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A regio- and stereo-controlled synthesis of β-D-Glc*p*NAc6SO_3-(1→3)-β-D-Gal*p*6SO_3-(1→4)-β-D-Glc*p*NAc6SO_3-(1→3)-D-Gal*p*, a linear acidic glycan fragment of keratan sulfate I*

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ABSTRACT

A stereocontrolled systhesis of β-D-Glc*p*NAc6SO_3-(1→3)-β-D-Gal*p*6SO_3-(1→4)-β-D-Glc*p*NAc6SO_3-(1→3)-D-Gal*p*, was achieved by use of benzyl *O*-(2-acetamido-3,4 di-*O*-benzyl-2-deoxy-6-*O*-*p*-methoxyphenyl-β-D-glucopyranosyl)-(1→3)-*O*-(2,4-di-*O*-*tert*-butyldiphenylsilyl-β-D-galactopyranosyl-(1→4)-*O*-(2-acetamido-3-*O*-benzyl-2-deoxy-6-*O*-*p*-methoxyphenyl-β-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside as a key intermediate, which was in turn prepared by employing two glycosyl donors, 3,4-di-*O*-benzyl-2-deoxy-6-*O*-*p*-methoxyphenyl-2-phthalimido-β-D-glucopyranosyl trichloroacetimidate and *O*-(3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-*p*-methoxyphenyl-2-phthalimido-β-D-glucopyranosyl trichloroacetimidate, and a glycosyl acceptor, benzyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside.

INTRODUCTION

Keratan sulfate proteoglycans[2] may be classified into two types, keratan sulfate I and keratan sulfate II. Keratan sulfate I is exclusively located in the cornea, and the oligosaccharide chains are linked to protein by an *N*-glycosylic linkage[3] between *N*-acetyl-D-glucosamine and L-asparagine. In 1983 Hascall and his co-workers[4] clearly demonstrated that the linkage region of keratan sulfate I isolated from monkey cornea was derived from a complex type of *N*-linked glycan precursor. Keratan sulfate II is found in skin, cartilage and bone, and the oligosaccharide chains are bound to protein by an *O*-glycosidic linkage[5] between *N*-acetyl-D-galactosamine and L-serine or L-threonine. Recently, Feizi and her co-workers[6] successfully characterized the structures of a series of oligosaccharides up to nona-*O*-sulfoglycodecaose released from keratan sulfate I of bovine cornea. Based upon these structural studies, a putative structure for keratan sulfate I may be depicted as **1** (Scheme 1). Synthetic experiments on keratan sulfate I may be directed toward structural units, such as a sulfated glycooligose **2** and a

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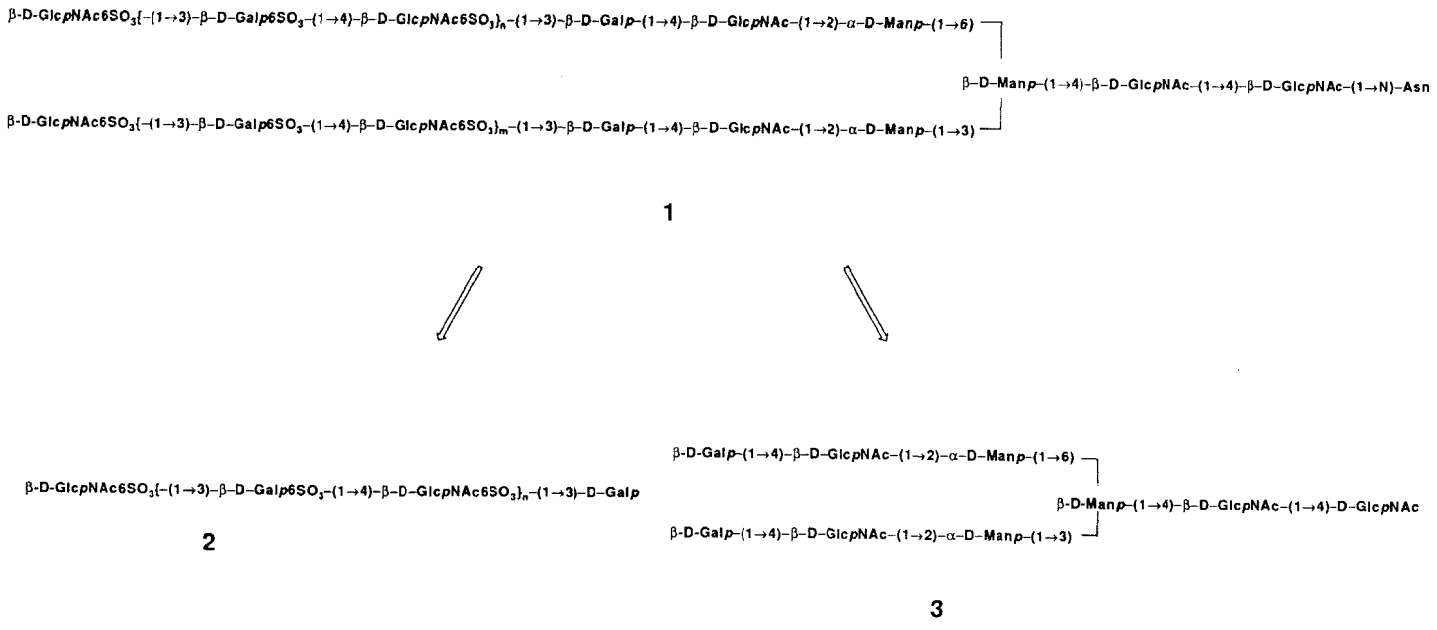
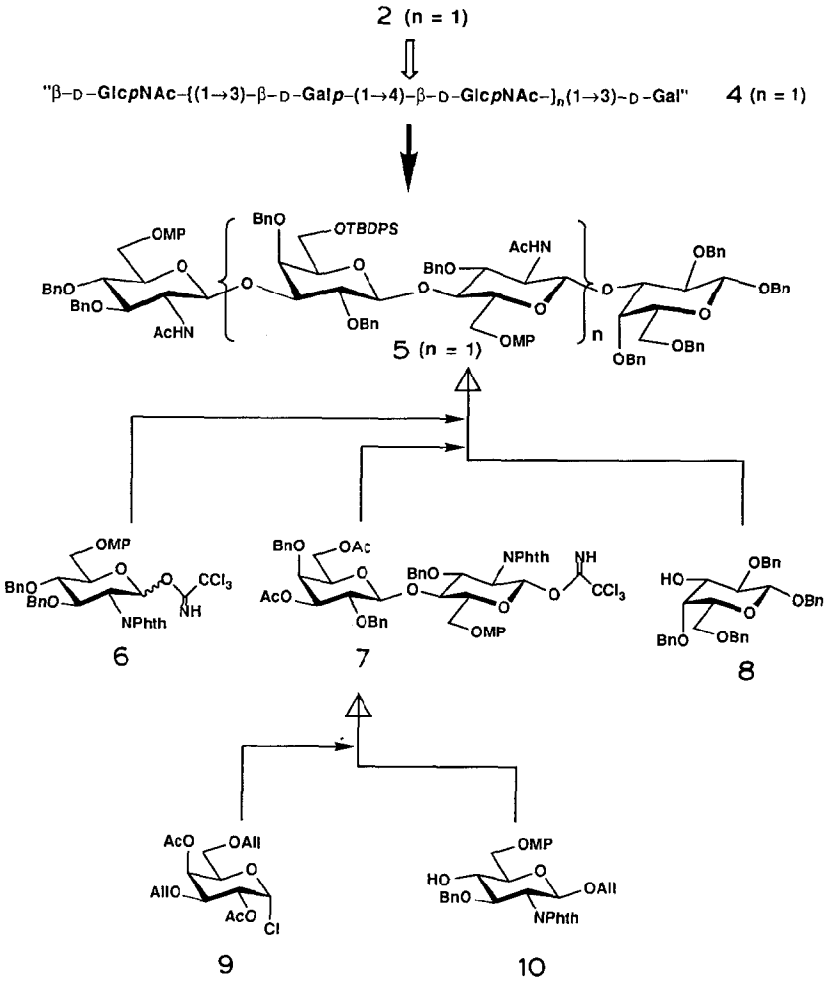

β-D-GlcpNAc6SO3{-(1→3)-β-D-Galp6SO3-(1→4)-β-D-GlcpNAc6SO3}n-(1→3)-β-D-Galp-(1→4)-β-D-GlcpNAc-(1→2)-α-D-Manp-(1→6)
β-D-Manp-(1→4)-β-D-GlcpNAc-(1→4)-β-D-GlcpNAc-(1→N)-Asn
β-D-GlcpNAc6SO3{-(1→3)-β-D-Galp6SO3-(1→4)-β-D-GlcpNAc6SO3}m-(1→3)-β-D-Galp-(1→4)-β-D-GlcpNAc-(1→2)-α-D-Manp-(1→3)
1
β-D-GlcpNAc6SO3{-(1→3)-β-D-Galp6SO3-(1→4)-β-D-GlcpNAc6SO3}n-(1→3)-D-Galp
2
β-D-Galp-(1→4)-β-D-GlcpNAc-(1→2)-α-D-Manp-(1→6)
β-D-Manp-(1→4)-β-D-GlcpNAc-(1→4)-D-GlcpNAc
β-D-Galp-(1→4)-β-D-GlcpNAc-(1→2)-α-D-Manp-(1→3)
3

Scheme 1.

neutral biantennary complex type glycan **3**. Since a synthetic approach to compound **3** had been described[7], a versatile route to acidic glycooligose **2** has now been undertaken[8].

