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Syntheses of the methyl glycosides of the repeating units of chondroitin 4- and 6-sulfate

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ABSTRACT

3,4,6-Tri-*O*-acetyl-D-galactal was transformed into methyl 6-*O*-acetyl-2-azido-4-*O*-benzyl-2-deoxy-β-D-galactopyranoside and its 4-*O*-acetyl-6-*O*-benzyl analogue, each of which was glycosylated with activated, *O*-acetylated derivatives of methyl D-glucopyranosyluronate. The resulting β-(1→3)-linked disaccharide derivatives were each reductively *N*-acetylated, hydrogenolysed, *O*-sulfated, and saponified to afford the disodium salts of methyl 2-acetamido-2-deoxy-3-*O*-(β-D-glucopyranosyluronic acid)-4-*O*-sulfo-β-D-galactopyranoside and the 6-*O*-sulfo analogue. D-Galactal was also transformed into activated derivatives of 2-azido-3,6-di-*O*-benzyl-2-deoxy-D-galactopyranose and their 3,4-di-*O*-benzyl analogues with various substituents at O-4 and O-6. These glycosyl donors were condensed with 6-*O*-protected derivatives of methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside to give the β-(1→4)-linked disaccharide derivatives, which were selectively deprotected, then oxidised at C-6 of the *gluco* unit, reductively *N*-acetylated, selectively deprotected, *O*-sulfated at C-4 or C-6 of the *galacto* unit, and hydrogenolysed to give the disodium salts of methyl 4-*O*-(2-acetamido-2-deoxy-4-*O*-sulfo-β-D-galactopyranosyl)-β-D-glucopyranosiduronic acid and the 6-*O*-sulfo analogue.

INTRODUCTION

Chondroitin sulfates occur in many tissues as side chains of proteoglycans[1]. Although chondroitin 4-sulfate is the major variant, articular cartilage, particularly of older individuals, has high contents of the 6-sulfated variant. However, copolymeric chondroitin 4-/6-sulfate may be a common form. Over- and under-sulfated structures have also been described. Chondroitin sulfate proteoglycans are also present in plasma[2] and as a complex with platelet factor 4. The inhibitor of the complement factor Cl_q was identified as a chondroitin sulfate proteoglycan[3]. Recently, purified fractions of chondroitin sulfate proteoglycans were found[4] to accelerate the reactions of thrombin-AT III and factor Xa-AT III.

Structural studies showed chondroitins to be essentially copolymers built from repeating units (Fig. 1) composed of D-glucuronic acid (GlcA) and 4- or 6-*O*-sulfated 2-acetamido-2-deoxy-D-galactose (GalNAc). This microheterogeneity complicates chemical and enzymic studies. Thus, the availability of synthetic fragments and ^1H- and ^{13}C-n.m.r. data are of prime importance for the study of such structures. This approach has been undertaken with heparin[5] and dermatan sulfate[6]. Syntheses of the methyl

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$R^4 = SO_3^-, R^6 = H$ chondrointin 4-sulfate
$R^4 = H\ R^6 = SO_3^-$ chondrointin 6-sulfate

glycosides **35**, **36**, **51**, and **60**, four possible repeating units of chondroitin 4- and 6-sulfate, from 3,4,6-tri-*O*-acetyl-D-galactal (**1**) are now reported.

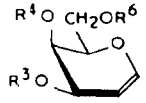
RESULTS AND DISCUSSION

The 4- (**35**) and 6-sulfate (**36**) of β-GlcA-(1→3)-β-GalNAc-OMe were obtained via reactions of the glycosyl acceptors **4** and **5** with the glycosyl donors **25** and **26**. The 4′- (**51**) and 6′-sulfate (**60**) of β-GalNAc-(1→4)-β-GlcA-OMe were obtained via reactions of the glycosyl donors **14** or **15** and **20** or **23** with glycosyl acceptors **38** and **39.**

Methyl 2-azido-2-deoxy-β-D-galactopyranoside[6] (**2**), obtained from (**1**), was 3,6-di-*O*-silylated with *tert*-butyldimethylsilyl chloride and imidazole in *N,N*-dimethylformamide. Treatment of the product with benzyl bromide and sodium hydride in *N,N*-dimethylformamide gave a complex mixture, even at low temperatures, in which the tri-*O*-benzyl derivative was the major component. This kind of reductive cleavage of *tert*-butyldimethylsilyl ethers was reported recently[7]. With tetrahydrofuran as the solvent, reaction was slow and incomplete, even with an excess of the reagents but, with 4:1 tetrahydrofuran–*N,N*-dimethylformamide at 0°, reaction was complete within 30 min. Although *tert*-butyldimethylsilyl ethers are known[8] to be stable in alcoholic bases, *in situ O*-desilylation of the benzylated product gave 72% of crystalline **3**. Selective-6-*O*-acetylation of **3** with 1-acetylimidazole gave the crystalline glycosyl acceptor methyl 6-*O*-acetyl-2-azido-4-*O*-benzyl-2-deoxy-β-D-galactopyranoside (**4**, 78%), the structure of which was indicated by the ^{1}H-n.m.r. spectrum.

The glycosyl acceptor methyl 4-*O*-acetyl-2-azido-6-*O*-benzyl-2-deoxy-β-D-galactopyranoside (**5**) was prepared from **2** essentially as reported[6].

The various glycosyl donors were synthesised as follows. D-Galactal (**6**) was prepared as described[9], but the physical properties reported were slightly at variance with those found. The structure of **6** was apparent from the ^{1}H-n.m.r. spectrum in which, in addition to the known ($J_{1,3}$) long-range coupling, $J_{2,4}$ 2.0 Hz, was observed. Attempts to selectively 3,6-di-*O*-benzylate **6** with benzyl chloride–sodium hydride gave mainly the 4,6-di-*O*-benzyl derivative as reported[10]. However, treatment of **6** with benzoyl chloride at 0° gave 76% of the crystalline 3,6-dibenzoate **7**. Attempted 4-*O*-*tert*-butyldimethylsilylation of **7** failed. Reaction was possible only in concentrated media



1 $R^3 = R^4 = R^6 = Ac$

6 $R^3 = R^4 = R^6 = H$

7 $R^3 = R^6 = Bz$, $R^4 = H$

8 $R^3 = R^6 = {}^tBuMe_2Si$, $R^4 = H$

9 $R^3 = R^6 = H$, $R^4 = MeOCH_2CH_2OCH_2$

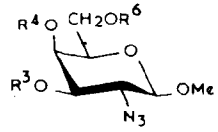
10 $R^3 = R^6 = Bn$, $R^4 = MeOCH_2CH_2OCH_2$

16 $R^3 = R^4 = H$, $R^6 = {}^tBuMe_2Si$

17 $R^3 = R^4 = Bn$, $R^6 = H$

18 $R^3 = R^4 = Bn$, $R^6 = MeOCH_2CH_2OCH_2$

21 $R^3 = R^4 = Bn$, $R^6 = Bz$

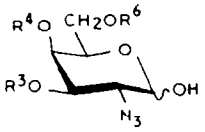


2 $R^3 = R^4 = R^6 = H$

3 $R^3 = R^6 = H$, $R^4 = Bn$

4 $R^3 = H$, $R^4 = Bn$, $R^6 = Ac$

5 $R^3 = H$, $R^4 = Ac$, $R^6 = Bn$

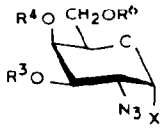


11 $R^3 = R^6 = Bn$, $R^4 = MeOCH_2CH_2OCH_2$

12 $R^3 = R^6 = Bn$, $R^4 = Ac$

19 $R^3 = R^4 = Bn$, $R^6 = MeOCH_2CH_2OCH_2$

22 $R^3 = R^4 = Bn$, $R^6 = Bz$



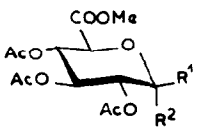
13 $X = Br$, $R^3 = R^6 = Bn$, $R^4 = MeOCH_2CH_2OCH_2$

14 $X = OC(NH)CCl_3$, $R^3 = R^6 = Bn$, $R^4 = MeOCH_2CH_2OCH_2$

15 $X = OC(NH)CCl_3$, $R^3 = R^6 = Bn$, $R^4 = Ac$

20 $X = OC(NH)CCl_3$, $R^3 = R^4 = Bn$, $R^6 = MeOCH_2CH_2OCH_2$

23 $X = OC(NH)CCl_3$, $R^3 = R^4 = Bn$, $R^6 = Bz$



24 $R^1 = OAc$, $R^2 = H$

25 $R^1 = H$, $R^2 = OC(NH)CCl_3$

26 $R^1 = H$, $R^2 = Br$

with a large excess of reagents and heating, but extensive 3→4 benzoyl migration occurred (^{1}H-n.m.r. data). Hence, **6** was selectively *tert*-butyldimethylsilylated[11], as described, to give the 3,6-di-*O*-*tert*-butyldimethylsilyl derivative **8** (95%). Treatment of **8** with 2-methoxyethoxymethyl chloride[12] and sodium hydride in tetrahydrofuran–*N*,*N*-dimethylformamide, as described for the preparation of **3**, gave 63% of the crystalline 4-*O*-(2-methoxyethoxymethyl) derivative **9**. Reaction of **9** with benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide afforded the 3,6-di-*O*-benzyl derivative **10** (96%), which was rather unstable.

Azidonitration[13] of **10** proceeded readily within 2 h at −20°, and the crude *α*,*β*-mixture was treated with sodium nitrite[14] in aqueous 1,4-dioxane to give the crystalline 2-azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-(2-methoxyethoxymethyl)-D-galacto-pyranose (**11**, 69%). The *galacto* structure of **11** was apparent from the ^{1}H-n.m.r. data ($J_{2,3}$ 10.40, $J_{3,4}$ 3.0, $J_{4,5}$ 0.80 Hz), as was the non-substitution at C-1 (δ 5.34, t, $J_{1,2} = J_{1,OH}$ = 3.60 Hz, H-1*α*).

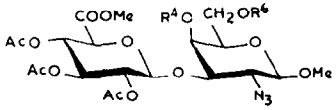
In the route to **51**, the 4-(2-methoxyethoxymethyl) group in **11** was replaced by acetyl. When **11** was treated with anhydrous zinc bromide[12] in dichloromethane, the

reaction was not clean and was incomplete even after 24 h, and treatment with titanium tetrachloride[12] at low temperature led to extensive degradation (mainly *O*-debenzylation). However, treatment of **11** with aqueous 90% trifluoroacetic acid for 15 min, followed by acetylation and then selective 1-*O*-deacetylation with benzylamine[15] in ether, gave **12** (83%), which had resonances for H-4α and H-4β at δ 5.57 and 5.48, respectively.

Treatment of **11** with (bromomethylene)dimethylammonium bromide, prepared[16] *in situ*, gave the crystalline bromide **13** (81%). Glycosyl trichloroacetimidates that have non-participating groups at C-2 undergo inversion at the anomeric centre when treated with boron trifluoride etherate at low temperature[17]. Reaction of **11** with trichloroacetonitrile and 1,8-diazabicyclo[5.4.0]undec-7-ene gave 81% of the glycosyl donor 2-azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-(2-methoxyethoxymethyl)-α-D-galactopyranosyl trichloroacetimidate (**14**). That **14** was α was indicated by the $[\alpha]_D$ value ($+78°$) and the resonance for H-1 at δ 6.41 (d, $J_{1,2}$ 3.60 Hz). An ~ 1:1 mixture (14%) of **14** and its β-isomer (δ 5.56, d, $J_{1,2}$ 8.40 Hz, H-1β) was also obtained, from which **11** could be regenerated. Likewise, **12** was converted into the glycosyl donor 4-*O*-acetyl-2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-galactopyranosyl trichloroacetimidate (**15**, 81%).

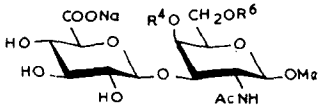
The glycosyl donors **20** and **23** were obtained as follows. Selective 6-*O*-*tert*-butyldimethylsilylation of **6** gave **16** (80%) together with 11% of the 3,6-di-*O*-silyl ether **8**. Benzylation of **16** followed by *in situ* *O*-desilylation gave crystalline 3,4-di-*O*-benzyl-D-galactal (**17**, 85%). That HO-6 was unsubstituted was evident from the ^{1}H-n.m.r. spectrum [δ 2.31, dd, $J_{6a,OH}$ 4.20, $J_{6b,OH}$ 8.50 Hz, HO-6). Treatment of **17** with 2-methoxyethoxymethyl chloride[12] and sodium hydride gave **18** (92%), azidonitration of which followed by hydrolysis afforded 60% of crystalline **19**. The reaction of **19** with trichloroacetonitrile and 1,8-diazabicyclo[5.4.0]undec-7-ene gave only 65% of the glycosyl donor 2-azido-3,4-di-*O*-benzyl-2-deoxy-6-*O*-(2-methoxyethoxymethyl)-α-D-galactopyranosyl trichloroacetimidate (**20**), and 25% of the β isomer (δ 5.57, d, $J_{1,2}$ 8.20 Hz, H-1β) was isolated. The reduced stereoselectivity contrasted with those for **14** and **15**. 6-*O*-Benzoylation of **17** gave **21** (95%), azidonitration of which followed by hydrolysis afforded **22** (66%). Treatment of **22** with trichloroacetonitrile, as described above, gave the glycosyl donor 2-azido-6-*O*-benzoyl-3,4-di-*O*-benzyl-2-deoxy-α-D-galactopyranosyl trichloroacetimidate (**23**, 79%).

Activated acetylated derivatives of methyl D-glucopyranuronate were required for the syntheses of the target molecules **35** and **36**. Treatment of the β-acetate **24**[19] with dibutyltin oxide in methanol was reported[20] to give 80% of the free hemiacetal that was converted into the crystalline glycosyl donor methyl (2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate)uronate (**25**, 74% overall yield). Condensation of **25** (1.33 equiv.) with **4** (1 equiv.), catalysed by trimethylsilyl triflate (5% based on **25**) in toluene at $-20°$, gave the crystalline β-linked disaccharide-glycoside **27** (75% from **4**; δ 4.87, d, $J_{1',2'}$ 7.80 Hz, H-1'). Condensation of **4** (1 equiv.) with **26** (1.4 equiv.) in the presence of silver triflate and 4 Å molecular sieves also gave **27** (90% from **4**). Condensation of **5** with imidate **25** in the presence of trimethylsilyl triflate (5% based on **25**) gave a major product, the spectrum of which indicated it to be an orthoester [δ 5.97 (d, 1 H, $J_{1',2'}$ 5.0



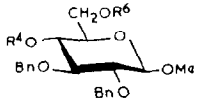
27 R^4 = Bn , R^6 = Ac

28 R^4 = Ac , R^6 = Bn



35 R^4 = SO_3Na, R^6 = H

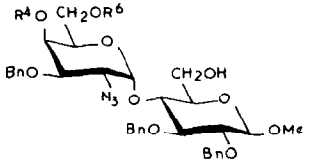
36 R^4 = H , R^6 = SO_3Na



37 R^4 = R^6 = H

38 R^4 = H , R^6 = $COCH_2Cl$

39 R^4 = H , R^6 = $^tBuMe_2Si$

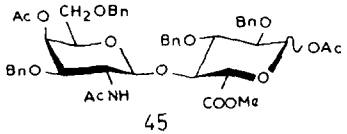


41 R^4 = $MeOCH_2CH_2OCH_2$, R^6 = Bn

47 R^4 = Ac , R^6 = Bn

53 R^4 = Bn , R^6 = $MeOCH_2CH_2OCH_2$

55 R^4 = Bn , R^6 = Bz



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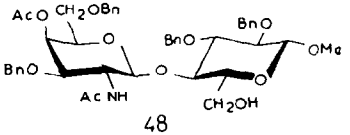

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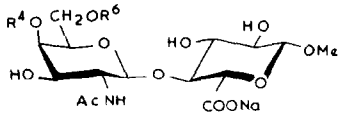
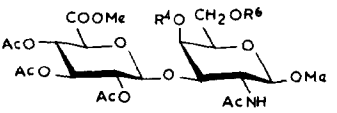


51 R^4 = SO_3Na , R^6 = H

60 R^4 = H , R^6 = SO_3Na



29 R^4 = Bn , R^6 = Ac

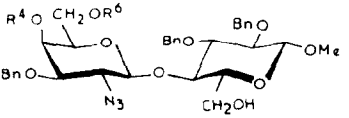
30 R^4 = Ac , R^6 = Bn

31 R^4 = H , R^6 = Ac

32 R^4 = Ac , R^6 = H

33 R^4 = SO_3Na , R^6 = Ac

34 R^4 = Ac , R^6 = SO_3Na

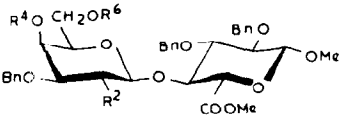


40 R^4 = $MeOCH_2CH_2OCH_2$, R^6 = Bn

46 R^4 = Ac , R^6 = Bn

52 R^4 = Bn , R^6 = $MeOCH_2CH_2OCH_2$

54 R^4 = Bn , R^6 = Bz



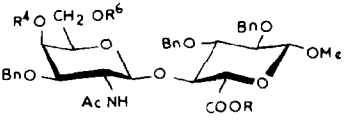
42 R^2 = N_3, R^4 = $MeOCH_2CH_2OCH_2$, R^6 = Bn

43 R^2 = NHAc, R^4 = $MeOCH_2CH_2OCH_2$, R^6 = Bn

44 R^2 = NHAc, R^4 = H , R^6 = Bn

56 R^2 = N_3, R^4 = Bn , R^6 = Bz

57 R^2 = NHAc, R^4 = Bn , R^6 = Bz



49 R = R^4 = H , R^6 = Bn

50 R = Na , R^4 = SO_3Na , R^6 = Bn

58 R = R^6 = H , R^4 = Bn

59 R = Na , R^4 = Bn , R^6 = SO_3Na

Hz, H-1'), 4.36 (dd, 1 H, $J_{1',2'}$ 5.0, $J_{2',3'}$ 4.0 Hz, H-2'), and 1.82 (s, 3 H, C-Me)]. The formation of this undesirable intermediate was avoided by using 10% of catalyst, and 72% of the crystalline β-linked disaccharide derivative **28** (δ 4.81, d, $J_{1',2'}$ 7.80 Hz, H-1') was obtained. Condensation of **5** (1 equiv.) and the glycosyl donor[18] methyl (2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl bromide)uronate (**26**, 1.5 equiv.) in the presence of silver triflate afforded 80% of **28**. Therefore, glycosylation with the bromide **26**–silver triflate system was the better method.

