Stereospecific Synthesis of α- and β-*C*-Aryl-Δ²-Glycopyranosides from *p-tert*-Butylphenyl α-*O*-Δ²-Glycopyranoside *via* Grignard Reagents

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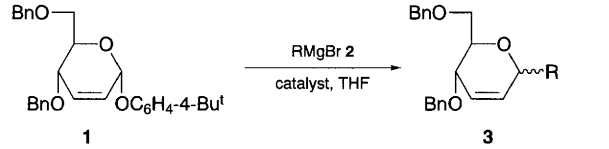
Palladium-catalysed coupling of *p-tert*-butylphenyl α-*O*-Δ²-glycopyranoside with various substituted arylmagnesium bromides provides the corresponding *C*-α-aryl-Δ²-glycopyranosides, while nickel-mediated reaction allows the preparation of the *C*-β-aryl anomers.

Recently, there has been interest in the synthesis of *C*-aryl-glycosides,[1] because many natural products containing this structural framework show antibiotic and/or antiviral activities. Furthermore, these types of derivatives are valuable synthetic intermediates to more complex targets. In particular, *C*-arylglycosides bearing a double bond in position 2,3 are particularly versatile synthons, since this unsaturation can further be functionalised for total synthesis of natural products.

The usual approaches to such structures involve palladium(II)-mediated arylation of glycals,[2] addition of arylzinc derivatives to hex-2-enopyranosides in the presence of a catalytic amount of palladium(0),[3] Lewis acid promoted reaction of phenols with glycals,[4] or addition of bromomagnesium phenates to the same unsaturated glycals.[5] However, one of the major drawback of these different methodologies is the lack of selectivity observed, the α anomer being generally preponderant.

As part of our continuing interest in the field of palladium-catalysed functionalisation at the anomeric centre of carbohydrates,[6] we describe herein a new procedure that allows the regio- and stereo-specific introduction of an aryl group at the anomeric position of 2,3-unsaturated glycopyranosides.



1 **3**

a R = Ph
b R = 4-MeOC$_6$H$_4$
c R = 2-MeOC$_6$H$_4$
d R = 3,4-(CH$_2$O$_2$)C$_6$H$_3$
e R = 4-MeC$_6$H$_4$
f R = 2-MeC$_6$H$_4$
g R = 4-ClC$_6$H$_4$
h R = PhCH$_2$
i R = 2-thienyl

Scheme 1

p-tert-Butylphenyl 4,6-di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **1**, very easily prepared in multigram quantities from 3,4,6-tri-*O*-acetyl-D-glucal,[7] was chosen as the model substrate for our arylation studies. Treatment of unsaturated compound **1** with phenylmagnesium bromide **2a** in the presence of PdCl$_2$(dppf) [palladium dichloro {1,1′-bis(diphenylphosphino) ferrocene}] led very cleanly to the 2,3-unsaturated *C*-α-phenylglycopyranoside **3a** in quite good yield (run 1). The use of other palladium catalytic systems like Pd(PPh$_3$)$_4$ or PdCl$_2$(PPh$_3$)$_2$ gave practically no reaction. This transformation was thereafter successfully extended to various other arylbromides bearing methyl, methoxy, chloro or methylenedioxy substituents, to give stereospecifically and in excellent chemical yields the corresponding unsaturated *C*-α-arylglycopyranosides **3b–g**, (runs 3, 5, 7, 9, 11 and 12). Even 2-thienylmagnesium bromide provided *C*-α-(2-thienyl) glycopyranoside **3i** in 81% yield (run 14). This palladium-catalysed carbon–carbon bond formation at the anomeric centre was not restricted to aromatic magnesium bromides. For example, 2,3-unsaturated *C*-α-benzylated glycopyranoside **3j** was obtained under the same conditions in 70% yield (run 13).

The use of a nickel catalyst NiCl$_2$(dppe) [nickel dichloro {1,2-bis(diphenyl phosphino) ethane}], instead of the palladium catalyst, together with the arylmagnesium bromides, between −40 and 0 °C, lead now stereospecifically to the 2,3-unsaturated *C*-β-arylglycopyranosides **3** (runs 2, 4, 6, 8 and 10) in quite good yields. However, at room temp., only by-products arising from the ring opening of the carbohydrate moiety[8] by a second molecule of arylmagnesium bromide or the attack of the nucleophile at the other electrophilic site of the π-allyl intermediate were observed.

The anomeric configuration was assigned by ^{1}H and ^{13}C NMR spectroscopy.[9] Having in hand both epimers of **3a–e**, the ^{13}C NMR spectra allowed in these cases the unambiguous assignment of the anomeric configuration by examination of the C-5 chemical shift. Indeed, this value for the α anomer is always

Table 1 Arylation of *p-tert*-butylphenyl 4,6-di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **1** with RMgBr **2**[a]

