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Candida antarctica B lipase-catalysed alcoholysis of peracetylated alkyl D-ribofuranosides

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Abstract

Candida antarctica B lipase (CAL-B) catalysed alcoholysis of a series of peracetylated alkyl *α*, *β*-D-ribofuranosides was assayed. Methyl and ethyl 2,3-di-*O*-acetyl-*α*, *β*-D-ribofuranosides enriched in the *α*-anomer were regioselectively prepared through this enzymatic deacetylation in 33% and 43% yield, respectively, the latter being a new compound. Isopropyl 2,3,5-tri-*O*-acetyl-*β*-D-ribofuranoside gave the new isopropyl 2,3-di-*O*-acetyl-*β*-D-ribofuranoside in 24% yield. The anomeric substituent affects the regioselectivity of the reaction, since n-propyl and n-butyl *α*, *β*-D-ribofuranosides reacted without selectivity.

Keywords: *Enzymatic alcoholysis,* Candida antarctica *B lipase, regioselectivity, ribofuranosides*

Introduction

Hydrolytic enzymes, such as lipases, catalyse regioselective transformations of polyhydroxylated molecules such as carbohydrates (Bornscheuer & Kazlauskas 2004) and nucleosides (Ferrero & Gotor 2000), give access to partially acylated derivatives. Regioselective acylated carbohydrates find applications as biodegradable surfactants (Queneau et al. 2008) and as synthetic precursors of oligosaccharides, glycopeptides and nucleosides (Pathak 2002); their efficient synthesis requires discrimination of similar reactive hydroxyl groups and the regioselectivity provided by hydrolases (Bornscheuer & Kazlauskas 2004) can avoid the use of protective groups. However, in the field of hydrolase-catalysed transformation of carbohydrates, hexapyranosic substrates (Bornscheuer & Kazlauskas, 2004; Gonçalves et al. 2004; Filice et al. 2007) have been studied more extensively than pentofuranoses (Fernández-Lorente et al. 2003; Bornscheuer & Kazlauskas 2004; Chien & Chern 2004; D'Antona et al. 2005; Jun et al. 2005; Prasad et al. 2007).

In our laboratory we have prepared partially acylated nucleosides carrying free 5'-hydroxyl groups using regioselective *Candida antarctica* B lipase (CAL-B) catalysed alcoholysis of peracetylated precursors (Zinni et al. 2004; 2007; Sabaini et al. 2010) and extended the scope of this biotransformation to pentofuranoses. At first (Iñigo et al. 2005), we studied the CAL-B catalysed alcoholysis of isolated methyl 2,3,5-tri-*O*-acetyl-*α*-D-ribofuranoside (1a, Scheme 1) and methyl 2,3,5-tri-*O*-acetyl-*β*-D-ribofuranoside (1b); each anomer was recognized differently by the enzyme, the former regioselectively affording methyl 2,3-di-*O*-acetyl-*α*-D-ribofuranoside (6a, Scheme 2) and the latter, methyl *β*-D-ribofuranoside. We then studied CAL-B catalysed alcoholysis of a set of pentofuranoses and recently reported the regio- and diasteroselective preparation of methyl 3-*O*-acetyl-2-deoxy-*α*-D-ribofuranoside, 1,3-di-*O*-acetyl-2-deoxy-*α*-D-ribofuranose and 1,2,3-tri-*O*-acetyl-*α*-D-arabinofuranose in de = 100% from the anomeric mixtures of the corresponding 5-*O*-acetylated compounds (Gudiño et al. 2009).

Taking into account these antecedents, and to have more information about the regio- and stereoselective performance of *O*-acetylated pentofuranosides in CAL-B catalysed alcoholysis, we considered

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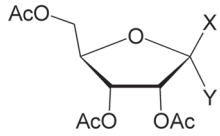


1a X = H, Y = OMe
1b X = OMe, Y = H
2a X = H; Y = OEt
2b X = OEt, Y = H
3 X = OiPr, Y = H
4a X = H, Y = OnPr
4b X = OnPr , Y = H
5a X = H, Y = OnBu
5b X = OnBu , Y = H

Scheme 1. Structure of substrates 1–5 assayed in CAL-B-catalysed alcoholysis.

it of interest to assay a set of peracetylated alkyl D-ribofuranosides (2–5, Scheme 1), studying the influence of the anomeric substituent on the selectivity of the biotransformation and we report herein the obtained results.

