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Preparation of 1-*C*-glycosyl aldehydes by reductive hydrolysis

Szabolcs Sipos, István Jablonkai *

Institute of Biomolecular Chemistry, Chemical Research Center, Hungarian Academy of Sciences, PO Box 17, 1525 Budapest, Hungary

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Dedicated to Professor Dr. András Lipták on the occasion of his 75th birthday

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ABSTRACT

Reductive hydrolysis of various protected glycosyl cyanides was carried out using DIBAL-H to form aldimine alane intermediates which were then hydrolyzed under mildly acidic condition to provide the corresponding aldehyde derivatives. While 1-*C*-formyl glycal and 2-deoxy glycosyl derivatives were stable during isolation and storage 1-*C*-glycosyl formaldehydes in the *gluco*, *galacto* and *manno* series were sensitive and decomposition occurred by 2-alkyloxy elimination. A one-pot method using *N*,*N*′-diphenylethylenediamine to trap these aldehydes in stable form was developed. Reductive hydrolysis of glycosyl cyanides offers valuable aldehyde building blocks in a convenient way which can be applied in the synthesis of complex *C*-glycosides.

1. Introduction

The design of glycomimetics offers a useful tool to modify the structure of biologically active peptides and glycoconjugates. Introduction of formyl group at the anomeric position of carbohydrates affords valuable intermediates for synthesis of complex *C*-glycosides. In addition to regular *C*-glycosides, by the use of unsaturated analogs the conformation of glycopeptides can be further modified.

The most practical methods for the preparation of multigram quantities of 1-formyl-*C*-glycosides include oxidative cleavage of aldehyde precursor *C*-glycosides possessing alkenyl or nitromethyl substituents or introduction of an aldehyde-equivalent group at the anomeric center followed by unmasking the aldehyde functionality. Ozonolysis of *C*-glycosyl-allene,[1] prop-1-ene,[2] styrene,[3–6] and 1-allyl-4-phenyl-1,2,4-triazolidine-3,5-dione[7] derivatives provided the respective anomer carbon-linked aldehydes. pH-controlled ozonolysis of C-glycosylated nitromethane[8] as well as two-step oxidation of *C*-glycosyl-enoxysilane[9] have also been developed for the synthesis of 1-formyl-*C*-glycosides. Due to the harsh oxidizing conditions by which the anomeric substituents were converted to a formyl group the common hydroxyl protecting group such as benzyl was readily oxidized[10] and the conversion of the desired aldehyde to an acid[8] was also observed. Addition of an aldehyde-equivalent group such as thiazole[11,12] benzothiazole,[13] dithiane[5] and bis-(methylthio)methyl[14] to glyconolactones followed by unmasking the aldehyde functionality is another way to introduce formyl group at the anomeric position. However, these syntheses are often strenuous and offer α/β anomeric mixtures.[11]

Glycosyl cyanides can be readily available starting materials as aldehyde equivalents for the preparation of 1-formyl-*C*-glycosides by reductive hydrolysis. Reductive hydrolysis of nitriles employing various metal hydrides as reducing agents such as lithium trialkoxyaluminum hydrides, sodium dialkylaluminum hydrides, and diisobutylaluminum hydride (DIBAL-H) have been described for mostly aromatic nitriles.[15] Nevertheless no such hydrides have been applied for the conversion of glycosyl cyanides to the corresponding aldehydes. Raney nickel and sodium hypophosphite in aqueous pyridine-acetic acid[16–18] as well as $LiAlH_4$ in THF[19] were used exclusively in the preparation of 1-formyl-*C*-glycosides by reductive hydrolysis. However, formation of unsaturated aldehydes by 2- and 3-acetoxy/benzoyloxy elimination was observed with Raney Ni/NaH_2PO_2 that can be avoided by trapping the resulting saturated aldehyde with *N*,*N*′-diphenylethylenediamine (Wanzlick's reagent).[16,17,19] Reduction of perbenzylated α-D-glucopyranosyl cyanide with $LiAlH_4$ in THF followed by hydrolysis of the intermediate aldimine was reported to afford the respective *C*-1-formyl derivative.[20] However, in the reported NMR spectrum the chemical shift (9.20 ppm) of the CHO proton is rather consistent with the formation of 3,4,6-tri-*O*-benzyl-D-glucal aldehyde since in all 1-formyl-*C*-glycosyl derivatives of the *gluco*, *galacto*, and *manno* series higher chemical shifts (9.60–9.98 ppm) were reported[12] for the CHO proton. In contrast, no synthetic procedure for the

* Corresponding author. Tel.: +36 1 438 1100x130; fax: +36 1 4381145.
E-mail address: jabi@chemres.hu (I. Jablonkai).

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preparation of 1-formyl-2-deoxy-*C*-glycosyl derivatives has been published.

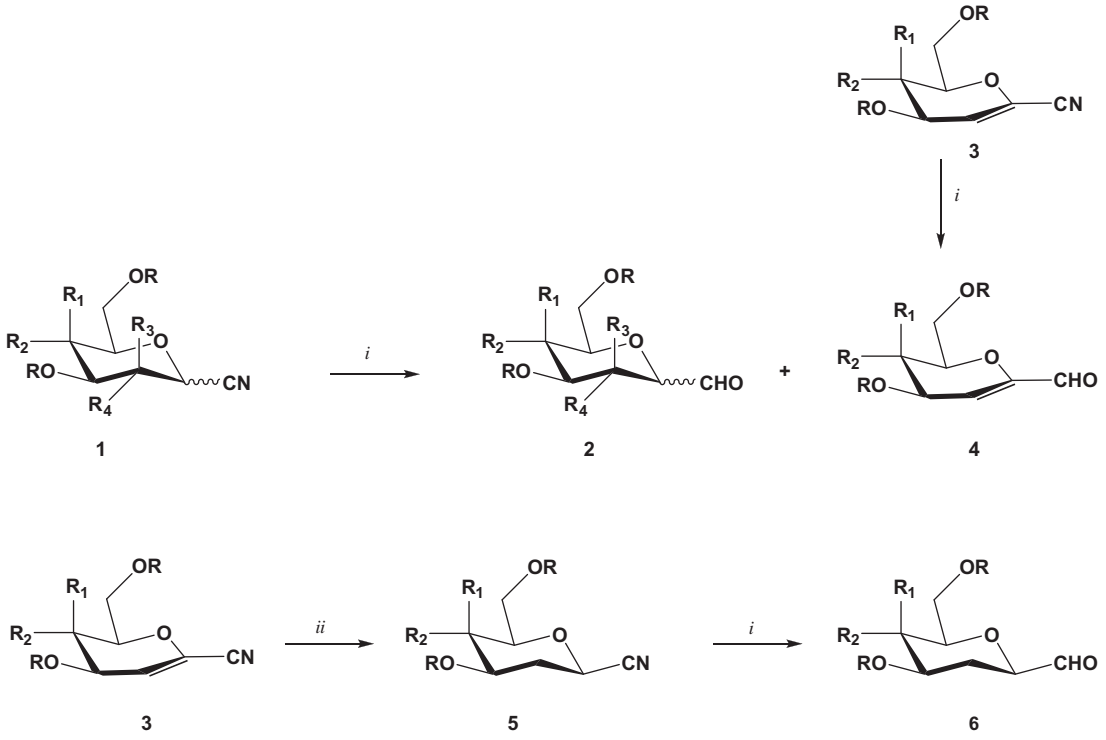
The objective of this study was to prepare 1-*C*-glycosyl, 1-*C*-2-deoxy-glycosyl formaldehydes and 1-*C*-formyl-glycals by reductive hydrolysis of the corresponding cyanides employing complex aluminum-hydrides such as DIBAL-H and RedAl (sodium bis(2-methoxyethoxy)aluminum dihydride). The effect of solvent and temperature on the product formation was also studied.

2. Results and discussion

Protected glycosyl cyanides (Scheme 1, Table 1) were prepared by standard literature methods. Perbenzyl α-galactosyl and glucosyl cyanides (**1a-α** and **1d-α**) were synthesized via α-trichloroacetimidate derivatives.[21] Perbenzyl β-galactosyl cyanide (**1a-β**) was obtained from peracetyl β-galactopyranosyl cyanide[22] after Zemplen deacetylation[23] and benzylation.

