Carbohydrate Research, 174 (1988) 253–264
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

CHEMICAL SYNTHESIS OF L-IDURONIC ACID-CONTAINING DISACCHARIDIC FRAGMENTS OF HEPARIN*,†

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(Received September 2nd, 1987; accepted for publication, September 26th, 1987)

ABSTRACT

Condensation of methyl 3-*O*-benzyl-2-benzyloxycarbonylamino-6-*O*-chloroacetyl-2-deoxy-α-D-glucopyranoside with methyl (2,3,4-tri-*O*-acetyl-α-L-idopyranosyl bromide)uronate in 1,2-dichloroethane, in the presence of silver triflate and molecular sieves, provided 83% of crystalline methyl 3-*O*-benzyl-2-benzyloxycarbonylamino-6-*O*-chloroacetyl-2-deoxy-4-*O*-(methyl 2,3,4-tri-*O*-acetyl-α-L-idopyranosyluronate)-α-D-glucopyranoside. Dechloroacetylation followed successively by *O*-sulfation with the sulfur trioxide–trimethylamine complex, acetylation, and saponification gave the disodium salt of methyl 2-acetamido-2-deoxy-4-*O*-(α-L-idopyranosyluronic acid)-6-*O*-sulfo-α-D-glucopyranoside. The *N*-sulfated analogue of this disaccharide was also synthesized, the acetylation being replaced by a selective *N*-sulfation. Condensation of methyl (methyl 2,3-di-*O*-benzyl-β-L-idopyranosid)uronate with 6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl bromide in dichloromethane, in the presence of silver triflate and 2,4,6-trimethylpyridine, gave methyl [methyl 4-*O*-(6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-2,3-di-*O*-benzyl-β-L-idopyranosid]uronate. Saponification followed successively by esterification, *O*-sulfation, saponification, catalytic hydrogenolysis, and selective *N*-sulfation gave the trisodium salt of methyl 4-*O*-(2-deoxy-6-*O*-sulfo-2-sulfoamino-α-D-glucopyranosyl)-β-L-idopyranosiduronic acid.

INTRODUCTION

Following the hypothesis that a pentasaccharide sequence constituted the binding site of heparin to antithrombin[1], we launched a program on the chemical synthesis of specific heparin sequences. The above hypothesis could thus be con-

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*Dedicated to Professor Hans Paulsen.

†Part of this work has been presented; Maurice Petitou, PhD Thesis, Université d'Orléans, 1984.

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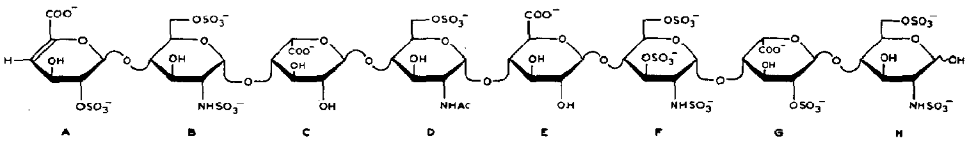


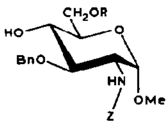
Fig. 1. The octasaccharide fragment of heparin, which has selective anti-Xa activity.

firmed[2] through the use of a well defined chemically synthesized pentasaccharide DEFGH[3] which is present in all heparin fragments having affinity for antithrombin, and particularly in the octasaccharide ABCDEFGH (Fig. 1), which was isolated after treatment of heparin with heparinase[4].

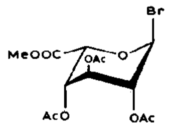
We now report the chemical synthesis of the methyl glycosides of the disaccharides CD and BC which are more useful than the reducing disaccharides in synthesis and subsequent n.m.r. analysis.

RESULTS AND DISCUSSION

The known methyl 3-*O*-benzyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside[5] (**1**) was selectively chloroacetylated by reaction with chloroacetic anhydride for 1 h at 0° in pyridine to give 71% of crystalline **2**. Acylation of HO-6 caused the expected downfield displacement of the signals of H-6 in **1**. Methyl (2,3,4-tri-*O*-acetyl-α-L-idopyranosyl bromide)uronate (**3**), recently prepared[6] from the commercially available D-glucofuranurono-6,3-lactone, was condensed with **2** in 1,2-dichloroethane in the presence of silver triflate and powdered 4 Å molecular sieves to give 83% of the crystalline α-linked disaccharide derivative **4**. The *J* values ($J_{1,2}$ 3.3, $J_{2,3}$ 4.8, $J_{3,4}$ 4.8, $J_{4,5}$ 3.8 Hz) observed for the α-L-idopyranosyluronate unit are rather large and indicate a significant departure from the $^1C_4$ conformation in chloroform solution and a substantial contribution of the $^4C_1$ form. Similar values were observed for the α-L-idopyranosyl unit of **5** ($J_{1,2}$ 3.0, $J_{2,3}$ 4.2, $J_{3,4}$ 4.2, $J_{4,5}$ 3.1 Hz) and **6** ($J_{1,2}$ 2.8, $J_{2,3}$ 4.0, $J_{3,4}$ 4.0, $J_{4,5}$ not determined) which were derived from **4** in excellent yields by *O*-dechloroacetylation with thiourea in pyridine–ethanol[7] (45 min at 100°) and *O*-sulfation with the sulfur trioxide–trimethylamine complex in *N*,*N*-dimethylformamide (1.5 h at 60°). Sulfation of HO-6 of **5** (→**6**) caused a down-field shift of the signals for H-6a,6b of 0.35 p.p.m., which is in agreement with previous observations[8]. Catalytic hydrogenolysis (Pd/C) of **6** followed by *N*- and *O*-acetylation with acetic anhydride in pyridine gave the amorphous sulfated and acetylated disaccharide derivative **7** in 91% yield. Compound **7** was saponified with sodium hydroxide in tetrahydrofuran–water to give the disaccharide glycoside **8**. The *J* values ($J_{1,2}$ 4.8, $J_{2,3}$ 7.2, $J_{3,4}$ 6.0, $J_{4,5}$ 3.8 Hz) observed for the α-L-idopyranosyluronate unit of **8** are similar to those reported for the synthetic methyl 2-acetamido-2-deoxy-3-*O*-(α-L-idopyranosyluronic acid)-4-*O*-sulfo-β-D-galactopyranoside disodium salt[9] and for an α-L-idopyranosyluronate residue located at the non-reducing terminus of two tetrasaccharides isolated from heparan sulfate, where the population[10] of the $^4C_1$ form was 65%. These values accord with an equilibrium of the $^1C_4$ and $^4C_1$ forms, with the participation of the $^2S_0$ conformation being insignificant on the basis of the rather large $J_{3,4}$ value[11].



