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Lipases Aided Esterification of (2,2-Dimethyl-1,3-dioxolan-4-yl)methanol

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Abstract: Racemic solketal (2,2-Dimethyl-1,3-dioxolan-4-yl)methanol 1, was treated with carboxylic acids of varying chain length or their vinyl esters in the presence of different lipases. The esterification reaction was carried out in *n*-hexane or diisopropyl ether as a solvent. The yield of the solketal esters and their enantiopurity were satisfactory, as indicated by gas chromatography using chiral column. Lipases from *Rhizopus oryzae* and *Pseudomonas fluorescence* gave the best enantiomeric excess (*ee*) when the solketal was treated with vinyl butyrate in a solution of diisopropyl ether at room temperature.

Keywords: Esterification, solketal, lipases, enantiopurity, biocatalysis.

INTRODUCTION

The development of biodiesel production (FAME) and fatty acids demand for the pharmacy and cosmetics industry resulted in an excess of glycerol, being a second product of fats processing [1]. The glycerol is partially utilised in the production of chloromethyloxirane and glycerol acetate or nitrate [2-4]. The important utilisation of glycerol is its conversion into solketal, (2,2-Dimethyl-1,3-dioxolan-4-yl) methanol, valuable product, especially in the form of pure enantiomers for pharmacy as a chiral, three-carbons building block [5, 6]. Solketal, is a chiral synthetic precursor of acylglycerols [7, 8] and glycerophospholipids [9, 10], β-blockers [11, 12] and polymers [13, 14]. Enantiomerically enriched (*R*)- and (*S*)- solketal are commercially available but at a high price since their production according to standard synthetic protocols is expensive and laborious [15 - 18], whereas racemic solketal is an inexpensive reagent, obtained in reaction of glycerol with acetone [19]. Consequently, new and efficient synthetic routes are required to produce optically pure solketal as a building block based on glycerol. Herein, we described an approach for the enantioselective synthesis of solketal esters using lipases as a biocatalyst. Lipases (EC3.1.1.3) are a subgroup of carboxylesterases specifically hydrolyse the triacylglycerols in the presence of water. Due to the natural activity of lipases the hydrolysis of the appropriate esters is the most reported attitudes applied for synthesis of enantiomerically enriched esters or alcohols. Lipases are also able to form esters in organic solvents in the presence of traces of water necessary for the formation of their enzymatically-active shape. When racemic substrate is used in esterification reaction both enantiomers can be formed in competitive reactions. Such reaction is kinetically controlled and depends on the activation energy of both products formation, especially in chiral environment formed by enzyme. The enantiomer having a lower activation energy is formed faster and this is reflected by enantiopurity of product. If the esterification is performed under conditions which enable an equilibrium, the more thermodynamically stable product with higher activation energy is formed [20]. It is typical for esterification of alcohols using acid as an acyl donor. Under condition of irreversible esterification, usually kinetically favoured product predominates [21, 22].

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RESULTS AND DISCUSSION

The racemic solketal **1** was obtained in reaction of glycerol with anhydrous acetone catalysed by *p*-TSA in *n*-pentane under reflux [19]. The enantiomerically enriched solketals, namely (*S*)-(+)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol **2a** were obtained in three-step synthesis starting from D-mannitol [16]. The (*R*)-enantiomer **2b** was a commercially available product. The standards of reference, esters of (*R*)- and (*S*)-solketal were obtained according to elaborated procedure in condensation reaction of carboxylic acids with the appropriate enantiomers in the presence of *N*,*N*'-dicyclohexylcarbodiimide (DCC) in methylene chloride solution (Scheme **1**).

The esters of racemic solketal **1** were obtained under the same conditions. In primary trials, **1** was treated with equimolar amount of carboxylic acids **3a-d** in a solution of an organic solvent (*n*-hexane or diisopropyl ether) in the presence of lipases preparations, namely Novozyme 435 and Lipozyme RMIM (Scheme **2**), used in a weight ratio 1:10 with respect to racemic solketal. The reaction was performed at room temperature. The progress of reaction was monitored by gas chromatograph system equipped with chiral capillary column (Table **1** and **2**). Tables **1** and **2** also contains E-values, a measure of the enantioselectivity in kinetic resolution, defined as the ratio of the specificity constants $kcat/K_M$ for the two competing enantiomeric substrates [23]. Both enzymes to some extent, exhibit activity towards **1**.