Permethyl α- and β-D-galactosyl cyanides (**1b-α** and **1b-β**) were synthesized from 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-α/β-D-galactose[24] with TMSCN in the presence of boron trifluoride etherate[20] and the anomers were separated by column chromatography. Perallyl β-D-galactosyl cyanide (**1c-β**) was prepared by the same procedure as described for **1a-β**. Perbenzyl β-D-glucosyl cyanide (**1d-β**) was obtained from benzobromoglucose[25] which was transformed into the benzoylated β-D-glucopyranosyl cyanide[26] followed by deacetylation[23] and benzylation. Permethyl α- and β-D-glucosyl and mannosyl cyanides (**1e-α**, **1e-β**, **1f-α**, and **1f-β**) were synthesized from 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-α/β-D-glucose/mannose[24] as described earlier for **1b-α** and **1b-β**. Benzyl-protected glycal nitriles (**3a** and **3b**) were available in our laboratory as unexpected products during the standard benzylation (NaH, benzylbromide, DMF) of β-D-glucopyranosyl, β-D-galactopyranosyl, and α-D-mannopyranosyl cyanides by 2-benzyloxy elimination. When β-D-galactosyl nitrile was benzylated in addition to the perbenzylated β-D-galactosyl nitrile about 20% of tribenzyl galactal cyanide (**3a**) was isolated. 1-Cyano-3,4,6-tri-*O*-benzyl-D-glucal (**3b**) was obtained in 12% yield during the benzylation of β-D-glucopyranosyl nitrile. On the other hand, exclusively **3b** formed during the perbenzylation of α-D-mannosyl nitrile. To our best knowledge no such benzylated glycal nitriles were reported in the literature. Acetylated 1-cyanoglycals were prepared by direct elimination of acetic acid from the appropriate peracetylated glycosyl nitriles with 1,8-diazabicyclo[5.4.0]undec-7-ene in aprotic solvents.[27,28] 2-Deoxy-β-D-galactosyl (**5a-β**) and glucosyl (**5b-β**) cyanides were prepared from the respective glycal cyanide by hydrogenation over palladium on charcoal at atmospheric pressure. The amount of catalyst seemed to be important in the formation of desired product since in addition to the saturation of the double bond the reduction of the cyano group to an amine also took place. When 5% (w Pd/w substrate) of palladium on charcoal catalyst was used at atmospheric pressure, the reaction proceeded quickly but both functionalities were reduced. Reducing the amount of the catalyst to 1% the reaction was sluggish and only the double bond reduction occurred yielding the deoxy nitriles (**5a-β** and **5b-β**) in moderate yields (50–60%). Surprisingly, hydrogenation of these glycal cyanides was stereospecific and resulted in almost exclusively the β-anomers indicating that the hydrogen addition occurs from the less hindered α-face of the sugar. Depending on the batch of the catalyst the amount of the α-anomer accounted for 6%.

The reductive hydrolysis of various glycosyl, 2-deoxy-glycosyl and glycal cyanides was carried out with DIBAL-H and RedAl (Scheme 1). In these experiments the workup of the resulting aldimine alane from the reaction of the nitrile and the hydride was crucial on the product formation. Initially when the aldimine alane was hydrolyzed with 1 N HCl almost exclusively 1-formyl-*C*-glycal formation was observed. The use of 1 N NH_4Cl for the hydrolysis of the aldimine greatly reduced the glycal aldehyde formation by 2-benzyloxy elimination. In order to find the optimal



Scheme 1. Preparation of 1-*C*-glycosyl aldehydes by reductive hydrolysis (see Table 1 for structural details). Reagents and conditions: (i) DIBAL-H, −78 °C, 30 min then 1 M NH_4Cl; (ii) Pd/C, EtOH.

Table 1
Structure of glycosyl cyanides and the derived aldehydes as well as synthesis methods for the preparation of the starting cyanides

Cyanide	Method of preparation	R_1	R_2	R_3	R_4	R	Aldehyde
1a-α	Ref.[20]	OBn	H	H	OBn	OBn	**2a-α**
1a-β	Refs.[21,22]	OBn	H	H	OBn	OBn	**2a-β**
1b-α	Refs.[19,23]	OMe	H	H	OMe	OMe	**2b-α**
1b-β	Refs.[19,23]	OMe	H	H	OMe	OMe	**2b-β**
1c-β	Refs.[21,22]	OAll	H	H	OAll	OAll	**4c**[a]
1d-α	Ref.[20]	H	OBn	H	OBn	OBn	**2d-α**
1d-β	Refs.[22,24,25]	H	OBn	H	OBn	OBn	**2d-β**
1e-α	Refs.[19,23]	H	OMe	H	OMe	OMe	**2e-α**
1e-β	Refs.[19,23]	H	OMe	H	OMe	OMe	**2e-β**
1f-α	Refs.[19,23]	H	OMe	OMe	H	OMe	**2f-α**
1f-β	Refs.[19,23]	H	OMe	OMe	H	OMe	**2f-β**
3a	Formed during benzylation of unprotected cyanides	OBn	H	—	—	OBn	**4a**
3b		H	OBn	—	—	OBn	**4b**
5a-β	Hydrogenation of **3a**, **3b**	OBn	H	—	—	OBn	**6a-β**
5b-β		H	OBn	—	—	OBn	**6b-β**

[a] Only galactal derivative formed by β-allyloxy elimination.

reaction conditions experiments with **1a-β** were carried out by changing the temperature and amount of the respective hydride (Table 2).

When 2 equiv of DIBAL-H was used no expected **2a-β** formed, instead 1-*C*-formyl galactal derivative **4a** and a significant amount of amine byproduct were detected. Lowering the excess of DIBAL-H up to 1.4 equiv 52% isolated yield of **2a-β** was obtained and only low amount of 2-benzyloxy-eliminated galactal aldehyde was observed with no over-reduction to the amine. At 1.2 equiv of DIBAL-H no β-eliminated product **4a** was detected in the crude product but during the chromatography decomposition of **2a-β** led to this compound. These results suggested that purification of the crude product should be avoided in case of 1-*C*-glycosyl formaldehydes since the acidity of silica gel appears to favor the elimination reaction. During flash chromatography decomposition and epimerization were also reported when 1-*C*-formyl-α-D-glucosyl derivative was purified.[12] Nevertheless, elevation of temperature favored for over-reduction to the amine and only 2-benzyloxy-eliminated product was observed.

Red-Al in toluene or THF at −78 °C was unreactive and no product formation during 2 h was detected. However, at room temperature formation of both aldehydes was observed. We could not find conditions using RedAl which favored exclusively for the formation of **2a-β** therefore RedAl was considered unsuitable for reductive hydrolysis of such glycosyl cyanides.

Further reductive hydrolysis experiments with various D-glycosyl, 2-deoxy-D-glycosyl and D-glycal cyanides were accomplished with 1.4 equiv of DIBAL-H at −78 °C (Table 3). Since in the initial experiments decomposition of **2a-β** yielding glycal aldehyde took place during the chromatography ^{1}H NMR spectrum of crude products was always taken immediately after the work-up. Results suggested that the aldehydes were pure enough to be used in further synthesis without purification. All glycosyl cyanides except **1c-β** were converted into the expected aldehyde derivatives. Interestingly when tetraallyl β-D-galactosyl cyanide **1c-β** was subjected to reductive hydrolysis only unsaturated product (**4c**) formation was noticed. Despite similar leaving group abilities of benzyloxy and methoxy groups replacement of the benzyl protective groups in the galactosyl derivatives with methyl groups (**1b-α** and **1b-β**) increased the stability of these derivatives during purification. No byproduct formation was found in the reaction of glycal (**3a** and **3b**) and 2-deoxy-β-D-glycosyl (**5a-β** and **5b-β**) cyanides and yields for the respective aldehydes were moderate (52–63%). Such 2-deoxy-glycosyl aldehydes have not been previously reported. β-Elimination has also been noticed in the synthesis and reaction of such 1-*C*-glycosyl aldehydes.[1,12,29,30] Under mild basic conditions epimerization of benzyl-protected α-D-glycopyranosyl aldehydes were transformed into an equilibrium α/β ratio 1:8–20 accompanied by β-elimination of the benzyloxy groups.[1] In case of mannose derivative the degree of elimination was not significantly different from that of galactose and glucose derivatives despite the favorable trans-diaxial disposition between the C-1 hydrogen and C-2 *O*-benzyl group. Nevertheless, in a Mannich reaction from benzyl-protected β-D-mannosyl and β-D-arabinosyl aldehydes promoted by Lewis acid ($InCl_3$) formation of glycal aldehydes was also observed.[31] Decomposition of selected aldehydes was studied by ^{1}H NMR spectroscopy in $CDCl_3$. The benzyl-protected **2a-β** decomposed fairly rapidly and half of the starting alde-

