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Carbohydrate Research 324 (2000) 210–217

CARBOHYDRATE
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Note

Unexpected formation of glycals upon attempted C-alkylation of protected glycosylacetylenes

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Received 5 October 1999; accepted 5 November 1999

Abstract

Treatment of 3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-1,2-dideoxy-D-*glycero*-D-*galacto*-oct-1-ynitol (β-D-mannosyl acetylene, **1**) with 5 equivalents of *n*-butyllithium at either 0 or −78 °C resulted in the elimination of benzyl alcohol to yield 3,7-anhydro-5,6,8-tri-*O*-benzyl-1,2,4-trideoxy-D-*arabino*-oct-3-en-1-ynitol (glycal acetylene, **3**) as the major product. Additional studies showed that **3** is also produced from two isomers of **1** with α-D-mannosyl and β-D-glucosyl stereochemistry, but in lower yields. Furthermore, substrates in which the acetylene moiety is replaced by either a methyl or phenyl group do not produce a glycal product under these conditions. Finally, treatment of **1** with phenyllithium provides **3** in low yield. Deuterium labeling studies suggest that the reaction proceeds through an E2, rather than an E1cB, mechanism. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Glycals; *C*-Glycosides; Glycosylacetylenes

1. Introduction

Glycosyl acetylenes (e.g., 3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-1,2-dideoxy-D-*glycero*-D-*galacto*-oct-1-ynitol (**1**)) have been shown in recent years to be versatile synthetic intermediates, having been used for the preparation of a variety of targets including *C*-aryl glycosides [1–3], C-linked glycosyl amino acid conjugates [4], and polysaccharide mimics [5,6]. In the course of other investigations, we needed to C-alkylate the alkyne moiety of **1** with ethyl iodide. Using standard conditions, *n*-butyllithium (2.0 equivalents), THF, 0 °C, followed by iodoethane (3 equivalents), **1** provided **2** in only 35% yield, the major product being unreacted starting material. An excess of base was needed due to adventitious water present in the reaction mixture. In an attempt to improve the yield of the desired product, the reaction was then carried out by treatment of **1** with 5 equivalents of the base, followed by 10 equivalents of iodoethane. The major product formed, in 63% yield, was not **2** but instead the glycal acetylene **3**. Only two such substituted glycals, **4** [1,2] and **5** [1], have been reported, and both have been shown to be useful intermediates in the synthesis of *C*-aryl glycosides [1,2]. Previously, the only access to acetylenic glycals of this type has been via the addition of magnesium trimethylsilylacetylide to 2-deoxyglycosyl lactones, followed by dehydrative elimination [1,2,7].

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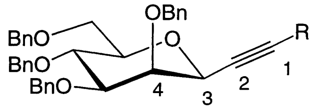
PII: S0008-6215(99)00296-7



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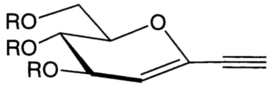
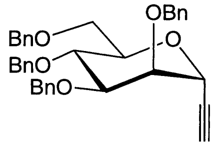
2 R = CH_2CH_3
6 R = CH_3



3 R = Bn
4 R = t-BuMe_2Si
5 R = Ac



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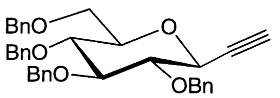

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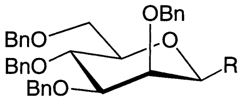

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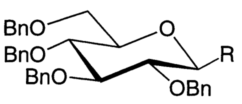
10 R = Ph



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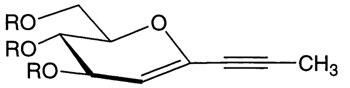
12 R = Ph



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The structure of **3** was determined through the use of NMR spectroscopy in $CDCl_3$. Characteristic absorptions in the ^{1}H NMR spectrum included those arising from the vinylic hydrogen, H-4 (5.38 ppm, doublet, J 2.9 Hz), and the alkyne hydrogen, H-1 (2.93 ppm, singlet). The alkyne hydrogen in **1** is coupled to H-3 and therefore appears in the ^{1}H NMR spectrum as a doublet (J 2.3 Hz). The fact that this signal appears as a singlet in the spectrum of **3** suggests that H-3 has been lost. Furthermore, integration of the aromatic protons identified the presence of only three benzyl groups. Taken together, these data indicate the loss of benzyl alcohol from across the C-3–C-4 bond. In the ^{13}C NMR spectrum of **3**, the resonances for C-3 and C-4 appeared at 137.25 and 107.76 ppm, respectively. The structure of the product was further supported by the assignments of all other resonances, which could be done straightforwardly via ^{1}H–^{1}H and ^{1}H–^{13}C correlation experiments.

