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PREPARATION OF DERIVATIVES LEADING TO 2-AMINO-2-DEOXY-D-GULURONIC ACID

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INTRODUCTION

The availability of 2-amino-2-deoxy-D-gulose derivatives by interconversion from 2-amino-2-deoxy-D-glucose derivatives[1], and the importance of the former structure in natural products[2], have led us to begin a systematic study of 2-amino-2-deoxy-D-gulose derivatives. Uronic acids are of value[3,4] as intermediates for a variety of preparative purposes in the amino sugar field. It is possible that 2-amino-2-deoxy-D-guluronic acid may eventually be found in Nature, as have been 2-amino-2-deoxy-D-galacturonic acid[5], 2-amino-2-deoxy-D-glucuronic acid[6], and 2-amino-2-deoxy-D-mannuronic acid[7]. This first report is concerned with possible routes to derivatives of 2-amino-2-deoxy-D-guluronic acid.

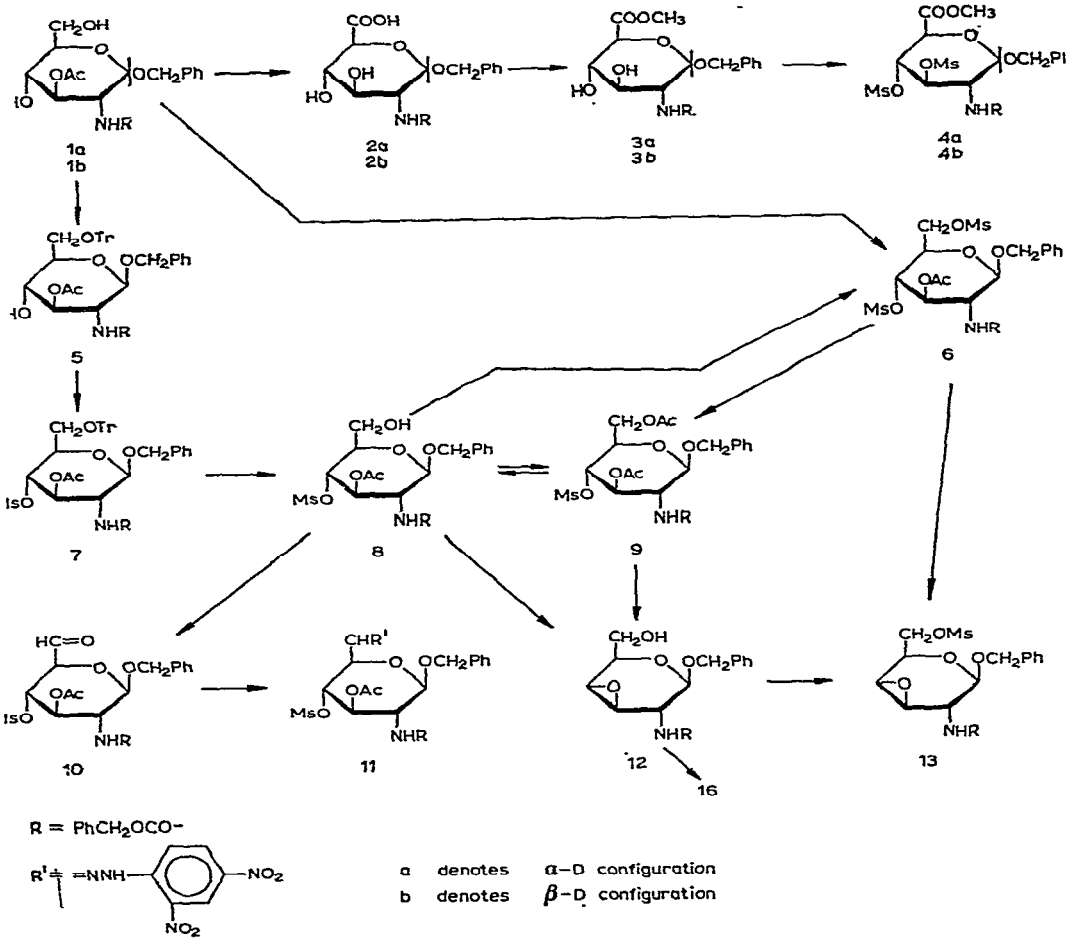
RESULTS AND DISCUSSION

Initially, a route through the known 2-amino-2-deoxy-D-glucuronic acid[8] appeared convenient, provided that the 3-*O*-acetyl derivative (**1**) could be oxidized to the acid, to furnish an intermediate which could be subjected to configurational inversions[1,9] at C-3 and C-4 and give the desired material in only four subsequent steps. However, catalytic oxidation of each of the anomeric 3-*O*-acetyl derivatives (**1a** and **1b**)* proved to be accompanied by deacetylation, leading to **2a** and **2b**, respectively. Both products were identified and further characterized by their known[10,11] methyl esters (**3a** and **3b**). The 3,4-dimethanesulfonate of this ester, **4b**, was prepared, with a view to conversion into **21** by treatment with base, by the well-known procedure for preparing an epoxy sugar[12] from a vicinal disulfonate. However, all efforts in that direction were unsuccessful.

