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MODIFICATIONS AT C-3 AND C-4 OF 2-AMINO-2-DEOXY-D-GLUCOSE*†

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ABSTRACT

Modifications at C-3 and C-4 of 2-amino-2-deoxy-D-glucose have been developed. A 3,4-double bond was introduced into benzyl 2-acetamido-2-deoxy-3,4-di-*O*-methylsulfonyl-α-D-glucopyranoside by treatment with NaI and Zn. Epoxidation of the double bond with *m*-chloroperoxybenzoic acid gave an *exo*-epoxide exclusively. The stereochemistry of the epoxidation product has been confirmed by an alternative synthesis. An analysis of the ^{1}H-n.m.r. spectra indicates that both the 3,4-unsaturated derivatives and the epoxide exist in the $^{O}H_{1}$ (D) conformation. Nucleophilic reagents (F^-, I^-) opened the 3,4-epoxide to give 4-substituted derivatives having the D-*gulo* configuration. Thus, 2-acetamido-1,3,6-tri-*O*-acetyl-2,4-dideoxy-4-iodo-α-D-gulopyranose and 2-acetamido-1,3,6-tri-*O*-acetyl-3,4-dideoxy-4-fluoro-α-D-gulopyranose have been synthesized. Reduction of the double bond in the key intermediate and deprotection gave 2-acetamido-2,3,4-trideoxy-D-glucopyranose. Some of the derivatives were active as inhibitors of growth of mouse, mammary adenocarcinoma cells in culture.

INTRODUCTION

Analogs of 2-amino-2-deoxy-D-glucose, in which the groups at C-3 and -4 have been modified, could potentially interfere with the biosynthesis of glycoconjugates in two different ways: (a) These analogs would be incorporated into the glycoconjugate but, as OH-3 and -4 are modified, they would terminate any further chain elongation. (b) Even before being converted into the nucleotide sugars, these analogs would interfere with biosynthesis, *e.g.*, of sialic acid for which 2-amino-2-deoxy-D-glucose is a precursor.

A convenient route for the modification of OH-3 and -4 in 2-amino-2-deoxy-D-glucose appeared to be the generation of a double bond between C-3 and -4 which could be hydrogenated to give the 3,4-dideoxy analog. Alternatively, the double bond could be epoxidated, and the resulting compound could serve to introduce halogen

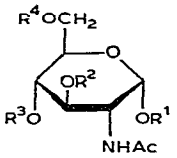
*A preliminary report has been published[1].

†This paper is dedicated in memory of the late John A. Mills.

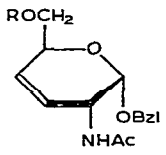
atoms by appropriate stereo- and regio-selective substitution reactions resulting in ring opening.

RESULTS AND DISCUSSION

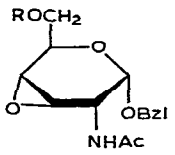
The starting material for these syntheses was benzyl 2-acetamido-2-deoxy-3,4-di-*O*-methylsulfonyl-6-*O*-trityl-α-D-glucopyranoside (**1**). For the purpose of biological testing, a sample of **1** was hydrogenolyzed to a crystalline di-*O*-mesyl derivative **2**, which was subsequently acetylated to give **3**. Treatment of **1** with sodium iodide and zinc in boiling *N*,*N*-dimethylformamide[2] yielded the unsaturated derivative **7**



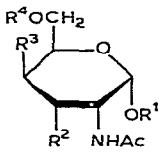
1 R^1 = Bzl, R^2 = R^3 = Ms, R^4 = Tr
2 R^1 = R^4 = H, R^2 = R^3 = Ms
3 R^1 = R^4 = Ac, R^2 = R^3 = Ms
4 R^1 = Bzl, R^2 = Ms, R^3 = R^4 = H
5 R^1 = Bzl, R^2 = Ms, R^3 = H, R^4 = Tr
6 R^1 = Bzl, R^2 = Ms, R^3 = R^4 = Ac



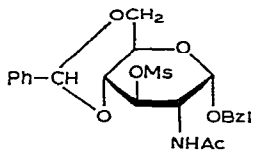
7 R = Tr
8 R = H
9 R = Ac



10 R = Tr
11 R = H
12 R = Ac



13 R^1 = R^4 = Ac, R^2 = OAc, R^3 = F
14 R^1 = Ac, R^2 = OH, R^3 = R^4 = H
15 R^1 = Bzl, R^2 = R^3 = H, R^4 = Tr
16 R^1 = Bzl, R^2 = OH, R^3 = I, R^4 = Tr
17 R^1 = R^4 = Ac, R^2 = OAc, R^3 = H
18 R^1 = R^2 = R^3 = R^4 = H
19 R^1 = R^4 = Ac, R^2 = R^3 = H
20 R^1 = Bzl, R^2 = OH, R^3 = F, R^4 = Tr
21 R^1 = Bzl, R^2 = OAc, R^3 = F, R^4 = Tr
22 R^1 = R^3 = H, R^2 = OAc, R^4 = F



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(68% yield). It should be pointed out that unless the reaction had been conducted under scrupulously dry conditions, the yield was decreased, and some detritylation took place as evidenced by the appearance of triphenylmethanol in the reaction product. The unsaturated compound **7** was hydrogenolyzed to give **18**, which was

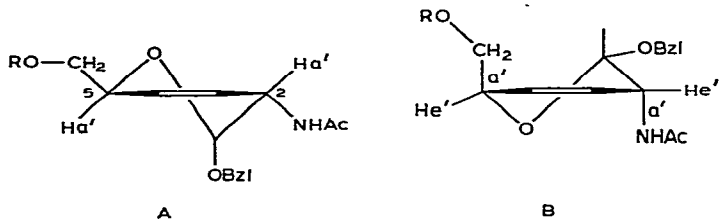
acetylated to give **19**. In addition to the usual characterization of new compounds, acetylation provided biologically lipophylic derivatives. Whereas *N*-acetyl derivatives of aminodeoxy sugars have been found to be only sparingly permeable[3], *O*-acetylation increased their lipophylicity to the extent that they were being absorbed by passive diffusion[4]. Based on earlier experiments, *O*-acetyl groups of the acetylated sugar are hydrolyzed inside the cells[4]. Any remaining *O*-acetyl derivative could potentially inhibit hexokinase, as has been shown for 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α,β-D-glucopyranose[5].

