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Formation of hemiacetal esters in lipase-catalysed reactions of vinyl esters with hindered secondary alcohols

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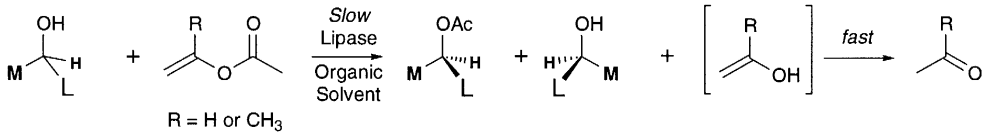
Abstract

Normally many lipases are efficient catalysts for the acetylation of alcohols with vinyl acetate. Unexpectedly, we found that some sterically hindered secondary alcohols react slowly to yield hemiacetal esters as mixtures of diastereomers. Their formation can be explained by the reaction of the alcohol with acetaldehyde that is produced by the lipase-catalysed splitting of vinyl acetate and subsequent acetylation of the resulting hemiacetal by the lipase.

Keywords: lipase; hindered alcohol; hemiacetal ester.

Lipase-catalysed transesterification[1] in organic solvents[2] is a widely used method for the resolution of racemic secondary alcohols. Either vinyl or isopropenyl acetate is often used as the acyl donor, because the resulting vinyl alcohols are rapidly converted to acetaldehyde or acetone, respectively, making the transesterification irreversible (Scheme 1).



Scheme 1. Lipase-catalysed enantioselective transesterification of vinyl acetates with racemic alcohols

While tertiary alcohols are almost unreactive,[3] sterically hindered secondary alcohols react slowly in such transesterifications.[4] In attempts to kinetically resolve the latter type of alcohols, e.g. racemic borneol **1**[5a] and the racemic bicyclic alcohol **2**[5b] (Scheme 2), we noticed that incubation of these alcohols with vinyl acetate in organic solvents using certain lipases led to the formation of a new type of product. In addition to the expected acetate **1**-Ac,[6] a diastereomeric mixture of the acetylated hemiacetal **3** was obtained (Scheme 2). Alcohol **2** gave the acylated hemiacetal **4** as the only product. To our knowledge this

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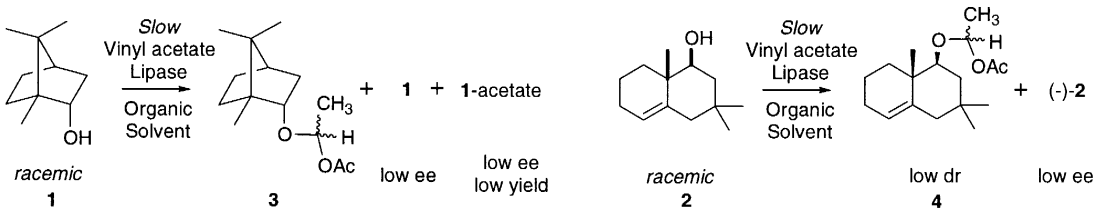
is the first observation of such products in lipase catalysed transesterifications of vinyl esters. However, acetal esters have been used as substrates in lipase catalysed enantioselective hydrolytic reactions.[7] The hemiacetal esters **3** and **4** appeared to be formed via enzyme-mediated reactions. This induced us to study the structures of these products and their mechanism of formation in more detail.



Scheme 2. Formation of normal and abnormal acylation products

A number of lipases and conditions were studied with the two substrates **1** and **2** (see Table 1). Only lipases from *Candida antarctica* (Lipase B: Chirazyme™ L2, Novozyme SP435) and *Pseudomonas* sp. (Lipase PS, Chirazyme™ L6) afforded products **3** or **4** in appreciable yields. If the enzyme was excluded, no formation of hemiacetal esters was observed. When inactivated enzyme[8] or bovine serum albumin were added as protein components, no **4** was obtained from alcohol **2**. Borneol **1** and a mixture of acetaldehyde, acetic acid and acetic anhydride without enzyme gave only a low yield of bornyl acetate **1**-Ac. In the presence of enzyme and added acetaldehyde, higher yields of products were obtained (entries 5, 6, 13, 14). Incubation of CALB with **2** and isopropenyl acetate as the acyl donor gave no acetylated hemiketal from liberated acetone. However, after addition of acetaldehyde, the formation of **4** started (entry 14).

