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A Short Route for Large-Scale Synthesis of Per-*O*-acetylated *C*-1 Hydroxyglycopyranose

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A short route for large scale synthesis of *C*-1 hydroxypyranose was developed starting from L-rhamnose and D-mannose. The selective hydrolysis at anomeric carbon was carried out in the presence of catalytic amount of zinc. In the current paper, X-ray crystallographic studies of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranose was also exploited, which crystallizes in tetragonal space group *I*4 along with three water molecules in asymmetric unit.

Keywords: Nucleosides, Glycosylation, *O*-Deacetylated, Oligosaccharides, Hydroxyglucopyranoses, L-Rhamnose, D-Mannose.

INTRODUCTION

The development of practical and efficient route for the synthesis of drug-like small molecules is of considerable interest to medicinal chemists and chemical biologists[1-5]. 2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranose and 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranose are considered as the versatile synthetic intermediate for the synthesis of *C*-and *O*-nucleosides and other biologically active molecules[6-8]. They also serve as the key building blocks in the synthesis of optically active natural products and glycosides as well as the glycosyl donors and acceptors[9-11].

Selective deprotection at anomeric carbon is often a key step in glycosylation reactions in carbohydrate chemistry[12]. Among the chemical methods for the selective deprotection of anomeric acetates of pyranoses, the procedure involving glycosyl trichloroacetimidate is highly efficient and widely employed[13]. In an attempt to deacetylate anomeric acetate, potassium and ammonium carbonate was used but yields in more by-products[14]. Imidazole[15] and piperidine[16] was also used for the synthesis of per *O*-deacetylated rhamnose and mannose, but longer reaction time and harsh reaction conditions fails to get the desired products in good yields. Over the years, numerous basic reagents such as 1,2-diaminoethane[17], phenylmethanamine[18] and tributyltin alkoxides[19] were used but due to tedious workup and toxic reagents, the methods were not suitable for large scale synthesis. In view of the importance of anomeric deprotected sugars and their derivates in the synthesis of oligosaccharides and natural products and in continuation to our interest in its chemistry a simple, less toxic and user-friendly reaction protocol for the synthesis is highly desirable.

EXPERIMENTAL

General procedure for the synthesis of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranose (3) and 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranose (6): To a suspension of L-rhamnose/D-mannose (10.00 g) in acetic anhydride (7.0 mol equiv) was added 1 g of 33 wt % HBr/acetic acid at room temperature. The temperature of the reaction mixture was maintained at room temperature by adding ice occasionally in the water bath. Stirring was continued for 3 h during which time the suspended solid went into solution. This solution was then treated with an additional 9.5 g of 33 wt % HBr/acetic acid and the resulting solution was stirred overnight at room temperature. Anhydrous sodium acetate (8.0 g) was then added to neutralize the excess HBr. The resulting mixture was dried under *vacuo* and to the syrup obtained was added $CuSO_4.5H_2O$ (0.5 g) and zinc (2.0 g) in a solution of water (50 mL) and acetic acid (50 mL). The resultant reaction mixture was stirred vigorously using mechanical stirrer at room temperature for 3 h. The solid was then removed by filtration and washed with ethyl acetate (500 mL) and water (200 mL). The organic layer of the filtrate was washed with saturated aqueous $NaHCO_3$ then with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranose (**3**) (90 % yield) and 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranose (**6**) (87 % yield) as colorless syrups.

RESULTS AND DISCUSSION

The structures of the synthesized compounds were identified by nuclear magnetic resonance (^{1}H NMR (500.133 MHz) and ^{13}C NMR (125.75 MHz) analyses in $CDCl_3$ with TMS as internal standard. Infrared analysis (Perkin Elmer spectrum BX FT-IR spectrometer) and mass spectra were recorded on a Jeol JMS-700 mass spectrometer. Chromatographic data of compounds **3** and **6** are in accordance with the literature data[20,21].

The compound **3** was recrystallized by slow evaporation in toluene-ethylacetate (3:1) mixture to get the crystals suitable for X-ray crystallography (Fig. 1).

