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PII: S0008-6215(18)30052-1

DOI: 10.1016/j.carres.2018.02.010

Reference: CAR 7526

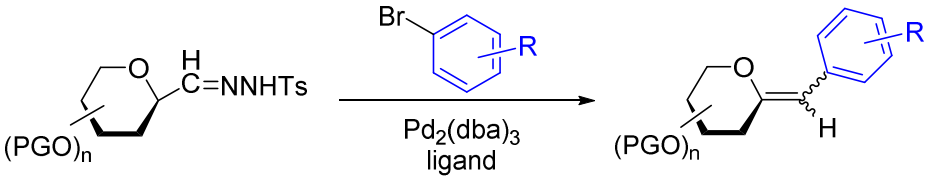
To appear in: *Carbohydrate Research*

Received Date: 29 January 2018

Revised Date: 16 February 2018

Accepted Date: 16 February 2018

Please cite this article as: Tí. Kaszás, A. Ivanov, M. Tóth, P. Ehlers, P. Langer, Láó. Somsák, Pd-catalyzed coupling reactions of anhydro-aldose tosylhydrazones with aryl bromides to produce substituted *exo*-glycals, *Carbohydrate Research* (2018), doi: 10.1016/j.carres.2018.02.010.



Sugar configuration:
D-*gluco*, D-*galacto*
PG = Bz, Ac, Me

12 examples (11-75 %)
R = H, 4-CH_3, 4-OCH_3, 4-F,
4-Cl, 4-NO_2, 3-CN, 4-CN

Pd-catalyzed coupling reactions of anhydro-aldose tosylhydrazones with aryl bromides to produce substituted *exo*-glycals

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Abstract

Palladium-catalyzed cross-couplings of *O*-peracylated and *O*-permethylated 2,6-anhydro-aldose tosylhydrazones with aryl halides were studied under thermic conditions in the presence of LiO*t*Bu and phosphine ligands. The reactions gave the corresponding aryl substituted *exo*-glycals as mixtures of diastereomers in 11-75% yields. The transformations represent a new access to these types of glycomimetic compounds. The double bond of some aryl substituted *exo*-glycals was saturated to give good yields of benzylic *C*-glycosyl derivatives.

Keywords: Cross coupling; Pd-catalysis; Anhydro-aldose tosylhydrazones; Carbenes; Substituted *exo*-glycals.

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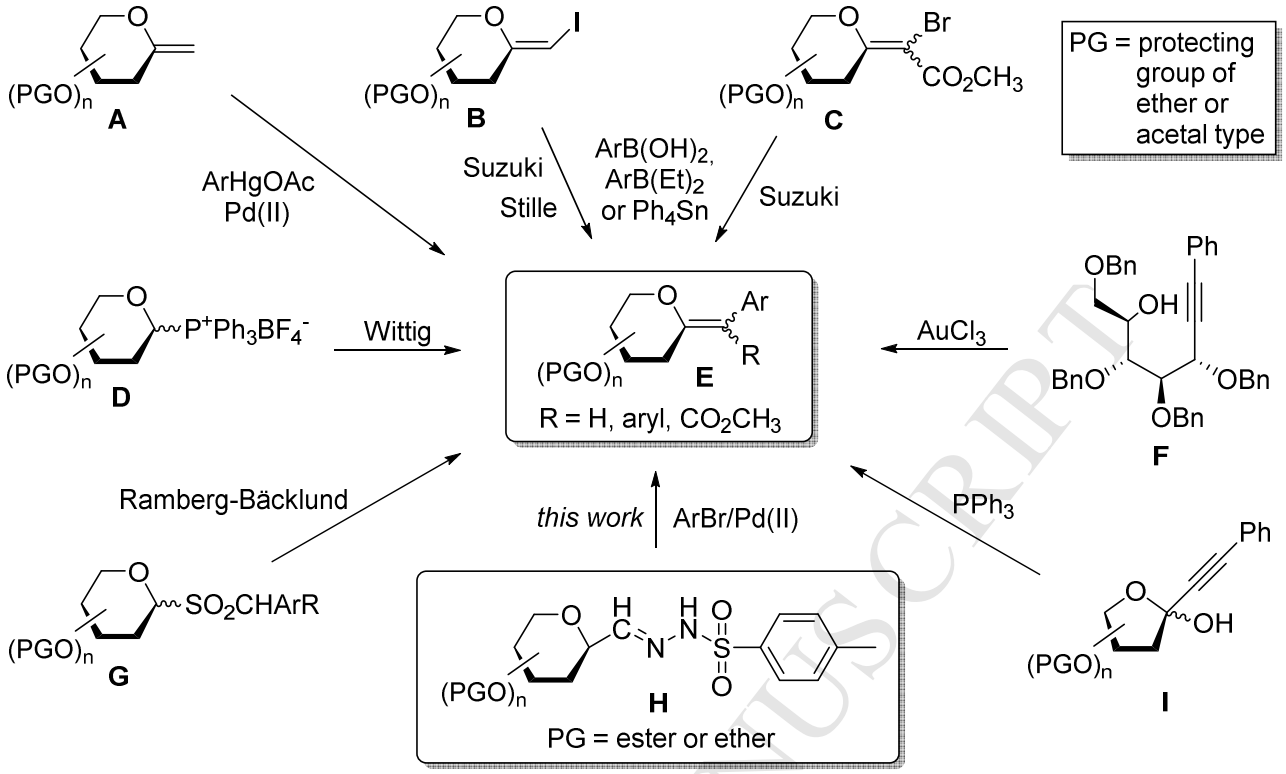
1. Introduction

Formation of a carbon-carbon bond at the anomeric position of carbohydrates has received great attention due to the versatile applicability of such sugar derivatives as chiral synthons in syntheses of complex natural products as well as to manyfold biological activities of *C*-glycosyl compounds [1-3]. As a part of a program targeting the systematic study of applications of anhydro-aldose tosylhydrazones (compounds **H** in Scheme 1) as coupling partners in metal-free [4, 5] and transition metal-catalyzed coupling reactions we have been interested in the Pd-catalyzed coupling of **H** with bromobenzenes. According to general mechanistic considerations, such coupling reactions [6-8] are expected to result in substituted *exo*-glycals (compounds **E** in Scheme 1). Aryl substituted pyranoid *exo*-glycals represent valuable starting compounds for the syntheses of benzylic *C*-glycosyl derivatives [9-11], also elaborated to porphyrine glycoconjugates [12], *C*-glycosyl benzyl alcohols used to get glycosidase inhibitors [13], ketopyranose derivatives [14] including disaccharides [15], and spiro-oxazolines [16].

In the literature only a few methods have been published for the preparation of aryl substituted *exo*-glycals with a pyranoid ring. In the earliest report *O*-perbenzylated *exo*-glucal **A** was applied as the starting material (Scheme 1) in a Pd(II)-catalyzed reaction with arylmercury(II) acetate to yield substituted *exo*-glucal **E** [17]. (*Z*)-Configured iodo-*exo*-glycals **B** of the D-*gluco*-, D-*manno*- and D-*galacto*- series underwent Suzuki or B-alkyl Suzuki cross-coupling reactions with boronic acids or boranes to yield aryl and hetaryl functionalized *exo*-glycals **E** in a stereoselective manner [18]. *O*-Permethylated (*Z*)-*exo*-glucal **E** could be conveniently prepared in a convergent way by a Stille cross-coupling of (*Z*)-iodo-

exo-glucal **B** with tetraphenyl stannane [19]. Stereoselective palladium-catalyzed Suzuki cross-couplings of acetal-protected bromo methoxycarbonyl-*exo*-mannals **C** with boronic acids were carried out to obtain phenyl methoxycarbonyl-*exo*-glycals **E** [20]. Wittig reactions of an anomeric mixture of the *O*-perbenzylated 2-deoxy-D-galactopyranosyl phosphonium salt **D** with arenecarboxaldehydes gave mixtures of *E/Z*-isomers of **E** [11, 15, 16]. Ramberg-Bäcklund rearrangement of protected glycosyl sulfones **G** yielded the corresponding *E/Z*-isomeric mixtures of phenyl- or diphenyl substituted *exo*-glycals **E** [12, 21]. A gold-catalyzed ring-closure reaction of alkyne **F** was developed for the synthesis of *O*-perbenzylated (*Z*)-phenyl-*exo*-glucal **E** [10]. Phosphine-mediated cycloisomerization of alkynyl-substituted hemiketals **I** resulted in acetal-protected phenyl-substituted *exo*-glycals **E** as single *Z*-diasteromers with a 2-keto functionality in the pyranoid ring [22].

In most of the above methods base stable protecting groups had to be applied and/or the reagents like boronic acids [23] or stannanes [24] needed be prepared from aryl halides. In the present work we have investigated the formation aryl substituted *exo*-glycals **E** in the first Pd-catalyzed cross coupling reactions of ester or ether protected anhydro-aldose tosylhydrazones **H** with easily available aryl bromides.



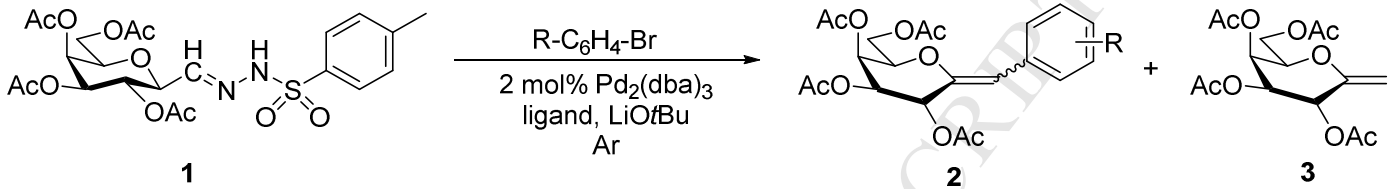
Scheme 1. Strategies for the synthesis of aryl-substituted exo-glycals.

