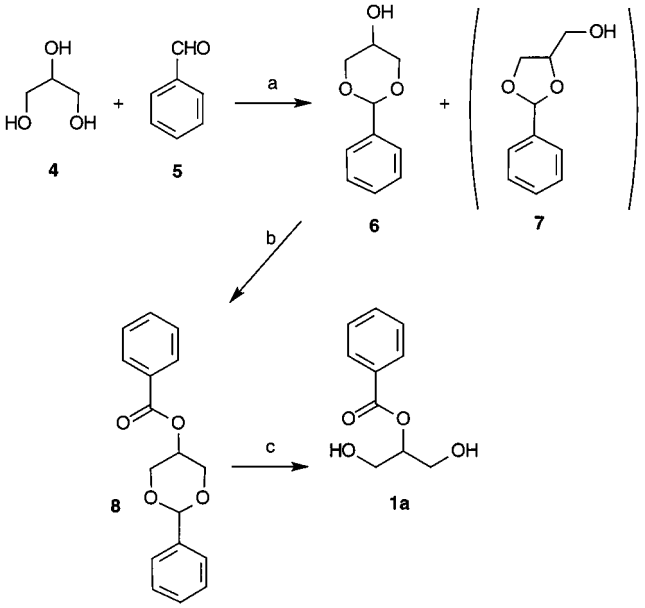
Key words: 2-*O*-benzoylglycerol, enantiotope selective, acetylation, lipase

Chiral glycerol derivatives are considered to be useful C_3 building blocks for the preparation of homochiral biologically active molecules such as phospholipids[1], phospholipase A_2 inhibitors[2], PAF (platelet-activating factor)[3], and many others[4].

Biocatalytical preparation of these chiral C_3 units were carried out either by enantiomer selective or enantiotope selective manner. The kinetic resolution of racemic glycerol derivatives such as glycerol acetonide[5,6] , glycerol-2,3-carbonate [7] provided moderate selectivity and 50% theoretical limit of the desired enantiomer. On the other hand, enantiotope selective transformation of prochiral 1,3-propanediols (**1**) or their diacyl derivatives (**3**) provide theoretically 100% of a single enantiomer (**2** or *ent*-**2**).

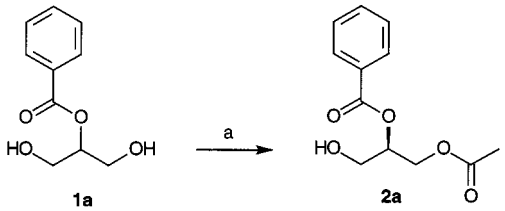


Enzyme-catalyzed acylation of several 2-*O*-alkylglycerol derivatives (**1**, R_1,R_2= *O*-alkyl, H), such as the 2-*O*-methyl-,[8,9] 2-*O*-ethyl-, [8,9] or 2-*O*-benzylglycerol[8] gave optically active monoacetates (**2**). Hydrolyses of the corresponding diacyl compound (**3**, R_1, R_2= OBn, H) with different enzymes under various conditions were also performed.[11-15] In the case of the 2-*O*-alkyl substituents, the lipase-catalyzed process proved to be *pro-S* selective. Consequently, acylation of the 2-*O*-benzylglycerol (**1**, R_1, R_2= OBn, H) provided (*S*)-1-*O*-acetyl-2-*O*-benzylglycerol (**2**, R_1= H, R_2= OBn) [11] and hydrolyses of the corresponding diacyl derivative (**3**, R_1= H, R_2= OBn) gave the (R)-enantiomer (*ent*-**2**, R_1= OBn, R_2= H).[11,12] The slow ra-



(a) cat. cc. H_2SO_4, RT, 4 h, 28%; (b) BzCl (1.1 eq.), Et_3N (1.2 eq.), cat. DMAP, CH_2Cl_2, RT, 2 h, 96 %; (c) H_2, cat. 10 %Pd/C, EtOAc, RT, 8 h, 73 %.

Scheme 1



Entry	Enzyme (mg)	Time	2a	
		(h)	Y %	e.e. %
1	Novozym 435 (250)	0.5	5*	1
2	Lipase G (100)	72	5*	3
3	Lipase AK (100)	1	32	7
4	PsL (100)	2.5	36	19
5	Lipase N (100)	72	13	20
6	CcL (50)	72	10	33
7	PPL (300)	1	63	96

* According to TLC data, most of the diol **1a** was converted to diacetate.

