Synthesis and Biological Evaluation of Modified 2-Deoxystreptamine Dimers

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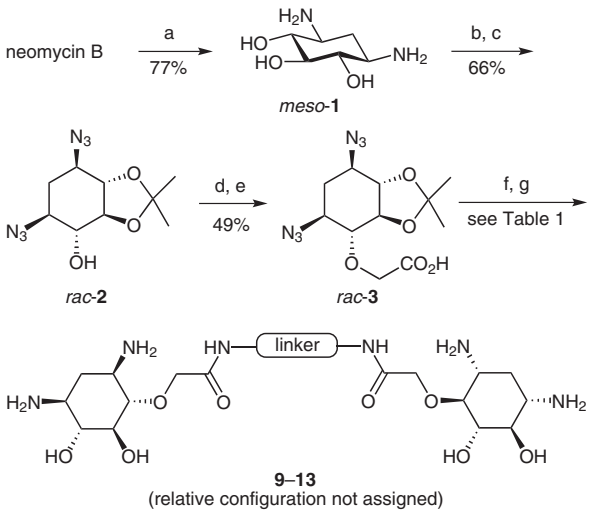
Dedicated to Prof. Pierre Vogel on the occasion of his 65th birthday

Abstract: Aminoglycosides are powerful antibiotics, but the emergence of resistant bacterial strains has prompted the search for analogues with better pharmacological profiles. The synthesis of 2-deoxystreptamine (2-DOS) dimers linked by polyamines and analogues based on furylcarbopeptoid skeletons is described. Potent and selective ligands for bacterial 16S rRNA were identified using microarray techniques by determining the affinity of these derivatives toward bacterial and human ribosomal RNAs.

Key words: antibiotics, 2-deoxystreptamine dimers, microarray, ribosomal RNA, solid-phase synthesis

Many human diseases are associated with RNA processing malfunction. At least 15% of all genetic disorders involve aberrant mRNA processing.[1] Despite some early scepticism, RNA, in particular ribosomal RNA, has become a well-established drug target. Aminoglycosides, a large family of clinically used antibiotics, were the first compounds to be recognized as effectors of RNA function.[2] Despite their wide use for the treatment of enterococcal, mycobacterial, and severe Gram-negative bacterial infections, aminoglycosides show ototoxicity and cause renal damage.[3] These side effects and the emergence of aminoglycoside resistant strains[4] have prompted the development of aminoglycoside analogues. Several approaches were based on the chemical modification of the natural antibiotics.[5] The affinity and specificity of aminoglycosides for their viral or bacterial RNA targets have been significantly enhanced by the formation of dimers[6] or conjugation to other binding molecules such as aromatic structures and peptides.[7] In view of the complex synthesis of aminosugars and aminocyclitols, an appealing strategy is based on the generation of simpler structural analogues that are amenable to straightforward medicinal chemistry exploration. The central core of all aminoglycosides, 2-deoxystreptamine (2-DOS), is a good starting point for aminoglycoside analogues.[8] Here, we report on the preparation and RNA affinity evaluation of 2-DOS dimers as well as polyamine and aminopolyketide linked analogues.[9,10]

Enhancement of the RNA binding affinities for dimeric aminoglycosides may result from an increased overall positive charge and from the possibility to target multiple binding sites within large RNA molecules. In particular, long and conformationally flexible spacers should allow the resulting conjugates to search for several binding sites by screening variable conformations.[2a,6a] While linkers containing ether, thioether, amide, aromatic and disulfide moieties have already been used to dimerize aminoglycosides,[6b–d] we intended to combine both flexibility and enhanced cationic density through polyamine spacers. Based on the variety of accessible polyamines, the preparation of 2-DOS dimers was thus envisaged through the conjugation with diamino linkers **4**–**6** and with more complex aminopolyketides **7** and **8** (Scheme 1). These differ-



Scheme 1 Synthesis of 2-deoxystreptamine dimers. *Reagents and conditions*: (a) HBr, 120 °C; (b) TfN3, CuSO4 (cat.), MeOH–PhH–Et3N, 25 °C; (c) 2,2-dimethoxypropane, CSA (cat.), MeCN, 25 °C; (d) NaH, BrCH2CO2Me, MeCN, 25 °C; (e) LiOH, THF–MeOH–H_2O, 25 °C; (f) **4**–**8**, PyBOP, Et_3N, CH_2Cl_2, 25 °C; (g) Method A: i) CF_3CO_2H–MeOH–H_2O, 25 °C, ii) H_2 1 atm, $Pd(OH)_2$/C (cat.), MeOH, 25 °C. Method B: i) H_2 1 atm, $Pd(OH)_2$/C (cat.), AcOH, ii) CF_3CO_2H–MeOH–H_2O, 25 °C.

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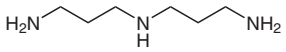
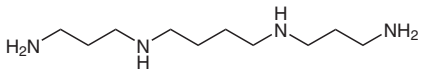
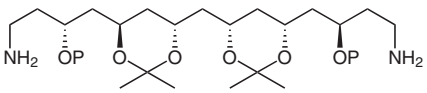
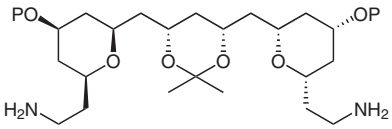
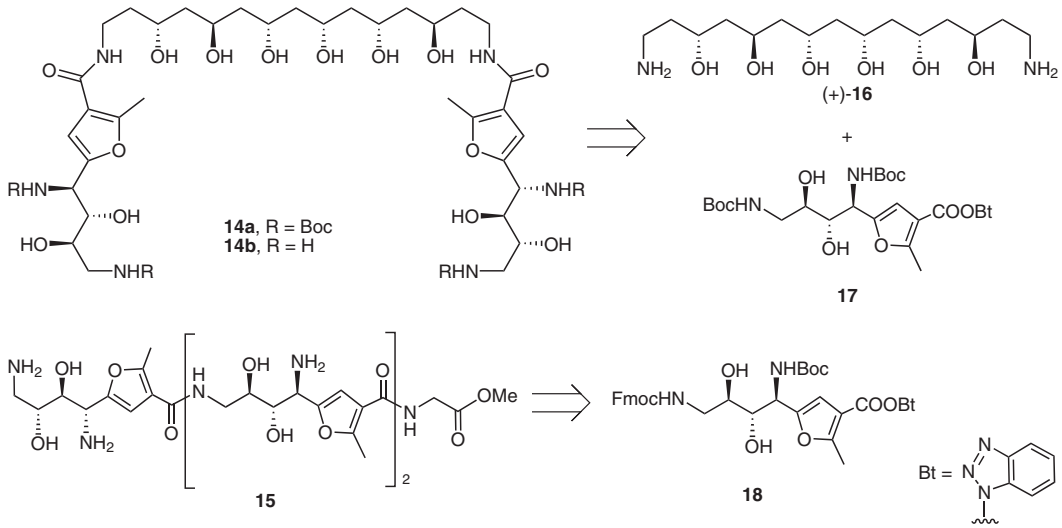
Table 1 Synthesis of 2-DOS Dimers

Linker	Method	Dimer	Yield (%, 3 steps)
 **4**	A	**9**	50
 **5**	A	**10**	42
 **6**	A	**11**	19
 **7** (P = BOM)	B	**12**	10
 **8** (P = BOM)	B	**13**	23

ent spacers will give some insights in the influence of the linker length and polarity on RNA affinity.

Following established procedures, diazido alcohol *rac*-**2** was obtained by acidic degradation of neomycin B[11] followed by copper-mediated azide transfer[12] and protection of the remaining diol as an acetonide. S_N2 displacement of methyl bromoacetate by the corresponding alkoxide and saponification of the resulting methyl ester afforded carboxylic acid *rac*-**3** in 49% yield. Conjugation with various diamines **4**–**8** (Table 1) was followed by different deprotection sequences. Starting from amines **4**–**6**, acid-mediated cleavage of the acetonide moieties and final hydrogenolysis of the azido groups afforded dimers **9**–**11**. Starting from *rac*-**3**, the formation of a *meso*-conjugate and a *threo*-conjugate (mixture of 2 enantiomers) was expected. After purification by column chromatography, the isolated dimers **9**–**11** displayed only one set of signals in the ^{13}C NMR spectra (see Supporting Information) and thus appeared as single isomers. Starting from optically active diamines **7** and **8**, the reverse order of deprotection as well as stronger hydrogenolysis conditions were required for the cleavage of anti acetonides and BOM (benzyloxymethyl) ethers to deliver 2-DOS conjugates **12** and **13** in modest overall yield. While several stereoisomers could be produced, HPLC purification allowed the isolation of the major products from this reaction sequence.

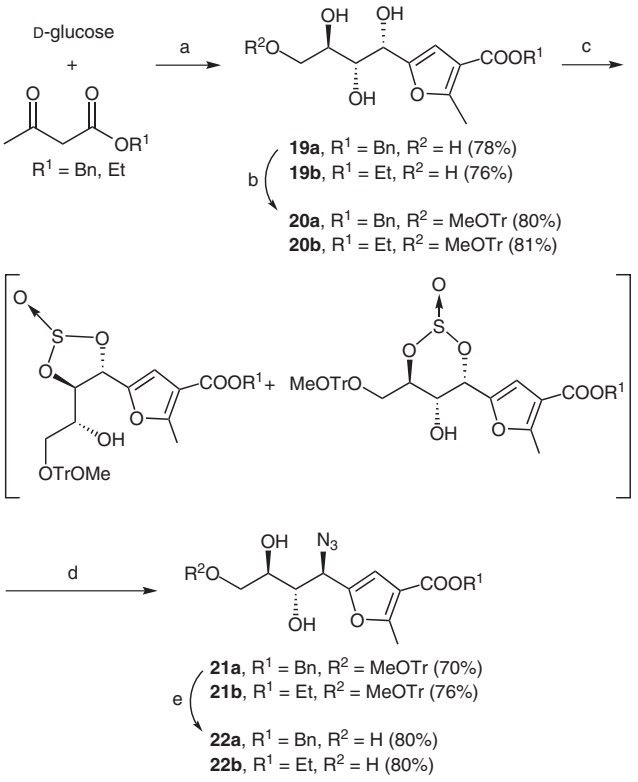
To test whether the 2-DOS RNA recognition element can be replaced by other binding motifs, such as aromatic moieties, conjugates between furyl residues and 1,3-hydroxyamine fragments were designed. Compounds **14b** and **15** were prepared from furyl amino acids **17** and **18** following the retrosynthetic analysis outlined in Scheme 2. Compound **15** can be considered as an amino-polyketide with furyl moieties as spacers containing the



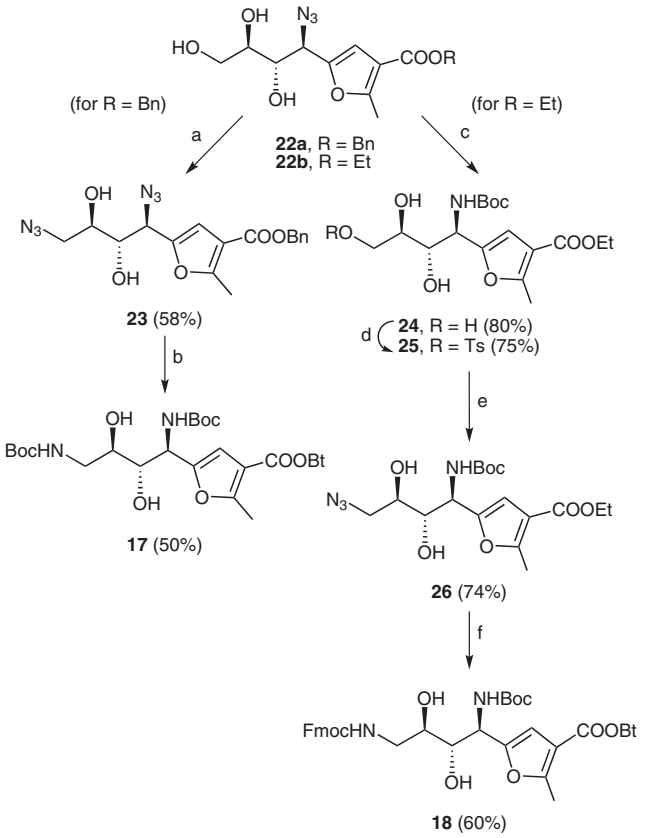
Scheme 2 Retrosynthetic analysis to furylcarbopeptoids

structural motifs needed for potential interaction with RNA. The aromatic moieties could increase the binding affinity, as reported.[7]

