References and Notes

(1) Syntex Postdoctoral Fellow, 1970–1972.
(2) See, *e.g.*, (a) P. Greengard, R. Paoletti, and G. A. Robison, Ed., "Advances in Cyclic Nucleotide Research," Vol. I, Raven Press, New York, N. Y., 1972; (b) G. A. Robison, R. W. Butcher, and E. W. Sutherland, "Cyclic AMP," Academic Press, New York, N. Y., 1971; (c) P. Greengard and E. Costa, Ed., "Role of Cyclic AMP in Cell Function," Raven Press, New York, N. Y., 1970.
(3) See, *e.g.*, (a) T. Posternak, I. Marcus, A. Gabbai, and G. Cehovic, *C. R. Acad. Sci., Ser. D*, **269**, 2409 (1969); (b) R. B. Meyer, D. A. Shuman, R. K. Robins, R. J. Bauer, M. K. Dimmitt, and L. N. Simon, *Biochemistry*, **11**, 2704 (1972); (c) G. Weimann, E. Haid, K. Mühlegger, H. U. Bergmeyer, K. Dietmann, G. Michal, and M. Nelboeck-Hochstetter, U. S. Patent 3,712,885 (1973).
(4) K. Muneyama, R. J. Bauer, D. A. Shuman, R. K. Robins, and L. N. Simon, *Biochemistry*, **10**, 2390 (1971).
(5) G. H. Jones, H. P. Albrecht, N. P. Domodaran, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **92**, 5510 (1970).
(6) F. Eckstein, *J. Amer. Chem. Soc.*, **92**, 4718 (1970).
(7) (a) A. Murayama, B. Jastorff, F. Cramer, and H. Hettler, *J. Org. Chem.*, **36**, 3029 (1971); (b) R. B. Meyer, D. A. Shuman, and R. K. Robins, *Tetrahedron Lett.*, 269 (1973).
(8) G. I. Drummond, M. W. Gilgan, E. J. Reiner, and M. Smith, *J. Amer. Chem. Soc.*, **86**, 1626 (1964).
(9) (a) W. W. Lee, L. V. Fisher, and L. Goodman, *J. Heterocycl. Chem.*, **8**, 179 (1971); (b) T. A. Khwaja, R. Harris, and R. K. Robins, *Tetrahedron Lett.*, 4681 (1972).
(10) M. Hubert-Habart and L. Goodman, *Chem. Commun.*, 740 (1969).
(11) D. V. K. Murthy and R. Golling, in preparation.
(12) Symposium on the Chemistry and Biochemistry of Cyclic AMP, Pacific Conference on Chemistry and Spectroscopy, San Francisco, Calif., Oct 1972, Papers 131 (G. H. Jones) and 133 (D. V. K. Murthy and R. Golling).
(13) E. J. Reist, L. Goodman, R. R. Spencer, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 3962 (1958).
(14) E. J. Reist, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 5775 (1958).
(15) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **85**, 3027 (1963).
(16) *E.g.*, G. H. Jones and J. G. Moffatt, *J. Amer. Chem. Soc.*, **90**, 5337 (1968).
(17) G. H. Jones and J. G. Moffatt, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, CARB 16.
(18) S. Chládek and J. Smrt, *Collect. Czech. Chem. Commun.*, **29**, 214 (1964).
(19) (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661 (1965). (b) For a review on sulfoxide-based oxidations, see J. G. Moffatt in "Techniques and Applications in Organic Synthesis. Oxidation," Vol. II, Marcel Dekker, New York, N. Y., 1971, p 1.
(20) (a) H. W. Wanzlick and W. Löchel, *Chem. Ber.*, **86**, 1463 (1953); (b) N. P. Damodaran, G. H. Jones, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **93**, 3812 (1971).
(21) Unpublished work by G. H. Jones, D. Tegg, G. B. Howarth, N. P. Damodaran, A. Rudinskas, and J. G. Moffatt.
(22) H. Kaufmann, P. Mühlradt, and T. Reichstein, *Helv. Chim. Acta*, **50**, 2287 (1967).
(23) Kindly provided by Professor T. Reichstein.
(24) P. Howgate and A. Hampton, *Carbohyd. Res.*, **21**, 309 (1972).
(25) We would like to thank Dr. M. L. Maddox for clarification of this point.
(26) G. M. Tener, *J. Amer. Chem. Soc.*, **83**, 159 (1961).
(27) A. Franke, K. H. Scheit, and F. Eckstein, *Chem. Ber.*, **101**, 2998 (1968).
(28) M. Smith, G. I. Drummond, and H. G. Khorana, *J. Amer. Chem. Soc.*, **83**, 698 (1961).
(29) (a) C. D. Jardetzky, *J. Amer. Chem. Soc.*, **84**, 62 (1962); (b) B. J. Blackburn, R. D. Lapper, and I. C. P. Smith, *ibid.*, **95**, 2873 (1973).
(30) R. F. Nutt and E. Walton, *J. Med. Chem.*, **11**, 151 (1968).
(31) P. J. Harper and A. Hampton, *J. Org. Chem.*, **35**, 1688 (1970).
(32) R. R. Schmidt, U. Schloz, and D. Schwiele, *Chem. Ber.*, **101**, 590 (1968).
(33) H. J. Fritz, R. Machat, and R. R. Schmidt, *Chem. Ber.*, **105**, 642 (1972).
(34) T. A. Khwaja and C. B. Reese, *Tetrahedron*, **27**, 6189 (1971).
(35) R. K. Ralph and H. G. Khorana, *J. Amer. Chem. Soc.*, **83**, 2926 (1961).
(36) It has previously been noted that the cleavage of trichloroethyl esters in different compounds may optimally require different acids. See, *e.g.*, R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. José, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, **36**, 1259 (1971).
(37) *Cf.* methyl groups in carbocyclic chair conformations. See L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, London, 1969, p 240.
(38) J. Parrick and J. W. Rasbun, *Can. J. Chem.*, **43**, 3453 (1965).
(39) W. E. Trevelyan, D. P. Procter, and J. S. Harnson, *Nature (London)*, **166**, 444 (1950).
(40) Prepared by treatment as above of methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside[13] kindly provided by Dr. Leon Goodman.