2. Results and discussion

Optimal reaction conditions were sought for by applying literature conditions [25] to tosylhydrazone **1** [26-28] and bromobenzene (1,4-dioxane, 70 ^{o}C with 2 mol% tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) catalyst in the presence of LiO*t*Bu and XPhos, Table 1). Both short and longer reaction times resulted in moderate yields with the XPhos ligand (entries 1 and 2). Other ligands such as SPhos, RuPhos and P(4-F-$C_6H_4)_3$ were found to be also effective (entries 3-5, respectively), however, the yield did not improve significantly. On the other hand, P(2-furyl)$_3$ proved ineffective in this reaction (entry 6). It was observed that 4 mol% of CataCXium A gave the better result both in short and longer times (entries 7 and 8), however, application of 10 mol% did not affect the yield (entry 9).

The application of toluene as the solvent was not favourable in this reaction (entry 10). Reducing the reaction temperature to 60 ^{o}C (entry 11) resulted in the formation of exo-galactal **3** only, while raising the temperature to 100 ^{o}C did not improve the the yield as compared to that of the reaction at 70 ^{o}C (entry 12). Reducing the amount of LiO*t*Bu resulted in a diminished yield (entry 13). Performing the reaction with 1-bromo-chlorobenzene or 4-bromoanisole gave only low yields of the expected products (entries 14, 15). The target compounds **2** were always obtained as inseparable mixtures of diastereoisomers and the formation of the by-product *exo*-galactal **3** could never be avoided.

Table 1. Optimization of the reaction conditions and coupling of tosylhydrazone **1** with aryl bromides



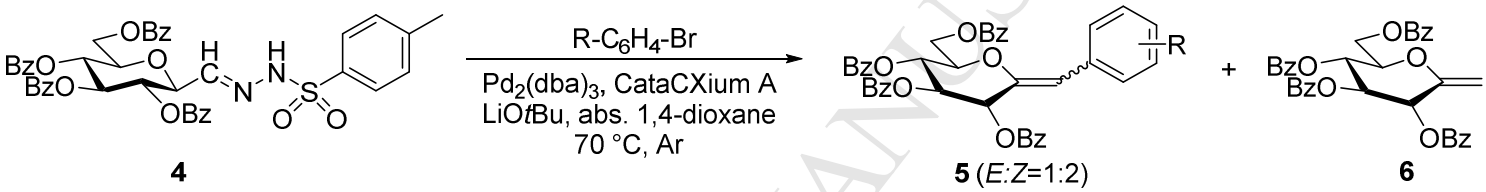
Entry		R	R-C_6H_4-Br equiv.	LiOtBu equiv.	Ligand (mol%)	Solvent	T (°C)	t (h)	Yield (%)[a]		
									2	*E:Z* for **2**	**3**[b]
1	**a**	H	3	2.2	XPhos (4)	1,4-Dioxane	70	2	31		+
2	**a**	H	3	2.2	XPhos (4)	1,4-Dioxane	70	18	24	1:4	31
3	**a**	H	3	2.2	SPhos (4)	1,4-Dioxane	70	18	40		+
4	**a**	H	3	2.2	RuPhos (4)	1,4-Dioxane	70	18	28		+
5	**a**	H	3	2.2	P(4-F-C_6H_4)$_3$ (4)	1,4-Dioxane	70	18	34		+
6	**a**	H	3	2.2	P(2-furyl)$_3$ (4)	1,4-Dioxane	70	18	-	-	+
7	**a**	H	3	2.2	CataCXium A (4)	1,4-Dioxane	70	3	44	1:3	22
8	**a**	H	3	2.2	CataCXium A (4)	1,4-Dioxane	70	18	44	1:3	19
9	**a**	H	3	2.2	CataCXium A (10)	1,4-Dioxane	70	18	44		+
10	**a**	H	3	2.2	CataCXium A (4)	Toluene	70	18	10	1:4	18
11	**a**	H	3	2.2	CataCXium A (4)	1,4-Dioxane	60	18	-		+

12	**a**	H	3	2.2	CataCXium A (4)	1,4-Dioxane	100	18	42	1:3	25
13	**a**	H	6	1.5	CataCXium A (4)	1,4-Dioxane	70	20	17	1:6	3
14	**b**	4-Cl	6	2.2	CataCXium A (4)	1,4-Dioxane	70	16	6	1:3	2
15	**c**	4-CH_3O	3	2.2	CataCXium A (4)	1,4-Dioxane	70	3	21	1:4	16

[a] Yields calculated on the basis of the proton NMR spectra of the worked-up reaction mixture.
[b] Observation of *exo*-glycal **3** without determination of its proportion is denoted by +.

The examinations were extended to the D-*gluco* configured tosylhydrazone **4** [27, 28] (Table 2). The corresponding phenyl substituted *exo*-glucal **5a** was isolated in moderate yields (entries 1, 2). The coupling was found to be not significantly affected by the substituents on the aromatic ring; both electron-rich (entries 3, 4) and electron-deficient (entries 5-8) bromobenzenes gave more or less similar yields of the expected products. The *exo*-glucal by-product **6** always formed in significant quantitities.

Table 2. Pd-catalyzed coupling of tosylhydrazone **4** with aryl bromides

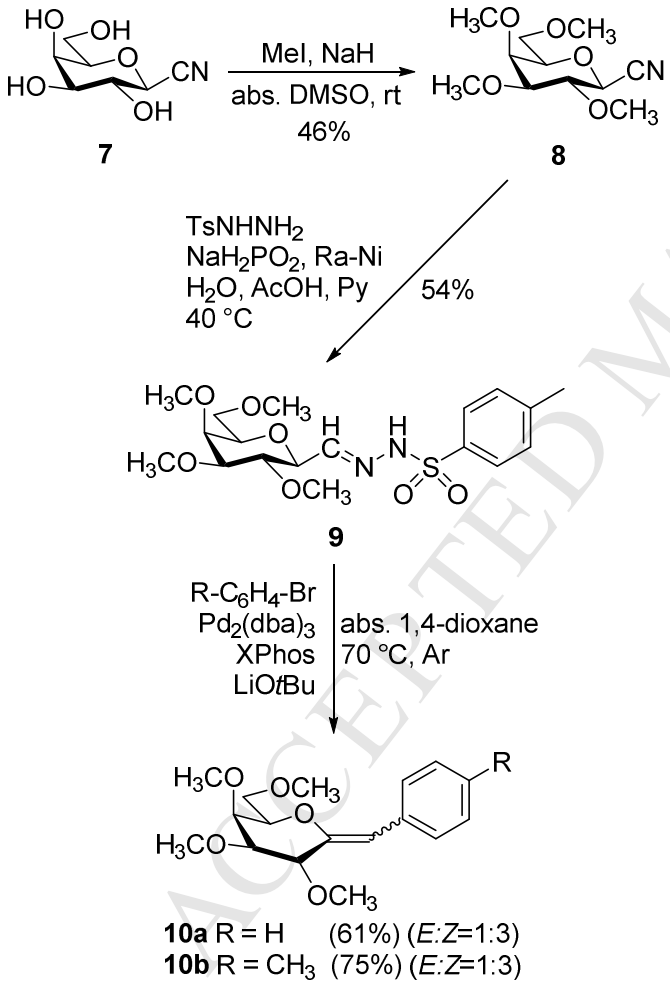


Entry		R	R-C_6H_4-Br equiv.	LiO*t*Bu equiv.	t (h)	Yield (%)		
						5	*E:Z* for **5**	**6**[b]
1	**a**	H	3	2.2	1.5	24[a]	1:2	36[a]
2	**a**	H	6	1.5	20	17[a]	1:2.5	20[a]
3	**b**	4-CH_3	6	2.2	15	41[a]	1:2	19[a]
4	**c**	4-CH_3O	3	2.2	2.5	11	1:2	27
5	**d**	4-F	6	2.2	15	32[a]	1:2	16[a]
6	**e**	4-NO_2	6	1.5	16	33	1:2	24
7	**f**	4-CN	6	2.2	15	46	1:2	4
8	**g**	3-CN	6	1.5	16.5	20	1:2	+

[a] Yields calcdulated on the basis of the proton NMR spectra of the worked-up reaction mixture.
[b] Observation of *exo*-glycal **6** without determination of its proportion is denoted by +.

To get an insight into the effect of an ether type protecting group on the outcome of the studied coupling reaction, the known β-D-galactopyranosyl cyanide [29] (**7**, Scheme 2) was

O-permethylated under Hakomori conditions to give **8** [30]. Reduction of **8** in the presence of tosylhydrazine under literature conditions [26-28] furnished the *O*-methyl protected anhydro-aldose tosylhydrazone **9** in medium yield. Coupling of **9** with aryl bromides gave the substituted *exo*-galactals **10** in good yields. The corresponding unsubstituted *exo*-glycal by-product was not present in the reaction leading to **10a**, and a very minor amount of it could be detected in the ^{1}H NMR spectrum of the crude mixture giving **10b**.



Scheme 2. Preparation of an ether protected anhydro-aldose tosylhydrazone and its coupling with aryl bromides.

In the case of compounds **5f** nuclear Overhauser effects were observed between the *ortho* protons of the phenyl ring and the olefinic hydrogen as well as H-2 allowed to assign the *E*-

configuration of the double bond while only the *ortho* protons and the olefinic one were in the vicinity of each other in the *Z*-isomer (Fig. 1). In addition, a significant difference in the chemical shift of the olefinic proton was observed for the isomers which proved to be general and was used as a diagnostic means to determine the configuration of the double bond in these series of compounds (D-*galacto* series: 6.54-6.46 ppm for (*E*)-**2**, 5.76-5.70 ppm for (*Z*)-**2**, 6.34, 6.30 ppm for (*E*)-**10**, 5.83, 5.82 ppm for (*Z*)-**10**; D-*gluco* series: 6.68-6.57 ppm for (*E*)-**5**, 5.98-5.85 ppm for (*Z*)-**5**).