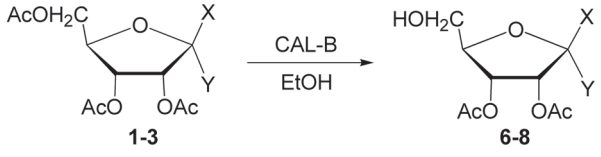
Materials and methods

General methods

NMR spectra were recorded on a Bruker AC-500 spectrometer in $CDCl_3$, at 500 MHz for ^1H and 125 MHz for ^{13}C using TMS and $CDCl_3$ as internal standards, respectively. Electrospray-ionization (ESI) mass spectra were recorded on a Bruker microTOF-Q II spectrometer, dissolving compounds in a methanolic solution of ammonium acetate. Optical rotations were measured on a Perkin Elmer Polarimeter 343 at 589 nm.

All reagents and solvents were of analytical grade and were obtained from commercial sources. The alcohols and pyridine were dried and distilled prior to use. Absolute ethanol was used for the enzymatic alcoholysis.

TLC was performed on silica gel 60 F_{254} plates (Merck, Darmstadt, Germany) and the resulting plates were developed using ethanol–sulphuric acid 80:20 v/v with heating. Silica gel Merck 60 was used for flash column chromatography.



1a, 6a X = H, Y = OMe
1b, 6b X = OMe, Y = H
2a, 7a X = H; Y = OEt
2b, 7b X = OEt, Y = H
3, 8 X = OiPr, Y = H

Scheme 2. CAL-B-catalysed regioselective alcoholysis of substrates 1–3.

Lipase B from *C. antarctica* (CAL-B, Novozym 435, 10000 PLU mg^{-1} solid; PLU: Propyl Laurate Units) was a generous gift from Novozymes (Brazil) and *C. rugosa* lipase (CRL, 875 units activity mg^{-1} solid) was purchased from Sigma Chemical Co (St Louis, MO, USA). Both enzymes were used without any further treatment or purification.

Enzymatic reactions were carried out in a temperature-controlled incubator shaker (Sontec OS 11, Argentina) at 200 rpm and 30°C or 45°C.

Preparation of substrates 1–5

Substrates 1–5 were prepared through standard protocols (Gudiño et al. 2009). Purification of the crude products by column chromatography employing dichloromethane–methanol 98:2 v/v as the eluent afforded the desired substrates as a mixture of *α* and *β* anomers, except for 3, which was obtained as the *β*-anomer. Yields are given in brackets: methyl 2,3,5-tri-*O*-acetyl-*α*,*β*-D-ribofuranoside (1a,b, 60%), ethyl 2,3,5-tri-*O*-acetyl-*α*, *β*-D-ribofuranoside (2a,b, 43%), isopropyl 2,3,5-tri-*O*-acetyl-*β*-D-ribofuranoside (3, 38%), n-propyl 2,3,5-tri-*O*-acetyl-*α*, *β*-D-ribofuranoside (4a,b, 50%) and n-butyl 2,3,5-tri-*O*-acetyl-*α*, *β*-D-ribofuranoside (5a,b, 43%). Satisfactory NMR data were obtained for these compounds.

CAL-B catalysed alcoholysis of substrates 1–5

Analytical procedure. In a typical analytical protocol, the substrate (10 mg) was dissolved in the alcohol at an alcohol/substrate molar ratio (A/S) = 1200 or 120 and CAL-B (300 mg $mmol^{-1}$ substrate) was added.

The resulting reaction mixture was shaken at 200 rpm and 30°C or 45°C. Samples were taken at different times and, after removal of the enzyme, monitored by TLC using dichloromethane–methanol 95:5 v/v as eluent.

Control experiments carried out in the absence of the enzyme showed no appreciable reaction.