Synthesis of building blocks **17** and **18** started from readily available **19a** and **19b** (Scheme 3). Intermediate **19a** was obtained from D-glucose and benzyl acetoacetate following a high-yielding modified procedure of the García-González reaction.[13] The introduction of the azido moiety at the benzylic position was carried out utilizing the procedure for the stereoselective synthesis of α-furfurylamines.[14] Regioselective tritylation of **19a** (80% yield) followed by reaction with thionyl chloride and triethylamine afforded a mixture of cyclic sulfites, which were not isolated. Subsequent S_N2 displacement with trimethylsilyl azide, in the presence of TBAF, gave azide **21a** in 70% yield from **19a**. Removal of the *p*-methoxytrityl group in **21a** was successfully performed under mild acidic conditions using triisopropylsilane as scavenger (Scheme 3). As previously described,[15] compound **22b** was obtained similarly but using ethyl acetoacetate as starting material. Regioselective tosylation of benzyl ester **22a** followed by nucleophilic displacement using tetrabutylammonium azide afforded diazido derivative **23** in 58% overall yield (Scheme 4). Hydrogenation of **23** under atmospheric pressure in methanol containing $(Boc)_2O$ furnished the corresponding protected diamino acid derivative, which was isolated as the stable benzotriazol-1-yl activated ester **17** by reaction with PyBOP and DIPEA in 50% overall yield. Hydrogenation of **22b** in methanol containing $(Boc)_2O$ afforded **24** in good yield. Regioselective tosylation followed by displacement with $TMSN_3$/TBAF gave **26**. Saponification of **26** (LiOH/EtOH), followed by reduction of the azido group and protection of the resulting amino function with Fmoc, afforded the corresponding orthogonally protected diamino acid derivative, which was isolated as the benzotriazol-1-yl activated ester **18** in 60% overall yield (Scheme 4). Both activated esters **17** and **18** were purified by column chromatography.



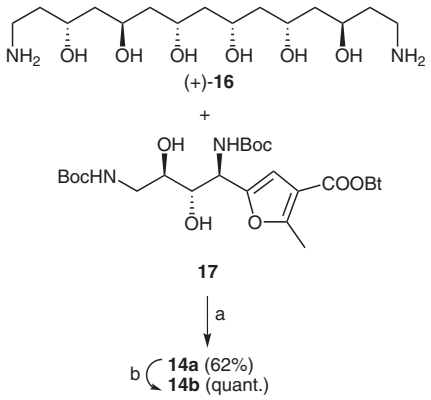
Scheme 3 *Reagents and conditions*: (a) NaI, $CeCl_3$, SiO_2, 50 °C, 9 days; (b) MeOTrCl, Py; (c) $SOCl_2$, CH_2Cl_2, 0 °C; (d) $TMSN_3$, TBAF, THF, r.t., 24 h; (e) 2% TFA–CH_2Cl_2, triisopropylsilane.



Scheme 4 *Reagents and conditions*: (a) (i) TsCl, Py, –15 to 0 °C, (ii) Bu_4NN_3, THF, 50 °C, 2 h; (b) (i) H_2 1 atm, Pd/C, $(Boc)_2O$, MeOH, (ii) PyBOP, DIPEA, DMF; (c) H_2, 1 atm, Pd/C, $(Boc)_2O$, MeOH; (d) TsCl, Py, –15 to 0 °C; (e) $TMSN_3$, TBAF, THF, 60 °C; (f) (i) LiOH, EtOH, 50 °C, (ii) H_2, 1 atm, Pd/C, EtOH, (iii) Fmoc-OSu, aq $NaHCO_3$, 1,4-dioxane, (iv) PyBOP, DIPEA, DMF, 60%.

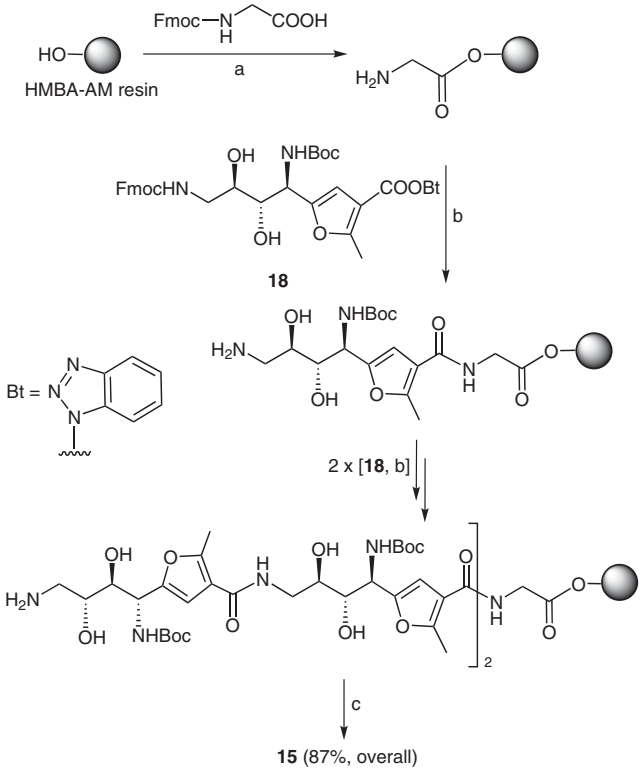
Furyl carbopeptoids containing 1,3-hydroxyamine motifs were prepared from building blocks **17** and **18** that are protected furyldiamino acids activated for amido coupling as stable benzotriazol-1-yl (Bt) esters. Acetonide hydrolysis and hydrogenation of (+)-**7** afforded aminopolyol (+)-**16**, which was immediately coupled with **17** upon treatment with DIPEA and DMF in 62% yield (Scheme 5). Furyl carbopeptoid **14b** was obtained after removal of the Boc groups in quantitative yield.

On the other hand, orthogonally N-protected **18** was oligomerized using solid-phase peptide synthesis methodology (Fmoc strategy/HMBA-AM resin) (Scheme 6). Fmoc-glycine was first attached to the hydroxyl resin to facilitate the final cleavage of the furylcarbopeptoid from the resin.[16] Iterative couplings with excess **18** in the pres-



Scheme 5 *Reagents and conditions*: (a) DIPEA, DMF; (b) 20% TFA–CH_2Cl_2.

ence of DIPEA in DMF, afforded the polymer-bound compound, which was removed from the solid support by treatment with MeOH–Et_3N (2:1) overnight using DMF as cosolvent. Due to the stability of the activated ester derivative **18**, excess of this compound was recovered from the resin by washing with DMF and recycled to optimize the overall yield. Final Boc deprotection with TFA (20%)–CH_2Cl_2 gave furylcarbopeptoid **15** in 87% overall yield.



Scheme 6 *Reagents and conditions*: (a) (i) 2,6-dichlorobenzoyl chloride, Py–DMF; (ii) 20% piperidine–CH_2Cl_2; (b) (i) DIPEA, DMF, (ii) 20% piperidine–CH_2Cl_2; (c) (i) DMF, MeOH–Et_3N (2:1), (ii) 20% TFA–CH_2Cl_2.

Binding of rRNA mimics to the 2-DOS dimers, analogues, and aminoglycosides was analyzed using microarrays. The aminoglycosides, analogues, and controls were

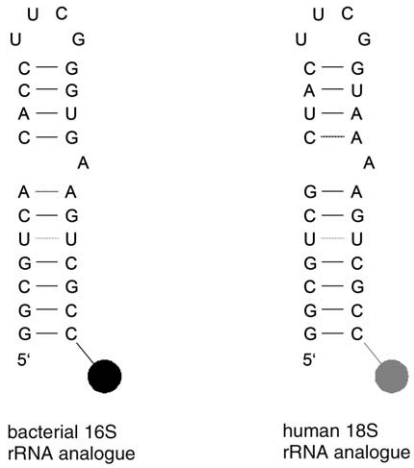


Figure 1 Structure of the 3′-fluorescence-labeled rRNA mimics (bacterial 16S rRNA analogue fluorescence label = tetramethylrhodamine, human 18S rRNA analogue fluorescence label = fluorescein)

printed onto amine-reactive microarray slides and incubated with fluorescence-labeled RNA mimics (Figure 1).

Bacterial and human rRNA mimics bound well and in a concentration dependent manner to several compounds on the microarray, including neomycin, kanamycin, spermidine, **9**, **11**, and (+)-**16** (Figure 2 and Supporting Information). Binding of some structures was even higher than to the immobilized aminoglycosides. For instance, the binding level of the 16S rRNA mimic was higher for compounds **9**, **11**, and (+)-**16** than for streptomycin or paranomycin. These long and flexible structures, as well as spermidine, were recognized particularly well. Apparently, the flexibility allows for improved interactions with the rRNA mimics. However, no distinct structural feature that is essential for rRNA binding could be determined. Furthermore, no structure displayed any pronounced preference for binding bacterial versus human rRNA.

The antibiotic properties of the compounds were analyzed using a disc diffusion assay (data not shown). Aminoglycosides, 2-DOS dimers, analogues, or controls were added to sterile filter plates that were placed on top agar plates containing *E. coli* bacteria. Plates were incubated overnight and checked for a zone of inhibition around the filter plates. Standard aminoglycosides (neomycin, paranomycin, streptomycin, and kanamycin A) inhibited bacterial growth, while none of the 2-DOS dimers or their analogues acted as inhibitors.

Several 2-DOS dimers and analogues interacted well with rRNA in vitro, demonstrating their utility as scaffolds for aminoglycoside analogues. However, the factors that are responsible for binding specificity and in vivo antibiotic activity remain elusive.

In summary, we have synthesized 2-deoxystreptamine dimers linked by naturally occurring polyamines or aminofunctionalized polyketides.[9] Some analogues containing substituted furyl moieties have been prepared from furyl amino acid building blocks. Evaluation of the bind-

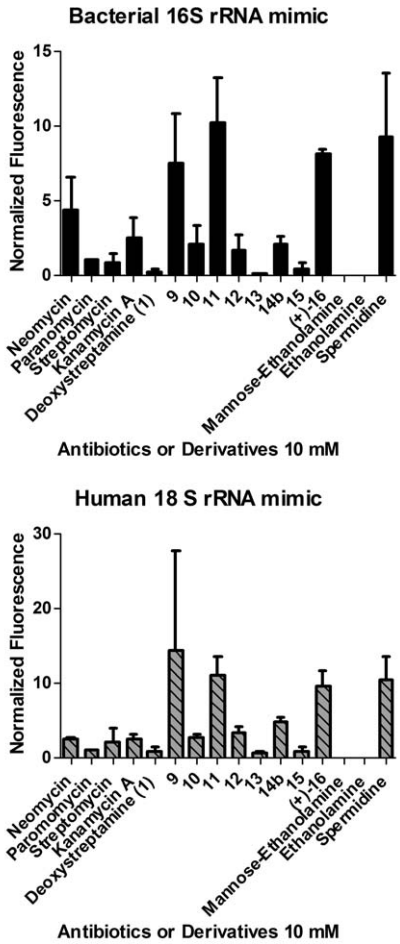


Figure 2 Binding of the bacterial 16S rRNA mimic or the human 18S rRNA mimic to aminoglycosides, 2-DOS dimers, and analogues. Aminoglycosides, 2-DOS dimers, and analogues were printed onto microarrays, incubated with rRNA analogues and evaluated as described in the experimental section. Error bars show standard error.

ing of rRNA mimics to these derivatives revealed high affinity of the flexible polyketide (+)-**16**. In addition, the affinity of 2-deoxystreptamine dimers appeared to be dependent on the length of the amino containing linker. Spermine-derived dimer **11** bound well to rRNA mimics but not selectively to bacterial rRNA. While furyl moieties were expected to provide stacking interactions with rRNA mimics, none of the furyl carbopeptoids displayed high affinity toward rRNA fragments. These results highlight that amino-functionalized derivatives may be used as interesting scaffolds for the preparation of new aminoglycoside mimics, but need to be further derivatized to improve binding selectivity.