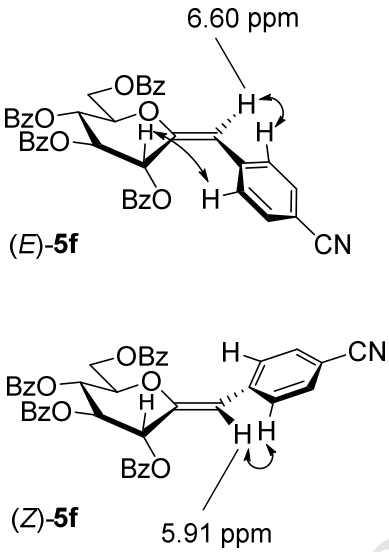
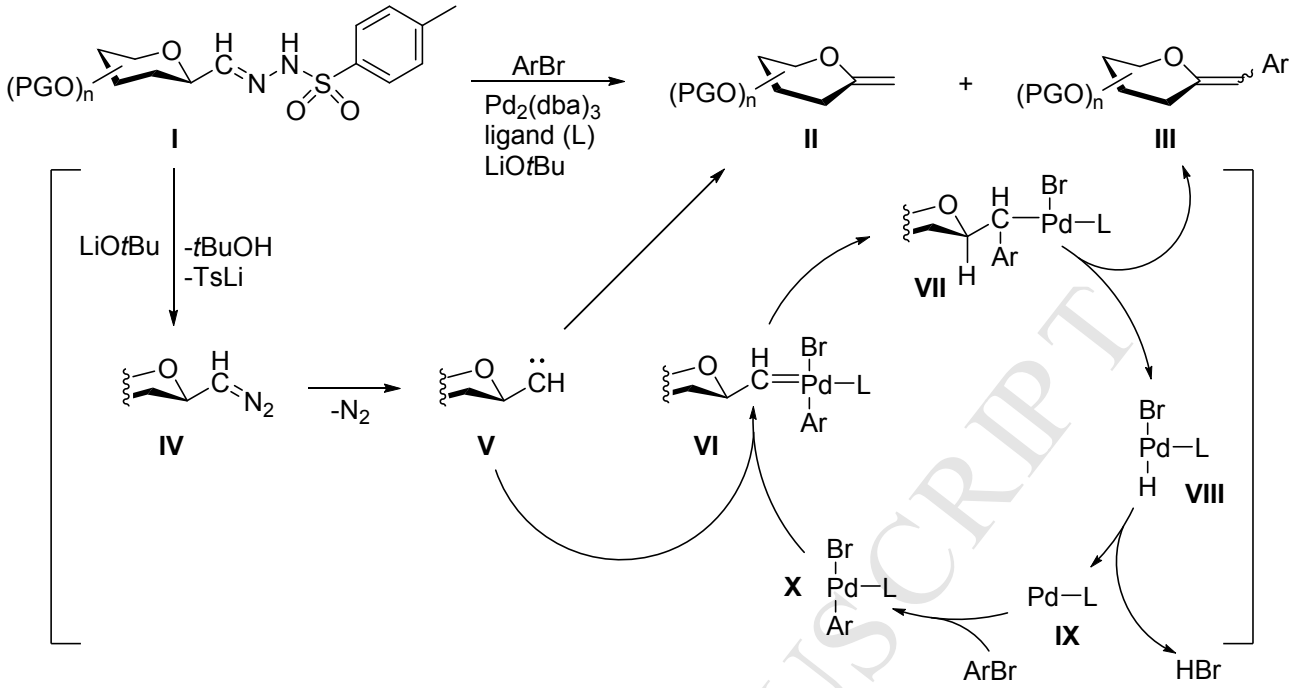


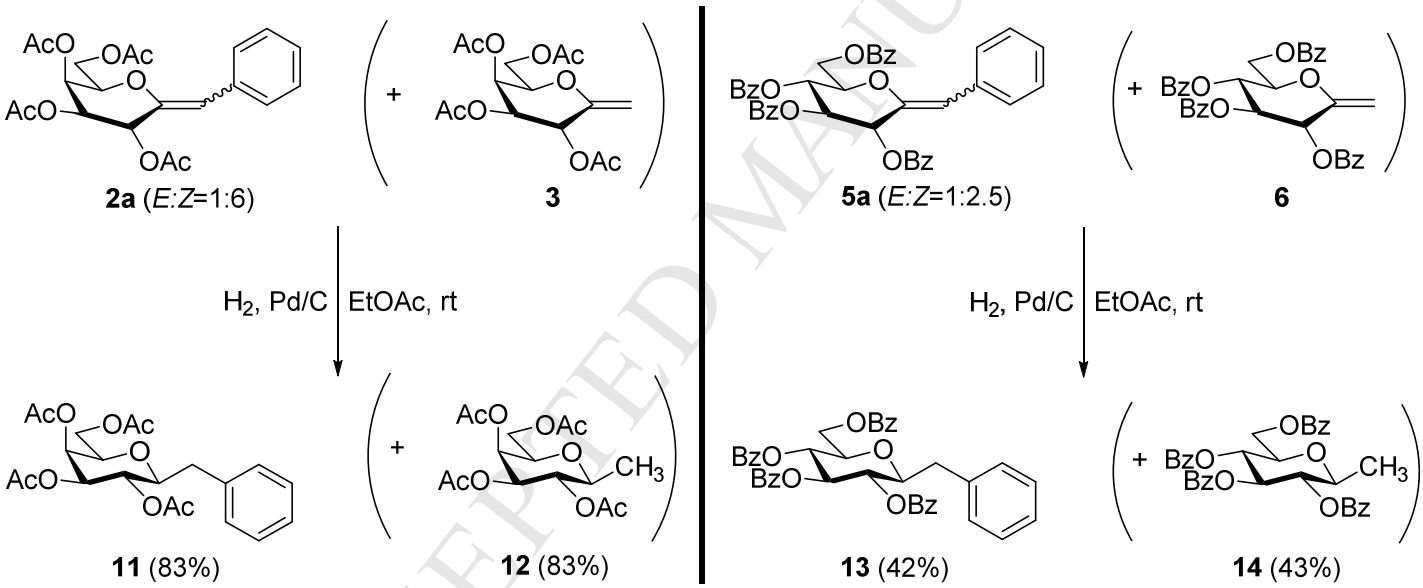
Figure 1. Characteristic NMR data for the configuration of the double bond in *E/Z* isomers of compounds **5f** (↔ denotes observed n. O. e.).



Scheme 3. Plausible mechanism of the transformations.

The formation of mixtures of substituted and unsubstituted *exo*-glycals in the studied transformations can be explained by considering the mechanistic possibilities outlined in Scheme 3. Tosylhydrazones **I** upon deprotonation and loss of a sulfinate ion may lead to the diazo intermediate **IV** which can give rise to carbene **V** by eliminating a nitrogen molecule. Carbene **V** may either undergo an intramolecular C–H insertion to form the *exo*-glycal **II** [27, 28] or enter the usual catalytic cycle to produce **VI** by coordinating to the arylpalladium species **X** formed by an oxidative addition of ArBr to **IX**. Migration of the Ar moiety leads to **VII** which, upon β-hydride elimination, furnishes the substituted *exo*-glycal **III** and the Pd-complex **VIII** which loses HBr to complete the catalytic cycle. Since the intramolecular carbene insertion (**V→II**) competes with the intermolecular complexation (**V→VI**) the formation of **II** is practically unavoidable.

In order to assess the synthetic utility of these *exo*-glycals, the mixtures **2a** + **3** and **5a** + **6** were subjected to catalytic hydrogenation over Pd/C (Scheme 4). These reactions gave good yields of the expected benzylic *C*-glycosyl derivatives **11** and **13**, as well as the by-products **12** and **14**, respectively (isolated yields refer to the substituted *vs* unsubstituted *exo*-glycal components of the respective mixtures). The configuration of the „anomeric" carbon in these compounds was assigned as β on the basis of the vicinal proton-proton coupling constanst (**11**: *J* 9.6 Hz, **12**: *J* 9.0 Hz, **13**: *J* 9.8 Hz, **14**: *J* 9.7 Hz). The very high stereoselectivity of these reductions is in accord with previous literature results [9-11].



Scheme 4. Hydrogenation of the double bonds of the *exo*-glycals.

In conclusion, this study on the Pd-catalyzed couplings of *O*-peracylated 2,6-anhydro-aldose tosylhydrazones with bromobenzenes revealed that the reactions gave the expected aryl substituted *exo*-glycals as mixtures of diastereomers in low to good yields. The method resulted in very good yields with *O*-permethylated sugar tosylhydrazones. The sugar configuration seemed not to have any effect on the outcome of the transformations. Thus,

such coupling reactions provide a new general method for the preparation of aryl substituted *exo*-glycals whose synthetic utility was demonstrated by their reduction to give benzylic *C*-glycosyl compounds.

