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Fatty acylamino-trisaccharides. Synthesis and some stereochemical properties.

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Abstract: The synthesis of the lipooligosaccharide β-D-Glc*p*NR-(1→4)-β-D-Glc*p*-(1→4)-β-D-Glc (**15**) where R is COC17:2(*trans,cis*-Δ2,9) starting from octaacetyl-α-cellobiose is described. The preparation of *O*-protected acetamidotrisaccharides β-D-Glc*p*NR-(1→4)-β-D-Glc*p*-(1→4)-β-D-Glc[**11**, R=COC17:1(*cis*-Δ11); **12** R=COC17:2(*trans,cis*-Δ2,9); **13**, R=Ac] is also reported. The *EZ* ⇆ *ZZ* is the most probable conformational equilibrium for the unsaturated amido moiety of **12** Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Recently glycolipids and polysaccharides have been described as immunomodulators[1]. Most of the vaccines used in veterinary and human medicine consist of weakened or killed bacteria and viruses. However in the last few years vaccines have been developed, using antigen refined surface structures of pathogens or peptidic immunodominant epitopes hybridized with proteins. These types of antigen have the advantage of the absence of the virulence of the pathogen, but to elicit the protective effect they frecuently need the simultaneous use of adjuvants which increase the specific immune response to the antigen[2]. Among these adjuvants are several classes of conjugates of carbohydrates and lipids such as lipid A [1,3,4], natural glycosphingolipids[5] and glycoglycerolipids[6], and synthetic glycosyl amides[1]. All these compounds have an amino mono- to trisaccharides (aminosugar and glycosylamine) as glycosyl moiety and one or several fatty acid chains frequently on the amino group. The best compounds for biological studies[1] are those containing a non protected di- or tri-saccharide structure due to their water solubility.

At the same time legumes and their symbiotic bacteria of the genus *Rhizobium* are responsible for the largest contribution to global biological nitrogen fixation. *Rhizobia* elicit on their host in a specific manner, the formation of particular organs, the nodules, in which they reduce molecular nitrogen to ammonia[7]. The

symbiosis is specific and both partners exchange low molecular weight signal molecules. The plants control the bacteria by secreting flavonoids and betains and the rhizobia respond to plants by secreting specific signal molecules named *Nod-Rm* factors. These signal molecules have been found to be N-acylated chitoligomers, bearing several substituents at both ends[8,9]. In the majority of the *Nod-Rm* factors there is a fatty N-acyl group on the non-reducing aminosugar end[7,9]. These fatty acyl moieties are C16 or C18 chains which contain one, two, three or four double bonds. There is a *cis*-double bond located between C11 and C12 or between C9 and C10 in the C18 or C16 acyl moiety respectively, whereas the other double bonds are *trans*-conjugated to the carbonyl group.

Chemical and biological properties of organic compounds strongly depend on their configuration and conformation. Although the amide *Z/E* isomerism due to hindered rotation about the C-N bond has been studied in both non-sugar[10] and sugar[11,12] amido derivatives, as far as we know there are no data on N-acylamino sugars where the N-acyl group has a double bond conjugated with the amido carbonyl group. The ^{1}H- and ^{13}C NMR spectra of 2-acylamino-2-deoxy sugars of the type Su-NHCOR show only one signal set and the antiperiplanar conformation of the Z-configuration (figure 1) has been proposed[11] based on the $J_{NH,CH}$ coupling constant. On the other hand, for glycolipids of the type Su-NR^1-COR^2 (R^1,R^2 alkyl chains)[1], the presence of two conformational isomers in solution has been observed, but NMR signals for individual conformers were not identified and nor was the preferred conformation established.

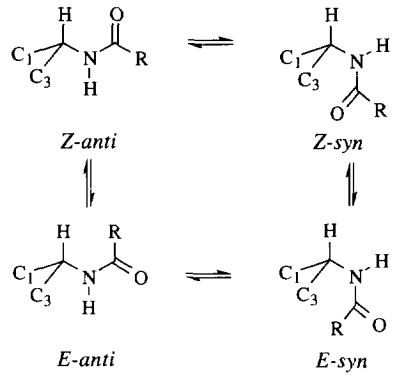


Figure 1. *Anti* and *syn* periplanar conformations of *Z* and *E* isomers.

In this paper we describe the synthesis of the lipotrisaccharides **11**, **12** and **15** with only one amido group whose structures are related to those of rhizobia *Nod*-factors[7] and glycolipid immunomodulators[1]. The synthetic route, starting from cellobiose, is shown in figure 2. The synthesis of the α and β-trisaccharides **8**, precursors of the target lipooligosaccharides, was performed using the trichloroacetimidate glycosylation method[13]. Based on the NMR data of **12**, which has a *trans* double bond conjugated to the carbonyl group, we proposed that this compound exists in chloroformic solutions in a *EZ* ⇋ *ZZ* equilibrium.

RESULTS AND DISCUSSION

The synthesis of the suitably protected acceptor **5** was performed using well-precedented procedures. Thus the reaction of octaacetyl cellobiose **1** with *p*-methoxyphenol in 1,2-dichloroethane in the presence of TMSOTf afforded[14] a mixture 1:1 of the α, β *p*-methoxyphenylcellobiosides heptaacetate (**2**). The following steps were carried out with this anomeric mixture. Zemplén deacetylation of **2** followed by benzylidenation with benzaldhyde and zinc chloride afforded **3** in 95% overall yield. Subsequent treatment with benzyl bromide under phase transfer catalysis conditions[15-16] gave **4** in 65% yield. Regioselective reduction with sodium cyanoborohydride of the benzylidene acetal group of **4** afforded the glycosyl acceptor **5** in 94% yield.

