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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 67–81

Novel glycine like amino acids from glyco-α-aminonitriles as building blocks for peptide synthesis

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Received 30 October 2007; accepted 30 November 2007
Available online 26 December 2007

Abstract—Our interest in the glycoaminocyanation reaction led us to apply this methodology to introduce amino acids on a monosaccharide using the N-terminal position. The GAAs described in this paper are characterized by having the amino and carboxylic acid functionalities on a disubstituted position of the saccharide backbone leading to α,α-disubstituted glycines. These new sugar amino acids showed a restricted conformation involving a spontaneous intramolecular cyclization between the C- and N-terminal positions during hydrolysis or hydrogenolysis to give the corresponding oxopiperazine. Tripeptide mimics were obtained by the introduction of an additional amino acid using one-pot conditions starting from these cyclic by-products under basic media. We demonstrated that these pseudo tripeptides are good candidates for extension of the peptidic scaffold and cyclization.

1. Introduction

Among the natural products, amino acids and carbohydrates are two of the most potent compounds for biological interactions. Over the last decade, an increased interest in unnatural α-amino acids has been noted in the literature.[1–5] Such compounds have been used to study enzymatic reaction mechanisms and as optically active starting materials for a variety of synthetic applications. Hybrids of sugars and amino acids (SAAs), also termed as glycosamino acids (GAAs), are molecules that combine the structural features of simple amino acids (amino and carboxylic acid functions) with those of simple carbohydrates (cyclic polyols, which may contain additional acetamido or amino functions).[1,6] The resulting hybrid is a highly substituted polyfunctionalized monomer, which can be used for the synthesis of compound libraries by means of combinatorial synthesis.[7,8] This class of conformationally restricted building block has been used extensively for the preparation of unnatural glycopeptides,[9–14] oligomer, and foldamers[15–19] or cyclic peptides and macrocycles,[20–22] among others. Their predisposition to induce novel secondary structures is well established.[21,23,24]

Recently Martinková described a novel furanoid α-substituted amino acid as a potent β-turn mimic, applying a [3,3]-sigmatropic rearrangement of an allylic thiocyanate.[25] Moreover, the synthesis of unnatural glycopeptides was extensively studied. In this case, the amino acid functionality was implemented on the anomeric position.

2. Results and discussion

In keeping with our earlier work, we have studied the scope and limitations of the aminocyanation reaction[26–30] to elaborate glycopeptide mimics by introducing an α-amino acid segment onto a saccharide moiety such that the N-terminal group is directly linked to a sugar carbon atom (amino sugar–amino acid hybrid) (Fig. 1).

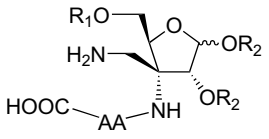

Figure 1. General structure of target glycoamino acids.

Thus, L- and D-amino acids were first protected by conversion into their methyl esters using classical conditions [$(MeO)_2C(Me)_2$; HCl; H_2O] and then stereoselectively coupled with uloses **1**, **2**, and **3** using our aminocyanation procedure, which employs $Ti(OiPr)_4$ as a mild and effective

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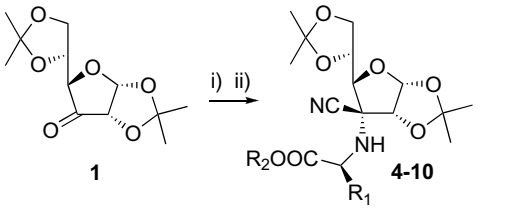
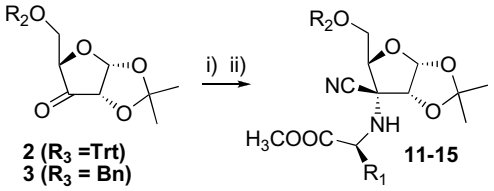
doi:10.1016/j.tetasy.2007.11.038

Lewis acid (Scheme 1).[26–30] Relatively low yields of the α-substituted L-amino acid derivatives **5**–**10**, **12**, and **14** (15–31%) were obtained. In contrast, higher yields were afforded for the glycine derivatives **4**, **11**, and **13** (56%, 53%, and 78%, respectively) and of the phenylalanine derivative **15** (57%).



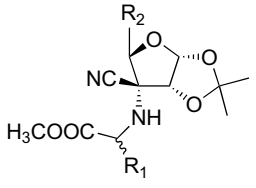
4- R_1= H, R_2=CH_3 (56%)
5- R_1= CH_3, R_2=CH_3 (18%)
6- R_1= $CH_2CH(CH_3)_2$, R_2=CH_3 (20%)
7- R_1= $CH_2CH_2SCH_3$, R_2=CH_3 (16%)
8- R_1= $CH_2CH_2COOCH_3$, R_2=CH_3 (15%)
9- R_1= CH_2Ph, R_2=CH_3 (30%)
10-R_1= H, R_2=tBu (35%)



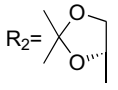
11- R_1= H, R_2= Bn (63%)
12- R_1= $CH_2CH(CH_3)_2$, R_2= Bn (20%)
13- R_1= H, R_2=Trt (78%)
14- R_1= CH_3, R_2=Trt (31%)
15- R_1= CH_2Ph, R_2=Trt (57%)

Scheme 1. Reagents and conditions: (i) $Ti(OiPr)_4$ (1.2 equiv), R_2OOC–CHR_1–NH_2·HCl, TEA (1.1 equiv), MeOH (24 h); (ii) TMSCN (1 equiv) (12 h).

Many attempts involving modifications in the equivalents of aminoacid, the nature and equivalents of Lewis acid [$Ti(OiPr)_4$, $TiCl_4$] and/or an excess of amino acids, the solvents (MeOH, CH_3CN, Et_2O, CH_2Cl_2) and an increasing temperature did not permit an improvement in the yield. D-Amino acids led to better reactivities (Fig. 2).



(L- series) (D- series)

R_2= 

5- R_1 = CH_3 (18%) **16**- R_1 = CH_3 (33%)
9- R_1 = CH_2Ph (30%) **17**- R_1 = CH_2Ph (40%)

R_2= CH_2OTrt **14**- R_1 = CH_3 (31%) **18**- R_1 = CH_3 (58%)
15- R_1 = CH_2Ph (57%) **19**- R_1 = CH_2Ph (62%)

Figure 2.

Thus, D-alanine was introduced on uloses **1** and **2** in 33% and 58%, respectively (vs 18% and 31% in the L-series) and D-phenylalanine in 40% and 62%, respectively (vs 30% and 40% in the L-series). These differences in the reactivity could be attributed to an enhancement of the steric constraint on the Ti-complexed transition state induced by the α- substituent for the L- versus the D-series (Fig. 3).

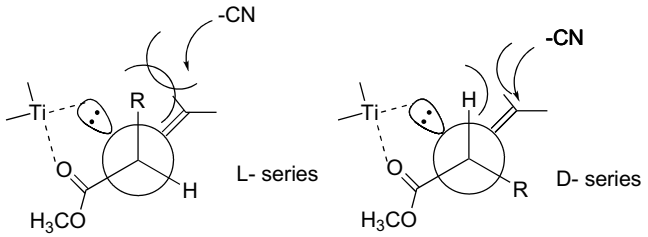


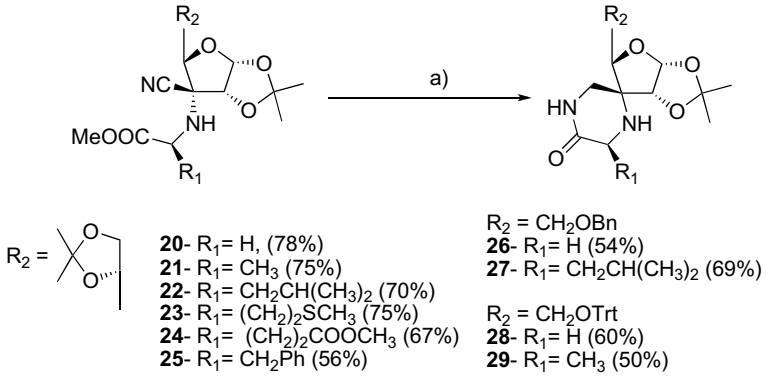
Figure 3.

To extend the peptidic scaffold, selective reduction of the CN group of compounds **4**–**15** with $NaBH_4$–$CoCl_2$ was effected.

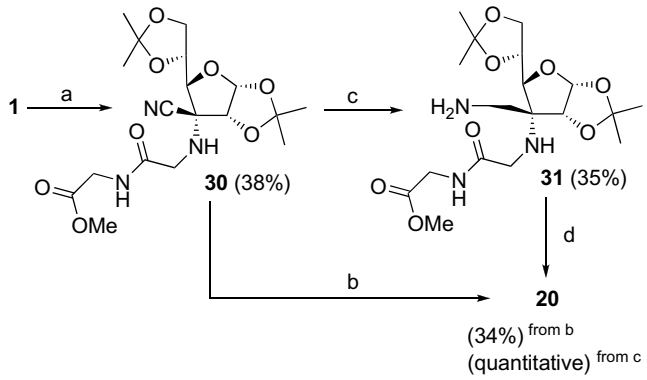
In all cases, the derivatives were obtained, which cyclized spontaneously to the corresponding oxopiperazines **20**–**29** with good yield (Scheme 2). Removal of Co^{II} derivatives was achieved by filtration through a silica gel pad. Compound **20** was also obtained (82%) from *t*-butyl ester protected amino acid derivative **10** that is less prone to aminolysis (Scheme 2).

To avoid spontaneous intramolecular aminolysis aided by the formation of a stable piperazine ring, we chose to use the dipeptide glycylglycine instead of a monomeric amino acid. Thus, the corresponding glycopeptidonitrile **30** was obtained from **1** in 38% yield. Selective reduction of the cyano group of **30** was achieved in the same fashion as used for **4**–**15**. Contrary to previous experiments, the Co^{II}–glycopeptide complex appeared to be relatively stable, such that filtration through a layer of silica gel was found to be inefficient in removing the cobalt moiety. However, extraction using aqueous HCl (5 M) resulted in cyclization to give piperazine **20** in low yield (34%). These results demonstrate the effective and selective reduction of the cyano group without affecting the carbonyl group and the capability of the subsequent amines to efficiently cyclize and to give the required piperazine derivative. A hypothesis for the high reactivity is the formation of a cobalt–amino acid complex involving the oxygen and nitrogen atoms of the same amino acid unit. Displacement of the peptide derivative from the complex by adding KCN followed by extraction into $CHCl_3$ led successfully to the amino glycopeptide **31** in 35% yield. Nevertheless, **31** gave piperazine **20** quantitatively by silica gel chromatography (Scheme 3).

To circumvent the oxopiperazine formation, the reduction step was carried out in the presence of an acylating agent (Boc_2O or Ac_2O) to quench the amino methyl ester as a carbamate or an amide. Under these conditions, compound **4** yielded the *N*-Boc and *N*-Ac compounds **32** and **33** in 54% and 45% yield, respectively. Oxopiperazine **20** was additionally formed in 33% yield using the acetylating conditions. Finally, the replacement of Boc_2O/Ac_2O by an



Scheme 2. Reagents and conditions: (a) $CoCl_2{\cdot}4H_2O$ (2 equiv), $NaBH_4$ (10 equiv), MeOH (30 min).

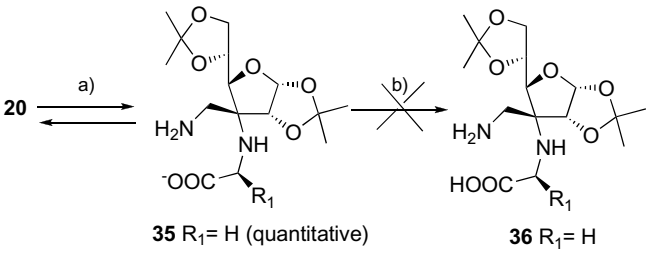


Scheme 3. Reagents and conditions: (a) (i) $Ti(OiPr)_4$ (1.2 equiv) MeOOC-Gly-Gly-NH_2, HCl (1.1 equiv), TEA (1.1 equiv), MeOH; (ii) TMSCN (1 equiv); (b) (i) $CoCl_2{\cdot}4H_2O$ (3 equiv), $NaBH_4$ (10 equiv), MeOH; (ii) HCl (0.5 M); (c) (i) $CoCl_2{\cdot}4H_2O$ (3 equiv), $NaBH_4$ (10 equiv), MeOH; (ii) KCN, H_2O; (d) silica gel chromatography.

amino acid anhydride such as L-glycine symmetrical anhydride [*N*-*Z*-Gly; DDC (0.5 equiv); CH_2Cl_2; 0 °C; 65%] gave the target compound **34** in modest yield (18%) together with oxopiperazine **20** (56%) (Scheme 4).

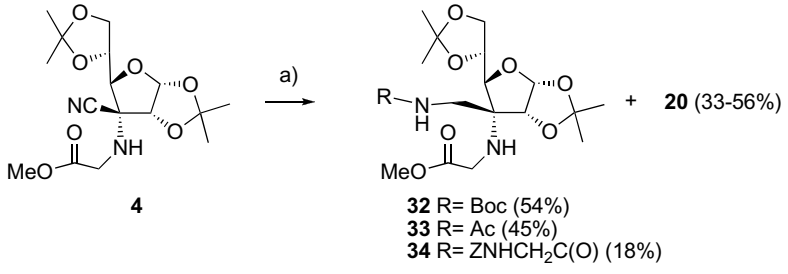
This poor result prompted us to explore the route to synthesize the target compounds starting from the oxopiperazine. Firstly, the hydrolysis of the spiro-ring was performed from **20** using aqueous NaOH (3 equiv) in refluxing dioxane/H_2O mixture overnight. Acyclic sodium carboxylate **35** was formed exclusively from **20** in quantitative yield (Scheme 5).

Piperazines **21**–**25** were unreactive under the same conditions or using $Ba(OH)_2$, known to be efficient for the hydrolysis of spirohydantoin rings.[28] Surprisingly, acidic displacement (IRA 120) of **35** to get the corresponding carboxylic acid **36** yielded the starting oxopiperazine **20** (Scheme 5). This phenomenon was also observed when we realized the hydrolysis of **4** to **37** (89%) followed by a subsequent hydrogenation step using H_2–Pd/C. Spiro oxopiperazine **20** was formed in 59% and 83% yield, respectively, using AcOEt or MeOH as solvent (Scheme 6).

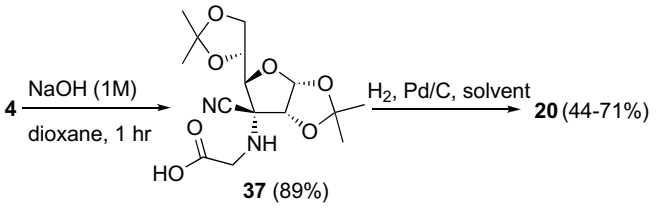


Scheme 5. Reagents and conditions: (a) NaOH (3 N) dioxane–H_2O, reflux (12 h); (b) IR 120 resin.

Because of his stability in basic media, carboxylate **35** has been exploited as an intermediate to introduce further amino acid units. When **20** was treated with NaOH (3 equiv) and *p*-nitrophenyl esters of amino acids (Gly; Ala; Leu; Phe), the tripeptide mimic compounds **38**–**41** were obtained in 42–56% yield. Starting from **38**, methylated L-alanine was coupled using DCC to afford the pseudotetrapeptide **42** in 67% yield (Scheme 7).



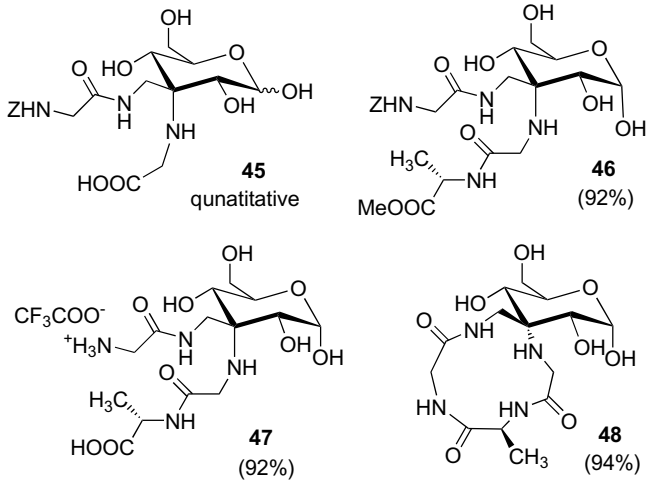
Scheme 4. Reagents and conditions: (a) $CoCl_2{\cdot}4H_2O$ (2 equiv), Boc_2O, Ac_2O or $(ZNH\text{-}Gly\text{-}CO)_2O$ (3 equiv), MeOH and then $NaBH_4$ (10 equiv).

