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Synthesis of *C*-glycosyl compounds of *N*-acetylneuraminic acid from D-gluconolactone

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Dedicated to Professor Derek Horton on the occasion of his 70th birthday

Abstract

A general strategy towards the synthesis of *C*-glycosyl compounds of *N*-acetylneuraminic acid (Neu5Ac) has been developed and successfully applied to the synthesis of *C*-methyl and *C*-phenyl derivatives. The key strategic elements are (i) chain extension of a D-gluconolactone derivative as C_6-precursor with an allyl Grignard reagent as C_3-precursor having in 2 position the C-linked aglycon moiety, (ii) stereoselective C-4/C-5 erythro-diol formation, (iii) 6-exo-trig selective heterocyclization, and (iv) instalment of the 5-acetylamino and C-1 carboxylate functionalities. The efficiency and potential versatility of this approach was exemplified in the synthesis of *C*-methyl derivative **1** as target molecule.

Keywords: *C*-Glycosides; Synthesis; Neuraminic acid; Cyclization; Chain extension

1. Introduction

As terminating constituents of many glycoconjugates, sialic acids are often found at the nonreducing end of the oligosaccharide moiety, and, due to this peripheral position they are involved in a significant number of biological events.[‡] Thus, they mediate numerous molecular recognition events.[2–10] The most ubiquitous member of this class of structurally unique carbohydrates is *N*-acetylneuraminic acid (Neu5Ac) (Scheme 1, **1**, R OH).[1] Typically, Neu5Ac is attached via an α-*O*-glycosidic linkage to the carbohydrate chain of these glycoconjugates.[§] In vivo, terminal Neu5Ac is removed from the glycoconjugate by neuraminidases, specific hydrolytic enzymes. Following cleavage, antigenic oligosaccharides are unmasked, thereby permitting the catabolism of the entire glycoconjugate. The replacement of the glycosidic oxygen by a corresponding carbon substituent provides an interesting approach to rationally control many of these important processes in glycobiology, since this structural transformation renders the natural *O*-glycoside a nonhydrolyzable *C*-glycosyl analogue which is inert to catabolism.

Despite numerous methodologies available for the synthesis of *C*-glycosyl derivatives of aldoses,[¶] only a few syntheses of *C*-glycosyl derivatives of sialic acids have been reported.[12] The work of Linhardt and coworkers,[13] using samarium iodide for sialyl intermediate generation, provided more complex *C*-glycosyl derivatives of various sialic acids. Herein, we extend our previously reported strategy to the synthesis of the highly valuable Neu5Ac-α(2-3)-Gal *C*-disaccharide,[14] to a general synthesis of Neu5Ac *C*-glycosyl derivatives (Scheme 1, **1**, R Me, Ph). This versatile approach is based on the electrophilic cyclization of open-chain

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[‡] For reviews, see Ref. 1.

[§] Important motifs are Neu5Acα(2-3)Gal-, Neu5Acα(2-6)Gal- and the Neu5Acα(2-8)-Neu5Ac-disaccharide moieties.

[¶] For reviews, see Ref. 11.

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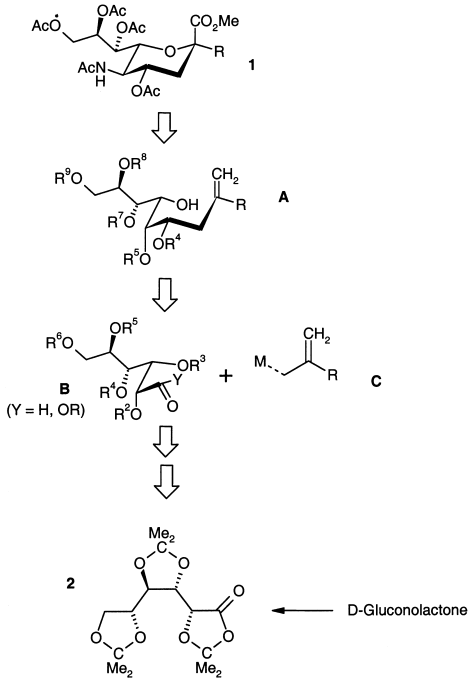
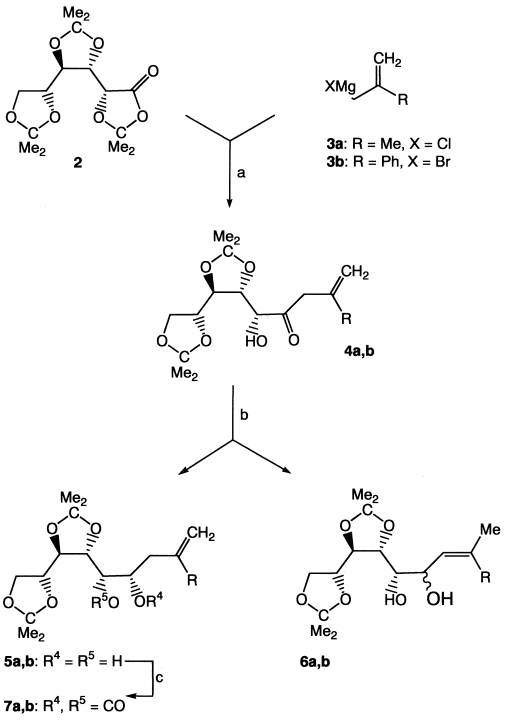
precursor **A** using phenylselenyl triflate[**,††] as cyclization reagent followed by the generation of the carboxylate moiety and introduction of the nitrogen. Intermediate **A** can be readily obtained from C_6- and C_3-precursors **B** and **C**, respectively. For **B**, D-gluconolactone seemed to be an ideal starting material because it can be efficiently transformed into tri-*O*-isopropylidene derivative **2**, which fulfils all demands for the required C_6-building block.

2. Results and discussion

Reaction of tri-*O*-isopropylidene-D-gluconate **2**[17] with 2-methyl- and 2-phenyl-allylmagnesium bromide (**3a** and **3b**) Grignard reagents at −95 °C led, after work-up, to addition products **4a** and **4b**, respectively, in very high yields (Scheme 2). Due to the low reaction temperature, no isomerization of **4a**,**b** to the thermodynamically more stable α,β-unsaturated enone system was observed; also further addition of the *C*-nucleophiles to the ketone carbonyl group of **4** were only minor byproducts (< 5%). Next, the α-hydroxyketone moiety of **4a**,**b** was stereoselectively reduced with zinc



Scheme 1. Retrosynthetic analysis for the generation of target molecule **1**.



Scheme 2. Transformation of gluconate **2** into nonenitol derivatives **7a**,**b**. Reagents and conditions: (a) 2:1, Et_2O–THF, −95 °C, **4a** (87%), **4b** (82%); (b) $Zn(BH_4)_2$, Et_2O, −10 °C, (**a**: 95%, **5a**:**6a** 30:1; **b**: 86%, **5b**:**6b** 13:1); (c) diphosgene, DMAP, pyr/CH_2Cl_2, 0 °C (**7a**: 88%; **7b**: 92%).

boronhydride[18] in Et_2O at −10 °C to afford diols **5a**, **6a** and **5b**, **6b**, respectively, in very high yields. Obviously, prior to carbonyl group reduction some double bond migration had occurred. As expected from previous experiments,[14,19] a 30:1 mixture of isomers **5a**/**6a** and a 13:1 mixture of isomers **5b**/**6b** in favour of **5a** and **5b**, respectively, with the desired C-4/C-5 erythro-configuration was obtained. The structural assignment of **5a**, **5b** was confirmed by the subsequent reactions. Transformation of **5a** and **5b** with diphosgene in the presence of Steglich's reagent (4-dimethylaminopyridine DMAP) in dichloromethane/pyridine furnished cyclic carbonate derivatives **7a**,**b** in high yields.

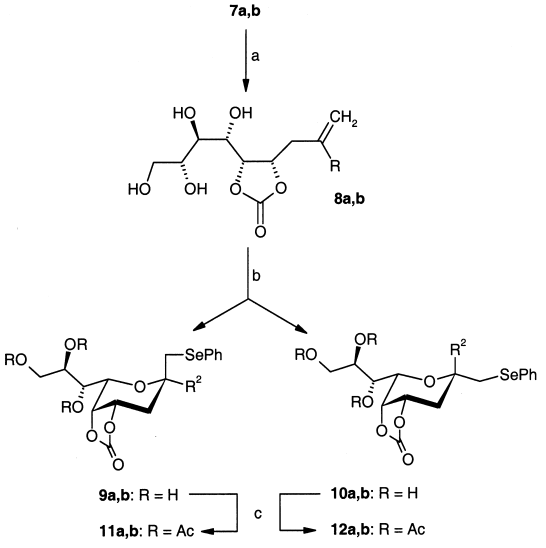
For the ring closure, the *O*-isopropylidene groups of **7a**,**b** were removed with trifluoroacetic acid (TFA) in THF/water, thus affording **8a** and **8b** (Scheme 3). We reasoned that out of four hydroxyl groups present in **8**, only the 6-hydroxy group leading to a six-membered cyclization product would participate in the cyclization step in an exo-trig selective manner,[20] thus rendering a selective protection of the other hydroxy groups unnecessary. In addition, we decided to postpone the introduction of the nitrogen to a later stage of the synthesis, i.e., after the cyclization step, in order to avoid a competitive participation of the nitrogen during the cyclization reaction. We furthermore anticipated that embedding of the erythro-diol unit of **5** into a cyclic

[**] For the use of phenylselenyl triflate for electrophilic cyclization see Ref. 15.

