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Synthesis of extended spacer-linked neooligodeoxysaccharides by metathesis olefination and evaluation of their RNA-binding properties

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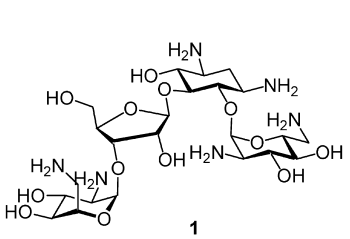
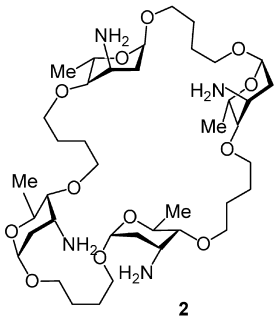
Abstract—The preparation of linear 1,4-butanediol-linked oligodeoxysugars **50**–**53**, **58** and **60** is described which are potential binders to polynucleotides. Various aminodeoxymonosaccharides **9**, **13**–**18**, **30**, **31** and **40**–**42** which are either allylated at the anomeric center or at C4 were subjected to the metathesis olefination protocol. Depending on the position of allylation *E*/*Z*-mixtures of C_2-symmetric head-to-head or tail-to-tail homodimers were formed. Among them, saccharides **13**, **30**, **31** and **40** were transformed into the corresponding 1,4-butanediol linked disaccharides **50**–**53** by catalytic hydrogenation of the central olefinic double bond and exhaustive deprotection. In order to target extended spacer-linked neooligosaccharides homodimeric aminoglycoside **37** was bisallylated and subjected to cross metathesis conditions using methyl 4-*O*-allyl daunosamide **40** as reaction partner which yielded two desired trimeric and tetrameric linearly spacer-linked daunosamine derivatives. After hydrogenation and deprotection two additional probes **58** and **60** for nucleic acid binding studies were at hand.

1. Introduction

Oligocationic compounds, like protonable polyamines and guanidines often play key roles in various biological processes. The pharmacological activity of these molecules is due to their ability to specifically bind to polynucleotides thus giving rise to the possibility of inhibiting DNA duplication[1] or RNA catalysis, or the forcing of RNA into an alternate conformation.[2] Aminodeoxy sugars present in glycoconjugates like the anthracycline antibiotic daunomycin as well as amino glycoside antibiotics like neomycin B (**1**) typically target polynucleotides. The major drawback of aminoglycosides in medicinal applications, however, is their significant oto- and nephrotoxicity.[2,3] Still, despite the emergence of aminoglycoside-modifying enzymes[4] some aminoglycosides such as gentamicin C_{1a} and tobramycin are used in clinical practice. Nevertheless, their basic scaffold together with a variety of different techniques for joining monomeric subunits make them ideal for the synthesis of new selective and potentially less toxic structures that can be used for studying ligand binding to oligonucleotides and thus lead to modified aminoglycosides with better resistance towards bacteria.[5]



1



2

Recently, we initiated a project on the preparation of new 1,4-butanediol-linked oligomeric deoxysugars, most of them containing amino groups.[6] The synthetic strategy allows to rapidly assemble extended linear and cyclic oligosaccharides like **2**[7–9] which can serve as probes for studying interactions with oligonucleotides. Their oligomeric character in association with the larger number of amino groups which are essential for efficient binding should lead to cooperative effects[10] and hence tighter binding to oligonucleotides. The major advantage of our synthetic approach is the fact that once the monomeric

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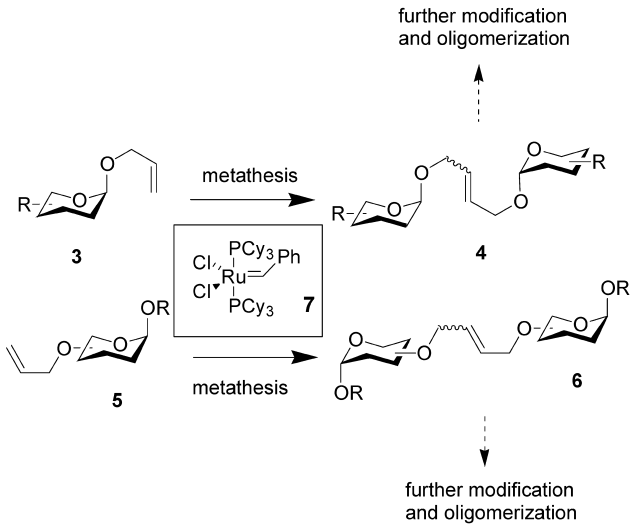
building blocks are at hand the problem of stereocontrol of the anomeric center does not need to be considered in the following coupling steps.

In this report we give a comprehensive summary of our synthetic studies towards novel linear 1,4-butanediol-linked neooligodeoxysaccharides. The 1,4-butane diol linkage between two adjacent deoxysugar moieties is efficiently constructed by metathesis-based alkene dimerization[11] of appropriately allylated glycosides using the Grubbs pre-catalyst **7** (Scheme 1). Depending on the attachment of the allyl group in hexoses **3** or **5** either head-to-head **4** or tail-to-tail **6** dimers are formed which can be further modified or oligomerized.

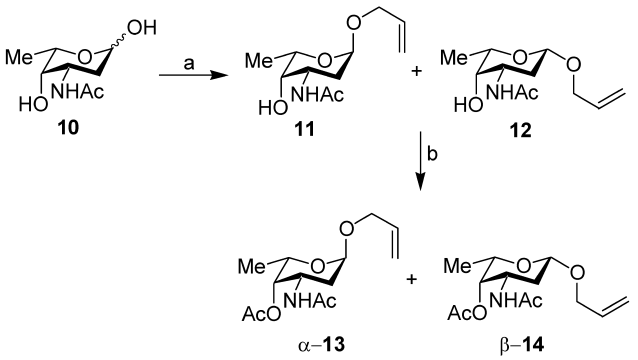


Scheme 1. Concepts for the homodimerization of pyranoses by metathesis olefination.

2. Results and discussions

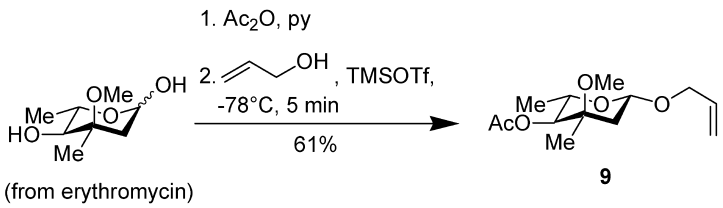
A diverse number of allylated hexoses had to be prepared prior to dimerization and oligomerization. The monomeric *O*-allylated building blocks **9**, **13**–**18**, **30**, **31** and **40**–**42** (Tables 1–3) were prepared as pure isomers according to literature procedures.[12,13] Most syntheses of these allylated products started from D-glucose, D-galactose, L-rhamnose and L-fucose. In contrast to these purely synthetic approaches, the methyl-branched allyl glycoside **9** (see also Table 1, entry 5) was obtained from erythromycin which had been degraded under strongly acidic conditions (0.75 N HCl, 20 h, rt, 90%) to furnish L-cladinose **8** (Scheme 2). L-Cladinose was transformed into allyl glycoside **9** by two standard reactions. Only the β-anomer is formed upon glycosidation which can be ascribed to the quaternary center at C-3 and the axial methyl group which limits access of the allyl alcohol from the α-face.

N-Protected L-daunosamine **10** was prepared in 20 g scale from D-mannose according to Horton and Weckerle.[14] *O*-Allylation afforded anomeric allyl glycosides **11** and **12** in 82% which could be separated by column chromatography. 4-*O*-Acylation yielded the two monomeric building blocks α-**13** and β-**14** (Scheme 3).



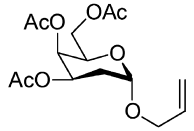
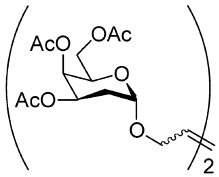
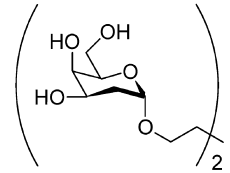
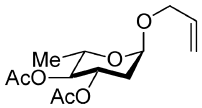
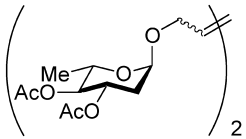
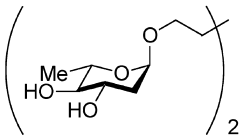
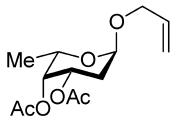
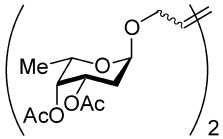
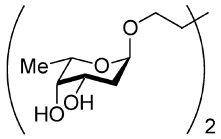
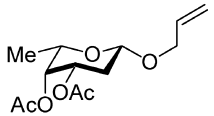
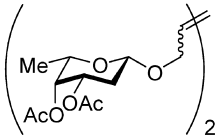
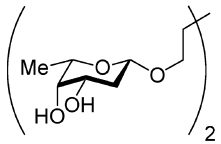
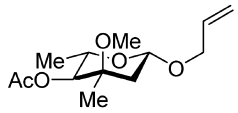
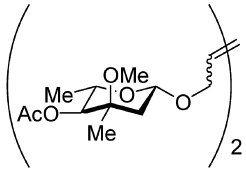
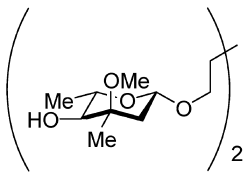
Scheme 3. Preparation of *N*-acetyl-daunosamides **13** and **14**. Reagents and conditions: (a) allyl alcohol, Dowex 50 ($H^{\oplus}$-form), 70 °C (82% for two steps), separation; (b) Ac_2O, py, 4-$DMAP_{cat.}$, rt (for **13**: quant.; for **14**: 94%).

In the following, a set of homodimeric 1,4-butanediol linked deoxyhexoses were prepared by utilizing Grubbs metathesis catalyst **7**. In Table 1 dimerization of allyl glycosides **9** and **15**–**18** is shown. Apart from β-allyl glycoside **18** the metathesis products **19**–**23** are commonly formed as *E*/*Z*-mixtures with similar ratios (commonly around 5–6:1; for **22**: *E*/*Z*=3.8:1 and for **23**: *E*/*Z*=3.5:1). The *E*-selectivity of this process is in full accordance with most intermolecular metathesis olefinations described in the literature. The preferential formation of *trans*-α,β-disubstituted metallocyclobutane intermediates is responsible for this preferred *E*-selectivity.[15] The ratios of the inseparable *E*/*Z*-mixtures described in this report were assigned by ^1H and ^{13}C NMR spectroscopy and the correlation spectra derived therefrom. Determination of the ratio has typically been achieved by indirect methods such as analysis of the chemical shifts of olefinic carbon atoms in the ^{13}C NMR spectrum.[16] It is based on the observation, that the carbon atom in the α-position of *Z*-configured olefines is magnetically more shielded than the allylic carbon atom in the corresponding *E*-configured isomer. This phenomenon is called γ-effect and leads to a ca. 5 ppm upfield shift for the *Z*-isomer. In conjunction with our synthetic efforts in this field, the group of Glaser recently developed a new NMR-technique which



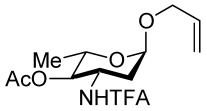
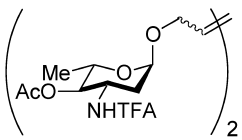
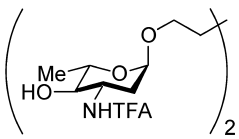
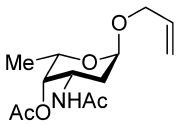
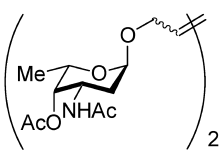
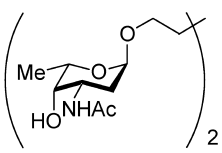
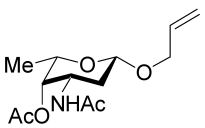
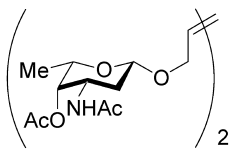
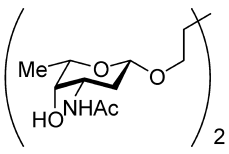
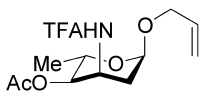
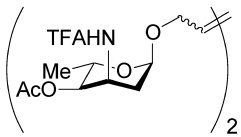
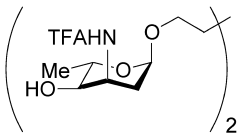
Scheme 2. Preparation of allyl cladinoside **9**.