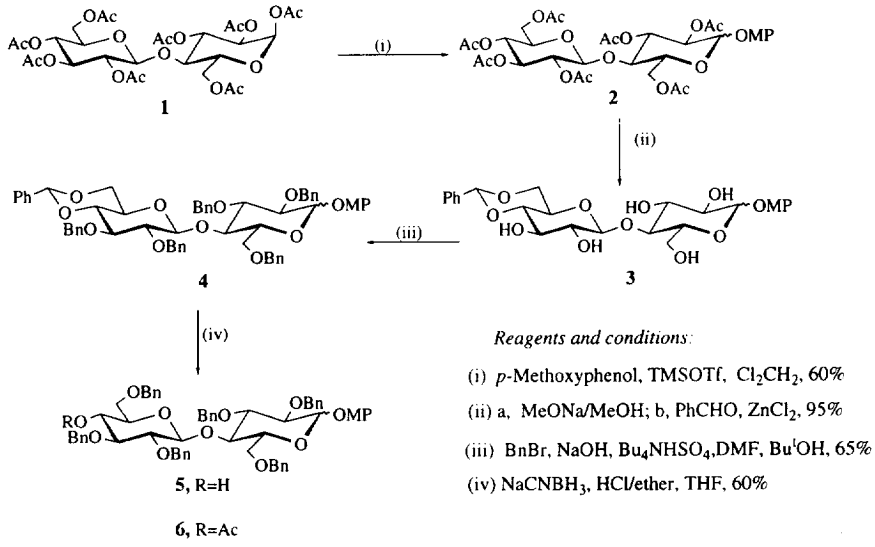
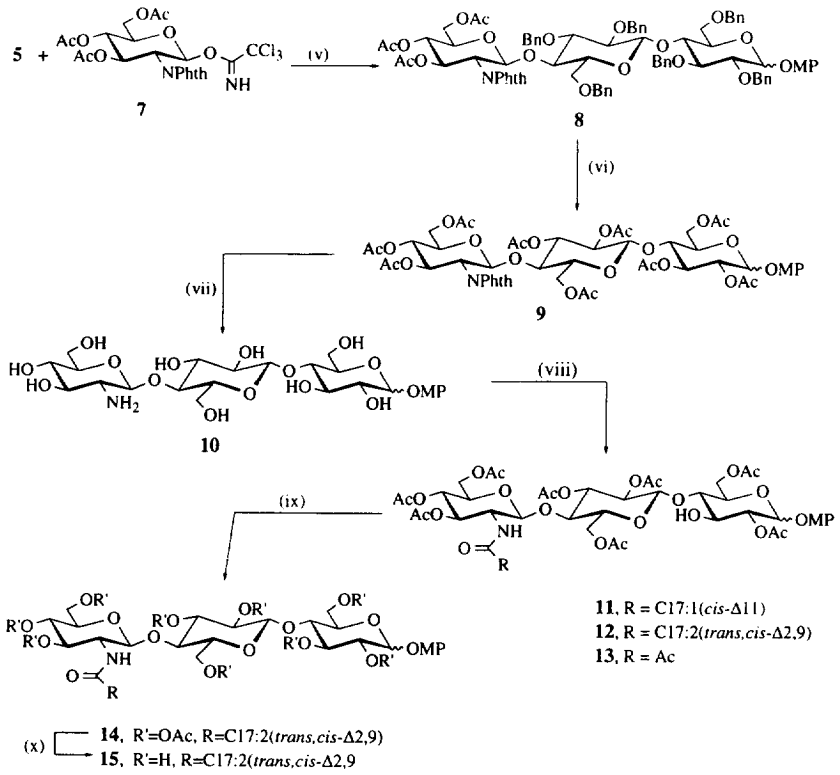


Figure 2a. Synthesis of the cellobiose-glycosyl acceptor

The structures of compounds **2-5** are supported by analytical and NMR (Table 1) and MS spectroscopic data. In the case of **5** the acetyl derivative **6** was prepared to confirm the position of the hydroxyl group. Both ^{1}H and ^{13}C NMR spectra show the doubling of the signals corresponding to ring A[17], confirming the presence of α- and β- anomers. The resonances for H-1α, H-1β, C-1α, and C-1β appeared at 5.24-5.52 ppm ($J_{1,2}$ ≈3.6 Hz), 4.50-4.90 ppm ($J_{1,2}$ 7.6-8.6 Hz), 94.7-96.7 ppm and 99.9-103.3 ppm respectively in accordance with reported data for related pairs of anomers[18-20]. The doubling of signals in ring B was practically not observed. The chemical shift for the resonance of H-4' in **6** was ≈4.9 ppm showing a downfield shift with respect to the same signal in **5**, as corresponding to the acetylation.

For the glycosylation of **5** we have chosen the trichloroacetimidate–silver triflate method[13, 21, 22]. The reaction of the glycosyl acceptors **5** with the imidate **7** in the presence of AgOTf in dichloromethane afforded with quantitative β-stereoselectivity (as expected from the directing effect of the phtalimido group)

the trisaccharides **8** in 65% yield. Hydrogenolysis in the presence of $Pd(OH)_2$ followed by acetylation gave the pairs of anomers **9** in 80% overall yield.



Reagents and conditions:

(v) AgOTf, Cl_2CH_2; 60% (vi) a. $H_2/Pd(OH)_2$; b. Ac_2O/Py, 80% (vii) $N_2H_4.H_2O$, EtOH, 55%

(viii) a. 2-chloro-1-methylpiridinium iodide, vaccenic acid, Et_3N, DMF, b. Ac_2O/Py, → **11**, 55%
a. 2-chloro-1-methylpiridinium iodide, 2,9-octadecadienoic acid, Et_3N, DMF, b. Ac_2O/Py, → **12**, 25%
Ac_2O/Py, → **13**, 60%

(ix) CAN, acetonitrile-toluene-water 4:1.3:1, 34%; (x) NaOMe/MeOH, 64%

Figure 2b. Strategy for the synthesis of the lipooligosaccharides **11**, **12** and **15**.

The analytical and spectroscopic data of **8** and **9** (Table 1 and experimental) were in agreement with the proposed structures. The resonances of H-1" (≈5.4 ppm) and H-3" (≈ 5.7 ppm) showed the described[10] deshielding influence of an equatorial diacylamino group on the adjacent axial protons. Nevertheless a shielding effect (≈3 ppm) was observed in the resonance of C-1".

The treatment of **9** with hydrazine acetate in ethanol under reflux gave the aminotrisaccharide **10** which was not isolated. N-acylation of 10 with vaccenic or 2,9-octadecadienoic acid[23] in the presence of 2-chloro-1-methyl-piridinium iodide[24] followed by acetylation produced the lipooligosaccharides glycosides **11** (55 % overall from **9**) or **12** (25 % overall from **9**) respectively. Conventional acetylation of **10** gave **13** which was prepared, as model compound, for spectroscopic characterization. Cleavage of the aromatic glycosidic bond of **12** with ceric ammonium nitrate (CAN) gave **14** which was characterized by HRFABMS, and finally deacetylation of **14** led to the water soluble target lipotrisaccharide **15.**

The chemical shifts for the resonances of H-1", H-2", C-1" and C-2" (Table 1 and experimental) for **11-13** confirmed the proposed structure and were in agreement with reported data on related 2-acylamino β-glycosides[11,25]. Additionally the ^{1}H NMR spectra of **13** showed the characteristic signal at 1.91 ppm corresponding to the equatorial acetamido group [25].

