# 5-Azido Derivatives of Neuraminic Acid − Synthesis and Structure

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*Dedicated to Professor Peter Köll on the occasion of his 60th birthday*

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Benzyl sialoside **1** was transformed into the corresponding 5-azido derivative **4** by *N*-nitrosation of the 5-acetylamino group and treatment with base followed by hydrazoic acid or, alternatively, by *N,O*-deacetylation followed by diazo group transfer to the amino moiety by means of $TfN_3$. Regioselective 4-*O*-acetylation and introduction of the MPM group at 9-*O* afforded glycosyl acceptor **11**. *N,O*-Deacetylation of ethyl 2-thiosialoside **13** afforded **14** which, after diazo group transfer to the amino group, furnished 5-azido derivative **16**, which can serve as a sialyl donor. Activation of the ethylthio leaving group in the absence of an acceptor afforded 2,3-dehydro derivative **17**. Regioselective 4-*O*-acetylation and 9-*O*-benzylation furnished glycosyl acceptor **22**. An X-ray analysis was obtained from crystals of the 7,8,9-*O*-unprotected intermediate **21**.

## Introduction

Chemical sialylation is mainly performed with per-*O*-acetyl-*N*-acetylneuraminic acid methyl ester derivatives possessing either phosphite or sulfide leaving groups at the anomeric position.[1−3] Because these sialyl donors do not always provide the desired high degree of α-linkage to acceptors, anchimeric assistance with the help of auxiliary groups at the 3-position of *N*-acetylneuraminic acid (Neu5Ac) has also been investigated.[4] The great influence of protective groups on the reactivity and stereoselectivity not only of glycosyl donors but also of glycosyl acceptors − for instance, the difficult α(2−8)-linkage between two Neu5Ac residues[5] − was an incentive to generate 5-azido derivatives of Neu5Ac from which the desired 5-acetylamino function might readily be generated. The azido derivatives will not form a hydrogen bond with the 8-hydroxy group,[5] which could lower the acceptor character. This effect of the 5-acetylamino function on the nucleophilicity of the 8-hydroxy group was deduced from a 1,7-lactone of Neu5Ac, possessing these two functionalities in a well separated state; this compound exhibited greatly increased acceptor reactivity.[6,7]

## Results and Discussion

5-Azido derivatives of neuraminic acid have previously been obtained by following the biosynthetic pathway; i.e., by treating 2-azidomannose with pyruvate in an aldolase-catalyzed reaction.[8−12] A chemical synthesis was based on *N*-nitrosation of Neu5Ac, subsequent treatment with base to yield the diazo intermediate, followed by treatment with hydrazoic acid.[13] Investigation of this reaction sequence required the transformation of Neu5Ac into known benzyl glycoside **1**[14,15] (Scheme 1). *N*-Nitrosation of **1** with $N_2O_4$ in the presence of sodium acetate[13] furnished *N*-nitroso derivative **2**; subsequent treatment with sodium trifluoroethanolate as base furnished the 5-diazo intermediate **2A**, which on addition of hydrazoic acid gave 5-azido derivative **4** in a one-pot procedure, but only in 43% overall yield. The configurational assignment at C-5 was confirmed by the $^1H$ NMR spectroscopic data ($J_{4,5}$ = 9.9, $J_{5,6}$ = 10.6 Hz). Therefore, diazo group transfer to the amino group was investigated.

To this end, **1** was transformed into the known **3**,[14−17] after which treatment of **3** with trifluoromethanesulfonyl azide ($TfN_3$) as the diazo transfer reagent[18,19] in the presence of sodium methoxide and 4-dimethylaminopyridine (DMAP, Steglich's base) furnished azido derivative **6**. This, on immediate *O*-acetylation with acetic anhydride in pyridine and treatment with diazomethane, afforded **4** in 70% overall yield. Removal of the *O*-acetyl groups under Zemplén conditions[20] (→ **5**), followed by treatment with 2,2-dimethoxypropane (DMP) in the presence of *p*-toluenesulfonic acid (*p*TsOH) as catalyst, afforded a high yield of 8,9-*O*-isopropylidene derivative **7**, offering regioselective access to the 4-hydroxy group. Thus, treatment of **7** with acetic anhydride/pyridine in dichloromethane regioselectively afforded the desired 4-*O*-acetyl derivative **8** in up to 78% yield; only minor amounts of the 4,7-di-*O*-acetyl compound **9** were obtained. De-*O*-isopropylidenation of **8** with ethanethiol as nucleophile in the presence of *p*TsOH as catalyst[21] resulted in 7,8,9-*O*-unprotected compound **10**. Regioselective introduction of a 4-methoxyphenylmethyl (MPM) group at *O*-9 could be carried out with the corresponding trichloroacetimidate [MPM−O−C(=NH)$CCl_3$][22] as MPM donor in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalyst, thus affording valuable acceptor **11**, permitting regioselective reaction at

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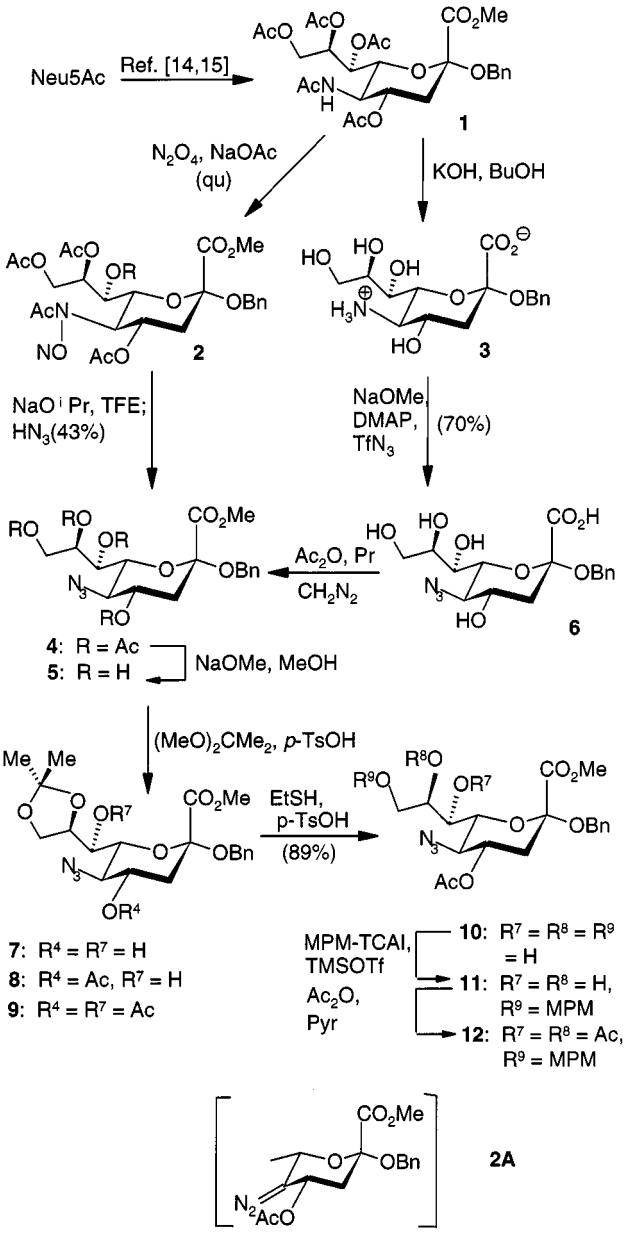
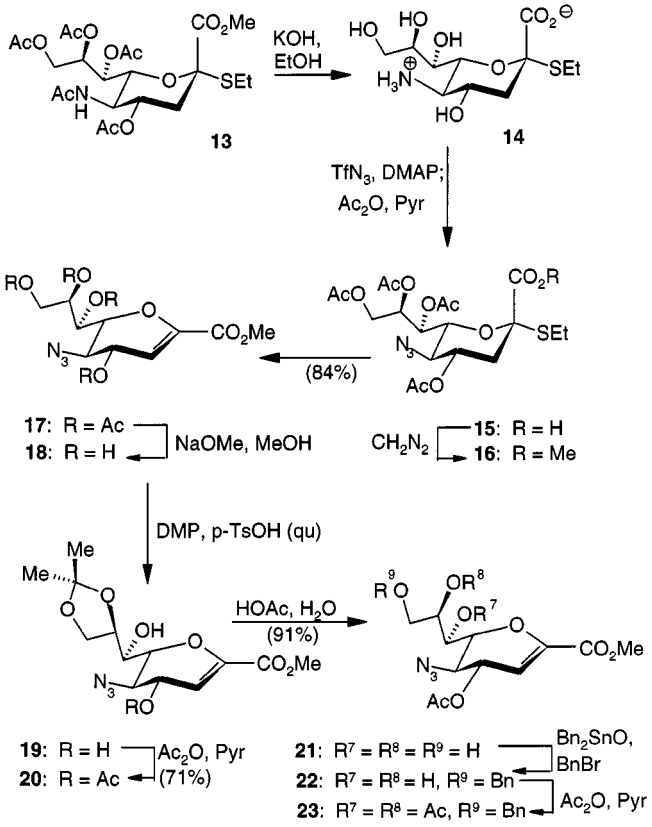



