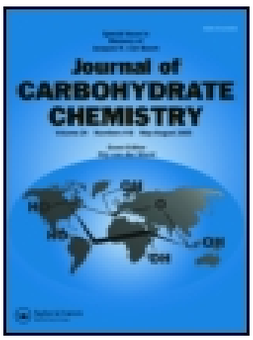

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Synthesis of unstable 4-benzoyl-1,6-anhydro-3-keto-β-D-mannopyranose *via* stereoselective photobromination of 2,3-isopropylidene-4-benzoyl-1,6-anhydro-β-D-mannopyranose

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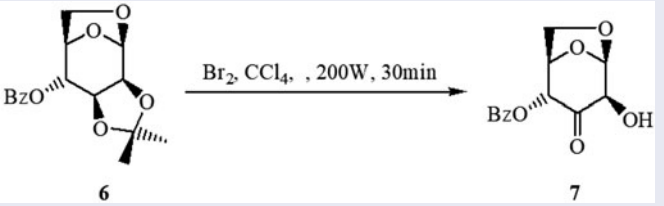
ABSTRACT

Stereoselective photobromination of 1,6-anhydro-β-D-glucopyranose derivatives occurs at *exo*-H6. However, photobromination of 4-benzoyl-2,3-isopropylidene-1,6-anhydro-β-D-mannopyranose **6** produced unstable 4-benzoyl-1,6-anhydro-3-keto-β-D-mannopyranose **7**. The mechanism of stereoselective oxidation at C-3 could be attributed to the facile radical proton abstraction at C-3, followed by the subsequent bromination of the isopropylidene group, which was subsequently eliminated during the aqueous workup. Thus, the aim of this article is to identify the molecular structure of the unstable compound **7**.

GRAPHICAL ABSTRACT



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1,6-anhydro-3-keto-β-D-mannopyranose; 6-bromo-1,6-anhydroglycopyranose; photobromination; synthesis

Introduction

1,6-Anhydro sugars with different orientations of stereocentres, allowing a wide range of chiral organic synthesis, are useful synthetic building blocks.[1] These natural product derivatives, including levoglucosan **1**, mannosan **2**, and galactosan **3** (Fig. 1), tend to have $^{1}C_{4}$ conformations. From a molecular structure point of view, both mannosan **2** and galactosan **3** possess two hydroxy groups cis to each other. Thus, isopropylidene and

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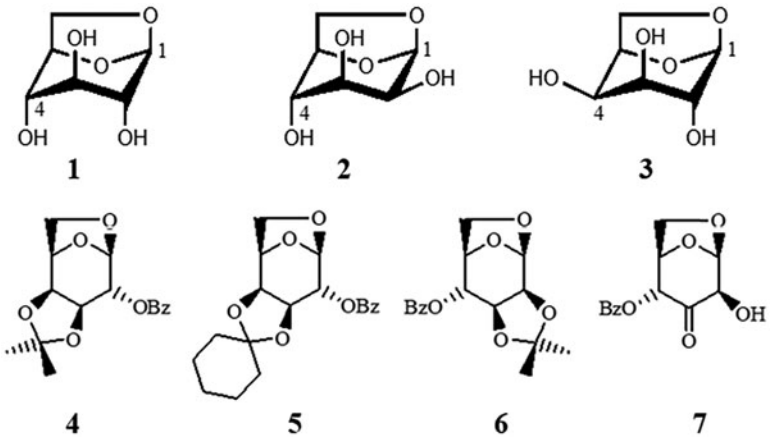


Figure 1. Structures of some common 1,6-anhydro sugars.

cyclohexylidene protecting groups can generate a second five-member ring in 1,6-anhydro-pyranose derivatives (Fig. 1). *Per se* these anhydro sugars **1**–**3** have considerable synthetic potentials due to the bicyclic rings and different stereochemical arrangement of hydroxyl groups. These characteristics contribute to enabling high regio- and stereo-controlled reactions in the synthesis of various chiral biologically active molecules.[1–3] In this respect, stereoselective bromination of monosaccharide derivatives provides an opportunity for extending the sugar chain at C-1 and C-6 *via* alkylation, for example. In addition, bromination of sugars is of potential interest, to gain access for unsaturated sugar derivatives, stereospecific S_N2' nucleophilic substitution, or as intermediates in radical carbon-carbon bond formation.[4–8] When 1,6-anhydro sugars undergo bromination or other reactions they often yield stable molecules. However, it has been reported that photobromination of 1,6-anhydro-2-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranose **4** and its cyclohexylidene derivative **5** gave decomposed products.[9] An attempt to photobrominate 2,3-isopropylidene-4-benzoyl-1,6-anhydro-β-D-mannopyranose **6** also gave unstable compounds. Therefore, this research was focused on the preparation and identification of the unstable 3-keto mannosan derivative **7**.

