ELSEVIER

Carbohydrate Research 258 (1994) 293–297

CARBOHYDRATE RESEARCH

Note

Stereoselective synthesis of β-D-glycopyranosyl-L-serinate or -threoninate derivatives with an unusual migration

Lajos Szabó, Robin Polt *

Chemistry Department, University of Arizona, Tucson, Arizona 85721 USA

(Received April 29th 1993; accepted in revised form December 19th, 1993)

Stereoselective glycosylation is the most important aspect of complex carbohydrate synthesis [1–4]. Generally, 1-*O*-acyl glycopyranoses have been used only as starting materials or intermediates for glycosylation reactions. In recent years, however, there has been increased interest in acyl-glycose [5] derivatives with biological activity, i.e., glycosylated opioid peptides [6,7] and derivatives of glucuronic acids [8–11].

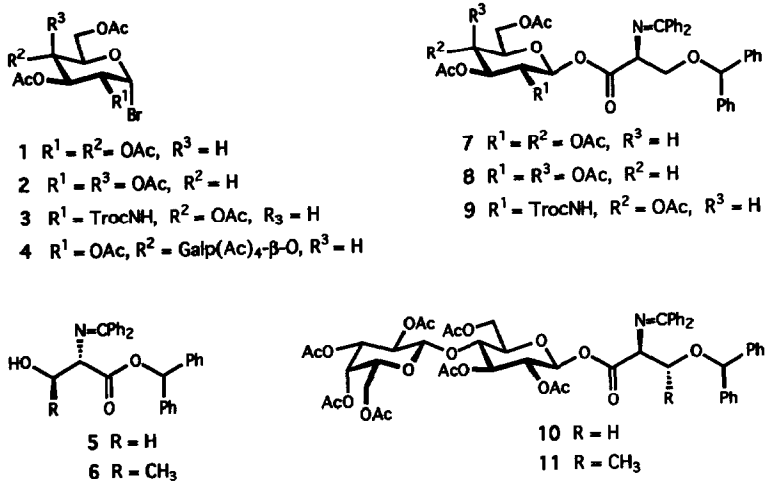
The synthesis of *O*-linked glycopeptides [2,4,12] is complicated by the acid lability of the glycosidic linkage, and the base lability of the β-hydroxy amino acid residue. Additional complications arise due to the poor nucleophilicity of the usual *N*-acylated (e.g., Boc, Cbz, Fmoc protection) serine and threonine substrates. Because of this decreased reactivity, harsh reaction conditions are required to effect glycosidic bond formation, and the yields suffer, as well as the α- vs. β-glycoside selectivity [13]. In order to avoid these problems, we have used the benzophenone Schiff base esters [14] of serine and threonine which have proved to be more reactive in both 1,2-*cis* and *trans*-glycosylations [15,16].

Various metal halides (Lewis acids) have been used as glycosylation promoters [17], but the use of $ZnCl_2$ has only been applied to very special cases – the preparation of aryl-1-thioglycosides [18], glycosides [19], and 2-amino-2-deoxy-glucopyranosides [20]. In a classic study, Lemieux studied the anomerization of glycosides in the presence of a variety of Lewis acids, including $ZnCl_2$ [21].

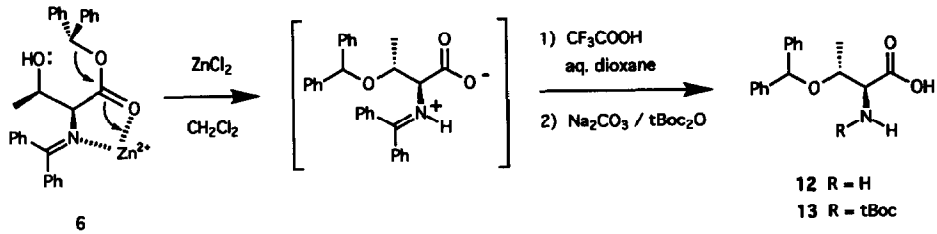
Our studies show that $ZnCl_2$ can be an efficient promoter in the synthesis of serine or threonine 1,2-*trans*-*O*-acyl-derivatives of carbohydrates via migration. In a typical procedure, a solution of acetobromo sugar (**1–4**, 1.5 mmol), fused and powdered $ZnCl_2$ (1.5 mmol), and the glycosyl acceptor (**5** and **6**, 1 mmol) in CH_2Cl_2 (10 mL) were stirred at room temperature under rigorously anhydrous

* Corresponding author.

