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Synthesis of a complex disaccharide precursor of phosphonate analogues of the antibiotic moenomycin A_{12}

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Abstract—An approach for the synthesis of moenomycin A_{12} C-glycoside partial structures is reported.

1. Introduction

In view of the problem of antibiotic resistance[1] anti-infectives with novel modes of action are desperately needed. The transglycosylation reaction,[2] the penultimate step in the biosynthesis of peptidoglycan (the main structural polymer of the bacterial cell wall), occurs at the outside of the cytoplasmic membrane and is catalyzed by membrane proteins designated as bifunctional (class A) high-molecular mass penicillin-binding proteins (PBPs).[3] The reaction came recently into focus as a promising new target for a number of reasons: (i) the methods for isolating the enzyme(s) involved have improved considerably;[4,5] (ii) a monofunctional glycosyltransferase from *Staphylococcus aureus* that shares considerable homology with the transglycosylase domain of bifunctional (class A) high-molecular mass PBPs has been expressed as a truncated protein lacking the membrane domain and purified to homogeneity;[6] (iii) one of the two substrates of the transglycosylation step, the so-called lipid II, can now be made in sufficient amounts;[7] (iv) new and efficient in vitro test systems have been developed which conveniently allow to monitor the inhibition of the incorporation of lipid II into uncross-linked peptidoglycan,[7,8] and binding of inhibitors to the enzyme, respectively.[9]

The assembly of the peptidoglycan polysaccharide strands from lipid II is blocked by certain glycopeptides,[10] ramoplanin,[11] lantibiotics such as nisin,[12] and the moenomycin-type antibiotics.[13] Of these, the moenomycins (see Fig. 1) are the only compounds known to inhibit the enzyme itself[2] (i.e. the transglycosylase domain of the bifunctional

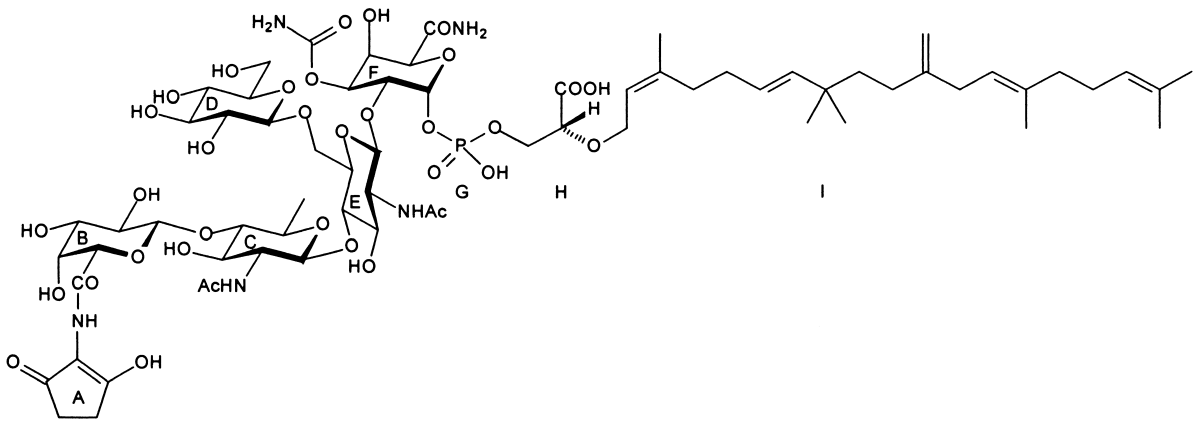

Figure 1. Moenomycin A_{12}.

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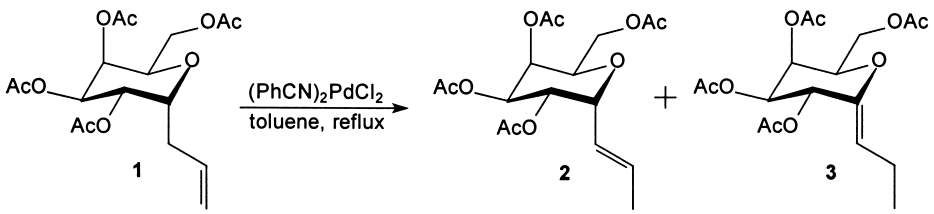


Scheme 1.

high-molecular PBPs), whereas ramoplanin and nisin interfere with lipid II. The mechanism of the glycopeptides that inhibit the transglycosylation reaction is not clear.[14] The moenomycins are, thus, unique tools for investigating both the transglycosylation step and the corresponding enzyme(s). In addition, they are highly promising lead compounds for new anti-infectives. Based on structure–activity relationships,[15] a mechanism for their mode of action has been proposed.[4,16–18] It is assumed that they are anchored to the cytoplasmic membrane via the lipid part[19] and bind then highly selectively to the binding site of the growing polysaccharide strand at the enzyme via the C-E-F trisaccharide.

The moenomycins do not induce resistance readily. However, a weak point in this respect may be the phosphate bond at unit F. Its cleavage by a yet poorly characterized enzyme is the only enzymatic degradation reaction of the moenomycins that is known to date.[20] Furthermore, some analogues which we expected to be antibiotically active were devoid of antibiotic activity. It has been speculated that these compounds are used as substrates by the transglycosylase.[17] With this in mind we started a program aimed at synthesizing analogues of moenomycin A_{12} in which the phosphate oxygen at C-1 of unit F is replaced by a CH_2 group.[21] It seemed important to retain all other functional groups in ring F as present in moenomycin A_{12} since they are known to be of major importance as far as antibiotic activity is concerned. Some mono- and disaccharide phosphonate models of moenomycin A have already been prepared by Qiao and Vederas[22] and by Brooks et al.[23] but obviously the structures were too simple to elicit antibiotic activity.[22,23]

2. Synthetic design

We decided to disconnect the target structure as indicated in formula **A** to give a precursor of type **B** (Scheme 1). **A** would be available from C-glycoside **B** (X=Br) by an Arbuzov reaction.[23] We have recently reported on a new approach for the synthesis of such C-glycosides which started from a tartaric acid-derived aldehyde of general structure **D** and a C-3 allyl stannane such as **E** to give an open-chain olefin of type **F**. Subsequent mercuric ion-induced cyclization and trapping the organomercurial provided **B** (X=I).[24] In the present publication, we describe a new synthetic approach which started from D-galactose (**C**, Fig. 2). For the synthesis of C-glycosides from ordinary sugars many methods exist. Carbocation, carbanion and radical chemistry can be used to add carbon appendages to C-1 of the starting sugar.[25]

3. Results and discussion

3.1. Synthesis of glycosyl acceptors 8c and 11d

Commercially available β-D-galactose-pentaacetate on BF_3-mediated reaction with allyltrimethylsilane was converted into 2,6-anhydro-7,8,9-trideoxy-D-*glycero*-L-*galacto*-non-8-enitol (**1**) as described by Giannis and

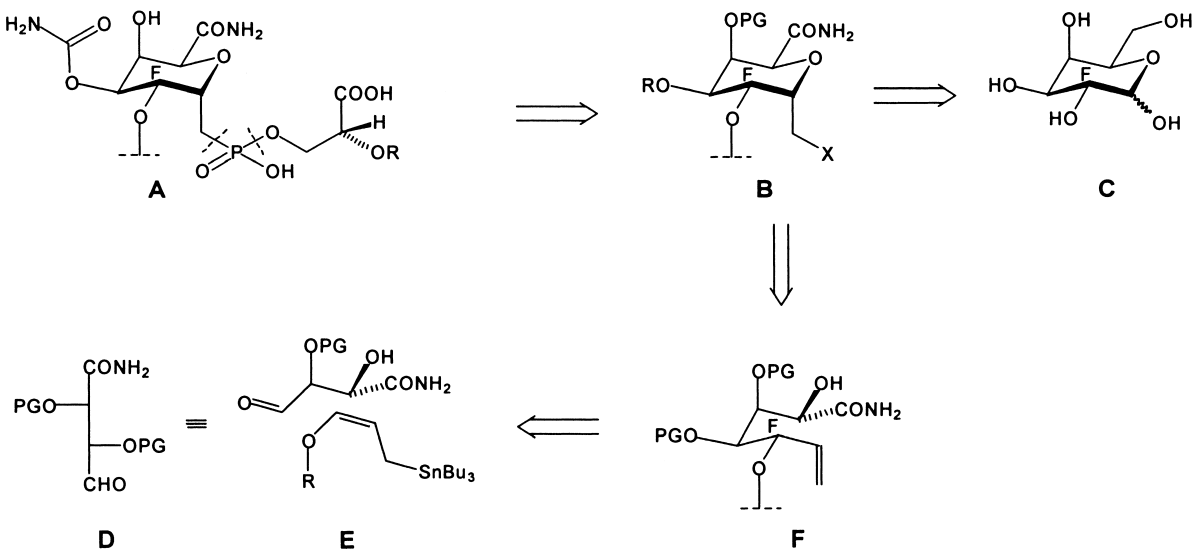
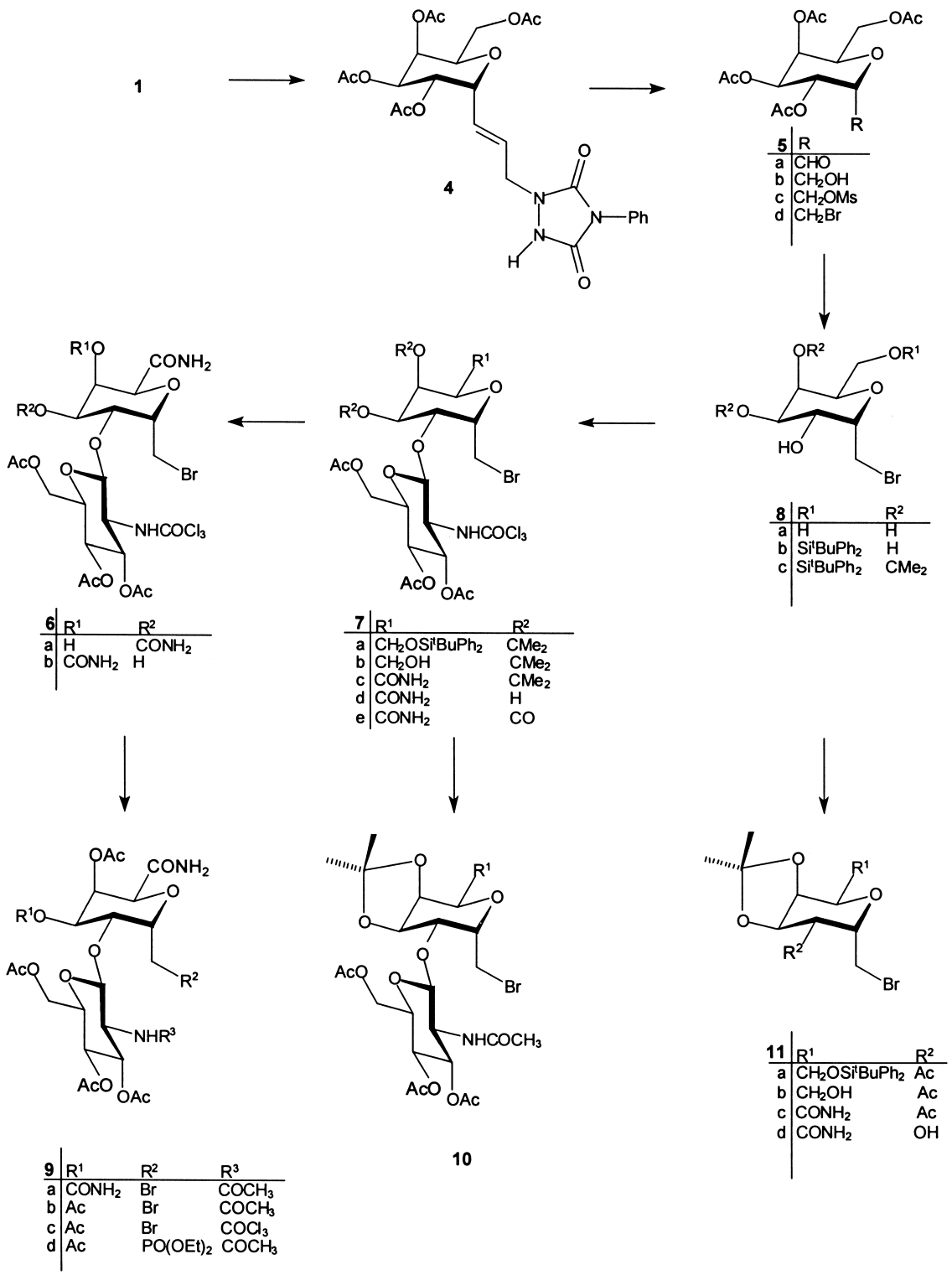


Figure 2. Synthetic design.



