Deoxysugar Synthesis. II.¹⁾ Deoxygenations of Methyl 2,6-Dibenzyloxy-carbonylamino-2,6-dideoxy- α -D-glucopyranoside

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The 3-*p*-toluenesulfonate (4) of methyl 2,6-dibenzyloxy carbonylamino-2,6-dideoxy- α -D-glucopyranoside was treated with sodium borohydride in dimethyl sulfoxide, giving 3-deoxy- and 4-deoxy- α -D-*ribo*-hexopyranosides (10 and 11) in a ratio of 1:5. On the other hand, analogous treatment of the 4-*p*-toluenesulfonate (5) afforded the *allo*-3,4-epoxide (19). Further, related study was described.

In connection with our studies in the field of aminoglycoside antibiotics,³⁾ it deemed expedient to develop a method for the removal of a 3- or 4-hydroxyl function in 2,6-diamino-2,6-dideoxy- α -D-glucopyranoside, which is an important structural unit of aminoglycoside antibiotics.⁴⁾ Thus, among several approaches attempted along this line, the metal hydride reduction of the 3- or 4-sulfonate or 3,4-anhydride of the diaminoglucoside derivatives was found to provide certain deoxy compounds which forms the topic of this paper.

Methyl 2,6-dibenzyloxy carbonylamino-2,6-dideoxy- α -D-glucopyranoside (1) was selected for this study and prepared in quantity from the known methyl 2-benzyloxy carbonylamino-2-deoxy-6-O-tosyl- α -D-glucopyranoside⁵⁾ (2) in the following way.⁶⁾ Treatment of 2 with sodium azide in dimethyl sulfoxide (DMSO) gave the 6-azide (3) which was converted into the starting material (1) on reduction with lithium aluminum hydride or zinc followed by N-benzyloxy-carbonylation.

Tosylation of the dibenzyloxy carbonylaminoglucoside (1) with two molar equivalents of *p*-toluenesulfonyl chloride (TsCl) in pyridine afforded a mixture containing the 3-sulfonate (4), the 4-sulfonate (5), and the 3,4-disulfonate in relative ratio of 7:3:1, each of which was isolated by chromatography over silica gel. Predominant formation of the 3-sulfonate (4) is supposedly due to the greater activity of the 3-hydroxy group for esterification and parallels the preceding observation on other related compounds.⁷⁾ The structures of these sulfonates were clarified based on an alternative synthesis of the 3-sulfonate (4) which was carried out by an unequivocal process as follows. Tosylation of methyl 4,6-O-benzylidene-2-benzyloxy carbonylamino-2-deoxy- α -D-glucopyranoside⁸⁾ (6) gave its 3-sulfonate (7) which was converted into the 3,6-disulfonate (8) by acid hydrolysis and successive tosylation of the 6-hydroxy group. Treat-

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3) H. Saeki, Y. Shimada, Y. Ohashi, M. Tajima, S. Sugawara, and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **22**, 1145 (1974); H. Saeki, Y. Shimada, S. Sugawara, and E. Ohki, *J. Antibiotics*, **28**, 530 (1975).

4) S. Hanessian and T.H. Haskell, "The Carbohydrates, Chemistry and Biochemistry," Vol. IIA, ed. by W. Pigman and D. Horton, Academic Press, New York & London, 1970, p. 139; S. Umezawa, "Advances in Carbohydrate Chemistry and Biochemistry," Vol. 30, ed. by R.S. Tipson and D. Horton, Academic Press, N.Y., San Francisco & London, 1974, p. 111.

5) A.B. Foster, M. Stacy, and S.V. Vardheim, *Acta Chem. Scand.*, **13**, 281 (1959).

6) cf. K.L. Rinehart, Jr., M. Hichens, K. Striegler, K.R. Rover, and S. Tatsuoka, *J. Am. Chem. Soc.*, **83**, 2964 (1961); W. Meyer zu Reckendorf and W.A. Bonner, *Chem. Ber.*, **96**, 2017 (1963).

7) M.W. Horner, L. Hough, and A.C. Richardson, *J. Chem. Soc. (C)*, **1970**, 1336; R. Khan and L. Hough, *Carbohydr. Res.*, **24**, 141 (1972); Y. Takagi, T. Miyake, T. Tsuchiya, S. Umezawa, and H. Umezawa, *J. Antibiotics*, **26**, 403 (1973).

8) S. Akiya and T. Osawa, *Yakugaku Zasshi*, **76**, 1276 (1956).

ment of the disulfonate (8) with sodium azide gave the 6-azide (9) without a substitution at the 3-tosyloxy group. Reduction of 9 with lithium aluminum hydride followed by N-benzyloxycarbonylation resulted in a formation of the 3-sulfonate (4) which was identified with the major product obtained by tosylation of 1.

In 1969, Bell, *et al.*⁹⁾ reported that treatment of several sulfonates with sodium borohydride in DMSO or diglyme furnishes a useful method for the reductive fission of their carbon-oxygen bonds; and this method has recently been used with carbohydrate derivatives for removal of a primary sulfonyloxy group.¹⁰⁾ Herein, we undertook the application of this method to these secondary sulfonates (4 and 5) obtained as above.

