Novel Synthesis of Aryl 2,3,4,6-Tetra-O-acetyl-D-glucopyranosides

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The glycosidation of phenols with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl fluoride in the presence of BF₃·OEt₂ to give, predominantly, α-anomers has been studied. In the presence of an amine base, 1,1,3,3-tetramethylguanidine, however, enhanced β-selectivity was achieved. The former reaction provides a novel and useful synthesis of aryl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside whilst the latter is effective for the glycosidation of relatively hindered phenols.

O-Aryl glucosides are widely found in natural products, and carbon–oxygen bond formation employing activated sugar derivatives and phenols has been extensively studied.[1] The stereoselective formation of anomeric centres is a major problem in synthesis, and various combinations of leaving group, promoter, and protecting group have been devised to achieve this; the popularity of fluoride as a leaving group is increasing.[2] Recently, the novel glycosidation of phenols utilizing 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl fluoride and BF₃·OEt₂–2,2,6,6-tetramethylpiperidin-4-one system as promoter was reported.[3,4] Although this interesting and complex reagent system was successfully applied to trans-glycoside synthesis, the role of the hindered base was not described in detail.[5] Employing 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl fluoride (1) we have re-examined the reaction, and our results are now presented.[6]
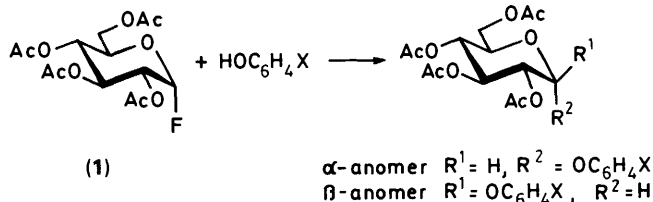
The reaction of 1-naphthol and the fluoride (1) was selected as a probe to understand the reaction. The addition of BF₃·OEt₂ to the above mixture in acetonitrile gave 1-naphthyl 2,3,4,6-tetra-O-acetyl-D-glucopyranoside in high yield as a mixture of α- and β-anomers (40:60). When an amine base was added prior to the Lewis acid, a dramatic enhancement of β-selectivity was observed. Especially effective was 1,1,3,3-tetramethylguanidine and 1,8-bis(dimethylamino)naphthalene, which gave the β-isomer almost exclusively. Inorganic bases (CsF, K₂CO₃, etc.) or weaker base (2,6-lutidine) inhibited the reaction. Other than acetonitrile, methylene dichloride, 1,2-dichloroethane, nitromethane etc., but not THF, could be used with a similar level of stereoselectivity. As for the Lewis acid, SiF₄, TMSOTf,[2b] and Sn(OTf)₂ were less effective. Variations in the order of addition of reagents resulted in no glucoside production. For example, addition of 1-naphthol to a mixture of (1), BF₃·OEt₂, and an amine gave no glucoside.

Several phenols were treated with (1) in the presence of BF₃·OEt₂ and tetramethylguanidine, and the results are summarized in Table 1. Except for p-nitrophenol, β-glucosides were obtained in high yields and with good selectivity. In general, phenols with electron-donating groups showed high β-selectivity. It was noted that the reaction was applicable to sterically hindered phenols such as 2,6-disubstituted phenols or anthrone.
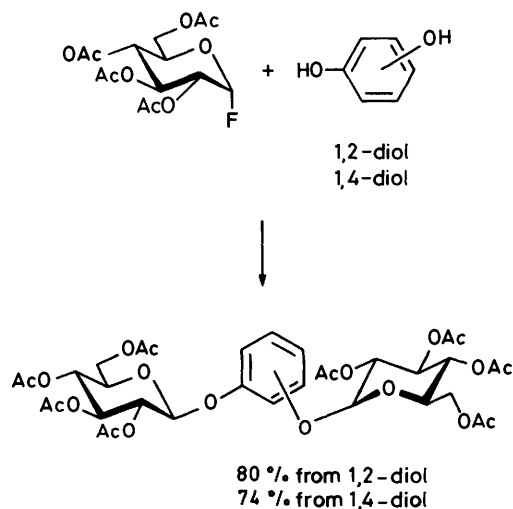
The effectiveness of this reaction was also shown by the high yielding bis-glycosidation of benzenediols (Scheme 1).

