Carbohydrate Research 393 (2014) 23–25

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Note

Synthesis of novel 2-deoxy-β-benzyl-C-glycosides by highly stereo- and chemoselective hydrogenation of *exo*-glycals

Gisela Díaz, Agustín Ponzinibbio *, Rodolfo Daniel Bravo

Laboratorio de Estudio de Compuestos Orgánicos (LADECOR), Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata. 47 y 115, (1900) La Plata, Argentina

ARTICLE INFO

Article history:
Received 17 February 2014
Received in revised form 5 April 2014
Accepted 12 April 2014
Available online 21 April 2014

Keywords:
Wittig reaction
exo-Glycals
Hydrogenation
Palladium catalyst
C-Glycosides

ABSTRACT

Novel 2-deoxy-β-benzyl-C-glycosides were prepared in good yields and excellent stereoselectivity by a route involving the Wittig reaction of glycosyl phosphonium salts and reduction of *exo*-glycals as key steps. Hydrogenation of benzyl protected enol ethers was performed with Pd/C(en) as an effective chemoselective catalyst to afford exclusively β anomers.

C-Glycosides are an important class of bioactive molecules of extensive therapeutic potential.[1] Preliminary structure–activity studies revealed some structural features related to the potency of the cytotoxic activity. In a large series of C-glycosides screened, β equatorial configuration at anomeric carbon, unsaturated aglycons, and *O*-benzyl protective groups, led to the highest antiproliferative and apoptotic activities against human cancer cell lines.[2] The *O*-benzyl group, besides increasing cell permeability, may favor an aromatic interaction with the receptor, resulting in increased binding affinity.[3] Since glycosylarenes exhibit diverse biological activities, including antitumor and antiviral action[4] and considering the characteristics mentioned above, we decided to carry out an effective synthesis of *O*-benzyl protected β-benzyl-C-glycosides.

C-Glycosides are well known carbohydrates and different synthetic pathways for their synthesis have been described over the years.[5] C-Glycosyl compounds having a carbon—carbon double bond at the anomeric center, for example, **1a**,**b**, are less familiar compounds. In principle, such olefins could be of interest as precursors of C-glycosides if the double bond can be transformed with high stereocontrol. For a long time we have been interested in the synthesis and reactivity of glycosyl phosphonium tetrafluoroborates salts.[6] This methodology was a key step in the preparation of galactopyranosyl alanine,[7] C-disaccharides, C,O-trisaccharides,[8] 2-deoxy ketopyranoses,[9] and carbohydrate derivatives with a spiro-isoxazoline moiety.[10]

We wish to report a method for the synthesis of *exo*-glycals and their further transformation to C-glycosides by a highly stereo- and chemoselective hydrogenation.

The *exo*-glycals were prepared by the Wittig reaction of the α,β-mixture of the 2-deoxigalactosyl phosphonium salt[11] with several aromatic aldehydes to give the olefinated sugars (Scheme 1).

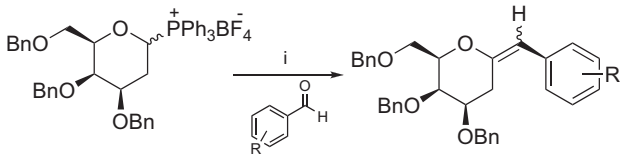
After filtration on silica gel the exocyclic enol ethers were obtained spectroscopically pure as a mixture of isomers in the yields and *E*/*Z* ratios shown in Table 1. To the best of our knowledge, compounds **1a**,**b**, **3a**,**b**, **4a**,**b**, **5a**,**b**, and **6a**,**b** were not yet described in the literature. The *E* and *Z* configurations were assigned on the basis of the chemical shift of the vinyl protons.[12] The mixture of *E* and *Z* isomers was not separated and used directly in the next steps.

The simple reduction of the double bond of *exo*-glycals has been investigated.[13] In order to obtain the desired C-glycosides we studied the *exo*-cyclic hydrogenation with Pd catalysts using *exo*-glycals **1a**,**b** and **2a**,**b** as model compounds (Scheme 2).