Experiments

Reactions were carried out under nitrogen atmosphere in AnalaR grade or freshly distilled solvents. They were monitored by thin-layer chromatography (0.2 mm Merck aluminum pre-coated Silica gel plates, 60 F254) with UV light and ethanolic phosphomolybdic acid and heat. Melting points were determined on a Kofler hot stage. High-resolution ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM 360 (360 MHz) pulsed Fourier

transform spectrometer. Chemical shifts are quoted in units relative to tetramethylsilane (δ). Mass spectra were recorded on Varian Mat CH5 05 Trio-1 spectrometer.

General procedure for photobromination of 1,6-anhydro-β-D-glycopyranose derivatives

A mixture of the 1,6-anhydro-β-D-glycopyranose (1 equiv) and bromine or NBS (1 equiv) in carbon tetrachloride (30 ml) was irradiated by a standard 150-W bulb wrapped with the flask by foil. After 2 h, the reaction mixture was cooled to room temperature, washed with sodium thiosulfate solution (2 × 10 ml), sodium bicarbonate (2 × 10 ml) and water (2 × 10 ml). The organic layer was then dried over sodium sulfate.[7,8] Evaporation of the solvent under reduced pressure gave:

1,6-Anhydro-2,3,4-tri-O-acetyl-6-bromo-β-D-glucopyranose 10 (0.57 g, 77% or 0.59 g, 80%, when Br_2 or NBS was used respectively) as a yellowish sirup, which was purified by flash silica, with 1,6-anhydro-2,3,4-tri-O-acetyl-β-D-glucopyranose **8** (0.6 g, 1.79 mmole) as starting material. MP = 95–98 °C. ^{1}H NMR ($CDCl_3$): δ 6.44(1 H, s, H6*endo*, 5.84 (1 H, s, H3), 4.92 (1 H, br.s., H4), 4.85 (1 H, s, H1). 4.69 (1 H, br,s, H2), 4.57 (1 H, br. s, H5), 2.19, 2.18, 2.13 (9 H, s, Me-Ac). ^{13}C NMR $CDCl_3$): δ 169.81, 169.55, 168.89 (C=O Ac), 102.20 (C1), 84.29 (C6), 79.32 (C5), 69.43 (C3), 68.07 (C4), 67.84 (C2), 20.85 ($\underline{C}H_3$-Ac). FD-MS ($C_{12}H_{15}O_8Br$): m/z 366.7 ($C_{12}H_{15}O_8Br$-H), 286.1 ($C_{12}H_{15}O_8$-H); EI-MS: m/z 367.0 $[M]^+$, 287.0 ($C_{12}H_{15}O_8$), 227.0 ($C_{10}H_{11}O_6$), 167.0 ($C_8H_7O_4$), 139.0, 97.0, 71.0.

1,6-Anhydro-2,3,4-tri-O-benzoyl-6-bromo-β-D-glucopyranose 11 (4.96 g, 85% and 0.59 g, 80%, when Br_2 or NBS was used respectively) as a yellowish sirup, which was crystallised from diethyl ether solvent, with 1,6-anhydro-2,3,4-tri-O-benzoyl-β-D-glucopyranose **9** (5.0 g, 10.5 mmole) as starting material. MP = 190–192 °C. ^{1}H NMR ($CDCl_3$): δ 8.147.25(15H, m, H-Ar), 6.69 (1 H, s, H6endo), 6.12 (1 H, br.s, H3), 5.48 (1 H, br, s, H4). 5.16 (1 H, br,s, H1), 5.13 (1 H, br. s, H2), 5.5 (1 H, br. s, H5). ^{13}C NMR $CDCl_3$): δ 165.01, 164.86, 164.44 (C=O Bz), 133.83, 133.74,133.72, 130.00–102.34 (C-Ar), 102.34 (C1), 84.28 (C6), 76.34 (C5), 69.41 (C3), 67.89 (C4), 67.67 ($\underline{C}2$). FD-MS ($C_{27}H_{21}O_8Br$-H): *m/z* 473.3.