1 R = H
2 R = ClCH$_2$CO



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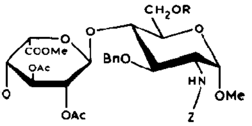
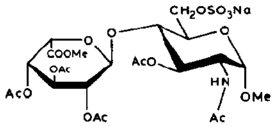
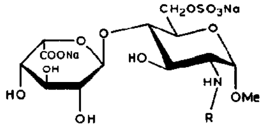


4 R = ClCH$_2$CO
5 R = H
6 R = SO$_3$Na



7

Z = COOCH$_2$Ph



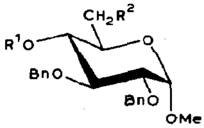
8 R = Ac
9 R = SO$_3$Na

Thus, **3** proved to be an excellent glycosyl donor for the stereoselective synthesis of the disaccharide CD$_{\mathrm{NAc}}$ which is part of the irregular domain of heparin.

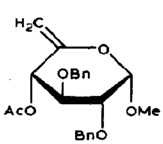
Replacement of the *N*-acetyl group of fragment D by a sulfoamino group occurs in beef-lung heparin[12]. The synthesis of CD$_{\mathrm{NSO_3Na}}$ was thus achieved from **6** after catalytic hydrogenolysis (Pd/C) in aqueous methanol followed by selective *N*-sulfation in aqueous solution of pH 9 at room temperature with the sulfur trioxide–trimethylamine complex, to give the disaccharide glycoside **9**. The *J* values ($J_{1,2}$ 4.8, $J_{2,3}$ 7.3, $J_{3,4}$ 6.2, $J_{4,5}$ 4.0 Hz) observed for the α-L-idopyranosyluronate unit are similar to those for **8** and correspond to an equilibrium of two chair forms. Therefore, the replacement of the *N*-acetyl group in the residue D by a sulfoamino group has practically no influence on the conformational equilibrium in aqueous solution of the neighboring α-L-idopyranosyluronate residue C.

Methyl (methyl 2,3-di-*O*-benzyl-β-L-idopyranosid)uronate (**18**) was selected as a glycosyl acceptor for the synthesis of the B–C sequence. Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[13] (**10**) was converted into crystalline methyl 4-*O*-acetyl-2,3-di-*O*-benzyl-6-deoxy-α-D-*xylo*-hex-5-enopyranoside (**14**) through a well-established four-step sequence. Hydroboration of **14** in tetrahydrofuran with a M solution of borane in tetrahydrofuran gave a 3:2 *ido:gluco* mixture of products. An improved selectivity towards the desired *ido* form was obtained upon similar hydroboration of deacetylated **14**, which gave methyl 2,3-di-*O*-benzyl-β-L-idopyranoside (**15**) and methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**10**) in yields of 70 and 21%, respectively. In a one-pot reaction, **15** was routinely converted into **16**, which was quantitatively detritylated at 0° in dichloromethane with a $BF_3:Et_2O$–methanol solution to give **17**. Oxidation of HO-6 of **17** with chromium trioxide in acetone–sulfuric acid at 0° gave, after *O*-debenzoylation and esterification with diazomethane, the glycosyl acceptor **18** (57% from **17**).

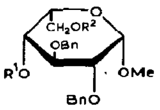
Condensation of the useful glycosyl donor **19**, introduced by Paulsen and Stenzel[14], with **18** in dichloromethane at 0°, in the presence of silver triflate and 2,4,6-trimethylpyridine, gave 83% of the amorphous disaccharide derivative **20**,



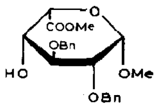
10 R^1 = H, R^2 = OH
11 R^1 = H, R^2 = OTs
12 R^1 = H, R^2 = I
13 R^1 = Ac, R^2 = I



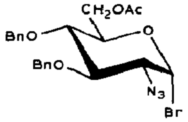
14



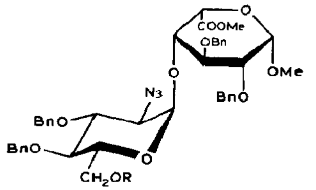
15 R^1 = R^2 = H
16 R^1 = Bz, R^2 = Tr
17 R^1 = Bz, R^2 = H



