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Cytotoxic effects of *C*-glycosides in HOS and HeLa cell lines

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Abstract—Fifty-two *C*-glycosides were synthesized and their in-vitro antiproliferative activity screened against human cervical carcinoma (HeLa) and osteosarcoma (HOS) cell lines. Nine of them had growth inhibitions (GI_{50} values) below 10 μM, the *C*-glucopyranoside **38** being the most active against HeLa (5.4 μM) and the dichlorocyclopropyl derivative **42** against HOS (1.6 μM). Some preliminary structure–activity relationships were established.
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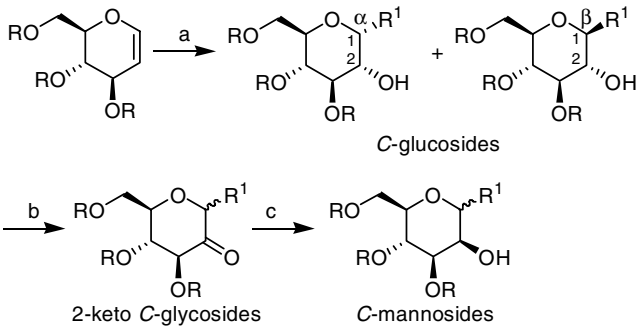
A large number of bioactive *C*-glycosides have been obtained from natural sources[1] as well as via different synthetic approaches.[2] In addition, they possess high stability against chemical and enzymatic hydrolysis and retain the biological properties of natural *O*-glycosides.[3] Therefore, *C*-glycosides are good candidates to test their cytotoxic activities.

In a previous study,[4] we reported the antiproliferative and apoptotic properties of structurally simple *C*-glycosides against human leukemia cancer cells (HL60).

However, solid tumors represent over 85% of all cancers and many of these show resistance to treatment with anticancer drugs, so the development of new drugs still plays a major role in the fight against cancer. Herein, we report the antiproliferative activity of a large series of *C*-glycosides against two types of human solid tumor cell lines: osteosarcoma (HOS) and cervical carcinoma (HeLa).

Most *C*-glycosides were synthesized using Danishefsky's procedure.[5] Epoxidation of a series of D-glucal derivatives (Scheme 1, R = benzyl, *n*-butyl, *n*-pentadecyl, 4-fluorobenzyl, and 2-methylenenaphthyl) using dimethyldioxirane in CH_2Cl_2 and subsequent epoxide ring opening by a stabilized carbanion,[6] such as Grignard reagents (R^1 = methyl, ethyl, *n*-propyl, *i*-butyl, allyl, *n*-pentyl, cyclohexylmethyl, phenyl, and benzyl), led to a mixture of *C*-glycosides, the α/β ratio being variable. The stereochemistry at the *pseudo*-anomeric carbon was established by analyzing the ^{1}H NMR $J_{1,2}$ value and the crosspeaks between H-1 and H-3 and H-5 from T-ROESY experiments.[7] Oxidation of the hydroxyl group at C-2 with dimethylsulfoxide/acetic anhydride[8] led to the corresponding 2-keto *C*-glycosides **44**–**52**.



Scheme 1. Synthesis of *C*-glycosides, 2-keto-*C*-glycosides, and *C*-mannosides. Reagents and conditions: (a) i—DMDO, CH_2Cl_2, 0 °C; ii—R^1MgX, Et_2O, −78 °C; (b) DMSO/Ac_2O (2:1), rt; (c) $NaBH_4$, CH_2Cl_2/MeOH (1:1) 0 °C.