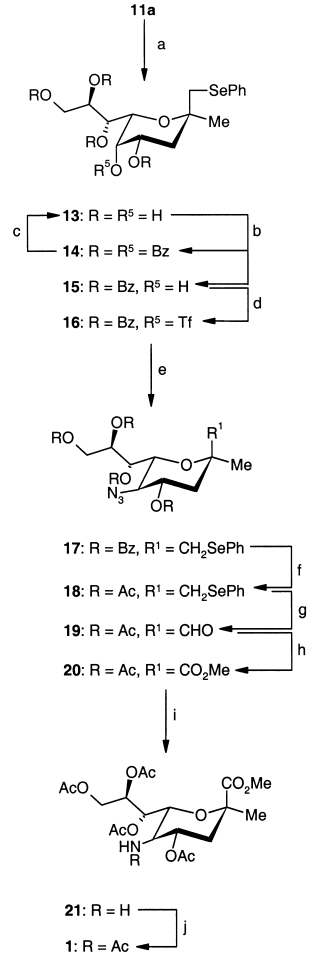
[††] For early work on electrophilic cyclization for the synthesis of C-glycosyl derivatives with other electrophiles see Ref. 16.

carbonate framework would decrease the combinatorial flexibility of the acyclic scaffold and facilitate the electrophilic cyclization.‡‡ Thus, open-chain precursors **8a** and **8b** were pivotal intermediates. On the basis of the potential and versatility of selenium based reagents[22] as well as our own results,[14,23] the capability of cationic selenium species to induce an electrophilic heterocyclization between the olefin moiety and the 6-hydroxy group was investigated. Addition of **8a** to phenylselenyl triflate at -80 °C in propionitrile resulted in almost quantitative formation of a 2:1 ratio of cyclization products **9a** and **10a**; application of the same reaction to **8b** led to a 1:2 ratio of cyclization products **9b** and **10b**. For further transformation and characterization, these compounds were *O*-acetylated to provide **11a**, **11b**, **12a**, and **12b**, which could be fully assigned by the NMR data. The assignment of the stereochemistry of the quaternary carbon centre formed in **11a**,**b** on one side and **12a**,**b** on the other side could be readily based on NOE cross-peaks between the protons of the corresponding axial methylene group in **11a**,**b** and 4-H and 6-H, respectively.

Following our strategy, the next task was the introduction of the nitrogen functionality§§ (Scheme 4). To this end, in **11a** all ester groups were cleaved by treatment with NaOMe in methanol affording *O*-unprotected derivative **13**. Regioselective *O*-benzoylation with benzoyl cyanide in the presence of triethylamine as base at 0 °C afforded, as expected,¶¶ 5-*O*-unprotected **15** together with fully *O*-benzoylated **14**, which could be readily converted into the starting material.[25] The regiochemical assignment can be derived from the chemical shift of 5-H (**14**: δ 5.86–5.95; **15**: δ 4.34). Next, the axial hydroxyl group of tetrabenzoate **15** was converted into a leaving group by triflate activation ($\rightarrow$**16**), which was then displaced by treatment with tetra-*n*-butylammonium azide to afford azido compound **17** in practically quantitative yield. The inversion of the configuration could be unambiguously confirmed by the value of the vicinal coupling constants $J_{4,5}$ $J_{5,6} \approx 10$ Hz.



Scheme 3. Ring closure of **8a**,**b**. Reagents and conditions: (a) TFA, THF/H_2O: **8a** (91%), **8b** (98%); (b) PhSeCl, AgOTf, EtCN, rt; **a**: 92% (**9a**:**10a** $\approx$ 2:1); **b**: 66% (**9b**:**10b** 1:2); (c) Ac_2O, DMAP, pyr; **11a** (95%), **11b** (86%), **12a** (96%), **12b** (84%).



Scheme 4. Synthesis of target molecule **1**. Reagents and conditions: (a) NaOMe, MeOH (98%); (b) BzCN, NEt_3, THF, 0 °C (67%; **14**/**15** 1:1); (c) NAOMe, MeOH (qu); (d) Tf_2O, pyr, 0 °C (qu); (e) TBAA, toluene (96%); (f) NaOMe, MeOH; Ac_2O, pyr (94%); (g) MCPBA, THF, -80 °C; Ac_2O, NaOAc, -80 °C $\rightarrow$ refl.; NaOMe, MeOH; Ac_2O, pyr (80%); (h) $NaClO_2$, KH_2PO_4, Me_2CCHMe, MeCN/^{t}BuOH; CH_2N_2, Et_2O (79%); (i) Pd/$CaCO_3$, H_2, MeOH (77%); (j) Ac_2O, pyr (91%).

‡‡ For an illustrative example, see Ref. 21.

§§ Successful transformation of 3-deoxy-2-glyculosonates into the corresponding 5-azido-3,5-dideoxy derivatives has been already described. See Ref. 24.

¶¶ Such regioselective benzoylations are not without precedent. See Ref. 25.

The next task was the installation of the carboxylate functionality. After transformation of **17** into *O*-acetyl protected **18**, this functional group transformation could be achieved in a straightforward manner by subjecting phenylselenide **18** to a selena-Pummerer rearrangement[14] to afford aldehyde **19** in four steps in 80% overall yield. Oxidation of the aldehyde and subsequent esterification of the carboxylic acid with diazomethane then provided methyl ester **20** in 79% yield. Liberation of the amino group from the azido functionality was performed by hydrogenation with $Pd/CaCO_3$ as catalyst affording amino derivative **21** which on immediate N-acetylation furnished target molecule **1**. The structural assignment could be based on the NMR data (NOE cross-peaks between H-4 and H-6, H-4 and H_{eq}-3, H-5 and H_{ax}-3).

3. Conclusion

We have developed a novel approach to the synthesis of *C*-glycosyl derivatives of Neu5Ac. Important features of this strategy are the following: (a) The approach is assumed to be general and should allow for variability within the *C*-glycosyl part as well as the sialic acid moiety; (b) the key steps of the strategy consist of a C_3-chain extension of a readily available gluconate derivative, diastereoselective generation of an erythro-diol moiety, and a 6-exo-trig selective electrophilic cyclization; (c) the strategy is not based on expensive Neu5Ac precursors but uses inexpensive and readily available precursors as starting materials; and (d) due to the masked amino functionality as an azide group, upon reduction a large variety of substituents other than *N*-acetyl can be attached.

4. Experimental

General methods.—All organometallic reactions were performed under an inert atmosphere of nitrogen and for reactions at low temperatures, cryostats were used in combination with threefold coated cryogenic flasks. Chemicals and solvents were either purchased puriss. p.A. from commercial suppliers or purified by standard techniques. THF was distilled from sodium-benzophenone. For analytical thin layer chromatography (TLC), silica gel plastic plates E. Merck 60 F_{254} were used and compounds were visualized by irradiation with UV light and/or by immersion into a soln of ammonium molybdate (20 g), $Ce(SO_4)_2$ (400 mg), 10% H_2SO_4 (400 mL) followed by heating or by treatment with 15% H_2SO_4 soln followed by heating. Preparative flash chromatography was performed at a pressure of 1.2–1.4 bar using J. T. Baker silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM). Melting points are uncorrected. Optical rotations were determined using a Perkin–Elmer Polarimeter 241MC (1 dm cell, temperature 21 °C, λ 589 nm). ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature either on Bruker AC 250 Cryospec or Bruker DRX 600. Chemical shifts are given in δ relative to Me_4Si, the coupling constants J are given in Hz. For ^{1}H NMR, Me_4Si served as internal standard (δ 0 ppm), and $CDCl_3$ was used as internal standard (δ 77.0 ppm), for ^{13}C NMR. Assignment of peaks and stereochemistry was based upon DQF-COSY, HMQC, HMBY and ROESY experiments. Geminal diastereotopic protons were distinguished by [a] and [b]. EIMS were recorded on a Finnigan MAT 312. MALDI-TOF mass spectra were recorded on a Kratos Kompact MALDI instrument, using a 2,5-dihydroxy benzoic acid matrix.

*1,2,3-Trideoxy-6,7:8,9-di-*O*-isopropylidene-2-methyl-*D*-gluco-non-1-eno-4-ulose* (**4a**).—1,2:3,4:5,6-Tri-*O*-isopropylidene-D-gluconate[17] (**2**) (4.00 g, 12.64 mmol) was dissolved in anhyd Et_2O (200 mL) and cooled to −95 °C. Then a −95 °C cold soln of freshly prepared β-methallyl magnesium chloride (**3a**) in anhyd THF (40 mmol in 100 mL) was quickly pumped to this soln via a transfer cannula and the mixture was stirred for 20 min at this temperature. The cold mixture was poured onto a 10% HCl soln (100 mL) and stirred for 5 min. The layers were separated, the aq layer was washed with Et_2O (2 × 20 mL), the combined organic layers were washed with brine (5 × 40 mL) and dried ($MgSO_4$). Filtration, concentration under diminished pressure and purification of the residue by flash chromatography (SiO_2, 9:1 petroleum ether–EtOAc) afforded hydroxy ketone **4a** (3.44 g, 87%) as a colourless syrup. TLC (2:1 petroleum ether–EtOAc): R_f 0.43; $[\alpha]_D$ −43.80° (*c* 2; $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.99 (1 H, s, 1-H[b]), 4.86 (1 H, s, 1-H[a]), 4.39 (1 H, br d, *J* 7.0 Hz, 5-H), 4.32 (1 H, br d, *J* 5.7 Hz, 6-H), 4.17–4.11 (3 H, m, 9-H[b], 7-H, 8-H), 4.00 (1 H, m, 9-H[a]), 3.53 (1 H, d, *J* 7.0 Hz, 5-OH), 3.34 (1 H, d, *J* 17.0 Hz, 3-H[b]), 3.30 (1 H, d, *J* 17.0 Hz, 3-H[a]), 1.78 (3 H, s, CH_3), 1.44, 1.35, 1.34 (12 H, 3 s, 2 × CMe_2); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ 206.7 (C-4). 138.1 (C-2), 115.7 (C-1), 110.1, 109.8 (2 × CMe_2), 79.9 (C-6), 77.5 (C-7), 76.7 (C-8), 75.0 (C-5), 67.9 (C-9), 47.4 (C-3), 27.1 (CH_3), 26.7, 26.4, 25.3, 22.6 (4 CH_3); EIMS: *m*/*z* 314 (M^+). Anal. Calcd for $C_{16}H_{26}O_6$ (314.4): C, 61.13; H, 8.34. Found: C, 60.72; H, 8.36.