Table 1. Preparation of head-to-head 1,4-butanediol linked 2-deoxy hexoses

Entry	Allyl glycoside	Head-to-head homodimers by metathesis[a,b]	Yield *E*/*Z*-ratio	Deprotected 1,4-butanediol linked homodimer[a,b]	Yield
1	 **15**		**19** (41%) *E*/*Z*=5:1[c]		**24** (99%)
2	 **16**		**20** (50%) *E*/*Z*=5:1[d]		**25** (99%)
3	 **17**		**21** (60%) *E*/*Z*=6:1		**26** (98%)
4	 **18**		**22** (84%) *E*/*Z*=3.8:1		**27** (99%)
5	 **9**		**23** (87%) *E*/*Z*=3.5:1		**28** (95%)

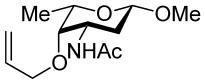
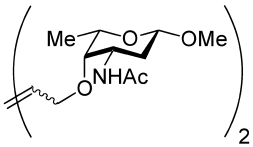
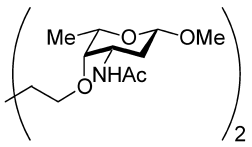
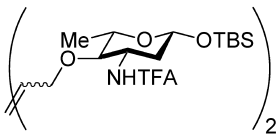
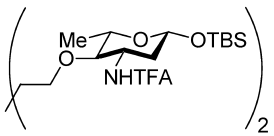
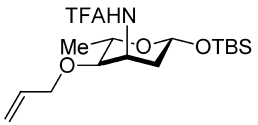
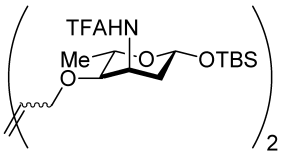
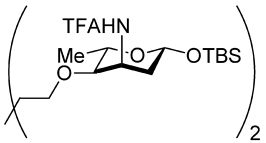
[a] For experimental details refer to Section 4.
[b] Product ratios were determined from the ^{1}H NMR spectra of the crude products; yields refer to isolated yields of pure products.
[c] Only 51% of starting material were transformed.
[d] Only 66% of starting material were transformed.

Table 2. Preparation of head-to-head 1,4-butanediol linked 3-amino-2,3-dideoxy hexoses

Entry	Allyl glycoside		Head-to-head homodimers by metathesis[a,b]	Yield *E*/*Z*-ratio	Deprotected 1,4-butanediol linked homodimer[b]	Yield
1		**30**		**32** (87%) *E*/*Z*=2.5:1		**36** (98%)
2		**13**		**33** (82%) *E*/*Z*=3.3:1		**37** (83%)
3		**14**		**34** (73%) *E*/*Z*=1:2		**38** (78%)
4		**31**		**35** (54%) *E*/*Z*=2.5:1		**39** (85%)

[a] For experimental details refer to Section 4.
[b] Product ratios were determined from the ^{1}H NMR spectra of the crude products; yields refer to isolated yields of pure products.

Table 3. Preparation of tail-to-tail 1,4-butanediol linked 3-amino-2,3-dideoxy hexoses

Entry	4-*O*-Allylated glycoside		Tail-to-tail homodimers by metathesis[a,b]	Yield *E*/*Z*-ratio	Deprotected 1,4-butanediol linked homodimer[b]	Yield
1		**40**		**43** (90%) *E*/*Z*=5:1		**46** (99%)
2		**41**		**44** (89%) *E*/*Z*=6:1		**47** (95%)
3		**42**		**45** (62%) *E*/*Z*=only *E*-isomer detected[c]		**48** (82%)

[a] For experimental details refer to Section 4.
[b] Product ratios were determined from the ^{1}H NMR spectra of the crude products; yields refer to isolated yields of pure products.
[c] Enolethers **49** were formed in 30% yield.

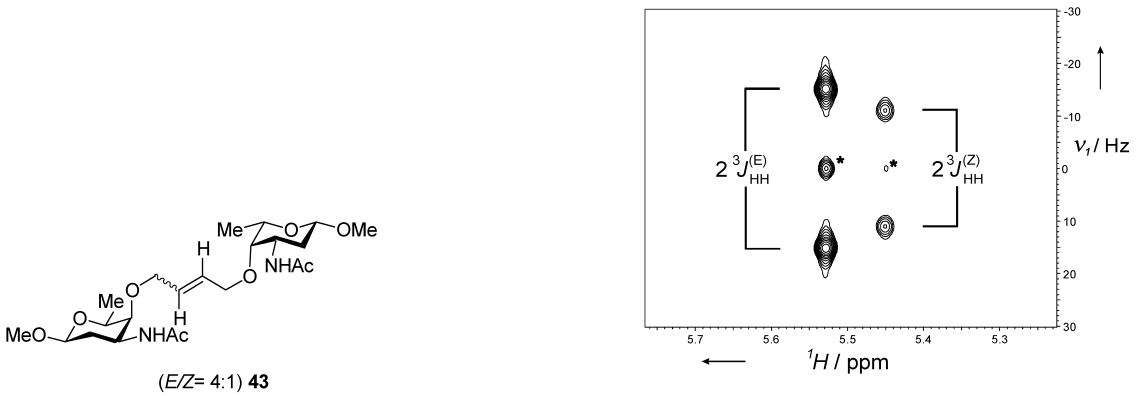
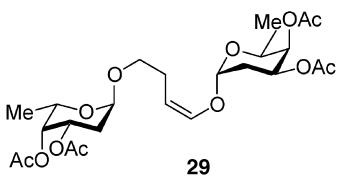


Figure 1. Determination of the double bond configuration of the homodimeric metathesis product **43** by NMR-spectroscopy.

allows to distinguish vicinal protons as found in C_2-symmetrical *E*- and *Z*- alkenes, respectively. In this two dimensional experiment the ^3J(H,H)-coupling of interest is evolved under selective isotopic mixing conditions and the proton signal is acquired. Besides a significant sensitivity gain the experiment permits a straightforward interpretation, since only the desired ^3J(H,H)-coupling gives rise to an observable splitting.[17] The advantages of this method are (i) short recording time and (ii) direct determination of coupling constants *J* of the central vicinal alkenic hydrogens in C_2-symmetric compounds. We routinely used this new NMR-tool for determining the *E*/*Z*-ratio of the metathesis products as exemplified for tail-to-tail homodimer **43** (vide supra) in Figure 1.

In some cases (entries 1 and 2), the reduced yields for the dimers is associated with incomplete transformation. The amount of catalyst **7** employed was substrate dependent. Often, the catalyst was added in up to three portions which in some cases accumulated to 10 mol%. In the case of allyl 2-deoxy-α-L-fucoside **17**, the metathesis step yielded an unsymmetrical byproduct which was characterized as the *Z*-configured enol ether **29** (17%). It is obvious that the catalyst is not only able to catalyze dimerization but also promotes prototopic rearrangements of double bonds in allyl ethers. This property of catalyst **7** has been observed before by various research groups.[5,18]

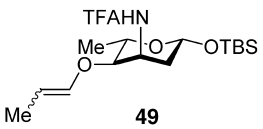


29

The primary olefination products were further modified by reduction of the olefinic double bond [10% Pd/C, H_2, trace Et_3N, MeOH/CH_2Cl_2 (2:1) or PtO_2, H_2, ethyl acetate, rt] and complete removal of the *O*-protection [NaOMe, MeOH, 0 °C to rt or Amberlyst A-21 (hydroxide form), MeOH, rt] to furnish C_2-symmetric dimers **24**–**28** in excellent yield.

In analogy to the deoxygenated allyl glycosides listed in Table 1, we utilized this synthetic sequence for the preparation of 1,4-butanediol-linked aminodeoxy saccharides **36**–**39** starting from **13**, **14**, **30** and **31** (Table 2). Under similar reaction conditions as described above, homodimers **32**–**35** were formed with less pronounced *E*/*Z*-selectivity which in the case of β-allyl glycoside **14** leads to reversed selectivity (Table 2, entry 3). Acetyl as well as trifluoracetyl protection of the amino groups were tolerable under the olefination conditions,[4] while the azido functionality is not compatible. The more polar 4-hydroxy analogue of allyl glycoside **13** is less suitable as a substrate for the metathesis olefination. The dimerization proceeded in only 47% (*E*/*Z*=4.5:1) isolated yield. Finally, catalytic hydrogenation of the intermediate alkene gave homodimer **37** in 95% yield.

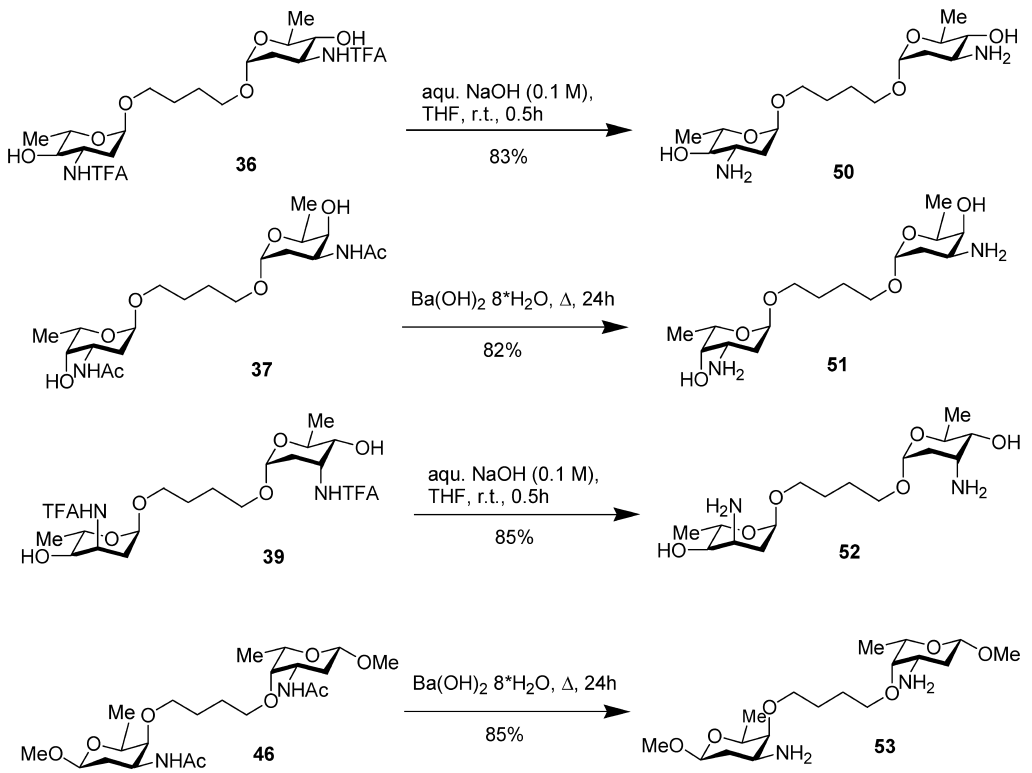
In addition, we conducted metathesis olefination reactions on 4-*O*-allylated aminoglycosides **40**–**42** which yield tail-to-tail homodimers **43**–**45** in very good yield and for substrates **40** and **41** with the expected *E*/*Z*-selectivity (Table 3). *Ribo*-configured aminoglycoside **42** which contains an axially orientated trifluoacetamido group yielded homodimer **45** with exclusive *E*-selectivity. The yield was reduced due to formation of enolether **49** which resulted from rearrangement of the olefinic double bond in the starting allyl ether.[7,16] As continuation of the work reduction of the alkenic double bond yielded 1,4-butanediols **46**–**48**. It should be noted that silyl glycosides **47** and **48** are very versatile dimers as two glycosyl donor functionalities are present which can conveniently be utilized for further derivatization or extension by glycosidation.[17,18]



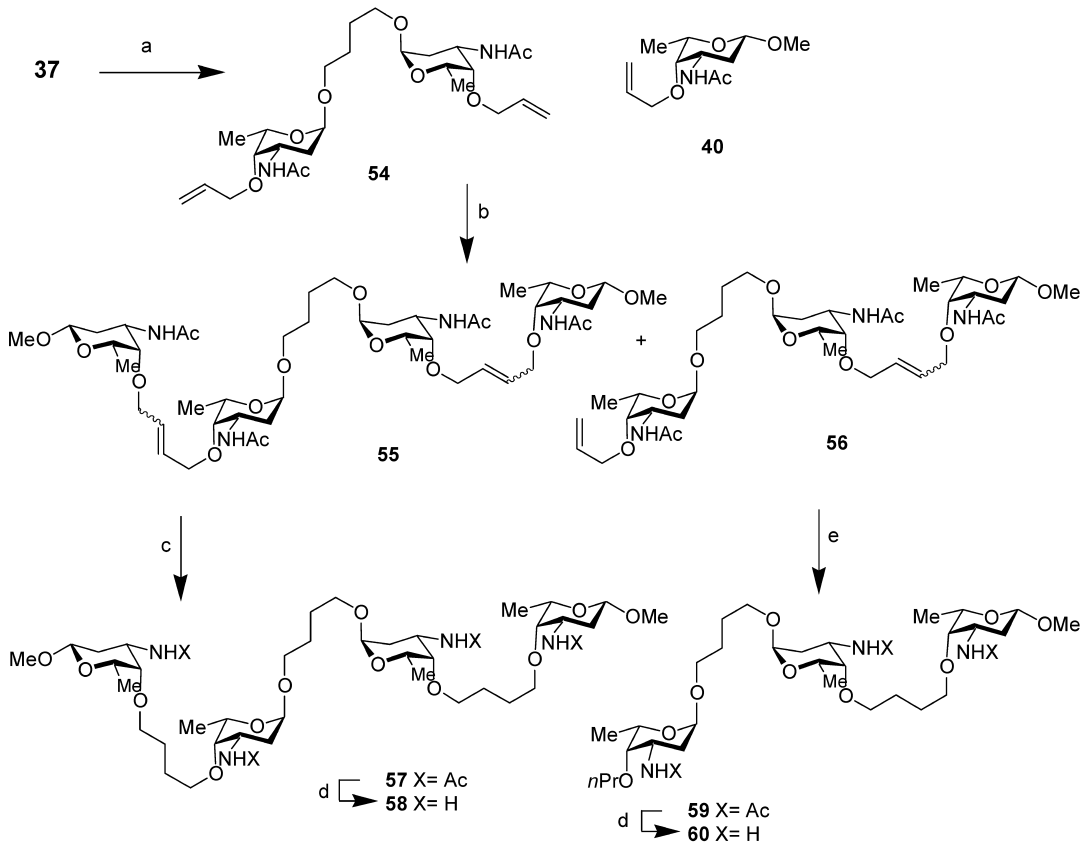
49

Removal of the amino protection is achieved under standard hydrolytic conditions as exemplified for homodimers **36**, **37**, **39** and **46** (Scheme 4). The resulting diamines **50**–**53** were isolated in good yields after chromatographic purification on a RP-18 phase.

