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Improved synthesis of per-*O*-acetylated C1 hydroxyglycopyranose and structural study as non-covalent organic framework

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ABSTRACT

An improved method for the synthesis of per-*O*-acetylated C-1-hydroxyglycopyranose was developed by hydrolysis of per-*O*-acetylated glycopyranosyl α-chlorides derived from sugars with C-2 axial acetates for example L-rhamnose and D-mannose. 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranose crystallized in tetragonal space group I4, a rare phenomenon in carbohydrate literature. The three dimensional packing of the molecule with the help of regular hydrogen bond and C–H···O interactions resulted in the formation of porous framework showing channels with pore size 7 Å.

Bacterial cell surface carbohydrate antigens are involved in host defense immunity against infections. The complex microheterogeneous structures of oligosaccharides and their very low availability in nature pose insurmountable problems in the structure–function correlations of carbohydrates. Chemical synthesis of oligosaccharides is a powerful tool in this regard. Stereo- and regioselective synthesis of structurally well defined oligosaccharides has indeed gained significant attention in recent years. Among the chemical methods for glycosidation, the procedure involving glycosyl trichloroacetimidate, introduced by Schmidt,[1,2] is highly efficient and widely employed. Protected glycosyl trichloroacetimidates are synthesized from per-*O*-acetylated C-1-hydroxyglycopyranoses. L-Rhamnose (Rha) is a 6-deoxyhexose frequently found on the cell surface of pathogenic bacteria for example *Mycobacterium tuberculosis*.[3] L-Rhamnose has similar structure as that of mannose except being mirror image of each other and unlike D-mannose, L-rhamnose is a 6-deoxyhexose. Chemical synthesis of L-rhamnose containing oligosaccharides and glycoconjugates is important in the area of chemical biology for the development of sugar containing pathologically important biomolecules. 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranose (**4**) is an important intermediate for the chemical synthesis of biologically important L-rhamnose containing glycans and glycoconjugates.[4] The conventional methods for the synthesis of per-*O*-acetylated C-1-hydroxyglycopyranoses involve the hydrolysis of glycosyl bromides in the presence of silver salts,[5] selective deacetylation of glycosyl C1-*O*-acetates,[6] hydrolysis of *O*-glycosides,[7] and thioglycosides.[8] Most of the methods are not sufficient for large scale synthesis of per-*O*-acetylated C1-hydroxyl glycopyranoses as they involve the use of expensive reagents (e.g., silver salts)[5] or laborious purification process (column chromatography). The development of simple and efficient method for the large scale preparation of per-*O*-acetylated C-1-hydroxyglycopyranoses would be a valuable contribution in the area of chemical synthesis of oligosaccharides and glycoconjugates containing biologically important sugars like L-rhamnose and D-mannose.

The synthesis of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranose (**4**) started with per-*O*-acetylation of L-rhamnose (**1**) followed by conversion of anomeric acetate (**2**) to α-chloride (**3**) using thionyl chloride in the presence of pre-catalyst bismuth oxychloride.[9] 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl chloride (**3**) was hydrolized in a mixture of acetone and water (2:1) at 60 °C. After complete conversion of the starting material as monitored by TLC, aqueous work-up of the reaction mixture gave the desired compound **4** in 92% yield (Scheme 1). Based on the good agreement between its physical and spectral data obtained and those reported in the literature, product **4** was unambiguously characterized as

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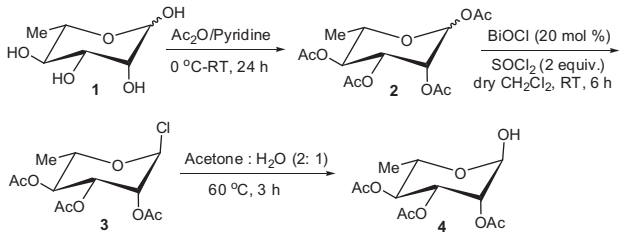


Scheme 1. Synthesis of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranose.

