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SYNTHESIS OF 2-ACETAMIDO-5-AMINO-2,5-DIDEOXY-D-GLUCO- AND -L-IDO-PYRANOSE DERIVATIVES*

AKIRA HASEGAWA, EIJI TANAHASHI, AND MAKOTO KISO
Department of Agricultural Chemistry, Gifu University, Kakamigahara, Gifu 504 (Japan)
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ABSTRACT

Methyl 2-acetamido-5,6-anhydro-2-deoxy-α-L-idofuranoside (**6**) was prepared from 2-acetamido-2-deoxy-D-glucose in six steps. Opening of the epoxide ring in the 3-(tetrahydropyran-2-yl) ether of **6** with aqueous sodium hydroxide gave methyl 2-acetamido-2-deoxy-3-*O*-(tetrahydropyran-2-yl)-α-L-idofuranoside (**8**). Tritylation of **8**, followed by 5-*O*-mesylation, gave methyl 2-acetamido-2-deoxy-5-*O*-mesyl-3-*O*-(tetrahydropyran-2-yl)-6-*O*-trityl-α-L-idofuranoside, which was converted, *via* partial hydrolysis and subsequent tritylation, into methyl 2-acetamido-2-deoxy-5-*O*-mesyl-6-*O*-trityl-α-L-idofuranoside (**12**). Tritylation of methyl 2-acetamido-3-*O*-benzoyl-2-deoxy-β-D-glucofuranoside, followed by 5-*O*-mesylation, afforded methyl 2-acetamido-3-*O*-benzoyl-2-deoxy-5-*O*-mesyl-6-*O*-trityl-β-D-glucofuranoside which was debenzoylated to compound **5** by alkaline treatment. Treatment of compounds **12** and **5** with sodium azide gave the 5-azido derivatives **13** and **15**, respectively, which were characterized as their *N*-acetyl-di-*O*-acetyl derivatives, **14** and **16**. Mild, acid hydrolysis of **14** and **16**, followed by acetylation, afforded the 2-acetamido-1,3,6-tri-*O*-acetyl-5-azido-2,5-dideoxy-D-gluco- and -L-ido-furanose derivatives **17** and **20**, respectively; these were converted, *via O*-deacetylation, *O*-(tetrahydropyran-2-yl)ation, and reduction, into the corresponding 5-amino derivatives **19** and **22**. When treated with sulfur dioxide in 1,4-dioxane–water, compounds **19** and **22** respectively yielded the title compounds. Evidence in support of the structures assigned to the new derivatives is presented.

INTRODUCTION

Hetero sugars, in which the ring-oxygen atom of normal sugars is replaced by such atoms as nitrogen or sulfur, are interesting, not only from the point of view of the chemistry involved, but also for their various, biological activities[2,3]. Our interest has been directed toward the synthesis of a variety of hetero sugars having an acetamido group on C-2 of aldoses. In previous papers[1,4] in this series, we described the synthesis of 2-acetamido-2-deoxy-5-thio-D-glucopyranose and 2-acetamido-5-amino-2,5-dideoxy-D-xylopyranose, starting from methyl 2-acetamido-2-deoxy-5,6-

*Studies on Hetero Sugars, Part V. For Part IV, see ref. 1.

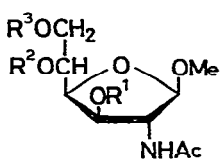
O-isopropylidene-β-D-glucofuranoside[6] (prepared from 2-acetamido-2-deoxy-D-glucose in one step). In continuation of these studies, we now describe the synthesis of 2-acetamido-5-amino-2,5-dideoxy-D-gluco- and -L-ido-pyranose derivatives.

RESULTS AND DISCUSSION

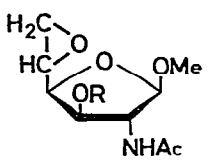
Methyl 2-acetamido-3,6-di-*O*-benzoyl-2-deoxy-5-*O*-mesyl-β-D-glucofuranoside[4] (**2**), prepared from methyl 2-acetamido-2-deoxy-5,6-*O*-isopropylidene-β-D-glucofuranoside[6] in four steps, served as a convenient starting-material for the synthesis of 2,5-diamino-2,5-dideoxy-D-glucose derivatives. Compound **2** in dry chloroform was treated with methanolic sodium methoxide at $-10 \pm 5°$, to give methyl 2-acetamido-5,6-anhydro-2-deoxy-α-L-idofuranoside (**6**) in almost quantitative yield. Compound **6** was treated with dihydropyran, to afford the 3-*O*-(tetrahydropyran-2-yl) derivative (**7**). Hydrolysis of the epoxide ring in **7** under mild, alkaline conditions gave methyl 2-acetamido-2-deoxy-3-*O*-(tetrahydropyran-2-yl)-α-L-idofuranoside (**8**) in good yield; the reaction did not involve inversion of C-5, because of predominant attack[7] at C-6 in **7** by hydroxyl ion.