In the next phase of the project extention of the linear homodimeric aminoglycosides was envisaged (Scheme 5). Starting from diol **37** bisallylation was achieved under neutral conditions using excess of allyl iodide in the presence of freshly prepared silver oxide. The bisallylated neodisaccharide **54** underwent metathesis olefination in the presence of 4-*O*-allylated methyl daunosamide **40** to give two olefination products **55** (16%) and **56** (27%) as complex



Scheme 4. Deprotection of acylated homodimers.



Scheme 5. Preparation of linear spacer-linked tri- and tetrasaccharides. Reagents and conditions: (a) 6 equiv. allyl iodide, Ag_2O, CH_3CN, Δ, 48 h (96%); (b) 4.6 equiv. **40** and **7** (3.6 mol%), $benzene_{abs.}$, rt, 1 h, then **7** (2.4 mol%), Δ, 14 h (**55**: 16%; **56**: 27%; **43**: 50%); (c) 10% Pd–C, H_2, trace Et_3N, MeOH, CH_2Cl_2 (2:1), rt, 24 h; (d) $Ba(OH)_2{\cdot}8H_2O$, H_2O, Δ, 30 h (**58**: 64% for two steps; **60**: 84% for two steps); (e) PtO_2, H_2, ethyl acetate, CH_2Cl_2, MeOH (16:8:1), rt, 20 h (92%).

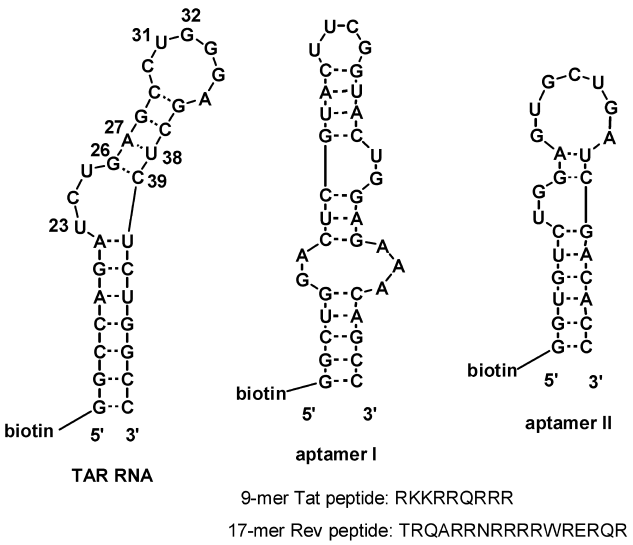


Figure 2. TAR-RNA, aptamers, 9-mer peptide and 17-mer peptide.

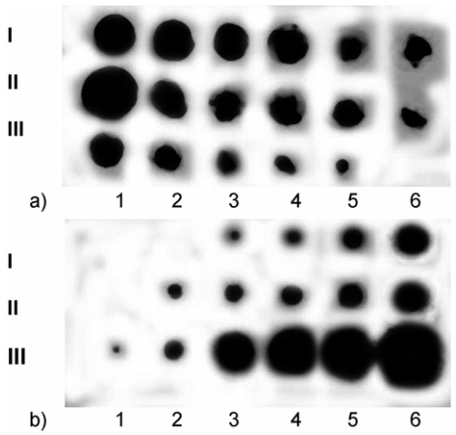


Figure 3. Dot blot analysis of Tat-TAR binding in the presence of the aminoglycosides **2**, **58** and **60**. Dot blot analysis of Tat-TAR binding in the presence of the aminoglycosides 2, 58 and 60 at concentrations varying from 1.2 to 22 mM. TAR 0.16 μM, 9-mer peptide 222 μM. Lane I, linear neotrisaccharide 58; lane II, linear neotetrasaccharide 60; lane III, cyclic neotetrasaccharide 2: (a) above: nitrocellulose membrane (retains peptide-bound RNA); (b) below: positively-charged nylon membrane (retains unbound RNA). The aminoglycoside concentration was increased from left to right.

mixtures of *E*/*Z*-isomers along with homodimer **43** (see Table 3, entry 1) (50% based on **40**) which resulted from dimerization of the starting monosaccharide. In order to suppress facile macrocyclization[5] the monomeric 4-*O*-allyl daunosamide **40** had to be employed in 6-fold excess.

In order to evaluate the RNA-affinity of these extended linear aminoglycosides we screened for aminoglycosides that interfere with the binding of proteins with RNA. Screening was conducted for about twenty aminoglycosides including 1,4-butanediol linked derivatives. For the three aminoglycosides **2**, **58** as well as **60** we observed non specific binding to RNA in a simplified HPLC system.[19] Then, three RNAs were chosen as the targets for further binding studies. First the HIV-1 TAR-RNA was selected for which binding of the Tat protein (Fig. 2) is well characterized and the known interaction between the RNA and the peptide could therefore be used in competitive binding studies.[20] In order compare the interaction with other RNAs, two aptamers selected for binding to the REV protein were investigated in competitive dot blot experiments with the 17-mer binding protein.[21] The interaction of the Tat protein with the TAR-RNA is a pivotal event in the life cycle of the HIV virus and inhibiting this particular interaction could be of great medicinal use.

For screening of the aminoglycoside library, the different behavior of peptide-bound and peptide-free RNA was utilized. In an typical binding-experiment the TAR-RNA (0.16 μM) and the 9-mer Tat peptide (222 μM) were incubated for 15 min. Then, the different aminoglycosides were added in concentrations varying from 1.2 to 22 mM for the individual aminoglycoside subunits.

After additional 15 min the mixture was filtered with the aid of a dot-blot apparatus in which first a nitrocellulose membrane (retains RNA-peptide complexes) and secondly a positively charged nylon membrane (retains all RNA) had been inserted. Filtration of the above mentioned individual binding-assays then results in separation of both, the peptide-bound and the aminoglycoside-bound RNA on separate membranes. In Figure 3 the dot blot results for the aminoglycosides **2**, **58** and **60** are shown. Figure 3 (top) shows the peptide bound fraction of the TAR-RNA at the nitrocellulose membrane.

The amount of aminoglycoside subunits increased from left to right (1.2–22 mM) with an concomitant decrease of the peptide bound RNA. Lane I depicts the dot blots for linear trimer **58**, lane II for linear tetramer **60** and lane III the cyclic tetramer **2**. Figure 3 (bottom) shows the results of the same experiments on the positively charged nylon membrane. It can be seen that in the case of the cyclic tetramer **2** most of the RNA at a aminoglycoside concentration higher than 5.6 mM is peptide free and has passed the nitrocellulose membrane. Surprisingly, an extraordinary increase in binding affinity was observed when cyclic tetramer **2** was employed implying that not only the increase of positive charges and the potential of forming hydrogen bonds but also the conformation of the ligand adds significantly to these interactions.[22] These findings suggest that particularly cyclic tetrameric structures interfere significantly with the TAR–Tat interaction. For comparison the two aptamers were also used in dot blot experiments. Here we used a 17-mer peptide with a binding constant of ca. 100 μM with respect to the two aptamer RNAs. These binding constants are approximately 10-fold stronger than the one for the Tat–TAR interaction (1 mM). As a consequence we had to use the aminoglycoside **2** at a 10-fold higher concentration compared to the Tat-TAR experiment. The dot blot experiments shown in Figure 4. In these dot blot experiments the aptamers (0.16 μM) and the 17-mer Rev peptide (100 μM) were incubated for 25 min. Then, aminoglycoside **2** was added in concentration ranging from 1 to 200 mM. In Figure 4 (top) the peptide-bound aptamers are shown. Figure 4 (bottom) represents the aptamer content that has passed the first membrane and was collected on the nylon membrane. It can be seen that aminoglycoside **2** substitutes the peptide from aptamer II at lower concentrations compared to aptamer I. Since this

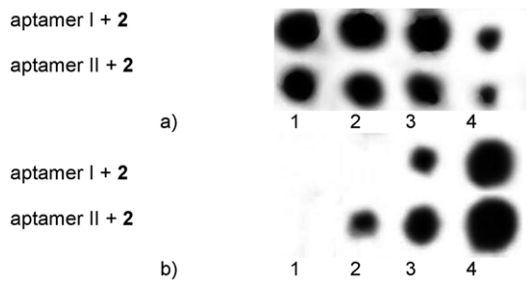


Figure 4. Dot blot analysis of aptamers in the presence of the aminoglycosides **2**. Dot blot analysis of aptamers in the presence of the aminoglycoside 2 at 80, 120, 160 and 200 mM. Aptamer 0.16 μM, 17-mer peptide 100 μM. Lane I: aptamerI+2; lane II: aptamerII+2: a) above: nitrocellulose membrane (retains peptide-bound RNA); b) below: positively-charged nylon membrane (retains unbound RNA). The aminoglycoside concentration was increased from left to right.

binding assay utilizes the different behavior of peptide-bound vs peptide-free RNA, no exact measurement of the aminoglycoside-RNA binding constant can be obtained since binding of the aminoglycoside can occur while the RNA is still bound to the peptide.

3. Conclusion

In summary, we described a rapid synthetic route towards 1,4-butanediol linked neoaminodeoxyoligosaccharides by employing the metathesis olefination. The synthetic strategy is based on a modular approach by using stereochemically defined hexose building blocks. The assembling of the chains is rapidly achieved without considering stereochemical aspects, which commonly arises when glycosidation protocols are exploited. Preliminary binding studies with selected RNAs revealed that in comparison to their linear counterparts macrocyclic spacer-linked aminoglycosides can efficiently bind to the TAR-RNA.

4. Experimental

4.1. General remarks and starting materials

All temperatures quoted are uncorrected. Optical rotations were recorded on a Perkin–Elmer 141 polarimeter (wavelength 589 nm) and are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR, ^{13}C NMR, ^{1}H, ^{1}H and ^{1}H, ^{13}C COSY as well as NOESY spectra were recorded on a Bruker DPX 200-NMR and a ARX 400-NMR spectrometer for solutions in $CDCl_3$ using residual $CHCl_3$ as internal standard (7.26 ppm) unless otherwise stated. Multiplicities are described using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Chemical shift values of ^{13}C NMR spectra are reported as values in ppm relative to residual $CHCl_3$ (77 ppm) as internal standards. The multiplicities refer to the resonances in the off-resonance spectra and were elucidated using the distortionless enhancement by polarization transfer (DEPT) spectral editing technique, with secondary pulses at 90 and 135°. Multiplicities are reported using the following abbreviations: s=singlet (due to quaternary carbon), d=doublet (methine), q=quartet (methyl), t=triplet (methylene). Mass spectra were recorded on a type LCT-spectrometer (Micromass). In addition, fast atom bombardment (FAB) mass spectra were obtained on a BG Analytical ZAB-2F (Ion Tech FAB gun, 8 kV, Xe carrier gas). Ion mass (*m*/*z*) signals are reported as values in atomic mass units followed, in parentheses, by the peak intensities relative to the base peak (100%). Combustion analyses were performed by the Institut für Pharmazeutische Chemie, Technische Universität Braunschweig and the Institut für Organische Chemie, Universität Hannover. All solvents used were of reagent grade and were further dried. Reactions were monitored by thin layer chromatography (TLC) on silica gel 60 F^{254} (E. Merck, Darmstadt) and spots were detected either by UV-absorption or by charring with H_2SO_4/4-methoxybenzaldehyde in methanol. Preparative column chromatography was performed on silica gel 60 (E. Merck, Darmstadt).

Compounds **11**, **13**, **14**, **21**, **26**, **33**, **34**, **37** and **38** were prepared according to reference.[6b] Hexoses **31**, **35**, **39**, **41**, **42**, **44**, **45**, **47** and **48** were obtained following the procedure described by us before.[7] Aminoglycoside **10** was prepared by a classical procedure accurately described in reference.[14] Hexose **15** was obtained according to the reported procedure in Ref. 23. The allyl aminoglycosides **17** and **18** were prepared as described in Ref. 24.

For the sake of convenience linear spacer-linked tri- and tetramers **55**, **56**, **57**, **58**, **59** and **60** are given the indices I, II, III for the individual pyranoses starting with the methyl glycoside moiety which is designated the label I.