Substance **1b** was selected for the remaining work, because of the generally superior crystallizing and handling properties noted with the β-D-glycosides. Substance **1b** was converted into the 4,6-dimethanesulfonate (**6**), and thence into the 3,6-di-*O*-acetyl-4-*O*-(methylsulfonyl) derivative (**9**). The relatively high yields in this direct route to **9** were not consistently reproducible. Moreover, although alkaline conversion

*The anomeric benzyl glycosides are indicated throughout by "a" for the α-D anomer and "b" for the β-D anomer.

of **9** into the 3,4-epoxy intermediate (**12**) gave excellent crude yields, the intensive recrystallization necessary to remove the last traces of sulfur-bearing contaminants from **12**—essential if poisoning of the catalyst was to be avoided in the following oxidation step— diminished the usable yield of epoxide to not greater than 65%.



Accordingly, an alternative route through the 6-trityl ether (**5**) derived from **1b** was examined. Substance **5** could be readily converted into the 4-methanesulfonate (**7**) and then be detritylated with aqueous acetic acid to give **8**. The structure of **8** was confirmed by methanesulfonation, to give the previously known[13] **6**, and by its conversion into **9**. Attempts at catalytic oxidation of **8** resulted in immediate poisoning of the catalyst, with no subsequent oxidation. It may be noted that the selectivity of the deacetylation of **9** at C-6 (pH 10 at 0°) to give **8** is a little surprising in view of the extraordinarily facile deacetylation at C-3 (pH 8 at 80°) observed during catalytic oxidation of **1a** and **1b**. It appears that the solvolysis of the 3-*O*-acetyl group can be facilitated or prevented, simply by a suitable adjustment of the temperature. Not

only was the overall yield of **9** from **1b** by the indirect route *via* the trityl ether slightly superior (75% *vs.* 73%) to that by the direct route, but, more important, the direct alkaline conversion of **8** into **12** immediately gave an uncontaminated product, suitable for oxidation to **16**.

A further advantage of the indirect route appeared when it was found that **8** could be specifically oxidized* to the 6-aldehyde (**10**) by methyl sulfoxide in the presence of *N,N'*-dicyclohexylcarbodiimide and phosphoric acid[15]. Substance **10** was not isolated, but was characterized as its (2,4-dinitrophenyl)hydrazone (**11**). The aldehyde **10** and analogous derivatives offer promise as intermediates for future study.

Alkaline conversion of **6** into **13**, as used for the α-D anomer[9] of **13**, provided a reference substance for further characterization of **12**. Methanesulfonation of the latter gave **13**. Treatment with hot, aqueous acetic acid converted **12** into the 2,3-carbamate** (**18**) having the 2-amino-2-deoxy-D-gulose configuration, and the same treatment of **13** gave the 2,3-carbamate **14**. The latter was characterized as the 4,6-dimethanesulfonate (**19**) and also as the 4-*O*-acetyl-6-*O*-(methylsulfonyl) derivative (**15**). Substance **19** also served as an aid in confirming the structure of **18**, which was also characterized as the diacetate (**22**). The 2-amino-2-deoxy-D-gulose structure of **18** was finally verified by alkaline hydrolysis to give benzyl 2-amino-2-deoxy-β-D-guloside (**23**), which could be converted by acid hydrolysis into the known[1] 2-amino-2-deoxy-D-gulose hydrochloride.

When **12** was subjected to catalytic oxidation, it readily provided benzyl 3,4-anhydro-2-[(benzyloxycarbonyl)amino]-2-deoxy-β-D-galactopyranosiduronic acid (**16**) in a yield (60%) comparable to that obtained by catalytic oxidation of otherwise unprotected benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-D-glucopyranosides[8,10,11] and -galactopyranosides [17,18]. It is evident from this fact that the 3,4-epoxide bridge is quite stable to the conditions required for this oxidation, in marked contrast to the 3-acetyl group, which is labile. Substance **16** was readily characterized as its methyl ester (**20**), which could be prepared in quantitative yield by treatment with diazomethane. The derivative **16** could also be converted, by aqueous acetic acid, into a hygroscopic carbamate (**17**) having the D-*gulo* configuration. The carbamate (**17**) was also obtained, but in markedly lower yield, by catalytic oxidation of **18**. Substance **18** showed a strong tendency to become adsorbed to the catalyst, hindering the oxidation. The hygroscopic carbamate **17** was characterized as its methyl ester (**21**) and 3-acetate (**24**). Attempts to cleave the carbamate **17** with alkali gave an uncrystallizable gum that was not characterized.