1,6-Anhydro-3-keto 4-bezoyl-β-D-mannopyranose 7 (0.78 g, 46.0%) as a yellow sirup, which was rapidly purified by column chromatography, with 1,6-anhydro-2,3-O-isopropylidene-4-benzoyl-β-D-mannopyranose **6** (2 g, 0.65 mmole) as starting material. ^{1}H ($CDCl_3$) δ 8.07-8.04 (2 H, d,d, $J_{1.12,1.34\,Hz}$, H-OBz); 7.63–7.60 (1 H, d,d, $J_{1.72,1.24\,Hz}$, H-OBz); 7.50–7.46 (2 H, d,d, $J_{7.65,1.67\,Hz}$, H-OBz); 5.72 (1 H, d, $J_{2.3\,Hz}$, 2.3 Hz, H1); 5.32(1 H, d, $J_{2.00\,Hz}$, H4); 5.10–5.08 (1 H, d,d, $J_{1.2,\ 2.0\,Hz}$, H5); 4.57 (1 H, d, $J_{2.2\,Hz}$, H2),

3.10–3.92 (1 H, d,d, $J_{1.1,\ 8.6\,Hz}$, H6-*exo*), 3.83–3.80 (1 H, d,d, $J_{5.7,\ 8.5\,Hz}$, H6, *endo*). ^{13}C ($CDC1_3$) δ 200.87 (C=O, C3); 165.06 (C=O, Bz); 134.09, 130.07, 128.74 (C-Ar); 103.93 (C1); 77.30, 76.94, 76.59 (C5, C2, C4), 65.69 (C6). EI-MS: *m/z* 142 (M-benzoic acid)$^+$, 121, 105, 77, 51; CI-MS: calculated for $C_{13}H_{13}O_6$ $[(M+H)^+]$ 265.0712, found 265.0712; 162, 147, 137, 120, 105.

Preparation of 1,6-anhydro-2,3-isopropylidene-β-D-mannopyranose 14

p-Toluene sulfonyl chloride (13.7 g, 72.2 mmole) in 20 ml of pyridine was added slowly to D-mannopyranose **12** (10 g, 44.6 mmole) in 100 ml of pyridine. The reaction mixture was stirred for 1 h at 0 °C-r.t. and then cooled before aqueous NaOH (2.3 g, 55.5 mmole) solution (10 ml) was added slowly. The reaction mixture was left stirring overnight then neutralized with HCl. The solvent was evaporated under reduced pressure, azeotroped with toluene (2 × 20 ml) and then extracted with ethanol. Evaporation of ethanol gave a light syrup which was dissolved in acetone (100 ml), before adding 2,2-dimethoxy propane (10 ml) and the reaction mixture was left overnight, neutralized with triethyl amine (7 ml) and evaporated to give a sirup which was crystallized with ethyl acetate to give **14** (4.2 g, 37%). MP = 161-163 °C. ^1H NMR ($CDC1_3$) δ 5.35 (1 H, d, $J_{2.9\,Hz}$, H1), 4.54 (1 H, d,d, $J_{1.4,\ 6.2\,Hz}$, H2), 4.22 (1 H, d,d $J_{1.0,5.1\,Hz}$, H6 *endo*), 4.10–4.07 (1 H, d,d, $J_{3.1,\ 6.2\,Hz}$, H5), 4.05–4.03 (1 H, d,d, $J_{1.1,\ 7.4\,Hz}$, H3), 3.96 (1 H, d, $J_{8.8\,Hz}$, H6-*exo*), 3.78 (1 H, t, $J_{6.8\,Hz}$, H4), 2.32 (1 H, br. s, 4-OH), 1.35, 1.33 (6 H, s, 2Me). ^{13}C NMR ($CDCl_3$): δ 110.22 (C-isopropy.), 99.53 (C1), 76.98 (C5), 75.80 (C4), 72.12 (C3), 69.48 (C2), 64.30 (C6), 25.95 (Me). EI-MS ($C_9H_{14}O_5$): M/Z 187.0 (M-CH_3), 127.0 ($C_2H_4O_2$), 100.0, 85.0. 59., 43.0.

