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Journal of Molecular Catalysis B: Enzymatic 54 (2008) 61–66
JOURNAL OF MOLECULAR CATALYSIS B: ENZYMATIC
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Chemo-enzymatic Baeyer–Villiger oxidation of cyclopentanone and substituted cyclopentanones

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Received 25 September 2007; received in revised form 20 November 2007; accepted 6 December 2007
Available online 23 December 2007

Abstract

Chemo-enzymatic oxidation of cyclopentanones and substituted cyclopentanones to the corresponding δ-valerolactones was investigated employing catalytic amount of *Candida antarctica* lipase-B in ethyl acetate and employing urea–hydrogen peroxide as the oxidant. In contrast to the smooth oxidation of cyclohexanones to the corresponding ε-caprolactones, the δ-valerolactones reacted further with the lipase delivering trans-esterified products and also acetylated alcohols, depending on the structural nature of the cyclopentanones.

Keywords: Chemo-enzymatic oxidation; *Candida antarctica* lipase-B; Baeyer–Villiger oxidation; Trans-esterification

1. Introduction

The Baeyer–Villiger oxidation is the oxidative cleavage of a carbon–carbon bond adjacent to a carbonyl group and the insertion of an oxygen atom between these two carbons. The Baeyer–Villiger oxidation involves the reaction of a ketone or an aldehyde with organic peroxyacids or alkyl hydroperoxides to deliver esters (or lactones). Several methodologies have been developed to achieve this high synthetic value transformation [1]. This oxidation can also be carried out with hydrogen peroxide in the presence of a Lewis acid and also enzymatically using Baeyer–Villiger monooxygenases [2,3].

We are particularly interested in developing new benign oxidative methodologies that can be practical and minimize the environmental impact [4]. Organic peracids are expensive and/or hazardous, which limits their industrial applications. Commercially available solution of peracetic acid also contains acetic acid, hydrogen peroxide, and traces of sulfuric acid which might be detrimental to some sensitive oxidized products. Efforts have been directed toward the *in situ* generation of organic peracids [5]. In this context, we recently developed a green chemo-enzymatic oxidation of unfunctionalized olefins [6]. This chemo-enzymatic approach was also successfully applied to Baeyer–Villiger oxidation of cyclohexanones [7].

Candida antarctica lipase-B, also called CAL-B, is a 317 aminoacid serine-hydrolase which has found many applications for the synthesis of fine chemicals [8]. This enzyme has been cloned and expressed in *Aspergillus orizae* and immobilized in a porous polyacrylic resin, Novozyme-435. This enzyme is highly valuable in the kinetic resolution of racemic primary and secondary alcohols [9]. It was also found that it could also carry out perhydrolysis and ammonolysis of esters and carboxylic acids [10,11].

We recently reported attractive environmentally benign procedures for the epoxidation of unfunctionalized olefins, and the Baeyer–Villiger oxidation of cyclohexanones utilizing *C. antarctica* lipase-B, Scheme 1 [6,7]. A chemo-enzymatic strategy was developed to generate the peracetic acid *in situ* in a mild and green fashion. In this transformation, ethyl acetate was utilized as solvent and also as a substrate for a lipase which oxidizes the ethyl acetate to peroxyacetic acid using hydrogen peroxide complexed with urea (UHP). The peracetic acid, formed *in situ*, oxidizes unfunctionalized olefins to the corresponding epoxides. The same reaction conditions were applied with success for the Baeyer–Villiger oxidation of cyclohexanone and substituted cyclohexanones for the preparation of caprolactones. The use of UHP, an anhydrous form of hydrogen peroxide [12], facilitated the addition of the oxidant, and avoided any dam-

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doi:10.1016/j.molcatb.2007.12.012

