Regioselectivity of Lipase-Catalysed Deacetylation of Methyl 2,3,5-tri-*O*-Acetyl-α,β-D-Furanosides in Ionic Liquid

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Abstract: Ionic liquids (ILs) were assayed as reaction medium for the enzymatic deacetylation of three methyl 2,3,5-tri-O-acetyl-α,β-D-furanosides and the obtained results show the influence of the IL and the furanose structure on the regioselectivity of hydrolyses catalysed by the tested lipases. In a reaction medium consisting of a 1:1 mixture of 30 mM phosphate buffer (pH 7) and 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]), *Candida rugosa* lipase catalysed the formation of methyl 2,3-di-*O*-acetyl-α,β-D-arabinofuranoside in 77 %, while in a 9:1 mixture of the same buffer and 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF_4]), methyl 2,3-di-*O*-acetyl-α,β-D-ribofuranoside was obtained in 62 %.

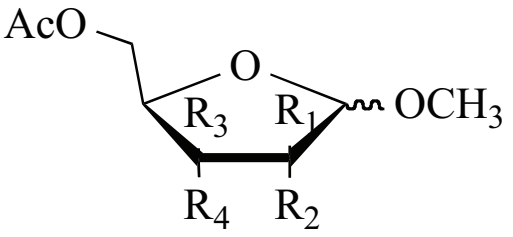
Keywords: Furanoses, furanosides, ionic liquids, lipases, *Candida antarctica* lipase B, *Candida rugosa* lipase, regioselectivity.

1. INTRODUCTION

Regioselectively acylated carbohydrates are synthetic precursors of natural products analogues such as glycopeptides and nucleosides. By overcoming limitations of chemical protection-deprotection procedures, biocatalysis is accepted nowadays to provide a convenient access to regioselectively acylated carbohydrates derivatives. However, most of the obtained products are hexopyranoses, acylated pentofuranoses having received less attention [1-9].

Over the last years we have been focusing our interest on the preparation of regioselectively acetylated furanoses carrying 5-hydroxyl groups. In many cases, *Candida antarctica* lipase B (CAL-B) catalysed alcoholysis of the corresponding 5-acetylated compounds at high alcohol/substrate ratio (A/S) afforded a simple and regioselective procedure to obtain the target products. Regarding to ribofuranoses, the anomeric substituent [10] and the stereochemistry of the anomeric carbon [10, 11] have shown to play a role in the selectivity of the reaction; application of CAL-B catalysed alcoholysis allowed us to prepare a set of alkyl 2,3-di-*O*-acetyl-α,β–D-ribofuranosides. The extension of this enzymatic alcoholysis to furanoses other than ribo conducted regioselectively to methyl 3-*O*-acetyl-2-deoxy–α–D-ribofuranoside, 1,3-di-*O*-acetyl-2-deoxy-α-D-ribofuranose, 1,2,3-tri-*O*-acetyl-α-D-arabinofuranose [12] and methyl 2,3-di-*O*-acetyl-α,β-D-xylofuranoside (Gudiño EG, Iribarren AM, Iglesias LE, submitted for publication). Except from the latter, products were obtained in 100% diasteroselectivity from the corresponding anomeric mixtures [12].

Prompted by the fact that CAL-B catalysed alcoholysis of methyl 2,3,5-tri-*O*-acetyl–α,β–D-arabinofuranoside



1 R_1=R_4=OAc, R_2=R_3=H
3 R_2=R_4=OAc, R_1=R_3=H
5 R_2=R_3=OAc, R_1=R_4=H

(**1**, Fig. **1**) afforded in low yield methyl 2,3-di-*O*-acetyl–α,β–D-arabinofuranoside (**2**), an useful synthetic precursor for natural products analogues such as modified arabinonucleosides, we decided to test ionic liquids (ILs), which over the last decade have shown to be alternative media for biotransformations [13]. In the field of carbohydrates, the application of ILs as reaction medium has shown a positive effect on the regioselectivity of lipase-catalysed biotransformations. For instance, in ILs CAL-B catalysed the 6-*O*-acylation of glucose with higher regioselectivity than by using solvents such as THF or acetone [14,15]; a fast complete regioselectivity could be attained in *Pseudomonas cepacia* lipase catalysed hydrolysis of a glucal acetate in a IL [16].