Scheme 2.

Sandhoff[26] The C_9 compound **1** had to be degraded to a C_7 compound after shifting of the double bond. It is well known that double bonds can be moved to thermodynamically more stable positions in palladium-mediated reactions. This approach that has been employed by Brooks et al.[23] was described to be not completely satisfactory since product mixtures resulted.

In the present work, the same observation was made (Scheme 1). When compound **1** was refluxed in toluene with varying amounts of bis(benzonitrile)palladium(II) chloride, TLC (using several solvent mixtures) showed a major spot with exactly the same R_f value as **1** and a minor spot with a slightly larger R_f. The major spot according to ^{13}C NMR corresponded to a 1:1 mixture of **1** and **2**. The CH_3 signal of

2 appeared at δ=18, while the CH_2 vinylic signals of the starting material appeared at δ=31. In the δ=115–135 range, the olefinic signals of the starting material **1** appeared at δ=118 and 133, whereas the signals at δ=119 and 123 were assigned to the olefinic carbons of product **2**. Changing the amount of the catalyst and the reaction time did not affect the result. The by-product, a white solid, was **3** according to the spectra. When a mixture of the two compounds **1** and **2** was ozonolyzed, again compounds with very close R_f values have been obtained (data not reported). As a conclusion, we preferred to look for a more practical route for the double bond rearrangement in compound **1**. Use of an ene reaction was an obvious option. An attempt in this direction was made using singlet oxygen. The photooxidation of **1** was tested using methylene blue and Rose bengal as sensitizers and methanol and dichloromethane as solvents. In neither case, a reaction was observed as indicated by TLC, using different eluents. Guided by this result we looked for a more reactive reagent. A good choice seemed to be 4-phenyl-3*H*-1,2,4-triazoline-3,5-dione (PTAD).[27–29] Compound **1** on reaction with PTAD in dichloromethane at rt provided **4** in 83% yield. Unreacted alkene (13%) were recovered (Scheme 2). The typical red color of PTAD was quickly discharged when PTAD was mixed with the alkene. Ozonolysis of **4** in dry CH_2Cl_2–MeOH (10:1) at −70°C, and subsequent quenching with dimethyl sulfide led to aldehyde **5a**. No effort has been made to obtain pure samples of the aldehyde. Reduction of the crude ozonolysis products of **4** with sodium acetoxyborohydride[23] (prepared in situ from $NaBH_4$ and AcOH in THF) furnished primary alcohol **5b** in a non-satisfying yield of 42%. An identified problem was the ready elimination of acetic acid to give the α,β-unsaturated aldehyde **12** (Fig. 3). The formation of this glycal was completely suppressed under dry conditions. When the reaction was performed using freshly distilled THF and acetic acid, the yield increased up to 85% with no trace of the aldehyde **12** observable by TLC. The primary hydroxyl group of **5b** was mesylated,[23] using methanesulfonyl chloride in pyridine, in the presence of catalytic amount of *p*-dimethylaminopyridine (DMAP) at 4°C to give methanesulfonate **5c** in 60% yield. The mesylate **5c** was converted in turn into **5d** (80%) when heated in toluene at 80°C with tetrabutylammonium bromide.[23] Hydrolysis of the acetate groups without harming the primary bromide was accomplished making use of the Zemplén method[30] (quantitative yield of **8a**). The primary hydroxyl group of **8a** was protected as *t*-butyldiphenylsilylether. Treatment of **8a** with *t*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of bases such as pyridine and triethylamine and catalytic amount of DMAP at 0°C yielded **8b** in 33% yield. On the other hand, treatment of **8a** with TBDPSCl in *N*,*N*′-dimethylformamide (DMF) solution in the presence of imidazole at 0°C afforded the 6-(*t*-butyldiphenylsilyl) ether **8b** in 85% yield. The free hydroxyl groups at C-3 and C-4 in compound **8b** were protected by acid-catalyzed acetonide formation with 2,2-dimethoxypropane in dry acetone to give **8c** in 88% yield.[31]

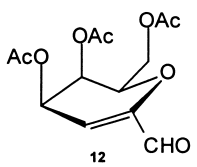


Figure 3.

As discussed above, the amide group at position 1 in unit F (position 6 in normal moenomycin analogues) is essential for the biological activity. Therefore, acceptor **8c** was converted into **11d**, which we planned to use as an alternative glycosyl acceptor. The hydroxyl group in **8c** was protected by acetylation to give **11a** (88%), the silyl ether of which was cleaved with a molar solution of TBAF in THF at rt, affording **11b** in 87% yield. The free hydroxyl group was then subjected to an oxidation using the TEMPO method (Flitsch conditions[32]) affording an aldehyde which was in turn oxidized with sodium chlorite[17] to the corresponding acid. The acid was converted into amide **11c**, making use of Staab's method.[33,34] The overall yield was 95%. The required glycosyl acceptor **11d** was obtained in quantitative yield by cleavage of the ester bond at position 5 under Zemplén conditions.

3.2. Disaccharide formation

Disaccharide formation was attempted employing the Jacquinet and Blatter method,[35] which involves the use of glycosyl donor 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-α-D-glucopyranosyl trichloroacetamidate and TMSOTf a promoter. No reaction was observed between this donor and acceptor **11d**, which may reflect the low nucleophilicity of the acceptor. On the contrary, glycosylation with acceptor **8c** gave **7a** in 79% yield. The reaction conditions had to be carefully optimized. A reaction time not longer than 10 min and 0°C are required to furnish **7a** in good yield. It was noticed by TLC that on longer reaction times decomposition occurred to give many products, and the desired disaccharide was obtained in low yield. Deprotection of the silyl group in disaccharide **7a** was easily accomplished on treatment with a molar solution of TBAF in THF at rt affording **7b** (89%). It should be recognized that the bromomethyl group survived the reaction conditions. Synthesis of the uronamide **7c** from **7b** was achieved in an overall yield of 98% by: (i) oxidation of the primary hydroxyl group in unit F to the corresponding aldehyde with sodium hypochlorite and TEMPO; (ii) oxidation of the crude aldehyde to the carboxylic acid with sodium chlorite; (iii) amide formation according to Staab. Removal of the isopropylidene group from **8c** with trifluoroacetic acid (TFA) at rt furnished diol **8d** (89%). No reaction was noticed when **8c** was treated with 80% AcOH at rt for 17 h.

3.3. Final reactions

For the introduction of the carbamoyl group into moenomycin analogues a number of methods have successfully been used, i.e. the reaction with trichloroacetylisocyanate (TAI)[36] to give the trichloroacetylurethane and subsequent removal of the trichloroacetyl group.[37,38] or the McLamore et al.[39] method which consists of the reaction with phenyl chloroformate to give the phenyl carbonate and subsequent treatment with ammonia.[15] An alternative method to form the urethane is the conversion of a 1,2-diol into the

corresponding cyclic carbonate. The carbonate ring can then be opened with ammonia from both sides in a non-selective reaction, thus leading to two isomeric *O*-carbamoyl compounds.[40,41] We found (vide infra) the 4-*O*-carbamoyl group in the C-glycosides of type **6a** to be much more base-labile than in the normal moenomycin unit F-type compounds that we have studied before. The reason may be that in the normal compounds the electron-withdrawing anomeric oxygen stabilizes the urethane. Thus, in the C-glycosides we were unable to prepare the urethane making use of the trichloroacetyl isocyanate procedure.[42] When we tried to apply the method of McLamore et al., the cyclic carbonate **7e** was formed in 72% yield reflecting again the instability of the urethane. The cyclic carbonate **7e** was also obtained on reaction of **7d** with carbonyl diimidazole (CDI) in CH_2Cl_2 solution (84%). Subsequent opening of the carbonate ring by bubbling a stream of gaseous ammonia into the CH_2Cl_2 solution at 0°C gave **6a** (62%) as well as its isomer **6b** (21%). Separation of the two isomers by MPLC was difficult and time consuming. Flash chromatography as well as reversed-phase chromatography were unsuccessful. Both isomers were fully characterized by two-dimensional NMR including H,H COSY, HMQC and HMBC. The 3- and the 4-*O*-carbamoyl derivatives were readily distinguishable. The 4-H signal of the 4-*O*-carbamoyl derivative **6a** was observed as a doublet of doublets at δ=5.68 with coupling constants of 3.5 and 8.3 Hz, as expected for an axial proton. In contrast, the 3-H signal of the 3-*O*-carbamoyl derivative **6b** was observed at δ=6.47 as a broad singlet.

It was clear from the beginning that for the dehalogenation of the N-trichloroacetyl group some of the usual reductive methods (radical dehalogenation with tributyltin hydride,[43–45] or $(Me_3Si)_3SiH$,[46] activated zinc–acetic acid in THF,[47] or activated Zn–Cu couple in acetic acid[15,48]) were unsuitable because of the presence of CH_2Br group. Unfortunately, many other methods that we tried were not compatible with the carbonate in **7e** and the carbamoyl group in urethane **6a**, respectively. Hydrolysis of **7e** with 0.5 M LiOH in MeOH–THF (1:1)[49] followed by acetylation gave **9c** (73%), while reduction of **7e** with $NaBH_4$ in ethanol[50,51] followed by acetylation gave **9b** (60°C, 85%; rt, 83%). Similarly, attempted reduction of **6a** with $NaBH_4$ in ethanol at 60°C followed by acetylation gave **9b** (78%), whereas performing the reduction step at 5°C (THF–MeOH, 4:1) or at rt (ethanol or isopropanol) gave **9c** in an average yield of 65%. The reaction between the N-trichloroacetyl group and $NaBH_3CN$ was fruitless. In one experiment ($NaBH_4$, EtOH, rt, then Ac_2O, pyridine, rt), the desired compound **9a** was formed in 42% yield accompanied by **9b** (46%). This result shows that it is possible to perform the conversion of **6a** to **9a** as desired. However, until now the reaction is capricous. The structure of **9a** was fully confirmed by ^1H and ^{13}C NMR as well as by high resolution ESI FT ICR mass spectrometry. The phosphonate grouping was installed making use of the Arbuzov reaction. **9d** was obtained from **9b** in 70% yield.

In conclusion, we have shown that C-glycoside **1** can easily be converted into structural analogues of unit F of the moenomycins.

4. Experimental

4.1. Methods and materials

See Ref. 52.

4.2. Pd-mediated rearrangement of 1

1 (1.00 g, 2.69 mmol) was added to a solution of bis(benzonitrile)palladium(II) chloride (0.15 g, 0.15 equiv.; 0.40 mmol) in dry toluene (200 mL) under an argon atmosphere. The reaction mixture was refluxed for 5 days. The reaction progress was controlled by TLC (e.g. ethyl acetate–petroleum ether 1:2) which showed the presence of a major spot with the same R_f value as the reactant **1**. The reaction mixture was filtered, evaporated, and chromatographed twice with ethyl acetate–petroleum ether 1:2. Evaporation of the solvents gave 0.98 g of a yellow oil, which appeared as a single spot, but was a 1:1 mixture of **1** and **2** as indicated by ^{13}C NMR. Furthermore, 0.005 g of **3** were obtained. Characteristic signals of **2** at δ=18 (CH_3), 119 and 123 (olefinic carbons). Characteristic signals of **1** at δ=31 (=CH_2), 118 and 133 (olefinic carbons).

4.2.1. 1,3,4,5-Tetra-*O*-acetyl-2,6-anhydro-7,8,9-trideoxy-D-*glycero*-L-*galacto*-non-6-enitol (3). R_f: 0.26 (ethyl acetate–petroleum ether 1:2). IR (KBr): $\tilde{\nu}$=1754 cm^{-1}. ^1H NMR (H,H COSY, 200 MHz, $CDCl_3$): δ=0.95 (t, 3H, CH_3-9, J=7.6 Hz), 2.00, 2.06, 2.12, 2.15 (4s, 12H, 4×CH_3COO), 2.22–2.25 (m, 2H, CH_2-8), 3.95 (ddd, 1H, 2-H, J=1.7, 5.7, 7.2 Hz), 4.14 (dd, 1H, 1-H, J=5.7, 11.4 Hz), 4.24 (dd, 1H, 1-H′, J=7.2, 11.4 Hz), 4.89 (dt, 1H, 7-H, J=1.8, 7.4 Hz), 5.02 (dd, 1H, 4-H, J=3.4, 9.9 Hz), 5.50 (dd, 1H, 3-H, J=1.7, 3.4 Hz), 5.62 (m, 1H, 5-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.48 (C-9), 17.99 (C-8), 21.04, 21.21 (4×*C*H_3COO), 62.13 (C-1), 67.68, 68.12, 71.97, 75.88, 114.71 (C-7), 145.56 (C-6), 170.08, 170.56, 170.71, 171.02 (4×CH_3*C*OO). $C_{17}H_{24}O_9$ (372.37, 372.14), ESI MS: m/z 373.1 $[M+H]^+$, 395.1 $[M+Na]^+$.

