Highlight Review

Stereoselective C-Alkynylation, Allenylation, and Prop-2-ynylation Leading to Sugar Glycosides

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Abstract

Carbohydrates have been recognized and utilized for a long time as the starting materials for target-oriented syntheses toward optically active compounds. C-Glycosides are often employed for this purpose because they have much potential for the introduction of new stereogenic centers to the side chain. We describe herein various methods for the introduction of carbon chains to the sugar rings under acidic conditions, particularly in the form of alkynyl, allenyl, or prop-2-ynyl group at the anomeric position with high stereoselectivity.

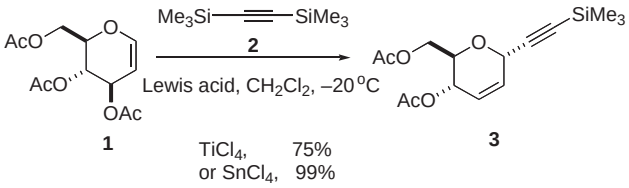
♦ 1. Introduction

The synthetic studies toward natural products often require multistep process from several starting materials in optically active forms. Sugar synthons have been playing indispensable roles as its availability from biomass products having various chirons in the molecules. The sugar molecule having tetrahydropyran or dihydropyran ring is of further importance due to the following facts; thus, asymmetric synthesis can often start by introducing a carbon chain to the ring and further by introducing new stereogenic centers on the chain using the tetrahydropyran ring as chiral template. In this sense, C-glycosidation is a quite essential reaction, and we have developed new methodologies for the introduction of various carbon chains at the anomeric position by C-glycosidation in a stereoselective manner. In fact, many examples have been demonstrated at the earlier stage of the multistep natural product synthesis on the basis of C-glycosidation.

♦ 2. C-Alkynylation

C-Alkynylation has been very useful reactions since it allows introduction of the carbon chains to sugar chirons. Application of the Hosomi–Sakurai reaction[1] to sugars was reported first from Danishefsky's group[2] and then from our group[3] in the syntheses toward natural products, which was shown to be highly stereoselective to a sugar nucleus as chiral pool. Introduction of an alkynyl (acetylenic) group to sugar nuclei has been developed for the synthesis of sugar–acetylenes, key compounds toward various natural products.[4]

Our earliest work in this area is the C-alkynylation of glycal **1** with bis(trimethylsilyl)acetylene (**2**). The reaction proceeded in the presence of Lewis acid at $-20\,^{\circ}C$ to give exclusively α-anomer product. The stronger Lewis acid $SnCl_4$[5] works better than $TiCl_4$[6] to give alkynyl glycoside **3** in quantitative yield (Scheme 1).



Scheme 1.

This strategy was then applied to the preparation of other alkynyl glycosides with different substituent at the other end of the acetylene.[7] The C-alkynylation of higher homologous silylacetylene **6**, **8**, and **10** were carried out in the presence of $SnCl_4$ at low temperature in dichloromethane for ca. 1 h. All glycoside products were obtained selectively as a single α-stereoisomer as shown in Table 1.

Use of other Lewis-acid catalysts was investigated by Yadav and co-workers,[8] and $InBr_3$ was found to be an effective catalyst in the C-alkynyl glycoside preparation. Treatment of the glycal with various alkynyltrimethylsilanes in the presence of 5 mol % $InBr_3$ at ambient temperature results in the formation of the corresponding alkynyl C-pseudoglycals in excellent yield. Reddy and Smitha[9] have also demonstrated that $ZrCl_4$ can be used as a catalyst in acetonitrile to promote C-alkynylation of $Me_3SiC{\equiv}CPh$ to D-glucal.

