Stereoselective Conjugate Addition of Nitrogen and Carbon Nucleophiles to Sugar-Derived Enones: Synthesis of Sialic Acid Analogues

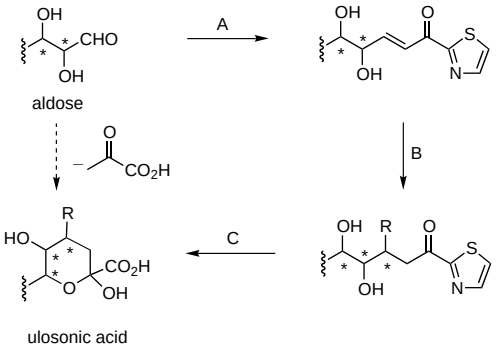
Alessandro Dondoni,* Alberto Marra, and Alessia Boscarato[a]

Abstract: The conjugate addition of benzylamine to three polyalkoxy α,β-enones derived from D-glyceraldehyde, D-erythrose, and D-mannose, whose carbonyls were flanked by the thiazole ring, proceeded with modest to good *syn*-selectivity. The resulting polyalkoxy β-amino ketones were converted by ketalization into methyl 1-(2-thiazolyl)-pyranosides that in turn were transformed into 4-amino-3,4-dideoxy-ulosonic acids by sequential cleavage of the thiazole ring into the formyl group and oxidation of the latter to carboxylate. Thus, starting from the enone derived from D-mannose, the 4-acetamido-nonulosonic acid *iso*-Neu4Ac, a positional isomer of sialic acid Neu5Ac, was prepared. Because of some unsatisfactory reactions, a more efficient synthesis of *iso*-Neu4Ac was carried out by the use of trimethylsilyl azide as a nitrogen nucleophile in the initial conjugate addition reaction. Also, in the presence of DBU the addition of nitromethane to the same enones proceeded with good *syn*-selectivity and chemical yield. The cyclization of the resulting ketones afforded methyl 3-nitromethyl-1-(2-thiazolyl)-pyranosides. Furthermore, the pyranoside derived from the enone incorporating the D-mannose moiety afforded after reduction of the nitro to the amino group and carboxylate generation from the thiazole ring, a 4-acetamidomethyl-3,4-dideoxy-ulosonic acid, which is a branched one-carbon higher homologue of *iso*-Neu4Ac.

Keywords: azides · carbohydrate mimetics · Michael additions · neuraminic acids · sialic acids

Introduction

Previous work in our laboratory demonstrated a viable route to 3-deoxy-2-ulosonic acids by three-carbon chain elongation of aldehydo sugars[1] (Scheme 1). In this method, the open-chain skeleton of the target molecule is constructed by Wittig-type olefination of the polyhydroxylated aldehyde with a thiazole-armed carbonylphosphorane (step A) and 1,4-conjugate addition of an oxygen nucleophile to the resulting α,β-enone (step B). The synthesis is completed by intramolecular ketalization, followed by conversion of the thiazole ring into the formyl group and oxidation of the latter to carboxylate (step C). The reaction sequence A, B, and C (R = OH) corresponds to the addition of the pyruvate carbanion to the starting aldose.[2] A demonstration of the synthetic utility of the above olefination–addition route was provided[1] by the preparation of 3-deoxy-D-*glycero*-D-*galacto*-nonulopyranosonic acid, KDN (**2**) (Figure 1), a special type of sialic acid[3] that can be considered as the deaminated analogue of *N*-acetylneuraminic acid Neu5Ac (**1**), the most common member of the sialic acid class of carbohydrates.[4] In the reaction sequence culminating with the synthesis of **2**, the benzyl oxide anion was employed as the oxygen nucleophile in step B. Hence it became evident to us that extension of the above olefination–addition route to the preparation of ulosonic acids carrying other groups than OH at C4 could be achieved just by changing the type of nucleophile employed in step B. For example, the use of nitrogen nucleophiles would lead to 4-aminated ulosonic acids (R = NH_2).[5] A special target in this context was represented by the 4-acetamido-nonulosonic acid (**3**), a positional isomer of *N*-acetylneuraminic acid (**1**). Given



Scheme 1. Synthesis of 3-deoxy-ulosonic acids: A) Wittig olefination with $Ph_3PCHC(O)Th$-2; B) conjugate addition of the nucleophile R; C) cyclization and conversion of the thiazole ring to the carboxylate group.

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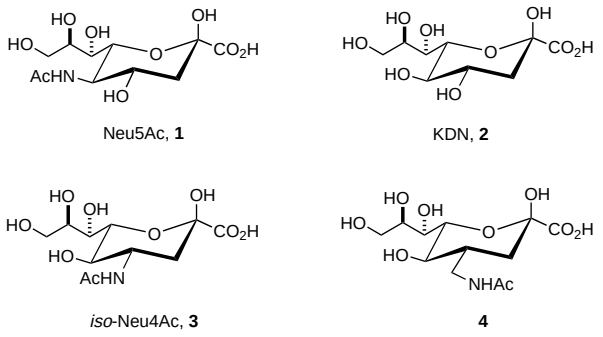


Figure 1. Natural nonulosonic acids **1** and **2** and nonnatural synthetic targets **3** and **4**.

the widespread occurrence of **1** in glycoproteins, glycolipids, and oligosaccharides and the essential role that these sialyl conjugates play in molecular recognition of infectious pathogens and in cell adhesion and differentiation phenomena,[6] it appeared important to prepare analogues of sialic acids[7] since these compounds are potential inhibitors of the above biological processes. For the same reasons we thought it would be interesting to prepare a homologue of **3**, that is the ulosonic acid **4**, in which the acetamido group is attached to the pyranose ring through a methylene bridge.[8] The aminomethyl group ($R = CH_2NH_2$) at C4 of the ulosonic acid can be introduced through the carbanion derived from nitromethane as nucleophile in step B.

Results and Discussion

Addition of benzylamine: The attachment of the amino group to a carbon atom by asymmetric 1,4-conjugate addition reactions of nitrogen nucleophiles[9, 10] (ammonia synthons) to enones, enoates, and other activated olefins has been described in various instances. As in most 1,4-conjugate addition reactions[11] the stereochemical outcome varied depending on several factors, which include solvent, temperature, nucleophile, and substituents on stereocenters adjacent to the double bond. Thus, we focused on the use of benzylamine as the nitrogen nucleophile and decided to study the feasibility of the synthetic approach to 4-aminated ulosonic acids starting from γ,δ-dialkoxy enones **5** and **6** (Figure 2).[5] These compounds were available in pure *E*-geometry by olefination of protected D-glyceraldehyde and D-erythrose, respectively, with a thiazole-armed phosphorous ylide.[1]

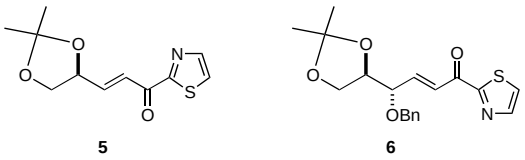
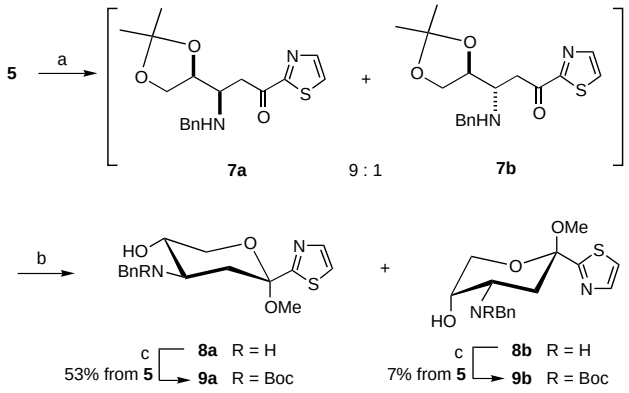


Figure 2. Enones **5** and **6** employed for model studies.

Thus, the reaction of a slight excess of benzylamine (1.2 equiv) with the enone **5** at $-70\,^{\circ}C$ in CH_2Cl_2 afforded after five hours a mixture of β-amino ketones **7a** and **7b** (Scheme 2). The NMR spectrum of this mixture at room temperature revealed that these compounds were present in a nearly 1:1 ratio. However, quenching the reaction mixture at



Scheme 2. Addition of benzylamine to the enone **5** and cyclization of the adducts. a) $BnNH_2$, CH_2Cl_2, $-70\,^{\circ}C$; b) HCl, MeOH, $-70\,^{\circ}C$ to RT; c) Boc_2O, dioxane, RT.

$-70\,^{\circ}C$ with methanolic HCl afforded a mixture of 1-(2-thiazolyl)-pentopyranosides **8a** and **8b** in 9:1 ratio by NMR analysis. The same ratio was assumed reasonably for their precursors **7a** and **7b** at $-70\,^{\circ}C$ while epimerization occurred at room temperature, very likely through a retro-Michael-type process.[12] While the separation of epimeric methyl pyranosides **8a** and **8b** was unsuccessful, the first-order 300 MHz ^1H NMR spectrum of the mixture gave unequivocal information on their structure. The all *trans*-diaxial sequence of protons in the major product **8a** ($J_{2ax,3} = 12.7$, $J_{3,4} = 12.0$, $J_{4,5ax} = 9.3$ Hz) indicated the equatorial arrangement of both the benzylamino and hydroxy groups and consequently

Abstract in Italian: *L' addizione coniugata di benzilammina a tre polialcossi tiazolil-α,β-enoni derivanti da* D-*gliceraldeide,* D-*eritrosio e* D-*mannosio conduce stereoselettivamente ai corrispondenti sin β-amminochetoni. Questi composti sono stati trasformati in metil 1-(2-tiazolil)-piranosidi mediante chetalizzazione e successivamente in acidi 4-ammino-3,4-didesossi-ulosonici attraverso la conversione dell' anello tiazolico in gruppo formilico seguita dall' ossidazione di quest' ultimo a gruppo carbossilico. Utilizzando questo schema sintetico è stato preparato l' acido 4-acetammido-nonulosonico iso-Neu4Ac, un isomero di posizione dell' acido sialico Neu5Ac, a partire dall' α,β-enone ottenuto dal* D-*mannosio. Una sintesi più efficiente dell' iso-Neu4Ac è stata eseguita impiegando la trimetilsilil azide come nucleofilo azotato. Anche l' addizione coniugata di nitrometano in presenza di DBU agli stessi tre enoni avviene in resa elevata e con una buona sin selettività per dare β-nitrometilchetoni che sono stati in seguito ciclizzati in ambiente acido nei corrispondenti metil piranosidi. Partendo dal piranoside ottenuto dal* D-*mannosio è stato preparato un acido 4-acetamidometil-3,4-didesossi-ulosonico, un omologo superiore dell' iso-Neu4Ac, mediante riduzione del gruppo nitro a gruppo amminico e trasformazione dell' anello tiazolico in gruppo carbossilico.*

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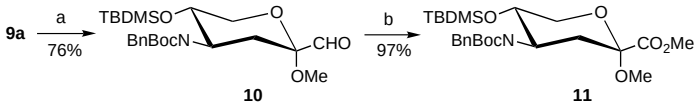
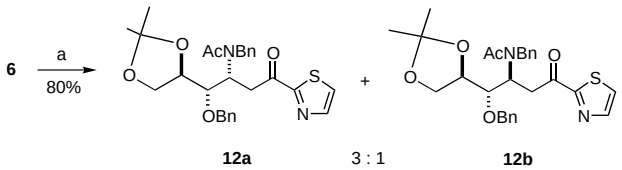
demonstrated that the precursor β-amino ketone was the *syn*-isomer **7a**. The NMR spectrum of the minor isomer **8b** ($J_{2ax,3} = 12.7$, $J_{3,4} = 3.1$, $J_{4,5eq} = 1.8$ Hz) consistently confirmed that the above ring substituents are located in an axial–equatorial arrangement and therefore the original addition product was the *anti*-isomer **7b**. Finally, compounds **8a** and **8b** were converted into the *N*-Boc derivatives **9a** and **9b** (53 and 7% yield, respectively, from **5**) whose assigned structure was confirmed by ^{1}H NMR spectra after separation.[13, 14]

The final reaction sequence highlighted the role of the thiazole ring at the anomeric carbon in this synthetic approach to amino ulosonic acids. Having been compatible with the various reaction conditions under which the adducts **7a** and **7b** were formed and then converted into the methyl pyranosides **9a** and **9b**, the main service of thiazole stemmed from its equivalence with the formyl group.[15] Thus, after protection of the hydroxy group of compound **9a** as *tert*-butyldimethylsilyl ether, application of the standard one-pot thiazole-to-formyl deblocking protocol[16] (N-methylation, reduction, hydrolysis) afforded the aldosulose **10** in 76% isolated yield[17] (Scheme 3). The double protection of the amino group as *N*-benzyl-*N*-*tert*-butoxycarbonyl (*N*-BnBoc) proved to be necessary in this step since the single protection as *N*-benzyl was incompatible with the reaction sequence of the unmasking protocol.[18] Finally, the oxidation of **10** (Ag_2O, THF/H_2O) followed by esterification with diazomethane gave the 4-amino substituted 3-deoxy ulosonate **11** in almost quantitative yield (39% overall yield from the enone **5**).