According to the above discussion, in this paper we report the obtained results by assaying ILs for the enzymatic deacetylation of methyl 2,3,5-tri-*O*-acetyl–α,β–D-arabinofuranoside (**1**), methyl 2,3,5-tri-*O*-acetyl–α,β–D-ribofuranoside (**3**) and methyl 2,3,5-tri-*O*-acetyl–α,β–D-xylofuranoside (**5**) (Fig. **1**). The assayed lipases were CAL-B, a versatile enzyme applied in a wide variety of enantio-

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and regioselective transformations [17], and lipase from *Candida rugosa* (CRL), one of the most employed lipases in biotransformations [18], which is particular useful for peracylated monosaccharides primary ester deacylation [2].

2. MATERIALS AND METHODS

General

Lipase from *Candida rugosa* (CRL, Sigma Type VII, 875 U/mg solid) was purchased from Sigma-Aldrich Co. and lipase B from *Candida antarctica* (CAL B, Novozym 435, 10000 PLU/mg solid; PLU: Propyl Laurate Units) was a generous gift from Novozymes (Brazil). The enzymes were used straight 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 30º C. Control experiments carried out in the absence of the enzyme showed no appreciable conversion of the substrates.

All employed reagents and solvents were of analytical grade and obtained from commercial sources.

The assayed ionic liquids, purchased from Sigma-Aldrich, were: 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF_4]), 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]) and 1-butyl-3-methylimidazolium methanesulfonate ([BMIM][MeSO]).

TLC was performed on Silicagel 60 F_{254} plates (Merck) using dichloromethane/methanol (95:5 v/v) as the mobile phase; detection of the spots was done by spraying the plates with ethanolic sulphuric acid (20% v/v) and subsequent heating. Flash column chromatography was carried out using silicagel Merck 60 and exchange ion chromatography was performed employing a Dowex 50WX2-200 Na resin, 100-200 mesh (Sigma-Aldrich)

HPLC analyses were carried out using a C18 column with detection at 215 nm. Selection of this wavelenght was done on the basis of the UV spectra of methyl 2,3,5-tri-*O*-acetyl−α,β−D-arabinofuranoside (**1**), methyl 2,3-di-*O*-acetyl−α,β−D-arabinofuranoside (**2**) and that of a mixture of methyl α,β−D-arabinofuranoside monoacetylated derivatives, isolated from an enzymatic deacetylation. A 20 min gradient of water/acetonitrile from 95:5 (v/v) to 80:20 (v/v) at a flow rate of 1 ml/min was employed, and reported conversions in Table **1** were calculated based on the corresponding calibration curve.

NMR spectra were recorded on a Bruker AC-500 spectrometer in $CDCl_3$, at 500 MHz for ^{1}H and 125 MHz for ^{13}C using TMS and $CDCl_3$ as internal standards, respectively.

Preparation of Substrates 1, 3 and 5

According to standard protocols [11], substrates **1**, **3** and **5** were prepared by treatment of the corresponding D-furanose in an excess of methanol containing sulphuric acid and copper sulphate, to afford the corresponding methyl α,β−D-furanoside, which by subsequent reaction with acetic anhydride and dimethylaminopyridine in pyridine gave the triacetylated compounds. Purification of the crude products by column chromatography afforded methyl 2,3,5-tri-*O*-acetyl-α, β-D-arabinofuranoside (**1**, 77 %), methyl 2,3,5-tri-*O*-acetyl−α,β−D-ribofuranoside (**3,** 60%) and methyl 2,3,5-tri-*O*-acetyl−α,β−D-xylofuranoside (**5,** 58%), which gave satisfactory NMR data.

