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SYNTHESIS OF 1,6-ANHYDRO-2,3-DI-*O*-BENZOYL-4-*O*-(METHYL 2,3,4-TRI-*O*-BENZOYL-α-L-IDOPYRANOSYLURONATE)-β-D-GLUCOPYRANOSE FROM CELLOBIOSE†

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ABSTRACT

The title compound (**21**) was synthesized from cellobiose as a synthon of a heparin-related oligosaccharide. The per-*O*-benzyl and per-*O*-benzoyl derivatives of 1,6-anhydro-4-*O*-(6-deoxy-β-D-*xylo*-hex-5-enopyranosyl)-β-D-glucopyranose were treated with a nonsolvated borane to give a 1:2 mixture of the corresponding 4-*O*-α-L-idopyranosyl- and 4-*O*-β-D-glucopyranosyl-D-glucopyranose derivatives in total yields of 90 and 39%, respectively. Jones oxidation of 1,6-anhydro-2,3-di-*O*-benzoyl-4-*O*-(2,3,4-tri-*O*-benzoyl-α-L-idopyranosyl)-β-D-glucopyranose and 1,6-anhydro-2,3-di-*O*-benzoyl-4-*O*-(2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-β-D-glucopyranose gave the corresponding uronic acid derivatives, namely, the α-L-idopyranosyluronate (**21**) and the β-D-glucosyluronate, in good yields.

INTRODUCTION

Our new program on the synthesis of a partial structure of heparin necessitates the use of several disaccharides, including an L-idopyranosyluronic acid moiety, as the building blocks of that oligosaccharide. Hitherto, we have made some efforts to utilize the readily available disaccharides as the starting materials for various syntheses[1–3]. Along this line, the chemical transformation of cellobiose into a 4-*O*-(α-L-idopyranosyluronic acid)-D-glucopyranose derivative was attempted.

We now describe the synthesis of 1,6-anhydro-2,3-di-*O*-benzoyl-4-*O*-(methyl 2,3,4-tri-*O*-benzoyl-α-L-idopyranosyluronate)-β-D-glucopyranose (**21**) through configurational inversion at C-5′ of cellobiose, and oxidation of the hydroxymethyl group in the product.

RESULTS AND DISCUSSION

The essential starting-material, 1,6-anhydro-β-cellobiose (**2**), was obtained by

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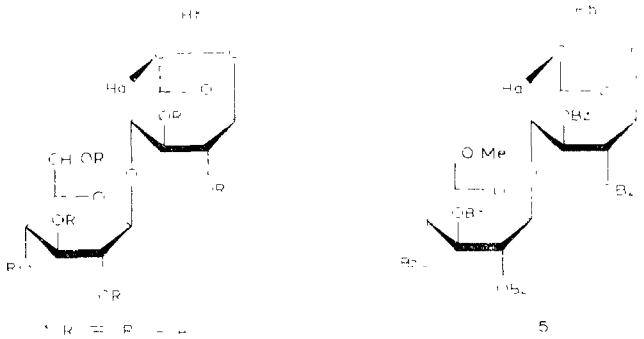
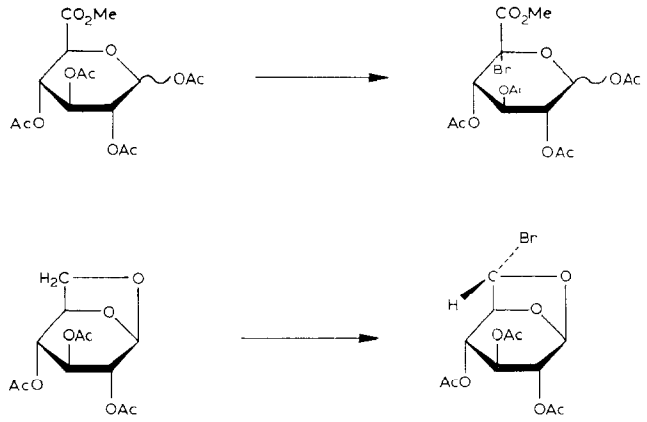
base hydrolysis of the corresponding peracetate[3] (**1**), and it was used for two series of syntheses without being purified. The procedures that have been developed for configurational inversion at C-5 of aldohexoses by utilizing their furanosyl[4] or acyclic form[5] as the intermediates are not applicable to our synthesis of an *O*-α-L-idopyranosyl-(1→4)-D-glucopyranose derivative, because the starting material (**2**) is a disaccharide consisting of two pyranose forms. Therefore, we planned to examine two different ways for configurational inversion at C-5 in the (nonreducing) D-glucosyl group of cellobiose. The first approach included selective halogenation at C-5′ in an intermediary disaccharide derivative, and subsequent, reductive removal of the halogen atom, with configurational inversion. Alternatively, the second approach consisted of the formation of a 6-deoxy-5-enopyranosyl group therein, and hydroboration of the double bond in it.

In the first route, **2** was subjected to tritylation and benzoylation, to give the mono-*O*-tritylated penta-*O*-benzoyl derivative (**3**) as crystals in 88% yield. Removal of the trityl group in **3** was achieved by treatment with perchloric acid in chloroform during 5 min at room temperature, to afford the corresponding 6-hydroxy compound (**4**) in good yield. For oxidation of the 5′-hydroxymethyl group in **4**, we did not use the conventional methods, such as air oxidation[6] or permanganate oxidation[7], but employed Jones oxidation[8,9], found to proceed very readily at room temperature. After esterification of the resulting acid with diazomethane, crystalline methyl ester **5** was obtained in 83% yield.



