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Lipase-catalyzed enantiotope selective acetylation of 2-acyloxypropane-1,3-diols. Influence of the acyl moiety on the selectivity

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Abstract

Preparation and lipase-catalyzed enantiotope selective acetylation of the prochiral 2-acyloxypropane-1,3-diols (**1a–h**) including sulfonic ester (**1a–c**) and carboxylic ester (**1d–h**) series is described. A strong influence of the acyl moiety in these diols on the enantiotope selectivity of the porcine pancreatic lipase (PPL)-catalyzed reaction with vinyl acetate was observed. The best results were achieved with the 2-(4-methylbenzoyl)oxy- and cyclohexanecarbonyloxypropane-1,3-diols (**1g** and **1h**) resulting in acetylated products (**2g**) of $\geq 98\%$ e.e. in 77% yield and (**2h**) of 95% e.e. in 66% yield, respectively.

Keywords: Enzymes and enzyme reactions; Acylation; Enantioselection; Substituent effects

1. Introduction

In the preparation of homochiral biologically active molecules, such as platelet-activating factor (PAF) [1], phospholipids [2], phospholipase A_2 inhibitors [3], and many others [4], chiral glycerol derivatives of high enantiomeric purity might be useful C_3 building blocks.

Enantiomer selective biocatalytical methods [5–7], e.g. kinetic resolution of racemic glycerol derivatives such as glycerol acetonide [8,9], glycerol-2,3-carbonate [10], 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**) (Fig. 1).

Among the 2-*O*-alkylglycerol derivatives (**1** or **3**, R_1,R_2 = O-alkyl, H), the enantiotope selective biotransformations of 2-benzyloxy substituted compounds are the most studied. Hydrolyses of the corresponding diacyl compound (**3**, R_1,R_2 = OBn, H) with different enzymes under various conditions were performed [11–14,16].

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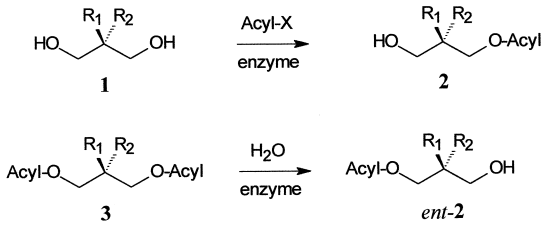


Fig. 1. Enantiotope selective biotransformation of prochiral 1,3-propanediol derivatives (**1** and **2**).

The slow racemization (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 [16]. Enzyme-catalyzed acylation of 2-*O*-benzylglycerol (**1**) R_1,R_2 = OBn, H) [15–18] and other 2-*O*-alkyl-(**1**, R_1,R_2 = *O*-alkyl, H) such as the 2-*O*-methyl– [17,18], 2-*O*-ethylglycerols [17,18] yielding optically active monoacetates (**2**, R_1,R_2 = O-alkyl, H) were also studied. The lipase-catalyzed processes proved to be *pro-S* selective for the 2-*O*-alkylglycerol derivatives. Consequently, acetylation of **1** yielded **2** [16] and hydrolyses of the corresponding diacyl derivative (**3**, R_1 = H, R_2 = OBn) afforded the (*R*)-enantiomer (*ent*-**2**, R_1 = OBn, R_2 = H) [11,16].

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 enzymatic enantiotope selective acylation of 2-*O*-acylglycerol derivatives (**1**, R_1,R_2 = *O*-acyl, H) was found. It is worthwhile 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* [19].

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 (**1a–h**, R_1,R_2 = *O*-acyl, H). In our preliminary work, the 2-benzoyloxypropane-1,3-diol (**1**, R_1 = OBz, R_2 = H) was selected as the first representative of this class [20]. This diol was tested with several hydrolases for the enantiotope selective acetylation. The best result was achieved with porcine pancreatic lipase (PPL) and vinyl acetate in hexane-THF yielding monoacetate (**2**, R_1 = OBz, R_2 = H) of 96% e.e. [20]. In this study our aim was to investigate the influence of the 2-acyloxy moiety on the enantiotope selectivity of enzymatic acetylation of these prochiral 1,3-diols. Hence, several prochiral carboxylic and sulfonic ester derivatives of glycerol were prepared and tested for enzymatic acetylation.

2. Experimental

2.1. Materials and methods

The ^{1}H NMR spectra were recorded on a Bruker AW-250 spectrometer operating at 250 MHz. For enantiomeric excess determinations, a Bruker DRX-500 spectrometer operating at 500 MHz was used. All spectra were taken in $CDCl_3$ solution and chemical shift values are expressed in ppm values from TMS as internal standard on δ scale. IR spectra of thin film samples were taken on a Specord 2000 spectrometer. Optical rotations were determined on a Perkin-Elmer 241 polarimeter at 20°C. Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} alumina sheets (using hexane:acetone 10:4, if otherwise not stated). Spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating of the dried plates. Preparative chromatographic separations were performed using vacuum chromatography [21] on Merck Kieselgel 60 (0.063–0.200 mm). Chemicals were products of Fluka or Aldrich. All solvents used were freshly distilled. CcL (lipase from *Candida rugosa*, formerly *C. cylindracea*), PPL (lipase from porcine pancreas) and papain were obtained from Sigma. PfL (lipase from *Pseudomonas fluorescens*) was a product of Fluka. Novozym 435 (immobilized lipase of *C. antarctica*) and Lipozym IM (immobilized lipase of *Mucor miehei*) were gifts from Novo Nordisk. Lipase A (lipase from *As-*

pergillus niger), Lipase AK (lipase from *P. fluorescens*); Lipase G (lipase from *Penicillium camembertii*), Lipase M (lipase from *M. javonicus*), Lipase N (lipase from *Rhisopus niveus*) and Lipase PS (lipase from *Pseudomonas* spp.) were gifts from Amano.

2.2. cis-5-Hydroxy-2-phenyl-1,3-dioxane (6)

The reaction between glycerol (**4**) (50 g, 0.54 mol) and benzaldehyde (**5**) (50 g, 0.47 mol) according to the known method [22] gave crystalline product (**6**, 30 g, 35%).

^{1}H NMR: 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); IR (KBr, cm^{-1}): 3285, 3190, 2985, 2920, 2855, 1450, 1390, 1340, 1280, 1240, 1230, 1155, 1090, 1015, 995, 975, 950, 930, 830, 810, 740. (Spectra are in agreement with literature data [22].)

2.3. Preparation of cis-5-(aryl- or alkylsulfonyl)oxy-2-phenyl-1,3-dioxanes (7a–c)

General procedure: To a solution of *cis*-5-hydroxy-2-phenyl-1,3-dioxane (**6**, 3.73 g, 20 mmol) and triethylbenzylammonium chloride (50 mg) in diethyl ether (25 ml) finely powdered KOH (3.36 g, 60 mmol) was added and the mixture was cooled to −5°C. At this temperature aryl- or alkylsulfonyl chloride (22 mmol) was added portionwise. The resulting mixture was vigorously stirred at −5°C for 40 min and at room temperature for 15 min. The white suspension was diluted with ethyl acetate (25 ml) and washed with water (15 ml). The aqueous phase was re-extracted with ethyl acetate (2 × 25 ml). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent in vacuo afforded the desired acylated products (**7a–c**).

2.3.1. cis-2-Phenyl-5-(p-toluenesulfonyl)oxy-1,3-dioxane (7a)

According to the general procedure, 6.15 g (92%) of white crystalline solid was prepared.

M.p.: 120–123°C (ethyl acetate); ^{1}H NMR: 2.40 (s, 3H, CH_3), 4.01 and 4.23 (m(A_2B_2), 4H, 2 CH_2), 4.43 (s, 1H, CH–O), 5.45 (s, 1H, O–CH–O), 7.26–7.65 (m, 7H, ArH), 7.82 (d, 2H, ArH); IR (KBr, cm^{-1}): 3445, 2860, 1650, 1465, 1395, 1355, 1190, 1175, 1145, 1080, 1015, 985, 930, 745; Calcd. for $C_{17}H_{18}O_5S$: C 61.06, H 5.43, S 9.59; found C 60.89, H 5.42, S 9.61.

