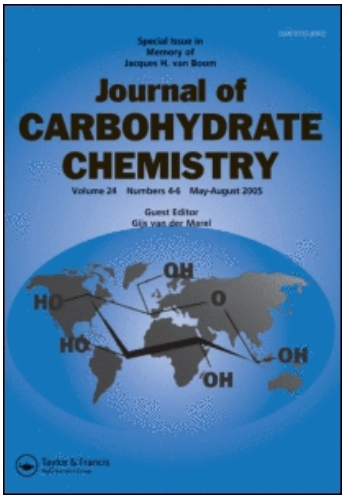

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Comparison of Several Glucuronate Glycosyl Donors

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ABSTRACT

Methyl 3,4-di-*O*-benzyl-[(*S*)-1,2-*O*-(1-cyanoethylidene)]-α-D-glucopyranuronate (**12**), methyl 3,4-di-*O*-benzyl-[(*S*)-1,2-*O*-(1-ethoxyethylidene)]-α-D-glucopyranuronate (**14**), methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-D-glucopyranuronate bromide (**15**), methyl (2-*O*-acetyl-3,4-di-*O*-benzyl-α-D-glucopyranosyl)uronate trichloroacetimidate (**17**), and methyl (2,3,4-tri-*O*-benzyl-α/β-D-glucopyranosyl)uronate trichloroacetimidate (**30**) were synthesized and used as glycosyl donors. Glycosylation reactions of **12** with (5-*R*)-2,3,4,5−tetrahydro-5-trityloxymethyl-2-furanone (**32**) and **14**,**15**,**17** with the corresponding (5-*R*)-2,3,4,5-tetrahydro-5-hydroxymethyl-2-furanone (**31**) provided the exclusively β-linked glucuronide **33** in 69%, 28%, 45%, and 71% yield, respectively. The coupling of donor **30** with acceptor **31** furnished the glucuronated lactone **35** in 70% yield with a surprisingly high content (20%) of the undesired α-linked sugar residue. The structure of **33** was proved by NMR and X-ray diffraction studies. In a model reaction a complete deprotection procedure of the glucuronic acid lactone conjugation was demonstrated.

Key Words: D-glucuronic acid derivatives; Orthoesters; Trichloroacetimidates; Cyanoethylidene derivatives; Glycosylation; X-ray structures.

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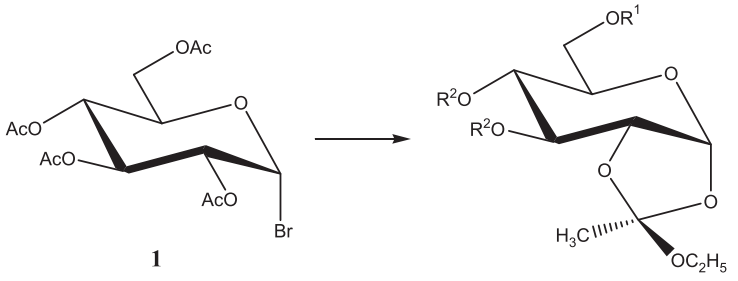
INTRODUCTION

In a program directed towards the synthesis of biologically active lactone *O*-glucuronides, the development of new and more effective uronic acid glycosyl donors became necessary. Two general strategies of synthesizing *O*-glucuronides have been applied: the most commonly used glycosylation with readily accessible but sluggish acyl glucuronate donors, or, rarely, glycosylation with more active benzyl or silyl ether protected glucuronates.[2,3] Generally, the anchimeric assistance of an acyl substituent on *O*-2 leads predominantly to the β-configuration, whereas stereochemical control of the glycosylation by using ether protected intermediates is more complicated.[4] We now report the application of several glucuronate glycosyl donors, potentially of value in both strategies, bearing not only the participating *O*-2 acyl substituent but also the activating benzyl ethers for protection of the remaining hydroxyl groups. As model substances for highly sensitive lactones the commercially available (5-*R*)-2,3,4,5-tetrahydro-5-hydroxymethyl-2-furanone (**31**) and the corresponding (5-*R*)-2,3,4,5−tetrahydro-5-trityloxyethyl-2-furanone (**32**) were chosen.

RESULTS AND DISCUSSION

For the preparation of the orthoester **6**, suitable as a potential intermediate for a series of glucuronate glycosyl donors, it is possible to proceed from the acetylated glucopyranose 1,2-orthoester **2**. The latter one was synthesized by classical in situ anomerization from the peracetylated α-D-glucopyranosyl bromide (**1**)[5] in the presence of *sym*-collidine, ethanol and tetra-*n*-butylammonium bromide (Scheme 1).[6] After Zemplén deacetylation the more accessible primary hydroxyl group of **3** was selectively protected as a *tert*-butyldimethylsilyl ether by a procedure of Sinaÿ et al.[7]



1

2: $\mathbf{R^1} = \mathbf{R^2} = Ac$
3: $\mathbf{R^1} = \mathbf{R^2} = H$
4: $\mathbf{R^1} = Si(CH_3)_2C(CH_3)_3$ $\mathbf{R^2} = H$
5: $\mathbf{R^1} = Si(CH_3)_2C(CH_3)_3$ $\mathbf{R^2} = Bn$
6: $\mathbf{R^1} = H$ $\mathbf{R^2} = Bn$

Scheme 1.

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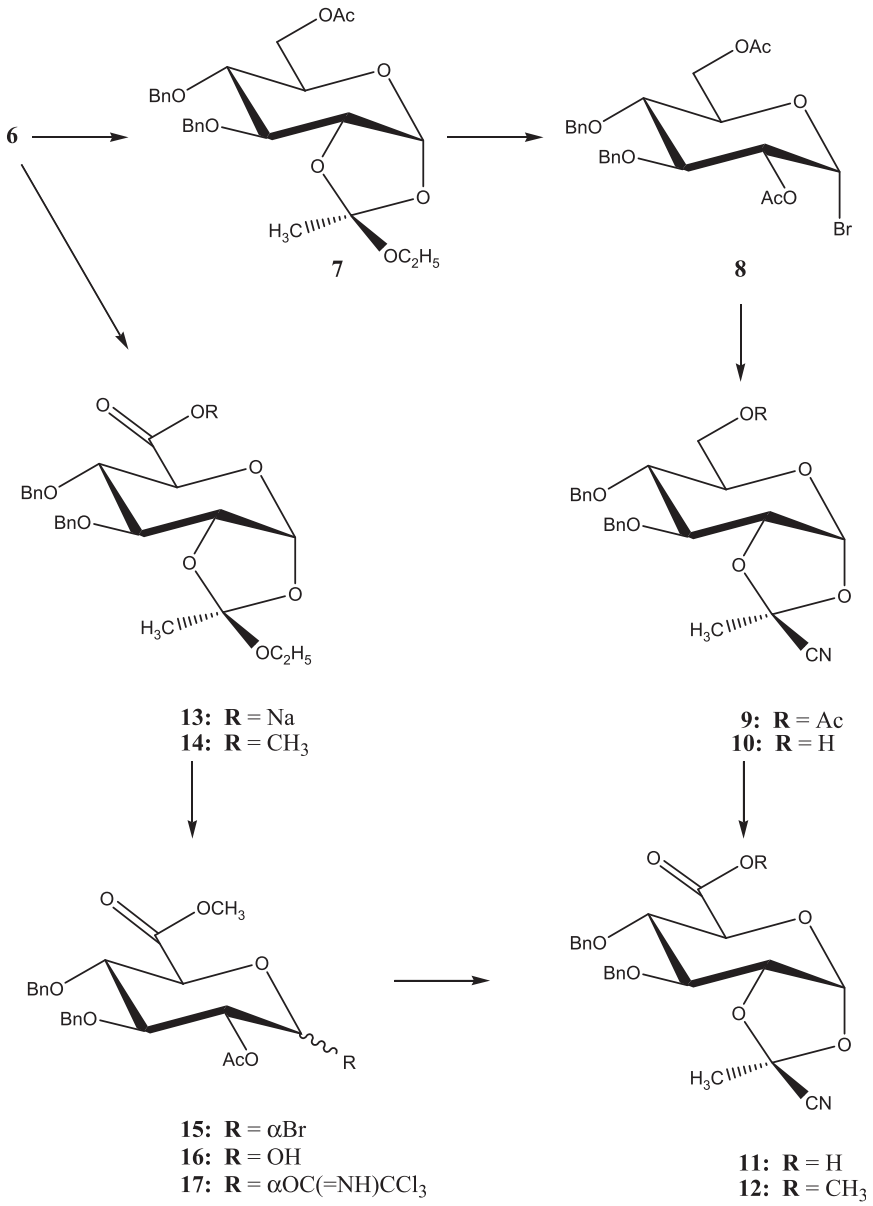
Chromatographic purification provided the *S*-configured 1,2-*O*-(1-ethoxyethylidene) derivative **4** in 87% yield. The benzylation of **4** with benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide (**5**, 71% yield), followed by cleavage of the silyl ether bond with tetra-*n*-butylammonium fluoride trihydrate provided compound **6** (96% yield). Temporary protection of the primary hydroxyl function was then taken over by a simple *O*-6 acetylation of **6** to give **7** which is sufficiently stable in the following steps for the synthesis of the cyanoethylidene derivative **9**. For this purpose, the fully protected orthoester **7** was converted into the bromide **8** by a procedure of Lemieux et al.[8] and then treated with carefully powdered sodium cyanide, tetra-*n*-butylammonium bromide in dry acetonitrile[9] to provide the *exo*/*endo* mixture of **9** in 58% and 15% yield, respectively.

X-Ray and ^{1}H NMR studies[10] were employed to address the absolute configuration of the cyano group in peracetylated 1,2-*O*-(1-cyanoethylidene)-α-D-glycopyranoses. From these results it could be concluded that for cyanoethylidene derivatives with the cyano group in an *exo*-orientation (*S*-configuration), the proton signal for this methyl group appeared downfield ($\delta > 1.80$ ppm) in comparison to those from a methyl group in an *exo*-orientation (*R*-configuration; $\delta < 1.80$ ppm). Owing to the observed values for $\mathbf{9}_{exo}$ [δ 1.87 ppm, C(CN)CH_3] and $\mathbf{9}_{endo}$ [δ 1.76 ppm, C(CN)CH_3], the configurations of the 1,2-*cis*-fused five membered rings could be described as having *endo*- and *exo*-cyanoethylidene groups, respectively. In order to simplify monitoring, the *exo*-isomer $\mathbf{9}_{exo}$ was used exclusively, in the following reaction steps.

Gentle cleavage of the acetyl group was achieved with 0.28 M methanolic hydrochloric acid at room temperature to afford **10** in 69% yield.[11] The oxidation of the partially protected compound **10** with the Jones reagent [chromium(VI)oxide–sulfuric acid] was carried out in 1:5 dichloromethane-acetone,[12] and the resulting glucopyranuronic acid **11** was treated with diazomethane to give the methyl ester **12** in 63% yield (Scheme 2).

Shortening the preparation of **12** was achieved via the orthoester **14** which was obtained by oxidation of **6** with the TEMPO/hypochlorite system[13] and subsequent esterification under phase transfer condition in 65% yield.[14] Treatment of the glucuronate orthoester **14** with acetyl bromide in the presence of tetra-*n*-butylammonium bromide[8] then provided the glycosyl bromide **15**. In contrast to the formation of the methyl 3,4-di-*O*-acetyl-1,2-*O*-[(1-exocyano)ethylidene]-α-D-glucopyranuronate that required drastic reaction conditions (an excess of silver cyanide in boiling xylene[15]) the 3,4-di-*O*-benzyl bromide **15** reacted smoothly with sodium cyanide, tetra-*n*-butylammonium bromide in dry acetonitrile at room temperature to give the desired cyanoethylidene derivative **12** in 65% yield. Thus, the introduction of the benzyl ethers at the *O*-3 and *O*-4 position instead of the acetyl groups increases the reactivity of the bromide **15** significantly.[16,17] Surprisingly, the reaction was very stereoselective because no *endo*-configured cyanoethylidene derivative was observed. Comparing both synthetic pathways for **12** with respect to the overall yield from **6**, the latter (41%) is more efficient than the first one (24%).

Starting from orthoester **14**, a further glucuronate glycosyl donor was prepared. Acid catalyzed hydrolysis of the orthoester[18] leads quantitatively to an α/β-mixture (4:1) of **16**. Treatment of this mixture with sodium hydride and trichloroacetonitrile[19] in dry dichloromethane delivers after three hours at room temperature the benzylated α-trichloroacetimidate **17** bearing an anchimeric acetyl group at position *O*-2 in excellent



Scheme 2.

(94%) yield. Noteworthy, the quality of the sodium hydride sets the limits for the introduction of the trichloroacetimidate function and in some cases appreciable amounts of the β-isomer could be observed. Typically, the small coupling constant $J_{1,2}$ of 3.5 Hz for the α-anomer **17** and the considerable bigger one of 7.1 Hz for **17β** in the ^{1}H NMR spectra illustrated the situation at the anomeric center.