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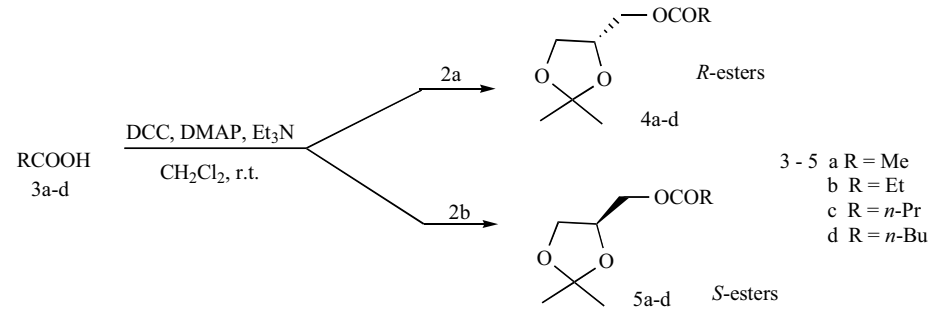
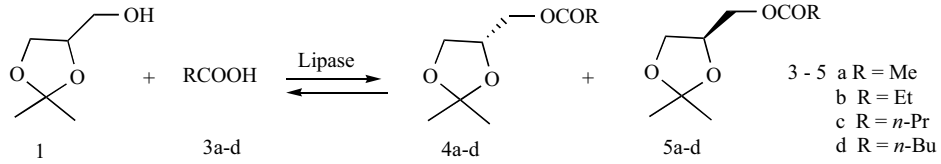


Scheme 1. Synthesis of references compounds.



Scheme 2. Esterification of solketal by carboxylic acids in the presence of lipases.

Table 1. The Primary Trials of Solketal Esterification Using Novozyme 435

Enzyme	Entry	Acid 3	Time [h]	*n*-Hexane			*i*-Pr_2O		
				Yield [%]	ee_S [%]	E	Yield [%]	ee_S [%]	E
Novozyme 435	**1**	**a**	0.75	6	71	6	9	33	2
	2	**b**	0.75	24	12	1	11	40	2.5
	3	**c**	0.75	39	10	1.3	21	25	1.8
	4	**d**	0.75	42	7	1.3	31	11	1

In experiments ratio of enzyme : solketal was 1:10 (w/w)

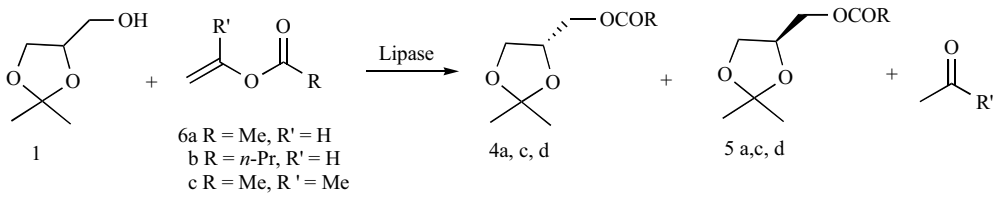
Table 2. The Esterification of Solketal in the Presence of Lipozyme RMIM

Entry	Acid 3	Time [h]	Yield [%]	ee_R [%]	E
1	**a**	No reaction	-	-	-
2	**b**	0.75	8	17	1.4
3	**c**	0.75	11	19	1.5
4	**d**	0.75	16	22	1.6

In experiments ratio of enzyme : solketal was 1:10 (w/w)