Scheme 1




Scheme 2

*O*-8 of the neuraminic acid residue. For further characterization, compound **11** was transformed into 4,7,8-tri-*O*-acetyl derivative **12**.

Similar reactions were carried out with a different neuraminic acid derivative. 2-Alkyl/-aryl thiosialosides have been successfully employed as sialyl donors in chemical glycosylation reactions.[3] Therefore, the known ethyl thioglycoside **13**[23,24] (Scheme 2) was saponified with KOH in ethanol to afford **14** in quantitative yield. Treatment of crude **14** with $TfN_3$ [18] in the presence of DMAP, followed by acetic anhydride in pyridine, furnished tetra-*O*-acetyl-5-azido derivative **15**, which, on treatment with diazomethane, produced the corresponding methyl ester **16** in 63% overall yield. Compound **16** should be a versatile sialyl donor.

It was found that 2,3-dehydro derivatives of neuraminic acid are particularly reactive glycosyl acceptors at the 8-hydroxy group.[23,24] It is also possible to generate anchimerically assisted sialyl donors from these precursors.[4] Therefore, activation of **16** with *N*-iodosuccinimide (NIS)/TfOH[25] in the absence of an acceptor was performed, furnishing known 2,3-dehydro derivative **17**[26,27] in 84% yield. De-*O*-acetylation under Zemplén conditions[20] (→ **18**), followed by regioselective 8,9-*O*-isopropylidenation, gave **19**, which was again regioselectively 4-*O*-acetylated with acetic anhydride and pyridine in dichloromethane to provide **20** in 71% yield. De-*O*-isopropylidenation with aqueous acetic acid afforded 7,8,9-*O*-unprotected derivative **21**, which was obtained in the form of crystals suitable for X-ray analysis (see below). Regioselective 9-*O*-benzylation was performed with dibutyltin oxide followed by benzyl bromide treatment, thus providing **22**, which again is a useful acceptor for glycosylations at *O*-8 of the neuraminic acid skeleton. For further characterization, **22** was transformed into 4,7,8-tri-*O*-acetyl derivative **23**.

The X-ray structural analysis obtained from crystals of **21** represents the first detailed structural information available for a 2,3-dehydro-neuraminic acid derivative (Figure 1).[28] The expected $^6H_5$ half-chair conformation of the dihydropyran moiety could be confirmed. C-2 is almost planar (bond angles: 125.7°, 124.1°, and 110.2°), and the 8-hydroxy group is now readily accessible; it displays interactions with neither the azido group, nor the caboxylate group.

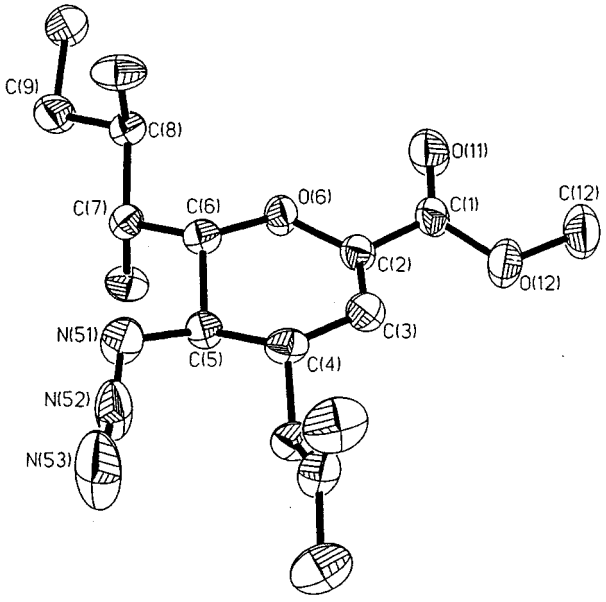



Figure 1. Structure of compound **21** in ORTEP drawing

## Conclusion

In conclusion, it proved possible to obtain versatile azido derivatives of neuraminic acid, with variable protecting group patterns. These compounds are useful as acceptors for reactions at the 4- and the 8-hydroxy groups (compounds **7**, **19** and **11**, **22**) and as sialyl donors (compounds **16** and **17**) in sialylation reactions.

## Experimental Section

**General Methods:** Solvents were purified according to the standard procedures. − Flash chromatography was performed on J. T. Baker silica gel (40−63 μm) or RP-18 silica gel (40 μm) at a pressure of 0.4 bar. − TLC was performed on Merck 60 $F_{254}$ silica gel plastic plates or Merck RP-18 60 $F_{254S}$ silica gel glass plates; compounds were viewed by treatment with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (20 g) and $Ce(SO_4)_2$ (0.4 g) in 10% sulfuric acid (400 mL) and heating at 150 °C. − Optical rotations were measured on a Perkin−Elmer 241 polarimeter in a 1 dm cell at 22 °C. − NMR Measurements were recorded on a Bruker AC250 Cryospec, Bruker DRX500, or a Bruker DRX600 spectrometer. − MALDI mass spectra were recorded on a Kratos Kompact MALDI instrument, using a 2,5-dihydroxybenzoic acid matrix. FAB mass spectra were recorded on a Finnigan MAT 312/AMD 5000 spectrometer, using a 1:1 (3-nitrobenzyl)alcohol/glycerol matrix.

The diffraction measurements for compounds **21** were carried out on a Siemens SMART 1000 area detector system with graphite-monochromated Mo-$K_\alpha$ radiation (λ = 0.7107 Å). Data collection was performed by ω scans (Δω = 2.0°). Absorption effects were considered negligible. The structures were determined by direct methods (SHELXS-86) and refined by full-matrix, least-squares, with the non-hydrogen atoms anisotropic and hydrogen atoms treated as isotropic (SHELXL-93). Most hydrogens were located from difference electron density maps and the remainder were fixed at calculated positions with U-values 1.2 times those of the corresponding carbon atoms.

