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Note

The synthesis of some 4-substituted derivatives of 1,2,3-tri-*O*-acetyl-6-deoxy-L-glucopyranose having cytotoxic activity

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The surface-membrane architecture of normal cells, and of those transformed by oncogenic viruses and chemical carcinogens, differs considerably with respect to structural and compositional features[1]. Although the possibility of exploiting such differences by employing membrane carbohydrate analogs that might be incorporated into the surface of neoplastic cells and thereby potentially altering their immunogenicity or oncogenicity (or both) appears to exist, little effort has been expended in this area. Attempts have therefore been made in this investigation to fashion a chemotherapeutic attack on neoplastic-cell membranes. This report describes the synthesis and cell-culture evaluation of a number of 4-substituted analogs of L-fucose peracetate having the 6-deoxy-L-glucopyranose configuration. An approach similar to that of our laboratory is independently being carried out by Bernacki *et al.*[2]; these investigators have synthesized a number of membrane sugar analogs and have shown that 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose is more potent than 2-amino-2-deoxy-D-glucose as an inhibitor of the growth of L-1210 leukemic cells in culture.

Methyl 6-deoxy-α-L-galactopyranoside was prepared from L-fucose (6-deoxy-L-galactose) according to the method of Zehavi and Sharon[3], whereupon selective benzoylation and subsequent mesylation of methyl 6-deoxy-α-L-galactopyranoside, as described by Richardson and Williams[4], afforded the respective 2,3-dibenzoate **1** and 4-mesylate **2**. Treatment of **2** with sodium azide in hexamethylphosphoric triamide displaced the sulfonyloxy group with inversion of configuration, to give the 4-azide derivative **3** as an analytically pure syrup in 82% yield, the structure of which was supported by examination of the 270-MHz ^{1}H-n.m.r. spectrum (Table I). *O*-Debenzoylation afforded crystalline methyl 4-azido-4,6-dideoxy-α-L-glucopyranoside (**4**) in 70% yield, from which the triacetate **10** was obtained as a syrupy product in 70% yield upon acetolysis. The n.m.r. spectrum of **10** indicated a mixture of α and β anomers in the ratio of 4:1. Base-catalyzed hydrolysis of **10** gave crystalline 4-azido-4,6-dideoxy-L-glucopyranose (**11**) in 53% yield.

TABLE I

FIRST-ORDER ^{1}H-N.M.R. DATA (δ VALUES) IN CHLOROFORM-*d* AT 270 MHz

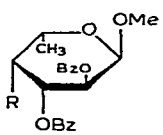
Compound	*Chemical shifts*						*Coupling constants (Hz)*					*OMe*	*OAc, NAc*
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$		
3	5.08	5.15	5.90	3.43	3.85	1.42	3.6	10.3	10.3	10.3	5.9	3.40	
5[a,b]	5.04	4.13	4.01	4.33	4.70	1.48	3.6				6.6	3.38	
6	5.18	5.26	6.11	5.35	4.17	1.33	3.7	9.5	9.5	9.5	5.9	3.46	
8	5.16	5.11	5.97	3.78	4.09	1.47		9.6	9.6	9.6	6.6	3.43	
10	6.24	5.02	5.41	3.28	3.80	1.35	3.7	9.9	9.9	9.9	5.9		2.17, 2.12, 2.02
12[c,d]	6.30	5.08	5.25	4.04	3.84	1.24	3.7	10.3	10.3	10.3	5.9		2.15, 2.06, 2.01, 1.96
14[d]	6.27	5.07	5.43	4.86	4.02	1.20	3.6	10.3	10.3	10.3	5.9		2.17, 2.06, 2.03, 2.02
16	6.28	4.99	5.48	3.59	4.07	1.39	3.6	9.9	9.9	9.9	5.9		2.19, 2.11, 2.01

[a]In pyridine-d_5. [b]NH 8.75, $J_{NH,4}$ 10.3 Hz, NAc 2.13. [c]NH 5.51, $J_{NH,4}$ 10.3 Hz. [d]α Anomer.

