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A MILD METHOD FOR THE SYNTHESIS OF ANOMERICALLY ALLYLATED C-GLYCOPYRANOSIDES AND C-GLYCOFURANOSIDES

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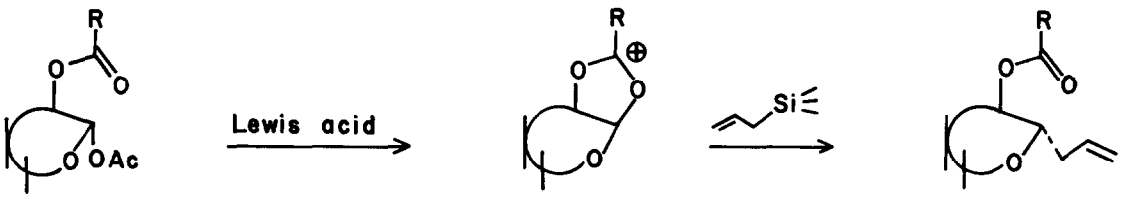
Summary: The reaction of glycosyl acetates with allyltrimethylsilane in the presence of zinc bromide has been investigated as a new method for C-glycoside construction.

During the course of our efforts to develop a carbohydrate-based approach to the antibiotic pseudomonic acids A, B and C,[1] we had the occassion to examine some new methods for C-glycoside construction. In particular, we were intrigued by the possibility of utilizing an allylsilane as a nucleophile to intercept the oxonium ion intermediate formed on exposure of a glycosyl acetate to a Lewis acid.[2] We did, of course, anticipate that the reaction might be rendered stereospecific in cases where neighboring group participation was possible.[3]



To test this notion experimentally, we employed several readily available derivatives of D-ribose and L-lyxose. While we did examine a variety of Lewis acids (e.g., TMSOTf,[4] $TiCl_4$, $SnCl_4$, $BF_3 \cdot OEt_2$ and $ZnBr_2$), solvents, and reaction temperatures and times, we have been most pleased with a very simple procedure which calls for heating the sugar derivative with neat allyltrimethylsilane in the presence of 2.5 equivalents of zinc bromide at 110°C for 3 h. Good yields of C-allylated products are obtained from both the five- and six-membered ring sugars (Table).

It is interesting to note that both silyl and ketal groups survived these reaction conditions admirably. Bond cleavage of a ketal carbon-oxygen bond is among other reasons presumably made less favorable than cleavage of the anomeric

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carbon-oxygen bond as a consequence of poor orbital alignment.[5]

With regard to the stereochemistry of this new functionalization process, it can be seen readily from the Table that in cases where anchimeric assistance could mediate product stereochemistry, no such directing effect was in fact observed. With 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (1), the reaction actually appears superficially to have taken on more of the character of an S_N2 process. This result is to be compared with a report by Hanessian in which the same ribose derivative was shown to react with the trimethylsilyl enol ether of cyclohexanone in the presence of stannic chloride to provide exclusively 2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)cyclohexanone.[6] The stereochemistry of our isomers was established in an unambiguous manner by subjecting each to ozonolysis and working up the ozonide in an oxidative fashion to afford the corresponding carboxylic acid. Diazomethane treatment then provided the methyl ribofuranosyl-acetates which could be correlated with the product prepared from 5-O-t-butyl-dimethylsilyl-2,3-O-isopropylidene-D-ribofuranose by Wittig reaction with (methoxycarbonylmethylidene)triphenylphosphorane followed by hydroxyl group deprotection with aqueous trifluoroacetic acid and reprotection with benzoyl chloride/pyridine. Since the Wittig process is well known to yield the β-isomer as the major kinetic product,[7] these experiments allowed us to assign α-stereochemistry to the major product of the allylsilane reaction.

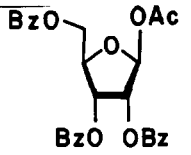
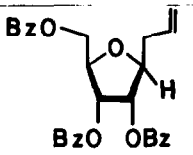
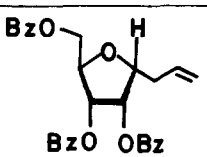
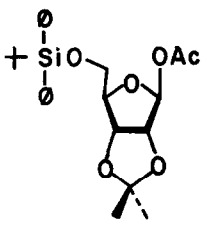
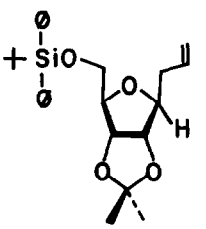
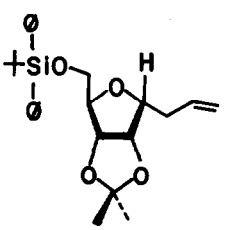
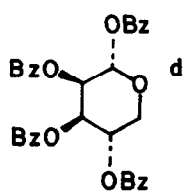
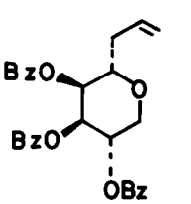
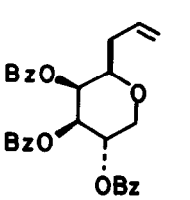
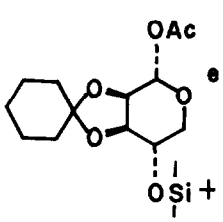
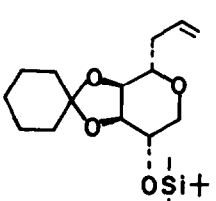
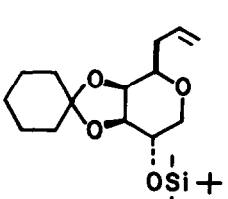
In the lyxose series, the tetrabenzoate 3 displayed no stereoselectivity in its reaction with the allyltrimethylsilane. The cyclohexylidene derivative 4, on the other hand, did show a preference for formation of the product of retained C-1 stereochemistry. Thus, in this latter case attack upon an open oxonium ion intermediate may for steric reasons occur preferentially on the convex-like face of the molecule.

