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Synthesis of Silylallene Glycosides and Diene Diglycosides by *C*-Glycosidation of D-Glucal with 1,4-Bis(trimethylsilyl)-2-butyne

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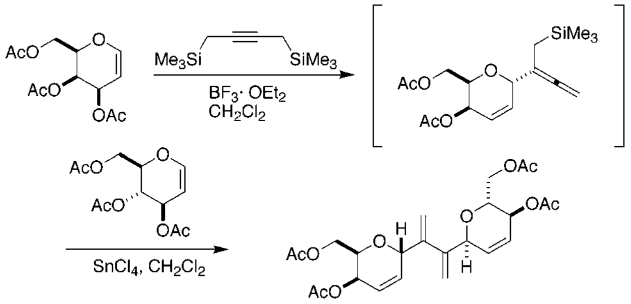
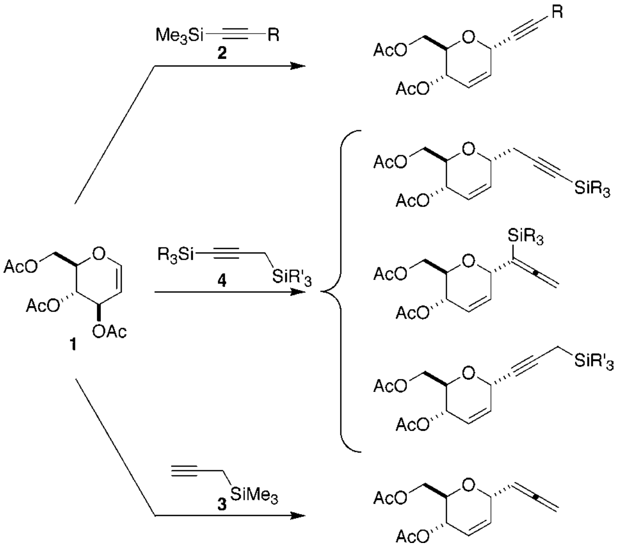
ABSTRACT



Silylmethylallenyl glycosides, symmetrical and unsymmetrical diene glycosides, were synthesized by *C*-glycosidation with 1,4-bis(trimethylsilyl)-2-butyne in good yield. The nature of the product is controlled by the choice of Lewis acid, $BF_3{\cdot}OEt_2$, or $SnCl_4$. The efficient construction of unsymmetrical diene glycosides was achieved in one pot on the basis of the order of addition of sugar starting materials.

We previously demonstrated the *C*-glycosidation of glucal **1** with bis-silylacetylenes (**2**, R = $SiMe_3$) under acidic conditions (Scheme 1).[1] For the functionalization of tetrahydropyran rings, *C*-glycosidation of alkynyl or propargyl silanes by oxocarbenium ion intermediates has proven to be a useful method. We have extended this stereoselective *C*-glycosidation methodology using terminal alkynyl silanes **2** with various R groups to obtain different types of acetylenic glycosides,[2] as well as using propargyl silanes **3** to introduce the allenyl group to sugar nuclei.[3] We have also been able to select for the formation of allenic, acetylenic or propargylic glycosides by choice of silyl groups on each side of the acetylene nucleophile **4**.[4] While most of these approaches have been developed to provide sugar fragments for bioactive

Scheme 1. C-Glycosidation of D-Glucal



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‡ Nagoya University.

[1] (a) Ichikawa, Y.; Isobe, M.; Konobe, M.; Goto, T. *Tetrahedron Lett.* **1984**, *25*, 5049−5052. (b) Ichikawa, Y.; Isobe, M.; Konobe, M.; Goto, T. *Carbohydr. Res.* **1987**, *171*, 193−199. (c) Tsukiyama, S.; Isobe, M. *Tetrahedron Lett.* **1992**, *33*, 7911−7914.

[2] Isobe, M.; Saeeng, R.; Nishizawa, R.; Konobe, M.; Nishikawa, T. *Chem. Lett.* **1999**, 467−468.

[3] Huang, G.; Isobe, M. *Tetrahedron* **2001**, *57*, 10241−10246.

