Synthesis of a Conformationally Constrained Heparin-Like Pentasaccharide

Nobuo Sakairi, Jan E. M. Basten, Gijsbert A. van der Marel, Constant A. A. van Boeckel* and Jacques H. van Boom*

Abstract: An octasulfated pentasaccharide **1** having an L-iduronic acid moiety in a fixed $^1C_4$ conformation was synthesized by the coupling of a triosyl donor **3** with a disaccharide acceptor **4** followed by deprotection and *O*-sulfation. The acceptor **4** was prepared from the fully acetylated 5-*C*-allyl-β-D-glucose building block **7** by means of a TMSOTf-promoted glycosylation, intramolecular substitution and ozonolysis of the olefinic bond as the key reactions. Compound **1** showed very low activity in an antithrombin III-mediated anti-Xa assay; this reflects the importance of the presence of a flexible L-iduronic acid moiety in heparin-like antithrombotics.

Keywords
antithrombotics · conformation · molecular recognition · oligosaccharides

Introduction

Since Lindahl and Choay's proposal[1, 2] that a unique pentasaccharide fragment in heparin (also known as fragment DEFGH) binds specifically to antithrombin III (ATIII), more than fifty analogues with pentasaccharide structures have been synthesized and tested, such as desulfated,[3] open-chain[4] and "non-glycosamino" glycan analogues.[5] It is now well recognized that the three-dimensional orientation of negative charges of the pentasaccharide is of particular importance in eliciting the inhibitory activity of ATIII against blood coagulation factors.[6]

In addition to these structure–activity relationship studies, conformational analysis of the pentasaccharide has been carried out with the aid of ^{1}H NMR spectroscopy[7] and force-field calculations.[8] These studies revealed the flexibility of the L-iduronic acid residue, which shows up in an equilibrium between the $^1C_4$ and $^2S_0$ conformation. However, it is still a matter of debate as to whether the flexibility of L-iduronic acid is necessary for the binding and activation of ATIII or alternatively both the $^1C_4$ and $^2S_0$ conformations are recognized. In order to obtain a deeper insight into molecular recognition between ATIII and the pentasaccharide, we have started the synthesis of pentasaccharide analogues containing conformationally constrained L-iduronic acid residues. This paper deals with the first synthesis of a pentasaccharide containing a 3-*O*,5-*C*-methylene-bridged L-idopyranuronate moiety in a fixed $^1C_4$ conformation (compound **1**).

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Results and Discussion

On the basis of the structure of a potent "non-glycosamino" glycan pentasaccharide analogue,[5] we designed the target compound **1** with a rigidified 3-*O*,5-*C*-methylene L-idopyranuronate residue. Its retrosynthetic analysis is illustrated in Scheme 1. Octasulfated pentasaccharide **1** can be synthesized from the appropriately protected derivative **2**, which has to be constructed by coupling of the readily available triosyl donor **3**[9] and the 3',5'-bridged disaccharide acceptor **4**. Retrosynthesis of **4** leads to synthon **5**, in which the propenyl group at C-5' and the tosyl group at C-6' are envisioned as precursor of the carboxyl group and the methylene bridge, respectively. The C-5' propenyl group of **5** can be introduced through radical C–C bond formation[10] between the glycosyl halide **6** and allyl tri-*n*-butyltin followed by the olefin isomerization. The 5-*C*-bromo derivative **6** is equipped with an equatorial substituent at the C-1 position in order to avoid unfavourable 1,3-diaxial interaction during axial allylation at C-5.

Keeping the retrosynthetic strategy above in mind, we started the synthesis of the acceptor **4** from the bromide **6**, which was prepared by photobromination[11] of penta-*O*-acetyl-β-D-glucopyranose. Compound **6** was treated with allyl tri-*n*-butyltin and 2,2'-azobis(2-methylpropionitrile) (AIBN) under modified Keck and Yates conditions.[12] The product, isolated in 75% yield, consisted of a mixture of the desired (5*R*)-5-*C*-allyl derivative **7a** and its (5*S*)-isomer **7b** in a ratio of 10:3. The stereoselectivity is explained by attack of the stabilized axially oriented σ radical at the C-5 position. One-dimensional difference NOE spectra of the mixture showed that the H-1 of major product **7a** ($\delta = 6.01$) exhibited NOE to H-7 ($\delta = 2.88$) whereas that of **7b** ($\delta = 6.06$) exhibited NOE to H-6 ($\delta = 4.74$), supporting the assigned structures. As efforts to isolate the desired pure **7a** were unsuccessful, the mixture **7a,b** was directly subjected to glycosidation by the trichloroacetimidate method.[13] To this end, **7a,b** was converted into the imidate **9a,b** in two steps and

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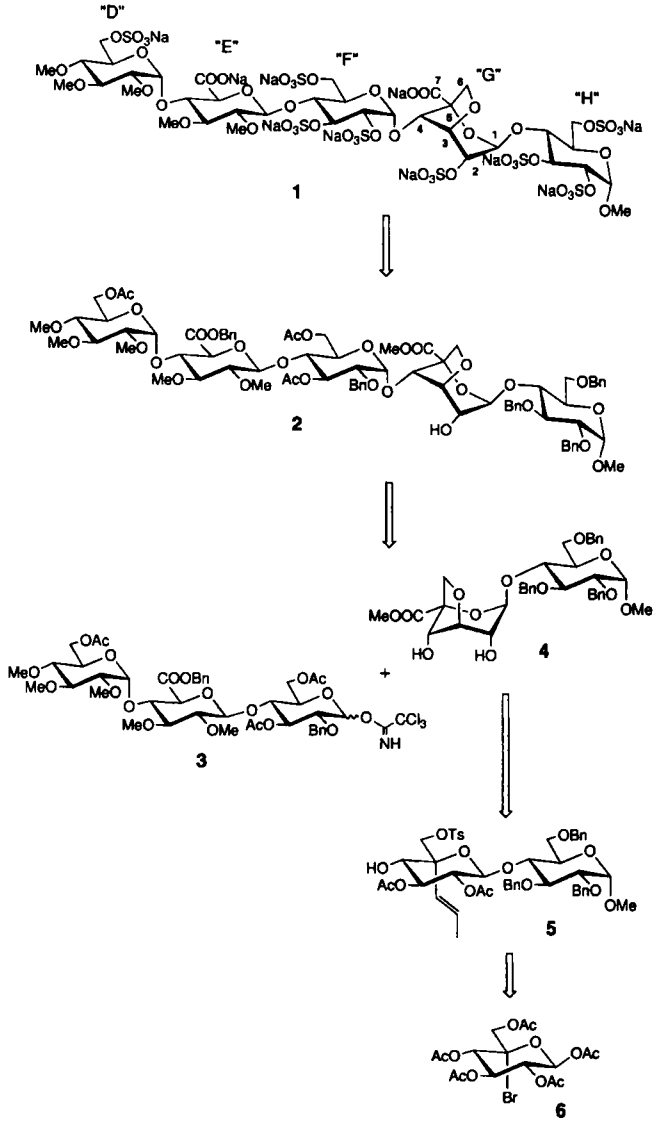
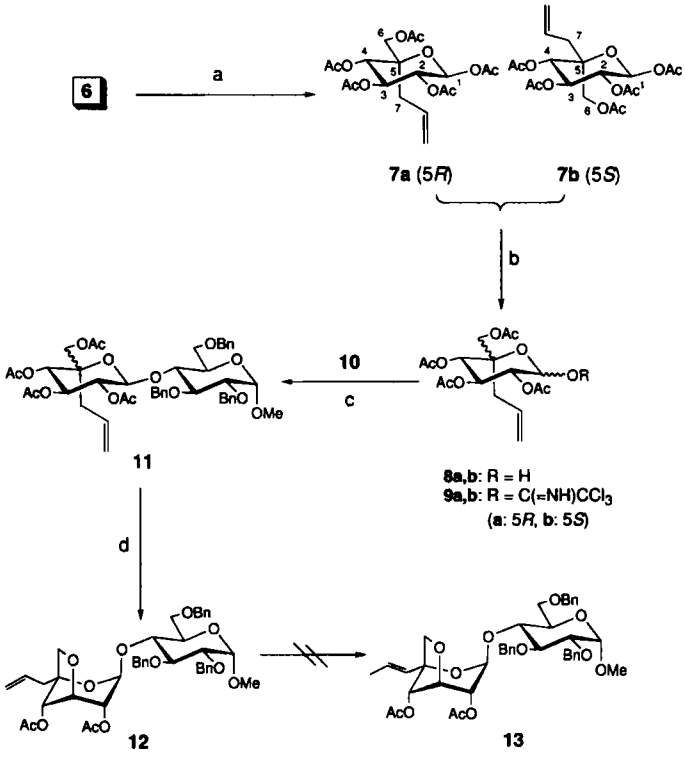


Scheme 1. Retrosynthetic analysis of heparin "DEFGH analogue" 1.



Scheme 2. Synthesis of the 5'-*C*-allyl disaccharide **12**. Reagents and conditions: a) allyl tri-*n*-butyltin/AIBN, toluene, 80–85 °C, 1.5 h (76%); b) $BnNH_2$, CH_2Cl_2/MeOH, RT, 8 h (48%); CCl_3CN, Cs_2CO_3, CH_2Cl_2, 0 °C, 4 h (65%); c) TMSOTf, MS AW-300, CH_2Cl_2, 0 °C, 1 h (50%); d) NaOMe/MeOH; TsCl, pyridine/CH_2Cl_2, RT, overnight; 0.4 M KOH, 80 °C; 2 h; Ac_2O/pyridine (29% in 4 steps).

treated with methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **10** in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane (Scheme 2). After column chromatography on silica gel, pure methyl 4-*O*-(2,3,4,6-tetra-*O*-acetyl-5-*C*-allyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**11**) was isolated in 74% yield. Zemplén deacetylation of **11** gave crude tetrol, which was subjected to selective tosylation of the primary hydroxyl group followed by base-mediated ring closure. After acetylation, the product was isolated as the 2',4'-diacetate **12** in an overall yield of 29% from **11**. However, subsequent olefin isomerization of **12** with bis(acetonitrile)palladium dichloride as the catalyst[14, 15] led to an inseparable mixture of **12** and the desired 5-*C*-propen-1-yl derivative **13** in a ratio of 4:1.