Keywords: *C*-Glycosides; 2-Keto-*C*-glycosides; *C*-Mannosides; Osteosarcoma (HOS); Cervical carcinoma (HeLa); Cytotoxic; Cancer.
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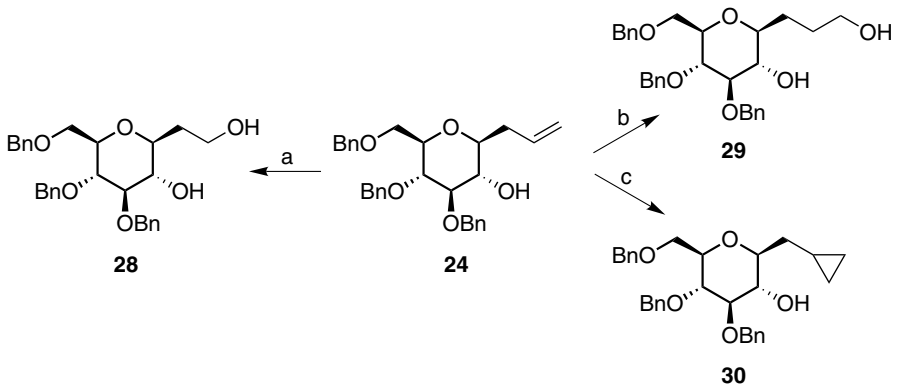
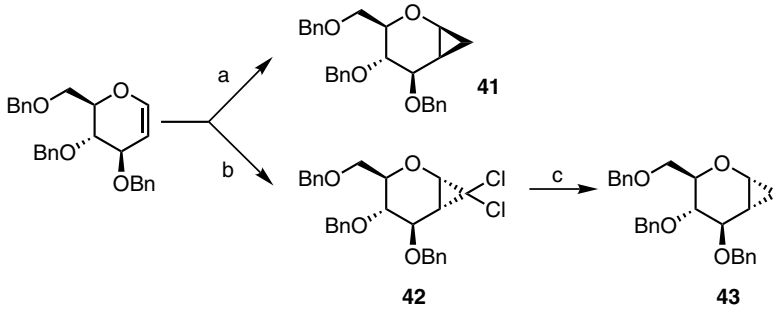


Scheme 2. Synthesis of *C*-glucosides **28**–**30**. Reagents and conditions: (a) 1—O_3, CH_2Cl_2/MeOH (1:1), −78 °C; 2—$NaBH_4$; (b) 1—TBSOTf, Et_3N, CH_2Cl_2, rt; 2—$BH_3{\cdot}Me_2S$, THF, rt, then H_2O_2; 3—Bu_4NF, CH_2Cl_2, rt; (c) $ZnEt_2$, CH_2I_2, Et_2O, rt.



Scheme 3. Synthesis of cyclopropyl derivatives. Reagents and conditions: (a) $ZnEt_2$, CH_2I_2, Et_2O, rt; (b) $CHCl_3$, NaOH, rt; (c) $LiAlH_4$, THF, rt.

Reduction of compounds **46** and **48** with $NaBH_4$ gave the corresponding mannopyranoside derivatives **10** and **22**.[9]

The tetra-*O*-benzyl derivatives **26** and **35** were obtained from **24** and **34**, respectively, by treatment with BnBr and NaH in DMF. Compounds with an acetyl group at C-2 (**4**, **7**, **17**, **23**, and **25**) were obtained from the corresponding alcohols by acetylation with Ac_2O/Py. Compounds **36**–**40** were obtained from the benzyl *C*-glucoside **34** by partial catalytic hydrogenolysis with H_2/Pd(C) in ethanol and, for some of them, consecutive acetylation with Ac_2O/Py.

The 2-hydroxyethyl *C*-glucoside **28** was obtained from the β allyl derivative **24** (Scheme 2) by ozonolysis and subsequent reduction with $NaBH_4$, while the hydroxymethyl derivative **27** was obtained similarly from the corresponding β vinyl *C*-glycoside. The 3-hydroxypropyl derivative **29** was obtained in three steps from **24**: protection of the hydroxyl group at C-2 with *tert*-butyl dimethyl silyl triflate, hydroboration with $BH_3{\cdot}Me_2S$ in THF, and finally, deprotection of silyl group with Bu_4NF. The cyclopropylmethyl derivative **30** was obtained from **24** by means of a Simmons–Smith cyclopropanation.

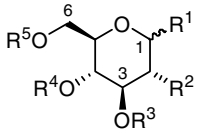
The cyclopropyl derivatives **41**–**43** were synthesized from 3,4,6-tri-*O*-benzyl D-glucal (Scheme 3).[12,13] The effective use of the Simmons–Smith reagent[14] led to the β-cyclopropyl **41**, while dichlorocarbene gave the α-dichlorocyclopropyl **42**, which after reduction with $LiAlH_4$ provided the α-cyclopropyl **43**.