3. Experimental

3.1. General methods

Optical rotations were determined with a Perkin–Elmer 241 polarimeter at room temperature. NMR spectra were recorded with Bruker Avance 250 II (250/63 MHz for $^{1}H/^{13}C$), Bruker Avance 300 III (300/75 MHz for $^{1}H/^{13}C$), Bruker 360 AM Avance (360/90 MHz for $^{1}H/^{13}C$) or Bruker DRX 400 (400/100 MHz for $^{1}H/^{13}C$) spectrometers. Chemical shifts are referenced to TMS as the internal reference (^{1}H), or to the residual solvent signals (^{1}H, ^{13}C). The assignments of the ^{1}H and ^{13}C NMR signals of compounds **2**, **5**, **10-13** were performed by their NOE (**5f**), COSY (**2a**, **5a-c**, **5e-g**, **10a**, **10b**, **11-13**), HSQC (**2a**, **5a-c**, **5e-g**, **11-13**), HMBC (**2a**, **5a-c**, **5g**) and NOESY (**10a**) spectra. Mass spectra were obtained by an Agilent HP GC / MS 5890 / 5973 instrument (EI, 70 eV) by GC inlet or by a MX-1321 and Finnigan MAT 95 XP (Thermo Electron Corp., San Jose, CA, USA) instruments (EI, 70 eV) by direct inlet or by an Agilent 1969A Time-of-Flight LC-MS or by a Thermo Scientific LTQ XL (Thermo Electron Corp., San Jose, CA, USA) LC-MS. LC-MS mass spectrometers operated in a full scan positive ion ESI mode. TLC was performed on DCAlurolle Kieselgel 60 F254 (Merck). TLC plates were visualized under UV light, and by gentle heating. For column chromatography Kieselgel 60 (Merck, particle size (0.063–0.200 mm) or Al_2O_3 neutral (Across Organics, particle size: (0.050–0.200 mm, 60A) was applied. 1,4-Dioxane and THF was distilled from sodium benzophenone ketyl and stored over sodium wires.

3.2. General procedure I for the reaction of anhydro-aldose tosylhydrazones with aryl bromides

A bromobenzene, LiO*t*Bu, (in a ratio relative to **1** or **4** indicated in Tables 1 and 2, respectively) CataCxium A (4 mol% toward **2** and **5**) or XPhos (4 mol% toward **10**) and $Pd_2(dba)_3$ (2 mol%), was added to abs. 1,4-dioxane (3 mL). The suspension was stirred and heated to 70 °C (bath temp) under an argon atmosphere, and then a solution of a tosylhydrazone **1** [26-28] (0.1 g, 0.19 mmol), **4** [27, 28] (0.1 g, 0.13 mmol) or **9** (0.1 g, 0.24 mmol) in abs. 1,4-dioxane (2 mL) was added dropwise in 15 minutes. When TLC (1:1 EtOAc–hexane or 1:1 EtOAc–heptane for **1**, 1:2 EtOAc–hexane or 1:2 EtOAc–hexane for **4**, 1:1 EtOAc–heptane for **9**) indicated complete consumption of the starting compound (1 h–1 day), the mixture was cooled and the insoluble material filtered off through a pad of celite and washed thoroughly with abs. 1,4-dioxane (3 × 3 mL). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (neutral Al_2O_3) with eluents indicated for the particular compounds to give aryl substituted *exo*-glycals.

3.2.1. 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-phenyl-D-*galacto*-hept-1-enitol (2a)

Prepared from tosylhydrazone **1** (0.1 g, 0.19 mmol), 4-bromobenzene (3 equiv., 0.06 mL, 0.09 g, 0.57 mmol) and LiO*t*Bu (2.2 equiv., 0.03 g, 0.41 mmol) according to General procedure I. Purified by column chromatography (1:1 EtOAc–heptane) to yield 49 mg yellow amorphous product containing **2a** (*E*:*Z* = 1:3) and **3** in 2 : 1 ratio. R_f: 0.45 (1:1 EtOAc–hexane). NMR: *E* isomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.26–7.18 (m, 3H, aromatics), 7.13 (d, 2H, *J* 7.6 Hz, aromatics), 6.54 (s, 1H, H-1), 5.84 (dd, 1H, $J_{1,3}$ 0.7, $J_{3,4}$ 7.3 Hz, H-3), 5.55 (pseudo t, 1H, $J_{5,6}$ 3.3 Hz, H-5), 5.22 (dd, 1H, $J_{4,5}$ 3.4 Hz, H-4), 4.39 (dd, 1H, $J_{6,7a}$ 7.5, $J_{7a,7b}$ 11.1 Hz, H-7_a), 4.36–4.07 (m, 2H, H-6, H-7_b), 2.13, 2.11, 2.04, 2.00 (4s, 12H, 4×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.0, 169.6, 169.5 (4×CO), 145.5 (C-2), 134.5–126.6 (aromatics), 118.1 (C-

1), 75.2 (C-6), 70.2 (C-4), 66.7 (C-3, C-5), 61.5 (C-7), 21.1–20.3 (4×CH_3). *Z* isomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.62 (d, 2H, *J* 8.7 Hz, aromatics), 7.35–7.19 (m, 3H, aromatics), 5.81 (dd, 1H, $J_{1,3}$ 1.6, $J_{3,4}$ 10.0 Hz, H-3), 5.76 (d, 1H, H-1), 5.58 (dd, 1H, $J_{5,6}$ 1.6 Hz, H-5), 5.13 (dd, 1H, $J_{4,5}$ 3.3 Hz, H-4), 4.32 (dd, 1H, $J_{7a,7b}$ 11.7 Hz, H-7_a), 4.23 (dd, 1H, H-7_b), 4.16 (ddd, 1H, $J_{6,7a}$ 4.7, $J_{6,7b}$ 7.8 Hz, H-6), 2.20, 2.19, 2.10, 2.03 (4s, 12H, 4×CH_3). ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.5, 170.1, 170.0, 169.5 (4×CO), 146.8 (C-2), 134.5–126.6 (aromatics), 111.2 (C-1), 75.8 (C-6), 71.5 (C-4), 67.7 (C-5), 67.4 (C-3), 62.4 (C-7), 21.0, 20.8, 20.7 (4×CH_3). HR-ESI-MS positive mode (m/z): calcd. for $[M+Na]^+$=443.1313, found: $[M+Na]^+$=443.1316, $C_{21}H_{24}O_9$ (420.14).

3.2.2. 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-(4-chlorophenyl)-1-deoxy-D-*galacto*-hept-1-enitol (2b)

Prepared from tosylhydrazone **1** (0.5 g, 0.95 mmol), 1-bromo-4-chlorobenzene (6 equiv., 1.09 g, 5.68 mmol) and Li*O*t*B*u (2.2 equiv., 0.17 g, 2.08 mmol) according to General procedure I. Purified by column chromatography (1:8 EtOAc–hexane) to yield 34 mg yellow amorphous product containing **2b** (*E*:*Z* = 1:3) and **3** in 3 : 1 ratio. R_f: 0.41 (1:1 EtOAc–hexane). NMR: *E* isomer:^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.23 (m, 2H, aromatics), 7.07 (d, 2H, *J* 8.2 Hz, aromatics), 6.46 (s, 1H, H-1), 5.80 (strongly coupled, 1H, H-3), 5.55 (pseudo t, 1H, $J_{5,6}$ 3.1 Hz, H-5), 5.21 (dd, 1H, $J_{4,5}$ 3.3 Hz, H-4), 4.39 (dd, 1H, $J_{6,7a}$ 7.6, $J_{7a,7b}$ 12.2 Hz, H-7_a), 4.36–4.11 (m, 2H, H-6, H-7_b), 2.13, 2.11, 2.09, 2.02 (4s, 12H, 4×CH_3). ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.7, 170.0, 169.6, 169.5 (4×CO), 146.2 (C-2), 133.4–127.9 (aromatics), 116.9 (C-1), 75.2 (C-6), 70.1 (C-4), 66.7, 66.6 (C-3, C-5), 61.4 (C-7), 21.1–20.3 (4×CH_3). *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 2H, *J* 8.4 Hz, aromatics), 7.26 (d, 2H, *J* 8.1 Hz aromatics), 5.80 (dd, 1H, $J_{1,3}$ 1.6, $J_{3,4}$ 9.8 Hz, H-3), 5.71 (d, 1H, H-1), 5.57 (dd, 1H, $J_{5,6}$ 1.5 Hz, H-5), 5.13 (dd, 1H, $J_{4,5}$ 3.1 Hz, H-4), 4.29 (dd, 1H, $J_{7a,7b}$ 11.4 Hz, H-7_a), 4.24 (dd, 1H, H-7_b), 4.16 (ddd, 1H,

$J_{6,7a}$ 4.5, $J_{6,7b}$ 8.3 Hz, H-6), 2.20, 2.19, 2.10, 2.03 (4s, 12H, 4×CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.2, 170.0, 169.5 (4×CO), 147.4 (C-2), 133.2–128.1 (aromatics), 110.0 (C-1), 75.9 (C-6), 71.3 (C-4), 67.6 (C-5), 67.3 (C-3), 62.4 (C-7), 21.0, 20.9, 20.8 (4×CH_3). ESI-MS positive mode (m/z): calcd. for $[M+Na]^+$=477.09, found: $[M+Na]^+$=477.25, $C_{21}H_{23}ClO_9$ (454.10).