RESULTS AND DISCUSSION

As the simplest target for our synthetic experiments, we chose tri-*O*-sulfoglycotetraose **2** (n = 1), for which a synthetic plan is outlined in Scheme 2. A fully protected glycotetraose **5** is designed as a direct precursor for compound **4** (n = 1), which is suitable for sulfation and subsequent deprotection. Compound **4** can be prepared by two successive glycosylations of a known glycosyl acceptor[9] **8**, first with a



Scheme 2

glycobisoyl donor **7**, and then with a glycosyl donor **6**. The glycobiosyl donor **7** can be prepared from a glycosyl donor[10] **9** and a glycosyl acceptor[11] **10**.

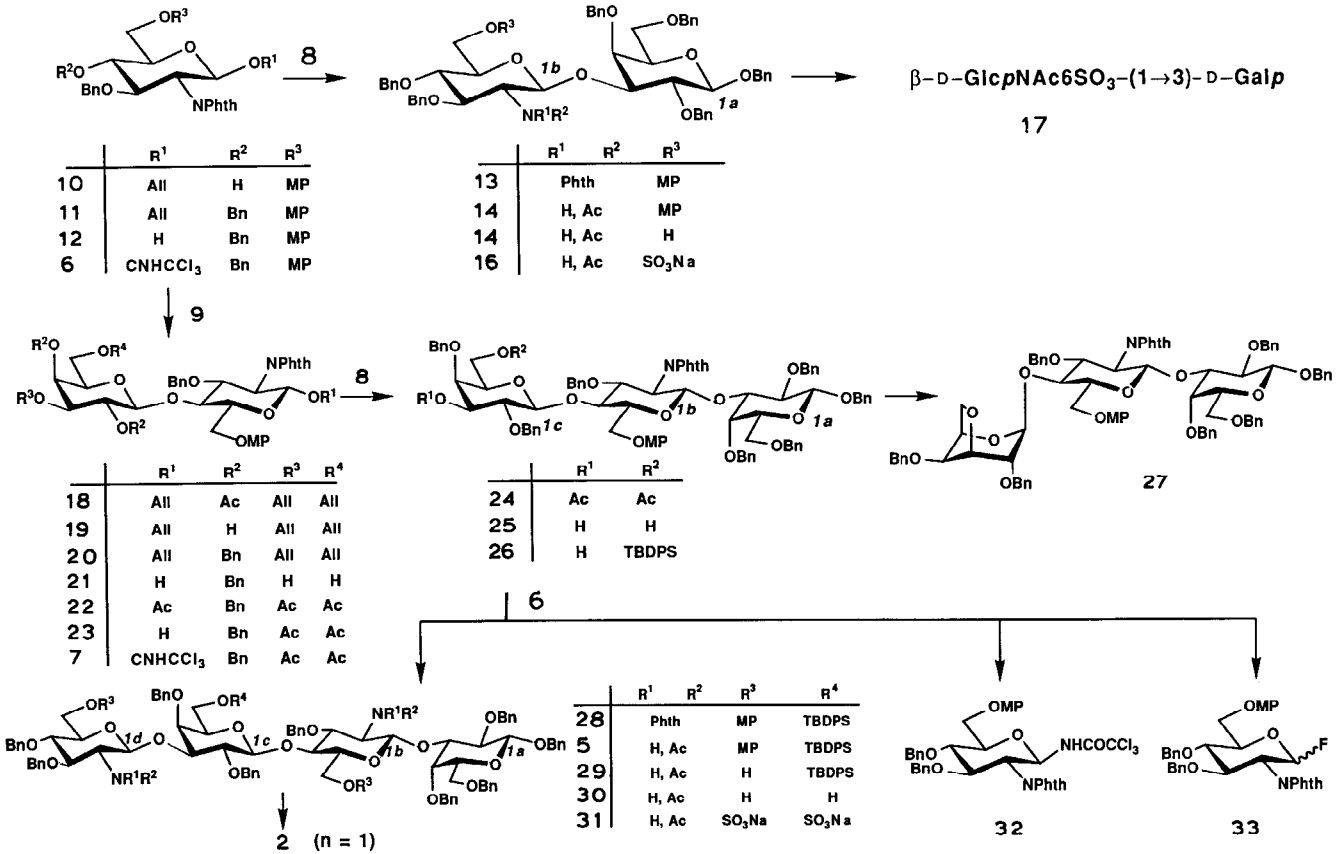
Glycosyl donor **6** was prepared from allyl glycoside **10** in three steps in 62% overall yield via compounds **11** and **12**: (*i*) benzyl bromide, silver(I) oxide and potassium iodide in DMF at 0°, (*ii*) tris(triphenylphosphine)rhodium(I) chloride and 1,4-diazabicyclo[2.2.2]octane (DABCO) in 7:3:1 ethanol–benzene–water under reflux, then mercury(II) oxide and mercury(II) chloride in 10% aq. acetone[12] at 20°, (*iii*) trichloroacetonitrile[13] and 1,8-diazabicyclo[5.4.0]undec-7-ene.

In order to determine both the reactivity of the imidate **6**, as well as the suitability of the chosen protective groups, transformation of compound **8** into sulfoglycobiose **17** was first examined (see Scheme 3). Coupling of the donor **6** with a glycosyl acceptor **8** was performed at $-30°$ to $-40°$ in the presence of boron trifluoride etherate[14] to give a 76% yield of the glycobioside **13**. The configuration of the newly introduced anomeric linkage at C-1b was assignable from the ^{1}H-n.m.r. data which showed a signal for H-1b as a doublet at δ 5.490 with a $^3J_{H,H}$ value of 8.6 Hz. Compound **13** was smoothly converted into monosulfoglycobiose **17** in 4 steps in 60% overall yield via compounds **14**, **15**, and **16**; (*i*) hydrazine hydrate in ethanol under reflux[15], then acetic anhydride and pyridine, (*ii*) ammonium cerium(IV) nitrate (CAN) in 10% aq. acetonitrile[16], (*iii*) sulfur trioxide–trimethylamine complex[17] in DMF at 50°, (*iv*) 10% palladium–carbon and H_2 in 9:1 methanol–water at 50°.

Having successfully prepared monosulfoglycobiose **17**, synthetic experiments toward the target trisulfoglycotetraose **2** were then undertaken. Silver triflate promoted glycosylation of a glycosyl acceptor **10** with a glycosyl donor **9** afforded a 92% yield of allyl glycobioside **18**. The configuration at C-1b in compound **18** was expected to be β-D by the presence in the glycosyl donor **9** of an *O*-2 acetyl group as an auxiliary capable of neighbouring group participation. The β-D configuration was confirmed by the ^{1}H-n.m.r. data which contained a doublet at δ 4.537 ($^3J_{H,H}$ 7.9 Hz) for H-1b. Deacetylation of compound **18** was successfully achieved by lithium hydroxide and hydrogen peroxide[18] in THF to give a 91% yield of the diol **19**. Benzylation of compound **19** with benzyl bromide in the presence of potassium iodide and silver(I) oxide afforded the product **20** in 90% yield. Subsequent stepwise deallylation of compound **20** was achieved as previously described to give the crude hemiacetal **21** that was directly acetylated to afford a 71% overall yield of the triacetate **22** as a mixture of β- and α-anomers in a ratio of 11:1. As a minor side product from this reaction sequence, a partially hydrogenated product, propyl *O*-(3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-3-*O*-benzyl-2-deoxy-6-*O*-*p*-methoxyphenyl-2-phthalimido-β-D-glucopyranoside, was isolated in 24% overall yield.

Chemoselective deacetylation of triacetate **22** was achieved by hydrazine acetate[19] in DMF to afford a 73% yield of the hemiacetal **23**, which was then smoothly converted into the imidate **7** in 87% yield. The β-D configuration at C-1a in compound **7** was confirmed by the ^{1}H-n.m.r. data that revealed a doublet at δ 6.443 ($^3J_{H,H}$ 8.4 Hz) for H-1a.

Boron trifluoride etherate promoted glycosylation of compound **8** with the



	R¹	R²	R³
10	All	H	MP
11	All	Bn	MP
12	H	Bn	MP
6	$CNHCCl_3$	Bn	MP

	R¹	R²	R³
13	Phth		MP
14	H, Ac		MP
14	H, Ac		H
16	H, Ac		SO_3Na

	R¹	R²	R³	R⁴
18	All	Ac	All	All
19	All	H	All	All
20	All	Bn	All	All
21	H	Bn	H	H
22	Ac	Bn	Ac	Ac
23	H	Bn	Ac	Ac
7	$CNHCCl_3$	Bn	Ac	Ac

	R¹	R²
24	Ac	Ac
25	H	H
26	H	TBDPS

	R¹	R²	R³	R⁴
28	Phth		MP	TBDPS
5	H, Ac		MP	TBDPS
29	H, Ac		H	TBDPS
30	H, Ac		H	H
31	H, Ac		SO_3Na	SO_3Na

Scheme 3.

imidate **7** gave a desired glycotrioside **24** in 83% yield. The configuration of newly introduced anomeric carbon C-1b was expected to be β-D due to the presence of the *N*-2 phthaloyl group[15] in the glycosyl donor which favors the formation of 1,2-*trans* stereochemistry. The β-D configuration was confirmed by the ^{1}H-n.m.r. data which showed a doublet at δ 5.478 ($^3J_{H,H}$ 8.2 Hz) for H-1b.

