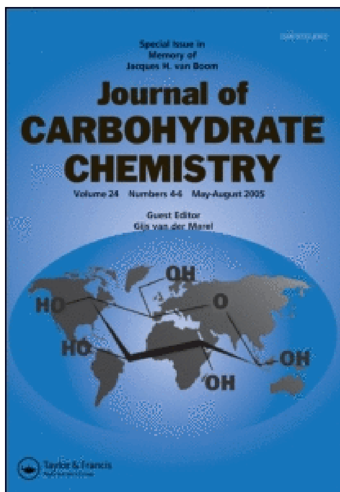
This article was downloaded by:
On: *23 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



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

Selective Acylation of 4,6-*O*-Benzylidene Glycopyranosides by Enzymatic Catalysis

Luigi Panza[a]; Monica Luisetti[a]; Emanuela Crociati[b]; Sergio Riva[b]
[a] Dipartimento di Chimica Organicae, Industriale and Centro di Studio per le Sostanze Organiche Naturali del CNR, Milano, Italy [b] Istituto di Chimica degli Ormoni, CNR, Milano, Italy

To cite this Article Panza, Luigi , Luisetti, Monica , Crociati, Emanuela and Riva, Sergio(1993) 'Selective Acylation of 4,6-*O*-Benzylidene Glycopyranosides by Enzymatic Catalysis', Journal of Carbohydrate Chemistry, 12: 1, 125 — 130
To link to this Article: DOI: 10.1080/07328309308018546
URL: http://dx.doi.org/10.1080/07328309308018546

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

J. CARBOHYDRATE CHEMISTRY, 12(1), 125-130 (1993)

COMMUNICATION

SELECTIVE ACYLATION OF 4,6-*O*-BENZYLIDENE GLYCOPYRANOSIDES BY ENZYMATIC CATALYSIS

Luigi Panza,[a*] Monica Luisetti,[a] Emanuela Crociati,[b] and Sergio Riva[b*]

[a] Dipartimento di Chimica Organica e Industriale and Centro di Studio per le Sostanze Organiche Naturali del CNR, via Venezian, 21 - 20133 Milano - Italy.[b] Istituto di Chimica degli Ormoni, CNR via Mario Bianco, 9 - 20131 Milano - Italy

Downloaded At: 10:12 23 January 2011

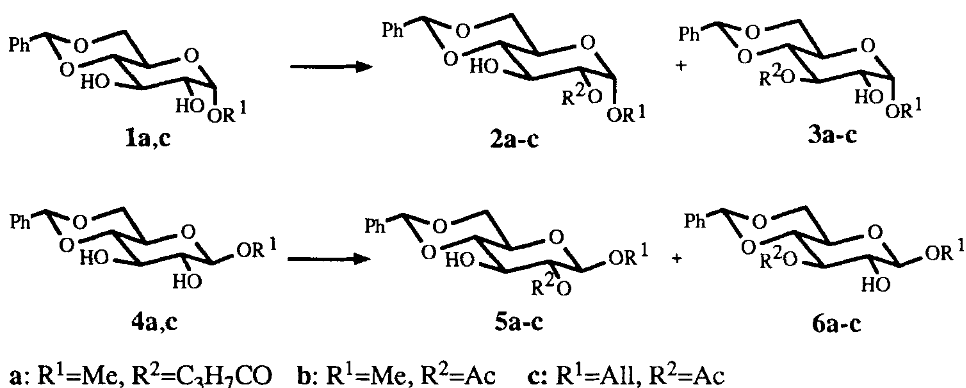
Received February 20, 1992 - Final Form September 9, 1992

Selective acylation of different hydroxyls is of great importance, and widespread applications are found in carbohydrate chemistry.[1] As protecting groups, esters offer the advantage of being easily prepared and easily removed, and accordingly, partially acylated monosaccharides have been used for the preparation of other *O*-substituted derivatives as well as for the synthesis of oligosaccharides. For this latter purpose 4,6-*O*-benzylidene-D-glycopyranosides like **1a**, once selectively modified at one of their two free hydroxy groups, are particularly suitable compounds.

