Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6111–6116

TETRAHEDRON LETTERS

Stereoselective synthesis of substituted *exo*-glycals from 1-*exo*-methylene pyranoses

Ana M. Gómez,* Ana Pedregosa, Serafín Valverde and J. Cristóbal López*

Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain

Received 14 April 2003; revised 9 June 2003; accepted 9 June 2003

Abstract—Halo-*exo*-glycals of the *gluco*-, *manno*- and *galacto*- series, readily prepared by reaction of 1-*exo*-methylene pyranoses with iodonium dicollidinium triflate (IDCT), undergo Suzuki or B-alkyl Suzuki cross-coupling reactions with boronic acids or alkyl boranes to yield, in a stereoselective manner, functionalized *exo*-glycals.

1-*exo*-Methylene pyranoses (2,6-anhydro-1-deoxyhept-1-enitols), currently known as *exo*-glycals, **1**,[1–3] are interesting compounds from a biological and from a synthetic standpoint (Scheme 1). They have been used as glycosidase inhibitors,[4] and have proven to be valuable synthetic intermediates owing to the versatility supplied by the enol ether double bond for further elaboration.[5–15] The first methods for the preparation of *exo*-glycals had focused on the methylenation of the corresponding lactones using the Tebbe, or Petasis, reagents.[1,2,16] Very recently, Tóth and Somsák[17] have described a novel method for the preparation of **1**. However, the preparation of substituted *exo*-glycals, **2**, also of considerable interest, has only been addressed recently. Contributions in this area include: Wittig olefination of glycosyl phosponium salts[18] or sugar lactones,[19] Keck reaction of glycosyl dihalides,[20] [2,3]-Wittig sigmatropic rearrangement,[21] nucleophilic addition to sugar lactones followed by elimination[22] and Ramberg–Bäcklund rearrangement of *S*-glycosides.[23,24] The latter approach, reported independently by the groups of Taylor[23] and Franck,[24] is the most general in terms of scope.[23b]

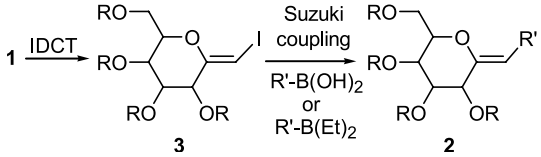
Scheme 1. *exo*-Glycal (**1**) and substituted *exo*-glycal (**2**).

In this context, we have reported two methods for the preparation of substituted furanosidic *exo*-glycals (2,5-anhydro-1-deoxyhex-1-enitols),[25,26] and in this Letter, we report on the extension of one of these strategies[26] for the stereoselective preparation of pyranosidic *exo*-glycals.

The approach is based on the stereoselective iodination of *exo*-glycals with IDCT (iodonium dicollidinium triflate),[27] followed by Suzuki,[28] or B-alkyl Suzuki[29] cross-coupling reaction of the ensuing halo-glycals, **3**, with boronic acids or alkyl boranes, respectively (Scheme 2). We illustrate the potential of the method with the preparation of substituted *exo*-glycals derived from D-*gluco*-, D-*manno*- and D-galactopyranose.

Accordingly, methylenation of lactones **4**–**6**,[30] with the Petasis reagent,[31] generated *exo*-glycals, **7**,[2,32] **8**,[16b] **9**,[33] which upon treatment with IDCT[27] yielded halo-*exo*-glycals **10**,[6] **11**, and **12** (Scheme 3).

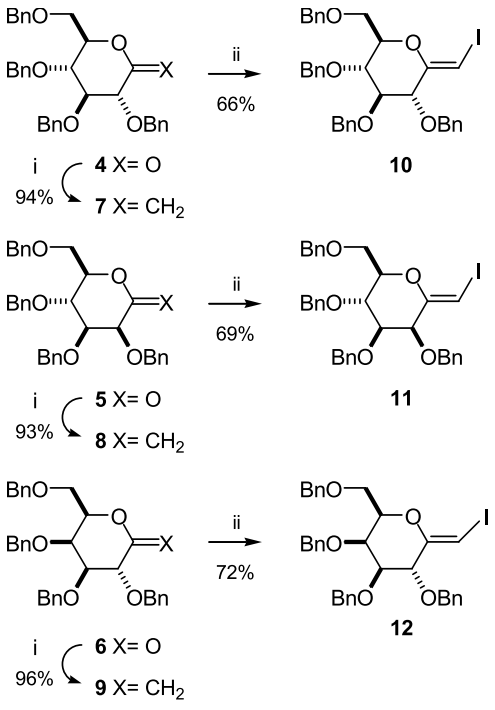
In order to evaluate the scope of the synthetic method we chose diethyl borane, **13**, and boronic acids **14**–**16** (Fig. 1) as coupling partners for the halo-*exo*-glycals



Scheme 2. General strategy for the preparation of substituted *exo*-glycals from 1-*exo*-methylene pyranoses.