Concomitant hydrogenation (Pd–C) of benzyl ethers and reduction of an azide group is unsatisfactory[6] in the presence of methyl esters, and a two-step procedure was examined that involved reductive *N*-acetylation of the azide group using thioacetic acid[21]. Treatment of **27** with thioacetic acid for 24 h at room temperature gave 87% of the crystalline 2-acetamido-2-deoxy derivative **29** [δ 5.67 (d, 1 H, $J_{2,NH}$ 7.0 Hz, NH) and 1.95 (s, 3 H, NAc)]. Likewise, **28** gave crystalline **30** (82%). Hydrogenolysis (10% Pd–C) of **29** in methanol gave 95% of crystalline **31**. Hydrogenolysis of **30** in methanol gave up to 20% of the 6-acetate **31**, due to 4→6 acetyl migration. The yield of this by-product was decreased to 6% by using ethyl acetate as solvent, and 82% of the crystalline alcohol **32** was obtained. Treatment of **31** with the sulfur trioxide–trimethylamine complex in *N,N*-dimethylformamide afforded the 4-sulfate derivative, isolated as the crystalline sodium salt **33** (94%). Comparison of the ^{1}H-n.m.r. spectra of **33** and **31** showed the expected downfield shift[6] (0.78 p.p.m.) of the signal of H-4 of **33**. Likewise, sulfation of **32** gave the 6-sulfate derivative, isolated as the crystalline sodium salt (**34**, 92%). The expected downfield shifts of the signals for H-6a (0.47 p.p.m.) and H-6b (0.54 p.p.m.) were observed. These data accord with previous observations[6]. Treatment of **33** and **34** with sodium hydroxide in aqueous methanol gave the crystalline target compounds **35** (83%) and **36** (86%), respectively. The relevant ^{1}H-n.m.r. data of **35** and **36** in Table I accord with observations based on synthetic models[6,22].

For the syntheses of **51** and **60**, benzylated derivatives of methyl β-D-glucopyranoside were required. Treatment of methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside[23] (**37**)

TABLE I

^{1}H-N.m.r. parameters[a] (300 MHz) for the sulfated disaccharide methyl glycosides (Na salts)

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6b*	*H-1'*	*H-2'*	*H-3'*	*H-4'*	*H-5'*
4-Sulfate **35**	4.48	4.08	4.09	**4.81**[b]	3.84	3.84	3.84	4.49	3.37	3.47	3.55	3.68
6-Sulfate **36**	4.46	4.04	3.86	4.25	3.95	**4.27**	**4.22**	4.52	3.35	3.51	3.52	3.71
	H-1'	*H-2'*	*H-3'*	*H-4'*	*H-5'*	*H-6'a*	*H-6'b*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*
4-Sulfate **51**	4.56	3.91	3.89	**4.69**	3.84	3.84	3.84	4.39	3.34	3.60	3.77	3.72
6-Sulfate **60**	4.53	3.93	3.75	3.99	3.97	**4.26**	**4.23**	4.40	3.36	3.62	3.76	3.72

[a] In D_2O at 25°; chemical shifts in p.p.m. from internal 3-(trimethylsilyl)propionic acid, sodium salt (TSP).
[b] Values in bold type reflect the locations of the sulfate groups.

with 1-chloracetylimidazole in 1,2-dichloroethane gave the crystalline glycosyl acceptor methyl 2,3-di-*O*-benzyl-6-*O*-chloroacetyl-β-D-glucopyranoside (**38**, 79%). Selective 6-*O*-*tert*-butyldimethylsilylation of **37** gave the glycosyl acceptor methyl 2,3-di-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranoside (**39**, 92%).

TABLE II

Glycosylations of **38** and **39**

Donor	*Acceptor*	*Solvent*[c]	*Product*	*Yield*[d] *(%)*	*αβ-Ratio*
13[a]	**38**	A	**40**	20	~1
13[a]	**39**	A	**40**	26	~1
14[b]	**38**	A	**40**	30	1:6
14[b]	**38**	B	**40**	66	1:10[e]
14[b]	**39**	B	**40**	40	1:9
15[b]	**38**	B	**46**	50	1:3
15[b]	**39**	B	**46**	65	1:20[e]
20[b]	**38**	B	**52**	35	2:3
20[b]	**39**	B	**52**	32	1:3
23[b]	**38**	B	**54**	40	2:3
23[b]	**39**	A	**54**	32	1:8
23[b]	**39**	B	**54**	60	1:11[e]

[a] Catalysis with silver silicate. [b] Catalysis with boron trifluoride etherate. [c] A, 1,2-dichloroethane; B, toluene. [d] Yields refer to compounds isolated after removal of the 6-substituent in the Glc moiety. [e] Selected preparative conditions.

Glycosylation reactions that involved the donors **13–15**, **20**, and **23**, and the acceptors **38** and **39**, are summarized in Table II. Most of the coupling products could be isolated by chromatography only after deprotection at O-6 of the Glc unit. Excess of acceptor (1.5 equiv.) was routinely used. When the bromide **13** was condensed with **38** or **39** under the catalysis of silver silicate[24], the stereoselectivity was high, although the yields were low, probably due to the well-known low nucleophilicity of O-4 of hexopyranosides. Much better yields were obtained from the imidates **14**, **15**, **20**, or **23**, and the acceptors **38** or **39**, by reaction in toluene at −20° rather than in 1,2-dichloroethane. Compound **39** appeared to be the best acceptor except in the reaction with **14**. Imidates **14**, **15**, and **23** gave reasonable yields of products with acceptable selectivity, but poor selectivity occurred with **20**. The ^{1}H-n.m.r. spectrum of each β-linked disaccharide derivative contained a doublet ($J_{1',2'}$ 7.80–8.0 Hz) for H-1′ and signals (dd or t) at δ 2–3 characteristic of HO-6.

Several conditions for oxidizing **40** to the uronic acid derivative **42** were examined. Oxidation[25] of **40** with chromic anhydride–sulfuric acid was slow and incomplete,

even with a large excess of the oxidant. Compound **40** (as well as **46** and **54**) was poorly soluble in acetone at low temperature, and only 40% of **42** was isolated after esterification with diazomethane. A two-step procedure involving oxidation[26] with dimethyl sulfoxide–oxalyl chloride and treatment of the crude *aldehydo* derivative with bromine[27] in buffered ($NaHCO_3$) methanol–water afforded 35% of **42**. However, 75% of crystalline **42** was obtained by oxidation of **40** with pyridinium dichromate[28] (5 equiv.) in *N,N*-dimethylformamide for 20 h, followed by esterification with diazomethane. Also formed in this reaction was 20% of an intermolecular tetrasaccharidic ester[29], by the reaction of **40** with the aldehyde, formed on oxidation, to give a hemiacetal. Compound **42**, the structure of which was confirmed by the ^{1}H-n.m.r. data [δ 3.95 (d, 1 H, $J_{4,5}$ 9.50 Hz, H-5) and 3.82 (s, 3 H, COOMe)] was treated with thioacetic acid to give the crystalline 2-acetamido derivative **43** (76%). Attempted removal of the 4-*O*-(2-methoxyethoxymethyl) group with zinc bromide[12] or titanium tetrachloride[12] was unsuccessful. Acetolysis of **43** with 5% trifluoroacetic acid in acetic anhydride at low temperature resulted in *O*-debenzylation, but treatment for 30 min with aqueous 85% trifluoroacetic acid afforded 60% of crystalline **44** together with 25% of **45**, identified after *O*-acetylation. Thus, substituted methyl ethers were not good temporary protecting-groups.

The following route was used for the preparation of the target compound **51**. The azido derivative **46** was reduced with sodium borohydride, nickel dichloride hexahydrate, and boric acid, and the resulting amine was *N*-acetylated to give crystalline **48** (81%). Oxidation of **48** with pyridinium dichromate in *N,N*-dimethylformamide for 24 h, followed by saponification, gave crystalline **49** (78%), which was obtained (88%) also by saponification of the methyl uronate **44**. Sulfation, as described above, of the sodium salt **44** gave the amorphous disodium salt **50** (93%). Comparison of the ^{1}H-n.m.r. spectra of **50** and **49** showed the expected downfield shift (0.95 p.p.m.) for the signal of H-4′ of **50**. Catalytic hydrogenation (Pd–C) of **50** then gave the target molecule **51** (87%). ^{1}H-N.m.r. data for **51**, reported in Table I, accord with previous observations.

The target molecule **60** was prepared from the 6-*O*-benzoylated disaccharide derivative **54**. Thus, oxidation of **54** with pyridinium dichromate in *N,N*-dimethylformamide and esterification of the product with etheral diazomethane gave **56** (73%), which was subjected in sequence to reductive *N*-acetylation (→**57**, 78%), saponification (→**58**, 83%) and sulfation (→**59**, 86%). Comparison of the ^{1}H-n.m.r. spectra of **59** and **58** also showed downfield displacement of the signals for H-6′a and H-6′b (0.52 and 0.65 p.p.m., respectively) in the former. Catalytic hydrogenolysis (Pd–C) of **59** then gave the amorphous target molecule **60** (89%). The ^{1}H-n.m.r. data for **60** in Table I accord with previous observations.

The ^{13}C-n.m.r. data (Table III) for **35**, **36**, **51**, and **60** accord with those for model compounds[6]. 4-Sulfation caused downfield displacements of 7.50 and 8.30 p.p.m., respectively, for C-4 in the disaccharide-glycosides **35** and **51**, and 6-sulfation caused downfield displacements of 6.60 and 6.0 p.p.m. in the signal for C-6 in the disaccharide-glycosides **36** and **60**, respectively. These data accord with those for polymeric chondroitin 4- and 6-sulfates[30,31].

TABLE III

^{13}C-N.m.r. parameters[a] (75.4 MHz) for the sulfated disaccharide methyl glycosides (Na salts)

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-1'*	*C-2'*	*C-3'*	*C-4'*	*C-5'*	*C-6'*
4-Sulfate **35**	102.25	51.97	76.76	**75.48**[b]	74.83	61.32	103.44	72.03	75.08	72.76	76.66	175.00
6-Sulfate **36**	102.44	51.24	80.28	68.00	73.05	**67.95**	104.34	72.08	75.67	73.01	76.39	175.15
	C-1'	*C-2'*	*C-3'*	*C-4'*	*C-5'*	*C-6'*	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
4-Sulfate **51**	103.51	52.84	72.83	**75.97**	74.18	61.24	101.32	70.30	74.73	80.22	76.78	174.36
6-Sulfate **60**	103.56	52.41	72.80	67.70	72.94	**67.28**	101.80	71.12	74.33	81.24	76.78	174.12

[a] In D_2O at 30°; chemical shifts in p.p.m. from internal acetone (30.50 p.p.m.). [b] Values in bold type reflect the locations of the sulfate groups.

The syntheses of **35**, **36**, **51**, and **60** now reported open the way to the synthesis of fragments of higher molecular weight.

EXPERIMENTAL

General methods. — Melting points were determined in capillary tubes with a Büchi apparatus and are uncorrected. Optical rotations were measured at 20–25° with a Perkin–Elmer Model 141 polarimeter. The ^{1}H- (300 MHz) and ^{13}C-n.m.r. (75 MHz) spectra were recorded with a Bruker AM-300 spectrometer. Chemical shifts (δ) are given from the signal of internal Me_4Si unless otherwise stated. Unprimed numbers refer to the "reducing" unit and primed numbers to the non-reducing unit. 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), and flash-column chromatography on Silica Gel (Merck, 40–63 μm). Elemental analyses were performed by the Service Central de Micro-Analyse du Centre National de la Recherche Scientifique (Vernaison, France).

*Methyl 2-azido-4-O-benzyl-2-deoxy-β-*D*-galactopyranoside (***3***).* — A mixture of methyl 2-azido-2-deoxy-β-D-galactopyranoside[6] (**2**, 440 mg), imidazole (580 mg), and *tert*-butyldimethylsilyl chloride (642 mg) in dry *N,N*-dimethylformamide (10 mL) was stirred for 45 min at 0°, then poured into cold aqueous 5% ammonium chloride, and extracted with dichloromethane (3 × 20 mL). The combined extracts were washed with cold brine and water, dried ($MgSO_4$), and concentrated. A mixture of the crude residue and sodium hydride (92 mg) in dry tetrahydrofuran (10 mL) was stirred at 0°. Benzyl bromide (0.3 mL) and then dry *N,N*-dimethylformamide (2 mL) were added dropwise, and the mixture was stirred for 30 min at 0°. Methanol (0.5 mL) was added and stirring was continued for 16 h at room temperature. The mixture was concentrated, and the residue was applied to a column (3 × 5 cm) of silica gel and eluted with ethyl acetate–hexane (1:1). Crystallization of the product from the same solvents gave **3** (445 mg,

72%, m.p. 136–137°, $[\alpha]_D$ −8° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.35 (m, 5 H, Ph), 4.76 (ABq, 2 H, CH_2Ph), 4.17 (d, 1 H, $J_{1,2}$ 7.80 Hz, H-1), 3.57 (s, 3 H, OMe), 2.29 (d, 1 H, $J_{3,OH}$ 6.50 Hz, HO-3), 1.63 (dd, 1 H, $J_{6a,OH}$ 4.0, $J_{6b,OH}$ 7.0 Hz, HO-6).

Anal. Calc. for $C_{14}H_{19}N_3O_5$: C, 54.36; H, 6.19; N, 13.58. Found: C, 54,38; H, 6.12; N, 13.41.

Methyl 6-O-acetyl-2-azido-4-O-benzyl-2-deoxy-β-D-galactopyranoside (**4**). — A mixture of **3** (402 mg) and 1-acetylimidazole (180 mg) in dry 1,2-dichloroethane (6 mL) was stirred at 65° with exclusion of moisture for 18 h, then cooled, diluted with dichloromethane (50 mL), washed with cold 0.01 M hydrochloric acid, brine, and water, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel (30 g) with hexane–ethyl acetate (3:2) and crystallized from ether to give **4** (356 mg, 78%), m.p. 90–91°, $[\alpha]_D$ −18° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.35 (m, 5 H, Ph), 4.32 (dd, 1 H, $J_{5,6a}$ 6.60 $J_{6a,6b}$ 11.10 Hz, H-6a), 4.16 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.13 (dd, 1 H, $J_{5,6b}$ 6.60, $J_{6a,6b}$ 11.10 Hz, H-6b), 3.76 (dd, 1 H, $J_{3,4}$ 3.20, $J_{4,5}$ 1.0 Hz, H-4), 3.62 (m, 1 H, $J_{4,5}$ 1.0, $J_{5,6a} = J_{5,6b}$ = 6.60 Hz, H-5), 3.58 (dd, 1 H, $J_{1,2}$ 7.80, $J_{2,3}$ 10.30 Hz, H-2), 3.56 (s, 3 H, OMe), 3.47 (dd, 1 H, $J_{2,3}$ 10.30, $J_{3,4}$ 3.20 Hz, H-3), 2.27 (d, 1 H, $J_{3,OH}$ 6.50 Hz, HO-3), 2.02 (s, 3 H, OAc).