4.1.1. Allyl 4-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-β-L-ribo-hexopyranoside (9). L-Cladinose **8** (1.0 g, 5.7 mmol) was dissolved in pyridine (20 ml) and acetic anhydride (6.4 mol, 9 ml) with stirring at 0 °C for 2 h. To this solution was added a mixture of water and dichloromethane (1:1, 14 ml). The aqueous phase was extracted with dichloromethane (3×10 ml). The combined organic extracts were washed with brine (40 ml), dried ($MgSO_4$) and evaporated in vacuum. The residue was dissolved in absolute allyl alcohol (0.6 ml) and absolute ether (10 ml) and stirred at −78 °C. After 15 min trimethyltrifluoromethane sulfonate (0.5 equiv., 556 mg) in ether was added and stirring was continued for 5 min. The mixture was hydrolyzed with aqueous saturated ammonium chloride and was allowed to warm up to rt. After washing with dichloromethane (3×10 ml) the combined organic extracts were dried ($MgSO_4$) and evaporated in vacuum. The crude product was purified by column chromatography over silica gel (petroleum ether/ethyl acetate=5:1) to yield momomer **9** (0.90 g, 3.5 mmol; 61%).

Compound **9**. Colorless oil; $[\alpha]_D^{20}=-33.5$ ($CHCl_3$, $c=1$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.91 (ddd, 1H, J=17.2, 10.4, 5.1 Hz, CH=), 5.27 (dq, 1H, J=17.3, 1.9 Hz, C*H*H′=CH–), 5.17 (ddd, 1H, J=10.4, 3.5, 1.9 Hz, CH*H*′=CH–), 4.72 (dd, 1H, J=9.7, 2.0 Hz, 1-H), 4.65 (d, 1H, J=9.7 Hz, 4-H), 4.35 (ddt 1H, J=12.7, 5.2, 1.5 Hz, OC*H*H′), 4.02 (ddt, 1H, J=12.8, 6.2, 1.4 Hz, OCH*H*′), 3.95 (dq, 1H, J=9.7, 6.3 Hz, 5-H), 3.26 (s, 3H, CH_3O), 2.22 (dd, 1H, J=14.2, 2.0 Hz, 2_{eq}-H), 2.12 (s, 3H, CH_3CO), 1.52 (dd, 1H, J=14.2, 9.7 Hz, 2_{ax}-H), 1.14 (d, 3H, J=6.3 Hz, 6-H), 1.12 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.5, 134.3, 117.1, 97.2, 78.6, 74.6, 69.6, 67.9,

49.6, 39.3, 20.9, 20.6, 17.6; HRMS for $C_{13}H_{22}O_5$ (M^++ MeCN+Na): calcd 322.1630, found 322.1637.

4.1.2. Allyl 3-acetamido-2,3,6-trideoxy-α-L-lyxo-hexopyranoside (11) and allyl 3-acetamido-2,3,6-trideoxy-β-L-lyxo-hexopyranoside (12). Methyl 3-acetamido-2,3,6-trideoxy-β-L-lyxo-hexopyranoside (500 mg, 2.46 mmol) was hydrolyzed to yield **10**. The crude product was not further purified but was directly employed for the next allylation step. In the following the suspension of Dowex-50 (H^+-form) in allyl alcohol was heated under reflux for 30 min, filtered and finally washed with absolute allyl alcohol. The resin (1.19 g) was added to a solution of the crude material **10** which was dissolved in absolute allyl alcohol (25 ml). The suspension was stirred at 70 °C for 1 h, at which time TLC dichloromethane/methanol=10:1) indicated that the allylation was complete. The mixture was filtered with suction while hot and washed with acetone. After addition of triethyl amine (2 ml) the combined filtrates were concentrated in vacuum to give an oily residue. This crude material was purified by column chromatography (dichloromethane/methanol=10:1) to afford two fractions of the α- and β-isomers (α/β=5.8:1) of the title compounds **11** and **12** (461 mg, 2.01 mmol; 82% for two steps). The physical and spectroscopic data for α-isomer were reported in Refs. 6b,7.

Compound **12**. Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.38 (d, 1H, *J*=8.4 Hz, NH), 5.89 (dddd, 1H, *J*=17.2, 10.4, 6.0, 5.2 Hz, CH=), 5.25 (dq, 1H, *J*=17.2, 1.8 Hz, C*H*H′=CH–), 5.21 (d, 1H, *J*=4.2 Hz, 1-H), 5.18 (dq, 1H, *J*=10.4, 1.5 Hz, CH*H*′=CH–), 4.36 (ddt, 1H, *J*=8.6, 2.8, 1.8 Hz, 3-H), 4.20 (ddt, 1H, *J*=12.8, 5.2, 1.5 Hz, OC*H*H′), 3.97 (ddt, 1H, *J*=12.8, 6.0, 1.4 Hz, OCH*H*′), 3.75 (q, 1H, *J*=6.0 Hz, 5-H), 3.73 (d, 1H, *J*=3.0 Hz, 4-H), 2.88 (d, 1H, *J*=3.6 Hz, OH), 2.19 (ddd, 1H, *J*=13.8, 8.6, 4.8 Hz, 2-H_{ax}), 1.94 (s, 3H, CH_3CO), 1.82 (dd, 1H, *J*=13.8, 1.8 Hz, 2-H_{eq}), 1.20 (d, 3H, *J*=6.0 Hz, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.6, 134.2, 117.1, 102.9, 89.6, 67.9, 67.8, 49.5, 38.9, 23.2, 18.7); calcd (%) for $C_{11}H_{19}NO_4$ (229.13): C 57.62, H 8.35, N 6.10, found C 57.81, H 8.31, N 5.98.

4.1.3. Allyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-β-L-lyxo-hexopyranoside (14). Allyl 3-acetamido-2,3,6-trideoxy-β-L-lyxo-hexopyranoside **12** (208 mg, 0.91 mmol) was dissolved under nitrogen in dry dichloromethane (10 ml). To this solution were added triethyl amine (1 ml) and acetic anhydride (1.2 equiv., 0.10 ml). After addition of a small amount of 4-dimethylamino pyridine (0.2 equiv., 22 mg) the mixture was stirred at rt for 1 h, whereupon TLC (petroleum ether/ethyl acetate 5:1) revealed that the acetylation was completed. The mixture was concentrated in vacuum and the crude product was purified by passing it through a silica gel column (dichloromethane, methanol, trace of triethyl amine) to give the pure title compound **14** (232 mg, 0.86 mmol; 94%). The hexopyranoside **14** was directly used for the next step without further characterization.

4.1.4. Allyl 3,4-di-*O*-acetyl-2,6-didesoxy-α-L-arabino-hexopyranoside (16). To a stirred solution of 3,4-di-*O*-acetyl-L-rhamnal (5 g, 23 mmol) and allyl alcohol (2 g, 34.5 mmol, 1.5 equiv.) in dry dichloromethane (50 ml) was added polymer-bound PPh_3·HBr (20 mg). The reaction mixture was stirred at rt for 24 h, filtered through a pad of Celite and concentrated under reduced pressure. The crude product was finally purified by column chromatography (ethyl acetate/petroleum ether=1:6) to furnish the pure title compound **16** (2.6 g, 9.6 mmol; 41%).

Compound **16**. Colorless oil; $[\alpha]_D^{20}=-156.3$ (*c*=1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.89 (dddd, *J*=16.7, 11.0, 5.8, 5.3 Hz, 1H, C*H*=), 5.30 (ddd, 1H, *J*=9.3, 5.4, 2.1 Hz, 3-H), 5.29 (dq, *J*=17.1, 1.6 Hz, 1H, C*H*H′=CH), 5.18 (dq, 1H, *J*=10.4, 1.4 Hz, CH*H*′=CH), 4.90 (d, 1H, *J*=3.1 Hz, 1-H), 4.73 (t, 1H, *J*=9.6 Hz, 4-H), 4.13 (ddt, 1H, *J*=12.9, 5.1, 1.5 Hz, OC*H*H′), 3.94 (ddt, 1H, *J*=13.0, 6.1, 1.3 Hz, OCH*H*′), 3.86 (dq, 1H, *J*=9.8, 6.2 Hz, 5-H), 2.24 (ddd, 1H, *J*=12.9, 5.4, 1.2 Hz, 2-H_{ax}), 2.04, 1.99 (2s, 6H, 2×CH_3CO), 1.79 (ddd, 1H, *J*=12.8, 11.7, 3.7 Hz, 2-H_{eq}), 1.17 (d, 3H, *J*=6.3 Hz, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.51, 134.27, 117.46, 96.21, 75.20, 69.40, 66.00, 68.21, 35.58, 21.30, 21.12, 17.82; LRMS (ESI) for $C_{13}H_{20}O_6$: 336.15 (100) [M+CH_3CN+Na]$^+$.

4.1.5. 1,4-Di-(3′,4′,6′-tri-*O*-acetyl-2′-deoxy-α-D-lyxo-hexopyranosidyl)-2-butene (19). Allyl 2-deoxy-3,4,6-tri-*O*-acetyl-α-D-lyxo-hexopyranoside **15** (50 mg, 0.15 mmol) was dried under reduced pressure (10^{-2} Torr) for about 5 h and dissolved under nitrogen in absolute benzene (6 ml). To this solution was added the Grubbs catalyst **7** (15 μmol, 10 mol %). The purple solution was stirred at 50 °C for 4 h, at which time the reaction mixture was concentrated under reduced pressure. After addition of 15 ml diethyl ether and 0.5 ml triethyl amine stirring was continued under air for 2 h. Then, the solvent was removed in vacuum to yield a crude product, which was subsequently purified by column chromatography (R_f=0.24, petroleum ether/ethyl acetate=1:1) to furnish the pure title compound **19** (39 mg, 61.6 μmol; 41%, *E*/*Z*=5:1) as an inseparable mixture of stereoisomers. The material was directly used for the next step. Selected spectroscopic date: ^{13}C NMR (50 MHz, $CDCl_3$): δ=170.5, 170.3, 170.0, 128.6, 77.0, 66.7, 66.6, 66.1, 62.4, 30.0, 20.8, 20.7, 20.6.

4.1.6. 1,4-Di-(3′,4′-di-*O*-acetyl-2′,6′-dideoxy-α-D-arabino-hexopyranosidyl)-2-butene (20). Allyl 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-arabino-hexopyranoside **16** (21 mg, 77 μmol) was dried in vacuum (10^{-2} Torr) for about 5 h and was dissolved under nitrogen in absolute benzene (3 ml). To this solution the Grubbs catalyst **7** (8 μmol, 10 mol %) was added. The purple solution was stirred at 50 °C for 4 h, at which time the reaction mixture was concentrated under reduced pressure. After addition of 10 ml diethyl ether and 0.3 ml triethyl amine stirring was continued under air for 2 h. Then, the solvent was removed in vacuum to afford a crude product, which was subsequently purified by column chromatography (R_f=0.55, petroleum ether/ethyl acetate=1:1) to furnish the title compound **20** (10 mg, 19.4 μmol; 50%, *E*/*Z*=5:1) as an inseparable mixture of stereoisomers. The material was directly used for the next step. Selected spectroscopic data: ^{13}C NMR (50 MHz, $CDCl_3$) δ=170.3, 128.6, 96.0, 74.8, 69.0, 65.7, 66.9, 35.2, 21.0, 20,8, 17.5; LRMS (ESI) for $C_{24}H_{36}O_{12}$: 539.4 (M^++Na^+).

4.1.7. 1,4-Di-(3′,4′-di-*O*-acetyl-2′,6′-dideoxy-β-L-lyxo-hexopyranosyl)-2-butene-1,4-diol (22). Allyl 3,4-di-*O*-acetyl-2,6-dideoxy-β-L-lyxo-hexopyranoside **18** (25 mg, 0.092 mmol) was dried in vacuum (10^{-2} Torr) for about 5 h and dissolved under nitrogen in absolute benzene (10 ml). To this solution the Grubbs catalyst **7** (5 mg, 6.6 mol%, after 14 h a second portion of 4 mg, 5.3 mol%) was added. The purple solution was stirred for 14 h at rt and then at 50 °C for 5 h, at which time the reaction mixture was concentrated under reduced pressure. After addition of diethyl ether (30 ml) and triethyl amine (1 ml) stirring was continued for 2 h under air. Then, the solvent was removed in vacuum to afford a crude product, which was subsequently purified by column chromatography (R_f=0.20; petroleum ether/ethyl acetate 4:1) to give the title compound **22** (20 mg, 39 μmol; 84.4%, *E*/*Z*=3.8:1) as an inseparable mixture of stereoisomers. The material was directly used for the next step. Selected spectroscopic data: ^{1}H NMR (200 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=5.83 (t, 2H, *J*=2.9 Hz, 2×=CH), 5.09 (dd, 2H, *J*=2.8, 0.8 Hz, 2×4-H), 4.97 (ddd, 2H, *J*=11.6, 6.0, 3.2 Hz, 2×3-H), 4.55 (dd, 2H, *J*=8.0, 3.8 Hz, 2×1-H), 4.41 (dm, 2H, *J*=12.6 Hz, 2×OC*H*H′), 4.08 (dm, 2H, *J*=12.8 Hz, 2×OCH*H*′), 3.66 (dq, 2H, *J*=6.4, 1.0 Hz, 2×5-H), 2.15 (s, 6H, 2×CH_3CO), 2.06–1.86 (m, 4H, 2×2-H_{eq} and 2×2-H_{ax}), 2.00 (s, 6H, 2×CH_3CO), 1.22 (d, 6H, *J*=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=170.8, 170.2, 129.0, 98.8, 69.2, 69.0, 68.6, 68.7, 31.7, 20.9, 20.8, 16.5; Selected ^{1}H NMR data for *Z*-isomer: ^{1}H NMR (200 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=5.75 (t, 2H, *J*=4.1 Hz, 2×CH=).