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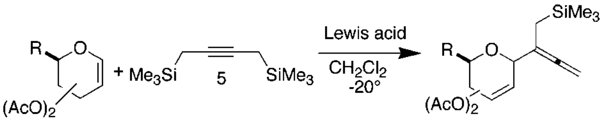
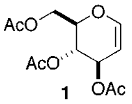
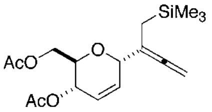
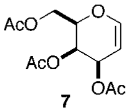
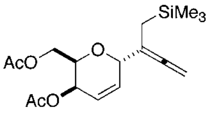
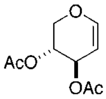
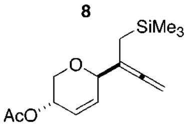
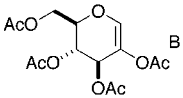
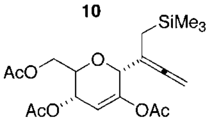
Table 1. Silylallene Glycosides from C-Glycosidation with 1,4-Bis(trimethylsilyl)-2-butyne[a]



R= H, CH_2OAc

entry	sugar	condition	time	Product	Yield (%)
1	 **1**	A B C	20 min	 **6**	66 82 5
2	 **7**	B	3 hr	 **8**	73
3	 **9**	B	30 min	 **10**	69
4	 **11**	B	7 h	 **12**	34

[a] Conditions: (A) sugar/**5** = 1:1, Lewis acid = $BF_3{\cdot}OEt_2$; (B) sugar/**5** = 1:1.2, Lewis acid = $BF_3{\cdot}OEt_2$; (C) sugar/**5** = 1:1, Lewis acid = $SnCl_4$.

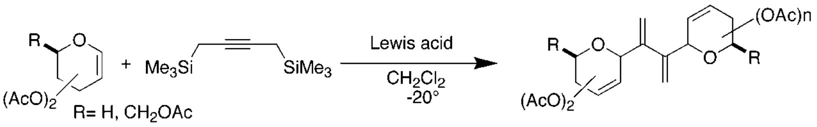
natural product synthesis, none have involved the construction of new types of glycosides. The synthesis of those new types of glycosides, diene diglycosides and silylmethylallene glycosides, is now reported here by *C*-glycosidation with 1,4-bis(trimethylsilyl)-2-butyne **5**.

The nucleophile, 1,4-bis(trimethylsilyl)-2-butyne **5**, was prepared by metal−halogen exchange of 1,4-dichloro-2-butyne with lithium dispersion (30% in paraffin liquid) in the presence of a catalytic amount of DTBB, followed by silylation with trimethylsilyl chloride.

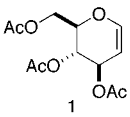
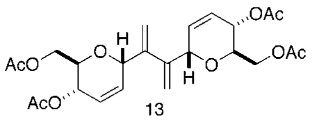
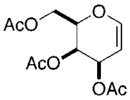
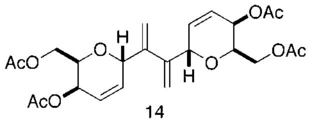
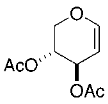
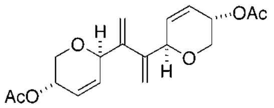
Initially, 1 equiv of D-glucal **1** reacted with 1 equiv of **5** in the presence of $BF_3{\cdot}OEt_2$ (Table 1, entry 1). The reaction led to the silylallene glycoside **6** with α-orientation in 66% yield with high selectivity (condition A). Use of 1.2 equiv of **5** raised the yield to 82% (condition B). In the presence of $SnCl_4$, *C*-glycosidation gave only a low yield of the expected product (condition C). The *C*-glycosidation was then performed under condition B with a range of carbohydrates (entries 2−4), and these reactions led to the silylallene glycoside products **8**, **10**, and **12** in moderate to good yields. In the case of D-galactal **7**, the product was obtained in 73% yield after 3 h whereas for *C*-glycosidation of 2-acetoxy-D-glucal **11**, the glycoside product was formed in only 34% yield after conducting the reaction for as long as 7 h. On the basis of these results, the rate of *C*-glycosidation of D-glucal is suggested to be similar to that of D-xylal but faster than both D-galactal and 2-acetoxy-D-glucal.

