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DE NOVO SYNTHETIC ROUTE TO A COMBINATORIAL LIBRARY OF PEPTIDYL NUCLEOSIDES

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□ *A stereoselective synthetic route has been developed for the combinatorial synthesis of a structurally unique class of C-4′ side chain modified peptide-linked nucleosides. The synthetic strategy and approach involves initial synthesis of a strategically functionalized amino butenolide template, utilizing L-serine as a chiral starting material. Subsequent transformation of the above lactone to C4′ aminoalkyl substituted nucleosides, followed by the peptidic coupling of the C4′ side chain amine with various amino acids completed the syntheses of the target peptidyl nucleosides. Employing the above route, and utilizing a combination of easily available nucleobases (4) and amino acids (6) as the two diversity elements, synthesis of a 24-member combinatorial library of the title peptide-linked nucleosides has been accomplished.*

Keywords Peptide-nucleoside hybrid; C4′-homologation; combinatorial synthesis; L-serine; chiral aminobutenolide

INTRODUCTION

The design and synthesis of biomimetic molecular entities is an integral part of contemporary drug discovery endeavors. In this context, construction of multifunctional scaffolds, grafting various biologically relevant structural units on a common framework, is a highly attractive strategy for the development of new chemical entities of potential biomedical application.[1] Amino acids and nucleosides are among the most common and fundamental building blocks of a vast array of natural macromolecules. Therefore, creation of designer molecules via a judicious combination of the above building blocks provides an opportunity to access new and diverse classes of 'nature-like' and yet non-natural organic compounds.[2] Along the

above lines, and as part of an ongoing program[3] investigating the complex peptidyl nucleoside families of antifungal antibiotics,[4] we recently initiated studies exploring the combinatorial synthesis of a new class of structurally unique amino acid-nucleoside hybrids. Details of the synthesis leading to a 24-member library of peptide-linked nucleosides are reported herein.

In recent times, structurally modified nucleoside building blocks and oligonucleotides thereof have gained much attention by virtue of their significant biological profiles, including their use in antisense, antiviral, and anticancer therapies.[5] This awareness of the potential therapeutic utility of nucleoside analogs has stimulated an intensive effort in the search for newer generations of structurally modified analogs, designed to improve their potency and circumvent the various physical and biological limitations.[6] Not surprisingly therefore, synthesis of various nucleoside combinatorial libraries continues to be an active area of research.[7,8] However, almost all of the nucleoside library construction efforts reported so far are directed at generating libraries by derivatization of the nucleobase component of preformed nucleosides. Moreover, the usual approaches in these library syntheses endeavors employed readily available carbohydrate precursors to access the central nucleoside scaffold, thereby limiting the opportunities towards sugar core modification. The above carbohydrate approach in nucleoside core construction has considerable merit when it can be applied in an efficient manner, however, when the desired end product incorporates unusual residues or nonnatural stereochemistry, the relative inflexibility of the carbohydrate scaffold toward core modifications and the multiple hydroxyl groups as present in the starting material, often necessitates lengthy reaction sequence and extensive protection-deprotection protocols. To circumvent the disadvantages inherent in the carbohydrate approach, an alternative reaction strategy, involving stereoselective de novo construction of the nucleoside core of the desired targets, starting from a more simple non-carbohydrate synthon, is an attractive proposition.[9] Accordingly, employing an amino acid chiral pool approach, we devised a strategy involving utilization of easily available L-serine towards initial construction of a pivotal alkylamino substituted chiral butenolide **1** (Figure 1), its subsequent conversion to a C4′ homologated and alkylamino substituted enantiopure nucleoside **2**, followed by peptidic coupling of the strategic side chain amine functionality with various amino acids to form the desired peptidyl nucleoside scaffold **3**.

RESULTS AND DISCUSSION

Following a recently developed protocol from our laboratory,[3b,10] readily available L-serine was converted to the corresponding multifunctional aminobutenolide **1** (Scheme 1) in 42% overall yield. As evident from its
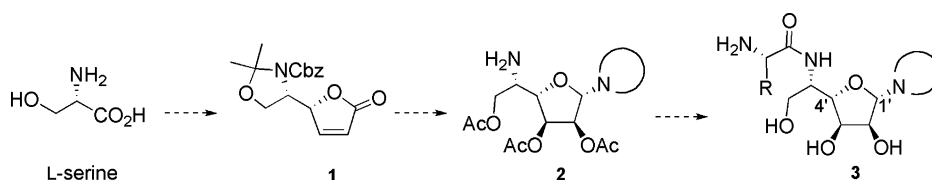
FIGURE 1 Strategy for combinatorial synthesis of a C4'-homologated peptidyl nucleoside library.

structure, the strategically functionalized lactone **1** already incorporates the desired dual modifications at C4' (nucleoside numbering), amine substitution and homologation of the side chain. Furthermore, the ring olefinic bond is an ideal precursor for its eventual conversion to a *vic*-diol functionality. Additionally, the enone moiety of **1** also provides an easy handle for potential structural modifications (epoxidation, nucleophilic/electrophilic addition, deoxygenation, halogenation, hydrogenation, etc.) at these sites. Similarly, the lactone carbonyl is well suited for the desired introduction of nucleobases. Importantly, the chirality of the starting amino acid (L- or D-) can be easily utilized towards stereoselective formation of various possible stereoisomers of the lactone **1**. The resident chirality of **1** in turn will dictate the induction and control of asymmetry in the subsequent reactions (vide infra), thereby providing selective access to various stereoisomeric end products.

In conformity with our earlier developed protocol, potassium osmate catalyzed stereoselective dihydroxylation of **1** resulted in the corresponding diol **4** (Scheme 1) as the only product.[3b] Subsequent partial reduction of the lactone, followed by treatment of the resulting lactol with an excess of acetic anhydride provided the triacetate derivative **5** in good overall yield. The desired nucleobase introduction was performed by reacting **5** with bis-silylated thymine in the presence of TMSOTf (Vorbrüggen protocol),[11] resulting in a highly regio- (N-1 selective), and stereoselective formation of the nucleoside derivative **6a**. The observed stereoselectivity[3b] in the nucleobase incorporation can be attributed to the neighboring C2-acetoxy group-assisted stabilization of the oxonium ion intermediate, resulting in blocking of the *β*-face and consequent approach of the nucleobase exclusively from the *α*-face. Interestingly, the acidic reaction condition employed also led to clean cleavage of the side chain *N*,*O*-acetonide protection. To achieve diversification, the nucleoside forming reaction was then extended to synthesize the corresponding uridine, 5-fluorouridine, and cytidine analogs. Accordingly, condensation of **5** with the respective bis-silylated nucleobases[11] resulted in the expected nucleoside derivatives in respectable yields. In order to facilitate purification, without isolation, the free primary hydroxyl containing nucleosides as obtained from the above reaction were directly subjected to acetylation under standard conditions to result in the corresponding fully protected nucleoside derivatives **7a–d**.
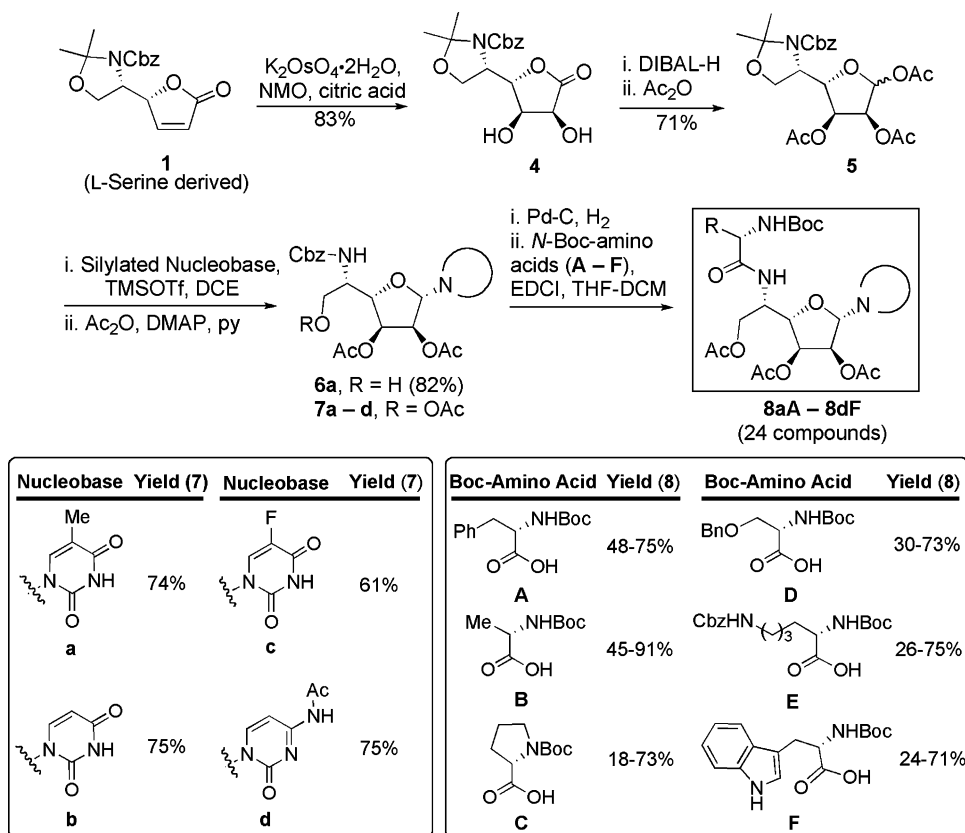
SCHEME 1 Synthesis of peptidyl nucleoside library.