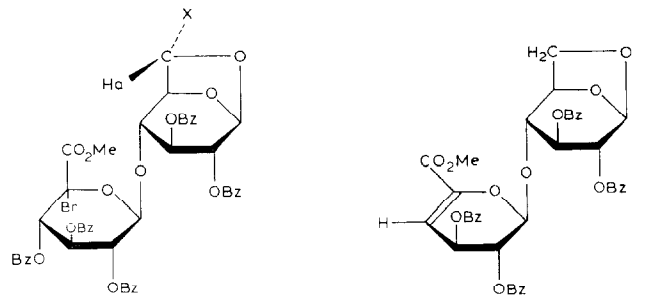
Ferrier and Furneaux[10] reported the photo-bromination reactions of some monosaccharide derivatives as shown in Scheme 1. On treatment with bromine or *N*-bromosuccinimide (NBS) under ordinary light, the peracetate of methyl D-glucuronate undergoes[10] bromination at C-5, whereas the peracetate of 1,6-anhydro-β-D-glucopyranose gives the 6*exo*-bromo derivative[11]. Our disaccharide substrate (**5**)



Scheme 1

consists of both types of monosaccharide components, but selective bromination at C-5′ was desired.

Photo-bromination of **5** with 1.1 mol. equiv. of bromine resulted in a mixture of the 5′-bromo and the *6exo*, 5′-dibromo compounds (**6** and **7**) in 47 and 7% yield, respectively. Furthermore, the reaction of **5** with 1.2 mol. equiv. of NBS (instead of bromine) gave **6** only, in 61% yield, if an appropriate reaction-time was employed. The structures of **6** and **7** were elucidated on the basis of their ^{1}H-n.m.r. spectra. The ^{1}H-n.m.r. spectrum of **5** exhibited signals due to H-6a, H-6b, H-4′, and H-5′, at δ 4.05 as a doublet with $J_{6a,6b}$ 7.82 Hz, at δ 3.80 as a broad triplet with J 7.32 Hz, at δ 5.75 as a triplet with $J_{3',4'} = J_{4',5'} = 9.27$ Hz, and at δ 4.55 as a doublet with $J_{4',5'}$ 9.27 Hz. On the other hand, the ^{1}H-n.m.r. spectrum of **6** revealed the H-4′ resonance at δ 5.68 as a doublet with $J_{3',4'}$ 9.28 Hz, and no H-5′ resonance. Product **7** showed no resonance for either H-5′ or H-6b in its ^{1}H-n.m.r. spectrum.

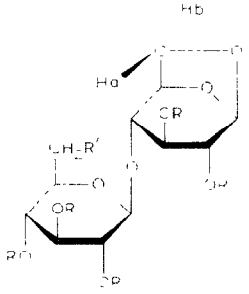


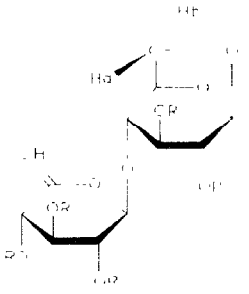
6 X = H
7 X = Br

8

Reductive replacement of the bromo atom in **6** with configurational inversion at C-5′ was necessary for preparation of the target compound (**21**). However, all attempts failed, and the only products obtained from various reductions of **6** were the D-glucosyluronate-containing disaccharide **5** and the 4′-alkenic compound **8**. When

zinc or sodium borohydride in various polar or nonpolar solvents was used, **8** was obtained in high yield. The use of triphenyltin hydride (neat) or sodium cyanoborohydride in nonpolar solvents gave **5** exclusively. These results suggested that the lone pair of the oxygen atom in the pyranose ring stabilizes the C-5′ carbenium ion produced during the reaction, to result in the formation of the thermodynamically stable **5**, instead of **21**.





9 R = Ac, R′ = OTr

10 R = Bn, R′ = OTr

11 R = Bn, R′ = OH

12 R = Bn, R′ = OTs

13 R = Bn, R′ = I

14 R = Bz, R′ = OTs

15 R = Bz, R′ = I

Ts = $SO_2C_6H_4Me$-*p*

16 R = Bn

17 R = Bz

The second approach was examined with compounds bearing benzyl or benzoyl groups as protection for the secondary alcohol groups. 1,6-Anhydro-6′-*O*-trityl-cellobiose, produced *in situ* from the corresponding peracetate (**9**), was benzylated in *N*,*N*-dimethylformamide with sodium hydride and benzyl bromide in the usual way, giving crystalline, per-*O*-benzyl derivative **10**. The trityl group in **10** was removed as described for the preparation of **4**, to afford **11** in 79% yield. Treatment of **11** with *p*-toluenesulfonyl chloride in the presence of 4-(dimethylamino)pyridine, and replacement of the resulting 6′-tosyloxy group with an iodo anion gave iodide **13** in 75% overall yield. On treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in oxolane (tetrahydrofuran, THF), **13** underwent elimination of hydrogen iodide to afford alkene **16** almost quantitatively.

To the best of our knowledge, there is only one report[12] dealing with the hydroboration of a double bond between C-5 and C-6 in a hexose derivative, but none concerning that of disaccharides. The foregoing work showed[12] that treatment of methyl 6-deoxy-α-D-*xylo*-hex-5-enopyranoside with borane gave a 2.5:1 mixture of methyl β-L-idopyranoside and methyl α-D-glucopyranoside. Incidentally, according to some[13,14], the direction of attack of electrophiles on C-5 is greatly influenced by

TABLE I

HYDROBORATION OF **16**

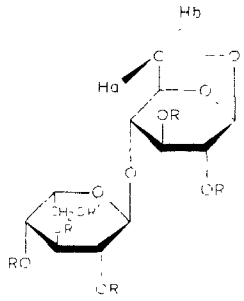
Reagents	*Solvent*	*Products*	
		Yield (%)	*Ratio of* **18:11**
$BH_3 \cdot THF$	THF	0	—
$BH_3 \cdot SMe_3$	THF	90	1:8
BH_3	CH_2Cl_2	90	1:2

the anomeric configuration of the substrate, giving a preponderance of the product bearing the main groups at C-1 and C-5 in *cis* relationship. This situation was very unsuitable for our project, the preparation of an α-L-idopyranosyl compound from a β-D-linked disaccharide of the D series (such as **16**), but had to be overcome to the fullest extent possible.