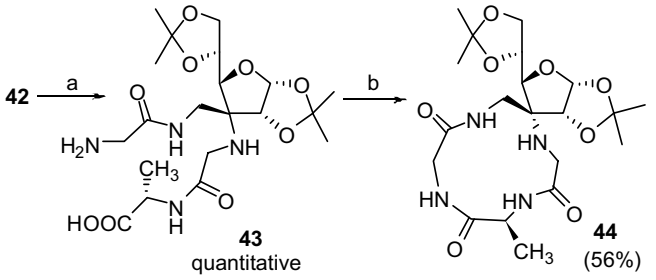


Scheme 6. Reagents and conditions: (a) NaOH (1 M), dioxane (40 min); (b) H_2, Pd/C MeOH or AcOEt (12 h).

Expecting to benefit from the spontaneous cyclization between the N-terminal position and the methyl ester group previously observed in the formation of the oxopiperazine, we afforded the cleavage of the benzyloxycarbonyl protecting group. Hydrogenolysis of **42** followed by deprotection of the C-terminal position quantitatively gave **43**, which cyclized using DPPA as a coupling agent to give the cyclic pseudotetrapeptide **44** in 56% yield (Scheme 8).

Removal of the isopropylidene groups in **38** and **42**–**44** under classical conditions (TFA/H_2O 9:1) gave pseudotripeptide **45**, acyclic pseudo tetrapetide **46**, **47** and cyclic tetrapeptide **48** in 92% to quantitative yields.





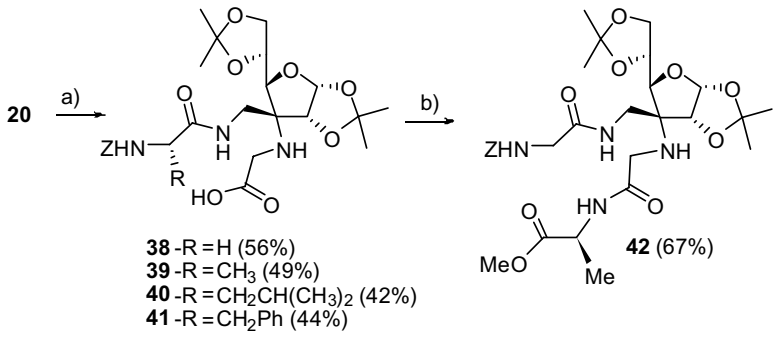
Scheme 8. Reagents and conditions: (a) (i) K_2CO_3, MeOH, H_2O; (ii) H_2, Pd/C MeOH or AcOEt (12 h); (b) DPPA (1.2 equiv), TEA (2 equiv), DMF.

3. Conclusion

In conclusion, we have demonstrated that α-amido nitriles derived from sugar templates are key intermediates for accessing restricted disubstituted glycine like compounds. A series of L- and D-amino acids have been used to explore the scope and limits of the aminocyanation reaction. Furthermore, extension on the C- and N-terminal position was achieved to obtain acyclic and cyclic pseudotetrapeptide. Further works concerning the synthesis of cyclic peptides incorporating SAAs are currently in progress and will be reported in due course.

4. Experimental

Melting points were determined on a digital melting point apparatus (Electrothermal) and are uncorrected. Optical rotations were recorded in $CHCl_3$, H_2O with a digital polarimeter model 343 (Perkin Elmer) using a 1 mL cell. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, MeOD-d_3, Me_2SO, D_2O (internal Me_4Si), respectively, at 300.13 MHz and at 75.47 MHz (Bruker Avance-300). TLC was performed on Silica F254 (Merck) and detection by UV light at 254 nm or by charring with phosphomolybdic acid–H_2SO_4 reagent. Column chromatography was effected on Silica Gel 60 (Merck, 230 mesh). Elemental analyses have been carried out in Madrid (IQOG, CSIC).



Scheme 7. Reagents and conditions: (a) NaOH (3 equiv), H_2O–dioxane, ZNH-gly-CO–O–Ph–NO_2 (1.2 equiv); (b) L-Ala-OMe (2 equiv), DCC (2 equiv), *N*-hydroxysuccinimide (2 equiv), DMF, MeCN −10 °C to ambient temperature (24 h).

^{13}C NMR resonances have been assigned by using standard NMR (DEPT, COSY, HSQC) experiments. FTIR spectra were obtained on an AVATAR 320 neat using ATR and are reported in cm^{-1}. Mass spectral data were acquired on a WATERS Micromass ZQ spectrometer or a WATERS Micromass Q-TOFF spectrometer.

4.1. General procedure for esterification of amino acids

To a solution of amino acid (20 mmol) in 2,2-dimethoxypropane was added concentrated HCl (20 mL) dropwise. The reaction mixture was stirred at room temperature overnight and then evaporated to dryness. To the residue was added a small amount of MeOH and Et_2O (250 mL). After one night at −4 °C, the crude was filtered to afford the methyl protected aminoacids as the corresponding hydrochloride salt.

4.2. General procedure for α-aminocyanation A

$Ti(OiPr)_4$ (1.2 equiv) was added to a solution of ulose derivative (1 equiv), $H_3COOC–CHR–NH_2$ (1.1 equiv) and triethylamine (1.1 equiv) in MeOH. The reaction mixture was stirred at room temperature for 5 h, and then TMSCN (1 equiv) was added and the reaction mixture stirred for 12 h. A few drops of water and EtOAc were added until oxidation of the titanium residue was complete. The solvent was evaporated to dryness and the crude product was purified by flash chromatography (EtOAc/hexane).

4.3. General procedure for oxopiperazine synthesis B

To a solution of compounds **20**–**25** (1 equiv) and $CoCl_2{\cdot}4H_2O$ (2 equiv) in MeOH was added $NaBH_4$ (10 equiv) portionwise. After stirring for 30 min, the reaction mixture was filtered through a silica pad until decolorization of the filtrate. The solvent was eliminated under vacuum and the crude was purified by flash chromatography (EtOAc/hexane).

4.4. 3-*C*-Cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[(methoxycarbonyl)methyl]amino]-α-D-allofuranose 4

Following General Method **A**, **1** (4.0 g, 16 mmol), MeOOCCH$_2$NH$_2$ (2.2 g, 18 mmol), TEA (2.47 mL, 18 mmol), and TMSCN (2.15 mL, 16 mmol) in MeOH (33 mL) gave after flash chromatography (EtOAc/hexane, 2:8) compound **4** (3.17 g, 56%) as a colorless syrup: $[\alpha]_D^{25} = +30.8$ (*c* 1.20; $CHCl_3$); IR (ATR): *v* 2927, 1748, 1375, 1255, 1260, 1141, 1059 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.85 (d, 1H, H-1, $J_{1,2}$ 3.6 Hz), 4.66 (d, 1H, H-2), 4.30 (ddd, 1H, H-5, $J_{5,6b}$ 6.1 Hz), 4.11 (dd, 1H, H-6b, $J_{6a,6b}$ 9.0 Hz), 3.96 (dd, 1H, H-6a, $J_{5,6a}$ 4.0 Hz), 3.84 (d, 1H, H-4, $J_{5,4}$ 9.0 Hz), 3.70 (s, 3H, OCH_3), 3.58 (s, 2H, C*H*$_2$NH), 2.93 (s, 1H, NH), 1.50 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.9 (C=O), 117.1 (CN), 114.1 (CH_3CCH_3), 110.3 (CH_3CCH_3), 104.4 (C-1), 82.5 (C-2), 80.8 (C-4), 75.0 (C-5), 68.0 (C-3), 67.6 (C-6), 52.1 (OCH_3), 46.5 (CH_2NH), 26.6 (2 × CH_3), 26.5 (CH_3), 24.9 (CH_3); MS (ES) $[M+Na]^+$ 379.16. Anal. Calcd for $C_{16}H_{24}N_2O_7$ (356.37 g/mol): C, 53.92; H, 6.79; N, 7.86. Found: C, 52.75; H, 6.24; N, 7.54.

4.5. 3-*C*-Cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[(*S*)-1-(methoxycarbonyl)ethyl] amino]-α-D-allofuranose 5

Following General Method **A**, **1** (0.6 g, 2.32 mmol), L-MeOOCCH(CH_3)NH_2 (0.35 g, 2.51 mmol), TEA (0.36 mL, 2.50 mmol), and TMSCN (0.31 mL, 2.32 mmol) in MeOH (5 mL) gave after flash chromatography (EtOAc/hexane, 2:8) compound **5** (0.10 g, 18%) as a colorless syrup: $[\alpha]_D^{25} = +8.8$ (*c* 1.09; $CHCl_3$); IR (ATR): *v* 2988, 2901, 1740, 1375, 1255, 1216, 1166, 1075, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.83 (d, 1H, H-1, $J_{1,2}$ 3.6 Hz), 4.71 (d, 1H, H-2), 4.28 (ddd, 1H, H-5, $J_{5,6b}$ 6.3 Hz), 4.10 (dd, 1H, H-6b, $J_{6a,6b}$ 8.9 Hz), 3.96 (dd, 1H, H-6a, $J_{5,6a}$ 4.6 Hz), 3.81 (d, 1H, H-4, $J_{5,4}$ 8.1Hz), 3.77 (m, 1H, $CH_{(ala)}$), 3.67 (s, 3H, OCH_3), 2.50 (s, 1H, NH), 1.49 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.34 (d, 3H, $CH_{3(ala)}$, $J_{H,CH_3(ala)}$ 7.0 Hz), 1.31 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}C NMR ($CDC1_3$) δ 174.8 (C=O), 117.2 (CN), 113.5 (CH_3CCH_3), 109.8 (CH_3CCH_3), 104.0 (C-1), 82.6 (C-2), 81.6 (C-4), 74.6 (C-5), 67.1 (C-6), 66.8 (C-3), 53.6 (CHNH), 51.9 (OCH_3), 26.4 (CH_3), 26.3 (CH_3), 26.2 (CH_3), 24.8 (CH_3), 19.0 ($CH_{3(ala)}$); HRMS: calcd $[M+Na]^+$ 393.1638; found, 393.1634. Anal. Calcd for $C_{17}H_{26}N_2O_7$ (370.40 g/mol): C, 55.13; H, 7.08; N, 7.56. Found: C, 55.42; H, 6.95; N, 7.64.

4.6. 3-*C*-Cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[(*S*)-1-(methoxycarbonyl)-3-methyl butyl]amino]-α-D-allofuranose 6

Following General Method **A**, **1** (1.06 g, 4.11 mmol), L-MeOOCCH[CH(CH_3)$_2$]NH_2 (0.89 g, 4.93 mmol), TEA (0.69 mL, 4.93 mmol), and TMSCN (0.55 mL, 4.11 mmol) in MeOH (8 mL) gave after flash chromatography (EtOAc/hexane, 2:8) compound **6** (0.34 g, 20%) as a colorless syrup; $[\alpha]_D^{20} = -2.0$ (*c* 1.00, $CHCl_3$); IR (ATR): *v* 2987, 2955, 1738, 1374, 1253, 1216, 1166, 1075, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.89 (d, 1H, H-1, $J_{1,2}$ 3.5 Hz), 4.73 (d, 1H, H-2), 4.35 (ddd, 1H, H-5, $J_{5,6b}$ 6.2 Hz), 4.2 (dd, 1H, H-6b, $J_{6a,6b}$ 8.8 Hz), 3.98 (dd, 1H, H-6a, $J_{5,6a}$ 5.5 Hz), 3.93 (d, 1H, H-4, $J_{5,4}$ 7.9 Hz), 3.76 (s, 3H, OCH_3), 3.74 (m, 1H, C*H*NH), 2.59 (d, 1H, N*H*, $J_{NH,CH}$ 5.5 Hz), 1.68 (m, 1H, CH), 1.60 (d, 2H, CH_2 J_{CH,CH_2} 7.1 Hz), 1.56 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 0.98 (d, 3H, CH_3, J_{CH,CH_3} 1.3 Hz), 0.96 (d, 3H, CH_3 J_{CH,CH_3} 1.3 Hz); ^{13}C NMR ($CDCl_3$) δ 175.2 (C=O), 117.6 (CN), 114.3 (CH_3CCH_3), 110.5 (CH_3CCH_3), 104.8 (C-1), 83 (C-2), 81.7 (C-4), 75.2 (C-5), 68.7 (C-3), 67.9 (C-6), 57.8 (*C*HNH), 52.4 (OCH_3), 42.6 (CH_2), 26.8 (3 × CH_3), 25.5 (CH_3), 25.0 (CH), 23.2 (*C*H_3CH), 22.6 (*C*H_3CH); HRMS: Calcd. $[M+Na]^+$ 435.2107; found, 435.2092. Anal. Calcd for $C_{20}H_{32}N_2O_7$ (412.22 g/mol): C, 58.24; H, 7.82; N, 6.79. Found: C, 58.10; H, 7.57; N, 6.71.

4.7. 3-*C*-Cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[(*S*)-1-(methoxycarbonyl)-3-methyl thio-propyl]amino]-α-D-allofuranose 7

Following General Method **A**, **1** (1.06 g, 4.11 mmol), L-MeOOCH(CH_2SCH_3)NH_2 (0.98 g, 4.93 mmol), TEA (0.69 mL, 4.93 mmol), and TMSCN (0.55 mL, 4.11 mmol) in MeOH (8 mL) gave after flash chromatography (EtOAc/hexane, 2:8) compound **7** (0.28 g, 16%) as a colorless syrup;

$[\alpha]_D^{20} = +8.0$ (*c* 1.60, $CHCl_3$); IR (ATR): *v* 2988, 2936, 1739, 1375, 1253, 1217, 1165, 1076, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.90 (d, 1H, H-1, $J_{1,2}$ 3.7 Hz), 4.77 (d, 1H, H-2), 4.37 (ddd, 1H, H-5, $J_{5,6b}$ 6.2 Hz), 4.19 (dd, 1H, H-6b, $J_{6a,6b}$ 8.8 Hz), 4.01 (dd, 1H, H-6a, $J_{5,6a}$ 5.4 Hz), 3.84 (m, 2H, CH, H-4, $J_{5,4}$ 7.4 Hz), 3.76 (s, 3H, OCH_3), 2.6 (m, 3H, NH, CH_2S), 2.11 (s, 3H, SCH_3), 2.09 (m, 1H, H-a), 1.92 (m, 1H, H-b (CH–$CH_{2(a,b)}$)), 1.55 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.36 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.7 (C=O), 117.6 (CN), 114.2 (CH_3CCH_3), 110.5 (CH_3CCH_3), 104.6 (C-1), 83.1 (C-2), 82.4 (C-4), 75.0 (C-5), 67.8 (C-3), 67.6 (C-6), 58.0 (CH), 52.6 (OCH_3), 33.2 (CH_2), 30.5 (CH_2SH), 27.1 (CH_3), 27.0 (CH_3), 26.8 (CH), 25.5 (CH_3CH), 15.8 (SCH_3); HRMS: calcd $[M+Na]^+$ 453.1671; found, 435.1657. Anal. Calcd for $C_{19}H_{30}N_2O_7S$ (430.18 g/mol): C, 53.01; H, 7.02; N, 6.51; S, 7.45. Found: C, 54.15; H, 7.03; N, 7.24; S, 7.80.

