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On the alkoxybromination of glucal esters: 2-acetamido-α-D-mannosyl bromides from 2-acetamidoglucal

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Abstract—While the alkoxybromination of glucal and 2-acyloxyglucal esters leads to 2-bromo-2-deoxy-α-D-glycosides and α-D-glycosulosyl bromides, respectively, the exposure of 2-acetamido-D-glucal triacetate to NBS/ROH yields 2-*O*-alkyl-2-*C*-acetamido-α-D-mannosyl bromides. Although the final products of these reactions are distinctly different, mechanistic considerations show the initial step to consistently be the capture of a bromonium ion by C-2 from the axial side, followed by a *trans*-addition of ROH. In contrast, fluoro-acetoxylations of the same glucal esters invariably lead to *cis*-addition products due to a quasi-concerted SET-induced mechanism involving a solvent cage-trapped biradical.
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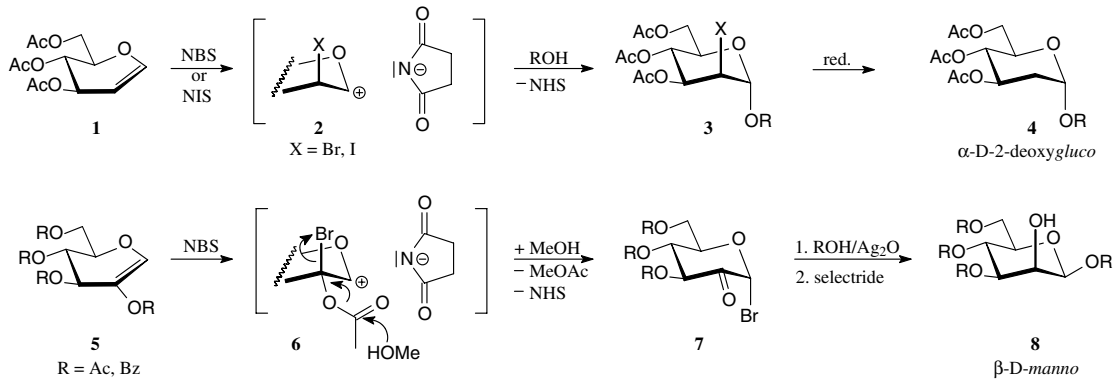
1. Introduction

Ample evidence has been obtained with regard to the alkoxyhalogenation of glycal esters to proceed in a regiospecific and highly stereospecific manner,[1–3] such that the electrophilic halogen Br^+ or I^+ generated from *N*-bromo- or *N*-iodosuccinimide, for example, is captured from the axial side by C-2, the more nucleophilic olefinic carbon, followed by an equally axial attack of the alcohol at the oxocarbenium intermediate, that is, **1**→**2**→**3**. The resulting 2-halo-2-deoxy-glycosides can be readily dehalogenated, for example, **3**→**4**, and hence are of appreciable significance for the preparation of anomerically pure 2-deoxy-α-glycosides (Scheme 1).[2,3]

A quite different course is observed for the alkoxybromination of 2-acyloxyglycal esters of type **5**. When exposed to NBS in the presence of methanol, oxocarbonium intermediate **6** initially formed is not attacked by the *O*-nucleophile (MeOH) at the anomeric carbon, but at the 2-acyloxy



Scheme 1. Mechanism of the alkoxyhalogenation of glucal and 2-acyloxyglucal esters, and the utilization of the products (NBS = *N*-bromosuccinimide, NHS = succinimide).