The final steps toward library construction involved hydrogenolytic unmasking of the side chain amine functionality of the above nucleosides, followed by standard peptidic coupling of the resulting free amine with a variety of suitably protected amino acids. Employing the above sequence of reactions, the combination of the four nucleosides **7a–d** with six different amino acids (A–F) resulted in the construction of the 24-member library of peptidyl nucleosides **8aA–8dF** (Scheme 1). It is worth mentioning that, in the final library-forming step (**7** to **8**), the two step yields as reported are not the optimized yields, resulting in the rather large variation (18–91%) in the product yields.

To demonstrate the feasibility of removal of the protecting groups, two representative peptidyl nucleosides **8aB** and **8bC** (Scheme 2) also were subjected to global deprotection. Thus, following a sequence of initial alkaline hydrolysis of the acetate groups and subsequent acidic cleavage of the t-butylcarbamate under standard conditions afforded the fully deprotected nucleoside derivatives **9** and **10,** respectively, in high overall yields
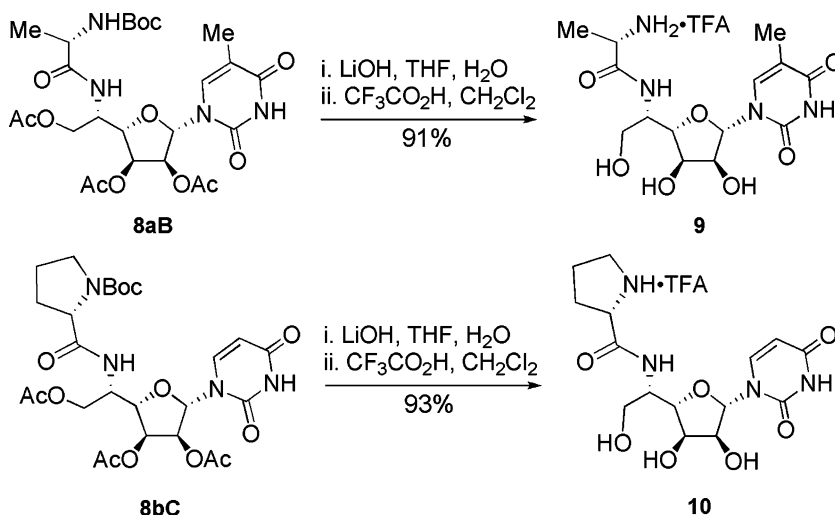
SCHEME 2 Removal of protecting groups.

(Scheme 2). The above library members are presently being evaluated against various biological screens.

CONCLUSION

In conclusion, starting from an L-serine derived chiral aminobutenolide intermediate, *de novo* synthetic route to a unique class of C4′ homologated aminoalkyl nucleoside has been developed. Subsequent anchoring of various amino acids on the side chain amine functionality of the nucleosides resulted in a structurally novel nucleoside-peptide hybrid. Utilizing readily available nucleobases (4) and amino acids (6) as the two diversity elements, the above method was successfully employed to construct a 24-member training library of peptidyl nucleosides. In addition to allowing easy access to a novel structural scaffold of potential biological significance, the other advantages of the present synthesis are expected to be the inherent flexibility of the method towards extensive structural modifications, stereocontrolled reactions, and the presence of multiple functional sites for further derivatization/library construction.

EXPERIMENTAL SECTION

All of the solvents and reagents used were obtained commercially and used as such unless noted otherwise. Moisture or air sensitive reactions were conducted under argon atmosphere in oven dried (120°C) glass apparatus. Diethyl ether and THF were distilled from sodium benzophenone ketyl, while dichloromethane was distilled over calcium hydride, prior to use.

Solvents were removed under reduced pressure using standard rotary evaporators. Flash column chromatography was carried out using Silica gel 60 (230–400 mesh), while thin layer chromatography (TLC) was carried out on Silica Gel HLF, precoated glass plates. All yields reported refer to isolated material judged to be homogeneous by TLC and NMR spectroscopy. Proton and carbon nuclear magnetic resonance spectra were recorded using a Bruker DRX 400 MHz or Bruker DRX 500 MHz spectrometer (Bruker Biospin Corp., Billerica, MA, USA). Unless noted otherwise, NMR spectra were recorded with the chemical shifts (δ) reported in ppm relative to Me_4Si (for ^1H) and $CDCl_3$ (for ^{13}C) as internal standards respectively. Mass spectra were obtained from a ZAB HS mass spectrometer (VG Analytical Ltd., Manchester, UK) equipped with a 11/250 data system. Fast-atom bombardment mass spectrometry (FAB-MS) experiments were performed with a Xenon gun operated at 8 Kev energy and 0.8 mA emission at the MS laboratory at the University of Kansas. Fast-atom bombardment high resolution mass spectra (FAB-HRMS) were recorded at 1:10,000 resolution using linear voltage scans under data system control and collected in a multi-channel analyzer mode (MCA). A Shimadzu FTIR-8400S spectrophotometer was used to record infrared spectra (Shimadzu Scientific Instruments, Columbia, MD, USA).

Starting from L-serine, the lactone **1**, diol **4**, and the triacetate derivative **5** were prepared following an earlier reported procedure from our laboratory.[3b] The spectral and analytical data of all of the above compounds were in good agreement with those reported for the corresponding enantiomeric products reported previously.[3b]

(2*S*,3*S*,4*S*,5*R*)-2-((*S*)-1-(Benzyloxycarbonylamino)-2-hydroxyethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl diethanoate (6a). To a solution of the triacetate $5^{[3b]}$ (1 g, 2.09 mmol) in anhydrous $(CH_2Cl)_2$ (25 mL) was added bis(trimethylsilyl)thymine (1.41 g, 5.21 mmol; 2.5 equiv), followed by freshly distilled TMSOTf (1.9 mL, 10.43 mmol; 5 equiv). After stirring at room temperature for 2 hours, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extract was washed with brine (10 mL), dried over Na_2SO_4, concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc: hexanes = 3/2 to 4/1) to yield pure **6a** (842 mg, 80%) as a foamy semisolid: $[\alpha]_D^{25} -4.0$ (*c* 1, $CHCl_3$); IR (neat) broad 3306, 1751, 1747, 1693 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.46–7.33 (m, 5H), 7.08 (s, 1H), 5.79 (d, $J = 5.5$ Hz, 1H), 5.63 (br s, 1H), 5.51–5.48 (m, 1H), 5.37–5.34 (m, 1H), 5.14–5.13 (m, 2H), 4.39–4.31 (m, 1H), 4.22–4.05 (m, 1H), 4.0–3.92 (m, 1H), 3.78–3.70 (m, 1H), 2.65 (br s, 1H, exchangeable with D_2O), 2.09 (s, 6H), 1.90 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.5, 170.3, 164.2, 157.1, 151.2, 137.1, 136.6, 128.9, 128.6, 128.5, 112.3, 89.4, 81.9, 72.9, 71.2, 67.5, 61.8, 53.9, 20.9,

20.8, 12.8; HRMS calcd. for $C_{23}H_{28}N_3O_{10}$ m/z (M+H) 506.1775, found 506.1764.

