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Crystallographic studies of some cyclic benzylidene acetals: Key synthons for *o*-glycoamino acid building blocks and solid-phase oligosaccharide synthesis

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Synthesis of methyl 2-azido-2-deoxy-4,6-*O*-benzylidene-β-D-galactopyranoside (**1**), one of the key components in the synthesis of *O*-glycoamino acids, was undertaken in order to synthesize Tn and TF[3] antigen building blocks. In pursuit of an alternative approach, benzylidenation of the crude D-galactal (**2a**) afforded methyl 2-deoxy-4,6-*O*-benzylidene-α-D-galactopyranoside (**3c**) and 3,4-*O*-benzylidene-D-galactal (**3b**) besides the expected 4,6-*O*-benzylidene-D-galactal (**3a**). Formation of compound **3c** was explained based on the presence of methyl 2 deoxy-α-D-galactopyranoside (**2b**) isomer and/or trace amount of methanol in the crude mixture of deacetylated product of **2** prior to benzylidenation. On the other hand, formation of **3b** in substantial quantities appears to be a thermodynamically controlled product and its formation is found to be common during prolonged Lewis-acid catalyzed benzylidenation reaction. Crystal structures of these important and useful precursors were deduced by X-ray diffraction methods to enumerate their complete molecular structure as well as to understand the effect of the cyclic acetal on the pyranose ring conformation. Compound **1** crystallizes in the orthorhombic space group $P2_12_12_1$ with cell dimensions a = 5.058(7), b = 12.766(7), c = 22.557(7) Å; **3b** crystallizes in the hexagonal space group $P6_1$ with cell dimensions a = 18.265(4), b = 18.265(3), c = 6.323(2) Å; **3c** crystallizes in the monoclinic space group $P2_1$ with cell dimensions a = 10.614(3), b = 4.963(2), c = 12.730(3) Å, and β = 95.47(3)°.

KEY WORDS: *O*-glycoamino acid; D-galactal; azidonitration; benzylidenation; benzylidene acetals; structural analysis; X-ray diffraction; nmr

Introduction

Structural glycobiology is now being immensely pursued in several laboratories due to the pivotal role of oligosaccharides which endow some unique functional niches.[1] Despite the large number of naturally occurring glycoproteins, the types of covalent bonds between the protein and the saccharide moiety show limited variation. One of the most common types of linkages found in many secreted and cell surface proteins is the covalent attachment of GalNAc to Ser and/or Thr *via* an α-*O*-glycosidic bond.[2] For instance, mucins from various organs and species displayed microheterogeneous nature of their carbohydrate chains attached to the protein core *via* *O*-glycosidic and/or *N*-glycosidic bond.[3] Strategies for the creation of an *O*-glycosidic bond selectively between a carbohydrate and an aglycon either by enzymatic or by chemical synthesis have been immensely pursued for the preparation of glycoconjugates for many years. As part of our ongoing project directed towards the

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[3] Abbreviations used: 2D-NMR, two-dimensional nuclear magnetic resonance; e.s.d's, estimated standard deviations; Fmoc, N^{α}-fluorenylmethoxycarbonyl; Gal, galactose; GalNAc, N-acetyl galactosamine; MUC7, human salivary mucin; OPfp, pentafluorophenyl ester; TF, Thomsen-Friedenreich antigen [D-Galβ(1-3)-D-GalNAc α 1-*O*-serine and/or threonine]; Tn antigen [D-GalNAc α 1-*O*-serine and/or threonine].

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synthesis and structure-function studies of human salivary mucin (MG2, also designated as MUC7) derived *O*-linked glycopeptides, we are currently developing a simple and versatile synthetic methodology for the preparation of *O*-glycosylated threonine and serine building blocks.[4]

Out of the various methods available for carrying out *O*-glycosylation of *N*- and *C*-terminal protected amino acids, the Koenigs-Knorr reaction is the most commonly used method where an acetylated glycosyl halide is stereoselectively linked to *N*-, *C*-protected Ser/Thr in the presence of various catalysts.[5] The resultant product from this method will always have the β-glycosidic linkage due to neighboring group participation. To obtain an α-glycosidic linkage, numerous methods are now available whereby introducing a non-participating groups at C-2 position such as dinitrophenylamino or azido or arylideneamino group, stereoselectivity can be reversed to favor the formation of an α-isomer.[6] In this context, we choose to make a series of derivatives that would help to ease some of the practical difficulties encountered in getting the carbohydrates stereoselectively α-linked to *N*- and *C*-terminal protected amino acids. Herein, we report the X-ray crystal structure data procured for benzylidene acetals of few sugar derivatives belonging to *galacto* series and their synthesis by benzylidenation of azido methyl galactoside and D-galactal. The cyclic acetal precursors synthesized were determined to be important intermediates for the synthesis of glycosylated amino acid building blocks; thus making them prospective candidates for solid-phase oligosaccharide and glycopeptide synthesis.

Experimental

All chemicals and solvents were of analytical grade and used without any further purification. Dimethylformamide, and methanol were purchased anhydrous from Aldrich (Milwaukee, WI). 3,4, 6-Tri-*O*-acetyl-D-galactal was obtained from Pfanstiehl Laboratories Inc., (Waukegan, IL). The progress of the reaction was monitored by thin layer chromatography (TLC) on Merck Silica Gel 60 F_{254} plates, visualized by charring with 5% sulfuric acid in ethanol and/or by UV light when applicable. Concentration of the organic solvent was performed under aspirator pressure using temperatures below 40°C unless otherwise mentioned. Column chromatography was performed on Silica Gel (60–200 mesh, JT Baker) using ethyl acetate and petroleum ether (hexane) as the solvent systems. Melting points were determined on a Fisher-Johns melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Varian VXR-500 spectrometer equipped with SUN Sparcstation 5 at 500 MHz. Samples were prepared in $CDCl_3$ (99.9%, Cambridge Isotope Laboratories) using trimethylsilane (Me_4Si) as an internal standard at 300 K. Chemical shifts are reported in δ_{ppm} using Me_4Si as the standard reference.

*Synthesis of methyl 2-azido-2-deoxy-4,6-O-benzylidene-β-D-galacto-pyranoside(**1**)*

Synthesis of the title compound was performed according to the procedure of Evans.[7] Methyl 2-azido-2-deoxy-β-D-galactopyranoside[8] (4.35 g), freshly distilled α,α-dimethoxytoluene (5.42 mL) and *p*-toluenesulfonic acid monohydrate (50 mg) were placed in a 250 mL round-bottomed flask. The flask was then attached to a Buchi evaporator, evacuated and rotated on a water bath for 3 h at 60°C. The mixture was then neutralized with triethylamine and concentrated. Column chromatography of the crude mixture over silica gel (3:1, ethyl acetate:hexane) afforded a pure crystalline product (**1**). Yield was 8.3 g (69%); R_f 0.44 (1:1, ethyl acetate:hexane); mp 174–176°C; lit.[7] mp 174–176 °C; ^{1}H NMR (500 MHz, CDC_3); δ 7.52-7.50 (m, 2H, Ar), 7.40–7.35 (m, 3H, Ar), 5.58 (s, 1H, PhCH), 4.36 (dd, 1H, J = 12.6 Hz, 1.6 Hz), 4.20 (d, 1H, J = 7.6 Hz), 4.18 (dd, 1H, J = 3.2 Hz, 1.0 Hz), 4.09 (dd, 1H, J = 2.0 Hz), 3.64-3.59 (m, 2H), 3.60 (s, 3H, OCH_3), 3.45 (m, 1H), 2.60 (brs, 1H, OH).

*Benzylidenation of the product of 3,4,6-tri-O-acetyl-D-galactal deacetylation and isolation of 4,6-O-benzylidene-D-galactal (**3a**), 3,4-O-benzylidene-D-galactal (**3b**), and methyl 2-deoxy-4,6-O-benzylidene-β-D-galactopyranoside (**3c**)*

3,4,6-Tri-*O*-acetyl-D-galactal (**2**) (20 g, 73.44 mmol) was dissolved in dry MeOH (500 mL) and a 25% NaOMe solution in MeOH was added drop wise with constant stirring until the reaction mixture attained a pH of 8–9. Stirring was stopped when the TLC (50% ethyl acetate in hexane, v/v) showed that all starting material had been consumed. The reaction mixture was neutralized with Amberlite IRC-50(H^+) resin, filtered and concentrated to give crude D-galactal; yield = 10 g (93%). The D-galactal obtained (10 g, 68.44 mmol) was treated with purified benzaldehyde

