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Syntheses and structures of anomeric quaternary ammonium β-glucosides and comments on the anomeric C–N bond lengths

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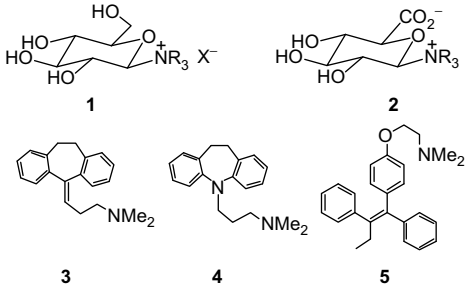
ABSTRACT

We report convenient syntheses of anomeric quaternary ammonium β-glucosides in both protected and deprotected forms, together with X-ray structural investigations of two of the products. Both the quaternisation of a protected anomeric *N*,*N*-(dimethylamino)glucose, derived in two high-yielding steps from the anomeric azide, and the direct reaction of glucose or 6-*O*-trityl glucose with a secondary amine, followed by protection and quaternisation, are viable routes. We also discuss the significance, in terms of stereoelectronic effects, of the observed C–N bond lengths and the stabilities of the products.

1. Introduction

Anomeric quaternary ammonium β-glucosides of type **1** are of both theoretical and practical interest: some compounds of this type appeared in the early carbohydrate literature.[1–3] More recently it has been recognised that structurally similar zwitterionic N^+-glucuronides, of general structure **2**, are important metabolites for a wide range of drugs that contain a tertiary amino group.[4,5] Thus amitriptyline **3**,[5] imipramine **4**[5] and tamoxifen **5**[6] are all metabolised at least in part in this way and a very recent report confirmed the isolation of a similar metabolite of 1-hydroxymidazolam.[7] *N*-Glucuronide metabolites are often unique to humans and are therefore not detected in pre-clinical studies. *N*-Glucoside drug metabolites are also known, e.g., of barbiturates,[8] though these do not possess quaternary nitrogen. Also, in the plant kingdom, transferases responsible for N-glucosidation have been identified.[9]

In connection with a wider interest in glucuronides and methods for their synthesis,[10,11] we wished to establish general methods for the synthesis of *N*-glucuronides, especially the quaternary ammonium zwitterionic type. Syntheses of some metabolites of this type were reported by Kaspersen and van Boeckel.[12]



The most obvious access to such metabolites would appear to be the direct reaction of a tertiary amine with an anomeric bromosugar such as **6**. This works well for relatively weak bases, including heterocycles such as pyridine[13] and for anilines[14] but is much less satisfactory for aliphatic tertiary amines. Invariably elimination predominates with such strong bases, leading to the glycal **7** as the major product:[15] we have obtained similar results in the glucose series. While this work was being written a new report appeared,[16] describing quaternisation via an anomeric mesylate, but this was still ineffective for aliphatic tertiary amines.

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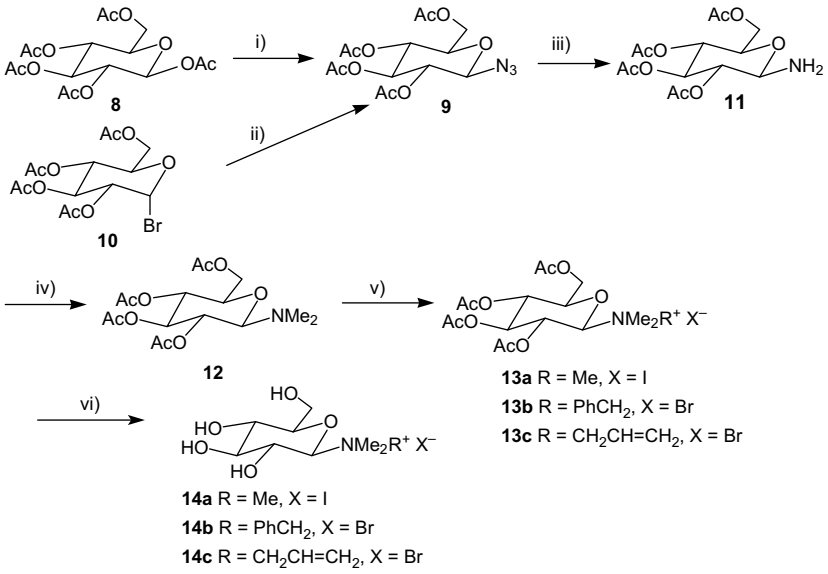


Scheme 1. Synthesis of 1β-quaternary ammonium glucosides: azide route. Reagents: (i) Me_3SiN_3, $SnCl_4$, CH_2Cl_2, 95%; (ii) Me_3SiN_3, TBAF, THF, ca. 80%; (iii) Pd/H_2, EtOAc, 75%; (iv) HCHO aq, *i*-PrOH/THF, Pd/H_2, 92%; (v) MeI, $PhCH_2Br$ or $CH_2{=}CH{\cdot}CH_2Br$, MeCN, 50 °C, 3–4 h, 51–82%; (vi) aq Na_2CO_3, MeOH, AR-120 (H^+), 72–92%.

We note that others[17] have reported extremely low yields by this method or a related two-phase procedure.[4] Interestingly, the direct reaction of **5** with bromosugar **6** *did* give a very modest yield of tamoxifen N^+-glucuronide after deprotection.[6] This more favourable outcome is probably due to the relatively weaker base strength of the β-alkoxyamine **5**. We decided it was important to understand first the synthesis and chemistry of anomeric quaternary ammonium glucosides, then later apply this knowledge to N^+-glucuronide synthesis. In the following we describe three methods for the synthesis of different classes of anomeric quaternary N^+-glucosides and report on the structures and stabilities of the products.

2. Results and discussion

2.1. Syntheses and structures

One of the best ways of introducing anomeric nitrogen into monosaccharides is via an azide. Reaction (Scheme 1) of glucose β-pentaacetate **8** with Me_3SiN_3 and $SnCl_4$[18] (the most effective Lewis acid, we have found) affords the β-azide **9** *only*, in excellent yield. Alternatively, reaction of acetobromoglucose **10** with Me_3SiN_3 and TBAF[19] also affords **9**, but in lower yield.

Reduction of **9** by catalytic hydrogenation in EtOAc affords the primary amine **11**[20] as a single β-anomer in excellent yield. Reductive *N*,*N*-dimethylation of *anomeric* pyranose amines has not previously been reported, though it has been used for other ring positions.[21] After much experimentation, we found that Pd-catalysed hydrogenation of a solution of **11** in THF/*i*-PrOH and aq formaldehyde afforded the desired tertiary amine **12** in very good yield; this material slowly crystallised and was quite stable at 20 °C in neutral conditions. The use of Eschweiler–Clarke conditions or $HCHO/NaCNBH_3/AcOH$ was unsuccessful, almost certainly owing to the acid instability of the product.