This problem forced us to isomerize the allyl group in an earlier stage of the synthesis. Fortunately, the isomerization of monosaccharide **7a,b** proceeded smoothly in the presence of the palladium catalyst in toluene under argon atmosphere at 80–90 °C. Column chromatography of the reaction mixture on silica gel afforded crystalline 1,2,3,4,6-penta-*O*-acetyl-5-*C*-(propen-1-yl)-β-D-glucopyranose (**14**) in 46% yield (Scheme 3). The ^{1}H NMR spectrum of **14** showed the presence of signals due to H-7 and H-8 at $\delta = 5.59$ and 6.31 with a coupling constant of 16.0 Hz, indicative of the *trans* olefinic structure. The glycosyl acetate **14** was coupled with the acceptor **10** in the presence of TMSOTf[16] to give the β-disaccharide **15** in 79% yield. Subsequent de-*O*-acetylation of the propenyl derivative **15** followed by selective tosylation, treatment with aqueous potassium hydroxide, and acetylation gave the 3,6-anhydro derivative **13** in 20% overall yield. The small coupling constants ($J_{1',2'} < 1$ Hz, $J_{2',3'} = 3.4$ Hz, and $J_{3',4'} = 5.3$ Hz) observed in the ^{1}H NMR spectrum of **13** correspond to the observed[17, 18] and calculated[18, 19] coupling constants of 3,6-anhydro-D-glucosides. The low overall yield of **13** may be attributed to the low site selectivity of tosylation caused by the neopentylic nature of the 6'-hydroxy group. Use of the 4',6'-acetonide **16** as the key intermediate resulted in a better yield. After treatment of the tetraacetate **15** with methanolic sodium methoxide, the intermediate tetrol was treated with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid monohydrate and subsequently with acetic anhydride/pyridine to give the 2',3'-di-*O*-acetyl-4',6'-*O*-isopropylidene derivative **16** in 91% yield. Cleavage of the acetonide of **16** with aqueous acetic acid at 50–60 °C gave a 79% yield of the 4',6'-diol **17**, which could be selectively converted into the monotosylated derivative **5** (74% yield based on consumed **17**). On treatment with aqueous potassium hydroxide at 70–80 °C for 4 h, compound **5** was saponified and intramolecularly substituted by its released 3'-hydroxy group to form the required 3',6'-anhydro bridge. After acetylation, the product was isolated as the diacetate **13** in 84% yield.

We then turned our attention to the oxidative cleavage of the olefinic bond of **13** by ozonolysis. To this end, compound **13** was treated with ozone at −78 °C in dichloromethane/methanol, after which the reaction was quenched with dimethylsulfide. The resulting crude aldehyde was subjected to sodium chlorite oxi-

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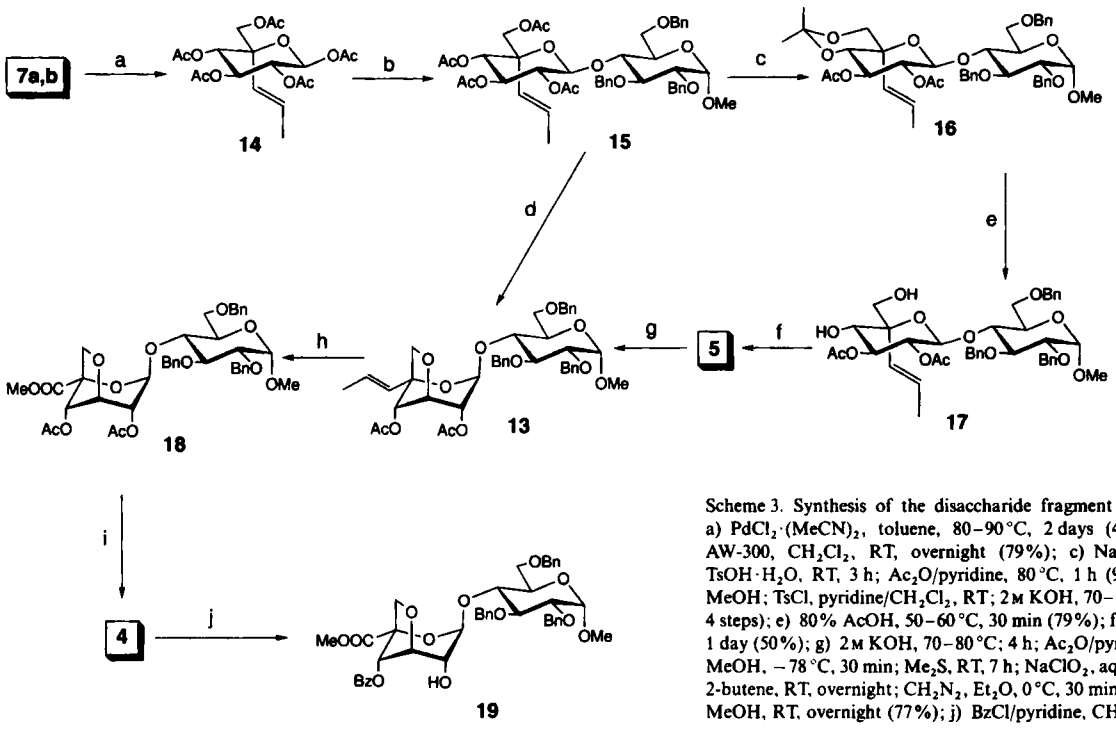
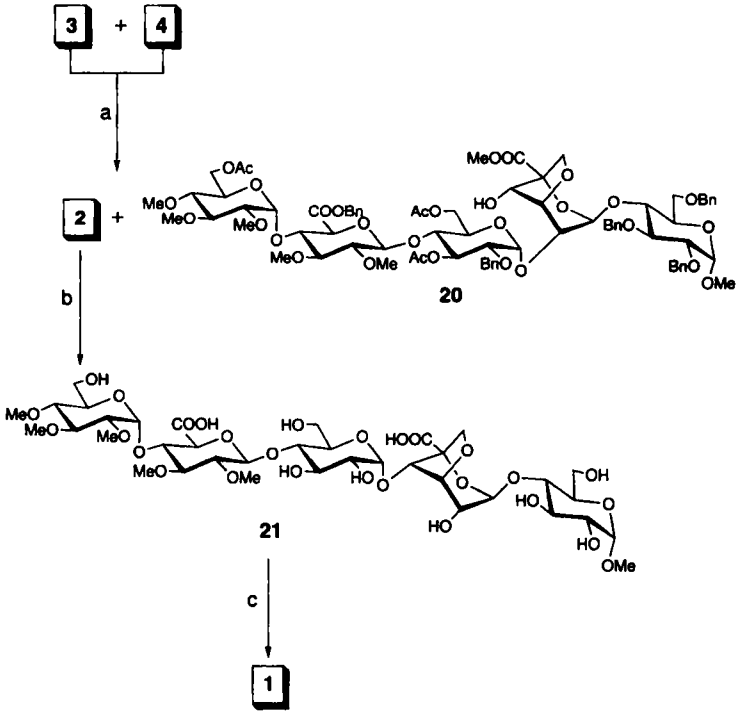


Scheme 3. Synthesis of the disaccharide fragment **4**. Reagents and conditions: a) $PdCl_2(MeCN)_2$, toluene, 80–90 °C, 2 days (46%); b) **10**, TMSOTf, MS AW-300, CH_2Cl_2, RT, overnight (79%); c) NaOMe/MeOH; $Me_2C(OMe)_2$/TsOH·H_2O, RT, 3 h; Ac_2O/pyridine, 80 °C, 1 h (91% in 3 steps); d) NaOMe/MeOH; TsCl, pyridine/CH_2Cl_2, RT; 2 M KOH, 70–80 °C; Ac_2O/pyridine (20% in 4 steps); e) 80% AcOH, 50–60 °C, 30 min (79%); f) TsCl, pyridine/CH_2Cl_2, RT, 1 day (50%); g) 2 M KOH, 70–80 °C; 4 h; Ac_2O/pyridine (84%); h) O_3, CH_2Cl_2/MeOH, −78 °C, 30 min; Me_2S, RT, 7 h; $NaClO_2$, aq. NaH_2PO_4/*t*BuOH/2-methyl-2-butene, RT, overnight; CH_2N_2, Et_2O, 0 °C, 30 min (31% in 4 steps); i) NaOMe/MeOH, RT, overnight (77%); j) BzCl/pyridine, CH_2Cl_2, RT, 2 days (48%).

dation[20] in sodium dihydrogen phosphate buffer in the presence of *tert*-butyl alcohol and 2-methyl-2-butene, followed by methylation with ethereal diazomethane. However, the desired methyl ester **18** was isolated in a low yield of 31%, while the product was contaminated with small amounts of *O*-benzoyl derivatives owing to competitive oxidation[21] of the *O*-benzyl groups during ozonolysis. After treatment with methanolic sodium methoxide, the debenzoylated impurities could be removed by column chromatography to give the methyl 3-*O*,5-*C*-methylene-α-L-idopyranuronate "diol" **4** in 77% yield from **18**.