The cytotoxic activity of the whole series was measured as growth inhibition or decreased viability of the two human solid tumor cell lines. Tables 1 and 2 show the antiproliferative activities for all synthesized products, while Schemes 3 and 4 show the structure of those compounds with a 50% growth inhibition (GI_{50}) below 20 μM. Cytotoxicity data were determined by the SRB assay[15] and calculated from at least three independent experiments.

The *C*-glucopyranosides **15** and **38** (Scheme 4) exhibited the best activity against the HeLa cell line (GI_{50} = 5.6 and 5.4 μM, respectively), whereas the α-dichlorocyclopropyl derivative **42** (Scheme 5) was the most active on HOS (GI_{50} = 1.6 μM).

The present study reveals some structure–activity relationships. For example, the presence of benzyl or 4-fluorobenzyl groups at C-3, C-4, and C-6 favored the cytotoxicity against both cell lines (Table 1). However, derivatization of the hydroxyl groups at these positions with other alkyl or acyl groups, such as *n*-butyl, *n*-pentadecyl, 2-naphthylmethyl, and acetyl, led to no activity or to a lower activity. In addition, the lack of one or more of these benzyl groups (**39** and **40**) decreases or annuls antiproliferative activity (compare with **34**). See also, for example, the tetrol **18** versus the tri-*O*-benzyl derivative **8**. *C*-Glucosides with 4-fluorobenzyl groups (compounds

Table 1. Effects of *C*-glycosides **1**–**43** on the growth of HeLa and HOS cell lines[10,11]



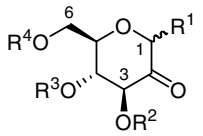
Compound	Config.[a]	R^1	R^2	R^3	R^4	R^5	HeLa		HOS	
							GI_{50}[b]	SD[c]	GI_{50}	SD
1	—	H	H	Bn	Bn	Bn	33.3	4.6	22.2	0.8
2	—	H	OH	Bn	Bn	Bn	n.a.[d]	—	37.9	6.1
3	β	Methyl	OH	Bn	Bn	Bn	n.a.	—	n.a.	—
4	β	Methyl	OAc	Bn	Bn	Bn	n.a.	—	8.8	7.0
5	β	Ethyl	OH	Bn	Bn	Bn	19.8	6.7	34.2	14.7
6	α	Ethyl	OH	Bn	Bn	Bn	n.a.	—	n.a.	—
7	β	Ethyl	OAc	Bn	Bn	Bn	n.a.	—	n.a.	—
8	β	*n*-Propyl	OH	Bn	Bn	Bn	18.9	7.1	38.6	6.1
9	α	*n*-Propyl	OH	Bn	Bn	Bn	17.4	5.9	23.6	5.9
10	β	*n*-Propyl	OH[e]	Bn	Bn	Bn	23.3	4.4	n.a.	—
11	β	*n*-Propyl	OH	*n*-Butyl	*n*-Butyl	*n*-Butyl	n.a.	—	n.a.	—
12	β	*n*-Propyl	OH	*n*-Pentadecyl	*n*-Pentadecyl	*n*-Pentadecyl	n.a.	—	n.a.	—
13	α	*n*-Propyl	OH	*n*-Pentadecyl	*n*-Pentadecyl	*n*-Pentadecyl	28.7	8.4	29.9	0.3
14	β	*n*-Propyl	OH	4-F–Bn	4-F–Bn	4-F–Bn	12.3	7.3	17.2	6.3
15	α	*n*-Propyl	OH	4-F–Bn	4-F–Bn	4-F–Bn	5.6	1.1	n.a.	—
16	β	*n*-Propyl	OH	2-Naphthylmethyl	2-Naphthylmethyl	2-Naphthylmethyl	n.a.	—	n.a.	—
17	β	*n*-Propyl	OAc	2-Naphthylmethyl	2-Naphthylmethyl	2-Naphthylmethyl	n.a.	—	n.a.	—
18	β	*n*-Propyl	OH	OH	OH	OH	n.a.	—	n.a.	—
19	β	*n*-Butyl	OH	Bn	Bn	Bn	n.a.	—	40.1	3.1
20	β	*i*-Butyl	OH	Bn	Bn	Bn	n.a.	—	45.2	10.4
21	α	*i*-Butyl	OH	Bn	Bn	Bn	43.9	8.2	44.5	17.7
22	β	*i*-Butyl	OH[e]	Bn	Bn	Bn	24.6	4.1	26.3	1.1
23	α	*i*-Butyl	OAc	Bn	Bn	Bn	n.a.	—	n.a.	—
24	β	Allyl	OH	Bn	Bn	Bn	26.2	6.9	44.1	5.1
25	β	Allyl	OAc	Bn	Bn	Bn	n.a.	—	11.0	1.4
26	β	Allyl	OBn	Bn	Bn	Bn	n.a.	—	n.a.	—
27	β	Hydroxymethyl	OH	Bn	Bn	Bn	25.8	16.1	27.3	11.2
28	β	2-Hydroxyethyl	OH	Bn	Bn	Bn	30.2	14.9	39.7	16.5
29	β	3-Hydroxypropyl	OH	Bn	Bn	Bn	n.a.	—	n.a.	—
30	β	Cyclopropylmethyl	OH	Bn	Bn	Bn	n.a.	—	n.a.	—
31	β	Cyclohexylmethyl	OH	Bn	Bn	Bn	9.5	2.9	4.4	0.2
32	α	Cyclohexylmethyl	OH	Bn	Bn	Bn	n.a.	—	20.7	2.7
33	β	Phenyl	OH	Bn	Bn	Bn	n.a.	—	n.a.	—
34	β	Benzyl	OH	Bn	Bn	Bn	17.4	3.1	29.2	3.9
35	β	Benzyl	OBn	Bn	Bn	Bn	n.a.	—	n.a.	—
36	β	Benzyl	OAc	Bn	Ac	Ac	n.a.	—	n.a.	—
37	β	Benzyl	OAc	Ac	Ac	Bn	n.a.	—	n.a.	—
38	β	Benzyl	OAc	Bn	Ac	Bn	5.4	3.5	6.1	4.1
39	β	Benzyl	OH	Bn	Bn	OH	38.0	0.1	31.6	2.1
40	β	Benzyl	OH	OH	Bn	Bn	47.9	8.6	33.5	5.9
41	β	$–CH_2–$[e]		Bn	Bn	Bn	n.a.	—	n.a.	—
42	α	$–CCl_2–$		Bn	Bn	Bn	n.a.	—	1.6	0.1
43	α	$–CH_2–$		Bn	Bn	Bn	n.a.	—	n.a.	—