Iodine is generally regarded as an I^+ equivalent reagent that can work as a catalyst to promote O-glycosidation reactions[10] and C-glycosidation of allyltrimethylsilane.[11] Accordingly, we developed a convenient and easy procedure for C-alkynylation of tri-*O*-acetyl-D-glucal using iodine-promoted reactions. The series of silylacetylene with different substituents were examined and the results are summarized in Table 2. The stereoselective formation of α-anomer products was observed in all cases and the reaction was proposed to proceed via an iodo-oxonium intermediate.

Subsequent to these experiments, the efficiency of iodine was tested for the C-alkynylation of a larger silylacetylene compound. Silylpropynyl-sugar **12** was allowed to react with D-glucal at room temperature to furnish exclusively α-acetylene glycoside **13** in 88% yield, proving the generality of this methodol-

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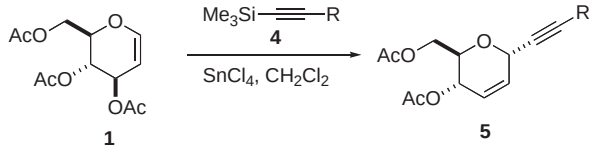
Table 1. Alkynylation with various silylacetylenes



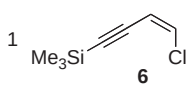
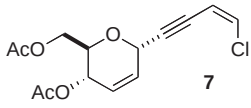
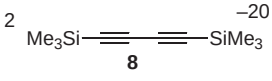
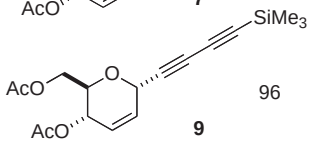
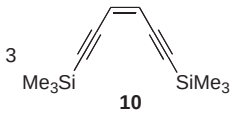
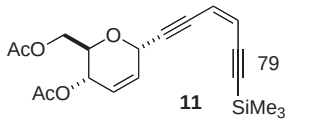
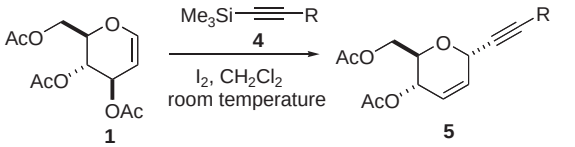
Entry	Nucleophile	Temperature	Product	Yield/%
1		0 °C		81
2		–20 °C		96
3		–78 °C		79

Table 2. Alkynylation by iodine as a catalyst

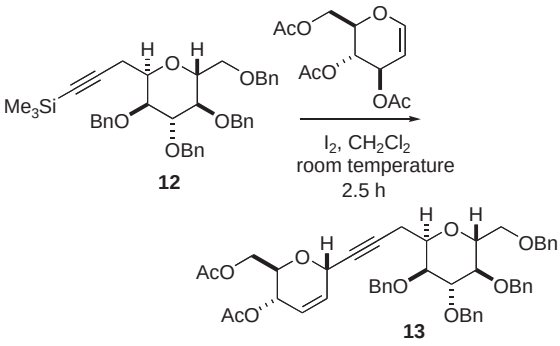


Entry	R	Time	Yield/%
1	$SiMe_3$	16 h	78
2	CH_3	1 h	80
3	Ph	1 h	90
4	SPh	45 min	38
5	H	24 h	0
6	CH_2SiMe_3	2 h	30
7	CH_2SiiPr_3	3.5 h	53
8	CH_2OTBPS	4 h	74
9	$(CH_2)_2OTBPS$	1 h	83
10	$(CH_2)_3OTBPS$	45 min	80
11	$C{\equiv}CSiMe_3$	5 h	67

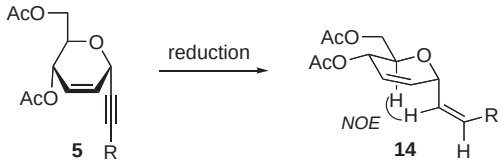
ogy (Scheme 2).[12]

Stereochemistry at the C-1 position of the acetylene glycoside products **5** was proved to be exclusively α-orientation through partial hydrogenation of the acetylene group to the corresponding vinyl **14**, α-proton of the vinyl group showing NOE with the H-5 (Scheme 3).

