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Different C-Glycosidation Products of Glucal with Alkynyl or Propargyl Silanes under Acidic Conditions

Minoru Isobe,* Wanna Phoosaha, Rungnapha Saeeng, Kazunobu Kira, and Chavi Yenjai

Laboratory of Organic Chemistry, Graduate School of Bioagricultural Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan

isobem@agr.nagoya-u.ac.jp

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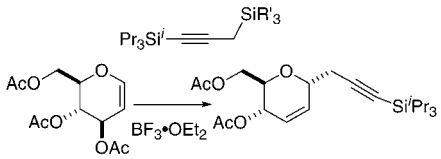
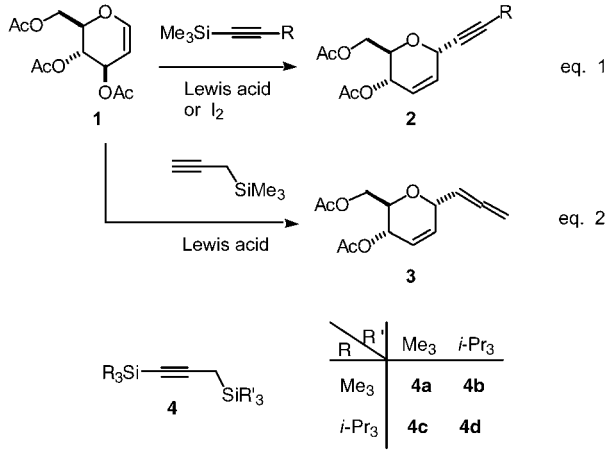
ABSTRACT



Propargylic and acetylenic silyl groups on propyne control the C-glycosidation products depending on the trimethylsilyl and triisopropylsilyl groups used. Some mechanistic discussions are included.

C-Glycosidation holds a key position in organic synthesis as a means to obtain starting materials for complex natural molecules, while many practical methods have become available to extend the carbon chains with functional groups. Among these methods, we have been using the alkynylation of oxocarbenium derivatives generated from glucals such as **1** with silyl acetylenes. We reported this reaction in 1984[1] and have developed it as a method to prepare sugar acetylenes such as **2**.[2] A stereochemical switching method, from α to *β*, was established during the syntheses of tautomycin and okadaic acid analogues.[3,4] We have also reported that the current reaction is conducted by molecular iodine.[5,6]



We have also reported the C-glycosidation of propargyl trimethylsilane, which afforded the allene **3** (eq 2) exclusively as the α-axial isomer.[7] These are remarkably selective reactions.

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(2) Tsukiyama, S.; Isobe, M. *Tetrahedron Lett.* **1992**, *33*, 7911−7914.

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(5) Saeeng, R.; Sirion, U.; Sahakitpichan, P.; Isobe, M. *Tetrahedron Lett.* **2003**, *44*, 6211−6214.

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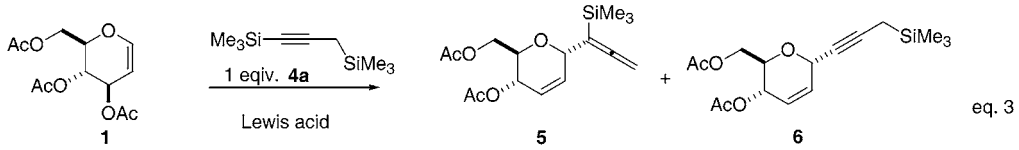
Table 1.



entry	Lewis acid	solvent	time	% yield of **5** + **6**	**5**/**6**
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	1.0 h	74	1:2.5
2	$BF_3{\cdot}OEt_2$	CH_2Cl_2	1.5 h	87	1:2.5
3	$SnCl_4$	CH_2Cl_2	15 min	83	1:2
4	$SnCl_4$	CH_3CN	15 min	60	4:1

