Tetrahedron Letters No. 9, pp 661 - 664, 1976. Pergamon Press. Printed in Great Britain.

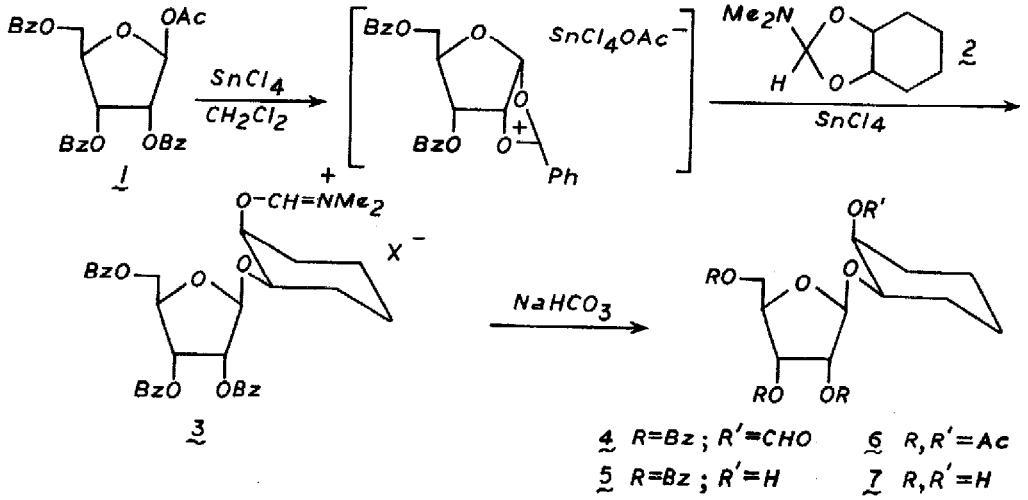
CHEMISTRY OF THE GLYCOSIDIC LINKAGE. β-D RIBOFURANOSYL DISACCHARIDES VIA GLYCOSIDATION WITH CYCLIC AMIDE ACETALS.

Stephen Hanessian and Joseph Banoub
Department of Chemistry, University of Montreal
Montreal, Quebec, Canada.

(Received in USA 20 October 1975; received in UK for publication 20 January 1976)

Newer preparative routes to O-glycosides are in constant demand, particularly with the current interest in biologically relevant areas such as the aminoglycoside,[1] and related sugar-containing antibiotics,[2] and various types of oligosaccharides, including those of the blood group substances.[3] Current synthetic objectives along these lines necessitate the union of specific saccharide units, in which the anomeric integrity of the natural prototype compound is preserved, in order to ensure the maintenance of the anticipated biochemical effects.

We describe in this paper, a novel synthesis of disaccharides and pseudodisaccharides containing the O-β-D-ribofuranosyl unit, based on the reaction illustrated below (only one diastereomer is shown).

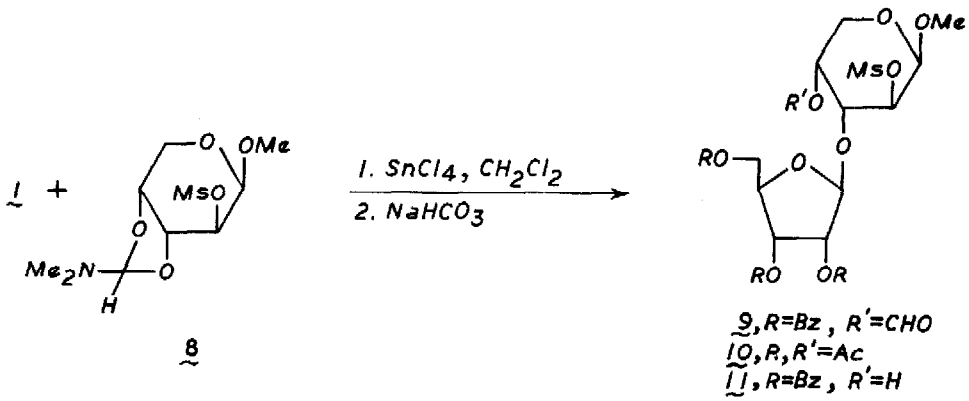


1 + 2 → 3 → 4 R=Bz ; R'=CHO; 5 R=Bz ; R'=H; 6 R,R'=Ac; 7 R,R'=H

The anticipated success of this reaction was based on the premise that cyclic amide acetals (e.g. dimethylaminomethylene acetals) of vicinal diols, may be sufficiently reactive as glycosidating agents toward anomerically activated sugar derivatives particularly in the presence of a Lewis acid. [4]