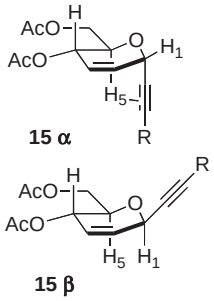
Stereochemitry of the products was assigned as follows: Chemical shifts of H-5 are found in ^{1}H NMR between δ 4.07 and 4.09 in the case of R = TMS or C≡CTMS due to the anisotropic effect of the α-acetylene at the C-1 (**15 α**). Comparing with β-acetylene glycosides (**15 β**), which were prepared through epimerization of the cobalt–alkyne complexes of α-isomers, the chemical shifts at the H-5 were observed between δ



Scheme 2.



Scheme 3.



compds	R	Chemical shift H-1	H-5
15 α	*SiMe3*	4.96	*4.09*
	C≡CSiMe3,	5.00	*4.07*
15 β	*SiMe3*	4.99	*3.75*
	C≡CSiMe3,	5.04	*3.74*

Figure 1.

3.74 and 3.77 (Figure 1) as reported by Tanaka, et al. due to the absence of anisotropic effect.[7b] All of the H-5 chemical shifts of acetylene glycoside products in our experiments were observed at δ 4.05–4.18.[12] These results confirm α-orientation of the acetylene-glycoside products.

The electronic factors of the silylpropynyl alcohol derivatives have been found to control their reactivity in C-alkynylation of glycals.[13] The presence of an electron-withdrawing acyloxy group at the propynylic position interrupted the formation of product, the silylpropynylic derivative having an acetyl or pivaloyl group never afforded the product.

On the other hand, when the benzyl- or *tert*-butyldiphenylsilyl group was employed as the protecting group for the propynylic alcohol to react with D-glucal, the corresponding products were obtained in 44 and 84% yields, respectively (Scheme 4). These facts indicate that different reactivity is derived from different degree of electronegativity by the acyl group to destabilize cationic intermediate **17**.

When the carbon chain (X = $(CH_2)_n$OAc, $n > 1$) was elongated, yields of the products increased with the larger n as shown in Scheme 5. This is due to a relief of the destabilization effect caused by the acetate group.

Electronic effect in nucleophilic silylacetylene was also observed in C-alkynylation by a larger silylacetylene compound

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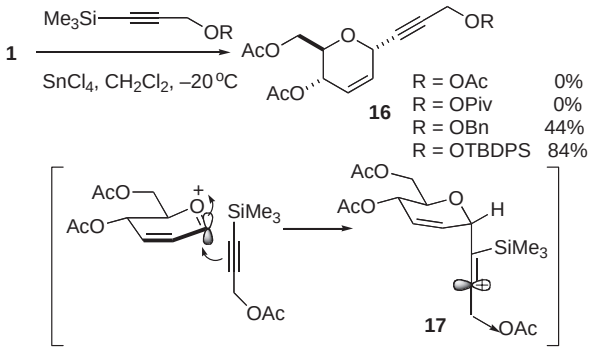
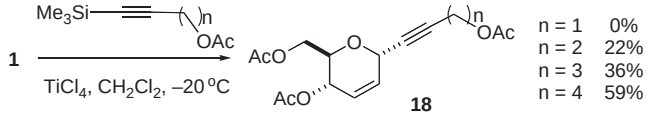
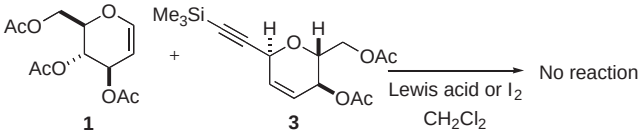


Scheme 4.



Scheme 5.



Scheme 6.