4.8. 3-*C*-Cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[(*S*)-(1,3)-di-(methoxycarbonyl)propyl]amino]-α-D-allofuranose 8

Following General Method **A**, **1** (1.12 g, 4.34 mmol), L-MeOOCH(CH_2CH_2COOMe)NH_2 (1.10 g, 5.21 mmol), TEA (0.73 mL, 5.21 mmol), and TMSCN (0.58 mL, 4.34 mmol) in MeOH (8 mL) gave after flash chromatography (EtOAc/hexane, 2:8) compound **8** (0.29 g, 15%) as a colorless syrup; $[\alpha]_D^{20} = +22.0$ (*c* 1.55, $CHCl_3$); IR (ATR): *v* 2989, 2937, 1734, 1376, 1260, 1213, 1165, 1065, 1042 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.89 (d, 1H, H-1, $J_{1,2}$ 3.7 Hz), 4.76 (d, 1H, H-2), 4.35 (ddd, 1H, H-5, $J_{5,6b}$ 6.3 Hz), 4.19 (dd, 1H, H-6b, $J_{6a,6b}$ 8.7 Hz), 4.00 (dd, 1H, H-6a, $J_{5,6a}$ 5.5 Hz), 3.83 (d, 1H, H-4, $J_{5,4}$ 7.5 Hz), 3.75 (m, 4H, OCH_3, CH), 3.69 (s, 3H, OCH_3), 2.58 (d, 1H, N*H*, $J_{NH,CH}$ 8.5 Hz), 2.48 (m, 2H, CH_2), 2.11 (m, 1H, H′(CH_2CO)), 1.96 (m, 1H, H″(CH_2CO)), 1.55 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.39 (s, 3H, CH_3,), 1.36 (s, 3H, CH_3);^{13}C NMR ($CDCl_3$) δ 174.7 (C=O), 173.6 (C=O), 117.5 (CN), 114.2 (CH_3CCH_3), 110.5 (CH_3CCH_3), 104.5 (C-1), 83.1 (C-2), 82.6 (C-4), 75.0 (C-5), 67.6 (C-3, C-6), 58.1 (CH), 52.6 (OCH_3), 52.1 (OCH_3), 30.5 (CH_2), 28.7 (CH_2CO), 27.1 (CH_3), 26.9 (CH_3), 26.8 (CH_3), 25.5 (CH_3); HRMS: calcd $[M+Na]^+$ 465.1849; found, 465.1845. Anal. Calcd for $C_{20}H_{30}N_2O_9$ (442.20 g/mol): C, 54.29; H, 6.83; N, 6.33. Found: C, 54.15; H, 6.75; N, 6.17.

4.9. 3-*C*-Cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[(*S*)-1-(methoxycarbonyl)-2-phenylethyl]amino]-α-D-allofuranose 9

Following General Method **A**, **1** (1.02 g, 3.95 mmol), L-MeOOCH(CH_2Ph)NH_2 (1.02 g, 4.74 mmol), TEA (0.67 mL, 4.74 mmol), and TMSCN (0.53 mL, 3.95 mmol) in MeOH (8 mL) gave after flash chromatography (EtOAc/hexane, 2:8) compound **9** (0.52 g, 30%) as a colorless syrup; $[\alpha]_D^{20} = +16$ (*c* 0.21, $CHCl_3$); IR (ATR): *v* 2991, 2901, 1739, 1374, 1251, 1215, 1166, 1079, 1027 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (m, 5H, Ph), 5.86 (d, 1H, H-1, $J_{1,2}$ 3.6 Hz), 4.71 (d, 1H, H-2), 4.22 (ddd, 1H, H-5, $J_{H5,H6a}$ 6.3 Hz), 4.11 (dd, 1H, H-6a, $J_{H6a,H6b}$ 8.7 Hz), 4.04 (ddd, 1H, CH, $J_{CH,Ha}$ 5.9 Hz), 3.91 (dd, 1H, H-6b, $J_{5,6a}$ 5.2 Hz), 3.88 (d, 1H, H-4, $J_{5,4}$ 8.2 Hz), 3.70 (s, 3H, OCH_3), 3.14 (d, 1H, H-a, $J_{Ha,Hb}$ 13.9 Hz), 3.05 (d, 1H, H-b, $J_{Hb,CH}$ 8.2 Hz), 2.72 (1H, NH, $J_{NH,CH}$ 4.9 Hz), 1.54 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.24 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.1 (C=O), 136.0 (C*q*), 129.8, 129.0, 127.5 (5C, Ph), 117.4 (CN), 114.3 (CH_3CCH_3), 110.5 (CH_3CCH_3), 104.8 (C-1), 83.0 (C-2), 81.8 (C-4), 75.0 (C-5), 68.7 (C-3), 67.9 (C-6), 60.1 (CH), 52.5 (OCH_3), 39.2 (CH_2), 26.7 (CH_3), 26.9 (CH_3), 26.8 (CH_3), 25.3 (CH_3); MS (ES) $[M+Na]^+$ 469.4; $[M+K]^+$ 485.3, $[2M+Na]^+$ 915.4. Anal. Calcd for $C_{23}H_{30}N_2O_7$ (446.21 g/mol): C, 61.87; H, 6.77; N, 6.27. Found: C, 61.59; H, 6.56; N, 6.01.

4.10. 3-*C*-Cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[(*tert*-butoxycarbonyl)methyl]amino]-α-D-allofuranose 10

Following General Method **A**, **1** (0.50 g, 1.94 mmol), L-*t*BuOOCCH_2NH_2 (0.39 g, 2.15 mmol), TEA (0.30 mL, 2.13 mmol), and TMSCN (0.26 mL, 1.90 mmol) in MeOH (5 mL) gave after flash chromatography (EtOAc/hexane, 1:9) compound **10** (0.27 g, 35%) as a colorless syrup; $[\alpha]_D^{28} = +18.7$ (*c* 0.33, $CHCl_3$); IR (ATR): *v* 2988, 1736, 1372, 1246, 1160, 1077, 1041, 1002, 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.90 (d, 1H, H-1, $J_{1,2}$ 3.6 Hz), 4.72 (d, 1H, H-2), 4.31 (ddd, 1H, H-5, J_{5-6b} 6.0 Hz), 4.20 (dd, 1H, H-6b, J_{6b-6a} 9.0 Hz), 4.00 (dd, 1H, H6a, J_{6a-5} 4.0 Hz), 3.91 (d, 1H, H-4, J_{4-5} 9.5 Hz), 3.50 (d, 2H, CH_2, $J_{CH_2,NH}$ 5.8 Hz), 2.90 (t, 1H, NH), 1.54 (s, 3H, CH_3), 1.45 (s, 9H, *t*-Bu), 1.46 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.7 (C=O), 117.7 (CN), 114.5 (CH_3CCH_3), 110.8 (CH_3CCH_3), 104.8 (C-1), 83.1 (C-2), 82.3 (Cq *t*-Bu), 81.3 (C-4), 75.4 (C-5), 68.6 (C-3), 68.0 (C-6), 47.9 (CH_2NH), 28.4 (4C, CH_3, $3 \times CH_{3(t\text{-Bu})}$), 27.1 ($CH_3$), 26.9 ($CH_3$), 25.4 ($CH_3$); HRMS: calcd $[M+Na]^+$ 421.1951; found, 421.1967. Anal. Calcd for $C_{19}H_{30}N_2O_7$ (398.21 g/mol): C, 57.27; H, 7.59; N, 7.03. Found: C, 56.98; H, 7.45; N, 7.21.

4.11. 5-*O*-Benzyl-3-*C*-cyano-3-deoxy-1,2-*O*-isopropylidene-3-[[(methoxycarbonyl)methyl]amino]-α-D-ribofuranose 11

Following General Method **A**, **3** (5.81 g, 20 mmol), L-MeOOCCH_2NH_2 (2.87 g, 20 mmol), TEA (7.50 mL, 20 mmol), and TMSCN (2.80 mL, 20 mmol) in MeOH (45 mL) gave after flash chromatography (EtOAc/hexane, 1:9) compound **11** (4.93 g, 63%) as a colorless syrup; $[\alpha]_D^{29} = +29.6$ (*c* 0.63, $CHCl_3$); IR (ATR): *v* 2989, 2868, 1742, 1376, 1255, 1217, 1165, 1097, 1026 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (m, 5H, Ph), 5.91 (d, 1H, H-1, $J_{1,2}$ 3.7 Hz), 4.71 (d, 1H, H-2), 4.58 (s, 2H, CH_2(*Bn*)), 4.16 (t, 1H, H-4, $J_{4,5}$ 6.1 Hz), 3.86 (dd, 2H, H-a ($NHCH_{2(a,b)}$), H-5a, $J_{H5a,H5b}$ 9.3Hz), 3.62 (s, 3H, OCH_3), 3.60 (dd, 2H, H-5b, H-b, $J_{Ha,Hb}$ 5.9Hz), 2.70 (t, 1H, N*H*, $J_{NH,CH}$ 6.3 Hz), 1.53 (s, 3H, CH_3), 1.26 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.3 (C=O), 137.7 (C*q*), 128.8–128.2 (5C, Ph), 117.3 (CN), 114.1 (CH_3CCH_3), 104.8 (C-1), 82.0 (C-4), 79.7 (C-2), 74.2 ($CH_{2(Bn)}$), 69.4 (C-5), 67.7 (C-3), 52.4 (OCH_3), 47.2 (CH_2), 27.0 (CH_3), 26.7 (CH_3); HRMS: calcd $[M+Na]^+$ 399.1532; found, 399.1525. Anal. Calcd for $C_{19}H_{24}N_2O_6$ (376.16 g/mol): C, 60.73; H, 6.43; N, 7.44. Found: C, 60.74; H, 6.27; N, 7.19.

4.12. 5-*O*-Benzyl-3-*C*-cyano-3-deoxy-1,2-*O*-isopropylidene-3-[[(*S*)-1- (methoxycarbonyl)-3-methylbutyl]amino]-α-D-ribofuranose 12

Following General Method **A**, **3** (3.0 g, 10 mmol), L-MeOOCCH(CH_2–*i*Pr)NH_2 (2.94 g, 20 mmol), TEA (2.27 mL, 20 mmol), and TMSCN (1.45 mL, 10 mmol) in MeOH (25 mL) gave after flash chromatography (EtOAc/hexane, 1:9) compound **12** (0.92 g, 20%) as a colorless syrup; $[\alpha]_D^{20} = -11.0$ (*c* 1.80, $CHCl_3$); IR (ATR): *v* 2954, 2872, 1739, 1376, 1255, 1216, 1165, 1101, 1028, 740, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (m, 5H, Ph), 5.94 (d, 1H, H-1, $J_{1,2}$ 3.7 Hz), 4.70 (d, 1H, H-2), 4.65 (d, 1H, H′(Bn), $J_{H'H''}$ 11.8 Hz), 4.57 (d, 1H, H″(Bn)), 4.08 (t, 1H, H-4, $J_{4,5}$ 5.5 Hz), 3.86 (d, 2H, 2 × H-5), 3.70 (s, 3H, OCH_3), 3.61 (m, 1H, C*H*NH), 2.43 (d, 1H, N*H*, $J_{NH,CH}$ 7.9 Hz), 1.64 (m, 1H, CH), 1.55 (s, 3H, CH_3), 1.45 (m, 2H, CH_2), 1.36 (s, 3H, CH_3), 0.88 (d, 6H, 2 × CH_3 J_{CH,CH_3} 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 175.5 (C=O), 138.7 (C*q*), 128.8, 128.3, 128.3 (5C, Ph), 117.3 (CN), 113.9 (CH_3CCH_3), 104.8 (C-1), 82.2 (C-2), 80.6 (C-4), 74.3 ($CH_{2(Bn)}$), 69.6 (C-5), 67.4 (C-3), 57.5 (*C*HNH), 52.4 (OMe), 42.9 (CH_2), 27.1 (CH_3), 26.8 (CH_3), 24.9 (CH), 23.9 (*C*H_3CH), 22.3 (*C*H_3CH); HRMS: calcd $[M+Na]^+$ 455.2158; found, 455.2162.

4.13. 3-*C*-Cyano-3-deoxy-1,2-*O*-isopropylidene-3-[[(methoxycarbonyl)methyl]amino]-5-*O*-trityl-α-D-ribofuranose 13

Following General Method **A**, **2** (2.0 g, 4.65 mmol), L-MeOOCCH_2NH_2 (0.63 g, 5.12 mmol), TEA (0.72 mL, 5.11 mmol), and TMSCN (0.62 mL, 4.65 mmol) in MeOH (16 mL) gave after flash chromatography (EtOAc/hexane, 2:8) compound **13** (1.91 g, 78%) as a colorless syrup; $[\alpha]_D^{25} = +20.6$ (*c* 1.00, $CHCl_3$); IR (ATR): *v* 2987, 1751, 1449, 1376, 1218, 1162, 1085, 1030, 761, 748, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56–7.34 (m, 15H, Ph, H trityl), 5.94 (d, 1H, H-1, $J_{1,2}$ 3.7 Hz), 4.76 (d, 1H, H-2), 4.13 (dd, 1H, H-4, $J_{4,5a}$ 5.5 Hz), 3.80 (dd, 1H, H-5b, $J_{4,5b}$ 7.0 Hz), 3.74 (s, 3H, OCH_3), 3.68 (s, 2H, CH_2NH), 3.56 (dd, 1H, H-5a, $J_{5a,5b}$ 10.1 Hz), 2.83 (t, 1H, N*H* J_{NH-CH_2NH} 5.9 Hz), 1.62 (s, 3H, CH_3), 1.38 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.4 (C=O), 143.1 (3C, C_{ipso}), 128.5, 127.8, 127.1 (15C, trityl), 116.7 (CN), 113.5 (CH_3CCH_3), 104.1 (C-1), 87.7 (*Cq* Ph_3), 81.7 (C-2), 79.2 (C-4), 67.3 (C-3), 63.1 (C-5), 51.8 (OCH_3), 46.7 (CHNH), 26.4 (CH_3), 26.3 (CH_3); MS (ES) $[M+Na]^+$ 551.4.

4.14. 3-*C*-Cyano-3-deoxy-1,2-*O*-isopropylidene-3-[[(*S*)-1-(methoxycarbonyl)ethyl]amino]-5-*O*-trityl-α-D-ribofuranose 14

Following General Method **A**, **2** (0.88 g, 2.05 mmol), L-MeOOCCH(CH_3)NH_2 (0.57 g, 4.08 mmol), TEA (0.50 mL, 3.45 mmol), and TMSCN (0.27 mL, 2.05 mmol) in MeOH (7 mL) gave after flash chromatography (EtOAc/hexane, 1.5:8.5) compound **14** (0.35 g, 31%) as a colorless solid; mp = 133–135 °C; $[\alpha]_D^{25} = -24.9$ (*c* 1.18, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.51–7.32 (m, 15H, Ph, H trityl), 5.91 (d, 1H, H-1, $J_{1,2}$ 3.7 Hz), 4.72 (d, 1H, H-2), 4.00 (dd, 1H, H-4, $J_{4,5a} = J_{4,5b}$ 5.7 Hz), 3.74 (s, 4H, OCH_3, C*H*NH), 3.69 (dd, 1H, H-5a), 3.48 (dd, 1H, H-5b, $J_{5a,5b}$ 10.3 Hz), 2.58 (d, 1H, N*H* $J_{NH,CH(ala)}$ 5.5 Hz), 1.61 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.33 (d, 1H, $CH_{3(ala)}$ $J_{CH,CH_{3(ala)}}$ 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 174.9 (C=O), 143.3 (3C, C_{ipso}), 128.6, 127.9, 127.2 (15C, trityl), 116.9 (CN), 113.4 (CH_3CCH_3), 104.1 (C-1), 87.6 (*Cq* Ph_3), 81.8 (C-2), 80.0 (C-4), 66.9 (C-3), 63.0 (C-5), 53.9 (CHNH), 52.1 (OMe), 26.6 (CH_3), 26.4 (CH_3), 19.5 (1C, $CH_{3(ala)}$).

4.15. 3-*C*-Cyano-3-deoxy-1,2-*O*-isopropylidene-3-[[(*S*)-1-(methoxycarbonyl)-2-phenylethyl]amino]-5-*O*-trityl-α-D-ribofuranose 15

Following General Method **A**, **2** (0.88 g, 2.05 mmol), L-MeOOCCH(CH_3)NH_2 (0.57 g, 4.08 mmol), TEA (0.50 mL, 3.45 mmol), and TMSCN (0.27 mL, 2.05 mmol) in MeOH (7 mL) gave after flash chromatography (EtOAc/hexane, 1.5:8.5) compound **15** (0.35 g, 31%) as a colorless syrup; $[\alpha]_D^{20} = +32.0$ (*c* 0.21, $CHCl_3$); IR (ATR): *v* 2988, 1741, 1491, 1449, 1377, 1218, 1164, 1078, 1056, 875, 737, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49–7.03 (m, 20H, $Ph_{(ala)}$, H trityl), 5.91 (d, 1H, H-1, $J_{1,2}$ 3.7 Hz), 4.65 (d, 1H, H-2), 3.88 (dd, 1H, H-4, $J_{4,5a}$ 5.8 Hz), 3.80 (m, 1H, CH, J_{CH,CH_2} 6.9 Hz), 3.67 (s, 3H, OCH_3), 3.65 (dd, 1H, H-5a), 3.42 (dd, 1H, H-5b, $J_{4,5b}$ 4.8 Hz, $J_{5a,5b}$ 10.5 Hz), 2.96 (dd, 1H, H-a, $CH_{2(Ph\text{-}ala)}$ J_{Ha-Hb} 13.6 Hz), 2.90 (dd, 1H, H-b ($CH_{2(Ph\text{-}ala)}$)), 2.50 (d, 1H, N*H* $J_{NH,CH(Ph\text{-}ala)}$ 7.4 Hz), 1.57 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.0 (C=O), 143.8 (3 × C*q*), 136.5 (C*q*), 131.3–127.2 (20C, trityl, $Ph_{(ala)}$), 117.2 (CN), 113.8 (CH_3CCH_3), 104.6 (C-1), 88.1 (*Cq* Ph_3), 82.1 (C-2), 80.5 (C-4), 67.5 (C-3), 63.8 (C-5), 60.2 (CH), 52.4 (OMe), 40.2 (CH_2), 27.0 (CH_3), 26.8 (CH_3); MS (ES) $[M+Na]^+$ 641.3.