3.2.3. 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-(4-methoxyphenyl)-D-*galacto*-hept-1-enitol (2c)

Prepared from tosylhydrazone **1** (0.1 g, 0.19 mmol), 1-bromo-4-methoxybenzene (3 equiv., 0.07 mL, 0.11 g, 0.57 mmol) and Li*O*t*Bu (2.2 equiv., 0.03 g, 0.41 mmol) according to General procedure I. Purified by column chromatography (1:1 EtOAc–heptane) to yield 15 mg (18%) of **5c** (*E*:*Z* = 1:4) as a grey amorphous product. R_f: 0.39 (1:1 EtOAc–hexane). NMR: *E* isomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.06 (d, 2H, *J* 8.2 Hz, aromatics), 6.90–6.79 (m, 2H, aromatics), 6.48 (s, 1H, H-1), 5.82 (dd, 1H, $J_{1,3}$ 0.8, $J_{3,4}$ 6.6, Hz, H-3), 5.55 (pseudo t, 1H, $J_{5,6}$ 3.5 Hz, H-5), 5.24 (dd, 1H, $J_{4,5}$ 3.5 Hz, H-4), 4.47–4.08 (m, 3H, H-6, H-7_a, H-7_b), 3.79 (1s, 3H, O–CH_3), 2.11, 2.04, 2.01, 1.99 (4s, 12H, 4×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.0, 169.6, 169.5 (4×CO), 144.3 (C-2), 158.9–113.4 (aromatics), 118.7 (C-1), 75.1 (C-6), 69.8 (C-4), 66.8, 66.5 (C-3, C-5), 61.4 (C-7), 55.4 (O–CH_3), 21.1, 20.9, 20.8 (4×CH_3). *Z* isomer: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.57 (d, 2H, *J* 8.9 Hz, aromatics), 6.83 (d, 2H, *J* 8.9 Hz, aromatics), 5.79 (dd, 1H, $J_{1,3}$ 1.5, $J_{3,4}$ 9.7 Hz, H-3), 5.70 (d, 1H, H-1), 5.57 (dd, 1H, $J_{5,6}$ 1.6 Hz, H-5), 5.11 (dd, 1H, $J_{4,5}$ 3.4 Hz, H-4), 4.31 (dd, 1H, $J_{7a,7b}$ 11.6 Hz, H-7_a), 4.23 (dd, 1H, H-7_b), 4.14 (ddd, 1H, $J_{6,7a}$ 4.6, $J_{6,7b}$ 8.0 Hz, H-6), 3.81 (1s, 3H, O–CH_3), 2.19, 2.18, 2.10, 2.02, (4s, 12H, 4×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 170.3, 170.1, 169.6 (4×CO), 145.0 (C-2), 158.9–113.4 (aromatics), 110.9 (C-1), 75.7 (C-6), 71.5 (C-4), 67.8 (C-5), 67.5 (C-3),

62.4 (C-7), 55.4 (O–CH_3), 21.1, 20.9, 20.8 (4×CH_3). HR-ESI-MS positive mode (m/z): calcd. for $[M+Na]^+$=473.1418, found: $[M+Na]^+$=473.1414, $C_{22}H_{26}O_{10}$ (450.15).

3.2.4. 2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-deoxy-1-phenyl-D-*gluco*-hept-1-enitol (5a)

Prepared from tosylhydrazone **4** (0.1 g, 0.13 mmol), bromobenzene (3 equiv., 0.04 mL, 0.06 g, 0.39 mmol) and LiO*t*Bu (2.2 equiv., 0.02 g, 0.28 mmol) according to General procedure I. Purified by column chromatography (1:5 EtOAc–heptane) to yield 48 mg yellow amorphous product containing **5a** (*E*:*Z* = 1:2) and **6** in 1 : 1.5 ratio. R_f: 0.42 (1:2 EtOAc–hexane). NMR: *E* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–7.03 (m, 25H, aromatics), 6.67 (s, 1H, H-1), 6.16 (dd, 1H, $J_{1,3}$ 0.4, $J_{3,4}$ 3.6 Hz, H-3), 5.94–5.74 (m, 1H, H-4), 5.72 (dd, 1H, $J_{4,5}$ 7.8, $J_{5,6}$ 3.0 Hz, H-5), 4.86–4.82 (m, 1H, H-6), 4.81–4.55 (m, 2H, H-7_a, H-7_b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 165.0, 164.7 (4×CO), 146.4 (C-2), 134.5–125.2 (aromatics), 116.6 (C-1), 74.8 (C-6), 70.1 (C-4), 69.1 (C-5), 67.6 (C-3), 63.4 (C-7). *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–7.03 (m, 25H, aromatics), 6.06 (dd, 1H, $J_{1,3}$ 0.8, $J_{3,4}$ 7.5 Hz, H-3), 5.92 (d, 1H, H-1), 5.87 (pseudo t, 1H, $J_{4,5}$ 7.3 Hz, H-4), 5.94–5.74 (m, 1H, H-5), 4.80 (dd, 1H, $J_{6,7a}$ 2.5, $J_{7a,7b}$ 12.2 Hz, H-7_a), 4.77–4.55 (m, 2H, H-6, H-7_b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.6, 165.3, 165.0 (4×CO), 145.9 (C-2), 134.5–125.2 (aromatics), 112.2 (C-1), 76.3 (C-6), 73.1 (C-4), 70.5 (C-3), 69.4 (C-5), 63.7 (C-7). HR-ESI-MS positive mode (m/z): calcd. for $[M+Na]^+$=691.1939, found: $[M+Na]^+$=691.1935, $C_{41}H_{32}O_9$ (668.21).

3.2.5. 2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-deoxy-1-(4-methylphenyl)-D-*gluco*-hept-1-enitol (5b)

Prepared from tosylhydrazone **4** (0.3 g, 0.39 mmol), 1-bromo-4-methylbenzene (6 equiv., 0.29 mL, 0.40 g, 2.32 mmol) and LiO*t*Bu (2.2 equiv., 0.07 g, 0.85 mmol) according to General procedure I. Purified by column chromatography (1:8 EtOAc–heptane) to yield 152 mg yellow amorphous product containing **5b** (*E*:*Z* = 1:2) and **6** in 2 : 1 ratio. R_f: 0.42 (1:2

EtOAc–hexane). NMR: *E* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–6.89 (m, 24H, aromatics), 6.65 (s, 1H, H-1), 6.16 (dd, 1H, $J_{1,3}$ 0.4, $J_{3,4}$ 3.9 Hz, H-3), 5.85–5.75 (m, 1H, H-4), 5.71 (dd, 1H, $J_{4,5}$ 7.7, $J_{5,6}$ 2.6 Hz, H-5), 4.85–4.82 (m, 1H, H-6), 4.81–4.49 (m, 2H, H-7_a, H-7_b), 2.21 (s, 3H, CH_3). ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.2, 165.0, 164.7 (4×CO), 145.9 (C-2), 143.5–125.4 (aromatics), 116.6 (C-1), 74.8 (C-6), 70.5 (C-4), 69.1 (C-5), 67.3 (C-3), 63.6 (C-7), 21.1 (CH_3). *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–6.89 (m, 24H, aromatics), 6.05 (dd, 1H, $J_{1,3}$ 0.8, $J_{3,4}$ 7.6 Hz, H-3), 5.90 (s, 1H, H-1), 5.87 (pseudo t, 1H, $J_{4,5}$ 7.3 Hz, H-4), 5.85–5.75 (m, 1H, H-5), 4.78 (dd, 1H, $J_{6,7a}$ 2.5, $J_{7a,7b}$ 12.2 Hz, H-7_a), 4.75–4.61 (m, 1H, H-7_b), 4.60–4.49 (m, 1H, H-6), 2.26 (s, 3H, CH_3). ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.2, 165.5, 165.3, 165.0 (4×CO), 145.2 (C-2), 143.5–125.4 (aromatics), 112.2 (C-1), 76.3 (C-6), 73.2 (C-4), 70.5 (C-3), 69.5 (C-5), 63.7 (C-7), 21.3 (CH_3). HR-ESI-MS positive mode (m/z): calcd. for $[M+Na]^+$=705.2095, found: $[M+Na]^+$=705.2089, $C_{42}H_{34}O_9$ (682.22).

3.2.6. 2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-deoxy-1-(4-methoxyphenyl)-D-*gluco*-hept-1-enitol (5c)

Prepared from tosylhydrazone **4** (0.1 g, 0.13 mmol), 1-bromo-4-methoxybenzene (3 equiv., 0.05 mL, 0.07 g, 0.39 mmol) and Li*Ot*Bu (2.2 equiv., 0.02 g, 0.28 mmol) according to General procedure I. Purified by column chromatography (1:8 EtOAc–heptane) to yield 10 mg (11%) of **5c** (*E*:*Z* = 1:2) as a brown amorphous product. R_f: 0.41 (1:2 EtOAc–heptane). NMR: *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22–6.86 (m, 22H, aromatics), 6.73 (d, 2H, *J* 8.8 Hz, aromatics), 6.62 (s, 1H, H-1), 6.14 (d, 1H, $J_{1,2}$ 0.4, $J_{3,4}$ 4.0 Hz, H-3), 5.90–5.64 (m, 2H, H-4, H-5), 4.83–4.42 (m, 3H, H-6, H-7_a, H-7_b), 3.69 (1s, 3H, O–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 165.0, 164.7, 164.5 (4×CO), 143.5 (C-2), 161.0–110.3 (aromatics), 114.2 (C-1), 75.6 (C-6), 71.7 (C-4), 69.5 (C-5), 68.4 (C-3), 62.7 (C-7), 55.3 (O–CH_3). *Z* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22–6.86 (m, 22H, aromatics), 6.65 (d, 2H, *J* 8.9 Hz

aromatics), 6.03 (dd, 1H, $J_{1,3}$ 1.2, $J_{3,4}$ 7.5 Hz, H-3), 5.85 (d, 1H, H-1), 5.90–5.64 (m, 2H, H-4, H-5), 4.83–4.42 (m, 3H, H-6, H-7_a, H-7_b), 3.71 (1s, 3H, O–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 165.4, 165.2, 164.9 (4×CO), 144.1 (C-2), 161.0–110.3 (aromatics), 113.9 (C-1), 76.3 (C-6), 73.3 (C-4), 70.5 (C-3), 69.5 (C-5), 62.7 (C-7), 55.3 (O–CH_3). HR-ESI-MS positive mode (m/z): calcd. for $[M+Na]^+$=721.2044, found: $[M+Na]^+$=721.2041, $C_{42}H_{34}O_{10}$ (698.22).

