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SYNTHESIS OF TWO STRUCTURAL ANALOGUES OF THE SMALLEST ANTIBIOTICALLY ACTIVE DEGRADATION PRODUCT OF MOENOMYCIN A

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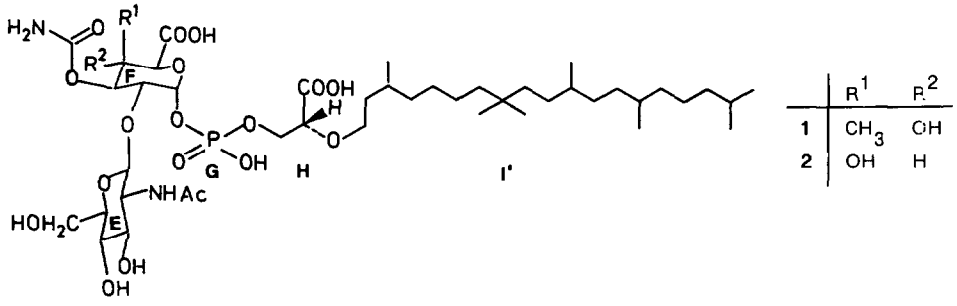
Abstract - The disaccharide analogues **19** and **2** of moenomycin A have been synthesized. In contrast to the moenomycin A degradation product **1**, synthetic compounds **19** and **2** do not show antibiotic activity.

Introduction

Moenomycin A and related antibiotics interfere with the biosynthesis of peptidoglycan, the main structural component of the bacterial cell wall. With cell-free systems from Escherichia coli it was demonstrated that moenomycin A inhibits the formation of the linear glycan strands of peptidoglycan from the last membrane precursor by its inhibitory effect on the enzyme penicillin-binding protein 1b (PBP 1b).[1] From degradation and biochemical work it is known that compound **1** represents the smallest fully active portion of moenomycin A. Removal of unit E or the carbamoyl grouping from **1** as well as esterification of the carboxyl group of unit H destroy the antibiotic activity completely.[2]



Scheme 1.

There is a need in biologically active derivatives of **1** that can be used

- for localizing the transglycosylase domain in PBP 1b (a bifunctional protein that catalyses the two successive final reactions in the biosynthesis of cross-linked peptidoglycan[1]) by irreversible binding
- as ligands in affinity chromatographic purification of the enzyme PBP 1b.

Furthermore, derivatives of **1** with better transport properties in living organisms would be highly welcome. It may be recalled that moenomycin A and related antibiotics a) belong to the most active antibiotics, b) inhibit a step which is not affected by any other antibiotic, c) cause little resistance, and d) nevertheless cannot be used in human therapy because of their unsuitable physical properties.[3] Until now we have been unable to find efficient methods to further derivatize **1**.[4] We therefore resorted to synthetic methods to arrive at structural analogues of **1**.

Synthetic planning

A retrosynthetic analysis of **1** revealed the ordinary precursors D-glucosamine (E) and 3-phospho-D-glycerate (G-H), accompanied by unusual ones such as the D-moenuronic acid moiety (F) and the perhydromoenocinol part (I'). In approaching the problems associated with the synthesis of type **1**

compounds experimentally it was realized that the synthesis of both D-moenuronic acid buildung blocks[5] and 2-O-alkylated glyceric acid derivatives[6] is a rather complicated task. In view of this situation we decided to start our efforts towards moenomycin A analogues by

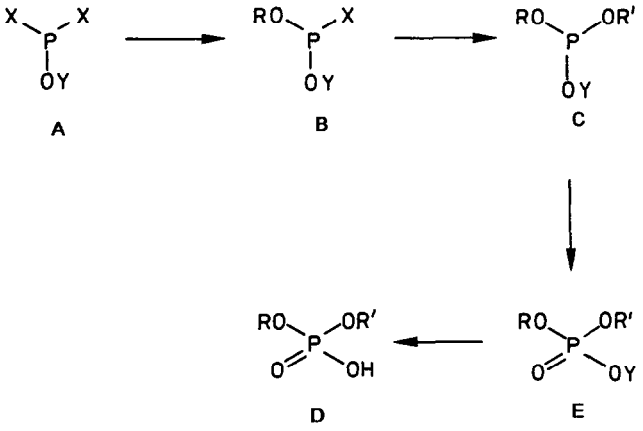
a) using as a starting material the H-I' fragment **16**, obtained from moenomycin A by degradation,[7] and

b) replacing the D-moenuronic acid part (F) by a common carbohydrate moiety. The latter decision led to the further question, which structural changes in unit F are tolerated without loss of the antibiotic activity.

In the present publication we report the synthesis of compound **2** in which unit F is derived from D-galacturonic acid. **2** differs from **1** only in unit F by the configuration at C-4 and the missing 4-C-methyl group.

Formation of the phosphoric acid diester grouping at the anomeric carbon of unit F was anticipated to cause the main synthetic difficulties.[8,9] There are only scarce examples in the literature,[10] using

- the reaction of orthoesters with phosphoric acid monoesters (this method is inapplicable in the present case for structural reasons)[11]
- activation of a saccharide-1-phosphate and subsequent reaction with an appropiate alcohol (this corresponds to the diester methodology in nucleotide synthesis)[12]
- the Ramirez cyclic enediol phosphate method[13]
- Schmidt's trichloroacetimidate procedure[14]
- the so-called phosphite methodology[8,15]
- 1-H-phosphonate intermediates.[16]



(Y = protecting group)

Scheme 2.

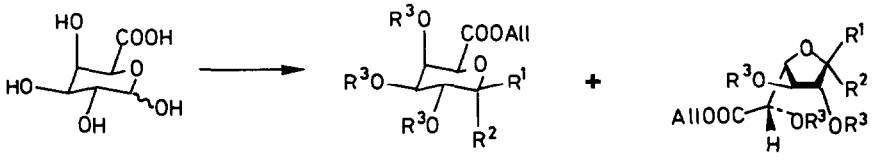
We decided to use the phosphite-triester approach as summarized in Scheme 2. It is known that dichlorophosphites of type **A** (X=Cl) are more reactive than the monochlorophosphites **B** (X=Cl), especially when a bulky protecting group Y is employed.[17] This reactivity difference can be utilized to introduce sequentially and selectively first OR and then OR'. According to Ugi[18] the selectivity is even more pronounced when in **A** and **B** Cl is replaced by 1,2,4-triazol-1-yl residues.

As protecting group Y (see Scheme 2) the bulky 2,2,2-trichloro-1,1-dimethyl-ethyl residue was chosen for the reason mentioned above. Furthermore, phosphite- and phosphate-triesters with this protecting group can be expected to be quite stable as a consequence of steric hindrance.[17,18]

For the oxidation of aldose-1-phosphite-triester to phosphate-triester intermediates (**C**→**E**) until now tert-butyl hydroperoxide and O_2/AIBN have been employed.[9,15] We selected bis(trimethylsilyl)peroxide which should be a superior reagent for this purpose.[19] Finally, a number of methods is available for the reductive removal of 2,2,2-trichloroethyl-type protecting groups (step **E**→**D** in Scheme 2).[20]

Synthesis of the galacturonic acid derivative 6.

In a straightforward route to **6**, which contains two different protecting groups in the 1- and the 6-position, D-galacturonic acid was treated with anhydrous allyl alcohol in the presence of Dowex-50 (H^+ form) resin[21] to furnish a 1:1 mixture of **4a/4b** and **5a/5b**. The furanoid fraction was recycled (2x) to give eventually a 56 % yield of a 1:3.5 mixture of **4a** and **4b**. The structural assignments are based on very careful NMR analyses of **4a**, **4b**, **5a**, and **5b**, and their respective acetyl derivatives **4c**, **4d**, **5c**, and **5d** (see Tables 1-3). Routinely, **4a** and **4b** were not separated. Transesterification of this mixture with sodium methoxide in methanol yielded a mixture of **6** and its ß-isomer, the separation of which was easier than that of **4a** and **4b**. This method for the synthesis of compounds of type **6** compares well with that recently reported by Ogawa for similar galacturonic acid derivatives.[22]



