Enzymatic Regioselective Acylation of Hexoses and Pentoses Using Oxime Esters

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Hexoses and pentoses have been acylated with Amano PS, and *Candida antarctica* (Novo SP435) lipases, using oxime esters as acyl donors. This method represents the first report of the enzymatic acylation of free pentoses. The selectivity of the process depends on the structure of the starting material.

The synthetic transformation of carbohydrates, important both as constituents of many biological materials[1] and as energy sources in living organisms, is a considerable challenge because of the presence of multiple hydroxy groups of similar reactivity.[2]

Two routes have been mainly developed for the regioselective synthesis of carbohydrate esters. They involve the nucleophilic attack of a carboxylate anion at the anomeric carbon of the carbohydrate,[3] or the reaction of the primary hydroxy group with a suitable acyl donor.[4] In addition, some chemical esterifications of free substrates have been achieved using: (i) organometallic reagents[5] to enhance selectively the nucleophilicity of hydroxy groups; (ii) bulky reagents in order to acylate selectively the primary hydroxy groups, *e.g.*, application of the Mitsunobu reaction[6] to the carbohydrates; (iii) 3-acylthiazole derivatives as specific reagents.[7] These chemical methods are prone to certain general drawbacks such as cumbersome protection–deprotection reactions, tedious purification steps and, in some cases, acyl migrations under the reaction conditions employed.[8] The enzymatic transesterification of sugars is an alternative to classical synthetic methods. Enzyme-catalyzed esterification of glycosides and free sugars has been extensively studied recently.[9] Lipases[10] and proteases[11] successfully catalyze the monoacylation of sugars. Due to the poor solubility of carbohydrates in common organic solvents these reactions are carried out in polar solvents using activated acylating agents.[10,11] Some interesting examples, in which the acylation has been achieved by means of free acids in absence of solvent, are also known.[12]

Results and Discussion

Two important aspects in enzyme-catalyzed esterifications are the role of the solvent[13] and the irreversibility of the process which is conditioned by the acylating agent. Moreover, the reactivity of the acylating agent may affect the overall performance of the enzyme. Thus, anhydrides and vinyl esters can react with the free amino groups of the enzyme causing loss of activity or inactivation.[14]

On the other hand, oxime esters have an intermediate reactivity, with respect to the above mentioned acyl donors and can, therefore, be employed under mild conditions in enzymatic reactions.[15] In addition, oxime esters are easy to obtain by enzymatic methods.[16]

In a preliminary communication we reported an efficient method for the regioselective acylation of α-D-glucopyranose and methyl α-D-glucopyranoside with oxime esters as acyl donors.[17] Lipase from *Pseudomonas cepacia* (PSL) allowed the selective acylation of the primary hydroxy group of the carbohydrates tested. The length of the acyl moiety in the oxime ester used did not change the selectivity, and with long chain esters increased yields were obtained.

To study the scope and limitations of the enzymatic acylation of carbohydrates through oxime esters we applied the method to other hexoses, both aldoses and ketoses, as well as to some pentoses.

(A) *Acylation of Hexoses.*—D-Galactose and D-mannose react with oxime esters in the presence of lipase from *Pseudomonas cepacia* under the conditions previously reported[17] (dry pyridine, room temperature and an inert atmosphere) to afford regioselectively acylated derivatives of the primary hydroxy group, compounds **3a–f**. No reaction was observed in the absence of enzyme (Scheme 1). These results are summarized in Table 1. Yields were similar to those obtained with α-D-glucopyranose and methyl α-D-glucopyranoside, showing that changes in the configuration of the C-2 or of the C-4 in the hexose seem not to affect the preference of the enzyme for the primary hydroxy group.

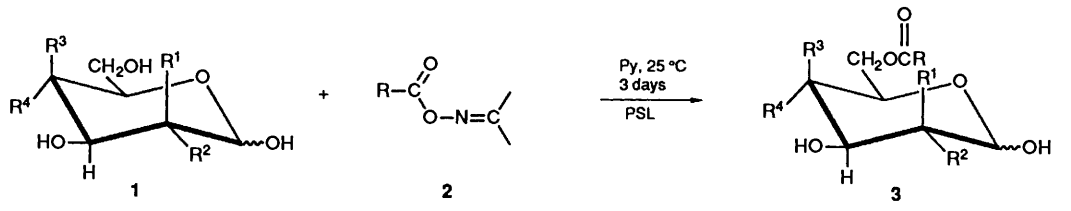
The primary hydroxy group of the ketohexose L-sorbopyranose **4** was similarly acylated to give 1-*O*-acyl derivatives, compounds **5** (Scheme 2, Table 2). In contrast, D-fructose yielded mixtures of variable complexity under all reaction conditions tested. Nevertheless, in pyridine at room temperature two major products (70%) were identified by ^{13}C NMR as 6-*O*-acetyl-β-D-fructofuranose and 1-*O*-acetyl-β-D-fructofuranose in the same proportion. This behaviour is in agreement with the results from Klibanov *et al.*[12]