4.16. 3-*C*-Cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[(*R*)-1-(methoxycarbonyl)ethyl]amino]-α-D-allofuranose 16

Following General Method **A**, **1** (1.07 g, 4.13 mmol), D-MeOOCCH(CH_3)NH_2 (0.87 g, 4.95 mmol), TEA (0.87 mL, 4.95 mmol), and TMSCN (0.55 mL, 4.13 mmol) in MeOH (10 mL) gave after flash chromatography (EtOAc/hexane, 1.5:8.5) compound **16** (0.49 g, 33%) as a colorless syrup; $[\alpha]_D^{20} = +30$ (*c* 0.26, $CHCl_3$); IR (ATR): *v* 2989, 2929, 1740, 1375, 1255, 1216, 1167, 1072, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (d, 1H, H-1, $J_{1,2}$ 3.6 Hz), 4.75 (d, 1H, H-2), 4.25 (ddd, 1H, H-5, $J_{5,6a}$ 6.1 Hz), 4.09 (dd, 1H, H-6a, $J_{6a,6b}$ 9.0 Hz), 3.92 (dd, 1H, H-6b, $J_{5,6b}$ 4.2 Hz), 3.80 (d, 1H, H-4, $J_{5,4}$ 9.0 Hz), 3.69 (s, 3H, OCH_3), 3.55 (m, 1H, $CH_{(ala)}$), 3.09 (s, 1H, NH), 1.48 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.29 (d, 3H, $CH_{3(ala)}$, J_{H,CH_3} 7.2 Hz), 1.28 (s, 6H, 2 × CH_3); ^{13}C NMR ($CDCl_3$) δ 175.1 (C=O), 117.7 (CN), 114.3 (CH_3CCH_3), 110.6 (CH_3CCH_3), 104.8 (C-1), 83.1 (C-2), 81.4 (C-4), 75.3 (C-5), 68.0 (C-6), 67.9 (C-3), 53.8 (CHNH), 52.4 (OCH_3), 27.0 (CH_3), 26.9 (CH_3), 26.8 (CH_3), 25.3 (CH_3), 20.4 ($CH_{3(ala)}$); HRMS: calcd $[M+Na]^+$ 393.1638; found, 393.1640. Anal. Calcd for $C_{17}H_{26}N_2O_7$ (370.40 g/mol): C, 55.13; H, 7.08; N, 7.56. Found: C, 54.98; H, 6.99; N, 7.45.

4.17. 3-*C*-Cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[(*R*)-1-(methoxycarbonyl)-2-phenylethyl]amino]-α-D-allofuranose 17

Following General Method **A**, **1** (1.00 g, 3.87 mmol), D-MeOOCCH(CH_2Ph)NH_2 (1.00 g, 4.64 mmol), TEA (0.65 mL, 4.64 mmol), and TMSCN (0.52 mL, 3.87 mmol) in MeOH (10 mL) gave after flash chromatography (EtOAc/hexane, 2:8) compound **17** (0.69 g, 40%) as a colorless syrup; $[\alpha]_D^{20} = -36.6$ (*c* 0.50, $CHCl_3$); IR (ATR): *v* 2991, 2901, 1740, 1374, 1251, 1215, 1167, 1078, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (m, 5H, Ph), 5.90 (d, 1H, H-1, $J_{1,2}$ 3.7 Hz), 4.75 (d, 1H, H-2), 4.35 (ddd, 1H, H-5, $J_{5,6a}$ 6.2 Hz), 4.13 (dd, 1H, H-6a, $J_{6a,6b}$ 9.1 Hz), 4.03 (dd, 1H, H-6b, $J_{5,6a}$ 3.7 Hz), 3.82 (d, 1H, H-4, $J_{5,4}$ 9.3 Hz), 3.80 (m, 1H, CH), 3.73 (s, 3H, OCH_3), 3.02 (d, 1H, NH, $J_{NH,CH}$ 6.5 Hz), 2.98 (d, 2H, CH_2, J_{CH,CH_2} 8.5 Hz), 1.47 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.1 (C=O), 137.1 (C*q*), 128.9, 128.7, 127.0 (Ph), 118.1 (CN), 114.3 (CH_3CCH_3), 110.0 (CH_3CCH_3), 104.0 (C-1), 83.0 (C-2), 81.0 (C-4), 75.0 (C-5), 67.0 (C-6), 67.0 (C-3), 59.0 (CH), 52.4 (OCH_3), 40.7 (CH_2), 27.3 (CH_3), 27.1 (CH_3), 26.8 (CH_3), 25.3 (CH_3); MS (ES) $[M+Na]^+$ 469.4; $[M+K]^+$ 485.4. Anal. Calcd for $C_{23}H_{30}N_2O_7$ (446.21 g/mol): C, 61.87; H, 6.77; N, 6.27. Found: C, 61.59; H, 6.48; N, 6.30.

4.18. 3-*C*-Cyano-3-deoxy-1,2-*O*-isopropylidene-3-[[(*R*)-1-(methoxycarbonyl)ethyl]amino]-5-*O*-trityl-α-D-ribofuranose 18

Following General Method **A**, **2a** (0.87 g, 2.01 mmol), D-MeOOCCH(CH_3)NH_2 (0.34 g, 2.42 mmol), TEA (0.34 mL, 2.42 mmol), and TMSCN (0.29 mL, 2.01 mmol) in MeOH (8 mL) gave after flash chromatography (EtOAc/hexane, 1.5:8.5) compound **18** (0.64 g, 58%) as a colorless syrup; $[\alpha]_D^{20} = +36.2$ (*c* 0.50, $CHCl_3$); IR (ATR): *v* 2989, 1741, 1491, 1449, 1376, 1218, 1168, 1079, 1012, 737, 706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54–7.29 (m, 15H, Ph, H trityl), 5.89 (d, 1H, H-1, $J_{1,2}$ 3.7 Hz), 4.89 (d, 1H, H-2), 4.12 (dd, 1H, H-4, $J_{4,5a}$ 4.9 Hz), 3.74 (dd, 1H, H-5a), 3.70 (s, 3H, OCH_3), 3.63 (m, 1H, CH), 3.53 (dd, 1H, H-5b, $J_{4,5b}$ 8.4 Hz, $J_{5a,5b}$ 9.6 Hz), 3.09 (d, 1H, N*H* $J_{NH,CH(ala)}$ 9.9 Hz), 1.60 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.38 (d, 1H, $CH_{3(ala)}$ $J_{CH,CH_{3(ala)}}$ 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 174.9 (C=O), 143.6 (3 × C*q*), 129.1, 128.4, 127.7 (trity1), 117.7 (CN), 114.2 (CH_3CCH_3), 104.8 (C-1), 88.5 (*Cq* Ph_3), 82.9 (C-2), 79.7 (C-4), 67.7 (C-3), 63.5 (C-5), 54.2 (CHNH), 52.3 (OCH_3), 27.1 (CH_3), 26.9 (CH_3), 20.6 ($CH_{3(ala)}$); MS (ES) $[M+Na]^+$ 565.4; $[M+K]^+$ 581.4.

4.19. 3-*C*-Cyano-3-deoxy-1,2-*O*-isopropylidene-3-[[(*R*)-1-(methoxycarbonyl)-2-phenylethyl]amino]-5-*O*-trityl-α-D-ribofuranose 19

Following General Method **A**, **2** (0.95 g, 2.22 mmol), D-MeOOCCH(CH_2Ph)NH_2 (0.57 g, 2.66 mmol), TEA (0.37 mL, 2.66 mmol), and TMSCN (0.30 mL, 2.22 mmol) in MeOH (8 mL) gave after flash chromatography (EtOAc/hexane, 1.5:8.5) compound **19** (0.74 g, 62%) as a colorless syrup; $[\alpha]_D^{20} = -22.0$ (*c* 0.17, $CHCl_3$); IR (ATR): *v* 2987, 1741, 1491, 1449, 1377, 1218, 1165, 1078, 1028, 910, 733, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.03 (m, 20H, $Ph_{(ala)}$, H trityl), 5.90 (d, 1H, H-1, $J_{1,2}$ 3.3 Hz), 4.65 (d, 1H, H-2), 3.88 (dd, 1H, H-4, $J_{4,5a}$ 5.8 Hz), 3.78 (m, 1H, CH, J_{CH,CH_2} 6.9 Hz), 3.67 (s, 3H, OCH_3), 3.65 (dd, 1H, H-5a), 3.43 (dd, 1H, H-5b, $J_{4,5b}$ 4.7 Hz, $J_{5a,5b}$ 10.4 Hz), 2.96 (dd, 1H, H-a, $CH_{2(Ph\text{-}ala)}$ $J_{Ha,Hb}$ 13.6 Hz), 2.93 (dd, 1H, H-b, $CH_{2(Ph\text{-}ala)}$), 2.50 (d, 1H, N*H* $J_{NH,CH(Ph\text{-}ala)}$ 7.3 Hz), 1.56 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.1 (C=O), 143.8 (3 × C*q*), 136.5 (C*q*), 129.7–127.2 (20C, trityl, $Ph_{(ala)}$), 117.2 (CN), 113.8 (CH_3CCH_3), 104.6 (C-1), 88.1 (*Cq* Ph_3), 82.1 (C-2), 80.5 (C-4), 67.4 (C-3), 63.8 (C-5), 60.1 (CH), 52.4 (OCH_3), 40.2 (CH_2), 27.0 (CH_3), 26.7 (CH_3); HRMS: Anal. Calcd $[M+Na]^+$ 641.2628; found, 641.2635.

4.20. (3*R*)-1,2:5,6-Di-*O*-isopropylidenespiro[3-deoxy-α-D-*ribo*-hexofuranose-3,5′-piperazine]-2′-one 20

Following General Procedure **B**, $NaBH_4$ (0.34 g, 9.13 mmol) was added to a solution of **4** (0.34 g, 0.91 mmol) and $CoCl_2{\cdot}4H_2O$ (0.23 g, 1.80 mmol) in MeOH (9 mL). After flash chromatography (EtOAc/hexane, 5:5), compound **20** (0.23 g, 78%) was isolated as a colorless syrup; $[\alpha]_D^{25} = +67.8$ (*c* 1.19, $CHCl_3$); IR (ATR): *v* 2994, 2931, 1672, 1373, 1250, 1213, 1165, 1073, 1010, 875, 846 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (d, 1H, NH($CH_{2(\alpha,\beta)}$)), 5.81 (d, 1H, H-1, $J_{1,2}$ 3.8 Hz), 4.70 (d, 1H, H-2), 4.15 (dd, 1H, H-6b, $J_{6a,6b}$ 8.2 Hz), 4.05 (ddd, 1H, H-5, $J_{5,6b}$ 5.9 Hz), 3.92 (dd, 1H, H-6a, $J_{5,6a}$ 5.0 Hz), 3.85 (d, 1H, H-4, $J_{5,4}$ 8.5 Hz), 3.70 (d, 1H, H-α, $J_{H\text{-}\alpha,H\text{-}\beta}$ 12.3 Hz), 3.64 (d, 1H, H-a), 3.50 (d, 1H, H-b, $J_{H\text{-}a,H\text{-}b}$ 18.1 Hz), 3.55 (dd, H-β, $J_{H\text{-}\beta,NH}$ 4.4 Hz), 2.6 (s, 1H, NH), 1.60 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.9 (C=O), 113.3 (CH_3CCH_3), 110.4 (CH_3CCH_3), 104.3 (C-1), 81.7 (C-2), 80.9 (C-4), 73.7 (C-5), 68.6 (C-6), 62.6 (C-3), 46.8 ($CH_{2(gly)}$), 44.1 ($CH_{2(\alpha,\beta)}NH$), 27.1 (CH_3), 27.0 (CH_3), 26.7 (CH_3), 25.5 (CH_3); HRMS: calcd $[M+Na]^+$ 351.1532; found, 351.1534. Anal. Calcd for $C_{15}H_{24}N_2O_6$ (328.36 g/mol): C, 54.87; H, 7.37; N, 8.53. Found: C, 54.76; H, 7.54; N, 8.54.

4.21. (3*R*,3′*S*)-1,2:5,6-Di-*O*-isopropylidene-3′-methylspiro[3-deoxy-α-D-*ribo*-hexofuranose-3,5′-piperazine]-2′-one 21

Following General Procedure **B**, $NaBH_4$ (0.10 g, 2.65 mmol) was added to a solution of **5** (0.10 g, 0.27 mmol) and $CoCl_2{\cdot}4H_2O$ (0.07 g, 0.53 mmol) in MeOH (3 mL). After flash chromatography (EtOAc/hexane, 5:5), compound **21** (0.08 g, 75%) was isolated as a colorless syrup; $[\alpha]_D^{25} = +23.3$ (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.9 (d, 1H, NH($CH_{2(\alpha,\beta)}$)), 5.7 (d, 1H, H-1, $J_{1,2}$ 3.8 Hz), 4.35 (d, 1H, H-2), 4.12 (dd, 1H, H-6b, $J_{6a,6b}$ 7.8 Hz), 4.05 (ddd, 1H, H-5, $J_{5,6b}$ 5.9 Hz), 3.92 (dd, 1H, H-6a, $J_{5,6a}$ 5.0 Hz), 3.85 (d, 1H, H-4, $J_{5,4}$ 8.1 Hz), 3.72 (d, 1H, CH, J_{CH,CH_3} 6.8 Hz), 3.6 (d, 1H, H-α, $J_{H\text{-}\alpha,H\text{-}\beta}$ 12.8 Hz), 3.15 (dd, H-β, $J_{H\text{-}\beta,NH}$ 4.3 Hz), 2.2 (s, 1H, NH), 1.60 (s, 3H, CH_3), 1.4 (s, 3H, CH_3), 1.34 (d, 3H, $CH_{3(ala)}$), 1.33 (s, 3H, CH_3), 1.26 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 176.4 (C=O),113.1 (CH_3CCH_3), 110.1 (CH_3CCH_3), 103.3

(C-1), 83.6 (C-2), 83.1 (C-4), 73.8 (C-5), 68.7 (C-6), 63.6 (C-3), 50.7 ($CH_{(ala)}$), 42.7 ($CH_{2(\alpha,\beta)}$), 27.1 (CH_3), 26.9 (CH_3), 26.8 (CH_3), 25.6 (CH_3), 17.9 ($CH_{3(ala)}$).