To further extend the scope to double glycosidation, 2 equiv of D-glucal was employed with 1 equiv of 1,4-bis(trimethylsilyl)-2-butyne **5**. The reaction was carried out using $BF_3{\cdot}OEt_2$ as Lewis acid to provide a new type of symmetrical diene glycoside **13** with the monoglycosidation

Table 2. Symmetric Diene Glycosides from *C*-Glycosidation with 1,4-Bis(trimethylsilyl)-2-butyne[a]



R= H, CH_2OAc

entry	sugar	condition	Lewis acid	time	Product	Yield (%)
1	 1	A B C D	$BF_3{\cdot}OEt$ $SnCl_4$ $SnCl_4$ TMSOTf	3.5 h 15 min 35 min 2.5 h	 13	50 92 43 29
2	 7	B	$SnCl_4$	7 h	 14	62
3	 9	B	$SnCl_4$	25 min	 15	78

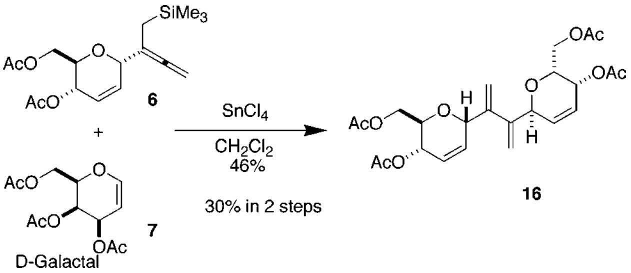
[a] Conditions: (A) sugar/**5** = 1:2; (B) sugar/**5** = 1:3; (C) sugar/**5** = 1:2; (D) sugar/**5** = 1:2.

product **6** in similar amounts (50:50) after stirring the reaction for 3.5 h (entry 1, Table 2). On changing from $BF_3{\cdot}OEt_2$ to TMSOTf and $SnCl_4$, only low to moderate yields of the diene glycoside product were observed, but without the silylallene glycoside. However when 3 equiv of D-glucal were used in the presence of $SnCl_4$, there was a dramatic change in the outcome of the reaction, and diene glycoside **13** was obtained in 92% in 15 min (condition B).

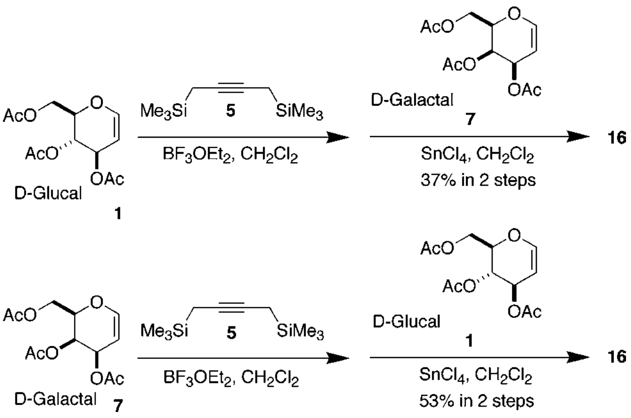
D-Galactal and D-xylal were also employed in the C-glycosidation using condition B to produce the diene glycosides **14** and **15** steroselectively and in good yields. The 2-acetoxy-D-glucal failed to afford the diene glycoside. It was found that either the silylallene glycoside or the diene glycoside could be accessed in excellent yield as the sole product by using either $BF_3{\cdot}OEt_2$ or $SnCl_4$ as the Lewis acid.

The scope was further extended to unsymmetrical diene glycosides by reaction of silylallene glycosides with different glycals. Initially, D-galactal was employed to react with silylallene glycoside **6** in the presence of $SnCl_4$ to give the unsymmetrical diene glycoside **16** in 30% yield in two steps (Scheme 2). Alternatively, this reaction could be performed in one pot without isolation of the silylallene glycoside, resulting in an increased yield of 37% (Scheme 3). The *C*-Glycosidation of D-glucal with 1,4-bis(trimethylsilyl)-2-butyne **5** was first carried out in the presence of $BF_3{\cdot}OEt_2$, followed by addition of D-galactal **7** and $SnCl_4$. On the other hand, a better yield (53%) of **16** was observed by reversing the order of addition of the sugar starting materials. Thus, D-galactal first reacted with alkyne **5**, followed by addition of D-glucal. Scheme 4 shows two examples of unsymmetrical diene glycosides that can be formed by this one pot reaction. Interestingly, all of the unsymmetrical diene glycosides could be produced in improved yields when the reaction was performed first with the *C*-glycosidation of the faster-reacting sugar followed by the slower one (using the results from Table 1).