In order to study the difference in reactivity between the two hydroxy groups at C-2′ and C-4′, the diol **4** was treated with benzoyl chloride in pyridine/dichloromethane. A monobenzoylated product was isolated in 48% yield, which, to our surprise, was characterized as the 4′-*O*-benzoyl derivative **19**. The presence of the 4′-*O*-benzoyl group was unambiguously corroborated by two-dimensional NMR spectroscopy; for instance, the H-4′, appearing at low field ($\delta = 5.53$), showed a crosspeak with the H-$6'_{exo}$ ($\delta = 4.16$) in the 2D NOESY spectrum. The unexpected higher reactivity of OH-4′ relative to OH-2′ in compound **4** might be rationalized by the bulkiness of the tri-*O*-benzyl-D-glucopyranosyl moiety at the anomeric position and/or intramolecular hydrogen bridge formation between the OH-4′ and the methyl ester function at C-5′. The regioselectivity found in this experiment prompted us to examine coupling of the diol acceptor **4** with the triosyl donor **3** (Scheme 4). After treatment of **4** with an equimolar amount of **3** in the presence of TMSOTf and 4 Å molecular sieves in dichloromethane at −20 °C for 1 h and subsequent column chromatography on silica gel, two products were isolated in a yield of 43% and 18%. In spite of a significant difference in the TLC retention time ($R_f = 0.65$ and 0.33, 88:12 dichloromethane/acetone), 400 MHz ^{1}H NMR spectroscopy suggested that both products were α-coupled pentasaccharides. Further structural elucidation was carried out by 600 MHz ^{1}H NMR spectroscopy including two-dimensional COSY, HOHAHA and NOESY experiments. Signals assignable to protons of the idopyranuronate residue (unit G) of the major product were observed at $\delta = 5.43$ (H-1G), 3.82 (H-2G), 4.50–4.55 (H-4G, OH-2), 3.88 (H-6G) and 4.52 (H-6G) with cou-



Scheme 4. Coupling of fragments **3** and **4** and synthesis of the pentasaccharide **1**. Reagents and conditions: a) TMSOTf, MS 4 Å, CH_2Cl_2, −20 °C, 1 h (**2**: 43%, **20**: 18%); b) 10% Pd/C/H_2, *t*BuOH/H_2O, RT, overnight; 0.5 M NaOH, RT, overnight (75%); c) SO_3·Et_3N, DMF, 55 °C, overnight (100%).

pling constants of $J_{1G,2G}<1$, $J_{2G,3G}=3.3$, $J_{2G,OH}=13.0$ and $J_{6G,6G}=9.3$ Hz. Moreover, interresidual NOE crosspeaks for H(1D)–H(4E), H(1F)–H(4G,OH) and H(1G)–H(3H,4H) were observed in its NOESY spectrum. These results clearly revealed that the major product is the desired pentasaccharide **2** coupled at the O-4′ position of **4**. The minor product turned out to be the O-2′ coupled pentasaccharide **20**. The fully protected pentamer **2** was then hydrogenated in aqueous *tert*-butyl alcohol with palladium on carbon as a catalyst, in order to remove all benzyl groups. Subsequent saponification of the debenzylated pentasaccharide with 0.5 M aqueous sodium hydroxide afforded a 75% yield of fully deprotected pentasaccharide **21**. *O*-Sulfation of the latter with sulfur trioxide triethylamine complex in *N*,*N*-dimethylformamide (DMF) at 55 °C gave the target pentasaccharide **1** in quantitative yield. The structure and homogeneity of the product **1** were ascertained by ^{1}H NMR spectroscopy, matrix-assisted laser desorption ionization (Maldi) mass spectrometry, HPLC analysis on ion-exchange column (Mono Q)[22] as well as capillary electrophoresis (CE).[5] The $^1C_4$ conformation of the idopyranuronate moiety was confirmed by ^{1}H NMR spectroscopy, which revealed coupling constants of $J_{1G,2G}<1$ Hz and $J_{3G,4G}$ ca. 4.0 Hz. Since compound **1** showed a very low activity of 65 units mg^{-1} in an AT III-mediated anti-Xa assay, we may conclude that the $^1C_4$ conformation of L-iduronic acid moiety is not the active one.

Conclusion

An octasulfated pentasaccharide **1** having a 3-*O*,5-*C*-methylene bridged L-iduronic acid moiety in a fixed $^1C_4$ conformation has been synthesized. Compound **1** showed a very low activity in an AT III-mediated anti-Xa assay. Since the activity of closely related compounds containing the flexible L-iduronic acid moiety is in the range of 800–1500 anti-Xa units mg^{-1},[6] we conclude that either the $^2S_0$ conformation of L-iduronic acid is essential for optimal interaction with AT III or, alternatively, that flexibility of L-iduronic acid (i.e., the presence of both $^2S_0$ and $^1C_4$ conformations) is required to impose conformational change on AT III in a so-called induced fit.

Experimental Procedure

General methods: Pyridine, toluene, *N*,*N*-dimethylformamide (DMF) and tetrahydrofuran (THF) were dried by refluxing with calcium hydride and then distilled. Dichloromethane was dried over anhydrous calcium chloride and then distilled from calcium hydride. All anhydrous solvents were stored over 4 Å molecular sieves. Methanol was distilled from magnesium methoxide and stored over 3 Å molecular sieves. Petroleum ether used was of low boiling point (40–60 °C). Molecular sieves were activated at 150 °C for several hours in vacuo before use. TLC and HPTLC analyses were performed on silica gel 60 F_{254} precoated on glass plates (layer thickness 0.25 and 0.2 mm, Merck); spots were visualized by UV light (254 nm) and by charring with 20% methanolic sulfuric acid. Column chromatography was performed on silica gel (0.063–0.20 mm, J. T. Baker, Holland). M.p. were measured in a capillary with a Büchi melting-point apparatus. Optical rotations were determined with a Propol polarimeter. ^{1}H NMR (200 MHz) and ^{13}C NMR (50.1 MHz) spectra were recorded with a Jeol JNM FX-200 spectrometer. ^{1}H NMR spectra at 300.13, 400.13 and 600.13 MHz were recorded with Bruker WM-300, WM-400 and DMX-600 spectrometers for solution in [D$_1$]chloroform or deuterium oxide. Chemical shifts (δ) are given relative to tetramethylsilane (TMS) or HDO (δ = 4.60) as internal standards. Capillary electrophoresis (CE) was performed in 5 mM sulfosalicylic acid buffer (pH 3.0) at 30 °C by application of a potential of 7.5 kV across the capillary. Electropherograms were recorded by means of indirect UV detection by quenching signal at 214 nm. Mass spectra of the intermediates were recorded with a Finnigan MAT SSQ-710 mass spectrometer equipped with an electrospray interface (ESI) from Analytica (Broadford). The Maldi mass spectrum of compound 1 was recorded with a Vision 2000 spectrometer with $(Arg-Gly)_{10}$ as basic peptide for ionic complex formation and 3-hydroxypicolic acid as matrix [23]. Analytical samples were dried over phosphorous pentoxide for 3–5 h at 60 °C.

1,2,3,4,6-Penta-*O*-acetyl-5-*C*-allyl-β-D-glucopyranose (7a) and 1,2,3,4,6-penta-*O*-acetyl-5-*C*-allyl-α-L-idopyranose (7b): The bromide [11] **6** (920 mg, 2 mmol) and allyl tri-*n*-butyltin (4 mL, 12 mmol) were dissolved in dry toluene (20 mL). The solution was degassed under reduced pressure and stirred under argon atmosphere at 80–85 °C. To the resulting solution was added dropwise over 55 min a solution of AIBN (490 mg, 3 mmol) in dry and degassed toluene (12 mL). The mixture was stirred at 80–90 °C for 35 min; TLC analysis with 15:1 (v/v) toluene/acetone (development 3 times) showed complete disappearance of the starting material **6**. The resulting solution was cooled and concentrated. The residue was partitioned between acetonitrile (150 mL) and petroleum ether (100 mL). The acetonitrile layer was washed with petroleum ether (4 × 50 mL) and concentrated. The residue (1.2 g) was chromatographed on a column of silica gel (3 × 20 cm) employing 50:3 (v/v) toluene/acetone as the eluant, giving a 10:3 mixture of **7a** and **7b** (648 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): for compound **7a**: δ = 6.01 (d, J = 8.3 Hz, 1H; H-1), 5.90–5.99 (m, 1H; H-8), 5.41–5.46 (m, 2H; H-3,4), 5.05–5.38 (m, 3H; H-2,9,9′), 4.07 (d, J = 12.2 Hz, 1H; H-6), 3.94 (d, J = 12.3 Hz, 1H; H-6′), 2.88 (ddt, J = 1.3, 5.0, 15.7 Hz, 1H; H-7), 2.39 (dd, J = 9.2, 15.4 Hz, 1H; H-7′), 2.11, 2.10, 2.041, 2.035, 2.01 (5 × s, 15H; 5 × OAc) (NOE was observed between H-7 (irradiation) and H-1,3 and between H-1 (irradiation) and H-7); for **7b**: δ = 6.06 (d, J = 7.8 Hz, 0.3H; H-1), 5.62–5.79 (m, 0.3H; H-8), 5.59 (t, J = 9.6 Hz, 0.3H; H-3), 5.05–5.38 (m, 1.2H; H-2,4,9,9′), 4.74 (d, J = 12.7 Hz, 0.3H; H-6), 4.02 (d, J = 12.8 Hz, 0.3H; H-6′), 2.35–2.43 (m, 0.3H; H-7) (NOE was observed between H-1 and H-6); ^{13}C NMR (50 MHz, $CDCl_3$): for **7a**: δ = 168.6, 168.4, 129.5 (C-8), 119.5 (C-9), 87.6 (C-1), 76.7 (C-5), 70.5, 70.0, 68.2 (C-2,3,4), 64.2 (C-6), 32.3 (C-7), 20.8, 20.1, 19.9 (Ac); for **7b**: δ = 169.7, 169.3, 168.5, 130.0 (C-8), 119.5 (C-9), 88.7 (C-1), 76.8 (C-5), 70.9, 70.3 (C-2,3,4), 64.2 (C-6), 39.6 (C-7), 20.8, 20.1, 19.9 (Ac). ESI-MS: $C_{19}H_{26}O_{11}$ (M) for 430.15; found: m/e 469 (M + K$^+$), 453 (M + Na$^+$), 371 (M − OAc)$^+$.