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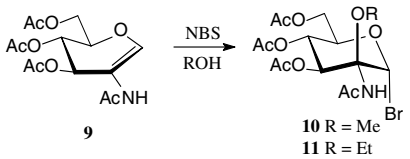
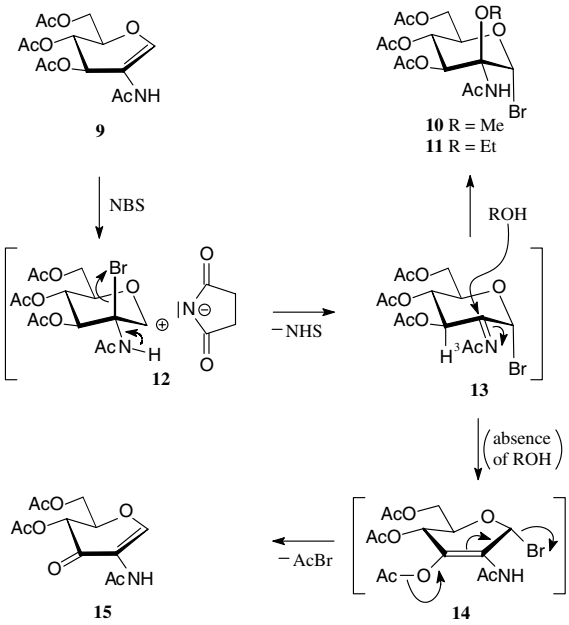
group (arrows in **6**), thereby elaborating 2-oxohexosyl bromides of type **7**. Due to their generation in nearly quantitative yields,[4] their essentially β-specific glycosidation,[5] and the *manno*-specific carbonyl reduction **7**→**8**,[6] the ulosyl bromides have proven to be highly useful glycosyl donors for the efficient generation of oligosaccharides containing β-D-mannosidic linkages.[7] As shown in this paper with the alkoxybromination of 2-acetamidoglucal **9**, the reaction again takes a different course inasmuch as 2-acetamido-α-D-mannosyl bromides **10** and **11** are formed, with the alkoxy group ending up at C-2 and the bromine at the anomeric carbon.



2. Results and discussion

Exposure of acetamidoglucal **9**, in a dichloromethane solution, to equimolar amounts of NBS in the presence of two equivalents of methanol or ethanol, smoothly (1.5 h, rt) afforded a single product each (TLC), isolable in 71% and 75% yields, respectively. Their NMR data, with the appearance of the anomeric protons as low as at 7.45 ppm, clearly indicated that the bromine was located at the anomeric centre, thus verifying the products to be either 2-*C*-acetamido-α-D-mannosyl bromides **10** and **11**, or their 2-epimeric α-D-glucosyl isomers. Proof for the (*S*)-configuration at the tertiary carbon, that is, **10** and **11** being 2-acetamido-mannose derivatives, was unambiguously established from the X-ray structural analysis of **11** (Fig. 1), which clearly showed the 1-bromo and 2-ethoxy groups in a diaxial arrangement.



Scheme 2. Plausible mechanisms for the reaction of 2-acetamidoglucal triacetate **9** with NBS in the presence (→**10** or **11**) and the absence of an alcohol (→**15**) [NHS = succinimide].

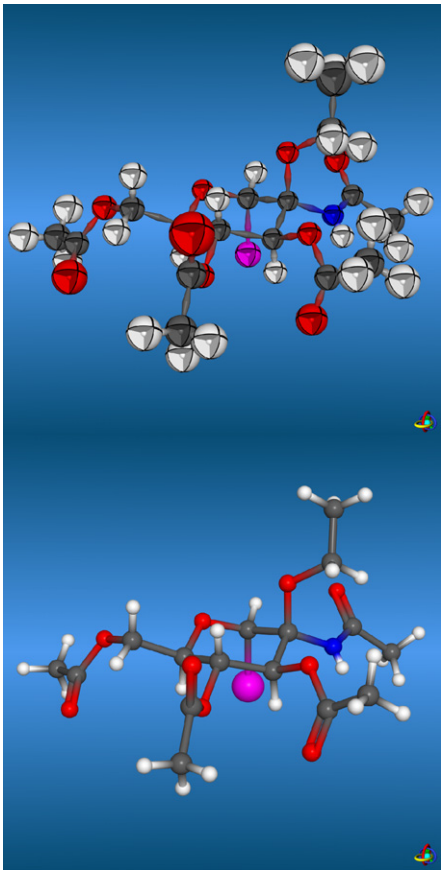
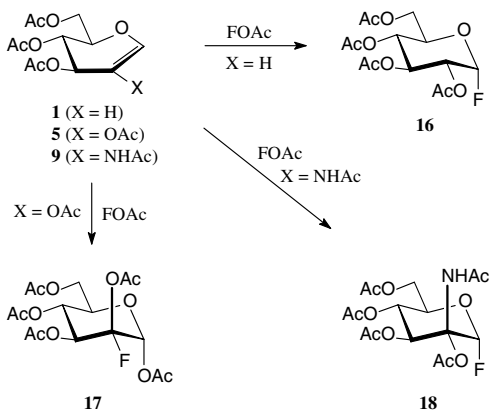


Figure 1. X-ray structure of 2-*C*-acetamido-3,4,6-tri-*O*-acetyl-2-*O*-ethyl-α-D-mannopyranosyl bromide **11** as anisotropic thermal ellipsoids (top) and in ball-and-stick model form. The pyranose ring adopts a nearly perfect $^4C_1$ chair conformation with an essentially antiparallel arrangement of the 1-Br and 2-OEt moieties. Selected dihedral angles [°]: Br–C1–C2–O2 +170.5, Br–C1–C2–N +48.4, O2–C2–C3–O3 −58.1, N–C2–C3–O3 +69.0, N–C2–C1–O5 −64.8.