We became interested in the new system **4** having both alkynyl and propargyl silanes and the question of which group would predominantly control the reaction. In this paper, we show that the reactivity depends on the kind and position of the silyl groups and report the formation of a novel product, a propargylic glycoside. In the case of the reaction between 1,3-bis(trimethylsilyl)propyne **4a** and glucal **1**, we obtained mixtures of the two possible products, allene **5** and alkyne **6** (Table 1). In dichloromethane, the major product was alkyne **6**, while in acetonitrile, allene **5** was the major product. The α-stereochemistry of **6** was proven by comparison of the NMR signal of H-5 (δ 3.74 1H, ddd, J = 9.0, 6.0, 2.5 Hz) with related compounds.[5]

The ratios of **5** and **6** are reversed on changing solvent. This may be due to the stabilization of the cationic intermediate by acetonitrile (Figure 1). The initial oxocarbenium ion **A** might receive little solvent stabilization judging from the absence of the β-isomer. On the other hand, the sp^2 cationic intermediate **B** seems to receive a dramatic effect. Elimination of one trimethylsilyl group via process "**B-a**" occurs in dichloromethane to yield the alkyne **6**, while elimination "**B-b**" is favored in acetonitrile, perhaps through component orientation **C**.

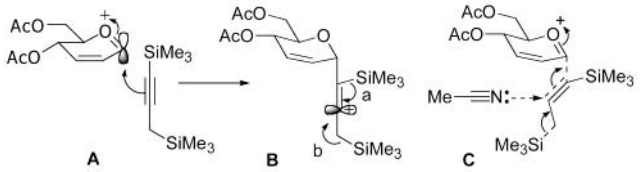
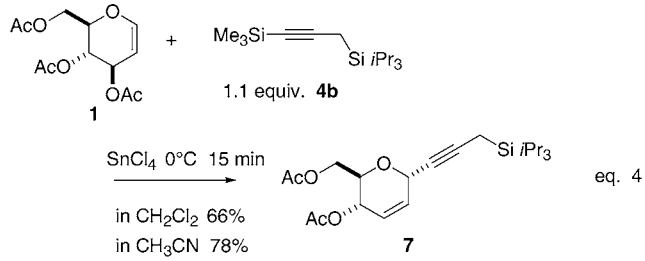


Figure 1. Solvent effect on the cation intermediate.

We have examined substrates containing two different silyl groups **4a**−**d**. The system with two triisopropyl groups **4d** was unreactive, and no product was obtained. When the triisopropylsilyl group was in the propargylic position, **4b**, only the trimethylsilyl group was lost to give exclusively the alkyne **7**, regardless of the choice of solvent (equation 4).



With substrate **4c** having the triisopropylsilyl group in the acetylenic position (Table 2), there was a striking contrast to previous examples. Besides the minor allenic product **8**, the major product was the propargylic compound **9**, which has not been previously observed in these reactions. The ratio of allene **8** to propargyl compound **9** in dichloromethane depended on the reaction time (entries 1−3), though prolonged times resulted in a drop in yield. In acetonitrile, **9** was much more strongly favored (entries 4−6). This suggests that formation of **9** occurs by a multistep pathway.

We then searched for other products from the reaction of 1,3-bis(trimethylsilyl)propyne **4a** and an excess of glucal **1**. Compounds **10**, **11**, **12**, and **13** were isolated in 13, 25, 29, and 9% yields, respectively (total 76%).

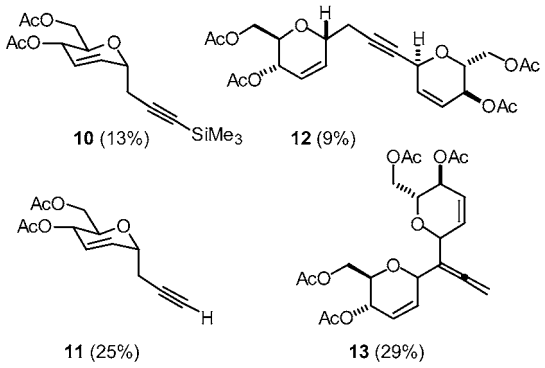
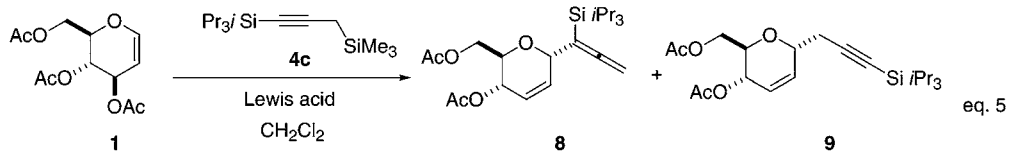