Table 2
Reductive hydrolysis of **1a-β** using DIBAL-H and RedAl and effect of reaction conditions on the product formation and the yields

Hydride	Equiv	Solvent	Temp (°C)	Time (min)	Products	Yield (%)[a]	
						2a-β	**3a**
DIBAL-H	2.0	CH_2Cl_2	−78	**30**	**4a + Gal(OBn)$_4$CH$_2$NH$_2$**[b]	—	45
DIBAL-H	1.8	CH_2Cl_2	−78	**30**	**2a-β + 4a + Gal(OBn)$_4$CH$_2$NH$_2$**	12	51
DIBAL-H	1.4	CH_2Cl_2	−78	**30**	**2a-β + 4a**	52	10
DIBAL-H	1.2	CH_2Cl_2	−78	**30**	**2a-β + 1a-β**	23	12
DIBAL-H	1.4	CH_2Cl_2	−40	**30**	**4a + Gal(OBn)$_4$CH$_2$NH$_2$**	—	38
DIBAL-H	1.8	CH_2Cl_2	−40	**30**	**4a + Gal(OBn)$_4$CH$_2$NH$_2$**	—	27
RedAl	2.0	Toluene or THF	−78	**120**	—	—	—
RedAl	2.5	THF	20	**120**	**2a-β + 4a**	Traces	54
RedAl	1.0	Toluene or THF	20	**120**	**2a-β + 4a**	—	12
RedAl	2.5	THF	20	**120**	**2a-β + 4a**	10	50
RedAl	2.5	Toluene	−20 then rt	**20 + 30**	**2a-β + 4a**	36	30

[a] Yields of the respective aldehyde after silica gel flash chromatography.
[b] The amine byproduct was not isolated but detected in the reaction mixture by MS and TLC.

Table 3
Reductive hydrolysis of various glycosyl, 2-deoxy-glycosyl, and glycal cyanides. Effect of purification on decomposition of glycosyl aldehydes by 2-alkyloxy elimination.

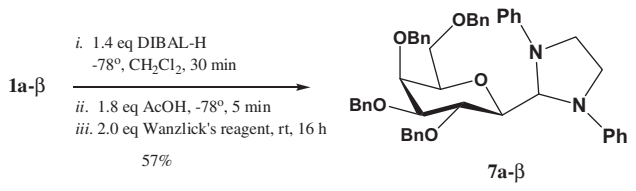
Cyanide	Hydride	Aldehyde in crude product (%)[a]		Isolated aldehyde (%)	
		1-*C*-Glycosyl aldehyde	1-Formyl-*C*-glycal	1-*C*-Glycosyl aldehyde	1-Formyl-*C*-glycal
1a-α	DIBAL-H	90	10	18	36
1a-β	DIBAL-H	91	9	52	10
1a-β	Red-Al	N/A	N/A	36	30
1b-α	DIBAL-H	100	0	71	8
1b-β	DIBAL-H	100	0	60	0
1c-β	DIBAL-H	0	100	0	63
1c-β	Red-Al	0	100	0	22
1d-α	DIBAL-H	92	8	0	38
1d-α	Red-Al	N/A	N/A	0	54
1d-β	DIBAL-H	98[b] (0[c])	2[b] (100[c])	0	41
1e-α	DIBAL-H	95	5	N/A	N/A
1e-β	DIBAL-H	98	2	N/A	N/A
1f-α	DIBAL-H	88	12	29	26
1f-β	DIBAL-H	80	20	38	28
3a	DIBAL-H	—	—	—	63
3b	DIBAL-H	—	—	—	52
5a-β	DIBAL-H	—	—	53	—
5b-β	DIBAL-H	—	—	59	—

[a] Based on the ratio of integral values for CHO protons in the ^{1}H NMR spectrum of crude products.
[b] Work-up of the aldimine alane was with 1 M NH_4Cl.
[c] Work-up of the aldimine alane was with 1 M HCl.

hyde converted to **4a** in 180 min at 40 °C while the same degree of decomposition for the methyl protected mannosyl aldehyde **2f-β** required 60 days at 20 °C. Storage of these aldehydes in freezer however is strongly recommended.[12] Addition of a strong base DBU (0.2 equiv) to **2a-β** increased the rate of decomposition and the epimerized product **2a-α** is also appeared. In the presence of 0.2 equiv of TFA β-benzyloxy elimination took place instantly. Nevertheless, both glycal and 2-deoxy aldehydes were stable for a longer period in refrigerator. Since **2a-f** glycosyl aldehydes cannot be prepared in high purity form and were not stable for long-term storage the reductive hydrolysis procedure was modified to trap the aldehyde as 1,3-diphenylimidazolidine derivative.[16,17] In our procedure **1a-β** was treated with DIBAL-H (1.4 equiv) at −78 °C for 30 min then the excess of hydride was quenched with acetic acid followed by addition of the Wanzlick's reagent[19] (2 equiv) (Scheme 2). The product formed overnight at room temperature was purified without decomposition by silica gel chromatography to provide **7a-β** (57%).

3. Conclusion

In conclusion, reductive hydrolysis of various protected glycosyl cyanides was carried out using DIBAL-H to form aldimine alane intermediates which were then hydrolyzed under mildly acidic condition to provide the corresponding aldehyde derivatives. While 1-*C*-formyl glycal and 2-deoxy glycosyl derivatives were stable during isolation and storage 1-*C*-glycosyl formaldehydes in the *gluco*, *galacto* and *manno* series were sensitive and decomposition occurred by 2-alkyloxy elimination. A one-pot method using *N*,*N*′-diphenylethylenediamine to trap these sensitive aldehydes as stable derivatives was developed. Reductive hydrolysis of glycosyl cyanides offers valuable aldehyde building blocks in a convenient way which can gain application in the synthesis of complex *C*-glycosyl derivatives.



Scheme 2. Preparation of 1,3-diphenylimidazolidine derivative from **1a-β**.

4. Experimental

4.1. General methods

All chemicals and solvents were purchased from Sigma–Aldrich Kft. (Budapest, Hungary). TLC aluminum sheets (Silica Gel 60 F_{254}, 0.2 mm layer thickness) for following the proceeding of the reactions and silica gel for column chromatography (Silica Gel 60, 0.040–0.063 mm) was from Merck Kft. (Budapest, Hungary). Spots of compounds were visualized under UV light or heating the plates after immersion in 5% (v/v) H_2SO_4 in EtOH or 0.4% (w/v) 2,4-dinitrophenylhydrazine in 2 N HCl or 0.2% (w/v) ninhydrin in EtOH. Melting points were determined by a Boetius PHMK05 melting point apparatus (MLW, Dresden, Germany) and are uncorrected. The NMR spectra were recorded with Varian Gemini-3000 (300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometer (Varian Inc., Palo Alto, CA, USA). Mass spectrometric measurements were run on an Applied Biosystems 3200QTrap hybrid mass spectrometer in electrospray ionization mode. Optical rotations were measured using an Optical Activity AA-10R polarimeter (Optical Activity Ltd, Ramsey, UK) at 20 °C.

4.2. 2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl cyanide (1a-α)

Preparation of **1a-α** was carried out via an α-trichloroacetimidate intermediate as described previously.[21] Mp 45–49 °C; $[\alpha]_D^{20}$ +3.0 (*c* 1.3, $CHCl_3$); R_f 0.35 (hexanes–EtOAc, 8:2); ^{1}H NMR ($CDCl_3$): δ 3.50 (m, 2H, H-6a, H-6b), 3.82 (dd, 1H, $J_{3,4}$ 2.8 Hz, H-3), 3.99 (m, 2H, H-4, H-5), 4.11 (dd, 1H, $J_{2,3}$ 9.8 Hz, H-2), 4.68 (d, 1H, $J_{1,2}$ 6 Hz, H-1), 4.4–4.8 (m, 8H, $PhCH_2$), 7.20–7.40 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$): δ 67.6 (C-1), 68.0 (C-6), 73.3, 73.4, 73.6, 75.0 ($PhCH_2$), 73.6 (C-2), 74.0, 74.2 (C-4, C-5), 80.3 (C-3), 115.8 (CN), 127.0–129.0 (Ph), 137.5, 137.6, 138.0, 138.1 (C_q); MS (ESI): *m*/*z* 550.7 $[M+H]^+$.