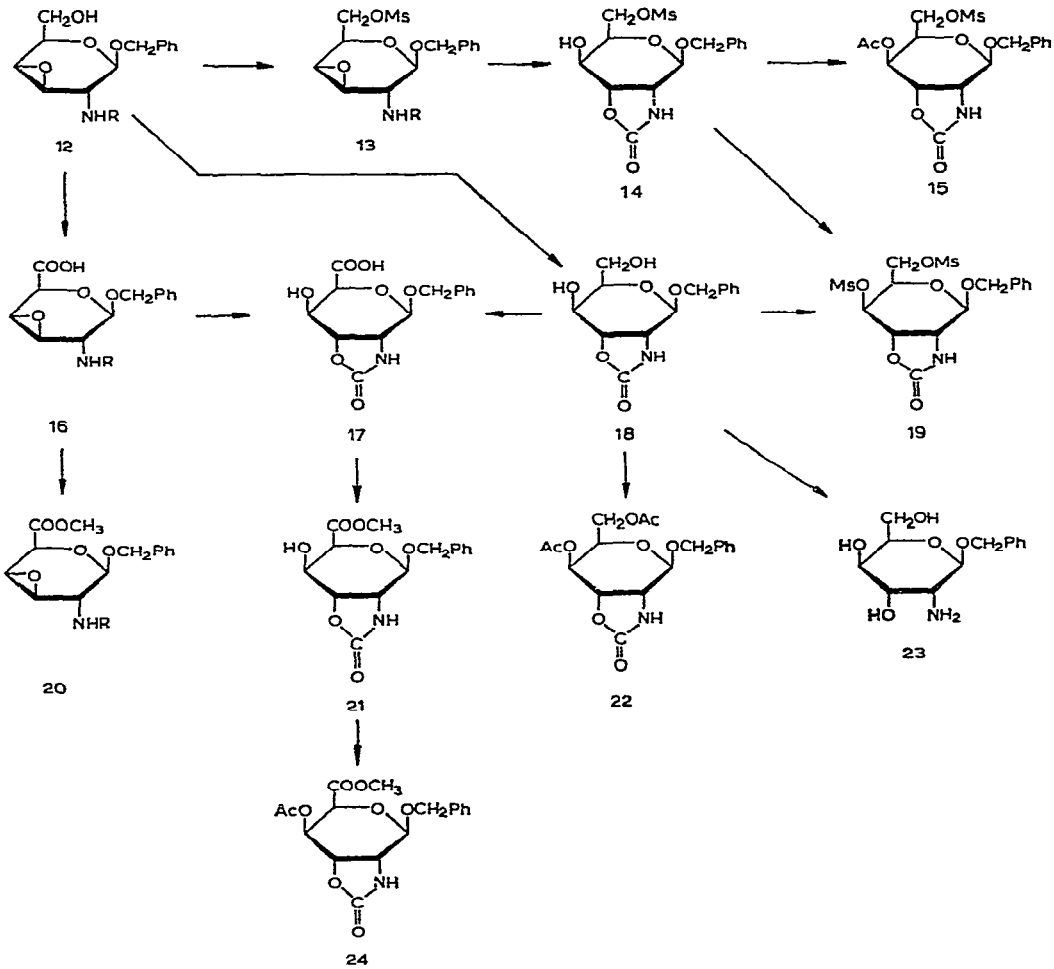
The preferred route from **1b** to **17** is considered to be as follows: **1b**→**6**→**7**→**8**→**12**→**16**→**18**. However, the ester derivative (**21**) obviously affords a more felicitous material for handling and storage than does the acid **17**.

*Using conditions similar to those above, Horton *et al.*[14] have converted the primary alcohol function in 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose into an aldehyde function.

**This class of compound has been referred to as oxazolidone in earlier publications[16].

EXPERIMENTAL

All melting points are uncorrected. Thin-layer chromatograms were made on silica gel, with benzene–methanol mixtures, usually in a 19:1 ratio, as developer. In a few cases, slight deviations from these proportions were required in order to assure satisfactory migration of the spots.



Benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-α-D-glucopyranosiduronic acid (**2a**)

A suspension of 3.2 g of **1a**[13] in 700 ml of distilled water was heated to 80° with stirring at 4000 to 5000 rpm, and 1.2 g of pre-hydrogenated platinum dioxide was added. Oxygen was bubbled through the stirred mixture for 4 h, during which time the pH was maintained at 8 by continual addition of sodium hydrogen carbonate. After

being cooled to 10°, the suspension was filtered, and the filtrate was concentrated to 50 ml. This solution was cooled to 5°, filtered, and acidified to pH 3 by careful addition of concentrated hydrochloric acid. After storage for 2h at 0°, the product was filtered off, washed at 0° with water, and recrystallized from 60% methanol, to give 1.1 g (30%) of long, white needles having properties identical with those given in the literature[8,10] for **2a**.

Benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-β-D-glucopyranosiduronic acid (**2b**)

Treatment of **1b**[13] in a manner identical to that given above gave **2b** (yield 30%) having properties identical with those previously described[11].

Methyl (benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-3,4-di-O-(methylsulfonyl)-α-D-glucopyranosid)uronate (**4a**)

Substance **2a** was converted into the methyl ester (**3a**) by treatment with diazomethane, as described in the literature [10]. To 0.5 g of **3a** in pyridine at −5° was added 0.5 ml of methanesulfonyl chloride. After storage at −5° for 2 days, the mixture was poured into ice-water to precipitate a gum, which was separated by decantation and recrystallized from 80% aqueous methanol, to afford 0.37 g (64%) of long, white needles, m.p. 141–2°, $[\alpha]_D^{27}$ +93° (*c* 2.4, pyridine).

Anal. Calc. for $C_{24}H_{29}NO_{12}S_2$: C, 49.06; H, 4.97; N, 2.39. Found: C, 49.43; H, 4.98; N, 2.41.

Methyl (benzyl 2-[(benzyloxycarbonyl)amino]-2-deoxy-3,4-di-O-(methylsulfonyl)-β-D-glucopyranosid)uronate (**4b**)

Substance **2b** was converted into the methyl ester (**3b**) with diazomethane[11]. The ester (0.7 g) was methanesulfonated as described for **4a**. The crystals which formed when the product was poured into ice-water were filtered off and recrystallized from methanol, to provide 0.8 g (85%) of needles, m.p. 180°, $[\alpha]_D^{27}$ −10° (*c* 1.2, pyridine).

Anal. Calc. for $C_{24}H_{29}NO_{12}S_2$: C, 49.06; H, 4.97; N, 2.39; O, 32.67; S, 10.91. Found: C, 49.29; H, 5.11; N, 2.42; O, 32.98; S, 10.66.

Benzyl 3-O-acetyl-2-[(benzyloxycarbonyl)amino]-2-deoxy-6-O-trityl-β-D-glucopyranoside (**5**)

Substance **1b** (13 g), which had been dried for 24 h at 90° and 3 mm over P_2O_5, was dissolved in 30 ml of absolute pyridine, treated with 8.2 g of chlorotriphenylmethane, and shaken for 48 h at room temperature. The bulk of this solution of **5** was used, without isolation of **5**, for the preparation of **7**. A small aliquot was removed, poured into ice-water, and the precipitated syrup dissolved in hot methanol. Crystals of **5** were formed upon cooling, m.p. 130–1°, $[\alpha]_D^{27}$ −32° (*c* 1.8, pyridine).

Anal. Calc. for $C_{42}H_{41}NO_8$: C, 73.34; H, 6.01; N, 2.04; O, 18.61. Found: C, 73.05; H, 6.06; N, 2.33; O, 18.61.

Benzyl 3-O-acetyl-2-[(benzyloxycarbonyl)amino]-2-deoxy-4-O-(methylsulfonyl)-6-O-trityl-β-D-glucopyranoside (7)

A further 40 ml of pyridine was added to the solution of **5** described above, the whole was cooled to −5°, and 13 ml of methanesulfonyl chloride was added slowly with stirring. The mixture was kept for 48 h at −5°, poured into ice-water, and filtered, and the precipitate was recrystallized from isopropyl alcohol to give 21.3 g (90%) of **7**, m.p. 135–6°, $[\alpha]_D^{27}$ −11° (*c* 1.0, pyridine).

Anal. Calc. for $C_{43}H_{43}NO_{10}S$: C, 67.44; H, 5.66; N, 1.83; O, 20.89; S, 4.19. Found: C, 66.47; H, 5.77; N, 1.94; O, 21.11; S, 4.74.

Benzyl 3-O-acetyl-2-[(benzyloxycarbonyl)amino]-2-deoxy-4-O-(methylsulfonyl)-β-D-glucopyranoside (8)

(a) To a solution of **7** (19.4 g) in glacial acetic acid (200 ml) at 95° was added water (200 ml) during 45 min. After refrigeration overnight, the mixture was filtered. The precipitate was successively extracted with four 100-ml portions of benzene, and the residual product (10.8 g, 84%) was recrystallized from chloroform–isopropyl ether, m.p. 166–7°, $[\alpha]_D^{27}$ −14° (*c* 2.0, pyridine).