Chemical esterification of these glycosides has been achieved by different approaches, exploiting either steric effects or the differences in acidity of the two hydroxyls. More specifically, acyl chlorides have been used with dialkyl stannylene acetals, trialkyltin ethers,[2] or complexes with divalent cations.[3] Other reactions have been carried out under phase transfer conditions[4-6] or using other acylating agents[7-9] or under controlled conditions.[10]

Some general trends can be extrapolated from the data in the literature. α-Glucopyranosides such as **1a** give the 2-*O*-acyl derivatives in good yields[2,3,5-8] while the corresponding β anomers **4a** prefer the 3-OH but with lower selectivity.[2,8,10] α-Galactopyranosides and α-mannopyranosides can be esterified either at the 2-OH or at the 3-OH, depending on the reaction conditions, but with poor or moderate

Copyright © 1993 by Marcel Dekker, Inc.



SCHEME 1

Downloaded At: 10:12 23 January 2011

selectivity.[2,4-6] β-Galactopyranosides can be efficiently acylated at the 3-OH.[9] To our knowledge, no data are available at present about the chemical acylation of β-mannopyranosides.

In recent years, the use of hydrolases (lipases and proteases) in aqueous or organic media has been continuously growing.[11] When applied to carbohydrates, these enzymes have shown remarkable regioselectivity of action, often allowing the isolation of monoacyl derivatives in good yields.[12]

In this paper we report the results of the use of this methodology with 4,6-*O*-benzylidene derivatives of different simple monosaccharides. A preliminary screening of the lipases we had available was performed with methyl 4,6-*O*-benzylidene-α- and β-D-glucopyranosides **1a** and **4a**, using trifluoroethyl butanoate as acylating agent.

As shown in Table 1, lipase PS (from *Pseudomonas cepacia*) was the enzyme which gave higher conversion, had the best selectivity on both anomers and, therefore, was chosen for further studies. Using this lipase, the reaction protocol was further simplified by using vinyl acetate both as solvent and acylating agent and made more reproducible by adsorbing the enzyme on celite.[13]

In a typical procedure 200 mg of **1a** in 10 ml of vinyl acetate were shaken 7 hours at 45 °C with lipase PS adsorbed on celite (1 g). HPLC analysis showed 98% conversion to a single new product. Filtration of the enzyme and evaporation of the solvent yielded 220 mg (98%) of **2b**. Under similar conditions the corresponding β anomer **4a** showed a 98% conversion to a mixture of **5b** and **6b** in a 6:92 ratio after 1 hour. Usual work-up and purification by flash-chromatography (hexane-ethyl acetate 1:1) yielded 192 mg (86%) of **6b**.

Downloaded At: 10:12 23 January 2011

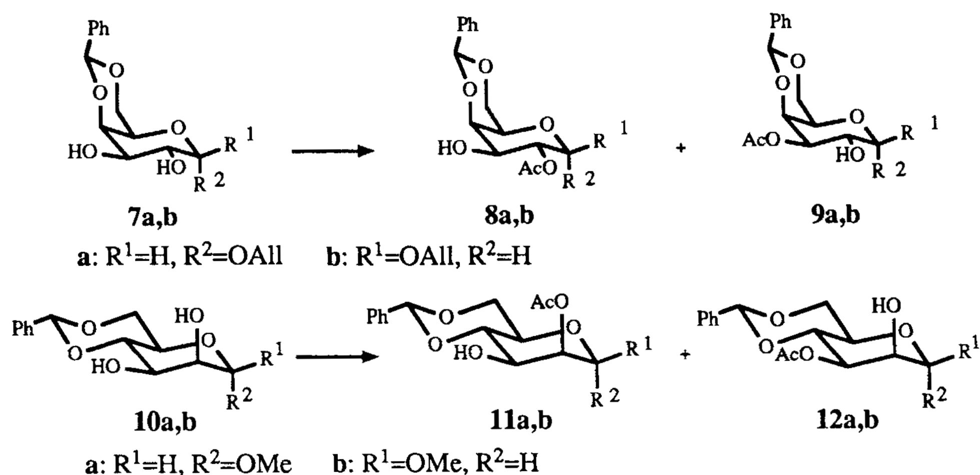
TABLE 1. Enzymatic Acylation of Methyl 4,6-*O*-Benzylidene α- and β-D-Glucopyranosides by Different Lipases.

