solids were filtered off and washed with tetrahydrofuran and the combined filtrates were evaporated to dryness. The residue was taken up in chloroform and washed with water. The chloroform extract was dried ($MgSO_4$) and evaporated to give 1,3,2′,6′,3″-penta-*N*-acetyl-1,3,2′,6′-tetra-*N*-methyl-5,2″,4″-tri-*O*-methylsisomicin (**25**) as a clear gum, *m/e* 755 ($M\cdot^+$), 614, 509, 500, 271, 239, 230.

The pseudotrisaccharide **25** was heated under reflux on a steam bath with 6 *N* hydrochloric acid (30 ml) for 2 hr. The solution was cooled and passed over Amberlite IR45 resin and the eluate was evaporated to dryness. The latter was taken up in methanol (5 ml), and acetic anhydride (1 ml) was added. After 25 min at 25° the mixture was evaporated to dryness and the residue was azeotroped with toluene and then chromatographed on a silica gel column (50 × 1 cm) using the lower phase of a chloroform–methanol–7% ammonium hydroxide (2:1:1) system as the eluent to give 1,3-di-*N*-acetyl-1,3-di-*N*-methyl-5-*O*-methyl-2-deoxystreptamine (**26**) as a colorless, amorphous solid, 11 mg (25%), *m/e* 288 ($M\cdot^+$), 270 ($M - H_2O$), which was identical (melting point, tlc, mass spectrum, ir) with an authentic sample.[9] The deoxystreptamine derivative (**26**) showed no CD in Cupra A solution.

Acknowledgment. The authors express their thanks to Dr. R. D. Guthrie for some of the CD spectra and Dr. M. D. Yudis and his associates for providing the spectroscopic and analytical data.

Registry No.—**1**, 32385-11-8; **5**, 51056-65-6; **7**, 51056-66-7; **8**, 51153-06-1; **9**, 51153-05-0; **10**, 34323-04-1; **11**, 51056-67-8; **13**, 34323-05-2; **17**, 34356-18-8; **17** hydrochloride, 51153-07-2; **18**, 34356-19-9; **19**, 34356-20-2; **20**, 51056-68-9; **21**, 51056-69-0; **22**, 51056-70-3; **23**, 49751-51-1; **24**, 51056-71-7; **25**, 51056,72,5.

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(19) Mixture of rotamers at ambient temperature.

(20) Aminocyclitol antibiotics are notorious for their tendency to absorb atmospheric CO_2.[18]

Preparative Routes to 4-Amino-4-deoxy-D-galactose[1]

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Received November 15, 1973

The elaboration of two synthetic routes to methyl 4-acetamido-4-deoxy-α-D-galactopyranoside (**15**) is described, involving the displacement of the sulfonyloxy group by azide in methyl 4-*O*-methanesulfonyl-α-D-glucosides, in which the hydroxyl functions are blocked by benzoyl groups (**4**, route A) or by benzyl and trityl moieties (**6**, route B). With respect to yields and crystallinity of products, route A (**4** → **5** → **8** → **15**) proved to be the more efficient. Free 4-amino-4-deoxy-D-galactose, characterized in the form of its hydrochloride (**18**), its highly crystalline *N*-acetate (**20**), and its α- and β-pentaacetyl derivatives (**19**), was readily obtained by acetolysis of methyl tri-*O*-acetyl-4-azido-4-deoxy-α-D-galactoside **9** and subsequent hydrogenation. Nmr data and rotations unambiguously confirm the assigned structures and configurations, and are in excellent agreement with those of the respective 2-amino-2-deoxy and 3-amino-3-deoxy derivatives of D-galactose.

As a prelude to the synthesis of 4-aminogalactosyl nucleosides,[2] required for further assessing structure–activity relationships in the aminoacyl aminohexosyl cytosine group of antibiotics,[3,4] the elaboration of an adequate preparative sequence was considered essential, that not only would make 4-amino-4-deoxy-D-galactose accessible in a form suitable for subsequent nucleosidation, but also would be applicable to simple hexopyranosyl nucleosides without major modifications. We have, by consequence, initiated work on synthetic routes meeting these requirements,[1a] and herein report the details of these investigations. The preliminary published portions thereof[1c] already had sufficed to disprove an earlier structure of the nucleoside antibiotic gougerotin, the sugar part of which had erroneously been assigned the 4-aminogalacto configuration.[5]