Methyl 4-*O*-(2,3,4,6-tetra-*O*-acetyl-5-*C*-allyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (11): A solution of **7a,b** (0.86 g, 2 mmol) in 10:10:1 (v/v/v) dichloromethane/methanol/benzylamine (21 mL) was stirred at room temperature for 8 h. The solution was diluted with dichloromethane (100 mL), washed successively with 1 M hydrochloric acid, aqueous sodium hydrogencarbonate and brine, dried with anhydrous sodium sulfate and evaporated. Column chromatography of the residue on silica gel with 2:1 (v/v) toluene/ethyl acetate gave the hemiacetal **8a,b** (370 mg, 48%) [^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81–5.56 (m, 1H; H-8), 4.84 (d, J = 7.9 Hz, 1H; H-6), 2.74 (dd, J = 6.2, 15.4 Hz, 1H; H-7), 2.10–1.99 (m, OAc)], together with unchanged **7a,b** (400 mg, 46%). To a stirred ice-cold solution of **8a,b** (470 mg, 1.21 mmol) in dry dichloromethane (10 mL) was added trichloroacetonitrile (1 mL) and caesium carbonate (200 mg). The suspension was stirred at 0 °C for 4 h, filtered and concentrated. Chromatography of the residue on a short column of silica gel with 75:24:1 (v/v/v) toluene/ethyl acetate/triethylamine afforded the imidate **9a,b** (420 mg, 65%). A mixture of the imidate **9a,b** (420 mg, 0.79 mmol) and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside [24] **10** (800 mg, 1.72 mmol) was dried by coevaporation with toluene (3 × 5 mL) and dissolved in dichloromethane. Powdered molecular sieves AW-300 (2 g) were added to the solution and the suspension was stirred at 0 °C for 1 h. TMSOTf (0.05 mL, 0.26 mmol) was added to the suspension. The mixture was stirred at 0 °C for 2 h and at room temperature overnight, quenched with triethylamine (0.2 mL) and filtered through Hyflo Super Cell® (Fluka). The filtrate was concentrated and the residual syrup was subjected to column chromatography on silica gel with 10:1 → 3:1 (v/v) toluene/ethyl acetate to give unchanged **10** (378 mg) and the disaccharide **11** (493 mg, 74%); R_f = 0.26 (3:1 toluene/ethyl acetate); $[\alpha]_D^{21}$ = − 22 (c = 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.82 (m, 1H; H-8′), 5.32 (d, J = 9.3 Hz, 1H; H-4′), 5.21 (t, J = 9.3 Hz, 1H; H-3′), 5.12 (d, J = 16.5 Hz, 1H; H-9′), 5.10 (d, J = 12.0 Hz, 1H; H-9′), 5.09, 4.66 (2 × d, 2H, J = 11.6 Hz, CH_2Ph), 5.07 (brs, 1H; H-9′), 4.96 (t, J = 8.2 Hz, 1H; H-2′), 4.87 (d, J = 8.1 Hz, 1H; H-1′), 4.72, 4.56 (2 × d, 2H, J = 12.0 Hz, CH_2Ph), 4.71, 4.48 (2 × d, 2H, J = 12.1 Hz, CH_2Ph), 4.57 (d, J = 3.8 Hz, 1H; H-1), 4.02 (d, J = 12.1 Hz, 1H; H-6′), 3.81–3.75, 3.60–3.53 (m, 5H; H-3,4,5,6,6), 3.68 (d, J = 12.1 Hz, 1H; H-6′), 3.47 (dd, J = 3.9, 9.2 Hz, 1H; H-2), 3.35 (s, 3H; MeO), 2.53 (dd, J = 5.7, 15.6 Hz, 1H; H-7′), 2.24 (dd, J = 8.5, 15.6 Hz, 1H; H-7′), 1.99, 1.98, 1.95, 1.84 (4 × s, 12H; AcO); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.24, 169.91, 168.81 (C=O), 139.37, 138.17, 137.18 (Ph_q), 129.68 (C-8′), 128.42–126.84 (Ph), 119.81 (C-9′), 98.32 (C-1′), 95.48 (C-1), 79.89, 78.61, 77.44, 75.57, 74.93, 73.89, 73.41, 72.42, 70.84, 69.53, 69.00, 67.36, 64.94, 55.16 (MeO), 32.30 (C-7′), 20.50, 20.36 (AcO); ESI-MS: $C_{45}H_{54}O_{15}$ (M) for 834.35; found: m/e 857 (M + Na$^+$).

Methyl 4-*O*-(2,6-di-*O*-acetyl-3,6-anhydro-5-*C*-allyl-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (12): To a solution of compound **11** (410 mg, 0.49 mmol) in 1:1 (v/v) methanol/tetrahydrofuran (20 mL) was added sodium methoxide (50 mg). The solution was stirred at room temperature overnight, neutralized with Dowex 50 (H$^+$ form), filtered and evaporated. To a solution of the residue (370 mg) in 1:1 (v/v) pyridine/dichloromethane (20 mL) was added *p*-toluenesulfonyl chloride (190 mg, 1 mmol). The mixture was stirred at room temperature overnight and then cooled in an ice bath. To the resulting solution were added ethanol (10 mL) and then 0.4 M potassium hydroxide (10 mL). The solvent was evaporated to half of its original volume. The mixture was stirred at 80 °C for 2 h, diluted with 10% aqueous ammonium chloride and extracted with dichloromethane. The extract was washed successively with 10% aqueous ammonium chloride, saturated aqueous sodium hydrogencarbonate and brine, dried with

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anhydrous sodium sulfate and evaporated. The residue was acetylated with 2:1 (v/v) pyridine/acetic anhydride at room temperature overnight to give the 3′,6′-anhydro derivative **12** (105 mg, 29%) after column chromatography on silica gel with 4:1 (v/v) toluene/ethyl acetate; $R_f = 0.33$ (3:1 toluene/ethyl acetate); $[\alpha]_D^{20} = +19$ ($c = 0.24$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.62$ (ddt, $J = 7.2$, 10.1, 17.1 Hz, 1H; H-8′), 5.19 (s, 1H; H-1′), 5.07, 4.84 (2 × d, 2H, $J = 11.1$ Hz, CH_2Ph), 4.99 (dd, $J = 1.7$, 10.1 Hz, 1H; H-9′), 4.92 (d, $J = 3.5$ Hz, 1H; H-2′), 4.91 (dd, $J = 1.8$, 17.1 Hz, 1H; H-9′), 4.70, 4.58 (2 × d, $J = 12.1$ Hz, 2H; CH_2Ph), 4.60 (d, $J = 3.4$ Hz, 1H; H-1), 4.57 (d, $J = 5.4$ Hz, 1H; H-4′), 4.53 (s, 2H, CH_2Ph), 4.46 (dd, $J = 3.4$, 5.3 Hz, 1H; H-3′), 4.31 (d, $J = 9.7$ Hz, 1H; H-6′), 3.96 (t, $J = 8.8$ Hz, 1H; H-3), 3.92 (t, $J = 8.7$ Hz, 1H; H-4), 3.77–3.68 (m, 3H; H-5,6,6), 3.58 (dd, $J = 3.4$, 9.2 Hz, 1H; H-2), 3.53 (d, $J = 9.7$ Hz, 1H; H-6′), 3.36 (s, 3H, MeO), 2.27 (dd, $J = 7.2$, 14.3 Hz, 1H; H-7′), 2.20 (dd, $J = 7.5$, 14.3 Hz, 1H; H-7′), 2.05, 1.90 (2 × s, 6H; AcO); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 139.14$, 137.97 (Ph_q), 131.49 (C-8′), 128.36–127.20 (Ph), 118.96 (C-9′), 99.81 (C-1′), 97.79 (C-1), 80.39, 79.25, 74.81, 74.61, 73.23, 72.71, 72.07, 70.63, 70.52, 69.85, 68.85, 55.16 (MeO), 36.47 (C-7′), 20.59 (Ac); ESI-MS: $C_{41}H_{48}O_{12}$ (M) for 732.31; m/e 755 ($M + Na^+$), 771 ($M + K^+$).

1,2,3,4,6-Penta-*O*-acetyl-5-*C*-(propen-1-yl)-β-D-glucopyranose (14): A solution of a 10:3 mixture of the 5-*C*-allyl derivatives **7a,b** (1.10 g, 2.56 mmol) and bis(acetonitrile)palladium dichloride (30 mg) in degassed toluene (20 mL) was stirred under an argon atmosphere at 80–90 °C for 1 d. The dark brown precipitate was filtered through a short column of silica gel and the column was washed with 4:1 (v/v) toluene/ethyl acetate. The combined filtrate and the washings were concentrated and the residue was treated again with bis(acetonitrile)palladium dichloride (30 mg) as described above. Column chromatography on silica gel of the resulting dark brown suspension with 3:1 (v/v) petroleum ether/EtOAc gave the 5-*C*-propenyl derivative **14** (508 mg, 46%); $[\alpha]_D^{20} = -79$ ($c = 0.42$, $CHCl_3$); m.p. 111–112 °C (from diethyl ether/petroleum ether); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 6.31$ (qd, $J = 6.6$, 16.0 Hz, 1H; H-8), 5.91 (d, $J = 8.1$ Hz, 1H; H-1), 5.59 (br d, $J = 16.0$ Hz, 1H; H-7), 5.37 (d, $J = 10.5$ Hz, 1H; H-4), 5.25 (t, $J = 9.9$ Hz, 1H; H-3), 5.16 (t, $J = 8.5$ Hz, 1H; H-2), 4.14 (d, $J = 12.6$ Hz, 1H; H-6), 3.68 (d, $J = 12.6$ Hz, 1H; H-6), 2.10–2.01 (5 × s, 15H; AcO), 1.86 (dd, $J = 1.5$, 6.6 Hz, 3H; H-9); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 170.09$ (C=O), 134.06, 121.88 (C-7,8), 88.39 (C-1), 76.36 (C-5), 71.13, 70.87, 68.04 (C-2,3,4), 65.26 (C-6), 20.85, 20.59 (Ac), 18.43 (C-9). $C_{19}H_{26}O_{11}$: calcd C 53.02, H 6.09; found: C 53.21, H 6.09. Further elution of the column with the same solvent gave a mixture of **14** and its isomers (410 mg, 37%).

