Site Selectivity in the α-Silyl Lithiation of 3,4,6-Tris-*O*-(*tert*-butyldimethylsilyl)-D-glucal and 3,4-Bis-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-L-glucal with *tert*-Butyllithium

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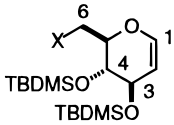
Glycals that are lithiated at the vinylic C1 position are versatile synthons that can be reacted with a variety of electrophiles.[1] Typically, the lithiated glycal is prepared by simple deprotonation at C1 using a strong base such as ^{t}BuLi or Schlosser's base (nBuLi /KO^{t}Bu).[1,2] In a previous paper, we described a series of experiments concerned with the metalation (^{t}BuLi) and subsequent deuteration (D_2O) of 3,4,6-tris-O-(*tert*-butyldimethylsilyl)-D-glucal (**1**).[3] In summary, it was demonstrated that



1 X = OTBDMS
2 X = H

deprotonation of the vinylic C1-H by ^{t}BuLi occurred in competition with lithiation α to silicon on one or more of the TBDMS protecting groups.[4] Lithiation reactions that resulted in complete C1 deprotonation of **1** provided a significant amount of a polyanionic species that was trapped with deuterium both at C1 and α to silicon. Several other groups have reported examples of α-silyl metalation when deprotonating glycals that contain silyl protecting groups.[5] For example, Crich and Ritchie isolated a mono(phenylthio) derivative of **1** that had been formed upon treatment of **1** with ^{t}BuLi followed by trapping with $(PhS)_2$.[5b] They proposed that the phenylthio moiety had been introduced into the (*tert*-butyldimethylsilyl)oxy (TBDMSO) group at C6 although no evidence in support of this proposal was given.

In contrast, it has been demonstrated by several groups that 3,4-bis-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-L-glucal (**2**)[6] behaves quite differently than **1** and is cleanly deprotonated with ^{t}BuLi at C1, apparently without competing metalation α to silicon.[1g,h,7] On the basis of this latter observation, it seems likely that the C6 TBDMSO moiety is responsible for the problems that are encountered in attempts to metalate **1** cleanly at C1 and presumably is the site of α-silyl lithiation.

In light of these reports and our previous investigations into the metalation of **1**, we thought it would be of interest to determine which TBDMSO groups in **1** were being lithiated and to establish whether α-silyl lithiation takes place with any degree of site selectivity. In addition, we wanted to study the corresponding lithiation reactions of **2** to confirm that no TBDMSO groups are lithiated and to find out if the apparent stability of glucal **2** with respect to α-silyl metalation is related to the absence of the silyloxy moiety at C6. Herein, we describe the results of our studies that (1) demonstrate that *both* glucals **1** and **2** undergo lithiation on TBDMSO moieties and (2) clearly reveal a site selectivity in the α-silyl lithiation of both of these silyl-protected glucals.

Results and Discussion

(a) Assignment of Methyl Resonances. It is known that the ^{1}H NMR resonance position of the protons in a deuterated methyl group (CH_2D) moves upfield by approximately 0.015 ppm from the original chemical shift of the CH_3 protons due to a deuterium isotope shift.[8] Therefore, our approach to studying the issues outlined above was to metalate glucals **1** and **2** with ^{t}BuLi, as had been described previously, and then treat the resulting lithiated species with D_2O. Comparison of the ^{1}H NMR spectra of the lithiated/deuterated products with those of the parent glucals, specifically in the region of the TBDMSO methyl resonances, would allow us to assess the site of α-silyl lithiation. In order to successfully employ this strategy, it was imperative that the ^{1}H NMR resonances of the diastereomeric TBDMSO methyl groups in glucals **1** and **2** would be resolved and unambiguously assigned.