**Methyl (Benzyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-(*antilsyn*-*N*-nitrosoacetamido)-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid)onate (2):**[13] A mixture of sodium acetate (454 mg, 6.880 mmol) and **1** (400 mg, 0.668 mmol) in dichloromethane (8 mL) was treated at 0 °C with $N_2O_4$ (commercially available from Aldrich) until nitrosation was complete, as judged by TLC (ethyl acetate/hexane, 1:1). After 2 h, the reaction mixture was poured into ice water (30 mL) and extracted with dichloromethane (2 × 30 mL). The organic layer was then washed with sat. sodium hydrogen carbonate solution (30 mL) and water (30 mL), dried with $MgSO_4$, and filtered. The solvent was evaporated in vacuo without additional warming. The two isomers of compound **2** (400 mg, 0.655 mmol, 95%) were obtained without further purification. − TLC (ethyl acetate/petroleum ether, 1:1): $R_f$ = 0.65 and 0.69. − $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.80, 1.97, 2.07, 2.14 (4 s, 12 H, 4 OAc), 1.80−2.20 (hidden, 1 H, 3-$H_{ax}$), 2.66 (s, 3 H, $MeCON_a$), 3.77 (s, 3 H, $MeCON_b$), 2.75 (dd, $^2J_{3,3'}$ = 12.9 Hz, $^3J_{3',4}$ = 5.1 Hz, 1 H, 3-$H_{equiv.}$), 3.69 (s, 3 H, $MeO_a$), 3.77 (s, 3 H, $MeO_b$), 4.03 (dd, $^3J_{8,9}$ = 5.0 Hz, $^2J_{9,9'}$ = 12.6 Hz, 1 H, 9-H), 4.20 (dd, $^3J_{8,9'}$ = 2.8 Hz, $^2J_{9,9'}$ = 12.6 Hz, 1 H, 9′-H), 4.41−5.39 (m, 5 H, 8-H, 7-H, 6-H, 5-H, 4-H), 7.23−7.39 (m, 5 H, Ph).

**Methyl (Benzyl 4,7,8,9-tetra-*O*-acetyl-5-azido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid)onate (4). − a) By Treatment of 2 with $HN_3$:**[13] A solution of **2** (400 mg, 0.655 mmol) in dry dichloromethane (7 mL) was cooled to −15 °C and treated successively with trifluoroethanol (80 μL, 1.032 mmol) and a cool, freshly prepared solution of sodium isopropoxide in 2-propanol (0.2 N, 4.05 mL, 0.826 mmol). The compound **2A** was obtained in situ. After exactly one minute, a cooled solution of $HN_3$ in toluene (approx. 1.7 M, 2 mL, approx. 3.4 mmol) was added by syringe. After stirring for 12 h, the reaction mixture was diluted with dichloromethane (40 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 50 mL) and sat. aq. NaCl (20 mL), dried with $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography (toluene/acetone, 20:1) on silica gel to give the azide **4** (160 mg, 0.282 mmol, 43%).

**b) From Compound 6:** The crude compound **6**, obtained by treatment of compound **3**[14−17] (2.09 g, 5.87 mmol) with $TfN_3$,[18] was treated overnight with a mixture of acetic anhydride and pyridine (24 mL, 1:1). After evaporation in vacuo, the residue was diluted with ethyl acetate (300 mL) and afterwards washed with water (2 × 150 mL) and sat. aq. NaCl (50 mL). The combined aqueous layers were acidified with 1 N HCl and reextracted with ethyl acetate (100 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue **6A** was dissolved in dichloromethane (40 mL) and treated with a fresh solution of diazomethane in diethyl ether, monitoring by TLC (toluene/acetone, 20:1). After completion, in order to destroy excess diazomethane, a few drops of acetic acid were added before evaporation in vacuo. Column chromatography (toluene/acetone, 20:1) of the residue afforded the azide **4** (2.324 g, 4.109 mmol) with an overall yield of 70%. − TLC (toluene/acetone, 20:1)**:** $R_f$ = 0.46. − $[\alpha]_D$ = −6.6 (*c* = 1, $CHCl_3$). − $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.80 (dd, $^2J_{3,3'}$ = 12.8 Hz, $^3J_{3,4}$ = 12.5 Hz, 1 H, 3-$H_{ax}$), 2.06, 2.09, 2.15, 2.18 (4 s, 12 H, 4 OAc), 2.77 (dd, $^2J_{3,3'}$ = 12.8 Hz, $^3J_{3',4}$ = 4.7 Hz, 1 H, 3-$H_{equiv.}$), 3.22 (dd, $^3J_{4,5}$ = 9.9 Hz, $^3J_{5,6}$ = 10.6 Hz, 1 H, 5-H), 3.67 (s, 3 H, COOMe), 3.86 (dd, $^3J_{5,6}$ = 10.6 Hz, $^3J_{6,7}$ = 1.5 Hz, 1 H, 6-H), 4.20 (dd, $^3J_{8,9}$ = 4.0 Hz, $^2J_{9,9'}$ = 12.7 Hz, 1 H, 9-H), 4.30 (dd, $^3J_{8,9'}$ = 2.4 Hz, $^2J_{9,9'}$ = 12.7 Hz, 1 H, 9′-H), 4.38 (d, $^2J$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.75 (d, $^2J$ = 12.0 Hz, 1 H, C$H_2$Ph), 4.82 (ddd, $^3J_{3,4}$ = 4.7 Hz, $^3J_{3',4}$ = 12.5 Hz, $^3J_{4,5}$ = 9.9 Hz, 1 H, 4-H), 5.43 (ddd, $^3J_{7,8}$ = 9.3 Hz, $^3J_{8,9}$ = 4.0 Hz, $^3J_{8,9'}$ = 2.4 Hz, 1 H, 8-

H), 5.52 (dd, $^3J_{6,7}$ = 1.5 Hz, $^3J_{7,8}$ = 9.3 Hz, 1 H, 7-H), 7.10−7.31 (m, 5 H, Ph). − $C_{25}H_{31}N_3O_{12}$ (565.5): calcd. C 53.10, H 5.53, N 7.43; found C 53.25, H 5.59, N 7.14.

**Methyl (Benzyl 5-azido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid)onate (5):** Compound **4** (1.950 g, 3.448 mmol) was treated overnight with a solution of NaOMe (0.09 M, 30 mL). After neutralization with Amberlite IR 120 ($H^+$-form) and filtration, the solvent was evaporated in vacuo to give a colorless syrup of compound **5** (1.335 g, 3.332 mmol, 97%). − TLC (toluene/acetone, 2:1): $R_f$ = 0.24. − $[\alpha]_D$= −54.7 (*c* = 0.17, $CHCl_3$). − $^1$H NMR (500 MHz, MeOD): δ = 1.80 (dd, $^2J_{3,3'} = {}^3J_{3,4}$ = 12.6 Hz, 1 H, 3-$H_{ax}$), 2.68 (dd, $^2J_{3,3'}$ = 12.7 Hz, $^3J_{3',4}$ = 4.7 Hz, 1 H, 3-$H_{equiv.}$), 3.32−3.88 (m, 10 H, 5-H, 6-H, 7-H, 8-H, 9-H, 9′-H, COOMe), 4.46 (d, $^2J$ = 11.6 Hz, 1 H, C$H_2$Ph), 4.77 (d, $^2J$ = 11.6 Hz, 1 H, C$H_2$Ph), 7.21−7.30 (m, 5 H, Ph). − MS (MALDI positive mode): *m*/*z*: 393 [($M_R$ − $N_2$)$Na^+$]. − $C_{17}H_{23}N_3O_8$ × 0.25 $H_2O$ (401.9): calcd. C 50.80, H 5.84, N 10.45; found C 50.72, H 5.98, N 9.86.

