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STEREOSELECTIVE SYNTHESIS OF α- C-ALLYL-GLYCOPYRANOSIDES

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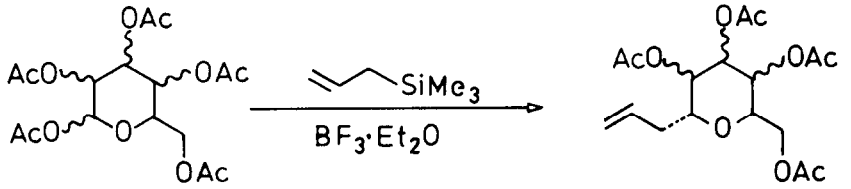
Summary: A simplified procedure for the synthesis of C-glycosides has been developed. Fully or partially acetylated glycopyranoses are reacted, in a single step, with allyltrimethylsilane in the presence of a Lewis acid. This method also offers the advantage that stereoselectivity can be induced by using appropriate solvents.

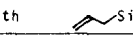
C-glycopyranosides occur as subunits of a variety of natural products (1). They have been used as enzyme inhibitors (2) and as chiral sources for organic syntheses (3). Procedures published to date require the use of complex starting materials and/or HPLC-separation procedures (4). In our biochemical studies on properties and mechanisms of glycosidases, we wanted to employ a variety of C-glycosides as potential inhibitors and as affinity ligands.

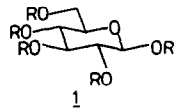
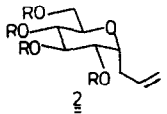
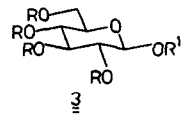
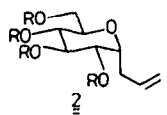
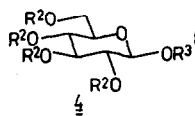
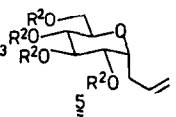
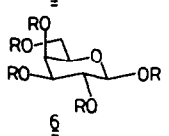
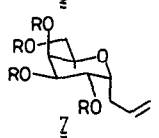
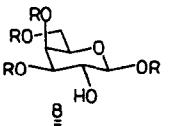
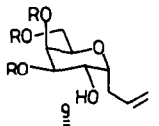
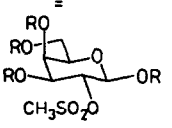
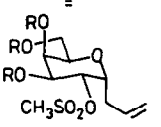
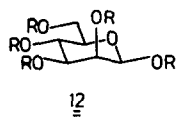
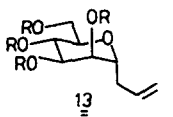
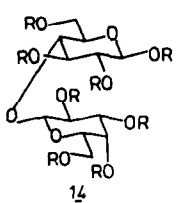
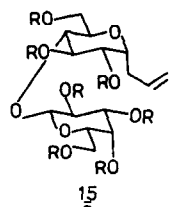
A simple procedure for the synthesis of allyl-C-glycopyranosides has therefore been developed using easily accessible peracetylated glycopyranoses as starting materials:



The choice of the solvent considerably affected the stereoselectivity of the reaction, as shown in Table 1.

Thus, while the reaction in dichloroethane as solvent yielded about equimolar quantities of the α and β anomers, running the reaction in acetonitrile produced a selective abundance (up to 95 %) of the α anomer. An even more extreme stereoselectivity could be demonstrated using compound 8 (5) as reactant. In this case, in either solvent only the α-anomer of compound 9 was produced. This was ascertained by physical measurements (^{1}H-NMR, ^{13}C-NMR) and with an enzymatic assay in which the product (e.g. compound 9 R = H) inhibited selectively α-galactosidase, but hat no effect on β-galactosidase.

Table 1: C-glycosylation with 

STARTING MATERIAL[a]	PRODUCT[6]	REACTION CONDITIONS	α/β-RATIO[b]	YIELD[c] (%)
 1	 2	I. $CLCH_2CH_2CL$ 50°, 6 h	1 : 1	72
		II. CH_3CN 4°, 48 h	95 : 5	81
 3	 2	CH_3CN 65°, 4 h	9 : 1	69
 4	 5	CH_3CN 65°, 4 h	9 : 1	71
 6	 7	I. $CLCH_2CH_2CL$ 50°, 6 h	1 : 1	78
		II. CH_3CN 4°, 48 h	95 : 5	80
 8	 9	I. $CLCH_2CH_2CL$ 80°, 24 h	1 : 0	40[d]
		II. CH_3CN 80°, 24 h	1 : 0	25
 10	 11	CH_3CN 80°, 24 h	99 : 1	88[7]
 12	 13	CH_3CN 20°, 72 h	4 : 1	68
 14	 15	CH_3CN 20°, 6 h	99 : 1	55

a) R = Acetyl, R^1 = 2, 4, 6 trimethylbenzoyl, R^2 = benzoyl, R^3 = formyl.

