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Syntheses of sugar-related pyrrolidine derivatives by reductive amination reactions

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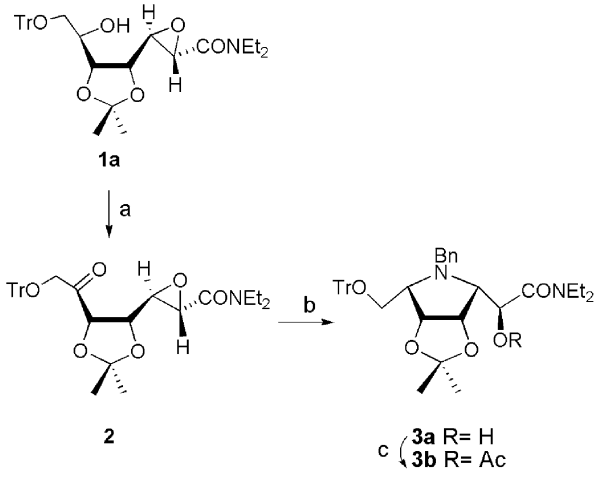
Dedicated to the memory of Dr. Fidel Jorge López Herrera

Abstract—Several pyrrolidine iminosugar derivatives have been stereoselectively synthesised from a chiral keto-epoxyamide, by reductive amination procedures. An unexpected cyanide addition was observed when a mixture of $SnCl_2$ and $NaCNBH_3$ was employed.

1. Introduction

Iminosugars (or azasugars) represent an important class of transition state analogue inhibitors of glycosidases and glycosyl transferases.[1–3] These compounds can be considered as useful biological tools for a better understanding of glycoconjugate function, because of the key role of carbohydrates in cellular recognition and signalling phenomena. Some iminosugars are arousing great interest as potential therapeutic agents against HIV infection,[4,5] cancer,[6,7] diabetes[8] and other genetic or metabolic disorders.[9] Some of them have already found clinical application[10,11] but efforts are still required to create novel structures with improved potency and selectivity towards a target enzyme. Many syntheses of polyhydroxylated pyrrolidines and piperidines have been focused on derivatives of D-gluco, D-manno or D-galacto configurations because their targeting enzymes are essential for living organism, but there are few reports on L-derivatives and other diastereomers.[12]

These antecedents encouraged us to develop our own synthetic approach to these compounds, from chiral epoxyamides as starting materials.[13,14] Among the strategies followed by our group to reach several iminosugar types, the most direct synthesis employed reductive amination as the key step (Scheme 1). Several approaches to iminosugars have been described previously using this reaction,[15,16] and a number of them were based in a double reductive amination,[17,18] with the possibility of stereoisomer mixtures being formed. We planned to combine reductive amination with intramolecular epoxide opening.



Scheme 1. Reagents and conditions: (a) DMSO, Ac_2O, 24 h; (b) $BnNH_2$, $ZnCl_2$, $NaBH_3CN$, EtOH, 7 h; (c) Ac_2O, py, 48 h.

2. Results and discussion

Our strategy starts with the oxidation of the epoxyamide **1a** to the ketone **2**. The best results were obtained

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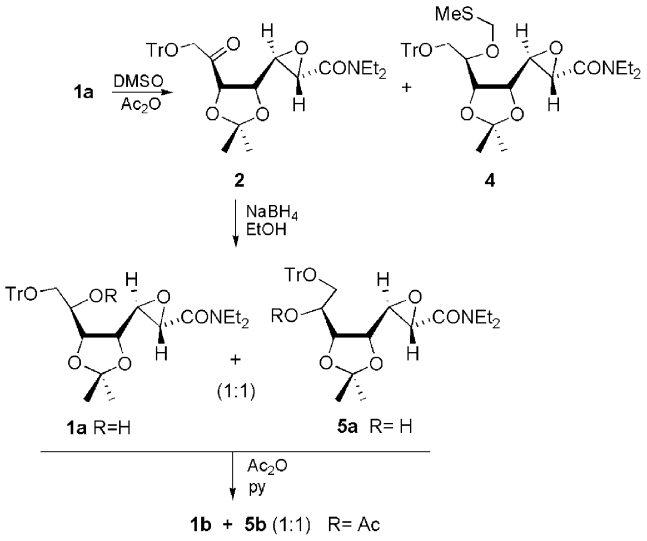
treating **1a** with DMSO and Ac_2O, although a small quantity of methylthiomethylether **4** was isolated with the oxidation product **2**. Both products could be structurally determined by spectroscopy. To test a possible C-5 epimerisation in the oxidation product, we reduced **2** obtaining an inseparable mixture of **1a** and its C-6 epimer **5a** in approximately 1:1 relation. The epimers were acetylated giving the mixture of **1b**,[19] and **5b**. Thus, it was confirmed that **2** had not epimerised (Scheme 2).