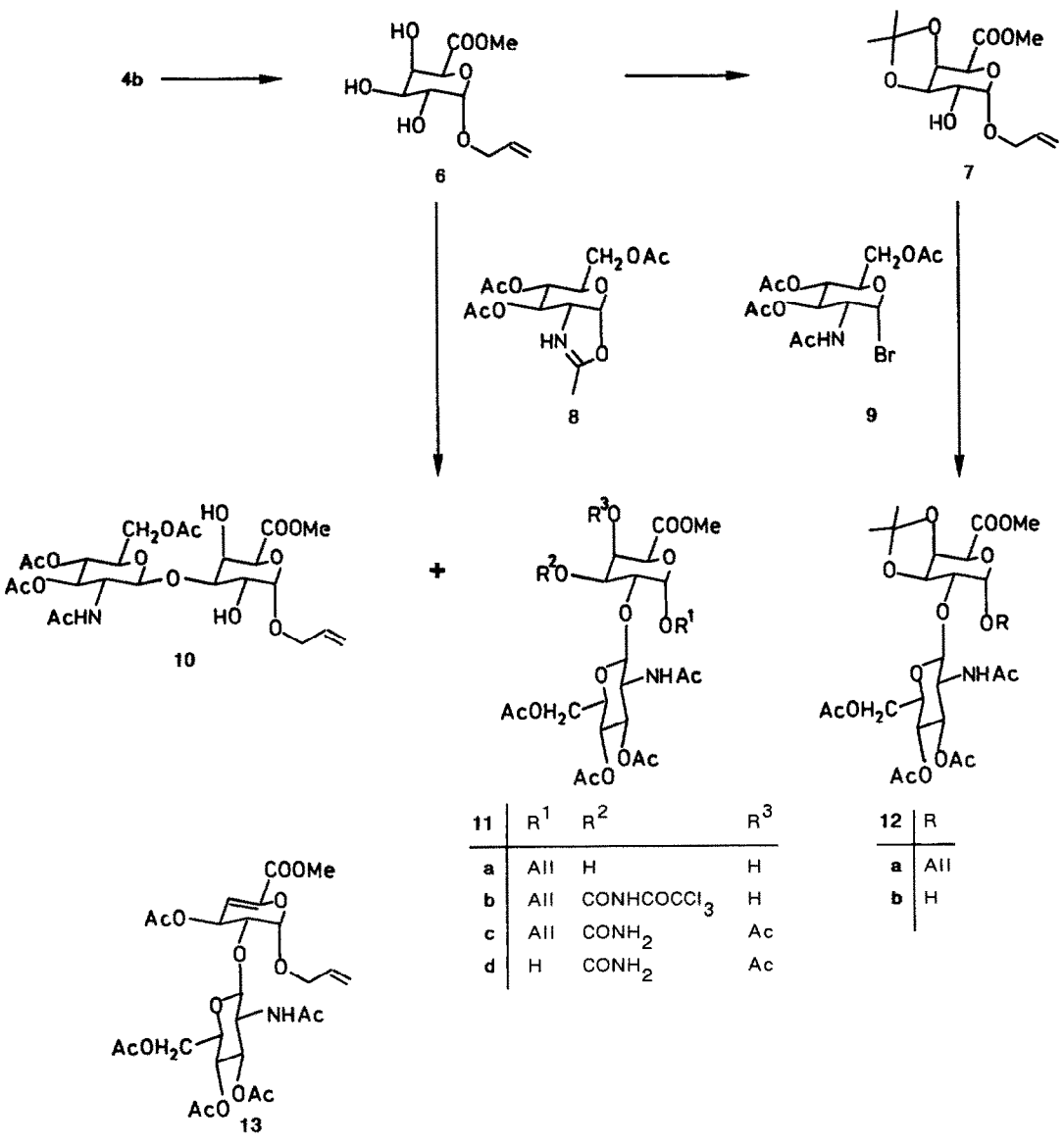
4,5	R^1	R^2	R^3
a	OAll	H	H
b	H	OAll	H
c	OAll	H	Ac
d	H	OAll	Ac

Scheme 3.

Synthesis of disaccharides **11a** and **12a**[23]

If **6** without further protecting group chemistry was directly treated with the oxazoline **8**[24] in toluene-nitromethane solution in the presence of anhydrous p-toluenesulfonic acid,[25] the two isomeric disaccharides **10** and **11a** were obtained in a 1:1 ratio (33 % and 36 % yield). Under the conditions of the Helferich modification of the Koenigs-Knorr method[23] - reaction of **6** with 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-glucopyranosyl bromide (**9**)[26] in CH_2Cl_2 solution in the presence of $Hg(CN)_2$-$HgBr_2$[27] - 53 % of the undesired 1-3-linked disaccharide **10** were obtained whereas **11a** was formed in moderate 35 % yield.[28] In order to suppress the formation of the 1-3-linked disaccharide, **6** was converted into the isopropylidene derivative **7**.[27] Coupling of **7** with **8** in CH_2Cl_2 solution at 60°C in the presence of 4 Å molecular sieves with anhydrous camphorsulfonic acid as catalyst provided disaccharide **12a** in 70 % yield. The acetonide protecting group was then removed by treatment with 20% aq. acetic acid[27] to give the desired **11a** in 99 % yield.

The structures of **10** and **11a** were assigned on the basis of extensive NMR experiments (see Experimental), the results of which are collected in Table 4. Most specifically, the low-field position of the C-2 signal of the galacturonic acid moiety in **11a** (δ = 78.69 as compared to δ = 69.84 in **6**) has its origin in the glycosidic linkage at this position (ß-effect). Attachment of the glucosamine residue to the 2-position of the uronic acid part in **11a** was confirmed by a H,C-COLOC experiment (^1H,^{13}C correlation spectroscopy via long range couplings[29]) which showed a coupling from the uronic acid C-2 across the glycosidic bridge to 1-H of the amino sugar moiety (alongside with cross peaks from C-2 to 2-H, 3-H and 4-H and from C-3 to 1-H, 3-H, and 4-H of the uronic acid part).



11	R^1	R^2	R^3
a	All	H	H
b	All	$CONHCOCCl_3$	H
c	All	$CONH_2$	Ac
d	H	$CONH_2$	Ac

12	R
a	All
b	H

Scheme 4.

Synthesis of 11d

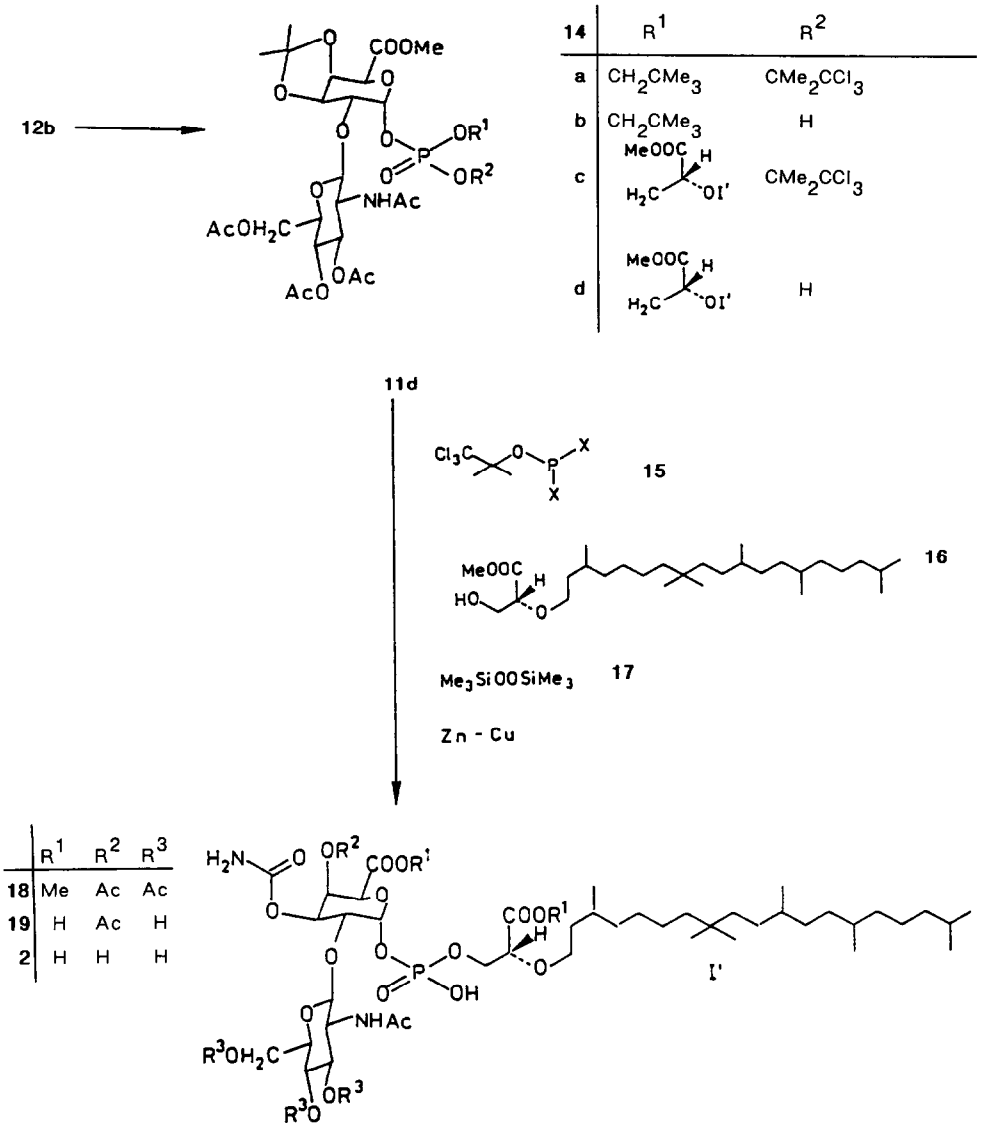
In the next phase of the synthesis the following reactions had to be accomplished: a) introduction of the 3-O-carbamoyl group into **11a**, b) acetylation of the free 4-OH group, and c) removal of the allyl group. We wanted to protect the 4-OH group in order to prevent unwanted side-reactions associated with the deallylation (furanoid ring formation) and phosphorylation steps.

The urethane grouping was introduced[6b,30] by reacting **11a** with trichloroacetyl isocyanate[31] (1 equiv, in order to suppress the attack of the very reactive isocyanate at the 4-OH group[32]) at -40°C. According to TLC analysis **11b** was the sole reaction product. Acylation in the 3-position was clearly visible in the ^1H NMR spectrum of **11b** (1 ppm down-field shift[33] of the 3-H signal as compared with **11a**). In the IR spectrum the CO band appeared at 1795 cm^{-1}.

11b turned out to be rather sensitive and decomposed partly (by loss of the trichloroacetyl group[34]) on attempted chromatographic purification.[35] Normally, **11b** was, therefore, directly converted into its acetyl derivative with acetic anhydride-pyridine, using Steglich's DMAP[36] as catalyst. Under the conditions of the work-up procedure and the chromatographic separation the trichloroacetyl group was lost and **11c** was obtained in 58 % yield alongside with the elimination

product **13** (25 %). The chemical processes leading to **13** were not investigated. It seems reasonable to assume that migration of the trichloroacetylcarbamoyl group from the 3- to the 4-position under the acetylation conditions followed by elimination[37] and acetylation of the 3-OH group are responsible for this side reaction.

Finally, the allyl ether in **11c** was cleaved[38] with $PdCl_2$ in a 0.1 molar solution of NaOAc in 20:1 acetic acid-water[39] to provide **11d** (anomeric mixture) in 81 % yield. Similarly, from **12a** the allyl group was removed to give **12b** as a mixture of anomers (83 %).



Scheme 5.

