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Synthesis of sialic acid derivatives as ligands for the myelin-associated glycoprotein (MAG)

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Abstract—The trisaccharide substructure **13** of the ganglioside GQ1bα shows a remarkable affinity for the myelin-associated glycoprotein (MAG). In the search for structurally simplified and pharmacokinetically improved mimics of **13**, sialosides with modifications at the reducing and non-reducing end were synthesized. The biological evaluation of mimics **12a–o** was performed in a competitive target-based assay. It was found that the relative inhibitory potency (rIP) of antagonist **12h** was enhanced by more than 1000-fold in comparison to the reference trisaccharide **13**, despite the former having a much simpler structure. In addition, the sialic acid derivatives, for example, **12h**, have clearly improved pharmacokinetic properties due to the presence of aromatic moieties, a lower molecular weight, and a reduced number of polar hydroxy functions compared to the reference compound **13**.

1. Introduction

The adult mammalian central nervous system (CNS) inherently lacks the capacity for regeneration.[1] However, it could be shown that neurite outgrowth is principally possible,[2] but actively inhibited by inhibitor proteins expressed by myelinating glia cells, oligodendrocytes, and Schwann cells.[3] Three major inhibitor proteins have been identified so far: Nogo A,[4] oligodendrocyte myelin glycoprotein (OMpg),[5] and myelin-associated glycoprotein (MAG).[6] All three inhibitor proteins bind to the Nogo receptor (NgR)[7] located on the neuron surface. The NgR then forms a complex with the coreceptor $p75^{NTR}$ to transduce the inhibitory signal to the cytosol of the neuron.[8] There, it activates the RhoA-ROCK[9] cascade, which finally leads to growth cone collapse. This same cascade is probably also triggered by MAG binding to gangliosides. Again, it is believed that the interaction with the coreceptor $p75^{NTR}$[10] initiates the inhibitory cascade.

MAG has been identified as a sialic acid-binding immunoglobulin-like lectin (Siglec-4). Its role[11] as one of several myelin components inhibiting axonal regrowth after injury has drawn a lot of attention.[12] Although the mechanism is still unclear, it is believed that blocking this inhibitory activity of MAG could support the regeneration after injury to the CNS. Schnaar[13] reported that GQ1bα, GD1a, and GT1b, known to be expressed on myelinated neurons in vivo, are functional ligands of MAG. These gangliosides have been synthesized in preparative amounts,[14] and were therefore used to establish a structure affinity relationship (SAR). Thereafter, the SAR profile was refined by numerous synthetic contributions based on neuraminic acid derivatives and ganglioside fragments.[15] The recently reported ability to reverse MAG inhibition with monovalent glycosides[16] encourages further exploration of glycans and glycan mimics as inhibitors of MAG-mediated axonal outgrowth inhibition.

The binding properties of all siglecs studied so far rely on their interactions with sialylated glycans, strongly suggesting that these Sia-dependent interactions are also important for their biological function in vivo. Several potential sialylated binding partners for MAG have been identified,[15] however, the full biological role of its sialic acid-binding activity has remained unclear. A

Keywords: Sialic acid derivatives; Myelin-associated glycoprotein (MAG); Topliss operational scheme.
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potent and selective inhibitor with drug-like properties would provide a tool required to further investigate both, the role of sialic acid-dependent interactions of MAG and the therapeutic potential of MAG antagonists.

In this report, we describe the synthesis and biological evaluation of the sialic acid derivative **12a** obtained by combining the reported beneficial modifications in the 2- and 9-position of one molecule.[15,17] This new lead **12a** was then further optimized applying a Topliss approach.[18]

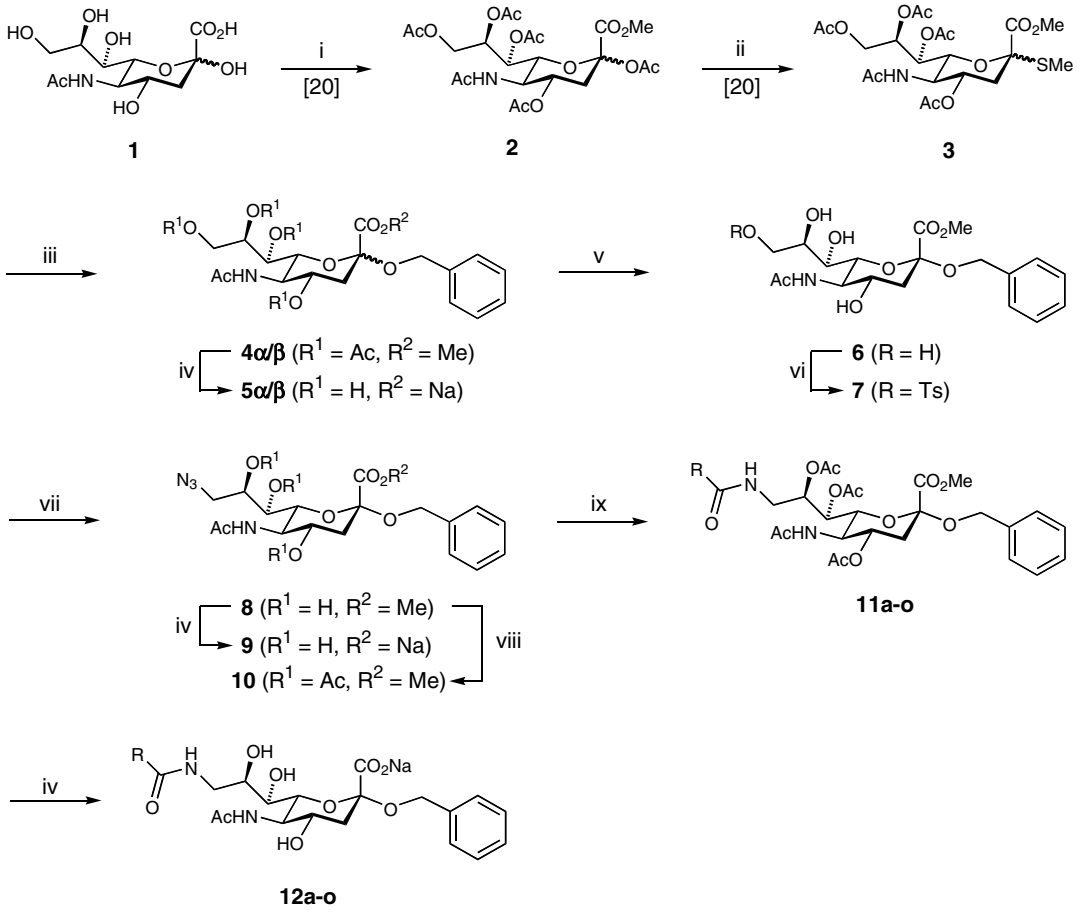
2. Results and discussion

Kelm et al. reported that Neu5AcαBn has a 10-fold higher affinity for MAG than the corresponding methyl sialoside.[15a] In addition, substitution of the hydroxy group in the 9-position of sialic acid by an amino group also enhanced binding, while substitution by halogens abolished binding, suggesting the important role of a hydrogen donor at this position.[15a] Finally, acylation of the amino group in the 9-position further increased the affinity for MAG significantly.[15f,19]

In order to obtain MAG antagonists with further enhanced affinity, we combined the various modifications reported to date in one molecule (→**12a**, Scheme 1). This new lead structure was then the starting point for a lead optimization program.

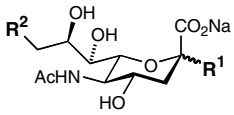
Starting from neuraminic acid (**1**), the sialyl donor **3** was synthesized according to a reported procedure.[20] The reaction of **3** with benzyl alcohol in the presence of NIS/TfOH yielded an anomeric mixture of the benzyl sialosides **4α** (41%) and **4β** (18%), which were chromatographically separated.[21] Subsequent saponification of **4α** and **4β** gave the test compounds **5α** and **5β** (Table 1, entries b and c).

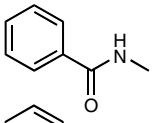
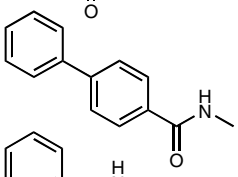
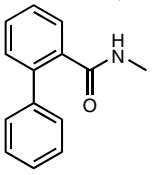
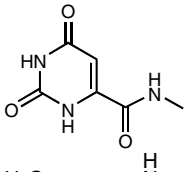
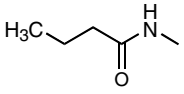
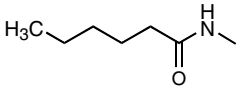
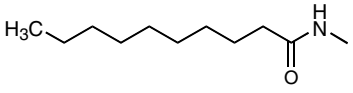
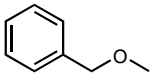
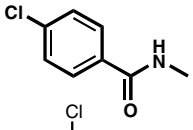
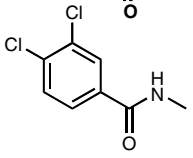
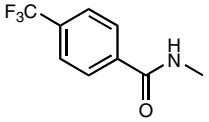
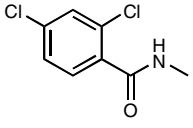
For the extension of the non-reducing end of **4α**, the acetate protection was removed under Zemplén conditions (→**6**), the 9-OH selectively tosylated (→**7**),[22] and then transformed into the corresponding azide **8** using sodium azide and 18-crown-6 in DMF.[23] Subsequent saponification afforded the test compound **9** (Table 1, entry d). Alternatively, acetylation of **8** using acetic anhydride and pyridine gave compound **10**, which was used for amidation under modified Staudinger conditions[24] with a wide range of aromatic and aliphatic acyl



Scheme 1. Reagents: (i) a—MeOH, Amberlyst 15, b—Ac_2O, DMAP, pyr, 81%; (ii) TMSSMe, TMSOTf, MS 3 Å, DCE 82%; (iii) $PhCH_2OH$, NIS/TfOH, MeCN, 41% α, 18% β; (iv) a—10% NaOH, MeOH, b—Dowex 50 × 8 (Na^+), 70–95%; (v) NaOMe, MeOH, 2 h, 82%; (vi) *p*TsCl, pyr, 56%; (vii) NaN_3, DMF, 18-C-6, 75%; (viii) Ac_2O, DMAP, pyr, 73%; (ix) RCOCl, PPh_3, DCM, 54–70%.

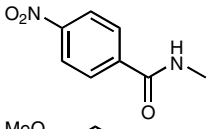
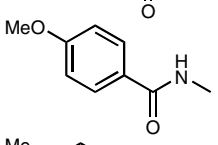
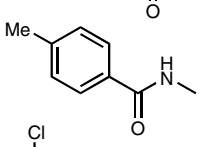
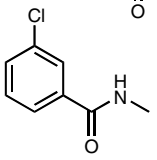
Table 1. Relative inhibitory potencies (rIPs) of sialosides



Entry	Compound	R^1	R^2	rIP
a	**13**	Gal-β(1–3)-Gal*N*Ac-OSE	HO–	1
b	**5α**	αOBn	HO–	0.62
c	**5β**	βOBn	HO–	n.a.
d	**9**	αOBn	N_3–	0.05
e	**12a**	αOBn		690
f	**12b**	αOBn		191
g	**12c**	αOBn		75
h	**12d**	αOBn		6.7
i	**12e**	αOBn		8.6
j	**12f**	αOBn		12
k	**12g**	αOBn		12
l	**16**	αOBn		2.8
m	**12h**	αOBn		**1074**
n	**12i**	αOBn		690
o	**12j**	αOBn		207
p	**12k**	αOBn		35

(*continued on next page*)

Table 1 (*continued*)

Entry	Compound	R^1	R^2	rIP
q	**12l**	αOBn		414
r	**12m**	αOBn		290
s	**12n**	αOBn		806
t	**12o**	αOBn		483

The rIP of each sialoside was calculated by dividing the IC_{50} of the reference compound **13** by the IC_{50} of the compound of interest. This results in rIPs above 1.0 for derivatives binding better than **13** and rIPs below 1.0 for compounds with a lower affinity than **13**; n.a., not applicable, less than 50% inhibition at the highest concentration tested (20 mM).

