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Antagonists of the myelin-associated glycoprotein: A new class of tetrasaccharide mimics

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Abstract—The tetrasaccharide substructure **1** 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 **1**, biphenyl was identified as a feasible replacement for the core disaccharide Galβ(1–3)Gal*N*Ac according to saturation transfer difference (STD) NMR and molecular modeling investigations. Using Suzuki coupling, a convergent synthesis of the mimics was achieved. To optimize the yields of the coupling reactions, the catalytic effects of microwave irradiation and conventional heating were compared. The biological evaluation of mimics **3** and **4** was performed in a competitive target-based assay. It was found that the relative inhibitory potency (rIP) of antagonist **3** was clearly enhanced in comparison to the reference trisaccharide **2**, despite the former having a much simpler structure. In addition to the improved synthetic feasibility, an increase of the partition coefficient between octanol and water (log *P*), and therefore a beneficial change in the pharmacokinetic properties of **3** and **4** was achieved.

1. Introduction

The adult mammalian central nervous system (CNS) has—unlike the peripheral nervous system (PNS)—no capacity for regeneration.[1] It was believed that this lack of regeneration is inherent to the CNS. However, it is now known that neurite outgrowth is principally possible,[2] but actively inhibited by inhibitor proteins expressed by myelinating glia cells, oligodendrocytes and Schwann cells.[3] Three inhibitor proteins have been identified so far: Nogo A,[4] oligodendrocyte myelin glycoprotein (OMpg)[5] and myelin-associated glycoprotein (MAG).[6] It appears that these three proteins all bind to the same receptor, Nogo-66,[7] that then forms a complex with the coreceptor $p75^{NTR}$.[8] This leads to the transduction of the inhibitory signal into the cytosol of the neuron, where it activates RhoA,[9] which in turn causes growth cone collapse. This cascade has also been proved to be triggered by MAG binding to gangliosides with $p75^{NTR}$ as coreceptor[10] (Fig. 1).

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 reverting this inhibitory activity of MAG could be a way of supporting the regeneration after injury to the central nervous system. Schnaar[13] reported that a limited set of structurally related gangliosides, known to be expressed on myelinated neurons in vivo, are functional ligands of MAG. The gangliosides GD1a, GT1b, and GQ1bα (Fig. 2) have been synthesized in preparative amounts[14] and have therefore been available for the establishment of 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.

In conclusion, although several potential binding partners for MAG have been identified, the full biological role of its sialic acid-binding activity has remained unclear. A potent and selective inhibitor of this activity would provide the tool required to investigate this

Keywords: Axonal regeneration; Binding affinity; Carbohydrate-binding epitope; Myelin-associated glycoprotein (MAG); Biphenyl; Suzuki coupling; Miyaura boronation.
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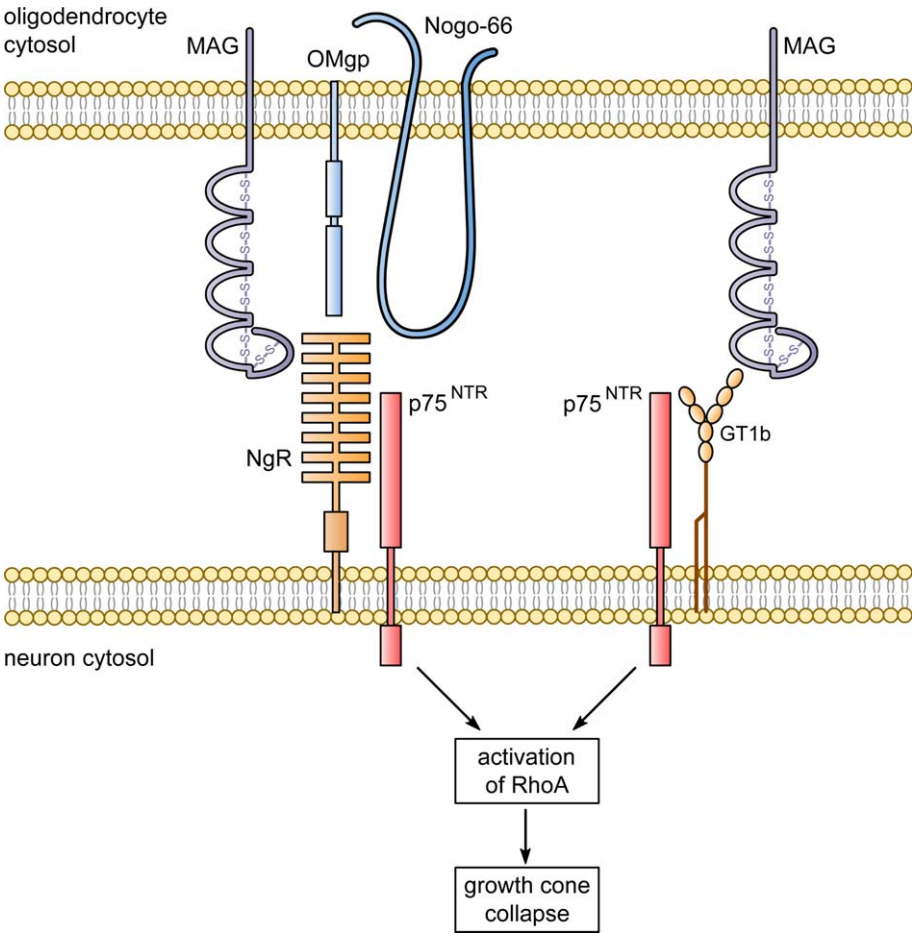


Figure 1. MAG, Nogo-66, and oligodendrocyte myelin glycoprotein (OMgp) all bind to the Nogo-66 receptor (NgR). The inhibitory signal is transduced into the cytosol of the neuron via the coreceptor $p75^{NTR}$. MAG also binds to GT1b with $p75^{NTR}$ as coreceptor and thereby transduces the inhibitory signal into the cytosol. Intracellularly, the small GTPase RhoA is activated, which leads to a collapse of the growth cone.

question. Furthermore, although numerous sialic acid derivatives and oligosaccharides with antagonistic activity are available,[15] no MAG antagonist mimicking the carbohydrate nature of the physiological ligands and at the same time having drug-like properties has been published so far.

In an earlier study,[17] we investigated the binding properties of the terminal tetrasaccharide of GQ1bα (see **1**, Fig. 2). In the present study, mimics of the tetrasaccharide **1**, where the core disaccharide Galβ(1–3)Gal*N*Ac is replaced by a non-carbohydrate linker, are presented.

2. Results and discussion

By comparing the carbohydrate structures of the gangliosides GD1a, GT1b, and GQ1bα, tetrasaccharide **1** was identified as the relevant part for binding to MAG.[13,17] Recently, the binding, that is, the proximity of individual parts of **1** to MAG (see **1**, Fig. 2), has been determined by Saturation Transfer Difference (STD) NMR. [17] The largest STD response was observed at the N-acetyl function of the α(2–3)-linked sialic acid. Further significant interactions originate from H-6 and H-7 of the α(2–3)-linked sialic acid. For the α(2–6)-linked sialic acid, the only sizeable STD effect detected stems from the N-acetyl group. In analogy to the knowledge gained from the crystal structure of the N-terminal domain of sialoadhesin (Siglec-1) in complex with 3′-sialyllactose,[18] we can assume that the carboxylic acid of the α(2–3)-linked sialic acid forms an important salt bridge with Arg118.[19] In addition, docking of tetrasaccharide **1** to a homology model of MAG[20] indicates that the carboxylic acid of the α(2–6)-linked sialic acid forms a second salt bridge with Lys67.[20] Finally, the low STD values found for protons of the core disaccharide Galβ(1–3)Gal*N*Ac indicate that only marginal contributions to binding originate from this part of tetrasaccharide **1**. We therefore decided to replace the core disaccharide by a linker, which positions the two sialic acid residues in the required spacial orientation (Fig. 2, mimic **3**), and at the same time improves the pharmacokinetic properties of lead structure **1**. Molecular modeling revealed that a biphenyl core would fulfill such spacial requirements. In addition, a dramatic reduction of the high polarity of **1**, and therefore an improvement of log *P*, can be expected. It has been reported that, in the search for selectin antagonists, the biphenyl moiety has already successfully been applied for mimicking the core disaccharide Galβ(1–4)Glc*N*Ac of sialyl $Lewis^x$.[21]