Preparative procedure. According to the above protocol, for preparative purposes, the substrate (0.31 mmol) was dissolved in the alcohol, as indicated in Table I, at the alcohol/substrate molar ratio (A/S) cited and CAL-B (93 mg) was added. The reaction mixture was shaken at 200 rpm at the temperatures and times reported in Table I. Then the lipase was filtered off, washed with dichloromethane and the resulting filtrates evaporated; the crude product was purified by silica gel column chromatography using dichloromethane–methanol 98:2.

Table I. CAL-B-catalysed alcoholysis of D-ribofuranosides 1–5 (Scheme 2).

Entry	Substrate	Substrate α/β ratio[a]	T (°C)	t (h)	Alcohol	A/S[b]	Product (yield, %)[c]	Product α/β ratio[a]	α-Anomer recovery (%)[d]
1	1[a,b]	1.0/3.0	45	4	Ethanol	120	6[a,b] (33)	2.0/1.0	89
2	2[a,b]	1.0/3.2	30	6	Ethanol	120	7[a,b] (43)	1.3/1.0	79
3	3	0/1.0	30	48	Ethanol	1200	8 (24)	0/1.0	—
4	4[a,b]	1.0/3.7	45	24	Ethanol	1200	51[e]	nd[f]	nd[f]
5	5[a,b]	1.0/4.9	30	48	1-Butanol	1200	27[e]	nd[f]	nd[f]

[a]Anomeric ratio, determined by ^{1}H NMR. [b]Alcohol/substrate molar ratio. [c]Yield determined after isolation by silica gel column chromatography. [d]Yield calculated on the basis of α-anomer content in isolated product and in the substrate. [e]A mixture of regioisomers was formed. [f]nd: not determined.

Methyl 2,3-di-O-acetyl-α, β-D-ribofuranoside (6a,b). Application of this procedure gave 6a,b (anomeric ratio: 2.0/1.0) in 33% yield, affording satisfactory NMR data consistent with those previously reported for 6 (Hennen et al. 1988).

Ethyl 2,3-di-O-acetyl-α, β-D-ribofuranoside (7a,b). Following the general procedure described above, 7a,b (anomeric ratio: 1.3/1.0) was isolated in 43% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.23 (2t, 6H, J = 7.1 Hz, $CH_2C\underline{H}_3$s, α, β anomers), 2.06 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 3.53–3.67 (m, 3H, H-5, H-5′, α-anomer; H-5, β-anomer), 3.76–3.82 (m, 4H, OCH_2s, α, β anomers), 3.85 (dd, 1H, J = 12.0, 3.1 Hz, H-5′, β-anomer), 4.14–4.16 (m, 1H, H-4, α-anomer), 4.21–4.24 (m, 1H, H-4, β-anomer), 4.95 (dd, 1H, J = 7.2, 4.3 Hz, H-2, α-anomer), 5.02 (s, 1H, H-1, β-anomer), 5.18 (dd, 1H, J = 7.2, 4.1 Hz, H-3, α-anomer), 5.23 (d, 1H, J = 5.0 Hz, H-2, β-anomer), 5.27 (d, 1H, J = 4.3 Hz, H-1, α-anomer), 5.39 (dd, 1H, J = 6.6, 5.0 Hz, H-3, β-anomer). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 15.06, 15.11 ($CH_2\underline{C}H_3$s), 20.40, 20.60, 20.62, 20.88 ($CO\underline{C}H_3$s), 62.21, 62.87 (C-5s), 63.04, 64.32 ($\underline{C}H_2$s), 69.99, 71.13, 71.28 (C-2, C-3s), 75.54 (C-2), 81.78, 82.38 (C-4s), 100.27, 105.22 (C-1s), 169.70, 170.04, 170.08, 170.80 (COs); MS (ESI, *m/z*): 285 (100%, M+Na); HRMS: calcd for $C_{11}H_{18}O_7 \cdot Na$ (M+Na): 285.0945; found: 285.0940.

