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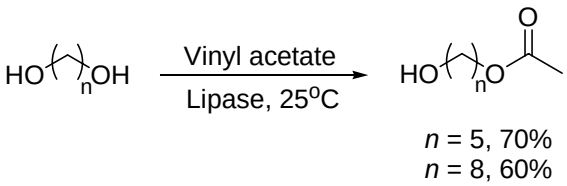
A simple enzymatic methodology for the selective monoacetylation of 1,*n*-diols (*n*=5,8) using immobilized *Thermomyces lanuginosus* lipase in different organic media is reported.



Lipase-catalysed selective monoacylation of 1,*n*-diols with vinyl acetate

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Abstract

A simple enzymatic methodology for the selective monoacetylation of 1,*n*-diols (n=5,8) using vinyl acetate is reported. Monoacetylation excesses of 81-87% at 74-90% 1,*n*-diol conversions were obtained in toluene and diisopropyl ether using *Thermomyces lanuginosus* lipase (TLL) immobilised on polypropylene powder as catalyst.

Keywords: symmetric diols, lipases, selective monoacetylation

In the course of an ongoing project for the application of green methodology to the synthesis of insect sex pheromones, we have sought for alternatives to the selective monoesterification of polymethylene-1,*n*-diols, an important step in the preparation of lepidopteran sex pheromones.[1-4] Chemical and enzymatic methods to perform this reaction in an efficient way still remains a current challenge.[5-11] Selective chemical monoacylation can be accomplished by metal sulfates supported on silica gel[12,13] or with acetyl chloride with the diol adsorbed on silica gel.[14] The latter methodology providing both high yields and selectivity. Recently, a new chemical method for monoesterification of diols with aromatic and aliphatic acids has been reported,[2] in which the selectivity was accomplished by using $Al_2O_3/MeSO_3H$. A simple process

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based on the selective enzymatic hydrolysis of diacetates was reported by Houille *et al.*[15] This approach considers that the hydrophobic diacetate is bounded to the enzyme tighter than the monoacetate in aqueous media and, therefore, the hydrolysis of the former is kinetically favoured. Monoacetylation of diols in moderate to good yields was reported using pronase E (*i.e.* a mixture of proteases from *Streptomyces griseus*) in anhydrous pyridine and *p*-nitrophenyl acetate as acyl-donor.[16] Ciuffreda *et al*,[17] have reported that *Mucor miehei* lipase (MML) was, among five lipases tested, the most suitable enzyme for the selective monobenzoylation of 1,4-diols using vinyl benzoate as acyl transfer reagent in organic media. Regioselective acetylation and hydrolysis of acyclic terpene-1,*n*-diols and their diacetates was also accomplished using *Pseudomonas cepacia* lipase.[7] However, in most of the aforementioned methods the longer the distance between the two alcohol groups the lower the monoacylation yield obtained. Hence, none of these methods, gave satisfactory yields for the monoacylation of medium-long chain polymethylene-1,*n*-diols with *n*>5.

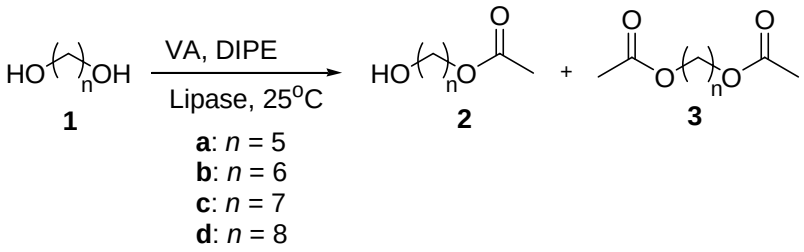

Figure 1

These previous publications prompted us to screen a number of commercially available lipases for the selective monoacetylation of 1,*n*-diols with *n* = 5, 6, 7 and 8 methylene groups (Figure 1) using simple vinyl acetate (VA) as acylating substrate. Eight lipases were investigated to assess their suitability to carry out the monoacetylation reaction (Table 1). First, the screening was conducted at analytical level with both pentane-1,5-diol (**1a**) and octane-1,8-diol (**1d**). The reactions were carried out in diisopropyl ether (DIPE) using the lipases immobilised onto a

polypropylene support (Accurel EP100) as catalysts.[18] The progress of mono and diacetylated products was monitored by glc under the conditions described below. An inspection of the time-evolution of the reactions indicated that the monoacetylation excesses (*me*) decreased with the 1,*n*-diol conversion. Hence, the results summarised in Table 1 were the optimum considering a convenient balance between *me* and substrate conversions. In most cases, the larger the number of methylene units between the alcohol groups the lower the *me* values obtained. CAL-B showed high activity but low *me* values (Table 1, entries 1-2). Both, RNL and PPL gave good selectivity but 1,*n*-diol conversions were too low for preparative scale (Table 1 entries 15-18). Rather good results were achieved with RAL, ROL and CRL (Table 1 entries 5-8 and 13-14) Remarkably, TLL gave both high *me* and conversions suitable for the selective monoacetylation of 1,*n*-diols, with n = 5, 6, 7, 8, at preparative scale (Table 1, entries 9-12). The influence of the organic solvent on the TLL selectivity was also investigated. To this end, the acetylation reaction was also conducted in toluene, methyl *tert*-butyl ether (MTBE), tetrahydrofuran (THF) and diethyleneglycol dimethyl ether (Diglyme). The results, summarised in Table 2, show that the best *me* and conversion were achieved in toluene and DIPE. Interestingly, the lower the hydrophobicity of the solvent (i.e. log P) the lower the *me* values. This may be explained by the different solvation, akin to the partition coefficient, of the diol and the corresponding monoacetate between the organic solvent and the predominantly aqueous microenvironment of the enzyme.[19]