SSDI 0008-6215(94)00006-2



Scheme 1.



Scheme 2.

Table 1
Yields and selected physical properties of β-acyl-glycoses

Entry	Aceto-bromo donor	Alcohol	Product [a]	Yield (%)	$[\alpha]_D$	R_f ($CHCl_3$)	Selected NMR parameters ($CDCl_3$)				
							H-1 δ (ppm)	$^3J_{H\text{-}1,H\text{-}2}$ (Hz)	$CHPh_2$ δ (ppm)	C-1 δ (ppm)	$^1J_{C\text{-}1,H\text{-}1}$ (Hz)
1	1	5 [16]	7	68	−71°	0.5 [b]	5.66	7.8	5.32	91.8	169.9
2	2	5	8	63	−0.4°	0.4 [c]	5.66	8.4	5.33	92.4	168.8
3	3 [23]	5	9	65	−67°	0.6 [d]	5.67	8.7	5.33	92.5	168.8
4	4	5	10	78	−27°	0.7 [e]	5.64	8.1	5.33	91.7	166.2
										100.8	158.1
5	4	6 [16]	11	76	−58°	0.7 [d]	5.68	8.1	5.52	91.4	167.5
										100.7	159.5

[a] All product were characterized by ^1H NMR (250 and 500 MHz), COSY (500 MHz), ^{13}C NMR (62.5 MHz), and FABMS. The $^1J_{C\text{-}1,H\text{-}1}$ correlated to Bock et al.'s data [24]. The yields reported are for the isolated products after SiO_2 flash chromatography. Chromatographic solvents used: [b] 62:38 C_6H_{14}–EtOAc; [c] 75:25 C_6H_{14}–EtOAc; [d] 95:5 CH_2Cl_2–acetone; [e] 65:10:25 CH_2Cl_2–C_6H_{14}–EtOAc.

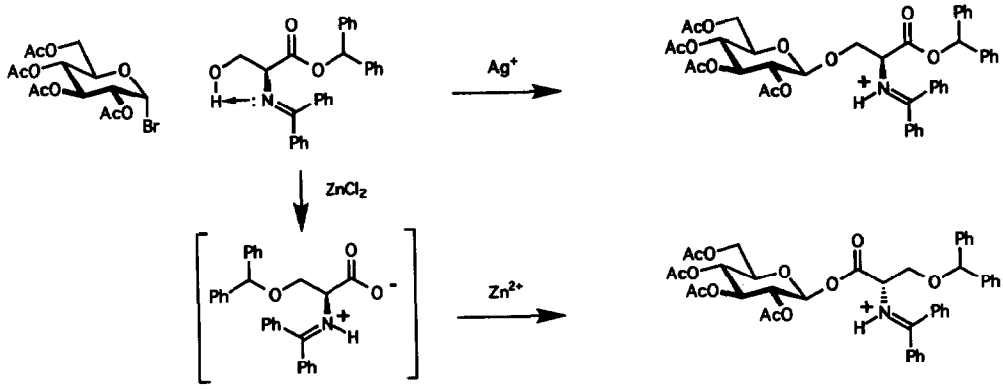
conditions for 16 h (Scheme 1, Table 1). The reaction was quenched with Et_3N (3 mmol), diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, then H_2O, dried ($MgSO_4$), and concentrated under vacuum. The residue was flash chromatographed on silica gel. The reaction conditions were not optimized.

The method is extremely stereoselective for acyl β-glycoses (> 18:1). None of the corresponding *O*-glycosides could be detected in the crude reaction mixtures by ^1H NMR (comparison with authentic β-products by ^1H NMR). Control experiments show that [diphenylmethyl-*N*-(diphenylmethylene)-L-serinate-3-yl]-2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranoside [16] was not isomerized to **7** under the same reaction conditions.