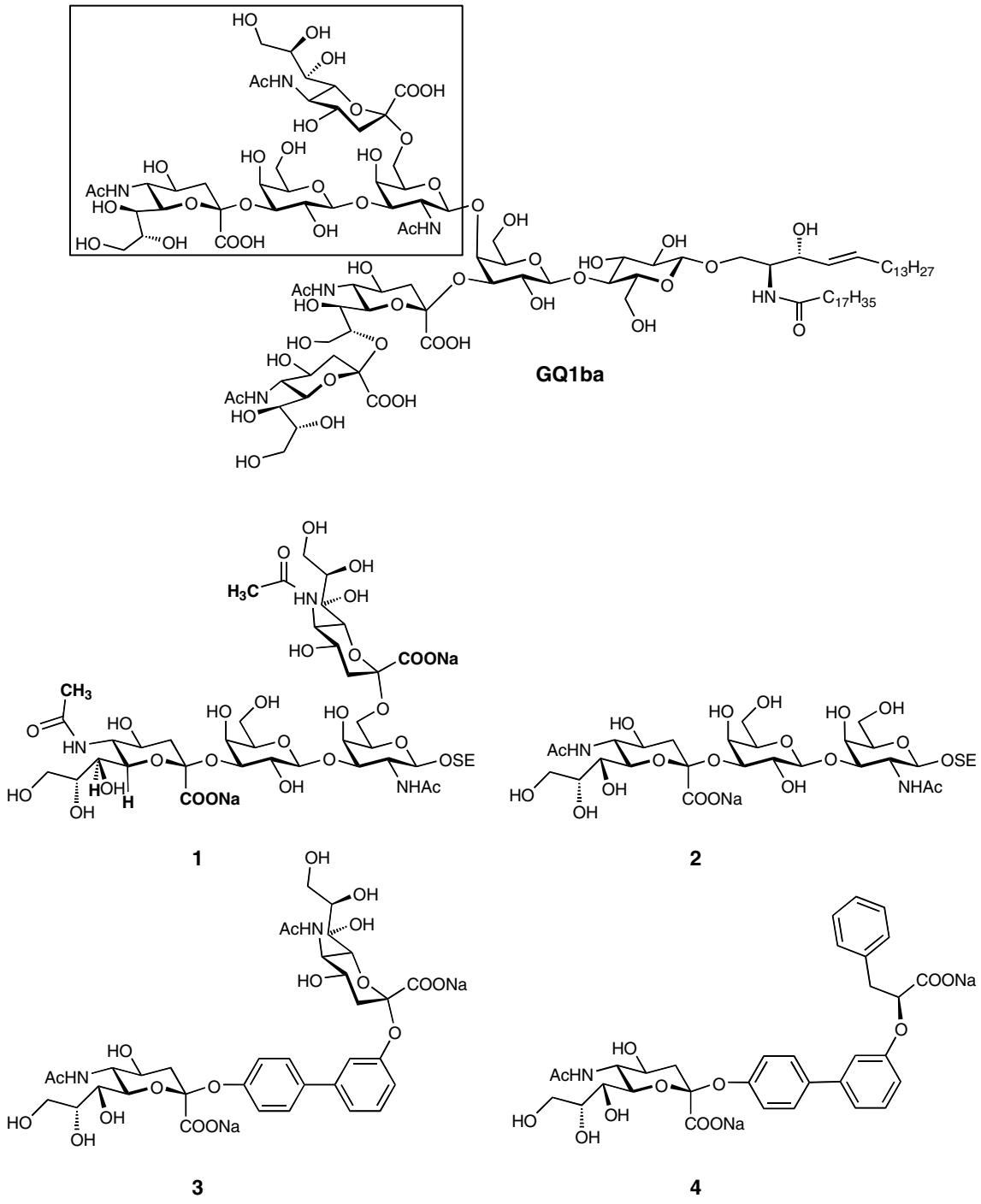


Figure 2. GQ1bα, bis-sialylated lead structure **1**, reference compound **2**, and biphenyl derivatives **3** and **4**. In **1** the pharmacophores are indicated in bold-face type.

With the second mimic, the contribution of the α(2–6)-linked sialic acid was explored. Since its interaction with MAG is limited to a lipophilic contact of the N-acetyl group and a salt bridge formed by the carboxylate, its replacement by (*S*)-phenyllactic acid was envisaged (Fig. 2, mimic **4**). Models for the 3D-structures of lead **1** and mimic **3** were generated using MacroModel 5.0,[22] optimized in aqueous solution on the basis of the improved AMBER 4.0 force field for carbohydrates published by Still,[23] and partially modified by Kolb and Ernst.[24] The superimposition was performed manually with the PrGen software.[25] The illustrations were finally prepared with SAMOA©[26] (Fig. 3).

For the synthesis of **3** and **4**, a convergent approach based on Suzuki coupling[27] was anticipated. The building blocks for this approach, phenylhalides **8**–**10** and **12**, and the boronic esters **13** were obtained by standard procedures.

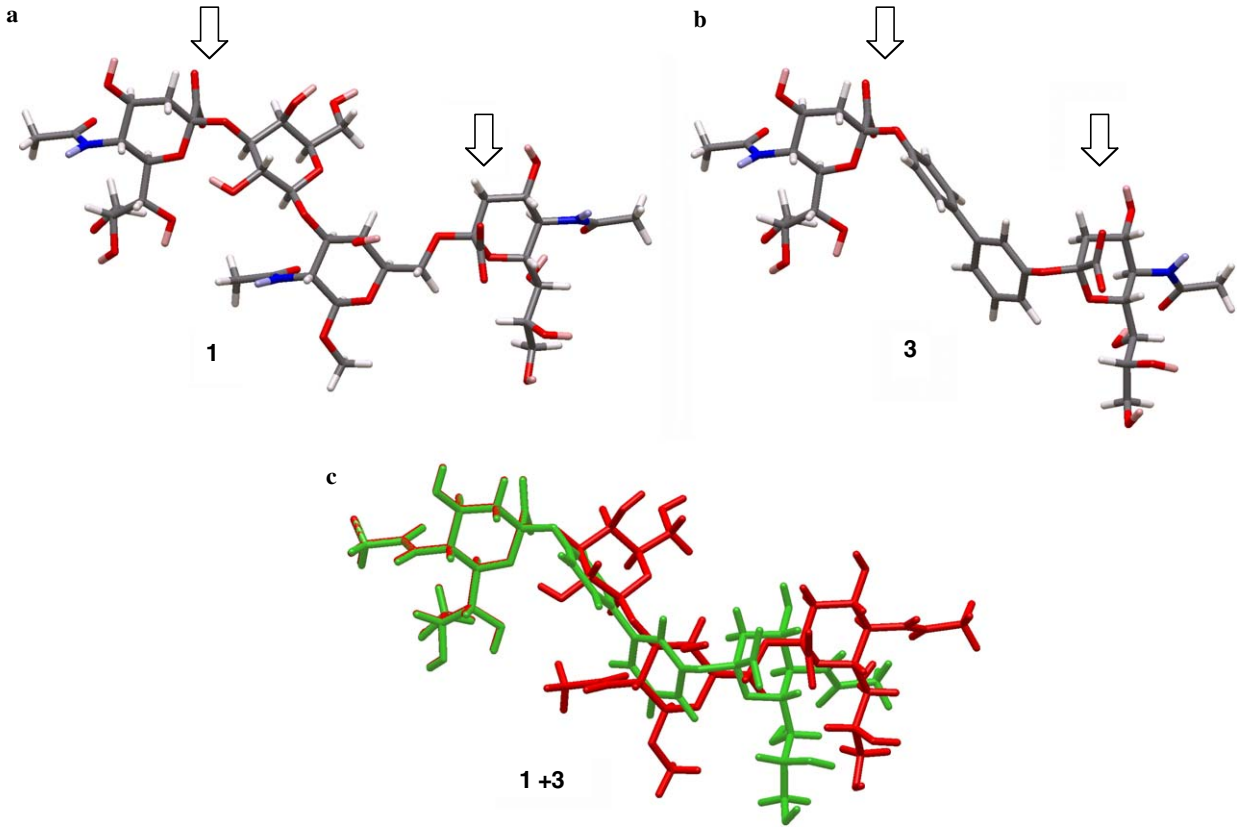
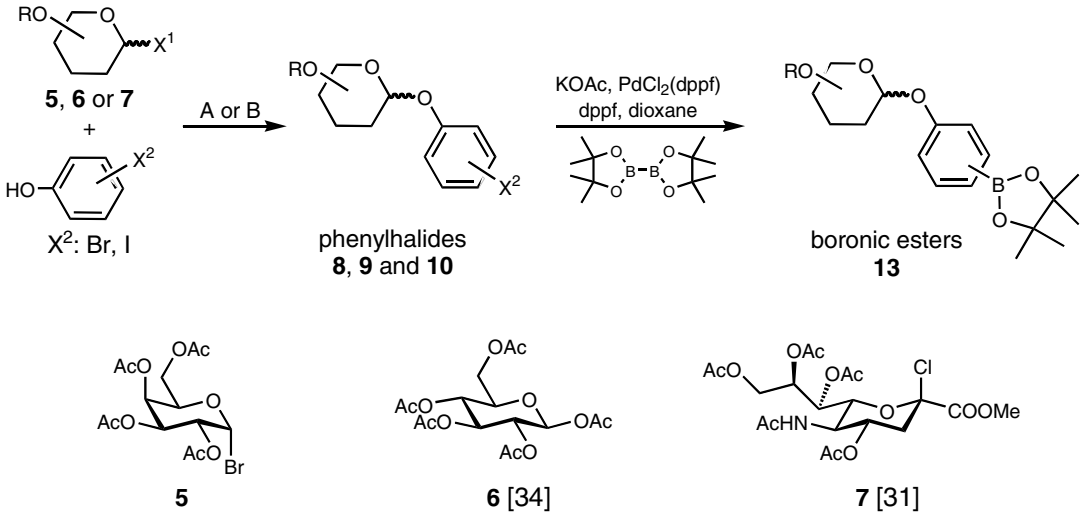


Figure 3. Replacement of the Galβ(1–3)Gal*N*Ac core of **1** by biphenyl; (a) 3D-structure of **1**; (b) 3D-structure of **3**; (c) superposition of the 3D-structure of **1** (red) and **3** (green).

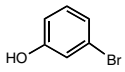
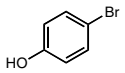
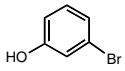
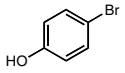
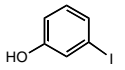
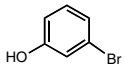
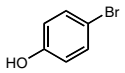
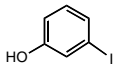
Although phase transfer catalysis (PTC) proved to be a valuable method for synthesizing the aryl galactosides **8a** and **8b** starting from the commercially available tetra-*O*-acetyl-α-D-galactopyranosylbromide (**5**) (Scheme 1, Table 1), it gave unsatisfactory yields in the glucose series due to a competing 1,2-elimination reaction.[28] However, acceptable yields of the β-isomers **9a**–**c** were obtained by using BF_3·etherate as catalyst.[29] The sialosides **10a**–**c** were prepared by PTC[30] from sialylchloride **7**. [31] For the synthesis of the phenylbromide **12**, benzyl (*R*)-phenyllactate **11** was treated with 3-bromophenol (Scheme 2) under Mitsunobu conditions.[32]

For the boronation of the phenylbromides **8a**,**b**, **9a**,**b** and **10b** (Scheme 1, Table 1), the procedure published by Miyaura[32,33,35] was optimized using microwave technique. The best results were obtained with $PdCl_2$(dppf) catalysis in the presence of additional dppf in dioxane.