Desilylation of isomers 11 and 12 does make it possible to effect their separation by flash chromatography. The major isomer, whose stereochemistry was readily assigned by 300 MHz ^1H NMR decoupling experiments, should prove to be a useful intermediate in enantiospecific syntheses of the pseudomonic acids. The allyl appendage of this molecule can, of course, function as a latent acetonyl unit, for a simple Wacker type reaction will effect the necessary unmasking operation.[8]

An exemplary procedure follows:

A mixture of 1,2,3,4-tetra-O-benzoyl-α-L-lyxose (56 mg, 0.1 mmol), zinc bromide (56 mg, 0.25 mmol), and allyltrimethylsilane was heated in a Kimax culture tube at 110°C for 3 h. The reaction mixture was cooled, diluted with saturated sodium bicarbonate, and extracted with ether (3 X). The organic extracts were dried ($MgSO_4$) and concentrated to leave a two component mixture (ratio = 1:1, 100%) of high purity as judged by TLC, HPLC, and 300 MHz ^1H NMR analysis. Separation of the two isomers was accomplished by HPLC on a μ-porisil

Table. Anomeric Functionalization of Some Selected Carbohydrate Derivatives

Starting Material	Products[a,b] and Isomer Ratios[c]	Yield (%)
 1	 5 +  6 (1:4)	85
 2	 7 +  8 (1:1)	89
 3	 9 +  10 (1:1)	100
 4	 11 +  12 (4:1)	85

[a]The reaction conditions in all cases are as described in the exemplary procedure.

[b]All products gave satisfactory NMR, IR, and mass spectral data.

[c]Isomer ratios were determined by 300 MHz ^{1}H NMR integrations and hplc analysis.

[d]H. G. Fletcher, Jr., R. K. Ness, and C. S. Hudson, J. Am. Chem. Soc., 73, 3698 (1951).

[e]The reaction of 4 was complete within 15 min.

[f]No change was observed when pure 11 was resubjected to the reaction conditions for a 3 h period.

column using 10% ethyl acetate-hexanes as eluent with a flow rate of 2.5 ml/min: α-isomer (retention time = 3.3 min) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32-2.56 (m, 2, H_3), 4.04-4.25 (m, 3, H_4 and H_8), 5.10-5.18 (m, 2, H_1), 5.32-5.33 (m, 1, H_6), 5.52 (dd, 1, J = 9.5, 3.2 Hz, H_5), 5.86-5.89 (m, 1, H_7), 5.86-6.01 (m, 1, H_2), 7.13-8.15 (m, 15, Aromatics); IR ($CHCl_3$) 3000, 1720, 1640, 1600, 1585, 1420, 1250, 1100, 1080, 1025, 920 cm^{-1}. β-isomer (retention time = 3.80 min) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35-2.48 (m, 2, H_3), 3.55 (dd, 1, J = 10.9, 10.3, H_{8a}), 3.84 (ddd, 1, J = 7.3, 6.7, 1.0, H_4), 4.46 (dd, 1, J = 10.1, 5.2, H_{8e}), 5.06-5.12 (m, 2, H_1), 5.63 (dd, 1, J = 10.1, 3.2, H_6), 5.72 (dt, 1, J = 10.1, 5.2, H_7), 5.82 (dd, 1, J = 3.2, 1.0, H_5), 5.78-5.87 (m, 1, H_2), 7.25-8.18 (m, 15, Aromatics); IR ($CHCl_3$) 3000, 2925, 2850, 1715, 1640, 1600, 1585, 1470, 1250, 1090, 1065, 1025, 920 cm^{-1}; mass spectrum (70 eV) m/e = 486 (M^+).

Acknowledgements. We are indebted to the National Institutes of Health (Grant No. AI-16138) and the Ciba-Geigy Corporation for support of this work.

References and Notes

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