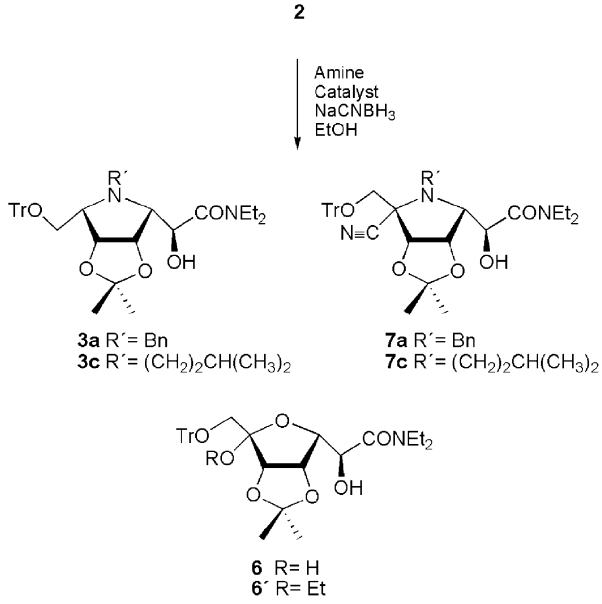
Scheme 2.

The reductive amination process permitted us to obtain the pyrrolidine products in a one-pot procedure. The ketone **2** was treated with benzylamine and zinc chloride in ethanolic solution in the presence of sodium cyanoborohydride. The reduction of the imine with subsequent regioselective epoxide opening gave the pyrrolidine **3a** by a 5-*exo* intramolecular process. Surprisingly, only a pyrrolidine derivative with the (*S*)-configuration (L-series) was isolated. The (*R*)-isomer was not detected. The ^1H NMR data showed the symmetrical structure of **3a**, with similar coupling constants $J_{3,4} = 6.3$ Hz and $J_{5,6} = 6.4$ Hz.[20] The complete connectivity of the carbon and hydrogen atoms was ascertained by 2D NMR experiments. These signals: C-3 = 67.6 ppm, C-6 = 66.4 ppm, C-4 = 80.56 ppm and C-5 = 78.69 ppm are consistent with a pyrrolidine ring. Additionally, the acetylation of **3a** giving **3b**, confirmed the structural assignment. Our strategy takes advantage on earlier procedures due to the complete stereoselectivity in both processes: reduction and subsequent oxirane opening.

The low yield in the synthesis of **3a** could be due to the formation of hemiacetal **6**, formed from **2** after several hours of reaction. This product was isolated in several experiments. The chromatographic mobility of product **6** was similar to that of **2** (slightly more polar), it being sometimes difficult to determine the completion of the reaction with accuracy. NMR experiments permitted us to elucidate the structure of **6** but not the absolute configuration at C-6.

In an experiment, the ethanol addition product **6′** (R = Et) was detected.

To study the influence of the catalyst we repeated the reaction of **2** with $BnNH_2$ and $NaCNBH_3$ using $SnCl_2$ (Scheme 3), isolating **3a** as major product (42%) along with an α-aminonitrile **7a** (12%) that could be formed by cyanide addition to the imine intermediate before cyclisation. The spectroscopy data confirmed this structure, (^{13}C NMR: 117.5 ppm, C≡N; quaternary C-6 in SEFT), but not the absolute configuration at C-6. To our knowledge this subproduct type has been not described in literature in reductive amination reactions with $NaCNBH_3$ as reductor. The α-aminonitriles are useful as α-aminoacids precursors and among the wide range of synthetic routes to α-aminoacids, the related Strecker synthesis is the most predominant (Table 1).



Scheme 3.

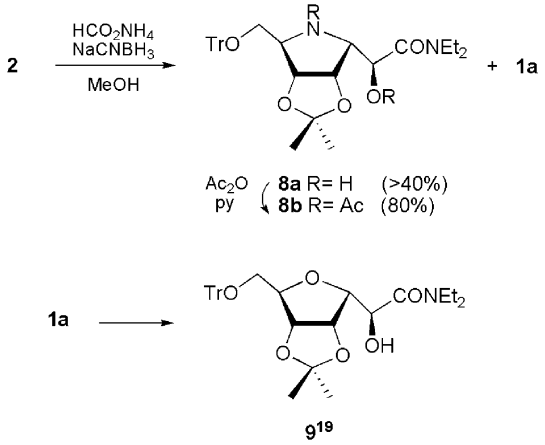
Table 1. Isolated products in the reductive amination reactions of Scheme 3[23]

Amine	Catalyst	**3** (%)	**7** (%)	**6** (%)
$BnNH_2$	$ZnCl_2$	**3a** (60)	—	(25)
$BnNH_2$	$SnCl_2$	**3a** (42)	**7a** (12)	Not determined
$(CH_3)_2CH(CH_2)_2NH_2$	$ZnCl_2$	**3c** (67)	—	(3)
$(CH_3)_2CH(CH_2)_2NH_2$	$SnCl_2$	**3c** (42)	**7c** (15)	Not determined

With the object of studying the influence of the nature of protecting group in the stereoselectivity of the reduction process, we tested the reaction with a bulky aliphatic amine. Moreover, *N*-alkylated azasugars have been demonstrated to be stronger glycosidase inhibitors than the corresponding nonalkylated derivatives.[21] Using isoamylamine we obtained similar results to those of the benzyl amine with $ZnCl_2$ or $SnCl_2$ as catalysts (Scheme 3). The formation of the product **3c** showed that the complete stereoselectivity, in the reductive amination reaction, cannot be simply justified by a possible