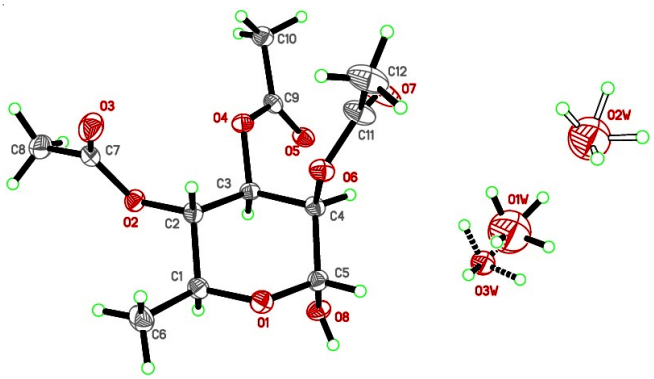
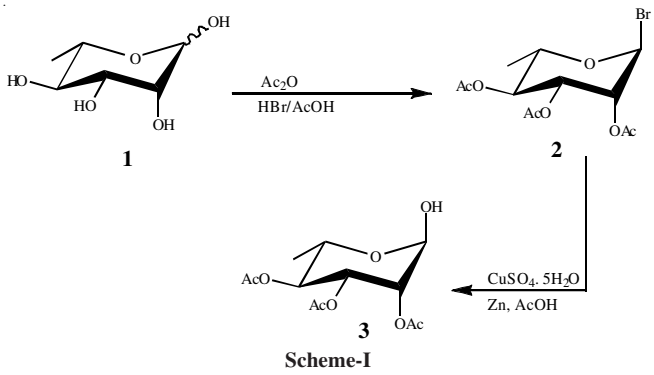


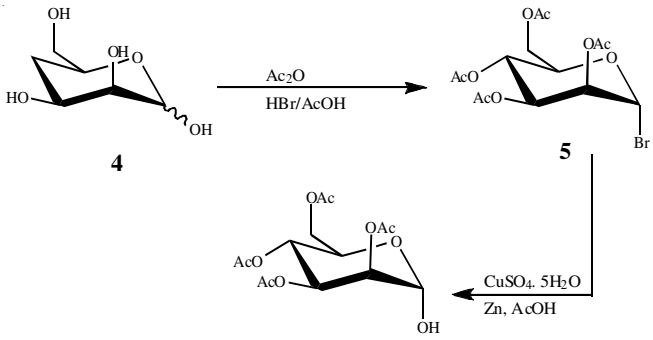
Fig. 1. Molecular structure of the title compound **3** with atom labelling scheme drawn at 30 % probability displacement elliposids

We report herein a very efficient protocol for the large scale synthesis of *C*-1-hydroxyglycopyranoses. L-Rhamnose (**Scheme-I**) and D-mannose (**Scheme-II**) were selected because both are mirror images of each other except that former is a 6-deoxyhexose. Typical procedure starts with the formation of per acetylated products using excess of acetic anhydride followed by the replacement of anomeric acetate with halide in the presence of HBr/acetic acid to form anomeric peracetyl-glycosyl bromides[22]. Hydrolysis of glycosyl bromides was carried out in the presence of catalytic amount of zinc and copper sulfate pentahydrate in acetic acid. In the formation of compound **3** (**Scheme-I**) only α anomer was obtained which could be explained due to the anchimeric assistance or the neighboring group participation of *C*-2 axial acetate. High yield were obtained in the stereoselective synthesis of **6** (**Scheme-II**) but mixture of α/β was obtained when glucose and galactose were used under the same reaction conditions. It is noteworthy to mention that overhead mechanical stirring was vital in this reaction because no products were obtained under magnetic stirring. Thus, it is believed that the reaction required vigorous stirring therefore; mechanical stirring strongly promotes the formation of desired products in high yields.

