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X-Ray Crystal Structure Determinations of Galactosylacetylene Building Blocks

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We report the crystal structures of two galactosylacetylenes: 3,7-anhydro-4,5,6,8-tetra-O-benzyl-1,1,2,2-tetradehydro-1,2-dideoxy-1-C-(trimethylsilyl)-D-glycero-L-mann ooctitol (7) and 3,7-anhydro-4,5,6,8-tetra-O-benzyl-1,1,2,2-tetradehydro-1,2-D-glycero-L-mannooctitol (8). A short overview of the synthetic chemistry used to obtain these targets is mentioned.

Keywords X-ray crystal structure; Galactosylacetylene; Structure; Synthesis

INTRODUCTION

Glycosylacetylene building blocks have been appearing in the literature^[1,2] and are proving to be valuable building blocks in carbohydrate chemistry. Galactosylacetylenes are an important member of this group and have been used in the ever expanding area of 1,3-dipolar cycloaddition of terminal azides and alkynes (Huisgen reactions), which are a subset of "click" chemistry.^[3–6] "Click" chemistry of azides and alkynes has been heavily utilized due to its robust nature in facilitating aqueous or oxygenated conditions, uncomplicated operation and workup, and high-yielding transformations.^[7,8] The glycosylacetylenes, including the galactosylacetylenes, have also been used in C-glycosylamino acid and

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glycopeptide synthesis.^[5,6,9–13] Due to 7 and 8 being widely used as building blocks for C-glycosylamino acids, glycopeptides, and other carbohydrate-based structures, it is important to confirm the anomeric configurations.

RESULTS AND DISCUSSION

The synthesis of compounds 7 and 8 is shown in Scheme 1. Key to the synthesis of the anomer-substituted galactosylacetylene 8 was the alkynyl addition to the lactone intermediate 5. Accordingly, the synthesis of D-galactonolactone 5 was readily achieved by oxidation of the methyl 2,3,4,6-tetra-O-benzyl-D-galactoside 3 via the methyl-D-galactopyranoside 2.^[14–16]



Scheme 1: Synthesis of galactosylacetylenes 7 and 8.

Reagents and conditions: (i) Amberlite IR 120, 115°C, MeOH, 92% (lit.^[17] 78%); (ii) BnBr, NaH, Bu₄NI, DMF, 84% (lit.^[14] 82%); (iii) AcOH (80%), 1M H₂SO₄, 145°C, 70% (lit.^[14] 62%); (iv) Ac₂O, DMSO, 88% (lit.^[16] 90%); (v) Li-TMS acetylene, CeCl₃, THF, 80% (lit.^[9] 91%); (vi) Et₃SiH, BF₃·OEt₂, CH₃CN-CH₂Cl₂, 73% (lit.^[9] 71%); (vii) NaOH, MeOH-CH₂Cl₂, 90% (lit.^[9] 99%).

Deprotection of the methyl acetal **3** to the hemiacetal **4** was carried out with 80% AcOH and 1M H₂SO₄ at reflux.^[14] The oxidation method used for the tetraacetate analogue of galactonolactone **5** was used successfully for the oxidation of compound **4** to **5**.^[15,16] We noted, however, that insufficiently pure methyl α/β -D-galactoside gave unwanted 2,3,4,6-tetra-O-benzyl-D-galactonofurano- δ -lactone, which was evidenced by the ¹³C NMR analysis, where the furano carbonyl peak was deshielded by δ 2.2 ppm relative to the corresponding pyrano carbonyl signal.^[16,18–21] Alkyne addition to the galactolactone **5** was mediated by lithiated trimethylsilyl (TMS)-acetylene in the presence of $CeCl_3$ affording the hemiacetal **6** in 80% yield.^[9] Treatment of **6** with a Lewis acid promoted the formation of the oxonium ion, which was stereoselectively intercepted by triethylsilane to afford the protected alkynylgalactose **7** in good yield.^[9] The structure of this compound was verified by X-ray crystallography (Fig. 1), which showed that the product is in the beta configuration and is the pyranose isomer. 3,7-Anhydro-4,5,6,8-tetra-O-benzyl-1,1,2,2-tetradehydro-1,2-D-glycero-L-mannooctitol **8** was also successfully crystallized and analyzed by X-ray crystallography (Fig. 2), which again confirmed the beta configuration of the alkyne and the pyranose form.

We noted that **7** was successfully crystallized, while previous workers reported this compound as an oil.^[9]

Both compounds 7 and 8 crystallized in the monoclinic space group $P2_1$, compound 7 having two independent molecules in the asymmetric unit. The two molecules differed slightly with respect to the conformations of the 2- and



Figure 1: Thermal ellipsoid plot for compound 7, molecule 1. Ellipsoids are at the 20% probability level.



Figure 2: Thermal ellipsoid plot for compound 8. Ellipsoids are at the 20% probability level.

3-*O*-benzyl substituents; however, the bond distances and angles for the two molecules were not significantly different from one another. Selected bond distances and angles for the pyranose rings of **7** and **8** and of the anomeric alkyne substituents are presented in Table 1.