Anal. Calc. for $C_{24}H_{29}NO_{10}S$: C, 55.06; H, 5.55; N, 2.68; O, 30.56; S, 6.14 Found: C, 54.33; H, 5.38; N, 2.72; O, 31.55; S, 6.25.

(b) A solution of 3 g of **9** in 50 ml of *p*-dioxane was cooled to 0°, and 0.5N aqueous potassium hydroxide was added during 3 h, at a rate sufficient to maintain the pH at 10. The solution was then neutralized with a few drops of glacial acetic acid, and concentrated to give a gel. This residue was suspended in 100 ml of water, and the suspension was shaken for 12 h, and filtered. The solid was recrystallized from chloroform–isopropyl ether, to provide 2.0 g (80%) of product identical in all respects (m.p., specific rotation, t.l.c., i.r. spectrum) with the product obtained by method (a).

Benzyl 3,6-di-O-acetyl-2-[(benzyloxycarbonyl)amino]-2-deoxy-4-O-(methylsulfonyl)-β-D-glucopyranoside (9)

(a) A mixture of 5 g of **6**[13], 10 g of potassium acetate, and 32 ml of a 3:1 (v/v) mixture of glacial acetic acid and acetic anhydride was heated for 10 h at 105°, and then evaporated at 12–15 mm pressure.

The residue was successively re-evaporated with two 10-ml portions of glacial acetic acid, and then two 20-ml portions of toluene, to give a solid which was twice extracted with 75-ml portions of tetrahydrofuran. The combined extracts were filtered through a thin layer of silica gel, and the solution was evaporated to a syrup and re-evaporated twice with toluene; the residue was crystallized from ethanol, to afford 3.5 g (76% crude) of **9**, m.p. 158° (dec.), $[\alpha]_D^{21}$ −16° (*c* 1.9, pyridine).

Anal. Calc. for $C_{26}H_{31}NO_{11}S$: C, 55.21; H, 5.53; N, 2.48; O, 31.11; S, 5.68. Found: C, 54.65; H, 5.42; N, 2.52; O, 31.94; S, 5.88.

(b) A solution of **8** (0.5 g) in the minimal volume of pyridine was cooled to 0°, and acetylated at room temperature for 12 h with acetic anhydride (0.5 ml), after which time it was poured into ice-water to give 0.7 g (quantitative yield) of **9**, which

was recrystallized from ethanol. This material was identical (m.p., specific rotation, t.l.c., i.r. spectrum) with that prepared by method (a).

Benzyl 3-O-acetyl-2-[(benzyloxycarbonyl)amino]-2-deoxy-4-O-(methylsulfonyl)-β-D-gluco-hexodialdo-1,5-pyranoside 6-(2,4-dinitrophenyl)hydrazone (**11**)

To a stirred solution of **8** (0.913 g) in 20 ml of methyl sulfoxide at 21°, which had been treated with 1.47 g of *N,N'*-dicyclohexylcarbodiimide, was added dropwise 0.46 ml of anhydrous orthophosphoric acid. Stirring was continued for 21 h at room temperature (25°), after which time the mixture was filtered, and the residue was washed with small portions of methyl sulfoxide and acetone. The filtrate and washings were combined and diluted with an excess of chloroform, followed by water and sufficient 2.4N potassium hydrogen carbonate solution to give a pH of 8. The aqueous layer was extracted repeatedly with chloroform, and the combined organic layers were washed with water until they were neutral. The organic solution was evaporated to a syrup, which was dissolved in methanol; a product was precipitated by addition of water. Thin-layer chromatography of this product showed the presence of starting material (**8**) and one other component (presumably **10**). This mixture was dissolved in the minimal volume of methanol, and treated with an excess of alcoholic (2,4-dinitrophenyl)hydrazine. After 45 min, the product was filtered off and recrystallized from ethyl acetate–methanol to give 0.47 g (27% based on **8**) of yellow crystals, m.p. 219° (dec.).

Anal. Calc. for $C_{30}H_{31}N_5O_{13}$: C, 51.35; H, 4.45; N, 9.98. Found C, 51.44; H, 4.44; N, 9.80.

Benzyl 3,4-anhydro-2-[(benzyloxycarbonyl)amino]-2-deoxy-β-D-galactopyranoside (**12**)

(a) A solution of **9** (6.5 g) in 30 ml of absolute *p*-dioxane was cooled to 0°, ice-cold 0.51M sodium methoxide (33 ml) was added, and the mixture was stirred for 3 h, and kept overnight at 0°. The mixture was filtered, the residue was washed thoroughly with tetrahydrofuran, and the filtrate and washings were combined, filtered through a thin layer of silica gel, and evaporated to dryness at 12–15 mm. The residual solid was recrystallized by dissolving it in ethyl acetate and adding isopropyl ether, to give 4.1 g (95%) of **12**, m.p. 159–60°, $[\alpha]_D^{22}$ −106° (*c* 1.3, pyridine), ν_{max}^{KBr} 3500 (hydroxyl), 3350, 1700, 1520 (urethan), 1250 (epoxide), 730, 700 (phenyl) cm^{-1}.