4.3. 2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl cyanide (1a-β)

Synthesis of **1a-β** was started from acetobromogalactose from which peracetyl β-galactopyranosyl cyanide[22] was prepared followed by Zemplen deacetylation[23] and benzylation. Mp 87–88 °C; $[\alpha]_D^{20}$ +25.1 (*c* 3.0, $CHCl_3$); R_f 0.30 (hexanes–EtOAc, 8:2); ^1H NMR ($CDCl_3$): δ 3.4–3.6 (m, 3H, H-5, H-6a, H-6b), 3.49 (dd, 1H, $J_{3,4}$ 3.0 Hz, H-3), 3.93 (d, 1H, H-4), 4.02 (d, 1H, $J_{1,2}$ 11.0 Hz, H-1), 4.17 (dd, 1H, $J_{2,3}$ 9.0 Hz, H-2), 4.30–5.0 (8H, $PhCH_2$), 7.18–7.41 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$): δ 68.0 (C-1), 68.3 (C-6), 72.7, 73.3, 73.7, 74.8 ($PhCH_2$), 76.0 (C-2), 76.3 (C-4), 78.2 (C-5), 83.0 (C-3), 116.8 (CN), 127.0–129.0 (Ph), 137.2, 137.5, 137.7, 138.1 (C_q); MS (ESI): *m/z* 550.8 $[M+H]^+$.

4.4. 2,3,4,6-Tetra-*O*-methyl-α-D-galactopyranosyl cyanide (1b-α)

Permethyl α-D-galactopyranosyl cyanide (**1b-α**) was synthesized from 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-α/β-D-galactopyranose[24] with TMSCN in the presence of boron trifluoride etherate[20] and the anomeric mixture was separated by column chromatography. $[\alpha]_D^{20}$ +110.3 (*c* 1.1, $CHCl_3$); R_f 0.28 (hexanes–EtOAc, 1:1); ^1H NMR ($CDCl_3$): δ 3.35–3.70 (m, 6H, H-2, H-3, H-4, H-5, H-6a, H-6b), 3.40, 3.55, 3.56, 3.57 (s, 12H, CH_3), 4.95 (d, 1H, $J_{1,2}$ 5.8 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 58.51, 59.28, 59.71, 61.59 (CH_3), 66.93 (C-1), 70.39 (C-6), 74.81, 75.14, 75.33, 81.98 (CH), 115.61 (CN), MS (ESI): *m/z* 268.3 $[M+Na]^+$.

4.5. 2,3,4,6-Tetra-*O*-methyl-β-D-galactopyranosyl cyanide (1b-β)

Permethyl α-galactopyranosyl cyanide (**1b-β**) was synthesized from 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-α/β-galactopyranose[24] with TMSCN in the presence of boron trifluoride etherate[20] and the anomers were separated by column chromatography. Mp 73–75 °C; $[\alpha]_D^{20}$ +36.4 (*c* 1.1, $CHCl_3$); R_f 0.22 (hexanes–EtOAc, 1:1); ^1H NMR ($CDCl_3$): δ 3.11 (m, 1H, CH), 3.33–3.73 (m, 5H, CH, H-6a, H-6b), 3.36, 3.50, 3.53, 3.64 (s, 12H, CH_3), 3.88 (d, 1H, $J_{1,2}$ 9.8 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 58.34, 59.34, 61.50, 61.52 (CH_3), 67.83 (C-1), 70.58 (C-6), 74.97, 75.29, 78.02, 84.96 (CH), 116.86 (CN); MS (ESI): *m/z* 268.3 $[M+Na]^+$.

4.6. 2,3,4,6-Tetra-*O*-allyl-β-D-galactopyranosyl cyanide (1c-β)

Synthesis of **1c-β** was started from acetobromogalactose from which peracetyl β-galactopyranosyl cyanide[22] was prepared followed by Zemplen deacetylation[23] and allylation using allyl bromide. $[\alpha]_D^{20}$ −41.1 (*c* 1.1, $CHCl_3$); R_f 0.35 (hexanes–EtOAc, 8:2); ^1H NMR ($CDCl_3$): δ 3.32 (m, 1H, CH), 3.53–3.83 (m, 5H, CH, H-6a, H-6b), 3.91–4.41 (m, 8H, OCH_2), 5.12–5.35 (m, 8H, CH_2=CH), 5.64 (m, 1H, H-1), 5.81–6.07 (m, 4H, CH_2=CH); ^{13}C NMR ($CDCl_3$): δ 67.59 (C-6), 71.92, 72.94, 73.46, 73.95 (OCH_2), 72.63, 75.23, 77.00, 77.59, 81.93 (CH), 114.62 (CN), 116.26, 116.49, 116.62, 117.00 (CH_2=CH), 133.44, 133.67, 134.10, 134.44 (CH_2=CH); MS (ESI): *m/z* 350.2 $[M+H]^+$.

4.7. 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl cyanide (1d-α)

Preparation of **1d-α** was carried out via an α-trichloroacetimidate intermediate as described previously.[21] $[\alpha]_D^{20}$ +34.7 (*c* 2.2, $CHCl_3$); R_f 0.30 (hexanes–EtOAc, 8:2); ^1H NMR ($CDCl_3$): δ 3.70 (dd, 1H, $J_{5,6a}$ 2.2 Hz, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.71 (dd, 1H, $J_{4,5}$ 9.9 Hz, H-4), 3.72 (dd, 1H, $J_{2,3}$ 9.5 Hz, H-2), 3.77 (dd, 1H, $J_{5,6b}$ 3.3 Hz, H-6b), 3.88 (1H, ddd, H-5), 3.95 (1H, dd, $J_{3,4}$ 9.3 Hz, H-3), 4.67 (d, 1H, $J_{1,2}$ 6 Hz, H-1), 4.50–5.0 (m, 8H, $PhCH_2$), 7.00–7.40 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$): δ 67.0 (C-1), 67.9 (C-6), 73.6, 74.0, 75.2, 76.0 ($PhCH_2$), 76.2 (C-5), 76.3, 76.4 (C-2, C-4), 83.2 (C-3), 115.5 (CN), 127.0–130.0 (Ph), 137.0, 137.4, 138.3, 138.5 (C_q); MS (ESI): *m/z* 572.7 $[M+Na]^+$.

4.8. 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl cyanide (1d-β)

Synthesis of **1d-β** was started from benzobromoglucose[25] which was transformed into the benzoylated β-D-glucopyranosyl cyanide[26] followed by deacetylation[23] and benzylation. $[\alpha]_D^{20}$ +25.0 (*c* 1.5, $CHCl_3$); R_f 0.23 (hexanes–EtOAc, 8:2); ^1H NMR ($CDCl_3$): δ 3.40 (ddd, 1H, $J_{5,6a}$ 3.8 Hz, $J_{5,6b}$ 2.4 Hz, H-5), 3.59 (dd, 1H, $J_{3,4}$ 9.2 Hz, H-3), 3.64 (dd, 1H, $J_{4,5}$ 9.4 Hz, H-4), 3.69 (m, 2H, H-6a, H-6b), 3.76 (dd, 1H, $J_{2,3}$ 8.6 Hz, H-2), 4.05 (d, 1H, $J_{1,2}$ 10.0 Hz, H-1), 4.40–5.0 (m, 8H, $PhCH_2$), 7.00–7.40 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$): δ 67.64 (C-1), 68.29 (C-6), 73.70, 75.28, 75.84, 77.02 (C-4), 79.75 (C-2), 80.00 (C-5), 85.60 (C-3), 116.85 (CN), 127.74 – 128.59 (Ph), 136.93, 137.58, 137.77, 138.08 (C_q); MS (ESI): *m/z* 572.6 $[M+Na]^+$.