Synthesis and Reactions of Azido Halo Sugars

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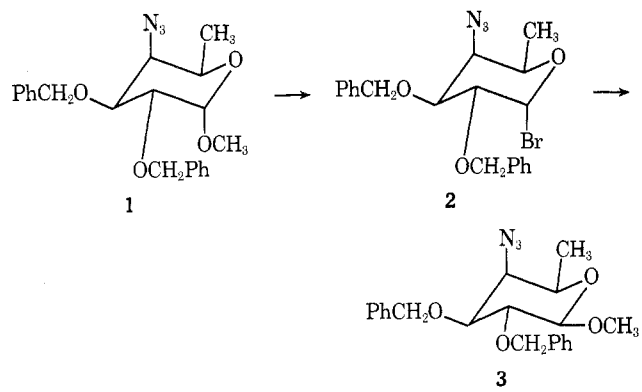
The syntheses of several crystalline 4-azido-4,6-dideoxy-1-halo hexoses, which are useful intermediates in the chemical synthesis of natural products containing amino hexoses, are described. The reactions of these compounds with methanol and ethanol in the presence of silver carbonate are shown to be stereospecific. The uses of azido halo sugars in the synthesis of cardiac glycosides, antibiotics, and amino sugar nucleosides are indicated.

Many amino sugars have been isolated from biologically important natural sources such as antibiotics,[2,3] cell wall polysaccharides,[2] and cardiac glycosides.[4] Because an azide can be conveniently used as an amine precursor, azido halo sugars are extremely useful intermediates for the chemical synthesis of these natural products and their structural anaogs of potential biological activity. However, except for the recent reports on the isolation of 6-azido-1-chloro hexoses by Umezawa and coworkers,[5] azido halo sugars have not been prepared. Earlier attempts to obtain this class of compounds were reported to be unsuccessful.[6,7] We now describe the synthesis and reactions of several crystalline 4-azido-4,6-dideoxy-1-halo sugars as part of our investigation of the chemistry of 4-amino-4,6-dideoxy hexoses and their derivatives.[8]

Treatment of methyl 4-azido-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-galactopyranoside[9] (**1**) with acetyl bromide at room temperature for 30 min gave the crystalline 4-azido-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-galactopyranosyl bromide (**2**). The α configuration for the bromo sugar **2** was indicated by its nmr spectrum, which showed the anomeric proton as a doublet ($J_{1,2}$ = 3.5 Hz) at δ 6.43. Also, reaction of **2** with methanol in the presence of silver carbonate gave clean inversion at the anomeric center, providing methyl 4-azido-4,6-dideoxy-2,3-di-*O*-benzyl-β-D-galactopy-

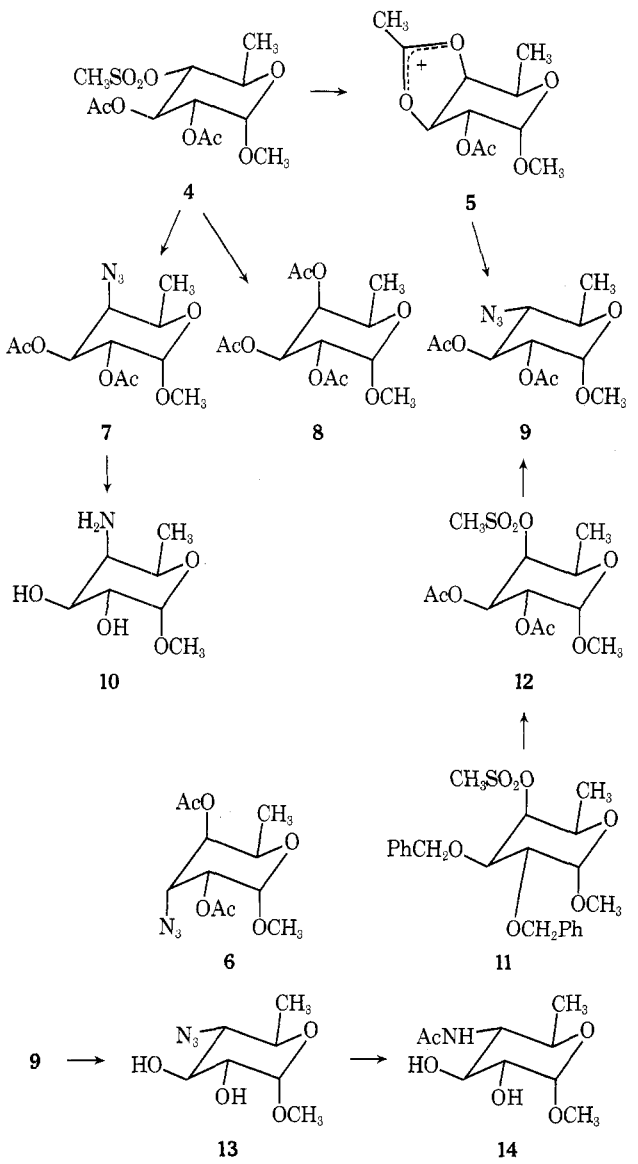


1 2

3

ranoside (3), which was identical with a sample previously characterized in our laboratory.[10]