4.22. (3*R*,3′*S*)-3′-Isobutyl-1,2:5,6-di-*O*-isopropylidenespiro[3-deoxy-α-D-*ribo*-hexofuranose-3,5′-piperazine]-2′-one 22

Following General Procedure **B**, $NaBH_4$ (0.19 g, 5.12 mmol) was added to a solution of **6** (0.21 g, 0.51 mmol) and $CoCl_2{\cdot}4H_2O$ (0.24 g, 0.10 mmol) in MeOH (10 mL). After flash chromatography (EtOAc/MeOH, 9:1), compound **22** (0.14 g, 70%) was isolated as a colorless syrup; $[\alpha]_D^{20} = -13.0$ (*c* 1.80, $CHCl_3$); IR (ATR): *v* 2987, 2955, 1682, 1373, 1250, 1216, 1165, 1073, 1046 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (s, 1H, NH($CH_{2(\alpha,\beta)}$)), 5.70 (d, 1H, H-1, $J_{1,2}$ 3.8 Hz), 4.32 (d, 1H, H-2), 4.12 (dd, 1H, H-6a, $J_{6a,6b}$ 7.6 Hz), 4.08 (ddd, 1H, H-5, $J_{5,6a}$ 6.0 Hz), 3.90 (dd, 1H, H-6b, $J_{5,6b}$ 5.8 Hz), 3.82 (d, 1H, H-4, $J_{5,4}$ 7.9 Hz), 3.62 (dd, 1H, CH, J_{CH,CH_2} 9.9 Hz), 3.58 (d, 1H, H-α, $J_{H\text{-}\alpha,H\text{-}\beta}$ 12.9 Hz), 3.07 (dd, H-β, $J_{H\text{-}\beta,NH}$ 4.2 Hz), 1.92 (m, 1H, NH, $J_{NH,CH}$ 3.9 Hz), 1.85 (m, 1H, CH, J_{CH,CH_3} 6.4 Hz), 1.78 (m, 2H, $CH_{2(leu)}$), 1.55 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.34 (d, 3H, CH_3), 1.32 (s, 3H, CH_3), 0.92 (d, 3H, $CH_{3(leu)}$), 0.88 (d, 3H, $CH_{3(leu)}$); ^{13}C NMR ($CDCl_3$) δ 176.5 (C=O), 112.7 (CH_3CCH_3), 110.1 (CH_3CCH_3), 103.3 (C-1), 83.6 (C-2), 83.2 (C-4), 73.7 (C-5), 68.7 (C-6), 63.4 (C-3), 53.0 (CH), 42.5 ($CH_{2(\alpha,\beta)}NH$), 40.9 (CH_2), 27.0 (CH_3), 26.9 (CH_3), 26.8 (CH_3), 25.6 (CH_3), 24.0 ($CH(CH_3)_2$), 23.8 ($CH_{3(leu)}$), 21.7 ($CH_{3(leu)}$); HRMS: calcd $[M+H]^+$ 385.2339; found, 385.2335. Anal. Calcd for $C_{19}H_{32}N_2O_6$ (384.23 g/mol): C, 59.36; H, 8.39; N, 7.29. Found: C, 59.16; H, 8.15; N, 7.60.

4.23. (3*R*,3′*S*)-1,2:5,6-Di-*O*-isopropylidene-3′-(2-methylthioethyl)spiro[3-desoxy-α-D-*ribo*-hexofuranose-3,5′-piperazine]-2′-one 23

Following General Procedure **B**, $NaBH_4$ (0.14 g, 3.69 mmol) was added to a solution of **7** (0.16 g, 0.37 mmol) and $CoCl_2{\cdot}4H_2O$ (0.18 g, 0.74 mmol) in MeOH (7 mL). After flash chromatography (EtOAc/MeOH, 9:1), compound **23** (0.11 g, 75%) was isolated as a colorless syrup; $[\alpha]_D^{20} = -20.0$ (*c* 1.40, $CHCl_3$); IR (ATR): *v* 2987, 2935, 1674, 1373, 1249, 1216, 1166, 1074, 1014 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (s, 1H, NH($CH_{2(\alpha,\beta)}$)), 5.70 (d, 1H, H-1, $J_{1,2}$ 3.8 Hz), 4.32 (d, 1H, H-2), 4.13 (dd, 1H, H-6a, $J_{6a,6b}$ 7.9 Hz), 4.05 (ddd, 1H, H-5, $J_{5,6a}$ 6.0 Hz), 3.89 (dd, 1H, H-6b, $J_{5,6b}$ 5.4 Hz), 3.82 (d, 1H, H-4, $J_{5,4}$ 8.3 Hz), 3.76 (dd, 1H, CH, $J_{CH,Ha}$ 4.6 Hz), 3.56 (dd, 1H, H-α, $J_{H\text{-}\alpha,H\text{-}\beta}$ 12.8 Hz, $J_{H\text{-}\alpha,NH}$ 2.7 Hz), 3.10 (dd, H-β, $J_{H\text{-}\beta,NH}$ 3.8 Hz), 2.70 (t, 2H, CH_2S, $J_{CH_2,Ha} = J_{CH_2,Hb}$ 7.3 Hz), 2.12 (m, 4H, CH_3, H-a), 1.88 (ddt, 1H, H-b, $J_{CH,Hb}$ 8.0 Hz), 1.56 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 175.2 (C=O), 112.8 (CH_3CCH_3), 110.2 (CH_3CCH_3), 103.3 (C-1), 83.8 (C-2), 83.1 (C-4), 73.6 (C-5), 68.9 (C-6), 63.2 (C-3), 53.9 (CH), 42.0 ($CH_{2(\alpha,\beta)}$), 31.8 (CH_2S), 31.0 ($CH_{2(a,b)}$), 27.1 (CH_3), 27.0 (CH_3), 26.8 (CH_3), 25.6 (CH_3), 15.65 (SCH_3); HRMS: calcd $[M+Na]^+$ 403.1903; found, 403.1896. Anal. Calcd for $C_{18}H_{31}N_2O_6S$ (402.18 g/mol): C, 53.71; H, 7.51; N, 6.96; S, 7.97. Found: C, 54.01; H, 7.52; N, 6.85; S, 6.74.

4.24. (3*R*,3′*S*)-1,2:5,6-Di-*O*-isopropylidene-3′-[2-(methoxycarbonyl)ethyl]spiro[3-deoxy-α-D-*ribo*-hexofuranose-3,5′-piperazine]-2′-one 24

Following General Procedure **B**, $NaBH_4$ (0.17 g, 4.30 mmol) was added to a solution of **8** (0.20 g, 0.43 mmol) and $CoCl_2{\cdot}4H_2O$ (0.21 g, 0.88 mmol) in MeOH (7 mL). After flash chromatography (EtOAc/MeOH, 9:1), compound **24** (0.12 g, 67%) was isolated as a colorless syrup; $[\alpha]_D^{20} = +11$ (*c* 0.17, $CHCl_3$); IR (ATR): *v* 2987, 2901, 1733, 1674, 1374, 1250, 1216, 1166, 1073, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (s, 1H, NH($CH_{2(\alpha,\beta)}$)), 5.70 (d, 1H, H-1, $J_{1,2}$ 3.8 Hz), 4.28 (d, 1H, H-2), 4.10 (dd, 1H, H-6a, $J_{6a,6b}$ 8.0 Hz), 4.02 (ddd, 1H, H-5, $J_{5,6a}$ 5.8 Hz), 3.86 (dd, 1H, H-6b, $J_{5,6b}$ 5.7 Hz), 3.78 (d, 1H, H-4, $J_{5,4}$ 8.4 Hz), 3.66 (m, 4H, OCH_3, CH), 3.50 (dd, 1H, H-α, $J_{\alpha,\beta}$ 12.8 Hz, $J_{H\alpha\text{-}NH}$ 3.1 Hz), 3.12 (dd, H-β, $J_{H\beta,NH}$ 3.1 Hz), 2.50 (t, 2H, CH_2–*CO*, $J_{CH_2\text{–}H(a,b)}$ 7.4 Hz), 2.18 (m, 2H, NH, H-a), 1.98 (q, 1H, H-b, $J_{CH,Hb} = J_{CH,Ha}$ 7.4 Hz), 1.54 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.31 (s, 6H, $2 \times CH_3$); ^{13}C NMR ($CDCl_3$) δ 174.9 (C=O), 174.5 (C=O), 112.8 (CH_3 *C*CH_3), 110.1 (CH_3CCH_3), 103.1 (C-1), 84.0 (C-2), 83.3 (C-4), 73.6 (C-5), 68.9 (C-6), 63.0 (C-3), 54.4 (CH), 51.8 (OCH_3), 42.7 ($CH_{2(\alpha,\beta)}$), 30.9 ($CH_{2(a,b)}$), 27.8 (CH_2CO), 27.0 (CH_3), 26.9 (CH_3), 26.8 (CH_3), 25.5 (CH_3); HRMS: calcd for $C_{19}H_{30}N_2O_8Na$ $[M+Na]^+$ 437.1900; found, 437.1897.

4.25. (3*R*,3′*S*)-3′-Benzyl-1,2:5,6-di-*O*-isopropylidenespiro[3-deoxy-α-D-*ribo*-hexofuranose-3,5′-piperazine]-2′-one 25

Following General Procedure **B**, $NaBH_4$ (0.19 g, 5.00 mmol) was added to a solution of **9** (0.22 g, 0.50 mmol) and $CoCl_2{\cdot}4H_2O$ (0.24 g, 1.00 mmol) in MeOH (8 mL). After flash chromatography (EtOAc/MeOH, 9:1), compound **25** (0.12 g, 56%) was isolated as a colorless syrup; $[\alpha]_D^{20} = +18.0$ (*c* 0.32, $CHCl_3$); IR (ATR): *v* 2966, 1680, 1375, 1254, 1210, 1165, 1073, 1041, 756, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (m, 6H, NH($CH_{2(\alpha,\beta)}$), 5H (Ph)), 5.70 (d, 1H, H-1, $J_{1,2}$ 3.8 Hz), 4.31 (d, 1H, H-2), 4.05 (m, 2H, CH, H-5, $J_{5,6a}$ 4.4 Hz), 3.94 (dd, 1H, H-6a, $J_{6a,6b}$ 9.5 Hz), 3.83 (dd, 1H, H-6b, $J_{5,6b}$ 6.6 Hz), 3.70 (d, 1H, H-4, $J_{5,4}$ 7.3 Hz), 3.48 (dd, 1H, H-α, $J_{H\text{-}\alpha,H\text{-}\beta}$ 12.5 Hz, $J_{H\text{-}\alpha,NH}$ 2.6 Hz), 3.38 (dd, 1H, H-a, $J_{Ha,Hb}$ 13.8 Hz, $J_{Ha,CH}$ 3.4 Hz), 3.03 (dd, H-β, $J_{H\text{-}\beta,NH}$ 3.6 Hz), 2.82 (dd, 1H, H-b, $J_{Hb,CH}$ 9.6 Hz), 2.03 (s, 1H, NH), 1.50 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.30 (s, 6H, $2 \times CH_3$); ^{13}C NMR ($CDCl_3$) δ 174.6 (C=O), 139.0 (C*q*), 129.8, 128.7, 126.7 (Ph), 112.7 (CH_3CCH_3), 110.0 (CH_3CCH_3), 103.2 (C-1), 83.6 (C-2), 82.9 (C-4), 73.5 (C-5), 68.4 (C-6), 63.1 (C-3), 56.6 (CH), 43.1 ($CH_{2(\alpha,\beta)}NH$), 38.8 ($CH_{2(a,b)}$), 27.0 (CH_3), 26.9 (CH_3), 26.7 (CH_3), 25.5 (CH_3). Anal. Calcd for $C_{21}H_{28}N_2O_6$ (404.19 g/mol): C, 62.36; H, 6.98; N, 6.93. Found: C, 62.27; H, 6.91; N, 6.99.

4.26. (3*R*)-5-*O*-Benzyl-1,2-*O*-isopropylidenespiro[3-deoxy-α-D-*erythro*-pentofuranose-3,5′-piperazine]-2′-one 26

Following General Procedure **B**, $NaBH_4$ (1.23 g, 32.66 mmol) was added to a solution of **11** (1.23 g, 3.26 mmol) and $CoCl_2{\cdot}4H_2O$ (0.84 g, 6.52 mmol) in MeOH (40 mL). After flash chromatography (EtOAc/MeOH, 9:1), com-

pound **26** (0.61 g, 54%) was isolated as a colorless syrup; $[\alpha]_D^{29} = +71.6$ (*c* 0.38, $CHCl_3$); IR (ATR): *v* 2986, 2926, 2865, 1672, 1380, 1255, 1213, 1164, 1074, 1051, 1001 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (d, 1H, NH, $J_{NH-H\beta}$ 3.2 Hz), 7.27 (m, 5H, Ph), 5.75 (d, 1H, H-1, $J_{1,2}$ 3.9 Hz), 4.49 (d, 1H, H-2), 4.48 (s, 2H, CH_2(Bn)), 3.88 (dd, 1H, H-4, $J_{5a,4}$ 3.0 Hz), 3.58 (m, 2H, H-a, H-5a, $J_{5a,5b}$ 10.5 Hz), 3.45 (d, 1H, H-b, $J_{H\text{-}a,H\text{-}b}$ 17.5 Hz), 3.49 (dd, 1H, H-5b, $J_{5b,4}$ 6.8 Hz), 3.27 (d, 1H, H-α, $J_{H\text{-}\alpha,H\text{-}\beta}$ 12.4 Hz), 2.79 (dd, 1H, H-β), 1.97 (s, 1H, NH), 1.49 (s, 3H, CH_3), 1.27 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.2 (C=O), 138.0 (C_{ipso}), 128.8, 128.2, 128.1 (5C, Ph), 112.6 (CH_3CCH_3), 104.4 (C-1), 80.3 (C-4), 79.4 (C-2), 73.9 ($CH_2(Z)$), 68.3 (C-5), 62.7 (C-3), 46.9 ($CH_{2(a,b)}$), 42.9 ($CH_{2(\alpha,\beta)}$), 26.9 (CH_3), 26.7 (CH_3).

4.27. (3*R*,3′S)-5-*O*-Benzyl-3′-isobutyl-1,2-*O*- isopropylidenespiro[3-deoxy-α-D-*erythro*-pentofuranose-3,5′-piperazine]-2′-one 27

Following General Procedure **B**, $NaBH_4$ (0.70 g, 18.50 mmol) was added to a solution of **12** (0.79 g, 1.85 mmol) and $CoCl_2{\cdot}4H_2O$ (0.88 g, 3.70 mmol) in MeOH (25 mL). After flash chromatography (EtOAc/MeOH, 9:1), compound **27** (0.51 g, 69%) was isolated as a colorless syrup; $[\alpha]_D^{20} = +13.0$ (*c* 0.85, $CHCl_3$); IR (ATR): *v* 2957, 2901, 1674, 1383, 1250, 1216, 1166, 1076, 1066, 737, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (d, 1H, NH, $J_{NH-H\beta}$ 4.4 Hz), 7.32 (m, 5H, Ph), 5.78 (d, 1H, H-1, $J_{1,2}$ 3.7 Hz), 4.55 (s, 2H, $CH_{2(Bn)}$), 4.31 (d, 1H, H-2), 3.95 (dd, 1H, H-4, $J_{5a,4}$ 3.2 Hz), 3.71 (m, 1H, H-5a, $J_{5a,5b}$ 10.6 Hz), 3.60 (dd, 1H, H-5b, $J_{5b,4}$ 6.0 Hz), 3.40 (m, 2H, CH, H-α, $J_{H\text{-}\alpha,H\text{-}\beta}$ 13.3 Hz), 3.00 (dd, 1H, H-β), 1.97 (s, 1H, NH), 1.76 (m, 3H, $CH(CH_3)_2$, CH_2), 1.53 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 0.94 (d, 3H, $CH_{3(leu)}$), 0.87 (d, 3H, $CH_{3(leu)}$); ^{13}C NMR ($CDCl_3$) δ 175.9 (C=O), 138.0 (C_{ipso}), 128.8, 128.3, 128.2 (5C, Ph), 112.4 (CH_3CCH_3), 103.8 (C-1), 81.9 (C-2), 81.2 (C-4), 74.0 (CH_2(Bn)), 68.2 (C-5), 63.1 (C-3), 53.4 (CHNH), 42.2 ($CH_{2(\alpha,\beta)}$), 41.2 ($CH_{2(leu)}$), 26.9 (CH_3), 26.8 (CH_3), 24.7 (CH), 23.9 ($CH_{3(leu)}$), 21.4 ($CH_{3(leu)}$); HRMS: calcd $[M+Na]^+$ 427.2209; found, 427.2203. Anal. Calcd for $C_{22}H_{32}N_2O_5$ (404.23 g/mol): C, 65.32; H, 7.97; N, 6.93. Found: C, 65.08; H, 7.95; N, 6.82.