4.9. 2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl cyanide (1e-α)

Permethyl α-D-glucopyranosyl cyanide (**1e-α**) was synthesized from 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-α/β-D-glucopyranose[24] with TMSCN in the presence of boron trifluoride etherate[20] and the anomers were separated by column chromatography. Mp 73–75 °C; $[\alpha]_D^{20}$ +108 (*c* 0.80, $CHCl_3$); R_f 0.35 (hexanes–EtOAc, 1:1); ^1H NMR ($CDCl_3$): δ 3.21 (dd, 1H, *J* 9.0, 9.3 Hz, CH), 3.34 (m, 1H, CH), 3.38 (m, 1H, CH), 3.41, 3.53, 3.55, 3,66 (s, 12H, CH_3), 3.62 (m, 2H, H-6a, H-6b), 3.69 (m, 1H, CH), 4.90 (d, 1H, $J_{1,2}$ 5.7 Hz, H-1), ^{13}C NMR ($CDCl_3$): δ 59.13, 59.38, 60.59, 61.07 (CH_3), 66.12 (C-1), 70.29 (C-6), 75.87 (CH), 77.94 (CH), 79.00 (CH), 84.52 (CH), 115.10 (CN); MS (ESI): *m/z* 246.3 $[M+H]^+$.

4.10. 2,3,4,6-Tetra-*O*-methyl-β-D-glucopyranosyl cyanide (1e-β)

Permethyl β-D-glucopyranosyl cyanide (**1e-β**) was synthesized from 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-α/β-D-glucopyranose[24] with TMSCN in the presence of boron trifluoride etherate[20] and the anomers were separated by column chromatography. $[\alpha]_D^{20}$ +44.0 (*c* 1.0, $CHCl_3$); R_f 0.46 (hexanes–EtOAc, 1:1); ^1H NMR ($CDCl_3$): δ 3.14 (dd, 1H, $J_{3,4}$ 8.3, H-3), 3.17 (dd, 1H, $J_{2,3}$ 8.6 Hz, H-2), 3.25 (m, 1H, H-5), 3.33 (m, 1H, H-4), 3.40, 3.53, 3.65, 3,68 (s, 12H, CH_3), 3.57 (m, 1H, H-6a), 3.60 (m, 1H, H-6b), 3.91 (d, 1H, $J_{1,2}$ 10.0 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 59.61, 60.91, 61.31, 61.39 (CH_3), 67.59 (C-1), 70.92 (C-6), 78.67 (C-2), 79.84 (C-5), 81.83 (C-4), 87.70 (C-3), 116.88 (CN); MS (ESI): *m/z* 268.3 $[M+Na]^+$.

4.11. 2,3,4,6-Tetra-*O*-methyl-α-D-mannopyranosyl cyanide (1f-α)

Permethyl α-D-mannopyranosyl cyanide (**1f-α**) was synthesized from 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-α/β-D-mannopyranose[24] with TMSCN in the presence of boron trifluoride etherate[20] and the anomers were separated by column chromatography. $[\alpha]_D^{20}$ +11.9 (*c* 1.0, $CHCl_3$); R_f 0.35 (hexanes–EtOAc, 1:1); ^1H NMR ($CDCl_3$): δ 3.46 (dd, 1H, $J_{4,5}$ 9.0 Hz, H-4), 3.53 (dd, 1H, $J_{3,4}$ 9.0 Hz, H-3), 3.38, 3.49, 3.51, 3.69 (s, 12H, CH_3), 3.64 (m, 1H, H-5), 3.60 (m, 2H, H-6a, H-6b), 3.74 (dd, 1H, $J_{2,3}$ 3.0 Hz, H-2), 4.87 (d, 1H, $J_{1,2}$ 2.4 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 58.18, 58.65, 59.19, 60.73 (CH_3), 64.38 (C-1), 70.85 (C-6), 75.34 (C-4), 76.59 (C-5), 77.20 (C-2), 81.32 (C-3), 115.32 (CN); MS (ESI): *m/z* 268.3 $[M+Na]^+$.

4.12. 2,3,4,6-Tetra-*O*-methyl-β-D-mannopyranosyl cyanide (1f-β)

Permethyl α-D-mannopyranosyl cyanide (**1f-β**) was synthesized from 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-α/β-D-mannopyranose[24] with TMSCN in the presence of boron trifluoride etherate[20] and the anomeric mixture was separated by column chromatography. $[\alpha]_D^{20}$ −9.9 (*c* 1.2, $CHCl_3$), R_f 0.30 (hexanes–EtOAc, 1:1); ^1H NMR

($CDCl_3$): δ 3.18 (dd, 1H, $J_{3,4}$ 9.2 Hz, H-3), 3.25 (m, 1H, H-5), 3.40 (dd, 1H, $J_{4,5}$ 8.8 Hz, H-4), 3.38, 3.49, 3.51, 3.69 (s, 12H, CH_3), 3.56 (dd, 1H, $J_{5,6a}$ 5.4 Hz, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.61 (dd, 1H, $J_{5,6b}$ 2.2 Hz, H-6b), 3.80 (dd, 1H, $J_{2,3}$ 3.0 Hz, H-2), 4.19 (d, 1H, $J_{1,2}$ 1.3 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 58.16, 59.37, 60.90, 61.62 (CH_3), 67.11 (C-1), 71.26 (C-6), 75.47 (C-4), 76.47 (C-2), 80,07 (C-5), 84.3 (C-3), 115.76 (CN); MS (ESI): *m/z* 268.3 $[M+Na]^+$.

4.13. General procedure for the reductive hydrolysis of glycosyl cyanides

Glycosyl cyanides (**1a-f**, **3a-b**, **5a-b**, 0.2 mmol) were dissolved in dry CH_2Cl_2 (3 mL) and DIBAL-H (280 μL of 1 M soln in CH_2Cl_2, 0.28 mmol) was added by a syringe at −78 °C under N_2 and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and 1 M NH_4Cl solution (8 mL) was added and stirred at room temperature for 10 min. The layers were separated and the organic layer was dried over Na_2SO_4 and the solvent evaporated in vacuo. The residue was purified by silica gel column chromatography with hexanes–EtOAc eluents.

4.13.1. (2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)methanal (2a-α)

R_f 0.19 (hexanes–EtOAc, 6:4); ^1H NMR ($CDCl_3$): δ 3.61 (m, 1H, H-5), 3.64 (dd, 1H, $J_{3,4}$ 4.4 Hz, H-3), 3.85 (dd, 1H, $J_{2,3}$ 10.6 Hz, H-2), 4.01 (m, 1H, H-6a), 4.12 (m, 1H, H-6b), 4.29 (d, 1H, H-4), 4.32 (m, 1H, H-1), 4.45–4.91 (m, 8H, $PhCH_2$), 7.11–7.41 (m, 20H, Ph), 9.79 (s, 1H, CHO); MS (ESI): *m/z* 553.6 $[M+H]^+$.

4.13.2. (2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl)methanal (2a-β)

R_f 0.17 (hexanes–EtOAc, 6:4); ^1H NMR ($CDCl_3$): δ 3.50–3.65 (m, 3H, H-5, H-6a, H-6b), 3.66 (dd, 1H, $J_{3,4}$ 2.7 Hz, H-3), 3.75 (dd, 1H, $J_{1,2}$ 9.8 Hz, H-1), 3.98 (d, 1H, H-4), 4.05 (dd, 1H, $J_{2,3}$ 9.4 Hz, H-2), 4.42–4.99 (m, 8H, $PhCH_2$), 7.03–7.41 (m, 20H, Ph), 9.64 (d, 1H, *J* 1.4 Hz, CHO); MS (ESI): *m/z* 585.4 $[M+Na]^+$.

4.13.3. (2,3,4,6-Tetra-*O*-methyl-α-D-galactopyranosyl)methanal (2b-α)

R_f 0.15 (hexanes–EtOAc, 1:1); ^1H NMR ($CDCl_3$): δ 3.32–3.99 (dd, 5H, H-4), 3.40, 3.53, 3.56, 3.57 (s, 12H, CH_3), 4.27 (m, 1H, CH), 4.42 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 9.81 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 58.57, 59.20, 59.32, 59.75 (CH_3), 66.99 (CH), 70.42 (C-6), 74.86, 75.20, 75.40, 82.04 (CH), 202.49 (CHO); MS (ESI): *m/z* 271.3 $[M+Na]^+$.