*1,2,3-Trideoxy-6,7:8,9-di-*O*-isopropylidene-2-phenyl-*D*-gluco-non-1-eno-4-ulose* (**4b**).—Triacetonide **2** (4.00 g, 12.64 mmol) was dissolved in anhyd Et_2O (200 mL) and cooled to −95 °C. Then a −95 °C cold soln of freshly prepared α-bromomagnesium methylstyrene (**3b**) in anhyd THF (40 mmol in 100 mL) was quickly pumped to this soln via transfer cannula and the mixture was stirred for 20 min at this temperature. The cold mixture was poured onto a 10% HCl soln (100

mL) and stirred for 5 min. The layers were separated, the aq layer was washed with Et_2O (2 × 20 mL), the combined organic layers were washed with brine (5 × 40 mL) and dried ($MgSO_4$). Filtration, concentration under diminished pressure and purification of the residue by flash chromatography (SiO_2, 9:1 petroleum ether–EtOAc) afforded the hydroxy ketone **4b** (3.90 g, 82%) as a colourless syrup. TLC (95:5 CH_2Cl_2–MeOH): R_f 0.40; $[\alpha]_D$ −1.71° (*c* 0.7; $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.36–7.21 (5 H, m, Ar-H), 5.58 (1 H, s, 1-H^b), 5.19 (H, s, 1-H^a), 4.33 (1 H, d, *J* 6.5 Hz, 5-H), 4.10–4.01 (4 H, m, 9-H^b, 7-H, 8-H, 6-H), 3.93 (1 H, m, 9-H^a), 3.82 (1 H, d, *J* 17.0 Hz, 3-H^b), 3.70 (1 H, d, *J* 17.0 Hz, 3-H^a), 3.48 (1 H, d, *J* 7.3 Hz, 5-OH), 1.37, 1.35, 1.28 (12 H, 3 s, 2 × CMe_2); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 207.2 (C-4), 141.0 (C-2), 129.1, 128.6, 126.6, 118.0 (C-Ar), 110.8, 110.5 (2 × *C*Me_2), 80.7 (C-6), 78.2 (C-7), 78.1 (C-8), 75.7 (C-5), 68.5 (C-9), 46.1 (C-3), 27.8, 27.3, 27.1, 26.0 (4 CH_3); EIMS: *m*/*z* 376 (M^+). Anal. Calcd for $C_{21}H_{28}O_6$ (376.4): C, 67.00; H, 7.50. Found: C, 66.87; H, 8.00.

1,2,3-Trideoxy-6,7:8,9-di-O-*isopropylidene-2-methyl*-D-glycero-D-gulo-*non-1-enitol* (**5a**) *and 1,2,3-trideoxy-6,7:8,9-di*-O-*isopropylidene-2-methyl*-D-glycero-D-gulo/ido-*non-2-enitol* (**6a**).—A soln of hydroxy ketone **4a** (3.40, 10.86 mmol) in anhyd Et_2O (50 mL) was cooled to −10 °C and a soln of $Zn(BH_4)_2$ in anhyd Et_2O[3] (25 mL) was added. The mixture was stirred for about 1 h at this temperature until the reaction was complete (monitored by TLC). Then a 1N HCl soln (25 mL) was carefully added, the mixture was stirred for 5 min and the layers were separated. The aq layer was extracted with Et_2O (2 × 50 mL), the combined organic layers were washed with brine until the aq layer showed pH 6–7 and dried ($MgSO_4$). Filtration, concentration under diminished pressure and purification of the residue by flash chromatography (SiO_2, 2:1 petroleum ether–EtOAc) afforded diol **5a** (3.16 g, 92%) and diol **6a** (10 mg, 3%) as colourless syrups.

5a: TLC (2:1 petroleum ether–EtOAc): R_f 0.25; $[\alpha]_D$ +8.86° (*c* 0.7; $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 4.87 (1 H, br s, 1-H^b), 4.82 (1 H, br s, 1-H^a), 4.24 (1 H, dd, *J* 1.5, 7.2 Hz, 6-H), 4.17–3.91 (4 H, m, 9-H^a, 7-H, 8-H, 9-H^b), 3.76 (1 H, m, 4-H), 3.56 (1 H, m, 5-H), 2.46 (1 H, dd, *J* 3.1, 14.1 Hz, 3-H^b), 2.40–2.30 (2 H, m, C(4)-OH, C(5)-OH), 2.17 (1 H, dd, *J* 9.8, 14.1 Hz, 3-H^a), 1.77 (1 H, s, CH_3), 1.42, 1.40, 1.33 (12 H, 3 s, 2 × CMe_2); EIMS: *m*/*z* 316 (M^+). Anal. Calcd for $C_{16}H_{28}O_6$ (316.39): C, 60.74; H, 8.92. Found: C, 60.65; H, 9.14.

6a: ^1H NMR (250 MHz, $CDCl_3$): δ 5.26 (1 H, dd, *J* 1.3, 7.4 Hz, 3-H), 4.43 (1 H, m, 4-H), 4.18–3.90 (5H, 7-H, 8-H, 9-H^a, 9-H^b, 6-H), 3.57 (1 H, dd, *J* 6.6, 6.9 Hz, 5-H), 2.60 (1 H, d, *J* 9.2, C(5)-OH), 2.34 (1 H, d, *J* 9.0 Hz, C(4)-OH), 1.75 (3 H, d, *J* 1.1 Hz, CH_3), 1.69 (3 H, d, *J* 1.1 Hz, CH_3), 1.39, 1.37, 1.36, 1.31 (12 H, 4s, 2 × CMe_2). Anal. Calcd for $C_{16}H_{28}O_6 \cdot 0.25\ H_2O$ (320.9): C, 59.89; H, 8.95. Found: C, 59.93; H, 9.05.

1,2,3-Trideoxy-6,7:8,9-di-O-*isopropylidene-2-phenyl*-D-glycero-D-gulo-*non-1-enitol* (**5b**) *and 1,2,3-trideoxy-6,7:8,9-di*-O-*isopropylidene-2-phenyl*-D-glycero-D-gulo/ido-*non-1-enitol* (**6b**).—A soln of hydroxy ketone **4b** (1.88, 5.00 mmol) in anhyd Et_2O (25 mL) was cooled to −10 °C and a soln of $Zn(BH_4)_2$ in anhyd Et_2O[18] (12 mL) was added. The mixture was stirred for about 1 h at this temperature until the reaction was complete (TLC). Then 1N HCl soln (12 mL) was carefully added, the mixture was stirred for 5 min and the layers were separated. The aq layer was extracted with Et_2O (2 × 50 mL), the combined organic layers were washed with brine until the aq layer showed pH 6–7, and dried ($MgSO_4$). Filtration, concentration under diminished pressure and purification of the residue by flash chromatography (SiO_2, 2:1 petroleum ether–EtOAc) afforded diol **5b** (1.52 g, 80%) as a white foams and diol **6b** (120 mg, 6%) as a colourless syrup.

5b: TLC (2:1 petroleum ether/EtOAc): R_f 0.35; $[\alpha]_D$ +11.00° (*c* 0.7; $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 7.42 (2 H, d, *J* 7.4 Hz, Ar-H), 7.28 (3 H, m, Ar-H), 5.41 (H, s, 1-H^b), 5.22 (1 H, s, 1-H^a), 4.25 (1 H, d, *J* 7.2 Hz, 6-H), 4.12 (1 H, dd, *J* 5.8, 8.4, 9-H^b), 4.05 (1 H, m, 8-H), 4.02 (1 H, m, 7-H), 3.95 (1 H, dd, *J* 4.6, 8.5 Hz, 9-H^a), 3.70 (1 H, m, 4-H), 3.61 (1 H, m, 5-H), 3.13 (1 H, dd, *J* 3.16, 14.5 Hz, 3-H^b), 2.62 (1 H, dd, *J* 9.3, 14.5 Hz, 3-H^a), 2.50 (1 H, br d, *J* 7.0 Hz, C(5)-OH), 2.15 (1 H, br.s, C(4)-OH), 1.40, 1.37, 1.33 (12 H, 3 s, 2 × CMe_2); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ 144.9, 140.4, 140.4, 128.4, 127.7, 126.2 (C-Ar), 115.4 (C-1), 109.7, 109.6 (2 × *C*Me_2), 79.5 (C-6), 77.1 (C-8), 71.5 (C-4), 71.2 (C-5), 67.7 (C-9), 40.3 (C-3), 27.1, 26.8, 26.6, 25.2 (4 CH_3); EIMS: *m*/*z* 378 (M^+). Anal. Calcd for $C_{21}H_{30}O_6 \cdot 0.25\ H_2O$ (383.0): C, 65.86; H, 8.03. Found: C, 65.60; H, 8.16.