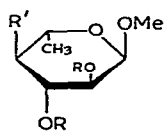
Interest in the 4-amino-4,6-dideoxy-hexose class of compounds was initially stimulated by their isolation from antibiotics and bacterial cell-walls. 4-Amino-4,6-dideoxy-D-glucose (viosamine) has been isolated from *C. violaceum*[5], and it occurs as its dimethylamino derivative (amosamine)[6] as a constituent of the antibiotic amicetin[7]. The epimeric amino sugar 4-amino-4,6-dideoxy-D-galactose (thomosamine) has been isolated from *P. pseudotuberculosis*[8], while the isolation and characterization of both 4-amino-4,6-dideoxy-D-glucose and -D-galactose from various strains of *E. coli*, linked to thymidine diphosphate[9] and as constituents of their lipopolysaccharides[10], has been reported. 4-Amino-4,6-dideoxy-D-mannose (perosamine) occurs in *V. cholerae*[11], is a component[12] of the heptaenic antibiotic perimycin[13], and was recently identified[14] as a degradation product of the new aromatic heptaenic antibiotic flavumycin A. The chemical syntheses of all eight possible 4-amino-4,6-dideoxy-D-hexoses have been reported[15,16]. In contrast, only the *manno*[17] and *talo*[18] isomers of the L-series have been prepared; the natural occurrence of the 4-amino-4,6-dideoxy-L-hexoses has not as yet been reported. In part, these data have encouraged the synthesis of a new member of this class, namely 4-amino-4,6-dideoxy-L-glucopyranose.

Hydrogenation of the 4-azide **4** with palladium-on-charcoal afforded the corresponding 4-amino derivative, which was treated further *in situ* with acetic anhydride. The resulting crystalline methyl 4-acetamido-4,6-dideoxy-α-L-glucopyranoside (**5**), isolated in 72% yield, was then converted by acetolysis into the triacetate **12**, which crystallized as the α anomer. Base-catalyzed hydrolysis of **12** with 25% methanolic ammonia afforded crystalline 4-acetamido-4,6-dideoxy-L-glucopyranose (**13**) in 75% yield.

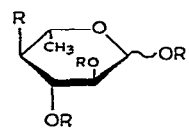
The synthesis of 6-deoxy-L-glucopyranose was of interest, as this stereoisomer of L-fucose appears to have the potential to be incorporated into cell membranes. Adopting a slight modification of the procedure of Richardson and Williams[4], the 4-mesylate **2** was readily converted, in 57% yield, into the crystalline tribenzoate **6** by treatment with sodium benzoate in hexamethylphosphoric triamide. The structure of **6** was supported by examination of the n.m.r. spectrum (Table I), which showed the H-4 resonance to lower field of the other ring protons as a triplet exhibiting a



1 R = OH
2 R = OMs



3 R = Bz, R' = N_3
4 R = H, R' = N_3
5 R = H, R' = NHAc
6 R = Bz, R' = OBz
7 R = H, R' = OH
8 R = Bz, R' = Cl
9 R = H, R' = Cl



10 R = Ac, R' = N_3
11 R = H, R' = N_3
12 R = Ac, R' = NHAc
13 R = H, R' = NHAc
14 R = Ac, R' = OAc
15 R = H, R' = OH
16 R = Ac, R' = Cl
17 R = H, R' = Cl

splitting of 9.5 Hz. Base-catalyzed hydrolysis of **6** gave crystalline methyl 6-deoxy-α-L-glucopyranoside (**7**) in 58% yield. The physical data for **7** compared well with those obtained for the D-enantiomer[19]. Acetolysis of **7** with acetic anhydride–sulfuric acid gave the crystalline tetraacetate **14** in 68% yield, the n.m.r. spectrum (Table I) of which indicated a mixture with about 10% of the β-L form present. Crystalline 6-deoxy-L-glucopyranose (**15**) was then obtained in 72% yield by base-catalyzed hydrolysis of **14** as described previously for **13**.

The synthesis of methyl 2,3-di-*O*-benzoyl-4-chloro-4,6-dideoxy-α-L-glucopyranoside (**8**), isolated as an analytically pure syrup in 67% yield, was achieved by treatment of the 2,3-dibenzoate **1** with sulfuryl chloride in pyridine. Base-catalyzed hydrolysis of **8** gave the glycoside **9**, which was readily converted into the triacetate **16** by treatment with acetic anhydride under acidic conditions. The triacetate **16**, isolated as a syrupy product in 69% yield, was shown from its n.m.r. spectrum to be a mixture of the α and β anomers in the ratio of 17:3. Base-catalyzed hydrolysis of **16** with 25% methanolic ammonia afforded crystalline 4-chloro-4,6-dideoxy-L-glucopyranose (**17**) in 51% yield.