Table 1. Selected NMR data (δ, ppm; *J*, Hz) of compounds **2 - 6, 8 - 9, 11 - 13** and **15**

Comp.	$\delta_{H\text{-}1\alpha}$	$\delta_{H\text{-}1\beta}$	$J_{1,2\alpha}$	$J_{1,2\beta}$	$\delta_{H\text{-}1'}$	$J_{1',2'}$	$\delta_{H\text{-}1''}$	$J_{1'',2''}$	$\delta_{C\text{-}1\alpha}$	$\delta_{C\text{-}1\beta}$	$\delta_{C\text{-}1'}$	$\delta_{C\text{-}1''}$
2[a]	5.52	4.90	3.7	8.6	4.53	8.0	-	-	94.7	99.9	100.6	-
3[b]	5.24	4.77	3.7	7.6	4.52	7.8	-	-	98.4	103.3	103.1	-
4[a]	5.30	4.85	3.6	7.6	4.55	7.7	-	-	96.5	102.7	102.8	-
5[a]	5.30	4.50	3.7	7.6	4.36	7.2	-	-	96.6[c]	102.4[c]	102.7[c]	-
6[a]	5.28	4.85	3.6	7.7	4.51	7.4	-	-	96.7[c]	102.2[c]	102.6[c]	-
8[a]	5.25	4.79	3.6	8.2	4.28[d]	-[d]	5.51	8.30	96.5	102.6	102.1	96.7
9[a]	5.48	4.41[d]	3.7	-[d]	4.85	7.9	5.37	8.30	94.7	100.4	99.8	97.4
11[a]	5.53	4.90	3.8	7.8	4.50	7.9	4.55[d]	-[d]	95.0	99.9	100.5	100.7
12[a]	5.53[d]	4.89[d]	-[d]	-[d]	4.50[d]	-[d]	4.53[d]	-[d]	94.9	100.7	100.6	100.0
13[a]	5.53	4.90	3.7	6.4	4.50	6.4	4.56[d]	-[d]	95.2	99.9	100.5	100.7
15[b]	5.10[d]	4.50[d]	-[d]	-[d]	4.50[d]	-[d]	4.50[d]	-[d]	93.7	104.3	103.0	98.7

[a] In $CDCl_3$, 500 MHz (^{1}H), 125.7 MHz (^{13}C); [b] In Me_2SO-d_6, 500 MHz (^{1}H), 125.7 MHz (^{13}C); [c] 75.4 MHz; [d] Overlapped signal

All the vicinal coupling constants that could be measured for **2**, **3-6**, **8**, **9**, and **11-13** indicated that the $^4C_1$ conformation is the main conformation for each sugar ring in chloroformic solution (dimethyl sulphoxide-d_6 for **2**).

The ^{1}H NMR spectrum of the pair of anomers **12** showed four (two for each anomer) doublets ($J_{2'',NH}$ 8.3 - 9.0 Hz and intesities ≈1:1:1:1) for the NH of the amido group. These *J* values indicate in every

case *trans*-relationship between the corresponding protons. When the spectrum was registered in chloroform-*d* the NH signals were markedly upfield shifted on increasing the temperature from 303 to 333°K but coalescence did not take place. The spectrum in dimethyl sulphoxide-d_6 was similar and in this case the coalescence of every pair of doublets took place at 363°K, a temperature value very close to that reported for the coalescence of signals corresponding to N-alkyl-N-glycosyl saturated fatty acid amides[1] (Su-NR[1]-COR[2]). The $J_{2,NH}$ (8.7 Hz) did not change on increasing the temperature. Both the ^1H and ^{13}C NMR spectra showed the doubling of some other signals, whose coalescences took place at the same temperature. As we said above it is described[11] that amidosugars of the type Su-NHCOR exist in the *anti-Z* configuration, however the discussed facts indicated for **12** the presence of two conformational isomers in solution. In this conformers H-2" and NH are always in antiperiplanar relationship.

For an amide of a 2,3-unsaturated fatty acid, such as **12**, the conjugation (figure 3) hinders the rotation around the C-N and C-C bonds; which have to some extent, double bond character. This character is higher in the C-N bond, because of the situation of the charges in the structure A and the experimental coalescence temperature[1]. Consequently the four interchangeable stereoisomers indicated in the figure are possible.

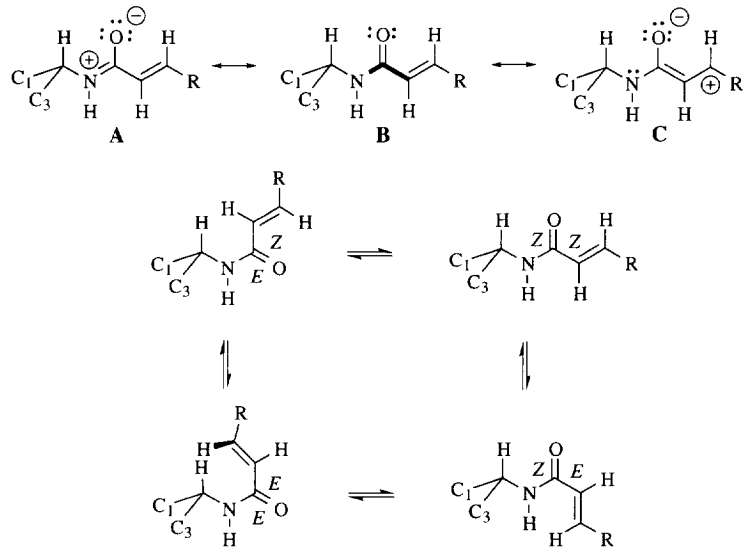


Figure 3.- Resonance hybrid and possible rotational stereoisomers for **12**

A ROESY[26] experiment performed on **12** showed n.O.e. between H-2" of the carbohydrate moiety and H-2 of the lipid chain, which indicates that these two protons are close to each other and hence the presence of the *EZ* configuration. Taking into account the antecedents on conformational equilibria of sugar amides of the type Su-NH-COR[11] and the experimental value of the coalescence temperature (363 °K), the other probable stereoisomer is *ZZ*, although an equilibrium *EZ* = *ZZ* can not wholy be ruled out. No doubling of signals was observed in the NMR spectra of **11** and **13**.

As the fatty acid amide moiety of **12** is similar to that for several natural and synthetic [27-29] *Nod-Rm* factors the stereochemical observations on **12** could be extended to them.