When the 3-sulfonate (4) was treated with sodium borohydride in DMSO at 80°, two deoxygenated compounds, methyl 2,6-dibenzyloxycarbonylamino-2,3,6-trideoxy- α -D-ribo-hexopyranoside (10) and its 2,4,6-trideoxy isomer (11) were obtained in a ratio of 1:5. Both were acetylated to give the corresponding acetates whose mass spectra and nuclear magnetic resonance (NMR) spectra exhibited data reflecting a molecular formula corresponding to a monodeoxy mono-O-acetyl derivative of the starting material (1). These analyses, however, did not give any reliable data for structural elucidation. Consequently, their structures were confirmed on the basis of the following synthetic study.

First, an authentic sample of the minor deoxygenated product (10) was prepared by an unequivocal route and identified. 4,6-O-Benzylidenation of methyl 2-deoxy-2-methoxycarbonylamino- α -D-glucopyranoside¹¹⁾ (12) followed by tosylation gave the 3-sulfonate¹²⁾ (13). Removal of the benzylidene group from 13 with acid and treatment of the resulting 3-sulfonate (14) with sodium iodide in hot N,N-dimethylformamide (DMF) afforded a 3-iodide (15).¹³⁾ Hydrogenation of 15 over Raney nickel gave methyl 2,3-dideoxy-2-methoxycarbonylamino- α -D-ribo-hexopyranoside (16) which was identified with the sample derived from the known 4,6-O-isopropylidene derivative of 16.¹⁾ Compound 16 was converted into the desired compound 10 by a sequence of reactions; 6-O-tosylation, displacement of the 6-tosyloxy group with sodium azide, hydrogenation over palladium on charcoal, alkaline hydrolysis and N-benzyloxycarbonylation.

On the other hand, the structure of the major deoxygenated product (11) was determined as follows. Oxidation of 11 with DMSO and acetic anhydride¹⁴⁾ afforded a ketone (17) which was different from the 4-ketone (18) analogously prepared from the minor product (10). This fact suggests that the major product (11) was a 4-deoxy derivative of the starting material (1). Although the configuration at C-3 in 11 was still ambiguous, it was assumed that the formation of a 4-deoxy product can be illustrated by an initial participation of the 4-hydroxy group

- 1: $R_1=R_2=H$, $R_3=NHCBz$
 2: $R_1=R_2=H$, $R_3=OTs$
 3: $R_1=R_2=H$, $R_3=N_3$
 4: $R_1=Ts$, $R_2=H$, $R_3=NHCBz$
 5: $R_1=H$, $R_2=Ts$, $R_3=NHCBz$
 8: $R_1=Ts$, $R_2=H$, $R_3=OTs$
 9: $R_1=Ts$, $R_2=H$, $R_3=N_3$

- 6: $R=H$
 7: $R=Ts$

Ph=phenyl
 Cbz=COOCH₂C₆H₅

Chart 1

9) H.M. Bell, C.W. Vanderslice, and A. Spehar, *J. Org. Chem.*, **34**, 3923 (1969).

10) H. Weidmann, N. Wolf, and W. Timpe, *Carbohydr. Res.*, **24**, 184 (1972); L.M. Lerner, *ibid.*, **36**, 392 (1974).

11) D. Ikeda, T. Tsuchiya, and S. Umezawa, *Bull. Chem. Soc., Japan*, **44**, 2529 (1971).

12) Sodium borohydride reduction of the 3-sulfonate (13) or displacement reaction with an iodide was attempted; but it was found that 13 was quite inert under these reaction conditions.

13) In the case of using the N-benzyloxycarbonyl analog of 14, the displacement reaction of its 3-tosyloxy group was not successful.

14) J.D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4214 (1965).

in a displacement of the 3-tosyloxy group to give a 4,3-epoxide which is subject to a hydride attack at C-4. Therefore, we next attempted a preparation of an epoxide from the 3-sulfonate (4) and examined its ring opening reaction¹⁵⁾ in order to certify the structure of the 4-deoxy product (11).

Chart 2

a) configuration uncertain

Treatment of the 3-sulfonate (4) with sodium methoxide in methanol afforded the *D-allo*-epoxide (19) slowly but in a good yield. Contrary to our expectation, 19 was found to be inert to further reduction with sodium borohydride in DMSO; however, lithium aluminum hydride reduction of 19 resulted in the formation of the same 4-deoxy compound (11) that was obtained by sodium borohydride reduction of the 3-sulfonate (4). Further, treatment of the epoxide (19) with hydrogen iodide and hydrogenolysis of the subsequent iodohydrin (20) over Raney nickel afforded the same 4-deoxy compound (11). These results indicate that lithium aluminum hydride reduction of the *allo*-epoxide (19) proceeded under a hydride attack, preferentially at its 4-position (diaxial opening), to give methyl 2,6-dibenzylamino-2,4,6-trideoxy- α -*D*-ribo-hexopyranoside (11) and the iodohydrin formation from 19 was also conducted under diaxial opening of the epoxide ring to give the 4-iodo-*D*-gulo derivative (20). Thus, the structure of the 4-deoxy compound (11) mainly obtained by the reduction of the 3-sulfonate (4) was conclusively confirmed. These facts suggest that the borohydride reduction of 4 does not always imply a simple displacement of the tosyloxy group by a hydride, due to the significant participation by the neighboring hydroxyl group. As for the formation of the 3-deoxy product (10) from 4, it is not obvious so far whether it occurred *via* hydride attack of the epoxide intermediate at C-3 or by direct substitution of the 3-tosyloxy group with hydride.