(B) *Acylation of Pentoses: L-Arabinose, D-Ribose, D-Xylose and D-Lyxose.*—Selective acylation of the primary hydroxy functions of methylfuranosides with 2,2,2-trifluoroethyl acetate with porcine pancreatic lipase (PPL) as catalysts has been previously reported.[18] Our best results were obtained with L-arabinose and D-ribose in dry pyridine using PSL as catalyst (Schemes 3, 4). A careful control of the temperature allowed us to isolate the furanoses **7** selectively acylated at *O*-5 as a mixture of α and β anomers, according to their NMR spectra (see below).

With moderate or long-chain oxime esters (C_4, C_{10}) the process must be carried out at 0 °C, since at higher temperatures polyacylated compounds are formed. However, with acetone *O*-acetyloxime ester the reaction goes smoothly at room temperature and for L-arabinose only the monoacylation product at *O*-5 is isolated. The trials with a different lipase, Novo SP435, gave monoacylated products in the same way, allowing us to carry out all the reactions at room temperature (Schemes 5, 6).

D-Xylose and D-lyxose yielded complex mixtures of products, which were not isolated, under the same reaction conditions

Scheme 1 Reaction of D-mannose (R^1=R^4=OH, R^2=R^3=H) and D-galactose (R^1=R^4=H, R^2=R^3=OH) with oxime esters



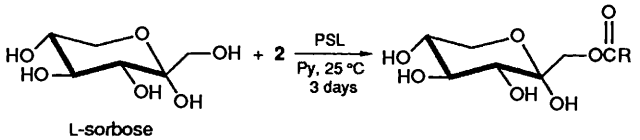
1 2 3

Table 1 Reaction of D-mannose (R^1=R^4=OH, R^2=R^3=H) and D-galactose (R^1=R^4=H, R^2=R^3=OH) with oxime esters catalysed by *Pseudomonas cepacia* lipase

Entry	R	R^1	R^2	R^3	R^4	Yield (%)[a]	$[\alpha]_D^{25}$ (*c*, solvent)	M.p.	R_f (solvent)[c]
3a	Me	OH	H	H	OH	65	16.9 (0.8, H_2O)	Syrup	0.31 (A)
3b	$CH_3(CH_2)_2$	OH	H	H	OH	73	22.5 (1.3, MeOH)[b]	Syrup	0.27 (B)
3c	$CH_3(CH_2)_8$	OH	H	H	OH	80	14.1 (1.1, MeOH)[b]	Syrup	0.41 (B)
3d	Me	H	OH	OH	H	70	95.6 (1.0, MeOH)	130–132	0.30 (A)
3e	$CH_3(CH_2)_2$	H	OH	OH	H	74	93.3 (0.9, H_2O)	152–156	0.35 (B)
3f	$CH_3(CH_2)_8$	H	OH	OH	H	85	53.4 (0.9, H_2O)	156–158	0.52 (C)

[a] Calculated with respect to **1**. [b] λ = 578 nm (Hg lamp). [c] Solvent A: AcOEt–MeOH–H_2O (20:2:1); solvent B: CH_2Cl_2–MeOH (9:1); solvent C: CH_2Cl_2–MeOH (85:15).

Scheme 2 Reaction of α-L-sorbose with oxime esters



L-sorbose
4 5

Table 2

Entry[a]	R	Yield (%)[b]	$[\alpha]_D^{25}$ (*c*, solvent)	R_f (solvent)
4a	Me	72	−24.5 (1.0, H_2O)	0.35 (A)
4b	$CH_3(CH_2)_2$	68	−10.2 (1.6, MeOH)	0.22 (B)
4c	$CH_3(CH_2)_8$	86	−4.5 (1.4, MeOH)	0.35 (B)

[a] All compounds were obtained as syrups. [b] Calculated with respect to **4**.