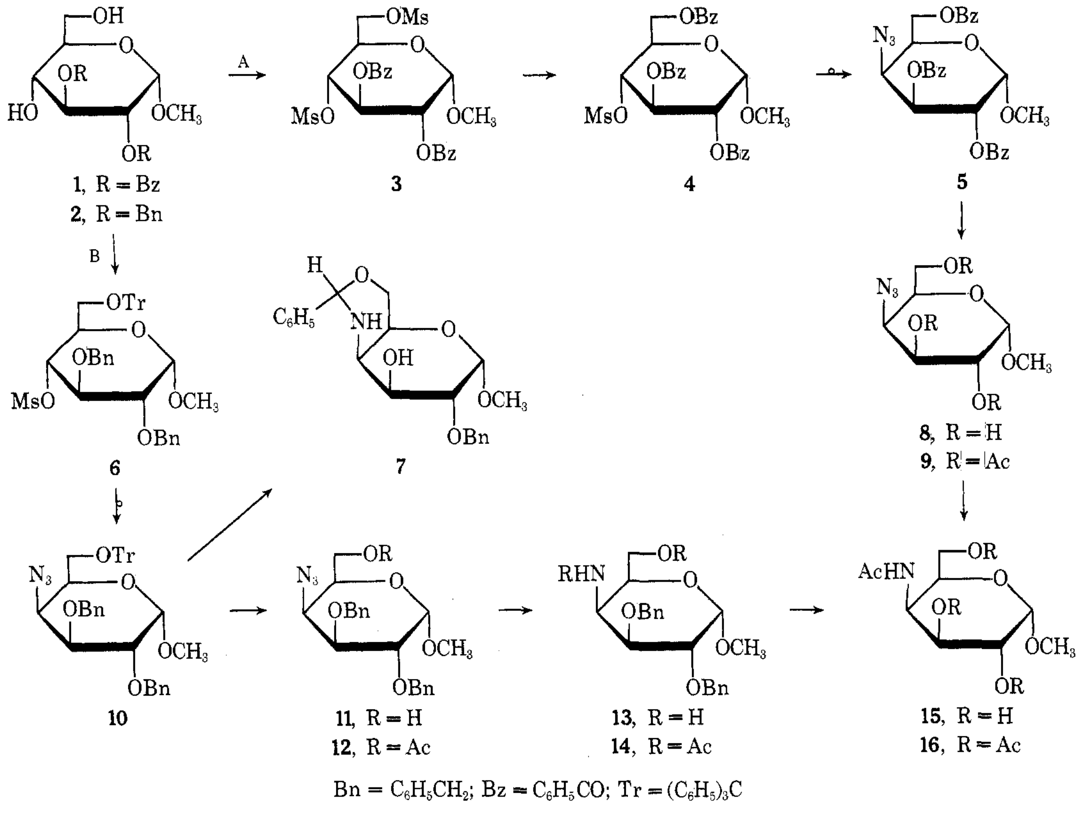
Of the conceivable synthetic approaches to 4-aminogalactose or its derivatives, the oxidation of readily available methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside[6] to its 4-hexuloside followed by oximation, reduction of the oxime, and removal of the protecting groups appeared to be the most propitious. Although this procedure has proved effective with hex-4-uloses carrying alkylidene protecting groups,[7-10] including a synthesis of 4-amino-4-deoxy-D-galactose from open-chain sugar derivatives,[10] its success appeared doubtful with an acylated glycopyranosid-4-ulose owing to extreme sensitivity toward β elimination under acidic and basic conditions.[11,12] Hence, another approach was deemed more promising, involving azide displacement of a 4-sulfonyl ester group in a suitable protected glucopyranoside. This route, which, at the outset of this work,[1] had been utilized in preparing 4-amino-4,6-dideoxy-[13] 4,6-diamino-4,6-dideoxy-,[14] and 2,3,4,6-tetramino-D-galactose derivatives,[15] was also used with two methyl 4-*O*-methylsulfonylglucopyranosides, in which the hydroxyl functions at C-2, C-3, and C-6 were protected by benzoyl groups (**4**, route A) or by benzyl and trityl moieties (**6**, route B), respectively.

1,4-Amino-4-deoxy-α-D-galactosides. Route A. The more efficient synthetic sequence with respect to yields and crystallinity of products, proved to be route A. In the readily accessible methyl 2,3-di-*O*-benzoyl-4,6-di-*O*-methylsulfonyl-α-D-galactopyranoside (**3**), the primary C-6 mesyloxy function can be displaced selectively by azide.[16] An analogous displacement on **3** with sodium benzoate in *N,N*-dimethylformamide (5 hr, 80°) gave methyl 2,3,6-tri-*O*-benzoyl-4-*O*-mesyl-α-D-glucoside (**4**), which, under somewhat more forcing conditions (60 hr, 100° or 5 hr, 150°), was readily converted to the syrupy azido tribenzoate **5** in 85% yield. Deesterification afforded crystalline **8**, which in turn gave methyl 4-acetamido-4-deoxy-α-D-galactopyranoside (**15**) in 64% yield in the form of well-shaped needles. All attempts, however, by various methods of acetylation and purification, to obtain the tetraacetyl derivative **16** in crystalline form were unsuccessful. The product (**16**) was characterized as a syrup of $[\alpha]^{25}\mathrm{D}$ +119°, which was sufficiently different from reported values of a gougerotin degradation product (mp 193°, $[\alpha]\mathrm{D}$ +87°)[17] as to disprove[1c] structure **16** that had been assigned.[5]

Route B. The alternate procedure to the 4-aminogalactosides **15** and **16** started from methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**2**),[18] which by tritylation and subsequent mesylation was converted in 79% yield into the fully protected derivative **6**, suitable for an ensuing azidolysis. When heated with sodium azide in *N,N*-dimethylformamide for 30 hr at 100°, the 4-azido-galactoside **10** was readily obtained (93%). In **10**, the azido function as well as the trityl and benzyl protecting groups are sensitive toward hydrogenolysis conditions; yet its conversion into methyl 4-aminogalactoside could not be accomplished in one step. On hydrogenolysis of **10** over 10% palladium on carbon in methanol, only the azido function was reduced with partial detritylation, while methanolic hydrochloric acid—conditions that proved effective for the debenzylation of methyl 2,3-di-*O*-benzyl-4-amino-4,6-dideoxy-α-D-galactopyranoside[13]—removed only one of the benzyl groups, presumably the one located at C-3. The resulting product was characterized as its benzylidene derivative formed on treatment with benzaldehyde, which appeared to be the 4,6-*N,O*-benzylidene compound **7**[19] rather than the expected Schiff base. Owing to these difficulties, the conversion **10** → **16** was made stepwise: de-O-tritylation by acid afforded syrupy **11**, which was characterized as its crystalline 6-*O*-acetyl derivative **12**; subsequent treatment with lithium aluminum hydride gave the 2,3-dibenzyl-4-aminogalactoside **13**, similarly characterizable as its 4-*N*,6-*O*-diacetate (**14**); the removal of the benzyl groups was finally effected by sodium in liquid ammonia, giving on subsequent acetylation in 43% yield methyl tri-*O*-acetyl-4-acetamido-4-deoxy-α-D-galactoside (**16**), indistinguishable from a sample prepared by route A.