Quaternisation of **12** worked well for highly electrophilic halides, and derivatives **13a–c** were obtained using MeI, $PhCH_2Br$ and $CH_2{=}CHCH_2Br$, respectively: the reaction was accompanied by a characteristic downfield shift of H(1), e.g., from δ 4.05 (1H, d, J=9.3 Hz) to 5.30 (1H, d, J=8.4 Hz) for the transformation **12**→**13a**. However, the use of less reactive halides, including primary halides, led to decomposition, probably via formation of the hemiacetal initially (cf. Scheme 3 below): we have not investigated the use of higher acyl derivatives in this reaction. A single-crystal X-ray structure determination† on compound **13a** (Fig. 1, crystals from MeOH) gave a similar result to the corresponding[22,23] bromide.

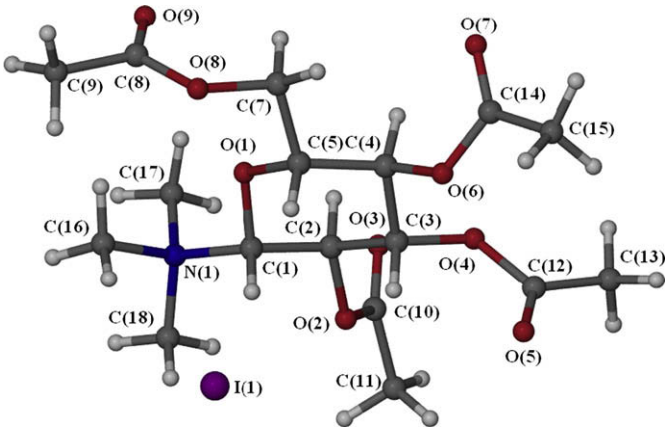


Figure 1. X-ray structure of anomeric quaternary ammonium glucoside **13a**. The anomeric C–N^+ length is 1.523 Å (cf. 1.534 Å for the bromide).

It was crucial to establish reliable conditions for deprotection of **13a** without loss of the $^+NR_3$ group. Reports in earlier literature suggested that such compounds are unstable in strong base, [2,3,5] leading to the generation of anhydro-sugars, but we obtained clean deacetylation of **13a** using aq Na_2CO_3/MeOH, giving the free sugar **14** in good yield. This product crystallised from MeOH, allowing

† Crystal data for **13a**: $C_{17}H_{28}INO_9$, M=517.30, colourless prism, 0.44×0.42×0.29 mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), a=8.6160(17), b=11.244(2), c=24.390(5) Å, V=2362.9(8) $Å^3$, Z=4, D_c=1.454 g/cm^3, F_{000}=1048, STOE IPDS, Mo Kα radiation, λ=0.71073 Å, T=173(2) K, $2\theta_{max}$=48.4°, 18,276 reflections collected, 3557 unique (R_{int}=0.0456). Final GooF=0.854, $R1$=0.0274, $wR2$=0.0519, R indices based on 2812 reflections with $I>2\sigma(I)$ (refinement on F^2), 260 parameters, 0 restraints. Lp and absorption corrections applied, μ=1.397 mm^{-1}. Absolute structure parameter=−0.030(17) (Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876–881).

a further single-crystal X-ray structure determination[‡]: two aspects are shown in Figure 2.[24]

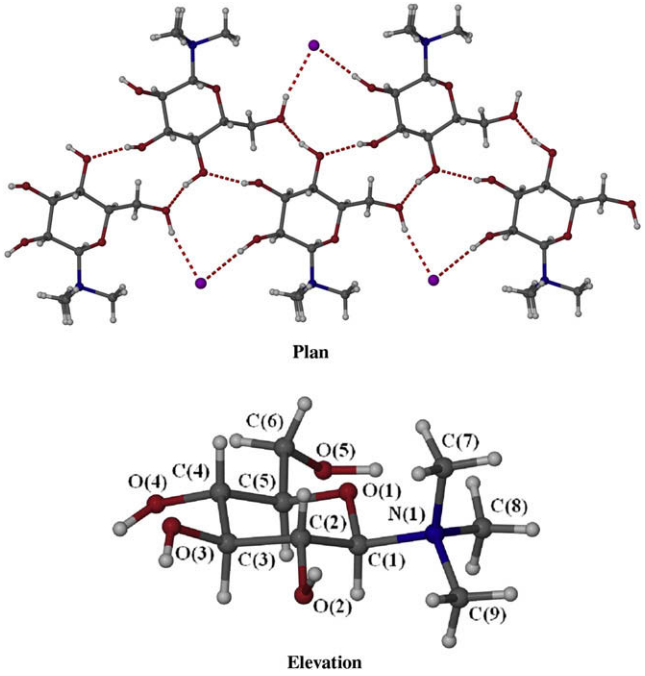
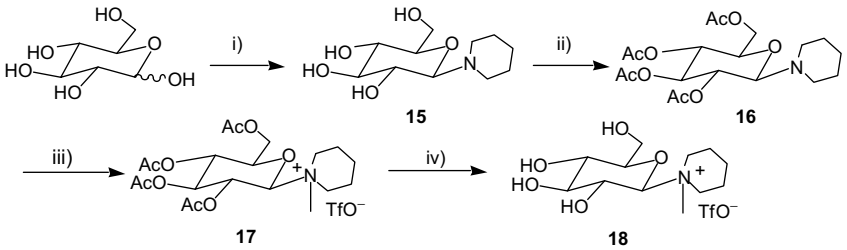


Figure 2. Two views of the structure of anomeric quaternary ammonium glucoside **14**: the intermolecular hydrogen bonding involving the iodide ions (*plan*), and the conformation of the ring system (*elevation*).

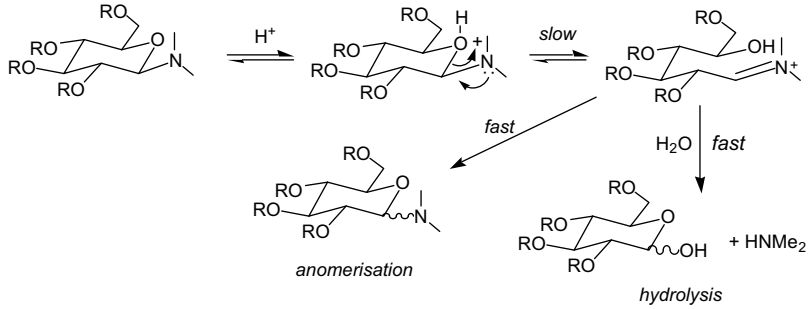
This is the first X-ray structure determination of such a carbohydrate in unprotected form, and the pattern of bond lengths at the anomeric centre is of special interest. The anomeric C–N^+ bond lengths for **13a** (1.523 Å; cf. 1.534 Å for the corresponding bromide) and **14**, at 1.522 Å are the same within experimental error (±0.005 Å), and fall into the region expected for a trimethylammonium group attached to secondary carbon. Thus the length of the N^+–CH bond in 29 structures in the Cambridge Crystallographic database with the substructure Me_3N^+–CHR_2 (R=alkyl) is 1.537±0.008 Å. A discussion of the implications of the observed bond lengths is given at the end of this section.