Next, our attention was directed to the reaction in the absence of the amine base. As mentioned before, the absence of base resulted in an increase of the α-anomer. Especially with phenols possessing electron-withdrawing groups, a high level of α-selectivity was observed (Table 2). The observation was interesting since the reaction of silylated 4-methylumbelliferone

Table 1. Glycosidation of phenols with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl fluoride (1) in the presence of BF₃·OEt₂ and 1,1,3,3-tetramethylguanidine in MeCN at room temp. during 3 h.

$$\alpha\text{-anomer} \quad R^1 = H, \ R^2 = OC_6H_4X$$
$$\beta\text{-anomer} \quad R^1 = OC_6H_4X, \ R^2 = H$$

HOC₆H₄X X	Yield (%)	α:β
p-OMe	66	β
2,6-Me₂	70	β
2,6-(OMe)₂	69	β
o-Cl	quant.	10:90
p-CO₂Me	88	13:87
H	85	22:78
p-NO₂	67	32:68
1-Naphthol	90	3:97
Anthrone	43	β

1,2-diol
1,4-diol

80 % from 1,2-diol
74 % from 1,4-diol

Scheme 1. Reagents and conditions: BF₃·OEt₂, MeNC(:NH)NMe₂ in MeCN at room temp. during 3 h.

with β-glucosyl fluoride in the presence of BF₃·OEt₂ was reported to give β-glucosides.[3b]

Table 2. Glycosidation of phenols with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl fluoride (1) in the presence of $BF_3 \cdot OEt_2$ in MeCN at room temp. during 3 h.

(1)

α-anomer $R^1 = H$, $R^2 = OC_6H_4X$
β-anomer $R^1 = OC_6H_4X$, $R^2 = H$

HOC_6H_4X	Yield (%)	α:β
X		
p-NO_2	67	82:18
p-Cl	60	75:25
o-Cl	76	80:20
p-Br	50	84:16
p-CO_2Me	84	80:20
p-Ac	53	87:13
p-Ph	55	78:22
H	63	66:34
p-MeO	54	51:49
1-Naphthol	93	40:60

It is well-known that 2-acylated glucose derivatives give β-glucosides as a result of the neighbouring group participation of the carbonyl oxygen at the 2-position (Scheme 2).[7] In other words, the synthesis of α-anomers from acylated glucose derivatives has been rather difficult. Classically, aryl α-glucosides were obtained by heating neat penta-O-acetylglucose and phenols in the presence of zinc chloride at high temperatures.[8] The use of tin(IV) chloride in refluxing benzene for a long period has also been reported.[9,10] Yields of the α-anomer were generally low, although exceptions have been reported, e.g., phenyl α-D-glucoside in ref. 8a. Compared with these conventional methods, the present reaction proceeded effectively under mild reaction conditions, and could be a useful method for the synthesis of aryl α-D-glucopyranosides.

A drawback of the present reaction is that it could not be applied where the phenolic hydroxy group was strongly hydrogen bonded to neighbouring groups. For example, o-hydroxyacetophenone, o-nitrophenol, or 8-methoxy-1-hydroxyanthraquinone failed to undergo glycosidation either by the BF_3 method or the BF_3–tetramethylguanidine method.

An explanation for the above α-stereoselectivity is presented in Scheme 2. As is generally accepted, attack of phenolic oxygen on the oxonium intermediate (2) is considered to take place kinetically from the equatorial site.[11] When an amine base is present in solution, the proton is rapidly removed from eq-(3) to give β-anomers selectively. In the absence of a proton captor, interconversion between eq-(3) and ax-(3) occurs, and the thermodynamically more stable α-anomers are formed via ax-(3).[4] The effects of phenol substituents on the stereochemistry can also be explained by this Scheme. Since the anomeric carbon–oxygen bond of eq-(3) is weaker for phenols with electron-withdrawing groups than for those with electron-donating groups, the former are more susceptible to isomerization to ax-(3). Accordingly, α-anomers are obtained with more acidic phenols.

In summary, a novel synthesis of 2,3,4,6-tetra-O-acetyl-D-glucopyranosides from 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl fluoride (1) has been developed.

Experimental

M.p.s are uncorrected. NMR spectra were obtained on a JEOL JNM-FX-60, and chemical shift values are given in ppm relative to internal Me_4Si. IR spectra were recorded on a Shimadzu IR-408. Elemental analysis were performed with a YANACO MT-3 CHN Corder. Optical rotations were obtained with HORIBA SEPA-200 High Sensitive Polarimeter.