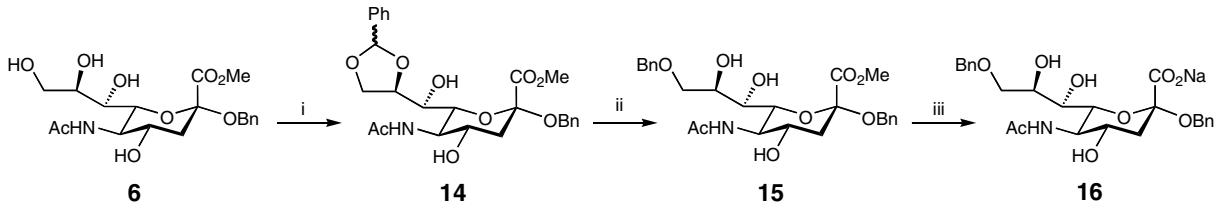
chlorides. 9-amido-substituted sialosides **11a**–**g** were obtained in 54–70% yield. Finally, deprotection yielded the amides **12a**–**g** ready for biological investigation in a hapten inhibition assay (Table 1, entries e–k).

For the inhibition assays, a recombinant protein consisting of the three *N*-terminal domains of MAG and the Fc part of human IgG (Fc-$MAG_{d1–3}$) was produced by expression in CHO cells and affinity purification on protein A-agarose.[25] The relative inhibitory potencies (rIP) of the benzyl sialosides **5α**, **5β**, **9**, and **12a**–**g** were determined in microtiter plates coated with covalently attached sialic acids as binding target for Fc-$MAG_{d1–3}$.[26] By complexing the Fc-part with alkaline phosphatase-labeled anti-Fc antibodies and measuring the initial velocity of fluorescein release from fluorescein diphosphate, the amount of bound MAG could be determined. At least three independent titrations were performed for each compound. To ensure comparability with earlier reported results,[15] the affinities were measured relative to the reference compound **13** (Table 1, entry a),[27] which has an IC_{50} of 265 μM and rIP of 1. Compound **13** was selected as the reference compound because it represents the minimal carbohydrate epitope required for binding to MAG as identified by Schnaar et al. in their studies on gangliosides.[13] High rIPs represent compounds with high affinity, whereas low rIPs indicate low affinity compounds.

As reported earlier,[15a] only α-sialosides fulfill the geometrical requirements for binding to MAG. It was found that the α-sialoside **5α** showed an affinity slightly below the one of the trisaccharide **13**, which was used as a reference compound. For the corresponding β-anomer, no activity could be observed at concentrations up to 20 mM. These results correspond entirely with the binding mode deduced from the crystal structure of siglec-7 in complex with a sialylated ligand, the ganglioside analogue α(2–3)/α(2–6)disialyllactotetraosyl 2-(trimethylsilyl)ethyl.[28] Only in the case of the α-anomer the vital salt bridge between the carboxylate of the ligand and the guanidinium group of Arg97 can be formed.

Similar to the finding of Kelm et al. with methyl α-sialosides,[15f,19] a benzamide in the 9-position of benzyl α-sialoside (**12a**) improves binding affinity by almost three orders of magnitude as well. The sterically more demanding biphenyls **12b** and **12c** (entries 6 and 7) led to decreased activity. However, aromatic amides (**12a**–**c**) generally turned out to be significantly more active than their aliphatic counterparts (**12e**–**g**). Finally, a derivative with a heteroaromatic substituent in the 9-position also exhibited reduced affinity (**12d**).

Unlike the other test compounds in Table 1, the 9-azido derivative **10** is lacking the hydrogen donor properties at the non-reducing end. This might be the reason for the 20-fold reduction in affinity compared to the reference compound **13**, similar to the reduced affinity reported for 9-halogeno derivatives.[15a] In order to confirm the importance of the hydrogen bond formation initiated by the hydroxy group in the 9-position, the corresponding benzyl ether **16** was synthesized (Scheme 2). In contrast to the benzamide, the benzyl ether has the advantage of higher flexibility facilitating the formation of possible hydrophobic interactions. On the other hand, it is missing the hydrogen bond donor potential. Starting from **6**, the 8,9-diol was regioselectively protected as benzylidene acetal to afford **14** as a diastereomeric mixture[29] which was then regioselectively transformed into the 9-*O*-Bn derivative **15** using $BH_3{\cdot}NMe_3$, $AlCl_3$ and traces of H_2O in THF. After hydrolysis with LiOH in dioxane-H_2O and ion exchange chromatography the sodium salt **16** was obtained in a good overall yield.



Scheme 2. Reagents and conditions: (i) α,α-Dimethoxytoluene, *p*TsOH·H_2O, CH_3CN, rt, 1.5 h; (ii) BH_3·NMe_3, $AlCl_3$, THF, cat. H_2O, rt, 4 h (**6** → **15**, 70%); (iii) a—LiOH, H_2O-dioxane, rt, 1.5 h, b—Dowex 50 × 8 (Na^+), 87%.

The replacement of the benzamide in **12a** by a benzyl ether (**16**) led to a reduction in the affinity by more than two orders of magnitude (Table 1, entry l). The nonexistence of a hydrogen bridge donor at the 9-position in **16** might therefore be the reason for the dramatic drop in activity.

A very common problem in drug design is to find the optimal substitution on an aromatic ring in an active lead compound (e.g. **12a**) in order to maximize its potency. Since there are many possible substitutions and several different ring positions, the number of potential compounds to be considered is very large. With the development of the Hansch method for treatment of structure activity correlations,[30] a more rational approach to this problem became available. Thus, a limited group of substituents, which will give good discrimination between π (hydrophobic effects), σ (electronic effects), and E_S (steric effects) can be selected.

The Topliss operational scheme is a manual, non-mathematical application of the Hansch analysis to drug design, developed to guide towards the most active analogue of a lead compound with the least synthetic investment.[18] The Topliss scheme starts with the unsubstituted benzamide **12a** (Scheme 1). The first derivative to be synthesized is the *p*-Cl-benzamide **12h**. It turned out to have a higher affinity than the parent compound **12a** (rIP: 690 vs 1074), which most probably can be attributed to a $+\pi$-effect, a $+\sigma$-effect or to a combination of both. *m*,*p*-Dichloro-benzamide **12i** was synthesized next, because of the increase in both π- and σ-values when summed for the two substituents. Since the potency of **12i** was lower than that of the precursor **12h** (rIP: 1074 vs 690), **12j–l** were the next synthetic targets. All three compounds showed decreased affinities, which might be ascribed to either an unfavorable steric effect of 2,4-substitution in **12k** or to the exceedance of the optimal lipophilicity or the electron withdrawing capacity of the substituents. To cross check, the derivatives **12m**, **12n**, and **12o** were also synthesized. As expected they turned out to have lower affinity than the best compound identified so far, the *p*-chloro-benzamide **12h**.

3. Conclusions

Although the Topliss approach can be highly useful in lead optimization, it did not furnish a significantly more potent compound in the presented case. The increase in potency from **12a** (rIP 690) with an unsubstituted phenyl group to the most potent compound **12h** (rIP 1074) is less than one order of magnitude in difference.

2,4-Substitution (**12k**) was found to be detrimental to the affinity. Steric limitations within the binding site or a change in the torsional angle between the phenyl group and the carbonyl carbon may explain this result. For substituents in the 3,4-position (**12i**), the electronic and steric effects seem to compensate each other. Finally, 4-substitution with CF_3, having a strongly increased π- and σ-effect also led to a decrease in affinity.

Compared to the trisaccharide **13**, which was used as reference compound, the new mono-sialoside **12h** shows an improvement of affinity toward MAG of more than a factor 1000. In addition, it is supposed to have improved pharmacokinetic properties because the number of hydrogen donors and acceptors is dramatically reduced compared to the reference compound, the molecular weight is close to 500, and the Clog P (1.47) is in the range of oral availability.[31] A further important issue to be addressed is the metabolic stability of the presented sialosides. In general, the substrate specificity of sialidases from mammalian tissues is determined by the type of bond at the terminal sialic acid residue (2–3, 2–6 or 2–8) and does not depend on the structure of the glycoconjugate chain.[32] Therefore, it cannot be excluded that the presented mimics are metabolically cleaved by sialidases.

4. Experimental

4.1. Chemistry

NMR spectra were recorded on a Bruker Avance DMX-500 (500 MHz) spectrometer. Assignment of ^1H and ^{13}C NMR spectra was achieved using 2D methods (COSY, HSQC, TOCSY). Chemical shifts are expressed in ppm using residual $CHCl_3$, CHD_2OD, and HDO as references. Optical rotations were measured using Perkin-Elmer Polarimeters 241 and 341. ESI-MS analyses were carried out using a Waters Micromass ZQ Detector system. The spectra were recorded in positive ESI mode. HR-MS were measured on a Bruker micrOTOF detector in positive mode. Reactions were monitored by TLC using glass plates coated with silica gel 60 F_{254} (Merck) and visualized by using UV light and/or by charring with a molybdate solution (a 0.02 M solution of ammonium cerium sulfate dihydrate and ammonium molybdate tetrahydrate in aqueous 10% H_2SO_4). Column chromatography was performed on silica gel (Fluka, 40–60 mesh). Methanol (MeOH) was dried by refluxing with sodium methoxide and distilled immediately before use. Pyridine was freshly distilled under

argon over CaH_2. Dichloromethane (DCM), dichloroethane (DCE), acetonitrile (MeCN), toluene, and benzene were dried by filtration over Al_2O_3 (Fluka, type 5016 A basic). Molecular sieves (3 Å) were activated in vacuo at 500 °C for 2 h immediately before use.

4.2. General procedure A for the synthesis of 9-substituted amides 11a–o

To a solution of **10** (1 equiv) and acid chloride (2–4 equiv) in toluene, DCM or DCE was added a solution of triphenyl phosphine (1.2–2.2 equiv) in DCM, DCE or toluene. After stirring for 1–3 h at room temperature, the solvent was evaporated. Purification by column chromatography on silica gel (DCM/MeOH 100:1 to 20:1) yielded **11a**–**11o** as solids.

4.3. General method B for deprotection

To a solution of the protected compound (25–50 mg) in MeOH (2 mL) was added 10% aq NaOH (0.2 mL). The mixture was stirred at room temperature for 3 h. The solution was concentrated and the residue was purified by reversed phase chromatography (RP-18 column, 5% gradient MeOH in water), Dowex 50 × 8 (Na^+ type) ion-exchange chromatography, and Sephadex G-15 size exclusion chromatography to afford the target molecule as colorless solid after a final lyophilization from water.

4.4. Methyl (5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (2)[20]

N-Acetyl neuraminic acid (**1**) (6.18 g, 20.0 mmol) and ion-exchange resin Amberlyst 15 (5.00 g) were stirred at rt in MeOH (300 mL) for 16 h. The reaction mixture was filtered and the residual solid thoroughly washed with MeOH. After evaporation of the solvent, the methyl ester (5.50 g) was obtained and taken as such for the acetylation step. The above product was dissolved in pyridine (68 mL) and stirred at 0 °C for 15 min under argon before DMAP (323 mg, 2.70 mmol) and Ac_2O (76.6 mL, 715 mmol) were added at 0 °C. The mixture was stirred at rt for 14 h and then concentrated in vacuo. Chromatography of the residue on silica gel (DCM/MeOH 20:1) yielded **2** (7.25 g, 81%) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.90 (s, 3H, NHCOCH_3), 2.04 (m, 10H, H-3a, 3 OCOCH_3), 2.14, 2.15 (2s, 6H, 2 OCOCH_3), 2.66 (dd, J = 5.0, 13.5 Hz, 1H, H-3e), 3.79 (s, 3H, OCH_3), 4.12 (m, 3H, H-5, H-6, H-9a), 4.49 (dd, J = 2.5, 12.4 Hz, 1H, H-9b), 5.08 (m, 1H, H-8), 5.26 (m, 1H, H-4), 5.38 (m, 2H, H-7, NH); ESI-MS Calcd for $C_{22}H_{31}NNaO_{14}$ [M+Na^+]: 556.2; Found: 556.1.