Deacetylation of compound **24** to diol **25**, followed by the subsequent Mitsunobu reaction [20] of **25** in the presence of *p*-methoxyphenol, triphenylphosphine, and diethyl azodicarboxylate, led to the quantitative isolation of the 3,6-anhydro derivative **27** instead of the desired product from the introduction of the *p*-methoxyphenyl group at *O*-6c. However, treatment of diol **25** with *tert*-butylchlorodiphenylsilane[21] and imidazole in DMF gave the monosilyl ether **26** in 78% yield. The crucial glycosylation of compound **26** with two equiv. of the imidate **6** was carried out in the presence of boron trifluoride etherate at −23° in 1,2-dichloroethane to afford a 48% yield of the desired glycotetraoside **28**, along with a 33% recovery of the unreacted glycosyl acceptor **26**. The configuration of the newly introduced anomeric center at C-1d of **28** was confirmed as β-D by its ^{1}H n.m.r. data, which contained two doublets at δ 5.435 and 5.266 ($^3J_{H,H}$ 8.2 Hz) for H-1b and H-1d, respectively. Due to the low reactivity of the hydroxy group at C-3c in compound **26**, the glycosyl donor **6**, which was employed in excess, was largely transformed into a rearranged trichloroacetamide **32** (48%), as well as into fluorides **33** (8%), which were shown to be a mixture of α and β anomers in a ratio of 1:1.2. It is to be noted that reaction of the same glycosyl donor **6**, under similar glycosylation conditions, proceeded quite smoothly with acceptor **8**. The different reactivity observed for the C-3 hydroxy groups of compounds **8** and **26** may be ascribed to a steric impediment in compound **26** that is most likely brought about by the unfavorable conformation of the 4-*O*-benzyl group, which, in turn is caused by the presence of the bulky 6-*O*-*tert*-butyldiphenylsilyl group, which was not present in compound **8**. Dephthaloylation of the glycotetraoside **28** and subsequent acetylation of the product afforded the key intermediate **5** in 63% yield.

Having prepared the key intermediate **5**, further conversion into the target compound **2** was achieved as follows. Removal of the *p*-methoxyphenyl group was achieved by oxidation with ammonium cerium(IV) nitrate[16] in aq. acetonitrile to give diol **29** in 75% yield. Subsequent desilylation of compound **29** by treatment with fluoride anion[22] in THF gave a 78% yield of the triol **30**, which was sulfated by the sulfur trioxide–trimethylamine complex to give a 93% yield of the tri-*O*-sulfoderivative **31**. The ^{13}C-n.m.r. spectrum of compound **31** in 1:1 $CDCl_3$–CD_3OD showed a similar low-field shift of the chemical shifts for three signals for C-6bcd that were observed at about δ 61 p.p.m. for compound **30**, indicating successful introduction of three sulfate groups at O-6bcd. Finally, hydrogenolysis of compound **30**, afforded the target compound **2** whose ^{1}H-n.m.r. spectral data taken in D_2O was found to be in good agreement with that[6] of the natural product, thus providing synthetic evidence for such structures as depicted in **2**.

In summary, a versatile synthetic route to the tri-*O*-sulfoglycotetraose **2**, a part structure of the acidic glycan chain for keratan sulfate I, was developed for the first time

in a regio- and stereo-controlled way. Since the synthetic route to the glycononaose **3** has already been established, it may be noted that further synthetic experiments directed toward an assembly of an acidic glycooligose **2** with a neutral complex type glycan **3** remain to be undertaken for the reconstruction of keratan sulfate I glycan **1**.

EXPERIMENTAL

General. — Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter, for solutions in $CHCl_3$ at 25°, unless noted otherwise. Column chromatography was performed on Silica Gel-60 (Merck 70–230 mesh ASTM). Flash chromatography was performed on columns of Wako Gel C-300 (200–300 mesh ASTM). T.l.c. and high-performance (h.p.) t.l.c. were carried out on Silica Gel-60 F_{254} (Merck). Molecular sieves were purchased from Nakarai Chemicals. N.m.r. spectra were recorded with either JEOL GX500 [^{1}H(500 MHz)] or FX90Q [^{13}C (22.50 MHz)] spectrometers. The values of δ_C and δ_H are expressed in p.p.m. downfield from the signal for internal Me_4Si, for solutions in $CDCl_3$, unless noted otherwise.

*Allyl 3,4-di-*O*-benzyl-2-deoxy-6-*O*-p-methoxyphenyl-2-phthalimido-β-*D*-glucopyranoside* (**11**). — To a solution of compound **10** (5.39 g, 9.88 mmol) in DMF (150 mL) were added successively at 0° Ag_2O (13.5 g, 58.3 mmol), benzyl bromide (10.1 g, 59.3 mmol), and KI (3.94 g, 23.7 mmol). After being stirred for 4 h at 0–20°, the reaction mixture was poured into ether (350 mL) and filtered through Celite. The filtrate was washed with water (300 mL), and the aqueous layer was back-extracted with ether (350 mL). The combined organic layers were washed with brine (300 mL) and dried ($MgSO_4$), and the solvent was evaporated. Chromatography of the residue on silica gel using 2:1 hexane–EtOAc afforded **11** (6.20 g, 99%): m.p. 54–55° (hexane–$CHCl_3$), $[\alpha]_D$ +50.0° (*c* 0.4), R_F 0.65 (1:2 hexane–EtOAc); ^{1}H-n.m.r. data: δ 3.771 (s, 3 H, OCH_3), 3.898 (dd, 1 H, *J* 8.7, 10.7 Hz, H-4), 3.974 (m, 1 H, CH_2–CH=CH_2), 4.128 (dd, 1 H, *J* 4.4, 10.4 Hz, H-6), 4.252 (dd, 1 H, *J* 8.4, 10.7 Hz, H-2), 4.402 (dd, 1 H, *J* 8.6, 10.6 Hz, H-3), 4.454 and 4.806 (2 d, 2 H, *J* 12.2 Hz, OCH_2Ph), 4.628 and 4.867 (2 d, 2 H, *J* 10.8 Hz, OCH_2Ph), 5.210 (d, 1 H, *J* 8.3 Hz, H-1), and 5.655 (m, 1 H, CH=CH_2).

Anal. Calc. for $C_{38}H_{37}NO_8 \cdot 0.05\ CHCl_3$: C, 71.22; H,5.82; N, 2.18. Found: C, 71.25; H, 5.85; N, 2.16

*3,4-Di-*O*-benzyl-2-deoxy-6-*O*-p-methoxyphenyl-2-phthalimido-*D*-glucopyranose* (**12**). — A solution of **11** (3.0 g, 4.72 mmol) in EtOH–PhH–H_2O (7:3:1, 250 mL) was heated under reflux for 1 h under Ar and then cooled to 20°. To this solution were added $(PPh_3)_3Rh(I)Cl$ (175 mg, 188 μmol) and DABCO (63 mg, 562 μmol). After heating the mixture under reflux for 4 h, additional $(PPh_3)_3Rh(I)Cl$ (174 mg, 188 μmol) and DABCO (64 mg, 571 μmol) were added, and the mixture was heated under reflux for an additional 4.5 h. After evaporation of the solvent, HgO (433 mg, 2.00 mmol) and $HgCl_2$ (10.3 g, 47.2 mmol) were added to a solution of the residue in 10% aq. acetone (210 mL). After being stirred for 2.5 h at 20°, the reaction mixture was poured into chloroform (1.0 L) and washed with water (1.0 L). The aqueous layer was extracted with chloroform (500 mL), and the combined organic layers were washed successively with 10% KI

solution (500 mL) and brine (500 mL) and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and chromatography of the residue on silica gel using 1:1 hexane–EtOAc afforded **12** (1.74 g, 62%): m.p. 176–178° (hexane–$CHCl_3$), $[\alpha]_D$ +87.1° (*c* 0.6); R_F 0.26 (1:1 hexane–EtOAc); ^{1}H-n.m.r. data: δ 3.740 (s, 2.4 H, OCH_3), 3.755 (s, 0.6 H, OCH_3), 5.023 (d, 0.2 H, $J_{1,OH}$ 3.7 Hz, O*H*), 5.374 (t, 0.2 H, *J* 3.7 Hz, H-1*α*), and 5.444 (t, 0.8 H, $J_{1,2;1,OH}$ 8.1 Hz, H-1*β*).

Anal. Calc. for $C_{35}H_{33}NO_8$: C, 70.58; H, 5.58; N, 2.35. Found: C, 70.45; H, 5.60; N, 2.35.