Although the bromine in the alkoxybromination of **9** ends up at the anomeric center, a plausible mechanism (Scheme 2) precludes direct attack of the NBS-derived bromonium ion at C-1. Instead, Br^+ is captured by C-2 from the axial face—in analogy to the glucal (**1**→**2**)[2,3] and 2-acyloxyglucal (**5**→**6**)[8] additions.[9] Oxocarbenium ion **12** then undergoes HBr elimination utilizing the NH proton (arrows in **12**), followed by the axial addition of the alcohol to acetylimine intermediate **13**.

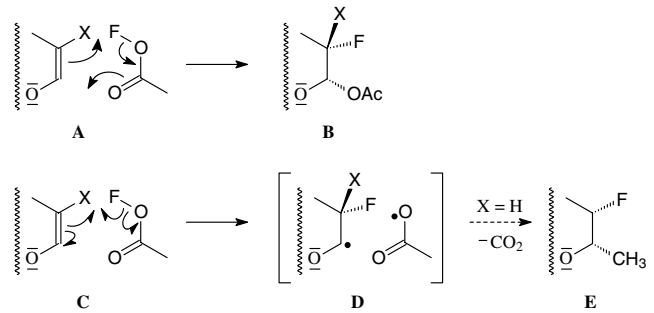
Exposure of acetamidoglucal **9** to NBS in the absence of an alcohol leads to dihydropyranone **15**, isolable in crystalline form in 56% yield. Although surprising at first, its formation can be readily rationalized in such (cf. Scheme 2) that acetylimine intermediate **13**, due to the absence of a nucleophile, undergoes tautomerization utilizing H-3 to give an enaminol-type intermediate **14**, which stabilizes to dihydropyrone **15** by excision of the elements of acetyl bromide.

In view of the consistency of these mechanistic rationalizations which may safely be extended to other glycal additions, it must be emphasized that they are valid for additions involving distinct halonium ions, which fluorine, unlike other halogens, cannot form. Thus, reactions of fluorination agents with glycal esters are a priori presumed to proceed along different mechanistic veins—a conjecture substantiated by the experimental findings that 1,2-*cis*-adducts are obtained with high preference on addition of elemental fluorine,[11] of trifluoromethyl hypofluorite (CF_3OF),[12] and, most extensively studied,[13–17] of acetyl hypofluorite (AcOF). Tri-*O*-acetyl-D-glucal **1** generates tetra-*O*-acetyl-2-fluoro-2-deoxy-α-D-glucose **16** either exclusively (AcOF, in 9:1 $CFCl_3$/HOAc, 5 min, −78 °C[13]) or with a high preference[15,16] (Scheme 3); 2-acetoxyglucal **5** reacts to give (2*R*)-acetoxy analogue **17** (AcOF in $CFCl_3$/CH_3CN, 0 °C, 23% isol. yield[17]), whereas 2-acetamidoglucal **9**, in a reverse addition of AcOF, gives glucosyl fluoride **18**, isolated in 30% yield, its (2*S*)-configuration established by analogy.[17]



Scheme 3. Fluoro-acetoxylations of tri-*O*-acetyl-D-glucal **1**→**16**,[13,15,16] and of its 2-acetoxy-**5**→**17**[17] and 2-acetamido-analogs **9**→**18**.[17]

In contrast to NBS with its electrophilic bromine, which entails ionic transition states such as **2**, **6** and **12** (Schemes 1 and 2) and, hence, 1,2-*trans*-diaxial adducts of types **3** and **10**, the 1,2-*cis* additions of acetyl hypofluorite, devoid of predisposed fluoronium ions, obviously proceed in a different fashion: a concerted mechanism of the type **A**→**B** (Scheme 4), or, as suggested by Visser and Herscheid,[18] a quasi-concerted mechanism with intermediate radicals emerging from single-electron transfers (SET), that is, electron transfer from the double bond to the fluorine atom to generate a carbon-centered and an acetoxy radical (**C**→**D**), which immediately collapse within the solvent cage (**D**→**B**). A strong indication for the AcOF additions passing through such biradical transition states is provided, in fact, by the detection (2%) of α-*C*-methyl 2-fluoroglucoside **E** (Scheme 4) in the reaction mixture resulting from fluoro-acetoxylation of D-glucal triacetate,[15,18] readily explained by excision of CO_2 from the acetoxy radical in **D**.