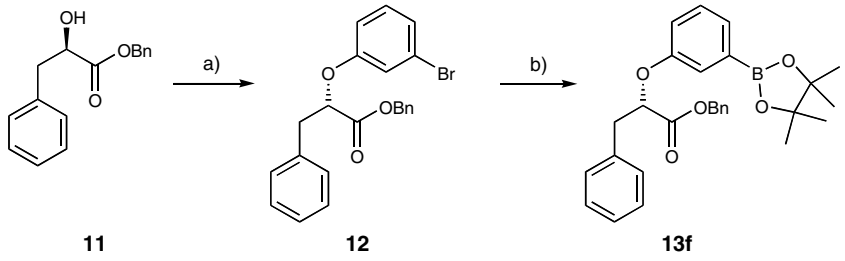


Scheme 1. Synthesis of the reactants for the Suzuki coupling: phenylhalides and boronic esters. (See above-mentioned references for further information).[34]

Table 1. Synthesis of the reactants for the Suzuki coupling

Glycosyl donor	Glycosyl acceptor	Method	Phenylhalide	Yield (%)	Reaction conditions	Boronic ester	Yield (%)
5		A	**8a**, β	77	1.5 h, 120 °C, μW	**13a**, β	89
			**8b**, β	74	1.5 h, 120 °C, μW	**13b**, β	86
6		B	**9a**, β	56	2 h, 120 °C, μW	**13c**, β	80
			**9b**, β	49	2.25 h, 120 °C, μW	**13d**, β	89
			**9c**, β	49	—	—	—
7		A	**10a**, α	40	—	—	—
			**10b**, α	56	0.75 h, 120 °C, μW	**13e**, α	85
			**10c**, α	46	—	—	—

Method A, phase transfer catalysis starting from sugar halides; method B, Lewis acid-catalysis starting from peracetylated β-D-glucose.



Scheme 2. Synthesis of the (*S*)-phenyl-lactic acid derivative **13f**. Reagents and conditions: (a) PPh_3, DEAD, THF, 3-bromophenol (66%); (b) bis(picanolato)diborane, KOAc, $PdCl_2$(dppf), dppf, dioxane, 80 °C (66%).

The boronide **13f** was obtained by standard procedures. Finally, all boronides were purified by filtration through a short silica column, although slight decomposition could not be avoided.

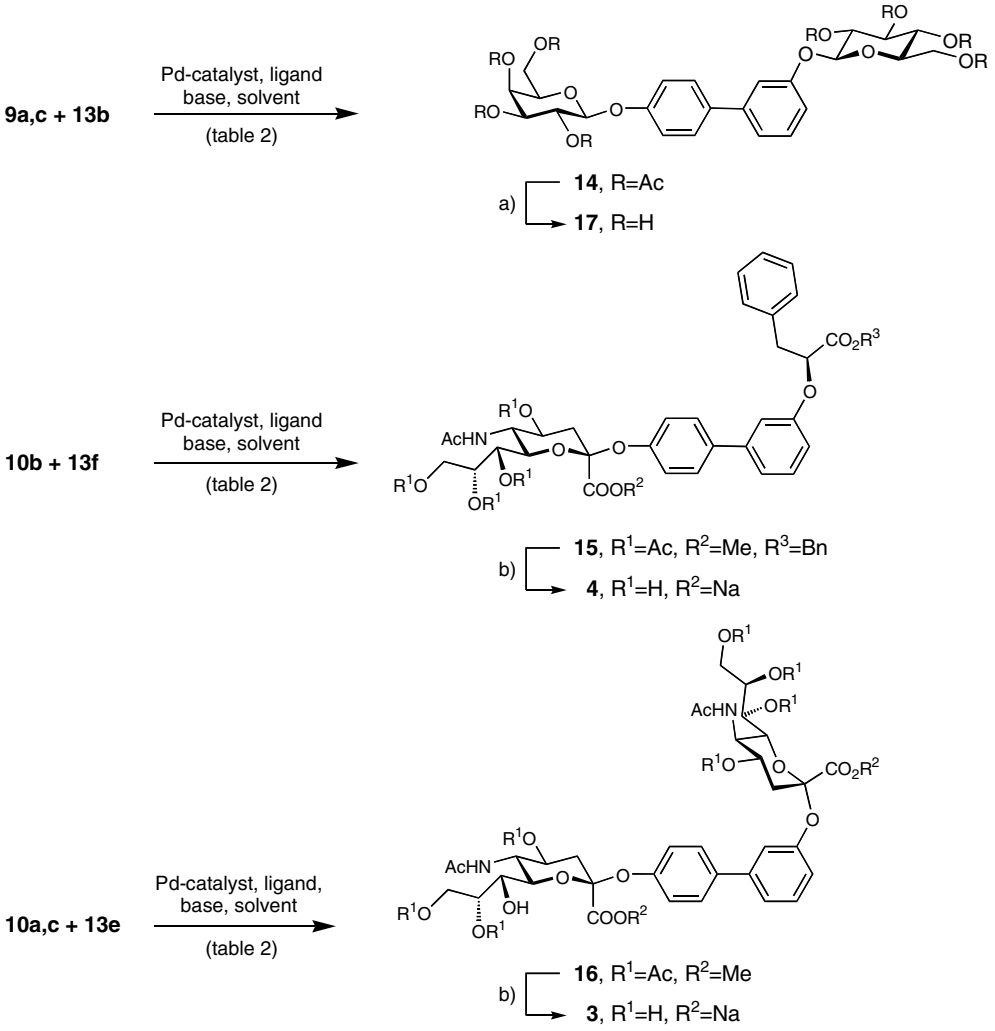
In a first step, the Suzuki coupling leading to the biphenyl derivative **14** was carefully optimized with the glucose derivatives **9a**,**c** and the boronic ester of galactose **13b**. (Table 2, entries 1–9). Initially, the influence of elevated temperature (oil bath) and microwave irradiation on the Suzuki coupling was compared in two test reactions (entries 1 and 2). As expected,[36] microwave irradiation gave an improvement in the yield by more than 50% compared to conventional heating. To prevent deprotection of the reactants, mild bases like K_3PO_4 or $NaHCO_3$ were initially used,[27] However, only modest yields were obtained for galactose or glucose derivatives (entries 3–6), and even lower yields for the more sensitive sialic acid derivatives **10a**–**c** (entries 10–13). Change of solvent (entry 6) or prolonged reaction times at lower temperature (entry 13) did not lead to improved yields. Also the addition of 2,6-di-*tert*-butyl-*p*-cresol as a radical scavenger did not affect the outcome of the reaction,[37] Stronger bases like Cs_2CO_3 or Ag_2CO_3, however, had a significant impact on the yields of Suzuki coupling with galactose and glucose derivatives (see entries 2 and 7–9). With Ag_2CO_3, a 77% yield of **16** was obtained (entry 14), whereas Cs_2CO_3 led to the formation of various side products (entry 15). In general, iodides gave slightly higher yields than the corresponding bromides (entries 8 and 9 vs 2 and 7), and the use of cesium carbonate resulted in shorter reaction times compared to silver carbonate (entries 2 and 9 vs 7 and 8) (Scheme 3).

Deprotection of **14**, **15**, and **16** was performed under standard Zemplén conditions to afford **3** (56%), **4** (52%), and **17** (91%). After transformation into the corresponding sodium salts, the biphenyls were purified by filtration through a size-exclusion column (P-2) prior to biological testing.

Table 2. Microwave-assisted Suzuki coupling leading to the formation of the biphenyl core of **14**, **15**, and **16**

Entries	Reactants	Pd-catalyst	Ligand	Base	Solvent	Time, conditions	Prod.	Yield[a] (%)
1	**9a** + **13b**	$Pd(PPh_3)_4$[c]	—	Cs_2CO_3	Dioxane	4.5 h, 120 °C[d]	**14**	54
2		$Pd(PPh_3)_4$[c]	—	Cs_2CO_3	Dioxane	4.5 h, 120 °C, μW	**14**	83
3		$Pd(PPh_3)_4$[c]	—	$NaHCO_3$	H_2O/dioxane	10 h, 150 °C, μW	**14**	39
4		$PdCl_2(dppf)$[b]	dppf	K_3PO_4	Dioxane	1.75 h, 170 °C, μW	**14**	38
5		$PdCl_2(dppf)$[b]	dppf	K_3PO_4	Dioxane/BHT	1.75 h, 170 °C, μW	**14**	40
6		$PdCl_2(dppf)$[b]	dppf	K_3PO_4	THF	1.75 h, 170 °C, μW	**14**	41
7		$Pd(PPh_3)_4$[c]	—	Ag_2CO_3	Dioxane	8 h, 120 °C, μW	**14**	73
8	**9c** + **13b**	$Pd(PPh_3)_4$[c]	—	Ag_2CO_3	Dioxane	8 h, 120 °C, μW	**14**	83
9		$Pd(PPh_3)_4$[c]	—	Cs_2CO_3	Dioxane	4.5 h, 120 °C, μW	**14**	87
10	**10a** + **13e**	$PdCl_2(dppf)$[b]	dppf	K_3PO_4	Dioxane/BHT	1.75 h, 170 °C, μW	**16**	8
11	**10b** + **13f**	$PdCl_2(dppf)$[b]	dppf	K_3PO_4	Dioxane/BHT	2.25 h, 170 °C, μW	**15**	28
12	**10c** + **13e**	$PdCl_2(dppf)$[b]	dppf	K_3PO_4	Dioxane/BHT	1.5 h, 170 °C, μW	**16**	10
13		$PdCl_2(dppf)$[b]	dppf	K_3PO_4	Dioxane/BHT	58.5 h, 100 °C, μW	**16**	12
14		$Pd(PPh_3)_4$[b]	—	Ag_2CO_3	Dioxane	7 h, 120 °C, μW	**16**	77
15		$Pd(PPh_3)_4$[c]	—	Cs_2CO_3	Dioxane	7 h, 120 °C, μW	**16**	11

[a] Isolated yield.
[b] 0.03 equiv of the catalyst was used.
[c] 0.01 equiv of the catalyst was used.
[d] Reaction heated in oil-bath.



