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An Improved Method for the Synthesis of Anomerically Allylated C-Glycopyranosides and C-Glycofuranosides.

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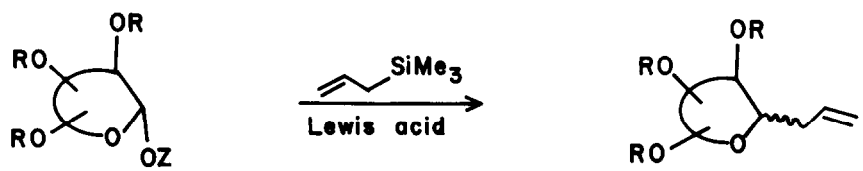
Summary: *An improved procedure for the anomeric C-allylation of several carbohydrate derivatives is described.*

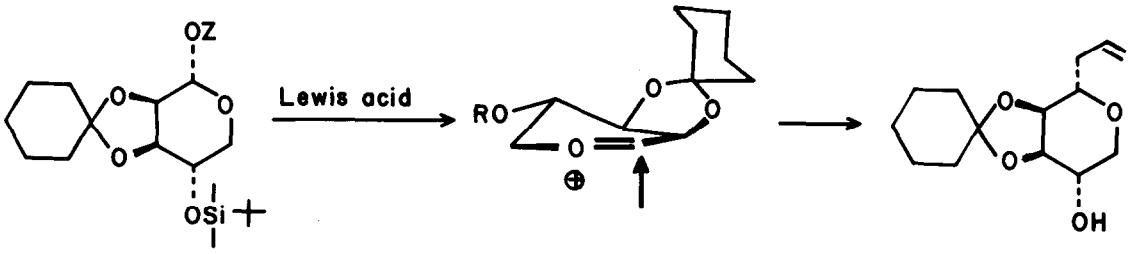
In continuation of our efforts to devise new ways of effecting the stereoselective C-functionalization of the anomeric site of carbohydrates, we wish to disclose further details of our C-allylation process utilizing allyltrimethylsilane which allow one to carry the reaction out under a milder set of reaction conditions and with higher stereoselectivity.[1] Previously, we had reported that zinc bromide could be used to effect the marginally stereoselective C-allylation of derivatives of both L-lyxose and D-ribose at 110°C employing allyltrimethylsilane as the solvent.[2]



On further varying the nature of the Lewis acid used to promote this reaction as well as the nature of the leaving group used to activate the carbohydrate, we have discovered that the protected lyxose derivative 1 can be converted exclusively to the desired α-product 2. While our original reaction conditions utilizing the acetate derivative 1 (Z=Ac) delivered a 4:1 mixture of the α and β products, this same acetate on reaction with allyltrimethylsilane in acetonitrile with $BF_3 \cdot OEt_2$ as catalyst (0°C → rt) afforded an 88% yield of the C-allylated product which consisted of >95% of the α-isomer 2.[3]

When the p-nitrobenzoate derivative 1 (Z=PNB) of L-lyxose was reacted under these same conditions, only the α-isomer could be detected by HPLC analysis. The better leaving group ability of the PNB group must favor complete production of

an open oxonium ion, which subsequently reacts by the stereoelectronically (and sterically) preferred axial addition mode. When this same PNB derivative was reacted under the zinc bromide catalysis conditions, a 5:1/α:β isomer ratio was generated. The zinc bromide method may thus lead to substitution via mechanistic pathways involving both the S_N1 and the S_N2 (or extended transition state)[4] processes.



In order to completely insure our previous ^1H NMR based structural assignments of these products, a single crystal X-ray analysis has been carried out on the undesired isomer 3. As Figure 1 reveals, our original assignment of structure was made correctly.