In another control experiment, threonine Schiff base **6** was treated with $ZnCl_2$, and the migration of the diphenylmethyl group was also observed *in the absence of a glycosyl donor*. While the relatively soft Ag^+ cation attacks the bromo sugar to promote normal glycosylation, the more Lewis acidic and harder Zn^{2+} cation can promote ionization of the ester moiety, perhaps via a Zn-chelate with the imine nitrogen (Scheme 2). The resonance-stabilized diphenylmethyl cation can easily migrate to the hydroxyl oxygen via a six-membered cyclic transition state. The nucleophilic carboxylate can then react with the oxocarbenium cation (oxonium ion) generated by the $ZnCl_2$.

Since α-imino acid Schiff bases can spontaneously decarboxylate in situ [22], attempts to isolate the unstable imino acid proved futile. Instead, the $Ph_2C{=}N-$ group was cleaved to provide amino acid **12**, and the amino group was reprotected to give the *t*-Boc derivative **13** using the following procedure: Schiff base **6** (225 mg) was treated with $ZnCl_2$ (108 mg, 1.5 equiv) in 5 mL CH_2Cl_2 (cf. Entries 1–5, Table 1). After 16 h the mixture was evaporated under vacuum, and the residue was dissolved in 1:1 H_2O–1,4-dioxane (2 mL), stirred with CF_3CO_2H (0.2 mL) for 15 min, then Na_2CO_3 (350 mg) and di-*tert*-butyl dicarbonate (164 mg, 1.5 equiv) were added. After stirring for 14 h the mixture was evaporated, dissolved in CH_2Cl_2 (25 mL), washed with H_2O (3 × 10 mL), dried (Na_2SO_4), evaporated and purified on a short column (9:1 CH_2Cl_2–CH_3OH) to give **13** (151 mg, 78%) as a syrup; $[\alpha]_D$ −20.1° (*c* 4.1, $CHCl_3$). ^1H NMR data ($CDCl_3$): δ 7.33–7.18 (m, 10 H, 2 Ph), 5.45 (s, 1 H, C*H*Ph_2), 5.40 (d, 1 H, $J_{NH,\alpha H}$ 9.6 Hz, NH), 4.35 (dd, 1 H $J_{\alpha H,\beta H}$ 2.1 Hz, αH), 4.15 (dq, 1 H, $J_{\beta H,Me}$ 6.2 Hz, βH), 1.46 [s, 9 H, $C(CH_3)_3$], 1.24 (d, 3 H, CH_3). ^{13}C NMR data ($CDCl_3$): δ 176.26 (COOH), 156.20 (NH–CO), 142.16 and 140.81 (quat. Ph), 128.44–126.64 (Ph), 81.00 (*C*HPh_2), 80.21 [*C*$(CH_3)_3$], 72.25 (βC), 58.24 (αC), 28.26 [C(*C*$H_3)_3$], 16.22 (CH_3). High resolution FABMS: Calcd. for $C_{22}H_{27}O_5N$: 385.1889. Found [MH^+]: 386.1893.

The lower yields in the monosaccharide cases (Table 1, Entries 1–3) is a reflection of the small R_f differences between the starting materials and products, since the mixed fractions were not re-separated and not included in the mass balance. The disaccharides (Entries 4 and 5) were more easily separated. The threonine Schiff base **6**, bearing a secondary hydroxyl group, provided the same excellent yields (Entry 5) as the protected serine **5** which bears a primary hydroxyl (Entry 4). The Troc-protected glucosamine **3** [23] also provided excellent yields of the acyl-glycose (Entry 3).



Scheme 3.

In summary, the $ZnCl_2$-catalyzed glycosylation method described is very useful since acyl-glycoses of serine or threonine can be synthesized stereoselectively from the same starting materials that have been used previously for the preparation of the corresponding β-glycosides with AgOTfl as a promoter [16]. Deprotection of the products to the free amino alcohols was easily accomplished with H_2/Pd–C.

Acknowledgments

We thank the National Science Foundation (Grant No. CHE-9201112), and Selectide Corporation of Tucson, Arizona for the financial support of this work.