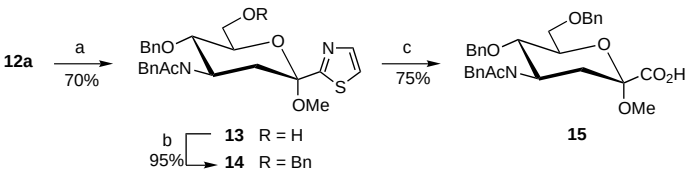
Scheme 3. Cleavage of the thiazole ring of **9a** and oxidation to the ulosonate **11**. a) tBuMe$_2$SiCl, imidazole, DMF, 80 °C; then MeOTf, CH_3CN, RT; then $NaBH_4$, MeOH, RT; then $CuCl_2$, CuO, CH_3CN/H_2O, RT; b) Ag_2O, THF/H_2O, RT; then CH_2N_2, Et_2O, RT.

An essentially identical procedure was followed starting from the D-erythrose derived enone **6**. Succinctly, the addition of benzylamine to **6** at low temperature in CH_2Cl_2 followed by treatment with acetic anhydride afforded a mixture of non-epimerizable *N*,*N*-diprotected amino ketones **12a** and **12b** in 3:1 ratio and 80% overall yield (Scheme 4). These compounds



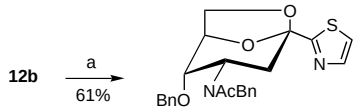
Scheme 4. Addition of benzylamine to the enone **6**. a) $BnNH_2$, CH_2Cl_2, -50 to -20 °C; then Ac_2O.

were separated by preparative HPLC and adequately characterized through their methyl pyranosides. Thus, **12a** treated with methanolic HCl afforded the 1-(2-thiazolyl)-hexopyranoside[14] **13** (Scheme 5) whereas the epimer **12b** gave the 1,6-



Scheme 5. Cyclization of the amino ketone **12a** and unmasking of the ulosonate **15**. a) HCl, MeOH, RT; b) BnBr, NaH, DMF, 0 °C to RT; c) MeOTf, CH_3CN, RT; then $NaBH_4$, MeOH, RT; then $CuCl_2$, CuO, CH_3CN/H_2O, RT; then Ag_2O, THF/H_2O, RT.

anhydro sugar derivative **16** (Scheme 6). Compound **13** was first converted into **14** by protection of the free hydroxy group as *O*-benzyl ether and then into the methyl ulosonidonic acid **15** (75% yield) by the same reaction sequence described above for **9a** involving the aldehyde liberation from the thiazole ring and oxidation to carboxylic acid. The double protection of nitrogen with the benzyl and acetyl group (*N*-AcBn) proved equally suitable in this synthesis.



Scheme 6. Cyclization of the amino ketone **12b**. a) HCl, MeOH, RT.

In conclusion, the addition of benzylamine to the α,β-enones **5** and **6** occurred with good to modest levels of *syn*-selectivity. The same selectivity was observed in the reactions of these enones with sodium benzyl oxide.[1] Thus, the same modified Felkin-type model[19] as exemplified in Figure 3 can be assumed for these conjugate addition reactions. Quite important, particularly for synthetic purposes, is the observation that the reaction with benzylamine is reversible and consequently requires appropriate reaction conditions and workup procedures of the reaction mixture for the isolation of the products of kinetic selectivity.

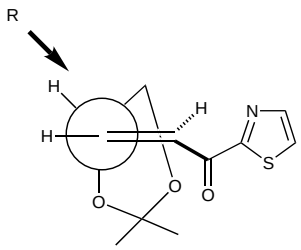


Figure 3. Transition state model for the addition of benzyl oxide anion ($R = BnO^-$) and benzylamine ($R = BnNH_2$) to the enone **5**.

Synthesis of 4-acetamido-nonulosonic acid 3: With the above set of information at hand, we were able to complete[20] the synthesis of the neuraminic acid analogue **3**. For this task we considered the D-mannose derived α,β-enone **17** as substrate for the conjugate addition of benzylamine (Scheme 7). This enone was previously employed in our synthesis of KDN **2** through reaction with sodium benzyl oxide.[1] Thus, the

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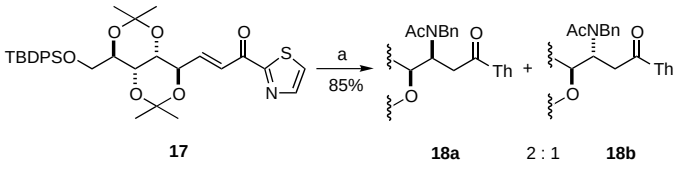
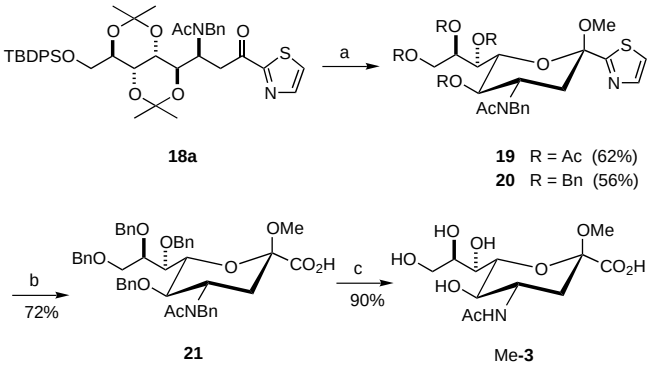


Scheme 7. Addition of benzylamine to the enone **17**. Th = 2-thiazolyl. a) $BnNH_2$, CH_2Cl_2, $-50\,^{\circ}C$; then Ac_2O.

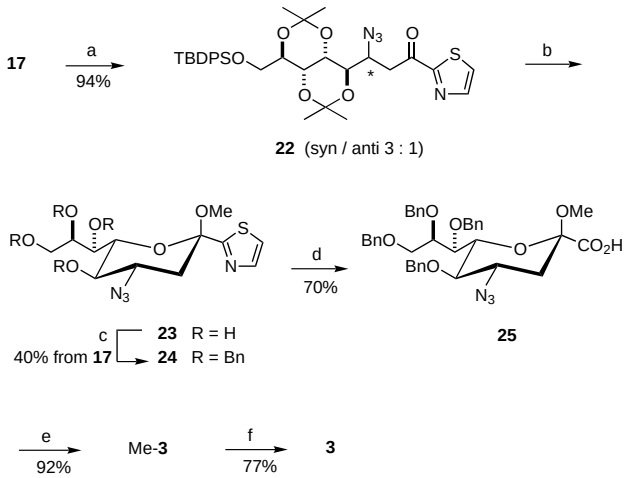
addition of benzylamine to **17** and acetylation at low temperature, as described above for the reaction with **6**, afforded the *syn*-adduct **18a** and the *anti*-isomer **18b** in 2:1 ratio and 85% overall yield after separation by preparative HPLC (Scheme 7). The configuration at the newly formed stereocenter of the major isomer **18a** was assigned following its conversion into the peracetylated methyl pyranoside **19** (Scheme 8). The ^1H NMR spectrum of this compound showed large coupling constant values for the pyranoside ring protons ($J_{2ax,3} = 13.2$, $J_{3,4} = J_{4,5} = 9.9$ Hz), thus indicating a *trans*-diequatorial arrangement of the *N*-benzylacetamido and acetoxy groups at C-3 and C-4 in a $^1C_4$ conformation. The β-D anomeric configuration was proven by the NOE between the methoxy group and the axial proton at C-5.



Scheme 8. Synthesis of methyl *iso*-Neu4Ac Me-**3** by the benzylamine route. a) HCl, MeOH, RT; then Ac_2O, pyridine, RT or BnBr, NaH, DMF, 0 °C to RT; b) MeOTf, CH_3CN, RT; then $NaBH_4$, MeOH, RT; then $CuCl_2$, CuO, CH_3CN-H_2O, RT; then Ag_2O, THF/H_2O, RT; c) Li, refluxing NH_3.

For the prosecution of the synthesis, compound **18a** was converted into the perbenzylated derivative **20** in order to facilitate the protective group removal in the final stage. Then, compound **20** was subjected to the usual cleavage of the thiazole ring and oxidation to give the all protected nonulosonic acid **21**. While O-debenzylation of **21** was easily carried out by catalytic hydrogenation, the removal of the *N*-benzyl group was problematical. Both O- and N-debenzylation were simultaneously carried out by the use of lithium in liquid ammonia to give the methyl *O*-glycoside derivative Me-**3.** Unfortunately, this compound was contaminated by numerous by-products as shown by NMR analysis. Several efforts to remove these impurities by reverse-phase or ion-exchange chromatography were unsuccessful.

Instead of looking for improved conditions that could overcome the above difficulties, we considered a synthetic approach to the target product **3** by the replacement of benzylamine with the azide ion as an ammonia equivalent. This drastic change of synthetic plan was also dictated by the modest level of selectivity of the conjugate addition of benzylamine to the enone **17**. By contrast, the reaction of **17** with trimethylsilyl azide ($TMSN_3$) and 10% Bu_4NF in CH_2Cl_2 at $-20\,^{\circ}C$ proceeded with a more substantial stereoselectivity to give the β-azido ketone **22** (94% yield) as a mixture of diastereomers in a 3:1 ratio determined by ^1H NMR analysis (Scheme 9). No epimerization was observed when the reaction mixture was stirred at room temperature for several

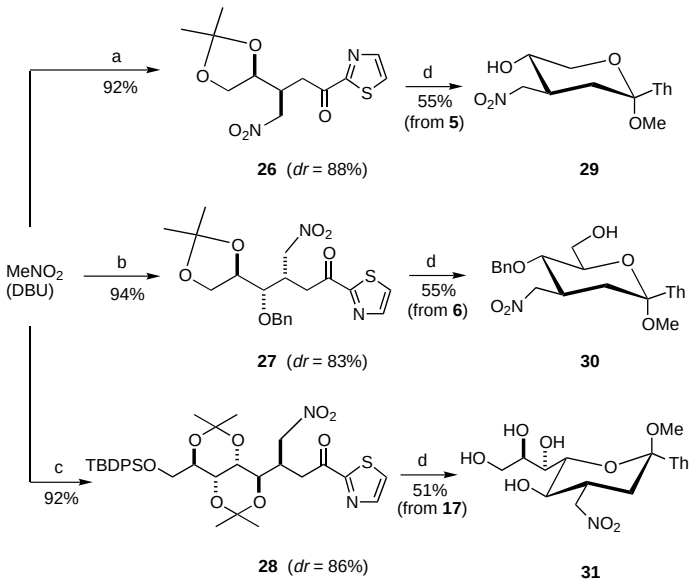


Scheme 9. Synthesis of *iso*-Neu4Ac **3** by the azide route. a) $TMSN_3$, TBAF, CH_2Cl_2, $-20\,^{\circ}C$; b) HCl, MeOH, RT; c) BnBr, NaH, DMF, 0 °C to RT; d) MeOTf, CH_3CN, RT; then $NaBH_4$, MeOH, RT; then $CuCl_2$, CuO, CH_3CN/H_2O, RT; then Ag_2O, THF/H_2O, RT; e) Li, refluxing NH_3; then Ac_2O, MeOH, RT; f) AcOH/H_2O, 100 °C.

hours although the separation of the individual *syn*- and *anti*-stereoisomers by chromatography was unsuccessful as a result of considerable decomposition. Thus, the mixture was processed as in previous reaction schemes, that is treated with methanolic HCl to remove the hydroxy protective groups and induce ketalization. The major product methyl pyranoside **23** was isolated in a pure form by preparative HPLC after perbenzylation to **24** (40% overall yield from **17**). The latter compound was suitable for a complete structural characterization by NMR analysis. The unequivocally established stereochemistry of the azido group in **24** ($J_{2ax,3} = 12.2$, $J_{3,4} = 9.0$, $J_{4,5} = 10.0$ Hz) confirmed that the *syn*-adduct was the major product of the 1,4-conjugate addition of $TMSN_3$ to the α,β-enone **17**. The synthesis was continued from **24** by the standard conversion of the thiazole-to-formyl and oxidation to the carboxylic group to give the 4-azido-ulosonic acid **25**. As expected on the basis of our earlier work,[21] the unmasking of the aldehyde from the thiazole ring was compatible with the presence of the azido group. Next, the reduction of the azido to amino group proceeded rapidly and cleanly by treatment of **25** with lithium in liquid ammonia, which concomitantly removed the *O*-benzyl groups. The *N*-acetylation of the resulting crude material afforded Me-**3** (92%) that was easily isolated in a pure form. Finally, this compound was transformed into *iso*-Neu4Ac (**3**) by hydrolysis of the glycosidic linkage with AcOH/H_2O at 100 °C for one hour.[22]