4.5. Methyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (3)[20]

To a stirred solution of **2** (7.20 g, 13.5 mmol) in DCE (100 mL) containing activated molecular sieves (3 Å, 5.0 g), TMSSMe (2.26 g, 18.9 mmol) and TMSOTf (2.24 g, 10.1 mmol) were added. The mixture was stirred under argon at 50 °C for 5 h and then for 16 h at rt After dilution with DCM (25 mL) the reaction mixture was subsequently washed with satd aqueous $NaHCO_3$ (100 mL) and H_2O (100 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography on silica gel (DCM/MeOH 40:1) yielded **3** (5.75 g, 82%) as a colorless foam, which was directly used in the next step.

4.6. Methyl (benzyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α- and β-D-*galacto*-2-nonulopyranosid)onate (4α and 4β)

A suspension of **3** (5.20 g, 10.0 mmol), benzyl alcohol (1.62 g, 15.0 mmol), and molecular sieves (3 Å, 5.0 g) in MeCN (100 mL) was cooled to −40 °C under argon. NIS (2.68 g, 12.0 mmol) and TfOH (600 mg, 4.00 mmol) were added successively at −40 °C. After stirring for 30 min, the reaction mixture was warmed to −30 °C and stirring was continued for additional 14 h. The mixture was diluted with DCM and filtered through a pad of Celite. After washing with 20% aqueous $Na_2S_2O_3$ (200 mL) and satd aqueous $NaHCO_3$ (200 mL), the organic layer was dried (Na_2SO_4), filtered, and concentrated to give a syrup. Purification by column chromatography on silica gel (petrol ether/DCM/*i*-PrOH 8:4:1) afforded **4α** (2.40 g, 41%) and **4β** (1.04 g, 18%).

Compound **4α**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.90 (s, 3H, NHCOCH_3). 2.03 (s, 3H, OCOCH_3), 2.03 (m, 4H, H-3a, OCOCH_3), 2.05, 2.14, 2.17 (3s, 9H, 3 OCOCH_3), 2.66 (dd, J = 4.6, 12.9 Hz, 1H, H-3e), 3.67 (s, 3H, OCH_3), 4.09–4.15 (m, 3H, H-5, H-6, H-9a), 4.33 (dd, J = 2.7, 12.4 Hz, 1H, H-9b), 4.43, 4.82 (A, B of AB, J = 12.0 Hz, 2H, CH_2Ph), 4.87 (m, 1H, H-4), 5.21 (m, 1H, NH), 5.35 (dd, J = 2.1, 8.5 Hz, 1H, H-7), 5.47 (m, 1H, H-8), 7.25–7.37 (s, 5H, C_6H_5); ESI-MS Calcd for $C_{27}H_{35}NNaO_{13}$ [M+Na^+]: 604.2; Found: 604.2.

Compound **4β**: ^{1}H NMR (500 MHz, $CDCl_3$): 1.87 (s, 3H, NHCOCH_3), 1.96 (m, 4H, H-3a, OCOCH_3), 2.01, 2.03, 2.16 (3s, 9H, 3 OCOCH_3), 2.56 (m, 1H, H-3e), 3.73 (s, 3H, OCH_3), 3.99 (dd, J = 2.2, 10.5 Hz, 1H, H-9a), 4.10–4.15 (m, 2H, H-5, H-9b), 4.52 (A, B of AB, J = 11.9 Hz, 2H, CH_2Ph), 4.84 (dd, J = 2.5, 12.5 Hz, 1H, H-6), 5.28–5.41 (m, 4H, H-4, H-7, H-8, NH), 7.28–7.36 (m, 5H, C_6H_5); ESI-MS Calcd for $C_{27}H_{35}NNaO_{13}$ [M+Na^+]: 604.2; Found: 604.3.

4.7. Sodium (benzyl 5-acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (5α)

According to General procedure B, compound **4α** (50.0 mg, 86.0 μmol) was treated with 10% aqueous NaOH (0.2 mL). Compound **5α** (33.9 mg, 94%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 4.3 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.60 (t, J = 11.9 Hz, 1H, H-3a), 1.89 (s, 3H, NHCOCH_3), 2.68 (dd, J = 3.5, 12.0 Hz, 1H, H-3e), 3.49–3.77 (m, 7H, H-4, H-5, H-6, H-7, H-8, H-9), 4.42, 4.65 (A, B of AB, J = 11.0 Hz, 2H, CH_2Ph), 7.30 (m, 5H, C_6H_5); ^{13}C NMR (125 MHz, D_2O): δ 22.4

(NHCOCH_3), 40.9 (C-3), 52.2 (C-5), 62.9 (C-9), 67.5 (CH_2Ph), 68.5 (C-7), 68.7 (C-4), 72.0 (C-8), 73.1 (C-6), 101.3 (C-2), 128.7, 129.0, 129.1, 137.4 (6C, C_6H_5), 173.9, 175.4 (2 CO); HR-MS Calcd for $C_{18}H_{24}NNa_2O_9$ [M+Na^+]: 444.1246; Found: 444.1245.

4.8. Sodium (benzyl 5-acetamido-3,5-dideoxy-D-*glycero*-β-D-*galacto*-2-nonulopyranosid)onate (5β)

According to General procedure B, compound **4β** (50.0 mg, 86.0 μmol) was treated with 10% aqueous NaOH (0.2 mL). Compound **5β** (34.0 mg, 94%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 1.3 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.68 (t, *J* = 12.1 Hz, 1H, H-3a), 1.90 (s, 3H, NHCOCH_3), 2.38 (dd, *J* = 4.7, 13.1 Hz, 1H, H-3e), 3.57 (d, *J* = 9.6 Hz, 1H, H-7), 3.67 (dd, *J* = 6.5, 12.0 Hz, 1H, H-9a), 3.83–3.97 (m, 4H, H-5, H-6, H-8, H-9b), 4.02 (m, 1H, H-4), 4.27, 4.60 (A, B of AB, *J* = 10.1 Hz, 2H, CH_2Ph), 7.39–7.47 (m, 5H, C_6H_5); ^{13}C NMR (125 MHz, D_2O): δ 23.6 (NHCOCH_3), 40.3 (C-3), 52.4 (C-5), 63.9 (C-9), 65.3 (CH_2Ph), 67.4 (C-4), 68.6 (C-7), 70.3 (C-8), 70.6 (C-6), 100.5 (C-2), 128.7, 129.1, 129.2, 137.5 (6C, C_6H_5), 175.1, 181.9 (2 CO); HR-MS Calcd for $C_{18}H_{24}NNa_2O_9$ [M+Na^+]: 444.1246; Found: 444.1248.

4.9. Methyl (benzyl 5-acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (6)

A solution of **4α** (2.38 g, 3.95 mmol) in MeOH (90 mL) was treated with 1 M NaOMe/MeOH (10.5 mL) at rt for 2 h. The reaction mixture was neutralized with Amberlyst 15 ion-exchange resin and filtered through a pad of Celite. The Celite was washed thoroughly with methanol (3 × 5 mL), and the combined filtrates were evaporated to dryness to give **6** as colorless foam (1.40 g, 82%).

^{1}H NMR (500 MHz, CD_3OD): δ 1.85 (t, *J* = 12.6 Hz, 1H, H-3a), 2.05 (s, 3H, NHCOCH_3), 2.78 (dd, *J* = 4.6, 12.8 Hz, 1H, H-3e), 3.58 (dd, *J* = 1.6, 11.0 Hz, 1H, H-9a), 3.67–3.74 (m, 3H, H-4, H-6, H-9b), 3.81 (s, 3H, OCH_3), 3.83–3.95 (m, 4H, H-5, H-7, H-8, NH), 4.56, 4.86 (A, B of AB, *J* = 11.6 Hz, 2H, CH_2Ph), 7.28–7.33 (m, 5H, C_6H_5); ESI-MS Calcd for $C_{19}H_{27}NNaO_9$ [M+Na^+]: 436.2; Found: 436.1.

4.10. Methyl [benzyl 5-acetamido-3,5-dideoxy-9-*O*-(4-toluenesulfonyl)-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (7)

To a solution of **6** (1.20 g, 2.90 mmol) in pyridine was added *p*-TsCl (608 mg, 3.20 mmol) at 0 °C. After 2 h, an additional portion of *p*-TsCl (220 mg, 1.16 mmol) was added and stirring continued for 16 h at 5 °C. The reaction mixture was warmed to rt, diluted with MeOH (40 mL), and stirring continued for 30 min. After removal of the solvents the remaining syrup was purified by chromatography on silica gel (DCM/MeOH 19:1) to yield **7** (929 mg, 56%) as a colorless foam.

^{1}H NMR (500 MHz, CD_3OD): δ 1.80 (t, *J* = 12.7 Hz, 1H, H-3a), 2.04 (s, 3H, NHCOCH_3), 2.45 (s, 3H, CH_3), 2.74 (dd, *J* = 4.6, 12.8 Hz, 1H, H-3e), 3.52 (dd, *J* = 1.5, 8.5 Hz, 1H, H-7), 3.65 (dd, *J* = 1.5, 10.4 Hz, 1H, H-6), 3.69 (m, 1H, H-4), 3.77 (m, 1H, H-5), 3.79 (s, 3H, OCH_3), 4.05 (ddd, *J* = 2.1, 6.4, 9.4 Hz, 1H, H-8), 4.13 (dd, *J* = 6.4, 10.1 Hz, 1H, H-9a), 4.40 (dd, *J* = 2.2, 10.1 Hz, 1H, H-9b), 4.49, 4.77 (A, B of AB, *J* = 11.6 Hz, 2H, CH_2Ph), 7.33, 7.45, 7.83 (m, 9H, C_6H_4, C_6H_5); ESI-MS Calcd for $C_{26}H_{33}NNaO_{11}S$ [M+Na^+]: 590.2; Found: 590.2.

4.11. Methyl (benzyl 5-acetamido-9-azido-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (8)

A suspension of **7** (910 mg, 1.60 mmol), crown ether 18-C-6 (169 mg, 0.64 mmol), and NaN_3 (520 mg, 8.00 mmol) was stirred in DMF (30 mL) at 60 °C for 24 h. The mixture was filtered through a pad of Celite and the filtrate was evaporated to dryness. Purification by column chromatography on silica gel (DCM/acetone 7:3) gave **8** (525 mg, 75%) as a white solid.

^{1}H NMR (500 MHz, CD_3OD): δ 1.84 (t, *J* = 12.6 Hz, 1H, H-3a), 2.06 (s, 3H, NHCOCH_3), 2.77 (dd, *J* = 4.6, 12.8 Hz, 1H, H-3e), 3.43 (dd, *J* = 6.2, 12.9 Hz, 1H, H-9a), 3.54 (dd, *J* = 1.4, 8.9 Hz, 1H, H-7), 3.60 (dd, *J* = 2.5, 12.8 Hz, 1H, H-9b), 3.75 (m, 2H, H-4, H-6), 3.81 (s, 3H, OCH_3), 3.83 (m, 1H, H-5), 4.06 (m, 1H, H-8), 4.57, 4.85 (A, B of AB, *J* = 11.6 Hz, 2H, CH_2Ph), 7.34–7.38 (m, 5H, C_6H_5); ESI-MS Calcd for $C_{19}H_{26}N_4NaO_8$ [M+Na^+]: 461.2; Found: 461.1.