[a] Configuration of R^1 (*C*-aglycon).
[b] GI_{50}, μM.
[c] SD, standard deviation.
[d] n.a., not active ($GI_{50} > 50$ μM).
[e] Axial configuration (R^2).

14 and **15**) were more cytotoxic than those with underivatized benzyl groups (**8** and **9**). Other structure–activity relationships depend on the particular tumor cell line.

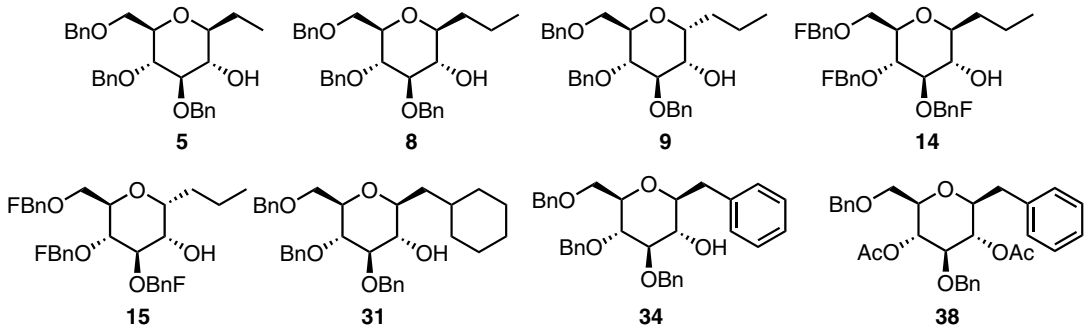
Cervical carcinoma (HeLa). Analysis of the data in Tables 1 and 2, and of the chemical structures, particularly those shown in Scheme 4, reveals further structure–activity relationships for this cell line. The underivatized hydroxyl group at C-2 in all active compounds, except the di-acetyl compound **38**, seems to favor antiproliferative activity. This was also observed in the corresponding study of the cytotoxic activity of *C*-glycosides against leukemia (HL60), although in the present study the configuration at C-2 is not so critical. Either