	7 (M1)	7 (M2)	8	9	10
C1-C2	1.547(3)	1.544(3)	1.540(4)	1.528	1.544
C1-C7	1.471(4)	1.476(4)	1.462(4)	1.475	1.484
C2-C3	1.507(4)	1.517(4)	1.517(4)	1.513	1.521
C3-C4	1.528(3)	1.525(4)	1.538(4)	1.534	1.545
C4-C5	1.518(4)	1.522(3)	1.520(4)	1.543	1.528
C5-O1	1.432(3)	1.431(3)	1.427(3)	1.434	1.441
01-C1	1.433(3)	1.431(3)	1.433(3)	1.416	1.425
C2-O2	1.421(3)	1.419(3)	1.434(3)	1.421	1.427
C3-O3	1.426(3)	1.433(3)	1.430(3)	1.419	1.410
C4-O4	1.426(3)	1.422(3)	1.418(3)	1.422	
O1-C1-C2	110.8(2)	111.6(2)	110.7(2)	110.3	110.3
C1-C2-C3	107.5(2)	109.1(2)	109.8(2)	110.7	111.7
C2-C3-C4	109.7(2)	110.9(2)	111.2(2)	110.1	109.2
C3-C4-C5	108.0(2)	107.6(2)	107.5(2)	110.2	109.5
C4-C5-O1	110.8(2)	113.6(2)	110.1(2)	108.9	109.0
C5-O1-C1	111.5(2)	112.4(2)	110.6(2)	114.0	113.2
01-C1-C7	108.6(2)	107.5(2)	107.5(2)	112.0	113.2
C2-O2 C3-O3 C4-O4 O1-C1-C2 C1-C2-C3 C2-C3-C4 C3-C4-C5 C4-C5-O1 C5-O1-C1 O1-C1-C7	1.421(3) 1.426(3) 1.426(3) 107.5(2) 109.7(2) 108.0(2) 110.8(2) 111.5(2) 108.6(2)	1.419(3) 1.433(3) 1.422(3) 111.6(2) 109.1(2) 109.(2) 107.6(2) 113.6(2) 112.4(2) 107.5(2)	1.434(3) 1.430(3) 1.418(3) 110.7(2) 109.8(2) 111.2(2) 107.5(2) 110.1(2) 110.6(2) 107.5(2)	1.421 1.419 1.422 110.3 110.7 110.1 110.2 108.9 114.0 112.0	1. 110. 111. 109. 109. 109. 113. 113.

Table 1: Selected bond distances (Å) and angles (°) for compounds 7 (both molecules), 8, 9, and 10

Both alkynes **7** and **8** have the β -configuration and the C1–C7 bond distances are not significantly different from one another. It is of interest to compare these structures with other anomeric alkynes, particularly those with the α -configuration, as these may reveal structural effects arising from the anomeric effect. A survey of the Cambridge Crystallographic database^[22] gave the structures **9** and **10**, which were deemed accurate enough and suitable for comparison.^[23] The C1-C7 bond distance in compound **9**, which is an anomeric alkyne having the α -configuration, is not significantly different from either **7** or **8**; however, the C–C bond distance in the anomeric alkyne **10** is lengthened slightly compared to the nonanomeric alkyne at the 4-position in the same structure, suggesting that the $n_0-\sigma^*_{CC}$ interaction is lengthening this bond. Comparison with a larger range of structures needs to be made before any conclusions can be made as to whether there are any significant structural differences between α - and β -anomeric alkynes.



CONCLUSION

We have successfully solved the X-ray crystal structures of 3,7-anhydro-4,5,6,8-tetra-O-benzyl-1,1,2,2-tetradehydro-1,2-dideoxy-1-C-(trimethylsilyl)-D-glycero-L-mannooctitol **7** (Fig. 1) and 3,7-anhydro-4,5,6,8-tetra-O-benzyl-1,1, 2,2-tetradehydro-1,2-D-glycero-L-mannooctitol **8** (Fig. 2), which were successfully synthesized via Scheme 1. These novel XRD crystal structures clearly confirmed the relative configuration of **7** and **8**. Compounds such as **8** are proving to be useful building blocks in carbohydrate synthesis.

EXPERIMENTAL

Crystallography

Intensity data for compound 8 was collected with an Oxford Diffraction Sapphire CCD diffractometer using Cu-Ka radiation (graphite crystal monochromator $\lfloor = 1.54184$); intensity data for 7 was collected with a Bruker SMART Apex CCD detector using Mo-Ka radiation (graphite crystal monochromator $\lfloor = 0.71073$). The temperature during data collection was maintained at 130.0(1) K.

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Crystal data for 7

The crystals obtained for **7** were recrystallized from hexanedichloromethane, mp 78–80°C. $C_{39}H_{44}O_5Si$, M = 620.83, T = 130.0(2) K, $\downarrow = 0.71073$ Å, Monoclinic, space group P2₁ a = 18.607(1), b = 7.5190(5), c = 25.337(2) Å, [®] = 99.639(1)°. V 3494.8(4) Å³, Z = 4, D_c = 1.180 mg M⁻³ \lceil (Mo-K() 0.109 mm⁻¹, F(000) = 1328, crystal size 0.5 × 0.45 × 0.40 mm. 18212 reflections measured, 9143 independent reflections (R_{int} = 0.0335); the final R was 0.042, [I > 2 \lceil (I)] and wR(F²) was 0.0987 (all data).

Crystal data for 8

The crystals obtained for **8** were recrystallized from hexanedichloromethane, mp 81–83°C (lit.^[11] 79–80°C (pentane)). $C_{36}H_{36}O_5$, M = 548.65, T = 130.0(2) K, \lfloor = 1.54184 Å, Monoclinic, space group P2₁ a = 11.2772(3), b = 8.4295(2), c = 16.5947(2) Å, [®] = 109.206(2)°. V 1489.71(6) Å³, Z = 2, D_c = 1.223 mg M⁻³ [(Mo-K $\langle\rangle$) 0.642 mm⁻¹, F(000) = 584, crystal size 0.5 × 0.45 × 0.40 mm. 5898 reflections measured, 4399 independent reflections (R_{int} = 0.0351); the final R was 0.045, [I > 2[(I)] and wR(F²) was 0.0984 (all data).

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