*3,4-Di-*O*-benzyl-2-deoxy-6-*O-p-*methoxyphenyl-2-phthalimido-β-*D*-glucopyranosyl trichloroacetimidate* (**6**). — Trichloroacetonitrile (848 mg, 5.88 mmol) and DBU (13 mg, 84 μmol) were added to a solution of **12** (91 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) at O°. After being stirred for 2 h at 0°, the mixture was carefully transferred onto the top of a column of silica gel and chromatographed using 2:1 hexane–EtOAc to give **6** (111 mg, 99%): $[\alpha]_D$ +73.7° (*c* 0.8); R_F 0.45 (1:1 hexane–EtOAc); ^{1}H-N.m.r. data: δ 3.762 (s, 3 H, OMe), 3.958 (ddd, 1 H, $J_{5,6'}$ 1.9, $J_{5,6}$ 3.5, $J_{4,5}$ 9.8 Hz, H-5), 4.201 (dd, 1 H, $J_{5,6}$ 3.5, $J_{6,6'}$ 10.7 Hz, H-6), 4.262 (dd, 1 H, $J_{5,6'}$ 1.9, $J_{6,6'}$ 10.7 Hz, H-6'), 4.501 and 4.845 (2 d, 2 H, *J* 12.3 Hz, OCH_2Ph), 4.678 and 4.893 (2 d, 2 H, *J* 10.8 Hz, OCH_2Ph), 6.453 (d, 1 H, $J_{1,2}$ 8.7 Hz, H-1), and 8.554 (s, 1 H, C=N*H*).

*Benzyl-*O*-(3,4-di-*O*-benzyl-2-deoxy-6-*O-p-*methoxyphenyl-2-phthalimido-β-*D*-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-β-*D*-galactopyranoside* (**13**). — To a mixture of **8** (237 mg, 439 μmol) and AW-300 molecular sieves (1.58 g) in $(ClCH_2)_2$ (8 mL), were added successively a solution of **6** (253 mg, 348 μmol) in $(ClCH_2)_2$ (2 mL) and a solution of BF_3·OEt_2 (59 μL, 0.40 mmol) in $(ClCH_2)_2$ (2 mL) at −30°. After being stirred for 2 h at −30°, the mixture was filtered through Celite. The filtrate was diluted with EtOAc (40 mL) and washed with aq. $NaHCO_3$ (40 mL). The aqueous layer was extracted with EtOAc (40 mL), and the combined organic layers were washed with brine (40 mL) and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and chromatography of the residue on silica gel using 15:1 toluene–EtOAc afforded recovered **8** (57 mg, 15%) and **13** (287 mg, 76% based on **6**): $[\alpha]_D$ +4.9° (*c* 0.4), R_F 0.60 (1:1 hexane–EtOAc); ^{1}H-n.m.r. data: δ 3.560 (dd, 1 H, $J_{1,2}$ 7.6, $J_{2,3}$ 9.9 Hz, H-2a), 3.704 (dd, 1 H, $J_{3,4}$ 3.0, $J_{2,3}$ 9.9 Hz, H-3a), 3.761 (s, 3 H, OCH_3), 3.909 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-4a), 4.291 (d, 1 H, *J* 7.9 Hz, H-1a), and 5.490 (d, 1 H, *J* 8.6 Hz, H-1b).

Anal. Calc. for $C_{69}H_{67}NO_{13}$·EtOAc: C, 72.68; H, 6.27; N, 1.16. Found: C, 72.76; H, 5.92; N, 1.39.

*Benzyl-*O*-(2-acetamido-3,4-di-*O*-benzyl-2-deoxy-6-*O-p-*methoxyphenyl-β-*D*-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-β-*D*-galactopyranoside* (**14**). — A mixture of **13** (103 mg, 92.4 μmol) and NH_2NH_2·H_2O (1.5 mL, 29 mmol) in ethanol (4.5 mL) was heated under reflux for 2 h. After evaporation of the solvent, the residue was dissolved in 1:1 pyridine–acetic anhydride (3 mL) and stirred for 1 h at 20°. The mixture was filtered to remove the precipitated white solid, and the filtrate was concentrated *in vacuo*. Residual volatiles were co-evaporated with toluene *in vacuo*, and chromatography of the residue on silica gel using 1:1 hexane–EtOAc afforded **14** (78 mg, 82%): m.p. 149–150° (EtOAc–hexane), $[\alpha]_D$ −14.1° (*c* 1.0), R_F 0.59 in 1:2 hexane–EtOAc; ^{1}H-n.m.r.

data: δ 1.478 (s, 3 H, COCH_3), 3.747 (s, 3 H, OCH_3), 3.872 (d, 1 H, $J_{3,4}$ 2.6 Hz, H-4a), 4.053 (dd, 1 H, $J_{5,6}$ 4.8, $J_{6,6'}$ 10.4 Hz, H-6b), 4.152 (dd, 1 H, $J_{5,6'}$ 2.0, $J_{6,6'}$ 10.4 Hz, H-6'b), and 4.406 (d, 1 H, J 7.9, H-1a).

Anal. Calc. for $C_{63}H_{67}NO_{12}$: C, 73.45; H. 6.55; N, 1.36. Found: C, 73.36; H, 6.59; N, 1.39.

Benzyl O-*(2-acetamido-3,4-di-*O*-benzyl-2-deoxy-β-*D*-glucopyranosyl)-(1→3)-2, 4,6-tri-*O*-benzyl-β-*D*-galactopyranoside* (**15**). — Ceric ammonium nitrate (CAN) (53 mg, 97 μmol) was added at 0° to a solution of **14** (50 mg, 48 μmol) in 10% aq. acetonitrile (10 mL). After stirring for 5 h at 0°, additional CAN (26 mg, 49 μmol) was added to the solution, and the mixture was stirred for 1 h at 0–20°. The reaction mixture was poured into EtOAc (40 mL) and washed with water (40 mL). The aqueous layer was extracted with EtOAc (40 mL), and the combined organic layers were washed with brine (40 mL) and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and chromatography of the residue on silica gel using 1:1 hexane–EtOAc afforded **15** (34 mg, 76%): m.p. 96–98° (hexane–$CHCl_3$), $[\alpha]_D$ −17.7° (*c* 0.9); R_F 0.43 (1:2 hexane–EtOAc); ^{1}H-n.m.r. data: δ 1.500 (s, 3 H, COCH_3), 4.420 (d, 1 H, J 7.6 Hz, H-1a), and 4.846 (d, 1 H, J 8.2 Hz, H-1b).

Anal. Calc. for $C_{56}H_{61}NO_{11}\cdot 0.14\ CHCl_3$: C, 71.65; H, 6.55; N, 1.49. Found: C, 71.64; H, 6.54; N, 1.76.

Benzyl O-*(2-acetamido-3,4-di-*O*-benzyl-2-deoxy-6-*O*-sulfo-β-*D*-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-β-*D*-galactopyranoside, sodium salt* (**16**). — To a solution of **15** (5.0 mg, 5.4 μmol) in DMF (0.2 mL) was added sulfur trioxide–trimethylamine complex (2.4 mg, 17 μmol), and the mixture was stirred for 22 h at 50°. Then additional sulfur trioxide–trimethylamine complex (2.4 mg, 17 μmol) was added, and after being stirred for 3 h at 50°, the mixture was diluted with 1:1 chloroform–methanol (3 mL). The solution was carefully transferred onto the top of a column of Sephadex LH-20 and eluted with 1:1 chloroform–methanol. The product was converted to the sodium salt by passing a solution of the compound in 1:1 methanol–water through a column of Dowex-50 (Na^+) resin to yield **16** (5.4 mg, 98%): m.p. 221–223° (toluene–hexane), $[\alpha]_D$ −15.2° (*c* 0.6), R_F 0.71 (3:1 $CHCl_3$–MeOH); ^{1}H-n.m.r. data (1:1 $CDCl_3$–CD_3OD): δ 1.641 (s, 3 H, COCH_3), 4.150 (d, 1 H, J 2.8 Hz, H-4a), 4.296 (dd, 1 H, $J_{5,6}$ 4.6, $J_{6,6'}$ 10.7 Hz, H-6b), 4.440 (dd, 1 H, $J_{5,6'}$ 1.7, $J_{6,6'}$ 10.8 Hz, H-6'b), and 4.461 (d, $J_{1,2}$ 7.6, H-1a).

Anal. Calc. for $C_{56}H_{60}NO_{14}SNa\cdot 0.5\ H_2O$: C, 64.98; H, 6.04; N, 1.35. Found: C, 64.83; H, 6.04; N, 1.66.

Deprotection of compound **16** *to give* **17**. — A mixture of **16** (5.4 mg, 5.2 μmol) and 10% Pd–C (6 mg) in 9:1 methanol–water (0.5 mL) was stirred for 24 h at 20° under H_2, at the end of which time, additional 10% Pd–C (7 mg) was added. After being stirred for an additional 42 h at 50° under H_2, the mixture was filtered through Celite, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on Sephadex G-10 using water. Further purification of the product was carried out by chromatography on Biogel P-4 using water to give **17** (2.5 mg, 98%): $[\alpha]_D$ +10.5° (*c* 0.2, H_2O), R_F 0.13 (6:5:1 BuOH–Acetone–H_2O); ^{1}H-n.m.r. data (D_2O): δ 2.033 (s, 3 H, COCH_3), 4.558 (d, 0.75 H, J 8.3 Hz, H-1a), 4.702 (d, J 8.6 Hz, H-1b), 4.723 (d, J 8.6 Hz, H-1b), and 5.222 (d, 0.25 H, J 3.3 Hz, H-1a).