Table 2. Effects of 2-keto *C*-glycosides **44**–**52** on the growth of HeLa and HOS cell lines

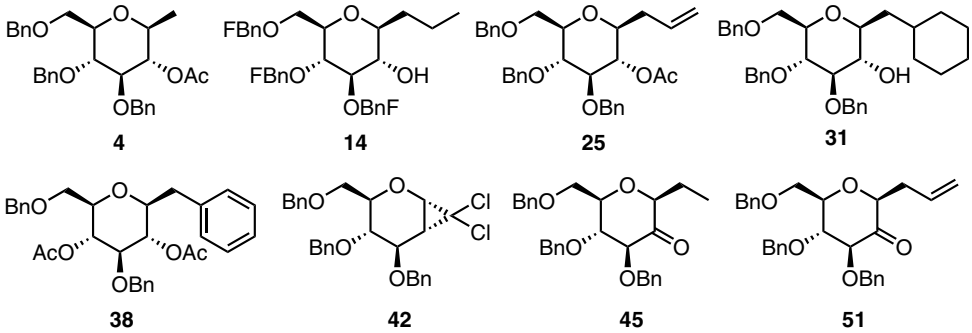


Compound	Config.[a]	R^1	R^2	R^3	R^4	HeLa		HOS	
						GI_{50}[b]	SD[c]	GI_{50}	SD
44	β	Methyl	Bn	Bn	Bn	n.a.[d]	—	n.a.	—
45	β	Ethyl	Bn	Bn	Bn	n.a.	—	4.3	0.8
46	β	*n*-Propyl	Bn	Bn	Bn	n.a.	—	n.a.	—
47	α	*n*-Propyl	Bn	Bn	Bn	n.a.	—	n.a.	—
48	β	*i*-Butyl	Bn	Bn	Bn	n.a.	—	n.a.	—
49	β	*n*-Pentyl	Bn	Bn	Bn	n.a.	—	n.a.	—
50	β	Benzyl	Bn	Bn	Bn	n.a.	—	n.a.	—
51	β	Allyl	Bn	Bn	Bn	n.a.	—	7.6	1.6
52	β	*n*-Propyl	*n*-Butyl	*n*-Butyl	*n*-Butyl	n.a.	—	n.a.	—

[a] Configuration of R^1.
[b] GI_{50}, μM.
[c] SD, standard deviation.
[d] n.a., not active (GI_{50} > 50 μM).



Scheme 4. Structures of *C*-glycosides with antiproliferative activity against the HeLa cell line below 20 μM.



Scheme 5. Structures of *C*-glycosides with antiproliferative activity against the HOS cell line below 20 μM.

an equatorial or an axial configuration provides cytotoxicity (for instance, the *C*-glucoside **8** or its stereoisomer the *C*-mannoside **10**). In addition, even the *C*-mannoside **22** showed some activity, while its epimer at C-2 (*C*-glucoside **20**) was not cytotoxic.

To test the relationship between antiproliferative activity and the *C*-aglycon (R^1), different alkyl and aryl groups were introduced at C-1. The length of the chain in compounds having a linear *C*-aglycon seems to be critical for cytotoxicity. Thus, *C*-glycosides with a hydrogen, a methyl, or a *n*-butyl group as aglycon (R^1) were not active (compounds **2**, **3**, and **19**), while those with an ethyl (**5**), a *n*-propyl (**8**), or an allyl (**24**) group were antiproliferative (GI_{50} 19.8, 18.9, and 26.2 μM, respectively). On the other hand, compounds

having a hydroxyl group in the aglycon, as do **27**–**29**, exhibited a moderate cytotoxicity, their activity decreasing as the length of the chain increased. Thus, while the hydroxymethyl group had a GI_{50} of 25.8 μM (compound **27**), the 2-hydroxyethyl showed a higher value of 30.2 μM (**28**) and the 3-hydroxypropyl had no activity (**29**). β-*C*-Glucosides with branched or cyclic aglycons, like the *iso*-butyl **20**, phenyl **33**, or cyclopropyl compounds **41**–**43**, were inactive. However, those compounds having a cyclohexylmethyl (**31**) or benzyl group (**34**) as aglycon were cytotoxic (GI_{50} 9.5 and 17.4 μM, respectively).