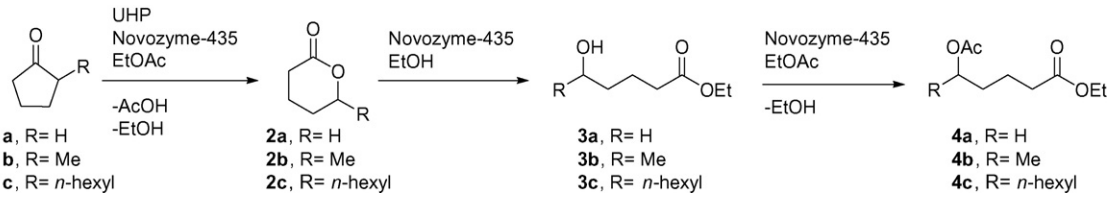
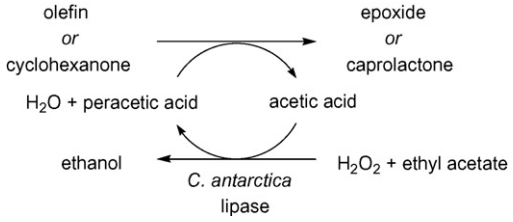


Fig. 1. Chemo-enzymatic oxidation of cyclopentanone.



Scheme 1. Overall catalytic cycle.

age of the oxidant to the enzyme. In this paper, we report this chemo-enzymatic oxidation applied to cyclopentanones.

2. Results and discussion

A smooth conversion of cyclohexanone and substituted cyclohexanones to the corresponding ε-caprolactones occurred when the oxidation was carried out with UHP in the presence of lipase and ethyl acetate as the solvent [7]. However, we observed that when cyclopentanones were subjected to the same chemo-enzymatic conditions, formation of several other products occurred. Reaction of ethyl acetate and Novozyme-435 in the presence of UHP generates peracetic acid and also an equivalent of ethanol (Fig. 1). The peracetic acid readily oxidizes cyclopentanone to δ-valerolactone (**2a**) generating also acetic acid. Now, the δ-valerolactone generated can also compete with ethyl acetate and acetic acid for binding to the active site of the lipase to form the acyl enzyme complex with serine-105 of *C. antarctica* lipase-B. Reaction of ethyl acetate or acetic acid with the lipase forms the acetyl–enzyme complex, nucleophilic attack of ethanol regenerates ethyl acetate, and nucleophilic attack of hydrogen peroxide forms peroxyacetic acid. In addition, reaction of the lactone with the lipase can potentially generate a hydroxyester with the serine group in the binding site (the acyl enzyme complex). It appears that δ-valerolactone reacts faster than ε-caprolactone with the lipase. Once generation of peracetic acid occurs, ethanol and hydrogen peroxide can compete for nucleophilic attack to other acyl enzyme complex. Attack of ethanol to the acyl enzyme complex formed with valerolactone can deliver ethyl 5-hydroxypentanoate (**3a**). The new alcohol formed, can also compete for nucleophilic attack to acyl enzyme complexes. In this manner, ethyl 5-acetoxypentanoate (**4a**) is also formed.

The oxidation of cyclopentanone using the chemo-enzymatic conditions was carefully monitored by NMR, Fig. 2a. We observed that as soon as cyclopentanone (**1a**) was oxidized, valerolactone **2a** reacted smoothly with the lipase and ethanol delivering the hydroxyester **3a**. Furthermore, 5-hydroxyester **3a** was also readily acetylated to the diester **4a**. After 7 days, the major product was the acetylated alcohol **4a**. In the case of 2-methyl cyclopentanone (**1b**), the Baeyer–Villiger oxidation occurred faster than with the unsubstituted cyclopentanone, Fig. 2b. Again, we observed ethanolysis of the valerolactone furnishing the corresponding 5-hydroxy ethyl ester **3b**. But this time, acetylation of the secondary alcohol was more difficult, being the alcohol **3b** the major product after 7 days. With the more hindered 2-*n*-hexylcyclopentanone (**1c**), Baeyer–Villiger oxidation was also relatively fast, having a 50% conversion after 3 days, Fig. 2c. Trans-esterification of valerolactone **2c**