In conclusion, instead of the planned route involving benzylamine, the synthesis of **3** was more conveniently carried out by the use of $TMSN_3$, in which the azido group serves as the amino precursor. In pursuing this synthetic target, some information on the preferential *syn*-selectivity of the conjugate addition reactions of these nitrogen nucleophiles to some chiral polyalkoxy enones was obtained.[23] While the stereoselective addition of benzylamine to a chiral γ-alkoxy enoate is well documented,[9a,b,c,f,g] the use of $TMSN_3$ as a reaction partner in 1,4-conjugate addition reactions has been reported in a few instances with simple nonchiral model systems.[24]

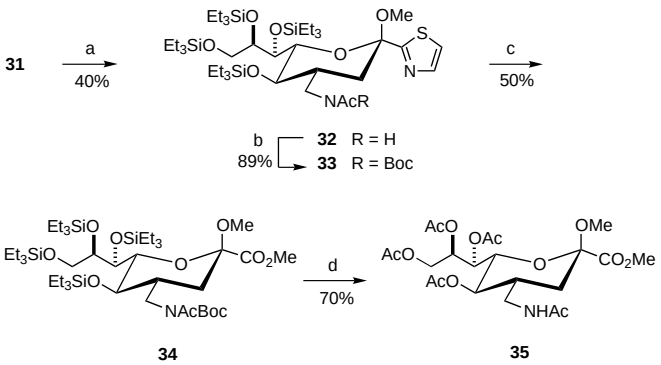
Addition of nitromethane: As for the second main target of our program, the branched amino-ulosonic acid **4**, it was quite logical to consider nitromethane as an appropriate reagent for the introduction of the aminomethyl group. A study of the Michael addition to the enones **5**, **6**, and **17** was initially carried out in order to obtain some information on the efficiency and selectivity of this reaction (Scheme 10). Guided



Scheme 10. Addition of nitromethane to the enones **5**, **6**, and **17** and cyclization of the adducts. Th = 2-thiazolyl. a) **5**, CH_2Cl_2, $-20\,^{\circ}C$; b) **6**, CH_2Cl_2, $-20\,^{\circ}C$; c) **17**, CH_2Cl_2, $-20\,^{\circ}C$; d) HCl, MeOH, RT.

by the recent work of others[25] and after considerable experimentation, the reactions were carried out in CH_2Cl_2 at $-20\,^{\circ}C$ with 5 equivalents of nitromethane and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.7 equiv) as a base. Under these optimized conditions, each reaction proceeded with good selectivity (*dr* 83–88% by ^1H NMR analysis) to give the corresponding *syn*-adduct as a main product (compounds **26**–**28**). These products, contaminated by the *anti*-isomers (not shown), were isolated in fairly good yields (92–94%). Because of the difficult purification, crude compounds **26**, **27**, and **28** were submitted to the usual treatment with methanolic HCl to give the corresponding methyl pyranosides **29** (55%), **30** (55%), and **31** (51%) in the indicated isolated yield from the corresponding starting enone. These compounds were adequately characterized by NMR spectroscopy.[26] In particular they all showed coupling constant values ($J_{3,4} = 9.8-11.1$ Hz) consistent with the *trans*-diequatorial disposition of the nitromethyl and hydroxy groups, thus confirming the structure of the *syn*-adducts **26**–**28**. The same main stereochemical outcome has been recently reported for the conjugate addition of nitromethane-DBU to chiral enoates.[25]

Synthesis of 4-acetamidomethyl-nonulosonate 35: After a satisfactory access to the methyl pyranoside **31** was established, the reduction of the nitromethyl to aminomethyl group and the conversion of the thiazole ring into the carboxylate function remained to be carried out for the synthesis of **4**. The convenient order of these transformations was far from being a trivial problem. Nevertheless, the procedure adopted was as follows. After various unsuccessful attempts to protect the free hydroxy groups[27] of **31**, the reduction of the nitro group was carried out directly on this compound with $LiAlH_4$ in refluxing THF. The selective acetylation of the resulting amino group and protection of the hydroxy groups as *O*-triethylsilyl ether afforded compound **32** (Scheme 11). Since



Scheme 11. Synthesis of acetamidomethyl ulosonate **35**, a protected derivative of **4**. a) $LiAlH_4$, THF, reflux; then Ac_2O, MeOH, RT; then Et_3SiOTf, pyridine, RT; b) Boc_2O, Et_3N, DMAP, RT; c) MeOTf, CH_3CN, RT; then $NaBH_4$, MeOH, RT; then $CuCl_2$, CuO, CH_3CN/H_2O, RT; then I_2, KOH, MeOH, RT; d) CF_3CO_2H, CH_2Cl_2, RT; then Ac_2O, pyridine, RT.

we found that the reaction sequence involved in the thiazole-to-formyl conversion was incompatible with the presence of the acetamido group,[28] a temporary double protection was achieved by the *tert*-butoxycarbonyl group. Compound **33** obtained in this way was transformed into the methyl ester **34** by sequential cleavage of the thiazole ring and oxidation of the formyl group. Finally the *N*-Boc group was removed with trifluoroacetic acid (TFA) while O-desilylation occurred at the same time. The acetylation of the tetrol afforded the peracetylated methyl ulosonate **35**, a suitably protected derivative of the target 4-*N*-acetylaminomethyl-nonulosonic acid **4**.

Conclusion

In summary, a route to 4-amino- and 4-aminomethyl-3-deoxy-ulosonic acids has been disclosed. This route is mainly based on the conjugate addition of the nitrogen nucleophiles

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benzylamine and trimethylsilyl azide, and the carbanion of nitromethane to sugar-derived enones. It was mainly the sense and level of stereoselectivity of these initial reactions that established the feasibility and the efficiency of the method. The conversion to the final products of the Michael-type adducts was straightforward through well established methods that in some cases needed some optimized conditions. Extension of this chemistry for the preparation of various aminated ulosonic acids should be easily achieved.

Experimental Section

All moisture-sensitive reactions were performed under a nitrogen atmosphere with oven-dried glassware. Anhydrous solvents were dried over standard drying agents[29] and freshly distilled prior to use. Commercially available powdered 4 Å molecular sieves (50 μm average particle size) were used without further activation. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid. Flash column chromatography[30] was performed on silica gel 60 (230–400 mesh). Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at $20 \pm 2\,^{\circ}C$ in the stated solvent. ^1H (300 MHz) NMR were recorded at RT for $CDCl_3$ solutions, unless otherwise specified. Assignments were aided by homo- and heteronuclear two-dimensional NMR experiments. Enones **5**, **6**, and **17** were prepared as reported.[1]

(3*R*,4*S*)- and **(3*S*,4*S*)-3-*N*-Benzylamino-4,5-dihydroxy-4,5-*O*-isopropylidene-1-(2-thiazolyl)-1-pentanone (7a** and **7b)**: Freshly distilled benzylamine (438 µL, 4.01 mmol) was slowly added to a cooled ($-70\,^{\circ}C$), stirred solution of **5** (800 mg, 3.34 mmol) in anhydrous CH_2Cl_2 (34 mL). The solution was stirred at $-70\,^{\circ}C$ for 5 h, then diluted with saturated aqueous $NaHCO_3$ (20 mL) and warmed to room temperature. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (50 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated to give a 1:1 mixture of **7a** and **7b** (980 mg). ^1H NMR of **7a**: $\delta = 7.97$, 7.56 (2 d, 2 H, $J = 3.1$ Hz), 7.30 (m, 5 H, Ph), 4.25 (ddd, 1 H, $J = 2.4$, 4.9, 11.3 Hz), 4.00 (dd, 1 H, $J = 6.5$, 8.1 Hz), 3.88, 3.79 (2 d, 2 H, $J = 13.3$ Hz), 3.83 (ddd, 1 H, $J = 3.3$, 4.9, 6.5 Hz), 3.76 (dd, 1 H, $J = 3.3$, 8.1 Hz), 3.38 (dd, 1 H, $J = 5.7$, 11.3 Hz), 3.30 (dd, 1 H, $J = 2.4$, 5.7 Hz), 1.35, 1.25 (2 s, 6 H); ^1H NMR of **7b**: $\delta = 7.97$, 7.64 (2 d, 2 H, $J = 3.1$ Hz), 7.30 (m, 5 H, Ph), 4.17 (m, 1 H), 4.07 (dd, 1 H, $J =$ 6.5, 8.1 Hz), 3.88, 3.79 (2 d, 2 H, $J = 13.3$ Hz), 3.86 (m, 1 H), 3.76 (dd, 1 H, $J = 3.3$, 8.1 Hz), 3.38 (dd, 1 H, $J = 5.7$, 11.3 Hz), 3.30 (dd, 1 H, $J = 2.4$, 5.7 Hz), 1.35, 1.25 (2 s, 6 H).

Methyl 3-*N*-benzylamino-2,3-dideoxy-1-(2-thiazolyl)-*α*-D-*threo*- and **-*β*-D-*erythro*-pentopyranoside (8a** and **8b)**: Freshly distilled benzylamine (438 µL, 4.01 mmol) was slowly added to a cooled ($-70\,^{\circ}C$), stirred solution of **5** (800 mg, 3.34 mmol) in anhydrous CH_2Cl_2 (50 mL). The solution was stirred at $-70\,^{\circ}C$ for 5 h, then diluted with an 8% (*w*/*w*) solution of HCl in anhydrous MeOH (12 mL). The solution was stirred at room temperature for 14 h, then concentrated. The residue was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with AcOEt (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give a 9:1 mixture of **8a** and **8b** (930 mg). ^1H NMR of **8a** ($CDCl_3 + D_2O$): $\delta = 7.81$, 7.30 (2 d, 2 H, $J = 3.1$ Hz, Th), 7.30–7.20 (m, 5 H, Ph), 4.00 (dd, 1 H, $J_{4,5eq} = 4.4$, $J_{5eq,5ax} = 9.5$ Hz, H-5eq), 3.92, 3.67 (2 d, 2 H, $J = 12.6$ Hz, PhCH_2), 3.60 (dd, 1 H, $J_{4,5ax} = 9.3$ Hz, H-5ax), 3.45 (ddd, 1 H, $J_{2eq,3} = 4.4$, $J_{3,4} = 12.0$, $J_{2ax,3} = 12.7$ Hz, H-3), 3.44 (ddd, 1 H, H-4), 3.10 (s, 3 H, MeO), 2.90 (dd, 1 H, $J_{2ax,2eq} = 13.5$ Hz, H-2eq), 1.50 (dd, 1 H, H-2ax); ^1H NMR selected data of **8b** ($CDCl_3 + D_2O$): $\delta = 7.80$ (d, 1 H, $J = 3.1$ Hz, Th), 7.30–7.20 (m, 6 H, Ph, Th), 4.07 (dd, 1 H, $J_{4,5eq} = 1.8$, $J_{5eq,5ax} = 8.1$ Hz, H-5eq), 3.83, 3.75 (2 d, 2 H, $J = 12.6$ Hz, PhCH_2), 3.28 (ddd, 1 H, $J_{3,4} = 3.1$, $J_{2eq,3} = 4.8$, $J_{2ax,3} = 12.7$ Hz, H-3), 3.09 (s, 3 H, MeO), 2.20 (dd, 1 H, $J_{2ax,2eq} =$ 13.5 Hz, H-2eq), 1.80 (dd, 1 H, H-2ax). This crude mixture was used for the next step without further purification.