Materials.—2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl fluoride was prepared according to a literature method.[12] Acetonitrile was distilled from CaH_2, and stored over MS 4A.

Glycosidation in the Absence of 1,1,3,3-Tetramethylguanidine: Typical Procedures.—Under a nitrogen atmosphere, $BF_3 \cdot OEt_2$ (0.20 ml, 1.6 mmol) was added to a mixture of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl fluoride (1) (105 mg, 0.3 mmol) and p-methoxyphenol (12 mg, 0.1 mmol) in acetonitrile (2 ml) at room temperature. After the mixture had been stirred for 3 h, saturated aqueous $NaHCO_3$ was added. Organic materials were extracted twice with ethyl acetate, washed with water and brine, dried (Na_2SO_4) and concentrated, and the residue chromatographed on silica gel to give p-methoxyphenyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside (23 mg, 50%) and p-methoxyphenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (20 mg, 43%).

Glycosidation in the Presence of 1,1,3,3-Tetramethylguanidine: Typical Procedures.—Under a nitrogen atmosphere, $BF_3 \cdot OEt_2$ (0.05 ml, 0.4 mmol) was added to a mixture of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl fluoride (53 mg, 0.15 mmol), p-methoxyphenol (12 mg, 0.1 mmol), and 1,1,3,3-tetramethylguanidine (35 mg, 0.3 mmol) in acetonitrile (2 ml) at room temperature. After the mixture had been stirred for 2 h, saturated aqueous $NaHCO_3$ was added. Organic materials were extracted twice with ethyl acetate, washed with saturated aqueous $KHSO_4$ and brine, dried (Na_2SO_4), concentrated, and the residue chromatographed on silica gel to give p-methoxyphenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (28 mg, 63%).

The reactions of p-chlorophenol, p-bromophenol, and p-phenylphenol were also carried out in 0.6 mmol scale, and products were obtained in similar yields and selectivities.

p-*Methoxyphenyl* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside.* M.p. 80.5–82.5 °C (methanol) [lit.,[8e] 81–82 °C (methanol)], $[\alpha]_D^{23}$ +112.7° (c 0.66, chloroform) [lit.,[8e] +158.9° (c 1.1, chloroform)].

p-*Methoxyphenyl* 2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranoside.* M.p. 98.5 °C (chloroform–hexane) [lit.,[14] 90–92 °C (ethanol)], $[\alpha]_D^{23}$ −15.5° (c 1.0, chloroform) [lit.,[14] −14° (c 1, chloroform)].