An *exo* cyclic double bond conjugated to an aromatic moiety requires higher hydrogen pressure conditions to be reduced than aliphatic chains.[14] Unfortunately double bond reduction without removal of benzyl-protecting groups was not achieved under mild conditions so that an intractable mixture of products was obtained.

* Corresponding author. Tel.: +54 221 4243104; fax: +54 221 4226947.
E-mail address: ponzinibbio@quimica.unlp.edu.ar (A. Ponzinibbio).

http://dx.doi.org/10.1016/j.carres.2014.04.009
0008-6215/



Scheme 1. Reagents and conditions: (i) BuLi, THF, −90 °C (1 h), −90 °C to rt (12 h).

Table 1
Wittig reaction of 2-deoxigalactosyl phosphonium salt with several aldehydes

Starting aldehydes	Product/yield	Ratio (*E*/*Z*)[a]
Benzaldehyde	**1a**,**b**/55	36/64
4-Chlorobenzaldehyde	**2a**,**b**/53	35/65
2-Chlorobenzaldehyde	**3a**,**b**/50	37/63
4-Isopropylbenzaldehyde	**4a**,**b**/55	32/68
4-(Dimethylamino)benzaldehyde	**5a**,**b**/56	39/61
4-Anisaldehyde	**6a**,**b**/58	36/64

[a] *E*/*Z* ratios determined by ^{1}H NMR of the reaction mixture.

Longer reaction times and higher hydrogen pressure promoted debenzylation and catalytic hydrodechlorination (HDC) reactions to afford the unprotected C-glycoside **9** using both **1a**,**b** and **2a**,**b** as substrates.

The development of modified Pd catalysts for chemoselective hydrogenation has been a long-standing goal in synthetic chemistry.[15] The Pd/C-ethylenediamine complex, a non pyrophoric catalyst compared to commercial Pd/C, was first prepared by Sajiki et al.[16] Catalytic hydrogenations with Pd/C(en) catalyst display good selectivity in the reduction of reducible functionalities such as olefin, acetylene, nitro, and azido in the presence of an *O*-benzyl protective group.[17] Therefore, we planned to use the Pd/C(en) as a catalyst for the chemoselective hydrogenation of the enol ether function with retention of benzyl protective groups.

At first we examined the reaction of **1a**,**b** in several solvents and pressure conditions as seen in Table 2. The results show that the hydrogenation of the *exo*-cyclic double bond proceeded smoothly with excellent yields in EtOH under 2.5 atm hydrogen pressure. The obtained C-glycosylarene was fully characterized by NMR spectroscopy. As expected, the C-glycosyl chain lies on the β face as shown by the proton coupling constants and the presence of NOE effect between H-2 and H-6. This high stereoselectivity has been previously described in the hydrogenation of *exo*-glycals.[13,18]

Encouraged by the initial results, the reaction was then carried out with a variety of *exo*-glycals under the experimental conditions shown below. (Table 3)

As seen in entries 1–4 and 7 the desired products were obtained in excellent yields and no products derived from debenzylation or hydrodechlorination reactions were detected. As expected the Pd/C(en) catalyst inhibits the halogen removal from the aromatic moiety typically produced in hydrogenations with Pd/C.[19] The

Table 2
exo-Glycal (**1a**,**b**) hydrogenation using Pd/C(en) catalyst

Pressure (atm)	Solvent	Cat.[a] (wt %)	Time (h)	Yield (%)
1	THF	10	12	0
1	THF	25	12	0
2,5	THF	10	3	76
2,5	MeOH	10	3	82
2,5	MeOH	25	3	85
2,5	EtOH	10	3	95

[a] Prepared as previously reported.[19]