Scheme 3. Reagents and conditions: (a) 1 M NaOMe, MeOH, 17 h, rt (91%); (b) i—1 M NaOMe, MeOH, 17 h, rt, ii—addition of H_2O, 6 h, rt, iii—Dowex 50 × 8 (Na^+), **3**, 52%; **4**, 56%.

Table 3. Rel. inhibitory potencies (rIP) and C log *P* values[36] of parent compound **1**, reference **2**, and mimics **3** and **4**

Compound	**1**	**2**[a]	**3**	**4**
rIP	3.30	1.0	1.38	0.91
C log *P*[36]	−8.91	−5.54	−2.55	+1.68

[a] Compound **2**[38] was used as reference compound with a relative rIP of 1.

For the biological evaluation, a competitive target-based assay was used.[15,17] The relative inhibitory potentials (rIP) of mimics **3** and **4** were determined in microtiter plates containing covalently attached sialic acids. To determine the bound MAG, the Fc-part of MAG was complexed with alkaline phosphatase-labeled anti-Fc antibodies. The amount of MAG bound to the sialylated plates was then determined by the initial velocity of fluorescein release from fluorescein diphosphate. The affinities were determined relative to trisaccharide **2**,[38] which was used as a standard compound, and has a relative inhibitory potency (rIP) of 1.

The rIP of compound **3** is less (1.38) than that of its tetrasaccharide counterpart **1** (3.3). However, compound **3** is still more active than the reference trisaccharide **2**. Replacement of the α(2–6)-linked sialic acid with (*S*)-phenyllactic acid results in a lower biological activity in comparison to **3**. The decline in potency of compounds **3** and **4** can be rationalized by a spacial shift of ca. 1 Å for the carboxylate of the α(2–6)-linked sialic acid and the (*S*)-phenyllactic acid (see Fig. 3), when compared to its original position in the tetrasaccharide **1**. However, the ease of synthesis and the assumed improvement in the pharmacokinetic properties of compounds **3** and **4** (for C log *P*,[39] see Table 3) may countervail the modest increase in potency for mimic **3** and the decrease in biological activity for compound **4**.

3. Conclusions

Two mimics of the tetrasaccharide Siaα(2–3)Galβ(1–3)[Siaα(2–6)]Gal*N*Ac (**1**) were prepared. Based on STD data[17] and molecular modeling considerations,[20] the core disaccharide Galβ(1–3)Gal*N*Ac was substituted with a biphenyl moiety. Employing Suzuki coupling, a convergent synthesis of the biphenyl structures **3** and **4** could be achieved. To improve the yields of the coupling reaction, the catalytic effect of microwave irradiation and conventional heating was compared.

The biological evaluation of mimics **3** and **4** was performed in a competitive target-based assay. It was found that the rIP of antagonist **3** was clearly enhanced compared to that of the reference trisaccharide **2**, despite the former having a much simpler structure. Mimics **4**, however, showed an rIP similar to the reference compound, indicating that the (*S*)-phenyllactate moiety is only incompletely mimicking the α(2–6)-linked sialic acid.

In addition to the improved synthetic feasibility, a beneficial change in the pharmacokinetic properties of both mimics could be achieved. Thus, a critical parameter for bioavailability of **3** and **4**, that is, C log *P*, could decisively be improved by six and ten orders of magnitude, respectively, compared to the parent tetrasaccharide **1** (Table 3). 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.[40] Therefore, it cannot be excluded that the presented mimics **3** and **4** are cleaved metabolically by sialidases.

The data presented in this study constitute an important step toward the development of potent and drug-like oligosaccharide mimics. A further optimization of the core replacement by modified biphenyls and phenoxyphenyls is currently being investigated.

4. Experimental

4.1. General

Optical rotations were measured at 21 °C on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. NMR spectra were obtained on a Bruker Avance 500 Ultra Shield in $CDCl_3$, D_2O or CD_3OD with either solvent peak (H^1 NMR: $CDCl_3$ 7.26 ppm, CD_3OD 3.31 ppm, D_2O 4.79 ppm; ^{13}C NMR: $CDCl_3$ 77.0 ppm, CD_3OD 49.0 ppm) or dioxane (^{13}C NMR: 67.2 ppm) as an internal reference. Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer. Microwave-assisted reactions were carried out with CEM Discover and Explorer. Electron spray ionization mass spectra (ESI-MS) were obtained on a Waters micromass ZQ. 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 Mostain (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 Fluka silica gel C60 40/60 or Merck LiChroprep® RP-18 40/60. Methanol (MeOH) and dioxane were dried by refluxing with sodium methoxide and sodium, respectively, and distilled immediately before use. Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were freshly distilled from CaH_2. Dichloromethane (CH_2Cl_2), toluene, and tetrahydrofurane (THF) were dried by filtration over Al_2O_3 (Fluka, type 5016A basic).

4.2. 3′-Bromophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (8a)

At room temperature, NaOH (1.25 M, 10 ml) was added to a stirred solution of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosylbromide (**5**) (2.00 g, 4.86 mmol), benzyltriethylammonium bromide (1.11 g, 4.07 mmol), and 3-bromophenol (1.68 g, 9.73 mmol) in CH_2Cl_2 (80 ml). The reaction mixture was refluxed for 4 h at 40 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2× 40 ml). The combined organic layers were then washed with NaOH (1.25 M, 4×

30 ml) and water (30 ml), and dried over Na_2SO_4. The solvent was rotavaped off to yield **8a** (1.89 g, 77%), which was used in the Suzuki coupling without further purification.

$[\alpha]_D^{21}$ +1.0 (*c* 0.64, $CHCl_3$); ^1H NMR ($CDCl_3$, 500.1 MHz) δ: 2.01, 2.07, 2.09, 2.18 (4 s, 12H, 4 C(O)CH_3), 4.08 (m, 1H, H-5), 4.20 (m, 2H, H-$6_{a,b}$), 5.02 (d, J = 7.9 Hz, 1H, H-1), 5.48 (m, 1H, H-4), 5.48 (dd, J = 7.9, 10.4 Hz, 1H, H-2), 5.10 (dd, J = 3.5, 10.4 Hz, 1H, H-3), 6.92–7.22 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 20.6, 20.6, 20.7 (4 C(O)CH$_3$), 61.6 (C-6), 66.9 (C-4), 68.5 (C-2), 70.7 (C-3), 71.3 (C-5), 99.4 (C-1), 115.9 (aromat. C–Br), 120.0, 122.7, 126.4, 130.7 (aromat. C–H), 157.4 (aromat. C–O), 169.3, 170.1, 170.2, 170.5 (4 C=O); IR (KBr) ν: 3469, 2982, 1752 (C=O), 1590, 1477, 1429, 1371, 1227, 1080 cm^{-1}.

4.3. 4′-Bromophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (8b)

2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosylbromide (**5**) (0.540 g, 1.31 mmol) was treated with 4-bromophenol (0.455 g, 2.63 mmol), benzyltriethylammonium bromide (0.298 g, 1.09 mmol), and NaOH (1.25 M, 2.71 ml) according to the above procedure to afford the colorless solid **8b** (489 mg, 74%).

$[\alpha]_D^{21}$ +5.7 (*c* 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 500.1 MHz) δ: 2.01, 2.06, 2.07, 2.18 (4s, 12H, 4 C(O)CH_3), 4.05 (m, 1H, H-5), 4.15 (dd, J = 6.2, 11.4 Hz, 1H, H-6_a), 4.22 (dd, J = 7.0, 11.4 Hz, 1H, H-6_b), 4.99 (d, J = 8.0 Hz, 1H, H-1), 5.10 (dd, J = 3.4, 10.4 Hz, 1H, H-3), 5.45 (m, 1H, 4-H), 5.48 (dd, J = 8.0, 10.4, 1H, H-2), 6.88–6.90, 7.39–7.41 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 20.6, 20.7, 20.7 (4 C(O)CH$_3$), 61.3 (C-6), 66.8 (4 C(O)CH$_3$), 68.5 (C-2), 70.7 (C-3), 71.1 (C-5), 99.6 (C-1), 115.9 (aromat. C–Br), 118.8 (2 aromat. C–H), 132.5 (2 aromat. C–H), 164.0 (aromat. C–O), 170.3 (4 C=O); IR (KBr) ν: 3482, 2983, 1753 (C=O), 1582, 1488, 1432, 1371, 1228, 1165, 1067 cm^{-1}.

4.4. 3′-Bromophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (9a)

To a stirred solution of penta-*O*-acetyl-β-D-glucose (**6**) (0.601 g, 1.54 mmol) and 3-bromophenol (0.292 g, 1.69 mmol) in toluene (5 ml) under argon, $BF_3{\cdot}Et_2O$ (20.5 μl, 0.154 mmol) was added. The reaction was stirred at room temperature for 48 h and then diluted with toluene (5 ml) and quenched with water (10 ml). The layers were separated and the aqueous layer was extracted with toluene (3× 20 ml). The combined organic layers were then washed with NaOH (1.25 M, 2× 20 ml) and water (20 ml), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1 to 2:1) to yield **9a** (437 mg, 56%) as a white foam.

$[\alpha]_D^{21}$ −15.4 (*c* 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 500.1 MHz) δ: 2.03, 2.05, 2.07, 2.11 (4 s, 12H, 4 C(O)CH_3), 3.89 (ddd, J = 2.4, 6.0, 10.0 Hz, 1H, H-5), 4.19 (dd, J = 2.4, 12.3 Hz, 1H, H-6_a), 4.25 (dd, J = 6.0, 12.3 Hz, 1H, H-6_b), 5.06 (d, J = 7.5 Hz, 1H, H-1), 5.14 (m, 1H, H-4), 5.26 (dd, J = 7.5, 9.3 Hz, 1H, H-2), 5.30 (m, 1H, H-3), 6.91–6.93, 7.14–7.22 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 20.6, 20.6, 20.7 (4 C(O)CH$_3$), 62.0 (C-6), 68.3 (C-4), 71.0 (C-2), 72.2 (C-5), 72.6 (C-3), 98.8 (C-1), 116.0 (aromat. C–Br), 120.1, 122.7, 126.4, 130.7 (aromat. C–H), 157.4 (aromat. C–O), 169.3, 169.4, 170.6 (4 C=O); IR (KBr) ν: 3474, 2969, 1752 (C=O), 1589, 1475, 1434, 1370, 1228, 1063 cm^{-1}.