4.28. (3*R*)-1,2-*O*-Isopropylidene-5-*O*-trityl-spiro[3-deoxy-α-D-*erythro*-pentofuranose-3,5′-piperazine]-2′-one 28

Following General Procedure **B**, $NaBH_4$ (0.31 g, 8.22 mmol) was added to a solution of **13** (0.43 g, 0.82 mmol) and $CoCl_2{\cdot}4H_2O$ (0.21 g, 1.63 mmol) in MeOH (8 mL). After flash chromatography (EtOAc/MeOH, 5:5), compound **28** (0.24 g, 60%) was isolated as a colorless syrup; $[\alpha]_D^{27} = +51.1$ (*c* 0.28, $CHCl_3$); IR (ATR): *v* 2987, 2901, 1671, 1393, 1250, 1226, 1066, 1056, 879, 750, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.20 (m, 15H, trityl), 7.18 (d, 1H, NH($CH_{2(\alpha,\beta)}$)), 5.81 (d, 1H, H-1, $J_{1,2}$ 3.9 Hz), 4.50 (d, 1H, H-2), 4.00 (dd, 1H, H-4, $J_{5a,4}$ 6.4 Hz), 3.70 (d, 1H, H-a, $J_{H\text{-}a,H\text{-}b}$ 17.7 Hz), 3.45 (d, 1H, H-b), 3.40 (dd, 1H, H-5a, $J_{5a,5b}$ 10.1 Hz), 3.2 (dd, 1H, H-5b, $J_{5b,4}$ 4.6 Hz), 3.15 (d, 1H, H-α, $J_{H\text{-}\alpha,H\text{-}\beta}$ 12.4 Hz), 2.8 (dd, 1H, H-β, $J_{H\text{-}\beta,NH}$ 4.4 Hz), 2.06 (s, 1H, NH), 1.59 (s, 3H, CH_3), 1.36 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.4 (C=O), 143.9 (3 × C_{ipso}), 129.0, 128.4, 127.6 (15C, trityl), 112.7 (CH_3CCH_3), 104.4 (C-1), 87.7 (C*q*), 80.1 (C-2), 79.7 (C-4), 62.6 (C-5), 62.3 (C-3), 47.0 ($CH_{2(a,b)}$), 43.2 ($CH_{2(\alpha,\beta)}$ NH), 27.0 (CH_3), 26.7 (CH_3); HRMS: calcd $[M+Na]^+$ 523.2209; found, 523.2216. Anal. Calcd for $C_{30}H_{32}N_2O_5$ (500.59 g/mol): C, 71.98; H, 6.44; N, 5.60. Found: C, 71.54; H, 6.21; N, 5.34.

4.29. (3*R*,3′*S*)-1,2-*O*-Isopropylidene-3′-methyl-5-*O*-trityl-spiro[3-deoxy-α-D-*erythro*-pentofuranose-3,5′-piperazine]-2′-one 29

Following General Procedure **B**, $NaBH_4$ (0.16 g, 4.2 mmol) was added to a solution of **14** (0.23 g, 0.42 mmol) and $CoCl_2{\cdot}4H_2O$ (0.11 g, 0.84 mmol) in MeOH (4.5 mL). After flash chromatography (EtOAc/MeOH, 5:5), compound **29** (0.107 g, 50%) was isolated as a colorless syrup; $[\alpha]_D^{27} = +10.6$ (*c* 0.39, $CHCl_3$); IR (ATR): *v* 2987, 1680, 1373, 1213, 1161, 1080, 1012, 765, 747, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.52 (m, 15H, trityl), 7.11 (d, 1H, NH, ($CH_{2(\alpha,\beta)}$)), 5.84 (d, 1H, H-1, $J_{1,2}$ 3.9 Hz), 4.35 (d, 1H, H-2), 4.15 (q, 1H, CH, J_{CH,CH_3} 7.1 Hz), 4.08 (dd, 1H, H-4, $J_{4,5a} = J_{4,5b}$ 5.4 Hz), 3.40 (dd, 1H, H-5b), 3.32 (m, 1H, H-α, $J_{H\text{-}\alpha,H\text{-}\beta}$ 13.0 Hz), 3.24 (dd, 1H, H-5a, $J_{5a,5b}$ 10.3 Hz), 2.92 (dd, 1H, H-β, $J_{H\text{-}\beta,NH}$ 4.4 Hz), 2.12 (s, 1H, NH), 1.60 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.27 (d, 3H, $CH_{3(ala)}$); ^{13}C NMR ($CDCl_3$) δ 176.6 (C=O), 144.1 (3 × C_{ipso}), 128.9, 128.6, 128.0 (trityl), 112.4 (CH_3CCH_3), 103.9 (C-1), 87.5 (C*q*), 81.8 (C-2), 80.8 (C-4), 63.9 (C-5), 61.7 (C-3), 50.8 (CH), 44.8 ($CH_{2(\alpha,\beta)}$NH), 26.9 (CH_3), 26,8 (CH_3),17,2 (1C, $CH_{3(ala)}$); HRMS: calcd $[M+Na]^+$ 537.2365; found, 537.2379. Anal. Calcd for $C_{31}H_{34}N_2O_5$ (514.61 g/mol): C, 72.35; H, 6.66; N, 5.44. Found: C, 72.47; H, 6.91; N, 5.48.

4.30. 3-*C*-Cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[[(methoxycarbonyl)methyl]carbamoyl]methyl]amino]-α-D-allofuranose 30

Following General Method **A**, **1** (1.00 g, 3.88 mmol), Gly-Gly-OMe (0.78 g, 4.26 mmol), TEA (0.60 mL, 4.26 mmol), and TMSCN (0.52 mL, 3.87 mmol) in MeOH (8 mL) gave after flash chromatography (EtOAc/hexane, 1:9) compound **30** (0.65 g, 41%) as a colorless syrup; $[\alpha]_D^{28} = +1.4$ (*c* 0.38, $CHCl_3$); IR (ATR): *v* 2988, 1747, 1683, 1531, 1446, 1375, 1213, 1165, 1076, 1034, 874, 841 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (t, 1H, NH, $J_{NH,CH_{2\alpha}}$ 5.4 Hz), 5,81 (d, 1H, H-1, $J_{1,2}$ 3.6 Hz), 4.70 (d, 1H, H-2), 4.26 (ddd, 1H, H-5, $J_{5,6b}$ 6.2 Hz), 4.08 (dd, 1H, H-6b, $J_{6a,6b}$ 9.2 Hz), 3.95 (d, 2H, $CH_{2\alpha}$), 3.91 (dd, 1H, H-6a, $J_{6a,5}$ 4.4 Hz), 3.72 (d, 1H, H-4, $J_{5,4}$ 9.0 Hz), 3.60 (s, 3H, OCH_3), 3.50 (dd, 1H, H-β gly $J_{H\text{-}\beta,NH}$ 6.1 Hz), 3.36 (dd, 1H, H-β′ gly, $J_{H\text{-}\beta,H\text{-}\beta'}$ 16.7 Hz), 2.8 (dd, 1H, NH, $J_{NH,H\text{-}\beta'}$ 7.8 Hz), 1.46 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.23 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 170.7 (C=O), 170.3 (C=O), 117.3 (CN), 114.4 (CH_3CCH_3), 110.8 (CH_3CCH_3), 104.8 (C-1), 82.2 (C-2), 80.6 (C-4), 72.2 (C-5), 68.9 (C-3), 67.9 (C-6), 52.5 (OCH_3), 48.7 ($CH_{2\beta}$), 41.2 ($CH_{2\alpha}$), 26.9 (2 × CH_3), 26.7 (CH_3), 25.2 (CH_3); HRMS: calcd $[M+Na]^+$ 436.1696; found, 436.1697. Anal. Calcd for $C_{18}H_{27}N_3O_8$ (413.18 g/mol): C, 52.29; H, 6.58; N, 10.16. Found: C, 52.41; H, 6.53; N, 9.97.

4.31. 3-*C*-Aminomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[[(methoxycarbonyl)methyl]carbamoyl]-methyl]amino]-α-D-allofuranose 31

Following General Procedure **B**, $NaBH_4$ (0.30 g, 7.94 mmol) was added to a solution of **30** (0.33 g, 0.79 mmol) and $CoCl_2{\cdot}4H_2O$ (0.31 g, 2.38 mmol) in MeOH (8 mL). After extraction with CH_2Cl_2 and water, the organic layer was separated, dried, filtered, and evaporated to give compound **31** (0.12 g, 35%) as a slightly yellow syrup; ^{13}C NMR ($CDCl_3$) δ 173.5 (C=O), 170.7 (C=O), 112.4 (CH_3CCH_3), 110.2 (CH_3CCH_3), 104.6 (C-1), 83.4 (C-2), 83.0 (C-4), 73.7 (C-5), 69.1 (C-6), 67.8 (C-3), 52.6 (OMe), 47.3 ($CH_{2\beta}$), 41.7 (CH_2NH_2), 41.0 ($CH_{2\alpha}$), 27.2 (CH_3), 27.0 (CH_3), 26.7 (CH_3), 25.7 (CH_3). MS (ES) $[M+Na]^+$ 440.2.

4.32. 3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[(methoxycarbonyl)methyl]amino]-3-*C*-[(*tert*-butoxycarbonyl)-aminomethyl]-α-D-allofuranose 32

To a solution of compound **4** (0.38 g, 1.07 mmol) and $CoCl_2{\cdot}4H_2O$ (0.27 g, 2.14 mmol) in MeOH (10 mL) were added successively Boc_2O (0.69 g, 3.21 mmol) and $NaBH_4$ (0.40 g, 10.7 mmol) portionwise. After stirring for 1 h, a few drops of water were added followed by addition of KCN until the reaction mixture became homogeneous 5 min later, the residue was extracted with CH_2Cl_2. After the usual work-up and flash chromatography (EtOAc/hexance, 1:1), compound **32** was isolated (0.27 g, 54%) as a slightly yellow solid; mp = 101–105 °C; $[\alpha]_D^{32} = +13.3$ (*c* 1.38; $CHCl_3$); IR (ATR): *v* 2977, 2930, 1747, 1698, 1509, 1374, 1249, 1216, 1163, 1072, 1016 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.63 (d, 1H, H-1, $J_{1,2}$ 3.8 Hz), 5.50 (m, 1H, $NHCH_{2(\alpha,\beta)}$), 4.25 (d, 1H, H-2), 4.08 (dd, 1H, H-6a, $J_{6a\text{-}5}$ 6.0 Hz), 3.92 (dt, 1H, H-5, $J_{6b\text{–}5}$ 6.1 Hz), 3.77 (dd, 1H, H-6b, $J_{6a\text{–}6b}$ 8.3 Hz), 3.70 (1H, H-4, $J_{4\text{–}5}$ 8.7 Hz), 3.66 (s, 3H, OCH_3), 3.60 (d, 1H, H-a, $J_{H\text{-}a,H\text{-}b}$ 17.3 Hz), 3.45 (d, 1H, H-b), 3.18 (m, 2H, $CH_{2(\alpha,\beta)}$), 2.18 (s, 1H, NH), 1.49 (s, 3H, CH_3), 1.37 (s, 9H, CH_3), 1.34 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.24 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.3 (C=O), 156.6 (C=O), 112.6 (CH_3CCH_3), 110.1 (CH_3CCH_3), 103.7 (C-1), 83.4 (C-2), 83.1 (C-4), 79.7 (Cq(*t*-Bu)), 73.2 (C-5), 69.2 (C-6), 67.3 (C-3), 52.2 (OCH_3), 45.3 ($CH_{2(gly)}$), 39.7 ($CH_{2(\alpha,\beta)}$), 28.7 ($3 \times CH_3$-(*t*-Bu)), 27.2 (CH_3), 26.7 ($2 \times CH_3$), 25.6 (CH_3); HRMS: calcd for $C_{21}H_{37}N_2O_9$ $[M+H]^+$ 461.2499; found, 461.2480.

4.33. 3-*C*-(Acetamidomethyl)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[(methoxycarbonyl) methyl]amino]-α-D-allofuranose 33

To a solution of compound **4** (0.19 g, 0.53 mmol) and $CoCl_2{\cdot}4H_2O$ (0.14 g, 1.10 mmol) in MeOH (10 mL) were added successively Ac_2O (0.15 mL, 1.66 mmol) and $NaBH_4$ (0.20 g, 5.33 mmol) portionwise. After stirring for 1 h, a few drops of water were added followed by addition of KCN until the reaction mixture became homogeneous. After 5 min, the residue was extracted with CH_2Cl_2. After the usual work-up and flash chromatography (EtOAc/MeOH, 1:1), compound **33** was isolated (0.10 g, 45%) as a slight yellow syrup; $[\alpha]_D^{20} = +47$ (*c* 0.16, $CHCl_3$); IR (ATR): *v* 2981, 2936, 1658, 1544, 1373, 1250, 1167, 1071, 1014 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.93 (m, 1H, $NHCH_{2(\alpha,\beta)}$), 5.65 (d, 1H, H-1, $J_{1,2}$ 3.7 Hz), 4.20 (d, 1H, H-2), 4.11 (dd, 1H, H-6a, $J_{6a,5}$ 6.0 Hz), 3.93 (dt, 1H, H-5, $J_{6b,5}$ 6.0 Hz), 3.84 (dd, 1H, H-6b, $J_{6a,6b}$ 8.4 Hz), 3.70 (d, 1H, H-4, $J_{4,5}$ 9.0 Hz), 3.70 (s, 3H, OCH_3), 3.54 (s, 2H, $CH_{2(gly)}$), 3.43 (dd, 1H, H-α, $J_{H\alpha,NH}$ 6.3 Hz), 3.21 (dd, 1H, H-β, $J_{H\alpha,H\beta}$ 14.2 Hz, $J_{H\beta,NH}$ 3.5 Hz), 2.00 (s, 1H, NH), 1.98 (s, 1H, CH_3) 1.49 (s, 3H, CH_3), 1.51 (s, 9H, CH_3), 1.38 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.27 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.3 (C=O), 171.2 (C=O), 112.8 (CH_3CCH_3), 110.3 (CH_3CCH_3), 103.7 (C-1), 83.5 (C-2), 83.2 (C-4), 73.2 (C-5), 69.4 (C-6), 67.3 (C-3), 52.4 (OCH_3), 45.1 ($CH_{2(gly)}$), 38.4 ($CH_{2(\alpha,\beta)}$), 27.2 (CH_3), 26.8 ($2 \times CH_3$), 25.7 (CH_3), 23.5 (CH_3); HRMS: calcd $[M+Na]^+$ 425.1900; found, 425.1885. Anal. Calcd for $C_{18}H_{30}N_2O_8$ (402.20 g/mol): C, 53.72; H, 7.51; N, 6.96. Found: C, 54.01; H, 7.65; N, 6.79.

4.34. 3-*C*-[[[(Benzyloxy)carbonyl]glycyl]aminomethyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[(methoxycarbonyl)methyl]amino]-α-D-allofuranose 34

To a solution of compound **4** (0.36 g, 1.00 mmol) and $CoCl_2{\cdot}4H_2O$ (0.26 g, 2.00 mmol) in MeOH (10 mL) were added successively $ZNHCH_2COOCOtBu$(0.88 g, 3.00 mmol) and $NaBH_4$ (0.38 g, 10.0 mmol) portionwise. After stirring for 1 h, few drops of water were added followed by addition of KCN until the reaction mixture became homogeneous. After 5 min, the residue was extracted with CH_2Cl_2. After usual work-up and flash chromatography (EtOAc/hexane, 8:2), compound **34** was isolated (0.15 g, 28%) as a slight yellow syrup; $[\alpha]_D^{31} = -1.7$ (*c* 0.92, $CHCl_3$); IR (ATR): *v* 2986, 2940, 1728, 1675, 1525, 1373, 1216, 1165, 1070, 1049 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (m, 7H, 5H phenyl, $2 \times NH$), 5.69 (d, 1H, H-1, $J_{1,2}$ 3.7 Hz), 5.11 (s, 2H, $CH_{2(Z)}$), 4.25 (d, 1H, H-2), 4.11 (dd, 1H, H-6a, $J_{6a,5}$ 6.0 Hz), 3.90 (m, 4H, H-5, H-6b, $CH_{2(gly\text{-}Z)}$), 3.72 (d, 1H, H-4, $J_{4,5}$ 8.9 Hz), 3.69 (s, 3H, OCH_3), 3.54 (d,1H, H-a, $J_{H\text{-}a,H\text{-}b}$ 17.5 Hz), 3.52 (d, 1H, H-b), 3.46 (dd, 1H, H-α, $J_{H\alpha,NH}$ 5.5 Hz), 3.23 (dd, 1H, H-β, $J_{H\alpha,H\beta}$ 14.0 Hz, $J_{H\beta,NH}$ 3.0 Hz), 2.30 (s, 1H, NH), 1.54 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.29 (s, 6H, $2 \times CH_3$); ^{13}C NMR ($CDCl_3$) δ 173.9 (C=O), 169.8 (C=O), 156.9 (C=O), 136.6 (C_{ipso}), 128.9, 128.8, 126.6 (phenyl), 112.9 (CH_3CCH_3), 110.4 (CH_3CCH_3), 103.7 (C-1), 83.4 (C-2, C-4), 73.3 (C-5), 69.3 (C-6), 67.5 ($CH_{2(Z)}$), 67.4 (C-3), 52.4 (OCH_3), 45.2 ($CH_{2(a,b)}$), 44.9 ($CH_{2(gly\text{-}Z)}$), 38.3 ($CH_{2(\alpha,\beta)}$), 27.3 (CH_3), 26.9 (CH_3), 26.8 (CH_3), 25.6 (CH_3); HRMS: calcd $[M+Na]^+$ 574.2377; found, 574.2358. Anal. Calcd for $C_{26}H_{37}N_3O_{10}$ (555.59 g/mol): C, 56.61; H, 6.76; N, 7.62. Found: C, 56.48; H, 6.74; N, 8.02.