* Corresponding author. Tel.: +34-91-5622900; fax: +34-91-5644853; e-mail: anago@iqog.csic.es; clopez@iqog.csic.es

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01455-2



Scheme 3. Synthesis of halo-*exo*-glycals, **10–12**, from lactones, **4–6**, by methylenation and halogenation. *Reagents and conditions*: (i) Cp_2TiMe_2 (Petasis reagent), toluene; (ii) IDCT, CH_2Cl_2.

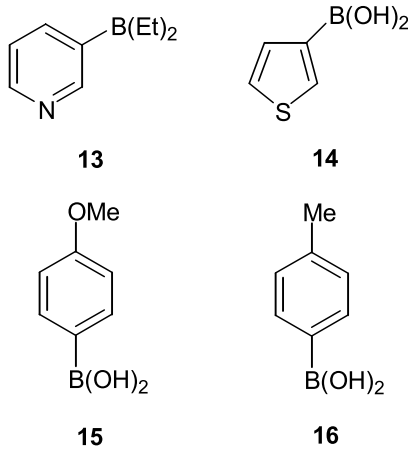


Figure 1.

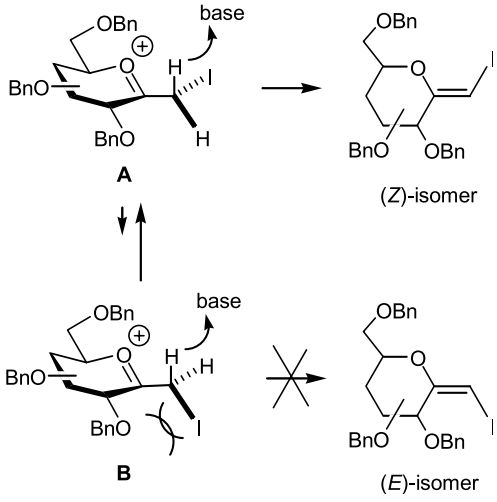
(**10–12**) in the B-alkyl- and Suzuki cross-coupling reactions, respectively. Our results are displayed in Table 1.

The B-alkyl Suzuki cross-coupling reaction of alkyl borane **13**, with halo-*exo*-glycals **10–12**, was carried out with $Pd(PPh_3)_4$ in the presence of NaOH, in THF/H_2O (9:1), and afforded good yields of coupled products (**17–19**) in short reaction times (entries *i–iii*, Table 1). For the Suzuki cross-coupling reactions we evaluated three different sets of experimental conditions (B, C, and D, Table 1). We have found slight differences in terms of yields, and significant differences in reaction times depending on the reaction conditions employed. The use of KF as a base, as recommended by Fu and co-workers,[34] resulted in higher yields and reduced reaction times (compare entries *vii* and *viii*; *ix* and *x*; *xii*, *xiii* and *xiv*; *xvii* and *xviii*, Table 1).

The stereochemistry at the terminal position of the exocyclic double bond was assigned as (*Z*-) for compounds **17**, **18**, **19** and **21** on the basis of observed NOEs between the vinylic protons (1-H) and the 3-H protons and assumed, by analogy, to be the same for the rest of the compounds. This assignment is in agreement with mechanistic considerations on the preferred formation of a (*Z*)-iodide isomer (Scheme 4), and with the fact that Suzuki cross-coupling reactions take place with retention of the configuration.[28]

