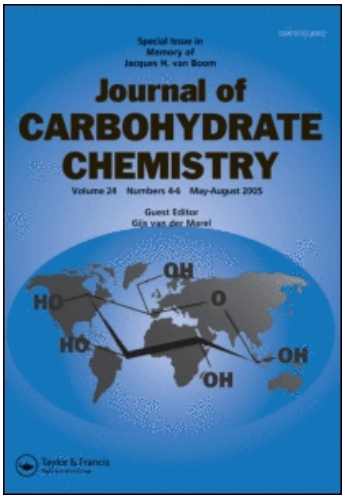

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GLYCOSIDATION OF 3,4,6-TRI-*O*-BENZYL-2-ETHENYL-D-GLUCAL – A ROUTE TO 2-*C*-(β-METHYL)METHYLENE GLYCOSIDES

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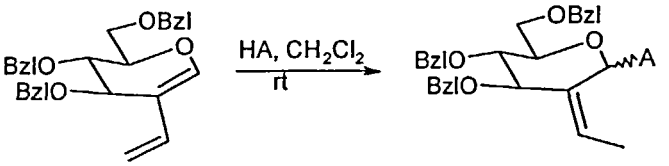
ABSTRACT

Monosaccharidic and disaccharidic 2-*C*-(β-methyl)methylene glycosides were synthesized by an electrophilic conjugate addition reaction of ROH-type compounds in the presence of $Ph_3\overset{+}{P}H\ Br^-$ to 2-ethenyl-3,4,6-tri-*O*-benzyl-D-glucal **1**, functioning as a model glycosyl donor. This 2-vinyl glucal derivative represents a series of 2-vinyl and 2-butadienyl glycals, prepared by Wittig-type methylenation of pyranosidic conjugated enals, derived from glucal, galactal and lactal. The exo-(β-methyl)methylene group paves the way for further chemical transformations.

INTRODUCTION

It has recently been reported that 2-deoxy glycosides, including disaccharides, can be prepared by an acid-catalyzed addition of hydroxylic compounds to glycals, using $Ph_3\overset{+}{P}H\ Br^-$ as a catalyst.[1] The acid-catalyzed Ferrier rearrangement reaction[2] is completely

suppressed under these conditions. A study of the feasibility of analogous electrophilic conjugate addition reactions of HA-type compounds to 2-vinyl derivatives of glycals functioning as glycosyl donors, to yield the corresponding 2-*C*-(β-methyl)methylene glycosides, is reported herein (Eq. 1):



(1)

1

2-Ethenyl-3,4,6-tri-*O*-benzyl-D-glucal **1**, used in the present study, is representative of a series of 2-vinyl and 2-butadienyl glycals, the synthesis of which is also reported herein.

Glycopyranosides and furanosides, having a methylenic double bond at the anomeric position, as well as at the other positions, are valuable precursors for the synthesis of diversely functionalized sugar derivatives. Pyranoid and furanoid-type carbohydrates, having an exo-methylene group at C-1, were prepared by direct methylenation of sugar lactones.[3] The reaction of the triphenylphosphonium bromide derivative obtained in the addition reaction of $Ph_3\overset{+}{P}H\ Br^-$ to 3,4,6-tri-*O*-benzyl-D-glucal, was reacted with aliphatic aldehydes under the conditions of the Wittig reaction to give the corresponding 2-deoxy-*C*-1-methylene-D-glucose derivatives.[1b] 1-*C*-methylene sugars were used as precursors to methylene bridged *C*-disaccharides,[4] which are interesting as potential enzyme inhibitors. A convenient method for the synthesis of 2-deoxy-2-*C*-methylene methyl and aryl glycosides, from the corresponding readily accessible *C*-2 formyl glycals, was also recently reported.[5] A glycal, having a conjugated exo-methylene group at C-3 was prepared in good yield from the corresponding, readily available 2,3-dihydro-γ-pyranone.[6] Benzyl 2,3,6-tri-*O*-benzyl-4-deoxy-4-*C*-methylene-α-D-xylohexopyranoside has been used as a precursor for the synthesis of unnatural glycosidase inhibitor.[7] Two other 4-*C*-methylene hexopyranoses were used as precursors for the synthesis of some methylene-bridged *C*-disaccharides,[8] of interest as potential glycosidase inhibitors, to affect HIV activity.[9] Sinäy et. al.[10] described a synthesis of methyl and benzyl 4-*C*-methylene glucoside derivatives and their use for constructing a novel class of non-natural analogues of C-dissaccharides.[11] A glucosyl ceramide analogue

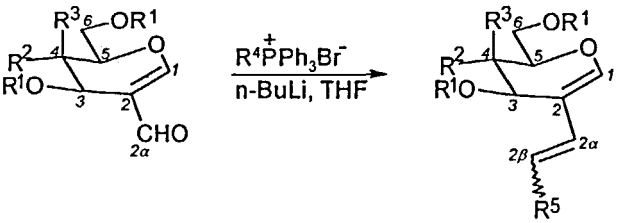
was prepared by introducing a 4-deoxy-4-*C*-methylene group at C-4 of the glucosyl moiety.[12] This was converted into products which are potential competitive inhibitors of UDP-galactosyl transferase. Much attention has also been focused on 6-deoxy-5-eno-pyranosides.[11,13-15] These very highly functionalized chiral cyclohexanones are very useful intermediates for the synthesis of natural products having six-membered ring systems.[14b]

RESULTS AND DISCUSSION

Wittig-type methylenation of pyranosidic conjugated enals was reported, in a few cases[16, 17] for the synthesis of carbohydrate-based conjugated dienes. A dithiane-based approach[17] and an acidic hydrolysis of carbohydrate enol ethers[18] represent two other methodologies used to prepare pyranosidic conjugated enals. Furthermore, the recently reported application of the Vilsmeier-Haack reaction to glycals[19] afforded a facile direct route to the synthesis of *C*-2-formyl glycals (from the corresponding glycals) in a one-pot synthesis. This paved the way to a convenient synthesis of *C*-2-vinyl and *C*-2-butadienyl glycals, reported in this paper.