Analysis of the data also reveals that the antiproliferative activity is strongly dependent on the configuration at C-1, although sometimes favoring the β stereoisomer and other times the α. Thus, while the β stereoisomers of the ethyl and cyclohexylmethyl glucosides (compounds **5** and **31**) were active, their α stereoisomers **6** and **32** were not. However, both stereoisomers of the *n*-propyl glucosides **8** and **9** showed similar antiproliferative activities. On the other hand, the α stereoisomer of the *n*-propyl tri-*O*-(4-fluoro-benzyl) glucoside **15** was more active (GI_{50} 5.6 μM) than the β **14** (GI_{50} 12.3 μM). This α preference was also observed in the stereoisomers of *n*-propyl tri-*O*-(*n*-pentadecyl) glucosides **12** and **13**, and in those of the *iso*-butyl tri-*O*-benzyl derivatives **20** and **21**.

Osteosarcoma (HOS). Structural analysis of the *C*-glycosides (Scheme 5) and of their corresponding data (Tables 1 and 2) reveals some structure–activity relationships for this cell line. Besides the already-mentioned preference for the benzyl groups as substituents for the hydroxyl groups at C-3, C-4, and C-6, other features can be established. In contrast to that observed with HeLa and HL60 cell lines, some *C*-glycosides with an acetyl or carbonyl group at position 2 were more cytotoxic than those with an underivatized hydroxyl group. Thus, while the methyl glucoside **3** was inactive, its acetyl derivative **4** had a GI_{50} of 8.8 μM. Moreover, acetylation of the hydroxyl group at C-2 in the allyl glucoside **24** (GI_{50} 44.1 μM), giving the allyl derivative **25**, led to higher antiproliferative activity (GI_{50} 11.0 μM). The 2-keto *C*-glycosides **45** and **51** (Table 2) also showed higher cytotoxicity (GI_{50} 4.3 and 7.6 μM,) than their respective reduced compounds **5** and **24** (GI_{50} 34.2 and 44.1 μM, respectively). Note that none of these 2-keto *C*-glycosides had antiproliferative activity against HeLa.

Concerning the aglycon, *C*-glycosides having a cyclic aglycon, such as the cyclohexylmethyl β-glucoside **31** (GI_{50} 4.4 μM), or the benzyl derivatives **34** and **38** (29.2 and 6.1 μM, respectively), were more cytotoxic than compounds with linear aglycons ($GI_{50} > 35$ μM) (Table 1). However, 2-keto *C*-glycosides (Table 2) do not seem to follow this relationship, since the ethyl (**45**) and the allyl (**51**) were cytotoxic but not the benzyl (**50**).

Regarding the configuration at C-1, all *C*-glucosides with high antiproliferative activity against the HOS cell line (Scheme 5) possessed a β configuration, with the sole exception of the dichlorocyclopropyl **42**. For instance, the *n*-propyl β-*C*-glucoside **14** had a GI_{50} of 17.2 μM, while its α stereoisomer **15** was not active. Similarly, the cyclohexylmethyl β-*C*-glucoside **31** showed significant antiproliferative activity (GI_{50} 4.4 μM), while its α stereoisomer **32** was less active (GI_{50} 20.7 μM).

In summary, a large series of *C*-glycosides were synthesized and screened against cervical carcinoma (HeLa) and osteosarcoma (HOS) cell lines. Several *C*-glucosides had high antiproliferative activity against these cell lines. Thus, compounds **15**, **31**, and **38** showed GI_{50} values below 10 μM against the HeLa cell line, while compounds **4**, **31**, **38**, **41**, **45**, and **51** against HOS. The easy synthetic access to these *C*-glycosides, together with their high activities, makes them promising substrates against these cancer cell lines. Some significant structure–activity relationships were established.