4.13.4. (2,3,4,6-Tetra-*O*-methyl-β-D-galactopyranosyl)methanal (2b-β)

R_f 0.12 (hexanes–EtOAc, 1:1); ^1H NMR ($CDCl_3$): δ 3.15 (m, 1H, CH), 3.30–3.79 (m, 5H, CH), 3.40, 3.50, 3.55, 3.58 (s, 12H, CH_3), 4.27 (m, 1H, CH), 3.93 (m, 1H, H-1), 9.69 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 58.51, 59.28, 59.70, 61.59 (CH_3), 66.94 (CH), 70.55 (C-6), 74.80 (CH), 75.13 (CH), 75.34 (CH), 85.02 (CH), 202.46 (CHO); MS (ESI): *m/z* 249.3 $[M+H]^+$.

4.13.5. (2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)methanal (2d-α)

R_f 0.18 (hexanes–EtOAc, 6:4); ^1H NMR spectrum was identical with the reported one.[13] MS (ESI): *m/z* 553.4 $[M+H]^+$.

4.13.6. (2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)methanal (2d-β)

R_f 0.18 (hexanes–EtOAc, 6:4); ^1H NMR ($CDCl_3$): δ 3.52 (ddd, 1H, $J_{5,6a}$ 4.3 Hz, $J_{5,6b}$ 2.0 Hz, H-5), 3.63 (dd, 1H, $J_{4,5}$ 9.6 Hz, H-4), 3.67 (dd, 1H, $J_{2,3}$ 8.7 Hz, H-2), 3.70–3.75 (m, 2H, H-6a, H-6b), 3.76 (dd, 1H, $J_{3,4}$ 8.4 Hz, H-3), 3.82 (dd, 1H, $J_{1,2}$ 9.8 Hz, H-1), 4.52–4.90 (m, 8H, $PhCH_2$), 7.02–7.41 (m, 20H, Ph), 9.65 (d, 1H, *J* 1.6 Hz, CHO); MS (ESI): *m/z* 585.6 $[M+Na]^+$.

4.13.7. (2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl)methanal (2e-α)

R_f 0.12 (hexanes–EtOAc, 1:1); ^1H NMR ($CDCl_3$): δ 3.14–3.68 (m, 4H, CH), 3.40, 3.53, 3.55, 3.66 (s, 12H, CH_3), 3.59 (m, 2H, H-6a, H-6b), 4.47 (d, 1H, $J_{1,2}$ 6.3 Hz, H-1), 9.88 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 59.44, 59.68, 60.88, 61.38 (CH_3), 66.45 (CH), 71.26 (C-6), 76.21, 78.29, 79.35, 84.86 (CH), 201.81 (CHO); MS (ESI): *m/z* 249.4 $[M+H]^+$.

4.13.8. (2,3,4,6-Tetra-*O*-methyl-β-D-glucopyranosyl)methanal (2e-β)

R_f 0.10 (hexanes–EtOAc, 1:1); ^1H NMR ($CDCl_3$): δ 3.09–3.40 (m, 4H, H-2, H-3, H-4, H-5), 3.33, 3.47, 3.60, 3.68 (s, 12H, CH_3), 3.65 (m, 2H, H-6a, H-6b), 3.91 (m, 1H, H-1), 9.68 (d, 1H, *J* 1.5 Hz, CHO); ^{13}C NMR ($CDCl_3$): δ 59.49, 60.38, 60.61, 61.35 (CH_3), 68.08 (CH), 71.84 (C-6), 78.63 (CH), 79.33 (CH), 79.92 (CH), 89.07 (CH), 197.87 (CHO); MS (ESI): *m/z* 271.5 $[M+Na]^+$.

4.13.9. (2,3,4,6-Tetra-*O*-methyl-α-D-mannopyranosyl)methanal (2f-α)

R_f 0.14 (hexanes–EtOAc, 1:1); ^1H NMR ($CDCl_3$): δ 3.07 (dd, 1H, $J_{3,4}$ 9.0 Hz, H-3), 3.39 (dd, 1H, $J_{4,5}$ 8.8 Hz, H-4), 3.38, 3.42, 3.44, 3.46 (s, 12H, CH_3), 3.53 (m, 1H, H-5), 3.58 (dd, 1H, $J_{5,6}$ 5.2 Hz, $J_{6a,6b}$ 9.9 Hz, H-6a), 3.63 (dd, 1H, $J_{5,6b}$ 1.6 Hz, H-6b), 3.98 (dd, 1H, $J_{2,3}$ 3.3 Hz, H-2), 4.39 (d, 1H, $J_{1,2}$ 2.8 Hz, H-1), 9.87 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 57.6, 58.1, 59.2, 60.6 (CH_3), 71.8 (C-6), 74.9 (C-2), 75.6 (C-4), 76.9 (C-5), 79.1 (C-1), 81.6 (C-3), 202.90 (CHO); MS (ESI): *m/z* 271.4 $[M+Na]^+$.

4.13.10. (2,3,4,6-Tetra-*O*-methyl-β-D-mannopyranosyl)methanal (2f-β)

R_f 0.12 (hexanes–EtOAc, 1:1); ^1H NMR ($CDCl_3$): δ 3.19 (m, 1H, CH), 3.30–3.70 (m, 17H, m, CH, H-6a, H-6b, CH_3), 4.01 (m, 1H, CH), 9.67 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 57.8, 59.3, 60.9, 61.3 (CH_3), 72.0 (C-6), 76.2, 76.5, 79.2, 82.1, 85.6 (CH), 201.9 (CHO); MS (ESI): *m/z* 271.4 $[M+Na]^+$.

4.14. Preparation of glycal cyanides

Unprotected β-D-glucosyl[32] or galactosyl[23,32] nitrile (5 mmol) was dissolved in DMF (60 mL) and sodium hydride (1.3 equiv per OH group) were added portionwise in 30 min at ice-bath temperature under nitrogen with vigorous stirring. Benzyl bromide (1.5 equiv per OH group) was added dropwise to the cooled solution and the mixture was allowed to stir at 0 °C for 4 h then overnight at room temperature. The excess sodium hydride was quenched with methanol under cooling and the solvents were removed in motor vacuum. The residue was diluted with CH_2Cl_2 and was washed with water. The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed on silica gel with hexanes–EtOAc (9:1) eluent to afford the corresponding glycal nitriles.

4.14.1. 1-Cyano-3,4,6-tri-*O*-benzyl-D-galactal (3a)

$[\alpha]_D^{20}$ −49.6 (*c* 2.06, $CHCl_3$); R_f 0.26 (hexanes–EtOAc, 8:2); ^1H NMR ($CDCl_3$): δ 3.65 (m, 2H, H-6a, H-6b), 3.97 (dd, 1H, $J_{4,5}$, 1.8 Hz, H-4), 4.16 (m, 1H, H-5), 4.22 (dd, 1H, $J_{3,4}$ 4.0 Hz, H-3), 4.20–4.90 (m, 6H, $PhCH_2$), 5.65 (dd, 1H, $J_{2,3}$ 2.0 Hz, H-2), 7.20–7.40 (m, 15H, Ph); ^{13}C NMR ($CDCl_3$): δ 67.77 (C-6), 69.37, 71.66, 71.91 (CH), 73.65, 74.45, 77.85 ($PhCH_2$), 114.03 (CN), 115.17 (C-2), 127.80–128.85 (Ph), 129.68 (C-1), 137.61, 137.75, 138.15 (C_q); MS (ESI): *m/z* 464.4 $[M+Na]^+$.