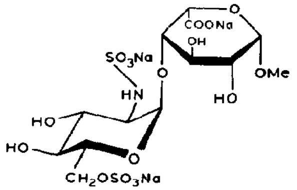
18



19



20 R = Ac
21 R = H
22 R = SO_3Na



23

the ^{1}H-n.m.r. data for which (δ 5.09, d, $J_{1',2'}$ 3.5 Hz, H-1') demonstrated that the new glycosidic bond was α. *O*-Deacetylation of **20** with aqueous methanolic sodium hydroxide at room temperature, followed by esterification with diazomethane, gave the amorphous derivative **21** (71% after chromatography on silica gel) which had no ^{1}H-n.m.r. signal for acetyl. *O*-Sulfation of **21** was achieved with the sulfur trioxide–trimethylamine complex in *N,N*-dimethylformamide, and the product was isolated as the sodium salt **22** in 80% yield. Sulfation of HO-6 of **21** caused a downfield shift of the signals of H-6a,6b of 0.5 p.p.m. Compound **22** was saponified and the disodium salt was catalytically hydrogenated (Pd/C) in aqueous methanol and then *N*-sulfated in aqueous solution of pH 9.5 at room temperature with the sulfur trioxide–trimethylamine complex to give the disaccharide glycoside **23** in 52% yield. The J values ($J_{1,2}$ 1.5, $J_{2,3}$ 3, $J_{3,4}$ 3, $J_{4,5}$ 1.9 Hz) observed for the β-L-idopyranosyluronate unit in **23** are all small and indicate the almost exclusive existence of the $^1C_4$ conformation in aqueous solution. The tendency of a non-sulfated β-L-idopyranosyluronate residue to adopt a $^1C_4$ conformation in aqueous solution has been noted for methyl 2-acetamido-2-deoxy-3-*O*-(β-L-idopyranosyluronic acid)-4-*O*-sulfo-β-D-galactopyranoside disodium salt[9]. The J values ($J_{1,2}$ 1.5, $J_{2,3}$ 3.2, $J_{3,4}$ 3.0, $J_{4,5}$ 1.6 Hz) observed in aqueous solution for the β-L-idopyranosyluronate unit of the synthetic disaccharide related to dermatan sulfate are similar to those for **23**. Whether this is a general conformational property of β-L-idopyranosiduronates remains to be established.

EXPERIMENTAL

General methods. — Melting points were determined in capillary tubes with a Büchi apparatus and are uncorrected. Optical rotations were measured at 20–24° with a Perkin–Elmer Model 141 polarimeter. ^{1}H-N.m.r. spectra were recorded with a Bruker AM-300 (300 MHz) instrument. The purity of products was determined by t.l.c. on Silica Gel 60 F_{154} (Merck) with detection by charring with sulfuric acid. Column chromatography was performed on Silica Gel 60 (Merck, 63–200 μm), which was used without pretreatment. Elemental analyses were performed by the Service Central de Micro-Analyse du Centre National de la Recherche Scientifique (Vernaison, France).

Methyl 3-O-benzyl-2-benzyloxycarbonylamino-6-O-chloroacetyl-2-deoxy-α-D-glucopyranoside (**2**). — A solution of chloroacetic anhydride (479 mg) in dichloromethane (5 mL) was added dropwise at 0° to a solution of methyl 3-*O*-benzyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (**1**, 1 g) in pyridine (15 mL), and the mixture was stirred for 1 h at 0°. Ice was added, and the mixture was diluted with dichloromethane (50 mL), washed with aqueous 10% $KHSO_4$, water, dilute aqueous $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel (50 g) with dichloromethane–acetone (15:1) to give **2** (840 mg, 71%), m.p. 101–102° (from ethyl acetate–hexane), $[\alpha]_D$ +65° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 10 H, 2 Ph), 4.94 (d, 1 H, $J_{2,NH}$ 9.80 Hz, NH), 4.67 (d, 1 H, $J_{1,2}$ 3.60 Hz, H-1), 4.57 (dd, 1 H, $J_{5,6a}$ 4.50, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.52 (dd, 1 H, $J_{5,6b}$ 2.0, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.10 (s, 2 H, $COCH_2Cl$), 3.98 (m, 1 H, $J_{1,2}$ 3.50, $J_{2,NH} = J_{2,3} = 9.80$ Hz, H-2), 4.76 (m, 1 H, H-5), 3.36 (s, 3 H, OMe), 2.43 (d, 1 H, J 2.40 Hz, OH).

Anal. Calc. for $C_{24}H_{28}ClNO_8$: C, 58.36; H, 5.71; N, 2.83. Found: C, 58.17; H, 5.74; N, 2.93.

Further elution gave **1** (201 mg, 20%).

Methyl 3-O-benzyl-2-benzyloxycarbonylamino-6-O-chloroacetyl-2-deoxy-4-O-(methyl 2,3,4-tri-O-acetyl-α-L-idopyranosyluronate)-α-D-glucopyranoside (**4**). — A mixture of **2** (296 mg), freshly prepared **3** (318 mg), activated 4 Å powdered molecular sieves (300 mg), and dry 1,2-dichloroethane (7 mL) was stirred for 15 min at room temperature under dry argon and then cooled to −20°. Silver triflate (325 mg) was added, and the mixture was stirred for 1 h at −20° and then allowed to attain room temperature during 3 h. The mixture was diluted with dichloromethane (50 mL), filtered through Celite, washed with water, cold 0.1M hydrochloric acid, dilute aqueous $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel (50 g) with ethyl acetate–hexane (1:1) to give **4** (403 mg, 83%), m.p. 191–192° (from ethyl acetate–hexane), $[\alpha]_D$ +20° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 10 H, 2 Ph), 5.26 (d, 1 H, $J_{1',2'}$ 3.30 Hz, H-1'), 5.13 (t, 1 H, $J_{2',3'} = J_{3',4'} = 4.80$ Hz, H-3'), 5.04 (dd, 1 H, $J_{3',4'}$ 4.80, $J_{4',5'}$ 3.80 Hz, H-4'), 5.02 (s, 2 H, $COOCH_2Ph$), 4.88 (d, 1 H, $J_{4',5'}$ 3.80 Hz, H-5'), 4.85 (d, 1 H, $J_{2,NH}$ 10.0 Hz, NH), 4.77 (dd, 1 H, $J_{1',2'}$ 3.30, $J_{2',3'}$ 4.80 Hz, H-2'), 4.73 (AB system, 2 H, OCH_2Ph), 4.66 (d, 1 H, $J_{1,2}$ 3.70 Hz, H-1), 4.63 (dd, 1 H, $J_{5,6a}$ 2.0, $J_{6a,6b}$ 12.20 Hz, H-6a), 4.32 (dd, 1 H, $J_{5,6b}$ 4.0, $J_{6a,6b}$ 12.20 Hz, H-6b), 4.17 (AB system, 2 H, $COCH_2Cl$), 4.05 (m, 1 H, H-2), 3.94 (dd, 1 H,

$J_{3,4}$ 9.0, $J_{4,5}$ 10.0 Hz, H-4), 3.82 (m, 1 H, H-5), 3.58 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 9.0 Hz, H-3), 3.48 (s, 3 H, COOMe), 3.35 (s, 3 H, OMe), 2.14, 2.08, and 2.04 (3 s, 9 H, 3 OAc).