Run	RMgBr **2**	Catalyst	*T*/°C	Product **3**	Yield[b] (%)	α/β[c]
1	**a**	PdCl$_2$(dppf)	25	**a**	95	100/0
2	**a**	NiCl$_2$(dppe)	−40	**a**	70	0/100
3	**b**	PdCl$_2$(dppf)	25	**b**	73	100/0
4	**b**	NiCl$_2$(dppe)	−40	**b**	75	0/100
5	**c**	PdCl$_2$(dppf)	25	**c**	87	100/0
6	**c**	NiCl$_2$(dppe)	−20	**c**	64	0/100
7	**d**	PdCl$_2$(dppf)	25	**d**	95	100/0
8	**d**	NiCl$_2$(dppe)	−40	**d**	70	0/100
9	**e**	PdCl$_2$(dppf)	25	**e**	70	100/0
10	**e**	NiCl$_2$(dppe)	−40	**e**	85	0/100
11	**f**	PdCl$_2$(dppf)	25	**f**	80	100/0
12	**g**	PdCl$_2$(dppf)	25	**g**	76	100/0
13	**h**	PdCl$_2$(dppf)	25	**h**	70	100/0
14	**i**	PdCl$_2$(dppf)	25	**i**	81	100/0

[a] Typical experimental procedure: To a stirred solution of **1** (200 mg, 0.44 mmol) in dry THF (2 ml) under nitrogen was added PdCl$_2$(dppf) (0.044 mmol), obtained by mixing PdCl$_2$(MeCN)$_2$ and dppf, or NiCl$_2$(dppe) (0.023 mg, 0.04 mmol). A solution of RMgBr (2.18 mmol) in THF (2 ml) was added dropwise at the indicated temperature. After 2–4 h, the resultant mixture was hydrolysed and the organic products were extracted with dichloromethane. Concentration of the solution and purification of the residue by silica gel chromatography afforded compounds **3**. [b] Isolated yield of pure product (not optimised). All new compounds gave satisfactory analytical and spectroscopic data. [c] Determined by ^{1}H and ^{13}C NMR spectroscopy.

shielded with respect to the corresponding carbon of the β isomer due to the γ-*gauche* effect described by Stothers.[10] These characterisations were later confirmed by NOE experiments. For example, irradiation of the H-1 signal at δ 5.3 of *C*-arylglycopyranoside **3a**† obtained by palladium-catalysed reaction results in less than 3% increase of the H-5 signal at δ 3.6. Conversely, irradiation of the H-1 signal at δ 5.18 of **3a**† prepared *via* nickel catalysis gives rise to a strong NOE effect (10%) of the H-5 signal at δ 3.75, in agreement with a *syn* disposition of these two protons. In the case of compound **3h** obtained by palladium-catalysed reaction, the irradiation of the benzylic protons at δ 2.82 and 3.08 produces a 7% increase of the H-5 signal at δ 3.91.

Although the overall inversion of configuration obtained in the case of the nickel catalyst agrees well with the literature data,[11] the overall retention of configuration observed in the case of palladium-mediated reaction was unexpected. It should be noticed that palladium-catalysed substitution of allylic derivatives by Grignard reagents is quite rare, but it was nevertheless recently shown that such a transformation generally occurs with inversion of configuration in the case of linear compounds.[12] However, more experiments are needed to clear up the mechanistic pathway of this last reaction.

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Footnote

† Selected data for **3a**: α anomer: $[\alpha]_D^{20}$ + 18.5 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.50–3.70 (3 H, m, H-5, H-6, H-6′), 4.20 (1 H, br d, $J_{4,5}$ 7.3 Hz, H-4), 4.43 (1 H, d, J_{gem} 12.1 Hz, OCH_2Ph), 4.46 (1 H, d, J_{gem} 11.5 Hz, OCH_2Ph), 4.58 (1 H, d, J_{gem} 12.1 Hz, OCH_2Ph), 4.61 (1 H, d, J_{gem} 11.5 Hz, OCH_2Ph), 5.30 (1 H, br s, H-1), 6.00 (1 H, br d, $J_{2,3}$ 10.9 Hz, H-2), 6.16 (1 H, br d, $J_{3,2}$ 10.9 Hz, H-3), 7.20–7.50 (15 H, m, H_{arom}); ^{13}C NMR (50 MHz, $CDCl_3$) δ 69.0 (C-6), 70.1 and 70.7 (C-4, C-5), 71.0 and 73.2 (OCH_2Ph), 74.0 (C-1), 127.0–130.0, 138.2 and 139.5 (C-2, C-3, C_{arom}). β anomer: $[\alpha]_D^{20}$ + 60.8 (*c* 0.65, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.60–3.90 (3 H, m, H-5, H-6, H-6′), 4.20 (1 H, br d, $J_{4,5}$ 8.6 Hz, H-4), 4.51 (1 H, d, J_{gem} 11.5 Hz, OCH_2Ph), 4.56 (1 H, d, J_{gem} 12.1 Hz, OCH_2Ph), 4.64 (1 H, d, J_{gem} 12.1 Hz, OCH_2Ph), 4.66 (1 H, d, J_{gem} 11.5 Hz, OCH_2Ph), 5.20 (1 H, br s, H-1), 5.86 (1 H, br d, $J_{2,3}$ 10.3 Hz, H-2), 6.00 (1 H, br d, $H_{3,2}$ 10.3 Hz, H-3), 7.20–7.40 (15 H, m, H_{arom}); ^{13}C NMR (50 MHz, $CDCl_3$) δ 69.9 (C-6), 70.5 (C-4), 71.3 and 73.4 (OCH_2Ph), 77.4 (C-5), 77.8 (C-1), 125.9–131.7, 138.0, 138.4 and 140.7 (C-2, C-3, C_{arom}).

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