We have developed an alternative synthesis of anomeric quaternary ammonium glucosides (Scheme 2), giving access to structures other than the *N*,*N*-dimethyl type. It is well known that free sugars will react directly with amines to form glycosylamines,[25,26] and these can be valuable intermediates for the quaternary compounds provided the Amadori rearrangement can be avoided. The reaction is particularly efficient for cyclic secondary amines, e.g., piperidine with glucose[26] affords the glycosylamine **15** in high yield as mainly the β product without acid catalysis. For such cyclic amines, the Amadori rearrangement[27] is relatively slow: the derivative remains in the pyranose form long enough to allow peracetylation, giving solely the known β-product **16**[26] (NMR) in good yield. We obtained similar reactions using morpholine, pyrrolidine and *N*-methylpiperazine.[28]

Quaternisation of the tertiary amine **16** to give **17**[29] required MeOTf (MeI gave only slow decomposition: nor was direct quaternisation of **15** possible) but a good yield of product was obtained. Here again mild deprotection, using catalytic NaOMe/MeOH, afforded the free sugar **18** in excellent yield.



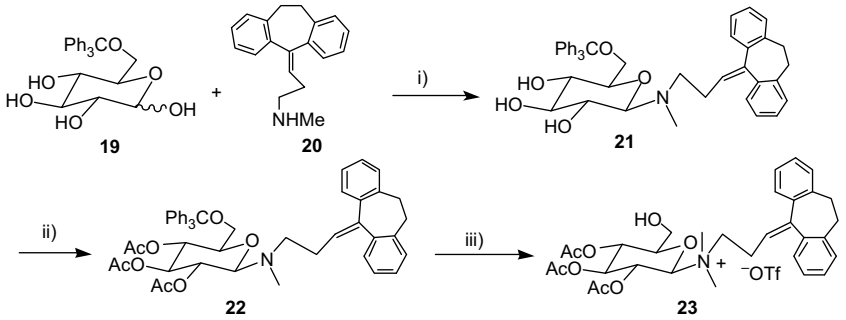
Scheme 2. Direct synthesis of anomeric glycosylamines and their quaternary derivatives from glucose. Reagents: (i) piperidine, 80 °C; (ii) Ac_2O, pyridine, CH_2Cl_2 [74% for steps (i) and (ii)]; (iii) MeOTf, CH_2Cl_2, 62%; (iv) NaOMe, MeOH, 20 °C, 100%.



Scheme 3. Hydrolysis of glycosylamines, illustrated for an *N*,*N*-dimethyl example.

In the above sequence, and elsewhere, the acid instability of tertiary amines such as **12** and **16** frequently makes their handling and chromatographic purification difficult. This is understood to be a consequence of reversible protonation on the pyranose oxygen followed by ring opening and rapid hydrolysis or anomerisation of the resulting iminium species, Scheme 3.[30] In contrast, quaternary ammonium species show greater acid stability, as do the HCl salts of the tertiary amines, since no N lone pair is available to participate: thus the HCl salt of **15** is stable in aqueous solution for 18 h at 20 °C.

[‡] Crystal data for **14**: $C_9H_{20}INO_5$, M=349.16, colourless prism, 0.32×0.19×0.15 mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), a=9.3032(19), b=9.985(2), c=14.663(3) Å, V=1362.0(5) $Å^3$, Z=4, Dc=1.703 g/cm^3, $F000$=696, Bruker D8 diffractometer with APEX detector, Mo Ka radiation, l=0.71073 Å, T=100(2) K, $2q_{max}$=55.0°, 8145 reflections collected, 3038 unique (R_{int}=0.0177). Final GooF=1.026, $R1$=0.0182, $wR2$=0.0477, R indices based on 3024 reflections with $I>2\sigma(I)$ (refinement on $F2$), 189 parameters, 8 restraints. Lp and absorption corrections applied, m=2.358 mm^{-1}. Absolute structure parameter=0.02(2) (Flack, H. D. *Acta Cryst.*. **1983**, *A39*, 876–881).



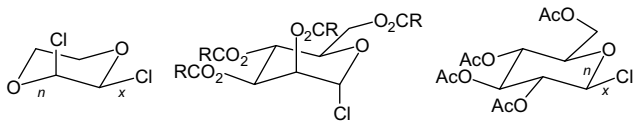
Scheme 4. Quaternary ammonium glucosides via 6-*O*-trityl glucose. Reagents: (i) **19**+**20**, CH_2Cl_2, 40 °C, 49%; (ii) Ac_2O, pyridine, CH_2Cl_2, 79%; (iii) MeOTf, CH_2Cl_2, 59%.

A more general procedure for less reactive (acyclic) secondary amines, which can also avoid difficulties arising from Amadori rearrangement, uses 6-*O*-trityl glucose **19** (Scheme 4).[31] In this way both the sugar and the amine (the example shown employs nortriptyline **20**,[32] the secondary amine related to amitriptyline **2**) may be kept in solution using an organic solvent (CH_2Cl_2 is suitable). Even at a 1:1 ratio of **19**/**20**, the equilibrium is strongly (>9:1) in favour of glycosylamine **21** by NMR spectroscopy, though again there are losses on chromatography (cf. Scheme 3). It is important to purify **21** *rapidly* to forestall rearrangement, but after triacetylation a stable pyranose product **22** is obtained. Similarly to Scheme 2, quaternisation of **21** is not possible, but **22** may be quaternised using MeOTf, with concomitant loss of the trityl group, to give **23** in good yield.

2.2. Observed bond lengths: stereoelectronic implications

The pattern of bond lengths at the anomeric centre of a glycoside is subject to a combination of effects, which however are minimised in systems like **13a** and **14** with equatorial trialkylammonium groups. Electron withdrawal by the four OH or OAc groups of a hexapyranoside is sufficient to make the ring oxygen more electronegative than the oxygen of an alkoxyl group, so that the endocyclic C–O bond *n* at the glycosidic centre (cf. structures **24** and **25** below) is typically longer than the exocyclic bond *x* for an *O*-glycoside; though both are shortened, compared to alkyl ether/alcohol C–O bonds, by mutual n_O–σ^*_{C-O} overlap.[33] However, the Me_3N^+ group can only act as a σ-acceptor, because there is no lone pair on N for n_N–σ^*_{C-O} donation. On the other hand, n_O–σ^*_{C-N} donation would be possible if the exocyclic C–N were axial but is not expected for equatorial C–N. In this respect the Me_3N^+ group is best compared with a halogen, except that the halogen atom of a glycosyl halide is generally axial, while in the handful of known examples the Me_3N^+ group in systems like **13a** and **14** is always equatorial. The electronic anomeric effect of a Me_3N^+ group would be expected to be at least as large as that of Cl; but the combined steric effects of equatorial Me_3N^+ and the 6-CH_2OR group of a hexapyranoside are decisive, as are the combined anomeric effect of an axial halogen and the steric effect of equatorial 6-CH_2OR.