The *C*-2-formyl derivatives of the tri-*O*-methyl and the tri-*O*-benzyl ethers of glucal (**2** and **3**) and galactal (**4** and **5**) were prepared in yields which were comparable to, or in some cases higher than, the reported ones.[19] The hitherto unknown *C*-2-formyl glycal derivatives of hexa-*O*-methyl and hexa-*O*-benzyl ethers of the disaccharide lactal (**13** and **14**) were similarly prepared, but the yields were rather low (15% and 37%, respectively, cf. Experimental Section). All the *C*-2-formyl glycals prepared were reacted in a Wittig reaction, with a two-fold excess of the ylides derived from $Me\overset{+}{P}Ph_3\ Br^-$ and from $CH_2{=}CH{-}CH_2\overset{+}{P}Ph_3\ Br^-$ to yield the corresponding *C*-2-vinyl (**1**, **6-8**, **15** and **16**) and *C*-2-butadienyl (**9-12** and **17**) derivatives, respectively (Eqs. 2 and 3).

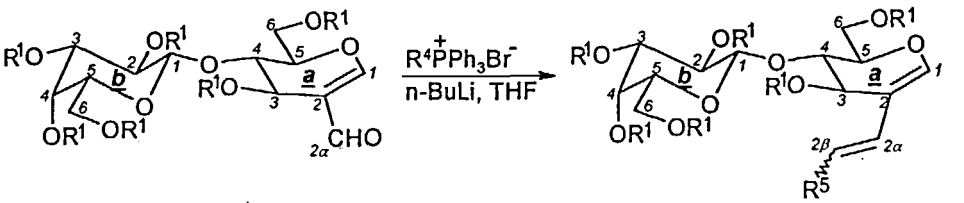
The results summarized in Table 1 show that carrying out the reaction between the ylide and the *C*-2-formyl glycal (in THF) at a higher temperature (-10 °C as compared to -30 °C) resulted in higher yields. The *C*-2-butadienyl derivatives were obtained as a mixture of *cis* and *trans* isomers (with respect to the butadienyl group). Representative ^1H NMR data of the *C*-2-vinyl and the *C*-2-butadienyl derivatives of the glycals prepared (**1**, **8**, **9**, **12**, **16** and **17**) are given in the experimental section. The rest (**6**, **7**, **10**, **11** and **15**) are detailed in the supplementary section.[21]



(2)

R^1 = Bzl, R^2 = OBzl, R^3 = H: **2**
R^1 = Me, R^2 = OMe, R^3 = H: **3**
R^1 = Bzl, R^2 = H, R^3 = OBzl: **4**
R^1 = Me, R^2 = H, R^3 = OMe: **5**

1: R^5 = H, **9**: R^5 = CH=CH_2, (E) & (Z)
6: R^5 = H, **10**: R^5 = CH=CH_2, (E) & (Z)
7: R^5 = H, **11**: R^5 = CH=CH_2, (*E*) & (Z)
8: R^5 = H, **12**: R^5 = CH=CH_2, (*E*) & (Z)

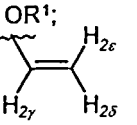


(3)

R^1 = Bzl: **13**
R^1 = Me: **14**

15: R^5 = H, **17**: R^5 = CH=CH_2, (E) & (Z)
16: R^5 = H

For both equations (2) and (3): R^1 = OBzl, OMe; R^2, R^3 = OR^1, H; H, OR^1;

R^4 = CH_3, CH_2-CH=CH_2; R^5 = $H_{2\gamma}$, 

The glycosidation of 2-ethenyl-3,4,6-tri-*O*-benzyl-D-glucal **1** with ROH-type compounds (R = Et, carbohydrate moiety) was carried out in CH_2Cl_2 at room temperature in the presence of catalytic amounts of $Ph_3\overset{+}{P}H\ Br^-$. Electrophilic additions of other HA-type compounds, namely 4-toluenesulfinic acid **18** and benzotriazole **19**, were also carried out, but in absence of $Ph_3\overset{+}{P}H\ Br^-$. 1,4-Conjugate addition products were the only addition products obtained. The results are summarized in Table 2. The structure of the glycosidation products was determined based on their ^{1}H NMR, ^{13}C NMR and MS spectral data. The data from several representative products (**27**, **32- 34** and **36**) are given in the experimental section and the rest (**28-31** and **35**) – in the supplementary.[21] Only one isomer was formed in the reaction of 4-toluenesulfinic acid (**18**). ^{1}H NMR data was not clear enough to indicate whether it was the α- or the β-isomer, due to the absence of a vicinal H-atom at C-2. We have assumed that the product formed in this case is the β-isomer based on the fact that a β-isomer was obtained in the addition reaction of this acid (under the same reaction conditions) to 3,4-dihydro-2H-pyran.[20]

Table 1. Synthesis of *C*-2-vinyl and *C*-2-butadienyl glycals - Experimental conditions and results

