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C-Glycosidation with Silylacetylenes to *D*-Glucals

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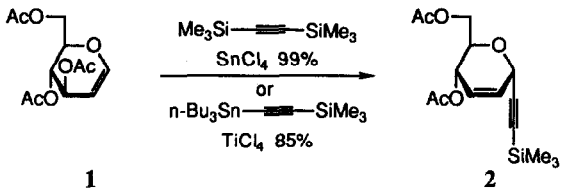
Key Words: C-Glycosidation; D-glucals; silylacetylene; tin acetylene; Lewis Acids

Abstract C-Glycosidation is of significance for introducing carbon chains to sugar nuclei from the chiral pool. Silylacetylenes have been shown to be sufficiently reactive for the selective introduction of acetylenic groups, useful for organic synthesis.

Synthesis of optically active compounds has posed challenges directed toward new methodologies with more practical sources. Sugars have been used as sources as well as templates in synthesis for expansion of stereogenic center(s) on extended side chain from tetrahydropyranyl ring.[1] C-Glycosidation is considered as a key reaction for introducing the carbon chain to sugars. A generalization of acetylenic group introduction into *D*-glucals is described here in the presence of Lewis acid as catalyst.

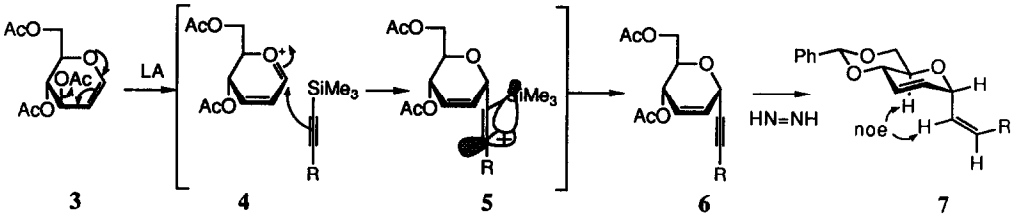


1 **2**

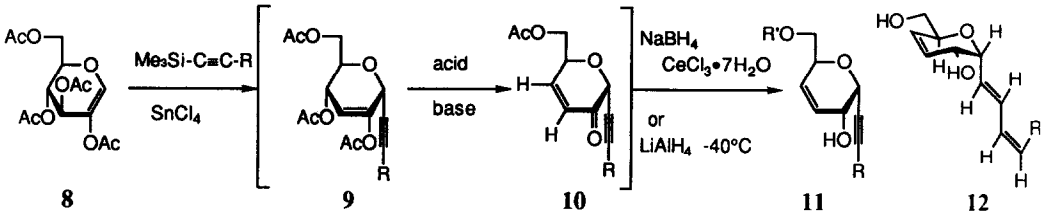
The first example between tri-*O*-acetyl-D-glucal **1** and bistrimethylsilyl acetylene as shown above was the initiation of the current method which gave the glycosidation product **2** in quantitative yield.[2] This reaction can also be done with tributylstannyl- and trimethylsilyl-acetylene in high yields.[3] The more readily available silylacetylenes proved to be sufficiently reactive for the C-glycosidation. The reaction mechanism, as illustrated in Scheme 1, involves elimination of the 3-acetoxy group in **3** (= **1**), and subsequent formation of the oxonium intermediate **4** to which pi-electrons of the silylacetylene should participate. A possible cationic charge would develop on the beta carbon in **5**, which is highly stabilized by the silicon atom.[4] Departure of the trimethylsilyl group results in the formation of the product **6**. Four more examples of C-glycosidation with Me3Si-C≡C-R on tri-*O*-acetyl-D-glucal **1** in the presence of Lewis acid at low temperatures in dichloromethane for ca. 1 hr are shown in Table 1 (entry 2-5). This glycosidation was completely stereoselective to obtain single stereoisomers, **2, 6a, 6b, 6c** and **6d.** Partial hydrogenation of product **2** (**6**, R= SiMe3) afforded **7** (R= SiMe3), of which the noe between H-5 and the olefinic H showed the alpha orientation. All others are assigned to have the alpha configuration at the C-1 position. The thiophenyl

derivative **6a** was obtained with a weaker catalyst $BF_3 \cdot OEt_2$ instead of $SnCl_4$ due to the additional stabilization effect by the sulfur atom for the cation **5** (R= SPh). Three products, **2**, **6b**, **6d**, containing trimethylsilylacetylenic moiety on the other end, which would potentially be reactive with another *D*-glucal molecule under the given conditions. In fact, the enediyne type product **6d** [FAB-MS m/z 361 (M+1)], in entry 5, was further reactive to allow us to isolate the twice reacted product [**14** shown in ref. 5, m/z 501 (M+1) in 10% yield beside **6d** in 79% yield].[5] The doubly glycosidated products, analogous to **14**, were not obtained under the ordinal condition in entry 1 and 3 in Table 1.