4.12. Sodium (benzyl 5-acetamido-9-azido-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (9)

According to General procedure B, compound **8** (25.0 mg, 45.0 μmol) was treated with 10% aqueous NaOH. Compound **9** (17.0 mg, 85%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 3.6 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.67 (t, *J* = 12.2 Hz, 1H, H-3a), 2.03 (s, 3H, NHCOCH_3), 2.76 (dd, *J* = 4.6, 12.4 Hz, 1H, H-3e), 3.46 (dd, *J* = 6.1, 13.2 Hz, 1H, H-9a), 3.57 (dd, *J* = 1.8, 9.1 Hz, 1H, H-7), 3.63 (dd, *J* = 2.6, 13.2 Hz, 1H, H-9b), 3.68 (ddd, *J* = 4.1, 4.6, 11.8 Hz, 1H, H-4), 3.74 (d, *J* = 10.4 Hz, 1H, H-6), 3.79–3.83 (m, 2H, H-5, H-8), 4.53, 4.72 (A, B of AB, *J* = 11.0 Hz, 2H, CH_2Ph), 7.39–7.43 (m, 5H, C_6H_5); ^{13}C NMR (125 MHz, D_2O): δ 20.5 (NHCOCH_3), 39.1 (C-3), 50.4 (C-5), 51.5 (C-9), 65.8 (CH_2Ph), 66.8 (C-4), 67.4 (C-7), 68.8 (C-8), 71.0 (C-6), 99.6 (C-2), 126.8, 127.2, 127.2, 135.7 (6C, C_6H_5), 172.0, 173.6 (2 CO); HR-MS Calcd for $C_{18}H_{24}N_4NaO_8$ [M+H^+]: 447.1492; Found: 447.1490.

4.13. Methyl (benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-9-azido-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (10)

Compound **8** (480 mg, 1.09 mmol) was dissolved in pyridine (4.38 mL, 54.3 mmol) and stirred at 0 °C for 15 min under argon before DMAP (21.4 mg, 0.175 mmol) and Ac_2O (3.27 mL, 46.0 mmol) were added at 0 °C. The mixture was stirred at rt for 14 h and then concentrated in va-

cuo. Chromatography of the residue on silica gel (DCM/MeOH 20:1) yielded **10** (470 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.89 (s, 3H, NHC-OCH_3), 2.03 (s, 3H, $OCOCH_3$), 2.04 (t, J = 12.6 Hz, 1H, H-3a), 2.17, 2.19 (2s, 6H, 2 $OCOCH_3$), 2.67 (dd, J = 4.6, 12.9 Hz, 1H, H-3e), 3.28 (dd, J = 5.9, 13.5 Hz, 1H, H-9a), 3.59 (dd, J = 3.0, 13.5 Hz, 1H, H-9b), 3.70 (s, 3H, OCH_3), 4.12 (m, 1H, H-5), 4.44, 4.80 (A, B of AB, J = 11.9 Hz, 2H, CH_2Ph), 4.87 (m, 1H, H-4), 5.19 (m, 1H, NH), 5.36 (m, 3H, H-6, H-7, H-8), 7.28–7.34 (m, 5H, Ar-H); ESI-MS Calcd for $C_{25}H_{32}N_4NaO_{11}$ [M+Na$^+$]: 587.2; Found: 587.4.

4.14. Methyl (benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-9-benzamido-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (11a)

According to General procedure A, **10** (42.0 mg, 74.4 μmol) was reacted with benzoyl chloride (20.0 mg, 142 μmol) and PPh_3 (24.0 mg, 91.5 μmol) in toluene (2 mL) for 1 h. After purification **11a** (25.0 mg, 54%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.99 (s, 3H, $NHCOCH_3$), 2.05 (m, 4H, H-3a, $OCOCH_3$), 2.15, 2.27 (2s, 6H, 2 $OCOCH_3$), 2.67 (dd, J = 4.6, 12.8 Hz, 1H, H-3e), 2.96 (dd, J = 3.3, 11.5 Hz, 1H, H-9a), 3.65 (s, 3H, OCH_3), 4.06 (d, J = 10.7 Hz, 1H, H-6), 4.21 (q, J = 10.7 Hz, 1H, H-5), 4.39 (m, 1H, H-9b), 4.44, 4.83 (A, B of AB, J = 12.0 Hz, 2H, CH_2Ph), 4.85 (m, 1H, H-4), 5.16–5.18 (m, 2H, NH-5, H-7), 5.33 (m, 1H, H-8), 7.09 (m, 1H, NH-9), 7.33–7.44, 7.84 (m, 10H, 2 C_6H_5); ESI-MS Calcd for $C_{32}H_{38}N_2NaO_{12}$ [M+Na$^+$]: 665.2; Found: 665.3.

4.15. Methyl [benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-9-(4-biphenylcarboxamido)-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (11b)

According to General procedure A, **10** (50.0 mg, 88.6 μmol) was reacted with biphenyl-4-carbonyl chloride (36.3 mg, 168 μmol) and PPh_3 (26.2 mg, 100 μmol) in toluene (2 mL) for 2 h. After purification **11b** (14.0 mg, 24%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.91 (s, 3H, NHC-OCH_3), 2.06 (m, 3H, H-3a, $OCOCH_3$), 2.16, 2.28 (2s, 6H, 2 $OCOCH_3$), 2.67 (dd, J = 4.6, 12.7 Hz, 1H, H-3e), 2.98 (m, 1H, H-9a), 3.65 (s, 3H, OCH_3), 4.07 (dd, J = 2.0, 10.8 Hz, 1H, H-6), 4.22 (dd, J = 10.3, 10.8 Hz, 1H, H-5), 4.41 (m, 1H, H-9b), 4.45, 4.85 (A, B of AB, J = 12.0 Hz, 2H, CH_2Ph), 4.86 (m, 1H, H-4), 5.20 (m, 2H, H-7, NH-5), 5.35 (m, 1H, H-8), 7.15 (m, 1H, NH-9), 7.33–7.39, 7.47, 7.62–7.67, 7.91 (m, 14H, C_6H_4, 2 C_6H_5); ESI-MS Calcd for $C_{38}H_{42}N_2NaO_{12}$ [M+Na$^+$]: 741.3; Found: 741.2.

4.16. Methyl [benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-9-(2-biphenylcarboxamido)-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (11c)

According to General procedure A, **10** (50.0 mg, 88.6 μmol) was reacted with biphenyl-2-carbonyl chloride (72.5 mg, 336 μmol) and PPh_3 (48.4 mg, 184 μmol) in DCM (2 mL) for 1 h. After purification **11c** (40.0 mg, 66%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.02 (m, 4H, H-3a, NHC-OCH_3), 2.08, 2.15, 2.17 (3s, 9H, $OCOCH_3$), 2.63–2.70 (m, 2H, H-3e, H-9a), 3.69 (s, 3H, OCH_3), 3.94 (dd, J = 2.3, 10.7 Hz, 1H, H-6), 4.06–4.15 (m, 2H, H-5, H-9b), 4.39, 4.79 (A, B of AB, J = 12.0 Hz, 2H, CH_2Ph), 4.67 (dd, J = 2.2, 9.4 Hz, 1H, H-7), 4.83 (m, 1H, H-4), 4.99 (m, 1H, NH-5), 5.12 (m, 1H, H-8), 5.99 (m, 1H, NH-9), 7.31–7.59 (m, 14H, C_6H_4, 2 C_6H_5); ESI-MS Calcd for $C_{38}H_{42}N_2NaO_{12}$ [M+Na$^+$]: 741.3; Found: 741.3.

4.17. Methyl (benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-3,5,9-trideoxy-9-orotinoylamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (11d)

According to General procedure A, **10** (50.0 mg, 88.6 μmol) was reacted with orotinoyl chloride (63.8 mg, 336 μmol) and PPh_3 (48.4 mg, 184 μmol) in DCM (2 mL) for 1 h. After purification **11d** (40.0 mg, 70%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.92 (s, 3H, $NHCOCH_3$), 2.05 (m, 4H, H-3a, $OCOCH_3$), 2.13, 2.26 (2s, 6H, $OCOCH_3$), 2.67 (dd, J = 4.6, 12.7 Hz, 1H, H-3e), 2.93 (m, 1H, H-9a), 3.99 (s, 3H, OCH_3), 4.03 (dd, J = 2.0, 10.7 Hz, 1H, H-6), 4.21 (m, 1H, H-5), 4.27 (m, 1H, H-9b), 4.41, 4.79 (A, B of AB, J = 12.0 Hz, 2H, CH_2Ph), 4.84 (m, 1H, H-4), 5.04 (dd, J = 2.0, 9.9 Hz, 1H, H-7), 5.32 (m, 2H, NH-5, H-8), 6.08 (s, CH= C), 6.40 (s, C= CH) 7.30–7.34 (s, 5H, C_6H_5), 7.49 (m, 1H, NH-9), 8.65 (m, 1H, allylic NH), 8.82 (s, 1H, NH); ESI-MS Calcd for $C_{30}H_{37}N_4NaO_{14}$ [M+H$^+$]: 677.2; Found: 677.2.

4.18. Methyl (benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-9-butyrylamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (11e)

According to General procedure A, **10** (50.0 mg, 88.6 μmol) was reacted with butyryl chloride (35.8 mg, 336 μmol) and PPh_3 (48.4 mg, 184 μmol) in DCM (2 mL) for 3 h. After purification **11e** (43.0 mg, 84%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (t, J = 8.3 Hz, 3H, H-4′), 1.63–1.68 (m, 2H, H-3′), 1.91 (s, 3H, NHC-OCH_3), 2.04 (m, 4H, H-3a, $OCOCH_3$), 2.13 (s, 3H, $OCOCH_3$), 2.17 (t, J = 7.4 Hz, 2H, H-2′), 2.21 (s, 3H, $OCOCH_3$), 2.66 (dd, J = 4.5, 12.8 Hz, 1H, H-3e), 2.78 (m, 1H, H-9a), 3.66 (s, 3H, OCH_3), 4.04–4.20 (m, 3H, H-5, H-6, H-9b), 4.42, 4.82 (A, B of AB, J = 12.0 Hz, 2H, CH_2Ph), 4.86 (m, 1H, H-4), 5.09 (d, J = 10.6 Hz, 1H, H-7), 5.21–5.25 (m, 2H, H-8, NH-5), 6.17 (m, 1H, NH-9), 7.32 (m, 5H, C_6H_5); ESI-MS Calcd for $C_{29}H_{40}N_2NaO_{12}$ [M+Na$^+$]: 631.2; Found: 631.3.

4.19. Methyl (benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-3,5,9-trideoxy-9-hexanoylamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (11f)

According to General procedure A, **10** (50.0 mg, 88.6 μmol) was reacted with caproyl chloride (45.6 mg,

336 μmol) and PPh_3 (48.4 mg, 184 μmol) in DCM (2 mL) for 3 h. After purification **11f** (25.9 mg, 49%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (t, J = 6.9 Hz, 3H, H-6′), 1.28–1.32 (m, 4H, H-4′, H-5′), 1.62 (m, 2H, H-3′), 1.91 (s, 3H, $NHCOCH_3$), 2.04 (m, 4H, H-3a, $OCOCH_3$), 2.13 (s, 3H, $OCOCH_3$), 2.18 (t, J = 6.9 Hz, 2H, H-2′), 2.21 (s, 3H, $OCOCH_3$), 2.56 (dd, J = 4.6, 12.8 Hz, 1H, H-3e), 2.79 (m, 1H, H-9a), 3.66 (s, 3H, OCH_3), 4.09 (m, 2H, H-6, H-9b), 4.18 (q, J = 10.4 Hz, 1H, H-5), 4.42, 4.82 (A, B of AB, J = 12.0 Hz, 2H, CH_2Ph), 4.86 (ddd, J = 5.7, 6.5, 10.4 Hz, 1H, H-4), 5.01 (dd, J = 2.1, 9.7 Hz, 1H, H-7), 5.23–5.25 (m, 2H, H-8, NH-5), 6.14 (m, 1H, NH-9), 7.26–7.33 (m, 5H, C_6H_5); ESI-MS Calcd for $C_{31}H_{44}N_2NaO_{12}$ [M+Na^+]: 659.3; Found: 659.3.