Tritylation of **8** gave the 6-*O*-trityl derivative **9**, which was treated with methanesulfonyl chloride to afford the 5-*O*-mesyl derivative **10**. Attempts to displace the 5-*O*-mesylate group in **10** with sodium azide in boiling *N*,*N*-dimethylformamide gave only a low yield of the desired azide, and the starting material was recovered, presumably due to the steric hindrance of the substituents at C-1 and C-3 in **10** toward bimolecular, nucleophilic displacement. Partial hydrolysis of **10** with aqueous acetic acid, and subsequent 6-*O*-tritylation, gave methyl 2-acetamido-2-deoxy-5-*O*-mesyl-6-*O*-trityl-α-L-idofuranoside (**12**), which readily exchanged the mesyloxyl group on being heated at 120–125° with sodium azide in *N*,*N*-dimethylformamide, to form methyl 2-acetamido-5-azido-2,5-dideoxy-6-*O*-trityl-β-D-glucofuranoside (**13**). Hydrolysis of the trityl group in compound **13**, and subsequent acetylation, afforded the diacetate **14**. The structure of **14** was assigned on the basis of elemental analysis and n.m.r. data. The n.m.r. spectrum of **14** exhibited three sharp singlets, each integrating for three protons, at δ 2.00, 2.10, and 2.12, which demonstrated the presence of one *N*-acetyl and two *O*-acetyl groups; H-1 appeared at δ 4.89 (1.5 Hz) as a doublet, and H-3 as a doublet of doublets at δ 5.37 ($J_{2,3}$ 1.3, $J_{3,4}$ 5.0 Hz), indicating structure **14**.

On the other hand, methyl 2-acetamido-3-*O*-benzoyl-2-deoxy-β-D-glucofuranoside[4] (**1**) was used as the starting material for the synthesis of 2,5-diamino-2,5-dideoxy-L-idose derivatives. Treatment of **1** with chlorotriphenylmethane gave methyl 2-acetamido-3-*O*-benzoyl-2-deoxy-6-*O*-trityl-β-D-glucofuranoside (**3**), which was converted into the 5-*O*-mesyl derivative **4**. In view of the steric hindrance arising from the 3-*O*-benzoyl group in **4** (see the foregoing procedure), it was deemed necessary to remove this bulky group. Partial hydrolysis of **4** with methanolic sodium methoxide gave methyl 2-acetamido-2-deoxy-5-*O*-mesyl-6-*O*-trityl-β-D-glucofurano-

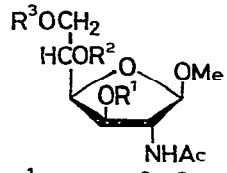


1 R^1=Bz, R^2,R^3=H
2 R^1,R^3=Bz, R^2=Ms
3 R^1=Bz, R^2=H, R^3=Tr
4 R^1=Bz, R^2=Ms, R^3=Tr
5 R^1=H, R^2=Ms, R^3=Tr

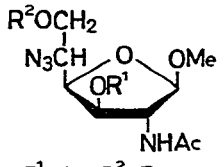


6 R=H
7 R=THP

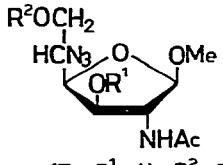
THP = tetrahydropyran-2-yl
Tr = Ph_3C



8 R^1=THP, R^2,R^3=H
9 R^1=THP, R^2=H, R^3=Tr
10 R^1=THP, R^2=Ms, R^3=Tr
11 R^1,R^3=H, R^2=Ms
12 R^1=H, R^2=Ms, R^3=Tr



13 R^1=H, R^2=Tr
14 R^1,R^2=Ac



15 R^1=H, R^2=Tr
16 R^1,R^2=Ac

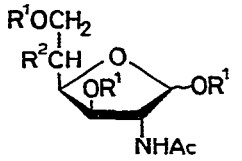
side (**5**). On treatment with sodium azide in *N*,*N*-dimethylformamide for 12 h at 120–125°, compound **5** afforded the azide derivative **15** in good yield.

Mild hydrolysis of **15**, and subsequent acetylation, gave methyl 2-acetamido-3,6-di-*O*-acetyl-5-azido-2,5-dideoxy-α-L-idofuranoside (**16**). The structure of **16** was assigned on the basis of elemental analysis, and i.r. and n.m.r. spectroscopy; the i.r. spectrum showed a characteristic absorption at 2090 cm^{-1} (N_3), and the n.m.r. spectrum revealed the presence of one *N*-acetyl and two *O*-acetyl groups, at δ 1.99, 2.08, and 2.12, H-1 as a doublet at δ 4.94 (2.5 Hz), and H-3 at δ 5.30 ($J_{2,3}$ 3.0, $J_{3,4}$ 5.0 Hz). All of the spectral features were in harmony with structure **16**.