Reaction of **7** with *m*-chloroperoxybenzoic acid in dichloromethane afforded the epoxide **10** as a homogeneous, crystalline product in 82% yield. The *exo* configuration of the epoxide **10** was shown by the independent synthesis of **10** from benzyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-methylsulfonyl-α-D-glucopyranoside (**23**). Hydrolysis of the 4,6-benzylidene group of **23** gave **4**, which was then tritylated and treated with sodium methoxide. The resulting epoxide **10** was identical in all respects to that obtained by direct epoxidation. The structure of the epoxide is consistent with the ^{1}H-n.m.r. spectra of the compounds (see below).

Initially, the reason for the high stereospecificity of the epoxidation was thought to be due to the steric effect of the trityl group preventing the access of the reagent from the *endo* side. In order to test this hypothesis, **7** was detritylated with acetic acid to give **8**, and the latter compound acetylated to **9**. Both **8** and **9** were subjected to direct epoxidation, which resulted in the formation of **11** and **12** in high yield. The structure of these epoxides was ascertained by detritylation of **10** to give **11**, which was acetylated to **12**. Thus, the configuration of the products of the epoxidation reaction is not dependent on the bulk of the substituent at C-6. In studies on the epoxidation reaction with peracids of cyclic allylic hydroxyolefins, it was shown that the resulting epoxide is predominantly in *cis* position to the vicinal hydroxyl group[6]. This was explained by hydrogen bonding of the reagent with the hydroxyl group vicinal to the double bond. It is possible that an analogous hydrogen bonding with the vicinal NH of the *N*-acetyl group may affect the configuration of the products of epoxidation reactions on **7**, **8**, and **9**. In connection with the synthesis of the aforementioned 3,4-epoxide, it may be recalled that 3,4-*endo* epoxides of 2-amino-2-deoxy-D-glucose have been postulated as intermediates in some reactions[7,8]. Nevertheless, their instability due to the participation of the neighboring acetamido group has precluded their isolation[7,8].

Although n.m.r. spectroscopy and conformational aspects of 1,2- and 2,3-unsaturated pyranose derivatives have been investigated extensively, relatively little work has been reported on the 3,4-unsaturated compounds and the corresponding epoxides. The ^{1}H-n.m.r. spectrum of **7** in dimethyl sulfoxide-d_6 was analyzed, for the most part, by first order methods (see Table I). As the vinylic H-3 and H-4 are only weakly coupled to H-2 and H-5, respectively, they appeared as an AB quadruplet, which gave directly $J_{3,4}$. The doublet peaks due to H-3 (δ 5.81) are split by 1.9 Hz, which is due to coupling to H-2, as shown by decoupling experiments. Similarly, the width of the doublet due to H-4 (δ 5.59) was reduced on irradiation of H-5; a simula-

tion of the partial spectrum provided $J_{4,5}$ 0.9 Hz. Likewise, spectral simulation indicated long-range coupling constants $J_{2,4}$ and $J_{3,5}$ of the order of 1 Hz. The conformation of the molecule is discussed in terms of two half-chair forms, **A** ($^{O}H_{1}$-D) and **B** ($^{1}H_{O}$-D) (See Scheme 1). The vinyl-allylic couplings $J_{2,3}$ and $J_{4,5}$ were of



Scheme 1

considerable value in determining the conformation[9-11]; a small value indicated a torsion angle between the allylic positions, and the olefin plane is approaching 90°. Since both coupling constants are small (<5 Hz), the molecules assumes the $^{O}H_{1}$ conformation, as shown in **A**. It should also be mentioned that the long-range coupling constants were small, which further substantiates the proposed conformation[12]. In the conformation thus adopted by the 3,4-unsaturated derivative, BzlO-1 is axial, which is consistent with the preponderance of the anomeric effect in the half-chair conformers, and with the bulky substituted CH_2OH-6 being *pseudo*-equatorial[13].

The n.m.r. spectrum of the epoxide **10** was determined for a chloroform-*d* solution, and the coupling constants were established by double-irradiation experiments and by the use of europiumtris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) [Eu(fod)$_3$] shift reagent (Table I). The benzyl methylene protons appeared as an AB quadruplet in the region of the H-2 signal. The latter, on irradiation of N–H, appeared as a quadruplet, for which $J_{2,3}$ 2.4 Hz could be determined. H-5 appeared as a triplet, which is almost entirely due to its coupling to H-6, as shown by decoupling experiments on the spectrum shifted by Eu(fod)$_3$. Addition of increasing amounts of Eu(fod)$_3$ resulted in the selective shift and broadening of N-H, H-2, and methyl protons[14]. This indicates that Eu(III) is strongly coordinated with the nitrogen atom of the 2-amino-2-deoxy-D-glucose residue. The shift reagent resolved the H-3, H-4, and H-6 resonances, which moved downfield in this order (Fig. 1), and the assignments of which were established by decoupling experiments. It was observed that $J_{1,2}$ 4.90 Hz remained constant on addition of the shift reagent and, thus, it may be assumed that the conformation of **10** was not significantly affected by formation of the complex. H-4 appeared clearly as a doublet (J 4.2 Hz), but the irradiation of H-5 decreased the splitting to J 3.3 Hz, indicating a coupling of H-4 to H-5 by $J_{4,5}$ 0.9 Hz, and $J_{3,4}$ 3.3 Hz. Thus, the coupling constants of all the ring protons were established.