3.2.7. 2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-deoxy-1-(4-fluorophenyl)-D-*gluco*-hept-1-enitol (5d)

Prepared from tosylhydrazone **4** (0.3 g, 0.39 mmol), 1-bromo-4-fluorobenzene (6 equiv., 0.25 mL, 0.41 g, 2.32 mmol) and LiO*t*Bu (2.2 equiv., 0.07 g, 0.85 mmol) according to General procedure I. Purified by column chromatography (1:4 EtOAc–heptane) to 122 mg yellow amorphous product containing **5d** (*E*:*Z* = 1:2) and **6** in 2 : 1 ratio. R_f: 0.39 (1:2 EtOAc–hexane). NMR: *E* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25–7.01 (m, 24H, aromatics), 6.68 (s, 1H, H-1), 6.17 (dd, 1H, $J_{1,3}$ 0.4 Hz, $J_{3,4}$ 3.6 Hz, H-3), 5.87–5.74 (m, 1H, H-4), 5.73 (dd, 1H, $J_{4,5}$ 7.8, $J_{5,6}$ 2.5 Hz, H-5), 4.87–4.81 (m, 1H, H-6), 4.74 (dd, 1H, $J_{6,7a}$ 3.1, $J_{7a,7b}$ 7.9 Hz, H-7_a), 4.87–4.49 (m, 1H, H-7_b). ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.2, 165.0, 164.7 (4×CO), 146.4 (C-2), 143.7–123.2 (aromatics), 116.5 (C-1), 74.8 (C-6), 70.5 (C-4), 69.2 (C-5), 67.2 (C-3), 63.6 (C-7). *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25–7.01 (m, 24H, aromatics), 6.07 (dd, 1H, $J_{1,3}$ 1.0, $J_{3,4}$ 7.5 Hz, H-3), 5.93 (d, 1H, H-1), 5.88 (pseudo t, 1H, $J_{4,5}$ 7.4 Hz, H-4), 5.87–5.74 (m, 1H, H-5), 4.80 (dd, 1H, $J_{7a,7b}$ 12.2 Hz, H-7_a), 4.76 (dd, 1H, H-7_b), 4.49 (dd, 1H, $J_{5,6}$ 9.1 $J_{6,7a}$ 2.3, $J_{6,7a}$ 6.6 Hz, H-6). ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.2, 165.5, 165.3, 165.0 (4×CO), 145.9 (C-2), 143.7–123.2 (aromatics), 112.3 (C-1), 76.3 (C-6), 73.2 (C-4), 70.5 (C-3), 69.5 (C-5), 63.7 (C-7). ESI-MS positive mode (m/z): calcd. for $[M+H]^+$=687.20, found: $[M+H]^+$=686.25, $C_{41}H_{31}FO_9$ (686.20).

3.2.8. 2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-deoxy-1-(4-nitrophenyl)-D-*gluco*-hept-1-enitol (5e)

Prepared from tosylhydrazone **4** (0.3 g, 0.39 mmol), 1-bromo-4-nitrobenzene (6 equiv., 0.47 g, 2.32 mmol) and LiO*t*Bu (1.5 equiv., 0.05 g, 0.58 mmol) according to General procedure I. Purified by column chromatography (1:8 EtOAc–heptane) to yield 90 mg (33%) of **5e** (*E*:*Z* = 1:2) as a yellow amorphous product. R_f: 0.39 (1:2 EtOAc–hexane). NMR: *E* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–7.14 (m, 24H, aromatics), 6.63 (s, 1H, H-1), 6.18 (strongly coupled, 1H, H-3), 5.84–5.76 (m, 2H, H-4, H-5), 4.89–4.77 (m, 1H, H-6), 4.75–4.60 (m, 2H, H-7_a, H-7_b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.0, 164.8, 164.5 (4×CO), 149.1 (C-2), 147.0–123.2 (aromatics), 114.0 (C-1), 75.2 (C-6), 71.0, 69.1 (C-4, C-5), 67.1 (C-3), 60.4 (C-7). *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–7.14 (m, 24H, aromatics), 6.07 (dd, 1H, $J_{1,3}$ 0.7, $J_{3,4}$ 7.0 Hz, H-3), 5.98 (d, 1H, H-1), 5.88 (pseudo t, 1H, $J_{4,5}$ 6.7 Hz, H-4), 5.84–5.76 (m, 1H, H-5), 4.88–4.77 (m, 1H, H-7_a), 4.75–4.60 (m, 2H, H-6, H-7_b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.4, 165.3, 164.9 (4×CO), 149.5 (C-2), 147.0–123.2 (aromatics), 110.3 (C-1), 76.5 (C-6), 72.6 (C-4), 70.3 (C-3), 69.2 (C-5), 63.4 (C-7). HR-ESI-MS positive mode (m/z): calcd. for $[M+Na]^+$=736.1789, found: $[M+Na]^+$=736.1781, $C_{41}H_{31}NO_{11}$ (713.19).

3.2.9. 2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-(4-cyanophenyl)-1-deoxy-D-*gluco*-hept-1-enitol (5f)

Prepared from tosylhydrazone **4** (0.3 g, 0.39 mmol), 4-bromobenzonitrile (6 equiv., 0.42 g, 2.32 mmol) and LiO*t*Bu (2.2 equiv., 0.07 g, 0.85 mmol) according to General procedure I. Purified by column chromatography (1:4 EtOAc–heptane) to yield 122 mg (46%) of **5f** (*E*:*Z* = 1:2) as a pale yellow amorphous product. R_f: 0.33 (1:2 EtOAc–hexane). NMR: *E* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–7.16 (m, 24H, aromatics), 6.60 (s, 1H, H-1), 6.14 (strongly coupled, 1H, H-3), 5.82–5.71 (m, 2H, H-4, H-5), 4.86–4.75 (m, 1H, H-6), 4.74–4.60 (m, 2H,

H-7_a, H-7_b). ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.2, 165.0, 164.8, 164.6 (4×CO), 148.7 (C-2), 139.4–118.5 (aromatics), 114.4 (C-1), 110.7 (CN), 75.2 (C-6), 71.0 (C-4), 69.1 (C-5), 67.1 (C-3), 63.4 (C-7). *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–7.16 (m, 24H, aromatics), 6.05 (dd, 1H, $J_{1,3}$ 0.5, $J_{3,4}$ 7.00 Hz, H-3), 5.91 (d, 1H, H-1), 5.86 (pseudo t, 1H, $J_{4,5}$ 6.9 Hz, H-4), 5.82–5.71 (m, 1H, H-5), 4.85–4.77 (m, 1H, H-7_a), 4.74–4.60 (m, 2H, H-6, H-7_b). ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.1, 165.4, 165.2, 164.9 (4×CO), 149.0 (C-2), 139.4–118.5 (aromatics), 110.7 (C-1), 110.4 (CN), 76.4 (C-6), 72.7 (C-4), 70.4 (C-3), 69.2 (C-5), 63.4 (C-7). HR-ESI-MS positive mode (m/z): calcd. for $[M+Na]^+$=716.1891, found: $[M+Na]^+$=716.1887, $C_{42}H_{31}NO_9$ (693.20).

3.2.10. 2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-(3-cyanophenyl)-1-deoxy-D-*gluco*-hept-1-enitol (5g)

Prepared from tosylhydrazone **4** (0.2 g, 0.26 mmol), 3-bromobenzonitrile (6 eqiuv., 0.28 g, 1.54 mmol) and Li*O*t*Bu (1.5 equiv., 0.03 g, 0.39 mmol) according to General procedure I. Purified by column chromatography (1:7 EtOAc–hexane) to yield 36 mg (20%) of **5g** (*E*:*Z* = 1:2) as a yellow amorphous product. R_f: 0.33 (1:2 EtOAc–hexane). NMR: *E* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–7.08 (m, 24H, aromatics), 6.57 (s, 1H, H-1), 6.09 (strongly coupled, 1H, H-3), 5.82–5.73 (m, 2H, H-4, H-5), 4.82–4.75 (m, 1H, H-6), 4.72–4.61 (m, 2H, H-7_a, H-7_b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.0, 164.6, 164.5 (4×CO), 148.5 (C-2), 135.5–118.3 (aromatics), 113.8 (C-1), 112.8 (CN), 75.2 (C-6), 71.1 (C-4), 69.1 (C-5), 67.1 (C-3), 63.4 (C-7). *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–7.08 (m, 24H, aromatics), 6.04 (dd, 1H, $J_{1,3}$ 0.8, $J_{3,4}$ 6.6 Hz, H-3), 5.89 (d, 1H, H-1), 5.84 (pseudo t, 1H, $J_{4,5}$ 6.5 Hz, H-4), 5.82–5.73 (m, 1H, H-5), 4.93–4.83 (m, 1H, H-7_a), 4.78 (d, 1H, H-7_b), 4.72–4.61 (m, 1H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.4, 165.2, 164.9 (4×CO), 148.1 (C-2), 135.5–118.3 (aromatics), 112.6 (CN), 110.3 (C-1), 76.3 (C-6), 72.6 (C-4), 70.4 (C-3), 69.2 (C-5),

63.3 (C-7). ESI-MS positive mode (m/z): calcd. for $[M+Na]^+$=716.19, found: $[M+Na]^+$=716.67, $C_{42}H_{31}NO_9$ (693.20).