2,3,4-tri-*O*-acetyl-L-rhamnopyranose that exists predominantly as the α-anomer.[10, 22]

The stereoselective formation of compound **4** only as α-anomer can be explained due to anchimeric assistance of the neighboring axial C-2 acetate group during hydrolysis of the α-chloride. To explore the generality of this methodology for the synthesis of per-*O*-acetylated C-1-hydroxyglycopyranoses with the C-2 axial acetate group 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl chloride[9] was reacted under identical condition (Scheme 2). This also resulted in the complete conversion of the chloride (**7**) to 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranose (**8**)[11] as the only product in 91% yield.[22]

Efforts to use the same methodology for other sugars like D-glucose, 2-deoxy-2-acetamido-D-glucopyranose, D-arabinose, and L-arabinose resulted in a mixture of α and β isomers of the per-*O*-acetylated C-1-hydroxyglycopyranoses with slower rate of hydrolysis of the α-chlorides. This observation supported the importance of the C-2 axial acetate group for the rapid hydrolysis of α-chloride and formation of single isomer as the product. In case of D-mannose and L-rhamnose the neighboring group participation involving the axial C2 acetate group during hydrolysis of the anomeric α-chloride facilitate the formation of a more stable (due to anomeric effect) α isomer of the C1 hydroxyl derivative (Scheme 3). Similar neighboring group participation is not possible in D-glucose and other glycopyranoses, where a mixture of isomers is formed as the product with a relatively slow rate of hydrolysis.

Interestingly, a survey of the literature revealed no report on the crystal structure of any per-*O*-acetylated C-1 hydroxy sugars. Single crystals of compound **4** suitable for an X-ray study were obtained by recrystallizing from a mixture of ethyl acetate and hexane at about 10 °C by the slow evaporation method. The structure of **4** was solved in the *tetragonal* space group *I4*, a rare phenomenon in carbohydrate literature (Fig. 1). All the C–C bond lengths are close to 1.54 Å, in good agreement with the observed sugar derivatives.[12] The ring C1–O5 bond length (1.418 Å) in compound **4** is shorter than that of C5–O5 (1.437 Å). The shortening may be attributed to the delocalization of oxygen lone pair of electrons into the anti bonding orbital of the C1–O5 bond. The *O*-glycosidic torsion angle (*Φ*), H1–C1–O1–H(O1), is found to be 40.5° pointing out near the *gauche* orientation of hydroxyl hydrogen with respect to the anomeric hydrogen atom.

The profound significance of this conformation became evident while analyzing the hydrogen bonding network in the molecule. As shown in Table 1, only a single regular hydrogen bond involving anomeric oxygen as the donor and carbonyl oxygen atom (O7) of the C3 acetoxy moiety is observed (Fig. 2).

In addition to conventional hydrogen bonds, weak interactions like C–H···O interactions have gained enormous importance in the recent literature for their involvement in deciding the structure and activity of biomolecules which is useful in the area of medicinal chemistry.[13] Meticulous analysis of the molecular packing unraveled five distinct and fairly strong C-H···O interactions, listed in Table 1 and depicted in Figure 1.

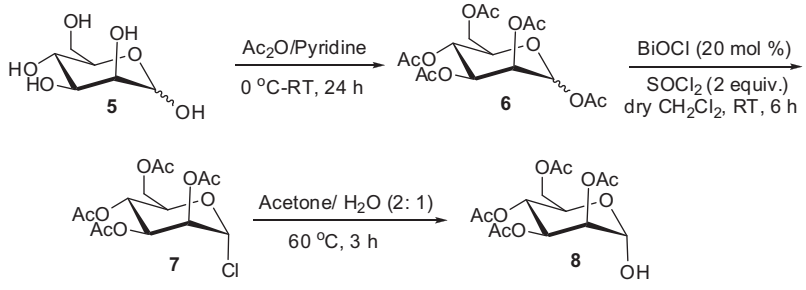
The regular hydrogen bond (O1–H1 ···O7) interconnects four molecules of compound **4** related through four fold rotation symmetry forming a *crystallographic synthon*, which is further stabilized by two C–H···O interactions (C1–H1′···O6 and C10–H10A···O5) as depicted in Figure 3.

As each molecule of **4** is endowed with a valency of twelve, two of which are of the regular hydrogen bonding type and the rest ten owing to C–H···O interactions, the *crystallographic synthon* consisting of four molecules derives a gigantic valency of 48, half of which are satisfied by mutual interactions among these while the remaining valency of 24 are available to expand the network in three dimension (Fig. 4).