The consequent effects on bond lengths are illustrated by results with simpler systems. The crystal structure of the *cis*-dichlorodioxan **24** shows a classical chair conformation, with one Cl atom necessarily equatorial, and thus antiperiplanar to ring bonds rather than lone pair electron density. As a result the C–Cl bond length (*x*=1.781 Å) and that of the corresponding endocyclic C–O bond (*n*=1.425 Å) are normal for alkyl halides or ethers. The corresponding bond lengths at the centre with *axial* Cl, by contrast, at 1.820 and 1.394 Å, show the marked lengthening and shortening, respectively, characteristic of the anomeric effect.[33]



24 **25** R = Me or Ph **26**

Similar effects are observed at the anomeric centres of glycopyranosides, where the electrophilicity of Cl can elicit a substantial anomeric effect even from the ring oxygen of tetraacyl derivatives. Thus the bond lengths *x* and *n* of the tetraacyl α-D-mannosyl chlorides **25** are 1.859 and 1.364 Å (R=Me), and 1.812 and 1.398 Å (R=Ph), respectively.[34,35] By comparison, those of the equatorial tetraacetyl β-D-glucosyl chloride **26**, with n_O–σ^*_{C-O} overlap 'turned off', are 1.767 and 1.429 Å.[36,37] These values are not very different from those for the equatorial centre in **24**.

In summary, the limited amount of data available suggest that the exocyclic C–N^+ bond lengths at the anomeric centres of systems, like **13a** and **14**, with equatorial trialkylammonium groups, are indeed subject to a combination of effects, which largely cancel out. Systems with the trialkylammonium group axial are expected to show a more substantial anomeric effect, and will be of considerable interest if the substantial synthetic difficulties can be overcome.

3. Conclusions

In summary, we have demonstrated general methods for the syntheses of tertiary glucosylamines and their quaternisation. Both the quaternisation of a protected anomeric *N*,*N*-dimethylaminoglucoside and the direct reaction of glucose or 6-*O*-trityl glucose with a secondary amine, followed by protection and quaternisation, are viable routes. While the tertiary glycosylamines are rather unstable, particularly in acid conditions, after quaternisation the products may be deprotected by mild base-catalysed hydrolysis to deliver the free glucosides, in good yields. These quaternary derivatives are in general more stable over the intermediate (3–10) pH range. Both protected and deprotected quaternary ammonium derivatives exhibit well-defined crystal structures with essentially undistorted chair conformations and C–N^+ bond lengths within the previously observed range.

4. Experimental

4.1. General experimental methods

All organic solvents were anhydrous and of AR grade. Vacuum rotary evaporation was carried out at <30 °C. Analytical thin-layer chromatography was performed using Merck Kieselgel 60 F_{254} silica plates; preparative column chromatography was performed on

Merck 938S silica gel. Infra-red spectra were obtained using an FT/IR-4100 type A instrument. Both ^{1}H and ^{13}C NMR spectra were recorded for the solvents noted using either Bruker 250 MHz or 400 MHz instruments (the latter operating at 100 MHz for ^{13}C observation) with tetramethylsilane as internal standard. Mass spectra in the chemical ionisation (CI) mode were obtained using a VG7070E mass spectrometer. Both low and high resolution electrospray mode (ES) mass spectra were obtained using a Micromass LCT mass spectrometer operating in the +ve or −ve ion mode as indicated. Elemental microanalysis was performed by Mr. Steve Apter (Liverpool). 3-[2,2,3,3-$^{2}H_4$] Trimethylsilyl propionate sodium salt (TSP), sodium dihydrogen phosphate and disodium hydrogen phosphate, were purchased from Sigma–Aldrich Company, Ltd (Gillingham, Dorset, UK). HPLC–NMR grade deuterium oxide ($^{2}H_2O$) was obtained from Goss Scientific Instruments (Essex, UK).

4.2. 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-*N*,*N*-dimethylamine (12)

To a solution of **11** (0.397 g, 1.15 mmol) in THF (15 mL) was added Pd/C (20 mol %) and isopropanol (15 mL), followed by the addition of 37% aqueous formaldehyde solution (11.5 mmol). The flask was then placed under vacuum before purging with hydrogen. The reaction was stirred at room temperature under a positive pressure of hydrogen for 5 h. The solution was filtered through a pad of Celite, and washed with ethyl acetate. The solvent was removed in vacuo and the residue was chromatographed using a gradient from 30% to 70% EtOAc/hexane, to afford the product **12** (0.395 g, 92%) as a hygroscopic solid. Found: C, 46.5; H, 6.6; N, 3.4; *m*/*z*, 398.1424. $C_{16}H_{25}NO_9\cdot 2H_2O$ requires C, 46.7; H, 7.05; N, 3.4%; $C_{16}H_{25}NO_9\cdot Na$ requires *m*/*z*, 398.1427; ^{1}H NMR: δ ($CDCl_3$) 2.00, 2.02, 2.04, 2.08 (12H, 4s, 4×CH_3CO), 2.40 (6H, s, 2×CH_3N), 3.59 (1H, ddd, *J*=9.9, 4.9 and 2.7 Hz, 5-H), 4.05 (1H, d, *J*=9.3 Hz, 1-H), 4.12 (1H, dd, *J*=12.1 and 2.5 Hz, H-6a), 4.23 (1H, dd, *J*=12.1 and 4.9 Hz, H-6b), 5.00 (1H, t, *J*=9.9 Hz, H-4), 5.12 (1H, t, *J*=9.3 Hz, H-2), 5.20 (1H, t, *J*=9.3 Hz, H-3); ^{13}C NMR: δ ($CDCl_3$) 21.0, 21.1, 21.2, 23.0, 39.9 (×2), 62.8, 68.7, 69.4, 73.3, 74.5, 93.8, 169.9, 170.0, 170.6 and 171.0; *m*/*z* (ES +ve mode) 398 (MNa^+, 100%).

4.3. General procedure for the quaternisation of (12)

To a solution of **12** (0.13 mmol) in acetonitrile (1 mL) under argon was added MeI, $PhCH_2Br$ or $CH_2{=}CHCH_2Br$ (1.33 mmol), and then the reaction was heated to 50 °C for 5 h. The acetonitrile was removed in vacuo and the solid residue was recrystallised from ethanol to give the product **13a**, **b** or **c**.

