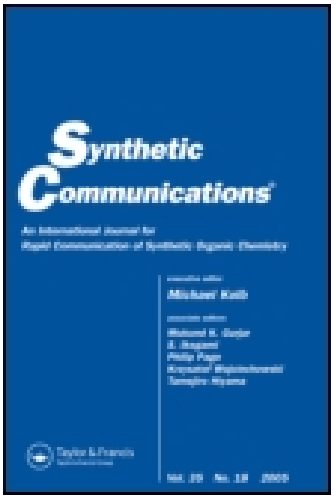

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LIPOZYME-MEDIATED REGIOSELECTIVE ESTERIFICATION OF ISOSORBIDE UNDER SOLVENT-FREE CONDITIONS

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Abstract: Monoesters of isosorbide were obtained with high regioselectivity in Lipozyme catalysed esterification by fatty acids under solvent-free conditions.

1,4:3,6-dianhydro-D-glucitol (isosorbide) **1** is an important by-product of starch industry[1], interesting by its low cost, and its availability in large quantities. It is a substrate in synthesis of pharmaceuticals, polymers and it has been used as chiral synthon in asymmetric synthesis[2]. A number of chemical methods describe the preparation of its derivatives with variable selectivity as regard to the two heterotopic hydroxyl groups[3-5]. Transesterification catalysed by lipase SAM

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II from *Pseudomonas sp.* using vinyl acetate as acyl donor is described as the most selective. However this reaction necessitates the use of expensive activated esters and its time is very long (3-5 days)[6] and even longer for vinyl esters of fatty acids[7].

With the purpose of obtaining regioselective fatty monoesters of isosorbide we have tested esterification catalysed by lipases from *Candida antarctica* and *Mucor miehei*. Free acids were acyl donors for the commercial preparation of these enzymes immobilized on organic support (ca. 10 % w/w): Novozym and Lipozyme[8] which were used in solvent-free reactions. Under dry anhydrous conditions the enzyme support plays the role of the solvent. Substrats co-impregnation on the solid support allows to form a homogeneous reaction medium with products of different polarity[9]. The esterification usually provides good yields in an easy work up; furthermore the enzymes can be easily recovered. The Novozyme catalysed reaction was found to be fast and to give good yields but with low regioselectivity. Nevertheless, isosorbide can be esterified with high regioselectivity within few hours with long-chain carboxylic acids in presence of Lipozyme. For instance in the case of octanoic acid (2 equivalents), after one hour at 40°C the conversion of isosorbide reaches 42%; however it is only 17% at 80°C. The optimal temperature was 60°C. Under these conditions, the half-life time of Lipozyme is 1800 hours[10]. At this temperature, the endo monooctylester of isosorbide was obtained as the sole product in 90% yield after 6 hours. As a comparison, after 1 hour Novozym gives 63% of conversion with the following distribution of products: 30% **3**, 13% **4**, 20% **5**.

Scheme

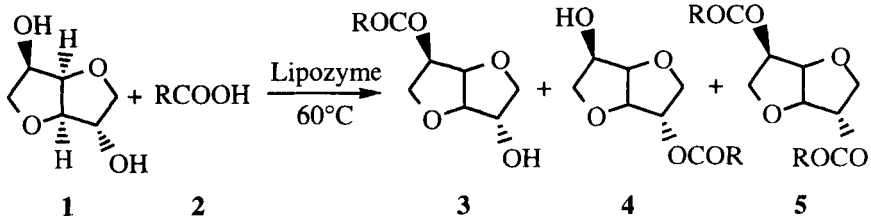

Table 1: Esterification of isosorbide with fatty acids in presence of Lipozyme

	R	t (h)	c_1 (%)	$Yield_3$ (%)	$Yield_4$ (%)	$Yield_5$ (%)
a	C_7H_{15}	1	54	49	0	0
a	C_7H_{15}	3	72	70	0	0
a	**C_7H_{15}**	**6**	**91**	**90**	**0**	**<1**
b	C_9H_{19}	1	29	28	<1	<1
b	C_9H_{19}	2	37	35	<1	1
b	C_9H_{19}	3	45	42	<1	2-3
c	$C_{11}H_{23}$	6	53	43	<1	10
d	$C_{13}H_{27}$	0.5	75	70	<1	4
e	$C_{15}H_{31}$	3	61	56	1	3

Convertions (c) and yields were determined by GC[11] using an internal standard. Products were analysed by NMR[12] and GC-MS[13].

As it is shown in Table 1 the best regioselectivity with Lipozyme was obtained with octanoic acid. For shorter acids (butanoic or hexanoic), yields were very low even whith a large excess of acyl donor. We proved previously that microwave irradiation can displace equilibrium of the enzymatic reaction and

increase its selectivity[14,15]. Unfortunately, we found that in the case of Lipozyme the reaction carried in microwave reactor stopped after half an hour at 25% of conversion to isosorbide endooctylester **3a**.