Anal. Calc. for $C_{37}H_{44}ClNO_{17}$: C, 54.85; H, 5.47; N, 1.73. Found: C, 54.74; H, 5.49; N, 1.71.

Methyl 3-O-benzyl-2-benzyloxycarbonylamino-2-deoxy-4-O-(methyl 2,3,4-tri-O-acetyl-α-L-idopyranosyluronate)-α-D-glucopyranoside (**5**). — A solution of **4** (203 mg) in pyridine (5 mL) and ethanol (1 mL) was heated for 45 min at 100° in the presence of thiourea (38 mg), then cooled, and concentrated. The residue was taken up in dichloromethane–water (1:1, 50 mL) and decanted, and the organic layer was washed with saturated aqueous ammonium chloride and water, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel (10 g) with dichloromethane–methanol (15:1) to give **5** (155 mg, 89%), m.p. 142–143° (from ethyl acetate–hexane), $[\alpha]_D$ +11° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.25 (m, 10 H, 2 Ph), 5.29 (d, 1 H, $J_{1',2'}$ 3.0 Hz, H-1'), 5.09 (t, 1 H, $J_{2',3'} = J_{3',4'} = 4.20$ Hz, H-3'), 5.01 (dd, 1 H, $J_{3',4'}$ 4.20, $J_{4',5'}$ 3.10 Hz, H-4'), 4.99 (s, 2 H, COOCH_2Ph), 4.94 (d, 1 H, $J_{4',5'}$ 3.10 Hz, H-5'), 4.88 (d, 1 H, $J_{2,NH}$ 10.0 Hz, NH), 4.76 (dd, 1 H, $J_{1',2'}$ 3.0, $J_{2',3'}$ 4.20 Hz, H-2'), 4.75 (AB system, 2 H, OCH_2Ph), 4.67 (d, 1 H, $J_{1,2}$ 3.70 Hz, H-1), 4.07 (m, 1 H, H-2), 3.99 (t, 1 H, $J_{3,4} = J_{4,5} = 9.80$ Hz, H-4), 3.84 (m, 2 H, H-6a,6b), 3.63 (m, 1 H, H-5), 3.57 (t, 1 H, $J_{2,3} = J_{3,4} = 9.80$ Hz, H-3), 3.40 (s, 3 H, COOMe), 3.34 (s, 3 H, OMe), 2.17, 2.08, and 2.03 (3 s, 9 H, 3 OAc), 1.88 (1 H, OH).

Anal. Calc. for $C_{35}H_{43}NO_{16}$: C, 57.29; H, 5.91; N, 1.91. Found: C, 57.49; H, 6.00; N, 1.91.

Methyl 3-O-benzyl-2-benzyloxycarbonylamino-2-deoxy-4-O-(methyl 2,3,4-tri-O-acetyl-α-L-idopyranosyluronate)-6-O-sulfo-α-D-glucopyranoside (**6**). — A mixture of **5** (242 mg), *N,N*-dimethylformamide (3.5 mL), and the sulfur trioxide–trimethylamine complex (186 mg) was stirred for 1.5 h at 60° and then cooled. Methanol (0.5 mL) was added, and the mixture was eluted from a column (35 × 600 mm) of Sephadex LH-20 with chloroform–methanol (1:1) to give a product that was eluted from a column (15 × 300 mm) of Sephadex SP-C25 (Na^+ form) with methanol–water (9:1) to afford **6** (256 mg, 93%), isolated as a colorless glass, $[\alpha]_D$ +14° (*c* 1, methanol). ^{1}H-N.m.r. data (CD_3OD): δ 7.25 (m, 10 H, 2 Ph), 5.27 (d, 1 H, $J_{1',2'}$ 2.80 Hz, H-1'), 5.03 (t, 1 H, $J_{2',3'} = J_{3',4'}$ 4.0 Hz, H-3'), 5.00 (s, 2 H, COOCH_2), 4.95 (m, 2 H, H-4',5'), 4.88 (dd, 1 H, $J_{1',2'}$ 2.80, $J_{2',3'}$ 4.0 Hz, H-2'), 4.79 (s, 2 H, OCH_2Ph), 4.64 (d, 1 H, $J_{1,2}$ 3.70 Hz, H-1), 4.23 (dd, 1 H, $J_{5,6a}$ 2.0, $J_{6a,6b}$ 11.20 Hz, H-6a), 4.16 (dd, 1 H, $J_{5,6b}$ 3.60, $J_{6a,6b}$ 11.20 Hz, H-6b), 3.95 (m, 2 H, H-2,4), 3.83 (m, 1 H, $J_{4,5}$ 9.30 Hz, H-5), 3.72 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 9.30 Hz, H-3), 3.41 (s, 3 H, COOMe), 3.35 (s, 3 H, OMe), 2.18, 2.08, and 2.00 (3 s, 9 H, 3 OAc).

Anal. Calc. for $C_{35}H_{42}NNaO_{19}S \cdot H_2O$: C, 49.23; H, 5.19; N, 1.64. Found: C, 49.24; H, 5.43; N, 1.63.