4.2.2. (7*E*)-1,3,4,5-Tetra-*O*-acetyl-2,6-anhydro-7,8,9-trideoxy-9-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-D-*glycero*-L-*galacto*-non-7-enitol (4). To a solution of compound **1** (0.518 g, 1.39 mmol) in dry dichloromethane (20 mL), a solution of PTAD (0.244 g, 1.0 equiv.; 1.39 mmol) in dichloromethane (20 mL) was added slowly with stirring. The reaction mixture was stirred at rt, until the red color had disappeared (overnight). The reaction progress was controlled by TLC (ethyl acetate–petroleum ether 1:1). Evaporation of the solvent left a slightly yellow semisolid, which was purified by FC eluting with a gradient of ethyl acetate–petroleum ether 2:1→ethyl acetate. Evaporation left **4** (0.631 g, 83%) as a pale yellow solid. Compound **1** of 0.067 g, 13% were recovered. Mp: 75–76°C (ethyl acetate–petroleum ether). $[\alpha]_D^{23}$=+46.15 (*c* 0.26, CH_2Cl_2). R_f: 0.36 (ethyl acetate). IR (KBr): $\tilde{\nu}$=1229, 1709, 1749, 3440 cm^{-1}. ^1H NMR (H,H COSY, 300 MHz, $CDCl_3$): δ=2.06, 2.07, 2.09, 2.18 (4 s, 12H, 4×CH_3COO), 3.99 (m, 1H, 1-H), 4.13 (m, 1H, 1-H′), 4.23 (m, 1H, 2-H), 4.28–4.32 (m, 2H, CH_2-9), 4.84 (m, 1H, 6-H), 5.13 (dd, 1H, 4-H, J=3.3, 9.9 Hz), 5.32 (m, 1H), 5.36 (m, 1H), 5.96–6.02 (m, 2H, 7-H, 8-H), 7.50–7.54 (m, 5H, aromatic). ^{13}C NMR (APT, HETCOR, 75 MHz, $CDCl_3$): δ=20.96, 21.00, 21.05, 21.09

(−, 4×CH_3COO), 49.04 (+, C-9), 62.14 (+, C-1), 68.07 (−), 68.19 (−), 68.62 (−, C-4), 68.88 (−, C-2), 71.99 (−, C-6), 125.85, 128.52, 128.68, 128.76, 129.49 (−, 5×C^{Ar}, C-7 and C-8), 131.35 (+, NC^{Ar}), 153.00, 154.20 (+, 2×NCON), 170.26, 170.34, 170.39 (+, 4×CH_3*C*OO). $C_{25}H_{29}N_3O_{11}$ (547.52, 547.18), FAB MS: *m/z* 548.1 $[M+H]^+$, 570.1 $[M+Na]^+$, ESI MS: *m/z* 548.2 $[M+H]^+$, 570.0 $[M+Na]^+$.

4.3. Preparation of alcohol 5b

(a) **4** (0.254 g, 0.464 mmol) was dissolved in dry dichloromethane (20 mL) and dry methanol (2 mL), then the solution was cooled to −70°C. Ozone was bubbled through the solution for ca. 1 h. Progress of the reaction was controlled by TLC (ethyl acetate–petroleum ether 1:1). Excess ozone was removed by purging with oxygen and with argon. Dimethyl sulfide (1 mL) was added, and the solution was left overnight at rt. The solvents were evaporated, and the crude product **5a** was redissolved in THF (10 mL), and added to a mixture of sodium borohydride (0.019 g, 1.1 equiv.; 0.510 mol) and acetic acid (40 μL, 1.1 equiv.; 0.510 mmol) in THF (2 mL). The mixture was left overnight, diluted with brine, and extracted with ethyl acetate (3×20 mL). The extract was dried, evaporated and left 0.192 g as a crude product mixture, which on FC (ethyl acetate–petroleum ether 2:1) gave **5b** (0.071 g, 42%) and **12** (0.070 g, 50%) as pale yellow oils.

(b) **4** (0.116 g, 0.212 mmol) was treated as above. However, carefully dried solvents were used. **5b** of 0.065 g (85%) were obtained (pale yellow oil).

4.3.1. 4,5,7-Tri-*O*-acetyl-2,6-anhydro-3-deoxy-D-*lyxo*-hept-2-enose (12). R_f: 0.60 (ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.07, 2.09, 2.12 (3s, 9H, 3×CH_3COO), 4.28–4.34 (m, 2H), 4.45 (m, 1H), 5.51 (m, 1H), 5.70 (m, 1H), 5.77 (m, 1H), 9.23 (s, 1H, 1-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.03, 21.09, 21.19 (3×*C*H_3COO), 61.76, 62.98, 65.16, 74.31, 116.23 (C-3), 152.54 (C-2), 170.39, 170.52, 170.89 (3×CH_3*C*OO), 185.69 (C-1).

4.3.2. 1,3,4,5-Tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-L-*galacto*-heptitol (5b). $[\alpha]_D^{23}$=+44.44 (*c* 0.18, CH_2Cl_2). R_f: 0.45 (ethyl acetate). IR (film): $\tilde{\nu}$=1080, 1142, 1296, 1724, 2929, 3491 cm^{-1}. ^{1}H NMR (H,H COSY, 200 MHz, $CDCl_3$): δ=2.05, 2.06, 2.10, 2.11 (4 s, 12H, 4×CH_3COO), 3.65 (dd, 1H, 7-H, *J*=4.6, 12.0 Hz), 3.83 (dd, 1H, 7-H′, *J*=7.5, 12.0 Hz), 4.07 (dd, 1H, 1-H, *J*=4.0, 11.0 Hz), 4.27 (m, 1H, 6-H), 4.31 (m, 1H, 2-H), 4.41 (dd, 1H, 1-H′, *J*=7.8, 11.0 Hz), 5.27 (m, 1H, 5-H), 5.29 (m, 1H, 4-H), 5.44 (t, 1H, 3-H, *J*=3.0 Hz). ^{13}C NMR (APT, HETCOR, 50 MHz, $CDCl_3$): δ=21.15, 21.22 (−, 4×*C*H_3COO), 60.37 (+, C-7), 61.48 (+, C-1), 67.50 (−, C-3), 68.37 (−, C-4), 68.58 (−, C-5), 70.82 (−, C-2), 71.77 (−, C-6), 170.20, 170.40, 170.63, 171.30 (+, 4×CH_3*C*OO). $C_{15}H_{22}O_{10}$ (362.33, 462.12), FAB MS: *m/z* 303.1 $[M+H-AcOH]^+$, 345.1 $[M+H-H_2O]^+$, 363.1 $[M+H]^+$, 385.1 $[M+Na]^+$, ESI MS: *m/z* 385.1 $[M+Na]^+$.

4.3.3. 1,3,4,5-Tetra-*O*-acetyl-2,6-anhydro-7-*O*-methysulfonyl-D-*glycero*-L-*galacto*-heptitol (5c). 5b (0.046 g, 0.127 mmol) was dissolved in dry pyridine (4 mL) containing DMAP (0.002 g, cat. amount) and the mixture was cooled to 4°C. Methanesulfonyl chloride (12 μL, 1.2 equiv.; 0.152 mmol) was added, and the orange-red mixture was stirred at 4°C for 5 h (TLC, ethyl acetate). The mixture was diluted with dichloromethane and 2 M sulfuric acid. The organic layer was washed with aqueous sodium hydrogencarbonate and with brine. Drying, evaporation, and FC (ethyl acetate–petroleum ether 1:1) gave **5c** (0.034 g, 60%) as a pale yellow oil. $[\alpha]_D^{23}$=+39.28 (*c* 0.56, CH_2Cl_2). R_f: 0.56 (ethyl acetate). IR (film): $\tilde{\nu}$=1055, 1175, 1227, 1367, 1749, 3446 cm^{-1}. ^{1}H NMR (H,H COSY, 200 MHz, $CDCl_3$): δ=2.05, 2.06, 2.11, 2.12 (4s, 12H, 4×CH_3COO), 3.09 (s, 3H, SO_2CH_3), 4.11 (dd, 1H, 1-H, *J*=2.6, 8.8 Hz), 4.20 (m, 1H, 2-H), 4.30 (m, 1H, 1-H′), 4.32 (m, 1H, 7-H), 4.48 (m, 1H, 6-H), 4.51 (m, 1H, 7-H′), 5.21 (dd, 1H, 4-H, *J*=3.1, 8.5 Hz), 5.31 (dd, 1H, 5-H, *J*=4.0, 8.5 Hz), 5.43 (m, 1H, 3-H). ^{13}C NMR (APT, HETCOR, 50 MHz, $CDCl_3$): δ=20.73, 20.79, 20.84 (−, 4×*C*H_3COO), 38.05 (−, SO_2CH_3), 60.95 (+, C-1), 65.59 (+, C-7), 67.02 (−, C-3), 67.11 (−, C-5), 67.81 (−, C-4), 69.81 (−, C-6), 70.36 (−, C-2), 169.64, 169.69, 169.89, 170.64 (−, 4×CH_3*C*OO). $C_{16}H_{24}O_{12}S$ (440.42, 440.10), FAB MS: *m/z* 345.1 $[M+H-MeSO_3H]^+$, 381.0 $[M+H-AcOH]^+$, 441.1 $[M+H]^+$, 463.0 $[M+Na]^+$, ESI MS: *m/z* 463.1 $[M+Na]^+$.

4.3.4. 1,3,4,5-Tetra-*O*-acetyl-2,6-anhydro-7-bromo-7-deoxy-D-*glycero*-L-*galacto*-heptitol (5d). The methanesulfonate **5c** (0.054 g, 0.122 mmol) was dissolved in dry toluene (5 mL) containing tetrabutylammonium bromide (0.098 g, 2.5 equiv.; 0.305 mmol), and the mixture was heated at 80°C for 20 h (TLC, ethyl acetate–petroleum ether 80:20). The mixture was partitioned between water (10 mL) and ethyl acetate (20 mL), the organic layer was washed with aqueous sodium hydrogencarbonate, and with brine. Drying and evaporation left a crude mixture, which on FC (ethyl acetate–petroleum ether 80:20) gave **5d** (0.042 g, 80%) as a pale yellow oil. $[\alpha]_D^{23}$=+64.86 (*c* 0.3, CH_2Cl_2). R_f: 0.60 (ethyl acetate–petroleum ether 80:20). IR (film): $\tilde{\nu}$=1049, 1227, 1371, 1749, 3435 cm^{-1}. ^{1}H NMR (H,H COSY, 200 MHz, $CDCl_3$): δ=2.05, 2.08, 2.11, 2.13 (4s, 12H, 4×CH_3COO), 3.44 (dd, 1H, 7-H, *J*=5.1, 11.4 Hz), 3.55 (dd, 1H, 7-H′, *J*=9.2, 11.4 Hz), 4.11 (m, 1H, 2-H), 4.16 (m, 1H, 1-H), 4.30 (m, 1H, 1-H′), 4.45 (m, 1H, 6-H), 5.19 (dd, 1H, 4-H, *J*=3.3, 8.7 Hz), 5.35 (dd, 1H, 5-H, *J*=4.9, 8.7 Hz), 5.43 (t, 1H, 3-H, *J*=2.9 Hz). ^{13}C NMR (APT, HETCOR, 50 MHz, $CDCl_3$): δ=20.77, 20.82 (−, 4×*C*H_3COO), 27.49 (+, C-7), 61.06 (+, C-1), 67.22 (−, C-3), 67.71 (−, C-5), 68.13 (−, C-4), 69.39 (−, C-2), 71.74 (−, C-6), 169.62, 169.79, 170.02, 170.74 (+, 4×CH_3*C*OO). $C_{15}H_{21}BrO_9$ (425.23, 424.04), FAB MS: *m/z* 345.1 $[M+H-HBr]^+$, 365.0 $[M+H-AcOH]^+$, 425.0 $[M+H]^+$, 447.0 $[M+Na]^+$, ESI MS: *m/z* 447.1 $[M+Na]^+$.