In contrast to the case of the 3-sulfonate (4), analogous treatment of the 4-sulfonate (5) with sodium borohydride did not give a deoxygenated product, but resulted in a facile formation of the *D-galacto*-epoxide (21), suggesting that the reagent reacted simply as a base in this case. Actually, the same epoxide (21) was easily obtained by treatment of the 4-sulfonate (5) with

Chart 3

15) N.R. Williams, "Advances in Carbohydrate Chemistry and Biochemistry," Vol. 25, ed. by R.S. Tipson and D. Horton, Academic Press, N.Y. & London, 1970, p. 109.

sodium methoxide in methanol. Lithium aluminum hydride reduction of **21** gave a new isomeric deoxy compound (**22**) which was not identical with either of the afore-mentioned deoxy compounds (**10** and **11**). Compound **22** was oxidized with DMSO and acetic anhydride or with chromium trioxide pyridine complex to give the 4-ketone (**18**). Based on these facts, compound **22** was determined to be methyl 2,6-dibenzyloxycarbonylamino-2,3,6-trideoxy- α -D-xylo-hexopyranoside, indicating that an attack of a hydride occurred at the 3-position of the D-galacto-epoxide (**21**).

Experimental

Melting points (mp) are not corrected. Infrared (IR) spectra were recorded on a JASCO A-2 spectrometer, NMR spectra on a Hitachi-Perkin Elmer R-24 spectrometer, and mass spectra (MS) on a JEOL JMS-01SG mass spectrometer. Optical rotations were measured on a Perkin-Elmer Model 141 automatic polarimeter in 1 dm tubes. Thin-layer chromatography (TLC) was performed on TLC-plates, Silica gel F₂₅₄ pre-coated, layer thickness 0.25 mm (E. Merck, AG) and spots were visualized by spraying with vanadic acid-sulfuric acid reagent or with an ethanolic solution of phosphomolybdic acid. For column chromatography on silica gel, Wakogel C-200 (Wako Pure Chemical Industries, Ltd., Osaka) was used. Solvents were removed by rotary flash evaporator at diminished pressures and usually at 35–50°.

Methyl 6-Azido-2-benzyloxycarbonylamino-2,6-dideoxy- α -D-glucopyranoside (3)—A stirred solution of 15.2 g of methyl 2-benzyloxycarbonylamino-2-deoxy-6-O-tosyl- α -D-glucopyranoside⁴ (**2**) and 2.5 g of NaN₃ in 60 ml of DMSO was heated at 90–100° for 2 hr under N₂ atmosphere. The cooled mixture was diluted with H₂O and extracted with CHCl₃. The extract was washed with H₂O, dried and evaporated *in vacuo*, leaving a crystalline mass which was recrystallized from EtOH-hexane to 8.68 g of **3**, mp 120°, fine needles, $[\alpha]_D^{20} + 53.9^\circ$ ($c=0.38$, CHCl₃). IR $\nu_{\max}^{\text{Nujol}}$: 2100 cm⁻¹ (azide), no absorption of OTs. Anal. Calcd. for C₁₅H₂₀O₆N₄·1/2H₂O: C, 50.49; H, 5.79; N, 15.70. Found: C, 50.46; H, 5.98; N, 15.57.

Methyl 2,6-Dibenzyloxycarbonylamino-2,6-dideoxy- α -D-glucopyranoside (1)—(i) To a stirred solution of 20.5 g of **3** in 450 ml of tetrahydrofuran was added portionwise 6.64 g of LiAlH₄ at 0° under N₂ atmosphere. After further stirring for 2 hr at 0°, aq. MeOH was added dropwise for decomposition of the excess reagent. The precipitates were filtered off and the filtrate was made basic with Na₂CO₃ (solid). To the solution was added dropwise 19.6 g of benzyloxycarbonyl chloride at 0° and the mixture was stirred for another 1 hr. Then, the mixture was diluted with ice-water and extracted with CHCl₃. The extract was washed with H₂O, dried and evaporated *in vacuo*, leaving a crystalline mass which was recrystallized from EtOH to 16.5 g of **1**, mp 172–174°, prisms, $[\alpha]_D^{20} + 15.3^\circ$ ($c=0.36$, CHCl₃). Anal. Calcd. for C₂₃H₂₈O₈N₂: C, 59.99; H, 6.13; N, 6.08. Found: C, 60.00; H, 6.15; N, 6.44.

ii) To a stirred mixture of 10 g of **3**, 100 ml of acetone, 25 ml of H₂O, and 30 g of zinc powder was added dropwise 10 ml of conc. HCl with cooling and vigorous stirring. After 30 min, the mixture was filtered and the filtrate was concentrated to half volume *in vacuo* then 25 ml of H₂O, 20 g of Na₂CO₃ (solid) and 15 g of benzyloxycarbonyl chloride was added successively with stirring. Stirring was continued for 3 hr and the resulting precipitates were extracted with CHCl₃. The extract was evaporated and recrystallized to 5.2 g of **1**.