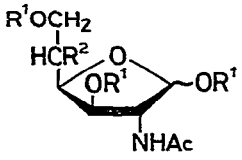
Hydrolytic removal of the methoxyl group in **14** with 15:1 acetic acid–2M hydrochloric acid for 5 h at 40°, and subsequent acetylation, afforded 2-acetamido-1,3,6-tri-*O*-acetyl-5-azido-2,5-dideoxy-α-D-glucofuranose (**17**). The n.m.r. spectrum of **17** exhibited three singlets, integrating for twelve protons, at δ 1.93, 2.04, and 2.12, which demonstrated the presence of one *N*-acetyl and three *O*-acetyl groups. A low-field doublet appearing at δ 6.37 (5.0 Hz) was assigned to the anomeric proton of the α-acetate. The H-3 atom appeared at δ 5.60 (8.0 Hz) as a triplet, due to coupling with H-2 and H-4, indicating the structure of a furanose derivative[4,8–11] having a 1-*O*-acetyl or -alkyl group *cis* to the group on C-2. *O*-Deacetylation of compound **17**, and subsequent (tetrahydropyran-2-yl)ation gave 2-acetamido-5-azido-2,5-dideoxy-1,3,6-tri-*O*-(tetrahydropyran-2-yl)-D-glucofuranose (**18**) in 93% yield.

Reduction of the azide group in **18** (in methanol–triethylamine) with hydrogen in the presence of 10% Pd–C catalyst afforded **19** quantitatively. Treatment of the amino compound **19** with sulfur dioxide according to the procedure reported[1,12] yielded compound **23**. In the same way, the 2-acetamido-5-amino-2,5-dideoxy-L-idose derivative **24** was synthesized from compound **16**. Mild, acid hydrolysis of **16**, and

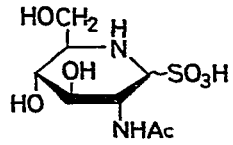
subsequent acetylation, gave 2-acetamido-5-azido-1,3,6-tri-*O*-acetyl-2,5-dideoxy-β-L-idofuranose (**20**); significant signals in the n.m.r. spectrum were a one-proton doublet of doublets at δ 4.42 ($J_{3,4}$ 8.5, $J_{4,5}$ 2.5 Hz, H-4), a one-proton triplet at δ 5.53 ($J_{2,3}$ = $J_{3,4}$ = 8.5 Hz, H-3), and a low-field, one-proton doublet at δ 6.32 ($J_{1,2}$ 4.5 Hz, H-1). Other n.m.r. data are given in the Experimental section, and all are consistent with structure **20**. *O*-Deacetylation of **20** with sodium methoxide in methanol, and subsequent (tetrahydropyran-2-yl)ation, gave compound **21** in good yield. The amino compound **22**, derived from **21** by hydrogenation, was treated with sulfur dioxide in 1,4-dioxane–water as already described, to afford compound **24**.



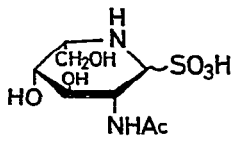
17 R^1 = Ac, R^2 = N_3
18 R^1 = THP, R^2 = N_3
19 R^1 = THP, R^2 = NH_2



20 R^1 = Ac, R^2 = N_3
21 R^1 = THP, R^2 = N_3
22 R^1 = THP, R^2 = NH_2



23



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EXPERIMENTAL

General methods. — Melting points were determined with a Yanagimoto micro melting-point apparatus, and are uncorrected. Specific rotations were determined with a Yanagimoto OR-50 polarimeter, and i.r. spectra were recorded with a Jasco IRA-1 spectrophotometer. N.m.r. spectra were recorded at 60 and 90 MHz with Hitachi R-24 and R-22 spectrometers. N.m.r. data were confirmed by use of decoupling techniques. Preparative chromatography was performed on silica gel (Waco Co.; 300 mesh) with the solvent systems specified. Evaporations were conducted *in vacuo*.

Methyl 2-acetamido-5,6-anhydro-2-deoxy-α-L-idofuranoside (**6**). — To a solution of methyl 2-acetamido-3,5-di-*O*-benzoyl-2-deoxy-5-*O*-mesyl-β-D-glucofuranoside[4] (**2**, 7.0 g) in dry chloroform (70 mL), cooled to −15°, was slowly added, with stirring, an ice-cooled solution of freshly prepared, sodium methoxide in methanol (450 mg of sodium in 18 mL of methanol). The mixture was stirred at −5 to −10°, the progress of the reaction being monitored by t.l.c.; after ~5 h, the salts were removed by stirring

for 15 min with a mixture of Amberlite IR-120B (H^+) and Amberlite IR-45 (OH^-) ion-exchange resins. The resin mixture was filtered off, successively washed with water and methanol, and the filtrate and washings were combined, and evaporated at 45° to a syrup which was chromatographed on a column of silica gel (60 g) with chloroform, and then with 30:1 chloroform–methanol. The latter eluate gave compound **6** as a syrup (2.8 g, 96%), $[\alpha]_D^{20}$ −45° (*c* 1.0, methanol); ν_{max}^{film} 3420 (OH), 3270 (NH), and 1620 and 1560 cm^{-1} (amide); n.m.r. data at 60 MHz (in chloroform-*d*): δ 1.90 (s, 3 H, AcN), 2.50–2.95 (m, 2 H, H-6,6'), 3.34 (s, 3 H, MeO), 3.05–4.40 (m, 5 H, H-2–H-5, OH-3), 4.83 (s, 1 H, H-1), and 7.48 (d, 1 H, $J_{2,NH}$ 8.0 Hz, NH).

Anal. Calc. for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.78; H, 6.99; N, 6.41.