In reactions catalysed by Novozyme 435 **5a** was obtained after 45 minutes with *ee* excided 70% (Table **1**, entry 1). Extension of alkyl chain in the molecule of acyl donor **3a-d** gave the highest conversion of solketal but the enantiomeric excess and E-value of formed esters **5a-d** decreased (Table **1**, entry 2-4). Acylation in the presence of lipozyme RMIM gave the appropriate esters **4b-d** with (*R*)-absolute configuration (Table **2**, entry 1-4). The yield of esters **4b-d** is rather low, the best result was obtained for solketal valerate **4d**. When acetic acid **3a** was used as an acyl donor the formation of solketal acetate **4a** was not observed. The observed behaviour remains in an agreement with a recent work by Machado *et al.* who found longer acyl chains preferential for kinetic resolution of solketal esters *via* hydrolysis by lipases [24]. These primary tests clearly indicated that the esterification of solketal using our enzyme preparations is possible. Tests performed using enzymes such as lipozyme TLIM, lipase from *Candida rugosa*, *Rhizopus oryzae*, *Aspergillus niger*, spawn from *Mucor circinelloides* and *Pancreatin*, clearly indicated that the investigated preparations did not show sufficient activity in this reaction.

To increase the yield of esters another approach was considered. An alternative reaction pathway for ester synthesis by using carboxylic acids was irreversible esterification involving vinyl esters. Biotransformations were carried out using racemic solketal **1** and acyl donor **6b**, which gave the best yield of solketal's ester. Reactants were used in a ratio 1 : 2 (solketal : acyl donor) in a solution of diisopropyl ether



Scheme 3. Irreversible esterification of solketal.

Table 3. Esterification of Solketal using Vinyl Butyrate 6b in Diisopropyl Ether

Entry.	Lipase	Amount of Enzyme prep. [mg]	Time [h]	Yield [%]	*ee* [%]	E
1	Lipozyme RMIM	10	**2**	99	0	0
2	Immobilised on Sol-gel-AK lipase from *Candida cylindracea*	10	2	-	-	-
3	Amano lipase A from *Aspergillius niger*	10	2	<3	7_S	1.1
4	Lipase from *Aspergillus niger*	10	2	-	-	-
5	Lipozyme TLIM	10	2	92	1_R	1.1
6	Novozyme 435	10	2	99	0	0
7	Lipase from *Candida rugosa*	10	2	4	26_R	1.6
8	Lipase from *Rhizopus oryzae*	10	2	-	-	-
9	Lipase from *Rhizopus oryzae*	20	120.0	28.5	55.3_R	4.3
10	Pork pancreatin	10	2	9	45_R	2.8
11	Lipase from porcine pancreas type II	10	2	7	47_R	2.9
12	Spawn from *Mucor circinelloides*	10	2	43	33_R	2.5
13	Amano lipase from Pseudomonas fluorescens	10	2	15	80_R	10.3
14	Amano lipase from *Pseudomonas fluorescens*	10	4	26	76_R	9.5
15	Lipase from *Candida antarctica* CLEA	10	2	41	24_R	1.9

**calculated for 100 mg of solketal.

at 25 °C. Several preparations of lipases were applied, the ratio enzyme : acyl donor was constant, despite enzymes specific activity (Scheme **3**, Table **3**).

The best activity was observed for the lipase from *Pseudomonas fluorescens*. The satisfactory *ee* was obtained after 2 h without significant decrease of enantiomeric excess when reaction time was extended to 4 h (Table **3**, entry 13, 14). Lipozyme RMIM and Novozyme 435 gave the high yield of solketal ester, but unfortunately, ester is produced as a racemate (Table **3**, entries 1, 6). In the presence of lipase from *Rhizopus oryzae* the ester formation took more time and the yield and *ee* were moderate. For the further experiments three lipases were selected, namely spawn from *Mucor circinelloides*, *Rhizopus oryzae* and *Pseudomonas fluorescens*. These preparations gave the best result when the yield versus *ee* was compared (Table **4**). The reaction of esterification was performed under conditions applied above with usage of **6a-c** as an acyl donor.

Inspection of (Table **4**) indicated the high affinity of lipase from *Pseudomonas fluorescens* as a catalyst for esterification of solketal (entry 19-27), especially when vinyl butyrate **6b** was applied (entry 25-27). The variation of the proportion solketal **1** to vinyl butyrate **6b** does not have a significant influence on the yield and *ee* of formed **4c** (Table **5**, Fig. **1**).