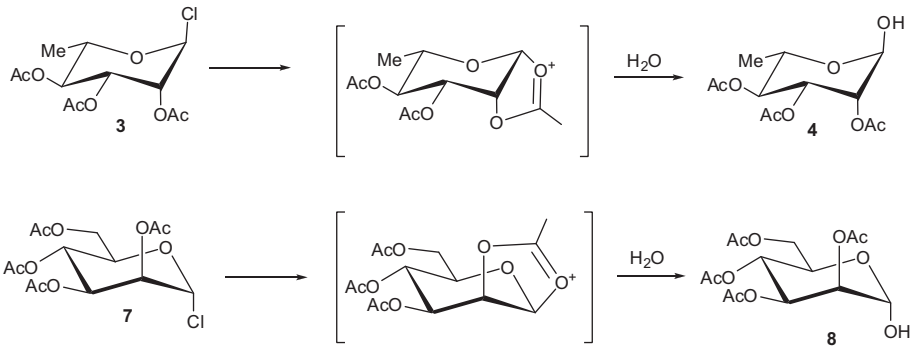
These large valencies of 24 through C–H···O interactions enable the tetramer *crystallographic synthon* to expand the network indefinitely in three dimensions. The result of this expansion is the exquisite molecular assembly (Fig. 5) consisting of channels of 7 Å diameter with a polar interior, formed by criss-crossing of molecular backbone in which the nonpolar acetyl groups are grouped together leading to hydrophobic patches.

To the best of our knowledge, the unique molecular packing observed in the present work is hitherto unknown in the area of carbohydrate crystallography.

Elucidation of the correlation between the complex structures of cell surface glyconjugates and their myriad biological functions is a challenging problem in glycobiology. X-ray crystallographic investigation undertaken during the present study has unraveled a unique molecular assembly driven by a combination of one regular hydrogen bond and five C–H···O interactions in the crystal structure of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranose (**4**). The occurrence of channels of 7 Å diameters in the crystal of compound **4** is a rather rare phenomenon in the realm of small organic molecules. Unlike conventional inorganic porous materials for example zeolite,[14] porous organic–inorganic hybrid materials such as metal organic frameworks (MOFs)[15] and covalent organic frameworks (COFs);[16,17] stabilized by non-covalent interactions have scope for targeted application because their constituent building blocks can be readily diversified using simple organic transformation.[18] Such compounds have scope for application in the area of



Scheme 2. Synthesis of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranose.



Scheme 3. Plausible mechanism for hydrolysis of α-chlorides involving the neighboring group participation.

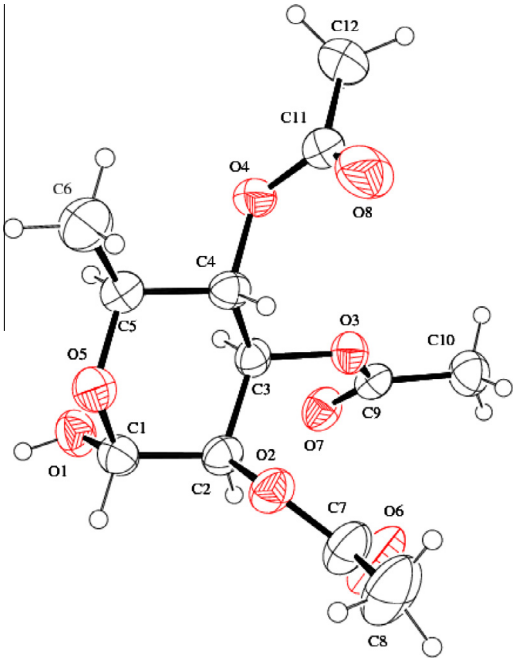


Figure 1. ORTEP diagram of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranose.