All commercially available reagents and solvents (Fluka, Aldrich, Acros) were used without further purification. For reactions requiring anhydrous conditions, anhydrous solvents were bought (Fluka) or dried by filtration (Innovation Technology). Petroleum ether (PE) used refers to the fraction boiling in the range 40–60 °C. Experiments were carried out under argon atmosphere unless noted otherwise. Reactions were monitored by TLC (Merck silica gel $60F_{254}$ plates). Detection by UV light, $KMnO_4$, or Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O]. Purifications were performed by flash chromatography on silica gel (Merck No. 9385 silica gel 60, 240–400 mesh). ^1H NMR spectra : Bruker spectrometers at 300, 400, and 500 MHz. Chemical shifts in ppm relative to the solvent's residual ^1H signal (MeOD: 3.34 ppm, $CDCl_3$: 7.27 ppm, C_6D_6: 7.30 ppm) as internal reference. ^1H assignments were confirmed by 2D-COSY-45 spectra. Coupling constants *J* in Hz. ^{13}C NMR spectra: Same spectrometers as for ^1H NMR spectra at 75.4, 100, and 125.7 MHz. Reference for solvent used as internal reference in ppm (MeOD: 49 ppm, $CDCl_3$: 77 ppm, C_6D_6: 128.5 ppm). Coupling constants *J* in Hz. IR spectra: Perkin-Elmer Paragon 1000 FT-IR spectrometer. Mass spectra: GC-MS spectrometer [Nermag R-10-10C, chemical ionization (NH_3) mode *m/z*]; MALDI-TOF spectrometer (Axima-CFR+, Kratos, Manchester); ESI-Q spectrometer (Finnigan SSQ 710C, Thermoquest, UK); ESI-QT spectrometer (Ultima spectrometer, Micromass, Manchester); FAB mass spectra were obtained using glycerol or 3-nitrobenzyl alcohol as the matrix. Optical rotations were measured in a 1.0 cm or 1.0 dm tube with a Perkin-Elmer 241MC spectropolarimeter.

Microarray Printing: Microarrays were fabricated according to published methods.[17] In brief, DOS dimers, analogues, aminoglycosides and controls were dissolved in buffer (50 mM sodium phosphate, pH 8.5) and printed onto amine-reactive slides (CodeLink) in concentrations ranging from 10 mM to 10 μM using an automated arraying robot (Genetix). Spotted slides were incubated for 24 h in a humidity chamber to complete the immobilization reaction and stored under a dry atmosphere until usage.

Binding Experiments: Fluorescence-labeled human and bacterial rRNA mimics were obtained from Biomers and were refolded by incubation for 5 min at 60 °C in 20 mM Hepes, pH 7.4 and 200 mM NaCl and slow cooling to r.t. Refolded rRNA mimics were incubated on the microarrays (500 pmol/slide with 40U RNAse inhibitor (Invitrogen) in 20 mM Hepes pH 7.4 with 200 mM NaCl) for 1 h at r.t. Slides were washed with buffer, centrifuged to dryness, and scanned using a fluorescence microarray reader (Tecan). Spot intensities were evaluated using the GeneSpotter software (MicroDiscovery).

Disc Diffusion Test: LB top agar plates containing *E. coli* [strain BL21(DE3), Stratagene] bacteria were prepared. Sterile filter plates were placed onto the agar and 10 μL of the test solution (aminoglycosides, analogues or controls, each 5 mM in H_2O) was added to the filters. Plates were incubated overnight at 37 °C and inhibition of bacterial growth was assessed.

Coupling of Acid *rac*-3 with Diamines; General Procedure

To a solution of acid *rac*-**3** (0.20 to 0.50 mmol, 2 equiv) in CH_2Cl_2 (0.15 to 0.1 M) were added Et_3N (0.60 to 1.50 mmol, 6 equiv) and PyBOP (0.22 to 0.55 mmol, 2.2 equiv) at 25 °C. Diamine (0.10 to 0.25 mmol, 1 equiv) was added to this mixture and the white suspension was stirred for 2 h. The reaction mixture was concentrated in vacuo. Purification of the residue by flash chromatography (4–10% of MeOH in CH_2Cl_2) afforded diamides as colorless oils.

Deprotection of Dimers; General Procedures

Method A: Diamides obtained as above were dissolved in MeOH–TFA–H_2O (0.5:1:0.5, 2 to 4 mL) and stirred at 25 °C for 3 h. The reaction mixture was concentrated in vacuo. Purification of the residue by flash chromatography (2–10% of aq NH_4OH in MeCN) afforded the corresponding azides as colorless oils. The intermediate azides were dissolved in MeOH (2 to 4 mL) with a catalytic amount of $Pd(OH)_2$ on activated charcoal and stirred at 25 °C under 1 atm of H_2 for 3 h. The reaction mixtures were filtered through a pad of Celite, the filtrates were concentrated in vacuo. Purification of the residues by flash chromatography (40–60% of aq NH_4OH in MeCN) afforded products as white foams.

Method B: Diamides obtained as above were dissolved in AcOH (2 to 4 mL) and stirred with a catalytic amount of $Pd(OH)_2$ on activated

charcoal at 25 °C under 1 atm of H_2 for 5 h. The reaction mixtures were filtered though a pad of Celite and the filtrates were concentrated in vacuo. The residues were dissolved in MeOH–TFA–H_2O (0.5:1:0.5, 2 to 4 mL) and stirred at 25 °C for 5 h. The reaction mixtures were concentrated in vacuo. Purification of the residues by semi-preparative HPLC (0–100% of MeCN in H_2O–TFA in 30 min at 18 mL/min) afforded 2-DOS dimers as white foams.

(3a*RS*,4*SR*,5*RS*,7*SR*,7a*RS*)-5,7-Diazido-2,2-dimethylhexahydro-1,3-benzodioxolo-4-ol (*rac*-2)

A solution of neomycin trisulfate (10.0 g, 11 mmol) in aq 48% HBr (60 mL) was heated under reflux for 17 h. HBr was evaporated in vacuo and the remaining black oil was dissolved in H_2O (60 mL) with activated charcoal. After mixing for 1 h, the black solution was filtered though a pad of Celite and the filter was washed with H_2O (180 mL). The brown aqueous solution was concentrated in vacuo. MeOH (60 mL) was added to the brown oil, which solidified upon mixing. The white suspension was filtered and dried 12 h before being loaded on an anion resin exchanger column. Fractions with a basic pH were collected and lyophilized to obtain aminocyclitol *meso*-**1** as a white powder (1.37 g, 77%). To a solution of *meso*-**1** (1.05 g, 6.474 mmol) in MeOH (64 mL) and Et_3N (6.55 g, 9 ml, 65 mmol, 10 equiv) was added $CuSO_4$ (52 mg, 0.324 mmol, 0.05 equiv). A 0.4 M solution of TfN_3 in CH_2Cl_2 was added dropwise at 0 °C, the green mixture was stirred for 24 h, and concentrated in vacuo. The green oil was purified by flash chromatography (20% of pentane in EtOAc then 20% of MeOH in EtOAc) affording diazide intermediate as a white solid (1.25 g, 90%). A solution of the intermediate (1.25 g, 5.836 mmol) in MeCN (30 mL) and 2,2-dimethoxypropane (30 mL) was treated with CSA (135 mg, 0.584 mmol, 0.1 equiv) at 25 °C for 5 h. The reaction mixture was poured into sat. aq $NaHCO_3$ (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (70 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash chromatography (30% of EtOAc in pentane) afforded alcohol *rac*-**2** as a white solid (1.09 g, 73%). Preparation of the 0.4 M solution of TfN_3 in CH_2Cl_2–Tf_2O (5.19 g, 3.05 mL, 18.5 mmol, 0.2 equiv) was added to a solution of NaN_3 (6.01 g, 92.5 mmol) in CH_2Cl_2 (25 mL) and H_2O (15 mL). The mixture was stirred at 0 °C for 5 h. The aqueous phase was extracted with CH_2Cl_2 (2 × 8 mL). The combined organic layers were washed with sat. aq Na_2CO_3 (15 mL).

IR (film): 3410, 2100, 1450, 1370, 1240, 1190, 1140, 1060, 960, 830, 780 cm^{-1}.

^1H NMR (400 MHz, MeOD): δ = 3.80–3.65 (m, 1 H, H-7), 3.63 (dd, *J* = 6.9, 6.8 Hz, 1 H, H-4), 3.46–3.40 (m, 5-H, H-3a, H-7a), 2.2 (dt, *J* = 4.8, 13.4 Hz, 1 H, H-6), 1.45 (s, 6 H, 2-CH_3), 1.34 (dt, *J* = 12.2, 13.4 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, MeOD): δ = 113.1 (2 s, C-2), 81.1, 80.9 (2 d, C-3a, C-7a), 75.2 (d, C-4), 64.3 (d, C-5), 58.9 (d, C-7), 34.8 (t, C-6), 27.1, 26.9 (2 q, CH_3-2).

CI-MS: *m*/*z* = 255 $[M + H]^+$.

Anal. Calcd for $C_9H_{14}N_6O_3$ (254.25): C, 42.52; H, 5.55; N, 33.05. Found: C, 42.58; H, 5.52; N, 33.01.

{[(3a*RS*,4*SR*,5*RS*,7*SR*,7a*RS*)-5,7-Diazido-2,2-dimethylhexahydro-1,3-benzodioxolo-4-yl]oxy}acetic Acid (*rac*-3)

To a solution of alcohol *rac*-**2** (1.09 g, 4.267 mmol) in MeCN (20 mL) were added NaH (60% in mineral oil, 340 mg, 8.535 mmol, 2 equiv) and methyl bromoacetate (976 mg, 606 μL, 6.4 mmol, 1.5 equiv). The mixture was stirred at 25 °C for 2 h. The reaction mixture was poured into sat. aq NH_4Cl (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (70 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash chromatography (20% of EtOAc in pentane) afforded an intermediate methyl ester as a colorless oil (445 mg, 64% yield based on recovered starting material). To a solution of methyl ester (445 mg, 1.364 mmol) in THF (35 mL), MeOH (5 mL), and H_2O (5 mL), a 1 M LiOH solution (20 mL, 20 mmol, 15 equiv) was added. The mixture was stirred at 25 °C for 15 h. THF was removed in vacuo and the aqueous solution was saturated with NaCl, the pH of the solution was adjusted to 4–5 with aq 2 M HCl and extracted with EtOAc (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography (20% of MeOH in CH_2Cl_2) afforded *rac*-**3** as a white foam; yield: 325 mg (76%).

IR (film): 3215, 2920, 2500, 2355, 2100, 1730, 1595, 1450, 1060, 840, 785 cm^{-1}.