In conclusion, based on the collection of 13 lipases applied in the synthesis of solketal esters, the best results were obtained in irreversible esterification of racemic **1** using the lipase from *Pseudomonas fluorescens*. These results will be used for the optimisation of explored reaction as a starting point. The immobilisation of lipase on support of different types is considered at present. The mesoporous silica SBA-15 modified with octyl groups and oxidised multi-wall carbon nanotubes (*O*-MWCNTs) are chosen for the preliminary tests. Due to the published reports, immobilisation of an enzyme may improve its activity and enantioselectivity. Immobilisation alters physicochemical properties of enzyme changing its environment (hydrophilicity or hydrophobicity) or increasing enzyme rigidification. For lipases immobilisation may become a way to keep "open form" where the active site is exposed to the medium [25].

Table 4. The Influence of Acyl Donor on Esterification Reaction of Solketal

Entry	Lipase	Amount of Enzyme [mg]	Acyl Donor 6	Time [h]	Yield of Ester [%]	ee %	E
1	Spawn from Mucor circinelloides	20	c	8	9.5	38.5 R	2.3
2				24	21	36 R	
3				32	44.5	29 R	
4		20	a	0.5	6	42 R	2.5
5				2	18	40 R	
6				3	26	38.5 R	
7		20	b	0.5	28	37 R	2.5
8				1	47	31 R	
9				1.5	64	25 R	
10	Rhizopus oryzae	40	c	24	No reaction		
11				48			
12				72			
13		40	a	24	3	57R	3.7
14				48	5	57R	
15				72	7	57R	
16		40	b	24	22	57 R	4.3
17				48	38	52 R	
18				72	52	46 R	
19	Pseudomonas fluorescens	20	c	1	9	59 R	4.2
20				3	23	55 R	4.1
21				4	30	53 R	4.0
22		20	a	1	24	55 R	4.0
23				3	62	38 R	4.0
24				4	72	34 R	4.4
25		20	b	1	16	80 R	10.4
26				3	42	72 R	10.2
27				4	51	65 R	9.6

EXPERIMENTAL

NMR spectra were recorded at 300 MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR on a Varian Inova 300 MHz in $CDCl_3$ solution if not indicated else; δ values are in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard. Alcohol and ester concentrations were determined by GC analysis on the Agilent Technologies model 6890N Network GC System gas-chromatograph equipped with a flame ionisation detector (FID) and a chiral capillary column MEGA-DEX DMP Beta, (MEGA, Legnano, Italy, diameter 0.25 mm, length 25 m, thickness 0.25μm).

Esters of (*R*)- and (*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol; (*R*)-solketal and (*S*)-solketal esters (4,5 a-d)

General Procedure

The enantiomerically enriched (*S*)-solketal **2a** or (*R*)-solketal **2b** (1.32 g, 10 mmol) was dissolved in anhydrous methylene chloride (18 ml), DMAP (0.12 g, 1mmol), DCC (2.27g, 11 mmol) and carboxylic acid **3a-d** (10 mmol) was added at room temperature while stirring. After 24 h, the reaction mixture was filtered off by a thin pad of silica gel. The deposit formed on silica surface was rinsed with anhy-

Table 5. The Influence of Ratio Solketal : Acyl Donor 6b on Esterification of 1

Lipase	Ratio 1 : 6b	Time [h]	Yield of Ester [%]	ee_R %	E
Pseudomonas fluorescens	1:1	1	10	81	10.3
		3	33	74	9.5
		4	45	69	9.5
	1:2	1	16	80	10.5
		3	42	72	10.2
		4	51	65	9.6
	1:4	1	22	77	9.6
		3	51	64	8.9
		4	61	54	8.2
Spawn from *Mucor circinelloides*	1:2	0.5	28	37	2.5
		1.0	47	31	2.5
	1:6	0.5	39	30	2.2
		1.0	64	21	2.2