4.5. 4′-Bromophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (9b)

Penta-*O*-acetyl-β-D-glucopyranose (**6**) (601 mg, 1.54 mmol) was treated with 4-bromophenol (293 mg, 1.69 mmol) and $BF_3{\cdot}Et_2O$ (20.5 μl, 0.154 mmol) according to the procedure for **9a**. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1 to 2:1) to afford **9b** (383 mg, 49%) as a colorless solid.

$[\alpha]_D^{21}$ −16.8 (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$, 500.1 MHz) δ: 2.03, 2.05, 2.06, 2.08 (4 s, 12H, 4 C(O)CH_3), 3.85 (ddd, J = 2.4, 5.4, 9.9 Hz, 1H, H-5), 4.16 (dd, J = 2.4, 12.3 Hz, 1H, H-6_a), 4.28 (dd, J = 5.4, 12.3 Hz, 1H, H-6_b), 5.03 (d, J = 7.4 Hz, 1H, H-1), 5.16 (m, 1H, H-4), 5.25 (m, 1H, H-2), 5.28 (m, 1H, H-3), 6.87–6.89, 7.39–7.41 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 20.6, 20.6, 20.7 (4 C(O)CH$_3$), 61.9 (C-6), 68.2 (C-4), 71.1 (C-3), 72.1 (C-5), 72.6 (C-2), 99.1 (C-1), 115.9 (aromat. C–Br), 118.8 (2 aromat. C–H), 132.5 (2 aromat. C–H), 155.8 (aromat. C–O), 169.4, 170.2, 170.5 (4 C=O); IR (KBr) ν: 3482, 2960, 1749 (C=O), 1490, 1441 1378, 1235, 1055 cm^{-1}.

4.6. 3′-Iodophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (9c)

Penta-*O*-acetyl-β-D-glucopyranose (**6**) (501 mg, 1.28 mmol) was treated with 3-iodophenol (311 mg, 1.41 mmol) and $BF_3{\cdot}Et_2O$ (17.1 μl, 0.136 mmol) according to the procedure for **9a**. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 4:1 to 2:1) to afford **9c** (344 mg, 49%) as a colorless solid.

$[\alpha]_D^{21}$ −16.4 (*c* 0.59, $CHCl_3$); ^1H NMR ($CDCl_3$, 500.1 MHz) δ: 2.03, 2.05, 2.06, 2.12 (4 s, 12H, 4 C(O)CH_3), 3.88 (ddd, J = 2.4, 5.9, 10.0 Hz, 1H, H-5), 4.18 (dd, J = 2.4, 12.3 Hz, 1H, H-6_a), 4.25 (dd, J = 5.9, 12.3 Hz, 1H, H-6_b), 5.06 (d, J = 7.5 Hz, 1H, H-1), 5.13 (m, 1H, H-4), 5.25 (dd, J = 7.6, 9.3 Hz, 1H, H-2), 5.29 (m, 1H, H-3), 6.94–7.42 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 20.6, 20.6, 20.8 (4 C(O)CH$_3$), 62.0 (C-6), 68.2 (C-4), 71.0 (C-2), 72.2 (C-5), 72.6 (C-3), 94.1 (aromat. C–I), 98.8 (C-1), 116.6, 125.9, 130.9, 132.5 (aromat. C), 157.1 (aromat. C–O), 169.4, 170.2, 170.6 (4 C=O); IR (KBr) ν: 3474, 2960, 1759 (C=O), 1585, 1474, 1369, 1226, 1039 cm^{-1}; Anal. Calcd for $C_{20}H_{23}O_{10}I$: C, 43.65; H, 4.21; O, 29.07. Found: C, 43.82; H, 4.22; O, 29.18.

4.7. Methyl (3′-bromophenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosid)onate (10a)

NaOH (0.2 M, 75 ml) was added to a stirred solution of methyl 2-deoxy-2-chloro-4,7,8,9-tetra-*O*-acetyl-*N*-acetyl-neuraminidate (**7**) (1.47 g, 2.88 mmol), benzyltriethylammonium bromide (1.73 g, 6.35 mmol), and 3-bromophenol (2.49 g, 14.4 mmol) in CH_2Cl_2 (60 ml). The mixture was refluxed for 2.5 h at 40 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3× 20 ml). The combined organic layers were washed with NaOH (0.2 M, 2× 40 ml) and water (20 ml), and dried over Na_2SO_4. The solvent was removed at high vacuo and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 80:1 to 16:1) to yield **10a** (738 mg, 40%) as a white foam.

$[\alpha]_D^{21}$ +12.1 (*c* 0.61, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500.1 MHz) *δ*: 1.91, 2.04, 2.05, 2.13, 2.14 (5 s, 15H, 5 C(O)CH_3), 2.18 (m, 1H, H-3$_{ax}$), 2.67 (dd, *J* = 4.7, 13.0 Hz, 1H, H-3$_{eq}$), 3.70 (s, 3H, OCH_3), 4.06 (m, 1H, H-5), 4.18 (dd, *J* = 4.6, 12.5 Hz, 1H, H-9$_a$), 4.31 (dd, *J* = 2.2, 12.5 Hz, 1H, H-9$_b$), 4.36 (dd, *J* = 1.0, 10.6 Hz, 1H, H-6), 4.97 (m, 1H, H-4), 5.22 (d, *J* = 10.0 Hz, 1H, NH), 5.33 (m, 1H, H-7), 5.36 (m, 1H, H-8), 7.04–7.24 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) *δ*: 20.8, 20.8, 20.8, 21.0, 23.2 (5 C(O)*C*H$_3$), 37.7 (C-3), 49.4 (C-5), 53.1 (OCH_3), 62.0 (C-9), 67.3 (C-7), 68.6 (C-4), 69.1 (C-8), 73.4 (C-6), 100.0 (C-2), 118.8, 122.3, 124.0, 127.4, 130.5 (aromat. C), 154.2 (aromat. C–O), 167.8, 170.0, 170.0, 170.2, 170.6, 170.9 (6 C=O); IR (KBr) *ν*: 3374, 3070, 2960, 1748 (C=O), 1666 (N–C=O), 1586, 1542, 1472, 1434, 1370, 1218, 1131, 1040 cm^{-1}; Anal. Calcd for $C_{26}H_{32}NO_{13}Br$: C, 48.31; H, 4.99; N, 2.17. Found: C, 48.27; H, 4.79; N, 2.39.

4.8. Methyl (4′-bromophenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-galacto-2-nonulopyranosid)onate (10b)

Methyl 2-deoxy-2-chloro-4,7,8,9-tetra-*O*-acetyl-*N*-acetyl-neuraminidate (**7**) (2.00 g, 3.92 mmol) was treated with 4-bromophenol (3.40 g, 19.7 mmol), benzyltriethylammonium bromide (2.35 g, 8.63 mmol), and NaOH (0.2 M, 100 ml) according to the procedure for **10a**. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 80:1 to 20:1) to afford **10b** (1.43 g, 56%) as a colorless solid.

$[\alpha]_D^{21}$ +6.4 (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500.1 MHz) *δ*: 1.91, 2.04, 2.05, 2.13, 2.15 (5 s, 15H, 5 C(O)CH_3), 2.21 (m, 1H, H-3$_{ax}$), 2.70 (dd, *J* = 4.6, 13.0 Hz, 1H, H-3$_{eq}$), 3.65 (s, 3H, OCH_3), 4.08 (m, 1H, H-5), 4.14 (dd, *J* = 4.9, 12.5 Hz, 1H, H-9$_a$), 4.27 (m, 1H, H-9$_b$), 4.43 (m, 1H, H-6), 4.94 (ddd, *J* = 4.6, 10.4, 12.2 Hz, 1H, H-4), 5.21 (d, *J* = 10.0 Hz, 1H, NH), 5.35 (m, 1H, H-7), 5.36 (m, 1H, H-8), 6.94–6.95, 7.37–7.39 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) *δ*: 20.8, 20.8, 20.8, 21.0, 23.2 (5 C(O)*C*H$_3$), 38.3 (C-3), 49.4 (C-5), 53.1 (OCH_3), 62.0 (C-9), 67.2 (C-7), 68.6 (C-4), 68.9 (C-8), 73.4 (C-6), 100.0 (C-2), 116.7 (aromat. C–Br), 121.5, 132.3 (4 aromat. C–H), 152.9 (aromat. C–O), 167.9, 170.0, 170.1, 170.2, 170.6, 170.9 (6 C=O); IR (KBr) *ν*: 3381, 3073, 2961, 1748 (C=O), 1663 (N–C=O), 1542, 1486, 1371, 1220, 1131, 1040 cm^{-1}; Anal. Calcd for $C_{26}H_{32}NO_{13}Br$: C, 48.31; H, 4.99; N, 2.17. Found: C, 48.13; H, 4.75; N, 2.03.

4.9. Methyl (3′-iodophenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-*galacto*-2-nonulopyranosid)onate (10c)

Methyl 2-deoxy-2-chloro-4,7,8,9-tetra-*O*-acetyl-*N*-acetyl-neuraminidate (**7**) (0.670 g, 1.31 mmol) was treated with 3-iodophenol (1.46 g, 6.64 mmol), benzyltriethylammonium bromide (0.797 g, 2.93 mmol), and NaOH (0.2 M, 34 ml) according to the procedure for **10a**. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 1:0 to 25:1) to afford **10c** (442 mg, 46%) as a colorless solid.