π–π stacking interaction between the trityl and benzyl groups as we supposed at first. The role of the free hydroxyl groups in the formation of D-products[22] has been previously noted and accordingly, the presence of isopropylidene group should favour the L-products. In our case, the reaction could not be tested with the deprotected ketone to compare possible changes in the stereoselectivity because the hydrolysis of the protecting groups could provoke secondary reactions. Additionally, some results revealed a discrepancy between the soluble hydride and catalytic hydrogenation methods.[17]

In contrast, employing a combination of ammonium formate and sodium cyanoborohydride in methanol, (Scheme 4) we obtained the D-isomer **8a** and the direct reduction product **1a**. The C-6 epimer was not detected. The structural assignment of **8a** and that of its acetate **8b** was by NMR data ($J_{5,6} = 0$). Compound **1a** cyclised easily to the C-glycoside **9**.[19]



Scheme 4.

3. Conclusion

In conclusion, with substituted amines and $ZnCl_2$ or $SnCl_2$, the hydride delivery is from the least hindered face to afford, after cyclisation, the L-isomers. With ammonium formate, a less hindered imine is formed, which leads to the product **8a** (D-series) with a 5,6-*trans*-relationship.

We have described a method to achieve pyrrolidine derivatives in a highly stereocontrolled manner, in five steps from D-ribose. Therefore, this methodology can be extended to the synthesis of various pyrrolidine azasugars having suitable side chains for further synthetic elaborations. This research program is underway in our laboratory.

4. Experimental

4.1. General

All reactions were carried out under argon or nitrogen atmosphere using distilled solvents. Reactions were monitored by thin layer chromatography (TLC) on E. Merck silica gel plates (0.25 mm) and visualised using UV light (254 nm) and/or heating with 7% ethanolic phosphomolybdic acid solution. Flash chromatography was performed on E. Merck silica gel (60, particle size 0.040–0.063 mm). After chromatographic purification, the formation of solid foam is favoured solving syrupy products in some of Et_2O and evaporating. NMR spectra were recorded at on a Bruker WP200SY spectrometer at room temperature. Chemical shifts (ppm) are reported relative to the residual solvent peak. Multiplicities are designated as: singlet (s), doublet (d), triplet (t) and multiplet (m). Coupling constants are expressed as *J* values in Hertz units. Mass spectra (EI, CI and FAB) were recorded with a Kratos MS-80RFA or a Micromass AutoSpecQ instrument with a resolution of 1000 or 60,000 (10% valley definition). For the FAB spectra, ions were produced by a beam of xenon atoms (67 keV), using 3-nitrobenzyl alcohol or thioglycerol as matrix and NaI as salt. Exact masses were recorded on a Kratos MS-80RFAa instrument of the University of Seville. Specific rotations were measured with a Perkin–Elmer 241 polarimeter.

4.2. *N*,*N*-Diethyl 2,3-anhydro-4,5-*O*-isopropylidene-7-*O*-trityl-D-*altro*-6-heptulosonamide 2

To a solution of **1a**[19] (0.7 g, 1.3 mmol) in DMSO (3.6 mL, 51.3 mmol) cooled with ice bath was added Ac_2O (2.4 mL, 25.6 mmol). The mixture was allowed to reach room temperature and stirred for 24 h. TLC ($CHCl_3$–hexanes–MeOH, 10:10:1) showed the depletion of **1a** and the formation of two faster-running compounds. Ethyl ether was added (10 mL) and the reaction mixture washed with water and the aqueous layer extracted with Et_2O (2×10 mL). The combined organic layers were dried over anhyd $MgSO_4$ and concentrated. The residue was chromatographed (AcOEt–hexanes, 4:6) to give **4** (123 mg, 27%) and the ketone **2** (430 mg, 61%) as a white foam. Compound **2**: $[\alpha]_D^{26} = -20$ (*c* 0.53, $CHCl_3$). R_f: 0.6 (AcOEt–hexanes, 4:6); 0.7 ($CHCl_3$–hexanes–MeOH, 10:10:1). ^{1}H NMR δ (400 MHz, $CDCl_3$): 1.09 (t, 3H, CH_2CH_3), 1.19 (t, 3H, CH_2CH_3), 1.29 (s, 3H, $C(CH_3)_2$), 1.44 (s, 3H, $C(CH_3)_2$), 3.18 (dd, 1H, H-3, $J_{3,4} = 5.4$, $J_{3,2} = 2.1$), 3.30–3.46 (m, 4H, CH_2CH_3), 3.49 (d, 1H, H-2), 4.04 (d, 2H, H-7, H-7′, $J_{7,7'} = 6.9$), 4.39 (dd, 1H, H-4, $J_{4,5} = 7$), 4.84 (d, 1H, H-5), 7.21–7.43 (m, 15H, Tr). ^{13}C NMR δ (100 MHz, $CDCl_3$): 12.8 and 14.6 ($2CH_2CH_3$), 25.0 and 26.9 ($C(CH_3)_2$), 40.6 and 41.3 ($2CH_2CH_3$), 51.5 (C-2), 55.2 (C-3), 69.3 (C-4), 76.2 (C-7), 80.1 (C-5), 88.1 (CPh_3), 110.5 [$C(CH_3)_2$], 127.4, 128.1, 128.6, 142.9 (Ph), 165.1 ($CONEt_2$), 203.1 (CO). FAB HRMS *m/z*: 566.251641, [MNa^+] $C_{33}H_{37}NO_6Na$ requires 566.251858.

