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Conformational effects on lipase-mediated acylations of 2-substituted cyclohexanols

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Abstract—Lipase-mediated acetylations of *trans*- and *cis*-2-substituted cyclohexanols gave the corresponding (1*R*)-cyclohexyl acetates and (1*S*)-cyclohexanols in high yields and ee, but *c*-4-*tert*-butyl-*c*-2-ethenyl-*r*-1-cyclohexanol was unreactive owing to the steric interaction between the axial OH group and the axial H atoms at the 3- and 5-positions. In the *cis*-isomer the OH group occupies an equatorial position to bind to the lipase, and less bulky axial alkenyl and alkynyl groups might not so much prevent acetylations than an alkyl group.

Lipase PS (lipase from *Pseudomonas cepacia*) is one of the most frequently utilized enzymes in organic synthesis because it is inexpensive, and it has high enantioselectivity and a broad substrate specificity.[1–4] Some lipases including lipase PS are well known to react with (*R*)-alcohols faster to give the corresponding acetates for secondary alcohols.[5,6] To comprehend the mechanistic aspects, many active site models were reported, [6–10] and hence it seems to be favorable for a binding model to use a compound having a rigid conformation. Although some examples of lipase-mediated resolutions of cyclohexanols have been reported,[6,10–13] the relationship between reactivities and conformations including ring inversion had not been discussed. Here, we report conformational effects on the lipase-mediated acetylations of 2-substituted cyclohexanols **1**–**5** as a reasonable model.

The *trans*-2-substituted cyclohexanols **1** were prepared by the ring-opening reaction of cyclohexene oxide using RLi or RMgBr, while the *cis*-isomers **2** were synthesized by the reduction of the corresponding cyclohexanones with diisobutylaluminium hydride, followed by purification with silica gel column. The reduction of 4-*tert*-butyl-2-ethenylcyclohexanone with $NaBH_4$ gave a diastereoisomeric mixture of 4-*tert*-butyl-2-ethenylcyclohexanols, and the subsequent separation by column chromatography on silica gel afforded diastereoisomers **3b**–**5b**, but no *c*-4-*tert*-butyl-*t*-2-ethenyl-*r*-1-cyclohexanol was obtained.

The structures of these diastereoisomers were deduced by the synthetic mechanism, and also confirmed by a combination of H–C COSY measurements and the detections of large coupling constants *J* between an axial H(1) and a neighboring axial H(2) in the NMR spectra of **1a**–**e**, **3b**.[14]

In a typical experiment, a suspension of 2-substituted cyclohexanols **1**–**5** (2.0 mmol), lipase PS (Amano) (0.5 g), vinyl acetate (2.0 mmol), and molecular sieves 4 Å (2.0 g) in toluene (20 ml) was stirred at 30°C. In order to learn the conversion, samples were withdrawn at intervals, and the mixture was kept stirred until about 50% conversion. Thereafter the enzyme was filtered off, and the filtrate was found to contain only cyclohexyl acetates **6**–**10** and **1**–**5**. After concentration in vacuo the residue was purified by chromatography on silica gel to afford (1*R*)-cyclohexyl acetates ***R*-6**–**10** and (1*S*)-alcohols ***S*-1**–**5**. Treatments of ***S*-1**–**5** with acetic anhydride (2 equiv.), 4-(dimethylamino)pyridine (2 equiv.) in acetonitrile (10 ml) provided the corresponding (1*S*)-acetates ***S*-6**–**10** nearly quantitatively.

The ee values of ***S*-1**–**5** and ***S*-6**–**10** were determined by HPLC equipped with a chiral column (Daicel chiralcel OD-H) or capillary GC with Chrompack WCOT. The absolute structures of the products were assigned according to the empirical rule,[5,6] and were further

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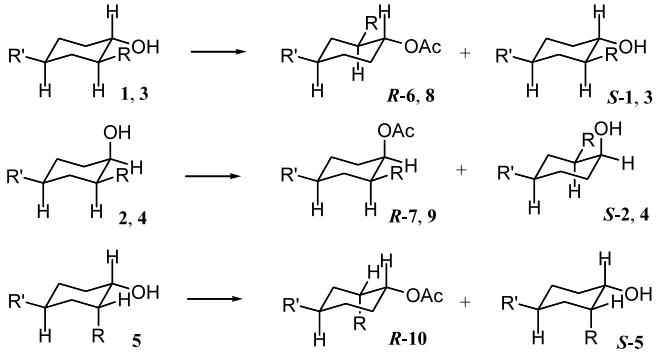
confirmed on the basis of the octant rule in the CD spectra[15] of the corresponding cyclohexanones, which were obtained by Swern oxidation of a OH group and the reduction of C=C and C≡C group using $NaBH_4$–$CoCl_3$.[16] These results are given in Table 1.