It may be reasonable to assume that the 3,4-epoxide **10** would assume a conformation similar to that of the unsaturated derivative **7**, although this is less evident

TABLE I

CHEMICAL SHIFTS (δ VALUES) AND MULTIPLET SPLITTINGS (Hz) FOR 3,4-UNSATURATED (**7–9**) AND 3,4-ANHYDRO (**10–12**) DERIVATIVES[a]

Compounds	*Solvent*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*CH_3 (NAc)*	*CH_3 (OAC)*	CH_2-*Ph*	*NH*
7	Me_2SO-d_6	5.02 (d) $J_{1,2}$ 3.80	4.55 (m)	5.82 (d) $J_{3,4}$ 11.50	5.58 (d) $J_{3,4}$ 11.50	4.25 (m)	3.15 (m)	1.90 (s)		4.68 (q) *J* 13.50	8.05 (d) *J* 9.50
8	Me_2SO-d_6	4.95 (d) $J_{1,2}$ 3.80	4.50 (m)	5.85 (d) $J_{3,4}$ 12.0	5.50 (d) $J_{4,3}$ 12.0	4.12 (m)	3.35 (m)	1.88 (s)		4.65 (q) *J* 13.5	7.90 (d) *J* 9.50
9	Me_2SO-d_6	4.98 (d) $J_{1,2}$ 3.9	4.50 (m) $J_{2,3}$ 1.90	5.82 (d) $J_{3,4}$ 12.0	5.58 (d) $J_{4,3}$ 12.0	4.35 (m)	4.15 (m)	1.87 (s)	2.08 (s)	4.70 (q) *J* 13.5	8.00(d) *J* 9.50
10	Me_2SO-d_6	4.75 (d) $J_{1,2}$ 4.90	4.35 (m)	3.30 (m)	3.30 (m)	3.92 (m)	3.30 (m)	1.92 (s)		4.50 (q) *J* 13.50	8.1 (d) *J* 9.50
	$CDCl_3$	4.86 (d) $J_{1,2}$ 4.90	4.57 (m) $J_{2,3}$ 2.40	3.40 (m) $J_{3,4}$ 3.30	3.35 (m) $J_{4,5} \approx 0.90$	4.08 (m)	3.35 (m)	1.99 (s)		4.58 (q) *J* 13.50	6.04 (d) *J* 9.50
11	$CDCl_3$	4.95 (d) $J_{1,2}$ 4.95	4.55 (m)	3.40 (m)	3.40 (m)	4.09 (m)	3.85 (m)	2.05 (s)		4.60 (q) *J* 13.50	6.99 (d) *J* 9.50
12	$CDCl_3$	4.85 (d) $J_{1,2}$ 4.95	4.55 (m)	3.38 (m)	3.38 (m)	4 18 (m)	4.25 (m)	1.95 (s)	2.12 (s)	4.60 (q) *J* 13.50	6.1 (d) *J* 9.50

[a]Signal multiplicities: d, doublet; m, multiplet; q, quadruplet; and s, singlet.

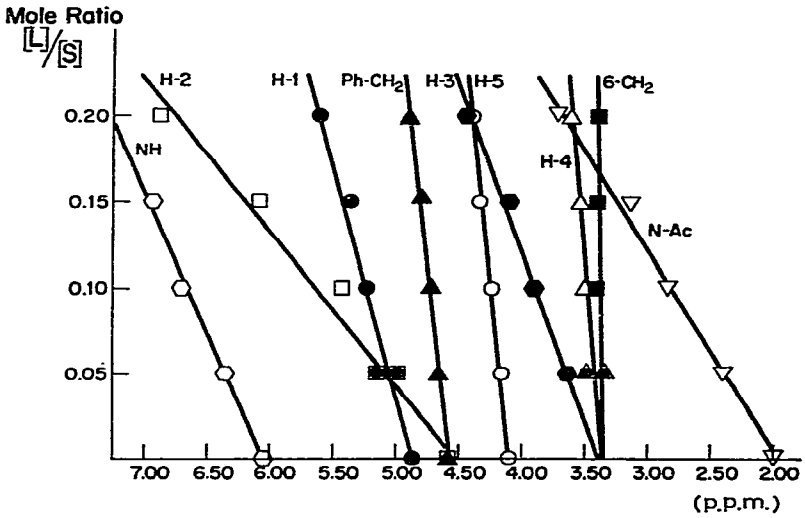


Fig. 1. The effects of addition of Eu(fod)$_3$ on the chemical shifts of **10**.

from its n.m.r. spectrum. The small value of $J_{2,3}$ is consistent with the dihedral angle approaching 90° in the $^{O}H_1$(D) conformation, and is not consistent with an angle approaching 0° in the $^{1}H_O$(D) conformation. However, the $J_{4,5}$ value of 3.3 Hz does not distinguish between a ~60° dihedral angle in the $^{1}H_O$(D), and a ~120° angle in the $^{O}H_1$(D) conformation. This evidence favors a $^{O}H_1$(D) conformation for the epoxide **10**. The higher $J_{1,2}$ value indicates an interaction between the axial BzlO-1 and the 3,4-epoxide group, causing a general flattening of the ring, and a decrease in H-1–H-2 dihedral angle. The ^{13}C-n.m.r. spectrum of the epoxide **10** showed an upfield shift of the C-1 signal as compared to that of the unsaturated derivative **7**, which could be ascribed to the steric compression due to the epoxide ring. Although a $^{O}H_1$(D) conformation was established for **7**, stereochemical and other considerations make it possible that the epoxidation proceeds *via* the $^{1}H_O$(D) or one of the boat conformations. The latter conformations would make possible a hydrogen bonding between the 2-acetamido group and the peracid reagent, and could determine the *cis* configuration to the 2-acetamido group of the product of the epoxidation reaction.

The epoxide **10** was treated with tetrabutylammonium fluoride in acetonitrile to give the fluoro derivative **20** which was isolated as the acetyl derivative **21**. The axial configuration of the fluoro group was established[15] from the *gem* coupling constant ($^{2}J_{H_4,F}$ 54 Hz) in agreement with the Fürst–Plattner rules postulating a diaxial epoxide ring-opening by nucleophiles[16], which have been shown to be applicable to carbohydrate epoxides[17]. In an analogous reaction, the epoxide **10** was treated with lithium iodide to give the iodo derivative **16**. Hydrogenolysis of **16**, followed by acetylation gave the 4-deoxy derivative **14**, which was isolated as the acetyl derivative **17**.