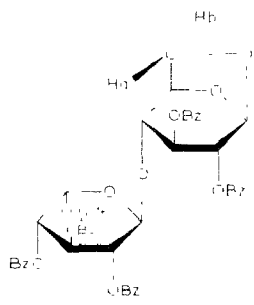
The results of the hydroboration of **16** are shown in Table I. Use of the stoichiometric amount of the borane–THF complex under the standard conditions resulted in no reaction, and complete recovery of **16**. When the concentration of borane was increased by a factor of 10, by using borane–methyl sulfide complex in THF, the hydroboration proceeded, to give the products in 90% yield. Two isomers, prepared by benzoylation thereof, were separated by column chromatography. The compound obtained by basic hydrolysis of the major benzoate (moving the more slowly in thin-layer chromatography) was identified with **11** on the basis of their spectral data and other physical properties. The compound derived from the minor benzoate (moving the faster in thin-layer chromatography) was identified as the α-L-idopyranosyl-containing disaccharide **18**; *i.e.*, its ^{1}H-n.m.r. spectrum exhibited the H-5′ resonance at δ 4.03, as a broad singlet. This spectrum was in sharp contrast to that of **11**, revealing the H-5′ resonance at δ 3.02 as a doublet having a large coupling-constant ($J_{4',5'}$ 8.79 Hz). These n.m.r. data indicated that the dihedral angle between H-4′ and H-5′ in **18** is nearly 90°, and that the glycosyl group in **18** has the $^1C_4$(L) conformation.

Although the (nonreducing) glycosyl group of cellobiose could be partially converted into the expected L-*ido* component, the ratio of the hydroboration products, **18**:**11**, was only 1:8.

To improve the ratio, a nonsolvated borane prepared according to a procedure reported by Brändström and co-workers[15] was employed for the hydroboration of **16**. When **16** was treated with tetrabutylammonium borohydride and methyl iodide in dichloromethane, and the product treated with hydrogen peroxide in aqueous sodium hydroxide, a 1:2 mixture of **18** and **11** was obtained in 90% yield. The undesired product **11** could be converted into alkene **16** by the aforementioned procedure, thus allowing it to be recycled. In a similar way to the preparation of **5**, **18** underwent



18 R = Bn, R' = H
19 R = Bz, R' = Tr
20 R = Bz, R' = H



21

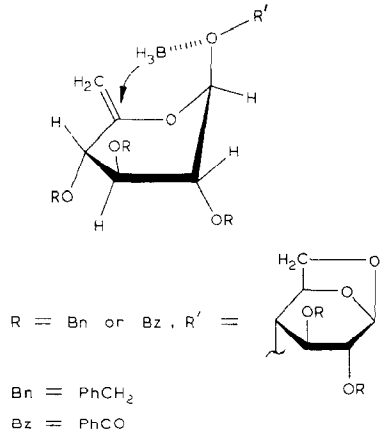
the Jones oxidation, but gave several products in rather low yield, probably because some of the benzyl groups were oxidized.

Therefore, instead of the benzylated disaccharide **18**, it was decided to synthesize the corresponding, benzoylated compound **20**. As in the preparation of **16** from **11**, **4** was transformed into the benzoylated alkene **17**, *via* the 6′-*O*-tosyl (**14**) and the 6′-deoxy-6′-iodo compound (**15**), in 42% overall yield. Hydroboration of **1** with the nonsolvated borane was conducted as described for that of **16**, but it unexpectedly gave a mixture of several compounds that were detectable by thin-layer chromatography. Because this probably occurred as the result of migration, or hydrolysis, of some of the benzoyl groups during the treatment under basic conditions, the mixture of hydroboration products was benzoylated before isolation, to give two perbenzoates in the ratio of 1 : 2 (in a total yield of 53%, based on **17**). The major was more polar than the minor product, as far as behavior on thin-layer chromatograms was concerned.

For the elucidation of their structures, and the preparation of a substrate for the next oxidation reaction, both perbenzoates were converted into the corresponding penta-*O*-benzoyl-6′-*O*-trityl derivatives in good yield, as described for the preparation of **3** from **1**. The compound derived from the more polar perbenzoate was identified as **3**. The other 6′-*O*-trityl derivative, obtained from the less-polar product, gave a ^{1}H-n.m.r. spectrum revealing the H-4′ resonance at δ 5.27 as a broad singlet, and the H-5′ resonance at δ 4.90 as a broad doublet of doublets with $J_{5',6a'}$ 5.86 and $J_{5',6b'}$ 9.76 Hz. This spectrum was in sharp contrast to that of **3**, exhibiting H-4′ and H-5′ resonances at δ 5.46 as a triplet with a spacing of 9.76 Hz, and δ 3.93 as a doublet of doublets of doublets with $J_{4',5'}$ 9.76 Hz. These spectral data indicated that this compound was the L-idopyranosyl derivative (**19**).