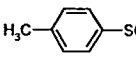
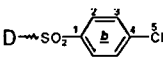
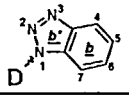
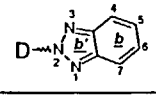
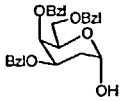
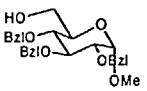
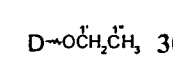
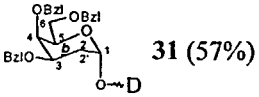
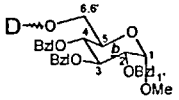
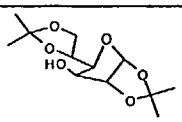
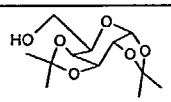
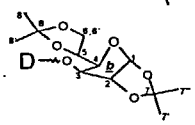
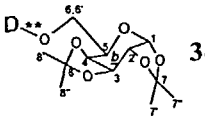
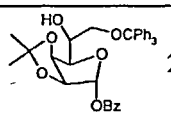
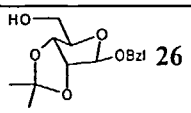
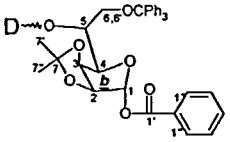
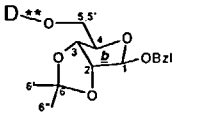
Entry		2-formyl glycal			$R^4P^+Ph_3Br^-$			*n*-BuLi	T_1	t_1	T_2	t_2		Product
	Type[a]	R^1	R^2	R^3	Mmol	R^4	Mmol	Mmol	(°C)	(min)	(°C)	(m)	R^5	Yield[b](%)
1	(I)	Bzl	OBzl	H	0.67	Me	1.35	1.35	-30	40	-10	90	H	**1** (78)
2	(I)	Bzl	OBzl	H	5.78	Me	11.56	11.56	-30	40	-10	90	H	**1** (69)
3	(I)	Me	OMe	H	1.39	Me	4.16	4.16	-30	40	-10	210	H	**6** (48)
4	(I)	Bzl	H	OBzl	0.67	Me	1.35	1.35	-30	40	-10	100	H	**7** (71)
5	(I)	Me	H	OMe	1.39	Me	2.77	2.77	-30	30	-10	20	H	**8** (81)
6	(I)	Bzl	OBzl	H	1.12	Allyl	2.25	2.25	-30	15	-30	90	$CH=CH_2$	**9** (43)
7	(I)	Me	OMe	H	1.34	Allyl	2.68	2.68	-30	30	-10	10	$CH=CH_2$	**10** (52)
8	(I)	Bzl	H	OBzl	1.12	Allyl	2.25	2.25	-30	40	-30	50	$CH=CH_2$	**11** (49)
9	(I)	Me	H	OMe	1.39	Allyl	2.77	2.77	-30	30	-10	50	$CH=CH_2$	**12** (65)
10	(II)	Bzl	-	-	0.57	Me	1.14	1.14	-30	40	-10	90	H	**15** (74)
11	(II)	Me	-	-	0.63	Me	1.26	1.26	-30	40	-10	120	H	**16** (70)
12	(II)	Bzl	-	-	0.57	Allyl	1.14	1.14	-30	40	-10	210	$CH=CH_2$	**17** (64)

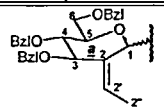
a. The type (I) substrates and products are monosaccharides (cf. eq. 2) and type (II) are disaccharides.
b. Yields of analytically pure products isolated by column chromatography.

The reaction with benzotriazole was carried out in CCl_4. Two isomers of the addition product, 1'-benzotriazolyl **28** and 2'-benzotriazolyl **29** derivatives, were obtained. Each of these two products consisted of a 1:1 mixture of the α and β or the (*E*) and (*Z*) isomers. Each of the compounds **30-36** was obtained as a single isomer. The anomeric configuration and the *E*/*Z* stereochemistry of the disaccharides **34** and **36** were determined based on correlations of ROESY measurements. A (*Z*) geometry was assigned to the 2-*C*-(β-methyl)methylene double bond of the other disaccharides (**30-33, 35**), based on the comparison of the vinylic protons of **34** and **36** chemical shifts.

In conclusion, the herein reported application of 2-*C*-vinyl glycal derivatives as glycosyl donors, extends the scope of the analogous application of glycals themselves as glycosyl donors[1] yielding 2-deoxy glycoside-type products. The present glycosidation of the readily prepared 2-*C*-vinyl glycals leads to formation of a class of glycosides, namely - 2-*C*-methylene derivatives of oligosaccharides, which are prone to further chemical elaboration via the exo-2-(β-methyl)methylene group.

Table 2. The addition products of HA type compounds to tri-*O*-benzyl-2-ethenyl-D-glucal **1**

HA	 **18**	 **19**	
Product/s (yield)	 **27** (76%)	 **28** (37%)	 **29** (22%)
HA	EtOH **20**	 **21**	 **22**
Product/s (yield)	 **30** (42%)	 **31** (57%)	 **32** (31%)
HA	 **23**	 **24**	
Product/s (yield)	 **33** (68%)	 **34** (74%)	
HA	 **25**	 **26**	
Product/s (yield)	 **35** (37%)	 **36** (53%)	

* D = 

** The ROESY measurement indicated the anomeric configuration as α.

EXPERIMENTAL

General methods. ^{1}H and ^{13}C NMR spectra were obtained on Bruker AC-200 (200 MHz), Bruker AC-250 Cryospec (250 MHz), Bruker ARX-500 (500 MHz) and Bruker DRX-600 (600 MHz) spectrometers, in $CDCl_3$, downfield from tetramethylsilane as internal standard. Values of chemical shifts (δ) and couplings (J) are given in ppm and Hz, respectively. Integrations other than 1H are indicated. FABMS were obtained using a Finnigan MAT 312 Mass Spectrometer (70 ev) and the EIMS were obtained using a