*Methyl 2-acetamido-5,6-anhydro-2-deoxy-3-*O*-(tetrahydropyran-2-yl)-*α*-*L*-idofuranoside* (**7**). — To a stirred solution of **6** (3.2 g) in dry 1,4-dioxane (30 mL) were added dihydropyran (6.2 g) and *p*-toluenesulfonic acid monohydrate (30 mg). The mixture was stirred for 16 h at room temperature, treated with Amberlite IR-45 (OH^-) ion-exchange resin to remove the acid, and evaporated to a syrup which was chromatographed on a column of silica gel (80 g) with chloroform, and then with 50:1 chloroform–methanol. The latter eluate gave compound **7** (3.9 g, 88%) as a syrup, $[\alpha]_D^{20}$ −44° (*c* 0.8, methanol); ν_{max}^{film} 3260 (NH), and 1650 and 1540 cm^{-1} (amide); n.m.r. data at 60 MHz (in chloroform-*d*): δ 1.58 (s, 6 H, tetrahydropyranyl methylene, C-CH_2-C), 1.94 (s, 3 H, AcN), 2.45–2.88 (m, 2 H, H-6,6'), 3.40 (s, 3 H, MeO), and 4.85 (s, 1 H, H-1).

Anal. Calc. for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.72; H, 7.83; N, 4.60.

*Methyl 2-acetamido-2-deoxy-3-*O*-(tetrahydropyran-2-yl)-*α*-*L*-idofuranoside* (**8**). — A solution of **7** (3.7 g) in 2M sodium hydroxide (20 mL) was heated, with stirring, for 12 h at 45–50°, cooled, and treated with Amberlite IRC-50 (H^+) ion-exchange resin to remove the base. The resin was filtered off, washed successively with water and methanol, and the combined filtrate and washings were evaporated to a syrup which was purified by chromatography on a column of silica gel (40 g) with chloroform, and 50:1 and then 20:1 chloroform–methanol. The third eluate gave compound **8** (3.1 g, 78%) as a syrup, $[\alpha]_D^{20}$ −33° (*c* 1.0, chloroform); ν_{max}^{film} 3440 (OH), 3290 (NH), and 1620 and 1560 cm^{-1} (amide).

Anal. Calc. for $C_{14}H_{25}NO_7$: C, 52.65; H, 7.89; N, 4.39. Found: C, 52.48; H, 7.98; N, 4.21.

*Methyl 2-acetamido-2-deoxy-3-*O*-(tetrahydropyran-2-yl)-6-*O*-trityl-*α*-*L*-idofuranoside* (**9**). — To a solution of **8** (1.45 g) in dry pyridine (20 mL) was added trityl chloride (2.0 g). The mixture was heated for 6 h at 55–60°, evaporated, and the residue extracted with chloroform. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated. The residue was chromatographed on a column of silica gel (50 g) with chloroform, and then with 100:1 chloroform–methanol. The latter eluate yielded **9** as a syrup (2.25 g,

88%); ν_{max}^{film} 3500–3250 (OH, NH), 1650 and 1540 (amide), and 740 and 690 cm^{-1} (phenyl).

Methyl 2-acetamido-2-deoxy-5-O-mesyl-3-O-(tetrahydropyran-2-yl)-6-O-trityl-α-L-idofuranoside (**10**). — To a stirred solution of **9** (2.0 g) in dry pyridine (20 mL) was added methanesulfonyl chloride (600 mg) at 0°. The mixture was stirred for 12 h at 0°; the excess of reagent was decomposed by adding water, and the mixture was evaporated to a syrup which was extracted with chloroform. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated. The residue was chromatographed on a column of silica gel (30 g) with chloroform, and then with 100 : 1 chloroform–methanol. The latter eluate yielded **10** (2.1 g, 92%), which was crystallized from ether–hexane; m.p. 97°, $[\alpha]_D^{20}$ −45° (*c* 1.0, methanol); ν_{max}^{Nujol} 3240 (NH), 1650 and 1540 (amide), 1170 (SO_2), and 740 and 690 cm^{-1} (phenyl).

Anal. Calc. for $C_{34}H_{41}NO_9S$: C, 63.83; H, 6.46; N, 2.19. Found: C, 63.68; H, 6.45; N, 2.16.

Methyl 2-acetamido-2-deoxy-5-O-mesyl-6-O-trityl-α-L-idofuranoside (**12**). — A solution of **10** (2.1 g) in 70% aqueous acetic acid (30 mL) was heated for 4 h at 40°, and then evaporated at 40° to a syrup. To a solution of the residue in dry pyridine (20 mL) was added trityl chloride (1.5 g); the mixture was heated for 6 h at 55–60°, evaporated, and then extracted with chloroform. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated. The residue was chromatographed on a column of silica gel (50 g) with chloroform, and then with 100 : 1 chloroform–methanol. The latter eluate afforded **12** (1.5 g, 82%) as needles, m.p. 85°, $[\alpha]_D^{20}$ −51° (*c* 0.4, methanol); ν_{max}^{Nujol} 3500–3250 (OH, NH), 1650 and 1540 (amide), and 740 and 690 cm^{-1} (phenyl); n.m.r. data at 60 MHz (in chloroform-*d*): δ 1.89 (s, 3 H, AcN), 3.01 (s, 3 H, MeS), 3.36 (s, 3 H, MeO), 3.35–4.45 (m, 6 H, H-2–H-6′, OH-3), 4.84 (s, 1 H, H-1), 5.02 (m, 1 H, H-5), 6.03 (d, 1 H, $J_{2,NH}$ 7.5 Hz, NH), and 7.15–7.55 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{29}H_{33}NO_8S$: C, 62.68; H, 5.99; N, 2.52. Found: C, 62.65; H, 6.08; N, 2.52.