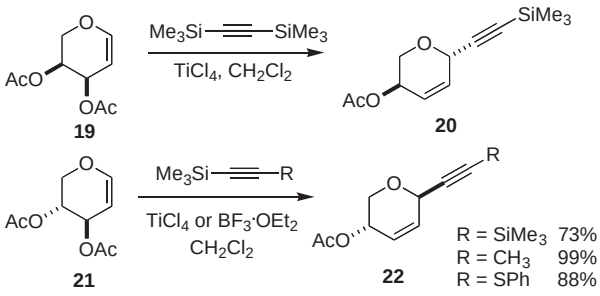
as shown in Scheme 6. Silylacetylene glycoside **3** failed to react with D-glucal **1** owing to a polarizing destabilization effect of the ether ring oxygen atom.

We also demonstrated the C-alkynylation by silylacetylene nucleophiles to pentopyranose derivatives such as di-*O*-acetyl-L-arabinal (**19**) and di-*O*-acetyl-D-xylal (**21**). The stereochemical induction turned out to contrast strikingly to the previous cases. The addition of silylacetylene to the hexopyranoglycals produces only the α-alkynylated products with 1,4-syn selectivity as for **5**, **16**, **18**, etc. Galactal, however, afforded 1,4-anti product; thus, hexopyranosides always give α-anomer owing to the conformational preference at the transition state to induce stereoelectronic control.[3] On the other hand, a similar addition of silylacetylene to pentopyranoseglycals affords the opposite results; thus, complete 1,4-anti stereochemistry is observed in the pentopyranose cases as shown in Scheme 7.[14]

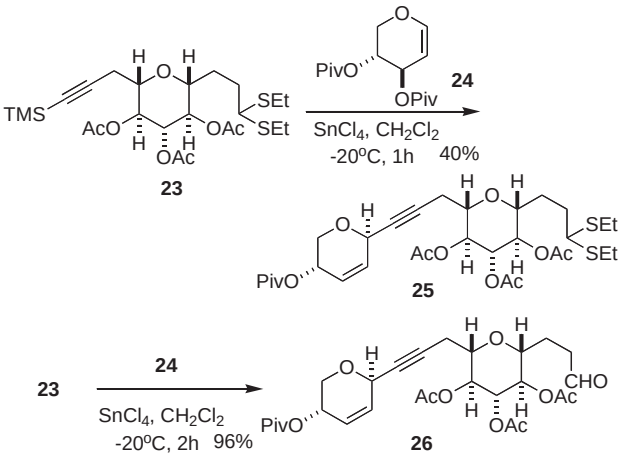
It was of initial interest for us to attempt to extend this study to the preparation of an intermediate for the synthesis of the ABC fragment of ciguatoxin.[15] C-Alkynylation of silylacetylene **23** with D-xylal yielded the anti products as shown in Scheme 8. After longer reaction time (2 h), the dithioacetal underwent hydrolysis to give the corresponding aldehyde **26**.[16]

♦ 3. C-Allenylation and Prop-2-ynylation

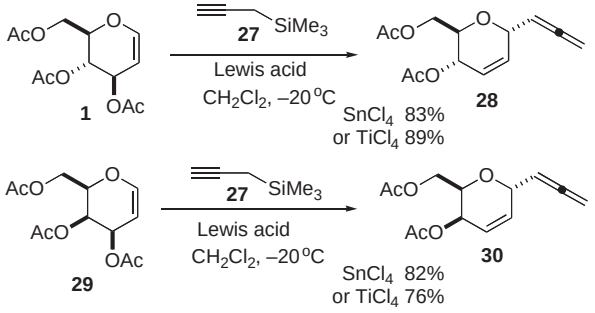
Over the past years, trimethyl(prop-2-ynyl)silane has been shown to be a useful starting material for the synthesis of monosubstituted allenes.[17] Accordingly, we selected this reagent as carbon sources of allenyl groups for introduction to sugar ring.[18] At first, the reaction of tri-*O*-acetyl-D-glucal (**1**) with trimethyl-



Scheme 7.