Methyl 2-acetamido-3-O-acetyl-2-deoxy-4-O-(methyl 2,3,4-tri-O-acetyl-α-L-

idopyranosyluronate)-6-O-sulfo-α-D-glucopyranoside (**7**). — A solution of **6** (51 mg) in methanol–water (4:1, 5 mL) was hydrogenated in the presence of 10% Pd/C (50 mg) for 24 h, then filtered, and concentrated. Toluene (2 × 10 mL) was evaporated from the residue, which was then acetylated (acetic anhydride–pyridine) for 6 h at room temperature. Elution of the product from a column (12 × 250 mm) of Sephadex SP-C25 (Na^+ form) with methanol–water (9:1) afforded **7** (38 mg, 91%), isolated as a colorless glass, $[\alpha]_D$ −1° (*c* 1, methanol). ^{1}H-N.m.r. data (CD_3OD): δ 5.21 (dd, 1 H, $J_{2,3}$ 10.60, $J_{3,4}$ 8.80 Hz, H-3), 5.19 (s, 1 H, $J_{1',2'}$ 2.60 Hz, H-1'), 5.04 (dd, 1 H, $J_{3',4'}$ 4.60, $J_{4',5'}$ 2.30 Hz, H-4'), 5.03 (t, 1 H, $J_{2',3'} = J_{3',4'} = 4.70$ Hz, H-3'), 4.84 (dd, 1 H, $J_{1',2'}$ 2.60, $J_{2',3'}$ 4.70 Hz, H-2'), 4.82 (d, 1 H, $J_{4',5'}$ 2.30 Hz, H-5'), 4.63 (d, 1 H, $J_{1,2}$ 3.70 Hz, H-1), 4.24 (dd, 1 H, $J_{5,6a}$ 1.80, $J_{6a,6b}$ 11.40 Hz, H-6a), 4.17 (dd, 1 H, $J_{5,6b}$ 2.40, $J_{6a,6b}$ 11.40 Hz, H-6b), 4.16 (dd, 1 H, $J_{1,2}$ 3.70, $J_{2,3}$ 10.60 Hz, H-2), 3.93 (t, 1 H, $J_{3,4} = J_{4,5} = 8.80$ Hz, H-4), 3.91 (m, 1 H, H-5), 3.75 (s, 3 H, COOMe), 3.42 (s, 3 H, OMe), 2.10, 2.09, 2.04, and 1.98 (4 s, 12 H, 4 OAc), 1.91 (s, 3 H, NAc).

Anal. Calc. for $C_{24}H_{34}NO_{19} \cdot H_2O$: C, 40.39; H, 5.08; N, 1.96. Found: C, 40.39; H, 4.78; N, 2.41.

Methyl 2-acetamido-2-deoxy-4-O-(α-L-idopyranosyluronic acid)-6-O-sulfo-α-D-glucopyranoside, disodium salt (**8**). — M Sodium hydroxide (1 mL) was added dropwise at 0° to a solution of **7** (52 mg) in tetrahydrofuran (1 mL), and the mixture was stirred for 16 h at 4°. The pH of the solution was then adjusted to 7.5 with dilute acetic acid and the mixture was concentrated. The residue was eluted from a column (22 × 900 mm) of Sephadex G-10 with water to give a fraction that was eluted from a column (25 × 900 mm) of Sephadex SP-C25 (Na^+ form) with water to give **8** (32 mg, 80%), isolated as a white foam, $[\alpha]_D$ +35° (*c* 1, water). ^{1}H-N.m.r. data (D_2O, internal TSP): δ 4.89 (d, 1 H, $J_{1',2'}$ 4.80 Hz, H-1'), 4.77 (d, 1 H, $J_{1,2}$ 3.60 Hz, H-1), 4.58 (d, 1 H, $J_{4',5'}$ 3.80 Hz, H-5'), 4.37 (dd, 1 H, $J_{5,6a}$ 2.40, $J_{6a,6b}$ 11.20 Hz, H-6a), 4.31 (dd, 1 H, $J_{5,6b}$ 4.50, $J_{6a,6b}$ 11.20 Hz, H-6b), 4.02 (m, 1 H, $J_{4,5}$ 9.80 Hz, H-5), 3.98 (dd, 1 H, $J_{1,2}$ 3.60, $J_{2,3}$ 10.20 Hz, H-2), 3.91 (dd, 1 H, $J_{3',4'}$ 6.0, $J_{4',5'}$ 3.80 Hz, H-4'), 3.82 (dd, 1 H, $J_{3,4}$ 9.50, $J_{4,5}$ 9.80 Hz, H-4), 3.75 (dd, 1 H, $J_{2',3'}$ 7.20, $J_{3',4'}$ 6.0 Hz, H-3'), 3.74 (dd, 1 H, $J_{2,3}$ 10.20, $J_{3,4}$ 9.50 Hz, H-3), 3.57 (dd, 1 H, $J_{1',2'}$ 4.20, $J_{2',3'}$ 7.20 Hz, H-2'), 3.40 (s, 3 H, OMe), 2.04 (s, 3 H, NAc).

Anal. Calc. for $C_{15}H_{23}O_{15}NNa_2S \cdot 2\ H_2O$: C, 31.53; H, 4.76; N, 2.45. Found: C, 31.76; H, 4.88; N, 2.33.

Methyl 2-deoxy-4-O-(α-L-idopyranosyluronic acid)-6-O-sulfo-2-sulfoamino-α-D-glucopyranoside, trisodium salt (**9**). — Compound **6** (66 mg) was hydrogenolyzed as described for the preparation of **7**. The pH of a solution of the residue in water (3 mL) was adjusted to 9 with M NaOH. Sulfur trioxide–pyridine complex (125 mg) was added portionwise with stirring, the pH was maintained at 9 by subsequent addition of M NaOH, and the mixture was stirred for 2 h, then neutralized with dilute acetic acid, and concentrated to 1.5 mL. The product was eluted from a column (22 × 900 mm) of Sephadex G-10 with water to afford a fraction that was eluted from a column (25 × 900 mm) of Sephadex SP-C25 (Na^+ form) with water to give **9** (35 mg, 75% from **6**), isolated as a white foam, $[\alpha]_D$ +22° (*c* 1, water). ^{1}H-N.m.r. data (D_2O, internal TSP): δ 5.04 (d, 1 H, $J_{1,2}$ 3.50 Hz, H-1), 4.88 (d, 1 H, $J_{1',2'}$ 4.80 Hz, H-1'), 4.59 (d, 1 H, $J_{4',5'}$ 4.0 Hz, H-5'), 4.37 (dd, 1 H, $J_{5,6a}$ 2.50, $J_{6a,6b}$ 11.20 Hz, H-6a), 4.31 (dd, 1 H, $J_{5,6b}$ 4.60, $J_{6a,6b}$ 11.20 Hz, H-6b), 3.99 (m, 1 H, $J_{4,5}$ 9.60 Hz, H-5), 3.89 (dd, 1 H, $J_{3',4'}$ 6.20, $J_{4',5'}$ 4.0 Hz, H-4'), 3.74 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 9.60 Hz, H-4), 3.73 (dd, 1 H, $J_{2',3'}$ 7.30, $J_{3',4'}$ 6.20 Hz, H-3'), 3.67 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 9.60 Hz, H-3), 3.56 (dd, 1 H, $J_{1',2'}$ 4.80, $J_{2',3'}$ 7.30 Hz, H-2'), 3.43 (s, 3 H, OMe), 3.31 (dd, 1 H, $J_{1,2}$ 3.50, $J_{2,3}$ 10.0 Hz, H-2).

