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Towards New MraY Inhibitors: A Serine Template for Uracil and 5-Amino-5-deoxyribosyl Scaffolding

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The bacterial translocase MraY is a good target for the development of new antitbiotics as it is ubiquitous and essential for bacterial growth. The goal of this work was the synthesis of simplified analogues of naturally occurring inhibitors of this enzyme to investigate the essential character of the uridine moiety of these inhibitors with regards to biological activity. Thus, the structure of the targeted enantiomerically pure *N*-(uracilylpentyl)-β-D-*O*-(5-amino-5-deoxyribosyl)-L-serine retains uracil and 5-amino-5-deoxyribose parts linked by a serinyl template. The synthetic strategy towards this compound relies on sequential *O*-glycosylation and *N*-alkylation by reductive amination of a serine derivative.

Introduction

The world-wide emergence of bacterial resistance to various antibiotics[1] such as β-lactams, vancomycin, methicillin and other clinically important antibiotics has forced the scientific community to discover novel structures that are able to treat the resistant bacterial strains. The enzymes involved in peptidoglycan biosynthesis appear to be the targets of choice in the development of new antibacterials since the peptidoglycan layer forms part of the bacterial cell wall and protects the cell from osmotic stress. Indeed, most of the enzymes involved in its biosynthesis have been demonstrated to be ubiquitous and essential for bacterial growth.[2] Owing to its transmembrane localisation,[3] the translocase MraY has only recently been characterised and purified to homogeneity[4] and no therapeutic drugs targeting this essential enzyme[5] exist so far. Nevertheless,

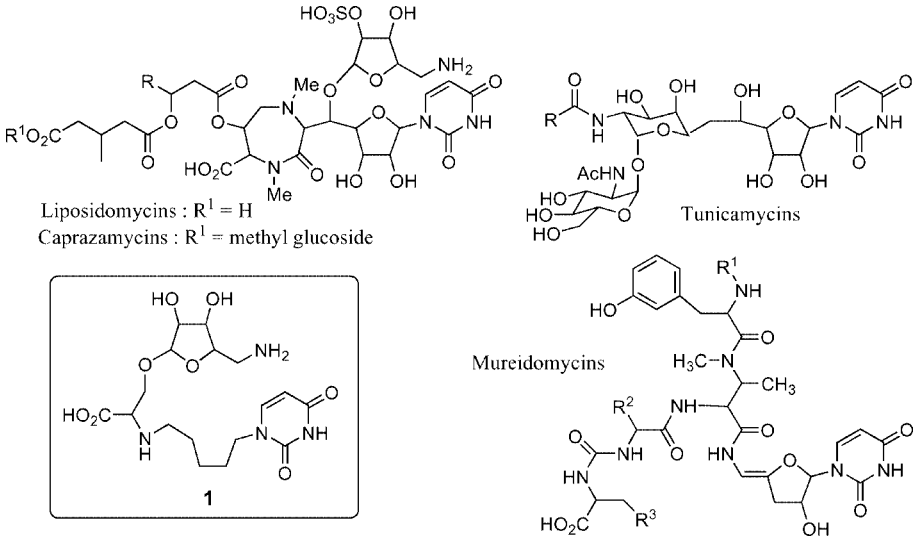

Figure 1. MraY inhibitors and the target compound **1**.

several families of naturally occurring inhibitors have been identified such as liposidomycins,[6] tunicamycins,[7] mureidomycins[8] and caprazamycins[9] (Figure 1).

However, although most of these compounds display high activity in vitro, their antibacterial activity is limited

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due to their high hydrophilicity or their lack of specificity leading to toxicity.[10] In an ongoing program directed towards the inhibition of new targets for fighting antibiotics resistance, our goal was to develop access to new MraY inhibitors displaying simplified structures compared with the natural ones and enhanced biological activity. The described approach focuses on the right-hand part of liposidomycins and caprazamycins and takes into account the following motivations: on the one hand, to gain a better stability of the synthesised inhibitors, and on the other hand, bearing in mind that the two hydroxy groups at the 2′,3′ positions of the uridine moiety may be unnecessary to retain biological activity,[11] our plan was to replace the sugar part of uridine by a C_5 acyclic alkyl chain (Figure 1). Thus, the hypothesis intended to be tested is that only the uracil template and not the uridine would be crucial to ensure possible recognition of the resulting inhibitors by the enzyme. Thus, uracil, aminoribose and amino acid moieties, being the three key fragments of the naturally occurring inhibitors, were retained in the targeted inhibitor **1**. It is evident that, if inhibitory activity was demonstrated for such a compound, other modifications related to the chemical linkage between the uracil and serine moieties and that allow modulations in either its flexibility or polarity would also be evaluated later on.

Results and Discussion

The retrosynthetic analysis of the target compound **1** (Figure 2) relies on two complementary strategies involving either *N*-alkylation of a serinyl derivative followed by *O*-glycosylation as the key steps (path a) or, inversely, *O*-glycosylation and subsequent *N*-alkylation (path b).

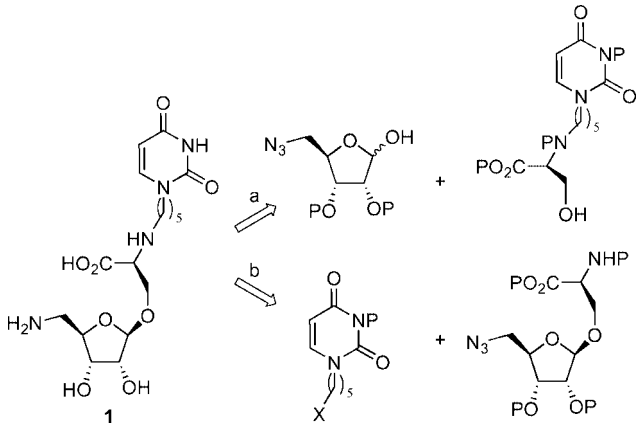
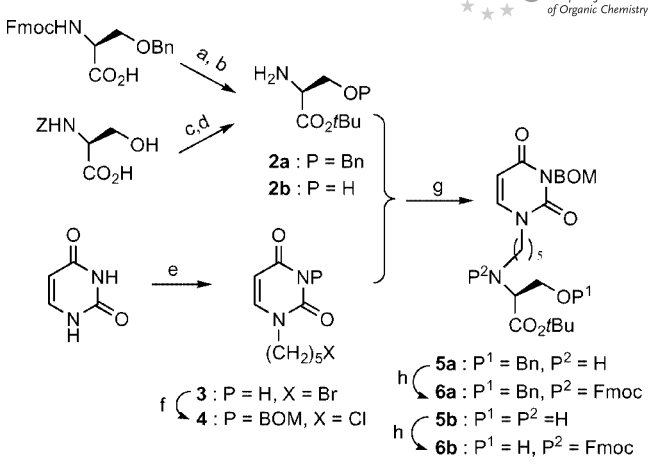


Figure 2. Retrosynthetic pathways: a) *O*-glycosylation of the *N*-(uracilylalkyl)serine derivative or b) *N*-alkylation of the *O*-(azidoribosyl)serine derivative.

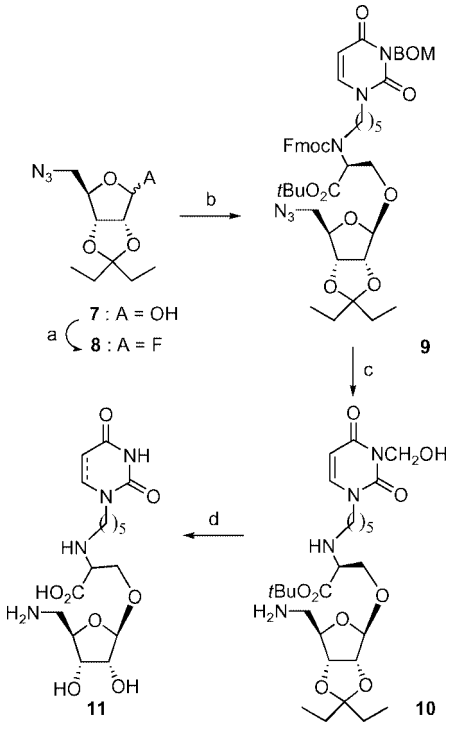
So, in accord with path a, we embarked on the synthesis of a conveniently protected *N*-(uracilylpentyl)-L-serine derivative (Scheme 1) from commercially available *N*-Fmoc-*O*-benzyl-L-serine.



Scheme 1. Reagents and conditions: a) $Cl_3CC(NH)OtBu$, cyclohexane, 50 °C (100%); b) DBU, THF, room temp. (100% for **2a**); c) *t*BuBr, $BnEt_3NCl$, K_2CO_3, MeCN, 50 °C (88%); d) H_2, Pd/C, EtOAc (100% for **2b**); e) i. $(Me_3Si)_2NH$, Me_3SiCl, 80 °C, ii. $Br(CH_2)_5Br$, DMF, 80 °C (41%); f) BOMCl, DBU, DMF, room temp. (77%); g) **4**, NaI, Cs_2CO_3, DMF (63% for **5a** and 37% for **5b**); h) FmocCl, DIPEA, CH_2Cl_2, room temp. (81% for **6a** and 73% for **6b**).