2.3.2. cis-5-Benzenesulfonyloxy-2-phenyl-1,3-dioxane (7b)

According to the general procedure, 4.8 g (75%) of white crystalline solid was prepared.

M.p.: 127–130°C (diethyl ether); ^{1}H NMR: 4.09 and 4.27 (m(A_2B_2), 4H, 2 CH_2), 4.52 (s, 1H, CH–O), 5.49 (s, 1H, O–CH–O), 7.26–7.68 (m, 7H, ArH), 7.97 (d, 2H, ArH); IR (KBr, cm^{-1}): 3445, 2855, 1685, 1640, 1445, 1350, 1185, 1145, 1075, 1015, 910, 870, 850, 755; Calcd. for $C_{16}H_{16}O_5S$: C 59.99, H 5.03, S 10.01; found C 60.07, H 5.02, S 10.03.

2.3.3. cis-5-Methanesulfonyloxy-2-phenyl-1,3-dioxane (7c)

The general procedure followed preparative vacuum column chromatography (silica gel, hexane:acetone 10:1) yielded 2.22 g (43%) of white crystals.

M.p.: 128–130°C (ethyl acetate); ^{1}H NMR: 3.14 (s, 3H, CH_3), 4.18 and 4.44 (m(A_2B_2), 4H, 2CH_2), 4.68 (s, 1H, CH–O), 5.56 (s, 1H, O–CH–O), 7.37 (mc, 3H, ArH), 7.50 (mc, 2H, ArH); IR (KBr, cm^{-1}): 3425, 3025, 1450, 1385, 1330, 1170, 1135, 1080, 1015, 980, 955, 940, 910, 870, 740; Calcd. for $C_{11}H_{14}O_5S$: C 51.15, H 5.46, S 12.41; found C 51.24, H 5.47, S 12.43.

2.4. Preparation of cis-5-acyloxy-2-phenyl-1,3-dioxanes (7d–i)

General procedure: To a solution of **6** (3.73 g, 20 mmol), pyridine (1.95 ml, 24 mmol) and 4-(dimethylamino)pyridine (50 mg) in dichloromethane (30 ml), acyl chloride (22

mmol) was added at room temperature and the mixture was stirred for 1–12 h. The resulting mixture was washed with 5% HCl solution (2 × 10 ml), 10% Na_2CO_3 solution (10 ml) and brine (10 ml). After drying over Na_2SO_4 and evaporation of the solvent, the solid residue was recrystallized to give white crystals (**7d–i**).

*2.4.1. cis-5-Acetyloxy-2-phenyl-1,3-dioxane (**7d**)*

Yield: 84%; M.p.: 98–101°C (hexane:ethyl acetate 1:1); ^{1}H NMR: 2.16 (s, 3H, CH_3), 4.10–4.28 (2 × dd, 4H, $2CH_2$), 4.70 (d, 1H, CH–O), 5.55 (s, 1H, O–CH–O), 7.35 (m, 3H, Ar–H), 7.49 (m, 2H, Ar–H); IR (KBr, cm^{-1}): 3440, 1730, 1460, 1390, 1375, 1245, 1140, 1085, 1020, 985, 950, 920, 745; Calcd. for $C_{12}H_{14}O_4$: C 64.85, H 6.35; found C 64.79, H 6.36.

*2.4.2. cis-5-Diphenylacetyloxy-2-phenyl-1,3-dioxane (**7e**)*

Yield: 86%; M.p.: 116–119°C (hexane:ethyl acetate 1:1); ^{1}H NMR: 4.12–4.33 (m(A_2B_2), 4H, $2CH_2$), 4.76 (br s, 1H, CH–O), 5.19 (s, 1H, Ph–CH–Ph), 5.55 (s, 1H, O–CH–O), 7.16–7.56 (m, 15H, Ar–H); IR (KBr, cm^{-1}): 3435, 1725, 1495, 1450, 1390, 1330, 1310, 1270, 1195, 1160, 1140, 1085, 1020, 745. Calcd. for $C_{24}H_{22}O_4$: C 76.99, H 5.92; found C 76.81, H 5.93.

*2.4.3. cis-2-Phenyl-5-pivaloyloxy-1,3-dioxane (**7f**)*

Yield: 83%; M.p.: 106–111°C (hexane:ethyl acetate 1:1); ^{1}H NMR: 1.29 (s, 9H, $3CH_3$), 4.11–4.27 (m(A_2B_2), 4H, $2CH_2$), 4.65 (br s, 1H, CH–O), 5.53 (s, 1H, O–CH–O), 7.37 (m, 3H, Ar–H), 7.49 (m, 2H, Ar–H); IR (KBr, cm^{-1}): 3400, 2985, 1705, 1455, 1395, 1284, 1165, 1140, 1085, 1015, 990, 955, 745; Calcd. for $C_{15}H_{20}O_4$: C 68.16, H 7.63; found C 68.15, H 7.64.

*2.4.4. cis-5-(4-methylbenzoyl)oxy-2-phenyl-1,3-dioxane (**7g**)*

Yield: 80%; M.p.: 119–122°C (hexane:ethyl acetate 1:1); ^{1}H NMR: 2.41 (s, 3H, CH_3), 4.21–4.46 (m(A_2B_2), 4H, $2CH_2$), 4.94 (br s, 1H, CH–O), 5.61 (s, 1H, O–CH–O), 7.24 (d, 2H, Ar–H), 7.38 (m, 3H, Ar–H), 7.51 (m, 2H, Ar–H), 8.06 (d, 2H, Ar–H),; IR (KBr, cm^{-1}): 3445, 1775, 1710, 1610, 1455, 1390, 1275, 1210, 1145, 1115, 1085, 1020, 980, 950, 900, 755, 745; Calcd. for $C_{18}H_{18}O_4$: C 72.47, H 6.08; found C 72.34, H 6.07.

*2.4.5. cis-5-Cyclohexanecarbonyloxy-2-phenyl-1,3-dioxane (**7h**)*

Yield: 96%; M.p.: 73–75°C (hexane); ^{1}H NMR: 1.20–1.36 (m, 3H), 1.44–1.56 (m, 2H), 1.65 (mc, 1H), 1.72–1.80 (m, 2H), 1.94–2.0 (m, 2H), 2.45 (mc, 1H, CH–CO), 4.15 and 4.25 (m(A_2B_2), 4H, 2 CH_2–O), 4.69 (br s, 1H, CH–Ph), 5.54 (s, 1H, O–CH–O), 7.32–7.40 (m, 3H, Ar–H), 7.48–7.52 (m, 2H, Ar–H); IR (KBr, cm^{-1}): 2936, 2880, 1712, 1456, 1392, 1365, 1312, 1248, 1176, 1140, 1084, 1000, 744, 696; Calcd. for C_{17} H_{22} O_4: C 70.32, H 7.64; found C 70.18, H 7.72.

*2.4.6. cis-5-Lauryloxy-2-phenyl-1,3-dioxane (**7i**)*

Yield: 60% (purified by chromatography on silica gel using hexane–acetone 10:1); waxy solid; ^{1}H NMR: 0.87 (t, 3H, CH_3), 1.20–1.38 (m, 16H, 8 CH_2), 1.67 (mc, 2H, CH_2), 2.44 (t, 2H, CH_2–CO), 4.16 and 4.27 (m(A_2B_2), 4.72 (br s, 1H, CH–Ph), 5.56 (s, 1H, O–CH–O), 7.33–7.40 (m, 3H, Ar–H), 7.49–7.53 (m, 2H, Ar–H); IR (KBr, cm^{-1}): 2920, 2880, 1736, 1456, 1432, 1392, 1360, 1276, 1240, 1200, 1176, 1144, 1088, 1016, 744, 696; Calcd. for C_{22} H_{34} O_4: C 72.89, H 9.45; found C 73.01, H 9.52.