Methyl 3-(*N*-benzyl-*N*-*tert*-butoxycarbonylamino)-2,3-dideoxy-1-(2-thiazolyl)-*α*-D-*threo*- and **-*β*-D-*erythro*-pentopyranoside (9a** and **9b)**: A solution of crude **8a** and **8b** (930 mg, ~2.8 mmol) and di-*tert*-butyl dicarbonate (1.20 g, 5.5 mmol) in 1,4-dioxane (30 mL) was kept at room temperature for 14 h, then concentrated. The residue was dissolved in Et_2O (100 mL), washed with saturated aqueous $NaHCO_3$ (20 mL), dried (Na_2SO_4), and concentrated. The crude product was eluted from a column of silica gel with 4:1 petroleum ether/Et_2O to give first **9a** (750 mg, 53% from **5**) as a white foam: $[\alpha]_D = +21.7$ ($c = 0.2$, $CHCl_3$); ^1H NMR ([D]$_6$DMSO, 150 °C): $\delta = 7.80$, 7.60 (2 d, 2 H, $J = 3.1$ Hz, Th), 7.30–7.10 (m, 5 H, Ph), 4.51, 4.39 (2 d, 2 H, $J = 16.2$ Hz, PhCH_2), 4.08 (ddd, 1 H, $J_{2eq,3} =$ 4.0, $J_{3,4} = 12.1$, $J_{2ax,3} = 12.9$ Hz, H-3), 3.98 (ddd, 1 H, $J_{4,5eq} = 6.0$, $J_{4,5ax} =$ 10.1 Hz, H-4), 3.85 (dd, 1 H, $J_{5ax,5eq} = 10.1$ Hz, H-5eq), 3.50 (dd, 1 H, H-5ax), 3.0 (s, 3 H, MeO), 2.23 (dd, 1 H, $J_{2ax,2eq} = 12.1$ Hz, H-2eq), 2.01 (dd, 1 H, H-2ax), 1.40 (s, 9 H, *t*Bu); anal. calcd for $C_{21}H_{28}N_2O_5S$: C 59.98, H 6.71, N 6.66; found: C 59.76, H 6.67, N 6.62; eluted second was **9b** (98 mg, 7% from **5**) as a white foam: $[\alpha]_D = -21.8$ ($c = 0.3$, $CHCl_3$); ^1H NMR ([D]$_6$DMSO, 110 °C): $\delta = 7.75$, 7.60 (2 d, 2 H, $J = 3.1$ Hz, Th), 7.30–7.10 (m, 5 H, Ph), 4.63, 4.41 (2 d, 2 H, $J = 17.4$ Hz, PhCH_2), 4.18 (ddd, 1 H, $J_{3,4} =$ 3.0, $J_{2eq,3} = 4.1$, $J_{2ax,3} = 13.1$ Hz, H-3), 3.91 (ddd, 1 H, $J_{4,5eq} = 1.0$, $J_{4,5ax} =$ 2.6 Hz, H-4), 3.87 (dd, 1 H, $J_{5ax,5eq} = 12.1$ Hz, H-5eq), 3.81 (dd, 1 H, H-5ax), 3.20 (s, 3 H, MeO), 2.27 (dd, 1 H, $J_{2ax,2eq} = 12.3$ Hz, H-2ax), 2.10 (dd, 1 H, H-2eq), 1.40 (s, 9 H, *t*Bu); anal. calcd for $C_{21}H_{28}N_2O_5S$: C 59.98, H 6.71, N 6.66; found: C 59.63, H 6.60, N 6.57.

Methyl 4-(*N*-benzyl-*N*-*tert*-butoxycarbonylamino)-5-*O*-*tert*-butyldimethylsilyl-3,4-dideoxy-*α*-D-*threo*-hexosulopyranoside (10): A solution of **9a** (500 mg, 1.19 mmol), imidazole (162 mg, 2.38 mmol), and *tert*-butyldimethylsilyl chloride (197 mg, 1.31 mmol) in anhydrous DMF (24 mL) was stirred at 80 °C for 2 h, then cooled to room temperature and concentrated under high vacuum. The residue was dissolved in Et_2O (100 mL), washed with saturated aqueous $NaHCO_3$ (20 mL), dried (Na_2SO_4), and concentrated. The crude product was eluted from a column of silica gel with 1.5:1 petroleum ether/Et_2O to give methyl 3-(*N*-benzyl-*N*-*tert*-butoxycarbonylamino)-4-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-1-(2-thiazolyl)-*α*-D-*threo*-pentopyranoside (603 mg, 95%) as a white solid: M.p. 115–116 °C (from AcOEt/hexane); $[\alpha]_D = -31.1$ ($c = 0.9$, $CHCl_3$); ^1H NMR ([D]$_6$DMSO, 140 °C): $\delta = 7.75$, 7.61 (2 d, 2 H, $J = 3.0$ Hz, Th), 7.40–7.20 (m, 5 H, Ph), 4.65, 4.25 (2 d, 2 H, $J = 15.6$ Hz, PhCH_2), 4.35 (ddd, 1 H, $J_{4,5eq} = 6.2$, $J_{3,4} = 8.3$, $J_{4,5ax} = 10.4$ Hz, H-4), 3.90 (ddd, 1 H, $J_{2eq,3} = 4.2$, $J_{2ax,3} = 13.3$ Hz, H-3), 3.85 (dd, 1 H, $J_{5ax,5eq} = 10.4$ Hz, H-5eq), 3.48 (dd, 1 H, H-5ax), 3.0 (s, 3 H, MeO), 2.30 (dd, 1 H, $J_{2ax,2eq} = 13.5$ Hz, H-2ax), 2.18 (dd, 1 H, H-2eq), 1.40 (s, 9 H, *t*BuO), 0.90 (s, 9 H, *t*BuSi), 0.15, 0.10 (2 s, 6 H, Me_2Si); anal. calcd for $C_{27}H_{42}N_2O_5SSi$: C 60.64, H 7.92, N 5.24; found: C 60.45, H 7.89, N 5.23.

A mixture of the silylated derivative (534 mg, 1.00 mmol), activated 4 Å powdered molecular sieves (2.0 g), and anhydrous CH_3CN (10 mL) was stirred at room temperature for 10 min, then methyl triflate (147 µL, 1.30 mmol) was added. The suspension was stirred at room temperature for 15 min and then concentrated to dryness. $NaBH_4$ (83 mg, 2.20 mmol) was added to a cooled (0 °C), stirred suspension of the crude *N*-methylthiazolium salt in CH_3OH (10 mL). The mixture was stirred at room temperature for an additional 5 min, diluted with acetone (2 mL), filtered through a pad of celite, and concentrated. A solution of the crude mixture of diastereomeric thiazolidines in CH_3CN (10 mL) and H_2O (1 mL) was treated, under vigorous stirring, with CuO (636 mg, 8.00 mmol) and then $CuCl_2 \cdot 2H_2O$ (170 mg, 1.00 mmol). The mixture was stirred at room temperature for 15 min, then filtered through a pad of celite, and concentrated to remove acetonitrile and most of the water (bath temperature not exceeding 40 °C); the brown residue was triturated with Et_2O (4 × 10 mL), and the liquid phase was pipetted and filtered through a pad (3 × 1 cm, d × h) of Florisil (100–200 mesh) to afford a colorless solution. After a further washing of Florisil with AcOEt (10 mL), the combined organic phases were concentrated to yield almost pure (NMR analysis) aldehyde **10** (384 mg, ~80%) as a syrup. ^1H NMR ([D]$_6$DMSO, 140 °C): $\delta = 9.40$ (s, 1 H, CHO), 7.35–7.20 (m, 5 H, Ph), 4.63, 4.22 (2 d, 2 H, $J = 15.7$ Hz, PhCH_2), 4.30 (ddd, 1 H, $J_{5,6eq} =$ 7.0, $J_{5,6ax} = 10.5$, $J_{4,5} = 10.5$ Hz, H-5), 3.80 (dd, 1 H, $J_{6ax,6eq} = 10.5$ Hz, H-6eq), 3.75 (ddd, 1 H, $J_{3eq,4} = 5.2$, $J_{3ax,4} = 12.5$ Hz, H-4), 3.35 (dd, 1 H, H-6ax), 3.20 (s, 3 H, MeO), 2.10 (dd, 1 H, $J_{3ax,3eq} = 13.0$ Hz, H-3ax), 1.60 (dd, 1 H, H-3eq), 1.40 (s, 9 H, *t*BuO), 0.95 (s, 9 H, *t*BuSi), 0.11, 0.10 (2 s, 6 H, Me_2Si).

Methyl [methyl 4-(*N*-benzyl-*N*-*tert*-butoxycarbonylamino)-5-*O*-*tert*-butyldimethylsilyl-3,4-dideoxy-*α*-D-*threo*-hexopyranosid]onate (11): A freshly prepared solution of NaOH (258 mg, 6.40 mmol) in H_2O (5 mL) was added to a stirred solution of silver nitrate (543 mg, 3.20 mmol) in H_2O (5 mL). A solution of crude aldehyde **10** (384 mg, ~0.80 mmol) in freshly distilled THF (3 mL) was added to the resulting suspension of silver oxide. The mixture was stirred at room temperature for 48 h, then acidified with acetic

acid, filtered through celite, and concentrated. The residue was dissolved in CH_2Cl_2 (50 mL), washed with H_2O (5 mL), dried (Na_2SO_4), and concentrated.

A cooled (0 °C), stirred solution of the crude acid in Et_2O (10 mL) was treated with an excess of ethereal diazomethane for 10 min, then concentrated. The residue was eluted from a column of silica gel with 5:1 petroleum ether/AcOEt to give **11** (395 mg, 97 %) as a syrup: $[\alpha]_D = -6.1$ ($c = 0.9$, $CHCl_3$); ^{1}H NMR ([D]$_6$DMSO, 120 °C): $\delta = 7.36-7.20$ (m, 5H, Ph), 4.61, 4.22 (2d, 2H, $J = 16.0$ Hz, PhCH_2), 4.27 (ddd, 1H, $J_{5,6eq} = 5.5$, $J_{4,5} = J_{5,6ax} = 10.4$ Hz, H-5), 3.75 (dd, 1H, $J_{6ax,6eq} = 10.4$ Hz, H-6eq), 3.75 (ddd, 1H, $J_{3eq,4} = 6.8$, $J_{3ax,4} = 13.0$ Hz, H-4), 3.67, 3.13 (2s, 6H, 2Me), 3.28 (dd, 1H, H-6ax), 2.25 (dd, 1H, $J_{3ax,3eq} = 13.0$ Hz, H-3ax), 1.79 (dd, 1H, H-3eq), 1.40 (s, 9H, *t*BuO), 0.90 (s, 9H, *t*BuSi), 0.12, 0.11 (2s, 6H, Me_2Si); anal. calcd for $C_{26}H_{43}NO_7Si$: C 61.27, H 8.50, N 2.75; found: C 61.25, H 8.59, N 2.63.

(3*R*,4*S*,5*S*)- and **(3*S*,4*S*,5*S*)-3-(*N*-Acetyl-*N*-benzylamino)-4-*O*-benzyl-4,5,6-trihydroxy-5,6-*O*-isopropylidene-1-(2-thiazolyl)-1-hexanone (12a** and **12b)**: Freshly distilled benzylamine (2.13 mL, 19.47 mmol) was slowly added to a cooled (−50 °C), stirred solution of **6** (2.00 g, 5.56 mmol) in anhydrous CH_2Cl_2 (56 mL). The solution was stirred at −50 °C for 5 h, warmed to −20 °C and stirred for an additional 14 h, then diluted with acetic anhydride (1.84 mL, 19.47 mmol). The solution was stirred at −20 °C for 30 min, then warmed to room temperature and concentrated. The crude products were purified by preparative HPLC (silica, 6 μm, 60 Å, 3:1 cyclohexane/AcOEt, UV detection $\lambda = 254$ nm). Eluted first was **12a** (1.70 g, 60 %) as a white foam: $[\alpha]_D = +74.3$ ($c = 0.7$, $CHCl_3$); ^{1}H NMR ([D]$_6$DMSO, 140 °C): $\delta = 8.0$, 7.95 (2d, 2H, $J = 3.0$ Hz, Th), 7.40–7.00 (m, 10H, 2Ph), 4.80 (m, 1H), 4.78, 4.51 (2d, 2H, $J = 16.0$ Hz, PhCH_2N), 4.71, 4.58 (2d, 2H, $J = 11.3$ Hz, PhCH_2O), 4.15 (q, 1H, $J = 5.9$ Hz), 4.04–3.96 (m, 2H), 3.86 (dd, 1H, $J = 5.9$, 8.9 Hz), 3.56 (d, 2H, $J = 6.5$ Hz), 2.10 (s, 3H, Ac), 1.35, 1.25 (2s, 6H, 2Me); anal. calcd for $C_{28}H_{32}N_2O_5S$: C 66.12, H 6.34, N 5.51; found: C 66.30, H 6.58, N 5.50; eluted second was **12b** (565 mg, 20 %) as a white foam: $[\alpha]_D = -68.5$ ($c = 0.3$, $CHCl_3$); ^{1}H NMR ([D]$_6$DMSO, 140 °C): $\delta = 7.99$, 7.95 (2d, 2H, $J = 3.0$ Hz, Th), 7.40–7.10 (m, 10H, 2Ph) 4.84 (q, 1H, $J = 6.5$ Hz), 4.70, 4.54 (2d, 2H, $J = 16.6$ Hz, PhCH_2N), 4.69, 4.56 (2d, 2H, $J = 11.3$ Hz, PhCH_2O), 4.16 (m, 1H), 4.00 (dd, 1H, $J = 4.1$, 5.9 Hz), 3.90 (dd, 1H, $J = 6.5$, 7.7 Hz), 3.81 (dd, 1H, $J = 6.5$, 7.7 Hz), 3.67 (dd, 1H, $J = 5.3$, 17.8 Hz), 3.39 (dd, 1H, $J = 7.1$, 17.8 Hz), 2.10 (s, 3H, Ac), 1.35, 1.25 (2s, 6H, 2Me); anal. calcd for $C_{28}H_{32}N_2O_5S$: C 66.12, H 6.34, N 5.51; found: C 65.82, H 6.52, N 5.29.