EXPERIMENTAL

General. Melting points are uncorrected. Optical rotations were measured at 22±1° for solutions in dichloromethane or chloroform. ^{1}H NMR spectra (300 and 500 MHz) were obtained for solutions in $CDCl_3$ or MeOH-d_4, *J* values are given in Hz. Assignments were confirmed by decoupling, H-D exchange, and homonuclear 2D COSY correlated experiments. ^{13}C NMR spectra were recorded at 75.4, and 125.7 MHz. Heteronuclear 2D correlated spectra were obtained in order to assist in carbon resonance assignments. EI-Mass spectra (70 eV) were measured with a KRATOS MS-80RFA instrument, with an ionising current or 100 μA, an accelerating voltage of 4 kV, and a resolution of 1000 (10% valley definition). The FABMS spectra were measured with the same instrument. Ions were produced by a beam of xenon atoms (6-7 KeV) using a matrix consisting of glycerol or thioglycerol and NaI as salt, $(CsI)_{37}Cs$ was used as reference. TLC was performed on Silica Gel HF_{254} (Merck), with detection by UV light or charring with H_2SO_4. Silica Gel 60 (Merck, 230 mesh) was used for preparative chromatography.

p-*Methoxyphenyl 2,3,6,2',3',4',6'-hepta-O-acetyl-α and β-cellobiosides* (**2**). To a mixture of octaacetyl-α-cellobiose **1** (1g, 1.48 mmol), TMSOTf (0.4 mL, 2.32 mmol), 1,2-dicloroethane (30 mL) and 4Å molecular sieves, a solution of *p*-methoxyphenol (0.35 g, 2.91 mmol) in 1,2-dichloroethane (30 mL)was transferred at 0° C under nitrogen. The reaction mixture was warmed to room temperature and stirred for 18 h under nitrogen, filtered and diluted with dichloromethane. The solution was washed successively with aq $NaHCO_3$ and water, dried ($MgSO_4$) and evaporated in vacuo. Chromatography of the residue (1.40g) on silica gel (6:1 toluene-acetone) gave **2** (0.68, 60%), which crystallised from ethanol had m.p. 194-196°; $[\alpha]_D$ +8.0° (*c* 1.0, dichloromethane). ^{1}H NMR (500 MHz, Cl_3CD) , Table 1 and δ 7.02-6.78 (m, 4H, $C_6H_4OCH_3$), 5.65 (t, 0.25H, $J_{3,4}$ 9.3 Hz, H-3α), 5.24 (t, 0.75H, $J_{3,4}$ 9.6 Hz, H-3β), 5.15 (t, 1H, $J_{3,4}$ 9,1 Hz, H-3'), 5,06 (t, 1H, $J_{4,5}$ 9.1 Hz, H-4'), 5.19-5.12 (m, 0.75H, H-2β), 4.97-4.89 (m, 1.25H, H-2α, H-2'), 4.53 (dd, 0.75H, $J_{5,6a}$ 1.8 Hz, $J_{6a,6b}$ 11.6 Hz, H-6aβ), 4.46 (dd, 0.25H, $J_{6a,6b}$ 11.8 Hz, H-6aα), 4.37 (dd, 1H, $J_{6a,6b}$ 12,5 Hz, H-6'a), 4.17-4.03 (m, 1.75H, H-6bα, H-6bβ, H-5β), 4.06 (dd, 1H, $J_{5,6b}$ 2.5 Hz, H-6'b), 3.3 (ddd, 0.25H, $J_{5,6a}$ 3,5 Hz, $J_{5,6b}$ 11.6 Hz, H-5α), 3.36 (ddd, 1H, $J_{5,6a}$ 4.4 Hz , $J_{5,6b}$ 2.5 Hz, H-5'), 3.77 (s, 3H, OCH_3), 3.85 (t, 0.75H, $J_{4,5}$ 9.6 Hz, H-4β), 3.80 (t, 0.25H, $J_{4,5}$ 9.3 Hz, H-4α), 2.08, 2.06, 2.05, 2.03, 2.01, 2.00 and 1.98 (7s, 21H, 7Ac). ^{13}C NMR (125.7 MHz in Cl_3CD) Table 1 and δ 170.3,- 168.8 (7*CO* of CH_3), 155.5, 155.2 (C-4" β and α of $C_6H_4OCH_3$), 150.7, 150.0 (C-1" α and β of $C_6H_4OCH_3$), 118.4, 114.3, 117.6, 114.4 (4C, aromatic), 76.4 (C-4α), 76.2 (C-4β), 72.7 (C-5β), 72.3 (C-5'), 72.6 (C-3'), 71.8 (C-3β), 71.4 (C-2'), 71.2 (C-2β), 70.5 (C-2α), 69.3 (C-3α), 68.6 (C-5α), 67.6 (C-4'), 61.7 (C-6β), 61.4 (C-6α) and 61.3 (C-6'), 20.6 - 20.5 (7 $COCH_3$). FABMS: *m/z* 742 (2%, $M^{+\bullet}$) and 765 [100%, $(M+Na)^{+\bullet}$].

p-*Methoxyphenyl 4',6'-O-benzylidene-α and β-cellobiosides* (**3**). To a solution of **2** (2.69g, 3.60 mmol) in methanol (100 mL) was added dropwise a solution of 1M NaMeO/MeOH until pH 9-10. The mixture was stirred for 1 h at r.t., made neutral with Amberlyst IRA-120(H^+), and evaporated in vacuo. The residue was dissolved in freshly distilled PhCHO (31 mL) and $ZnCl_2$ (0.99g, 7.26 mmol) was added. The reaction mixture was stirred for 16 h at r.t. and then washed with water (3x30 mL). Hexane was added to the organic layer to give a white solid which was filtered off. Column chromatography of the crude product on silica gel (1:1 chloroform-acetone) gave **3** (1.44g, 95%) that recrystallised from ethanol had m.p. 188-190°; $[\alpha]_D$ +13.0° (*c* 1.0, methanol). ^1H NMR (500 MHz, DMSO-d_6), Table 1 and δ 7.44-7.36 (m, 5H, Ph), 7.02-6.84 (m, 4H, $C_6H_4OCH_3$), 5.58 (s, 1H, PhC*H*), 5.52, 5.49, 5.42, 5.37, 5.36, 5.16, 4.66, 4.60, 4.51, 4.37 (d or bs, 5H, O*H*), 3.74-3.43 (m 9.5H, sugar ring protons), 3.45-3.39 (m, 1H, H-3β, H-2α), 3.33 (s, 3H, OCH_3), 3.27-3.25 (m, 0.5H, H-2β) and 3.14-3.11 (m, 1H, H-2'). ^{13}C NMR (75.4 MHz, DMSO-d_6), Table 1 and δ 154.5, 154.4 (1C, C-4" α and β of $C_6H_4OCH_3$), 151.4, 150.9 (1C, C1" α and β of $C_6H_4OCH_3$), 137.8, 128.9, 128.1, 126.4 (10C, aromatic), 100.8, 101.2 (1C, Ph*C*H α and β), 80.4 (0.5C, C-4β), 80.4 (C-4'), 78.6 (0.5C, C-5β), 74.5 (C-2'), 72.9 (C-3'), 67.8 (C-6'), 66.1 (C-5'), 59.9 (0.5C, C-6β), 73.3, 71.6, 71.2, 72.8, 78.8, 59.7 (3.5C, C-2,3,4α,5α and 6α) and 55.5 (1C, $C_6H_4OCH_3$). FABMS: *m/z* 536 (2%, $M^{+\bullet}$) and 559 [100%, $(M+Na)^{+\bullet}$].

