

Acceptor Site Recognition of Transglycosylase Inhibitors A β -D-glucopyranosyl-(1 \rightarrow 2)- α -D-glucopyranuronamide-derived Moenomycin Analogue

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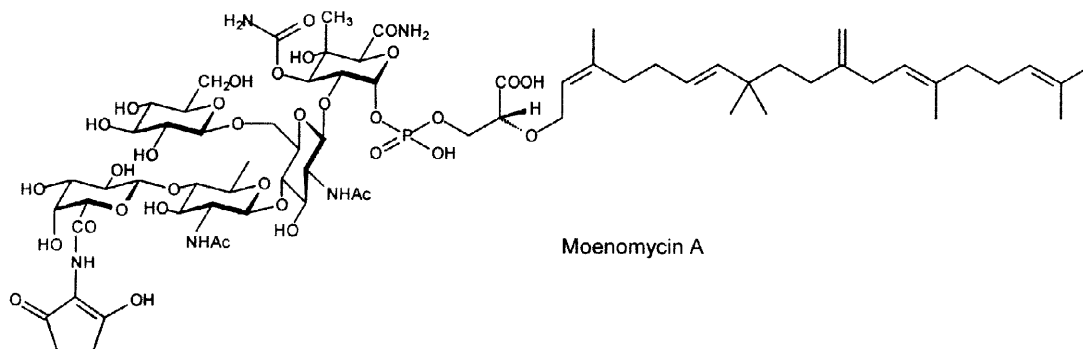
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Abstract - The synthesis, the antibiotic and the transglycosylase inhibiting properties of a disaccharide analogue of moenomycin A in which the NHAc group of unit E is replaced by a hydroxyl function are described. It can be concluded that this NHAc group is essential for eliciting transglycosylase inhibiting properties, in agreement with a recently established solution structure of moenomycin A. © 1999 Elsevier Science Ltd. All rights reserved.

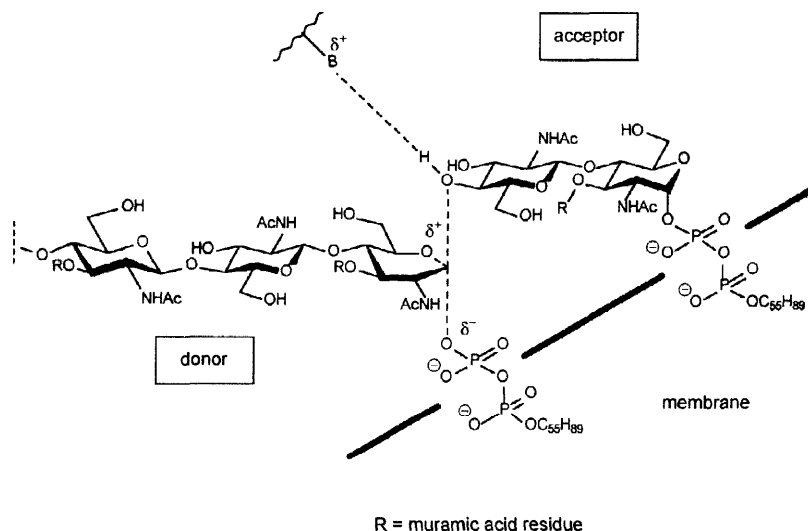
Key words: Antibiotics, carbohydrates, phospholipids, structure-activity

Introduction

Transglycosylases such as penicillin binding protein 1b (PBP 1b) catalyze the formation of un-crosslinked peptidoglycan from a disaccharide intermediate (Lipid II).¹ This glycosyltransfer reaction is believed to proceed in such a way that the growing peptidoglycan chain is the glycosyl donor substrate whereas lipid II is the glycosyl acceptor (see Scheme 1).²

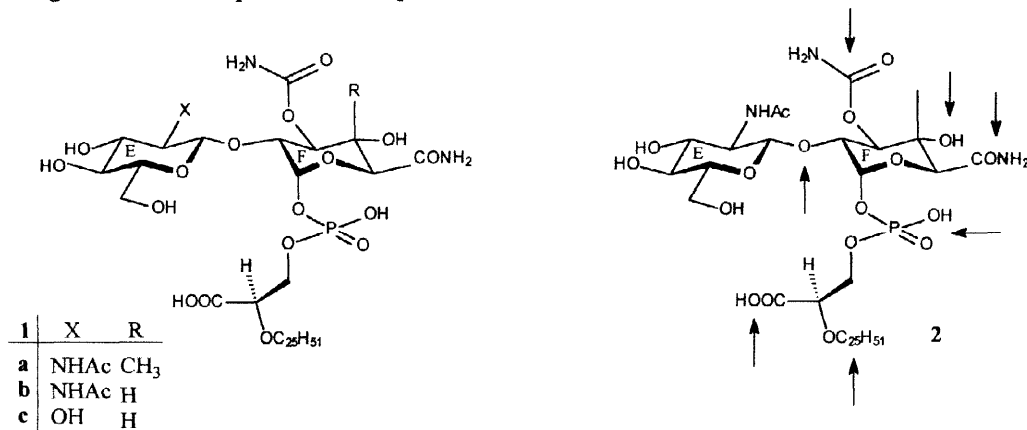


The moenomycin antibiotics have been shown to inhibit PBP 1b and related enzymes.³ The structure-activity relationships indicate that there are two recognition sites for moenomycin-type transglycosylase inhibitors at the enzyme, one at the donor and one at the acceptor binding site. The moenomycins themselves and struc-



Scheme 1: Transition state of the transglycosylation reaction (speculative)

tural analogues with at least three sugar units bind presumably to the donor binding site.^{4,5} They are active *in vivo* (against gram-positive bacteria) as well as in the *in vitro* test systems. Moenomycin analogues with two sugars are antibiologically more or less inactive but they do inhibit the enzyme in the test systems provided that they have the right substitution pattern.⁵ Compounds **1a** and **1b** fulfil these conditions.

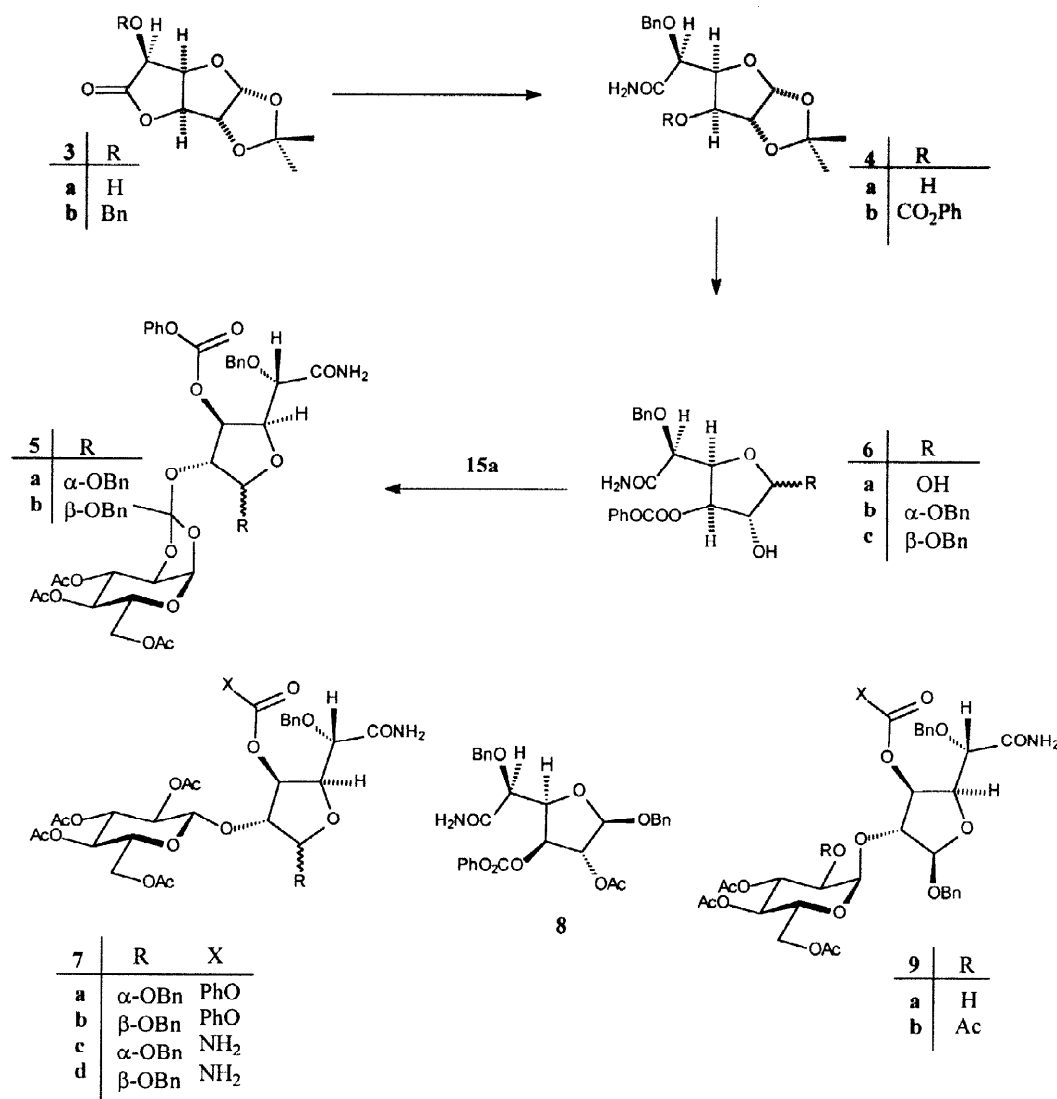


It is believed that these analogues bind to the acceptor binding site. Formula **2** indicates the groups that have been shown with the help of structural analogues to be indispensable for transglycosylase inhibition to be elicited.⁵ From a recently determined NMR conformation of moenomycin A in aqueous solution⁶ it may be concluded that in addition to the previously established pharmacophoric groups (see arrows in formula **2**) the NHAc group of unit E should also be an obligatory structural feature of transglycosylase inhibitors.

It was the purpose of the work outlined herein to test this conclusion. Described are (i) the synthesis, (ii) the antibiotic, and (iii) the transglycosylase inhibiting properties of compound **1c**, a disaccharide analogue of moenomycin A in which the NHAc group of unit E is replaced by a hydroxyl function.

Synthesis of glycosyl acceptor

The disaccharide part of **1c** was constructed from a suitably functionalized D-glucuronic acid derivative (glycosyl acceptor) and a D-glucose-derived glycosyl donor.



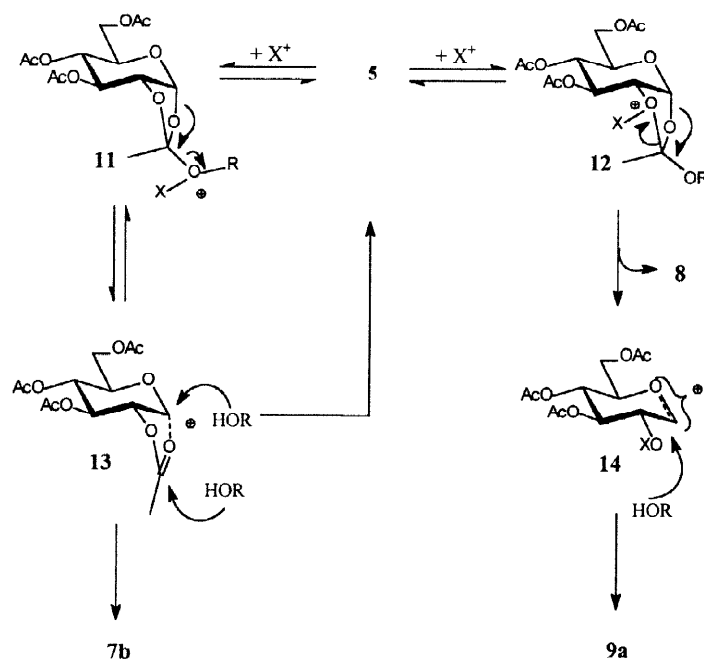
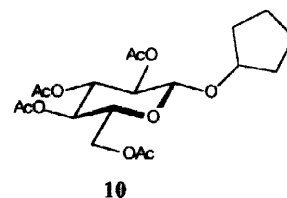
It has been shown previously, that the synthesis of compounds like **1b** is plagued by the high polarity of intermediates with the uronamide and carbamoyl functionalities.⁷ A number of measures have been taken to overcome these problems, including development of a new lipophilic protecting group for the anomeric centre.⁸ In the present work we used benzyl groups for both the 1- and the 5-position of unit F to render the compounds less polar. Recently, we found out that replacing the carbamoyl group in unit F by a latent functionality, a phenyl carbonate, solved most of the solubility and polarity problems.⁵ This method was used for the present synthesis, too, but in addition, we performed some preliminary experiments with a glycosyl donor in which the acetyl were replaced by butyryl groups.

Alkylation⁹ of the 5-OH group of **3a** using benzyl trichloroacetimidate^{10,11} in a trifluoromethanesulfonic acid-mediated reaction gave benzyl ether **3b** in 60% yield. The lactonic ring in **3b** was opened with NH₃ in THF solution to furnish the uronamide **4a**.¹² **4a** on reaction with phenyl chloroformate in dichloromethane in

the presence of 1.0 eq of DMAP and triethylamine (procedure of McLamore et al.¹³) provided phenyl carbonate **4b**. The acetonide protecting group was then removed with 90 per cent trifluoroacetic acid at 20°C^{14,15} to form **6a** in quantitative yield as a mixture of anomers which was in turn converted under Fischer conditions¹⁶ to a mixture of benzyl glycosides **6b** (56%) and **6c** (26%).