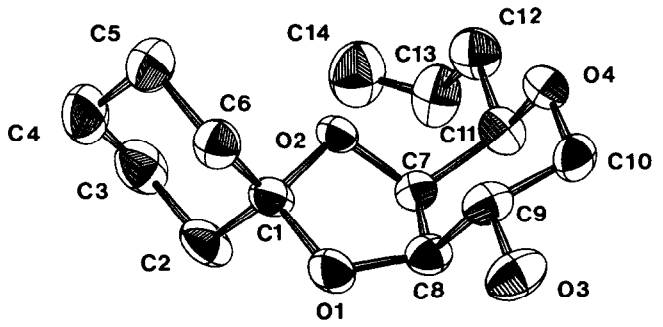
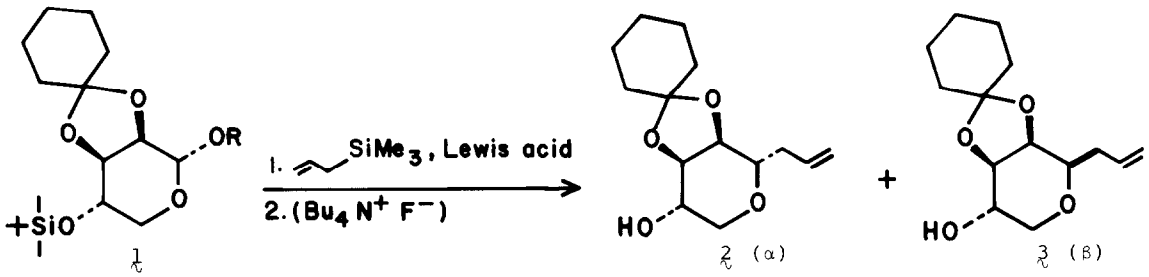


Figure 1. X-ray structure of 3 with hydrogens omitted for clarity.

We have also been able to achieve complete stereoselectivity in the trimethylsilyl triflate (TMSOTf) assisted reaction of the acetate 1 with allyltrimethylsilane. The yield obtained for this reaction was, however, a disappointing 42%.

When the $BF_3 \cdot OEt_2$ conditions were applied to the tetrabenzoate derivative of L-lyxose (4), it was quite curious to observe that a 1:5 mixture of the α/β products was generated. This is to be contrasted with the 1:1 ratio generated by the zinc bromide process. Even with the ribose derivative 7, the $BF_3 \cdot OEt_2$ conditions led to the production of more of what would appear to be the product of inversion. While a conformational change brought about by complexation and thus the operation of the reverse anomeric effect could be invoked,[6] this explanation is

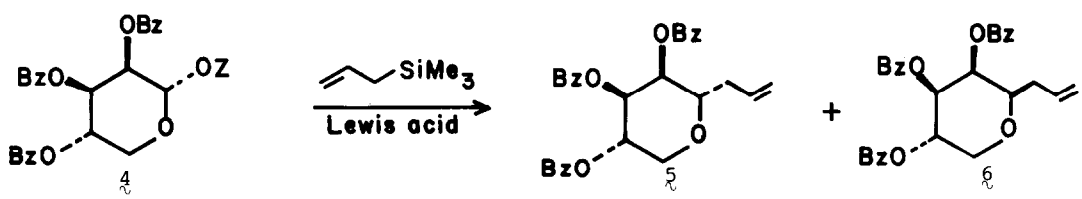
Table. Anomeric Functionalization of Some Selected Carbohydrate Derivatives.



1 → 2 (α) + 3 (β)

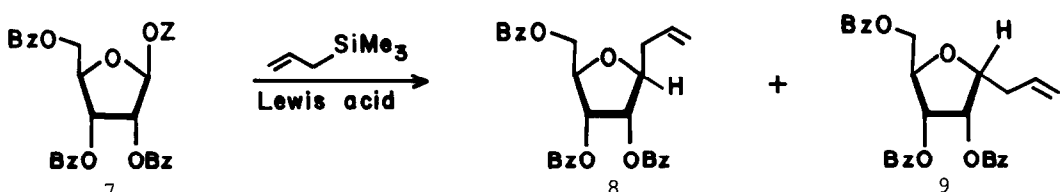
Entry	Z	Lewis Acid/Reaction Conditions	α/β ratio[a]	(Yield)
1	Ac	$ZnCl_2$, neat, 110°C, 2 h	3:1	(90)
2	Ac	$ZnBr_2$, neat, 110°C, 15 min	4:1	(84)
3	Ac	$BF_3 \cdot OEt_2$, CH_3CN, 0° → rt, 3 h	>95:5	(88)
4	PNB	$ZnBr_2$, neat, 110°C, 15 min	5:1	(84)
5	PNB	$BF_3 \cdot OEt_2$, CH_3CN, 0° → rt, 2 h	1:0	(88)
6	Ac	TMSOTf, CH_2Cl_2, rt	1:0	(42)

[a]The isomer ratios were determined by ^1H NMR and HPLC analysis after complete desilylation.