Synthesis of model compounds **14b** and **14d**

In exploratory experiments the dichlorophosphite **15** (X = Cl) was converted into the ditriazolide **15** (X = 1,2,4-triazol-1-yl).[18] This reagent in THF-pyridine solution was sequentially treated with the disaccharide **12b** and neopentyl alcohol to give the corresponding triphosphite. For the subsequent oxidation with bis(trimethylsilyl)peroxide **19** (to give **14a**) a solvent change (THF-pyridine→CH_2Cl_2) had to be performed which was accompanied by some hydrolytic cleavage of the triphosphite to give **12b** back. **14a** was also sensitive towards hydrolysis and during chromatographic purification extensive decomposition (formation of **12b**) occurred, even in the presence of triethylamine. In the ^1H NMR spectrum of **12a** $J_{1,2}$ = 3.2 Hz was indicative of the α-configuration at C-1 in the uronic

acid part. The phosphate protecting group of **14a** was reductively removed with Zn-Cu couple[40] to give **14b** in quantitative yield.

To circumvent the unwanted hydrolysis associated with the change of solvent necessary for $(Me_3SiO)_2$ oxidation, in a second model experiment the phosphorylation reaction was performed in CH_2Cl_2 solution. Thus, reaction of **15** (X = 1,2,4-triazol-1-yl) with **12b** and then with **16** in CH_2Cl_2 solution followed by oxidation with bis(trimethylsilyl)peroxide provided **14c** in 20 % overall yield alongside with 12 % of a compound presumed to be the ß-anomer.[34] According to ^1H NMR spectroscopy **14c** was a mixture of two diastereoisomers (isomeric at the phosphate chiral center). Reductive elimination of the 2,2,2-trichloro-1,1-dimethylethyl group proceeded again uneventfully to give diphosphate **14d** in quantitative yield. Here again, the α-configuration at C-1 of unit F was evident from the ^1H NMR spectrum ($J_{1,2}$ = 3.3 Hz).

Synthesis of **2** from **11d**

The most advantageous experimental conditions found in the model series were used. Reaction of **15** (X = 1,2,4-triazol-1-yl) with disaccharide **11a** and the moenomycin degradation product **16** in CH_2Cl_2 solution followed by $(Me_3SiO)_2$ oxidation and subsequent Zn-Cu-induced reductive elimination of the phosphate protecting group[40] gave **18** (21 %) and a fraction containing (on the basis of an incomplete spectral analysis) the ß-phosphate;[34] 36 % of **11a** were recovered. The structure of **18** is well-supported by spectral data, such as the 1-H signal of unit F at δ = 6.53 (dd, $J_{1,2}$ = 3.5 Hz and $J_{1,P}$ = 7.0 Hz), and the ^{13}C NMR signals at δ = 95.88 (C-1 of unit F) and δ = 157.12 (signal of the carbamoyl carbon). The ester protecting groups were finally removed by hydrolysis with LiOH in THF-water.[41] TLC indicated that first **19** was formed which on longer exposure to the basic conditions was converted to **2**. In view of the interesting relation between chemical structure and biological activity of these compounds both **19** and **2** were isolated. Their structures are fully supported by the spectroscopic properties (^{13}C NMR and FAB-MS, see Table 6 and Experimental).

Biological properties of **19** and **2** and conclusions

In van Heijenoort's *in vitro* assay for inhibition of the transglycosylation reaction[1,2] **19** and **2** turned out to have no inhibitory effect at a final concentration of 10 µg/ml.

In conclusion, we have developed a synthetic scheme for disaccharide analogues of moenomycin A. Compounds **19** and **2** which differ from the moenomycin A degradation product **1** only at C-4 of unit F are in contrast to **1** biologically inactive which means that the structural requirements in unit F for antibiotic activity are very strict.

EXPERIMENTAL

General

All reactions were performed in oven-dried glassware under a positive pressure of argon. Liquids and solutions were transferred by syringes, and were introduced into reaction flasks through rubber septa. All solvents were carefully dried prior to use. Usual work-up means partitioning the reaction mixture between water and an organic solvent (given in parenthesis), drying the combined organic solutions over Na_2SO_4 and removal of solvent either by distillation in vacuo using a rotatory evaporator or by lyophilization.

The instrumentation used was: ^1H NMR: WP 80 (Bruker); AM 400 (Bruker); ^{13}C NMR: AM 400 (Bruker); IR: Perkin Elmer 257 and 1310; Liquid SIMS: a) MAT 731/SS 200 instrument (Varian) with a modified Saddle Field Ion Source (Ion Tech Ltd.); b) MAT-CH-5 instrument (Varian) with a modified thermal ion emitter and a Cs ion gun, MPLC: Medium pressure chromatography using 20.0 cm x 1.5 cm glass tubes (column A, short, 9 g SiO_2), 37.0 cm x 1.5 cm glass tubes (column A, long, 17 g SiO_2), 31.0 cm x 2.5 cm glass tubes (column B, 60 g SiO_2), or 40.0 cm x 4.5 cm glass tubes (column C, 270 g

SiO_2), silica gel Grace (35-70 µm), and a Duramat pump (CfG).
The following methods were employed for the NMR spectroscopical structural assignments (if necessary): a) normal ^1H and ^{13}C NMR spectroscopy (DEPT technique[42]), b) standard two dimensional (2D) $^1H,^1H$ chemical shift correlation spectroscopy (COSY[43]), heteronuclear $^1H,^{13}C$ 2D shift correlation using large ($^1J_{CH}$) C,H couplings,[44] and heteronuclear $^1H,^{13}C$ correlation spectroscopy via long range couplings (COLOC[29]).
Carbon and proton numbering in the subunits (see NMR and MS spectral data) follows the moenomycin A nomenclature (see formula 1).

Reaction of 3 with allyl alcohol.

a) A mixture of D-galacturonic acid monohydrate (3, 530 mg, 2.50 mmol), Dowex-50 W-X2 resin (H^+ form, 100-200 mesh, 0.5 g) and anhydrous allyl alcohol (2.0 ml) was stirred for 15 h at 85°C. The resin was filtered off and washed with methanol. The combined filtrates after solvent evaporation and MPLC (column B, hexanes-$CHCl_3$-ethanol 12:1:1) furnished **5a** (137 mg, 20 %, colourless sirup), **5b** (42 mg, 7 %, colourless sirup), and a mixture of **4a** and **4b** (187 mg, 28 %, colourless sirup).

b) A mixture of D-galacturonic acid monohydrate (3, 6.00 g, 28.3 mmol), Dowex-50 W-X2 resin (H^+ form, 100-200 mesh, 1.8 g) and anhydrous allyl alcohol (60.0 ml) was stirred for 46 h at 80°C. The resin was filtered off and washed with methanol. After solvent evaporation of the combined filtrates **5a/5b** were separated from **4a/4b** by MPLC (column B, hexanes-$CHCl_3$-ethanol 12:1:1). **5a/5b** were treated again with Dowex-50 W-X2 and allyl alcohol. After three cycles a mixture of **5a/5b** (0.30 g, 5 %) and a mixture of **4a/4b** (3.45 g, 56 %) were obtained. The **4a/4b** fraction formed a brownish sirup, which after boiling in dry ether (15 ml per 2 g) furnished a colourless solid. 200 mg of this sample were separated by MPLC (column B, hexanes-$CHCl_3$-ethanol 7:1:1) to give pure **4a** (40 mg) and **4b** (144 mg).

Allyl (allyl ß-D-galactopyranosid)uronate (4a).

M.p. 137-139°C (from $CHCl_3$-hexanes).- ^1H NMR (400 MHz, $CDCl_3$, $^1H,^{13}C$ correlation): see Table 1.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): see Table 2.- IR ($CHCl_3$): 3630-3130 (OH), 1760 cm^{-1} (CO).- MS (Cs^+, matrix: DMSO/glycerol): m/z(%) = 549 (0.7, $[2M+H]^+$), 275 (15, $[M+H]^+$), 217 (100), 199 (14), 181 (12), 171 (12), 159 (6), 145 (14).- (Found: C, 52.54; H, 6.70. $C_{12}H_{18}O_7$ (274.3) requires C, 52.55; H, 6.62).

Allyl (allyl α-D-galactopyranosid)uronate (4b).

M.p. 112-113.5°C (from $CHCl_3$-hexanes).- ^1H NMR (400 MHz, $CDCl_3$, $^1H,^{13}C$ correlation): see Table 1.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): see Table 2.- IR ($CHCl_3$): 3640-3130 (OH), 1760 cm^{-1} (CO).- MS (Cs^+, matrix: DMSO/glycerol): m/z(%) = 549 (3, $[2M+H]^+$), 275 (18, $[M+H]^+$), 217 (100), 199 (10), 181 (9), 171 (11), 159 (5), 157 (10).- (Found: C, 52.66; H, 6.65. $C_{12}H_{18}O_7$ (274.3) requires C, 52.55; H, 6.62).

Allyl (allyl ß-D-galactofuranosid)uronate (5a).

^1H NMR (400 MHz, $CDCl_3$, $^1H,^{13}C$ correlation): see Table 1.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): see Table 2.- IR ($CHCl_3$): 3640-3200 (OH), 1750 cm^{-1} (CO).- MS (Cs^+, matrix: DMSO/glycerol): m/z(%) = 275 (5, $[M+H]^+$), 259 (2), 217 (34), 199 (6), 181 (7), 141 (3).- (Found: C, 52.61; H, 6.71. $C_{12}H_{18}O_7$ (274.3) requires C, 52.55; H, 6.62).

Allyl (allyl α-D-galactofuranosid)uronate (5b).