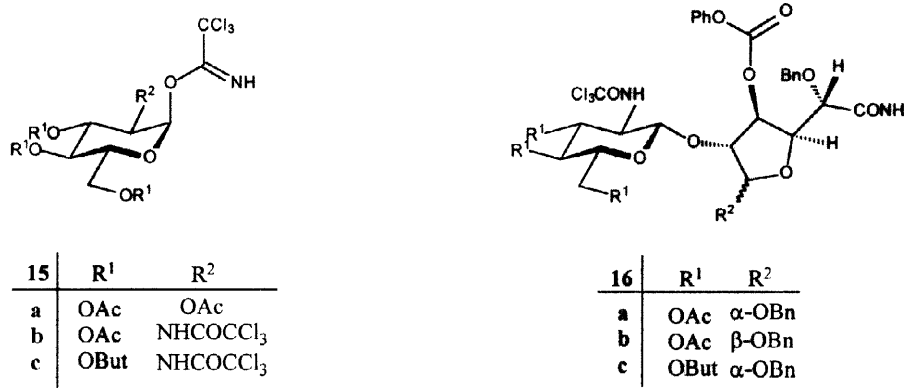
Glycosidation experiments

For the synthesis of **1c** we used the known trichloroacetimidate **15a** as glycosyl donor.¹⁷ In a model experiment **15a** was treated with cyclopentanol (0°C, BF₃·Et₂O-mediated) to provide **10**¹⁸ in an unexceptional reaction (66% yield, not optimized). On the other hand, on reaction of **15a** with the glycosyl acceptor **6c** at -20°C (BF₃·Et₂O-mediated) in a clean reaction solely orthoester **5b** was formed (93%). The configuration at the orthoester carbon was not determined. When the reaction was repeated at 20°C three products could be isolated. One of them was the desired disaccharide **7b** (17%), the others were



Scheme 2: Proposed mechanism for the formation of **7b**, **8** and **9a**

disaccharide **9a** with an α - glucopyranosyl unit lacking the acetyl group of position 2 (29% yield) and glycosyl acceptor derivative **8** in which the accepting OH group of **6c** was acetylated. Scheme 2 indicates how these compounds are probably formed. When the orthoester reacts as indicated in **13** (lower arrow), **7b** is the product. Opening of the bond between the 2-oxygen of the glucose unit and the orthoester carbon leads to the other products. Similar reactions have been found on attempted glycosylation reactions of some steroid aglycons.¹⁹ When the same reaction was repeated with **6b** as glycosyl acceptor **5a** and **7a** were isolated.



In some model experiments glycosyl acceptors **6b** and **6c** were treated with the Beau-Jacquet glucosamine glycosyl donor **15b**.²⁰ Here the reactions were again straightforward and provided disaccharides **16a** and **16b**, respectively. As already mentioned above we exchanged **15b** against the butyryl analogue **15c** (for the preparation, see Experimental). The disaccharide formation proceeded as desired and indeed, the disaccharide **16c** was much less polar when compared with **16a**. This example shows that the previously encountered solubility problems can also be solved by the proper choice of acyl protecting groups at least as far as disaccharide intermediates are involved.⁵

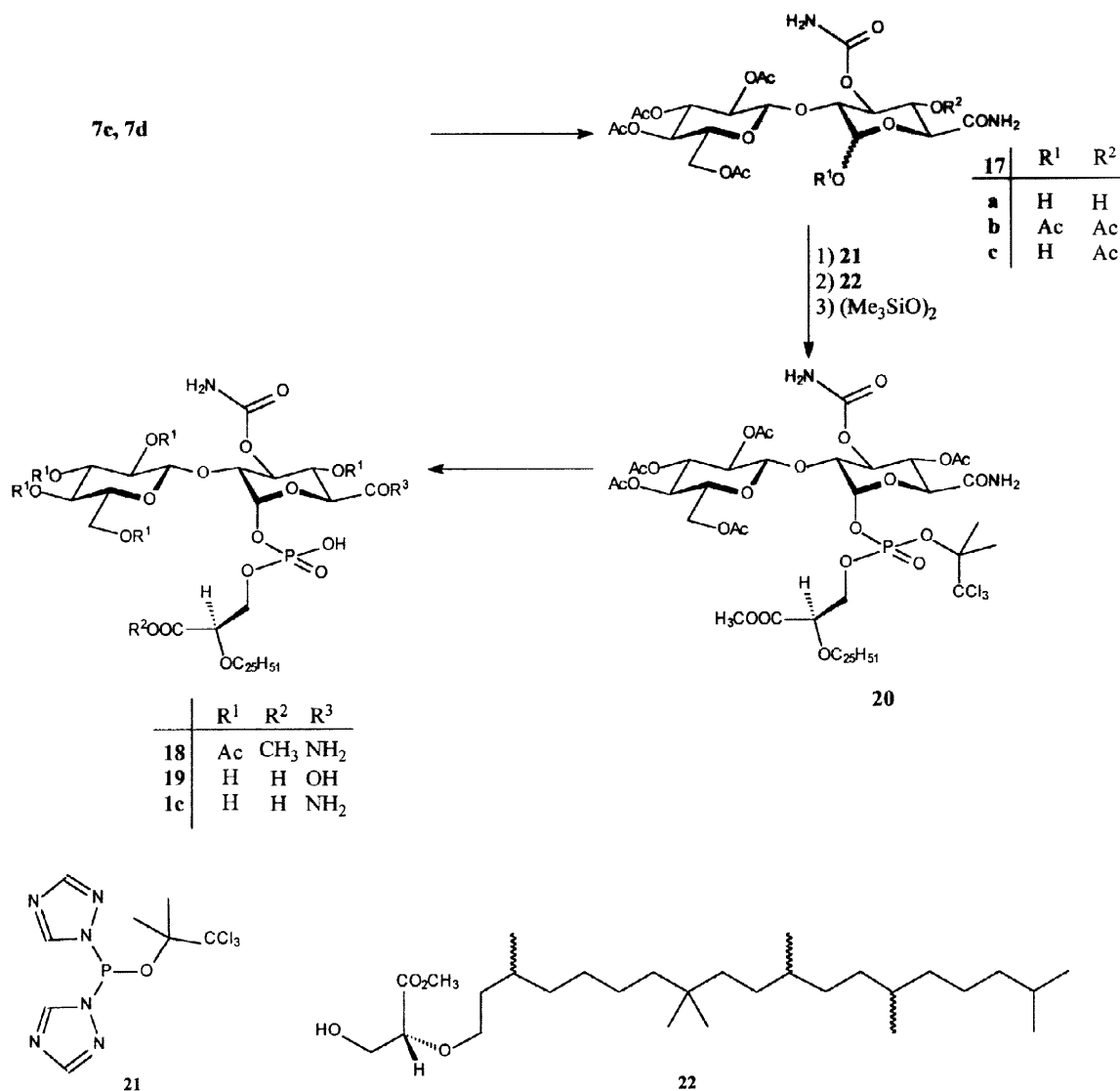
Completion of the synthesis of **1c**

Treatment of **7a** and **7b** with NH₃ in THF solution²¹ provided **7c** (63%) and **7d** (41%) which on hydrogenation furnished **17a**.^{22,23} The anomeric mixture was acetylated to give a mixture of anomeric acetates which was then selectively deacetylated to provide the desired compound **17c**.²⁴ Treatment of **17c** with reagent **21**, prepared *in-situ* from 1H-1,2,4-triazol and 2,2,2-trichloro-1,1-dimethylethyl dichlorophosphite, followed by reaction with the moenomycin-derived building block **22**²⁵ furnished a phosphite which was oxidized with bis(trimethylsilyl)peroxide²⁶ to form phosphoric acid triester **20**.²⁷ Two diastereoisomers were obtained, the configuration at the phosphate unit was not determined. Deprotection occurred in two steps: (i) reductive removal of the phosphate protecting group (zinc-copper couple under Imai conditions)²⁸ and (ii) base hydrolysis of the ester protecting groups.²⁹ As usual, the glyceric acid methyl ester reacted most reluctantly. Besides the target compound **1c** uronic acid **19** was isolated. The structure of **1c** was secured by FAB MS and ¹³C and ³¹P NMR.

Antibiotic and transglycosylase inhibiting properties of **1c**

1c was antibiotically inactive (Staph. aureus SG 511). In van Heijenoort's test system³⁰ the compound was devoid of activity even at 10 µg / mL.

The results mean that the N-acetyl group of unit E is indeed a prerequisite of transglycosylase inhibiting properties. The suggestion of the NMR analysis is, thus, corroborated by our results. Most probably the NHAc group supplies an important contribution of the binding of moenomycin disaccharide analogues to the enzyme.



EXPERIMENTAL

General

Organic solvent evaporations were performed *in vacuo* at 40 °C using a rotary evaporator, water was removed by lyophilization (Leybold-Heraeus GT2 or Christ Alpha 1-2). Solvents were purified by standard procedures. If necessary, solvents were degassed by sonication (Bandelin, Sonorex Super RK 106).- O₂- or moisture-sensitive reactions were performed in oven-dried glassware under a positive pressure of argon. Liquids and solutions were transferred by syringe. Small-scale reactions were performed in Wheaton serum bottles sealed with aluminium caps with open top Teflon-faced septum (Aldrich).- The instrumentation used was: NMR: Gemini 200 and Gemini 2000 (Varian, ¹H NMR 200 MHz, ¹³C NMR 50.3 MHz), Gemini 300 (Varian, ¹H NMR 300 MHz, ¹³C NMR 75.5 MHz, ³¹P NMR 121.5 MHz), Unity 400 (Varian, ¹H NMR 400 MHz, ¹³C NMR 100.6 MHz, ³¹P NMR 161.9 MHz), Bruker DMX 600 spectrometer (¹H NMR 600.13 MHz, processed on a SGI O2 workstation using the X-WINNMR program), chemical shifts are given in δ values, the ³¹P NMR shifts are based on external phosphoric acid; FT-IR: ATI Mattson spectrometer, Genesis series; FAB MS: VG AUTOSPEC (matrix: lactic acid or 3- nitrobenzyl alcohol), two molecular masses are always

communicated, the first was calculated using the International Atomic Masses, the second refers to ^{12}C , ^1H , ^{16}O , ^{14}N , ^{31}P , ^{35}Cl (mono-isotopic masses), carbon and proton numbering in the subunits (see NMR data) as well as naming of the MS fragments follows the moenomycin nomenclature³¹ (see formula); melting points (corrected, determined in capillary tubes): Büchi (B-540); analytical TLC: Merck precoated silica gel 60 F₂₅₄ plates (0.2 mm), spots were identified under a UV lamp ($\lambda = 254$ nm and $\lambda = 366$ nm) and by dipping into a 2.22 mol/L H₂SO₄ solution containing Ce(SO₄)₂·xH₂O (10.0 g/L) and H₃[PO₄(Mo₃O₉)₄]·xH₂O (25.0 g/L)³² and subsequent heating at 140°C or with the phosphate-specific spraying reagent of Dittmer and Lester;³³ flash chromatography (FC)³⁴: silica gel (ICN Biomedical Silica 32-63 μm), Optima pump (Model 10007); medium-pressure liquid chromatography (MPLC): silica gel 20-40 μm (Merck), 35-70 μm (Amicon) or 50 μm (Fa. Grace), the samples were applied to a precolumn (3-5 g Kieselgel, 63-100 μm) and eluted at 1-2·10⁵ Pa using a dosage pump (Promint Dosiertechnik, Heidelberg or Kronlab Chromatographie und Labortechnik, Sinsheim).

1,2-*O*-Isopropylidene-5-*O*-benzyl- α -D-glucofuranosidurono-6,3-lactone (**3b**)

Trifluoromethanesulfonic acid (96 μL) was added to a solution of **3a** (2.3 g, 10.64 mmol) and benzyl trichloroacetimidate⁹ (5.5 g, 21.78 mmol) in diethylether – dichloromethane (1:1, 13 mL) at 20°C. The solution was stirred at 20°C for 3 h and then triethylamine (0.2 mL) was added. The mixture was cooled to 0°C, solids were filtered off. The residue was washed several times with petrol-dichloromethane (3:1). Solvent evaporation from the combined solutions and FC (dichloromethane-ethyl acetate 99:1 \rightarrow ethyl acetate) gave **3b** (1.85 g, 60%).- ^1H NMR (200 MHz, ^1H - ^1H COSY, CDCl₃): $\delta = 1.34$, 1.51 (6H, 2 s, O₂C(CH₃)₂), 4.26 (1H, d, 5-H, $J_{4,5} = 4.3$ Hz), 4.71 (1H, d, 3-H, $J_{3,4} = 2.9$ Hz), 4.79 (1H, d, 2-H, $J_{1,2} = 3.7$ Hz), 4.86 (1H, dd, 4-H, $J_{3,4} = 3.0$ Hz, $J_{4,5} = 4.4$ Hz), 4.92 (2H, s, OCH₂Ph), 6.04 (1H, d, 1-H, $J_{1,2} = 3.7$ Hz), 7.32-7.48 (m, Ph); impurity: 5.30 (CH₂Cl₂).- ^{13}C NMR (50 MHz, CDCl₃): $\delta = 27.0$, 27.4 (O₂C(CH₃)₂), 73.0, 75.0, 77.9, 82.2, 83.0 (C-2, C-3, C-4, C-5, OCH₂Ph), 107.5 (C-1), 113.7 (O₂C(CH₃)₂), 128.9, 129.1, 136.6 (Ar-Cs), 172.4 (CO).- IR (CHCl₃): 1804 cm⁻¹.- C₁₆H₁₈O₆ (306.28, 306.11), FAB MS: m/z 329.0 [M+Na]⁺, 307.0 [M+H]⁺, 305.0 [M+H-H₂]⁺.

