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PORCINE PANCREATIC LIPASE MEDIATED SELECTIVE ACYLATION OF PRIMARY ALCOHOLS IN ORGANIC SOLVENTS

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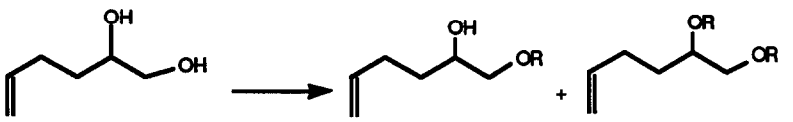
Abstract: Porcine pancreatic lipase mediated acylation of 1,n-diols and triols affords primary acylated products in high yields.

The regio- and stereospecificity of enzyme catalyzed reactions are the envy of synthetic chemists.[1] The use of enzymes in organic synthesis has become increasingly popular since it was realized that many enzymes can function in organic solvents without loss of specificity.[2]
While investigating the kinetic resolution of racemic 1,3-butanediol using porcine pancreatic lipase (PPL) in Et_2O with trifluoroethyl butyrate as the acylating agent, we noted that acylation of the primary hydroxyl was essentially complete before reaction occurred at the secondary hydroxyl.[3] This enzyme-catalyzed reaction offered promise as a convenient method for the acylation of primary hydroxyls in the presence of secondary hydroxyls. Conventional procedures for such selective protection using acetic anhydride - pyridine in dichloromethane afford substantial amounts of diacylated product even at temperatures below 0°C (Scheme 1).



$(CH_3CO)_2O$, Pyridine	(R = $COCH_3$)	5	:	1
$(CH_3CO)_2O$, K_2CO_3	(R = $COCH_3$)	8	:	1
$(CH_3CO)_2O$, PPL	(R = $COCH_3$)	98	:	2
$(C_3H_7CO)_2O$, PPL	(R = COC_3H_7)	99	:	1

Scheme 1

Biphasic systems employing acetic anhydride and solid K_2CO_3 yield somewhat less diacylated product but substantial amounts of starting material remain. Attempts to drive these reactions to completion by addition of excess anhydride result in increased yields of the diacylated product.

Lipase mediated acylations in organic solvents have been demonstrated to be regiospecific for the primary hydroxyls of carbohydrates.[5] We have now applied this technique to aliphatic diols, using porcine pancreatic lipase (PPL) and acetic or butyric anhydride as the acylating agent.[6] These reactions produce high yields of the primary acylated product which contain only traces (1-2%) of diester. Systematic investigation of this method using 1,n-diols 1-4 and triol 5 (Figure 1), reveal the method to be general.

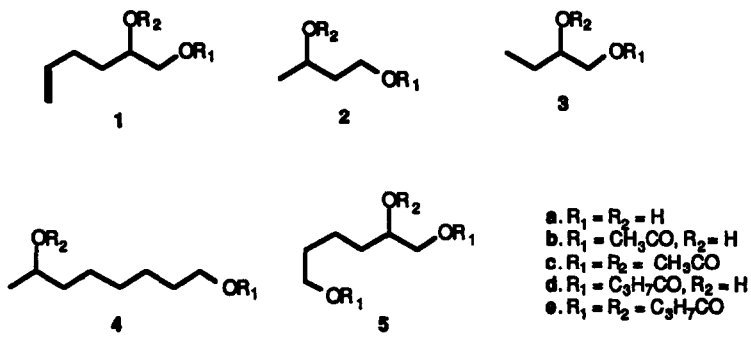


Figure 1

Reactions were carried out by vigorously stirring a mixture of the diol with 1.5 eq of the anhydride and PPL in ether. Because of the poor solubility of triol 5 in ether, THF was used as a solvent for this substrate.

There was a remarkable selectivity for primary acylation in the case of both vicinal and distal diols (entries 1-4) and butyrylation proceeded faster than acetylation (see entries 1 and 5). This might be expected since the natural substrates for lipases are the triglycerides of long-chain fatty acids. Selectivity was poor between sterically differentiated primary alcohols (entry 5).[7]

Lipase Catalyzed Acylation of 1-5. The following general procedure was followed: PPL[8] (50 mg of solid per mmol of the substrate) was added to a stirred solution of 1eq of diol or triol and 1.5 eq of anhydride in Et_2O or THF (1M solution). The reaction was stirred at room temperature for the indicated time (Table 1), after which the PPL was removed by filtration. The organic phase was diluted with ether and excess anhydride was removed by washing with aqueous 2M NaOH in the case of acetic anhydride, or by distillation in the case of butyric anhydride (50°C at 0.1 torr). The product was then either distilled (Kugelrohr) or isolated by column chromatography. Analytical samples were obtained by column chromatography.[9] In conclusion, the method reported here illustrates the potential of PPL in selective hydroxyl protection.

Table 1. Porcine Pancreatic Lipase Mediated Acylation on Diols and Triols

Entry	Substrate	Acylating agent	Time (h)	yield* (%)	Products obtained	Product Ratio**
1	1a	$(CH_3CO)_2O$	18	92	1b, 1c	98:2
		$(C_3H_7CO)_2O$	3	95	1d, 1e	99:1
2	2a	$(C_3H_7CO)_2O$	7	68	2d, 2e	99:1
3	3a	$(C_3H_7CO)_2O$	24	87	3d, 3e	94:6
4	4a	$(C_3H_7CO)_2O$	7	89	4d, 4e	97:3
5	5a	$(CH_3CO)_2O$	48	92	5b, 5c	98:2
		$(C_3H_7CO)_2O$	15	94	5d, 5e	99:1

* Isolated yields

** Ratios determined by gas chromatographic analysis

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3. When the reaction proceeded beyond monoacylation, only minor degree of kinetic resolution was observed. A mixture of 1,3-butanediol (3.0 g, 33.7 mmol), trifluoroethyl butyrate (15.2 g, 89.1 mmol) and PPL (5 g) was stirred in Et_2O (50 mL) for 119 h. After removal of the enzyme, the mono- and dibutyrate were separated by column chromatography. Hydrolysis of the dibutyrate, followed by derivatization with (S)-acetyl lactyl chloride[4] yielded an ee_p value of 0.376. A similar derivatization of the monobutyrate yielded ee_s of 0.132. From these values the calculated conversion was 26.0%, and the selectivity (E) was 2.5.

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7. A similar lack of selectivity was observed in the acylation of 1,3 propanediol, 1,4-butanediol and 2-methyl-1,4-butanediol. In the case of 1,2-ethanediol, acylation with 1.0 equivalent of butyric anhydride in the presence of PPL yielded a 5 : 1 ratio of mono- to dibutyrate, as determined by GC analysis. However this ratio fell to 3 : 1 as the water-soluble monoester was extracted during aqueous work-up.

8. PPL was purchased from Sigma Chemical Company (Type II); the listed activity was 16 units per mg solid using olive oil at pH 7.7, with a 30 min incubation.

9. All compounds were analyzed by a combination of ^{1}H and ^{13}C NMR, CIMS, IR, and elemental analysis.

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