^1H NMR (400 MHz, $CDCl_3$, $^1H,^{13}C$ correlation): see Table 1.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): see

Table 1. ^{1}H NMR spectral data of compounds 4a, 4b, 5a, and 5b

Assignment	4a	4b	5a	5b
unit F				
1-H	4.31 (d)	5.02 (d)	5.02 (s)	4.92 (d)
2-H	3.64-3.77	3.89*	4.01 (d)	4.08
3-H		3.89*	4.12 (t)	4.40 (t, broad)
4-H	4.27 (dd)	4.27 (dd)	4.44	4.19 (dd)
5-H	4.12 (d)	4.40 (d)		4.29 (dd)
OH			3.31 (s, broad)	3.21 (s, broad)
	3.70-4.25	3.95-4.35	4.10 (s, broad)	3.23 (d, broad)
			4.25 (s, broad)	3.76 (s, broad)

4a: $J_{1,2}$ = 7.5 Hz, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 1.5 Hz.
4b: $J_{1,2}$ = 3.0 Hz, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 1.5 Hz.
5a: $J_{2,3} = J_{3,4}$ = 0.8 Hz, $J_{4,5}$ < 1.5 Hz.
5b: $J_{1,2}$ = 5.0 Hz, $J_{2,3} = J_{3,4}$ = 7.5 Hz, $J_{4,5}$ = 2.5 Hz, $J_{5,OH}$ = 9.0 Hz.

allyl groups[48]				
1-H	4.12	4.02	3.95	4.05
	4.68-4.71	4.63-4.67	4.63-4.81	4.63-4.73
1'-H	4.41	4.15	4.13	4.23
	4.68-4.71	4.63-4.67	4.63-4.81	4.63-4.73

4a: 1-H, $|J_{AB}|$ = 13.0 Hz, ^3J = 6.5 Hz; 1'-H, ^3J = 5.5 Hz.
4b: 1-H, $|J_{AB}|$ = 13.0 Hz, ^3J = 6.0 Hz; 1'-H, ^3J = 5.5 Hz.
5a, 5b: 1-H, $|J_{AB}|$ = 13.0 Hz, ^3J = 6.0 Hz, $|^4J|$ = 1.5 Hz; 1'-H, ^3J = 6.0 Hz, $|^4J|$ = 1.5 Hz.

*Overlapping multiplets

Table 2. ^{13}C NMR spectral data of compounds 4a, 4b, 5a, and 5b

Assignment	4a	4b	5a	5b
unit F				
C-1	101.66	98.16	107.69	100.02
C-2	70.74*	68.25*	79.20*	77.94
C-3	72.98*	69.87*	77.87*	74.97
C-4	69.81	70.40	86.73	82.64
C-5	73.98	70.51	70.05	69.96
C-6	167.74	168.69	171.59	171.78
allyl groups[48]				
C-1	66.13	66.01	66.67	66.23
	70.43	69.02	68.28	69.41

*Assignments based on literature data.[50]

Table 2.- IR ($CHCl_3$): 3640-3130 (OH), 1740 cm^{-1} (CO).- MS (Cs^+, matrix: DMSO/glycerol): m/z(%) = 549 (2, $[2M+H]^+$), 491 (22), 275 (14, $[M+H]^+$), 217 (100, $[M+H-AllOH]^+$), 199 (13), 181 (14), 159 (7), 141 (17).- (Found: C, 52.63; H, 6.65. $C_{12}H_{18}O_7$ (274.3) requires C, 52.55; H, 6.62).

Acetylation of **4a**, **4b**, **5a**, and **5b**.

5a, **5b**, and a mixture of **4a** and **4b** were individually acetylated using acetic anhydride-pyridine to furnish **5c** (99 %), **5d** (100 %), and a mixture of **4c** and **4d** (96 %). The mixture of **4c** and **4d** was separated by MPLC (hexanes-$CHCl_3$-ethanol 10:1:1) to give **4c** (34 %) and **4d** (57 %).

Allyl (allyl 2,3,4-tri-O-acetyl-β-D-galactopyranosid)uronate (**4c**).

^1H NMR (400 MHz, $CDCl_3$, COSY): see Table 3.- IR ($CHCl_3$): 1745 cm^{-1} (CO).- MS (Xe, matrix: glycerol): m/z(%) = 393 (18), 362 (5), 344 (13), 343 (100), 326 (6), 303 (29), 301 (9).- (Found: C, 53.94; H, 6.10. $C_{18}H_{24}O_{10}$ (400.4) requires C, 54.00; H, 6.04).

Allyl (allyl 2,3,4-tri-O-acetyl-α-D-galactopyranosid)uronate (**4d**).

^1H NMR (400 MHz, $CDCl_3$, COSY): see Table 3.- IR ($CHCl_3$): 1745 cm^{-1} (CO).- MS (Cs^+, matrix: DMSO/glycerol): m/z(%) = 401 (3, $[M+H]^+$), 343 (73), 243 (13), 241 (6), 223 (26), 199 (7), 181 (100), 153 (32), 137 (28).- (Found: C, 53.86; H, 6.10. $C_{18}H_{24}O_{10}$ (400.4) requires C, 54.00; H, 6.04).

Table 3. ^1H NMR spectral data of compounds **4c**, **4d**, **5c**, and **5d**

Assignment	**4c**	**4d**	**5c**	**5d**
unit F				
1-H	4.53 (d)	5.25 (d)	5.08 (s)	5.18 (d)
2-H	5.23 (dd)	5.16 (dd)	5.09 (d)	5.04 (dd)
3-H	5.06 (dd)	5.41 (dd)	5.02 (dd)	5.57 (dd)
4-H	5.71 (dd)	5.77 (dd)	4.54 (dd)	4.38 (dd)
5-H	4.29 (d)	4.64 (d)	5.39 (d)	5.26 (d)
$COCH_3$	1.97 (s)	1.96 (s)	2.07 (s)	2.15 (s)
	2.23 (s)	2.04 (s)	2.08 (s)	2.19 (s)
	2.28 (s)	2.05 (s)	2.18 (s)	2.26 (s)

4c: $J_{1,2}$ = 7.5 Hz, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.5 Hz.
4d: $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.5 Hz.
5c: $J_{2,3}$ = 2.0 Hz, $J_{3,4}$ = 6.0 Hz, $J_{4,5}$ = 3.0 Hz.
5d: $J_{1,2}$ = 4.5 Hz, $J_{2,3}$ = 8.0 Hz, $J_{3,4}$ = 6.5 Hz, $J_{4,5}$ = 3.5 Hz.

allyl groups[48]				
1-H	4.12	4.03	3.95	3.90
	4.55-4.69	4.53-4.68	4.58-4.74	4.58-4.70
1'-H	4.41	4.20	4.19	4.23
	4.55-4.69	4.53-4.68	4.58-4.74	4.58-4.70

4c: 1-H, $|J_{AB}|$ = 13.5 Hz, ^3J = 6.5 Hz, $|^4J|$ = 1.5 Hz; 1'-H, ^3J = 5.0 Hz, $|^4J|$ = 1.5 Hz.
4d: 1-H, $|J_{AB}|$ = 13.0 Hz, ^3J = 6.0 Hz, $|^4J|$ = 1.2 Hz; 1'-H, ^3J = 5.2 Hz, $|^4J|$ = 1.2 Hz.
5c: 1-H, $|J_{AB}|$ = 13.0 Hz, ^3J = 6.0 Hz, $|^4J|$ = 1.5 Hz; 1'-H, ^3J = 6.0 Hz, $|^4J|$ = 1.5 Hz.
5d: 1-H, $|J_{AB}|$ = 13.0 Hz, ^3J = 6.0 Hz, $|^4J|$ = 1.5 Hz; 1'-H, ^3J = 5.0 Hz, $|^4J|$ = 1.5 Hz.

Allyl (allyl 2,3,5-tri-O-acetyl-β-D-galactofuranosid)uronate (5c).

^{1}H NMR (400 MHz, $CDCl_3$, COSY): see Table 3.- IR ($CHCl_3$): 1745 cm^{-1} (CO).- MS (Xe, matrix: glycerol): m/z(%) = 401 (3, $[M+H]^+$), 343 (10), 303 (18), 301 (25), 261 (10), 259 (25), 243 (21), 223 (23), 183 (24), 181 (25), 155 (14), 141 (25), 127 (17), 115 (18).- (Found: C, 54.04; H, 6.09. $C_{18}H_{24}O_{10}$ (400.4) requires C, 54.00; H, 6.04).

Allyl (allyl 2,3,5-tri-O-acetyl-α-D-galactofuranosid)uronate (5d).

^{1}H NMR (400 MHz, $CDCl_3$, COSY): see Table 3.- IR ($CHCl_3$): 1745 cm^{-1} (CO).- MS (Cs^+, matrix: DMSO/glycerol): m/z(%) = 533 (0.1, $[M+Cs]^+$), 459 (0.3), 401 (0.7, $[M+H]^+$), 343 (6), 325 (2), 283 (2), 243 (5), 225 (2), 223 (8), 183 (4), 181 (5).- (Found: C, 53.93; H, 5.97. $C_{18}H_{24}O_{10}$ (400.4) requires C, 54.00; H, 6.04).

Methyl (allyl α-D-galactopyranosid)uronate (6).

To a solution of **4a/4b** (140 mg, 511 μmol) in methanol (2.5 ml) a solution of sodium methoxide in methanol (2.0 ml, aliquot of 30 mg of sodium in 20 ml of methanol) was added. The solution was left at 20°C for 30 min and was then neutralized with Dowex 50 W-X2 resin (H^+-Form, 100-200 mesh, 0.5 g). The resin was filtered off and washed with methanol. The combined filtrates after solvent evaporation and MPLC (column A, hexanes-$CHCl_3$-ethanol 6:1:1) furnished **6** (78 mg, 62 %), along with the corresponding β-configurated product (22 mg, 18 %);[34] 7 mg (5 %) of **4a/4b** were recovered.- M.p. 119-121°C (from $CHCl_3$-hexanes, colourless needles).- ^{1}H NMR (400 MHz, [D_5] pyridine): see Table 4.- ^{13}C NMR (100.6 MHz, [D_5] pyridine, DEPT): see Table 4.- IR ($CHCl_3$): 3640-3100 (OH), 1760 cm^{-1} (CO).- MS (Cs^+, matrix: DMSO/glycerol): m/z(%) = 745 (0.6, $[3M+H]^+$), 497 (5, $[2M+H]^+$), 249 (22, $[M+H]^+$), 191 (100), 173 (21), 155 (17), 145 (9), 131 (18), 119 (20).- (Found: C, 48.48; H, 6.48. $C_{10}H_{16}O_7$ (248.2) requires C, 48.39; H, 6.50).