General procedure for the synthesis of the nucleoside triacetates 7a-d. Following the same procedure as in **6a** above, the triacetate **5** was separately reacted with the corresponding bis-silylated nucleobases derived from uracil, 5-fluorouracil, and N^4-acetylcytosine, respectively. After standard workup of the reaction mixture as above, the crude nucleoside adducts obtained were subjected to acetylation without any further purification.

After dissolving the above nucleoside adducts (**6a-d**) in anhydrous CH_2Cl_2 (100 mg/mL), the solution was cooled to 0°C (ice-bath), followed by sequential addition of pyridine (4 equiv), 4-DMAP (10 mol%), and acetic anhydride (2 equiv). The cooling bath was removed and stirring continued at room temperature for 1 hour. The reaction was quenched by the addition of a saturated solution of aqueous $NaHCO_3$. After stirring for 15 minutes, the organic layer was separated and the aqueous layer extracted with $CHCl_3$ (3 times). The combined extract was dried over anhydrous Na_2SO_4, concentrated under vacuum, and the crude product purified by flash chromatography (EtOAc: hexanes = 1/1 to 2/1) to provide the acetylated nucleoside derivatives **7a-d**.

(2S,3S,4S,5R)-2-((S)-1-(Benzyloxycarbonylamino)-2-(ethanoyloxy)ethyl) -5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4- diyl diethanoate (7a): Purified by column chromatography (hexane/ethyl acetate: 1/2) to obtain the product as a white solid (183 mg, 74%). ^{1}HNMR (400 MHz, $CDCl_3$): δ 9.12 (s, 1H), 7.35–7.33 (m, 5H), 7.05 (s, 1H), 5.89 (s, 1H), 5.52–5.38 (m, 3H), 5.15–5.08 (m, 2H), 4.27 (m, 3H), 4.12–4.10 (m, 1H), 2.07 (s, 3H), 2.06(s, 3H), 2.04 (s, 3H), 1.91 (s 3H). ^{13}CNMR (100.6 MHz, $CDCl_3$): δ 170.6, 169.6, 169.5, 163.4, 156.2, 150.4, 135.9, 135.7, 128.6, 128.3, 128.2, 112.1, 88.1, 80.7, 72.1, 70.7, 67.3, 62.9, 51.4, 20.7, 20.4, 12.5. HRMS (ES+) found 548.1875 (M+H) (calc for $C_{25}H_{30}N_3O_{11}$: 548.1880).

(2S,3S,4S,5R)-2-((S)-1-(Benzyloxycarbonylamino)-2-(ethanoyloxy)ethyl) -5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyldieth anoate (7b). Purified by column chromatography (hexane/ethyl acetate: 1/1 to 1/2) to obtain the product as a white solid (210 mg, 75%). ^{1}HNMR (400 MHz, $CDCl_3$): δ 9.00 (brs, 1H), 7.35–7.31 (m, 5H), 7.24–7.21 (m, 1H), 5.84 (s, 1H), 5.73 (d, $J = 7.6$ Hz, 1H), 5.52–5.49 (m, 1H), 5.42–5.38 (m, 2H), 5.11 (s, 2H), 4.24 (s, 3H), 4.14–4.11 (m, 1H), 2.08, 2.06, 2.05 (3s, 9H). ^{13}CNMR (125.8 MHz, $CDCl_3$): δ 170.6, 169.6, 169.5, 162.5, 156.1, 150.1, 140.2, 136.0, 128.6, 128.4, 128.2, 103.5, 88.7, 80.9, 72.2, 70.7, 67.3, 62.9, 51.3, 34.6, 34.5, 31.6, 29.0, 25.3, 22.6, 20.7, 20.4, 14.1, 11.4. HRMS (ES+) found 534.1725 (M+H) (calc for $C_{24}H_{28}N_3O_{11}$: 534.1724).

(2S,3S,4S,5R)-2-((S)-1-(Benzyloxycarbonylamino)-2-(ethanoyloxy)ethyl) -5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4- diyl diethanoate (7c). Purified by column chromatography (hexane/ethyl

acetate: 1/1 to 1/2) to obtain the product as a white solid (161 mg, 61%).
^{1}HNMR (500 MHz, CDCl$_3$): δ 8.82 (brs, 1H), 7.40–7.31 (m, 6H), 5.87 (brs, 1H), 5.50–5.48 (m, 1H), 5.37–5.34 (m, 2H), 5.16–5.10 (m, 2H), 4.28–4.23 (m, 3H), 4.14–4.11 (m, 1H), 2.08–2.06 (3s, 9H). ^{13}CNMR (125.8 MHz, CDCl$_3$): δ 170.6, 169.7, 169.5, 156.4, 156.2, 156.1, 148.7, 141.8, 139.9, 135.8, 128.6, 128.4, 128.3, 124.5, 124.2, 88.2, 81.2, 72.1, 70.5, 67.5, 62.9, 51.3, 29.7, 21.1, 20.7, 20.4. HRMS (ES+) found 574.1447 (M+Na) (calc for C$_{24}$H$_{26}$FN$_3$O$_{11}$Na: 574.1449).

**(2S,3S,4S,5R)-2-((S)-1-(Benzyloxycarbonylamino)-2-(ethanoyloxy)ethyl)
-5-(4-ethanamido-2-oxopyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl
diethanoate (7d).** Purified by column chromatography (methylene chloride/methanol: 98/2 to 96/4) to obtain the product as a white solid (174 mg, 75%). ^{1}HNMR (500 MHz, CDCl$_3$): δ 9.78 (brs, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 7.0 Hz, 1H), 7.34–7.28 (m, 5H), 5.91 (d, J = 5.0 Hz, 1H), 5.60–5.55 (m, 2H), 5.50 (bs, 1H), 5.10 (s, 2H), 4.29–4.22 (m, 4H), 2.24 (s, 3H), 2.05–2.02 (m, 9H). ^{13}CNMR (125.8 MHz, CDCl$_3$): δ 170.9, 170.7, 169.5, 169.4, 163.2, 156.2, 154.9, 145.1, 136.2, 128.5, 128.2, 128.1, 97.4, 90.6, 81.0, 73.2, 70.9, 67.2, 62.9, 60.3, 51.4, 34.6, 34.5, 32.5, 29.7, 29.0, 25.3, 24.9, 22.6, 20.7, 20.4, 20.3, 14.2, 14.1, 11.4. HRMS (ES+) found 575.2009 (M+H) (calc for C$_{26}$H$_{31}$N$_4$O$_{11}$: 575.1989).

General procedure for the synthesis of the peptidyl nucleosides 8aA-8dF. *Step 1* (Cbz-deprotection): Each of the side chain *N*-Cbz protected nucleoside derivatives **7a-d**, dissolved separately in ethyl acetate (100 mg/mL) were treated with 10% palladium on activated carbon (wt. of nucleoside/wt. of Pd-C = 1/0.1), and the resulting mixture stirred at room temperature under H$_2$ atmosphere (balloon). After stirring for 2–3 hours (monitored by TLC), the reaction mixtures were filtered through Celite and the residue washed thoroughly with ethyl acetate (3×) and methanol (3×). Removal of solvent under vacuum and drying of the resulting oily residue under high vacuum provided the corresponding free amino derivatives. The crude amines thus obtained were used directly for the peptidic coupling reaction without any further purification.

Step 2 (Peptidic coupling): Each of the the aminoalkyl nucleoside derivatives as obtained above, were divided into six equal portions, dissolved in a mixture of anhydrous THF/CH$_2$Cl$_2$ (1:1, 10% solution by wt.), followed by sequential addition of the different *N*-Boc amino acids A–F (1.5 equiv) and EDCI (2 equiv) into the six different reaction flasks. The resulting mixtures were stirred at room temperature overnight and then quenched by the addition of water. After separating each of the organic layers, the aqueous layers were extracted with ethyl acetate (3x), combined extract dried over anhydrous Na$_2$SO$_4$ and the solvent concentrated under vacuum. Purification of the crude residues by flash chromatography (EtOAc:

hexanes $= 1/1$ to $2/1$) provided the pure peptidyl nucleoside derivatives **8aA-8dF** (24 compounds).