X-Ray crystallographic study of compound 3: The ORTEP diagram of the title compound **3** with atom labeling scheme drawn at 30 % probability displacement ellipsoids is depicted in Fig. 1. The compound crystallizes in tetragonal space group *I*4, with a, b = 19.8444 (6) Å, c = 8.0598 Å, α = β = γ = 90°, V = 3174 (2) Å^3 and *Z* = 8. The asymmetric unit of the title compound contains one 4,5-*bis*(acetyloxy)-6-hydroxy-2-methyloxan-3-yl acetate and three water molecules (Fig. 1).



Scheme-I



Scheme-II

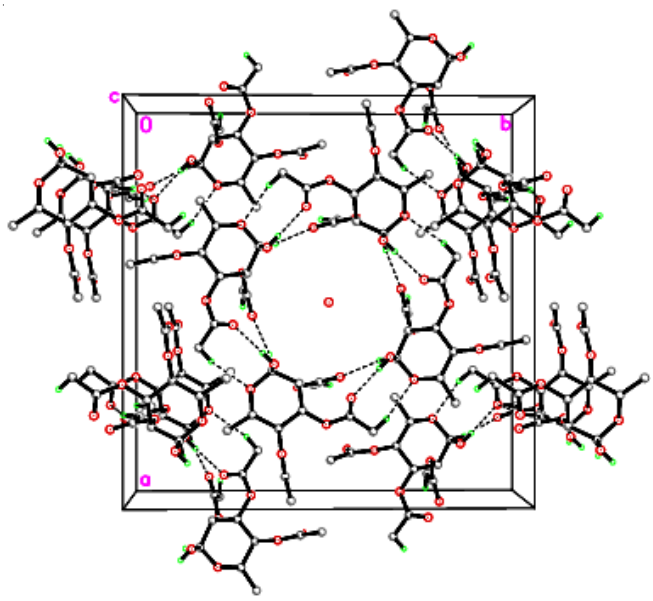


Fig. 2. Crystal packing of the title compound **3** viewed along *c* axis

The H-atoms of the water molecules are distorted. The six member oxan (C1–C5/O1) ring adopts chair conformation with the puckering parameters Q = 0.583(3) Å, θ = 3.6(3) and ψ = 115(4). In the crystal structure, the adjacent molecules are connected *via* intermolecular O–H···O and C–H···O hydrogen bonding (Symmetry codes: y, –x+1, z; –y+1, x, z; x, y, z–1) interactions (Fig. 2) incorporating $R_2^2(8)$ and $R_2^2(12)$ ring motifs. The O5 acts as a bifurcated acceptor producing a two dimensional structure. The bond lengths and bond angles of the title compound are in normal ranges. The crystal data and structure refinement parameters are given in Table-1. The CIF and FCF of this structure have been deposited (CCDC 1030446 & CCDC 1030447 respectively).

TABLE-1
CRYSTAL DATA AND REFINEMENT PARAMETERS

Crystal data	
$C_{12}H_{18.40}O_{8.20}$	F(000) = 1248
M_r = 293.87	D_x = 1.230 Mg m^{-3}
Tetragonal, *I*4	MoKα radiation, λ = 0.71073 Å
a = 19.8444 (6) Å	μ = 0.11 mm^{-1}
c = 8.0598 (3) Å	T = 293 K
V = 3174.0 (2) $Å^3$	Z = 8
Data collection	
68144 measured reflections	θ_{max} = 26.4°, θ_{min} = 2.7°
3248 independent reflections	h = –24→24
3015 reflections with I > 2σ(I)	k = –24→24
R_{int} = 0.044	l = –10→10
Refinement	
Refinement on F^2	Hydrogen site location: mixed
Least-squares matrix: full	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)]$ = 0.046	$w = 1/[\sigma^2(F_o^2) + (0.0864P)^2 + 1.2863P]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2)$ = 0.134	$(\Delta/\sigma)_{max}$ = 0.002
S = 1.13	$\Delta\rho_{max}$ = 0.63 e $Å^{-3}$
3248 reflections	$\Delta\rho_{min}$ = –0.29 e $Å^{-3}$
195 parameters	Absolute structure: Flack x determined using 1340 quotients [(I+)-(I-)]/[(I+)+(I-)]
1 restraint	Absolute structure parameter: 0.00 (19)

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