The compounds synthesized in this study were tested as inhibitors of growth of mouse mammary-adenocarcinoma (TA-3) cells grown in cell culture in Eagle's medium[18]. The ID_{50} value of the compounds that was greater than mM was not determined. Compounds **2**, **3**, **13**, and **17** had ID_{50} values of 60, 15, 60, and 300 μM respectively. The 2-amino-2-deoxy-D-glucose derivatives **8**, **9**, **11**, **12**, and **19** had no effect on the growth of TA-3 cells.

EXPERIMENTAL

General methods. — Melting points (uncorrected) were determined by the capillary method. I.r. spectra were recorded with a Perkin–Elmer 457 spectrophotometer, and n.m.r. spectra with a Varian A60A or Varian XL-100 instrument. The latter instrument was also used for the determination of ^{13}C-n.m.r. spectra. Positions of the peaks are expressed in δ from the signal of tetramethylsilane as an internal standard. Optical rotations were determined with a Perkin–Elmer 141 polarimeter. Thin-layer chromatograms were obtained on Merck MF-254 silica gel plates, the spots being detected by u.v. absorption or by spraying with a sulfuric acid solution.

*Benzyl 2-acetamido-2-deoxy-3,4-di-*O*-methylsulfonyl-6-*O*-trityl-α-*D*-glucopyranoside* (**1**). — A solution of benzyl 2-acetamido-2-deoxy-6-*O*-trityl-α-D-glucopyranoside[19] (3.7 g) in dry pyridine (30 mL) was treated with a solution of methanesulfonyl chloride (2.61 g) in dry pyridine (5 mL) at 0°. The mixture was kept overnight at 0–5°. It was poured into ice–water, and the crystalline solid product was filtered off, washed with water, dried, and recrystallized from methanol (4.4 g, 88%), m.p. 128–130°, $[\alpha]_D^{22}$ +71.4° (*c* 1, chloroform); ν_{max}^{KBr} 3310 (NH), 1675 (amide C=O), 1350 SO_2), 1180 (SO_2), and 700 cm^{-1} (aromatic); ^{1}H-n.m.r. ($CDCl_3$): δ 2.15 (s, 3 H), 2.6 (s, 3 H), 3.5 (s, 3 H), 4.7 (q, 2 H, *J* 14 Hz), 5.5 (d, 1 H, *J* 3.5 Hz), 6.25 (d, 1 H, *J* 10 Hz), and 7.4 (m, 2 OH); ^{13}C-n.m.r. ($CDCl_3$): δ 170.4 (C=O), 143.3 (q, Ph of Tr), 136.3 (q, Ph of Bzl), 127.3–128.9 (aromatic), 96.3 (C-1), 87.1 (q, Tr), 77.6 (C-3), 74.7 (C-4), 70.1 (C-5), 69.5 (benzylic CH_2), 62.2 (C-6), 51.9 (C-2), 38.9, 38.6 (CH_3 of mesyl), and 23.2 (CH_3 of NAc).

Anal. Calc. for $C_{36}H_{39}NO_{10}S_2 \cdot H_2O$: C, 59.41; H, 5.64; N, 1.92; S, 8.80. Found: C, 59.71; H, 5.97; N, 1.74; S, 8.95.

*2-Acetamido-2-deoxy-3,4-di-*O*-methylsulfonyl-α-*D*-glucopyranose* (**2**). — A suspension of **1** (1.2 g) in acetic acid (35 mL) was hydrogenolyzed in the presence of palladium-on-charcoal (0.5 g, 10%) for 48 h. The suspension was filtered, and the filtrate evaporated. The colorless, crystalline product was recrystallized from methanol–ether (500 mg, 78.6%), m.p. 180–181°, $[\alpha]_D^{22}$ +45.4° (*c* 1, methanol); ν_{max}^{KBr} 3500 (OH), 3300 (NH), 1650 (amide CO), 1350 (SO_2), and 1170 cm^{-1} (SO_2); ^{1}H-n.m.r. (Me_2SO-d_6): δ 1.85 (s, 3 H), 3.20 (s, 3 H, OMs), 3.31 (s, 3 H, OMs), and 8.05 (d, 1 H, *J* 10 Hz).

Anal. Calc. for $C_{10}H_{19}NO_{10}S_2$: C, 31.88; H, 5.04; N, 3.71; S, 16.97. Found: C, 31.93; H, 5.17; N, 3.97; S, 17.09.

*2-Acetamido-1,6-di-*O*-acetyl-2-deoxy-3,4-di-*O*-methylsulfonyl-α-*D*-glucopyranose*

(3). — A solution of **2** (150 mg) in dry pyridine (7 mL) was acetylated with acetic anhydride (3 mL). After isolation, the product crystallized from methanol–ether (170 mg, 92%), m.p. 165° (dec.), $[\alpha]_D^{25}$ +86.4° (*c* 1, chloroform); ν_{max}^{KBr} 3300 (NH), 1755 (CO), 1660 and 1540 (amide CO), 1350 and 1180 cm^{-1} (SO_2); ^{1}H-n.m.r. (Me_2SO-d_6): δ 1.85 (s, 3 H), 2.01 (s, 3 H), 2.20 (s, 3 H), 3.29 (s, 3 H, OMs), 3.34 (s, 3 H, OMs), 5.89 (d, 1 H, 3.5 Hz), and 8.20 (d, 1 H, *J* 10 Hz).

Anal. Calc. for $C_{10}H_{19}NO_{10}S_2$: C, 36.44; H, 5.02; N, 3.04; S, 13.88. Found: C, 36.55; H, 5.24; N, 3.12; S, 13.62.