Scheme 8.

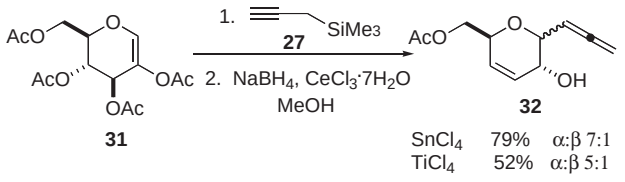


Scheme 9.

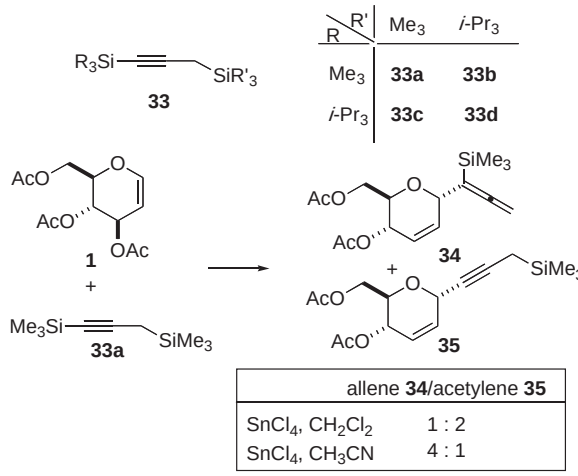
(prop-2-ynyl)silane (**27**) (Scheme 9) was examined. At the same time, Voegle et al.[19] reported this reaction during a disaccharide synthesis. Glycal **1** was stirred with 1.5 equiv. of $HC{\equiv}CCH_2SiMe_3$ in dichloromethane at $-20\,^{\circ}C$ to obtain exclusively the α-*C*-allenyl derivative **28** in 83% yield with $SnCl_4$ as catalyst. This reaction can also be catalyzed by $TiCl_4$ to give **28** in 89% yield.

Reaction between tri-*O*-acetyl-D-galactal (**29**) and trimethyl(prop-2-ynyl)silane under the catalysis of $SnCl_4$ or $TiCl_4$ also provided the α-*C*-allenyl product **30** in 82 or 76% yield, respectively.

Similarly, 2,3,4,6-tetra-*O*-acetyl-D-glucal (**31**) was allowed to react with trimethyl(prop-2-ynyl)silane in the presence of $SnCl_4$ or $TiCl_4$, and the product was then reduced with $NaBH_4/CeCl_3{\cdot}7H_2O$ to give α- and β-allenyl products **32** in 79 or 52%



Scheme 10.



Scheme 11.

combined yields, with ratios of α/β being 7:1 by $SnCl_4$ and 5:1 by $TiCl_4$, respectively (Scheme 10).

Then, we turned our attention on a new system (**33**) having two silyl groups at acetylenic and propynylic positions and raised the question of which group would predominantly be fixed at the anomeric position.

We found that propynylic and acetylenic silyl groups in **33** control the C-glycosidation products depending on the kind of silyl groups used (Scheme 11).[20] In the case of the reaction of 1,3-bis(trimethylsilyl)propyne (**33a**) with glucal **1**, we obtained a mixtures of the two possible products, allene **34** and alkyne **35**. In dichloromethane, the major product was alkyne **35**, while in acetonitrile, allene **34** was the major product. The ratio of **34** and **35** was reversed by changing the solvent. This may be due to the stabilization of a cationic intermediate by acetonitrile (Figure 2). Elimination of one trimethylsilyl group via process "**B**-**a**" occurs in dichloromethane to yield alkyne **35**, while elimination "**B**-**b**" is favored in acetonitrile, perhaps through the transition structure **C**.

Then, we examined the other substrates of this series **33b**–**33d**. The system (**33d**) with two triisopropyl groups was unreactive and no product was obtained at all. When the triisopropylsilyl group was placed at the propynylic position in **33b**, only a trimethylsilyl group was lost to give exclusively alkyne **36**, regardless of the choice of solvent (Scheme 12).