$[\alpha]_D^{21}$ +19.9 (*c* 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500.1 MHz) *δ*: 1.91, 2.04, 2.05, 2.13, 2.14 (5 s, 15H, 5 C(O)CH_3), 2.17 (m, 1H, H-3$_{ax}$), 2.67 (dd, *J* = 4.7, 13.0 Hz, 1H, H-3$_{eq}$), 3.70 (s, 3H, OCH_3), 4.06 (m, 1H, H-5), 4.18 (dd, *J* = 4.6, 12.4 Hz, 1H, H-9$_a$), 4.31 (m, 1H, H-9$_b$), 4.35 (dd, *J* = 0.9, 10.8 Hz, 1H, H-6), 4.96 (ddd, *J* = 4.6, 10.4, 12.0 Hz, 1H, H-4), 5.22 (d, *J* = 10.0 Hz, 1H, NH), 5.35 (m, 2H, H-7, H-8), 6.99–7.44 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) *δ*: 20.3, 20.8, 20.8, 21.0, 23.2 (5 C(O)*C*H$_3$), 37.7 (C-3), 49.4 (C-5), 53.1 (OCH_3), 61.9 (C-9), 67.3 (C-7), 68.6 (C-4), 69.1 (C-8), 73.4 (C-6), 100.0 (C-2), 93.6 (aromat C–I), 119.5, 129.9, 130.8, 133.3 (4 aromat C), 153.9 (aromat C–O), 167.8, 170.0, 170.0, 170.2, 170.9 (6 C=O); IR (KBr) *ν*: 3373, 3067, 2959, 1748 (C=O), 1665 (N–C=O), 1580, 1468, 1436, 1371, 1219, 1131, 1040 cm^{-1}; ESI-MS Calcd. for $C_{26}H_{33}INO_{13}$ [M+H$^+$]: 694.1; Found: 694.1.

4.10. Benzyl (*S*)-2-(3′-bromophenoxy)-3-phenylpropanoate (12)

To a cooled (0 °C) solution of benzyl D-3-phenyllactate (420 mg, 1.64 mmol), 3-bromophenol (441 mg, 2.55 mmol), and triphenylphosphine (643 mg, 2.45 mmol) in THF was added diethylazodicarboxylate (382 μl, 2.46 mmol). The mixture was stirred at room temperature for 2$\frac{1}{2}$ h. The solvent was evaporated in vacuo and the resulting residue was suspended in 20 ml of hexane and diethyl ether (1:1), and then filtered. The triphenylphosphine oxide crystals were thoroughly washed with a hexane-diethyl ether-mixture (60 ml, 1:1). The filtrate was washed with 0.6 M NaOH (2× 15 ml) and water (15 ml), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (toluene/petroleum ether, 1:1 to 2:1) to give 448 mg (66%, 1.09 mmol) of crystalline **12**.

$[\alpha]_D^{21}$ +17.3 (*c* 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500.1 MHz) *δ*: 3.22–3.24 (m, 2H, H-3), 4.81 (dd, *J* = 5.7, 7.4 Hz, 1H, H-2), 5.10–5.17 (m, 2H, H-1′), 6.71–6.73, 6.98–7.08 (m, 4H, C_6H_4), 7.19–7.34 (m, 10H, 2× C_6H_5); ^{13}C NMR ($CDCl_3$, 125.8 MHz) *δ*: 38.9 (C-3), 67.2 (C-1′), 77.9 (C-2), 114.0, 118.9, 123.4, 124.9, 127.1, 128.4, 128.5, 128.6, 129.4, 130.6 (15

aromat. C), 135.0, 135.9 (2 aromat. C–C), 158.3 (aromat. C–O), 170.5 (C-1); IR (KBr) *v*: 3464, 3062, 3031, 2961, 2925, 1743 (C=O), 1585, 1470, 1454, 1388, 1357, 1280, 1232, 1198, 1172, 1061 cm^{-1}.

4.11. General procedure for the preparation of boronides

A microwave tube was charged with the appropriate phenylbromide (1 mmol), potassium acetate (3 mmol), bis(picanolato)diborane (1.2 mmol), $PdCl_2$(dppf) (3 mol%), and dppf (3 mol%). The tube was closed, evacuated through a needle, and flushed with argon. Dioxane (2.5 ml) was added with vigorous stirring. The solvent was degassed in an ultrasonic bath for 15 min and flushed with argon for another 5 min. The tube was heated by microwave irradiation to 120 °C for 1.5 to 2.25 h. The solvent was evaporated in vacuo and the residue dissolved in CH_2Cl_2 (50 ml), washed with brine (2× 25 ml), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography.

4.12. 3′-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolane-2-yl)-phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (13a)

Phenylbromide **8a** (103 mg, 0.204 mmol) was treated with bis(picanolato)diborane (60.6 mg, 0.239 mmol) following the general procedure (μW, 120 °C, 1.5 h). The residue was purified by flash chromatography (toluene/ethyl acetate, 5:1) to afford 100 mg (89%, 0.182 mmol) of **13a** as a colorless solid.

$[\alpha]_D^{21}$ +1.3 (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$, 500.1 MHz) *δ*: 1.33 (s, 12H, 4 CH_3), 2.03, 2.05, 2.06, 2.08 (4 s, 12H, 4 C(O)CH_3), 3.89 (ddd, *J* = 2.3, 5.5, 10.0 Hz, 1H, H-5), 4.16 (dd, *J* = 2.3, 12.3 Hz, 1H, H-6_a), 4.28 (dd, *J* = 5.5, 12.3 Hz, 1H, H-6_b), 5.14 (d, *J* = 7.5 Hz, 1H, H-1), 5.17 (m, 1H, H-3), 5.26–5.32 (m, 2H, H-2, H-4), 7.08–7.52 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) *δ*: 20.6, 20.7, 20.7, 20.6 (4 C(O)*C*H_3), 24.8, 24.9 (2 C(*C*H_3)$_2$), 61.5 (C-6), 67.0 (C-4), 68.7 (C-2), 70.9 (C-3), 71.0 (C-5), 84.0 (2 *C*(CH_3)$_2$), 99.4 (C-1), 120.2, 122.3, 129.0, 129.8 (4 aromat. C–H), 156.4 (aromat. C–O), 169.4, 170.1, 170.3, 170.4 (4 C=O); IR (KBr) *v*: 3444, 2981, 2937, 1753 (C=O), 1577, 1491, 1431, 1372, 1356, 1321 (B-O), 1225, 1145, 1078 cm^{-1}.

4.13. 4′-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolane-2-yl)-phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (13b)

Phenylbromide **8b** (102 mg, 0.203 mmol) was treated with bis(picanolato)diborane (61.0 mg, 0.240 mmol) following the general procedure (μW, 120 °C, 1.5 h). The residue was purified by flash chromatography (toluene/ethyl acetate, 4:1) to afford 95.6 mg (86%, 0.174 mmol) of **13b** as a colorless solid.

$[\alpha]_D^{21}$ +6.6 (*c* 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 500.1 MHz) *δ*: 1.33 (s, 12H, 4 CH_3), 2.01, 2.05, 2.07, 2.18 (4 s, 12H, 4 C(O)CH_3), 4.09 (m, 1H, H-5), 4.17 (dd, *J* = 6.0, 11.4 Hz, 1H, H-6_a), 4.21 (dd, *J* = 7.3, 11.4 Hz, 1H, H-6_b), 5.09 (d, *J* = 8.0 Hz, 1H, H-1), 5.11 (dd, *J* = 3.4, 10.5 Hz, 1H, H-3), 5.41 (m, 1H, H-4), 5.50 (dd, *J* = 7.9, 10.5 Hz, 1H, H-2), 6.97–6.99, 7.75–7.76 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) *δ*: 20.6, 20.7, 20.7, 20.7 (4 C(O)*C*H_3), 24.8, 24.8 (2 C(*C*H_3)$_2$), 61.5 (C-6), 66.9 (C-4), 68.6 (C-2), 70.8 (C-3), 71.1 (C-5), 83.8 (2 *C*(CH_3)$_2$), 99.1 (C-1), 115.9 (2 aromat. C–H), 136.5 (2 aromat. C–H), 159.3 (aromat. C–O), 169.4, 170.1, 170.2, 170.4 (4 C=O); IR (KBr) *v*: 3475, 2981, 2937, 1755 (C=O), 1605, 1575, 1514, 1364, 1322 (B-O), 1229, 1166, 1144, 1076 cm^{-1}.

4.14. 3′-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolane-2-yl)-phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (13c)

Phenylbromide **9a** (100 mg, 0.199 mmol) was treated with bis(picanolato)diborane (60.9 mg, 0.240 mmol) following the general procedure (μW, 120 °C, 2 h). The residue was purified by flash chromatography (toluene/ethyl acetate, 7:1) to afford 87.9 mg (80%, 0.160 mmol) of **13c** as a colorless solid.

$[\alpha]_D^{21}$ −12.4 (*c* 0.76, $CHCl_3$); ^1H NMR ($CDCl_3$, 500.1 MHz) *δ*: 1.33 (s, 12H, 4 CH_3), 2.01, 2.07, 2.07, 2.19 (4 s, 12H, 4 C(O)CH_3), 4.09 (m, 1H, H-5), 4.17 (dd, *J* = 6.0, 11.3 Hz, 1H, H-6_a), 4.22 (dd, *J* = 7.2, 11.3 Hz, 1H, H-6_b), 5.11 (d, *J* = 8.0 Hz, 1H, H-1), 5.12 (m, 1H, H-4), 5.46 (m, 1H, H-2), 5.50 (dd, 1H, *J* = 7.9, 10.5 Hz, H-3), 7.09–7.53 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) *δ*: 20.6, 20.6, 20.7, 20.7 (4 C(O)*C*H_3), 24.8, 24.9 (2 C(*C*H_3)$_2$), 62.0 (C-6), 68.3 (C-4), 71.2 (C-2), 72.0 (C-5), 72.8 (C-3), 84.0 (2 *C*(CH_3)$_2$), 98.9 (C-1), 120.1, 122.4, 129.1, 129.8 (4 aromat. C–H), 156.3 (aromat. C–O), 170.7 (4 C=O); IR (KBr) *v*: 3475, 2981, 1760 (C=O), 1577, 1492, 1433, 1357, 1322 (B-O), 1224, 1145, 1046 cm^{-1}.

4.15. 4′-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolane-2-yl)-phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (13d)

Phenylbromide **9b** (101 mg, 0.201 mmol) was treated with bis(picanolato)diborane (60.4 mg, 0.238 mmol) following the general procedure (μW, 120 °C, 2.25 h). The residue was purified by flash chromatography (toluene/ethyl acetate, 5:1) to afford 98.2 mg (89%, 0.178 mmol) of **13d** as a colorless solid.