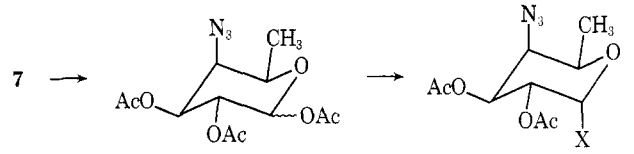
In order to obtain azido halo sugars with acetate protection of the hydroxyl groups, methyl 6-deoxy-2,3-di-*O*-acetyl-4-*O*-methylsulfonyl-α-D-glucopyranoside[8c] (4) was treated with sodium azide in dimethylformamide at 140° for 16 hr. Acetylation of the reaction mixture followed by preparative thin layer chromatography provided methyl 4-azido-4,6-dideoxy-2,3-di-*O*-acetyl-α-D-galactopyranoside (7) in 77% yield. Small amounts of the triacetate 8 (3.5%) and the gluco azide 9 (2.5%) were also isolated. As the methyl sulfonate and the acetate groups are trans to each other, the displacement reactions of 4 may be expected to proceed through the intermediate 5 owing to neighboring group participation.[11] However, surprisingly, the major process taking place was the direct displacement (SN2) of the methyl sulfonate by the azide anion to give the galacto azide 7. Similarly, compound 8 must have resulted from displacement of the methyl sulfonate by the acetate formed in the reaction mixture by partial deacetylation. The formation of the small amount of the gluco azide 9 may be explained as resulting from neighboring group participation. However, methyl 3-azido-3,6-dideoxy-2,4-di-*O*-acetyl-α-D-gulopyranoside (6), which is also expected to result from the intermediate 5, was not isolated, probably because it was formed only in very small amounts.



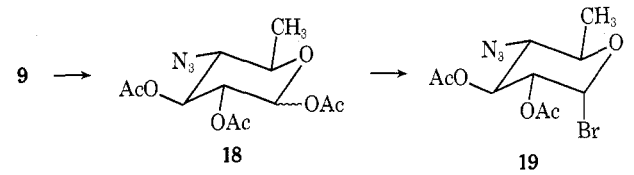
The structure of 7 was confirmed by its deacetylation followed by hydrogenation in the presence of 10% Pd/C as a catalyst to give the known methyl 4-amino-4,6-dideoxy-α-D-galactopyranoside[9] (10), which was characterized as its crystalline hydrochloride. Compound 8 was identified by relating it to the known methyl 6-deoxy-2,3,4-tri-*O*-acetyl-α-L-galactopyranoside[12] (the L isomer of 8). Also, deacetylation of 8 with sodium methoxide in methanol gave methyl 6-deoxy-α-D-galactopyranoside with the same physical properties as reported in the literature.[13] In order to establish the structure of 9, it was independently synthesized as described below.

Methyl 6-deoxy-2,3-di-*O*-benzyl-4-*O*-methylsulfonyl-α-D-galactopyranoside[14] (11) was converted to the diacetate 12 by reductive debenzylation of 11 followed by acetylation with acetic anhydride in pyridine. Treatment of 12 with sodium azide in refluxing dimethylformamide and subsequent purification of the product by column chromatography gave compound 9 as a syrup, identical with the sample obtained from the azide displacement of 4. The structure of 9 was confirmed by its deacetylation with sodium methoxide in methanol to give 13, which was then reduced and selectivity N-acetylated to obtain methyl 4-acetamido-4,6-dideoxy-α-D-glucopyranoside[14] (14), identical with an authentic sample.

Treatment of 7 with acetic anhydride in the presence of sulfuric acid as a catalyst gave the triacetate 15 as a mixture of anomers from which the pure α isomer was obtained as a crystalline material by preparative thin layer chromatography. The mixture 15 on treatment with titanium tetrachloride in chloroform gave the crystalline chloro sugar 16.



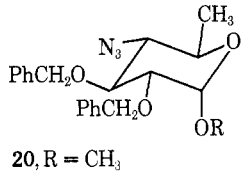
Similarly, the bromo sugar 17 was obtained by treatment of 15 with titanium tetrabromide in chloroform. Acetolysis of 9 with acetic anhydride in the presence of sulfuric acid yielded the triacetate 18 as an anomeric mixture from which the pure α isomer crystallized out on standing. The bromo sugar 19 was prepared by treatment of 18 with titanium tetrabromide in chloroform. Compounds 16, 17, and 19 were shown to have the α configuration at the anomeric center by their nmr spectra.[15]



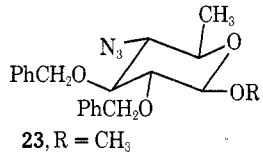
Azido halo sugars in the gluco series, with the hydroxyl groups protected as the benzyl ethers, were synthesized in the following way. Reaction of methyl 4-azido-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-glucopyranoside[14] (20) with acetic acid and acetic anhydride in the presence of sulfuric acid as a catalyst gave the 1-acetate 26 as a mixture of α and β anomers. Treatment of 26 with titanium tetrachloride in chloroform provided the α-chloro sugar 28 as a syrup. The nmr spectrum of 28 showed a low-field doublet with a small coupling constant as expected for an α anomer.[15]

Deacetylation of 26 with sodium methoxide in methanol provided the crystalline free sugar 27. Although 27 did not

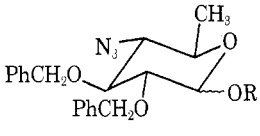
show any appreciable mutarotation in a variety of solvents, an nmr spectrum in DMSO-d_6–acetone-d_6 indicated that it consisted of 71% of the α and 29% of the β anomers in this solvent system.[16] Treatment of **27** with *p*-nitrobenzoyl chloride in pyridine at room temperature gave a mixture of the α- and β-*p*-nitrobenzoates **22** and **25** in equal amounts, from which the pure isomers were obtained by fractionl crystallization. While the nmr ($CDCl_3$) of **22** showed a clean doublet ($J_{1,2}$ = 3.5 Hz) at δ 6.6 as expected for an α isomer,[15] the C-1 hydrogen of **25** appeared as an inverted triplet at δ 5.9. The unusual shape of this nmr signal is explained by the concept of virtual coupling.[17] This phenomenon was also observed in the nmr ($CDCl_3$) spectra of compounds **23**, **24**, and **29**, all of which have β substituents at the anomeric center. When the solvent was changed to benzene-d_6, the anomeric hydrogens appeared as clean doublets ($J_{1,2}$ = 8 Hz), showing that virtual coupling is indeed solvent dependent.