Table 3
Stereo- and chemoselective catalytic hydrogenation of *exo*-glycals

Entry	*exo*-Glycal	Pd catalyst	Product	Yield (%)
1	**1a**,**b**	Pd/C(en)	7	95
2	**2a**,**b**		8	97
3	**3a**,**b**		10	90
4	**4a**,**b**		11	94
5	**5a**,**b**		**5a**,**b**	—
6	**5a**,**b**	Pd/C 5%	12	91
7	**6a**,**b**	Pd/C(en)	13	97

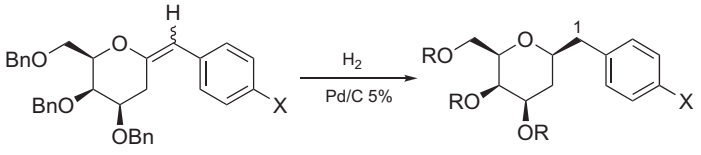
hydrogenation reaction of *exo*-glycals **5a**,**b** described above failed due to the poisoning effect of reagents over the palladium catalyst,[20] the reaction was successfully accomplished with Pd/C 5% in EtOH at 2.5 atm. Here again, the double bond reduction proceeded with high stereocontrol, compound **12** being obtained as a single anomer in excellent yields.

In conclusion, our methodology allowed us to prepare C-glycosides in very good yields and excellent stereoselectivity from *exo*-glycals. We have used an effective and chemoselective hydrogenation method with retention of benzyl protective groups using Pd/C(en) as a catalyst in EtOH under which enol ethers were easily hydrogenated. Further applications of the above method for the synthesis of various C-glycosides linked to a heterocyclic moiety will be presented in due course. Also studies on the antiproliferative activity against human hepatocellular liver carcinoma (HepG2) and human lung adenocarcinoma (A549) cell lines are currently in progress.[21]

1. Experimental

1.1. General

Thin layer chromatography (TLC) was performed on Merck 60 F_{254} plates. Reactions were monitored by TLC on silica gel, with detection by UV light (254 nm) or by charring with sulfuric acid. Flash chromatography was performed using silica gel (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 200 (200.055 and 50.309 MHz, respectively) using Me_4Si as



1a,b X = H
2a,b X = Cl

7 X = H, R = Bn
8 X = Cl, R = Bn
9 X = H, R = H

Scheme 2. Formation of C-glycosides by hydrogenation of *exo*-glycals **1a**,**b** and **2a**,**b**.

the internal standard in $CDCl_3$ or DMSO-d_6. HSQC and COSY spectra were used to establish peak assignments in ^1H and ^{13}C NMR. High-resolution mass spectra were recorded on a Finnigan Model MAT 95 mass spectrometer. Tetrahydrofuran (THF) was refluxed with sodium and benzophenone until a characteristic blue color was evident and then fractionally distilled. All reactions sensitive to moisture were carried out under argon atmosphere using oven-dried glassware. The hydrogenation experiments were performed in a glass reactor.

1.2. Wittig reaction

To a suspension of (3,4,6-tri-*O*-benzyl-2-deoxy-αβ-D-galactopyranosyi)-triphenylphosphonium tetrafluoroborate (770 mg, 1 mmol) in abs THF (5 mL) at −90 °C, *n*-BuLi (625 L, 1.6 M in hexane, 1 mmol) was added over a period of 5 min. A solution of benzaldehyde (107 mg, 1 mmol) in abs THF (2 mL) was added over a period of 10 min and the reaction was kept for 1 h at −90 °C and then allowed to come to room temperature overnight. After evaporation in vacuo the solution of the residue in ethyl acetate was washed twice with $NaHCO_3$ (5%), twice with water, dried over $MgSO_4$, and concentrated in vacuo. The oily residue was treated with ethyl acetate/diethyl ether and then filtrated to separate off the triphenylphosphine oxide. After evaporation of the solvent in vacuo the residue was chromatographed on silica gel (eluent: hexane/ethyl acetate 8:2, containing 0.1% triethylamine) to afford **1a**,**b** as spectroscopically pure oil (458 mg, 55%, mixture *E*/*Z* = 15:85).