*4.3.1. 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl(trimethylammonium)iodide (**13a**)*

Yield of **13a**, 0.034 g (51%); off-white solid, mp 173–174 °C. Found: C, 39.2; H, 5.5; N, 2.6; *m*/*z*, 390.1765. $C_{17}H_{28}INO_9$ requires C, 39.5; H, 5.4; N, 2.7%; $C_{17}H_{28}NO_9$ requires *m*/*z*, 390.1764; ν_{max} (diamond) cm^{-1} 2974, 2920, 1740, 1612, 1446, 1376 and 1211; ^{1}H NMR: δ (D_2O) 2.20, 2.22, 2.25 and 2.28 (12H, 4s, 4×CH_3CO), 3.32 [9H, s, $(CH_3)_3N^+$], 4.38–4.42 (1H, m, 5-H), 4.45–4.65 (2H, m, 2×6-H), 5.30 (1H, d, *J*=8.4 Hz, 1-H), 5.36 (1H, t, *J*=9.2 Hz, 4-H), 5.58 (1H, t, *J*=8.8 Hz, 3-H) and 5.75 (1H, t, *J*=8.4 Hz, 2-H); ^{13}C NMR: δ (D_2O) 20.5, 20.6, 20.7, 20.8, 51.7, 62.1, 67.6, 68.4, 74.2, 75.2, 93.8, 100.0, 172.2, 173.0, 173.3 and 174.2; *m*/*z* (ES +ve mode) 390 (cation M^+, 100%).

*4.3.2. 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl(benzyldimethylammonium)bromide (**13b**)*

Yield of **13b**, 0.068 g (64%): solid, mp 160–162 °C. Found: *m*/*z*, 466.2072. $C_{23}H_{32}NO_9$ requires *m*/*z*, 466.2077; ^{1}H NMR: δ (D_2O) 2.18, 2.22, 2.29 (12H, 3s, 4×CH_3CO; two signals coincident), 3.21, 3.33 (6H, 2s, 2×CH_3N^+), 4.41–4.45 (1H, m, 5-H), 4.55–4.70 (2H, m, 2×6-H), 4.85–5.00 (2H, ABq, $PhCH_2N^+$), 5.11 (1H, d, *J*=8.7 Hz, 1-H), 5.37 (1H, t, *J*=9.3 Hz, 4-H), 5.49 (1H, t, *J*=9.2 Hz, 3-H), 5.78 (1H, t, *J*=8.4 Hz, 2-H) and 7.65–7.75 (5H, m, ArH); ^{13}C NMR: δ (D_2O) 20.5, 20.6, 20.8, 21.1, 47.6, 49.1, 62.3, 67.5, 68.0, 68.8, 74.2, 74.9, 91.1, 126.7, 130.1, 132.0, 133.4, 172.2, 173.0, 173.2 and 174.2; *m*/*z* (ES +ve mode) 466 (cation M^+, 100%).

*4.3.3. 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl(dimethyl-2-propenyl)ammonium bromide (**13c**)*

Yield of **13c**, 82%; amorphous glass. Found: C, 44.6; H, 5.9; N, 2.25; *m*/*z*, 416.1900. $C_{19}H_{30}BrNO_9\cdot H_2O$ requires C, 44.4; H, 6.2; N, 2.7%; $C_{19}H_{30}NO_9$ requires *m*/*z*, 416.1921; ^{1}H NMR: δ [$(CD_3)_2CO$] 1.98, 2.03, 2.06 and 2.17 (12H, 4s, 4×CH_3CO), 3.42 (two signals, 6H, 2s, 2×CH_3N^+), 4.26 (1H, dd, *J*=12.5 and 5.6 Hz, H-6a), 4.38 (1H, dd, *J*=12.5 and 2.4 Hz, H-6b), 4.47–4.65 (2H, 2 m, $N^+CH_2CH{=}CH_2$), 4.70 (1H, approx. dd, *J*=10.1 and 3.2 Hz, 5-H), 5.22 (1H, dd, *J*=10.1 and 9.3 Hz, 4-H), 5.52 (1H, t, *J*=9.1 Hz, H-3), 5.67 (1H, t, *J*=8.9 Hz, H-2), 5.72 (1H, dd, *J*=10.1 and 1.6 Hz, CH=CH_2 *cis*-olefinic H), 5.89 (1H, dd, *J*=16.8 and 1.4 Hz, CH=CH_2 *trans*-olefinic H), 6.26 (1H, d, *J*=9 Hz, 1-H) and 6.30–6.35 (1H, m, $CH_2CH{=}CH_2$); ^{13}C NMR: δ [$(CD_3)_2CO$] 20.9, 21.0, 21.2, 21.5, 48.6, 49.4, 62.6, 67.0, 68.6, 69.1, 74.5, 75.9, 91.9, 127.1, 129.7, 170.5 (×2), 170.7 and 171.2; *m*/*z* (ES +ve mode) 416 (cation M^+, 100%).

4.4. General procedure for the hydrolysis of peracetates (13a)–(13c)

To a solution of perester **13a**, **13b** or **13c** (0.058 mmol) in MeOH (1 mL) was added solid anhydrous Na_2CO_3 (0.17 mmol) at ambient temperature. The reaction was left stirring at room temperature for 3 h, followed by quenching with Amberlite H^+ resin (0.17 mmol) until pH 7 was reached. The resin was then filtered and washed with methanol, followed by evaporation in vacuo: the residue was recrystallised from ethanol to afford the product **14a**, **14b** or **14c**.

*4.4.1. β-D-Glucopyranosyl(trimethylammonium)iodide (**14a**)*

White solid, yield, 87%. Found: C, 30.88, H, 5.78, N, 4.00; *m*/*z*, 222.1349. $C_9H_{20}INO_5$ requires C, 30.94, H, 5.78, N, 4.01%; $C_9H_{20}NO_5$ requires *m*/*z*, 222.1341; ^{1}H NMR: δ [$(CD_3)_2SO$] 3.11 [9H, s, $(CH_3)_3N^+$], 3.10–3.40 (3H, m, 2-H+3-H+4-H), 3.45–3.50 (2H, m, 2×6-H), 3.70–3.75 (1H, m, 5-H) and 4.54 (1H, d, *J*=8.9 Hz, 1-H); ^{13}C NMR: δ [$(CD_3)_2SO$] 50.7, 60.8, 69.2, 70.5, 77.3, 80.6 and 95.4; *m*/*z* (ES +ve mode) 222 (cation M^+, 100%).

*4.4.2. β-D-Glucopyranosyl(benzyldimethylammonium)-bromide (**14b**)*

Yield, 72%; amorphous glass. Found: *m*/*z*, 298.1660. $C_{15}H_{24}NO_5$ requires *m*/*z*, 298.1654; ^{1}H NMR: δ [$(CD_3)_2SO$] 3.10, 3.12 (6H, 2s, 2×CH_3N^+), 3.16 (1H, t, *J*=9.4 Hz, 4-H), 3.28 (1H, t, *J*=8.7 Hz, 3-H), 3.39 (1H, m, 5-H), 3.56 (1H, dd, *J*=12.3 and 6.7 Hz, 6-Ha; other 6-H is below $CH_3N^+$by COSY), 3.65 (1H, t, *J*=8.7 Hz, 2-H), 4.24 (1H, d, *J*=8.9 Hz, 1-H), 4.56, 4.88 (2H, ABq, $ArCH_2N^+$), 7.49–7.59 (3H, m, ArH) and 7.63–7.68 (2H, m, ArH); ^{13}C NMR: δ [$(CD_3)_2SO$] 46.9, 48.2, 61.1, 66.1, 69.2, 70.1, 77.2, 80.5, 92.9, 127.9, 129.4, 130.8 and 133.5; *m*/*z* (ES +ve mode) 298 (cation M^+, 100%).