Anal. Calc. for $C_{16}H_{21}N_3O_6$: C, 54.69; H, 6.02; N, 11.96. Found: C, 54.58; H, 5.95; N, 11.86.

*1,5-Anhydro-*D-arabino-*hex-1-enitol (*D-*galactal)* (**6**). — To a solution of 3,4,6-tri-*O*-acetyl-D-galactal (**1**, 16.35 g) in methanol (100 mL) was added sodium (20 mg). The mixture was stirred overnight and then concentrated. The residue was eluted from a column (4 × 4 cm) of silica gel with dichloromethane–methanol (5:1) and crystallized from ethyl acetate to give **6** (7.80 g, 89%), m.p. 93–94°, $[\alpha]_D$ −23° (*c* 1, methanol); lit.[9] m.p. 104°, $[\alpha]_D$ +5° (*c* 1.2, methanol). ^{1}H-N.m.r. data (D_2O, internal TSP): δ 5.87 (dd, 1 H, $J_{1,2}$ 6.20, $J_{1,3}$ 2.0 Hz, H-1), 4.74 (m, 1 H, $J_{1,2}$ 6.20, $J_{2,3}$ 2.0, $J_{2,4}$ 2.0 Hz, H-2), 4.50 (m, 1 H, $J_{1,3} = J_{2,3}$ = 2.0 Hz, $J_{3,4}$ 4.60 Hz, H-3), 4.07 (m, 1 H, $J_{4,5}$ 0.80, $J_{5,6a}$ 4.80, $J_{5,6b}$ 8.0 Hz, H-5), 3.96 (m, 1 H, $J_{3,4}$ 4.60, $J_{4,5}$ 0.80, $J_{2,4}$ 2.0 Hz, H-4), 3.86 (dd, 1 H, $J_{5,6a}$ 8.0, $J_{6a,6b}$ 12.0 Hz, H-6a), 3.78 (dd, 1 H, $J_{5,6b}$ 4.80, $J_{6a,6b}$ 12.0 Hz, H-6b).

Anal. Calc. for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.35; H, 6.92.

*3,6-Di-O-benzoyl-*D-*galactal* (**7**). — A solution of benzoyl chloride (0.81 mL) in 1,2-dichloromethane (2 mL) was added dropwise at 0° within 15 min to a solution of **6** (438 mg) in pyridine (2 mL) and 1,2-dichloroethane (3 mL), and the mixture was stirred for 45 min at 0°. Methanol (1 mL) was then added, and the mixture was stirred for 30 min at room temperature, then diluted with dichloromethane (50 mL), washed with aqueous 10% potassium hydrogensulfate, saturated aqueous sodium hydrogencarbonate, and water, dried ($MgSO_4$), and concentrated. The residue was crystallized from ethyl acetate–hexane to give **7** (808 mg, 76%), m.p. 120–121°, $[\alpha]_D$ +106° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.10–7.30 (m, 10 H, 2 Ph), 6.57 (dd, 1 H, $J_{1,2}$ 6.20, $J_{1,3}$ 1.80 Hz, H-1), 5.23 (m, 1 H, $J_{1,3}$ 1.80 $J_{2,3}$ 2.0, $J_{3,4}$ 2.20 Hz, H-3), 4.87 (m, 1 H, $J_{1,2}$ 6.20, $J_{2,3}$ 2.0, $J_{2,4}$ 1.80 Hz, H-2), 4.73 (dd, 1 H, $J_{5,6a}$ 7.0, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.66 (dd, 1 H, $J_{5,6b}$ 5.20, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.46 (m, 1 H, $J_{3,4}$ 2.20, $J_{4,5}$ 1.0, $J_{2,4}$ 1.80 Hz, H-4), 4.42 (m, 1 H, $J_{4,5}$ 1.0, $J_{5,6a}$ 7.0, $J_{5,6b}$ 5.20 Hz, H-5), 2.32 (d, 1 H, $J_{4,OH}$ 6.40 Hz, HO-4).

Anal. Calc. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.81; H, 5.08.

3,6-Di-O-tert-butyldimethylsilyl-D-galactal[11] (**8**). — A mixture of **6** (877 mg), imidazole (2.040 g), and *tert*-butyldimethylsilyl chloride (2.040 g) in dry *N,N*-dimethylformamide (20 mL) was stirred for 45 min at 0°, then diluted with dichloromethane (100 mL), washed with aqueous 5% ammonium chloride, brine, and water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel (20 g) with hexane–ethyl acetate (24:1) to give **8**, isolated as a mobile syrup (2.145 g, 95%), $[\alpha]_D$ −41° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.35 (dd, 1 H, $J_{1,2}$ 6.40, $J_{1,3}$ 1.80 Hz, H-1), 4.53 (m, 1 H, $J_{1,2}$ 6.40, $J_{2,3}$ 2.0, $J_{2,4}$ 1.80 Hz, H-2), 4.45 (m, 1 H, $J_{1,3}$ 1.80, $J_{2,3}$ 2.0, $J_{3,4}$ 5.0 Hz, H-3), 2.70 (d, 1 H, $J_{4,OH}$ 1.5 Hz, HO-4), 0.91 and 0.89 (2 s, 18 H, ^{t}Bu), 0.10 and 0.09 (2 s, 12 H, Me).

4-O-(2-Methoxyethoxymethyl)-D-galactal (**9**). — A mixture of **8** (2.81 g), sodium hydride (345 mg), and 2-methoxyethoxymethyl chloride (1.14 mL) in dry tetrahydrofuran (20 mL) was stirred at 0° with the exclusion of moisture. Dry *N,N*-dimethylformamide (5 mL) was added dropwise and stirring was continued for 45 min at 0°. Methanol (1 mL) was added, and the mixture was stirred for 4 h at 40°, then concentrated. The residue was eluted from a column (3 × 8 cm) of silica gel with dichloromethane–methanol (12:1). The resulting yellow syrup was triturated in ether (50 mL) and then crystallized from ethyl acetate to give **9** (1.106 g, 63%), m.p. 98–99°, $[\alpha]_D$ −53° (*c* 1, methanol). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 6.27 (dd, 1 H, $J_{1,2}$ 6.40, $J_{1,3}$ 1.80 Hz, H-1), 4.80 (ABq, 2 H, OCH_2O), 4.74 (d, 1 H, $J_{3,OH}$ 6.50 Hz, HO-3), 4.70 (t, 1 H, $J_{6a,OH} = J_{6b,OH}$ = 5.50 Hz, HO-6), 4.54 (m, 1 H, $J_{1,2}$ 6.40, $J_{2,3} = J_{2,4}$ = 2.0 Hz, H-2), 3.25 (s, 3 H, OMe).

Anal. Calc. for $C_{10}H_{18}O_6$: C, 51,27; H, 7.74. Found: C, 51.18; H, 7.81.

3,6-Di-O-benzyl-4-O(2-methoxyethoxymethyl)-D-galactal (**10**). — Sodium hydride (290 mg) was added to a stirred solution of **9** (703 mg) in dry *N,N*-dimethylformamide (10 mL). After 30 min, benzyl bromide (1.07 mL) was added dropwise and the mixture was stirred for 1 h. Excess of reagent was then destroyed by the addition of methanol (1 mL) and stirring for 30 min. The mixture was diluted with dichloromethane (50 mL), washed with brine and water, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel (50 g) with hexane–ethyl acetate (5:2) to give **10**, isolated as an unstable syrup (1.20 g, 96%), $[\alpha]_D$ −48° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDC1_3$): δ 7.30 (m, 10 H, 2 Ph), 6.38 (d, 1 H, $J_{1,2}$ 6.20 Hz, H-1), 4.90 (ABq, 2 H, OCH_2O),4.84 (dd, 1 H, $J_{1,2}$ 6.20, $J_{2,3}$ 4.0 Hz, H-2), 3.34 (s, 3 H, OMe).

Anal. Calc. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.29. Found: C, 69.70; H, 7.11.

2-Azido-3,6-di-O-benzyl-2-deoxy-4-O-(2-methoxyethoxymethyl)-D-galactopyranose (**11**). — A solution of **10** (415 mg) in dry acetonitrile (8 mL) was transferred under dry argon to a mixture of dry sodium azide (98 mg) and powdered ceric ammonium nitrate (1.65 g). The resulting suspension was stirred vigorously for 2 h at −20°. Cold ether (50 mL) was then added and the mixture was washed twice with ice-cold water (with back-extraction with ether of the aqueous layer), dried (Na_2SO_4), and concentrated. A mixture of the residue and sodium nitrite (172 mg) in 1,4-dioxane (8 ml) and water (0.5 mL) was stirred for 1 h at 80°, then cooled, poured into ice-cold water (100 mL), and extracted with dichloromethane (4 × 10 mL). The combined extracts were washed with

water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel (25 g) with hexane–ethyl acetate (3:2) and crystallized from the same solvents to give **11** (326 mg, 69%), m.p. 74–75°, $[\alpha]_D$ +11° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 10 H, 2 Ph), 5.34 (t, $J_{1,2} = J_{1,OH}$ = 3.60 Hz, H-1α), 4.47 (m, $J_{1,2}$ 8.0, $J_{1,OH}$ 5.50 Hz, H-1β), 4.23 (m, $J_{4,5}$ 0.80, $J_{5,6a} = J_{5,6b}$ = 6.50 Hz, H-5α), 4.16 (dd, $J_{3,4}$ 3.0, $J_{4,5}$ 0.80 Hz, H-4α), 4.06 (dd, $J_{3,4}$ 3.0, $J_{4,5}$ 0.60 Hz, H-4β), 3.92 (dd, $J_{2,3}$ 10.40, $J_{3,4}$ 3.0 Hz, H-3α), 3.81 (dd, $J_{1,2}$ 3.60, $J_{2,3}$ 10.40 Hz, H-2α), 3.31 and 3.30 (2 s, 3 H, OMe), 3.30 (dd, $J_{2,3}$ 10.40, $J_{3,4}$ 3.0 Hz, H-3β).

Anal. Calc. for $C_{24}H_{31}N_3O_7$: C, 60.87; H, 6.60; N, 8.87. Found: C, 60.86; H, 6.51; N, 8.62.

*4-O-Acetyl-2-azido-3,6-di-O-benzyl-2-deoxy-*D*-galactopyranose* (**12**). — A solution of **11** (284 mg) in aqueous 90% trifluoroacetic acid (2 mL) was stirred for 15 min at room temperature, then concentrated to dryness. Water (10 mL) and then toluene (2 × 10 mL) were evaporated from the residue which was acetylated (acetic anhydride–pyridine) overnight. The mixture was concentrated to dryness, and toluene (2 × 10 mL) was evaporated from the residue which was then stirred with benzylamine (1 mL) in ether (4 mL) for 2 h at room temperature. The mixture was concentrated, diluted with dichloromethane (30 mL), washed with cold 0.1M hydrochloric acid, brine, and water, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel (20 g) with hexane–ethyl acetate (2:1) to give amorphous **12** (212 mg, 83%), $[\alpha]_D$ +36° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 10 H, 2 Ph), 5.57 (dd, $J_{3,4}$ 3.0, $J_{4,5}$ 1.0 Hz, H-4α), 5.48 (dd, $J_{3,4}$ 3.20, $J_{4,5}$ 0.80 Hz, H-4β), 5.32 (t, $J_{1,2} = J_{1,OH}$ = 3.60 Hz, H-1α),4.48 (dd, $J_{1,2}$ 7.80, $J_{1,OH}$ 4.0 Hz, H-1β), 4.33 (m, $J_{4,5}$ 1.0, $J_{5,6a} = J_{5,6b}$ = 5.50 Hz, H-5α), 3.97 (dd, $J_{2,3}$ 10.40, $J_{3,4}$ 3.0 Hz, H-3α), 3.67 (dd, $J_{1,2}$ 3.60, $J_{2,3}$ 10.40, Hz, H-2α), 3.36 (dd, $J_{2,3}$ 10.40, $J_{3,4}$ 3.20 Hz, H-3β), 2.08 and 2.06 (2 s, 3 H, OAc).

Anal. Calc. for $C_{22}H_{25}N_3O_6$: C, 61.82; H, 5.89; N, 9.83. Found: C, 61.92; H, 6.00; N, 9.78.

*2-Azido-3,6-di-O-benzyl-2-deoxy-4-O-(2-methoxyethoxymethyl)-α-*D*-galactopyranosyl bromide* (**13**). — A solution of oxalyl bromide (0.15 mL) in 1,2-dichloroethane (1 mL) was added dropwise at 0° to a stirred solution of **11** (142 mg) in 1,2-dichloroethane (4 mL) and *N,N*-dimethylformamide (0.25 mL). The mixture was stirred for 1.5 h at 0°, then diluted with cold ether (30 mL), washed with cold aqueous 2% sodium hydrogencarbonate and water, dried ($MgSO_4$), and concentrated. The residue was quickly eluted from a column (1 × 3 cm) of silica gel with hexane–ethyl acetate (5:2) and crystallized from ether–hexane to give **13** (130 mg, 81%), m.p. 63–64°, $[\alpha]_D$ +133° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 10 H, 2 Ph), 6.49 (d, 1 H, $J_{1,2}$ 3.40 Hz, H-1), 4.85 (ABq, 2 H, OCH_2O), 4.25 (dd, 1 H, $J_{3,4}$ 2.80, $J_{4,5}$ 0.80 Hz, H-4),4.24 (m, 1 H, $J_{4,5}$ 0.80, $J_{5,6a} = J_{5,6b}$ = 6.50 Hz, H-5), 4.01 (dd, 1 H, $J_{1,2}$ 3.40, $J_{2,3}$ 10.40 Hz, H-2), 3.93 (dd, 1 H, $J_{2,3}$ 10.40, $J_{3,4}$ 2.80 Hz, H-3), 3.30 (s, 3 H, OMe).

Anal. Calc. for $C_{24}H_{30}BrN_3O_6$: C, 53.74; H, 5.64; N, 7.83. Found: C, 53.61; H, 5.48; N, 7.59.

*2-Azido-3,6-di-O-benzyl-2-deoxy-4-O-(2-methoxyethoxymethyl)-α-*D*-galactopyranosyl trichloroacetimidate* (**14**). — A mixture of **11** (355 mg), trichloroacetonitrile

(0.75 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (45 μL) in 1,2-dichloroethane (8 mL) was stirred for 2 h at room temperature, then concentrated. The dark residue was eluted from a column of silica gel (30 g) with hexane–ethyl acetate (5:2, containing 0.2% of triethylamine) to give, first, amorphous **14** (375 mg, 81%), $[\alpha]_D$ +78° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.67 (s, 1 H, C=NH), 7.30 (m, 10 H, 2 Ph), 6.41 (d, 1 H, $J_{1,2}$ 3.60 Hz, H-1), 4.88 (ABq, 2 H, OCH_2O), 4.32 (dd, 1 H, $J_{3,4}$ 2.80, $J_{4,5}$ 0.80 Hz, H-4), 4.17 (m, 1 H, $J_{4,5}$ 0.80, $J_{5,6a} = J_{5,6b}$ = 6.50 Hz, H-5), 4.08 (dd, 1 H, $J_{1,2}$ 3.60, $J_{2,3}$ 10.40 Hz, H-2), 3.97 (dd, 1 H, $J_{2,3}$ 10.40, $J_{3,4}$ 2.80 Hz, H-3), 3.30 (s, 3 H, OMe).

Anal. Calc. for $C_{26}H_{31}Cl_3N_4O_7$: C, 50.54; H, 5.06; N, 9.07. Found: C, 50.60; H, 5.00; N, 8.81.

Further elution gave a fraction (64 mg, 14%) that contained **14** and its β isomer (δ 5.56, d, $J_{1,2}$ 8.40 Hz, H-1β). A solution of this fraction in acetone–water (9:1, 2 mL) was stirred at room temperature with *p*-toluenesulfonic acid monohydrate (10 mg) for 30 min, then concentrated. A solution of the residue in toluene (10 mL) was washed with aqueous 5% sodium hydrogencarbonate, brine, and water, dried (Na_2SO_4), and concentrated to give solid **11** (45 mg).