(a) **1a** (300 mg), enzyme, vinyl acetate (1 ml), THF (3 ml), hexane (3 ml), RT

Scheme 2

cemisation (*ca.* 2 %/h) found when optically active (*S*)-1-*O*-acetyl-2-*O*-benzylglycerol (**2**, R_1= H, R_2= OBn) was incubated in phosphate buffer pH 7 without enzyme is the drawback of the hydrolytic method.[11]

Although the enantiotope selective biotransformations of 2-*O*-alkylglycerol derivatives (**1** or **3**, R_1,R_2= *O*-alkyl, H) are well documented, no example of enzymic enantiotope selective acylation of 2-O-acylglycerol derivatives (**1**, R_1, R_2= *O*-acyl, H) was found.

It is worthwile noting that two compounds of this family (**2**, R_1, R_2= *O*-acyl, H), namely 1-*O*-acetyl-2-*O*-(16-methyl)heptadecanoyl- and 1-*O*-acetyl-2-*O*-(18-methyl)nonadecanoylglycerol, were isolated from *Nicotina benthamiana*.[16]

As a part of our interest in exploring new stereoselective biocatalytic methods, we decided to investigate the lipase-catalyzed acetylation of the 2-*O*-acylglycerol derivatives (**1**, R_1,R_2= *O*-acyl, H). Hence, 2-*O*-benzoyloxyglycerol (**1a**, R_1=OBz, R_2=H) was selected as a representative of this class.

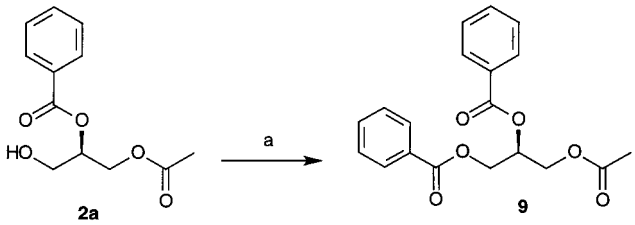
Preparation of the desired diol (**1a**) was straightforward (Scheme 1). Condensation reaction [17] of glycerol (**4**) and benzaldehyde (**5**) provided *cis*-5-hydroxy-2-phenyl-1,3-dioxane (**6**).[18] Consequent benzoylation and deprotection of the benzylidene protected intermediate (**8**)[19] by catalytic hydrogenation yielded the desired diol (**1a**)[20] in pure crystalline form.

With the desired prochiral diol (**1a**) in hand, the enantiotope selectivity of acetylation by several commercially available lipases was tested (Scheme 2).

Among the enzymes investigated, lipase from porcine pancreas (PPL) proved to be the most selective providing almost enantiomerically pure product (**2a**)[21] in good yield (Entry 7). The enantiomeric purity of the product (**2a**) was determined from the ^{1}H-NMR signals of its MTPA ester.[22] The composition of the solvent in this reaction catalyzed by PPL played an important role. Since the crystalline diol (**1a**) is poorly soluble in apolar solvents, the reaction was slow in hexane. Enzymatic acetylations using vinyl acetate as acylating agent in more polar solvents like chloroform, ethyl acetate or vinyl acetate gave decreased enantiotope selectivity compared to that obtained in the best solvent system (THF:hexane 1:1).

Prediction of the sense of enantiotopic selectivity seemed to be not obvious for lipase-catalyzed acylation of this new class of prochiral 1,3-propanediols. The lipase-catalyzed acylation of 2-*O*-alkyl-1,3-propanediols (**1**, R_1, R_2= *O*-alkyl, H) proved to be *pro-S* selective. In the case of 2-alkyl-1,3-propanediols (**1**, R_1, R_2= alkyl, H) bearing apolar substituent at position 2, enantiotope preference is inverted in a geometrical sense, although as a result of the sequence rules, the affected group is still labelled *pro-S*.[23] Acetylation of the diol bearing 2-*N*-benzyloxycarbonyl group by PPL was found to be *pro-R*.[11]

The absolute configuration of our product (**2a**) was determined by chemical correlation (Scheme 3.).



(a) BzCl (1.1 eq.), Et_3N (1.2 eq.), THF, 0-20°C, 2 h, 88 %.

Scheme 3

The optical rotation of our dibenzoyl compound (**9**)[24] ($[\alpha]_D$= -2.78; c = 0.78, methanol) comparing to the literature data for (*S*)-(**9**) ($[\alpha]_D$= -0.8; c = 0.13, methanol) [25]proved its (*S*)-configuration, and therefore (*R*)-configuration of our enzymic product (**2a**).

