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# ENZYME REACTIONS IN APOLAR SOLVENT. 6.§ THE EFFECT OF DOUBLE BOND ISOMERISM ON THE RATE OF PPL-CATALYZED ACYLATION OF ALLYLIC ALCOHOLS

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**Abstract:** (*E*)- and (*Z*)-isomers of allylic alcohols showed a difference in the rate of porcine pancreatic lipase (PPL) catalyzed acylation. Enzyme-catalyzed acylation was applied to the purification of two terpenic alcohols.

## INTRODUCTION

Enzymes have become increasing popular as catalysts in synthetic organic chemistry due to their ability to form isomerically pure compounds.[1] Lipases have attracted much attention as they are realtively inexpensive, show broad substrate specificity with often high selectivity, and can operate in both aqueous and anhydrous organic solutions.[2] As a cheap, crude preparation, porcine pancreatic lipase (PPL) has been widely used, and examples of its chemoselectivity,[3] regioselectivty,[4] enantioselectivity [5] and prochiral selectivity[6] have all been described. However, little has been reported on the ability of PPL to distinguish between E/Z stereoisomers. Herein we report our observations on the PPL-catalyzed transesterification of E/Z mixtures of primary and secondary allylic alcohols.

## RESULTS

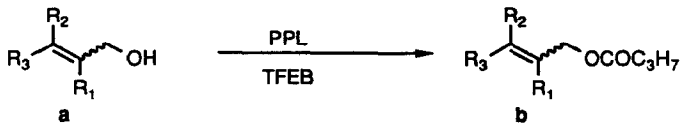
### A. 1° ALLYLIC ALCOHOLS

While examining the PPL-catalyzed acylation of isomerically pure 2° allylic alcohols, it was noted that the enzyme exerted a large difference in both reactivity and enantioselectivity between (*E*)- and (*Z*)-2° allylic alcohols.[5b]

Competition reactions, using mixtures of (*E*)- and (*Z*)-1° allylic alcohols, also showed a difference in reactivity.

When an equimolar mixture of (*E*)- and (*Z*)-2-nonenol (**1**)[7] was subjected to PPL-catalyzed transesterification in $Et_2O$ with a deficiency of trifluoroethyl butyrate (TFEB) as acylating agent, 2-3 times as much of the (*E*)-butyrate was formed over the course of the reaction (Table 1).

Table 1. PPL-Catalyzed Acylation of 1° Allylic Alcohols

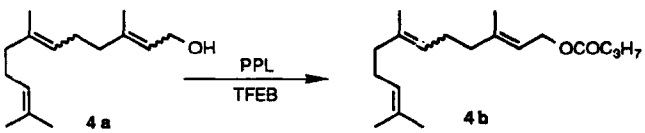



| Substrate | a E : Z[a] | Time (min) | b E : Z[a] |
|---|---|---|---|
| $C_6H_{13}$ OH 1 | 1 : 1 | 5-390 | 2.8-2.2 : 1 |
| $C_7H_{15}$ OH 2 | 5.3 : 1 | 15-300 | 15-13 : 1 |
| OH 3 | 1 : 6.2 | 5-235 | 2.5-0.9 : 1 |

Conditions: Substrate (0.3-0.4M), TFEB (0.2-0.35M), PPL (0.2 g) in $Et_2O$ (5 mL). [a]E : Z calculated from the GC signal area ratio[8]

Introduction of a methyl group at the 2-position was expected to change the stereoselectivity, so the acylation of 2-methyl-2-decenol (**2**)[9] was carried out. While the E/Z ratio of the starting alcohol was 5.3:1, the E/Z ratio of the butyrate formed was approximately 14:1, again showing an almost 3-fold preference for reaction with the (E)-isomer.

A sample of commercial nerol was found to be a 6.2:1 mixture of nerol and geraniol when examined by GC. Although a 6-fold excess of nerol was present, *twice* as much geranyl butyrate was initially formed when the mixture was submitted to PPL-catalyzed transesterification. It was surprising that the more remote 3-methyl group ion **3** should affect selectivity to a greater extent than the 2-methyl substituent in **2**. This result is in agreement with those of other groups who have also observed high selectivity in the enzyme-catalyzed acylation of nerol/geraniol mixtures using PPL[10] and mycelia from *Rhizopus arrhizus*.[11]




An attempt was made to apply this selective acylation technique to the purification of farnesol. When examined by GC, a sample of old technical farnesol (**4a**) was found to be a 1:3.3:2.4 mixture of isomers, presumed to be the (2Z,6Z), (2E,6Z) and (2E,6E) isomers respectively. (A sample of technical farnesyl butyrate (**4b**), chemically prepared, was also a 1:3.4:2.7 mixture of isomers, while the butyrate prepared from *trans,trans*-farnesol displayed a single peak on GC.) A solution of technical farnesol in $Et_2O$ was treated with TFEB (0.5 equiv.) in the presence of PPL. Whilst the starting alcohol was a 1:3.3:2.4 mixture

of isomers, the initially formed butyrates were in the ratio 1:10:26, declining to 1:8:14 after stirring overnight. $^1$H NMR of the vinylic region indicated that significant purification had occurred (Fig. 1).