4-O-Acetyl-2-azido-3,6-di-O-benzyl-2-deoxy-α-D-galactopyranosyl trichloroacetimidate (**15**). — A mixture of **12** (260 mg), trichloroacetonitrile (0.6 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (45 μL) in 1,2-dichloroethane (5 mL) was stirred for 2.5 h at room temperature, then concentrated. The residue was eluted from a column of silica gel (25 g) with hexane–ethyl acetate (5:2, containing 0.2% of triethylamine) to give, first, amorphous **15** (280 mg, 81%) $[\alpha]_D$ +65° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.69 (s, 1 H, C = NH), 7.30 (m, 10 H, 2 Ph), 6.40 (d, 1 H, $J_{1,2}$ 3.60 Hz, H-1), 5.78 (dd, 1 H, $J_{3,4}$ 3.0, $J_{4,5}$ 1.0 Hz, H-4), 4.30 (m, 1 H, $J_{4,5}$ 1.0, $J_{5,6a}$ 5.50, $J_{5,6b}$ 7.20 Hz, H-5), 4.06 (dd, 1 H, $J_{2,3}$ 10.60 $J_{3,4}$ 3.0 Hz, H-3), 3.82 (dd, 1 H, $J_{1,2}$ 3.60, $J_{2,3}$ 10.40 Hz, H-2), 3.55 (dd, 1 H, $J_{5,6a}$ 5.50, $J_{6a,6b}$ 12.0 Hz, H-6a), 3.47 (dd, 1 H, $J_{5,6b}$ 7.20, $J_{6a,6b}$ 12.0 Hz, H-6b), 2.07 (s, 3 H, Ac).

Anal. Calc. for $C_{24}H_{25}Cl_3N_4O_6$: C, 50.41; H, 4.40; N, 9.80. Found: C, 50.29; H, 4.52; N, 9.72.

Further elution gave a fraction (42 mg, 10%) that contained **15** and its β isomer, which was hydrolyzed as described for the preparation of **14**.

6-O-tert-Butyldimethylsilyl-D-galactal (**16**). — A mixture of **6** (877 mg), imidazole (921 mg), and *tert*-butyldimethylsilyl chloride (990 mg) in *N,N*-dimethylformamide (15 mL) was stirred for 40 min at 0°, then diluted with chloroform (50 mL), washed with aqueous 5% ammonium chloride, brine, and water, dried (Na_2SO_4), and concentrated. Flash-column chromatography of the residue on silica gel (30 g) with hexane–ethyl acetate (3:2) gave, first, the 3,6-di-*O*-silylated derivative **8** (250 mg, 11%), then **16**, isolated as a mobile syrup (1.25 g, 80%), $[\alpha]_D$ +4° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.38 (dd, 1 H, $J_{1,2}$ 6.20, $J_{1,3}$ 2.0 Hz, H-1), 4.73 (m, 1 H, $J_{1,2}$ 6.20, $J_{2,3} = J_{1,3}$ = 2.0 Hz, H-2), 4.30 (m, 1 H, $J_{1,3} = J_{2,3}$ = 2.0, $J_{3,4}$ 4.80 Hz, H-3), 3.20 (d, 1 H, $J_{3,OH}$ 6.20 Hz, HO-3), 2.76 (d, 1 H, $J_{4,OH}$ 9.0 Hz, HO-4), 0.91 (s, 9 H, ^{t}Bu), 0.10 and 0.09 (2 s, 6 H, Me).

Anal. Calc. for $C_{12}H_{24}O_4Si$: C, 55.35; H, 9.29. Found: C, 55.23. H. 9.11.

3,4-Di-O-benzyl-D-galactal (**17**). — A mixture of **16** (1.075 g) and sodium hydride

(600 mg) in dry tetrahydrofuran (10 mL) was stirred at 0° with the exclusion of moisture. After 15 min, benzyl bromide (1.44 mL) and then *N,N*-dimethylformamide (2 mL) were added dropwise, and the mixture was stirred for 1 h at 0°. Methanol (2 mL) was added and stirring was continued overnight at room temperature. The mixture was concentrated, diluted with dichloromethane (50 mL), washed with water, brine, and water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel (80 g) with hexane–ethyl acetate (7:4) and crystallized from ether–hexane to give **17** (1.145 g, 85%), m.p. 54–55°, $[\alpha]_D$ −103° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 10 H, 2 Ph), 6.38 (dd, 1 H, $J_{1,2}$ 6.20, $J_{1,3}$ 1.0 Hz, H-1), 4.84 (dd, 1 H, $J_{1,2}$ 6.20, $J_{2,3}$ 3.60 Hz, H-2), 4.17 (m, 1 H, $J_{2,3} = J_{3,4}$ = 3.60, $J_{1,3}$ 1.0 Hz, H-3), 3.98 (dd, 1 H, $J_{5,6a}$ 5.0, $J_{6a,6b}$ 12.0 Hz, H-6a), 3.74 (dd, 1 H, $J_{5,6b}$ 6.0 $J_{6a,6b}$ 12.0 Hz, H-6b), 2.31 (dd, 1 H, $J_{6a,OH}$ 4.20 $J_{6b,OH}$ 8.50 Hz, HO-6).

Anal. Calc. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.68; H, 6.81.

3,4-Di-O-benzyl-6-O-(2-methoxyethoxymethyl)-D-galactal (**18**). — A mixture of **17** (1.632 g), sodium hydride (184 mg), and 2-methoxyethoxymethyl chloride (0.80 mL) in *N,N*-dimethylformamide (15 mL) was stirred for 30 min at 0°. Methanol (1 mL) was added, and, after 30 min, the mixture was diluted with dichloromethane (50 mL), washed with water, brine, and water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel (80 g) with hexane–ethyl acetate (2:1, containing 0.1% of triethylamine) to give syrupy **18** (1.906 g, 92%), $[\alpha]_D$ −45° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.35 (m, 10 H, 2 Ph), 6.37 (dd, 1 H, $J_{1,2}$ 6.40, $J_{1,3}$ 1.80 Hz, H-1), 4.87 (m, 1 H, $J_{1,2}$ 6.40, $J_{2,3} = J_{2,4}$ = 1.80 Hz, H-2), 4.76 (ABq, 2 H, OCH_2O), 4.18 (m, 1 H, $J_{1,3} = J_{2,3}$ = 1.80, $J_{3,4}$ 4.80 Hz, H-3), 3.36 (s, 3 H, OMe).

Anal. Calc. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.29. Found: C, 69.66; H, 7.18.

2-Azido-3,4-di-O-benzyl-2-deoxy-6-O-(2-methoxyethoxymethyl)-D-galactopyranose (**19**). — Compound **18** (1.886 g) was treated as described for the preparation of **11**. The product was eluted from a column of silica gel (100 g) with ethyl acetate–hexane (1:1) and crystallized from ether–hexane to give **19** (1.293 g, 60%), m.p. 75–76°, $[\alpha]_D$ +59° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 10 H, 2 Ph), 5.34 (t, $J_{1,2} = J_{1,OH}$ = 3.20 Hz, H-1α), 4.50 (dd, $J_{1,2}$ 8.0, $J_{1,OH}$ 4.50 Hz, H-1β), 4.22 (m, 1 H, $J_{4,5}$ 1.0, $J_{5,6a}$ 4.80, $J_{5,6b}$ 8.0 Hz, H-5), 4.01 (dd, 1 H, $J_{2,3}$ 10.40, $J_{3,4}$ 2.80 Hz, H-3), 3.94 (dd, 1 H, $J_{1,2}$ 3.20, $J_{2,3}$ 10.40 Hz, H-2), 3.90 (dd, 1 H, $J_{3,4}$ 2.80, $J_{4,5}$ 1.0 Hz, H-4), 3.38 (s, 3 H, OMe).

Anal. Calc. for $C_{24}H_{31}N_3O_7$: C, 60.87; H, 6.60; N, 8.87. Found: C, 60.92; H, 6.48; N, 8.62.

2-Azido-3,4-di-O-benzyl-2-deoxy-6-O-(2-methoxyethoxymethyl)-α-D-galactopyranosyl trichloroacetimidate (**20**). — A mixture of **19** (483 mg), trichloroacetonitrile (1 mL), and 1,8-diazabicylco[5.4.0]undec-7-ene (80 μL) in 1,2-dichloroethane (7 mL) was stirred for 3 h at room temperature, then concentrated. The residue was eluted from a column of silica gel (40 g) with hexane–ethyl acetate (7:4, containing 0.1% of triethylamine) to give, first, amorphous **20** (420 mg, 65%), $[\alpha]_D$ +93° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.66 (s, 1 H, C=NH), 7.30 (m, 10 H, 2 Ph), 6.41 (d, 1 H, $J_{1,2}$ 3.40 Hz, H-1), 4.20 (dd, 1 H, $J_{1,2}$ 3.40, $J_{2,3}$ 10.50 Hz, H-2), 4.12 (m, 1 H, $J_{4,5}$ 0.80, $J_{5,6a} = J_{5,6b}$ = 6.5 Hz, H-5), 4.11 (dd, 1 H, $J_{3,4}$ 2.80, $J_{4,5}$ 0.80 Hz, H-4), 4.05 (dd, 1 H, $J_{2,3}$ 10.50, $J_{3,4}$ 2.80 Hz, H-3), 3.36 (s, 3 H, OMe).

Anal. Calc. for $C_{26}H_{31}Cl_3N_4O_7$: C, 50.54; H, 5.06; N, 9.07. Found: C, 50.48; H, 5.12; N, 8.88.

Further elution gave the β isomer of **20**, isolated as a colourless glass (157 mg, 25%), $[\alpha]_D$ +8° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.65 (s, 1 H, C=NH), 5.57 (d, 1 H, $J_{1,2}$ 8.40 Hz, H-1). The latter was hydrolyzed, as described for the preparation of **14**, to afford **19** (106 mg).

*6-O-Benzoyl-3,4-di-O-benzyl-*D-galactal (**21**). — Benzoyl chloride (0.5 mL) was added dropwise at 0° to a solution of **17** (981 mg) in pyridine (1 mL) and dichloromethane (12 mL), and the mixture was stirred for 1 h at 0°. Methanol (0.5 mL) was added, and the mixture was stirred for 30 min, then diluted with dichloromethane (25 mL), washed with aqueous 10% potassium hydrogensulfate, aqueous 5% sodium hydrogencarbonate, and water, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel (20 g) with hexane–ethyl acetate (5:1) to give **21**, isolated as a colorless syrup (1.23 g, 95%), $[\alpha]_D$ −60° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.10–7.30 (m, 15 H, 3 Ph), 6.37 (dd, 1 H, $J_{1,2}$ 6.40, $J_{1,3}$ 1.60 Hz, H-1), 4.93 (dd, 1 H, $J_{1,2}$ 6.40, $J_{2,3}$ 3.60 Hz, H-2), 4.76 (dd, 1 H, $J_{5,6a}$ 8.40, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.55 (dd, 1 H, $J_{5,6b}$ 4.0, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.18 (m, 1 H, $J_{2,3} = J_{3,4}$ = 3.60, $J_{1,3}$ 1.60 Hz, H-3), 3.98 (dd, H, $J_{3,4}$ 3.60, $J_{4,5}$ 3.0 Hz, H-4).

Anal. Calc. for $C_{27}H_{26}O_5$: C, 75.33; H, 6.09. Found: C, 73.11; H, 6.14.

*2-Azido-6-O-benzoyl-3,4-di-O-benzyl-2-deoxy-*D-*galactopyranose* (**22**). — Compound **21** (1.20 g) was treated as described for the preparation of **11**, except for the hydrolysis of the glycosyl nitrate, which required 3 h at 80°. The product was eluted from a column of silica gel (60 g) with hexane–ethyl acetate (5:2) to give amorphous **22** (901 mg, 66%), $[\alpha]_D$ −1° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.0–7.30 (m, 15 H, 3 Ph), 5.37 (dd, 1 H, $J_{1,2}$ 3.0, $J_{1,OH}$ 2.80 Hz, H-1α), 4.53 (dd, 1 H, $J_{1,2}$ 8.0, $J_{1,OH}$ 6.0 Hz, H-1β), 4.45–4.30 (m, 2 H, H-6a,6b$\alpha\beta$), 4.00 (dd, $J_{1,2}$ 3.0, $J_{2,3}$ 10.50 Hz, H-2α), 3.82 (dd, $J_{1,2}$ 8.0, $J_{2,3}$ 10.40 Hz, H-2β), 3.32 (d, $J_{1,OH}$ 6.0 Hz, HO-1β), 2.86 (d, $J_{1,OH}$ 2.80 Hz, HO-1α).

Anal. Calc. for $C_{27}H_{27}N_3O_6$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.08; H, 5.71. N, 8.38.

*2-Azido-6-O-benzoyl-3,4-di-O-benzyl-2-deoxy-α-*D-*galactopyranosyl trichloroacetimidate* (**23**). — Compound **22** (245 mg) was treated as described for the preparation of **14**. The product was eluted from a column of silica gel (20 g) with hexane–ethyl acetate (9:2, containing 0.1% of triethylamine) to give, first, amorphous **23** (250 mg, 79%), $[\alpha]_D$ +60° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.67 (s, 1 H, C=NH), 8.10–7.30 (m, 15 H, 3 Ph), 6.46 (d, 1 H, $J_{1,2}$ 3.60 Hz, H-1), 4.40 (m, 3 H, H-5,6a,6b), 4.24 (dd, 1 H, $J_{1,2}$ 3.60, $J_{2,3}$ 10.20 Hz, H-2), 4.08 (dd, 1 H, $J_{2,3}$ 10.20, $J_{3,4}$ 3.0 Hz, H-3), 4.05 (dd, 1 H, $J_{3,4}$ 3.0, $J_{4,5}$ 0.80 Hz, H-4).

Anal. Calc. for $C_{29}H_{27}Cl_3N_4O_6$: C, 54.95; H, 4.29; N, 8.84. Found: C, 54.72; H, 4.31; N, 8.72.

Further elution gave a mixture (45 mg, 14%) of **23** and its β isomer (δ 5.60, d, $J_{1,2}$ 8.20 Hz, H-1β). Acid hydrolysis, as described for the preparation of **14**, gave **22** (33 mg).

*Methyl (2,3,4-tri-O-acetyl-α-*D-*glucopyranosyl trichloroacetimidate)uronate* (**25**). — A mixture of **24**[19] (1.13 g) and dibutyltin oxide (374 mg) in dry methanol (6 mL) was

stirred for 45 min at 55°, then cooled, and concentrated. Immediate flash-column chromatography of the residue on a column of silica gel (30 g) with hexane–ethyl acetate (3:2) gave the hemiacetal (804 mg, 80%), which was dissolved in 1,2-dichloroethane (15 mL) in the presence of trichloroacetonitrile (3 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.15 mL). The mixture was stirred for 1 h at room temperature, then concentrated. The residue was eluted from a column of silica gel (70 g) with hexane–ethyl acetate (3:2) and crystallized from ether–hexane to give **26** (1.06 g, 74% from **24**), m.p. 106–107°, $[\alpha]_D$ +93° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.73 (s, 1 H, C=NH), 6.65 (d, 1 H, $J_{1,2}$ 3.60 Hz, H-1), 5.64 (t, 1 H, $J_{3,4} = J_{4,5}$ = 10.0 Hz, H-4), 5.28 (t, 1 H, $J_{2,3} = J_{3,4}$ 10.0 Hz, H-3), 5.16 (dd, 1 H, $J_{1,2}$ 3.60, $J_{2,3}$ 10.0 Hz, H-2), 4.51 (d, 1 H, $J_{4,5}$ 10.0 Hz, H-5), 3.76 (s, 3 H, COOMe), 2.06, 2.05, and 2.02 (3 s, 9 H, 3 Ac).

Anal. Calc. for $C_{15}H_{18}Cl_3NO_{10}$: C, 37.64; H, 3.79; N, 2.92. Found: C, 37.61; H, 3.86; N, 2.74.