In order to explain the phenomenon that employment of the nonsolvated borane (instead of the usual, solvated one) as the reagent for hydroboration of **16** or **17** resulted in increase of the ratio of the products, the α-idopyranosyl : β-D-glucopyranosyl compound, the conformation of the substrates (**16** or **17**) and factors dominating the direction of attack of the reagent should be taken into consideration. According

to Ferrier *et al.*[16], when the $J_{1,2}$ values of the exocyclic, alkene-containing β-D-glucopyranoside derivatives are in the range of 3 to 5 Hz, they retain the $^1C_4$ conformation. Thus, the $J_{1',2'}$ values of 6.34 Hz for **16** and 4.39 Hz for **17** indicate that the β-glycosidic bond of the unsaturated-monosaccharide component in **16** and **17** is axially oriented, as shown. When the solvated borane was used, the β-glycosidic oxygen



atom, bearing a bulky aglycon, sterically hindered attack of the reagent on the double bond from this side, whereas the nonsolvated borane could attack the double bond from this side *via* formation of a chelate with the β-glycosidic oxygen atom. This situation is shown in the depiction.

The conversion of **17** into the uronate **21** was performed as described for the preparation of **5**; thus, **19** was subjected to *O*-detritylation, the product to Jones oxidation, and the oxidation product to esterification, to afford **21** in 84% overall yield. The ^{1}H-n.m.r. spectrum of **21** showed the H-3′, H-4′, and H-5′ signals, each as a broad singlet, which indicated that the oxidation had proceeded without any epimerization at C-5′ in **19**.

EXPERIMENTAL

General methods. — Melting points were determined with a Yamato micro melting-point apparatus, and are uncorrected. Optical rotations were determined with a Perkin–Elmer Model 241MC polarimeter. Chromatography was performed in a column of Silica Gel Merck (70–230 mesh; E. Merck, Darmstadt, Germany). Thin-layer chromatography was conducted on precoated plates (layer thickness, 0.25 mm; E. Merck, Darmstadt, Germany) of Silica Gel 60 F_{254}. I.r. spectra were recorded with a Shimadzu IR-27 spectrophotometer, as Nujol mulls for crystalline samples and as neat films for liquid samples. ^{1}H-N.m.r. spectra were recorded with a JEOL JNM-FX 400 spectrometer, using tetramethylsilane as the internal standard,

for solutions in chloroform-*d*. Solutions were evaporated under diminished pressure: solvent extracts were dried with magnesium sulfate unless specified otherwise.

*1,6-Anhydro-2,3-di-*O*-benzoyl-4-*O*-(2,3,4-tri-*O*-benzoyl-6-*O*-trityl-β-*D*-glucopyranosyl)-β-*D*-glucopyranose* (**3**). — A mixture of **1** (27.3 g, 47.4 mmol) and sodium methoxide (180 mg) in methanol (150 mL) was stirred for 10 h at room temperature. After being stirred for 30 min with Dowex 50 (H^+) resin (15 mL), the mixture was filtered, and the filtrate was evaporated, to give a syrup, which was dissolved in pyridine (300 mL). Trityl chloride (28.6 g, 103 mmol) was added, and, after 10 h, benzoyl chloride (72 g, 512 mmol) was added dropwise at 0–5°, and the mixture stirred for 10 h at room temperature, poured into ice–water, and extracted with ethyl acetate. The extract was successively washed with cold, dilute hydrochloric acid, aqueous sodium hydrogencarbonate, and water, dried, and evaporated. The residual syrup was chromatographed on silica gel with 10:1 (v/v) hexane–ethyl acetate as the eluant, to give **3** (45.5 g, 88%): m.p. 134–135°, $[\alpha]_D^{28}$ +34° (*c* 1.00, chloroform); δ_H 3.33 (dd, 1 H, *J* 2.93 and 10.7 Hz, H-6′a), 3.40 (dd, 1 H, *J* 5.86 and 10.7 Hz, H-6′b), 3.80 (dd, 1 H, *J* 5.35 and 7.32 Hz, H-6b), 3.87 (s, 1 H, H-4), 3.93 (ddd, *J* 2.93, 5.86, and 9.76 Hz, H-5′), 4.05 (d, 1 H, *J* 7.33 Hz, H-6a), 5.10 (s, 1 H, H-1), 5.35 (d, 1 H, *J* 8.30 Hz, H-1′), 5.46 (t, 1 H, *J* 9.76 Hz, H-4′), 5.63 (dd, 1 H, *J* 8.30 and 9.76 Hz, H-2′), 5.68 (s, 1 H, H-2), 5.76 (s, 1 H, H-3), and 5.83 (t, 1 H, *J* 9.77 Hz, H-3′).

Anal. Calc. for $C_{66}H_{57}O_{15}$: C, 72.92; H, 5.00. Found: C, 72.53; H, 4.99.

*1,6-Anhydro-2,3-di-*O*-benzoyl-4-*O*-(methyl 2,3,4-tri-*O*-benzoyl-β-*D*-glucopyranosyluronate)-β-*D*-glucopyranose* (**5**). — A solution of **3** (10.0 g, 9.2 mmol) in chloroform (100 mL) and 60% perchloric acid (0.5 mL) was stirred for 5 min at room temperature, and then diluted with chloroform. The organic layer was successively washed with aqueous sodium hydrogencarbonate and water, dried (calcium chloride), and evaporated. Jones reagent (4M chromium trioxide, 24 mL) was added dropwise during 20 min at 0–5° to a cold solution of the residual syrup in acetone (100 mL), and the mixture was stirred for 6 h at room temperature. The excess of the reagent was decomposed by addition of methanol, and the mixture was evaporated, the residue suspended in ethyl acetate–water, and the aqueous layer extracted with ethyl acetate. The extract was successively washed with aqueous sodium hydrogencarbonate and water, dried, and evaporated. The residue was chromatographed on silica gel with 50:1 (v/v) chloroform–methanol as the eluant, to give the uronic acid, which was esterified with diazomethane in dichloromethane–diethyl ether, to give **5** (5.3 g, 66% from **3**); m.p. 185.5–186.5°, $[\alpha]_D^{25}$ +23° (*c* 0.42, chloroform); δ_H: 3.41 (s, 3 H, CO_2CH_3), 3.80 (br t, 1 H, *J* 7.32 Hz, H-6b), 3.84 (s, 1 H, H-4), 4.05 (d, 1 H, *J* 7.82 Hz, H-6a), 4.55 (d, 1 H, *J* 9.27 Hz, H-5′), 4.59 (d, 1 H, *J* 5.37 Hz, H-5), 5.02 (s, 1 H, H-1), 5.42 (d, 1 H, *J* 7.81 Hz, H-1′), 5.63–5.69 (m, 3 H, H-2,3,2′), 5.75 (t, 1 H, *J* 9.27 Hz, H-4′), 5.97 (t, 1 H, H-3′), and 7.25–8.20 (m, 25 H, 5 Ph).