(2S,3S,4S,5R)-2-((6S,9S)-6-Benzyl-2,2-dimethyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diethanoate (8aA). Purified by column chromatography (hexane/ethyl acetate: $1/1$ to $1/2$) to obtain the product as a white solid (81 mg, 75%). ^{1}HNMR (400 MHz, CDCl$_3$, mixture of rotamers): δ 9.43 (s, 1H), 7.29–7.22 (m, 5H), 7.11 (d, $J = 16.8$ Hz, 1H), 6.88 & 6.62 (2brs, 1H), 5.90 (brs, 1H), 5.38–5.12 (m, 3H), 4.50–4.35 (m, 2H), 4.30–3.90 (m, 3H), 3.20–3.00 (m, 2H), 2.11–2.03 (m, 9H), 1.96 (s, 3H), 1.39 (s, 9H). ^{13}CNMR (100.6 MHz, CDCl$_3$, mixture of rotamers): δ 171.9, 170.6, 169.7, 169.5, 163.5, 155.3, 150.5, 136.5, 135.7, 129.3, 128.5, 126.8, 112.2, 87.9, 80.4, 71.7, 70.8, 70.6, 62.5, 55.8, 49.1, 38.6, 29.6, 28.1, 20.7, 20.5, 20.4, 12.4. HRMS (ES+) found 661.2729 (M+H) (calc for C$_{31}$H$_{41}$N$_4$O$_{12}$: 661.2721).

(2R,3S,4S,5S)-2-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-5-((6S,9S)-2,2,6-tri-methyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)tetrahydrofuran-3,4-diyldiethanoate (8aB). Purified by column chromatography (hexane/ethyl acetate: $1/2$ to $1/4$) to obtain the product a white solid (90 mg, 81%). ^{1}HNMR (400 MHz, CDCl$_3$, mixture of rotamers): δ 9.13 (brd, $J = 15.2$ Hz, 1 H), 7.11 (d, $J = 16.8$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 1H), 5.93 (brs, 1H), 5.90 (d, $J = 6$ Hz, 1H), 5.44–5.41 (m, 1H), 5.37 (dd, $J = 12, 6$ Hz, 1H), 4.48 (brs, 1H), 4.25–4.10 (m, 4H), 2.11 (s, 3H), 2.06 (s, 3H, s, 3H), 1.94 (s, 3H), 1.43 (d, $J = 2.4$ Hz, 9H), 1.35 (dd, $J = 6.8, 3.2$ Hz, 3H). ^{13}CNMR (125.8 MHz, CDCl$_3$, mixture of rotamers): δ 173.3, 170.7, 169.6, 163.2, 155.8, 150.4, 135.8, 112.2, 87.7, 81.2, 80.8, 71.8, 70.7, 70.5, 62.5, 50.2, 49.4, 29.7, 28.3, 20.7, 20.6, 20.4, 12.4. HRMS (ES+) found 585.2416 (M+H) (calc for C$_{25}$H$_{37}$N$_4$O$_{12}$: 585.2408).

(2S,3S,4S,5R)-2-((S)-1-((S)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carbox-amido)-2-(ethanoyl-oxy)ethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diethanoate (8aC). Purified by column chromatography (hexane/ethyl acetate: $1/4$) to obtain the product as a white solid (76 mg, 73%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 9.34 (brs, 1H), 7.15 (s, 1H), 6.03 (d, $J = 7$ Hz, 1H), 5.39–5.23 (m, 3H), 4.46 (brs, 1H), 4.27–4.06 (m, 5H), 3.40–3.30 (m, 3H), 2.12–1.99 (m, 11H), 1.93 (d, $J = 5.5$ Hz, 3H), 1.42 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 170.5, 169.3, 163.5, 150.5, 135.1, 112.4, 86.6, 80.8, 71.4, 70.9, 70.3, 49.1, 49.1, 47.2, 31.6, 29.7, 28.3, 22.6, 20.6, 20.5, 20.3, 12.4. HRMS (ES+) found 611.2569 (M+H) (calc for C$_{27}$H$_{39}$N$_4$O$_{12}$: 611.2565).

(2S,3S,4S,5R)-2-((6S,9S)-6-(Benzyloxymethyl)-2,2-dimethyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyl diethanoate (8aD). Purified by column chromatography (hexane/ethyl acetate: $1/2$ to $1/4$)

to obtain the product as a white solid (80 mg, 72%). ^{1}HNMR (400 MHz, CDCl$_3$, mixture of rotamers): δ 8.71 (m, 1H), 7.36–7.28 (m, 5H), 7.17–7.07 (m, 2H), 5.92–5.89 (m, 1H), 5.44–5.37 (m, 3H), 4.58–4.47 (m, 3H), 4.38–4.26 (brs, 1H), 4.25–4.16 (m, 2H), 4.11–4.04 (m, 1H), 3.93–3.89 (m, 1H), 3.68–3.57 (m, 1H), 2.09 (s, 3H), 2.07 & 2.04 (2s, 6H), 1.95 & 1.93 (2s, 3H), 1.45 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 170.8, 170.6, 169.6, 169.5, 163.1, 155.7, 155.5, 150.2, 137.4, 135.6, 128.5, 128.0, 128.9, 127.7, 127.6, 112.2, 112.1, 87.9, 87.6, 80.9, 80.8, 80.5, 73.4, 73.3, 71.9, 71.8, 70.9, 70.4, 69.7, 69.5, 62.6, 54.1, 49.6, 49.3, 28.3, 20.6, 20.5, 20.4, 12.5, 12.4. HRMS (ES+) found 691.2842 (M+H) (calc for $C_{32}H_{43}N_4O_{13}$: 691.2827).

(2*S*,3*S*,4*S*,5*R*)-2-((9*S*,12*S*)-9-(*tert*-Butoxycarbonylamino)-3,10,15-trioxo-1-phenyl-2,14-dioxa -4,11-diazahexadecan-12-yl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetra-hydrofuran-3,4-diyl diethanoate (8aE). Purified by column chromatography (hexane/ethyl acetate: 1/2) to obtain the product as a white solid (69 mg, 75%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 9.58 & 9.51 (2s, 1H), 7.32–7.28 (m, 6H), 7.15–6.98 (m, 2H), 5.93 & 5.83 (2s, 1H), 5.42–5.29 (m, 3H), 5.18–5.11 (m, 1H), 5.07 (s, 2H), 4.47 (m, 1H), 4.29–4.22 (m, 1H), 4.16–4.02 (m, 4H), 3.17–3.15 (m, 2H), 2.07 (s, 3H), 2.03 (s,6H), 1.92 (s, 3H), 1.88 & 1.77 (m, 1H), 1.64–1.45 (m, 3H), 1.41 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 172.8, 170.7, 169.7, 169.6, 163.7, 156.7, 150.7, 136.6, 135.9, 128.5, 128.1, 112.1, 87.8, 80.8, 80.3, 72.0, 70.7, 66.6, 54.5, 49.5, 40.3, 29.4, 28.3, 22.5, 20.7, 20.5, 20.4, 12.4. HRMS (ES+) found 798.3170 (M+Na) (calc for $C_{36}H_{49}N_5O_{14}Na$: 798.3174).