*2.5. Preparation of 2-(aryl-or alkylsulfonyl)oxypropane-1,3-diols (**1a–c**)*

General procedure: To a 20% methanolic solution of the *cis*-5-(aryl-or alkylsulfonyl)oxy-2-phenyl-1,3-dioxane (**7a–c**, 9–18 mmol), equimolar amount of concentrated hydrochloric acid was added and the mixture was refluxed for 1 min. After cooling to room temperature, most of

the methanol was removed in vacuo, the solution was neutralized with saturated Na_2CO_3 solution, and further diluted with water (up to a final volume of 20–30 ml. After complete evaporation of the methanol, the residue was extracted with hexane (2×15 ml, removal of benzaldehyde), and with ethyl acetate (3×20 ml). The combined ethyl acetate layers were dried over Na_2SO_4. Evaporation in vacuo resulted the corresponding product (**1a–c**).

*2.5.1. 2-(p-Toluenesulfonyl)oxypropane-1,3-diol (**1a**)*

Oil. Yield: 76%; ^{1}H NMR: 2.42 (s, 3H, CH_3), 3.74 (m, 4H, $2CH_2$–O), 4.53 (m(t), 1H, CH–O), 7.33 (d, 2H, Ar), 7.81 (d, 2H, Ar); IR (film, cm^{-1}): 3395 (br), 2950, 1700, 1600, 1455, 1360, 1175, 1095, 1055, 925, 815; Calcd. for $C_{10}H_{14}O_5S$: C 48.77, H 5.73, S 13.02; found C 48.70, H 5.74, S 13.00.

*2.5.2. 2-Benzenesulfonyloxypropane-1,3-diol (**1b**)*

Oil. Yield: 74%; ^{1}H NMR: 3.76 (m, 4H, $2CH_2$–O), 4.59 (m(t), 1H, CH–O), 7.56 (t, 2H, Ar), 7.69 (t, 1H, Ar), 7.94 (d, 2H, Ar); IR (film, cm^{-1}): 3385 (br), 3945, 1450, 1360, 1185, 1095, 1055, 1010, 925, 790, 755; Calcd. for $C_9H_{12}O_5S$: C 46.54, H 5.21, S 13.80; found C 46.52, H 5.20, S 13.79.

*2.5.3. 2-Methanesulfonyloxypropane-1,3-diol (**1c**)*

Yield: 69%; M.p.: 65–68°C (hexane–ethyl acetate 1:1); ^{1}H NMR (MeOH-d_4): 3.07 (s, 3H, CH_3), 3.68 (m, 4H, $2CH_2$–O), 4.53 (m, 1H, CH–O); IR (film, cm^{-1}): 3385 (br), 1340, 1170, 1085, 1040, 1010, 985, 930, 795; Calcd. for $C_4H_{10}O_5S$: C 28.23, H 5.92, S 18.84; found C 28.28, H 5.93, S 18.83.

*2.6. Preparation of 2-acyloxypropane-1,3-diols (**1d–h**)*

General procedure: To a 20% isopropanolic solution of the *cis*-5-acyloxy-2-phenyl-1,3-dioxane (**7d–h**, 16–18 mmol), Pd–C (5%) was added and the mixture was vigorously stirred under hydrogen at room temperature. After uptaking the calculated amount of hydrogen (2 equivalents), the catalyst was filtered off. Evaporation of the solvent in vacuo yielded the corresponding product (**1d–h**).

*2.6.1. 2-Acetoxypropane-1,3-diol (**1d**)*

Oil. Yield: 67%; ^{1}H NMR: 2.13 (s, 3H, CH_3), 3.81 (m(d), 4H, $2CH_2$–O), 4.89 (mc, 1H, CH–O); IR (film, cm^{-1}): 3380 (br), 2940, 1735, 1245, 1045, 960, 830; Calcd. for $C_5H_{10}O_4$: C 44.77, H 7.51; found C 44.70, H 7.52.

*2.6.2. 2-Diphenylacetoxypropane-1,3-diol (**1e**)*

Oil. Yield: 75%; ^{1}H NMR: 3.74 (mc, 4H, $2CH_2$–O), 4.87 (mc, 1H, CH–O), 5.06 (s, 1H, Ph–CH–Ph), 7.10–7.28 (m, 10H, Ar–H); IR (film, cm^{-1}): 3405 (br), 1735, 1495, 1455, 1305, 1190, 1150, 1050, 1010, 745, 700; Calcd. for $C_{17}H_{18}O_4$: C 71.31, H 6.34; found C 71.43, H 6.33.

*2.6.3. 2-Pivaloyloxypropane-1,3-diol (**1f**)*

Oil. Yield: 77%; ^{1}H NMR: 1.22 (s, 9H, CH_3), 3.77 (m(d), 4H, $2CH_2$-O), 4.86 (m(t), 1H, CH–O); IR (film, cm^{-1}): 3415 (br), 2970, 2845, 1710, 1480, 1460, 1400, 1370, 1285, 1170, 1040, 980, 770; Calcd. for $C_8H_{16}O_4$: C 54.53, H 9.15; found C 54.64, H 9.17.

*2.6.4. 2-(4-Methylbenzoyl)oxypropane-1,3-diol (**1g**)*

Yield: 76%; M.p..: 84–90°C (hexane:ethyl acetate 1:1); ^{1}H NMR: 2.38 (s, 3H, CH_3), 3.90 (m(d), 4H, $2CH_2$–O), 5.11 (m(t), 1H, CH–O), 7.20 (d, 2H, Ar–H), 7.91 (d, 2H, Ar–H); IR (film, cm^{-1}): 3410 (br), 1685, 1610, 1460, 1420, 1355, 1305, 1185, 1130, 1085, 1055, 1040, 835, 760, 700; Calcd. for $C_{11}H_{14}O_4$: C 62.85, H 6.71; found C 62.79, H 6.72.

*2.6.5. 2-Cyclohexanecarbonyloxypropane-1,3-diol (**1h**)*

Semisolid. Yield: 96%; ^{1}H NMR: 1.19–1.35 (m, 3H), 1.38–1.50 (m, 2H), 1.65 (mc, 1H),

1.71–1.81 (m, 2H), 1.87–1.96 (m, 2H), 2.34 (mc, 1H, CH–CO) 3.75–3.84 (m(dd), 4H, $2CH_2$–O), 4.89 (m(t), 1H, CH–O); IR (film, cm^{-1}): 3400 (br), 2936, 2856, 1710, 1452, 1428, 1384, 1312, 1248, 1172, 1136, 1040; Calcd. for $C_{10}H_{18}O_4$: C 59.39, H 8.97; found C 59.29, H 9.02.

*2.7. Preparation of racemic 3-acetyloxy-2-acyloxypropan-1-ols (rac-**2a–g**)*

General procedure: To a solution of the 2-acyloxypropane-1,3-diol (**1a–g**, 5 mmol) in ethyl acetate (10 ml), pyridine (0.45 ml), 4-(dimethylamino)pyridine (25 mg) and acetic acid anhydride (0.47 ml) were added. The mixture was stirred at room temperature for 1 h and then washed with 5% HCl solution (2×5 ml), 10% Na_2CO_3 solution (5 ml) and brine (5 ml). After drying over Na_2SO_4 the solvent was removed in vacuo and the residue was purified by preparative vacuum column chromatography (silica gel, hexane–acetone) affording the product (*rac*-**2a–g**) as an oil.

*2.7.1. 3-Acetoxy-2-(p-toluenesulfonyl)oxypropan-1-ol (rac-**2a**)*

Yield: 51%; ^{1}H NMR: 1.92 (s, 3H, CH_3–CO), 2.45 (s, 3H, Ar–CH_3), 3.75 (mc, 2H, CH_2–O), 4.14–4.26 (m, 2H, CH_2–OAc), 4.70 (mc, 1H, CH–O), 7.34 (d, 2H, Ar), 7.82 (d, 2H, Ar); IR (film, cm^{-1}): 3415 (br), 2955, 1745, 1600, 1360, 1240, 1190, 1175, 1100, 1050, 930, 915, 775; Calcd. for $C_{12}H_{16}O_6S$: C 49.99, H 5.59, S 11.12; found C 49.98, H 5.61, S 11.11.