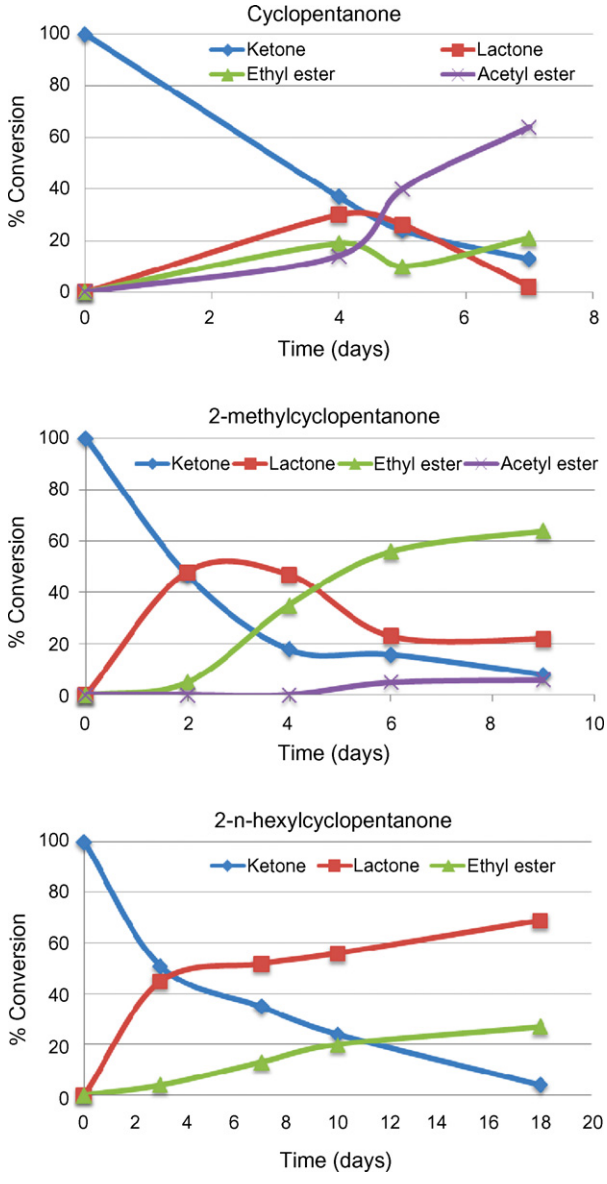
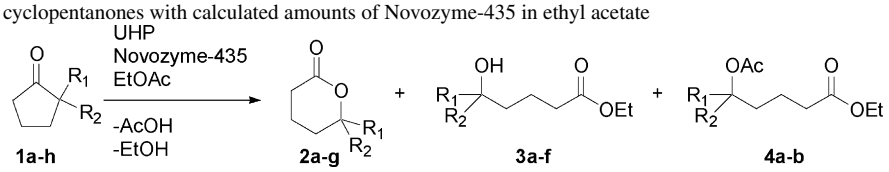


Fig. 2. Chemo-enzymatic oxidation of cyclopentanones.

Table 1
Baeyer–Villiger oxidation of cyclopentanones with calculated amounts of Novozyme-435 in ethyl acetate



Entry	Ketone	Time (days)	**1** (%)	**2** (%)	**3** (%)	**4** (%)	Conversion (%)
1	**1a**, R_1 = H, R_2 = H	4	37	30	19	14	63
		5	24	26	10	40	76
		7	13	2	21	64	87
2	**1b**, R_1 = H, R_2 = Me	2	47	48	5	0	53
		4	18	47	35	0	82
		6	16	23	56	5	84
		9	8	22	64	6	92
3	**1c**, R_1 = H, R_2 = *n*-hexyl	3	51	45	4	0	49
		7	35	52	13	0	65
		10	24	56	20	0	76
		18	4	69	27	0	96
4	**1d**, R_1 = H, R_2 = *n*-pentyl	7	28	58	14	0	72
5	**1e**, R_1 = H, R_2 = benzyl	8	3	75	22	0	97
6	**1f**, R_1 = H, R_2 = allyl	7	15	76	9	0	85
		9	9	71	9	0	91[a]
7	**1g**, R_1 = Me, R_2 = Me	5	85	15	0	0	15
		7	83	17	0	0	17
		13	76	24	0	0	24
		20	75	25	0	0	25
8	**1h**, R_1 = benzyl, R_2 = benzyl	20	100	0	0	0	0