Compound **4**: R_f: 0.7 (AcOEt–hexanes, 4:6) ^{1}H NMR δ (400 MHz, $CDCl_3$): 1.14 (t, 3H, CH_2CH_3), 1.25 (t, 3H, CH_2CH_3), 1.37 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$), 2.10 (s, 3H, CH_2SCH_3) 3.37 (dd, 1H, H-3, $J_{3,4} = 6,3$, $J_{3,2} = 1.8$), 3.4–3.52 (m, 6H, H-7, H-7′, $2CH_2CH_3$), 3.54 (d, 1H, H-2), 4.02 (t, 1H, H-4, $J_{4,5} = 6.4$), 4.06 (m, 1H, H-6), 4.55 (dd, 1H, H-5,

$J_{5,6}$ = 8.2), 4.67 (2d, 2H, CH_2SCH$_3$), 7.22–7.49 (m, 15H, Tr). ^{13}C NMR δ (50 MHz, CDCl$_3$): 12.9 and 14.6 (2CH$_2$*C*H$_3$), 14.7 (CH$_2$S*C*H$_3$) 24.9 and 27.5 [C(*C*H$_3$)$_2$], 40.6 and 41.3 (2*C*H$_2$CH$_3$), 51.8 (C-2), 55.1 (C-3), 62.5, 73.8, 74.8, 75.8, 77.1, 86.6 (CPh$_3$), 108.7 [*C*(CH$_3$)$_2$], 126.9, 127.7, 128.7, 143.7 (Ph), 165.9 (CONEt$_2$).

4.3. Reduction of 2 with $NaBH_4$ and acetylation of 1a and 5a

To a cooled solution (0 °C) of **2** (70 mg, 0.13 mmol) in EtOH (0.5 mL) was added $NaBH_4$ (4.8 mg, 0.13 mmol) stirring for 15 min. The reaction mixture was diluted with aq $KHSO_4$ and extracted with Et_2O. The organic layer was dried over anhyd $MgSO_4$, filtered and evaporated. The residue was purified by preparative TLC (AcOEt–hexanes, 1:1), yielding an inseparable mixture of **1a** and **5a** (50 mg, 71%). A solution of the mixture **1a** and **5a** (42 mg, 0,08 mmol) and Ac_2O (0.02 mL, 0.15 mmol) in pyridine (0.5 mL) was stirred at room temperature for 24 h. The mixture was diluted with cold water and extracted with Et_2O. The organic layer was dried over anhyd $MgSO_4$, filtered and evaporated. The residue was purified in preparative TLC (hexanes–Et_2O–NEt_3, 5:10:2), yielding a mixture (R_f: 0.4) of the acetylated products **1b**[19] and **5b** (1:1, 30 mg, 65%). Selected ^{1}H NMR data for compound **5a**: 3.48 (d, H-2), 3.55 (m, H-3), 3.80 (t, H-4), 4.05 (m, H-6), 4.42 (dd, H-5). Compound **5b**: 4.72 (m, 2H, H-5 of **5a** and **5b**), 5.39 (m, H-6).

4.4. Typical procedure for reductive amination reaction with metal chlorides

To a solution of the carbonyl compound **2** in EtOH was added the amine and then a solution of $NaCNBH_3$ and the catalyst ($ZnCl_2$ or $SnCl_2$) in EtOH, stirring the mixture at rt. After completion of the reaction, the mixture was diluted with water and extracted with Et_2O (2×). The combined organic layers were dried over anhyd $MgSO_4$, filtered and evaporated and later purified.

4.5. *N*,*N*-Diethyl 3,6-dideoxy-3,6-imino-*N*′-benzyl-4,5-*O*-isopropylidene-7-*O*-trityl-L-*glycero*-D-*manno*-heptonamide 3a