Anal. Calc. for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.01; N, 3.64. Found : C, 65.44; H, 5.99 N, 3.82.

(b) Treatment of **8** in the manner described in method (a) above gave **12** (77% yield), having properties (m.p., specific rotation, t.l.c., i.r. spectrum) identical with those of the foregoing product.

Benzyl 3,4-anhydro-2-[(benzyloxycarbonyl)amino]-2-deoxy-6-O-(methylsulfonyl)-β-D-galactopyranoside (**13**)

(a) To an ice-cold solution of 3 g of **6**[13] in 50 ml of absolute *p*-dioxane was added

17 ml of ice-cold 0.38M sodium isopropoxide. With continued stirring, the partially frozen material dissolved completely. After stirring the mixture for 12 h in the cold, tetrahydrofuran (30 ml) was added, the mixture was filtered, and the filtrate was concentrated to a syrup at 12–15 mm. The residue was dissolved in tetrahydrofuran, the mixture was filtered through a thin layer of silica gel, and the product was precipitated from the filtrate with isopropyl ether containing a little heptane. It was recrystallized from methanol–isopropyl ether to give 1.8 g (78%) of white crystals, m.p. 145–6°, $[\alpha]_D^{25}$ −101° (*c* 1.4, pyridine), ν_{max}^{KBr} 3350, 1700, 1550 (urethan), 1260 (epoxide), 1185 (sulfonate), 735, 700 (phenyl) cm^{-1}.

Anal. Calc. for $C_{22}H_{25}NO_8S$: C, 57.01; H, 5.44; N, 3.02. Found: C, 57.19; H, 5.44; N, 3.02.

(b) To **12** (0.22 g) in the minimal volume of pyridine at −5° was added methanesulfonyl chloride (0.25 ml), and the mixture was kept for 2 days at −5°. When poured over crushed ice, it gave 0.23 g (89%) of product, which was recrystallized as in (a) and was identical in all respects (m.p., specific rotation, t.l.c., i.r. spectrum) with the preceding preparation.

Benzyl 2-amino-2-deoxy-β-D-gulopyranoside 2,3-carbamate (**18**)

To a solution of **12** (1.5 g) in 60 ml of glacial acetic acid at 105° was added 60 ml of water during 1 h, after which time the solution was evaporated at 12–15 mm. The residue was re-evaporated with ethanol and then with toluene, to give a dry syrup which was dissolved in a small volume of methanol; the product crystallized on addition of isopropyl ether. Recrystallization from the same solvent afforded 0.9 g (82%) of needles, m.p. 115°, $[\alpha]_D^{23}$ −101° (*c* 2.6, pyridine) ν_{max}^{KBr} 3500 (hydroxyl), 3350, 1750 (carbamate), 740, 700 (phenyl) cm^{-1}; amide-II band at 1500–1550 cm^{-1} absent because of ring formation.

Anal. Calc. for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.75; O, 32.51. Found: C, 56.63; H, 5.97; N, 4.83; O, 32.63.

Benzyl 4,6-di-O-(methylsulfonyl)-β-D-gulopyranoside 2,3-carbamate (**19**)

(a) Compound **13** (1 g) was treated as described above for **18**, and after evaporation, the product was re-evaporated once with glacial acetic acid and twice with toluene, to give **14** as a syrup. The latter was dissolved in a small volume of pyridine, cooled to −5°, and cold methanesulfonyl chloride (1 ml) was added. The mixture was kept for 2 days at −5°, and then poured over ice, to give 0.6 g (67%, based on **13**) of crystals which were recrystallized from acetone–isopropyl ether, m.p. 202°, $[\alpha]_D^{25}$ −69° (*c* 1.5, pyridine).

Anal. Calc. for $C_{16}H_{21}NO_{10}S_2$: C, 42.57; H, 4.69; N, 3.10. Found: C, 42.78; H, 4.73; N, 3.13.

(b) Treatment of 0.14 g of **18** with methanesulfonyl chloride, and recrystallization as in method (a), gave 0.17 g (76%) of product identical (m.p., specific rotation, t.l.c., i.r. spectrum) with that described above.

Benzyl 3-O-acetyl-6-O-(methylsulfonyl)-β-D-gulopyranoside 2,3-carbamate (**15**)

Substance **13** (7.5 g) was converted into **14** by the method described in the preparation of **19**. To a cold solution of syrupy **14** in pyridine was added acetic anhydride (3 ml), and the solution was kept for 12 h at room temperature. When poured into ice-water, it afforded 6.6 g (98% based on **13**) of product, which was recrystallized from methanol, m.p. 180°, $[\alpha]_D^{27}$ −55° (*c* 2.2, pyridine).

