Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 6293–6295
Tetrahedron Letters

Highly regioselective lipase-catalyzed acetylation and hydrolysis of acyclic α,α′-alkenediols and their diacetates

Takaya Hisano, Kotoko Onodera, Yasuhiro Toyabe, Nobuyuki Mase, Hidemi Yoda and Kunihiko Takabe*

Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan

Received 24 June 2005; revised 8 July 2005; accepted 11 July 2005

Abstract—Highly regioselective transformation of acyclic α,α′-alkenediols and their corresponding diacetates to monoacetates using lipase was accomplished. The acetylation of the α,α′-alkenediol regioselectively gave (*E*)-monoacetate, whereas the (*Z*)-monoacetate were obtained by hydrolysis of the α,α′-diacetate.

The differentiation of sterically and electronically similar functional groups is a challenging research for organic synthetic chemists. Generally, it is more difficult to differentiate similar functional groups, as the difference of physical properties of those groups become smaller. For example, acetylation of acyclic α,ω-terpenediols with acetic anhydride under standard conditions resulted in the mixture of α-monoacetoxyterpene, ω-monoacetoxyterpene and α,ω-terpenediacetate.[1] Therefore, synthesis of either the α or ω-monoacetoxyterpene was previously achieved by multi-step transformation.[2] The best and simplest approach to such acyclic terpenes is one-step transformation of terpenes having the same α- and ω-functional groups (Fig. 1). 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.[3] Their pioneering work encouraged us to investigate highly regioselective acetylation and hydrolysis of the unsymmetrical α,ω-terpenediols and their acetates using lipase, which enables the direct synthesis of α,ω-functionalized terpenoids.[1]

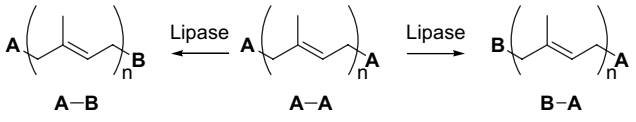


Figure 1. Lipase-catalyzed one-step transformation of terpenes bearing different functional groups.

In order to develop broadly useful enzymes[4] for this class of differentiation, we investigated a regioselective acetylation and hydrolysis of unsymmetrical α,α′-alkenediols and acetates using lipase (Fig. 2). To the best of our knowledge, this study represents the first example of a direct transformation of unsymmetrical α,α′-alkenediols bearing two primary hydroxy groups with a high level of regioselectivity.[5]

α,α′-Alkendiol **2** was prepared from 1,3-bis[(tetrahydro-2*H*-pyran-2-yl)oxy]-2-propanone (**1**) by Wittig reaction following deprotection as shown in Scheme 1. The two-step synthesis afforded various acyclic α,α′-alkendiols **2** in 37–71% yield.

At first, acetylation of the acyclic α,α′-alkendiols **2** was examined under standard conditions. The acetylation is carried out using acetic anhydride (1 equiv) and pyridine (1 equiv) in a solution of dichloromethane.

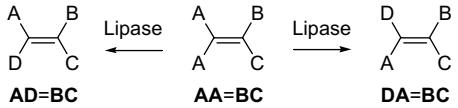
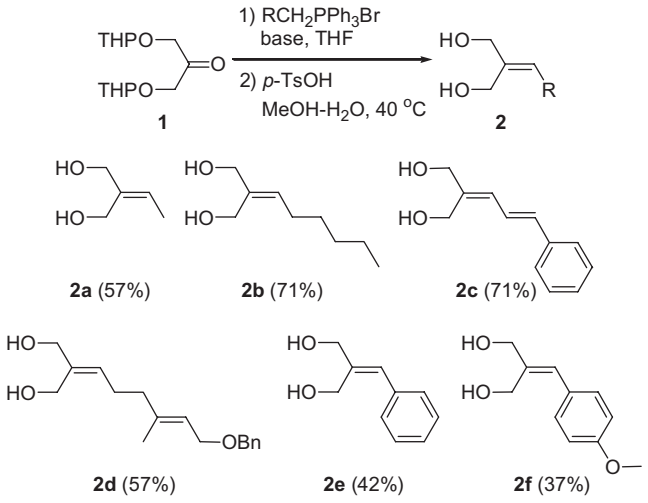


Figure 2. Lipase-catalyzed one-step transformation of alkenes bearing different functional groups.