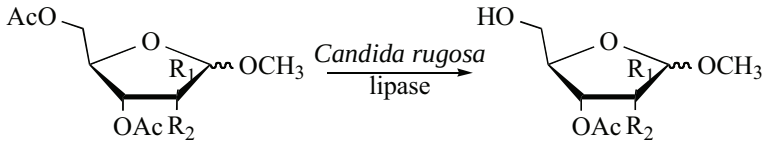
Enzymatic Hydrolysis of 1, 3 and 5

Lipase-catalysed hydrolyses were carried out by adding the assayed hydrolase (CRL or CAL-B, 9 mg) to a mixture of the substrate (10 mg) in sodium phosphate buffer (30 mM, pH 7) and the assayed IL. When [BMIM][BF_4] and [BMIM][MeSO] were tested, 10 % (v/v) (0.05 ml) of the reaction total volume and 20 % (v/v) (0.1 ml) were added to the mixture. By employing [BMIM][PF_6], different percentages (25, 50 and 75 %, v/v) were assayed and the reaction total volume kept constant at 0.5 ml.

The reaction mixtures were shaken at 200 rpm at 30 ºC, samples taken at different times and the enzyme removed. The resulting aliquots were monitored by TLC; for mixtures containing [BMIM][PF_6] both phases were analysed, verifing that the aqueous one did not contain the target product. Prior to TLC, [BMIM][PF_6] phases were extracted with ethanol; for HPLC analysis, the remaining IL in the ethanolic extract was completely removed by means of cation exchange chromatography.

Preparation of Methyl 2,3-di-O-acetyl−α,β−D-Arabinofuranoside (2)

In view of the obtained results, the preparative synthesis of **2** involved the addition of CRL (90 mg) to a 1:1 mixture of sodium phosphate buffer (30 mM, pH 7; 2.5 ml) and [BMIM][PF_6] (2.5 ml) containing **1** (100 mg). The system was shaken for 24 h at 30 ºC and 200 rpm, the lipase filtered off and washed with methanol and dichloromethane. Filtrates were concentrated *in vacuo*, giving a crude which was dissolved in methanol, passed through a cation-exchange chromatography column in its sodium form and eluted with methanol. Free IL elutes containing the mixture of **2** and unreacted **1** were evaporated in vacuo; the resulting crude was subsequently dissolved in dichloromethane and purified through a silicagel flash column. Elution with dichloromethane/methanol (98:2 v/v) afforded **2** in 68% yield: ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 2.11 (s, 3H, $COCH_3$), 2.12 (2s, 6H, $COCH_3$), 2.13 (s, 3H, $COCH_3$), 3.41 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.77-3.81, 3.90-3.92 (2m, 4H, H-5, H-5′, α and β anomers), 4.03-4.06, 4.10-4.13 (2m, 2H, H-4, α and β anomers), 4.93 (s, 1H, H-1, α-anomer), 4.98 (dd, 1H, $J_{3,2}$ 1.2 Hz, $J_{3,4}$ 4.6 Hz, H-3, α-anomer), 5.03 (d, 1H, $J_{2,3}$ 1.2 Hz, H-2, α-anomer), 5.07 (dd, 1H, $J_{2,1}$ 4.6 Hz, $J_{2,3}$ 6.8 Hz, H-2, β-anomer), 5.09 (d, 1H, $J_{1,2}$ 4.6 Hz, H-1, β-anomer), 5.33 (dd, 1H, $J_{3,2}$ 6.8 Hz, $J_{3,4}$ 5.3 Hz, H-3, β-anomer). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 19.99, 20.53, 20.70, 20.78 ($CO\underline{C}H_3$s, α and β anomers), 54.81, 55.81 (OCH_3, α and β anomers), 61.92 (C-5, α anomer), 64.02 (C-5, β anomer), 77.00, 77.12, 77.16, 77.19, 77.24, 77.42 (C-2, C-3 and C-4, α and β anomers), 100.73 (C-1, β anomer), 106.51 (C-1, α anomer), 169.72, 170.31, 170.62, 170.94 (COs, α and β anomers).