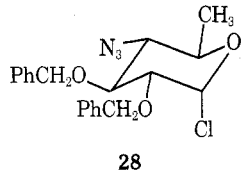
20, R = CH_3
21, R = C_2H_5
22, R = *p*-nitrobenzoyl



23, R = CH_3
24, R = C_2H_5
25, R = *p*-nitrobenzoyl



26, R = Ac
27, R = H



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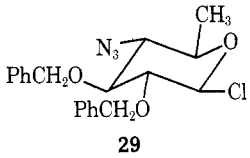

29

Treatment of the 1-*p*-nitrobenzates **22** and **25**, either as pure isomers or as a mixture, with dry hydrogen chloride in ethanol-free chloroform produced the β-chloro sugar **29** in very high yields. Thus, when **25** was treated with hydrogen chloride at room temperature for 4 hr, a mixture consisting of 92% of **29** and 8% of **28** was formed from which 85% of **29** was isolated by crystallization. Reaction of hydrogen chloride with the α-*p*-nitrobenzoate **22** gave 90% of **29** and 10% of **28** in 36 hr, whereas a 53:47 mixture of **22** and **25** was converted to 88% chloro sugar containing 83% of **29** and 17% of **28** in 32 hr. These estimations were carried out by nmr spectrometry. It may be noted here that no evidence was obtained for the isomerization of **22** to **25** or vice versa under the reaction conditions.

If the reactions were allowed to continue for longer periods of time, the β-chloro sugar **29** was slowly converted to the α-chloro sugar **28**, which is expected to be more stable owing to the anomeric effect.[18] Pure **29** itself was slowly isomerized to **28** when treated with hydrogen chloride in chloroform. The formation of the β-chloro sugar **29** from both **22** and **25** was not totally unexpected, as similar results have been reported earlier in the formation of bromo sugars.[19]

The α-chloro sugar **28** reacted stereospecifically with methanol and ethanol in the presence of silver carbonate or mercuric cyanide, giving the β-glycosides **23** and **24**, respectively. In these experiments, the α anomers, **20** and **21**, were not formed in detectable amounts. The reactions of the β-chloro sugar with methanol and ethanol were also stereospecific, yielding only the α-glycosides **20** and **21**, respectively.

Preliminary accounts on the use of these azido halo sugars in the synthesis of cardiac glycosides,[20] antibiotics,[21] and amino sugar nucleosides[22] have been recorded previously. Details of these investigations will be published elsewhere.

Experimental Section[23]

4-Azido-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-galactopyranosyl Bromide (2). A solution of 750 mg (2.0 mmol) of methyl 4-azido-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-galactopyranoside[9] (**1**) in 7.5 ml of acetylbromide was left at room temperature for 30 min. The solvent was removed under vacuum and the pink residue was redissolved in dry ether and decolorized with charcoal. Filtration, evaporation of the solvent, and recrystallization of the residue from hexane gave 510 mg (60%) of **2**: mp 114–116°; $[\alpha]^{26}D$ +194° (*c* 0.82, $CHCl_3$); nmr ($CDCl_3$) δ 6.43 (d, $J_{1,2}$ = 3.5 Hz, 1, C-1 H).

Anal. Calcd for $C_{20}H_{22}BrN_3O_3$: C, 55.56; H, 5.13; N, 9.72. Found: C, 55.37; H, 5.11; N, 9.76.

Treatment of 250 mg (0.5 mmol) of **2** with 7.0 ml of anhydrous CH_3OH and 300 mg of Ag_2CO_3 under stirring at room temperature for 3 hr followed by filtration, evaporation, and recrystallization of the residue from hexane gave 77 mg (35%) of methyl 4-azido-4,6-dideoxy-2,3-di-*O*-benzyl-β-D-galactopyranoside (**3**), mp 57–58°, $[\alpha]^{25}D$ +17.1° (*c* 1.0, $CHCl_3$). A mixture melting point of **3** with an authentic sample[10] was undepressed.

Methyl 4-Azido-4,6-dideoxy-2,3-di-*O*-acetyl-α-D-galactopyranoside (7). A solution of 20 g (59 mmol) of methyl 6-deoxy-2,3-di-*O*-acetyl-4-*O*-methylsulfonyl-α-D-glucopyranoside[8c] (**4**) in 100 ml of *N*,*N*-dimethylformamide was heated with 15.0 g of sodium azide at 140° for 16 hr. The cooled mixture was diluted with 300 ml of $CHCl_3$ and filtered. The filtrate was washed with water, and the $CHCl_3$ layer was dried (Na_2SO_4) and concentrated. The syrupy residue was treated with 70 ml of a 1:1 mixture of acetic anhydride and pyridine at room temperature overnight. The mixture was poured into ice–water and stirred for 30 min and the solid that separated was collected by filtration and recrystallized twice from hexane to give 11.4 g (66.5%) of **7**, mp 76–77°, $[\alpha]^{25}D$ +95.6° (*c* 0.35, $CHCl_3$).

Anal. Calcd for $C_{11}H_{17}N_3O_6$: C, 45.98; H, 5.96; N, 14.63. Found: C, 45.75; H, 6.06; N, 14.65.

Deacetylation of a sample of **7** with sodium methoxide in CH_3OH followed by hydrogenation in the presence of 10% Pd/C gave methyl 4-amino-4,6-dideoxy-α-D-galactopyranoside (**10**) isolated as its hydrochloride, mp 227–229° dec. A mixture melting point with an authentic sample[9] was undepressed.