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(18) Data for *cis*-5-hydroxy-2-phenyl-1,3-dioxane (**6**): ν_{max} (KBr)/cm^{-1} 3285, 3190, 2987, 2920, 2855, 1452, 1391, 1340, 1279, 1239, 1231, 1156, 1089, 1017,996, 977, 948, 930, 831, 808, 741; δ_H (500 MHz, $CDCl_3$): 3.15 (1H, d, *J*= 10.0 Hz, OH), 3.58 (1 H, br d, *J*= 10.0 Hz), 4.09 (2H, dd, *J*= 12.0 and 1.5 Hz), 4.17 (2H, dd, *J*= 12.0 and 1.5 Hz), 5.54 (1H, s) , 7.36 (3H, m), 7.49 (2H, m). Spectra are in agreement with literature data.[17]
(19) Data for *cis*-5-benzoyloxy-2-phenyl-1,3-dioxane (**7**): m.p. 92-93°C (ethanol); ν_{max} (KBr)/cm^{-1} 3060, 2990, 2850, 1720, 1595, 1450, 1390, 1360, 1310, 1280, 1265, 1145, 1110, 1010,

790, 750, 710; δ_H (500 MHz, $CDCl_3$): 4.27 and 4.43 (2H, d, *J*=12 Hz, 2 CH_2), 4.96 (1H, s, CH-OBz), 5.72 (1H, s, CH-Ph), 7.39 (3H, m, Ar-H), 7.46 (2H, t, *J*= 7.5 Hz, Ar-H), 7.56 (3H, m, Ar-H), 8.17 (2H, d, *J*= 7.5 Hz, Ar-H).

(20) Data for 2-benzoyloxy-1,3-propanendiol (**1a**): m.p. 72-73°C (toluene-hexane 2:1); ν_{max} (KBr)/cm^{-1} 3300, 2950, 2920, 2850, 1720, 1590, 1450, 1350, 1270, 1105, 1020, 955, 705; δ_H (500 MHz, $CDCl_3$): 2.59 (2H, 2 OH), 3.87 (m, 4H, 2 CH_2-O), 5.08 (m, 1H, CH-O), 7.36 (t, 2H, *J*= 7.5 Hz, 2 *m*-Ar-H), 7.50 (t, 1H, *J*= 7.5 Hz, *p*-Ar-H), 7.89 (d, 2H, *J*= 7.5 Hz, 2 *o*-Ar-H).

(21) The prochiral diol (1a, 300 mg, 1.53 mmol) was dissoved in dry THF (3 ml). To this solution vinyl acetate (1 ml), hexane (3 ml) and lipase from porcine pancreas (PPL, 300 mg) were added and the resulting suspension was stirred at RT for 1 h. The lipase (which after washing by acetone and drying proved to be active in a subsequent reaction) was removed by filtration. The oily residue remaining after evaporation of the filtrate was purified by low pressure chromatography on silica gel using hexane - acetone 4 : 1 eluant mixture.
Data for (*R*)-3-acetoxy-2-benzoyloxy-1-propanol (**2a**, 230 mg, 63 %): $[\alpha]_D$= -27.4 (c 1, ethanol), 96 %e.e.; ν_{max} (KBr)/cm^{-1} 3400, 2960, 2910, 2850, 1730, 1720, 1590, 1470, 1450, 1350, 1270, 1110, 1020, 960, 705; δ_H (500 MHz, $CDCl_3$): 2.04 (s, 3H, O=C-CH_3), 3.32 (br s, 1H, OH), 3.85 (m, 2H, CH_2-OH), 4.40 (m, 2H, CH_2-OAc), 5.33 (m, 1H, CH-O), 7.43 (t, 2H, *J*= 7.5 Hz, 2 *m*-Ar-H), 7.56 (t, 1H, *J*= 7.5 Hz, 1 *p*-Ar-H), 8.04 (d, 2H, *J*= 7.5 Hz, 2 *o*-Ar-H).

(22) Reaction of **2a** with (*R*)-MTPA-Cl (1.2 eqv., CCl_4, pyridine) gave diastereomeric MTPA esters. Useful signals (δ_H, 500 MHz, $CDCl_3$): 3.517 [s, OCH_3, (*R*)-2a MTPA ester], 3.544 [s, OCH_3, (*S*)-2a MTPA ester].

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(24) Data for (*S*)-1-acetoxy-2,3-benzoyloxypropane (**9**): $[\alpha]_D$= -2.78 (c 0.78, methanol); ν_{max} (KBr)/cm^{-1} 3050, 2950, 1740, 1720, 1600, 1580, 1485, 1450, 1360, 1315, 1250, 1175, 1100, 1070, 1045, 1025, 935, 850, 710, 680; δ_H (500 MHz, $CDCl_3$): 2.09 (3H,s), 4.47 (2H, mc, CH_2OAc), 4.62 (2H, mc, CH_2OBz), 5.68 (1H, m, CH-OBz), 7.26 (4H, mc, 4 *m*-ArH), 7.44 (2H, mc, 2 *p*-Ar-H), 8.04 (4H, mc, 4 *o*-Ar-H). Spectra are in agreement with literature data.[25]

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