Finnigan MAT 8430 Mass Spectrometer (70 ev). Silica gel 60 (Baker: 0.04-0.063 mm or ICN: 0.03-0.063 mm) was used for flash chromatography. Medium pressure liquid chromatography (MPLC) was performed on LiChroprep Si 60 (Merck: 0.040-0.063 mm) silica gel, pressure: 0.2-0.4 bar, detector: refractive index (Knaur), flow: 10 mL/min. All solvents were purified and dried by standard methods. The 2-formyl derivatives of the glycals used (3,4,6-tri-*O*-benzyl-D-glucal, 3,4,6-tri-*O*-methyl-D-glucal, 3,4,6-tri-*O*-benzyl-D-galactal, 3,6,2',3',4',6'-hexa-*O*-benzyl-D-lactal, 3,6,2',3',4',6'-hexa-*O*-methyl-D-lactal) were prepared by a recently reported method.[19]

3,6,2',3',4',6'-Hexa-*O*-benzyl-2-*C*-formyl-D-lactal (13). Freshly distilled phosphorus oxychloride (2.48 g, 44.52 mmol) was added dropwise to a solution of 3,6,2',3',4',6'-hexa-*O*-benzyl-D-lactal (12.60 g, 14.84 mmol) in absolute DMF (80 mL), cooled in an ice-bath. The reaction mixture was stirred at room temperature for two days, and then poured into a cooled 4.9 M aqueous solution of sodium acetate. This was followed by extraction with methylene chloride. All manipulations and the reaction itself were carried out under anhydrous conditions and under nitrogen. The product recovered from the organic extracts was purified by flash chromatography (petroleum ether : ethyl acetate, 8:2). 4.77 g (37%) of the 3,6,2',3',4',6'-hexa-*O*-benzyl-*C*-2-formyl-D-lactal **13** were obtained as a slightly yellow viscous oil. The formyl lactal **13** was not fully characterized. The general ^{1}H NMR (250 MHz) features of the product are as follows: δ: 9.31 (s, CHO), 7.2-7.4 (m, 31H, Ar, H-1a), 4.4-5.0 (15H), 4.2 (1H), 3.4-3.9 (8H).

General procedure for preparation of the *C*-2-vinyl and the *C*-2-butadienyl glycals: The reaction was carried out in a two neck flask equipped with a nitrogen inlet, a rubber septum and magnetic stirring, under strictly dry conditions. The methyltriphenylphosphonium bromide or the allyltriphenylphosphonium bromide was introduced into the reaction flask followed by 2-3 mL of THF (a suspension was obtained), and the mixture cooled to T_1 °C (cf. Table 1). The required amounts of *n*-BuLi (1.6 M solution in hexane) was introduced dropwise into the reaction mixture during 5 min via syringe, and the mixture stirred for t_1 min. A solution of the *C*-formyl glycal in THF (10 mL) was then introduced dropwise via syringe, and the reaction mixture stirred for t_2 min at T_2 °C. The reaction mixture was then quenched with methanol, the solvent removed and the residue subjected to flash chromatography on silica gel column. Mixtures

of petroleum ether and ethyl acetate were used as eluents. Yields reported are those of the isolated pure products. Compounds **1**, **6-12** and **15-17** were prepared according to this procedure. The experimental conditions and the results are summarized in Table 1. MS, ^1H and ^{13}C NMR data of representative *C*-2-vinyl and the *C*-2-butadienyl derivatives of the glycals prepared (**1**, **8**, **9**, **12**, **16** and **17**) are given hereby. These data for the rest (**6**, **7**, **10**, **11** and **15**) are detailed in the supplementary section.[21]

3,4,6-Tri-*O*-benzyl-2-ethenyl-D-glucal (1). Compound **1** was prepared according to the general procedure. ^1H NMR (250 MHz) δ: 7.09-7.27 (m, 15H, Ar), 6.54 (s, H-1), 6.12 (dd, J= 17.5, 11.0 Hz, H-2α), 4.90 (dd, J= 17.5, 1 Hz, H-2β), 4.77 (dd, J= 11.0, 1 Hz, H-2γ), 4.58 (s, 2H, 2Bzl), 4.41 (d, J= 12.0 Hz, Bzl), 4.35 (m, 4H, H-5, 3Bzl), 4.14 (sh.m, H-3), 3.88 (t, J= 3.5 Hz, H-4), 3.68 (dd, J= 10.4, 6.7 Hz, H-6), 3.56 (dd, J= 10.4, 5.8 Hz, H-6').

Anal. Calcd for $C_{29}H_{30}O_4$: C, 78.71; H, 6.83. Found: C, 79.05; H, 6.94.

2-Ethenyl-3,4,6-tri-*O*-methyl-D-galactal (8). Compound **8** was prepared according to the general procedure. ^1H NMR (250 MHz) δ: 6.44 (s, H-1), 6.18 (dd, J= 17.4, 11.0 Hz, H-2α), 5.05 (dd, J= 17.4, < 1 Hz, H-2β), 4.88 (dd, J= 11.0, < 1 Hz, H-2γ), 4.38 (m, H-5), 4.12 (dd, J= 3.7, < 1 Hz, H-3), 3.82 (dd, J= 11.2, 8.6 Hz, H-6), 3.72 (dd, J= 4.5, 3.7 Hz, H-4), 3.64 (dd, J= 11.2, 2.5 Hz, H-6'), 3.55 (s, 3H, OMe), 3.52 (s, 3H, OMe), 3.37 (s, 3H, OMe).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.31; H, 8.49.