Methyl 6-Deoxy-2,3-4-tri-*O*-acetyl-α-D-galactopyranoside (8). The aqueous solution (from the preparation of **7**) after the filtration of **7** was extracted with $CHCl_3$, dried (Na_2SO_4), combined with the mother liquors from the hexane recrystallizations of **7**, and evaporated to dryness to give 3.5 g of a syrup. This material was separated by preparative thin layer chromatography (20 × 20 cm plates, 1 mm thickness) using a hexane–ether–acetone (1:1:0.2) system. Fraction 1 (R_f 0.45) gave 1.8 g more of **7**, mp 73–76°, for a total yield of 13.4 g (77%). Fraction 2 (R_f 0.50) yielded 438 mg (2.5%) of compound **9** which was also prepared by another method as described later. Fraction 3 (R_f 0.41) provided 570 mg (3.5%) of **8** as a syrup which crystallized on standing. It was recrystallized from hexane, mp 64–65°, $[\alpha]^{26}D$ +149.1° (*c* 0.97, $CHCl_3$) [lit.[12] L isomer mp 67°, $[\alpha]^{20}D$ −149.7° (*c* 1.8, $CHCl_3$)].

Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.30; H, 6.62. Found: C, 51.58; H, 6.34.

A small portion of **8** was deacetylated with sodium methoxide in CH_3OH to give methyl 6-deoxy-α-D-galactopyranoside, mp 153–154°, $[\alpha]^{26}D$ +192.7° (*c* 0.9, H_2O) [lit.[13] mp 154°, $[\alpha]D$ +190° (*c* 10, H_2O)].

Methyl 6-Deoxy-2,3-di-*O*-acetyl-4-*O*-methylsulfonyl-α-D-galactopyranoside (12). A solution of 5.85 g (13.4 mmol) of methyl 6-deoxy-2,3-di-*O*-benzyl-4-*O*-methylsulfonyl-α-D-galactopyranoside[14] (**11**) in 40 ml of THF and 40 ml of ethanol was hydrogenated in the presence of 0.6 g of 10% Pd/C and 0.1 ml of concentrated hydrochloric acid until reduction was complete. Neutralization with Dowex 1-X_2 (OH^-), filtration, and evaporation of the solvent *in vacuo* gave the intermediate diol, which was acetylated with 10 ml of acetic anhydride in 10 ml of pyridine at room temperature for 16 hr. The mixture was poured into ice–

water, filtered, dried, and recrystallized from benzene–ether–pentane to give 3.5 g (78%) of **12**, mp 65–67°, $[\alpha]^{26}D$ +151° (*c* 0.49, $CHCl_3$).

Anal. Calcd for $C_{12}H_{20}O_9S$: C, 42.35; H, 5.92; S, 9.42. Found: C, 42.39; H, 5.96; S, 9.56.

Methyl 4-Azido-4,6-dideoxy-2,3-di-*O*-acetyl-α-D-glucopyranoside (9). A mixture of 11.1 g (32 mmol) of **12** in 40 ml of dimethylformamide and 9 g (128 mmol) of sodium azide was heated at 120° for 12 hr with vigorous stirring. The mixture was cooled, diluted with 300 ml of $CHCl_3$, and filtered and the filtrate was washed with 3 × 100 ml of water. The $CHCl_3$ layer was dried (Na_2SO_4) and evaporated to dryness under vacuum to give a brown liquid, which was chromatographed on a column of silica gel (80 g). Elution with 15% ether–pentane gave 5.48 g (67%) of **9** as a syrup, $[\alpha]^{26}D$ +174° (*c* 0.61, $CHCl_3$).

Anal. Calcd for $C_{11}H_{17}N_3O_6$: C, 45.98; H, 5.96; N, 14.63. Found: C, 46.21; H, 6.04; N, 14.75.

Further elution of the column with ether yielded 2.2 g of a mixture containing mostly the starting material, **12**.

Methyl 4-Azido-4,6-dideoxy-α-D-glucopyranoside (13). A solution of 115 mg (0.4 mmol) of **9** in 5 ml of CH_3OH was heated under reflux on a steam bath with 5 drops of 0.5% sodium methoxide in methanol for 1 hr. The sodium methoxide was neutralized with CO_2 and the solvent was removed under vacuum. The residue was extracted with ether, the ether solution was concentrated, and the product crystallized on addition of hexane to give 74 mg (91%) of **13**, mp 139–140°, $[\alpha]^{26}D$ +240.1° (*c* 1.1, $CHCl_3$).

Anal. Calcd for $C_7H_{13}N_3O_4$: C, 41.38; H, 6.45; N, 20.68. Found: C, 41.28; H, 6.46; N, 20.94.

A small portion of **13** was hydrogenated in the presence of 10% Pd/C and the amine was acetylated with acetic anhydride in methanol to give methyl 4-acetamido-4,6-dideoxy-α-D-glucopyranoside (**14**), mp 189–190°. A mixture melting point with an authentic sample[12] was undepressed.

4-Azido-4,6-dideoxy-1,2,3-tri-*O*-acetyl-D-galactopyranose (15). A solution of 350 mg (1.2 mmol) of **7** in 10 ml of acetic anhydride containing 0.1 ml of H_2SO_4 was stirred at room temperature for 2 hr. The mixture was poured into ice–water and extracted with ether, and the ether layer was washed with $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness to yield 344 mg (90%) of **15** as a colorless syrup. This material showed two spots on tlc (ether–hexane–acetone, 1:1:0.2 system) corresponding to the α and β anomers. Separation of a portion of the mixture by preparative tlc using the above solvent system gave the major isomer as a gum which was crystallized from hexane to give 4-azido-4,6-dideoxy-1,2,3-tri-*O*-acetyl-α-D-galactopyranose, mp 92–93°, $[\alpha]^{26}D$ +91° (*c* 0.83, $CHCl_3$).

Anal. Calcd for $C_{12}H_{17}N_3O_7$: C, 45.71; H, 5.43; N, 13.33. Found: C, 46.00; H, 5.69; N, 13.61.