To demonstrate the usefulness of the methodology developed, the monoacetylation of pentane-1,5-diol and octane-1,8-diol catalysed by TLL was performed at preparative scale. A typical procedure was as follows: **1a** (2g, 19.2 mmol) was dissolved in diisopropyl ether (300 mL) and immobilized TLL (12 g) was

added. To this solution, was added vinyl acetate (1.79 mL, 19.2 mmol). The mixture was placed in a reciprocal shaker at 25°C and the progress of the reaction was monitored by glc: capillary column BPX5 (30 m, 0.25 mm internal diameter and 0.25 μm stationary phase thickness), temperature program from 50°C to 200°C over 5 min and then from 200°C to 300°C over 7 min. When the reaction reached the 80% conversion, the enzyme was filtered off and washed with diisopropyl ether. The solvent was evaporated under vacuum and the residue purified by flash chromatography on silica gel. Elution was performed with a hexane:ethyl acetate stepwise gradient from 7:1 to 1:1 in volumes of 400 mL each. Pure compound **2a** was obtained as a colourless oil (1.94 g 70% yield). ^{1}H NMR spectrum is consistent with that reported in the literature[3]. ^{13}C NMR (175 MHz, $CDCl_3$) δ 171.3 (CO), 64.3 (CH_2OCOCH_3), 62.2 (CH_2OH), 32.0 (CH_2CH_2OH), 28.2 ($CH_2CH_2OCOCH_3$), 22.1 ($CH_2CH_2CH_2CH_2CH_2$), 20.8 (CH_3). An analogous procedure was used for the selective monoacetylation of **1d**. The elution conditions for the purification of **2d** were: hexane:ethyl acetate stepwise gradient from 7:1 to 2:1 in volumes of 400 mL. Pure product was obtained as an oil (1.52 g, 60% yield). ^{1}H NMR spectrum is consistent with that reported in the literature[4]. ^{13}C NMR (175 MHz, $CDCl_3$) δ 171.22 (CO), 64.51 (CH_2OCOCH_3), 62.80 (CH_2OH), 32.58, 29.16, 29.07, 28.45 ($CH_2CH_2CH_2OH$ and $CH_2CH_2CH_2OCOCH_3$), 25.70, 25.5 ($CH_2CH_2CH_2(CH_2)_2CH_2CH_2CH_2$), 20.90 ($CH_3$).

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Table 1. Lipase-catalysed acetylation of 1,*n*-diols.[a]

Entry	Enzyme[b]	Diol	Immobilised enzyme (mg)	*me*[c]	Reaction Conversion	Reaction time min
1	CAL-B	**1a**	5	52	79	40
2	CAL-B	**1d**	5	41	75	40
3	RML-IM	**1a**	10	74	80	30
4	RML-IM	**1d**	10	70	62	90
5	RAL	**1a**	15	77	78	120
6	RAL	**1d**	15	69	71	90
7	ROL	**1a**	10	78	73	120
8	ROL	**1d**	10	71	70	120
9	TLL	**1a**	50	81	86	60
10	TLL	**1b**	40	85	77	240
11	TLL	**1c**	30	84	77	198
12	TLL	**1d**	50	85	74	120
13	CRL	**1a**	40	75	74	1440
14	CRL	**1d**	40	75	72	360
15	RNL	**1a**	40	85	52	60
16	RNL	**1d**	40	79	47	60
17	PPL	**1a**	10	77	32	120
18	PPL	**1d**	10	85	27	60

[a]Reactions were performed in a 4 ml screw-capped flat bottom vials. To a mixture of the corresponding 1,*n*-aliphatic diol (0.032 mmol) and immobilised lipase (5-50 mg) in 1 mL of diisopropyl ether, was added vinyl acetate (19.4 μL, 0.032 mmol). The resulting mixture was shaken reciprocally (125 rpm) at 25 ^{o}C. At different reaction times, samples were withdrawn from the reaction mixture, dissolved in hexane and subsequently analysed by glc. The 1,*n*-diol consumption, mono and diacetate formation were quantified from the peak areas by the external standard method. [b]*Candida antarctica* (CAL-B) (i.e. Novozyme® 435), *Rhizomucor miehei* (RML-IM), *Rhizopus arrhizus* (RAL), *Rhizopus oryzae* (ROL), *Thermomyces lanuginosus* (TLL) (i.e. Novozyme® 871), *Candida rugosa* (CRL), *Rhizopus niveus* (RNL) and porcine pancreatic lipase (PPL). [c]Monoacetylation excess (*me*) = %monoacetylated - %diacetylated/%monoacetylated + %diacetylated.

Table 2. TLL-catalysed monoacetylation of pentane-1,5-diol and octane-1,8-diol in different organic solvents.[a]

		Diol **1a**		Diol **1d**		
Solvent	Log P[b]	*me*[c]	Conversion (time, h)	*me*[c]	Conversion (time. h)	Immobilised. enzyme (mg)
Toluene	2.73	80	90 (24)	87	84(4)[d]	10
DIPE	1.52	81	86(1)	85	74(2)	50
MTBE	0.94	76	77(2)	75	78(2)	5
THF	0.46	62	83(48)	78	73(48)	150
Diglyme	-0.36	64	84(48)	68	81(72)	50

[a]Reactions conditions are described in the footnote of Table 1. [b]logarithm of the octanol-water partition coefficient of the solvent; experimental data available from Syracuse Research Corporation (http://www.syrres.com (main page) and http://esc.syrres.com/interkow/kowdemo.htm to find the specific Log P values). [c]Monoacetylation excess. [d]5 mg of immobilised preparation was used.