*Benzyl 2-acetamido-2,3,4-trideoxy-6-*O*-trityl-α-*D*-erythro-hex-3-enopyranoside* (**7**). — Compound **1** (3.5 g) in dry *N*,*N*-dimethylformamide (70 mL) was heated under reflux with a mixture of anhydrous sodium iodide (25 g) and zinc dust (15 g) with stirring for 2.5 h. The reaction mixture was poured into a beaker, allowed to cool, and then diluted with chloroform. Lumps of zinc were broken up, filtered off, and washed with *N*,*N*-dimethylformamide and then with chloroform. The filtrate was evaporated to dryness *in vacuo* and the residue was taken up in ethyl acetate, and the solution washed with water, dried (Na_2SO_4), and then evaporated. Compound **7** was crystallized from methanol (1.7 g, 68%), m.p. 166–167°, $[\alpha]_D^{22}$ −10.4° (*c* 1, chloroform); t.l.c. (ethyl acetate): R_F 0.7; ν_{max}^{KBr} 3290 (NH), 1640 and 1545 (amide CO), and 710 cm^{-1} (aromatic); ^{1}H-n.m.r. ($CDCl_3$): δ 1.9 (s, 3 H), 4.7 (q, 2 H, *J* 14 Hz), 5.05 (d, 1 H, *J* 4.5 Hz), 5.7 (q, broad, 2 H, *J* 12 Hz), and 7.35 (m, 20 H); ^{13}C-n.m.r. ($CDCl_3$): δ 169.3 (CO), 143.3 [q, $(C_6H_5)_3CH$], 137.2 (q, $C_6H_5CH_2$), 128.4–126.8 (aromatic), 124.7 (olefinic), 94.8 (C-1), 86.5 (q, Tr), 69.6 (CH_2Ph), 67.7 (C-5), 65.8 (C-6), 45.4 (C-2), and 23.2 (CH_3).

Anal. Calc. for $C_{33}H_{33}NO_4$: C, 78.08; H, 6.55; N, 2.76. Found: C, 78.33; H, 6.59; N, 2.51.

*Benzyl 2-acetamido-3,4-anhydro-2-deoxy-6-*O*-trityl-α-*D*-allopyranoside* (**10**). — *From* **7**. To a stirred and cooled (0°) solution of **7** (2.5 g) in dry dichloromethane (30 mL) was added a solution of 3-chloroperoxybenzoic acid (4 g) in dry dichloromethane (40 mL). Stirring was continued for 24 h at room temperature. Anhydrous sodium carbonate (2 g) was added and the stirring continued for another 15 min. The suspension was filtered, and the dichloromethane solution was washed with a solution of sodium carbonate, then water, dried (Na_2SO_4), and evaporated. The residue was a clear, thick syrup that crystallized from ether; it was recrystallized from chloroform–ether (2.10 g, 81.7%), m.p. 198–199°, $[\alpha]_D^{22}$ +24.8° (*c* 1, chloroform); ν_{max}^{KBr} 3220 (NH), 1635 and 1540 (amide CO), and 705 cm^{-1} (aromatic); ^{1}H-n.m.r. ($CDCl_3$): δ 2.00 (s, 3 H), 4.55 (q, 2 H, *J* 14 Hz), 4.85 (d, 1 H, *J* 5 Hz), and 6.1 (d, 1 H, *J* 9 Hz); ^{13}C-n.m.r. ($CDCl_3$): δ 170.1 (CO), 143.7 [q, $(C_6H_5)_3CH$], 137.1 (q, $C_6H_5CH_2$), 128.7–127.2 (aromatic), 94.4 (C-1), 86.9 (q, Tr), 70.3 ($C_6H_5CH_2$), 67.1 (C-5), 64.0 (C-6), 54.9 (C-3), 50.9 (C-4), 46.2 (C-2), and 23.2 (CH_3).

Anal. Calc. for $C_{33}H_{33}NO_5$: C, 75.70; H, 6.35; N, 2.67. Found: C, 75.99; H, 6.39; N, 2.58.

From **5**. Compound **5** (620 mg) was dissolved in anhydrous methanol (10 mL) containing sodium methoxide (prepared from sodium, 50 mg), and the solution

was heated for 1 h at 60–65°. The white precipitate was filtered off, washed with cold methanol, and recrystallized from chloroform–ether (502 mg, 95%), m.p. 197–198°, $[\alpha]_D^{25}$ +22.8° (*c* 1, chloroform). This compound was identical with that obtained from **4** by the epoxidation reaction by mixed m.p., and i.r. and ^{1}H-n.m.r. spectra.

Hydrolysis of **10**. — The anhydride **10** (260 mg) was heated in acetic acid at 90–95°, and water (1 mL) was added dropwise. The mixture was stirred at that temperature for 1 h. The solution was diluted with water and extracted with ethyl acetate. The extract was washed once with water, dried (Na_2SO_4), and evaporated. The residue was freed from acetic acid by co-distillation with toluene. Triphenylmethanol was removed by washing with ether. The semisolid residue crystallized slowly from chloroform–pet. ether (75 mg, 51%), m.p. 110–111° alone or in admixture with **11**, $[\alpha]_D^{25}$ +66.8° (*c* 1, chloroform).

A sample was acetylated with acetic anhydride and pyridine. The product isolated was identical with **12**, on the basis of mixed m.p. (155–156°), $[\alpha]_D^{25}$ +222.7° (*c* 1, chloroform).

*Benzyl 2-acetamido-2-deoxy-3-*O*-methylsulfonyl-α-*D*-glucopyranoside* (**4**). — A solution of **23** (ref. 20, 2 g) in acetic acid (32 mL) was heated to 90°; 20 mL of water was slowly added with stirring which was continued for 1 h. After removal of the solvent *in vacuo*, the residue was chromatographed on a column of silica gel. Benzaldehyde was eluted with ether, and the product with 9 : 1 (v/v) chloroform–methanol. Evaporation of the solvent gave an amorphous solid (1.2 g, 75%), m.p. 72–75°, $[\alpha]_D^{25}$ +110.2° (*c* 1, chloroform); ν_{max}^{KBr} 3300, 3550 (broad, OH and NH), 1660 and 1535 (amide CO), 1350 and 1175 (SO_2), and 700 cm^{-1} (aromatic); ^{1}H-n.m.r. ($CDCl_3$): δ 1.95 (s, 3 H), 3.1 (s, 3 H), 4.55 (q, 2 H, *J* 14 Hz), 4.95 (d, 1 H, *J* 3.5 Hz), 6.00 (d broad, *J* 10 Hz), and 7.35 (s, 5 H).