Anal. Calc. for $C_{48}H_{40}O_{16}$: C, 66.05; H, 4.62; Found: C, 65.95; H, 4.63.

*1,6-Anhydro-2,3-di-*O*-benzoyl-4-*O*-(methyl 2,3,4-tri-*O*-benzoyl-5-bromo-β-*D*-glucopyranosyluronate)-β-*D*-glucopyranose* (**6**). — A stirred solution of **5** (3.0 g, 3.4

mmol) and *N*-bromosuccinimide (740 mg, 4.1 mmol) in carbon tetrachloride (200 mL) was refluxed under irradiation with a tungsten lamp (200 W) until two products appeared in t.l.c. The mixture was cooled, poured into ice–water, and extracted with chloroform. The extract was successively washed with 10% aqueous sodium hydrogensulfate, aqueous sodium hydrogencarbonate, and water, dried (calcium chloride), and evaporated. The residual syrup was chromatographed on silica gel, with 60:1 (v/v) benzene–ethyl acetate as the eluant, to give **6** (1.1 g, 61%); m.p. 129.5–131.5°, $[\alpha]_D^{24}$ −58° (*c* 0.08, chloroform); δ_H: 3.47 (s, 3 H, CO_2CH_3), 3.38 (dd, 1 H, *J* 5.86 and 7.81 Hz, H-6b), 3.94 (s, 1 H, H-4), 4.13 (d, 1 H, *J* 7.82 Hz, H-6a), 4.65 (d, 1 H, *J* 5.87 Hz, H-5), 5.04 (s, 1 H, H-6b), 5.48 (s, 1 H, H-2), 5.59 (s, 1 H, H-3), 5.81 (t, 1 H, *J* 8.30 Hz, H-2′), 5.85 (d, 1 H, *J* 7.80 Hz, H-1′), 5.86 (d, 1 H, *J* 9.28 Hz, H-4′), and 6.17 (t, 1 H, *J* 9.28 Hz, H-3′).

Anal. Calc. for $C_{48}H_{39}BrO_{16}$: C, 60.57; H, 4.13; Br, 8.40. Found: C, 60.26; H. 4.18; Br, 8.37.

*1,6-Anhydro-2,3-di-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-β-*D*-glucopyranosyl)-β-*D*-glucopyranose* (**10**). — 1,6-Anhydro-6′-*O*-trityl-β-cellobiose was prepared from **1** (25 g, 43 mmol) as described for the synthesis of **3**, and isolated as peracetate **9** (21 g, 63%); m.p. 190–190.5°, $[\alpha]_D^{25}$ −12° (*c* 0.31, chloroform).

Anal. Calc. for $C_{41}H_{44}O_{15}$: C, 63.39; H, 5.71. Found: C, 63.25; H, 5.73.

A suspension of **9** (20 g, 26 mmol) and sodium methoxide (800 mg) in methanol (200 mL) was stirred for 3 h at room temperature, and then evaporated. Sodium hydride (18.5 g, 50% mineral oil dispersion) was added portionwise during 10 min at 0–5° to a cooled solution of the residual syrup in *N*,*N*-dimethylformamide (650 mL), and the mixture was stirred for 30 min at room temperature. Benzyl bromide (125 g, 731 mmol) was added dropwise during 30 min at 0–5° to the cooled mixture, and the mixture was stirred for 2 h at room temperature. The excess of the reagent was decomposed by addition of methanol, and the mixture was poured into ice–water, and extracted with diethyl ether. The extract was washed with water, dried, and evaporated. The residual syrup was chromatographed on silica gel, with 10:1 (v/v) hexane–ethyl acetate as the eluant, to give **10** (20.9 g, 49% from **1**); m.p. 153–154.5°, $[\alpha]_D^{25}$ −18°; (*c* 1.30, chloroform); ν_{max} 1950–1700, 1590, 1150, 1070, 910, and 695 cm^{-1}; δ_H: 3.24 (dd, 1 H, *J* 5.39 and 9.71 Hz), 3.43 (s, 1 H, H-4), 4.34 (d, 1 H, *J* 10.3 Hz), and 5.52 (s, 1 H, H-1).

Anal. Calc. for $C_{66}H_{64}O_{10}$: C, 77.93; H, 6.34. Found: C, 77.86; H, 6.29.

*1,6-Anhydro-2,3-di-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-β-*D*-glucopyranosyl)-β-*D*-glucopyranose* (**11**). — A solution of **10** (20.5 g, 20.2 mmol) in chloroform (200 mL) and 60% perchloric acid (0.4 mL) was stirred for 5 min at room temperature, and then diluted with chloroform. The organic layer was successively washed with aqueous sodium hydrogencarbonate and water, dried (calcium chloride), and evaporated. The residual syrup was chromatographed on silica gel, with 10:1 (v/v) hexane–ethyl acetate as the eluant, to give syrupy **11** (12.4 g, 79%); $[\alpha]_D^{20}$ −30° (*c* 1.27, chloroform); ν_{max} 3460 cm^{-1}; δ_H: 1.70 (s, 1 H, O*H*), 3.20 (ddd, 1 H, *J* 2.90, 2.90, and 8.79 Hz, H-5′), 3.38 (s, 1 H, H-4), 3.47 (dd, 1 H, *J* 7.82 and 8.79 Hz, H-2′), 3.54 (t,

1 H, *J* 8.79 Hz, H-4′), 3.62 (t, 1 H, *J* 8.79 Hz, H-3′), 3.57–3.72 (m, 2 H, H-6′a,6′b), 3.71 (dd, 1 H, *J* 6.34 and 7.32 Hz, H-6b), 3.74 (s, 1 H, H-2), 3.80 (s, 1 H, H-3), 3.97 (d, 1 H, *J* 7.33 Hz, H-6a), 4.50 (d, 1 H, *J* 7.82 Hz, H-1′), and 5.51 (s, 1 H, H-1).