Although it is known that glycals are formed by the treatment of either glycosyl halides [8] or sulfoxides [9] with n-butyllithium, to the best of our knowledge this is the first report of the formation of these products upon reaction of this base with a *C*-glycoside. We have therefore explored the scope of this elimination reaction by treating substrates **6**–**12** with an excess of n-butyllithium. In order to test the requirement that the benzyloxy leaving group be trans to H-3, compounds **7** and **8** were prepared. The necessity of the alkyne functionality was probed by synthesizing substrates **9**–**12**, the β-*C*-methyl and β-*C*-phenyl glycosides of D-mannose and D-glucose. Finally, to investigate if the reaction proceeded with internal alkynes, **6** was synthesized and subjected to the reaction. *C*-Glycosides **7**–**12** have been reported [4,10–12], and their preparation proceeded without incident using known protocols. The synthesis of **6** was done by reacting iodomethane with **1**

Table 1
Formation of an elimination product upon treatment of **1** and **6**–**12** with n-butyllithium or phenyllithium [a]

Entry	Substrate	RLi	Temperature (°C)	Yield of elimination product [b] (%)
1	**1**	n-BuLi	0	63
2	**1**	n-BuLi	−78	56
3	**7**	n-BuLi	−78	40
4	**8**	n-BuLi	−78	8
5	**9**	n-BuLi	−78	ND [c]
6	**10**	n-BuLi	−78	ND
7	**11**	n-BuLi	−78	ND
8	**12**	n-BuLi	−78	ND
9	**6**	n-BuLi	−78	ND
10	**1**	PhLi	−78	11

[a] See Section 2 for reaction conditions.

[b] Yield after chromatography.

[c] ND, no product detected by TLC or by ^{1}H NMR spectroscopy of crude reaction mixtures following workup.

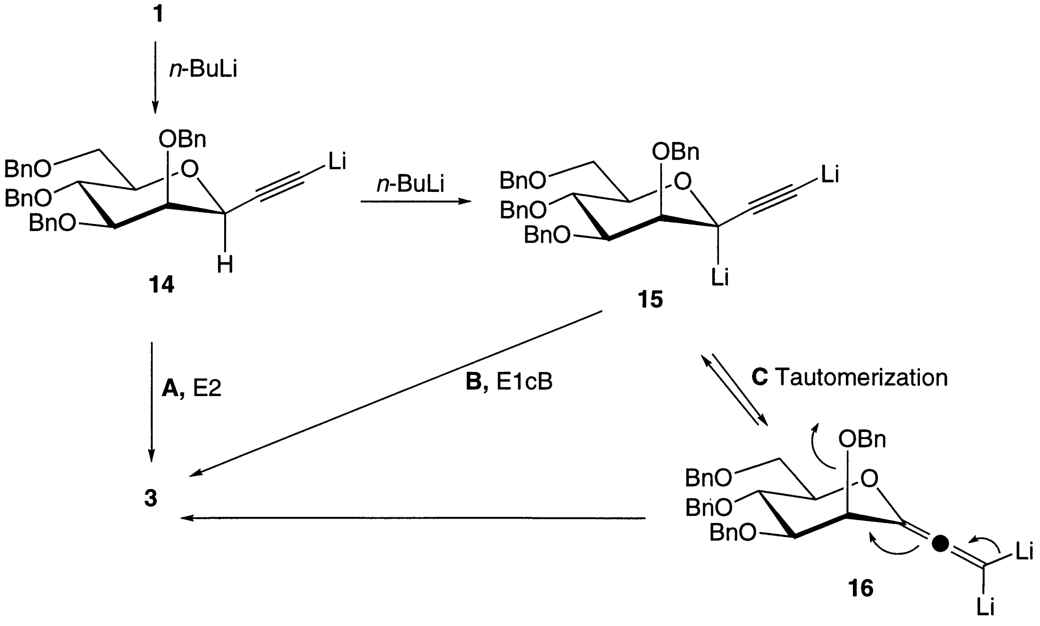


Fig. 1. Possible reaction pathways for the formation of **3**.

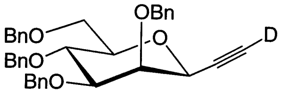
using the method described for the preparation of **2**. The desired methylated product was obtained in 54% yield along with a 29% yield of the methylated glycal acetylene **13**.

The results (Table 1) show that the best yields of **3** are obtained when the β-mannosyl acetylene **1** is treated with *n*-butyllithium. The reaction proceeds in approximately the same yield regardless of whether the reaction is carried out at 0 or −78 °C (entries 1 and 2). Furthermore, although better yields are seen with **1**, in which H-3 and the C-4 benzyloxy leaving group are 1,2-trans diaxial, there does not appear to be an absolute requirement for this stereochemistry, as a significant amount of **3** is also formed from the α-D-mannosyl acetylene **7** (entry 3). Similarly, the β-D-glucosyl acetylene **8** also affords the product, albeit in low yield (entry 4). The alkyne moiety appears to be necessary for the reaction to proceed because neither the *C*-methyl (**9**, **11**) nor *C*-phenyl (**10**, **12**) glycosides give an elimination product (entries 5–8). In order for the elimination to proceed, it is also necessary to use a terminal alkyne, as **6** gave none of the alkene product (entry 9). Finally, base strength is important as treatment of **1** with phenyllithium, a weaker base than *n*-butyllithium, resulted in only low yields of **3** (entry 10).