Anal. Cald. for $C_{26}H_{32}O_{12}$; C, 58.21; H, 5.97. Found: C, 58.36; H, 5.73.

p-*Methoxyphenyl 2,3,6,2',3'-penta-O-benzyl-* 4',6'-*O-benzylidene-α and β-cellobiosides* (**4**). To a solution of **3** (2.64g, 4.93 mmoles) in DMF (26 mL), powdered NaOH (3g, 73.62 mL) and a solution of tetrabutylammonyum hydrogensulphate (170 mg, 0.50 mmol) in *t*-butanol (26 mL) was added. The mixture was vigorously stirred for 15 minutes, and then benzyl bromide (6 mmol, 50 mL) was added dropwise. After 7 h with vigorous stirring at r.t., the reaction mixture was diluted with dichloromethane and the unreacted NaOH was filtered off through Celite. The solution was washed with water (3x30mL), dried ($MgSO_4$) and evaporated to dryness. Column chromatography of the residue (5.40 g) on silica gel (35:1 toluene-acetone) gave **4** (2.95 mg, 65%) as a white solid, that recrystallised from ethanol had m.p. 154-156°; $[\alpha]_D$ -6.0° (*c* 1.0, dichloromethane). ^1H NMR (500 MHz, Cl_3CD) Table 1 and δ 7.49-7.22 (m, 30 H, *Ph*CH and $5CH_2Ph$), 7.03-6.78 (m, 4H, $C_6H_4OCH_3$), 5.49 (s, 1H, PhC*H*), 4.99, 4.98, 4.94, 4.91, 4.81, 4.80, 4.72, 4.66, 4.53, 4.38, 4.27 (11d, 10H, $^2J_{H,H}$ 10.9, 10.6, 10.7, 11.3, 11.2, 10.0, 11.2, 12.0, 11.7, 11.9, 12.0 Hz, $5CH_2Ph$), 4.22-4.18 (m , 0.25H, H-6aα), 4.20 (dd, 1H, $J_{6'a,6'b}$ 10.3 Hz, H-6'a), 4.05-3.99 (m, 1.25H, H-3α, H-3'), 3.85-3.33 (m, 6.5H, sugar ring protons), 3.77 (s, 3H, OCH_3), 3.50 (dd, 1H, H-6'b), 3.19 (ddd, 1H, $J_{5',6'a}$ 5.0, $J_{5',6'b}$ 3.5 Hz, H-5') and 3.11 (ddd, 0.25H, $J_{5,6a}$ 4.9, $J_{5,6b}$ 9.7, $J_{6a,6b}$ 14.2 Hz, H-5α). ^{13}C NMR: (125.7 MHz, Cl_3CD), Table 1 and δ 155.1, 154.9 (1C, C-4" α and β of $C_6H_4OCH_3$), 151.4, 150.8 (1C, C-1" α and β of $C_6H_4OCH_3$), 139.1-114.4 (40C, aromatic), 100.9 (1C, Ph*C*H), 82.7-65.6 (7.25C, sugar ring carbons), 75.4, 75.1, 75.0, 74.9, 74.8, 73.1 (6C, CH_2Ph), 68.6 (1C, C-6'), 67.8 (0.75C, C-6β), 66,6 (1C, C-5') and 55.5 (1C, $C_6H_4OCH_3$). FABMS: *m/z* 986 (3%, $M^{+\bullet}$) and 1009 [28%, $(M+Na)^{+\bullet}$].

Anal. Calcd. for $C_{61}H_{62}O_{12}$; C, 74.24; H, 6.29. Found: C, 74.24; H, 6.44.

p-*Methoxyphenyl 2,3,6,2',3',6'-hexa-O-benzyl-α and β-cellobiosides* (**5**) Dry hydrogen chloride in diethyl ether was added at 0°C to a solution of **4** (5.45g, 5.5 mmoles) and $NaCNBH_3$ (3.0g, 47.65 mmols) in dry THF (75 mL) containing 4Å molecular sieves until pH 3-4. After 3h at 0°C, a t.l.c. analysis (4:1 toluene-ethyl acetate) indicated complete reaction. The reaction mixture was poured into ice-water and extracted with dichloromethane (3x40 mL). The organic layer was washed sucessively with aq NaCl, aq $NaHCO_3$ and water, dried and evaporated in vacuo to dryness. Column chromatography of the residue on silica gel (1:1 ether-petroleum ether) gave **5** (5.08, 94%), which crystallised from 1:1 ether-petroleum ether had m.p. 98-100°; $[\alpha]_D$ +12.2° (*c* 0.9, dichloromethane). ^1H NMR (500 MHz, Cl_3CD), Table 1 and δ 7.34-7.23 (m, 30H, $6CH_2Ph$), 7.06-7.01 (m, 4H, $C_6H_4OCH_3$), 5.03, 4.98, 4.65, 4.58, 4.56, 4.33 (6d, 1H each, $^2J_{H,H}$ 10.9, 11.0, 12.0, 11.9, 12.0, 12.0 Hz, CH_2Ph), 4.89-4.63, 4.48-4.38 (2m, 6H, CH_2Ph), 4.05-4.00, 3.82-3.77, 3.66-3.21 (3m, 12H, sugar ring protons), 3.79, 3.78 (2s, each 3H, OCH_3 α and β) and 2.90 (bs, 1H, O*H*). ^{13}C NMR (75.4 MHz, Cl_3CD), Table 1 and δ 155.1, 154.9 (1C, C-4" α and β of $C_6H_4OCH_3$), 151.4, 150.8 (1C, C-1" α and β of $C_6H_4OCH_3$), 139.0-114.4 (40C, aromatic), 100.9 (1C, PhCH), 84.2-70.5 (4.5C, sugar ring carbons), 75.2-73.0 (6C, CH_2Ph) 68.0 (1C, C-6'), 67.6 (0.5C, C-6β) and 55.5 (1C, $C_6H_4OCH_3$). FABMS: *m/z* 987 (1%, $M^{+\bullet}$) and 1010 [545, $(M+Na)^{+\bullet}$].