Anal. Calc. for $C_{13}H_{20}NNa_3O_{17}S_2 \cdot 1.5\ H_2O$: C, 25.00; H, 3.71; N, 2.24. Found: C, 24.87; H, 3.91; N, 2.01.

*Methyl 2,3-di-O-benzyl-6-O-tosyl-α-*D*-glucopyranoside* (**11**). — A solution of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**10**, 1 g), toluene-*p*-sulphonyl chloride (0.56 g), 4-dimethylaminopyridine (16 mg), and triethylamine (0.67 mL) in dichloromethane (20 mL) was stirred for 12 h at room temperature. The mixture was stirred for 2 h with ice, diluted with dichloromethane, washed successively with 2M HCl, water, saturated aqueous $NaHCO_3$, and water, and concentrated to give amorphous **11** (1.38 g, 97%), $[\alpha]_D$ +70° (*c* 0.8, *N*,*N*-dimethylformamide).

Anal. Calc. for $C_{28}H_{32}O_8S$: C, 63.61; H, 6.10. Found: C, 63.50; H, 6.15.

*Methyl 2,3-di-O-benzyl-6-deoxy-6-iodo-α-*D*-glucopyranoside* (**12**). — A mixture of **11** (31.8 g) and sodium iodide (39 g) in acetonitrile (250 mL) was boiled under reflux for 3 h, then cooled, filtered, and concentrated. The residue was diluted with chloroform, washed with water, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with ether–hexane (1:1) to give **12** (24.7 g, 71.5%), $[\alpha]_D$ +24° (*c* 1, chloroform).

Anal. Calc. for $C_{21}H_{25}IO_5$: C, 52.07; H, 5.20. Found: C, 52.59; H, 5.59.

*Methyl 4-O-acetyl-2,3-di-O-benzyl-6-deoxy-6-iodo-α-*D*-glucopyranoside* (**13**). — Compound **12** (22.2 g) was acetylated conventionally with acetic anhydride (43 mL) in pyridine (200 mL) at room temperature to give amorphous **13**, $[\alpha]_D$ +4.5° (*c* 1.29, chloroform).

Anal. Calc. for $C_{23}H_{27}IO_6$: C, 52.48; H, 5.17. Found: C, 52.31; H, 5.15.

*Methyl 4-O-acetyl-2,3-di-O-benzyl-6-deoxy-α-*D-xylo*-hex-5-enopyranoside* (**14**). — A solution of **13** (4 g) in pyridine was stirred for 2.5 h at room temperature in the presence of silver fluoride (6.86 g), then diluted with chloroform–ether (1 L, 1:1), filtered, and concentrated. The residue was diluted with chloroform, washed with cold aqueous 5% potassium hydrogensulfate and water, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel (100 g) with hexane–ethyl acetate (4:1) to give **14** (1.62 g, 54%), m.p. 81–82° (from ether–hexane), $[\alpha]_D$ −20° (*c* 1, chloroform).

Anal. Calc. for $C_{23}H_{26}O_6$: C, 69.33; H, 6.57. Found: C, 69.11; H, 6.64.

*Methyl 2,3-di-O-benzyl-β-*L*-idopyranoside* (**15**). — A solution of **14** (2 g) in a mixture of dry methanol (20 mL) and chloroform (20 mL) was treated with methanolic 2M sodium methoxide (2 mL) for 1.5 h at room temperature, then diluted with chloroform, washed with water, and concentrated. A solution of the colorless residue (1.78 g, 99%) in dry tetrahydrofuran (50 mL) was stirred for 1 h at room temperature in the presence of a commercial M solution of borane in tetrahydrofuran (20 mL). Ethanol was added, and the mixture was diluted with tetrahydrofuran (100 mL) and stirred for 2 h at 50° in the presence of 3M sodium hydroxide (12 mL) and hydrogen peroxide (8 mL). The mixture was diluted with chloroform (500 mL), washed with 2M hydrochloric acid and water, and concentrated. The residue (1.9 g) was eluted from a column of silica gel (120 g) with chloroform–methanol (30:1) to give amorphous **15** (1.3 g, 70%), $[\alpha]_D$ +86° (*c* 1.2, chloroform).

Anal. Calc. for $C_{21}H_{26}O_6$: C, 67.36; H, 6.99. Found: C, 67.05; H, 6.94.

Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**10**; 0.39 g, 21%) was also eluted from the column.