4-Amino-4-deoxy-D-galactose. Attempts to obtain reducing sugars from methyl 4-acetamido-4-deoxy-α-D-galactoside (**15**) or its tri-*O*-acetate **16** by hydrolysis were unsuccessful. Even short heating in 4 *N* hydrochloric acid at 80° resulted in extensive decomposition, as indicated by a black solution and the detection of at least four compounds by tlc. Less forcing acetolysis conditions,[20] which favor formation of acetyliminofuranose derivatives with 4-acetamido-4-deoxyaldosides,[21,22] were employed with the azido-tri-*O*-acetate **9** and gave tetraacetate **17** as a 10:1 α/β-anomeric mixture in 81% yield. De-O-acetylation of **17** with sodium methoxide in methanol followed by hydrogenolysis over 5% palladium on carbon in methanol containing hydrochloric acid gave the hydrochloride of 4-amino-4-deoxy-D-galactose (**18**) as an amorphous solid, exhibiting data, *e.g.*, $[\alpha]^{25}\mathrm{D}$ +51°, that are practically identical with those observed for the same product from a different synthetic route.[10]

On conversion of the azido function in **17** into an acetamido group by hydrogenolysis and subsequent acetylation, a pentaacetyl derivative **19**, $[\alpha]^{25}\mathrm{D}$ +82°, is obtained, comprising an approximate 10:1 anomeric mixture in

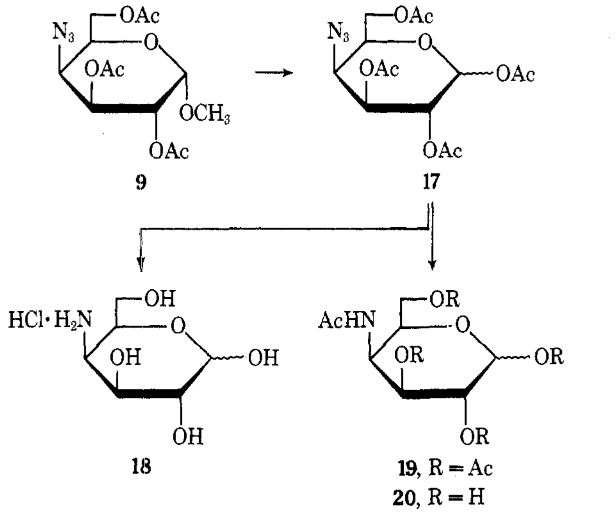


Bn = $C_6H_5CH_2$; Bz = C_6H_5CO; Tr = $(C_6H_5)_3C$

Table I
Nmr Data in $CDCl_3$ and Rotations of Peracetylated α-D-Galactopyranoses

		Chemical shifts[a]							
Peracetyl derivative of α-D-hexopyranose	Registry no.	H-1	H-2	H-3	H-4	a-OAc	e-OAc a-NHAc 6-OAc	e-NHAc	$[\alpha]_D$ in $CHCl_3$, deg
α-D-Galactose	4163-59-1	3.64	4.65[d]	4.65[d]	4.48	7.85 (2)	7.97 7.99 8.00		+107[f]
2-Amino-2-deoxy-α-D-galactose[b]	10385-50-9	3.75	5.34	4.75	4.59	7.81 (2)	7.97 (2)	8.05	+102[g]
3-Amino-3-deoxy-α-D-galactose[c]	23743-53-5	3.72	4.80	5.36	4.56	7.83 (2)	7.96 (2)	8.03	+119
4-Amino-4-deoxy-α-D-galactose (**19**)		3.65	4.70[d]	4.70[d]	5.20	7.84	7.95 (2) 7.97 7.99		+89[h]
Methyl α-D-galactoside	5019-22-7	5.05[d]	5.05[d]	4.93	4.58	7.86	7.95 (2) 8.01		+133[i]
Methyl 3-amino-3-deoxy-α-D-galactoside	51015-64-6	5.07[d]	5.07[d]	5.31	4.49	7.87	7.93 7.95	8.09	+91[j]
Methyl 4-amino-4-deoxy-α-D-galactoside (**16**)		5.03[e]	5.05[e]	4.73	5.27		7.91 7.94 (2) 8.01		+119

[a] Coupling constants observed are $J_{1,2} = 2.0–3.8$, $J_{2,3} = 10–11$, $J_{3,4} = 3.0–4.1$, $J_{4,5} = 1.0–1.5$ Hz. [b] Nmr data from T. D. Inch, J. R. Plimmer, and H. G. Fletcher, *J. Org. Chem.*, **31,** 1825 (1966). [c] Data from F. W. Lichtenthaler, G. Bambach, and U. Scheidegger, *Chem. Ber.*, **102,** 986 (1969). [d] Unresolved 2 H multiplets. [e] Calculated values on the basis of an AB system with $J_{1,2} = 3.8$ and $J_{2,3} = 10.5$ Hz. [f] C. S. Hudson and P. O. Parker, *J. Amer. Chem. Soc.*, **37,** 1589 (1915). [g] M. Stacey, *J. Chem. Soc.*, 272 (1944). [h] Calculated value; *cf.* ref 23. [i] F. Micheel and O. Littmann, *Justus Liebigs Ann. Chem.*, **466,** 115 (1928). [j] H. H. Baer, *J. Amer. Chem. Soc.*, **84,** 83 (1962).



favor of the α anomer on the basis of its rotation and nmr data (*cf.* Table I). The most suitable derivative for characterization appears to be the 4-acetamido-4-deoxy-D-galactopyranose, readily isolated in crystalline form from a de-O-acetylation of **19**. Expectedly, it shows mutarotation in water from +45 to +65°, which is interesting insofar as 4-acetamido-4-deoxy-D-glucose, although having a different initial rotation, features the same rotational value for the anomeric equilibrium ($[\alpha]^{20}D$ +91 → +66°, in water[10]). On treatment with pyridine–acetic anhydride, the 4-acetamido-4-deoxy-D-galactose **20** is converted to a syrupy pentaacetyl derivative **19**, in which now the β anomer preponderates by an approximate ratio of 9:1, as indicated by nmr data and its rotation of $[\alpha]^{25}D$ +15°.[23] It is interesting to note that no product corresponding to 1,2,3,5,6-penta-*O*-acetyl-4-acetamido-4-deoxy-D-galactofuranose[22] or to dimeric forms thereof[10] could be detected by either tlc or nmr in this tetra-*O*-acetyl-4-acetamido-4-deoxy-β-D-galactopyranose **19**, containing 10% of the α anomer.