Anal. Calcd. for $C_{61}H_{63}O_{12}$; C, 74.16; H, 6.38. Found: C, 74.14; H, 6.60.

p-*Methoxyphenyl 4'-O-acetyl-2,3,6,2',3',6'-hexa-O-benzyl-α and β-cellobiosides* (**6**). Conventional acetylation of **5** (0.02g, 0.02 mmol) with acetic anhydride (0.5 mL) and pyridine (1 mL) gave **6** (0.02g, 99%) as a white solid that crystallised from 1:1 ether-petroleum ether had m.p. 108-110°; $[\alpha]_D$ +29.0° (*c* 1.5, chloroform). ^1H NMR (500 MHz, Cl_3CD), Table 1 and δ 7.42-7.22 (m, 30 H, $6CH_2Ph$), 7.06-7.01 (m, 4H, $C_6H_4OCH_3$), 5.03, 4.99, 4.97, 4.82, 4.75, 4.72, 4.70, 4.63, 4.59, 4.57, 4.44, 4.42, 4.38, 4.35, 4.25, 4.22 (16d, 12H, $^2J_{H,H}$ 12.0 Hz, CH_2Ph), 5.03-4.88 (m, H-4'), 4.05-3.31 (m, 11H, sugar ring protons), 3.78, 3.77 (2s, each 3H, OCH_3 α and β) and 1.83, 1.82 (2s, each, 3H, Ac). ^{13}C NMR (75.4 MHz, Cl_3CD), Table 1 and δ 169.7 ($COCH_3$), 155.1, 154.9 (1C, C-4" α and β of $C_6H_4OCH_3$), 151.4, 150.8 (1C, C-1" α and β of $C_6H_4OCH_3$), 113.9-114.3 (40C, aromatic), 82.6 - 69.8 (8.5C, sugar ring carbons), 75.4-73.1 (6C, CH_2Ph), 68.0 (1C, C-6'), 67.6 (0.5C, C-6β), 55.5 (1C, $C_6H_4OCH_3$), 20.2 (1C, $COCH_3$). FABMS: *m/z* 1054 [100%, $(M+Na)^{+\bullet}$].

Anal. Calcd. for $C_{63}H_{65}O_{13}$; C, 73.40; H, 6.31. Found: C, 73.38; H, 6.30.

p-*Methoxyphenyl O-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-O-(2,3,6-tri-O-benzyl-β-D-glucopyranosyl)-(1→4)-2,3,6-tri-O-benzyl-α and β-D-glucopyranosides* (**8**). To a mixture of *O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)trichloroacetimidate (**7**, 1.08 g, 1.9 mmol), *p*-methoxyphenyl 2,3,6,2',3',6'-hexa-*O*-benzyl-α and β-cellobiosides (**4**, 1.50 g, 1.50 mmol), AgOTf (0.50 g, 1.5 mmol) and powdered molecular sieves AW-300 (7.5 g), dry dichloromethane (10 mL) at 15°C under Ar was added. The reaction mixture was stirred for 48 h at 15°C and then diluted with dichloromethane, filtered and washed sucessively with aq $NaHCO_3$ and water, dried ($MgSO_4$) and

evaporated in vacuo. Chromatography of the residue on silica gel (1:1 ether-petroleum ether) gave **8** (1.21g, 65%) which crystallysed from ether-petroleum ether had m.p. 174-176°; $[\alpha]_D$ +14.9° (*c* 1.1, dichloromethane). ^{1}H NMR (500 MHz, Cl_3CD) Table 1 and δ 7.87-7.08 (m, 34 H, 6CH_2*Ph*, NPhth), 6.98-6.76 (m, 4H, $C_6H_4OCH_3$), 5.74-5.68 (m 1H, H-3"), 5.08-5.14 (m, 1H, H-4"), 5.68-4.74, 5.07-4.92, 4.78-4.68, 4.57-4.55 (3m, 12H, CH_2Ph), 4.40 - 4.22 (m, 6H, sugar ring protons), 3.97 (t, 0.5H, $J_{2,3}$ 8.9, $J_{3,4}$ 8.9 Hz, H-3α), 3.95-3.22 (m, 7.5H, sugar ring protons), 3.77, 3.76 (2s, 3H, OCH_3 α and β) 3.63-3.52 (m, 0.5H, H-2β), 3.58-3.54 (m, 0.5H, H-2α) and 1.97-1.83 (2s, 9H, 3Ac). ^{13}C NMR (125.7 MHz, Cl_3CD), Table 1 and δ 170.5, 169.9 (3C, *C*OCH_3), 169.2 (2CO of NPhth), 155.0, 154.8 (1C, C-4" α and β of $C_6H_4OCH_3$), 151.4, 150.8 (1C, C-1" α and β of $C_6H_4OCH_3$), 138.9-114.3 (46C, aromatic), 82.9-67.8 (13C, sugar carbons), 75.1-74.0 (6C, *C*H_2Ph), 61.2 (C-6"), 55.4 ($C_6H_4OCH_3$) , 55.2, 55.1 (C-2"), 20.5, 20.4, 20.2 (3C, CO*C*H_3). FABMS: *m/z* 1405 (2%, $M^{+\bullet}$) y 1429 [70%, $(M+Na)^{+\bullet}$].

Anal. Calcd. for $C_{81}H_{83}NO_{21}$; C, 69.18; H, 5.91; N, 1.00. Found: C, 69.06; H, 5.81; N, 1.00.

p-*Methoxyphenyl O-(3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→4)-O-(2,3,6) -tri-O- acetyl-β-D-glucopyranosyl)-(1→4)-2,3,6-tri-O-acetyl-α and β-D-glucopyranosides* (**9**). Compounds **8** (0.78 g, 0.55 mmol) were dissolved in 1:3 ethyl acetate-methanol (50 mL) and $Pd(OH)_2$-C, 20% (0.38 g) was added. After 13 hours of hydrogenolysis at r.t. and 1 atm the reaction mixture was filtered through Celite and the solution concentrated to dryness to give a residue {500 mg, [FABMS: *m/z* 865 (1%, $M^{+\bullet}$) and 888 (48%, $M+Na)^{+\bullet}$]}, that was conventionally acetylated with 1:1 pyridine-acetic anhydride (20 mL). Column chromatography of the residue on silica gel (toluene-acetone 4:1) gave **9** as an amorphous solid (520 mg, 80%); $[\alpha]_D$ +10.0° (*c* 0.2, dichloromethane). ^{1}H NMR (500 MHz, Cl_3CD) Table 1 and δ 7.86-7.75 (m, 4H, NPhth), 6.96-6.88 (m, 4H, $C_6H_4OCH_3$), 5.76 (dd 1H, $J_{3,4}$ 9.2 Hz H-3"), 5.18-5.10 (m, 3.5H, H-3α, H-3', H-4', H-4"), 5.07 (t 1H, $J_{2,3}$ 7.9 Hz, H-2'), 4.85-4.79 (m, 0.5H, H-2α), 4.51-4.41 (m, 2H, H-6aα, H-6bα, H-6"a), 4.22 (dd 1H, $J_{2,3}$ 10.5 Hz , H-2"), 4.17 (dd, 1H, $J_{5,6a}$ 1.6 Hz, $J_{6a,6b}$ 11.3 Hz, H-6'a), 4.15-3.95 (m, 1H, H-5), 4.10 (dd, 1H, $J_{5,6a}$ 2.9 Hz, $J_{6a,6b,}$ 12.3 Hz, H-6'a), 3.82 (m, 1H, H-5"), 3.80-3.75 (m, 1H, H-4), 3.62-3.59 (m, 1H, H-6'b), 3.75 (s, 3H, OCH_3), 3.48-3.45 (m, 1H, H-5') and 2.12-2.01 (m, 27H, Ac). ^{13}C NMR (125.7 MHz, Cl_3CD), Table 1 and δ 170.4-168.2 (9C, *C*OCH_3), 169.2, 169.1 (2CO of NPhth), 155.5, 155.1 (1C, C-4" α and β of $C_6H_4OCH_3$), 150.7, 150.0 (1C, C-1" α and β of $C_6H_4OCH_3$), 74.6 (C-4"), 72.6-72.2 (8C, C-2', C-5', C-3', C-3, C-4', C-5", C-2, C-4), 71.8 (C-2α), 70.3 (C-3"), 68.1 (C-5), 61.9-61.2 (3C, C-6, C-6', C-6"), 55.5, 55.4 (1C, $C_6H_4OCH_3$ α and β), 54.5 (C-2") and 20.6, 20.5, 20.45, 20.4, 20.39, 20.37, 20.3, 20.2, 20.1 (9C, CO*C*H_3). FABMS: *m/z* 1117 (4%, $M^{+\bullet}$) and 1140 [100%, $(M+Na)^{+\bullet}$].