**Benzyl 5-Azido-3,4-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosidonic Acid (6):** Compound **3** (2.09 g, 5.87 mmol) was dissolved in dry methanol (10 mL) and treated with a freshly prepared solution of NaOMe (1.48 M, 4.70 mL, 6.96 mmol). After ten min, the reaction mixture was diluted with methanol (68 mL). Dimethylaminopyridine (766 mg, 6.27 mmol) and a solution (approx. 0.26 M) of freshly prepared $TfN_3$[18] ($Tf_2O$ needs to be distilled before use!) in dichloromethane (50 mL, approx. 13 mmol) was added slowly to the reaction mixture. The progress of the reaction was monitored by TLC (*n*BuOH/acetone/acetic acid/aq. ammonia (5%)/water, 7:5:3:3:2). In order to avoid precipitation, additional methanol may be necessary. The mixture was stirred at room temp. for 12−48 h, then evaporated in vacuo at temperatures below 30 °C to obtain crude compound **6**, which was acetylated to compound **4** without further purification.

**Methyl (Benzyl 5-azido-3,5-dideoxy-8,9-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid)onate (7):** Compound **5** (1.30 g, 3.24 mmol) in dry acetone (30 mL) was treated with 2,2-dimethoxypropane (10 mL, 0.11 mol), in the presence of *p*-toluenesulfonic acid monohydrate catalyst (15 mg, 0.08 mmol). After 17 h, the reaction was quenched by addition of one drop of triethylamine and evaporated in vacuo. The residue was purified by flash chromatography (silica gel/toluene acetone, 9:1) to give **7** (1.20 g, 2.74 mmol, 85%) as a colorless syrup. − TLC (toluene/acetone, 9.5:0.5): $R_f$ = 0.09. − $[\alpha]_D$= −12.5 (*c* = 1, $CHCl_3$). − $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.36, 1.41 (2 s, 6 H, 2 Me), 1.85 (dd, $^2J_{3,3'} = {}^3J_{3,4}$ = 11.9 Hz, 1 H, 3-$H_{ax}$), 2.40 (d, $^3J_{4,OH}$ = 2.4 Hz, 1 H, 4-OH), 2.72 (dd, $^3J_{3',4}$ = 4.7 Hz, $^2J_{3,3'}$ = 11.9 Hz, 1 H, 3-$H_{equiv.}$), 2.94 (d, $^3J_{7,OH}$ = 4.4 Hz, 1 H, 7-OH), 3.49−3.57 (m, 2 H, 5-H, 6-H), 3.61−3.69 (s, 3 H, COOMe), 3.88−3.92 (m, 1 H, 7-H), 4.04−4.12 (m, 3 H, 8-H, 9-H, 9′-H), 4.48 (d, $^2J$ = 11.8 Hz, 1 H, C$H_2$Ph), 4.10 (d, $^2J$ = 11.8 Hz, 1 H, C$H_2$Ph), 7.25−7.33 (m, 5 H, Ph). − $C_{20}H_{27}N_3O_8$ (437.5): calcd. C 54.91, H 6.22, N 9.61; found C 54.84, H 6.40, N 9.32.

**Methyl (Benzyl 4-*O*-acetyl-5-azido-3,5-dideoxy-8,9-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid)onate (8) and Methyl (Benzyl 4,7-di-*O*-acetyl-5-azido-3,5-dideoxy-8,9-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid)onate (9):** A solution of **7** (1.033 g, 2.364 mmol) in dry dichloromethane (30 mL) was treated with acetic anhydride (570 μL, 6.041 mmol) and pyridine (900 μL) at 5 °C. The reaction was quenched after 48 h with a drop of methanol and evaporated in vacuo. The oily residue was subjected to column chromatography (silica gel, petroleum ether/ethyl acetate, 3:1) to give compound **8** (885 mg, 1.848 mmol, 78%) and **9** (265 mg, 0.508 mmol, 21%) as a by-product. The yield of **8** (75 mg, 0.157 mmol) could be improved to 83% by treating compound **7** (90 mg, 0.188 mmol) at room temp. with acetic anhydride (100 μL) and pyridine (100 μL) in dry dichloromethane (1.5 mL) overnight and analogous workup.

**Compound 8:** TLC (petroleum ether/ethyl acetate, 3:1): $R_f$ = 0.34. − $[\alpha]_D$= −27.8 (*c* = 1, $CHCl_3$). − $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.36, 1.40 (2 s, 6 H, 2 Me), 1.81 (dd, $^2J_{3,3'} = {}^3J_{3,4}$ = 12.8 Hz, $^3J_{3,4}$ = 11.9 Hz, 1 H, 3-$H_{ax}$), 1.85 (b, 1 H, 7-OH), 2.08 (s, 3 H, OAc), 2.78 (dd, $^2J_{3,3'}$ = 12.8 Hz, $^3J_{3',4}$ = 4.9 Hz, 1 H, 3-$H_{equiv.}$), 3.65−3.74 (m, 2 H, 5-H, 6-H), 3.71 (s, 3 H, COOMe), 3.90 (dd, $^3J_{6,7} \approx$ 1.0 Hz, $^3J_{7,8}$ = 4.4 Hz, 1 H, 7-H), 4.03−4.12 (m, 3 H, 8-H, 9-H, 9′-H), 4.48 (d, $^2J$ = 11.9 Hz, 1 H, C$H_2$Ph), 4.71 (d, $^2J$ = 11.9 Hz, 1 H, C$H_2$Ph), 4.74−4.96 (m, 1 H, 4-H), 7.24−7.38 (m, 5 H, Ph). − $C_{22}H_{29}N_3O_9$ (479.5): calcd. C 55.11, H 6.10, N 8.76; found C 55.29, H 6.30, N 8.74.

**Compound 9:** TLC (toluene/acetone, 5:1): $R_f$ = 0.55. − $[\alpha]_D$= −4.8 (*c* = 1, $CHCl_3$). − $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.36, 1.40 (2 s, 6 H, 2 Me), 1.81 (dd, $^2J_{3,3'} = {}^3J_{3,4}$ = 12.2 Hz, 1 H, 3-$H_{ax}$), 2.08 (s, 3 H, OAc), 2.18 (s, 3 H, OAc), 2.81 (dd, $^2J_{3,3'}$ = 12.2 Hz, $^3J_{3',4}$ = 4.9 Hz, 1 H, 3-$H_{equiv.}$), 3.30 (dd, $^3J_{4,5} = {}^3J_{5,6}$ = 10.4 Hz, 1 H, 5-H), 3.70 (dd, $^3J_{5,6}$ = 10.4 Hz, $^3J_{6,7}$ = 1.3 Hz, 1 H, 6-H) 3.76 (s, 3 H, COOMe), 3.99 (dd, $^3J_{8,9}$ = 6.7 Hz, $^2J_{9,9'}$ = 8.4 Hz, 1 H, 9-H), 4.12 (dd, $^3J_{8,9'}$ = 6.5 Hz, $^3J_{9,9'}$ = 8.4 Hz, 1 H, 9′-H), 4.35 (ddd, $^3J_{7,8}$ = 4.5 Hz, $^3J_{8,9'}$ = 6.5 Hz, $^3J_{8,9}$ = 6.7 Hz, 1 H, 8-H), 4.44 (d, $^2J$ = 11.5 Hz, 1 H, C$H_2$Ph), 4.73 (d, $^2J$ = 11.5 Hz, 1 H, C$H_2$Ph), 4.85 (ddd, $^3J_{3,4}$ = 12.2 Hz, $^3J_{3',4}$ = 4.9 Hz, $^3J_{4,5}$ = 10.4 Hz, 1 H, 4-H), 5.53 (dd, $^3J_{6,7}$ = 1.3 Hz, $^3J_{7,8}$ = 4.5 Hz, 1 H, 7-H), 7.24−7.34 (m, 5 H, Ph). − $C_{24}H_{31}N_3O_{10}$ (521.5): calcd. C 55.27, H 5.99, N 8.06; found C 55.00, H 5.91, N 7.83.