Anal. Calc. for $C_{47}H_{50}O_{10}$: C, 72.85; H, 6.50. Found: C, 72.46; H, 6.50.

*1,6-Anhydro-2,3-di-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-*p*-tolylsulfonyl-β-*D*-glucopyranosyl)-β-*D*-glucopyranose* (**12**). — A solution of **11** (16.3 g, 21 mmol), *p*-toluenesulfonyl chloride (16 g, 84 mmol), and 4-(dimethylamino)pyridine (2.6 g, 21 mmol) in pyridine (200 mL) was stirred for 10 h at room temperature, poured into ice–water, and extracted with diethyl ether. The extract was successively washed with cold, aqueous hydrochloric acid, aqueous sodium hydrogencarbonate, and water, dried, and evaporated. The residual syrup was chromatographed on silica gel, with 10:1 (v/v) hexane–ethyl acetate as the eluant, to give syrupy **12** (17.3 g, 89%): $[\alpha]_D^{27}$ −21° (*c* 0.37, chloroform); ν_{max} 1186 cm^{-1}; δ_H: 2.34 (s, 3 H, ArCH_3).

Anal. Calc. for $C_{54}H_{50}O_{12}S$: C, 69.81; H, 6.07; S, 3.45. Found: C, 69.66; H, 6.06; S, 3.24.

*1,6-Anhydro-2,3-di-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-β-*D*-glucopyranosyl)-β-*D*-glucopyranose* (**13**). — A suspension of **12** (12.8 g, 13.8 mmol) and sodium iodide (7.0 g, 46.9 mmol) in 2-butanone (200 mL) was boiled under reflux, with stirring, for 10 h, cooled, poured into ice–water, and extracted with diethyl ether. The extract was successively washed with 10% aqueous sodium hydrogensulfate, aqueous sodium hydrogencarbonate, and water, dried, and evaporated. The residual syrup was chromatographed on silica gel, with 10:1 (v/v) hexane–ethyl acetate as the eluant, to give syrupy **13** (10.3 g, 84%); $[\alpha]_D^{25}$ −19° (*c* 0.23, chloroform); δ_H: 3.67 (t, 1 H, *J* 9.28 Hz), 4.02 (d, 1 H, *J* 7.32 Hz), and 5.51 (s, 1 H, H-1).

Anal. Calc. for $C_{54}H_{49}IO_9$: C, 63.80; H, 5.58; I, 14.35. Found: C, 63.98; H, 5.48; I, 14.15.

*1,6-Anhydro-2,3-di-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-6-deoxy-β-*D*-xylo-hex-5-enopyranosyl)-β-*D*-glucopyranose* (**16**). — A stirred solution of **13** (9.8 g, 12.9 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (5.9 g, 38.8 mmol) in dry oxolane (90 mL) was boiled under reflux for 10 h under a nitrogen atmosphere, cooled, poured into ice–water, and extracted with diethyl ether. The extract was washed with water, dried, and evaporated. The residual syrup was chromatographed on silica gel (Silicar CC-7 special, Mallinckrodt), with 10:1 (v/v) hexane–ethyl acetate as the eluant, to give syrupy **16** (9.65 g, 98%); $[\alpha]_D^{21}$ −54 (*c* 1.4, chloroform); ν_{max} 1660 cm^{-1}; δ_H: 3.36 (s, 1 H, H-4), 3.64 (br t, 1 H, *J* 7.32 Hz, H-3′), 3.66 (br t, 1 H, *J* 6.34 Hz, H-2′), 3.70 (br t, 1 H, *J* 6.35 Hz, H-6b), 3.79 (s, 1 H, H-2), 3.86 (s, 1 H, H-3), 3.99 (d, 1 H, *J* 7.32 Hz, H-6), 4.03 (d, 1 H, *J* 7.32 Hz, H-4′), 4.86 (d, 1 H, *J* 6.34 Hz, H-1′), and 5.48 (s, 1 H, H-1).

Anal. Calc. for $C_{47}H_{48}O_9$: C, 74.58; H, 6.39. Found: C, 74.56; H, 6.24.

*1,6-Anhydro-2,3-di-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-α-*L*-idopyranosyl)-β-*D*-glucopyranose* (**18**). — Methyl iodide (85 mg, 0.6 mmol) was added dropwise during 5 min at 0–5° under a nitrogen atmosphere to a cold solution of **16** (380 mg, 0.5 mmol) and tetrabutylammonium borohydride (153 mg, 0.6 mmol) in dry dichloromethane

(2 mL), and the mixture was stirred for 3 h at room temperature. To the cooled mixture were successively added, dropwise, water (0.15 mL), 3M sodium hydroxide (0.15 mL), and 33% hydrogen peroxide (0.15 mL), and the mixture was stirred for 3 h at room temperature. After the mixture turned yellow, it was diluted with dichloromethane. The organic layer was washed with water, dried (calcium chloride), and evaporated. Benzoyl chloride (1.0 mL) was added dropwise to a cooled solution of the residue in pyridine (5 mL), and the mixture was stirred for 10 h at room temperature, poured into ice–water, and extracted with diethyl ether. The extract was successively washed with cold, aqueous hydrochloric acid, aqueous sodium hydrogencarbonate, and water, dried, and evaporated. The residual syrup was chromatographed on silica gel, with 20:1 (v/v) hexane–ethyl acetate as the eluant, to give a less-polar benzoate (130 mg, 30% from **16**) and a more-polar benzoate (260 mg, 60% from **16**).