Structural and Configurational Assignments. While the mode of preparation in itself is conclusive proof for the galacto configuration of compounds **5** and **7–20**, corroborative evidence is readily furnished by nmr data. In contrast to the respective gluco derivatives **3**, **4**, and **6**, in which coupling constants of 9–10 Hz ($J_{3,4}$ and $J_{4,5}$) are observed for the proton at C-4, in the galacto derivatives H-4 consistently appears as a quartet with $J_{3,4}$ = 3–4 and $J_{4,5}$ = 1–1.5 Hz. In the acetamido derivatives **14**, **16**, **19**, and **21**, this quartet is further split by coupling with the NH proton ($J_{4,NH}$ = 9 Hz), which, however, is eliminated on deuteration or on addition of trifluoroacetic acid.

These configurational assignments are further substantiated by the chemical shifts of the acetyl resonances of the peracetylated amino galacto derivatives **16** and **19**, which nicely comply with the empirical principles laid down in the "acetyl resonance rule" for cyclitols[24] and hexopyranoses,[25] as well as with the data for the other galactopyranose peracetates collected in Table I. Accordingly, **16** and the two anomers of **19** exhibit no acetyl resonances (in $CDCl_3$) attributable to an equatorial acetamido group (around τ 8.07), the signal at highest field appearing at τ 8.01. Similarly, a low-field resonance around τ 7.85 is only observed in the case of the α anomer of **19**, as expected for the C-1 acetoxy group.

Equally distinct configurational proof is provided by the nmr characteristics of the ring protons H-1–H-4 of **16** and **19**, particularly when juxtaposed with the corresponding derivatives of galactose, 2-aminogalactose, and 3-aminogalactose (Table I). In the pentaacetyl compounds the axially oriented anomeric proton appears within the narrow range of 3.64–3.75 ppm, while in the glycosides H-1a is shifted toward higher field by approximately 1.3 ppm. Another obvious relationship appears to be the consistent upfield shift of the ring protons by 0.7 ppm when replacing an acetoxy group at C-2, C-3, or C-4 in pentaacetyl-α-D-galactopyranose by an acetamido function.

Since replacement of an acetoxy by an acetamido group does not substantially affect rotational values,[26] their sign and magnitude should also be indicative of configuration. Indeed, all peracetylated α-D-galactopyranoses in Table I exhibit a high positive rotation in chloroform, the somewhat scattered values being within the limitations of this type of comparisons. Thus, the $[\alpha]^{25}$D of +119° observed for **16** compares well with those for other peracetylated α-D-galactosides (*cf.* Table I). For the respective β anomer of **16**, as yet unknown, a small negative or at best a small positive rotation must necessarily be predicted on the basis of $[\alpha]$D −14° for methyl tetra-*O*-acetyl-β-D-galactopyranoside,[27] −17° for the 2-acetamido-2-deoxy,[28] and −5° for the 3-acetamido-3-deoxy compounds,[25] respectively. Nevertheless, Fox, *et al.*,[29] pretended that the tetraacetate of methyl 4-amino-4-deoxy-β-D-galactopyranoside could well have a rotation of +87°.

Experimental Section

Melting points were determined on a Bock Monoskop, and are uncorrected. Spectral measurement were effected with Perkin-Elmer 125 (ir), Perkin-Elmer 137 (uv), and Varian A-60A (nmr) instruments. Thin layer chromatography on Kieselgel F_{254} plastic sheets (Merck, Darmstadt) was used to monitor the reactions and to ascertain the purity of the reaction products; preparative tlc was done on 20 × 40 cm glass plates coated with a 1.5-mm layer of Merck Kieselgel HF. Developers employed (A) benzene–ethyl acetate (10:1); (B) chloroform–ethyl acetate (10:1); (C) ethyl acetate–ethanol–water (15:2:1). The spots were visualized by uv light, by iodine vapor, or by spraying with 80% aqueous sulfuric acid and charring at 110° for 5 min. Column chromatography was carried out on silica gel 70–230 mesh (Kieselgel 60, Merck, Darmstadt).

Route A. Methyl 2,3,6-Tri-*O*-benzoyl-4-*O*-methylsulfonyl-α-D-glucopyranoside (4). To a solution of methyl 2,3-di-*O*-benzoyl-4,6-di-*O*-mesyl-α-D-glucopyranoside[16] (**3**, 9.3 g, 16.7 mmol) in *N,N*-dimethylformamide (50 ml) was added sodium benzoate (2.7 g, 18.5 mmol), and the mixture was heated for 5 hr at 80° with stirring, followed by evaporation to dryness *in vacuo*. A chloroform solution of the residue was washed with water, dried, and concentrated to a syrup, that was purified *via* elution from a silica gel column (2 × 50 cm) with solvent system B. An 8.7-g (89%) yield of a colorless, uniform (tlc in A) syrup was obtained: $[\alpha]^{25}$D +139° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) τ 1.9 and 2.5 (broad m, 6 and 9, 3 C_6H_5), 4.88 (t, 1, $J_{3,4} = J_{4,5} = 9$ Hz, H-4), 5.2–5.8 (m, 3, H-5 and 6-CH_2), 6.55 (s, 3, OCH_3), 7.10 (s, 3, OMs); H-1, H-2, and H-3 give an ABX spectrum, the AB part (seven lines centered around τ 4.7) and X portion (11 lines around τ 3.86) indicating $J_{1,2} = 3.5$ and $J_{2,3} = 9.5$ Hz as well as the chemical shifts for H-1 (4.75) and H-2 (4.71); a spectrum calculated on the basis of these data was in excellent agreement with the observed one.

Anal. Calcd for $C_{29}H_{28}O_{11}S$: C, 59.58; H, 4.83; S, 5.49. Found: C, 59.56; H, 4.80; S, 5.25.