The enzymatic nature of the hemiacetal ester formation was substantiated by the observations that the (*S*,*S*)-isomer of **2** was converted preferentially into **4** ($E=2.8\pm0.2$)[9] and that also one of the enantiomers of *rac*-borneol **1** was converted preferentially (entry 1). In the latter case, the preferred enantiomer varied depending on the enzyme used.

The enantioselectivity of the acylation step was evident from the fact that two different major diastereomers were obtained from (−)- and (+)-borneol **1** (entries 2, 3, 6). The stereogenic centre in the hemiacetal moiety determined which diastereomer of **3** was produced preferentially. Thus, the minor diastereomer from (+)-**1** was the enantiomer of the major one from (−)-**1** and vice versa.

From the results above, the formation of **3** and **4** can be explained as follows (Scheme 3). The alcohol adds to acetaldehyde, which is produced by the reaction of the enzyme with vinyl acetate,[10] giving the hemiacetals. Subsequently, these are acetylated by the enzyme. The high selectivity and conversion obtained in entry 6 can only be explained, if it is assumed that the hemiacetal is rapidly equilibrated prior to the slow but stereoselective enzyme-catalysed esterification.

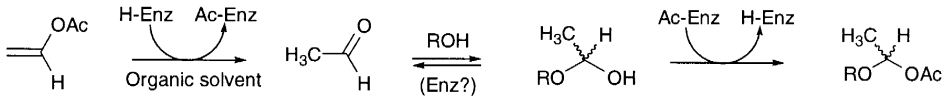
The hemiacetal esters were first recognised because of their long retention times on GC analysis. Conventional aqueous work-up resulted in hydrolysis of the hemiacetal esters with recovery of the substrate (along with acetaldehyde and acetic acid). This might explain why these products have not been noticed before. However, when using a non-aqueous work up under virtually non-acidic conditions, compounds **3** and **4** could be isolated and the latter was purified using preparative GC. The structures of these hemiacetal esters were evident from their spectroscopic data.[11]

In order to investigate the scope of the hemiacetal ester formation, some additional sterically hindered secondary alcohols were also investigated. Thus, in the presence of lipase and vinyl acetate in an organic solvent, compounds **5**–**8**[11] gave mixtures of acetates and hemiacetal esters whereas compounds **9**–**11** just gave the usual acetates.

Table 1
Reaction of alcohols **1**, **2**, **7** and **8** with lipases under various conditions

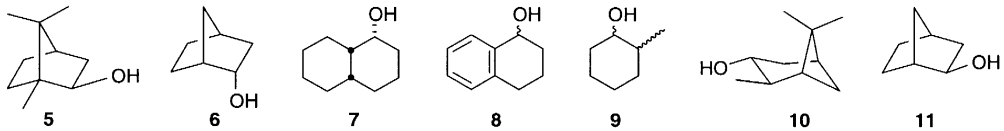
entry	enzyme[a]	Sub-strate	solvent	+alde-hyde	temp. (°C)	hemiacetal acetate formed (%)[b] 2 d	1 w	2 w	3 w	4 w	d.r.
1	PCL-L-6	*rac*-**1**	TBME	no	22	-[c]	5	17[e]	-	-	2:1[d]
2	PCL-L-6	(-)-**1**	TBME	no	22	-	7	17[e]	-	-	1:9 (1 w)
3	PCL-L-6	(+)-**1**	TBME	no	22	-	12	33[e]	-	-	3:1
4	PCL-L-6	(-)-**1**	TBME	no	30	-	17	50-60[e]	-	-	-
5	PCL-L-6	(-)-**1**	TBME	yes[f]	22	-	52	68[e]	-	-	-
6	PCL-L-6	(-)-**1**	TBME	yes[f]	22	-	-	-	>99		2:98
7	PCL-L-6	*rac*-**1**	heptane	no	22	-	5	6[e]	-	-	-
8	CALB-435	*rac*-**1**	TBME	no	22	-	9	19[e]	-	-	1:3[d]
9	PCL-PS	**2**	octane	no	45	<1	10	-	-		-
10	CALB-L-2	**2**	octane	no	45	21	31	38	36[g]	34	-
11	CALB-L-2	**2**	octane	no	25	17	31	37	45	52	-
12	CALB-L-2	**2**	*t*BuOH[h]	no	25	<1	9	-	-	-	-
13	CALB-L-2	**2**	octane	yes	25	-	30[i]	59	65	77	-
14	CALB-L-2	**2**	octane	yes[k]	25	-	0[i]	16[l]	27	30	-
15	CALB-L-2	**7**[m]	octane	no	25	30	37	45	47	46	-
16	CALB-L-2	**8**	octane	no	25	27	37	46	47	47	-