A solution of the less-polar benzoate (1.06 g, 1.2 mmol) and 3M sodium hydroxide (5 mL) in oxolane (30 mL) and methanol (10 mL) was stirred for 4 h at room temperature, evaporated, and the residue extracted with diethyl ether. The extract was washed with water, dried, and evaporated. The residual syrup was chromatographed on silica gel, with 5:1 (v/v) hexane–ethyl acetate as the eluant, to give syrupy **18** (881 mg, 95%; 29% from **16**); $[\alpha]_D^{20}$ −38° (*c* 0.93, chloroform); δ_H: 4.03 (s, 1 H, $J_{4',5'}$ ~0 Hz, H-5').

Anal. Calc. for $C_{47}H_{50}O_{10}$: C, 72.85; H, 6.50. Found: C, 72.49; H, 6.53.

The more-polar benzoate (260 mg, 0.3 mmol) was treated with 2M sodium hydroxide (0.5 mL) in oxolane (5 mL) and methanol (1 mL), to give an alcohol (216 mg, 95%) which was identified as **1** on the basis of their ^{1}H-n.m.r. spectra, specific rotations, and elemental analysis.

*1,6-Anhydro-2,3-di-*O*-benzoyl-4-*O*-(2,3,4-tri-*O*-benzoyl-β-*D*-glucopyranosyl)-β-*D*-glucopyranose* (**4**). — The per-*O*-benzoylated trityl derivative **3** (4.5 g, 4.1 mmol) in chloroform (50 mL) was treated with 60% perchloric acid (0.25 mL) as described for the synthesis of **11**, to give **4** (2.8 g, 80%) as an amorphous powder; $[\alpha]_D^{22}$ −12° (*c* 0.81, chloroform); ν_{max} 3460 cm^{-1}.

Anal. Calc. for $C_{47}H_{40}O_{15}$: C, 66.82; H, 4.77. Found: C, 66.85; H, 4.74.

*1,6-Anhydro-2,3-di-*O*-benzoyl-4-*O*-(2,3,4-tri-*O*-benzoyl-6-*O*-p-tolylsulfonyl-β-*D*-glucopyranosyl)-β-*D*-glucopyranose* (**14**). — Alcohol **4** (1.8 g, 2.1 mmol) in pyridine (30 mL) was treated with *p*-toluenesulfonyl chloride (487 mg, 2.6 mmol) and 4-(dimethylamino)pyridine (256 mg, 2.1 mmol) as described for the synthesis of **12**, to give **14** (1.67 g, 79%); m.p. 141–142.5°, $[\alpha]_D^{20}$ +11° (*c* 0.92, chloroform); ν_{max} 1168 cm^{-1}; δ_H: 2.21 (s, 3 H, ArCH_3), 3.77 (m, 2 H, H-4,6'a), 3.98–4.07 (m, 2 H), 4.15–4.27 (m, 2 H), 4.56 (d, 1 H, *J* 5.37 Hz, H-5), 4.93 (s, 1 H, H-1), 5.30 (d, 1 H, *J* 8.30 Hz, H-1'), 5.41 (t, 1 H, *J* 9.77 Hz. H-4'), 5.53 (s, 1 H, H-2), 5.58 (dd, 1 H, *J* 8.30 and 9.76 Hz, H-2'), 5.63 (s, 1 H, H-3), 5.89 (t, 1 H, *J* 9.77 Hz, H-3'), and 6.95–8.16 (m, 29 H, 5 Ph + C_6H_4).

Anal. Calc. for $C_{54}H_{46}O_{17}S$: C, 64.92; H, 4.64; S, 3.21. Found: C, 64.86; H, 4.56; S, 3.17.

*1,6-Anhydro-2,3-di-*O*-benzoyl-4-*O*-(2,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-β-*D*-glucopyranosyl)-β-*D*-glucopyranose* (**15**). — The tosylate **14** (27.9 g, 28 mmol) in 2-butanone (300 mL) was treated with sodium iodide (14.3 g, 95 mmol) as described for the preparation of **13**, to give **15** (23.4 g, 87%); m.p. 128–129.5°, $[\alpha]_D^{20}$ +7.9 (*c* 0.41, chloroform); δ_H: 2.98 (dd, 1 H, *J* 8.79 and 10.76 Hz, H-6'a), 3.29 (dd, 1 H, *J* 2.44 and 10.74 Hz, H-6'b), 3.79 (dd, 1 H, *J* 5.38 and 7.81 Hz, H-6b), 3.82 (s, 1 H, H-4), 4.01 (ddd, 1 H, *J* 2.44, 8.79, and 9.77 Hz, H-5'), 4.05 (d, 1 H, *J* 7.81 Hz, H-6a), 4.56 (d, 1 H, *J* 5.37 Hz, H-5), 5.14 (s, 1 H, H-1), 5.38 (t, 1 H, *J* 9.78 Hz, H-4'), 5.40 (d, 1 H, *J* 8.31 Hz, H-1'), 5.62–5.67 (m, 2 H, H-2,2'), 5.81 (s, 1 H, H-3), and 5.93 (t, 1 H, *J* 9.76 Hz, H-3').

Anal. Calc. for $C_{47}H_{39}IO_{14}$: C, 59.13; H, 4.12; I, 13.29. Found: C, 59.09; H, 4.19; I, 13.55.