**Methyl (Benzyl 4-*O*-acetyl-5-azido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid)onate (10):** Compound **8** (570 mg, 1.189 mmol) was dissolved in dry dichloromethane (10 mL) under $N_2$ atmosphere. After cooling to 0 °C, ethanethiol (530 μL, 7.17 mmol) and a catalytic amount of anhydrous *p*-toluenesulfonic acid (approx. 20 mg, 0.12 mmol) were added. The reaction mixture was warmed slowly to room temp. and, after a further 4 h, quenched by addition of a drop of triethylamine (the reaction process was monitored by TLC; toluene/acetone, 2:1). The solvent was evaporated in vacuo and the residue was purified by column chromatography (toluene/acetone, 4:1) to give **10** (465 mg, 1.058 mmol, 89%) as a colorless syrup. TLC (toluene/acetone, 2:1): $R_f$ = 0.33. − $[\alpha]_D$= −34.5 (*c* = 1, $CHCl_3$). − $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.87 (dd, $^2J_{3,3'} = {}^3J_{3,4}$ = 12.5 Hz, 1 H, 3-$H_{ax}$), 2.07 (s, 3 H, OAc), 2.85 (dd, $^2J_{3,3'}$ = 12.5 Hz, $^3J_{3',4}$ = 5.0 Hz, 1 H, 3-$H_{equiv.}$), 2.90−3.30 (b, 3 H, 7-OH, 8-OH, 9-OH), 3.58 (dd, $^3J_{5,6}$ = 10.4 Hz, $^3J_{6,7}$ = 1.5 Hz, 1 H, 6-H), 3.61−3.90 (m, 8 H, COOMe, 5-H, 7-H, 8-H, 9-H, 9′-H), 4.42 (d, $^2J$ = 11.9 Hz, 1 H, C$H_2$Ph), 4.70 (d, $^2J$ = 11.9 Hz, 1 H, $CH_2$Ph), 4.82 (ddd, $^3J_{3,4}$ = 5.0 Hz, $^3J_{3',4}$ = 12.5 Hz, $^3J_{4,5}$ = 9.6 Hz, 1 H, 4-H), 7.19−7.33 (m, 5 H, Ph). − $C_{19}H_{25}N_3O_9$ (439.4): calcd. C 51.93, H 5.73, N 9.56; found C 52.25, H 5.88, N 9.56.

**Methyl (Benzyl 4-*O*-acetyl-5-azido-3,5-dideoxy-9-*O*-(4-methoxybenzyl)-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid)onate (11):** A solution of compound **11** (46 mg, 0.105 mmol) in dry acetonitrile (1.5 mL) was cooled to −23 °C under $N_2$ atmosphere. Freshly prepared *p*-methoxybenzyl trichloroacetimidate[22] (42 mg, 0.126 mmol) in dry acetonitrile and a solution of trimethylsilyl triflate in acetonitrile (0.1 M, 100 μL, 0.01 mmol) were added successively by syringe. The reaction was quenched after 30 min by addition of one drop of triethylamine. After evaporation of the solvent

in vacuo, the residue was purified by column chromatography (petroleum ether/ethyl acetate; gradient: 3:1 → 3:2) to give compound **11** (35 mg, 0.063 mmol, 60%) as a colorless oil. TLC (toluene/acetone, 6:1): $R_f$ = 0.4. − $[\alpha]_D$= −26.5 ($c$ = 1, $CHCl_3$). − $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.90 (dd, $^2J_{3,3'}$ = 13.0 Hz, $^3J_{3,4}$ = 12.1 Hz, 1 H, 3-$H_{ax}$), 2.12 (s, 3 H, OAc), 2.88 (dd, $^2J_{3,3'}$ = 13.0 Hz, $^3J_{3',4}$ = 4.9 Hz, 1 H, 3-$H_{equiv.}$), 3.64−3.97 (m, 12 H, 5-H, 6-H, 7-H, 8-H, 9-H, 9′-H, OMe, COOMe), 4.45 (d, $^2J$ = 11.9 Hz, 1 H, C$H_2$Ph), 4.54 (s, 2 H, C$H_2$C$_6$H$_4$OMe), 4.75 (d, $^2J$ = 11.9 Hz, 1 H, C$H_2$Ph), 4.86 (ddd, $^3J_{3,4}$ = 4.9 Hz, $^3J_{3',4}$ = 12.1 Hz, $^3J_{4,5}$ = 9.8 Hz, 1 H, 4-H), 6.73−7.25 (m, 9 H, 2 Ar). − $C_{27}H_{33}N_3O_{10}$ (559.6): calcd. C 57.95, H 5.94, N 7.51; found C 58.18, H 5.99, N 7.45.

**Methyl (Benzyl 4,7,8-tri-*O*-acetyl-5-azido-3,5-dideoxy-9-*O*-(4-methoxybenzyl)-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid)onate (12):** Compound **11** (23 mg, 0.041 mmol) was treated overnight with acetic anhydride (0.5 mL) and pyridine (0.5 mL). After concentration in vacuo, the residue was subjected to column chromatography (petroleum ether/ethyl acetate, 3:1) to give compound **12** (24 mg, 0.037 mmol, 91%) after lyophilization. TLC (petroleum ether/ethyl acetate, 3:1): $R_f$ = 0.35. − $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.73 (dd, $^2J_{3,3'}$ = $^3J_{3,4}$ = 12.7 Hz, 1 H, 3-$H_{ax}$), 1.98, 2.04, 2.10 (3a, 9 H, 3 OAc), 2.70 (dd, $^2J_{3,3'}$ = 12.7 Hz, $^3J_{3',4}$ = 4.8 Hz, 1 H, 3-$H_{equiv.}$), 3.18 (dd, $^3J_{4,5}$ = 9.7 Hz, $^3J_{5,6}$ = 10.7 Hz, 1 H, 5-H), 3.45 (dd, $^3J_{8,9}$ = 4.4 Hz, $^2J_{9,9'}$ = 11.1 Hz, 1 H, 9-H), 3.55 (dd, $^3J_{8,9}$ = 3.2 Hz, $^2J_{9,9'}$ = 11.1 Hz, 1 H, 9′-H), 3.63 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.83 (dd, $^3J_{5,6}$ = 10.6 Hz, $^3J_{6,7}$ = 1.5 Hz, 1 H, 6-H), 4.29 (d, $^2J$ = 11.7 Hz, 1 H, C$H_2$Ph), 4.31 (d, $^2J$ = 11.9 Hz, 1 H, C$H_2$Ph), 4.45 (d, $^2J$ = 11.7 Hz, 1 H, C$H_2$Ph), 4.70 (d, $^2J$ = 11.9 Hz, 1 H, C$H_2$Ph), 4.70−4.83 (m, 1 H, 4-H), 5.34 (ddd, $^3J_{7,8}$ = 9.3 Hz, $^3J_{8,9}$ = 3.2 Hz, $^3J_{8,9'}$ = 4.4 Hz, 1 H, 8-H), 5.34 (dd, $^3J_{6,7}$ = 1.6 Hz, $^3J_{7,8}$ = 9.3 Hz, 1 H, 7-H), 6.81−7.26 (m, 9 H, 2 Ar). − $C_{31}H_{37}N_3O_{12}$ (643.7): calcd. C 57.85, H 5.79, N 6.53; found C 57.78, H 6.00, N 6.44.