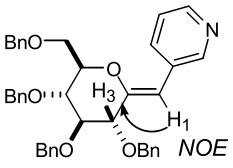
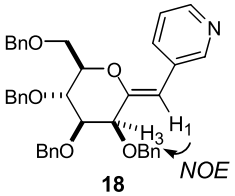
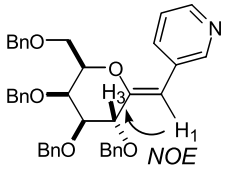
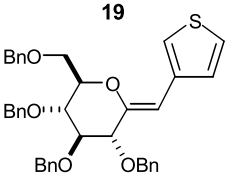
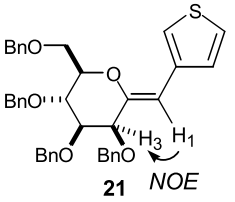
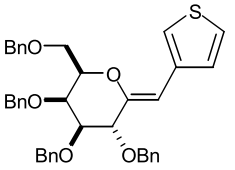
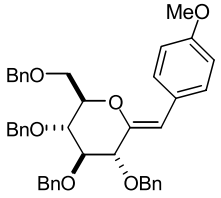
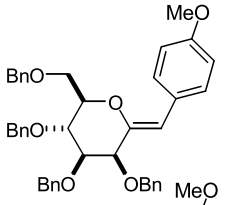
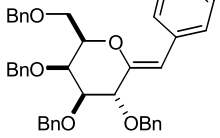
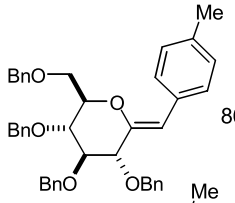
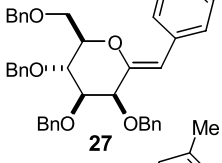
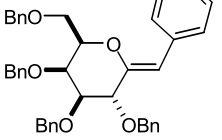
Thus, formation of (*Z*)-halo-*exo*-glycals is considered to proceed via an intermediary oxonium ion. Accordingly, the in-situ released *sym*-collidine would abstract a proton from a 1-iodomethyloxocarbenium ion to generate the iodo-*exo*-glycal. The deprotonation would take place from a preferred conformer (**A**, Scheme 4) which has a C–H bond antiperiplanar to the *p*-orbitals of the oxocarbenium and that would place the bulky iodine atom away from the benzyl substituent at C-2.[22c]

In summary, we have disclosed a novel synthetic route that permits the transformation of, readily available, 1-*exo*-methylene pyranoses into substituted (*Z*)-*exo*-glycals through a synthetic sequence, which involves: stereoselective halogenation with IDCT, followed by Suzuki, or B-alkyl Suzuki, cross coupling reaction.[35–37] The use of KF in the Suzuki cross coupling reaction results in reduced reaction times and good to excellent yields. Further synthetic transformation of the substituted *exo*-glycals are under study and will be reported in due course.



Scheme 4. Preferred formation of a (*Z*)-halo isomer.

Table 1.

Entry	Halo-glycal	Coupling partner	Reaction conditions and time	Product	Yield (%)
i	**10**	**13**	*A*[a]; 3h	 **17**	89
ii	**11**	**13**	*A;* 3h	 **18**	82
iii	**12**	**13**	*A;* 4h	 **19**	77
iv	**10**	**14**	*B*[a]; 3h	 **20**	72
v	**11**	**14**	*B;* 2h	 **21**	69
vi	**11**	**14**	*C*[a]; 24h	**21**	68
vii	**12**	**14**	*B;* 1h	 **22**	79
viii	**12**	**14**	*C;* 24h	**22**	72
ix	**10**	**15**	*B;* 5h	 **23**	88
x	**10**	**15**	*D;* 24h	**23**	75
xi	**11**	**15**	*C;* 24h	 **24**	73
xii	**12**	**15**	*B;* 3h	 **25**	78
xiii	**12**	**15**	*C;* 24h	**25**	74
xiv	**12**	**15**	*D*[a]; 48h	**25**	66
xv	**10**	**16**	*B;* 2h	 **26**	86
xvi	**11**	**16**	*C;* 24h	 **27**	76
xvii	**12**	**16**	*B;* 5h	 **28**	84
xviii	**12**	**16**	*C;* 24h	**28**	77

a) Reaction conditions: (*A*) NaOH (3 equiv.), alkyl borane (1.3 equiv.), $Pd(PPh_3)_4$ (10%), THF:H_2O (9:1), reflux. (*B*) KF (3 equiv.), boronic acid (1.3 equiv.), $Pd(PPh_3)_4$ (10%), THF, reflux. (C) $Ba(OH)_2$, boronic acid (1.3 equiv.), $Pd(PPh_3)_4$ (10%), DME:H_2O (8:2), reflux. (*D*) K_2CO_3, boronic acid (1.3 equiv.), $Pd(PPh_3)_4$ (10%), DME, reflux.

Acknowledgements

Generous financial support from Janssen-Cilag is gratefully acknowledged. This research was supported with funds from the Dirección General de Enseñanza Superior (Grants: PB96-0822, PB97-1244, PPQ2000-1330, and BQU2001-0582). A.P. thanks Janssen-Cilag for financial support.