Figure 2. Various products between **4a** and an excess of **1**.

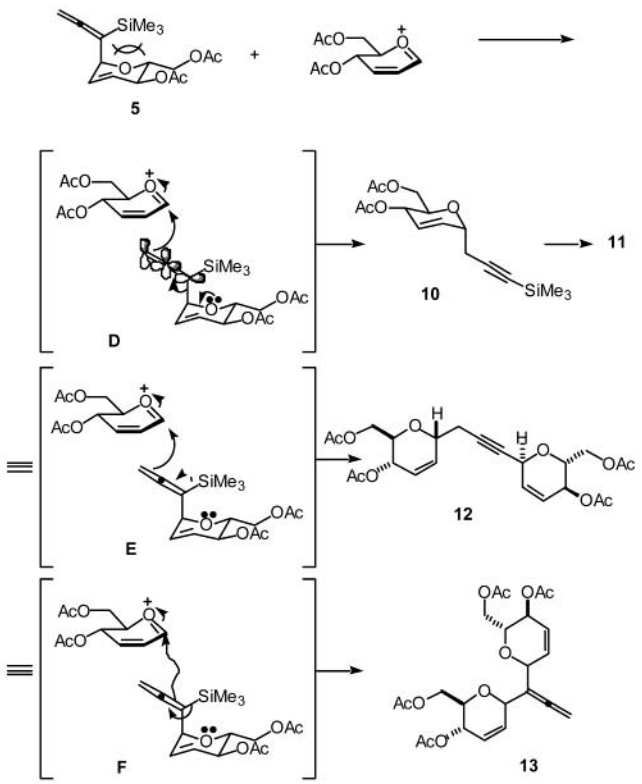
Table 2.



entry	equiv of **4**	Lewis acid	solvent	time	% yield of **8** + **9**	**8**/**9**
1	2	$SnCl_4$	CH_2Cl_2	15 min	74	1:2.5
2	1.1	$TiCl_4$	CH_2Cl_2	15 min	87	1:2.5
3	1.1	$SnCl_4$	CH_2Cl_2	45 min	69	1:5
4	1.1	$SnCl_4$	CH_3CN	1 h	58	1:9
5	1.1	$SnCl_4$	CH_3CN	15 min	60	1:9
6	0.5	$SnCl_4$	CH_3CN	1.5 h	30	1:80

The nature of these products suggests that the mechanism is as shown in Scheme 1, in which the initially formed allenic glycoside continues to attack further oxocarbenium ions. All of these four compounds are new and not derived simply from the starting materials. Compounds **10** and **11** are the first examples with propargylic substituents and should have interesting applications in polyether synthesis.[8] Formation of such propargylic products seems to be via mechanism **D** in which the initially formed allenic compound **5** attacks an additional oxocarbenium ion. The ring oxygen lone pair appears to drive the transfer of the three-carbon unit from one glycoside to another. Coupled products **12** and **13** appear to be formed by attack of different allene π-systems on an oxocarbenium ion via mechanisms **E** and **F**.[9]

Scheme 1. Bimolecular Mechanism for **10**−**13** Formation



In conclusion, we have established the ability to select between the formation of different C-glycosides by appropriate choice of conditions and silyl group. Further studies and application to the synthesis of CTX intermediates are now in progress and will be reported in due course.

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Supporting Information Available: Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Attempted preparation of the allenic compounds (**5** and **8**) in large amount was difficult as shown in eq 5.