4.14.2. 1-Cyano-3,4,6-tri-*O*-benzyl-D-glucal (3b)

$[\alpha]_D^{20}$ −1.80 (*c* 1.08, $CHCl_3$); R_f 0.30 (hexanes–EtOAc, 8:2); ^1H NMR ($CDCl_3$): δ 3.75 (m, 1H, H-6a), 3.79 (m, 1H, H-6b), 3.91 (dd, 1H, $J_{4,5}$ 8.4 Hz, H-4), 4.13 (m, 1H, H-5), 4.20 (dd, 1H, $J_{3,4}$ 6.0 Hz, H-3), 4.49–4.81 (m, 6H, $PhCH_2$), 5.68 (d, 1H, $J_{2,3}$ 3.0 Hz, H-2), 7.18–7.39 (m, 15H, Ph); ^{13}C NMR ($CDCl_3$): δ 67.73 (C-6), 71.74, 73.85, 74.33 ($PhCH_2$), 73.26, 75.18, 78.95 (CH), 113.95 (CN), 114.55 (C-2), 128.00 – 129.25 (Ph), 130.13 (C-1), 137.56, 137.86, 137.89 (C_q); MS (ESI): *m/z* 459.4 $[M+NH_4]^+$.

4.15. 1-*C*-Formyl-3,4,6-tri-*O*-benzyl-D-galactal (4a)

Reductive hydrolysis of **3a** was carried out according to the general procedure described in Section 4.13. $[\alpha]_D^{20}$ −84.0 (*c* 1.10, $CHCl_3$); R_f 0.18 (hexanes–EtOAc, 8:2); ^1H NMR ($CDCl_3$): δ 3.75 (m, 2H, H-6a, H-6b), 4.10 (dd, 1H, $J_{3,4}$ 3.5 Hz, H-3), 4.17 (m, 1H, H-5), 4.41 (m, 1H, H-4), 4.30–5.00 (m, 6H, $PhCH_2$), 5.81 (dd, 1H, $J_{2,3}$ 2.2 Hz, H-2), 7.20–7.40 (m, 15H, Ph), 9.16 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 67.70 (C-6), 69.53 (C-4), 71.57 ($PhCH_2$), 73.03 (C-3), 73.78, 74.62 ($PhCH_2$), 76.75 (C-5), 119.25 (C-2), 127.78–128.82 (Ph), 137.83, 137.84, 138.38 (C_q), 151.64 (C-1), 186.28 (CHO); MS (ESI): *m/z* 467.2 $[M+Na]^+$.

4.16. 1-*C*-Formyl-3,4,6-tri-*O*-benzyl-D-glucal (4b)

Reductive hydrolysis of **3b** was carried out according to the general procedure described in Section 4.13. $[\alpha]_D^{20}$ −23.90 (*c* 0.50, $CHCl_3$); R_f 0.20 (hexanes–EtOAc, 85:15); ^1H NMR ($CDCl_3$): δ 3.85 (m, 2H, H-6a, H-6b), 3.99 (dd, 1H, $J_{4,5}$ 8.7 Hz, H-4), 4.16, (ddd, 1H, $J_{5,6a}$ 3.4, $J_{5,6b}$ 3.4 Hz, H-5), 4.35 (dd, 1H, $J_{3,4}$ 6.4 Hz, H-3), 4.50–4.80 (m, 6H, $PhCH_2$), 5.82 (d, 1H, $J_{2,3}$ 3.0 Hz, H-2), 7.19–7.36 (m, 15H, Ph), 9.21 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 67.95 (C-6), 71.80, 73.81 ($PhCH_2$), 73.87 (C-4), 74.30 ($PhCH_2$), 75.93 (C-3), 77.90 (C-5), 117.26 (CN), 127.93–138.15 (C_q), 151.79 (C-1), 186.40 (CHO); MS (ESI): *m/z* 467.4 $[M+Na]^+$.

4.17. 1-*C*-Formyl-3,4,6-tri-*O*-allyl-D-galactal (4c)

Reductive hydrolysis of **1c-β** carried out as described in Section 4.13. resulted in only this product. $[\alpha]_D^{20}$ −117 (*c* 0.60, $CHCl_3$). R_f 0.32 (hexanes–EtOAc, 1:1); ^1H NMR ($CDCl_3$): δ 3.58 (m, 1H, CH), 3.71–3.83 (m, 4H, CH), 3.96–4.40 (m, 8H, OCH_2), 5.12–5.38 (m, 8H, CH_2=CH), 5.78 (m, 1H, H-2), 5.75–6.03 (m, 4H, CH_2=C*H*), 9.14 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 67.51 (C-6), 69.18 (CH), 70.45, 72.94, 73.70 (OCH_2), 72.56, 72.75, 76.48 (CH), 117.41, 117.56, 117.70 (CH_2=CH), 134.21, 134.33, 134.96 (CH_2=CH), 151.51 (C-1), 186.09 (CHO); MS (ESI): *m/z* 312.1 $[M+H]^+$.

4.18. Preparation of 2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glycopyranosyl cyanides (5a-β, 5b-β)

Protected glycal cyanides (**3a**, **3b**) (1 mmol) were dissolved in ethanol (60 mL) and palladium on carbon (0.8% w/w catalyst/substrate, 36 mg, 10% Pd/C) was added under H_2 in a round-bottomed flask sealed with septum. The mixture was stirred for 4 days supplying H_2 from a balloon. The catalyst was filtered off and the filtrate was evaporated. The residue was chromatographed on silica gel with hexanes–EtOAc (95:5) eluent to afford the corresponding deoxy derivatives.

4.18.1. 2-Deoxy-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl cyanide (5a-β)

Mp 56–58 °C; $[\alpha]_D^{20}$ +4.6 (*c* 1.97, $CHCl_3$); R_f 0.30 (hexanes–EtOAc, 8:2); ^1H NMR ($CDCl_3$): δ 2.08 (m, 1H, H-2a), 2.44 (m, 1H, H-2b), 3.43–3.60 (m, 4H, H-3, H-5, H-6a, H-6b), 3.83 (m, 1H, H-4), 4.18 (dd, 1H, $J_{1,2a}$ 12.0 Hz, $J_{1,2b}$ 2.0 Hz, H-1), 4.38–4.94 (m, 6H, $PhCH_2$), 7.17–7.35 (m, 15H, Ph); ^{13}C NMR ($CDCl_3$): δ 30.86 (C-2), 64.40 (C-1), 69.21 (C-6), 70.71 ($PhCH_2$), 72.22 (C-4), 73.88, 74.77 ($PhCH_2$), 77.31, 78.85 (CH), 117.34 (CN), 127.68–128.88 (Ph), 137.97, 137.99, 138.67 (C_q); MS (ESI): *m/z* 444.0 $[M+H]^+$.

4.18.2. 2-Deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl cyanide (5b-β)

$[\alpha]_D^{20}$ +24.4 (*c* 0.90, $CHCl_3$); R_f 0.34 (hexanes–EtOAc, 8:2); ^1H NMR ($CDCl_3$): δ 1.97 (m, 1H, H-2a), 2.40 (m, 1H, H-2b), 3.38 (m, 1H, H-4), 3.51–3.65 (m, 2H, H-3, H-5), 3.70 (m, 2H, H-6a, H-6b), 4.19 (dd, 1H, $J_{1,2a}$ 12.0 Hz, $J_{1,2b}$ 2.1 Hz, H-1), 4.47–4.90 (m, 6H, $PhCH_2$), 7.17–7.35 (m, 15H, Ph); ^{13}C NMR ($CDCl_3$): δ 35.33 (C-2), 63.89 (C-1), 68.85 (C-6), 72.16 ($PhCH_2$), 73.85 ($PhCH_2$), 75.51 ($PhCH_2$), 77.24 (CH), 79.42 (CH), 80.27 (C-4), 117.13 (CN), 127.95–128.78 (Ph), 138.00, 138.06, 138.19 (C_q); MS (ESI): *m/z* 444.3 $[M+H]^+$.

4.19. (2-Deoxy-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)methanal (6a-β)

Reductive hydrolysis of **5a-β** was carried out according to the general procedure described in Section 4.13. $[\alpha]_D^{20}$ +5.50 (*c* 0.37, $CHCl_3$); R_f 0.17 (hexanes–EtOAc, 6:4); ^1H NMR ($CDCl_3$): δ 1.99 (q, 1H, *J* 12.3 Hz, H-2a), 2.11 (m, 1H, H-2b), 3.59 (m, 2H, H-6a, H-6b), 3.60 (dd, 1H, $J_{5,6a}$ 5.1 Hz, $J_{5,6b}$ 5.4 Hz, 1H, H-5), 3.62 (dd, *J* 2.1, 9.0 Hz, 1H, CH), 3.80 (dd, 1H, *J* 2.7, 12.0 Hz, 1H, CH), 3.86 (br, 1H, H-4), 4.41–4.96 (m, 6H, $PhCH_2$), 7.18–7.39 (m, 15H, Ph), 9.68 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 27.44 (CH_2), 69.77 (C-6), 70.45 ($PhCH_2$), 72.86 (C-4), 73.85 ($PhCH_2$), 74.69 ($PhCH_2$), 78.13 (CH), 78.20 (C-5), 80.34 (CH), 127.55–128.74 (Ph), 138.05, 138.31, 138.78 (C_q), 201.43 (CHO); MS (ESI): *m/z* 469.4 $[M+Na]^+$.