1,2-*O*-Isopropylidene-5-*O*-benzyl-3-hydroxy- α -D-glucofuranosiduronamide (**4a**)

Ammonia was slowly bubbled into a solution of **3b** (4.16 g, 13.6 mmol) in dry THF (25 mL) for 1.5 h. The reaction mixture was stirred at 20°C overnight. Solvent evaporation furnished pure **4a** (4.07 g, 93%).- M.p. 136°C, lit.¹² 135°C.- ^1H NMR (200 MHz, CDCl₃): $\delta = 1.32$, 1.47 (6H, 2 s, C(CH₃)₂), 4.22 (1H, m, 3-H, $J_{3,\text{OH}} = 5.4$ Hz, $J_{3,4} = 3.2$ Hz), 4.37 (1H, d, 5-H, $J_{4,5} = 2.0$ Hz), 4.50 (1H, d, 2-H, $J_{1,2} = 3.6$ Hz), 4.56 (1H, t, 4-H, $J_{3,4} = 3.2$ Hz, $J_{4,5} = 2.2$ Hz), 4.69, 4.77 (2H, AB system, OCH₂Ph, $^2J = 11.6$ Hz), 5.24 (1H, d, OH, $J_{3,\text{OH}} = 5.4$ Hz), 5.90 (1H, d, 1-H, $J_{1,2} = 3.6$ Hz), 5.95, 6.82 (2H, 2bs, CONH₂), 7.30-7.45 (5H, m, Ph).- ^{13}C NMR (50 MHz, CDCl₃): $\delta = 26.6$, 27.4 (O₂C(CH₃)₂), 74.4, 75.8, 76.9, 81.2, 86.0 (C-2, C-3, C-4, C-5, OCH₂Ph), 105.4 (C-1), 112.5 (O₂C(CH₃)₂), 128.7, 129.1, 129.3, 136.7 (Ar-Cs), 173.8 (CONH₂).- IR (KBr): 1662 cm⁻¹.- C₁₆H₂₁NO₆ (323.35, 323.14), FAB MS: m/z 346.0 [M+Na]⁺, 324.0 [M+H]⁺.

1,2-*O*-Isopropylidene-5-*O*-benzyl-3-*O*-phenoxy-carbonyl- α -D-glucofuranosiduronamide (**4b**)

To a solution of **4a** (2.1 g, 6.5 mmol) and phenyl chloroformate (1.02 g, 0.82 mL, 1.0 eq.) in dichloromethane (24 mL) DMAP (803 mg, 1.0 eq.) and triethylamine (0.9 mL) were added at 20°C. The solution was stirred at 20°C for 1 h. Dichloromethane (30 mL) was added. The solution was washed twice with a saturated NaHCO₃ solution and with water. After drying, solvent evaporation and FC (chloroform-ethyl acetate 7:3) pure **4b** (2.55 g, 88%) was obtained.- M.p. 187°C.- ^1H NMR (200 MHz, CDCl₃): $\delta = 1.32$, 1.50 (6H, 2 s, O₂C(CH₃)₂), 4.28 (1H, d, 5-H, $J_{4,5} = 6.8$ Hz), 4.58 (1H, dd, 4-H, $J_{3,4} = 2.8$ Hz, $J_{4,5} = 6.8$ Hz), 4.64, 4.77 (2H, AB system, OCH₂Ph, $^2J = 11.4$ Hz), 4.68 (1H, d, 2-H), 5.34 (1H, d, 3-H, $J_{3,4} = 2.8$ Hz), 6.04 (1H, d, 1-H, $J_{1,2} = 3.8$ Hz), 6.14, 6.41 (2H, 2 bs, CONH₂), 6.95-7.38 (10H, m, Ar-Hs).- ^{13}C NMR (50 MHz, CDCl₃): $\delta = 26.7$, 27.0 (O₂C(CH₃)₂), 74.3, 77.3, 79.3, 80.2, 83.3 (C-2, C-3, C-4, C-5, OCH₂Ph), 105.3 (C-1), 113.2 (O₂C(CH₃)₂), 121.2, 126.7, 128.70, 128.75, 129.1, 130.0, 137.3 (Ar-Cs), 151.4, 153.1 (ipso-Ar-C, carbonate-C), 172.8 (CONH₂).- IR (KBr): 1766, 1678, 1380, 1300, 1256, 1213, 1163, 1094, 1077, 1026 cm⁻¹.- C₂₃H₂₅NO₈ (443.45, 443.16), FAB MS: m/z 466.1 [M+Na]⁺, 444.1 [M+H]⁺.

5-O-Benzyl-3-O-phenoxy-carbonyl-D-glucofuranuronamide (mixture of anomers) (6a)

4b (600 mg, 1.35 mmol) was treated with 90 per cent trifluoroacetic acid (6.6 mL). The solution was stirred at 20°C for 90 min. Lyophilization furnished pure **6a** (545 mg, 100%).- ¹H NMR (200 MHz, DMSO-d₆): δ = 3.97 (1H, d, 5-H^α, J_{4,5} = 8.1 Hz), 4.03 (1H, m (w_{1/2} = 2.0 Hz), 2-H^β), 4.10 (1H, d, 5-H^β, J_{4,5} = 9.0 Hz), 4.17 (1H, t, 2-H^α, J = 4.2 Hz), 4.37-4.62 (6H, m, 2×OCH₂Ph, 4-H^α and 4-H^β), 5.03 (1H, dd, 3-H^β, J_{2,3} = 1.4 Hz, J_{3,4} = 4.5 Hz), 5.09 (1H, s, 1-H^β, J_{1,2} < 1.0 Hz), 5.19 (1H, dd, 3-H^α, J_{2,3} = 4.4 Hz, J_{3,4} = 4.8 Hz), 5.26 (1H, d, 1-H^α, J_{1,2} = 4.2 Hz), 6.20–6.70 (4H, m, probably OH signals), 7.05-7.50 (10H, m, Ar-Hs), 7.63, 7.69 (CONH₂).- ¹³C NMR (50 MHz, CDCl₃): δ = 71.4, 71.7 (OCH₂Ph of both anomers), 73.8, 75.3, 77.9, 78.1, 79.1, 81.6, 82.1 (C-2, C-3, C-4 and C-5 of both anomers), 96.3 (C-1^α), 103.3 (C-1^β), 121.2, 121.3, 126.4, 127.67, 127.75, 127.8, 128.4, 129.8, 129.9, 137.90, 137.93 (Ar-Cs), 150.8, 152.8 (carbonate-C of both anomers), 171.4, 171.5 (CONH₂ of both anomers).- C₂₀H₂₁NO₈ (403.39, 403.13), FAB MS: m/z 426.1 [M+Na]⁺, 404.1 [M+H]⁺, 391.2 [M+H-H₂O]⁺.

Conversion of 6a to benzyl glycosides 6b and 6c

A mixture of **6a** (294 mg, 0.73 mmol), Dowex 50 WX2[®] (H⁺ form, ≈ 1 g) and benzyl alcohol (15 mL) was stirred at 20°C for 7 h. After filtration, the resin was washed with ethyl acetate. From the combined solutions ethyl acetate and benzyl alcohol were removed by distillation (benzyl alcohol at 80°C and p = 0.7 Pa). Purification by FC (chloroform-ethyl acetate 7:3) yielded **6b** (92 mg, 26%) and **6c** (202 mg, 56%).

Benzyl 5-O-benzyl-3-O-phenoxy-carbonyl-D-α-glucofuranosiduronamide (6b)

M.p. 176°C (decomp.).- ¹H NMR (200 MHz, pyridine-d₅): δ = 4.68 (1H, d, OCH₂H_bPh, ²J = 11.9 Hz), 4.76 (1H, d, 5-H), 4.87-5.08 (4H, m, 2-H, J_{1,2} = 4.6 Hz, J_{2,3} = 6.8 Hz, OCH_aH_bPh, OCH₂Ph'), 5.41-5.48 (2H, m, 1-H, 4-H), 6.22 (1H, t, 3-H, J_{2,3} = J_{3,4} = 6.8 Hz), 7.09-7.54 (15H, m, Ar-Hs), 8.30, 8.64 (2H, 2 s, CONH₂).- ¹³C NMR (50 MHz, pyridine-d₅): δ = 69.5, 73.5, 75.5, 76.7, 79.9, 81.9 (C-2, C-3, C-4, C-5 and 2×OCH₂Ph), 100.5 (C-1), 121.2, 125.9, 127.6, 127.7, 127.9, 128.0, 128.3, 128.4, 129.3, 138.0 (Ar-Cs), 151.4, 153.7 (OCOOPh, ipso-Ar-C), 172.2 (C-6).- IR (KBr): 1752, 1676, 1657, 1261, 1214 cm⁻¹.- C₂₇H₂₇NO₈ (493.51, 493.17), FAB MS: m/z 516.3 [M+Na]⁺, 494.4 [M+H]⁺.

Benzyl 5-O-benzyl-3-O-phenoxy-carbonyl-D-β-glucofuranosiduronamide (6c)

M.p. 98°C.- ¹H NMR (200 MHz, pyridine-d₅): δ = 4.75, 5.20 (2H, AB system, OCH₂Ph, ²J = 11.9 Hz), 4.83, 4.99 (2H, AB system, OCH₂Ph, ²J = 11.4 Hz), 4.90 (1H, d, 5-H, J_{4,5} = 8.6 Hz), 5.08 (1H, bs (w_{1/2} = 0.4 Hz), 2-H), 5.46 (1H, dd, 4-H, J_{3,4} = 5.1 Hz, J_{4,5} = 8.7 Hz), 5.60 (1H, bs, 1-H), 5.92 (1H, dd, 3-H, J_{2,3} = 1.9 Hz, J_{3,4} = 5.1 Hz), 7.12-7.53 (15H, m, Ar-Hs), 8.52, 8.54 (2H, 2 s, CONH₂).- ¹³C NMR (50 MHz, APT, pyridine-d₅): δ = 70.2, 73.0 (2×OCH₂Ph), 79.3, 80.1, 80.9, 82.6 (C-2, C-3, C-4, C-5), 108.9 (C-1), 121.8, 126.6, 128.2, 128.3, 128.5, 128.7, 128.9, 130.1, 138.6, 138.9 (Ar-Cs), 152.0, 153.9 (OCOOPh, ipso-Ar-C), 173.3 (CONH₂).- IR (KBr): 1760, 1683, 1259, 1212, 1093, 1045 cm⁻¹.- C₂₇H₂₇NO₈ (493.51, 493.17), FAB MS: m/z 516.2 [M+Na]⁺, 494.3 [M+H]⁺.

Cyclopentyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (10)

To a solution of **15a** (327 mg, 0.664 mmol) and cyclopentanol (60 μL, 0.664 mmol) in dichloromethane (3 mL) BF₃·Et₂O (21 μL, 0.25 eq.) was added at 0°C. The mixture was stirred at 20°C for 90 min. Triethylamine (0.1 mL) was added. After solvent evaporation, water addition (5 mL) and lyophilization the ¹³C NMR spectrum of the crude reaction product (397 mg) proved the absence of an orthoester (no signal between 115 and 125 ppm). FC (petroleum ether-ethyl acetate 1:1) furnished **10** (184 mg, 66%).- ¹H NMR (200 MHz, homodecoupling, CDCl₃): δ = 1.40-1.75 (8H, m, CH₂-2^{cyclopentyl} and CH₂-3^{cyclopentyl} covered by an impurity signal), 1.94, 1.95, 1.96, 2.02 (12H, 4 s, COCH₃), 3.62 (1H, ddd, 5-H, J_{5,6a} = 2.6 Hz, J_{5,6b} = 4.8 Hz, J_{4,5} = 9.7 Hz), 4.06, 4.20 (2H, part of an ABX system, CH₂-6, ²J = 12.3 Hz, J_{5,6a} = 2.6 Hz, J_{5,6b} = 4.8 Hz), 4.21 (1H, m, 1^{cyclopentyl}-H, covered by 6-H), 4.46 (1H, d, 1-H, J_{1,2} = 8.0 Hz), 4.87 (1H, dd, 2-H, J_{1,2} = 8.0 Hz, J_{2,3} = 9.3 Hz), 5.00 (1H, dd, 4-H, J_{3,4} = 9.3 Hz, J_{4,5} = 9.7 Hz), 5.14 (1H, dd, 3-H, J = 9.3 and 9.7 Hz); impurities: δ = 1.98, 2.04, 5.37-5.49 (t), 5.54-5.56 (m), 5.79-5.85 (m), 6.00-6.06 (m).- ¹³C NMR (50 MHz,

APT, CDCl₃): δ = 21.1 (3 \times), 21.2 (COCH₃), 23.5, 23.8 (C-3'), 32.6, 33.6 (C-2'), 62.6 (C-6), 69.1, 71.9, 72.2, 73.4, 82.1 (C-2, C-3, C-4, C-5, C-1'), 100.0 (C-1), 169.7, 169.9, 170.8, 172.2 (COCH₃); impurity: δ = 67.8, 69.9.- C₁₉H₂₈O₁₀ (416.43, 416.17), FAB MS: *m/z* 439.1 [M+Na]⁺, 417.1 [M+H]⁺.

Benzyl 2-O-(2-trichloroacetamido-3,4,6-tri-O-acetyl-2-deoxy- β -D-glucopyranosyl)-5-O-benzyl-3-O-phenoxy-carbonyl- α -D-glucufuranosiduronamide (16a)

A suspension of **6b** (31 mg, 0.063 mmol), **15b** (49.4 mg, 0.082 mmol), 3 Å molecular sieves (44 mg) in 1,2-dichloroethane (0.6 mL) was stirred at 20°C. After 1 h the mixture was cooled to 0°C and a solution of TMSOTf in toluene (1 M, 12 μ L) was added. Stirring was continued for 4.5 h, before the reaction was stopped by adding of triethylamine (11 μ L). Ethyl acetate (5 mL) was added and the organic layers were extracted with a saturated NaHCO₃ solution, with 10 per cent tartaric acid and with water. The organic layer was dried with NaSO₄. Solvent evaporation and FC (chloroform - ethyl acetate 7:3) gave **16a** (40 mg, 68 %).- ¹H NMR (200 MHz, ¹³C-¹H COSY, DMSO-d₆): δ = 1.91, 1.93, 2.01 (9H, 3 s, COCH₃), 3.77-3.93 (2H, m, 2-H^E, 5-H^E), 4.10 (1H, d, 5-H^F, *J*_{4,5} = 6.5 Hz), 4.15 (2H, d (w_{1/2} = 0.4 Hz), 6-H^E, *J*_{5,6} = 2.9 Hz), 4.40-4.73 (6H, m, containing: 2-H^F δ = 4.43, dd, *J*_{1,2} = 4.3 Hz, *J*_{2,3} = 7.3 Hz; 2 \times CH₂Ph, 4-H^F), 4.99 (1H, t, 4-H^F, *J* = 9.5 Hz), 5.01 (1H, d, 1-H^E, *J*_{1,2} = 8.5 Hz), 5.17 (1H, d, 1-H^F, *J*_{1,2} = 4.2 Hz), 5.30-5.44 (2H, m, 3-H^F, 3-H^E), 6.97-7.39 (16H, m, Ph and CONHH'), 7.51 (1H, s, CONHH'), 9.17 (1H, d, NH, *J*_{2,NH} = 8.9 Hz).- ¹³C NMR (50 MHz, DMSO-d₆): δ = 20.5, 20.7 (2 \times) (COCH₃), 55.3 (C-2^E), 62.0 (C-6^F), 68.8, 72.7 (2 \times CH₂Ph), 69.8, 71.4, 71.9, 74.6, 78.3, 79.0, 81.2 (C-3^E, C-4^E, C-5^E, C-2^F, C-3^F, C-4^F, C-5^F), 92.8 (CCl₃), 99.9 (1-H^E), 100.3 (1-H^E), 121.1, 126.4, 127.7, 127.8, 128.0, 128.4, 129.7, 137.8, 138.1 (Ar-Cs), 150.8, 152.6 (ipso-Ar-C, carbonate-C), 161.9, 169.6, 169.7, 170.2, 170.9 (COCCl₃, COCH₃, CONH₂).- C₄₁H₄₃N₂O₁₆Cl₃ (926.16, 924.17) FAB MS: *m/z* 947.1 [M+Na]⁺, 925.1 [M+H]⁺.