To a solution of **2** (200 mg, 0.37 mmol) in EtOH (1.2 mL) were successively added benzylamine (0.16 mL 1.47 mmol) and a mixture of $NaBH_3CN$ (23 mg, 0.37 mmol) and $ZnCl_2$ (25 mg 0.18 mmol) in EtOH (0.4 mL), stirring the mixture for 7 h at room temperature. After following the work-up procedure for reductive amination reactions, the residue was purified by preparative TLC (MeOH–AcOEt–hexanes, 1:1:8), obtaining pure **3a** (120 mg, 60%) and **6** (28 mg, 25%) as white foams. Compound **3a**: $[\alpha]_D^{26} = +16$ (*c* 1, $CHCl_3$). ^{1}H NMR δ (400 MHz, CDCl$_3$): 1.08 (t, 3H, CH$_2$C*H*$_3$), 1.07 (t, 3H, CH$_2$C*H*$_3$), 1.33 (s, 3H, C(C*H*$_3$)$_2$), 1.41 (s, 3H, C(C*H*$_3$)$_2$), 2.66–2.72 (m, 2H, H3, H-6), 3.06–3.21 (m, 3H, H-7, C*H*$_2$CH$_3$), 3.33–3.51 (m, 3H, H-7′, C*H*$_2$CH$_3$, C*H*$_2$Ph), 3.56 (d, 1H, C*H*$_2$Ph), 4.57 (d, 1H, H-2, $J_{2,3}$ = 5.3), 4.70 (dd, 1H, H-4, $J_{4,3}$ = 6.3, $J_{4,5}$ = 5.2), 4.93 (dd, 1H, H-5, $J_{5,6}$ = 6.4), 6.98 (m, 2H, CH$_2$*Ph*), 7.15 (m, 3H, CH$_2$*Ph*), 7.18–7.41 (m, 15H, Tr). ^{13}C NMR δ (100 MHz, CDCl$_3$): 12.6 and 14.2 (2CH$_2$*C*H$_3$), 25.1 and 26.0 (C(*C*H$_3$)$_2$), 40.0 and 41.6 (2CH$_2$*C*H$_3$), 54.4 (*C*H$_2$Ph), 61.6 (C-7), 66.4 (C-6), 67.5 (C-3), 67.7 (C-2), 78.7 (C-4), 80.6 (C-5), 86.8 (*C*Ph$_3$), 110.9 (*C*(CH$_3$)$_2$), 126.8, 127.6, 128.7, 137.0, 144.1 (Ph), 171.9 (*C*ONEt$_2$). FAB HRMS *m*/*z*: 635.3456 [MH$^+$] $C_{40}H_{47}N_2O_5$ requires 635.3484. Compound **6**: ^{1}H NMR δ (400 MHz, CDCl$_3$): 1.10 (t, 3H, CH$_2$C*H*$_3$), 1.18 (t, 3H, CH$_2$C*H*$_3$), 1.26 (s, 3H, C(C*H*$_3$)$_2$), 1.28 (s, 3H, C(C*H*$_3$)$_2$), 3.04 (m, 1H, C*H*$_2$CH$_3$), 3.16 (m, 1H, C*H*$_2$CH$_3$), 3.32 (d, 1H, H-7, $J_{7,7'}$ = 3.6), 3.83 (m, 1H, C*H*$_2$CH$_3$), 3.65 (m, 1H, C*H*$_2$CH$_3$), 4.01 (dd, 1H, H-4, $J_{4,3}$ = 3.6, $J_{4,5}$ = 9.15), 4.47 (d, 1H, H-2, $J_{2,3}$ = 5.5), 4.68 (d, 1H, H-5), 4.92 (dd, 1H, H-4), 7.16–7.41 (m, 15H, Tr). ^{13}C NMR δ (100 MHz, CDCl$_3$): 12.7 and 13.8 (2CH$_2$*C*H$_3$), 24.6 and 25.9 (C(*C*H$_3$)$_2$), 40.4 and 40.9 (2CH$_2$*C*H$_3$), 64.4 (C-7), 64.8 (C-2), 80.3, 81.4, 84.8 (C-3, C-4, C-5), 86.7 (*C*Ph$_3$), 104.5 (C-6), 112.5 (*C*(CH$_3$)$_2$), 127.2, 127.7, 128.6, 143.2 (Ph), 172.0 (*C*ONEt$_2$). FAB HRMS *m*/*z*: 561.270062, [MH$^+$] $C_{33}H_{39}N_1O_7$ requires 561.272653.

4.6. Acetylation of 3a

A solution of **3a** (100 mg, 0.16 mmol) and Ac_2O (0.5 mL) in 1.2 mL of pyridine was stirred for 48 h at rt. After addition of cold water and extraction with Et_2O (2 × 5 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by preparative TLC (AcOEt–hexanes, 1:1, R_f: 0.5) afforded pure **3b** (74 mg, 80%) as a foam. ^{1}H NMR δ (400 MHz, CDCl$_3$): 0.91 (t, 3H, CH$_2$C*H*$_3$), 1.20 (t, 3H, CH$_2$C*H*$_3$), 1.32 (s, 3H, C(C*H*$_3$)$_2$), 1.40 (s, 3H, C(C*H*$_3$)$_2$), 2.06 (s, 3H, OCOC*H*$_3$), 2.73 (m, 1H, H6), 3.06 (dd, 1H, H-3, $J_{3,2}$ = 8.2, $J_{3,4}$ = 4.6), 3.10–3.17 (m, 2H, C*H*$_2$CH$_3$), 3.29–3.35 (m, 3H, H-7′, C*H*$_2$CH$_3$), 3.35 (d, 1H, C*H*$_2$Ph), 3.43 (t, 1H, H-7, $J_{7,7'}$ = 8.3), 3.53 (d, 1H, C*H*$_2$Ph), 3.70–3.77 (m, 1H, C*H*$_2$CH$_3$), 4.60 (dd, 1H, H-5, $J_{5,4}$ = 6.0), 4.72 (dd, 1H, H-4), 5.51 (d, 1H, H-2), 6.93 (m, 2H, CH$_2$*Ph*), 7.14 (m, 3H, CH$_2$*Ph*), 7.20–7.40 (m, 15H, Tr). ^{13}C NMR δ (100 MHz, CDCl$_3$): 12.3 and 13.3 (2CH$_2$*C*H$_3$), 20.8 (OCO*C*H$_3$) 25.4 and 26.1 (C(*C*H$_3$)$_2$), 40.9 and 42.2 (2CH$_2$*C*H$_3$), 54.2 (*C*H$_2$Ph), 61.2 (C-7), 65.1 (C-2), 65.7 (C-6), 69.3 (C-3), 78.8 (C-4), 79.5 (C-5), 86.7 (*C*Ph$_3$), 110.8 (*C*(CH$_3$)$_2$), 126.8–144.1 (Ph), 168.7 (*C*ONEt$_2$), 170.1 (O*C*OCH$_3$).