Scheme 4. Transition states for the 1,2-*cis* additions of AcOF onto glucal esters **1** and **5** (X = H and OAc).

Further support for this quasi-concerted biradical mechanism can be derived from density functional theory (DFT) calculations[19] for the reaction of AcOF with ethylene as a model compound, clearly indicating the presence of a planar transition state. The attack occurs perpendicular to the double bond (that is, in plane with the π-orbitals), but parallel to the carbon–carbon axis (Fig. 2). The reaction appears to be initiated by the electrophilic attack of the fluorine on the double bond by interaction of the $LUMO_{AcOF}$ (σ^*_{O-F}) with the $HOMO_{C_2H_4}$ ($\pi_{C=C}$). Formation of the C_β–F bond (transition state atomic distances $d_{C_\beta F}$ 1.885 Å) and breaking of the F–O bond (d_{O-F} 1.819 Å) occur simultaneously. Surprising at first sight is the rather large separation between the C-2 of ethylene and the carbonyl group of AcOF (d_{C-O} 2.784 Å), yet computations in the restricted versus unrestricted B3LYP scheme indicated the elaboration of a singlet biradical character in the transition state ($\Delta H^* \approx 55$ kJ mol^{-1}), with a spin density accumulating at C-2 of ethylene and the oxygen atom of the O–F bond. In the sequel, seamless and transition state free recombinations of the acetoxy and carbon centered radicals yield the 2-fluoroethyl acetate reaction product. Although the formation of the newly created bonds does not occur simultaneously, this type of mechanism can be regarded as a concerted process with a single transition state, in which an electrophilic fluorine atom (not

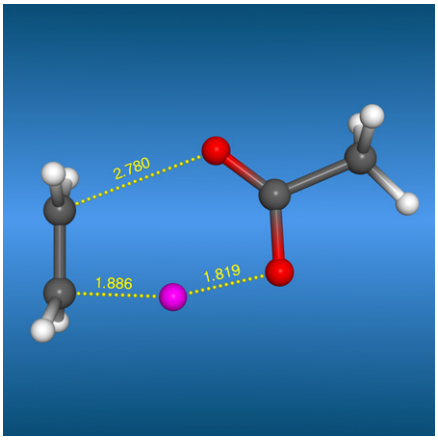
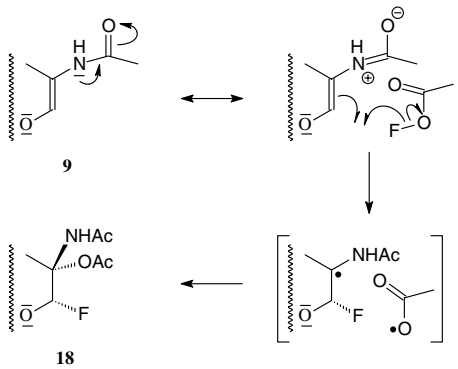


Figure 2. Transition state for the reaction of ethylene with FOAc (B3LYP/6-311G+(p,d) optimized structures, atomic distances given in Å), based on DFT calculations.[19]

F^+) is transferred from AcOF to ethylene with immediate recombination of the radical centers.

The isolation of 2-*C*-acetamido-α-D-glucosyl fluoride **18** on the fluoro-acetoxylation of **9**, albeit in only 30% yield and without firm configurational proof at the tertiary carbon atom,[17] implies that the AcOF addition occurs in a sense opposite to the parent glucal, as depicted in Scheme 5; a course which has been attributed[17] 'to stabilization of the developing carbonium ion at C-2 by electron donation from the amide nitrogen'.[20] However, since AcOF, due to its inability to release genuine fluoronium species, reacts with the parent glucal (Scheme 4) through homolytic rather than heterolytic cleavage of the F–O bond, it appears more persuasive to assume an analogous course for its addition to the acetamidoglucal: capture of the fluorine through a quasi-concerted single-electron-transfer (SET) via a solvent cage-trapped biradical transition state (Scheme 5). As a result, the 'inverse' regioselectivity may be attributable to the electron-withdrawing effect of the nitrogen enhanced by resonance of its lone electron pair with the amide carbonyl, which engenders an Umpolung of the double bonds's polarity.