Benzyl 2-O-(2-trichloroacetamido-3,4,6-tri-O-acetyl-2-deoxy- β -D-glucopyranosyl)-5-O-benzyl-3-O-phenoxy-carbonyl- β -D-glucufuranosiduronamide (16b)

16b was prepared from **6c** and **15b** as described for **16a**. Yield: 83 %.- ¹H NMR (200 MHz, ¹³C-¹H COSY, DMSO-d₆): δ = 1.92, 1.96, 1.99 (9H, 3 s, COCH₃), 3.69-3.96 (2H, m, 2-H^E, 5-H^E), 3.98-4.27 (3H, m, 5-H^F, CH₂-6^E), 4.40-4.59 (5H, m, CH₂Ph, CH_aH_bPh', 2-H^F (δ = 4.48, s), 4-H^F), 4.81 (1H, part of an AB system, CH_aH_bPh', ²*J* = 11.7 Hz), 4.94 (1H, t, 4-H^E, *J* = 9.6 Hz), 5.137 (1H, s, 1-H^F) 5.144 (1H, d, 1-H^E, *J*_{1,2} = 8.1 Hz), 5.28 (1H, t, 3-H^E, *J* = 9.6 Hz), 5.40 (1H, d, 3-H^F, *J*_{3,4} = 4.8 Hz), 7.05-7.42 (16H, m, Ph and CONHH'), 7.74 (1H, s, CONHH'), 9.22 (1H, d, NH, *J*_{2,NH} = 9.2 Hz).- ¹³C NMR (50 MHz, DMSO-d₆): δ = 20.4, 20.6 (2 \times) (COCH₃), 54.8 (C-2^E), 61.8 (C-6^E), 68.6 (C-4^F), 69.0 (CH₂Ph), 71.3 (CH₂Ph'), 71.8 (C-5^E), 72.0 (C-3^E), 77.9 (C-5^F), 78.2 (C-3^F), 79.4 (C-4^F), 83.9 (C-2^F), 92.9 (CCl₃), 98.5 (C-1^E), 105.6 (C-1^F), 121.1, 126.6, 127.7, 127.9, 128.1, 128.4, 128.5, 130.0, 137.7, 137.9 (Ar-Cs), 150.7, 152.4 (ipso-Ar-C, carbonate-C), 162.1, 169.5, 169.6, 170.2, 171.1 (COCCl₃, COCH₃, CONH₂).- C₄₁H₄₃N₂O₁₆Cl₃ (926.16, 924.17) FAB MS: *m/z* 947.1 [M+Na]⁺, 925.1 [M+H]⁺.

1,3,4,6-Tetra-O-n-butyryl-2-deoxy-2-trichloroacetamido-D-glucopyranose (mixture of anomers, formula not shown)

To a solution of 2-deoxy-2-trichloroacetamido-D-glucopyranose (6.43 g, 19.8 mmol) in pyridine (110 mL) butyric anhydride (50 mL) was added at 0°C. The mixture was heated to 20°C. After 16 h the reaction was stopped by solvent removal. Repeated FC (petroleum ether-ethyl acetate 2:1) yielded 1,3,4,6-Tetra-O-n-butyryl-2-deoxy-2-trichloroacetamido-D-glucopyranose (9.63 g, 80%).- ¹H NMR (200 MHz, CDCl₃): δ = 0.82-0.99 (12H, COCH₂CH₂CH₃ signals), 1.48-1.77 (8H, COCH₂CH₂CH₃ signals), 2.16-2.42 (8H, COCH₂CH₂CH₃ signals), 3.95-4.36 (4H, m, 2-H, 5-H, CH₂-6), 5.17 (1H, t, 4-H ^{β} , covered by 4-H ^{α}), 5.23 (1H, t, 4-H ^{α} , *J* = 9.7 Hz), 5.35 (1H, dd, 3-H, *J* = 9.5, 10.3 Hz), 5.81 (1H, d, 1-H ^{β} , *J* = 8.9 Hz), 6.30 (1H, d, 1-H ^{α} , *J* = 3.7 Hz), 6.89 (1H, d, NH ^{α} , *J* = 8.1 Hz), 7.17 (1H, d, NH ^{β}); ratio of anomers: α/β = 5:1 (based on the 1 H signal integrals).- ¹³C NMR (50 MHz, CDCl₃): δ = 13.96 (3 \times), 14.00 (COCH₂CH₂CH₃), 18.6 (2 \times), 18.7, 18.8 (COCH₂CH₂CH₃), 36.20, 36.24, 36.29 (2 \times) (COCH₂CH₂CH₃), 54.0 (C-2), 61.7 (C-6), 67.2, 70.3, 70.5 (C-3, C-4, C-5), 89.7 (C-1), 92.2 (COCCl₃), 162.5, 162.7 (β ?) (COCCl₃), 171.5, 172.2, 173.8, 175.1

(COCH₂CH₂CH₃)- C₂₄H₃₆Cl₃NO₁₀ (604.91, 603.14).- FAB MS: m/z 626.3 [M+Na]⁺, 516.3 [M+H-C₄H₈O₂]⁺.

3,4,6-Tri-*O*-*n*-butyryl-2-deoxy-2-trichloroacetamido- α -D-glucopyranose (formula not shown)

A solution of 1,3,4,6-tetra-*O*-*n*-butyryl-2-deoxy-2-trichloroacetamido-D-glucopyranose (2.17 g, 3.59 mmol) and hydrazinium acetate (583 mg, 6.3 mmol) in DMF (20 mL) was stirred at 20°C for 20 min. Ethyl acetate (80 mL) was added. The remaining solution was extracted with water, a saturated NaHCO₃ solution and again with water. After drying the organic layer with MgSO₄ and solvent removal pure 3,4,6-tri-*O*-*n*-butyryl-2-deoxy-2-trichloroacetamido- α -D-glucopyranose (1.64 g, 85%) was obtained.- ¹H NMR (200 MHz, CDCl₃): δ = 0.83-0.97 (9H, COCH₂CH₂CH₃ signals), 1.45-1.73 (6H, COCH₂CH₂CH₃ signals), 2.18-2.37 (6H, COCH₂CH₂CH₃ signals), 4.12-4.26 (4H, m, 2-H, 5-H, CH₂-6), 5.23 (1H, t, 4-H, *J* = 9.5 Hz), 5.34 (1H, d, 1-H, *J* = 3.5 Hz), 5.41 (1H, dd, 3-H, *J* = 9.7, 10.4 Hz), 7.07 (1H, d, NH, *J* = 9.0 Hz).- ¹³C NMR (50 MHz, CDCl₃): δ = 14.06, 14.11 (2 \times) (COCH₂CH₂CH₃), 18.7, 18.8 (2 \times) (COCH₂CH₂CH₃), 36.35, 36.42 (2 \times) (COCH₂CH₂CH₃), 54.8 (C-2), 62.1 (C-6), 68.1, 68.4, 70.5 (C-3, C-4, C-5), 91.4 (C-1), 92.5 (COCCl₃), 162.5 (COCCl₃), 172.4, 174.0, 174.4 (COCH₂CH₂CH₃)- C₂₀H₃₀Cl₃NO₉ (534.82, 533.10).- FAB MS: m/z 556.3 [M+Na]⁺, 516.3 [M+H-H₂O]⁺.

O-(3,4,6-Tri-*O*-*n*-butyryl-2-deoxy-2-trichloroacetamido-D-glucopyranosyl)-trichloroacetimidate (15c)

A mixture of 1,3,4,6-tetra-*O*-*n*-butyryl-2-deoxy-2-trichloroacetamido-D-glucopyranose (1.64 g, 3.07 mmol), trichloroacetonitrile (2.4 mL, 23.2 mmol), dichloromethane (12 mL) and DBU (170 μ L) was stirred at 20°C for 30 min. Evaporation and FC (petroleum ether-ethyl acetate 2:1 + 0.1% NEt₃) gave **15c** (1.74 g, 83%).- ¹H NMR (200 MHz, homodecoupling, pyridine-d₅): δ = 0.80-0.89 (9H, COCH₂CH₂CH₃ signals), 1.53-1.71 (6H, COCH₂CH₂CH₃ signals), 2.28-2.42 (6H, COCH₂CH₂CH₃ signals), 4.41-4.75 (3H, m, 5-H, CH₂-6), 5.19 (1H, ddd, 2-H, *J* = 3.1, 8.2, 10.8 Hz), 5.84 (1H, t, 4-H, *J* = 9.6 Hz), 6.04 (1H, dd, 3-H, *J* = 9.6, 10.7 Hz), 7.13 (1H, bs, 1-H, *J* = 3.0 Hz), 8.58 (1H, d, NH, *J* = 8.1 Hz), 10.64 (1H, s, =NH); impurity: 4.77-4.90 (m), 5.59 (dd, *J* = 9.5, 9.9 Hz), 9.35 (d, *J* = 8.8 Hz), 9.79 (d, *J* = 3.1 Hz).- ¹³C NMR (50 MHz, CDCl₃): δ = 13.80, 13.83, 13.9 (COCH₂CH₂CH₃), 18.7 (3 \times) (COCH₂CH₂CH₃), 36.04, 36.07, 36.2 (COCH₂CH₂CH₃), 54.7 (C-2), 62.1 (C-6), 68.2, 70.9, 71.5 (C-3, C-4, C-5), 93.1, 94.5 (C-1, COCCl₃, NHCCl₃), 159.6 (C=NH), 163.1 (COCCl₃), 172.5, 173.3, 174.3 (COCH₂CH₂CH₃). The ¹³C spectrum contained an other set of signals with low intensity at δ = 13.76, 36.4, 55.7, 62.9, 68.0, 69.7, 71.56 (shoulder), 91.4, 91.8, 172.7, 163.1 (shoulder), 173.4, 173.6 probably belonging to the oxazoline.- C₂₂H₃₀Cl₃N₂O₉ (679.21, 676.01).- FAB MS: m/z 699.3 [M+Na]⁺, 516.3 [M+H-Cl₃CCONH₂]⁺.

Benzyl 2-*O*-(3,4,6-tri-*O*-*n*-butyryl-2-deoxy-2-trichloroacetamido- β -D-glucopyranosyl)-5-*O*-benzyl-3-*O*-carbamoyl- α -D-glucofuranosiduronamide (16c)

16c was prepared from **6c** and **15c** as described for **16a**. Yield: 66 % after FC (petroleum ether-chloroform-acetone 1:1:1).- ¹H NMR (400 MHz, ¹H-¹H COSY, ¹³C-¹H COSY, pyridine-d₅): δ = 0.77-0.90 (9H, COCH₂CH₂CH₃ signals), 1.51-1.73 (6H, COCH₂CH₂CH₃ signals), 2.16-2.45 (6H, COCH₂CH₂CH₃ signals), 3.96 (1H, dt, 5-H^E, *J*_{4,5} = 9.8 Hz), 4.42-4.59 (3H, m, CH₂-6^E, 2-H^E), 4.73 (1H, d, 5-H^F, *J*_{4,5} = 4.9 Hz), 4.77/5.00 (2H, AB system, OCH₂Ph, ²*J* = 12.1 Hz), 4.89/4.94 (2H, AB system, OCH₂Ph, the second signal was covered by the H₂O signal), ²*J* = 11.6 Hz), 5.04 (1H, dd, 2-H^F, *J*_{1,2} = 4.4 Hz, *J*_{2,3} = 8.1 Hz), 5.41 (1H, dd, 4-H^F, *J*_{3,4} = 7.5 Hz, *J*_{4,5} = 5.1 Hz), 5.52 (1H, d, 1H^E, *J*_{1,2} = 8.6 Hz), 5.55 (1H, d, 1-H^F, *J*_{1,2} = 4.4 Hz), 5.58 (1H, d, 4-H^E, the signal was partly covered by 1-H^F, *J*_{4,5} = 9.7 Hz), 6.15 (1H, dd, 3-H^E, *J* = 9.8, 10.2 Hz), 6.27 (1H, t, 3-H^F, *J* = 7.8 Hz), 7.09-7.35 and 7.49-7.53 (15H, 2 m, Ar-Hs), 8.24, 8.69 (2H, 2s, CONH₂), 10.94 (1H, d, NH, *J*_{2,NH} = 8.3 Hz); impurities: 9.57, 9.75 (2 bs).- ¹³C NMR (50 MHz, ¹³C-¹H COSY, DEPT, pyridine-d₅): δ = 13.8 (2 \times), 14.0 (COCH₂CH₂CH₃ signals), 18.66, 18.74, 18.84 (COCH₂CH₂CH₃ signals), 36.04, 36.14, 36.3 (COCH₂CH₂CH₃ signals), 57.0 (C-2^E), 62.3 (C-6^E), 69.3 (C-4^E), 70.6 (OCH₂Ph), 72.1 (C-3^E), 72.9 (C-5^E), 74.4 (OCH₂Ph), 76.2 (C-4^F), 79.6 (C-3^F), 81.0 (C-5^F), 82.5 (C-2^F), 94.2 (CCl₃), 100.7, 101.4 (C-1^E, C-1^F), 121.9, 126.6, 128.1, 128.3, 128.5, 128.9, 129.1, 130.0, 138.6, 138.9 (Ar-Cs), 152.0, 154.0 (ipso-Ar-C, carbonate-C), 163.5 (COCCl₃), 172.5, 172.6, 173.3, 173.4 (CO(CH₂)₂CH₃, CONH₂)- C₄₇H₅₅Cl₃N₂O₁₆ (1010.32, 1008.26).- FAB MS: m/z 1031.3 [M+Na]⁺, 901.3 [M+H-BnOH]⁺.

