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A SIMPLE DIASTEREOSELECTIVE SYNTHESIS OF 2',3'-UNSATURATED ARYL C-GLUCOPYRANOSIDES

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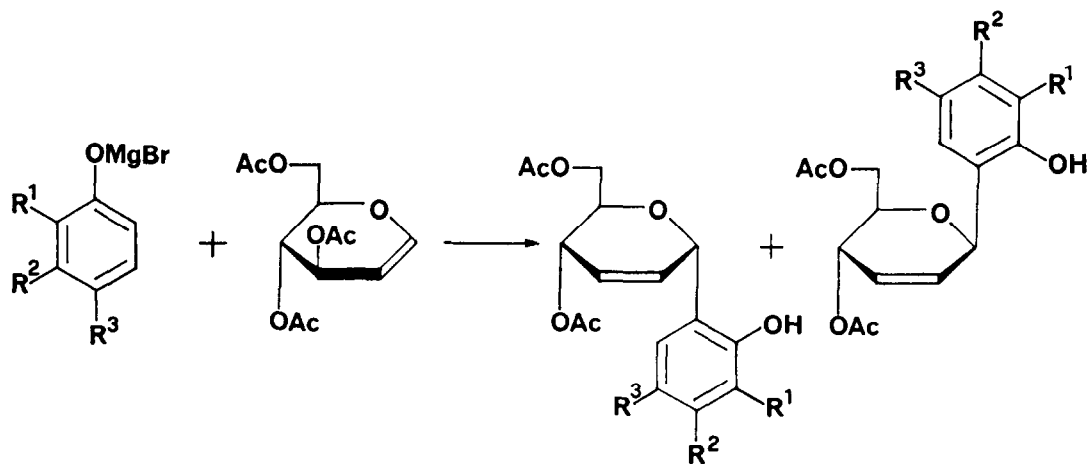
Abstract: The regio- and stereoselective arylation at the anomer center of 3,4,6-tri-O-acetyl-D-glucal (**2**) by means of bromomagnesium phenolates (**1**) allows direct preparation of 2',3'-unsaturated 1-C-aryl- α-D-glycosides (**3**).

Aryl C-glycosides are widespread in Nature and often show biological activity.[1] Furthermore they have proven to be versatile synthetic intermediates for the assembly of more complex targets.[2] As a consequence, much attention has been paid to their synthesis either by using Diels-Alder chemistry or dipolar cycloaddition reactions in the construction of the carbohydrate fragment[3] or by formation of a carbon-carbon bond at the anomer center of a sugar precursor.[4]

We have now elaborated a highly regio- and diastereoselective approach to the 2',3'-unsaturated axial C-glycopyranosides (**3**) via direct arylation of available tri-O-acetyl-D-glucal (**2**) by means of bromomagnesium salts of phenols (**1**) under ultrasonic irradiation.[5]



1 **2** **3** **4**

As a general procedure, the appropriate phenol (**1**) (4 equiv.) was added to a solution of ethylmagnesium bromide in diethyl ether. After 10 min the ether was removed completely under vacuum and ethanol-free CH_2Cl_2 added. The reaction vessel was placed into a ice-cooled sonication bath and glucal (**2**) added dropwise as a solution in CH_2Cl_2.
After the reaction was completed (6-8 hr; 15-20°C), the mixture was quenched by pouring into a saturated aq. NH_4Cl solution and extracted with CH_2Cl_2. The solvent was then removed and pure C-α and C-β-glycopyranosyl derivatives (**3**) and (**4**) separated from the crude by flash chromatography (silica-gel) by using hexane-ethyl acetate as an eluant.

Table 1. Reaction of bromomagnesium phenolates (**1**) with 3,4,6-tri-O-acetyl-D-glucal (**2**)

entry	phenol	R^1	R^2	R^3	products	yield,[a] %	**3**:**4**[b] ratio
1	**1a**	H	H	H	**3a**+**4a**	63	29:1
2	**1b**	H	OMe	H	**3b**+**4b**	69	21:1
3	**1c**	H	H	OMe	**3c**	82	>100:1
4	**1d**	H	H	t-Bu	**3d**	71	>100:1
5	**1e**	t-Bu	H	Me	**3e**+**4e**	66	58:1
6	**1f**	H	$-OCH_2O-$		**3f**+**4f**	80	27:1

[a] Combined yield for pure anomers, based on the amount of the glucal (**2**) used. [b] Determined on crude products by reverse-phase HPLC (Pecosphere-5CC18 column; methanol/water solvent system).