6b: TLC (2:1 petroleum ether–EtOAc): R_f 0.30; $[\alpha]_D$ −3.57° (*c* 0.7; $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.38–7.16 (5 H, m, Ar-H), 5.78 (1 H, dd, *J* 1.3, 8.3 Hz, 3-H), 4.58 (1 H, dd, *J* 5.6, 8.1 Hz, 4-H), 4.16–3.81 (5 H, 7-H, 8-H, 9-H^a, 9-H^b, 6-H), 3.69 (1 H, m, 5-H), 2.70 (1 H, br d, *J* 9.2 Hz, C(5)-OH), 2.55 (1 H, br d, *J* 9.0 Hz, C(4)-OH), 2.05 (3 H, d, *J* 1.3 Hz, CH_3), 1.36, (12 H, 3 s, 2 × CMe_2), 1.33, 1.23; EIMS: *m*/*z* 378 (M^+). Anal. Calcd for $C_{21}H_{30}O_6 \cdot 0.25\ H_2O$ (383.0): C, 65.86; H, 8.03. Found: C, 65.65; H, 8.03.

4,5-O-*Carbonylidene-1,2,3-trideoxy-6,7:8,9-di*-O-*isopropylidene-2-methyl*-D-glycero-D-gulo-*non-1-enitol* (**7a**).—A soln of diol **5a** (3.13, 9.90 mmol) and DMAP (cat.) in anhyd 4:1 CH_2Cl_2–pyridine (75 mL) was cooled to 0 °C, then diphosgene (0.69 mL, 5.46 mmol) was added via a syringe and the mixture was allowed to warm to rt. After stirring for 30 min, MeOH was added and the mixture was stirred further for 5 min. Then the solvents were removed under diminished pressure and

the residue was dissolved in Et_2O followed by addition of water with vigorous stirring. The layers were separated and the aq layer was extracted with Et_2O (6 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtration, concentrated under diminished pressure and purified by flash chromatography (SiO_2, 9:1 petroleum ether–EtOAc) to afford diol **7a** (3.00 g, 88%) as a white foams. TLC (2:1 petroleum ether–EtOAc): R_f 0.70; $[\alpha]_D$ + 25.86° (*c* 0.7; $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 4.95 (2 H, m, 1-H^b, 4-H), 4.83 (2 H, m, 5-H, 1-H^a), 4.16 (1 H, dd, *J* 6.1, 8.4 Hz, 9-H^b), 4.06–3.96 (4 H, m, 9-H^a, 7-H, 8-H, 6-H), 2.77 (1 H, dd, *J* 8.8, 15.6 Hz, 3-H^b), 2.55 (1 H, dd, *J* 4.7, 15.6 Hz, 3-H^a), 1.82 (3 H, s, CH_3), 1.42, 1.41, 1.40, 1.33 (12 H, 4s, 2 × CMe_2); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ 154.5 (CO); 140.2 (C-2), 113.2 (C-1), 111.0, 109.9 (2 × CMe_2), 78.0 (C-6), 77.8 (C-4), 77.0 (C-8), 76.5 (C-5, C-7), 68.0 (C-9), 36.7 (C-3), 27.1, 26.9, 26.0, 25.2 (2 × CMe_2), 22.9 (CH_3); EIMS: *m*/*z* 342 (M^+). Anal. Calcd for $C_{17}H_{26}O_7$ (343.0): C, 59.64; H, 7.65. Found: C, 59.72; H, 7.77.

4,5-O-*Carbonylidene*-*1,2,3*-*trideoxy*-*6,7:8,9*-*di*-O-*isopropylidene*-*2*-*phenyl*-D-glycero-D-gulo-*non*-*1*-*enitol* (**7b**).—A soln of diol **5b** (1.36, 3.60 mmol) and DMAP (cat.) in anhyd 4:1 CH_2Cl_2–pyridine (25 mL) was cooled 0 °C, then diphosgene (0.25 mL, 2.00 mmol) was added via a syringe and the mixture was allowed to warm to rt. After stirring for 30 min, MeOH was added and the mixture was stirred further for 5 min. Then the solvents were removed under diminished pressure and the residue was dissolved in Et_2O followed by addition of water with vigorous stirring. The layers were separated and the aq layer was extracted with Et_2O (6 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtration, concentrated under diminished pressure and purified by flash chromatography (SiO_2, 9:1 petroleum ether–EtOAc) to afford diol **7b** (1.34 g, 92%) as a white foam. TLC (2:1 petroleum ether–EtOAc): R_f 0.50; $[\alpha]_D$ + 24.62° (*c* 0.8; $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 5.52 (1 H, s, 1-H^b), 5.24 (1 H, s, 1-H^a), 4.88 (1 H, ddd, *J* 5.6, 8.1, 13.0 Hz, 4-H), 4.76 (1 H, d, *J* 7.6 Hz, 5-H), 4.18–3.93 (5 H, m, 9-H^a, 9-H^b, 7-H, 8-H, 6-H), 3.28 (1 H, dd, *J* 8.1, 15.5, 3-H^b), 3.10 (1 H, dd, *J* 5.6, 15.5 Hz, 3-H^a), 1.42, 1.41, 1.39, 1.34 (12 H, 4 s, 2 × CMe_2). Anal. Calcd for $C_{22}H_{28}O_7 \cdot 0.25\ H_2O$ (409.0): C, 64.62; H, 7.02. Found: C, 64.47; H, 7.25.

4,5-O-*Carbonylidene*-*1,2,3*-*trideoxy*-*2*-*methyl*-D-glycero-D-gulo-*non*-*1*-*enitol* (**8a**).—Cyclic carbonate **7a** (2.57 g, 7.50 mmol) was dissolved in 1:1 THF/water (100 mL) and TFA (50 mL) was added. After stirring at rt for 10 min cleavage of the primary isopropylidene ketal moiety was complete (monitored by TLC). Then the mixture was stirred at 70 °C until cleavage of the second *O*-isopropylidene ketal moiety was complete (60–70 min, monitored by TLC). The solvents were removed under diminished pressure and the residue was purified by flash chromatography (SiO_2, 1:0 to 19:1 $CHCl_3$–MeOH) to afford diol **8a** (1.79 g, 91%) as a white solid, mp 134–136 °C. TLC (4:1 $CHCl_3$–MeOH): R_f 0.50; $[\alpha]_D$ + 46.75° (*c* 0.8; $CHCl_3$); ^1H NMR (250 MHz, Me_2SO-d_6 + D_2O): δ 5.01 (1 H, m, 4-H), 4.92 (1 H, m, 5-H), 4.82 (1 H, s, 1-H^b), 4.81 (1 H, m, 6-H), 4.75 (1 H, s, 1-H^a), 3.57 (1 H, dd, *J* 2.5, 10.3 Hz, 9-H^b), 3.50–3.32 (3 H, m, 7-H, 8-H, 9-H^a), 2.58 (1 H, dd, *J* 9.4, 15.5 Hz, 3-H^b), 2.40 (1 H, dd, *J* 3.8, 15.6 Hz, 3-H^a), 1.71 (1 H, s, CH_3). Anal. Calcd for $C_{11}H_{18}O_7$ (262.3): C, 50.38; H, 6.92. Found: C, 50.10; H, 7.36.

4,5-O-*Carbonylidene*-*1,2,3*-*trideoxy*-*2*-*phenyl*-D-glycero-D-gulo-*non*-*1*-*enitol* (**8b**).—Cyclic carbonate **7b** (1.18 g, 2.92 mmol) was dissolved in 1:1 THF/water (50 mL) and TFA (25 mL) was added. After stirring at rt for 10 min cleavage of the primary isopropylidene ketal moiety was complete (monitored by TLC). Then the mixture was stirred at 70 °C until cleavage of the second *O*-isopropylidene ketal moiety was complete (60–70 min, monitored by TLC). The solvents were removed under diminished pressure and the residue was purified by flash chromatography (SiO_2, 1:0 to 19:1 $CHCl_3$–MeOH) to afford diol **8b** (0.93 g, 98%) as a white solid, mp 152–155 °C. TLC (4:1 $CHCl_3$–MeOH): R_f 0.40; $[\alpha]_D$ + 43.50° (*c* 0.6; $CHCl_3$); ^1H NMR (250 MHz, CD_3COCD_3): δ 7.47–7.28 (5 H, m, Ar-H), 5.42(1 H, s, 1-H^b), 5.25 (1 H, s, 1-H^a), 4.92 (1 H, m, 4-H), 4.14 (1 H, dd, *J* 1.9, 3.5 Hz, 5-H), 3.77–3.58 (5 H, m, 9-H^a, 9-H^b, 7-H, 8-H, 6-H), 3.30 (2 H, m, 3-H^a 3-H^b). Anal. Calcd for $C_{16}H_{20}O_7 \cdot 0.5\ H_2O$ (333.3): C, 57.65; H, 6.35. Found: C, 57.88; H, 6.49.