Benzyl 5-O-benzyl-3-O-(phenoxy-carbonyl)-2-O-[(E)-1,1-(3,4,6-O-triacetyl- α -D-glucopyranose-1-O, 2-O-diyl)ethyl]- α -D-glucofuranosiduronamide (5a)

To a suspension of **15a** (480 mg, 974 μ mol) and **6b** (397 mg, 804 μ mol) in dichloromethane (20 mL) a solution of TMSOTf in dichloromethane (0.5 M, 100 μ L, 0.06 eq.) was added at -20°C . The mixture was stirred at -20°C for 7 h. After quenching with triethylamine (0.2 mL), solvent evaporation and FC (chloroform-ethyl acetate 2:1) furnished **5a** (505 mg, 76%).- ^1H NMR (400 MHz, ^1H - ^1H COSY, ^{13}C - ^1H COSY, homodecoupling, pyridine- d_5): δ = 1.89, 1.95, 1.99, 2.01 (12H, 4 s, COCH₃, CH₃CO₃), 4.30-4.36 (1H, m, 5-H^E), 4.46-4.50 (2H, m, CH₂-6^F), 4.58 (1H, part of an AB system, OCH₂H_bPh, 2J = 12.0 Hz), 4.73 (1H, d, 5-H^F, $J_{4,5}$ = 5.3 Hz), 4.76-4.79 (1H, m, 2-H^E), 4.84-5.03 (4H, m, 2-H^F, OCH₂H_bPh, OCH₂Ph'), 5.30-5.37 (2H, m, 4-H^F, 4-H^E), 5.48 (1H, d, 1-H^F, $J_{1,2}$ = 4.4 Hz), 5.59 (1H, t, 3-H^E, J = 2.6 Hz), 5.89 (1H, d, 1-H^E, $J_{1,2}$ = 5.1 Hz), 6.08 (1H, t, 3-H^F, J = 7.2 Hz), 7.10-7.40 and 7.49-7.55 (15H, 2 m, Ar-Hs), 8.26, 8.63 (2H, 2bs, CONH₂).- ^{13}C NMR (50 MHz, APT, ^{13}C - ^1H COSY, pyridine- d_5): δ = 20.17, 20.20 (2 \times), 20.7 (COCH₃, CO₃CH₃), 63.3 (C-6^F), 67.4 (C-5^E), 68.6 (C-4^F or C-4^E), 69.2 (OCH₂Ph), 70.2 (C-3^E), 73.6 (C-2^F), 73.9 (OCH₂Ph), 75.7 (C-2^F), 75.9 (C-4^F or C-4^E), 79.5 (C-3^F), 80.1 (C-5^F), 97.3 (C-1^E), 99.3 (C-1^F), 121.5 (CO₃), 121.2, 126.0, 127.7, 127.78, 127.82, 128.0, 128.3, 128.4, 128.5, 129.4, 137.7, 137.9, (Ar-Cs), 151.4, 153.4 (ipso-Ar-C, carbonate-C), 168.8, 169.5, 170.2, 171.9 (COCH₃, CONH₂).- C₄₁H₄₅NO₁₇ (823.80, 823.27), FAB MS: m/z 846.3 [M+Na]⁺, 824.3 [M+H]⁺, 716.2 [M+H-BnOH]⁺, 331.1 [e]⁺.

Benzyl 2-O-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-5-O-benzyl-3-O-phenoxy-carbonyl- α -D-glucofuranosiduronamide (7a)

i) To a mixture of **6b** (232 mg, 470.1 μ mol), **15a** (304 mg, 616.6 μ mol) and 1,2-dichloroethane (5.0 mL) at 0°C BF₃·Et₂O (8.5 μ L, 0.25 eq.) was added. The mixture was stirred at 0°C until the solids dissolved (15 min) and was then left at 20°C for 18 h. Triethylamine was added (0.1 mL). Evaporation at 40°C and MPLC (petroleum ether-chloroform-methanol 10:10:1) furnished **7a** (133 mg, 34%) and a fraction of not identified products (125 mg).

ii) To a mixture of **6b** (153 mg, 310.6 μ mol), **15a** (167 mg, 338.2 μ mol), 4 Å molecular sieves and dichloromethane (5.0 mL) BF₃·Et₂O (5.6 μ L, 0.25 eq.) was added at 0°C . The reaction mixture was stirred at 0°C until solid materials dissolved (15 min). The mixture was then left at 20°C for 2 d. Pyridine (0.2 mL) was added. Evaporation at 40°C and HPLC (petrol-chloroform-methanol 10:10:1) furnished **7a** (37 mg, 34%, 9.0 min) and a fraction of not identified products (80 mg, 10.4 min).- HPLC conditions: 10 mL/min, p = 1.3 MPa, λ = 254 nm.- ^1H NMR (400 MHz, ^1H - ^1H COSY, pyridine- d_5): δ = 1.98, 1.99, 2.03, 2.05 (12H, 4s, COCH₃), 4.08 (1H, ddd, 5-H^E, $J_{4,5}$ = 10.1 Hz, $J_{5,6a}$ = 4.8 Hz, $J_{5,6b}$ = 2.6 Hz), 4.41/4.52 (2H, part of an ABX system, CH₂-6^E, 2J = 12.3 Hz, $J_{5,6a}$ = 4.8 Hz, $J_{5,6b}$ = 2.6 Hz), 4.73 (1H, d, 5-H^F, $J_{4,5}$ = 5.3 Hz), 4.73/4.89 (2H, AB system, OCH₂Ph, 2J = 12.1 Hz), 4.90/4.99 (2H, AB system, OCH₂Ph, 2J = 11.6 Hz), 4.98 (1H, dd, 2-H^F, $J_{1,2}$ = 4.1 Hz, $J_{2,3}$ = 7.4 Hz), 5.20 (1H, d, 1-H^E, $J_{1,2}$ = 7.9 Hz), 5.34 (1H, dd, 4-H^F, $J_{3,4}$ = 7.5 Hz, $J_{4,5}$ = 5.3 Hz), 5.48-5.54 (3H, m, 1-H^F, 2-H^E, 4-H^E), 5.75 (1H, t, 3-H^E, J = 9.6 Hz), 6.21 (1H, t, 3-H^F, J = 7.6 Hz), 7.13-7.38 (10H, m, Ar-Hs), 7.47-7.56 (5H, m, Ar-Hs), 8.18, 8.66 (2H, 2s, CONH₂).- ^{13}C NMR (50 MHz, APT, ^{13}C - ^1H COSY, pyridine- d_5): δ = 19.87, 19.89 (2 \times), 20.01 (COCH₃), 61.8 (C-6^F), 68.5 (C-4^E), 69.6 (OCH₂Ph), 71.5 (C-2^E), 72.0 (C-5^F), 72.7 (C-3^E), 73.8 (OCH₂Ph), 75.7 (C-4^F), 79.2 (C-3^F), 80.0 (C-5^F), 82.6 (C-2^F), 99.5 (C-1^E), 101.4 (C-1^F), 121.2, 126.0, 127.4, 127.6, 127.8, 127.9, 128.2, 128.4, 129.4, 137.9, 138.0 (Ar-Cs), 151.3, 153.4 (ipso-C, carbonate-C), 169.2, 169.4, 169.9, 170.2, 171.9 (COCH₃, CONH₂).- IR (KBr): 1757, 1688, 1372, 1251, 1073, 1042 cm⁻¹.- C₄₁H₄₅NO₁₇ (823.80, 823.27), FAB MS: m/z 846.1[M+Na]⁺, 824.1 [M+H]⁺, 716.1 [M+H-BnOH]⁺.- HR MS: [M+H]⁺ calc 824.2766, found 824.2794.

Benzyl 5-O-benzyl-3-O-(phenoxy-carbonyl)-2-O-[(E)-1,1-(3,4,6-O-triacetyl- α -D-glucopyranose-1-O, 2-O-diyl)ethyl]- β -D-glucofuranosiduronamide (5b)

The reaction of **6c** and **15a** under the condition described for the formation of **5a** provided **5b** (93 %).- ^1H NMR (200 MHz, ^1H - ^1H COSY, ^{13}C - ^1H COSY, homodecoupling, pyridine- d_5): δ = 1.95 (2 \times), 1.98, 2.02 (12H, 3 s, COCH₃, CH₃CO₃), 4.37 (1H, dt, 5-H^E, $J_{4,5}$ = 9.2 Hz, $J_{5,6a,6b}$ = 4.0 Hz), 4.48-4.52 (2H, m, CH₂-6^F), 4.67/5.12 (2H, AB, OCH₂Ph, 2J = 11.7 Hz), 4.78/4.95 (2H, AB, OCH₂Ph, 2J = 11.4 Hz), 4.80 (1H, d, 5-H^F,

$J = 8.4$ Hz), 4.84 (1H, dd, 2-H^E, $J_{2,3} = 2.9$ Hz), 5.04 (1H, bs ($w_{1/2} = 5.6$ Hz), 2-H^F), 5.25 (1H, dd, 4-H^F, $J_{3,4} = 5.1$ Hz, $J_{4,5} = 8.4$ Hz), 5.35 (1H, dd, 4-H^E, $J_{3,4} = 2.9$ Hz, $J_{4,5} = 9.2$ Hz), 5.44 (1H, s, 1-H^F), 5.63 (1H, t, 3-H^E, $J = 2.9$ Hz), 5.79 (1H, dd, 3-H^F, $J_{2,3} = 2.2$ Hz, $J_{3,4} = 5.1$ Hz), 6.19 (1H, d, 1-H^E, $J_{1,2} = 5.1$ Hz), 7.13–7.55 (15H, m, Ar-Hs), 8.43, 8.53 (2H, 2bs, CONH₂).- ¹³C NMR (50 MHz, APT, ¹³C-¹H COSY, pyridine-d₅): $\delta = 19.27, 19.34$ (2 \times), 21.1 (COCH₃, CO₃CH₃), 62.4 (C-6^E), 66.9 (C-5^E), 67.5 (C-4^E), 68.9 (OCH₂Ph), 69.5 (C-3^E), 71.6 (OCH₂Ph), 73.0 (C-2^E), 78.5 (C-5^F), 78.9 (C-2^F), 79.0 (C-4^F), 79.3 (C-3^F), 96.6 (C-1^E), 105.7 (C-1^F), 121.2 (CO₃), 120.2, 125.2, 126.8, 127.0, 127.2, 127.3, 127.4, 127.5, 127.7, 128.6, 137.0 (Ar-Cs), 150.4, 152.2 (ipso-Ar-C, carbonate-C), 168.1, 168.7, 169.3, 171.4 (COCH₃, CONH₂).- IR (CHCl₃): 1753, 1699, 1371, 1251, 1045 cm⁻¹.- C₄₁H₄₅NO₁₇ (823.80, 823.27), FAB MS: m/z 862.0 [M+K]⁺, 846.2 [M+Na]⁺, 824.2 [M+H]⁺, 331.1 [e]⁺.

Glycosylation of 6c with 15a

To a mixture of 6c (575 mg, 1.16 mmol) and 15a (620 mg, 1.26 mmol) in dichloromethane (10.0 mL) BF₃·Et₂O (46 μ L, 0.29 mmol, 0.25 eq.) was added (TLC indicated the immediate formation of 5b). The reaction mixture was stirred at 20°C for 27 h. Triethylamine (0.2 mL) was added. After solvent evaporation and MPLC (chloroform-ethyl acetate = 1:1) 7b (164 mg, 17%), 8 (117 mg, 19%) and 9a (334 mg, 29%) were obtained.

Benzyl 2-O-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-5-O-benzyl-3-O-phenoxy-carbonyl- β -D-glucofuranosiduronamide (7b)

¹H NMR (400 MHz, ¹H-¹H COSY, ¹³C-¹H COSY, pyridine-d₅): $\delta = 1.96, 2.00, 2.02, 2.03$ (12H, 4 s, COCH₃), 4.09 (1H, ddd, 5-H^E, $J_{4,5} = 9.9$ Hz, $J_{5,6a} = 2.4$ Hz, $J_{5,6b} = 4.3$ Hz), 4.28/4.49 (2H, part of an ABX system, CH₂-6^E, $J_{5,6a} = 2.2$ Hz, $J_{5,6b} = 4.3$ Hz, $J_{6a,6b} = 12.3$ Hz), 4.68/5.14 (2H, AB system, OCH₂Ph, ² $J = 11.8$ Hz, signal at 5.14 ppm covered by 2-H^F-signal), 4.80/4.96 (2H, AB system, OCH₂Ph, ² $J = 11.3$ Hz), 4.83 (1H, d, 5-H^F, $J_{4,5} = 8.5$ Hz), 5.16 (1H, bs, 2-H^F, partly hidden), 5.19 (1H, dd, 4-H^F, $J_{3,4} = 5.3$ Hz, $J_{4,5} = 8.4$ Hz), 5.41 (1H, d, 1-H^E, $J_{1,2} = 8.0$ Hz), 5.46–5.56 (3H, m, containing: $\delta = 5.48$, dd, 2-H^E, $\delta = 5.53$, t, 4-H^E, $\delta = 5.56$, s, 1-H^F), 5.76 (1H, t, 3-H^E, $J = 9.5$ Hz), 5.81 (1H, dd, 3-H^F, $J_{2,3} = 1.5$ Hz, $J_{3,4} = 5.3$ Hz), 7.16–7.34 and 7.47–7.55 (15H, 2m, Ar-Hs), 8.45, 8.57 (2H, 2 bs, CONH₂); 4.36–4.45 (m, impurity).- ¹³C NMR (50 MHz, ¹³C-¹H COSY, pyridine-d₅): $\delta = 20.6$ (3 \times) and 20.7 (COCH₃), 62.2 (C-6^E), 69.0 (C-4^E), 70.4 (OCH₂Ph), 72.0 (C-2^E), 72.7 (C-5^E), 73.0 (OCH₂Ph), 73.5 (C-3^E), 79.5 (C-5^F), 80.0 (C-3^F), 80.5 (C-4^F), 86.3 (C-2^F), 100.8 (C-1^E), 106.8 (C-1^F), 121.8, 126.9, 128.3, 128.4, 128.6, 128.7, 129.0, 130.1, 130.2, 138.51, 138.52 (Ar-Cs), 151.9, 153.8 (ipso-Ar-C, carbonate-C), 170.0, 170.1, 170.6, 170.8, 172.9 (COCH₃, CONH₂).- C₄₁H₄₅NO₁₇ (823.80, 823.27), FAB MS: m/z 846.1 [M+Na]⁺, 824.1 [M+H]⁺, 716.1 [M+H-BnOH]⁺, 331.0 [e]⁺.- HR MS: [M+H]⁺ calc 824.2766, found 824.2775.