On the one hand, esterification with *tert*-butyl trichloroacetimidate followed by Fmoc deprotection efficiently led to *O*-benzyl-L-serine ester **2a**. On the other hand, 3-(benzyloxymethyl)-1-(5′-chloropentyl)uracil (**4**) was prepared in three steps from uracil. Persilylation of uracil in the presence of trimethylsilyl chloride and hexamethyldisilazane followed by N^1-alkylation with 1,5-dibromopentane[12] afforded the N^1-(bromopentyl)uracil (**3**).[13] N^3-Protection of **3** with benzyloxymethyl chloride (BOMCl)[14] was accompanied by simultaneous halogen exchange leading to N^1-(chloropentyl)uracil **4**. Then, *N*-alkylation of *O*-benzyl-L-serine ester **2a** with the uracil derivative **4** was carried out in the presence of caesium carbonate[15] at 50 °C for 4 d in DMF to deliver the *N*-alkylated serine **5a** in 63% yield. Then, further *N*-protection of **5a** as its *N*-Fmoc derivative **6a** cleanly occurred and was followed by attempts to deprotect the primary alcohol function prior to glycosylation. However, all the conditions assayed for this reaction proved unsuccessful, while concomitant *N*-Fmoc deprotection was observed. So we decided to reproduce the same sequence of reactions, without *O*-protection, starting from L-serine ester **2b**, the preparation of which was easily carried out from commercially available *N*-(benzyloxycarbonyl)-L-serine by esterification with *tert*-butyl bromide[16] followed by hydrogenolysis. Then, *N*-alkylation of **2b** with **4** was carried out under the same conditions as described previously except that completion of the reaction required heating at 80 °C for 2 d in DMF to afford the corresponding *N*-alkylated serine **5b** in a modest 37% yield. All attempts to improve the yield of this reaction, notably by using other bases (e.g., potassium carbonate, *N*,*N*′-diisopropylethylamine) and by varying the temperature, resulted in lower yields. Finally, *N*-protection of **5b** as its *N*-Fmoc derivative **6b** cleanly occurred, thus shortening the reaction sequence for its synthesis.

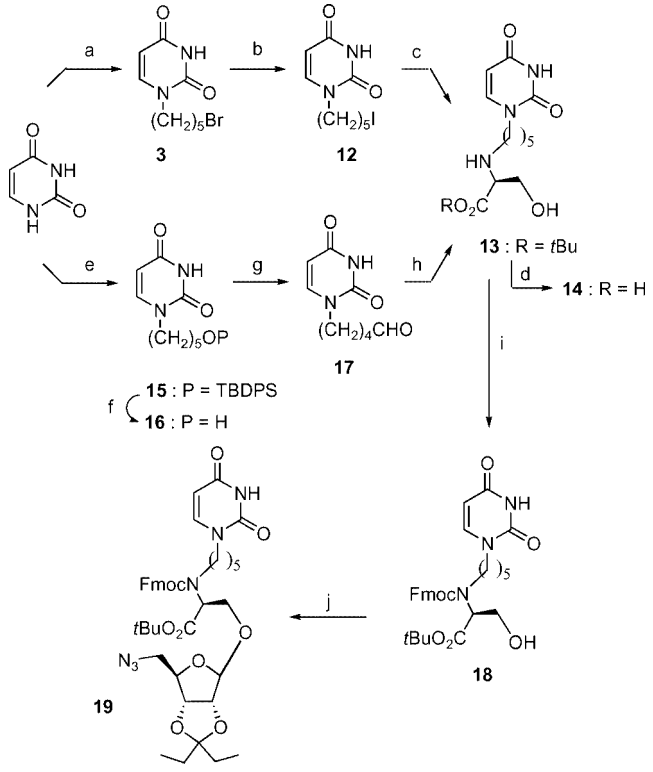
We next turned to the introduction of the aminoribosyl moiety (Scheme 2) onto the (uracilylalkyl)serine template by *O*-glycosylation with the 5-azido-5-deoxy-2,3-*O*-isopentylidene-D-ribofuranose (**7**),[14,17] the use of which was expected to promote the introduction of the serine derivative onto the β face of the ribose-like molecule due to steric hindrance at its α face.



Scheme 2. Reagents and conditions: a) DAST, CH_2Cl_2, –30 to 20 °C (β: 66%; α: 22%); b) **6b**, $BF_3{\cdot}OEt_2$, –45 to 10 °C (46%); c) H_2, $Pd(OH)_2$, MeOH; d) i. TFA/H_2O/THF, 4:3:1; ii. TFA (44%).

The glycosylation reaction involved first the activation of the anomeric position of the ribose derivative as a fluoride leading to **8** as a mixture of β/α anomers which could either be separated by column chromatography [isolated yields: 66% for the β anomer (1-H: doublet in ^1H NMR, $^2J_{H1-F}$ = 61.5 Hz) and 22% for the α anomer (1-H: dd, $^2J_{H1-F}$ = 63.5, $^3J_{H1-H2}$ = 3.6 Hz)] or used as a mixture. Indeed, condensation of the *N*-alkylated L-serine **6b** in the presence of boron trifluoride–diethyl ether with either the pure β anomer or a β/α mixture of anomers of the ribose led to the major formation of the expected β anomer of the *O*-glycosyl-*N*-(uracilylalkyl)serine **9** in the same β/α = 9:1 ratio. Thus, the pure β anomer of **9** (1-H: singlet) could be isolated in 46% yield. Reduction of the azido group to a primary amine and deprotection of the N^3-BOM of the uracil part were performed by hydrogenolysis in the presence of Pearlman's catalyst. Surprisingly, these conditions only resulted in the partial deprotection of the *N*-BOM moiety while deprotection of the *N*-Fmoc protecting group occurred, thus affording **10**. Removal of the remaining BOM and isopentylidene protecting groups required treatment with a mixture of trifluoroacetic acid/H_2O/THF followed by neat trifluoroacetic acid. The *O*-(5-amino-5-deoxyribosyl)-*N*-(uracilylpentyl)-serine derivative **11** was isolated in 44% yield. However, careful analysis of its NMR spectra revealed both partial reduction of the uracil double bond (20%) and partial epimerisation at the asymmetric carbon of serine. These by-products were respectively attributed to the conditions of hydrogenolysis and to the drastic conditions required for *N*-alkylation of the serine (80 °C, DMF for 2 d). It has to be pointed out that this epimerisation was not detected in compound **9** which was identified as a mixture of atropoisomers resulting from the presence of the Fmoc group and increasing the complexity of spectra.

This disappointing result prompted us to explore new routes for the preparation of the target compound **1** and we decided to not protect the N^3 position of the uracil moiety since its possible participation later in the reaction sequence had not been ascertained. The alternative preparation of the *N*-(uracilylalkyl)serine was carried out following to two different pathways (Scheme 3).

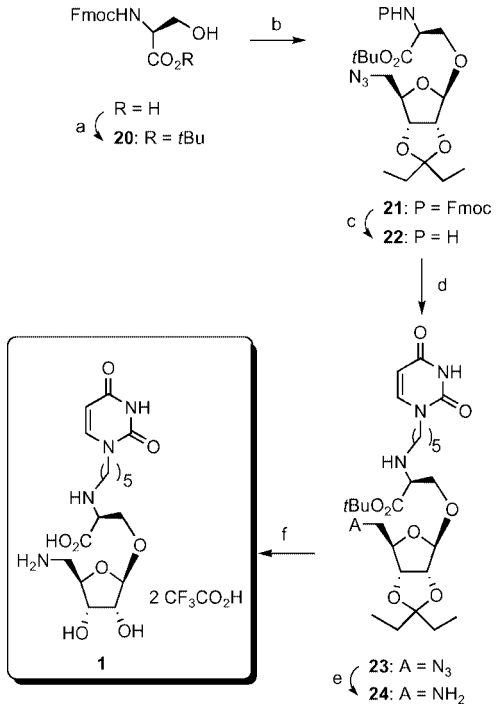


Scheme 3. Reagents and conditions: a) i. $(Me_3Si)_2NH$, Me_3SiCl, 80 °C; ii. $Br(CH_2)_5Br$, DMF, 80 °C (41%); b) NaI, acetone, 55 °C (65%); c) **2b**, K_2CO_3, MeCN, 60 °C (43%); d) TFA, CH_2Cl_2, room temp. (83%); e) $MsO(CH_2)_5OTBDPS$, Cs_2CO_3, DMF, 50 °C (67%); f) HCl, MeOH, room temp. (77%); g) Dess–Martin periodinane, CH_2Cl_2, room temp. (77%); h) i. **2b**, 4 Å MS, THF; ii. $NaBH(OAc)_3$ (71%); i) FmocCl, DIPEA, CH_2Cl_2, room temp. (71%); j) **8**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –45 to 10 °C (71%).

First, halogen exchange of the previously obtained N^1-(bromopentyl)uracil (**3**) with sodium iodide afforded the corresponding more reactive iodo derivative **12** which was then used for *N*-alkylation of the L-serine ester **2b** to give

13. However, completion of the reaction required heating at 60 °C and thus did not allow the milder conditions desired for this reaction. The second pathway proved more promising and involved *N*-alkylation of L-serine ester **2b** by reductive amination with N^1-formylbutyluracil (**17**). This latter was prepared in three steps from uracil and involved N^1-alkylation with 1-mesyloxy-5-(*tert*-butyldiphenylsilyloxy)pentane readily synthesised from commercially available pentane-1,5-diol by sequential monosilylation and mesylation.[18] The chemoselectivity of the uracil alkylation was checked by a 2D-NOESY NMR experiment which showed spatial coupling between 1-H of the side-chain and 6-H of the uracil. The *tert*-butyldiphenylsilyl protecting group of the resulting **15** was then removed under acidic conditions affording the alcohol **16** which was subsequently oxidised under Dess–Martin conditions to give the aldehyde **17**. Finally, *N*-alkylation of the L-serine ester **2b** by reductive amination with the aldehyde **17** afforded *tert*-butyl *N*-(uracilylpentyl)serine **13** in an improved 71% yield and in the required mild conditions. For further biological evaluation purposes, acidolysis of the *tert*-butyl ester in **13** was carried out and afforded the *N*-(uracilylpentyl)serine **14**. We could then turn to the second key step, the introduction of the ribosyl-like moiety.