Methyl 3-(*N*-acetyl-*N*-benzylamino)-4-*O*-benzyl-2,3-dideoxy-1-(2-thiazolyl)-α-D-*arabino*-hexopyranoside (13): A solution of **12a** (1.52 g, 3.00 mmol) in an 8 % (*w*/*w*) solution of HCl in anhydrous MeOH (15 mL) was kept at room temperature for 14 h, then concentrated. The residue was diluted with saturated aqueous $NaHCO_3$ (30 mL) and extracted with AcOEt (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 1.5:1 AcOEt/cyclohexane to give **13** (1.01 g, 70 %) as a white foam: $[\alpha]_D = +15.2$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR ([D]$_6$DMSO + D_2O, 120 °C): $\delta = 7.75$, 7.60 (2d, 2H, $J = 3.0$ Hz, Th), 7.40–7.10 (m, 10H, 2Ph), 4.66–4.24 (m, 5H), 4.08 (m, 1H), 3.88–3.66 (m, 3H), 3.05 (s, 3H, MeO), 2.30 (dd, 1H, $J_{2eq,3} = 3.6$, $J_{2eq,2ax} = 12.1$ Hz, H-2eq), 2.20–1.95 (m, 4H, H-2ax, Ac); anal. calcd for $C_{26}H_{30}N_2O_5S$: C 64.70, H 6.27, N 5.80; found: C 64.82, H 6.38, N 5.70.

Methyl 3-(*N*-acetyl-*N*-benzylamino)-4,6-di-*O*-benzyl-2,3-dideoxy-1-(2-thiazolyl)-α-D-*arabino*-hexopyranoside (14): To a cooled (0 °C), stirred solution of **13** (965 mg, 2.00 mmol) in DMF (8 mL) was added portionwise NaH (160 mg, 4.00 mmol, of a 60% dispersion in oil) and, after 30 min, benzyl bromide (357 μL, 3.00 mmol). The mixture was stirred at room temperature for 30 min, then treated with MeOH (1 mL), stirred for an additional 10 min, diluted with H_2O (30 mL), and extracted with Et_2O (2 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 1:1 cyclohexane/AcOEt to give **14** (1.09 g, 95 %) as a syrup: $[\alpha]_D = +30.8$ ($c = 0.3$, $CHCl_3$); ^{1}H NMR ([D]$_6$DMSO, 120 °C): $\delta = 7.78$, 7.65 (2d, 2H, $J = 3.0$ Hz, Th), 7.40–7.15 (m, 15H, 3Ph), 4.75–4.20 (m, 8H), 3.90–3.80 (m, 3H), 3.05 (s, 3H, MeO), 2.40–2.25 (m, 1H, H-2eq), 2.15–1.95 (m, 4H, H-2ax, Ac); anal. calcd for $C_{33}H_{36}N_2O_5S$: C 69.21, H 6.34, N 4.89; found: C 69.53, H 6.46, N 4.98.

[Methyl 4-(*N*-acetyl-*N*-benzylamino)-5,7-di-*O*-benzyl-3,4-dideoxy-α-D-*arabino*-heptulopyranosidonic] acid (15): The thiazolyl derivative **14** (1.00 g, 1.75 mmol) was treated as described for the preparation of **10** to give syrupy methyl 4-(*N*-acetyl-*N*-benzylamino)-5,7-di-*O*-benzyl-3,4-dideoxy-α-D-*arabino*-heptosulopyranoside (723 mg, ∼80 %) at least 95 % pure by NMR analysis. ^{1}H NMR ([D]$_6$DMSO, 120 °C): $\delta = 9.40$ (s, 1H, CHO), 7.40–7.10 (m, 15H, 3Ph), 4.70–4.20 (m, 8H), 3.80–3.60 (m, 3H), 3.20 (s, 3H, MeO), 2.15–1.95 (m, 4H, H-3ax, Ac), 1.70 (dd, 1H, $J_{3eq,4} = 3.5$, $J_{3eq,3ax} = 12.5$ Hz, H-3eq).

The crude aldehyde was oxidized as described for the preparation of **11** to afford the crude acid which was eluted from a column of Sephadex LH-20 (2 × 80 cm) with 1:1 CH_2Cl_2/CH_3OH to give **15** (699 mg, 75 % from **14**) as a white foam: $[\alpha]_D = +53.4$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR ([D]$_6$DMSO, 120 °C): $\delta = 7.40-7.15$ (m, 15H, 3Ph), 4.70–4.20 (m, 8H), 3.80–3.60 (m, 3H), 3.20 (s, 3H, MeO), 2.15–1.85 (m, 5H, H-3ax, H-3eq, Ac); anal. calcd for $C_{31}H_{35}NO_7$: C 69.77, H 6.61, N 2.62; found: C 70.00, H 6.80, N 2.51.

1,6-Anhydro-3-(*N*-acetyl-*N*-benzylamino)-4-*O*-benzyl-2,3-dideoxy-1-(2-thiazolyl)-β-D-*ribo*-hexopyranose (16): Ketone **12b** (508 mg, 1.00 mmol) was treated as described for the synthesis of **13** to give, after column chromatography on silica gel (4:1 cyclohexane/AcOEt), **16** (274 mg, 61 %) as a syrup: $[\alpha]_D = -76.8$ ($c = 0.9$, $CHCl_3$); ^{1}H NMR ([D]$_6$DMSO, 140 °C): $\delta = 7.70$, 7.65 (2d, 2H, $J = 3.0$ Hz, Th), 7.40–7.10 (m, 10H, 2Ph), 5.00 (ddd, 1H, $J_{3,4} = 2.8$, $J_{2eq,3} = 5.6$, $J_{2ax,3} = 13.3$ Hz, H-3), 4.98 (ddd, 1H, $J_{5,6a} = 0.7$, $J_{5,6b} = 4.9$, $J_{4,5} = 4.9$ Hz, H-5), 4.82, 4.71 (2d, 2H, $J = 17.6$ Hz, PhCH_2N), 4.72, 4.53 (2d, 2H, $J = 11.9$ Hz, PhCH_2O), 4.05 (dd, 1H, $J_{6a,6b} = 7.7$ Hz, H-6a), 3.96 (dd, 1H, H-6b), 3.88 (dd, 1H, H-4), 2.49 (dd, 1H, $J_{2eq,2ax} = 13.3$ Hz, H-2ax), 2.17 (dd, 1H, H-2eq), 2.00 (s, 3H, Ac); anal. calcd for $C_{25}H_{26}N_2O_4S$: C 66.64, H 5.82, N 6.22; found: C 66.50, H 5.63, N 6.11.

(3*S*,4*R*,5*R*,6*S*,7*S*)- and **(3*R*,4*R*,5*R*,6*S*,7*S*)-3-(*N*-Acetyl-*N*-benzylamino)-8-*O*-*tert*-butyldiphenylsilyl-4,5,6,7,8-pentahydroxy-4,6:5,7-di-*O*-isopropylidene-1-(2-thiazolyl)-1-octanone (18a** and **18b)**: Freshly distilled benzylamine (1.26 mL, 11.52 mmol) was slowly added to a cooled (−50 °C), stirred solution of **17** (2.00 g, 3.29 mmol) in anhydrous CH_2Cl_2 (33 mL). The solution was stirred at −50 °C for 3.5 h, then diluted with acetic anhydride (1.09 mL, 11.52 mmol). The solution was stirred at −50 °C for 30 min, then warmed to room temperature and concentrated. The crude products were purified by preparative HPLC (silica, 6 μm, 60 Å, 85:15 cyclohexane/AcOEt, UV detection $\lambda = 254$ nm). Eluted first was **18b** (697 mg, 28 %) as a white foam: $[\alpha]_D = +46.0$ ($c = 0.6$, $CHCl_3$); ^{1}H NMR ([D]$_6$DMSO, 140 °C): $\delta = 8.00$, 7.92 (2d, 2H, $J = 3.1$ Hz, Th), 7.70–7.65, 7.50–7.35, 7.20–7.0 (3m, 15H, 3Ph), 4.94 (m, 1H, H-3), 4.77, 4.43 (2d, 2H, $J = 16.6$ Hz, PhCH_2), 4.00–3.70 (m, 6H), 3.52 (dd, 1H, $J_{2a,3} = 5.5$, $J_{2a,2b} = 17.6$ Hz, H-2), 3.31 (dd, 1H, $J_{2b,3} = 7.4$ Hz, H-2b), 2.20 (s, 3H, Ac), 1.45, 1.39, 1.30, 1.20 (4s, 12H, 4Me), 1.18 (s, 9H, *t*Bu); anal. calcd for $C_{42}H_{52}N_2O_7SSi$: C 66.64, H 6.92, N 3.70; found: C 66.59, H 6.85, N 3.58.

Eluted second was **18a** (1.42 g, 57 %) as a white foam: $[\alpha]_D = -60.0$ ($c = 0.7$, $CHCl_3$); ^{1}H NMR ([D]$_6$DMSO, 160 °C): $\delta = 8.02$, 7.98 (2d, 2H, $J = 3.1$ Hz, Th), 7.70–7.65, 7.50–7.35, 7.20–7.0 (3m, 15H, 3Ph), 4.84 (q, 1H, $J = 6.5$ Hz, H-3), 4.71, 4.47 (2d, 2H, $J = 16.8$ Hz, PhCH_2), 4.02–3.70 (m, 6H), 3.62–3.45 (m, 2H, 2 H-2), 2.12 (s, 3H, Ac), 1.33, 1.25, 1.22, 1.20 (4s, 12H, 4Me), 1.05 (s, 9H, *t*Bu); anal. calcd for $C_{42}H_{52}N_2O_7SSi$: C 66.64, H 6.92, N 3.70; found: C 66.79, H 6.75, N 3.58.

Methyl 4,6,7,8-tetra-*O*-acetyl-3-(*N*-acetyl-*N*-benzylamino)-2,3-dideoxy-1-(2-thiazolyl)-β-D-*glycero*-D-*galacto*-octopyranoside (19): A solution of **18a** (757 mg, 1.00 mmol) in a 2 % (*w*/*w*) solution of HCl in anhydrous MeOH (10 mL) was kept at room temperature for 14 h, then concentrated. A solution of the residue in MeOH was neutralized with Amberlyst A-26 ion exchange resin (HO^- form) and concentrated to afford crude methyl 3-(*N*-acetyl-*N*-benzylamino)-2,3-dideoxy-1-(2-thiazolyl)-β-D-*glycero*-D-*galacto*-octopyranoside: ^{1}H NMR ([D]$_6$DMSO + D_2O, 160 °C): $\delta = 7.72$, 7.55 (2d, 2H, $J = 3.0$ Hz, Th), 7.30–7.10 (m, 5H, Ph), 4.70, 4.38 (2d, 2H, $J = 15.5$ Hz, PhCH_2), 4.50–4.42 (m, 1H), 4.06–3.92 (m, 2H), 3.86 (dd, 1H, $J = 1.1$, 8.8 Hz), 3.80–3.68 (m, 2H), 3.60 (dd, 1H, $J = 5.5$, 11.1 Hz), 3.10 (s, 3H, MeO), 2.30 (dd, 1H, $J_{2eq,3} = 4.4$, $J_{2eq,2ax} = 13.3$ Hz, H-2eq), 2.10 (s, 3H, Ac), 1.94 (dd, 1H, $J_{2ax,3} = 13.0$ Hz, H-2ax).

A solution of the crude product in 1:1 pyridine/acetic anhydride (10 mL) was kept at room temperature for 14 h, then concentrated. The residue was eluted from a column of silica gel with AcOEt to give **19** (384 mg, 62 %) as a white foam: $[\alpha]_D = +24.0$ ($c = 0.3$, $CHCl_3$); ^{1}H NMR ([D]$_6$DMSO, 160 °C): $\delta = 7.76$, 7.63 (2d, 2H, $J = 3.0$ Hz, Th), 7.32–7.18 (m, 5H, Ph), 5.35–5.28 (m, 2H, H-6, H-7), 5.21 (dd, 1H, $J_{3,4} = J_{4,5} = 9.9$ Hz, H-4), 4.66 (ddd, 1H, $J_{2eq,3} = 4.4$, $J_{2ax,3} = 13.2$ Hz, H-3), 4.55, 4.36 (2d, 2H, $J = 17.3$ Hz, PhCH_2), 4.47 (dd,

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1H, $J_{7,8a}=3.3$, $J_{8a,8b}=12.4$ Hz, H-8a), 4.24 (dd, 1H, $J_{5,6}=2.5$ Hz, H-5), 4.19 (dd, 1H, $J_{7,8b}=5.8$ Hz, H-8b), 3.10 (s, 3H, MeO), 2.40 (dd, 1H, $J_{2eq,2ax}=13.2$ Hz, H-2eq), 2.25 (dd, 1H, H-2ax), 2.10, 2.04, 1.98 (3s, 15H, 5Ac); anal. calcd for $C_{29}H_{36}N_2O_{11}S$: C 56.12, H 5.85, N 4.51; found: C 56.10, H 5.89, N 4.48.