4.20. Methyl (benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-9-decanoylamido-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (11g)

According to General procedure A, **10** (50.0 mg, 88.6 μmol) was reacted with decanoyl chloride (65.2 mg, 336 μmol) and PPh_3 (48.4 mg, 184 μmol) in DCM (2 mL) for 3 h. After purification **11g** (30.2 mg, 51%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, J = 6.8 Hz, 3H, H-10′), 1.26–1.31 (m, 14H, H-4′, H-5′, H-6′, H-7′, H-8′, H-9′), 1.60 (m, 2H, H-3′), 1.91 (s, 3H, $NHCOCH_3$), 2.04 (m, 4H, H-3a, $OCOCH_3$), 2.13 (s, 3H, $OCOCH_3$), 2.18 (t, J = 7.9 Hz, 2H, H-2′), 2.21 (s, 3H, $OCOCH_3$), 2.66 (dd, J = 4.5, 12.7 Hz, 1H, H-3e), 2.79 (m, 1H, H-9a), 3.65 (s, 3H, OCH_3), 4.06–4.20 (m, 3H, H-5, H-6, H-9b), 4.42, 4.82 (A, B of AB, J = 12.0 Hz, 2H, CH_2Ph), 4.86 (ddd, J = 4.9, 6.2, 10.3 Hz, 1H, H-4), 5.09 (d, J = 8.8 Hz, 1H, H-7), 5.18–5.25 (m, 2H, H-8, NH-5), 6.13 (m, 1H, NH-9), 7.27–7.33 (m, 5H, C_6H_5); ESI-MS Calcd for $C_{35}H_{52}N_2NaO_{12}$ [M+Na^+]: 715.3; Found: 715.4.

4.21. Methyl [benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-9-(4-chlorobenzamido)-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (11h)

According to General procedure A, **10** (40.0 mg, 70.9 μmol) was reacted with *p*-chlorobenzoyl chloride (49.0 mg, 280 μmol) and PPh_3 (40.3 mg, 154 μmol) in DCE (2 mL) for 14 h. After purification **11h** (32.0 mg, 68%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.89 (s, 3H, NHC-OCH_3), 2.04 (m, 4H, H-3a, $OCOCH_3$), 2.14, 2.26 (2s, 6H, 2 $OCOCH_3$), 2.67 (dd, J = 4.6, 12.8 Hz, 1H, H-3e), 2.96 (m, 1H, H-9a), 3.64 (s, 3H, OCH_3), 4.06 (dd, J = 2.0, 10.7 Hz, 1H, H-6), 4.20 (q, J = 10.4 Hz, 1H, H-5), 4.35 (m, 1H, H-9b), 4.43 (A of AB, J = 12.0 Hz, 1H, CH_2Ph), 4.83 (m, 2H, H-4, CH_2Ph), 5.15 (dd, J = 2.0, 9.9 Hz, 1H, H-7), 5.27 (d, J = 10.1 Hz, 1H, NH-5), 5.34 (m, 1H, H-8), 7.09 (m, 1H, NH-9), 7.25–7.43, 7.77 (m, 9H, C_6H_4, C_6H_5); ESI-MS Calcd for $C_{32}H_{37}ClN_2NaO_{12}$ [M+Na^+]: 699.2; Found: 699.2.

4.22. Methyl [benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-9-(3,4-dichlorobenzamido)-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (11i)

According to General procedure A, **10** (40.0 mg, 70.9 μmol) was reacted with 3,4-dichlorobenzoyl chloride (58.5 mg, 280 μmol) and PPh_3 (40.3 mg, 154 μmol) in DCE (2 mL) for 14 h. After purification **11i** (31.1 mg, 63%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.91 (s, 3H, NHC-OCH_3), 2.04 (m, 4H, H-3a, $OCOCH_3$), 2.14, 2.27 (2s, 6H, 2 $OCOCH_3$), 2.67 (dd, J = 4.6, 12.8 Hz, 1H, H-3e), 2.95 (m, 1H, H-9a), 3.65 (s, 3H, OCH_3), 4.06 (dd, J = 2.0, 10.7 Hz, 1H, H-6), 4.22 (q, J = 10.4 Hz, 1H, H-5), 4.35 (m, 1H, H-9b), 4.43 (A of AB, J = 12.0 Hz, 1H, CH_2Ph), 4.85 (m, 2H, H-4, CH_2Ph), 5.14 (dd, J = 2.1, 9.9 Hz, 1H, H-7), 5.25 (d, J = 10.1 Hz, 1H, NH-5), 5.33 (m, 1H, H-8), 7.12 (m, 1H, NH-9), 7.33, 7.51, 7.62, 7.94 (m, 8H, C_6H_3, C_6H_5); ESI-MS Calcd for $C_{32}H_{36}Cl_2N_2NaO_{12}$ [M+Na^+]: 733.2; Found: 733.1.

4.23. Methyl [benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-3,5,9-trideoxy-9-(4-trifluoromethyl-benzamido)-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (11j)

According to General procedure A, **10** (40.0 mg, 70.9 μmol) was reacted with 4-trifluoromethyl-benzoyl chloride (58.2 mg, 280 μmol) and PPh_3 (40.3 mg, 154 μmol) in DCE (2 mL) for 14 h. After purification **11j** (30.0 mg, 60%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.82 (s, 3H, NHC-OCH_3), 1.97 (m, 4H, H-3a, $OCOCH_3$), 2.07, 2.20 (2s, 6H, $OCOCH_3$), 2.60 (dd, J = 4.6, 12.8 Hz, 1H, H-3e), 2.92 (m, 1H, H-9a), 3.57 (s, 3H, OCH_3), 3.99 (m, 1H, H-6), 4.14 (q, J = 10.4 Hz, 1H, H-5), 4.29 (m, 1H, H-9b), 4.36 (A of AB, J = 12.0 Hz, 1H, CH_2Ph), 4.76 (m, 2H, H-4, CH_2Ph), 5.08 (dd, J = 2.1, 9.9 Hz, 1H, H-7), 5.29 (m, 2H, H-8, NH-5), 7.13–7.26, 7.63, 7.86 (m, 10H, NH-9, C_6H_4, C_6H_5); ESI-MS Calcd for $C_{33}H_{37}F_3N_2NaO_{12}$ [M+Na^+]: 733.2; Found: 733.2.

4.24. Methyl [benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-9-(2,4-dichlorobenzamido)-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (11k)

According to General procedure A, **10** (40.0 mg, 70.9 μmol) was reacted with 2,4-dichlorobenzoyl chloride (58.5 mg, 280 μmol) and PPh_3 (40.3 mg, 154 μmol) in DCE (2 mL) for 14 h. After purification **11k** (30.8 mg, 62%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.82 (s, 3H, NHC-OCH_3), 1.97 (m, 4H, H-3a, $OCOCH_3$), 2.09, 2.15 (2s, 6H, 2 $OCOCH_3$), 2.60 (dd, J = 4.6, 12.8 Hz, 1H, H-3e), 2.87 (m, 1H, H-9a), 3.59 (s, 3H, OCH_3), 4.01 (dd, J = 2.0, 10.8 Hz, 1H, H-6), 4.11 (q, J = 10.4 Hz, 1H, H-5), 4.29 (m, 1H, H-9b), 4.37, 4.76 (A, B of AB, J = 12.0 Hz, 2H, CH_2Ph), 4.80 (m, 1H, H-4), 5.11 (dd, J = 1.9, 9.7 Hz, 1H, H-7), 5.22–5.24 (m, 2H, H-8, NH-5), 6.84 (m, 1H, NH-9), 7.18–7.26, 7.35, 7.49 (m, 8H,

C_6H_3, C_6H_5); ESI-MS Calcd for $C_{32}H_{36}Cl_2N_2NaO_{12}$ [M+Na^+]: 733.2; Found: 733.2.

4.25. Methyl [benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-3,5,9-trideoxy-9-(4-nitrobenzamido)-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (11l)

According to General procedure A, **10** (40.0 mg, 70.9 μmol) was reacted with *p*-nitrobenzoyl chloride (51.8 mg, 280 μmol) and PPh_3 (40.3 mg, 154 μmol) in DCE (2 mL) for 14 h. After purification **11l** (28.1 mg, 58%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.82 (s, 3H, $NHCOCH_3$), 1.99 (m, 4H, H-3a, $OCOCH_3$), 2.08, 2.20 (2s, 6H, 2 $OCOCH_3$), 2.60 (dd, *J* = 4.6, 12.7 Hz, 1H, H-3e), 2.93 (m, 1H, H-9a), 3.58 (s, 3H, OCH_3), 3.99 (dd, *J* = 2.0, 10.7 Hz, 1H, H-6), 4.15 (q, *J* = 10.4 Hz, 1H, H-5), 4.30 (m, 1H, H-9b), 4.36 (A of AB, *J* = 11.9 Hz, 1H, C*H*$_2$Ph), 4.76 (m, 2H, H-4, C*H*$_2$Ph), 5.08 (dd, *J* = 2.0, 9.8 Hz, 1H, H-7), 5.27 (m, 2H, H-8, NH-5), 7.18–7.30, 7.91, 8.20 (m, 10H, NH-9, C_6H_4, C_6H_5); ESI-MS Calcd for $C_{32}H_{37}N_3NaO_{14}$ [M+Na^+]: 710.2; Found: 710.2.

4.26. Methyl [benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-3,5,9-trideoxy-9-(4-methoxybenzamido)-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (11m)

According to General procedure A, **10** (40.0 mg, 70.9 μmol) was reacted with *p*-anisoyl chloride (47.6 mg, 280 μmol) and PPh_3 (40.3 mg, 154 μmol) in DCE (2 mL) for 14 h. After purification **11m** (25.0 mg, 53%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.89 (s, 3H, $NHCOCH_3$), 2.04 (m, 4H, H-3a, $OCOCH_3$), 2.14, 2.25 (2s, 6H, 2 $OCOCH_3$), 2.67 (dd, *J* = 4.6, 12.7 Hz, 1H, H-3e), 2.95 (m, 1H, H-9a), 3.64, 3.84 (2s, 6H, 2 OCH_3), 4.06 (dd, *J* = 2.1, 10.7 Hz, 1H, H-6), 4.21 (q, *J* = 10.4 Hz, 1H, H-5), 4.35 (m, 1H, H-9b), 4.44 (A of AB, *J* = 11.9 Hz, 1H, C*H*$_2$Ph), 4.84 (m, 2H, H-4, C*H*$_2$Ph), 5.18 (dd, *J* = 2.0, 9.8 Hz, 1H, H-7), 5.26 (d, *J* = 10.1 Hz, 1H, NH-5), 5.33 (m, 1H, H-8), 6.92, 6.96, 7.24, 7.34, 7.79 (m, 10H, NH-9, C_6H_4, C_6H_5); ESI-MS Calcd for $C_{33}H_{40}N_2NaO_{13}$ [M+Na^+]: 695.2; Found: 695.3.