Methyl 4-*O*-(2,3,4,6-tetra-*O*-acetyl-5-*C*-(propen-1-yl)-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (15): A mixture of the pentaacetate **14** (330 mg, 0.77 mmol) and **10** (700 mg, 1.5 mmol) was dried by coevaporation with toluene (2 × 10 mL) and dissolved in dry dichloromethane (5 mL). To the solution were added powdered molecular sieves AW-300 (2 g), and the suspension was stirred at room temperature for 1 h. To the resulting suspension was added TMSOTf (0.2 mL, 1 mmol), and the mixture was stirred overnight at room temperature. After addition of triethylamine (0.3 mL), the precipitates were filtered through Hyflo Super Cell® (Fluka) and washed with ethyl acetate. The filtrate and washings were combined, washed successively with aqueous sodium hydrogencarbonate and brine, dried over anhydrous sodium sulfate and evaporated. The residue was subjected to column chromatography on silica gel with 4:1 to 2:1 (v/v) petroleum ether/ethyl acetate, giving the disaccharide **15** (509 mg, 79%); $R_f = 0.19$ (3:1 toluene/ethyl acetate); $[\alpha]_D^{24} = -26$ ($c = 1.13$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.16$ (qd, $J = 6.6$, 16.0 Hz, 1H; H-8′), 5.63 (dd, $J = 1.5$, 16.0 Hz, 1H; H-7′), 5.35 (d, $J = 10.3$ Hz, 1H; H-4′), 5.19 (d, $J = 11.3$ Hz, 1/2CH_2Ph), 5.18 (t, $J = 10.3$ Hz, 1H; H-3′), 5.03–4.98 (m, 2H; H-1′,2′), 4.74–4.66 (m, 3H; 3/2CH_2Ph), 4.57 (d, $J = 3.7$ Hz, 1H; H-1), 4.56 (d, $J = 12.3$ Hz, 1H; 1/2CH_2Ph), 4.50 (d, $J = 12.3$ Hz, 1H; 1/2CH_2Ph), 4.11 (d, $J = 12.4$ Hz, 1H; H-6′), 3.81–3.78 (m, 2H; H-3,4), 3.68 (dd, $J = 2.6$, 10.9 Hz, 1H; H-6), 3.56–3.41 (m, 4H; H-2,5,6,6′), 3.38 (s, 3H; MeO), 2.02, 1.98, 1.85, 1.80 (4 × s, 12H; 4 × AcO), 1.73 (dd, $J = 1.0$, 6.5 Hz, 3H; H-9′); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 169.45$, 168.37, 168.28 (C=O), 137.68, 132.45, 127.89, 127.57, 127.34, 127.25, 126.96, 126.55, 126.35, 122.99, 97.79 (C-1′), 95.36 (C-1), 79.60, 78.02, 77.12, 76.36, 75.69, 74.63, 73.35, 72.91, 71.95, 70.58, 69.03, 67.66, 64.91, 54.66 (MeO), 19.89 (Ac), 17.64 (C-9′). $C_{45}H_{54}O_{15} \cdot 0.5\,H_2O$: calcd C 64.05, H 6.57; found: C 64.09, H 6.58.

Methyl 4-*O*-(2,3-di-*O*-acetyl-4,6-*O*-isopropylidene-5-*C*-(propen-1-yl)-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (16): To a solution of the disaccharide **15** (450 mg, 0.54 mmol) in methanol (20 mL) was added methanolic sodium methoxide (1 M, 0.5 mL). The mixture was stirred at room temperature for 2 h, neutralized with Dowex 50 (H^+ form), concentrated and dried by coevaporation with toluene. The residue was dissolved in acetone (5 mL) and 2,2-dimethoxypropane (1 mL). To the solution was added *p*-toluenesulfonic acid monohydrate (100 mg). The mixture was stirred at room temperature for 3 h, quenched with pyridine (1 mL) and evaporated to dryness. The residue was dissolved in pyridine (6 mL) and acetic anhydride (2 mL). The solution was stirred at 80 °C for 1 h, cooled to room temperature, quenched with methanol (3 mL) and diluted with ethyl acetate (100 mL). The resulting solution was washed successively with cold 1 M hydrochloric acid, saturated aqueous sodium hydrogencarbonate and water, dried over anhydrous sodium sulfate and evaporated. The residue was subjected to column chromatography on silica gel with 9:1 → 4:1 (v/v) petroleum ether/ethyl acetate, giving the acetonide **16** (390 mg, 91%); $R_f = 0.43$ (3:1 toluene/ethyl acetate); $[\alpha]_D^{20} = -8.1$ ($c = 0.34$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.09$ (qd, $J = 6.5$, 16.2 Hz, 1H; H-8′), 5.79 (dd, $J = 1.6$, 16.2 Hz, 1H; H-7′), 5.17 (dd, $J = 9.2$, 10.4 Hz, 1H; H-3′), 5.02 (d, $J = 8.0$ Hz, 1H; H-1′), 4.98, 4.79 (2 × d, $J = 11.2$ Hz, 2H; CH_2Ph), 4.88 (dd, $J = 8.2$, 9.1 Hz, 1H; H-2′), 4.80, 4.64 (2 × d, $J = 12.3$ Hz, 2H; CH_2Ph), 4.72, 4.51 (2 × d, $J = 12.4$ Hz, 2H; CH_2Ph), 4.58 (d, $J = 3.7$ Hz, 1H; H-1), 3.83–3.79 (m, 2H; H-3,4), 3.74 (d, $J = 10.5$ Hz, 1H; H-4′), 3.64 (dd, $J = 2.3$, 10.4 Hz, 1H; H-6), 3.56 (m, 1H; H-5), 3.53 (dd, $J = 3.5$, 9.5 Hz, 1H; H-2), 3.44–3.37 (m, 2H; H-6′,6′), 3.35 (s, 3H; MeO), 2.04, 1.78 (2 × s, 6H; 2 × AcO), 1.70 (dd, $J = 1.4$, 6.6 Hz, 3H; H-9′), 1.42, 1.39 (2 × s, 6H; 2 × Me); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 169.94$, 169.07 (C=O), 139.34, 138.15, 137.24 (Ph_q), 128.33, 126.87 (C-7′,8′), 128.07–127.05 (Ph), 100.07 ($C_{isopropyl}$), 98.20 (C-1′), 96.39 (C-1), 79.83, 78.69, 76.80, 73.96, 73.74, 73.32, 73.12, 69.64, 55.07 (MeO), 28.96, 28.73 ($Me_{isopropyl}$), 20.56, 20.30 (Ac), 18.46 (C-9′). $C_{44}H_{54}O_{13} \cdot 0.25\,H_2O$: calcd C 66.44, H 6.91; found C 66.12, H 6.83.

Methyl 4-*O*-(2,3-di-*O*-acetyl-5-*C*-(propen-1-yl)-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (17): To a solution of the isopropylidene derivative **16** (380 mg, 0.48 mmol) in acetic acid (8 mL) water (2 mL) was added dropwise. The mixture was stirred at 50–60 °C for 30 min, poured into water (100 mL) and extracted with ethyl acetate (100 mL). The extract was washed successively with saturated aqueous sodium hydrogencarbonate and brine, dried and evaporated. The residual syrup was subjected to column chromatography on silica gel with 4:1 → 2:1 (v/v) toluene/ethyl acetate to give the 4′,6′-diol **17** (283 mg, 79%); $R_f = 0.34$ (1:1 toluene/ethyl acetate); $[\alpha]_D^{20} = -19$ ($c = 0.76$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.99$ (qd, $J = 6.5$, 16.1 Hz, 1H; H-8′), 5.62 (dd, $J = 1.6$, 16.1 Hz, 1H; H-7′), 5.04 (t, $J = 9.8$ Hz, 1H; H-3′), 4.98, 4.84 (2 × d, 2H, $J = 12.9$ Hz, CH_2Ph), 4.91 (d, $J = 8.1$ Hz, 1H; H-1′), 4.81 (dd, $J = 8.3$, 10.0 Hz, 1H; H-2′), 4.78, 4.65 (2 × d, $J = 11.3$ Hz, 2H; CH_2Ph), 4.70, 4.49 (2 × d, $J = 12.4$ Hz, 2H; CH_2Ph), 3.91 (dd, $J = 5.3$, 10.1 Hz, 1H; H-4′), 3.80–3.76 (m, 2H; H-3,4), 3.64 (dd, $J = 3.1$, 10.9 Hz, 1H; H-6), 3.57 (m, 1H; H-5), 3.54 (dd, $J = 3.8$, 9.6 Hz, 1H; H-2), 3.43 (dd, $J = 1.5$, 10.7 Hz, 1H; H-6), 3.35 (s, 3H; MeO), 3.26 (dd, $J = 1.8$, 11.9 Hz, 1H; H-6′), 3.11 (dd, $J = 4.4$, 12.2 Hz, 1H; H-6′), 2.92 (d, $J = 5.3$ Hz, 1H; H-4′), 2.05, 1.79 (2 × s, 6H, 2 × AcO), 1.69 (dd, $J = 1.5$, 5.5 Hz, 3H; H-9′); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 170.96$, 169.24 (C=O), 139.34, 138.26, 137.30 (Ph_q), 131.31, 124.60 (C-7′,8′), 128.54–126.49, 98.37 (C-1′), 95.60 (C-1), 79.92, 78.93, 78.52, 76.56, 74.84, 73.58, 73.47, 73.00, 69.88, 68.94, 67.13, 66.96, 55.28 (MeO), 20.79, 20.56 (Ac), 18.40 (C-9′). $C_{41}H_{50}O_{13}$: calcd C 65.59, H 6.71; found C 65.56, H 6.73.