Preparation of 1,6-anhydro-2,3-isopropylidene-4-benzoyl-β-D-mannopyranose 6

Benzoyl chloride (13.91 g, 9.89 mmole) in dichloromethane (100 ml) was added to 2,3-isopropylidene 1,6-anhydro-β-D-mannopyranose (20 g, 9.89 mmole) in pyridine (100 ml). The reaction mixture was refluxed overnight then cooled to r.t. before a saturated $NaCO_3$ (50 ml). The crude product was extracted with dichloromethane (250 ml), washed with water (3 × 50 ml) and dried over Na_2SO_4. Evaporation of dichloromethane under reduced pressure gave brown sirup which was crystallised with chloroform and methanol to give **6** (23.02 g, 76%). ^1H NMR ($CDC1_3$) δ ^1H NMR ($CDC1_3$) δ 8.10, 7.60, 7.46 (5 H, Ar); 5.43 (1 H, d, $J_{2.7\,Hz}$, H1); 5.27 (1 H, s, H2); 4.70 (1 H, d,d, $J_{1.4,\ 1.2\,Hz}$, H5); 4.30 (1 H, d, $J_{5.4\,Hz}$, H3); 4.17 (1 H, d,d, $J_{3.0,6.3\,Hz}$, H4); 4.12(1 H, d,d, $J_{6.6,\ 7.1\,Hz}$, H6*endo*); 3.83 (1 H, d,d, $J_{1.0,7.4\,Hz}$,

H6-*exo*). ^{13}C NMR ($CDCl_3$) δ 165.41 (C=O, Bz); 133.74, 129.85 (C, Ar); 129.36 (C- isopropy); 99.33 (C1); 73.85 (C3); 73.31 (C5); 72.20 (C2); 71.43 (C4); 64.65 (C6); 25.95, 25.86 (2 C-CH_3- isopropy).

X-Ray crystal structure analysis of 1,6-anhydro-2,3-isopropylidene-4-benzoyl-β-D-mannopyranose 6

Data were obtained using a FAST TV area detector diffractometer with graphite mononchromated Mo-Kα radiation (λ = 0.71069 Å), crystal system – orthorhombic. Crystal data: $C_{16}H_{18}O_6$, M_r=306.30, Unit cell dimensions: space group 2_1, $a = 6.3829(11)$ Å, $b = 10.689(3)$ Å, $c = 22.579(4)$ Å, $\gamma = 89.979(11)^\circ$, $V = 1540.4(6)$ Å^3, $Z = 4$, $D = 1.321$ MgM^{-3}, $T = 239(2)$ K, Absorption confinement = 0.101 mm^{-1}, crystal size 0.02 × 0.03 × 0.02 mm. Data were recorded within $-4 \leq h \leq 7^\circ$, $-4 \leq k \leq 11^\circ$, $-26 \leq 1 \leq 25^\circ$, giving 6502 measurements and 2386 unique (R_{int}=0.0603),. Refinement with 271 parameter gave R_1=0.0339, wR_2=0.0643 for 2386 data with $I > 2\sigma$ (0.0492, 0.0668 respectively for all data) Goodness-Of-Fit on F^2=0.812. Carbon and oxygen atoms were refined anisotropically. Hydrogens were inserted in idealized positions with U_{iso}-values.

Preparation of 1,6-anhydro-2,4-dibenzoly-β-D-glucopyranose 18 and 1,6-anhydro-2,3,4-tribenzoly-β-D-glucopyranose 19

Benzoyl chloride (2.674 g, 19.02 mmole) in dichloromethane (20 ml) was added to 1,6-anhydro-β-D-glucoyranose **1** (1.5 g, 19.02 mmole) in pyridine (10 ml). The reaction mixture was refluxed overnight then cooled to r.t. before saturated $NaCO_3$ (2 × 5 ml) was added. The crude product was extracted with dichloromethane (20 ml), washed with water (3 × 15 ml) and dried over Na_2SO_4. Evaporation of dichloromethane under reduced pressure gave a brown sirup which was subjected to crystallization with chloroform and methanol to give **18** (2.15 g, 7.36%) and **19** (0.38 g, 12.5%) after purified by column chromatography. **18**: ^{1}H NMR ($CDCl_3$) δ 8.05–8.10 (4 H, m, H-Bz), 7.66–7.58 (3 H, m, H-Bz), 7.45–7.38 (4 H, m, H-Bz), 5.72 (1 H, s, H1), 5.06 (1 H, s, H3). 4.93 (1 H, s, H5), 4.86–4.80 (1 H, d, J5.2 Hz, H2), 4.38–4.00 (1 H, d, J7.02, H4), 4.10 (1 H, s, H6endo), 3.90–3.85 (1 H, d,d, J2.10, 5.20 Hz, H6-*exo*). ^{13}C NMR ($CDCl_3$) δ 166.09 (C=O, Bz); 129.7, 128.3, 133.81 (C-Ar); 101.33 (C1); 73.17, 73.50, 72.11 (C5, C2, C4), 65.10 (C3), 68.02 (C6). **19**: ^{1}H NMR ($CDCl_3$) δ 8.18-8.07 (4 H, m, H-Bz), 7.66–7.58 (3 H, m, H-Bz), 7.51–7.40 (4 H, m, H-Bz), 5.73 (1 H, s, H1), 5.45 (1 H, s, H2). 5.44 (1 H, s, H2), 4.43 (1 H, s, H4), 5.10 (1 H, d, J0.56 Hz, H5), 4.40–4.38 (1 H, d, J7.7 Hz, H6endo), 3.99–3.98 (1 H, d,d, J6.79, 5.71 Hz, H6-*exo*). ^{13}C NMR ($CDCl_3$) δ 165.32, 165.08, 164.68 (C=O-Bz), 133.67,