4.27. Methyl [benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-3,5,9-trideoxy-9-(4-methylbenzamido)-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (11n)

According to General procedure A, **10** (40.0 mg, 70.9 μmol) was reacted with *p*-toluyl chloride (43.1 mg, 280 μmol) and PPh_3 (40.3 mg, 154 μmol) in DCE (2 mL) for 14 h. After purification **11n** (26.2 mg, 56%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.89 (s, 3H, $NHCOCH_3$), 2.04 (m, 4H, H-3a, $OCOCH_3$), 2.14, 2.26 (2s, 6H, 2 $OCOCH_3$), 2.39 (s, 3H, PhC*H*$_3$), 2.67 (dd, *J* = 4.6, 12.8 Hz, 1H, H-3e), 2.96 (m, 1H, H-9a), 3.64 (s, 3H, OCH_3), 4.06 (dd, *J* = 1.9, 10.8 Hz, 1H, H-6), 4.20 (q, *J* = 10.4 Hz, 1H, H-5), 4.36 (m, 1H, H-9b), 4.43 (A of AB, *J* = 12.0 Hz, 1H, C*H*$_2$Ph), 4.84 (m, 2H, H-4, C*H*$_2$Ph), 5.17 (dd, *J* = 1.9, 9.8 Hz, 1H, H-7), 5.24 (d, *J* = 10.1 Hz, 1H, NH-5), 5.33 (m, 1H, H-8), 7.04 (m, 1H, NH-9), 7.22–7.33, 7.73 (m, 9H, C_6H_4, C_6H_5); ESI-MS Calcd for $C_{33}H_{40}N_2NaO_{12}$ [M+Na^+]: 679.2; Found: 679.2.

4.28. Methyl [benzyl 5-acetamido-4,7,8-tri-*O*-acetyl-9-(3-chlorobenzamido)-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (11o)

According to General procedure A, **10** (40.0 mg, 70.9 μmol) was reacted with *m*-chlorobenzoyl chloride (49.0 mg, 280 μmol) and PPh_3 (40.3 mg, 154 μmol) in DCE (2 mL) for 14 h. After purification **11o** (28.0 mg, 59%) was obtained as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.84 (s, 3H, $NHCOCH_3$), 1.99 (m, 4H, H-3a, $OCOCH_3$), 2.07, 2.19 (2s, 6H, $OCOCH_3$), 2.60 (dd, *J* = 4.6, 12.9 Hz, 1H, H-3e), 2.87 (m, 1H, H-9a), 3.57 (s, 3H, OCH_3), 3.99 (d, *J* = 10.7 Hz, 1H, H-6), 4.14 (q, *J* = 10.7 Hz 1H, H-5), 4.29 (m, 1H, H-9b), 4.36 (A of AB, *J* = 12.0 Hz, 1H, C*H*$_2$Ph), 4.77 (m, 2H, H-4, C*H*$_2$Ph), 5.09 (d, *J* = 9.9 Hz, 1H, H-7), 5.22 (m, 2H, H-8, NH-5), 7.04 (m, 1H, NH-9), 7.14–7.41, 7.60, 7.76 (m, 9H, C_6H_4, C_6H_5); ESI-MS Calcd for $C_{32}H_{37}ClN_2NaO_{12}$ [M+Na^+]: 699.2; Found: 699.2.

4.29. Sodium (benzyl 5-acetamido-9-benzamido-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (12a)

According to General procedure B, compound **11a** (25.0 mg, 38.0 μmol) was treated with 10% aqueous NaOH. Compound **12a** (19.0 mg, 95%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 2.0 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.65 (t, *J* = 11.8 Hz, 1H, H-3a), 1.99 (s, 3H, $NHCOCH_3$), 2.77 (dd, *J* = 3.5, 11.8 Hz, 1H, H-3e), 3.46–3.52 (m, 2H, H-7, H-9a), 3.68 (m, 1H, H-4), 3.75–3.84 (m, 4H, H-5, H-6, H-8, H-9b), 4.53, 4.70 (A, B of AB, *J* = 11.2 Hz, 2H, C*H*$_2$Ph), 7.27–7.39, 7.52, 7.60, 7.78 (m, 10H, 2 C_6H_5); ^{13}C NMR (125 MHz, D_2O): δ 21.5 (NHCO*C*H3), 40.1 (C-3), 42.1 (C-9), 51.4 (C-5), 66.9 (*C*H$_2$Ph), 67.8 (C-4), 69.4 (C-7), 69.8 (C-8), 72.2 (C-6), 101.0 (C-2), 126.6, 127.7, 128.2, 128.3, 131.7, 133.2, 136.8 (12C, 2 C_6H_5), 170.7, 172.5, 174.6 (3 CO); HR-MS Calcd for $C_{25}H_{30}N_2NaO_9$ [M+H^+]: 525.1849; Found: 525.1850.

4.30. Sodium [benzyl 5-acetamido-9-(4-biphenylcarboxamido)-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (12b)

According to General procedure B, compound **11b** (14.0 mg, 19.0 μmol) was treated with 10% aqueous NaOH. Compound **12b** (7.1 mg, 64%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 4.8 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.69 (t, *J* = 12.2 Hz 1H, H-3a), 2.01 (s, 3H, $NHCOCH_3$), 2.77 (dd, *J* = 4.6, 12.2 Hz, 1H, H-3e), 3.44 (dd, *J* = 8.5, 14.7 Hz 1H, H-9a), 3.54 (d, *J* = 8.5 Hz, 1H, H-7), 3.68

(m, 1H, H-4), 3.79–3.83 (m, 4H, H-5, H-6, H-8, H-9b), 4.48, 4.68 (A, B of AB, $J = 11.2$ Hz, 2H, CH_2Ph), 7.22–7.32, 7.39, 7.54, 7.72 (m, 14H, 2 C_6H_5, C_6H_4); ^{13}C NMR (125 MHz, D_2O): δ 22.3 (NHCOCH_3), 40.5 (C-3), 42.5 (C-9), 52.2 (C-5), 67.5 (CH_2Ph), 68.6 (C-4), 70.4 (C-7), 70.8 (C-8), 73.0 (C-6), 101.5 (C-2), 127.3, 127.9, 128.4, 128.6, 128.8, 128.9, 129.4, 132.5, 137.4, 139.6, 144.2 (18C, 2 C_6H_5, C_6H_4), 171.5, 174.6, 176.3 (3 CO); HR-MS Calcd for $C_{31}H_{33}N_2Na_2O_9$ [M+Na$^+$]: 623.1981; Found: 623.1981.

4.31. Sodium [benzyl 5-acetamido-9-(2-biphenylcarboxamido)-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (12c)

According to General procedure B, compound **11c** (40.0 mg, 55.1 μmol) was treated with 10% aqueous NaOH. Compound **12c** (31.9 mg, 97%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 2.7 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.51 (t, $J = 11.4$ Hz, 1H, H-3a), 1.92 (s, 3H, NHCOCH_3), 2.63 (dd, $J = 4.3$, 10.5 Hz, 1H, H-3e), 2.97 (dd, $J = 9.0$, 13.9 Hz, 1H, H-9a), 3.27 (d, $J = 9.1$ Hz, 1H, H-7), 3.47 (m, 1H, H-8), 3.55–3.59 (m, 4H, H-4, H-5, H-6, H-9b), 4.36, 4.58 (A, B of AB, $J = 10.7$ Hz, 2H, CH_2Ph), 6.93, 7.02 7.07, 7.18–7.34 (m, 14H, 2 C_6H_5, C_6H_4); ^{13}C NMR (125 MHz, D_2O): δ 22.4 (NHCOCH_3), 40.7 (C-3), 43.5 (C-9), 52.2 (C-5), 67.5 (CH_2Ph), 68.6 (C-4), 70.2 (C-8), 70.4 (C-7), 72.8 (C-6), 101.2 (C-2), 127.9, 128.0, 128.1, 128.7, 128.9, 129.0, 129.3, 130.5, 130.9, 135.1, 137.2, 129.9, 140.1 (18C, 2 C_6H_5, C_6H_4), 173.5, 173.8, 175.4 (3 CO); HR-MS Calcd for $C_{31}H_{33}N_2Na_2O_9$ [M+Na$^+$]: 623.1981; Found: 623.1984.

4.32. Sodium (benzyl 5-acetamido-3,5,9-trideoxy-9-orotinoylamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (12d)

According to General procedure B, compound **11d** (40.0 mg, 58.9 μmol) was treated with 10% aqueous NaOH. Compound **12d** (32.1 mg, 96%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 3.7 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.69 (t, $J = 12.1$ Hz, 1H, H-3a), 2.01 (s, 3H, NHCOCH_3), 2.76 (dd, $J = 4.5$, 12.4 Hz, 1H, H-3e), 2.97 (m, 1H, H-9a), 3.44–3.52 (m, 2H, H-7, H-9b), 3.66–3.84 (m, 4H, H-4, H-5, H-6, H-8), 4.54, 4.69 (A, B of AB, $J = 11.3$ Hz, 2H, CH_2Ph), 6.07, 6.22 (2s, 2H, orotinoyl-H), 7.31–7.41 (m, 5H, C_6H_5); ^{13}C NMR (125 MHz, D_2O): δ 23.6 (NHCOCH_3), 42.1 (C-3), 44.9 (C-9), 52.2 (C-5), 67.7 (CH_2Ph), 68.6 (C-4), 70.1 (C-7), 70.4 (C-8), 72.9 (C-6), 98.2 (HN–C=*C*–), 100.8 (HN-*C*= C-), 128.5, 128.9, 129.1, 137.7 (6C, C_6H_5), 161.4, 166.7, 174.0, 176.0, 182.0 (5 CO); HR-MS Calcd for $C_{23}H_{27}N_4Na_2O_{11}$ [M+Na$^+$]: 581.1472; Found: 581.1460.

4.33. Sodium (benzyl 5-acetamido-9-butyrylamido-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (12e)

According to General procedure B, compound **11e** (42.0 mg, 69.0 μmol) was treated with 10% aqueous NaOH. Compound **12e** (31.8 mg, 96%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 1.2 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 0.88 (t, $J = 7.4$ Hz, 3H, H-4′), 1.59 (m, 2H, H-3′), 1.68 (t, $J = 12.2$ Hz, 1H, H-3a), 2.01 (s, 3H, NHCOCH_3), 2.24 (t, $J = 7.3$ Hz, 2H, H-2′), 2.75 (dd, $J = 4.7$, 12.4 Hz, 1H, H-3e), 3.30 (dd, $J = 7.1$, 14.2 Hz, 1H, H-9a), 3.45 (dd, $J = 1.7$, 9.0 Hz, 1H, H-7), 3.53 (dd, $J = 2.8$, 14.1 Hz, 1H, H-9b), 3.68 (ddd, $J = 2.9$, 4.7, 11.8 Hz, 1H, H-4), 3.72–3.82 (m, 3H, H-5, H-6, H-8), 4.51, 4.70 (A, B of AB, $J = 12.0$ Hz, 2H, CH_2Ph), 7.38 (m, 5H, C_6H_5); ^{13}C NMR (125 MHz, D_2O): δ 12.1 (C-4′), 18.4 (C-3′), 22.6 (NHCOCH_3), 37.0 (C-2′), 39.8 (C-3), 41.0 (C-9), 51.2 (C-5), 66.5 (CH_2Ph), 67.6 (C-4), 68.9 (C-7), 69.3 (C-8), 71.9 (C-6), 100.4 (C-2), 127.6, 128.0, 128.0, 136.5 (6C, C_6H_5), 174.3, 176.7, 180.8 (3 CO); HR-MS Calcd for $C_{22}H_{31}N_2Na_2O_9$ [M+Na$^+$]: 513.1825; Found: 513.1825.