4.3.5. 2,6-Anhydro-7-bromo-7-deoxy-D-*glycero*-L-*galacto*-heptitol (8a). To a solution of compound **5d** (0.050 g, 0.118 mmol) in dry methanol (10 mL) at 0°C, a solution of sodium methoxide (0.013 g, 2.0 equiv.; 0.236 mmol) in dry methanol (5 mL) was added. The reaction mixture was stirred at rt for about 3 h until the reactant was consumed, as shown by TLC (CH_3OH–$CHCl_3$ 15:85). The mixture was diluted with methanol, neutralized with Dowex 50-W X2 (H^+). The mixture was stirred for a few minutes, and then

the resin was filtered off, washed with methanol (3×5 mL). The combined filtrate was concentrated. The residue was applied to FC eluting with $CH_3OH-CHCl_3$ 15:85, and provided after solvent evaporation **8a** (0.030 g, quant.) as a white solid. Mp: 115–116°C (EtOH–petroleum ether). $[\alpha]_D^{23}=+73.68$ (*c* 0.38, EtOH). R_f: 0.16 ($CHCl_3$–MeOH 85:15). IR (KBr): $\tilde{\nu}=1055$, 1080, 3365, 3419 cm^{-1}. ^1H NMR (H,H COSY, 200 MHz, pyridine-d_5): $\delta=4.20-4.30$ (m, 2H, CH_2-7), 4.32–4.38 (m, 2H), 4.52–4.55 (m, 2H, CH_2-1), 4.75–4.85 (m, 3H). ^{13}C NMR (APT, HETCOR, 50 MHz, pyridine-d_5): $\delta=31.09$ (+, C-7), 61.40 (+, C-1), 69.44 (−), 69.77 (−), 71.79 (−), 74.51 (−), 76.03 (−). $C_7H_{13}BrO_5$ (257.08, 255.99), FAB MS: *m/z* 257.0 $[M+H]^+$, ESI MS: *m/z* 278.8 $[M+Na]^+$.

4.3.6. 2,6-Anhydro-7-bromo-1-*O*-(*t*-butyldiphenylsilyl)-7-deoxy-D-*glycero*-L-*galacto*-heptitol (8b). To a cold (0°C) stirred solution of **8a** (0.200 g, 0.781 mmol) and imidazole (0.105 g, 2.0 equiv.; 1.56 mmol) in dry DMF (4 mL) TBDPSCl (0.16 mL, 1.2 equiv.; 0.937 mmol) was added. The mixture was stirred at 0°C for about 2 h until the reaction was complete (TLC, $CH_3OH-CHCl_3$ 10:90). The mixture was poured into ice-water (10 mL) and extracted with chloroform (5×20 mL). The organic layer was extracted with saturated aqueous sodium hydrogencarbonate, water, dried, and evaporated. The residue was applied to FC. Elution with a gradient $CHCl_3 \rightarrow CH_3OH-CHCl_3$ 2:98 and solvent evaporation afforded **8b** (0.328 g, 85%) as a white solid. Mp: 77–78°C ($CHCl_3$–petroleum ether). $[\alpha]_D^{23}=+50$ (*c* 0.24, CH_2Cl_2). R_f: 0.42 ($CHCl_3$–MeOH 90:10). IR (KBr): $\tilde{\nu}=703$, 1079, 1110, 2930, 3405–3456 cm^{-1}. ^1H NMR (H,H COSY, 200 MHz, $CDCl_3$): $\delta=1.07$ (s, 9H, $(CH_3)_3CSi$), 3.38 (m, 1H, 7-H), 3.50–3.55 (m, 2H), 3.65 (dd, 1H, 7-H′, *J*=3.4, 11.6 Hz), 3.80–3.91 (m, 2H, CH_2-1), 4.08–4.10 (m, 2H), 4.25 (m, 1H), 7.26–7.43 (m, 6H, aromatic), 7.66–7.73 (m, 4H, aromatic). ^{13}C NMR (APT, HETCOR, 50 MHz, $CDCl_3$): $\delta=19.54$ (+, $(CH_3)_3CSi$), 27.25 (−, $(CH_3)_3CSi$), 28.24 (+, C-7), 64.04 (+, C-1), 69.45 (−), 70.29 (−), 71.15 (−), 71.59 (−), 76.24 (−), 128.39, 128.44, 130.51 (−, C^{Ar}), 133.18, 133.40 (+, SiC^{Ar}), 136.10, 136.22 (−, C^{Ar}). $C_{23}H_{31}BrO_5Si$ (495.49, 494.11), FAB MS: *m/z* 413.2 $[M+H-HBr]^+$, 437.1 $[M+Na-HBr]^+$, 495.0 $[M+H]^+$, 517.0 $[M+Na]^+$.

4.3.7. 2,6-Anhydro-7-bromo-1-*O*-(*t*-butyldiphenylsilyl)-3,4-*O*-isopropylidene-7-deoxy-D-*glycero*-L-*galacto*-heptitol (8c). To a solution of **8b** (0.045 g, 0.091 mmol) in dry acetone (5 mL) 2,2-dimethoxypropane (2 mL) and *p*-toluenesulfonic acid monohydrate (0.009 g) were added. The reaction mixture was stirred at rt for 2 h until the starting material was consumed (TLC, ethyl acetate–petroleum ether 1:1). The reaction mixture was neutralized by adding triethylamine and concentrated. The residue was applied to FC (ethyl acetate–petroleum ether 1:1) to give **8c** (0.043 g, 88%) as a pale yellow oil. $[\alpha]_D^{23}=+12.5$ (*c* 0.32, CH_2Cl_2). R_f: 0.50 (ethyl acetate–petroleum ether 1:1). IR (film): $\tilde{\nu}=1225$, 1745 cm^{-1}. ^1H NMR (H,H COSY, 200 MHz, $CDCl_3$): $\delta=1.06$ (s, 9H, $(CH_3)_3CSi$), 1.36, 1.46 (2s, 6H, $(CH_3)_2COO$), 3.37 (dd, 1H, 7-H, *J*=5.4, 9.9 Hz), 3.51 (dd, 1H, 7-H′, *J*=8.8, 9.9 Hz), 3.78–3.84 (m, 2H, CH_2-1), 4.12 (m, 1H, 2-H), 4.17 (m, 1H, 6-H), 4.18 (m, 1H, 5-H), 4.36 (dd, 1H, 4-H, *J*=2.6, 7.6 Hz), 4.47 (dd, 1H, 3-H, *J*=1.6, 7.6 Hz), 7.33–7.43 (m, 6H, aromatic), 7.66–7.73 (m, 4H, aromatic). ^{13}C NMR (APT, HETCOR, 50 MHz, $CDCl_3$): $\delta=19.76$ (+, $(CH_3)_3CSi$), 24.91, 27.11 (−, $(CH_3)_2COO$), 27.31 (−,$(CH_3)_3CSi$), 30.46 (+, C-7), 63.63 (+, C-1), 67.53 (−, C-5), 71.24 (−), 71.33 (−), 72.11 (−), 74.59 (−), 110.02 (+, $(CH_3)_2COO$), 128.05, 128.12, 130.10 (−, C^{Ar}), 134.04, 134.07 (+, SiC^{Ar}), 136.11, 136.15 (−, C^{Ar}). $C_{26}H_{35}BrO_5Si$ (535.55, 534.14), FAB MS: *m/z* 535.1 $[M+H]^+$, 557.1 $[M+Na]^+$.

4.3.8. 5-*O*-Acetyl-2,6-anhydro-7-bromo-1-*O*-(*t*-butyldiphenylsilyl)-7-deoxy-3,4-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptitol (11a). 8c (1.00 g, 1.87 mmol) was dissolved in dry pyridine (10 mL) and acetic anhydride (5 mL) and was stirred at rt for 3 h, during which the reaction progress was monitored by TLC (petroleum ether–ethyl acetate 2:1). Coevaporation with toluene, followed by FC (petroleum ether–ethyl acetate 2:1) gave the acetylated compound **11a** (0.950 g, 88%) as a pale yellow oil. $[\alpha]_D^{23}=-16.67$ (*c* 0.48, CH_2Cl_2). R_f: 0.51 (ethyl acetate–petroleum ether 2:1). IR (film): $\tilde{\nu}=1068$, 1105, 1153, 1221, 1751, 2854, 3498 cm^{-1}. ^1H NMR (H,H COSY, 600 MHz, $CDCl_3$): $\delta=1.08$ (s, 9H, $(CH_3)_3CSi$), 1.35, 1.49 (2s, 6H, $(CH_3)_2COO$), 2.14 (s, 3H, CH_3COO), 3.27–3.31 (m, 2H, CH_2-7), 3.83 (dd, 1H, 1-H, *J*=6.2, 9.9 Hz), 3.86 (dd, 1H, 1-H′, *J*=7.7, 9.9 Hz), 3.98 (m, 1H, 2-H), 4.29 (ddd, 1H, 6-H, *J*=2.6, 6.2, 8.7 Hz), 4.34 (dd, 1H, 4-H, *J*=2.6, 7.5 Hz), 4.45 (dd, 1H, 3-H, *J*=1.3, 7.5 Hz), 5.25 (t, 1H, 5-H, *J*=2.6 Hz), 7.38–7.44 (m, 6H, aromatic), 7.68–7.76 (m, 4H, aromatic). ^{13}C NMR (APT, HMQC, HMBC, 100 MHz, $CDCl_3$): $\delta=19.42$ (+, $(CH_3)_3CSi$), 20.98 (−, CH_3COO), 24.48, 26.68 (−, $(CH_3)_2COO$), 26.99 (−, $(CH_3)_3CSi$), 29.39 (+, C-7), 63.26 (+, C-1), 68.63 (−, C-5), 70.08 (−, C-6), 71.19 (−, C-2), 71.56 (−, C-3), 71.76 (−, C-4), 110.02 (+, $(CH_3)_2COO$), 127.70, 127.75, 129.71, 129.78 (−, C^{Ar}), 133.62, 133.74 (+, SiC^{Ar}), 135.72, 135.77 (−, C^{Ar}), 169.51 (+, CH_3COO). $C_{28}H_{37}BrO_6Si$ (577.59, 576.15), ESI MS: *m/z* calculated $[M+Na]^+$ 599.14350, found 599.14379.

4.3.9. 5-*O*-Acetyl-2,6-anhydro-7-bromo-7-deoxy-3,4-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptitol (11b). To a solution of compound **11a** (0.550 g, 0.955 mmol) in THF (20 mL) at rt, TBAF solution (1.0 M in THF, 1.15 mL, 1.2 equiv.; 1.146 mmol) was added. The reaction was stirred at rt for 3 h (TLC, petroleum ether–ethyl acetate 1:1). Water was added and the mixture was extracted with chloroform (5×20 mL). The combined organic layers were dried, and the solvent was removed by evaporation. The residue was submitted to FC (petroleum ether–ethyl acetate 1:1) to give **11b** (0.281 g, 87%) as a pale yellow oil. $[\alpha]_D^{23}=+8$ (*c* 0.25, CH_2Cl_2). R_f: 0.28 (ethyl acetate–petroleum ether 1:1). IR (film): $\tilde{\nu}=1061$, 1221, 1745 cm^{-1}. ^1H NMR (H,H COSY, 400 MHz, $CDCl_3$): $\delta=1.26$, 1.43 (2s, 6H, $(CH_3)_2COO$), 2.06 (s, 3H, CH_3COO), 2.50 (bs, 1H, OH), 3.25–3.35 (m, 2H, CH_2-7), 3.67 (dd, 1H, 1-H, *J*=4.7, 11.6 Hz), 3.78 (dd, 1H, 1-H′, *J*=6.7, 11.6 Hz), 3.93 (ddd, 1H, 2-H, *J*=1.6, 4.7, 6.7 Hz), 4.23 (dd, 1H, 3-H, *J*=1.6, 7.5 Hz), 4.27 (m, 1H, 4-H), 4.30 (m, 1H, 6-H), 5.21 (m, 1H, 5-H). ^{13}C NMR (APT, HMQC, HMBC, 100 MHz, $CDCl_3$): $\delta=20.91$(−, CH_3COO), 24.36, 26.46 (−, $(CH_3)_2COO$), 29.31 (+, C-7), 63.10 (+, C-1), 67.98 (−, C-5), 70.13 (−, C-4), 70.99 (−, C-2), 71.70 (−, C-6), 72.35 (−, C-3), 110.47 (+, $(CH_3)_2COO$), 169.54 (+, CH_3COO).