[a] Other product obtained as diastereomeric mixture (11%) was the hydroxy-epoxide **4k** (R = CH_2CHOCH_2).

with ethanol occurred slowly and no acetylation of the alcohol was observed. Trans-esterification of the larger valerolactone **2c** was so slow that the major product of this reaction was the valerolactone. It should be noted, that only starting cyclopentanones and no other products were observed when no enzyme was added. From these three examples, we can see clearly that lipase-mediated trans-esterification of valerolactones depends on the structural nature of the lactones, and that acetylation of alcohols is also dependent on the structural nature of the alcohol.

Other substituted cyclopentanones were investigated using these chemo-enzymatic conditions, Table 1. As expected, *n*-pentylcyclopentanone **1d** behaved similarly than *n*-hexylcyclopentanone **1c**. Oxidation of benzylcyclopentanone **1e** was almost complete after 8 days yielding a mixture of valerolactone **2e** and alcohol **3e**. Oxidation of allyl-cyclopentanone **1f** gave valerolactone **2f** in good yield after 7 days without oxidizing the terminal olefin. Interestingly, no acetylated ester **3f** was observed, but instead, epoxidation of the terminal alkene was observed after 9 days. Oxidation of the α, α-disubstituted cyclopentanones was more difficult furnishing modest yields of valerolactone **2g** after 7 days and no valerolactone **2h** was observed even after 20 days.

The chemo-enzymatic Baeyer–Villiger was also investigated in 1- and 2-indanones, Fig. 3. Oxidation of 1-indanone (**1i**) was extremely slow providing dihydrocoumarin (**2i**) in only 5% yield after 12 days. On the other hand, oxidation of 2-indanone (**1j**) gave 3-isochromanone (**2j**) in 50% yield after 7 days. No trans-esterification products were observed with these products.

In order to avoid further trans-esterification of the valerolactones in the chemo-enzymatic oxidation, we replaced the solvent for acetonitrile and added catalytic amounts of octanoic acid and Novozyme-435 [10b,13]. The oxidation of 2-methyl cyclopentanone (**1b**) was studied at different temperatures and conversion was measured by NMR after 24 h, Table 2. Under these conditions (inert solvent), octanoic acid reacts with the

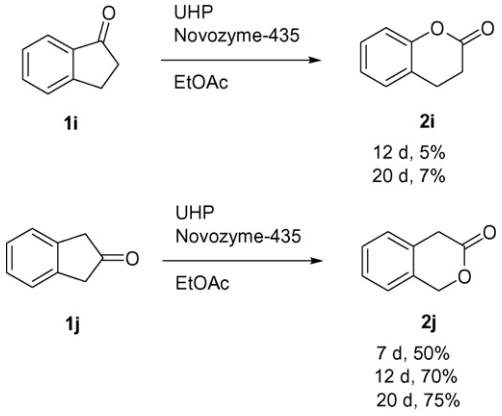
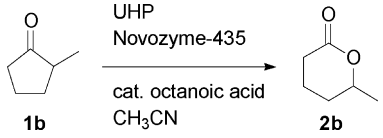


Fig. 3. Chemo-enzymatic oxidation of 1-indanone and 2-indanone.

Table 2
Baeyer–Villiger oxidation of 2-methyl cyclopentanone (**1b**) with calculated amounts of octanoic acid and Novozyme-435 in acetonitrile after 24 h



Entry	Temperature (°C)	Conversion (%)	
		1b	**2b**
1	24	75	25
2	40	48	52
3	60	17	73

lipase and UHP forming peroxyoctanoic acid and water. Now, the peroxyoctanoic acid oxidizes the cyclopentanone to the corresponding δ-valerolactone. As expected, no product other than valerolactone **2b** was detected. The absence of ethanol avoids the formation of the hydroxy ethyl ester product **3b**. A 25% conversion was achieved at room temperature and 73% conversion was reached when the reaction was run at a higher temperature.