[a] PCL = lipase from *Pseudomonas sp.*: PS = Amano PS; L-6: Boehringer Chirazyme™ L-6, lyo. CALB = *Candida antarctica* lipase B: L-2: Boehringer Chirazyme™ L-2, lyo; 435: Novozyme 435.
[b] d = days; w = weeks; Conditions: Entries 1-5,7,8: Enzyme 5 mg/ml (entry 6: 61,5 mg/ml), 0.1 M **1**, 2 M vinyl acetate, shaken. Entry 6: Enzyme 10 mg/ml, 0.2 M **1**, 1 M acetaldehyde, 1 M vinyl acetate, shaken. Entries 9-16: enzyme, 100 mg/ml, 0.1 M substrate, 2 M vinyl acetate (entry 13: isopropenyl acetate), 350 rpm.
[c] - = not determined.
[d] d.r. = diastereomeric ratio of the two major diastereomers derived from (-)-**1** and from (+)-**1**, respectively.
[e] **1**-Ac was also formed, entry/*yield%*: 1/*2*; 2/*1*; 3/*3*; 4/*15*; 5/*0*; 6/<*1*; 7/*1*; 8/*2*.
[f] 4 and 5 eq acetaldehyde (entries 5 and 6, respectively) added at start.
[g] Byproducts started to appear.
[h] Performing the reaction in toluene or iPr$_2$O gave even lower yields
[i] 2 eq acetaldehyde added.
[k] Isopropenyl acetate was used instead of vinyl acetate.
[l] 3 eq acetaldehyde added.
[m] One diastereomer reacted much faster than the other.



Scheme 3. Formation of hemiacetal esters

In summary we have shown that when some sterically hindered secondary alcohols and vinyl acetate were treated with certain lipases in an organic solvent, hemiacetal esters were formed. We have demonstrated that at least one step in this reaction, namely ester formation, was enzyme catalysed.