Methyl 2-acetamido-3-O-benzoyl-2-deoxy-6-O-trityl-β-D-glucofuranoside (**3**). — To a solution of methyl 2-acetamido-3-*O*-benzoyl-2-deoxy-β-D-glucofuranoside[4] (**1**, 8.0 g) in dry pyridine (25 mL) was added trityl chloride (10.0 g); the mixture was heated for 3 h at 55°, evaporated, and then extracted with chloroform. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated to a syrup. The product was purified by chromatography on a column of silica gel (200 g) with chloroform, and then 100 : 1 chloroform–methanol. The latter eluate afforded 12.9 g (94%) of product; crystallization from ethyl acetate–hexane gave needles, m.p. 203–204°, $[\alpha]_D^{20}$ −22° (*c* 1.0, chloroform); ν_{max}^{Nujol} 3300 (OH), 3250 (NH), 1720 and 1285 (ester), 1660 and 1540 (amide), and 780–695 cm^{-1} (phenyl).

Anal. Calc. for $C_{35}H_{35}NO_7$: C, 72.27; H, 6.07; N, 2.41. Found: C, 72.30; H, 6.13; N, 2.39.

Methyl 2-acetamido-3-O-benzoyl-2-deoxy-5-O-mesyl-6-O-trityl-β-D-glucofuranoside (**4**). — To a solution of **3** (5.5 g) in dry pyridine (17 mL) was added methanesulfonyl chloride (1.7 g) at 0°, and the mixture was kept for 16 h at 0°. The procedures described for the preparation of compound **10** afforded a crystalline mass of **4**. Recrystallization from ethyl acetate–hexane gave needles, wt. 4.8 g (77%), m.p. 204–205°, $[\alpha]_D^{20}$ −4.0° (*c* 1.0, chloroform); ν_{max}^{Nujol} 3360 (NH), 1725 and 1265 (ester), 1685 and 1520 (amide), 1180 (SO_2), and 750–690 cm^{-1} (phenyl); n.m.r. data at 60 MHz (in chloroform-*d*): δ 1.92 (s, 3 H, AcN), 2.76 (s, 3 H, MeS), 3.22 (s, 3 H, MeO), 3.32–3.70 (m, 2 H, H-6,6'), 4.09 (near d, 1 H, $J_{2,NH}$ 7.0 Hz, H-2), 4.72 (d of d, 1 H, $J_{3,4}$ 5.0, $J_{4,5}$ 7.2 Hz, H-4), 4.90 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 5.25 (m, 1 H, H-5), 5.52 (d of d, 1 H, $J_{2,3}$ 1.0, $J_{3,4}$ 5.0 Hz, H-3), 6.40 (d, 1 H, NH), and 7.0–8.15 (m, 20 H, 4 Ph).

Anal. Calc. for $C_{36}H_{37}NO_9S$: C, 65.54; H, 5.65; N, 2.12. Found: C, 65.81; H, 5.88; N, 2.15.

Methyl 2-acetamido-2-deoxy-5-O-mesyl-6-O-trityl-β-D-glucofuranoside (**5**). — To a solution of **4** (1.5 g) in chloroform (25 mL) was added sodium methoxide in methanol (250 mg of sodium in 5 mL of methanol) at −10°; after 10 min, the base was removed by stirring with Amberlite IRC-50 (H^+) ion-exchange resin. The resin was filtered off, and washed with methanol, and the filtrate and washings were combined, and evaporated to a syrup which was chromatographed on a column of silica gel (20 g) with chloroform, and 30:1 chloroform–methanol. The latter eluate afforded a crystalline mass of **5**. Recrystallization from ether–hexane gave needles, wt. 1.19 g (94%), m.p. 98°, $[\alpha]_D^{20}$ −25° (*c* 0.6, chloroform); ν_{max}^{Nujol} 3480 (OH), 3260 (NH), 1650 and 1530 (amide), 1170 (SO_2), and 750 and 690 cm^{-1} (phenyl); n.m.r. data at 60 MHz (in chloroform-*d*): δ 1.92 (s, 3 H, AcN), 3.00 (s, 3 H, MeS), 3.10 (s, 3 H, MeO), 3.24–3.76 (m, 2 H, H-6,6'), 4.09–4.44 (m, 4 H, H-2–H-4, OH-3), 4.72 (s, 1 H, H-1), 5.09 (m, 1 H, H-5), 6.22 (d, 1 H, $J_{2,NH}$ 7.0 Hz, NH), and 7.15–7.50 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{29}H_{33}NO_8S$: C, 62.68; H, 5.99; N, 2.52. Found: C, 62.53; H, 5.91; N, 2.48.