$[\alpha]_D^{21}$ −9.6 (*c* 0.69, $CHCl_3$); ^1H NMR ($CDCl_3$, 500.1 MHz) *δ*: 1.33 (s, 12H, 4 CH_3), 2.03, 2.04, 2.05, 2.08 (4 s, 12H, 4 C(O)C*H*3), 3.89 (ddd, *J* = 2.3, 5.6, 10.0 Hz, 1H, H-5), 4.16 (dd, *J* = 2.2, 12.3 Hz, 1H, H-6_a), 4.27 (dd, *J* = 5.5, 12.3 Hz, 1H, H-6_b), 5.12 (d, *J* = 7.5 Hz, 1H, H-1), 5.15 (m, 1H, H-4), 5.26–5.32 (m, 2H, H-2, H-3), 6.96–6.98, 7.74–7.76 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) *δ*: 20.6, 20.6, 20.7 (4 C(O)*C*H_3), 24.8 (2 C(*C*H_3)$_2$), 62.0 (C-6), 68.3 (C-4), 71.1 (C-2), 72.1 (C-5), 72.7 (C-3), 83.8 (2 *C*(CH_3)$_2$), 98.6 (C-1), 115.9 (2 aromat. C–H), 136.5 (2 aromat. C–H), 159.3 (aromat. C–O), 169.4, 170.2, 170.6 (4 C=O); IR (KBr) *v*: 3476, 2980, 1748 (C=O), 1605, 1366, 1323 (B-O), 1231, 1143, 1062 cm^{-1}.

4.16. Methyl [4′-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-galacto-2-nonulopyranosid]onate (13e)

Phenylbromide **10b** (251 mg, 0.388 mmol) was treated with bis(picanolato)diborane (118 mg, 0.465 mmol) following the general procedure (μW, 120 °C, 0.75 h). The residue was purified by flash chromatography (toluene/CH_2Cl_2/2-propanol, 15:10:0.1 to 15:10:3) to afford 228 mg (85%, 0.329 mmol) of **13e** as a brownish solid.

$[\alpha]_D^{21}$ +16.4 (*c* 0.59, $CHCl_3$); ^1H NMR ($CDCl_3$, 500.1 MHz) *δ*: 1.33 (s, 12H, 4 CH_3), 1.92, 2.04, 2.06, 2.12, 2.17 (5 s, 15H, 5 C(O)CH_3), 2.22 (m, 1H, H-3_{ax}), 2.68 (m, 1H, H-3_{eq}), 3.63 (s, 3H, OCH_3), 4.11 (m, H-5), 4.16 (m, 1H, H-9_a), 4.28 (m, 1H, H-9_b), 4.51 (m, 1H, H-6), 4.96 (m, 1H, H-4), 5.23 (m, 1H, N-H), 5.33 (m, 2H, H-7, H-8), 7.02–7.04, 7.71–7.73 (m, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) *δ*: 20.7, 20.8, 20.9, 21.0, 24.6 (5 C(O)*C*H_3), 24.8, 24.9 (2 C(*C*H_3)$_2$), 38.3 (C-3), 49.4 (C-5), 53.0 (CH_3), 62.0 (C-9), 67.4 (C-7), 68.7 (C-4), 69.3 (C-8), 73.6 (C-6), 83.7 (2 *C*$(CH_3)_2$), 99.6 (C-2), 118.3 (2 aromat. C–H), 136.3 (2 aromat. C–H), 159.5 (aromat. C–O), 168.4, 170.1, 171.0 (6 C═O); IR (KBr) *ν*: 3373, 2979, 1750 (C═O), 1663 (N–C═O), 1604, 1542, 1448, 1365, 1321 (B–O), 1223, 1145, 1083, 1039 cm^{-1}.

4.17. Benzyl (*S*)-2-[3′-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenoxy]-3-phenylpropanoate (13f)

A flask was charged with phenylbromide **12** (300 mg, 0.729 mmol), potassium acetate (215 mg, 2.19 mmol), dppf (13.3 mg, 24.0 μmol), and dioxane (15 ml). The flask was flushed with argon and degassed in ultrasonic bath for 15 min. Bis(picanolato)diborane (278 mg, 1.09 mmol) and $PdCl_2$(dppf) (17.9 mg, 21.9 μmol) were added and the mixture was heated to 80 °C for 27 h. The solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (25 ml), washed with water (2× 20 ml), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/toluene/ethyl acetate, 10:1:0.5) to afford 221 mg (66%, 0.482 mmol) of **13f** as a yellowish oil.

$[\alpha]_D^{21}$ −9.1 (*c* 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 500.1 MHz) *δ*: 1.32 (s, 12H, 4 CH_3), 3.21–3.29 (m, 2H, H-3), 4.93 (dd, *J* = 5.4, 7.6 Hz, 1H, H-2), 5.09–5.14 (m, 2H, H-1′), 6.91–7.40 (m, 14H, C_6H_4, 2× C_6H_5); ^{13}C NMR ($CDCl_3$, 125.8 MHz) *δ*: 24.8, 24.9 (2 C(*C*H_3)$_2$), 39.1 (C-3), 67.0 (C-1′), 77.4 (C-2), 83.8 (2 *C*$(CH_3)_2$), 118.4, 120.8, 126.9, 128.1, 128.3, 128.4, 128.5, 129.0, 129.5 (14 aromat. C), 135.2, 136.9 (2 aromat. C–C), 157.1 (aromat. C–O), 171.1 (C-1); IR (KBr) *ν*: 3492, 3064, 3032, 2978, 2931, 1752 (C═O), 1575, 1491, 1430, 1358, 1272, 1215, 1145, 1085 cm^{-1}.

4.18. General procedure for Suzuki coupling

A microwave tube was charged with phenylboronide (0.109 mmol), the appropriate phenylhalogenide (0.120 mmol), base (0.326 mmol), and catalyst (1.09 μmol). The tube was closed, evacuated through a needle, and flushed with argon. Dioxane (1 ml) was added under vigorous stirring. The solvent was degassed in ultrasonic bath for 20 min and flushed with argon for another 10 min. The tube was heated by microwave irradiation to 120 °C for an appropriate time. The solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (20 ml), washed twice with brine (2× 30 ml), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography to yield the corresponding biphenyl.

4.19. 4-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-3′-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-biphenyl (14)

Phenylhalide **9c** (50.2 mg, 91.2 μmol) and boronide **13b** (45.6 mg, 82.9 μmol) were treated with cesium carbonate (81.1 mg, 249 μmol) and $Pd(PPh_3)_4$ (1.4 mg, 1.21 μmol) in dioxane (1 ml) according to the general procedure (μW, 120 °C, 4.5 h). The residue was purified by flash chromatography (toluene/ethyl acetate, 3:1 to 2.5:1) to afford 61.0 mg (87%, 72.0 μmol) of **14** as a colorless solid.

$[\alpha]_D^{21}$ −1.6 (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 500.1 MHz) *δ*: 1.98, 2.02, 2.03, 2.04, 2.06, 2.06, 2.08, 2.19 (8 s, 24H, 8 C(O)CH_3), 3.88 (m, 1H, H-5′), 4.08 (m, 1H, H-5), 4.15–4.28 (m, 4H, H-6, H-6′), 5.08 (d, *J* = 7.9 Hz, 1H, H-1), 5.12 (dd, *J* = 3.5, 10.5 Hz, 1H, H-3), 5.15 (d, *J* = 7.6 Hz, 1H, H-1′), 5.16 (m, 1H, H-4′), 5.29–5.31 (m, 2H, H-2′, H-3′), 5.47 (dd, *J* = 0.7, 3.4 Hz, 1H, H-4), 5.51 (dd, *J* = 7.9, 10.5 Hz, 1H, H-2), 6.94–7.49 (m, 8H, 2× C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) *δ*: 20.5, 20.6, 20.6, 20.6, 20.7 (8 C(O)*C*H_3), 61.3 (C-6), 62.0 (C-6′), 66.8 (C-4), 68.3 (C-4′), 68.6 (C-2), 70.8 (C-3), 71.0 (C-5), 71.1 (C-3′), 72.0 (C-5′), 72.7 (C-2′), 98.9 (C-1′), 99.6 (C-1), 115.2, 115.7, 121.9, 129.9, 117.2, 128.3 (8 aromat. C–H), 135.7, 142.2 (2 aromat. C–C), 156.6, 157.1 (2 aromat. C–O), 169.3, 169.4, 170.1, 170.2, 170.3, 170.5 (8 C═O); Anal. Calcd for $C_{40}H_{46}O_{20}$: C, 56.74; H, 5.48. Found: C, 56.60; H, 5.73.

4.20. Methyl (3′-(*S*)-(1-benzyloxycarbonyl-2-phenyl-2-ethoxy)-biphenyl-4-yl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-galacto-2-nonulopyranosid)onate (15)

Phenylhalide **10b** (282 mg, 436 μmol) and boronide **13f** (220 mg, 480 μmol) were treated with K_3PO_4 (280 mg, 1.32 mmol), dppf (7.7 mg, 13.9 μmol), BHT (67.7 mg, 307 μmol), and $PdCl_2$(dppf) (12.0 mg, 14.7 μmol) in dioxane (6.5 ml) according to the general procedure (μW, 170 °C, 2.5 h). The mixture was heated with microwaves to 170 °C for 2 1/4 h. The residue was purified by flash chromatography (toluene/CH_2Cl_2/2-propanol, 15:10:0 to 15:10:2) to afford 108 mg (28%, 120 μmol) of **15** as colorless solid.