Methyl 4-*O*-(2,4-di-*O*-acetyl-3,6-anhydro-5-*C*-(propen-1-yl)-β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (13): To a solution of the diol **17** (183 mg, 0.24 mmol) in dichloromethane (7 mL) and pyridine (1.5 mL) was added *p*-toluenesulfonyl chloride (100 mg). The mixture was stirred at room temperature overnight and then additional *p*-toluenesulfonyl chloride (300 mg) was added to the mixture. The solution was further stirred at room temperature for 9 h, poured into ice-water and extracted with ethyl acetate. The extract was washed successively with 1 M hydrochloric acid, saturated aqueous sodium hydrogencarbonate and brine, dried over anhydrous sodium sulfate and evaporated. Chromatography of the residue on a column of silica gel with 4:1 (v/v) toluene/ethyl acetate gave unchanged **17** (55 mg, 30%) and the 6′-tosylate **5** (108 mg, 50%); $R_f = 0.62$ (1:1 toluene/ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.06$ (qd, $J = 6.5$, 16.0 Hz, 1H; H-8′), 5.66 (dd, $J = 1.6$, 16.1 Hz, 1H; H-7′), 5.11–5.06 (m, 2H; 1/2CH_2Ph, H-3′), 4.92–4.90 (m, 2H; H-1′,2′), 4.74–4.45 (m, 6H; 5/2CH_2Ph, H-1), 4.14 (d, $J = 11.7$ Hz, 1H; H-6′), 4.08 (dd, $J = 5.5$, 10.1 Hz, 1H; H-4′), 3.79 (t, $J = 10.1$ Hz, 1H; H-3), 3.70 (t, $J = 9.7$ Hz, 1H; H-4), 3.66 (dd, $J = 2.6$, 10.8 Hz, 2H; H-6), 3.58 (d, $J = 11.7$ Hz, 1H; H-6′), 3.53 (br d, $J = 9.3$ Hz, 1H; H-5), 3.49–3.38 (m, 2H; H-6,2′), 3.32 (s, 3H; MeO), 3.04 (d, $J = 5.6$ Hz, OH-4′), 2.42 (s, 3H; Ts), 2.10, 1.81 (2 × s, 6H, 3 × AcO), 1.65 (dd, $J = 1.5$, 6.5 Hz, 3H; H-9′); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 133.47$, 122.64 (C-7′,8′), 129.82–126.84 (Ph), 98.29 (C-1′), 96.18 (C-1), 80.39, 79.04, 77.91, 73.93, 73.50, 72.77, 72.33, 71.13, 69.64, 68.44, 55.25 (MeO), 21.55, 20.79, 20.53 (Ac), 18.25 (C-9′). The tosylate **5** (180 mg, 0.20 mmol) was dissolved in a mixture of ethanol (20 mL) and 2 M potassium hydroxide (20 mL). The solution was stirred at 70–80 °C for 4 h, cooled to room temperature and partitioned between 10% aqueous ammonium chloride and ethyl acetate. The organic layer was washed successively with 10% aqueous ammonium chloride and brine, dried with anhydrous sodium sulfate and evaporated. The residue was dissolved in 2:1 (v/v) pyridine/acetic anhydride (15 mL). The solution was stirred at 60 °C for 5 h, evaporated and coevaporated with toluene. The residue was chromatographed on a column of silica gel with 4:1 (v/v) toluene/ethyl acetate to give the 3′,6′-anhydro derivative **13** (123 mg, 84%); $R_f = 0.68$ (7:3 toluene/ethyl acetate); $[\alpha]_D^{20} = +14.9$ ($c = 0.89$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.76$ (qd, $J = 6.6$, 15.7 Hz, 1H; H-8′), 5.20 (dd, $J = 1.9$, 15.0 Hz, 1H; H-7′), 5.21 (s, 1H; H-1′), 5.05, 4.83 (2d, $J = 11.4$ Hz, 2H; CH_2Ph), 4.98 (d, $J = 3.4$ Hz, 1H; H-2′), 4.69 (d, $J = 12.0$ Hz, 1/2CH_2Ph), 4.68 (d, $J = 5.3$ Hz, 1H; H-4′), 4.59–4.50 (m, 5H, 3/2CH_2Ph, H-1,3′), 4.38 (d, $J = 9.6$ Hz, 1H; H-6′), 3.99–3.96 (m, 2H; H-3,4), 3.78–3.73 (m, 2H; H-5,6), 3.68 (dd, $J = 2.6$, 11.6 Hz, 1H; H-6), 3.60 (dd, $J = 3.8$, 9.1 Hz, 1H; H-2), 3.58 (d, $J = 9.5$ Hz, 1H; H-6′), 3.56 (s, 3H, MeO), 2.04, 1.91 (2 × s, 6H, 2 × AcO), 1.59 (dd, 3H, $J = 1.6$, 6.6 Hz, 1H; H-9′); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 139.14$, 137.97, 131.49, 128.36, 128.10, 127.37, 127.46, 127.20, 118.96, 99.81 (C-1′), 97.79 (C-1), 80.39, 74.81, 74.61, 73.23, 72.71, 72.06, 70.63, 70.52, 69.85, 68.85, 55.47 (MeO), 20.38, 20.15 (Ac), 17.55 (C-9′). $C_{41}H_{48}O_{12} \cdot 0.25\,H_2O$: calcd C 66.79, H 6.63; found C 66.72, H 6.69.

Methyl 4-*O*-(methyl-3-*O*,5-*C*-methylene-α-L-idopyranuronate)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (4): Compound **13** (130 mg, 0.18 mmol) was dissolved in 4:1 (v/v) dichloromethane/methanol (10 mL), the solution was stirred at −78 °C, and then ozone was bubbled through the solution for 30 min with stirring at −78 °C. The solution became pale blue. Dimethylsulfide (1 mL) was added to the solution and then the cooling bath was removed. The mixture was allowed to stand at room temperature for 7 h and was then evaporated under reduced pressure. The residue was suspended in *tert*-butyl alcohol (8 mL), 2-methyl-2-butene (3 mL) and water (8 mL). To the mixture were successively added sodium dihydrogen phosphate dihydrate (350 mg) and sodium chlorite (350 mg). The suspension was vigorously stirred at room temperature overnight and partitioned between water (100 mL) and ethyl acetate (80 mL). The organic layer was washed with 10% aqueous sodium thiosulfate and then brine, dried (Na_2SO_4) and evaporated. The residue was dissolved in diethyl ether (20 mL) and cooled in an ice bath. An ethereal solution of diazomethane (ca. 10 mL), prepared from 1-methyl-3-nitro-1-nitrosoguanidine (ca. 100 mg) and 40% (w/w) aqueous potassium hydroxide (10 g) in diethyl ether (40 mL) at 0 °C, was added dropwise to the solution. The pale yellow solution was shaken in an ice bath for 30 min, quenched by adding acetic acid and evaporated to dryness. The residue was subjected to column chromatography on silica gel with 9:1 (v/v) toluene/EtOAc giving a mixture of unknown products (32 mg) and the crude methyl ester **18** (45 mg, 31%); $R_f = 0.28$ (3:1 petroleum ether/ethyl acetate), 0.36 (10:1 toluene/acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.10-8.04$, 7.63–7.55, 7.48–7.13 (m, 15H; Ph), 5.32 (s, 1H; H-1'), 5.17–4.87 (m, 4H; CH_2Ph, H-2',4'), 4.79–4.54 (m, 7H; 2 × CH_2Ph, H-1,3',6'), 4.07–3.97 (m, 2H; H-3,4), 3.63 (s, 3H; MeO), 3.38 (s, 3H; MeO), 2.06, 1.91 (2 × s, 6H, 2 × AcO) [minor signals: $\delta = 5.29$ (s, 0.2H; H-1'), 2.00 (s, 0.6H; AcO), 1.93 (s, 0.6H; AcO)]; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 170.12$, 168.95, 167.64 (C=O), 139.20, 138.11, 137.97 (Ph_q), 132.98, 129.74, 128.39, 127.37, 127.22, 127.05, 100.33 (C-1'), 97.85 (C-1), 80.27, 75.77, 74.55, 73.90, 73.29, 73.20, 72.74, 72.42, 72.33, 70.86, 69.79, 68.82, 55.22, 52.79 (MeO), 20.53 (AcO). To a solution of **18** (45 mg, 60 μmol) in dry methanol (1 mL) was added 1 M methanolic sodium methoxide (0.05 mL). The mixture was stirred overnight at room temperature, neutralized with Dowex 50 (H^+ form) and evaporated. Chromatography of the residue with 4:1 to 1:1 (v/v) petroleum ether/ethyl acetate gave the diol **4** (28 mg, overall 24%) as hygroscopic amorphous solid; $R_f = 0.48$ (HPTLC: 88:12 dichloromethane/acetone); $[\alpha]_D^{20} = +0.4$; $[\alpha]_{546\,nm}^{20} = +4.4$ ($c = 0.46$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.26$ (s, 1H; H-1'), 5.04, 4.83 (2 × s, $J = 11.1$ Hz, 2H; CH_2Ph), 4.68 (d, $J = 12.0$ Hz, 2H; CH_2Ph), 4.63–4.52 (m, 5H; 3/2CH_2Ph, H-1, OH-4'), 4.53 (d, $J = 9.8$ Hz, 1H; H-6'), 4.44 (brs, 1H; H-4'), 4.18 (dd, $J = 4.0$, 5.4 Hz, 1H; H-3'), 3.96 (d, $J = 9.7$ Hz, 1H; H-6'), 3.96 (t, $J = 8.9$ Hz, 1H; H-3), 3.91 (t, $J = 8.9$ Hz, 1H; H-4), 3.77–3.69 (m, 3H; H-5,6,2'), 3.66 (dd, $J = 2.1$, 10.7 Hz, 1H; H-6), 3.59 (dd, $J = 3.6$, 9.2 Hz, 1H; H-2), 3.54 (s, 3H; MeO), 3.35 (s, 3H; MeO), 3.23 (d, $J = 8.9$ Hz, OH-2'); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 168.72$ (C=O), 138.99, 137.85, 129.79, 128.98, 128.39, 128.13, 128.04, 127.90, 127.75, 127.37, 127.28, 127.20, 127.11, 125.34, 104.39 (C-1'), 97.94 (C-1), 81.44, 80.04, 79.92, 76.50, 74.14, 73.53, 73.29, 73.23, 72.82, 72.36, 72.30, 69.76, 68.53, 55.25 (MeO), 52.71 (MeO). $C_{36}H_{42}O_{12} \cdot 2.5\,H_2O$: calcd C 60.75, H 6.66; found C 60.50, H 6.67.

Further elution of the column with the same solvent gave a small amount of di-*O*-benzyl derivative; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.42-7.23$ (m, 10H; 2 × Ph), 5.38 (s, 1H; H-1'), 5.02, 4.85 (2 × d, $J = 11.0$ Hz, 2H; CH_2Ph), 4.71 (d, $J = 12.0$ Hz, 1/2 × CH_2Ph), 4.62–4.49 (m, 4H; 1/2 × CH_2Ph, H-1,4',6'), 4.30 (dd, $J = 3.9$, 5.5 Hz, 1H; H-3'), 4.02–3.90 (m, 3H; H-3,4,2'), 3.60 (s, 3H; Me), 3.53 (dd, $J = 3.5$, 9.4 Hz, 1H; H-2), 3.36 (s, 3H; Me).

