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Highly regioselective lipase-catalyzed acetylation and hydrolysis of acyclic α,ω-terpenediols and their diacetates

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Abstract—Highly regioselective transformations of the acyclic α,ω-terpenediols and their diacetates to the monoacetates using lipase were accomplished. The acetylation of the α,ω-terpenediols gave regioselectively the ω-monoacetates **3**, whereas the α-monoacetates **2** were obtained by hydrolysis of the α,ω-diacetates.

Acyclic terpenes having different α- and ω-functional groups are valuable building blocks for the synthesis of natural products.[1] The best and simplest approach to such acyclic terpenes is one-step transformation of the terpenes having the same α- and ω-functional groups (Fig. 1), though this approach is rarely found in the literature. Recently, Itoh et al. reported highly regioselective partial hydrolysis of (*E*)-4-acetoxy-2-methylbut-2-enyl acetate, in which thiacrown ether remarkably accelerated the lipase-catalyzed hydrolysis.[2] Their pioneering work encouraged us to investigate the above challenge. We report herein regioselective lipase-catalyzed monoesterification of various acyclic α,ω-terpenediols and their diacetates.

At first, standard chemical acetylation of the acyclic α,ω-terpenediols **1** using acetic anhydride and pyridine was examined, in which no regioselectivity was observed (Scheme 1).

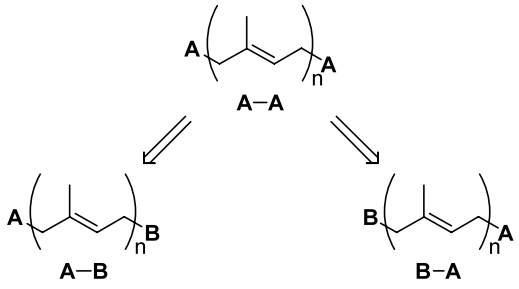
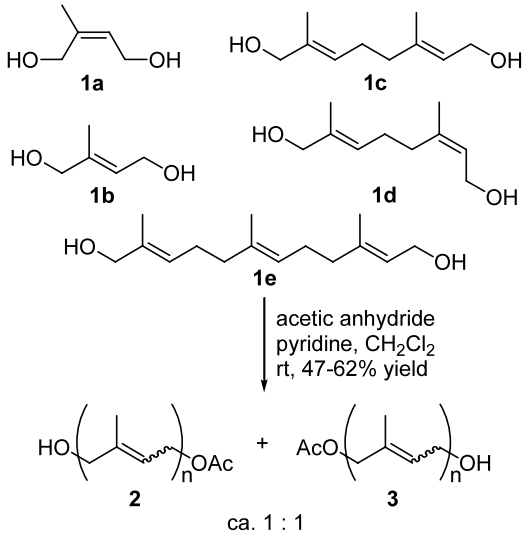


Figure 1. One-step transformation to different functional group-substituted terpenes.

Next, regioselective lipase-catalyzed acetylation of the acyclic α,ω-terpenediols **1** was investigated as shown in Table 1. Reactions were carried out in shaking apparatus at 25°C.[3,4] Lipase PS-D (*Pseudomonas cepacia*, Amano) marked the best regioselectivity among the lipases tested.[5] Acetylation of (*Z*)-2-methylbut-2-ene-1,4-diol **1a** regioselectively proceeded to give the ω-monoacetate **3a** in a **2a**/**3a** ratio of <1/>99 (entry 1).[6] The stereoisomer **1b** also showed high regioselectivity (entry 2). Similarly, acyclic mono- and sesqui-terpenediols **1c**–**e** were acetylated in shorter reaction time to afford the ω-monoacetate **3c**–**e** with high regioselectivity (entries 3–5). Generally, the synthesis of the ω-monoacetate **3** was more difficult than that of the



Scheme 1. Standard chemical acetylation of the acyclic α,ω-terpenediols **1**.