Tosylation of Methyl 2,6-Dibenzyloxycarbonylamino-2,6-dideoxy- α -D-glucopyranoside (1)—To a stirred solution of 350 mg of **1** in 3 ml of pyridine was added in portions 296 mg of TsCl at room temperature and the mixture was allowed to stand overnight. After working up in the usual manner, the product was dissolved in CHCl₃ and was charged on a column of silica gel (10 g) packed with benzene. After washing with benzene, the column was eluted with AcOEt-benzene (1:4, v/v). Evaporation of fast-running fractions gave a crystalline mixture (266 mg) which was recrystallized from EtOH to 45 mg of the 4-*p*-toluenesulfonate (**5**), needles, mp 170°, $[\alpha]_D^{21} + 39.6^\circ$ ($c=2.6$, CHCl₃). IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3460, 3400, 3270 (OH, NH), 1600, 1190, 1180 (OTs). NMR (CDCl₃) δ ppm: 2.41 (3H, s, CH₃ of tosyl), 3.25 (3H, s, OCH₃), 4.67 (1H, d, $J=3$ Hz, H-1). Anal. Calcd. for C₃₀H₃₄O₁₀N₂S: C, 58.62; H, 5.58; N, 4.56; S, 5.23. Found: C, 58.22; H, 5.66; N, 4.52; S, 5.37.

In succession, fractions obtained by further elution with the same solvent system were evaporated, leaving 100 mg of the pure 3-*p*-toluenesulfonate (**4**), mp 122°, prisms (from EtOH-hexane), $[\alpha]_D^{21} + 42.1^\circ$ ($c=2.87$, CHCl₃). IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3580 (OH), 3320 (NH), 1600, 1190, 1180 (OTs). NMR (CDCl₃) δ ppm: 2.37 (3H, s, CH₃ of tosyl), 3.28 (3H, s, OCH₃), 4.70 (1H, d, $J=3$ Hz, H-1). Anal. Calcd. for C₃₀H₃₄O₁₀N₂S: C, 58.62; H, 5.58; N, 4.56; S, 5.23. Found: C, 58.11; H, 5.52; N, 4.46; S, 5.09.

Further, the mother liquor left by recrystallization of these sulfonates was collected and evaporated. The residue (194 mg) was separated by preparative TLC (solvent system: AcOEt: benzene=2:3, v/v, silica gel 2×200×200 mm), giving 34 mg of the 4-sulfonate (**5**) and 73 mg of the 3-sulfonate (**4**), along with 25 mg of the 3,4-disulfonate, powder (from hexane), mp 56–60°. The analytical sample of the 3,4-disulfonate was not obtained, but its NMR spectrum exhibited two kinds of methyl signals of the tosyl groups at δ 2.41 and 2.35.

Methyl 4,6-O-Benzylidene-2-benzylloxycarbonylamino-2-deoxy-3-O-tosyl- α -D-glucopyranoside (7)—To a solution of 3.1 g of methyl 4,6-O-benzylidene-2-benzylloxycarbonylamino-2-deoxy- α -D-glucopyranoside⁸⁾ (6) in 20 ml of pyridine was added 3.6 g of TsCl and the mixture was allowed to stand for 2 days at room temperature. Working up in the usual manner and recrystallization of the product (3.8 g) from EtOH gave 7, mp 119–121° (softening at 81°), $[\alpha]_D^{20} +5.9^\circ$ ($c=0.78$, CHCl_3). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1600, 1190, 1175 (OTs), NMR (CDCl_3) δ ppm: 2.23 (3H, s, CH_3 of tosyl), 3.37 (3H, s, OCH_3), 4.78 (1H, d, $J=3.5$ Hz, H-1). Anal. Calcd. for $\text{C}_{29}\text{H}_{31}\text{O}_9\text{NS}$: C, 61.14; H, 5.49; N, 2.46; S, 5.63. Found: C, 61.11; H, 5.53; N, 2.47; S, 5.58.

Methyl 2-Benzylloxycarbonylamino-2-deoxy-3,6-di-O-tosyl- α -D-glucopyranoside (8)—A mixture of 1.5 g of 7, 19 ml of AcOH, and 6 ml of H_2O was warmed on a steam bath for 15 min, then, after cooling, diluted with 20 ml of H_2O and evaporated *in vacuo* below 45°. The residue was dissolved in EtOH and hexane was added. The resulting amorphous product was tosylated with 0.7 g of TsCl in 6 ml of pyridine, giving 1.7 g of a crude 8, which was purified by silica gel chromatography (30 g of silica gel packed with CHCl_3 , eluted with 1% MeOH- CHCl_3 , v/v) to give 0.81 g of 8, amorphous powder, $[\alpha]_D^{20} +65.7^\circ$ ($c=0.77$, CHCl_3). NMR (CDCl_3) δ ppm: 2.33 (3H, s, CH_3 of tosyl), 2.40 (3H, s, CH_3 of tosyl). Anal. Calcd. for $\text{C}_{29}\text{H}_{33}\text{O}_{11}\text{NS}_2$: C, 54.79; H, 5.23; N, 2.20; S, 10.09. Found: C, 54.62; H, 5.24; N, 2.44; S, 9.93.

Methyl 2,6-Dibenzylloxycarbonylamino-2,6-dideoxy-3-O-tosyl- α -D-glucopyranoside (4)—A mixture of 670 mg of 8, 100 mg of NaN_3 , and 3 ml of DMSO was stirred at 110–120° for 1 hr under N_2 atmosphere. The cooled mixture was treated in the usual manner, giving 477 mg of a 6-azido-3-sulfonate (9) as a syrup. IR $\nu_{\text{max}}^{\text{liq.}}$: 2100 cm^{-1} (azide). NMR (CDCl_3) δ : 2.30 ppm (3H, s, CH_3 of tosyl).