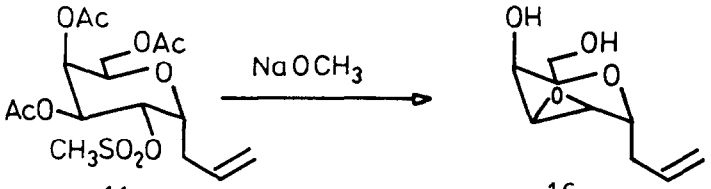
b) The ratio α/β was determined by ^{1}H-NMR spectroscopy (400 MHz) and by ^{13}C-NMR spectroscopy (without NOE).

c) The yield refers to the product isolated.

d) An identical amount of 7 is formed simultaneously.

The Table also demonstrates that mono- as well as disaccharides could be used as starting materials for this reaction. Furthermore, the acetyl groups at

C-1 could be replaced by other acyl residues. This might be best exemplified by the reactions in which compounds 2 and 5 were produced from compounds (8) 3 and 4, correspondingly. Of interest were the observations that even the 2, 4, 6-trimethylbenzoyl residue could be used as a substituent on the C-1 position of the starting material, and that compound 11 when dissolved in methanol and treated with sodium methoxide, produced a quantitative yield of compound 16. A similar β-C-galactoside has been described as suicide inhibitor for β-galactosidase from E. coli (9).



11 16

Finally, attempts to produce the corresponding C-allyl glycoside from 2 deoxy-2-acetamidoglucose were unsuccessful.

The following N-protecting groups have been tried:
Acetyl, phthaloyl, trifluoroacetyl, tosyl, p-methoxybenzyliden, benzyloxycarbonyl, tert. butyloxycarbonyl in combination with different Lewis acids: $BF_3 \cdot Et_2O$, $SnCl_4$, $AlCl_3$, $FeCl_3$, ZnJ_2.

Experimental procedure

10 mmol of the respective starting material were dissolved in 50 ml of absolute acetonitrile or dichlorethane, then 30 mmol allyltrimethylsilane and 50 mmol of bortrifluorideethylether complex were added successively under an atmosphere of nitrogen. The reaction was monitored by tlc and after completion the mixture was poured into a saturated solution of $NaHCO_3$. The product was extracted 3 times with dichloromethane (50 ml each), the organic solution dried with Na_2SO_4 and the solvent evaporated. Finally the product was isolated by flash-chromatography using toluene/ethylacetate (4:3, v/v) for elution.

References and Comments:

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6. All products gave satisfactory IR-, ^{1}H NMR-, ^{13}C NMR-, and mass spectra, consistent with the assigned structures. In the following selected data are given for products 7, 11, and 15:

7: ^{1}H-NMR (δ, $CDCl_3$) 2.00 (s, 3 H), 2.02 (s, 3 H), 2.04 (s, 3 H), 2.10 (s, 3 H), 2.20 - 2.50 (m, 2 H), 4.02 - 4.22 (m, 3 H), 4.24 - 4.31 (m, 1 H), 5.00 - 5.41 (m, 5 H), 5.67 - 5.80 (m, 1 H)

^{13}C-NMR (δ, $CDCl_3$) 20.68, 20.74, 20.81, 30.97, 61.49, 67.64, 67.97, 68.32, 68.84, 71.50, 117.72, 133.42, 169.93, 170.02, 170.19, 170.67

11: ^{1}H-NMR (δ, $CDCl_3$) 2.01 (s, 3 H), 2.02 (s, 3 H), 2.13 (s, 3 H), 2.40 - 2.58 (m, 2 H), 3.03 (s, 3 H), 4.00 - 4.15 (m, 3 H), 4.32 - 4.40 (m, 1 H), 4.97 - 5.50 (m, 5 H), 5.70 - 5.85 (m, 1 H)

^{13}C-NMR (δ, $CDCl_3$) 20.66, 30.07, 38.47, 61.50, 67.84, 67.90, 68.08, 73.00, 74.64, 118.21, 132.96, 169.76, 170.19, 170.61

15: ^{1}H-NMR (δ, $CDCl_3$) 1.96 (s, 3 H), 2.04 (s, 6 H), 2.05 (s, 3 H), 2.06 (s, 3 H), 2.09 (s, 3 H), 2.14 (s, 3 H), 2.20 - 2.60 (m, 2 H), 3.65 - 3.91 (m, 3 H), 4.06 - 4.20 (m, 4 H), 4.35 (dd, 1 H), 4.49 (d, 1 H), 4.94 - 5.00 (m, 2 H), 5.08 - 5.18 (m, 3 H), 5.31 - 5.36 (m, 2 H), 5.67 - 5.78 (m, 1 H)

^{13}C-NMR (δ, $CDCl_3$) 20.48, 20.61, 20.74, 20.81, 31.04, 60.91, 62.27, 66.74, 69.10, 69.78, 70.04, 70.75, 71.01, 71.50, 76.58, 101.34, 117.78, 133.12, 169.21, 169.63, 169.96, 170.09, 170.15, 170.41, 170.48

7. The molar ratio of borontrifluoride etherate/allyltrimethylsilane/10 was 6:6:1.

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