# A New Micro-Scale Synthesis of Lactose.[1]

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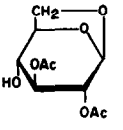
**Received August 1, 1969**

Labeled lactose has been prepared for the first time from 3-O-β-D-galactopyranosyl-D-arabinose via the cyanhydrin by means of $NaC^{14}N$.[2] The method is rather tedious and suffers from the disadvantage that it limits the labeling to the glucose moiety.

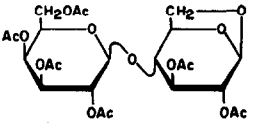
The chemical synthesis of lactose has been hampered by the well known low reactivity of the C-4 hydroxyl of the glucopyranose molecule. Hudson first prepared the disaccharide by a series of reactions proceeding via the epimeric galactosyl (1⟶4)mannose.[3] Curtis and Jones[4] have circumvented the difficulty by using the open-chain glucose in form of its diethyl acetal and separating the mixture of mono- and di-saccharides by charcoal- and paper-chromatography.

During the course of our studies on the gangliosides,[5,6] whose structure contains a lactose unit, it became imperative to devise a glucose derivative in which the 4-OH would have enhanced reactivity. It was found that 2,3-di-O-acetyl-1,6-anhydro-β-D-glucopyranose (I) meets this requirement. The synthesis of I involves cyclization of phenyl 2,3,6-tri-O-acetyl-4-O-t-butyl-β-D-glucopyranoside to 2,3-di-O-acetyl-4-O-t-butyl-1,6-anhydro-β-D-glucopyranose and subsequent removal of the protective butyl group

with trifluoroacetic acid. Details concerning the synthesis of I will be reported in a forthcoming paper.




I




II

Condensation of I with acetobromogalactose in the presence of mercuric cyanide gave a 49% yield of the hexaacetate II, whose physical properties were identical with those reported in the literature.[7] Since II has been earlier converted into lactose in high yield,[7] the present route constitutes a convenient micro-scale synthesis of the disaccharide. Moreover, since it permits labeling of either of the two hexose units, this method may provide useful substrates for the metabolic studies of glycolipids and mucopolysaccharides.

2,3-Di-O-acetyl-1,6-anhydro-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-glucopyranose (II).-

To a solution of I (200 mg, 0.81 mmole) in nitromethane-benzene (3:1, 20 ml) were added mercuric cyanide (250 mg) and tetra-O-acetyl-α-D-galactopyranosyl bromide (335 mg, 0.81 mmole), and the mixture was stirred with exclusion of moisture at 50°. After 24 hr, mercuric cyanide (120 mg) and bromide (150 mg) were added, and the reaction was allowed to proceed for further 24 hr.

The cooled solution was diluted with benzene and shaken thoroughly with cold 5% sodium hydrogen carbonate, then washed with water, dried over sodium sulfate and evaporated in vacuo. The crude product was passed through a silica gel column. Benzene-ethyl acetate 2:3 eluted 230 mg (49%) of II. It was homogeneous on tlc and identical in infrared spectrum and mobility (benzene-ethyl

acetate 1:1) with a sample prepared according to Hudson. After recrystallization from ethanol it melted at 206-208° (reported[7] 206-208°). $[\alpha]_D^{22}$ -39.5° (c 2.6, $CHCl_3$) (lit.[7,8] -40.8°, -38.9°). The same yield was obtained by using two moles of I per mole of the bromide.

1. Supported by National Institutes of Health, PL 480, Agreement No. 425115.

2. H.L. Frush and H.S. Isbell, J. Res. Natl. Bur. Stand., 50, 133 (1953).

3. W.T. Haskins, R.M. Hann and C.S. Hudson, J. Am. Chem. Soc., 64, 1852 (1942).

4. E.J.C. Curtis and J.K.N. Jones, Can. J. Chem., 37, 358 (1959).

5. D. Shapiro, A.J. Acher and E.S. Rachaman, J. Org. Chem., 32, 3767 (1967).

6. A.J. Acher and D. Shapiro, J. Org. Chem., in press.

7. E.M. Montgomery, N.K. Richtmyer and C.S. Hudson, J. Am. Chem. Soc., 65, 1848 (1943).

8. P. Karrer and S.C. Harloff, Helv. Chim. Acta, 16, 962 (1933).