Anal. Calc. for $C_{17}H_{21}NO_9S$: C, 49.15; H, 5.10; N, 3.37; O, 34.66; S, 7.74. Found: C, 49.26; H, 5.39; N, 3.53; O, 34.78; S, 7.63.

Benzyl 4,6-di-O-acetyl-β-D-gulopyranoside 2,3-carbamate (**22**)

Substance **18** (0.17 g) was acetylated in pyridine–acetic anhydride for 12 h at 0°, and, after being poured onto ice, it gave 0.13 g (60%) of product, which was recrystallized from methanol, m.p. 168–9°, $[\alpha]_D^{27}$ −71° (*c* 1.0, pyridine.)

Anal. Calc. for $C_{18}H_{21}NO_8$: C, 56.99; H, 5.58; N, 3.69; O, 33.74. Found: C, 56.82; H, 5.70; N, 4.04; O, 33.45.

Benzyl 2-amino-2-deoxy-β-D-gulopyranoside (**23**)

To 12 ml of a 15% aqueous potassium hydroxide solution was added **18** (2.5 g), and the mixture was heated for 4 h at 55°. After the mixture had been cooled, the precipitate was filtered off, thoroughly washed with ice-water, and crystallized from methanol by the addition of isopropyl ether, to afford 2.2 g (96%) of short, white needles, m.p. 146–7°, $[\alpha]_D^{21}$ −75° (*c* 1.0, pyridine).

Anal. Calc. for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20; O, 29.71. Found: C, 57.12; H, 7.11; N, 5.01; O, 31.16.

Benzyl 3,4-anhydro-2-[(benzyloxycarbonyl)amino]-2-deoxy-β-D-galactopyranosiduronic acid (**15**)

Substance **12** (2.2 g) was oxidized by the procedure described for the preparation of **2a**. After the product from the hydrochloric acid solution had been collected, it was dissolved in methanol, and the mixture was filtered through a thin layer of silica gel; the product crystallized from the filtrate on adding water. Recrystallization from 50% aqueous methanol gave 1.6 g (60%) of long, white needles, m.p. 131°, $[\alpha]_D^{26}$ −151° (*c* 1.1, pyridine), ν_{max}^{KBr} 3300, 1690, 1550 (urethan), 1720 (carbonyl), 1250 (epoxide), 730, 700 (phenyl) cm^{-1}.

Anal. Calc. for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51; O, 28.04. Found: C, 62.87; H, 5.27; N, 4.07; O, 28.03.

Methyl (benzyl 3,4-anhydro-2-[(benzyloxycarbonyl)amino]-2-deoxy-β-D-galactopyranosid)uronate (**20**)

To an ice-cold solution of **16** (0.5 g) in anhydrous methanol was added an ethereal solution of diazomethane until the yellow color persisted. The mixture was kept overnight at 0°, and then evaporated at 40°/12–15 mm. The residue was crystallized from hot methanol, to yield 0.6 g (quantitative) of long, white needles, m.p. 177–8°, $[\alpha]_D^{26}$ −137° (*c* 1.3, pyridine).

Anal. Calc. for $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39; O, 27.09. Found: C, 64.28; H, 5.69; N, 3.50; O, 26.91.

Benzyl β-D-gulopyranosiduronic acid 2,3-carbamate (**17**)

(a) Substance **18** (0.7 g) was oxidized in the manner described for the preparation of **2a**. After acidification of the cold, concentrated solution, it was saturated with potassium chloride and extracted three times with tetrahydrofuran. The combined organic extracts were evaporated to dryness. The residue was dissolved in a small volume of hot tetrahydrofuran, isopropyl ether was added to incipient opalescence, and the solution was kept for several hours in the cold. The resulting crystals turned to a gum immediately after exposure to the air. The compound was, therefore, characterized as its methyl ester (**21**).

(b) Substance **16** (1.5 g) was treated in hot, aqueous acetic acid as described for the preparation of **18**. Crystallization of the product as in method (a) above gave crystals which turned to a gum, and the product was characterized as its methyl ester.

Methyl (benzyl β-D-gulopyranosid)uronate 2,3-carbamate (**21**)

The gummy products from (a) and (b) of the preceding experiment were separately dissolved in absolute methanol and cooled to 0°. To each solution was added ethereal diazomethane, after which it was treated as described for the preparation of **20**. Addition of a large excess of isopropyl ether to the methanolic solution gave crystals which were recrystallized in the same way. From **18**, there was obtained 0.1 g (13% for the two steps), and from **16**, 1.0 g (78% for the two steps) of product, m.p. 146–7°, $[\alpha]_D^{21}$ −125° (*c* 1.1, pyridine), ν_{max}^{KBr} 3490 (hydroxyl), 3350, 1750 (carbamate), 1750 (carbonyl), 740, 700 (phenyl) cm^{-1}; amide-II band between 1550 and 1500 cm^{-1} was absent.