Obviously, Baeyer–Villiger oxidation of substituted cyclopentanones with peracetic acid does not provide any enantioselectivity [1d]. However, lipase-mediated hydrolysis [14] or trans-esterification of the substituted valerolactones might be an enantioselective process depending on reaction conditions. For example, substituted caprolactones have been enantioselectively trans-esterified via lipase when the reaction is solventless [15]. Therefore, we measured optical activity of valerolactones **2b–f** and hydroxyl esters **3b–d** and also prepared diastereomeric esters from **3b** to **3d** with (*S*)-*O*-acetylmandeloyl chloride [16]. In all cases, we did not observe any enantioselectivity when ethyl acetate was used as solvent [17].

3. Conclusions

In summary, we observed that cyclopentanone and substituted cyclopentanones with small substituents are oxidized by peracetic acid generated *in situ* in the enzymatic reaction of ethyl acetate with UHP and Novozyme-435. In contrast to ε-caprolactones, δ-valerolactones react faster with Novozyme-435 and ethanol in ethyl acetate yielding the corresponding trans-esterification products. Primary alcohols and not hindered secondary alcohols can also be acetylated under these conditions. If the δ-valerolactone is the desired product, replacing the solvent for acetonitrile and adding a catalytic amount of octanoic acid will deliver the desired valerolactone. These chemo-enzymatic oxidation methods should be a green alternative to chemical processes.

4. Experimental section

4.1. Materials and equipment

Cyclopentanones **1a** and **1b**, and indanones **1i** and **1j** were purchased from Aldrich and used without purification. Substituted cyclopentanones **1c–h** were prepared according to published procedures [18]. Urea–hydrogen peroxide complex was purchased from Acros. Novozyme-435 was a gift from Novozymes. Solvents were Reagent grade and used without purification. GC analyses were performed using a Shimadzu GC-17A equipped with a FID. The column was a Chiraldex B-PH (20 m × 0.25 mm). ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ (δ, ppm) on a Bruker Avance 300 instrument. Optical rotations were determined in a Jasco P-1020 polarimeter.

4.2. General procedure for the chemo-enzymatic Baeyer–Villiger oxidation in ethyl acetate

To a solution of cyclopentanone (1 mmol) in ethyl acetate (3.0 mL) was added urea–hydrogen peroxide (188 mg, 2 mmol) and Novozyme-435 (25 mg). The reaction mixture was stirred at room temperature and monitored by ^{1}H NMR (a 0.1 mL sample from the reaction mixture was diluted with $CDCl_3$). Reaction mixture was filtered through a plug of celite and the solid washed with more solvent. The organic layer was washed with water to remove the urea, and the organic layer was dried over Na_2SO_4, filtered and solvent evaporated. Products were purified by flash column chromatography.

4.3. Procedure for the chemo-enzymatic Baeyer–Villiger oxidation in acetonitrile

To a solution of cyclopentanone (1 mmol) in acetonitrile (3.0 mL) was added urea–hydrogen peroxide (188 mg, 2 mmol) and Novozyme-435 (25 mg), and a catalytic amount of octanoic acid (1 small drop). The reaction mixture was stirred at room temperature and monitored by ^{1}H NMR. Reaction mixture was filtered through a plug of celite and the solid washed with more solvent. The organic layer was washed with saturated $NaHCO_3$ solution, and the organic layer was dried over Na_2SO_4, filtered and solvent evaporated. Products were purified by flash column chromatography.

4.3.1. δ-Valerolactone (**2a**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (2H, t, J = 5.8 Hz, H-5), 2.56 (2H, t, J = 7.0 Hz, H-2), 1.89 (4H, m, H-3, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.47 (C, C-1), 69.45 (CH_2, C-5), 29.79 (CH_2, C-2), 22.26 (CH_2, C-3), 19.04 (CH_2, C-4).

4.3.2. 6-Methyl-tetrahydropyran-2-one (**2b**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45 (1H, m, H-5), 2.65–2.35 (2H, m, H-2), 2.00–1.75 (3H, m), 1.63–1.44 (1H, m), 1.38 (3H, d, J = 6.5 Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.12 (C, C-1), 77.82 (CH, C-5), 29.84, and 29.48 (CH_2, C-2, C-4), 21.96 (CH_3, C-6), 18.80 (CH_2, C-3).