^1H NMR (400 MHz, MeOD): δ = 4.31 (s, 2 H, H-2′), 3.73 (ddd, *J* = 4.7, 10.0, 11.7 Hz, 1 H, H-7), 3.68 (t, *J* = 8.4 Hz, 1 H, H-4), 3.64 (ddd, *J* = 4.7, 8.4, 9.2 Hz, 1 H, H-5), 3.55 (dd, *J* = 8.4, 9.2 Hz, 1 H, H-3a), 3.44 (dd, *J* = 9.2, 10.0 Hz, 1 H, H-7a), 2.2 (dt, *J* = 4.7, 13.4 Hz, 1 H, H-6), 1.44, 1.43 (2 s, 6 H, CH_3-2), 1.34 (dt, *J* = 11.7, 13.4 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, MeOD): δ = 174.4 (s, C-1′), 112.4 (s, C-2), 81.6 (d, $^1J_{C,H}$ = 155 Hz, C-4), 80.0, 79.9 (d, $C_{3a,7a}$, $^1J_{C,H}$ = 147 Hz, C-3a, C-7a), 68.1 (t, $^1J_{C,H}$ = 145 Hz, C-2′), 60.9 (d, $^1J_{C,H}$ = 143 Hz, C-5), 57.6 (d, $^1J_{C,H}$ = 145 Hz, C-7), 33.8 (t, $^1J_{C,H}$ = 134 Hz, C-6), 26.1, 25.9 (2 q, $^1J_{C,H}$ = 126 Hz, CH_3-2).

MALDI-TOF-HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{16}N_6O_5$ + Na: 335.1080; found: 335.1080.

Anal. Calcd for $C_9H_{14}N_6O_3$ (312.28): C, 42.31; H, 5.16; N, 26.91. Found: C, 42.50; H, 5.09; N, 26.75.

***N*,*N*′-Pentane-1,5-diylbis(2-{[(1*SR*,2*SR*,3*RS*,4*SR*,6*RS*)-4,6-diamino-2,3-dihydroxycyclohexyl]oxy}acetamide) (9)**

Name corresponding to the (±)-*threo* isomer. Starting from 1,5-diaminopentane (19 μL, 0.16 mmol), and following Method A, **9** (32 mg, 50% over 2 steps) was obtained as a white foam. The major product isolated by flash chromatography appeared as a single stereoisomer, which displayed a single set of signals in the ^{13}C NMR spectrum (see Supporting Information). No other isomer could be isolated in sufficient amount for characterization.

IR (film): 3380, 2940, 2505, 2105, 1655, 1550, 1450, 1375, 1260, 1235, 1110, 840 cm^{-1}.

^1H NMR (400 MHz, D_2O): δ = 4.24, 4.14 (2 d AB, *J* = 15.3 Hz, 4 H, H-2′), 3.59, 3.41 (2 t, $J_{2,3}$ = 9.3 Hz, 4 H, H-2, H-3), 3.33 (t, *J* = 9.3 Hz, 2 H, H-1), 3.26, 3.11 (td, *J* = 3.5, 9.3 Hz, 4 H, H-4, H-6), 3.03 (t, *J* = 6.8 Hz, 4 H, H-1″, H-5″), 2.26 (dt, *J* = 3.5, 12.4 Hz, 2 H, H-5), 1.63 (d, *J* = 12.4 Hz, 2 H, H-5), 1.4–1.3 (m, 4 H, H-2″, H-4″), 1.2–1.1 (m, 4 H, H-3″).

^{13}C NMR (100 MHz, D_2O): δ = 174.4 (s, C-1′), 83.8 (d, $^1J_{C,H}$ = 148 Hz, C-1), 77.5, 74.8 (2 d, $^1J_{C,H}$ = 146, 141 Hz, C-2, C-3), 73.1 (t, $^1J_{C,H}$ = 146 Hz, C-2′), 52.3 (d, $^1J_{C,H}$ = 143 Hz, C-4), 51.5 (d, $^1J_{C,H}$ = 147 Hz, C-6), 41.5 (t, $^1J_{C,H}$ = 139 Hz, C-1″, C-5″), 30.6 (t, $^1J_{C,H}$ = 127 Hz, C-5), 30.5 (t, $^1J_{C,H}$ = 125 Hz, C-2″, C-4″), 25.9 (t, $^1J_{C,H}$ = 128 Hz, C-3″).

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{42}N_6O_8$: 507.3142; found: 507.3145.

***N*,*N*′-Pentane-1,5-diylbis(2-{[(3a*RS*,4*SR*,5*RS*,7*SR*,7a*RS*)-5,7-diazido-2,2-dimethylhexahydro-1,3-benzodioxolo-4-yl]oxy}acetamide)**

Data for the intermediate, name corresponding to the (±)-*threo* isomer.

IR (film): 3380, 2940, 2505, 2105, 1655, 1550, 1450, 1375, 1260, 1235, 1110, 840 cm^{-1}.

^1H NMR (400 MHz, MeOD): δ = 4.27, 4.18 (2 d AB, *J* = 15.6 Hz, 4 H, H-2′), 3.79 (ddd, *J* = 4.7, 10.0, 11.4 Hz, 2 H, H-7), 3.73–3.66

(m, 2 H, H-5), 3.60 (t, *J* = 8.6 Hz, 2 H, H-4), 3.58 (dd, *J* = 4.7, 8.6 Hz, 2 H, H-3a), 3.52 (dd, *J* = 4.7, 10.0 Hz, 2 H, H-7a), 3.40–3.35 (m, 4 H, H-1″, H-5″), 2.26 (dt, *J* = 4.7, 13.3 Hz, 2 H, H-6), 1.62–1.52 (m, 4 H, H-2″, H-4″), 1.46, 1.45 (2 s, 12 H, CH_3-2), 1.45–1.13 (m, 4 H, H-6, H-3″).

^{13}C NMR (100 MHz, MeOD): δ = 171.1 (s, C-1′), 112.6 (s, C-2), 82.3 (d, $^1J_{C,H}$ = 155 Hz, C-4), 79.9, 79.5 (2 d, $^1J_{C,H}$ = 147, 148 Hz, C-3a, C-7a), 70.0 (t, $^1J_{C,H}$ = 145 Hz, C-2′), 61.4 (d, $^1J_{C,H}$ = 147 Hz, C-5), 57.6 (d, $^1J_{C,H}$ = 144 Hz, C-7), 38.9, 38.8 (2 t, $^1J_{C,H}$ = 137 Hz, C-1″, C-5″), 33.6 (t, $^1J_{C,H}$ = 134 Hz, C-6), 29.1 (t, $^1J_{C,H}$ = 121 Hz, C-2″, C-4″), 26.1, 26.0 (2 q, $^1J_{C,H}$ = 126 Hz, CH_3-2), 24.2 (t, $^1J_{C,H}$ = 125 Hz, C-3″).

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{42}N_{14}O_8$: 691.3388; found: 691.3384.

N,*N*′-(Iminodipropane-3,1-diyl)bis(2-{[(1*SR*,2*SR*,3*RS*,4*SR*,6*RS*)-4,6-diamino-2,3-dihydroxycyclohexyl]oxy}acetamide) (10)

Name corresponding to the (±)-*threo* isomer. Starting from 3,3′-diaminopropylamine (27 μL, 0.192 mmol), and following Method A, **10** (32 mg, 42% over 3 steps) was obtained as a white foam. The major product isolated by flash chromatography appeared as a single stereoisomer, which displayed a single set of signals observed in the ^{13}C NMR spectrum (see Supporting Information). No other isomer could be isolated in sufficient amount for characterization.

IR (film): 3320, 3095, 2940, 2105, 1670 1440, 1370, 1260, 1135, 1065, 840, 800 cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ = 4.30 (2 d AB, *J* = 15.4 Hz, 4 H, H-2′), 3.45–3.25 (m, 6 H, H-1, H-2, H-3), 3.26 (td, *J* = 3.8, 8.1 Hz, 2 H, H-4), 3.14 (t, *J* = 7.0 Hz, 4 H, H-3″), 3.11 (td, *J* = 8.1, 3.8 Hz, 2 H, H-6), 2.87 (t, *J* = 7.0 Hz, 4 H, H-1″), 2.26 (dt, *J* = 3.8, 12.5 Hz, 2 H, H-5), 1.76–1.65 (m, 4 H, H-4″), 1.64 (2 H, d, *J* = 12.5 Hz, 2 H, H-5).

^{13}C NMR (100 MHz, D_2O): δ = 175.1 (s, C-1′), 83.7 (d, $^1J_{C,H}$ = 143 Hz, C-1), 77.5, 74.8 (2 d, $^1J_{C,H}$ = 146, 149 Hz, C-2, C-3), 73.1 (t, $^1J_{C,H}$ = 146 Hz, C-2′), 52.3, 51.5 (2 d, $^1J_{C,H}$ = 143, 146 Hz, C-4, C-6), 47.7 (t, $^1J_{C,H}$ = 142 Hz, C-1″), 38.3 (t, $^1J_{C,H}$ = 140 Hz, C-3″), 30.6 (t, $^1J_{C,H}$ = 134 Hz, C-5), 28.1 (t, $^1J_{C,H}$ = 130 Hz, C-2″).

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{45}N_7O_8$: 536.3408; found: 536.3411.

N,*N*′-(Iminodipropane-3,1-diyl)bis(2-{[(1*SR*,2*SR*,3*RS*,4*SR*,6*RS*)-4,6-diazido-2,3-dihydroxycyclohexyl]oxy}acetamide)

Data for the intermediate; name corresponding to the (±)-*threo* isomer.

IR (film): 3320, 3095, 2940, 2105, 1670, 1440, 1370, 1260, 1135, 1065, 840, 800 cm^{-1}.

^{1}H NMR (400 MHz, MeOD): δ = 4.30 (2 d AB, *J* = 3.1 Hz, 4 H, H-2′), 3.57 (ddd, *J* = 4.3, 9.4, 12.9 Hz, 2 H, H-4), 3.0–3.3 (m, 8 H, H-2, H-6, H-3″), 3.23 (t, *J* = 9.4 Hz, 2 H, H-1), 3.12 (t, *J* = 9.4 Hz, 2 H, H-3), 2.98 (t, *J* = 7.2 Hz, 4 H, H-1″), 2.10 (dt, *J* = 4.3, 12.5 Hz, 2 H, H-5), 1.95–1.83 (m, 4 H, H-2″), 1.28 (dd, *J* = 12.9, 12.5 Hz, 2 H, H-5).

^{13}C NMR (100 MHz, MeOD): δ = 173.0 (s, C-1′), 85.5 (d, $^1J_{C,H}$ = 142 Hz, C-1), 76.7, 75.3 (2 d, $^1J_{C,H}$ = 142, 143 Hz, C-2, C-3), 71.4 (t, $^1J_{C,H}$ = 146 Hz, C-2′), 61.0, 60.8 (2 d, $^1J_{C,H}$ = 143, 143 Hz, C-4, C-6), 45.5 (t, $^1J_{C,H}$ = 143 Hz, C-1″), 35.5 (t, $^1J_{C,H}$ = 135 Hz, C-2″), 32.1 (t, $^1J_{C,H}$ = 133 Hz, C-5), 26.5 (t, $^1J_{C,H}$ = 129 Hz, C-3″).

MALDI-TOF-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{37}N_{15}O_8$: 640.3028; found: 640.3025.

N,*N*′-[Butane-1,4-diylbis(iminopropane-3,1-diyl)]bis(2-{[(1*SR*,2*SR*,3*RS*,4*SR*,6*RS*)-4,6-diamino-2,3-dihydroxycyclohexyl]oxy}acetamide) (11)

Name corresponding to the (±)-*threo* isomer. Starting from spermine (46 mg, 0.229 mmol), and following Method A, **11** (40 mg, 19% over 3 steps) was obtained as a white foam. The major product isolated by flash chromatography appeared as a single stereoisomer, which displayed a single set of signals in the ^{13}C NMR spectrum (see Supporting Information). No other isomer could be isolated in sufficient amount for characterization.