(pyridine as solvent, and PSL or Novo SP435 as catalysts). Two different monoacylated products were obtained when D-ribose was used as starting material and PS lipase as catalyst. They were separated from the crude reaction mixture by column chromatography, together with small quantities of starting material, and identified as 5-*O*-acyl-D-ribofuranose **9** (35%, mixture of α and β anomers) and 1-*O*-acyl-β-D-ribopyranose **10** (32%) by NMR. No further separation was accomplished. Nevertheless, with the *Candida antarctica* lipase (Novo SP435), products **9** of monoacylation of ribofuranose at *O*-5 were exclusively formed when pyridine was employed as solvent at room temperature. In addition, with this lipase, products **12** of acylation of D-lyxose at the anomeric hydroxy group were isolated. With neither D-lyxose nor D-xylose products of monoacylation at *O*-5 were obtained.

Analogously to the hexoses, higher reaction rates are obtained with the more lipophilic esters (C_4, C_{10}), which produce a small decrease in the selectivity achieved. Lowering the temperature favours the discrimination by the acyl–enzyme complex between the primary and secondary hydroxy groups, especially between the more reactive anomeric β hydroxy group of the pyranose form and the primary hydroxy of the furanose form.*

D-Ribose is present in solution as a mixture of pyranose and furanose configurations, both as α and β anomers, the β-pyranose isomer (62%) being predominant.[19] The higher reactivity of the β anomeric OH in the pyranose configuration is probably the reason that even at low temperature (0 °C) mixtures of products **9** and **10** are obtained.

Structure Determination.—^{13}C NMR spectra of the acylated carbohydrates were assigned by a combination of homo- and hetero-nuclear 2D correlation spectroscopy. Proton–proton connectivities established by COSY experiments with a double quantum filter were used to assign the ^{13}C signal by means of H, C-COSY correlations.[20] Anomeric configurations were determined from the coupling patterns and literature data of signals from anomeric protons. These were further confirmed by NOE-difference experiments for the pentoses. Anomerization rates are greatly reduced in solvents other than in D_2O, so that only one anomer was measured.[19,21]

Acylation of hexoses **3**, **5** and **11** at the primary hydroxy group was easily deduced from their ^{13}C NMR spectra. The β and γ carbons with respect to the acyl moiety showed the expected[22] downfield and upfield shifts, respectively. Identification of the esterified hydroxy group was further confirmed by long-range correlation between the methylenic protons of the sugar and the carbonyl carbon of the side-chain.

A mean coupling constant of *ca.* 10 Hz was assumed. In some cases, one-bond coupling modulation of the HC long-range coupling caused a severe decrease in the intensity of the key cross peaks. For those compounds a second H, C-COSY experiment was performed with the defocusing and refocusing delays equal to 145 ms.[23]

The same procedure outlined above was applied to identification of the acylation products of pentoses. In this case, cross peaks correlating the carbonyl group with the sugar moiety were difficult to recognize above the noise in 2D spectra based on polarizaton transfer.[20] A more satis-

* The reaction between L-arabinose and C_4 or C_{10} oxime esters carried out at room temperature under the conditions described in the Experimental section for pentoses gave predominantly a mixture of 1-*O*-acyl-β-L-arabinopyranose and 5-*O*-acyl-L-arabinofuranoses (mixture of α and β anomers).

Scheme 3 Reaction of L-arabinose with oxime esters

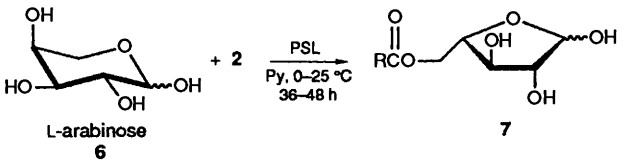


Table 3

Entry[a]	R	Yield (%)[b]	T(°C)	$[\alpha]_D^{25}$ (c, solvent)	R_f (solvent)[c]
7a	Me	70	25	−9.8 (0.7, H_2O)	0.30 (D)
7b	$CH_3(CH_2)_2$	45	0	0 (1.0, MeOH)	0.44 (B)
7c	$CH_3(CH_2)_8$	48	0	8.2 (1.0, MeOH)	0.54 (B)

[a] All compounds were obtained as syrups. [b] Calculated respect to **6**. [c] Solvent D: AcOEt–MeOH (98:2).