Phenyl 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside.* M.p. 111.0–111.5 °C (chloroform–hexane) [lit.,[8c] 115 °C (ethanol)], $[\alpha]_D^{23}$ +153.5° (c 1.0, chloroform) [lit.,[8c] +168.7° (c 2, chloroform)]. H NMR spectra agreed with those reported.[15]
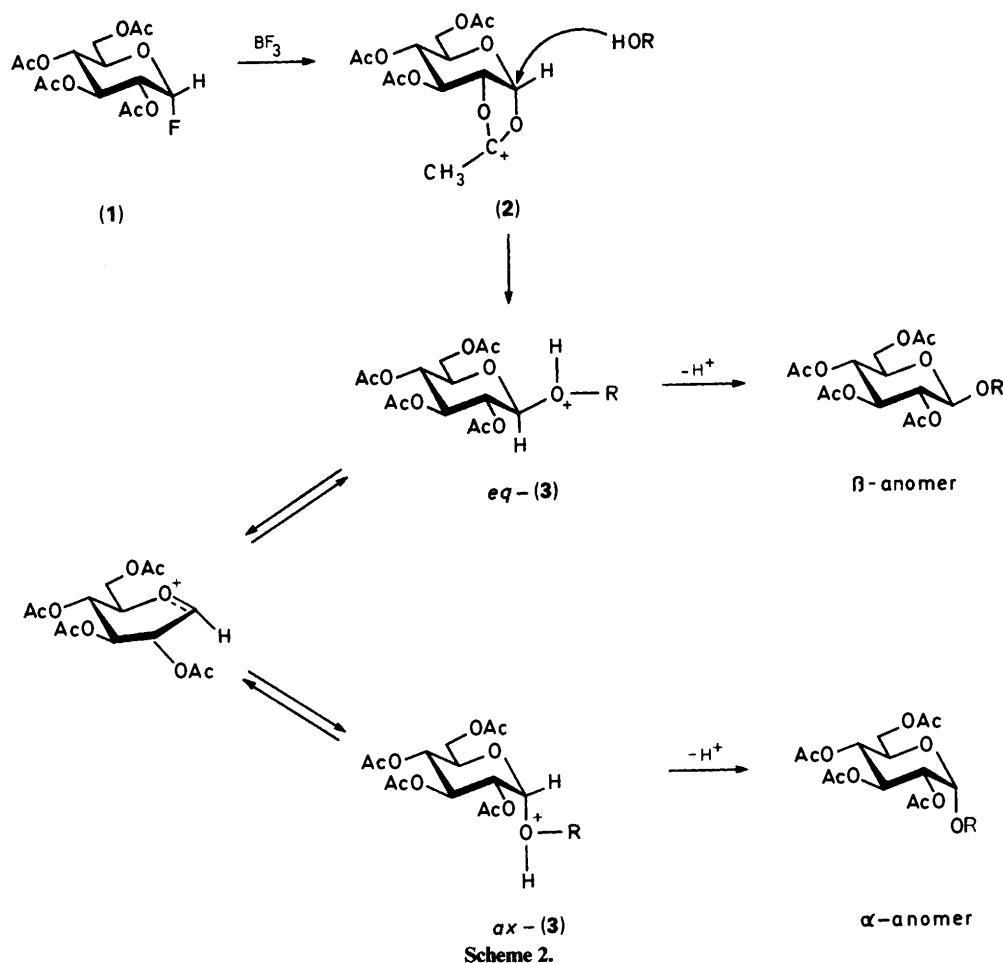
Phenyl 2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranoside.* M.p. 125 °C (chloroform–hexane) [lit.,[8c] 125–126 °C (chloroform)], $[\alpha]_D^{23}$ −21.0° (c 1.0, chloroform) [lit.,[8c] −22.5° (c 2, chloroform)]. H NMR spectra agreed with those reported.[15]

p-*Nitrophenyl* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside.* M.p. 112.0–112.5 °C (chloroform–hexane) [lit.,[8c] 113 °C (chloroform)], $[\alpha]_D^{23}$ +210.6° (c 0.12, chloroform) [lit.,[8c] +200° (c 2, chloroform)]. H NMR spectra agreed with those reported.[15]

p-*Nitrophenyl* 2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranoside.* M.p. 174.0–174.5 °C (chloroform–hexane) [lit.,[8c] 174–175 °C (ethanol)], $[\alpha]_D^{23}$ −34.0° (c 0.85, chloroform) [lit.,[8c] −41.0° (c 2, chloroform)]. H NMR spectra agreed with those reported.[15]

p-*Chlorophenyl* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside.* M.p. 100.2–100.5 °C (chloroform–hexane) [lit.,[9a] 102 °C (ethanol)], $[\alpha]_D^{23}$ +163.0° (c 1.0, chloroform) [lit.,[9a] +166° (c 1.5, chloroform)].

p-*Chlorophenyl* 2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranoside.* M.p. 124 °C (chloroform–hexane) [lit.,[9a] 124 °C (ethanol)],

Scheme 2.

$[\alpha]_D^{23}$ −19.3° (c 0.65, chloroform) [lit.,[9a] −20.5° (c 1.0, chloroform)].

o-*Chlorophenyl* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside*. M.p. 94–95 °C (ethanol) [lit.,[9a] 78 °C (ethanol)], $[\alpha]_D^{23}$ +156° (c 1.0, chloroform) [lit.,[9a] +128.4° (c 1.2, chloroform)] (Found: C, 52.15; H, 5.1. Calc. for $C_{20}H_{23}ClO_{10}$: C, 52.35; H, 5.05%).

o-*Chlorophenyl* 2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranoside*. M.p. 149–151 °C (chloroform–hexane) [lit.,[9a] 141 °C (ethanol)], $[\alpha]_D^{23}$ −43° (c 1.0, chloroform) [lit.,[9a] −45.9° (c 1.25, chloroform)].

p-*Bromophenyl* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside*. M.p. 112.5 °C (chloroform–hexane) [lit.,[13] 113 °C (propan-2-ol)], $[\alpha]_D^{23}$ +152.0° (c 1.0, chloroform) [lit.,[13] +159.6° (c 1.505, chloroform)].