$C_{12}H_{19}BrO_6$ (339.18, 338.04), ESI MS: *m/z* calculated $[M+Na]^+$ 361.02572, found 361.02609.

4.3.10. 5-*O*-Acetyl-2,6-anhydro-7-bromo-7-deoxy-3,4-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptonamide (11c). *TEMPO oxidation*. To a mixture of **11b** (0.330 g, 0.940 mmol) TEMPO (0.161 g, 1.06 equiv.; 0.996 mmol), tetrabutylammonium chloride (0.261 g, 1.0 equiv.; 0.940 mmol), potassium bromide (0.113 g, 1.0 equiv.; 0.95 mmol) and dichloromethane (20 mL) at 0°C, a mixture of saturated aqueous sodium chloride (10 mL), saturated aqueous sodium hydrogencarbonate (11 mL), and saturated aqueous sodium hypochlorite (1 mL, 12–14% active chlorine) was added slowly. The reaction mixture was vigorously stirred at rt for 3 h (TLC, petroleum ether–$CHCl_3$–EtOH 5:2:2). The pH was adjusted to 2–3 with concentrated HCl. The organic layer was separated and the aqueous layer was extracted five times with dichloromethane (10 mL portions). The combined organic extracts were dried, and the solvent was removed.

Sodium chlorite oxidation. The crude product of the TEMPO oxidation (max. 0.940 mmol), sodium chlorite (0.846 g, 10.0 equiv.; 9.4 mmol), and sodium dihydrogenphosphate monohydrate (0.97 g, 7.5 equiv.; 7.0 mmol) were placed in a reaction flask, and with stirring successively 2-methyl-2-butene (4.0 mL), *t*-butanol (18 mL) and water (7.0 mL) were added. The reaction mixture was stirred at rt for 4 h (TLC, petroleum ether–$CHCl_3$–EtOH 5:2:2), and then it was diluted with water (20 mL) and dichloromethane (50 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2×20 mL). The aqueous layer was adjusted to pH 2 with concentrated HCl and extracted with dichloromethane (3×10 mL). The combined organic extracts were dried, and the solvent was removed. The residue was dried at 0.1 mbar for ca. 2 h.

Amide formation according to Staab. The crude acid (max. 0.94 mmol) and CDI (0.386 g, 2.5 equiv.; 2.4 mmol) were dissolved in dry dichloromethane (30 mL), and the mixture was stirred at rt for 5 h. Through this solution at 0°C, gaseous ammonia was bubbled for 40 min (TLC, petroleum ether–$CHC1_3$–EtOH 5:2:2), then the mixture was stirred at rt for 1 h. The solvent was evaporated, and the residue was purified by FC (petroleum ether–$CHC1_3$–EtOH 8:2:2) to give amide **11c** (0.286 g, 95%, based on **11b**) as a pale yellow oil. $[\alpha]_D^{23}=-18.18$ (*c* 0.22, CH_2Cl_2). R_f: 0.50 (petroleum ether–$CHCl_3$–EtOH 5:2:2). IR (film): $\tilde{\nu}$= 1752, 1697, 1367, 1215, 1151, 1060 cm^{-1}. ^1H NMR (H,H COSY, 400 MHz, $CDCl_3$): δ=1.26, 1.43 (2s, 6H, $(CH_3)_2COO$), 2.06 (s, 3H, CH_3COO), 3.26–3.36 (m, 2H, CH_2-7), 4.31 (dd, 1H, 4-H, *J*=2.7, 7.5 Hz), 4.35 (d, 1H, 2-H, *J*=1.6 Hz), 4.37 (dd, 1H, 6-H, *J*=2.2, 7.0 Hz), 4.65 (dd, 1H, 3-H, *J*=1.6, 7.5 Hz), 5.15 (t, 1H, 5-H, *J*=2.2 Hz), 6.15, 6.65 (2bs, 2H, H_2NCO). ^{13}C NMR (APT, HMQC, HMBC, 100 MHz, $CDCl_3$): δ=20.82 (−, *C*H_3COO), 24.19, 26.50 (−, $(CH_3)_2$COO), 30.06 (+, C-7), 68.38 (−, C-5), 70.47 (−, C-6), 71.56 (−, C-4), 71.67 (−, C-2), 72.50 (−, C-3), 110.60 (+, $(CH_3)_2$*C*OO), 169.33 (+, CH_3*C*OO), 171.50 (+, H_2NCO). $C_{12}H_{18}BrNO_6$ (352.18, 351.04), ESI MS: *m/z* $[M+H]^+$ (calculated 352.03903, found 352.03928), $[M+Na]^+$ (calculated 374.02097, found 374.02106), $[M+K]^+$ (calculated 389.99491, found 389.99513).

4.3.11. 2,6-Anhydro-7-bromo-7-deoxy-3,4-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptonamide (11d). A solution of compound **11c** (0.300 g, 0.855 mmol) in dry methanol (10 mL) was treated at rt with sodium methoxide (0.092 g, 2.0 equiv.; 1.71 mmol). The reaction mixture was stirred for 1 h (TLC, petroleum ether–$CHCl_3$–EtOH, 5:2:2). The mixture was diluted with methanol and neutralized with Dowex 50-W X2 (H^+). The mixture was stirred for a few minutes, and then the resin was filtered off, washed with methanol (5×10 mL), and the filtrate was concentrated. The residue was chromatographed (FC) eluting with petroleum ether–$CHCl_3$–EtOH (8:2:2) to furnish compound **11d** (0.264 g, quant.) as a pale yellow oil. $[\alpha]_D^{23}=-31.58$ (*c* 0.19, CH_2Cl_2). R_f: 0.47 (petroleum ether–$CHCl_3$–EtOH 5:2:2). IR (film): $\tilde{\nu}$=1687, 3432 cm^{-1}. ^1H NMR (H,H COSY, 400 MHz, $CDCl_3$): δ=1.27, 1.41 (2s, 6H, $(CH_3)_2COO$), 3.41 (dd, 1H, 7-H, *J*=6.6, 10.2 Hz), 3.48 (dd, 1H, 7-H′, *J*=7.8, 10.2 Hz), 4.07 (bs, 1H, 5-H), 4.20 (m, 1H, 6-H), 4.35 (dd, 1H, 4-H, *J*=2.5, 7.8 Hz), 4.50 (bs, 1H, 2-H), 4.66 (d, 1H, 3-H, *J*=7.8 Hz), 5.74, 6.64 (2bs, 2H, H_2NCO). ^{13}C NMR (APT, HMQC, HMBC, 100 MHz, $CDCl_3$): δ=24.28, 26.52 (−, $(CH_3)_2COO$), 30.98 (+, C-7), 66.39 (−, C-5), 71.33 (−, C-2), 71.65 (−, C-6), 72.69 (−, C-3), 73.83 (−, C-4), 110.11 (+, $(CH_3)_2COO$), 172.69 (+, H_2NCO). $C_{10}H_{16}BrNO_5$ (310.14, 309.02), ESI MS: *m/z* $[M+H]^+$ (calculated 310.02846, found 310.02861), $[2M+H]^+$ (calculated 619.05019, found 619.05060).

4.3.12. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-glucopyranosyl-(1→5)-2,6-anhydro-7-bromo-7-deoxy-3,4-*O*-isopropylidene-1-*O*-(*t*-butyldiphenylsilyl)-D-*glycero*-L-*galacto*-heptitol (7a). A mixture of **8c** (0.034 g, 0.064 mmol), 3,4,6-tri-*O*-acetyl-3-deoxy-2-trichloroacetamido-α-D-glucopyranosyl trichloroacetamidate[35] (0.045 g, 1.2 equiv.; 0.077 mmol) and activated 3 Å molecular sieves in anhydrous 1,2-dichloroethane (5 mL) was stirred for 1 h at rt under an argon atmosphere, then cooled to 0°C. Trimethylsilyl triflate (1.5 μL, 0.1 equiv., 0.006 mmol) was added, and the mixture was stirred at 0°C for ca. 5 min (TLC, ethyl acetate–petroleum ether 1:1). Triethylamine (0.1 mL) was added to stop the reaction, and the mixture was diluted with CH_2Cl_2 (10 mL) and filtered. The molecular sieves were washed with CH_2Cl_2 (3×5 mL) and the combined filtrate was concentrated. The residue was subjected to FC (petroleum ether–ethyl acetate 2:1) to furnish **7a** (0.048 g, 79%) as a white solid. Mp: 227–228°C ($CHCl_3$–petroleum ether), decomposition. $[\alpha]_D^{23}=-16$ (*c* 0.25, CH_2Cl_2). R_f: 0.36 (ethyl acetate–petroleum ether 1:1). IR (KBr): $\tilde{\nu}$=1047, 1108, 1237, 1526, 1750, 3437 cm^{-1}. ^1H NMR (H,H COSY, 300 MHz, $CDCl_3$): δ=1.03 (s, 9H, $SiC(CH_3)_3$), 1.31, 1.46 (2s, 6H, $(CH_3)_2COO$), 2.05 (s, 6H, 2×CH_3COO), 2.09 (s, 3H, CH_3COO), 3.30 (dd, 1H, 7^F-H, *J*=5.9, 10.0 Hz), 3.55 (dd, 1H, 7^F-H′, *J*=8.1, 10.0 Hz), 3.75 (m, 1H, 5^E-H), 3.77–3.80 (m, 2H, CH_2-1^F), 3.94 (m, 1H, 2^E-H), 4.02 (m, 1H, 2^F-H), 4.10 (m, 1H, 5^F-H), 4.15 (m, 1H, 6^F-H), 4.21 (m, 1H, 4^F-H), 4.24–4.27 (m, 2H, CH_2-6^E), 4.47 (dd, 1H, 3^F-H, *J*=1.4, 7.1 Hz), 4.89 (d, 1H, 1^E-H, *J*= 8.5 Hz), 5.14 (dd, 1H, 4^E-H, *J*=9.6, 9.9 Hz), 5.39 (dd, 1H, 3^E-H, *J*=9.6, 10.7 Hz), 7.02 (d, 1H, $NHCOCCl_3$, *J*= 8.8 Hz), 7.35–7.41 (m, 6H, aromatic), 7.65–7.70 (m, 4H, aromatic). ^{13}C NMR (APT, HETCOR, 75 MHz, $CDCl_3$): δ=19.51 (+, $SiC(CH_3)_3$), 20.85, 20.91, 21.09 (−, 3× *C*H_3COO), 24.62, 27.15 (−, $(CH_3)_2$COO), 27.06 (−,

$SiC(CH_3)_3$), 30.33 (+, C-7^F), 56.42 (−, C-2^E), 62.29 (+, C-6^E), 63.05 (+, C-1^F), 68.55 (−, C-4^E), 70.19 (−), 71.09 (−, C-6^F), 71.69 (−, C-3^E), 71.96 (−, C-3^F), 72.37 (−, C-4^F), 72.49 (−, C-5^E), 75.29 (−), 93.00 (+, $NHCOCCl_3$), 99.92 (−, C-1^E), 109.86 (+, $(CH_3)_2COO$), 127.87, 127.93, 129.87, 129.91 (−, C-^{Ar}), 133.60, 133.67 (+, SiC^{Ar}), 135.86, 135.97 (−, C-^{Ar}), 162.19 (+, $NHCOCCl_3$), 169.60, 171.05, 171.34 (+, 3×CH_3COO). $C_{40}H_{51}BrCl_3NO_{13}Si$ (968.19, 965.14), FAB MS: *m/z* 966.1 $[M+H]^+$, 988.1 $[M+Na]^+$, ESI MS: *m/z* calculated $[M+NH_4]^+$ 983.17169, found 983.17325.