Methyl 4-Azido-2,3,6-tri-*O*-benzoyl-4-deoxy-α-D-galactopyranoside (5). A mixture of mesylate **4** (9.5 g, 16.3 mmol) and sodium azide (3.3 g, 3 molar equiv) in *N,N*-dimethylformamide (100 ml) was heated at 150° for 5 hr, followed by evaporation to dryness *in vacuo*. A chloroform solution of the residue was filtered, washed with water, and taken to dryness, leaving a syrup that was purified by elution from a silica gel column with solvent system A: 7.4 g (85%) of **5** as a chromatographically uniform syrup of $[\alpha]^{25}$D +17° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{28}H_{25}N_3O_8$: C, 63.27; H, 4.74; N, 7.91. Found: C, 63.18; H, 4.78; N, 8.02.

Methyl 4-Azido-4-deoxy-α-D-galactopyranoside (8). De-O-benzoylation of tribenzoate **5** (7.0 g, 13.2 mmol) was effected by standing overnight in methanol (50 ml) containing 1 *N* sodium methoxide (2 ml), followed by deionization with an acidic resin (Merck IV, H^+ form) and evaporation to dryness. The residue was dissolved in water and extracted twice with ether for removal of methyl benzoate, to give, on evaporation of the aqueous phase to dryness, a residue that crystallized on gradual addition of benzene to a 2-propanol solution. Recrystallization from methanol-benzene afforded 1.99 g (69%) of azidogalactoside **8** as colorless crystals: mp 153–155°; $[\alpha]^{25}$D +120° (*c* 0.5, CH_3OH); ir (KBr) 2130 cm^{-1} (N_3); nmr (D_2O) τ 5.18 (d, 1, $J_{1,2} = 3.5$ Hz, H-1), 6.61 (s, 3, OCH_3); CD_{max} 277 nm, θ in dioxane, +0.13, in methanol +0.09, in water +0.08.

Anal. Calcd for $C_7H_{13}N_3O_5$: C, 38.35; H, 5.98; N, 19.17. Found: C, 38.77; H, 6.03; N, 19.13.

Methyl 4-Azido-2,3,6-tri-*O*-acetyl-4-deoxy-α-D-galactopyranoside (9). A mixture of 2.5 g (11.4 mmol) of azidogalactoside **8** was kept in 2:1 pyridine–acetic anhydride (60 ml) for 24 hr at room temperature, followed by concentration to dryness and several reevaporations from water. The residue was purified by elution from a silica gel column with solvent system A, to give on evaporation and drying (50°, 0.1 mm) 2.8 g (72%) of a syrup, uniform by tlc (C): $[\alpha]^{25}$D +93° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) τ 4.56 (q, 1, $J_{2,3} = 10$ and $J_{3,4} = 3.5$ Hz, H-3), 4.84 (q, 1, $J_{1,2} = 3$ Hz, H-2), 5.05 (d, 1, H-1), 5.81 (m, 4, H-4, H-5, and 6-CH_2), 6.62 (s, 3, OCH_3), 7.88 (s, 3, 3-OAc), 7.92 (s, 6, 2- and 6-OAc).

Anal. Calcd for $C_{13}H_{19}N_3O_8$: C, 45.21; H, 5.55; N, 12.17. Found: C, 44.99; H, 5.57; N, 11.97.

Methyl 4-Acetamido-4-deoxy-α-D-galactopyranoside (15). A. From 4-Azidogalactoside 8 by Hydrogenation and N-Acetylation. A methanolic solution of **8** (1.0 g in 200 ml) was hydrogenated over 10% Pd/C for 6 hr, followed by removal of the catalyst and concentration of the filtrate to a volume of about 50 ml. Acetic anhydride (5 ml) was added, and, after being kept overnight at ambient temperature, the mixture was evaporated to dryness. Several reevaporations of the residue from benzene gave a product which slowly crystallized from a 2:1 ethanol-benzene solution on standing. Recrystallization from ethanol–acetone afforded 830 mg (76%) of **15** as needles: mp 203–205°; $[\alpha]^{25}$D +182° (*c* 1, CH_3OH); nmr (DMSO-d_6) τ 2.40 (d, 1, $J_{4,\mathrm{NH}} = 9$ Hz, NH), 6.70 (s, 3, OCH_3), 8.08 (s, 3, NHAc).

Anal. Calcd for $C_9H_{17}NO_6$: C, 45.95; H, 7.28; N, 5.96. Found: C, 45.86; H, 7.21; N, 6.00.

B. De-O-acetylation of Tetraacetate 16. A solution of **16** (2.5 g, 7 mmol) in methanolic ammonia (100 ml) was kept at room temperature overnight, followed by evaporation to dryness and trituration of the residue with methanol–benzene, which resulted in crystallization of 1.38 g (82%) of needles, indistinguishable from **15** prepared by method A.

Methyl 4-Acetamido-2,3,6-tri-*O*-acetyl-4-deoxy-α-D-galactopyranoside (16) by Acetylation of the *N*-Acetate (15). A solution of **15** (900 mg) in 2:1 pyridine–acetic anhydride (20 ml) was kept overnight at ambient temperature and subsequently evaporated to dryness followed by repeated coevaporations with water. The syrupy residue was applied to a silica gel column (2 × 30 cm) and eluted with solvent system C. The appropriate fraction was evaporated and dried (0.1 mm), affording **16** as a syrup: $[\alpha]^{25}$D +119° (*c* 1, $CHCl_3$); 100-MHz nmr in $CDCl_3$, *cf.* Table I; in DMSO-d_6 τ 1.85 (d, 1, $J_{4,\mathrm{NH}} = 10$ Hz, NH), 4.94 (m, 3, ABC system of H-1, H-2, and H-3), 5.44 (m, 1, H-4), 5.95 (m, 3, H-5 and 6-CH_2), 6.64 (s, 3, OCH_3), acetyl resonances at 7.96, 7.98, and 8,08 (2).

Anal. Calcd for $C_{15}H_{23}NO_9$: C, 49.86; H, 6.42; N, 3.88. Found: C, 50.02; H, 6.58; N, 3.89.