3,4,6-Tri-*O*-benzyl-2-(*E*)-butadienyl-D-glucal (9a). Compound **9** was prepared according to the general procedure. The product was obtained as a mixture of (*E*) - **9a** and (*Z*) - **9b** isomers and separated by flash chromatography. The ratio of the isomers (*E*):(*Z*) was 3.0:1.0, respectively, according to the integration of H-1 of each isomer in the ^1H NMR spectrum of the crude reaction mixture, before the separation. ^1H NMR (250 MHz) δ: 7.17-7.35 (m, 15H, Ar), 6.65 (s, H-1), 6.29 (dt, J= 16.8, 10.0 Hz, H-2γ), 6.07 (d, J= 15.5 Hz, H-2α), 5.92 (dd, J= 15.5, 10.0 Hz, H-2β), 4.97 (dd, J= 16.8, 1.4 Hz, H-2ε), 4.92 (dd, J= 10.0, 1.4 Hz, H-2δ), 4.67 (s, 2H, Bzl), 4.35-4.54 (m, 5H, 4Bzl, H-5), 4.10 (sh.m, H-3), 3.99 (t, J= 3.5 Hz, H-4), 3.77 (dd, J= 10.4, 6.7 Hz, H-6), 3.65 (dd, J= 10.4, 4.9 Hz, H-6').

Anal. Calcd for $C_{31}H_{32}O_4$: C, 79.46; H, 6.88. Found: C, 79.63; H, 6.98.

3,4,6-Tri-*O*-benzyl-2-(*Z*)-butadienyl-D-glucal (9b). ^{1}H NMR (250 MHz) δ: 7.20-7.34 (m, 15H, Ar), 6.76 (dddd, J= 16.9, 11.0, 10.5, 1 Hz, H-2γ), 6.54 (s, H-1), 6.04 (t, J= 11.0 Hz, H-2β), 5.73 (dd, J= 11.0, 1 Hz, H-2α), 5.22 (dt, J= 16.9, 1 Hz, H-2ε), 5.09 (dd, J= 10.5, 1 Hz, H-2δ), 4.70 (d, J= 11.7 Hz, Bzl), 4.63 (d, J= 11.7 Hz, Bzl), 4.53 (s, 2H, 2Bzl), 4.49 (s, 2H, 2Bzl), 4.25 (m, H-5), 4.13 (d, J= 4.6 Hz, H-3), 3.94 (dd, J= 6.1, 4.6 Hz, H-4), 3.80 (dd, J= 10.6, 6.0 Hz, H-6), 3.69 (dd, J= 10.6, 3.7 Hz, H-6').

2-(*E*)-Butadienyl-3,4,6-tri-*O*-methyl-D-galactal (12a). Compound **12** was prepared according to the general procedure. The ratio of the isomers (*E*):(*Z*) was 2.1:1.0, respectively, according to the integration of H-1 of each isomer in the ^{1}H NMR spectrum of the crude reaction mixture. The isomers were not separated. ^{1}H NMR (250 MHz) (from a mixture of *E* and *Z* isomers) δ: 6.47 (s, H-1), 6.38 (ddt, J= 16.7, 10.0, 1.6 Hz, H-2γ), 6.21 (d, J= 15.4 Hz, H-2α), 6.08 (dd, J= 15.4, 9.6 Hz, H-2β), 5.12 (dd, J= 16.7, 1.6 Hz, H-2ε), 4.98 (dd, J= 10.0, 1.6 Hz, H-2δ), 4.37 (m, H-5), 4.12 (sh.m, H-3), 3.82 (dd, J= 11.1, 8.5 Hz, H-6), 3.59-3.81 (m, 2H, H-4, H-6'), 3.58 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.37 (s, 3H, OMe).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.13; H, 8.18.

2-(*Z*)-Butadienyl-3,4,6-tri-*O*-methyl-D-galactal (12b). ^{1}H NMR (250 MHz) (from a mixture of *E* and *Z* isomers) δ: 6.73 (dt, J= 16.9, 11.2 Hz, H-2γ), 6.41 (s, H-1), 6.03 (t, J= 11.2 Hz, H-2β), 5.77 (d, J= 11.2 Hz, H-2α), 5.22 (dt, J= 16.9, 1 Hz, H-2ε), 5.07 (dd, J= 11.2, 1 Hz, H-2δ), 4.26 (m, H-5), 3.95 (sh.m, H-3), 3.59-3.81 (m, 3H, H-4, H-6, H-6'), 3.55 (s, 3H, OMe), 3.47 (s, 3H, OMe), 3.40 (s, 3H, OMe).

2-Ethenyl-3,6,2',3',4',6'-hexa-*O*-methyl-D-lactal (16). Compound **16** was prepared according to the general procedure. ^{1}H NMR (250 MHz) δ: 6.51 (s, H-1a), 6.15 (dd, J= 17.5, 11.0 Hz, H-2αa), 5.00 (dd, J= 17.5, < 1 Hz, H-2βa), 4.85 (dd, J= 11.0, < 1 Hz, H-2γa), 4.40 (m, H-5a), 4.37 (d, J= 7.8 Hz, H-1b), 4.13 (m, H-3a), 4.05 (m, H-3b), 3.68 (dd, J= 10.4, 7.4 Hz, H-6a), 3.61 (m, 2H), 3.44-3.56 (m, 2H), 3.54 (s, 3H, OMe), 3.49 (s, 3H, OMe), 3.48 (s, 3H, OMe), 3.47 (dd, J= 10.4, 4.8 Hz, H-6'a), 3.39 (s, 3H, OMe), 3.37 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.25 (dd, J=9.7, 7.5 Hz, H-6b), 3.09 (dd, J= 9.7, 3.0 Hz, H-6'b).