References

1. Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett*. **1984**, *25*, 395.
2. Rajanbabu, T. V.; Reddy, G. S. *J. Org. Chem*. **1986**, *51*, 5458.
3. For a review, see: Taylor, R. J. K. *Chem. Commun*. **1999**, 217.
4. (a) Brockhaus, M.; Lehmann, J. *Carbohydr. Res*. **1977**, *53*, 349; (b) Lehmann, J.; Schwesinger, B. *Carbohydr. Res*. **1982**, *107*, 43; (c) Fritz, H.; Lehmann, J.; Schlesselmann, P. *Carbohydr. Res*. **1983**, *113*, 71; (d) Hehre, E. J.; Brewer, C. F.; Uchiyama, T.; Schlesselmann, P.; Lehmann, J. *Biochemistry* **1980**, *19*, 3557.
5. Thiem, J.; Kleeberg, M. *Carbohydr. Res*. **1990**, *205*, 333.
6. Noort, D.; Veeneman, G. H.; Boons, G.-J. P. H.; van der Marel, G. A.; Mulder, G. J.; van Boom, J. H. *Synlett* **1990**, 205.
7. (a) Nicotra, F.; Panza, L.; Russo, G. *Tetrahedron Lett*. **1991**, *32*, 4035; (b) Lay, L.; Nicotra, F.; Panza, L.; Russo, G.; Caneva, E. *J. Org. Chem*. **1992**, *57*, 1304; (c) Lay, L.; Nicotra, F.; Panza, L.; Russo, G. *Synlett* **1995**, 167; (d) Cipolla, L.; Liguori, L.; Nicotra, F.; Torri, G.; Vismara, E. *Chem. Commun*. **1996**, 1253; (e) Lay, L.; Nicotra, F.; Panza, L.; Russo, G.; Sello, G. *J. Carbohydr. Chem*. **1998**, *17*, 1269.
8. Link, J. T.; Gallant, M.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1993**, *115*, 3782.
9. Gervay, J.; Flaherty, T. M.; Holmes, D. *Tetrahedron* **1997**, *53*, 16335.
10. (a) Johnson, C. R.; Johns, B. A. *Synlett* **1997**, 1406; (b) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc*. **1997**, *119*, 4856.
11. (a) Alcaraz, M.-L.; Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Lett*. **1998**, *39*, 8183 and references cited therein; (b) Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Angew. Chem., Int. Ed*. **1999**, *38*, 2939; (c) Campbell, A. D.; Paterson, D. E.; Raynham, T. M.; Taylor, R. J. K. *Chem. Commun*. **1999**, 1599; (d) Paterson, D. E.; Griffin, F. K.; Alcaraz, M.-L.; Taylor, R. J. K. *Eur. J. Org. Chem*. **2002**, 1323.
12. Haase, W. C.; Nieger, M.; Dötz, K. H. *Chem. Eur. J*. **1999**, *5*, 2014.
13. Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett*. **1999**, *1*, 1075.
14. (a) Yang, G.; Franck, R. W.; Byun, H.-S.; Bittman, R.; Samadder, P.; Arthur, G. *Org. Lett*. **1999**, *1*, 2149; (b) Pasetto, P.; Chen, X. C.; Drain, M.; Franck, R. W. *Chem. Commun*. **2000**, 81.
15. Gallos, J. K.; Sarli, V. C.; Koftis, T. V.; Coutouli-Argyropoulou, E. *Tetrahedron Lett*. **2000**, *41*, 4819.
16. (a) Ali, M. H.; Collins, P. M.; Overend, W. G. *Carbohydr. Res*. **1990**, *205*, 428; (b) Csuk, R.; Glänzer, B. I. *Tetrahedron* **1991**, *47*, 1655; (c) Audrechy, A.; Sinaÿ, P. *J. Org. Chem*. **1992**, *57*, 4142; (d) Faivre-Buet, V.; Eynard, I.; Nga, H. N.; Descotes, G.; Grouiller, A. *J. Carbohydr. Chem*. **1993**, *12*, 349.
17. Tóth, M.; Somsák, L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 942.
18. (a) Ousset, J. B.; Mioskowski, C.; Yang, Y.-L.; Falck, J. R. *Tetrahedron Lett*. **1984**, *25*, 5903; (b) Lieberknecht, A.; Griesser, H.; Bravo, R. D.; Colinas, P. A.; Grigera, R. J. *Tetrahedron* **1998**, *54*, 3159.
19. (a) Lakhrissi, M.; Chapleur, Y. *J. Org. Chem*. **1994**, *59*, 5752; (b) Lakhrissi, M.; Chapleur, Y. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 750; (c) Molina, A.; Czernecki, S.; Xie, J. *Tetrahedron Lett*. **1998**, *39*, 7507; (d) Xie, J.; Molina, A.; Czernecki, S. *J. Carbohydr. Chem*. **1999**, *18*, 481.
20. (a) Praly, J.-P.; Chen, G.-R.; Gola, J.; Hetzer, G.; Raphoz, C. *Tetrahedron Lett*. **1997**, *38*, 8185; (b) Praly, J.-P.; Chen, G.-R.; Gola, J.; Hetzer, G. *Eur. J. Org. Chem*. **2000**, 2831.
21. Lay, L.; Meldal, M.; Nicotra, F.; Panza, L.; Russo, G. *J. Chem. Soc., Chem. Commun*. **1997**, 1469.
22. (a) Yang, W.-B.; Chang, C.-F.; Wang, S.-H.; Teo, C.-F.; Lin, C.-H. *Tetrahedron Lett*. **2001**, *42*, 4657; (b) Yang, W.-B.; Bu, C.-Y.; Chang, C.-C.; Wang, S.-H.; Teo, C.-F.; Lin, C.-H. *Tetrahedron Lett*. **2001**, *42*, 6907; (c) Yang, W.-B.; Yang, Y.-Y.; Gu, Y. F.; Wang, S.-H.; Chang, C.-C.; Lin, C.-H. *J. Org. Chem*. **2002**, *67*, 3773.
23. (a) Griffin, F. K.; Murphy, P. V.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Lett*. **1998**, *39*, 8179; (b) Griffin, F. K.; Paterson, D. E.; Murphy, P. V.; Taylor, R. J. K. *Eur. J. Org. Chem*. **2002**, 1305.
24. Belica, P. S.; Franck, R. W. *Tetrahedron Lett*. **1998**, *39*, 8225.
25. Gómez, A. M.; Pedregosa, A.; Valverde, S.; López, J. C. *Chem. Commun*. **2002**, 2022.
26. Gómez, A. M.; Danelón, G. O.; Pedregosa, A.; Valverde, S.; López, J. C. *Chem. Commun*. **2002**, 2024.
27. Veeneman, G. H.; Van Leeuwen, S. H.; Zuurmond, H.; Van Boom, J. H. *J. Carbohydr. Chem*. **1990**, *9*, 783.
28. (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457; (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; VCH: Weinheim, 1998; pp. 49–97; (c) Suzuki, A. *J. Organomet. Chem*. **1999**, *576*, 147.
29. Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **2001**, *40*, 4544.
30. Overkleeft, H. S.; van Wiltenburg, J.; Pandit, U. *Tetrahedron* **1994**, *50*, 4215.
31. Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc*. **1990**, *112*, 6392.
32. Lancelin, J.-M.; Pougny, J.-R.; Sinaÿ, P. *Carbohydr. Res*. **1985**, *136*, 369.
33. Cipolla, L.; Liguori, L.; Nicotra, F.; Torri, G.; Vismara, E. *J. Chem. Soc., Chem. Commun*. **1996**, 1253.
34. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc*. **2000**, *122*, 4020.