In the cases where the formation of an elimination product was not observed, thin-layer chromatograms showed that the major product was unreacted starting material. This was confirmed by ^{1}H NMR analysis of the crude reaction mixtures following workup. Aside from containing a few minor, unidentified reaction by-product impurities, these spectra were identical to those of the starting *C*-glycoside. In all cases, a signal for the vinylogous hydrogen in **3** was absent.

The formation of **3** from the β-D-mannosyl acetylene **1** presumably proceeds through the initial formation of an alkynyl lithium intermediate **14** (Fig. 1), which then eliminates the C-4 benzyloxy group. Three alternative mechanistic pathways are conceivable for the formation of **3** from **14**. The first (A) is direct loss of the C-4 benzyloxy group via a β-elimination. The second (B) is the formation of the dilithio species **15** from **14**, which in turn eliminates via an E1cB pathway. The third (C) is the rapid tautomerization of **15** to **16**, followed by elimination.

In order to probe the mechanism of this reaction, **1** was treated with *n*-butyllithium at −78 °C and after 15 min the reaction was quenched with an excess of CD_3OD. After the experiment was carried out, unconverted start ing material was recovered by chromatography and analyzed by NMR spectroscopy. This study showed that nearly complete deuteration occurred only at C-1 giving a mixture of **1** and **17**, which was isolated in 76% yield. A 10% yield of the glycal **3** and its deuterated analog **18** was also obtained. Deuterium incorporation was first determined by a diminution in the signal of the acetylenic hydrogen in the ^{1}H NMR spectrum of the product mixture. Unfortunately, in the proton-decoupled ^{13}C NMR spectrum of this mixture, the intensity of the signal for C-1 in **17**, which was expected to be a triplet, was very weak, thus preventing its unambiguous assignment. Therefore, the product was hydrogenated to give a mixture of **19** and **20**. The presence of deuterium in **20** was readily apparent in the ^{13}C NMR spectrum as the signal for C-1 appeared as a triplet at 9.32 ppm, slightly upfield from this resonance in **19** (9.60 ppm, singlet). All other carbons appeared as singlets, indicating no deuterium incorporation at any other position.



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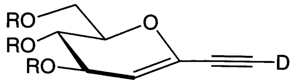

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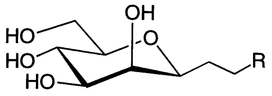
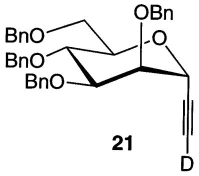


19 R = H
20 R = D



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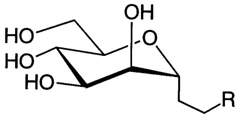

22 R = H
23 R = D

If the reaction proceeds via an E1cB mechanism, it would be expected that deuterium would be incorporated at both C-1 and C-3 in the recovered starting material. Because the label is found only at C-1, pathway B (Fig. 1) can be ruled out. The absence of deuterium incorporation at C-3 could also be attributed to the very rapid tautomerism of **15** to give **16** (C, Fig. 1) However, if this pathway is operative it would be expected that the starting material, re-isolated after the deuterium trapping experiment, would be a mixture of α- and β-*C*-glycosides. No scrambling of the stereochemistry was detected. Furthermore, no product arising from the trapping of **16** was detected and consequently pathway C can be ruled out. Therefore, based on these isotope