Anal. Calcd for $C_{20}H_{34}O_9$: C, 57.40; H, 8.19. Found: C, 57.32; H, 8.29.

3,6,2',3',4',6'-Hexa-*O*-benzyl-2-(*Z*)-butadienyl-D-lactal (17). Compound **17** was prepared according to the general procedure. The ratio of the isomers (*E*):(*Z*) was 1.0:2.7,

respectively, according to the integration of H-1 of each isomer in the ^{1}H NMR spectrum of the crude reaction mixture. The ^{1}H NMR spectrum reported is that of the major product - the (*Z*) isomer, after deduction from the spectrum of the (*E*) and (*Z*) isomers mixture. ^{1}H NMR (250 MHz) δ: 7.22-7.34 (m, 30H, Ar), 6.76 (dt, J= 17.0, 11.3 Hz, H-2γa), 6.56 (s, H-1a), 6.02 (t, J=11.3 Hz, H-2βa), 5.72 (d, J= 11.3 Hz, H-2αa), 5.22 (d, J= 17.0 Hz, H-2εa), 5.05 (d, J= 11.3 Hz, H-2δa), 4.26-4.98 (m, 17H), 4.16 (sh.m), 3.77-3.90 (m, 3H), 3.45-3.65 (m, 5H).

Anal. Calcd for $C_{58}H_{60}O_9$: C, 77.31; H, 6.71. Found: C, 77.55; H, 6.92.

(4'-Toluenesulfonyl)-3,4,6-tri-*O*-benzyl-2-deoxy-2-(ethylidene)-D-*arabino*-hexopyranoside (27). A solution of 3,4,6-tri-*O*-benzyl-2-ethenyl-D-glucal **1** (0.221 g, 0.50 mmol) in dry dichloromethane (5 mL) was added dropwise, via syringe, to a stirred solution of 4-toluenesulfinic acid (0.078 g, 0.50 mmol) in dry dichloromethane (5 mL) at room temperature, under argon. After a few minutes the colourless reaction mixture turned to pink. After stirring for 2 h at room temperature the solvent was evaporated. Flash chromatography (petroleum ether : ethyl acetate, 6:4) gave 0.227 g (76%) of **27** as colourless viscous oil. The ^{1}H and ^{13}C NMR spectral data are given in Tables 4 and 5, respectively. FABMS ($C_{36}H_{38}O_6S$, FW= 598.77): *m/z* (%): 771 (100) [(M+NaI)Na$^+$], 621 (4) [MNa$^+$].

(Benzotriazol-1'-and-2'-yl)-3,4,6-tri-*O*-benzyl-2-deoxy-2-(ethylidene)-D-*arabino*-hexopyranoside (28) and (29). A solution of 3,4,6-tri-*O*-benzyl-2-ethenyl-D-glucal **1** (0.442 g, 1.00 mmol) in dry carbon tetrachloride (1 mL) was added via a syringe, to a solution of benzotriazole (0.119 g, 1.00 mmol) in the same solvent (3 mL), under argon. The solution was refluxed for 3 h. Concentration under reduced pressure and purification of the residue by flash chromatography (petroleum ether : ethyl acetate, 85:15) gave two separate mixtures of different isomer pairs of the appropriate 1,4-conjugate addition products, as colourless viscous oils. The separated two mixtures were (α and β) or (*E* and *Z*) mixture of the benzotriazol-1'-yl adduct **28** 0.210 g (37%) and (α and β) or (*E* and *Z*) mixture of the benzotriazol-2'-yl adduct **29** 0.125 g (22%). The total yield of the addition reaction was 59%. The ^{1}H, ^{13}C NMR and MS spectral data of **28** and **29** are given in the supplementary.[21]

General procedure for the addition of ROH type compounds to 3,4,6-tri-*O*-benzyl-2-ethenyl-D-glucal (1). 3,4,6-Tri-*O*-benzyl-2-ethenyl-D-glucal **1**,

Table 3. The experimental conditions and the results of the addition of ROH type compounds to 3,4,6-tri-*O*-benzyl-2-ethenyl-D-glucal (**1**)

Entry	**1** [g (mmol)]	ROH[a] [g (mmol)]	Ph_3P·HBr [g (mmol)]	T (h)	Chromatography Eluents: PE:EtOAc (v/v)	Product[a]	Yield (%)
1	0.100 (0.23)	**20** 0.031 (0.68)	0.012 (0.034)	3	9 : 1[b]	**30**	0.047 g (42%)
2	0.059 (0.13)	**21** 0.173 (0.40)	0.007 (0.020)	1.5	9 : 1[b]	**31**	0.067 g (57%)
3	0.067 (0.152)	**22** 0.280 (0.48)	0.008 (0.024)	2	9 : 1[c]	**32**	0.043 g (31%)
4	0.100 (0.23)	**23** 0.176 (0.68)	0.012 (0.034)	3	9 : 1[b]	**33**	0.029 g (68%)
5	0.100 (0.23)	**24** 0.176 (0.68)	0.012 (0.034)	3	8 : 2[b]	**34**	0.118 g (74%)
6	0.100 (0.23)	**25** 0.384 (0.68)	0.012 (0.034)	2	8 : 2[c]	**35**	0.085 g (37%)
7	0.100 (0.23)	**26** 0.190 (0.68)	0.012 (0.034)	2	8 : 2[c]	**36**	0.087 g (53%)

a. cf. Table 2 b. The crude reaction mixture was separated by flash chromatography. c. The crude reaction mixture was separated on MPLC.