*2.7.2. 3-Acetoxy-2-benzenesulfonyloxypropan-1-ol (rac-**2b**)*

Yield: 47%; ^{1}H NMR: 1.92 (s, 3H, CH_3–CO), 3.78 (mc, 2H, CH_2–O), 4.15–4.28 (m, 2H, CH_2–OAc), 4.72 (mc, 1H, CH–O), 7.57 (t, 2H, Ar–H), 7.69 (t, 1H, Ar–H), 7.94 (d, 2H, Ar–H); IR (film, cm^{-1}): 3415 (br), 2955, 1745, 1450, 1365, 1215, 1190, 1125, 1100, 1050, 930, 790, 755; Calcd. for $C_{11}H_{14}O_6S$: C 48.17, H 5.14, S 11.69; found C 48.24, H 5.14, S 11.72.

*2.7.3. 3-Acetoxy-2-methanesulfonyloxypropan-1-ol (rac-**2c**)*

Yield: 45%; ^{1}H NMR: 2.12 (s, 3H, CH_3–CO), 3.13 (s, 3H, CH_3–S), 3.85 (mc, 2H, CH_2–O), 4.22–4.41 (m, 2H, CH_2–OAc), 4.88 (mc, 1H, CH–O); IR (film, cm^{-1}): 3520 (br), 3030, 2940, 1745, 1350, 1235, 1175, 1050, 975, 930, 805, 740; Calcd. for $C_6H_{12}O_6S$: C 33.96, H 5.70, S 15.11; found C 33.96, H 5.71, S 15.15.

*2.7.4. 2,3-Diacetoxypropan-1-ol (rac-**2d**)*

Yield: 54%; ^{1}H NMR: 2.11 (s, 3H, CH_3–CO), 2.16 (s, 3H, CH_3–CO), 3.71–3.77 (m, 2H, CH_2–O), 4.12–4.38 (m, 2H, CH_2–OAc), 5.08 (mc, 1H, CH–O); IR (film, cm^{-1}): 3465 (br), 2960, 1745, 1440, 1375, 1230, 1050, 960,845; Calcd. for $C_7H_{12}O_5$: C 47.73, H 6.87; found C 47.81, H 6.85.

*2.7.5. 3-Acetoxy-2-diphenylacetoxypropan-1-ol (rac-**2e**)*

Yield: 51%; ^{1}H NMR: 1.96 (s, 3H, CH_3–CO), 3.70 (mc, 4H, $2CH_2$–O), 4.16–4.31 (m, 2H, CH_2–OAc), 5.05 (mc, 1H, CH–O), 5.07 (s, 1H, Ph–CH–Ph), 7.30 (mc, 10H, Ar–H); IR (film, cm^{-1}): 3460 (br), 3030, 2955, 1740, 1585, 1495, 1450, 1370, 1235, 1190, 1150, 1045, 1015, 745, 700; Calcd. for $C_{19}H_{20}O_5$: C 69.50, H 6.14; found C 69.67, H 6.15.

*2.7.6. 3-Acetoxy-2-pivaloyloxypropan-1-ol (rac-**2f**)*

Yield: 48%; ^{1}H NMR: 1.22 (s, 9H, $3CH_3$), 2.07 (s, 3H, CH_3–CO), 3.74 (mc, 2H, CH_2–O), 4.19–4.37 (m, 2H, CH_2–OAc), 5.07 (mc, 1H, CH–O); IR (film, cm^{-1}): 3475 (br), 2970, 1730, 1480, 1460, 1400, 1370, 1285, 1235, 1160, 1050; Calcd. for $C_{10}H_{18}O_5$: C 55.03, H 8.31; found C 55.12, H 8.30.

*2.7.7. 3-Acetoxy-2-(4-methylbenzoyl)oxypropan-1-ol (rac-**2g**)*

Yield: 50%; ^{1}H NMR: 2.08 (s, 3H, CH_3–CO), 2.42 (s, 3H, Ar–CH_3), 3.87 (m(t), 2H, CH_2–O), 4.41 (m(d), 2H, CH_2–OAc), 5.31 (m(t), 1H, CH–O), 7.26 (d, 2H, Ar–H), 7.93 (d,

2H, Ar–H); IR (KBr, cm^{-1}): 3455 (br), 2955, 1715, 1610, 1510, 1445, 1410, 1370, 1275, 1180, 1110, 1045, 1020, 920, 840, 750; Calcd. for $C_{13}H_{16}O_5$: C 61.90, H 6.39; found C 62.04, H 6.41.

2.8. Enzymatic acetylation of 2-acyloxypropane-1,3-diols (**1a–h**)

General procedure: For solvents, enzymes, reaction times and yields, see Tables 1–3. To a solution of the prochiral diol (**1a–h**, 250 mg) in the solvent indicated, vinyl acetate and enzyme were added. After stirring the mixture at room temperature for the given time, the enzyme was filtered off, the solvent was removed from the filtrate in vacuo and the residue was purified by preparative vacuum column chromatography (silica gel, hexane:acetone 10:1.5). For yields, optical rotation and enantiomeric composition of the products (**2a–h**), see Tables 1–3. Spectral (^{1}H NMR and IR) data for the products (**2a–g**) were indistinguishable from that of the racemic 3-acetoxy-2-acyloxypropan-1-ols (*rac*-**2a–g**).

2.8.1. 3-Acetoxy-2-cyclohexanecarbonyloxypropan-1-ol (**2h**)

^{1}H NMR: 1.19–1.34 (m, 3H), 1.39–1.52 (m, 2H), 1.65 (mc, 1H), 1.72–1.80 (m, 2H), 1.87–1.96 (m, 2H), 2.07 (s, 3H, CH_3–CO), 2.36 (mc, 1H, CH–CO), 3.73 (mc, 2H, CH_2–O), 4.21–4.35 (m, 2H, CH_2–OAc), 5.08 (mc, 1H, CH–O); IR (KBr, cm^{-1}): 3464 (br), 2936, 2856, 1736, 1452, 1416, 1372, 1244, 1168, 1048; Calcd. for $C_{12}H_{20}O_5$: C 59.00, H 8.25; found C 59.08, H 8.33.

2.9. Preparation of MTPA esters from the racemic and optically active 3-acetyloxy-2-acyloxypropan-1-ols (**2a–g**)

The racemic or optically active 3-acetyloxy-2-acyloxypropan-1-ols (**2a–g**, 9–12 mg), pyridine (25 μl) and (4-dimethylamino)pyridine (2 mg) were added to a solution of 5% (*R*)-MTPA-Cl in carbon tetrachloride (350 μl) and the mixture was heated in a sealed ampoule at 50°C for 3 h. The resulting mixture was successively washed with 5% HCl solution (1 ml), saturated Na_2CO_3 solution (1 ml) and brine (1 ml). The organic phase was dried over Na_2SO_4 and the solvent was evaporated. The diastereomeric ratio of the forming MTPA esters were determined from their ^{1}H NMR spectra (500 MHz, $CDCl_3$, TMS). Several signals used for enantiomeric purity determination are listed in Table 1.