Methyl 4-*O*-(methyl-4-*O*-benzoyl-3-*O*,5-*C*-methylene-α-L-idopyranuronate)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (19): After coevaporation with toluene, compound **4** (18 mg, 27 μmol) was dissolved in 1:2 (v/v) pyridine/dichloromethane (1.5 mL) and a 1 M solution of benzoyl chloride in dichloromethane (80 μL) was added. The mixture was stirred at room temperature for 2 d, quenched with methanol and evaporated. The residue was chromatographed on silica gel with 3:1 → 2:1 (v/v) toluene/ethyl acetate to give unchanged **4** (6 mg, 33%) and the 4'-benzoate **19** (10 mg, 48%); $R_f = 0.52$ (1:1, toluene/ethyl acetate); $[\alpha]_D^{20} = 0$; $[\alpha]_{546\,nm}^{20} = +12$ ($c = 0.15$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 5.53$ (d, $J = 5.3$ Hz, 1H; H-4'), 5.43 (d, $J = 1.3$ Hz, 1H; H-1'), 5.03, 4.89 (2 × d, $J = 10.9$ Hz, 2H; CH_2Ph), 4.72, 4.59 (2 × d, $J = 12.1$ Hz, 2H; CH_2Ph), 4.60 (d, $J = 2.5$ Hz, 1H; H-1), 4.57, 4.52 (2 × d, $J = 11.9$ Hz, 2H; CH_2Ph), 4.46 (dd, $J = 2.9$, 5.8 Hz, 1H; H-3'), 4.45 (d, $J = 9.7$ Hz, 1H; H-6'), 4.16 (d, $J = 9.6$ Hz, 1H; H-6'), 3.99 (t, $J = 9.0$ Hz, 1H; H-3), 3.95 (t, $J = 9.1$ Hz, 1H; H-4), 3.82 (brs, 1H; H-2'), 3.80 (dd, $J = 3.3$, 11.0 Hz, 1H; H-6), 3.74 (ddd, $J = 2.3$, 3.3, 9.6 Hz, 1H; H-5), 3.67 (dd, $J = 2.2$, 11.0 Hz, 1H; H-6), 3.57 (dd, $J = 2.4$, 9.1 Hz, 1H; H-2'), 3.59 (s, 3H; MeO), 3.37 (s, 3H; MeO); crosspeaks from H(4')–H($6'_{exo}$), H(4)–H(2') and H(4)–H(1') were observed in a 2D NOESY spectrum; ESI-MS: $C_{43}H_{46}O_{13}$ (*M*) 770.29; *m/e*: 793 (*M* + Na^+), 809 (*M* + K^+).

Methyl 4-*O*-(methyl-4-*O*-(4-*O*-(benzyl-4-*O*-(6-*O*-acetyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-2,3-di-*O*-methyl-β-D-glucopyranuronate)-3,6-di-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-3-*O*,5-*C*-methylene-α-L-idopyranuronate)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (2) and **methyl 4-*O*-(methyl-2-*O*-(4-*O*-(benzyl-4-*O*-(6-*O*-acetyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-2,3-di-*O*-methyl-β-D-glucopyranuronate)-3,6-di-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl)-3-*O*,5-*C*-methylene-α-L-idopyranuronate)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (20)**: The diol **4** (29 mg, 44 μmol) was dried by coevaporation with toluene and dissolved in dry dichloromethane (1.5 mL). To the solution were successively added powdered 4 Å molecular sieves (65 mg) and a 1:1 anomeric mixture of 4-*O*-(benzyl-4-*O*-(6-*O*-acetyl-2,3,4,-tri-*O*-methyl-α-D-glucopyranosyl)-2,3-di-*O*-methyl-β-D-glucopyranuronate)-3,6-di-*O*-acetyl-2-*O*-benzyl-D-glucopyranosyl trichloroacetimidate **3** (45 mg, 44 μmol). The suspension was stirred under a nitrogen atmosphere at −20 °C for 30 min. To the suspension was added a solution of TMSOTf (1.27 μL, 6.6 μmol) in dichloromethane (127 μL). The mixture was stirred at −20 °C for 1 h, after which TLC showed complete disappearance of the starting materials **3** and **4**. Sodium hydrogencarbonate (50 mg) was added to quench the reaction. The mixture was stirred at the same temperature for 30 min and filtered. The filtrate was washed successively with aqueous sodium hydrogencarbonate and water, dried with anhydrous magnesium sulfate and evaporated. Column chromatography of the residue on Sephadex LH-20 with 1:1 (v/v) dichloromethane/methanol followed by silica gel chromatography with gradient elution with 0% to ca. 20% (v/v) acetone/dichloromethane gave the pentasaccharide **2** (29 mg, 43%) and its 2'-isomer **20** (12 mg, 18%).

Compound 2: $R_f = 0.65$ (HPTLC: 88:12 dichloromethane/acetone); $[\alpha]_D^{20} = +58$ ($c = 0.10$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 5.54$ (d, $J = 3.5$ Hz, 1H; H-1D), 5.34 (t, $J = 9.5$ Hz, 1H; H-3F), 5.34 (s, 1H; H-1G), 5.22, 5.08 (2 × d, $J = 12.0$ Hz, 2H; CH_2Ph), 5.07, 4.82 (2 × d, $J = 11.6$ Hz, 2H; CH_2Ph), 4.82 (d, $J = 4.0$ Hz, 1H; H-1F), 4.69 (d, $J = 12.0$ Hz, 1H; 1/2CH_2Ph), 4.62 (d, $J = 11.0$ Hz, 1/2CH_2Ph), 4.60 (d, $J = 12.0$ Hz, 1/2CH_2Ph), 4.57 (d, $J = 12.5$ Hz, 1/2CH_2Ph), 4.56 (d, $J = 3.0$ Hz, 1H; H-1H), 4.55–4.50 (m, 4H; 3/2CH_2Ph, H-3G), 4.52 (d, $J = 9.3$ Hz, 1H; H-6G), 4.51 (d, $J = 11.8$ Hz, 1H; H-6F), 4.32 (dd, $J = 2.0$, 12.0 Hz, 1H; H-6D), 4.30–4.27 (m, 2H; H-4G, OH), 4.25 (dd, $J = 4.0$, 11.7 Hz, 1H; H-6D), 4.21 (dd, $J = 3.0$, 11.8 Hz, 1H; H-6F), 4.13 (d, $J = 8.8$ Hz, 1H; H-1E), 4.00 (t, $J = 9.0$ Hz, 1H; H-4H), 3.98 (t, $J = 9.0$ Hz, 1H; H-3H), 3.95 (t, $J = 9.3$ Hz, 1H; H-4E), 3.88 (d, $J = 9.3$ Hz, 1H; H-6G), 3.85 (d, $J = 9.5$ Hz, 1H; H-5E), 3.82 (dd, $J = 3.3$, 13.0 Hz, 1H; H-2G), 3.78–3.73 (m, 2H; H-5H, 5F), 3.71 (brs, 2H; H-6H), 3.64–3.60 (m, 2H; H-4F, 2H), 3.57 (s, 6H; 2 × MeO), 3.55, 3.52, 3.48, 3.46, 3.37 (5 × s, 15H; 5 × MeO), 3.54 (dd, $J = 4.2$, 9.6 Hz, 1H; H-2F), 3.46–3.44 (m, 1H; H-5D), 3.38 (t, $J = 9.5$ Hz, 1H; H-3D), 3.34 (t, $J = 9.9$ Hz, 1H; H-3E), 3.15 (dd, $J = 3.7$, 10.0 Hz, 1H; H-2D), 3.07 (t, $J = 9.5$ Hz, 1H; H-4D), 3.00 (dd, $J = 9.0$, 9.9 Hz, 1H; H-2E), 2.14, 2.09, 1.89 (3 × s, 9H; 3 × AcO); NOESY crosspeaks for H(1D)–H(4E), H(1G)–H(3H,4H) and H(1F)–H(4G,OH) were observed; ESI-MS: $C_{79}H_{98}O_{31}$ (*M*) 1542.61; found: *m/e* 1561 (*M* + NH_4^+), 1565 (*M* + Na^+), 1582 (*M* + K^+).

Compound 20: $R_f = 0.33$ (HPTLC: 88:12 dichloromethane/acetone); $[\alpha]_D^{20} = +70$ ($c = 0.13$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 5.48$ (d, $J = 3.7$ Hz, 1H; H-1D), 5.40 (s, 1H; H-1G), 5.26 (t, $J = 9.7$ Hz, 1H; H-3F), 5.17, 5.05 (2 × d, $J = 12.2$ Hz, 2H; CH_2Ph), 5.03, 5.84 (2 × d, 2H, $J = 11.1$ Hz, 2H; CH_2Ph), 4.86 (d, $J = 3.9$ Hz, 1H; H-1F), 4.68, 4.56 (2 × d, $J = 12.1$ Hz, 2H; CH_2Ph), 4.59 (d, $J = 3.6$ Hz, 1H; H-1H), 4.56, 4.50 (2 × d, $J = 12.4$ Hz, 2H; CH_2Ph), 4.47 (dd, $J = 1.4$, 11.1 Hz, 1H; H-6F), 4.47 (d, $J = 9.5$ Hz, 1H; H-6G), 4.37 (brt, 1H; H-4G), 4.32 (dd, $J = 3.5$, 5.5 Hz, 1H; H-3G), 4.31, 4.20 (2 × d, $J = 10.3$ Hz, 2H; CH_2Ph), 4.27 (dd, $J = 2.2$, 12.0 Hz, 1H; H-6D), 4.22 (dd, $J = 4.0$, 12.2 Hz, 1H; H-6D), 4.17 (dd, $J = 5.3$, 12.2 Hz, 1H; H-6F), 4.14 (d, $J = 7.8$ Hz, 1H; H-1E), 4.00 (d, $J = 9.5$ Hz, 1H; H-6G), 3.96–3.93 (m, 1H; H-5F), 3.95 (t, $J = 9.7$ Hz, 1H; H-3H), 3.93 (t, $J = 9.7$ Hz, 1H; H-4H), 3.90 (t, $J = 9.2$ Hz, 1H; H-4E), 3.89 (d, $J = 3.8$ Hz, 1H; H-2G), 3.82 (d, $J = 9.8$ Hz, 1H; H-5E), 3.77 (dd, $J = 3.2$, 11.5 Hz, 1H; H-6H), 3.64–3.51 (m, 4H; H-4F,2H,5H,6H), 3.61, 3.51, 3.38, 3.47, 3.32 (5 × s, 15H; 5 × MeO), 3.55 (s, 6H; 2 × MeO), 3.43 (m, 1H; H-5D), 3.37–3.29 (m, 3H; H-3D,3E,2F), 3.11 (dd, $J = 3.4$, 9.8 Hz, 1H; H-2D), 3.04 (dd, $J = 8.8$, 10.1 Hz, 1H; H-4D), 2.98 (dd, $J = 7.9$, 9.1 Hz, 1H; H-2E), 2.10, 2.04, 1.85 (3 × s, 9H; 3 × AcO); NOESY crosspeak for H(1F)–H(1G) was observed; ESI-MS: $C_{79}H_{98}O_{31}$ (*M*) for 1542.61; found: *m/e* 1565 (*M* + Na^+), 1580 (*M* + K^+).