4-Azido-4,6-dideoxy-2,3-di-*O*-acetyl-α-D-galactopyranosyl Chloride (16). A solution of 1.5 g (4.8 mmol) of **15** (mixture of anomers) and 0.3 ml (2.4 mmol) of titanium tetrachloride in 30 ml of ethanol-free $CHCl_3$ was heated under reflux for 1 hr. The solution was washed with ice water and $NaHCO_3$ solution, dried ($MgSO_4$), decolorized with charcoal, filtered, and evaporated to dryness. The residue was crystallized from hexane to give 1.2 g (88%) of **16**, mp 83–85°. An analytical sample was prepared by an additional recrystallization from hexane: mp 86–87°; $[\alpha]^{26}D$ +206° (*c* 0.53, $CHCl_3$); nmr ($CDCl_3$) δ 6.3 (d, $J_{1,2}$ = 3.5 Hz, 1, C-1 H).

Anal. Calcd for $C_{10}H_{14}ClN_3O_5$: C, 41.17; H, 4.84; Cl, 12.16; N, 14.41. Found: C, 41.82; H, 5.09; Cl, 12.15; N, 14.34.

4-Azido-4,6-dideoxy-2,3-di-*O*-acetyl-α-D-galactopyranosyl Bromide (17). A solution of 2.5 g (8.0 mmol) of **15** (mixture of anomers) and 2.2 g (6.0 mmol) of titanium tetrabromide in 35 ml of ethanol-free $CHCl_3$ was heated under reflux for 1.5 hr. As a tlc analysis indicated that the reaction was complete, the mixture was washed with ice–water followed by $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness to give 2.8 g of a syrup which was crystallized from ether–hexane. Recrystallization from ether–hexane yielded 2.2 g (79%) of **17**, mp 76–77°, $[\alpha]^{26}D$ +268° (*c* 0.55, $CHCl_3$).

Anal. Calcd for $C_{10}H_{14}BrN_3O_5$: C, 35.73; H, 4.19; N, 12.50. Found: C, 36.03; H, 4.19; N, 12.39.

4-Azido-4,6-dideoxy-1,2,3-tri-*O*-acetyl-D-glucopyranose (18). Treatment of 5.5 g (19 mmol) of **9** with acetic anhydride in the presence of H_2SO_4 as described for the preparation of **15** gave 5.55 g (94%) of a mixture of anomeric triacetate **18** as an oil. This material crystallized on standing and recrystallization from ether–hexane gave the α isomer, 4-azido-4,6-dideoxy-1,2,3-tri-*O*-acetyl-α-D-glucopyranose: mp 65–66°; $[\alpha]^{26}D$ +148.9° (*c* 1.04, $CHCl_3$); nmr ($CDCl_3$) δ 6.15 (d, $J_{1,2}$ = 3.5 Hz, 1, C-1 H).

Anal. Calcd for $C_{12}H_{17}N_3O_7$: C, 45.71; H, 5.43; N, 13.32. Found: C, 45.85; H, 5.36; N, 13.29.

4-Azido-4,6-dideoxy-2,3-di-*O*-acetyl-α-D-glucopyranosyl Bromide (19). A solution of 1.0 g (3.2 mmol) of triacetate **18** and 1.2 g (3.3 mmol) of titanium tetrabromide in 20 ml of ethanol-free $CHCl_3$ was stirred at room temperature for 5 hr. The mixture was washed with ice–water followed by $NaHCO_3$ solution and dried (Na_2SO_4), and the solvent was removed. The brown syrup was redissolved in ether and decolorized with charcoal, filtered, and evaporated to dryness to give 955 mg (93%) of **19** as a yellow syrup. Preparative tlc using ether–hexane (1:1) as the solvent system and recrystallization from hexane gave 613 mg (57%) of the pure material: mp 45–47°; $[\alpha]^{26}D$ +254.4° (*c* 1.14, $CHCl_3$); nmr ($CDCl_3$) δ 6.6 (d, $J_{1,2}$ = 4.0 Hz, 1, C-1 H).

Anal. Calcd for $C_{10}H_{14}BrN_3O_5$: C, 35.73; H, 4.19; Br, 23.77; N, 12.50. Found: C, 35.46; H, 4.15; Br, 23.63; N, 12.47.

4-Azido-4,6-dideoxy-1-*O*-acetyl-2,3-di-*O*-benzyl-D-glucopyranose (26). A solution of 2.0 g (4.8 mmol) of methyl 4-azido-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-glucopyranoside[14] (**20**) in 24 ml of acetic acid and 7 ml of acetic anhydride was cooled until it solidified and was then mixed with 2.1 ml of a 10% solution of H_2SO_4 in acetic acid. The mixture was allowed to warm up slowly and left at room temperature for 4 hr. The solution was poured into a mixture of ice–water and CCl_4, the CCl_4 layer was separated, and the aqueous phase was thoroughly extracted with CCl_4. The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness to give 2.107 g (98.2%) of an oil, **26**, as a mixture of anomers. A portion of this material was purified by preparative tlc using a hexane–ether–acetone (1:1:0.2) system for analysis.

Anal. Calcd for $C_{22}H_{25}N_3O_5$: C, 64.22; H, 6.12; N, 10.21. Found: C, 63.97; H, 6.24; N, 10.35.

4-Azido-4,6-dideoxy-2,3-di-*O*-benzyl-D-glucopyranose (27). A solution of 2.1 g (5.13 mmol) of **26** in 60 ml of CH_3OH was deacetylated with 0.8 ml of 1 *N* sodium methoxide in CH_3OH for 45 min at room temperature. Solid CO_2 was added to neutralize the reaction mixture and the solution was evaporated to dryness. The residue was extracted with CCl_4 and the solvent was removed under vacuum. The product was recrystallized from CCl_4–hexane to give 1.4 g (74%) of **27**: mp 92–93°; $[\alpha]^{26}D$ +103° (*c* 1.5, $CHCl_3$); nmr (DMSO-d_6–acetone-d_6) δ 6.25 (d, *J* = 4 Hz, 0.71 H, 1-α-OH), 6.7 (d, *J* = 7 Hz, 0.29 H, 1-β-OH).[16]

Anal. Calcd for $C_{20}H_{23}N_3O_4$: C, 65.03; H, 6.27; N, 11.37. Found: C, 64.98; H, 6.32; N, 11.36.