Methyl 2-acetamido-5-azido-2,5-dideoxy-6-O-trityl-β-D-glucofuranoside (**13**). — To a solution of **12** (1.3 g) in dry *N*,*N*-dimethylformamide (20 mL) was added sodium azide (2.2 g), and the mixture was heated for 20 h at 120–125°, evaporated, and the residue extracted with chloroform. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated. The residue was chromatographed on a column of silica gel (40 g) with chloroform and then with 100:1 chloroform–methanol. The latter eluate gave 600 mg (64%) of **13** as needles, m.p. 89°, $[\alpha]_D^{20}$ −5.0° (*c* 1.0, methanol); ν_{max}^{Nujol} 3500–3240 (OH, NH), 2080 (azide), 1650 and 1540 (amide), and 750 and 690 cm^{-1} (phenyl); n.m.r. data at 60 MHz (in chloroform-*d*): δ 1.87 (s, 3 H, AcN), 3.10 (s, 3 H, MeO), 3.30–3.47 (m, 3 H, H-5,6,6'), 3.62–4.22 (m, 4 H, H-2–H-4, OH-3), 4.67 (s, 1 H, H-1), 6.61 (d, 1 H, $J_{2,NH}$ 7.0 Hz, NH), and 7.10–7.52 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{28}H_{30}N_4O_5$: C, 66.91; H, 6.02; N, 11.15. Found: C, 66.88; H, 6.15; N, 11.40.

*Methyl 2-acetamido-3,6-di-*O*-acetyl-5-azido-2,5-dideoxy-β-*D*-glucofuranoside* (**14**). — A solution of **13** (1.5 g) in 70% aqueous acetic acid (30 mL) was heated for 3 h at 40°, cooled, and evaporated to a syrup which was acetylated with acetic anhydride (3 mL) and pyridine (10 mL) for 12 h at room temperature. The product was chromatographed on a column of silica gel (50 g) with chloroform and then 100:1 chloroform–methanol. The latter eluate gave **14** as a syrup (910 mg, 88%), $[\alpha]_D^{20}$ −40° (*c* 0.45, chloroform); ν_{max}^{film} 3300 (NH), 2080 (azide), 1750 and 1230 (ester), and 1650 and 1540 cm^{-1} (amide); n.m.r. data at 60 MHz (in chloroform-*d*): δ 2.00 (s, 3 H, AcN), 2.10, 2.12 (2 s, 6 H, 2 AcO), 3.40 (s, 3 H, MeO), 3.80–4.80 (m, 5 H, H-2–H-6′), 4.89 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 5.37 (d of d, 1 H, $J_{2,3}$ 1.3, $J_{3,4}$ 5.0 Hz, H-3), and 7.35 (d, 1 H, $J_{2,NH}$ 7.2 Hz, NH).

Anal. Calc. for $C_{13}H_{20}N_4O_7$: C, 45.34; H, 5.85; N, 16.27. Found: C, 45.38; H, 5.81; N, 16.09.

*Methyl 2-acetamido-5-azido-2,5-dideoxy-6-*O*-trityl-α-*L*-idofuranoside* (**15**). — To a solution of **5** (1.26 g) in dry *N*,*N*-dimethylformamide (10 mL) was added sodium azide (3.0 g), and the mixture was heated, with stirring, for 12 h at 120–125°, evaporated, and the residue extracted with chloroform. The extract was treated as described in the synthesis of **13**, and the residue was purified on a column of silica gel (20 g) with (*a*) chloroform, (*b*) 100:1, and (*c*) 30:1 chloroform–methanol. Eluant (*b*) gave compound **15** as needles (750 mg, 66%), m.p. 85–87°, $[\alpha]_D^{20}$ −8° (*c* 0.6, chloroform); ν_{max}^{Nujol} 3480–3250 (OH, NH), 2080 (azide), 1660 and 1545 (amide), and 750 and 690 cm^{-1} (phenyl); n.m.r. data at 90 MHz (in chloroform-*d*): δ 1.92 (s, 3 H, AcN), 3.10–3.52 (m, 3 H, H-5,6,6′), 3.35 (s, 3 H, MeO), 3.65–4.24 (m, 4 H, H-2–H-4, OH-3), 4.79 (s, 1 H, H-1), 5.93 (d, 1 H, $J_{2,NH}$ 7.0 Hz, NH), and 7.12–7.49 (m, 15 H, 3 Ph).

Anal. Calc. for $C_{28}H_{30}N_4O_5$: C, 66.91; H, 6.02; N, 11.15. Found: C, 66.73; H, 6.25; N, 11.08.

The starting material **5** (380 mg, 30%) was recovered from eluant (*c*).