4.3.13. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-glucopyranosyl-(1→5)-2,6-anhydro-7-bromo-7-deoxy-3,4-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptitol (7b). To a solution of **7a** (0.300 g, 0.311 mmol) in THF (30 mL) a TBAF solution (1.0 M in THF, 0.37 mL, 1.2 equiv.; 0.373 mmol) was added. The mixture was stirred at rt for 21 h (TLC, ethyl acetate–petroleum ether 1:1). Water (15 mL) was added and the mixture was extracted with chloroform (5×10 mL). The combined organic layers were dried, and the solvent was evaporated. The residue was chromatographed (FC) eluting with petroleum ether–ethyl acetate 1:1 to give **7b** (0.201 g, 89%) as a white solid. Mp: 230–231°C ($CHCl_3$–petroleum ether), decomposition. $[\alpha]_D^{23}=-30$ (*c* 0.20, CH_2Cl_2). R_f: 0.13 (ethyl acetate–petroleum ether 1:1). IR (KBr): $\tilde{\nu}$=1044, 1109, 1162, 1236, 1374, 1529, 1750, 2923, 3393, 3492 cm^{-1}. ^1H NMR (H,H COSY, 200 MHz, pyridine-d_5): δ=1.32, 1.54 (2s, 6H, $(CH_3)_2COO$), 2.01, 2.02. 2.10 (3s, 9H, 3×CH_3COO), 3.79 (dd, 1H, 7^F-H, *J*=7.0, 10.3 Hz), 3.92 (dd, 1H, 7^F-H′, *J*=6.6, 10.3 Hz), 4.05 (ddd, 1H, 5^E-H, *J*=2.2, 4.8, 9.9 Hz), 4.21 (m, 1H, 1^F-H), 4.24 (m, 1H, 1^F-H′), 4.35 (m, 1H, 2^E-H), 4.41 (m, 1H, 6^E-H), 4.51 (m, 1H, 3^F-H), 4.53 (m, 1H, 6^E-H′), 4.58 (m, 1H, 2^F-H), 4.58 (m, 1H, 6^F-H), 4.74 (dd, 1H, 4^F-H, *J*=3.1, 7.2 Hz), 4.88 (dd, 1H, 5^F-H, *J*=1.3, 7.2 Hz), 5.51 (m, 1H, 4^E-H), 5.67 (d, 1H, 1^E-H, *J*=8.4 Hz), 6.14 (dd, 1H, 3^E-H, *J*=9.2, 10.6 Hz), 10.67 (d, 1H, $NHCOCCl_3$, *J*=8.1 Hz). ^{13}C NMR (APT, HETCOR, 50 MHz, pyridine-d_5): δ=20.49, 20.65 (−, 3×CH_3COO), 24.55, 27.09 (−, $(CH_3)_2COO$), 31.86 (+, C-7^F), 57.18 (−, C-2^E), 62.08 (+, C-1^F), 62.43 (+, C-6^E), 69.61 (−, C-4^E), 71.73 (−, C-3^E, C-2^F), 71.96 (−, C-6^F), 72.39 (−, C-5^E), 72.82 (−, C-4^F), 72.92 (−, C-5^F), 75.51 (−, C-3^F), 93.73 (+, $NHCOCCl_3$), 99.37 (−, C-1^E), 109.78 (+, $(CH_3)_2COO$), 163.28 (+, $NHCOCCl_3$), 169.81, 170.36, 170.43 (+, 3×CH_3COO). $C_{24}H_{33}BrCl_3NO_{13}$ (729.79, 727.02), FAB MS: *m/z* 728.0 $[M+H]^+$, 750.0 $[M+Na]^+$, ESI MS: *m/z* calculated $[M+Na]^+$ 750.00931, found 750.00868.

4.3.14. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-glucopyranosyl-(1→5)-2,6-anhydro-7-bromo-7-deoxy-3,4-*O*-isopropylidene-1-*O*-D-*glycero*-L-*galacto*-heptonamide (7c). *TEMPO oxidation*. To a mixture of **7b** (0.068 g, 0.094 mmol), TEMPO (0.016 g, 1.06 equiv.; 0.099 mmol), tetrabutylammonium chloride (0.026 g, 1.0 equiv.; 0.094 mmol), potassium bromide (0.011 g, 1.0 equiv.; 0.095 mmol) and dichloromethane (2 mL) at 0°C, a mixture of saturated aqueous sodium chloride (1 mL), saturated aqueous sodium hydrogencarbonate (1.1 mL), and saturated aqueous sodium hypochlorite (1 mL, 12–14% active chlorine) was added slowly. The reaction mixture was vigorously stirred at rt for 3 h (TLC, petroleum ether–$CHCl_3$–EtOH 5:2:2). The pH was adjusted to 2–3 with concentrated HCl. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5×10 mL). The combined organic extracts were dried, and the solvent was removed.

Sodium chlorite oxidation. The crude product of the TEMPO oxidation (max. 0.094 mmol), sodium chlorite (0.085 g, 10 equiv.; 0.94 mmol), and sodium dihydrogenphosphate monohydrate (0.097 g, 7.5 equiv.; 0.70 mmol) were placed in a reaction flask, and with stirring successively 2-methyl-2-butene (0.4 mL), *t*-butanol (1.8 mL) and water (0.7 mL) were added. The reaction mixture was stirred at rt for 4 h (TLC, petroleum ether–$CHCl_3$–EtOH 5:2:2), then it was diluted with water (2 mL) and dichloromethane (5 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (4×10 mL). The aqueous layer was adjusted to pH 2 with concentrated HCl, and extracted with dichloromethane (3×10 mL). The combined organic extracts were dried, and the solvent was removed. The residue was dried at 0.1 mbar for ca. 2 h.

Amide formation according to Staab. The crude acid (max. 0.094 mmol) and CDI (0.039 g, 2.5 equiv.; 0.24 mmol) were dissolved in dry dichloromethane (10 mL), and the mixture was stirred at rt for 5 h. Through this solution at 0°C gaseous ammonia was bubbled for 40 min (TLC, petroleum ether–$CHCl_3$–EtOH 5:2:2), then the mixture was stirred at rt for 1 h. The solvent was evaporated, and the residue was subjected to FC (petroleum ether–$CHCl_3$–EtOH 8:2:2) to furnish amide **7c** (0.068 g, 98%, based on **7b**) as a white solid. Mp: 152–153°C ($CHCl_3$–petroleum ether), decomposition. $[\alpha]_D^{23}=-80$ (*c* 0.15, CH_2Cl_2). R_f: 0.49 (petroleum ether–$CHCl_3$–EtOH 5:2:2). IR (KBr): $\tilde{\nu}$=1046, 1108, 1148, 1233, 1374, 1531, 1685, 1750, 3378, 3475 cm^{-1}. ^1H NMR (H,H COSY, 600 MHz, $CDCl_3$): δ=1.33, 1.48 (2s, 6H, $(CH_3)_2COO$), 2.03, 2.05, 2.11 (3s, 9H, 3×CH_3COO), 3.45, (dd, 1H, 7^F-H, *J*=6.5, 10.2 Hz), 3.57 (dd, 1H, 7^F-H′, *J*=7.1, 10.2 Hz), 3.77 (ddd, 1H, 5^E-H, *J*=2.5, 4.7, 9.9 Hz), 3.95 (m, 1H, 2^E-H), 4.07 (m, 1H, 5^F-H), 4.21 (dd, 1H, 6^E-H, *J*=2.5, 12.2 Hz), 4.25 (dd, 1H, 6^E-H′, *J*=4.7, 12.2 Hz), 4.29 (m, 1H, 6^F-H), 4.37 (d, 1H, 2^F-H, *J*=2.1 Hz), 4.41 (dd, 1H, 4^F-H, *J*=2.4, 7.6 Hz), 4.70 (dd, 1H, 3^F-H, *J*=1.6, 7.3 Hz), 4.95 (d, 1H, 1^E-H, *J*=8.4 Hz), 5.12 (dd, 1H, 4^E-H, *J*=9.4, 9.9 Hz), 5.39 (dd, 1H, 3^E-H, *J*=9.4, 10.5 Hz), 6.07, 6.72 (2d, 2H, H_2NCO, *J*=3.7 Hz), 7.66 (d, 1H, $NHCOCCl_3$, *J*=8.4 Hz). ^{13}C NMR (APT, HETCOR, HMQC, HMBC, 150 MHz, $CDCl_3$): δ=20.99, 21.05, 21.21 (−, 3×CH_3COO), 24.65, 26.97 (−, $(CH_3)_2COO$), 31.30 (+, C-7^F), 56.60 (−, C-2^E), 62.36 (+, C-6^E), 68.75 (−, C-4^E), 71.41 (−, C-6^F), 71.49 (−, C-2^F), 71.55 (−, C-4^F), 71.84 (−, C-3^E), 72.75 (−, C-5^E), 73.04 (−, C-3^F), 74.08 (−, C-5^F), 92.65 (+, $NHCOCCl_3$), 99.48 (−, C-1^E), 110.85 (+, $(CH_3)_2COO$), 162.97 (+, $NHCOCCl_3$), 169.92, 171.26, 171.49 (+, 3×CH_3COO), 172.28 (+, H_2NCO). $C_{24}H_{32}BrCl_3N_2O_{13}$ (742.78, 740.02), FAB MS: *m/z* 741.0 $[M+H]^+$, 763.0 $[M+Na]^+$, ESI MS: *m/z* $[M+H]^+$ (calculated 741.022261, found 741.02190), $[M+Na]^+$ (calculated 763.00456, found 763.00636).

4.3.15. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-glucopyranosyl-(1→5)-2,6-anhydro-7-bromo-7-deoxy-D-*glycero*-L-*galacto*-heptonamide (7d). 7c (0.040 g,

0.054 mmol) was dissolved in CH_2Cl_2 (10 mL) and TFA (21 μL, 5 equiv.; 0.270 mmol) was added. The reaction mixture was stirred at rt for 2 h (TLC, petroleum ether–$CHCl_3$–EtOH 5:2:2). The solution was coevaporated three times with toluene (3 mL). The residue was submitted to FC (petroleum ether–$CHCl_3$–EtOH 8:2:2) to give **7d** (0.034 g, 89%) as a white solid. Mp: 241–242°C (EtOH–petroleum ether), decomposition. $[\alpha]_D^{23}=-50$ (*c* 0.12, CH_2Cl_2). R_f: 0.23 (petroleum ether–$CHCl_3$–EtOH 5:2:2). IR (KBr): $\tilde{\nu}$=1635, 1678, 1746, 3443 cm^{-1}. ^1H NMR (H,H COSY, 400 MHz, pyridine-d_5): δ=1.96, 1.99, 2.07 (3s, 9H, 3×CH_3COO), 3.82 (ddd, 1H, 5^E-H, *J*=2.5, 4.6, 9.8 Hz), 4.12 (dd, 1H, 7^F-H, *J*=3.7, ca. 11.7 Hz), 4.25 (dd, 1H, 7^F-H′, *J*=3.0, ca. 11.7 Hz), 4.42–4.50 (m, 2H, CH_2-6^E), 4.51 (m, 1H, 5^F-H), 4.65 (dd, 1H, 2^E-H, *J*=8.6, 10.6 Hz), 4.79 (d, 1H, 3^F-H, *J*=2.4 Hz), 4.83 (m, 1H, 2^F-H), 4.91 (m, 1H, 6^F-H), 5.01 (m, 1H, 4^F-H), 5.49 (m, 1H, 4^E-H), 5.58 (d, 1H, 1^E-H, *J*=8.4 Hz), 5.95 (dd, 1H, 3^E-H, *J*=9.3, 10.6 Hz), 8.00, 8.78 (2bs, 2H, H_2NCO), 10.63 (d, 1H, N*H*COCCl$_3$, *J*=8.6 Hz). ^{13}C NMR (APT, HMQC, HMBC, 100 MHz, pyridine-d_5): δ=20.28, 20.37, 20.48 (−, 3×*C*H_3COO), 30.83 (+, C-7^F), 56.64 (−, C-2^E), 62.15 (+, C-6^E), 69.40 (−, C-4^E), 69.86 (−, C-4^F), 70.07 (−, C-5^F), 72.00 (−, C-5^E), 72.55 (−, C-3^E), 73.39 (−, C-3^F), 75.11 (−, C-6^F), 78.19 (−, C-2^F), 93.76 (+, NHCO*C*Cl$_3$), 101.46 (−, C-1^E), 163.18 (+, NH*C*OCCl$_3$), 169.63, 170.30, 170.38 (+, 3×CH_3*C*OO), 173.59 (+, H_2NCO). $C_{21}H_{28}BrCl_3N_2O_{13}$ (702.72, 699.98), FAB MS: *m*/*z* 700.9 $[M+H]^+$, 722.9 $[M+Na]^+$, ESI MS: *m*/*z* calculated $[M+Na]^+$ 722.97326, found 722.97544.