35. *General procedure for the B-alkyl Suzuki cross-coupling reaction*: To a solution of the halo-*exo*-glycal (100 mg, 0.15 mmol) in THF/H_2O (9:1) were added 2 M NaOH solution (2.3 equiv.) and alkyl borane **13** (1.3 equiv.). Argon was then bubbled through the solution for 10 min and $Pd(PPh_3)_4$ (10%, 0.015 equiv.) was next added. The reaction mixture was heated at reflux, under an argon atmosphere, for the time indicated in Table 1. The reaction mixture was then allowed to cool and extracted with EtOAc. The organic layer was dried (anhydrous $MgSO_4$), filtered and concentrated. Flash chromatography of the residue (hexane:EtOAc) furnished the corresponding substituted glycal.
36. *General procedure for the Suzuki cross-coupling reaction*: To a solution of the halo-*exo*-glycal (75 mg, 0.11 mmol) in THF were added the corresponding boronic acid (1.3 equiv.) and KF (3.3 equiv.). Argon was then bubbled through the solution for 10 min, after which time $Pd(PPh_3)_4$ (10%, 0.015 equiv.) was added. The reaction mixture was heated at reflux, under argon, for the time indicated in Table 1. Work-up as above then furnished the expected glycals.
37. *Data for selected compounds*:
(*Z*)-2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(3-pyridyl)-D-*gluco*-hept-1-enitol (**17**). 74 mg (89%): α_D = +53.4 ($CHCl_3$, *c* 1.1); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.64–3.81 (m, 4H), 3.94–3.96 (m, 1H), 4.04–4.10 (m, 1H), 4.42–4.71 (m, 8H), 5.55 (s, 1H), 7.03 (dd, 1H, *J* = 4.8 and 8.0 Hz), 7.07–7.30 (m, 20H), 8.07 (ddd, 1H, *J* = 1.6, 2.0 and 8.0 Hz), 8.27 (dd, 1H, *J* = 1.6 and 4.8 Hz), 8.56 (d, 1H, *J* = 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 69.2, 72.0, 73.6, 73.7, 74.2, 77.0, 77.9, 79.0, 84.3, 106.0, 123.4, 127.9, 128.0, 128.1 (×2), 128.2, 128.6, 128.7, 129.0 (×2), 131.4, 135.5, 137.8, 138.2 (×2), 147.3, 150.0, 151.5. API-ES positive: 614.1 $[MH]^+$. Anal. calcd for $C_{40}H_{39}NO_5$: C, 78.28; H, 6.40. Found: C, 78.53; H, 6.61.
(*Z*)-2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(3-pyridyl)-D-*manno*-hept-1-enitol (**18**). 75 mg (82%): α_D = +17.5 ($CHCl_3$, *c* 1.6); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.75 (dd, 1H, *J* = 3.2, and 8.8 Hz), 3.84 (m, 3H), 4.14 (d, 1H, *J* = 3.2 Hz), 4.21 (dd, 1H, *J* = 8.8 and 9.0 Hz), 4.60 (m, 6H), 4.80 (d, 1H, *J* = 12.4 Hz), 4.97 (d, 1H, *J* = 10.9 Hz), 5.56 (s, 1H), 7.08 (dd, 1H, *J* = 4.8 and 8.0 Hz), 7.32 (m, 20H), 8.28 (ddd, 1H, *J* = 1.7, 1.9, and 8.0 Hz), 8.40 (dd, 1H, *J* = 1.7 and 4.8 Hz), 8.62 (d, 1H, *J* = 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 70.0, 70.2, 72.0, 73.8, 74.6, 75.3, 75.4, 80.2, 81.0, 111.0, 123.8, 127.6, 128.0, 128.1, 128.2, 128.5, 128.8 (×2), 129.5, 131.0, 136.0, 138.2, 138.4, 138.6 (×2), 148.2, 150.3, 151.3. API-ES positive: 614.1 $[MH]^+$. Anal. calcd for $C_{40}H_{39}NO_5$: C, 78.28; H, 6.40. Found: C, 78.47; H, 6.69.
(*Z*)-2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(3-pyridyl)-D-*galacto*-hept-1-enitol (**19**). 75 mg (77%): α_D = +44.5 ($CHCl_3$, *c* 1.5); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.67 (dd, 1H, *J* = 2.6, and 8.2 Hz), 3.74 (dd, 1H, *J* = 6.9, and 9.9 Hz), 3.90–3.95 (m, 1H), 4.01 (m, 1H), 4.30–4.40 (m, 3H), 4.53 (d, 1H, *J* = 11.5 Hz), 4.60–4.73 (m, 4H), 4.84 (d, 1H, *J* = 11.5 Hz), 5.84 (s, 1H), 6.95 (dd, 1H, *J* = 4.7 and 8.0 Hz), 7.10–7.30 (m, 20H), 8.10 (ddd, 1H, *J* = 1.5, 1.6, and 8.0 Hz), 8.24 (dd, 1H, *J* = 1.5 and 4.8 Hz), 8.51 (d, 1H, *J* = 1.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 68.2, 72.0, 72.5, 72.7, 73.1, 73.2, 76.1, 77.4, 80.6, 105.9, 122.2, 126.5, 126.7, 126.8 (×2), 126.9, 127.0 (×2), 127.3, 127.4, 127.5, 130.1, 134.5, 136.9, 137.2, 146.2, 148.9, 151.8. API-ES positive: 614.1 $[MH]^+$. Anal. calcd for $C_{40}H_{39}NO_5$: C, 78.28; H, 6.40. Found: C, 78.49; H, 6.58.