*Methyl 6-*O*-acetyl-2-azido-4-*O*-benzyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-*D*-glucopyranosyluronate)-β-*D*-galactopyranoside* (**27**). — (*a*) A mixture of **4** (53 mg), **25** (96 mg), and activated powdered 4 Å molecular sieves (50 mg) in dry toluene (2 mL) was stirred at room temperature under dry argon, then cooled to −20°. A M solution of trimethylsilyl trifluoromethanesulfonate (12 μL) in dichloromethane was added, and the mixture was stirred for 1 h at −20°. *N,N*-Di-isopropylethylamine (50 μL) was added, and the mixture was filtered, then concentrated. The residue was eluted from a column of silica gel (10 g) with ethyl acetate–hexane (3:2), and crystallized from the same solvents to give **27** (75 mg, 75%), m.p. 150–151°, $[\alpha]_D$ −52° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 5 H, Ph), 5.33 (t, 1 H, $J_{2',3'} = J_{3',4'}$ = 9.50 Hz, H-3'), 5.24 (t, 1 H, $J_{3',4'} = J_{4',5'}$ = 9.5 Hz, H-4'), 5.09 (dd, 1 H, $J_{1',2'}$ 7.80, $J_{2',3'}$ 9.50 Hz, H-2'), 4.87 (d, 1 H, $J_{1',2'}$ 7.80 Hz, H-1'), 4.77 (ABq, 2 H, OCH_2Ph), 4.18 (dd, 1 H, $J_{5,6a}$ 6.50, $J_{6a,6b}$ 11.20 Hz, H-6a), 4.11 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.06 (d, 1 H, $J_{4',5'}$ 9.50 Hz, H-5'), 3.98 (dd, 1 H, $J_{5,6b}$ 6.50, $J_{6a,6b}$ 11.20 Hz, H-6b), 3.86 (dd, 1 H, $J_{3,4}$ 3.0, $J_{4,5}$ 0.80, Hz, H-4), 3.77 (s, 3 H, COOMe), 3.72 (dd, 1 H, $J_{1,2}$ 7.80, $J_{2,3}$ 10.40 Hz, H-2), 3.54 (m, 1 H, $J_{4,5}$ 0.80, $J_{5,6a} = J_{5,6b}$ = 6.50 Hz, H-5), 3.53 (s, 3 H, OMe), 3.46 (dd, 1 H, $J_{2,3}$ 10.40, $J_{3,4}$ 3.0 Hz, H-3), 2.09, 2.05, 2.04, and 1.97 (4 s, 12 H, 4 Ac).

Anal. Calc. For $C_{29}H_{37}N_3O_{15}$: C, 52.17; H, 5.58; N, 6.29. Found: C, 52.25; H, 5.51; N, 6.11.

(*b*) A mixture of **4** (176 mg), **26**[18] (298 mg), and activated powdered 4 Å molecular sieves (200 mg) in dry 1,2-dichloroethane (6 mL) was stirred at room temperature under dry argon for 30 min, then cooled to −20°. Silver triflate (283 mg) was added, and the mixture was stirred for 1 h at −20°, allowed to attain room temperature overnight, diluted with dichloromethane (20 mL), filtered through Celite, washed with cold 0.1M hydrochloric acid, aqueous 5% sodium hydrogencarbonate, and water, dried ($MgSO_4$), and concentrated. Elution of the residue from a column of silica gel (35 g) with ethyl acetate–hexane (3:2), with crystallization from the same solvents, gave **27** (300 mg, 90%), m.p. 150–151°.

*Methyl 4-*O*-acetyl-2-azido-6-*O*-benzyl-2-deoxy-*3*-O-(methyl 2,3,4-tri-*O*-acetyl-β-*D*-glucopyranosyluronate)-β-*D*-galactopyranoside* (**28**). — (a) A mixture of **5** (53 mg)

and **25** (108 mg) was treated as described for the preparation of **27** from **25**, but with more catalyst (24 μL). The product was eluted from a column of silica gel (10 g) with hexane–ethyl acetate (3:2), and crystallized from ether to give **28** (72 mg, 72%), m.p. 152–153°, $[\alpha]_D$ −15° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 5 H, Ph), 5.38 (dd, 1 H, $J_{3,4}$ 3.0, $J_{4,5}$ 0.80 Hz, H-4), 5.26 (t, 1 H, $J_{2',3'} = J_{3',4'}$ = 9.50 Hz, H-3'), 5.23 (dd, 1 H, $J_{3',4'}$ 9.50, $J_{4',5'}$ 10.0 Hz, H-4'), 4.98 (dd, 1 H, $J_{1',2'}$ 7.80, $J_{2',3'}$ 9.50 Hz, H-2'), 4.81 (d, 1 H, $J_{1',2'}$ 7.80 Hz, H-1'), 4.50 (ABq, 2 H, OCH_2Ph), 4.17 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.00 (d, 1 H, $J_{4',5'}$ 10.0 Hz, H-5'), 3.74 (s, 3 H, COOMe), 3.68 (m, 1 H, $J_{4,5}$ 0.80, $J_{5,6a} = J_{5,6b}$ = 6.0 Hz, H-5), 3.59 (s, 3 H, OMe), 2.09, 2.07, 2.03, and 2.01 (4 s, 12 H, 4 Ac).

Anal. Calc. for $C_{29}H_{37}N_3O_{15}$: C, 52.17; H, 5.58; N, 6.29. Found: C, 52.11, H, 5.64; N, 6.13.

(*b*) A mixture of **5** (176 mg) and **26**[18] (298 mg) was treated as described for the preparation of **27** from **26**. Elution of the residue from a column (40 g) of silica gel with hexane–ethyl acetate (3:2) and crystallization from ether gave **28** (267 mg, 80%), m.p. 152–153°.

*Methyl 2-acetamido-6-*O*-acetyl-4-*O*-benzyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-*D*-glucopyranosyluronate)-β-*D*-galactopyranoside* (**29**). — A solution of **27** (279 mg) in thioacetic acid (1.5 mL) was stirred for 24 h at room temperature, then concentrated. The residue was eluted from a column of silica gel (20 g) with dichloromethane–methanol (18:1) and crystallized from hot ethanol to give **29** (250 mg, 87%), m.p. 197–198°, $[\alpha]_D$ −30° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 5 H, Ph), 5.67 (d, 1 H, $J_{2,NH}$ 7.0 Hz, NH), 5.27 (t, 1 H, $J_{2',3'} = J_{3',4'}$ = 9.0 Hz, H-3'), 5.24 (dd, 1 H, $J_{3',4'}$ 9.0, $J_{4',5'}$ 10.0 Hz, H-4'), 5.02 (dd, 1 H, $J_{1',2'}$ 7.80, $J_{2',3'}$ 9.0 Hz, H-2'), 4.81 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.77 (ABq, 2 H, OCH_2Ph), 4.74 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 4.73 (dd, 1 H, $J_{2,3}$ 11.20, $J_{3,4}$ 3.20 Hz, H-3), 4.17 (dd, 1 H, $J_{5,6a}$ 6.50, $J_{6a,6b}$ 11.20 Hz, H-6a), 4.06 (d, 1 H, $J_{4',5'}$ 10.0 Hz, H-5'), 3.98 (dd, 1 H, $J_{3,4}$ 3.20, $J_{4,5}$ 0.80 Hz, H-4), 3.96 (dd, $J_{5,6b}$ 6.50, $J_{6a,6b}$ 11.20 Hz, H-6b), 3.75 (s, 3 H, COOMe), 3.46 (s, 3 H, OMe), 3.37 (m, 1 H, $J_{1,2}$ 8.0, $J_{2,NH}$ 7.0, $J_{2,3}$ 11.20 Hz, H-2), 2.06, 2.05, 2.02, 2.01, and 1.95 (5 s, 15 H, 5 Ac).

Anal. Calc. for $C_{31}H_{41}NO_{16}$: C, 54.46; H, 6.05; N, 2.05. Found: C, 54.38; H, 6.01; N, 1.98.

*Methyl 2-acetamido-4-*O*-acetyl-6-*O*-benzyl-3-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-*D*-glucopyranosyluronate)-β-*D*-galactopyranoside* (**30**). — Compound **28** (186 mg) was treated as described for the preparation of **29**. Crystallization from ethanol gave **30** (152 mg, 82%), m.p. 140–141°, $[\alpha]_D$ +5° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 5 H, Ph), 5.69 (d, 1 H, $J_{2,NH}$ 8.0 Hz, NH), 5.45 (dd, 1 H, $J_{3,4}$ 3.40, $J_{4,5}$ 0.80 Hz, H-4), 5.21 (t, 1 H, $J_{2',3'} = J_{3',4'}$ = 9.0 Hz, H-3'), 5.19 (dd, 1 H, $J_{3',4'}$ 9.0, $J_{4',5'}$ 10.0 Hz, H-4'), 4.97 (dd, 1 H, $J_{1',2'}$ 7.80, $J_{2',3'}$ 9.0 Hz, H-2'), 4.91 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.71 (d, 1 H, $J_{1',2'}$ 7.80 Hz, H-1'), 4.67 (dd, 1 H, $J_{2,3}$ 10.80, $J_{3,4}$ 3.40, H-3), 3.99 (d, 1 H, $J_{4',5'}$ 10.0 Hz, H-5'), 3.73 (s, 3 H, COOMe), 3.52 (s, 3 H, OMe), 3.36 (m, 1 H, $J_{1,2} = J_{2,NH}$ = 8.0, $J_{2,3}$ 10.80 Hz, H-2), 2.07, 2.06, 2.03, 2.01, and 1.96 (5 s, 15 H, 5 Ac).

Anal. Calc. for $C_{31}H_{41}NO_{16}$: C, 54.46; H, 6.05; N, 2.05. Found: C, 54.51; H, 6.07; N, 2.00.

*Methyl 2-acetamido-6-*O*-acetyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-*D*-glu-*

*copyranosyluronate)-β-*D*-galactopyranoside* (**31**). — A solution of **29** (140 mg) in methanol (5 mL) was hydrogenated in the presence of 10% Pd–C (100 mg) for 2 h, then filtered, and concentrated. The residue was crystallized from hot ethanol to give **31** (115 mg, 95%), m.p. 210–212°, $[\alpha]_D$ −10° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.94 (d, 1 H, $J_{2,NH}$ 7.0 Hz, NH), 5.26 (dd, 1 H, $J_{3',4'}$ 9.0, $J_{4',5'}$ 9.50 Hz, H-4'), 5.21 (t, 1 H, $J_{2',3'} = J_{3',4'} = 9.0$ Hz, H-3'), 5.03 (dd, 1 H, $J_{1',2'}$ 7.80, $J_{2',3'}$ 9.0 Hz, H-2'), 4.87 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.77 (d, 1 H, $J_{1',2'}$ 7.80 Hz, H-1'), 4.63 (dd, 1 H, $J_{2,3}$ 11.0, $J_{3,4}$ 3.40 Hz, H-3), 4.34 (m, 2 H, H-6a,6b), 4.02 (d, 1 H, $J_{4',5'}$ 9.50 Hz, H-5'), 4.06 (m, 1 H, $J_{3,4}$ 3.40, $J_{4,5}$ 0.80, $J_{4,OH}$ 3.60 Hz, H-4), 3.76 (m, 1 H, $J_{4,5}$ 0.8, $J_{5,6a}$ 5.60, $J_{5,OH}$ 1.0 Hz, H-5), 3.75 (s, 3 H, COOMe), 3.50 (s, 3 H, OMe), 3.32 (m, 1 H, $J_{1,2}$ 8.0, $J_{2,NH}$ 7.0, $J_{2,3}$ 11.0 Hz, H-2), 2.83 (dd, 1 H, $J_{4,OH}$ 3.60, $J_{5,OH}$ 1.0 Hz, HO-4), 2.08, 2.05, 2.04, 2.03, and 1.97 (5 s, 15 H, 5 Ac).

Anal. Calc. for $C_{24}H_{35}NO_{16}$: C, 48.57; H, 5.94; N, 2.36. Found: C, 48.49; H, 6.03; N, 2.21.

*Methyl 2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-*D*-glucopyranosyluronate)-β-*D*-galactopyranoside* (**32**). — A solution of **30** (187 mg) in ethyl acetate (6 mL) was hydrogenated in the presence of 10% Pd–C (100 mg) for 2 h, then filtered, and concentrated. The residue was eluted from a column of silica gel (15 g) with ethyl acetate–methanol (15:1) to give, first, **31** (10 mg, 6%), m.p. 210–212° (from ethanol). Further elution gave a fraction that crystallized from ethanol to afford **32** (133 mg, 82%), m.p. 207–208°, $[\alpha]_D$ +14° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.87 (d, 1 H, $J_{2,NH}$ 8.0 Hz, NH), 5.32 (dd, 1 H, $J_{3,4}$ 3.40, $J_{4,5}$ 0.80 Hz, H-4), 5.22 (dd, 1 H, $J_{3',4'}$ 9.0, $J_{4',5'}$ 9.50 Hz, H-4'), 5.18 (t, 1 H, $J_{2',3'} = J_{3',4'} = 9.0$ Hz, H-3'), 4.98 (dd, 1 H, $J_{1',2'}$ 7.80, $J_{2',3'}$ 9.0 Hz, H-2'), 4.93 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.75 (dd, 1 H, $J_{2,3}$ 10.60, $J_{3,4}$ 3.40 Hz, H-3), 4.71 (d, 1 H, $J_{1',2'}$ 7.80 Hz, H-1'), 4.01 (d, 1 H, $J_{4',5'}$ 9.50 Hz, H-5'), 3.75 (s, 3 H, COOMe), 3.64 (m, 1 H, $J_{5,6a}$ 6.50, $J_{6a,OH}$ 5.50, $J_{6a,6b}$ 11.20 Hz, H-6a), 3.50 (s, 3 H, OMe), 3.40 (m, 1 H, $J_{5,6b}$ 6.50, $J_{6b,OH}$ 9.0, $J_{6a,6b}$ 11.20 Hz, H-6b), 3.33 (m, 1 H, $J_{1,2} = J_{2,NH} = 8.0$ Hz, $J_{2,3}$ 10.60 Hz, H-2), 3.00 (dd, 1 H, $J_{6a,OH}$ 5.50, $J_{6b,OH}$ 9.0 Hz, HO-6), 2.15, 2.05, 2.02, 2.01, and 1.97 (5 s, 15 H, 5 Ac).

Anal. Calc. for $C_{24}H_{35}NO_{16}$: C, 48.57; H, 5.94; N, 2.36. Found: C, 48.48; H, 6.03; N, 2.14.

*Methyl 2-acetamido-6-*O*-acetyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-*D*-glucopyranosyluronate)-4-*O*-sulfo-β-*D*-galactopyranoside, sodium salt* (**33**). — A mixture of **31** (100 mg), dry *N,N*-dimethylformamide (1.5 mL), and the sulfur trioxide–trimethylamine complex (140 mg) was stirred for 18 h at 60°, then cooled. Methanol (0.1 mL) was added, and the mixture was eluted from a column (3.5 × 60 cm) of Sephadex LH-20 equilibrated in dichloromethane–methanol (1:1) with the same solvent. The product was eluted from a column (1.5 × 30 cm) of Sephadex SP-C25 (Na^+) with methanol–water (9:1) and crystallized from aqueous ethanol to afford **33** (110 mg, 94%), m.p. 183–185° (dec.), $[\alpha]_D$ −16° (*c* 1, methanol). ^{1}H-N.m.r. data (CD_3OD): δ 5.32 (t, 1 H, $J_{2',3'} = J_{3',4'} = 9.50$ Hz, H-3'), 5.22 (dd, 1 H, $J_{3',4'}$ 9.50, $J_{4',5'}$ 10.0 Hz, H-4'), 5.07 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 9.50 Hz, H-2'), 4.94 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.84 (dd, 1 H, $J_{3,4}$ 3.0, $J_{4,5}$ 0.80 Hz, H-4), 4.44 (dd, 1 H, $J_{5,6a}$ 4.50, $J_{6a,6b}$ 11.80 Hz, H-6a), 4.42 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.36 (dd, 1 H, $J_{5,6b}$ 7.50, $J_{6a,6b}$ 11.80 Hz, H-6b), 4.26 (d, 1 H, $J_{4',5'}$ 10.0 Hz, H-5'), 4.02 (dd, 1 H,

$J_{1,2}$ 8.0, $J_{2,3}$ 11.0 Hz, H-2), 4.01 (dd, 1 H, $J_{2,3}$ 11.0, $J_{3,4}$ 3.0 Hz, H-3), 3.75 (s, 3 H, COOMe), 3.46 (s, 3 H, OMe), 2.07, 2.05, 2.02, 2.00, and 1.98 (5 s, 15 H, 5 Ac).

Anal. Calc. for $C_{25}H_{34}NNaO_{19}S \cdot 0.5H_2O$: C, 40.91; H, 5.01; N, 1.99. Found: C, 40.78; H, 5.17; N, 1.88.