Fortunately, the six methyl resonances in the ^{1}H NMR spectrum of **1** (acetone-d_6, 500 MHz) are separated into three groups of two resonances each (Figure 1a). The peak assignments were carried out using NOE experiments,[9] and the assignments are summarized in Table 1. The most informative results came from the following experiments. Irradiation at the resonance frequency of the C2 vinyl proton (δ 4.74 ppm) resulted in enhancement of the middle group of methyl resonances (δ 0.115 and 0.118 ppm), identifying them as the methyls of the C3 TBDMSO moiety (Figure 1b). Irradiation of the resonance associated with one of the C6 methylene protons (δ 3.81 ppm) resulted in enhancement of the most

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(2) (a) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron Lett.* **1977**, 4187. (b) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron***1981**, *23*, 3997.

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(5) (a) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553. (b) Crich, D.; Ritchie, T. J. *Tetrahedron* **1988**, *44*, 2319. (c) Imanieh, H.; Quayle, P.; Voaden, M.; Conway, C.; Street, S. D. A. *Tetrahedron Lett.* **1992**, *33*, 543. (d) Zhang, H.-C.; Brakta, M.; Daves,G. D., Jr. *Tetrahedron Lett.* **1993**, *34*, 1571.

(6) Note that glucal **2** is drawn as its enantiomer for ease of comparison to glucal **1**.

(7) (a) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107. (b) Parker, K. A.; Coburn, C. A.; Koh, Y. *J. Org. Chem.*

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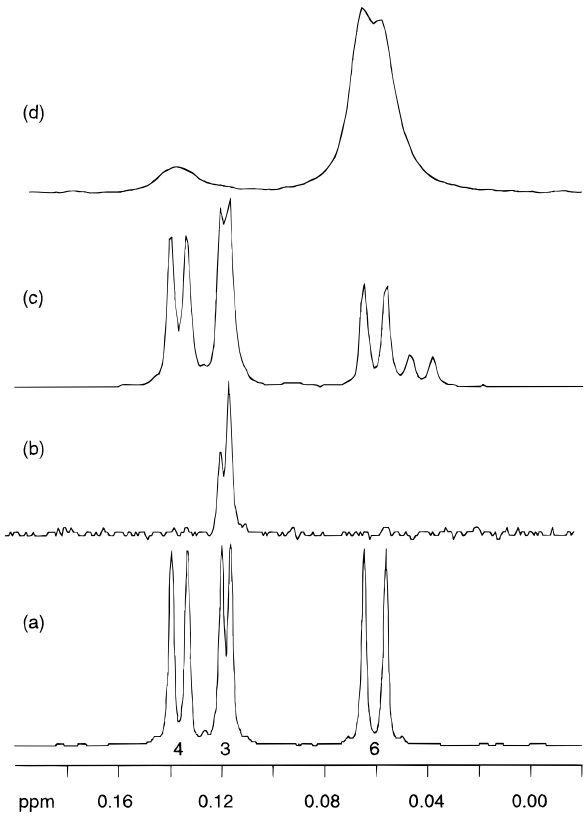

Figure 1. (a) 500 MHz ^{1}H NMR spectrum of **1** in acetone-d_6. (b) NOE spectrum[9] obtained upon irradiation at δ 4.74 ppm (C2 vinyl proton). (c) Deuterium-decoupled ^{1}H NMR spectrum obtained after lithiation (4 equiv ^{t}BuLi) and deuteration of **1** (Table 2, entry 3). (d) Proton-decoupled ^{2}H NMR spectrum (acetone) obtained after lithiation (4 equiv ^{t}BuLi) and deuteration of **1** (Table 2, entry 3).

Table 1. Chemical Shifts of SiC*H*$_3$ and SiCH$_2$*D* Resonances

glucal	methyl resonance	^{1}H chemical shift of SiCH_3 (ppm)	^{2}H chemical shift of SiCH$_2D$[a] (ppm)
1[b]	C3-OSi^{t}BuMe_2	0.115, 0.118	
	C4-OSi^{t}BuMe_2	0.132, 0.138	0.102
	C6-OSi^{t}BuMe_2	0.055, 0.064	0.025, 0.032
2[c]	C3-OSi^{t}BuMe_2	0.070, 0.079	
	C4-OSi^{t}BuMe_2	0.075, 0.092	0.094, 0.109