4.3.3. 6-Hexyl-tetrahydropyran-2-one (**2c**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (1H, m, H-5), 2.59 (1H, dt, J = 17.4, 7.3 Hz, H-2a), 2.44 (1H, dt, J = 17.4, 8.6 Hz, H-2b), 1.98–1.21 (14H, m, H-3, H-4, H-6, H-7, H-8, H-9, H-10), 0.88 (3H, t, J = 7.1 Hz, H-11); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.09 (C, C-1), 80.71 (CH, C-5), 35.95, 31.78, 29.58, 29.17, 27.90,

24.99, 22.65 and 18.61 (CH_2, C-2, C-3, C-4, C-6, C-7, C-8, C-9, C-10), 14.16 (CH_3, C-11).

*4.3.4. 6-Pentyl-tetrahydropyran-2-one (**2d**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (1H, m, H-5), 2.59 (1H, m, H-2a), 2.44 (1H, m, H-2b), 1.97–1.22 (12H, m, H-3, H-4, H-6, H-7, H-8, H-9), 0.89 (3H, t, J = 6.8 Hz, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.10 (C, C-1), 80.71 (CH, C-5), 35.90, 31.69, 29.57, 27.90, 24.71, 22.61 and 18.60 (CH_2, C-2, C-3, C-4, C-6, C-7, C-8, C-9), 14.16 (CH_3, C-10).

*4.3.5. 6-Benzyl-tetrahydropyran-2-one (**2e**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.14 (5H, m, Arom), 4.49 (1H, m, H-5), 3.08 (1H, dd, J = 13.8, 5.9 Hz, H-6a), 2.87 (1H, dd, J = 13.8, 6.9 Hz, H-6b), 2.56 (1H, dt, J = 18.2, 6.9 Hz, H-2a), 2.441 (1H, dt, J = 18.2, 8.6 Hz, H-2b), 1.95–1.68 and 1.60–1.42 (4H, m, H-3, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.67 (C, C-1), 136.56 (C, Arom), 129.67, 128.65 and 126.92 (CH, Arom), 81.11 (CH, C-5), 42.21 (CH_2, C-6), 29.54 (CH_2, C-4), 27.17 (CH_2, C-2), 18.49 (CH_2, C-3).

*4.3.6. 6-Allyl-tetrahydropyran-2-one (**2f**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (1H, ddt, J = 17.1, 10.2, 7.0 Hz, H-7), 5.17 (1H, m, H-8a), 5.12 (1H, m, H-8b), 4.35 (1H, dddd, J = 10.9, 7.0, 6.2, 3.0 Hz, H-5), 2.68–2.30 (4H, m, H-2, H-6), 2.00–1.74 (3H, m, H-4a, H-3), 1.67–1.44 (1H, m, H-4b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.78 (C, C-1), 132.78 (CH, C-7), 118.71 (CH_2, C-8), 79.95 (CH, C-5), 40.20 (CH_2, C-6), 29.63 (CH_2, C-4), 27.35 (CH_2, C-2), 18.60 (CH_2, C-3).

*4.3.7. 6,6-Dimethyl-tetrahydropyran-2-one (**2g**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (2H, t, J = 7.0 Hz, H-2), 1.83–1.95 (2H, m, H-3), 1.89–1.75 (2H, m, H-4), 1.41 (6H, s, H-6, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.36 (C, C-1), 82.27 (C, C-5), 33.91 (CH_2, C-4), 29.15 (CH_2, C-2), 28.75 (CH_3, C-6, C-7), 16.86 (CH_2, C-3).

*4.3.8. Dihydrocoumarin (**2i**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (4H, m, H-Arom), 5.32 (2H, s, H-5), 3.72 (2H, s, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.82 (C, C-1), 131.73 and 131.15 (C, C-Arom), 129.00, 127.55, 127.26 and 124.85 (CH-Arom), 70.26 (CH_2, C-5), 36.39 (CH_2, C-2).