4.34. Sodium (benzyl 5-acetamido-3,5,9-trideoxy-9-hexanoylamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (12f)

According to General procedure B, compound **11f** (26.1 mg, 40.1 μmol) was treated with 10% aqueous NaOH. Compound **12f** (20.2 mg, 96%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 1.15 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 0.81 (t, $J = 7.0$ Hz, 3H, H-6′), 1.23–1.27 (m, 4H, H-4′, H-5′), 1.57 (m, 2H, H-3′), 1.66 (t, $J = 12.2$ Hz, 1H, H-3a), 2.02 (s, 3H, NHCOCH_3), 2.25 (t, $J = 7.4$ Hz, 2H, H-2′), 2.75 (dd, $J = 4.7$, 12.5 Hz, 1H, H-3e), 3.22 (dd, $J = 7.7$, 14.2 Hz, 1H, H-9a), 3.46 (dd, $J = 1.7$, 9.0 Hz, 1H, H-7), 3.58 (dd, $J = 7.7$, 14.1 Hz, 1H, H-9b), 3.68 (ddd, $J = 6.6$, 9.8, 12.8 Hz, 1H, H-4), 3.72–3.80 (m, 3H, H-5, H-6, H-8), 4.50, 4.70 (A, B of AB, $J = 11.0$ Hz, 2H, CH_2Ph), 7.40 (s, 5H, C_6H_5); ^{13}C NMR (125 MHz, D_2O): δ 20.1 (C-6′), 20.6 (C-5′), 21.8 (NHCOCH_3), 23.7 (C-4′), 28.9 (C-3′), 34.2 (C-2′), 39.0 (C-3), 40.3 (C-9), 50.4 (C 5), 65.8 (CH_2Ph), 66.8 (C-4), 68.2 (C-7), 68.7 (C-8), 71.1 (C-6), 99.6 (C-2), 126.8, 127.2, 127.3, 135.6 (6C, C_6H_5), 173.6, 176.1, 180.1 (3 CO); HR-MS Calcd for $C_{24}H_{35}N_2Na_2O_9$ [M+Na$^+$]: 541.2138; Found: 541.2137.

4.35. Sodium (benzyl 5-acetamido-9-decanoylamido-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (12g)

According to General procedure B, compound **11g** (30.0 mg, 43.0 μmol) was treated with 10% aqueous NaOH. Compound **12g** (24.0 mg, 97%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 4.1 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 0.56 (t, $J = 6.8$ Hz, 3H, H-10′), 0.92–1.00 (m, 12H, H-4′, H-5′, H-6′, H-7′, H-8′, H-9′), 1.32 (m, 2H, H-3′), 1.46 (t, $J = 12.2$ Hz, 1H, H-3a), 1.81 (s, 3H, NHCOCH_3), 2.01 (t, $J = 7.2$ Hz, 2H, H-2′), 2.55 (dd, $J = 4.5$, 12.2 Hz, 1H, H-3e), 2.94 (dd, $J = 8.3$, 14.1 Hz, 1H, H-9a), 3.25 (d, $J = 11.1$ Hz, 1H, H-7), 3.42–3.50 (m, 2H, H-4, H-9b), 3.54–3.63 (m, 3H, H-5, H-6, H-8),

4.28, 4.49 (A, B of AB, $J = 10.9$ Hz, 2H, CH_2Ph), 7.10–7.17 (m, 5H, C_6H_5); ^{13}C NMR (125 MHz, D_2O): δ 13.9 (C-10′), 22.4 (C-9′), 22.5 (NHCOCH_3), 25.9 (C-8′), 28.7 (C-7′), 29.0 (2C, C-5′, C-6′), 29.2 (C-4′), 31.6 (C-3′), 36.2 (C-2′), 41.0 (C-3), 42.4 (C-9), 52.2 (C-5), 68.0 (CH_2Ph), 68.7 (C-4), 70.3 (C-7), 70.7 (C-8), 72.9 (C-6), 101.2 (C-2), 128.6, 129.0, 129.2, 137.4 (6C, C_6H_5), 173.6, 175.3, 177.3 (3 CO); HR-MS Calcd for $C_{28}H_{43}N_2Na_2O_9$ [M+Na$^+$]: 597.2764; Found: 597.2768.

4.36. Sodium [benzyl 5-acetamido-9-(4-chlorobenzamido)-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (12h)

According to General procedure B, compound **11h** (32.0 mg, 47.1 μmol) was treated with 10% aqueous NaOH. Compound **12h** (21.0 mg, 75%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 1.95 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.68 (t, $J = 12.2$ Hz, 1H, H-3a), 1.99 (s, 3H, NHCOCH_3), 2.76 (dd, $J = 4.6$, 12.4 Hz, 1H, H-3e), 3.45 (dd, $J = 8.0$, 14.4 Hz, 1H, H-9a), 3.51 (d, $J = 8.9$ Hz, 1H, H-7), 3.64–3.84 (m, 5H, H-4, H-5, H-6, H-8, H-9b) 4.51, 4.69 (A, B of AB, $J = 11.2$ Hz, 2H, CH_2Ph), 7.26–7.36, 7.46, 7.69 (m, 9H, C_6H_5, C_6H_4); ^{13}C NMR (125 MHz, D_2O): δ 22.3 (NHCOCH_3), 40.9 (C-3), 43.0 (C-9), 52.2 (C-5), 67.7 (CH_2Ph), 68.6 (C-4), 70.3 (C-7), 70.6 (C-8), 73.0 (C-6), 101.6 (C-2), 128.5, 128.9, 129.0, 129.0, 129.1, 132.4, 137.6, 137.9 (12C, C_6H_5, C_6H_4), 170.4, 173.5, 176.5 (3 CO); HR-MS Calcd for $C_{25}H_{28}ClN_2Na_2O_9$ [M+Na$^+$]: 581.1279; Found: 581.1278.

4.37. Sodium [benzyl 5-acetamido-9-(3,4-dichlorobenzamido)-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (12i)

According to General procedure B, compound **11i** (31.0 mg, 42.8 μmol) was treated with 10% aqueous NaOH. Compound **12i** (20.1 mg, 75%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 2.45 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.68 (t, $J = 12.1$ Hz, 1H, H-3a), 2.01 (s, 3H, NHCOCH_3), 2.76 (dd, $J = 4.6$, 12.4 Hz, 1H, H-3e), 3.39 (dd, $J = 14.4$, 8.5 Hz, 1H, H-9a), 3.52 (m, 1H, H-7), 3.64–3.85 (m, 5H, H-4, H-5, H-6, H-8, H-9b), 4.47, 4.69 (A, B of AB, $J = 11.1$ Hz, 2H, CH_2Ph), 7.21–7.32, 7.43, 7.53, 7.75 (m, 8H, C_6H_5, C_6H_3); ^{13}C NMR (125 MHz, D_2O): δ 22.4 (NHCOCH_3), 41.0 (C-3), 43.2 (C-9), 52.2 (C-5), 67.6 (CH_2Ph), 68.6 (C-4), 70.4 (C-7), 70.7 (C-8), 73.0 (C-6), 101.5 (C-2), 126.9, 128.5, 128.9, 129.4, 130.9, 132.5, 133.7, 135.8, 137.4 (12C, C_6H_5, C_6H_3), 168.5, 173.7, 175.4 (3 CO); HR-MS Calcd for $C_{25}H_{28}Cl_2N_2NaO_9$ [M+H$^+$]: 593.1070; Found: 593.1066.

4.38. Sodium [benzyl 5-acetamido-3,5,9-trideoxy-9-(4-trifluoromethyl-benzamido)-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (12j)

According to General procedure B, compound **11j** (36.0 mg, 50.0 μmol) was treated with 10% aqueous NaOH. Compound **12j** (21.0 mg, 70%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 2.37 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.68 (t, $J = 12.2$ Hz, 1H, H-3a), 2.00 (s, 3H, NHCOCH_3), 2.76 (dd, $J = 4.7$, 12.5 Hz, 1H, H-3e), 3.44–3.52 (m, 2H, H-7, H-9a), 3.68 (m, 1H, H-4), 3.75–3.84 (m, 4H, H-5, H-6, H-8, H-9b), 4.49, 4.68 (A, B of AB, $J = 11.2$ Hz, 2H, CH_2Ph), 7.24–7.35, 7.75, 7.84 (m, 9H, C_6H_5, C_6H_4); ^{13}C NMR (125 MHz, D_2O): δ 22.4 (NHCOCH_3), 40.9 (C-3), 43.1 (C-9), 52.3 (C-5), 67.6 (CH_2Ph), 68.6 (C-4), 70.3 (C-7), 70.6 (C-8), 73.0 (C-6), 101.6 (C-2), 126.0, (CF_3), 128.0, 128.5, 128.9, 129.0, 129.5, 129.6, 132.5, 137.5 (12C, C_6H_5, C_6H_4), 170.0, 173.8, 175.4 (3 CO); HR-MS Calcd for $C_{26}H_{29}F_3N_2NaO_9$ [M+H$^+$]: 593.1723; Found: 593.1722.

4.39. Sodium [benzyl 5-acetamido-9-(2,4-dichorobenzamido)-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (12k)

According to General procedure B, compound **11k** (31.0 mg, 42.9 μmol) was treated with 10% aqueous NaOH. Compound **12k** (18.0 mg, 72%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 1.17 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.66 (t, $J = 12.1$ Hz, 1H, H-3a), 2.01 (s, 3H, NHCOCH_3), 2.75 (dd, $J = 4.7$, 12.3 Hz, 1H, H-3e), 3.53–3.83 (m, 6H, H-4, H-5, H-6, H-7, H-9), 3.89 (m, 1H, H-8), 4.49, 4.71 (A, B of AB, $J = 11.0$ Hz, 2H, CH_2Ph), 7.33–7.41, 7.55 (m, 8H, C_6H_5, C_6H_3); ^{13}C NMR (125 MHz, D_2O): δ 20.0 (NHCOCH_3), 38.5 (C-3), 40.1 (C-9), 49.9 (C-5), 65.1 (CH_2Ph), 66.1 (C-4), 67.4 (C-7), 67.9 (C-8), 70.5 (C-6), 98.9 (C-2), 125.4, 126.2, 126.6, 126.7, 127.1, 127.4, 127.6, 129.0, 131.3, 134.1, 135.0 (12C, C_6H_5, C_6H_3), 167.6, 171.4, 173.0 (3 CO); HR-MS Calcd for $C_{25}H_{28}Cl_2N_2NaO_9$ [M+H$^+$]: 593.1070; Found: 593.1070.

4.40. Benzyl 5-acetamido-3,5,9-trideoxy-9-(4-nitrobenzamido)-D-*glycero*-α-D-*galacto*-2-nonulopyranosidic acid (12l)

According to General procedure B, compound **11l** (28.0 mg, 40.0 μmol) was treated with 10% aqueous NaOH. After workup the crude material was purified by reversed-phase chromatography (RP-18 column, 5% gradient MeOH in water), and Sephadex G-15 size exclusion chromatography to afford **12l** (21.0 mg, 95%) as colorless solid after a final lyophilization from water.

$[\alpha]_D^{25}$ − 2.45 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.67 (t, $J = 12.2$ Hz, 1H, H-3a), 1.99 (s, 3H, NHCOCH_3), 2.74 (dd, $J = 4.7$, 12.4 Hz, 1H, H-3e), 3.46 (dd, $J = 7.7$, 14.0 Hz, 1H, H-9a), 3.52 (dd, $J = 1.7$, 8.8 Hz, 1H, H-7), 3.67 (m, 1H, H-4), 3.74–3.84 (m, 4H, H-5, H-6, H-8, H-9b), 4.48, 4.67 (A, B of AB, $J = 11.2$ Hz, 2H, CH_2Ph), 7.23–7.34, 7.88, 8.25 (m, 9H, C_6H_4, C_6H_5); ^{13}C NMR (125 MHz, D_2O): δ 20.4 (NHCOCH_3), 39.0 (C-3), 41.3 (C-9), 50.3 (C-5), 65.7 (CH_2Ph), 66.6 (C-4), 68.4 (C-7), 68.6 (C-8), 71.1 (C-6), 99.6 (C-2), 122.3, 126.6, 126.8, 127.0, 127.0, 135.6,

138.1, 147.8 (12C, C_6H_4, C_6H_5), 172.4, 173.5, 176.5 (3 CO); HR-MS Calcd for $C_{25}H_{28}N_3Na_2O_{11}$ [M+Na$^+$]: 592.1519; Found: 592.1512.