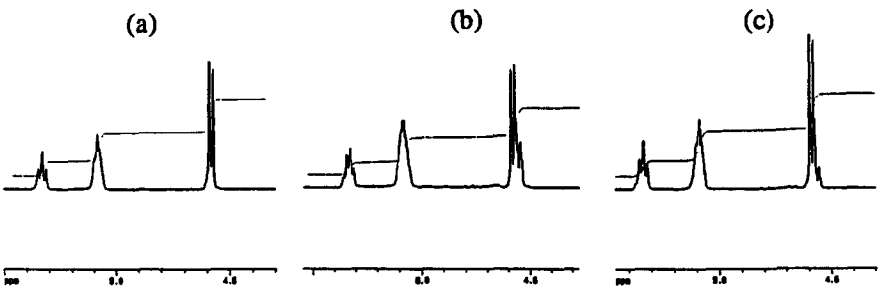
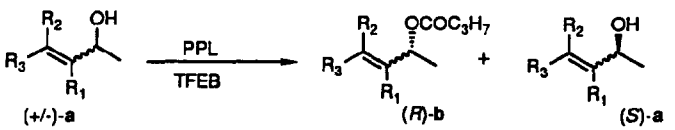



Fig. 1. Partial $^1$H NMR of the vinylic regions of: (a) pure (2*E*,6*E*) farnesyl butyrate; (b) technical farnesyl butyrate prepared chemically; (c) technical farnesyl butyrate prepared by PPL-catalyzed acylation.

## B. 2° ALLYLIC ALCOHOLS

For 3-undecen-2-ol (**5a**) and 4-phenyl-3-buten-2-ol (**6a**) the (*E*)-isomer reacted 20-40 times faster than the (*Z*)-isomer (Table 2). Because of the high enantioselectivity, the (*S*)-enantiomer of the (*E*)-isomer did not participate in the reaction, and the concentration of the of the (*E*)-isomer is essentially about half that of the (*Z*)-isomer.

Table 2. PPL-Catalyzed Kinetic Resolution of 2° Allylic Alcohols




| Substrate | a E : Z[a] | Time (h) | b E : Z[a] | E[b] (*E*)-a | (*Z*)-b |
|---|---|---|---|---|---|
| $C_7H_{15}$ OH **5** | 0.8 : 1 | 1-8 | 20-10 : 1 | >100 | 10[c] |
| OH **6** | 0.8 : 1 | 1-5 | 14-10 : 1 | >100 | 3[c] |
| OH **7** | 1.3 : 1 | 3-30 | 5.5-4.6 : 1 | 60 | 34 |

Conditions: Substrate (0.3 M), TFEB (0.5-0.9 M), PPL (1.0 g) in $Et_2O$ (5 ML).
[a] E : Z calculated from the GC signal area ratio.[8] [b] E value calculated as in ref. 12. [c] E values were determined from separate runs.[13]

As for 1° allylic alcohols, the presence of a methyl group in the 3-position had a dramatic effect on the selectivity of the reaction. However in the case of allylic alcohol **6a**[14] the acylation proceeded more

slowly and the (*E*)-isomer reacted only 3-4 times faster than the (*Z*)-isomer. Furthermore, the presence of the 3-methyl substituent resulted in an convergence of the E values for the two stereoisomers.

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**7**. E/Z-2-Nonenyl acetate (1.6 mmol) was deesterfied with $K_2CO_3$/MeOH and the crude product acylated with TFEB (0.95 mmol) and PPL (0.2 g). E/Z-2-nonenol (**1**) did not resolve on the GC column.

**8**. Gas chromatography was performed on a J/W fused silica DB-1 capillary glass column (15 m X 0.25 mm) using the following temperature program: initial temperature 60°C for 1 min; 20 deg/min; final temperature 250°C for 2 min.

**9**. Prepared by Wittig-Horner reaction of triethyl 2-phosphonopropionate with octanal, followed by $LiAlH_4$ reduction, as a 5.3:1 mixture of E/Z isomers (as shown by GC and $^1H$ NMR).

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**13**. The enantiomer excess (ee) of the unreacted alcohol (ees) and the product (eep)(after hydrolytic removal of the butyrate) was determined by derivatization with acetyl (*S*)-lactyl chloride followed by GC analysis of the diastereomers.

In the case of (*E*)- and (*Z*)-4-phenyl-3-buten-2-ol (**6**) the lactate esters did not resolve on the GC column. $ee_s$ and $ee_p$ for each isomer was determined in separate runs after hydrogenation of the reaction mixtures and derivatization with acetyl (*S*)-lactyl chloride.

In the case of (*E*)- and (*Z*)-3-undecen-2-ol (**5**), the (*Z*)-isomer was contaminated with a small amount of 2-undecanol which interfered with an accurate determination of $ee_s$ for the (*E*)-isomer. E values were determined in separate runs

**14**. Prepared by addition of MeLi to commercial citral.