The free compounds **11**, **13**, **15**, and **17** and the corresponding acetylated derivatives **10**, **12**, **14**, and **16** were tested for their capacities to inhibit the growth of P388 leukemia cells in culture. Although the free sugars tested lacked growth-inhibitory activity up to concentrations of 0.5mM, the acetylated derivatives tested at this concentration produced between 50 and 90% inhibition of cell growth. L-Fucose tetraacetate was also active within this concentration range, indicating little or no relationship between structure and activity.

EXPERIMENTAL

General methods. — All evaporations were performed under diminished pressure. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Hexamethylphosphoric triamide was dried in the presence of calcium hydride and then distilled under diminished pressure. Column chromatography was performed on Silica gel Merck 7734 (70–235 mesh), and all reactions were monitored by t.l.c. on Silica gel G (E. Merck A.G., Darmstadt, Germany). Petroleum ether refers to a fraction having b.p. 35–60°. Elemental analyses and optical rotations were performed by Baron Consulting Company, Orange, CT, U.S.A.

Methyl 4-azido-2,3-di-O-benzoyl-4,6-dideoxy-α-L-glucopyranoside (**3**). — To a solution of **2** (4 g) in hexamethylphosphoric triamide (50 ml) was added sodium azide (1.6 g). The reaction mixture was heated to 80° for 3 h, whereupon t.l.c. (4:1, v/v, petroleum ether–ethyl acetate) showed the reaction to be virtually complete. After cooling, the solution was diluted with ethyl acetate (200 ml) and extracted with water (2 × 100 ml). The combined aqueous layers where then re-extracted with ethyl acetate (2 × 50 ml), and the total solution was evaporated to a syrupy product.

Elution from a column of silica gel with 8:1 (v/v) petroleum ether–ethyl acetate afforded the syrupy 4-azide **3** (3 g, 82.4%), $[\alpha]_D^{25}$ −173° (*c* 1, chloroform).

Anal. Calc. for $C_{21}H_{21}N_3O_6$: C, 61.31; H, 5.11; N, 10.22. Found: C, 61.68; H, 5.44; N, 10.41.

*Methyl 4-azido-4,6-dideoxy-α-*L*-glucopyranoside* (**4**). — A saturated solution of methanolic ammonia (50 ml) was added to **3** (7 g), and the mixture was kept for 48 h at room temperature when t.l.c. (1:1, v/v, petroleum ether–ethyl acetate) indicated completion of the reaction. The solvent was evaporated to give a syrupy product, which was partitioned between petroleum ether and water. The aqueous phase was evaporated to dryness and the remaining water codistilled with ethanol. The syrupy product was crystallized from carbon tetrachloride–petroleum ether to afford **4** (2.4 g, 69.4%), m.p. 133–135°, $[\alpha]_D^{25}$ −194° (*c* 1, methanol).

Anal. Calc. for $C_7H_{13}N_3O_4$: C, 41.38; H, 6.40; N, 20.69. Found: C, 41.36; H, 6.56; N, 20.74.

*1,2,3-Tri-*O*-acetyl-4-azido-4,6-dideoxy-*L*-glucopyranose* (**10**). — A solution of **4** (0.128 g) in acetic anhydride (10 ml) containing sulfuric acid (0.2 ml) was kept for 16 h at room temperature; t.l.c. (4:1, v/v, petroleum ether–ethyl acetate) then showed one product. The mixture was diluted with chloroform (30 ml) and extracted with water (2 × 30 ml). Evaporation of the dried chloroform extract afforded a syrupy product, which was eluted from a column of silica gel with 6:1 (v/v) petroleum ether–ethyl acetate to give **5** (0.15 g, 70.4%), $[\alpha]_D^{25}$ −132° (*c* 1, chloroform).

Anal. Calc. for $C_{12}H_{17}N_3O_7$: C, 45.71; H, 5.40; N, 13.33. Found: C, 45.90; H, 5.49; N, 13.25.

*4-Azido-4,6-dideoxy-*L*-glucopyranose* (**11**). — To a solution of **10** (0.521 g) in methanol (15 ml) was added a saturated solution of methanolic ammonia (5 ml). The reaction mixture was kept for 16 h when t.l.c. (2:1, v/v, petroleum ether–ethyl acetate) showed the reaction to be complete. The mixture was evaporated, and the product was eluted from silica gel with 2:1 (v/v) petroleum ether–ethyl acetate to give **11** (0.165 g, 53%) as a crystalline product from ethyl acetate–petroleum ether, m.p. 119–120°, $[\alpha]_D^{25}$ −100° (*c* 1, water).