Methyl (allyl 3,4-O-isopropylidene-α-D-galactopyranosid)uronate (7).

A mixture of **6** (930 mg, 3.75 mmol) and anhydrous copper(II) sulphate (9.5 g) in acetone (100 ml) was stirred at 20°C for 4 d. The copper(II) sulphate was removed by centrifugation and washed with acetone. The combined solutions after solvent evaporation furnished pure **7** (1.05 g, 97 %, colourless solid).- M.p. 96-97.5°C (from ethanol).- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.31 (s, 3H, CCH_3); 1.46 (s, 3H, CCH_3); 3.79 (s, 3H, CO_2CH_3); 3.83-4.70 (7H, $-CH_2-CH=CH_2$, ring protons, OH); 5.01 (d, 1H, 1-H); 5.08-5.42 (2H, $=CH_2$); 5.65-6.16 (m, 1H, =CH-).- $J_{1,2}$ = 3.5 Hz.- IR($CHCl_3$): 3640-3140 (OH), 1760 cm^{-1} (CO).- MS (Cs^+, matrix: DMSO/glycerol): m/z(%) = 381 (5, $[M+gly+H]^+$), 327 (18), 249 (24), 191 (83), 173 (19), 157 (26), 155 (17), 131 (12), 119 (16), 93 (100, $[gly+H]^+$).- (Found: C, 54.21; H, 6.89. $C_{13}H_{20}O_7$ (288.3) requires C, 54.16; H, 6.99).

Methyl [allyl 2-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-3,4-O-isopropylidene-α-D-galactopyranosid]uronate (12a).

To a mixture of **7** (550 mg, 1.91 mmol), molecular sieves (4 Å, 30 mg), and **8** (1.40 g, 4.27 mmol) in CH_2Cl_2 (8.0 ml) a solution of anhydrous camphorsulfonic acid (0.58 g, 2.53 mmol) in CH_2Cl_2 (11.0 ml) was added. The mixture was stirred at 60°C for 20 h in a pressure vessel. After addition of another portion of **8** (560 mg, 1.71 mmol, dissolved in CH_2Cl_2 (2.0 ml)) and stirring at 60°C for 6.5 h the reaction was stopped by addition of pyridine (1.0 ml). The mixture was stirred at 20°C for 30 min. The molecular sieves were filtered off and washed with methanol. The combined filtrates after solvent evaporation and MPLC (column C, hexanes-$CHCl_3$-ethanol 6:1:1) furnished **12a** (0.82 g, 70 %): 58 mg (11 %) of **7** were recovered.- M.p. 232-233°C (from ethanol, colourless needles).- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.30 and 1.46 (2s, 6H, isopropylidene CH_3); 1.90 (s, 3H, NHAc); 2.00 (s, 3H, OAc); 2.01 (s, 3H, OAc); 2.05 (s, 3H, OAc); 3.79 (s, 3H, CO_2CH_3); 3.50-3.89 (1H, 5-H^E); 4.00-4.51 (8H)

and 4.57-5.43 (7H, ring protons, -CH_2-CH=CH_2); 5.52-6.10 (2H, =CH- and NH).- IR ($CHCl_3$): 3620-3180 (NH), 1740 (CO), 1680 (amide I), 1530 cm^{-1} (amide II).- MS (Cs^+, matrix: DMSO/glycerol); m/z(%) = 618 (6, $[M+H]^+$), 576 (2), 560 (4), 558 (2), 502 (2), 414 (2), 404 (4), 330 (100, $[E]^+$),^{45} 288 (16), 272 (15), 270 (14), 250 (22), 228 (25), 210 (64).- (Found: C, 52.42; H, 6.38. $C_{27}H_{39}NO_{15}$ (617.6) requires C, 52.51; H, 6.37).

10 and 11a from 6.

a) **6** (100 mg, 0.403 mmol) was dissolved in a 0.16 molar solution of **8** in 1:1 toluene-nitromethane (5.0 ml, 0.8 mmol). After addition of a 0.039 molar solution of anhydrous p-toluenesulfonic acid in toluene (0.6 ml, 23.4 µmol), the mixture was stirred at 70°C for 21 h. The reaction was then stopped by addition of pyridine (0.1 ml). After stirring at 20°C for 0.5 h and solvent evaporation (codestillation with toluene), MPLC (column B, methanol-$CHCl_3$ 1:15) furnished **10** (75 mg, 33 %) and **11a** (84 mg, 36 %); 28 mg (28 %) of **6** were recovered.

b) To a mixture of **6** (40 mg, 161 µmol), $Hg(CN)_2$ (35 mg, 140 µmol), and $HgBr_2$ (52 mg, 144 µmol) in CH_2Cl_2 (0.4 ml) a solution of **9** (210 mg, 514 µmol) in CH_2Cl_2 (1.0 ml) was added. After 3 d at 40°C another portion of **9** (210 mg, 514 µmol dissolved in CH_2Cl_2 (1.0 ml)) was added. After a total of 6 d at 40°C the mixture was filtered. The filtrate was extracted with saturated aq. sodium sulfide (4 ml). Usual work-up ($CHCl_3$) and MPLC (column B, methanol-$CHCl_3$ 1:15) furnished **10** (49 mg, 53 %) and **11a** (32 mg, 35 %); 0.5 mg (2 %) of **6** were recovered.

Methyl [allyl 3-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-α-D-galactopyranosid]uronate (10)

M.p. 214.5-218°C (from ethanol).- ^1H NMR (400 MHz, $CDCl_3$): see Table 4.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): see Table 4.- IR ($CHCl_3$): 3630-3150 (OH, NH), 1745 (CO), 1675 (amide I), 1520 cm^{-1} (amide II).- MS (Cs^+, matrix: DMSO/glycerol): m/z(%) = 578 (3, $[M+H]^+$), 520 (2), 436 (3), 330 (82, $[E]^+$),^{45} 288 (8), 270 (8), 228 (12), 210 (46), 168 (96), 150 (100), 126 (54), 108 (68).- (Found: C, 49.87; H, 6.15. $C_{24}H_{35}NO_{15}$ (577.5) requires C, 49.91; H, 6.11).

Methyl [allyl 2-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-α-D-galactopyranosid]uronate (11a)

M.p. 240-243°C (from ethanol, colourless needles).- ^1H NMR (400 MHz, $CDCl_3$, COLOC, COSY, ^1H,^{13}C correlation): see Table 4.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): see Table 4.- IR ($CHCl_3$): 3630-3150 (OH, NH), 1745 (CO), 1675 (amide I), 1530 cm^{-1} (amide II).- MS (Cs^+, matrix: DMSO/glycerol): m/z(%) = 578 (4, $[M+H]^+$), 520 (1), 502 (2), 484 (3), 460 (3), 330 (84, $[E]^+$),^{45} 288 (4), 270 (7), 228 (11), 210 (42), 168 (94), 150 (100), 126 (60), 108 (74).- (Found: C, 49.86; H, 6.10. $C_{24}H_{35}NO_{15}$ (577.5) requires C, 49.91; H, 6.11).

11a from 12a.

A solution of **12a** (0.81 g, 1.31 mmol) in 20% aq. acetic acid was stirred at 100°C for 30 min. Usual work-up (1. CH_2Cl_2, 2. ethyl acetate) furnished **11a** (0.75 g, 99 %).

Methyl [allyl 2-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-3-O-trichloroacetylcarbamoyl-α-D-galactopyranosid]uronate (11b).

To a solution of **11a** (31.6 mg, 54.8 µmol) in CH_2Cl_2 (0.3 ml) trichloroacetyl isocyanate (6.5 µl, 54.7 µmol) was added. The reaction mixture was left at -40°C for 15 min. The solution was then allowed to warm to 20°C. Addition of anhydrous methanol (0.1 ml) followed by MPLC (column A, hexanes-$CHCl_3$-ethanol 3:1:1) gave **11b** (41 mg, 98 %, the ^1H NMR spectra indicated the presence of an

Table 4. ^{1}H NMR and ^{13}C NMR spectral data of compounds **6**, **10** and **11a**.

Assignment unit E	^{1}H NMR data 6	10	11a	^{13}C NMR data 6	10	11a	Assignment unit E
					171.78	171.69	$NH\underline{C}OCH_3$
					170.89,	170.86,	$O\underline{C}OCH_3$
					170.71,	170.59,	
					168.99	169.39	
1-H		4.97 (d)	4.79 (d)		101.70	102.75	C-1
2-H		4.00-4.22	3.97 (m)		54.85	54.52	C-2
3-H		5.27 (dd)	5.16 (dd)		72.10	73.04	C-3
4-H		5.00 (t)	5.01 (t)		68.71	68.43	C-4
5-H		3.76 (m)	3.73 (m)		71.78	71.65	C-5
CH_2-6		4.00-4.22	4.10-4.15 (m)		62.18	62.18	C-6
NHAc		6.58 (d)	6.70 (d)				
$NHCOCH_3$		1.92 (s)	1.90 (s)		23.26	23.18	$NHCO\underline{C}H_3$
$OCOCH_3$		2.00,	2.00,		20.71,	20.72,	$OCO\underline{C}H_3$
		2.07 (s)	2.01,		20.61,	20.57	
			2.05 (s)		20.55		

10, **11a**: $J_{1,2}$ = 8.5 Hz, $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, $J_{NH,2}$ = 8.5 Hz.

unit F							unit F
1-H	5.41 (d)	5.03 (d)	5.18 (d)	100.22	97.92	97.67	C-1
2-H	4.55 (dd)*	3.90 (dd)	3.87 (dd)	69.84*	69.81#	78.69	C-2
3-H	4.67 (dd)*	4.00-4.22	4.08 (m, broad)	70.93*	79.44	67.69	C-3
4-H	4.85 (dd)	4.38 (dd, broad)	4.32 (m, broad)	72.05+	67.33#	70.54	C-4
5-H	4.93 (d)	4.42 (d)	4.46 (d)	72.41+	70.11	70.13	C-5
				170.39	169.34	169.53	C-6
CO_2CH_3	3.68 (s)	3.78 (s)	3.79 (s)	51.73	52.49	52.57	CO_2CH_3
OH	4.97 (s, broad)	4.00-4.30	3.92-4.29				
	6.73 (s, broad)						
	6.68 (s, broad)						