Scheme 4 Reaction of D-ribose with oxime esters catalyzed by PSL

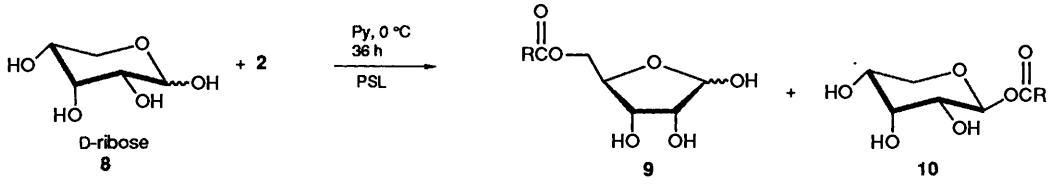
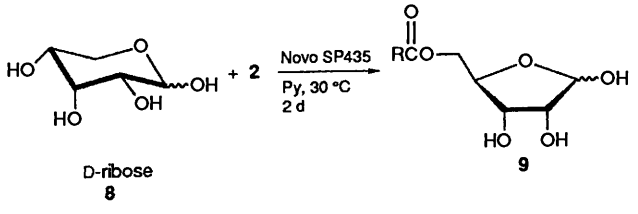


Table 4

Entry	R	Yield (%)[a]	R_f (solvent)	Entry	R	Yield (%)[a]	R_f (solvent)
9a	Me	35	0.35[b] (D)	**10a**	Me	32	0.29 (D)
9b	$CH_3(CH_2)_2$	34	0.46[c] (B)	**10b**	$CH_3(CH_2)_2$	33	0.40 (B)

[a] Calculated respect to **8**.

Scheme 5 Reaction of D-ribose with oxime esters catalysed by Novo SP435 lipase



Scheme 6 Reaction of D-lyxose with oxime esters catalysed by Novo SP435 lipase

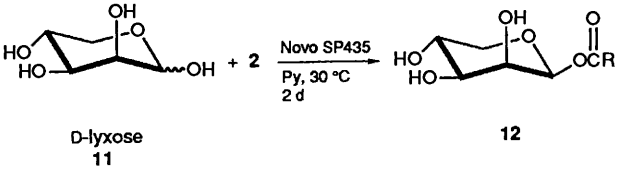


Table 5

Entry[a]	R	Yield (%)[b]	$[\alpha]_D^{25}$ (c, solvent)	R_f (solvent)
4a	Me	50	26.9 (1.2, MeOH)	0.35 (D)
4b	$CH_3(CH_2)_2$	56	26.2 (0.5, MeOH)	0.46 (B)
4c	$CH_3(CH_2)_8$	64	21.8 (0.7, MeOH)	0.20 (B)

[a] All compounds were obtained as syrups. [b] Calculated respect to **8**.

Table 6

Entry[a]	R	Yield (%)[b]	$[\alpha]_D^{25}$ (c, solvent)	R_f (solvent)
12a	Me	21	−20.0 (0.4, MeOH)	0.35 (D)
12b	$CH_3(CH_2)_8$	20	−16.1 (0.3, MeOH)	0.13 (B)

[a] All compounds were obtained as syrups. [b] Calculated respect to **11**.

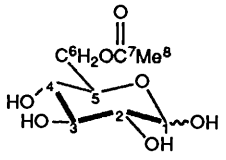
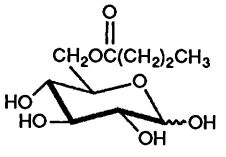
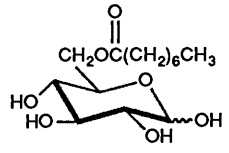
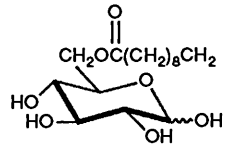
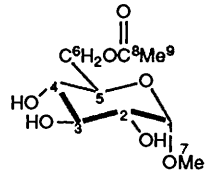
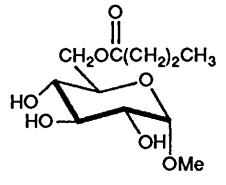
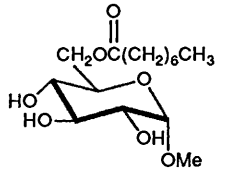
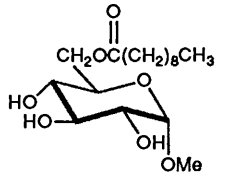
factory solution was obtained through proton detection of heteronuclear double quantum coherences generated during the evolution period.[24] A J low-pass filter was included in order to reduce responses derived from $^1J_{CH}$ coupling constant.[25]

Experimental

Pseudomonas cepacia lipase, Amano PS, was purchased from the Amano Pharmaceutical Co. The enzyme was kept under reduced pressure (10^{-6} mmHg) for 2 days prior to use. *Candida antarctica* lipase, Novo SP435, was kindly donated by Novo Nordisk A/S. All reagents were of commercial grade and were purchased from Aldrich Chemie Co.