Route B. Methyl 2,3-Di-*O*-benzyl-4-*O*-methylsulfonyl-6-*O*-trityl-α-D-glucopyranoside (6). To a solution of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[18] (**2**, 10.0 g, 27 mmol) in dry pyridine (125 ml) was added triphenylchloromethane (9.0 g, 32 mmol). The mixture was kept at ambient temperature overnight, followed by the addition of mesyl chloride (6 ml, 77 mmol) with cooling (0°), standing for 10 hr at room temperature, and evaporation to dryness *in vacuo*. The syrupy residue was dissolved in chloroform, which was washed with water and, after treatment with charcoal, dried ($MgSO_4$), followed by evaporation to dryness. Trituration of the residue with ethanol resulted in crystallization, amounting after recrystallization from the same solvent to 14.8 g (79%), as needles, mp 146–147°, $[\alpha]^{25}$D +24° (*c* 0.5, $CHCl_3$). Two recrystallizations of this product, which was used for further experiments, from acetone–methanol raised the melting point to 152–153° without change in rotation.

Anal. Calcd for $C_{41}H_{42}O_8S$: C, 70.78; H, 6.09; S, 4.62. Found: C, 70.78; H, 6.12; S, 4.64.

Methyl 4-Azido-2,3-di-*O*-benzyl-4-deoxy-6-*O*-trityl-α-D-galactopyranoside (10). The mesyl glucoside **6** (6.0 g, 8.7 mmol) and sodium azide (2.3 g, 4 molar equiv) were heated with stirring for 30 hr at 100° in dry *N,N*-dimethylformamide (60 ml). After cooling, the mixture was poured into ice–water and the solid, separated, was filtered off and recrystallized from methanol to give 5.3 g (93%) of azide **10** as colorless crystals: mp 50–52°; $[\alpha]^{25}$D +13° (*c* 2, $CHCl_3$);[30] ir (KBr) 2145 cm^{-1} (N_3).

Anal. Calcd for $C_{40}H_{39}N_3O_5$: C, 74.63; H, 6.13; N, 6.55. Found: C, 74.73; H, 6.10; N, 6.40.

Methyl 4-Amino-2-*O*-(3-*O*-)-benzyl-4-*N*,6-*O*-benzylidene-4-deoxy-α-D-galactopyranoside (7). To a prehydrogenated suspension of 10% Pd/C (500 mg) in methanol (75 ml) and 3.6 ml of concentrated hydrochloric acid was added 1.2 g (1.87 mmol) of azido galactoside **10** in 75 ml of methanol, and the hydrogenation was continued. After the uptake of H_2 had ceased (24 hr), the catalyst was filtered off and the filtrate was deionized by stirring with a strongly basic ion-exchange resin (Merck III, OH^- form). On concentration of the solution, triphenylmethane crystallized and was removed (0.35 g, mp 87-89°). Evaporation to dryness *in vacuo* afforded a syrup, which, being not amenable to crystallization, was allowed to react with benzaldehyde (1.0 ml) for 2 hr at 80°. The excessive benzaldehyde was distilled off (0.1 mm) and the syrupy residue was dissolved in ethyl acetate and washed consecutively with saturated sodium bicarbonate solution and water. Evaporation of the solvent and trituration of the residue with methanol gave 0.31 g (44%) of **7** as needles: mp 204-206°; ir (KBr) OH and NH around 3530 cm^{-1}, no absorption in the 1690-1630-cm^{-1} region (C=N); nmr ($CDCl_3$) τ 2.3-2.7 (m, 10, 2 C_6H_5), 3.05 (s, 1, NH), 3.92 (s, 1, benzylidene CH), 4.64 (d, 1, $J_{1,2}$ = 2 Hz, H-1), 5.15 (m, 2, H-2 and H-3), 5.85 (broad m, 1, H-4), 6.25 (m, 5, H-5, 6-CH_2 and $ArCH_2$), 6.51 (s, 3, OCH_3), 7.18 (s, 1, OH); the signals at τ 3.05 and 7.18 disappear on treatment with D_2O.

Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 68.01; H, 6.60; N, 3.86.

Methyl 4-Azido-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranoside (11). The trityl derivative **10** (16.4 g, 25.6 mmol) was heated for 30 min at 100° in 100 ml of 4:1 acetic acid-water. On cooling, triphenylmethanol crystallized and was removed (5.7 g), and a second crop (0.7 g, total 95%) was obtained on concentration of the solution to a small volume. Evaporation to dryness *in vacuo*, followed by repeated coevaporations with water, afforded crude **11** as a syrup (9.1 g, 89%), which contained traces of triphenylcarbinol (tlc in B), yet was used for further experiments. For the analytical sample, 0.35 g was applied to a preparative tlc plate and developed with solvent system B. The zone containing **11** (R_f 0.3) was scratched off and thoroughly eluted with chloroform-ethanol (1:1), followed by evaporation of the extract to dryness *in vacuo* to give 230 mg of a chromatographically uniform (tlc in A and B) syrup, $[\alpha]^{25}D$ +3° (*c* 1, $CHCl_3$), ir (film) 2150 cm^{-1} (N_3).

Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.14; H, 6.31; N, 10.52. Found: C, 62.89; H, 6.26; N, 10.38.

Methyl 6-*O*-Acetyl-4-azido-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranoside (12). The azido derivative **11** (140 mg) was kept in a mixture of pyridine (4 ml) and acetic anhydride (2 ml) overnight at ambient temperature. Concentration to dryness, several reevaporations from water to remove traces of solvents, treatment of an ethanolic solution with charcoal, and evaporation left a syrup, which crystallized on trituration with 2-propanol to give 72 mg (52%) of **12** as colorless needles: mp 76-78°; $[\alpha]^{25}D$ +8° (*c* 0.7, $CHCl_3$); nmr ($CDCl_3$) τ 6.65 (s, 3, OCH_3), 7.95 (s, 3, OAc).

Anal. Calcd for $C_{23}H_{27}N_3O_6$: C, 62.57; N, 6.16; N, 9.52. Found: C, 62.53; H, 6.15; N, 9.56.