Table 1. Crystal Data and Data Collection Summary for **1**, **3b** and **3c**

Summary	1	3b	3c
Empirical formula	$C_{14}H_{17}N_3O_5$	$C_{13}H_{14}O_4$	$C_{14}H_{18}O_5$
Formula weight	307.31	234.25	266.29
Crystal system	Orthorhombic	Hexagonal	Monoclinic
Space group	$P2_12_12_1$	$P6_1$	$P2_1$
a, Å	5.058(7)[a]	18.265(4)	10.614(3)
b, Å	12.766(7)	18.265(3)	4.963(2)
c, Å	22.557(7)	6.323(2)	12.730(3)
α, deg.	90	90	90
β, deg.	90	90	95.47(3)
γ, deg.	90	120	90
Volume, Å^3	1456.2	1826.8	667.5
Z	4	6	2
F(000)	648.0	744.0	264.0
Temperature, K	293(2)	293(2)	293(2)
Density$_{calc}$, mg/m^3	1.401	1.278	1.245
λ (CuK_α), Å	1.5418	1.5418	1.5418
Linear abs. coeff., mm^{-1}	0.909	0.786	0.808
Scan mode	ω-2θ	ω-2θ	ω-2θ
ω-scan width, deg.	0.60 + 0.14 tan θ	0.60 + 0.14 tan θ	0.60 + 0.14 tan θ
θ range, deg.	3.92 to 74.90	2.79 to 59.93	3.49 to 69.92
min/max of *h*, *k*, *l*	0/6, 0/15, 0/28	0/16, 0/17, 0/6	0/12, 0/6, −15/15
No. of reflections collected	1775	743	1293
No. of unique reflections	1775	680	1227
R(int)	0.0330	0.0335	0.0341
Final R_1 [$I > 2\sigma(I)$]	0.0346	0.0516	0.0373
Final wR_2	0.0954	0.0700	0.0904
Data/restraints/parameters	1775/0/219	680/1/157	1227/1/193
Goodness of fit	1.065	1.114	1.077
Absolute structure parameter	0.1(3)	0.1(8)	0.1(4)
Extinction coefficient	0.042(2)	0.0016(3)	0.021(2)
Largest Δ*F* peak and hole, eÅ^{-3}	0.147 and −0.163	0.180 and −0.187	0.243 and −0.153

[a] Values in the parentheses represent the estimated standard deviations.

(30 g, 0.28 mol) and freshly fused and powdered zinc chloride (8.4 g, 0.063 mol) and the mixture was stirred vigorously at room temperature for about 48 h, until a clear solution was obtained. After the customary processing, the residue (9.5 g, 57%) was subjected to column chromatography over silica gel using ethyl acetate and hexane as the solvent system. Compounds **3a**, **3b**, and **3c** were eluted using 30% to 40% ethyl acetate in hexane. Fractions were monitored by TLC and made into two major pools. The first pool contained a less polar compound (1 g, 5.6%) and had the following characteristics: R_f 0.63 (1:1 ethyl acetate:hexane); mp 175-177°C; ^{1}H NMR ∂ 7.52-7.49 (m, 2H, Ar), 7.38–7.34 (m, 3H, Ar), 5.59 (s, 1H, PhCH), 4.93 (t, 1H), 4.27 (dd, 1H, *J* = 12.5 Hz, 1.6 Hz), 4.12–4.09 (m, 2H), 4.07 (dd, 1H, *J* = 12.0 Hz, 2.0 Hz), 3.63 (brs, 1H), 3.35 (s, 3H, OCH_3), 1.96 (m, 2H, *J* = 8.5 Hz, 1.5 Hz). Based on the spectral data, the compound was tentatively identified as **3c**. The second pool showed the following features: R_f 0.60 (1:1 ethyl acetate:hexane); ^{1}H NMR ∂ 7.48-7.44 (m, 2H, Ar), 7.38-7.34 (m, 3H, Ar), 6.73 (d, 1H, *J* = 10 Hz), 6.00 (s, 1H, PhCH), 5.04 (dd, 1H, *J* = 7.5 Hz, 2.0 Hz), 4.85 (dd, 1H, *J* = 7.5 Hz, 2.0 Hz), 4.43 (d, 1H, *J* = 7.5 Hz), 4.05-3.97 (m, 2H), 3.88 (dd, 1H, *J* = 12 Hz, 2.4 Hz). While **3a** (2 g, 10.9%) after separation by crystallization showed a mp of 134–136°C, **3b** (6.2 g, 33.9%) showed mp of 82–84°C. Spectral data accounts for both **3a** and/or **3b** diastereomers, however, the structure of the major compound **3b** was confirmed by X-ray diffraction methods.

Crystal data collection

X-ray diffraction data were collected on an Enraf-Nonius CAD-4 automatic diffractometer with a graphite monochromatorized CuK_α radiation (λ = 1.5418

Å) following the procedure as described previously.[9] Suitable single crystals of all three compounds (**1**, **3b**, and **3c**) were obtained by slow evaporation at room temperature utilizing chloroform (in case of **1** and **3c**) and ethyl acetate (in the case of **3b**) as the solvent system. Table 1 summarizes the crystal data and data collection parameters for all the three compounds. Cell constants and an orientation matrix were obtained from a least-squares refinement utilizing the setting angles of 25 centered reflections in the range of $20° < \theta < 27°$. A check on crystal and electronic stability was carried out by monitoring three reflections every hour during data collection. The plot of intensity versus time indicated a loss in intensity of 1.5%.

Structure solution and refinement

The structure was solved by direct methods as applied in the program system SHELXS-86.[10] Refinement was done using full-matrix least-squares with non-hydrogen atoms refined anisotropically. The hydrogen atoms were located from difference electron density maps and were included in the refinement with individual isotropic thermal parameters. Hydrogen atoms bonded to carbon were positioned according to idealized geometry (C−H distance 0.95 Å). The final refinement on F^2 converged to the R indices given in Table 1. The final coordinates of C and O atoms for **1**, **3b**, and **3c** are listed in Tables 2, 4, and 6, respectively. Similarly, the corresponding bond angles and bond lengths for all the three compounds are given in Tables 3, 5, and 7. ORTEP[11] drawings of **1**, **3b**, and **3c** with the atom numbering schemes are shown in Figs. 1, 2, and 3, respectively. The least squares refinement was carried out using the program SHELXS-93, $(\Delta/\sigma)\text{max} < 0.73$ for all atoms.[10] Atomic scattering factors were taken from *International Tables for X-Ray Crystallography* (1974).[12]

Table 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) of **1** (with esd's in parentheses)

Atom	x	y	z	$U(eq)^a$
O(1)	−3378(4)	−4541(1)	−8675(1)	54(1)
O(3)	606(3)	−7154(1)	−9854(1)	52(1)
O(4)	−784(3)	−5358(1)	−10484(1)	44(1)
O(5)	−795(3)	−4044(1)	−9445(1)	45(1)
O(6)	−643(3)	−3565(1)	−10681(1)	50(1)
N(1)	−1305(4)	−6642(2)	−8724(1)	59(1)
N(2)	−3372(5)	−6730(2)	−8442(1)	59(1)
N(3)	−5079(6)	−6910(2)	−8143(1)	93(1)
C(1)	−1062(4)	−4766(2)	−8978(1)	44(1)
C(2)	−1327(4)	−5882(2)	−9215(1)	41(1)
C(3)	1005(4)	−6146(2)	−9611(1)	42(1)
C(4)	1391(4)	−5310(2)	−10079(1)	43(1)
C(5)	1503(4)	−4220(2)	−9801(1)	45(1)
C(6)	1514(5)	−3399(2)	−10284(1)	51(1)
C(7)	−497(5)	−4582(2)	−10929(1)	46(1)
C(8)	−2641(5)	−4709(2)	−11381(1)	46(1)
C(9)	−3707(6)	−5678(2)	−11507(1)	57(1)
C(10)	−5594(7)	−5780(2)	−11950(1)	67(1)
C(11)	−6439(6)	−4928(2)	−12269(1)	62(1)
C(12)	−5374(6)	−3958(2)	−12150(1)	65(1)
C(13)	−3501(6)	−3851(2)	−11709(1)	60(1)
C(14)	−3246(8)	−3576(2)	−8349(1)	71(1)

^{a} $U(eq)$ is defined as one third of the trace of the orthogonalized U_{ij} tensor (i.e., $U = 1/3\ [U(11) + U(22) + U(33)]$).

Results and discussion

The crucial step in the synthesis of suitably protected *O*-glycoamino acid building blocks required for glycopeptide synthesis is making the appropriate precursors which can be easily used for glycosylating the *N*-and *C*-terminal protected amino acids. Recently, Paulsen *et al.*[13] have reported the synthesis of TF antigen building block wherein methyl 2-azido-2-deoxy-4,6-*O*-benzylidene-β-D-galactopyranoside is one of the key intermediates in the proposed protocol. Hence, we synthesized methyl 2-azido-2-deoxy-4,6-*O*-benzylidene-β-D-galactopyranoside (**1**) by benzylidenation of methyl 2-azido-2-deoxy-β-D-galactopyranoside using α,α-dimethoxytoluene in the presence of *p*-toluenesulfonic acid as the catalyst. Compound **1** was purified using silica gel column chromatography which afforded highly purified material which was then crystallized for further studies. The spectral properties and melting point of this compound were found to be identical to the literature values.[13] However, there is no crystal structure report on this compound. Our rationale for synthesizing this compound was to make the protected disaccharide, methyl (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1-3)-4,6-*O*-benzylidene-2-azido-2-deoxy-β-D-galactopyranoside which could be eventually used for glycosylation of Fmoc−Ser−OPfp or Fmoc−Thr−OPfp.