Oxime esters were obtained by direct reaction of the acyl chlorides with the acetone oxime or by enzymatic methods according to procedures previously described.[16] Pyridine was dried by distillation over sodium hydroxide and stored under nitrogen. TLC was performed on precoated silica gel 60 sheets Merck F_{254} (for R_f see tables). For column chromatography Merck Silica gel 60 230–400 mesh was used. As eluents, mixtures

Table 7 ^{13}C NMR chemical shifts (δ_C in ppm) of the products **13a–h**[a]

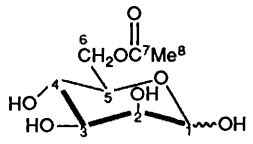
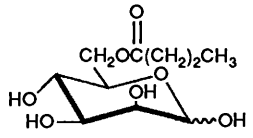
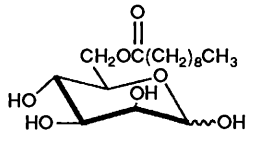
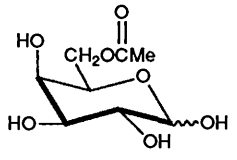
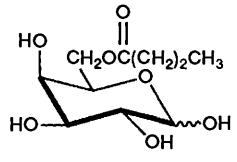
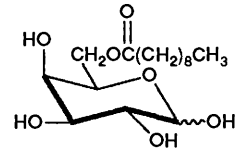
Compound	α-Pyranose						β-Pyranose					
	C-1	C-2	C-3	C-4	C-5	C-6	C-1	C-2	C-3	C-4	C-5	C-6
13a[b] 	92.3	71.5	72.7	69.6	69.2	63.6	96.2	74.1	75.7	69.6	73.5	63.6
13b[b] 	92.7	72.0	73.2	70.2	69.8	63.9	96.6	74.6	76.2	70.2	74.0	63.9
13c[c] 	93.9	73.7	74.7	71.8	70.6	64.8	—	—	—	—	—	—
13d[c] 	94.0	73.8	74.7	71.9	70.6	64.8	—	—	—	—	—	—
13e[b] 	100.0	71.8	73.5	70.1	69.8	64.0	—	—	—	—	—	—
13f[b] 	99.9	71.8	73.6	70.3	70.0	63.9	—	—	—	—	—	—
13g[c] 	100.0	71.9	73.5	70.2	69.9	63.9	—	—	—	—	—	—
13h[c] 	100.9	73.1	74.8	71.6	70.8	64.6	—	—	—	—	—	—

[a] Products collected in our previous work (see ref. 17). [b] D_2O as solvent. [c] CD_3OD as solvent, no β anomers are present.

of AcOEt–MeOH–H_2O (20:2:1 for hexoses), AcOEt–MeOH (98:2 for pentoses) or CH_2Cl_2–MeOH (90:10) were used. Mass spectra were obtained on a Hewlett-Packard 5897 A spectrometer.

^1H and ^{13}C spectra were obtained using a Bruker 300 AC spectrometer fitted with an Aspect 3000 computer, operating at 300.13 MHz and 75.5 MHz, respectively, with TMS as internal reference. Standard Bruker software and microprograms were

Table 8 ^{13}C NMR chemical shifts (δ_C in ppm) of the products **3a–f**

Compound	α-Pyranose						β-Pyranose					
	C-1	C-2	C-3	C-4	C-5	C-6	C-1	C-2	C-3	C-4	C-5	C-6
3a[a] 	94.8	71.2	70.7	67.4	70.6	64.4	94.4	71.7	73.5	67.1	74.2	64.4
3b[a, b] 	94.8 95.8	71.2 72.7	70.7 72.2	67.4 68.8	70.7 71.7	64.1 65.2	94.4 —	71.7 —	73.5 —	67.1 —	74.3 —	64.2 —
3c[b, c] 	95.8	72.7	72.1	68.8	71.6	65.1	95.6	73.0	75.1	68.4	75.5	65.1
3d[a] 	93.0	68.8	69.6	70.0	68.6	64.8	97.1	72.3	73.2	69.4	73.0	64.6
3e[a] 	93.0	68.8	69.6	69.9	68.7	64.6	97.1	72.4	73.2	69.4	73.1	64.4
3f[b] 	94.2	70.3	71.0	71.0	69.2	64.9	—	—	—	—	—	—