6: $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.5 Hz.
10: $J_{1,2}$ = 3.5 Hz, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 1.5 Hz.
11a: $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 10.0 Hz, $J_{4,5}$ = 1.0 Hz.

allyl group[48,49]							allyl group[48]
1-H	4.15	3.82-3.90 (m)	4.04	68.96	69.05	69.25	C-1
1'-H	4.36	4.00-4.22	4.16				

*,+Assignments based on comparison with **4a** and **4b**.
#Assignments may have to be reversed.

impurity (about 20 %)).- ^{1}H NMR (400 MHz, $CDCl_3$, COSY): see Table 5.- IR ($CHCl_3$): 3630-3100 (OH, NH), 1795 ($COCCl_3$), 1740 (CO), 1675 (amide I), 1500 cm^{-1} (amide II).- $C_{27}H_{35}Cl_3N_2O_{17}$ (765.9), MS (Cs^+, matrix: DMSO/glycerol): m/z(%) = 765[46] (36, $[M+H]^+$), 621 (37), 579 (19), 563 (21), 502 (42), 484 (41), 460 (100), 442 (23), 402 (22), 382 (18).- In a second MS experiment (Cs^+, matrix: DMSO/glycerol) the following result was obtained: m/z(%) = 330 (42, $[E]^+$),[45] 210 (35), 169 (100), 150 (98), 138 (46), 126 (78), 103 (99).

Methyl [allyl 2-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-4-O-acetyl-3-O-carbamoyl-α-D-galactopyranosid]uronate (**11c**).

The crude reaction mixture prepared from **11a** (230 mg, 398 µmol) and trichloroacetyl isocyanate as described above was filtered through SiO_2 (4.5 g, elution with hexanes-$CHCl_3$-ethanol 3:1:1) to give **11a** (8 %), and methyl [allyl-2-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-3-O-carbamoyl-α-D-galactopyranosid]uronate (4 %),[34] and as main product **11b** which was immediately acetylated with acetic anhydride-pyridine-4-dimethylaminopyridine. The reaction mixture was left at 20°C for 1 h. After addition of ethyl acetate and ethanol, solvent evaporation and MPLC (column B, hexanes-$CHCl_3$-ethanol 4:1:1) furnished **11c** (152 mg, 58 %) and **13** (60 mg, 25 %).- M.p. 119-121°C (from ethyl acetate-hexanes).- ^{1}H NMR (400 MHz, $CDCl_3$): see Table 5.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): see Table 5.- IR ($CHCl_3$): 3600-3200 (NH), 1740 (CO), 1670 (amide I), 1580, 1510 cm^{-1} (amide II).- MS (Cs^+, matrix: DMSO/glycerol); m/z(%) = 795 (1.4, $[M+Cs]^+$), 663 (3, $[M+H]^+$), 621 (1), 605 (1), 502 (1), 484 (0.4), 460 (0.4), 370 (1), 330 (66, $[E]^+$), 228 (10), 210 (35), 168 (91), 150 (9), 133 (100), 126 (59), 108 (86).- (Found: C, 49.00; H, 5.72. $C_{27}H_{38}N_2O_{17}$ (662.6) requires C, 48.94; H, 5.78).

Methyl [allyl 2-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-3-O-acetyl-4-deoxy-β-L-threo-hex-4-enopyranosid]uronate (**13**).

M.p. 138-139.5°C (from ethyl acetate-hexanes).- ^{1}H NMR (400 MHz, $CDCl_3$, COSY): see Table 5.- ^{13}C NMR (100.6 MHz, $CDCl_3$, DEPT): see Table 5.- IR ($CHCl_3$): 3600-3220 (NH), 1740 (CO), 1675 (amide I), 1505 cm^{-1} (amide II).- MS (Cs^+, matrix: DMSO/glycerol): m/z(%) = 602 (2, $[M+H]^+$), 560 (1), 542 (1), 484 (1), 443 (1), 361 (1), 330 (66, $[E]^+$),[45] 210 (32), 168 (94), 150 (82), 138 (47), 126 (76), 108 (100).- (Found: C, 52.00; H, 5.83. $C_{26}H_{35}NO_{15}$ (601.6) requires C, 51.91; H, 5.86).

Methyl 2-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-4-O-acetyl-3-O-carbamoyl-D-galactopyranuronate (**11d**).

A mixture of **11c** (200 µmol) and $PdCl_2$ (75 mg, 373 µmol) in a 0.1 molar solution of NaOAc in 20:1 acetic acid-water (4.0 ml) was stirred at 20°C for 24 h. Usual work-up (ethyl acetate) and MPLC (column A, hexanes-$CHCl_3$-ethanol 3:1:1.3) furnished **11d** (81 %); 6 % of **11c** were recovered.- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.91 (s, NHAc); 2.00 (s, OAc); 2.09 (s, OAc); 3.33-4.31 (ring protons), 3.71 (s, CO_2CH_3); 4.60-5.85 (ring protons, $-NH_2$); 6.31 (d, NHAc); 6.52 (d, NHAc). Appearance of two NHAc signals (ratio 1:1) is indicative of the two anomeric forms of **11d**.- $J_{NH,2(E)}$ = 8.5 Hz (for both signals).- IR ($CHCl_3$): 3610-3110 (OH, NH), 1730 (CO), 1665 (amide I), 1580, 1515 cm^{-1} (amide II).

Methyl 2-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-3,4-O-isopropylidene-D-galactopyranuronate (**12b**).

12b was prepared from **12a** exactly as described for **11d**. Yield 83 %.- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.30 (s, CCH_3); 1.47 (s, CCH_3); 1.90-2.10 (NHAc- and OAc-signals); 3.50-3.96 (ring protons), 3.80 (s, CO_2CH_3); 4.08-4.58 (ring protons); 4.77-5.42 (ring protons, $-NH_2$); 5.74 (d, NHAc); 5.79 (d, NHAc). Appearance of two NHAc signals (ratio 6:4) is indicative of the two anomeric forms of **12b**.- $J_{NH,2(E)}$ = 8.5 Hz (for both signals).- IR ($CHCl_3$): 3620-3150 (OH, NH), 1745 (CO), 1685 (amide I), 1520 cm^{-1} (amide II).

Table 5: ^{1}H NMR spectral data of compounds 11b, 11c, and 13 and ^{13}C NMR spectral data of 11c and 13

Assignment	^{1}H NMR data 11b	11c	13	^{13}C NMR data 11c	13	Assignment
unit E						unit E
				170.60, 170.40, 169.59#	170.41, 170.30, 170.16	$OCOCH_3$
				170.94	170.51	$NHCOCH_3$
1-H	5.05 (d)	5.11 (d)	5.20 (d)	100.66	100.02	C-1
2-H	3.77 (m)	3.72 (m)	3.67-3.79 (m)	56.04	56.27	C-2
3-H	5.29 (m)	5.57 (dd)	5.59 (dd)	74.21	71.66	C-3
4-H	5.01 (t)	5.00 (t)	4.95 (t)	68.58+	67.96+	C-4
5-H	3.78 (m)	3.38 (m)	3.31 (m)	71.57++	70.97+	C-5
CH_2-6	4.10-4.20	4.06-4.23	4.05-4.20	61.99	61.96	C-6
NHAc	6.27 (s, broad)	5.93 (d)	5.76-5.82			
$NHCOCH_3$	1.91 (s)	1.89 (s)**	1.85 (s)**	23.33	23.16	$NHCOCH_3$
$OCOCH_3$	2.00, 2.06 (s)	2.00**, 2.06** (s)	1.97**, 2.03** (s)	20.76##, 20.69##	20.96##, 20.66##, 20.60##	$OCOCH_3$

11b: $J_{1,2}$ = 8.5 Hz, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz.
11c: $J_{1,2}$ = 8.2 Hz, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, $J_{NH,2}$ = 8.0 Hz.
13: $J_{1,2}$ = 8.5 Hz, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz.

unit F						unit F
				167.78	162.08	$OCOCH_3$
				155.62		$OCONH_2$
1-H	5.20 (d)	5.22 (d)	5.31 (d)	97.75	98.51	C-1
2-H	4.22 (dd)*	3.99 (dd)	3.97 (dd)	77.20	75.56	C-2
3-H	5.11 (dd)*	5.18 (dd)	5.65 (dd)	68.81+	68.84+	C-3
4-H	4.75 (m)	5.75 (dd)	5.91 (d)	71.18++	109.24	C-4
5-H	4.56 (d)	4.61 (d)		69.87	141.15	C-5
				169.65#	169.56	C-6
CO_2CH_3	3.79 (s)	3.71 (s)	3.75 (s)	52.60	52.46	CO_2CH_3
$COCH_3$		2.09** (s)	2.07** (s)	20.64##	20.57##	$OCOCH_3$
OH	4.07-4.25					
NH/NH_2	9.75-10.50	4.95-5.06				

11b, 11c: $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.5 Hz.
13: $J_{1,2}$ = 3.0 Hz, $J_{2,3}$ = 9.0 Hz, $J_{3,4}$ = 2.8 Hz.

allyl group[48,49]						allyl group[48]
1-H	4.10	4.06-4.23	4.10-4.25	69.30	69.74	C-1
1'-H	4.21	4.06-4.23	4.10-4.25			

*Sharp signal, no coupling with the hydroxyl proton.
**,+,++,#,##Assignments may have to be reversed.

Methyl 2-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-1-O-[(2,2-dimethyl-propyl-oxy)-(2,2,2-trichloro-1,1-dimethyl-ethoxy)-phosphoryl]-3,4-O-isopropylidene-α-D-galactopyranuronate (14a).