Starting sugar	Lipase[a,b]	%Conversion[c]	% of acylation in position 2[c]	% of acylation in position 3[c]
1a	AP	0	-	-
"	CV	16	81	19
"	CC	32	84	16
"	PP	15	87	13
"	PS	85	100	0
"	G	0	-	-
4a	AP	0	-	-
"	CV	92	5	95
"	CC	33	0	100
"	PP	80	0	100
"	PS	94	5	95
"	G	0	-	-

a. The lipases were used as purchased; reaction conditions: **1a** or **4a**, 20 mg; trifluoroethyl butanoate, 100 uL; toluene-THF 4:1, 1 mL; lipase, 100 mg; molecular sieves 4 Å, 50 mg; 45 °C, 250 rpm, 18 hours.

b. AP: *Aspergillus niger* (Amano Pharmaceutical Corp.), CV: *Chromobacterium viscosum* (Finnsugar Biochemicals, INC.), CC: *Candida cylindracea* (Sigma Chemical Co.), PP: *Porcine pancreatic* (Sigma Chemical Co.), PS: *Pseudomonas cepacia* (Amano Pharmaceutical Corp.), G: *Pennicillum camembertii* (Amano Pharmaceutical Corp.).

c. Obtained by HPLC analysis: RP18 column, eluent acetonitrile -K_2HPO_4 10^{-2} M, pH 6, from 2:8 to 4:6.



SCHEME 2

TABLE 2. Lipase PS Catalyzed Acetylation of Different Benzylidene Glycopyranosides.

Starting sugar	Reaction time[a]	% 2-*O*-acetate[b]	% 3-*O*-acetate[b]	Isolated yield, % (product)[c]
1a (α-*gluco*)	7 hours	100	0	98 (**2a**)
4a (β-*gluco*)	1 hour	6	94	86 (**6b**)
1c (α-*gluco*)	7 hours	98	2	89 (**2c**)
4c (β-*gluco*)	1 hour	4	96	88 (**6c**)
7a (α-*galacto*)	4 days	0	0	-
7b (β-*galacto*)	4 days	2	98	91 (**9b**)
10a (α-*manno*)[d]	2 days	97	3	90 (**11a**)
10b (β-*manno*)	1 hour	2	98	92 (**12b**)
13	3 hours	30	70	23 + 46

a. The reaction was left until TLC showed disappearance of the starting sugar. **7a** was recovered unreacted.
b. No appreciable formation of diacetate was observed under the described reaction conditions.
c. Flash chromatography.
d. Reaction run at room temperature (~20 °C).

Downloaded At: 10:12 23 January 2011

Similar selectivities and degrees of conversion were obtained with the corresponding allyl α- or β-glucopyranosides **1c** and **4c**, which are much more useful from a synthetic point of view.

To study the scope of this methodology, we applied it to the corresponding benzylidene derivatives of galactose **7a,b** and mannose **10a,b**. Table 2 summarizes the results of acetylation of the different substrates.[14]

Some general trends can be deduced from Table 2. First of all, the nature of the sugar greatly affects the acylating power of *Pseudomonas* lipase, glucopyranosides and mannopyranosides being much more reactive than galactopyranosides.

The stereochemistry of the anomeric center greatly influences both the reactivity and the selectivity. β-Glycosides were acylated faster and preferentially at the 3-OH, while the corresponding α-anomers were acylated more slowly and preferentially at the 2-OH. The effect of the anomeric substitution on the selectivity was indirectly confirmed by the acylation of 4,6-*O*-benzylidene-D-glucose **13**, which was aspecific, giving the 3-*O* and 2-*O* acyl derivatives in about a 2:1 ratio because of the free anomeric position.

Compared to chemical acylations, this method provides selective acetylation of substrates such as the β-gluco, α- and β-manno benzylidene glycopyranosides **4a**, **8a** and **8b**, otherwise difficult to obtain, using very simple experimental conditions and even when the chemical acylation works well it can be a simple and useful alternative.