Isopropyl 2,3-di-O-acetyl-β-D-ribofuranoside (8). Analogously, according to the general protocol reported above, 8b was obtained in 24% yield. $[\alpha]_D^{20} = -22.5$ (*c* 0.014, CH_3CH_2OH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.18 (d, J = 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.22 (d, J = 6.1 Hz; $CH(C\underline{H}_3)_2$), 2.06 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.65 (dd, 1H, J = 12.1, 2.6 Hz, H-5), 3.81 (dd, 1H, J = 12.1, 3.0 Hz, H-5′), 3.93 (m, 1H, J = 6.1 Hz, OCH), 4.20–4.23 (m, 1H, H-4), 5.11 (s, 1H, H-1), 5.18 (d, 1H, J = 5.0 Hz, H-2), 5.41 (dd, 1H, J = 6.4, 5.0 Hz, H-3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 20.12, 20.16 ($\underline{C}OCH_3$s), 21.27, 22.76 ($CH(\underline{C}H_3)_2$s), 62.23 (C-5), 70.75, 70.78 (C-3, OCH), 75.55 (C-2), 81.75 (C-4), 103.84 (C-1), 169.9, 170.2 (COs); MS (ESI, *m/z*): 299 (100%, M+Na); HRMS: calcd for $C_{12}H_{20}O_7 \cdot Na$ (M+Na): 299.1101; found: 299.1099.

Results and discussion

Except for isopropyl 2,3,5-tri-*O*-acetyl-*β*-D-ribofuranoside (3), all other 2,3,5-tri-*O*-acetyl-D-ribofuranosides with methyl (1), ethyl (2), n-propyl (4) and n-butyl (5) aglycone were obtained and tested in CAL-B catalysed alcoholysis as anomeric mixtures (Table I); the enzymatic alcoholysis of 1 as a mixture of anomers was also carried out for comparison, since we had previously (Iñigo et al. 2005) assayed this reaction starting from isolated 1a and 1b.

Experiments were performed using alcohol/substrate ratios (A/S) = 1200 and 120; a high excess of nucleophile was employed because it allowed selective deacetylations in CAL-B catalysed alcoholysis of 1a and 1b (Iñigo et al. 2005), methyl 3,5-di-*O*-acetyl-2-deoxy-*α*, *β*-D-ribofuranoside and 1,2,3,5-tetra-*O*-acetyl-*α,β*-D-arabinofuranose (Gudiño et al. 2009). Table I (entries 1–3) reports the A/S ratio and times allowing maximal production of monodeacetylated products 6– from the corresponding substrates 1–3, using ethanol as nucleophile. After chromatographic isolation, ^{1}H NMR analysis of compounds 6–8 showed H-5 signals at ca. 3.65–3.85 ppm, this involving a shift towards higher fields of ca. 0.5–0.6 ppm in comparison with the corresponding signals of substrates 1–3, consistent with the removal of the 5-*O*-acetate. The product structures were confirmed by ^{13}C NMR; although C-5 chemical shifts of 6–8 did not show a significant difference in comparison with those of the substrates, a more appreciable shift was observed in most cases for C-4, which shifted, as expected, towards lower fields (ca. 2.5–3.5 ppm) in the monodeacetylated products. To the best of our knowledge, compounds 7 and 8 have not been previously reported in the literature.

Products 6–8 consisted only of the 5-*O*-deacetylated isomer, without the formation of other regioisomers; these results are in agreement with the regioselectivity displayed by CAL-B in the alcoholysis of pentofuranosides previously observed by us (Iñigo et al. 2005; Gudiño et al. 2009). However, when ribosides 4 and 5 were assayed in the enzymatic alcoholysis (entries 4 and 5, Table I), a loss of regioselectivity was observed in both cases, affording a mixture of monodeacetylated regioisomers.