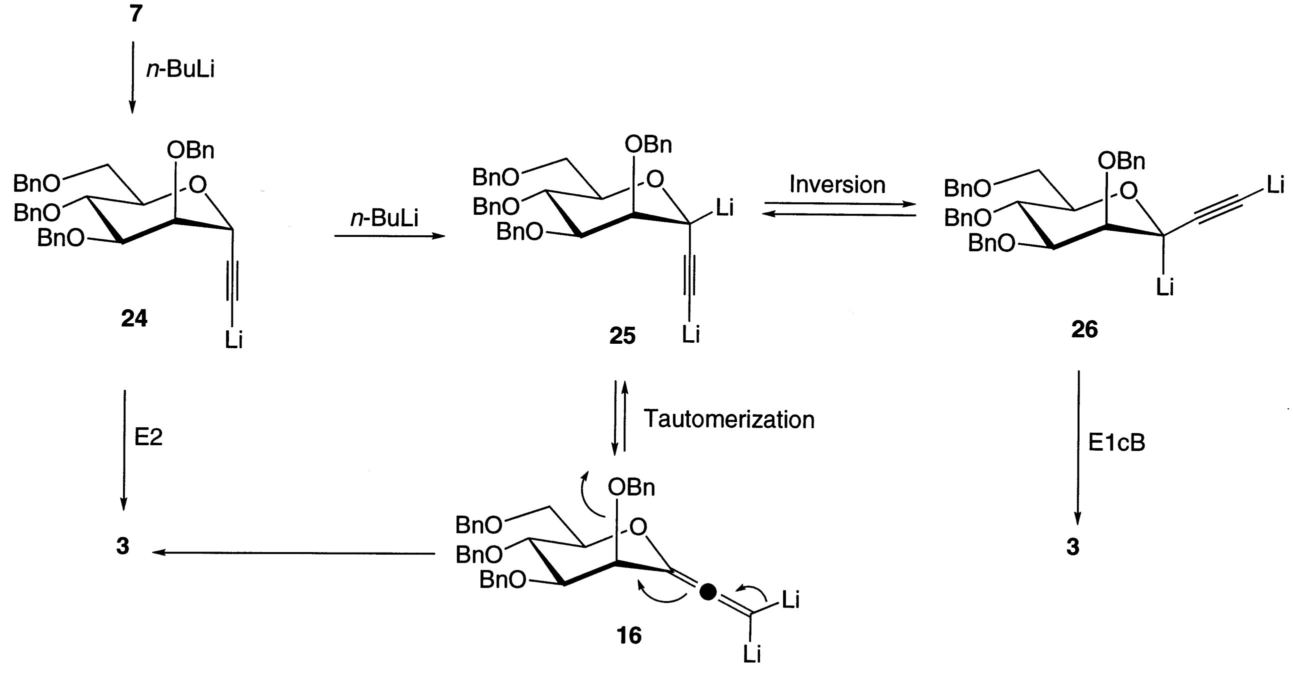

Fig. 2. Possible reaction pathways for the formation of **3** from **7**.

labeling experiments, we propose that in the case of **1** the reaction proceeds through an E2 mechanism.

The formation of **3** from **7** (Fig. 2) might be expected to involve an intermediate such as **16** given that due to the cis orientation of H-3 and the C-4 benzyloxy group, a concerted elimination would be expected to be less facile than in the case of **1**. To address this possibility, deuterium trapping experiments identical to those carried out on **1** were completed using the α-mannosyl acetylene **7** as the substrate. Upon completion of this experiment, a mixture of **7** and **21** was obtained in 67% yield, along with a 17% yield of **3**/**18**. Hydrogenation of the former gave a mixture of **22** and **23**, which were shown to have the same deuterium labeling patterns as the products obtained from **1**. Again, no equilibration of the stereochemistry at C-3 was observed.

When taken together these results suggest that neither allene **16** nor its alkyne tautomer **25** are intermediates in the reaction pathway leading to the formation of **3** from **7**. Although there is a possibility that upon the formation of **25**, a rapid inversion could occur to yield **26**, which could then eliminate via an E1cB pathway, the labeling studies do not support this pathway. Furthermore, such inversions have previously been shown not to occur in other glycosyl lithiums [13]. Consequently, we propose that the formation of **3** from **7** occurs via syn-elimination of the lithiated derivative **24**. An analogous pathway is also likely to be present in the elimination of **8**.

Finally, the lack of glycal formation from **10** and **12** is worth noting. In these *C*-glycosides, H-3 is a benzylic hydrogen and should be sufficiently acidic that upon reaction with *n*-butyllithium the elimination reaction should occur with ease. That it does not is curious and could possibly result from the size of the phenyl group, which precludes, through steric congestion, the abstraction of the H-3 by the base. Alternatively, it is also possible that, if formed, this anion is so stabilized by the aromatic ring that it is not prone to elimination.

In summary, we report here a novel elimination reaction of glycosyl acetylenes, which yield substituted glycals. We propose that this reaction proceeds though a concerted elimination mechanism.

2. Experimental

General methods.—All reaction solvents were distilled from the appropriate drying agents before use. Unless stated otherwise, all reactions were carried out at room temperature (rt) under a positive pressure of argon and were monitored by thin-layer chromatography (TLC) on Silica Gel 60 F_{254} (0.25 mm, E. Merck). Spots were detected under UV light and/or by charring with 10% H_2SO_4 in EtOH. Solvents were evaporated under reduced pressure and below 60 °C (bath). Solutions of the crude products were dried over anhyd Na_2SO_4. Column chromatography was performed on Silica Gel 60 (40–60 μM). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). Optical rotations were measured at 18 ± 2 °C. ^{1}H NMR spectra were recorded at 250, 400 or 500 MHz, and chemical shifts are referenced to either TMS (0.0, $CDCl_3$) or HOD (4.78, D_2O). ^{13}C NMR spectra were recorded at 62.5 or 100.6 MHz and ^{13}C chemical shifts are referenced to internal $CDCl_3$ (77.00, $CDCl_3$) or external dioxane (67.40, D_2O). The assignment of the resonances of **3** was made by two-dimensional homonuclear and heteronuclear shift correlation experiments. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. MALDI mass spectra were recorded on samples in an α-cyano-4-hydroxycinnamic acid matrix. Electrospray mass spectra were recorded on samples suspended in 3:1 CH_3OH–H_2O. *C*-glycosides **1** [4], **7** [4], **8** [10] and **9**–**12** [11,12] are known compounds.