2.10. Determination of the absolute configuration of the monoacetates (**2a–h**)

2.10.1. Enzymatic acetylation of 3-benzyloxypropane-1,2-diol (**9**) [24]

To a solution of **9** (9.5 g) in hexane (50 ml), THF (50 ml) and vinyl acetate (25 ml) Lipase

Table 1
PPL-catalyzed acetylation of 2-acyloxypropane-1,3-diols (**1a–h**)

Product	Time	Yield (%)	Configuration	E.e. (%)[a]	$[\alpha]_D$ (c 1, methanol)	^{1}H NMR signals of **2**-MTPA esters
2a	7 days	74	*S*	31	+9.2	1.93 (s); 1.93 (s)
2b	3 h	71	*S*	31	+6.2	4.59–4.62 (dd); 4.57–4.59 (dd)
2c	11 h	67	–	0	0.0	–
2d	6 h	79	*S*	40	+1.8	4.56 (dd), 4.61 (dd)
2e	2 days	80	*R*	16	−2.3	5.01 (s), 4.95 (s)
2f	6 h	82	*R*	67	−8.0	1.17 (d), 1.18 (d)
2g	11 h	77	*R*	≥ 98	−27.5	3.49 (d), 3.52 (d)
2h	5 h	66	*R*	> 95[b]	−8.7	–

Reaction conditions: 0.25 g of substrate (**1a–h**), 200 mg of PPL, 0.8 ml of vinyl acetate, 2.5 ml of THF and 2.5 ml of hexane, stirring at room temperature.

[a] Determined from the ^{1}H NMR spectra of the **2a–g** MTPA esters.

[b] Determined from optical rotation compared to **2h** prepared from **12h** of known e.e.

Table 2
Effect of the solvent on acetylation of 2-(*p*-toluenesulfonyl)oxypropane-1,2-diol (**1a**)

Solvent	Time	**2a**		
		Yield (%)	E.e. (%)	$[\alpha]_D$ (c 1, methanol)
Acetonitrile	7 days	0		
Chloroform	7 days	0		
Diethyl ether	7 days	0		
Ethyl acetate	10 h	64	0	0
Vinyl acetate	7.5 h	67	5	+1.6
THF	5 h	77	15	+4.5
t-Butanol	5 h	46	16	+4.7
Hexane:THF 1:1 (5 ml)	7 days	74	31	+9.2

Reaction conditions: 0.25 g of substrate (**1a**), 200 mg of porcine pancreas lipase (PPL), 0.6 ml of vinyl acetate, 3 ml of solvent, stirring at room temperature.

AK (1 g) was added and the mixture was stirred at room temperature for 27 h. The enzyme was filtered off, the solvent was evaporated from the filtrate and the residue was subjected to preparative vacuum column chromatography (silica gel, hexane:acetone 10:0.5 to 10:2) to give (*R*)-1-acetoxy-3-benzyloxypropan-2-ol [**10**, yield: 5.2 g, $[\alpha]_D = -3.3$ (c 1, chloroform); Ref. [24]: $[\alpha]_D = +4.1$ (c 1.04, chloroform), enantiomerically pure (*S*)-**10**] and (*S*)-1,2-diacetoxy-3-benzyloxypropane [**11**, yield: 5.2 g, $[\alpha]_D = +12.4$ (c 0.5, chloroform); Ref. [24]: $[\alpha]_D = +14.0$ (c 0.5, chloroform), enantiomerically pure (*S*)-**11**].

*2.10.2. Catalytic hydrogenation of (R)-1-acetoxy-3-benzyloxypropan-2-ol (**10**)*

A solution of **10** [2.0 g, 8.9 mmol, $[\alpha]_D = -3.3$ (c 1, chloroform)] in isopropanol (20 ml) was hydrogenated on 10% Pd–C (300 mg) at 40°C for 45 min. The catalyst was filtered off and solvent was evaporated in vacuo. Yield: 1.18 g (100%) of (*R*)-3-acetoxypropane-1,2-diol (**13**) [11] {$[\alpha]_D = -9.9$ (c 2, pyridine)}.

*2.11. Bis-sulfonylation of (R)-3-acetoxypropane-1,2-diol (**13**)*

General procedure: To a solution of **13** [0.40 g, 3.0 mmol, $[\alpha]_D = -9.9$ (c 2, pyridine)], triethylamine (1.0 ml, 7.2 mmol) and 4-(dimethylamino)pyridine (10 mg) in dichloromethane (3 ml) *p*-toluenesulfonyl chloride (1.26 g, 6.6 mmol, for *ent*-**8a**) or benzenesulfonyl chloride (1.17 g, 6.6 mmol, for *ent*-**8b**) was added and the resulting mixture was stirred at room temperature for 3 h. The mixture was then washed with 5% HCl solution (2 × 1 ml), 10% Na_2CO_3 solution (1 ml) and saturated $NaHCO_3$ (1 ml). The organic phase was dried over Na_2SO_4 and the solvent was evaporated in vacuo to leave the product (*ent*-**8a** or *ent*-**8b**) as an oil.

*2.11.1. (S)-1-acetoxy-2,3-di(p-toluenesulfonyl)oxypropane (ent-**8a**)*

Yield: 89%; $[\alpha]_D = -15.2$ (c 1, methanol); ^{1}H NMR: 1.91 (s, 3H, CH_3–CO), 2.45 (s, 3H, Ar–CH_3), 2.46 (s, 3H, Ar–CH_3), 4.02–4.23 (m, 4H, CH_2–OAc and CH_2–OTs), 4.76 (mc, 1H, CH–O), 7.32–7.37 (2 x d, 4H, Ar–H), 7.68–7.78 (2x d, 4H, Ar–H); IR (film, cm^{-1}): 2960, 1745, 1600, 1455, 1365, 1230, 1190, 1095, 1045, 1000, 935, 815, 765; Calcd. for $C_{19}H_{22}O_8S_2$: C 51.57, H 5.01, S 14.49; found C 51.57, H 5.02, S 14.47.

Table 3
Effect of the enzyme on acetylation of 2-(*p*-toluenesulfonyl)oxypropane-1,2-diol (**1a**)

Enzyme (mg)	Time	**2a**		
		Yield (%)	E.e. (%)	$[\alpha]_D$ (c 1, methanol)
Novozym 435 (50)[a]	1 day	0		
Papain (200)[a]	4 days	0		
PfL (20)[a]	1 day	0		
CcL (100)[a]	1 day	64	1	−0.2
Lipase G (100)[b]	7 days	51	1	+0.4
Lipase A (100)[b]	7 days	47	2	+0.6
Lipase AK (50)[a]	2 h	77	2	+0.7
Lipase PS (50)[a]	3 h	72	3	+0.9
Lipase N (100)[b]	7 days	47	4	+1.2
PPL (200)[b]	7 days	74	31	+9.2
Lipase M (50)[b]	2 days	75	34	+10.1
Lipozym IM (50)[b]	0.5 h	82	42	+12.5

Reaction conditions: 0.25 g of substrate in the solvent, RT.
[a] Solvent: vinyl acetate (2 ml).
[b] Solvent: THF (2.5 ml), hexane (2.5 ml), vinyl acetate (0.8 ml).

*2.11.2. (S)-1-acetoxy-2,3-di(benzenesulfonyl)oxypropane (ent-**8b**)*

Yield: 90%; $[\alpha]_D = -16.0$ (c 1, methanol); ^{1}H NMR: 1.89 (s, 3H, CH_3–CO), 4.07–4.23 (m, 4H, CH_2–OAc and CH_2–OSO_2Ph), 4.79 (mc, 1H, CH–O), 7.48–7.89 (m, 10H, Ar–H); IR (film, cm^{-1}): 2960, 1745, 1710, 1450, 1370, 1225, 1190, 1035, 1005, 935, 755; Calcd. for $C_{19}H_{18}O_8S_2$: C 49.27, H 4.38, S 15.47; found C 49.34, H 4.37, S 15.46.