Scheme 5. Quasi-concerted SET mechanism for the 'inverse' addition to acetamidoglucal **9**, proceeding through a solvent cage-trapped biradical.

The reasons underlying the inverse additions of AcOF to glucal **1** (→**16**) and its 2-acetamido analogue **8** (→**18**) may be attributed to the obviously opposite polarization of their double bond. That this is indeed the case can nicely be derived from calculations of the respective charge distributions. Figure 3 displays the molecular geometries of 3,4,6-tri-*O*-acetyl-glucal **1**, the corresponding 2-acetoxy glucal ester **5**, and 2-acetamido-glucal **9** alongside with their computed charge distribution in the form of Mulliken atomic charges mapped onto the atomic positions in color-coded form. Obviously, the double bond of the parent glucal (Fig. 3, left) becomes polarized by the electron donating effect of the ring oxygen in such a way that C-2 becomes more negatively (blue color) charged, and thus more nucleophilic than C-1. Consistently, the reaction with AcOF (1,2-*cis* rear face attack) results in the formation of the corresponding 2-deoxy-2-fluoro-α-D-glucoside with high preference.

A different picture emerges from the charge distribution of 2-acetamido-glucal **9** (Fig. 3, right), for which the electron

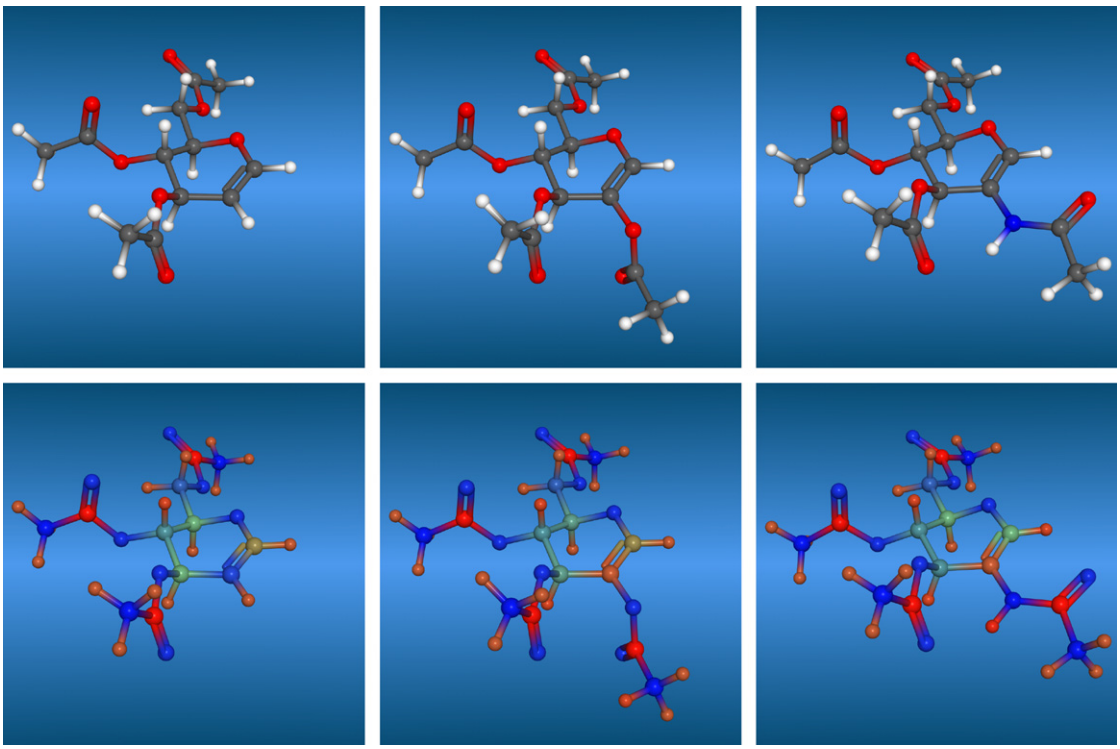


Figure 3. Molecular geometries (B3LYP/6-311G(d) optimized structures) of the tri-*O*-acetylderivatives of glucal **1** (left), 2-acetoxyglucal **5** (center), and 2-acetamidoglucal **9** (right). In the bottom row, atomic charges are mapped onto the structural models, with a color-code ranging from red (positive atomic charge) over green to blue (negative charge), revealing the antipodal polarization of the glucal double-bond.