*1,6-Anhydro-2,3-di-*O*-benzoyl-4-*O*-(2,3,4-tri-*O*-benzoyl-6-deoxy-β-*D*-xylo-hex-5-enopyranosyl)-β-*D*-glucopyranose* (**17**). — Iodide **15** (11.2 g, 11.7 mmol) in dry oxolane (130 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (6.5 g, 42.6 mmol) as described for the synthesis of **16**, to give **17** (8.4 g, 86%) as an amorphous powder; $[\alpha]_D^{22}$ −3.4 (*c* 0.74, chloroform); ν_{max} 1660 cm^{-1}; δ_H: 3.86 (m, 2 H, H-4,6b), 4.16 (d, 1 H, *J* 7.81 Hz, H-6a), 4.59 (m, 1 H, H-6'a), 4.78 (d, 1 H, *J* 4.88 Hz, H-5), 4.89 (m, 1 H, H-6'b), 5.02 (d, 1 H, *J* 0.79 Hz, H-1), 5.52 (d, 1 H, *J* 4.39 Hz, H-1'), 5.58 (dd, 1 H, *J* 4.39 and 5.37 Hz, H-2'), 5.66 (m, 1 H, H-2), 5.70 (s, 1 H, H-3), 5.74 (dd, 1 H, *J* 5.37 and 7.33 Hz, H-3'), and 5.97 (d, 1 H, *J* 7.33 Hz, H-4').

Anal. Calc. for $C_{47}H_{38}O_{14}$: C, 68.27; H, 4.63. Found: C, 68.27; H, 4.53.

*1,6-Anhydro-2,3-di-*O*-benzoyl-4-*O*-(2,3,4-tri-*O*-benzoyl-6-*O*-trityl-α-*L*-idopyranosyl)-β-*D*-glucopyranose* (**19**). — Methyl iodide (753 mg, 5.3 mmol) was added dropwise during 10 min at 0–5°, under a nitrogen atmosphere, to a cooled solution of **17** (4.0 g, 4.8 mmol) and tetrabutylammonium borohydride (1.36 g, 5.3 mmol) in dry dichloromethane (40 mL), and the mixture was stirred for 3 h at room temperature. To the cooled mixture were successively added water (1.5 mL), 3M sodium hydroxide (1.5 mL), and 33% hydrogen peroxide (1.5 mL), and the mixture was stirred for 3 h at room temperature. After the mixture turned yellow, it was diluted with dichloromethane. The organic layer was washed with water, dried (calcium chloride), and evaporated. A solution of the residue in pyridine (20 mL) was treated with benzoyl chloride (5 mL). The usual processing gave a mixture of two products, from which the less-polar one was isolated by chromatography on silica gel, with 30:1 (v/v) benzene–ethyl acetate as the eluant, to give a perbenzoate (818 mg, 18% from **17**). *O*-Debenzoylation of the less-polar perbenzoate (786 mg, 0.8 mmol) with sodium methoxide (60 mg) in methanol (2 mL), followed by treatment with Dowex 50 (H^+) resin, gave a syrup. A solution of the syrup in pyridine (15 mL) was successively treated with trityl chloride (2.0 g, 7.2 mmol) and benzoyl chloride (2.4 g, 17 mmol), as described for the synthesis of **3**, to give **19** (660 mg, 74%; 13% from **17**); m.p. 129–130.5°, $[\alpha]_D^{13}$ 12 (*c* 0.93, chloroform); δ_H: 3.36 (dd, 1 H, *J* 5.86 and 9.77 Hz, H-6'a), 3.58 (dd, 1 H, *J* 7.32 and 9.76 Hz, H-6'b), 3.95 (dd, 1 H, *J* 5.86 and 7.82 Hz, H-6b), 4.00 (s, 1 H, H-4), 4.23 (d, 1 H, *J* 7.82 Hz, H-6a), 4.90 (br s,

1 H, $J_{5',6'}$ 5.86, $J_{4',5'}$ ~0 Hz, H-5'), 4.98 (d, 1 H, *J* 5.86 Hz, H-5), 5.06 (s, 1 H, H-1), 5.27 (br s, 1 H, H-4'), 5.29 (br s, 1 H, H-2'), 5.37 (br s, 1 H, H-2), 5.52 (br s, 1 H, H-1'), 5.65 (br s, 1 H, H-3'), and 5.70 (s, 1 H, H-3).

Anal. Calc. for $C_{66}H_{54}O_{15}$: C, 72.92; H, 5.01. Found: C, 72.87; H, 4.93.

*1,6-Anhydro-2,3-di-*O*-benzoyl-4-*O*-(methyl 2,3,4-tri-*O*-benzoyl-α-*L*-idopyranosyluronate)-β-*D*-glucopyranose* (**21**). — Compound **19** (390 mg, 0.36 mmol) was treated as described for the synthesis of **5**, to give **21** (260 mg, 84% from **19**); m.p. 124–125.5°, $[\alpha]_D^{23}$ −25° (*c* 0.17, chloroform); δ_H: 3.56 (s, 3 H, CO_2CH_3), 3.93 (t, 1 H, *J* 6.83 Hz H-6b) 3.99 (s, 1 H, H-4), 4.17 (d, 1 H, *J* 7.32 Hz, H-6), 4.93 (d, 1 H, *J* 6.82 Hz, H-5), 5.10 (s, 1 H), 5.30 (s, 1 H), 5.38 (s, 1 H), 5.47 (s, 1 H), 5.49 (s, 1 H), 5.65 (s, 1 H), 5.66 (s, 1 H), and 5.74 (s, 1 H).

Anal. Calc. for $C_{47}H_{36}O_{16}$: C, 66.05; H, 4.62. Found: C, 65.96; H, 4.71.

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