To a solution of 1H-1,2,4-triazole (35.8 mg, 518 μmol) in 4:1 THF-pyridine (0.30 ml) 2,2,2-trichloro-1,1-dimethyl-ethyl phosphorodichlorodite (15, X = Cl) (24.8 μl, 124 μmol) was added at 0°C and the mixture was stirred at 0°C for 20 min. A solution of **12b** (65.0 mg, 113 μmol) in THF (0.80 ml) was added and the mixture was stirred at 0°C for 4 h. Then a solution of neopentyl alcohol (12.2 mg, 139 μmol) in THF (0.55 ml) was added and stirring was continued for 1 h. After solvent evaporation (25°C, argon stream) the residue was redissolved in CH_2Cl_2 (1.20 ml) and bis(trimethylsilyl)peroxide (17, 24 μl, 114 μmol) was added. Stirring at 20°C for 12 h, followed by solvent evaporation (25°C, argon stream) and MPLC (column A, hexanes-ethyl acetate-ethanol-triethylamine[47] 5:1:1:0.07) gave **14a** (23 mg, 23 %); 26 mg (41 %) of **12b** were recovered.- ^{1}H NMR (80 MHz, [D_5] pyridine): δ = 0.94 (s, 6H, $CH_2C(C\underline{H}_3)_3$); 1.06 (s, 3H, $CH_2C(C\underline{H}_3)_3$); 1.40 and 1.50 (2s, 6H, isopropylidene CH_3); 1.95-2.22 (18H, OAc, $C(CH_3)_2CCl_3$ signals); 3.77 (s, 3H, CO_2CH_3); 3.93 and 4.01 (2H, $C\underline{H}_2C(CH_3)_3$); 4.01-5.05 (7H, CH_2-6^E, ring protons); 5.27-5.60 (3H, ring protons); 5.71-6.04 (1H, ring proton), 6.45 (dd, 1H, 1-H^F); 9.33 (d, broad, 1H, N$\underline{H}$Ac).- $J_{1,2(F)}$ = 3.2 Hz, $J_{1,P(F)}$ = 5.5 Hz, $J_{NH,2(E)}$ = 9.0 Hz.- IR ($CHCl_3$): 3650-3200 (NH), 1750 (CO), 1695 (amide I), 1515 cm^{-1} (amide II).- $C_{33}H_{51}Cl_3NO_{18}P$ (887.1), MS (Xe, matrix: glycerol); m/z(%) = 886 (3, $[M+H]^+$), 728 (3), 560 (14, $[EF]^+$), 518 (3), 502 (7), 484 (5), 460 (5), 330 (99, $[E]^+$),[45] 278 (12), 270 (13), 210 (45), 168 (86), 150 (100), 138 (36), 126 (57), 118 (38), 108 (65).

Methyl 2-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-1-O-[(2,2-dimethylpropyl-oxy)-hydroxy-phosphoryl]-3,4-O-isopropylidene-α-D-galactopyranuronate (14b), triethylammonium salt.

To a solution of **14a** (5.6 mg, 6.3 μmol) in pyridine (0.2 ml) Zn-Cu couple (4.2 mg) and 2,4-pentanedione (10 μl) were added and the mixture was stirred under argon at 20°C for 4 h. Solids were filtered off, washed with ethyl acetate and methanol, and the combined filtrates were evaporated after addition of toluene. LC (SiO_2 (2.1 g), ethyl acetate-methanol-triethylamine 5:1:0.5) furnished the triethylammonium salt of **14b** (6 mg, 100 %).- ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 9H, $CH_2C(C\underline{H}_3)_3$); 1.32 and 1.47 (2 s, 6H, isopropylidene CH_3); 1.95 (s, 3H, NHAc); 2.00 (s, 6H, OAc); 2.06 (s, 3H, OAc); 3.49-3.57 (2H, $C\underline{H}_2C(CH_3)_3$); 3.62-3.68 (1H, ring proton); 3.74-3.85 (1H, ring proton); 3.78 (s, 3H, CO_2CH_3); 3.97-4.01 (1H, ring proton); 4.06 and 4.20 (2H, CH_2-6^E); 4.39 (dd, 1H, 3-H^F); 4.48 (dd, 1H, 4-H^F); 4.98 (t, 1H, 4-H^E); 4.99 (d, 1H, 5-H^F); 5.05 (d, 1H, 1-H^E); 5.26 (dd, 1H, 3-H^E); 5.65 (dd, 1H, 1-H^F); 6.52 (d, broad, 1H, N$\underline{H}$Ac).- $J_{1,2(F)}$ = 3.2 Hz, $J_{1,P(F)}$ = 7.2 Hz, $J_{2,3(F)}$ = 7.5 Hz, $J_{3,4(F)}$ = 5.5 Hz, $J_{4,5(F)}$ = 2.5 Hz.- $J_{1,2(E)}$ = 8.5 Hz, $J_{2,3(E)}$ = 10.5 Hz, $J_{3,4(E)}$ = $J_{4,5(E)}$ = 9.5 Hz, $J_{NH,2(E)}$ = 8.0 Hz, $J_{5,6(E)}$ = 2.5 Hz, $J_{5,6'(E)}$ = 5.0 Hz, $|J_{6,6'(E)}|$ = 12.0 Hz.

Preparation of 14c, 14d, and 18.

General procedures:

a) To a solution of 1H-1,2,4-triazole (95.0 mg, 1.37 mmol) in 4:1 CH_2Cl_2-pyridine (1.50 ml) **15** (X = Cl) (60.0 μl, 300 μmol) was added at 0°C and the mixture was stirred at 0°C for 10 min. The disaccharide (**11d** or **12b**) (265 μmol), dissolved in CH_2Cl_2 (1.35 ml), was added and the mixture was stirred at 0°C for 4 h. Then a solution of methyl (R)-3-hydroxy-2-(3,8,8,11,14,18-hexamethyl-nonadecyloxy)-propionate (**16**, 216 mg, 460 μmol) in CH_2Cl_2 (1.50 ml) was added. After 40 min and 110 min at 0°C additional amounts of **16** (70.6 mg, 150 μmol in each case, dissolved in CH_2Cl_2 (0.3 ml)) were added. Stirring at 0°C was continued for a total of 3 h. Then bis(trimethylsilyl)peroxide (17, 80.0 μl, 377 μmol) was added at 0°C and the mixture was stirred at 20°C for 15 h and then filtered through SiO_2. The filtrate was evaporated, the residue taken up in pyridine (5.4 ml) and then Zn-Cu couple (234 mg) and 2,4-pentandione (272 μl) were added and the mixture was stirred under argon at

20°C for 4 h. Solids were filtered off, washed with ethyl acetate and methanol and the combined filtrates were evaporated after addition of toluene.

b) The general procedure a) was used. After oxidation with bis(trimethylsilyl)peroxide and filtration through SiO_2, the filtrate was evaporated and the residue was separated by MPLC to give the pure phosphoric acid triester.

c) From the pure triester obtained using method b) the 2,2,2-trichloro-1,1-dimethyl-ethyl protecting group was reductively (Zn-Cu couple) removed as described in a).

Methyl 2-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-ß-D-glucopyranosyl)-3,4-O-isopropylidene-1-O-{[(R)-2-methoxycarbonyl-2-(3,8,8,11,14,18-hexamethyl-nonadecyloxy)-ethoxy]-(2,2,2-trichloro-1,1-dimethylethoxy)-phosphoryl}-α-D-galactopyranuronate (14c).

Pure **14c** was obtained using the general procedure b) (column B, hexanes-ethyl acetate-ethanol-triethylamine 7:1:1:0.08). Yields: 20 % of **14c** and 12 % of a compound supposed to be the ß-anomer.[34]- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 0.77-1.00 (21H, I); 1.03-1.40 (28H, I); 1.36 (s, 3H) and 1.52 (s, 3H, isopropylidene CH_3); 1.89-2.00 (9H, NHAc, $C(CH_3)_2CCl_3$); 2.02 (s, 6H, OAc); 2.09 (s, 3H, OAc); 3.43-3.91 (10H, ring protons), containing 3.78-3.83 (4s, 6H, CO_2CH_3); 3.91-4.60 (8H, ring protons); 4.85-5.86 (5H, ring protons, $-NH_2$); 5.95 (dd, 1H, 1-H^F).- $J_{1,2(F)}$ = 3.3 Hz, $J_{1,P(F)}$ = 6.2 Hz.

Methyl 2-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-ß-D-glucopyranosyl)-3,4-O-isopropylidene-1-O-{[(R)-2-methoxycarbonyl-2-(3,8,8,11,14,18-hexamethyl-nonadecyloxy)-ethoxy]-hydroxy-phosphoryl}-α-D-galactopyranuronate (**14d**), triethylammonium salt.

i) From **14c** pure **14d** was obtained using the general procedure c) followed by MPLC (column A, short, ethyl acetate-methanol-triethylamine 9:1:0.5). Yield: 100 %.
ii) The general procedure a) was used. For filtration of the phosphate-triester through SiO_2 (vide supra) hexanes-ethyl acetate-ethanol 2:1:1 was used as eluent. **14d** was purified by MPLC (column B, ethyl acetate-methanol-triethylamine 10:1:0.4). Yield: 22 % of **14d**, alongside with a compound presumed to be the ß-anomer (11 %);[34] 36 % of **12b** were recovered.
^{1}H NMR (80 MHz, $CDCl_3$): δ = 0.70-0.99 (21H, I); 1.00-1.45 (28H, I); 1.31 (t, $(CH_3CH_2)_3NH^+$); 1.32 (s, 3H) and 1.49 (s, 3H, isopropylidene-CH_3); 1.95 (s, 3H, NHAc); 2.00 (s, 6H, OAc); 2.05 (s, 3H, OAc); 3.03 (q, $(CH_3CH_2)_3NH^+$); 3.40-3.83 (10H, ring protons), containing 3.72 (s, 3H, CO_2CH_3) and 3.79 (s, 3H, CO_2CH_3); 4.00-4.56 (7H, ring protons); 4.82-5.48 (4H, ring protons, $-NH_2$); 5.59 (dd, 1H, 1-H^F); 6.59 (d, 1H, NHAc).- $J_{1,2(F)}$ = 3.3 Hz, $J_{1,P(F)}$ = 7.5 Hz, $J_{NH,2(E)}$ = 8.0 Hz.- ^{13}C NMR (100.6 MHz, [D_6] acetone, DEPT): see Table 6.- IR ($CHCl_3$): 3600-3200 (NH), 1740 (CO), 1670 (amide I), 1525 cm^{-1} (amide II).- $C_{53}H_{92}NO_{21}P$ (1110.3), MS (Xe, matrix: glycerol): m/z(%) = 1154 (100, $[M+2Na-H]^+$), 1132 (59, $[M+Na]^+$), 1110 (14, $[M+H]^+$), 1096 (32), 855 (13), 818 (9), 803 (14), 802 (6), 702 (13), 574 (4), 573 (9, $[GHI+Na]^+$).