Allyl O-*(2,4-di*-O-*acetyl-3,6-di*-O-*allyl-β*-D-*galactopyranosyl)-(1→4)-3*-O-*benzyl-2-deoxy-6*-O-p-*methoxyphenyl-2-phthalimido-β*-D-*glucopy* ranoside (**18**). — To a stirred mixture of **10** (1.09 g, 1.99 mmol), $AgOSO_3CF_3$ (1.02 g, 3.98 mmol), and 4A molecular sieves (6.0 g) in $(ClCH_2)_2$ (25 mL) was added at −10° under Ar a solution of **9** (1.20 g, 3.31 mmol). After being stirred for 18 h at −10–20°, the mixture was filtered through Celite, and the filtrate was diluted with EtOAc (50 mL), washed with aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography of the residue on silica gel using 2:1 hexane–EtOAc afforded **18** (1.6 g, 92%): m.p. 55–56° (hexane–$CHCl_3$), $[\alpha]_D$ +40.1° (*c* 0.9), R_F 0.22 (3:2 hexane–EtOAc); ^{1}H-n.m.r. data: δ 2.042 and 2.060 (2 s, 6 H, $COCH_3 \times 2$), 3.785 (s, 3 H, OCH_3), 4.462 and 4.869 (2 d, 2 H, *J* 12.3 Hz, CH_2Ph), 4.537 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1b), 5.184 (d, 1 H, $J_{1,2}$ 8.5 Hz, H-1a), and 5.380 (d, 1 H, $J_{3,4}$ 2.4 Hz, H-4b).

Anal. Calc. for $C_{47}H_{53}NO_{15}$: C, 64.74; H, 6.13; N, 1.61. Found: C, 64.52; H,6.26; N, 1.59.

Allyl O-*(3,6-di*-O-*allyl-β*-D-*galactopyranosyl)-(1→4)-3*-O-*benzyl-2-deoxy-6*-O-p-*methoxyphenyl-2-phthalimido-β*-D-*glucopyranoside* (**19**). — To a stirred solution of **18** (2.08 g, 2.39 mmol) in THF (45 mL) were added at 0° 1.25M LiOH (6 mL, 7.5 mmol) and 31% aq. H_2O_2 (17 mL). After stirring for 13 h at 0°, the reaction mixture was diluted with EtOAc (100 mL) and washed with H_2O (60 mL). The aqueous layer was extracted with EtOAc (100 mL), and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography of the residue on silica gel using 3:2 hexane–EtOAc afforded **19** (1.71 g, 91%): m.p. 55–57° ($CHCl_3$–hexane–Et_2O), $[\alpha]_D$ +42.5° (*c* 1.3), R_F 0.39 (1:2 hexane–EtOAc); ^{1}H-n.m.r. data: δ 3.777 (s, 3 H, OCH_3), 4.438 (d, 1 H, *J* 7.9 Hz, H-1b), 4.457 and 4.860 (2 d, 2 H, *J* 12.4 Hz, CH_2Ph), 5.201 (d, 1 H, *J* 8.2 Hz, H-1a), 5.654, 5.827 and 5.903 (3 m, 3 H, $CH=CH_2 \times 3$).

Anal. Calc. for $C_{43}H_{49}NO_{13}$: C, 65.55; H, 6.27; N, 1.78. Found: C, 65.31; H, 6.32; H, 1.76.

Allyl O-*(3,6-di*-O-*allyl-2,4-di*-O-*benzyl-β*-D-*galactopyranosyl)-(1→4)-3*-O-*benzyl-2-deoxy-6*-O-p-*methoxyphenyl-2-phthalimido-β*-D-*glucopyranoside* (**20**). — To a cooled solution of **19** (1.01 g, 1.28 mmol) in DMF (20 mL) were successively added at 0° benzyl bromide (1.9 mL, 15 mmol), Ag_2O (3.49 g, 15.1 mmol), and KI (1.03 g, 6.23 mmol). After being stirred for 5 h at 0–20°, the reaction mixture was poured into ether (50 mL) and filtered through Celite. The filtrate was washed with H_2O (50 mL), and the aqueous layer was extracted with ether (50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography of the residue on silica gel using 4:1 hexane–EtOAc afforded **20** (1.11 g, 90%): $[\alpha]_D$ +32.7° (*c* 0.5), R_F 0.37 (3:2 hexane–EtOAc); ^{1}H-n.m.r. data: δ 3.748 (s, 3 H, OCH_3), 3.800 (d, 1 H, $J_{3,4}$ 2.5 Hz, H-4b), 4.346 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1b), 4.479 and 4.894 (2 d, 2 H, *J* 11.9 Hz, CH_2Ph), 4.540 and 4.913 (2 d, 2 H, *J* 11.9 Hz, CH_2Ph), 4.793 and 4.864 (2 d, 2 H, *J* 11.0 Hz, CH_2Ph), 5.197 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1a), 5.662, 5.791, and 5.873 (3 m, 3 H, $CH=CH_2 \times 3$).

O-(3,6-Di-O-acetyl-2,4-di-O-benzyl-β-D-galactopyranosyl)-(1→4)-3-O-benzyl-2-deoxy-6-O-p-methoxyphenyl-2-phthalimido-β- and α-D-glucopyranosyl acetate (**22** *and its α-anomer), and propyl O-(3,6-di-O-acetyl-2,4-di-O-benzyl-β-D-galactopyranosyl)-(1→4)-3-O-benzyl-2-deoxy-6-O-p-methoxyphenyl-2-phthalimido-β-D-glucopyranoside.* — A solution of **20** (49 mg, 50 μmol) in 7:3:1 EtOH–PhH–H_2O (2.8 mL) was heated under reflux for 1 h under Ar, then cooled to 20°. To the solution were added $(PPh_3)_3Rh(I)Cl$ (6 mg, 6μmol) and DABCO (2 mg, 0.02 mmol), and after refluxing for 16 h under Ar, the solvent was evaporated. To a solution of the residue in 10:1 acetone–water (2.2 mL), were added HgO (5 mg, 0.02 mmol) and $HgCl_2$ (138 mg, 0.67 mmol), and after being stirred for 1 h, the reaction mixture was poured into chloroform (20 mL) and washed with water (20 mL). The aqueous layer was extracted with chloroform (20 mL) and EtOAc (20 mL), and the combined organic layers were washed with 10% aq. KI (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*.

The residue and a catalytic amount of DMAP was dissolved in 1:1 acetic anhydride–pyridine (1.5 mL) and stirred for 1 h at 20°. After evaporation of the solvent and coevaporation of the volatiles with toluene, the residue was chromatographed on silica gel using 2:1 hexane–EtOAc to afford **22** (35 mg, 71%, $\alpha:\beta$ = 1:11) and propyl glycoside (12 mg, 24%). Analytical samples for **22** and its α-anomer were obtained by rechromatography of the products under the same conditions as those in the foregoing.

Compound **22** had m.p. 153–154° ($CHCl_3$–Et_2O), $[\alpha]_D$ +41.7° (*c* 0.4); R_F 0.26 (1:1 hexane–EtOAc); ^{1}H-n.m.r. data: δ 1.928, 1.940, and 1.993 (3 s, 9 H, $COCH_3$ × 3), 3.766 (s, 3 H, OCH_3), 4.413 (d, 1 H, *J* 7.9 Hz, H-1b), 4.654 (dd, 1 H, $J_{3,4}$ 3.2, $J_{2,3}$ 10.2 Hz, H-3b), and 6.320 (d, 1 H, $J_{1,2}$ 8.9 Hz, H-1a).

Anal. Calc. for $C_{54}H_{55}NO_{16}$: C, 66.59; H, 5.59; N, 1.44. Found: C, 66.93; H, 5.71; N, 1.48.

The α-anomer of **22** had m.p. 55–57° ($CHCl_3$–hexane), $[\alpha]_D$ +56.1° (*c* 1.5), R_F 0.28 (1:1 hexane–EtOAc); ^{1}H-n.m.r. data: δ 1.931, 1.951, and 2.097 (3 s, 9 H, $COCH_3$ × 3), 3.773 (s, 3 H, OCH_3), 4.591 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 11.4 Hz, H-2a), 4.692 (dd, 1 H, $J_{3,4}$ 3.1, $J_{2,3}$ 10.1 Hz, H-3b), 5.085 (dd, 1 H, $J_{3,4}$ 9.2, $J_{2,3}$ 11.4 Hz, H-3a), and 6.270 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1a).

Anal. Calc. for $C_{54}H_{55}NO_{16}$: C, 66.59; H, 5.69; N, 1.44. Found: C, 66.13; H, 5.66; N, 1.44.

The propyl glycoside had $[\alpha]_D$ +32.9° (*c* 0.4), R_F 0.30 (1:1 hexane–EtOAc); ^{1}H-n.m.r. data: δ 1.002 (t, 3 H, *J* 7.2 Hz, $CH_2CH_2CH_3$), 1.929, 1.986 (2 s, 6 H, $COCH_3$ × 2), 3.768 (s, 3 H, OCH_3), 4.439 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1b), and 5.176 (d, 1 H, $J_{1,2}$ 8.5 Hz, H-1a).

Anal. Calc. for $C_{55}H_{59}NO_{15}$: C, 67.82; H, 6.10; N, 1.44. Found: C, 67.54; H, 5.98; N, 1.51.