4.7. Synthesis of 3a and *N*,*N*-diethyl 6(*R* or *S*)-cyano-3-deoxy-3,6-imino-*N*′-benzyl-4,5-*O*-isopropylidene-7-*O*-trityl-D-*manno*-heptonamide 7a

Following the general procedure were mixtured: **2** (100 mg, 0.18 mmol), EtOH (1 mL) and benzylamine (0.2 mL 1.08 mmol) with a solution of $NaBH_3CN$ (23 mg, 0.4 mmol) and $SnCl_2$ (17.24 mg 0.08 mmol, 0.5 equiv) in EtOH (0.4 mL), stirring the resulting mixture at room temperature. After 24 h, TLC (AcOEt–hexanes, 4:6) indicated the complete conversion of the starting material. After work-up as usual, the residue was subjected to flash chromatography on silica (AcOEt–hexanes, 3:7) to afford **3a** (49 mg, 42%) and **7a** (15 mg, 12%) as white foams. Compound **7a**: R_f:

0.6 (AcOEt–hexanes, 4:6), $[\alpha]_D^{22} = +26$ (*c* 0.54, $CHCl_3$) ^1H NMR δ (400 MHz, $CDCl_3$): 1.02–1.07 (m, 6H, $2CH_2CH_3$), 1.28 (s, 3H, $C(CH_3)_2$), 1.30 (s, 3H, $C(CH_3)_2$), 2.99–3.04 (m, 2H, H-7′, H-3), 3.12–3.26 (m, 3H, H-7, CH_2CH_3), 3.35 (m, 1H, CH_2CH_3), 3.72–3.85 (2d, 2H, CH_2Ph), 4.26 (d, 1H, –OH, $J_{OH,2} = 9.32$), 4.42 (dd, 1H, H-2, $J_{2,3} = 3.5$), 4.95 (d, 1H, H-5, $J_{5,4} = 6.4$), 5.26 (dd, 1H, H-4, $J_{4,3} = 4.1$, $J_{4,5} = 6.4$), 7.09–7.34 (m, 20H, Tr). ^{13}C NMR δ (100 MHz, $CDCl_3$): 12.7 and 14.4 ($2CH_2CH_3$), 25.3 and 25.7 ($C(CH_3)_2$), 40.3 and 41.7 ($2CH_2CH_3$), 53.3 (CH_2Ph), 63.1 (C-7), 67.0 (C-3), 67.8 (C-2), 71.5 (C-6), 80.6 (C-4), 81.9 (C-5), 87.3 (CPh_3), 112.4 ($C(CH_3)_2$), 117.5 (C≡N), 126.9, 127.7, 128.7, 138.6, 143.1 (Ph), 170.3 ($CONEt_2$). FAB HRMS *m*/*z*: 682.327324, $[MNa^+]$ $C_{41}H_{45}N_3O_5Na$ requires 682.325692.

4.8. *N*,*N*-Diethyl 3,6-dideoxy-3,6-imino-*N*′-(3′-methylbutyl)-4,5-*O*-isopropylidene-7-*O*-trityl-L-*glycero*-D-*manno*-heptonamide 3c