withdrawing effect of the nitrogen substituent, augmented by the resonance of the nitrogen lone-pair with the amide carbonyl group, becomes dominant. In total, the double bond displays a reversed polarity with regard to the parent glucal. An intermediate, slightly polarized C=C double bond prevails in 2-acetoxyglucal ester **5**, allowing the conjecture that either addition of AcOF as in glucal and inverse as in its 2-acetamido derivative should be possible. Currently, only the 'normal' glucal adduct **17** has been isolated.[17] As the yield was only 23%, it certainly will be worthwhile searching for the inverse adduct in the reaction mixture, and this the more, as in the fluoro-acetoxylation of triacetyl-glucal **1**, traces (1% each) of tetra-*O*-acetal-α-D-glucosyl and β-D-mannosyl fluoride, that is, products of the 'inverse' addition, have been detected.[15,18]

3. Conclusion

The alkoxyhalogenation of glucal, 2-acyloxyglucal and 2-acetamido glucal esters, although leading to distinctly different products, all have the first step in common: the capture of the bromonium ion by the more nucleophilic C-2 from the axial side towards a structurally and stereochemically analogous 2-bromo-oxocarbonium intermediate. Their follow-up reactions are dependent upon the nature of the 2-substituent: *trans*-addition of the alkoxy group to 2-bromo-α-D-glucosides in the case of glucal (**1** → **3**),[1–3] elaboration of ulosyl bromides from 2-acyloxyglucal esters due to methanolysis of the 2-acyloxy group (**5** → **7**),[4] and, as shown in this paper with 2-acetamido analogues, *trans*-addition of an alcohol onto a 2-ketimine intermediate to give α-D-mannosyl bromides (**9** → **10** or **11**). In contrast, the fluoro-acetoxylations (additions of FOAc) to the same glucal esters invariably lead to *cis*-addition products due to operation of a quasi-concerted radical mechanism that proceeds through SET transfer of the electrophilic fluorine (not F^+) via a solvent cage-trapped biradical.

4. Experimental

4.1. General

Melting points were determined with a Bock hot-stage microscope and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20 °C using a cell of 1 dm path length; concentration (*c*) in g/100 mL and solvents are given in parantheses. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer in $CDCl_3$. Mass spectra were acquired on Varian MAT 311 spectrometer. Microanalyses were determined on a Perkin–Elmer 240 elemental analyzer. Analytical thin layer chromatography (TLC) was performed on precoated Merck plastic sheets (0.2 mm silica gel 60 F_{254}) with detection by UV (254 nm) and/or spraying with H_2SO_4 (50%) and heating. Column and flash chromatography was carried out on Fluka silica gel 60 (70–230 mesh) using the specified eluents.

The starting material, 2-acetamido-3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol **9** (abridged term 'acetamidoglucal'), was prepared from *N*-acetyl-glucosamine by conversion into its peracetylated glycosyl chloride (78%[21]) followed by elimination of the HCl mediated either by base (24[21]) or by acid/isopropenyl acetate and subsequent de-*N*-acetylation of the 2-(*N*-acetylacetamido)glucal formed (64% for the two steps[21]).

The molecular geometries displayed in Figure 3 were derived from the X-ray structures of tri-*O*-acetyl-D-glucal **1**[22] and its 2-acetoxy analogue **5**,[22] that of the 2-acetamidoglucal **9** by homology modeling. DFT[19] calculations were carried out using GAUSSIAN03,[23] structural analysis and graphics were prepared using the Molarch$^+$ utility.[24]

All electronic structure calculations employed the Becke three parameter hybrid functionals[25] with the Lee–Young–Parr correlation part[26] (B3LYP) in combination with the 6-311G(d) basis set[27] for energy minimizations of the glucal derivatives, and 6-311++G(d,p) for the transition states of the fluoro-acetoxylation of ethylene (UB3LYP). All the stationary points identified (energy minima vs. transition states as first-order saddle-points) were verified by thermal frequency analysis.