This required *N*-Fmoc protection of the secondary amine of **13** (71% yield) and was followed by glycosylation of the resulting **18** with the 5-azido-5-deoxy-2,3-*O*-isopentylidene-1-fluoro-D-ribofuranose (**8**) under the same conditions as described previously and afforded **19** as a 5:1 mixture of β/α anomers in 71% isolated yield. Unfortunately, irrespective of the nature of the attempts made to separate these anomers, it was not possible to obtain the expected pure β anomer. Nevertheless, this difficulty could be overcome by inverting the sequence of reactions and by carrying out glycosylation prior to *N*-alkylation (Scheme 4).



Scheme 4. Reagents and conditions: a) $Cl_3CC(=NH)OtBu$, EtOAc, C_6H_{12}, 20 °C (90%); b) **8**, $BF_3{\cdot}OEt_2$, 4 Å MS, CH_2Cl_2, –45 °C to room temp. (28%); c) piperidine, DMF, room temp. (93%); d) i. **17**, Na_2SO_4, THF; ii. $NaBH(OAc)_3$, room temp. (65%); e) $(Ph_2PCH_2)_2$, THF, H_2O (84%); f) TFA, H_2O, THF (48%).

Thus, *O*-glycosylation of *tert*-butyl *N*-Fmoc-L-serine ester (**20**), obtained by esterification of the commercially available *N*-Fmoc-L-serine, with the 1-fluoro-D-ribofuranose derivative **8** led to the expected compound **21** which could be isolated as the pure β anomer in 28% yield. *N*-Fmoc deprotection with piperidine afforded the primary amine **22** which was then *N*-alkylated by reductive amination with the N^1-(formylbutyl)uracil (**17**) to afford the protected *N*-(uracilylpentyl)-*O*-(azidoribosyl)-L-serine derivative **23** in 65% yield. To avoid the partial reduction of the C5–C6 double bond of the uracil part observed during the hydrogenolysis of compound **9**, reduction of the azido group of the ribosyl moiety of **23** was carried out under Staudinger conditions in the presence of 1,2-bis(diphenylphosphanyl)ethane (84% yield) and was followed by acidic hydrolysis of the isopentylidene protecting group to give the targeted inhibitor **1** in 48% yield.

Conclusions

In conclusion, enantiomerically pure *N*-(uracilylpentyl)-β-D-*O*-aminoribosyl-L-serine has been synthesised by sequential *O*-glycosylation and *N*-alkylation by reductive amination of a serinyl derivative linker. This structure should be a promising lead in the development of MraY translocase inhibitors. Exploration of its inhibitory activity is currently in progress and should be reported in due course.

Experimental Section

^1H (250 or 500 MHz) and ^{13}C NMR (63 or 126 MHz) spectra were recorded with a Bruker AM250 spectrometer in $CDCl_3$ at 300 K (unless indicated otherwise). Chemical shifts (δ) are reported in ppm and coupling constants are given in Hz. Optical rotations were measured with a Perkin–Elmer 341 polarimeter equipped with a sodium (589 nm) or mercury (365 nm) lamp at 20 °C. Mass spectra, chemical ionisation (CI), and high-resolution (HRMS), were recorded by the Service de Spectrométrie de Masse, ICSN, Gif-sur-Yvette. All reactions were carried out under argon and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on glass. Unless indicated, flash chromatography was performed with Merck Kieselgel 60 (0.2–0.5 mm) or Bakerbond C_{18} (0.04 mm); the solvent systems are given as v/v. Spectroscopic (^1H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.[19]

***tert*-Butyl L-Serine Ester (2b):** 10% Pd/C (350 mg) was added to a solution of *tert*-butyl *N*-(benzyloxycarbonyl)-L-serine ester (1.48 g, 5.01 mmol) in EtOAc (100 mL). Hydrogenation was carried out in the presence of dihydrogen at room temp. for 90 min. After filtration through a Celite pad and concentration in vacuo, the L-serine ester **2b** was isolated as a colourless oil (770 mg, 95%). The product was used in subsequent steps without purification. $[\alpha]_D$ = –17.5 (c = 1, CH_2Cl_2). ^1H NMR: δ = 3.74 (dd, J_{3a-3b} = 10.5, J_{3a-2}

= 4.5 Hz, 1 H, 3a-H), 3.57 (dd, $J_{3b–3a}$ = 10.5, $J_{3b–2}$ = 6.3 Hz, 1 H, 3b-H), 3.44 (dd, $J_{2–3b}$ = 6.3, $J_{2–3a}$ = 4.5 Hz, 1 H, 2-H), 2.80 (br. s, 3 H, OH, NH), 1.45 (s, 9 H, *t*Bu) ppm. ^{13}C NMR: δ = 173.1 (C-1), 81.6 (*t*Bu), 64.2 (C-3) 56.6 (C-2), 28.1 (*t*Bu) ppm. HRMS (ESI): calcd. for $C_7H_{16}NO_3$ $[M + H]^+$ 162.1130; found 162.1144.

3-(Benzyloxymethyl)-1-(5′-chloropentyl)uracil (4): Benzyloxymethyl chloride (2.14 mL, 9.42 mmol) and DBU (1.4 mL, 9.42 mmol) were added to a solution of 1-(5-bromopentyl)uracil (**3**)[12,13] (3.1 g, 11.9 mmol) in DMF (13 mL) and the reaction mixture was stirred at room temp. for 24 h. The mixture was concentrated in vacuo. Purification by flash column chromatography (EtOAc/cyclohexane, 6:4) afforded compound **4** as a colourless oil (1.2 g, 77%). R_f = 0.30 (EtOAc/cyclohexane, 6:4). ^{1}H NMR: δ = 7.06 (d, $J_{6–5}$ = 7.9 Hz, 1 H, 6-H), 5.69 (d, $J_{5–6}$ = 7.9 Hz, 1 H, 5-H), 5.47, 4.69 (2s, 4 H, $CH_{2\,BOM}$), 3.70 (t, $J_{1′–2′}$ = 8.3 Hz, 2 H, 1′-H), 3.52 (t, $J_{5′–4′}$ = 6.4 Hz, 2 H, 5′-H), 1.90–1.61 (m, 4 H, 2′-H, 4′-H),1.60–1.40 (m, 2 H, 3′-H) ppm. ^{13}C NMR: δ = 162.9 (C-4), 151.3 (C-2), 143.2 (C-6), 137.9 ($C_{arom.}$), 128.1, 127.5 ($CH_{arom.}$), 101.3 (C-5), 72.0, 70.3 ($CH_{2\,BOM}$), 49.3 (C-1′), 44.5 (C-5′), 31.7 (C-4′), 27.9 (C-2′), 23.5 (C-3′) ppm. MS (ESI): *m*/*z* (%) = 359 (100) $[M + Na]^+$.

***tert*-Butyl (*S*)-3-(Benzyloxy)-2-[5′′-(3′-benzyloxymethyluracil-1′-yl)-pentylamino]propanoate (5a):** Caesium carbonate (130 mg, 0.40 mmol) and NaI (160 mg, 1.28 mmol) were added to a solution of *tert*-butyl *O*-benzyl-L-serine ester (**2a**)[17] (50 mg, 0.20 mmol) and 3-(benzyloxymethyl)-1-(5′-chloropentyl)uracil (**4**) (87 mg, 0.26 mmol) in DMF (1.3 mL). The reaction mixture was heated at 50 °C for 96 h. The solvent was removed in vacuo. H_2O was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. Flash chromatographic purification (EtOAc, 100%) afforded **5a** as a colourless oil (90 mg, 63%). R_f = 0.22 (EtOAc, 100%). $[\alpha]_D$ = –5 (c = 1, CH_2Cl_2). ^{1}H NMR: δ = 7.36–7.15 (m, 10 H, $H_{arom.}$), 7.02 (d, $J_{6′-5′}$ = 7.8 Hz, 1 H, 6′-H), 5.62 (d, $J_{5′–6′}$ = 7.8 Hz, 1 H, 5′-H), 5.43, 4.65 (2s, 4 H, $CH_{2\,BOM}$), 4.50, 4.48 (AB, $J_{A–B}$ = 12.1 Hz, 2 H, $CH_{2\ Bn}$), 3.69–3.53 (m, $J_{3–2}$ = 5.0 Hz, 4 H, 3-H, e-H), 3.27 (dd, $J_{2–3a}$ = $J_{2–3b}$ = 5.0 Hz, 1 H, H_2), 2.70–2.38 (m, 2 H, a-H), 1.93 (br. s, 1 H, *N*H), 1.71–1.26 (m, 15 H, b-H, c-H, d-H, *t*Bu) ppm. ^{13}C NMR: δ = 172.4 (C-1), 163.1 (C-4′), 151.5 (C-2′), 143.2 (C-6′), 138.1, 138.0 ($C_{arom.}$), 128.4, 128.3 ($CH_{arom.}$), 127.7 ($CH_{arom.}$), 101.6 (C-5′), 81.3 (*t*Bu), 73.3 ($CH_{2\,Bn}$), 73.3, 70.5 (2 $CH_{2\,BOM}$), 71.3 (C-3), 62.1 (C-2), 49.7 (C-e), 47.9 (C-a), 29.7 (C-b), 28.8 (C-d), 28.2 (*t*Bu), 24.1 (C-c) ppm. HRMS (ESI): calcd. for $C_{31}H_{42}N_3O_6$ $[M + H]^+$ 552.3074; found 552.3074.