Anal. Calc. for $C_{16}H_{23}NO_8S$: C, 49.36; H, 5.95; N, 3.60; S, 8.22. Found: C, 49.23; H, 6.10; N, 3.43; S, 8.26.

*Benzyl 2-acetamido-2-deoxy-3-*O*-methylsulfonyl-6-*O*-trityl-α-*D*-glucopyranoside* (**5**). — A solution containing **4** (1.4 g) and chlorotriphenylmethane (1.35 g) in anhydrous pyridine (17 mL) was stirred for 48 h at room temperature, and then the temperature was raised to 90–95° for 90 min. After being cooled, the reaction mixture was poured into ice–water, the semisolid material was washed with water, and then dissolved in chloroform. The chloroform solution was washed with water, dried (Na_2SO_4), and evaporated. The residue was washed with ether to remove triphenylmethanol, and finally crystallized from ethyl acetate–pet. ether (1.9 g, 86%), m.p. 176–7°, $[\alpha]_D^{25}$ +61.6° (*c* 1, chloroform); ν_{max}^{KBr} 3460 (OH), 3285 (NH), 1650 and 1550 (amide CO), 1350 and 1180 (SO_2), and 705 cm^{-1} (aromatic); ^{1}H-n.m.r. ($CDCl_3$): δ 1.95 (s, 3 H), 3.05 (s, 3 H), 4.55 (q, 2 H, *J* 14 Hz), 4.95 (d, 1 H, *J* 4 Hz), 5.85 (d broad, *J* 10 Hz), and 7.35 (m, aromatic).

Anal. Calc. for $C_{35}H_{37}NO_8S$: C, 66.55; H, 5.90; N, 2.22; S, 5.06. Found: C, 66.64; H, 6.08; N, 2.25; S, 5.30.

*Benzyl 2-acetamido-4,5-di-*O*-acetyl-2-deoxy-3-*O*-methylsulfonyl-α-*D*-glucopyranoside* (**6**). — Acetylation of **5** (200 mg) with acetic anhydride (2 mL) in dry pyridine

(6 mL), and the usual processing gave a product that crystallized from acetone–ether (220 mg, 88%), m.p. 127–128°, $[\alpha]_D^{25}$ +100.4° (*c* 1, chloroform); ν_{max}^{KBr} 3300 (NH), 1700 (CO), 1645 and 1530 (amide CO), 1350 and 1180 (SO_2), and 700 cm^{-1} (aromatic); ^{1}H-n.m.r. ($CDCl_3$): δ 1.98 (s, 3 H), 2.15 (s, 6 H), 2.98 (s, 3 H), 4.6 (q, 2 H, *J* 14 Hz), 4.98 (d, 1 H, *J* 3.5 Hz), 5.8 (d broad, *J* 10 Hz), and 7.35 (s, 5 H).

Anal. Calc. for $C_{20}H_{27}NO_{10}S$: C, 50.74; H, 5.70; N, 2.95. Found: C, 50.75; H, 5.69; N, 2.90.

*2-Acetamido-1,3,6-tri-*O*-acetyl-2,4-dideoxy-*α*-*D*-gulopyranose* (**17**). — *From* **10**. Compound **10** (500 mg) was hydrogenolyzed in acetic acid (20 mL) in the presence of Pd-on-charcoal (500 mg, 10%). The uptake of hydrogen ceased after 24 h. After the usual processing, the product obtained was a very hygroscopic solid. Triphenylmethane was removed by repeated washing with ether to yield an amorphous product (170 mg, 87%), ν_{max}^{KBr} 3600–3200 (OH and NH), and 1650 cm^{-1} (amide CO). The product was acetylated with acetic anhydride (2 mL) in pyridine (7 mL) under standard conditions to give crystalline **17** (120 mg, 76%), m.p. 160–161°, $[\alpha]_D^{25}$ +58° (*c* 1, chloroform): ν_{max}^{KBr} 3280 (NH), 1740 (CO), 1640 and 1550 cm^{-1} (amide CO).

Anal. Calc. for $C_{14}H_{21}NO_8$: C, 50.75; H, 6.39; N, 4.23. Found: C, 50.86; H, 6.26; N, 4.49.

From **16**. The iodo compound **16** (500 mg) was hydrogenolyzed in acetic acid (20 mL) in the presence of palladium-on-charcoal (400 mg, 10%) for 24 h. After the usual processing, the product was isolated as a very hygroscopic solid (180 mg); ν_{max}^{KBr} 3600–3200 (broad, OH and NH), 1650 cm^{-1} (amide), and absence of aromatic stretching. Compound **14** (180 mg) was acetylated with acetic anhydride (2 mL) in dry pyridine (7 mL) overnight, at room temperature. The excess of acetic anhydride was decomposed with ice–water, and the solution was evaporated to dryness. The residue crystallized on trituration with ether, and was recrystallized from ethanol–ether (210 mg, 87%), m.p. 160–161°, $[\alpha]_D^{22}$ +58.6° (*c* 1, chloroform); i.r. and n.m.r. spectra were identical with those of the compound obtained from **10**.