Anal. Calcd. for $C_{51}H_{59}NO_{27}$; C, 54.79; H, 5.28; N, 1.25. Found: C, 54.43; H, 5.51; N, 1.20.

p-*Methoxyphenyl O-{3,4,6-tri-O-acetyl-2-deoxy-2-[(11Z)-11-octadecaenylamido]-β-D-glucopyranosyl}-(1→4)-O-(2,3,6-tri-O-acetyl-β-D-glucopyranosyl)-(1→4)-2,3,6-tri-O-acetyl-α and β-D-glucopyranosides* (**11**). To a solution of **9** (89 mg, 0.08 mmol) in ethanol (10 mL), $N_2H_4.H_2O$ (0.3 mL, 6.4 mmol)

was added. The reaction mixture was refluxed for 48 hours and then concentrated to dryness. Traces of $N_2H_4.H_2O$ were eliminated by coevaporation with toluene and methanol. The crude product was dissolved in DMF (1 mL) and Et_3N (0.08 mL, 0.5 mmol), 2-chloro-1-methylpiridinium iodide (125 mg, 0.5 mmol) and vaccenic acid (110 mg 0.4 mmol) were added. The reaction mixture was strirred at r.t. for 6 hours and then concentrated to dryness. The residue was conventionally acetylated with 1:1 acetic anhydride-pyridine (2 mL). The crude product was purified by column chromatography (4:1 → 1:1 dichloromethane:methanol) to give **11** (40 mg, 55%) as an amorphous solid. $[\alpha]_D$ +12° (*c* 0.4, dichloromethane). ^{1}H NMR (500 MHz, Cl_3CD) Table 1 and δ 7.01-6.80 (m, 4H, $C_6H_4OCH_3$), 5.81 (d, 1H, $J_{2,NH}$ 8,8 Hz, N*H*), 5.37-5.35 (m, 2H, *cis*-H-11 and H-12 lipid chain), 5.25-5.21 (m, 1.75H, H-3β, H-3"), 5.02 (d, $J_{3,4}$ 9.8 Hz, $J_{4,5}$ 9.8 Hz, H-4"), 4.93 (dd, 0.25H, $J_{2,3}$ 7.9 Hz, H-2α), 4.89-4.85 (m, 1H, H-2"), 4.59-4.53, 4.40-3.55 (2m, 11.25H, sugar ring protons), 3.78 (s, 3H, OCH_3) y 2.16-2.00 (m, 29H, 9Ac, H-10 and H-12 lipid chain), 1.38-1.22 (m, 24H, CH_2 lipid chain) and 0.87-0.82 (m, 3H, CH_3 lipid chain). ^{13}C NMR: (125.7 MHz, Cl_3CD), Table 1 and δ 173.1-170.3 (10C, 9*C*OCH_3, NH*C*O), 155.0 (C-4" of $C_6H_4OCH_3$), 129.7-114.3 (4C, aromatic), 75.5, 72.3, 72.2, 72.0, 71.9, 71.8, 71.7, 71.5, 71.45, 71.3, 68.0, 62.0, 61.5, 61.0 (14C, sugar carbons), 55.5 (C_6H_4O*C*H_3), 54.5 (C-2"), 36.4 - 20.38 and 13.9 (26C, 9CO*C*H_3 and carbons of the lipid chain). FABMS: *m/z* 1274 [60%, $(M+Na)^{+\bullet}$].

p-*Methoxyphenyl O-{3,4,6-tri-O-acetyl-2-deoxy-2-[(2E, 9Z)-2,9- octadecadienylamido]-β-D-glucopyranosyl}-(1→4)-O-(2,3,6-tri-O-acetyl-β-D-glucopyranosyl)-(1→4)-2,3,6-tri-O-acetyl-α and β- D-glucopyrano-ides* (**12**). To a solution of **9** (234 mg, 0.21 mmol) in ethanol (30 mL), $N_2H_4.H_2O$ (0.84 mL, 18 mmol) was added. The reaction mixture was refluxed for 48 hours and then concentrated to dryness in vacuo. Traces of $N_2H_4.H_2O$ were eliminated by coevaporation with toluene and methanol. The crude product was dissolved in DMF (3.5 mL) and Et_3N (0.2 mL, 1.3 mmol), 2-chloro-1-methylpiridinium iodide (125 mg, 0.5 mmol) and (2*E*,9*Z*)-2,9-octadecadienoic acid (320 mg, 1.1 mmol) were added. The reaction mixture was strirred at r.t. for 2 hours and then concentrated to dryness. The residue was conventionally acetylated with 1:1 acetic anhydride-pyridine (2 mL). The crude product was purified by column chromatography (10:1 → 6:1 toluene:acetone) to give **12** (76 mg, 25%) as an amorphous solid $[\alpha]_D$ +20.0° (*c* 0.5, dichloromethane). ^{1}H NMR (500 MHz, Cl_3CD) Table 1 and δ 7.01-6.91 (m, 4H, $C_6H_4OCH_3$), 6.80-6.83 (m, 1H, H-3 lipid chain), 5.92, 5.90, 5.86, 5.85 (4d, 1H, $J_{2,NH}$ 8.3, 8.5, 8.7, 9.0 Hz, N*H* α and β), 5.72 (d, 1H, $^3J_{H,H}$ 15.2 Hz, H-2 lipid chain), 5.47-5.38 (m, 2H, *cis* H-9, H-10 of the lipid chain), 5.66-3.64 (m, 17H, sugar ring protons), 3.77 (s, 3H, OCH_3) and 2.16-2.00 (m, 29H, 9Ac, H-10 and H-12 of the lipid chain), 2.15-2.04 (27H, Ac), 2.05-1.98 (m, 3H, H-4, H-8, H-11 of the lipid chain), 1.33-1.26 (m, 14H, CH_2 lipid chain) and 0.93-0.89 (m, 3H, CH_3 lipid chain). ^{13}C NMR (125.7 MHz, Cl_3CD) Table 1 and δ 170.6-169.1 (10C, 9*C*OCH_3, NH*C*O), 167.6, 165.8 (2C, lipid chain), 155.7, 155.3 (1C, C-4" of $C_6H_4OCH_3$ α and β), 150.8, 150.1 (1C, C-1" of $C_6H_4OCH_3$ α and β), 135.0-114.4 (4C, aromatic), 76.4-61.4 (1C, sugar carbons), 55.2 (C_6H_4O*C*H_3), 54.5 (C-2"), 38.6 - 10.8 (24C, 9CO*C*H_3 and 15C of the lipid chain). FABMS: *m/z* 1272 [30%, $(M+Na)^{+\bullet}$. HRFABMS *m/z* obsd. 1382.4557. Calcd. for $C_{61}H_{87}NO_{26}$+Cs 1382.45694