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To avoid the crucial oxidation step during changing from glucose to the glucuronic acid series, we established an alternative synthetic route starting from the glucuronolactone **18**. Compound **18** was transformed, via the peracetylated glucopyranuronate **20**, into the methyl (glucopyranosyl bromide)uronate **21** by a procedure described by Bollenbeck et al.[20] The NMR data for **20** are published herein.

The reaction of **21** with dry ethanol in the presence of *sym*-collidine and tetra-*n*-butylammonium bromide provided the corresponding orthoester **22** in 90% yield. The structure of the orthoester **22** is supported by the analytical data and by the NMR data. The singlet at δ 1.69 in the ^{1}H NMR spectrum is assigned[21] to the *endo*-methyl group at *C*-2 of the dioxolane ring and indicates that the synthesized orthoacetate is an *exo*-isomer. Whereas deacetylation of **22** was achieved under Zemplén conditions, subsequent benzylation of **23** in a basic medium led to β-elimination.[22] Until now, we have not found conditions to avoid this undesired side reaction, even though a multitude of benzylation procedures was tested. In most cases, the main product was the enopyranuronate **24**, whose synthesis on a preparative scale is described in the Experimental.

For the purpose of comparison, the glucuronate glycosyl donor **30**, used by Schmidt et al. for the synthesis of β-glucuronides,[19] was prepared by an alternative route starting from a glucuronate precursor. Therefore, the bromide **21** was treated with allyl alcohol in a mercuric salt promoted glycosylation to provide the allyl β-glycoside **25** in excellent (97%) yield. The analytical data for **25** fully agree with the proposed structure. Thus, the vicinal coupling constant value $J_{1,2}$ = 7.7 Hz in the ^{1}H NMR spectrum indicates clearly the stereochemistry at the anomeric center. Removal of the acetyl groups of **25** was achieved with 0.28 M hydrochloric acid in dry methanol in 90% yield. For activation of the hydroxyl groups, the obtained triol **26** was converted into the trimethylsilyl derivative **27** in 81% yield. However, the reductive etherification of benzaldehyde with that alkoxytrimethylsilane[23] did not give the desired benzylated glucuronate **28** whose preparation succeeded with benzyl bromide in the presence of silver oxide. Strong exclusion of moisture is the fundamental requirement in this step and the benzylated uronate **28** was obtained in 38% average yield. After deallylation of compound **28** with the aid of palladium(II)chloride,[24] the introduction of the trichloroacetimidate group at the anomeric center of **27** in the presence of sodium hydride[19] furnished the trichloroacetimidate **30** as an α/β-mixture in 58% and 14% yield, respectively. The quality of the sodium hydride had again a strong influence on the outcome of the reaction with regard to both yield and ratio of the α/β-anomers, which were separated by HPLC. Characteristic signals in the ^{1}H NMR spectra appeared at δ 6.50 (d, 1H, $J_{1,2}$ = 3.4 Hz) and at δ 5.87 (d, 1H, $J_{1,2}$ = 7.3 Hz) for H-1 and in the ^{13}C NMR spectra at δ 93.96 and at δ 98.02 for C-1 of **30α** and **30β**, respectively (Scheme 3).

For the comparative study, the glucuronate donors **14**,**15**,**17**,**30** were coupled with the lactone **31** in a ratio of 1:1.1. The highest yields of the glucuronated lactones **33** and **35** were achieved with the trichloroacetimidates **17** (71%) and **30** (70%), respectively, in the presence of boron trifluoride etherate. In contrast to the results of Schmidt et al., who also applied the glycosyl donor **30** for the synthesis of β-D-glucopyranosyluronates under comparable conditions,[19] lactone **35** contains a surprisingly high content (20%) of the undesired α-coupled sugar residue,[25] whereas the anchimeric acetyl group at the *O*-2 position of the other donors guarantees the formation of the β-glycosidic linkage on lactone **33** (Scheme 4).

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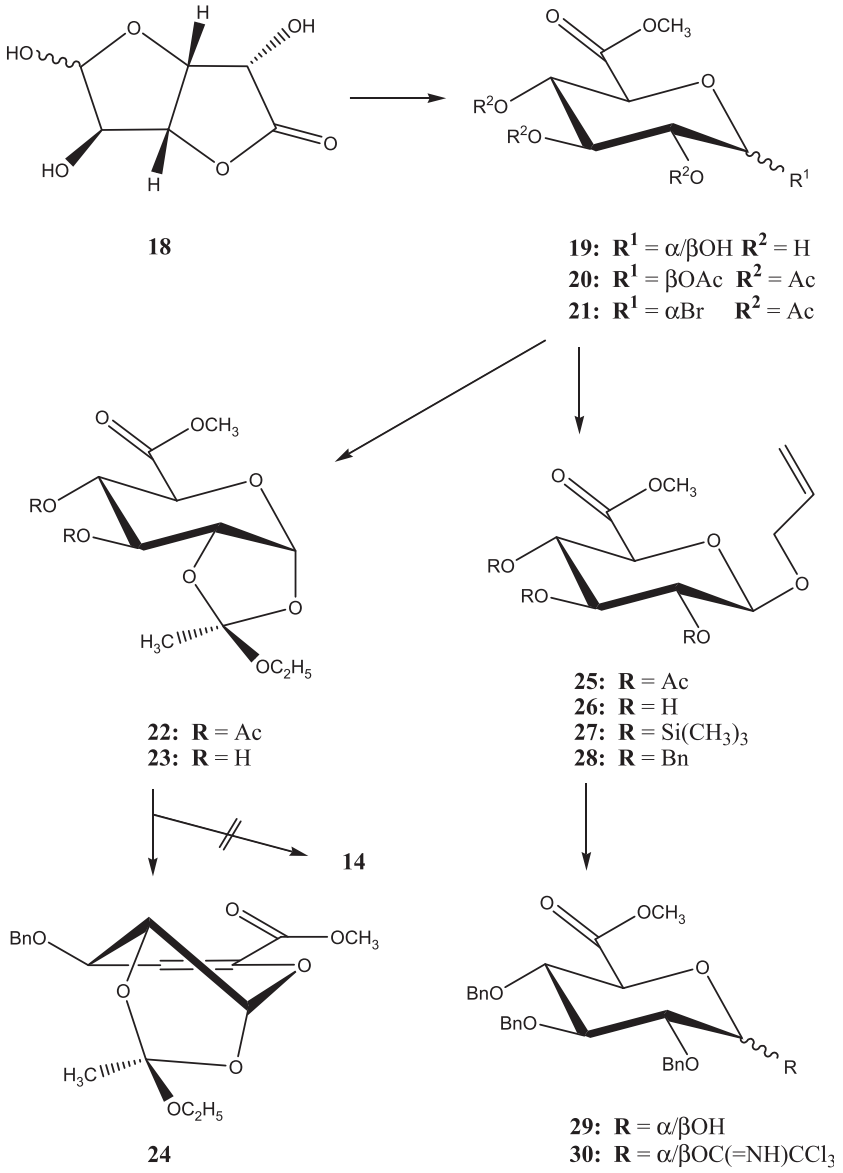
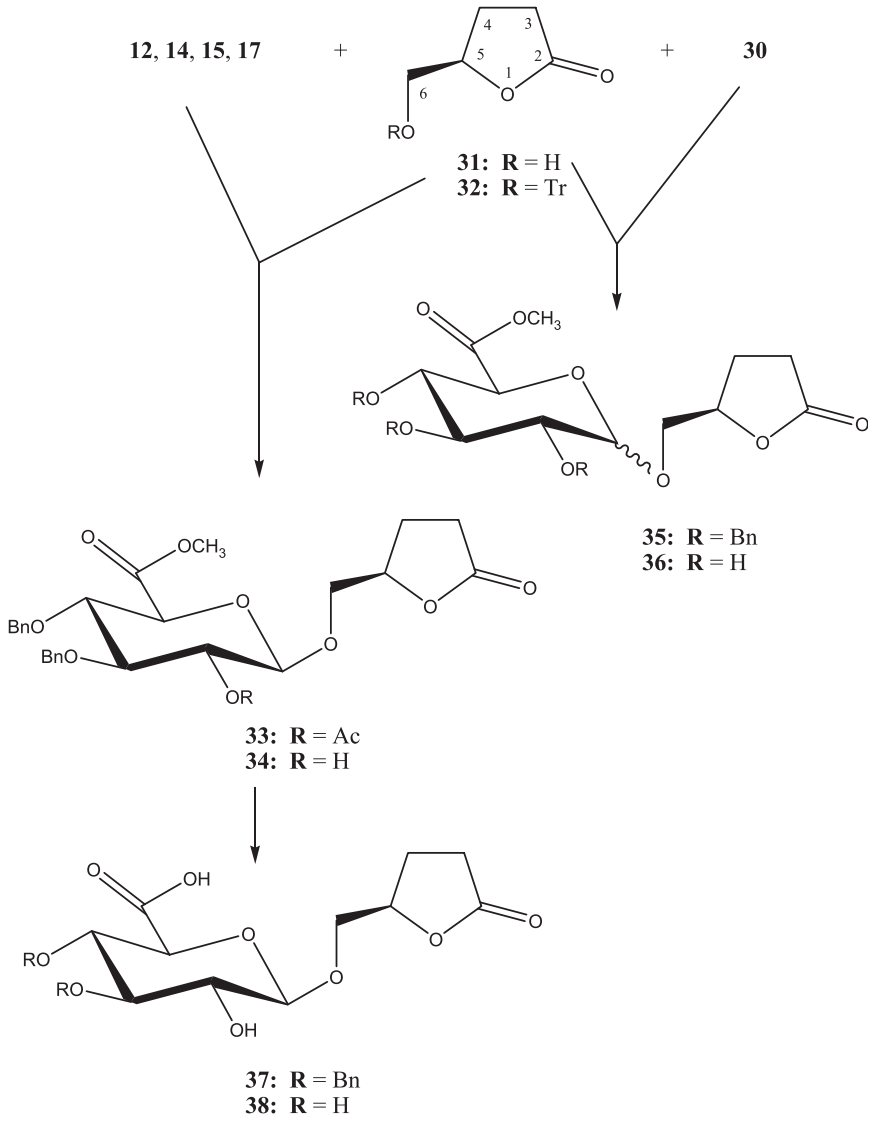


Scheme 3.

Comparable results afforded the tritylcyanoethylidene condensation[15] of the glycosyl donor **12** with the tritylated lactone **32** providing **33** in 69% yield. In the case of the bromide **15**, the glycosylation of **31** with the aid of silver perchlorate in acetonitrile[26] gave a moderate yield of 45%. Surprisingly low was the yield of lactone **33** when the orthoester **14** was used as glycosyl donor. The two-stage glycosylation,



Scheme 4.

involving re-esterification of the starting orthoester with the starting lactone **31** and glycosylation with the resulting orthoester,[27,28] yielded **33** only in 28% (Figure 1).

The NMR data secure the β-glycosidic linkage between the glucuronate residue and the lactone in compound **33**. Thus, the stereochemistry of the glycosidic linkage was assigned based on the large vicinal coupling constant $J_{1,2}$ = 7.5 Hz in the ^{1}H NMR and on the resonance of *C*-1 at δ 101.50 in the ^{13}C NMR spectra. Additionally, the X-ray diffraction studies were done to establish the structure of **33** and to gain

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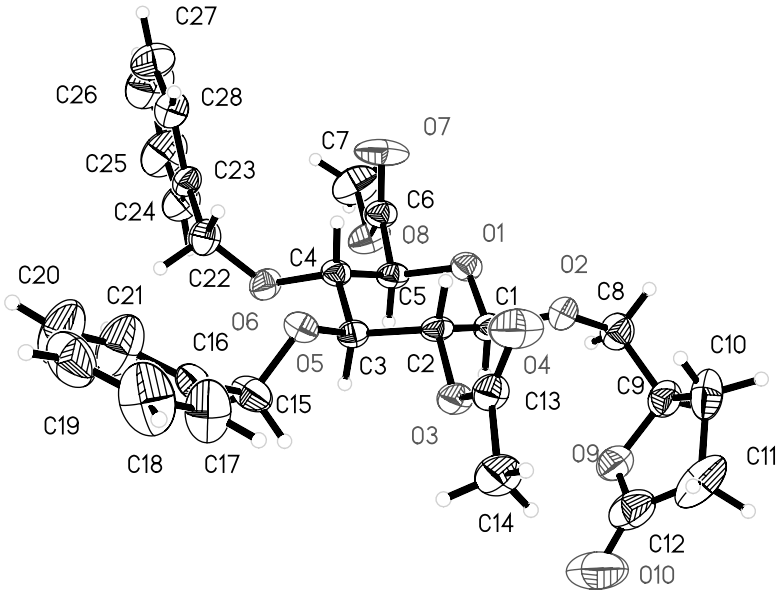

Figure 1. An ORTEP diagram of compound **33**. *(Go to www.dekker.com to view this figure in color.)*

information on the conformation of the pyranose ring. The solid crystallizes in the trigonal space group $P3_1$. The decision to assign $P3_1$ instead of the enantiomorphous space group $P3_2$ could not be made on the basis of the absolute structure parameter but was a result of considering the conformation of the precursor. The sugar ring adopts an almost ideal $^4C_1$ conformation, the puckering parameters are $Q = 0.575(4)$ Å, $\Theta = 4.7(4)^\circ$ and $\Phi = 357(6)^\circ$.