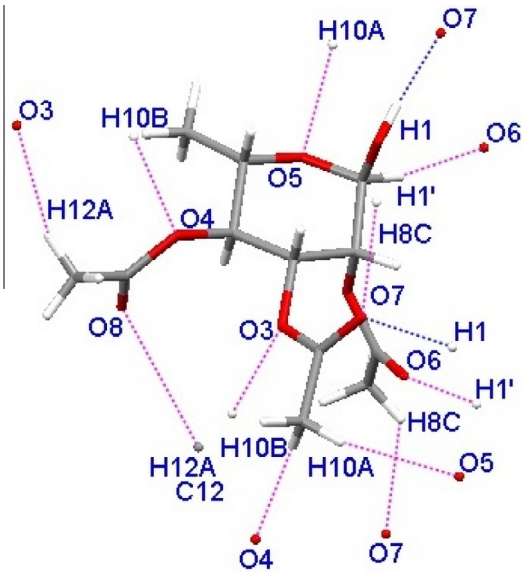


Figure 2. Non-covalent interactions (H-bonds and C–H···O interactions) in molecule **4**.

Table 1
Bond parameters of H-bond and C–H···O interactions.

H-bond		
D–H···A	D–A (Å)	Angle D–H···A (°)
O1–H1···O7	2.811	164.3
C–H···O interactions		
D–H···A	D–A (Å)	Angle D–H···A (°)
C1–H1′···O6	3.603	167.6
C8–H8C···O7	3.359	127.8
C10–H10B···O4	3.526	161.7
C10–H10A···O5	3.348	151.4
C12–H12A···O3	3.507	142.4

emerging technologies like heterogeneous catalysis, separation, adsorption, and storage of gas molecules and molecular recognition.[19–21] This present study using X-ray crystallography emphasized the importance of non-covalent interactions for the arrangement of complex organic molecules like carbohydrates to highly ordered structure like porous organic framework.

Thus the methodology of hydrolysis of per-*O*-acetylated glycopyranosyl-α-chloride with the C-2 axial acetate group will be useful for large scale synthesis of per-*O*-acetylated glycopyranosyl C-1

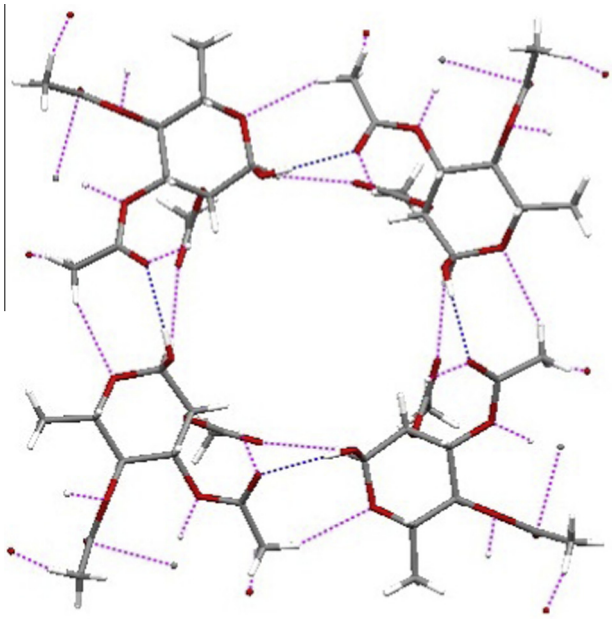


Figure 3. Tetramer *crystalographic synthon* of compound **4** (related by four fold rotation) formed by non-covalent interactions (H-bonds and C–H···O interactions).

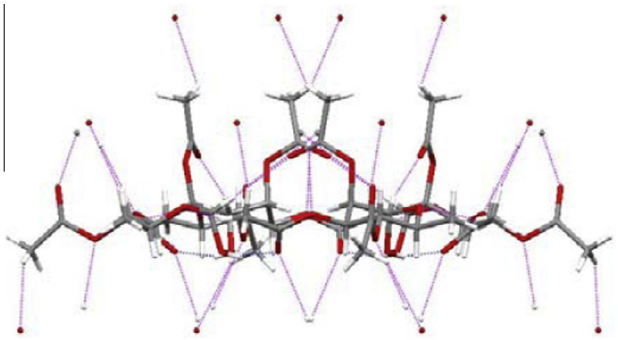


Figure 4. Multivalent non-covalent interactions (H-bonds and C–H···O interactions) in tetramer *crystallographic synthon* of molecule **4**.

