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1,4-*Anti* Induction in *C*-Glycosylation of Pentose Glycals

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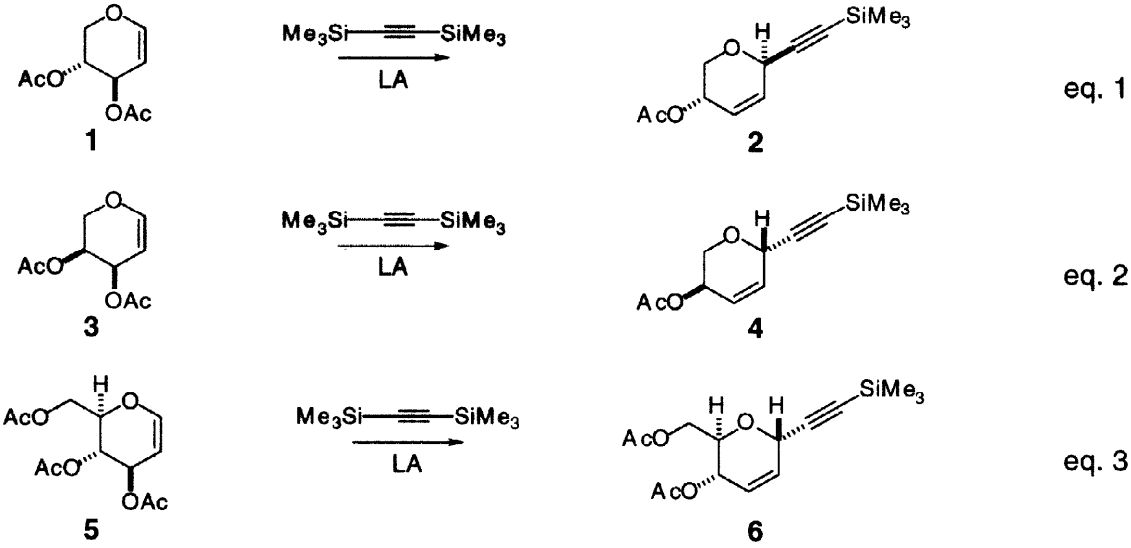
Abstract *: The C-glycosylation of pentose glycals with silylacetylenes or allylsilanes via oxocarbenium ion intermediates proceeded under high regio- and stereoselectivity giving the 1,4-anti products as the predominant products.*

We have been working on *C*-glycosylation of glycals with silylacetylene as one of the key steps in the total synthesis of natural products or their segments.[1] We have expanded similar *C*-glycosylations to pentopyranose derivatives such as di-*O*-acetyl-D-xylal (**1**) during the synthesis of an ABC-Segment of ciguatoxin and reported that the glycosylation led stereoselectively to a single isomer (**2**); and similarly the reaction with di-*O*-acetyl-L-arabinal (**3**) afforded **4**.[2] Initially, this stereogenic center was not so significant due to destruction of this center in the above mentioned synthesis (not even determined to be *alpha* or *beta*). Recently the results of the stereochemical induction turned out to be in striking contrast to the previous cases. For example, tri-*O*-acetyl-D-glucal (**5**) and bistrimethylsilylacetylene in the presence of Lewis acid react with highly stereospecific manner to give the *alpha-axial* orientation in the product **6**.[3] On the other hand 1,4-*anti* stereochemistry was the dominant or exclusive product **2** and **4** in the pentopyranose cases. In the present paper we describe the 1,4-*anti* selective introduction of carbon nucleophiles into pentose glycals with special reference to the stereochemical outcome and reaction mechanisms.



In order to determine the stereochemical outcome of the *C*-glycosylation with pentopyranoses, two compounds (**1**) and (**3**) were employed to show that the diastereoselection is due to 1,4-induction. The

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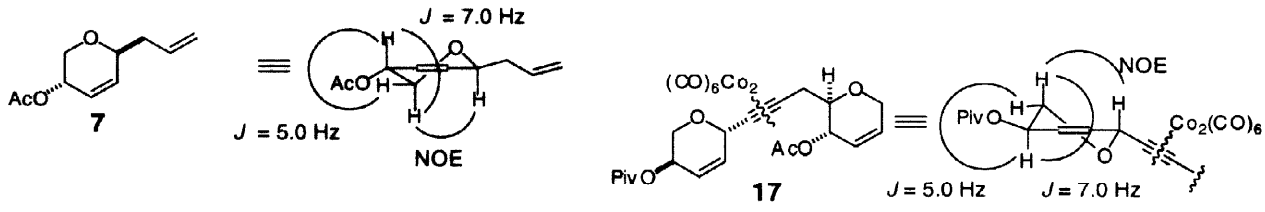
Hosomi-Sakurai reaction with allyltrimethylsilane with pentopyranosides (**1** or **3**) under similar condition also afforded the 1,4-anti products (**7** or **8**), respectively. These pairs of products (**2**, **4**) and (**7**, **8**) exhibited the same optical rotation with opposite sign to show the products are enantiomers to each other. Other examples of **1** proceeded with methyl(trimethylsilyl)acetylene or phenylthio(trimethylsilyl)-acetylene to provide the 1,4-*anti*-products **9** or **10**, respectively.