Methyl 4-Amino-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranoside (13). To a suspension of lithium aluminum hydride (2.5 g) in ether (100 ml) was added a solution of **11** (8.6 g, 21.5 mmol) in 200 ml of ether. After the reaction had ceased the mixture was refluxed for 1 hr. After cooling down, the excessive $LiAlH_4$ was destroyed by the addition of ethyl acetate, followed by evaporation to dryness. Suspension of the residue in ether (200 ml), gradual addition of water until coagulation occurred, decantation, and extraction of the residue with ether gave upon evaporation of the combined ether solutions a syrup (8.0 g), which was used for debenzylation although traces of triphenylcarbinol could be detected (tlc in B). For the analytical sample, 400 mg was applied to a preparative tlc plate and developed with solvent system B, followed by elution of the appropriate zone with ethyl acetate-methanol (1:1) and evaporation of the eluate to dryness *in vacuo* (finally 0.1 mm) to give 270 mg of a syrup, $[\alpha]^{25}D$ +54° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.32; H, 7.36; N, 3.68.

Methyl 4-Acetamido-6-*O*-acetyl-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranoside (14). Acetylation of **13** (300 mg) in 2:1 pyridine-acetic anhydride (15 ml) overnight at room temperature and evaporation to dryness gave a syrup, which was dissolved in chloroform and thoroughly washed with water. The residue either as such or after preparative tlc (as described for **11**) was not amenable to crystallization, affording 250 mg (68%) of a colorless syrup: $[\alpha]^{25}D$ +51° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) τ 4.27 (d, 1, $J_{4,NH}$ = 10 Hz, NH), 6.62 (s, 3, OCH_3), 7.95 and 7.98 (two s, 3-, 6-OAc and 4-NHAc).

Anal. Calcd for $C_{25}H_{31}NO_7$: C, 65.62; H, 6.83; N, 3.06. Found: C, 65.67; H, 6.83; N, 2.98.

De-O-benzylation of 13 with Liquid Ammonia. To a stirred suspension of 2,3-di-*O*-benzylgalactoside **13** (6.5 g, 17.4 mml) in liquid ammonia was added, in small portions, 3.0 g of sodium. After 3 hr, the excessive sodium was decomposed by the addition of ammonium chloride and the ammonia was allowed to evaporate. The residue was dissolved in water, followed by washing with chloroform and evaporation to dryness, leaving a uniform (tlc in C), ninhydrin-active syrup that was subsequently acetylated by standing overnight in 2:1 pyridine-acetic anhydride (100 ml). The mixture was concentrated to a syrup, which was repeatedly coevaporated with water and purified by elution from a silica gel column (3 × 50 cm) with solvent system C. The appropriate eluate was evaporated to dryness and dried (0.1 mm), giving 4.4 g (70%) of the tetraacetyl-4-aminogalactoside **16** as a syrup, indistinguishable with respect to nmr and rotational data from a sample of the same compound prepared by route A (*cf.* above).

Derivatives of 4-Amino-4-deoxy-D-galactose. 1,2,3,6-Tetra-*O*-acetyl-4-azido-4-deoxy-α-D-galactopyranose (17). To a cooled (0°) solution of azido galactoside **16** (2.0 g, 5.8 mmol) in acetic anhydride (40 ml) was slowly added with stirring acetic acid (20 ml) containing 2 ml of concentrated sulfuric acid, and the mixture was kept at 6-10° overnight, followed by pouring into ice-water (300 ml). After decomposition of excess acetic anhydride (20 min) the solution was extracted with chloroform (3 × 100 ml) and the combined extracts were washed with water, treated with charcoal, and subsequently evaporated to dryness *in vacuo*. The residue was applied to a silica gel column (3 × 50 cm) and eluted with 1:1 benzene-ethyl acetate, to afford after evaporation of the appropriate fraction and drying at 55° (0.1 mm) 1.75 g (81%) of **17** as a colorless foam, uniform by tlc (C), which was used for further experiments, although analytical data were somewhat too low: $[\alpha]^{25}D$ +56° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) τ 3.68 (narrow m, H-1), 7.88 s, 6, C-1 and C-3 OAc), 7.93 and 8.00 (two s, 3, C-2 and C-6 OAc); the content of the β anomer was below 10%.

4-Acetamido-1,2,3,6-tetra-*O*-acetyl-4-deoxy-D-galactopyranose (19). A. α Anomer (Containing 10% β). To a prehydrogenated suspension of 10% Pd/C in ethyl acetate (200 mg in 50 ml) was added 1.0 g (2.7 mmol) of syrupy azido tetraacetate **17**, and the hydrogenation was continued. After 6 hr the catalyst was removed, and the solution was evaporated to dryness followed by addition of 1:1 pyridine-acetic anhydride (10 ml). Standing overnight, concentration to a syrup with several coevaporations with water, and elution from a silica gel column (3 × 50 cm) with 1:1 benzene-ethyl acetate gave 0.68 g (65%) of a syrup, $[\alpha]^{25}D$ +82° (*c* 1, $CHCl_3$),[23] nmr ($CDCl_3$) *cf.* Table I.

Anal. Calcd for $C_{16}H_{23}NO_{10}$: C, 49.35; H, 5.95; N, 3.60. Found: C, 49.22; H, 6.21; N, 3.61.

B. β Anomer (Containing 10% α). The *N*-acetate **20** (150 mg) was kept in 1:1 pyridine-acetic anhydride (6 ml) at room temperature overnight, followed by concentration to a syrup which was reevaporated repeatedly from water and methanol. Treatment of a methanol solution with charcoal, evaporation to dryness, and drying (55°, 0.1 mm) left 220 mg (86%) of a colorless syrup: $[\alpha]^{25}D$ +15°;[23] nmr ($CDCl_3$) τ 3.79 (d, 1, $J_{4,NH}$ = 9 Hz, NH), 4.34 (d, $J_{1,2}$ = 8 Hz, H-1); acetyl resonances at 7.90 (1-OAc), 7.95 (2-, 6-OAc and 4-NHAc), 8.01 (3-OAc); the intensity of the acetyl resonance at τ 7.84 (axial 1-OAc) indicated approximately 10% of the α anomer.

Anal. Calcd for $C_{16}H_{23}NO_{10}$: C, 49.35; H, 5.95; N, 3.60. Found: C, 49.19; 5.90; N, 3.67.