Keywords: Lipase-catalyzed reaction; Regioselectivity; Building block.
* Corresponding author. Tel./fax: +81 53 478 1148; e-mail: tcktaka@ipc.shizuoka.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.07.039

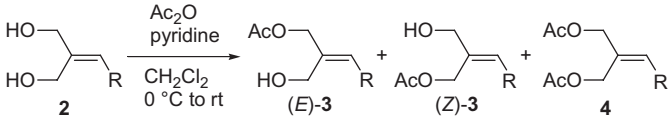


Scheme 1. Preparation of α,α′-alkendiols **2**.

Chemical yields of the monoacetate **3** were less than 59%, and poor regioselectivity was observed (Table 1). Control of over acetylation was very difficult, and then diacetates **4** are obtained in 5–25% yields.

Next, the regioselective lipase-catalyzed acetylation of α,α′-alkenediols **2** was investigated as shown in Table 2.[6] Reactions were carried out in a shaking apparatus at 25 °C. During lipase library screening, lipase PS-D (*Pseudomonas cepacia*, Amano) and AY (*Candida rugosa*, Amano) gave high regioselectivity (entries 1–5). The acetylation of 2-ethylidenepropane-1,3-diol (**2a**) regioselectively proceeded to give the monoacetate **3a** in a (*E*)-3/(*Z*)-3 ratio of 90/10 (entry 5). Alkyl and alkenyl substituents showed higher regioselectivity using lipase PS-D (entries 6–8). Similarly, aryl-substituted α,α′-alkenediols **2e**–**f** were acetylated within 4 h to afford the (*E*)-monoacetate **3e**–**f** with excellent regioselectivity (entries 10–11). A significant change of regioselectivity

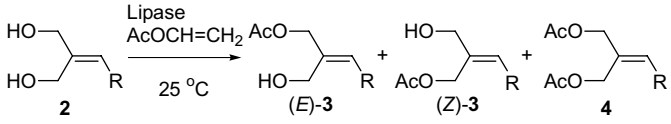
Table 1. Standard acetylation of α,α′-alkendiols **2** using acetic anhydride and pyridine[a]



Entry	Diol **2**	Time (h)	**3** Yield[b] (%)	Ratio[c] *E*:*Z*	**4** Yield[b] (%)	**2** yield[b] (%)
1	**2a**	7	48	55:45	12	37
2	**2b**	44	55	50:50	13	15
3	**2c**	31	59	46:54	10	21
4	**2d**	2	47	38:62	25	12
5	**2e**	4	54	70:30	17	24
6	**2f**	9	48	65:35	5	32

[a] The acetylation was carried out using acetic anhydride (1.0 equiv) and pyridine (1.0 equiv).
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis (entries 1–2) and HPLC analysis (entries 3–6).

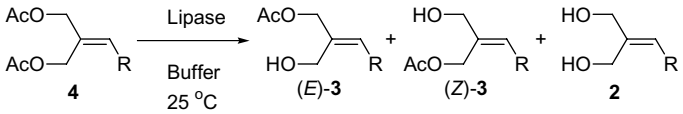
Table 2. Lipase-catalyzed acetylation of α,α′-alkendiols **2**[a]



Entry	Diol **2**	Lipase	Time (h)	**3** Yield[b] (%)	Ratio[c] *E*:*Z*	**4** Yield[b] (%)	**2** Yield[b] (%)
1	**2a**	—	24	0	—	—	Quant.
2	**2a**	Chirazyme	21	21	57:43	7	45
3	**2a**	AK	4	36	65:35	16	30
4	**2a**	PS-D	4	29	84:16	15	41
5	**2a**	AY	24	27	90:10	4	52
6	**2b**	PS-D	9	74	95:5	10	6
7	**2c**	PS-D	20	82	97:3	8	0
8	**2d**	PS-D	8	68	97:3	7	20
9	**2e**	PS-D	2	81	80:20	9	8
10	**2e**	AK	4	90	96:4	4	5
11	**2f**	PS-D	4	71	99:1	8	0

[a] The acetylation was carried out using vinyl acetate (1.0 equiv) and lipase (0.1 g equiv).
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis (entries 1–6) and HPLC analysis (entries 7–11).