(2*S*,3*S*,4*S*,5*R*)-2-((6*S*,9*S*)-6-(2-(1*H*-Indol-3-yl)ethyl)-2,2-dimethyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)-5-(5-methyl-2,4-dioxo-3,4-dihydro-pyrimidin-1(2*H*)-yl)tetrahydro-furan-3,4-diyl diethanoate (8aF). Purified by column chromatography (hexane/ethyl acetate: 1/2 to 1/4) to obtain the product as a light yellow solid (52 mg, 71%). ^{1}HNMR (400 MHz, CDCl$_3$, mixture of rotamers): δ 9.75 (2 brs, 1H), 8.75 (brs, 1H), 7.68–7.64 (m, 1H), 7.33–7.31 (m, 1H), 7.19–6.98 (m, 4H), 6.82 & 6.34 (2brs, 1H), 5.82–5.76 (m, 1H), 5.33–5.23 (m, 2H), 5.10–5.02 (m, 1H), 4.53–4.20 (m, 2H), 4.19–4.05 (m, 2H), 4.01–3.73 (m, 1H), 3.40–3.14 (m, 2H), 2.10 (s, 3H), 2.05–1.91 (m, 9H), 1.40 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 172.2, 170.6, 170.5, 169.6, 163.5, 155.5, 150.7, 136.2, 136.0, 127.4, 127.3, 123.3, 122.0, 119.5, 119.4, 118.7, 112.3, 112.1, 111.2, 110.2, 88.3, 80.3, 71.8, 71.6, 70.2, 62.4, 62.0, 55.5, 49.0, 28.2, 20.6, 20.4, 12.4. HRMS (ES+) found 700.2830 (M+H) (calc for $C_{33}H_{42}N_5O_{12}$: 700.2830).

(2*S*,3*S*,4*S*,5*R*)-2-((6*S*,9*S*)-6-Benzyl-2,2-dimethyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyldiethanoate (8bA). Purified by column chromatography (hexane/ethyl acetate: 1/2) to obtain the product as

a white solid (90 mg, 48%). ^{1}HNMR (400 MHZ, CDCl$_3$, mixture of rotamers): δ 8.45 (brs, 1H), 7.19–7.32 (m, 5H), 6.68 & 6.37 (2 brs, 1H), 5.80–5.78 (m, 2H), 5.40–5.35 (m, 1H), 5.32–5.29 (m, 1H), 5.12 (brs, 1H), 5.05–4.93 (m, 1H), 4.43–4.32 (m, 2H), 4.24–4.03 (m, 3H), 3.15–3.06 (m, 2H), 2.12–2.09 (m, 9H), 1.40–1.39 (s, 9H). ^{13}CNMR (100.6 Hz, CDCl$_3$, mixture of rotamers): δ 172.0, 171.8, 170.6, 170.4, 169.7, 169.6, 162.9, 155.4, 150.3, 140.4, 136.5, 129.4, 129.3, 128.6, 128.5, 128.4, 126.9, 126.8, 103.5, 88.3, 80.6, 71.9, 70.8, 70.6, 62.4, 62.2, 55.7, 49.0, 38.7, 31.5, 29.6, 28.1, 22.6, 21.0, 20.7, 20.5, 14.1. HRMS (ES+) found 647.2543 (M+H) (calc for C$_{30}$H$_{39}$N$_4$O$_{12}$: 647.2565).

(2*R*,3*S*,4*S*,5*S*)-2-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((6*S*,9*S*)-2, 2,6-trimethyl-4,7, 12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)tetrahydrofu-ran-3,4-diyldiethanoate (8bB). Purified by column chromatography (hexane/ethyl acetate: 1/3) to obtain the product as a white solid (122 mg, 91%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 8.92 (brs, 1H), 7.34–7.28 (m, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 5.91–5.87 (m, 1H), 5.80 (d, *J* = 7.5 Hz, 1H), 5.43–5.38 (m, 2H), 5.31–5.26 (m, 0.5H), 5.12–4.99 (m, 1.5H), 4.48 (brs, 1.5H), 4.31–4.10 (m, 5.5H), 2.12 (s, 3H), 2.08 (s, 6H), 1.43 (d, *J* = 5.0 Hz, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 173.3, 173.2, 170.7, 169.6, 169.3, 162.5, 155.8, 152.9, 150.3, 150.2, 140.3, 103.6, 88.4, 88.2, 85.8, 81.3, 80.9, 80.4, 79.8, 72.0, 71.9, 71.2, 70.7, 70.6, 62.6, 62.5, 50.2, 49.3, 49.2, 30.9, 29.7, 28.3, 28.2, 20.7, 20.6, 20.5, 20.4, 18.1, 17.6. HRMS (ES+) found 571.2245 (M+H) (calc for C$_{24}$H$_{35}$N$_4$O$_{12}$: 571.2251).

(2*S*,3*S*,4*S*,5*R*)-2-((*S*)-1-((*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxamido)-2-(ethanoyl-oxy)ethyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2*H*)-yl)tetrahydrofuran-3,4-diyl diethano-ate (8bC). Purified by column chromatography (hexane/ethyl acetate: 1/2 to 1/4) to obtain the product as a white solid (86 mg, 70%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 8.91 & 8.67 (2s, 1H), 7.89–7.53 (m, 1H), 7.42–7.35 (m, 1H), 6.05–6.00 (m, 1H), 5.80 (t, *J* = 6.5 Hz, 1H), 5.42–5.31 (m, 2H), 4.46 (bs, 1H), 4.30–4.04 (m, 4H), 3.54–3.31 (m, 2H), 2.72–2.32 (m, 1H), 2.12 & 2.11 (2s, 3H), 2.09–2.04 (m, 6H), 1.88 (brs, 3H), 1.45 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 172.5, 170.6, 169.7, 169.5, 169.2, 162.4, 162.3, 156.2, 152.8, 150.3, 150.1, 140.0, 139.5, 103.6, 87.1, 80.9, 80.6, 80.5, 71.9, 71.6, 70.8, 70.4, 62.9, 59.9, 49.4, 49.2, 49.1, 47.2, 30.9, 30.8, 29.7, 28.3, 27.7, 24.6, 22.6, 20.7, 20.6, 20.5, 20.4, 13.7. HRMS (ES+) found 597.2397 (M+H) (calc for C$_{26}$H$_{37}$N$_4$O$_{12}$: 597.2408).

(2*S*,3*S*,4*S*,5*R*)-2-((6*S*,9*S*)-6-(Benzyloxymethyl)-2,2-dimethyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl diethanoate (8bD). Purified by column chromatography (hexane/ethyl acetate: 1/2 to 1/4) to obtain the product as a white solid (66 mg, 44%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 8.65 (brs, 1H), 7.35–7.25 (m, 5H), 7.10–7.00 (m, 1H),

5.89–5.86 (m, 1H), 5.80–5.76 (m, 1H), 5.43–5.35 (m, 2H), 5.33–5.28 (m, 1H), 4.58–4.47 (m, 3H), 4.34–4.10 (m, 4H), 3.97–3.90 (m, 1H), 3.64–3.43 (m, 2H), 2.14–1.94 (m, 9H), 1.45 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 171.0, 170.9, 170.8, 170.6, 169.8, 169.7, 169.6, 169.5, 169.2, 169.1, 162.3, 155.7, 152.8, 150.1, 140.2, 137.4, 128.5, 128.0, 127.9, 127.7, 103.6, 103.5, 88.3, 88.1, 85.8, 85.7, 81.0, 80.9, 79.8, 73.4, 73.3, 72.0, 71.5, 71.1, 70.9, 70.4, 69.7, 69.5, 68.5, 62.5, 54.1, 49.6, 49.5, 49.3, 30.8, 29.7, 28.3, 20.7, 20.6, 20.5, 20.4, 14.1. HRMS (ES+) found 677.2669 (M+H) (calc for $C_{31}H_{41}N_4O_{13}$: 677.2670).

(2*S*,3*S*,4*S*,5*R*)-2-((9*S*,12*S*)-9-(*tert*-Butoxycarbonylamino)-3,10,15-trioxo-1-phenyl-2,14-dioxa-4,11-diazahexadecan-12-yl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydro-furan-3,4-diyl diethanoate (8bE). Purified by column chromatography (hexane/ethyl acetate: 1/2 to 1/4) to obtain the product as a white solid (39 mg, 34%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 9.12 & 8.90 (2 brs, 1H), 7.37–7.22 (m, 6H), 7.01–6.86 (m, 1H), 5.88–5.73 (m, 1.5H), 5.48–5.41 (m, 1.5H), 5.34–5.06 (m, 5H), 4.52–4.47 (brs, 1H), 4.32–4.02 (m, 4H), 3.19 (brs, 2H), 2.10–2.04 (m, 9H), 1.88 (brs, 2H), 1.62–1.51 (m, 4H), 1.42 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 172.9, 172.7, 170.7, 169.8, 169.3, 162.5, 156.9, 156.8, 156.7, 156.0, 150.3, 140.8, 140.6, 136.6, 136.5, 128.6, 128.1, 103.6, 81.0, 80.9, 80.4, 79.8, 72.4, 72.0, 71.3, 70.6, 70.5, 66.8, 66.7, 62.5, 62.4, 54.5, 49.7, 49.4, 49.2, 40.2, 40.1, 31.6, 31.1, 30.9, 29.7, 29.4, 28.3, 22.7, 22.5, 20.8, 20.7, 20.6, 20.5, 20.4, 14.2. HRMS (ES+) found 762.3201 (M+H) (calc for $C_{35}H_{48}N_5O_{14}$: 762.3198).