The 6-azide (9, 470 mg) thus obtained was dissolved in 3 ml of tetrahydrofuran and 100 mg of LiAlH_4 was added in portions with stirring and cooling. After 1.5 hr stirring, the mixture was worked up and was successively treated with 0.2 ml of benzylloxycarbonyl chloride as described earlier in the case of 3→1, affording 533 mg of a syrup which was purified by chromatography to give 301 mg of 4, mp 122°. The identification with the sample obtained before was carried out by infrared spectrometry, mixed mp and TLC.

Sodium Borohydride Reduction of Methyl 2,6-Dibenzylloxycarbonylamino-2,6-dideoxy-3-O-tosyl- α -D-glucopyranoside (4)—A mixture of 440 mg of 4, 60 mg of NaBH_4 , and 4.4 ml of DMSO was stirred at 80° (bath temp.) for 1 hr under nitrogen atmosphere. After another 20 mg of NaBH_4 was added, the reaction was continued for 4 hr. The cooled mixture was diluted with H_2O and the excess hydride was decomposed with AcOH. The mixture was extracted with CHCl_3 and the extract was washed with H_2O , dried and evaporated *in vacuo*. The residue was charged on a silica gel plate for preparative TLC ($2 \times 200 \times 200$ mm) and developed with AcOEt-benzene (1:1, v/v). After extraction of each component with MeOH- CHCl_3 (3:7, v/v) in the usual manner and evaporation of the solvent, 74 mg of the crude unchanged material (4) (fastest-moving), 20 mg of methyl 2,6-dibenzylloxycarbonylamino-2,3,6-trideoxy- α -D-ribo-hexopyranoside (10), mp 167–170°, needles, and 94 mg of the 2,4,6-trideoxy isomer (11), amorphous powder, $[\alpha]_D^{20} +41.8^\circ$ ($c=0.8$, CHCl_3) (slowest-moving), were obtained. NMR (CDCl_3) δ ppm for 10: 1.2–2.3 (2H, m, $-\text{CH}_2-$), 3.20 (3H, s, OCH_3), 4.45 (1H, d, $J=4$ Hz, H-1); for 11: 1.3–2.0 (2H, m, $-\text{CH}_2-$), 3.25 (3H, s, OCH_3). Mass Spectrum m/e for 10 and 11: 413 (M^+-OCH_3), 412 (M^+-HOCH_3). Anal. Calcd. for 10 as $\text{C}_{23}\text{H}_{28}\text{O}_7\text{N}_2$: C, 62.15; H, 6.35; N, 6.30; Found for 10: C, 61.70; H, 6.04; N, 6.43; Calcd. for 11 as $\text{C}_{23}\text{H}_{28}\text{O}_7\text{N}_2 \cdot 1/2\text{H}_2\text{O}$: C, 60.92; H, 6.45; N, 6.18; Found for 11: C, 61.06; H, 6.39; N, 6.27.

Acetylation of 10 and 11 with a mixture of Ac_2O and pyridine gave the acetate of 10, mp 156–158°, needles (from EtOH) and the acetate of 11, amorphous, respectively. IR ν_{max} cm^{-1} : for the acetate of 10 (Nujol): 3350 (NH), 1740 (OAc), 1710, 1680, 1530 (NHCOO); for the acetate of 11 (liq.): 1740 (shoulder, OAc), 1720, 1520 (NHCOO). NMR (CDCl_3) δ ppm for the acetate of 10: 1.92 (3H, s, CH_3CO); for the acetate of 11: 2.00 (3H, s, CH_3CO), 3.26 (3H, s, OCH_3), 1.3–2.0 (2H, m, $-\text{CH}_2-$). Mass Spectrum m/e for the acetate of 10: 486 (M^+), 455 (M^+-OCH_3), 454 (M^+-HOCH_3); for the acetate of 11: 486 (M^+), 455 (M^+-OCH_3), 426 ($\text{M}^+-\text{CH}_3\text{COOH}$), 395 ($\text{M}^+-\text{OCH}_3-\text{CH}_3\text{COOH}$). Anal. Calcd. for the acetate of 10 as $\text{C}_{25}\text{H}_{30}\text{O}_8\text{N}_2$: C, 61.72; H, 6.22; N, 5.76. Found: C, 61.31; H, 6.10; N, 5.78.

Methyl 4,6-O-Benzylidene-2-deoxy-2-methoxycarbonylamino-3-O-tosyl- α -D-glucopyranoside (13)—A mixture of 10 g of methyl 2-deoxy-2-methoxycarbonylamino- α -D-glucopyranoside (12), 50 g of benzaldehyde, and 20 g of ZnCl_2 (anhyd.) was stirred at room temperature for 2 hr. Then, after 100 ml of H_2O was added to the reaction mixture, the resulting crystals were washed with petroleum ether several times and recrystallized from EtOH to give 17 g of needles, mp 201–202°. Further recrystallization afforded silky needles, mp 214–215°, $[\alpha]_D^{20} +44.2^\circ$ ($c=1.4$, CHCl_3). Anal. Calcd. for $\text{C}_{16}\text{H}_{21}\text{O}_7\text{N}$: C, 56.63; H, 6.24; N, 4.13. Found: C, 56.69; H, 6.10; N, 4.11.