4-Acetamino-4-deoxy-D-galactopyranose (20). To a methanol solution of pentaacetate **19** (450 mg in 20 ml) was added 1 *N* sodium methoxide (2 ml) and the mixture was kept at ambient temperature for 12 hr. Deionization by stirring with an acidic resin (Merck IV, H^+ form), evaporation to dryness *in vacuo*, and trituration of the residue with 2-propanol-benzene gave a solid mass that was recrystallized from ethanol to give 240 mg (47%) of **20** as colorless crystals: mp 193-195° dec; $[\alpha]^{25}D$ +45° (3 min) → +65° (2 days) (*c* 1, H_2O); nmr (100 MHz, in D_2O) τ 4.72 and 5.39 (two d of total integration 1, $J_{1e,2}$ = 3.8 and $J_{1a,2}$ = 7.5 Hz, H-1e and H-1a), 5.63 (q, 1, $J_{3,4}$ = 4.0 Hz, H-4), 7.94 (s, 3, NHAc).

Anal. Calcd for $C_8H_{15}NO_6$: C, 43.43; H, 6.84; N, 6.33. Found: C, 43.47; H, 7.03; N, 6.28.

4-Amino-4-deoxy-D-galactopyranose Hydrochloride (18). The 4-azido tetraacetate **17** (500 mg) was subjected to de-O-acetylation by 1 *N* sodium methoxide (1 ml) in 10 ml of methanol (3 hr, 25°), and after deionization with an acidic resin (Merck IV, H^+ form) was taken to dryness. The syrupy residue was dissolved in 10 ml of 0.1 *N* hydrochloric acid and hydrogenated over 5% Pd/C (50 mg) for 3 hr. Removal of the catalyst and evaporation to dryness *in vacuo* (bath temperature below 30°), followed by repeated reevaporations from water, afforded a syrup which was precipitated from a methanol-ether solution in an amorphous form to give 185 mg (64%), melting gradually with decomposition from 110° on (after drying at 30°, 0.1 mm), $[\alpha]^{25}\mathrm{D}$ +51° (*c* 1, H_2O) (lit.[10] $[\alpha]^{20}\mathrm{D}$ +48.2°).

Anal. Calcd for $C_6H_{13}NO_5 \cdot HCl$: C, 33.41; H, 6.55; N, 6.50; Cl, 16.49. Found: C, 33.20; H, 6.70; N, 6.40; Cl, 16.04.

Registry No.—**2**, 17791-36-5; **3**, 22435-33-2; **4**, 19877-45-3; **5**, 51015-65-7; **6**, 19877-37-3; **7** 2-*O*-benzyl derivative, 51015-66-8; **7** 3-*O*-benzyl derivative, 51015-67-9; **8**, 21395-67-5; **9**, 51015-68-0; **10**, 19877-38-4; **11**, 19887-42-4; **12**, 19877-39-5; **13**, 19877-40-8; **14**, 19877-41-9; **15**, 19877-43-1; **16**, 19877-42-0; **17**, 51015-69-1; **18**, 24558-85-8; **18** hydrochloride, 51015-70-4; **19** α anomer, 51015-71-5; **19** β anomer, 51015-72-6; **20**, 51015-73-7.

References and Notes

(1) (a) Taken in part from the Doctoral Dissertation of P. H., Technische Hochschule Darmstadt, Feb 1969. (b) Financial support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. (c) A preliminary account on part of this work has appeared: F. W. Lichtenthaler and P. Heidel, *Angew. Chem.*, **80**, 441 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 458 (1968).

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Sulfur-Containing Carbohydrates. Synthesis of 1,3,4,6-Tetrathio-D-mannitol[1,2]

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Received September 19, 1973

The di-*O*-isopropylidene derivative (**2**) of 3,4-anhydro-D-talitol on reaction with potassium methyl xanthate gave a mixture of two diastereomeric trithiocarbonates. One of these, mp 117°, was assigned the D-manno configuration (**7**), the other, mp 127°, the D-ido configuration (**1**), primarily on the basis of optical rotation studies. The yellow trithiocarbonate **7** was hydrolyzed to the tetrol **8**, which was converted to its tetraacetate **9**. The compound **7** was only partially reduced by lithium aluminum hydride, giving the mercaptodithiolane **3**. When oxidized, the trithiocarbonate **7** gave the corresponding dithiocarbonate **6**. The latter on hydrolysis gave the tetrol **4**, which was converted to its tetraacetate **5**. The dithiocarbonate **6** on reaction with hydrogen bromide in acetic acid gave the 1,6-dibromide dithiocarbonate diacetate **10**. The trithiocarbonate **7** similarly gave the 1,6-dibromide dithiocarbonate diacetate **14**. The compound **10** on reaction with potassium thiolacetate gave the 1,6-dithiol dithiocarbonate tetraacetate **11**. Reduction of the latter finally gave the desired 1,3,4,6-tetrathio-D-mannitol (**12**), mp 124° (hexaacetate mp 165°). Evidence for the constitution, configuration, and conformation of the various products was obtained by a variety of physical methods.

In the course of a project for synthesis of perthio carbohydrates (all oxygen atoms to be replaced by sulfur), we recently prepared a large number of hexitol and cyclitol analogs and their derivatives, in which from two to four of the oxygen atoms were replaced by sulfur.[2a]

Since it has, unfortunately, been necessary to discontinue the perthio carbohydrate project, we are now reporting on some of these partially thiolated products. A literature survey indicates that very few carbohydrates (or other organic compounds) containing three or more mercapto groups are known.[4,5] We are hopeful that some of the compounds now reported will have valuable physical, chemical, and especially biological properties.

The 3-benzoate-4-mesylate derivative[6,7] of 1,2;5,6-di-*O*-isopropylidene-D-mannitol was prepared by an improved method and converted to the di-*O*-isopropylidene derivative, **2** (Chart I), of 3,4-anhydro-D-talitol[7] (equally well named 3,4-anhydro-D-altritol). This epoxide on reac-