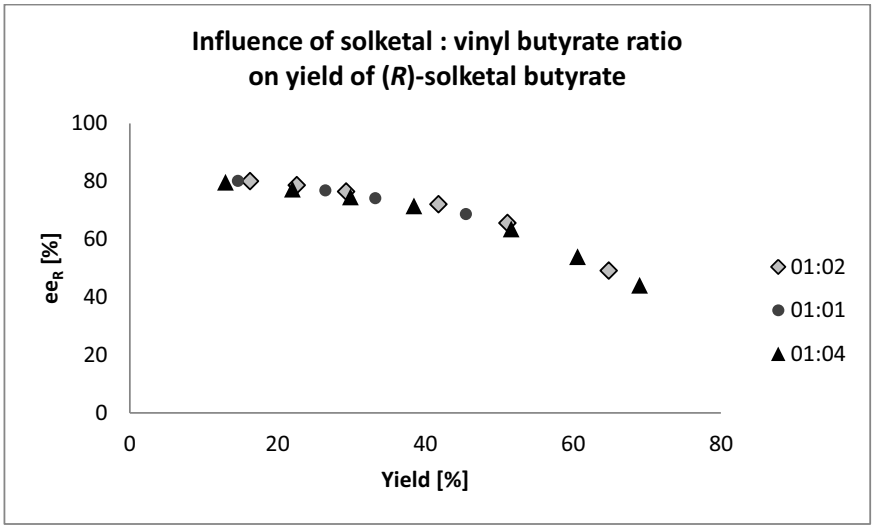


Fig. (1). Influence of solketal and vinyl butyrate ratio on yield of (*R*)-solketal butyrate.

drous CH_2Cl_2 (10 ml). The combined filtrates were washed with aqueous solution of sodium bicarbonate (3 x 15 ml) and water (1×15 ml). The organic layer was dried over anhydrous $MgSO_4$ and after evaporation on rotary evaporator at room temperature, the residual oil was purified on silica gel packed column using ethyl acetate : *n*-hexane as an eluent (3:7, v:v). Appropriate esters **4**,**5a-d** were obtained as colourless oils.

(R)-Solketal Acetate (4a)

Yield 75%; ^{1}H NMR ($CDCl_3$), δ (ppm): 1.38 (s, 3H, C$\underline{H}_3$), 1.44 (s, 3H, C$\underline{H}_3$), 2.10 (s, 3H, C$\underline{H}_3$CO), 3.74 (dd, 1H, ^2J=8.4Hz, ^3J=6.0Hz, H_a-5), 4.03-4.11 (m, 2H, H_b-5, H_b-6), 4.18 (dd,1H, ^2J=11.4 Hz, ^3J=4.5 Hz, H_a-6), 4.29-4.37 (m, 1H, C$\underline{H}$). ^{13}C NMR ($CDCl_3$), δ (ppm): 20.9, 25.5, 26.8, 64.9, 66.4, 73.7, 109.5, 170.9. $[\alpha]^{25}_D$ = +2.0 (neat); $[\alpha]^{25}_D$ = +1.9 (neat) [26].

(R)-Solketal Propionate (4b)

Yield 79%; ^{1}H NMR ($CDCl_3$), δ (ppm): 1.15 (t, ^3J=7.5 Hz, 3H, C$\underline{H}_3$), 1.26 (s, 3H, C$\underline{H}_3$), 1.32 (s, 3H, C$\underline{H}_3$), 2.38 (q, 2H, ^3J=7.5 Hz, CH_2), 3.74 (dd, 1H, ^2J=8.4 Hz, ^3J=6.0 Hz, H_a-5), 4.04-4.12 (m, 2H, H_b-5, H_b-6), 4.16-4.21 (dd, 1H, ^2J=11.5 Hz, ^3J=4.5 Hz, H_a-6), 4.29-4.37 (m, 1H, CH). ^{13}C NMR ($CDCl_3$), δ (ppm): 9.0, 20.9, 25.5, 26.8, 64.9, 66.4, 73.7, 109.5, 170.9. $[\alpha]^{25}_D$ = +4.4 (neat); $[\alpha]^{25}_D$ = +4.7 (neat) [26].