hydroxylic nucleophile (93 equiv) and catalytic amount of triphenylphoshine hydrobromide (0.15 equiv), in anhydrous dichloromethane (5 mL) were stirred for 1.5 - 3 h, at room temperature, under argon. The reaction mixture was washed with saturated sodium hydrogencarbonate solution, followed by saturated sodium chloride solution, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography to yield a colourless viscous oil. The experimental conditions and the results are summarized in Table 3. Representative MS, ^1H and ^{13}C NMR data of the addition products (**32-34** and **36**) are given hereby. These data for the rest (**30**, **31** and **35**) are detailed in the supplementary section.[21]

Methyl 6-*O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-ethylidene-D-*arabino*-hexopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (32). Compound **32** was prepared according to the general procedure. The ^1H and ^{13}C NMR spectral data are given in Tables 4 and 5, respectively. FABMS ($C_{57}H_{62}O_{10}$, FW= 907.11): *m/z* (%): 1079 (5) $[M+NaI]Na^+$, 945 (5) $[MK^+]$, 929 (100) $[MNa^+]$.

3-*O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-ethylidene-D-*arabino*-hexopyranosyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (33). Compound **33** was prepared according to the general procedure. The ^1H and ^{13}C NMR spectral data are given in Tables

Table 4. ^{1}H NMR Spectral Data of Compounds **27**, **32-34** and **36**.

H	27*	32**	33**	34**	36**
1a	3.01 (s)	5.63 (s)	5.83 (s)	5.65 (s)	5.55 (s)
2'a	4.53 (q, 7.3)	5.67 (dq, 7.2, 1.9)	5.75 (dq, 7.1, 1.5)	5.75 (dq, 7.0, 1.5)	5.75 (dq, 7.0, 1.6)
2"a	1.39 (d, 3H, 7.3)	1.62 (dd, 3H, 7.2, 1.9)	1.74 (dd, 3H, 7.1, 1.6)	1.74 (dd, 3H, 7.0, 1.5)	1.70 (dd, 3H, 7.0, 1.6)
3a	4.15 (d, 9.2)	4.31 (bd, 9.0)	4.32 (bd, 9.5)	4.38 (bd, 9.1)	4.37 (bd, 9.1)
4a	3.70 (t, 9.2)	3.52 (m, 3H-cf. 4b & 6b')	3.57 (t, 9.5)	3.58 (t, 9.4)	3.57 (dd, 9.7, 9.1)
5a	3.87 (ddd, 9.2, 4.4, 2.2)	3.72 (bd, 9.3)	3.95 (ddd, 9.5, 4.8, 2.9)	3.96 (bd, 8.9)	3.92 (bd, 9.7)
6a	3.70 (dd, 10.9, 4.4)	3.80 (dd, 10.6, 4.0)	3.79 (dd, 10.5, 4.8)	3.77 (m, 3H-cf. 5b & 6b')	3.72 (dd, 10.6, 3.7)
6'a	3.61 (dd, 10.9, 2.2)	3.74 (bd, 10.6)	3.73 (dd, 10.5, 2.9)	3.67 (dd, 10.5, 1.3)	3.63 (dd, 10.6, 1.4)
1b	-	4.52 (d, 3.4)	5.82 (d, 3.6)	5.53 (d, 5.0)	5.15 (s)
1'b	-	3.33 (s, 3H)	-	-	-
2b	7.57 (d, 10.3)	3.46 (dd, 9.4, 3.4)	4.58 (d, 3.6)	4.31 (dd, 4.8, 2.2)	4.68 (m, 5H-cf. Bzl)
3b	cf. Aryl	3.98 (t, 9.4)	4.35 (d, 2.4)	4.61 (dd, 7.9, 2.0)	
4b	-	3.52 (m, 3H-cf. 4a & 6b')	3.95 (m)	4.25 (dd, 7.9, 1.3)	4.40 (dd, 9.1, 5.8)
5b	2.43 (s, 3H)	3.87 (bd, 8.2)	4.17 (m)	3.77 (m, 3H-cf. 6a & 6b')	3.53 (dd, 10.0, 9.1)
5'b	-	-	-	-	3.78 (10.0, 5.8)
6b	-	3.63 (dd, 10.6, 3.9)	4.09 (dd, 8.6, 6.2)	4.02 (t, 6.8)	-
6'b	-	3.52 (m, 3H-cf. 4a & 4b)	3.96 (dd, 8.6, 5.6)	3.77 (m, 3H-cf. 5a & 5b)	-
Aryl	7.33 (m, 17H)	7.11-7.34 (m, 30H)	7.12-7.37 (m, 15H)	7.15-7.36 (15H, Ar)	7.14-7.37 (m, 20H)
Bzl	4.40 (d, 11.5), 4.51 (d, 12.2), 4.54 (d, 11.9), 4.57 (d, 11.5), 4.65 (d, 12.2), 4.75 (d, 11.9)	4.39 (d, 12.0), 4.44 (d, 11.0), 4.56 (d, 12.0), 4.57 (d, 10.9), 4.65 (d, 11.8, 2H), 4.69 (d, 11.8), 4.77 (d, 11.8), 4.79 (d, 10.6), 4.83 (d, 10.9), 4.87 (d, 11.0), 4.96 (d, 10.6)	4.86 (d, 10.6), 4.69 (bs, 2H), 4.62 (d, 12.1), 4.49 (d, 12.1), 4.45 (d, 10.6)	4.48 (d, 11.4, 2H), 4.71 (s, 2H), 4.85 (d, 10.8)	4.43 (d, 11.8), 4.46 (d, 11.4), 4.48 (d, 10.3), 4.61 (d, 11.4), 4.68 (m, 5H-cf. 2b & 3b), 4.85 (d, 10.3)
Me		-	1.24 (s, 3H), 1.29 (s, 3H), 1.40 (s, 3H), 1.48 (s, 3H)	1.33 (s, 6H), 1.44 (s, 3H), 1.53 (s, 3H)	1.31 (s, 3H), 1.47 (s, 3H)

* The ^{1}H NMR spectra were obtained on a 250 MHz spectrometer. ** The ^{1}H NMR spectra were obtained on a 600 MHz spectrometer.