[a] Glucals were fully lithiated and deuterated at C1 (see Table 2, entries 3 and 5). [b] ^{1}H NMR spectra (500 MHz) in acetone-d_6 referenced to acetone-d_5 at δ 2.04 ppm. Proton-decoupled ^{2}H NMR spectra (76.8 MHz) in acetone referenced to acetone-d_6 at δ 2.04 ppm. [c] ^{1}H NMR spectra (500 MHz) in $CDCl_3$ referenced to $CHCl_3$ at δ 7.24 ppm. Proton-decoupled ^{2}H NMR spectra (76.8 MHz) in $CHCl_3$ referenced to $CDCl_3$ at δ 7.24 ppm.

shielded methyl resonances (δ 0.055 and 0.064 ppm). Thus, these methyl resonances are assigned to the methyls of the C6 TBDMSO moiety while the most deshielded methyl resonances at δ 0.132 and 0.138 ppm are assigned, by default, to the methyls of the C4 TBDMSO moiety. The methyl resonances in Figure 1a are labeled as 3, 4, and 6, corresponding to the methyls of the TBDMSO moieties on C3, C4, and C6, respectively.

The four methyl resonances in the ^{1}H NMR spectrum of **2** ($CDCl_3$, 500 MHz) are not as well resolved as those of **1** (Figure 2a). However, definitive assignments were possible (Table 1) since irradiation at the resonance frequency of the C2 vinyl proton (δ 4.64 ppm) in a NOE experiment[9] resulted in enhancement of the methyl resonances at δ 0.070 and 0.079 ppm (Figure 2b),

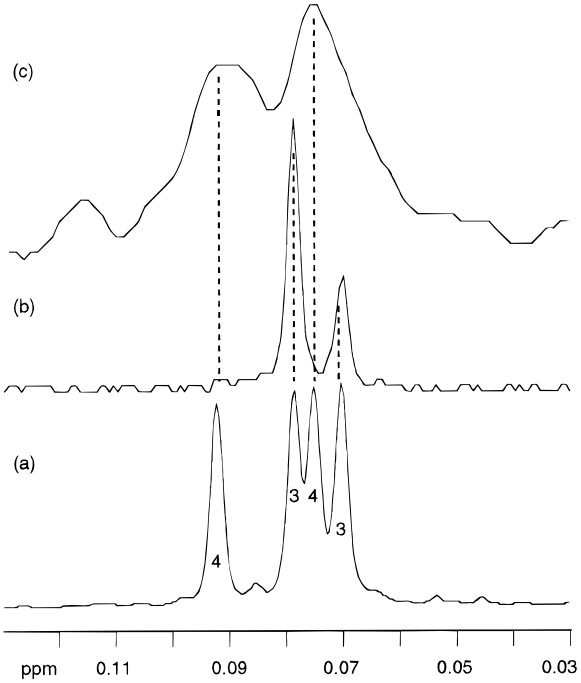

Figure 2. (a) 500 MHz ^{1}H NMR spectrum of **1** in $CDCl_3$. (b) NOE spectrum[9] obtained upon irradiation at δ 4.64 ppm (C2 vinyl proton). (c) Proton-decoupled ^{2}H NMR spectrum ($CHCl_3$) obtained after lithiation (2.2 equiv ^{t}BuLi) and deuteration of **1** (Table 2, entry 5).

Table 2. Lithiation of Glucals 1 and 2 with ^{t}BuLi

				D incorporation α to Si[c] (%)	
entry	glucal	equiv of ^{t}BuLi[a]	D incorporation at C1[b] (%)	C6 TBDMSO	C4 TBDMSO
1	1	2.2	55	27	4
2	1	3.2	84	57	6
3	1	4.0	>98	77	11
4	1	8.0	>98	85	25
5	2	2.2	>98		3
6	2	4.0	>98		8
7	2	8.0	>98		11

[a] See the Experimental Section for standard lithiation conditions. [b] From inspection of the integrated H1 and H2 resonances in the ^{1}H NMR spectra (500 MHz; acetone-d_6 for **1**, CDCl3 for **2**). [c] From integration of the D1 and SiCH$_2D$ resonances in the proton-decoupled ^{2}H NMR spectra (76.8 MHz; acetone for **1**, $CHCl_3$ for **2**).

identifying them as the methyls of the C3 TBDMSO moiety. The resonances at δ 0.075 and 0.092 ppm are thus assigned to the C4 TBDMSO methyls. The methyl resonances in Figure 2a are labeled as 3 and 4, corresponding to the methyls of the TBDMSO moieties on C3 and C4, respectively.