O-(3,6-Di-O-acetyl-2,4-di-O-benzyl-β-D-galactopyranosyl)-(1→4)-3-O-benzyl-2-deoxy-6-O-p-methoxyphenyl-2-phthalimido-D-glucopyranose (**23**). — A solution of **22** (418 mg, 429 μmol) and NH_2NH_2·AcOH (47 mg, 0.51 mmol) in DMF (5 mL) was stirred for 10 min at 50°, at the end of which time, additional NH_2NH_2·AcOH (46 mg, 0.50 mmol) was added. After being stirred for an additional 10 min at 50°, the mixture was

diluted with EtOAc (100 mL) and washed with 10% aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with EtOAc (100 mL), and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography of the residue on silica gel using 3:1 hexane–EtOAc afforded **23** (291 mg, 73%): $[\alpha]_D$ +49.3° (*c* 0.5), R_F 0.18 and 0.23 (1:1 hexane–EtOAc). ^{1}H-n.m.r. data: δ 1.931 and 1.979 (2 s, 4 H, $COCH_3$ × 2), 1.943 and 1.966 (2 s, 2 H, $COCH_3$ × 2), 3.754 (s, 2 H, OCH_3), 3.767 (s, 1 H, OCH_3), 5.297 (d, 0.33 H, $J_{1,2}$ 3.5 Hz, H-1a), and 5.378 (d, 0.67 H, $J_{1,2}$ 8.8 Hz, H-1a).

Anal. Calc. for $C_{52}H_{53}NO_{15}$: C, 67.01; H, 5.73; N, 1.50. Found: C, 66.77; H, 5.75; N, 1.53.

Conversion of compound **23** *to* O-*(3,6-di*-O-*acetyl-2,4-di*-O-*benzyl-β*-D-*galactopyranosyl-(1→4)-3*-O-*benzyl-2-deoxy-6*-O-p-*methoxyphenyl-2-phthalimido-β*-D-*glucopyranosyl trichloroacetimidate* **7**. — To a stirred solution of **23** (100 mg, 0.11 mmol) in dichloromethane (2 mL) were successively added at 0° Cl_3CCN (387 mg, 2.68 mmol) and DBU (8 mg, 0.05 mmol). After being stirred for 3.5 h at 0°, the reaction mixture was directly chromatographed on silica gel using 2:1 hexane–EtOAc to give trichloroacetimidate **7** (101 mg, 87%): $[\alpha]_D$ +57.9° (*c* 0.5); R_F 0.34 (1:1 hexane–EtOAc); ^{1}H-n.m.r. data: δ 1.939, 2.002 (2 s, 6 H, $COCH_3$ × 2), 3.765 (s, 3 H, OCH_3), 6.443 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1a), and 8.535 (s, 1 H, C=N*H*).

Benzyl O-*(3,6-di*-O-*acetyl-2,4-di*-O-*benzyl-β*-D-*galactopyranosyl)-(1→4)*-O-*(3*-O-*benzyl-2-deoxy-6*-p-*methoxyphenyl-2-phthalimido-β*-D-*glucopyranosyl)-(1→3)-2,4,6-tri*-O-*benzyl-β*-D-*galactopyranoside* (**24**). — To a stirred mixture of **8** (1.825 g, 3.38 mmol) and AW-300 molecular sieves (21.2 g) in 1,2-dichloroethane (80 mL) were successively added a solution of **7** (2.02 g, 1.88 mmol) in 1,2-dichloroethane (30 mL) and a solution of $BF_3{\cdot}OEt_2$ (0.4 mL, 2.7 mmal) in 1,2-dichloroethane (10 mL) at −25° to −30° under Ar. After being stirred for 2 h at −25 to −30°, the mixture was filtered through Celite, and the filtrate was diluted with EtOAc (350 mL) and washed with 1% aq. $NaHCO_3$ (300 mL). The aqueous layer was extracted with EtOAc (300 mL), and the combined organic layers were washed with brine (300 mL), dried ($MgSO_4$), and evaporated *in vacuo*. Chromatography of the residue on silica gel using in 3:1 hexane–EtOAc afforded **24** (2.26 g, 83% based on **7**): m.p. 56–58° (CH_3OH); $[\alpha]_D$ +9.1° (*c* 0.7); R_F 0.43 (1:1 hexane–EtOAc); ^{1}H-n.m.r. data: δ 1.943 and 1.954 (2 s, 6 H, $COCH_3$ × 2), 3.748 (s, 3 H, OCH_3), 3.801 (d, 1 H, $J_{3,4}$ 2.0 Hz) and 3.878 (d, 1 H, $J_{3,4}$ 2.4 Hz, H-4ac), 4.706 (dd, 1 H, $J_{3,4}$ 3.6, $J_{2,3}$ 9.8 Hz, H-3c), 5.478 (d, 1 H, *J* 8.2 Hz, H-1b), and 8.70–6.70 (m, 43 H, aromatic).

Anal. Calc. for $C_{86}H_{87}NO_{20}$: C, 71.01; H, 6.03; N, 0.96. Found: C, 71.17; H, 6.13; N, 1.04.

Benzyl-O-*(2,4-di*-O-*benzyl-β*-D-*galactopyranosyl)-(1→4)*-O-*(3*-O-*benzyl-2-deoxy-6*-O-p-*methoxyphenyl-2-phthalimido-β*-D-*glucopyranosyl)-(1→3)-2,4,6-tri*-O-*benzyl-β*-D-*galactopyranoside* (**25**). — *Procedure A*. To a stirred solution of **24** (77 mg, 53 μmol) in THF (1.2 mL) were added successively 1.25M aq. LiOH (0.11 mL, 88 μmol) and 31% aq. H_2O_2 (0.40 mL) at 0°. After being stirred for 34 h at 0°, the mixture was poured into EtOAc (40 mL) and washed with water (40 mL). The aqueous layer was extracted

with EtOAc (40 mL), and the combined organic layers were washed with brine (40 mL) and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and chromatography of the residue on silica gel using 2:1 hexane–EtOAc afforded **25** (66 mg, 90%).

Procedure B. To a stirred solution of **24** (709 mg, 487 μmol) in MeOH (10 mL) was added 0.1M NaOMe–MeOH solution (5 mL) at 20°. After being stirred for 2.5 h, the mixture was neutralised with Amberlyst-15 (H^+) resin. After removal of the resin by filtration, the filtrate was concentrated to dryness. Chromatography of the residue on silica gel in using 1:1 hexane–EtOAc afforded **25** (616 mg, 92%): $[\alpha]_D$ −3.7° (*c* 0.6); R_F 0.49 (1:2 hexane–EtOAc); n.m.r. data: δ_H 3.630 (d, 1 H, $J_{3,4}$ 3.4 Hz) and 3.878 (d, 1 H, $J_{3,4}$ 2.4 Hz, H-4ac), 3.742 (s, 3 H, OCH_3), 4.298 (d, 1 H, $J_{1,2}$ 7.6 Hz) and 4.348 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1ac), and 5.500 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1b); δ_C 55.7 and 56.3 (OCH_3 and C-2b), 61.9 (C-6c), 99.7 ($^1J_{C,H}$ 166.0 Hz, C-1b), 102.6 ($^1J_{C,H}$ 157.0 Hz, C-1a), and 103.3 ($^1J_{C,H}$ 160.0 Hz, C-1c).

Anal. Calc. for $C_{82}H_{83}NO_{18}$: C, 71.86; H, 6.10; N, 1.02. Found: C, 71.42; H, 6.11; N, 0.99.

Benzyl O-(*2,4-di*-O-*benzyl-6*-O-tert-*butyldiphenylsilyl-β*-D-*galactopyranosyl*)-(*1→4*)-O-(*3*-O-*benzyl-2-deoxy-6*-O-p-*methoxyphenyl-2-phthalimido-β*-D-*glucopyranosyl*)-(*1→3*)-*2,4,6-tri*-O-*benzyl-β*-D-*galactopyranoside* (**26**). — To the stirred mixture of *tert*-butylchlorodiphenylsilane (TBDPSCl) (0.11 mL, 0.41 mmol) and imidazole (32 mg, 047 mmol) in DMF (5 mL) was added a solution of **25** (378 mg, 274 μmol) in DMF (5 mL) at 20°. After stirring for 24 h, the mixture was poured into ether (200 mL) and washed with water (200 mL). The aqueous layer was extracted with ether (200 mL × 2), and the combined organic layers were washed with brine (150 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by silica gel column chromatography using 8:3 hexane–EtOAc to give **26** (344 mg, 78%): $[\alpha]_D$ −0.2° (*c* 1.1), R_F 0.65 (1:2 hexane–EtOAc); ^{1}H-n.m.r. data: δ 1.018 (s, 9 H, $C(CH_3)_3$), 3.757 (s, 3 H, OCH_3), 3.861 (d, 1 H, $J_{3,4}$ 2.4 Hz), 3.944 (d, 1 H, $J_{3,4}$ 3.1 Hz, 4ac), and 5.453 (d, 1 H, $J_{1,2}$ 8.5 Hz, H-1b).

Anal. Calc. for $C_{98}H_{101}NO_{18}Si \cdot 0.75$ EtOAc: C, 72.42; H, 6.44; N, 0.84. Found: C, 72.45; H, 6.31; N, 0.79.