*2.12. Arylsulfonylation of monoacetates (2a,b) from enzymatic acetylation of the prochiral diols (**1a,b**)*

General procedure: 3-Acetyloxy-2-(*p*-toluenesulfonyl)oxypropan-1-ol [**2a**, 0.33 mmol, $[\alpha]_D = +9.2$ (c 1, methanol)] or 3-acetyloxy-2-benzenesulfonyloxypropan-1-ol [**2b**, 0.33 mmol, $[\alpha]_D = +6.2$ (c 1, methanol)], 4-(dimethylamino)pyridine (1 mg) and triethylamine (0.05 ml) were dissolved in dichloromethane (0.7 ml) and *p*-toluenesulfonyl chloride (0.35 mmol, for **2a**) or benzenesulfonyl chloride (0.35 mmol, for **2b**) was added. The resulting mixture was stirred at room temperature for 3 h, and it was washed with 5% HCl solution, 10% Na_2CO_3 solution and saturated $NaHCO_3$. The organic phase was dried over Na_2SO_4 and solvent was evaporated in vacuo to leave the product (**8a** or **8b**) as an oil. Spectral (^{1}H NMR and IR) data were indistinguishable from those of the above products (*ent*-**8a** or *ent*-**8b**).

(*R*)-1-Acetoxy-2,3-di(*p*-toluenesulfonyl)oxypropane (**8a**): $[\alpha]_D = +8.8$ (c 1, methanol).

(*R*)-1-Acetoxy-2,3-di(benzenesulfonyl)oxypropane (**8b**): $[\alpha]_D = +4.8$ (c 1, methanol).

*2.13. Preparation of 1-acetoxy-2-acyloxy-3-benzyloxypropanes (**12d–h**)*

General procedure: To a solution of **10** [314 mg, 1.4 mmol, $[\alpha]_D = -3.3$ (c 1, chloroform)], triethylamine (0.23 ml) and 4-(dimethylamino)-pyridine (5 mg) in dichloromethane (1.5 ml) the corresponding acyl chloride (1.54 mmol) was added and the resulting mixture was stirred at room temperature for 1–6 h. The mixture was then washed with 5% HCl solution (2×0.5 ml), 10% Na_2CO_3 solution (0.5 ml) and saturated $NaHCO_3$ (0.5 ml). The organic phase was dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by preparative vacuum column chromatography (silica gel, hexane:acetone 5:1) to give the product (**12d–h**) as an oil.

*2.13.1. (R)-1,2-diacetoxy-3-benzyloxypropane (**12d**)*

Yield: 77%; $[\alpha]_D = -15.8$ (c 1, methanol); ^{1}H NMR: 2.02 (s, 3H, CH_3–CO), 2.07 (s, 3H, CH_3–CO), 3.58 (m(d), 2H, CH_2–OBn), 4.14–4.36 (m, 2H, CH_2–OAc), 4.53 (m, 2H, O–CH_2–Ph), 5.21 (mc, 1H, CH–O), 7.31 (mc, 5H, Ar–H); IR (film, cm^{-1}): 2865, 1745, 1455, 1370, 1225, 1100, 1050, 1020, 960, 740, 700; Calcd. for $C_{14}H_{18}O_5$: C 63.15, H 6.81; found C 63.30, H 6.82.

*2.13.2. (R)-1-acetoxy-3-benzyloxy-2-(diphenylacetoxy)propane (**12e**)*

Yield: 81%; $[\alpha]_D = -12.9$ (c 1, methanol); ^{1}H NMR: 1.89 (s, 3H, CH_3–CO), 3.57 (m(d), 2H, CH_2–OBn), 4.17–4.32 (m, 2H, CH_2–OAc), 4.44 (mc, 2H, O–CH_2–Ph), 5.05 (s, 1H, Ph–CH–Ph), 5.33 (mc, 1H, CH–O), 7.21–7.50 (m, 15H, Ar–H); IR (film, cm^{-1}): 2865, 1745, 1600, 1495, 1455, 1365, 1230, 1190, 1150, 1115, 1045, 975, 740; Calcd. for $C_{26}H_{26}O_5$: C 74.62, H 6.26; found C 74.75, H 6.26.

*2.13.3. (R)-1-acetoxy-3-benzyloxy-2-pivaloyloxypropane (**12f**)*

Yield: 81%; $[\alpha]_D = -14.6$ (c 1, methanol); ^{1}H NMR: 1.20 (s, 9H, $3CH_3$), 2.03 (s, 3H, CH_3–CO), 3.61 (m(d), 2H, CH_2–OBn), 4.17–4.33 (m, 2H, CH_2–OAc), 4.54 (s, 2H, O–CH_2Ph), 5.22 (mc, 1H, CH–O), 7.24–7.38 (m, 5H, Ar–H); IR (film, cm^{-1}): 2975, 2870, 1810, 1735, 1480, 1455, 1370, 1285, 1235, 1155,

1115, 1045, 740; Calcd. for $C_{17}H_{24}O_5$: C 66.21, H 7.84; found C 66.37, H 7.85.

*2.13.4. (R)-1-acetoxy-3-benzyloxy-2-(4-methylbenzoyl)oxypropane (**12g**)*

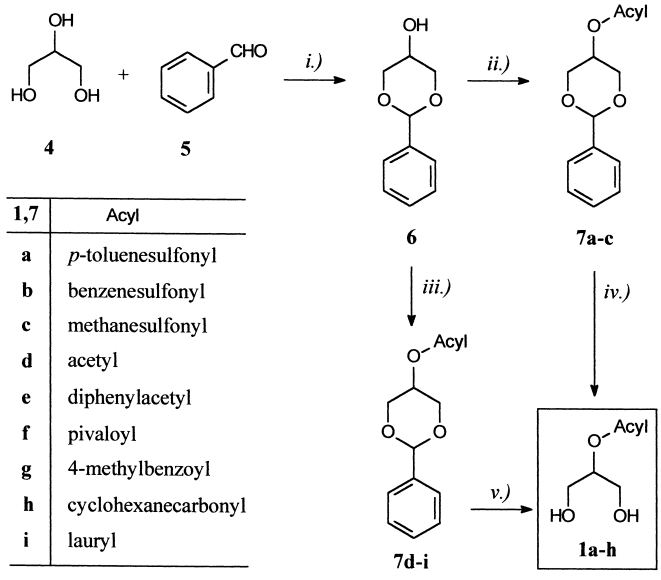
Yield: 78%; $[\alpha]_D = -9.2$ (c 1, methanol); ^{1}H NMR: 2.01 (s, 3H, CH_3–CO), 2.35 (s, 3H, Ar–CH_3), 3.69 (mc, 2H, CH_2–OBn), 4.26–4.49 (m, 2H, CH_2–OAc), 4.56 (m(d), 2H, O–CH_2–Ph), 5.45 (mc, 1H, CH–O), 7.22 (d, 2H, Ar–H), 7.30 (mc, 5H, Ar–H), 7.92 (d, 2H, Ar–H); IR (film, cm^{-1}): 2865, 1745, 1720, 1610, 1495, 1455, 1365, 1275, 1230, 1180, 1105, 1045, 910, 840, 750; Calcd. for $C_{20}H_{22}O_5$: C 70.16, H 6.48; found C 70.01, H 6.46.

*2.13.5. (R)-1-acetoxy-3-benzyloxy-2-cyclohexanecarbonyloxypropane (**12h**)*

Yield: 97%; $[\alpha]_D = -12.5$ (c 1, methanol); ^{1}H NMR: 1.18–1.34 (m, 3H), 1.38–1.51 (m, 2H), 1.64 (mc, 1H), 1.69–1.79 (m, 2H), 1.83–1.93 (m, 2H), 2.02 (s, 3H, CH_3–CO), 2.32 (mc, 1H, CH–CO), 3.58 (mc, 2H, CH_2–OBn), 4.18–4.37 (m, 2H, CH_2–OAc), 4.53 (mc, 2H, O–CH_2–Ph), 5.22 (mc, 1H, CH–O), 7.26–7.37 (m, 5H, Ar–H); IR (film, cm^{-1}): 2936, 2856, 1740, 1736, 1488, 1452, 1368, 1312, 1292, 1236, 1230, 1168, 1132, 1048, 740, 696; Calcd. for $C_{19}H_{26}O_5$: C 68.24, H 7.84; found C 68.09, H 7.93.