IR (KBr): 2965, 2790, 1650, 1590, 1455, 1005, 1290, 1195, 1145, 1100, 1060, 1005, 900 cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ = 4.29, 4.20 (2 d AB, *J* = 15.4 Hz, 4 H, H-2′), 3.5–3.25 (m, 8 H, H-1, H-2, H-4, H-5), 3.23–3.1 (m, 6 H, H-3, H-1″), 2.91 (br s, 8 H, H-3″, H-1‴), 2.37–2.25 (m, 2 H, H-6), 1.83–1.72 (m, 4 H, H-2″), 1.68 (dd, *J* = 12.4, 12.4 Hz, 2 H, H-5), 1.51 (br s, 4 H, H-2‴).

^{13}C NMR (100 MHz, D_2O): δ = 172.5 (s, C-1′), 82.6, 75.4, 72.7 (3 d, $^1J_{C,H}$ = 147, 146, 147 Hz, C-1, C-2, C-3), 71.0 (t, $^1J_{C,H}$ = 147 Hz, C-2′), 50.2, 49.3 (2 d, $^1J_{C,H}$ = 143, 147 Hz, C-4, C-6), 47.3, 45.5 (2 t, $^1J_{C,H}$ = 148 Hz, C-3″, C-2‴), 28.4 (t, $^1J_{C,H}$ = 132 Hz, C-5), 26.2 (t, $^1J_{C,H}$ = 140 Hz, C-1″), 25.9 (t, $^1J_{C,H}$ = 131 Hz, C-2″), 23.2 (t, $^1J_{C,H}$ = 132 Hz, C-2‴).

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{54}N_8O_8$: 607.4143; found: 607.4147.

N,*N*′-[Butane-1,4-diylbis(iminopropane-3,1-diyl)]bis(2-{[(3a*RS*,4*SR*,5*RS*,7*SR*,7a*RS*)-5,7-diazido-2,2-dimethylhexahydro-1,3-benzodioxolo-4-yl]oxy}acetamide)

Data for the intermediate; name corresponding to the (±)-*threo* isomer.

IR (film): 2930, 2105, 1670, 1550, 1535, 1450, 1380, 1230, 1105, 1050, 840, 750 cm^{-1}.

^{1}H NMR (400 MHz, MeOD): δ = 4.32, 4.22 (2 d AB, *J* = 15.5 Hz, 4 H, H-2′), 3.81 (m, 4 H, H-5, H-7), 3.64, 3.59 (2 t, *J* = 9.4 Hz, 4 H, H-3a, H-7a), 3.35 (2 t, *J* = 9.4 Hz, 2 H, H-4), 3.46–3.40, 3.33–3.28 (2 m, 4 H, H-1″), 3.07–2.95 (m, 8 H, H-3″, H-4‴), 2.27, 2.23 (dt, *J* = 4.9, 13.3 Hz, 2 H, H-6), 1.97–1.88 (m, 4 H, H-2″), 1.83–1.76 (m, 4 H, H-3‴), 1.45, 1.44 (2 s, 12 H, CH_3-2), 1.43, 1.37 (2 d, *J* = 13.3 Hz, 2 H, H-6).

^{13}C NMR (100 MHz, MeOD): δ = 172.3 (s, C-1′), 112.6 (s, C-2), 82.4 (d, $^1J_{C,H}$ = 145 Hz, C-3a), 80.0 (d, $^1J_{C,H}$ = 147 Hz, C-4), 79.5 (d, $^1J_{C,H}$ = 148 Hz, C-7a), 69.9 (t, $^1J_{C,H}$ = 145 Hz, C-2′), 61.4, 57.6 (2 d, $^1J_{C,H}$ = 143 Hz, C-5, C-7), 47.4, 45.4 (2 t, $^1J_{C,H}$ = 138, 137 Hz, C-3″, C-4‴), 35.7 (t, $^1J_{C,H}$ = 138 Hz, C-1″), 33.6 (t, $^1J_{C,H}$ = 133 Hz, C-6), 26.9 (t, $^1J_{C,H}$ = 125 Hz, C-2″), 26.1 (q, $^1J_{C,H}$ = 127 Hz, CH_3-2), 23.8 (t, $^1J_{C,H}$ = 126 Hz, C-3‴).

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{54}N_{16}O_8$: 791.4389; found: 791.4393.

2-{[(1*S*,2*S*,3*R*,4*S*,6*R*)-4,6-Diamino-2,3-dihydroxycyclohexyl]oxy}-*N*-{(3*R*,5*S*,7*R*,9*S*, 11*S*,13*R*)-15-[({[(1*S*,2*S*,3*R*,4*S*,6*R*)-4,6-diamino-2,3-dihydroxycyclohexyl]oxy}acetyl)amino]-3,5,7,9,11,13-hexahydroxypentadecyl}acetamide (12)

Indication of the configurations of one possible isomer. Starting from protected diamine **7** (85 mg, 0.129 mmol) and following method B, **12** (4 mg, 10% yield over 3 steps) was obtained as the major product; white foam; $[\alpha]_D^{25}$ –33 (*c* = 0.1, H_2O).

IR (KBr): 3415, 2940, 1680, 1650, 1200, 1140, 840, 800, 670 cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ = 4.41–4.20 (m, 4 H, H-2′, H-2‴), 4.05–3.72 (2 m, 6 H, H-3″, H-5″, H-9″, H-11″, H-13″), 3.60–3.10 (3 m, 14 H, H-1, H-2, H-3, H-4, H-6, H-1^{IV}, H-2^{IV}, H-3^{IV}, H-4^{IV}, H-

6^{IV}, H-1″, H-15″), 2.55–2.30 (2 m, 2 H, H-5, H-5^{IV}), 1.70–1.4 (m, 16 H, H-5, H-5^{IV}, H-2″, H-4″, H-6″, H-8″, H-10″, H-12″, H-14″).

^{13}C NMR (100 MHz, D_2O): δ = 140 (s, C-1′, C-1‴), 81.7, 81.5, 81.4 (3 d, C-1, C-2, C-3, C-1^{IV}, C-2^{IV}, C-3^{IV}), 75.2, 75.3 (2 t, C-1″, C-15″), 72.4, 71.1 (t, C-2′, C-2‴), 66.6, 66.5, 66.3, 66.1, 65.1, 65.0 (6 d, C-3″, C-5″, C-7″, C-9″, C-11″, C-13″), 59.2, 52.3, 52.1, 50.1, 49.8, 45.0, 44.9 (7 d, C-5, C-5^{IV}, C-2″, C-4″, C-6″, C-8″, C-10″, C-12″, C-14″), 37.2, 33.2 (2 d, C-4, C-6, C-4^{IV}, C-6^{IV}).

ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{31}H_{62}N_6O_{14}$: 743.4402; 743.4401.

2-{[(1*S*,2*S*,3*R*,4*S*,6*R*)-4,6-Diamino-2,3-dihydroxycyclohexyl]oxy}-*N*-{2-[(2*S*,4*R*,6*R*)-6-{(2*R*,4*S*)-5-[(2*R*,4*R*,6*S*)-6-{2-[({[(1*S*,2*S*,3*R*,4*S*,6*R*)-4,6-diamino-2,3-dihydroxycyclohexyl]oxy}acetyl)amino]ethyl}-4-hydroxytetrahydro-2*H*-pyran-2-yl]-2,4-dihydroxypentyl}-4-hydroxytetrahydro-2*H*-pyran-2-yl]ethyl}acetamide (13)

Indication of the configurations of one possible isomer. Starting from protected diamine **8** (95 mg, 0.141 mmol), and following method B, **13** (26 mg, 23% yield over 3 steps) was obtained as the major product as a white foam; $[\alpha]_D^{25}$ –18 (*c* = 0.2, H_2O).

IR (KBr): 2940, 2855, 2810, 1600, 1455, 1360, 1305, 1270, 1115, 1070, 1005, 915, 865 cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ = 4.29, 4.21 (2 d AB, *J* = 15.3 Hz, 4 H, H-2′), 4.17–3.75 (2 m, 12 H, H-2^{IV}, H-4^{IV}, H-6^{IV}, H-2^{V}, H-4^{V}, H-2^{VI}, H-4^{VI}, H-6^{VI}, H-1″, H-2‴), 3.47–3.28 (3 m, 6 H, H-1, H-2, H-3), 3.27–3.13 (m, 4 H, H-4, H-6), 2.51–2.17 (2 m, 2 H, H-5), 2.07–1.8 (2 m, 4 H, H-1^{V}, H-5^{V}), 1.83–1.70 (m, 2 H, H-5), 1.2–1.06 (m, 2 H, H-3^{V}), 1.67–1.43 (m, 8 H, H-3^{IV}, H-5^{IV}, H-3^{VI}, H-5^{VI}).

^{13}C NMR (100 MHz, D_2O): δ = 172.4 (s, C-1′), 81.6, 75.5, 75.4, 72.7, 71.7 (5 d, C-1, C-2, C-3), 70.9, 70.7 (2 t, C-2′), 67.4, 67.0, 65.9, 65.8, 63.9, 63.8 (6 d, C-2^{IV}, C-4^{IV}, C-6^{IV}, C-2^{V}, C-4^{V}, C-2^{VI}, C-4^{VI}, C-6^{VI}), 57.1 (d, C-4, C-6), 50.1, 49.3 (2 t, C-1″, C-2‴), 44.4 (t, C-3^{V}), 42.7, 42.6 (2 t, C-1^{V}, C-5^{V}), 40.4, 39.8 (2 t, C-5^{IV}, C-3^{IV}), 37.0, 36.3 (2 t, C-3^{VI}, C-5^{VI}), 30.3, 30.0 (2 t, C-2″, C-1‴), 28.5 (t, C-5).

ESI-HRMS: *m/z* [M + H]$^+$ calcd for $C_{35}H_{66}N_6O_{14}$: 795.4715; found: 795.4720.

Benzyl 5-(d-*arabino*Tetritol-1-yl)-2-methylfuran-3-carboxylate (19a)

Silica gel (2 g) was added to a mixture of $CeCl_3 \cdot 7H_2O$ (0.452 g, 1.2 mmol) and NaI (56 mg, 1.2 mmol) in MeCN (28 mL) and the mixture was stirred overnight. Then, D-glucose (720 mg, 4 mmol) was added to the mixture, and the suspension was stirred for 1 h. The solvent was evaporated, benzyl acetoacetate (1.0 g, 0.9 mL, 5.2 mmol) was added to the mixture and the solvent-free mixture was stirred for 9 days at 50 °C. After this period, MeOH was added to the mixture, the resulting suspension was filtered over Celite and the solid residue was washed several times with MeOH. The filtered solution was evaporated to dryness and the resulting crude was purified by column chromatography (CH_2Cl_2–MeOH, 15:1 → 5:1) to afford **19a** (1.05 g, 78%) as a colorless oil. The analytical data were in accord with the previously reported values.[13]

Benzyl 2-Methyl-5-[4-*O*-methoxytrityl-D-*arabino*teritol-1-yl]furan-3-carboxylate (20a)

To a cooled solution of **19a** (2.06 g, 6.12 mmol) in anhyd pyridine (10 mL) was added *p*-methoxytrityl chloride (2.27 g, 7.34 mmol) and the mixture stirred for 3 h at 25 °C. MeOH (2.5 mL) was added, the solution stirred for further 15 min, and then evaporated to dryness. The resulting residue was diluted with CH_2Cl_2 and the organic layer was washed with H_2O (2 × 40 mL) and brine (40 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography (CH_2Cl_2–acetone, 30:1 → acetone, adding 1% of Et_3N to the eluent) to afford **20a** (2.98 g, 80%) as a yellow oil; $[\alpha]_D^{23}$ +16 (*c* = 0.9, CH_2Cl_2).

IR (film): 3435 (OH), 2935, 1715 (C=O), 1610, 1510, 1445, 1250, 1075, 700 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.47–6.81 (m, 19 H_{arom}), 6.50 (s, 1 H, H-4), 5.26 (s, 2 H, CH_2Ph), 4.78 (d, $J_{1',2'}$ = 3.3 Hz, 1 H, H-1′), 3.87–3.78 (m, 2 H, H-2′, H-3′), 3.76 (s, 3 H, OCH_3), 3.26 (dd, $J_{4'a,4'b}$ = 9.5 Hz, $J_{4'a,3'}$ = 3.1 Hz, 1 H, H-4′a), 3.14 (dd, $J_{4'b,3'}$ = 5.9 Hz, 1 H, H-4′b), 2.49 (s, 3 H, CH_3).