*Methyl 2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-*D*-glucopyranosyluronate)-6-*O*-sulfo-β-*D*-galactopyranoside, sodium salt* (**34**). — Compound **32** (104 mg) was treated as described for the preparation of **33**. The residue crystallized from ethyl acetate–methanol to give **34** (111 mg, 92%), m.p. 178–180° (dec.), $[\alpha]_D$ −6° (*c* 1, methanol). ^{1}H-N.m.r. data (CD_3OD): δ 5.42 (dd, 1 H, $J_{3,4}$ 3.0, $J_{4,5}$ 0.80 Hz, H-4), 5.28 (t, 1 H, $J_{2',3'} = J_{3',4'}$ = 9.50 Hz, H-3'), 5.26 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 9.50 Hz, H-2'), 5.07 (dd, 1 H, $J_{3',4'}$ 9.50, $J_{4',5'}$ 10.0 Hz, H-4'), 4.86 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.35 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.22 (d, 1 H, $J_{4',5'}$ 10.0 Hz, H-5'), 4.11 (dd, 1 H, $J_{5,6a}$ 6.50, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.04 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 11.0 Hz, H-2), 3.97 (dd, 1 H, $J_{2,3}$ 11.0, $J_{3,4}$ 3.0 Hz, H-3), 3.94 (dd, 1 H, $J_{5,6b}$ 7.50, $J_{6a,6b}$ 12.0 Hz, H-6b), 3.74 (s, 3 H, COOMe), 3.46 (s, 3 H, OMe), 2.09, 2.03, 1.98, 1.96, and 1.95 (5 s, 15 H, 5 Ac).

Anal. Calc. for $C_{24}H_{34}NNaO_{19}S$: 41.44; H, 4.93; N, 2.01. Found: C, 41.20; H, 5.13; N, 1.89.

*Methyl 2-acetamido-2-deoxy-3-*O*-(β-*D*-glucopyranosyluronic acid)-4-*O*-sulfo-β-*D*-galactopyranoside, disodium salt* (**35**). — 3M Sodium hydroxide (1.5 mL) was added dropwise to a suspension of **33** (110 mg) in methanol–water (5:1, 3 mL), and the mixture was stirred for 6 h at room temperature. The pH of the solution was brought to ~8 with dilute acetic acid and the mixture was concentrated. The residue was eluted from a column (2.2 × 115 cm) of Sephadex G-10 with water to give a fraction that crystallized from aqueous ethanol to afford **35** (70 mg, 83%), m.p. 236–240° (dec.), $[\alpha]_D$ −36° (*c* 1, water). N.m.r. data: ^{1}H (D_2O, internal TSP), δ 4.81 (dd, 1 H, $J_{3,4}$ 2.80, $J_{4,5}$ 0.80 Hz, H-4), 4.49 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.47 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.09 (dd, 1 H, $J_{2,3}$ 11.0, $J_{3,4}$ 2.80 Hz, H-3), 4.08 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 11.0 Hz, H-2), 3.84 (m 3 H, H-5,6a,6b), 3.68 (d, 1 H, $J_{4',5'}$ 9.50 Hz, H-5'), 3.55 (dd, 1 H, $J_{3',4'}$ 9.0, $J_{4',5'}$ 9.50 Hz, H-4'), 3.53 (s, 3 H, OMe), 3.47 (t, 1 H, $J_{2,3'} = J_{3',4'}$ = 9.0 Hz, H-3'), 3.37 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 9.0 Hz, H-2'), 2.04 (s, 3 H, NAc); ^{13}C (D_2O, internal acetone), δ 176.17 (C=O), 175.00 (C-6'), 103.44 (C-1'), 102.25 (C-1), 76.76 (C-3), 76.66 (C-5'), 75.48 (C-4), 75.08 (C-3'), 74.83 (C-5), 72.76 (C-4'), 72.03 (C-2'), 61.32 (C-6), 57.41 (OCH_3), 51.97 (C-2), 22.55 (CO–CH_3).

Anal. Calc. for $C_{15}H_{23}NNa_2O_{15} \cdot H_2O$: C, 32.56; H, 4.55; N, 2.53. Found: C, 32.38; H, 4.76; N, 2.41.

*Methyl 2-acetamido-2-deoxy-3-*O*-(β-*D*-glucopyranosyluronic acid)-6-*O*-sulfo-β-*D*-galactopyranoside, disodium salt* (**36**). — Compound **34** (110 mg) was treated as described for the preparation of **35**. The product crystallized from aqueous ethanol to give **36** (72 mg, 86%), m.p. 245–248° (dec.), $[\alpha]_D$ −27° (*c* 1, water). N.m.r. data: ^{1}H (D_2O, internal TSP), δ 4.52 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 4.46 (d, 1 H, $J_{1,2}$ 8.20 Hz, H-1), 4.27 (dd, 1 H, $J_{5,6a}$ 4.50, $J_{6a,6b}$ 11.20 Hz, H-6a), 4.25 (dd, 1 H, $J_{3,4}$ 3.20, $J_{4,5}$ 1.0 Hz, H-4), 4.22 (dd, 1 H, $J_{5,6b}$ 7.20, $J_{6a,6b}$ 11.20 Hz, H-6b), 4.04 (dd, 1 H, $J_{1,2}$ 8.20, $J_{2,3}$ 11.0 Hz, H-2), 3.95 (m, 1 H, $J_{4,5}$ 1.0, $J_{5,6a}$ 4.50 $J_{5,6b}$ 7.20 Hz, H-5), 3.86 (dd, 1 H, $J_{2,3}$ 11.0, $J_{3,4}$ 3.20 Hz, H-3), 3.71 (d, 1 H, $J_{4',5'}$ 9.50 Hz, H-5'), 3.54 (s, 3 H, OMe), 3.52 (t, 1 H, $J_{3',4'} = J_{4',5'}$ = 9.50 Hz, H-4'), 3.51 (t, 1

H, $J_{2',3'} = J_{3',4'} = 9.50$ Hz, H-3'), 3.35 (dd, 1 H, $J_{1',2'}$ 7.80, $J_{2',3'}$ 9.50 Hz, H-2'), 2.04 (s, 3 H, NAc); ^{13}C (D_2O, internal acetone), δ 176.17 (C=O), 175.15 (C-6'), 104.34 (C-1'), 102.44 (C-1), 80.28 (C-3), 76.39 (C-5), 75.67 (C-3'), 73.05 (C-5), 73.01 (C-4'), 72.08 (C-2'), 68.00 (C-4), 67.95 (C-6), 57.32 (OCH_3), 51.24 (C-2), 22.58 (CO–CH_3).

Anal. Calc. for $C_{15}H_{23}NNa_2O_{15}S \cdot 0.5H_2O$: C, 33.09; H, 4.44; N, 2.57. Found: C, 32.91; H, 4.59; N, 2.39.

*Methyl 2,3-di-*O*-benzyl-6-*O*-chloroacetyl-β-*D*-glucopyranoside* (**38**). — A solution of chloroacetyl chloride (216 μL) in 1,2-dichloroethane (1 mL) was added dropwise to a solution of imidazole (368 mg) in 1,2-dichloroethane (10 mL). The mixture was stirred for 30 min, then cooled to 0°, and filtered. Methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside[23] (749 mg) was added to the filtrate, and the mixture was stirred for 20 min at 60°, then cooled, diluted with dichloromethane (50 mL), washed with water, brine, and water, dried (Na_2SO_4), and concentrated. Flash-column chromatography of the residue on silica gel (30 g) with hexane–ethyl acetate (3:1) and crystallization of the product from ether gave **38** (713 mg, 79%), m.p. 83–84°, $[\alpha]_D$ −22° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 10 H, 2 Ph), 4.47 (dd, 1 H, $J_{5,6a}$ 2.50, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.42 (dd, 1 H, $J_{5,6b}$ 7.60, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.33 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 3.98 (s, 2 H, CH_2Cl), 3.57 (s, 3 H, OMe), 2.29 (bs, 1 H, OH).

Anal. Calc. for $C_{23}H_{27}ClO_7$: C, 61.26; H, 6.03. Found: C, 61.31; H, 5.99.

*Methyl 2,3-di-*O*-benzyl-6-*O*-tert-butyldimethylsilyl-β-*D*-glucopyranoside* (**39**). — A mixture of **37** (200 mg), imidazole (82 mg), and *tert*-butyldimethylsilyl chloride (91 mg) in dry *N,N*-dimethylformamide (5 mL) was stirred for 30 min at 0°, then diluted with dichloromethane (25 mL), washed with aqueous 5% ammonium chloride, brine, and water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column (1 × 3 cm) of silica gel with hexane–ethyl acetate (5:1) to give **39**, isolated as a mobile syrup (240 mg, 92%), $[\alpha]_D$ −10° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 10 H, 2 Ph), 4.34 (d, 1 H, $J_{1,2}$ 7.80 Hz, H-1), 3.92 (dd, 1 H, $J_{5,6a}$ 5.0, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.86 (dd, 1 H, $J_{5,6b}$ 5.0, $J_{6a,6b}$ 11.0 Hz, H-6b), 3.62 (m, 1 H, $J_{3,4} = J_{4,5} = 9.0$, $J_{4,OH}$ 2.0 Hz, H-4), 3.55 (s, 3 H, OMe), 3.48 (t, 1 H, $J_{2,3} = J_{3,4} = 9.0$ Hz, H-3), 3.37 (dd, 1 H, $J_{1,2}$ 7.80, $J_{2,3}$ 9.0 Hz, H-2), 3.33 (m, 1 H, $J_{4,5}$ 9.0, $J_{5,6a} = J_{5,6b} = 9.0$ Hz, H-5), 2.86 (d, 1 H, $J_{4,OH}$ 2.0 Hz, HO-4), 0.91 (s, 9 H, ^{t}Bu), 0.10 (s, 6 H, 2 Me).

Anal. Calc. for $C_{27}H_{40}O_6Si$: C, 66.36; H, 8.25. Found: C, 66.34; H, 8.12.

*Methyl 4-*O*-[2-azido-3,6-di-*O*-benzyl-2-deoxy-4-*O*-(2-methoxyethoxymethyl)-β-*D*-galactopyranosyl]-2,3-di-*O*-benzyl-β-*D*-glucopyranoside* (**40**). — (*a*) A mixture of **39** (120 mg), freshly prepared silver silicate[24] (210 mg), and activated powdered 4 Å molecular sieves (100 mg) in dry 1,2-dichloroethane (1.5 mL) was stirred under dry argon, then cooled to −20°. A solution of **13** (80 mg) in 1,2-dichloroethane (1 mL) was added dropwise, and the mixture was stirred for 1 h at −20°, allowed to attain 0° within 3 h, diluted with dichloromethane (20 mL), filtered through Celite, and concentrated. The residue was eluted from a column of silica gel (15 g) with hexane–ethyl acetate (4:1) to give **39** (95 mg), and then a fraction (50 mg) that was directly stirred for 1 h at 0° with 0.2M Bu_4NF in tetrahydrofuran (1 mL). The mixture was diluted with dichloromethane (20 mL), washed with aqueous 5% ammonium chloride, brine, and water, dried

($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel (5 g) with dichloromethane–ethyl acetate (5:2) to give amorphous **40** (32 mg, 26% from **13**), $[\alpha]_D$ +5° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 20 H, 4 Ph), 4.41 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.35 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.07 (dd, 1 H, $J_{3',4'}$ 3.0, $J_{4',5'}$ 0.8 Hz, H-4'), 3.96 (m, 1 H, $J_{5,6a}$ 2.50, $J_{6a,6b}$ 12.40, $J_{6a,OH}$ 6.0 Hz, H-6a), 3.90 (m, 1 H, $J_{5,6b}$ 3.20, $J_{6a,6b}$ 12.40, $J_{6b,OH}$ 6.0 Hz, H-6b), 3.89 (t, 1 H, $J_{3,4} = J_{4,5}$ = 9.20 Hz, H-4), 3.70 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 10.60 Hz, H-2'), 3.56 (s, 3 H, OMe), 3.28 (s, 3 H, OMe), 2.02 (t, 1 H, $J_{6a,OH} = J_{6b,OH}$ = 6.0 Hz, HO-6).

Anal. Calc. for $C_{45}H_{55}N_3O_{12}$: C, 65.12; H, 6.68; N, 5.06. Found: C, 65.02; H, 6.77; N, 4.92.

(*b*) A mixture of **38** (340 mg), **14** (330 mg), and powdered 4 Å molecular sieves (200 mg) in dry toluene (7 mL) was stirred under dry argon, then cooled to −20°. M $BF_3 \cdot Et_2O$ in dichloromethane (27 μL) was added, and the mixture was stirred at −20°. More catalyst (16 μL each time) was added after 1 and 2 h. After 3 h, *N,N*-diisopropylethylamine (100 μL) was added, and the mixture was filtered and concentrated. The residue was eluted from a column of silica gel (50 g) with toluene–ethyl acetate (12:1) to give, first, a disaccharide fraction (430 mg) that was *O*-deacylated (methanolic sodium methoxide). The usual work-up and elution of the product from a column of silica gel (35 g) with dichloromethane–ethyl acetate (7:2) gave, first, the α-linked product **41**, isolated as a colorless glass (27 mg, 6% from **14**), $[\alpha]_D$ +33° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 20 H, 4 Ph), 5.72 (d, 1 H, $J_{1',2'}$ 3.80 Hz, H-1'), 4.35 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 3.65 (dd, 1 H, $J_{1',2'}$ 3.60, $J_{2',3'}$ 10.60 Hz, H-2'), 3.56 (s, 3 H, OMe), 3.29 (s, 3 H, OMe) 2.97 (t, 1 H, $J_{6a,OH} = J_{6b,OH}$ = 6.60 Hz, HO-6).

Anal. Found: C, 64.98; H, 6.81; N, 5.00.

Eluted next was **40** (266 mg, 60% from **14**).

Methyl {methyl 4-O-[2-azido-3,6-di-O-benzyl-2-deoxy-4-O-(2-methoxyethoxymethyl)-β-D-galactopyranosyl]-2,3-di-O-benzyl-β-D-glucopyranosid}uronate (**42**). — A mixture of **40** (162 mg) and pyridinium dichromate (375 mg) in dry *N,N*-dimethylformamide (2 mL) was stirred under dry argon for 20 h, then poured into vigorously stirred ice–water (50 mL). The mixture was extracted with chloroform (6 × 10 mL), and the combined extracts were washed with brine and water, dried (Na_2SO_4), and concentrated. To a solution of the residue in 1,2-dimethoxyethane (2.5 mL) at 0° was added M sodium hydroxide (1 mL). The mixture was stirred for 2 h at room temperature and then cooled to 0°, M hydrochloric acid was added to pH ~1, and the gelatinous precipitate was extracted with chloroform (5 × 10 mL). The combined extracts were washed with water, dried (Na_2SO_4), and concentrated. A solution of the residue in 1,2-dimethoxyethane (2 mL) was treated with excess of ethereal diazomethane, then concentrated. The residue was eluted from a column of silica gel (15 g) with hexane–ethyl acetate (3:2) and crystallized from ether–hexane to give **42** (128 mg, 75%), m.p. 87–88°, $[\alpha]_D$ +9° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 20 H, 4 Ph), 4.37 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.30 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.12 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.50 Hz, H-4), 4.05 (dd, 1 H, $J_{3',4'}$ 3.0, $J_{4',5'}$ 0.80 Hz, H-4'), 3.95 (d, 1 H, $J_{4,5}$ 9.50 Hz, H-5), 3.82 (s, 3 H, COOMe), 3.63 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 10.60 Hz, H-2'), 3.61 (t, 1 H, $J_{2,3}$

= $J_{3,4}$ = 9.0 Hz, H-3), 3.54 (s, 3 H, OMe), 3.42 (dd, 1 H, $J_{1,2}$ 8.0 $J_{2,3}$ 9.0 Hz, H-2), 3.28 (s, 3 H, OMe), 3.21 (dd, 1 H, $J_{2',3'}$ 10.60 $J_{3',4'}$ 3.0 Hz, H-3').

Anal. Calc. for $C_{46}H_{55}N_3O_{13}$: C, 64.40; H, 6.46; N, 4.90. Found: C, 64.32; H, 6.51; N, 4.72.

Further elution gave **40** (16 mg, 10%).

Methyl {methyl 4-O-[2-acetamido-3,6-di-O-benzyl-2-deoxy-4-O-(2-methoxyethoxymethyl)-β-D-galactopyranosyl]-2,3-di-O-benzyl-β-D-glucopyranosid}uronate (**43**). — A solution of **42** (195 mg) in thioacetic acid (1.5 mL) was stirred for 24 h at room temperature, then concentrated. The residue was eluted from a column of silica gel (15 g) with dichloromethane–acetone (9:1) and crystallized from methanol to give **43** (151 mg, 76%), m.p. 174–175°, $[\alpha]_D$ +17° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 20 H, 4 Ph), 5.43 (d, 1 H, $J_{2,NH}$ 8.0 Hz, NH), 4.88 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.33 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.11 (dd, 1 H, $J_{3',4'}$ 3.0, $J_{4',5'}$ 0.80 Hz, H-4'), 4.05 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.50 Hz, H-4), 4.03 (dd, 1 H, $J_{2',3'}$ 11.0, $J_{3',4'}$ 3.0 Hz, H-3'), 3.87 (d, 1 H, $J_{4,5}$ 9.50 Hz, H-5), 3.78 (s, 3 H, COOMe), 3.53 (s, 3 H, OMe), 3.29 (s, 3 H, OMe), 1.94 (s, 3 H, NAc).