4.35. 3-[(Carboxymethyl)amino]-3-*C*-cyano-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose 37

To a solution of compound **4** (1.04 g, 3.04 mmol) in dioxane was added NaOH 1 M (58 mL). After stirring for 40 min at room temperature, the reaction mixture was neutralized with acetic acid. The solvent was removed under vacuo and the residue extracted with $CHCl_3$ and water. The organic layer was separated, dried over Na_2SO_4, and evaporated. After flash chromatography (EtOAc), com-

pound **37** (0.89 g, 89%) was isolated as a white solid: mp = 93–95 °C, $[\alpha]_D^{29} = +26.8$ (*c* 0.47, $CHCl_3$); IR (ATR): *v* 2985, 2930, 1736, 1376, 1235, 1213, 1167, 1078, 1027 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.91 (d, 1H, H-1, $J_{1,2}$ 3.6 Hz), 4.73 (d, 1H, H-2), 4.35 (ddd, 1H, H-5, $J_{5,6b}$ 6.2 Hz), 4.18 (dd, 1H, H-6b, $J_{6a,6b}$ 9.0 Hz), 3.95 (dd, 1H, H-6a, $J_{5,6a}$ 4.1 Hz), 3.85 (d, 1H, H-4, $J_{5,4}$ 9.0 Hz), 3.70 (d, 1H, H-a, $CH_{2(gly)}$, $J_{Ha,Hb}$ 19.3 Hz), 3.62 (d, 1H, H-b), 2.03 (s, 1H, NH), 1.55 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.2 (C=O), 117.3 (CN), 114.7 (CH_3CCH_3), 110.9 (CH_3CCH_3), 104.9 (C-1), 82.8 (C-2), 81.1 (C-4), 75.3 (C-5), 68.4 (C-3), 68.0 (C-6), 46.9 ($CH_{2(gly)}$), 26.7 (2 × CH_3), 26.8 (CH_3), 25.2 (CH_3); HRMS: calcd $[M+Na]^+$ 365.1325; found, 365.1326. Anal. Calcd for $C_{15}H_{22}N_2O_7$ (342.14 g/mol): C, 52.63; H, 6.48; N, 8.18. Found: C, 52.48; H, 6.47; N, 7.99.

4.36. 3-*C*-[[[(Benzyloxy)carbonyl]glycyl]aminomethyl]-3-[(carboxymethyl)amino]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose 38

To a solution of compound **20** (0.68 g, 2.09 mmol) in 20 mL of (dioxane/H_2O, 1:1) was added NaOH (0.25 g, 6.26 mmol). The reaction mixture was heated at 100 °C overnight. After cooling at room temperature, $ZNHCH_2COOPhNO_2$ (1.38 g, 4.17 mmol) was added slowly and stirred for 1 h. After elimination of the solvent, the residue was extracted with EtOAc and a saturated solution of $NaHCO_3$. The aqueous layer was acidified with HCl 1 M until pH 4 then extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4, filtered, and the solvent eliminated under vacuum. After flash chromatography (EtOAc/MeOH/CH_3COOH, 80:19:1), compound **38** (0.45 g, 56%) was isolated as a solid; mp = 104–107 °C, $[\alpha]_D^{20} = +18$ (*c* 0.12, $CHCl_3$); IR (ATR): *v* 2989, 2931, 1728, 1666, 1530, 1382, 1267, 1223, 1166, 1071, 1050 cm^{-1}; ^1H NMR (CD_3OD) δ 7.37 (m, 5H, phenyl), 5.85 (d, 1H, H-1, $J_{1,2}$ 3.5 Hz), 5.12 (s, 2H, $CH_{2(Z)}$), 4.65 (d, 1H, H-2), 4.23 (m, 2H, H-5, H-6a), 3.89 (m, 2H, H-4, H-6b), 3.82 (s, 2H, $CH_{2(gly\text{-}Z)}$), 3.76 (d, 1H, H-a, CH_2COOH, $J_{Ha,Hb}$ 16.5 Hz), 3.70 (d, 1H, H-α, CH_2NH, $J_{Hα,Hβ}$ 14.9 Hz), 3.58 (d, 1H, H-b), 3.55 (d, 1H, H-β), 1.57 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR (CD_3OD) δ 172.6 (C=O), 172.2 (C=O), 158.1 (C=O), 137.0 (C_{ipso}), 128.5, 128.1, 128.0 (phenyl), 113.3 (CH_3CCH_3), 110.6 (CH_3CCH_3), 104.3 (C-1), 82.0 (C-2), 81.8 (C-4), 72.8 (C-5), 68.6 (C-3), 68.4 (C-6), 66.9 ($CH_{2(Z)}$), 46.0 ($CH_{2(a,b)}$), 44.2 ($CH_{2(gly\text{-}Z)}$), 37.2 ($CH_{2(α,β)}$), 25.8 (CH_3), 25.6 (CH_3), 25.4 (CH_3), 24.2 (CH_3); HRMS: calcd $[M+H]^+$ 538.2401; found, 538.2401. Anal. Calcd for $C_{25}H_{35}N_3O_{10}$ (537.23 g/mol): C, 55.86; H, 6.56; N, 7.82. Found: C, 55.99; H, 6.71; N, 7.90.

4.37. 3-*C*-[[[(Benzyloxy)carbonyl]-L-alanyl]aminomethyl]-3-[(carboxymethyl)amino]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose 39

To a solution of compound **20** (1.81 g, 3.60 mmol) in 18 mL of (dioxane/H_2O, 1:2) was added NaOH (0.43 g, 10.81 mmol). The reaction mixture was heated at 100 °C overnight. After cooling at room temperature, $ZNHCH(CH_3)COOPhNO_2$ (1.49 g, 4.32 mmol) was added slowly and stirred for 1 h. After elimination of the solvent, the residue was extracted with EtOAc and a saturated solution of $NaHCO_3$. The aqueous layer was acidified with HCl 1 M until pH 4 then extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4, filtered, and the solvent eliminated under vacuum. After flash chromatography (EtOAc/MeOH/CH_3COOH, 90:9:1), compound **39** (0.97 g, 49%) was isolated as a solid; mp = 108–111 °C, $[\alpha]_D^{20} = +20$ (*c* 0.11, $CHCl_3$); IR (ATR): *v* 2989, 2899, 1722, 1678, 1515, 1383, 1249, 1164, 1073, 1027 cm^{-1}; ^1H RMN ($CDCl_3$) δ 8.84 (s, 1H, NH), 7.33 (m, 5H, Ph), 6.35 (m, 2H, NH), 5.87 (m, 1H, H-1, $J_{1,2}$ 3.1 Hz), 5.11 (d, 1H, H′, $CH_{2(Z)}$, $J_{H',H''}$ 11.9 Hz), 5.02 (d, 1H, H″, $CH_{2(Z)}$), 4.58 (d, 1H, H-2), 4.25 (m, 2H, H-6a, CH), 4.13–3.92 (m, 5H, H-4, H-5, H-6b, H-a, H-α), 3.72 (d, 1H, H-b, CH_2COOH, $J_{Ha,Hb}$ 15.7 Hz), 3.64 (d, 1H, H-β, $J_{Hα,Hβ}$ 12.6 Hz), 1.55 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.34 (s, 6H, CH_3, $CH_{3(ala)}$, J_{CH,CH_3} 7.0 Hz), 1.27 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 175.1 (C=O), 172.5 (C=O), 156.5 (C=O), 136.6 (C_{ipso}), 128.9, 128.6, 128.3 (phenyl), 113.9 (CH_3CCH_3), 110.9 (CH_3CCH_3), 104.2 (C-1), 81.7 (C-2), 81.1 (C-4), 72.6 (C-5), 69.2 (C-6, C-3), 67.2 ($CH_{2(Z)}$), 51.2 (CH), 46.7 ($CH_{2(a,b)}$), 37.7 ($CH_{2(α,β)}$), 26.9 (CH_3), 26.5 (2 × CH_3), 25.3 (CH_3), 18.9 ($CH_{3(ala)}$); MS (ES) $[M+Na]^+$ 574.4, $[M+K]^+$ 590.4.

4.38. 3-*C*-[[[(Benzyloxy)carbonyl]-L-isoleucyl]aminomethyl]-3-[(carboxymethyl)amino]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose 40

To a solution of compound **20** (1.81 g, 3.60 mmol) in 18 mL of (dioxane/H_2O, 1:2) was added NaOH (0.43 g, 10.81 mmol). The reaction mixture was heated at 100 °C overnight. After cooling at room temperature, $ZNHCH(CH_3)COOPhNO_2$ (1.49 g, 4.32 mmol) was added slowly and stirred for 1 h. After elimination of the solvent, the residue was extracted with EtOAc and a saturated solution of $NaHCO_3$. The aqueous layer was acidified with HCl 1 M until pH 4 then extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4, filtered, and the solvent eliminated under vacuum. After flash chromatography (EtOAc/MeOH/CH_3COOH, 90:9:1), compound **40** (0.97 g, 49%) was isolated as a solid; mp = 92–95 °C, $[\alpha]_D^{20} = +27$ (*c* 0.15, $CHCl_3$); IR (ATR): *v* 1716, 1688, 1528, 1379, 1257, 1218, 1165, 1071, 1026 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.74 (s, 1H, $NH_{(CH_{2α,β})}$), 7.33 (m, 5H, Ph), 6.40 (m, 1H, $NH_{(leu)}$), 5.90 (m, 1H, H-1, $J_{1,2}$ 3.1 Hz), 5.68 (d, 1H, NH, $J_{NH,CH}$ 7.0 Hz), 5.08 (d, 1H, H′, $CH_{2(Z)}$, $J_{H',H''}$ 12.4 Hz), 4.98 (d, 1H, H″, $CH_{2(Z)}$), 4.57 (d, 1H, H-2), 4.28 (m, 3H, H-6a, H-6b, CH), 4.00 (m, 4H, H-4, H-5, H-a, H-α), 3.71 (d, 1H, H-b, CH_2COOH, $J_{Ha,Hb}$ 16.2 Hz), 3.38 (d, 1H, H-β, $J_{Hα,Hβ}$ 12.5 Hz), 1.64 (m, 3H, $CH_{2(leu)}$, $CH_{(CH_3)_2}$, J_{CH,CH_3} 6.0 Hz), 1.53 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 0.94 (d, 6H, $CH_{3(leu)}$); ^{13}C NMR ($CDCl_3$) δ 175.0 (C=O), 172.8 (C=O), 156.7 (C=O), 136.6 (C_{ipso}), 128.9, 128.5, 128.3 (phenyl), 113.7 (CH_3CCH_3), 110.8 (CH_3CCH_3), 104.3 (C-1), 81.8 (C-2), 81.3 (C-4), 72.8 (C-5), 69.2 (C-3), 69.1 (C-6), 67.3 ($CH_{2(Z)}$), 54.3 (CH), 46.7 ($CH_{2(a,b)}$), 41.8 ($CH_{2(leu)}$), 38.0 ($CH_{2(α,β)}$), 26.9 (CH_3), 26.5 (2 × CH_3),

25.4 (CH_3), 25.1 (CH), 23.4 ($CH_{3(leu)}$), 22.4 ($CH_{3(leu)}$); HRMS: calcd $[M+Na]^+$ 616.2846; found, 616.2827. Anal. Calcd for $C_{29}H_{43}N_3O_{10}$ (593.29 g/mol): C, 58.67; H, 7.30; N, 7.08. Found: C, 58.54; H, 7.25; N, 7.20.

4.39. 3-*C*-[[[(Benzyloxy)carbonyl]-L-phenylalanyl]aminomethyl]-3-[(carboxymethyl)amino]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose 41

To a solution of compound **20** (0.83 g, 2.52 mmol) in 30 mL of (dioxane/H_2O, 1:1) was added NaOH (0.30 g, 7.56 mmol). The reaction mixture was heated at 100 °C overnight. After cooling at room temperature, ZNH-$CH(CH_2Ph)COOPhNO_2$ (2.12 g, 5.04 mmol) was added slowly and stirred for 1 h. After elimination of the solvent, the residue was extracted with EtOAc and a saturated solution of $NaHCO_3$. The aqueous layer was acidified with HCl 1 M until pH 4 then extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4, filtered, and the solvent eliminated under vacuum. After flash chromatography (EtOAc/MeOH/CH_3COOH, 90:9:1), compound **41** (0.69 g, 44%) was isolated as a solid; mp = 92–93 °C, $[\alpha]_D^{20} = +21$ (*c* 0.12, $CHCl_3$); IR (ATR): *v* 2979, 1720, 1682, 1523, 1383, 1227, 1165, 1073, 1027 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 10H, phenyl), 5.78 (m, 2H, $NH_{(CH_{2\alpha,\beta})}$, H-1, $J_{1,2}$ 3.0 Hz), 5.61 (d, 1H, NH, J_{NHCH} 6.9 Hz), 5.06 (dd, 2H, $CH_{2(Z)}$, $J_{H',H''}$ 6.9 Hz), 4.45 (m, 2H, H-2, CH, $J_{CH,Hc}$ 6.4 Hz, $J_{CH,Hd}$ 7.9 Hz), 4.16 (dd, 1H, H-6a, $J_{6a,5}$ 5.2 Hz), 3.80–4.02 (m, 5H, H-4, H-5, H-a, $NH_{(CH_{2a,b})}$, H-6b, $J_{6a,6b}$ 10.9 Hz), 3.61 (d, 1H, H-b, C*H*$_2$COOH, $J_{Ha,Hb}$ 11.7 Hz), 3.35 (d, 1H, H-α, $J_{H\alpha,H\beta}$ 8.2 Hz), 3.14 (m, 2H, H-β, H-c, $J_{Hc,Hd}$ 13.8 Hz), 3.00 (dd, 1H, H-d), 1.49 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.16 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.2 (C=O), 172.8 (C=O), 156.4 (C=O), 136.7, 136.5 (2 × C_{ipso}), 129.7, 129.0, 128.9, 128.5, 128.3, 127.4 (10C, phenyl), 113.6 (CH_3CCH_3), 110.8 (CH_3CCH_3), 104.2 (C-1), 82.0 (C-2), 81.6 (C-4), 72.8 (C-5), 69.1 (C-6), 68.8 (C-3), 67.3 ($CH_{2(Z)}$), 58.8 (CH), 46.4 ($CH_{2(a,b)}$), 38.6 ($CH_{2(c,d)}$), 38.2 ($CH_{2(\alpha,\beta)}$), 26.9 (CH_3), 26. (2 × CH_3), 25.4 (CH_3); HRMS: calcd $[M+Na]^+$ 650.2690; found, 650.2708. Anal. Calcd for $C_{32}H_{41}N_3O_{10}$ (627.28 g/mol): C, 61.23; H, 6.58; N, 6.69. Found: C, 61.15; H, 6.81; N, 6.74.