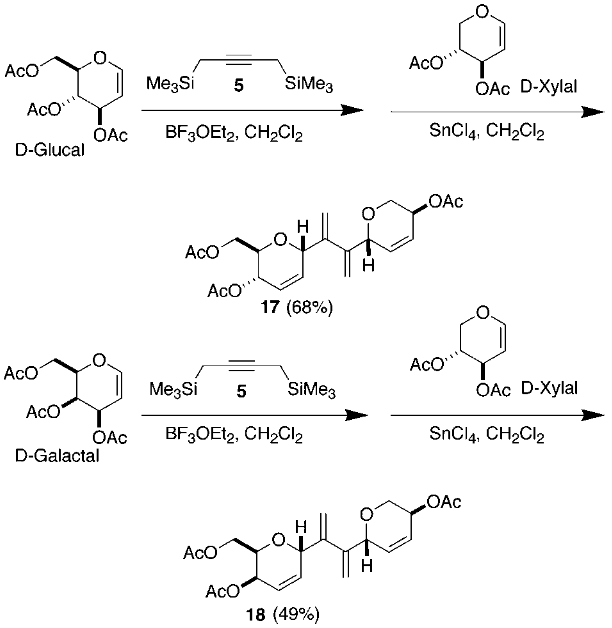
Scheme 2. Two-Step Synthesis of Asymmetric Diene Glycoside



Scheme 3. One-Pot Synthesis of **16** with Different Orders of Addition



Scheme 4. One-Pot Synthesis of Unsymmetrical Diene Glycosides



The stereochemistry of the silylallene glycosides and diene glycosides was supported by spectroscopic analyses. The configurations at C1 of silylallene glycosides **6** and **8** were both determined to be α on the basis of the observation of NOESY cross-peaks between H5 and H2′ and the coupling constants of H4 and H5 (Figure 1). Glycoside **10** is proposed to have a 1,4-anti configuration[5] based on the previous work on *C*-glycosidation of D-xylal.[6]

In diene glycosides **13** and **14**, an additional cross-peak was observed between H1 and H2′b. The 1,4-anti configu-

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(4) Isobe, M.; Phoosaha, W.; Saeeng, R.; Kira, K.; Yenjai, C. *Org. Lett.* **2003**, *5*, 4883−4885.

(5) Miljkovic, M.; Yeagley, D.; Deslongchamp, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597−7604. For other examples of 4-substituted tetrahydropyran acetals, see: Ayala, L.; Lucero, C. G.; Romero, J. C.; Tabacco, S. A.; Woerpel, K. A. *J. Org. Chem.* **2003**, *125*, 15521−15528.

(6) Hosokawa, S.; Kirschbaum, B., Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 1917−1920.

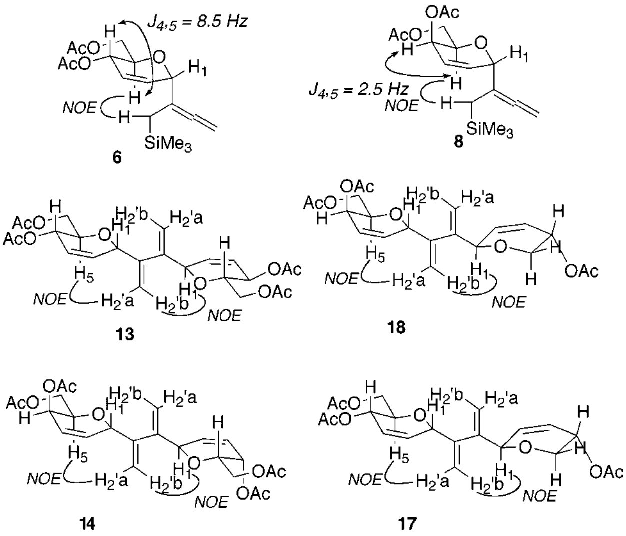

Figure 1. Stereochemistry of glycosides.

ration of **15** can be deduced from the X-ray structure shown in the Supporting Information. The 1,4-anti configuration of the xylyl-derived moiety is confirmed by the X-ray crystallographic data of compounds **17** and **18**.

In conclusion, we have established a synthesis of new types of symmetric and unsymmetrical diene glycosides and silylallene glycosides.

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Supporting Information Available: Experimental procedures and full spectroscopic data for **6**, **8**, **10**, and **13**−**18**. Details of the X-ray crystallographic analysis of **15**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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