A solution of 1.9 g of the benzylidene derivative and 6.4 g of TsCl in 11 ml of pyridine was allowed to stand at room temperature overnight. Working up in the usual manner, 2.4 g of 13 was obtained as powder. The analytical sample was obtained by recrystallization from EtOH, needles, mp 164–166°, $[\alpha]_D^{20} -4.8^\circ$ ($c=3.1$, CHCl_3). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1600, 1190, 1175 (OTs). NMR (CDCl_3) δ ppm: 2.23 (3H, s, CH_3 of tosyl), 3.38 (3H, s, OCH_3), 3.65 (3H, s, CH_3OCO), 4.76 (1H, d, $J=4$ Hz, H-1), 5.43 (1H, s, $=\text{CH}-\text{C}_6\text{H}_5$), 7.28 (5H, s, $-\text{C}_6\text{H}_5$), 6.93, 7.16 (2H each, d, $J=9$ Hz, C_6H_4 to tosyl). Anal. Calcd. for $\text{C}_{28}\text{H}_{27}\text{O}_9\text{NS}$: C, 55.97; H, 5.52; N, 2.84; S, 6.50. Found: C, 56.11; H, 5.48; N, 2.82; S, 6.19.

Methyl 2-Deoxy-2-methoxycarbonylamino-3-O-tosyl- α -D-glucopyranoside (14)—A mixture of 19 g of 13, 90 ml of AcOH, and 72 ml of H_2O was warmed on a steam bath for 5 min and evaporated *in vacuo*

to dryness. The residue was dissolved in CHCl_3 and the solution was washed with aq. NaHCO_3 and successively with H_2O , and dried. Evaporation of the solvent left a syrup, which on washing with hexane gave 15 g of **14**, as a thick syrup. The analytical sample was obtained by chromatography over silica gel using 3% (v/v) MeOH-CHCl_3 as eluant. NMR (CDCl_3) δ ppm: 2.40 (3H, s, CH_3 of Ts), 3.34 (3H, s, OCH_3), 3.55 (3H, s, $-\text{COOCH}_3$), 4.21 (1H, d, $J=4$ Hz, H-1), 7.25, 7.78 (2H each, d, $J=9$ Hz, C_6H_4 of Ts). Anal. Calcd. for $\text{C}_{16}\text{H}_{23}\text{O}_9\text{NS}\cdot 1/2\text{H}_2\text{O}$: C, 46.36; H, 5.84; N, 3.38; S, 7.74. Found: C, 46.57; H, 5.49; N, 3.11; S, 7.54.

Methyl 2,3-Dideoxy-2-methoxycarbonylamino- α -D-ribo-hexopyranoside (16)—A stirred mixture of 14.5 g of **14**, 4.5 g of NaI, and 75 ml of DMF was heated at 90–100° overnight. The cooled reaction mixture was diluted with H_2O and, after addition of 50 g of lead acetate (solid), was shaken. After filtration, the aqueous solution was evaporated *in vacuo* and residue was extracted with boiling CHCl_3 . The extract was dried and evaporated to give 3.25 g of the crude 3-iodide (**14**) which was recrystallized from MeOH-ether to give fine needles, mp 188–189°. Anal. Calcd. for $\text{C}_9\text{H}_{16}\text{O}_6\text{NI}$: C, 29.93; H, 4.47; N, 3.88; I, 35.14. Found: C, 29.80; H, 4.49; N, 3.85; I, 35.11.

A solution of 3.2 g of **15** and 47 mg of KOH in 100 ml of EtOH was stirred over 23.5 ml of Raney nickel under H_2 atmosphere at room temperature and 1 atm for 2 hr. The catalyst was filtered and washed with EtOH. The combined washings and filtrate were evaporated and the residue was extracted with CHCl_3 several times. The extract was evaporated and was recrystallized from MeOH-ether to give 1.2 g of **16**, needles, mp 170–171°, $[\alpha]_D^{25} + 98.5^\circ$ ($c=3.0$, H_2O). Mass Spectrum m/e : 204 (M^+-OCH_3). Anal. Calcd. for $\text{C}_9\text{H}_{11}\text{O}_6\text{N}$: C, 45.95; H, 7.28; N, 5.96. Found: C, 45.81; H, 7.30; N, 5.91.

A solution of methyl 2,3-dideoxy-4,6-O-isopropylidene-2-methoxycarbonylamino- α -D-ribo-hexopyranoside¹⁾ in 80% aq. AcOH was heated on a steam bath for 30 min. Evaporation of the solvent *in vacuo* gave solid of **16** which was recrystallized and identified with the sample obtained as above by mixed mp, infrared spectrometry and TLC.

Methyl 2,6-Dibenzyloxycarbonylamino-2,3,6-trideoxy- α -D-ribo-hexopyranoside (10)—To an ice-cold solution of 1.2 g of **16** in 13 ml of pyridine was added dropwise a solution of 680 mg of TsCl in 2 ml of pyridine with stirring and the mixture was allowed to stand overnight in a refrigerator. Working up in the usual manner, the product was recrystallized from EtOH to give 1.46 g of the 6-*p*-toluenesulfonate, powder-like crystals, mp 138°, $[\alpha]_D^{19} + 102^\circ$ ($c=0.7$, CHCl_3). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1190, 1170 (OTs). Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{O}_8\text{NS}$: C, 49.40; H, 5.71; N, 3.61; S, 8.26. Found: C, 49.54; H, 5.89; N, 3.68; S, 8.53.

A stirred solution of 1.46 g of the 6-*p*-toluenesulfonate thus obtained and 730 mg of NaN_3 in 37 ml of DMSO was heated at 90–100° in an atmosphere of N_2 for 2 hr, and was diluted with cold CHCl_3 . The solution was washed with aq. sat. NaCl, dried, and evaporated, leaving 0.8 g of the crude 6-azide which was recrystallized from EtOH-hexane to give needles, mp 115°, $[\alpha]_D^{25} + 34.1^\circ$ ($c=3.0$, CHCl_3). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 2100 (N_3), no absorption due to OTs. Anal. Calcd. for $\text{C}_9\text{H}_{16}\text{O}_5\text{N}_4$: C, 41.53; H, 6.20; N, 21.53. Found: C, 42.63; H, 6.34; N, 20.77.