*Benzyl 2-acetamido-2,3,4-trideoxy-6-*O*-trityl-*α*-*D*-glucopyranoside* (**15**). — The olefinic compound **7** (200 mg) was hydrogenated in ethanol–ethyl acetate in the presence of palladium-on-charcoal (50 mg, 5%). The uptake of hydrogen stopped after 8 h. After the usual processing, the colorless solid was recrystallized from chloroform–pet. ether, (180 mg, 90%), m.p. 177–178°, $[\alpha]_D^{22}$ +57.7° (*c* 1, chloroform); ν_{max}^{KBr} 3290 (NH), 1630 and 1540 (amide CO), and 705 cm^{-1} (aromatic); ^{1}H-n.m.r. ($CDCl_3$): δ 1.85 (s, 3 H), 4.7 (q, 2 H, *J* 15 Hz), 7.5 (d broad, 1 H, *J* 10 Hz, NH), and 7.3 (m, 20 H, aromatic).

Anal. Calc. for $C_{33}H_{35}NO_4$: C, 77.77; H, 6.92; N, 2.75. Found: C, 77.50; H, 7.02; N, 2.60.

*Benzyl 2-acetamido-2,4-dideoxy-4-iodo-6-*O*-trityl-*α*-*D*-gulopyranoside* (**16**). — A solution of **10** (1.15 g) in dry acetone was heated under reflux with lithium iodide (10 g) for 6 h. The solvent was evaporated, the residual, light-yellow thick syrup was taken up in chloroform, and the solution was washed with water, dried (Na_2SO_4), and evaporated. The residue, a thick syrup, crystallized from ether and was re-

crystallized from acetone–ether (1.5 g, 83%), m.p. 210–211°, $[\alpha]_D^{22}$ +60.5° (*c* 1, chloroform); ν_{max}^{KBr} 3220 (NH), 1640 and 1545 (amide CO), and 700 cm^{-1} (aromatic).

Anal. Calc. for $C_{34}H_{34}INO_5$: C, 61.69; H, 5.01; I, 19.15; N, 2.11. Found: C, 61.80; H, 5.34; I, 19.35; N, 2.15.

*2-Acetamido-1,6-di-*O*-acetyl-2,3,4-trideoxy-α-*D*-glucopyranose* (**19**). — A solution of **7** (250 mg) in acetic acid (50 mL) was hydrogenolyzed in the presence of palladium-on-charcoal (1 g, 10%) for 36 h. After the usual processing, the semisolid residue was freed from triphenylmethane by washing with ether. The product (**18**) crystallized slowly from ethyl acetate (600 mg, 68%), m.p. 101–102°, $[\alpha]_D^{22}$ +54° (*c* 1, methanol); ν_{max}^{KBr} 3400 (OH), 3250 (NH), 1650 and 1550 cm^{-1} (amide CO). It was too hygroscopic to be analyzed, and part of it (300 mg) was acetylated overnight with acetic anhydride and dry pyridine. The solution was diluted with ice–water and evaporated to dryness. The residue was freed from pyridine by codistillation with toluene and solidified by trituration with ether. It crystallized from ethanol–ether as clusters of needles (350 mg, 81%), m.p. 93–94°, $[\alpha]_D^{22}$ +117.5° (*c* 1, chloroform); ν_{max}^{KBr} 3300, (NH), 1735 (CO), 1640 and 1535 cm^{-1} (amide CO).

Anal. Calc. for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 53.03; H, 7.11; N, 4.97.

*Benzyl 2-acetamido-3-*O*-acetyl-2,4-dideoxy-4-fluoro-6-*O*-trityl-α-*D*-gulopyranoside* (**21**). — A solution of the epoxide **10** (1.0 g) and tetrabutylammonium fluoride (7.0 g) in dry acetonitrile (70 mL) was heated under reflux for 24 h. The solution was evaporated to dryness. The residue was dissolved in dry pyridine (70 mL) and acetic anhydride (15 mL) added. The mixture was kept overnight at room temperature, and then poured into ice–water and extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue was freed from pyridine by codistillation with toluene, and chromatographed on a column of silica gel. The product was eluted with chloroform and crystallized from chloroform–ether (750 mg, 65.7%), m.p. 184–185°, $[\alpha]_D^{25}$ +92.4° (*c* 1, chloroform); ν_{max}^{KBr} 3300 (NH), 1750 (CO), 1660 and 1550 (amide CO), and 710 cm^{-1} (aromatic); ^{1}H-n.m.r. ($CDCl_3$): δ 1.80 (s, 3 H, NAc), 2.05 (s, 3 H, OAc), 4.70 (q, 2 H, *J* 14 Hz), 5.05 (d, 1 H, *J* 4 Hz, H-1), 5.75 (d, 1 H, *J* 10 Hz, NH), and 7.35 (m, 20 H, aromatic); ^{19}F-n.m.r.: ($CDCl_3$–$CFCl_3$): δ −188.2 (q, J_{F,H_4} 54 Hz).

Anal. Calc. for $C_{36}H_{36}FNO_6$: C, 72.36; H, 6.03; F, 3.18; N, 2.34. Found: C, 72.33; H, 6.21; F, 3.38; N, 2.42.

*2-Acetamido-3-*O*-acetyl-2,4-dideoxy-4-fluoro-*D*-gulose* (**22**). — A solution of **21** (475 mg) in acetic acid (25 mL) was hydrogenolyzed in the presence of palladium-on-charcoal (10%, 400 mg) for 48 h. The mixture was filtered and the solvent evaporated to afford a semisolid product. Triphenylmethane was removed by washing the product with ether. The residue was a hygroscopic, waxy solid (188 mg, 83%), $[\alpha]_D^{22}$ +49.1° (*c* 1, methanol); ν_{max}^{KBr} 3500–3200 (OH and NH), 1700 (CO), and 1650 cm^{-1} (amide CO).

A portion of **22** (200 mg) was acetylated with acetic anhydride (2 mL) in pyridine (7 mL) overnight. The product (**13**) was crystallized from ether, and then

recrystallized from chloroform–pet. ether (205 mg, 78%), m.p. 80°, $[\alpha]_D^{22}$ +84.2° (*c* 1, chloroform); ν_{max}^{KBr} 3300 (NH), 1760 (CO), 1650 and 1545 cm^{-1} (amide CO).