***tert*-Butyl 3-(Benzyloxy)-2-[(*S*)-*N*-Fmoc-{5′′-[3′-(benzyloxymethyl)-uracil-1′-yl]pentylamino}]propanoate (6a):** Diisopropylethylamine (DIPEA) (84 μL, 0.48 mmol) and FmocCl (90 mg, 0.35 mmol) were added to a solution of the amine **5a** (130 mg, 0.24 mmol) in CH_2Cl_2 (3.5 mL) and the reaction mixture was stirred at room temp. for 3 h. The solution was concentrated in vacuo. Purification by flash column chromatography (EtOAc/cyclohexane, 1:1) afforded compound **6a** as a colourless oil (150 mg, 81%). R_f = 0.25 (EtOAc/cyclohexane, 1:1). $[\alpha]_D$ = –13 (c = 1, CH_2Cl_2). ^{1}H NMR (rotamer mixture): δ = 7.90–7.22 (m, 19 H, 6′-H, $H_{arom.}$), 5.65 (d, $J_{5′–6′}$ = 7.9 Hz, 1 H, 5′-H), 5.41 (s, 2 H, $CH_{2\,BOM}$), 4.70–4.53 (m, 4 H, $CH_{2\,BOM}$, $CH_{2\,Fmoc}$), 4.47, 4.39 (AB, $J_{A–B}$ = 11.8 Hz, 2 H, $CH_{2\ Bn}$), 4.33–4.15 (m, 2 H, 2-H, CH_{Fmoc}), 3.84–3.70 (m, 2 H, 3-H), 3.59 (t, $J_{e–d}$ = 7.6 Hz, 2 H, e-H), 3.00–2.69 (m, 2 H, a-H), 1.47–1.01 (m, 13 H, d-H, b-H, *t*Bu), 1.00–0.80 (m, 2 H, c-H) ppm. ^{13}C NMR (CD_3CN): δ = 169.5 (C-1), 164.0 (C-4′), 156.7 (CO_{Fmoc}), 152.6 (C-2′), 145.2 (C-6′, C_{Fmoc}), 142.3 (C_{Fmoc}), 139.5, 139.3 ($C_{arom.}$), 129.3, 129.2, 128.6, 128.5, 128.1, 125.5, 121.0 ($CH_{arom.}$), 101.5 (C-5′), 82.1 (*t*Bu), 73.6 (C-4), 72.5, 71.3 ($CH_{2\,BOM}$), 69.3 (C-3), 67.1 ($CH_{2\,Fmoc}$), 61.7 (C-2), 50.1 (C-e), 48.4 (C-a), 48.2 (CH_{Fmoc}), 48.2 (C-5), 29.4, 29.3 (C-b, C-d), 28.3 (*t*Bu), 24.4 (c-H) ppm. HRMS (ESI): calcd. for $C_{46}H_{51}N_3O_8Na$ $[M + Na]^+$ 796.3574; found 796.3603.

***tert*-Butyl (*S*)-2-[5′′-(3′-Benzyloxymethyluracil-1′-yl)pentylamino]-3-hydroxypropanoate (5b):** The procedure was similar to that used for the obtention of **5a** and involved L-serine ester **2b** (63 mg, 0.39 mmol), 3-(benzyloxymethyl)-1-(5′-chloropentyl)uracil (**4**) (159 mg, 0.47 mmol), caesium carbonate (254 mg, 0.78 mmol) and NaI (297 mg, 2.34 mmol) in DMF (1.3 mL). The mixture was heated at 80 °C for 48 h. Flash column chromatography (CH_2Cl_2/MeOH, 98:2→95:5) afforded **5b** as a colourless oil (67 mg, 37%). R_f = 0.17 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D$ = –9 (c = 1, CH_2Cl_2). ^{1}H NMR: δ = 7.45–7.25 (m, 5 H, $H_{arom.}$), 7.12 (d, $J_{6′-5′}$ = 7.9 Hz, 1 H, 6′-H), 5.72 (d, $J_{5′–6′}$ = 7.9 Hz, 1 H, 5′-H), 5.51, 4.73 (2s, 4 H, $CH_{2\,BOM}$), 3.71 (dd, $J_{3a–3b}$ = 10.7, $J_{3a–2}$ = 4.5 Hz, 1 H, 3a-H), 3.73 (t, $J_{e–d}$ = 7.5 Hz, 2 H), 3.56 (dd, $J_{3b–3a}$ = 10.7, $J_{3b–2}$ = 6.6 Hz, 1 H, 3b-H), 3.27 (dd, $J_{2–3b}$ = 6.6, $J_{2–3a}$ = 4.5 Hz, 1 H, 2-H), 2.82–2.49 (m, 2 H, a-H), 2.40 (br. s, 2 H, *O*H, *N*H), 1.85–1.35 (m, 15 H, b-H, c-H, d-H, *t*Bu) ppm. ^{13}C NMR: δ = 172.5 (C-1), 162.9 (C-4′), 151.2 (C-2′), 143.3 (C-6′), 137.7 ($C_{arom.}$), 128.0, 127.3 ($CH_{arom.}$), 101.0 (C-5′), 81.3 (*t*Bu), 71.8, 70.1 ($CH_{2\,BOM}$) 63.2 (C-2), 62.5 (C-3), 49.3 (C-e), 47.6 (C-a), 29.2 (C-b), 28.3 (C-d), 27.7 (*t*Bu), 23.7 (C-c) ppm. HRMS (ESI): calcd. for $C_{24}H_{36}N_3O_6$ $[M + H]^+$ 462.2604; found 462.2592.

***tert*-Butyl 2-[(*S*)-*N*-Fmoc-{5′′-[3′-(benzyloxymethyl)uracil-1′-yl]-pentylamino}]-3-hydroxypropanoate (6b):** DIPEA (0.22 mL, 1.27 mmol) and FmocCl (214 mg, 0.83 mmol) were added to a solution of the amine **5b** (306 mg, 0.66 mmol) in CH_2Cl_2 (7 mL) and the reaction mixture was stirred at room temp. for 2 h. The solution was concentrated in vacuo. Purification by flash column chromatography (CH_2Cl_2/MeOH, 98:2) afforded compound **6b** as a colourless oil (330 mg, 73%). R_f = 0.36 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D$ = –13 (c = 1, CH_2Cl_2). ^{1}H NMR (CD_3CN, 500 MHz, rotamer mixture): δ = 7.85–7.23 (m, 14 H, 6′-H, $H_{arom.}$), 5.63 (d, $J_{5′–6′}$ = 7.9 Hz, 1 H, 5′-H), 5.40 (s, 2 H, $CH_{2\,BOM}$), 4.64–4.48 (m, 4 H, $CH_{2\,BOM}$, $CH_{2\,Fmoc}$), 4.30–4.20 (m, 1 H, CH_{Fmoc}), 3.93 (dd, $J_{2–3a}$ = 7.7, $J_{2–3b}$ = 4.8 Hz, 1 H, 2-H), 3.85–3.54 (m, 4 H, 3-H, e-H), 2.99 (t, J = 3.1 Hz, 1 H, *O*H), 2.95–2.71 (m, 2 H, a-H), 1.49–1.40 (m, 2 H, d-H), 1.36 (s, 9 H, *t*Bu), 1.26–1.05 (m, 2 H, b-H), 0.99–0.85 (m, 2 H, c-H) ppm. ^{13}C NMR (CD_3CN, 126 MHz): δ = 169.4 (C-1), 163.1 (C-4′), 156.2 (CO_{Fmoc}), 151.6 (C-2′), 143.9, 141.5 138.0 ($C_{arom.}$), 143.1 (C-6′), 128.4, 127.7, 127.2, 124.8, 120.1 ($CH_{arom.}$), 101.6 (C-5′), 82.3 (*t*Bu), 72.3, 70.5 ($CH_{2\,BOM}$), 66.8 ($CH_{2\,Fmoc}$), 63.3 (C-2), 61.5 (C-3), 49.6 (C-e), 48.8 (C-a), 47.4 (CH_{Fmoc}), 28.6 (C-b, C-d), 28.0 (*t*Bu), 23.6 (c-H) ppm. HRMS (ESI): calcd. for $C_{39}H_{45}N_3O_8Na$ $[M + Na]^+$ 706.3104; found 706.3099.

***tert*-Butyl *O*-(5′-Azido-5′-deoxy-2′,3′-*O*-isopentylidene-β-D-ribos-1′-yl)-*N*-Fmoc-*N*-[5′′-(*N*^{3}-benzyloxymethyluracil-1-yl)pentyl]-L-serine (9):** Molecular sieves (4 Å, 1.3 g) were added to a solution of **6b** (298 mg, 0.50 mmol) and ribosyl fluoride **8**[14] (184 mg, 0.75 mmol) in CH_2Cl_2 (15 mL). After stirring for 1 h at room temp., boron trifluoride–diethyl ether (76 μL, 0.6 mmol) was added at –45 °C. After allowing to warm to 10 °C over 16 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL), filtered through a Celite pad and washed with a saturated aqueous solution of sodium hydrogen carbonate (30 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo. Flash column chromatography (cyclohexane/EtOAc, 6:4) afforded a β/*a* anomer mixture (9:1) of glycosylated product **9** (67%) from which anomer β could be isolated as a pure compound (220 mg, 46%). R_f = 0.4 (cyclohexane/EtOAc, 1:1). $[\alpha]_D$ = –27 (c = 1, CH_2Cl_2). ^{1}H NMR (CD_3CN, 500 MHz): δ = 7.90–7.22 (m, 14 H, 6-H, $H_{arom.}$), 5.57 (d, $J_{5–6}$ = 7.8 Hz, 1 H, 5-