*4.3.9. 3-Isochromanone (**2j**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.00 (4H, m, H-Arom), 3.00 (2H, dd, J = 8.0, 6.8 Hz, H-3), 2.78 (2H, dd, J = 8.0, 5.6 Hz, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.64 (C, C-1), 152.07 (C, C-5), 122.74 (C, C-4), 128.33, 128.12, 124.47 and 116.97 (CH-Arom), 29.30 (CH_2, C-3), 23.78 (CH_2, C-2).

*4.3.10. Ethyl-5-hydroxypentanoate (**3a**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (2H, q, J = 7.2 Hz, COO**CH_2**), 3.64 (2H, t, J = 6.4 Hz, H-5), 2.34 (2H, t, J = 7.0 Hz, H-2), 2.20 (1H, bs, OH), 1.72 (2H, m, H-3), 1.61 (2H, m, H-4), 1.26 (3H, t, J = 7.2 Hz, $COOCH_2$**CH_3**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.96 (C, C-1), 62.23 (CH_2, C-5), 60.46 (CH_2, COO**CH_2**), 34.04 (CH_2, C-2), 32.14 (CH_2, C-4), 21.22 (CH_2, C-3), 14.32 (CH_3, $COOCH_2$**CH_3**).

*4.3.11. Ethyl-5-hydroxyhexanoate (**3b**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (2H, q, J = 7.2 Hz, COO**CH_2**), 3.80 (2H, m, H-5), 2.33 (2H, t, J = 7.3 Hz, H-2), 1.73 (3H, m, OH, H-3), 1.47 (2H, m, H-4), 1.26 (3H, t, J = 6.9 Hz, $COOCH_2$**CH_3**), 1.20 (3H, d, J = 5.9 Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.91 (C, C-1), 67.64 (CH, C-5), 60.47 (CH_2, COO**CH_2**), 38.72 (CH_2, C-4), 34.26 (CH_2, C-2), 23.63 (CH_3, C-6), 21.20 (CH_2, C-3), 14.38 (CH_3, $COOCH_2$**CH_3**).

*4.3.12. Ethyl-5-hydroxyundecanoate (**3c**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (2H, q, J = 6.9 Hz, COO**CH_2**), 3.60 (1H, m, H-5), 2.33 (2H, t, J = 6.9 Hz, H-2), 1.85–1.27 (14H, m, H-3, H-4, H-6, H-7, H-8, H-9, H-10), 1.26 (3H, t, J = 7.2 Hz, $COOCH_2$**CH_3**), 0.88 (3H, t, J = 6.9 Hz, H-11); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.96 (C, C-1), 71.57 (CH, C-5), 60.47 (CH_2, COO**CH_2**), 37.66, 36.93, 34.36, 32.01, 29.51, 25.77, 22.79 and 21.17 (CH_2, C-2, C-3, C-4, C-6, C-7, C-8, C-9, C-10), 14.42 and 14.25 (CH_3, C-11, $COOCH_2$**CH_3**).

*4.3.13. Ethyl-5-hydroxydecanoate (**3d**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (2H, q, J = 7.1 Hz, COO**CH_2**), 3.60 (1H, m, H-5), 2.33 (2H, t, J = 7.2 Hz, H-2), 1.90–1.22 (13H, m, H-3, H-4, H-6, H-7, H-8, H-9), 1.23 (3H, t, J = 7.1 Hz, $COOCH_2$**CH_3**), 0.89 (3H, t, J = 6.7 Hz, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.94 (C, C-1), 71.39 (CH, C-5), 60.38 (CH_2, COO**CH_2**), 37.53, 36.81, 34.27, 31.98, 25.41, 22.72 and 21.10 (CH_2, C-2, C-3, C-4, C-6, C-7, C-8, C-9), 14.32 and 14.12 (CH_3, C-10, $COOCH_2$**CH_3**).