2,6-*Anhydro*-*4,5*-O-*carbonylidene*-*1,3*-*dideoxy*-*2*-*methyl*-*1*-*phenylseleno*-D-erythro-L-talo-*nonitol* (**9a**) *and* *2,6*-*anhydro*-*4,5*-O-*carbonylidene*-*1,3*-*dideoxy*-*2*-*methyl*-*1*-*phenylseleno*-D-erythro-L-galacto-*nonitol* (**10a**).—Compound **8a** was coevaporated several times with anhyd toluene prior to use and dried under diminished pressure. All operations were carried out under an inert atmosphere of argon. To a soln of phenylselenyl chloride (1.00 g, 5.20 mmol) in anhyd propionitrile (25 mL) silver trifluoromethanesulfonate (1.33 g, 5.20 mmol) was added at rt. A white solid precipitated and the yellow mixture was quickly cooled to −80 °C and stirred for 60 min. Then a soln of **8a** (1.05 g, 4 mmol) in anhyd propionitrile (50 mL) was added within 2 min via a syringe and the mixture was stirred for another 60 min. The reaction was worked up by pouring the cold reaction mixture on a cold (0 °C) mixture of CH_2Cl_2 and brine with vigorous stirring (5 min). The layers were separated, the aq layer was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried ($MgSO_4$). Filtration, concentration under diminished pressure and purification of the residue by flash chromatography (SiO_2, 19:1 CH_2Cl_2–MeOH) afforded **9a** (1.02 g, 61%) as a white foam and **10a** (0.52 g, 31%) as a white foam.

9a: TLC (4:1 $CHCl_3$–MeOH): R_f 0.50; $[\alpha]_D$ +5.66° (*c* 0.3; $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.48 (2 H, m, Ar-H), 7.25 (3 H, m, Ar-H), 5.06 (2 H, d, *J* 11.1 Hz, 4-H, 5-H), 3.90–3.60 (4 H, 7-H, 8-H, C(7)-OH, C(8)-OH), 3.40–3.02 (6 H, m, 1-H^a, 1-H^b, 9-H^a, 9-H^b, 6-H, C(9)-OH), 2.35 (1 H, d, *J* 15.7 Hz, 3-H^b), 1.80 (1 H, d, *J* 15.7 Hz, 3-H^a), 1.31 (3 H, s, CH_3); ^1H NMR (250 MHz, CD_3OD): δ 7.55–7.60 (2 H, m, Ar-H), 7.31–7.24 (3 H, m Ar-H), 5.09–4.98 (2 H, m, 5-H, 4-H), 3.90–3.62 (5 H, m, 6-H, 7-H, 8-H, 9-H^a, 9-H^b), 3.26 (2 H, s, 1-H^a, 1-H^b), 2.30 (1 H, dd, *J* 3.2, 16.0 Hz, 3-H^b), 1.90 (1 H, dd, *J* 3.0, 16.1 Hz, 3-H^a), 1.43 (3 H, s CH_3); MS: *m*/*z* 418 (M^+). Anal. Calcd for $C_{17}H_{22}O_7Se{\cdot}0.25\ H_2O$ (421.8): C, 48.41; H, 5.37. Found: C, 48.36; H, 5.72.

10a: TLC (4:1 $CHCl_3$–MeOH): R_f 0.45; $[\alpha]_D$ −8.60° (*c* 0.5; $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.49 (2 H, m, Ar-H), 7.21 (3 H, m, Ar-H), 4.86 (2 H, d, *J* 12.0 Hz, 4-H, 5-H), 4.30–3.36 (8 H, m, 6-H, 7-H, 8-H, 9-H^a, 9-H^b, C(9)-OH, C(8)-OH, C(7)-OH), 3.33 (1 H, d, *J* 12.4 Hz, 1-H^b), 3.05 (1 H, d, *J* 12.5 Hz, 1-H^a), 2.30 (1 H, d, *J* 15.5 Hz, 3-H^b), 1.80 (1 H, d, *J* 15.3 Hz, 3-H^a), 1.31 (3 H, s, CH_3); EIMS: *m*/*z* 418 (M^+). Anal. Calcd for $C_{17}H_{22}O_7Se{\cdot}0.25\ H_2O$ (421.8): C, 48.41; H, 5.37. Found: C, 48.83; H, 6.04.

*2,6-Anhydro-4,5-*O*-carbonylidene-1,3-dideoxy-2-phenyl-1-phenylseleno-*D-erythro-L-talo-*nonitol* (**9b**) *and 2,6-anhydro-4,5-*O*-carbonylidene-1,3-dideoxy-2-phenyl-1-phenylseleno-*D-erythro-L-galacto-*nonitol* (**10b**).—Compound **8b** was coevaporated several times with anhyd toluene prior to use and dried under diminished pressure. All operations were carried out under an inert atmosphere of argon. To a soln of phenylselenyl chloride (385 mg, 2.00 mmol) in anhyd propionitrile (25 mL), silver trifluoromethanesulfonate (520 mg, 2.03 mmol) was added at rt. A white solid precipitated and the yellow mixture was quickly cooled to −80 °C and stirred for 60 min. Then a soln of **8b** (500 mg, 1.54 mmol) in anhyd propionitrile (50 mL) was added within 2 min via a syringe and the mixture was stirred for another 60 min. The reaction was worked up by pouring the cold reaction mixture on a cold (0 °C) mixture of CH_2Cl_2 and brine with vigorous stirring (5 min). The layers were separated, the aq layer was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried ($MgSO_4$). Filtration, concentration under diminished pressure and purification of the residue by flash chromatography (SiO_2, 19:1 CH_2Cl_2–MeOH) afforded **9b** (147 mg, 20%) and **10b** (340 mg, 46%) as white foams.

9b: TLC (9:1 $CHCl_3$–MeOH): R_f 0.30; $[\alpha]_D$ −13.3° (*c* 0.3; $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.36–7.13 (10 H, m, Ar-H), 5.04 (1 H, d, *J* 9.1 Hz, 5-H), 4.86 (H, d, *J* 8.0 Hz, 4-H), 4.10–3.80 (8 H, m, 6-H, 7-H, 8-H, 9-H^a, 9-H^b, C(9)-OH, C(8)-OH, C(7)-OH), 3.48 (1 H, d, *J* 12.8 Hz, 1-H^b), 3.35 (1 H, d, *J* 12.0 Hz, 1-H^a), 2.60 (1 H, d, *J* 14.6 Hz, 3-H^b), 2.30 (1 H, d, *J* 14.6 Hz, 3-H^a). Anal. Calcd for $C_{22}H_{24}O_7Se{\cdot}0.5\ H_2O$ (488.4): C, 54.11; H, 5.16. Found: C, 53.65; H, 5.60.

10b: TLC (9:1 $CHCl_3$–MeOH): R_f 0.35; $[\alpha]_D$ −30.0° (*c* 0.3; $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.37–7.06 (10 H, m, Ar-H), 4.95 (1 H, dd, *J* 7.8, 15.6 Hz, 5-H), 4.76 (1 H, d, *J* 7.7 Hz, 4-H), 4.00–3.60 (8 H, m, 6-H, 7-H, 8-H, 9-H^a, 9-H^b, C(9)-OH, C(8)-OH, C(7)-OH), 3.40 (1 H, d, *J* 13.2 Hz, 1-H^b), 3.27 (1 H, d, *J* 12.7 Hz, 1-H^a), 2.55 (2 H, m, 3-H^a, 3-H^b). Anal. Calcd for $C_{22}H_{24}O_7Se{\cdot}0.5\ H_2O$ (488.4): C, 54.11; H, 5.16. Found: C, 53.75; H, 5.58.

*7,8,9-Tri-*O*-acetyl-2,6-anhydro-4,5-*O*-carbonylidene-1,3-dideoxy-2-methyl-1-phenyl-seleno-*D-erythro-L-talo-*nonitol* (**11a**).—Compound **9a** (0.26 g, 0.62 mmol) was dissolved in pyridine (6 mL), Ac_2O (4 mL) and DMAP (cat.) were added and the soln was stirred at rt for 12 h. The solvents were removed under diminished pressure and purification of the residue by flash chromatography (SiO_2, 1:1 petroleum ether–EtOAc) afforded **11a** (320 mg, 95%) as a white foam. TLC (1:1 petroleum ether–EtOAc): R_f 0.40; $[\alpha]_D$ +8.60° (*c* 0.6; $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 7.50 (2 H, m, Ar-H), 7.27 (3 H, m, Ar-H), 5.47 (1 H, dd, *J* 3.6, 6.2 Hz, 7-H), 5.30 (1 H, m, 8-H), 4.99 (1 H, m, 4-H), 4.76 (1 H, d, *J* 8.8 Hz, 5-H), 4.46 (1 H, dd, *J* 2.1, 12.3 Hz, 9-H^b), 4.15 (1 H, dd, *J* 5.9, 12.3 Hz, 9-H^a), 3.84 (1 H, d, *J* 3.6 Hz, 6-H), 3.07 (1 H, d, *J* 12.0, 1-H^b), 2.95 (1 H, d, *J* 12.0, 1-H^a), 2.27 (1 H, dd, *J* 3.2, 16.0 Hz, 3-H^b), 2.15, 2.04, 2.03 (9 H, 3 s, 3 × Ac), 1.81 (1 H, dd, *J* 3.0, 16.0 Hz, 3-H^a), 1.45 (3 H, s, CH_3); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ 170.7, 170.1, 169.8 (3 × Ac), 153.4 (CO), 133.0, 130.2, 129.4, 127.5 (C-Ar), 75.7 (C-2), 73.7 (C-5), 73.2 (C-4), 69.9 (C-8), 69.3 (C-7), 67.7 (C-6), 61.7 (C-9), 39.1 (C-1), 32.5 (C-3), 28.2 (CH_3), 21.0, 20.9, 20.7 (3 × Ac); EIMS: *m*/*z* 544 (M^+). Anal. Calcd for $C_{23}H_{28}O_{10}Se$ (543.4): C, 50.83; H, 5.19. Found: C, 50.66; H, 5.60.