3.3. 2,6-anhydro-3,4,5,7-tetra-*O*-methyl-D-*glycero*-L-*manno*-heptononitrile (8)

2,6-anhydro-D-*glycero*-L-*manno*-heptononitrile **7** (0.1 g, 0.53 mmol) and sodium hydride (3 equiv. / OH, 0.15 g, 6.34 mmol) were added to abs. dimethyl sulfoxide (1.4 mL). The suspension was stirred and cooled to 0 °C, iodomethane (3 equiv. / OH, 0.39 mL, 0.90 g, 6.34 mmol) was added dropwise, then the reaction mixture was allowed to warm up to rt. When TLC (1:1 EtOAc–hexane) indicated complete consumption of the starting compound (1 day), a few drops methanol was added to the suspension. The reaction mixture was diluted with diethyl ether, washed with water (3 × 3 mL) and dried on anhydrous magnesium sulfate. The solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 1:2 EtOAc–hexane) to give 60 mg (46%) of **8** as a yellow amorphous product. R_f: 0.53 (1:1 EtOAc–hexane); $[\alpha]_D$ +21 (*c* 0.55, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (d, $J_{2,3}$ 9.9 Hz, H-2), 3.74–3.64 (m, 2H, H-3, H-6), 3.59–3.46 (m, 3H, H-5, H-7_a, H-7_b), 3.67, 3.57, 3.53, 3.39 (4s, 12H, 4×CH_3), 3.13 (dd, 1H, $J_{3,4}$ 9.3, $J_{4,5}$ 2.7 Hz, H-4). ^{13}C NMR (90 MHz, $CDCl_3$) δ 116.8 (C-1), 84.9 (C-4), 78.0 (C-3, C-5), 74.8 (C-6), 70.5 (C-7), 67.8 (C-2), 61.6, 59.4, 58.3 (4×CH_3). $C_{11}H_{19}NO_5$ (245.13). Spectral data correspond to the published values.[30]

3.4. 2,6-Anhydro-3,4,5,7-tetra-*O*-methyl-D-*glycero*-L-*manno*-heptose tosylhydrazone (9)

Raney-nickel (6.0 g, an aqueous suspension, Merck) was added at room temperature to a vigorously stirred solution of pyridine (23 mL), acetic acid (14 mL), and water (14 mL). Then sodium hypophosphite (2.96 g, 33.6 mmol), tosylhydrazine (1.49 g, 8.00 mmol), and nitrile **8** (0.98 g, 4.00 mmol) were added to the mixture. When TLC (1:1 EtOAc–hexane) indicated

complete consumption of the starting compound (5 h), the insoluble material was filtered off through a pad of celite and washed with dichloromethane (3 × 40 mL). The organic layer of the filtrate was separated, washed with water (12 mL), 10% aqueous hydrogen chloride solution (2 × 12 mL), cold, saturated sodium hydrogencarbonate solution (2 × 12 mL), water (12 mL), and then dried on anhydrous magnesium sulfate. The solution was concentrated under reduced pressure, and traces of pyridine were removed by repeated co-evaporations with toluene. The residue was purified by silica gel column chromatography (eluent: 2:1 EtOAc–hexane) to give two unidentified isomers **9a** and **9b**.

9a 526 mg (32%); R_f: 0.33 (2:1 EtOAc–hexane).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (bs, 1H, NH), 7.79 (d, 2H, *J* 8.3 Hz, aromatics), 7.29 (d, 2H, *J* 8.1 Hz, aromatics), 7.10 (d, 1H, $J_{1,2}$ 6.2 Hz, H-1), 3.69 (dd, 1H, $J_{2,3}$ 9.6 Hz, H-2), 3.66 (dd, 1H, $J_{5,6}$ 0.8 Hz, H-5), 3.58–3.42 (m, 3H, H-6, H-7_a, H-7_b), 3.36 (pseudo t, 1H, $J_{3,4}$ 9.4 Hz, H-3), 3.21 (dd, 1H, $J_{4,5}$ 3.0 Hz, H-4), 3.53, 3.51, 3.35, 3.18 (4s, 12H, 4×CH_3), 2.40 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4 (C-1), 144.4–126.6 (aromatics), 85.1, 78.5, 77.8, 76.7, 75.5 (C-2–C-6), 71.1 (C-7), 61.4, 60.2, 59.1, 58.1 (4×CH_3), 21.6 (CH_3). ESI-MS positive mode (m/z): calcd. for $[M+H]^+$=417.17, found: $[M+H]^+$=417.58, $C_{18}H_{28}N_2O_7S$ (416.16).

9b 202 mg (12%); R_f: 0.74 (2:1 EtOAc–hexane).^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (bs, 1H, NH), 7.81 (d, 2H, *J* 8.2 Hz, aromatics), 7.31 (d, 2H, *J* 8.0 Hz, aromatics), 6.81 (d, 1H, $J_{1,2}$ 4.6 Hz, H-1), 3.99 (dd, 1H, $J_{2,3}$ 10.1 Hz, H-2), 3.69 (dd, 1H, $J_{5,6}$ 0.7 Hz, H-5), 3.63–3.34 (m, 4H, H-3 H-6, H-7_a, H-7_b), 3.55, 3.51, 3.39, 3.31 (4s, 12H, 4×CH_3), 3.26 (dd, 1H, $J_{4,5}$ 2.7 Hz, H-4), 2.42 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7 (C-1), 144.5–127.5 (aromatics), 85.9, 79.1, 77.1, 74.9, 74.1 (C-2–C-6), 70.8 (C-7), 61.4, 61.0, 59.2, 57.8 (4×CH_3), 21.6 (CH_3). ESI-MS positive mode (m/z): calcd. for $[M+H]^+$=417.17, found: $[M+H]^+$=417.58, $C_{18}H_{28}N_2O_7S$ (416.16)

3.5 2,6-Anhydro-1-deoxy-3,4,5,7-tetra-*O*-methyl-1-phenyl-D-*galacto*-hept-1-enitol (10a)

Prepared from tosylhydrazone **9** (0.1 g, 0.24 mmol), bromobenzene (3 equiv., 0.08 mL, 0.11 g, 0.72 mmol) and LiO*t*Bu (2.2 equiv., 0.04 g, 0.53 mmol) according to General procedure I. Purified by column chromatography (1:1 EtOAc–heptane) to yield 45 mg (61%) of **10a** (*E*:*Z* = 1:3) as a white amorphous product. *E* isomer: 11 mg (15%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.41–7.30 (m, 2H, aromatics), 7.28–7.19 (m, 3H, aromatics), 6.34 (s, 1H, H-1), 4.29 (ddd, 1H, $J_{5,6}$ 5.3, $J_{6,7a}$ 8.1, $J_{6,7b}$ 2.4 Hz, H-6), 4.22 (dd, 1H, $J_{1,3}$ 0.4, $J_{3,4}$ 3.9 Hz, H-3), 3.85 (dd, 1H, $J_{4,5}$ 3.1 Hz, H-5), 3.75 (pseudo t, 1H, H-4), 3.69 (dd, 1H, $J_{7a,7b}$ 11.3 Hz, H-7_a), 3.45 (dd, 1H, H-7_b), 3.37, 3.36, 3.29, 3.12 (4s, 12H, 4×CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 147.5 (C-2), 135.5–126.2 (aromatics), 117.6 (C-1), 76.8, 76.7, 74.0, 73.3 (C-3–C-6), 69.5 (C-7), 58.3, 58.1, 57.5, 55.2 (4×CH_3). HR-EI-MS positive mode (m/z): calcd. for $[M]^+$=308.1618, found: $[M]^+$=308.1620, $C_{17}H_{24}O_5$ (308.16). *Z* isomer: 34 mg (46%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.66 (d, 2H, *J* 8.6 Hz, aromatics), 7.33–7.22 (m, 2H, aromatics), 7.19–7.10 (m, 1H, aromatic), 5.83 (s, 1H, H-1), 4.04 (ddd, 1H, $J_{5,6}$ 2.9, $J_{6,7a}$ 2.7, $J_{6,7b}$ 5.3 Hz H-6), 3.89 (dd, 1H, $J_{1,3}$ 0.9, $J_{3,4}$ 7.8 Hz, H-3), 3.85 (pseudo t, 1H, $J_{4,5}$ 2.9 Hz, H-5), 3.62 (dd, 1H, $J_{7a,7b}$ 12.0 Hz, H-7_a), 3.57 (dd, 1H, H-7_b), 3.50 (dd, 1H, H-4), 3.43, 3.42, 3.41, 3.27 (4s, 12H, 4×CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.9 (C-2), 135.3–126.0 (aromatics), 109.8 (C-1), 81.3, 78.3, 77.3, 74.7 (C-3–C-6), 71.0 (C-7), 59.4, 58.3, 58.0, 57.5 (4×CH_3). HR-EI-MS positive mode (m/z): calcd. for $[M]^+$=308.1618, found: $[M]^+$=308.1617, $C_{17}H_{24}O_5$ (308.16).

3.6. 2,6-Anhydro-1-deoxy-3,4,5,7-tetra-*O*-methyl-1-(4-methylphenyl)-D-*galacto*-hept-1-enitol (10b)

Prepared from tosylhydrazone **9** (0.1 g, 0.24 mmol), 1-bromo-4-methylbenzene (3 equiv., 0.09 mL, 0.12 g, 0.72 mmol) and LiO*t*Bu (2.2 equiv., 0.04 g, 0.53 mmol) according to

General procedure I. Purified by column chromatography (1:1 EtOAc–heptane) to yield 58 mg (75%) of **10b** (*E*:*Z* = 1:3) as white amorphous products. *E* isomer: 15 mg (19%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.30–7.10 (m, 4H, aromatics), 6.30 (s, 1H, H-1), 4.25 (ddd, 1H, $J_{5,6}$ 5.3, $J_{6,7a}$ 8.1, $J_{6,7b}$ 2.4 Hz, H-6), 4.22 (dd, 1H, $J_{1,3}$ 0.4, $J_{3,4}$ 3.9 Hz, H-3), 3.85 (dd, 1H, $J_{4,5}$ 3.1 Hz, H-5), 3.73 (pseudo t, 1H, H-4), 3.68 (dd, 1H, $J_{7a,7b}$ 12.0 Hz, H-7_a), 3.45 (dd, 1H, H-7_b), 3.38, 3.36, 3.28, 3.10 (4s, 12H, 4×CH_3), 2.31 (s, 3H, CH_3). ^{13}C NMR (63 MHz, DMSO-d_6) δ 146.8 (C-2), 135.8–128.0 (aromatics), 117.7 (C-1), 76.7, 76.6, 73.9, 73.2 (C-3–C-6), 69.4 (C-7), 58.2, 58.1, 57.4, 55.1 (4×CH_3), 20.7 (CH_3). HR-EI-MS positive mode (m/z): calcd. for $[M]^+$=322.1775, found: $[M]^+$=322.1770, $C_{18}H_{26}O_5$ (322.18). *Z* isomer: 43 mg (56%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.58–7.48 (m, 2H, aromatics), 7.15–7.08 (m, 2H, aromatics), 5.82 (s, 1H, H-1), 4.02 (ddd, 1H, $J_{5,6}$ 2.9, $J_{6,7a}$ 2.7, $J_{6,7b}$ 5.3 Hz H-6), 3.90 (dd, 1H, $J_{1,3}$ 0.9, $J_{3,4}$ 7.8 Hz, H-3), 3.84 (pseudo t, 1H, $J_{4,5}$ 2.9 Hz, H-5), 3.60 (dd, 1H, $J_{7a,7b}$ 12.0 Hz, H-7_a), 3.54 (dd, 1H, H-7_b), 3.50 (dd, 1H, H-4), 3.43, 3.42, 3.41, 3.27 (4s, 12H, 4×CH_3), 2.30 (s, 3H, CH_3). ^{13}C NMR (63 MHz, DMSO-d_6) δ 149.0 (C-2), 135.5–128.1 (aromatics), 109.8 (C-1), 81.2, 78.3, 77.2, 74.7 (C-3–C-6), 71.0 (C-7), 59.3, 58.3, 57.9, 57.4 (4×CH_3), 20.7 (CH_3). HR-EI-MS positive mode (m/z): calcd. for $[M]^+$=322.1775, found: $[M]^+$=322.1772, $C_{18}H_{26}O_5$ (322.18).