*4.3.14. Ethyl-5-hydroxy-6-phenylhexanoate (**3e**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.16 (5H, m, Arom), 4.12 (2H, q, J = 6.9 Hz, COO**CH_2**), 3.81 (1H, m, H-5), 2.81 (1H, dd, J = 13.3, 4.4 Hz, H-6a), 2.66 (1H, dd, J = 13.3, 8.4 Hz, H-6b), 2.33 (2H, t, J = 6.9 Hz, H-2), 1.92–1.44 (4H, m, H-3, H-4), 1.24 (3H, t, J = 7.2 Hz, $COOCH_2$**CH_3**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.86 (C, C-1), 138.56 (C, Arom), 129.55, 128.70 and 126.62 (CH, Arom), 72.30 (CH, C-5), 60.45 (CH_2, COO**CH_2**), 44.20 (CH_2, C-6), 36.19 (CH_2, C-4), 34.25 (CH_2, C-2), 21.27 (CH_2, C-3), 14.38 (CH_3, $COOCH_2$**CH_3**).

*4.3.15. Ethyl-5-hydroxyoct-7-enoate (**3f**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (1H, m, H-7), 5.16 (1H, m, H-8a), 5.11 (1H, m, H-8b), 4.13 (2H, q, J = 7.2 Hz, COO**CH_2**), 3.66 (1H, m, H-5), 2.34 (2H, t, J = 7.2 Hz, H-2), 2.30 (1H, m, H-6a), 2.16 (1H, m, H-6b), 1.77 (3H, m, H-4a, H-3), 1.50 (1H, m, H-4b); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.86 (C, C-1), 134.82 (CH, C-7), 118.38 (CH_2, C-8), 70.32 (CH, C-5), 60.47 (CH_2, COO**CH_2**), 40.10 (CH_2, C-6), 36.25 (CH_2, C-4), 34.28 (CH_2, C-2), 21.21 (CH_2, C-3), 14.41 (CH_3, $COOCH_2$**CH_3**).

*4.3.16. Ethyl-5-acetoxypentanoate (**4a**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (2H, c, J = 7.2 Hz, COO**CH_2**), 4.08 (2H, t, J = 6.2 Hz, H-5), 2.34 (2H, t, J = 7.2 Hz, H-2), 2.05 (3H, s, CO**CH_3**), 1.69 (4H, m, H-3, H-4), 1.26 (3H,

t, $J = 7.2$ Hz, $COOCH_2\mathbf{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.44 (C, C-1), 171.27 (C, $\mathbf{CO}CH_3$), 64.14 (CH_2, C-5), 60.49 (CH_2, $COO\mathbf{CH_2}$), 33.97 (CH_2, C-2), 28.19 (CH_2, C-4), 21.63 (CH_2, C-3), 21.12 (CH_3, $CO\mathbf{CH_3}$), 14.40 (CH_3, $COOCH_2\mathbf{CH_3}$).

*4.3.17. Ethyl-5-acetoxyhexanoate (**4b**)*

^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (1H, m, H-5), 4.13 (2H, q, $J = 7.2$ Hz, $COO\mathbf{CH_2}$), 2.31 (2H, t, $J = 7.2$ Hz, H-2), 2.03 (3H, s, $CO\mathbf{CH_3}$), 1.75–1.43 (4H, m, H-3, H-4), 1.26 (3H, t, $J = 7.2$ Hz, $COOCH_2\mathbf{CH_3}$), 1.22 (3H, d, $J = 6.3$ Hz, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.75 (C, C-1), 171.10 (C, $\mathbf{CO}CH_3$), 70.66 (CH, C-5), 60.51 (CH_2, $COO\mathbf{CH_2}$), 35.41 (CH_2, C-4), 34.17 (CH_2, C-2), 21.54 (CH_3, C-6), 21.01 (CH_3, $CO\mathbf{CH_3}$), 20.08 (CH_2, C-3), 14.42 (CH_3, $COOCH_2\mathbf{CH_3}$).

Acknowledgements

This research was supported with funds provided by the Center for Environmentally Beneficial Catalysis under the National Science Foundation Engineering Research Grant (EEC-0310689). MYR is a Comexus Fulbright-Garcia Robles fellow and is thankful to Universidad Autónoma del Estado de Morelos for a sabbatical fellowship. We are also grateful to Novozymes for a gift of Novozyme-435.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcatb.2007.12.012.

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