An alternative approach to the aforementioned derivatives could start from D-galactal. Adverting to this strategy, direct benzylidenation of crude D-galactal using benzaldehyde and $ZnCl_2$ afforded two undesired by-products *viz.*, 3,4-*O*-benzylidene-D-galactal (**3b**)

Table 3. Molecular dimensions of 1 (with esd's in parentheses)

Bond lengths, Å					
C(1)–O(1)	1.387(3)	C(4)–C(5)	1.527(3)	C(8)–C(13)	1.391(3)
C(1)–O(5)	1.407(2)	C(5)–O(5)	1.431(3)	C(9)–C(10)	1.388(4)
C(1)–C(2)	1.527(3)	C(5)–C(6)	1.512(3)	C(10)–C(11)	1.372(4)
C(2)–N(1)	1.472(3)	C(6)–O(6)	1.427(3)	C(11)–C(12)	1.377(4)
C(2)–C(3)	1.517(3)	C(7)–O(6)	1.416(2)	C(12)–C(13)	1.381(4)
C(3)–O(3)	1.413(2)	C(7)–O(4)	1.417(2)	C(14)–O(1)	1.436(3)
C(3)–C(4)	1.516(3)	C(7)–C(8)	1.498(3)	N(1)–N(2)	1.229(3)
C(4)–O(4)	1.431(2)	C(8)–C(9)	1.379(3)	N(2)–N(3)	1.119(3)
Bond angles, deg.					
O(1)–C(1)–O(5)	108.3(2)	C(3)–C(4)–C(5)	111.1(2)	C(8)–C(9)–C(10)	120.0(2)
O(1)–C(1)–C(2)	107.0(2)	O(5)–C(5)–C(6)	107.3(2)	C(11)–C(10)–C(9)	121.2(2)
O(5)–C(1)–C(2)	110.9(2)	O(5)–C(5)–C(4)	110.1(2)	C(10)–C(11)–C(12)	119.2(2)
N(1)–C(2)–C(3)	106.8(2)	C(6)–C(5)–C(4)	109.6(2)	C(11)–C(12)–C(13)	119.9(2)
N(1)–C(2)–C(1)	110.5(2)	O(6)–C(6)–C(5)	110.3(2)	C(12)–C(13)–C(8)	121.3(2)
C(3)–C(2)–C(1)	110.2(2)	O(6)–C(7)–O(4)	110.9(2)	N(2)–N(1)–C(2)	116.3(2)
O(3)–C(3)–C(4)	112.9(2)	O(6)–C(7)–C(8)	109.3(2)	N(3)–N(2)–N(1)	170.7(3)
O(3)–C(3)–C(2)	108.7(2)	O(4)–C(7)–C(8)	109.4(2)	C(1)–O(5)–C(5)	113.3(2)
C(4)–C(3)–C(2)	110.7(2)	C(9)–C(8)–C(13)	118.4(2)	C(7)–O(4)–C(4)	110.0(2)
O(4)–C(4)–C(3)	108.4(2)	C(9)–C(8)–C(7)	121.4(2)	C(7)–O(6)–C(6)	110.1(2)
O(4)–C(4)–C(5)	109.3(2)	C(13)–C(8)–C(7)	120.2(2)	C(1)–O(1)–C(14)	113.0(2)
Torsion angles, deg.					
O(5)–C(1)–O(1)–C(14)	−69.4(2)		O(4)–C(4)–C(5)–C(6)	−52.8(2)	
C(2)–C(1)–O(1)–C(14)	171.0(2)		C(4)–C(5)–O(5)–C(1)	60.2(2)	
O(1)–C(1)–O(5)–C(5)	−178.3(2)		C(6)–C(5)–O(5)–C(1)	179.5(2)	
C(2)–C(1)–O(5)–C(5)	−61.2(2)		C(4)–C(5)–C(6)–O(6)	52.5(2)	
O(5)–C(1)–C(2)–N(1)	173.7(2)		O(5)–C(5)–C(6)–O(6)	−67.1(2)	
O(5)–C(1)–C(2)–C(3)	55.8(2)		C(5)–C(6)–O(6)–C(7)	−57.7(2)	
O(1)–C(1)–C(2)–N(1)	−68.4(2)		O(4)–C(7)–O(6)–C(6)	64.0(2)	
O(1)–C(1)–C(2)–C(3)	173.7(2)		C(8)–C(7)–O(6)–C(6)	−175.3(2)	
C(1)–C(2)–N(1)–N(2)	77.9(2)		C(8)–C(7)–O(4)–C(4)	174.6(2)	
C(1)–C(2)–C(3)–C(4)	−51.5(2)		O(6)–C(7)–O(4)–C(4)	−64.8(2)	
C(1)–C(2)–C(3)–O(3)	−176.1(2)		O(4)–C(7)–C(8)–C(13)	153.2(2)	
C(3)–C(2)–N(1)–N(2)	−162.2(2)		O(4)–C(7)–C(8)–C(9)	−30.4(3)	
N(1)–C(2)–C(3)–O(3)	63.9(2)		O(6)–C(7)–C(8)–C(13)	31.6(3)	
N(1)–C(2)–C(3)–C(4)	−171.6(2)		O(6)–C(7)–C(8)–C(9)	−152.0(2)	
C(2)–C(3)–C(4)–C(5)	51.5(2)		C(7)–C(8)–C(13)–C(12)	176.5(2)	
C(2)–C(3)–C(4)–O(4)	−68.6(2)		C(7)–C(8)–C(9)–C(10)	−176.6(2)	
O(3)–C(3)–C(4)–O(4)	53.5(2)		C(9)–C(8)–C(13)–C(12)	0.02(4)	
O(3)–C(3)–C(4)–C(5)	173.6(2)		C(13)–C(8)–C(9)–C(10)	−0.17(4)	
C(3)–C(4)–O(4)–C(7)	179.7(2)		C(8)–C(9)–C(10)–C(11)	−0.13(4)	
C(3)–C(4)–C(5)–C(6)	−172.3(2)		C(9)–C(10)–C(11)–C(12)	0.57(4)	
C(3)–C(4)–C(5)–O(5)	−54.5(2)		C(10)–C(11)–C(12)–C(13)	−0.72(4)	
C(5)–C(4)–O(4)–C(7)	58.5(2)		C(11)–C(12)–C(13)–C(8)	0.43(4)	
O(4)–C(4)–C(5)–O(5)	65.1(2)				

and methyl 2-deoxy-4,6-*O*-benzylidine-α-D-galactopyranoside (**3c**) besides the expected 4,6-*O*-benzylidene-D-galactal (**3a**). Scheme 1 represents the reaction profile for the formation of compounds **3a–3c**. Commercially available 3,4,6-tri-*O*-acetyl-D-galactal (**2**) was subjected to deacetylation using NaOMe in the presence of dry MeOH at room temperature for 2–3 h. Completely deacetylated crude product was treated with benzaldehyde and $ZnCl_2$ for 48 h until a clear solution was obtained. After customary processing, the residue obtained was purified over a silica gel column. The first pooled fraction eluted from the column contained the less polar compound and was identified as methyl 2-deoxy-4,6-*O*-benzylidene-α-D-galactopyranoside (**3c**) by ^{1}H NMR spectroscopy and confirmed by X-ray crystallography. The second pooled fraction had more than one compound which were essentially co-eluted during chromatography. Noteworthy that our initial attempts to differentiate these compounds either by TLC or by ^{1}H NMR analysis failed. However, after

Table 4. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) of **3b** (with esd's in parentheses)

Atom	*x*	*y*	*z*	*U*(eq)[a]
O(3)	5587(3)	6356(3)	916(10)	50(2)
O(4)	6482(3)	7649(3)	2325(11)	56(2)
O(5)	6861(3)	6988(3)	6196(10)	54(2)
O(6)	8584(3)	8678(3)	3312(14)	89(3)
C(1)	6182(5)	6213(5)	5970(18)	51(3)
C(2)	5900(5)	5842(4)	4124(19)	51(3)
C(3)	6219(5)	6262(5)	2074(16)	50(3)
C(4)	6920(5)	7183(5)	2357(15)	45(3)
C(5)	7397(4)	7332(4)	4397(19)	48(3)
C(6)	7966(4)	8258(5)	4904(18)	71(4)
C(7)	5619(5)	7085(4)	1785(16)	42(2)
C(8)	5296(5)	7468(4)	215(17)	40(2)
C(9)	4587(5)	7532(4)	692(17)	51(3)
C(10)	4283(5)	7876(5)	−802(22)	60(3)
C(11)	4674(5)	8150(5)	−2681(19)	61(3)
C(12)	5379(5)	8088(4)	−3165(16)	50(3)
C(13)	5685(5)	7754(5)	−1689(17)	48(3)

[a] *U*(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor (i.e., $U = 1/3\ [U(11) + U(22) + U(33)]$).

prolong storage of the sample at 4°C **3b** crystallized thus making it separated from **3a** and/or its diastereomer. The soluble supernatant layer was further processed to isolate another compound which showed different melting point than **3b**. We tentatively labeled this compound as **3a**. It should be noted that the complete structure of **3a** remains to be determined either by 2D-NMR spectroscopy or by X-ray crystallography, because one cannot rule out the possibility for the formation of diastereomer of **3b** due to the new stereogenic center at the acetal carbon. Diastereomer of **3b** can also show similar ^{1}H NMR spectral data but different melting point. Formation of diastereomers for acetals and their differentiation by ^{1}H NMR analysis has been reported and reviewed by Clode.[14] Therefore, in the present study, the representation of the formation of **3a** in Scheme 1 is tentative.