1.3. Hydrogenation procedure using Pd/C as catalyst

After three vacuum/H_2 cycles to replace air inside the reaction tube with hydrogen, the substrate (0.25 mmol) and 5% Pd/C (10 wt % of the substrate) were mixed in THF, MeOH, or EtOH (1.0 mL) and then vigorously stirred at room temperature under 2 atm of hydrogen for 12 h. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated in vacuo to afford a white solid.

1.3.1. *C*-Benzyl 2-deoxy-β-D-galactopiranoside (9)

White solid. ^1H NMR: (200 MHz, DMSO-d_6) δ: 1.24–1.60 (m, 2H, 3-H), 2.56 (dd, 1H, J = 6.8, J = 13.4, 1-Ha), 2.83 (dd, 1H, J = 6.3, J = 13.4, 1-Hb), 3.25–3.59 (m, 6H, 5-H, 4-H, 6-H, 7-H), 3.85–4.98 (vbs, 3H, –OH), 7.07–7.33 (m, 20H, Ph). ^{13}C NMR: (50,3 MHz, DMSO-d_6) δ: 34.7 (C-3), 42.4 (C-1), 61.6 (C-7), 67.6 (C-5), 69.6, 76.7, 79.6 (C-2, C-4, C-6), 126.6, 128.8, 129.9, 139.2 (Ph). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61; O, 26.86. Found: C, 65.53; H, 7.61; O, 26.86.

1.4. General procedure for the hydrogenation using Pd/C(en) as catalyst

After three vacuum/H_2 cycles to replace air inside the reaction tube with hydrogen, the mixture of substrate (0.25 mmol) and 5% Pd/C(en) (10 wt % of the substrate) in EtOH (1.0 mL) was vigorously stirred at room temperature under 2.5 atm of hydrogen for 3 h. The reaction mixture was then filtered through a pad of celite, and the filtrate was concentrated in vacuo to afford an oil. The crude product was chromatographed on silica gel (eluent: hexane/ethyl acetate 8:2 containing 0.1% triethylamine) to give the pure product as a colorless syrup.

1.4.1. *C*-Benzyl 3,4,6-tri-*O*-benzyl-2-deoxy-β-D-galactopiranoside (7)

Colorless syrup. ^1H NMR: (200 MHz, CD_3Cl) δ: 1.63–1.95 (m, 2H, 3-H), 2.63 (dd, 1H, J = 7.1, J = 13.7, 1-Ha), 2.98 (dd, 1H, J = 6.2, J = 13.7, 1-Hb), 3.35–3.56 (m, 5H, 4-H, 6-H, 7-H), 3.77 (br s, 1H, 5-H), 4.35 (s, 1H, CH_2Ph), 4.37 (s, 1H, CH_2Ph), 4.45 (s, 2H, CH_2Ph), 4.58 (AB, 1H, J = 11.8, CH_2Ph), 4.85 (AB, 1H, J = 11.8, CH_2Ph), 7.07–7.33 (m, 20H, Ph). ^{13}C RMN: (50,3 MHz, CD_3Cl) δ: 32.4 (C-3), 42.5 (C-1), 70.1 (C-7), 70.4 (CH_2Ph), 72.6 (C-5), 73.7 (CH_2Ph), 74.4 (CH_2Ph), 77.7, 79.2, 77.9 (C-2, C-4, C-6), 126.4–129.7 (Ph), 138.4 (C-Ph), 138.6 (C-Ph), 138.7 (C-Ph), 139.2 (C-Ph). Anal. Calcd for $C_{34}H_{36}O_4$: C, 80.28; H, 7.13; O, 12.58. Found: C, 80.28; H, 7.13; O, 12.58.

Acknowledgment

Authors wish to thank Comisión de Investigaciones Científicas de la Provincia de Buenos Aires (CICPBA), UNLP and CONICET for their financial support to the present work.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres. 2014.04. 009. These data include MOL files and InChiKeys of the most important compounds described in this article.