Scheme 1

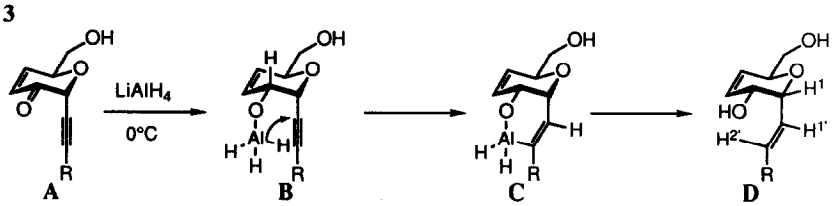


Scheme 2



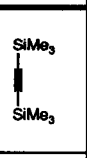
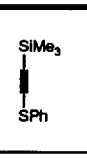
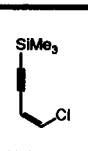
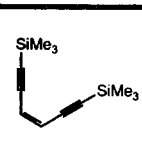
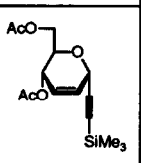
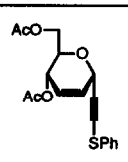
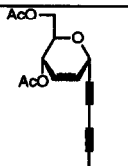
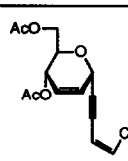
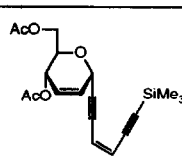
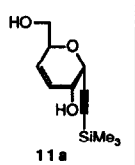
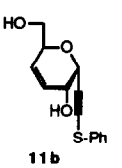
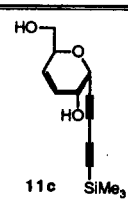
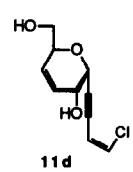
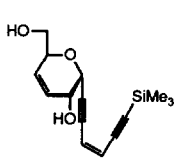
Similar C-glycosidation to 2-acetoxy-D-glucal **8** with the silyl acetylenes proceeded with tin tetrachloride at 0 ~ -20°C as illustrated in Scheme 2 to produce the acetylenic products **9**, most of which were unstable to acid, to base or even to silica gel for purification. These products were converted, after the aqueous work-up, into the α,β–unsaturated ketone **10**, which were stable to measure nmr (R= $SiMe_3$ α–H, δ 6.3 ppm & β–H 7.1 ppm), but were unstable to be isolated by silica gel chromatography. Usually the products (**10**) were treated with a reducing agent such as sodium borohydride in the presence of ceric trichloride to give the allylic alcohols **11** (R'= Ac). Reduction of **10** with lithium aluminumhydride at -40°C also provided the alcohols, **11a-e** (R'= H, overall yields being indicated in Table 1).[6]

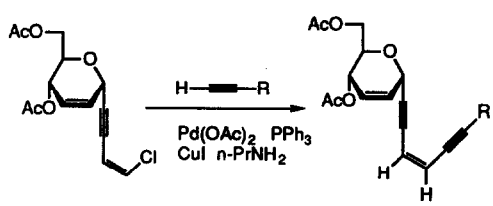
Scheme 3



On the other hand, reduction of **10** with $LiAlH_4$ at higher temperatures such as 0°C yielded the corresponding *trans* olefinic compounds **12** (R= Cl, R= -C≡C-SiMe3 in 36, 37% yield, respectively) together with the non-hydroalumination products (**11d,e** in ca. 30%, respectively). This hydroalumination proceeded due to the *cisoid* orientation of the acetylene and alkoxyaluminum at the neighboring positions. This assignment is suggested from the mechanism shown in Scheme 3. Stereochemistry of 2-hydroxy group is alpha by the hydride attack from the beta side in **A** to result in the formation of the intermediate **B**, which allows the hydroalumination (**C**), resulting in **D** after aqueous work-up. In fact, one of the product (**12**, R= -C≡C-SiMe3) showed noe between H-5 and H-1' as well as H-6 and H-1 to prove the stereochemistry of C-glycosidation being alpha.[7]

Table 1 C-Glycosidation of Silyl Acetylenes to *D*-glucals 1 and 8.

