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Regioselective Bromination of O-ß-Glycosylated Aromatics

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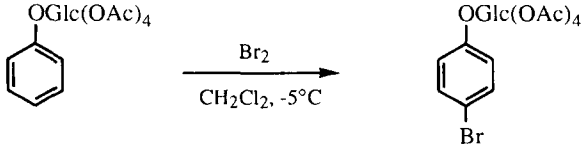
Abstract: The quasi quantitative and regioselective bromination of O-(2,3,4,6-tetra-O-acetyl-ß-D-glucopyranosyl) phenols is described. The orientating effect of the glycoside group is compared with those of other oxygenated groups and its usefulness illustrated with examples. These bromo-glycosylated aromatics are able to react with alkenes via a Heck reaction and could be used for the synthesis of natural products.

A large number of natural aromatic products are ß-glycosylated[1] and the glycoside group is frequently introduced by a phase-transfer reaction in the final stages of synthesis[2]. However, although this reaction is applicable to almost all phenols, it gives a low yield, a major drawback for the final stages of any synthesis. In addition, it would be useful to be able to introduce the glycoside moiety before the end of the synthesis but, at the present time, very few synthesis reactions have been developed for working in the presence of glucosides. In this work, we have studied the functionalization by bromination of ß-O-glycosylated aromatic rings. This reaction turns out to be especially effective in terms of the yields and regioselectivity obtained.

Bromination was performed by the classic method for bromination of activated aromatics[3], i.e. the addition, in the cold (-20°C), of bromine to a solution of glycosylated phenol in dichloromethane (scheme 1), followed by two hours reaction at -5°C[4], conditions under which the bromination yields are quantitative and the position of bromination completely selective. The bromination results for several mono- or di-substituted glycosylated phenols are shown in table 1[5].

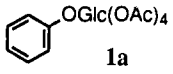
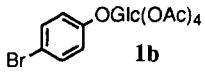
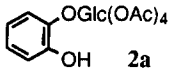
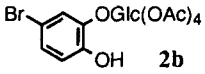
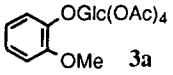
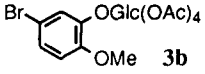
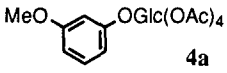
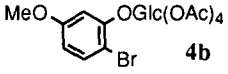
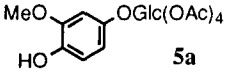
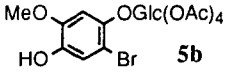
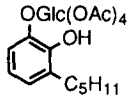
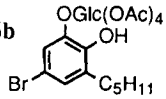
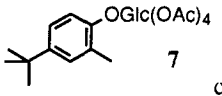
Scheme 1



In all cases we observed a regioselective monobromination except with compound **4a**. Indeed the reaction with 1-O-(2,3,4,6-tetra-O-acetyl-ß-D-glucopyranosyl)-3-methoxy-phenol **4a** for 2h at -5°C gave a 50%/50% mixture of bromination at positions 4 and 6, but reaction for 5h at -78°C resulted in bromination exclusively at position 6 (determined by nOe).

The results show that the 1-O-(2,3,4,6-tetra-O-acetyl-ß-D-glucopyranosyl) group is less strongly *ortho/para* directing than the methoxyl and so even less than the hydroxyl[6]. Selection of orientation between the

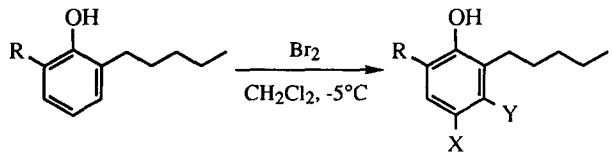
Table 1. Bromination of a Series of Substituted O-ß-Glycosylated Phenols

Entry	Starting material	Product	Yield %
1	 **1a**	 **1b**	94
2	 **2a**	 **2b**	94
3	 **3a**	 **3b**	94
4	 **4a** a,b	 **4b**	93
5	 **5a**	 **5b**	95
6	**6a** 	**6b** 	96
7	 **7** c	-	0

a) 50/50 mixture of bromination at positions 4 and 6 after reaction for 2h at -5°C.
b) 100% of bromination at position 6 after reaction for 5h at -78°C.
c) 0% yield after reaction for 5 hours at 25°C.

methoxyl and hydroxyl groups is sometimes difficult and the introduction of the glycoside group makes it possible to accentuate the differences in directing potential of the oxygenated groups. For example, 1-O-methyl-3-n-pentylcatechol gives a 75%/25% mixture of bromination (scheme 2) at the position *para* to the hydroxyl and methoxyl groups, while 1-O-(2,3,4,6-tetra-O-acetyl-ß-D-glucopyranosyl)-3-n-pentylcatechol **6a** is exclusively brominated at the position *para* to the hydroxyl group.