Since the two compounds in the second pool exhibited profound differences in physical properties, we determined the molecular structure of the major compound, **3b** by X-ray crystallography. It is noteworthy that neither the synthesis nor the crystal structure of **3b** has been reported. However, Richardson[15] and Blaha *et al.*[16] have reported the synthesis of methyl 2-deoxy-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranoside, a structural analog of methyl 2-deoxy-4,6-*O*-benzylidene-α-D-galactopyranoside. Interestingly, the physical properties of these compounds were in close agreement when compared to each other. The rationale for synthesizing 4,6-*O*-benzylidene-D-galactal is based on its use in constructing the oligosaccharide derivatives required for the synthesis of TF-and Sialyl Tn-antigen building blocks required for the synthesis of *O*-linked glycopeptides.

The formation of 3,4-*O*-benzylidene-D-galactal (**3b**) is quite common during prolonged Lewis-acid catalyzed benzylidenation reaction-conditions.[17] Although, it has been shown before that D-galactose reacts with paraldehyde in the presence of 0.3% of sulfuric acid, giving 4,6-*O*-ethylidene-α-D-galactopyranose and minor amounts of 3,4-*O*-ethylidene-α-D-galactopyranose, however, with more acid and longer times, the major product is 1,2:3,4-di-*O*-ethylidene-α-D-galactopyranose.[18] Thus, **3b** would have resulted due to the presence of more acid in the reaction mixture as well as due to the increased reaction time to 48 h. Generally, acid-catalyzed benzylidenation is a reversible process wherein the products formed are thermodynamically more stable.[17,19] On the contrary, it has been shown that benzylidenation under basic conditions are irreversible and gives kinetically controlled products that are unusual because of their thermodynamic instability.[20] It is interesting to note that Eklind *et al.*[21] and Garegg and Swahn[22] have shown that base catalyzed benzylidenation of methyl 6-deoxy-β-D-galactopyranoside and methyl-6-*O*-acetyl-β-D-galactopyranoside gives exclusively the kinetically controlled 3,4-*O*-benzylidene derivative. Therefore, though 4,6-*O*-benzylidene-D-galactal (**3a**) is thermodynamically more stable than 3,4-*O*-benzylidene-D-galactal (**3b**), formation of significant amounts of **3b** appears to be due to more acid and a longer reaction time. Besides, acid-catalyzed benzylidenation reactions are reversible which might have altered the stability of **3b** over **3a**.

The crystal structure of **3b** is hitherto unknown, however, Lemieux *et al.*[23] have reported the facile synthesis of its structural analog *viz.*, methyl 4,6-*O*-benzylidene-D-hex-2-enopyranosides. In addition, Sharma and Brown[24] have studied the synthesis of 4,6-benzylidene-D-glucal and the reaction of methyllithium with methyl 2,3-anhydro-4, 6-*O*-benzylidene-α-D-allopyranoside. They have elucidated the structure of 4,6-benzylidene-D-glucal and various structural analogs by ^{1}H NMR. Interestingly, Barili *et al.*[25] reported the structure of methyl 3,4-*O*-isopropylidene-α- and β-D-galactopyranosides by NMR and X-ray analysis, recently. They intended to study the conformational features of these two derivatives to explain their reac-

Table 5. Molecular Dimensions of **3b** (with esd's in parentheses)

Bond lengths, Å					
O(5)–C(1)	1.345(8)	C(1)–C(2)	1.318(12)	C(8)–C(9)	1.390(9)
O(5)–C(5)	1.426(10)	C(2)–C(3)	1.470(13)	C(9)–C(10)	1.394(12)
O(6)–C(6)	1.418(10)	C(3)–C(4)	1.532(9)	C(10)–C(11)	1.347(13)
O(3)–C(7)	1.414(8)	C(4)–C(5)	1.503(12)	C(11)–C(12)	1.381(10)
O(3)–C(3)	1.448(8)	C(5)–C(6)	1.512(9)	C(12)–C(13)	1.377(11)
O(4)–C(7)	1.428(7)	C(7)–C(8)	1.496(11)		
O(4)–C(4)	1.432(8)	C(8)–C(13)	1.362(12)		
Bond angles, deg.					
C(1)–O(5)–C(5)	116.6(8)	O(4)–C(4)–C(3)	104.0(7)	C(13)–C(8)–C(9)	119.3(9)
C(7)–O(3)–C(3)	104.8(6)	C(5)–C(4)–C(3)	113.0(7)	C(13)–C(8)–C(7)	120.9(8)
C(7)–O(4)–C(4)	108.5(6)	O(5)–C(5)–C(4)	113.4(6)	C(9)–C(8)–C(7)	119.8(9)
C(2)–C(1)–O(5)	123.6(9)	O(5)–C(5)–C(6)	105.1(8)	C(8)–C(9)–C(10)	119.2(10)
C(1)–C(2)–C(3)	124.2(7)	C(4)–C(5)–C(6)	113.4(8)	C(11)–C(10)–C(9)	120.6(9)
O(3)–C(3)–C(2)	112.1(7)	O(6)–C(6)–C(5)	111.8(9)	C(10)–C(11)–C(12)	120.5(10)
O(3)–C(3)–C(4)	102.0(7)	O(3)–C(7)–O(4)	106.5(6)	C(13)–C(12)–C(11)	119.2(9)
C(2)–C(3)–C(4)	111.4(8)	O(3)–C(7)–C(8)	110.0(8)	C(8)–C(13)–C(12)	121.3(8)
O(4)–C(4)–C(5)	110.5(7)	O(4)–C(7)–C(8)	111.9(6)		

Torsion angles, deg.			
C(1)–O(5)–C(5)–C(6)	166.8(8)	O(4)–C(4)–C(5)–O(5)	67.4(10)
C(1)–O(5)–C(5)–C(4)	42.5(12)	C(3)–C(4)–C(5)–O(5)	−48.6(12)
C(5)–O(5)–C(1)–C(2)	−14.1(15)	C(3)–C(4)–C(5)–C(6)	−168.4(9)
C(3)–O(3)–C(7)–C(8)	156.0(8)	O(4)–C(4)–C(5)–C(6)	−52.4(11)
C(3)–O(3)–C(7)–O(4)	34.4(9)	O(5)–C(5)–C(6)–O(6)	175.7(8)
C(7)–O(3)–C(3)–C(2)	81.8(9)	C(4)–C(5)–C(6)–O(6)	−59.9(11)
C(7)–O(3)–C(3)–C(4)	−37.7(9)	O(4)–C(7)–C(8)–C(9)	−123.1(9)
C(4)–O(4)–C(7)–O(3)	−16.1(9)	O(3)–C(7)–C(8)–C(9)	118.6(10)
C(4)–O(4)–C(7)–C(8)	−136.4(8)	O(4)–C(7)–C(8)–C(13)	57.1(12)
C(7)–O(4)–C(4)–C(3)	−7.5(9)	O(3)–C(7)–C(8)–C(13)	−61.2(12)
C(7)–O(4)–C(4)–C(5)	−128.8(8)	C(7)–C(8)–C(13)–C(12)	178.3(9)
O(5)–C(1)–C(2)–C(3)	−8.4(18)	C(7)–C(8)–C(9)–C(10)	−179.1(10)
C(1)–C(2)–C(3)–O(3)	−113.2(12)	C(9)–C(8)–C(13)–C(12)	−1.5(16)
C(1)–C(2)–C(3)–C(4)	0.4(15)	C(13)–C(8)–C(9)–C(10)	0.68(15)
O(3)–C(3)–C(4)–O(4)	27.5(9)	C(8)–C(9)–C(10)–C(11)	−0.21(17)
C(2)–C(3)–C(4)–O(4)	−92.6(9)	C(9)–C(10)–C(11)–C(12)	0.50(17)
C(2)–C(3)–C(4)–C(5)	27.1(12)	C(10)–C(11)–C(12)–C(13)	−1.23(16)
O(3)–C(3)–C(4)–C(5)	147.17(8)	C(11)–C(12)–C(13)–C(8)	1.72(16)

tivity towards t-BuOK and the role of the pyranose ring conformation in determining their reactivity. Barili *et al.*[26] noticed that *O*-protected β-anomers easily eliminate acetone to give high yields of the synthetically useful 4-deoxy-L-threo-hex-4-enopyranosides, however, the corresponding α-anomers were completely unreactive. From the crystal structure studies, they found that the presence of methyl or acetyl substituents in positions 2 and 6 causes very little or no conformational change. Therefore, they concluded that the resistance of α-anomer toward elimination, promoted by *t*-BuOK, cannot be attributed to deviations from the $^4C_1$ conformation of pyranoid rings of the α- and β-anomers, but rather to steric hindrance exerted by the axial anomeric group in the former. On the other hand, Lamba *et al.*[27] carried out the structural analysis of methyl α-L-fucopyranoside by X-ray crystallography, NMR spectroscopy, and molecular mechanics calculations and they found that the conformation of the pyranose ring in solution, derived from $^3J_{HH}$ values was similar to that in the crystal.