(b) Lithiation Experiments. With the assignment of each methyl resonance secured, it was now possible to carry out and analyze the results of the lithiation/deuteration experiments. We had previously shown that 4 equiv of ^{t}BuLi was sufficient to bring about complete C1 deprotonation of glucal 1.[3] Therefore, THF solutions of glucals **1** and **2** were treated with 2.2−8 equiv of ^{t}BuLi in pentane at −78 °C, stirred at 0 °C for 1 h, and then treated with D_2O. The resulting crude reaction products were filtered through a plug of silica, and ^{1}H and ^{2}H NMR spectra were acquired. The results are summarized in Tables 1 and 2.

Upon complete C1 lithiation and deuteration of **1** (Table 2, entry 3), one can clearly observe in the deuterium-decoupled ^{1}H NMR spectrum (Figure 1c) a decrease

in the intensity of the C6 OTBDMS methyl resonances at δ 0.055 and 0.064 ppm relative to the other methyl resonances (compare Figures 1a and 1c). In addition, two new proton resonances are readily apparent at δ 0.038 and 0.047 ppm (1:1:1 multiplets in the deuterium-coupled ^{1}H NMR spectrum (J_{H-D} = 2.2 Hz) that collapse to singlets upon deuterium-decoupling). The observed shielding of these resonances relative to the parent C6 OTBDMS methyl resonances ($\Delta\delta$ = 0.017 ppm) is consistent with the deuterium isotope shift one would expect for the residual protons on a monodeuterated methyl group.[8] Thus, these two new resonances can be assigned to deuterated methyl groups ($OSiCH_2D$) on the C6 TBDMSO moiety. While the C4 TBDMSO methyl resonances are slightly less intense than those of the C3 TBDMSO methyl resonances, no other changes to the ^{1}H NMR spectrum are readily apparent except, of course, the disappearance of the H1 signal. However, inspection of the corresponding proton-decoupled ^{2}H NMR spectrum (Figure 1d) clearly shows the presence of *three* resonances (Table 1) in addition to the C1 vinyl D resonance at δ 6.325 ppm (not shown).[10] The two furthermost upfield resonances are assigned to the $OSiCH_2D$ signals from the two diastereomeric methyl groups in the C6 TBDMSO moiety, consistent with the observation that the C6 TBDMSO methyl resonances are the most shielded in the ^{1}H NMR spectrum. The question then becomes, to which TBDMSO group does the most deshielded $OSiCH_2D$ resonance belong? Alignment of the C6 $OSiCH_3$ and $OSiCH_2D$ resonances, the most shielded resonances in their respective NMR spectra (Figure 1a,d), results in alignment of the most deshielded $OSiCH_2D$ resonance with the methyl resonances of the C4 TBDMSO moiety. Presumably, this broadened resonance is the product of two unresolved C4 $OSiCH_2D$ resonances. The $OSiCH_2D$ resonances from the C4 TBDMSO group are not observed in the ^{1}H NMR spectrum (Figure 1c) since they are buried under the C3 TBDMSO methyl resonances which are upfield from the C4 TBDMSO methyl resonances by approximately 0.017−0.020 ppm. Thus, lithiation and deuteration α to silicon in glucal **1** is occuring predominantly on the C6 TBDMSO protecting group and, to a lesser extent, on the C4 TBDMSO protecting group (Table 2, entries 1−4). Furthermore, the α-silyl lithiation is site selective with respect to the protecting groups on the secondary alcohols at C3 and C4. Lithiation is observed only on the C4 TBDMSO group and *not on the C3 TBDMSO group*, even when excess ^{t}BuLi is used (Table 2, entry 4). There is no indication of any metalation diastereoselectivity between the diastereomeric methyl groups in the C6 TBDMSO moiety since the integrated intensities of the new $OSiCH_2D$ resonances (Figure 1c) are approximately equal.