Acknowledgments

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10. Registry numbers for known compounds: **1**, 91780-41-5; **2**, 152840-34-1; **3**, 105938-03-2; **4**, 105938-04-3; **5**, 909533-21-

7; **6**, 151100-74-5; **8**, 320576-39-4; **9**, 909533-28-4; **10**, 909533-39-7; **11**, 909533-51-3; **12**, 909533-52-4; **13**, 909533-53-5; **18**, 3736-73-0; **19**, 909714-58-5; **20**, 909533-22-8; **21**, 909533-23-9; **22**, 909533-41-1; **24**, 161275-25-8; **25**, 193546-84-8; **26**, 81972-19-2; **27**, 135561-09-0; **29**, 288584-96-3; **30**, 909533-56-8; **31**, 909533-24-0; **32**, 909533-25-1; **33**, 130912-38-8; **34**, 130912-39-9; **35**, 155590-31-1; **39**, 909533-29-5; **40**, 909533-31-9; **41**, 162332-11-8; **42**, 162332-13-0; **43**, 162428-31-1; **51**, 192929-31-0.

11. Spectroscopic data for new representative *C*-glycosides: (a) 4,8-anhydro-1,2,3-trideoxy-6,7,9-tris-*O*-(4-fluorobenzyl)-D-glycero-D-gulo-nonitol (**14**): ^{1}H NMR (δ, ppm): 7.28–7.25 (m, 4H), 7.15–7.12 (m, 2H), 7.05–6.96 (m, 6H), 4.87 (d, J = 11.5 Hz, 1H), 4.71 (d, J = 11.0 Hz, 1H), 4.71 (d, J = 11.0 Hz, 1H), 4.60 (d, J = 12.2 Hz, 1H), 4.54–4.49 (m, 2H), 3.70–3.64 (m, H-9 and H-9′), 3.56 (dd, J = 9.0 and 9.0 Hz, H-7), 3.43 (dd, J = 9.0 and 9.0 Hz, H-6), 3.38 (ddd, J = 2.5, 3.9 and 9.7 Hz, H-8), 3.30 (dd, J = 9.0 and 9.0 Hz, H-5), 3.16 (ddd, J = 2.4, 8.8 and 8.8 Hz, H-4), 1.77 (m, H-3), 1.56 (m, H-2), 1.50–1.36 (m, H-2′, H-3′), 0.92 (dd, J = 7.3 and 7.3 Hz, 3H); ^{13}C NMR (δ, ppm): 129.4 (s), 129.3 (s), 129.3 (s), 129.2 (s), 129.2 (s), 129.2 (s), 115.5–114.8 (aromatic C′s), 86.6 (d, C-6), 79.0 (d, C-4), 78.7 (d, C-8), 78.2 (d, C-7), 74.2 (t), 73.8 (t), 73.7 (d, C-2), 72.5 (t), 68.6 (t, C-9), 33.6 (t, C-3), 18.3 (t, C-2), 13.9 (q, C-1). (b) 3,7-Anhydro-5,6,8-tri-*O*-benzyl-1,2-dideoxy-D-gluco-oct-4-ulose (**45**): ^{1}H NMR (δ, ppm): 7.35–7.18 (m, 15H), 5.01 (d, J = 11.3 Hz, 1H), 4.86 (d, J = 10.9 Hz, 1H), 4.62 (d, J = 12.2 Hz, 1H), 4.60 (d, J = 11.3 Hz, 1H), 4.56 (d, J = 12.2 Hz, 1H), 4.55 (d, J = 10.9 Hz, 1H), 4.18 (d, J = 8.6 Hz, H-5), 3.87 (dd, J = 9.0 and 9.0 Hz, H-6), 3.82–3.67 (m, H-3, H-7, H-8 and H-8′), 1.90 (m, H-2), 1.69 (m, H-2′), 1.02 (dd, J = 7.5 and 7.5 Hz, 3H-1); ^{13}C NMR (δ, ppm): 202.5 (s, C-4), 138.1 (s), 137.8 (s), 137.6 (s), 128.4–127.6 (aromatic C′s), 86.7 (d, C-5), 81.9 (d, C-3), 80.3 (d, C-6), 79.2 (d, C-7), 74.9 (t), 73.7 (t), 73.5 (t), 68.9 (t, C-8), 21.8 (t, C-2), 9.7 (q, C-1).
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