Next, a two-step saponification[29] was used for deesterification of **33**. Therefore, compound **33** was treated at first with sodium methoxide in methanol to provide deacetylated **34** (75%), and then with lithium hydroxide in water-acetone to remove the methyl ester group (**37**, 88%). Finally, the benzyl protective groups of **35** and **37** were removed by hydrogenolysis over Pd-C to give the partially deprotected glucuronate **36**, still containing 20% of the α-anomer, and the fully deprotected pure β-anomeric glucosyluronic acid derivative **38** in yields of 98% and 84%, respectively.

In conclusion, we synthesized several glucuronate derivatives potentially suitable as glycosyl donors. The following glycosylation reactions provided β-linked glucuronides of lactone **31**, which was used as a model compound. The best yields and the best stereoselectivity were obtained with the trichloroacetimidate **17** and with the cyanoethylidene derivative **12**. This result may be connected with the activation of the donors by benzyl protective groups and the anchimeric effect of the acetyl group at the *O*-2 position. It seems, that the glucuronate glycosyl donors **12** and **17** can compete with methyl (ethyl 2-*O*-acetyl-3,4-di-*O*-benzyl-1-thio-β-D-glucopyranosid)uronate and with methyl [ethyl 2-*O*-acetyl-3,4-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxane-1,3-diyl)-1-thio-β-D-glucopyranosid]uronate prepared and used by S. Oscarson et al.[2,3] regarding both accessibility and reaction capacity.

EXPERIMENTAL

General methods. Melting points were determined with a Boetius micro apparatus BHMK 05 (Rapido, Dresden) and are uncorrected. Optical rotations were measured for solutions in a 2-cm cell with an automatic polarimeter ''GYROMAT'' (Dr. Kernchen Co.). NMR spectra were recorded with Bruker AC-250 or ARX-300 spectrometers, at 250 MHz or 300 MHz for ^{1}H, and 62.9 MHz or 75.5 MHz for ^{13}C, respectively. Chemical shifts are given relative to the signal of internal standard tetramethylsilane ($\delta = 0$). First order chemical shifts and coupling constants were obtained from one-dimensional spectra, and assignment of proton resonances was based on COSY experiments. For the X-ray structure determination, a crystal of **33** was checked by a rotational photograph and a suitable reduced cell was found by the automatic cell determination routine. The data collection was performed in routine ω-scan, the structure was solved by direct methods (Siemens SHELXTL, 1990, Siemens Analytical X-ray Inst. Inc.) and refined by the full matrix least-squares method of Bruker SHELXTL, Vers.5.10, Copyright 1997, Bruker Analytical X-ray Systems. All non-hydrogen atoms were refined anisotropically. The hydrogens were put into theoretical positions and refined using the riding model. Additional parameters are as follows: Siemens P4 diffractometer; radiation: $\lambda = 0.71073$ Å (Mo-K_α), graphite monochromator; crystal size: $0.68 \times 0.48 \times 0.46$ mm^3; formula: $C_{28}H_{32}O_{10}$; formula weight: 528.54; temperature: 293(2) K; crystal system: trigonal; space group: $P3_1$; unit cell dimensions: $a = b = 13.294(2)$ Å, $c = 13.412(2)$ Å, $\alpha = \beta = 90°$, $\gamma = 120°$; volume: 2052.7(5) $Å^3$; $Z = 3$; density (calculated): 1.283 Mg/m^3; absorption coefficient: 0.097 mm^{-1}; F(000): 840; Θ range for data collection: 2.33 to 21.99°; index ranges: $-12 \leq h \leq 12$, $-13 \leq k \leq 13$, $-14 \leq l \leq 14$; reflections collected: 3719; independent reflections: 3294; R(int) = 0.0358, completeness to $\Theta = 21.99°$, 98.6%; data/restraints/parameters: 3294/1/344; goodness-of-fit on F2: 1.033; final R indices [$I > 2\sigma(I)$]: R1 = 0.0474, wR2 = 0.1221; R indices (all data): R1 = 0.0583, wR2 = 0.1322; absolute structure parameter: −0.6(14); extinction coefficient: 0.017(2); largest diff. peak/hole: 0.164/−0.182 e.Å-3. Crystallographic data (excluding structure factors) for the structure **33** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 147232. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int.code +(1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/conts/retrieving.html.

Thin-layer chromatography (TLC) on precoated plates of silica gel (Merck, Silica Gel 60, F_{254}, 0.25 mm) was performed with the following solvent systems (v/v): (A) 9:1, (B) 7:1, (C) 4:1, (D) 3:1, (E) 2:1, (F) 1:1, (G) 1:2 heptane–ethyl acetate, (H) 12:1, (I) 1:2 ethyl acetate–methanol, (J) 7:4:1, (K) 7:4:2 ethyl acetate–methanol–water. The spots were made visible by spraying with methanolic 10% H_2SO_4 solution and charring them for 3–5 min with a heat gun. Detection of benzyl derivatives was effected by UV fluorescence. Preparative flash chromatography and HPLC was performed by elution from columns of slurry-packed Silica Gel 60 (Merck, 40–63 μm) and Nucleosil 100-7 (Knauer, 7.0 μm), respectively, with the above solvent systems. All solvents and reagents were purified and dried according to standard procedures.[30] After classical work up of the reaction mixtures, the organic layers as a rule, were dried over $MgSO_4$, and then concentrated under reduced pressure (rotary evaporator).

6-*O*-*tert*-Butyldimethylsilyl-[(*S*)-1,2-*O*-(1-ethoxyethylidene)]-α-D-glucopyranose (4). Triethylamine (4.45 mL, 32.1 mmol), 4-dimethylaminopyridine (2.6 g, 21.4 mmol) and *tert*-butyldimethylsilyl chloride (4.2 g, 27.8 mmol) were added to a solution of orthoester **3** (5.36 g, 21.4 mmol) in dry dichloromethane (50 mL). After stirring for one hour at rt (TLC solvent G R_f 0.54), the solution was diluted with chloroform (50 mL) and heptane (200 mL), washed with cold sat aq NH_4Cl (3 × 50 mL), sat aq $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), dried and concentrated. The residue was purified by MPLC (eluent ethyl acetate gradient 25% → 50% in heptane with 1% triethylamine) to yield **4** (6.78 g, 87%) as an amorphous colorless solid: $[\alpha]_D^{[24]}$ + 19.7 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.05 [s, 6H, $Si(CH_3)_2C(CH_3)_3$], 0.86 [s, 9H, $Si(CH_3)_2(CH_3)_3$], 1.14 [t, 3H, $C(CH_3)OCH_2CH_3$], 1.64 [s, 3H, $C(CH_3)OCH_2CH_3$], 2.99 (bs, 2H, 2 × OH), 3.52 [q, 2H, $C(CH_3)OCH_2CH_3$], 3.66 (dd, 1H, $J_{4,5}$ = 7.6 Hz, H-4), 3.72 (ddd, 1H, H-5), 3.77 (dd, 1H, $J_{6,6'}$ = 10.8 Hz, $J_{6,5}$ = 4.2 Hz, H-6), 3.87 (dd, 1H, $J_{6',5}$ = 3.6 Hz, H-6′), 3.90 (dd, 1H, $J_{3,4}$ = 5.4 Hz, H-3), 4.24 (t, 1H, $J_{2,3}$ = 5.1 Hz, H-2), 5.72 (d, 1H, $J_{1,2}$ = 5.1 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ −5.50 [$Si(CH_3)_2C(CH_3)_3$ two signals are isochronic], 15.20 [$C(CH_3)OCH_2CH_3$], 18.21 [$Si(CH_3)_2C(CH_3)_3$], 22.19 [$C(CH_3)OCH_2CH_3$], 25.79 [$Si(CH_3)_2C(CH_3)_3$ three signals are isochronic], 58.61 [$C(CH_3)OCH_2CH_3$], 64.17 (C-6), 70.22 (C-5), 72.49 (C-3), 73.05 (C-4), 76.76 (C-2), 97.62 (C-1), 121.01 [$C(CH_3)OCH_2CH_3$].

Anal.Calcd for $C_{16}H_{32}O_7Si$ (364.51): C, 52.72; H, 8.85. Found: C, 52.49; H, 8.67.

3,4-Di-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-[(*S*)-1,2-*O*-(1-ethoxyethylidene)]-α-D-glucopyranose (5). Sodium hydride (3.6 g, 119 mmol, 80% dispersion in oil) was added to a stirred solution of compound **4** (6.2 g, 17 mmol) in dry *N,N*-dimethylformamide (60 mL) at 0°C. The solution was kept for 30 min at that temperature, and benzyl bromide (10 mL, 85 mmol) was then added dropwise. The mixture was allowed to attain rt and stirring was continued for further 2 h. When the reaction was complete (TLC solvent D R_f 0.58), methanol (10 mL) was added at 0°C and after stirring for further 20 min, the mixture was diluted with chloroform (50 mL) and heptane (100 mL). The organic layer was washed with water (4 × 50 mL), dried and concentrated. MPLC purification of the residue (eluent gradient ethyl acetate 0%→10 % in heptane with 1% triethylamine) afforded compound **5** (6.6 g, 71%) as a colorless syrup: $[\alpha]_D^{[24]}$ + 22.7 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.06 [s, 6H, $Si(CH_3)_2C(CH_3)_3$], 0.90 [s, 9H, $Si(CH_3)_2(CH_3)_3$], 1.19 [t, 3H, $C(CH_3)OCH_2CH_3$], 1.65 [s, 3H, $C(CH_3)OCH_2CH_3$], 3.54 [dq, 2H, $C(CH_3)OCH_2CH_3$], 3.64 (t, 1H, H-5), 3.72 (ddd, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 3.83 (dd, 2H, $J_{6,5}$ = $J_{6',5}$ = 3.0 Hz, H-6, H-6′), 3.85 (dd, 1H, $J_{3,4}$ = 3.6 Hz, H-3), 4.67 (ddd, 1H, $J_{2,3}$ = 5.1 Hz, H-2), 4.53, 4.67 (2d, 2H, J = 11.3 Hz, $CH_2C_6H_5$), 4.60, 4.71 (2d, 2H, J = 11.8 Hz, $CH_2C_6H_5$), 5.74 (d, 1H, $J_{1,2}$ = 5.6 Hz, H-1), 7.26−7.38 (m, 10H, 2 × $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ −5.24, −5.12 [$Si(CH_3)_2C(CH_3)_3$], 15.37 [$C(CH_3)OCH_2CH_3$], 18.39 [$Si(CH_3)_2C(CH_3)_3$], 22.23 [$C(CH_3)OCH_2CH_3$], 25.98 [$Si(CH_3)_2C(CH_3)_3$], 58.55 [$C(CH_3)OCH_2CH_3$], 62.74 (C-6), 72.04 (C-5), 72.06, 73.35 (2 × $CH_2C_6H_5$), 74.63 (C-4), 76.59 (C-2), 79.72 (C-3), 97.96 (C-1), 120.94 [$C(CH_3)OCH_2CH_3$], 127.79, 127.88, 128.00, 128.03, 128.41, 128.45, 137.87, 138.27 (2 × $CH_2C_6H_5$, four signals are isochronic).

Anal.Calcd for $C_{30}H_{44}O_7Si$ (544.76): C, 66.14; H, 8.14. Found: C, 66.41; H, 8.22.

3,4-Di-*O*-benzyl-[(*S*)-1,2-*O*-(1-ethoxyethylidene)]-α-D-glucopyranose (6). Tetrabutylammonium fluoride trihydrate (1.32 g, 4.2 mmol) was added to a solution of

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compound **5** (1.68 g, 3.0 mmol) in tetrahydrofuran (25 mL). After stirring for 30 min at rt (TLC solvent F R_f 0.57), the reaction mixture was diluted with chloroform (70 mL) and heptane (140 mL), and the organic layer was washed with water (5 × 50 mL), dried and concentrated. MPLC purification of the residue (eluent solvent C with 1% triethylamine) provided **6** (1.24 g, 96 %) as a colorless syrup: $[\alpha]_D^{[24]}$ + 35.2 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.20 [t, 3H, $C(CH_3)OCH_2CH_3$], 1.68 [s, 3H, $C(CH_3)OCH_2CH_3$], 2.20 (bs, 1H, OH), 3.53 [q, 2H, $C(CH_3)OCH_2CH_3$], 3.63 (dd, 1H, $J_{4,5}$ = 0.8 Hz, H-4), 3.68 (m, 1H, H-6), 3.69 (m, 1H, H-5), 3.80 (m, 1H, H-6′), 3.90 (t, 1H, $J_{3,4}$ = 3.4 Hz, H-3), 4.43 (ddd, 1H, $J_{2,3}$ = 5.3 Hz, H-2), 4.44, 4.58 (2d, 2H, J = 11.5 Hz, $CH_2C_6H_5$), 4.57, 4.67 (2d, 2H, J = 12.0 Hz, $CH_2C_6H_5$), 5.72 (d, 1H, $J_{1,2}$ = 5.0 Hz, H-1), 7.27–7.40 (m, 10H, 2 × $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 15.38 [$C(CH_3)OCH_2CH_3$], 21.41 [$C(CH_3)OCH_2CH_3$], 58.89 [$C(CH_3)OCH_2CH_3$], 62.57 (C-6), 70.66 (C-5), 71.95, 72.64 (2 × $CH_2C_6H_5$), 74.88 (C-2), 75.14 (C-4), 77.76 (C-3), 97.49 (C-1), 120.96 [$C(CH_3)OCH_2CH_3$], 127.99, 128.08, 128.11, 128.48, 128.55, 137.51, 137.77 (2 × $CH_2C_6H_5$, five signals are isochronic).