Methyl 2-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-ß-D-glucopyranosyl)-4-O-acetyl-3-O-carbamoyl-1-O-{[(R)-2-methoxycarbonyl-2-(3,8,8,11,14,18-hexamethyl-nonadecyloxy)-ethoxy]-hydroxy-phosphoryl}-α-D-galactopyranuronate (**18**), triethylammonium salt.

The general procedure a) was used. For the crude triester filtration through SiO_2 elution was performed with hexanes-ethyl acetate-ethanol-triethylamine 3:2:1:0.02 (20 % of **11d** were recovered at this stage). Purification of **18** by LC (ethyl acetate-methanol-triethylamine 7:1:0.3) provided **18** in 21 % yield alongside with the ß-anomer (7 %);[34] 16 % of **11d** were recovered.-^{1}H NMR (400 MHz, [D_5] pyridine, COSY, ^{1}H,^{13}C correlation): see Table 6.- ^{13}C NMR (100.6 MHz, [D_5] pyridine, DEPT): see Table 6.- IR ($CHCl_3$): 3620-3220 (NH), 1745 (CO), 1670 (amide I), 1590, 1540 cm^{-1} (amide II).- $C_{53}H_{91}N_2O_{23}P$ (1155.3), MS (Xe, matrix: triethanolamine): m/z(%) = 1194 (8, $[M+K]^+$), 1178 (18,

Table 6: ^{1}H NMR data of **18** and ^{13}C NMR data of compounds **2**, **18**, **19**, and **14d**

^{1}H NMR spectral data		^{13}C NMR spectral data				
Assignment	**18**	**14d**	**18**	**19**	**2**	Assignment
unit E						unit E
$\underline{C}OCH_3$		171.68, 171.02, 170.47	170.98, 170.75, 170.48			$O\underline{C}OCH_3$
$NH\underline{C}OCH_3$		172.14	171.63	169.2	169.4	$NH\underline{C}OCH_3$
1-H	5.72 (d)	100.59	101.51	102.6	102.7	C-1
2-H	4.33 (m)	55.05	55.43	55.5	55.5	C-2
3-H	5.95 (dd)	74.59	73.52	74.1	74.3	C-3
4-H	5.43 (t)	69.34*	69.69	70.7	70.7	C-4
5-H	3.89-3.96 (m)	72.61**	72.03	77.1	77.0	C-5
6-H	4.40 (m)	62.91	62.47	61.1	61.1	C-6
6'-H	4.55 (m)					
NHAc	9.13 (d)					
$NHCOCH_3$	1.91 (s)	23.32	23.40	23.0	23.1	$NHCO\underline{C}H_3$
$OCOCH_3$	2.06, 2.02, 1.99 (s)	20.88, 20.71, 20.67	20.74+, 20.66+, 20.54+			$OCO\underline{C}H_3$

18: $J_{1,2}$ = 8.5 Hz, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, $J_{NH,2}$ = 8.5 Hz, $|J_{6,6'}|$ = 12.0 Hz, $J_{5,6}$ = 2.5 Hz, $J_{5,6'}$ = 4.3 Hz.

unit F						unit F
			168.37	168.8		$O\underline{C}OCH_3$
$CONH_2$	5.05-5.55		157.12	155.8	156.4	$\underline{C}ONH_2$
		110.18				$(CH_3)_2\underline{C}$
1-H	6.53 (dd)	93.99	95.88	93.7	94.1	C-1
2-H	4.66	75.59	75.47	75.5	75.1	C-2
3-H	5.96 (dd)	71.11**	68.87	67.9	67.9	C-3
4-H	6.42 (dd)	73.23**	71.01	?	72.6	C-4
5-H	5.49 (d)	69.94*	69.94	69.6	?	C-5
		170.01++	169.86++	168.4++	170.4++	C-6
CO_2CH_3	3.75# (s)	52.29#	51.87#			$CO_2\underline{C}H_3$
$OCOCH_3$	2.23 (s)		20.42+	19.9		$OCO\underline{C}H_3$

18: $J_{1,2}$ = 3.5 Hz, $J_{1,P}$ = 7.0 Hz, $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.5 Hz, $|^{2}J_{C,P}|$ = 5.9 Hz, $|^{3}J_{C,P}|$ = 8.1 Hz.

unit G						unit G
$HN^{+}(C\underline{H}_2CH_3)_3$	3.04 (q)		45.79	45.4	45.3	$HN^{+}(\underline{C}H_2CH_3)_3$
$HN^{+}(CH_2C\underline{H}_3)_3$	1.28 (t)		8.75	8.7	8.6	$HN^{+}(CH_2\underline{C}H_3)_3$
unit H						unit H
C-1		169.81++	169.71++	172.2++	172.1++	C-1
2-H	4.51 (dd)	79.57	79.58	79.1	79.0	C-2
3-H	4.60-4.69 (m)	66.37	66.47	65.4	65.1	C-3
3'-H	4.71-4.79 (m)					
CO_2CH_3	3.68# (s)	52.68#	52.13#			$CO_2\underline{C}H_3$

18: $J_{2,3}$ = 4.5 Hz, $J_{2,3'}$ = 6.0 Hz, $|^{2}J_{C,P}|$ = 4.0 Hz, $|^{3}J_{C,P}|$ = 8.0 Hz. **14d**: $|^{3}J_{C,P}|$ = 8.0 Hz.

unit I						unit I
1-H	3.60-3.75	69.75	69.61	67.9	67.9	C-1
1'-H	3.77-3.86 (m)					
		33.09	32.70	32.2	32.2	C-8

14d: $|^{5}J_{C,P}|$ = 4.5 Hz, $|^{3}J_{C,P}|$ = 8.0 Hz.

#,+,++,*,** Assignments may have to be reversed.

$[M+Na]^+$), 1156 (2, $[M+H]^+$), 1136 (2), 1118 (2), 739 (4), 683 (3), 622 (2), 605 (5, $[EF]^+$), 590 (19), 573 (11, $[GHI+Na]^+$), 551 (4, $[GHI+H]^+$), 391 (2), 330 (100, $[E]^+$).[45]

Deprotecting of **18**.

To a solution of **18** (25.5 mg, 20.3 µmol) in anhydrous THF (2.35 ml) at 0°C a 0.29 molar aq. LiOH (570 µl) was added, and the mixture was stirred at 0°C for 90 min. Excess base was neutralized by addition of Dowex 50 W-X2 (H^+-Form, 100-200 mesh). Filtration, lyophilization, and MPLC (column A, $CHCl_3$-methanol-water 10:6:1) furnished **19** (7 mg, 32 %), **2** (13 mg, 61 %), and a fraction (2 mg) containing **19** and **2**.

2-O-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-4-O-acetyl-3-O-carbamoyl-1-O-{[(R)-2-carboxy-2-(3,8,8,11,14,18-hexamethyl-nonadecyloxy)-ethoxy]-hydroxy-phosphoryl}-α-D-galactopyranuronic acid (**19**).

The analytical sample was further purified by reversed-phase LC (HP 20, elution with water-methanol 10:0 to 0:10), followed by reversed phase MPLC (column A, 19 g of RP 18, methanol-water-acetonitrile 8:1:4).- ^{13}C NMR (100.6 MHz, [D_6] DMSO): see Table 6.- $C_{45}H_{81}N_2O_{20}P$ (1001.1), MS (Xe, matrix: triethanolamine): m/z(%) = 1062 (4, $[M+K+Na-H]^+$), 1046 (9, $[M+2Na-H]^+$), 1024 (5, $[M+Na]^+$), 1002 (4, $[M+H]^+$), 871 (2.7), 746 (4.7), 744 (3.8), 597 (6, $[GHI+K+Na-H]^+$), 581 (9, $[GHI+2Na-H]^+$), 560 (9), 557 (4), 487 (4, $[EF+Na]^+$), 337 (15), 286 (16), 241 (100).

2-O-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-3-O-carbamoyl-1-O-{[(R)-2-carboxy-2-(3,8,8,11,14,18-hexamethyl-nonadecyloxy)-ethoxy]-hydroxy-phosphoryl}-α-D-galactopyranuronic acid (**2**).

The analytical sample was further purified by reversed-phase MPLC (column A, 19 g of RP 18, methanol-water-acetonitrile 8:1:4).- ^{13}C NMR (100.6 MHz, [D_6] DMSO): see Table 6.- $C_{43}H_{79}N_2O_{19}P$ (959.0), MS (Xe, matrix: triethanolamine): m/z(%) = 1020 (11, $M+K+Na-H]^+$), 1004 (25, $[M+2Na-H]^+$), 998 (14, $[M+K]^+$), 982 (46, $[M+Na]^+$), 727 (10), 725 (27), 598 (17), 581 (30, $[GHI+2Na-H]^+$), 560 (73), 544 (12), 445 (20, $[EF+Na]^+$), 337 (58), 321 (68), 299 (100).

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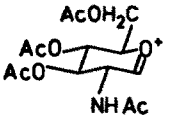
45) $[E]^+$ = 

46) Calculated for ^{35}Cl.

47) Addition of triethylamine to the solvent mixture was necessary, otherwise (for example with hexanes-$CHCl_3$-ethanol 7:1:1) extensive decomposition to **12b** occurred.

48) Only the signals of CH_2-1 and C-1, respectively, are recorded. A full account of all resonances is given in ref.[34]

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