References

[1] A.F. Bochkov and G.E. Zaikov, *Chemistry of the O-Glycosidic Bond: Formation and Cleavage*, Pergamon Press, Oxford, 1979, pp 1–79.
[2] H. Paulsen, *Angew. Chem. Int. Ed. Engl.*, 21 (1982) 155–173.
[3] R.R. Schmidt, *Angew. Chem. Int. Ed. Engl.*, 25 (1986) 212–235.
[4] H. Kunz, *Angew. Chem. Int. Ed. Engl.*, 26 (1987) 294–308.
[5] K. Kunz, R. Kullmann, P. Wernig, and J. Zimmer, *Tetrahedron Lett.*, 33 (1992) 1969–1972.
[6] S. Horvat, J. Horvat, D. Kantoci, and L. Varga, *Tetrahedron*, 45 (1989) 4579–4584.
[7] L. Varga-Defterdarovic, S. Horvat, N.N. Chung, and P.W. Schiller, *Int. J. Peptide Protein Res.*, 39 (1992) 12–17.
[8] D. Keglevic, N. Pravdic, and J. Tomasic, *J. Chem. Soc. C.*, (1968) 511–514.
[9] R. Bugianesi and T.Y. Shen, *Carbohydr. Res.*, 19 (1971) 179–187.
[10] A.B. Barua and J.A. Olson, *J. Lipid. Res.*, 26 (1985) 1277–1282.
[11] M. Tanaka, M. Okita, and I. Yamatsu, *Carbohydr. Res.*, 241 (1993) 81–88.
[12] H.G. Garg and R.W. Jeanloz, *Adv. Carbohydr. Chem. Biochem.*, 43 (1985) 135–201.
[13] (a) H. Kunz and M. Buchholz, *Angew. Chem. Int. Ed. Engl.*, 20 (1981) 894–895; (b) H. Kunz and H. Waldmann, *ibid.*, 23 (1984) 71–72; (c) H. Kunz and S. Birnbach, *ibid.*, 25 (1984) 360–362; (d) H. Kunz and W. Sager, *Helv. Chim. Acta*, 68 (1985) 283–287; (e) J.K.N. Jones, M.B. Perry, B. Shelton,

and D.J. Walton, *Can. J. Chem.*, 39 (1961) 1005–1016; (f) V.A. Derevitskaya, M.G. Vafina, and N.K. Kochetkov, *Carbohydr. Res.*, 3 (1967) 377–388; (g) N.J. Maeji, Y. Inoue, and R. Chujo, *ibid.*, 146 (1986) 174–176.

[14] M.J. O'Donnell and R.L. Polt, *J. Org. Chem.*, 47 (1982) 2663–2666.

[15] L. Szabó, Y. Li, and R. Polt, *Tetrahedron Lett.*, 32 (1991) 585–588.

[16] R. Polt, L. Szabó, J. Treiberg, Y. Li, and V.J. Hruby, *J. Am. Chem. Soc.*, 114 (1992) 10249–10258.

[17] J. Banoub and D.R. Bundle, *Can. J. Chem.*, 57 (1979) 2085–2090; M. Kiso and L. Anderson, *Carbohydr. Res.*, 136 (1985) 309–323.

[18] T. Shimadate, S. Chiba, K. Inouye, T. Iino and Y. Hosoyama, *Bull. Chem. Soc. Jpn.*, 55 (1982) 3552–3554.

[19] (a) P.J. Garegg, R. Johansson and B. Samuelsson, *Acta Chem. Scand. B*, 36 (1982) 249–250; (b) Y. Araki, K. Watanabe, F. Kuan, K. Itoh, N. Kobayashi, and Y. Ishido, *Carbohydr. Res.*, 127 (1984) c5–c9; (c) H. Lönn and J. Lönngren, *ibid.*, 132 (1984) 39–44. (d) E. Kallin, H. Lönn and T. Norberg, *J. Carbohydr. Chem.*, 9 (1990) 721–733; (e) S. Nilsson, H. Lönn and T. Norberg, *ibid.*, 10 (1991) 1023–1048.

[20] K. Higashi, K. Nakayama, T. Soga, E. Shioya, K. Uoto, and T. Kasama, *Chem. Pharm. Bull.*, 38 (1990) 3280–3282.

[21] R.U. Lemieux, *Adv. Carbohydr. Chem.*, 9 (1954) 1–57.

[22] R. Polt and X. Qian, unpublished results.

[23] M. Imoto, H. Yoshimura, T. Shimamoto, N. Sakaguchi, S. Kusamoto, and T. Shiba, *Bull. Chem. Soc. Jpn.*, 60 (1987) 2205–2214.

[24] K. Bock, I. Lundt, and C. Pedersen, *Tetrahedron Lett.*, 13 (1973) 1037–1040.