In contrast to glucal **1**, the C1 deprotonation of glucal **2** was found to be complete using only 2.2 equiv of ^{t}BuLi (Table 2, entry 5). This observation is consistent with the previously reported lithiations of **2**.[7] At this degree of C1 lithiation, no changes in the relative intensities of the TBDMSO methyl resonances in the resulting ^{1}H NMR spectrum are readily apparent. However, two $OSiCH_2D$ resonances ($\Delta\delta$ = 15 ppb) are observed in the proton-decoupled ^{2}H NMR spectrum (Table 1 and Figure 2c). These resonances integrate to only 3% of the deuterium signal due to the vinylic C1 deuterium (Table 2, entry 5). The chemical shift differences ($\Delta\delta$) between the resonances of the diastereomeric methyls within each of the C3 and C4 TBDMSO groups in the parent glucal **2** are 9 ppb and 17 ppb, respectively (see Table 1). These $\Delta\delta$ values are sufficiently and significantly different such that they can be used to identify the site of lithiation. The $\Delta\delta$ value of 15 ppb for the $OSiCH_2D$ resonances compares favorably with the $\Delta\delta$ value of 17 ppb observed for the methyl resonances of the C4 TBDMSO group. Alignment of Figure 2a,c clearly illustrates this relationship. Thus, lithiation of **2** has occurred only on the methyls of the C4 TBDMSO moiety and not on the C3 TBDMSO group. The degree of metalation on the methyls of the C4 TBDMSO group of **2** using 2.2−4 equiv of ^{t}BuLi is comparable to the amount of lithiation that is observed with glucal **1** on this TBDMSO residue (Table 2, entries 5 and 6).

These results demonstrate that, in addition to and in competition with vinylic deprotonation, lithiation of glucals **1** and **2** is occurring α to silicon on the C4 TBDMSO methyl groups and, in the case of **1**, on the C6 TBDMSO methyl groups. Under the reaction conditions employed in this study, no deprotonation is observed α to silicon on the C3 TBDMSO methyls in either of the glucals **1** or **2**. A simple explanation that would appear to account for some of the above observations is that the methyl protons α to silicon in the C6 TBDMSO moiety of glucal **1** are simply more sterically accessible to the bulky ^{t}BuLi reagent[11] than are the corresponding methyl hydrogens of the TBDMS groups attached to the secondary alcohols at C4 or C3. An explanation that would also rationalize the site selectivity of lithiation requires the internal delivery of the lithiating species *via* a precoordinated complex involving ^{t}BuLi and the pyran oxygen (and/or the primary C6 oxygen in the case of **1**).[12] The proximity of ^{t}BuLi to the C6 and C4 TBDMSO methyls in such a complex leads to lithiation on these groups. Lithiation of the C3 TBDMSO methyls via such a mechanism would require the initial complexation of ^{t}BuLi to the C4 oxygen which is in a much more sterically demanding environment. Lithiation at this site is therefore not observed.

In conclusion, we have demonstrated that glucal **1** is lithiated predominatly on the C6 TBDMSO group. It is also apparent that there is an inherent bias for lithiation of the C4 TBDMSO group compared to the TBDMS moiety on the alternative secondary alcohol at C3, irrespective of the type of substitution at C6. Clearly, the facile and efficient C1 lithiation of **2**, as has been reported,[1g,h,7] is due to the absence of the C6 TBDMSO group.

Experimental Section[13]

^{1}H NMR and ^{2}H NMR spectra were recorded at 500 and 76.8 MHz, respectively. The ^{1}H spectra were refer-

(10) Note that the reference peaks for spectra a and d are different (see footnotes a and b in Table 1). Spectrum d has been aligned with spectrum a (see text), and therefore, the chemical shifts in spectrum d cannot be read from the scale.