133.56, 133.54 (C-Ar), 130.02–128.44 (CH-Ar), 99.47 (C1), 73.83 (C5), 70.19 (C4), 69.81 (C2), 69.11 (C3), 65.53 (C6).

Preparation of 1,6-anhydro-2,4-dibenzoly 3-keto-β-D-glucopyranose 20

Pyridinium chlorochromate (PCC) (0.582 g, 2.7 mmol) was added to 1,6-anhydro-2.3-dibenzoyl-β-D-glucopyranose **18** (0.5 g, 1.35 mmol) in dry dichloromethane (20 ml). The reaction mixture was stirred overnight at r.t., before being filtered off and washed with 3×15 ml CH_2Cl_2. The solvent was then removed under reduced pressure. The crude product was then purified by column chromatography to give **20** (0.368 g, 72%). ^{1}H NMR ($CDCl_3$) δ 8.09–8.1 (4 H, d, J8.02 H-Bz), 7.61–7.57 (2 H, t, J7.67, 7.21, H-Bz), 7.45–7.41 (4 H, d,d, J1.41, 7.51 Hz, H-Bz), 5.85 (1 H,s, H1), 5.48 (1 H, s, H2). 5.43 (1 H, s, H2), 4.98 (1 H, d, J5.11 Hz, H5). 4.31 (1 H, d, J8.05 Hz, H6endo), 4.28–3.99 (1 H, d,d, J2.41, 5.17 Hz, H6-*exo*). ^{13}C NMR ($CDCl_3$) δ 201.65 (C=O, C3); 166.09 (C=O, Bz); 133.1, 130.2, 128.7 (3 C, C-Ar); 102.21 (C1); 78.17, 75.58, 76.21 (C5, C2, C4), 66.03 (C6).

Results and discussion

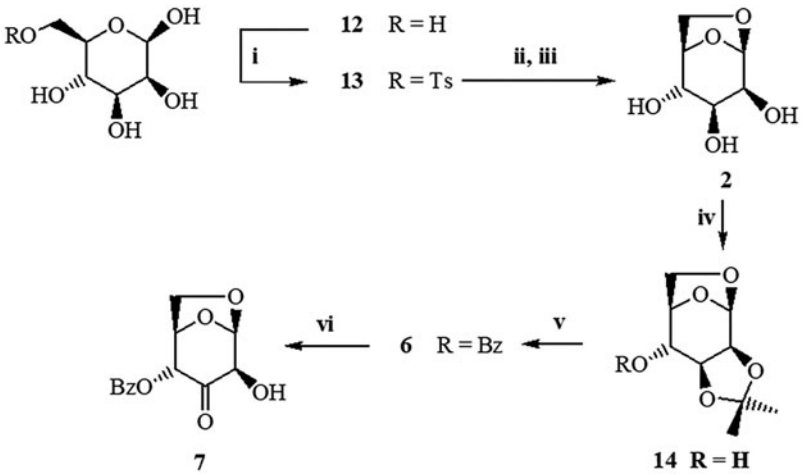
Synthesis of 3-keto mannosan derivative 7

The irradiation of a stoichiometric mixture of 2,3,4-triacetyl (**8**)/tribenzoyl (**9**)-1,6-anhydro-β-D-glucopyranose and bromine or N-bromo succinimide in carbon tetrachloride gave the corresponding bromo-compounds **10** and **11**, respectively (Sch. 1). The stereospecific photobromination at C6-*exo* proton of 1,6-anhydro-β-D-*hexo* glycopyranoses is due to the fact that the *axial* proton is more reactive than the equatorial proton. Ring protons in 1,6-Anhydro-β-D-glucopyranose **1** (H2, H3 and H4) are *equatorial* and thus are less reactive than the *axial* counterparts. Furthermore, the bridge-head protons (H1 and H5) are not reactive. In addition, H2, H3 and H4 protons in 1,6-anhydro sugars are deactivated by the *geminal* acetyl and benzoyl groups. In the case of 1,6-anhydro-β-D-mannopyranose **2** and 1,6-anhydro-β-D-galactopyranose **3**, each has an *axial* proton at C2 and C4,

Scheme 1. (i) Br_2 (or NBS), CCl_4, λ, 200 W, 30 min.

respectively. These protons are still deactivated by the acetyl or benzoyl protecting group, leaving the H6-*exo* proton only to undergo stereospecific photobromination.