3.7. General procedure II for catalytic hydrogenation

A degassed, vigorously stirred suspension of 10 % Pd/C (75 weight % of **2a** and **3**; 50 weight % of **5a** and **6**) in abs. EtOAc (3 mL) was saturated with H_2 (3 ×), and a solution of **2a** and **3** (0.17 mmol + 0.02 mmol) or **5a** and **6** (0.12 mmol + 0.15 mmol) in abs. EtOAc (3 mL) was added. The reaction mixture was stirred overnight under H_2 atmosphere at rt. The insoluble materials were filtered off through a pad of celite and washed thoroughly with EtOAc (3 × 3 mL). The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography with eluents indicated for the particular compounds.

3.7.1. 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-1-phenyl-D-*glycero*-L-*manno*-heptitol (11)

Prepared from **2a** (0.07 g, 0.17 mmol), according to the General procedure II. Purified by column chromatography (1:9 EtOAc–toluene) to yield 60 mg (83%) of **11** as a white amorphous product. R_f: 0.38 (1:1 EtOAc–hexane); $[\alpha]_D$ +11 (*c* 0.78, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.15 (m, 5H, aromatic), 5.41 (dd, 1H, $J_{5,6}$ 0.8 Hz, H-5), 5.19 (pseudo t, 1H, $J_{3,4}$ 10.0 Hz, H-3), 5.02 (dd, 1H, $J_{4,5}$ 3.4 Hz, H-4), 4.14 (dd, 1H, $J_{7a,7b}$ 11.2 Hz, H-7_a), 4.01 (dd, 1H, H-7_b), 3.80 (ddd, 1H, $J_{6,7a}$ 6.4, $J_{6,7b}$ 7.0 Hz, H-6), 3.63 (ddd, 1H, $J_{1a,2}$ 3.7, $J_{1b,2}$ 8.4, $J_{2,3}$ 9.6 Hz, H-2), 2.86 (dd, 1H, $J_{1a,1b}$ 14.5 Hz, H-1_a), 2.79 (dd, 1H, H-1_b), 2.16, 1.98, 1.97 (4s, 12H, 4×CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.4, 170.3, 170.0 (4×CO), 138.1–126.2 (aromatics), 79.1 (C-2), 74.2 (C-6), 72.4 (C-4), 69.7 (C-3), 67.9 (C-5), 61.7 (C-7), 38.2 (C-1), 20.8, 20.7 (4×CH_3). ESI-MS positive mode (m/z): calcd. for $[M+Na]^+$=445.15, found: $[M+Na]^+$=445.33, $C_{21}H_{26}O_9$ (422.16).

3.7.2. 3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-1-deoxy-D-*glycero*-L-*manno*-heptitol (12)

Prepared from **3** (0.008 g, 0.02 mmol), according to the General procedure II. Purified by column chromatography (1:9 EtOAc–toluene) to yield 7 mg (83%) of **12** as a white amorphous product. R_f: 0.33 (1:1 EtOAc–hexane); $[\alpha]_D$ +9 (*c* 0.26, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (dd, 1H, $J_{5,6}$ 1.0 Hz, H-5), 5.06 (pseudo t, 1H, $J_{3,4}$ 10.1 Hz, H-3), 5.00 (dd, 1H, $J_{4,5}$ 3.2 Hz, H-4), 4.11 (dd, 1H, $J_{7a,7b}$ 11.7 Hz, H-7_a), 4.07 (dd, 1H, H-7_b), 3.87 (ddd, 1H, $J_{6,7a}$ 6.6, $J_{6,7b}$ 6.8 Hz, H-6), 3.53 (dq, 1H, $J_{1,2}$ 6.2, $J_{2,3}$ 9.0 Hz, H-2), 2.16, 2.06, 2.05, 1.98 (4s, 12H, 4×CH_3), 1.24 (d, 3H, H-1). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.5, 170.4, 170.0 (4×CO), 74.8, 74.2 (C-2, C-6), 72.2 (C-4), 70.9 (C-3), 68.0 (C-5), 62.0 (C-1), 21.0,

20.9, 20.8 (4×CH_3), 17.8 (C-1). ESI-MS positive mode (m/z): calcd. for $[M+Na]^+$=369.12, found: $[M+Na]^+$=369.33, $C_{15}H_{22}O_9$ (346.13).

3.7.3. 2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-deoxy-1-phenyl-D-*glycero*-D-*gulo*-heptitol (13)

Prepared from **5a** (0.08 g, 0.12 mmol), according to the General procedure II. Purified by column chromatography (1:99 EtOAc–toluene) to yield 34 mg (42%) of **13** as a white amorphous product. R_f: 0.36 (1:2 EtOAc–hexane); $[\alpha]_D$ +18 (*c* 0.57, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–7.75 (m, 8H, aromatics), 7.64–7.08 (m, 17H, aromatics), 5.89 (pseudo t, 1H, $J_{4,5}$ 9.7 Hz, H-4), 5.61 (pseudo t, 1H, $J_{5,6}$ 9.6 Hz, H-5), 5.47 (pseudo t, 1H, $J_{3,4}$ 9.5 Hz, H-3), 4.59 (dd, 1H, $J_{7a,7b}$ 12.1 Hz, H-7_a), 4.42 (dd, 1H, H-7_b), 4.04 (ddd, 1H, $J_{6,7a}$ 2.8, $J_{6,7b}$ 6.3 Hz, H-6), 4.00 (ddd, 1H, $J_{1a,2}$ 4.8, $J_{1b,2}$ 6.8, $J_{2,3}$ 9.8 Hz, H-2), 2.96 (dd, 1H, $J_{1a,1b}$ 12.3 Hz, H-1_a), 2.92 (dd, 1H, H-1_b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 166.1, 165.6, 165.4 (4×CO), 138.3–126.0 (aromatics), 79.2 (C-2), 76.2 (C-6), 74.7 (C-4), 72.6 (C-3), 70.2 (C-5), 63.6 (C-7), 38.0 (C-1). ESI-MS positive mode (m/z): calcd. for $[M+Na]^+$=693.21, found: $[M+Na]^+$=693.50, $C_{41}H_{34}O_9$ (670.22).

3.7.4. 2,6-Anhydro-3,4,5,7-tetra-*O*-benzoyl-1-deoxy-D-*glycero*-D-*gulo*-heptitol (14)

Prepared from **6** (0.09 g, 0.15 mmol), according to the General procedure II. Purified by column chromatography (1:99 EtOAc–toluene) to yield 38 mg (43%) of **14** as a white amorphous product. R_f: 0.41 (1:2 EtOAc–hexane); $[\alpha]_D$ +43 (*c* 0.59, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–7.76 (m, 8H, aromatics), 7.61–7.06 (m, 12H, aromatics), 5.87 (pseudo t, 1H, $J_{4,5}$ 9.7 Hz, H-4), 5.67 (pseudo t, 1H, $J_{5,6}$ 9.8 Hz, H-5), 5.36 (pseudo t, 1H, $J_{3,4}$ 9.5 Hz, H-3), 4.61 (dd, 1H, $J_{7a,7b}$ 12.2 Hz, H-7_a), 4.45 (dd, 1H, H-7_b), 4.11 (ddd, 1H, $J_{6,7a}$ 3.0, $J_{6,7b}$ 5.1 Hz, H-6), 3.90 (dq, 1H, $J_{1,2}$ 6.1, $J_{2,3}$ 9.7 Hz, H-2), 1.36 (d, 3H, H-1). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 166.4, 166.1, 165.6, 165.4 (4×CO), 133.6–127.2 (aromatics), 76.2 (C-6), 75.0 (C-2), 74.5 (C-4), 74.1 (C-3), 70.1 (C-5), 63.6 (C-7), 18.0 (C-1). ESI-MS positive mode (m/z): calcd. for $[M+Na]^+$=617.18, found: $[M+Na]^+$=617.42, $C_{35}H_{30}O_9$ (594.19).

Acknowledgements

This work was supported by the Hungarian Scientific Research Fund (OTKA K109450) and the Alexander von Humboldt Foundation. Presentation of the work at Eurocarb 2017, Barcelona was financed by the EU and co-financed by the European Regional Development Fund under the project GINOP-2.3.2-15-2016-00008.

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- Pd-catalyzed cross coupling of anhydro-aldose tosylhydrazones with aryl bromides
- Formation of aryl-substituted *exo*-glycals
- Application to the preparation of benzylic *C*-glycosyl derivatives