Benzyl 2-O-acetyl-5-O-benzyl-3-O-phenoxy-carbonyl- β -D-glucofuranosiduronamide (8)

M.p. 88°C.- ¹H NMR (200 MHz, pyridine-d₅): $\delta = 1.92$ (3H, s, COCH₃), 4.74/5.19 (2H, AB system, OCH₂Ph, ² $J = 12.0$ Hz), 4.82/4.96 (2H, AB system, OCH₂Ph, ² $J = 12.8$ Hz, signal at 4.96 ppm covered by the water peak), 4.88 (1H, d, 5-H, $J_{4,5} = 8.8$ Hz), 5.27 (1H, dd, 4-H, $J_{3,4} = 5.3$ Hz, $J_{4,5} = 8.8$ Hz), 5.46 (1H, s, 1-H), 5.84 (1H, bs, 2-H), 5.94 (1H, dd, 3-H, $J_{2,3} = 1.3$ Hz, $J_{3,4} = 5.3$ Hz), 7.05–7.34 and 7.46–7.60 (15H, 2 m, Ar-Hs), 8.58, 8.63 (2H, 2 s, CONH₂).- ¹³C NMR (50 MHz, pyridine-d₅): $\delta = 20.0$ (COCH₃), 69.6, 72.1, 78.9, 79.1, 80.1, 80.5 (C-2^F, C-3^F, C-4^F, C-5^F, 2 \times OCH₂Ph), 105.4 (C-1^F), 121.1, 126.1, 127.6, 127.7, 127.8, 128.0, 128.3, 129.4, 137.7, 137.8 (Ar-Cs), 151.2, 152.9 (ipso-Ar-C, carbonate-C), 169.2, 172.3 (COCH₃, CONH₂).- C₂₉H₂₉NO₉ (535.55, 535.18), FAB MS: m/z 558.1 [M+Na]⁺, 536.1 [M+H]⁺, 428.1 [M+H-BnOH]⁺.- HR MS: [M+H]⁺ calc 536.1921, found 536.1913.

Benzyl 2-O-(3,4,6-tri-O-acetyl- α -D-glucopyranosyl)-5-O-benzyl-3-O-phenoxy-carbonyl- β -D-glucofuranosiduronamide (9a)

¹H NMR (400 MHz, ¹H-¹H COSY, DMSO-d₆): $\delta = 1.83, 1.95, 1.97$ (9H, 3 s, COCH₃), 3.63 (1H, ddd, 2-H^E, $J_{1,2} = 3.8$ Hz, $J_{2,3} = 9.9$ Hz, $J_{2,OH} = 6.9$ Hz), 3.93–3.98 (2H, m, 5-H^E, CH_aH_b-6^E), 4.07–4.13 (2H, m, 5-H^F, $J_{4,5} = 9.4$ Hz, CH_aH_b-6^E), 4.41 (1H, bs, 2-H^F), 4.44/4.57 (2H, AB system, OCH₂Ph, ² $J = 11.5$ Hz), 4.53/4.81

(2H, AB system, OCH₂Ph, ²J = 11.8 Hz), 4.64 (1H, dd, 4-H^F, J_{3,4} = 5.1 Hz, J_{4,5} = 9.2 Hz), 4.80 (1H, t, 4-H^F, J = 9.6 Hz), 5.05–5.09 (2H, m, 1-H^E, 3-H^E), 5.23 (1H, s, 1-H^F), 5.38 (1H, dd, 3-H^F, J_{2,3} = 1.0 Hz, J_{3,4} = 5.1 Hz), 5.45 (1H, d, OH, J_{2,OH} = 6.8 Hz, exchangeable with D₂O), 7.01–7.05 and 7.29–7.41 (15H, 2 m, Ar-Hs), 7.43, 7.73 (2H, 2 bs, CONH₂).- ¹H NMR (400 MHz, ¹H-¹H COSY, pyridine-d₅): δ = 1.98, 2.01, 2.04 (9H, 3 s, COCH₃), 4.19–4.26 (1H, m, 2-H^E), 4.38–4.43 (1H, m, CH₂H_b-6^E), 4.51–4.58 (3H, m, 5-H^E, OCH₂H_bPh, CH_aH_b-6^E), 4.77/4.94 (2H, AB, OCH₂Ph, signal at 4.94 ppm hidden by the water signal), 4.79 (1H, d, 5-H^F, J_{1,2} = 8.5 Hz), 5.11 (1H, bs (w_{1/2} = 4.2 Hz), 2-H^F), 5.18 (1H, d, OCH₂H_bPh, ²J = 11.6 Hz), 5.19 (1H, dd, 4-H^F, J_{3,4} = 5.8 Hz, J_{4,5} = 8.4 Hz), 5.47 (1H, dd, 4-H^E, J = 9.6 and 9.9 Hz), 5.56 (1H, d, 1-H^F, J_{1,2} = 1.4 Hz), 5.65 (1H, d, 1-H^E, J_{1,2} = 3.8 Hz), 5.95 (2H, dd and t, 3-H^F, J_{2,3} = 1.9 Hz, J_{3,4} = 5.6 Hz; 3-H^E, J = 9.6 Hz), 7.14–7.33 and 7.47–7.51 (15H, 2 m, Ar-Hs), 8.32, 8.56 (2H, 2 s, CONH₂); impurity: 5.68 (CH₂Cl₂).- ¹³C NMR (50 MHz, APT, pyridine-d₅): δ = 21.0, 20.8, 20.9 (COCH₃), 62.9 (C-6^E), 70.4, 73.1 (2×OCH₂Ph), 69.4, 69.8, 70.8, 74.2, 80.1, 80.4, 80.7, 85.8 (C-2^E, C-3^E, C-4^E, C-5^E, C-2^F, C-3^F, C-4^F, C-5^F), 100.3 (C-1^E), 106.8 (C-1^F), 121.8, 126.8, 128.2, 128.4, 128.58, 128.62, 128.98, 129.03, 130.1, 138.5, 138.6 (Ar-Cs), 151.9, 153.7 (ipso-Ar-C, carbonate-C), 170.3, 170.9, 171.0, 172.9 (COCH₃, CONH₂).- IR (CHCl₃): 1749, 1698, 1258, 1237, 1225, 1074, 1039 cm⁻¹.- C₃₉H₄₃NO₁₆ (781.77, 781.26), FAB MS: m/z 804.2 [M+Na]⁺, 782.2 [M+H]⁺, 674.1 [M+H-BnOH]⁺.- HR MS: [M+H]⁺ calc 782.2660, found 782.2663.

Benzyl 2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5-O-benzyl-3-O-phenoxy-carbonyl-α-D-glucofuranosiduronamide (9b)

9a (55 mg, 70 mmol) was acetylated with acetic anhydride in pyridine. Solvent evaporation and MPLC (petroleum ether-chloroform-methanol 10:10:1) yielded **9b** (59 mg, 98%).- ¹H NMR (400 MHz, ¹H-¹H COSY, pyridine-d₅): δ = 1.95, 2.00, 2.02, 2.04 (12H, 4s, COCH₃), 4.35–4.45 (1H, m, CH₂H_b-6^E), 4.49–4.57 (2H, m, 5-H^E, CH₂H_b-6^E), 4.70/5.20 (2H, AB system, OCH₂Ph, ²J = 11.7 Hz), 4.80 (1H, d, 5-H^F, J_{4,5} = 8.0 Hz), 4.81/4.94 (2H, AB system, OCH₂Ph, (signal at 4.94 ppm was partly covered by the water peak), ²J = 11.3 Hz), 5.11 (1H, dd, 2-H^F, J_{1,2} = 1.9 Hz, J_{2,3} = 2.4 Hz), 5.32 (1H, dd, 4-H^F, J_{4,5} = 8.2 Hz, J_{3,4} = 6.0 Hz), 5.36 (1H, dd, 2-H^E, J_{1,2} = 4.0 Hz, J_{2,3} = 10.3 Hz), 5.528 (1H, d, 1-H^F, J_{1,2} = 1.7 Hz), 5.535 (1H, t, 4-H^E, J_{3,4} = 9.6 Hz, J_{4,5} = 9.9 Hz), 5.82 (1H, d, 1-H^E, J_{1,2} = 4.0 Hz), 5.93–5.99 (2H, m, containing: δ = 5.95, dd, 3-H^F J = 2.6 Hz; δ = 5.96, t, 3-H^E, J = 9.9 Hz), 7.14–7.37 and 7.49–7.55 (15H, 2 m, Ar-Hs), 8.35, 8.61 (2H, 2 bs, CONH₂).- ¹³C NMR (50 MHz, pyridine-d₅): δ = 19.8, 19.9, 20.00, 20.04 (COCH₃), 61.7 (C-6^E), 68.4, 68.5, 69.8, 70.1, 70.7, 72.6, 79.59, 79.62, 79.68, 84.8 (C-2^E, C-3^E, C-4^E, C-5^E, C-2^F, C-3^F, C-4^F, C-5^F, 2×OCH₂Ph), 96.1 (C-1^E), 105.5 (C-1^F), 121.1, 127.97, 128.03, 128.36, 128.37, 129.4, 137.75, 137.81 (Ar-Cs), 151.2, 153.1 (ipso-Ar-C, carbonate-C), 169.5, 169.9, 170.2, 172.3 (COCH₃, CONH₂).- C₄₁H₄₅NO₁₇ (823.80, 823.27), FAB MS: m/z 846.1 [M+Na]⁺, 824.1 [M+H]⁺, 716.1 [M+H-BnOH]⁺.- HR MS: [M+H]⁺ calc 824.2766, found 824.2758.

Benzyl 2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5-O-benzyl-3-O-carbamoyl-α-D-glucofuranosiduronamide (7c)

Ammonia was slowly bubbled into a solution of **7a** (133 mg, 161.1 μmol) in dry THF (10 mL) for 18 h at 20°C. After solvent removal and FC (chloroform-methanol 10:1) **7c** (76 mg, 63%) and a fraction of compounds with an unprotected OH-function (32 mg) were obtained. The yield of **7c** increased to 85% after acetylation of the 32 mg fraction.- ¹H NMR (400 MHz, ¹H-¹H COSY, homodecoupling, pyridine-d₅): δ = 1.97, 1.99, 2.01, 2.06 (12H, 4s, COCH₃), 3.96 (1H, ddd, 5-H^E, J_{4,5} = 9.9 Hz, J_{5,6a} = 4.6 Hz, J_{5,6b} = 2.6 Hz), 4.36/4.49 (2H, part of an ABX system, CH₂-6^E, ²J = 12.3 Hz, J_{5,6a} = 4.6 Hz, J_{5,6b} = 2.5 Hz), 4.64 (1H, d, 5-H^F, J_{4,5} = 5.3 Hz), 4.69/4.87 (2H, AB system, OCH₂Ph, ²J = 12.3 Hz), 4.84 (2H, s, OCH₂Ph), 4.95 (1H, dd, 2-H^F, J_{1,2} = 4.4 Hz, J_{2,3} = 7.2 Hz), 5.18 (1H, d, 1-H^E, J_{1,2} = 8.0 Hz), 5.20 (1H, dd, 4-H^F, J_{3,4} = 7.4 Hz, J_{4,5} = 5.3 Hz), 5.45–5.53 (3H, m, containing: δ = 5.472, dd, 4-H^E, J = 9.4, 9.9 Hz, δ = 5.474, d, 1-H^F, J = 4.3 Hz, δ = 5.51 dd, 2-H^E, J = 8.0, 9.6 Hz), 5.66 (1H, t, 3-H^E, J_{2,3} = 9.5 Hz), 6.26 (1H, t, 3-H^F, J = 7.3 Hz), 7.14–7.36 and 7.46–7.54 (10H, 2m, Ar-Hs), 7.71 (2H, s, OCONH₂), 7.93, 8.47 (2H, 2s, CONH₂).- ¹³C NMR (50 MHz, ¹³C-¹H COSY, pyridine-d₅): δ = 19.2 (3×), 19.4 (COCH₃), 61.1 (C-6^E), 67.9 (C-4^E), 68.7 (OCH₂Ph), 70.7 (C-2^E), 71.1 (C-5^E), 72.2 (C-3^E), 72.8 (OCH₂Ph), 73.9 (C-3^F), 76.0 (C-4^F), 79.4 (C-5^F), 82.2 (C-2^F), 99.1 (C-1^E), 100.6 (C-1^F), 126.5, 126.7, 127.0, 127.4, 127.6, 137.2, 137.5 (Ar-Cs), 156.0

(OCONH₂), 168.4, 168.6, 169.1, 169.3, 171.5 (COCH₃, CONH₂)- IR (CHCl₃): 1751, 1689, 1376, 1231, 1211, 1042 cm⁻¹.- C₃₅H₄₂N₂O₁₆ (746.72, 746.25), FAB MS: m/z 769.2 [M+Na]⁺, 747.2 [M+H]⁺, 639.1 [M+H-BnOH]⁺.- HR MS: [M+H]⁺ calc 747.2613, found 747.2607.