However, photobromination of 2,3-isopropylidene-4-benzoyl-1,6-anhydro-β-D-mannopyranose **6** gave 1,6-anhydro-3-keto-4-benzoyl-β-D-mannopyranose **7**, as an unstable compound (Sch. 2). The synthesis of compound **7** started with the preparation of 2,3-isopropylidene-1,6-anhydro-β-D-mannopyranose **6** by a two-step, one-pot reaction (Sch. 2). The first step included the formation of 6-tosyl mannose, **13**, which gave 1,6-anhydro-2,3-isopropylidene-β-D-mannopyranose, **14**, after treatment with sodium hydroxide and then trimethyl orthoformate. Benzoylation of isopropylidene mannosan **14** with benzoyl chloride in dichloromethane gave 4-benzoyl-2-3-isopropylidene-1,6-anhydromannosan **6** in 78% yield.

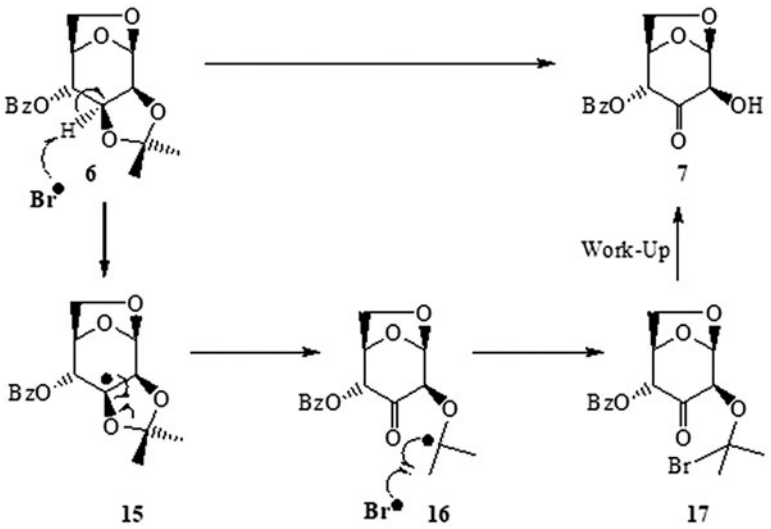


Scheme 2. (i) TsCl, Pyr, 0 °C-r.t.; (ii) aq. NaOH, 0 °C-r.t. overnight; (iii) aq. HCl; (iv) 2,2-dimethoxy propane, acetone (yield = 37%), (v) BzCl, K-^{t}Butoxide, CH_2Cl_2 (yield = 78%), (vi) Br_2, CCl_4, λ, 200 W, 30 min (yield = 46.0%).

The photobromination reaction of compound **6** was repeated three times. In the first, ketomannose compound **7** was obtained after flash silica purification in a solid-state; however, it decomposed within approximately 30 minutes. In the second run, close monitoring of the purified white powder compound **7** indicated that the decomposition started within approximately 10 minutes and became dark brown-syrup-like and dark solid substance(s) within two hours. In the third run, the ketomannose compound **7** was kept in the organic solvents (diethyl ether and petroleum ether) used for chromatography or chloroform-d to run spectroscopies. In addition, several organic solvents, including carbon tetrachloride, ethylacetate, and diethyl ether were used to test the stability of ketomannose

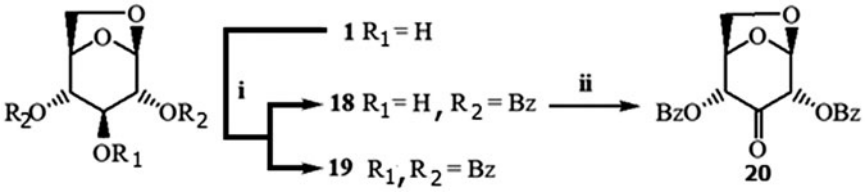
compound **7**. The results indicated that it was stable to certain extent, for no longer than three weeks in the above organic solvents.