Anal. Calc. for $C_{14}H_{20}FNO_8$: C, 48.12; H, 5.73; F, 5.44; N, 4.00. Found: C, 48.20; H, 5.84; F, 5.29; N, 3.84.

*Benzyl 2-acetamido-2,3,4-trideoxy-α-*D-erythro-*hex-3-enopyranoside* (**8**). — To a solution of **7** (600 mg) in acetic acid (10 mL) at 95° was added water with stirring, and the solution was stirred for 2 h. It was then cooled, poured into water, and filtered from triphenylmethanol. The filtrate was evaporated to dryness, and the residue was freed from acetic acid by codistillation with toluene and then crystallized from ether–methanol (285 mg, 87%), m.p. 150°, $[\alpha]_D^{22}$ +255° (*c* 0.5, chloroform); ν_{max}^{KBr} 3400 (OH), 3300 (NH), 1650 and 1550 (amide CO), and 700 cm^{-1} (aromatic); ^{1}H-n.m.r. (Me_2SO-d_6): δ 1.95 (s, 3 H, NAc), 4.65 (q, 2 H, *J* 14 Hz), 4.95 (d, 1 H, *J* 4 Hz), 5.68 (q, 2 H, *J* 12 Hz, olefinic), 7.35 (s, 5 H), and 7.9 (d, 1 H, *J* 10 Hz, AcNH).

Anal. Calc. for $C_{15}H_{19}NO_4$: C, 64.95; H, 6.92; N, 5.05. Found: C, 64.90; H, 6.80; N, 4.88.

*Benzyl 2-acetamido-6-*O*-acetyl-2,3,4-trideoxy-α-*D-erythro-*hex-3-enopyranoside* (**9**). — The unsaturated compound **8** (200 mg) was acetylated overnight with acetic anhydride and pyridine. The reaction mixture was poured into ice–water and evaporated to dryness. The product was crystallized from chloroform–pet. ether (200 mg, 86.9%), m.p. 111–112°, $[\alpha]_D^{22}$ +194° (*c* 1, chloroform); ν_{max}^{KBr} 3290 (NH), 1640 (CO), 1650 and 1550 (amide CO), and 720 cm^{-1} (aromatic); ^{1}H-n.m.r. (Me_2SO-d_6): δ 1.95 (s, 3 H, CH_3), 2.1 (s, 3 H, OAc), 4.7 (q, 2 H, *J* 14 Hz), 5.05 (d, 1 H, *J* 4 Hz), 5.7 (q, 2 H, *J* 12 Hz), and 7.35 (s, 5 H, aromatic).

Anal. Calc. for $C_{17}H_{21}NO_5$: C, 63.92; H, 6.64; N, 4.39. Found: C, 63.75; H, 6.64; N, 4.19.

*Benzyl 2-acetamido-3,4-anhydro-2-deoxy-α-*D*-allopyranoside* (**11**). — A solution of 3-chloroperoxybenzoic acid (400 mg) in dichloromethane (5 mL) was added to a solution of **9** (200 mg) in dichloromethane (5 mL) at 0°. The reaction mixture was stirred for 24 h at room temperature. Sodium carbonate (500 mg) was added at the end of the reaction and, after being stirred for 15 min, the reaction mixture was filtered. The filtrate was washed with a solution of sodium carbonate, then water, and dried (Na_2SO_4). On evaporation of the solvent, the product crystallized from chloroform–pet. ether (195 mg, 92%), m.p. 114°, $[\alpha]_D^{25}$ +68.8° (*c* 1, chloroform); ν_{max}^{KBr} 3480 (OH), 3300 (NH), 1640 and 1545 (amide CO), and 700 cm^{-1} (aromatic); ^{1}H-n.m.r. ($CDCl_3$): δ 1.95 (s, 3 H, CH_3), 4.62 (q, 2 H, *J* 14 Hz), 4.75 (d, 1 H, *J* 4 Hz), 7.35 (s, 5 H, aromatic), and 8.1 (d, 1 H, *J* 10 Hz).

Anal. Calc. for $C_{15}H_{19}NO_5$: C, 61.41; H, 6.54; N, 4.78. Found: C, 61.32; H, 6.48; N, 4.74.

*Benzyl 2-acetamido-6-*O*-acetyl-3,4-anhydro-2-deoxy-α-*D*-allopyranoside* (**12**). — *From* **11**. Compound **11** (200 mg) was acetylated with acetic anhydride (2 mL) in dry pyridine (6 mL) overnight at room temperature. After the usual processing, the product crystallized from chloroform–pet. ether (185 mg, 81%), m.p. 155–156°, $[\alpha]_D^{22}$ +224° (*c* 1, chloroform); ν_{max}^{KBr} 3310 (NH), 1730 (CO), 1640 and 1545 (amide

CO), and 700 cm^{-1} (aromatic); ^{1}H-n.m.r. ($CDCl_3$): δ 1.97 (s, 3 H CH_3), 2.12 (s, 3 H), 3.4 (broad s, 2 H), 4.55 (q, 2 H, J 14 Hz), 4.85 (d, 1 H, J 4 Hz), 6.1 (d, 1 H, J 10 Hz), and 7.32 (s, 5 H).

Anal. Calc. for $C_{17}H_{21}NO_6$: C, 60.88; H, 6.32; N, 4.18. Found: C, 60.68; H, 6.24; N, 4.05.

From **9**. A solution of **9** (510 mg) in dichloromethane (10 mL) was treated with a solution of 3-chloroperoxybenzoic acid (1.4 g) in dichloromethane (10 mL) at 0°. The mixture was stirred at room temperature for 22 h. Anhydrous sodium carbonate (1 g) was added, stirred for 15 min, and filtered off. The filtrate was washed with a solution of sodium carbonate, then water, dried (Na_2SO_4), and evaporated. The residue was a crystalline solid that was recrystallized from chloroform–pet. ether, (480 mg, 89%), m.p. 155–156°, alone or in admixture with the compound prepared from **11**.

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