Entry	1	2	3	4	5
Silyl acetylenes					
Lewis Acid	$SnCl_4$	$BF_3{\cdot}OEt_2$	$SnCl_4$	$SnCl_4$	$SnCl_4$
react. temp	-20°C	0°C	-20°C	0°C	-78°C
product from 1	 **2**	 **6a**	 **6b**	 **6c**	 **6d**
yield	99 %	84 %	96 %	81 %	79 %
product from 8	 **11a**	 **11b**	 **11c**	 **11d**	 **11e**
yield	50 %	72%	39 %	41 %	48 %



6c **13**

Table 2

R	OTHP **13a**	OEt OEt **13b**
yields	63 %	93 %

The current C-glycosidation with silyl acetylenes has to be conducted under acidic conditions, which means a limitation to the acid-sensitive functional group such as acetals and ketals. To overcome this limitation a two-step preparation through the vinyl chloride **6c** was employed, which coupled with some acetylenes with acetal or ketal in the presence of palladium and copper under basic conditions[8] to yield **13a,b** (olefinic H, J= 7.7 Hz).

The current method will be used for the synthesis of oxygenated carbon compounds in optically active form, and the studies are to be continued for further application.

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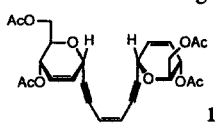
References and Notes

1. (a) M. Isobe, Y. Ichikawa, M. Kitamura and T. Goto; *Chemistry Lett.*, 457 (1981). (b) M. Kitamura, M. Isobe, Y. Ichikawa and T. Goto; *J. Am. Chem. Soc.*, **106**, 3252 (1984). (c) M. Isobe, Y. Funabashi, Y. Ichikawa, S. Mio and T. Goto, *Tetrahedron Lett.*, **25**, 2021 (1984). (d) M. Isobe, Y. Ichikawa, Y. Funabashi, S. Mio and T. Goto; *Tetrahedron*, **42**, 2863 (1986).
2. (a) Y. Ichikawa, M. Isobe, M. Konobe and T. Goto; *Carbohydrate Research*, **171**, 193 (1987).
3. Other acetylenic bond formations to acetals and ketals have been reported: (a) M. Hayashi, A. Inubushi, T. Mukaiyama, *Chemistry Lett.*, 1975 (1987). (b) W. S. Johnson, R. Elliott, J. D. Elliott, *J. Am. Chem. Soc.*, **105**, 2904 (1983).
4. (a) A. Hosomi and H. Sakurai; *Tetrahedron Lett.*, 1295 (1976). (b) M. Isobe, Y. Ichikawa and T. Goto; *Tetrahedron Lett.*, **27**, 963 (1986). (c) M. Isobe, Y. Ichikawa, D. Bai, H. Masaki and T. Goto; *Tetrahedron*, **43**, 4767 (1987). (d) S. Danishefsky and J. F. Kerwin, Jr.; *J. Org. Chem.*, **47**, 3805 (1982). (e) I. Fleming, *Comprehensive Organic Chemistry*, Chapter 13 Organo Silicon Chemistry, Pergamon Press (1979).
5. **6d** ($CDCl_3$ 200MHz), δ 0.22ppm (9H), 2.08(3H), 2.10(3H), 4.16(H-5, ddd, J= 9, 5, 2.5 Hz), 4.28(H-6,6), 5.20(H-1, m), 5.36 (H-4, ddt, J= 9, 4, 2), 5.84 (H-2, dt, J= 10.5, 2), 5.92 (side chain olefin 2H), 5.96 (H-3, ddd, J= 10.5, 4, 2); (50MHz), δ 0.1,* 20.8, 20.9, 62.9, 64.4, 64.7, 70.0, 83.7, 92.4, 101.5,* 103.4,* 119.3, 120.7,* 125.5, 128.7, 169.9, 170.5ppm.
The compound **14** showed no signals corresponding to the 13C-signal with asterisked*.



14

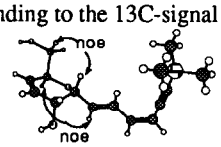


Fig 1 (see ref 7)

6. **11e** ($CDCl_3$ 200MHz), δ 0.22ppm(TMS), 3.64ppm (H-6), 4.36(H-2, br), 4.50(H-5), 5.14(H-1, brd, J= 6Hz), 5.88(olefinic 4H); (50MHz), δ 0.1, 63.9, 64.5, 68.0, 71.6, 85.5, 91.0, 101.7, 103.7, 110.9, 121.0, 127.6, a19.7ppm. FAB-MS m/z 259.2 (M-17). Doubly glycosidated product, analogous to **14** was not detected in reaction mixtures.
7. The NOESY spectrum was run with the olefin **12b**, and a twist boat conformation is suggested as shown in Fig. 1 in the space of Ref. 5.
8. (a) K. Sonogashira, Y. Tohda, N. Hagihara; *Tetrahedron Lett.*, 4467 (1975). (b) S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara; *Synthesis*, 627 (1980).

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