$[\alpha]_D^{21}$ +5.0 (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$, 500.1 MHz) *δ*: 1.86, 1.96, 1.98, 2.06, 2.08 (5 s, 15H, 5 C(O)CH_3), 2.17 (m, 1H, H-3_{ax}), 2.73 (dd, *J* = 4.6, 12.9 Hz, 1H, H-3_{eq}), 3.17–3.25 (m, 2H, H-3′), 3.62 (s, 3H, OCH_3), 4.04 (m, 1H, H-5), 4.11 (dd, *J* = 4.9,

12.5 Hz, 1H, H-9$_a$), 4.21 (m, 1H, H-9$_b$), 4.26 (dd, J = 2.4, 12.5 Hz, 1H, H-6), 4.85 (dd, J = 5.4, 7.7 Hz, 1H, H-2′), 4.92 (m, 1H, 4-H), 5.04–5.11 (m, 2H, H-1″), 5.29–5.34 (m, 2H, H-7, H-8), 5.35 (d, J = 5.0 Hz, 1H, N-H), 6.67–7.34 (m, 18H, 2× C_6H_4, 2× C_6H_5); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 20.7, 20.9, 21.0, 23.1 (5 C(O)CH_3), 38.0 (C-3), 39.1 (C-3′), 49.4 (C-5), 53.0 (OCH_3), 62.0 (C-9), 67.0 (C-1″), 67.3 (C-7), 68.8 (C-4), 69.2 (C-8), 73.3 (C-6), 77.8 (C-2′), 100.0 (C-2), 113.5, 114.2, 114.3, 116.7, 118.0, 120.1, 120.5, 121.5, 126.9, 128.0, 128.3, 128.4, 128.5, 128.5, 129.5, 129.7, 132.3, 135.1, 136.1, 136.3, 141.9 (22 aromat. C), 153.3, 158.0 (2 aromat. C–O), 168.1, 170.6, 170.9, 171.0 (8 C=O); HR-MS calcd for $C_{48}H_{51}NNaO_{16}$ [M+Na$^+$]: 920.3100; Found: 920.3074.

4.21. 3,4′-Di-[methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-*galacto*-2-nonulopyranosid)onat-2-yl]-biphenyl (16)

Phenylhalide **10c** (61.2 mg, 88.3 μmol) and boronide **13e** (41.6 mg, 60.0 μmol) were treated with silver carbonate (47.9 mg, 174 μmol) and $Pd(PPh_3)_4$ (2.2 mg, 1.91 μmol) in dioxane (1 ml) according to the general procedure (μW, 120 °C, 7 h). The residue was purified by flash chromatography (toluene/CH_2Cl_2/2-propanol, 15:10:1 to 15:10:2.5) to afford 52.6 mg (77%, 46.4 μmol) of **16** as colorless solid.

$[\alpha]_D^{21}$ +16.6 (c 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500.1 MHz) δ: 1.89, 1.91, 2.01, 2.02, 2.03, 2.05, 2.10, 2.12, 2.14 (9 s, 30H, 10 C(O)CH_3), 2.17–2.26 (m, 2H, H-3$_{ax}$, H-3′$_{ax}$), 2.67–2.73 (m, 2H, H-3$_{eq}$, H-3′$_{eq}$), 3.66, 3.70 (2 s, 6H, 2 OCH_3), 4.05–4.19 (m, 4H, H-5, H-5′, H-9$_a$, H-9′$_a$), 4.29–4.36 (m, 2H, H-9$_b$, H-9′$_b$), 4.36–4.45 (m, 2H, H-6, H-6′), 4.95–4.99 (m, 2H, H-4, H-4′), 5.33–5.40 (m, 4H, H-7, H-7′, H-8, H-8′), 5.46–5.50 (m, 2H, N-H, N′-H), 7.06–7.49 (m, 8H, 2× C_6H_4); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ: 20.6, 20.7, 20.8, 21.0, 23.1 (10 C(O)CH_3), 37.5, 38.1 (C-3, C-3′), 49.4 (C-5, C-5′), 53.0, 53.4 (2 OCH_3), 62.0 (C-9, C-9′), 67.3, 67.5 (C-7, C-7′), 68.8, 68.9 (C-4, C-4′), 69.1, 69.6 (C-8, C-8′), 73.3 (C-6, C-6′), 99.9, 100.0 (C-2, C-2′), 118.7, 119.2, 122.7, 129.6, 120.0, 127.9 (8 aromat. C–H), 153.4, 153.8 (2 aromat. C–O), 135.9, 141.6 (2 aromat. C–C), 168.1, 168.2, 170.1, 170.1, 170.6, 171.0 (12 C=O); Anal. Calcd for $C_{52}H_{64}N_2O_{26}$: C, 55.12; H, 5.69; N, 2.47. Found: C, 55.11; H, 5.75; N, 2.39.

4.22. General procedure for deprotection

To a solution of the biphenyl derivative (0.095 mmol) in methanol (3 ml) was added 1 M NaOMe in methanol (1 ml). After stirring at room temperature for 17 h, water (1 ml) was added and stirring continued for 6 h. The mixture was neutralized with Dowex 50 × 8 (H$^+$), filtered, and concentrated in vacuo. The residue was purified by reversed-phase chromatography (gradient methanol/water), treated with Dowex 50 × 8 (Na$^+$), and purified on a P2 column to give the sodium salt of the biphenyl derivative after a final lyophilization from dioxane/water.

4.23. 3,4′-Di-[sodium (5-acetamido-3,5-dideoxy-D-*glycero*-α-D-galacto-2-nonulopyranosid)onat-2-yl]-biphenyl (3)

Biphenyl **16** (31.6 mg, 27.9 μmol) was treated according to the general procedure to afford 12.7 mg (56%, 15.6 μmol) of **3** as a colorless solid.

^{1}H NMR (D_2O, 500.1 MHz) δ: 1.95 (m, 2H, H-3$_{ax}$, H-3′$_{ax}$), 2.04 (s, 6H, 2 C(O)CH_3), 2.91 (m, 2H, H-3$_{eq}$, H-3′$_{eq}$), 3.63 (m, 2H, H-7, H-7′), 3.65 (m, 2H, H-9$_a$, H-9′$_a$), 3.77 (m, 2H, H-4, H-4′), 3.80–3.89 (m, 2H, H-9$_b$, H-9′$_b$), 3.92 (m, 2H, H-5, H-5′), 3.87–3.94 (m, 4H, H-6, H-6′, H-8, H-8′), 6.86–7.60 (m, 8H, 2× C_6H_4); ^{13}C NMR (D_2O, 125.8 MHz) δ: 22.5 (2 CH_3), 52.1 (C-5, C-5′), 63.3 (C-9, C-9′), 68.7 (C-7, C-7′, C-4, C-4′), 72.5 (C-8, C-8′), 73.9 (C-6, C-6′), 103.2, 103.1 (C-2, C-2′), 114.4, 115.1, 116.7, 119.2, 119.8, 120.2, 122.4, 122.9, 128.4, 128.7, 130.5, 131.0 (12 aromat. C); HR-MS calcd for $C_{23}H_{26}NO_{10}$ [M−Sia]: 476.1562; Found: 476.1542.

4.24. Sodium [3′-(*S*)-(sodium 2-hydroxy-3-phenylpropionate-2-*O*-yl)-biphenyl-4-yl 5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosid]onate (4)

Biphenyl **15** (85.0 mg, 94.7 μmol) was treated according to the general procedure to afford 33.2 mg (52%, 49.6 μmol) of **4** as a colorless solid.

$[\alpha]_D^{21}$ +24.0 (c 0.52, H_2O); ^{1}H NMR (D_2O, 500.1 MHz) δ: 1.95 (m, 1H, H-3$_{ax}$), 2.05 (1 s, 3H, C(O)CH_3), 2.90 (dd, J = 4.0, 12.4 Hz, 1H, H-3$_{eq}$), 3.16–3.29 (m, 2H, H-3′), 3.61 (m, 1H, H-7), 3.66 (m, 1H, H-9$_a$), 3.78 (m, 1H, H-4), 3.87–3.89 (m, 1H, H-9$_b$), 3.91–3.92 (m, 3H, H-5, H-6, H-8), 4.80 (m, 1H, H-2′), 6.84–7.58 (m, 13H, 2× C_6H_4, C_6H_5); ^{13}C NMR (D_2O, 125.8 MHz) δ: 22.8 (CH_3), 41.2 (C-3), 52.5 (C-5), 63.3 (C-9), 68.9 (C-7), 68.6 (C-4), 72.4 (C-8), 74.0 (C-6), 80.5 (C-2′), 114.1, 114.2, 120.1, 122.1, 127.1, 128.2, 128.8, 129.6, 130.8 (18 aromat. C); Anal. Calcd for $C_{32}H_{33}NO_{12}Na_2{\cdot}5H_2O$: C, 50.59; H, 5.71; N, 1.84. Found: C, 50.83; H, 5.66; N, 2.02.

4.25. 4-β-D-Galactopyranosyl-3′-β-D-glucopyranosyl-biphenyl (17)

Biphenyl **14** (93.1 mg, 110 μmol) was treated according to the general procedure without addition of water to afford 51.2 mg (91%, 100 μmol) of **17** as a colorless solid.

$[\alpha]_D^{21}$ −62.0 (c 0.58, H_2O); ^{1}H NMR (D_2O, 500.1 MHz) δ: 3.49 (m, 1H, H-3′), 3.60 (m, 2H, H-2′, H-5′), 3.62–3.67 (m, 1H, H-4′), 3.72–3.81 (m, 2H, H-6), 3.78 (m, 1H, H-3), 3.83 (m, 1H, H-2), 3.88 (m, 1H, H-5), 3.92 (m, 2H, H-6′), 4.00 (m, 1H, H-4), 5.08 (d, 1H, J = 7.6 Hz, H-1), 5.16 (d, 1H, J = 7.3 Hz, H-1′), 7.10–7.65 (m, 8H, 2× C_6H_4); ^{13}C NMR (D_2O, 125.8 MHz) δ: 61.2 (C-6′), 61.4 (C-6), 69.1 (C-4), 70.2 (C-3′), 71.2 (C-2), 73.2, 73.6 (C-3), 76.1 (C-5), 76.2, 76.8, 100.8 (C-1′), 101.3 (C-1), 115.3, 116.0, 117.6, 122.2, 129.0, 131.1 (12 aromat. C); Anal. Calcd for $C_{24}H_{30}O_{12}{\cdot}2.5H_2O$: C, 51.89; H, 6.35. Found: C, 52.25; H, 6.16.

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