(2*S*,3*S*,4*S*,5*R*)-2-((6*S*,9*S*)-6-(2-(1*H*-Indol-3-yl)ethyl)-2,2-dimethyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl diethanoate (8bF). Purified by column chromatography (hexane/ethyl acetate: 1/2 to 1/4) to obtain the product as a white solid (42 mg, 51%). ^{1}HNMR (500 MHz, CDCl$_3$ mixture of rotamers): δ 9.10 (brs, 1H), 8.50 & 8.49 (2s, 1H), 7.67–7.62 (m, 1H), 7.33–7.31 (m, 1H), 7.21–7.12 (m, 4H), 6.62–6.14 (m, 1H), 5.77–5.71 (m, 2H), 5.41–5.06 (m, 3H), 4.10–3.60 (m, 3H), 3.42–3.05 (m, 2H), 2.10–1.97 (m, 9H), 1.42 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 172.2, 172.2, 170.6, 170.5, 169.9, 169.7, 169.6, 169.4, 169.2, 162.5, 155.6, 155.4, 153.0, 150.3, 150.1, 140.5, 140.2, 136.2, 127.4, 127.3, 123.4, 123.3, 122.2, 119.7, 119.6, 118.8, 111.3, 111.2, 110.3, 103.7, 103.5, 89.0, 87.9, 80.4, 80.3, 79.3, 72.0, 71.8, 70.9, 70.7, 70.3, 62.4, 62.0, 55.4, 53.4, 49.2, 49.0, 30.8, 29.7, 28.7, 28.3, 20.7, 20.6, 20.5, 20.4, HRMS (ES+) found 686.2680 (M+H) (calc for $C_{32}H_{40}N_5O_{12}$: 686.2673).

(2*S*,3*S*,4*S*,5*R*)-2-((6*S*,9*S*)-6-Benzyl-2,2-dimethyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)-5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl dietha- noate (8cA). Purified by column chromatography (hexane/ethyl acetate: 1/1 to 1/2) to obtain the product

as a white solid (67 mg, 53%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 9.48 (brs, 1H), 7.55–7.44(m, 1H), 7.29–7.20 (m, 5H), 6.02–5.85 (m, 1H), 5.40–5.16 (m, 2H), 5.14–5.02 (m, 1H), 4.48–4.35 (m, 2H), 4.30–4.04 (m, 3H), 3.95–3.61 (m, 1H), 3.19–3.05 (m, 2H), 2.13–2.00 (m, 9H), 1.35 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 172.1, 172.0, 170.6, 170.4, 169.9, 169.7, 169.6, 156.7, 156.5, 155.5, 149.1, 141.9, 140.0, 136.6, 129.3, 128.6, 128.5, 126.9, 124.6, 124.3, 88.1, 81.1, 80.9, 80.6, 71.8, 70.7, 70.5, 62.5, 62.4, 55.9, 49.5, 49.0, 38.6, 29.7, 28.2, 20.7, 20.6, 20.5, 20.3. HRMS (ES+) found 687.2291 (M+Na) (calc for C$_{30}$H$_{37}$FN$_4$O$_{12}$Na: 687.2290).

(2*R*,3*S*,4*S*,5*S*)-2-(5-Fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((6*S*,9*S*)-2,2,6-tri-methyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl) tetrahydrofuran-3,4-diyldiethanoate (8cB). Purified by column chromatography (hexane/ethyl acetate: 1/1 to 1/2) to obtain the product as a white solid (50 mg, 64%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 7.01–6.82 (m, 1H), 5.99–5.88 (m, 1H), 5.38–5.26 (m, 1H), 5.20–5.08 (m, 1H), 5.04–4.94 (m, 1H), 4.51 (brs, 1H), 4.38–4.28 (m, 1H), 4.26–4.10 (m, 3H), 4.03–3.81 (m, 1H), 3.69–3.63 (m, 1H), 2.16–2.02 (m, 9H), 1.45–1.44 (m, 9H), 1.37 (m, 3H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 173.6, 173.5, 173.4, 170.7, 170.0, 169.8, 169.4, 169.6, 165.6, 165.4, 156.9, 156.7, 155.7, 152.0, 149.2, 141.9, 140.0, 124.5, 124.3, 87.5, 85.6, 82.6, 81.4, 81.2, 81.1, 81.0, 80.5, 80.4, 80.2, 71.7, 71.4, 71.2, 70.7, 70.5, 68.7, 62.7, 50.1, 49.6, 49.4, 41.5, 41.3, 29.6, 28.2, 20.7, 20.6, 20.5, 20.4, 20.3, 17.9, 17.5. HRMS (ES+) found 611.1981 (M+Na) (calc for C$_{24}$H$_{33}$FN$_4$O$_{12}$Na: 611.1977).

(2*S*,3*S*,4*S*,5*R*)-2-((*S*)-1-((*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxamido)-2-(ethanoyl-oxy)ethyl)-5-(5-fluoro-2,4-dioxo-3,4-dihydro-pyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl diethanoate (8cC). Purified by column chromatography (hexane/ethyl acetate: 1/2) to obtain the product as a white solid (49 mg, 49%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 8.79 (brs, 1H), 7.96–7.85 (m, 0.5H), 7.64–7.44 (m, 1.5H), 6.00 (brs, 1H), 5.43–5.32 (m, 2H), 4.48 (brs 1H), 4.31–4.11 (m, 4H), 3.42–3.33 (m, 2H), 2.15–2.05 (m, 9H), 1.89 (brs, 4H), 1.46 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 170.6, 170.5, 169.5, 156.5, 156.3, 149.1, 149.0, 141.9, 124.0, 81.2, 80.7, 71.8, 71.5, 70.2, 63.0, 49.3, 47.3, 34.7, 29.7, 28.3, 27.9, 20.6, 20.5, 20.3, 14.1. HRMS (ES+) found 615.2314 (M+H) (calc for C$_{26}$H$_{36}$FN$_4$O$_{12}$: 615.2314).

(2*S*,3*S*,4*S*,5*R*)-2-((6*S*,9*S*)-6-(Benzyloxymethyl)-2,2-dimethyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)-5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl diethanoate (8cD). Purified by column chromatography (hexane/ethyl acetate: 1/1 to 1/2) to obtain the product as a white solid (50 mg, 46%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 8.88 (brs, 1H), 7.47–7.41 (m, 1H), 7.36–7.23

(m, 5H), 7.09 (d, $J = 9$ Hz, 1H), 5.98–5.86 (m, 1H), 5.41–5.34 (m, 2H), 5.33–5.25 (m, 1H), 4.58–4.46 (m, 3H), 4.34–4.31 (m, 1H), 4.25–4.18 (m, 2H), 4.13–4.10 (m, 1H), 3.97–3.91 (m, 1H), 3.66–3.58 (m, 1H), 2.10–1.94 (m, 9H), 1.45 (d, $J = 2$ Hz, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 171.2, 171.0, 170.6, 169.7, 169.6, 169.5, 156.6, 156.3, 149.0, 141.8, 139.9, 137.4, 128.5, 128.0, 127.9, 127.7, 127.5, 124.5, 124.3, 81.4, 81.2, 80.6, 80.3, 73.4, 73.3, 73.2, 71.9, 71.8, 70.7, 70.3, 69.6, 68.7, 62.7, 62.6, 54.2, 49.8, 49.6, 49.4, 29.7, 28.3, 20.6, 20.5, 20.3. HRMS (ES+) found 695.2573 (M+H) (calc for C$_{31}$H$_{40}$FN$_4$O$_{13}$: 695.2576).