**Ethyl 5-Amino-3,5-dideoxy-2-thio-D-*glycero*-α-D-*galacto*-non-2-ulopyranosidonic Acid (14):** Compound **13**[23,24] (1.00 g, 1.90 mmol) was dissolved in a mixture of KOH/water/ethanol (865 mg/1 mL/15 mL) and refluxed for 20 h. The reaction mixture was then neutralized with acidic resin (Amberlite IR 120, $H^+$-form); the resin was washed thoroughly afterwards with methanol. The solvent was evaporated in vacuo. Dissolution of the residue in water and lyophilization gave compound **14** (564 mg, 1.89 mmol, qu.) without further purification. TLC (1-propanol/water/acetic acid, 30:8:1): $R_f$ = 0.54. − $[\alpha]_D$= +1.3 ($c$ = 1, MeOH). − $^1$H NMR (250 MHz, $D_2O$): δ = 1.04 (m, $^3J$ = 7.5 Hz, 3 H, SCH$_2$C$H_3$), 1.62 (dd, $^2J_{3,3'}$ = 12.9 Hz, $^3J_{3,4}$ = 11.4 Hz, 1 H, 3-$H_{ax}$), 2.61−2.40 (m, 2 H, SC$H_2$CH$_3$), 2.67 (dd, $^2J_{3,3'}$ = 12.9 Hz, $^3J_{3',4}$ = 5.8 Hz, 1 H, 3-$H_{equiv.}$), 3.09 (dd, $^3J_{4,5}$ = $^3J_{5,6}$ = 10.3 Hz, 1 H, 5-H), 3.45−3.78 (m, 6 H, 4-H, 6-H, 7-H, 8-H, 9-H, 9′-H).

**Ethyl 4,7,8,9-Tetra-*O*-acetyl-5-azido-3,5-dideoxy-2-thio-D-*glycero*-α-D-*galacto*-non-2-ulopyranosidonic Acid (15) and Methyl (Ethyl 4,7,8,9-tetra-*O*-acetyl-5-azido-3,5-dideoxy-2-thio-D-*glycero*-α-D-*galacto*-non-2-ulopyranosid)onate (16):** Compound **14** (669 mg, 2.151 mmol) was dissolved in 0.15 M sodium methoxide (17.2 mL, 2.58 mmol). Then, 4-dimethylaminopyridine (315 mg, 2.578 mmol) and a freshly prepared solution of $TfN_3$[18] (approx. 0.26 M, 25 mL, ca. 6.5 mmol) was added slowly. After 24 h, the solvent was evaporated in vacuo (< 30 °C) to give a pale yellow foam, which was treated overnight with a mixture of acetic anhydride and pyridine (20 mL, 1:1). After evaporation of the solvent, the residue was redissolved in ethyl acetate (200 mL) and washed with water (2 × 100 mL). The aqueous layer was acidified by addition of 1 N HCl, and extracted twice more with ethyl acetate (2 × 70 mL). The combined organic layers were dried with $MgSO_4$. Evaporation of the solvent gave crude product **15** as a colorless syrup. An analytical quantity of **15** was purified by column chromatography (toluene/acetone, 20:1, 2% acetic acid). The crude product **15** was dissolved in ethyl acetate (10 mL) and treated at 0 °C with a solution of $CH_2N_2$ in diethyl ether (the completion of esterification was monitored by TLC; toluene/acetone, 2:1). Column chromatography (toluene/acetone, 20:1) gave compound **16** (703 mg, 1.353 mmol, 63%) as a colorless oil.

**Compound 15:** TLC (toluene/acetone, 2:1): $R_f$ = 0.51. − $[\alpha]_D$= +9.4 ($c$ = 1, $CHCl_3$). − $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.19 (m, $^3J$ = 7.5 Hz, 3 H, SCH$_2$C$H_3$), 1.77 (dd, $^2J_{3,3'}$ = $^3J_{3,4}$ = 12.0 Hz, 1 H, 3-$H_{ax}$), 2.04, 2.08, 2.09, 2.17 (4 s, 12 H, 4 OAc), 2.53−2.87 (m, 3 H, SC$H_2$CH$_3$, 3-$H_{equiv.}$), 3.22 (dd, $^3J_{4,5}$ = 4.7 Hz, $^3J_{5,6}$ = 10.6 Hz, 1 H, 5-H), 3.60 (dd, $^3J_{5,6}$ = 10.6 Hz, $^3J_{6,7}$ = 1.6 Hz, 1 H, 6-H), 4.17 (dd, $^3J_{8,9}$ = 4.1 Hz, $^2J_{9,9'}$ = 12.7 Hz, 1 H, 9-H), 4.23 (dd, $^3J_{8,9'}$ = 2.5 Hz, $^2J_{9,9'}$ = 12.7 Hz, 1 H, 9′-H), 4.92 (ddd, $^3J_{3,4}$ = 4.8 Hz, $^3J_{3',4}$ = 9.7 Hz, $^3J_{4,5}$ = 11.7 Hz, 1 H, 4-H), 5.32 (ddd, $^3J_{7,8}$ = 9.3 Hz, $^3J_{8,9}$ = 4.1 Hz, $^3J_{8,9'}$ = 2.5 Hz, 1 H, 8-H), 5.49 (dd, $^3J_{6,7}$ = 1.6 Hz, $^3J_{7,8}$ = 9.3 Hz, 1 H, 7-H), 7.25−7.60 (b, 1 H, COO$H$). − $C_{19}H_{27}N_3O_{11}S$ (505.5). − MS (MALDI negative mode): $m/z$ (%) = 505 (100) [$M_R^+$].

**Compound 16:** TLC (toluene/acetone, 4:1): $R_f$ = 0.67. − $[\alpha]_D$= +13.8 ($c$ = 1, $CHCl_3$). − $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.16 (m, $^3J$ = 6.6 Hz, 3 H, SCH$_2$C$H_3$), 1.75 (dd, $^2J_{3,3'}$ = 12.7 Hz, $^3J_{3,4}$ = 11.8 Hz, 1 H, 3-$H_{ax}$), 2.08, 2.13, 2.16, 2.40 (4 s, 12 H, 4 OAc), 2.40−2.84 (m, 3 H, SC$H_2$CH$_3$, 3-$H_{equiv.}$), 3.19 (dd, $^3J_{4,5}$ = 9.7 Hz, $^3J_{5,6}$ = 10.6 Hz, 1 H, 5-H), 3.53 (dd, $^3J_{5,6}$ = 10.6 Hz, $^3J_{6,7}$ = 1.7 Hz, 1 H, 6-H), 3.77 (s, 3 H, COOMe), 4.18 (dd, $^3J_{8,9}$ = 4.0 Hz, $^2J_{9,9'}$ = 12.7 Hz, 1 H, 9-H), 4.28 (dd, $^3J_{8,9'}$ = 2.4 Hz, $^2J_{9,9'}$ = 12.7 Hz, 1 H, 9′-H), 4.79 (ddd, $^3J_{3,4}$ = 4.7 Hz, $^3J_{3',4}$ = 11.8 Hz, $^3J_{4,5}$ = 9.7 Hz, 1 H, 4-H), 5.31 (ddd, $^3J_{7,8}$ = 9.4 Hz, $^3J_{8,9}$ = 3.9 Hz, $^3J_{8,9'}$ = 2.4 Hz, 1 H, 8-H), 5.46 (dd, $^3J_{6,7}$ = 1.7 Hz, $^3J_{7,8}$ = 9.3 Hz, 1 H, 7-H). − $C_{20}H_{29}N_3O_{11}S \times 0.25\ H_2O$ (524.0): calcd. C 45.48, H 5.67, N 8.02; found C 45.81, H 5.53, N 7.91. − MS (MALDI positive mode): $m/z$ (%) = 544 (15) [$MNa^+$], 560 (100) [$MK^+$].

