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Preparation of 3-Alkyl-4-hydroxy-2-butenyl Acetate through Highly Regioselective Lipase-Catalyzed Hydrolysis of Corresponding Diacetates

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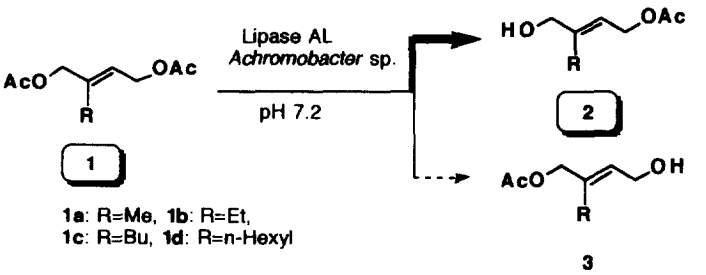
Abstract: Highly regioselective hydrolysis of diacetate of (E)-2-substituted-2-butene-1,4-diol has been demonstrated. Lipase AL (Meito) was chosen from among commercial enzymes as the one most able to preferentially hydrolyze the acetyl group at 1-position giving monoacetate.

Lipases are the most frequently used enzymes in organic synthesis because of their stability, availability and their acceptance of a broad range of substrates.[1] Numerous applications have been found in kinetic resolution or enantioselective synthesis of prochiral compounds, employing transesterification or ester hydrolysis. Enzyme-catalyzed regioselective acetylation or deacetylation are also known to be as useful means of preparing partially acetylated compounds.[1,2] To date, however, the reported examples of lipase-catalyzed regioselective deacetylation have been applied only to limited types of compounds.[1,2] We wish to report here the simple preparation of 4-hydroxy-2-butenyl acetate (**2**) through lipase-catalyzed regioselective deacetylation of corresponding diacetate **1** (Eq. 1).



1a: R=Me, **1b**: R=Et,
1c: R=Bu, **1d**: R=n-Hexyl

Twenty-eight commercially available lipases were screened for their activity and regioselectivity using diacetate **1a** (R=Me) as a model compound.[3,4] Reactions were performed in 0.1M phosphate buffer (pH7.2) at 35°C. Fortunately, separation of two regio isomers of monoacetate, **2a** and **3a**, was achieved by silica gel flash column chromatography (**2a**: R*f*=0.5, **3a**: R*f*=0.48, in hexane-ethyl acetate=1:1). Assignment of each isomer

Table 1. Lipase-catalyzed Regioselective Deacetylation of Diacetate 1 [a]

Entry	Substrate	R	Time (h)	Yield of monoacetate	Regioselectivity 2 : 3	Recovery of 1	Yield of the Diol
1	**1a**	Me	1.5 [b]	50%	88 : 12	40%	0%
2	**1a**	Me	26	61%	94 : 6	0%	4% [c]
3	**1b**	Et	1	65%	100 : 0 [d]	0%	5% [c]
4	**1c**	Bu	120	50%	100 : 0 [d]	0%	22%
5	**1d**	n-Heptyl	120	85%	100 : 0 [d]	0%	5%

a) Reaction was carried out at 0°C in 0.1 M phosphate buffer at pH 7.2. b) The reaction was carried out at 35°C. c) Due to the hydrophilicity of the diol produced, significant loss of amount was observed during the isolation process from the reaction media. d) No isomer was detected by capillary GC analysis using Chiraldex G-Ta(φ0.25 mm x20 M, He, 100°C).

was achieved by ^{1}H NMR analysis. The resulting monoacetates, a mixture of regioisomers, were converted to the corresponding t-butyldimethylsilyl ether and the regioselectivity determined by capillary GC analysis. Interestingly, many enzymes catalyzed to hydrolysis **1a** at the sterically bulky position to afford monacetate **2** preferentially. Lipase AL (*Achromobacter* sp., Meito) was chosen as the best enzyme to ensure high regioselectivity (88% selectivity, Entry 1 in Table 1). The regioselectivity was enhanced up to 94% when the reaction was carried out at 0°C, though longer reaction time was required (Entry 2 in Table 1); further reaction was conducted at 0°C. Change of R group of **1** from methyl to larger alkyl groups provided excellent results. Three types of diacetates, **2b-2d**, were prepared from corresponding propargyl alcohols through hydromagnesiation and the following reaction with paraformaldehyde.[5] *Perfect regioselectivity* was observed when substrate **1b** (R=Et), **1c** (R=Bu), or **1d** (R=n-Hept) were subjected to the reaction (Entries 3-5 in Table 1).

Because this type of regioselective hydrolysis of diacetate is impossible by a chemical reaction such as alkaline hydrolysis, the present enzymatic reaction is recommended as useful to obtain **2** very conveniently. The work represents not only a significant advance in preparation of partially acetylated compounds but also provides a new aspect in application of enzymatic reaction for organic synthesis. Further study of the scope and limitations of this reaction will make it even more beneficial.

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References and Notes

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2) For recent examples see: (a) Palmer, D. C.; Terradas, F. *Tetrahedron Lett.* **1994**, *35*, 1673. (b) Morimoto, T.; Murakami, N.; Nagata, A.; Sakakibara, *J. Pharm. Bull.* **1994**, *42*, 751. (c) Danieli, B.; Luisetti, M.; Riva, S.; Bertinotti, A.; Ragg, E.; Scaglioni, L.; Bombardelli, E. *J. Org.Chem.*, **1995**, *60*, 3637.
3) Four other types of enzymes can hydrolyze **1a** preferentially at the 1-position giving monoacetate in ca.60% yield with more than 70% regioselectivity; PL (Meito, *Alcaligenes sp.*, 90% at 0°C for 8h), Porcine Pancreatin (Sigma Type II, 89% at 0°C for 336 h). PS (Amano, *Pseudomonas cepacia*, 86% at 0°C for 4 h), OF (Meito, *Candida cylindracea*, 73% at 0°C for 0.75 h).
4) Diacetate **1a** was prepared from 2-methyl-1,3-butadiene; Oroshnik, W.; Mallory, R. A. *J. Am. Chem. Soc.*, **1950**, *72*, 4608.
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6) The authors are grateful to Professors Kenji Uneyama and Takashi Sakai of Okayama University for their valuable discussions throughout this work. They also grateful to the SC-NMR Laboratory of Okayama University for the NMR measurements.

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