(2*S*,3*S*,4*S*,5*R*)-2-((9*S*,12*S*)-9-(*tert*-Butoxycarbonylamino)-3,10,15-trioxo-1-phenyl-2,14-dioxa-4,11-diazahexadecan-12-yl)-5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-tetrahydrofuran-3,4-diyl diethanoate (8cE). Purified by column chromatography (hexane/ ethyl acetate: 1/1 to 1/2) to obtain the product as a white solid (65 mg, 47%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 9.89 & 9.70 (2brs, 1H), 7.56 & 7.48 (2s, 1H), 7.34–7.28 (m, 5H), 7.13–6.95 (m, 1H), 5.95 & 5.81 (2brs, 1H), 5.41–5.25 (m, 3H), 5.19–5.09 (m, 3H), 4.51–4.50 (brs, 1H), 4.34–3.99 (m, 4H), 3.18–3.17 (m, 2H), 2.16–2.01 (m, 9H), 1.95 (brs, 1H), 1.87 (brs, 1H), 1.70 (brs, 1H), 1.61 (brs, 2H), 1.43–1.42 (m, 10H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 173.0, 170.7, 170.0, 169.7, 156.9, 156.8, 156.7, 155.9, 149.1, 141.8, 139.9, 136.6, 128.5, 128.1, 81.2, 81.0, 80.4, 72.0, 71.8, 71.2, 70.5, 66.6, 62.5, 54.5, 49.4, 49.2, 40.3, 29.7, 29.4, 28.2, 22.5, 20.6, 20.5, 20.4, 20.3. HRMS (ES+) found 797.3386 (M+NH$_4$) (calc for C$_{35}$H$_{50}$FN$_6$O$_{14}$: 797.3370).

(2*S*,3*S*,4*S*,5*R*)-2-((6*S*,9*S*)-6-(2-(1*H*-indol-3-yl)ethyl)-2,2-dimethyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)-5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydro-furan-3,4-diyl diethanoate (8cF). Purified by column chromatography (hexane/ethyl acetate: 1/1 to 1/2) to obtain the product as a light yellow solid (33 mg, 27%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 9.62 (brs, 1H), 8.55 -8.48 (m, 1H), 7.67–7.62 (m, 1H), 7.47–7.43 (m, 2H), 7.18–7.06 (m, 3H), 6.68–6.57 (m, 1H), 5.86–5.72 (m, 1H), 5.42–5.05 (m, 3H), 4.54–4.35 (m, 2H), 4.22–3.58 (m, 3H), 3.36–3.12 (m, 2H), 2.22–1.94 (m, 9H), 1.42 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 172.4, 170.7, 170.5, 170.0, 169.8, 169.7, 156.7, 156.5, 155.5, 149.1, 149.0, 136.3, 136.2, 127.5, 127.3, 123.4, 122.2, 122.1, 119.6, 118.8, 111.3, 111.2, 110.3, 80.7, 80.6, 80.4, 71.9, 71.7, 70.8, 70.3, 62.5, 62.1, 49.2, 49.0, 29.7, 28.3, 22.7, 20.6, 20.5, 20.4, 14.1. HRMS (ES+) found 704.2592 (M+H) (calc for C$_{32}$H$_{39}$FN$_5$O$_{12}$: 704.2579).

(2*S*,3*S*,4*S*,5*R*)-2-((6*S*,9*S*)-6-Benzyl-2,2-dimethyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)-5-(4-ethanamido-2-oxopyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl diethanoate (8dA). Purified by column chromatography (ethyl acetate/methanol: 98/2) to obtain the product as white solid (55 mg, 51%). ^{1}HNMR (500 MHZ, CDCl$_3$, mixture of rotamers):

δ 9.81 & 9.60 (2s, 1H), 8.18–8.03 (m, 1H), 7.78–7.33 (m, 2H), 7.19–7.18 (brs, 5H), 6.07–5.87 (m, 1H), 5.69–5.37 (m, 2H), 5.31–5.17 (m, 1H), 4.92–4.67 (m, 1H), 4.39–4.10 (m, 4H), 3.12–3.06 (m, 1H), 2.90–2.83 (m, 1H), 2.13 (s, 3H), 2.04–1.98 (m, 9H), 1.36 & 1.33 (2s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 172.4, 172.3, 171.2, 170.8, 170.6, 169.6, 169.3, 169.0, 163.2, 162.9, 155.6, 144.5, 137.1, 136.9, 129.6, 129.5, 128.2, 126.6, 98.0, 97.3, 80.4, 79.6, 73.3, 73.1, 71.5, 62.4, 62.3, 55.1, 49.1, 40.0, 39.5, 29.6, 28.2, 24.9, 24.8, 20.8, 20.6, 20.4, 20.3. HRMS (ES+) found 688.2844 (M+H) (calc for C$_{32}$H$_{42}$N$_5$O$_{12}$: 688.2830).

(2*R*,3*S*,4*S*,5*S*)-2-(4-Ethanamido-2-oxopyrimidin-1(2*H*)-yl)-5-((6*S*,9*S*)-2,2,6-trimethyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)tetrahydrofuran-3,4-diyl diethanoate (8dB). Purified by column chromatography (ethyl acetate/methanol: 98/2) to obtain the product as white solid (62 mg, 45%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 9.88 & 9.61 (2s, 1H), 8.08–7.30 (m, 3H), 6.04 & 5.85 (2s, 1H), 5.66–5.33 (m, 3H), 4.81 & 4.68 (2s, 1H), 4.55 & 4.47 (2s, 1H), 4.38–4.11 (m, 3H), 2.29–2.23 (2s, 3H), 2.05–2.01 (m, 9H), 1.43 & 1.42 (2s, 9H), 1.33 (brs, 3H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 173.8, 173.5, 171.1, 170.8, 170.7, 169.5, 169.4, 169.2, 163.2, 162.9, 155.7, 155.6, 155.5, 155.4, 144.9, 144.8, 97.8, 97.2, 90.4, 90.0, 80.9, 79.8, 73.3, 73.1, 70.9, 69.9, 62.4, 62.3, 49.7, 49.0, 34.6, 31.5, 29.7, 28.3, 25.0, 24.8, 22.6, 20.7, 20.6, 20.4, 19.6, 18.8, 14.1. HRMS (ES+) found 612.2528 (M+H) (calc for C$_{26}$H$_{38}$N$_5$O$_{12}$: 612.2517).

(2*S*,3*S*,4*S*,5*R*)-2-((*S*)-1-((*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxamido)-2-(ethanoyl-oxy)ethyl)-5-(4-ethanamido-2-oxopyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl diethanoate (8dC). Purified by column chromatography (ethyl acetate/methanol: 98/2) to obtain the product as white solid (24 mg, 18%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 9.60 (bs, 1H), 7.87–7.56 (m, 2H), 7.47 (brs, 1H), 6.09 (brs, 1H), 5.44–5.31 (m, 2H), 4.53 (brs, 1H), 4.33–4.17 (m, 4H), 3.42–3.31 (m, 2H), 2.26 (s, 3H), 2.11–2.03 (m, 9H), 1.87 (brs, 4H), 1.43 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 170.5, 169.5, 163.0, 155.0, 97.5, 81.1, 80.5, 73.1, 70.6, 62.9, 59.9, 49.2, 47.2, 36.6, 34.6, 34.5, 31.5, 29.7, 28.3, 25.2, 24.9, 24.7, 22.6, 20.7, 20.5, 20.4, 14.1. HRMS (ES+) found 638.2665 (M+H) (calc for C$_{28}$H$_{40}$N$_5$O$_{12}$: 638.2673).