*7,8,9-Tri-*O*-acetyl-2,6-anhydro-4,5-*O*-carbonylidene-1,3-dideoxy-2-methyl-1-phenyl-seleno-*D-erythro-L-talo-*nonitol* (**12a**).—Compound **10a** (0.31 g, 0.62 mmol) was dissolved in pyridine (3 mL), Ac_2O (2 mL) and DMAP (cat.) were added with stirring at rt for 12 h. The solvents were removed under diminished pressure and purification of the residue by flash chromatography (SiO_2, 1:1 petroleum ether–EtOAc) afforded **12a** (162 mg, 96%) as a white foam. TLC (1:1 petroleum ether–EtOAc): R_f 0.20; $[\alpha]_D$ −7.60° (*c* 0.5; $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 7.53 (2 H, m, Ar-H), 7.26 (3 H, m, Ar-H), 5.50 (1 H, dd, *J* 3.5, 6.4 Hz, 7-H), 5.22 (1 H, ddd, *J* 2.4, 5.6, 8.4, 8-H), 4.93 (1 H, m, 4-H), 4.73 (1 H, dd, *J* 1.5, 8.4 Hz, 5-H), 4.46 (1 H, dd, *J* 1.9, 12.6 Hz, 9-H^b), 4.12 (1 H, dd, *J* 5.6, 12.6 Hz, 9-H^a), 3.78 (1 H, dd, *J* 1.5, 3.5 Hz, 6-H), 3.28 (1 H, d, *J* 12.7, 1-H^b), 3.14 (1 H, d, *J* 12.7, 1-H^a), 2.42 (1 H, dd, *J* 3.9, 15.9 Hz, 3-H^b), 2.12, 2.07, 2.03 (9H, 3 s, 3 × Ac), 1.72 (1 H, dd, *J* 3.2, 15.9 Hz, 3-H^a), 1.26 (3 H, s, CH_3); ^{13}C NMR

(150.8 MHz, $CDCl_3$): δ 170.2, 169.7, 169.2 (3 × Ac), 152.4 (CO), 132.2, 130.0, 128.7, 126.6 (C-Ar), 75.5 (C-2), 73.6 (C-5), 72.9 (C-4), 69.4 (C-8), 68.5 (C-7), 67.0 (C-6), 61.1 (C-9), 39.8 (C-1), 31.7 (C-3), 24.1 (CH_3), 20.4, 20.4, 20.2 (3 × Ac); EIMS: m/z 544 (M^+). Anal. Calcd for $C_{23}H_{28}O_{10}Se$ (543.4): C, 50.83; H, 5.19. Found: C, 51.08; H, 5.60.

7,8,9-Tri-O-*acetyl-2,6-anhydro-4,5*-O-*carbonylidene-1,3-dideoxy-2-phenyl-1-phenyl-seleno*-D-erythro-L-talo-*nonitol* (**11b**).—Compound **9b** (80 mg, 0.167 mmol) was dissolved in pyridine (4 mL), Ac_2O (2 mL) and DMAP (cat.) were added and the soln was stirred at rt for 12 h. The solvents were removed under diminished pressure and purification of the residue by flash chromatography (SiO_2, 1:1 petroleum ether–EtOAc) afforded **11b** (87 mg, 86%) as a white foam. TLC (2:1 petroleum ether–EtOAc): R_f 0.50; $[\alpha]_D$ −2.00° (*c* 0.5; $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44–7.23 (10 H, m, Ar-H), 5.62 (1 H, m, 7-H), 5.45 (1 H, m, 8-H), 4.99 (1 H, d, *J* 9.1 Hz, 4-H), 4.80 (1 H, d, *J* 9.1 Hz, 5-H), 4.60 (1 H, dd, *J* 1.1, 12.4 Hz, 9-H^b), 4.33 (1 H, d, *J* 3.6 Hz, 6-H), 4.28 (1 H, dd, *J* 5.8, 12.4 Hz, 9-H^a), 3.36 (1 H, d, *J* 12.9, 1-H^b), 3.26 (1 H, d, *J* 12.9, 1-H^a), 2.66 (1 H, dd, *J* 2.0, 15.9 Hz, 3-H^b), 2.60 (1 H, dd, *J* 3.3, 15.9 Hz, 3-H^a), 2.19, 2.14, 2.07 (9H, 3 s, 3 × Ac). Anal. Calcd for $C_{28}H_{30}O_{10}Se$ (605.5): C, 55.54; H, 4.99. Found: C, 55.09; H, 5.18.

7,8,9-Tri-O-*acetyl-2,6-anhydro-4,5*-O-*carbonylidene-1,3-dideoxy-2-phenyl-1-phenyl-seleno*-D-erythro-L-talo-*nonitol* (**12b**).—Compound **10b** (210 mg, 0.44 mmol) was dissolved in pyridine (6 mL), Ac_2O (4 mL) and DMAP (cat.) were added and the soln was stirred at rt for 12 h. The solvents were removed under diminished pressure and purification of the residue by flash chromatography (SiO_2, 1:1 petroleum ether–EtOAc) afforded **12b** (223 mg, 84%) as a white foam. TLC (2:1 petroleum ether–EtOAc): R_f 0.60; $[\alpha]_D$ −12.00° (*c* 0.5; $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34–7.12 (10 H, m, Ar-H), 5.50 (1 H, dd, *J* 4.6, 6.0 Hz, 7-H), 5.24 (1 H, m, 8-H), 4.98 (1 H, dd, *J* 7.2, 12.4 Hz, 4-H), 4.57 (1 H, dd, *J* 1.3, 7.2 Hz, 5-H), 4.40 (1 H, dd, *J* 2.3, 12.5 Hz, 9-H^b), 4.08 (1 H, dd, *J* 5.6, 12.5 Hz, 9-H^a), 3.65 (1 H, m, 6-H), 3.38 (1 H, d, *J* 12.5, 1-H^b), 3.31 (1 H, d, *J* 12.5 Hz, 1-H^a), 2.75 (1 H, dd, *J* 5.0, 14.9 Hz, 3-H^b), 2.54 (1 H, dd, *J* 7.5, 14.9 Hz, 3-H^a), 2.19, 2.17, 1.93 (9 H, 3 s, 3 × Ac). Anal. Calcd for $C_{28}H_{30}O_{10}Se$ (605.5): C, 55.54; H, 4.99. Found: C, 55.35; H, 5.40.

2,6-Anhydro-1,3-dideoxy-2-methyl-1-phenylseleno-D-erythro-L-talo-*nonitol* (**13**).—A soln of **11a** (1.60 g, 3 mmol) in anhyd MeOH (50 mL) was treated with a 1 M NaOMe in MeOH (1 mL) and the mixture was stirred at rt until the reaction was complete (TLC). Then the mixture was neutralized with Amberlite 120 (H^+), filtered, concentrated under diminished pressure and coevaporated with anhyd toluene several times to afford **13** (1.15 g, 98%) as a white foam. TLC (4:1 CH_2Cl_2–MeOH): R_f 0.27; $[\alpha]_D$ −22.86° (*c* 0.7; $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.49 (2 H, m, Ar-H), 7.26 (3 H, m, Ar-H), 4.10–3.70 (7 H, m, 6-H, 7-H, 8-H, 9-H^a, 9-H^b, 4-H, 5-H), 3.52 (1 H, d, *J* 11. 7 Hz, 1-H^b), 3.00 (1 H, d, *J* 11.7 Hz, 1-H^a), 2.75 (5 H, br s, 5 × OH), 1.86 (2 H, m, 3-H^a, 3-H^b), 1.44 (3 H, s, CH_3). Anal. Calcd for $C_{16}H_{24}O_6Se$ (391.3): C, 49.11; H, 6.18. Found: C, 49.68; H, 6.04.

2,6-Anhydro-4,5,7,8,9-penta-O-*benzoyl-1,3-dideoxy-2-methyl-1-phenylseleno*-D-erythro-L-talo-*nonitol* (**14**) *and 2,6-anhydro-4,7,8,9-tetra*-O-*benzoyl-1,3-dideoxy-2-methyl-1-phenylseleno*-D-erythro-L-talo-*nonitol* (**15**).—Deprotected **13** (2.08 g, 5.30 mmol) was dissolved in anhyd 1:1 THF–NEt_3 (200 mL) and cooled to 0 °C. Then, 2.65 mL of a freshly prepared soln of benzoyl cyanide (3.07 g, 23.32 mmol) in anhyd THF (10.60 mL) were added every 60 min while stirring at 0 °C. After complete addition, the reaction mixture was stirred at 0 °C (22 h). Then further benzoyl cyanide (0.76 g) was added and stirring was continued for 6 h. Then further benzoyl cyanide (1.74 g, 13.22 mmol) was added, the mixture was warmed up to +5 °C and stirring was continued for 36 h. For work-up, MeOH was added, the mixture was allowed to warm up to rt and stirred for 2 h. Removal of the solvents under diminished pressure and purification by flash chromatography (SiO_2, 99.5:0.5 CH_2Cl_2–MeOH) afforded **14** (1.65 g, 34%) as a white foam and **15** (1.40 g, 33%) as a white foam.