**Methyl 4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-5-azido-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (17):** A solution of **16** (1.160 g, 2.214 mmol) in dry propionitrile (20 mL) in the presence of molecular sieves (4 Å) was treated under argon at −60 °C with *N*-iodosuccinimide (1.00 g, 4.466 mmol) and TfOH (44 μL, 0.446 mmol). After 30 min, the reaction mixture was quenched with a drop of triethylamine, warmed to room temp. and diluted with ethyl acetate (150 mL). The organic layer was washed successively with sat. aq. $NaHCO_3$, $Na_2S_2O_3$, and NaCl. The combined aq. layers were extracted with ethyl acetate. The combined organic layers were dried with $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography (toluene/acetone, 7:1) to give **17** (857 mg, 1.875 mmol, 85%) as a colorless oil. The physical data corresponded to those reported in the literature.[26,27]

**Methyl 2,6-Anhydro-5-azido-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (18):** Compound **17** (857 mg, 1.875 mmol) was treated with sodium methoxide (1 N, 5 mL). After 2 h (TLC monitoring), the solution was neutralized by addition of acidic resin (Amberlite IR 120, $H^+$-form). The resin was washed with methanol. The combined organic layers were concentrated to dryness to give compound **18** (500 mg, 1.730 mmol, 92%) as a colorless oil. − TLC (methanol/ethyl acetate, 1:9): $R_f$ = 0.69. − $[\alpha]_D$ = −3.5 ($c$ = 0.75, $CHCl_3$/MeOH; 3:1). − $^1$H NMR (250 MHz, MeOD): δ = 3.77 (s, 3 H, OMe), 3.66−3.87 (m, 5 H, 5-H, 7-H, 8-H, 9-H, 9′-H), 4.08 (dd, $^3J_{5,6}$ = 10.9 Hz, $^3J_{6,7}$ = 1.1 Hz, 1 H, 6-H), 4.44 (ddd, $^3J_{3,4}$ =

2.4 Hz, $^3J_{4,5}$ = 8.4 Hz, 1 H, 4-H), 5.90 (d, $^3J_{3,4}$ = 2.4 Hz, 1 H, 3-H). − $C_{10}H_{15}N_3O_7 \times H_2O$ (307.3): calcd. C 39.09, H 5.56, N 13.68; found C 39.27, H 5.39, N 13.14.

**Methyl 2,6-Anhydro-5-azido-3,5-dideoxy-8,9-*O*-isopropylidene-D-*glycero*-D-*galacto*-non-2-enonate (19):** Compound **18** (500 mg, 1.730 mmol) was dissolved in dry acetone (12 mL), and 2,2-dimethoxypropane (1.6 mL) and *p*-toluenesulfonic acid (30 mg, 0.158 mmol) were then added. After 2 h, the reaction was quenched with one drop of triethylamine and the solvent was evaporated. The residue was subjected to column chromatography (toluene/acetone, 3:1) to give the crystalline compound **19** (567 mg, 1.722 mmol, 99%). − TLC (toluene/acetone, 3:1): $R_f$ = 0.31; m.p. 110 °C. − $[\alpha]_D$ = +4.5 (*c* = 0.95, $CHCl_3$). − $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.32, 1.38 (2 s, 6 H, 2 Me), 3.28−3.30 (b, 2 H, 2 OH), 3.70 (dd, $^3J_{4,5}$ = 8.2 Hz, $^3J_{5,6}$ = 10.6 Hz, 1 H, 5-H), 3.76 (s, 3 H, OMe), 3.82 (dd, $^3J_{6,7}$ = 1.1 Hz, $^3J_{7,8}$ = 7.8 Hz, 1 H, 7-H), 3.96 (dd, $^3J_{5,6}$ = 10.6 Hz, $^3J_{6,7}$ = 1.1 Hz, 1 H, 6-H), 4.04−4.12 (m, 2 H, 9-H, 9′-H), 4.15−4.24 (m, 1 H, 4-H), 4.43 (ddd, $^3J_{3,4}$ = 1.6 Hz, $^3J_{4,5}$ = 8.2 Hz, 1 H, 4-H), 5.90 (d, $^3J_{3,4}$ = 1.6 Hz, 1 H, 3-H). − $C_{13}H_{19}N_3O_7 \times 0.25\ H_2O$ (333.8): calcd. C 46.78, H 5.89, N 12.59; found C 46.79, H 6.01, N 12.21.

**Methyl 4-*O*-Acetyl-2,6-anhydro-5-azido-3,5-dideoxy-8,9-*O*-isopropylidene-D-*glycero*-D-*galacto*-non-2-enonate (20):** Compound **19** (567 mg, 1.722 mmol) was dissolved under argon in dry dichloromethane (10 mL) and cooled to 0 °C. Acetic anhydride (250 μL, 2.649 mmol) and pyridine (450 μL) were injected through a septum. The reaction mixture was stirred for 48 h at 0−4 °C. Before warming to room temp., the reaction was quenched with one drop of methanol. After evaporation of the solvent, the residue was subjected to column chromatography (toluene/acetone, 4:1) to yield the crystalline compound **20** (454 mg, 1.222 mmol, 71%). − TLC (toluene/acetone, 3:1): $R_f$ = 0.44. − m.p. 129 °C. − $[\alpha]_D$ = +35.6 (*c* = 0.8, $CHCl_3$). − $^1$H NMR (250 MHz, $CDCl_3$): δ = 1.34, 1.40 (2 s, 6 H, 2 Me), 2.12 (s, 3 H, OAc), 3.76 (s, 3 H, OMe), 3.92 (dd, $^3J_{6,7} \approx$ 1.0 Hz, $^3J_{7,8}$ = 7.2 Hz, 1 H, 7-H), 4.01−4.03 (m, 2 H, 5-H, 6-H), 4.11−4.14 (m, 3 H, 9-H, 9′-H, 8-H), 5.55 (dd, $^3J_{3,4}$ = 2.4 Hz, $^3J_{4,5}$ = 5.7 Hz, 1 H, 4-H), 5.91 (d, $^3J_{3,4}$ = 2.4 Hz, 1 H, 3-H). − $C_{15}H_{21}N_3O_8 \times 0.25\ H_2O$ (375.9): calcd. C 47.93, H 5.76, N 11.18; found C 48.13, H 5.93, N 11.23.

**Methyl 4-*O*-Acetyl-2,6-anhydro-5-azido-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (21):** Compound **20** (420 mg, 1.131 mmol) was dissolved in aqueous acetic acid (60%, 16 mL) and heated to 60 °C. After 30 min, the solvent was evaporated in vacuo and the residue was subjected to column chromatography (toluene/acetone, 2:1) to give the crystalline compound **21** (370 mg, 1.117 mmol, 91%). − TLC (toluene/acetone, 2:1): $R_f$ = 0.14.− m.p. 74 °C. − $[\alpha]_D$ = +31.5 (*c* = 1, $CHCl_3$). − $^1$H NMR (250 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, OAc), 2.35−2.84 (b, 3 H, 3 OH), 3.79 (s, 3 H, OMe), 3.80−4.05 (m, 4 H, 5-H, 6-H, 7-H, 8-H), 4.09−4.20 (m, 2 H, 9-H, 9′-H), 5.55 (dd, $^3J_{3,4}$ = 2.0 Hz, $^3J_{4,5}$ = 8.4 Hz, 1 H, 4-H), 5.94 (d, $^3J_{3,4}$ = 2.0 Hz, 1 H, 3-H). − $C_{12}H_{17}N_3O_8$ (331.3): calcd. C 43.51, H 5.17, N 12.68; found C 43.66, H 5.10, N 12.08.