*5,9-Anhydro-6,7,9,10-tetra-*O*-benzyl-1,2,3,4-tetradeoxy-*D-glycero-D-galacto-*dec-3-ynitol* (**2**).—Acetylene **1** (110 mg, 0.200 mmol) was dissolved in dry THF (2 mL) and cooled to 0 °C before the addition of *n*-butyllithium (1.6 M in hexanes, 0.25 mL, 0.40 mmol). After 1 h at 0 °C, iodomethane (0.05 mL, 0.6 mmol) was added and the mixture was allowed to stir for 1 h. At this point, the mixture was allowed to warm to rt and stirring continued for an additional 5.5 h. The mixture was then diluted with EtOAc and washed in succession with 0.1 M HCl, water, and brine. The organic layer was dried, filtered, and concentrated to give the crude product. Column chromatography (9:1 petroleum ether–EtOAc) gave product **2** (41 mg, 35%) as a syrup R_f 0.34 (6:1 petroleum ether–EtOAc); $[\alpha]_D$ − 29.8° (c 1.0, CHCl$_3$); ^{1}H NMR (250 MHz, CDCl$_3$): δ_H 7.55–7.47 (m, 2 H, PhH), 7.47–7.22 (m, 16 H, PhH), 7.22–7.14 (m, 2 H, PhH), 5.03 (s, 2 H, PhCH$_2$O), 4.91 (d, 1 H, J 10.7 Hz, PhCH$_2$O), 4.69–4.55 (m, 4 H, PhCH$_2$O), 4.55 (d, 1 H, J 10.7 Hz, PhCH$_2$O), 4.16 (m, 1 H, H-5), 3.97 (m, 1 H, H-6), 3.93 (dd, 1 H, J 9.3, 9.7 Hz, H-8), 3.79 (dd, 1 H, J 2.5, 10.9 Hz, H-10b), 3.73 (dd, 1 H, J 5.0, 10.9 Hz, H-10a), 3.56 (dd, 1 H, J 3.0, 9.3 Hz, H-7), 3.47 (ddd, 1 H, J 2.5, 5.0. 9.7 Hz, H-9), 2.27 (dq, 2 H, J 1.9, 7.5 Hz, H-2), 1.16 (t, 3 H, J 7.5 Hz, H-1); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ_C 138.63, 138.28, 138.25, 138.19 (Ph, quaternary), 128.38, 128.28, 128.25, 128.18, 128.03, 127.72, 127.63, 127.60, 127.54, 127.45, 127.41 (Ph, methine), 88.02 (C-3), 83.56 (C-7), 79.65 (C-9), 76.00 (C-6), 75.92 (C-4), 75.20 (PhCH$_2$O), 74.73 (C-8), 74.49 (PhCH$_2$O), 73.41 (PhCH$_2$O), 71.93 (PhCH$_2$O), 69.50 (2 C, C-5, C-10), 13.36 (C-2), 12.54 (C-1); ESIMS m/z Calcd for [C$_{38}$H$_{40}$O$_5$]Na$^+$ 599.2768. Found 599.2783.

3,7-Anhydro-5,6,8-tri-O-*benzyl-1,2,4-trideoxy*-D-arabino-*oct-3-en-1-ynitol* (**3**).—The acetylene **1** (117 mg, 0.213 mmol) was dissolved in dry THF (2 mL) and cooled to 0 °C before the addition of n-butyllithium (1.6 M in hexanes, 0.625 mL, 1.00 mmol). After 1 h at 0 °C, the reaction was cooled to − 78 °C and iodoethane (0.16 mL, 2.00 mmol) was added and the reaction mixture was stirred overnight, while allowing it to warm to rt. The mixture was then diluted with EtOAc, neutralized with 1.0 M HCl, and washed in succession with water and brine. The organic layer was dried, filtered, and concentrated. Chromatography gave pure **3** as a syrup (59 mg, 63%): R_f 0.51 (6:1 petroleum ether–EtOAc); $[\alpha]_D$ − 5.0° (c 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 7.36–7.16 (m, 15 H, PhH), 5.38 (d, 1 H, J 2.9 Hz, H-4), 4.81 (d, 1 H, J 11.2 Hz, PhCH_2O), 4.68–4.51 (m, 5 H, PhCH_2O), 4.23 (dd, 1 H, J 2.9, 6.3 Hz, H-5), 4.09 (ddd, 1 H, J 2.7, 4.4, 8.8 Hz, H-7), 3.91 (dd, 1 H, J 6.3, 8.8 Hz, H-6), 3.83 (dd, 1 H, J 4.4, 10.9 Hz, H-8a), 3.77 (dd, 1 H, J 2.7, 10.9 Hz, H-8b), 2.93 (s, 1 H, H-1); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ_C 138.09, 138.06, 138.04, (Ph, quaternary), 137.25 (C-3), 128.46, 128.41, 128.38, 127.92, 127.78, 127.64 (Ph, methine), 107.86 (C-4), 77.98 (C-2), 77.83 (C-7), 77.04 (C-1), 76.08 (C-5), 73.87 (PhCH$_2$O), 73.71 (C-6), 73.56 (PhCH$_2$O), 70.74 (PhCH$_2$O), 68.16 (C-8); HR-MALDI-MS m/z Calcd for [C$_{29}$H$_{28}$O$_4$]Na$^+$ 463.1885. Found 463.1905. Anal. Calcd for C$_{29}$H$_{28}$O$_4$: C, 79.07; H, 6.41. Found: C, 78.91; H, 6.54.