(11) It has been shown that while ^{t}BuLi and ether exist in a temperature-dependent equilibrium between tetra solvated dimers and unsolvated tetramers, it is the dimer that is the more reactive metalating species. Bates, T. F.; Clarke, M. T.; Thomas, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5109.

(12) Boeckman[2] has invoked the involvement of oxygen complexation of ^{t}BuLi for the requirement of excess ^{t}BuLi to effect metalation of 2-methoxy-3,4-dihydro-2(*H*)-pyran. There are several additional reports describing the necessity of a coordinating atom, such as oxygen or nitrogen, for the successful lithiation α to silicon by ^{t}BuLi. See, for example: (a) Bates, T. F.; Thomas, R. D. *J. Organomet. Chem.* **1989**, *359*, 285. (b) Hosomi, A.; Kohra, S.; Tominaga, Y.; Shoji, M.; Sakurai, H. *Chem. Pharm. Bull.* **1987**, *35*, 1663.

(13) See ref 3 for general experimental details.

enced to acetone-d_5 at δ 2.04 ppm or $CHCl_3$ at δ 7.24 ppm. The ^2H spectra were referenced to acetone-d_6 at δ 2.04 ppm or $CDCl_3$ at δ 7.24 ppm. The preparation of glucal **2** has been described.[7a] 3,4-Bis-O-acetyl-6-deoxy-L-glucal, the precursor to **2**, is commercially available.[14]

General Procedure for the Lithiation/Deuteration of Glucals 1 and 2. A solution of the appropriate glucal in THF (~1 mL/100 mg) at −78 °C was treated dropwise with ^{t}BuLi (1.4 M pentane solution) and allowed to react at 0 °C for 1 h upon completion of the addition. Excess D_2O was then added rapidly. After the solution was stirred at rt for approximately 30 min, $MgSO_4$ was added and the solution was filtered (ether) and concentrated. The crude deuterated reaction products were filtered through a plug of silica gel (hexane/ether) and inspected by ^1H and ^2H NMR spectroscopy.

Lithiation of 1. Following the general lithiation procedure, **1** (106 mg, 0.217 mmol) was treated with ^{t}BuLi (0.62 mL, 0.867 mmol). The extent of C1 deprotonation was measured, by ^1H NMR spectroscopy, to be >98%: ^2H NMR ($(CH_3)_2CO$) δ 0.025, 0.032, 0.102, 6.32; MS (DCI, CH_4) m/z (relative abundance, assignment) 473 (0.0, $(C_{23}H_{49}O_4Si_3)^+ = (M - CH_3)^+$), 474 (0.62, $(C_{23}H_{48}O_4Si_3D)^+$), 475 (1.0, $(C_{23}H_{47}O_4Si_3D_2)^+$), 476 (0.44, $(C_{23}H_{46}O_4Si_3D_3)^+$).

Lithiation of 2. Following the general lithiation procedure, **2** (133 mg, 0.371 mmol) was treated with ^{t}BuLi (0.58 mL, 0.816 mmol). The extent of C1 deprotonation was measured, by ^1H NMR spectroscopy, to be >98%: ^2H NMR ($CHCl_3$) δ 0.094, 0.109, 6.29; MS (DCI, CH_4) *m/z* (relative abundance, assignment) 343 (0.03, $(C_{17}H_{35}O_3Si_2)^+ = (M - CH_3)^+$), 344 (1.0, $(C_{17}H_{34}O_3Si_2D)^+$), 345 (0.12, $(C_{17}H_{33}O_3Si_2D_2)^+$).

Acknowledgment. We would like to thank C. Li for carrying out the mass spectral analysis of the deuterated compounds.

Supporting Information Available: ^1H NMR spectra of **1** and **2** and ^2H NMR spectra of the deuterated compounds resulting from complete lithiation of **1** and **2** at C1 (Table 2, entries 3 and 5) (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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