(*Z*)-2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(3-thiophenyl)-D-*gluco*-hept-1-enitol (**20**). 67 mg (72%): α_D = +11.0 ($CHCl_3$, *c* 0.3); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.55–3.90 (m, 8H), 4.03 (d, 1H, *J* = 5.6 Hz), 4.07–4.12 (m, 1H), 4.53–4.85 (m, 9H), 5.85 (s, 1H), 7.17–7.39 (m, 22H), 7.56 (d, 1H, *J* = 2.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 69.3, 71.8, 73.4, 73.6, 74.0, 76.8, 77.9, 78.9, 84.6, 104.3, 122.8, 124.4, 127.7 (×2), 127.8 (×2), 127.9 (×2), 128.3, 128.4, 128.5, 128.7, 135.6, 137.8, 138.0, 138.1, 147.9. API-ES positive: 636 $[M+H_2O]^+$.
(*Z*)-2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(3-thiophenyl)-D-*manno*-hept-1-enitol (**21**). 64 mg (69%): α_D = +15.6 ($CHCl_3$, *c* 0.3); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.64 (dd, 1H, *J* = 3.2, and 8.9 Hz), 3.67–3.85 (m, 3H), 3.99 (d, 1H, *J* = 3.2 Hz), 4.02–4.11 (m, 1H), 4.32–4.58 (m, 6H), 4.68 (d, 1H, *J* = 12.6 Hz), 4.90 (d, 1H, *J* = 10.9 Hz), 5.61 (s, 1H), 7.06 (dd, 1H, *J* = 2.9 and 4.9 Hz), 7.11–7.35 (m, 21H), 7.55 (dd, 1H, *J* = 0.7 and 2.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 68.1, 69.0, 70.4, 72.3, 73.4 (×2), 74.2, 78.6, 80.7, 108.7, 123.0, 123.8, 126.6 (×2), 126.7 (×2), 126.8 (×2), 126.9, 127.2, 127.4, 127.7, 134.2, 137.0, 137.2, 137.3, 146.1. API-ES positive: 641 $[M+Na]^+$.
(*Z*)-2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(3-thiophenyl)-D-*galacto*-hept-1-enitol (**22**). 73.5 mg (79%): α_D = +13.0 ($CHCl_3$, *c* 1.0); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.57 (dd, 1H, *J* = 4.5 and 9.9 Hz), 3.64 (dd, 1H, *J* = 2.7 and 8.2 Hz), 3.75 (dd, 1H, *J* = 7.1 and 9.9 Hz), 3.90–4.01 (m, 2H), 4.30–4.38 (m, 3H), 4.53 (d, 1H, *J* = 11.5 Hz), 4.60–4.74 (m, 4H), 4.83 (d, 1H, *J* = 11.5 Hz), 5.95 (s, 1H), 7.03 (dd, 1H, *J* = 2.9 and 4.8 Hz), 7.16–7.31 (m, 21H), 7.47 (dd, 1H, *J* = 1.0 and 2.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 70.0, 73.5, 73.7, 73.8, 74.4, 75.0, 77.0, 78.8, 82.0, 106.1, 123.5, 124.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.7, 128.8, 129.3, 136.1, 138.4, 138.5, 138.7, 138.8, 149.4. API-ES positive: 636.1 $[M+H_2O]^+$.
(*Z*)-2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(*p*-methoxyphenyl)-D-*gluco*-hept-1-enitol (**23**). 68.3 mg (88%): α_D = +73.5 ($CHCl_3$, *c* 0.4); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.68 (s, 3H), 3.69–3.94 (m, 5H), 4.43–4.75 (m, 9H), 5.61 (s, 1H), 6.68 (d, 2H, *J* = 8.9 Hz), 7.07–7.29 (m, 20H), 7.53 (d, 2H, *J* = 8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 55.6, 69.7, 72.2, 73.8, 74.0, 74.5 (×2), 78.3, 79.7, 85.2, 109.4, 114.0, 128.0, 128.1, 128.2, 128.3 (×3), 128.7 (×2), 128.8, 128.9, 130.3, 138.3, 138.5, 138.6, 147.7, 158.5. API-ES positive: 660.3 $[M+H_2O]^+$.
(*Z*)-2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(*p*-methoxyphenyl)-D-*manno*-hept-1-enitol (**24**). 56.6 mg (73%): α_D = +15.8 ($CHCl_3$, *c* 0.9); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.64–3.85 (m, 4H), 3.69 (s, 3H), 4.02 (d, 1H, *J* = 3.2 Hz), 4.13 (t, 1H, *J* = 9.1 Hz), 4.37–4.67 (m, 6H), 4.74 (d, 1H, *J* = 12.6 Hz), 4.95 (d, 1H, *J* = 10.9 Hz), 5.47 (s, 1H), 6.70 (d, 2H, *J* = 8.9 Hz), 7.21–7.38 (m, 20H), 7.60 (d, 2H, *J* = 8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 54.3, 68.0, 69.0, 70.4, 72.3, 73.5, 74.0, 74.2, 75.4, 81.0, 112.7 (×2), 113.9, 115.0, 126.2, 126.5, 126.7, 126.8 (×2), 126.9, 127.2, 127.4 (×2), 129.3, 137.2, 137.4, 145.6, 157.6.