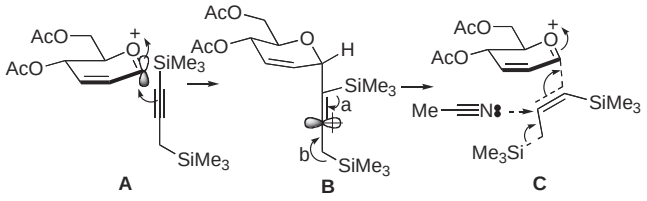
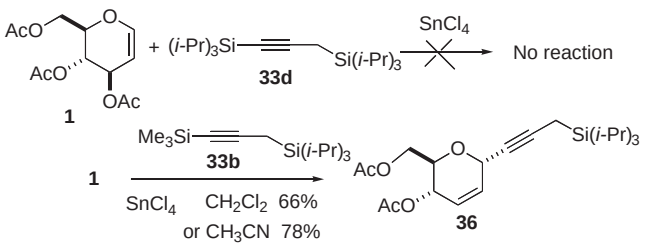
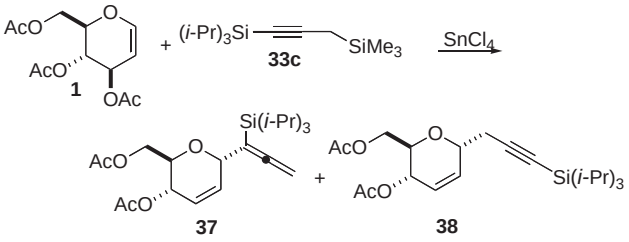


Figure 2.



Scheme 12.

Table 3. Effects of molar ratio and solvent for allenylation or propargylation



Entry	Equiv. of 1	Solvent	Yield of **37+38**/%	**37**/**38**
1	2	CH_2Cl_2	74	1:2.5
2	1.1	CH_2Cl_2	69	1:5
3	1.1	CH_3CN	60	1:9
4	0.5	CH_3CN	30	1:80

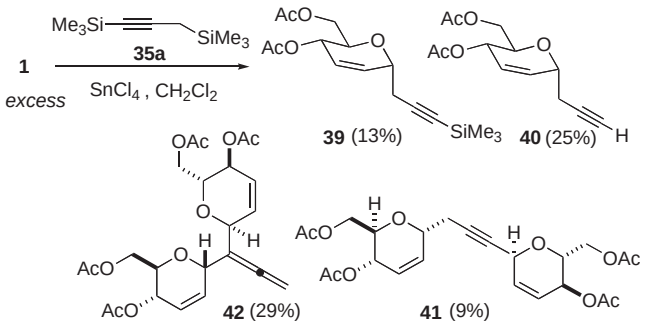
With substrate **33c** having a triisopropylsilyl group in the acetylenic position, there was a striking contrast to previous examples. Besides minor allenic product **37**, the major product was the propynylic compound **38** which was not previously observed in these reactions. The ratio of products **37** and **38** depended on the molar ratio of substrates and solvent used (Table 3).

We then searched for other products from the reaction of 1,3-bis(trimethylsilyl)propyne (**35a**) and an excess of glucal **1** (Scheme 13). Compounds **39**, **40**, **41**, and **42** were isolated in 13, 25, 29, and 9% yields respectively (total 76%).

The nature of these products suggests a mechanism shown in Figure 3, in which the initially formed allenic glycoside attacks another oxocarbenium ion. Compounds **41** and **42** are the first examples of dimer formation with propynylic substituents and should have interesting applications in polyether synthesis.[21] Formation of such propynylic products seems to take place via mechanism **D** in which the initially formed allenic compound **34** attacks an additional oxocarbenium ion. The ring oxygen lone pair appears to drive the transfer of a three carbon unit from one glycoside to another. Coupled products **41** and **42** seem to be formed by attack of the silyl allene moiety at either terminal on an oxocarbenium ion as shown in **E** and **F**.