Anal.Calcd for $C_{24}H_{30}O_7$ (430.49): C, 66.96; H, 7.02. Found: C, 67.19; H, 7.12.

6-*O*-Acetyl-3,4-di-*O*-benzyl-[(*S*)-1,2-*O*-(1-ethoxyethylidene)]-α-D-glucopyranose (7). Acetic anhydride (6.3 mL) was added dropwise to a solution of compound **6** (1.29 g, 3.0 mmol) in dry pyridine (10 mL) under an atmosphere of argon at 0°C. After stirring overnight at rt (TLC solvent E R_f 0.43), methanol (2 mL) was added dropwise at 0°C and after 30 min, the mixture was poured into ice–water (200 mL). The aqueous layer was extracted with chloroform (2 × 50 mL), the combined extracts were diluted with heptane (200 mL), and the organic layer was washed successively with sat aq NH_4Cl (3 × 50 mL), water (2 × 50 mL), sat aq $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), dried and concentrated. The crude material was purified by HPLC (eluent solvent C with 1% triethylamine) to yield **7** (1.13 g, 80%) as a colorless syrup: $[\alpha]_D^{[25]}$ +39.7 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.20 [t, 3H, $C(CH_3)OCH_2CH_3$], 1.68 [s, 3H, $C(CH_3)OCH_2CH_3$], 2.10 (s, 3H, $OCOCH_3$), 3.54 [q, 2H, $C(CH_3)OCH_2CH_3$], 3.58 (m, 1H, H-4), 3.86 (m, 1H, $J_{5,6}$ = 2.6 Hz, $J_{5,6'}$ = 4.8 Hz, H-5), 3.92 (t, 1H, $J_{3,4}$ = 3.6 Hz, H-3), 4.19 (dd, 1H, $J_{6,6'}$ = 11.9 Hz, H-6), 4.27 (dd, 1H, H-6′), 4.39, 4.60 (2d, 2H, J = 11.8 Hz, $CH_2C_6H_5$), 4.44 (ddd, 1H, $J_{2,3}$ = 5.2 Hz, H-2), 4.61, 4.72 (2d, 2H, J = 11,6 Hz, $CH_2C_6H_5$), 5.71 (d, 1H, $J_{1,2}$ = 5.3 Hz, H-1), 7.28–7.40 (m, 10H, 2×$CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 15.19 [$C(CH_3)OCH_2CH_3$], 20.64 ($OCOCH_3$), 21.36 [$C(CH_3)OCH_2CH_3$], 58.67 [$C(CH_3)OCH_2CH_3$], 63.52 (C-6), 68.37 (C-5), 71.75, 72.30 (2 × $CH_2C_6H_5$), 74.77 (C-4), 74.81 (C-2), 77.75 (C-3), 97.35 (C-1), 120.86 [$C(CH_3)OCH_2CH_3$], 127.81, 127.91, 127.98, 128.17, 128.29, 128.37, 137.37 (2 × $CH_2C_6H_5$, five signals are isochronic), 170.57 ($OCOCH_3$).

Anal.Calcd for $C_{26}H_{32}O_8$ (472.53): C, 66.09; H, 6.82. Found: C, 65.92; H, 6.74.

2,6-Di-*O*-acetyl-3,4-di-*O*-benzyl-α-D-glucopyranosyl bromide (8). Acetyl bromide (0.83 mL, 11.2 mmol) was added to a stirred mixture of compound **7** (2.66 g, 5.6 mmol), tetraethylammonium bromide (0.59 g, 2.8 mmol), and molecular sieves (4 Å, 3.0 g) in dry dichloromethane (20 mL). After stirring for 30 min at rt (TLC solvent E R_f 0.44), the reaction mixture was poured into a stirred ice-cold solution of sat aq $NaHCO_3$ (500 mL), chloroform (100 mL), and heptane (200 mL). The organic layer was separated, washed with water (2 × 50 mL), dried and concentrated. The crude bromide **8** (2.74 g, 96%) isolated as a light-yellow syrup was used immediately for the next step without further purification.

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6-*O*-Acetyl-3,4-di-*O*-benzyl-[1,2-*O*-(1-cyanoethylidene)]-α-D-glucopyranose (9). The heterogeneous mixture of glucosyl bromide **8** (2.74 g, 5.4 mmol), carefully powdered sodium cyanide (2.64 g, 54 mmol), and tetrabutylammonium bromide (0.87 g, 2.7 mmol) in dry acetonitrile (15 mL) was stirred at rt for 20 h in the dark followed by TLC. The mixture was then diluted with heptane (120 mL) and chloroform (60 mL), washed successively with water (4 × 50 mL), aq 5% $KHSO_4$ (2 × 50 mL), water (2 × 50 mL), sat aq $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), dried, and concentrated. The residue was dissolved in ethyl acetate (10 mL), and the resulting solution was filtered through a thin layer of silica gel and concentrated. The crude material was purified by MPLC (eluent ethyl acetate gradient 10%→25% in heptane).

6-*O*-Acetyl-3,4-di-*O*-benzyl-[(*S*)-1,2-*O*-(1-cyanoethylidene)]-α-D-glucopyranose ($\mathbf{9_{exo}}$). (1.41 g, 58%, TLC solvent E R_f 0.43), colorless crystals: mp 87–89°C; $[\alpha]_D^{[24]}$ +20.6 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.87 [s, 3H, C(CN)CH_3], 2.02 (s, 3H, $OCOCH_3$), 3.55 (ddd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 3.79 (ddd, 1H, $J_{5,6}$ = 2.7 Hz, $J_{5,6'}$ = 5.2 Hz, H-5), 3.96 (t, 1H, $J_{3,4}$ = 2.9 Hz, H-3), 4.16 (dd, 1H, $J_{6,6'}$ = 12.2 Hz, H-6), 4.25 (dd, 1H, H-6′), 4.35, 4.53 (2d, 2H, J = 11.6 Hz, C$H_2C_6H_5$), 4.48 (ddd, 1H, $J_{2,3}$ = 3.2 Hz, H-2), 4.58, 4.70 (2d, 2H, J = 11.7 Hz, C$H_2C_6H_5$), 5.78 (d, 1H, $J_{1,2}$ = 5.2 Hz, H-1), 7.21–7.41 (m, 10H, 2 × $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 20.75 ($OCOCH_3$), 24.55 [C(CN)CH_3], 63.42 (C-6), 68.63 (C-5), 72.06, 72.26 (2 × $CH_2C_6H_5$), 74.72 (C-4), 74.98 (C-2), 75.95 (C-3), 97.94 (C-1), 98.58 [C(CN)CH_3], 116.94 [C(CN)CH_3], 128.14, 128.36, 128.52, 128.68, 136.94 (2 × $CH_2C_6H_5$, seven signals are isochronic), 170.70 ($OCOCH_3$).

Anal.Calcd for $C_{25}H_{27}O_7N$ (453.49): C, 66.21; H, 6.00; N, 3.09. Found: C, 66.05; H, 5.92; N, 3.12.

6-*O*-Acetyl-3,4-di-*O*-benzyl-[(*R*)-1,2-*O*-(1-cyanoethylidene)]-α-D-glucopyranose ($\mathbf{9_{endo}}$). (0.36 g, 15%, TLC solvent E R_f 0.40), colorless syrup: $[\alpha]_D^{[24]}$ + 70.9 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.76 [s, 3H, C(CN)CH_3], 2.01 (s, 3H, $OCOCH_3$), 3.51 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 4.05 (m, 1H, H-5), 4.23 (d, 1H, $J_{3,4}$ = 8.1 Hz, H-3), 4.28 (m, 1H, H-6), 4.31 (m, 1H, H-6′), 4.36 (t, 1H, $J_{2,3}$ = 5.5 Hz, H-2), 4.56, 4.72 (2d, 2H, J = 11.4 Hz, C$H_2C_6H_5$), 4.80, 4.86 (2d, 2H, J = 11.6 Hz, C$H_2C_6H_5$), 5.65 (d, 1H, $J_{1,2}$ = 4.9 Hz, H-1), 7.23–7.40 (m, 10H, 2 × $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 20.78 ($OCOCH_3$), 24.40 [C(CN)CH_3], 62.87 (C-6), 71.17 (C-5), 73.39, 74.28 (2 × $CH_2C_6H_5$), 74.11 (C-4), 80.12 (C-2), 80.28 (C-3), 99.01 (C-1), 99.11 [C(CN)CH_3], 117.81 [C(CN)-CH_3], 128.02, 128.14, 128.48, 128.53, 137.49 (2 × $CH_2C_6H_5$, seven signals are isochronic), 170.53 ($OCOCH_3$).

Anal.Calcd for $C_{25}H_{27}O_7N$ (453.49): C, 66.21; H, 6.00; N, 3.09. Found: C, 66.04; H, 5.91; N, 3.20.

3,4-Di-*O*-benzyl-[(*S*)-1,2-*O*-(1-cyanoethylidene)]-α-D-glucopyranose (10). Methanolic HCl (0.28 M, 60 mL, prepared by adding 1.2 mL acetyl chloride to 60 mL ice-cold dry methanol) was added to a solution of $\mathbf{9_{exo}}$ (1.05 g, 2.3 mmol) in dry dichloromethane (20 mL) and the mixture was stirred for 15 h at rt (TLC solvent F R_f 0.46). The solution was made neutral by addition of $PbCO_3/Pb(OH)_2$ (5 g). The lead salts were filtered off and washed with dry methanol. The filtrate and washings were passed through a thin layer of silica gel and concentrated. The residue was purified by MPLC (eluent ethyl acetate gradient 0% → 50% in heptane) to yield **10** (0.65 g, 69%) as colorless crystals:

mp 114–115°C; $[\alpha]_D^{[26]}$ + 12.8 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.84 [s, 3H, C(CN)CH_3], 3.61–3.66 (m, 3H, H-4, H-5, H-6), 3.78 (m, 1H, H-6′), 3.93 (ddd, 1H, $J_{3,4}$ = 2.8 Hz, H-3), 4.39, 4.51 (2d, 2H, J = 11.6 Hz, C$H_2C_6H_5$), 4.44 (ddd, 1H, $J_{2,3}$ = 5.3 Hz, H-2), 4.54, 4.64 (2d, 2H, J = 11.8 Hz, C$H_2C_6H_5$), 5.77 (d, 1H, $J_{1,2}$ = 5.5 Hz, H-1), 7.21–7.40 (m, 10H, 2 × $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 24.30 [C(CN)CH_3], 62.18 (C-6), 70.71 (C-5), 71.84, 72.24 (2 × $CH_2C_6H_5$), 74.53 (C-4), 74.86 (C-2), 75.77 (C-3), 97.72 (C-1), 98.35 [C(CN)CH_3], 116.77 [C(CN)CH_3], 127.80, 127.85, 127.92, 128.04, 128.29, 128.43, 136.75, 137.21 (2 × $CH_2C_6H_5$, four signals are isochronic).

Anal.Calcd for $C_{23}H_{25}NO_6$ (411.45): C, 67.14; H, 6.12; N, 3.40. Found: C, 67.19; H, 6.20; N, 3.31.