4.40. 3-*C*-[[[(Benzyloxy)carbonyl]glycyl]aminomethyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-[[[(1*S*)-(methoxycarbonyl)ethyl]amino]carboxy]methylamino]-α-D-allofuranose 42

To a solution of compound **39** (2.92 g, 5.44 mmol) and L-Ala-OMe (1.52 g, 10.9 mmol) in CH_3CN/DMF (30 mL, 1:1) were added *N*-hydroxysuccinimide (1.25 g, 10.9 mmol) and TEA (1.53 mL, 10.9 mmol). After cooling at −10 °C under argon, DCC (2.25 g, 10.9 mmol) was added and the reaction mixture was stirred at room temperature overnight. After extraction with EtOAc and water, the organic layer was successively washed with a saturated solution of $NaHCO_3$ and water. The organic phase was separated, dried over Na_2SO_4, filtered, and evaporated. After flash chromatography (EtOAc) compound **42** (2.28 g, 67%) was isolated as a slight yellow syrup; $[\alpha]_D^{20} = +7.0$ (*c* 0.10, $CHCl_3$); IR (ATR): *v* 2988, 2901, 1726, 1664, 1525, 1455, 1375, 1217, 1167, 877, 844 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (s, 1H, NH), 7.34 (m, 5H, phenyl), 7.19 (s, 1H, $NH_{CH_{2(\alpha,\beta)}}$), 5.80 (s, 1H, $NH_{CH_{2(c,d)}}$), 5.77 (d, 1H, H-1, $J_{1,2}$ 3.5 Hz), 5.10 (dd, 2H, $CH_{2(Z)}$, $J_{H',H''}$ 12.3 Hz), 4.60 (q, 1H, CH, $J_{CH,NH}$ 7.5 Hz), 4.30 (d, 1H, H-2), 4.15 (dd, 1H, H-6a, $J_{6a,5}$ 5.9 Hz), 3.98–3.88 (m, 4H, H-6b, H-5, $CH_{2(c,d)}$), 3.74 (s, 3H, CH_3), 3.72 (m, 2H, H-4, H-α), 3.60 (d, 1H, H-a, J_{HaHb} 17.4 Hz), 3.45 (d, 1H, H-b), 3.22 (d, 1H, H-β, $J_{H\alpha,H\beta}$ 13.2 Hz, $J_{H\beta,NH}$ 3.2 Hz), 2.35 (s, 1H, $NH_{CH_{2(a,b)}}$), 1.55 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.40 (d, 3H, CH_3, J_{CH,CH_3} 7.5 Hz), 1.35 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.9 (C=O), 172.3 (C=O), 170.4 (C=O), 156.9 (C=O), 136.6 (C_{ipso}), 128.9, 128.6, 128.5 (5C, phenyl), 112.9 (CH_3CCH_3), 110.5 (CH_3CCH_3), 103.8 (C-1), 83.6 (C-2), 83.4 (C-4), 73.2 (C-5), 69.4 (C-6), 68.0 (C-3), 67.5 ($CH_{2(Z)}$), 53.1 (OMe), 47.9 (CH), 46.8 ($CH_{2(a,b)}$), 44.8 ($CH_{2(c,d)}$), 38.1 ($CH_{2(\alpha,\beta)}$), 27.3 (CH_3), 26.9 (CH_3), 26.8 (CH_3), 25.6 (CH_3), 18.5 ($CH_{3(ala)}$); HRMS: calcd $[M+Na]^+$ 645.2748; found, 645.2760. Anal. Calcd for $C_{29}H_{42}N_4O_{11}$ (622.09 g/mol): C, 55.94; H, 6.80; N, 9.00. Found: C, 55.79; H, 6.84; N, 8.93.

4.41. [1*S*,3*R*,4*R*,5*S*,10*S*]-1-[(4*R*)(2,2-Dimethyl-[1,3]dioxolan-4-yl)]-3,4-*O*-isopropylidene-10-methyl-2-oxa-6,9,12,15-tetraaza-spiro[4.11]hexadecane-8,11,14-trione 44

Compound **42** (169 mg, 0.30 mmol) and K_2CO_3 (46 mg, 0.33 mmol) were solubilized in 4 mL of a solution of MeOH/H_2O (9:1) and stirred at room temperature. After neutralization with resin IRA-120 (pH 6), the reaction mixture was filtered and the solvent removed under vacuo. To the crude material solubilized in EtOAc (3.5 mL) and EtOH (2 mL) were added 16 mg of Pd/C (10%) and stirred under hydrogen overnight. After filtration through a Celite pad and removal of the solvent, compound **43** was obtained quantitatively and used in the next step without further purification. To a solution of crude compound **43** (0.81 g, 1.70 mmol) in DMF (438 mL) at 0 °C under argon were introduced TEA (0.48 mL, 3.40 mmol) and DPPA (0.44 mL, 2.00 mmol). After 1 night, the solvent was eliminated and the residue extracted with EtOAc and a saturated solution of NaCl. After separation, the organic layer was dried over Na_2SO_4, filtered, and concentrated. After flash chromatography (EtOAc), compound **44** (0.43 g, 56%) was isolated as a white solid; mp = 143–146 °C, $[\alpha]_D^{20} = -13.0$ (*c* 0.15, $CHCl_3$); IR (ATR): *v* 2987, 1666, 1528, 1374, 1216, 1070, 1013, 842 cm^{-1}; ^1H NMR (DMSO-D_6) δ 7.48 (s, 1H, $NH_{CH_{2(c,d)}}$), 7.20 (d, 1H, $NH_{(ala)}$, $J_{CH,NH}$ 8.9 Hz), 6.39 (d, 1H, $NH_{CH_{2(\alpha,\beta)}}$, $J_{H\alpha,NH}$ 6.7 Hz), 5.67 (d, 1H, H-1, $J_{1,2}$ 3.5 Hz), 4.63 (m, 1H, CH), 4.32 (d, 2H, H-2, H-c, $J_{Hc,Hd}$ 13.8 Hz), 4.09 (m, 1H, H-5, $J_{6a,5}$ 6.4 Hz), 3.94 (dd, 1H, H-6a, $J_{6a,6b}$ 7.9 Hz), 3.83 (dd, 1H, H-6b, $J_{6b,5}$ 5.0 Hz), 3.66 (d, 1H, H-4, $J_{4,5}$ 9.1 Hz), 3.50 (m, 3H, H-a, H-d, H-α), 3.44 (d, 1H, H-b, $J_{Ha,Hb}$ 7.0 Hz), 3.09 (d, 1H, H-β, $J_{H\alpha,H\beta}$ 14.2 Hz), 2.60 (s, large, 1H, $NH_{CH_{2(a,b)}}$), 1.51 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.34 (d, 3H, CH_3, J_{CH,CH_3} 7.8 Hz), 1.32 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}C RMN (DMSO-d_6) δ 175.9 (C=O), 172.8 (C=O), 170.9 (C=O), 113.1 (CH_3CCH_3), 110.3 (CH_3CCH_3), 104.0 (C-1), 84.3 (C-4), 82.7 (C-2), 73.0 (C-5), 69.3 (C-6), 67.2 (C-3), 49.9 (CH), 47.4 ($CH_{2(a,b)}$), 44.7 ($CH_{2(c,d)}$), 39.8 ($CH_{2(\alpha,\beta)}$), 27.3 (CH_3), 27.0 (CH_3), 26.7

(CH_3), 25.5 (CH_3), 14.9 ($CH_{3(ala)}$); HRMS: calcd $[M+Na]^+$ 479.2118; found, 479.2130. Anal. Calcd for $C_{20}H_{32}N_4O_8$ (456.22 g/mol): C, 52.62; H, 7.07; N, 12.27. Found: C, 52.55; H, 7.07; N, 11.98.

4.42. 3-*C*-[[[(Benzyloxy)carbonyl]glycyl]aminomethyl]-3-[(carboxymethyl)amino]-3-deoxy-D-allopyranose 45

Compound **38** (0.51 g, 9.55 mmol) was solubilized in 6 mL of a solution of TFA/H_2O (9:1) and stirred at room temperature. After one night, the solvent was removed under reduced pressure, and the residue was co-evaporated successively with MeOH and toluene. Crystallization in diethyl ether gave after filtration compound **45** (0.44 g, 100%) as a white solid; mp = 200–203 °C; IR (ATR): *v* 1725, 1660, 1530, 1296, 1232, 1166 cm^{-1}; **45α**: ^{13}C NMR (DMSO-d_6) δ 172.2 (C=O), 168.4 (C=O), 157.4 (C=O), 137.7 (C*q*), 129.2–127.3 (phenyl), 92.7 (C-1), 68.8 (C-2), 67.6 (C-4), 66.5 (CH_2(*Z*)), 65.9 (C-5), 65.3 (C-3), 61.7 (C-6), 44.6 ($CH_{2(a,b)}$), 41.2 ($CH_{2(c,d)}$), 37.9 ($CH_{2(\alpha,\beta)}$). **45β**: ^{13}C NMR (DMSO-d_6) δ 172.2 (C=O), 170.7 (C=O), 157.4 (C=O), 137.7 (C*q*), 129.2–127.3 (phenyl), 92.7 (C-1), 69.0 (C-2), 67.9 (C-4), 66.5 (CH_2(*Z*)), 66.2 (C-5), 65.5 (C-3), 61.7 (C-6), 45.5 ($CH_{2(a,b)}$), 41.2 ($CH_{2(c,d)}$), 38.4 ($CH_{2(\alpha,\beta)}$); MS (ES) [M−H] −456,4. Anal. Calcd for $C_{19}H_{27}N_3O_{10}$ (457.17 g/mol): C, 49.89; H, 5.95; N, 9.19. Found: C, 49.71; H, 5.88; N, 8.99.

4.43. 3-*C*-[[[(Benzyloxy)carbonyl]glycyl]aminomethyl]-3-deoxy-3-[[[1-(methoxycarbonyl)ethyl]amino]carboxymethyl]amino]-α-D-allopyranose 46

Compound **42** (0.40 g, 6.43 mmol) was solubilized in 10 mL of a solution of TFA/H_2O (9:1) and stirred at room temperature. After one night, the solvent was removed under reduced pressure, and the residue was co-evaporated successively with MeOH and toluene. Crystallization in diethyl ether led after filtration to compound **46** (0.32 g, 92%) as a white solid; mp = 102–104 °C, $[\alpha]_D^{20} = +21$ (*c* 0.10, H_2O); IR (ATR): *v* 3391, 3207, 1672, 1540, 1454, 1201, 1138, 1052 cm^{-1}; ^1H NMR (D_2O) δ 7.32 (m, 5H, Ph), 5.18 (d, 1H, H-1, $J_{1,2}$ 2.2 Hz), 5.03 (s, 2H, CH_2(*Z*)), 4.36 (q, 1H, CH, J_{CH,CH_3} 7.3 Hz), 4.15 (m, 2H, $CH_{2(a,b)}$), 3.90 (d, 1H, H-2), 3.75 (m, 4H,$CH_{2(c,d)}$, $CH_{2(\alpha,\beta)}$), 3.70 (m, 4H, 2 × H-6, H-5, H-4), 3.64 (s, 3H, OCH_3), 1.31 (d, 3H, $CH_{3(ala)}$); ^{13}C NMR (D_2O) δ 174.9 (C=O), 173.4 (C=O), 166.8 (C=O), 158.4 (C=O), 136.9 (C_{ipso}), 129.1, 128.8, 128.1 (phenyl), 92.1 (C-1), 67.7 ($CH_{2(Z)}$), 67.6 (C-2), 66.6 (C-4), 66.1 (C-3), 64.8 (C-5), 60.8 (C-6), 53.4 (OMe), 49.4 (CH), 45.1 ($CH_{2(a,b)}$), 44.1 ($CH_{2(c,d)}$), 37.6 ($CH_{2(\alpha,\beta)}$), 16.3 ($CH_{3(ala)}$); HRMS: calcd $[M+H]^+$ 543.2302; found, 543.228. Anal. Calcd for $C_{23}H_{34}N_4O_{11}$ (542.22 g/mol): C, 50.92; H, 6.32; N, 10.33. Found: C, 50.89; H, 6.15; N, 10.21.

4.44. 3-Deoxy-3-[[[[1-(carboxy)ethyl]amino]carboxymethyl]amino]-3-*C*-[[[glycyl]amino]methyl]-α-D-allopyranose. Trifluoroactetate 47

Compound **42** (169 mg, 0.30 mmol) and K_2CO_3 (46 mg, 0.33 mmol) were solubilized in 4 mL of a solution of MeOH/H_2O (9:1) and stirred at room temperature. After neutralization with resin IRA-120 (pH 6), the reaction mixture was filtered and the solvent removed under vacuo. To the crude material solubilized in EtOAc (3.5 mL) and EtOH (2 mL) were added 16 mg of Pd/C (10%) and stirred under hydrogen overnight. After filtration through a Celite pad and removal of the solvent, compound **44** was obtained quantitatively and used in the next step without further purification. The crude compound **44** (0.40 g, 1.26 mmol) was solubilized in 6 mL of a solution of TFA/H_2O (9:1) and stirred at room temperature. After one night, the solvent was removed under reduced pressure. The residue was co-evaporated successively with MeOH and toluene. Crystallization in diethyl ether gave after filtration compound **47** (0.59 g, 92%) as a white solid; mp = 100–103 °C, $[\alpha]_D^{20} = +29$ (*c* 0.25; H_2O); IR (ATR): *v* 3394, 1670, 1556, 1434, 1198, 1135, 839, 800, 723 cm^{-1}; ^1H NMR (D_2O) δ 5.05 (d, 1H, H-1, $J_{1,2}$ 2.3 Hz), 4.36 (q, 1H, CH_{ala}, J_{CH,CH_3} 7.2Hz), 4.05 (d, 1H, H-a, $CH_{2(a,b)}$, $J_{Ha,Hb}$ 15.7 Hz), 3.99 (d, 1H, H-b), 3.90 (d, 1H, H-2), 3.73 (d, 1H, H-α, $CH_{2(\alpha,\beta)}$, $J_{H\alpha,H\beta}$ 8.9 Hz), 3.62–3.50 (m, 6H, H-4, H-5, H-β, H-6a, $CH_{2(c,d)}$), 3.46 (m, 1H, H-6b, $J_{6a,6b}$ 8.5Hz), 1.16 (d, 3H, $CH_{3(ala)}$); ^{13}C NMR (D_2O) δ 176.0 (C=O), 168.7 (C=O), 166.6 (C=O), 163.3, 162.8, 162.4, 161.9 (CF_3COO^-), 122.1, 118.2, 114.4, 110.5 (CF_3COO^-), 92.0 (C-1), 67.6 (C-2), 66.0 (C-4, C-3), 64.3 (C-5), 60.6 (C-6), 49.2 (CH), 44.9 ($CH_{2(a,b)}$), 40.7 ($CH_{2(c,d)}$), 37.0 ($CH_{2(\alpha,\beta)}$), 16.2 ($CH_{3(ala)}$); HRMS: calcd for $C_{14}H_{27}N_4O_9$ $[M+H]^+$ 395.1778; found, 395.1768.

4.45. [(1*R*,2*R*,4*S*,5*S*,11*S*)]-1,2,5-Trihydroxy-4-hydroxymethyl-11-methyl-3-oxa-7,10,13,16-tetraaza-spiro[5.11]heptadecane-9,12,15-trione 48

Compound **44** (0.118 g, 0.26 mmol) was solubilized in 2 mL of a solution of TFA/H_2O (9:1) and stirred at room temperature. After 48 h, the solvent was removed under reduced pressure. The residue was co-evaporated successively with MeOH and toluene. Crystallization in diethyl ether led after filtration to compound **48** (92 mg, 94%) as a white solid; mp = 204–207 °C, $[\alpha]_D^{20} = +76$ (*c* 0.10, H_2O); IR (ATR): *v* 3391, 3207, 1670, 1540, 1290, 1138 cm^{-1}; ^1H NMR (D_2O) δ 5.27 (d, 1H, H-1, $J_{1,2}$ 2.3 Hz), 4.90 (q, 1H, CH_{ala}, J_{CH,CH_3} 6.3 Hz), 4.05 (d, 1H, H-a, $CH_{2(a,b)}$, $J_{Ha,Hb}$ 16.8 Hz), 3.92 (m, 2H, H-2, H-4, $J_{4,5}$ 9.9 Hz), 3.78 (m, 4H, $CH_{2(c,d)}$, H-6a, H-6b), 3.69 (d, H-b, $CH_{2(a,b)}$), 3.64 (m, 1H, H-5), 3.10 (d, 1H, H-α, $J_{\alpha,\beta}$ 15.6 Hz), 3.01 (d, 1H, H-β), 1.13 (d, 3H, $CH_{3(ala)}$); ^{13}C NMR (D_2O) δ 175.3 (C=O), 172.0 (C=O), 165.9 (C=O), 91.9 (C-1), 69.5 (C-2), 68.2 (C-4), 66.9 (C-3), 65.9 (C-5), 60.4 (C-6), 45.9 (CH), 44.9 ($CH_{2(a,b)}$), 44.2 ($CH_{2(c,d)}$), 41.2 ($CH_{2(\alpha,\beta)}$), 157 ($CH_{3(ala)}$); MS (ES) $[M+Na]^+$ 399.4, $[M+K]^+$ 415.3.

Acknowledgments

H.D. thanks the Conseil Régional de Picardie for a fellowship. D.P. thanks the Conseil Régional de Picardie, the CNRS and the Ministère de la Recherche for financial support.

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