4.20. (2-Deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)methanal (6b-β)

Reductive hydrolysis of **5b-β** was carried out according to the general procedure described in Section 4.13. $[\alpha]_D^{20}$ +17.0 (*c* 0.94, $CHCl_3$); R_f 0.15 (hexanes–EtOAc, 6:4); ^1H NMR ($CDCl_3$): δ (ppm): 1.50 (m, 1H, H-2a), 2.39 (m, 1H, H-2b), 3.41–3.82 (m, 6H, H-1, H-3, H-4, H-5, H-6, H-6′), 4.42–4.93 (m, 6H, $PhCH_2$), 7.17–7.34 (m, 15H, Ph), 9.70 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ (ppm): 31.54 (C-2), 69.13 (C-6), 71.43, 73.57, 75.15 ($PhCH_2$), 77.74, 79.14, 79.44, 80.27 (C-1, C-3, C-4, C-5), 127.61–128.48 (Ph), 137.94, 138.11, 138.21 (C_q), 200.76 (CHO); MS (ESI): *m/z* 469.4 $[M+Na]^+$.

4.21. 1,3-Diphenyl-2-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-imidazolidine (7a-β)

Compound 1a-β (55 mg, 0.1 mmol) was dissolved in dry CH_2Cl_2 (2 mL) and DIBAL-H (140 μL of 1 M soln in CH_2Cl_2, 0.14 mmol) was added by a syringe at −78 °C under N_2 and the reaction mixture was stirred for 30 min. Glacial acetic acid (10 μL, 0.18 mmol) was added and the mixture was stirred for 5 min at −78 °C. Then *N*,*N*′-diphenylethylenediamine (43 mg, 0.2 mmol) dissolved in methanol (2 mL) was added and the stirring was continued overnight at room temperature. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1 M NH_4Cl solution (8 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated in vacuo. The residue was purified by silica gel column chromatography (hexanes–EtOAc, 9:1) to give **7a-β** as a white crystalline material. Mp 38–39 °C; $[\alpha]_D^{20}$ +80.0 (*c* 1.0, $CHCl_3$); R_f 0.37 (hexanes–EtOAc, 8:2); ^1H NMR ($CDCl_3$): δ (ppm): 3.42 (m, 2H, NCH_2), 3.51 (m, 1H, H-5), 3.52 (m, 2H, NCH_2), 3.55 (m, 1H, H-4), 3.62 (d, 1H, $J_{1,2}$ 9.9 Hz, H-1), 3.70 (d, 2H, *J* 6.6 Hz, H-6a, H6b), 3.92 (m, 1H, H-2), 3.93 (br s, 1H, H-3), 4.41–5.09 (m, 8H, $PhCH_2$), 5.50 (s, 1H, NCHN), 6.68–6.75 (m, 4H, CH), 6.85 (m, 2H, Ph), 7.13–7.35 (m, 24H, Ph);

^{13}C NMR ($CDCl_3$): δ (ppm): 46.38, 47.15 (NCH_2), 69.49 (C-6), 72.05, 73.72, 74.25, 74.37 ($PhCH_2$), 73.74 (C-3), 75.26 (C-2), 76.76 (C-5), 76.83 (NCHN), 80.63 (C-1), 86.12 (C-4), 112.89, 114.14, 117.18, 117.69 (Ph), 126.81–129.55 (Ph), 138.16, 138.36, 139.43, 139.74, 146.31, 147.13 (C_q); MS (ESI): *m/z* 747.6 $[M+H]^+$.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.04.019.

References

1. Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *Tetrahedron Lett.* **1992**, *33*, 737–740.
2. Wong, C.-H.; Moris-Varas, F.; Hung, S.-C.; Marron, T. G.; Lin, C.-C.; Gong, K. W.; Weitz-Schmidt, G. *J. Am. Chem. Soc.* **1997**, *119*, 8152–8158.
3. Zhai, D.; Williams, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 2501–2505.
4. Stork, G.; Suh, H. K.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054–7056.
5. Sánchez, M. E. L.; Michelet, V.; Besnier, I.; Genet, J. P. *Synlett* **1994**, 705–708.
6. Desire, J.; Veyrieres, A. *Carbohydr. Res.* **1995**, *268*, 177–186.
7. Ajaj, A. K.; Hennig, L.; Findeisen, M.; Giesa, S.; Muller, D.; Welzel, D. *Tetrahedron* **2002**, *58*, 8439–8451.
8. Petrusova, M.; BeMiller, J. N.; Krihova, A.; Petrus, L. *Carbohydr. Res.* **1996**, *295*, 57–67.
9. Zeitouni, J.; Norsikian, S.; Lubineau, A. *Tetrahedron Lett.* **2004**, *45*, 7761–7763.
10. Dondoni, A.; Marra, A.; Scherrmann, M.-C. *Tetrahedron Lett.* **1993**, *34*, 7323–7326.
11. Dondoni, A.; Scherrmann, M.-C. *Tetrahedron Lett.* **1993**, *34*, 7319.
12. Dondoni, A.; Schermann, M.-C. *J. Org. Chem.* **1994**, *59*, 6404.
13. Dondoni, A.; Marra, A. *Tetrahedron Lett.* **2003**, *44*, 13.
14. Labeguere, F.; Lavergne, J.-P.; Martinez, J. *Tetrahedron Lett.* **2002**, *43*, 7271–7272.
15. Hudlicky, M. Reduction of Nitriles. In *Reductions in Organic Chemistry*, 2nd ed.; ACS: Washington, 1996; pp 239–243.
16. Albrecht, H. P.; Repke, D. B.; Moffatt, J. G. *J. Org. Chem.* **1973**, *38*, 1836–1840.
17. Dettinger, H. M.; Kurz, G.; Lehmann, J. *Carbohydr. Res.* **1979**, *74*, 301–307.
18. Frische, K.; Schmidt, R. R. *Liebigs Ann. Chem.* **1994**, *3*, 297–304.
19. Wanzlick, H. W.; Löchel, W. *Chem. Ber.* **1953**, *86*, 1463–1466.
20. Garcia-Lopez, M.-T.; De las Heras, F. G.; San Felix, A. *J. Carbohydr. Chem.* **1987**, *6*, 273–279.
21. Hoffmann, M. G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1985**, *12*, 2403–2419.
22. Helferich, B.; Bettin, K. L. *Chem. Ber.* **1961**, *94*, 1159–1160.
23. Somsak, L. *Carbohydr. Res.* **1996**, *286*, 167–171.
24. Jensen, H. H.; Nordstroem, L. U.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205–9213.
25. Lockhoff, O. In *Methoden der Organischen Chemie (Houben-Weyl)*; Hagemann, H., Klamann, D., Eds.; Thieme: Stuttgart, 1992; Vol. E14a/3, p 708.
26. Somsak, L.; Nagy, V.; Docsa, B.; Toth, B.; Gergely, P. *Tetrahedron: Asymmetry* **2000**, *11*, 405–408.
27. Mahmoud, S. H.; Somsak, L. *Carbohydr. Res.* **1994**, *254*, 91–104.
28. Banaszek, A. *Tetrahedron* **1995**, *51*, 4231–4238.
29. Dondoni, A.; Zuurmond, H. M.; Boscarato, A. *J. Org. Chem.* **1997**, 8114–8124.
30. Somsak, L. *Chem. Rev.* **2001**, *101*, 81–135.
31. Dondoni, A.; Massi, A.; Sabbatini, S. *Chem. Eur. J.* **2005**, *11*, 7110–7125.
32. Myers, R. W.; Lee, Y. C. *Carbohydr. Res.* **1986**, *152*, 143–158.