Methyl 3,4-di-*O*-benzyl-[(*S*)-1,2-*O*-(1-ethoxyethylidene)]-α-D-glucopyranuronate (14). To a solution of orthoester **6** (861 mg, 2 mmol) in dichloromethane (20 mL) were added 2,2,6,6-tetramethylpiperidine **1**-oxide (TEMPO, 3.9 mg, 0.025 mmol), aq 5% $NaHCO_3$ (10 mL), KBr (48 mg, 0.4 mmol) and tetrabutylammonium chloride (14 mg, 0.05 mmol). After a few minutes, a solution of aq NaOCl (13% active chlorine, 12 mL), sat aq $NaHCO_3$ (5 mL) and sat aq NaCl (10 mL) was added at 0°C. The mixture was stirred vigorously for an additional 30 min at rt followed by TLC (solvent F). $NaHCO_3$ (1.5 g), tetrabutylammonium bromide (645 mg, 2.0 mmol) and methyl iodide (0.5 mL, 8.0 mmol) were then added and the resulting mixture was stirred vigorously overnight (TLC solvent E R_f 0.44). Chloroform (30 mL) and heptane (100 mL) were added and the organic layer was washed with water (3 × 50 mL), dried and concentrated. The purification of the residue by HPLC (eluent solvent A with 1% Et_3N) yielded **14** (595 mg, 65%) as a colorless syrup: $[\alpha]_D^{[24]}$ + 19.4 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.18 [t, 3H, C(CH_3)OCH$_2$CH_3], 1.68 [s, 3H, C(CH_3)OCH$_2$CH$_3$], 3.53 [q, 2H, C(CH_3)OCH_2CH$_3$], 3.69 (s, 3H, OCH_3), 3.91 (m, 1H, H-4), 3.93 (m, 1H, H-3), 4.30 (m, 1H, H-5), 4.36 (m, 1H, H-2), 4.53, 4.62 (2d, 2H, J = 11.60 Hz, C$H_2C_6H_5$), 4.54, 4.60 (2d, 2H, J = 12.0 Hz, C$H_2C_6H_5$), 5.79 (d, 1H, $J_{1,2}$ = 4.6 Hz, H-1), 7.24–7.36 (m, 10H, 2 × $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 15.28 [C(CH_3)OCH$_2$CH_3], 22.43 [C-(CH_3)OCH$_2$CH$_3$], 52.40 (OCH_3), 58.51 [C(CH_3)OCH_2CH$_3$], 71.14 (C-5), 72.13, 72.79 (2 × $CH_2C_6H_5$), 75.50 (C-4), 75.71 (C-2), 76.80 (C-3), 96.77 (C-1), 122.15 [C(CH_3)-OCH$_2$CH$_3$], 127.91, 128.02, 128.38, 128.49, 137.41, 137.65 (2 × $CH_2C_6H_5$, six signals are isochronic), 170.16 (C-6).

Anal.Calcd for $C_{25}H_{30}O_8$ (458.50): C, 65.49; H, 6.59. Found: C, 65.28; H, 6.71.

Methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-D-glucopyranosyluronate bromide (15). Acetyl bromide (0.3 mL, 4.0 mmol) was added to a mixture of compound **14** (367 mg, 0.8 mmol), tetraethylammonium bromide (84 mg, 0.4 mmol), and molecular sieves (4 Å, 0.5 g) in dry dichloromethane (5 mL) at ambient temperature. After stirring for 2 h (TLC solvent E R_f 0.46), chloroform (25 mL) and heptane (50 mL) were added and the resulting organic layer was washed with ice–water (2 × 50 mL), sat aq $NaHCO_3$ (2 × 50 mL), ice–water (2 × 50 mL), dried and concentrated. The crude bromide **15** (380 mg, 96%) obtained as a light-yellow syrup was used immediately for the next step without further purification.

Methyl 3,4-di-*O*-benzyl-[(*S*)-1,2-*O*-(1-cyanoethylidene)]-α-D-glucopyranuronate (12). Via **10**. Jones reagent (3.8 mL, prepared by adding 720 mg chromium(VI) oxide

to 3.6 mL 3.5 M sulfuric acid) was added dropwise to a solution of compound **10** (0.5 g, 1.2 mmol) in acetone (5 mL) and dichloromethane (1 mL) at 0°C. After stirring for 15 h at rt, ethanol was added (10 mL) and the solution was filtered. The neutralization of the filtrate was realized by addition of $NaHCO_3$ (1.5 g). The salts were filtered off and the filtrate was concentrated. After dissolving the residue in chloroform (7 mL), the resulting solution was treated with Dowex 50 [H^+] resin to reach pH 2–3, then filtered and concentrated to dryness. The obtained syrupy 3,4-di-*O*-benzyl-[(*S*)-1,2-*O*-(1-cyanoethylidene]-α-D-glucopyranuronic acid (**11**) was dissolved in dichloromethane (5 mL) and a solution of diazomethane in ether (ca. 10 mL) was added dropwise until the yellow color of the reaction mixture persisted (TLC solvent E R_f 0.45). The excess of diazomethane was destroyed by addition of acetic acid (3 mL) and the solution was then poured in water (50 mL). The layers were separated and the organic layer was washed with water (2 × 50 mL), sat aq $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), dried and concentrated. The purification of the residue by HPLC (solvent C) gave the ester **12** (0.34 g, 63%) as a colorless syrup.

Via **15**. The heterogeneous mixture of bromide **15** (400 mg, 0.8 mmol), carefully powdered sodium cyanide (780 mg, 16 mmol) and tetrabutylammonium bromide (130 mg, 0.4 mmol) in dry acetonitrile (8 mL) was vigorously stirred for **4** d under an argon atmosphere at rt in the dark (TLC solvent E R_f 0.45). The reaction mixture was then diluted with heptane (100 mL) and chloroform (50 mL), washed successively with water (4 × 50 mL), aq 15% $NaHSO_4$ (2 × 50 mL), water (2 × 50 mL), sat aq $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), dried and concentrated. The residue was dissolved in ethyl acetate (10 mL), the solution was filtered through a thin layer of silica gel and concentrated. The crude material was purified by HPLC to yield exclusively the pure *exo*-isomer **12** (230 mg, 65%) as a syrup: $[\alpha]_D^{[24]}$ − 6.3 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.88 [s, 3H, C(CN)CH_3], 3.72 (s, 3H, OCH_3), 4.05 (dd, 1H, $J_{4,5}$ = 7.6 Hz, H-4), 4.06 (m, 1H, H-3), 4.22 (d, 1H, H-5), 4.43 (m, 1H, H-2), 4.50, 4.55 (2d, 2H, J = 11.5 Hz, C$H_2C_6H_5$), 4.52, 4.58 (2d, 2H, J = 11.9 Hz, C$H_2C_6H_5$), 5.86 (d, 1H, $J_{1,2}$ = 4.9 Hz, H-1) 7.24–7.39 (m, 10H, 2 × $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 24.84 [C(CN)*C*H_3], 52.58 (OCH_3), 70.79 (C-5), 72.21, 72.62 (2 × *C*$H_2C_6H_5$), 75.00 (C-3), 75.21 (C-4), 75.45 (C-2), 97.04 (C-1), 99.37 [*C*(CN)CH_3], 116.84 [C(*C*N)CH_3], 127.99, 128.05, 128.29, 128.46, 128.63, 129.79, 136.84, 137.34 (2 × $CH_2C_6H_5$, four signals are isochronic), 169.49 (C-6); CI mass spectrum (isobutane): *m/z* 439 (M^+).

Anal.Calcd for $C_{24}H_{25}NO_7$ (439.46): C, 65.59; H, 5.73; N, 3.19. Found: C, 65.72; H, 5.56; N, 3.16.

Methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-D-glucopyranuronate (16). To a solution of orthoester **14** (1.83 g, 4.0 mmol) in 1.4-dioxane (40 mL) was added aq 60% acetic acid (80 mL). After stirring at rt for 1 h (TLC solvent F R_f 0.39), the solution was coevaporated with toluene (5 × 50 mL). The residue was purified by HPLC (eluent solvent E) to provide crystalline **16** (1.68 g, 98%, 4:1 ratio of the α,β anomers): ^{1}H NMR of **16α** ($CDCl_3$) δ 2.01 (s, 3H, $OCOCH_3$), 3.69 (s, 3H, OCH_3), 3.83 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 4.05 (dd, 1H, $J_{3,4}$ = 8.8 Hz, H-3), 4.48 (d, 1H, H-5) 4.61, 4.72 (2d, 2H, J = 11.0 Hz, C$H_2C_6H_5$), 4.75, 4.76 (2d, 2H, J = 9.7 Hz, C$H_2C_6H_5$), 4.85 (dd, 1H, $J_{2,3}$ = 9.7 Hz, H-2), 5.44 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1) 7.20–7.37 (m, 10H, 2 × $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 20.84 (OCO*C*H_3), 52.52 (OCH_3), 70.44 (C-5), 72.97 (C-2), 75.04,

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75.42 (2 × $CH_2C_6H_5$), 78.81 (C-3), 79.19 (C-4), 90.72 (C-1), 127.65, 127.76, 127.89, 127.98, 128.03, 128.42, 137.74, 138.24 (2 × $CH_2C_6H_5$, four signals are isochronic), 169.74 ($OCOCH_3$), 170.28 (C-6).

Anal.Calcd for $C_{23}H_{26}O_8$ (430.45): C, 64.18; H, 6.08. Found: C, 64.02; H, 6.05.

Methyl (2-*O*-acetyl-3,4-di-*O*-benzyl-α-D-glucopyranosyl)uronate trichloroacetimidate (17). A suspension of sodium hydride in oil (70%, 19.2 mg, 0.56 mmol) was added to a solution of compound **16** (340 mg, 0.8 mmol) and trichloroacetonitrile (0.8 mL, 8.0 mmol) in dry dichloromethane (8 mL).The mixture was stirred for 3 h at rt (TLC solvent F R_f 0.61), filtered then through a thin layer of silica gel and evaporated. The crude product was purified by HPLC (eluent solvent B) to yield **17** (430 mg, 94%) as colorless syrup: $[\alpha]_D^{[26]}$ + 68.4 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.93 (s, 3H, $OCOCH_3$), 3.72 (s, 3H, OCH_3), 3.94 (dd, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 4.11 (t, 1H, $J_{3,4}$ = 9.6 Hz, H-3), 4.43 (d, 1H, H-5), 4.63, 4.76 (2d, 2H, J = 10.7 Hz, $CH_2C_6H_5$), 4.82, 4.87 (2d, 2H, J = 11.3 Hz, $CH_2C_6H_5$), 5.09 (dd, 1H, $J_{2,3}$ = 9.9 Hz, H-2), 6.54 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 7.23–7.38 (m, 10H, 2 × $CH_2C_6H_5$), 8.64 [s, 1H, O(C═NH)CCl_3]; ^{13}C NMR ($CDCl_3$) δ 20.51 ($OCOCH_3$), 52.66 (OCH_3), 71.81 (C-5), 72.65 (C-4), 75.51 (2 × $CH_2C_6H_5$), 78.77 (C-3), 78.95 (C-2), 90.79 [O(C═NH)CCl_3], 93.57 (C-1), 127.89, 128.09, 128.22, 128.44, 128.49, 137.42, 137.99 (2 × $CH_2C_6H_5$, five signals are isochronic), 160.74 [O(C═NH)CCl_3], 168.66 ($OCOCH_3$), 168.86 (C-6); CI mass spectrum (isobutane): *m/z* 413 (M-trichloroacetimidate$^+$, 100%).

Anal.Calcd for $C_{25}H_{26}NO_8Cl_3$ (574.84): C, 52.23; H, 4.56; N, 2.44. Found: C, 52.38; H, 4.69; N, 2.57.

The quality of the sodium hydride has a strong influence on the outcome of the reaction. In some cases, the yield was remarkably lower and the formation of the β-anomer was observed: ^{1}H NMR of **17β** ($CDCl_3$) δ 1.92 (s, 3H, $OCOCH_3$), 3.71 (s, 3H, OCH_3), 3.77 (t, 1H, $J_{3,4}$ = 8.5 Hz, H-3), 4.04 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 4.15 (d, 1H, H-5), 4.63, 4.77 (2d, 2H, J = 11.1 Hz, $CH_2C_6H_5$), 4.69, 4.79 (2d, 2H, J = 11.6 Hz, $CH_2C_6H_5$), 5.28 (dd, 1H, $J_{2,3}$ = 8.5 Hz, H-2), 5.83 (d, 1H, $J_{1,2}$ = 7.1 Hz, H-1), 7.21–7.36 (m, 10H, 2 × $CH_2C_6H_5$), 8.66 [s, 1H, O(C═NH)CCl_3]; ^{13}C NMR of **17β** ($CDCl_3$) δ 20.69 ($OCOCH_3$), 52.63 (OCH_3), 71.60 (C-5), 74.88 (C-4), 74.67, 75.00 (2 × $CH_2C_6H_5$), 78.51 (C-3), 81.43 (C-2), 90.83 [O(C═NH)CCl_3], 95.96 (C-1), 127.89, 127.93, 128.01, 128.10, 128.45, 137.43, 137.74 (2 × $CH_2C_6H_5$, five signals are isochronic), 160.98 [O(C═NH)CCl_3], 168.31 ($OCOCH_3$), 168.96 (C-6).

Methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate (20). ^{1}H NMR ($CDCl_3$) δ 1.96, 1.97, 2.05 (3s, 12H, 4 × $OCOCH_3$), 3.80 (s, 3H, OCH_3), 4.14 (d, 1H, H-5), 5.08 (dd, 1H, $J_{2,3}$ = 8.8 Hz, H-2), 5.17 (t, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 5.22 (dd, 1H, $J_{3,4}$ = 12.7 Hz, H-3), 5.71 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 20.44, 20.52, 20.74 (4 × $OCOCH_3$), 52.99 (OCH_3), 68.87 (C-2), 70.09 (C-3), 71.75 (C-4), 72.90 (C-5), 91.29 (C-1), 166.79 (C-6), 168.80, 169.15, 169.39, 169.86 (4 × $OCOCH_3$).