Benzyl O-(*3,6-anhydro-2,4-di*-O-*benzyl-β*-D-*galactopyranosyl*)-(*1→4*)-O-(*3*-O-*benzyl-2-deoxy-6*-O-p-*methoxyphenyl-2-phthalimido-β*-D-*glucopyranosyl*)-(*1→3*)-*2,4,6-tri*-O-*benzyl-β*-D-*galactopyranoside* (**27**). — To a solution of *p*-methoxyphenol (37 mg, 0.30 mmol), triphenylphosphine (79 mg, 0.30 mmol), and **25** (136 mg, 99 μmol) in dichloromethane (5 mL) was added dropwise diethyl azodicarboxylate (53 mg, 0.30 mmol) in dichloromethane (1.5 mL) at 0° under Ar. After being stirred for 21 h at 0–20°, the reaction mixture was diluted with dichloromethane (50 mL) and washed with ice-water (50 mL). The aqueous layer was extracted with dichloromethane (50 mL), and the combined organic layers were washed with brine (50 mL), and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and chromatography of the residue on silica gel using 1:1 hexane–EtOAc afforded **27** (135 mg, quantitative): m.p. 40–41° (EtOAc), $[\alpha]_D$ −17.4° (*c* 1.0): R_F 0.43 (1:1 hexane–EtOAc); n.m.r. data: δ_H 3.731 (s, 3 H, OCH_3), 3.895 (d, 1 H, $J_{3,4}$ 3.1 Hz, H-4a), 5.015 (s, 1 H, H-1c), and 5.478 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1b); δ_C

55.7 (C-2b and OCH_3), 99.7 ($^1J_{C,H}$ 166 Hz, C-1b), 101.3 ($^1J_{C,H}$ 166 Hz, C-1c), and 102.6 ($^1J_{C,H}$ 158 Hz, C-1a).

Anal. Calc. for $C_{82}H_{81}NO_{17}$·0.5 EtOAc: C, 72.24; H, 6.13; N, 1.00. Found: C, 72.02; H, 6.12; N, 1.06.

Benzyl-O-(*3,4-di*-O-*benzyl-2-deoxy-6*-O-p-*methoxyphenyl-2-phthalimido-β*-D-*glucopyranosyl*)-(*1→3*)-*O*-(*2,4-di*-O-*benzyl-6*-O-tert-*butyldiphenylsilyl-β*-D-*galacto-pyranosyl*)-(*1→4*)-O-(*3*-O-*benzyl-2-deoxy-6*-O-p-*methoxyphenyl-2-phthalimido-β*-D-*glucopyranosyl*-(*1→3*)-*2,4,6-tri*-O-*benzyl-β*-D-*galactopyranoside* (**28**). — To a stirred solution of **26** (344 mg, 214 μmol) and AW-300 molecular sieves (2.1 g) in 1,2-dichloroethane (20 mL) were added successively a solution of **6** [prepared from **12** (302 mg, 506 μmol) in 1,2-dichloroethane (10 mL)] and BF_3·EtO_2 (15 μL, 0.1 mmol) at −23° under Ar. After being stirred for 1.5 h at −23° to −25°, the mixture was filtrated through Celite. The filtrate was diluted with EtOAc (200 mL), then washed with 1% aq. $NaHCO_3$ (200 mL). The aqueous layer was extracted with EtOAc (200 mL), and the combined organic layers were washed with brine (150 mL) and dried ($MgSO_4$). The solvent was then evaporated *in vacuo*. Purification of the residue by silica gel column chromatography using 15:1 $PhCH_3$–EtOAc and p.t.l.c. in 7:1 $PhCH_3$–EtOAc, afforded **28** (225 mg, 48%; 72% based on the consumed **26**; recovered **26** (114 mg, 33%), **32** (176 mg, 48% based on **12**), **33** (24 mg, 8% as a mixture of α and β anomers in a ratio of 1:1.2, based on **12**), and recovered **12** (58 mg, 20%).

Compound **28** had $[\alpha]_D$ −4.4° (*c* 0.9); R_F 0.57 (5:1 $PhCH_3$–EtOAc); N.m.r. data: δ_H 0.838 (s, 9 H, $C(CH_3)_3$), 3.704 and 3.789 (2 s, 6 H, OCH_3 × 2), 5.266 (d, 1 H, *J* 8.2 Hz, H-1d), and 5.435 (d, 1 H, *J* 8.2 Hz, H-1b); δ_C 99.3 ($^1J_{C,H}$ 162 Hz, C-1d), 99.8 ($^1J_{C,H}$ 166 Hz, C-1b), 102.6 ($^1J_{C,H}$ 156 Hz, C-1a), and 102.9 ($^1J_{C,H}$ 159 Hz, C-1c).

Anal. Calc. for $C_{133}H_{132}N_2O_{25}Si$·1.4 EtOAc: C, 72.06; H, 6.24; N, 1.21. Found: C, 71.82; H, 5.89; N, 1.34.

Compound **32** had m.p. 127–129° ($CHCl_3$–hexane); $[\alpha]_D$ +57.4° (*c* 0.6); R_F 0.23 (15:1 $PhCH_3$–EtOAc); ^{1}H-n.m.r. data: δ 3.779 (s, 3 H, OCH_3), 3.909 (ddd, 1 H, $J_{5,6}$ 1.7, $J_{5,6'}$ 3.1, and $J_{4,5}$ 10.2 Hz, H-5), 4.005 (t, 1 H, $J_{3,4}$ 9.3 Hz, H-4), 4.188 (dd, 1 H, $J_{5,6'}$ 3.1, $J_{6,6'}$ 10.7 Hz, H-6'), 4.254 (dd, 1 H, $J_{5,6}$ 1.8 Hz, $J_{6,6'}$ 10.7 Hz, H-6), 4.287 (t, 1 H, $J_{1,2}=J_{2,3}$ 10.1 Hz, H-2), 4.511 and 4.863 (2 d, 2 H, *J* 12.1 Hz, CH_2Ph), 4.651 and 4.877 (2 d, 2 H, *J* 10.7 Hz, CH_2Ph), 4.746 (dd, 1 H, $J_{3,4}$ 8.5, $J_{2,3}$ 10.5 Hz, H-3), and 5.771 (t, 1 H, $J_{1,2}=J_{1,NH}$ 9.6 Hz, H-1).

Anal. Calc. for $C_{37}H_{33}Cl_3N_2O_8$· 0.1 C_6H_{14}: C, 60.32; H, 4.63; N, 3.74. Found: C, 60.72; H, 4.62; N, 3.63.

Compound **33α** had $[\alpha]_D$ +76.3° (*c* 0.5); R_F 0.38 (15:1 $PhCH_3$–EtOAc); ^{1}H-n.m.r. data: δ 3.781 (s, 3 H, OCH_3), 4.016 (t, 1 H, $J_{3,4}=J_{4,5}$ 9.4 Hz, H-4), 4.193 (dd, 1 H, $J_{5,6'}$ 2.1, $J_{6,6'}$ 10.7 Hz, H-6'), 4.229 (dd, 1 H, $J_{5,6}$ 3.1, $J_{6,6'}$ 10.7 Hz, H-6), 4.290 (td, 1 H, $J_{5,6'}=J_{5,6}=2.5$, $J_{4,5}$ 10.1 Hz, H-5), 4.523 (ddd, 1 H, $J_{1,2}$ 2.9, $J_{2,3}$ 11.1, $^3J_{H,F}$ 30.5 Hz, H-2), 4.635 and 4.934 (2 d, 2 H, *J* 11.9 Hz, CH_2Ph), 4.647 and 4.873 (2 d, 2 H, *J* 10.1 Hz, CH_2Ph), 5.227 (dd, 1 H, $J_{3,4}$ 9.2, $J_{2,3}$ 11.0 Hz, H-3), and 5.643 (dd, 1 H, $J_{1,2}$ 2.9, $^2J_{H,F}$ 53.6 Hz, H-1).

Compound **33β** had m.p. 88–90° (EtOAc–toluene); $[\alpha]_D$ +56.8° (*c* 0.6); R_F 0.24

(15:1 $PhCH_3$–EtOAc); ^{1}H-n.m.r. data: δ 3.779 (s, 3 H, OCH_3), 3.887 (bd, 1 H, $J_{4,5}$ 10.0 Hz, H-5), 3.987 (dd, 1 H, $J_{3,4}$ 8.5, $J_{4,5}$ 10.1 Hz, H-4), 4.159 (dd, 1 H, $J_{5,6}$ 3.6, $J_{6,6'}$ 10.7 Hz, H-6), 4.222 (dd, 1 H, $J_{5,6'}$ 1.8, $J_{6,6'}$ 10.7 Hz, H-6'), 4.337 (ddd, 1 H, $J_{1,2}$ 7.9, $J_{2,3}$ 10.8, $^3J_{H,F}$ 12.5 Hz, H-2), 4.439 (dd, 1 H, $J_{3,4}$ 8.7, $J_{2,3}$ 10.8 Hz, H-3), 4.464 and 4.823 (2 d, 2 H, J 12.2 Hz, CH_2Ph), 4.666 and 4.886 (2 d, 2 H, J 11.0 Hz, CH_2Ph), and 5.912 (dd, 1 H, $J_{1,2}$ 7.8, $^2J_{H,F}$ 50.3 Hz, H-1).