Although the exact mechanism for the formation of compound **3c** is not known, it appears that the presence of minor amounts of methyl 2-deoxy-α-D-galactopyranoside (**2b**) isomer resulted after neutralization with Amberlite IRC-50(H^+) resin prior to benzylidenation and/or trace amount of methanol left after deacetylation of 3,4,6-tri-*O*-acetyl-D-galactal (**2**) would have a generated **3c** during the benzylidenation of methyl 2-deoxy-4, 6-*O*-benzylidene-α-D-galactopyranoside (**3c**). The formation of this compound is highly unlikely during benzylidenation under normal

Table 6. Atomic Coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) of **3c** (with esd's in parentheses)

Atom	*x*	*y*	*z*	*U*(eq)[a]
O(1)	−2166(2)	−340(6)	−6702(2)	58(1)
O(3)	−4504(2)	255(5)	−9582(1)	50(1)
O(4)	−6149(2)	−1556(4)	−8129(1)	38(1)
O(5)	−4147(2)	−2027(5)	−6400(2)	46(1)
O(6)	−6863(2)	−1794(5)	−6454(2)	49(1)
C(1)	−3072(3)	−2360(7)	−6957(2)	47(1)
C(2)	−3407(3)	−2313(7)	−8140(2)	43(1)
C(3)	−4137(3)	210(6)	−8478(2)	37(1)
C(4)	−5257(3)	545(6)	−7835(2)	37(1)
C(5)	−4854(3)	376(7)	−6656(2)	43(1)
C(6)	−6013(3)	284(9)	−6059(2)	53(1)
C(7)	−7209(3)	−1383(7)	−7547(2)	40(1)
C(8)	−8160(3)	−3487(6)	−7917(2)	40(1)
C(9)	−8118(3)	−4801(8)	−8863(2)	50(1)
C(10)	−9033(3)	−6716(9)	−9197(3)	61(1)
C(11)	−9998(3)	−7266(10)	−8587(3)	65(1)
C(12)	−10051(3)	−5940(10)	−7648(3)	68(1)
C(13)	−9144(3)	−4068(8)	−7314(3)	58(1)
C(14)	−1676(4)	−362(15)	−5620(3)	86(2)

[a] *U*(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor (i.e., U = 1/3 [U(11) + U(22) + U(33)]).

reaction conditions and hence it is essential to have the purified and dried D-galactal (**2a**) for benzylidenation reaction to get **3a** and/or **3b** in fair yields.

The relevant crystallographic data for **1**, **3b**, and **3c** are given in Table 1. A view of **1**, showing the thermal ellipsoids and the atomic numbering scheme is presented in Fig. 1. There are no unusual geometrical features in the structure of **1**. The bond lengths and bond angles all lie within the expected ranges (Table 3). However, the two ring C−O bond-lengths are significantly different, with C(1)−O(5) = 1.407(2) Å, and C(5)−O(5) = 1.431(3) Å. This difference is considerably larger than expected from observations and theoretical calculations relating to β-D-aldopyranosides.[28] Similarly, the C(1)−O(1) bond has a length [1.387(3) Å] which is much shorter than those of the other C−O bonds (on average 1.42 Å). This pattern of bond lengths is a common feature of carbohydrates and has been correlated with the anomeric effect.[29] As expected,[30] the pyranose ring and the dioxolane rings in **1** are in chair conformations. The absolute configuration at each pyranose carbon atom is found to be equivalent to that of β-pyranosides[31] as well as α-D-galactopyranoside.[28,29] Within the pyranose system, the mean C−C bond length is 1.52(3) Å, while that for C−O is 1.42(2) Å. Conformation angles in the pyranose ring range between 51.5° to 61.6° (Table 3) which by comparison with the idealized ring angle of 55.8° to 61.7°, suggests that the hexapyranosyl ring adopts a slightly distorted $^4C_1$ conformation.[28,29]

It has been well documented that as a result of the distortion of the chair conformation, the pyranoid ring gets flattened at the oxygen apex, allowing the C−O−C angle to increase while the other internal ring angles remain close to tetrahedral values.[32] Such an effect is clearly seen in **1** as the flattening of the ring-O atom and C(3) allows the ring angles C(1)−O(5)−C(5) and C(3)−C(4)−C(5) to widen to 113.3(2)° and 111.1(2)°, respectively. The glycosidic linkage is (−)*synclinal*, with O(5)–C(1)–O(1)–C(14) = −69.4(2)°, consistent with the *exo*-anomeric effect as found in isopropyl-1-thio-β-D-galactopyranoside.[33] Besides, the bond angle is found to be 113.0(2)° which is commonly observed for most simple methyl-glycosides and it depends upon the local substitution pattern.[34] The orientation of the phenyl ring is equitorial with respect to the dioxolane ring and the *O*-methyl group on the anomeric carbon is also found to be equitorial. As expected, the azido group on C(2) is equitorial and the bond angle spanning the atoms, C(2)−N(1)−N(2) and N(1)−N(2)−N(3) showed 116.3(2) and 170.7(3)°, respectively, indicating all the three nitrogen atoms are linear having cumulative double bonds and it is coplanar to the pyranose ring.

The perspective view and the numbering scheme for **3b** is given in Fig. 2. Bond lengths and valence angles (Table 5) conform to the tabulated values for pyranoses.[34] The six-membered pyranose ring has a slightly distorted half-chair of $^5H_4$ conformation[35] as the C(3) and O(5) are required to be planar owing to the presence of the C(1)−C(2) double bond [bond length = 1.318(12) Å]. This observation is found to be consistent with the X-ray structure of ethyl 6-*O*-benzoyl-4-iodo-2,3,4,-trideoxy-α-D-hex-2-enopyranoside.[36] The C(4) and C(5) are above and below the plane thereby the primary hydroxymethyl group on C(5) is forced into a quasi-equitorial position due to the double bond in the ring. The average bond angle and torsional angles in the pyranose ring of **3b** are 117.0(8) and 23.5(14)°, which clearly indicates that a more flattened conformation for the pyranose ring. Also, the ring C−O distances are short [1.35(8) and 1.43(10) Å] compared with those for most pyranoid sugars (1.40–1.45 Å). This observation further supports the flattening of the pyranose ring. Furthermore, the formation of a cyclic acetal induces a flattening effect in the five-membered dioxolane ring, as a conse-

Table 7. Molecular Dimensions of **3c** (with esd's in parentheses)