As starting material the pentopyranose derivatives, di-*O*-acetyl-D-xylal (**1**), di-*O*-pivaloyl-D-xylal (**11**), di-*O*-acetyl-L-arabinal (**3**) or di-*O*-pivaloyl-L-arabinal (**14**) were employed to examine the stereoselectivity in the *C*-glycosylation. The nucleophiles for the *C*-glycosylation were the silylacetylenes listed in Table 1. The silylacetylenes **12** and **14** are intermediates for the ciguatoxin (enantio-) AB or ABC fragments as reported. In these cases the glycals **11** and **16** having pivaloyl protection afforded higher yields than the corresponding acetates. We are now able to make a stereochemical assignment for the products **13**, **15**, **17**, and **18**. Another nucleophile, 4-(trimethylsilyloxy)pent-3-en-2-one (**19**), reacted with **1** to provide the C-C coupling product (**20**), which showed slightly lower selectivity. This might suggest that the products are usually formed under kinetic control for the silylacetylene while the last example may include a thermodynamic factor.[4]

A typical *C*-glycosylation reaction was carried out as follows: a solution of D-xylal **1** (113 mg, 565 μmol) and allyltrimethylsilane (150 μl, 944 μmol) in dichloromethane (3.0 ml) was cooled to -40°C under N_2 atmosphere, and an aliquot of $BF_3{\cdot}OEt_2$ (75 μl) was added to this solution with stirring. The stirring was continued at -15°C for 2 hr and the reaction mixture was poured into a cold sodium bicarbonate solution under vigorous stirring. The products were extracted with dichloromethane (3 times), and the extracts were washed with water and brine and concentrated in vacuo. The residue was purified by passing through a short column containing silica gel to afford the product **7** as a colorless oil in 102 mg in 99% yield (analytically pure; data as shown in Table 1). In the cases of the pivaloates (**11**, **16**), the reaction proceeded relatively slower to result in self-condensation as a side reaction, and some additional 0.2~0.5 equiv. of the glycals were added until the reaction was completed. All *C*-glycosylations proceeded in excellent yields with high stereoselectivity.