*Methyl 2-acetamido-3,6-di-*O*-acetyl-5-azido-2,5-dideoxy-α-*L*-idofuranoside* (**16**). — A solution of **15** (1.04 g) in 70% aqueous acetic acid (20 mL) was heated for 4 h at 40°, cooled, and evaporated to a syrup which was acetylated with acetic anhydride–pyridine. The product was purified by chromatography on a column of silica gel (15 g) with chloroform and then with 100:1 chloroform–methanol. The latter eluate afforded **16** as a syrup (585 mg, 82%), $[\alpha]_D^{20}$ −25° (*c* 0.97, chloroform); ν_{max}^{film} 3250 (NH), 2090 (azide), 1740 and 1250 (ester), and 1650 and 1540 cm^{-1} (amide); n.m.r. data at 60 MHz (in chloroform-*d*): δ 1.99, 2.08, 2.12 (3 s, 9 H, AcN, 2 AcO), 3.43 (s, 3 H, MeO), 3.70–4.48 (m, 5 H, H-2, H-4–H-6′), 4.94 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 5.30 (d of d, 1 H, $J_{2,3}$ 3.0, $J_{3,4}$ 5.0 Hz, H-3), and 7.40 (d, 1 H, $J_{2,NH}$ 7.0 Hz, NH),

Anal. Calc. for $C_{13}H_{20}N_4O_7$: C, 45.34; H, 5.85; N, 16.27. Found: C, 45.20; H, 5.93; N, 16.01.

*2-Acetamido-1,3,6-tri-*O*-acetyl-5-azido-2,5-dideoxy-α-*D*-glucofuranose* (**17**). — A solution of **14** (200 mg) in 15:1 acetic acid–2M hydrochloric acid (15 mL) was

heated for 5 h at 40°; at this time, the starting material was no longer detectable by t.l.c. Water (5 mL) was added to the mixture, and the solution was reheated for 2 h at 40°, to hydrolyze the oxazoline derivative formed. The mixture was treated with Amberlite IR-45 resin, and the resin was filtered off, and washed with methanol. The filtrate and washings were combined, and evaporated to a syrup which was acetylated with acetic anhydride (1 mL)–pyridine (3 mL) overnight at 0°. The product was purified by chromatography on a column of silica gel (20 g) with chloroform, and then 150:1 chloroform–methanol. The latter eluate afforded **17** (137 mg, 63%) as a syrup, $[\alpha]_D^{20}$ +20° (*c* 1.4, chloroform); ν_{max}^{film} 3300 (NH), 2080 (azide), 1750 and 1220 (ester), and 1650 and 1530 cm^{-1} (amide); n.m.r. data at 60 MHz (in chloroform-*d*): δ 1.93 (s, 3 H, AcN), 2.04 (s, 6 H, 2 AcO), 2.12 (s, 3 H, AcO), 3.63 (m, 1 H, H-5), 3.98–4.90 (m, 4 H, H-2,4,6,6'), 5.60 (t, 1 H, $J_{2,3} = J_{3,4}$ = 8.2 Hz, H-3), 6.37 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), and 6.65 (d, 1 H, $J_{2,NH}$ 8.0 Hz, NH).

Anal. Calc. for $C_{14}H_{20}N_4O_8$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.13; H, 5.70; N, 14.88.

*2-Acetamido-5-azido-2,5-dideoxy-1,3,6-tri-*O*-(tetrahydropyran-2-yl)-*D*-glucofuranose* (**18**). — To an ice-cooled solution of **17** (100 mg) in methanol (20 mL) was added M sodium methoxide (1 mL), and the mixture was kept for 1 h at 0°, and then treated with Amberlite IR-120-B resin to remove the base; the resin was filtered off, and washed with methanol. The filtrate and washings were combined, and evaporated to a syrup which was dissolved in dry 1,4-dioxane (10 mL). To the stirred solution were added dihydropyran (400 mg) and *p*-toluenesulfonic acid monohydrate (20 mg). The mixture was stirred overnight at room temperature, treated with Amberlite IR-410 (OH^-) ion-exchange resin to remove the acid, and then evaporated to a syrup. The product was chromatographed on a column of silica gel (20 g) with chloroform and then with 150:1 chloroform–methanol. The latter eluate yielded compound **18** as a syrup (125 mg, 93%); ν_{max}^{film} 3280 (NH), 2080 (azide), and 1650 and 1520 cm^{-1} (amide); n.m.r. data at 60 MHz (in chloroform-*d*): δ 1.40–1.80 (m, 18 H, tetrahydropyranyl methylene, C-CH_2-C), 1.95 (s, 3 H, AcN), 5.47 (d, $J_{1,2}$ 5.5 Hz, H-1α), and 6.34 (d, 1 H, $J_{2,NH}$ 8.0 Hz, NH).

Anal. Calc. for $C_{23}H_{38}N_4O_8$: C, 55.40; H, 7.68; N, 11.24. Found: C, 55.28; H, 7.80; N, 11.35.