Bond lengths, Å					
O(4)–C(7)	1.408(3)	O(6)–C(6)	1.430(4)	C(7)–C(8)	1.497(4)
O(4)–C(4)	1.433(3)	C(5)–C(6)	1.507(4)	C(8)–C(9)	1.374(4)
C(4)–C(3)	1.515(4)	C(3)–O(3)	1.422(3)	C(8)–C(13)	1.385(4)
C(4)–C(5)	1.524(4)	C(3)–C(2)	1.513(4)	C(9)–C(10)	1.395(5)
O(5)–C(1)	1.410(4)	C(2)–C(1)	1.514(4)	C(13)–C(12)	1.375(5)
O(5)–C(5)	1.430(4)	O(1)–C(1)	1.405(4)	C(11)–C(12)	1.370(6)
O(6)–C(7)	1.420(3)	O(1)–C(14)	1.426(4)	C(11)–C(10)	1.371(5)
Bond angles, deg.					
C(7)–O(4)–C(4)	111.1(2)	O(3)–C(3)–C(2)	112.2(3)	C(9)–C(8)–C(13)	118.4(3)
O(4)–C(4)–C(3)	108.2(2)	C(4)–C(3)–C(2)	110.1(2)	C(9)–C(8)–C(7)	122.0(3)
O(4)–C(4)–C(5)	109.5(2)	C(1)–C(2)–C(3)	111.2(3)	C(13)–C(8)–C(7)	119.5(3)
C(3)–C(4)–C(5)	111.4(2)	C(1)–O(1)–C(14)	113.4(3)	O(6)–C(6)–C(5)	111.3(3)
C(1)–O(5)–C(5)	114.5(2)	O(1)–C(1)–O(5)	111.6(3)	C(8)–C(9)–C(10)	120.7(3)
C(7)–O(6)–C(6)	109.7(2)	O(1)–C(1)–C(2)	108.1(3)	C(12)–C(13)–C(8)	120.8(4)
O(5)–C(5)–C(6)	107.2(3)	O(5)–C(1)–C(2)	111.9(2)	C(12)–C(11)–C(10)	119.6(4)
O(5)–C(5)–C(4)	111.2(3)	O(4)–C(7)–O(6)	111.2(2)	C(11)–C(12)–C(13)	120.6(4)
C(6)–C(5)–C(4)	109.4(2)	O(4)–C(7)–C(8)	109.9(2)	C(11)–C(10)–C(9)	119.9(4)
O(3)–C(3)–C(4)	112.1(2)	O(6)–C(7)–C(8)	108.2(2)		
Torsion angles, deg.					
C(4)–O(4)–C(7)–C(8)		176.4(2)	O(5)–C(5)–C(6)–O(6)		−68.4(3)
C(4)–O(4)–C(7)–O(6)		−63.8(3)	C(4)–C(3)–C(2)–C(1)		−52.2(3)
C(7)–O(4)–C(4)–C(3)		179.2(2)	O(3)–C(3)–C(2)–C(1)		−177.9(3)
C(7)–O(4)–C(4)–C(5)		57.6(3)	C(3)–C(2)–C(1)–O(5)		54.2(4)
O(4)–C(4)–C(3)–C(2)		−68.5(3)	C(3)–C(2)–C(1)–O(1)		−69.1(3)
O(4)–C(4)–C(3)–O(3)		57.3(3)	C(14)–O(1)–C(1)–C(2)		−174.0(3)
O(4)–C(4)–C(5)–C(6)		−51.7(3)	C(14)–O(1)–C(1)–O(5)		62.5(4)
O(4)–C(4)–C(5)–O(5)		66.7(3)	O(6)–C(7)–C(8)–C(9)		−137.9(3)
C(5)–C(4)–C(3)–C(2)		51.8(3)	O(4)–C(7)–C(8)–C(9)		−16.3(4)
C(5)–C(4)–C(3)–O(3)		177.6(3)	O(6)–C(7)–C(8)–C(13)		44.5(4)
C(3)–C(4)–C(5)–O(5)		−52.9(3)	O(4)–C(7)–C(8)–C(13)		166.1(3)
C(3)–C(4)–C(5)–C(6)		−171.3(3)	C(7)–C(8)–C(13)–C(12)		178.2(3)
C(1)–O(5)–C(5)–C(4)		55.8(3)	C(7)–C(8)–C(9)–C(10)		−178.8(3)
C(5)–O(5)–C(1)–C(2)		−56.7(4)	C(9)–C(8)–C(13)–C(12)		0.60(6)
C(5)–O(5)–C(1)–O(1)		64.6(3)	C(13)–C(8)–C(9)–C(10)		−1.17(5)
C(1)–O(5)–C(5)–C(6)		175.5(3)	C(8–C(9)–C(10)–C(11)		1.13(6)
C(6)–O(6)–C(7)–O(4)		62.7(3)	C(8)–C(13)–C(12)–C(11)		0.03(6)
C(7)–O(6)–C(6)–C(5)		−57.3(3)	C(12)–C(11)–C(10)–C(9)		−0.48(6)
C(6)–O(6)–C(7)–C(8)		−176.5(3)	C(10)–C(11)–C(12)–C(13)		−0.09(7)
C(4)–C(5)–C(6)–O(6)		52.44(4)			

quence the cyclohexane moiety is distorted in such a way that the two vicinal hydroxyl groups involved in the acetal become more coplanar.[37] This *cis*-fused 1,3-dioxolane ring induces a narrowing effect on both the exocylic O(3)–C(3)–C(4)–O(4) and endocyclic C(2)–C(3)–C(4)–C(5) torsion angles. Since it has been documented that a single *cis*-dioxolane fusion causes only minor distortions as noticed in the case of 3,4,6-tri-*O*-acetyl-1,2-*O*-isopropylidene-D-galactopyranose which adopts a distorted[4] C_1 conformation[38], distortion of the chair conformation in **3b** is mainly due to the double bond. The present finding confirm this trend, showing that the *cis*-dioxolane fusion in the 3,4-position, independently of the nature of substituents at 2 and 6 and in the dioxolane ring, causes only a marked flattening of the $^4C_1$ D-galactopyranoside conformation both in solution and in the solid state. Similar observation has been made recently by Barili *et al.*[25] in the case of 3,4-*O*-isopropylidene-α-and-β-D-galactopyranosides.

The orientation of the primary hydroxymethyl group in **3b** is *trans-gauche* with torsion angles O(5)–C(5)–C(6)–O(6) = 175.7(8)° and C(4)–C(5)–C(6)–O(6) = −59.9(11)° in contrast to methyl α-D-galactopyranoside which adopts a *gauche-trans* conformation.[34] These are the two preferred non-eclipsed conformers normally displayed in the solid state for monosaccharides having the *galacto* configu-

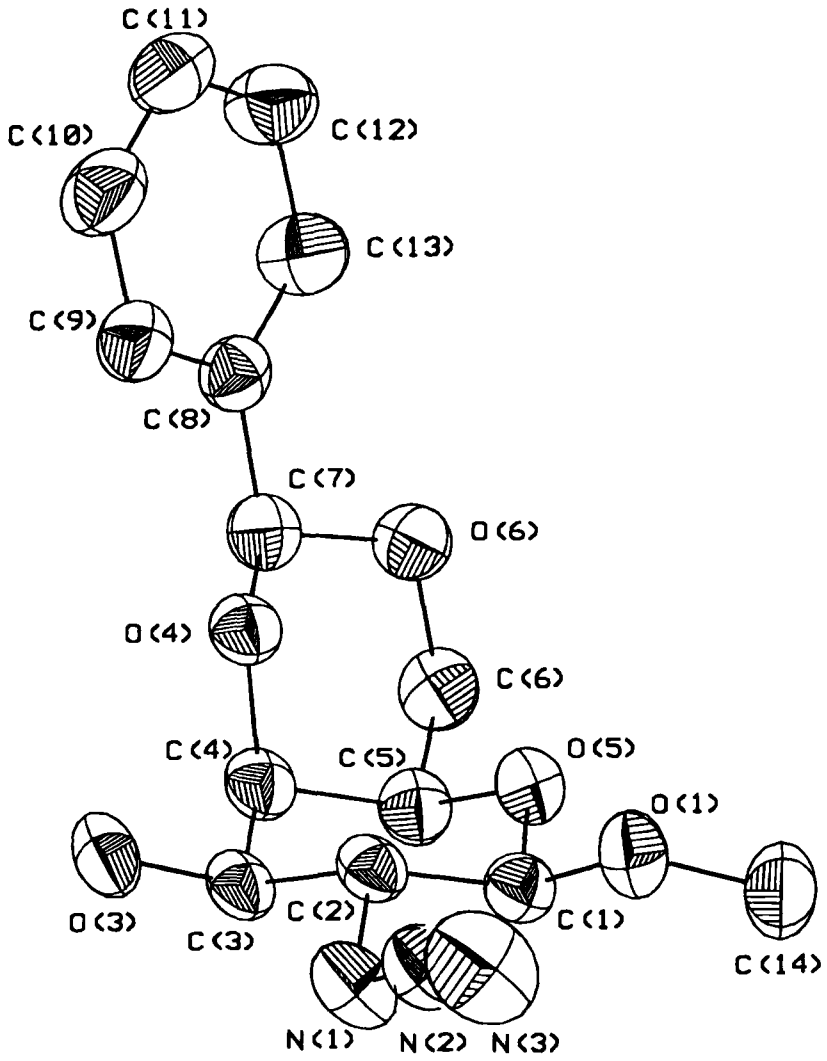


Fig. 1.

ration.[39] The stereoscopic representation of the crystal packing for 3,4-*O*-benzylidene-D-galactal (**3b**) is shown in Fig. 4. From packing diagram it appears that the thermal ellipsoids for O(6) of the primary hydroxymethyl group is surprisingly distorted. The hydrogen of the $-OH$ group in $-CH_2OH$ will undoubtedly hydrogen bond to another oxygen atom in the cell and the packing diagram shows that the hydrogen bond is to O(6) related by 6_1. The O···O distance of 2.72 Å is short and represents a strong hydrogen bond which should fix O(6) firmly in the cell. One possible explanation for this distortion comes from the fact that either the oxygen atom is disordered in two positions of the large central hole of the 6_1 axis contains a weakly bound water molecule(s) which will probably not show up very strongly in the difference map of this non-centrosymmetric structure.