Anal. Calc. for $C_{15}H_{16}NO_7$: C, 55.90; H, 5.00; N, 4.35; O, 34.75. Found: C, 55.79; H, 5.25; N, 4.15; O, 34.82.

Methyl (benzyl 4-O-acetyl-β-D-gulopyranosid)uronate 2,3-carbamate (**24**)

Acetylation of 0.5 g of **21** in pyridine–acetic anhydride for 24 h at 0° gave a crystalline product when the mixture was poured into ice-water. Recrystallization from methanol–isopropyl ether afforded 0.54 g (quantitative) of long needles, m.p. 205–6°, $[\alpha]_D^{21}$ −87° (*c* 1.3, pyridine).

Anal. Calc. for $C_{17}H_{19}NO_8$: C, 55.89; H, 5.24; N, 3.83; C, 35.03. Found: C, 55.96; H, 5.19; N, 3.96; O, 35.14.

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SUMMARY

Inversion of configuration at C-3 and C-4 of 2-amino-2-deoxy-D-glucose, *via* an anchimerically assisted cleavage of a 3,4-epoxide, has been explored as a route for the preparation of derivatives of 2-amino-2-deoxy-D-guluronic acid. It is shown that catalytic oxidation of the benzyl 3-*O*-acetyl-2-[(benzyloxycarbonyl)amino]-2-deoxy-D-glucopyranosides over platinum is accompanied by solvolysis of the 3-*O*-acetyl group in the product. On the other hand, oxidations could be achieved by the action of *N,N'*-dicyclohexylcarbodiimide–phosphoric acid–methyl sulfoxide, without affecting the substituents at C-3 and C-4, on benzyl 3-*O*-acetyl-2-[(benzyloxycarbonyl)-amino]-2-deoxy-4-*O*-(methylsulfonyl)-β-D-glucopyranoside (giving specifically the 6-aldehyde), and also on benzyl 3,4-anhydro-2-[(benzyloxycarbonyl)amino]-2-deoxy-β-D-galactopyranoside over platinum (giving the uronic acid). The latter acid could be transformed readily by aqueous acetic acid into benzyl β-D-gulopyranosiduronic acid 2,3-carbamate.

REFERENCES

1 P. H. GROSS, K. BRENDEL, AND H. K. ZIMMERMAN, *Ann.*, 680 (1964) 159.
2 J. D. DUTCHER, *Advan. Carbohydrate Chem.*, 18 (1963) 276.
3 H. WEIDMANN, *Ann.*, 687 (1965) 250.
4 H. WEIDMANN, E. FAULAND, R. HELBIG, AND H. K. ZIMMERMAN, *Ann.*, in press.
5 K. HEYNS, G. KIESSLING, W. LINDERBERG, H. PAULSEN, AND M. WEBSTER, *Chem. Ber.*, 92 (1959) 2435.
6 A. R. WILLIAMSON AND S. ZAMENHOFF, *J. Biol. Chem.*, 238 (1963) 2255.
7 H. R. PERKINS, *Biochem. J.*, 86 (1963) 475.
8 K. HEYNS AND H. PAULSEN, *Chem. Ber.*, 88 (1955) 188.
9 P. H. GROSS, K. BRENDEL, AND H. K. ZIMMERMAN, *Ann.*, 680 (1964) 155.
10 H. WEIDMANN AND H. K. ZIMMERMAN, *Ann.*, 639 (1961) 198.
11 S. M. BLOCK, P. H. GROSS, H. WEIDMANN, AND H. K. ZIMMERMAN, *Ann.*, in press.
12 F. H. NEWTH, *Quart. Rev.* (London), 13 (1959) 37.
13 P. H. GROSS AND H. K. ZIMMERMAN, *Ann.*, 674 (1964) 211.
14 D. HORTON, J. B. HUGHES, AND J. M. J. TRONCHET, *Chem. Commun.*, (1965) 481.
15 K. E. PFITZNER AND J. G. MOFFATT, *J. Am. Chem. Soc.*, 87 (1965) 211.
16 K. BRENDEL, P. H. GROSS, AND H. K. ZIMMERMAN, *Ann.*, 683 (1965) 182.
17 K. HEYNS AND M. BECK, *Chem. Ber.*, 90 (1957) 2443.
18 L. V. SMITH, P. H. GROSS, K. BRENDEL, AND H. K. ZIMMERMAN, *Ann.*, 681 (1965) 228.