Methyl 3,4-di-*O*-acetyl-[(*S*)-1,2-*O*-(1-ethoxyethylidene)]-α-D-glucopyranuronate (22). Dry ethanol (1.3 mL, 21.8 mmol), *sym*-collidine (2 mL, 15.3 mmol) and tetrabutylammonium bromide (0.46 g, 1.39 mmol) were added to a mixture of bromide **21** (5.5 g, 13.9 mmol) and molecular sieves (4Å, 0.5 g) in dry acetonitrile (8 mL). After stirring overnight (TLC solvent F R_f 0.57) at 40°C under an atmosphere of argon, the

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precipitated *sym*-collidine hydrobromide was filtered off and the filtrate was passed through a layer of silica gel. The solution was then diluted with chloroform (50 mL) and heptane (100 mL), washed with ice–water (5 × 50 mL), dried and concentrated. The purification of the residue by MPLC (eluent solvent B with 1% Et_3N) yielded **22** (4.7 g, 90%) as a colorless syrup: $[\alpha]_D^{[26]}$ + 11.5 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.13 [t, 3H, $C(CH_3)OCH_2CH_3$], 1.69 [s, 3H, $C(CH_3)OCH_2CH_3$], 2.04, 2.05 (2s, 6H, 2 × $OCOCH_3$), 3.49 [q, 2H, $C(CH_3)OCH_2CH_3$], 3.72 (s, 3H, OCH_3), 4.27 (m, 1H, H-2), 4.27 (d, 1H, H-5), 5.09 (ddd, 1H, $J_{4,5}$ = 7.5 Hz, H-4), 5.18 (t, 1H, $J_{3,4}$ = 2.6 Hz, H-3), 5.81 (d, 1H, $J_{1,2}$ = 4.6 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 15.17 [$C(CH_3)OCH_2CH_3$], 20.71 (2 × $OCOCH_3$), 21.53 [$C(CH_3)OCH_2CH_3$], 52.72 (OCH_3), 58.87 [$C(CH_3)OCH_2CH_3$], 68.18 (C-4), 68.37 (C-3), 68.98 (C-5), 72.81 (C-2), 96.01 (C-1), 122.24 [$C(CH_3)OCH_2CH_3$], 168.91 (2 × $OCOCH_3$), 169.38 (C-6).

Anal.Calcd for $C_{15}H_{22}O_{10}$ (362.33): C, 49.72; H, 6.12. Found: C, 49.85; H, 6.07.

Methyl [(*S*)-1,2-*O*-(1-ethoxyethylidene)]-α-D-glucopyranuronate (23). A methanolic sodium methoxide solution (0.5 M, 0.7 mL) was added to a solution of compound **22** (900 mg, 2.5 mmol) in dry methanol (15 mL). After stirring for 1 h at ambient temperature under an atmosphere of argon (TLC solvent G R_f 0.25), the solution was concentrated. The residue was dissolved in ethyl acetate, filtered through a layer of silica gel and concentrated. The purification of the crude material by MPLC (eluent solvent F with 1% Et_3N) afforded **23** (670 mg, 95%) as a colorless syrup: $[\alpha]_D^{[26]}$ + 19.7 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.16 [t, 3H, $C(CH_3)OCH_2CH_3$], 1.69 [s, 3H, $C(CH_3)OCH_2CH_3$], 3.54 [q, 2H, $C(CH_3)OCH_2CH_3$], 3.78 (s, 3H, OCH_3), 3.92 (dd, 1H, $J_{4,5}$ = 6.7 Hz, H-4), 4.09 (t, 1H, $J_{3,4}$ = 4.5 Hz, H-3), 4.27 (t, 1H, $J_{2,3}$ = 4.2 Hz, H-2), 4.29 (d, 1H, H-5), 5.82 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 15.17 [$C(CH_3)OCH_2CH_3$], 23.07 [$C(CH_3)OCH_2CH_3$], 52.69 (OCH_3), 58.64 [$C(CH_3)OCH_2CH_3$], 70.02 (C-4), 70.53 (C-3), 73.43 (C-5), 77.27 (C-2), 96.24 (C-1), 122.35 [$C(CH_3)OCH_2CH_3$], 170.88 (C-6).

Anal.Calcd for $C_{11}H_{18}O_8$ (278.25): C, 47.48; H, 6.52. Found: C, 47.33; H, 6.50.

Methyl 3-*O*-benzyl-[(*S*)-1,2-*O*-(1-ethoxyethylidene)]-4-deoxy-L-*threo*-hex-4-enopyranuronate (24). Molecular sieves (4 Å, 0.5 g) were added to a solution of compound **23** (0.56 g, 2.0 mmol) in dry *N,N*-dimethylformamide (20 mL) and the mixture was stirred for 15 min at ambient temperature. After cooling to −20°C, dry silver oxide (0.93 g, 4.0 mmol) and dry potassium iodide (0.33 g, 2.0 mmol) were added under an atmosphere of argon. A solution of benzyl bromide (0.71 mL, 6.0 mmol) in dry *N,N*-dimethylformamide (2 mL) was then added dropwise to the vigorously stirred reaction mixture during 30 min at −20°C. After stirring for 2 h at that temperature (TLC solvent F R_f 0.56), the mixture was filtered through bed of silica gel and the filtrate was diluted with chloroform (50 mL) and heptane (100 mL). The organic layer was washed with ice–water (2 × 50 mL), aq 10% sodium thiosulphate (3 × 50 mL), brine (2 × 50 mL), ice–water (2 × 50 mL), dried and concentrated. The crude material was purified by HPLC (eluent solvent A) to provide compound **24** (0.55 g, 78 %) as a colorless syrup: $[\alpha]_D^{[24]}$ + 140.2 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.17 [t, 3H, $C(CH_3)OCH_2CH_3$], 1.54 [s, 3H, $C(CH_3)OCH_2CH_3$], 3.55 [q, 2H, $C(CH_3)OCH_2CH_3$], 3.79 (s, 3H, OCH_3), 4.17 (dd, 1H, $J_{3,4}$ = 4.9 Hz, H-3), 4.50 (m, $J_{2,3}$ = 1.8 Hz, 1H, H-2), 4.55, 4.63 (2d, 2H, J = 11.6 Hz, $CH_2C_6H_5$), 5.73 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 6.24 (dd, 1H, H-4), 7.27–7.34 (m, 5H,

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$CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 14.97 [$C(CH_3)OCH_2CH_3$], 24.43 [$C(CH_3)OCH_2CH_3$], 52.52 (OCH_3), 57.95 [$C(CH_3)OCH_2CH_3$], 67.31 (C-3), 70.96 ($CH_2C_6H_5$), 77.39 (C-2), 96.15 (C-1), 107.32 (C-4), 123.06 [$C(CH_3)OCH_2CH_3$], 127.82, 128.02, 128.48, 137.11 ($CH_2C_6H_5$), 143.07 (C-5), 162.14 (C-6).

Anal.Calcd for $C_{25}H_{30}O_8$ (458.50): C, 65.49; H, 6.59. Found: C, 65.28; H, 6.71.

Methyl (allyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (25). Mercuric cyanide (3.46 g, 13.7 mmol) and mercuric bromide (0.49 g, 1.37 mmol) were added to a solution of bromide **21** (10.9 g, 27.4 mmol) in dry allyl alcohol (56 mL). The mixture was stirred for 15 h at ambient temperature under an atmosphere of argon (TLC solvent G R_f 0.43) and then concentrated. The residue was dissolved in a solution of chloroform (50 mL) and heptane (100 mL). The resulting solution was washed with ice–water (4 × 50 mL), aq 1 N potassium iodide (3 × 50 mL), ice–water (2 × 50 mL), dried and concentrated. The residue was purified by crystallization from ethyl acetate–heptane (1:4) to provide **25** (10.0 g, 97%) as colorless crystals: mp 134–135°C; $[\alpha]_D^{[24]}$ − 40.2 (*c* 1.0, chloroform); ^1H NMR ($CDCl_3$) δ 1.97, 2.05 (2s, 9H, 3 × $OCOCH_3$), 3.72 (s, 3H, OCH_3), 3.97 (d, 1H, H-5), 4.06, 4.33 (2m, 2H, $OCH_2CH{=}CH_2$), 4.57 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 5.00 (m, 1H, H-2), 5.21 (m, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 5.22 (m, 1H, H-3), 5.15–5.27 (m, 2H, $OCH_2CH{=}CH_2$), 5.79 (m, 1H, $OCH_2CH{=}CH_2$); ^{13}C NMR ($CDCl_3$) δ 20.52, 20.64 (3 × $OCOCH_3$ one signal is isochronic), 52.93 (OCH_3), 69.41 (C-4), 70.12 ($OCH_2CH{=}CH_2$), 71.17 (C-2), 72.04 (C-3), 72.56 (C-5), 99.45 (C-1), 117.88 ($OCH_2CH{=}CH_2$), 133.06 ($OCH_2CH{=}CH_2$), 167.29 (C-6), 169.29, 169.42, 170.17 (3 × $OCOCH_3$).

Anal.Calcd for $C_{16}H_{22}O_{10}$ (374.34): C, 51.34; H, 5.92. Found: C, 51.39; H, 5.98.

Methyl (allyl β-D-glucopyranosid)uronate (26). Compound **25** (2.27 g, 6 mmol) was dissolved in methanolic HCl (0.28 N, 184 mL, prepared by adding 4.3 mL acetyl chloride to 180 mL ice-cold dry methanol) and the solution was stirred for 10 h at rt (TLC solvent H R_f 0.48). The solution was then neutralized with solid $NaHCO_3$, filtered through a thin layer of alkaline alumina, concentrated and dried in high vacuum to give analytically pure **26** (1.34, 90%) as a colorless amorphous solid: $[\alpha]_D^{[25]}$ − 60.0 (*c* 1.0, chloroform); ^1H NMR ($CDCl_3$) δ 3.45 (m, 1H, H-2), 3.53 (m, 1H, H-3), 3.68 (m, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 3.75 (s, 3H, OCH_3), 3.83 (d, 1H, H-5), 4.06, 4.30 (m, 2H, $OCH_2CH{=}CH_2$), 4.34 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1), 4.70 (brs, 3H, 3 × OH), 5.14, 5.25 (2m, 2H, $OCH_2CH{=}CH_2$), 5.87 (m, 1H, $OCH_2CH{=}CH_2$); ^{13}C NMR ($CDCl_3$) δ 52.79 (OCH_3), 70.52 ($OCH_2CH{=}CH_2$), 71.34 (C-4), 72.83 (C-2), 74.67 (C-5), 75.54 (C-3), 101.76 (C-1), 118.30 ($OCH_2CH{=}CH_2$), 133.68 ($OCH_2CH{=}CH_2$), 169.72 (C-6).

Anal.Calcd for $C_{10}H_{16}O_7$ (248.23): C, 48.38; H, 6.49. Found: C, 48.24; H, 6.52.

Methyl (allyl 2,3,4-tri-*O*-trimethylsilyl-β-D-glucopyranosid)uronate (27). Hexamethyldisilazane (1.65 mL, 8 mmol) and trimethylsilyl chloride (0.5 mL, 4 mmol) were added to a mixture of **26** (496 mg, 2 mmol) and molecular sieves (4 Å, 0.5 g) in dry pyridine (25 mL). After stirring for 1 h at ambient temperature (TLC solvent E R_f 0.54), the mixture was diluted with chloroform (25 mL) and heptane (50 mL) and filtered. The filtrate was washed with ice–water (2 × 50 mL), sat aq NH_4Cl (2 × 50 mL), sat aq $NaHCO_3$ (2 × 50 mL), ice–water (2 × 50 mL), dried and concentrated. The residue was purified by HPLC (eluent solvent A) to provide **27** (0.76 g, 81%) as a colorless

syrup: $[\alpha]_D^{[24]}$ − 13.9 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 0.06, 0.10, 0.13 [3s, 9H, 3 × $Si(CH_3)_3$], 3.40 (m, 1H, H-2), 3.42 (m, 1H, H-3), 3.70 (m, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 3.75 (s, 3H, OCH_3), 3.78 (d, 1H, H-5), 3.97, 4.32 (2m, 2H, $OCH_2CH{=}CH_2$), 4.23 (d, 1H, $J_{1,2}$ = 7.0 Hz, H-1), 5.14, 5.23 (2m, 2H, $OCH_2CH{=}CH_2$), 5.87 (m, 1H, $OCH_2CH{=}CH_2$); ^{13}C NMR ($CDCl_3$) δ 0.11, 0.76, 0.96, 1.23, 1.43 [3 × $Si(CH_3)_3$, four signals are isochronic], 52.45 (OCH_3), 70.52 ($OCH_2CH{=}CH_2$), 73.33 (C-4), 75.45 (C-2), 76.42 (C-5), 78.57 (C-3), 102.65 (C-1), 117.89 ($OCH_2CH{=}CH_2$), 133.88 ($OCH_2CH{=}CH_2$), 169.39 (C-6).

Anal.Calcd for $C_{19}H_{40}O_7Si_3$ (464.77): C, 49.10; H, 8.67. Found: C, 49.01; H, 8.81.