*2.14. Catalytic hydrogenation of 1-acetoxy-2-acyloxy-3-benzyloxypropanes (**12d–h**)*

General procedure: The 1-acetoxy-2-acyloxy-3-benzyloxypropane (**12d–h**) from the previous reaction was dissolved in isopropanol (3 ml). Catalyst (10% Pd–C, 10% w/w of the substrate) was added and hydrogenation was carried out at room temperature for 0.5 to 2 hours. The catalyst was then filtered off and the solvent was evaporated from the filtrate to leave the (*R*)-monoacetates [(*R*)-**2d–h**] in yields between 66 and 82%. ^{1}H NMR and IR spectra were identical to those of the racemates (*rac*-**2d–g**) or monoacetates from the enzymatic reaction (**2d–h**).



1,7	Acyl
a	*p*-toluenesulfonyl
b	benzenesulfonyl
c	methanesulfonyl
d	acetyl
e	diphenylacetyl
f	pivaloyl
g	4-methylbenzoyl
h	cyclohexanecarbonyl
i	lauryl

Fig. 2. Preparation of 2-acyloxypropane-1,3-diols (**1a–h**). Reaction conditions: (i) cat. H_2SO_4, RT, 5 h, 35%; (ii) RSO_2-Cl, KOH, Et_2O, −5°C, 40 min, RT, 15 min, 43–92% ; (iii) Acyl-Cl, pyridine, cat. DMAP, CH_2Cl_2, RT, 1–12 h, 80–86%; (iv) cc. HCl, MeOH, reflux, 1 min, 69–76%; (v) H_2, 10% Pd/C, *i*-PrOH, RT, 67–77%.

2,3-Diacetoxypropan-1-ol [(*R*)-**2d**] $[\alpha]_D = -4.6$ (c 1, methanol);
3-Acetoxy-2-(diphenylacetoxy)propan-1-ol [(*R*)-**2e**] $[\alpha]_D = -28.7$ (c 1, methanol)
3-Acetoxy-2-pivaloyloxypropan-1-ol [(*R*)-**2f**] $[\alpha]_D = -8.2$ (c 1, methanol)
3-Acetoxy-2-(4-methylbenzoyl)oxypropan-1-ol [(*R*)-**2g**] $[\alpha]_D = -20.6$ (c 1, methanol)
3-Acetoxy-2-cyclohexanecarbonyloxypropan-1-ol [(*R*)-**2h**] $[\alpha]_D = -6.7$ (c 1, methanol)

3. Results and discussion

Preparation of the desired prochiral 2-acyloxypropane-1,3-diols (**1a–h**) was straightforward (Fig. 2). Condensation reaction [22] of glycerol (**4**) and benzaldehyde (**5**) provided *cis*-5-hydroxy-2-phenyl-1,3-dioxane (**6**). The benzylidene protected secondary alcohol (**6**) was transformed into sulfonic (**7a–c**) or carboxylic esters (**7d–i**) in slightly different ways. The sulfonic esters (**7a–c**) were obtained by reaction of the secondary alcohol (**6**) with alkyl- or arylsulfonyl chloride and powdered potassium hydroxide in diethyl ether at −5°C, whereas the carboxylic esters (**7d–i**) were obtained by acylation of the alcohol (**6**) with the corresponding acyl chloride using pyridine and catalytic amounts of 4-(dimethylamino)pyridine (DMAP) in dichloromethane at room temperature. Benzylidene deprotection of the two types of esters (**7a–c** and **7d–i**) was also different. Benzylidene removal from the sulfonic ester intermediates (**7a–c**) was performed by acid hydrolysis with concentrated hydrochloric acid in refluxing methanol, whereas carboxylic esters (**7d–i**) were deprotected by catalytic hydrogenation over 10% Pd–C in isopropanol at room temperature, providing the desired prochiral diols (**1a–g**) smoothly. In the case of the lauryl derivative (**7i**), however, deprotection proceeded with immediate acyl migration leading almost exclusively to 1-*O*-laurylglycerol. Although substantial degree of acyl migration was observed by the 2-*O*-diphenylacetyl (**1e**) and 2-*O*-cyclohexanecarbonyl (**1h**) products within days standing in standard glass flasks at room temperature, these prochiral diols (**1e** and **1h**) were suitable for enzymatic transformation immediately after the deprotection.

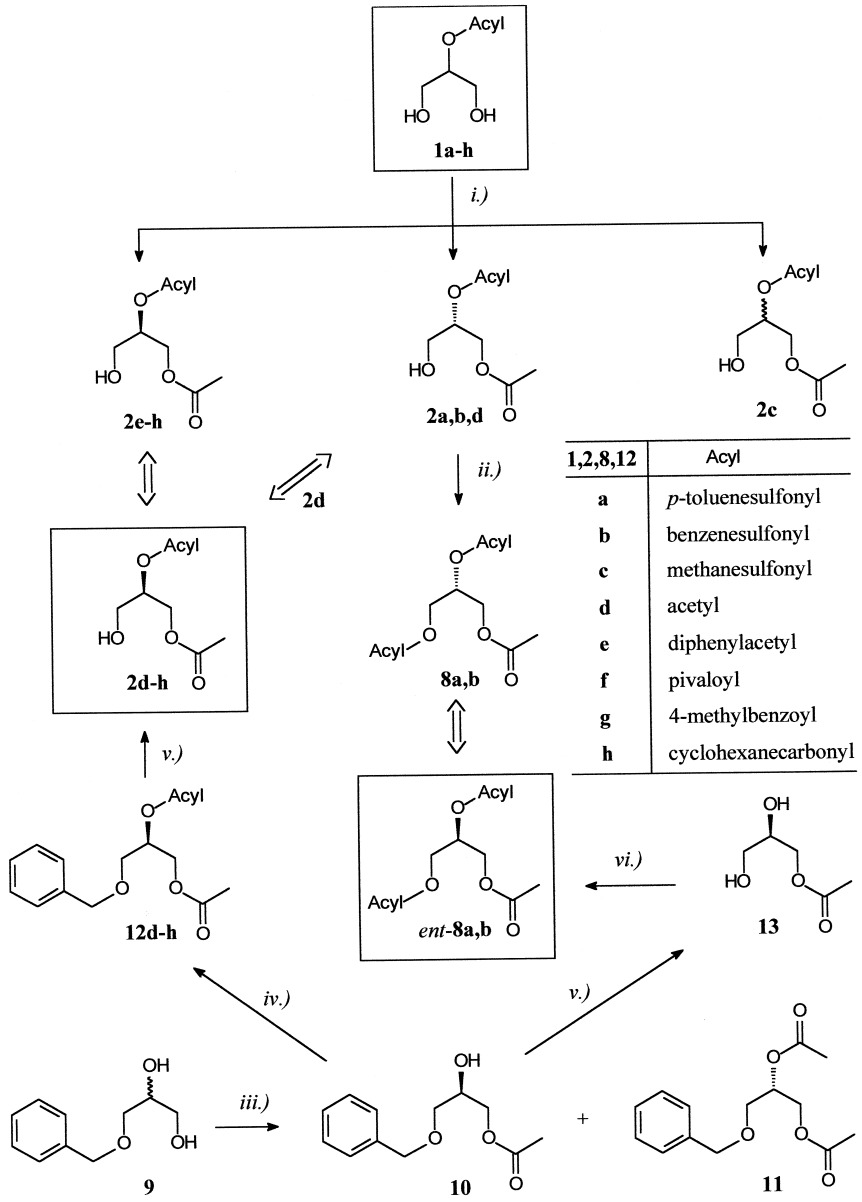
In our preliminary study, the enantiotope selective acetylation of 2-benzoyloxypropane-1,2-diol (**1**, R_1 = OBz, R_2 = H), which was considered as the first representant of the prochiral 2-acyloxy-1,3-propanediol family, was investigated [20]. The lipase from porcine pancreas (PPL) proved to be the most selective among the enzymes studied providing the acylated product (**2**, R_1 = OBz, R_2 = H) with 96% enantiomeric purity in good yield. Because of that promising result, the same inexpensive commercial lipase was chosen for the present study of the further 2-acyloxypropanediols (**1a–h**), too.