(2*S*,3*S*,4*S*,5*R*)-2-((6*S*,9*S*)-6-(Benzyloxymethyl)-2,2-dimethyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)-5-(4-ethanamido-2-oxopyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl diethanoate (8dD). Purified by column chromatography (ethyl acetate/methanol: 98/2) to obtain the product as white solid (36 mg, 30%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 9.47 & 9.55 (2s, 1H), 7.71–7.58 (m, 2H), 7.49–7.41 (m, 1H), 7.34–7.24 (m, 5H), 6.02 & 5.92 (2s, 1H), 5.66–5.38 (m, 3H), 4.67–4.62 (m, 1H), 4.55–4.46 (m, 3H), 4.28–4.18 (m, 3H), 3.88–3.84 (m, 1H), 3.67–3.62 (m, 1H), 2.22 & 2.21 (2s, 3H), 2.05–1.95 (m, 9H), 1.43 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$,

mixture of rotamers): δ 170.1, 170.9, 170.6, 169.4, 169.3, 163.1, 163.0, 155.8, 155.3, 155.2, 144.9, 144.7, 137.6, 128.4, 127.8, 127.7, 127.5, 97.6, 97.4, 89.8, 89.5, 73.3, 73.2, 73.0, 70.8, 70.5, 70.4, 70.1, 62.6, 62.4, 54.0, 49.8, 49.4, 29.7, 28.3, 24.9, 20.6, 20.4, 14.1. HRMS (ES+) found 718.2928 (M+H) (calc for $C_{33}H_{44}N_5O_{13}$: 718.2936).

(2*S*,3*S*,4*S*,5*R*)-2-((9*S*,12*S*)-9-(*tert*-Butoxycarbonylamino)-3,10,15-trioxo-1-phenyl-2,14-dioxa-4,11-diazahexadecan-12-yl)-5-(4-ethanamido-2-oxopyrimidin-1(2*H*)-yl)tetrahydro-furan-3,4-diyl diethanoate (8dE). Purified by column chromatography (ethyl acetate/methanol: 98/2) to obtain the product as white solid (37 mg, 26%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 11.42 & 11.00 (2s, 0.5H), 9.81 & 9.57 (2s, 0.5H), 8.15 & 7.87 (2s, 1H), 7.70–7.15 (m, 5H), 5.83–5.03 (m, 8H), 4.68–4.05 (m, 5H), 3.37–3.10 (m, 3H), 2.25–2.18 (m, 3H), 2.13–2.03 (m, 9H), 1.92–1.51 (m, 4H), 1.45 (brs, 11H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 173.5, 173.1, 171.6, 170.6, 170.2, 169.7, 169.4, 164.2, 163.2, 158.3, 156.7, 156.0, 155.7, 155.4, 136.8, 136.6, 128.5, 128.0, 127.7, 97.8, 97.6, 80.6, 79.3, 75.1, 73.3, 69.6, 66.6, 62.0, 60.8, 53.9, 49.9, 40.6, 38.9, 36.6, 32.2, 29.1, 28.3, 24.9, 24.8, 24.7, 24.6, 20.7, 20.6, 20.5, 20.4, 20.2, 14.1. HRMS (ES+) found 803.3471 (M+H) (calc for $C_{37}H_{51}N_6O_{14}$: 803.3464).

(2*S*,3*S*,4*S*,5*R*)-2-((6*S*,9*S*)-6-(2-(1*H*-Indol-3-yl)ethyl)-2,2-dimethyl-4,7,12-trioxo-3,11-dioxa-5,8-diazatridecan-9-yl)-5-(4-ethanamido-2-oxopyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl diethanoate (8dF). Purified by column chromatography (ethyl acetate/methanol: 98/2) to obtain the product as light yellow solid (30 mg, 24%). ^{1}HNMR (500 MHz, CDCl$_3$, mixture of rotamers): δ 9.58 (brs, 1H), 8.61 (brs, 1H), 7.60 (brs, 2H), 7.37–7.25 (m, 3H), 7.09–7.02 (m, 3H), 5.79 (brs, 1H), 5.54–5.26 (m, 3H), 4.84–4.73 (m, 1H), 4.63–4.15 (m, 3H), 4.06–4.00 (m, 1H), 3.21–3.13 (m, 2H), 2.16 (s, 3H), 2.05–1.84 (m, 9H), 1.39 (s, 9H). ^{13}CNMR (125.8 Hz, CDCl$_3$, mixture of rotamers): δ 172.6, 170.8, 170.6, 169.5, 162.9, 155.3, 155.2, 136.1, 127.6, 127.5, 123.4, 121.9, 119.3, 118.7, 111.2, 111.1, 110.6, 97.7, 80.3, 79.8, 73.2, 73.1, 62.5, 62.3, 55.1, 29.7, 28.3, 24.9, 24.8, 20.7, 20.6, 20.4, 20.3. HRMS (ES+) found 727.2935 (M+H) (calc for $C_{34}H_{43}N_6O_{12}$: 727.2939).

General deprotection procedure to form the free peptidyl nucleosides 9 and 10. *Step 1* (Deacetylation): To an ice-cooled solution of the fully protected peptidyl nucleoside (**8aB**, or, **8bC**) in THF (100 mg / mL) was added dropwise an aqueous solution of LiOH (5 equiv, 1g/10 mL) with stirring. After stirring at the same temperature for 2 hours, the reaction was quenched by addition of saturated aqueous NH$_4$Cl solution till pH 7–8. After addition of EtOAc (10 mL), the organic layer was separated, aqueous layer saturated by addition of solid NaCl and the resulting solution extracted with ethyl acetate (3x). After drying over anhydrous Na$_2$SO$_4$ and removal of solvent under vacuum, the corresponding deacetylated products were

obtained as white solid, which were taken to the next deprotection step without any further purification.

Step 2 (Boc-deprotection): The deacetylated nucleoside derivative as obtained above was added to an ice-cooled solution of CH_2Cl_2 / TFA (1/9, 10% solution by weight), stirred at the same temperature for 30 minutes followed by 1 hour at room temperature. Excess solvent was removed under vacuum and the residue triturated with CH_2Cl_2 and diethyl ether. The resulting solid was dried under high vacuum to provide the fully deprotected peptidyl nucleosides **9** and **10**.

(2*R*,3*S*,4*S*,5*S*)-5-((*S*)-1-((*S*)-2-Aminopropanamido)-2-hydroxyethyl)-4-hydroxy-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydro-furan-3-yl ethanoate (as the trifluoro-acetate salt) (9). Obtained as a white solid (22 mg, 91%). ^{1}HNMR (400 MHz, CD_3OD, mixture of rotamers): δ 7.45 (d, $J = 7.2$ Hz, 1H), 5.76 (apparent t, $J = 6.8$ Hz, 1H), 4.38–4.30 (2 t, $J = 5.6$ Hz, 1H), 4.24–4.17 (m, 1H), 4.13 (t, $J = 5.6$ Hz, 1H), 3.99–3.87 (m, 2H), 3.78–3.68 (m, 2H), 1.90 (s, 3H), 1.53 (d, $J = 6.8$ Hz, 3H). ^{13}CNMR (125.8 Hz, CD_3OD, mixture of rotamers): δ 171.6, 166.4, 152.7, 139.2, 138.9, 112.2, 92.1, 91.9, 84.2, 83.9, 73.9, 73.6, 72.6, 72.5, 62.1, 61.9, 54.5, 50.6, 30.9, 17.9, 12.4. HRMS (ES+) found 359.1561 (M+H) (calc for free amine $C_{14}H_{23}N_4O_7$: 359.1567).

(*S*)-*N*-((*S*)-1-((2*S*,3*R*,4*S*,5*R*)-5-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)-2-hydroxyethyl)pyrrolidine-2-carboxamide (as the trifluoroacetate salt) (10). Obtained as a white solid (31 mg, 93%). ^{1}HNMR (400 MHz, CD_3OD, mixture of rotamers): δ 7.62 (dd, $J = 8$, 2.4 Hz, 1H), 5.75–5.71 (m, 2H), 4.33–4.11 (m, 4H), 3.94–3.71 (m, 4H), 3.43–3.40 (m, 1H), 2.43–2.39 (m, 1H), 2.15–2.01 (m, 3H). ^{13}CNMR (125.8 Hz, CD_3OD, mixture of rotamers): δ 170.3, 166.1, 152.4, 143.5, 143.4, 103.3, 92.5, 84.1, 83.7, 74.2, 74.0, 72.8, 72.5, 62.0, 61.9, 61.5, 61.4, 54.8, 47.7, 31.3, 30.9, 30.7, 30.6, 30.3, 25.2. HRMS (ES+) found 371.1584 (M+H) (calc for $C_{15}H_{23}N_4O_7$: 371.1567).

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