Methyl 3-(*N*-acetyl-*N*-benzylamino)-4,6,7,8-tetra-*O*-benzyl-2,3-dideoxy-1-(2-thiazolyl)-β-D-*glycero*-D-*galacto*-octopyranoside (20): A solution of **18a** (1.38 g, 1.82 mmol) in a 2% (*w*/*w*) solution of HCl in anhydrous MeOH (18 mL) was kept at room temperature for 14 h, then concentrated. A solution of the residue in MeOH was neutralized with Amberlyst A-26 ion exchange resin (HO^- form) and concentrated. The crude methyl glycoside was perbenzylated as described for the synthesis of **14** to afford, after column chromatography on silica gel (1:1 cyclohexane/AcOEt), **20** (830 mg, 56%) as a syrup: $[\alpha]_D=-7.0$ ($c=0.9$, $CHCl_3$); ^{1}H NMR selected data ($[D]_6$DMSO, 140 °C): $\delta=7.75$, 7.60 (2d, 2H, $J=3.0$ Hz, Th), 7.40–7.15 (m, 25H, 5Ph), 2.97 (s, 3H, MeO), 2.36 (dd, 1H, $J_{2eq,3}=4.1$, $J_{2eq,2ax}=12.9$ Hz, H-2eq), 2.20–2.05 (m, 1H, H-2ax), 2.03 (s, 3H, Ac); anal. calcd for $C_{49}H_{52}N_2O_7S$: C 72.39, H 6.45, N 3.44; found: C 72.42, H 6.44, N 3.40.

[Methyl 4-(*N*-acetyl-*N*-benzylamino)-5,7,8,9-tetra-*O*-benzyl-3,4-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosidonic] acid (21): The thiazolyl derivative **20** (650 mg, 0.80 mmol) was treated as described for the preparation of **10** to give syrupy methyl 4-(*N*-acetyl-*N*-benzylamino)-5,7,8,9-tetra-*O*-benzyl-3,4-dideoxy-β-D-*glycero*-D-*galacto*-2-nonosulopyranoside (533 mg, ~88%) at least 95% pure by NMR analysis. ^{1}H NMR selected data ($[D]_6$DMSO, 140 °C): $\delta=9.35$ (s, 1H, CHO), 7.40–7.15 (m, 25H, 5Ph), 3.15 (s, 3H, MeO), 2.05 (s, 3H, Ac), 1.72 (dd, 1H, $J_{3eq,4}=4.1$, $J_{3ax,3eq}=13.0$ Hz, H-3eq), 1.62–1.50 (m, 1H, H-3ax).

The crude aldehyde was oxidized as described for the preparation of **11** to afford the crude acid which was eluted from a column of Sephadex LH-20 (2 × 80 cm) with 1:1 CH_2Cl_2/CH_3OH to give **21** (446 mg, 72% from **20**) as a syrup: $[\alpha]_D=-26.0$ ($c=0.5$, $CHCl_3$); ^{1}H NMR selected data: $\delta=10.0$ (br s, 1H, CO_2H), 7.40–7.10 (m, 25H, 5Ph), 2.10 (dd, 1H, $J_{3eq,4}=2.8$, $J_{3eq,3ax}=12.5$ Hz, H-3eq), 1.74 (dd, 1H, $J_{3ax,4}=13.8$ Hz, H-3ax); anal. calcd for $C_{47}H_{51}NO_9$: C 72.94, H 6.64, N 1.81; found: C 72.8, H 6.81, N 1.68.

[Methyl 4-acetamido-3,4-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosidonic] acid (Me-3): *Route A*: Lithium was added in small pieces to a cooled (−40 °C), stirred solution of **21** (387 mg, 0.50 mmol) in anhydrous THF (5 mL) and liquid ammonia (10 mL) until a persistent blue colored solution was obtained. The mixture was stirred for an additional 15 min, diluted with EtOH (0.5 mL), slowly warmed to room temperature, and concentrated. The residue was dissolved in MeOH, treated with Dowex 50 × 2 ion exchange resin (H^+ form), and concentrated. The crude acid was eluted from a column of Sephadex LH-20 (1 × 80 cm) with 1.5:1 CH_3OH/CH_2Cl_2 to give **Me-3** (145 mg, ~90%) contaminated by uncharacterized by-products (NMR analysis).

Route B: Acid **25** (267 mg, 0.40 mmol) was treated with lithium in liquid ammonia as described in Route A. Acetic anhydride was added dropwise to a stirred solution of the residue in MeOH (5 mL) until the starting material had disappeared by TLC analysis (5:5:3:1 AcOEt/pyridine/H_2O/AcOH). The solution was concentrated, the residue was dissolved in MeOH, treated with Dowex 50 × 2 ion exchange resin (H^+ form), and concentrated. The crude acid was eluted from a column of Sephadex LH-20 (1 × 80 cm) with 1.5:1 CH_3OH/CH_2Cl_2 to give **Me-3** (119 mg, 92%) as a white foam: $[\alpha]_D=-34.0$ ($c=0.4$, CH_3OH); ^{1}H NMR (D_2O): $\delta=4.00$ (ddd, 1H, $J_{3eq,4}=3.9$, $J_{3ax,4}=11.7$, $J_{4,5}=11.7$ Hz, H-4), 3.80–3.60 (m, 4H, H-6, H-7, H-8, H-9), 3.50 (dd, 1H, $J_{8,9a}=4.7$, $J_{9a,9b}=11.7$ Hz, H-9a), 3.40 (dd, 1H, $J_{5,6}=8.7$ Hz, H-5), 3.02 (s, 3H, MeO), 1.96 (dd, 1H, $J_{3ax,3eq}=13.6$ Hz, H-3eq), 1.80 (s, 3H, Ac), 1.40 (dd, 1H, H-3ax); anal. calcd for $C_{12}H_{21}NO_9$: C 44.58, H 6.55, N 4.33; found: C 44.50, H 6.43, N 4.30.

(3*S*,4*R*,5*R*,6*S*,7*S*)- and **(3*R*,4*R*,5*R*,6*S*,7*S*)-3-Azido-8-*O*-*tert*-butyldiphenylsilyl-4,5,6,7,8-pentahydroxy-4,6:5,7-di-*O*-isopropylidene-1-(2-thiazolyl)-1-octanone (*syn*-22** and ***anti*-22)**: To a cooled (−20 °C), stirred solution of **17** (790 mg, 1.30 mmol) in anhydrous CH_2Cl_2 (13 mL) was added trimethylsilyl azide (207 μL, 1.56 mmol) and then a solution of tetrabutylammonium fluoride (34 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (0.5 mL). The mixture was stirred at −20 °C for four days, then diluted with H_2O (10 mL), warmed to room temperature, diluted with CH_2Cl_2 (100 mL), washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and concentrated to give a 3:1 mixture of *syn*-**22** and *anti*-**22** (NMR analysis) as a syrup (794 mg, 94%). Attempts to separate the diastereomers by column chromatography on silica gel led to extensive decomposition of the adducts (~30% of enone **17** was recovered). ^{1}H NMR selected data of *syn*-**22**: $\delta=8.03$ (d, 1H, $J=3.0$ Hz, Th), 4.22–4.14 (m, 1H); 4.09–4.02 (m, 1H), 3.97 (dd, 1H, $J=5.7$, 7.4 Hz), 3.90 (dd, 1H, $J=4.0$, 8.0 Hz), 3.61 (dd, 1H, $J=9.2$, 17.2 Hz), 3.30 (dd, 1H, $J=4.0$, 17.2 Hz). ^{1}H NMR selected data of *anti*-**22**: $\delta=8.01$ (d, 1H, $J=3.0$ Hz, Th), 4.35–4.25 (m, 1H).

Methyl 3-azido-2,3-dideoxy-1-(2-thiazolyl)-β-D-*glycero*-D-*galacto*-octopyranoside (23): A solution of a 3:1 mixture of *syn*-**22** and *anti*-**22** (794 mg, 1.22 mmol) in a 2% (*w*/*w*) solution of HCl in anhydrous MeOH (13 mL) was kept at room temperature for 14 h, then concentrated. A solution of the residue in MeOH was neutralized with Amberlyst A-26 ion-exchange resin (HO^- form) and concentrated. The crude methyl glycoside was purified by preparative HPLC (silica C18, 6 μm, 60 å, 4:1 MeOH/H_2O, UV detection $\lambda=254$ nm) to give **23** (212 mg, ~50%) contaminated by an uncharacterized by-product. ^{1}H NMR selected data (D_2O): $\delta=7.66$, 7.45 (2d, 2H, $J=3.0$ Hz, Th), 3.88–3.68 (m, 5H), 3.64–3.50 (m, 2H), 2.97 (s, 3H, MeO), 2.46 (dd, 1H, $J_{2eq,3}=4.5$, $J_{2eq,2ax}=13.5$ Hz, H-2eq), 1.61 (dd, 1H, $J_{2ax,3}=10.9$ Hz, H-2ax).

Methyl 3-azido-4,6,7,8-tetra-*O*-benzyl-2,3-dideoxy-1-(2-thiazolyl)-β-D-*glycero*-D-*galacto*-octopyranoside (24): Tetrol **23** (212 mg, ~0.61 mmol) was perbenzylated as described for the preparation of **14** to afford, after column chromatography on silica gel (6:1 cyclohexane/AcOEt), **24** (367 mg, 40% from **17**) as a syrup: $[\alpha]_D=-36.0$ ($c=0.9$, $CHCl_3$); ^{1}H NMR selected data: $\delta=7.85$ (d, 1H, $J=3.0$ Hz, Th), 7.40–7.20 (m, 21H, 4Ph, Th), 4.28 (dd, 1H, $J_{5,6}=1.5$, $J_{6,7}=5.0$ Hz, H-6), 4.16 (ddd, 1H, $J_{2eq,3}=4.8$, $J_{3,4}=9.0$, $J_{2ax,3}=12.2$ Hz, H-3), 4.14 (dd, 1H, $J_{7,8a}=2.0$, $J_{8a,8b}=10.5$ Hz, H-8a), 4.08 (ddd, 1H, $J_{7,8b}=5.5$ Hz, H-7), 4.05 (dd, 1H, $J_{4,5}=10.0$ Hz, H-5), 3.81 (dd, 1H, H-8b), 3.61 (dd, 1H, H-4), 2.95 (s, 3H, MeO), 2.80 (dd, 1H, $J_{2ax,2eq}=13.3$ Hz, H-2eq), 1.80 (dd, 1H, H-2ax); anal. calcd for $C_{40}H_{42}N_4O_6S$: C 67.97, H 5.99, N 7.93; found: C 67.85, H 5.75, N 7.82.

[Methyl 4-azido-5,7,8,9-tetra-*O*-benzyl-3,4-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosidonic] acid (25): The thiazolyl derivative **24** (353 mg, 0.50 mmol) was treated as described for the preparation of **10** to give syrupy methyl 4-azido-5,7,8,9-tetra-*O*-benzyl-3,4-dideoxy-β-D-*glycero*-D-*galacto*-2-nonosulopyranoside (283 mg, ~87%) at least 95% pure by NMR analysis. ^{1}H NMR selected data: $\delta=9.35$ (s, 1H, CHO), 7.40–7.10 (m, 20H, 4Ph), 3.10 (s, 3H, MeO), 2.12 (dd, 1H, $J_{3eq,4}=4.8$, $J_{3ax,3eq}=12.9$ Hz, H-3eq), 1.56 (dd, 1H, $J_{3ax,4}=12.5$ Hz, H-3ax).

The crude aldehyde was oxidized as described for the preparation of **11** to afford the crude acid which was eluted from a column of Sephadex LH-20 (1 × 80 cm) with 1:1 CH_2Cl_2/CH_3OH to give **25** (234 mg, 70% from **24**) as a syrup: $[\alpha]_D=-52.0$ ($c=1.3$, $CHCl_3$); ^{1}H NMR selected data: $\delta=8.70$ (br s, 1H, CO_2H), 7.50–7.20 (m, 20H, 4Ph), 4.20 (dd, 1H, $J_{6,7}=1.6$, $J_{7,8}=4.9$ Hz, H-7), 4.04–3.92 (m, 3H, H-4, H-8, H-9a), 3.88 (dd, 1H, $J_{5,6}=10.0$ Hz, H-6), 3.70 (dd, 1H, $J_{8,9b}=3.8$, $J_{9a,9b}=10.5$ Hz, H-9b), 3.53 (dd, 1H, $J_{4,5}=9.4$ Hz, H-5), 3.10 (s, 3H, MeO), 2.48 (dd, 1H, $J_{3eq,4}=4.2$, $J_{3ax,3eq}=13.0$ Hz, H-3eq), 1.75 (dd, 1H, $J_{3ax,4}=12.0$ Hz, H-3ax); anal. calcd for $C_{38}H_{41}N_3O_8$: C 68.35, H 6.19, N 6.29; found: C 68.30, H 6.10, N 6.47.