4.41. Sodium [benzyl 5-acetamido-3,5,9-trideoxy-9-(4-methoxybenzamido)-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (12m)

According to General procedure B, compound **11m** (25.0 mg, 36.9 μmol) was treated with 10% aqueous NaOH. Compound **12m** (16.0 mg, 80%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 3.22 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.68 (t, *J* = 12.2 Hz, 1H, H-3a), 1.98 (s, 3H, NHCOCH_3), 2.76 (dd, *J* = 4.7, 12.4 Hz, 1H, H-3e), 3.44 (dd, *J* = 8.2, 14.6 Hz, 1H, H-9a), 3.51 (dd, *J* = 1.7, 8.7 Hz, 1H, H-7), 3.64–3.84 (m, 8H, H-4, H-5, H-6, H-8, H-9b, OCH_3), 4.51, 4.68 (A, B of AB, *J* = 11.2 Hz, 2H, CH_2Ph), 7.01, 7.24–7.36, 7.74 (m, 9H, C_6H_5, C_6H_4); ^{13}C NMR (125 MHz, D_2O): δ 22.4 (NHCOCH_3), 40.9 (C-3), 42.9 (C-9), 52.2 (C-5), 55.8 (OCH_3), 67.7 (CH_2Ph), 68.6 (C-4), 70.3 (C-7), 70.7 (C-8), 73.0 (C-6), 101.6 (C-2), 114.3, 126.3, 128.5, 128.9, 129.0, 129.5, 137.6, 162.3 (12C, C_6H_5, C_6H_4), 170.6, 173.8, 175.4 (3 CO); HR-MS Calcd for $C_{26}H_{31}N_2Na_2O_{10}$ [M+Na$^+$]: 577.1774; Found: 577.1773.

4.42. Sodium [benzyl 5-acetamido-3,5,9-trideoxy-9-(4-methylbenzamido)-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (12n)

According to General procedure B, compound **11n** (26.0 mg, 39.0 μmol) was treated with 10% aqueous NaOH. Compound **12n** (20.2 mg, 87%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 2.07 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.68 (t, *J* = 12.2 Hz, 1H, H-3a), 1.98 (s, 3H, NHCOCH_3), 2.38 (s, 3H, PhCH_3), 2.76 (dd, *J* = 4.6, 12.4 Hz, 1H, H-3e), 3.33–3.51 (m, 2H, H-7, H-9a), 3.67 (m, 1H, H-4), 3.72–3.83 (m, 4H, H-5, H-6, H-8, H-9b), 4.53, 4.69 (A, B of AB, *J* = 11.3 Hz, 2H, CH_2Ph), 7.26, 7.36, 7.69 (m, 9H, C_6H_5, C_6H_4); ^{13}C NMR (125 MHz, D_2O): δ 20.9 (PhCH_3), 22.3 (NHCOCH_3), 40.9 (C-3), 42.9 (C-9), 52.2 (C-5), 67.7 (CH_2Ph), 68.6 (C-4), 70.2 (C-7), 70.6 (C-8), 73.0 (C-6), 101.7 (C-2), 127.5, 128.5, 128.9, 129.0, 129.7, 131.0, 137.6, 143.6 (12C, C_6H_5, C_6H_4), 171.3, 173.8, 175.4 (3 CO); HR-MS Calcd for $C_{26}H_{31}N_2Na_2O_9$ [M+Na$^+$]: 561.1825; Found: 561.1821.

4.43. Sodium [benzyl 5-acetamido-9-(3-chlorobenzamido)-3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid]onate (12o)

According to General procedure B, compound **11o** (28.0 mg, 41.1 μmol) was treated with 10% aqueous NaOH. Compound **12o** (16.0 mg, 69%) was obtained as a colorless solid after purification.

$[\alpha]_D^{25}$ − 1.77 (*c* 1.00, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 1.69 (t, *J* = 11.8 Hz, 1H, H-3a), 2.00 (s, 3H, NHCOCH_3), 2.77 (dd, *J* = 4.6, 12.4 Hz, 1H, H-3e), 3.49 (m, 2H, H-7, H-9a), 3.63–3.83 (m, 5H, H-4, H-5, H-6, H-8, H-9), 4.53, 4.71 (A, B of AB, *J* = 11.2 Hz, 2H, CH_2Ph), 7.29–7.39, 7.44, 7.53, 7.62 (m, 9H, C_6H_5, C_6H_4); ^{13}C NMR (125 MHz, D_2O): δ 21.9 (NHCOCH_3), 40.5 (C-3), 42.6 (C-9), 51.8 (C-5), 67.2 (CH_2Ph), 68.2 (C-4), 69.8 (C-7), 70.1 (C-8), 72.6 (C-6), 101.2 (C-2), 125.3, 127.1, 128.1, 128.5, 128.5, 130.2, 131.8, 134.0, 135.3, 137.2 (12C, C_6H_5, C_6H_4), 169.5, 173.4, 175.0 (3 CO); HR-MS Calcd for $C_{25}H_{28}ClN_2Na_2O_9$ [M+Na$^+$]: 581.1279; Found: 581.1276.

4.44. Methyl (benzyl 5-acetamido-8,9-*O*-benzylidene-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (14)

To a stirred solution of **6** (36.0 mg, 87.1 μmol) and α,α-dimethoxytoluene (26.0 μL, 174 μmol) in MeCN (2 mL) at 0 °C was added *p*-TsOH·H_2O (1.30 mg, 6.70 μmol). The mixture was stirred at rt for 1.5 h and then quenched by adding a few drops of NEt_3. After concentration under reduced pressure, the residue (∼50 mg) was used directly in the next step. In accordance with,[29a] the ^{1}H NMR data of **14** showed a 1:1 mixture of *exo*/*endo* isomers.

4.45. Methyl (benzyl 5-acetamido-9-*O*-benzyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (15)

Compound **14** (87.1 μmol), BH_3·NMe_3 (25.4 mg, 348 μmol), and $AlCl_3$ (69.6 mg, 523 μmol) were dissolved in THF (2 mL) under argon. After 5 min, H_2O (2.60 μL, 131 μmol) was added and the mixture was stirred at rt for 4 h. The reaction was quenched by adding H_2O (1 mL) and 0.1 N HCl (1 mL). The solution was diluted with DCM (10 mL) and washed with 5% aq $NaHCO_3$ (2 × 5 mL) and H_2O (5 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (1% gradient MeOH in DCM) to afford **15** (34.8 mg, 70% **6** → **15**) as white foam.

$[\alpha]_D^{25}$ + 4.8 (*c* 0.51, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ 1.80 (t, *J* = 12.5 Hz, 1H, H-3a), 2.00 (s, 3H, NHCOCH_3), 2.74 (dd, *J* = 4.6, 12.8 Hz, 1H, H-3e), 3.60 (dd, *J* = 1.5, 8.9 Hz, 1H, H-7), 3.63–3.69 (m, 3H, H-4, H-6, H-9a), 3.76 (s, 3H, OCH_3), 3.78–3.83 (m, 2H, H-5, H-9b), 4.02 (ddd, *J* = 2.3, 5.8, 8.6 Hz, 1H, H-8), 4.50, 4.80 (A, B of AB, *J* = 11.7 Hz, 2H, CH_2Ph), 4.57, 4.59 (A, B of AB, 2H, CH_2Ph), 7.24–7.37 (m, 10H, 2 C_6H_5); ^{13}C NMR (125 MHz, CD_3OD): δ 22.6 (NHCOCH_3), 41.7 (C-3), 53.2 (OCH_3), 53.8 (C-5), 67.2 (CH_2Ph), 68.4 (C-4), 70.1 (C-7), 71.3 (C-8), 72.6 (C-9), 74.4 (CH_2Ph), 74.8 (C-6), 100.1 (C-2), 128.5, 128.6, 128.8, 128.8, 129.2, 129.2, 138.8 (12C, 2 C_6H_5), 170.9, 175.1 (2 CO); Anal. Calcd for $C_{26}H_{33}NO_9$+1/2 H_2O: C, 60.93; H, 6.69; N, 2.73. Found: C, 61.14; H, 6.62; N, 2.65.

4.46. Sodium (benzyl 5-acetamido-9-*O*-benzyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid)onate (16)

To a solution of **15** (35.0 mg, 69.5 μmol) in H_2O/dioxane (1:1, 4 mL) under argon was added LiOH (16.8 mg,

69.5 μmol). The mixture was stirred at rt for 1.5 h, then neutralized with 0.5% HCl and concentrated. The residue was purified by silica gel chromatography (10% gradient MeOH in DCM), Dowex 50 × 8 (Na^+ type) ion-exchange chromatography, and Sephadex G-15 size exclusion chromatography to afford **16** as a white solid (31.0 mg, 87%) after a final lyophilization from H_2O.

$[\alpha]_D^{25}$ − 16.1, (*c* 0.65, H_2O); ^1H NMR (500 MHz, D_2O): δ 1.68 (t, J = 12.2 Hz, 1H, H-3a), 2.03 (s, 3H, NHC-OCH_3), 2.77 (dd, J = 4.6, 12.4 Hz, 1H, H-3b), 3.60–3.64 (m, 2H, H-7, H-9a), 3.67–3.73 (m, 2H, H-4, H-6), 3.78–3.82 (m, 2H, H-5, H-9b), 3.86 (ddd, J = 2.0, 6.3, 8.6 Hz, 1H, H-8), 4.49, 4.69 (A, B of AB, J = 11.0 Hz, 2H, CH_2Ph), 4.58, 4.61 (A, B of AB, J = 12.0 Hz, 2H, CH_2Ph), 7.35–7.46 (m, 10H, 2 C_6H_5); ^{13}C NMR (125 MHz, D_2O): δ 22.0 (NHCO*C*H_3), 40.5 (C-3), 51.9 (C-5), 67.1 (*C*H_2Ph), 68.2, 68.4 (C-4, C-7), 70.4 (C-8), 70.8 (C-9), 72.6 (C-6), 73.0 (*C*H_2Ph), 101.0 (C-2), 128.2, 128.3, 128.3, 128.7, 128.7, 128.7, 137.1, 137.5 (12C, 2 C_6H_5), 173.5, 175.1 (2 CO); HR-MS Calcd for $C_{25}H_{31}NNaO_9$ [M+H^+]: 512.1897; Found: 512.1896.

4.47. In vitro binding assay

A recombinant protein consisting of the *N*-terminal three domains of MAG and the Fc part of human IgG (Fc-MAG_{d1-3}) was produced by expression in CHO cells and affinity purification on protein A-agarose as described.[25] For the hapten inhibition assay a modification of the previously described assay[15a] was used. Instead of human erythrocytes as target for sialic acid-dependent binding of MAG, commercially available microtiter plates with immobilized Neu5Ac (Lundonia, Lund, Sweden) were used. In brief, to each well 10 μL of an oligosaccharide solution was added followed by 20 μL of Fc-MAG_{d1-3} which had been precomplexed with an anti-Fc antibody labeled with alkaline phosphatase. After an overnight incubation at 4 °C unbound Fc-MAG complexes were removed by washing and the amount of bound Fc-MAG was determined via the alkaline phosphatase with fluorescein diphosphate as substrate. For each oligosaccharide at least eight concentrations were used to determine the concentration required for 50% inhibition (IC_{50}). In order to compare the results from different assays compound **13** was included in each test and used as a reference to calculate the relative inhibitory potencies (rIP). At least three independent titrations were performed for each compound.

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References and notes

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