4.3.16. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-glucopyranosyl-(1→5)-2,6-anhydro-7-bromo-3,4-*O*-carbonyl-7-deoxy-D-*glycero*-L-*galacto*-heptonamide (7e). To a solution of **7d** (0.313 g, 0.45 mmol) in dry CH_2Cl_2 (20 mL) CDI (0.146 g, 2.0 equiv.; 0.90 mmol) and DMAP (0.055 g, 1.0 equiv.; 0.45 mmol) were added. The reaction mixture was stirred at rt for 2 h (TLC, petroleum ether–$CHCl_3$–EtOH 5:2:2). Evaporation, FC (petroleum ether–$CHCl_3$–EtOH 8:2:2) afforded **7e** (0.272 g, 84%) as a white solid. Mp: 153–154°C ($CHCl_3$–petroleum ether). $[\alpha]_D^{23}=-13.33$ (*c* 0.15, CH_2Cl_2). R_f: 0.41 (petroleum ether–$CHCl_3$–EtOH 5:2:2). IR (KBr): $\tilde{\nu}$=1047, 1069, 1236, 1696, 1749, 1816, 3420, 3439 cm^{-1}. ^1H NMR (H,H COSY, 400 MHz, pyridine-d_5): δ=2.02, 2.03, 2.12 (3s, 9H, 3×CH_3COO), 3.76 (dd, 1H, 7^F-H, *J*=7.9, 10.9 Hz), 3.92 (dd, 1H, 7^F-H′, *J*=5.9, 10.9 Hz), 4.12 (ddd, 1H, 5^E-H, *J*=2.6, 4.8, 9.9 Hz), 4.38 (dd, 1H, 2^E-H, *J*=8.1, 10.6 Hz), 4.47 (dd, 1H, 6^E-H, *J*=2.6 12.0 Hz), 4.51 (dd, 1H, 6^E-H′, *J*=4.8, 12.0 Hz), 4.63 (ddd, 1H, 6^F-H, *J*=3.7, 5.9, 7.9 Hz), 4.93 (t, 1H, 5^F-H, *J*=3.7 Hz), 5.01 (d, 1H, 2^F-H, *J*=1.7 Hz), 5.53 (m, 1H, 4^E-H), 5.59 (m, 1H, 4^F-H), 5.82 (d, 1H, 1^E-H, *J*=8.4 Hz), 5.95 (dd, 1H, 3^F-H, *J*=1.7, 8.4 Hz), 6.17 (dd, 1H, 3^E-H, *J*=9.2, 10.6 Hz), 7.92, 8.90 (2s, 2H, H_2NCO), 10.78 (d, 1H, NHCOCCl$_3$, *J*=8.6 Hz). ^{13}C NMR (APT, HMQC, HMBC, 100 MHz, pyridine-d_5): δ=21.60, 21.77 (−, 3×*C*H_3COO), 31.79 (+, C-7^F), 58.11 (−, C-2^E), 63.42 (+, C-6^E), 70.64 (−, C-4^E), 72.02 (−, C-2^F), 72.72 (−, C-3^E), 73.28 (−, C-5^F), 73.43 (−, C-4^F), 73.76 (−, C-5^E), 74.66 (−, C-6^F), 76.52 (−, C-3^F), 94.70 (+, NHCO*C*Cl$_3$), 100.08 (−, C-1^E), 155.16 (+, OCOO), 164.80 (+, NH*C*OCCl$_3$), 170.71 (+, H_2NCO), 171.00, 171.57, 171.60 (+, 3×CH_3*C*OO). $C_{22}H_{26}BrCl_3N_2O_{14}$ (728.72, 725.96), FAB MS: *m*/*z* 727.1 $[M+H]^+$, 749.1 $[M+Na]^+$, ESI MS: *m*/*z* $[M+Na]^+$ (calculated 748.95252, found 748.95186), $[M+K]^+$ (calculated 764.92646, found 764.92556).

4.4. Treatment of 7d with phenyl chloroformate

A solution of **7d** (0.020 g, 0.028 mmol) and DMAP (0.004 g, 1.0 equiv.; 0.028 mmol) in dry CH_2Cl_2 (5 mL) was cooled to 0°C, then dry triethylamine (4 μL, 1.0 equiv.; 0.028 mmol) was added. Phenyl chloroformate (3.8 μL, 1.1 equiv., 0.031 mmol) was added dropwise at 0°C, and the reaction mixture was stirred at rt for 1 h (TLC, petroleum ether–$CHCl_3$–EtOH 5:2:2). The solvent was evaporated, and the residue was separated by FC, eluted with petroleum ether–$CHCl_3$–EtOH (8:2:2) to give compound **7e** (0.015 g, 72%).

4.5. Reaction of 7e with ammonia

Dry ammonia gas was bubbled through a solution of **7e** (0.150 g, 0.207 mmol) in CH_2Cl_2 (10 mL) at 0°C for 6 h (TLC, petroleum ether–$CHCl_3$–EtOH 5:2:2). The solvent was evaporated, and the residue was separated using repeated MPLC eluting with petroleum ether–ethyl acetate–EtOH 5:2:1 to give **6a** (0.095 g, 62%) and **6b** (0.032 g, 21%) as white solids.

4.5.1. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-glucopyranosyl-(1→5)-2,6-anhydro-7-bromo-4-carbamoyl-7-deoxy-D-*glycero*-L-*galacto*-heptonamide (6a). Mp: 261–262°C (EtOH–petroleum ether), decomposition. R_f: 0.14 (petroleum ether–$CHCl_3$–EtOH 5:2:2). IR (KBr): $\tilde{\nu}$=1690, 1706, 1743, 3310–3521 cm^{-1}. ^1H NMR (H,H COSY, 400 MHz, pyridine-d_5): δ=2.00, 2.03, 2.10, (3s, 9H, 3×CH_3COO), 3.84 (m, 1H, 5^E-H), 4.10 (dd, 1H, 7^F-H, *J*=3.3, 11.4 Hz), 4.30 (dd, 1H, 7^F-H′, *J*<1, 11.4 Hz), 4.31 (m, 1H, 6^E-H,), 4.42 (m, 1H, 6^E-H′), 4.43 (m, 1H, 2^E-H), 4.84 (d, 1H, 2^F-H, *J*=1.8 Hz), 4.96 (m, 1H, 6^F-H), 5.03 (m, 1H, 5^F-H), 5.40 (dd, 1H, 3^F-H, *J*=1.8, 3.5 Hz), 5.50 (dd, 1H, 4^E-H, *J*=9.5, 9.9 Hz), 5.57 (d, 1H, 1^E-H, *J*=8.4 Hz), 5.68 (dd, 1H, 4^F-H, *J*=3.5, 8.3 Hz), 6.08 (dd, 1H, 3^E-H, *J*=9.5, 10.6 Hz), 7.50 (bs, 2H, H_2NCOO), 7.80, 8.49 (2s, 2H, H_2NCO), 10.57 (d, 1H, NHCOCCl$_3$, *J*=8.1 Hz). ^{13}C NMR (APT, HMQC, HMBC, 100 MHz, pyridine-d_5): δ=20.12, 20.21, 20.31 (−, 3×*C*H_3COO), 30.32 (+, C-7^F), 56.76 (−, C-2^E), 61.83 (+, C-6^E), 67.63 (−, C-3^F), 69.27 (−, C-4^E), 71.58 (−, C-3^E), 71.73 (−, C-5^E), 72.71 (−, C-4^F), 73.17 (−, C-2^F), 75.11 (−, C-5^F), 75.66 (−, C-6^F), 93.46 (+, NHCO*C*Cl$_3$), 100.57 (−, C-1^E), 156.83 (+, H_2NCOO), 162.89 (+, NH*C*OCCl$_3$), 169.43, 170.06, 170.14 (+, 3×CH_3*C*OO), 171.98 (+, H_2NCO). $C_{22}H_{29}BrCl_3N_3O_{14}$ (745.74, 742.99), FAB MS: *m*/*z* 744.2 $[M+H]^+$, 766.2 $[M+Na]^+$, ESI MS: *m*/*z* calculated $[M+H]^+$ 743.99712, found 743.99616.

4.5.2. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-glucopyranosyl-(1→5)-2,6-anhydro-7-bromo-3-carbamoyl-7-deoxy-D-*glycero*-L-*galacto*-heptonamide (6b). Mp: 257–258°C (EtOH–petroleum ether), decomposition. R_f: 0.12 (petroleum ether–$CHCl_3$–EtOH 5:2:2). IR (KBr): $\tilde{\nu}$=1721, 3306–3445 cm^{-1}. ^1H NMR (H,H COSY, 400 MHz, pyridine-d_5): δ=2.01, 2.06, 2.10, (3s, 9H, 3×CH_3COOO), 3.84 (m, 1H, 5^E-H), 4.17 (dd, 1H, 7^F-H, *J*=3.2, 11.5 Hz), 4.29 (dd, 1H, 7^F-H′, *J*<1, 11.5 Hz), 4.34

(m, 1H, 6^E-H), 4.47 (dd, 1H, 6^E-H, J=4.7, 12.2 Hz), 4.64 (m, 1H, 4^F-H), 4.65 (m, 1H, 5^F-H), 4.71 (ddd, 1H, 2^E-H, J=8.5, 8.8, 10.4 Hz), 4.95 (m, 1H, 6^F-H), 5.47 (d, 1H, 1^E-H, J=8.5 Hz), 5.01 (d, 1H, 2^F-H, J=1.7 Hz), 5.52 (dd, 1H, 4^E-H, J=9.6, 9.9 Hz), 5.93 (dd, 1H, 3^E-H, J=9.6, 10.4 Hz), 6.47 (bs, 1H, 3^F-H), 7.60 (bs, 2H, H_2NCOO), 7.88, 8.54 (2s, 2H, H_2NCO), 10.73 (d, 1H, $NHCOCCl_3$, J=8.8 Hz). ^{13}C NMR (APT, HMQC, HMBC, 100 MHz, pyridine-d_5): δ=20.28, 20.40, 20.53 (−, 3×CH_3COO), 29.83 (+, C-7^F), 56.48 (−, C-2^E), 62.24 (+, C-6^E), 68.71 (−, C-4^F), 69.40 (−, C-4^E), 71.93 (−, C-2^F), 72.14 (−, C-5^E), 72.54 (−, C-3^F), 72.71 (−, C-3^E), 76.52 (−, C-6^F), 78.58 (−, C-5^F), 93.79 (+, $NHCOCCl_3$), 102.20 (−, C-1^E), 157.78 (+, H_2NCOO), 163.22 (+, $NHCOCCl_3$), 169.60, 170.32, 170.45 (+, 3×CH_3COO), 170.84 (+, H_2NCO). $C_{22}H_{29}BrCl_3N_3O_{14}$ (745.74, 742.99), FAB MS: m/z744.2 $[M+H]^+$, 766.2 $[M+Na]^+$, ESI MS: m/z calculated $[M+H]^+$ 743.99712, found 743.99605.

4.6. Attempted conversion of 7e into 10 by LiOH hydrolysis and acetylation

7e (0.015 g, 0.021 mmol) was treated with 0.5 M LiOH in THF–MeOH (1:1) (10 mL) for 2 h (TLC, petroleum ether–$CHCl_3$–EtOH 5:2:2). The solution was diluted with EtOH (10 mL), cooled to 0°C and neutralized with dry acetic acid. The solution was coevaporated with MeOH (3×2 mL). The crude product was dissolved in dry pyridine (5 mL) and stirred overnight with Ac_2O (5 mL). The solution was coevaporated with toluene, and the residue was purified by FC (petroleum ether–$CHCl_3$–EtOH 8:2:2) to give **9c** (0.012 g, 73%) as a white solid.