Benzyl 2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5-O-benzyl-3-O-carbamoyl-β-D-glucofuranosiduronamide (7d)

Ammonia was slowly bubbled into a solution of **7b** (156 mg, 316 μmol) in dry THF (10.0 mL) for 18 h at 20°C. After solvent removal and FC (chloroform-methanol 10:1) **7d** (58 mg, 41%) was isolated.- ¹H NMR (600 MHz, pyridine-d₅): δ = 1.96, 1.97, 1.99, 2.01 (12H, 4s, COCH₃), 4.09 (1H, ddd, 5-H^E, J_{4,5} = 10.1 Hz, J_{5,6a} = 2.4 Hz, J_{5,6b} = 4.1 Hz), 4.27/4.51 (2H, part of an ABX system, CH₂-6^E, J_{5,6a} = 2.3 Hz, J_{5,6b} = 4.3 Hz, J_{6a,6b} = 12.3 Hz), 4.69/5.18 (2H, AB system, OCH₂Ph, ²J = 12.0 Hz), 4.71/4.79 (2H, AB system, OCH₂Ph, ²J = 10.7 Hz), 4.72 (1H, d, 5-H^F, J = 9.0 Hz), 4.98-5.04 (4-H^F and 2-H^F, hidden by the H₂O signal), 5.45-5.53 (4H, m, containing: δ = 5.46, d, 1-H^E, J = 8.0 Hz and δ = 5.51, s, 1-H^F and 2-H^F, 4-H^E), 5.73 (1H, t, 3-H^E, J = 9.4 Hz), 5.85 (1H, d, 3-H^F, J = 6.0 Hz), 7.21-7.30 and 7.47-7.53 (10H, 2 m, Ar-Hs), 7.90 (2H, s, OCONH₂), 8.22, 8.44 (2H, 2 bs, CONH₂); impurity: 3.78-3.81 (m), 3.99-4.02 (m).- ¹³C NMR (50 MHz, pyridine-d₅): δ = 19.0, 19.1 (2×), 19.2 (COCH₃), 60.7 (C-6^E), 67.5, 68.7, 70.6, 71.1, 71.6, 72.1, 74.3, 78.4, 79.6, 85.7 (C-2^E, C-3^E, C-4^E, C-5^E, C-2^F, C-3^F, C-4^F, C-5^F, 2×OCH₂Ph), 99.2 (C-1^E), 105.7 (C-1^F), 126.6, 126.9, 127.1, 127.4, 137.1, 137.2 (Ar-Cs), 156.1 (OCONH₂), 168.5, 168.6, 169.1, 169.3, 172.1 (COCH₃, CONH₂)- IR (CHCl₃): 1752, 1689, 1231, 1070, 1042 cm⁻¹.- C₃₅H₄₂N₂O₁₆ (746.72, 746.25), FAB MS: m/z 769.2 [M+Na]⁺, 747.2 [M+H]⁺, 639.1 [M+H-BnOH]⁺, 331.1 [e]⁺.- HR MS: [M+H]⁺ calc 747.2613, found 747.2618.

2-O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-O-carbamoyl-α-D-glucopyranuronamide (17a)

i) A mixture of **7c** (116 mg, 155.5 μmol) and Pd(OH)₂/C (142 mg, 20%) in THF-acetic acid (10:1, 10 mL) was stirred in a hydrogen atmosphere for 18 h at 20°C. After filtration the catalyst was carefully washed with acetone. Solvent removal from the combined solutions and lyophilization provided **17a** (85 mg, 96%).

ii) A mixture of **7c** (57 mg, 76.5 μmol) and Pd/C (89 mg, 10%) in aqueous THF (4.5 mL) was stirred in a hydrogen atmosphere for 12 h at 20°C. After filtration the catalyst was carefully washed with THF. Solvent evaporation from the combined solutions and FC (chloroform-methanol 4:1) furnished **17a** (40 mg, 91%).- ¹H NMR (600 MHz, ¹H-¹H COSY, ¹³C-¹H COSY, pyridine-d₅, containing a trace of the β-anomer): δ = 1.92, 1.98, 2.01, 2.31 (12H, 4s, COCH₃), 3.91 (1H, ddd, 5-H^E, J_{4,5} = 9.9 Hz, J_{5,6a} = 4.7 Hz, J_{5,6b} = 2.4 Hz), 4.14 (1H, dd, 2-H^F, J_{1,2} = 3.4 Hz, J_{2,3} = 10.1 Hz), 4.34 (1H, part of an ABX system, CH_aH_b-6^E, J_{5,6} = 2.2 Hz, J_{6a,6b} = 12.1 Hz), 4.43-4.50 (2H, m, CH_aH_b-6^E, 4-H^F), 5.15 (1H, d, 1-H^E, J_{1,2} = 8.0 Hz), 5.17 (1H, d, 5-H^F, J_{4,5} = 9.9 Hz), 5.40 (1H, t, 4-H^E, J = 9.8 Hz), 5.51 (1H, dd, 2-H^E, J_{1,2} = 8.2 Hz, J_{2,3} = 9.5 Hz), 5.64 (1H, t, 3-H^E, J = 9.6), 6.00 (1H, d, 1-H^F, J_{1,2} = 3.4 Hz), 6.27 (1H, t, 3-H^F, J = 9.6 Hz), 7.52 (2H, bs, OCONH₂), 8.50, 8.55 (2H, 2 bs, CONH₂)- ¹³C NMR (50 MHz, ¹³C-¹H COSY, pyridine-d₅): δ = 19.96 (2×), 20.05, 20.1 (COCH₃), 61.9 (C-6^E), 68.7 (C-4^E), 71.17 (C-5^F), 71.24 (C-2^E), 71.7 (C-5^E), 72.1 (C-4^F), 73.3 (C-3^E), 74.2 (C-3^F), 79.8 (C-2^F), 93.1 (C-1^F), 102.2 (C-1^E), 157.7 (OCONH₂), 169.5, 169.8, 170.1, 170.2, 173.9 (COCH₃, CONH₂)- C₂₁H₃₀N₂O₁₆ (566.47, 566.16), FAB MS: m/z 589.1 [M+Na]⁺, 567.1, [M+H]⁺.- HR MS: [M+Na]⁺ calc 589.1493, found 589.1493.

1,4-Di-O-acetyl-2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-3-O-carbamoyl-α-D-glucopyranuronamide (17b)

A mixture of **7d** (48 mg, 64.7 μmol) and Pd(OH)₂/C (51 mg, 20%) in THF-acetic acid (10:1, 5 mL) was stirred in a hydrogen atmosphere for 18 h at 20°C. After filtration the catalyst was carefully washed with THF. After solvent evaporation from the combined solutions the crude product was treated with a mixture of pyridine and acetic anhydride (1:1, 1 mL), and the solution was stirred overnight. Solvent removal by lyophilization and FC (chloroform-methanol 10:1) yielded **17b** (42 mg, 100%).- ¹H NMR (200 MHz, homodecoupling, ¹H-¹H COSY, ¹³C-¹H COSY, pyridine-d₅): δ = 1.82, 1.98, 2.01, 2.07, 2.11, 2.23 (18H, 6s, COCH₃), 3.97 (1H, dt, 5-H^E, J_{4,5} = 9.9 Hz, J_{5,6} = 3.3 Hz), 4.26 (1H, dd, 2-H^F, J_{1,2} = 3.8 Hz, J_{2,3} = 9.7 Hz), 4.43-4.48 (2H, m, CH₂-6^E), 4.81 (1H, d, 5-H^F, J_{4,5} = 9.7 Hz), 5.09 (1H, d, 1-H^E, J_{1,2} = 7.7 Hz), 5.44 (2H, t,

2-H^E, 4-H^E, $J = 9.2$ Hz), 5.64 (1H, t, 3-H^E, $J = 9.4$ Hz), 5.90 (1H, dd, 4-H^F, $J_{3,4} = 9.5$ Hz, $J_{4,5} = 9.9$ Hz), 6.02 (1H, t, 3-H^F, $J = 9.6$ Hz), 6.83 (1H, d, 1-H^F, $J_{1,2} = 3.9$ Hz), 7.79 (2H, bs, OCONH₂), 8.32, 8.49 (2H, 2 bs, CONH₂); impurity: 5.68 (CH₂Cl₂)-¹³C NMR (50 MHz, ¹³C-¹H COSY, pyridine-d₅): $\delta = 19.88, 19.92, 19.95, 20.05, 20.13, 20.4$ (COCH₃), 61.6 (C-6^E), 68.4 (C-4^E), 70.1 (C-4^F), 70.9 (C-3^F), 71.1 (C-2^F, C-5^F), 71.7 (C-5^E), 72.8 (C-3^E), 76.9 (C-2^F), 90.6 (C-1^F), 101.7 (C-1^E), 156.8 (OCONH₂), 168.9, 169.42, 169.47, 169.55, 170.0, 170.4 (COCH₃, CONH₂)- IR (CHCl₃): 1755, 1705, 1373, 1228, 1211, 1077, 1041 cm⁻¹.- C₂₅H₃₄N₂O₁₈ (650.55, 650.18), FAB MS: m/z 673.1 [M+Na]⁺, 651.2 [M+H]⁺, 591.1 [M+H-AcOH]⁺.- HR MS: [M+Na]⁺ calc 673.1704, found 673.1718.

2-O-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)-4-O-acetyl-3-O-carbamoyl-D-glucopyranuronamide (mixture of anomers) (17c)

A mixture of **17b** (46 mg, 70.68 μ mol), hydrazinium acetate (9.3 mg, 100 μ mol, 1.4 eq.) and DMF (0.4 mL) was stirred at 20°C for 30 min. Ethyl acetate (0.3 mL), water (0.2 mL) and toluene (3 mL) were added. Solvent removal and FC (chloroform-methanol 10:1) furnished **17c** (26.4 mg, 67%) and a fraction containing non-identified products (5.6 mg).- ¹H NMR (400 MHz, homodecoupling, ¹H-¹H COSY, ¹³C-¹H COSY, pyridine-d₅, containing a trace of the β -anomer): $\delta = 1.94, 1.98, 2.02, 2.08, 2.28$ (15H, 5s, COCH₃), 3.94 (1H, ddd, 5-H^E, $J_{4,5} = 10.1$ Hz, $J_{5,6a} = 2.6$ Hz, $J_{5,6b} = 4.8$ Hz), 4.13 (1H, dd, 2-H^F, $J_{1,2} = 3.4$ Hz, $J_{2,3} = 10.1$ Hz), 4.36/4.48 (2H, part of an ABX system, CH₂-6^E, $J_{5,6a} = 2.6$ Hz, $J_{5,6b} = 4.8$ Hz, $J_{6a,6b} = 12.3$ Hz), 5.12 (1H, d, 1-H^E, $J_{1,2} = 8.0$ Hz), 5.17 (1H, d, 5-H^F, $J_{4,5} = 10.3$ Hz), 5.40 (1H, dd, 4-H^E, $J_{4,5} = 10.1$ Hz, $J_{3,4} = 9.4$ Hz), 5.48 (1H, dd, 2-H^E, $J_{1,2} = 8.0$ Hz, $J_{2,3} = 9.6$ Hz), 5.64 (1H, t, 3-H^E, $J = 9.5$ Hz), 5.89 (1H, dd, 4-H^F, $J_{3,4} = 9.6$ Hz, $J_{4,5} = 10.1$ Hz), 5.96 (1H, d, 1-H^F, $J_{1,2} = 3.3$ Hz), 6.24 (1H, t, 3-H^F, $J = 9.7$ Hz), 7.63 (2H, bs, OCONH₂), 8.18, 8.32 (2H, 2 bs, CONH₂)- ¹³C NMR (50 MHz, ¹³C-¹H COSY, pyridine-d₅): $\delta = 20.7$ (2 \times), 20.8 (2 \times), 21.3 (COCH₃), 62.6 (C-6^E), 69.4 (C-4^E), 69.6 (C-5^F), 71.95 (C-2^E), 72.02 (C-4^F), 72.5 (C-3^F, C-5^E), 73.9 (C-3^E), 80.0 (C-2^F), 93.5 (C-1^F), 102.8 (C-1^E), 157.7 (OCONH₂), 170.1, 170.3, 170.4, 170.6, 170.8, 171.7 (COCH₃, CONH₂)- C₂₃H₃₂N₂O₁₇ (608.51, 608.17), FAB MS: m/z 631.0 [M+Na]⁺.

2-O-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)-4-O-acetyl-3-O-carbamoyl-1-O-{(R)-2-methoxycarbonyl-2-(3,8,8,11,14,18-hexamethylnonadecyloxy)-ethoxy}-(2,2,2-trichloro-1,1-dimethylethoxy)-phosphoryl}- α -D-glucopyranuronamide (20)

To a solution of 1H-1,2,4-triazol (44.6 mg, 660.7 μ mol) in 1:4 pyridine-dichloromethane (1.2 mL) 2,2,2-trichloro-1,1-dimethylethyl dichlorophosphite (32 μ L, 161.7 μ mol) was added at 0°C, and the mixture was stirred at 0°C for 30 min. A solution of **17c** (78 mg, 127.5 μ mol) in pyridine-dichloromethane (1:1.8, 2.5 mL) was added dropwise. Stirring was continued for 90 min at 0°C. Within 90 min a solution of **22** (181 mg, 384 μ mol) in pyridine-dichloromethane (1:4, 2 mL) was added. After another 3 h stirring at 0°C bis(trimethylsilyl)-peroxide (56 μ L, 267.4 μ mol) was added, and the mixture stirred at 20°C overnight. After solvent removal and FC (chloroform-methanol 20:1) two P-diastereomers of **20** (unpolar product: 51 mg, 31%), polar product: 13 mg, 8%) and a fraction containing both diastereomers (40 mg, 23%) were obtained.