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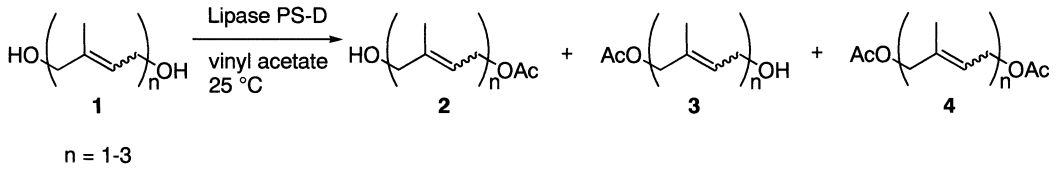
Table 1. Lipase-catalyzed acetylation of acyclic α,ω-terpenediols **1**[a]



Entry	Substrate	Time (h)	Yield (**2**+**3**, %)[b]	**2**+**3**:**4**:**1** Ratio[c]	**2**:**3** Ratio[c]
1	**1a**	24	27	31:32:37	<1:>99
2	**1b**	0.5	36	40:49:11	8:92[d]
3	**1c**	2.5	22	24:76:0	<1:>99
4	**1d**	1	43	49:41:10	<1:>99
5	**1e**	2	45	49:27:24	<1:>99

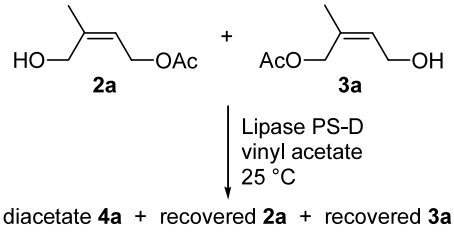
[a] Lipase PS-D/substrate=1/10 (w/w), vinyl acetate/substrate=2/1 (mol/mol).
[b] Isolated yield.
[c] Determined by GC using Shimadzu GC-17A fused silica capillary column (J&W Scientific DB-1, 30 m×0.25 mm).
[d] Determined by ^{1}H NMR analysis.

α-monoacetate **2**,[7] which were prepared by SeO_2 oxidation of prenyl, geranyl, neryl, and farnesyl acetates, respectively.[1] However, it has been found that such difficulties are solved by our regioselective lipase-catalyzed acetylation.

Interestingly, competitive lipase-catalyzed acetylation of 2-buten-1-ol (**5**) and 2-methyl-2-propen-1-ol (**6**) resulted in no chemoselectivity as shown in Scheme 2, that is, lipase PS-D could not differentiate between γ- and β-methyl groups to the hydroxyl group. The similar acetylation of a mixture of the monoacetates (**2a**:**3a**=56:44) gave a mixture of the diacetate **4a** and recovered monoacetates, the ratio of recovered **2a** and **3a** was remarkably changed as shown in Table 2. It became clear that the monoacetate **2a** was acetylated faster than **3a**. We, therefore, suggested that the first acetylation of the diol **1** to the monoacetate **2**,**3** was non-regioselective, while the second acetylation of **2**,**3** to the diacetate **4** was regioselective (Scheme 3). Since the acetylation was a reversible reaction, the hydrolysis of the diacetate **4** would give rise to high regioselectivity as well as high yield.

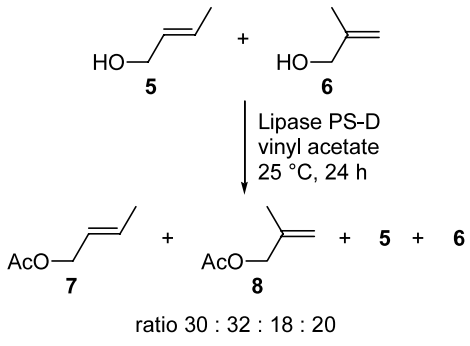
Lipase-catalyzed hydrolysis of the α,ω-diacetates **4** was investigated as shown in Table 3. Reactions were carried out in a similar manner to acetylation. As would be expected, the hydrolysis effectively proceeded to give the monoacetate **2** with better yield than in the case of acetylation. (*Z*)-4-Hydroxy-3-methyl-but-2-enyl acetate (**2a**) was obtained by the hydrolysis of the diacetate **4a** with high regioselectivity in a ratio of 97:3 (entry 1); however, the hydrolysis of mono- and sesqui-terpene diacetate **4b**–**e** slightly decreased the regioselectivity (entries 2–5).

Table 2. Competitive acetylation of **2a** and **3a**

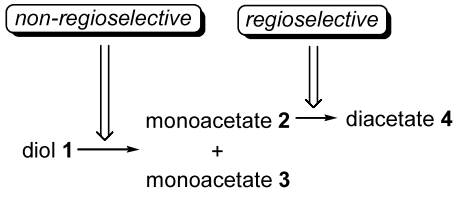


Time (min)	**2a**:**3a** Ratio[a]	**2a**+**3a**:**4a** Ratio[a]
0	56:44	100:0
10	47:53	95:5
30	40:60	51:49
50	19:81	30:70
70	6:94	18:82
90	<1:>99	12:88

[a] Determined by GC using Shimadzu GC-17A fused silica capillary column (J&W Scientific DB-1, 30 m×0.25 mm).