The triacetyl and tribenzoyl 1,6-anhydropyrinosides are often selectively photobrominated at the C-6 *exo* proton, but the presence of an isopropylidene group in 1,6-anhydromannosan **6** showed equatorial H3 is preferentially abstracted and not the *axial* H2 or H6-*exo*. The reaction for the formation of 4-benzoyl-1,6-anhydro-3-keto-β-D-mannopyranose **7** may suggest a mechanism that the radical abstraction took place at H3, forming the intermediate radical, **15** which rapidly cleaved off the O-C bond of isopropylidene group, forming the tertiary radical intermediate **16**. Then, compound **16** reacted with bromine radicals to give compound **17**. Hydrolysis of the ketobromo compound **17** during the aqueous work-up leads to the cleavage of the isopropylidene group (Sch. 3) giving the keto-mannosan 4-benzoylate compound **7**. It may be possible that compound **7** underwent β-elimination and subsequent decomposition.



Scheme 3. The reaction mechanism for the formation of keto mannosan 7.

In addition, the benzoylation of 1,6-anhydro-β-D-glucopyranose **1** with 2 equivalents of benzoyl chloride gave 2,4-dibenzoly-1,6-anhydro-glucopyranose **18** as a major product. The benzoylation occurred at the C-2 and C-4 positions, as the hydroxyl groups at these positions are more reactive than the counterpart at C-3. 2,4-Dibenzoyl-1,6-anhydro-β-D-glucopyranose **18** was then oxidized with pyridinium chlorochromate (PCC) or potassium permanganate[10] to yield 2,4-dibenzoyl-3-keto-1,6-anhydro β-D-glucopyranose **19** in 72% or 29% yield (Sch. 4).



Scheme 4. (i) BzCl (1.6equ), K-tButoxide, CH2Cl2 (yield of 18 = 70.36% and 19 = 12.48%); (ii) PCC, CH2Cl2, r.t. (yield = 72%)

Molecular structure analysis of keto mannopyranose 7

The ^{1}H-NMR spectrum of 3-keto-4-benzoyl-β-D-mannopyranose **7** showed three doublets at the resonances of 5.72, 5.31 and 4.57 ppm with coupling constants of 2.3, 2.0 and 2.2 Hz, which were respectively assigned as H1, H4 and H2. These three doublets exist only if the carbonyl is at C3, as each has one *vicinal* neighbor proton only. It is unlikely that these splitting results are from long-range coupling. The magnitude of the long-range coupling for H2 and H4 in 1,6-anhydro-levoglucosan is 1.1 Hz.[11] Furthermore, Table 1 shows close chemical shift values between the two 3-keto-1,6-anhydro-β-D-glycopyranose derivatives **7** and **20** for H1, H4, H5 and H6 *endo*. In addition, ^{13}C-NMR spectrum of 3-keto-4-benzoyl-1,6-anhydro-β-D-mannopyranose **7** showed two off resonance singlets at δ 200.87 and δ 165.06 for C=O (C3) and C=O (Bz), respectively, which are both similar to the shift value of the corresponding single carbon [C=O of C3: δ 201.65 and C=O of Bz: δ 166.09)] of 1,6-anhydro-2,4-dibenzoly-3-keto-β-D-glucopyranose **20**. Furthermore, the accurate mass spectrum of the mannosan derivative **7** gave a value of 265.0712, corresponding to $(C_{13}H_{12}O_6+H)^+$}.

Table 1. The Chemical shift (ppm) of the related 1,6-anhydrosugars.

1,6-Anhydrosugar	HI	H2	H3	H4	H5	H6-*Exo*	H6-*Endo*
2,3-Isopropylidene-4-benzoyl-mannosan **6**	5.43, d $J_{2.7Hz}$	4.17, d,d $J_{6.3.3.0HZ}$	4.30, d $J_{5.4Hz}$	5.27, s	4.70, d, $J_{1.4.1.2Hz}$	4.12, d,d, $J_{1.0,7.4Hz}$	3.83, d,d, $J_{7.1,6.6Hz}$
4-Benzoyl-3-ketomannosan **7**	5.72, d, $J_{2.3HZ}$	4.57, d, $J_{2.2Hz}$	–	5.32, d,d, $J_{2.2Hz}$	5.09, d,d, $J_{1.2,5.6Hz}$	3.82, d,d, $J_{1.1,8.6Hz}$	3.93, d,d, $J_{5.7,\ 8.5Hz}$
2,4-Dibenzoyl-3-ketolevoglucosan **20**	5.85, s	5.43, s	–	5.48, s	4.99, d, $J_{5.1Hz}$	4.30, d, $J_{8.1Hz}$	4.00, d,d, $J_{5.1.\ 8.1Hz}$