Anal. Calc. for $C_{48}H_{59}NO_{14}$: C, 65.96; H, 6.80; N, 1.60. Found: C, 66.02; H, 6.78; N, 1.51.

Methyl [methyl 4-O-(2-acetamido-3,6-di-O-benzyl-2-deoxy-β-D-galactopyranosyl)-2,3-di-O-benzyl-β-D-glucopyranosid]uronate (**44**). — A solution of **43** (95 mg) in aqueous 85% trifluoroacetic acid (1 mL) was stirred for 30 min at room temperature, then poured into ice-cold water (50 mL), and extracted with chloroform (4 × 10 mL), and the combined extracts were washed with aqueous 5% sodium hydrogencarbonate and water, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel (8 g) with dichloromethane–acetone (6:1) to give, first, **44** (51 mg, 60%), m.p. 173–174° (from ethanol), $[\alpha]_D$ +17° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 20 H, 4 Ph), 5.63 (d, 1 H, $J_{2,NH}$ 8.0 Hz, NH), 4.82 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.33 (d, 1 H, $J_{1,2}$ 7.80 Hz, H-1), 4.07 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.50 Hz, H-4), 4.05 (m, 1 H, $J_{3',4'}$ 3.0, $J_{4',5'}$ 0.80, $J_{4',OH}$ 2.40 Hz, H-4'), 3.95 (dd, 1 H, $J_{2',3'}$ 10.40, $J_{3',4'}$ 3.0 Hz, H-3'), 3.90 (d, 1 H, $J_{4,5}$ 9.50 Hz, H-5), 3.80 (s, 3 H, COOMe), 3.60 (m, 1 H, $J_{1',2'}$ = $J_{2',NH}$ = 8.0, $J_{2',3'}$ 10.40 Hz, H-2'), 3.53 (s, 3 H, OMe), 3.42 (dd, 1 H, $J_{1,2}$ 7,80 $J_{2,3}$ 9.0 Hz, H-2), 2.46 (d, 1 H, $J_{4,OH}$ 2.40 Hz, HO-4), 1.95 (s, 3 H, NAc).

Anal. Calc. for $C_{44}H_{51}NO_{12}$: C, 67.25; H, 6.54; N, 1.78. Found: C, 67.18; H, 6.62; N, 1.74.

Further elution gave a fraction (25 mg) that was acetylated (acetic anhydride–pyridine) overnight, then concentrated. The residue was eluted from a column of silica gel (3 g) with ethyl acetate–hexane (3:2) to give amorphous **45** (22 mg, 24% from **43**). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.35 (m, 20 H, 4 Ph), 6.25 (d, $J_{1,2}$ 3.60 Hz, H-1α), 5.64 (d, $J_{1,2}$ 8.0 Hz, H-1β), 5.58 (dd, $J_{3',4'}$ 3.0, $J_{4',5'}$ 1.0 Hz, H-4'β), 5.56 (dd, $J_{3',4'}$ 3.0, $J_{4',5'}$ 0.80 Hz, H-4'α), 5.42 (d, $J_{2,NH}$ 8.0 Hz, NHβ), 5.34 (d, $J_{2,NH}$ 8.0 Hz, NHα), 4.96 (d, $J_{1',2'}$ 8.0 Hz, H-1'β), 4.93 (d, $J_{1',2'}$ 8.0 Hz, H-1'α), 4.15 (dd, $J_{2',3'}$ 10.40, $J_{3',4'}$ 3.0 Hz, H-3'β), 4.06 (dd, $J_{2',3'}$ 10.40, $J_{3',4'}$ 3.0 Hz, H-3'α), 3.76 and 3.75 (2 s, 3 H, COOMe), 3.62 (dd, $J_{1,2}$ 3.60, $J_{2,3}$ 9.20 Hz, H-2α), 2.16, 2.15, 2.03, 2.02, 1.92, and 1.91 (6 s, 9 H, 3 Ac).

Anal. Calc. for $C_{47}H_{53}NO_{14}$: C, 65.95; H, 6.24; N, 1.63. Found: C, 66.00; H, 6.18; N, 1.47.

Methyl 4-O-(4-O-acetyl-2-azido-3,6-di-O-benzyl-2-deoxy-β-D-galactopyranosyl)-2,3-di-O-benzyl-β-D-glucopyranoside (**46**). — A mixture of **39** (237 mg), imidate **15** (185 mg), and activated powdered 4 Å molecular sieves (150 mg) in dry toluene (5 mL) was stirred under dry argon, then cooled to −20°. M $BF_3 \cdot Et_2O$ in dichloromethane (16 μL) was added, the mixture was stirred at −20°, and more catalyst (7 μL each time) was added after 1 and 2 h. After 3 h, *N,N*-di-isopropylethylamine (0.1 mL) was added, and the mixture was filtered and then concentrated. The residue was eluted from a column of silica gel (40 g) with toluene–ethyl acetate (24:1) to give, first, a disaccharide fraction (255 mg) that was *O*-desilylated for 20 min at 0° with 0.2M Bu_4NF in tetrahydrofuran (5 mL). The mixture was diluted with dichloromethane (40 mL), washed with aqueous 5% ammonium chloride, brine, and water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel (20 g) with dichloromethane–ethyl acetate (6:1) to give, first, the amorphous α-linked product **47** (8 mg, 3%), $[\alpha]_D$ +56° (*c* 1, chlorofom). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 20 H, 4 Ph), 5.70 (d, 1 H, $J_{1',2'}$ 4.0 Hz, H-1'), 5.62 (dd, 1 H, $J_{3',4'}$ 3.40, $J_{4',5'}$ 0.80 Hz, H-4'), 4.36 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 3.57 (s, 3 H, OMe), 3.52 (dd, 1 H, $J_{1',2'}$ 4.0, $J_{2',3'}$ 11.0 Hz, H-2'), 3.46 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.0 Hz, H-2), 2.72 (t, 1 H, $J_{6a,OH} = J_{6b,OH}$ = 6.60 Hz, HO-6), 2.03 (s, 3 H, Ac).

Anal. Calc. for $C_{43}H_{49}N_3O_{11}$: C, 65.89; H, 6.30; N, 5.36. Found: C, 65.69; H, 6.41; N, 5.18.

Further elution gave **46** (157 mg, 62%), m.p. 124–125° (from ethyl acetate–hexane), $[\alpha]_D$ −21° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 20 H, 4 Ph), 5.57 (dd, 1 H, $J_{3',4'}$ 3.0, $J_{4',5'}$ 0.80 Hz, H-4'), 4.44 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.35 (d, 1 H, $J_{1,2}$ 7.80 Hz, H-1), 3.97 (m, 1 H, $J_{5,6a}$ 2.50, $J_{6a,6b}$ 12.0, $J_{6a,OH}$ 5.0 Hz, H-6a), 3.92 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.50 Hz, H-4), 3.90 (m, 1 H, $J_{5,6b}$ 4.0, $J_{6a,6b}$ 12.0, $J_{6b,OH}$ 8.0 Hz, H-6b), 3.61 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.0 Hz, H-3), 3.58 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 10.40 Hz, H-2'), 3.56 (s, 3 H, OMe), 3.43 (dd, 1 H, $J_{2',3'}$ 10.40, $J_{3',4'}$ 3.0 Hz, H-3'), 3.33 (dd, 1 H, $J_{1,2}$ 7.80, $J_{2,3}$ 9.0 Hz, H-2), 2.03 (s, 3 H, OAc), 1.98 (dd, 1 H, $J_{6a,OH}$ 5.0, $J_{6b,OH}$ 8.0 Hz, HO-6).

Anal. Calc. for $C_{43}H_{49}N_3O_{11}$: C, 65.89; H, 6.30; N, 5.36. Found: C, 65.78; H, 6.33; N, 5.29.

Methyl 4-O-(2-acetamido-4-O-acetyl-3,6-di-O-benzyl-2-deoxy-β-D-galactopyranosyl)-2,3-di-O-benzyl-β-D-glucopyranoside (**48**). — Ethanolic 4% nickel dichloride hexahydrate containing 2% of boric acid (15 mL) was added to a solution of **46** (156 mg) in 1,2-dimethoxyethane (1 mL). A solution of sodium borohydride in ethanol (10 mg/mL) was then added dropwise with stirring until the green solution turned to persistent black (30 min). The mixture was then concentrated. Flash chromatography of the residue on a column (1 × 5 cm) of silica gel with dichloromethane–methanol (12:1) gave a colourless fraction that was dissolved in methanol (5 mL). The pH of the solution was adjusted to ~8 with 0.1M sodium hydroxide, acetic anhydride (1 mL) was added immediately, and the mixture was stirred for 10 min and then concentrated. A solution of the residue in ethyl acetate (10 mL) was filtered through Celite and concentrated, and the residue was crystallized from ethyl acetate–hexane to give **48** (126 mg, 81%), m.p. 159–160°, $[\alpha]_D$ +35° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.35 (m, 20 H, 4 Ph), 5.57 (d, 1 H, $J_{2,NH}$ 8.0 Hz, NH), 5.55 (dd, 1 H, $J_{3',4'}$ 3.40, $J_{4',5'}$ 0.80 Hz, H-4'), 5.11 (d, 1 H, $J_{1',2'}$ 8.0 Hz,

H-1'), 4.33 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.20 (dd, 1 H, $J_{2',3'}$ 10.60, $J_{3',4'}$ 3.40 Hz, H-3'), 3.85 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.50 Hz, H-4), 3.83 (m, 1 H, $J_{5,6a}$ 2.50, $J_{6a,6b}$ 12.0, $J_{6a,OH}$ 5.20 Hz, H-6a), 3.72 (m, 1 H, $J_{5,6b}$ 3.50, $J_{6a,6b}$ 12.0, $J_{6b,OH}$ 5.20 Hz, H-6b), 3.62 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.0 Hz, H-3), 3.54 (s, 3 H, OMe), 3.49 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 10.60 Hz, H-2'), 3.35 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.0 Hz, H-2), 2.10 (t, 1 H, $J_{6a,OH} = J_{6b,OH}$ = 5.20 Hz, HO-6), 2.03 (s, 3 H, Ac), 1.89 (s, 3 H, NAc).

Anal. Calc. for $C_{45}H_{53}NO_{12}$: C, 67.57; H, 6.68; N, 1.75. Found: C, 67.63; H, 6.57; N, 1.71.

Methyl 4-O-(2-acetamido-3,6-di-O-benzyl-2-deoxy-β-D-galactopyranosyl)-2,3-di-O-benzyl-β-D-glucopyranosiduronic acid (**49**). — (*a*) A mixture of **48** (89 mg) and pyridinium dichromate (240 mg) in dry *N,N*-dimethylformamide (1 mL) was stirred under argon for 24 h, then poured into vigorously stirred ice–water (30 mL). The mixture was extracted with chloroform (6 × 5 mL), and the combined extracts were washed with brine and water, then concentrated. To a solution of the residue in 1,2-dimethoxyethane (2 mL) and methanol (1 mL) was added M sodium hydroxide, and the mixture was stirred for 5 h at room temperature, then cooled to 0°. M Hydrochloric acid was added to pH ~1, the mixture was extracted with chloroform (6 × 5 mL), and the combined extracts were washed with water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel (5 g) with dichloromethane–methanol (6:1) and crystallized from aqueous ethanol to give **49** (67 mg, 78%), m.p. 175–177° (dec.), $[\alpha]_D$ +20° (*c* 0.5, chloroform). ^{1}H-N.m.r. data (CD_3OD): δ 7.30 (m, 20 H, 4 Ph), 4.64 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.40 (d, 1 H, $J_{1,2}$ 7.80 Hz, H-1), 4.05 (dd, 1 H, $J_{3',4'}$ 3.0, $J_{4',5'}$ 0.80 Hz, H-4'), 4.03 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.50 Hz, H-4), 3.97 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 10.60 Hz, H-2'), 3.87 (d, 1 H, $J_{4,5}$ 9.50 Hz, H-5), 3.54 (s, 3 H, OMe), 3.36 (dd, 1 H, $J_{1,2}$ 7.80, $J_{2,3}$ 9.0 Hz, H-2), 1.96 (s, 3 H, NAc).

Anal. Calc. for $C_{43}H_{49}NO_{12}\cdot H_2O$: C, 65.38; H, 6.51; N, 1.77. Found: C, 65.51; H, 6.60; N, 1.66.

(*b*) To a solution of **44** (45 mg) in 1,2-dimethoxyethane (1.5 mL) at 0° was added M sodium hydroxide (0.5 mL) dropwise, and the mixture was stirred for 5 h at 0°. M Hydrochloric acid was then added to pH ~1, the mixture was extracted with chloroform (5 × 5 mL), and the combined extracts were washed with water, dried (Na_2SO_4), and concentrated. The residue crystallized from aqueous ethanol to give **49** (39 mg, 88%).

Methyl 4-O-(2-acetamido-3,6-di-O-benzyl-2-deoxy-4-O-sulfo-β-D-galactopyranosyl)-2,3-di-O-benzyl-β-D-glucopyranosiduronic acid, disodium salt (**50**). M Sodium hydroxide (115 μL) was added to a solution of **49** (85 mg) in methanol–water (4:1, 5 mL). The mixture was stirred for 1 h at room temperature, then concentrated, and the residue was dried *in vacuo*. A mixture of the residue and the sulfur trioxide–trimethylamine complex (100 mg) in dry *N,N*-dimethylformamide (1.5 mL) was stirred for 36 h at 60°, then cooled. Methanol (0.5 mL) was added and the mixture was eluted from a column (3.5 × 60 cm) of Sephadex LH-20, equilibrated in dichloromethane–methanol (1:1), with the same solvent. The product was eluted from a column (1.5 × 30 cm) of Sephadex SP-C25 (Na^+) with methanol–water (9:1) to give **50**, isolated as a colorless glass (91 mg,

93%), $[\alpha]_D$ −32° (*c* 1, methanol). ^{1}H-N.m.r. data (CD_3OD): δ 7.30 (m, 20 H, 4 Ph), 5.00 (dd, 1 H, $J_{3',4'}$ 3.0, $J_{4',5'}$ 0.80 Hz, H-4'), 4.63 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.34 (d, 1 H, $J_{1,2}$ 7.80 Hz, H-1), 4.05 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 10.60 Hz, H-2'), 3.92 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.50 Hz, H-4), 3.70 (d, 1 H, $J_{4,5}$ 9.50 Hz, H-5), 3.52 (s, 3 H, OMe), 3.49 (dd, 1 H, $J_{2',3'}$ 10.60, $J_{3',4'}$ 3.0 Hz, H-3'), 3.28 (dd, 1 H, $J_{1,2}$ 7.80, $J_{2,3}$ 9.0 Hz, H-2), 2.00 (s, 3 H, NAc).

Anal. Calc. for $C_{43}H_{47}NNa_2O_{15}S\cdot 0.5H_2O$: C, 57.07; H, 5.34; N, 1.55. Found: C, 57.01; H, 5.46; N, 1.42.

*Methyl 4-O-(2-acetamido-2-deoxy-4-O-sulfo-β-*D*-galactopyranosyl)-β-*D*-glucopyranosiduronic acid, disodium salt* (**51**). — A solution of **50** (90 mg) in methanol–water (3:1, 4 mL) was hydrogenated in the presence of 10% Pd–C (50 mg) for 24 h, then filtered, and concentrated. The residue was eluted from a column (2.2 × 115 cm) of Sephadex G-10 with water to give **51**, isolated as a white amorphous powder (47 mg, 87%), $[\alpha]_D$ −13° (*c* 1, water). N.m.r. data: ^{1}H (D_2O, internal TSP), δ 4.69 (dd, 1 H, $J_{3',4'}$ 2.80, $J_{4',5'}$ 0.80 Hz, H-4'), 4.56 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.39 (d, 1 H, $J_{1,2}$ 7.80 Hz, H-1), 3.91 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 11.0 Hz, H-2'), 3.89 (dd, 1 H, $J_{2',3'}$ 11.0, $J_{3',4'}$ 2.80 Hz, H-3'), 3.84 (m, 3 H, H-5',6'a,6'b), 3.77 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.50 Hz, H-4), 3.72 (d, 1 H, $J_{4,5}$ 9.50 Hz, H-5), 3.60 (dd, 1 H, $J_{2,3}$ 9.50, $J_{3,4}$ 9.0 Hz, H-3), 3.56 (s, 3 H, OMe), 3.34 (dd, 1 H, $J_{1,2}$ 7.80, $J_{2,3}$ 9.50 Hz, H-2), 2.06 (s, 3 H, NAc); ^{13}C (D_2O, internal acetone), δ 175.24 (C=O), 174.36 (C-6), 103.51 (C-1'), 101.32 (C-1), 80.22 (C-4), 76.78 (C-5), 75.98 (C-4'), 74.73 (C-3), 74.18 (C-5'), 72.83 (C-3'), 70.30 (C-2), 61.24 (C-6'), 57.49 (OCH_3), 52.84 (C-2'), 22.70 (CO–CH_3).