[a] D_2O as solvent. [b] CD_3OD as solvent. [c] 18% of β anomer.

applied for all the NMR experiments. ^1H FIDs were recorded over 16 transients, covering a sweep width of 1700 Hz and digitalized in 16 K. They were zero filled prior to the Fourier transformation giving a resolution of 0.1 Hz per point. For the proton decoupled ^{13}C NMR spectra 200 scans were accumulated over a spectral width of 13 000 Hz in 32 K of memory space. An exponential multiplication with a line broadening factor of 2 Hz was applied before the Fourier transformation. NOE-difference experiments were performed with the NOEMULT microprogram using a presaturation power of 51L during 7 seconds. A 90° (10 μs) reading pulse was applied in order to minimize polarization transfer artifacts.

Typical experimental parameters were as follows.

Double-quantum filtered COSY (*COSYDQF*). Relaxation delay 2 s, sweep width 1700 Hz, 512 experiments, 16 scans per experiment, final matrix of 2048 × 1024 data points after zero filling in F1, squared sinus bell apodization (π/6) in both dimensions.

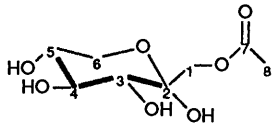
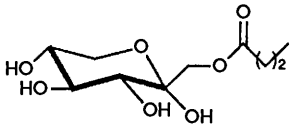
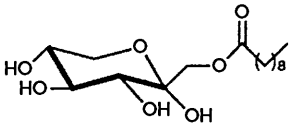
One-bond H, C-COSY (*XHCORR*). Relaxation delay 2 s, sweep width 7500 Hz and 1700 Hz, 128 increments of 128 scans each, size 2 K in F2 and 512 W in F1, zero filling in F1, squared sinus bell filter (π/4) in F2 and (π/4) in F1.

Long-range H, C-COSY (*XHCORR*). The same conditions as for the one bond correlation experiment were used, except that the sweep width in F2 was set to 13 000 Hz and the number of scans increased to 200. Defocusing–refocusing delays of 44 and 22 ms respectively. When modulation of the HC-long-range couplings by one-bond couplings were too severe, a second experiment was performed with both delays equal to 145 ms.[23]

HMBC with J low pass filter. A 5 mm BB reverse probe head was used. The ^1H pulses were generated *via* the decoupler channel while a PTS 160 MHz synthesizer was used for generating the X frequency. In this detection mode, both transmitter and decoupler offsets must be identical. 90° pulses were 10.6 μs for the ^1H (1 db attenuation) and 13 μs for the ^{13}C (4 db attenuation).

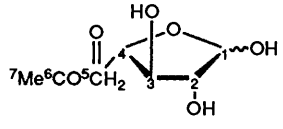
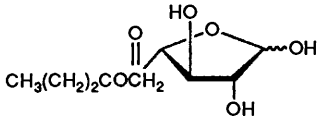
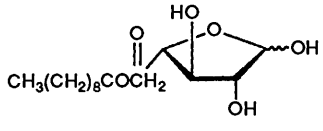
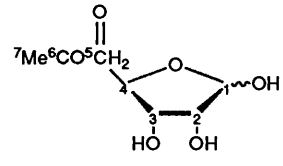
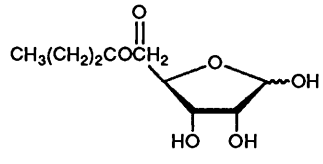
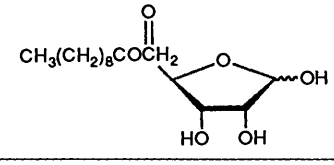
Relaxation delay 2 s, defocusing of long-range coupling during 60 ms, 512 increments of 32 scans each, sweep width in F2 1700 Hz and 13 000 Hz in F1. Zero filling F1 to a final matrix of 1024 × 1024 datapoints. Square sinus bell apodization of (π/4) in F2 and of (π/8) in F1.