4-Acetamido-3,4-dideoxy-β-D-*glycero*-D-*galacto*-2-nonulopyranosonic acid (3): A solution of **Me-3** (97 mg, 0.30 mmol, prepared from the azido derivative **25**) in a 4:1 mixture of AcOH and H_2O (6 mL) was stirred at 100 °C for 1 h, then concentrated. The residue was eluted from a column of Sephadex LH-20 (1 × 80 cm) with 1:1 CH_2Cl_2/CH_3OH to give **3** (79 mg, ~85%) contaminated by ~10% of unreacted **Me-3**. Prolonged hydrolysis led to decomposition products. ^{1}H NMR (D_2O): $\delta=4.04$ (ddd, 1H, $J_{3eq,4}=4.5$, $J_{4,5}=10.5$, $J_{3ax,4}=12.4$, Hz, H-4), 3.81 (dd, 1H, $J_{6,7}=\sim 0.5$, $J_{5,6}=9.5$ Hz, H-6), 3.72–3.52 (m, 3H, H-7, H-8, H-9), 3.44 (dd, 1H, $J_{8,9a}=5.8$, $J_{9a,9b}=11.9$ Hz, H-9b), 3.43 (dd, 1H, H-5), 1.87 (dd, 1H, $J_{3eq,3ax}=13.5$ Hz, H-3eq), 1.85 (s, 3H, Ac), 1.60 (dd, 1H, H-3ax).

(3*R*,4*S*)-4,5-Dihydroxy-4,5-*O*-isopropylidene-3-nitromethyl-1-(2-thiazolyl)-1-pentanone (26): To a cooled (−20 °C), stirred solution of **5** (800 mg, 3.34 mmol) in anhydrous CH_2Cl_2 (34 mL) was added freshly distilled nitromethane (904 μL, 16.70 mmol) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (333 μL, 2.23 mmol). The mixture was stirred at −20 °C for 14 h, then diluted with 1M phosphate buffer at pH 7 (10 mL), warmed to room temperature, and diluted with CH_2Cl_2 (100 mL). The phases were separated, the organic phase was washed with H_2O (20 mL), dried (Na_2SO_4), and concentrated to give a 7.3:1 mixture of **26** and its epimer *anti*-**26** (NMR analysis) as a syrup (923 mg, 92%). ^{1}H NMR of **26** (C_6D_6):

$\delta = 7.44$, 6.62 (2d, 2H, $J = 3.0$ Hz, Th), 4.22 (dd, 1H, $J = 3.7$, 13.1 Hz), 4.13 (dd, 1H, $J = 6.2$, 13.1 Hz), 3.81 (q, 1H, $J = 6.2$ Hz), 3.56 (dd, 1H, $J = 6.2$, 8.7 Hz), 3.32 (dd, 1H, $J = 6.8$, 8.7 Hz), 3.09 (dd, 1H, $J = 6.8$, 17.5 Hz), 3.01 (dd, 1H, $J = 5.6$, 17.5 Hz), 2.84 (m, 1H), 1.21, 1.10 (2s, 6H, 2Me). This crude mixture was used for the next step without further purification.

(3*R*,4*S*,5*S*)-4-*O*-Benzyl-4,5,6-trihydroxy-5,6-*O*-isopropylidene-3-nitromethyl-1-(2-thiazolyl)-1-hexanone (27): The enone **6** (1.00 g, 2.78 mmol) was treated with CH_3NO_2 and DBU as described for the preparation of **26** to give a 4.9:1 mixture of **27** and its epimer *anti*-**27** (NMR analysis) as a syrup (1.10 g, 94%). ^{1}H NMR of **27** (C_6D_6): $\delta = 7.42$, 6.56 (2d, 2H, $J =$ 3.1 Hz, Th), 7.20–7.0 (m, 5H, Ph), 4.48 (dd, 1H, $J = 7.5$, 13.6 Hz), 4.31, 4.08 (2d, 2H, $J = 11.3$ Hz, PhCH_2), 4.18 (dd, 1H, $J = 6.8$, 13.6 Hz), 4.02 (m, 1H), 3.82 (dd, 1H, $J = 6.0$, 8.3 Hz), 3.64–3.46 (m, 3H), 3.40 (dd, 1H, $J = 3.0$, 7.6 Hz), 3.02 (dd, 1H, $J = 6.8$, 16.6 Hz), 1.28, 1.16 (2s, 6H, 2Me). This crude mixture was used for the next step without further purification.

(3*S*,4*R*,5*R*,6*S*,7*S*)-8-*O*-*tert*-Butyldiphenylsilyl-4,5,6,7,8-pentahydroxy-4,6:5,7-di-*O*-isopropylidene-3-nitromethyl-1-(2-thiazolyl)-1-octanone (28): The enone **17** (800 mg, 1.32 mmol) was treated with CH_3NO_2 and DBU as described for the preparation of **26** to give a 6.1:1 mixture of **28** and its epimer *anti*-**28** (NMR analysis) as a syrup (810 mg, 92%). ^{1}H NMR of **28** (C_6D_6): $\delta = 7.84$–7.78, 7.22–7.18 (2m, 10H, 2Ph), 7.42, 6.58 (2d, 2H, $J =$ 2.9 Hz, Th), 4.39 (dd, 1H, $J = 5.7$, 12.7 Hz), 4.30 (dd, 1H, $J = 6.9$, 12.7 Hz), 3.98–3.70 (m, 5H), 3.65 (dd, 1H, $J = 4.2$, 8.5 Hz), 3.31 (m, 2H), 3.10–2.98 (m, 1H), 1.20, 1.19, 1.07, 1.03 (4s, 12H, 4Me), 1.17 (s, 9H, *t*Bu). This crude mixture was used for the next step without further purification.

Methyl 2,3-dideoxy-3-*C*-nitromethyl-1-(2-thiazolyl)-α-D-*threo*-pentopyranoside (29): A solution of **26** (923 mg, 3.07 mmol, of a 7.3:1 mixture of epimers) in an 8% (*w*/*w*) solution of HCl in anhydrous MeOH (30 mL) was kept at room temperature for 14 h, then concentrated. The residue was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with AcOEt (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 1.5:1 cyclohexane/AcOEt to give **29** (504 mg, 55% from **5**) as a white solid: M.p. 143–145 °C (from AcOEt/hexane); $[\alpha]_D = +56.8$ ($c = 0.7$, $CHCl_3$); ^{1}H NMR ($CDCl_3 + D_2O$): $\delta = 7.84$, 7.37 (2d, 2H, $J = 3.1$ Hz, Th), 4.65 (dd, 1H, $J_{3,3'} = 4.9$, $J_{3',3''} = 11.9$ Hz, H-3′), 4.47 (dd, 1H, $J_{3,3''} = 6.5$ Hz, H-3″), 3.98 (dd, 1H, $J_{4,5eq} = 3.2$, $J_{5ax,5eq} = 9.8$ Hz, H-5eq), 3.74 (ddd, 1H, $J_{4,5ax} = 10.7$, $J_{3,4} = 11.1$ Hz, H-4), 3.64 (dd, 1H, H-5ax), 3.13 (s, 3H, MeO), 2.89 (ddddd, 1H, $J_{2eq,3} = 3.3$, $J_{2ax,3} = 11.7$ Hz, H-3), 2.55 (dd, 1H, $J_{2ax,2eq} = 13.4$ Hz, H-2eq), 1.66 (dd, 1H, H-2ax); anal. calcd for $C_{10}H_{14}N_2O_5S$: C 43.79, H 5.14, N 10.21; found: C 43.60, H 5.20, N 10.02.

Methyl 2,3-dideoxy-3-*C*-nitromethyl-1-(2-thiazolyl)-α-D-*arabino*-hexopyranoside (30): A solution of **27** (1.10 g, 2.61 mmol, of a 4.9:1 mixture of epimers) in an 8% (*w*/*w*) solution of HCl in anhydrous MeOH (27 mL) was kept at room temperature for 14 h, then concentrated. The residue was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with AcOEt (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 1.5:1 AcOEt/cyclohexane to give **30** (603 mg, 55% from **6**) as a syrup: $[\alpha]_D = +37.7$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR ($CDCl_3 + D_2O$): $\delta = 7.80$ (d, 1H, $J = 3.1$ Hz, Th), 7.40–7.30 (m, 6H, Th, Ph), 4.78, 4.64 (2d, 2H, $J = 10.8$ Hz, PhCH_2), 4.49 (dd, 1H, $J_{3,3'} = 4.3$, $J_{3',3''} = 11.9$ Hz, H-3′), 4.28 (dd, 1H, $J_{3,3''} =$ 7.0 Hz, H-3″), 4.02 (dd, 1H, $J_{5,6a} = 2.1$, $J_{6a,6b} = 12.4$ Hz, H-6a), 3.94 (dd, 1H, $J_{5,6b} = 2.7$ Hz, H-6b), 3.80 (ddd, 1H, $J_{4,5} = 10.8$ Hz, H-5), 3.65 (dd, 1H, $J_{3,4} =$ 9.8 Hz, H-4), 3.15 (s, 3H, MeO), 3.0 (ddddd, 1H, $J_{2eq,3} = 4.0$, $J_{2ax,3} = 12.7$ Hz, H-3), 2.45 (dd, 1H, $J_{2ax,2eq} = 13.5$ Hz, H-2eq), 1.70 (dd, 1H, H-2ax); anal. calcd for $C_{18}H_{22}N_2O_6S$: C 54.81, H 5.62, N 7.10; found: C 54.95, H 5.60, N 7.15.

Methyl 2,3-dideoxy-3-*C*-nitromethyl-1-(2-thiazolyl)-β-D-*glycero*-D-*galacto*-octopyranoside (31): A solution of **28** (810 mg, 1.21 mmol, of a 6.1:1 mixture of epimers) in an 8% (*w*/*w*) solution of HCl in anhydrous MeOH (12 mL) was kept at room temperature for 14 h, then concentrated. A solution of the residue in MeOH was neutralized with Amberlyst A-26 ion exchange resin (HO^- form) and concentrated. The residue was eluted from a column of silica gel with 10:1 AcOEt/MeOH to give **31** (245 mg, 51% from **17**) as a white foam slightly contaminated by silica gel. An analytical sample was obtained by column chromatography on Sephadex LH-20 (1:1 CH_2Cl_2/CH_3OH): $[\alpha]_D = -47.5$ ($c = 1.0$, MeOH); ^{1}H NMR (CD_3OD): $\delta =$ 7.84, 7.66 (2d, 2H, $J = 2.8$ Hz, Th), 4.80 (dd, 1H, $J_{3,3'} = 4.5$, $J_{3',3''} = 12.3$ Hz, H-3′), 4.44 (dd, 1H, $J_{3,3''} = 8.4$ Hz, H-3″), 4.04 (dd, 1H, $J_{5,6} = 1.1$, $J_{4,5} =$ 10.0 Hz, H-5), 3.92 (dd, 1H, $J_{6,7} = 5.5$ Hz, H-6), 3.88 (dd, 1H, $J_{7,8a} = 1.0$, $J_{8a,8b} = 10.6$ Hz, H-8a), 3.84 (ddd, 1H, $J_{7,8b} = 5.0$ Hz, H-7), 3.70 (dd, 1H, H-8b), 3.63 (dd, 1H, $J_{3,4} = 10.7$ Hz, H-4), 3.20 (s, 3H, MeO), 2.90 (ddddd, 1H, $J_{2eq,3} = 3.9$, $J_{2ax,3} = 12.3$ Hz, H-3), 2.37 (dd, 1H, $J_{2ax,2eq} = 13.4$ Hz, H-2eq), 1.60 (dd, 1H, H-2ax); anal. calcd for $C_{13}H_{20}N_2O_8S$: C 42.85, H 5.53, N 7.69; found: C 42.52, H 5.42, N 7.60.