4.1.8. 1,4-Di-(4′-*O*-acetyl-2′,6′-dideoxy-3′-*C*-methyl-3′-*O*-methyl-β-L-ribo-hexopyranosyl)-2-butene-1,4-diol (23). Allyl 4-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-β-L-ribo-hexopyranoside **9** (100 mg, 0.39 mmol) was dried in vacuum (10^{-2} Torr) for about 5 h and dissolved under nitrogen in dry benzene (25 ml). To this solution was added the Grubbs catalyst **7** (19 mg, 6 mol%; after 14 h a second portion 13 mg, 4 mol%). The purple solution was stirred for 14 h at rt and then at 50 °C for 5 h, at which time the reaction mixture was concentrated under reduced pressure. After addition of diethyl ether (30 ml) and triethyl amine (1 ml) stirring under air was continued for 2 h. Then, the solvent was removed in vacuum to afford a crude product, which was subsequently purified by column chromatography (petroleum ether/ethyl acetate=5:1) to give the title compound **23** (70 mg, 0.17 mmol; 87%, *E*/*Z*=3.5:1) as an inseparable mixture of stereoisomers. The material was directly used for the next step. Selected spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.82 [t, 2H, *J*=3.0 Hz, 2×CH=(*trans*)], 5.71 [t, 2H, *J*=4.1 Hz, 2×CH=(*cis*)], 4.70 (dd, 2H, *J*=9.7, 2.0 Hz, 2×1-H), 4.64 (d, 2H, *J*=9.8 Hz, 2×4-H), 4.35 (ddd, 2H, *J*=11.5, 2.7, 1.2 Hz, 2×OC*H*H′), 4.02 (ddd, 2H, *J*=11.4, 3.3, 1.4 Hz, 2×OCH*H*′), 3.94 (dq, 2H, *J*=9.7, 6.3 Hz, 2×5-H), 3.26 (s, 6H, 2×CH_3O), 2.20 (dd, 2H, *J*=14.2, 2.0 Hz, 2×2$_{eq}$-H), 2.12 (s, 6H, 2×CH_3CO), 1.49 (dd, 2H, *J*=14.2, 9.7 Hz, 2×2$_{ax}$-H), 1.13 (d, 6H, *J*=6.3 Hz, 2×6-H), 1.11 (s, 6H, 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.5, 129.0, 97.3, 78.6, 74.6, 68.6, 67.9, 49.6, 39.3, 20.9, 20.6, 17.6.

4.1.9. 1,4-Di-(2′-deoxy-α-D-lyxo-hexopyranosidyl)-butane (24). To a stirred solution of 1, 4-di-(3′,4′,6′-tri-*O*-acetyl-2′-deoxy-α-D-lyxo-hexopyranosidyl)-butane **19** (40 mg, 0.063 mmol) in methanol (10 ml) Amberlite A-26 (OH^- form; 0.2 g) was added. The mixture was shaken at rt for 24 h, then filtered and the solvent was evaporated under reduced pressure. Finally, the product was dried under reduced pressure for 4 h to afford the title compound **24** (24 mg, 62.8 μmol, 99%).

Compound **24**. Colorless oil; $[\alpha]_D^{24}$=+4.2 (*c*=0.96, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD, CH_3OD=3.31 ppm): δ=4.87 (d, *J*=3.0 Hz, 1H, H-1), 3.93–3.83 (m, 1H), 3.76–3.57 (m, 5H), 3.40–3.24 (m, 1H), 1.90 (ddd, *J*=12.8, 12.0, 4.0 Hz, 1H, H-2$_{eq}$), 1.71 (dd, *J*=12.8, 4.4 Hz, 1H, H-2$_{ax}$), 1.67–1.55 (m, 2H, OCH_2CH_2); ^{13}C NMR (50 MHz, CD_3OD, CD_3OD=49.0 ppm): δ=98.9, 72.4, 69.6, 66.7, 68.1, 63.2, 33.7, 27.5; LRMS (ESI) for $C_{16}H_{30}O_{10}$: 405.2 (M^++Na^+).

4.1.10. 1,4-Di-(2′,6′-dideoxy-α-D-arabino-hexopyranosidyl)-butane (25). To a stirred solution of 1,4-di-(3′,4′-di-*O*-acetyl-2′,6′-dideoxy-α-D-arabino-hexopyranosidyl)-butane **20** (10 mg, 19.3 μmol) in methanol (5 ml) Amberlite A-26 (OH^- form; 0.05 g) was added. The mixture was shaken at rt for 12 h, then filtered and the solvent was evaporated under reduced pressure. Finally, the product was dried under reduced pressure for 4 h to afford the title compound **25** (6.8 mg, 19.3 μmol, 99%).

Compound **25**. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.83 (d, *J*=3.0 Hz, 1H, H-1), 3.95–3.82 (m, 1H), 3.71–3.55 (m, 1H), 3.13–3.00 (m, 1H), 2.73, 2.58 (2s, 2×1H, 2OH), 2.49–2.41 (m, 1H), 2.17–2.05 (m, 1H), 1.75–1.56 (m, 2H), 1.29 (d, *J*=6.2 Hz, 3H, H-6), 1.36–1.20 (m, 1H, H-2$_{eq}$), 0.96–0.83 (m, 1H, H-2$_{ax}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=97.3, 78.1, 69.2, 67.5, 67.0, 37.8, 26.5, 17.7; LRMS (ESI) for $C_{16}H_{30}O_6$: 373.1 (M^++Na^+).

4.1.11. 1,4-Di-(2′,6′-dideoxy-β-L-lyxo-hexopyranosyl)-1,4-butanediol (27). A suspension of 10% Pd/C (15 mg) in methanol (6 ml) was stirred under an hydrogen atmosphere for 30 min. 1,4-Di-(2′,6′-dideoxy-β-L-lyxo-hexopyranosyl)-2-butene-1,4-diol **22** (10 mg, 0.02 mmol) dissolved in a solvent mixture consisting of methanol (6 ml) and dichloromethane (6 ml) was added to the suspension. After successive addition of triethyl amine (0.1 ml) the mixture was stirred at rt for another 20 h, whereupon TLC analysis (R_f=0.28, dichloromethane/methanol=7:1) indicated that the hydrogenation was completed. The catalyst was filtered and washed with a mixture of dichloromethane and methanol (1:1). The combined filtrates were evaporated in vacuum to give a crude product, which was purified by flash column chromatography. However, the product was still contaminated with some ammonium salts. The material was taken up in aqueous sodium bicarbonate and the solution was evaporated again in vacuum to afford a residue which was extracted with chloroform. Filtration and concentration of the combined filtrates under reduced pressure afforded the title compound **27** (10 mg, 29 μmol, 99%).

Compound **27**. Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=4.32 (t, 2H, *J*=9.6, 2.2 Hz, 2×1-H), 3.87–3.76 (m, 2H, 2×OC*H*H′), 3.60 (ddd, 2H, *J*=12.0, 5.0, 3.2 Hz, 2×3-H), 3.42 (d, 2H, *J*=2.0 Hz,

2×4-H), 3.38–3.27 (m, 2H, 2×OCH*H′* and 2×5-H), 1.87 (ddd, 2H, *J*=12.6, 5.0, 2.0 Hz, 2×2-H_{eq}), 1.57 (m, 4H, CH_2CH_2), 1.62–1.51 (m, 2H, 2×2-H_{ax}), 1.23 (d, 6H, *J*=6.5 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=99.9, 70.4, 70.0, 68.6, 68.7, 34.3, 26.0, 16.4; HRMS ($C_{16}H_{30}NaO_8$): calcd. 373.1839 $[M+Na]^+$, found 373.1836.

4.1.12. 1,4-Di-(2′,6′-dideoxy-3′-*C*-methyl-3′-*O*-methyl-β-L-ribo-hexopyranosyl)-1,4-butanediol (28). To a solution of 1,4-di-(4′-*O*-acetyl-2′,6′-dideoxy-3′-*C*-methyl-3′-*O*-methyl-β-L-ribo-hexopyranosyl)-2-butene-1,4-diol **23** (70 mg, 0.17 mmol) in a mixed solvent system consisting of ethyl acetate, dichloromethane and methanol (16:8:1; 12.5 ml) was added PtO_2 (6.0 mg). The suspension was stirred under hydrogen atmosphere at rt for 24 h, after which time the hydrogenation was completed according to TLC analysis (petroleum ether/ethyl acetate 2:1). The reaction was terminated by addition of triethyl amine (1 ml), followed by filtration with suction and concentration under reduced pressure. To a solution of this crude material in methanol (10 ml) Amberlite A-26 (hydroxide form, 0.4 g) was added. The mixture was shaken at rt for 24 h and filtered. The filtrate was concentrated under reduced pressure. The crude material obtained was purified by flash column chromatography (petroleum ether/ethyl acetate=1:1) to furnish the hydrogenated product **28** (65 mg, 0.16 mmol, 95%).

Compound **28**. Colorless oil; $[\alpha]_D^{20}$=+18.7 (*c*=1; $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.54 (dd, 2H, *J*=9.7, 1.9 Hz, 2×1-H), 3.90–3.84 (m, 2H, 2×OC*H*H′), 3.56 (dq, 2H, *J*=9.4, 6.2 Hz, 2×5-H), 3.45–3.39 (m, 2H, 2×OC*H*H′), 3.24 (s, 6H, 2×CH_3O), 2.96 (dd, 2H, *J*=10.4, 9.7 Hz, 2×4-H), 2.21 (dd, 2H, *J*=14.4, 1.9 Hz, 2×2$_{eq}$-H), 2.09 (d, 2H, *J*=11.0 Hz, 2×OH), 1.67–1.63 (m, 4H, CH_2CH_2)1.38 (dd, 2H, *J*=14.4, 9.7 Hz, 2×2$_{ax}$-H), 1.29 (d, 6H, *J*=6.3 Hz, 2×6-H), 1.23 (s, 6H, 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=97.8, 78.1, 75.0, 70.9, 68.7, 49.0, 38.0, 26.3, 21.1, 18.2; HRMS for $C_{20}H_{38}O_8$ (M^++Na^+): calcd 429.2464, found 429.2457.

4.1.13. Allyl 4-*O*-acetyl-3-trifluoroacetamido-2,3,6-trideoxy-α-L-arabino-hexopyranoside (30). Allyl 3-trifluoroacetamido-2,3,6-trideoxy-α-L-arabino-hexopyranoside (crude product; about 3.92 mmol) was dissolved under nitrogen in dry dichloromethane (20 ml). To this solution were added triethyl amine (1.5 equiv., 0.79 ml) and acetic anhydride (1.5 equiv., 0.56 ml). After addition of a small amount of 4-dimethylamino pyridine (DMAP; about 5 mg) the mixture was stirred at rt for 1 h, whereupon TLC (petroleum ether/ethyl acetate=5:1) showed that acetylation was completed. The mixture was concentrated in vacuum to afford a crude material which was purified by passing it through a silica gel column (R_f=0.24; petroleum ether/ethyl acetate=5:1) containing 2% of triethyl amine to give the title compound **30** (1.09 g, 3.35 mmol; 86% for four steps).

Compound **30**. Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.02 (d, 1H, *J*=8.0 Hz, NH), 5.88 (ddt, 1H, *J*=17.4, 10.2, 5.4 Hz, CH=), 5.28 (dq, 2H, *J*=17.4, 1.8 Hz, C*H*H′=CH–), 5.18 (dq, 1H, *J*=10.2, 1.6 Hz, CH*H′*=CH–), 4.92 (t, 1H, *J*=3.0 Hz, 1-H), 4.63 (t, 1H, *J*=10.2 Hz, 4-H), 4.59–4.47 (m, 1H, 3-H), 4.14 (ddt, 1H, *J*=13.2, 5.0, 1.4 Hz, OC*H*H′), 3.95 (ddt, 1H, *J*=13.2, 5.0, 1.4 Hz, OCH*H′*), 3.94 (dq, 1H, *J*=9.2, 6.0 Hz, 5-H), 2.23 (ddd, 1H, *J*=12.8, 4.4, 1.0 Hz, 2-H_{eq}), 2.05 (s, 3H, CH_3CO), 1.75 (td, 1H, *J*=12.6, 3.6 Hz, 2-H_{ax}), 1.17 (d, 3H, *J*=6.4 Hz, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=172.0, 157.0, 133.8, 117.3, 115.6, 95.2, 75.4, 67.9, 65.6, 47.6, 35.5, 20.6, 17.6; calcd (%) for $C_{13}H_{18}F_3NO_5$ (325.28): C 48.00, H 5.58, N 4.31, found C 48.11, H 5.52, N 4.20.