We have established the synthesis of a new type of diene–diglycosides and silylmethylallene glycosides.[22] Synthesis of these new types of glycosides is successfully achieved by the C-propargylation with 1,4-bis(trimethylsilyl)but-2-yne (**43**).

D-Glucal **1** reacted with 1.2 equiv. of **43** in the presence of $BF_3 \cdot OEt_2$ (Table 4, entry 1) to give silylallene glycoside **44** with



Scheme 13.

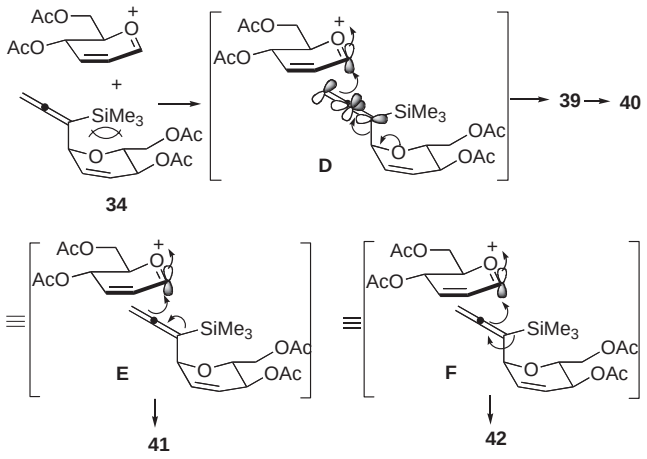


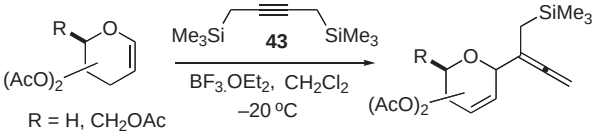
Figure 3.

α-orientation in 82% yield with high selectivity. In the presence of $SnCl_4$, the C-glycosidation gave only low yield of the expected product. The C-glycosidation was then performed in the presence of $BF_3 \cdot OEt_2$ with different carbohydrates (entries 2, 3, and 4) and these reactions led to the silylallene glycoside products **45**, **46**, and **47** in moderate to good yields. In the case of D-galactal **29**, product **45** was obtained in 73% after stirring 3 h, whereas for C-glycosidation of 2-acetoxy-D-glucal **31**, 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 the double glycosidation, 3 molar equiv. of D-glucal was employed for 1 equiv. of 1,4-bis(trimethylsilyl)-2-butyne (**43**) in the presence of $SnCl_4$ and diene glycoside **48** was obtained exclusively in 92% in 15 min (entry 1, Table 5). By changing $SnCl_4$ to $BF_3 \cdot OEt_2$, a mixture of symmetrical diene glycoside **48** and monoglycosidation product **44** was obtained in similar yields. It was found that either the silylallene glycoside or the diene glycoside could be obtained in excellent yield as the sole product by using either $BF_3 \cdot OEt_2$ or $SnCl_4$ as the Lewis acid.

D-Galactal and D-xylal could also be employed in the C-glycosidation using $SnCl_4$ to produce diene glycoside **49** and **50** steroselectively and in good yields (entries 2 and 3, Table 5), whereas 2-acetoxy-D-glucal **31** failed to afford the diene glycoside.