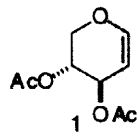
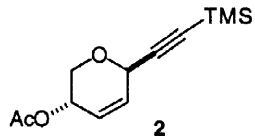
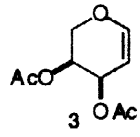
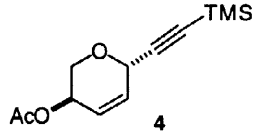
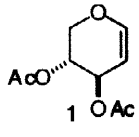
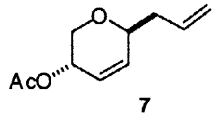
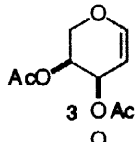
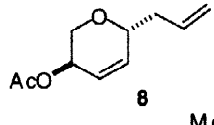
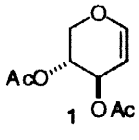
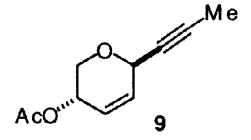
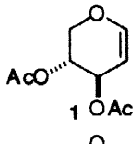
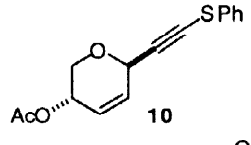
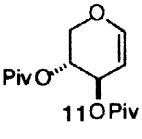
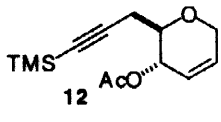
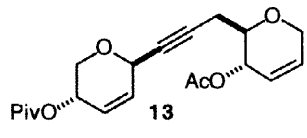
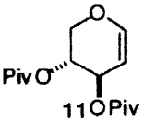
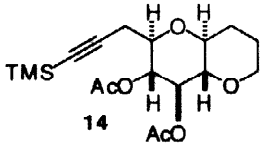
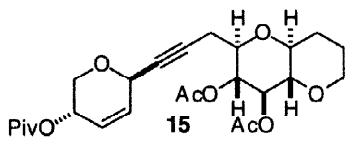
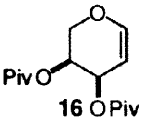
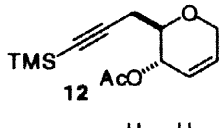
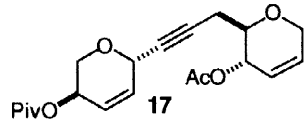
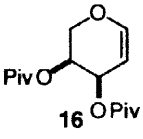
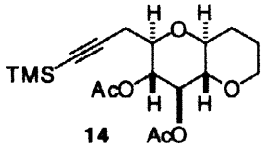
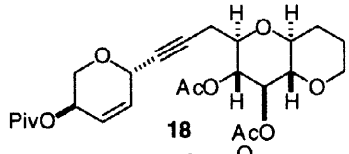
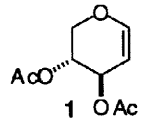
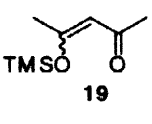
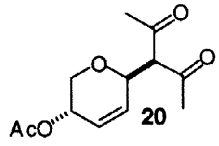
Several other nucleophiles were also employed for comparison. Besides bis-trimethylsilylacetylene were selected $Me_3SiC{\equiv}C$-R, with R= Me, SPh, etc. In the reaction with thiophenyl substituent the acid catalyst was the weakest among others due to stabilization effect to the cationic charge development next to the sulfuratom. Reactions with allylsilanes or alkynylsilanes could usually be carried out at such low temperatures as -40 to -15 °C. One vinylsilyl ether (**19**) was also employed. This turned out to react slower than the silylacetylenes, and the reaction was conducted at a higher temperature (0 °C as indicated in Table 1).[5]

The stereochemistry of the products was determined mainly by nmr studies; thus, the axial proton at C-1 (of the allylated product **7**, figure A) shows noe with the axial H-5, having the larger coupling constant (7.0 Hz) with H-4ax geminal to the 4-acetoxy group, while the H-4ax couples with the equatorial H-5eq with 5.0 Hz. On the other hand, the two dihydropyranosyl products **10** and **17** afforded similar results after converting them into the corresponding acetylenebiscobalt-hexacarbonyl complexes. The configurations of the products were determined using ^{1}H-NMR and NOESY experiments (Fig. A and B). All other acetylenic compounds were also transformed into their corresponding Co-complexes before carrying out NMR experiments to fix the conformation with the *C*-1 substituent in equatorial position. The result of the NMR-experiments led to the conclusion that the products of the *C*-glycosylations possess 1,4-*anti* configuration.

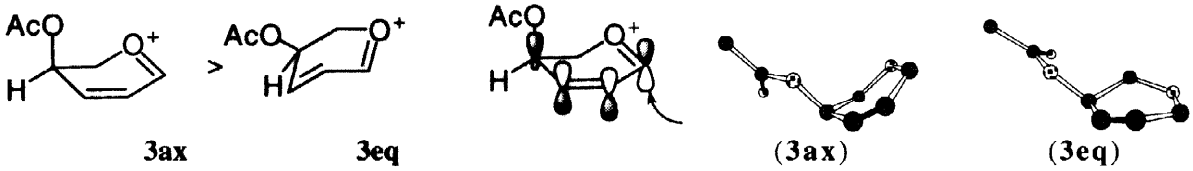


A B

Table 1 C-Glycosylation to pentopyranosyl derivatives with silylacetylene or allylsilane

entry	glycal	nucleophile	Lewis acid condition	major product	yield (*anti*:*syn*) $[\alpha]_D$
1	 **1**	TMS—≡—TMS	$TiCl_4$ -40~-15 °C 2 h	 **2**	73% (>95:5) +318.0
2	 **3**	TMS—≡—TMS	$TiCl_4$ -40~-15 °C 2 h	 **4**	97% (>95:5) -317.0
3	 **1**		BF_3•OEt_2 -40~-15 °C 2 h	 **7**	99% (>95:5) +176.1
4	 **3**		BF_3•OEt_2 -40~-15 °C 2 h	 **8**	95% (95:5) -174.7
5	 **1**	TMS—≡—Me	$TiCl_4$ -40~-15 °C 2 h	 **9**	99% (>95:5) +347.2
6	 **1**	TMS—≡—SPh	BF_3•OEt_2 0 °C 15 min	 **10**	88% (>95:5) +326.9
7	 **11**	 **12**	$TiCl_4$ -20 °C 2 h	 **13**	87% (>95:5) +199.1
8	 **11**	 **14**	$SnCl_4$ -20 °C 40 min	 **15**	96% (>95:5) +158.1
9	 **16**	 **12**	$TiCl_4$ -20 °C 2 h	 **17**	54% (>95:5) +10.3
10	 **16**	 **14**	$SnCl_4$ -20 °C 2 h	 **18**	83% (>95:5) -112.3
11	 **1**	 **19**	BF_3•OEt_2 -20~0 °C 1 h	 **20**	65% (85:15) -29.0