4-Azido-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-glucopyranosyl Cloride (28). A mixture of 445 mg (0.08 mmol) of **26** in 12 ml of ethanol-free $CHCl_3$ and 143 mg (0.75 mmol) of $TiCl_4$ was heated under reflux for 45 min. The solution was cooled, washed with ice–water and $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness to give 380 mg (90%) of **28** as an oil, slightly impure by tlc. This material was purified by preparative tlc (ether–hexane, 1:1 system) to give a syrup, $[\alpha]^{26}D$ +188.0° (*c* 0.9, $CHCl_3$), nmr ($CDCl_3$) δ 6.05 (d, $J_{1,2}$ = 3.5 Hz, 1, C-1 H).

Anal. Calcd for $C_{20}H_{22}ClN_3O_3$: C, 61.93; H, 5.73; Cl, 9.14; N, 10.83. Found: C, 62.17; H, 5.79; Cl, 9.34; N, 10.65.

4-Azido-4,6-dideoxy-2,3-di-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α-D-glucopyranose (22) and 4-Azido-4,6-dideoxy-2,3-di-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-β-D-glucopyranose (25). A solution of 3.3 g (8.8 mmol) of **27** in 56 ml of pyridine was stirred at room temperature while 3.3 g (17.6 mmol) of *p*-nitrobenzoyl chloride in 28 ml of pyridine was added. After 72 hr, the pyridine was removed under vacuum and the residue was treated with 220 ml of CCl_4 and 250 ml of 0.5 *M* $NaHCO_3$ solution. The organic layer was separated, washed with Na_2CO_3 solution, dried (K_2CO_3), and evaporated to dryness to give 4.5 g (98%) of a mixture of **22** and **25** in the ratio 1:1. This material was recrystallized from CCl_4–hexane to give 2.3 g (49%) of **25**, mp 132–133°, $[\alpha]^{26}D$ −10.8° (*c* 3.45, $CHCl_3$).

Anal. Calcd for $C_{27}H_{26}N_4O_7$: C, 62.54; H, 5.05; N, 10.80. Found: C, 62.34; H, 5.07; N, 10.94.

The mother liquor from the above crystallization was evaporated to dryness and crystallized from hexane to give **22**, mp 66–67°, $[\alpha]^{26}D$ +186° (*c* 1.2, $CHCl_3$).

Anal. Calcd for $C_{27}H_{26}N_4O_7$: C, 62.54; H, 5.05; N, 10.80. Found: C, 62.28; H, 5.16; N, 11.04.

4-Azido-4,6-dideoxy-2,3-di-*O*-benzyl-β-D-glucopyranosyl Chloride (29). A. From 25. A solution of 396 mg (0.77 mmol) of **25** in 30 ml of $CHCl_3$ saturated with HCl was stirred at room temperature for 4 hr. The mixture was cooled and filtered to remove the *p*-nitrobenzoic acid. The filtrate was evaporated to dryness under vacuum and the residue containing **29** and **28** in a ratio 92:8 was recrystallized from hexane to give 253 mg (85%) of

29: mp 94–95°; $[\alpha]^{26}D$ +115° (c 1.25, $CHCl_3$); nmr (C_6D_6) δ 5.0 (d, $J_{1,2}$ = 8 Hz, 1, C-1 H).

Anal. Calcd for $C_{20}H_{22}ClN_3O_3$: C, 61.93; H, 5.72; Cl, 9.14; N, 10.83. Found: C, 61.71; H, 5.78; Cl, 9.30; N, 10.91.

B. From 22. Treatment of 108 mg (0.2 mmol) of **22** with dry HCl in $CHCl_3$ for 32 hr at room temperature, as described above, gave 57 mg (67.5%) of **29**, mp 94–95°, identical with an analyzed sample. The crude product before recrystallization contained **29** and **28** in the ratio 9:1 as determined by nmr.

C. From a Mixture of 22 and 29. Treatment of 700 mg (1.35 mmol) of a mixture of **22** and **25** in a ratio of 53:47 with dry HCl in $CHCl_3$ at room temperature and monitoring the reaction by nmr showed that at 32 hr 88% reaction was complete and the product contained 83% of **29** and 17% of **28**. After leaving the mixture at 5° overnight, it was worked up as described earlier to give 325 mg (62%) of pure **29**, mp 94–95°.

A mixture of 33 mg of mercuric cyanide, 2 ml of CH_3OH, and 50 mg (0.13 mmol) of **29** was stirred at room temperature for 4 hr. The inorganic materials were removed by filtration, the filtrate was evaporated to dryness, and the residue was purified by preparative tlc (ether–hexane, 1:2 system) to give 39 mg (79%) of the α-methyl glycoside **20** as a syrup, $[\alpha]^{26}D$ +88° (c 1.0, $CHCl_3$). An ir spectrum of this material was superimposable on that of an authentic sample.[14]

Ethyl 4-Azido-4,6-dideoxy-2,3-di-*O*-benzyl-α-D-glucopyranoside (21). A mixture of 85 mg of silver carbonate, 100 mg of anhydrous $MgSO_4$, 4 ml of ethanol, and 125 mg (0.32 mmol) of **29** was stirred at room temperature for 4 hr and filtered and the filtrate was evaporated to dryness. The residue was distilled under reduced pressure to give 105 mg (82%) of **21**, bp 160° (0.05 mm), $[\alpha]^{26}D$ +97° (c 0.89, $CHCl_3$).

Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.84; N, 10.57. Found: C, 66.46; H, 7.11; N, 10.30.