The perspective drawing of **3c** with thermal ellipsoids and the atomic numbering scheme is shown in Fig. 3. The molecular geometry and torsion angles are given in Tables 6 and 7. As expected, the dioxolane and pyranose rings are *cis*-fused and in chair conformations. The pyranose ring adopts $^4C_1$ conformation, placing the glycosidic bond in an axial orientation and the C(3) hydroxyl-substituent equitorial. Some flattening of the pyranose chair was observed as suggested by the torsion angle O(5)−C(1)−C(2)−C(3) = 54.17° which agrees well with the earlier literature.[28,29] All C−C and C−O bond lengths [excluding those to O(1) and O(5)] are found to be 1.502(3) and 1.42(2) Å,

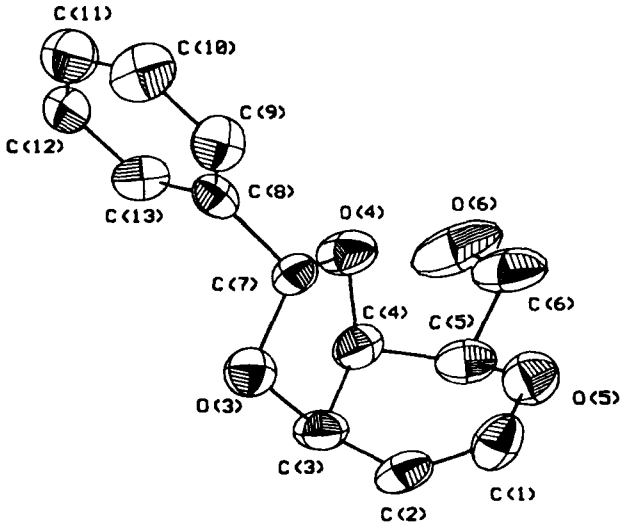


Fig. 2.

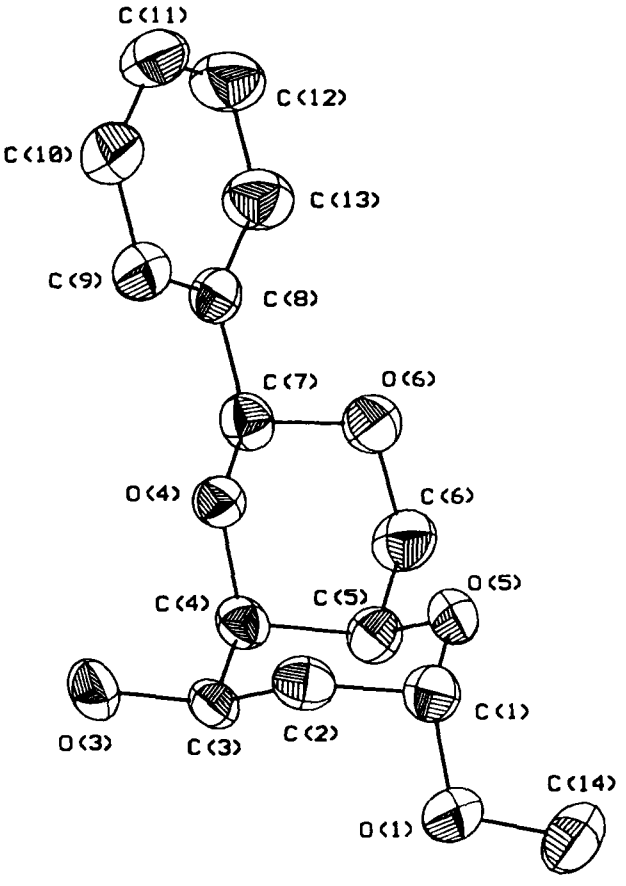
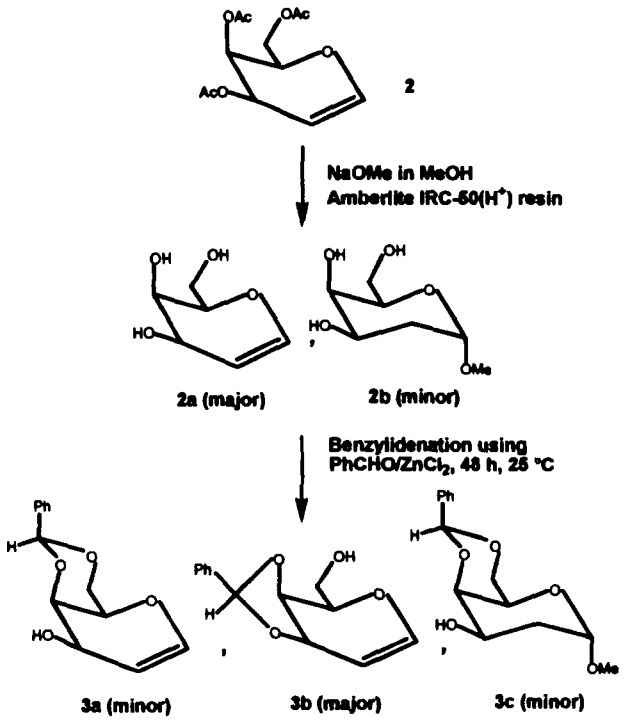


Fig. 3.



Scheme 1.

respectively. The observed C(5)–O(5) distance [1.43(4) Å] does not differ significantly from the mean value of 1.42(2) Å. In contrast to the C(1)–O(1) bond length of **1** which is 1.387(3) Å, the C(1)–O(1) bond length in **3c** is 1.405(4) Å. This observation is not unusual as in the averaged structure differing bond lengths are observed in the O(5)–C(1)–O(1)–R system depending upon the configuration of C(1) and the nature of **R**. This feature again explains the axial orientation (α) of the methoxyl substituent in **3c** as opposed to that of **1** which has the methoxyl substituent in equitorial orientation (β). The average bond angle and torsional angles in the pyranose ring of **3c** are 111.7(2) and 53.9(3)°, which indicates a more puckered conformation, possibly reflecting the absence of a substituent on C(2). Similar observation has been made in the X-ray structure of 1-*O*-benzoyl-4, 6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α-D-*arabino*-hexopyranose which also lacks a C(2) substituent.[40] Our X-ray data show that **3c** essentially contains the same structural feature of **1** except that it doesn't carry the azido functional group on C(2) and the glycosidic linkage is *(+)anticlinal*, with O(5)–C(1)–O(1)–C(14) = 62.5(4)°. For determining the pyranose ring conformation, torsional angles of methyl 3,4, 6-tri-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranoside were utilized[41]

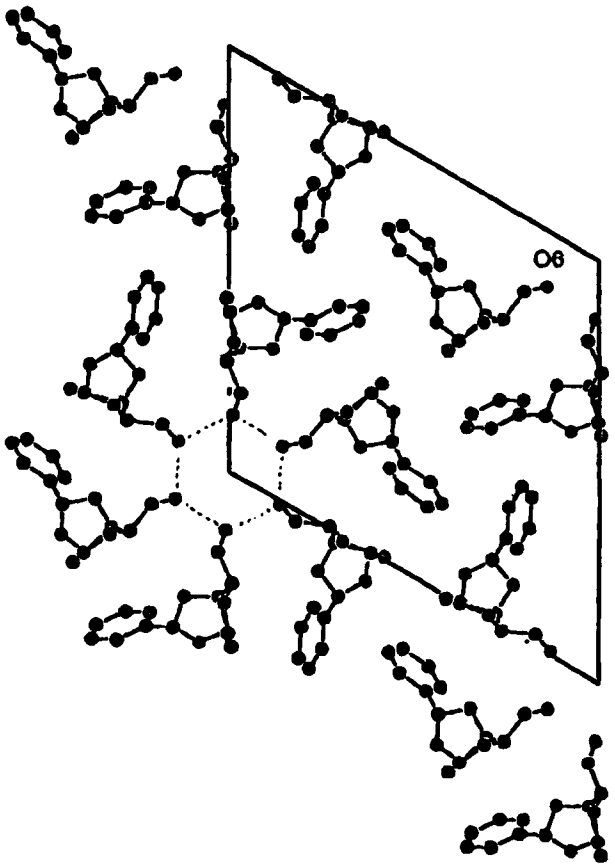


Fig. 4.

and compared with that of **3c**. No significant difference was noticed.

The cyclic benzylidene acetals of *galacto* series documented herein were found to have significant applications in the synthesis of oligosaccharide derivatives and appears to be prospective candidates for the synthesis of oligosaccharides by solid-phase methods.[42] In fact, one of its structural analogs 4,6-*O*-benzylidene-D-glucal has already been used for the synthesis of various oligosaccharides by solid-phase methods, recently.[43] In conclusion, the present study provides synthetic procedures and complete crystal structure of the three important derivatives, methyl 2-azido-2-deoxy-4, 6-*O*-benzylidene-β-D-galactopyranoside (**1**), 3,4-*O*-benzylidene-D-galactal (**b**), and methyl 2-deoxy-4,6-*O*-benzylidene-α-D-galactopyranoside (**3c**) used for the preparation of glycopeptide building blocks and oligosaccharides by solid-phase synthetic methods.