Apart from the regioselectivity, some observations can be made concerning the stereoselectivity of the biotransformation. The reported anomeric ratios (α/β ratios, Table I) for compounds 1 and 2 and their corresponding 5-hydroxyl free products 6 and 7, calculated on the basis of ^{1}H NMR integrations, show that while the β-isomer was the major component of both 2,3,5-tri-*O*-acetates 1 and 2, a reversal anomeric ratio was found for 2,3-di-*O*-acetates 6 and 7, respectively. This indicates a moderate preference of CAL-B towards the α-anomers 1a and 2a. In comparison, CAL-B catalysed alcoholysis of 1,2,3,5-tetra-*O*-acetyl-α, β-D-arabinofuranoside, methyl 3,5-di-*O*-acetyl-2-deoxy-α, β-D-ribofuranoside and 1,3,5-tri-*O*-acetyl-2-deoxy-α, β-D-ribofuranoside led to the respective 5-*O*-deacetylated product with α-configuration exclusively (Gudiño et al. 2009). These results confirm, as previously proposed (Gudiño et al. 2009), that the substitution at carbon 2 can affect the stereoselectivity of the biotransformation. This is also supported by the fact that alkyl 2,3,5-tri-*O*-acetyl-α, β-D-ribofuranosides 1a,b and 2a,b, 1,2,3,5-tetra-*O*-acetyl-α, β-D-ribofuranose (Gudiño et al. 2009) and methyl 2,3,5-tri-*O*-acetyl-α, β-D-arabinofuranoside (Gudiño et al. 2009) are transformed with lower stereoselectivity than 1,2,3,5-tetra-*O*-acetyl-α, β-D-arabinofuranoside, methyl 3,5-di-*O*-acetyl-2-deoxy-α, β-D-ribofuranoside and 1,3,5-tri-*O*-acetyl-2-deoxy-α, β-D-ribofuranose; all of these substrates differ in the substituent at carbon 2 whilst they have the same configuration at carbon 3. With regard to regioselectivity, the anomeric substituent would seem to have a more marked effect than the pentose substitution at carbons 2 and 3, since in the series of alkyl 2,3,5-tri-*O*-acetyl-α, β-D-ribofuranosides, n-propyl and n-butyl glycosides 4 and 5 reacted with no selectivity.

With the exception of 3, the yield of products (Table I) was calculated taking into account the mass of each substrate as anomeric mixtures. Additionally, a yield based on the mass of the α-anomer content in the substrate and in the product was also determined (% α-anomer recovery, Table I). This value shows that CAL-B catalysed alcoholysis allows the recovery of the α-anomer from anomeric mixtures of 1 and 2 in good yields. Thus, CAL-B catalysed alcoholysis provides a simple method to resolve pentofuranoside anomeric mixtures, which are usually difficult to separate through traditional chromatographic procedures.

Although differences in the behaviour of each anomer have been found in CAL-B catalysed transformation of pyranoses (Kadereit & Waldmann 2001; Gonçalves et al. 2004), few studies have dealt with CAL-B recognition of furanose anomers. Apart from the regioselective alcoholysis of the hexose 1, 2, 3, 4, 6-penta-*O*-acetyl-α,β-D-fructofuranose (D'Antona et al. 2005), in which different regioselectivity in the monodeacetylation of each anomer was observed, and our previous work (Iñigo et al. 2005; Gudiño et al. 2009), no other studies on the differential recognition of furanoses by CAL-B has been reported, as far as we know.

Conclusion

CAL-B catalysed alcoholysis of a series of peracetylated alkyl D-ribofuranoside derivatives has been used to study the determinants of substrate recognition by this lipase. The influence of the aglycone on the regioselectivity of the reaction was shown since n-propyl (4) and n-butyl (5) 2,3,5-tri-*O*-acetyl-α, β-D-ribofuranosides reacted without selectivity, while 5-*O*-acetyl groups of methyl (1) and ethyl (2) 2,3,5-tri-*O*-acetyl-α, β-D-ribofuranosides were removed regioselectively producing the respective 2,3-di-*O*-acetyl-D-ribofuranosides (6 and 7) enriched in the α-anomer, in 33% and 43% yield. In addition to the newly described product ethyl 2,3-di-*O*-acetyl-β-D-ribofuranoside (7), deacetylation of isopropyl 2,3,5-tri-*O*-acetyl-β-D-ribofuranoside (3) gave the new isopropyl 2,3-di-*O*-acetyl-β-D-ribofuranoside (8) in 24% yield.

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