The *trans*-cyclohexanols **1** and **3b** were found to be more reactive than the *cis*-isomers **2** and **5b**, (Run 1–5, 11, 6–10, and 13), and the substituent effects in **1a**–**c** are opposite to those in **2a**–**c** (Run 1→3 and 6→8). Interestingly, the *cis*-isomer **4b** containing an axial OH group was unreactive even after 600 h, because a binding of the axial OH group to the enzyme might be sterically hindered by the presence of two axial H atoms at the 3 and 5 positions (Run 12). On the other hand, in the other *cis*-isomer **5b** with an equatorial OH group an acetylation took place, though not so efficiently probably owing to a bulky 4-*tert*-butyl group (Run 13).

Molecular mechanics calculation of **2c** indicates that the conformer **2c-eq** having the OH group at the equatorial position is more stable than the other one **2c-ax** in 57:43 ratio. The compound numbers **2-eq** and **2-ax** mean that the compound **2** has the conformers containing an equatorial and an axial OH group, respectively, and the conformational inversion of **2-eq** and **2-ax** rapidly occurs at a room temperature. The NMR spectrum showed one singlet proton peak in the area of a ≡CH group at a room temperature, but at −99°C the spectrum revealed two distinct peaks in that area. The peak at the lower field is characteristic of a ≡CH proton at an equatorial position and the relative area of those two peaks was 62:38 in favor of **2c-eq**. The other **2-eq**/**2-ax** ratios predicted by MM calculations are as follows; **2a**; 9:91, **2b**; 17:83, **2d**; 5:95, and **2e**; 61:39 (69:31 found in NMR spectrum at −99°C).

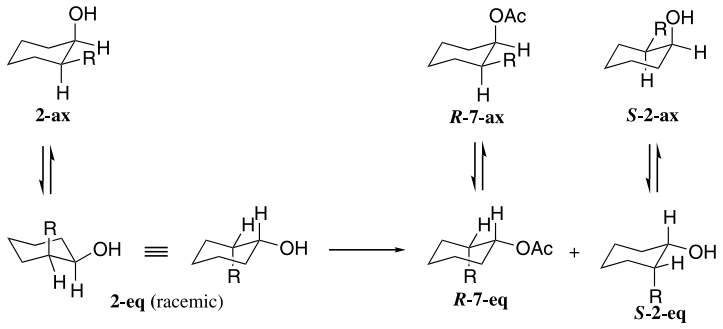
Cyclohexanol **4b** is unreactive to LPS because a 4-*tert*-butyl group ensures that the equilibrium lies heavily to the side having the *tert*-butyl group equatorial, that is, a hydroxy group axial. This finding strongly suggests that the conformer **2-ax** cannot react with the enzyme. In the *cis* isomers **2** a hydroxy group occupies an equatorial position to bind to the enzyme, and one enantiomer of racemic **2-eq** undergoes the acetylation

Table 1. Lipase-mediated acylations of cyclohexanols **1**–**5**[a]

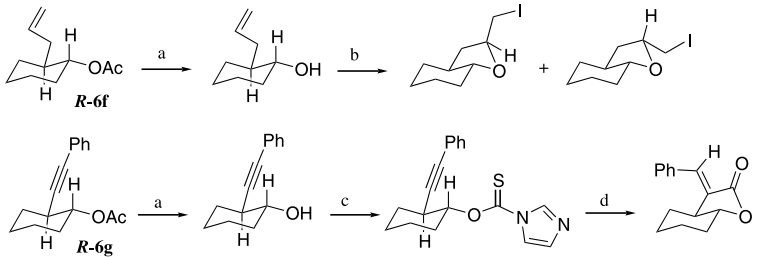


Run	Substrates	Reaction time (h)	Conversion (%)	e.e. (yield%)[b]		*E*
				***R*-6–10**	***S*-1–5**	
1	**1a**	7	43	99 (40)	75 (49)	>200
2	**1b**	9	42	99 (40)	72 (48)	>200
3	**1c**	12	42	99 (37)	72 (49)	>200
4	**1d**	8	40	99 (37)	78 (56)	>200
5	**1e**	13	44	94 (42)	79 (56)	>200
6	**2a**	46	43	96 (39)	74 (49)	111
7	**2b**	22	44	99 (38)	78 (45)	>200
8	**2c**	6	42	99 (40)	73 (48)	>200
9	**2d**	51	43	99 (39)	79 (50)	>200
10	**2e**	104	42	97 (32)	70 (64)	141
11	**3b**	48	14	82 (11)	13 (64)	11
12	**4b**	600	0[c]	–	–	–
13	**5b**	102	33	99 (26)	48 (64)	50

[a] Vinyl acetate, LPS, molecular sieves 4A, toluene, 30°C.
[b] Isolated yield.
[c] No reaction.