p-*Bromophenyl* 2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranoside*. M.p. 132 °C (chloroform–hexane) [lit.,[13] 133 °C (propan-2-ol)], $[\alpha]_D^{23}$ −17.2° (c 0.98, chloroform) [lit.,[13] −17.8° (c 1.32, chloroform)].

p-*Methoxycarbonylphenyl* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside*. M.p. 98–99 °C (ether–hexane), $[\alpha]_D^{23}$ +168° (c 1.0, chloroform); δ_H(CDCl$_3$–CCl$_4$) 2.07 (12 H, s), 3.7–4.5 (3 H, m), 3.89 (3 H, s), 4.9–5.9 (4 H, m), 7.13 (2 H, d, J 9 Hz), 8.01 (2 H, d, J 9 Hz); δ_C(CDCl$_3$) 20.5, 51.9, 61.4, 68.2, 68.3, 69.8, 70.2, 93.9, 116.0, 124.8, 131.5, 159.4, 166.2, 169.3, 169.9, and 170.2 (Found: C, 54.95; H, 5.8. Calc. for $C_{22}H_{26}O_{12}$: C, 54.79; H, 5.43%).

p-*Methoxycarbonylphenyl* 2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranoside*. M.p. 159.5–160.0 °C (ethanol) [lit.,[14] 147–149 °C (ethanol)]; $[\alpha]_D^{23}$ −25° (c 1.0, chloroform) [lit.,[14] −13° (c 1, chloroform)] (Found: C, 54.55; H, 5.4. Calc. for $C_{22}H_{26}O_{12}$: C, 54.79; H, 5.43%).

p-*Acetylphenyl* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside*.

M.p. 90.5–91.5 °C (chloroform–hexane), $[\alpha]_D^{23}$ +178.3° (c 1.0, chloroform); δ_H(CDCl$_3$–CCl$_4$) 2.01 (3 H, s), 2.03 (3 H, s), 2.05 (3 H, s), 2.06 (3 H, s), 2.55 (3 H, s), 3.7–4.4 (3 H, m), 4.8–5.9 (4 H, m), 7.14 (2 H, d, J 9 Hz), and 7.93 (2 H, d, J 9 Hz); δ_C(CDCl$_3$) 20.5, 26.2, 61.4, 68.2, 68.5, 69.9, 70.2, 94.0, 116.1, 130.4, 132.4, 159.5, 169.0, 169.5, 169.8, and 195.5 (Found: C, 56.6; H, 5.6. Calc. for $C_{22}H_{26}O_{11}$: C, 56.65; H, 5.62%).

p-*Acetylphenyl* 2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranoside*. M.p. 170.0–170.5 °C (chloroform) (lit.,[8c] 172–173 °C), $[\alpha]_D^{23}$ −27.3° (c 0.76, chloroform) [lit.,[8c] −28.6° (c 2, chloroform)].

p-*Phenylphenyl* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside*. M.p. 165 °C (chloroform–hexane) [lit.,[9a] 169 °C (ethanol)], $[\alpha]_D^{23}$ +161.7° (c 1.0, chloroform) [lit.,[9a] +198.5° (c 1.4, chloroform)].

p-*Phenylphenyl* 2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranoside*. M.p. 152 °C (chloroform–hexane) [lit.,[9a] 155 °C (ethanol)], $[\alpha]_D^{23}$ −12.7° (c 1.0, chloroform) [lit.,[9a] −12.3° (c 2.0, chloroform)].

1-*Naphthyl* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranoside*. M.p. 112–113 °C (chloroform–hexane) [lit.,[8d] 114.5 °C (propan-2-ol)], $[\alpha]_D^{23}$ 164° (c 1.03, chloroform) [lit.,[8d] 170.2° (c 1.273, chloroform)]. H NMR spectra agreed with those reported.[15]

1-*Naphthyl* 2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranoside*. M.p. 177–178 °C (chloroform–hexane) [lit.,[8f] 177–178 °C (ethanol)], $[\alpha]_D^{23}$ −71° (c 0.70, chloroform) [lit.,[8f] −76.4° (c 0.5, chloroform)]. H NMR spectra agreed with those reported.[15]

2,6-*Dimethylphenyl* 2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranoside*. M.p. 143.2–144.0 °C (chloroform–hexane), $[\alpha]_D^{23}$ −14° (c 0.35, chloroform); δ_H(CDCl$_3$–CCl$_4$) 2.02 (9 H, s), 2.10 (3 H, s), 2.27 (6 H, s), 3.3–3.8 (1 H, m), 4.0–4.3 (2 H, m), 4.7–5.7 (4 H, m), and 6.98 (3 H, s); δ_C(CDCl$_3$) 16.9, 20.6, 61.7, 68.6, 71.7, 71.8, 73.0,

101.5, 125.0, 128.9, 131.6, 152.8, 169.1, 169.3, 170.2, and 170.4 (Found: C, 58.35; H, 6.4. Calc. for $C_{22}H_{28}O_{10}$: C, 58.40; H, 6.24%).