Acknowledgements

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5. (a) Lindmark, M.; Isaksson, D.; Sjödin, K.; Högberg, H.-E., in press. (b) Compound **2** can be efficiently resolved by acylation with vinyl acetate catalysed by *Candida rugosa* lipase (CRL) in diisopropyl ether (Ref. 4) and is a key intermediate for the synthesis of the marasmane and lactarane sesquiterpenes: see: Ref. 4 and Bell, R. P. L.; Sobolev, A.; Wijnberg, J. B. P. A.; de Groot, Ae. *J. Org. Chem.* **1998**, *63*, 122–128.
6. The **1**-Ac formed was of low ee and varying configuration depending on the enzyme used. Thus Chirazyme™ L6 and Novozyme 435 gave (−)-**1**-Ac (E∼2) and (+)-**1**-Ac (E∼1.5), respectively.
7. (a) Franssen, M. C. R.; Goetheer, E. L. V.; Jongejan, H.; de Groot, Ae. *Tetrahedron Lett.* **1998**, *39*, 8345–8348. (b) Angelis Y.S.; Smnou, I. *Tetrahedron Lett.* **1997**, *38*, 8109–8112. (c) *ibid* **1998**, *39*, 2823–2826.
8. Boiled in water for 5 min, after which the water was removed by evaporation in vacuo.
9. The enantiopreference of CALB in this reaction is opposite to that of *Candida rugosa* lipase in the formation of **2**-Ac (Ref. 4).
10. Many lipases hydrolyse vinyl acetate, even under 'dry' conditions: Weber, H. K.; Weber, H.; Kazlauskas R. J. *Tetrahedron: Asymmetry* **1999**, *10*, 2635–2638.
11. Hemiacetal ester **3** from (−)-borneol, (−)-**1**: Colourless oil. ^{1}H NMR (C_6D_6): δ 0.76 (s, 3H), 0.78 (s, 3H), 0.92 (s, 3H), 1.05 (dd, 1H, *J*=13.0, 3.4 Hz), 1.18 (m, 1H), 1.25 (m, 1H), 1.32 (d, 3H, *J*=5.2 Hz), 1.55 (t, 1H, *J*=4.6 Hz), 1.66 (m, 1H), 1.75 (s, 3H), 2.17 (m, 2H), 3.95 (ddd, 1H, *J*=9.5, 3.2, 1.8 Hz), 6.06 (q, 1H, *J*=5.2 Hz). ^{13}C NMR (C_6D_6): δ 13.62, 18.89, 19.82, 21.10, 21.37, 26.83, 28.52, 36.37, 45.32, 47.75, 49.10, 82.59, 94.92, 170.29. MS: 180 (peak with highest *m/z*, M^+-CH_3COOH). Hemiacetal ester **3** from (+)-borneol, (+)-**1**: colourless oil, by prep. LC. ^{1}H NMR (C_6D_6): δ 0.76 (s, 3H), 0.77 (s, 3H), 0.84 (s, 3H), 1.15 (dd, 1H, *J*=13.0, 3.4 Hz), 1.25 (m, 1H), 1.28 (m, 1H), 1.32 (d, 3H, *J*=5.2 Hz), 1.53 (t, 1H, *J*=4.6 Hz), 1.68 (m, 1H), 1.77 (s, 3H), 2.13 (m, 2H), 3.89 (ddd, 1H, *J*=9.5, 3.2, 1.8 Hz), 6.05 (q, 1H, *J*=5.2 Hz). ^{13}C NMR (C_6D_6): δ 13.76, 18.86, 19.75, 21.19, 21.08, 26.93, 28.47, 37.47, 45.38, 47.31, 49.58, 85.97, 97.44, 169.96. MS: 180 (peak with highest *m/z*, M^+-CH_3COOH). Hemiacetal ester **4** from racemic **2**: colourless oil, by prep. GC. ^{1}H NMR (C_6D_6): δ 0.93 (s, 6H); 1.14 and 1.19 (s, 3H, two isomers); 1.35 and 1.38 (d, 3H, *J*=5.1 Hz, two isomers); 1.43–2.22 (m, 10H); 1.73 and 1.74 (s, 3H, two isomers), 3.65 (m, 1H, two isomers); 5.39 (m, 1H); 6.21 (q, 1H, *J*=5.1 Hz). ^{13}C NMR (C_6D_6): δ 18.31, 18.41, 19.10, 19.30, 20.84, 21.08, 21.47, 25.18, 25.45, 26.17, 31.91, 32.00, 32.29, 36.21, 36.44, 39.23, 40.21, 43.07, 45.31, 45.52, 80.77 and 85.17 (C1), 93.10 and 97.83 (O–C–O), 123.90 (C5), 140.18 and 140.43 (C4a), 170.00 and 170.21 (C=O). HRMS: theor. $C_{15}H_{24}O$ (M^+-CH_3COOH): 220.1827; found: 220.1818. Hemiacetal ester from **7**: colourless oil, by prep. GC. ^{1}H NMR (C_6D_6): δ 0.84–2.10 (m, 16H), 1.36 (d, 3H, *J*=5.4 Hz), 1.70 and 1.71 (s, 3H, two isomers), 3.66 (m, 1H, two isomers), 6.22 (m, 1H, two isomers). ^{13}C NMR (C_6D_6): δ 19.89, 20.78, 21.29, 21.41, 21.52, 24.47, 24.57, 26.24, 26.38, 26.53, 27.68, 31.83, 35.57, 35.84, 39.84, 42.31, 79.69 and 80.43 (C1), 94.24 and 95.17 (O−C−O), 170.29 (C=O). HRMS: theor. $C_{12}H_{20}O$ (M^+-CH_3COOH): 180.1514, found: 180.1511. Hemiacetal ester from **8**: colourless oil, by prep. GC; ^{1}H NMR (C_6D_6): δ 1.31 and 1.38 (2×d, 3H, *J*=5.1 Hz, two isomers); 1.40–2.72 (m, 6H); 1.73 (s, 3H CH_3), 4.74 (m, 1H, two isomers); 6.28 and 6.38 (q, 1H, *J*=5.1 Hz, two isomers); 6.90–7.70 (m, 4H). ^{13}C NMR (two isomers, C_6D_6): δ 14.10, 18.56, 18.86, 19.01, 20.71, 20.85, 21.18, 21.37, 22.54, 28.49, 28.71, 28.94, 29.10, 30.20, 73.37 and 75.16 (C1), 94.02 and 95.89 (O–C–O), 125.83–137.54 (6 aromatic carbons atoms, overlapped by the solvent), 169.94 and 170.17 (C=O). HRMS: theor. $C_{12}H_{14}O$ (M^+-CH_3COOH): 174.1045; found: 174.1041.