Through a stirred mixture of 496 mg of the 6-azide, 10 ml of MeOH, 5 ml of H_2O , and 300 mg of 10% Pd-C was bubbled hydrogen at room temperature for 30 min and filtered. After addition of 2 g of $\text{Ba}(\text{OH})_2$ (solid), the mixture was refluxed for 4 hr and the cooled mixture was filtered. Benzyloxycarbonyl chloride (5 ml) was added to the cooled filtrate with stirring and the mixture was stirred for 2 hr at room temperature. The resulting crystalline mass was collected by decantation, washed with H_2O and dissolved in CHCl_3 . The CHCl_3 solution was washed with aq. NaHCO_3 and with H_2O , dried and evaporated. The residue was triturated with ether and recrystallized from EtOH to give 70 mg of **10**, needles, mp 169–170°, $[\alpha]_D^{21} + 2.9^\circ$ ($c=3$, CHCl_3), which was identical with the sample obtained by NaBH_4 reduction of **4** as described earlier.

Methyl 2,6-Dibenzyloxycarbonylamino-2,4,6-trideoxy- α -D-erythro-hexopyranosid-3-ulose (17)—A solution of 40 mg of **11** in a mixture of 0.5 ml of Ac_2O and 0.5 ml of DMSO was allowed to stand overnight at room temperature. The reaction mixture was diluted with H_2O and the resulting precipitates were collected and dissolved in CHCl_3 . The CHCl_3 solution was washed with H_2O , dried and evaporated to give 38 mg of **17** as chromatographically homogeneous amorphous powder. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3300 (NH), 1730 (C=O), 1700, 1540 (NHCOO). Mass Spectrum m/e : 442 (M^+), 411 (M^+-OCH_3). Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{O}_7\text{N}_2$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.45; H, 5.98; N, 6.19.

Methyl 2,6-Dibenzyloxycarbonylamino-2,3,6-trideoxy- α -D-erythro-hexopyranosid-4-ulose (18)—A solution of 100 mg of **10** in a mixture of 0.5 ml of Ac_2O and 0.5 ml of DMSO was allowed to stand overnight at room temperature. Water was added to the solution to precipitate crystals, which revealed two spots on TLC (benzene-AcOEt, 1:1, v/v). The crude crystals were chromatographed on preparative TLC (silica gel, $2 \times 200 \times 200$ mm) with benzene-AcOEt (1:1, v/v). Extraction with $\text{CHCl}_3\text{-MeOH}$ (1:1, v/v) followed by evaporation of the solvent gave 56 mg of **18** (slower-moving component), mp 157–158° (from EtOH). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3350 (NH), 1730 (C=O), 1690, 1530 (NHCOO). Mass Spectrum m/e : 442 (M^+), 443 (M^++1). Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{O}_7\text{N}_2$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.45; H, 5.98; N, 6.19.

As a by-product, 20 mg of the 4-O-(methylthio)methyl derivative (faster-moving) was isolated and recrystallized from EtOH to needles, mp 153–154°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3350 (NH), 1690, 1540 (NHCFO). Mass Spectrum m/e : 504 (M^+), 505 (M^++1) (Calcd. for $\text{C}_{25}\text{H}_{32}\text{O}_7\text{N}_2\text{S}$: 504).

Methyl 3,4-Anhydro-2,6-dibenzyloxycarbonylamino-2,6-dideoxy- α -D-allopyranoside (19)—To a solution of 1 g of **4** in 15 ml of MeOH was added 0.9 ml of 2N NaOMe in MeOH and the mixture was allowed to stand

for 2 days at room temperature. Then, the mixture was diluted with H_2O and extracted with CHCl_3 . The extract was dried and evaporated and the residue was triturated with hexane-ether and recrystallized from EtOH, giving 0.6 g of **19**, fine needles, mp $134\text{--}136^\circ$, $[\alpha]_D^{20} -9.6^\circ$ ($c=1.8$, CHCl_3). NMR (CDCl_3) δ ppm: 4.60 (1H, d, $J_{1,2}=5.5$ Hz, H-1), 3.99 (1H, t, $J_{2,3}=5.5$ Hz, H-2), 4.3—3.9 (1H, m, H-5), 3.64—3.27 (2H, q, $J_{3,4}=5.5$ Hz, H-3,4), ~ 3.25 (2H, H-6,6'), 3.24 (3H, s, OCH_3). Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{O}_7\text{N}_2$: C, 62.43; H, 5.92; N, 6.33. Found: C, 61.95; H, 5.79; N, 6.33.

Methyl 2,6-Dibenzyloxycarbonylamino-2,4,6-trideoxy- α -D-ribo-hexopyranoside (11)—i) A mixture of 220 mg of **19**, 300 mg of NaI, 17 mg of anhyd. NaOAc, 0.32 ml of AcOH, and 3 ml of acetone was refluxed for 3 hr, then diluted with CHCl_3 and washed with H_2O . The organic layer was dried and evaporated, leaving 242 mg of the iodohydrin (**20**) which revealed one spot on TLC.