(R)-Solketal Butyrate (4c)

Yield 83%; ^{1}H NMR ($CDCl_3$), δ (ppm): 0.95 (t, 3H, ^3J=7.5 Hz, C$\underline{H}_3$), 1.37 (s, 3H, C$\underline{H}_3$), 1.44 (s, 3H, C$\underline{H}_3$), 1.66

(sextet, 2H, ^3J=7.5 Hz, C$\underline{H}_2$), 2.34 (t, 2H, ^3J=7.5 Hz, C$\underline{H}_2$), 3.74 (dd, 1H, ^2J=8.4 Hz, ^3J=6.0 Hz, H_a-5), 4.06-4.08 (m, 2H, H_b-5, H_b-6), 4.11-4.16 (dd, 1H, ^2J=11.4 Hz, ^3J=4.5 Hz, H_a-6), 4.28-4.36 (m, 1H, C$\underline{H}$). ^{13}C NMR ($CDCl_3$), δ (ppm): 13.8, 18.5, 25.5, 26.8, 36.1, 64.6, 66.5, 73.8, 109.9, 173.6. $[\alpha]^{25}_D$ = +4.9 (neat); $[\alpha]^{25}_D$ = +5.1 (neat) [26].

(R)-Solketal Valerate (4d)

Yield 89%; ^{1}H NMR ($CDCl_3$), δ (ppm): 0.92 (t, 3H, ^3J=7.5 Hz, C$\underline{H}_3$), 1.36 (quintet, 2H, ^3J=7.5 Hz, C$\underline{H}_2$), 1.37 (s, 3H, C$\underline{H}_3$), 1.44 (s, 3H, C$\underline{H}_3$), 1.66 (kwintet, 2H, J=7.5 Hz, C$\underline{H}_2$), 2.34 (t, 2H, ^3J=7.5 Hz, C$\underline{H}_2$), 3.74 (dd, 1H, ^2J=8.4 Hz, ^3J=6.3 Hz, H_a-5), 4.06-4.12 (m, 2H, H_b-5, H_b-6), 4.17 (dd, 1H, ^2J=11.5 Hz, ^3J=4.6 Hz, H_a-6), 4.28-4.36 (m, 1H, CH). ^{13}C NMR ($CDCl_3$), δ (ppm): 13.6, 22.3, 25.5, 26.8, 27.0, 31.0, 33.9, 70.3, 73.7, 96.2, 109.9, 173.7. $[\alpha]^{25}_D$ = +5.4 (neat); $[\alpha]^{25}_D$ = +5.7 (neat) [26].

Irreversible Esterification of Solketal (General Procedure)

(*R*, *S*)-Solketal (0.95 mmol) was dissolved in anhydrous diisopropyl ether (4 ml), and appropriate vinyl ester **6a-c** (1.90 mmol) was added followed by addition of enzyme preparation in amounts 10-40 mg as indicated in (Tables **3** and **4**). The resultant suspension was stirred at room temperature. In time intervals samples of volume 80-100 μl were taken of, diluted with diisopropyl ether to the volume of 800 μl and analysed on GC gas chromatograph system. The analyses were carried out using the following temperature program: oven temperature from 35 °C to 90 °C (5 °C/min), next from 90 °C to 150 °C (12 °C/min), and then held at 150 °C for 5 min. Injector temperature was 200 °C and the detector 250 °C. Carrier gas was held with a flow rate of 1.2 mL/min. The retention times of the enantiomers of 1,2-*O*-isopropylidene glycerol and its esters under these conditions were: (*R*)- solketal: 13.80 min, (*S*)-solketal: 13.90 min, (*S*)-solketal acetate: 14.50 min, (*R*)-solketal acetate: 14.60 min., (*S*)-solketal propionate: 15.80 min., (*R*)-solketal propionate 15.90 min., (*S*)-solketal butyrate: 17.50 min, (*R*)-solketal butyrate: 17.60 min., (*S*)-solketal valerate: 20.20 min., (*R*)-solketal valerate: 20.30 min.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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