In a typical example, a cooled solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose 1 (1 mmole) in dry dichloromethane (10 ml) was treated with stannic chloride (1.5 mmole) at 0°. After 10 min, a solution of the 1-(dimethylamino)methylene acetal derivative [5] of cis-1,2-cyclohexanediol (1 mmole) in the same solvent (1 ml) was added. After stirring overnight at 25°, the solution was poured into aqueous bicarbonate, and after extraction with chloroform and usual manipulation, the resulting product was purified by chromatography over silica gel (5% EtOAc-benzene), to give 2-O-formyl-1-cyclohexyl(2,3,5-tri-O-benzoyl-β-D-ribofuranoside), 4, as a colorless syrup (60%); $[\alpha]_D^{23}$ +14.9° (c 1.8, $CHC\ell_3$). [6,7] Methanolysis (reflux, 4h) of the O-formyl group, gave the 2-hydroxy derivative 5, as a colorless syrup in over 90% yield; $[\alpha]_D^{23}$ +49.8° (c 1.6, $CHC\ell_3$). Treatment with sodium methoxide, followed by acetylation (Ac_2O, pyr.) gave the peracetylated glycoside 6, as a syrup (quant.) $[\alpha]_D^{23}$ -17.1° (c 0.56, $CHC\ell_3$); M^+ -73, m/e 343 ($C_{16}H_{23}O_8$). Chromatographic separation of the mixture of glycosides 7 resulting from de-O-acylation, gave the two diastereoisomeric glycosides, mp 127-128°; $[\alpha]_D^{23}$ -30° (MeOH); and mp 142-143°; $[\alpha]_D^{23}$ -67° (MeOH) respectively.

Extension of the glycosidation to cyclic acetals derived from carbohydrates, [8] led to effective syntheses of disaccharides containing the β-D-ribofuranosyl unit. Thus, with methyl 3,4-O-[1-(dimethylamino)methylene]-2-O-methanesulfonyl-β-D-arabinopyranoside 8, there was formed the crystalline disaccharide 9 (70%); mp 164-165° (MeOH); $[\alpha]_D^{23}$ -43.16° (c 1.7, $CHC\ell_3$). Treatment with sodium methoxide followed by acetylation gave the tetracetyl derivative 10 as a syrup, $[\alpha]_D^{23}$ -80.3° (c 1.4, $CHC\ell_3$); M^+ 542; M^+ -32, m/e 510. Methanolysis of compound 9 gave the deformylated disaccharide derivative 11 as an amorphous solid (quant.); $[\alpha]_D^{23}$ -33.1° (c 0.9, $CHC\ell_3$).



8

9, R=Bz, R'=CHO
10, R, R'=Ac
11, R=Bz, R'=H

Chemical evidence for the structure of the disaccharide in this and other cases, was secured from different hydrolytic studies which, as expected, gave the component sugars. The position of linkage in compound 9, follows from its behavior in the presence of sodium methoxide (at 25°, or at reflux in MeOH). A 4-O-substituted disaccharide would have formed an epoxide with loss of the methanesulfonyloxy group, as shown in model experiments. Other disaccharides were similarly prepared.

Several unique features are worthy of comment with regard to this novel method of saccharide synthesis in this series: a. the reaction occurs under very mild conditions, with amide acetals derived from simple diols, as well as from those of sugar derivatives, b. there appears to be an apparent preference for glycosidation by one of the two oxygen atoms of the acetal function in the case of polyfunctional molecules, c. the glycosidations require no more than an equivalent amount of amide acetal derivative with respect to the substrate, and they are stereocontrolled. d. the hydroxyl group that is vicinal, and cis-disposed relative to the newly formed glycosidic bond in the aglycone portion, is protected in the form of a formyl ester in the product, most likely as a result of the hydrolysis of the intermediate iminoester salt (e.g. 3 → 4). [9] Subsequent selective cleavage of the formate ester, exposes an isolated hydroxyl group in the molecule that can be subjected to further chemical manipulations. This feature could have important preparative applications, particularly in a scheme that requires

the stepwise synthesis of pseudosaccharides of the aminoglycoside type,[1,10] and eventually of oligosaccharides in general. A common structural feature in one class of these important antibiotics, is the presence of the 5-O-(β-D-ribofuranosyl)deoxystreptamine unit.[11] Extension of the presently described glycosidation reaction to include cyclic amide acetals of polyfunctional cyclohexane 1,2-diols, would lead to a variety of biochemically relevant and synthetically useful pseudodisaccharides. Studies in this direction are in progress and will be reported in due course.

Acknowledgement. We thank the National Research Council of Canada for financial assistance.

REFERENCES and NOTES

1. S. Umezawa, Advan. Carbohyd. Chem. Biochem., 30, 111 (1974).

2. S. Hanessian and T.H. Haskell in "The Carbohydrates", W. Pigman and D. Horton, eds, Academic Press, N.Y., Vol. IIA, 139 (1970).

3. G.M.W. Cook and R.W. Stoddart, "Surface Carbohydrates of the Eukaryotic Cell", Academic Press, N.Y., 1973.

4. S. Hanessian and J. Banoub, preceding paper.

5. H. Neumann, Chimia, 23, 267 (1969).

6. Crystalline compounds gave correct microanalyses. All compounds exhibited n.m.r. spectral characteristics that were in agreement with their structures. All the glycosides were chemically characterized by hydrolytic studies.

7. The glycosides in this series (compds. 4-7) consist of mixtures of two diastereomers.

8. S. Hanessian and E. Moralioglu, Can. J. Chem., 50, 233 (1973).

9. This layer chromatographic examination of the reaction mixture indicates the formation of a highly polar compound presumably the iminoester stannate salt, e.g. 3, which persists, until the addition of aq. bicarbonate, whereby the disaccharide derivative, e.g. 4, is released and can be detected on the chromatoplates.

10. T. Ogawa, T. Takamoto and S. Hanessian, Tetrahedron Lett., 4013 (1974).

11. S. Hanessian, T. Takamoto and R. Massé, J. Antibiotics (Japan) 28, 835 (1975).