4.1.14. 1,4-Di-(3′-trifluoroacetamido-4′-*O*-acetyl-2′,3′,6′-trideoxy-α-L-arabino-hexopyranosyl)-2-butene-1,4-diol (32). Allyl 4-*O*-acetyl-3-trifluoroacetamido-2,3,6-trideoxy-α-L-arabino-hexopyranoside **30** (224 mg, 0.69 mmol) was dried in vacuum (10^{-2} Torr) for about 5 h and was dissolved under nitrogen in absolute benzene (40 ml). To this solution the Grubbs catalyst **7** was added in two portions (22 mg, 3.9 mol%; 9 mg, 1.6 mol %). The purple solution was stirred for 2 h at rt and then at 50 °C for 24 h, at which time the reaction mixture was concentrated under reduced pressure. After addition of diethyl ether (30 ml) and triethyl amine (1 ml) stirring was continued under air for 2 h. Then the solvent was removed in vacuum to afford a crude product, which was subsequently purified by column chromatography (petroleum ether/ethyl acetate=3:1 then 1:1, R_f=0.20, petroleum ether/ethyl acetate=2:1) to give the title compounds **32** (186 mg, 0.30 mmol, 87%, *E*/*Z*=2.5:1) as an inseparable mixture of stereoisomers. The material was directly used for the next step. Selected spectroscopic data: ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.67 (d, 2H, *J*=6.6 Hz, 2×NH), 5.83 (t, 2H, *J*=2.9 Hz, 2×CH=), 4.90 (d, 2H, *J*=3.2 Hz, 2×1-H), 4.57 (t, 2H, *J*=9.6 Hz, 2×4-H), 4.55–4.39 (m, 2H, 2×3-H), 4.22–4.09 (m, 2H, 2×OC*H*H′), 4.05–3.92 (m, 4H, 2×OCH*H′* and 2×5-H), 2.31 (ddd, 2H, *J*=13.0, 4.4, 1.2 Hz, 2×2-H_{eq}), 2.08 (s, 6H, 2×CH_3CO), 1.74 (dt, 2H, *J*=12.8, 3.6 Hz, 2×2-H_{ax}), 1.20 (d, 6H, *J*=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=170.0, 156.9, 128.6, 116.0, 95.4, 75.1, 66.9, 65.7, 48.1, 35.6, 20.6, 17.6; selected ^{1}H NMR data for the *Z*-isomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ=5.75 (t, 2H, *J*=4.0 Hz, 2×CH=), 1.19 (d, 6H, *J*=6.2 Hz, 2×6-H).

4.1.15. 1,4-Di-(4′-*O*-acetyl-3′-trifluoroacetamido-2′,3′,6′-trideoxy-α-L-arabino-hexopyranosyl)-1,4-butanediol (36). To a solution of 1,4-di-(3′-trifluoroacetamido-4′-*O*-acetyl-2′,3′,6′-trideoxy-α-L-arabino-hexopyranosyl)-2-butene-1,4-diol **32** (192 mg, 0.31 mmol) in ethyl acetate (20 ml) was added PtO_2 (6.0 mg). The suspension was stirred under an hydrogen atmosphere at rt for 24 h, after which time the reduction was completed according to TLC analysis (R_f=0.38, petroleum ether/ethyl acetate 2:1). The reaction was terminated by addition of triethyl amine (1 ml), which was followed by filtration with suction and evaporation under reduced pressure to afford a crude product. This material was purified by flash column chromatography (petroleum ether/ethyl acetate=1:1) to furnish the hydrogenated product **36** (188 mg, 0.30 mmol; 98%).

Compound **36**. Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.70 (d, 2H, *J*=8.2 Hz, 2×NH), 4.81 (d, 2H, *J*=2.8 Hz, 2×1-H), 4.54 (t, 2H, *J*=10.2 Hz, 2×4-H), 4.50–4.38 (m, 2H, 2×3-H), 3.87 (dq, 2H, *J*=10.0, 6.4 Hz, 2×5-H), 3.70–3.57

(m, 2H, 2×OC*H*H′), 3.42–3.31 (m, 2H, 2×OCH*H*′), 2.11 (ddd, 2H, *J*=13.0, 4.8, 1.0 Hz, 2×2-H_{eq}), 2.02 (s, 6H, 2×CH_3CO), 1.76 (dt, 2H, *J*=12.4, 3.2 Hz, 2×2-H_{ax}), 1.64 (m, 4H, CH_2CH_2), 1.14 (d, 6H, *J*=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=171.7, 156.8, 115.7, 96.0, 75.2, 67.2, 65.6, 47.3, 35.3, 26.2, 20.5, 17.5; calcd (%) for $C_{20}H_{30}F_6N_2O_8$ (540.45): C 44.45, H 5.59, N 5.18, found C 44.49, H 5.52, N 5.23.

4.1.16. Methyl 3-acetamido-4-allyl-2,3,6-trideoxy-β-L-lyxo-hexopyranoside (40). A nitrogen flask was equipped with a condenser and flushed with nitrogen. Methyl 3-acetamido-2,3,6-trideoxy-β-L-lyxo-hexopyranoside (118 mg, 0.58 mmol) dissolved in dry acetonitrile (10 ml) was added at rt under nitrogen. After addition of freshly precipitated and dry silver oxide (140 mg, 0.6 mmol) allyl iodide (0.2 ml, 2.18 mmol) was added dropwise to the suspension. The mixture was refluxed for 20 h, whereupon the suspension was filtered with suction through a pad of Celite and washed with the mixed solvent system of methanol and dichloromethane. The combined filtrates were evaporated under reduced pressure to afford a crude product. Purification by column chromatography (R_f=0.48; CH_2Cl_2/MeOH=10:1) afforded the pure title compound **40** (27 mg, 0.52 mmol, 90%).

Compound **40**. Colorless crystals; mp: 163–165 °C; $[\alpha]_D^{24}$=−48.4 (*c*=0.99, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ=5.92 (dddd, 1H, *J*=17.2, 10.0, 6.4, 5.4 Hz, CH=), 5.76 (d, 1H, *J*=8.3 Hz, NH), 5.26 (dq, 1H, *J*=17.2, 1.8 Hz, C*H*H′=CH–), 5.18 (dq, 1H, *J*=10.2, 1.4 Hz, CH*H*′=CH–), 4.35 (dd, 1H, *J*=9.6, 2.3 Hz, 1-H), 4.26 (ddt, 1H, *J*=12.7, 5.5, 1.4 Hz, OC*H*H′), 4.09 (m, 1H, 3-H), 3.96 (ddt, 1H, *J*=12.7, 5.5, 1.4 Hz, OCH*H*′), 3.54 (dq, 1H, *J*=6.4, 1.1 Hz, 5-H), 3.46 (s, 3H, OCH_3), 3.28 (d, 1H, *J*=3.0 Hz, 4-H), 1.97 (s, 3H, CH_3CO), 1.79 (ddd, 1H, *J*=12.2, 4.6, 2.3 Hz, 2-H_{eq}), 1.60 (dt, 1H, *J*=12.6, 9.4 Hz, 2-H_{ax}), 1.31 (d, 3H, *J*=6.6 Hz, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.3, 134.7, 117.5, 101.1, 76.7, 75.0, 71.6, 56.3, 47.9, 32.5, 23.4, 17.2; calcd (%) for $C_{12}H_{21}NO_4$ (243.30): C 59.24, H 8.70, N 5.76, found C 59.06, H 8.61, N 5.54.

4.1.17. 1,4-Bis (methyl-3′-acetamido-2′,3′,6′-trideoxy-β-L-lyxo-hexopyranos-4′-yl)-2-butene-1,4-diol (43). Methyl 3-acetamido-4-allyl-2,3,6-trideoxy-β-L-lyxo-hexopyranoside **40** (219 mg, 0.9 mmol) was dried in vacuum (10^{-2} Torr) for more than 5 h and was dissolved under nitrogen in absolute benzene (10 ml). To this solution was added the Grubbs catalyst **7** (56 mg, 0.068 mmol, 7.6 mol%). The purple solution was refluxed at 90–100 °C for 10 h, at which time the reaction mixture was cooled to rt and concentrated under reduced pressure. After addition of diethyl ether (30 ml) and triethyl amine (1 ml) stirring was continued under air for 2 h. Then, the solvent was removed in vacuum to afford a crude material, which was subsequently purified by column chromatography (ethyl acetate, then dichloromethane/methanol 10:1; R_f=0.30) to give the title compounds **43** (170 mg, 0.37 mmol, 90%; *E*/*Z*=4:1).

Compound **43**. Colorless oil; $[\alpha]_D^{24}$=−94.6 (*c*=1.86, $CHCl_3$/MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=7.12 (br d, 2H, 2×NH), 5.81 (t, 2H, *J*=3.0 Hz, 2×–)C*H*=CH_2), 4.39 (dd, 2H, *J*=8.4, 3.2 Hz, 2×1-H), 4.07 (br d, 2H, *J*=6.6 Hz, 2×OC*H*H′), 3.98–3.94 (m, 4H, 2×OCH*H*′ and 2×3-H), 3.58 (q, 2H, *J*=6.4 Hz, 2×5-H), 3.49 (s, 6H, 2×OCH_3), 3.35 (m, 2H, 2×4-H), 1.99 (s, 6H, 2×C*H*$_3$CO), 1.80–1.55 (m, 4H, 2×2-H_{eq} and 2×2-H_{ax}), 1.29 (d, 6H, *J*=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=170.5, 129.0, 101.2, 76.1, 73.7, 71.4, 56.2, 48.1, 31.6, 22.5, 16.8; selected ^{1}H NMR data for the alkenic double bond of the *Z*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=5.74 (t, 2H, *J*=4.0 Hz, 2×–C*H*=CH_2), 4.19 (m, 4H, 2×OCH_2), 2.01 (s, 6H, 2×C*H*$_3$CO), 1.32 (d, 6H, *J*=6.4 Hz, 2×6-H); calcd (%) for $C_{22}H_{38}N_2O_8$ (458.55): C 57.62, H 8.35, N 6.11, found C 57.79, H 8.18, N 6.00.

4.1.18. 1,4-Bis (methyl-3′-acetamido-2′,3′,6′-trideoxy-β-L-lyxo-hexopyranos-4′-yl)-1,4-butanediol (46). A solution of 10% Pd/C (17 mg) in methanol (6 ml) was stirred under an hydrogen atmosphere for 30 min. The metathesis product **43** (44 mg, 0.096 mmol) dissolved in a solvent system consisting of dichloromethane and methanol (3:1; 16 ml) was added to this suspension. After successive addition of triethyl amine (0.11 ml) the mixture was stirred at rt for additional 5 h, after which time the hydrogenation was terminated by addition of a second portion of triethyl amine (1 ml). The catalyst was filtered and washed with the solvent mixture consisting of dichloromethane and methanol (R_f=0.35, dichloromethane/methanol=10:1). The combined filtrates were evaporated in vacuum to give a crude material which was purified by passing it through a silica gel column to furnish the title compound **46** (44 mg, 0.096 mmol, 99%).

Compound **46**. Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=4.20 (dd, 2H, *J*=6.6, 3.2 Hz, 2×1-H), 4.05 (s, 2H, 2×NH), 3.80 (ddd, 2H, *J*=11.2, 6.6, 3.2 Hz, 2×3-H), 3.39 (q, 2H, *J*=6.2 Hz, 2×5-H), 3.42–3.33 (m, 4H, 2×OCH_2), 3.30 (s, 6H, 2×OCH_3), 3.11 (d, 2H, *J*=2.7 Hz, 2×4-H), 1.81 (s, 6H, 2×CH_3CO), 1.57–1.46 (m, 6H, 2×2-H_{eq} and CH_2CH_2), 1.49 (dt, 2H, *J*=12.4, 8.8 Hz, 2×2-H_{ax}), 1.29 (d, 6H, *J*=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=170.7, 101.1, 76.2, 74.0, 71.3, 55.9, 48.3, 31.2, 26.5, 22.0, 16.5; HRMS ($C_{22}H_{40}N_2NaO_2$): calcd. 483.2683 $[M+Na]^+$, found 483.2686.

4.1.19. 1,4-Di-(3′-amino-2′,3′,6′-trideoxy-α-L-arabino-hexopyranosyl)-1,4-butanediol (50). The hydrogenated product **36** was dissolved in a mixture of THF and 0.1M aqueous NaOH (1:3; 24 ml). This mixture was stirred at rt for 14 h, at which time TLC indicated that the deprotection was completed. After neutralization with dry ice (pH 7–8), the solution was concentrated to 2 ml under reduced pressure and the residue was subsequently subjected to a small column (800 mg of a reversed phase C-18; gradient water to methanol) to yield the target product **50** (21.4 mg, 61.4 μmol; 83.4%, for two steps).

Compound **50**. Colorless crystals; m.p.: 148–150 °C; $[\alpha]_D^{24}$=−121.4 (*c*=1.07; MeOH/$CHCl_3$ 2:1); ^{1}H NMR (200 MHz, $CDCl_3$ with CD_3OD): δ=4.68 (d, 2H, *J*=3.2 Hz, 2×1-H), 3.65 (br s, 4H, 2×NH_2), 3.60–3.50 (m,

2H, 2×OC*H*H′), 3.50 (dq, 2H, *J*=9.4, 6.0 Hz, 2×5-H), 3.80–3.69 (m, 2H, 2×3-H), 3.02–2.85 (m, 2H, 2×OCH*H*′), 2.73 (t, 2H, *J*=9.2 Hz, 2×4-H), 1.88 (dd, 2H, *J*=13.0, 4.0 Hz, 2×2-H_{eq}), 1.53 (m, 4H, CH_2CH_2), 1.42 (ddd, 2H, *J*=13.0, 12.0, 3.8 Hz, 2×2-H_{ax}), 1.27 (d, 6H, *J*=6.0 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$ with CD_3OD): δ=96.5, 77.7, 68.0, 66.7, 49.6, 37.7, 26.2, 17.4; LRMS (DCI) for $C_{16}H_{32}N_2O_6$: 349.3 (100) (M+H$^+$(, 697.7 (2) (2M+H$^+$).