These results are strikingly constrast with the cases of hexopyranoses as mentioned above, but the stereochemical course is conducted under a typical stereoelectronic effect. In the hexopyranose derivatives, all cationic intermediates should take a conformation with the C-6 in equatorial orientation, independent of the 4-AcO- group being in alpha or beta position; thus, the *alpha* orbital of the C-1(=O$^+$) is oriented *quasi-axial* to form a bond with the acetylene nucleophile to result allways in the *alpha* axial products. On the other hand, the pentopyranoses might have the C-4-AcO- group in an axial orientation in the transition state when reacting with a silylacetylene nucleophile. The assumption of this orientation is supported by molecular mechanic calculations (MMFF)[6] that indicates that the axial orientation of the 4-OAc group (**3ax**) is more stable than the equatorial one (**3eq**) by 1.5 kcal/mol. This result is consistent with the 0.63 kcal/mol energy difference of an Ab-initio calculation.[7] At the transition state of the *C*-glycosylation the α-*anti*-lobe to the acetoxy group at the C-3 α-lobe would become larger when according to the Felkin-Nguen model, while SN2' reaction should occur at the same face to result in the nucleophile addition at the C-1 from α-orientation.



3ax **3eq** **(3ax)** **(3eq)**

The overall process leads to a 1,4-*anti*-asymmetric induction in the above described *C*-glycosylations of pentose glycals. The nucleophilic attack is kinetically controlled. Under thermodynamic control (as indicated in entry 11), the selectivity usually drops according to the prolonged reaction time.

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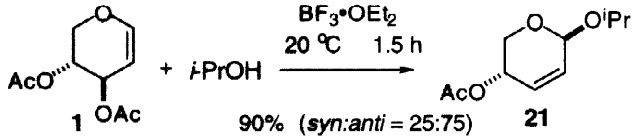
References and Notes

1. (a) Tsukiyama, T.; Isobe, M. *Tetrahedron Lett.*, **1992**, *33*, 7911-7914. (b) Tsukiyama, T.; Peters, S. C.; Isobe, M. *Synlett*, **1993**, 413-415. (c) Jiang Y-M.; Ichikawa, Y.; Isobe, M. *Synlett*, **1995**, 285-288. (d) Jiang, Y.; Isobe, M. *Tetrahedron*, **1996**, *52*, 2877-2892. (e) Ichikawa, Y.; Isobe, M.; Konobe, M.; Goto, T. *Carbohydrate Research*, **1987**, *171*, 193-199.
2. (a) Hosokawa, S.; Isobe, M. *Synlett*, **1995**, 1179-1180. (b) Hosokawa, S.; Isobe M. *Synlett*, **1996**, 351-352.
3. (a) Danishefsky, S.; Kerwin Jr., J. F.; *J. Org. Chem.*, **1982**, *47*, 3803. (b) S. Yougai, T. Miwa, *J. Chem. Soc. Chem. Commun.* **1983**, 68. (c) Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.*, **1987**, *52*, 1370-1372. See review: M. H. D. Postema, *C-Glycoside Synthesis*, CRC Press (1995). D. E. Levy, C. Tang, *The Chemistry Of C-Glycosides*, Pergamon (1995). S. Hanessian, *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon Press (1983).
4. R. L. Whistler, *et al. Methods in Carbohydrate Chemistry* **1962**, vol. 1, pp. 84, 184. M. W. Bredenkamp, C. W. Holzapfel, F. Toerien, *Synthetic Commun.* **1992**, *22*, 2459.
5. The oxygen nucleophile (2-propanol) gave **21** even in low selectivity as *syn:anti* = 25 : 75, which might be produced under equilibrium conditions.



6. Performed with MacroModel Version 6.0 employing MMFF94 force field as a package program. Merck Molecular Force Field, I. Basis from Scope Parametarization and performance of "MMFF94. Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490-512.
7. The authors are grateful to Prof. Deslongchamps to notify about their manuscript: Miljkovic, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. *J. Org. Chem., in press.*