4,8-Anhydro-5,6,7,9-tetra-O-*benzyl-1,2,3-trideoxy*-D-glycero-D-galacto-*non-2-ynitol* (**6**) *and 4,8-anhydro-6,7,9-tri*-O-*benzyl-1,2,3,5-tetradeoxy*-D-arabino-*non-4-en-2-ynitol* (**13**).—The acetylene **1** (82 mg, 0.15 mmol) was dissolved in dry THF (2 mL) and cooled to 0 °C before the addition of n-butyllithium (2.5 M in hexanes, 0.10 mL, 0.25 mmol). After 1 h at 0 °C, methyl iodide (0.028 mL, 0.45 mmol) was added, and the mixture was stirred for 40 min before being worked up as described for the synthesis of **2**. Column chromatography (6:1 petroleum ether–EtOAc) gave two products.

The more polar product was **6** (45 mg, 54%), which was obtained as a light-yellow syrup: R_f 0.16 (6:1 petroleum ether–EtOAc); $[\alpha]_D$ − 22.6° (c 0.9, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 7.55–7.40 (m, 2 H, PhH), 7.40–7.17 (m, 16 H, PhH), 7.17–7.08 (m, 2 H, PhH), 4.98 (s, 2 H, PhCH_2O), 4.86 (d, 1 H, J 10.8 Hz, PhCH_2O), 4.66–4.53 (m, 4 H, PhCH_2O), 4.52 (d, 1 H, J 10.8 Hz, PhCH_2O), 4.09 (m, 1 H, H-4), 3.93–3.86 (m, 2 H, H-5, H-7), 3.75 (dd 1 H, J 2.1, 10.8 Hz, H-9b), 3.70 (dd, 1 H, J 5.2, 10.8 Hz, H-9a), 3.53 (dd, 1 H, J 3.0, 9.4 Hz, H-6), 3.43 (ddd, 1 H, J 2.1, 5.2, 9.7 Hz, H-8), 1.83 (d, 3 H, J 2.1 Hz, H-1); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ_C 138.67, 138.38, 138.32, 138.23 (Ph, quaternary), 128.57, 128.42, 128.31, 128.28, 128.06, 128.03, 128.02, 127.67, 127.62, 127.58, 127.44 (Ph, methine), 83.66 (C-6), 82.47 (C-2), 79.72 (C-8), 75.79 (C-3), 75.23 (PhCH$_2$O), 74.79 (C-7), 74.47 (PhCH$_2$O), 73.46 (PhCH$_2$O), 72.03 (PhCH$_2$O), 69.56, 69.53 (C-4, C-9), 3.78 (C-1);

ESIMS *m/z* Calcd for $[C_{37}H_{38}O_5]Na^+$ 585.2611. Found 585.2787.

The less polar product was **13**, which was obtained (20 mg, 29%) as a yellow syrup: R_f 0.51 (6:1 petroleum ether–EtOAc); $[\alpha]_D$ + 25.3° (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.38–7.06 (m, 15 H, PhH), 5.21 (d, 1 H, *J* 2.9 Hz, H-5), 4.80 (d, 1 H, *J* 11.3 Hz, $PhCH_2O$), 4.65–4.50 (m, 3 H, $PhCH_2O$), 4.62 (d, 1 H, *J* 11.6 Hz, $PhCH_2O$), 4.53 (d, 1 H, *J* 11.6 Hz, $PhCH_2O$), 4.23 (dd, 1 H, *J* 2.9, 6.3 Hz, H-6), 4.07 (ddd, 1 H, *J* 2.9, 4.3, 8.8 Hz, H-8), 3.89 (dd, 1 H, *J* 6.3, 8.8 Hz, H-7), 3.82 (dd, 1 H, *J* 4.3, 10.9 Hz, H-9a), 3.77 (dd, 1 H, *J* 2.9, 10.9 Hz, H-9b), 1.94 (s, 3 H, H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 138.39, 138.19, 138.11 (Ph, quaternary), 128.67, 128.41, 128.36, 128.33, 127.92, 127.88, 127.78, 127.75, 127.70, 127.67, 127.58, 127.25 (Ph, methine), 115.30 (C-4), 105.21 (C-5), 86.12, 77.58 (C-8), 76.38 (C-6), 74.42, 73.84 ($PhCH_2O$), 73.77, 73.51 ($PhCH_2O$), 70.45 ($PhCH_2O$), 68.30 (C-9), 4.13 (C-1); ESIMS *m/z* Calcd for $[C_{30}H_{30}O_4]Na^+$ 477.2036. Found 477.2067.

General procedure for elimination reaction.—The reaction was run on a 100-mg scale in 2.5 mL of THF. The dried *C*-glycoside was dissolved in THF and cooled to − 78 °C before the addition of *n*-butyllithium (2.44 M solution in hexanes, 5 equiv). The reaction was stirred at − 78 °C for 1–2 h, then quenched with MeOH and diluted with EtOAc. The resulting mixture was washed in succession with 0.1 M HCl, water, and brine. The organic layer was dried, filtered, and evaporated to give the crude product. Column chromatography was carried out when an elimination product was formed, as determined by TLC.