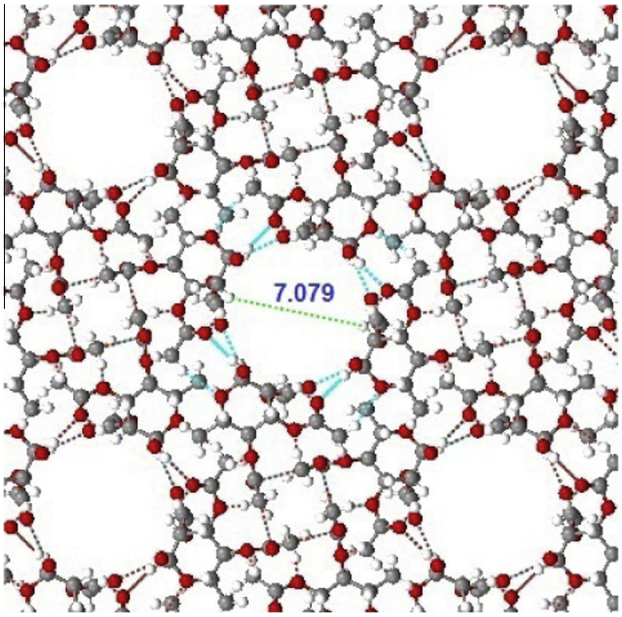


Figure 5. Porous Non-covalent organic framework of compound **4** formed by H-bonds and C–H···O interactions.

hydroxyl derivatives of therapeutically important sugars like L-rhamnose and D-mannose. The application of the synthesized per-*O*-acetylated glycopyranosyl C-1 hydroxyl derivatives in the synthesis of complex glycoconjugates is yet to be explored. Whereas the X-ray crystallographic study of the L-rhamnose derived compound (**4**) has enhanced the scope for the use of bio-molecules like carbohydrates for the design and synthesis of bio-degradable synthetic porous materials.

Acknowledgments

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X-ray crystallographic data: Complete crystallographic data for the structural analysis of compound **4** have been deposited with the Cambridge Crystallographic Data Centre, CCDC deposition number CCDC 936988.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.130.

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22. *General method for the synthesis of per-O-acetylated C-1- hydroxyglycopyranoses:* Per-*O*-acetylated glycopyranosyl α-chloride (5 mmol) was dissolved in acetone (20 mL) and to the stirred solution, water (10 mL) was added. The mixture was stirred at 60 °C until TLC (using ethylacetate and hexane 2:3) showed disappearance of the starting material. After completion of the reaction acetone was removed by applying vacuum. The compound was extracted with ethyl acetate (100 mL) and washed with water (20 mL × 2), followed by brine solution (20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness to give the desired compounds.
*2,3,4-Tri-O-acetyl-α-L-rhamnopyranose (**4**):* colorless solid, mp 89–90 °C; $[\alpha]_D$ −25.8° (*c* = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.37 (dd, 1H, *J* = 10 & 3.2 Hz, H-3), 5.28–5.27 (m, 1H, H-2), 5.17–5.16 (m, 1H, H-1), 5.08 (t, 1H, *J* = 10.0 Hz, H-4), 4.13–4.11 (m, 1H, H-5), 3.17 (d, 1H, *J* = 3.6 Hz, C1–OH), 2.16, 2.06, 2.00 (s, 9H, 3× –$COCH_3$), 1.22 (d, 3H, *J* = 6.4 Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 170.2 (2×), 92.2 (C-1), 71.2, 70.3, 68.9, 66.5, 21.0, 20.9, 20.8 (3× –$COCH_3$), 17.6 (–CH_3) ppm.
*2,3,4,6-Tetra-O-acetyl-α-D-mannopyranose (**8**):* colorless solid, mp 85-86 °C; $[\alpha]_D$ +24.0° (*c* = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.43 (dd, 1H, *J* = 10.1 & 3.4 Hz, H-3), 5.36–5.22 (m, 3H, H-1, H-2 & H-4), 4.30–4.10 (m, 3H, H-5, H-6a & H-6b), 3.42 (d, 1H, *J* = 4.2 Hz, C1–OH), 2.17, 2.11, 2.06, 2.01 (s, 12H, 4× –$COCH_3$) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0, 169.4, 169.2, 169.0 (4× –$COCH_3$), 91.5 (C-1), 69.2, 68.0, 67.8, 65.5, 61.8, 20.1, 20.0, 19.9, 19.8 (4× –$COCH_3$) ppm.