The iodohydrin (**20**) (180 mg) thus obtained was dissolved in 5 ml of EtOH and 1 ml of Raney nickel in EtOH and an excess amount of triethylamine was added. The mixture was shaken under H_2 (2.5 kg/cm 2) for 2 hr at room temperature, filtered, and evaporated *in vacuo* to dryness. The residue was dissolved in CHCl_3 and washed with H_2O , dried and evaporated, leaving 77 mg of **11** which was identical with the sample obtained before.

ii) To an ice-cold solution of 500 mg of **19** in 30 ml of tetrahydrofuran, 120 mg of LiAlH_4 was added with stirring. After having been stirred in an ice-bath for 2.5 hr, the mixture was diluted with 100 mg of CHCl_3 and with aq. MeOH for decomposition of the excess reagent. After filtration, the mixture was washed with aq. NaCl, dried and evaporated to leave 415 mg of an amorphous residue which was chromatographed on preparative TLC (silica gel, $2 \times 200 \times 200$ mm, AcOEt-benzene, 1:1, v/v). Thus, 138 mg of **11** was obtained as amorphous solid.

Methyl 3,4-Anhydro-2,6-dibenzyloxycarbonylamino-2,6-dideoxy- α -D-galactopyranoside (21)—i) A mixture of 307 mg of **5**, 57 mg of NaBH_4 and 3 ml of DMSO was stirred at 70° for 2.5 hr under N_2 atmosphere. The cooled mixture was worked up as before, giving a crystalline mass which was recrystallized from EtOH to give 140 mg of **21**, needles, mp 165° , $[\alpha]_D^{21} +33.3^\circ$ ($c=2.46$, CHCl_3). NMR (CDCl_3) δ ppm: 4.55 (1H, d, $J=5$ Hz, H-1), 4.2—3.7 (2H, m, H-2,5), 3.30 (3H, s, OCH_3), 3.10 (2H, s, H-6,6'), 3.6—3.2 (2H, m, H-3,4). Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{O}_7\text{N}_2$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.37; H, 5.82; N, 6.15.

ii) To a solution of 1.4 g of **5** in 35 ml of MeOH containing 1 ml of CHCl_3 was added 1.8 ml of 2N NaOCH_3 in MeOH and the mixture was stirred at room temperature for 1 hr. The resultant crystals were collected and recrystallized from EtOH to give 1.04 g of **21**.

Methyl 2,6-Dibenzyloxycarbonylamino-2,3,6-trideoxy- α -D-xyllo-hexopyranoside (22)—To an ice-cold solution of 2.0 g of **21** in 30 ml of tetrahydrofuran, 1.0 g of LiAlH_4 was added with stirring. After stirring for 2 hr with cooling, the mixture was diluted with CHCl_3 , then with aq. MeOH for decomposition of the reagent, and filtered. The filtrate was worked up as before and the product (1.5 g) was chromatographed over silica gel (44 g in benzene) with AcOEt-benzene (1:9 and 3:17, v/v), giving 200 mg of **22**, 470 mg of crude **22**, and 63 mg of an unidentified product which gave a positive ninhydrin test. The pure sample of **22** has mp $192\text{--}193^\circ$, $[\alpha]_D^{21} +61.2^\circ$ ($c=2.3$, CHCl_3). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm $^{-1}$: 3500 (OH), 3320 (NH), 1680, 1880, 1540 (NH-COO).

Acetylation of 50 mg of **22** with a mixture of 0.25 ml of pyridine and 0.25 ml of Ac_2O gave the acetate of **22**, granules, mp $173\text{--}175^\circ$ (from EtOH-hexane). NMR (CDCl_3) δ ppm: 2.10 (3H, s, OCOCH_3). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm $^{-1}$: 3350 (NH), 1730 (OAc), 1690, 1680, 1540 (NHCOO). Mass Spectrum m/e : 486 (M^+), 455 ($\text{M}^+ - \text{OCH}_3$), 454 ($\text{M}^+ - \text{HOCH}_3$). Anal. Calcd. for $\text{C}_{25}\text{H}_{30}\text{O}_8\text{N}_2$: C, 61.72; H, 6.22; N, 5.76. Found: C, 61.55; H, 6.28; N, 5.79.

Oxidation of Methyl 2,6-Dibenzyloxycarbonylamino-2,3,6-trideoxy- α -D-xyllo-hexopyranoside (22)—i) A solution of 60 mg of **22** in 0.4 ml of DMSO and 0.4 ml of Ac_2O was allowed to stand overnight at room temperature. Working up in the usual manner gave 70 mg of a crystalline mixture which revealed two spots on TLC. The preparative TLC on silica gel ($2 \times 100 \times 200$ mm, AcOEt-benzene, 1:1, v/v) gave 12 mg of a 4-O-(methylthio)methyl derivative (faster-moving, mp $180\text{--}185^\circ$; δ 2.06 ppm in CDCl_3 , SCH_3 ; Mass Spectrum m/e : 504, M^+) and 35 mg of **18** which was identified with the sample obtained before by mixed mp and infrared spectrometry.

ii) To an ice-cold, stirred mixture of 150 mg of CrO_3 and 5.5 ml of pyridine, 42 mg of **22** was added. Stirring was continued overnight at room temperature and the mixture was diluted with AcOEt. The resulting precipitates were filtered off and the filtrate was evaporated *in vacuo*. The residue was extracted with AcOEt and the extract was evaporated to dryness, leaving 30 mg of **18** which was recrystallized from EtOH.