*4.4.3. β-D-Glucopyranosyl(dimethyl-2-propenyl)-ammonium bromide (**14c**)*

Yield, 98%; amorphous glass. Found: C, 38.1; H, 6.9; N, 3.4; *m*/*z*, 248.1492. $C_{11}H_{22}BrNO_5.H_2O$ requires C, 38.15; H, 6.9; N, 4.0%; $C_{11}H_{22}NO_5$ requires *m*/*z*, 248.1498; ν_{max} (diamond) cm^{-1} 3700–2700 (br, vs), 2980, 2927, 1612, 1442, 1095 and 1060; ^{1}H NMR: δ [$(CD_3)_2SO$] 2.97, 3.02 (6H, 2s, 2×CH_3N^+), 3.16 (1H, t, *J*=9.4 Hz, 4-H), 3.32 (1H, t, *J*=8.7 Hz, 3-H), 3.30–3.40 (1H, m, 5-H, partly obscured), 3.49 (1H, dd, *J*=12.4 and 6.1 Hz, 6a-H), 3.56 (1H, t, *J*=8.8 Hz, 2-H), 3.72 (1H, dd, *J*=12.4 and 1.9 Hz, 6b-H), 3.90 (1H, dd, *J*=12.9 and 7.2 Hz, one of $CHCH_2N^+$), 4.16 (1H, dd, *J*=12.8 and 7.7 Hz, one of

CHCH_2N^+), 4.39 (1H, d, J=8.9 Hz, 1-H), 5.62 (1H, dd, J=10.0 and 1.5 Hz, CH=CH_2 *cis*-olefinic H), 5.66 (1H, dd, J=17.2 and 1.5 Hz, CH=CH_2 *trans*-olefinic H), and 5.90–6.00 (1H, m, CH_2CH=CH_2); ^{13}C NMR: δ [$(CD_3)_2SO$] 47.1, 48.3, 60.5, 65.9, 68.9, 70.1, 76.9, 80.1, 93.3, 125.4 and 129.0; m/z (ES +ve mode) 248 (cation M^+, 100%).

4.5. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-piperidine (16)

This was prepared essentially according to the reported procedure, Ref. 26 in the text as a white solid. Found: C, 55.1; H, 7.1; N, 3.2; m/z, 438.1718. $C_{19}H_{29}NO_9$ requires C, 54.9; H, 7.0; N, 3.4%; $C_{19}H_{29}NO_9Na$ requires m/z, 438.1740; ^{1}H NMR: δ ($CDCl_3$) 1.40–1.55 (6H, m, 3×CCH_2C), 2.02, 2.04, 2.07, 2.16 (12H, 4s, 4×CH_3CO), 2.49–2.56 and 2.88–2.96 (4H, 2m, 2×NCH_2), 3.59 (1H, ddd, J=10.0, 4.8 and 2.6 Hz, 5-H), 3.98 (1H, d, J=8.9 Hz, 1-H), 4.11 (1H, dd, J=12.1 and 2.6 Hz, 6a-H), 4.23 (1H, dd, J=12.1 and 4.8 Hz, 6b-H), 4.99 (1H, t, J=9.4 Hz, 4-H), 5.17 (1H, t, J=9.3 Hz, 2-H) and 5.20 (1H, t, J=8.5 Hz, 3-H); ^{13}C NMR: δ ($CDCl_3$) 21.0, 21.1 (×2), 21.2, 24.9, 26.7, 49.4, 62.8, 67.9, 69.4, 73.4, 74.3, 94.9, 169.9, 170.0, 170.7 and 171.0; m/z (ES +ve mode) 438 (MNa^+, 100%).

4.6. [*N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*-methyl]piperidinium trifluoromethanesulfonate (17)

To a solution of **16** (0.100 g, 0.24 mmol) in DCM (2 mL) under nitrogen was added MeOTf (0.48 mmol). The reaction was left stirring for 4 h at room temperature, and then the DCM was removed in vacuo. Column chromatography was carried out using 100% EtOAc, then 50:50 ethanol/DCM. The ethanol/DCM fractions were combined and solvent removed to give **17** in 62% yield as a foam. Found: m/z, 430.2064. $C_{20}H_{32}NO_9$ requires m/z, 430.2077; ^{1}H NMR: δ ($CDCl_3$) 1.70–1.80 (3H, m, CCH_2C), 1.98, 2.03, 2.05 and 2.12 (12H, 4s, 4×CH_3CO), 2.00–2.10 (3H, m, CCH_2C), 3.30 (3H, s, CH_3N^+), 3.60–3.95 (4H, m, 2×CH_2N^+), 4.27 (1H, dd, J=12.6 and 5.9 Hz, 6a-H), 4.36–4.44 (2H, m, 6b-H+5-H), 5.23 (1H, t, J=9.7 Hz, 4-H), 5.49 (1H, dd, J=9.4 and 8.3 Hz, 3-H), 5.69–5.78 (2H, m, 1-H+2-H); ^{13}C NMR: δ ($CDCl_3$) 20.7, 20.9, 21.0 (×2), 21.3, 21.8, 61.8, 62.2, 62.6, 68.4, 68.9, 74.6, 76.5, 90.9, 122.5 (CF_3, q, J=320 Hz), 170.5 (×2), 170.6 and 171.3; m/z (ES +ve mode) 430 (cation M^+, 100%).

4.7. [*N*-(β-D-Glucopyranosyl)-*N*-methyl]piperidinium trifluoromethanesulfonate (18)

To a solution of **17** (0.532 g, 0.92 mmol) in MeOH (6 mL) was added NaOMe (0.046 mmol). The reaction was left stirring at room temperature for 5 h, then quenched with Amberlite H^+ resin (0.046 mmol) to reach pH 7. The resin was filtered off and washed with methanol, and then the solvent was removed in vacuo to give the product **18** in quantitative yield as a non-crystalline foam. Found: m/z, 262.1661. $C_{12}H_{24}NO_5$ requires m/z, 262.1654; ^{1}H NMR: δ [$(CD_3)_2CO$] 1.69–1.78, 1.91–2.03, 2.05–2.12 (6H, m, 3×CCH_2C), 3.27 (3H, s, CH_3N^+), 3.48 (1H, t, J=9.5 Hz, 4-H), 3.45–3.75 (2H, m, CH_2N^+), 3.65–3.75 (2H, m, 2×6-H), 3.67 (1H, t, J=9.3 Hz, 3-H), 3.87–3.98 (2H, m, CH_2N^+), 3.90 (1H, t, J=8.8 Hz, 2-H), 4.10–4.20 (1H, m, 5-H) and 5.00 (1H, d, J=8.8 Hz, 1-H); ^{13}C NMR: δ [$(CD_3)_2CO$] 20.7, 20.8, 22.0, 45.5, 61.1, 61.8, 61.9, 70.2, 71.6, 78.7, 81.7, 93.5, 119.9 (CF_3, q, J=320 Hz); only the central two peaks of the CF_3 quartet can be assigned confidently as this is a weak spectrum; m/z (ES +ve mode) 262 (cation M^+, 100%).