4.1.20. 1,4-Di-(2′,3′,6′-trideoxy-α-L-lyxo-hexopyranosyl)-1,4-butanediol (51). Homodimer **37** (50.2 mg, 0.116 mmol) was dissolved at rt in water (20 ml) and barium hydroxide octahydrate (4.0 g, about 2 g/10 ml water) was added. The solution was stirred magnetically while it vigorously boiled under reflux (130–140 °C). After 24 h TLC (dichloromethane/methanol=5:1) indicated the completion of the saponification. To this mixture solid carbon dioxide was added and the precipitate was filtered. The filtrate was treated with Amberlite IRA-900 (OH$^-$ form, 20 ml) by stirring for 30 min. After filtration the filtrate was evaporated to give a residue, which, still containing some barium carbonate, was taken up in chloroform. The organic layer afforded the deprotected homodimer **51** (33 mg, 0.095 mmol, 82%) after evaporation in vacuum.

Compound **51**. Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.83 (d, 2H, *J*=2.0 Hz, 2×1-H), 3.87 (q, 2H, *J*=6.6 Hz, 2×5-H), 3.67–3.60 (m, 2H, 2×OC*H*H′), 3.41 (d, 2H, *J*=2.0 Hz, 2×4-H), 3.41–3.32 (m, 2H, 2×OCH*H*′), 3.23 (m, 2H, 2×3-H), 1.94 (br s, 8H, 2×2-H_{eq}, 2×NH_2 and 2×OH), 1.69–1.60 (m, 6H, 2×2-H_{ax} and CH_2CH_2), 1.26 (d, 6H, *J*=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=97.1, 71.0, 67.0, 65.8, 46.4, 32.9, 26.5, 17.0; DCI-MS: m/z (%)=349.2 (100) (M+H$^+$), 697.4 (2) (2M+H$^+$).

4.1.21. 1,4-Di-(3′-amino-2′,3′,6′-trideoxy-α-L-ribo-hexopyranosyl)-1,4-butanediol (52). 1,4-Di-(3′-trifluoroacetamino-2′,3′,6′-trideoxy-α-L-ribo-hexopyranosyl)-1,4-butanediol **39** (36.9 mg, 0.069 mmol) was dissolved in a mixture of tetrahydrofuran and 0.1M aqueous NaOH (1:3, 12 ml). The solution was stirred at rt for 30 min, at which time TLC indicated that the deprotection was completed. After neutralization with dry ice (pH 7–8), the solution was concentrated under reduced pressure to 2 ml. This residue was subjected to column chromatography (reversed phase C-18; gradient water to methanol) to afford the target product **52** (20.5 mg, 59 μmol, 85%).

Compound **52**. Colorless oil; $[\alpha]_D^{24}=-159.6$ (*c*=1.03; MeOH/$CHCl_3$=2:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.80 (s, 2H, 2×1-H), 3.73–3.62 (m, 2H, 2×OCHH′), 3.58 (dq, 2H, *J*=9.2, 6.2 Hz, 2×5-H), 3.38–3.25 (m, 2H, 2×OC*H*H′), 3.17–3.00 (m, 4H, 2×3-H and 2×4-H), 2.60–2.10 (b, 4H, 2×NH_2), 1.96 (bs, 4H, 2×2-H_{eq} and 2×2-H_{ax}), 1.63 (m, 4H, CH_2CH_2), 1.27 (d, 6H, *J*=6.4 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=97.4, 71.0, 67.3, 64.2, 47.4, 36.5, 26.6, 17.9; LRMS (DCI) for $C_{16}H_{32}N_2O_6$: 349.3 (100) (M+H$^+$), 697.7 (2) (2M+H$^+$).

4.1.22. 1,4-Bis (methyl-3′-amino-2′,3′,6′-trideoxy-β-L-lyxo-hexopyranos-4′-yl)-1,4-butanediol (53). Homodimer **46** (56 mg, 0.12 mmol) was dissolved in water (20 ml) at rt and barium hydroxide octahydrate (4.0 g, about 2 g/10 ml water) was added. The solution was stirred magnetically while it vigorously boiled under reflux (130–140 °C). After 48 h TLC (dichloromethane/methanol=5:1) indicated the completion of the saponification. Solid carbon dioxide was added to this suspension and the precipitate was filtered off. The filtrate was treated with Amberlite IRA-900 (OH$^-$ form, 20 ml) and the suspension was stirred for additional 30 min. After filtration, the solution was evaporated under reduced pressure to give a residue, which, still containing some barium carbonate, was taken up in chloroform. The organic layer afforded the deprotected homodimer **53** (16 mg, 42 μmol; 85%) after concentration in vacuum.

^{13}C NMR (50 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=101.5, 75.6, 74.4, 71.7, 56.3, 49.5, 29.6, 27.1, 17.5; LRMS (ES): $C_{18}H_{36}N_2O_6$: 377.4 (100) (M+H$^+$), 399.5 (31) (M+Na$^+$).

4.1.23. 1,4-Bis (3′-acetamido-4′-*O*-allyl-2′,3′,6′-trideoxy-α-L-lyxo-hexopyranosyl)-1,4-butanediol (54). A nitrogen flask was equipped with a condenser and was flushed with nitrogen. Diol **37** (80 mg, 0.185 mmol) in dry acetonitrile (20 ml) was added at rt under nitrogen. After addition of freshly precipitated and dry silver oxide (155 mg, 0.68 mmol) and allyl iodide (0.2 ml, 2.17 mmol, 6 equiv.) the suspension was refluxed at 100 °C for 1.5 h, whereupon the suspension was filtered with suction through a pad of Celite. After washing of the Celite with a mixture of methanol and dichloromethane the combined filtrates were concentrated under reduced pressure to afford a crude material. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH=10:1) yielded homodimer **54** (91 mg, 0.178 mmol; 96%).

Compound **54**. Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=5.92 (dddd, 2H, *J*=17.2, 10.4, 6.2, 5.4 Hz, 2×CH_2=C*H*CH_2O), 5.61 (d, 2H, *J*=8.8 Hz, 2×NH), 5.25 (dq, 2H, *J*=17.2, 1.5 Hz, 2×C*H*H′=$CHCH_2$O), 5.18 (dq, 2H, *J*=10.2, 1.3 Hz, 2×CH*H*′=$CHCH_2$O), 4.84 (d, 2H, *J*=2.4 Hz, 2×1-H), 4.45–4.31 (m, 2H, 2×3-H), 4.22 (ddt, 2H, *J*=12.8, 5.4, 1.4 Hz, 2×OC*H*H′CH=CH_2), 3.98 (ddt, 2H, *J*=12.8, 5.4, 1.4 Hz, 2×OCH*H*′CH=CH_2), 3.91 (q, 2H, *J*=6.4 Hz, 2×5-H), 3.58 (m, 2H, 2×OC*H*H′), 3.39 (d, 2H, *J*=2.2 Hz, 2×4-H), 3.38–3.21 (m, 2H, 2×OCH*H*′), 1.95 (s, 6H, 2×CH_3CONH), 1.79 (dt, 2H, *J*=12.6, 3.6 Hz, 2×2-H_{ax}), 1.71–1.61 (m, 2H, 2×2-H_{eq}), 1.59 (m, 4H, CH_2CH_2), 1.21 (d, 6H, *J*=6.6 Hz, 2×6-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.3, 134.7, 117.4, 96.8, 77.7, 75.0, 67.0, 65.9, 44.9, 30.8, 26.4, 23.4, 17.3; calcd (%) for $C_{28}H_{44}N_2O_8$ (512.64): C 60.92, H 8.65, N 5.46, found C 60.81, H 8.57, N 5.41.

4.1.24. Cross metathesis between 1,4-bis(3′-acetamido-2′,3′,6′-trideoxy-4′-*O*-allyl-α-L-lyxo-hexopyranosyl)-1,4-butanediol (54) and allyl ether 40 and preparation of trimer 56 and tetramer 55. Methyl 3-acetamido-4-allyl-2,3,6-trideoxy-β-L-lyxo-hexopyranoside **40** (127 mg, 0.522 mmol) and 1,4-bis (3′-acetamido-4′-*O*-allyl-2′,3′,6′-trideoxy-α-L-lyxo-hexopyranosyl)-1, 4-butanediol **54** (62 mg, 0.121 mmol) with a molar ratio of 4.3:1 were dried in high vacuum (10^{-2} Torr) for more than 5 h and dissolved under nitrogen in absolute benzene (20 ml). To this solution was added Grubbs's catalyst **7** in two portions (20 mg, 0.024 mmol then 14 mg, 0.017 mmol). The purple

solution was allowed to stir at rt for 14 h followed by additional stirring for 6 h at 95 °C. The reaction was terminated by concentration under reduced pressure. After addition of diethyl ether (30 ml) and triethyl amine (1 ml) stirring was continued under air for 2 h. The solvent was removed under reduced pressure to afford a mixture of crude products, which was subsequently purified by column chromatography (dichloromethane/methanol=10:1). Pure compounds of cross metathesis products **55** (18 mg, 19 μmol, 16%) and **56** (24 mg, 33 μmol, 27%), along with homodimer from methyl 3-acetamido-4-allyl-2,3,6-trideoxy-β-L-lyxo-hexopyranoside **40** (60 mg, 50.2%) were collected.

Compound **56**. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.07–5.82 (m, 1H, CH_2=C*H*CH_2O), 5.83 (t, 2H, *J*=3.0 Hz, O–CH_2–C*H*=C*H*–CH_2–O), 5.63, 5.56 (2d, 3H, *J*=8.8 Hz, NH^I, NH^{II}, NH^{III}), 5.28 (dq, 1H, *J*=17.2, 1.2 Hz, CH*H′*=CHCH_2O), 5.20 (dq, 1H, *J*=10.2, 1.0 Hz, CH*H′*=CHCH_2O), 4.85 (t, 2H, *J*=2.0 Hz, 1-H^{II}, 1-H^{III}), 4.46–4.34 (m, 2H, 3-H^{II}, 3-H^{III}), 4.36 (dd, 1H, *J*=9.2, 2.3 Hz, 1-H^I), 4.25–3.90 (m, 7H, 3-H^I, OCH_2CH=CH_2, O–CH_2–CH=CH–CH_2–O), 3.94 (q, 2H, *J*=6.4 Hz, 5-H^{II}, 5-H^{III}), 3.64–3.55 (m, 2H, 2×OCH*H′*-CH_2–), 3.56 (q, 1H, *J*=6.2 Hz, 5-H^I), 3.48 (s, 3H, OCH_3), 3.42–3.31 (m, 2H, 2×OCH*H′*-CH_2–), 3.40 (d, 2H, *J*=2.8 Hz, 4-H^{II}, 4-H^{III}), 3.31 (d, 1H, *J*=3.0 Hz, 4-H^I), 2.01, 2.00, 1.97 (3s, 9H, 3×CH_3CO–), 1.88–1.56 (m, 10H, 3×2-H, 2×OCH_2CH_2), 1.31 (d, 3H, *J*=6.4 Hz, 6-H^I), 1.23, 1.22 (2d, 6H, *J*=6.4 Hz, 6-H^{II} and 6-H^{III}); ^{13}C NMR (100 MHz, $CDCl_3$ with a trace amount of CD_3OD): δ=170.6, 170.4, 134.3, 129.1, 129.0, 117.2, 101.1, 96.6, 76.8, 76.7, 74.7, 73.5, 73.5, 71.3, 66.8, 65.7, 65.7, 56.0, 48.1, 45.0, 44.9, 31.4, 29.8, 26.0, 22.3, 22.2, 22.1, 16.7, 16.7, 16.6; HRMS ($C_{36}H_{61}N_3NaO_{12}$): calcd. 750.4153 $[M+Na]^+$, found 750.4147.

Compound **55**. Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ=5.86 (d, 2H, *J*=8.4 Hz, 2×NH^I), 5.83 (m, 4H, 2×–OCH_2–C*H*=C*H*–CH_2O–), 5.66 (d, 2H, *J*=8.6 Hz, 2×NH^{II}), 4.85 (d, 2H, *J*=2.6 Hz, 2×1-H^{II}), 4.43–4.30 (m, 2H, 2×3-H^{II}), 4.35 (dd, 2H, *J*=9.2, 2.0 Hz, 2×1-H^I), 4.25–4.07 (m, 2H, 2×3-H^I), 4.19 (d and m, 4H, *J*=12.8 Hz, 2×–OC*H′H*–CH=CH–C*H′H*O–), 4.04 (d and m, 4H, *J*=12.8 Hz, 2×–OC*H′H*–CH=CH–C*H′H*O–), 3.93 (q, 2H, *J*=6.4 Hz, 2×5-H^{II}), 3.63–3.41 (m, 4H, 2×OCH_2-CH_2–), 3.55 (q, 2H, *J*=6.4 Hz, 2×5-H^I), 3.45 (s, 6H, 2×OCH_3), 3.38 (d, 2H, *J*=2.4 Hz, 2×4-H^{II}), 3.31 (d, 2H, *J*=3.0 Hz, 2×4-H^I), 2.00, 1.99 (2s, 12H, 2×CH_3CO^I and 2×CH_3CO^{II}), 1.83–1.58 (m, 12H, 4×2-H, 2×OCH_2CH_2–), 1.30 (d, 6H, *J*=6.4 Hz, 2×6-H^I), 1.22 (d, 6H, *J*=6.5 Hz, 2×6-H^{II}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.6, 170.5, 129.7, 129.0, 101.1, 96.7, 77.0, 75.9, 73.6, 73.6, 71.4, 66.9, 65.7, 56.1, 48.1, 45.0, 31.6, 29.8, 26.2, 26.1, 25.9, 22.4, 22.3, 16.8, 16.7; HRMS ($C_{46}H_{78}N_4NaO_{16}$): calcd. 965.5311 $[M+Na]^+$, found 965.5302.