^{13}C NMR (75.4 MHz, CD_3OD): δ = 165.3 (*C*O_2Bn), 160.2 (C_{arom}), 160.0 (C-2), 155.1 (C-5), 150.1, 146.1, 138.4, 137.8, 136.9, 131.7, 129.7, 129.6, 128.7, 127.8, 125.6, 114.0 (23 C, C_{arom}), 114.9 (C-3), 108.8 (C-4), 87.7 [$(Ar)_3C$], 74.7 (C-2′), 72.3 (C-3′), 67.8 (C-1′), 67.0 (*C*H_2Ph), 66.6 (C-4′), 55.7 (OCH_3), 13.8 (CH_3).

MS (FAB): *m/z* (%) = 631 (4, [M + Na]$^+$).

HRMS-FAB: *m/z* [M + Na]$^+$ calcd for $C_{37}H_{36}O_8$ + Na: 631.2308; found: 631.2323.

Benzyl 5-(1-Azido-1-deoxy-4-*O*-methoxytrityl-D-*ribo*tetritol-1-yl)furan-3-carboxylate (21a)

To a solution of **20a** (2.950 g, 5.4 mmol) and Et_3N (2.43 g, 3.34 mL, 23.8 mmol) in anhyd CH_2Cl_2 (20 mL) cooled to 0 °C was slowly added a solution of $SOCl_2$ (1.62 g, 988 μL, 13.5 mmol) in anhyd CH_2Cl_2 (5 mL). The solution was stirred at 0 °C for 30 min. The mixture was diluted with Et_2O (120 mL) and the Et_2O layer was washed with H_2O and brine (3 × 40 mL), the organic phase was dried (Na_2SO_4), filtered, and evaporated to dryness. The resulting residue was dissolved in THF (10 mL), trimethylsilyl azide (1.96 g, 2.24 mL, 16.2 mmol) and TBAF (1 M in THF, 16.2 mL) were added and the mixture stirred for 24 h. The solution was evaporated to dryness and the resulting crude product purified by column chromatography (Et_2O–PE, 1:1, adding 1% of Et_3N to the eluent) to afford **21a** (2.30 g, 70%) as a colorless oil; $[\alpha]_D^{23}$ +42 (*c* = 1.33, CH_2Cl_2).

IR (film): 3480 (OH), 2935, 2100 (N_3), 1715 (C=O), 1610, 1510, 1445, 1250, 1225 (N_3), 1180, 1075, 830, 735, 700 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.48–6.83 (m, 19 H_{arom}), 6.72 (s, 1 H, H-4), 5.28 (s, 2 H, CH_2Ph), 4.62 (d, $J_{1',2'}$ = 4.5 Hz, 1 H, H-1′), 3.96 (dd, $J_{2',3'}$ = 7.5 Hz, 1 H, H-2′), 3.76 (s, 3 H, OCH_3), 3.58 (m, 1 H, H-3′), 3.35 (dd, $J_{4'a,4'b}$ = 9.7 Hz, $J_{4'a,3'}$ = 3.4 Hz, 1 H, H-4′a), 3.22 (dd, $J_{4'b,3'}$ = 6.2 Hz, 1 H, H-4′b), 2.55 (s, 3 H, CH_3).

^{13}C NMR (75.4 MHz, CD_3OD): δ = 165.1 (*C*O_2Bn), 161.0 (C_{arom}), 160.9 (C-2), 149.3 (C-5), 146.1, 137.7, 136.9, 131.7, 129.7, 129.6, 129.3, 128.7, 127.9, 114.0 (23 C, C_{arom}), 115.1 (C-3), 111.8 (C-4), 87.8 [$(Ar)_3C$], 74.7 (C-2′), 72.5 (C-3′), 67.1 (*C*H_2Ph), 66.5 (C-4′), 60.9 (C-1′), 55.7 (OCH_3), 13.9 (CH_3).

MS (FAB): *m/z* (%) = 656 (8, [M + Na]$^+$).

HRMS-FAB: *m/z* [M + Na]$^+$ calcd for $C_{37}H_{35}N_3O_7$ + Na: 656.2373; found: 656.2371.

Anal. Calcd for $C_{37}H_{35}O_7N_3$: C, 70.13; H, 5.57; N, 6.63. Found: C, 69.82; H, 5.80; N, 6.16.

Benzyl 5-(1-Azido-1-deoxy-D-*ribo*tetritol-1-yl)-2-methylfuran-3-carboxylate (22a)

Compound **21a** (2.25 g, 3.67 mmol) was dissolved in TFA–CH_2Cl_2 (2%, 45 mL) and triisopropylsilane (1.5 mL) was added. The mixture was stirred for 1 h and then evaporated to dryness. The resulting residue was purified by column chromatography (CH_2Cl_2–MeOH, 15:1) to afford **22a** (1.06 g, 80%) as a colorless oil; $[\alpha]_D^{23}$ +82 (*c* = 0.8, MeOH).

IR (film): 3415 (OH), 2925, 2105 (N_3), 1715 (C=O), 1610, 1430, 1225 (N_3), 1075, 775, 700 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.40–7.32 (m, 5 H_{arom}), 6.80 (s, 1 H, H-4), 5.28 (s, 2 H, CH_2Ph), 4.67 (d, $J_{1',2'}$ = 4.1 Hz, 1 H, H-1′), 3.92 (dd, $J_{2',3'}$ = 8.3 Hz, 1 H, H-2′), 3.74 (dd, $J_{4'a,4'b}$ = 11.3 Hz, $J_{4'a,3'}$ = 3.5 Hz, 1 H, H-4′a), 3.60 (dd, $J_{4'b,3'}$ = 5.8 Hz, 1 H, H-4′b), 3.43 (ddd, J = 8.3, 5.8, 3.5 Hz, 1 H, H-3′), 2.57 (s, 3 H, CH_3).

^{13}C NMR (75.4 MHz, CD_3OD): δ = 165.1 (CO_2Bn), 160.9 (C-2), 149.4 (C-5), 137.7, 129.6, 129.3 (6 C, C_{arom}), 115.1 (C-3), 111.8 (C-4), 74.6 (C-2′), 73.4 (C-3′), 67.1 (CH_2Ph), 64.5 (C-4′), 60.9 (C-1′), 13.8 (CH_3).

MS (FAB): m/z (%) = 384 (16, $[M + Na]^+$).

HRMS-FAB: m/z $[M + Na]^+$ calcd for $C_{17}H_{19}N_3O_6$ + Na: 384.1172; found: 384.1171.

Benzyl 5-(1,4-Diazido-1,4-dideoxy-D-*ribo*tetritol-1-yl)-2-methylfuran-3-carboxylate (23)

To a cooled solution of **22a** (271 mg, 0.906 mmol) in anhyd pyridine (5 mL) at –15 °C was added tosyl chloride (191 mg, 1.0 mmol) and the mixture stirred for 3 h at –15–20 °C. H_2O (0.3 mL) was added, the solution was stirred for 10 min, and the mixture evaporated to dryness. The resulting residue was diluted with cold CH_2Cl_2 (60 mL), and the organic layer washed with aq 1 M HCl (30 mL), sat. aq $NaHCO_3$ (30 mL), and brine (30 mL). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The resulting crude product was dissolved in THF (5 mL) and Bu_4NN_3 (284 mg, 1.0 mmol) was added to the solution. The mixture was heated at 60 °C for 2 h. Then, the solvent was evaporated and the resulting residue was purified by column chromatography (Et_2O–PE, 1:3→1:1) to afford **23** (203 mg, 58%) as a colorless oil; $[\alpha]_D^{26}$ +89 (c = 1.54, CH_2Cl_2).

^{1}H NMR (300 MHz, CD_3OD): δ = 7.32–7.44 (m, 19 H_{arom}), 6.79 (s, 1 H, 4-H), 5.28 (s, 2 H, CH_2Ph), 4.66 (d, J = 3.9 Hz, 1 H, H-1′), 3.90 (dd, $J_{2',3'}$ = 8.3 Hz, $J_{2',1'}$ = 3.9 Hz, 1 H, H-2′), 3.53 (m, 1 H, H-3′), 3.45 (dd, $J_{4'a,3'}$ = 2.9 Hz, 1 H, H-4′a), 3.36 (dd, $J_{4'b,4'a}$ = 12.8 Hz, $J_{4'b,3'}$ = 6.3 Hz, 1 H, H-4′b), 2.56 (s, 3 H, CH_3).

^{13}C NMR (75.4 MHz, CD_3OD): δ = 165.0 (CO_2Bn), 161.0 (C-2), 149.0 (C-5), 137.7, 129.6, 129.3 (6 C, C_{arom}), 115.1 (C-3), 111.9 (C-4), 74.2 (C-2′), 72.4 (C-3′), 67.2 (CH_2Ph), 60.7 (C-1′), 55.1 (C-4′), 13.9 (CH_3).

MS (FAB): m/z (%) = 409 (5, $[M + Na]^+$).

HRMS-FAB: m/z $[M + Na]^+$ calcd for $C_{17}H_{18}N_6O_5$ + Na: 409.1236; found: 409.1245.

Benzotriazol-1-yl 5-[1,4-Di-*N*-(*tert*-butoxycarbonyl)amino-1,4-dideoxy-D-*ribo*tetritol-1-yl]-2-methylfuran-3-carboxylate (17)

To a solution of **23** (149 mg, 0.4 mmol) in absolute EtOH (6 mL), Pd/C (catalytic amount) and $(Boc)_2O$ (134 mg, 0.6 mmol) were added. The mixture was hydrogenated for 3 h under atmospheric pressure. Then, the catalyst was filtered and washed several times with EtOH. The filtered solution was evaporated to dryness. To a solution of the resulting crude product in DMF (4 mL) were added PyBOP (215 mg, 0.4 mmol) and DIPEA (109 mg, 140 μL, 0.8 mmol) and the mixture was stirred for 1 h. The solution was concentrated to dryness. The resulting residue was dissolved in EtOAc (40 mL) and the organic phase washed with aq 1 M HCl (20 mL), sat. aq $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and evaporated. The resulting residue was purified by column chromatography (Et_2O–PE, 5:1) to afford **17** (111 mg, 50%) as a colorless oil; $[\alpha]_D^{23}$ –2 (c = 0.87, CH_2Cl_2).

^{1}H NMR (300 MHz, CD_3OD): δ = 8.08–7.51 (m, 4 H_{arom}), 6.88 (s, 1 H, H-4), 5.12 (br d, $J_{1',2'}$ = 3.5 Hz, 1 H, H-1′), 3.70 (dd, $J_{2',3'}$ = 8.4 Hz, 1 H, H-2′), 3.56–3.35 (m, 2 H, H-3′, H-4′a), 3.20 (dd, $J_{4'b,4'a}$ = 14.0 Hz, $J_{4'b,3'}$ = 6.3 Hz, 1 H, H-4′b), 2.67 (s, 3 H, CH_3), 1.46, 1.45 [2 s, 9 H each, 2 $(CH_3)_3$C].

^{13}C NMR (75.4 MHz, CD_3OD): δ = 164.5 (CO_2Bt), 161.1 (2 C, CO of Boc), 157.4 (C-2), 152.1 (C-5), 144.5, 130.3, 126.5, 120.8, 110.0 (6 C, C_{arom}), 109.5 (C-3), 108.7 (C-4), 80.8, 80.4 [$(CH_3)_3C$], 75.4 (C-2′), 72.2 (C-3′), 51.4 (C-1′), 44.7 (C-4′), 28.7 [$(CH_3)_3C$], 14.2 (CH_3).