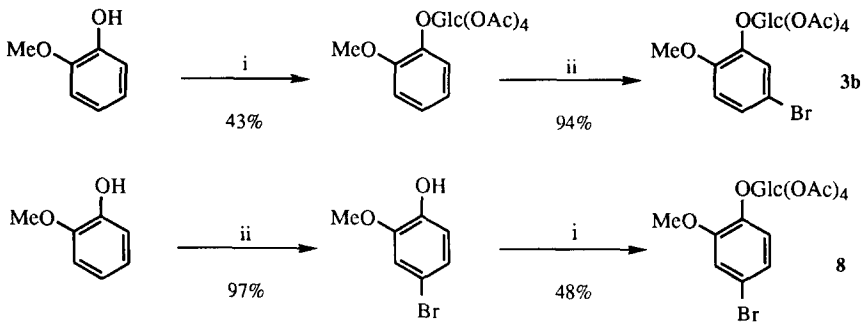
Scheme 2



R	X= H Y= Br	X= Br Y= H
OMe	25%	75%
O-ß-Glc(OAc)4 **6a**	0%	100% **6b**

This difference in orientation-inducing ability can also be exploited to obtain two bromination isomers by reversing the order of the glycosylation/bromination sequence (scheme 3); starting with guaïacol, glycosylation (i) by phase-transfer catalysed by triethylbenzylammonium chloride (TEBACl), followed by bromination (ii) gives isomer **3b** brominated in the position *para* to the methoxyl, while the reverse order of reaction, bromination[7] (ii) followed by glycosylation (i), gives derivative **8** brominated at the position *para* to the glycosyl[8].

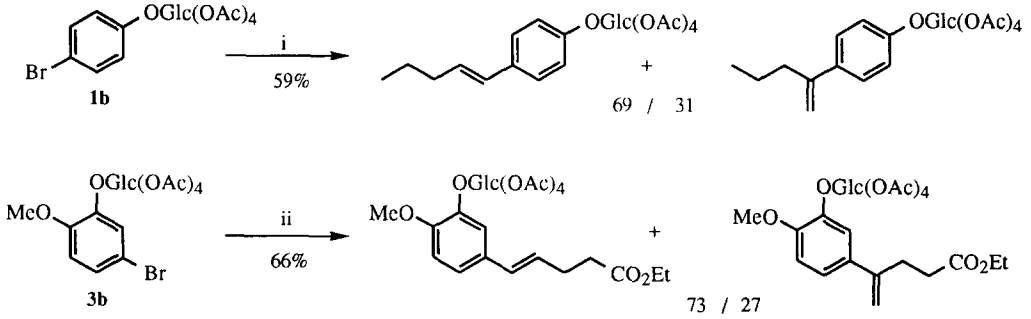
Scheme 3



i. $Glc(OAc)_4Br$, NaOH 1.25N, TEBACl, $CHCl_3$; ii. Br_2, CH_2Cl_2.

These brominated glycosylated aromatics can then be used as starting synthons for the branching of aliphatic chains, giving a point of access to the synthesis of natural products[9]. Two brominated aromatics were coupled to an alkene via a Heck reaction[10] (scheme 4)[11].

Scheme 4



i. 1-pentene (3 eq), $Pd(OAc)_2$ (0.1eq), $P(o\text{-}Tol)_3$ (0.4cq), NEt_3 (>3cq), 110°C, 24h
ii. Ethyl pent-4-enoate (3 eq), $Pd(OAc)_2$ (0.1eq), $P(o\text{-}Tol)_3$ (0.4cq), NEt_3 (>3cq), 110°C, 24h

In conclusion, new perspectives in strategies for the synthesis of natural O-ß-glycosylated products are opened up by the possibility of selective and quantitative functionalization by bromination of ß-glycosylated aromatic compounds. In addition, combined with the availability of developed effective methods for

glycosylation permitting the coupling of glycosides with excellent yields and with the high lability of the glycoside-phenol bond, the ability of glycosides to modify selective orientation in aromatic electrophilic substitution reactions should permit their use as true protecting groups.