2,6-*Dimethoxyphenyl* 2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranoside.* M.p. 138–139 °C (chloroform), $[\alpha]_D^{23}$ −12° (*c* 0.54, chloroform); δ_H(CDCl$_3$–CCl$_4$) 2.02 (12 H, s), 3.5–3.9 (1 H, m), 3.82 (6 H, s), 3.9–4.3 (2 H, m), 4.9–5.5 (4 H, m), 6.51 (1 H, d, *J* 9 Hz), 6.53 (1 H, d, *J* 7 Hz), and 7.00 (1 H, dd, *J* 7, 9 Hz); δ_C(CDCl$_3$) 20.7, 56.3, 62.4, 68.6, 71.9, 72.1, 73.2, 101.2, 105.7, 124.8, 134.7, 153.2, 169.2, 169.3, 170.3, and 170.5 (Found: C, 54.15; H, 5.85. Calc. for $C_{22}H_{28}O_{12}$: C, 54.54; H, 5.83%).

9-*Anthryl* 2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranoside.* M.p. 201–203 °C (chloroform–hexane), $[\alpha]_D^{23}$ +43° (*c* 0.47, chloroform); δ_H(CDCl$_3$–CCl$_4$) 1.75 (3 H, s), 1.99 (3 H, s), 2.07 (3 H, s), 2.22 (3 H, s), 3.3–3.8 (1 H, m), 3.78 (1 H, dd, *J* 3, 12 Hz), 4.23 (1 H, dd, *J* 6, 12 Hz), 5.0–5.9 (4 H, m), 7.2–7.7 (4 H, m), 7.7–8.1 (2 H, m), 8.1–8.5 (2 H, m), and 8.26 (1 H, s); δ_C(CDCl$_3$) 20.3, 20.6, 20.7, 20.9, 61.8, 68.8, 71.8, 72.2, 73.2, 102.7, 122.7, 123.9, 124.9, 125.4, 128.1, 132.1, 147.5, 169.2, and 170.2 (Found: C, 63.05; H, 5.4. Calc. for $C_{28}H_{28}O_{10}$: C, 64.11; H, 5.38%).

1,4-*Bis*-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy)benzene.* M.p. 195–196 °C (chloroform–hexane), $[\alpha]_D^{23}$ −16° (*c* 0.34, chloroform); δ_H(CDCl$_3$–CCl$_4$) 2.03 (12 H, s), 2.06 (6 H, s), 2.06 (6 H, s), 3.5–4.4 (6 H, m), 4.8–5.4 (8 H, m), and 6.91 (4 H, s); δ_C(CDCl$_3$) 20.6, 61.9, 68.4, 71.4, 72.2, 72.8, 99.8, 118.5, 152.9, 168.7, 169.0, 169.8, and 170.0 (Found: C, 52.55; H, 5.5. Calc. for $C_{34}H_{42}O_{20}$: C, 52.99; H, 5.49%).

1,2-*Bis*-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy)benzene.* M.p. 180.5–181.5 °C (chloroform–hexane), $[\alpha]_D^{23}$ −48° (*c* 0.24, chloroform); δ_H(CDCl$_3$–CCl$_4$) 2.01 (18 H, s), 2.06 (6 H, s), 3.5–4.0 (2 H, m), 4.0–4.4 (4 H, m), 4.8–5.5 (8 H, m), and 6.9–7.2 (4 H, m); δ_C(CDCl$_3$) 20.6, 61.8, 68.4, 71.6, 72.3, 99.9, 119.5, 124.1, 147.1, 168.9, 169.9, and 170.0 (Found: C, 52.8; H, 5.5. Calc. for $C_{34}H_{42}O_{20}$: C, 52.99; H, 5.49%).

Acknowledgements

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