MS (FAB): m/z (%) = 584 (52, $[M + Na]^+$).

HRMS-FAB: m/z $[M + Na]^+$ calcd for $C_{26}H_{35}N_5O_9$ + Na: 584.2332; found: 584.2326.

Ethyl 5-[1-*N*-(*tert*-Butoxycarbonyl)amino-1-deoxy-D-*ribo*tetritol-1-yl]-2-methylfuran-3-carboxylate (24)

To a solution of **22b** (340 mg, 1.14 mmol) in absolute EtOH (20 mL) were added $(Boc)_2O$ (373 mg, 1.14 mmol) and Pd/C (catalytic amount). The mixture was hydrogenated under atmospheric pressure for 2 h. Et_3N (175 mg, 240 μL, 1.71 mmol) was added and the mixture was stirred for 30 min. The Pd/C was filtered over Celite and washed with MeOH (20 mL). The filtered solution was evaporated to dryness and the resulting residue was purified by column chromatography (CH_2Cl_2–MeOH, 15:1) to afford **24** (328 mg, 77%) as a colorless oil; $[\alpha]_D^{20}$ +24 (c = 0.67, CH_2Cl_2).

IR (film): 3420 (OH), 2980, 2930, 1695 (CO), 1510, 1230, 1170, 1080, 780 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 6.54 (s, 1 H, H-4), 5.00 (br s, 1 H, H-1′), 4.26 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, CH_2CH$_3$), 3.77 (dd, $J_{2',3'}$ = 8.4 Hz, $J_{2',1'}$ = 3.7 Hz, 1 H, H-2′), 3.73 (dd, $J_{4'a,4'b}$ = 11.4 Hz, $J_{4'a,3'}$ = 3.3 Hz, 1 H, H-4′a), 3.59 (dd, $J_{4'b,3'}$ = 5.8 Hz, 1 H, H-4′b), 3.41 (ddd, J = 8.4, 5.8, 3.3 Hz, 1 H, H-3′), 2.54 (s, 3 H, CH_3), 1.44 [s, 9 H, $(CH_3)_3$C], 1.33 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3).

^{13}C NMR (75.4 MHz, CD_3OD): δ = 165.7 (CO_2Et)), 159.7 (C=O of Boc), 157.4 (C-2), 152.3 (C-5), 115.1 (C-3), 109.4 (C-4), 80.7 [$(CH_3)_3C$], 74.8 (C-2′), 73.2 (C-3′), 64.7 (C-4′), 61.3 (CH_2CH_3), 51.7 (C-1′), 28.7 [$(CH_3)_3C$], 14.7 (CH_2CH_3), 13.8 (CH_3).

MS (CI): m/z (%) = 374 (6, $[M + H]^+$), 257 (100, $[M – BocNH]^+$).

HRMS-CI: m/z $[M + H]^+$ calcd for $C_{17}H_{28}NO_8$: 374.1815; found: 374.1818.

Ethyl 5-[1-*N*-(*tert*-Butoxycarbonyl)amino-1-deoxy-4-*O*-tosyl-D-*ribo*tetritol-1-yl]-2-methylfuran-3-carboxylate (25)

To a cooled solution of **24** (697 mg, 1,32 mmol) in anhyd pyridine (5 mL) was added tosyl chloride (763 mg, 3.96 mmol) and the mixture was stirred for 2.5 h at –15 °C. H_2O (0.3 mL) was added, the solution was stirred for 10 min at –15 °C, and the mixture evaporated to dryness. The resulting residue was diluted with cold CH_2Cl_2 (70 mL), and the organic phase washed with aq 1 M HCl (2 × 40 mL), sat. aq $NaHCO_3$ (40 mL), and brine (40 mL). The organic phase was dried (Na_2SO_4), evaporated to dryness, and the resulting crude product was immediately purified by column chromatography (CH_2Cl_2–MeOH, 40:1) to afford **25** (525 mg, 75%) as a colorless oil; $[\alpha]_D^{21}$ +1 (c = 1.90, CH_2Cl_2).

IR (film): 3430 (OH), 2980, 1710 (C=O), 1510, 1365, 1230, 1175, 1080, 780 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.79 (d, J = 8.3 Hz, 2 H_{arom}), 7.41 (d, J = 8.3 Hz, 2 H_{arom}), 6.50 (s, 1 H, H-4), 4.94 (br s, 1 H, H-1′), 4.25 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, CH_2CH$_3$), 4.17 (dd, $J_{4'a,4'b}$ = 10.1 Hz, $J_{4'a,3'}$ = 2.4 Hz, 1 H, H-4′a), 4.02 (dd, $J_{4'b,3'}$ = 6.4 Hz, 1 H, H-4′b), 3.72 (dd, $J_{2',3'}$ = 8.4 Hz, $J_{2',1'}$ = 3.7 Hz, 1 H, H-2′), 3.55 (ddd, J = 8.4, 6.4, 2.4 Hz, 1 H, H-3′), 2.51 (s, 3 H, CH_3), 2.44 (s, 3 H, CH_3 of Ts), 1.42 [s, 9 H, $(CH_3)_3$C], 1.32 (t, J = 7.1 Hz, 3 H, CH$_2$CH_3).

^{13}C NMR (75.4 MHz, CD_3OD): δ = 165.7 (CO_2Et), 161.2 (C=O of Boc), 156.1 (C-2), 146.4 (C-5), 146.2, 134.2, 131.0, 129.8, 129.1, 126.9 (6 C, C_{arom}), 115.6 (C-3), 109.5 (C-4), 81.4 [$(CH_3)_3C$], 74.1 (C-2′), 73.4 (C-4′), 70.9 (C-3′), 61.3 (CH_2CH_3), 51.8 (C-1′), 28.7 [$(CH_3)_3C$], 21.6 (CH_3 of Ts), 14.7 (CH_2CH_3), 13.8 (CH_3).

MS (FAB): *m/z* (%) = 550 (56, [M + Na]$^+$).

HRMS-FAB: *m/z* [M + Na]$^+$ calcd for $C_{24}H_{33}NO_{10}S$ + Na: 550.1723; found: 550.1713.

Ethyl 5-[4-Azido-1-*N*-(*tert*-butoxycarbonyl)amino-1,4-dideoxy-D-*ribo*tetritol-1-yl]-2-methylfuran-3-carboxylate (26)

To a solution of **25** (447 mg, 0.85 mmol) in THF (3 mL) were added trimethylsilyl azide (413 mg, 471 μL, 3.4 mmol) and a 1 M solution of TBAF in THF (3.4 mL, 3.4 mmol). The mixture was heated at 60 °C and stirred for 4 h. The solution was evaporated to dryness and the resulting residue was purified by column chromatography (Et_2O–PE, 2:1) to afford **26** (251 mg, 74%) as a colorless oil; $[\alpha]_D^{23}$ +22 (*c* = 1.11, CH_2Cl_2).

IR (film): 3425 (OH), 2980, 2930, 2105 (N_3), 1690 (C=O), 1510, 1370, 1230 (N_3), 1170, 1085, 870, 810, 780 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 6.54 (s, 1 H, H-4), 4.97 (br d, $J_{1',2'}$ = 3.9 Hz, 1 H, H-1′), 4.26 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, CH_2CH_3), 3.75 (dd, $J_{2',3'}$ = 8.2 Hz, 1 H, H-2′), 3.54 (m, 1 H, H-3′), 3.45 (dd, $J_{4'a,4'b}$ = 12.8 Hz, $J_{4'a,3'}$ = 2.8 Hz, 1 H, H-4′a), 3.34 (dd, $J_{4'b,3'}$ = 6.7 Hz, 1 H, H-4′b), 2.54 (s, 3 H, CH_3), 1.44 [s, 9 H, $[CH_3)_3C]$, 1.33 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3).

^{13}C NMR (75.4 MHz, CD_3OD): δ = 165.7 (CO_2Et), 159.8 (C=O of Boc), 157.4 (C-2), 152.1 (C-5), 115.1 (C-3), 109.5 (C-4), 80.8 $[(CH_3)_3C]$, 75.1 (C-2′), 72.3 (C-3′), 61.3 (CH_2CH_3), 55.2 (C-4′), 51.5 (C-1′), 28.7 $[(CH_3)_3C]$, 14.7 (CH_2CH_3), 13.8 (CH_3).

MS (FAB): *m/z* (%) = 421 (46, [M + Na]$^+$).

HRMS-FAB: *m/z* [M + Na]$^+$ calcd for $C_{17}H_{26}N_4O_7$ + Na: 421.1699; found: 421.1723.

Benzotriazol-1-yl 5-[1-*N*-(*tert*-Butoxycarbonyl)amino-1,4-dideoxy-4-*N*-(fluorenylme-thoxycarbonyl)amino-D-*ribo*tetritol-1-yl]-2-methylfuran-3-carboxylate (18)

To a solution of **26** (153 mg, 0.38 mmol) in EtOH (3 mL) were added LiOH (74 mg, 3.4 mmol) and H_2O (2 mL), and the mixture was heated at 50 °C for 1.5 h. Aq 1 M HCl (3 mL) was added to the solution to reach pH ~7. The mixture was evaporated to dryness. The resulting residue was dissolved in EtOH (10 mL), Pd/C was added and the mixture was hydrogenated under atmospheric pressure for 2 h. The Pd/C was filtered over Celite, washed with EtOH, and the filtrate evaporated to dryness. The resulting crude product was dissolved in 1,4-dioxane (3 mL) and sat. aq $NaHCO_3$ (6 mL) and a solution of 9-fluorenylmethyloxycarbonylsuccinimide (158 mg, 0.46 mmol) in 1,4-dioxane (3 mL) were added. The mixture was stirred for 3 h and then evaporated to dryness. The resulting residue was diluted with EtOAc (50 mL), and the organic phase washed with aq 1 M HCl (25 mL) and brine (25 mL). The organic phase was dried (Na_2SO_4) and evaporated to dryness. To a solution of the crude product in DMF (4 mL) were added PyBOP (204 mg, 0.38 mmol) and DIPEA (104 mg, 133 μL, 0.76 mmol), and the mixture was stirred for 2 h. The solution was evaporated, the residue diluted with EtOAc (50 mL) and the organic phase washed with aq 1 M HCl (25 mL), sat. aq $NaHCO_3$ (25 mL) and brine (25 mL). Purification by column chromatography (Et_2O–PE, 5:1) afforded **18** (155 mg, 60%) as a colorless oil; $[\alpha]_D^{24}$ +11 (*c* = 0.57, CH_2Cl_2).

IR (film): 3390 (OH), 2920, 1795 (C=O), 1695 (C=O), 1160, 960, 740 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 8.05 (d, *J* = 8.3 Hz, 1 H_{arom}), 7.78 (d, *J* = 7.4 Hz, 2 H_{arom}), 7.65 (d, *J* = 7.4 Hz, 2 H_{arom}), 7.62 (d, *J* = 3.8 Hz, 2 H_{arom}), 7.51 (m, 1 H_{arom}), 7.38 (t, *J* = 7.4 Hz, 2 H_{arom}), 7.30 (t, *J* = 7.4 Hz, 2 H_{arom}), 6.88 (s, 1 H, H-4), 5.14 (br s, 1 H, H-1′), 4.43–4.32 (m, 2 H, CH_2 of Fmoc), 4.21 (m, 1 H, CH of Fmoc), 3.71 (dd, $J_{2',3'}$ = 8.3 Hz, $J_{2',1'}$ = 3.5 Hz, 1 H, H-2′), 3.54–3.45 (m, 2 H, H-3′, H-4′a), 3.25 (dd, $J_{4'a,4'b}$ = 14.8 Hz, $J_{4'b,3'}$ = 7.3 Hz, 1 H, H-4′b), 2.66 (s, 3 H, CH_3), 1.46 [s, 9 H, $(CH_3)_3C$].