14: TLC (99:1 CH_2Cl_2–MeOH): R_f 0.20; $[\alpha]_D$ −3.33° (*c* 0.3; $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.95–7.07 (30 H, m, Ar-H), 5.95–5.86 (3 H, m, 5-H, 8-H, 7-H), 5.24 (1 H, m, 4-H), 4.92 (1 H, dd, *J* 2.7, 12.4 Hz, 9-H^b), 4.43 (1 H, dd, *J* 5.2, 12.4 Hz, 9-H^a), 4.30 (1 H, d, *J* 3.4 Hz, 6-H), 3.28 (1 H, d, *J* 11.9, 1-H^b), 3.00 (1 H, d, *J* 11.9, 1-H^a), 2.07 (2 H, m, 3-H^a, 3-H^b), 1.44 (3 H, s, CH_3); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ 166.0 165.4, 165.3, 165.0 (5 × Bz), 133.1, 132.9, 132.9, 132.8, 132.7, 130.2, 130.0, 129.7, 129.7, 129.6, 129.5, 129.4, 129.2, 129.1, 128.8, 128.3, 128.1, 128.0, 127.9, 127.0, 126.5 (C-Ar), 76.0 (C-2), 71.3 (C-4), 70.7 (C-6), 69.4 (C-8), 68.6 (C-7), 67.7 (C-5), 62.5 (C-9), 34.2 (C-3), 34.0 (C-1), 29.0 (CH_3). Anal. Calcd for $C_{51}H_{44}O_{11}Se$ (911.8): C, 67.18; H, 4.86. Found: C, 67.04; H, 5.14.

15: TLC (99:1 CH_2Cl_2–MeOH): R_f 0.10; $[\alpha]_D$ +6.40° (*c* 0.5; $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.14–7.13 (25 H, m, Ar-H), 6.03–5.95 (2 H, m, 8-H, 7-H), 5.18 (1 H, m, 4-H), 5.02 (1 H, dd, *J* 3.2, 12.3 Hz, 9-H^b), 4.60 (1 H, dd, *J* 6.2, 12.3 Hz, 9-H^a), 4.34 (1 H, d, *J* 2.4 Hz, 5-H), 4.12 (1 H, d, *J* 5.1 Hz, 6-H), 3.32 (1 H, d, *J* 11.9, 1-H^b), 3.00 (1 H, d, *J* 11.9, 1-H^a), 2.10 (2 H, m, 3-H^a, 3-H^b), 1.40 (3 H, s, CH_3). Anal. Calcd for $C_{44}H_{40}O_{10}Se$ (807.7): C, 65.43; H, 4.99. Found: C, 65.47; H, 4.95.

*2,6-Anhydro-4,7,8,9-tetra-*O*-benzoyl-1,3-dideoxy-2-methyl-5-*O*-trifluoromethansulfonyl-1-phenylseleno-*D*-erythro-*L*-talo-nonitol* (**16**).—A soln of **15** (0.7 g, 0.86 mmol) in anhyd CH_2Cl_2 (50 mL) was cooled to 0 °C, pyridine (2.50 mL) was added followed by trifluoromethane sulfonic anhydride (2 mL) and the mixture was stirred for 12 h while warming up to rt. Then, the mixture was diluted with CH_2Cl_2 (100 mL), a satd aq $NaHCO_3$ soln (150 mL) was added, the layers were separated and the organic layer was extracted with CH_2Cl_2. The combined organic layers were concentrated under diminished pressure at rt and purified by rapid flash chromatography to afford triflate **16** (0.80 g, 99%) as a white foam which was immediately used in the next step. TLC (99:1 CH_2Cl_2–MeOH): R_f 0.60; $[\alpha]_D$ + 5.33° (*c* 0.6; $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.11–7.10 (25 H, m, Ar-H), 5.92–5.80 (2 H, m, 8-H, 7-H), 5.45 (1 H, d, *J* 2.5 Hz, 5-H), 5.20 (1 H, m, 4-H), 4.90 (1 H, dd, *J* 4.2, 12.1 Hz, 9-H^b), 4.45 (1 H, dd, *J* 5.4, 12.1 Hz, 9-H^a), 4.34 (1 H, d, *J* 7.6 Hz, 6-H), 3.26 (1 H, d, *J* 12.2, 1-H^b), 2.90 (1 H, d, *J* 12.2, 1-H^a), 2.10 (2 H, m, 3-H^a, 3-H^b), 1.26 (3 H, s, CH_3).

*2,6-Anhydro-5-azido-4,7,8,9-tetra-*O*-benzoyl-1,3-dideoxy-2-methyl-1-phenylseleno-*D*-erythro-*L*-manno-nonitol* (**17**).—The triflate **16** (0.80 g, 0.85 mmol) was dissolved in anhyd toluene (50 mL) and treated with tetra-*n*-butylammonium azide (2.60 g). After stirring for 15 min the mixture was concentrated under diminished pressure and purified by flash chromatography (SiO_2, 99.07:0.03 CH_2Cl_2–MeOH) to afford azide **17** (0.68 g, 96%) as a white foam. TLC (99:1 CH_2Cl_2–MeOH): R_f 0.60; $[\alpha]_D$ + 60.00° (*c* 0.3; $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19–7.16 (25 H, m, Ar-H), 6.12 (1 H, d, *J* 6.8 Hz, 7-H), 5.94 (1 H, m, 8-H), 5.28 (1 H, m, 4-H), 5.09 (1 H, dd, *J* 1.8, 12.4 Hz, 9-H^b), 4.56 (1 H, dd, *J* 5.7, 12.5 Hz, 9-H^a), 3.90 (1 H, d, *J* 10.2 Hz, 6-H), 3.45 (1 H, dd, *J* 10.2 Hz, 5-H), 3.27 (1 H, d, *J* 11.8, 1-H^b), 3.05 (1 H, d, *J* 11.8, 1-H^a), 2.55 (1 H, dd, *J* 4.8, 12.6 Hz, 3-H^b), 1.65 (1 H, dd, *J* 12.5, 12.6 Hz, 3-H^a), 1.44 (3 H, s, CH_3); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ 166.2, 165.5, 165.3 (4 × Bz), 133.7, 133.4, 133.2, 132.9, 130.1, 129.8, 129.7, 129.7, 129.3, 129.1, 128.7, 128.5, 128.3, 127.1 (C-Ar), 76.0 (C-2), 72.7 (C-4), 71.0 (C-8), 70.9 (C-6), 70.0 (C-7), 63.1 (C-9), 61.3 (C-5), 39.1 (C-3), 33.9 (C-1), 28.7 (CH_3). Anal. Calcd for $C_{44}H_{39}N_3O_9Se$ (832.8): C, 63.46; H, 4.72; N, 5.05. Found: C, 63.33; H, 5.21; N, 4.71.

*4,7,8,9-Tetra-*O*-acetyl-2,6-anhydro-5-azido-1,3-dideoxy-2-methyl-1-phenylseleno-*D*-erythro-*L*-manno-nonitol* (**18**).—To a stirred suspension of the protected compound **17** (0.66 g, 0.80 mmol) in anhyd MeOH (25 mL) was added portionwise MeONa (172 mg, 3.2 mmol) in anhyd MeOH (25 mL) at rt and the soln was stirred for 12 h. Then the mixture was neutralized with Amberlite IR 120 (H^+) and filtered. Concentration under diminished pressure and coevaporation with toluene several times afforded 2,6-anhydro-5-azido-1,3-dideoxy-2-methyl-1-phenylseleno-*D*-*erythro*-*L*-*manno*-nonitol, which was directly subjected to acetylation without further purification. 2,6-Anhydro-5-azido-1,3-dideoxy-2-methyl-1-phenylseleno-*D*-*erythro*-*L*-*manno*-nonitol was dissolved in pyridine (6 mL), Ac_2O (4 mL) and DMAP (cat.) were added and the mixture stirred at rt for 12 h. Evaporation of the solvents under reduced pressure gave the product which was purified by flash chromatography (SiO_2, 9:1 petroleum ether–EtOAc) to afford **18** (0.44 g, 94%) as a colourless syrup. TLC (95:5 CH_2Cl_2–MeOH): R_f 0.40; $[\alpha]_D$ − 23.50° (*c* 0.8; $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 (2 H, m, Ar-H), 7.26 (3 H, m, Ar-H), 5.51 (1 H, dd, *J* 1.4, 7.0 Hz, 7-H), 5.30 (1 H, m, 8-H), 5.08 (1 H, m, 4-H), 4.53 (1 H, dd, *J* 2.1, 12.6 Hz, 9-H^b), 4.23 (1 H, dd, *J* 5.1, 12.6 Hz, 9-H^a), 3.56 (1 H, dd, *J* 1.4, 10.5, 6-H), 3.37 (1 H, d, *J* 12.4 Hz, 1-H^b), 3.14 (1 H, dd, *J* 10.0, 10.1 Hz, 5-H), 2.96 (1 H, d, *J* 12.4 Hz, 1-H^a), 2.33 (1 H, dd, *J* 5.0, 13.2 Hz, 3-H^b), 2.17, 2.09, 2.05, 2.03 (12 H, 4 s, 4 × Ac), 1.57 (1 H, m, 3-H^a), 1.36 (3 H, s, CH_3); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ 170.78, 170.06, 169.93 (4 × Ac), 132.89, 129.77, 129.30, 129.30, 127.30 (C-Ar), 75.60 (C-2), 71.84 (C-4), 70.36 (C-8), 70.32 (C-6), 68.93 (C-7), 61.94 (C-9), 60.85 (C-5), 39.22 (C-3), 33.94 (C-1), 28.51 (CH_3), 21.21, 20.98, 20.81, 20.74 (4 × Ac). Anal. Calcd for $C_{24}H_{31}N_3O_9Se$ (584.5): C, 49.32; H, 5.35; N, 7.19. Found: C, 49.36; H, 5.76; N, 6.86.