20 (unpolar diastereomer)

¹H NMR (400 MHz, ¹H-¹H COSY, ¹³C-¹H COSY, pyridine-d₅): $\delta = 0.87-0.97$ (23H, m, signals of the lipid part), 1.10-1.60 (32H, m, signals of the lipid part), 1.99, 2.02, 2.07, 2.12, 2.25 (15H, 5s, COCH₃), 2.17, 2.18 (6H, 2s, (CH₃)₂CCl₃), 3.65-3.74, 3.83-3.93 (2H, 2m, CH₂-1¹), 3.78 (3H, s, COOCH₃), 3.99 (1H, ddd, 5-H^E, $J_{4,5} = 9.9$ Hz, $J_{5,6a} = 2.9$ Hz, $J_{5,6b} = 3.9$ Hz), 4.21 (1H, m, 2-H^F, $J_{1,2} = 3.4$ Hz), 4.43-4.54 (3H, m, CH₂-6^E, 2-H^H), 4.64-4.80 (2H, m, CH₂-3^H), 4.93 (5-H^F hidden by the H₂O peak), 4.95-5.01 (m, ?), 5.07 (1H, d, 1-H^E, $J_{1,2} = 8.0$ Hz), 5.47 (1H, dd, 2-H^E, $J_{1,2} = 8.0$ Hz, $J_{2,3} = 9.7$ Hz), 5.52 (1H, t, 4-H^E, $J = 9.7$ Hz), 5.64 (1H, t, 3-H^E, $J = 9.6$ Hz), 5.91 (1H, t, 3-H^F or 4H^F, $J = 7.1$ Hz), 5.93 (1H, t, 3-H^F or 4H^F, $J = 7.1$ Hz), 6.41 (1H, dd, 1-H^F, $J_{1,2} = 3.6$ Hz, $J_{1,p} = 5.6$ Hz), 7.74 (2H, bs, OCONH₂), 8.01, 8.59 (2H, 2 bs, CONH₂)- ¹³C NMR (50 MHz, ¹³C-¹H COSY, APT, pyridine-d₅): $\delta = 19.3-41.1$ (signals of the lipid part and protecting group signals); 52.0 (OCH₃), 61.7 (C-6^E), 68.2 (d, C-3^H, $J_{C,p} = 5.5$ Hz), 68.6 (C-4^E), 69.7 (C-1¹), 69.8, 70.8 (C-5^F and C-3^F), 70.9 (C-4^F), 71.0 (C-2^E), 71.9 (C-5^E), 73.1 (C-3^E), 77.4 (d, C-2^H, $J_{C,p} = 10.1$ Hz), 78.0 (d, C-2^F,

$J_{C,P} = 9.1$ Hz), 90.6 (d, $O\overline{C}(CH_3)_2CCl_3$, $J_{C,P} = 5.5$ Hz), 97.1 (d, $C-1^F$, $J_{C,P} = 6.4$ Hz), 102.1 ($C-1^E$), 105.6 (d, CCl_3 , $J_{C,P} = 14.6$ Hz), 156.7 ($OCONH_2$), 168.9, 169.38, 169.43, 169.5, 170.0, 170.1, 170.3 ($\overline{COCH_3}$, $CONH_2$).- ^{31}P NMR (80 MHz, pyridine- d_5): $\delta = -4.03$ (phosphate).- IR (KBr): 1752 cm^{-1} .- $C_{56}H_{94}Cl_3N_2O_{23}P$ (1300.69, 1298.51), FAB MS: m/z 1321.6 $[M+Na]^+$, 1299.7 $[M+H]^+$, 1179.5 $[M+K-C_4H_5Cl_3]^+$, 1163.5 $[M+Na-C_4H_5Cl_3]^+$.

20 (polar diastereomer)

1H NMR (400 MHz, 1H - 1H COSY, pyridine- d_5): $\delta = 0.80$ -1.95 (51H, m, signals of the lipid part), 2.02, 2.03, 2.04, 2.06, 2.07, 2.16, 2.27 (21H, 7s, $COCH_3$, $(CH_3)_2CCl_3$), 3.77-3.84 (1H, m, $CH_aH_b-1^1$), 3.96-4.05 (5H, m, containing: $\delta = 3.96$ (d, OCH_3 , $J \sim 2$ Hz, the sample did not contain the other diastereomer, the splitting might be due to 1H , ^{31}P coupling), $CH_aH_b-1^1$, 5- H^E), 4.22-4.30 (1H, m, 2- H^F), 4.35-4.44 (m, plasticizer), 4.50-4.66 (3H, m, CH_2-6^E , 2- H^H), 4.79-ca. 5.00 (2H, m, CH_2-3^H , signal partly covered by water), 4.98 (1H, d, 5- H^F , $J_{4,5} = 10.4$ Hz), 5.12 (1H, d, 1- H^E , $J_{1,2} = 8.0$ Hz), 5.50-5.57 (2H, m, 2- H^E , 4- H^E), 5.68 (1H, t, 3- H^E , $J = 9.6$ Hz), 5.84 (1H, dd, 4- H^F , $J_{3,4} = 9.8$ Hz, $J_{4,5} = 10.4$ Hz), 5.98 (1H, t, 3- H^F , $J = 9.9$ Hz), 6.51 (1H, m ($w_{1/2} = 12.8$ Hz), 1- H^F), 7.78 (2H, bs, $OCONH_2$), 8.08, 8.55 (2H, 2 bs, $CONH_2$).- ^{13}C NMR (50 MHz, pyridine- d_5): $\delta = 19.1$ -41.8 (signals of the lipid part and the protecting group signals); 51.8 (OCH_3), 61.7 ($C-6^E$), 68.0 ($C-3^H$, broad signal), 68.5, 69.5, 69.6, 69.8, 70.5 (2 \times), 70.9, 71.9, 72.9 ($C-2^E$, $C-3^E$, $C-4^E$, $C-5^E$, $C-3^F$, $C-4^F$, $C-5^F$, $C-1^1$), 77.5 (broad signal) and 77.8 (d, $J = 8.7$ Hz, $C-2^H$, $C-2^F$, assignment based on the assignment of the other stereoisomer), 90.3 (d, $(CH_3)_2\overline{C}Cl_3$, $J_{C,P} = 4.5$ Hz), 96.4 (d, $C-1^F$, $J_{C,P} = 5.3$ Hz), 102.0 ($C-1^E$), 105.6 (d, CCl_3 , $J_{C,P} = 15.5$ Hz), 156.5 ($OCONH_2$), 169.35, 169.38, 169.5, 169.6, 169.9, 170.2, 170.4 ($COCH_3$, $CONH_2$).- ^{31}P NMR (80 MHz, pyridine- d_5): $\delta = -4.69$ (phosphate).- IR (KBr): 1755 cm^{-1} .- $C_{56}H_{94}Cl_3N_2O_{23}P$ (1300.69, 1298.51), FAB MS: m/z 1321.1 $[M+Na]^+$, 1299.2 $[M+H]^+$, 1179.2 $[M+K-C_4H_5Cl_3]^+$, 1163.2 $[M+Na-C_4H_5Cl_3]^+$, 331 $[e]^-$.

2-O-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)-4-O-acetyl-3-O-carbamoyl-1-O-[(R)-2-methoxycarbonyl-2-(3,8,8,11,14,18-hexamethylnonadecyloxy)-ethoxy]-hydroxy-phosphoryl]- α -D-glucopyranuronamide (18)

A mixture of both diastereomers of **20** (23 mg, 17.6 μ mol) and freshly prepared zinc-copper couple (26 mg), pyridine (1.4 mL) and 2,4-pentandione (30 μ L) was stirred at 20°C for 2 h. After filtration the residue was carefully washed with pyridine and ethanol. From the combined solutions the solvent was evaporated. The crude product was dissolved in 8:1 water-ethanol and treated with Dowex 50W X 2 (200 mg, H^+ -form) for 20 min. The resin was removed by filtration and washed with 8:1 water-ethanol. From the combined solutions after solvent removal (lyophilization) and FC (toluene-chloroform-methanol 1:1:1) **18** (20 mg, 100%) was obtained.- 1H NMR (400 MHz, 1H - 1H COSY, pyridine- d_5): $\delta = 0.85$ -0.95, 1.10-1.70 (2m, signals of the lipid part), 2.01, 2.02, 2.04 (broad), 2.18 (broad), 2.25 (15H, 5s, $COCH_3$), 3.75-4.03 (6H, m, CH_2-1^1 , $COOCH_3$ ($\delta = 3.87$), 5- H^E), 4.07-4.11 (1H, m, 2- H^F), 4.45-4.69 (4H, m, CH_2-6^E , 2- H^H , $CH_aH_b-3^H$), 4.76-4.85 (1H, m, $CH_aH_b-3^H$, covered by an impurity signal), 5.05 (1H, d, 1- H^E , covered by the H_2O signal), 5.19 (1H, m, 5- H^F), 5.44 (2H, t (broad signal), 2- H^E , 4- H^E , $J = 9.4$ Hz), 5.63 (1H, t, 3- H^E , $J = 9.5$ Hz), 5.86 (1H, t, 4- H^F , $J = 9.7$ Hz), 5.93 (1H, t, 3- H^F , $J = 9.5$ Hz), 6.36 (1H, bs ($w_{1/2} = 14.5$ Hz), 1- H^F), 7.60 (2H, bs, $OCONH_2$), 8.09, 8.30 (2H, m, $CONH_2$).- ^{13}C NMR (50 MHz, ^{13}C - 1H COSY, APT, pyridine- d_5): $\delta = 19.7$ -42.5 (signals of the lipid part and protecting group signals), 52.3 (OCH_3), 62.5 ($C-6^E$), 66.7 ($C-3^H$, broad signal), 69.3 ($C-2^E$ or $C-4^E$), 69.6 ($C-1^1$), 70.0 ($C-4^F$), 70.8 ($C-5^F$), 71.9 ($C-2^E$ or $C-4^E$), 72.4 ($C-5^E$), 72.8 ($C-3^F$), 73.7 ($C-3^E$), 78.9 ($C-2^F$, broad signal), 79.8 ($C-2^H$, broad signal), 95.3 ($C-1^F$, broad signal), 102.6 ($C-1^E$), 157.6 ($OCONH_2$), 170.0, 170.2, 170.5, 170.6, 171.2 (broad signal), 171.6, 172.3 ($\overline{COCH_3}$, $\overline{COOCH_3}$, $CONH_2$).- ^{31}P NMR (80 MHz, pyridine- d_5): $\delta = +0.78$ (phosphate).- $C_{52}H_{89}N_2O_{23}P$ (1141.25, 1140.5594), FAB MS: m/z 1185.5 $[M+2Na-H]^+$, 1179.4 $[M+K]^+$, 1163.5 $[M+Na]^+$.

Deprotection of 18

A degassed solution of **18** (58 mg, 50.65 μ mol) in methanol-water (2:1, 4.0 mL) was treated with an aqueous lithium hydroxide solution (degassed, 1 mol \cdot L $^{-1}$, 100 μ L, 2 eq.) at 20°C. After 2 h, 3 h and 6 h further 100 μ L portions of the lithium hydroxide solution were added. The reaction was quenched by addition of 300 mg

Dowex 50W X2 (H⁺-form). Stirring was continued for 30 min. After filtration the resin was washed with ethanol. The combined filtrates were concentrated and the remaining solution was lyophilized. MPLC (chloroform-methanol-water 18:11:1.8→18:11:2.7) and Sephadex[®] filtration (water) gave **1c** (29.5 mg, 63%) and the uronic acid **19** (13.3 mg, 29%).

2-O-(β-D-Glucopyranosyl)-3-O-carbamoyl-1-O-{{(R)-2-carboxy-2-(3,8,8,11,14,18-hexamethylnonadecyloxy)-ethoxy}-hydroxyphosphoryl}-α-D-glucopyranuronamide (1c)

¹³C NMR (50 MHz, D₂O): signals of the lipid part: δ = 19.8, 20.0, 22.8, 22.9, 24.6, 25.0, 27.2, 28.0, 29.8 (b), 32.6, 33.2 (b), 34.0, 34.6, 37.4 (b), 37.7 (b), 39.5, 39.7, 42.6 (b) saccharide signals: δ = 60.6 (C-6^E), 69.6 (very broad signal), 71.8 (s), 72.9, 75.9 (very broad signal), 78.0, 95.6 (b, C-1^F), 104.1 (b, C-1^E), 159.1 (b, OCONH₂), 172.6 (b), 174.6? (b, COOH, CONH₂); impurities or unknown signals: 14.2, 125.5, 129.4 (weak intensity).- ³¹P NMR (80 MHz, D₂O): δ = - 1.86 (phosphate).- C₄₁H₇₇N₂O₁₈P (916.04, 916.49), FAB MS: m/z 977.4 ([M+Na+K-H]⁺, 961.5 ([M+2Na-H]⁺, 955.4 [M+K]⁺, 939.5 [M+Na]⁺.- HR MS: [M+Na]⁺ calc 939.4807, found 939.4799.

2-O-(β-D-Glucopyranosyl)-3-O-carbamoyl-1-O-{{(R)-2-carboxy-2-(3,8,8,11,14,18-hexamethylnonadecyloxy)-ethoxy}-hydroxyphosphoryl}-α-D-glucopyranuronic acid (19)

¹³C NMR (50 MHz, D₂O): signals of the lipid part: δ = 16.9, 22.6, 22.8, 25.6, 27.7 (broad signal), 29.8 (broad signal), 30.8, 32.6, 33.2, 37.5 (broad signal), 40.2, 40.4, 42.3; saccharide signals: δ = 62.0 (C-6^E), 72.6, 78.7, 78.8, 79.0 (no other saccharide carbon signals could be detected).- ³¹P-NMR (80 MHz, D₂O): δ = - 2.17 (phosphate).- C₄₁H₇₆NO₁₉P (918.02, 917.48), FAB MS: m/z 978.4 [M+Na+K-H]⁺, 962.4 [M+2Na-H]⁺, 956.4 [M+K]⁺, 940.5 [M+Na]⁺.- HR MS: [M+Na]⁺ calc 940.4647, found 940.4665.

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