Table 9 ^{13}C NMR chemical shifts (δ_C in ppm) of the products **5a–c**

Configuration	C-1	C-2	C-3	C-4	C-5	C-6
5a[a] 	66.0	97.2	71.5	74.1	69.9	62.5
5b[a] 	65.6	97.3	71.5	74.1	69.9	62.5
5c[b] 	66.2	97.7	72.8	75.7	71.5	63.5

[a] D_2O as solvent. [b] CD_3OD as solvent.

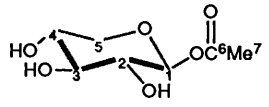
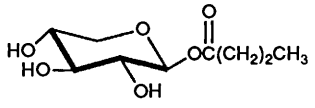
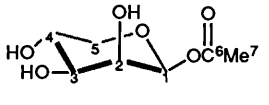
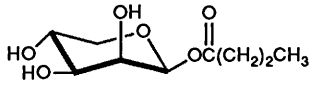
Table 10 ^{13}C NMR chemical shifts (δ_C in ppm) of the products **7a–c** and **9a, b**

	α-Anomer					β-Anomer				
Compound	C-1	C-2	C-3	C-4	C-5	C-1	C-2	C-3	C-4	C-5
7a[a] 	101.8	81.8	76.6	81.1	64.7	95.9	74.8	79.1	76.5	65.7
7b[b] 	103.5	83.6	78.5	82.0	65.2	97.4	77.0	80.8	78.3	66.7
7c[b] 	103.6	83.6	78.6	82.1	65.3	97.5	77.1	80.9	78.4	66.8
9a[a] 	97.0	71.2	70.8	80.6	65.0	101.7	75.6	71.2	80.1	65.6
9b[b] 	97.0	71.3	70.9	80.7	64.6	101.7	75.6	71.2	80.2	65.3
9c[a] 	98.0	72.7	72.3	81.5	65.3	102.3	76.9	72.7	81.1	66.7

[a] D_2O as solvent. [b] CD_3OD as solvent.

General Procedure for the Synthesis of Hexose Monoesters.—To the hexose (0.45 g, 2.5 mmol), in dry pyridine (10 cm^3) *O*-acetone oxime ester (2.5 mmol) and Amano PS Lipase (1 g) were added. The reaction mixture was magnetically stirred under a nitrogen atmosphere at room temperature. TLC monitoring of the reaction showed that after 2–3 days it was complete and the enzyme was then filtered off and washed with methanol (2 × 15 cm^3). The combined filtrate and washings were

Table 11 ^{13}C NMR chemical shifts (δ_C in ppm) of the products **10a–b** and **12a, b**

Configuration		C-1	C-2	C-3	C-4	C-5
10a[a]		94.6	70.2	73.0	66.3	64.0
10b[a]		94.5	70.0	72.8	66.3	64.1
12a[a]		94.6	71.4	68.6	70.5	61.5
12b[b]		95.8	72.3	69.8	72.1	61.6

[a] D_2O[9] as solvent. [b] CD_3OD as solvent.

evaporated under reduced pressure and the resulting syrup was purified by column chromatography to yield the corresponding monoester. (Physical and spectroscopical data are shown in Tables 1–11).

General Procedure for the Synthesis of Pentose Monoesters.—To the pentose (0.76 g, 5 mmol) in dry pyridine (10 cm^3), *O*-acetone oxime ester (5 mmol) and Amano PS lipase (2 g) were added. The mixture was magnetically stirred for 2 days under nitrogen atmosphere its temperature being kept at 25 °C for the reaction giving product **7a** and at 0 °C for all others (**7b, c**, **9** and **10a, b**). After this time the enzyme was filtered off and washed twice with methanol. The combined filtrate and washings were evaporated under reduced pressure and the residue purified by column chromatography. Catalysed acylation of D-ribose (0.38 g, 2.5 mmol) or D-lyxose in dry pyridine (10 cm^3) with *O*-acetone oxime esters (2.5 mmol) gave products **9a–c** or **11a, b**, respectively, following the procedure described above.

Characterization of Products.—Tables 1–11 show the reaction conditions, yields, optical rotations and ^1H-, and ^{13}C NMR spectra. IR data, mass spectra, and ^{13}C NMR spectra of the acyl side-chain of all compounds have been treated as a Supplementary publication.* All compounds gave satisfactory microanalyses which also form part of the Supplementary publication.

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* Supplementary publication no. 56897 (11 pages). For details of the Scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1992, Issue 1.

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