H), 5.40 (s, 2 H, $CH_{2\,BOM}$), 5.06 (s, 1 H, 1′-H), 4.69–4.46 (m, $J_{CH2-CHFmoc}$ = 5, $J_{2'-3'}$ = 6 Hz, 6 H, 2′-H, 3′-H, $CH_{2\,Fmoc}$, $CH_{2\,BOM}$), 4.35–4.21 (m, $J_{CH-CH2\,Fmoc}$ = 7.2 Hz, 2 H, 4′-H, CH_{Fmoc}), 4.07–4.02 (m, 1 H, 2′′-H), 3.91 (dd, $J_{3''a-3''b}$ = 10.6, $J_{3''a-2''}$ = 8.4 Hz, 1 H, 3′′a-H), 3.78 (dd, $J_{3''b-3''a}$ = 10.6, $J_{3''b-2''}$ = 4.7 Hz, 1 H, 3′′b-H), 3.71–3.55 (m, 2 H, e-H), 3.28 (dd, $J_{5'a-5'b}$ = 12.5, $J_{5'a-4'}$ = 7.9 Hz, 1 H, 5′a-H), 3.15 (dd, $J_{5'b-5'a}$ = 12.5, $J_{5'b-4'}$ = 6.4 Hz, 1 H, 5′b-H), 2.97–2.70 (m, 2 H, a-H), 1.72–1.42 (m, 6 H, 2 CH_2CH$_3$, d-H), 1.38, 1.35, 1.34 (s, 9 H, *t*Bu), 1.18–1.05 (m, 2 H, b-H), 1.02–0.76 (m, 6 H, 2 CH_2CH_3, c-H) ppm. ^{13}C NMR (CD_3CN, 126 MHz): δ = 169.2 (C-1′′), 164.0 (C-4), 156.4 (CO_{Fmoc}), 152.6 (C-2), 145.3 (C-6, $C_{arom.}$), 142.3, 139.5 ($C_{arom.}$), 129.2, 128.6, 128.4, 128.1, 125.5, 120.9 ($CH_{arom.}$), 117.4 [$C(CH_2CH_3)_2$], 109.4 (C-1′), 101.5 (C-5), 86.5 (C-4′), 86.3 (C-2′), 83.2 (C-3′), 82.3 (*t*Bu), 72.5, 71.2 ($CH_{2\,BOM}$), 67.4 ($CH_{2\,Fmoc}$), 66.4 (C-3′′), 61.6 (C-2′′), 54.0 (C-5′), 50.1 (C-e), 49.3 (C-a), 48.1 (CH_{Fmoc}), 30.0, 29.5 (CH_2CH_3), 29.3 (C-d), 29.0 (C-b), 28.2 (*t*Bu), 24.3 (C-c), 8.7, 7.7 (CH_2CH_3) ppm. HRMS (ESI): calcd. for $C_{49}H_{60}N_6O_{11}Na$ [M + Na]$^+$ 931.4218; found 931.4238.

1-(5′-Iodopentyl)uracil (12): A solution of 1-(5′-bromopentyl)uracil (**3**) (3.1 g, 11.9 mmol) and sodium iodide (8.9 g, 59.3 mmol) in acetone (190 mL) was heated at 55 °C for 3 h. The solvent was then removed in vacuo. The residue was taken up in EtOAc (100 mL) and washed with 10% aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with H_2O (100 mL), dried with $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography with CH_2Cl_2/MeOH (95:5) afforded compound **12** as a white solid (2.4 g, 65%). R_f = 0.30 (CH_2Cl_2/MeOH, 95:5). M.p. 88–90 °C. ^{1}H NMR: δ = 8.37 (br. s, 1 H, *N*H), 7.10 (d, J_{6-5} = 7.9 Hz, 1 H, 6-H), 5.66 (dd, J_{5-6} = 7.9, J_{5-3} = 2.3 Hz, 1 H, 5-H), 3.70 (t, $J_{1'-2'}$ = 7.3 Hz, 2 H, 1′-H), 3.15 (t, $J_{5'-4'}$ = 6.8 Hz, 2 H, 5′-H), 1.90–1.60 (m, 4 H, 2′-H, 4′-H), 1.50–1.35 (m, 2 H, 3′-H) ppm. ^{13}C NMR: δ = 164.4 (C-4), 151.1 (C-2), 144.6 (C-6), 102.3 (C-5), 48.6 (C-1′), 32.7 (C-4′), 27.9 (C-2′), 27.2 (C-3′), 6.5 (C-5′) ppm. HRMS (ESI): calcd. for $C_9H_{14}N_2O_2I$ [M + H]$^+$ 309.0100; found 309.0118.

***tert*-Butyl (*S*)-3-Hydroxy-2-[5′′-(uracil-1′-yl)pentylamino]propanoate (13):** From 1-(5′-iodopentyl)uracil (**12**): K_2CO_3 (52 mg, 0.38 mmol) was added to a solution of L-serine ester **2b** (54 mg, 0.33 mmol) and 1-(5′-iodopentyl)uracil (**12**) (59 mg, 0.19 mmol) in CH_3CN (1.5 mL). The reaction mixture was heated at 60 °C for 30 h. The solvent was removed in vacuo. H_2O was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo prior to flash chromatographic purification (CH_2Cl_2/MeOH, 98:2→95:5) affording **13** as colourless oil (30 mg, 43%).

From 5-(Uracil-1′-yl)pentanal (17): Serine ester **2b** (800 mg, 4.97 mmol) in THF (35 mL) was added to a solution of the aldehyde **17** (974 mg, 4.97 mmol) in THF (35 mL) in the presence of 4 Å molecular sieves. The reaction mixture was stirred at room temp. for 24 h then cooled to 0 °C. Sodium triacetoxyborohydride (3.16 g, 14.91 mmol) was added and the heterogeneous reaction mixture was stirred at room temp. for 40 h. After filtration through a Celite pad, the solvent was removed in vacuo. The residue was diluted with CH_2Cl_2/MeOH (95:5, 100 mL) and washed with 10% aq. Na_2CO_3 (50 mL). The aqueous layer was extracted with CH_2Cl_2/MeOH (95:5, 2 × 50 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography with CH_2Cl_2/MeOH (95:5) as eluent afforded compound **13** as a colourless oil (1.2 g, 71%). R_f = 0.22 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D$ = –16 (c = 1, CH_2Cl_2). ^{1}H NMR: δ = 7.20 (d, $J_{6'-5'}$ = 7.8 Hz, 1 H, 6′-H), 5.70 (d, $J_{5'-6'}$ = 7.8 Hz, 1 H, 5′-H), 3.78 (dd, J_{3a-3b} = 10.8, J_{3a-2} = 4.4 Hz, 1 H, 3a-H), 3.73 (t, J_{e-d} = 7.4 Hz, 2 H, e-H), 3.57 (dd, J_{3b-3a} = 10.8, J_{3b-2} = 6.4 Hz, 1 H, 3b-H), 3.25 (dd, J_{2-3b} = 6.4, J_{2-3a} = 4.4 Hz, 1 H, 2-H), 2.78–2.47 (m, 2 H, a-H), 1.80–1.30 (m, 15 H, b-H, c-H, d-H, *t*Bu) ppm. ^{13}C NMR: δ = 172.5 (C-1), 164.6 (C-4′), 151.2 (C-2′), 144.6 (C-6′), 102.4 (C-5′), 82.1 (*t*Bu), 63.5 (C-2), 62.8 (C-3), 48.9 (C-e), 48.0 (C-a), 29.7 (C-b), 29.0 (C-d), 28.3 (*t*Bu), 24.1 (C-c) ppm. HRMS (ESI): calcd. for $C_{16}H_{28}N_3O_5$ [M + H]$^+$ 342.2029; found 342.2052.

(*S*)-3-Hydroxy-2-[5′′-(uracil-1′-yl)pentylamino]pentanoic Acid (14): TFA (0.3 mL) was added to a solution of the amino acid ester **13** (41 mg, 0.12 mmol) in CH_2Cl_2 (1.5 mL) and the reaction mixture was stirred at room temp. for 16 h. The solution was concentrated in vacuo. After purification by C_{18} reversed-phase column chromatography (100% H_2O), compound **14** was obtained as a hygroscopic white solid (40 mg, 83%). R_f = 0.4 (100% H_2O). ^{1}H NMR (CD_3OD): δ = 7.58 (d, $J_{6'-5'}$ = 7.8 Hz, 1 H, 6′-H), 5.66 (d, $J_{5'-6'}$ = 7.8 Hz, 1 H, 5′-H), 4.10–3.90 (m, 3 H, 2-H, 3-H), 3.77 (t, J_{e-d} = 7.2 Hz, 2 H, e-H), 3.09 (m, 2 H, a-H), 1.85–1.65 (m, 4 H, b-H, d-H), 1.50–1.30 (m, 2 H, c-H) ppm. ^{13}C NMR (CD_3OD): δ = 170.3 (C-1), 166.7 (C-4′), 152.9 (C-2′), 147.2 (C-6′), 102.3 (C-5′), 63.1 (C-2), 59.8 (C-3), 49.1 (C-e), 47.3 (C-a), 29.3 (C-b), 26.6 (C-d), 24.3 (C-c) ppm.

1-[5′-(*tert*-Butyldiphenylsilyloxy)pentyl]uracil (15): Uracil (11.05 g, 38.7 mmol) and caesium carbonate (23.3 g, 71.5 mmol) were stirred in dry DMF (450 mL) at room temp. for 15 min. Then 5-(*tert*-butyldiphenylsilyloxy)pentyl methanesulfonate[18] (27.6 g, 65.8 mmol) in dry DMF (50 mL) was added and the reaction mixture was heated at 50 °C for 24 h. Water (300 mL) was added and the organic layer was extracted with EtOAc (3 × 300 mL) and dried with $MgSO_4$. After concentration in vacuo and purification by flash column chromatography with CH_2Cl_2/MeOH (95:5), compound **15** was obtained as a colourless oil (19.2 g, 67%). R_f = 0.41 (CH_2Cl_2/MeOH, 95:5). ^{1}H NMR: δ = 8.40 (br. s, 1 H, *N*H), 7.65–7.30 (m, 10 H, $H_{arom.}$), 7.05 (d, J_{6-5} = 7.9 Hz, 1 H, 6-H), 5.64 (d, J_{5-6} = 7.9 Hz, 1 H, 5-H), 3.67 (t, $J_{1'-2'}$ = 6.6 Hz, 2 H, 1′-H), 3.64 (t, $J_{5'-4'}$ = 6.1 Hz, 2 H, 5′-H), 1.75–1.50 (m, 4 H, 2′-H, 4′-H), 1.45–1.30 (m, 2 H, 3′-H), 1.02 (s, 9 H, *t*Bu) ppm. ^{13}C NMR: δ = 164.3 (C-4), 151.1 (C-2), 144.6 (C-6), 135.6, 129.7, 127.7 ($CH_{arom.}$), 134.0 ($C_{arom.}$), 63.5 (C-5′), 48.9 (C-1′), 32.0 (C-4′), 28.8 (C-2′), 26.9 (*t*Bu), 22.8 (C-3′), 19.3 (*t*Bu) ppm. HRMS (ESI): calcd. for $C_{25}H_{32}N_2O_3NaSi$ [M + Na]$^+$ 459.2080; found 459.2067.