Table 3. Lipase-catalyzed hydrolysis of α,α′-alkendiacetates **4**[a]



Entry	Diacetate **4**	Lipase	Time (h)	**3** Yield[b] (%)	Ratio[c] *E*:*Z*	**2** Yield[b] (%)	**4** Yield[b] (%)
1	**4a**	AY	33	24	28:72	18	31
2	**4b**	AY	72	51	21:79	28	17
3	**4c**	AY	44	41	15:85	6	25
4	**4d**	PS-D	24	49	9:91	26	21
5	**4e**	AK	48	52	4:96	7	30
6	**4f**	PS-D	26	50	4:96	7	38

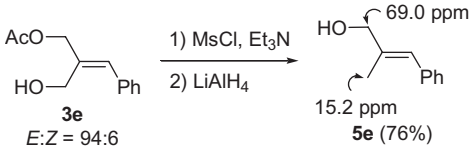
[a] The hydrolysis was carried out using lipase (0.1 g equiv).
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis (entries 1–2) and HPLC analysis (entries 3–6).

as well as chemical yield was observed. The (*E*)-monoacetates **3** are obtained in over 68% yield, and the diacetylated product **4** was reduced to less than 10% yield, with the exception of **2a**. Standard conditions for the chemical acetylation of α,α′-alkenediols **2** result in no regioselectivity and chemoselectivity. However, such difficulties are resolved by regioselective lipase-catalyzed acetylation, even of methyl-substituted alkenediol **2a**.

Lipase-catalyzed hydrolysis of α,α′-alkendiacetates **4** was investigated as shown in Table 3. Reactions are carried out in a similar manner to the reactions in Table 2. The hydrolysis proceeds slowly to give monoacetate **3** with high regioselectivity but lower chemical yield compared with that of acetylation. Interestingly, the (*Z*)-regioisomer is obtained as a major product in the lipase-catalyzed hydrolysis. The (*E*)-regioisomer is selectively obtained by lipase-catalyzed acetylation, therefore, we can regioselectively synthesize both of the regioisomers.

The structure of monoacetate **3** cannot be directly determined by ^{1}H NMR analysis, since signals of the methylene protons were overlapped. Structure determination of monoacetate **3e** is performed by ^{13}C NMR analysis, after derivatization of **3e** to **5e** as shown in Scheme 2. Mesylation following reduction furnished alcohol **5e** in 76% yield. ^{13}C NMR spectra of **5e** is in accordance with the reported data for (*E*)-2-methyl-3-phenylprop-2-en-1-ol (*E*)-**5e** ((*E*)-isomer 15.2, 68.8 ppm, (*Z*)-isomer 21.7, 62.2 ppm).[7]

In conclusion, we have shown high regioselectivity in lipase-catalyzed reactions of α,α′-alkendiols and their acetates. These acetates may now be used directly as building blocks in natural product synthesis. Although the detailed mechanism of the regioselectivity is not presently obvious, the results described here will lead to further application of the methodology.



Scheme 2. Determination of structure.

Acknowledgements

We are grateful to Amano Enzyme Inc. for a generous gift of Lipases. We gratefully acknowledge Dr. D. D. Steiner for a scientific discussion.

References and notes

1. Takabe, K.; Mase, N.; Hisano, T.; Yoda, H. *Tetrahedron Lett.* **2003**, *44*, 3267–3269.
2. (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; (c) Ferroud, D.; Gaudin, J. M.; Genet, J. P. *Tetrahedron Lett.* **1986**, *27*, 845–846.
3. (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.
4. (a) Aehle, W. *Enzymes in Industry: Production and Applications*; Wiley-VCH: Weinheim, 2004; (b) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook*; Wiley-VCH: Weinheim, 2002; (c) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994.
5. Enzyme-catalyzed hydrolysis of the α,α′-alkenedioate, see the following report: Schirmeister, T.; Otto, H. H. *J. Org. Chem.* **1993**, *58*, 4819–4822.
6. Typical procedure (Table 2, entry 10): To a solution of the α,α′-alkenediols **2e** (164 mg, 1.0 mmol, 1.0 equiv) and vinyl acetate (92 μL, 1.0 mmol, 1.0 equiv) in 1,4-dioxane (1.0 mL) was added Lipase AK (16 mg), and stirred for 4 h at 25 °C. The reaction mixture was filtrated to remove the Lipase AK, concentrated to give the crude acetate. The crude product was purified by column chromatography (silica gel, hexane/AcOEt = 70/30) to give the monoacetates **3e** (186 mg, 90%), the diacetate **4e** (12 mg, 5%) and the recovered diol **2e** (8 mg, 5%).
7. Daub, G. W.; Edwards, J. P.; Okada, C. R.; Allen, J. W.; Maxey, C. T.; Wells, M. S.; Goldstein, A. S.; Dibley, M. J.; Wang, C. J.; Ostercamp, D. P.; Chung, S.; Cunningham, P. S.; Berliner, M. A. *J. Org. Chem.* **1997**, *62*, 1976–1985.