Methyl (allyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranosid)uronate (28). Molecular sieves (4 Å, 1 g) were added to a solution of carefully dried **27** (500 mg, 2 mmol) in dry *N,N*-dimethylformamide (22 mL) under an atmosphere of argon. After stirring for 15 min, dry silver oxide (5.56 g, 24 mmol) and dry potassium iodide (1.66 g, 1.0 mmol) were added at −23°C. To the vigorously stirred mixture was then added benzyl bromide (2.85 mL, 24 mmol) in dry *N,N*-dimethylformamide (2 mL) during 30 min at the same temperature. After stirring for 8 h (TLC solvent E R_f 0.53) at that temperature, the mixture was filtered through a layer of silica gel. The filtrate was then diluted with chloroform (50 mL) and heptane (100 mL), washed with ice–water (2 × 50 mL), aq 10% sodium thiosulphate (3 × 50 mL), brine (2 × 50 mL), ice–water (2 × 50 mL), dried and concentrated. The crude material was purified by HPLC (eluent solvent A) to provide **28** (0.39 g, 38%) as colorless crystals: mp 112–113°C; $[\alpha]_D^{[25]}$ − 5.4 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 3.53 (dd, 1H, $J_{2,3}$ = 9.1 Hz, H-2), 3.67 (t, 1H, $J_{3,4}$ = 8.5 Hz, H-3), 3.72 (s, 3H, OCH_3), 3.84 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 3.91 (d, 1H, H-5), 4.12, 4.42 (2m, 2H, $OCH_2CH{=}CH_2$), 4.51 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.60, 4.72 (2d, 2H, J = 11.2 Hz, $CH_2C_6H_5$), 4.77, 4.81 (2 bs, 2H, J = 12.5 Hz, $CH_2C_6H_5$), 4.92, 4.94 (2d, 2H, J = 10.7 Hz, $CH_2C_6H_5$), 5.21, 5.34 (2m, 2H, $OCH_2CH{=}CH_2$), 5.93 (m, 1H, $OCH_2CH{=}CH_2$), 7.20–7.39 (m, 15H, 3 × $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 52.32 (OCH_3), 70.42 ($OCH_2CH{=}CH_2$), 74.44 (C-5), 74.81, 74.95, 75.60 (3 × $CH_2C_6H_5$), 79.22 (C-4), 81.73 (C-2), 83.79 (C-3), 102.82 (C-1), 117.51 ($OCH_2CH{=}CH_2$), 133.62 ($OCH_2CH{=}CH_2$), 127.56, 127.64, 127.72, 127.76, 127.88, 128.09, 128.28, 137.82, 138.21, 138.37 (3 × $CH_2C_6H_5$, eight signals are isochronic), 168.94 (C-6); CI mass spectrum (isobutane): *m/z* 517.6 ($M-H^+$).

Anal.Calcd for $C_{31}H_{34}O_7$ (518.60): C, 71.79; H, 6.61. Found: C, 71.95; H, 6.67.

Methyl 2,3,4-tri-*O*-benzyl-D-glucopyranuronate (29). Sodium acetate (496 mg, 6.1 mmol) and palladium(II)chloride (390 mg, 2.2 mmol) were added to a solution of **28** (287 mg, 0.55 mmol) in acetic acid–water (20:1, 14 mL) and the mixture was stirred for 12 h at 40°C (TLC solvent F R_f 0.43). After filtration through Celite, the solution was diluted with chloroform (35 mL) and heptane (70 mL) and successively washed with ice–water (2 × 50 mL), sat aq $NaHCO_3$ (2 × 50 mL), ice–water (2 × 50 mL), dried and concentrated. The crude material was purified by HPLC (eluent solvent B) to give **29** (210 mg, 80%, 4:1 ratio of the α,β anomers) as colorless crystals: ^{1}H NMR of **29α** ($CDCl_3$) δ 3.58 (dd, 1H, $J_{2,3}$ = 9.0 Hz, H-2), 3.68 (s, 3H, OCH_3), 3.73 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 3.97 (t, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 4.46 (d, 1H, H-5) 4.64, 4.75 (2d, 2H, J = 11.9 Hz, $CH_2C_6H_5$), 4.72, 4.77 (2d, 2H, J = 10.7 Hz, $CH_2C_6H_5$), 4.80, 4.88 (2d, 2H, J = 11.0 Hz, $CH_2C_6H_5$), 5.19 (d,

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1H, $J_{1,2}$ = 3.4 Hz, H-1) 7.20–7.35 (m, 15H, 3 × $CH_2C_6H_5$); ^{13}C NMR of **29α** ($CDCl_3$) δ 52.54 (OCH_3), 70.39 (C-5), 73.49, 75.07, 75.77 (3 × $CH_2C_6H_5$), 79.17 (C-4), 79.26 (C-2), 80.77 (C-3), 91.63 (C-1), 127.80, 127.90, 128.00, 128.05, 128.18, 128.23, 128.46, 128.48, 128.61, 137.61, 137.87, 138.40 (3 × $CH_2C_6H_5$, six signals are isochronic), 170.06 (C-6).

Anal.Calcd for $C_{28}H_{30}O_7$ (478.54): C, 70.28; H, 6.32. Found: C, 70.14; H, 6.30.

Methyl (2,3,4-tri-*O*-benzyl-D-glucopyranosyl)uronate trichloroacetimidate (30). The glucuronate **29** (479 g, 1.0 mmol) was converted into the trichloroacetimidate **30** as described by Schmidt et al.[19] The quality of the sodium hydride has a strong influence on the outcome of the reaction with regard to both yield and ratio of the α,β-anomers. The α,β-anomers were separated by HPLC (eluent solvent A).

Methyl (2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)uronate trichloroacetimidate (30α). (360 mg, 58%, TLC solvent F R_f 0.61), colorless syrup: $[\alpha]_D^{[24]}$ + 45.8 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H, OCH_3), 3.78 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.82 (dd, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 4.06 (t, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 4.41 (dd, 1H, H-5), 4.58 (d, 1H, J = 11.0 Hz, $CH_2C_6H_5$), 4.71 (d, 2H, J = 11.0 Hz, $CH_2C_6H_5$), 4.82 (d, 2H, J = 11.0 Hz, $CH_2C_6H_5$), 4.95 (d, 1H, J = 11.0 Hz, $CH_2C_6H_5$), 6.50 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 7.20–7.35 (m, 15H, 3 × $CH_2C_6H_5$), 8.65 [s, 1H, O(C═NH)CCl_3]; ^{13}C NMR ($CDCl_3$) δ 52.64 (OCH_3), 74.52 (C-5), 73.11, 75.47, 75.84 (3 × $CH_2C_6H_5$), 78.75 (C-2), 78.86 (C-4), 80.70 (C-3), 90.99 [O(C═NH)CCl_3], 93.96 (C-1), 127.73, 127.78, 127.91, 128.03, 128.08, 128.20, 128.44, 128.48, 137.63, 137.68, 138.32 (3 × $CH_2C_6H_5$, seven signals are isochronic), 161.05 [O(C═NH)CCl_3], 169.23 (C-6).

Anal.Calcd for $C_{30}H_{30}Cl_3NO_7$ (622.93): C, 57.84; H, 4.85; N, 2.25. Found: C, 58.06; H, 4.91; N, 2.40.

Methyl (2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl)uronate trichloroacetimidate (30β). (90 mg, 14%, TLC solvent F R_f 0.60), colorless crystals: mp 106°C; $[\alpha]_D^{[24]}$ +15.2 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H, OCH_3) 3.76 (m, 1H, H-2), 3.78 (m, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 3.92 (t, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 4.09 (d, 1H, $J_{5,4}$ = 9.5 Hz, H-5), 4.60, 4,80 (2d, 2H, J = 11.1 Hz, $CH_2C_6H_5$), 4.74, 4.92 (2d, 2H, J = 10.7 Hz, CHC_6H_5), 4.78, 4.88 (2d, 2H, J = 10.4 Hz, $CH_2C_6H_5$), 5.87 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1), 7.20-7.34 (m, 15H, 3 × $CH_2C_6H_5$), 8.72 [s, 1H, O(C═NH)CCl_3]; ^{13}C NMR ($CDCl_3$) δ 52.64 (OCH_3), 74.82 (C-5), 74.86, 75.06, 75.63 (3 × $CH_2C_6H_5$), 78.74 (C-4), 80.43 (C-3), 83.64 (C-2), 91.47 [O(C═NH)CCl_3], 98.02 (C-1), 127.80, 127.85, 127.92, 127.97, 128.02, 128.08, 128.19, 128.45, 128.58, 137.60, 137.66, 138.12 (3 × $CH_2C_6H_5$, six signals are isochronic), 160.91 [O(C═NH)CCl_3], 168.70 (C-6).

Anal.Calcd for $C_{30}H_{30}Cl_3NO_7$ (622.93): C, 57.84; H, 4.85; N, 2.25. Found: C, 57.76; H, 4.82; N, 2.31.

Methyl [(2-*R*)-2,3,4,5-tetrahydro-5-oxo-2-furylmethyl 2-*O*-acetyl-3,4-di-*O*-benzyl-β-D-glucopyranosid]uronate (33). *Via* **12** and **32**. The cyanoethylidene derivative **12** (88 mg, 0.2 mmol) and (5-*R*)-tetrahydro-5-trityloxymethyl-2-furanone (**32**, 79 mg, 0.22 mmol, FLUKA 93461) were dissolved in dry dichloromethane (10 mL) and the solvent then evaporated. The residue was dried under high vacuum for about 2 h and then dissolved in dry dichloromethane (3 mL, twice distilled over CaH_2). Trityl

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perchlorate (7 mg, 0.02 mmol) was added and the mixture was stirred in the dark under an inert atmosphere at rt. After 24 h followed by TLC (solvent G R_f 0.43), aq pyridine (2% water, 0.2 mL) was added. The reaction mixture was then filtered, diluted with heptane (40 mL) and chloroform (20 mL), washed with water (3 × 30 mL), dried and concentrated. The purification by HPLC (eluent solvent F) afforded compound **33** (73 mg, 69%).

Via **14** and **31**. A solution of orthoester **14** (229 mg, 0.5 mmol) and (5-*R*)-2,3,4,5-tetrahydro-5-hydoxymethyl-2-furanone (**31**, 64 mg, 0.55 mmol, FLUKA 55621) in dry 1,2-dichloroethane (3 mL) was evaporated at atmospheric pressure by addition of fresh solvent to keep the volume constant. When 10 mL of the solvent had been distilled off, *p*- toluenesulfonic acid (1.1 mg, 6.7 μmol) in dry dichloroethane (1 mL) was added, and the mixture was distilled under the same conditions until the formation of the new orthoester was nearly complete (ca. 1 h) while **14** disappeared in the TLC (solvent F). Pyridinium perchlorate (1.2 mg, 6.7 μmol) was then added and the mixture was refluxed for 2 h (TLC solvent G R_f 0.43). The solution was treated with pyridine (0.1 mL) and evaporated. The residue was purified by HPLC to give 33 (74 mg, 28%).

Via **15** and **31**. Anhyd silver perchlorate (112 mg, 0.54 mmol) was added to a stirred solution of bromide **15** (222 mg, 0.45 mmol) in dry acetonitrile (5 mL) at −15°C. After 40 min, a solution of the lactone **31** (58 mg, 0.5 mmol) in dry acetonitrile (2 mL) was added and stirring was continued at rt for 16 h (TLC solvent G R_f 0.43). The reaction mixture was then neutralized with anhydr sodium carbonate, diluted with chloroform (30 mL) and heptane (60 mL) and filtered. The organic layer was washed with water (3 × 50 mL), dried and concentrated. The crude product was purified by HPLC to give **33** (107 mg, 45%).

Via **17** and **31**. A solution of boron trifluoride etherate (5.8 μL, 46 μmol) in dry dichloromethane (0.5 mL) was added to a mixture of trichloroacetimidate **17** (161 mg, 0.28 mmol), lactone **31** (36 mg, 0.31 mmol) and molecular sieves (4 Å, 1 g) in dry dichloromethane (5 mL) under an atmosphere of argon at −20°C. After stirring for 2 h at that temperature (TLC solvent G R_f 0.43), the mixture was treated with anhyd $NaHCO_3$ (50 mg) and passed through a layer of silica gel. The filtrate was washed with sat aq $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), dried and concentrated. The crude material was purified by HPLC to yield **33** (105 mg, 71%) as colorless crystals: mp 128°C (from ethyl acetate–heptane); $[\alpha]_D^{[24]}$ − 13.6 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3H, $OCOCH_3$), 2.22 (m, 2H, lactone: H-4, H-4′), 2.36, 2.61 (2m, 2H, lactone: H-3, H-3′), 3.64 (dd, 1H, J = 11.2 Hz, lactone: H-6), 3.66 (dd, 1H, $J_{3,4}$ = 11.1 Hz, H-3), 3.71 (s, 3H, OCH_3), 3.86 (dd, 1H, $J_{4,5}$ = 8.0 Hz, H-4), 3.90 (ddd, 1H, $J_{5,4}$ = 9.7 Hz, H-5), 3.94 (dd, 1H, lactone: H-6′), 4.43 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 4.62 (m, 1H, lactone: H-5), 4.59, 4.66 (2d, 2H, J = 11.8 Hz, $CH_2C_6H_5$), 4.76, 4.77 (2d, 2H, J = 11.2 Hz, $CH_2C_6H_5$), 5.04 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 7.20–7.34 (m, 10H, 2 × $CH_2C_6H_5$); ^{13}C NMR ($CDCl_3$) δ 20.65 ($OCOCH_3$), 23.56 (lactone: C-4), 28.05 (lactone: C-3), 52.59 (OCH_3), 71.18 (lactone: C-6), 72.37 (C-2), 74.44 (C-5), 75.08 (2 × $CH_2C_6H_5$, two signals are isochronic), 77.78 (lactone: C-5), 79.24 (C-4), 81.79 (C-3), 101.50 (C-1), 127.87, 128.03, 128.46, 137.51, 137.81 (2 × $CH_2C_6H_5$, seven signals are isochronic), 168.68 (C-6), 169.80 ($COCH_3$), 177.52 (lactone: C-2); CI mass spectrum: *m/z* 527.6 ($M-H^+$), 413 (M-lactone$^+$, 100%).