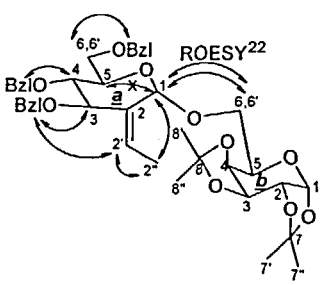
4 and 5, respectively. FABMS ($C_{41}H_{50}O_{10}$, FW= 702.79): *m/z* (%): 875 (3) $[M+NaI]Na^+$, 741 (3) MK^+, 725 (100) MNa^+, 443 (29) 3,4,6-tri-*O*-benzyl-2-deoxy-2-ethylidene-D-*arabino*-hexopyranosyl cation.

6-*O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-ethylidene-D-*arabino*-hexopyranosyl)-1',2':3',4'-di-*O*-isopropylidene-α-D-galactopyranoside (34). Compound **34** was prepared

Table 5. ^{13}C NMR Spectral Data for Compounds **27**, **32-34** and **36**.

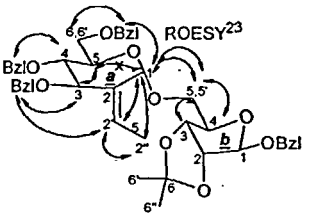
C	27*	32**	33**	34**	36**
1a	95.76	95.92	96.40	95.33	96.17
2a	144.66	cf. Aryl	132.18	132.84	132.76
2'a	cf. aryl	119.17	120.16	119.85	119.73
2"a	14.58	12.72	12.65	12.62	12.76
3a	68.88	81.11	81.28	81.49	81.37
4a	70.30	77.72/79.61	79.61	79.69	79.62
5a	68.77	70.36	72.19	71.40	71.47
6a	60.17	65.06	68.87	68.78	68.68
1b	cf. Aryl	97.93	105.22	96.33	107.19
2b	cf. Aryl	79.83	84.08	70.65	82.35 / 85.33
3b	cf. Aryl	82.06	78.75	71.63	82.35 / 85.33
4b	cf. Aryl	77.72/79.83	81.47	70.81	85.17
5b	21.64	71.21	72.22	64.87	68.32
6b	-	68.80	67.53	65.38	112.37
7b/8b	-	-	109.38, 111.89	108.50, 109.23	-
Aryl	127.58, 128.42-127.73, 129.22, 129.50, 131.73, 132.64, 133.97, 137.82, 137.91, 138.22	128.45, 128.45-128.48, 135-140	127.64-128.44, 138.17, 138.35	127.54-128.51, 138.15, 138.47, 138.54, 145.93	127.56-128.47, 137.05, 138.06, 138.39
Bzl	71.16, 71.35, 73.36	73.32, 73.36, 73.44, 74.81, 74.91, 75.84	73.53, 73.69, 75.15	73.41, 73.68, 74.83	69.20, 73.43, 73.65, 74.88
Me	-	55.11	25.26, 26.15, 26.74, 26.87	24.51, 24.88, 26.00, 26.12	25.04, 26.43

* The ^{13}C NMR spectra were obtained on a 250 MHz spectrometer. ** The ^{13}C NMR spectra were obtained on a 600 MHz spectrometer. The assignment was determined according to the HMQC spectrum.



according to the general procedure. The ^{1}H and ^{13}C NMR spectral data are given in Tables 4 and 5, respectively. FABMS ($C_{41}H_{50}O_{10}$, FW= 702.84): *m/z* (%):741 (3) [MK^+], 725 (100) [MNa^+], 701 (3) [$M-H]^+$, 635 (3) [(M-H-Bzl)Na^+], 443 (20) 3,4,6-tri-*O*-benzyl-2-deoxy-2-ethylidene-D-*arabino*-hexopyranosyl cation.

Benzyl 5-*O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-ethylidene-D-*arabino*-hexopyranosyl)-2,3-*O*-isopropylidene-α-D-ribofuranoside (36). Compound **36** was prepared according to the general procedure. The ^{1}H and ^{13}C NMR spectral data are given in



Tables 4 and 5, respectively. FABMS ($C_{44}H_{50}O_9$, FW=722.87): *m/z* (%):896 (3) [M+NaI]Na^+, 761 (5) [MK^+], 745 (100) [MNa^+].

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21. The supplementary section can be obtained from Ben-Ami Feit.
22. The ROESY (600 MHz) spectrum was measured at 1.0-6.0 ppm, and only the interactions, necessary for establishing the structures, are noted by the arrows. The anomeric configuration of the glycosyl donor (α) and the stereochemistry of the double bond (*Z*) was established based on the ROESY spectrum.
23. The ROESY (600 MHz) spectrum was measured at 1.1-6.0 ppm, and most of the important interactions, necessary for establishing the structures, are noted by the arrows. The anomeric configuration of the glycosyl donor (α) and the stereochemistry of the double bond (*Z*) was established based on the ROESY spectrum.