Methyl 4-O-benzoyl-2,3-di-O-benzyl-6-O-trityl-β-L-idopyranoside (**16**). — A solution of **15** (0.65 g) in pyridine (10 mL) was heated for 12 h at 80° in the presence of chlorotriphenylmethane (1.11 g), then cooled to 0°, treated for 2 h with benzoyl chloride (0.4 mL), and concentrated. A solution of the residue in chloroform (50 mL) was washed with aqueous 10% potassium hydrogensulfate, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel (60 g) with toluene–acetone (30:1) to give amorphous **16** (1.07 g, 85%), $[\alpha]_D$ +37° (*c* 1.5, chloroform). ^{1}H-N.m.r. data ($CDCl_3$) : δ 7.03–7.85 (m, 3 OH, Ph), 3.91 (t, 1 H, $J_{2,3} = J_{3,4}$ = 3 Hz, H-3), 3.50 (s, 3 H, OMe).

Anal. Calc. for $C_{47}H_{44}O_7 \cdot 0.75\ H_2O$: C, 76.86; H, 6.25. Found: C, 76.97; H, 6.30.

Methyl 4-O-benzoyl-2,3-di-O-benzyl-β-L-idopyranoside (**17**). — A solution of **16** (1 g) in dichloromethane (50 mL) was stirred for 6 h at room temperature in the presence of methanolic 2M $BF_3{:}Et_2O$ (1 mL), then washed with water, and dried (Na_2SO_4). The residue was eluted from a column of silica gel (40 g) with chloroform to give amorphous **17** (0.61 g, 93%), $[\alpha]_D$ −9° (*c* 1, chloroform).

Anal. Calc. for $C_{28}H_{30}O_7 \cdot 0.25\ H_2O$: C, 69.62; H, 6.36. Found: C, 69.66; H, 6.38.

Methyl (methyl 2,3-di-O-benzyl-β-L-idopyranosid)uronate (**18**). — A portion (1.5 mL) of a solution of chromium trioxide (1.17 g) in 3.5M sulfuric acid (5 mL) was added dropwise at 0° to a stirred solution of **17** (0.57 g) in acetone (20 mL). After 2 h at room temperature, more oxidant (2 mL) was added, and the mixture was stirred for 3 h at room temperature, then diluted with ice-cold water, and extracted with chloroform (3 × 50 mL). The combined extracts were washed with water, dried (Na_2SO_4), and concentrated. A solution of the residue (0.55 g) in methanol (70 mL) was treated for 12 h at 0° with 3M sodium hydroxide (10 mL). The methanol was evaporated, and the mixture was diluted with water (100 mL) and extracted with ether. The aqueous layer was acidified and extracted with ether (4 × 50 mL). The combined extracts were treated with an ethereal diazomethane and concentrated. The residue was eluted from a column of silica gel (15 g) with hexane–ethyl acetate (2:1) to give amorphous **18** (274 mg, 57%), $[\alpha]_D$ +109° (*c* 2.7, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 3.70 (s, 3 H, COOMe), 3.50 (s, 3 H, OMe).

Anal. Calc. for $C_{22}H_{26}O_7$: C, 65.65; H, 6.51. Found: C, 65.27; H, 6.43.

*Methyl [methyl 4-O-(6-O-acetyl-2-azido-3,4-di-O-benzyl-2-deoxy-α-*D*-glucopyranosyl)-2,3-di-O-benzyl-β-*L*-idopyranosid]uronate* (**20**). — A mixture of **18** (230 mg), 6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl bromide (**19**, 570 mg), 2,4,6-trimethylpyridine (0.18 mL), and dry dichloromethane (10 mL) was stirred for 15 min at 0° under dry argon. Silver triflate (330 mg) was added, and the mixture was stirred for 1 h at 0°, then diluted with dichloromethane (100 mL), filtered, washed with aqueous 10% potassium hydrogensulfate and water, dried (Na_2SO_4), and concentrated. Elution of the residue from a column of silica gel (25 g) with hexane–ethyl acetate (2:1) gave amorphous **20** (384 mg, 83%), $[\alpha]_D$ +54° (*c* 2, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 20 H, Ph), 5.09 (d, 1 H, $J_{1',2'}$ 3.5 Hz, H-1′), 4.55 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.37 (t, 1 H, $J_{2,3} = J_{3,4} = 6.5$ Hz, H-3), 3.76 (s, 3 H, COOMe), 3.50 (dd, 1 H, $J_{1,2}$ 3, $J_{2,3}$ 6.5 Hz, H-2), 3.43 (s, 3 H, OMe), 3.32 (dd, 1 H, $J_{1',2'}$ 3.5, $J_{2',3'}$ 10.5 Hz, H-2′), 2.0 (s, 3 H, OAc).

Anal. Calc. for $C_{44}H_{49}N_3O_{12}\cdot 0.5\ H_2O$: C, 64.37; H, 6.13; N, 5.11. Found: C, 64.38; H, 6.10; N, 5.10.

*Methyl [methyl 4-O-(2-azido-3,4-di-O-benzyl-2-deoxy-α-*D*-glucopyranosyl)-2,3-di-O-benzyl-β-*L*-idopyranosid]uronate* (**21**). — A solution of **20** (340 mg) in methanol (15 mL) was stirred for 3 h at room temperature in the presence of M sodium hydroxide (3 mL) and chromatographed on a column (15 mL) of Dowex 50 (H^+) resin (20–50 mesh), equilibrated with methanol. Elution with methanol gave a product a solution of which in ether was esterified with ethereal diazomethane and then concentrated. The residue was eluted from a column of silica gel (15 g) with ether–hexane (8:1) to give amorphous **21** (228 mg, 71%), $[\alpha]_D$ +55° (*c* 1, chloroform). ^{1}H-N.m.r. data (CD_3OD): δ 7.30 (m, 20 H, Ph), 5.0 (d, 1 H, $J_{1',2'}$ 3.5 Hz, H-1′), 4.67 (d, 1 H, $J_{1,2}$ 2.6 Hz, H-1), 4.52 (d, 1 H, $J_{4,5}$ 3.4 Hz, H-5), 4.23 (t, 1 H, $J_{2,3} = J_{3,4} = 5.6$ Hz), 3.95 (dd, 1 H, $J_{3,4}$ 5.6, $J_{4,5}$ 3.4 Hz, H-4), 3.80 (dd, 1 H, $J_{2',3'}$ 10.5, $J_{3',4'}$ 9 Hz, H-3′), 3.77 (s, 3 H, COOMe), 3.52 (dd, 1 H, $J_{1,2}$ 2.6, $J_{2,3}$ 5.6 Hz, H-2), 3.47 (s, 3 H, OMe), 3.36 (dd, 1 H, $J_{1,',2'}$ 3.5, $J_{2',3'}$ 10.5 Hz, H-2′).