*3,7-Anhydro-4,5,6,8-tetra-*O*-benzyl-1,2-dideoxy-*D-glycero-D-galacto*-oct-1-ynitol-1-d* (**17**) *and 3,7-anhydro-5,6,8-tri-*O*-benzyl-1,2,4-trideoxy-*D-arabino*-oct-3-en-1-ynitol-1-d* (**18**).—The acetylene **1** (89 mg, 0.16 mmol) was dissolved in THF (2 mL) and cooled to − 78 °C. *n*-Butyllithium (2.44 M in hexanes, 0.33 mL, 0.81 mmol) was added, and the reaction mixture was stirred at − 78 °C for 15 min before the addition of CD_3OD (0.15 mL, 3.7 mmol). The reaction mixture was diluted with EtOAc and washed successively with 0.1 M HCl, water, and brine. The organic layer was dried, filtered, evaporated and the resulting residue purified by column chromatography (6:1 hexane–EtOAc) to give two products.

The more polar product was a mixture of **1** and **17** (68 mg, 76%) obtained as a colorless syrup, which solidified upon standing: R_f 0.14 (6:1 petroleum ether–EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.49–7.39 (m, 2 H, PhH), 7.39–7.18 (m, 16 H, PhH), 7.18–7.05 (m, 2 H, PhH), 4.98 (s, 2 H, $PhCH_2O$), 4.86 (d, 1 H, *J* 10.8 Hz, $PhCH_2O$), 4.66–4.50 (m, 5 H, $PhCH_2O$), 4.12 (d, 1 H, *J* 0.8 Hz, H-3), 3.95 (dd, 1 H, *J* 0.8, 2.9 Hz, H-4), 3.91 (dd, 1 H, *J* 9.4, 9.7 Hz, H-6), 3.76 (dd, 1 H, *J* 2.1, 11.0 Hz, H-8b), 3.71 (dd, 1 H, *J* 5.1, 11.0 Hz, H-8a), 3.53 (dd, 1 H, *J* 2.9, 9.4 Hz, H-5), 3.44 (ddd, 1 H, *J* 2.1, 5.1, 9.7 Hz, H-7), 2.46 (d *J* 2.3 Hz, residual H-1); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 138.48, 138.31, 138.22, 138.12 (Ph, quaternary), 128.52, 128.42, 128.32, 128.27, 128.16, 128.09, 128.04, 127.99, 127.69, 127.65, 127.55, 127.47 (Ph, methine), 83.41 (C-5), 80.01 (C-7), 79.68 (C-2) 75.92 (C-4), 75.26 ($PhCH_2O$), 74.67 (C-6), 74.60 ($PhCH_2O$), 73.48 ($PhCH_2O$), 72.07 ($PhCH_2O$), 69.43 (C-8), 69.04 (C-3).

The less polar product was a mixture of **3** and **18** (7 mg, 10%) obtained as a syrup: R_f 0.51 (6:1 petroleum ether–EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.40–7.13 (m, 15 H, PhH), 5.38 (d, 1 H, *J* 3.0 Hz, H-4), 4.81 (d, 1 H, *J* 11.2 Hz, $PhCH_2O$), 4.65 (d, 1 H, *J* 11.2 Hz, $PhCH_2O$), 4.65–4.52 (m, 4 H, $PhCH_2O$), 4.23 (dd, 1 H, *J* 3.0, 6.3 Hz, H-5), 4.09 (ddd, 1 H, *J* 2.9, 4.3, 8.7 Hz, H-7), 3.91 (dd, 1 H, *J* 6.3, 8.7 Hz, H-6), 3.83 (dd, 1 H, *J* 4.3, 11.0 Hz, H-8a), 3.78 (dd, 1 H, *J* 2.9, 11.0 Hz, H-8b) 2.94 (s, residual H-1).

*3,7-Anhydro-4,5,6,8-tetra-*O*-benzyl-1,2-dideoxy-*D-glycero-D-talo*-oct-1-ynitol-1-d* (**21**).—Acetylene **7** (97 mg, 0.18 mmol) was treated as described for the preparation of **17** from **1** to provide **21** as a mixture with **7** (65 mg, 67%) as a syrup. Also formed was the glycal product **3**/**18** (13 mg, 17%): R_f 0.24 (6:1 petroleum ether–EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.40–7.10 (m, 20 H, PhH), 4.88 (d, 1 H, *J* 10.7 Hz, $PhCH_2O$), 4.81 (d, 1 H, *J* 2.2 Hz, H-3), 4.76–4.58 (m, 4 H, $PhCH_2O$), 4.65 (d, 1 H, *J* 12.2 Hz, $PhCH_2O$), 4.54 (d, 1 H, *J* 12.2 Hz, PhC*H*$_2$O), 4.52 (d, 1 H, *J* 10.7 Hz, PhC*H*$_2$O), 4.05–3.92 (m, 3 H, H-5, H-6, H-7), 3.83 (dd, 1 H, *J* 2.2, 2.5 Hz, H-4), 3.82–3.70 (m, 2 H, H-8a,b); 2.50 (d, *J* 2.3 Hz, residual H-1); ^{13}C NMR (100.6 MHz, CD$_3$OD): δ_C 140.24, 139.98, 139.94, 139.85 (Ph, quaternary), 130.36, 129.84, 129.79, 129.72, 129.65, 129.63, 129.53, 129.24, 129.20, 129.09, 129.07 (Ph, methine), 81.59 (C-5), 79.38 (C-1), 78.26, 76.48 (PhCH$_2$O), 76.35, 76.25, 74.78 (Ph*C*H$_2$O), 73.41 (Ph*C*H$_2$O), 73.24 (Ph*C*H$_2$O), 70.69 (C-8), 67.53 (C-3).