4.1.25. Hydrogenation of tetramer 55 to tetramer 57 with saturated spacer linkers. A solution of 10% Pd–C (12 mg) in 6 ml methanol was stirred under hydrogen for 30 min and to this suspension was added the metathesis product **55** (17 mg, 18 μmol) in a solvent system consisting of methanol (12 ml) and dichlormethane (4 ml). After a successive addition of triethyl amine (0.1 ml) the mixture was allowed to stir at rt for additional 24 h, after which time the hydrogenation was terminated by adding triethyl amine (1 ml). The catalyst was filtered off and washed with the mixed solvent (dichloromethane/methanol=10:1). The combined filtrates were evaporated in vacuum to give a crude product **57**. The material was directly employed in the next step.

Selected spectroscopic data: ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.94 (d, 2H, *J*=8.6 Hz, 2×NH^I), 5.77 (d, 2H, *J*=8.2 Hz, 2×NH^{II}), 4.82 (d, 2H, *J*=3.0 Hz, 2×1-H^{II}), 4.44–4.38 (m, 2H, 2×3-H^{II}), 4.32 (dd, 2H, *J*=9.4, 2.0 Hz, 2×1-H^I), 4.09–4.03 (m, 2H, 2×3-H^I), 3.89 (q, 2H, *J*=6.4 Hz, 2×5-H^{II}), 3.64–3.30 (m, 12H, 6×OCH_2-CH_2–), 3.51 (q, 2H, *J*=6.4 Hz, 2×5-H^I), 3.45 (s, 6H, 2×OCH_3), 3.36 (d, 2H, *J*=3.0 Hz, 2×4-H^{II}), 3.23 (d, 2H, *J*=2.4 Hz, 2×4-H^I), 1.99, 1.98 (2s, 12H, 2×CH_3CO^I and 2×CH_3CO^{II}), 1.80–1.55 (m, 20H, 4×2-H, 6×OCH_2CH_2–), 1.27 (d, 6H, *J*=6.2 Hz, 2×6-H^I), 1.19 (d, 6H, *J*=6.2 Hz, 2×6-H^{II}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.5, 169.4, 101.2, 96.8, 77.8, 76.8, 74.2, 74.0, 71.6, 66.9, 65.9, 56.3, 48.2, 45.2, 32.3, 30.5, 27.3, 27.0, 26.3, 23.4, 23.3, 17.2, 17.1; LRMS (DCI) for $C_{46}H_{82}N_4O_{16}$: 947.9 (100) ($M+H^+$), 964.9 (14) ($M+NH_4^+$).

4.1.26. Hydrolysis of tetramer 57 to the target 1,4-butanediol-linked tetradaunosamides 58. Tetramer **57** (17 mg, 0.018 mmol) was dissolved at rt in water (10 ml) and barium hydroxide octahydrate (2.0 g in 10 ml water) was added. The solution was stirred under refluxing conditions (130–140 °C) for 30 h. To this mixture solid carbon dioxide was added and the precipitate was filtered off. The filtrate was treated with Amberlite IRA-904 (OH^- form, 10 ml) and stirred for 30 min. After filtration the solution was evaporated to give a residue, which still contained traces of barium carbonate. It was taken up in chloroform and the crude product **58** (9 mg, 12 μmol, 64.3% for two steps) was purified by column chromatography over a RP-18 (800 mg).

Compound **58**. Colorless oil; $[\alpha]_D^{24}$=−73.3 (*c*=0.32, $CHCl_3$/MeOH 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.81 (d, 2H, *J*=2.4 Hz, 2×1-H^{II}), 4.26 (dd, 2H, *J*=9.6, 2.0 Hz, 2×1-H^I), 3.82 (q, 2H, *J*=6.4 Hz, 2×5-H^{II}), 3.69–3.65 (m, 4H, 4×OCH*H′*-CH_2–), 3.63–3.57 (m, 6H, 6×OCH*H′*-CH_2–), 3.46 (s, 6H, 2×OCH_3), 3.45 (q, 2H, *J*=6.4 Hz, 2×5-H^I), 3.38–3.31 (m, 2H, 2×OCH*H′*-CH_2–), 3.15 (d, 2H, *J*=2.5 Hz, 2×4-H^{II}), 3.11 (m, 2H, 2×3-H^{II}), 3.06 (d, 2H, *J*=3.0 Hz, 2×4-H^I), 2.80 (ddd, 2H, *J*=12.0, 4.2, 3.4 Hz, 2×3-H^I), 1.77–1.52 (m, 28H, 4×NH_2, 4×2-H, 6×OCH_2CH_2–), 1.31 (d, 6H, *J*=6.4 Hz, 2×6-H^I), 1.22 (d, 6H, *J*=6.4 Hz, 2×6-H^{II}); ^{13}C NMR (100 MHz, $CDCl_3$): δ=101.6, 97.3, 80.8, 79.8, 74.5, 74.4, 72.1, 66.9, 66.9, 56.2, 51.1, 47.0, 36.9, 35.5, 27.2, 27.1, 26.4, 17.5, 17.2; LRMS (DCI) for $C_{38}H_{74}N_4O_{12}$: 779.0 (100) ($M+H^+$).

4.1.27. Hydrogenation of trimer 56 for preparation of trimer 59 with saturated aliphatic linkages. To a solution of **56** (25 mg, 0.034 mmol) in 12.5 ml of a mixed solvent (ethyl acetate/dichloromethane/methanol=16:8:1) was added PtO_2 (7.7 mg). The suspension was stirred under hydrogen at rt for 16 h, after which time the reduction was complete (TLC: petroleum ether/ethyl acetate=4:1). The reaction was terminated by addition of triethyl amine (1 ml),

followed by filtration with suction and evaporation under reduced pressure. The crude product obtained was purified by flash column chromatography (petroleum ether/ethyl acetate=6:1) to furnish the hydrogenated product **59** (23 mg, 31 μmol, 92%).

Compound **59**. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.84 (d, 1H, J=8.5 Hz, NH^{I}), 5.68 (d, 1H, J=8.6 Hz, NH^{II}), 5.58 (d, 1H, J=8.5 Hz, NH^{III}), 4.84 (t, 2H, J=3.2 Hz, 1-H-b, 1-H^{III}), 4.42–4.33 (m, 2H, 3-H^{II}, 3-H^{III}), 4.34 (dd, 1H, J=9.4, 2.0 Hz, 1-H^{I}), 4.12–4.04 (m, 1H, 3-H^{I}), 3.91 (dq, 2H, J=6.4, 2.2 Hz, 5-H^{II}, 5-H^{III}), 3.67–3.50 (m, 7H, $OCHH'CH_2CH_3$, 2×OCH_2-CH_2-, 2×$OCHH'$-CH_2–), 3.53 (q, 1H, J=6.4 Hz, 5-H^{I}), 3.47 (s, 3H, OCH_3), 3.41 (dt, 1H, J=9.6, 7.2 Hz, $OCHH'CH_2CH_3$), 3.38–3.32 (m, 2H, 2×$OCHH'$-CH_2–), 3.31 (d, 2H, J=2.8 Hz, 4-H-b, 4-H^{III}), 3.24 (d, 1H, J=2.6 Hz, 4-H^{I}), 2.00, 1.99, 1.97 (3s, 9H, 3×CH_3CO), 1.80–1.56 (m, 16H, 3×2-H, 4×OCH_2CH_2, $OCH_2CH_2CH_3$), 1.29 (d, 3H, J=6.4 Hz, 6-H^{I}), 1.22, 1.21 (2d, 6H, J=6.4 Hz, 6-H^{II} and 6-H^{III}), 0.94 (t, 3H, J=7.3 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ=169.4, 169.2, 101.2, 96.8, 77.8, 76.9, 76.0, 74.2, 74.1, 71.6, 67.0, 66.1, 56.4, 48.2, 45.0, 32.4, 30.8, 27.4, 27.1, 26.4, 23.5, 23.4, 23.3, 17.3, 17.1, 10.7; LRMS (DCI) for $C_{36}H_{65}N_3O_{12}$: 732.8 (100) ($M+H^+$), 747.8 (11) ($M+NH_4^+$).

4.1.28. Hydrolysis of trimer 59 and synthesis of 1,4-butanediol-linked tridaunosamides 60. Trimer **59** (23 mg, 31 μmol) was dissolved at rt in water (20 ml) and barium hydroxide octahydrate (4.5 g) was added. The solution was stirred under refluxing conditions (130–140 °C) for 24 h. To this mixture solid carbon dioxide was added and the precipitate was filtered off. The filtrate was treated with Amberlite IRA-904 (OH^- form, 20 ml) and stirred for 30 min. After filtration the solution was evaporated to give a residue, which, still containing some barium carbonate, was taken up in chloroform. The organic layer afforded the deprotected trimer **60** (16 mg, 26 μmol, 84%) after evaporation in vacuum.

Compound **60**. Colorless oil; $[\alpha]_D^{24}=-70.9$ (c=0.46, $CHCl_3$/MeOH=3:1); ^{1}H 1NMR (400 MHz, $CDCl_3$): δ=4.80 (t, 2H, J=3.4 Hz, 1-H^{II}, 1-H^{III}), 4.24 (dd, 1H, J=9.5, 2.0 Hz, 1-H^{I}), 3.81 (qd, 2H, J=6.4, 2.2 Hz, 5-H^{II}, 5-H^{III}), 3.69–3.61 (m, 3H, $OCHH'CH_2CH_3$, 2×$OCHH'$-CH_2–), 3.63–3.54 (m, 4H, 4×$OCHH'$-CH_2–), 3.51 (dt, 1H, J=8.8, 7.2 Hz, $OCHH'CH_2CH_3$), 3.44 (s, 3H, OCH_3), 3.42 (q, 1H, J=6.4 Hz, 5-H^{I}), 3.37–3.29 (m, 2H, 2×$OCHH'$-CH_2–), 3.13 (br s, 2H, 4-H^{II}, 4-H^{III}), 3.11–3.05 (m, 2H, 3-H^{II}, 3-H^{III}), 3.04 (d, 1H, J=2.8 Hz, 4-H^{I}), 2.78 (ddd, 1H, J=12.3, 4.1, 3.2 Hz, 3-H^{I}), 1.74–1.53 (m, 22H, 3×NH_2, 3×2-H, 6×OCH_2CH_2-, $OCH_2CH_2CH_3$), 1.28 (d, 3H, J=6.4 Hz, 6-H^{I}), 1.21, 1.20 (2d, 6H, J=6.4 Hz, 6-H^{II}, 6-H^{III}), 0.91 (t, 3H, J=7.3 Hz, $OCH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=101.5, 97.2, 80.7, 79.7, 76.2, 74.4, 74.3, 72.1, 66.9, 66.8, 56.2, 51.0, 46.9, 36.9, 35.4, 27.1, 27.1, 26.4, 23.5, 17.3, 17.2, 10.5; LRMS (DCI) for $C_{30}H_{59}N_3O_9$: 606.6 (100) (M+H+).

4.2. Additional information on RNA dot blot experiments

For the sake of better comparison in the dot blot experiments the aminoglycoside concentrations are give in concentrations of the individual carbohydrate subunits (22, 11.2, 7.6, 5.6, 2.4 and 1.2 mM). The actual concentration for the trimer: 0.4, 0.8, 1.8, 2.5, 3.7 and 7.3 mM; for the tetramers: 0.3, 0.6, 1.4, 1.9, 2.8 and 5.5 mM. Dot blot experiments with the two aptamers were performed with an aptamer concentration of 0.16 μM, 100 μM 17-mer Rev peptide and aminoglycoside **2** ranging from 1 to 200 mM in an overalls volume of 20 μl. Binding experiments were performed in an overall volume of 40 μl, containing 10 mM Tris·HCl (pH=7.5), 70 mM NaCl, 0.2 mM EDTA, 5% glycerol. The TAR-RNA (0.16 μM) and the 9-mer Tat peptide (222 μM) were first incubated for 30 min. Then the aminoglycosides had been added and the mixture was incubated for additional 30 min. After that time the mixture was filtered through a dot blot apparatus in which two membranes, on top a nitrocellulose membrane and below a positively charged nylon membrane had been inserted. After filtration the two membranes were separated and the nylon membrane was 'backed' at 80 °C for 30 min. The RNA on the nitrocellulose membrane was blotted onto a positively nylon membrane and was then further treated as mentioned above. After immobilization at 80 °C followed by the wash protocol from Ambion, the RNA was visualized with streptavidin/alkaline phosphatase and CDP-star on kodak film.

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