Anal. Calc. for $C_6H_{11}N_3O_4$: C, 38.10; H, 5.82; N, 22.22. Found: C, 38.31; H, 5.93; N, 21.98.

*Methyl 4-acetamido-4,6-dideoxy-α-*L*-glucopyranoside* (**5**). — A solution of **4** (0.257 g) in ethanol (40 ml) was hydrogenated over 10% palladium-on-charcoal at 2 bar for 1.5 h, whereupon t.l.c. (4:1, v/v, ethyl acetate–methanol) indicated a single product. The reaction mixture was filtered, and acetic anhydride (0.4 ml) was added to the filtrate; t.l.c. indicated complete reaction within 0.5 h, and the solvent was evaporated to give a syrupy product. Crystallization from ethanol–petroleum ether afforded **5** (0.2 g, 72%), m.p. 187–188.5°, $[\alpha]_D^{25}$ −169° (*c* 1, methanol); lit.[15] (D series) m.p. 188–189°, $[\alpha]_D^{25}$ +173° (*c* 0.39, water).

*4-Acetamido-1,2,3-tri-*O*-acetyl-4,6-dideoxy-α-*L*-glucopyranose* (**12**). — A solution of **5** (0.1 g) in acetic anhydride (2 ml) containing 4% (v/v) of sulfuric acid was kept for 18 h at room temperature; t.l.c. (1:1, v/v, petroleum ether–ethyl acetate)

then indicated the presence of one major product. The reaction mixture was diluted with chloroform (15 ml) and extracted with water (2 × 15 ml). The dried chloroform extract was evaporated, and the product was crystallized from ethyl acetate–petroleum ether to give **12** (0.125 g, 82.8%). Recrystallization afforded pure **12** (0.99 g, 65.6%), m.p. 147–148.5°, $[\alpha]_D^{25}$ −140° (*c* 1, chloroform); lit.[15] (D series) m.p. 149–149.5°; $[\alpha]_D^{25}$ +142° (*c* 0.895, chloroform).

*4-Acetamido-4,6-dideoxy-*L*-glucopyranose* (**13**). — Base-catalyzed hydrolysis of **12** (0.29 g) was carried out in a manner similar to that described for the preparation of **11**. The resulting product was purified by elution from a column of silica gel with 9:1 (v/v) ethyl acetate–methanol. The 4-acetamido derivative **13** (0.135 g, 75%) was obtained as a crystalline product from ethyl acetate–methanol, m.p. 192–194°, $[\alpha]_D^{25}$ −75° (*c* 1, water).

Anal. Calc. for $C_8H_{15}NO_5$: C, 46.83; H, 7.32; N, 6.83. Found: C, 46.69; H, 7.33; N, 6.76.

*Methyl 6-deoxy-α-*L*-glucopyranoside* (**7**). — Base-catalyzed hydrolysis of the tribenzoate[9] **6** (2.57 g), as described for the preparation of **4**, gave an impure crystalline product. Elution from a column of silica gel with 9:1 (v/v) ethyl acetate–methanol afforded **7** (0.53 g, 58.4%), which was obtained as a crystalline product from ethyl acetate–petroleum ether, m.p. 97–98.5°, $[\alpha]_D^{25}$ −154° (*c* 1, chloroform); lit.[19] (D series) m.p. 99°, $[\alpha]_D^{25}$ +158° (*c* 1.0, water).

*1,2,3,4-Tetra-*O*-acetyl-6-deoxy-*L*-glucopyranose* (**14**). — Acetolysis of **7** (0.25 g) under conditions similar to those described for the preparation of **10** afforded a syrupy product. Elution of this material from silica gel with 6:1 (v/v) petroleum ether–ethyl acetate gave **14** (0.318 g, 68%), which crystallized from ethanol as needles, m.p. 113–116°, $[\alpha]_D^{25}$ −115° (*c* 1 chloroform); lit. (α-L-isomer)[20] m.p. 122–124.5°, $[\alpha]_D^{23}$ −104° (*c* 1.01, chloroform); (α-D isomer)[21] m.p. 117°, $[\alpha]_D^{23}$ +122° (*c* 1.3, chloroform).