*3,7-Anhydro-1,2-dideoxy-*D-glycero-D-galacto-*octitol* (**19**) *and 3,7-anhydro-1,2-dideoxy-*D-glycero-D-galacto-*octitol-1-d* (**20**).—The mixture of **1** and **17** (68 mg, 0.12 mmol) was dissolved in glacial acetic acid (2 mL) and 10% Pd–C (15.0 mg) was added. Hydrogen was bubbled through the solution for 1 min, and the flask was then flushed with hydrogen, before being stirred at rt for 4 h. The reaction was then diluted with CH$_2$Cl$_2$ and filtered through Celite. The solid was rinsed with MeOH and the filtrate concentrated. Column chromatography of the residue (5:1 CHCl$_3$–MeOH) gave the product **19**/**20** (20 mg, 83%) as a colorless syrup. R_f 0.32 (4:1 CHCl$_3$–MeOH); ^{1}H NMR (400 MHz, D$_2$O): δ_H 3.68 (dd, 1 H, *J* 2.2, 12.1 Hz, H-8b), 3.68 (d, 1 H, *J* 3.3 Hz, H-4), 3.47 (dd, 1 H, *J* 6.5, 12.1 Hz, H-8a), 3.40 (dd, 1 H, *J* 3.3, 9.6 Hz, H-5), 3.33 (dd, 1 H, *J* 9.6, 9.7 Hz, H-6), 3.24 (t, 1 H, *J* 7.1 Hz, H-3), 3.12 (ddd, 1 H, *J* 2.2, 6.5, 9.7 Hz, H-7), 1.48–1.32 (m, 2 H, H-2), 0.74–0.67 (m, 2 H, H-1); ^{13}C NMR (100.6 MHz, D$_2$O): δ_C 80.36 (C-7), 80.06 (C-3), 74.79 (C-5), 70.24 (C-4), 67.80 (C-6), 61.72 (C-8), 23.51 (unlabelled C-2), 23.43 (C-2), 9.60 (unlabelled C-1), 9.32 (t, *J* 19.2 Hz, C-1); ESIMS *m*/*z* Calcd for [C$_8$H$_{15}$O$_5$D]Na$^+$ 216.0953. Found 216.0941.

*3,7-Anhydro-1,2-dideoxy-*D-glycero-D-talo-*octitol* (**22**) *and 3,7-anhydro-1-1,2-dideoxy-*D-glycero-*D*-talo-*octitol-1-d* (**23**).—The products **22**/**23** were obtained (10 mg, 43%) as a colorless syrup from the mixture of **7** and **21** (65 mg, 0.12 mmol) using the procedure described for the preparation of **19**/**20**. R_f 0.32 (4:1 CHCl$_3$–MeOH); ^{1}H NMR (400 MHz, D$_2$O): δ_H 3.84 (dd, 1 H, *J* 1.8, 3.2 Hz, H-4), 3.80 (dd, 1 H, *J* 2.2, 12.1 Hz, H-8b), 3.78–3.73 (m, 2 H, H-3, H-5), 3.66 (dd, 1 H, *J* 6.1, 12.1 Hz, H-8a), 3.57 (dd, 1 H, *J* 9.5, 9.6 Hz, H-6), 3.47 (ddd, 1 H, *J* 2.2, 6.1, 9.6 Hz, H-7), 1.76–1.63 (m, 1 H, H-2a), 1.53–1.43 (m, 1 H, H-2b), 0.91–0.82 (m, 2 H, H-1); ^{13}C NMR (100.6 MHz, D$_2$O): δ_C 80.34 (C-5 or C-3), 73.73 (C-7), 71.64 (C-4), 71.23 (C-3 or C-5), 67.80 (C-6), 61.71 (C-8), 21.20 (unlabelled C-2), 21.12 (C-2), 9.92 (unlabelled C-1), 9.64 (t, *J* 19.2 Hz, C-1); ESIMS *m*/*z* Calcd for [C$_8$H$_{15}$O$_5$D]Na$^+$ 216.0953. Found 216.0962.

Acknowledgements

This work was supported by The Ohio State University, the National Institutes of Health (AI44045-01), and the donors of the Petroleum Research Fund, administered by the American Chemical Society. We thank Dr Christopher M. Hadad for helpful discussions.

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