Methyl 3-*C*-acetammidomethyl-2,3-dideoxy-4,6,7,8-tetra-*O*-triethylsilyl-1-(2-thiazolyl)-β-D-*glycero*-D-*galacto*-octopyranoside (32): A stirred mixture of **31** (255 mg, 0.70 mmol), $LiAlH_4$ (531 mg, 14.0 mmol), and anhydrous THF (24 mL) was refluxed for 3 h, then cooled at 0 °C and diluted with H_2O (~2 mL). The mixture was filtered trough celite and concentrated. Acetic anhydride was added dropwise to a stirred solution of the residue in MeOH (10 mL)until the starting material had disappeared by TLC analysis (5:5:3:1 AcOEt/pyridine/H_2O/AcOH). The solution was concentrated, the residue was dissolved in pyridine (10 mL) and treated with triethylsilyl triflate (1.58 mL, 7.00 mmol). The mixture was stirred at room temperature for 14 h, diluted with MeOH (1 mL), and concentrated. The residue was eluted from a column of silica gel with 1:1 cyclohexane/AcOEt (containing 0.2% of Et_3N) to give **32** (233 mg, 40%) as a syrup: $[\alpha]_D = -6.2$ ($c = 1.2$, $CHCl_3$); ^{1}H NMR: $\delta = 7.79$, 7.32 (2d, 2H, $J = 3.1$ Hz, Th), 5.55 (dd, 1H, $J_{NH,3'} = 5.5$, $J_{NH,3''} = 6.5$ Hz, NH), 4.11 (dd, 1H, $J_{7,8a} = 1.5$, $J_{8a,8b} = 10.5$ Hz, H-8a), 4.04 (dd, 1H, $J_{5,6} = 0.5$, $J_{6,7} = 4.5$ Hz, H-6), 3.89 (ddd, 1H, $J_{7,8b} =$ 9.0 Hz, H-7), 3.75 (dd, 1H, $J_{4,5} = 9.0$, Hz, H-5), 3.60 (dd, 1H, H-4), 3.59 (ddd, 1H, $J_{3,3'} = 5.7$, $J_{3',3''} = 13.5$ Hz, H-3′), 3.56 (dd, 1H, H-8b), 3.12 (s, 3H, MeO), 3.09 (ddd, 1H, $J_{3,3''} = 9.5$ Hz, H-3″), 2.41 (dd, 1H, $J_{2eq,3} = 3.8$, $J_{2ax,2eq} = 13.5$ Hz, H-2eq), 2.29 (ddddd, 1H, $J_{2ax,3} = 12.0$ Hz, H-3), 1.91 (s, 3H, Ac), 1.43 (dd, 1H, H-2ax), 1.04–0.86 (m, 36H, 12CH_3CH_2), 0.74–0.50 (m, 24H, 12CH_3CH_2); anal. calcd for $C_{39}H_{80}N_2O_7SSi_4$: C 56.20, H 9.67, N 3.36; found: C 56.41, H 9.50, N 3.48.

Methyl 3-*C*-(*N*-acetyl-*N*-*tert*-butoxycarbonylamino)methyl-2,3-dideoxy-4,6,7,8-tetra-*O*-triethylsilyl-1-(2-thiazolyl)-β-D-*glycero*-D-*galacto*-octopyranoside (33): A solution of **32** (250 mg, 0.30 mmol), di-*tert*-butyl dicarbonate (327 mg, 1.50 mmol), and 4-(dimethylamino)pyridine (7 mg, 0.06 mmol) in Et_3N (3.0 mL) was kept at room temperature for 14 h, then concentrated. The residue was eluted from a column of silica gel with 10:1 cyclohexane/AcOEt (containing 0.2% of Et_3N) to give **33** (249 mg, 89%) as a syrup: $[\alpha]_D = -8.7$ ($c = 1.4$, $CHCl_3$); ^{1}H NMR: $\delta = 7.78$, 7.31 (2d, 2H, $J = 3.2$ Hz, Th), 4.11 (dd, 1H, $J_{7,8a} = 1.5$, $J_{8a,8b} = 10.5$ Hz, H-8a), 4.08 (dd, 1H, $J_{3,3'} = 4.0$, $J_{3',3''} = 13.0$ Hz, H-3′), 4.03 (dd, 1H, $J_{5,6} = 0.5$, $J_{6,7} = 4.5$ Hz, H-6), 3.89 (ddd, 1H, $J_{7,8b} = 8.5$ Hz, H-7), 3.75 (dd, 1H, $J_{4,5} = 9.0$ Hz, H-5), 3.58 (dd, 1H, $J_{3,4} = 11.0$ Hz, H-4), 3.57 (dd, 1H, H-8b), 3.56 (dd, 1H, $J_{3,3''} = 10.5$ Hz, H-3″), 3.08 (s, 3H, MeO), 2.61 (ddddd, 1H, $J_{2eq,3} = 3.5$, $J_{2ax,3} = 12.5$ Hz, H-3), 2.45 (s, 3H, Ac), 2.16 (dd, 1H, $J_{2eq,2ax} = 13.5$ Hz, H-2eq), 1.44 (dd, 1H, H-2ax), 1.43 (s, 9H, *t*Bu), 1.04–0.87 (m, 36H, 12CH_3CH_2), 0.80–0.52 (m, 24H, 12CH_3CH_2); anal. calcd for $C_{44}H_{88}N_2O_9SSi_4$: C 56.61, H 9.50, N 3.00; found: C 56.66, H 9.42, N 2.91.

Methyl [methyl 4-*C*-(*N*-acetyl-*N*-*tert*-butoxycarbonylamino)methyl-3,4-dideoxy-5,7,8,9-tetra-*O*-triethylsilyl-β-D-*glycero*-D-*galacto*-nonulopyranosid]onate (34): The thiazolyl derivative **33** (280 mg, 0.30 mmol) was treated as described for the preparation of **10** to give syrupy methyl 4-*C*-(*N*-acetyl-*N*-*tert*-butoxycarbonylamino)methyl-3,4-dideoxy-5,7,8,9-tetra-*O*-triethylsilyl-β-D-*glycero*-D-*galacto*-nonosulopyranoside (213 mg, ~81%) at least 95% pure by NMR analysis. ^{1}H NMR: $\delta = 9.43$ (s, 1H, CHO), 3.99 (dd, 1H, $J_{4,4'} = 4.7$, $J_{4',4''} = 13.5$ Hz, H-4′), 3.97 (dd, 1H, $J_{8,9a} = 1.5$, $J_{9a,9b} = 10.4$ Hz, H-9a), 3.96 (dd, 1H, $J_{6,7} = 0.3$, $J_{7,8} = 7.0$ Hz, H-7), 3.88 (ddd, 1H, $J_{8,9b} =$ 7.6 Hz, H-8), 3.81 (dd, 1H, $J_{5,6} = 9.0$ Hz, H-6), 3.68 (dd, 1H, $J_{4,4''} =$ 10.9 Hz, H-4″), 3.54 (dd, 1H, $J_{4,5} = 10.8$ Hz, H-5), 3.50 (dd, 1H, H-9b), 3.25 (s, 3H, MeO), 2.46 (s, 3H, Ac), 2.40 (ddddd, 1H, $J_{3eq,4} = 4.0$, $J_{3ax,4} =$ 12.4 Hz, H-4), 1.58 (dd, 1H, $J_{3ax,3eq} = 13.3$ Hz, H-3eq), 1.51 (s, 9H, *t*Bu), 1.29 (dd, 1H, H-3ax), 1.02–0.90 (m, 36H, 12CH_3CH_2), 0.74–0.58 (m, 24H, 12CH_3CH_2).

A 1M solution of KOH in MeOH and a 0.5M solution of I_2 in MeOH were added, dropwise and simultaneously, to a vigorously stirred solution of the crude aldehyde in 1:1 MeOH/Et_2O (5 mL) until the intermediate methyl hemiacetals formed in situ had disappeared by TLC analysis (5:1 cyclohexane/AcOEt), then the mixture was neutralized with AcOH and concentrated. The crude methyl ester was diluted with CH_2Cl_2 (100 mL), washed with aqueous 10% $Na_2S_2O_3 \cdot 5H_2O$ (10 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with 10:1 cyclohexane/AcOEt to give **34** (136 mg, 50%) as a syrup: $[\alpha]_D = -10.0$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR: $\delta = 4.03$ (dd, 1H, $J_{8,9a} = 1.5$, $J_{9a,9b} = 10.5$ Hz, H-9a), 3.98 (dd, 1H, $J_{4,4'} = 3.5$, $J_{4',4''} = 13.5$ Hz, H-4′), 3.94 (dd, 1H, $J_{6,7} = 0.3$,

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$J_{7,8}$ = 7.7 Hz, H-7), 3.88 (ddd, 1H, J = 7.0 Hz, H-8), 3.74 (s, 3H, CO_2Me), 3.72 (dd, 1H, $J_{5,6}$ = 9.5 Hz, H-6), 3.67 (dd, 1H, $J_{4,4''}$ = 11.0 Hz, H-4″), 3.54 (dd, 1H, $J_{4,5}$ = 11.0 Hz, H-5), 3.50 (dd, 1H, 9b), 3.24 (s, 3H, MeO), 2.47 (s, 3H, Ac), 2.42 (ddddd, 1H, $J_{3eq,4}$ = 4.0, $J_{3ax,4}$ = 13.0 Hz, H-4), 1.82 (dd, 1H, $J_{3ax,3eq}$ = 13.5 Hz, H-3eq), 1.51 (dd, 1H, H-3ax), 1.50 (s, 9H, *t*Bu), 1.00–0.82 (m, 36H, 12 CH_3CH_2), 0.80–0.50 (m, 24H, 12 CH_3CH_2); anal. calcd for $C_{43}H_{89}NO_{11}Si_4$: C 56.85, H 9.87, N 1.54; found: C 56.60, H 9.67, N 1.42.

Methyl (methyl 4-*C*-acetamidomethyl-5,7,8,9-tetra-*O*-acetyl-3,4-dideoxy-β-D-*glycero*-D-*galacto*-nonulopyranosid)onate (35): A solution of **34** (118 mg, 0.13 mmol) in a 1.5:1 mixture of anhydrous CH_2Cl_2 and trifluoroacetic acid (3 mL) was kept at room temperature for 15 min, then concentrated. A solution of the crude tetrol in 1:1 pyridine/acetic anhydride (5 mL) was kept at room temperature for 4 h, then concentrated. The residue was eluted from a column of silica gel with AcOEt/cyclohexane (from 4:1 to 1:0) to give **35** (67 mg, 70%) as a syrup: $[\alpha]_D = +78.1$ (c = 0.2, $CHCl_3$); ^{1}H NMR: δ = 6.09 (dd, 1H, $J_{4'',NH}$ = 3.7, $J_{4',NH}$ = 8.7 Hz, NH), 5.46 (dd, 1H, $J_{6,7}$ = 2.4, $J_{7,8}$ = 4.9 Hz, H-7), 5.30 (ddd, 1H, $J_{8,9a}$ = 2.4, $J_{8,9b}$ = 6.9 Hz, H-8), 4.75 (dd, 1H, $J_{9a,9b}$ = 12.4 Hz, H-9a), 4.54 (dd, 1H, $J_{5,6}$ = 9.9, $J_{4,5}$ = 11.5 Hz, H-5), 4.18 (dd, 1H, H-9b), 4.03 (dd, 1H, H-6), 3.80 (s, 3H, CO_2Me), 3.75 (ddd, 1H, $J_{4,4'}$ = 2.5 Hz, $J_{4',4''}$ = 14.8 Hz, H-4′), 3.25 (s, 3H, MeO), 2.69 (ddd, 1H, $J_{4,4''}$ = 4.0 Hz, H-4″), 2.27 (ddddd, 1H, $J_{3eq,4}$ = 4.0, $J_{3ax,4}$ = 12.3 Hz, H-4), 2.14 (dd, 1H, $J_{3eq,3ax}$ = 13.4 Hz, H-3eq), 2.12, 2.10, 2.09, 2.01, 1.98 (5s, 15H, 5Ac), 1.63 (dd, 1H, H-3ax); anal. calcd for $C_{22}H_{33}NO_{13}$: C 50.86, H 6.40, N 2.70; found: C 50.70, H 6.24, N 2.53.

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[13] In general the NMR spectra at room temperature of compounds containing an *N*,*N*-dialkyl-*N*-Boc amine function show a double set of signals arising from the hindered rotation around the σ-bonds. Hence the spectrum of a mixture of epimers can be rather complex due to the presence of the corresponding rotamers. At higher temperatures (120–160 °C) the spectra become simpler because of the coalescence of signals.

[14] The α-D anomeric configuration of **9a** and **13**, and the β-D configuration of **9b** were supported by a substantial NOE between the methoxy group and H-5ax.

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[28] Very likely the N-methylation of the thiazole ring was accompanied by the formation of an unstable methyl imidate function from the acetamido group at C-4. On the other hand the thiazole-to-formyl deblocking protocol is fully compatible with the presence of a NHBoc group, see [ref. 16] and A. Dondoni, D. Perrone, P. Merino, *J. Org. Chem.* **1995**, *60*, 8074 – 8080.
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