4.2. 2-*C*-Acetamido-3,4,6-tri-*O*-acetyl-2-*O*-methyl-α-D-mannopyranosyl bromide 10

N-Bromosuccinimide (275 mg, 1.55 mmol) and methanol (0.1 mL, 2.5 mmol) were added to a solution of 2-acetamidoglucal **9**[21] (500 mg, 1.52 mmol) in CH_2Cl_2 (12 mL) and the mixture was stirred at ambient temperature for 1.5 h, followed by dilution with CH_2Cl_2 (40 mL) and consecutive washings with water (40 mL), 10% aqueous $Na_2S_2O_3$ solution (40 mL) and again water (40 mL). Drying over Na_2SO_4 and removal of the solvent in vacuo left a yellowish syrup which was purified by elution from a silica gel column (1.5 × 20 cm) with toluene/EtOAc (1:1): 475 mg (71%) of **10** as a colorless syrup; $[\alpha]_D^{20} = +141$ (*c* 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02, 2.07, 2.10, 2.16 (from 3H-s, AcCH_3), 3.50 (3H-s, OCH_3), 4.15 and 4.29 (two 1H-dd, 6-H_2), 4.21 (m, 1H, H-5), 5.43 (dd, 1H, H-4), 5.46 (d, 1H, H-3), 6.67 (br s, 1H, N*H*), 7.45 (s, 1H, H-1); $J_{3,4} = 8.7$, $J_{4,5} = 9.7$, $J_{5,6} = 1.7$ and 4.5, $J_{6,6'} = 11.7$ Hz; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.7, 20.8, 21.0, 24.2 (4 COCH_3), 53.6 (OCH_3), 61.6 (C-6), 66.1 (C-4), 72.7 (C-5) 75.3 (C-3), 87.2 (C-2), 88.6 (C-1), 169.4, 170.8, 170.9, 172.9 (4 *C*OCH_3). MS (FD, 20 mA): $m/z = 440$ [M^+]. Anal. Calcd for $C_{15}H_{22}NO_9Br$ (440.25): C, 40.93; H, 5.04; N, 3.18. Found: C, 41.05: H, 4.93; N, 3.07.

4.3. 2-*C*-Acetamido-3,4,6-tri-*O*-acetyl-2-*O*-ethyl-α-D-mannopyranosyl bromide 11

NBS (445 mg, 2.5 mmol) and dry ethanol (0.3 mL, 5 mmol) were added to a CH_2Cl_2 solution of acetamidoglucal **9**[21] (825 mg, 2.5 mmol, in 15 mL) followed by stirring at room temperature for 2 h. Dilution was done with CH_2Cl_2 (50 mL), and washings were done with 50 mL each of water, $Na_2S_2O_3$ solution, and again water. Drying over Na_2SO_4 and removal of the solvent in vacuo left a syrup

which was purified by elution from silica gel (2×25 cm column) with toluene/EtOAc (1:1). Evaporation of the product carrying fractions to dryness and trituration of the residue with EtOAc resulted in crystallization: 850 mg (75%) of **11** as colorless prisms of mp 110–111 °C; $[\alpha]_D^{20} = +127$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 3H, EtCH_3), 2.01, 2.07, 2.10, 2.16 (four 3H-s, 4 COCH_3), 375 (2H-m, EtCH_2), 4.14–4.25 (3H-m, H-5, 2 H-6), 5.43–5.46 (2H-m, H-3, H-4), 6.67 (br s, 1H, N*H*), 7.46 (s, 1H, H-1); $J_{3,4} = 8.7$, $J_{4,5} = 9.8$, $J_{5,6} = 1.7$ and 4.6, $J_{6,6'} = 11.6$ Hz; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.7 (Et*C*H$_3$), 20.7, 20.8, 21.0, 24.2 (4 CO*C*H$_3$), 61.5 (Et*C*H$_2$), 61.6 (C-6), 66.2 (C-4), 72.6 (C-5), 75.2 (C-3), 86.9 (C-2), 89.1 (C-1), 169.4, 170.6, 170.7, 172.9 (4 *C*OCH$_3$). Anal. Calcd for $C_{16}H_{24}NO_9Br$ (454.28): C, 43.85; H, 5.52; N, 3.19. Found: C, 43.76; H, 5.48; N, 3.11.