1,3 **2,4**

1,2 R_1=OAc, R_2=H buffer:[BMIM][PF_6] 1:1
3,4 R_1=H, R_2=OAc buffer:[BMIM][BF_4] 9:1

Scheme 1. *Candida rugosa lipase* (CRL) catalysed hydrolysis of methyl 2,3,5-tri-*O*- acetyl-α,β-D-arabinofuranoside (**1**) and methyl 2,3,5-tri-*O*- acetyl-α,β–D-ribofuranoside (**3**) in mixtures of buffer / ionic liquid.

Preparation of Methyl 2,3-di-O-acetyl-α,β-D-Ribofuranoside (4)

Analogously to the above reported procedure, CRL (90 mg) was added to a 9:1 mixture of sodium phosphate buffer (30 mM, pH 7; 4.5 ml) and [BMIM][BF_4] (0.5 ml) containing **3** (100 mg). The system was shaken for 5 h at 30 ºC and 200 rpm, the lipase filtered off and washed with methanol. Filtrates were extracted with dichloromethane and concentrated *in vacuo*, giving a crude that was purified through a silicagel flash column. Elution with dichloromethane/methanol (98:2 v/v) afforded **4** in 62% yield, which provided satisfactory NMR data [11].

CAL B-catalysed Alcoholysis of 1, 3 and 5

Typically, experiments of enzymatic alcoholyses were performed by adding CAL-B (9 mg) to a solution of the substrate (10 mg) in the assayed alcohol at the tested alcohol/ substrate ratio (A/S) = 120, 660 and 1200 and shaking the resulting mixtures at 200 rpm and 30 °C. When employing a solvent, 10 % (v/v) of the reaction total volume was added, except for the case A/S = 3, where the total volume contained 99.3 % (v/v) of the solvent. The same ratios and volumes were applied when assaying the reported ILs. Aliquots from the biotransformations were withdrawn at different times, the enzyme separated and after extracting with ethanol, analysed by TLC.

3. RESULTS AND DISCUSSION

As previously outlined in the Introduction, attempts to prepare **2** through CAL-B catalysed alcoholysis of methyl 2,3,5-tri-*O*-acetyl-α, β-D-arabinofuranoside (**1**) using either alcohols such as ethanol, 1-butanol and isopropanol at many alcohol/substrate (A/S) ratios (A/S = 120, 660 and 1200) or cosolvents (petroleum ether, dichloromethane, terbutylmethylether, acetone, dioxane, acetonitrile) at A/S = 3, 120 and 1200 afforded low yields (35-49%).

We decided then to assay ethanolysis in the presence of some ILs: [BMIM][BF_4], [BMIM][PF_6] and [BMIM][MeSO] (see Materials and Methods, General). Many examples testify that lipases such as CAL B and CRL are catalytically active in the two first ILs [13,19]. The same A/S ratios above reported for alcoholysis in presence of organic cosolvents were tested with the mentioned ILs (see Materials and Methods); with [BMIM][BF_4] and [BMIM][MeSO] the reaction mixtures were homogeneous, while [BMIM][PF_6] gave a biphasic system. None of the assayed experimental conditions afforded satisfactory results: poor **1** conversion was reached from biotransformations containing [BMIM][PF_6] and [BMIM][MeSO], and non regioselective reaction profils resulted from [BMIM][BF_4].

For comparative purposes, CAL B-catalysed ethanolysis of methyl 2,3,5-tri-*O*-acetyl–α,β–D-ribofuranoside (**3**) in ILs was also carried out, and again none of the assayed conditions was satisfactory, affording non selective mixtures of products, in contrast to the results obtained using only ethanol [10, 11]. When methyl 2,3,5-tri-*O*-acetyl–α,β–D-xylofuranoside (**5**) was assayed, no satisfactory conversion of the substrate was attained.

Taking into account these results, enzymatic hydrolysis was then considered and in this case, *Candida rugosa* lipase (CRL) was also tested as the biocatalyst, but unsatisfactory results were obtained in buffer phosphate (pH 7). CRL had already been reported to achieve the regioselective preparation of the α anomer of **2** in high yield [20], and prompted by the fact that Gervaise et al. [21] recently employed [BMIM][PF_6] for CRL-catalysed regioselective deacetylation of a thioglucopyranoside, demonstrating that the ILs and its content in the reaction mixture modulate the enzyme regioselectivity, we decided to explore the influence of ILs on enzymatic hydrolysis of triacetylated furanosides **1, 3** and **5**.