*4,7,8,9-Tetra-*O*-acetyl-1-aldehydo-2,6-anhydro-5-azido-3-deoxy-2-methyl-*D*-erythro-*L*-manno-nonitol* (**19**).—A soln of **18** (0.42 g, 0.72 mmol) in THF (30 mL) was cooled to − 80 °C and then 70% *m*-chloroperbenzoic acid (177 mg, 0.73 mmol) in THF (12 mL) was added dropwise via a syringe within 2 min. After stirring for 30 min, Ac_2O (324 μL) was added followed by anhyd sodium acetate (209 mg). Then the mixture was allowed to warm up to rt and was finally heated to reflux for 90 min. The solvents were removed under diminished pressure, the residue was dissolved in EtOAc and water was added with vigorous stirring. The layers were separated, the aq layer was extracted with EtOAc (3 × 30 mL) and the combined organic layers were dried ($MgSO_4$). Filtration, concentration under diminished pressure and purification of the residue (R_f 0.50–0.60, 2:1 petroleum ether–EtOAc) by flash chromatography (SiO_2, 9:1 petroleum ether–EtOAc) afforded a mixture of acetoxy selenides (0.42 g, 91%) that was immediately subjected to further conversion by dissolution in anhyd 3:1 MeOH–THF (40 mL) and treatment with a 1 M NaOMe in MeOH (1 mL). After stirring for 24 h, the mixture was neutralized by addition of Amberlite IR 120 (H^+), filtered and concentrated, and the residue was peracetylated in a mixture of pyridine and Ac_2O. Coevaporation with toluene and flash chromatography (SiO_2, 99:1 CH_2Cl_2–MeOH) afforded **19** (0.25 g, 80%) as a colourless syrup which was

immediately used in the next step. TLC (95:5 CH_2Cl_2–MeOH): R_f 0.55; ^1H NMR (250 MHz, $CDCl_3$): δ 9.39 (1 H, s, CHO), 5.46 (2 H, m, 8-H, 7-H), 4.82 (1 H, ddd, J 5.1, 9.7, 13.9 Hz, 4-H), 4.38 (1 H, dd, J 2.0, 12.7, 9-H^b), 4.17 (1 H, dd, J 4.2, 12.7, 9-H^a), 3.55 (1 H, dd, J 1.2, 10.5 Hz, 6-H), 3.18 (1 H, dd, J 10.1, 10.2 Hz, 5-H), 2.64 (1 H, dd, J 5.1, 13.9 Hz, 3-H^b), 2.20, 2.16, 2.12, 2.07 (12 H, 4 s, 4 × Ac), 1.54 (1 H, dd, J 12.4, 12.6 Hz, 3-H^a), 1.29 (3H, s, CH_3).

Methyl 4,7,8,9-tetra-O-*acetyl-2,6-anhydro-5-azido-3-deoxy-2-methyl*-D-erythro-L-manno-*nononate* (**20**).—A soln of $NaClO_2$ (0.50 g, 5.50 mmol) and KH_2PO_4 (0.69 g, 5.07 mmol) in water (3.63 mL) was added to a soln of aldehyde **19** (0.25 g, 0.56 mmol) in 4:4:1 CH_3CN–*t*-BuOH–2-methyl-2-butene (24.20 mL, 4:4:1). The mixture was stirred for 10 min at rt, then a 10% aq hydrogen chloride soln (60.5 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were concentrated, and the residue, TLC (SiO_2): R_f 0.25 (19:1 CH_2Cl_2–MeOH), was dissolved in Et_2O (30 mL) and treated with an excess of diazomethane in anhyd Et_2O, the excess being consumed by addition of AcOH. Concentration under diminished pressure, coevaporation with toluene and purification of the residue by flash chromatography (SiO_2, 99:1 CH_2Cl_2–MeOH) afforded the methyl ester **20** (0.21 g, 79%) as a colourless syrup which was immediately used in the next step. TLC (19:1 CH_2Cl_2–MeOH): R_f 0.50; $[\alpha]_D$ −30.00° (c 1; $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 5.46 (1 H, dd, J 1.5, 8.6 Hz, 7-H), 5.32 (1 H, ddd, J 2.3, 4.5, 6.8 Hz, 8-H), 4.80 (1 H, ddd, J 4.7, 9.8, 11.8 Hz, 4-H), 4.32 (1 H, dd, J 2.3, 12.6 Hz, 9-H^b), 4.20 (1 H, dd, J 4.6, 12.6 Hz, 9-H^a), 3.71 (3 H, s, OCH_3), 3.65 (1 H, dd, J 1.5, 10.6 Hz, 6-H), 3.12 (1 H, dd, J 10.3, 9.9 Hz, 5-H), 2.66 (1 H, dd, J 4.8, 13.0 Hz, 3-H^b), 2.14, 2.10, 2.06, 2.02 (12H, 4 s, 4 × Ac), 1.50 (1 H, dd, J 12.7, 12.1 Hz, 3-H^a), 1.38 (3 H, s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 172.2, 170.7, 169.9, 169.7, 169.6 (5 × CO), 77.3 (C-2), 72.0 (C-6), 71.9 (C-4), 68.8 (C-8), 68.3 (C-7), 61.9 (C-9), 60.4 (C-5), 52.5 (OCH_3), 38.5 (C-3), 26.6 (CH_3), 21.0, 20.8, 20.7 (4 × Ac); MALDI-MS: m/z 496 [MNa^+].

Methyl 5-amino-4,7,8,9-tetra-O-*acetyl-2,6-anhydro-3-deoxy-2-methyl*-D-erythro-L-manno-*nononate* (**21**).—To a soln of azide **20** (44 mg, 0.09 mmol) in MeOH (5 mL) was added 5% $Pd/Ca(CO_3)_2$ (25 mg) and the mixture was stirred at rt for 2 h under H_2. After monitoring of the reaction mixture (TLC), it was filtered through a Celite pad and washed with MeOH. The solvent was evaporated and the residue was purified by flash chromatography (SiO_2, 99:1 CH_2Cl_2–MeOH) afforded **21** (31 g, 77%) as a colourless syrup. TLC (19:1 CH_2Cl_2–MeOH): R_f 0.30; ^1H NMR (250 MHz, $CDCl_3$): δ 4.60 (1 H, ddd, J 4.5, 6.0, 11.5 Hz, 4-H), 4.39–4.21 (2 H, m, 8-H, 7-H), 3.72 (2 H, m, 9-H^a, 9-H^b), 3.70 (3 H, s, OCH_3), 3.62 (1 H, d, J 10.0 Hz, 6-H), 2.62 (1 H, dd, J 4.6, 12.8 Hz, 3-H^b), 2.47 (1 H, dd, J 9.9, 10.0 Hz, 5-H), 2.12, 2.11, 2.05, 2.02 (12 H, 4 s, 4 × Ac), 1.40 (1 H, m, 3-H^a), 1.37 (3 H, s, CH_3); EIMS: m/z 447 (M^+).

Methyl 5-acetamido-4,7,8,9-tetra-O-*acetyl-2,6-anhydro-3-deoxy-2-methyl*-D-erythro-L-manno-*nononate* (**1**).—Compound **21** (20 mg, 0.045 mmol) was dissolved in pyridine (3 mL), Ac_2O (2 mL) and DMAP (cat.) were added under stirring at rt for 24 h. The solvents were removed under diminished pressure and purification of the residue by flash chromatography (SiO_2, 49:1 CH_2Cl_2–MeOH) afforded **1** (20 mg, 91%) as a white solid, mp 60–62 °C. TLC (19:1 CH_2Cl_2–MeOH): R_f 0.37; $[\alpha]_D$ −33.66° (c 0.3; $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 5.36 (1 H, ddd, J 2.4, 6.4, 9.3 Hz, 8-H), 5.31 (2 H, dd, J 1.8, 6.9 Hz, 7-H), 5.13 (1 H, d, J 10.1 Hz, NH), 4.83 (H, ddd, J 4.3, 12.0, 12.0 Hz, 4-H), 4.43 (1 H, dd, J 2.3, 12.3 Hz, 9-H^b), 4.11 (1 H, dd, J 6.1, 12.3 Hz, 9-H^a), 4.02 (1 H, dd, J 10.3, 10.5 Hz, 5-H), 3.92 (1 H, dd, J 1.8, 10.5 Hz, 6-H), 3.75 (3 H, s, OCH_3), 2.55 (1 H, dd, J 4.5, 12.5 Hz, 3-H^b), 2.10, 2.09, 2.05, 2.01 (12 H, 3 s, 4 × Ac), 1.98 (3 H, s, NHAc), 1.74 (1 H, dd, J 12.3, 12.5 Hz, 3-H^a), 1.44 (3 H, s, CH_3), ^{13}C NMR (150.8 MHz, $CDCl_3$): δ 172.7, 171.0, 170.6, 170.3, 170.2, 170.1 (6 × CO), 77.7 (C-2), 73.5 (C-6), 70.2 (C-4), 70.0 (C-8), 67.9 (C-7), 62.4 (C-9), 52.5 (OCH_3), 49.6 (C-5), 39.0 (C-3), 26.7 (CH_3), 23.2 (NHAc), 21.1, 20.9, 20.8 (4 × Ac); EIMS: m/z 489 (M^+). Anal. Calcd for $C_{21}H_{31}NO_{12}$ (489.5): C, 51.53; H, 6.40; N, 2.86. Found: C, 51.30; H, 6.89; N, 2.77.

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