Composition of the solvent in the PPL-catalyzed acetylation reaction of carboxylic ester type 2-benzoyloxypropane-1,2-diol (**1**, R_1 = OBz, R_2 = H) played an important role [20], i.e. enzymatic acetylations in polar solvents like chloroform, ethyl acetate or vinyl acetate gave significantly decreased enantiotope selectivity compared to that obtained in the best solvent system (hexane:THF 1:1). Therefore, we investigated the solvent dependence of the PPL-catalyzed acetylation process for the *p*-toluenesulfonic ester (**1a**) representing the prochiral 2-sulfonyloxy diols as well (Table 2). Unfortunately, the degree of enantiotope selectivity remained low (**2a**: 31% e.e.) even in the best hexane:THF 1:1 solvent system.

After finding the solvent system which provided the highest selectivity in the acetylation of a representant of the sulfonic ester series (**1a**) and a member of the carboxylic ester series (**1**, R_1 = OBz, R_2 = H) [20], the further diols (**1b–**

h) were subjected to PPL-catalyzed enantiotope selective acetylation under this conditions (hexane:THF 1:1) (Table 1, Fig. 2).

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 =



1,2,8,12	Acyl
a	*p*-toluenesulfonyl
b	benzenesulfonyl
c	methanesulfonyl
d	acetyl
e	diphenylacetyl
f	pivaloyl
g	4-methylbenzoyl
h	cyclohexanecarbonyl

Fig. 3. Enzymatic acetylation of 2-acyloxypropane-1,3-diols (**1a–h**) and configuration of the products (**2a–h**). Reagents: (i) PPL, vinyl acetate, hexane:THF 1:1, RT; (ii) RSO_2–Cl, KOH, Et_2O, −5°C, 40 min, RT, 15 min, 43–92%; (iii) Lipase AK, vinyl acetate, THF, RT; (iv) Acyl-Cl, pyridine, cat. DMAP, CH_2Cl_2, RT, 1–12 h, 80–86%; (iv) cc. HCl, MeOH, reflux, 1 min, 69–76%; (v) H_2, 10% Pd/C, *i*-PrOH, RT, 67–77%.

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 labeled *pro-S* [5]. Acetylation of the diol bearing 2-*N*-benzyloxycarbonyl [16] or 2-O benzoyloxy [20] group by PPL was found to be *pro-R* selective.

Because of the above discussed uncertainty and since all the products (**2b–h**) except (**2a**) [23] were new compounds, absolute configuration determination of the acetates (**2a–h**) was necessary (Fig. 3). The configurations were determined by chemical correlation starting from (*R*)-1-acetoxy-3-benzyloxypropan-2-ol (**10**). The monoacetate (**10**) with known *R* configuration was obtained from Lipase AK catalyzed enantiomer selective acetylation of racemic 3-benzyloxypropane-1,2-diol (**9**) [24]. This secondary alcohol (**10**) was acylated into the benzyl protected compounds (**12d–h**) from which debenzylation gave the authentic (*R*)-3-acetoxy-2-acyloxypropan-1-ols [(*R*)-**2b–h**]. Comparing the optical rotation of these products [(*R*)-**2b–h**] with those of obtained from the PPL-catalyzed process proved the *R* configuration of bulkier carboxylic ester products (**2e–h**), while the smaller 2-acetoxy compound (**2d**) was found to have *S* configuration. The authentic (*S*)-bis-sulfonic esters (*ent*-**8a,b**) were also prepared from (*R*)-(**10**) via debenzylation and subsequent bis-sulfonylation of the chiral diol (**13**). The same bis-sulfonic esters having opposite sign of optical rotation (**8a,b**) were obtained by sulfonylation of the enzymatic products (**2a,b**) proving their *S* configuration.

The results listed in Table 1 indicated that the degree and even the sense of enantiotope selectivity of the PPL-catalyzed enantiotope acetylation of the prochiral 2-acyloxypropane-1,3-diols (**1a–h**) was strongly dependent on the moiety at position 2. It should be mentioned that similar stereopreference-change dependence on the substituent at the *sn*-2-position have already been observed with *Rhisopus* lipase — of which structure is known — [25,26]. Data obtained with the carboxylic ester series (**1d–h**) showed that there is a size optima at the size of the 4-benzoyloxy [**1g** → **2g** (≥ 98% e.e.)] moiety for the substituent at position 2. High but somewhat lower *pro-R* selectivity was obtained for the compounds bearing benzoyloxy {(**1**, R_1 = OBz, R_2 = H) → (**2**, R_1 = OBz, R_2 = H) (96% e.e. [20]} or cyclohexanecarbonyloxy [**1h** → **2h** (> 95% e.e.)] moieties having similar bulkiness, whereas the more bulky pivaloyloxy [**1f** → **2f** (67% e.e.)] or diphenylacetoxy [**1e** → **2e** (16% e.e.)] derivatives were transformed with decreased but still *pro-R* selectivity. The small acetoxy [**1c** → **2c** (40% e.e.)] moiety resulted in a moderate *pro-S* selectivity. Results for the sulfonic esters (**1a–c**) showed that increasing the bulkiness in the closer vicinity of the prochiral center (i.e. change of the O–CO– to the sterically more demanding O–SO_2– structural unit) alters the sense of the enantiotopic preference, too. The prochiral diol with methanesulfonyloxy [**1c** → **2c** (~ 0% e.e.)] moiety was acetylated with no selectivity, while the (*p*-toluenesulfonyl)oxy [**1a** → **2a** (31% e.e.)] or benzenesulfonyloxy [**1b** → **2b** (31% e.e.)] compounds were acetylated with a moderate *pro-S* selectivity.

The carboxylic ester type 2-(4-methylbenzoyl)oxy product (**2g**) allows the introduction of a leaving group at a primary hydroxylic function of an almost enantiomerically pure glycerol unit. The homochiral form of the sulfonic ester products (**2a–c**) bearing a leaving group at position 2 would represent a different valuable class of synthetically useful chiral C_3 units. Unfortunately, the results for the PPL-catalyzed acetylation of the prochiral sulfonic esters (**1a–c**) providing racemic product for the mesylate (**2c**) or products with low enantiomeric purity for the arylsulfonates (**2a,b**), were disappointing. As a representative of the prochiral sulfonic esters, 2-(*p*-toluenesulfonyl)oxypropane-1,2-diol (**1a**) was therefore investigated with further enzymes (Table 3).

This study of the acetylation of the prochiral tosylate (**1a**) with further enzymes was only partially successful. Although lipases from *Mu-*

cor sp. [Lipase M (from *M. javanicus*) and Lipozyme IM (from *M. miehei*)] catalyzed the acetylation with better enantiotope selectivities than that observed with PPL, enantiomeric purities of the product (**2a**, 34% and 42% e.e., respectively) were still too low for synthetic purposes.

4. Conclusions

In conclusion, a strong dependence of the degree and even the sense of selectivity on the 2-acyloxy moiety in the PPL-catalyzed acetylation of the prochiral 2-acyloxypropane-1,3-diols (**1a–h**) was found. The slight increase of size of the 2-acyloxy moiety from benzoyloxy (**1**, R_1 = OBz, R_2 = H) [20] to (4-methylbenzoyl)oxy (**1g**) resulted in pronounced enantiotope selectivity (from 96% e.e. [20] to $\geq$ 98% e.e.) providing the C_3 compound (**2g**) in almost enantiomerically pure form. Although the diol bearing cyclohexanecarbonyloxy moiety at position 2 (**1h**) was transformed also with high enantiotope selectivity (**2h**, $>$ 95% e.e.), usefulness of this acyl derivative is limited by the slow but significant acyl migration. 1,3-diols with significantly smaller (**1c,d**) or sterically more demanding (**1a,b,e,f**) moieties at position 2 showed moderate, no or even altered selectivities.

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