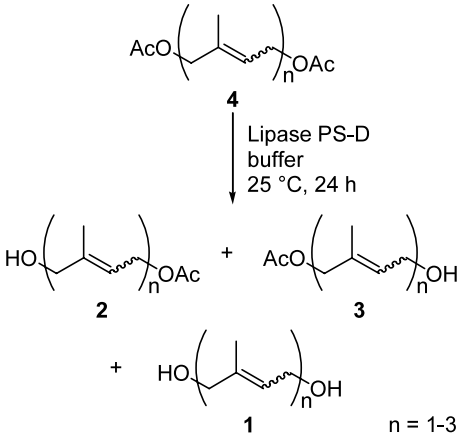


Scheme 2. Competitive acetylation of **5** and **6**.



Scheme 3. Proposed mechanism of regioselectivity.

Table 3. Lipase-catalyzed hydrolysis of the acyclic α,ω-terpenediacetates **4**[a]



Entry	Substrate	Yield (**2**+**3**, %)[b]	**2**+**3**:**1**:**4** Ratio[c]	**2**:**3** Ratio[c]
1	**4a**	62	78:15:7	97:3
2	**4b**	63	75:14:11	92:8[d]
3	**4c**	43	44:5:51	89:11
4	**4d**	58	74:17:9	91:9
5	**4e**	34	34:13:53	75:25

[a] Lipase PS-D/substrate = 1/10 (w/w).
[b] Isolated yield.
[c] Determined by GC using Shimadzu GC-17A fused silica capillary column (J&W Scientific DB-1, 30 m×0.25 mm).
[d] Determined by ^{1}H NMR analysis.

We have shown the high regioselectivity attained in lipase-catalyzed reactions of the unsymmetrical α,ω-terpenediols and their acetates, which may enable the direct and ready synthesis of terpenoids. Although the detailed mechanism of the regioselectivity is not presently obvious, the results described here will lead to further application of the methodology.

Acknowledgements

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2. (a) Itoh, T.; Mitsukura, K.; Kaihatsu, K.; Hamada, H.; Takagi, Y.; Tsukube, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2275–2278; (b) Itoh, T.; Uzu, A.; Kanda, N.; Takagi, Y. *Tetrahedron Lett*. **1996**, *37*, 91–92.
3. Typical procedure: a suspension of (*Z*)-2-methylbut-2-ene-1,4-diol **1a** (100 mg, 0.979 mmol) and Lipase PS-D (10 mg) in vinyl acetate (169 mg, 1.96 mmol) was stirred at 25°C for an appropriate time; then, Lipase PS-D was removed through filtration, and concentrated to give a crude oil, which was purified by column chromatography (silica gel, eluent: hexane-AcOEt) to give the monoacetates **2a**, **3a**, the diacetate **4** and the recovered diol **1a**.
4. All compounds were identified by comparing its spectrum with the reported value. Registry No. **1a**: 40560-13-2, **1b**: 53627-41-1, **1c**: 26488-97-1, **1d**: 26488-98-2, **1e**: 69809-46-7, **2a**:132032-87-2, **2b**: 70473-55-1, **2c**: 37905-03-6, **2d**: 70238-37-8, **2e**: 93787-91-8, **3a**: 104411-04-3, **3b**: 53170-98-2, **3c**: 177408-49-0, **3d**: 156700-81-1, **4a**: 59055-00-4, **4b**: 59054-99-8, **4c**: 67604-16-4, **4e**: 71135-55-2.
5. The regioselectivities were dependent upon the nature of the lipase catalysts, for instance, Lipase AY (*Candida rugosa*, Amano) showed reverse regioselectivity in a **2a**/**3a** ratio of 79/21.
6. (*Z*) or (*E*)-4-Hydroxy-2-methylbut-2-enyl acetate **3a** or **3b** has been difficult to prepare regioselectively a pure form according to reported procedure, see: Ferroud, D.; Gaudin, J. M.; Genet, J. P. *Tetrahedron Lett*. **1986**, *27*, 845–846.
7. Commonly, the synthesis of the ω-monoacetate **3** was achieved by protection/deprotection method, see: (a) Aldrich, J. R.; Oliver, J. E.; Waite, G. K.; Moore, C.; Waters, R. M. *J. Chem. Ecol*. **1996**, *22*, 729–738; (b) Hiroi, K.; Hirasawa, K. *Chem. Pharm. Bull*. **1994**, *42*, 1036–1040.