**Methyl 4-*O*-Acetyl-2,6-anhydro-5-azido-9-*O*-benzyl-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (22):** Compound **21** (220 mg, 0.664 mmol) and dibutyltin oxide (264.4 mg, 1.063 mmol) were suspended in dry benzene (16 mL) and refluxed with azeotropic removal of water. After 3 h, tetrabutylammonium bromide (428 mg, 1.328 mmol) and benzyl bromide (158 μL, 1.328 mmol) were added to the reaction mixture. After two more hours, the solvent was removed by distillation. The residue was purified by gradient column chromatography (toluene/acetone, 4:1 → 2:1). Compound **22** (170 mg, 0.403 mmol, 61%) was obtained as a colorless syrup, together with recovered starting material **21** (26 mg, 0.078 mmol, 12%). − TLC (toluene/acetone, 2:1): $R_f$ = 0.65. − $[\alpha]_D$ = +15.4 (*c* = 1, $CHCl_3$). − $^1$H NMR (250 MHz, $CDCl_3$): δ = 2.14 (s, 3 H, OAc), 2.18−2.32 (b, 2 H, 7-OH, 8-OH), 3.71−3.76 (m, 2 H, 5-H, 9′-H), 3.75 (s, 3 H, OMe), 3.93−4.16 (m, 4 H, 6-H, 7-H, 8-H, 9-H), 4.54 (d, $^2J$ = 12.2 Hz, 1 H, C$H_2$Ph), 4.60 (d, $^2J$ = 12.2 Hz, 1 H, C$H_2$Ph), 5.49−5.50 (m, 1 H, 4-H), 5.91 (d, $^3J_{3,4}$ = 2.5 Hz, 1 H, 3-H), 7.29−7.39 (m, 5 H, Ph). − $C_{19}H_{23}N_3O_8 \times 0.5\ H_2O$ (430.4): calcd. C 53.00, H 5.62, N 9.76; found C 52.74, H 5.58, N 9.30.

**Methyl 4,7,8-Tri-*O*-acetyl-2,6-anhydro-5-azido-9-*O*-benzyl-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (23):** Compound **22** (23 mg, 0.053 mmol) was treated overnight with a mixture of acetic anhydride and pyridine (2 mL, 1:1). After evaporation in vacuo, the residue was subjected to column chromatography (toluene/acetone, 20:1) to yield compound **23** (25 mg, 0.050 mmol, 95%) as a colorless oil. − TLC (toluene/acetone, 4:1): $R_f$ = 0.70. − $[\alpha]_D$ = +43.7 (*c* = 1, $CHCl_3$). − $^1$H NMR (250 MHz, $CDCl_3$): δ = 2.06, 2.08, 2.13 (3 s, 9 H, 3 Ac), 3.56 (dd, $^3J_{8,9'}$ = 5.0 Hz, $^2J_{9,9'}$ = 10.6 Hz, 1 H, 9′-H), 3.77 (s, 3 H, OMe), 3.72−3.85 (m, 2 H, 9-H, 5-H), 4.20 (dd, $^3J_{5,6}$ = 8.9 Hz, $^3J_{6,7}$ = 3.6 Hz, 1 H, 6-H), 4.49 (d, $^2J$ = 11.9 Hz, 1 H, $CH_2$Ph), 4.57 (d, $^2J$ = 11.9 Hz, 1 H, $CH_2$Ph), 5.33 (m, 1 H, 8-H), 5.46 (dd, $^3J_{3,4}$ = 3.1 Hz, $^3J_{4,5}$ = 6.8 Hz, 1 H, 4-H), 5.63 (dd, $^3J_{6,7}$ = 3.6 Hz, $^3J_{7,8}$ = 5.8 Hz, 1 H, 7-H), 5.98 (d, $^3J_{3,4}$ = 3.1 Hz, 1 H, 3-H), 7.28−7.36 (m, 5 H, Ph). $C_{23}H_{27}N_3O_{10}$ (505.5). MS (MALDI positive mode): *m*/*z* (%) = 528 (100) [$M_RNa^+$], 501 (7) [($M_R$- $N_2$)$Na^+$].

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[1] T. J. Martin, R. R. Schmidt, *Tetrahedron Lett.* **1992**, *33*, 6123−6126.
[2] T. J. Martin, R. Brescello, A. Toepfer, R. R. Schmidt, *Glycoconjugate J.* **1993**, *10*, 16−25.
[3] A. Hasegawa, T. Nagahama, H. Ohki, K. Kotta, H. Ishida, M. Kiso, *J. Carbohydr. Chem.* **1991**, *10*, 493−498.
[4] J. C. Castro-Palomino, Y. E. Tsvetkov, R. R. Schmidt, *J. Am. Chem. Soc.* **1998**, *120*, 5434−5440; and references therein.
[5] J. C. Castro-Palomino, Y. E. Tsvetkov, R. Schneider, R. R. Schmidt, *Tetrahedron Lett.* **1997**, *38*, 6837−6840.
[6] Y. E. Tsvetkov, R. R. Schmidt, *Tetrahedron Lett.* **1994**, *35*, 8583−8586.
[7] R. Schneider, Dissertation, Universität Konstanz, **1998**.
[8] C. Augé, B. Bouxan, B. Cavayé, C. Gautheron, *Tetrahedron Lett.* **1988**, *30*, 2217−2220.
[9] C. Augé, S. David, A. Malleron, *Carbohydr. Res.* **1989**, *188*, 201−205.
[10] A. Schrell, G. M. Whitesides, *Liebigs Ann. Chem.* **1990**, 1111−1114.
[11] C. H. Wong, C. H. Lin, *PCT Int. Appl.* **1993**, 41−43.
[12] U. Kragl, A. Gödde, C. Andrey, W. Kinzy, J. J. Cappon, J. Lugtenburg, *Tetrahedron: Assym.* **1993**, *6*, 1193−1202.
[13] E. Schreiner, E. Zbiral, *Liebigs Ann. Chem.* **1990**, 581−586
[14] N. E. Byramova, A. B. Tuzikov, N. V. Bovin, *Carbohydr. Res.* **1992**, *237*, 161−175
[15] Y. E. Tsvetkov, Universität Konstanz, **1994**.
[16] G. Dufner, Dissertation, Universität Konstanz, **1997**.
[17] G. Dufner, R. Schwörer, B. Müller, R. R. Schmidt, *Eur. J. Org. Chem.* **2000**, 1467−1482.

[18] A. Vasella, C. Witzig, J.-L. Chiara, M. Martín-Lomas, *Helv. Chim. Acta* **1991**, *74*, 2073−2077.
[19] P. B. Alper, S.-C. Hung, C.-H. Wong, *Tetrahedron Lett.* **1996**, *37*, 6029−6032.
[20] G. Zemplén, *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1555−1564.
[21] D. R. Williams, S. Y. Sith, *J. Am. Chem. Soc.* **1984**, *106*, 2949−2954.
[22] N. Nakajima, K. Horita, R. Abe, D. Yonenitsu, *Tetrahedron Lett.* **1988**, *29*, 4139−4142.
[23] A. Lubineau, J. LeGallic, *J. Carbohydr. Chem.* **1991**, *10*, 263−268.
[24] Y. E. Tsvetkov R. R. Schmidt, *Carbohydr. Lett.* **1996**, *2*, 149−156.
[25] G. H. Veeneman, S. H. van Laeuwen, F. H. van Boom, *Tetrahedron Lett.* **1990**, *31*, 1331−1334.
[26] G. B. Kok. B. L. Mackey, M. v. Itzstein, *Carbohydr. Res.* **1996**, *289*, 67−75.
[27] E. Schreiner, E. Zbiral, R. G. Kleineidam, R. Schauer, *Carbohydr. Res.* **1991**, *216*, 61−66.
[28] Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 133827. Copies of the data can be obtained free of charge on application to CCDC, 12, Union Road, Cambridge CB 21 EZ, UK; Fax: (+44)1223/336-033.

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