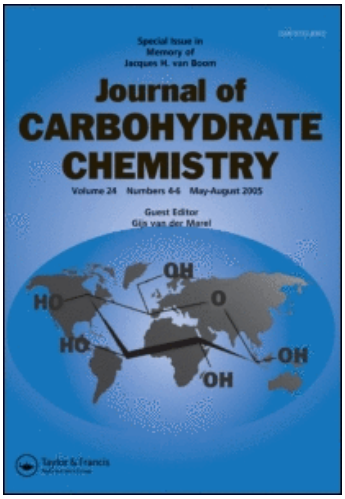

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Ciuffreda, Pierangela , Ronchetti, Fiamma and Toma, Lucio(1990) 'Acylation of 6-Deoxy-L-Hexoses: Regioselectivity in the Enzymatic Transesterification as Compared to Chemical Esterification', Journal of Carbohydrate Chemistry, 9: 1, 125 — 129

To link to this Article: DOI: 10.1080/07328309008545804

URL: http://dx.doi.org/10.1080/07328309008545804

J. CARBOHYDRATE CHEMISTRY, 9(1), 125-129 (1990)

COMMUNICATIONS

ACYLATION OF 6-DEOXY-L-HEXOSES: REGIOSELECTIVITY IN THE ENZYMATIC TRANSESTERIFICATION AS COMPARED TO CHEMICAL ESTERIFICATION

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Received April 25, 1989 - Final Form September 19, 1989

INTRODUCTION

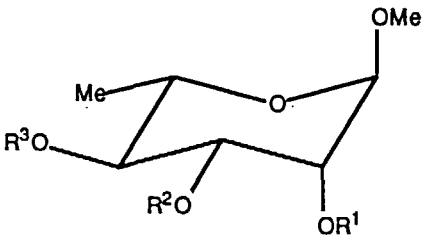
Regioselective esterification of sugars may represent a valuable tool for providing useful intermediates in the synthesis of more complex structures. A relatively easy solution to the problem can be found when discrimination between a primary *vs* secondary hydroxyl function is needed, but it seems to be quite unsolvable in a single chemical step when two or more secondary alcoholic groups are competing in the reaction with a given acylating reagent. Hydrolytic enzymes were found to be catalysts of great utility in this respect. Several cases are described in the literature concerning the selective deprotection of acylated sugars in aqueous media,[1] and the esterification of free sugars or their alkyl glycosides in non-polar organic solvents[1a,2] which first involve the primary alcohol function.[3] Enzyme-catalyzed acylation in organic media at secondary alcohol positions was also studied[4] in the case of 6-*O*-butyryl-glucose, -mannose, and -galactose and the

2-OH and/or 3-OH esterifications were shown to be preferred, with no reactivity observed at the 4 position.

RESULTS AND DISCUSSION

As suitable models to test the relative reactivity of the secondary alcoholic functions in the absence of a polar substituent in the primary position, we chose the 6-deoxy-L-hexoses L-rhamnose and L-fucose. These sugars occur widely throughout nature, contrary to the 6-deoxy-hexoses belonging to the D series. Moreover, L-rhamnose and L-fucose have opposite stereochemistry at C-4 and at C-2. The reactivity of these two sugars toward chemical acylation, *e.g.*, benzoylation or acetylation, is known and in both the cases the 4-OH was found to be the less reactive functional group.[5]

Here we report the results of the enzymatic butyrylation of methyl α-L-rhamnopyranoside **1a** and methyl α-L-fucopyranoside **2a** which was found to be a complementary tool in the regioselective acylation of these 6-deoxy-hexosides. In contrast, when the reaction was carried out chemically in pyridine with a 1 molar equivalent of butyryl chloride at room temperature,[6] a complex mixture[7] of mono- (**1b-d** and **2b-d**),[8] di- (**1e-g** and **2e-g**), and tri- (**1h** and **2h**) butyryl derivatives was obtained, with the monoesters prevailing. The product composition from this reaction is reported in Table 1 (entries 1 and 2). The relative percentage of the three monobutyrates reflects the reactivity of the three functions with 3-OH>2-OH>4-OH for the rhamnopyranoside and 2-OH>3-OH>4-OH for the fucopyranoside.



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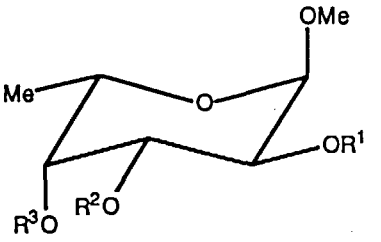

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a: $R^1=R^2=R^3=H$; **b**: $R^1=COCH_2CH_2CH_3$, $R^2=R^3=H$;

c: $R^1=R^3=H$, $R^2=COCH_2CH_2CH_3$; **d**: $R^1=R^2=H$, $R^3=COCH_2CH_2CH_3$;

e: $R^1=R^2=COCH_2CH_2CH_3$, $R^3=H$; **f**: $R^1=R^3=COCH_2CH_2CH_3$, $R^2=H$;

g: $R^1=H$, $R^2=R^3=COCH_2CH_2CH_3$; **h**: $R^1=R^2=R^3=COCH_2CH_2CH_3$.

TABLE 1. Butyrylation of 1a and 2a.

entry	substrate	isolated ester yields (%)			monoesters ratio[a]
		mono-	di-	tri-	b : c : d
1	**1a**	54	13[b]	2[b]	19 : 77 : 4
2	**2a**	45	23[b]	[c]	69 : 31 : [c]
3	**1a**	80	-	-	8 : 4 : 88
4	**2a**	66	[c]	-	4 : 28 : 68

a. Determined by ^{1}H NMR.

b. Identified by ^{1}H NMR spectroscopy.

c. Trace quantity (by TLC).