p-*Methoxyphenyl O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→4)-O-(2,3,6-tri-O-acetyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-O-acetyl-α and β-D-glucopyranosides* (**13**). To a solution of **9** (223 mg, 0.20 mmol) in ethanol (30 mL), $N_2H_4.H_2O$ (0.84 mL, 18 mmol) was added. The reaction mixture was refluxed for 48 hours and then concentrated to dryness in vacuo. Traces of $N_2H_4.H_2O$ were eliminated by coevaporation with toluene and methanol. The crude product was dissolved at 0° in pyridine-acetic anhydride 1:1 (8 mL) and kept at r.t. for 24 h. The conventional work-up of the reaction afforded **13** (0.13 g, 60%) as hygroscopic syrup. $[\alpha]_D$ +8.0° (*c* 0.4, dichloromehane). ^{1}H NMR (500 MHz, Cl_3CD) Table 1 and δ 7.01-6.80 (m, 4H, $C_6H_4OCH_3$), 5.91, 5.90 (d, $J_{2,NH}$ 8.9 Hz, N*H* α and β), 5.25-5.20 (m, 1.5H, H-3β, H-3"), 5.20-5.12 (m, 1,5H, H-2β, H-3'), 5.03 (t, 1H, $J_{3,4}$ 9.7 Hz, $J_{4,5}$ 9.7 Hz, H-4"), 4.57-4.54 (m, 1.5H, H-6aβ, H-6'a), 4.94 (dd, 0.5H, $J_{2,3}$ 9.7 Hz, H-2α), 4.89-4.85 (m, 1H, H-2'), 4.39-4.36 (m, 1.5H, H-6aα, H-6"a), 3.87-3.55 (m, 5.5H, H-5β, H-2", H-6"b, H-5", H-5', H-4'), 3.78 (s, 3H, O*CH*$_3$), 3.64 (t, 0.5H, $J_{3,4}$ 9.7 Hz, H-4α), 1.91 (s, 3H, NAc), 2.17-1.80 (27 H, 9Ac). ^{13}C NMR (125.7 MHz, Cl_3CD), Table 1 and δ 170.8-169.1 (10C, 9*C*OCH$_3$, NH*C*O), 155.6, 155.2 (1C, C-4" α and β of $C_6H_4OCH_3$), 150.7, 150.0 (1C, C-1" α and β of $C_6H_4OCH_3$), 76.3 (1C, C-4β), 75.6 (1C, C-5β), 72.9-71.7 (5C, C-3', C-4', C-3", C-2β, C-3β), 71.5 (C-5"), 71.3 (C-2'), 70.5 (0.5C, C-2α), 69.4 (0.5C, C-3α), 68.6(0.5C, C-5α), 61.6, 61.5, 61.4, 61.3 (3C, C-6α, C-6β, C-6', C-6"), 55.7, 55.5 (2C, C-2", α and β of $C_6H_4OCH_3$), 20.8-20.4 (10C, 9CO*C*H$_3$, NHAc). FABMS: *m/z* 1053 [100%, $(M+H+Na)^{+\bullet}$].

Anal. Calcd. for $C_{45}H_{59}NO_{26}$; C, 52.48; H, 5.73; N, 1.37. Found: C, 52.31; H, 5.84; N, 1.42

O-{3,4,6-tri-O-acetyl-2-deoxy-2-[(2E, 9Z)-2,9-octadecadienylamido]-β-D-glucopyranosyl}-(1→4)-O-(2,3,6- tri-O-acetyl-β-D-glucopyranosyl)-(1→4)-2,3,6-tri-O-acetyl-D-glucopyranose (**14**). A mixture of **12** (59 mg, 0.05 mmol) and CAN (48 mg, 0.1 mmol) in 4:1.3:1 acetonitrile-toluene-water (0.63 mL) was stirred at r.t. for 4 hours. The solid was evaporated and the residue purified by preparative thin layer chromatography eluting with 2:1 toluene-acetone, to give **14** (18 mg, 34%) as an oil. FABMS: *m/z* 1166 [10%, $(M+Na)^+$]. HRFABMS. *m/z* Obsd. 1166.49560. Calcd. for $C_{54}H_{81}NO_{25}$+Na 1166.49952.

O-{2-deoxy-2-[(2E,9Z)-2,9-octadecadienylamido]-β-D-glucopyranosyl}-(1→4)-O-β-D-glucopyranosyl-(1→4)-D-glucopyranose (**15**). To a solution of **14** (7 mg, 0.006 mmol) in methanol (2 mL) 1M NaOMe/MeOH (0.5 mL) was added. The reaction mixture was left at r.t. for 45 min and then neutralised with Amberlyst IRA-120(H^+), filtered and concentrated in vacuo. The residue was purified through column chromatography on biogel P-2, eluting with 1:1 methanol-water to give **15** (3 mg, 64%) as an amorphous hygroscopic solid. ^{1}H NMR (500 MHz, DMSO-*d*$_6$), Table 1 and δ 6.82 (m, 1H, H-3 lipid chain), 5.86 (dd, 1H, $J_{H,H}$ 15.3, 1.2 Hz, H-2 lipid chain), 5.32-5.28 (m, 2H, H-9, H-10 lipid chain), 5.15-5.05, 4.52-4.47, 3.95-3.30 (3m, 18H, sugar ring), 2.25-2.08 (m, 3H, H-4, H-8, H-11 lipid chain), 1.45-1.15 (m, 14H, CH_2 lipid chain), 0.80 (m, 3H, CH_3 lipid chain). ^{13}C NMR (125.7 MHz, DMSO-*d*$_6$) Table 1 and δ 80.6-57.3 (15C sugar carbons), 33.6, 33.0, 30.8, 30.6, 30.4, 23.7, 14.4 (carbons of the lipid chain). FABMS: *m/z* 894 [8%, $(M+Na)^{+\bullet}$].

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