Benzyl- O-(*2-acetamido-3,4-di*-O-*benzyl-2-deoxy-6*-O-p-*methoxyphenyl-β*-D-*glucopyranosyl*)-(*1→3*)-O-(*2,4-di*-O-*benzyl-6*-O-tert-*butyldiphenylsilyl-β*-D-*galactopyranosyl*)-(*1→4*)-O-(*2-acetamido-3*-O-*benzyl-2-deoxy-6*-O-p-*methoxyphenyl-β*-D-*glucopyranosyl*)-(*1→3*)-*2,4,6-tri*-O-*benzyl-β*-D-*galactopyranoside* (**5**). — A mixture of **28** (107 mg, 52.9 μmol) and $NH_2NH_2 \cdot H_2O$ (1.54 mL, 31.7 mmol) in EtOH (10 mL) was heated under reflux for 3 h. After evaporation of the solvent, the residue was dissolved in 1:1 pyridine–acetic anhydride (6 mL). After being stirred for 23 h at 20°, the solvent was evaporated, and the residual volatiles were co-evaporated with toluene and ethanol *in vacuo*. Chromatography of the residue on silica gel using 10:1, and then 3:1 $PhCH_3$–EtOAc, afforded **5** (62 mg, 63%): $[\alpha]_D$ −6.4° (*c* 0.3); R_F 0.78 (3:1 $PhCH_3$–acetone); n.m.r. data: δ_H 0.884 (s, 9 H, $C(CH_3)_3$), 1.382 and 1.438 (2 s, 6 H, $COCH_3$ × 2), 3.715, 3.737 (2 s, 6 H, OCH_3 × 2), and 7.55–6.65 (m, 63 H, aromatic); δ_C 101.7 ($^1J_{C,H}$ 161 Hz) and 101.8 ($^1J_{C,H}$ 161 Hz, C-1bd), 102.6 ($^1J_{C,H}$ 158 Hz), and 103.2 ($^1J_{C,H}$ 162 Hz, C-1ac).

Anal. Calc. for $C_{121}H_{132}N_2O_{23}Si$: C, 72.29; H, 6.62; N, 1.39. Found: C, 71.85; H, 6.70; N, 1.22.

Benzyl O-(*2-acetamido-3,4-di*-O-*benzyl-2-deoxy-β*-D-*glucopyranosyl*)-(*1→3*)-O-(*2,4-di*-O-*benzyl-6*-O-tert-*butyldiphenylsilyl-β*-D-*galactopyranosyl*)-(*1→4*)-O-(*2-acetamido-3*-O-*benzyl-2-deoxy-β*-D-*glucopyranosyl*)-(*1→3*)-*2,4,6-tri*-O-*benzyl-β*-D-*galactopyranoside* (**29**). — To a stirred solution of **5** (22 mg, 11 μmol) in 10% aq. acetonitrile (3 mL) was added CAN (40 mg, 73 μmol) at 0°. After being stirred for 1.5 h at 0°, the mixture was diluted hsth EtOAc (20 mL) and washed hsth water (10 mL). The aqueous layer was back-extracted hsth EtOAc (20 mL × 2). The combined organic layers were washed hsth brine (10 mL) and dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. Chromatography of the residue on silica gel using 3:1 $PhCH_3$–acetone afforded **29** (15 mg, 75%), $[\alpha]_D$ −19.2° (*c* 0.7); R_F 0.36 (3:1 $PhCH_3$-acetone); n.m.r. data: δ_H 1.016 (s, 9 H, $C(CH_3)_3$), 1.431 and 1.466 (2 s, 6 H, $COCH_3$ × 2), 7.6–7.0 (m, 55 H, aromatic); δ_C 101.6 and 101.7 (C-1bd), and 102.6 and 103.1 (C-1ac).

Anal. Calc. for $C_{107}H_{120}N_2O_{21}Si \cdot 2\ H_2O$: C, 70.06; H, 6.70; N, 1.52. Found: C, 70.01; H, 6.74; N, 1.46.

Benzyl O-(*2-acetamido-3,4-di*-O-*benzyl-2-deoxy-β*-D-*glucopyranosyl*)-(*1→3*)-O-(*2,4-di*-O-*benzyl-β*-D-*galactopyranosyl*)-(*1→4*)-O-(*2-acetamido-3*-O-*benzyl-2-deoxy-β*-D-*glucopyranosyl*)-(*1→3*)-*2,4,6-tri*-O-*benzyl-β*-D-*galactopyranoside* (**30**). — To a stirred solution of **29** (21 mg, 12 μmol) in THF (2 mL) was added a M solution of Bu_4NF in THF (0.07 mL, 0.07 mmol) at 0° under Ar. After being stirred for 3 h at 0–20°, the mixture was diluted hsth toluene (10 mL), and the solvent was evaporated *in vacuo*. The residue was diluted hsth EtOAc (20 mL) and washed hsth water (10 mL). The aqueous layer was back-extracted hsth EtOAc (20 mL × 2), and the combined organic layers

were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and chromatography of the residue on silica gel using 5:4 $PhCH_3$–acetone afforded **30** (14 mg, 78%): $[\alpha]_D$ −17.3° (*c* 0.4); R_F 0.32 (1:1 $PhCH_3$–acetone); n.m.r. data: δ_H 1.474 and 1.506 (2 s, 6 H, $COCH_3$ × 2), 4.393 (d, 1 H, *J* 7.6 Hz, H-1), and 7.45–7.15 (m, 45 H, $CH_2C_6H_5$ × 9); δ_C 22.3 ($COCH_3$ × 2), 55.2 and 55.5 (C-2bd), 60.0, 60.3, 61.1, and 61.7 (C-6bcd and one unassigned signal), 101.8 (C-1), 102.1 (C-1 × 2), 102.2 (C-1), and 170.9 and 171.0 ($COCH_3$ × 2).

Anal. Calc. for $C_{91}H_{102}N_2O_{21}\cdot H_2O$: C, 69.27; H, 6.64; N, 1.78. Found: C, 69.12; H, 6.78; N, 1.62.

Benzyl O-(*2-acetamido-3,4-di*-O-*benzyl-2-deoxy-6*-O-*sulfo-β*-D-*glucopyranosyl-(1→3)*-O-(*2,4-di*-O-*benzyl-6*-O-*sulfo-β*-D-*galactopyranosyl)-(1→4)*-O-(*2-acetamido-3*-O-*benzyl-2-deoxy-6*-O-*sulfo-β*-D-*glucopyranosyl-(1→3)-2,4,6-tri*-O-*benzyl-β*-D-*galactopyranoside, trisodium salt* (**31**). — To a solution of **30** (9.7 mg, 6.2 μmol) in DMF (2 mL) was added sulfur trioxide–trimethylamine complex ($SO_3\cdot NMe_3$) (7.8 mg, 56 μmol), and the mixture was stirred for 22 h at 50–60°. Then additional $SO_3\cdot NME_3$ (7.2 mg, 52 μmol) was added. After being stirred for an additional 24 h at 60–70°, the mixture was diluted with 1:1 chloroform–methanol (3 mL), and the solution was carefully transferred onto the top of a column of Sephadex LH-20 and eluted with 1:1 chloroform–methanol. Conversion of the product into the sodium salt was carried out by passing a solution of the compound in 1:1 methanol–water through a column of Dowex-50 [Na^+] resin to yield **31** (10.8 mg, 93%): $[\alpha]_D$ −10.5° (*c* 1.2); R_F 0.27 (3:1 $CHCl_3$–MeOH); n.m.r. data: δ_H (1:1 $CDCl_3$–CD_3OD) only broad signals; δ_C (1:1 $CDCl_3$–CD_3OD) 22.2 and 22.4 ($COCH_3$ × 2), 54.4 and 55.1 (C-2bd), 65.1, 100.9, 101.8, 102.0, and 102.6 (C-1 × 4), and 171.1 and 171.2 ($COCH_3$ × 2).

Anal. Calc. for $C_{91}H_{99}N_2O_{30}S_3Na_3\cdot 5\,H_2O$: C, 55.88; H, 5.62; N, 1.44. Found: C, 55.99; H, 5.68; N, 1.94.

Deprotection of compound **32** *into compound* **2**. — A mixture of **31** (2.5 mg, 1.3 μmol) and 10% Pd/C (3.1 mg) in 9:1 methanol–water (0.5 mL) was stirred for 21 h at 20° under H_2. After filtration of the mixture through Celite, the filtrate was evaporated *in vacuo*, and the residue was chromatographed using a column of Sephadex G-10 in water. The fractions containing **2** were combined and lyophilized to give pure **2** (1.3 mg, 92%): $[\alpha]_D$ +12° (*c* 0.1, H_2O); R_F 0.50 (6:5:4 BuOH–acetone–H_2O); n.m.r. data*: δ_H (D_2O) 2.032 and 2.043 (2 s, 6 H, $COCH_3$ × 2), 4.531 (d, $J_{1,2}$ 8.1 Hz, H-1a), 4.534 (d, $J_{1,2}$ 7.7 Hz, H-1c), 4.561 (d, 0.6 H, $J_{1,2}$ 8.1 Hz, H-1a), 5.226 (d, 0.4 H, $J_{1,2}$ 3.3 Hz, H-1a); δ_C [D_2O, $(CH_3)_2CO$, 30.3 p.p.m.] 22.27 and 22.30 ($COCH_3$ ×2), 55.23 and 55.62 (C-2bd), 96.60 (C-1a), and 102.65, 102.98, and 103.03 (C-1bcd).

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* The ^{1}H-n.m.r. spectrum was identical with that of the natural product (ref. 6).

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