4.6.1. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroacetamido)-β-D-glucopyranosyl-(1→5)-3,4-di-*O*-acetyl-2,6-anhydro-7-bromo-7-deoxy-D-*glycero*-L-*galacto*-heptonamide (9c). $[\alpha]_D^{23}$=+61.54 (c 0.13, CH_2Cl_2). R_f: 0.44 (petroleum ether–$CHCl_3$–EtOH 5:2:2). IR (KBr): $\tilde{\nu}$= 1043, 1234, 1749, 3558 cm^{-1}. ^1H NMR (H,H COSY, 400 MHz, pyridine-d_5): δ=2.01, 2.02, 2.05, 2.13, 2.21 (5s, 15H, 5×CH_3COO), 4.05 (m, 1H, 5^E-H), 4.15 (dd, 1H, 7^F-H, J=3.3, 11.7 Hz), 4.27 (m, 1H, 2^E-H), 4.43–4.47 (m, 2H, CH_2-6^E), 4.54 (dd, 1H, 7^F-H′, J<1, 11.7 Hz), 4.90 (m, 1H, 5^F-H), 5.07 (m, 1H, 6^F-H), 5.09 (d, 1H, 2^F-H, J=1.5 Hz), 5.52 (dd, 1H, 4^E-H, J=9.2, 9.9 Hz), 5.77 (d, 1H, 1^E-H, J=8.1 Hz), 5.87 (dd, 1H, 4^F-H, J=3.6, 10.6 Hz), 6.20 (dd, 1H, 3^E-H, J=9.2, 10.6 Hz), 6.57 (dd, 1H, 3^F-H, J=1.5, 3.6 Hz), 8.02, 8.84 (2s, 2H, H_2NCO), 10.67 (d, 1H, $NHCOCCl_3$, J=7.7 Hz). ^{13}C NMR (APT, HMQC, HMBC, 100 MHz, pyridine-d_5): δ=20.04, 20.08, 20.12, 20.26, 20.94 (−, 5×CH_3COO), 29.45 (+, C-7^F), 57.24 (−, C-2^E), 62.20 (+, C-6^E), 69.52 (−, C-4^E), 69.77 (−, C-3^F), 70.22 (−, C-4^F), 70.94 (−, C-2^F), 71.38 (−, C-3^E), 72.24 (−, C-5^E), 75.04 (−, C-5^F), 76.79 (−, C-6^F), 93.00 (+, $NHCOCCl_3$), 100.85 (−, C-1^E), 162.67, 169.44, 169.84, 169.90, 169.98, 170.08 (+, 5×CH_3COO, $NHCOCCl_3$, H_2NCO). $C_{25}H_{32}BrCl_3N_2O_{15}$ (786.80, 784.00), ESI MS: m/z calculated $[M+Na]^+$ 806.99439, found 806.99427.

4.7. Attempted conversion of 7e into 10 by $NaBH_4$ reduction and acetylation

A solution of **7e** (0.025 g, 0.034 mmol) and $NaBH_4$ (0.001 g, 1.0 equiv.; 0.034 mmol) in dry ethanol (10 mL) was stirred at 0°C for 15 h. The reaction progress was controlled by TLC (petroleum ether–$CHCl_3$–EtOH 5:2:2), which showed no reaction. The temperature was then raised to rt, and the reaction mixture was stirred for further 10 h. The solution was diluted with dry EtOH (10 mL), cooled to 0°C and neutralized with dry acetic acid. The solution was coevaporated twice with MeOH (5 mL portions), and taken up in dry pyridine (5 mL), and stirred overnight with Ac_2O (3 mL). The solution was coevaporated with toluene, and the residue was purified by FC (petroleum ether–$CHCl_3$–EtOH 8:2:2) to furnish **9b** (0.023 g, 83%) as a white solid.

4.7.1. 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl-(1→5)-3,4-di-*O*-acetyl-2,6-anhydro-7-bromo-7-deoxy-D-*glycero*-L-*galacto*-heptonamide (9b). Mp: 179–180°C ($CHCl_3$–petroleum ether), decomposition. $[\alpha]_D^{23}$ +142.8 (c 0.07, CH_2Cl_2). R_f: 0.28 (petroleum ether–$CHCl_3$–EtOH 5:2:2). IR (KBr): $\tilde{\nu}$=1236, 1745, 3423 cm^{-1}. ^1H NMR (H,H COSY, 400 MHz, pyridine-d_5): δ=2.00, 2.01, 2.04, 2.05, 2.09, 2.16 (6s, 18H, 5×CH_3COO, $NHCOCH_3$), 4.03 (m, 1H, 5^E-H), 4.08 (m, 1H, 2^E-H), 4.15 (m, 1H, 7^F-H), 4.43–4.44 (m, 2H, CH_2-6^E), 4.55 (m, 1H, 7^F-H′), 4.80 (dd, 1H, 5^F-H, J=3.3, 10.5 Hz), 5.02 (m, 1H, 6^F-H), 5.08 (d, 1H, 2^F-H, J=1.5 Hz), 5.45 (dd, 1H, 4^E-H, J=9.5, 10.3 Hz), 5.64 (d, 1H, 1^E-H, J=8.4 Hz), 5.85 (dd, 1H, 4^F-H, J=3.4, 10.5 Hz), 6.08 (dd, 1H, 3^E-H, J=9.5, 10.6 Hz), 6.48 (dd, 1H, 3^F-H, J=1.5, 3.4 Hz), 7.90, 8.80 (2bs, 2H, H_2NCO), 9.27 (d, 1H, $NHCOCH_3$, J=8.1 Hz). ^{13}C NMR (APT, HMQC, HMBC, 100 MHz, pyridine-d_5): δ=20.45, 20.49, 20.49, 20.67, 20.83 (−, 5×CH_3COO), 23.13 (−, $NHCOCH_3$), 29.52 (+, C-7^F), 56.15 (−, C-2^E), 62.50 (+, C-6^E), 69.68 (−, C-4^E), 69.87 (−, C-3^F, C-4^F), 71.04 (−, C-2^F), 72.09 (−, C-5^E), 72.55 (−, C-3^E), 75.72 (−, C-5^F), 76.83 (−, C-6^F), 101.89 (−, C-1^E), 169.84, 169.87, 170.14, 170.47 (+, 5×CH_3COO, $NHCOCH_3$, H_2NCO). $C_{25}H_{35}BrN_2O_{15}$ (683.46, 682.12), FAB MS: m/z 683.1 $[M+H]^+$, 705.11 $[M+Na]^+$, ESI MS: m/z $[M+H]^+$ (calculated 683.12936, found 683.12523), $[M+Na]^+$ (calculated 705.11185, found 705.11001).

4.7.2. 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl-(1→5)-3-*O*-acetyl-2,6-anhydro-7-bromo-4-*O*-carbamoyl-7-deoxy-D-*glycero*-L-*galacto*-heptonamide (9a). A solution of **6a** (0.040 g, 0.054 mmol) and $NaBH_4$ (0.002 g, 1.0 equiv.; 0.054 mmol) in dry ethanol (10 mL) was stirred at 0°C for 48 h, after which TLC (petroleum ether–$CHCl_3$–EtOH 5:2:2) showed no reaction. The temperature was then raised to rt, and the solution was stirred for further 17 h. The solution was diluted with dry EtOH (6 mL), cooled to 0°C and neutralized with dry acetic acid. The solution was coevaporated with MeOH (2×2 mL). The crude product was dissolved in dry pyridine (10 mL), and stirred overnight with Ac_2O (3 mL). The solution was coevaporated with toluene, and the residue was purified by FC eluting with petroleum ether–$CHCl_3$–EtOH (8:2:2) furnishing **9a** (0.015 g, 42%) and **9b** (0.017 g, 46%) as white solids. R_f: 0.12 (petroleum ether–$CHCl_3$–EtOH 5:2:2). ^1H NMR (H,H COSY, 400 MHz, pyridine-d_5): δ=1.99, 2.00, 2.06, 2.07, 2.16 (5s, 15H, 4×CH_3COO, $NHCOCH_3$), 4.00 (m, 1H, 5^E-H), 4.08 (m, 1H, 2^E-H),

4.14–4.18 (m, 2H, CH_2-7^F), 4.40–4.45 (m, 2H, CH_2-6^E), 4.76 (dd, 1H, 5^F-H, J=6.4, 10.8 Hz), 4.97 (m, 1H, 6^F-H), 5.07 (d, 1H, 2^F-H, J=1.5 Hz), 5.43 (dd, 1H, 4^E-H, J=9.1, 10.2 Hz), 5.70 (d, 1H, 1^E-H, J=8.2 Hz), 5.93 (dd, 1H, 4^F-H, J=3.2, 11.0 Hz), 6.20 (dd, 1H, 3^E-H, J=9.1, 10.8 Hz), 6.65 (dd, 1H, 3^F-H, J=1.5, 3.2 Hz), 7.70 (bs, 2H, H_2NCOO), 7.90, 8.60 (2s, 2H, H_2NCO), 9.31 (d, 1H, N*H*COCH$_3$, J=7.8 Hz). ^{13}C NMR (APT, HMQC, 100 MHz, pyridine-d_5): δ=20.60, 20.71, 20.95 (−, 4×*C*H$_3$COO), 23.29 (+, NHCO*C*H$_3$), 29.92 (+, C-7^F), 56.34 (−, C-2^E), 62.53 (+, C-6^E), 69.73, 69.87 (−, C-4^F, C-4^E), 70.32 (−, C-3^F), 71.32 (−, C-5^F), 71.96 (−, C-2^F), 72.46 (−, C-5^E), 76.66 (−, C-3^E), 77.01 (−, C-6^F), 102.09 (−, C-1^E), 157.08 (+, H_2NCOO), 169.51, 169.89, 170.11, 170.40, 170.50, 171.01 (−, 4×CH$_3$*C*OO, NH*C*OCH$_3$, H_2NCO). $C_{24}H_{34}BrN_3O_{15}$ (684.45, 683.12), ESI MS: *m/z* calculated [M+Na]$^+$ 706.106551, found 706.10766.

4.7.3. 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-gluco-pyranosyl-(1→5)-3,4-di-*O*-acetyl-2,6-anhydro-7-deoxy-7-(diethoxyphosphoryl)-D-*glycero*-L-*galacto*-heptonamide (9d). Compound **9c** (0.010 g, 0.015 mmol) was dissolved in degassed triethyl phosphite (5 mL) and heated overnight in an oil bath to 180°C, while purging the solution with an argon stream. The solution was cooled, and triethyl phosphite was coevaporated with toluene under reduced pressure. FC eluting with petroleum ether–$CHCl_3$–EtOH (8:2:2) gave **9d** (0.007 g, 70%) as a white solid. R_f: 0.19 (petroleum ether–$CHCl_3$–EtOH 5:2:2). IR (KBr): $\tilde{\nu}$=1236, 1747, 3437 cm^{-1}. ^{1}H NMR (H,H COSY, 600 MHz, pyridine-d_5): δ=1.22 (t, 3H, POCH$_2$C*H*$_3$, J=7.0 Hz), 1.26 (t, 3H, POCH$_2$C*H*$_3$, J=7.0 Hz), 2.00, 2.03, 2.04, 2.08, 2.11, 2.19 (6s, 18H, 5×CH$_3$COO; NHCOC*H*$_3$), 2.69 (m, 1H, 7^F-H), 3.06 (m, 1H, 7^F-H′), 4.03 (m, 1H, 5^E-H), 4.06 (m, 1H, 2^E-H), 4.17–4.22 (m, 4H, PO(OC*H*$_2$CH$_3$)$_2$), 4.39 (dd, 1H, 6^E-H, J=2.4, 12.2 Hz), 4.53 (dd, 1H, 6^E-H′, J=4.4, 12.2 Hz), 4.75 (m, 1H, 5^F-H), 5.16 (m, 1H, 2^F-H, partially hidden by the water signal), 5.34 (m, 1H, 6^F-H), 5.45 (t, 1H, 4^E-H, J=9.7 Hz), 5.68 (d, 1H, 1^E-H, J=8.4 Hz), 5.89 (dd, 1H, 4^F-H, J=3.3, 9.9 Hz), 6.11 (t, 1H, 3^E-H, J=9.8 Hz), 6.48 (m, 1H, 3^F-H), 8.22, 8.62 (2s, 2H, H_2NCO), 9.36 (d, 1H, N*H*COCH$_3$, J=8.1 Hz). ^{13}C NMR (50 MHz, pyridine-d_5): δ=16.44 (d, *C*H$_3$CH$_2$OP, $^3J_{C,P}$=6.1 Hz), 16.51 (d, *C*H$_3$CH$_2$OP, $^3J_{C,P}$=6.1 Hz), 20.45, 20.52, 20.61, 20.61, 20.94 (5×*C*H$_3$COO), 23.16 (NHCO*C*H$_3$), 26.98 (C-7^F), 56.20 (C-2^E), 61.59 (d, CH$_3$*C*H$_2$OP, $^2J_{C,P}$=6.5 Hz), 61.91 (d, CH$_3$*C*H$_2$OP, $^2J_{C,P}$=6.5 Hz), 62.57 (C-6^E), 69.54, 70.58, 71.80, 72.03, 72.54 (probably more than one signal), 75.67, 75.96, 101.85 (C-1^E), 169.84, 170.21, 170.27, 170.44, 170.47, 170.60 (5×CH$_3$*C*OO, NH*C*OCH$_3$, H_2NCO). ^{31}P NMR (121 MHz, pyridine-d_5): δ=27.94. $C_{29}H_{45}N_2O_{18}P$ (740.65, 740.24), FAB MS: *m/z* 741.2 [M+H]$^+$, 763.2 [M+Na]$^+$, ESI MS: *m/z* [M+H]$^+$ (calculated 741.24778, found 741.24687), [M+Na]$^+$ (calculated 763.22972, found 763.22925).

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