The enantioselectivity of *Pseudomonas* lipase has been widely used for resolution of racemic mixtures.[15] Here we have shown that other properties of this enzyme can be successfully exploited. The interesting relationship between the nature of the substrate and the regioselectivity of this enzyme deserves further study. Unfortunately, we cannot provide a rationale based on the interaction between these sugar derivatives and the active site of the enzyme because the tridimensional structure of *Pseudomonas* lipase has not yet been elucidated.

Work is in progress to extend the scope of the methodology to other carbohydrate derivatives.

ACKNOWLEDGMENTS

We thank italian CNR - Comitato per le biotecnologie e la biologia molecolare (Progetto speciale oligosaccaridi) for financial support.

Downloaded At: 10:12 23 January 2011

REFERENCES and FOOTNOTES

1. A. H. Haines, *Adv. Carbohydr. Chem. Biochem.*, **33**, 11 (1976).
2. S. David and S. Hanessian, *Tetrahedron*, **41**, 643 (1985) and references cited therein.
3. S. Hanessian and M. Kagotani, *Carbohydr. Res.*, **202**, 67 (1990).
4. W. Szeja, *Synthesis*, **10**, 821 (1979).
5. W. Szeja, *Carbohydr. Res.*, **115**, 240 (1983).
6. V. G. S. Box, L. L. Box and E. V. E. Roberts, *Carbohydr. Res.*, **119**, 273 (1983).
7. Y. Chapleur, B. Castro and R. Toubiana, *J. Chem. Soc., Perkin Trans 1*, 1940 (1980).
8. S. Kim, H. Chang and W. J. Kim, *J. Org. Chem.*, **50**, 1751 (1985).
9. I. F. Pelyvás, T. K. Lindhorst, H. Streicher and J. Thiem, *Synthesis,* 1015 (1991).
10. J. Stanek Jr. and J. Jary, *Liebigs Ann. Chem.*, 163 (1976).
11. a. A. Margolin, *CHEMTECH*, **21**, 160 (1991);
b. A. M. Klibanov, *Acc. Chem. Res.*, **23**, 114 (1990).
12. a. D. G. Drueckhammer, W. J. Hennen, R. L. Pederson, C. F. Barbas III, C. M. Gautheron, T. Krach and C. H. Wong, *Synthesis,* 499 (1991); b. F. Nicotra, S. Riva, F. Secundo and L. Zucchelli, *Tetrahedron Lett.*, **30**, 1703 (1989); c. S. Riva, J. Chopineau, A. P. G. Kieboom and A. M. Klibanov, *J. Am. Chem. Soc.*, **110**, 584 (1988); d. M. Therisod and A. M. Klibanov, *J. Am. Chem. Soc.,* **108**, 5638 (1986).

13. R. Bovara, C. Carrea, L. Ferrara and S. Riva, *Tetrahedron Asymmetry*, **2**, 931 (1991).

14. Selected ^{1}H NMR data ($CDCl_3$ sol.): **2a** δ 4.79 (dd, $J_{1,2}$=3.6 Hz, $J_{2,3}$=9.6 Hz, H-2); **2b** δ 4.79 (dd, $J_{1,2}$=3.8 Hz, $J_{2,3}$=9.7 Hz, H-2); **2c** δ 4.81 (dd, $J_{1,2}$=3.8 Hz, $J_{2,3}$=9.7 Hz, H-2); **6a** δ 5.22 (t, $J_{2,3}$=$J_{3,4}$=9.2 Hz, H-3); **6b** δ 5.23 (t, $J_{2,3}$=$J_{3,4}$=9.1 Hz, H-3); **6c** δ 5.22 (t, $J_{2,3}$=$J_{3,4}$=9.2 Hz, H-3); **9b** δ 4.85 (dd, $J_{2,3}$=10.1 Hz, $J_{3,4}$=3.8 Hz, H-3); **11a** δ 5.20 (dd, $J_{1,2}$=1.4 Hz, $J_{2,3}$=3.7 Hz, H-2); **12b** δ 5.05 (dd, $J_{2,3}$=3.0 Hz, $J_{3,4}$=10.3 Hz, H-3).

15. R. Kazlauskas, A. N. E. Weissfloch, A. T. Rappaport and L. A. Cuccia, *J. Org. Chem.*, **56**, 2656 (1991) and references cited therein.

Downloaded At: 10:12 23 January 2011