1-(5′-Hydroxypentyl)uracil (16): A 37% solution of HCl (1.65 mL) was added to a solution of silyl ether **15** (3.7 g, 8.47 mmol) in MeOH (13 mL) . The reaction mixture was stirred at room temp. for 4 h. The solvent was concentrated in vacuo and the crude product was purified by flash column chromatography with CH_2Cl_2/MeOH (95:5). Alcohol **16** was obtained as a white solid (1.3 g, 77%). R_f = 0.18 (CH_2Cl_2/MeOH, 90:10). M.p. 78–80 °C. ^{1}H NMR: δ = 9.19 (br. s, 1 H, *N*H), 7.12 (d, J_{6-5} = 7.9 Hz, 1 H, 6-H), 5.65 (d, J_{5-6} = 7.9 Hz, 1 H, 5-H), 3.70 (t, $J_{1'-2'}$ = 7.1 Hz, 2 H, 1′-H), 3.61 (t, $J_{5'-4'}$ = 6.0 Hz, 2 H, 5′-H), 1.80–1.50 (m, 4 H, 2′-H, 4′-H), 1.45–1.30 (m, 2 H, 3′-H) ppm. ^{13}C NMR: δ = 164.6 (C-4), 151.4 (C-2), 145.0 (C-6), 102.1 (C-5), 61.9 (C-5′), 48.7 (C-1′), 32.0 (C-4′), 28.8 (C-2′), 22.6 (C-3′) ppm. HRMS (ESI): calcd. for $C_9H_{14}N_2O_3Na$ [M + Na]$^+$ 221.0902; found 221.0910.

5-(Uracil-1′-yl)pentanal (17): Dess–Martin periodinane (3 g, 7.07 mmol) was added to a solution of 1-(5′-hydroxypentyl)uracil (**16**) (1.3 g, 6.56 mmol) in CH_2Cl_2 (140 mL). The resulting heterogeneous mixture was stirred at room temp. for 75 min. After dilution with CH_2Cl_2 (200 mL), a saturated aqueous $NaHCO_3$ solution (120 mL) and $Na_2S_2O_3$ (18.8 g, 118.9 mmol) were added and

the resulting biphasic solution was stirred at room temp. for 30 min. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 200 mL). After drying with $MgSO_4$ and concentrating in vacuo, the product was purified by flash column chromatography with CH_2Cl_2/MeOH (95:5) as eluent. The aldehyde **17** was obtained as a white solid (1 g, 77%). R_f = 0.23 (CH_2Cl_2/MeOH, 90:10). M.p. 82–84 °C. ^{1}H NMR: δ = 9.72 (s, 1 H, 1-H), 9.29 (br. s, 1 H, *N*H), 7.12 (d, $J_{6'-5'}$ = 7.8 Hz, 1 H, 6′-H), 5.66 (dd, $J_{5'-6'}$ = 7.8, $J_{5'-3'}$ = 2.2 Hz, 1 H, 5′-H), 3.70 (t, J_{5-4} = 6.8 Hz, 2 H, 5-H), 2.49 (t, J_{2-3} = 6.0 Hz, 2 H, 2-H), 1.80–1.50 (m, 4 H, 3-H, 4-H) ppm. ^{13}C NMR: δ = 202.0 (C-1), 164.6 (C-4′), 151.3 (C-2′), 144.8 (C-6′), 102.2 (C-5′), 48.4 (C-5), 43.0 (C-2), 28.3 (C-4), 18.7 (C-3) ppm. HRMS (ESI): calcd. for $C_9H_{12}N_2O_3Na$ [M + Na]$^+$ 219.0746; found 219.0769.

***tert*-Butyl (*S*)-3-Hydroxy-2-{*N*-Fmoc-[(5′′-uracil-1′-yl)-pentylamino]}propanoate (18):** DIPEA (70 μL, 0.41 mmol) and FmocCl (97 mg, 0.37 mmol) were added to a solution of the amine **13** (103 mg, 0.3 mmol) in CH_2Cl_2 (3.5 mL) and the reaction mixture was stirred at room temp. for 2 h. The solution was concentrated in vacuo. Purification by flash column chromatography (CH_2Cl_2/MeOH, 95:5) afforded compound **18** as a white solid (121 mg, 71%). R_f = 0.32 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D$ = –8.4 (*c* = 1, CH_2Cl_2). ^{1}H NMR (CD_3CN, 350 K): δ = 7.90–7.27 (m, 9 H, 6′-H, $H_{arom.}$), 5.66 (d, $J_{5'-6'}$ = 7.8 Hz, 1 H, 5′-H), 4.70–4.45 (m, 2 H, $CH_{2\,Fmoc}$), 4.34–4.24 (m, 1 H, CH_{Fmoc}), 4.15–4.01 (m, 1 H, 2-H), 3.90 (dd, J_{3a-3b} = 11.3, J_{3a-2} = 4.3 Hz, 1 H, 3a-H), 3.80–3.68 (m, 1 H, 3b-H), 3.66 (t, J_{e-d} = 6.7 Hz, 2 H, e-H), 3.25–2.75 (m, 2 H, a-H), 1.65–1.50 (m, 2 H, d-H), 1.44 (s, 9 H, *t*Bu), 1.45–1.30 (m, 2 H, b-H), 1.20–1.05 (m, 2 H, c-H) ppm. ^{13}C NMR (CD_3CN): δ = 170.0 (C-1), 165.1 (C-4′), 156.9 (CO_{Fmoc}), 152.1 (C-2′), 146.6 (C-6′), 145.3, 142.3 ($C_{arom.}$), 128.6, 128.1, 125.6, 120.9 ($CH_{arom.}$), 101.9 (C-5′), 82.1 (*t*Bu), 67.1 ($CH_{2\,Fmoc}$), 64.1 (C-2), 61.2 (C-3), 49.1 (C-a, C-e), 48.2 (CH_{Fmoc}), 29.3, 29.1 (C-b, C-d), 28.2 (*t*Bu), 24.3 (c-H) ppm. HRMS (ESI): calcd. for $C_{31}H_{37}N_3O_7Na$ [M + Na]$^+$ 586.2529; found 586.2504.

***tert*-Butyl *O*-(5′-Azido-5′-deoxy-2′,3′-*O*-isopentylidene-D-ribos-1′-yl)-*N*-Fmoc-*N*-(5′′-uracil-1-ylpentyl)-L-serine Ester (19):** Molecular sieves (4 Å, 280 mg) were added to a solution of **18** (51 mg, 0.11 mmol) and ribosyl fluoride **8**[14] (39 mg, 1.22 mmol) in CH_2Cl_2 (3 mL). After stirring for 2 h at room temp., boron trifluoride–diethyl ether (15 μL, 0.12 mmol) was added at –45 °C. After allowing the mixture to warm to 10 °C over 18 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL), filtered through a Celite pad and washed with a saturated aqueous solution of sodium hydrogen carbonate (10 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo. Flash column chromatography (CH_2Cl_2/MeOH, 99:1) afforded an inseparable (5:1) β/α anomer mixture of glycosylated product **19** (71%). R_f = 0.17 (CH_2Cl_2/MeOH, 97:3). ^{1}H NMR (CD_3CN, 350 K): δ = 8.79 (br. s, 1 H, *N*HCO), 7.90–7.22 (m, 9 H, 6-H, $H_{arom.}$), 5.57 (d, J_{5-6} = 7.8 Hz, 1 H, 5-H), 5.01 (s, 1 H, 1′-H), 4.75–4.45 (m, 4 H, 2′-H, 3′-H, $CH_{2\,Fmoc}$), 4.35–4.21 (m, 2 H, 4′-H, CH_{Fmoc}), 4.14 (m, 1 H, 2′′-H), 4.01–3.74 (m, 2 H, 3′′-H), 3.66 (t, J_{e-d} = 7.2 Hz, 2 H, e-H), 3.35 (dd, $J_{5'a-5'b}$ = 12.3, $J_{5'a-4'}$ = 7.8 Hz, 1 H, 5′a-H), 3.26 (dd, $J_{5'b-5'a}$ = 12.3, $J_{5'b-4'}$ = 7.1 Hz, 1 H, 5′b-H), 3.18–2.80 (m, 2 H, a-H), 1.79–1.50 (m, 6 H, 2 CH_2CH$_3$, d-H), 1.49–1.24 (m, 11 H, b-H, *t*Bu), 1.23–1.02 (m, 2 H, c-H), 1.00–0.82 (m, 6 H, 2 CH$_2$CH_3) ppm. ^{13}C NMR: δ = 168.3 (C-1′′), 163.9 (C-4), 156.0 (CO_{Fmoc}), 144.6, 144.5 ($C_{arom.}$), 144.1 (C-6), 141.6 ($C_{arom.}$), 127.9, 127.2, 124.8, 120.1, ($CH_{arom.}$), 117.4 (*t*Bu), 108.9 (C-1′), 102.2 (C-5), 85.7 (C-4′), 85.6 (C-2′), 82.5 (C-3′), 82.3 (*t*Bu), 67.6 (C-3′′), 66.9 ($CH_{2\,Fmoc}$), 60.8 (C-2′′), 53.5 (C-5′), 48.8 (C-a, C-e), 47.5 (CH_{Fmoc}), 29.6 (*C*H$_2$CH$_3$, C-d), 29.0 (C-b, *C*H$_2$CH$_3$), 28.2 (*t*Bu), 23.7 (C-c), 8.6, 7.6 (2 CH$_2$*C*H$_3$) ppm. HRMS (ESI): calcd. for $C_{41}H_{52}N_6O_{10}Na$ [M + Na]$^+$ 811.3643; found 811.3610.