4.8. [*N*-(6-*O*-Trityl)-β-D-glucopyranosyl]-*N*-methyl-3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-propanamine (21)

To a solution of 6-*O*-trityl glucose **19** (2.83 mmol) in DCM (15 mL) under nitrogen was added nortriptyline **20** (2.83 mmol). The reactants were stirred at rt for 24 h: the DCM was then removed in vacuo. Column chromatography was carried out using EtOAc to afford the product **21** (49%) as a solid, mp 91–92 °C. Found: m/z, 668.3407. $C_{44}H_{46}NO_5$ (MH^+) requires m/z, 668.3376; ^{1}H NMR: δ (CD_3CN) 2.40–2.47 (2H, m, =CHCH_2), 2.40 (3H, s, NCH_3), 2.90–3.00 (2H, m, NCH_2CH_2), 2.95–3.15 (4H, br m, ArCH_2CH_2Ar), 3.18 (1H, dd, J=10.0 and 5.5 Hz, 6a-H), 3.25–3.32 (3H, m, 4-H+5-H+6b-H), 3.33 (1H, t, J=9 Hz, 3-H), 3.40 (1H, t, J=8.5 Hz, 2-H), 3.91 (1H, d, J=8.8 Hz, 1-H), 5.92 (1H, t, J=7.6 Hz, =$CH$$CH_2$), 7.05–7.33 (17H, m, ArH) and 7.49–7.53 (6H, m, ArH); ^{13}C NMR: δ (CD_3CN) 27.6, 31.2, 33.0, 34.3, 53.3, 63.4, 69.5, 70.1, 76.1, 77.4, 85.7, 93.6, 125.4, 125.5, 126.7, 126.8, 127.1, 127.4, 127.6, 127.7, 128.0, 128.3, 129.0, 129.7, 136.6, 139.1, 139.8, 140.8, 143.1 and144.0; m/z (ES +ve mode) 668 (MH^+, 100%).

4.9. [*N*-[(6-*O*-Trityl)-2,3,4-tri-*O*-acetyl]-β-D-glucopyranosyl]-*N*-methyl-3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-propanamine (22)

To a solution of **21** (1.5 mmol) in pyridine (15 mL) at 0 °C under nitrogen was added acetic anhydride (9 mmol). The reaction was allowed to reach room temperature on addition of the acetic anhydride and left stirring for 4 h. The reaction was basified using satd $NaHCO_3$ until pH 7 was reached, then the solution was diluted with DCM (60 mL) and the organic layer was separated. The aqueous layer was then extracted with DCM (3×50 mL) and the combined DCM layers were washed with water (100 mL), brine (100 mL) and dried over Na_2SO_4. After evaporation, column chromatography was carried out using 50:50 ether/hexane to afford the product **22** (79%) as an amorphous foam. Found: m/z, 794.3710. $C_{50}H_{52}NO_8$ (MH^+) requires m/z, 794.3693; ^{1}H NMR: δ (CD_3CN) 1.73, 1.77 and 1.95 (9H, 3s, 3×CH_3CO), 2.39 (5H, m, =CHCH_2+NCH_3), 2.75–3.20 (6H, m, ArCH_2CH_2Ar+NCH_2CH_2), 3.25–3.60 (3H, m, 2×6-H+5-H), 4.15–4.35 (1H, br d, 1-H), 5.10–5.25 (3H, br m, 2-H+3-H+4-H), 5.87 (1H, t, =$CH$$CH_2$), 7.04–7.06 (1H, m, ArH), 7.09–7.17 (3H, m, ArH), 7.22–7.34 (13H, m, ArH) and 7.42–7.51 (6H, m, ArH); the ^{1}H NMR spectrum showed very broad signals and meaningful coupling constants cannot be quoted; ^{13}C NMR: δ (CD_3CN) 19.4 (×2), 19.6, 22.0, 27.4, 31.0, 31.3, 33.0, 33.4, 61.6, 67.9, 68.1, 73.4, 73.6, 85.7, 92.2, 125.3, 125.7, 126.7, 127.1, 127.5, 127.7, 128.1, 128.2, 129.2, 129.7, 136.7, 139.1, 139.8, 141.0, 142.9, 143.6, 168.6, 169.0 and 169.6; m/z (ES +ve mode) 794 (MH^+, 100%).

4.10. [*N*-[2,3,4-Tri-*O*-acetyl]-β-D-glucopyranosyl]-*N*,*N*-dimethyl-3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-propanammonium trifluoromethanesulfonate (23)

To a solution of **22** (0.38 mmol) in DCM (8 mL) under nitrogen was added MeOTf (0.76 mmol). The reaction was left stirring at 20 °C for 17 h. The DCM was removed in vacuo and column chromatography was carried out using 100% EtOAc, and then 20% EtOH/DCM to afford the product **23** (59%) as an amorphous foam. Found: m/z, 566.2740. $C_{32}H_{40}NO_8$ requires m/z, 566.2754; ν_{max} (diamond) cm^{-1} 3347 (br s), 1751, 1604, 1520 and 1452; ^{1}H NMR: δ (CD_3CN, 343 K) 2.01, 2.03 and 2.09 (9H, 3d, 3×CH_3CO; fluxional effects), 2.64 (2H, m, =CHCH_2), 3.02, 3.04 (6H, 2d, 2×CH_3N^+), 2.95–3.30 (4H, br m, $ArCH_2CH_2Ar$), 3.30–3.45 (1H, br m, one N^+CH_2), 3.50–3.70 (4H, br m, 2×6-H+5-H+one N^+CH_2), 4.86 (1H, approx. d, J=6.5 Hz, 1-H), 5.08 (1H, approx. t, J=9 Hz, 4-H), 5.26 (1H, approx. t, J=7.8 Hz, 3-H), 5.41 (1H, dd, J=9.2 and 7.5 Hz, 2-H), 5.79 (1H, t, J=6.4 Hz, =$CH$$CH_2$) and 7.05–7.45 (8H, m, ArH); ^{13}C NMR: δ (CD_3CN) 19.5, 19.6, 19.8, 22.5, 31.2, 32.9, 48.3, 59.2, 63.6, 66.3, 67.0, 72.8, 77.5, 91.0, 120.5 (CF_3, q, J=310 Hz), 122.8, 125.9, 127.1, 127.4, 127.7, 128.1, 130.0, 136.9, 138.6, 139.1, 169.3, 169.6 and 169.8; only the central two peaks of

the CF_3 quartet can be assigned confidently as this is a weak spectrum (cf. **18**); *m*/*z* (ES +ve mode) 566 (cation M^+, 100%).

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Supplementary data

Cif files for structures **13a** and **14**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.086.