Table 4. Silylmethylallene glycosides with $BF_3 \cdot OEt_2$



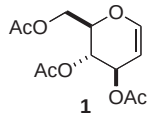
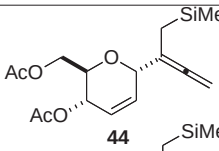
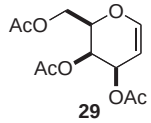
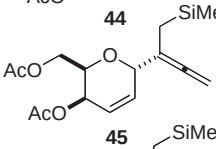
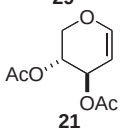
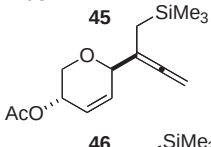
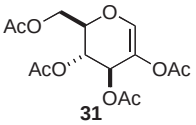
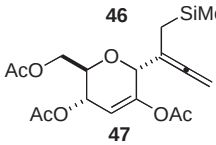
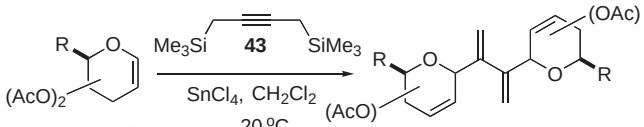
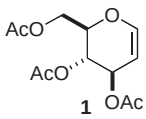
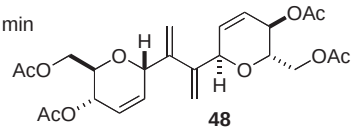
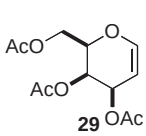
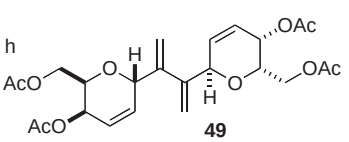
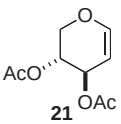
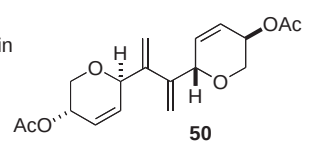
Entry	Sugar	Time	Product	Yield/%
1	 **1**	20 min	 **44**	82
2	 **29**	3 h	 **45**	73
3	 **21**	30 min	 **46**	69
4	 **31**	7 h	 **47**	34

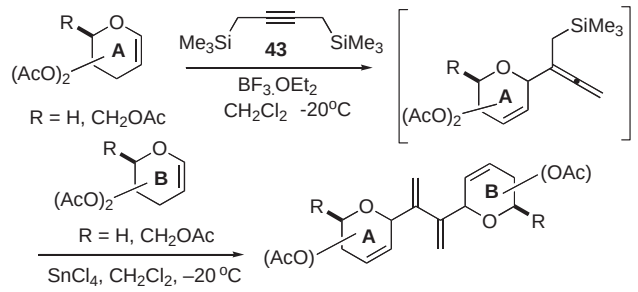
Table 5. Diene diglycosides with $SnCl_4$



Entry	Sugar	Time	Product	Yield/%
1	 **1**	15 min	 **48**	92
2	 **29**	7 h	 **49**	62
3	 **21**	25 min	 **50**	78

The scope was further extended to unsymmetrical diene glycosides by performing the reaction with different glycals in one pot without isolation of the silylallene glycoside. The C-glycosidation of D-glucal with 1,4-bis(trimethylsilyl)but-2-yne (**43**) was first carried out in the presence of $BF_3 \cdot OEt_2$, followed by addition of D-galactal **29** and $SnCl_4$ to obtain dieneglycoside **51** in 37% yield (entry 1, Table 6). It was found that, reversing the order of addition of the sugar starting materials, a better yield (53%) of **51** was observed (entry 2); thus, D-galactal was first

Table 6. Unsymmetrical diene glycosides



Entry	Sugar A	Sugar B	Product	Yield/%
1	**1**	**29**	**51**	37
2	**29**	**1**	**51**	53
3	**1**	**21**	**52**	68
4	**29**	**21**	**53**	49

allowed to react with alkyne **43** and then with D-glucal. Table 6 shows two more examples of unsymmetrical diene glycosides **52** and **53** that can be formed by this one-pot reaction. Interestingly, all of unsymmetrical diene glycosides could be produced in improved yields when the reaction was performed first with the C-glycosidation of a faster-reacting sugar followed by a slower one (using the results from Table 4).

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