*2-Acetamido-1,3,6-tri-*O*-acetyl-5-azido-2,5-dideoxy-β-*L*-idofuranose* (**20**). — A solution of **16** (400 mg) in 20:1 acetic acid–2M hydrochloric acid (20 mL) was heated for 9 h at 45°. Water (5 mL) was added to the mixture, and the solution was reheated for 2 h at 40°. The solution was processed as described for the preparation of **17**, and the product was acetylated with acetic anhydride (2 mL)–pyridine (10 mL) overnight at 0°. The acetylated compound was purified by chromatography on a column of silica gel (40 g) with chloroform and then with 150:1 chloroform–methanol. The latter eluate afforded **20** (250 mg, 58%) as a syrup, $[\alpha]_D^{20}$ +68° (*c* 1.0, chloroform); ν_{max}^{film} 3280 (NH), 2080 (azide), 1720 and 1210 (ester), and 1650 and 1520 cm^{-1} (amide); n.m.r. data at 60 MHz (in chloroform-*d*): δ 1.93 (s, 3 H, AcN), 2.04 (s, 6 H, 2 AcO), 2.13 (s, 3 H, AcO), 3.62 (m, 1 H, H-5), 4.19–4.30 (m, 2 H, H-6,6'),

4.42 (d, of d, $J_{3,4}$ 8.5, $J_{4,5}$ 2.5 Hz, H-4), 4.90 (m, 1 H, H-2), 5.53 (t, 1 H, $J_{2,3} = J_{3,4} = 8.5$ Hz, H-3), 6.32 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1), and 6.38 (d, 1 H, $J_{2,NH}$ 8.0 Hz, NH).

Anal. Calc. for $C_{14}H_{20}N_4O_8$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.24; H, 5.38; N, 15.23.

2-Acetamido-5-azido-2,5-dideoxy-1,3,6-tri-O-(tetrahydropyran-2-yl)-L-idofuranose (**21**). — Compound **20** (200 mg) was converted, *via O*-deacetylation and subsequent (tetrahydropyran-2-yl)ation according to the procedures described in the preparation of **18**, into **21**. Elution of the product from silica gel (30 g) with 150:1 chloroform–methanol afforded a pure syrup (240 mg, 90%) of **21**; ν_{max}^{film} 3280 (NH), 2080 (azide), and 1650 and 1540 cm^{-1} (amide); n.m.r. data at 60 MHz (in chloroform-*d*): δ 1.20–1.75 (m, 18 H, tetrahydropyranyl methylene, C-CH_2-C), 1.96 (s, 3 H, AcN), 5.48 (d, $J_{1,2}$ 5.0 Hz, H-1α), and 6.43 (d, 1 H, $J_{2,NH}$ 7.0 Hz, NH).

Anal. Calc. for $C_{23}H_{38}N_4O_8$: C, 55.40; H, 7.68; N, 11.24. Found: C, 55.38; H, 7.62; N, 11.03.

2-Acetamido-5-amino-2,5-dideoxy-D-glucopyranosyl hydrogensulfite (**23**). — A solution of **18** (100 mg) in methanol (20 mL) and triethylamine (2 mL) was hydrogenated in the presence of 10% Pd–C catalyst (50 mg) for 1.5 h at 30–40°; at this time, t.l.c. showed the reaction to be complete. The suspension was filtered, and the filtrate was evaporated, to give **19** as a syrup which was used without purification for the next reaction. The amino compound was dissolved in 1,4-dioxane (15 mL) and water (10 mL), and sulfur dioxide was vigorously bubbled through for 30 min at 0°. The reaction vessel was sealed, and kept for 10 h at room temperature. The mixture was evaporated at 30°, to give a crystalline mass which was dissolved in water (5 mL). The solution was heated for 4 min at 100°, decolorized with active charcoal, and then evaporated at 30°, to give a mass of crystals. Recrystallization from water–acetone gave **23** (32 mg, 56%), m.p. 139–145° (dec.), $[\alpha]_D^{20}$ +21° (*c* 0.5, methanol); ν_{max}^{KBr} 3400–3300 (OH, NH), 1650 and 1540 (amide), and 1210 cm^{-1} (SO_2); n.m.r. data at 90 MHz (in D_2O): δ 1.95 (s, 3 H, AcN) and 5.32 (d, $J_{1,2}$ 3.0 Hz, H-1α).

Anal. Calc. for $C_8H_{16}N_2O_7S$: C, 33.80; H, 5.67; N, 9.85. Found: C, 33.51; H, 5.89; N, 9.58.

2-Acetamido-5-amino-2,5-dideoxy-L-idopyranosyl hydrogensulfite (**24**). — Compound **20** (200 mg) in methanol (20 mL) and triethylamine (3 mL) was hydrogenated in the presence of 10% Pd–C catalyst (100 mg) for 2.5 h at 30–40°. The amino compound **22** was converted into **24** as described for **23**. Recrystallization of the product from water–acetone gave **24** (72 mg, 63%), m.p. 138–142° (dec.), $[\alpha]_D^{20}$ +27° (*c* 0.3, methanol); ν_{max}^{KBr} 3400–3300 (OH, NH), 1650 and 1550 (amide), and 1210 cm^{-1} (SO_2); n.m.r. data at 90 MHz (in D_2O): δ 1.93 (s, 3 H, AcN) and 5.30 (d, $J_{1,2}$ 2.8 Hz, H-1β).

Anal. Calc. for $C_8H_{16}N_2O_7S$: C, 33.80; H, 5.67; N, 9.85. Found: C, 33.68; H, 5.88; N, 9.63.

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