References and notes

1. The original preparation was given by Karrer, P.; Smirnoff, A. P. *Helv. Chim. Acta* **1921**, *4*, 817–821.
2. Micheel, F. *Ber. Dtsch. Chem. Ges.* **1929**, *62B*, 687–693.
3. McCloskey, C. M.; Coleman, G. H. *J. Org. Chem.* **1945**, *10*, 184–193; Also a quaternisation of a protected glycosylamine disaccharide (cellobiose) has been reported: Karrer, P.; Harloff, J. C. *Helv. Chim. Acta* **1933**, *16*, 962–968 and here again (cf. above) vigorous hydrolysis led to an anhydrosugar, with no isolation of the free quaternary ammonium salt.
4. Luo, H.; Hawes, E. M.; McKay, G.; Midha, K. K. *J. Pharm. Sci.* **1992**, *81*, 1079–1083.
5. Hawes, E. M. *Drug Metab. Dispos.* **1998**, *26*, 830–837.
6. Kaku, T.; Ogura, K.; Nishiyama, T.; Ohnuma, T.; Muro, K.; Hiratsuka, A. *Biochem. Pharmacol.* **2004**, *67*, 2093–2102.
7. Zhu, B.; Bush, D.; Doss, G. A.; Vincent, S.; Franklin, R. B.; Xu, S. *Drug Metab. Dispos.* **2008**, *36*, 331–338.
8. Palbir, S. G.; Soine, H. *J. Chromatogr., B* **1997**, *691*, 111–117.
9. Hou, B. K.; Lim, E. K.; Higgins, G. S.; Bowles, D. J. *J. Biol. Chem.* **2004**, *279*, 47822–47832.
10. Stachulski, A. V.; Jenkins, G. N. *Nat. Prod. Rev.* **1998**, *15*, 173–188.
11. Stachulski, A. V.; Harding, J. R.; Lindon, J. C.; Maggs, J. L.; Park, B. K.; Wilson, I. D. *J. Med. Chem.* **2006**, *49*, 6931–6945.
12. Kaspersen, F. M.; van Boeckel, C. A. A. *Xenobiotica* **1987**, *17*, 1451–1471.
13. Aboul-Enein, H. Y. *J. Carbohydr., Nucleosides, Nucleotides* **1977**, *4*, 77–81; (*Chem. Abstr.* **1977**, *87*, 85188).
14. Salekh, M. A.; Krasavina, L. S.; Vigdorchik, M. M.; Turchin, K. F.; Kuleshova, E. F.; Suvorov, N. N. *Zh. Org. Khim.* **1989**, *25*, 2613–2619; (*Chem. Abstr.* **1990**, *113*, 115694).
15. (a) Collins, P. M.; Ferrier, R. J. *Monosaccharides*; Wiley: Chichester, UK and New York, NY, 1995; pp 318–319; (b) Ref. 15a, p 175; cf. Baker, J. W. *J. Chem. Soc., Chem. Commun.* **1929**, 1205–1210; This elimination may be due in part to the acetate groups: thus a trimethyl ether anomeric chloroglucose derivative was successfully quaternised using Me_3N: Freudenberg, K.; Braun, E. *Justus Liebigs Ann. Chem.* **1928**, *460*, 288–304.
16. Araya, I.; Akita, H. *Heterocycles* **2008**, *75*, 1213–1223.
17. Mey, U.; Wachsmuth, H.; Breyer-Pfaff, U. *Drug Metab. Dispos.* **1999**, *27*, 1281–1292.
18. (a) Bianchi, A.; Bernardi, A. *J. Org. Chem.* **2006**, *71*, 4565–4577; (b) Paulsen, H.; Gyorgydeak, Z.; Friedman, M. *Chem. Ber.* **1974**, *107*, 1590–1613.
19. Marmuse, L.; Nepogodiev, S. A.; Field, R. A. *Org. Biomol. Chem.* **2005**, *3*, 2225–2227; Unverzagt, C.; Kunz, H. *J. Prakt. Chem.* **1992**, *335*, 570–578.
20. Shiozaki, M.; Mochizuki, T.; Hanazawa, H.; Haruyama, H. *Carbohydr. Res.* **1996**, *288*, 99–108.
21. Liberek, B.; Melcer, A.; Osuch, A.; Wakiec, R.; Milewski, S.; Wisniewski, A. *Carbohydr. Res.* **2005**, *340*, 1876–1884.
22. Skorupowa, E.; Kurszewska, M.; Konitz, A.; Wojnowski, W.; Wisniewski, A. *Carbohydr. Res.* **2001**, *331*, 343–346. The authors used the procedure of Karrer and Smirnoff, Ref. 1.
23. An earlier report described the crystallisation of both quaternary halides, viz. **13a** and the corresponding bromide, and noted that they both adopted an orthorhombic space group but without structural detail: Krouvine, Y.; Stora, C. *Comput. Rend.* **1945**, *220*, 328–330; (*Chem. Abstr.* **1945**, *41*, 3555).
24. Compounds**13b** and **13c** were also successfully deprotected to give the corresponding free sugars; see Experimental.
25. Paulsen, H.; Pflughaupt, K.-W. In *The Carbohydrates*, 2nd ed.; Pigman, W., Horton, D., Eds.; Academic: New York, NY, 1980; Vol. 1B, pp 881–927.
26. Hodge, J. E.; Rist, C. E. *J. Am. Chem. Soc.* **1952**, *74*, 1494–1497.
27. Hodge, J. E. *Adv. Carbohydr. Chem.* **1955**, *10*, 169–205. The first product from the Amadori rearrangement of a glucopyranosylamine is usually a fructosylamine.
28. Iddon, L. Ph. D. thesis, University of Liverpool, in preparation.
29. A similar intermediate was used in an intramolecular glycosidation study: Bols, M. *Acta Chem. Scand.* **1993**, *47*, 829–834; (*Chem. Abstr.* **1994**, *120*, 77532).
30. David, S. *The Molecular and Supramolecular Chemistry of Carbohydrates*; OUP: Oxford, 1997; pp 60–62.
31. cf. De Vries, N. K.; Buck, H. M. *Carbohydr. Res.* **1987**, *165*, 1–16; (*Chem. Abstr.* **1988**, *108*, 187084).
32. Available as its HCl salt from Sigma–Aldrich Co.
33. Briggs, A. J.; Glenn, R.; Jones, P. G.; Kirby, A. J.; Ramaswamy, P. *J. Am. Chem. Soc.* **1984**, *106*, 6200–6206.
34. Romers, C.; Altona, C. *Acta Crystallogr.* **1963**, *16*, 1225–1232.
35. Herpin, P.; Famery, R.; Augé, J.; David, S.; Guibé, L. *Acta Cryst., Sect. B: Struct. Sci.* **1976**, *32*, 209–215.
36. Lichtenthaler, F. W.; Sakakibara, T.; Oeser, E. *Carbohydr. Res.* **1977**, *59*, 47–61.
37. Lichtenthaler, F. W.; Ronninger, S.; Kreis, U. *Liebigs Ann. Chem.* **1990**, 1001–1006.