Anal. Calc. for $C_{15}H_{23}NNa_2O_{15}S\cdot 2H_2O$: C, 31.53; H, 4.76; N, 2.45. Found: C, 31.38; H, 4.89; N, 2.28.

*Methyl 4-O-[2-azido-3,4-di-O-benzyl-2-deoxy-6-O-(2-methoxyethoxymethyl)-β-*D*-galactopyranosyl]-2,3-di-O-benzyl-β-*D*-glucopyranoside* (**52**). — A mixture of **39** (269 mg), **20** (230 mg), and activated powdered 4 Å molecular sieve (150 mg) was treated as described for the preparation of **46**. The residue was eluted from a column of silica gel (40 g) with hexane–ethyl acetate (4:1) to give a disaccharide fraction (150 mg) which was *O*-desilylated as described for the preparation of **46**. The residue was eluted from a column of silica gel (20 g) with dichloromethane–acetone (7:1) to give, first, amorphous α-linked product **53** (25 mg, 8%), $[\alpha]_D$ +48° (*c* 1, chloroform). ^{1}H-N-m.r. data ($CDCl_3$): δ 7.30 (m, 20 H, 4 Ph), 5.71 (d, 1 H, $J_{1',2'}$ 3.80 Hz, H-1'), 4.36 (d, 1 H, $J_{1,2}$ 7.80 Hz, H-1), 3.94 (t, 1 H, $J_{3,4} = J_{4,5} = 9.0$ Hz, H-4), 3.57 (s, 3 H, OMe), 3.37 (s, 3 H, OMe), 2.95 (t, 1 H, $J_{6a,OH} = J_{6b,OH} = 6.60$ Hz, HO-6).

Anal. Calc. for $C_{45}H_{55}N_3O_{12}$: C, 65.12; H, 6.68; N, 5.06. Found: C, 65.33; H, 6.51; N, 4.78.

Further elution afforded amorphous **52** (74 mg, 24%), $[\alpha]_D$ +2° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.30 (m, 20 H, 4 Ph), 4.43 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.34 (d, 1 H, $J_{1,2}$ 7.80 Hz, H-1), 3.93 (t, 1 H, $J_{3,4} = J_{4,5} = 9.20$ Hz, H-4), 3.56 (s, 3 H, OMe), 3.32 (s, 3 H, OMe), 2.04 (dd, 1 H, $J_{6a,OH}$ 5.40, $J_{6b,OH}$ 8.20 Hz, HO-6).

Anal. Found: C, 65.02; H, 6.80; N, 4.97.

*Methyl-4-O-(2-azido-6-O-benzoyl-3,4-di-O-benzyl-2-deoxy-β-*D*-galactopyranosyl)-2,3-di-O-benzyl-β-*D*-glucopyranoside* (**54**). — A mixture of **39** (635 mg), **23** (412 mg), and activated powdered 4 Å molecular sieve (300 mg) in dry toluene (10 mL) was

stirred under dry argon, then cooled to −20°. 2M $BF_3 \cdot Et_2O$ in dichloromethane (16 μL) was added and the mixture was stirred at −20°. More catalyst (10 μL each time) was added after 1 and 2 h. After 4 h, *N,N*-di-isopropylethylamine (200 μL) was added, and the mixture was filtered and concentrated. The residue was eluted from a column of silica gel (70 g) with toluene–ethyl acetate (24:1) to give a disaccharide fraction (450 mg) that was *O*-desilylated as described for the preparation of **46**. The residue was eluted from a column of silica gel (35 g) with dichloromethane–ethyl acetate (10:1) to give, first, amorphous α-linked product **55** (28 mg, 5%), $[\alpha]_D$ +43° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.0–7.30 (m, 25 H, 5 Ph), 5.72 (d, 1 H, $J_{1',2'}$ 3.80 Hz, H-1'), 4.46 (dd, 1 H, $J_{5',6'a}$ 6.50, $J_{6'a,6'b}$ 11.20 Hz, H-6'a), 4.35 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.31 (dd, 1 H, $J_{5',6'b}$ 6.50, $J_{6'a,6'b}$ 11.20 Hz, H-6'b), 3.55 (s, 3 H, OMe), 2.17 (t, 1 H, $J_{6a,OH} = J_{6b,OH}$ = 6.20 Hz, HO-6).

Anal. Calc. for $C_{48}H_{51}N_3O_{11}$: C, 68.15; H, 6.07; N, 4.97. Found: C, 68.21; H, 6.02; N, 4.72.

Further elution afforded amorphous **54** (303 mg, 55%), $[\alpha]_D$ −27° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.0–7.30 (m, 25 H, 5 Ph), 4.46 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.36 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.28 (dd, 1 H, $J_{5',6'a}$ 5.80, $J_{6'a,6'b}$ 11.0 Hz, H-6'a), 4.18 (dd, 1 H, $J_{5',6'b}$ 7.40, $J_{6'a,6'b}$ 11.0 Hz, H-6'b), 3.94 (t, 1 H, $J_{3,4} = J_{4,5}$ = 9.0 Hz, H-4), 3.86 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 10.20 Hz, H-2'), 3.55 (s, 3 H, OMe), 3.42 (dd, 1 H, $J_{2',3'}$ 10.20, $J_{3',4'}$ 3.0 Hz, H-3'), 3.35 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.0 Hz, H-2), 1.98 (dd, 1 H, $J_{6a,OH}$ 5.50, $J_{6b,OH}$ 8.0 Hz, HO-6).

Anal. Found: C, 68.10; H, 6.17; N, 4.88.

Methyl [methyl 4-O-(2-azido-6-O-benzoyl-3,4-di-O-benzyl-2-deoxy-β-D-galacto-pyranosyl)-2,3-di-O-benzyl-β-D-glucopyranosid]uronate (**56**). — A mixture of **54** (246 mg) and pyridinium dichromate (700 mg) in dry *N,N*-dimethylformamide (3 mL) was stirred at room temperature under dry argon for 24 h, then poured into vigorously stirred ice–water (100 mL). The mixture was extracted with chloroform (6 × 10 mL), and the combined extracts were washed with brine and water, dried ($MgSO_4$), and concentrated. A solution of the residue in 1,2-dimethoxyethane (3 mL) was treated with excess of ethereal diazomethane and then concentrated. Elution of the residue from a column of silica gel (10 g) with hexane–ethyl acetate (2:1) afforded amorphous **56** (185 mg, 73%), $[\alpha]_D$ −17° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.0–7.30 (m, 25 H, 5 Ph), 4.38 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.36 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.28 (dd, 1 H, $J_{5',6'a}$ 7.0, $J_{6'a,6'b}$ 11.0 Hz, H-6'a), 4.17 (dd, 1 H, $J_{5',6'b}$ 6.0, $J_{6'a6'b}$ 11.0 Hz, H-6'b), 4.15 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.50 Hz, H-4), 3.97 (d, 1 H, $J_{4,5}$ 9.50 Hz, H-5), 3.84 (s, 3 H, COOMe), 3.55 (s, 3 H, OMe), 3.43 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.0 Hz, H-2), 3.31 (dd, 1 H, $J_{2',3'}$ 10.40, $J_{3',4'}$ 3.0 Hz, H-3').

Anal. Calc. for $C_{49}H_{51}N_3O_{12}$: C, 67.34; H, 5.88; N, 4.81. Found: C, 67.19; H, 5.92; N, 6.42.

Methyl [methyl 4-O-(2-acetamido-6-O-benzoyl-3,4-di-O-benzyl-2-deoxy-β-D-ga-lactopyranosyl)-2,3-di-O-benzyl-β-D-glucopyranosid]uronate (**57**). — A solution of **56** (155 mg) in thioacetic acid (1.5 mL) was stirred at room temperature for 24 h and then concentrated. The residue was eluted from a column of silica gel (12 g) with dichloro-methane–acetone (10:1) and crystallized from ethyl acetate – hexane to give **57** (123 mg, 78%), m.p. 138–139°, $[\alpha]_D$ −13° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.0–7.30

(m, 25 H, 5 Ph), 5.57 (d, 1 H, $J_{2,NH}$ 7.50 Hz, NH), 5.02 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.34 (d, 1 H, $J_{1,2}$ 7.80 Hz, H-1), 4.27 (dd, 1 H, $J_{5',6'a}$ 7.20, $J_{6'a,6'b}$ 11.0 Hz, H-6'a), 4.17 (dd, 1 H, $J_{5',6'b}$ 6.0, $J_{6'a,6'b}$ 11.0 Hz, H-6'b), 4.10 (dd, 1 H, $J_{3',4'}$ 9.0, $J_{4',5'}$ 9.50 Hz, H-4'), 3.88 (d, 1 H, $J_{4,5}$ 9.50 Hz, H-5), 3.83 (dd, 1 H, $J_{3',4'}$ 3.0, $J_{4',5'}$ 0.80 Hz, H-4'), 3.80 (s, 3 H, COOMe), 3.57 (m, 1 H, $J_{1',2'}$ 8.0, $J_{2',NH}$ 7.50, $J_{2,3}$ 11.0 Hz, H-2'), 3.53 (s, 3 H, OMe), 3.42 (dd, 1 H, $J_{1,2}$ 7.80, $J_{2,3}$ 9.0 Hz, H-2), 1.96 (s, 3 H, NAc).

Anal. Calc. for $C_{51}H_{55}NO_{13}$: C, 68.83; H, 6.23; N, 1.57. Found: C, 68.67; H, 6.34; N, 1.52.

Methyl 4-O-(2-acetamido-3,4-di-O-benzyl-2-deoxy-β-D-galactopyranosyl)-2,3-di-O-benzyl-β-D-glucopyranosiduronic acid (**58**). — To a solution of **57** (106 mg) in 1,2-dimethoxyethane (2 mL) and methanol (1 mL) was added M sodium hydroxide (2 mL) dropwise at 0°. The mixture was stirred overnight at room temperature and cooled to 0°, and M hydrochloric acid was added to pH ~1. The mixture was extracted with chloroform (6 × 10 mL), and the combined extracts were washed with water, dried (Na_2SO_4), and concentrated. The residue was triturated with cold ether (20 mL) and then crystallized from ethyl acetate–hexane to give **58** (77 mg, 83%), m.p. 188–190° (dec.), $[\alpha]_D$ +4° (*c* 0.5, chloroform). ^{1}H-N.m.r. data (CD_3OD): δ 7.30 (m, 20 H, 4 Ph), 4.57 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.41 (d, 1 H, $J_{1,2}$ 7.80 Hz, H-1), 4.15 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 11.0 Hz, H-2'), 4.03 (dd, 1 H, $J_{3,4}$ 9.20, $J_{4,5}$ 9.50 Hz, H-4), 3.87 (d, 1 H, $J_{4,5}$ 9.50 Hz, H-5), 3.74 (dd, 1 H, $J_{5',6'a}$ 7.0, $J_{6'a,6'b}$ 12.0 Hz, H-6'a), 3.56 (s, 3 H, OMe), 3.48 (dd, 1 H, $J_{5',6'b}$ 4.0, $J_{6'a,6'b}$ 12.0 Hz, H-6'b), 3.35 (dd, 1 H, $J_{1,2}$ 7.80, $J_{2,3}$ 9.20 Hz, H-2), 1.96 (s, 3 H, NAc).

Anal. Calc. for $C_{43}H_{49}NO_{12}\cdot 0.5H_2O$: C, 66.14; H, 6.45; N, 1.79. Found: C, 66.28; H, 6.51; N, 1.72.

Methyl 4-O-(2-acetamido-3,4-di-O-benzyl-2-deoxy-6-O-sulfo-β-D-galactopyranosyl)-2,3-di-O-benzyl-β-D-glucopyranosiduronic acid, disodium salt (**59**). — M Sodium hydroxide (86 μL) was added to a solution of **58** (64 mg) in methanol–water (3:1, 4 mL). The mixture was stirred for 1 h at room temperature, then concentrated, and the residue was dried *in vacuo*. A mixture of the residue and the sulfur trioxide–trimethylamine complex (35 mg) in dry *N,N*-dimethylformamide (1 mL) was stirred for 3 h at 60° and then cooled. Methanol (0.1 mL) was added, and the mixture was chromatographed, as described for the preparation of **50**, to give amorphous **59** (64 mg, 86%), $[\alpha]_D$ −2° (*c* 1, methanol). ^{1}H-N.m.r. data (CD_3OD): δ 7.30 (m, 20 H, 4 Ph), 4.64 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.34 (d, 1 H, $J_{1,2}$ 7.80 Hz, H-1), 4.28 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 10.60 Hz, H-2'), 4.26 (dd, 1 H, $J_{5',6'a}$ 8.0, $J_{6'a,6'b}$ 10.0 Hz, H-6'a), 4.17 (dd, 1 H, $J_{3',4'}$ 3.0, $J_{4',5'}$ 0.80 Hz, H-4'), 4.13 (dd, 1 H, $J_{5',6'b}$ 5.0, $J_{6'a,6'b}$ 10.0 Hz, H-6'b), 3.70 (d, 1 H, $J_{4,5}$ 9.50 Hz, H-5), 3.53 (s, 3 H, OMe), 3.32 (dd, 1 H, $J_{1,2}$ 7.80, $J_{2,3}$ 9.0 Hz, H-2), 2.00 (s, 3 H, NAc).

Anal. Calc. for $C_{43}H_{47}NNa_2O_{15}S\cdot H_2O$: C, 56.51; H, 5.40; N, 1.53. Found: C, 56.66; H, 5.51; N, 1.43.

Methyl 4-O-(2-acetamido-2-deoxy-6-O-sulfo-β-D-galactopyranosyl)-β-D-glucopyranosiduronic acid, disodium salt (**60**). — A solution of **59** (64 mg) in methanol–water (3:1, 4 mL) was hydrogenated in the presence of 10% Pd–C (40 mg) for 24 h, then filtered, and concentrated. The residue was eluted from a column (2.2 × 115 cm) of Sephadex G-10 with water to give **60**, isolated as a white foam (34 mg, 89%), $[\alpha]_D$ −7° (*c*

1, water). N.m.r. data: ^1H (D_2O, internal TSP), δ 4.53 (d, 1 H, $J_{1',2'}$ 8.40 Hz, H-1'), 4.40 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.26 (dd, 1 H, $J_{5',6'a}$ 5.50, $J_{6'a,6'b}$ 11.0 Hz, H-6'a), 4.23 (dd, 1 H, $J_{5',6'b}$ 7.0, $J_{6'a,6'b}$ 11.0 Hz, H-6'b), 3.99 (dd, 1 H, $J_{3',4'}$ 3.0, $J_{4',5'}$ 0.80 Hz, H-4'), 3.97 (m, 1 H, $J_{4',5'}$ 0.80, $J_{5',6'a}$ 5.50, $J_{5',6'b}$ 7.0 Hz, H-5'), 3.93 (dd, 1 H, $J_{1',2'}$ 8.40, $J_{2',3'}$ 11.0 Hz, H-2'), 3.76 (t, 1 H, $J_{3,4} = J_{4,5} = 9.50$ Hz, H-4), 3.75 (dd, 1 H, $J_{2',3'}$ 11.0, $J_{3',4'}$ 3.0 Hz, H-3'), 3.72 (d, 1 H, $J_{4,5}$ 9.50 Hz, H-5), 3.62 (t, 1 H, $J_{2,3} = J_{3,4} = 9.50$ Hz, H-3), 3.56 (s, 3 H, OMe), 3.36 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.50 Hz, H-2), 2.06 (s, 3 H, NAc); ^{13}C (D_2O, internal acetone), δ 175.29 (C=O), 174.12 (C-6), 103.56 (C-1'), 101.80 (C-1), 81.24 (C-4), 76.78 (C-5), 74.33 (C-3), 72.94 (C-5'), 72.80 (C-3'), 71.12 (C-2), 67.70 (C-4'), 67.28 (C-6'), 57.49 (OCH_3), 52.41 (C-2'), 22.75 (CO–CH_3).

Anal. Calc. for $C_{15}H_{23}NNa_2O_{15}S \cdot H_2O$: C, 32.56; H, 4.55; N, 2.53. Found: C, 32.32; H, 4.77; N, 2.32.

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