*6-Deoxy-*L*-glucopyranose* (**15**). — Base-catalyzed hydrolysis of **14** (0.316 g) under mild conditions, as described for the preparation of **11**, afforded an impure product that was fractionated on silica gel with 9:1 (v/v) ethyl acetate–methanol as eluent. Evaporation of the eluate gave **15** (0.112 g, 71.8%) as a white material that crystallized from acetone, m.p. 145–146.5°, $[\alpha]_D^{25}$ −25° (*c* 1, water; equil.); lit.[22] m.p. 143–145°, $[\alpha]_D^{25}$ −30.1° (*c* 2, water; equil.); lit.[23] m.p. 151°, $(\alpha)_D^{24}$ −30° (*c* 2, water; equil.); lit.[24] m.p. 143–146°, $[\alpha]_D^{23}$ −29.8° (*c* 5.5, water; equil.); lit.[25] m.p. 142–145°, $[\alpha]_D^{24}$ −30.2° (*c* 1.53, water; equil.).

*Methyl 2,3-di-*O*-benzoyl-4-chloro-4,6-dideoxy-α-*L*-glucopyranoside* (**8**). — To a solution of **1** (26.3 g) in pyridine (250 ml) cooled to −20° was added sulfuryl chloride (8 ml). The reaction mixture was maintained for 72 h at 0°, at which time t.l.c. (6:1, v/v, petroleum ether–ethyl acetate) indicated completion of the reaction. The mixture was then diluted with water to destroy any residual reagent, and evaporated to a small volume. This material was then evaporated, after addition of water, to remove the remaining pyridine. Elution of the product from a column of silica gel

with 15:1 (v/v) petroleum ether–ethyl acetate gave **8** (18.4 g, 67%) as a syrupy product, $[\alpha]_D^{25}$ −151° (*c* 1, chloroform).

Anal. Calc. for $C_{21}H_{21}ClO_6$: C, 62.30; H, 5.19; Cl, 8.78. Found: C, 62.16; H, 5.26; Cl, 8.67.

*Methyl 4-chloro-4-deoxy-α-*L*-glucopyranoside* (**9**). — *O*-Debenzoylation of **8** (0.8 g) was performed as described for the preparation of **4**. Column chromatography of the impure product on silica gel with 1:1 (v/v) petroleum ether–ethyl acetate as eluent afforded **9** (0.26 g, 66.8%), which was crystallized from carbon tetrachloride–petroleum ether, m.p. 87–88.5°, $[\alpha]_D^{25}$ −173° (*c* 1, chloroform).

Anal. Calc. for $C_7H_3ClO_4$: C, 42.75; H, 6.62; Cl, 18.07. Found: C, 42.99; H, 6.62; Cl, 17.87.

*1,2,3-Tri-*O*-acetyl-4-chloro-4,6-dideoxy-*L*-glucopyranose* (**16**). — Acetolysis of **9** (0.58 g) under conditions similar to those described for the preparation of **10** afforded a syrupy product. Fractionation of this material from a column of silica gel with 10:1 (v/v) petroleum ether–ethyl acetate as eluent gave **16** (0.595 g, 69%), which was obtained as fine white crystals from ethyl acetate–petroleum ether, m.p. 80–82°, $[\alpha]_D^{25}$ −76° (*c* 1, methanol).

Anal. Calc. for $C_{12}H_{17}ClO_7$: C, 46.68; H, 5.51; Cl, 11.51. Found: C, 46.41; H, 5.61; Cl, 11.85.

*4-Chloro-4,6-dideoxy-*L*-glucopyranose* (**17**). — A solution of **16** (0.411 g) in methanol (15 ml) was treated similarly to the procedure outlined for the preparation of **11**. The product was eluted from a column of silica gel with 2:1 (v/v) ethyl acetate–petroleum ether to yield **17** (0.217 g, 85%). Recrystallization from ethyl acetate–petroleum ether afforded pure **17** (0.13 g, 50.8%) m.p. 95–97°, $[\alpha]_D^{25}$ −17° (*c* 1, water; equil.).

Anal. Calc. for $C_6H_{11}ClO_4$: C, 39.45; H, 6.03; Cl, 19.45. Found: C, 39.34; H, 6.22; Cl, 19.27.

Assay of cell-culture activity. — Log-phase P388 leukemia cells were treated with each compound under test at a concentration of 0.5mM for 72 h. Cells were inoculated at an initial concentration of 10^4 cells/ml in Fischer's medium supplemented with 10% horse serum, and were incubated at 37°. At 72 h, cell numbers were determined with a Model ZBI Coulter counter.

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