***tert*-Butyl *N*-(Fluorenylmethoxycarbonyl)serine Ester (20):** A solution of *tert*-butyl trichloroacetimidate (14.5 g) in cyclohexane (70 mL) was added to a solution of *N*-Fmoc-serine (5.43 g, 16.6 mol) in ethyl acetate (150 mL) and the mixture was stirred at room temp. for 24 h. Concentration in vacuo and purification by column chromatography with cyclohexane/EtOAc (7:3 to 6:4) afforded **20** as a white solid (5.76 g, 90%). R_f = 0.27 (cyclohexane/EtOAc, 6:4). $[\alpha]_D$ = +2 (*c* = 1, CH_2Cl_2). M.p. 130 °C. ^{1}H NMR: δ = 7.81–7.21 (m, 8 H, $H_{arom.}$), 5.78 (d, J_{NH-2} = 5.7 Hz, 1 H, *N*H), 4.45 (d, 2 H, $J_{CH2-CH\,Fmoc}$ = 6.9 Hz, $CH_{2\,Fmoc}$), 4.25 (t, $J_{CH-CH2\,Fmoc}$ = 6.9 Hz, 1 H, CH_{Fmoc}), 3.98–3.94 (m, 2 H, 3-H), 1.52 (s, 9 H, *t*Bu) ppm. ^{13}C NMR: δ = 170.0 (C-1), 156.8 (CO_{Fmoc}), 144.1, 141.7 ($C_{arom.}$), 128.1, 127.5, 125.5, 120.4 ($CH_{arom.}$), 83.3 (*t*Bu), 67.6 ($CH_{2\,Fmoc}$), 64.0 (C-3), 57.1 (C-2), 47.5 (CH_{Fmoc}), 28.4 (*t*Bu) ppm. HRMS (ESI$^+$): calcd. for $C_{22}H_{26}NO_5$ [M + H]$^+$ 401.2076; found 401.2079.

5-Azido-1-*O*-(*tert*-butyl *N*-fluorenylmethoxycarbonyl-L-serin-3′-yl)-5-deoxy-2,3-*O*-(isopentylidene)-β-D-ribofuranose (21): Molecular sieves (4 Å, 2 g) were added to a solution of *tert*-butyl *N*-Fmoc-L-serine ester (**20**)[17] (318 mg, 0.83 mmol) and ribosyl fluoride **8**[14] (300 mg, 1.22 mmol) in CH_2Cl_2 (25 mL). After stirring for 2 h at room temp., boron trifluoride–diethyl ether (125 μL, 0.99 mmol) was added at –45 °C. After allowing the mixture to warm up to room temp. over 65 h, the reaction mixture was filtered through a Celite pad. A saturated aqueous solution of sodium hydrogen carbonate (20 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The organic layer was dried with $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography with cyclohexane/EtOAc (90:10) as eluent afforded the glycosylated compound **21** as a white solid (140 mg, 28%). R_f = 0.29 (cyclohexane/EtOAc, 8:2). $[\alpha]_D$ = –8.4 (*c* = 1, CH_2Cl_2). ^{1}H NMR: δ = 7.84–7.31 (m, 8 H, $H_{arom.}$), 5.58 (d, J_{NH-2} = 8.4 Hz, 1 H, *N*H), 5.14 (s, 1 H, 1′-H), 4.70 (d, $J_{2'-3'}$ = 5.9 Hz, 1 H, 2′-H), 4.61 (d, $J_{3'-2'}$ = 5.9 Hz, 1 H, 3′-H), 4.55–4.41 (m, 3 H, H_2, $CH_{2\,Fmoc}$), 4.35 (dd, $J_{4'-5'a}$ = $J_{4'-5'b}$ = 7.5 Hz, 1 H, 4′-H), 4.27 (dd, $J_{CH-CH2\,Fmoc}$ = 7 Hz, 1 H, CH_{Fmoc}), 4.13 (dd, J_{3a-3b} = 10.0, J_{3a-2} = 3.1 Hz, 1 H, 3a-H), 3.67 (dd, J_{3b-3a} = 10.0, J_{3b-2} = 3.1 Hz, 1 H, 3b-H), 3.42 (dd, $J_{5'a-5'b}$ = 12.5, $J_{5'a-4'}$ = 7.5 Hz, 1 H, 5′a-H), 3.20 (dd, $J_{5'b-5'a}$ = 12.5, $J_{5'b-4'}$ = 7.3 Hz, 1 H, 5′b-H), 1.80–1.55 (m, 4 H, 2 CH_2CH$_3$), 1.46 (m, 9 H, *t*Bu), 1.00–0.80 (m, 6 H, 2 CH$_2$CH_3) ppm. ^{13}C NMR: δ = 169.0 (C-1), 156.0 (CO_{Fmoc}), 144.0, 143.9, 141.4 ($C_{arom.}$), 127.8, 127.2, 125.3, 120.1 ($CH_{arom.}$), 117.3 [*C*(CH$_2$CH$_3$)$_2$], 109.7 (C-1′), 85.8 (C-4′), 85.5 (C-2′), 82.9 (*t*Bu), 82.4 (C-3′), 68.6 (C-3), 67.2 ($CH_{2\,Fmoc}$), 54.6 (C-2), 53.5 (C-5′), 47.3 (CH_{Fmoc}), 29.5, 29.0 (2 *C*H$_2$CH$_3$), 28.2 (*t*Bu), 8.5, 7.5 (2 CH$_2$*C*H$_3$) ppm. HRMS (ESI): calcd. for $C_{32}H_{40}N_4O_8Na$ [M + Na]$^+$ 631.2744; found 631.2759.

5-Azido-1-*O*-(*tert*-butyl L-serin-3′-yl)-5-deoxy-2,3-*O*-(isopentylidene)-β-D-ribofuranose (22): Piperidine (0.52 mL, 5.34 mmol) was added to a solution of compound **21** (330 mg, 0.54 mmol) in DMF (3.5 mL) . After stirring for 2 h at room temp., the reaction mixture was concentrated in vacuo. Purification by column chromatography with CH_2Cl_2/MeOH/NEt_3 (97:3:0.001) as eluent afforded the amine **22** as a colourless oil (195 mg, 93%). R_f = 0.21 (CH_2Cl_2/MeOH/NEt_3, 97:3:0.001). $[\alpha]_D$ = –36 (*c* = 1, CH_2Cl_2). ^{1}H NMR: δ = 5.14 (s, 1 H, 1′-H), 4.67 (d, $J_{2'-3'}$ = 6.0 Hz, 1 H, 2′-H), 4.60 (d, $J_{3'-2'}$ = 6.0 Hz, 1 H, 3′-H), 4.33 (dd, $J_{4'-5'a}$ = 7.1, $J_{4'-5'b}$ = 7.8 Hz, 1 H, 4′-H), 3.95 (dd, J_{3a-3b} = 9.7, J_{3a-2} = 5.0 Hz, 1 H, 3a-H), 3.62 (dd, J_{3b-3a} = 9.7, J_{3b-2} = 4.0 Hz, 1 H, 3b-H), 3.51 (dd, J_{2-3a} = 5.0, J_{2-3b} = 4.0 Hz, 1 H, 2-H), 3.45 (dd, $J_{5'a-5'b}$ = 12.5, $J_{5'a-4'}$ = 7.7 Hz,

1 H, 5′a-H), 3.21 (dd, $J_{5'b-5'a}$ = 12.5, $J_{5'b-4'}$ = 7.1 Hz, 1 H, 5′b-H), 1.90–1.76 (br. s, 1 H, NH_2), 1.69 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 1.57 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 1.47 (m, 9 H, *t*Bu), 0.91 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.87 (t, J = 7.4 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR: δ = 172.7 (C-1), 117.2 [$C(CH_2CH_3)_2$], 109.5 (C-1′), 85.9 (C-4′), 85.5 (C-2′), 82.4 (C-3′), 81.7 (*t*Bu), 70.5 (C-3), 55.1 (C-2), 53.6 (C-5′), 29.5 (2 CH_2CH_3), 28.9, 28.0 (*t*Bu), 8.4, 7.4 (2 CH_2CH_3) ppm. HRMS (ESI): calcd. for $C_{17}H_{31}N_4O_6$ [M + H]$^+$ 387.2244; found 387.2231.