Methyl 4-*O*-(sodium 4-*O*-(4-*O*-(sodium 4-*O*-(6-*O*-sulfo-2,3,4,-tri-*O*-methyl-α-D-glucopyranosyl)-2,3-di-*O*-methyl-β-D-glucopyranuronate)-2,3,6-tri-*O*-sulfo-α-D-glucopyranosyl)-3-*O*,5-*C*-methylene-2-*O*-sulfo-α-L-idopyranuronate)-2,3,6-tri-*O*-sulfo-α-D-glucopyranoside octasodium salt (1): To a solution of **2** (25 mg, 16 μmol) in a mixture of *tert*-butyl alcohol (4 mL) and water (0.5 mL) was added 10% palladium on carbon (25 mg). The suspension was shaken under a hydrogen atmosphere at room temperature for 5 h. Water (1.5 mL) was added to the suspension and the mixture was shaken under a hydrogen atmosphere overnight. TLC analysis of the mixture with 16:7:1.6:4 (v/v/v/v) ethyl acetate/pyridine/acetic acid/water showed a single spot ($R_f = 0.58$). The catalyst was filtered off and the filtrate was concentrated to give the product (14 mg), for which the ^{1}H NMR spectrum in D_2O showed complete disappearance of aromatic protons. The residue was dissolved in 0.5 M sodium hydroxide (2 mL). The solution was stirred overnight at room temperature, neutralized with 2 M hydrochloric acid and concentrated to ca. 1 mL. The solution was chromatographed on a column of Sephadex G-25 (1.6 × 60 cm) with 9:1 (v/v) water/acetonitrile to give the unprotected pentasaccharide **21** (11.5 mg, 75%); $R_f = 0.67$ (16:7:1.6:4 ethyl acetate/pyridine/acetic acid/water); ^{1}H NMR (400 MHz, D_2O): $\delta = 5.39$ (d, $J = 3.7$ Hz, 1H; H-1D), 5.08 (d, $J = 1.7$ Hz, 1H; H-1G), 5.03 (d, $J = 4.0$ Hz, 1H; H-1F), 4.74 (d, $J = 4.0$ Hz, 1H; H-1H), 4.64 (d, $J = ca.$ 6 Hz, 1H; H-4G overlapping with HDO), 4.49 (d, $J = 8.0$ Hz, 1H; H-1E), 4.39 (dd, $J = 2.5$, 5.7 Hz, 1H; H-3G), 4.30 (d, $J = 10.0$ Hz, 1H; H-6G), 4.07 (d, $J = 10.0$ Hz, 1H; H-6G), 3.57, 3.56, 3.55, 3.49, 3.46, 3.44 (6 × s, 18H; 6 × MeO), 3.24 (dd, $J = 3.7$, 10.0 Hz, 1H; H-2D), 3.21 (t, $J = 9.5$ Hz, 1H; H-4D), 3.19 (dd,

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J = 8.0, 9.2 Hz, 1H; H-2E). Compound **21** (11.5 mg, 12 μmol) was dissolved in water (2 mL), passed through a short column of Dowex 50 (H^+ form) and concentrated. The residue was dried by coevaporation three times with DMF and dissolved in DMF (0.8 mL). To this solution was added sulfur trioxide triethylamine complex (88 mg, 0.48 mmol), and the mixture was stirred under nitrogen overnight at 55 °C. The reaction mixture was quenched by addition of sodium hydrogencarbonate (163 mg) and water (1.4 mL), stirred for 1 h and concentrated. The residue was subjected to chromatography on a column (2.6 × 70 cm) of Sephadex G-25 with 9:1 (v/v) water/acetonitrile as the eluant to give the octasulfate **1** (22 mg, 100%); $[\alpha]_D^{20}$ = + 58 (c = 1.0, H_2O); ^{1}H NMR (400 MHz, D_2O): δ = 5.51 (s, 1H; H-1G), 5.31 (d, J = 3.8 Hz, 1H; H-1D), 5.24 (d, J = 3.6 Hz, 1H; H-1F), 5.00 (d, J = 3.6 Hz, 1H; H-1H), 4.61 (t, J = 8.9 Hz, 1H; H-3H overlapping with the signal of HDO), 4.56–4.49 (m, 4H; H-1E,3F,2G,3G), 4.43 (dd, J = 1.5, 11.5 Hz, 1H; H-6H), 4.33 (d, J = 10.2 Hz, 1H; H-6G), 4.29 (dd, J = 3.0, 12.0 Hz, 1H; H-6F), 4.28 (d, J = 4.0 Hz, 1H; H-4G), 4.21 (dd, J = 3.8, 9.8 Hz, 1H; H-2H), 4.20–4.10 (m, 4H; H-6D,2F,6F,6H), 4.00 (d, J = 11.2 Hz, 1H; H-6G), 3.97 (dd, J = 2.4, 12.4 Hz, 1H; H-6D), 3.97 (m, 1H; H-5F), 3.92–3.89 (m, 2H; H-4H, 5H), 3.83 (dd, J = 8.9, 9.7 Hz, 1H; H-4F), 3.72 (dd, J = 9.2, 9.5 Hz, 1H; H-4E), 3.72 (td, J = 1.7, 10.7 Hz, 1H; H-5D), 3.56 (d, J = 9.8 Hz, 1H; H-5E), 3.49, 3.47, 3.46, 3.42, 3.39, 3.31 (6 × s, 18H; 6 × MeO), 3.39 (dd, J = 8.6, 10.7 Hz, 1H; H-3D), 3.36 (dd, J = 9.1, 9.3 Hz, 1H; H-3E), 3.17 (t, J = 10.0 Hz, 1H; H-4D), 3.16 (dd, J = 3.8, 10.0 Hz, 1H; H-2D), 3.11 (dd, J = 7.9, 9.3 Hz, 1H; H-2E); Maldi mass: (*M* ($C_{37}H_{60}O_{52}S_8$) + (Arg–Gly)$_{10}$ + H)$^+$ for 3743.5; found: *m/e* 3745.2.

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[1] J. Choay, J. C. Lormeau, M. Petitou, *Ann. Pharm. Fr.* **1981**, *39*, 37; B. Casu, P. Oreste, G. Torri, G. Zoppetti, J. Choay, J. C. Lormeau, M. Petitou, P. Sinaÿ, *Biochem. J.* **1981**, *197*, 599.

[2] L. Thunberg, G. Bäckström, U. Lindahl, *Carbohydr. Res.* **1982**, *100*, 393; U. Lindahl, L. Thunberg, G. Bäckström, J. Riesenfeld, K. Nordling, I. Björk, *J. Biol. Chem.* **1984**, *259*, 12368.

[3] M. Petitou, P. Duchaussoy, L. Lederman, J. Choay, P. Sinaÿ, *Carbohydr. Res.* **1988**, *179*, 163.

[4] C. A. A. van Boeckel, G. N. Wagenaars, J.-R. Mellema, *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 649; T. Nukada, H. Lucas, P. Konradsson, C. A. A. van Boeckel, *Synlett* **1991**, 365.

[5] P. Westerduin, C. A. A. van Boeckel, J. E. M. Basten, M. A. Broekhoven, H. Lucas, A. Rood, H. van der Heijden, R. G. M. van Amsterdam, T. G. van Dinther, D. G. Meuleman, A. Visser, G. M. T. Vogel, J. B. L. Damm, G. T. Overklift, *Bioorg. Med. Chem.* **1994**, *2*, 1267.

[6] C. A. A. van Boeckel, M. Petitou, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1671.

[7] C. A. A. van Boeckel, T. Beetz, S. F. van Aelst, *Tetrahedron Lett.* **1988**, *29*, 803; D. R. Ferro, A. Provasoli, M. Ragazzi, B. Casu, G. Torri, V. Bossennec, B. Perly, P. Sinaÿ, M. Petitou, J. Choay, *Carbohydr. Res.* **1990**, *195*, 157.

[8] M. Ragazzi, D. R. Ferro, B. Perly, P. Sinaÿ, M. Petitou, J. Choay, *Carbohydr. Res.* **1990**, *195*, 169; P. D. J. Grootenhuis, C. A. A. van Boeckel, *J. Am. Chem. Soc.* **1991**, *113*, 2743.

[9] Trisaccharide imidate **3** was prepared analogously to the similar *O*-methylated derivative [5]; the preparation will be reported elsewhere.

[10] B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Oxford, **1986**.

[11] R. Blattner, R. J. Ferrier, *J. Chem. Soc. Perkin Trans. 1* **1980**, 1523.

[12] G. E. Keck, J. B. Yates, *J. Am. Chem. Soc.* **1981**, *104*, 5829.

[13] R. R. Schmidt, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212, and references cited therein.

[14] C. S. Wilcox, G. W. Long, H. Suh, *Tetrahedron Lett.* **1984**, *25*, 395.

[15] F. Nicotra, L. Panza, G. Russo, *J. Org. Chem.* **1987**, *52*, 5627.

[16] H. Paulsen, M. Paal, *Carbohydr. Res.* **1984**, *135*, 53.

[17] V. Durier, K. Mazeau, C. Gey, H. Driguez, F. R. Taravel, *New J. Chem.* **1993**, *17*, 843.

[18] P. L. Durette, L. Hough, A. C. Anderson, *J. Chem. Soc. Perkin Trans. 1* **1974**, 88.

[19] C. A. G. Haasnoot, F. A. A. M. de Leeuw, C. Altona, *Tetrahedron* **1980**, *36*, 2783.

[20] B. S. Bal, W. E. Childers, H. W. Pinnik, *Tetrahedron* **1981**, *37*, 2091; G. S. Arora, H. Shirahama, T. Matsumoto, *Chem. Ind.* **1983**, 318.

[21] A. B. Smith, III, E. G. Nolen, Jr., R. Shirai, F. R. Blase, M. Ohta, N. Chida, R. A. Hartz, D. M. Fitch, W. M. Clark, P. A. Sprengeler, *J. Org. Chem.* **1995**, *60*, 7837.

[22] J. N. Vos, M. W. P. Kat van den Nieuwenhof, J. E. M. Basten, C. A. A. van Boeckel, *J. Carbohydr. Chem.* **1990**, *9*, 501.

[23] P. Juhasz, K. Biemann, *Carbohydr. Res.* **1995**, *270*, 13.

[24] P. J. Garegg, H. Hultberg, *Carbohydr. Res.* **1981**, *93*, C10.