Anal.Calcd for $C_{28}H_{32}O_{10}$ (528.55): C, 63.63; H, 6.10. Found: C, 63.55; H, 6.17.

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Methyl [(2-*R*)-2,3,4,5-tetrahydro-5-oxo-2-furylmethyl 3,4-di-*O*-benzyl-β-D-glucopyranosid]uronate (34). Methanolic sodium methoxide (0.5 M, 0.7 mL) was added to a solution of **33** (158 mg, 0.3 mmol) in dry dichloromethane (2 mL) and dry methanol (10 mL). After stirring for 4 h at ambient temperature (TLC solvent G R_f 0.35), the solution was neutralized with Dowex-50 (H^+) resin, filtered and concentrated. The purification of the residue by HPLC (eluent solvent F) afforded compound **34** (110 mg, 75%), as colorless crystals: mp 112°C; $[\alpha]_D^{[24]}$ − 23.5 (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.22 (m, 2H, lactone: H-4, H-4′), 2.52 (m, 2H, H-3, H-3′), 3.57 (dd, 1H, $J_{2,3}$ = 7.9 Hz, H-2), 3.58 (dd, 1H, $J_{3,4}$ = 8.2 Hz, H-3), 3.72 (s, 3H, OCH_3), 3.80 (dd, 1H, $J_{4,5}$ = 8.0 Hz, H-4), 3.81 (d, 1H, lactone: H-6), 3.91 (d, 1H, $J_{5,4}$ = 9.6 Hz, H-5), 3.99 (dd, 1H, lactone: H-6′), 4.37 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.59, 4.80 (2d, 2H, J = 11.1 Hz, C*H*$_2$C$_6$H$_5$), 4.68 (m, 1H, lactone: H-5), 4.83, 4.92 (2d, 2H, J = 11,3 Hz, C*H*$_2$C$_6$H$_5$), 7.20−7.40 (m, 10H, 2 × CH$_2$C$_6$*H*$_5$); ^{13}C NMR ($CDCl_3$) δ 23.73 (lactone: C-4), 28.31 (lactone: C-3), 52.48 (OCH_3), 70.96 (lactone: C-6), 73.96 (C-2), 74.41 (C-5), 74.95, 75.16 (2 × *C*H$_2$C$_6$H$_5$), 78.21 (lactone: C-5), 78.76 (C-4), 83.37 (C-3), 103.25 (C-1), 127.76, 127.84, 127.91, 128.36, 128.42, 137.61, 138.21 (2 × CH$_2$*C*$_6$H$_5$, five signals are isochronic), 168.87 (C-6), 177.42 (lactone: C-2).

Anal.Calcd for $C_{26}H_{30}O_9$ (486.51): C, 64.18; H, 6.21. Found: C, 64.37; H, 6.36.

Methyl [(2-*R*)-2,3,4,5-tetrahydro-5-oxo-2-furylmethyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranosid]uronate (35). A solution of boron trifluoride etherate (3.5 μL, 25 μmol) in dry dichloromethane (1.0 mL) was added to a mixture of trichloroacetimidate **30** (95 mg, 0.15 mmol), lactone **31** (19 mg, 0.17 mmol) and molecular sieves (4 Å, 1 g) in dry dichloromethane (3 mL) under an atmosphere of argon at −20°C. After stirring for 2 h at that temperature (TLC solvent F R_f 0.33), the mixture was treated with anhyd $NaHCO_3$ (50 mg) and passed through a layer of silica gel. The filtrate was washed with sat aq $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), dried and concentrated. The residue was purified by HPLC (eluent solvent F) to provide compound **35** (61 mg, 70%, containing ca. 20% of the α-anomer) as colorless syrup: ^{1}H NMR of **35** ($CDCl_3$) δ 2.24 (m, 2H, lactone: H-4, H-4′), 2.50 (m, 2H, lactone: H-3, H-3′), 3.48 (dd, 1H, $J_{2,3}$ = 8.7 Hz, H-2), 3.66 (t, 1H, $J_{4,5}$ = 8.7 Hz, H-4), 3.71 (s, 3H, OCH_3), 3.81 (dd, 1H, lactone: H-6), 3.83 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 3.89 (d, 1H, $J_{5,4}$ = 9.5 Hz, H-5), 3.99 (dd, 1H, lactone: H-6′), 4.48 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1) 4.56, 4.66 (2d, 2H, J = 11.00 Hz, C*H*$_2$C$_6$H$_5$), 4.67 (m, 1H, lactone: H-5), 4.77, 4.78 (2d, 2H, J = 11.4 Hz, C*H*$_2$C$_6$H$_5$), 4.80, 4.89 (2d, 2H, J = 11.0 Hz, C*H*$_2$C$_6$H$_5$), 7.17−7.35 (m, 15H, 3 × CH$_2$C$_6$*H*$_5$); ^{13}C NMR of **35** ($CDCl_3$) δ 23.91 (lactone: C-4), 28.45 (lactone: C-3), 52.55 (OCH_3), 70.52 (lactone: C-6), 74.35 (C-5), 74.86, 75.07, 75.71 (3 × *C*H$_2$C$_6$H$_5$), 78.20 (lactone: C-5), 79.07 (C-3), 81.57 (C-2), 83.70 (C-4), 103.57 (C-1), 127.77, 127.81, 127.88, 127.93, 128.02, 128.09, 128.44, 128.56, 137.71, 137.95, 138.22 (3 × CH$_2$*C*$_6$H$_5$, seven signals are isochronic), 169.06 (C-6), 177.01 (lactone: C-2).

Anal.Calcd for $C_{33}H_{36}O_9$ (576.64): C, 68.73; H, 6.29. Found: C, 68.61; H, 6.40.

Methyl [(2-*R*)-2,3,4,5-tetrahydro-5-oxo-2-furylmethyl β-D-glucopyranosid]uronate (36). To a solution of **35** (49 mg, 85 μmol) in ethyl acetate (2 mL) and ethanol (3 mL) 10% was added palladium-on-charcoal (65 mg). The mixture was stirred in an atmosphere of hydrogen at rt. When the reaction was complete (TLC solvent H R_f 0.20), the mixture was filtered over Celite, eluted successively with ethanol, and the

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combined filtrates were concentrated to yield compound **36** (26 mg, 98%, containing 20% of the α-anomer) as a colorless powder: ^{1}H NMR of **36** (D_2O) δ 2.14, 2.37 (2 m, 2H, lactone: H-4, H-4′), 2.67 (m, 2H, lactone: H-3, H-3′), 3.36 (dd, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 3.57 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 3.59 (dd, 1H, $J_{4,5}$ = 8.6 Hz, H-4), 3.84 (s, 3H, OCH_3), 3.93, 4.01 (2dd, 2H, lactone: H-6, H-6′), 4.09 (dd, 1H, $J_{5,4}$ = 9.4 Hz, H-5), 4.57 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1), 4.88 (m, 1H, lactone: H-5); ^{13}C NMR of **36** (D_2O) δ 25.74 (lactone: C-4), 31.26 (lactone: C-3), 55.90 (OCH_3), 73.97 (lactone: C-6), 74.05 (C-4), 75.45 (C-2), 77.37 (C-5), 77.88 (C-3), 83.37 (lactone: C-5), 102.17 (C-1), 169.67 (C-6), 178.63 (lactone: C-2).

Anal.Calcd for $C_{12}H_{18}O_9$ (306.26): C, 47.06; H, 5.92. Found: C, 47.20; H, 5.84.

(2-*R*)-2,3,4,5-Tetrahydro-5-oxo-2-furylmethyl 3,4-di-*O*-benzyl-β-D-glucopyranosiduronic acid (37). Aq 1 M lithium hydroxide (3 mL) was added to a solution of **34** (107 mg, 0.22 mmol) in acetone (7 mL). After stirring for 3 h at ambient temperature (TLC solvent J R_f 0.30), the solution was treated with Dowex-50 (H^+) resin, filtered, and successively coevaporated with toluene (3 × 5 mL), ethanol (3 × 5 mL), and chloroform (3 × 5 mL). The residue was purified by preparative TLC (eluent solvent K R_f 0.45) to afford compound **37** (91 mg, 88%) as colorless crystals: mp 133°C; $[\alpha]_D^{[24]}$ − 94.1 (*c* 1.0, methanol); ^{1}H NMR (CD_3OD) δ 2.23 (m, 2H, lactone: H-4, H-4′), 2.56 (m, 2H, lactone: H-3, H-3′), 3.45 (dd, 1H, $J_{2,3}$ = 8.5 Hz, H-2), 3.52 (dd, 1H, $J_{4,5}$ = 9.1 Hz, H-4), 3.79 (d, 1H, $J_{5,4}$ = 9.0 Hz, H-5), 3.80 (dd, 1H, $J_{3,4}$ = 8.6 Hz, H-3), 3.81, 3.95 (2dd, 2H, lactone: H-6, H-6′), 4.37 (d, 1H, $J_{1,2}$ = 7.3 Hz, H-1), 4.67, 4.75 (2d, 2H, J = 10.7 Hz, $CH_2C_6H_5$), 4.74 (m, 1H, lactone: H-5), 4.77, 4.91 (2d, 2H, J = 11.2 Hz, $CH_2C_6H_5$), 7.18–7.36 (m, 10H, 2 × $CH_2C_6H_5$); ^{13}C NMR (CD_3OD) δ 24.69 (lactone: C-4), 29.26 (lactone: C-3), 71.78 (lactone: C-4), 75.32 (C-2), 75.50, 76.12 (2 × $CH_2C_6H_5$), 78.81 (C-5), 80.91 (lactone: C-5), 81.95 (C-3), 85.79 (C-4), 104.63 (C-1), 128.38, 128.86, 129.04, 129.13, 129.19, 140.04, 140.34 (2 × $CH_2C_6H_5$, five signals are isochronic), 176.23 (C-6), 180.26 (lactone: C-2); CI mass spectrum: *m/z* 473.2 ($M + H^+$).

Anal.Calcd for $C_{25}H_{28}O_9$ (472.49): C, 63.55; H, 5.97. Found: C, 63.29; H, 5.84.

(2-*R*)-2,3,4,5-Tetrahydro-5-oxo-2-furylmethyl β-D-glucopyranosiduronic acid (38). To a solution of compound **37** (38 mg, 0.08 mmol) in ethyl acetate (2 mL) and ethanol (5 mL) was added 10% palladium-on-charcoal (20 mg). The mixture was stirred in an atmosphere of hydrogen at rt. When the reaction was complete (TLC solvent I R_f 0.26), the mixture was filtered over Celite, eluted successively with ethanol, and the combined filtrates were concentrated. The residue was purified by preparative TLC (eluent solvent K R*f* 0.30). After concentration of the extracts, the residue was dissolved in water and lyophilized to provide compound **38** (20 mg, 84%) as a colorless powder: $[\alpha]_D^{[24]}$ − 9.7 (*c* 1.0, water); ^{1}H NMR ($CDCl_3$) δ 2.20–2.45 (m, 4H, lactone: H-3, H-3′, H-4, H-4′), 3.34 (dd, 1H, $J_{2,3}$ = 7.5 Hz, H-2), 3.50 (d, 1H, $J_{3,4}$ = 7.6 Hz, H-3), 3.51 (d, 1H, $J_{4,5}$ = 7.9 Hz, H-4), 3.71 (d, 1H, $J_{5,4}$ = 8.1 Hz, H-5), 3.82, 4.10 (2dd, 2H, lactone: H-6, H-6′), 4.49 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 4.66 (m, 1H, lactone: H-5); ^{13}C NMR (D_2O) δ 24.02 (lactone: C-4), 29.46 (lactone: C-3), 71.87 (lactone: C-6), 72.82 (C-4), 73.90 (C-2), 74.01 (lactone: C-5), 76.57 (C-3), 76.98 (C-5), 103.35 (C-1), 172.58 (C-6), 183.06 (lactone: C-2).

Anal.Calcd for $C_{11}H_{16}O_9$ (292.24): C, 45.21; H, 5.52. Found: C, 44.93; H, 5.44.

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