Isoamylamine (0.04 mL, 0.36 mmol) was added to a solution of **2** (50 mg, 0.09 mmol) in EtOH (0.4 mL) with stirring at room temperature. Then was added a solution of $NaBH_3CN$ (5.8 mg, 0.09 mmol) and $ZnCl_2$ (6.3 mg, 0.04 mmol, 0.5 equiv) in EtOH (0.4 mL). After stirring for 3 h, TLC (AcOEt–hexanes, 4:6) showed a more faster-running compound (R_f: 0.45). The reaction was worked up as above and the residue subjected to flash chromatography on silica (AcOEt–hexanes, 3:7) to afford **3c** (38 mg, 67%) and hemiacetal **6** (1.5 mg, 3%) as white foams. Compound **3c**: $[\alpha]_D^{26} = -25$ (*c* 0.53, $CHCl_3$) ^1H NMR δ (400 MHz, $CDCl_3$): 0.71–0.73 (2d, 6H, $-CH_2CH_2CH(CH_3)_2$), 0.98 (m, 1H, $-CH_2CH_2CH(CH_3)_2$), 1.07–1.13 (m, 6H, $2CH_2CH_3$), 1.17 (m, 1H, $-CH_2CH_2CH(CH_3)_2$), 1.27 (s, 3H, $C(CH_3)_2$), 1.31 (s, 3H, $C(CH_3)_2$), 2.42–2.57 (m, 2H, $-CH_2CH_2CH(CH_3)_2$), 2.67 (dd, 1H, H-3), 2.74 (dd, 1H, H-6), 3.10 (dd, 1H, H-7′, $J_{7',6} = 5.3$, $J_{7',7} = 9.1$), 3.23–3.4 (m, 3H, CH_2CH_3), 3.48 (m, 1H, CH_2CH_3), 3.56 (dd, 1H, H-7, $J_{7,6} = 6.4$), 4.09 (d, 1H, –OH, $J_{OH,2} = 8.6$), 4.49 (dd, 1H, H-2, $J_{2,3} = 4.8$), 4.63 (dd, 1H, H-5, $J_{5,4} = 6.4$, $J_{5,6} = 5.3$), 4.92 (dd, 1H, H-4, $J_{4,3} = 4.8$), 7.15–7.45 (m, 15H, Tr). ^{13}C NMR δ (100 MHz, $CDCl_3$): 12.7 and 14.3 ($2CH_2CH_3$), 22.5 and 22.7 ($CH_2CH_2CH(CH_3)_2$), 24.9, 25.7 and 26.6 [$C(CH_3)_2$, $-CH_2CH_2CH(CH_3)_2$], 31.3 [$-CH_2CH_2CH(CH_3)_2$], 40.5 and 41.6 ($2C_2CH_3$), 47.1 [$-CH_2CH_2CH(CH_3)_2$], 62.4 (C-7), 64.5 (C-6), 65.8 (C-3), 67.4 (C-2), 79.0 (C-5), 80.7 (C-4), 86.8 (CPh_3), 110.9 ($C(CH_3)_2$), 126.8, 127.6, 128.7, 138.6, 144.1 (Ph), 171.7 ($CONEt_2$). CI mass spectra: 614 $[M^+]$(<1), 615 $[MH^+]$(1), 484 (64), 485 (22), 243 (100). FAB HRMS *m*/*z*: 637.361743 $[MNa^+]$ $C_{38}H_{50}N_2O_5Na$ 637.357259.

4.9. Synthesis of 3c and *N*,*N*-diethyl 6(*R* or *S*)-cyano-3,6-imino-*N*′-(3′-methylbutyl)-4,5-*O*-isopropylidene-7-*O*-trityl-D-*manno*-heptonamide 7c

Isoamylamine (0.08 mL, 0.73 mmol) was added to a solution of **2** (100 mg, 0.18 mmol) in EtOH (1 mL) with stirring at room temperature. Then was added a solution of $NaBH_3CN$ (11.5 mg, 0.18 mmol) and $SnCl_2$ (17.3 mg, 0.09 mmol) in EtOH (0.4 mL). After stirring for 3 h, TLC (AcOEt–hexanes, 4:6) showed two new less polar products than **2**. The reaction was worked up as above and the residue subjected to flash chromatography on silica (AcOEt–hexanes, 4:6) to afford **3c** (47 mg, 42%) and **7c** (18 mg, 15%) as white foams. Compound **7c**; R_f: 0.7 (AcOEt–hexanes, 4:6). $[\alpha]_D^{22} = +7.5$ (*c* 0.48, $CHCl_3$). ^1H NMR δ (400 MHz, $CDCl_3$): 0.67 (2d, 6H, $-CH_2CH_2CH(CH_3)_2$), 0.98 (m, 1H, $-CH_2CH_2CH(CH_3)_2$), 1.07–1.13 (m, 6H, $2CH_2CH_3$), 1.17 (m, 1H, $-CH_2CH_2CH(CH_3)_2$), 1.20 (s, 3H, $C(CH_3)_2$), 1.23 (s, 3H, $C(CH_3)_2$), 2.36 and 2.56 (2m, 2H, $-CH_2CH_2CH(CH_3)_2$), 2.81 (dd, 1H, H-3), 3.11 (d, 1H, H-7′, $J_{7',7} = 8.5$), 3.21–3.42 (m, 4H, $2CH_2CH_3$), 3.53 (d, 1H, H-7, $J_{7,7'} = 8.5$), 4.30 (d, 1H, –OH, $J_{OH,2} = 10.2$), 4.43 (dd, 1H, H-2, $J_{2,3} = 3.2$), 4.81 (d, 1H, H-5, $J_{5,4} = 6.4$), 5.11 (dd, 1H, H-4, $J_{4,3} = 4.3$), 7.15–7.46 (m, 15H, Tr). ^{13}C NMR δ (100 MHz, $CDCl_3$): 12.8 and 14.5 ($2CH_2CH_3$), 22.3 and 22.4 ($CH_2CH_2CH(CH_3)_2$), 25.3, 25.5 and 26.3 [$C(CH_3)_2$, $CH_2CH_2CH(CH_3)_2$], 37.9 [$CH_2CH_2CH(CH_3)_2$], 40.4 and 41.9 ($2CH_2CH_3$), 47.5 [$CH_2CH_2CH(CH_3)_2$], 62.9 (C-7), 66.0 (C-3), 68.0 (C-2), 70.4 (C-6), 80.6 (C-4), 82.3 (C-4), 87.5 (CPh_3), 112.6 ($C(CH_3)_2$), 118.3 (CN), 127.1, 127.7, 128.7, 143.1, 144.1 (Ph), 170.3 ($CONEt_2$). FAB HRMS *m*/*z*: 662.357131 $[MNa^+]$ $C_{39}H_{49}N_3O_5Na$ requires 662.356992.