This methodology was shown to be quite general allowing the preparation of a variety of ring-hydroxylated 2',3'-unsaturated C-α-arylglycosides (**3a-f**) with good chemical efficiency and very high, often complete, α-stereoselectivity. The results are shown in Table 1 while a selection of physical and ^1H NMR spectroscopic data for the synthesized major α-glycosides (**3a-f**) are collected in Table 2.

The assignments of structures to α and β anomeric pairs (**3**) and (**4**) was made mainly on the basis of spectroscopic evidence. In the ^1H NMR spectra, the observed value for $J_{4',5'}$ proved to be particularly distinctive, ranging from 5.8 to 6.6 Hz in the major α-anomers (**3**) and from 8.8 to 9.1 Hz in the minor β-anomers (**4**).[6,7] In addition, these assignments were corroborated by NOE experiments. In the α-anomer series, no enhancement of H-1' was observed upon irradiation of H-5' while in the β-series a strong NOE enhancement was shown, in accordance with closely related studies in the C-glycoside domain.[8,9]

As far as this direct glycosidation is concerned, two points are worthy of mention. First, the reaction is regiospecific with respect to both the arylation sense and the substitution site, being the glucal anomeric carbon only arylated and the phenol ortho-carbon only substituted. Second, the reaction is strereoselective with proclivity to give α-anomers predominantly, likely as a result of a kinetic discrimination of the two diastereotopic faces of (**1**), wherein the aromatic ortho-carbon preferentially enters the anomeric carbon anti to the equatorial C-5' substituent.[10]

Table 2. 2-(4',6'-Di-O-acetyl-2',3'-dideoxy-α-D-erythro-hex-2'-enopyranosyl)-phenols (**3**) synthesized

				^{1}H NMR[b,c]			
Entry	Compd	Appearence or M.p,°C	$[\alpha]_D^{20}$,deg[a]	H-2'	H-3'	H-5'	$J_{4',5'}$
1	**3a**	syrup	+77	6.28	6.04	3.99	6.3
2	**3b**	syrup	+78	6.27	6.01	3.94	6.5
3	**3c**	syrup	+34	6.28	6.04	3.94	6.2
4	**3d**	syrup	+58	6.22	5.97	3.95	6.4
5	**3e**	77-79	+53	6.30	5.95	3.90	6.2
6	**3f**	126-128	-24	6.22	6.02	3.91	6.5

[a] For solutions in $CHCl_3$, c = 1. [b] Selected significant resonances in ppm relative to internal tetramethylsilane; coupling constants (J) in Hz. The spectra for solutions in $CDCl_3$ were taken on a Bruker AM-270 instrument at ambient temperature. [c] H-2', H-3', and H-5' resonances appear as ddd in all compounds. The related coupling constants are consistent with literature values for 2',3'-unsaturated C-α-glycosides (see ref. 6 and 7).

In conclusion, what we have presented is a preparatively useful procedure for carbon-carbon bond formation at the anomer center of a 1,2-unsaturated carbohydrate by means of bromomagnesium salts of hydroxylated aromatics. The extension of this reaction to suitable aromatic aglycones en route to pharmacologically important C-arylglycosides will be the subject of future work from this laboratory.

References and Notes

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7. The equatorial disposition of all the three pyran substituents in **4f** was unambiguously ascertained by single crystal X-ray analysis.

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9. In the ^{13}C NMR spectra, for a given pair, the C-5' resonance in the less dextrorotatory major α-anomers invariably was ca. 4 ppm further upfield than in the more dextrorotatory minor β-anomers.

10. Treatment of the kinetically favored C-α-glycoside (**3f**) with potassium tert-butoxide in benzene at ambient temperature resulted in the formation of a 1:2 mixture of starting (**3f**) and thermodinamically more stable C-β-glycoside (**4f**).

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