Methyl 4-Azido-4,6-dideoxy-2,3-di-*O*-benzyl-β-D-glucopyranoside (23). A mixture of 524 mg (1.35 mmol) of **28** in 2 ml of dry ether, 14 ml of CH_3OH, 413 mg of silver carbonate, and 233 mg of anhydrous $MgSO_4$ was stirred at room temperature for 30 min and filtered and the filtrate was evaporated to dryness. The residue was purified by preparative tlc (pentane–ether, 5:1 system) and crystallized from pentane to give 200 mg (40%) of **23**, mp 57–58°, $[\alpha]^{26}D$ +109° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{21}H_{25}N_3O_4$: C, 65.78; H, 6.57; N, 10.96. Found: C,65.51; H, 6.29; N, 10.72.

Ethyl 4-Azido-4,6-dideoxy-2,3-di-*O*-benzyl-β-D-glucopyranoside (24). A solution of 498 mg (1.3 mmol) of **28** in 2 ml of ether was stirred with 14 ml of ethanol, 205 mg of $MgSO_4$, and 395 mg of silver carbonate at room temperature for 48 hr. The mixture was filtered, the filtrate was evaporated to dryness, and the residue was purified by preparative tlc (pentane–ether, 4:1 system) and recrystallized from cold hexane to give 306 mg (60%) of **24**, mp 81–82°, $[\alpha]^{26}D$ +108° (c 0.64, $CHCl_3$).

Anal. Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.84; N, 10.57. Found: C, 66.83; H, 7.00; N, 10.55.

Isomerization of 29 to 28. A solution of 150 mg (0.4 mmol) of **29** in 2 ml of $CHCl_3$ saturated with HCl was kept at room temperature for isomerization. The progress of the reaction was followed by evaporating the solvent, redissolving the residue in $CDCl_3$, and determining the nmr spectrum at various intervals. The isomerization was slow, showing only 10% of **28** after 40 hr. Continuation of the reaction for over 300 hr showed a steady linear conversion of **29** to **28**, giving 66.8% of **28** at 316 hr. Further isomerization could not be followed as the chloro sugars were found to decompose giving insoluble materials.

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References and Notes

(1) Taken in part from the Ph.D. Dissertation of G. H. Ransford, Wayne State University, 1970.
(2) N. Sharon in "The Amino Sugars," Vol. 2A, E. A. Balazs and J. W. Jeanloz, Ed., Academic Press, New York, N. Y., 1965, p 1.
(3) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970.
(4) M. M. Janot, M. Leboeuf, A. Cave, R. Vijesekera, and R. Goutarel, *C. R. Acad. Sci., Ser. C*, **267**, 1050 (1968); R. Goutarel, C. Monneret, P. Choay, I. Kabore, and Q. K-Huu, *Carbohyd. Res.*, **24**, 297 (1972).
(5) S. Umezawa, T. Tsuchiya, R. Muto, Y. Nishimura, and H. Umezawa, *J. Antibiot.*, **24**, 274 (1971); Y. Nishimura, T. Tsuchiya, and S. Umezawa, *Bull. Chem. Soc. Jap.*, **44**, 2521 (1971).
(6) P. A. S. Smith and B. B. Brown, *J. Amer. Chem. Soc.*, **73**, 2438 (1951).
(7) K. A. Watnabe, M. P. Kotick, and J. J. Fox, *J. Org. Chem.*, **35**, 231 (1970); K. A. Watnabe, I. M. Wempen, and J. J. Fox, *Carbohyd. Res.*, **21**, 148 (1972).
(8) (a) C. L. Stevens, R. P. Glinski, K. G. Taylor, P. Blumbergs, and S. K. Gupta, *J. Amer. Chem. Soc.*, **92**, 3160 (1970), and references cited therein; (b) C. L. Stevens and K. K. Balasubramanian, *Carbohyd. Res.*, **21**, 166 (1972); (c) C. L. Stevens, K. K. Balasubramanian, C. P. Bryant, J. B. Filippi, and P. M. Pillai, *J. Org. Chem.* **38**, 4311 (1973).
(9) C. L. Stevens, P. Blumbergs, and D. H. Otterbach, *J. Org. Chem.*, **31**, 2817 (1966).
(10) C. L. Stevens and J. W. Stoddard, unpublished results.
(11) For reviews, see (a) L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 109 (1967); (b) B. Capon, *Chem. Rev.*, **69**, 407 (1969).
(12) R. C. Hockett, F. P. Phelps, and C. S. Hudson, *J. Amer. Chem. Soc.*, **61**, 1658 (1939).
(13) E. Votocek and F. Valentin, *Collect. Czech. Chem. Commun.*, **2**, 36 (1930).
(14) C. L. Stevens, P. Blumbergs, F. A. Daniher, D. H. Otterbach, and K. G. Taylor, *J. Org. Chem.*, **31**, 2822 (1966).
(15) R. U. Lemieux, R. K. Kulling, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958).
(16) For estimation of α and β anomers in a free sugar by nmr, see J. C. Jochims, G. Taigel, A. Seeliger, P. Lutz, and H. E. Dreisen, *Tetrahedron Lett.*, 4363 (1967).
(17) J. I. Musher and E. J. Corey, *Tetrahedron*, 791 (1962).
(18) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 377.
(19) T. Ishikawa and H. G. Fletcher, Jr., *J. Org. Chem.*, **34**, 563 (1969).
(20) C. L. Stevens, G. H. Ransford, and G. E. Gutowski, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1968, No. MED-09.
(21) C. L. Stevens, J. Němec, and G. H. Ransford, *J. Amer. Chem. Soc.*, **94**, 3280 (1972).
(22) C. L. Stevens, P. M. Pillai, and R. Radhakrishnan, Abstracts, 165th National Meeting of the American Chemical Society, Dallas, Texas, April 1973, No. CARB-18.
(23) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin layer chromatography was carried out using silica gel H from Brinkman Instruments. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. The nmr spectra were obtained on a Varian A-60 or T-60 spectrometer using tetramethylsilane as an internal standard. Infrared spectra were taken on a Perkin-Elmer Model 237B grating spectrophotometer. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.