X-ray structure, solved by direct methods using SHELXS-97:[28] Space group $P2_1$, monoclinic, unit cell dimensions $a = 8.713$, $b = 14.534$, $c = 8.798$, $\alpha = 90°$, $\beta = 114.96°$, $\gamma = 90°$, $V = 1010.1(4)$, Å$^3 = 2$, $D_c = 1.494$ g/cm^3, μ(Mo-K$_\alpha$) $= 0.066$ mm^{-1}, $1.71° < \theta < 24.02°$, crystal size $0.625 \times 0.55 \times 0.175$ mm, 4165 reflections collected/3769 unique ($R_{int} = 0.0636$) data | parameters = 2107 | 247, Goof = 1.078, $R_{indices}$ ($I > 2\sigma\pm$): $R_1 = 0.0395$, $wR_2 = 0.0916$, $R_{indices}$ (all data): $R_1 = 0.0416$, $wR_2 = 0.0935$; Refinement by full matrix least-squares on F^2 for all data using SHELX-97XL.[29] Stereostructure and selected torsional angles: Figure 1.

Full crystallographic details have been deposited (No. CCDC 630548) with the Cambridge Crystallographic Data Centre. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk.

4.4. 2-Acetamido-4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-ulose[(2*R*,3*R*)-5-acetamido-3-acetoxy-2-acetoxymethyl-2,3-dihydro-4*H*-pyran-4-one] 15

To a solution of acetamidoglucal **9**[21] (825 mg, 2.5 mmol) in CH_2Cl_2 (15 mL) was added *N*-bromosuccinimide (445 mg, 2.5 mmol) and the mixture was stirred overnight (14 h). Dilution with CH_2Cl_2 (50 mL) and consecutive washings with water (50 mL), 10% aqueous $Na_2S_2O_3$ solution (50 mL) and again water (50 mL), drying (Na_2SO_4) and removal of the solvent in vacuo gave a syrup which was purified by elution from a silica gel column (2×20 cm) with toluene/EtOAc (2:1). The product was obtained as a syrup, which gradually crystallized: 415 mg (56%) of **15**; mp 141–142 °C; $[\alpha]_D^{20} = +234.9$ (*c* 1.1, $CHCl_3$); lit.[30]: mp 142 °C (dec), $[\alpha]_D^{24} = +234.4$ (*c* 1, CH_2Cl_2). ^{1}H and ^{13}C NMR data in $CDCl_3$ correlated with those previously described.[30]

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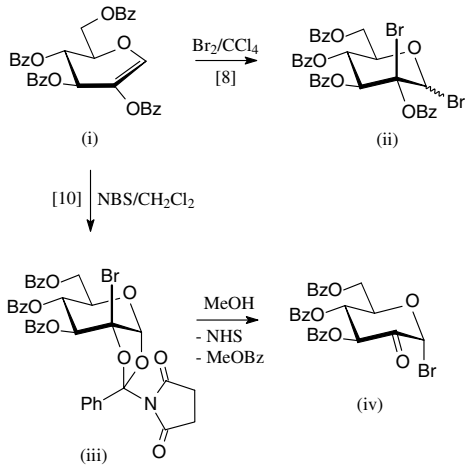
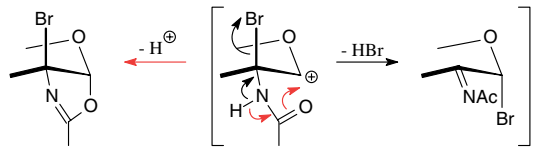
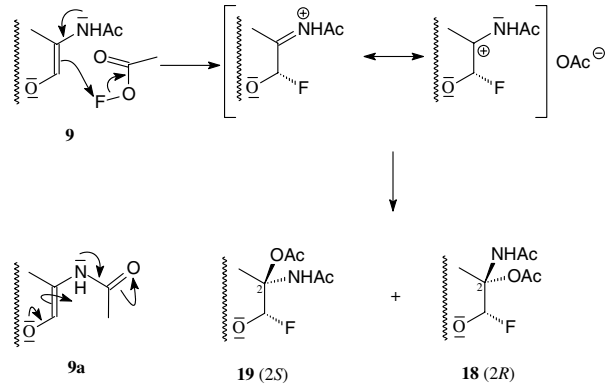


Attempts to isolate an intermediate analogous to (iii) from the NBS/CH_2Cl_2 bromination of acetamidoglucal **9** were unsuccessful, understandably as in the primary adduct **12**, a proton is directly available for HBr elimination to imine **13** (black arrows in **12**); the alternate possibility, elaboration of

the oxazoline (v) (red arrows) is not followed due to the strong inductive effect of the bromine.



(v) **12** **13**



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Also, besides *cis*-adduct **18**, the respective *trans*-isomer **19** would be expected as the major product, as the acetate ion is likely to attack the acetyliminium ion from the face opposite to the fluorine.

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