(*Z*)-2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(*p*-methoxyphenyl)-D-*galacto*-hept-1-enitol (**25**). 75.6.3 mg (78%): $\alpha_D = +13.4$ ($CHCl_3$, *c* 0.4); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.58–3.81 (m, 3H), 3.66 (s, 3H), 3.92–4.00 (m, 2H), 4.29–4.36 (m, 3H), 4.55 (d, 1H, $J = 11.5$ Hz), 4.59–4.74 (m, 4H), 4.84 (d, 1H, $J = 11.5$ Hz), 5.82 (s, 1H), 6.64 (d, 2H, $J = 8.9$ Hz), 7.16–7.30 (m, 20H), 7.55 (d, 2H, $J = 8.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 54.3, 68.5, 72.2, 72.5, 73.0, 73.5, 75.7, 76.1, 76.5, 80.5, 109.8, 112.6, 126.6, 126.7, 126.8 (×2), 127.0 (×2), 127.4 (×2), 127.5 (×2), 129.2, 137.2, 137.5, 137.6, 147.1, 157.2. API-ES positive: 665.2 $[M+Na]^+$.

(*Z*)-2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(*p*-tolyl)-D-*gluco*-hept-1-enitol (**26**). 64.5 mg (86%): $\alpha_D = +11.2$ ($CHCl_3$, *c* 0.6); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.32 (s, 3H), 3.77–3.90 (m, 4H), 4.03 (d, 1H, $J = 5.0$ Hz), 4.05–4.09 (m, 1H), 4.54–4.83 (m, 8H), 5.73 (s, 1H), 7.08 (d, 2H, $J = 8.0$ Hz), 7.26–7.40 (m, 20H), 7.60 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.6, 66.2, 69.6, 72.2, 73.8, 74.0, 74.4, 77.0, 79.7, 85.1, 109.8, 128.0, 128.1, 128.2 (×2), 128.3 (×2), 128.7, 128.8 (×2), 128.9, 129.0, 129.3, 130.6, 135.6, 135.7, 138.6, 148.7. API-ES positive: 649.3 $[M+Na]^+$.