References

1. Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300–2324.
2. Sanhueza, C. S.; Mayato, C.; García-Chicano, M.; Díaz-Peñate, R.; Dorta, R. L.; Vázquez, J. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4223–4227.
3. Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210–1250.
4. Suzuki, K.; Matsumoto, T. In *Synthesis of Glycosylarenes in Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp 527–542.
5. For review see: (a) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Elsevier Science: Amsterdam, 1995; (b) Postema, M. H. D. *C-Glycoside Synthesis*; CRC: USA, 1995. p 8476; (c) Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1–54; (d) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55–83; (e) Sinay, P. *Pure Appl. Chem.* **1997**, *69*, 459–464; (f) Du, Y.; Lindhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913–9959.
6. Lieberknecht, A.; Griesser, H.; Bravo, R. D.; Colinas, P. A.; Grigera, R. J. *Tetrahedron* **1998**, *54*, 3159–3168.
7. Lieberknecht, A.; Griesser, H.; Krämer, B.; Bravo, R. D.; Colinas, P. A.; Grigera, R. J. *Tetrahedron* **1999**, *55*, 6475–6482.
8. Colinas, P. A.; Ponzinibbio, A.; Lieberknecht, A.; Bravo, R. D. *Tetrahedron Lett.* **2003**, *44*, 7985–7988.
9. Ponzinibbio, A.; Colinas, P. A.; Lieberknecht, A.; Bravo, R. D. *Lett. Org. Chem.* **2006**, *3*, 459–462.
10. Colinas, P. A.; Jäger, V.; Lieberknecht, A.; Bravo, R. D. *Tetrahedron Lett.* **2003**, *44*, 1071–1074.
11. Frey, W.; Lieberknecht, A.; Griesser, H.; Bravo, R. D.; Colinas, P. A.; Grigera, R. J. *Z. Kristallogr.—New Cryst. Struct.* **1998**, *213*, 75–76.
12. The chemical shift of the vinyl protons was assigned according to increment calculations carried out for olefinic compounds. See: (a) Pascual, C.; Meier, J.; Simon, W. *Helv. Chim. Acta* **1969**, *49*, 164–168; (b) Pretsch, E.; Buhlmann, P.; Affolter, C. *Structure Determination of Organic Compounds*, 3rd English ed.; Springer Verlag: Berlin, 2000. Also the assignment was confirmed by comparison with earlier *exo*-glycals prepared by us. See: Refs. 5,8.
13. Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263–292.
14. Novoa, A.; Pellegrini-Moïse, N.; Lamandé-Langle, S.; Chapleur, Y. *Tetrahedron Lett.* **2009**, *50*, 6484–6487.
15. (a) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley-Interscience: New York, 2001; (b) Hudlickey, M. *Reductions in Organic Chemistry*, 2nd ed.; American Chemical Society: Washington, DC, 1996; (c) Rylander, P. N. *Hydrogenation Methods*, 3rd ed.; Academic: New York, 1985.
16. Sajiki, H.; Hattori, K.; Hirota, K. *J. Org. Chem.* **1998**, *63*, 7990–7992.
17. Sajiki, H.; Hirota, K. J. *Synth. Org. Chem.* **2001**, *59*, 109–120. and references cited therein.
18. Belica, P. S.; Franck, R. W. *Tetrahedron Lett.* **1998**, *39*, 8225–8228.
19. Further studies on the catalytic hydrogenation without dehalogenation of halonitrobenzenes to the corresponding haloanilines with Pd/C(en) are still ongoing, and the results will be reported in due course.
20. Sajiki, H.; Hirota, K. *Tetrahedron Lett.* **1998**, *54*, 13981–13996.
21. Crespo, R.; De Bravo, M. G.; Colinas, P. A.; Bravo, R. D. *Bioorg. Med. Chem. Lett.* **2010**, *22*, 6469–6471.