4 → 5 + 6

7	Bz	$ZnBr_2$, neat, 110°C, 2 h	1:1	(100)
8	Bz	$BF_3 \cdot OEt_2$, CH_3CN, 0° → rt, 10 h	1:5	(95)



7 → 8 + 9

9	Ac	$ZnBr_2$, neat, 110°C, 2 h	1:4	(85)
10	Ac	$BF_3 \cdot OEt_2$, CH_3CN, 0° → rt, 3 h	1:7	(93)
11	Ac	$BF_3 \cdot OEt_2$, CH_2Cl_2, 0° → rt, 24 h	1:2.5	(48)

still far from satisfactory. Further experiments are required in order to resolve this apparent stereochemical dilemma.

Exemplary $BF_3 \cdot OEt_2$ Procedure:

To an ice cold mixture of the L-lyxose derivate 7 (Z=Ac) (82 mg, 0.20 mmol) and allyltrimethylsilane (68 mg, 0.60 mmol) in 2 mL of acetonitrile was added dropwise $BF_3 \cdot OEt_2$ (31 mg, 0.22 mmol). The reaction mixture was allowed to warm to rt over a 3 h period, and then diluted with saturated sodium bicarbonate and extracted with ether. The organic extracts were dried ($MgSO_4$) and concentrated. The oily residue was chromatographed on silica gel with 25% ethyl acetate-hexanes as eluent to afford a pure sample of the desilylated product 2 (43 mg, 86%): C-13 NMR ($CDCl_3$) 134.36 (d, J = 153.8 Hz), 117.05 (t, J = 153.8 Hz), 110.06 (s), 78.49 (d, J = 146.8 Hz), 75.09 (d, J = 122.1 Hz), 73.47 (d, J = 119.6 Hz), 68.55 (t, J = 141.6 Hz), 66.55 (d, J = 146.5 Hz), 38.11 (t, J = 126.9 Hz), 37.20 (t, J = 126.5 Hz), 35.52 (t, J = 129.4 Hz), 28.98 (t, J = 201.9 Hz), 23.97 (t, J = 151.4 Hz), 23.65 (t, J = 129.4 Hz): ^1H NMR (300 MHz, $CDCl_3$) δ 1.30-1.80 (m, 10 H), 2.13-2.19 (m, 1 H), 2.20-2.26 (m, 1 H), 2.47-2.56 (m, 1 H), 3.29 (ddd, J = 9.0, 8.5, 3.8 Hz, 1 H), 3.75 (dd, J = 12.3, 1.8 Hz, 1 H), 3.85 (ddd, J = 12.3, 1.2, 1.2 Hz, 1 H), 3.92 (dd, J = 9.0, 5.1 Hz, 1 H), 3.97-4.01 (m, 1 H), 4.23-4.27 (m, 1 H), 5.08-5.19 (m, 2 H), and 4.82-5.95 (m, 1 H) ppm: IR ($CHCl_3$) 3560, 3000, 2920, 2845, 1638, 1510, 1445, 1365, 1270, 1200, 1180, 1105, 1080, 985, 920, and 840 cm^{-1}: mass calcd. for $C_{14}H_{22}O_4$: 254.151; found 254.151: $[\alpha]_D^{24} = -36.9^\circ$ (c = 1.72, $CHCl_3$).

References and Notes

1. A. P. Kozikowski, R. J. Schmiesing and K. L. Sorgi, J. Am. Chem. Soc., 102, 6577 (1980).
2. A. P. Kozikowski and K. L. Sorgi, Tetrahedron Lett., 23, 2281 (1981). The publication of some related work prompts us to disclose our additional findings at this time. See, M. D. Lewis, J. K. Cha and Y. Kishi, J. Am. Chem. Soc., 104, 4976 (1982); S. Danishefsky and J. F. Kerwin, J. Org. Chem., 47, 3805 (1982).
3. Desilylation does take place under these reaction conditions.
4. S. Murata and R. Noyori, Tetrahedron Lett., 23, 2601 (1982).
5. Details of the X-ray structure will be published elsewhere.
6. V. G. S. Box, Heterocycles, 19, 1939 (1982).

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