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3. Brittain, R. and de la Mare, P.B.D., in Patai and Rappoport, "*The Chemistry of Functional Groups, Supplement D*", Wiley, New-York, 1983, pt.1, pp. 522-532.
4. ***Typical procedure***: To a stirred solution of 1-O-(2,3,4,6-tetra-O-acetyl-ß-D-glucopyranosyl)phenol **1a** (424mg, 1mmol) in CH_2Cl_2 at -78°C, bromine (1.1 mmol, 50mL) is added dropwise and the reaction allowed to proceed for 2h at -5°C. A solution of $Na_2S_2O_3$ (5mL) is added and the reaction mixture stirred for 5 min. The organic material is then extracted using CH_2Cl_2 and the organic phase dried over $MgSO_4$ and evaporated under reduced pressure. After silica gel chromatography, the 1-O-(2,3,4,6-tetra-O-acetyl-ß-D-glucopyranosyl)-4-bromo-phenol **1b** (473mg, 0.94mmol) is obtained as a white crystal with a 94% yield.
5. All compounds were isolated as chromatographically pure materials which gave ^{1}H-NMR, ^{13}C-NMR, infrared and elementary analysis consistent with their assigned structures.
6. De la Mare, P.B.D. and Vernon, C.A. *J. Chem. Soc.*, **1951**, 1764-1772.
7. a) Robertson, P. *J. Chem. Soc.*, **1908**, *93*, 788-796. b) Moir, R.Y.; Purves, C.B. *Can. J. Research.* **1948**, B, *26*, 694-701.
8. **3b**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 6.81 (1H, d, J=8.6Hz), 6.59 (1H, d, J=2.6Hz), 6.50 (1H, dd, J=2.6Hz, 8.6Hz), 5.25 (3H, m), 4.97 (1H, d, J=7.6Hz), 4.28 (1H, dd, J=5.2Hz, 12.3Hz), 4.23 (1H, dd, J=2.6Hz, 12.3 Hz), 3.89 (3H, s), 3.83 (1H, ddd, J=2.6Hz, 5.2Hz, 10.0Hz), 2.09 (3H, s), 2.08 (3H, s), 2.05 (3H, s), 2.03 (3H, s). ^{13}C-NMR (50 MHz, $CDCl_3$) δ 170.7, 170.3, 169.5, 169.3, 149.9, 146.9, 127.3, 122.9, 114.1, 112.4, 100.6, 72.5, 72.2, 71.1, 68.5, 62.2, 56.3, 20.8, 20.7. IR ($CHCl_3$) ν 3030, 1752, 1235, 1214, 1060, 789. mp 143-144°C. Anal. Calcd. for $C_{21}H_{25}BrO_{11}$: C, 47.29; H, 4.73. Found: C, 46.89; H, 4.72. **8**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.00 (3H, m), 5.24 (2H, m), 5.14 (1H, dd, t like, J=9.9Hz), 4.90 (1H, d, J=8.0Hz), 4.25 (1H, dd, J=12.2Hz, 4.8Hz), 4.14 (1H, dd, J=12.2Hz, 2.4Hz), 3.80 (3H, s), 3.74 (1H, ddd, J=2.4Hz, 4.8Hz, 10.0Hz), 2.09 (3H, s), 2.08 (3H, s), 2.03 (3H, s), 2.02 (3H, s). ^{13}C-NMR (50 MHz, $CDCl_3$) δ 170.6, 170.2, 169.4, 169.3, 150.5, 145.8, 124.2, 119.4, 117.4, 114.6, 110.6, 72.3, 71.1, 68.5, 62.2, 56.5, 20.8, 20.6. IR ($CHCl_3$) ν 3026, 1752, 1234, 1210, 1056, 788. mp 137-138°C. Anal. Calcd. for $C_{21}H_{25}BrO_{11}$: C, 47.29; H, 4.73. Found: C, 47.14; H, 4.88.
9. a) Freundenberg, B et al, *Ber.* **1952**, *81*, 641-649. b) Urban, R., Rogowski, D., *Arch. Exp. Pathol. Pharmakol.* **1950**, *194*, 211-221. c) Thorpe, W., Williams, T., *J. Chem. Soc.* **1937**, 494-498.
10. Heck, R.F. *Org. Reactions*, **1982**, 345-391.
11. Five-fold more equivalents of $Pd(OAc)_2$ and P(o-Tol)$_3$ were required compared with the classic conditions (0.02%, 0.08%) to achieve coupling, which can be explained by complexing of the palladium by the acetoxy groups of the glycoside.

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