^{13}C NMR (75.4 MHz, CD_3OD): δ = 164.5 (CO_2Bt), 161.1 (C-2), 159.5 (C-5), 157.4, 154.1 (C=O of Fmoc, C=O of Boc), 145.3, 144.5, 142.6, 130.3, 128.8, 126.5, 126.2, 120.9, 120.7, 109.9 (18 C, C_{arom}), 109.5 (C-3), 108.8 (C-4), 80.9 $[(CH_3)_3C]$, 75.4 (C-2′), 72.1 (C-3′), 67.9 (CH_2 of Fmoc), 51.4 (C-1′), 48.2 (CH of Fmoc), 45.2 (C-4′), 28.7 $[(CH_3)_3C]$, 14.2 (CH_3).

MS (FAB): *m/z* (%) = 706 (25, [M + Na]$^+$).

HRMS-FAB: *m/z* [M + Na]$^+$ calcd for $C_{36}H_{37}N_5O_9$ + Na: 706.2489; found: 706.2443.

N-Protected Furylcarbopeptoid 14a

To a solution of **17** (95.4 mg, 0.17 mmol) and aminopolyol (+)-**16** (50 mg, 0.15 mmol) in DMF (8 mL) was added DIPEA (178 mg, 227 μL, 1.3 mmol) and the mixture was stirred overnight. Then, the solution was evaporated to dryness. The resulting residue was purified by column chromatography (CH_2Cl_2–MeOH, 10:1 → 4:1) to afford **14a** (62.5 mg, 62%) as a colorless oil; $[\alpha]_D^{22}$ +29 (*c* = 0.42, MeOH).

^{1}H NMR (500 MHz, CD_3OD): δ = 6.54 (s, 2 H, 2 H-4′), 5.00 (br s, 2 H, 2 H-1″), 4.04–3.89 (m, 6 H, H-3, H-5, H-7, H-9, H-11, H-13), 3.63 (dd, $J_{2'',3''}$ = 8.2 Hz, $J_{2'',1''}$ = 3.5 Hz, 2 H, 2 H-2″), 3.54–3.35 (m, 8 H, H-1, H-15, 2 H-3″, 2 H-4″a), 3.16 (dd, $J_{4''b,4''a}$ = 14.1 Hz, $J_{4''b,3''}$ = 6.5 Hz, 2 H, 2 H-4″b), 2.51 (s, 6 H, 2 CH_3), 1.72–1.53 (m, 14 H, H-2, H-4, H-6, H-8, H-10, H-12, H-14), 1.45 [s, 36 H, 4 $(CH_3)_3C$].

^{13}C NMR (125.7 MHz, CD_3OD): δ = 166.8 (2 C, 2 CONH), 159.2 (2 C, 2 C-2′), 157.3, 157.0 (4 C, 4 CO of Boc), 151.8 (2 C, 2 C-5′), 117.3 (2 C, 2 C-3′), 108.0 (2 C, 2 C-4′), 80.7, 80.4 [4 C, 4 $(CH_3)_3C$], 75.4 (2 C, 2 C-2″), 72.3 (2 C, 2 C-3″), 70.2, 68.3, 68.0, 67.2, 67.0, 66.1 (C-3, C-5, C-7, C-9, C-11, C-13), 51.4 (2 C, 2 C-1″), 46.3, 46.2, 45.9, 45.8, 45.7 (C-4, C-6, C-8, C-10, C-12), 44.7 (2 C, 2 C-4″), 38.7 (2 C, C-2, C-14), 37.4 (2 C, C-1, C-15), 28.7 [12 C, 4 $(CH_3)_3C$], 13.6 (2 C, 2 CH_3).

MS (FAB): *m/z* (%) = 1214 (5, [M + Na]$^+$), 813 (11, [M – 4 Boc + Na]$^+$).

HRMS-FAB: *m/z* [M + Na]$^+$ calcd for $C_{55}H_{94}N_6O_{22}$ + Na: 1213.6319; found: 1213.6371,

Furylcarbopeptoid 14b

Compound **14a** (30 mg, 0.025 mmol) was dissolved in TFA–CH_2Cl_2 (20%, 1.5 mL) and the mixture was stirred for 20 min. Then, the solvent was evaporated to afford **14b** (19 mg, quant) as a yellow oil; $[\alpha]_D^{25}$ –0.9 (*c* = 0.97, MeOH).

^{1}H NMR (500 MHz, CD_3OD): δ = 6.92 (s, 2 H, 2 H-4′), 4.73 (d, $J_{1'',2''}$ = 3.3 Hz, 2 H, 2 H-1″), 4.12–3.90 (m, 6 H, H-3, H-5, H-7, H-9, H-11, H-13), 3.89 (dd, $J_{2'',3''}$ = 9.2 Hz, 2 H, 2 H-2″), 3.56 (ddd, *J* = 9.1, 3.1, 2.5 Hz, 2 H, 2 H-3″), 3.52–3.35 (m, 4 H, H-1, H-15), 3.23 (dd, $J_{4''a,4''b}$ = 13.2 Hz, $J_{4''a,3''}$ = 3.1 Hz, 2 H, 2 H-4″a), 2.94 (dd, $J_{4''b,3''}$ = 2.51 Hz, 2 H, 2 H-4″b), 2.56 (s, 6 H, 2 CH_3), 1.99–1.50 (m, 14 H, H-2, H-4, H-6, H-8, H-10, H-12, H-14).

^{13}C NMR (125.7 MHz, CD_3OD): δ = 165.9 (2 C, 2 CONH), 158.6 (2 C, 2 C-2′), 145.8 (2 C, 2 C-5′), 118.3 (2 C, 2 C-3′), 111.8 (2 C, 2 C-4′), 73.1 (2 C, 2 C-2″), 69.5 (2 C, 2 C-3″), 68.4, 68.2, 68.1, 67.4, 67.1, 66.2 (C-3, C-5, C-7, C-9, C-11, C-13), 51.6 (2 C, 2 C-1″), 46.3, 46.2, 45.9, 45.8, 45.7 (C-4, C-6, C-8, C-10, C-12), 43.8 (2 C, 2 C-4″), 38.6 (2 C, C-2, C-14), 37.6 (2 C, C-1, C-15), 13.6 (2 C, 2 CH_3).

MS (FAB): *m/z* (%) = 813 (1, [M + Na]$^+$).

HRMS-FAB: *m/z* [M + Na]$^+$ calcd for $C_{35}H_{62}N_6O_{14}$ + Na: 813.4222; found: 813.4240.

Esterification of HMBA-AM Resin

A mixture of HMBAAM resin (59 mg, 0.068 mmol, substitution = 1.6 mmol/g) and Fmoc-glycine (81.5 mg, 0.274 mmol) in anhyd DMF (1.8 mL) was stirred for 15 min. Then a mixture of pyridine (59 mg, 60 μL, 0.75 mmol) and 2,6-dichlorobenzoyl chloride (93 mg, 64 μL, 0.274 mmol) was added and the resulting solution was stirred for 12 h. The reaction mixture was filtered and the resin washed with DMF (5 × 3 mL) and CH_2Cl_2 (3 × 3 mL). The resin was dried under vacuum affording 80 mg of a solid residue (100% substitution). The residue was treated with piperidine in DMF (20%, 2 mL) and stirred for 10 min. The resin was collected by filtration, washed with DMF (3 × 2 mL) and CH_2Cl_2 (4 × 2 mL), and dried under vacuum to afford H-Gly-OResin (81 mg).

Successive Coupling of Benzotriazol-1-yl 5-[1-*N*-(*tert*-Butoxycarbonyl)amino-1,4-dideoxy-4-*N*-(fluorenylmethoxycarbonyl)amino-D-*ribo*tetritol-1-yl]-2-methylfuran-3-carboxylate (18) Units to H-Gly-OResin

To H-Gly-OResin (81 mg, 0.068 mmol) in a reaction tube fitted with a glass frit in the side arm was added a solution of **18** (116.6 mg, 0.171 mmol) in DMF (2 mL) and DIPEA (46 mg, 58.5 μL, 0.342 mmol). The reaction mixture was stirred for 1 h. The resin was collected by filtration, washed with DMF (4 × 3 mL) and CH_2Cl_2 (4 × 3 mL), and dried. The same treatment was repeated until constant weight of the dipeptide bound resin (101 mg, 100% substitution) was obtained. The Fmoc/Boc protected resin bound dipeptide was treated with a solution of piperidine in DMF (20%, 2 mL) and stirred for 10 min. The resin was collected by filtration, washed with DMF (3 × 2 mL) and CH_2Cl_2 (4 × 2 mL), and dried under vacuum to afford the Boc protected dipeptide (87 mg). Subsequent couplings with **18** as described above were repeated twice to give the Boc-protected tetrapeptide bound resin (95% substitution).

Cleavage from the Resin and Final deprotection; Synthesis of 15

To the resin-bound tetrapeptide suspended in DMF (1 mL) was added a solution of MeOH–Et_3N (2:1) and the mixture was stirred overnight. Then, the resin was filtered and washed with DMF (3 × 2 mL) and MeOH (3 × 2 mL). The combined filtrates were evaporated to dryness and the residue was purified by preparative TLC (CH_2Cl_2–MeOH, 10:1) to afford pure Boc protected tetrapeptide. This product was dissolved in a solution of TFA–CH_2Cl_2 (20%, 2 mL) and the mixture was stirred for 15 min. Then the solution was evaporated to dryness and the unprotected tetrapeptide **15** was obtained as a white solid (42.5 mg, 92%); $[\alpha]_D^{25}$ –13 (*c* = 0.47, MeOH).

^{1}H NMR (500 MHz, CD_3OD): δ = 6.98, 6.95, 6.94 [3 s, 1 H each, H-4(A, B, C)], 4.74 (d, $J_{1'A,2'A}$ = 3.3 Hz, 1 H, H-1′A), 4.71, 4.70 [2 d, $J_{1'B,2'B} = J_{1'C,2'C}$ = 3.4 Hz, 1 H each, H-1′ (B, C)], 4.05 (s, 2 H, H-2′D), 3.88 (dd, $J_{2'A,3'A}$ = 9.2 Hz, 1 H, H-2′A), 3.79 [dd, $J_{2'B,3'B} = J_{2'C,3'C}$ = 9.2 Hz, 2 H, H-2′(B, C)], 3.74 (s, 3 H, OCH_3), 3.61–3.54 [m, 5 H, H-3′A, H-4′a(B, C), H-4′b(B, C)], 3.49–3.44 [m, 2 H, H-3′(B, C)], 3.24 (dd, $J_{4'aA,4'bA}$ = 12.9 Hz, $J_{4'aA,3'A}$ = 3.5 HZ, 1 H, H-4′aA), 2.95 (dd, $J_{4'bA,3'A}$ = 8.2 Hz, 1 H, H-4′bA), 2.57 [s, 9 H, CH_3(A, B, C)].

^{13}C NMR (125.7 MHz, CD_3OD): δ = 172.0 (C-1′D), 167.2, 166.2 [3 C, CONH(A, B, C)], 159.3, 159.0 [3 C, C-2(A, B, C)], 146.4, 145.9 [3 C, C-5(A, B, C)], 117.7 [3 C, C-3(A, B, C)], 111.8, 111.5, 111.5 [C-4(A, B, C)], 73.1 (C-2′A), 72.6, 72.5 [C-2′(B, C)], 72.4, 72.4 [C-3′(B, C)], 69.4 (C-3′A), 52.7 (OCH_3), 51.7 [3 C, C-1′(A, B, C)], 44.2, 44.0 [C-4′(B, C)], 43.8 (C-4′A), 41.8 (C-2′D), 13.7, 13.6 [3 C, CH_3(A, B, C)].

MS (FAB): *m*/*z* (%) = 790 (15, $[M + Na]^+$).

HRMS-FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{49}N_7O_{14}$ + Na: 790.3235; found: 790.3250.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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