Molecular modeling of five-member rings in compound 6

Molecular modeling studies were based on the X-ray diffraction structure of compound **6** (Fig. 2) at which the molecular geometry was optimized under GAMESS using A 3-21 G basis set and the resultant low energy structure was studied with CHEM-X.[12,13] In this respect, the molecular geometry of the five-member rings was also based on the X-ray diffraction

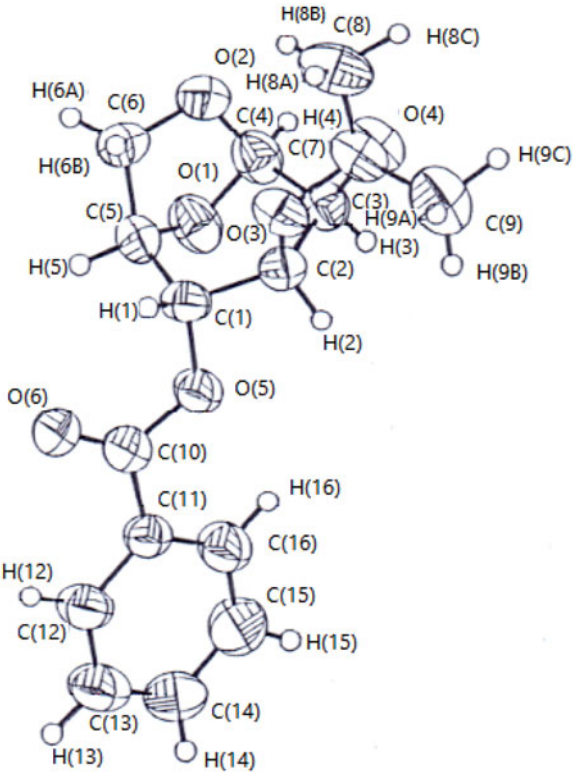


Figure 2. X-ray crystal structure of 4-benzoyl-2,3-isopropylidene-1,6-anhydromannosan **6**.

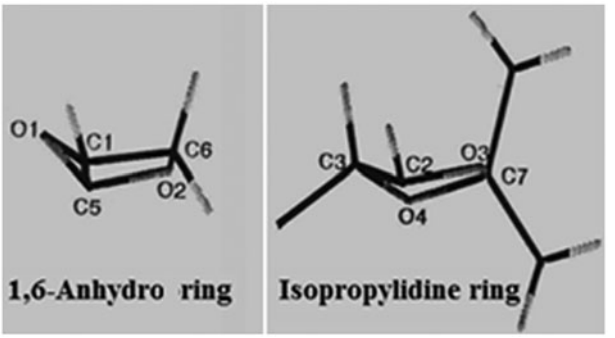


Figure 3. Envelope conformations of optimized five rings of 4-benzoyl-2.3-isopropylidene-1,6-anhydromannosan **6**.

data of compound **6**. The results showed conformational differences between the two five-member rings (Fig. 3).

Both the isopropylidene and 1,6-anhydro ring adopt an envelope conformation,[14] although not with the same atom out of the plane (isopropylidene ring q_2=0.327 Å, ϕ_2=103°; 1,6-anhydro ring q_2=0.384 Å, ϕ_2=356°; Fig. 3). According to the crystallographic structure of **6**, the isopropylidene ring adopts a different conformation, namely a twist (isopropylidene ring

q_2 = 0.304, Å, ϕ_2=86°; 1,6-anhydro ring q_2=0.405 Å, ϕ_2=357°). The twist conformation is most likely due to crystal packing forces. This is, however, unlikely to have a great effect on the H2, H6-*exo* and H3 protons, as all are freely available for reaction and the oxygen atoms in the ring are unlikely to undergo any stereoelectronic effect. The equatorial H3 proton is most likely abstracted, due to the proximity of the benzoyl group, which is three bonds away from H3 and four bonds away from H2 and H6-*exo*.

Conclusion

This article was focused on the identification of the chemical structure of the unstable 1,6-anhydro-3-keto-4-benzoyl-β-D-mannopyranose **7**. Although molecular geometry results showed conformational differences between the five-member rings, further study is required to find the transition states using quantum software, such as Gaussian or Jaguar.

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