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Supplementary material Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1003/ 5413 (for **1**), CCDC-1003/5414 (for **3b**), and CCDC-1003/5415 (for **3c**). Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

References

1. (a) Hokomori, S.-I. *Adv. Cancer Res.* **1989**, *52*, 257. (b) Varki, A. *Glycobiology* **1993**, *3*, 97. (c) Kim, Y.S.; Gum, J.R.; Brockhausen, I. *Glycoconjugate J.* **1996**, *13*, 693.
2. (a) Schachter, H.; Brockhausen, I. In *Glycoconjugates: Composition, Structure and Function*; Allen, H.J.; Kisailus, E.C.; Eds.; Marcel Dekker: New York, 1992; pp 263–332. (b) Hounsell, E.F.; Davies, M.J.; Renouf, D.V. *Glycoconjugate J.* **1996**, *13*, 19.
3. (a) Strous, G.J.; Dekker, J. *CRC Rev. Biochem. Mol. Biol.* **1992**, *27*, 57. (b) Kornfeld, R.; Kornfeld, S. *Ann. Rev. Biochem.* **1985**, *54*, 631.
4. (a) Gururaja, T.L.; Ramasubbu, N.; Levine, M.J. *Letts. Pept. Sci.* **1996**, *3*, 79. (b) Satyanarayana, J.; Gururaja, T.L.; Naganagowda, G.A.; Ramasubbu, N.; Levine, M.J. *J. Peptide Res.* **1998**, *52*, 165.
5. (a) Bonchkov, A.F.; Zaikov, G.E. *Chemistry of the O-glycosidic bond: Formation and Cleavage*; Pergmon Press: Oxford, 1979. (b) Paulsen, H. *Chem. Soc. Rev.* **1984**, *13*, 15.
6. (a) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21. (b) Paulsen, H. *Angew. Chem.* **1990**, *102*, 851. (c) Kunz, H. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 294.
7. Evans, M.E. *Carbohydr. Res.* **1972**, *21*, 473.
8. Paulsen, H.; Paal, M. *Carbohydr. Res.* **1984**, *135*, 71.
9. (a) Venugopalan, P.; Burgi, H.B. *Helv. Chim. Acta* **1994**, *77*, 1475. (b) Venugopalan, P.; Weiss, R.G.; Venkatesan, K. *J. Org. Chem.* **1992**, *57*, 276.
10. (a) Sheldrick, G.M. In *Crystallographic Computing*; Sheldrick, G.M.; Kruger, C.; Goddard, R., Eds.; Vol. 3, Oxford Univ. Press: Oxford, 1985. (b) Sheldrick, G.M. *SHELXL-93, Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1993.
11. Johnson, C.K. *ORTEP-II, Report ORNL-5138*; Oak Ridge National Laboratory, TN, 1976.
12. *International Tables for X-Ray Crystallography*, Kynoch Press: Birmingham, Vol. IV, 1974, Present distributor: Kluwer Academic Publishers, Dordrecht.
13. Paulsen, H.; Peters, S.; Bielfeldt, T.; Meldal, M.; Bock, K. *Carbohydr. Res.* **1995**, *268*, 17.
14. Clode, D.M. *Chem. Rev.* **1979**, *79*, 491.
15. Richardson, A.C. *Carbohydr. Res.* **1967**, *4*, 42.
16. Blaha, K.; Hermankova, V.; Jary, J.; Zobacova, A. *Collection Czechoslov. Chem. Commun.* **1972**, *37*, 4050.

17. (a) de Belder, A.N. *Adv. Carbohydr. Chem.* **1965**, *20*, 219. (b) Gelas, J. *Adv. Carbohydr. Chem.* **1981**, *39*, 71.
18. (a) Buchanan, J.G.; Miller, K.J. *Chem. Ind. (London)* **1958**, *625*. (b) Ball, D.H.; Jones, J.K.N. *J. Chem. Soc.* **1958**, *905*.
19. (a) Dobinson, B.; Foster, A.B.; Stacey, M. *Tetrahedron Lett.* **1959**, *1*. (b) Evans, M.E.; Parrish, F.W. *Tetrahedron Lett.* **1966**, 3805.
20. (a) Baggett, N.; Mosihuzzaman, Md.; Webber, J.M. *Carbohydr. Res.* **1969**, *11*, 263. (b) Garegg, P.J.; Maron, L.; Swahn, C.-G. *Acta Chem. Scand.* **1972**, *26*, 518.
21. Eklind, K.; Garegg, P.J.; Gotthammar, B. *Acta Chem. Scand.* **1972**, *B29*, 633.
22. Garegg, P.J.; Swahn, C.-G. *Methods Carbohydr.* **1980**, *VIII*, 317.
23. Lemieux, R.U.; Fraga, E.; Watanabe, K.A. *Can. J. Chem.* **1968**, *46*, 61.
24. Sharma, M.; Brown, R.K. *Can. J. Chem.* **1966**, *44*, 2825.
25. Barili, P.L.; Catelani, G.; Fabrizi, G.; Lamba, D. *Carbohydr. Res.* **1993**, *243*, 165.
26. Barili, P.L.; Berti, G.; Catelani, G.; Colonna, F.; D'Andrea, F. *Carbohydr. Res.* **1989**, *190*, 13.
27. Lamba, D.; Segre, A.L.; Fabrizi, G.; Matsuhiro, B. *Carbohydr. Res.* **1993**, *243*, 217.
28. Jeffrey, G.A.; Pople, J.A.; Binkley, J.S.; Vishveshwara, S. *J. Am. Chem. Soc.* **1978**, *100*, 373.
29. (a) Berman, H.M.; Chu, S.S.C.; Jeffrey, G.A. *Science* **1967**, *157*, 1576. (b) Gatehouse, B.M.; Poppleton, B.J. *Acta Crystallogr. Sect. B* **1971**, *27*, 654. (c) Jeffrey, G.A. *Acta Crystallogr. Sect. B*, **1990**, *46*, 89.
30. (a) Baggett, N.; Duxbury, J.M.; Foster, A.B.; Webber, J.M. *Carbohydr. Res.* **1965**, *1*, 22. (b) Puliti, R.; Mattia, A; Barone, G. *Carbohydr. Res.* **1988**, *182*, 148.
31. Chu, S.S.C.; Jeffrey, G.A. *Acta Crystallogr. Sect. B* **1968**, *24*, 830.
32. (a) Cremer, D.; Pople, J.A. *J. Am. Chem. Soc.* **1975**, *97*, 1354. (b) Sundaralingam, M. *Biopolymers* **1968**, *6*, 189.
33. Matias, P.M.; Jeffery, G.A. *Carbohydr. Res.* **1986**, *153*, 217.
34. (a) Arnott, S.; Scott, W.E. *J. Chem. Soc. Perkin Trans. 2* **1972**, 324. (b) Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **1987**, S1–S19.
35. Schwarz, J.C.P. *J. Chem. Soc. Chem. Commun.* **1973**, 505.
36. Stokhuyzen, R.; Chieh, C. *J. Chem. Soc. Perkin Trans 2* **1976**, 481.
37. Koll, P.; Saak, W.; Pohl, S.; Steiner, B.; Koos, M. *Carbohydr. Res.* **1994**, *265*, 237.
38. Cano, F.H.; Foces-Foces, C.; Jimenez-Barbero, J.; Alemey, A.; Bernabe, M.; Martin-Lomas, M. *Carbohydr. Res.* **1988**, *175*, 119.
39. Marchessault, R.H.; Perez, S. *Biopolymers* **1979**, *18*, 2369.
40. Guthrie, R.D.; Irvine, R.W.; Davison, B.E.; Henrick, K.; Trotter, J. *J. Chem. Soc. Perkin Trans. 2* **1981**, 468.
41. Lee, E.; Melody, N.; McArdle, P.; Cunningham, D. *Carbohydr. Res.* **1991**, *219*, 229.
42. (a) Veeneman, G.H.; Notermans, S.; Liskamp, R.M.J.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.* **1987**, *28*, 6695. (b) Douglas, S.P.; Whitfield, D.M.; Krepinsky, J.J. *J. Am. Chem. Soc.* **1991**, *113*, 5095. (c)Schuster, M.; Wang, P.; Paulson, J.C.; Wong, C-H. *J. Am. Chem. Soc.* **1994**, *116*, 1135.
43. (a) Danishefsky, S.J.; McClure, K.F.; Randolph, J.T.; Ruggeri, R.B. *Science* **1993**, *260*, 1307. (b) Danishefsky, S.J.; Bilodeau, M.T. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380.