***tert*-Butyl *O*-(5′-Azido-5′-deoxy-2′,3′-*O*-isopentylidene-β-D-ribos-1′-yl)-*N*-(5′′-uracil-1-ylpentyl)-L-serine Ester (23):** A solution of the amine **22** (114 mg, 0.30 mmol) in THF (2.5 mL) and Na_2SO_4 (920 mg, 6.48 mmol) were successively added to a solution of the aldehyde **17** (64 mg, 0.33 mmol) in THF (2.5 mL). After stirring for 21 h at room temp., sodium triacetoxyborohydride was added and the heterogeneous mixture was stirred at room temp. over 24 h. After filtration through a Celite pad and elution with CH_2Cl_2 (30 mL), the organic layer was washed with a saturated aqueous solution of sodium carbonate (15 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL). After drying with $MgSO_4$ and concentration in vacuo, the oily residue was purified by column chromatography with CH_2Cl_2/MeOH/NEt_3 (95:5:0.001) as eluent to afford **23** as a colourless oil (108 mg, 65%). R_f = 0.19 (CH_2Cl_2/MeOH/NEt_3, 95:5:0.001). $[\alpha]_D$ = –26 (c = 1, CH_2Cl_2). ^{1}H NMR: δ = 7.14 (d, J_{6-5} = 7.9 Hz, 1 H, 6-H), 5.67 (d, J_{5-6} = 7.9 Hz, 1 H, 5-H), 5.0 (s, 1 H, 1′-H), 4.63 (d, $J_{2'-3'}$ = 6.0 Hz, 1 H, 2′-H), 4.57 (d, $J_{3'-2'}$ = 6.0 Hz, 1 H, 3′-H), 4.30 (dd, $J_{4'-5'a}$ = $J_{4'-5'b}$ = 7.6 Hz, 1 H, 4′-H), 3.87 (dd, $J_{3''a-3''b}$ = 9.8, $J_{3''a-2''}$ = 4.8 Hz, 1 H, 3′′a-H), 3.70 (t, J_{e-d} = 7.2 Hz, 2 H, e-H), 3.54 (dd, $J_{3''b-3''a}$ = 9.8, $J_{3''b-2''}$ = 5.0 Hz, 1 H, 3′′b-H), 3.44 (dd, $J_{5'a-5'b}$ = 12.5, $J_{5'a-4'}$ = 7.8 Hz, 1 H, 5′a-H), 3.25 (dd, $J_{2''-3''a}$ = 4.8, $J_{2''-3''b}$ = 5.0 Hz, 1 H, 2′′-H), 3.21 (dd, $J_{5'b-5'a}$ = 12.5, $J_{5'b-4'}$ = 7.0 Hz, 1 H, 5′b-H), 2.72–2.41 (m, 2 H, a-H), 1.77–1.62 (m, 4 H, d-H, CH_2CH_3), 1.61–1.49 (m, 4 H, b-H, CH_2CH_3), 1.46 (m, 9 H, *t*Bu), 1.45–1.30 (m, 1 H, c-H), 0.92 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.89 (t, J = 7.6 Hz, CH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz, 300 K): δ = 172.2 (C-1′′), 164.1 (C-4), 151.0 (C-2), 144.5 (C-6), 117.2 ($C[CH_2CH_3]_2$), 109.4 (C-1′), 102.2 (C-5), 85.9 (C-4′), 85.5 (C-2′), 82.4 (C-3′), 81.8 ($C[CH_3]_3$), 69.3 (C-3′′), 61.8 (C-2′′), 53.6 (C-5′), 48.8 (C-e), 47.8 (C-a), 29.8 (C-b), 29.5 ($C[CH_2CH_3]_2$), 29.0 (C-d, $C[CH_2CH_3]_2$), 28.2 (*t*Bu), 24.1 (C-c), 8.5, 7.5 (2 CH_2CH_3) ppm. HRMS (ESI): calcd. for $C_{26}H_{43}N_6O_8$ [M + H]$^+$ 567.3142; found 567.3167.

***tert*-Butyl *O*-(5′-Amino-5′-deoxy-2′,3′-*O*-isopentylidene-β-D-ribos-1′-yl)-*N*-(5′′-uracil-1-ylpentyl)-L-serine Ester (24):** 1,2-Bis(diphenylphosphanyl)ethane (34 mg, 0.09 mmol) was added to the azido derivative **23** (88 mg, 0.16 mmol) in a 9:1 mixture of THF/H_2O (2.2 mL). After stirring for 18 h at room temp., the reaction mixture was concentrated in vacuo and the residue was purified by column chromatography with CH_2Cl_2/MeOH/NEt_3 (90:10:0.003) to afford **24** as a colourless oil (70 mg, 84%). R_f = 0.21 (CH_2Cl_2/MeOH/NEt_3, 80:20:0.025). $[\alpha]_D$ = –36 (c = 1, CH_2Cl_2). ^{1}H NMR: δ = 7.14 (d, J_{6-5} = 7.9 Hz, 1 H, 6-H), 5.67 (d, J_{5-6} = 7.9 Hz, 1 H, 5-H), 5.07 (s, 1 H, 1′-H), 4.58 (s, 2 H, 2′-H, 3′-H), 4.18 (dd, $J_{4'-5'a}$ = $J_{4'-5'b}$ = 6.8 Hz, 1 H, 4′-H), 3.83 (dd, $J_{3''a-3''b}$ = 9.7, $J_{3''a-2''}$ = 5.0 Hz, 1 H, 3′′a-H), 3.72 (t, J_{e-d} = 7.2 Hz, 2 H, e-H), 3.55 (dd, $J_{3''b-3''a}$ = 9.7, $J_{3''b-2''}$ = 5.1 Hz, 1 H, 3′′b-H), 3.25 (dd, $J_{2''-3''a}$ = 5.0, $J_{2''-3''b}$ = 5.1 Hz, 1 H, 2′′-H), 3.05 (br. s, 2 H, 5′-H), 2.77 (d, $J_{NH-5'}$ = 6.8 Hz, 1 H), 2.70–2.41 (m, 2 H, a-H), 1.76–1.61 (m, 4 H, b-H, CH_2CH_3), 1.61–1.50 (m, 4 H, d-H, CH_2CH_3), 1.46 (m, 9 H, *t*Bu), 1.45–1.30 (m, 1 H, c-H), 0.90 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.85 (t, J = 7.5 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR: δ = 173.3 (C-1′′), 165.0 (C-4), 152.2 (C-2), 146.3 (C-6), 116.9 [$C(CH_2CH_3)_2$], 110.0 (C-1′), 102.0 (C-5), 89.9 (C-4′), 86.6 (C-2′), 83.5 (C-3′), 81.8 (*t*Bu), 69.9 (C-3′′), 62.8 (C-2′′), 48.9 (C-e), 48.3 (C-a), 45.9 (C-5′), 30.3, 30.0, 29.5, (C-b, C-d, CH_2CH_3), 28.3 (*t*Bu), 24.6 (C-c), 8.8, 7.7 (2 CH_2CH_3) ppm. HRMS (ESI): calcd. for $C_{26}H_{44}N_4O_8Na$ [M + Na]$^+$ 563.3057; found 563.3063.

***O*-(5′-Amino-5′-deoxy-β-D-ribos-1′-yl)-*N*-(5′′-uracil-1-ylpentyl)-L-erine (1):** ′TFA (0.3 mL) was added to the amino compound **24** (70 mg, 0.13 mmol) in CH_2Cl_2 (1.5 mL). After stirring for 24 h at room temp., the reaction mixture was concentrated in vacuo. The oily residue was diluted in a 3:1 mixture of THF/H_2O (1.5 mL), TFA (1 mL) was added and the mixture was stirred at room temp. for 24 h. Concentration in vacuo and purification by C_{18} reversed-phase column chromatography (MeOH/H_2O, 1:1) afforded the target compound **1** as a white solid (40 mg, 48%). R_f = 0.18 (MeOH/H_2O, 1:1). $[\alpha]_{365nm}$ = –5 (c = 1, H_2O). ^{1}H NMR (CD_3OD): δ = 7.59 (d, J_{6-5} = 7.9 Hz, 1 H, 6-H), 5.67 (d, J_{5-6} = 7.9 Hz, 1 H, 5-H), 4.92 (s, 1 H, 1′-H), 4.32 (dd, $J_{3''a-3''b}$ = 10.7, $J_{3''a-2''}$ = 2.5 Hz, 1 H, 3′′a-H), 4.19–3.95 (m, 3 H, 2′-H, 3′-H, 4′-H), 3.93–3.63 (m, $J_{3''b-3''a}$ = 10.7, $J_{3''b-2''}$ = 2.5, J_{e-d} = 6.9 Hz, 4 H, 3′′b-H, e-H, 2′′-H), 3.22 (d, $J_{5'a-5'b}$ = 12.1 Hz, 1 H, 5′-H), 3.15–2.95 (m, 3 H, 5′b-H, a-H), 1.89–1.62 (m, 4 H, b-H, d-H), 1.52–1.33 (m, 2 H, c-H) ppm. ^{13}C NMR (CD_3CN): δ = 171.5 (C-1′′); 166.7 (C-4), 163.0 (q, $^2J_{C-F}$ = 35 Hz, $COCF_3$), 152.9 (C-2), 147.3 (C-6), 118.2 (q, $^1J_{C-F}$ = 293 Hz, $COCF_3$), 108.6 (C-1′), 102.4 (C-5), 80.4 (C-4′), 76.0 (C-2′), 74.1 (C-3′), 65.8 (C-3′′), 62.8 (C-2′′), 49.1 (C-e), 47.8 (C-a), 44.2 (C-5′), 29.4 (C-d), 26.5 (C-b), 24.4 (C-c) ppm. HRMS (ESI): calcd. for $C_{17}H_{29}N_4O_8$ [M – CF_3CO_2H + H]$^+$ 417.1985; found 417.1989.

Acknowledgments

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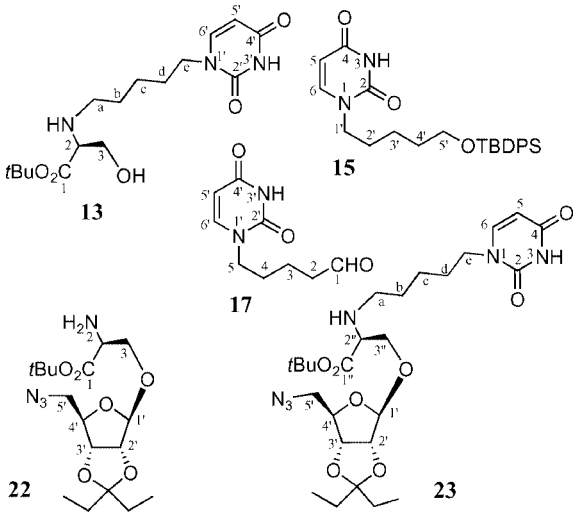
[19] To facilitate the understanding of NMR spectroscopic data, the numbering of atoms for the following representative compounds is as indicated below.



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