Scheme 1. Acylations of *cis*-2-substituted cyclohexanols **2**.



Scheme 2. *Reagents and conditions*: (a) NaOH, EtOH–H_2O, rt (98%); (b) *N*-iodosuccinimide, MeCN, rt (52+44%); (c) 1,1′-thiocarbonydiimidazole, THF, reflux (73%); (d) Et_3B, Bu_3SnH, toluene, −78°C, then aq. HCl (78%).

to give ***R*-7-eq** as shown in Scheme 1. Less bulky axial 2-alkenyl and 2-alkynyl groups in **2-eq** do not much prevent acetylations than an alkyl group (Run 7 and 8). This explains the tendency for the reactivities of **2a**, **2b**, and **2c**, though completely enough to exclude the stability by π-electrons.

These nonracemic chiral 2-alkenyl- and 2-alkynyl-cyclohexanols can be utilized in a wide variety of synthetic reactions, for example, formation of oxygen heterocycles.[17 18] The examples of ionic and radical cyclizations using ***R*-6f** and ***R*-6g** obtained by the above method (99% ee, $E=>200$) are given in Scheme 2.

Further details including the stereochemistry of these reactions will be reported in the near future.

References

1. Wong, C.- H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Elsevier: Oxford, 1994; pp. 41–130.
2. Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis*; Wiley-VCH: Weinheim, 1999; pp. 65–129.
3. Faber, K. *Biotransformations in Organic Chemistry*, 4th ed.; Springer: Berlin, 2000; pp. 29–176.
4. Gais, H. J.; Theil, F. In *Enzyme Catalysis in Organic Synthesis*, 2nd ed.; Drauz, K.; Waldmann, H., Eds.; Hydrolysis and Formation of Carboxylic Acid Esters; Wiley-VCH: Weinheim, 2002; Vol. II, pp. 335–578 and references cited therein.
5. Kazlauskas, R. J.; Alexandra, N. E.; Weissfloch, N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.
6. Cygler, M.; Grochulski, P.; Kazlaukas, R. J.; Schrag, J. D.; Bouthillier, F.; Rubin, B.; Serreqi, A. N.; Gupta, A. K. *J. Am. Chem. Soc.* **1994**, *116*, 3180–3186.
7. Toone, E. J.; Werth, M. J.; Jones, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 4946–4952.
8. Naemura, K.; Fukuda, R.; Murata, M.; Konishi, M.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2385–2394.
9. Nishizawa, K.; Ohgami, Y.; Matsuo, N.; Kishida, H.; Hirohara, H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1293–1298.
10. Ema, T.; Kobayashi, J.; Maeno, S.; Sakai, T.; Utaka, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 443–453.
11. Whitesell, J. K.; Chen, H.-H.; Lawrence, R. M. *J. Org. Chem.* **1985**, *50*, 4663–4665.
12. Esser, P.; Buschmann, H.; Meyer-Stork, M.; Scharf, H.-D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1190–1192.
13. Fukuzawa, T.; Shimoji, Y.; Hashimoto, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1649–1658.
14. Coupling constants $J_{H(1),H(2)}$ are as follows. $J_{ax\text{-}H(1),ax\text{-}H(2)}$: **1a**, 9.2; **1b**, 9.3; **1c**, 9.7; **1d**, 10.0; **1e**, 9.7; **3b**, 15.6 Hz. $J_{eq\text{-}H(1),ax\text{-}H(2)}$: **2b**, 5.6 Hz; **2a**, **2c**, **2d**, **2e**, **4b**, invisible under a broad singlet peak. $J_{ax\text{-}H(1),eq\text{-}H(2)}$: **5b**, 4.5 Hz.
15. Lightner, D. A.; Gurst, J. E. *Organic Conformational Analysis and Stereochemistry from Circular Dichroism Spectroscopy*; Wiley-VCH: New York, 2000; pp. 95–137.
16. Chung, S.-H. *J. Org. Chem.* **1979**, *44*, 1014–1016.
17. Bartlett, P. A. In *Asymmetric Synthesis*, *Vol. 3*, *Part B*; Morrison, J. D., Ed.; Olefin Cyclization Processes that Form Carbon-Heteroatom Bonds; Academic Press: Orlando, 1984; pp. 411–501
18. Srikrishna, A. In *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Radical Cyclizations and Rearrangements; Wiley-VCH: Weinheim, 2001; Vol. 2, pp. 151–278