TABLE 2. ^{1}H NMR data of compounds 1b-d and 2b-d.

	chemical shifts, δ							coupling constants, Hz				
	H-1	H-2	H-3	H-4	H-5	H_3-6	MeO	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
1b	4.63	5.07	3.92	3.44	3.66	1.32	3.36	1.5	3.5	9.5	9.5	6.5
1c	4.65	3.99	5.02	3.60	3.69	1.34	3.38	1.5	3.5	9.5	9.5	6.5
1d	4.71	3.91	3.84	4.77	3.77	1.22	3.37	1.5	3.5	9.5	9.5	6.5
2b	4.84	4.96	3.98	3.80	3.98	1.30	3.36	4	10.5	3	1	6.5
2c	4.78	3.94	5.07	3.83	4.00	1.28	3.43	4	10.5	3	1	6.5
2d	4.79	3.76	3.94	5.20	4.03	1.14	3.42	4	10	3.5	1	6.5

When the esterification was carried out using porcine pancreatic lipase (PPL)[9] as the catalyst and 2,2,2-trifluoroethyl butyrate (TFEB) as the acyl donor,[10] only monoesterification occurred with formation of the monobutyrates **1b-d** and **2b-d**[11,12] (Table 1, entries 3 and 4). Moreover, a great change in the regioselectivity was observed; Table 1 shows that the 4-OH becomes the largely preferred butyrylation site in both cases in spite of the different orientation of this functional group, equatorial in **1a** and axial in **1b**.[13,14]

Enzymatic acylation is a complementary method to chemical acylation, and furnishes products which are not easy to obtain by direct chemical transformation. The large enhancement of the reactivity of the 4-OH function in the enzymatic esterification might be due to the presence of a methyl rather than an acyloxymethyl group[4] at C-5 or it might depend on whether a sugar belongs to the L or D series. Interestingly, the stereochemistry at the reacting site (C-4) or at C-2 seems to have no influence on the regioselectivity of the reaction.

ACKNOWLEDGMENT

We thank Prof. Alberto Fiecchi for helpful discussions.

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3. The enzyme-catalyzed deacylation in tri-*O*-acetyllaevoglucosan was described[1d,e] as occurring preferentially at C-4 or at C-3 depending on the enzyme utilized.

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6. Substrate 1 g, butyryl chloride 0.59 mL, pyridine 10 mL, 0° C to r.t., 30 min.

7. The reaction mixture from **1a** was separated by column chromatography on silica gel eluted with toluene-acetone (9:1 to 3:1). Under these conditions the products eluted in the order: (i) the tributyrate **1h**; (ii) the dibutyrates **1e-g** collected as a mixture; (iii) the monobutyrate **1c**; (iv) a mixture of **1b** and **1d**. These last two butyrates were separated by careful column chromatography on silica gel eluted with chloroform-methanol (20:1).
Column chromatographic separation on the reaction mixture from **2a** as above yielded: (i) **2h**; (ii) a mixture of the dibutyrates **2e-g**; (iii) a mixture of **2b** and **2c**; (iv) the monobutyrate **2d**. **2b** and **2c** were separated as **1b** and **1d** in the above case.

8. Satisfactory elemental analyses were obtained for all compounds. The ^1H NMR spectra (500MHz, C^2HCl_3) are reported in Table 2. **1b**, oil, $[\alpha]_D^{20}$ -29° (*c* 1.2, $CHCl_3$); **1c**, oil, $[\alpha]_D^{20}$ -32° (*c* 1.2, $CHCl_3$); **1d**, mp 64-65 °C (methylene chloride), $[\alpha]_D^{20}$ -93° (*c* 1.2, $CHCl_3$); **2b**, oil, $[\alpha]_D^{20}$ -145° (*c* 1.8, $CHCl_3$); **2c**, oil, $[\alpha]_D^{20}$ -178° (*c* 1.8, $CHCl_3$); **2d**, oil, $[\alpha]_D^{20}$ -135° (*c* 1.2, $CHCl_3$).

9. PPL was purchased from Sigma; specific activity 11.8 triacetin units/mg solid.

10. Substrate 200 mg, PPL 1 g, TFEB 1 mL, solvent 4 mL (tetrahydrofuran for **1a** and tetrahydrofuran-pyridine 4:1 for **2a**), 45 °C, 288 h. PPL was kept under vacuum prior to use in order to lower the water content to 0.5%.[4] Tetrahydrofuran and pyridine were distilled just prior to use from, respectively, Na/benzophenone and calcium hydride.

11. The monoesters fractions were obtained from the crude reaction mixtures by column chromatography on silica gel eluted with toluene-acetone (3:1).

12. In the case of **2a** trace amounts of the diesters were obtained.

13. The observed regioselectivity was time-dependent: after 96 h the monoesters ratios were 5:2:93 (34% yield) for **1b:1c:1d** and 2:18:80 (26% yield) for **2b:2c:2d**. This fact might indicate that the reverse reaction is not completely negligible or, alternatively, that an acyl migration from the 4 to the 3 and 2 positions occurs to a small extent.

14. When **1a** and **2a** were reacted under the same conditions as described in note 10 except that vinyl acetate was used as the acyl carrier, reactions were very slow and less regioselective.