None of the two enzymes allowed a significant conversion of **1** in phosphate buffer (pH 7) containing either 10 % (v/v) or 20 % (v/v) of water miscible [BMIM][BF_4] and [BMIM][MeSO], a higher IL content being detrimental for reaction conversion.

In contrast to **1**, substrate **3** afforded methyl 2,3-di-*O*-acetyl–α,β–D-ribofuranoside (**4**, Scheme **1**) in 62 % yield when CRL was assayed in buffer / [BMIM][BF_4] 90:10 (v/v); however, **5** gave non selective mixtures of partially acetylated products. These results suggest a strong influence of the furanose structure on the regioselectivity of hydrolysis catalysed by the assayed lipases in ILs.

More convenient results were reached for the hydrolysis of **1** in systems containing the immiscible water [BMIM][PF_6]. We tested CAL B and CRL-catalysed hydrolysis of **1** in biphasic mixtures containg 25, 50 and 75 % of [BMIM][PF_6]; preliminary TLC analysis showed the regioselective formation of a diacetylated product. In order to quantify **2** by C18-HPLC, [BMIM][PF_6] was removed prior to analysis. Attempts to achieve this by silicagel column chromatography were unsuccessfull; thus, removal was accomplished by means of a cation exchange resin. As it can be seen (Table **1**), in a 1:1 buffer / [BMIM][PF_6] mixture

Table 1. Enzymatic Hydrolysis of Methyl 2,3,5-tri-*O*-acetyl–α,β–D-Arabinofuranoside (1) in a Mixture of Buffer / [BMIM]PF_6[a]

Entry	Enzyme	% LI (v/v)[b]	2 (%)[c]
1	CRL	50	77
2	CRL	75	51
3	CAL B	50	50
4	CAL B	75	17

[a]See Material and Methods. [b]Percentage of [BMIM]PF_6 in the reaction mixture. [c]Determined by HPLC (see Material and Methods) at 24 h.

CRL catalysed the regioselective formation of **2** in 77 % (Entry 1; Scheme **1**); after column chromatography this product was isolated in 68 % yield. NMR-^{1}H analysis of **2** also showed that the reaction proceeded without stereoselectivity: while the anomeric α/β ratio of **1** was 1.0/1.1, it was 1.0/1.0 for **2**. Analysis of the products obtained under the reaction conditions reported in Entries 2-4 (Table **1**) also showed similar ratios.

It can also be mentioned that **3** and **5** were non regioselectively deacetylated by CRL in [BMIM][PF_6] under the conditions assayed for **1**, showing again the influence of the furanose structure on the enzyme recognition and regioselectivity.

In summary, in this work we explore application of ILs to the enzymatic deacetylation of furanosides. The obtained results were very dependent on the furanose structure, the IL and its content. Among the tested ILs, [BMIM][PF_6] gave the best results and its effect on CRL-catalysed hydrolysis of **1** correlates with that observed in the hydrolysis of thioglucopyranose derivative, a structure related substrate [21]; in both cases, a 50 % of [BMIM][PF_6] enhanced the lipase regioselectivity. Moreover, it can be mentioned that when applying *Pseudomonas cepacia* lipase on Celite, the same IL afforded a fast and almost complete regioselective hydrolysis of 3,4,6-tri-*O*-acetyl-D-glucal, while hydrolysis and alcoholysis in [BMIM][BF_4] were slow and poorly selective [16].

The methodology herein presented allowed the regioselective preparation of products **2** and **4** in good yields. The interest in **2** lies in the fact that regioselectively acylated arabinofuranosides are useful precursors for oligosaccharides; for instance, arabino oligosaccharides are part of glycans found in the cell walls of some human pathogens, such as *Mycobacterium*, and their multi-milligram synthesis provides material for subsequent biochemical studies [22]. Moreover, **2** and **4** find applications as precursors for the chemoenzymatic synthesis of modified nucleosides [23].

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