(*Z*)-2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(*p*-tolyl)-D-*manno*-hept-1-enitol (**27**). 57.0 mg (76%): $\alpha_D = +7.4$ ($CHCl_3$, *c* 1.2); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.32 (s, 3H), 3.74 (dd, 1H, $J = 3.1$ and 8.8 Hz), 3.77–3.91 (m, 3H), 4.11 (d, 1H, $J = 3.2$ Hz), 4.22 (t, 1H, $J = 9.2$ Hz), 4.45–4.73 (m, 6H), 4.80 (d, 1H, $J = 12.6$ Hz), 5.01 (d, 1H, $J = 10.9$ Hz), 5.56 (s, 1H), 7.05 (d, 2H, $J = 8.3$ Hz), 7.24–7.44 (m, 20H), 7.60 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.5, 69.3, 70.1, 71.6, 73.6, 74.6, 75.2, 75.4, 80.0, 82.2, 115.3, 127.7, 127.9 (×3), 128.0, 128.2, 128.4, 128.6 (×2), 129.1, 129.3, 131.8, 137.2, 138.4 (×2), 138.7, 147.9. API-ES positive: 649.2 $[M+Na]^+$.

(*Z*)-2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-(*p*-tolyl)-D-*galacto*-hept-1-enitol (**28**). 78.9 mg (84%): $\alpha_D = +14.7$ ($CHCl_3$, *c* 1.8); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.23 (s, 3H), 3.65 (dd, 1H, $J = 4.1$ and 9.5 Hz), 3.70–3.81 (m, 2H), 3.92–4.06 (m, 2H), 4.32–4.78 (m, 8H), 4.85 (d, 1H, $J = 11.3$ Hz), 5.87 (s, 1H), 6.96 (d, 2H, $J = 8.0$ Hz), 7.16–7.30 (m, 20H), 7.50 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.6, 69.7, 73.5, 73.6, 73.8, 74.4, 74.8, 77.0, 78.6, 81.9, 111.3, 127.9, 128.0 (×2), 128.1, 128.2, 128.4 (×2), 128.7, 128.8 (×3), 129.2 (×2), 132.7, 136.5, 138.6, 149.7. API-ES positive: 644.2 $[M+H_2O]^+$.