4.10. *N*,*N*-Diethyl 3,6-dideoxy-3,6-imino-4,5-*O*-isopropylidene-7-*O*-trityl-D-*glycero*-D-*manno*-heptonamide 8a

In a flask containing 14 mg of dried molecular sieves were dissolved 100 mg (0.18 mmol) of **2** in dried MeOH (1.7 mL). Ammonium formate was added (15.1 mg, 0.23 mmol) and the mixture stirred for 20 min. Then was added $NaCNBH_3$ (25.9 mg, 0.41 mmol). After 11 h TLC (Et_3N–AcOEt–hexanes, 1:3:6) showed the complete conversion of **2**. The reaction mixture was filtered through Celite® that was washed with methanol. The filtrates were concentrated under vacuo and the residue was subjected to flash chromatography on silica (AcOEt–hexanes, 1:1) to afford product **6** (15 mg, 14%), pure **8a** (40 mg, 40%) as white foam, and 10 mg (**8a** + degradation products). Compound **8a**: $[\alpha]_D^{22} = +17$ (*c* 0.48, CH_2Cl_2). ^1H NMR δ (400 MHz, $CDCl_3$): 1.05 (t, 3H, CH_2CH_3), 1.12 (t, 3H, CH_2CH_3), 1.24 (s, 3H, $C(CH_3)_2$), 1.45 (s, 3H, $C(CH_3)_2$), 2.90–3.0 (m, 2H, H-7′, H-6), 3.05–3.22 (m, 3H, CH_2CH_3, H-3), 3.55–3.78 (m, 3H, CH_2CH_3, –OH), 4.33 (d, 1H, H-5, $J_{5,4} = 5.9$), 4.61 (dd, 1H, H-2), 4.69 (dd, 1H, H-4, $J_{4,3} = 5.37$), 7.15–7.33 (m, 15H, Tr). ^{13}C NMR δ (100 MHz, $CDCl_3$): 12.9 and 14.1 ($2CH_2CH_3$), 24.3 and 26.0 ($C(CH_3)_2$), 40.2 and 41.6 ($2CH_2CH_3$), 62.7, 63.0 (C-7, C-6), 63.9 (C-3), 67.3 (C-2), 81.0 (C-4), 82.4 (C-5), 86.8 (CPh_3), 111.36 ($C(CH_3)_2$), 127.08, 127.8, 128.4, 143.5 (Ph), 172.0 ($CONEt_2$). CI mass spectra: 545 $[MH^+]$(1), 271 (3), 243 (100). FAB HRMS: *m*/*z* 545.301417, $[M+H^+]$ $C_{33}H_{41}N_2O_5$ requires 545.301548.

4.11. Acetylation of 8a

To a solution of **8a** (30 mg, 0.05 mmol) in pyridine (1 mL) was added Ac_2O (0.2 mL) with stirring at rt. TLC showed the slow formation of a new compound.

After 5 days, cold water was added and the mixture extracted with Et_2O (2×5 mL). The organic layers were dried (anhyd $MgSO_4$) and concentrated to give a residue that was subjected to flash chromatography on silica (AcOEt–hexanes, 1:1) to afford **8b** (25 mg, 80%) as a white foam. R_f: 0.4 (AcOEt–hexanes, 1:1) ^{1}H NMR δ (400 MHz, $CDCl_3$): 1.10 (m, 6H, $2CH_2CH_3$), 1.24 (s, 3H, $C(CH_3)_2$), 1.41 (s, 3H, $C(CH_3)_2$), 1.84 (s, 3H, $NCOCH_3$), 2.0 (s, 3H, $OCOCH_3$), 3.12 (dd, 1H, H-7′), 3.25 (dd, 1H, H-7, $J_{7,7'} = 9.4$), 3.36 (m, 3H, CH_2CH_3), 3.62 (m, 1H, CH_2CH_3), 3.93 (dd, 1H, H-6, $J_{6,7} = 5.9$, $J_{6,7'} = 6.9$), 4.49 (d, 1H, H-5, $J_{5,4} = 5.37$), 4.62 (dd, 1H, H-4, $J_{4,3} = 4.83$), 6.35 (d, 1H, H-2, $J_{2,3} = 8.6$), 7.20–7.37 (m, 15H, Tr). ^{13}C NMR δ (100 MHz, $CDCl_3$): 12.3 and 13.7 ($2CH_2CH_3$), 20.8 ($OCOCH_3$), 22.7 ($NCOCH_3$), 24.8 and 26.4 ($C(CH_3)_2$), 40.0 and 41.5 ($2CH_2CH_3$), 61.9 (C-7), 62.1 (C-3), 66.0 (C-6), 67.4 (C-2), 79.9 (C-5), 80.3 (C-4), 87.5 (CPh_3), 111.3 ($C(CH_3)_2$), 126.8–143.2 (Ph), 167.6 ($CONEt_2$), 168.7 and 169.7 (2Ac).

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