Anal. Calc. for $C_{42}H_{47}N_3O_{11}$: C, 65.52; H, 6.15; N, 5.45. Found: C, 64.94; H, 6.15; N, 5.49.

*Methyl [methyl 4-O-(2-azido-3,4-di-O-benzyl-2-deoxy-6-O-sulfo-α-*D*-glucopyranosyl)-2,3-di-O-benzyl-β-*L*-idopyranosyl]uronate* (**22**). — A mixture of **21** (200 mg), *N*,*N*-dimethylformamide (5 mL), and the sulfur trioxide–trimethylamine complex (94 mg) was stirred for 1 h at 50° and then cooled. Methanol (2 mL) was added and the mixture was eluted from a column of silica gel (10 g) with chloroform–methanol (5:1) to give a pure fraction, a solution of which in methanol was eluted from a column of Dowex 50 (Na^+) resin (20–50 mesh) to afford amorphous **22** (188 mg, 80%), $[\alpha]_D$ +29° (*c* 0.9, chloroform). ^{1}H-N.m.r. data (CD_3OD): δ 7.30 (m, 20 H, Ph), 4.96 (d, 1 H, $J_{1',2'}$ 3.5 Hz, H-1′), 4.68 (d, 1 H, $J_{4,5}$ 2.7 Hz, H-5), 4.55 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 4.24 and 4.30 (2 dd, 2 H, $J_{5',6'}$ 2.5 Hz, 2 H-6′), 4.18 (t, 1 H,

$J_{2,3} = J_{3,4}$ = 4.5 Hz, H-3), 3.99 (dd, 1 H, $J_{3,4}$ 4.5, $J_{4,5}$ 2.7 Hz, H-4), 3.80 (s, 3 H, COOMe), 3.75 (t, 1 H, $J_{2',3'} = J_{3',4'}$ = 10 Hz, H-3'), 3.61 (t, 1 H, $J_{3',4'} = J_{4',5'}$ = 10 Hz, H-4'), 3.51 (dd, 1 H, $J_{1,2}$ 2.5, $J_{2,3}$ 4.5 Hz, H-2), 3.50 (s, 3 H, OMe), 3.40 (dd, 1 H, $J_{1',2'}$ 3.5, $J_{2',3'}$ 10 Hz, H-2').

Anal. Calc. for $C_{42}H_{46}N_3NaO_{14}S$: C, 57.85; H, 5.31; N, 4.81. Found: C, 57.78; H, 5.56; N, 4.71.

*Methyl 4-O-(2-deoxy-6-O-sulfo-2-sulfoamino-α-*D*-glucopyranosyl)-β-*L*-idopyranosiduronic acid, trisodium salt* (**23**). — 5M Sodium hydroxide (1.1 mL) was added to a solution of **22** (166 mg) in methanol (5 mL). The mixture was stirred for 1 h at room temperature, chromatographed first on a column (12 mL) of Dowex 50 (H^+) resin (20–50 mesh) and then on a column (12 mL) of Dowex 50 (Na^+) resin (20–50 mesh), both equilibrated and eluted with methanol–water (4:1). The product was eluted from a column of silica gel (10 g) with ethyl acetate–pyridine–acetic acid–water (6:2:0.6:1) to give a pure fraction which was eluted slowly from a column of Sephadex SP-C25 (Na^+ form) with methanol–water (4:1) to give a powder (135 mg, 81%), $[\alpha]_D$ +30.5° (*c* 2.6, methanol), which was hydrogenolyzed in methanol–water (4:1, 12 mL) in the presence of 5% Pd/C (150 mg) for 7 days, the catalyst being changed after 3 days. The mixture was filtered and concentrated, and the pH of a solution in water (6 mL) was adjusted to 9.5 with M NaOH. Sulfur trioxide–pyridine complex (86 mg) was added portionwise with stirring and the pH was maintained at 9.5 for 48 h. The mixture was filtered and eluted from a column (1.25 × 145 cm) of Sephadex G-25 with 0.2M sodium chloride to give a fraction that was eluted from a column (16 × 120 mm) of AG 1-X2 (Na^+) resin (200–400 mesh) with a gradient (0.5→3M) of aqueous sodium chloride. Final elution from a column of Sephadex G-25 with water gave **23** (39 mg, 52%), isolated as a white powder, $[\alpha]_D$ +94° (*c* 1.1, water). ^{1}H-N.m.r. data (D_2O, internal TSP): δ 5.28 (d, 1 H, $J_{1',2'}$ 3.5 Hz, H-1'), 4.75 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.40 (d, 1 H, $J_{4,5}$ 1.9 Hz, H-5), 4.33 (t, 1 H, $J_{2,3}$ 3, $J_{3,4}$ 3 Hz, H-3), 4.17 and 4.39 (2 dd, 2 H, $J_{5',6'}$ 2 Hz, 2 H-6'), 3.99 (dd, 1 H, $J_{3,4}$ 3, $J_{4,5}$ 1.9 Hz, H-4), 3.93 (d, 1 H, $J_{4',5'}$ 9.8 Hz, H-5'), 3.76 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 3 Hz, H-2), 3.61 (s, 3 H, OMe), 3.23 (dd, 1 H, $J_{1',2'}$ 3.5, $J_{2',3'}$ 10 Hz, H-2').

Anal. Calc. for $C_{13}H_{20}NNa_3O_{17}S_2 \cdot 3\,H_2O$: C, 24.04; H, 4.03; N, 2.15. Found: C, 24.15; H, 4.71; N, 2.09.

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