Typical experimental procedure: 1 mmol of isosorbide and 2 mmol of acid dissolved in 5 ml of acetone were impregnated on 500 mg of Lipozyme. The solvent was evaporated under reduced pressure. After heating under conditions defined in scheme and table 1, the reaction mixture was eluted with acetone in an ultrasound bath. The monosubstituted products **3** were separated on silica gel column with diethylether and pentane (1:1) as an eluent.

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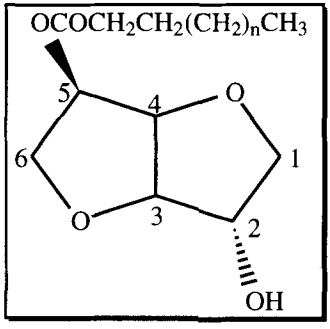
11.

Table 2: GC Retention times (min) of esters of isosorbide.

Products	a	b	c	d	e
4 (exo)	9.15	11.15	13.56	14.66	16.23
3 (endo)	9.77	11.73	14.14	15.16	16.68
5 (di)	15.64	18.71	24.66	38.12	51.05

GC analyses were performed on a Fisons Instruments GC 8000 series chromatograph with flame ionization and capillary column OV 1 12m, ID 0.22 mm, ef 0.1 μm, (carrier gas He at 70kPa) with the same gradient for the products **a**, **b**, **c**, **d**: 100°C to 270°C (10°C/min) then 270°C. For the products **e** the conditions were: 100°C to 280°C (10°C/min) then 280°C during 35 min. The retention time of isosorbide was 2,43 min. Internal standard for calibration in GC was methyl myristate.

12. ^{1}H NMR spectra were recorded on Brüker 250 MHz spectrometer in $CDCl_3$ with TMS as an internal standard. The optical rotations were measured at 20 °C on P20 Bellingham+Stanley Ltd. Polarimeter.



3a: $[\alpha]_D$=+86.6 (c 1 CH_3OH)

^{1}H-NMR ($CDCl_3$): 0,8-0,95 (3H, t, CH_3); 1,15-1,42 (8H, m, $4CH_2$); 1,54 -1,73 (2H, m, CH_2); 2,27-2,33 (1H, d, OH); 2,33-2,43 (2H, t, CH_2); 3,72-3,82 (1H, q, H6a); 3,85-3,97 (3H, m, H1a, 1b, 6b); 4,28-4,37 (1H, broad,H2); 4,37-4,43 (1H, d, H3); 4,81-4,89 (1H, t, H4); 5,1-5,2 (1H, q, H5).

3b: $[\alpha]_D$=+78.2 (c 1 CH_3OH)

^{1}H-NMR ($CDCl_3$): 0,8-0,95 (3H, t, CH_3); 1,15-1,4 (12H, m, 6CH_2); 1,55 -1,72 (2H, m, CH_2); 2,27-2,34 (1H, broad, OH); 2,32-2,42 (2H, t, CH_2); 3,72-3,81 (1H, q, H6a); 3,85-3,96 (3H, m, H1a, 1b, 6b); 4,28-4,37 (1H, broad, H2); 4,37-4,43 (1H, d, H3); 4,82-4,89 (1H, t, H4); 5,1-5,19 (1H, q, H5).

3c: $[\alpha]_D$=+72.6 (c 1 CH_3OH), mp=21-22 °C

^{1}H-NMR ($CDCl_3$): 0,8-0,93 (3H, t, CH_3); 1,15-1,42 (16H, m, 8CH_2); 1,55-1,78 (2H, m, CH_2); 2,32-2,42 (2H, t, CH_2); 3,72-3,82 (1H, q, H6a); 3,85-3,98 (3H, m, H1a, 1b, 6b); 4,3-4,38 (1H, broad, H2); 4,38-4,44 (1H, d, H3); 4,81-4,89 (1H, t, H4); 5,11-5,2 (1H, q, H5).

3d: $[\alpha]_D$=+65.0 (c 1 CH_3OH), mp=37-38 °C

^{1}H-NMR ($CDCl_3$): 0,8-1 (3H, t, CH_3); 1,15-1,45 (20H, m, 10CH_2); 1,5-1,8 (2H, m, CH_2); 2,3-2,45 (2H, t, CH_2); 3,72-3,82 (1H, q, H6a); 3,87-3,98 (3H, m, H1a, 1b, 6b); 4,3-4,38 (1H, broad,H2); 4,38-4,45 (1H, d,H3); 4,81-4,9 (1H, t, H4); 5,1-5,22 (1H, q, H5).

3e: $[\alpha]_D$=+62.8 (c 1 CH_3OH), mp=48.5-49.5 °C

^{1}H-NMR ($CDCl_3$): 0,8-0,95 (3H, t, CH_3); 1,15-1,45 (24H, m, 12CH_2); 1,55-1,75 (2H, m, CH_2); 2,3-2,43 (2H, t, CH_2); 3,72-3,83 (1H, q, H6a); 3,85-3,98 (3H, m, H1a, 1b, 6b); 4,3-4,38 (1H, broad, H2); 4,38-4,45 (1H, d, H3); 4,82-4,9 (1H, t, H4); 5,12-5,22 (1H, q, H5).

13. Mass analyses were performed on NERMAG R10-10 equipped with CPSil-5, 25m capillary column.
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