N-Glycosylation with Sulfoxide Donors for the Synthesis of Peptidonucleosides

This article is dedicated to the memory of our esteemed colleague Dr. Mazen Es-Sayed

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Abstract : We report here the synthesis of peptidonucleosides obtained after glycosylation of different pyrimidine bases with glucopyranosyl donors carrying an azide group at the C4 position. A methodological study involving different anomeric leaving groups (acetate, phenylsulfoxide and *ortho*-hexynylbenzoate) showed that a sulfoxide donor in combination with trimethylsilyl triflate as the promoter led to the best yields.

Fungicides represent a class of pesticides used to prevent the development of a fungus in the plant and / or to fight a fungal infection caused by a pathogen.[1] Their use has become essential over time to avoid contamination of whole crops and improve agricultural yields in a context of increasing urbanization that continues to decrease the area of cultivable land.[2] The continuous use of agrochemicals has led to the development of pest resistance to active substances, which makes some pesticides ineffective.[3] Thus, finding new structural motifs with new antifungal modes of action to fight against pathogens is essential to circumvent resistances. Natural products remain an important source of inspiration for the discovery of new active molecules. Among them gougerotin, isolated for the first time in 1962 from strains of *Streptomyces gougerotii*,[4] caught the attention of researchers.[5] This peptidylnucleoside consists of a glucan-type pyranose saccharide motif that has a carboxamide group at the 6-position. It is also substituted at the 4-position by a dipeptide made of D-serine and sarcosine and *N*-linked at the anomeric position by a cytosine base. Since its discovery, gougerotin has been the subject of three total syntheses, including two described in the 1970s[6] and a more recent one in 2005 using solid- and solution-phase methodology.[7] Gougerotin has a very broad spectrum of biological activities: antiviral,[8] antifungal,[5] antiparasitic and antibacterial[9] by inhibiting protein synthesis in procaryotic and eucaryotic systems. It is active on various varieties of plants whether in preventive or curative tests but its phytotoxicity limits its direct use on plants.[10] In order to optimize its crop specificity, we were interested in the preparation of a few gougerotin analogues. The main modifications will concern the replacement of the natural nucleic base by other pyrimidine bases while preserving the glucopyranosyl skeleton of the parent molecule (Figure 1). The carboxamide function at C5 will also be replaced by a free hydroxymethyl group. To access these compounds, different bases will first be glycosylated with a donor carrying an azide group at the C4 position. Following this glycosylation step, the azide will be reduced to the corresponding amine allowing a dipeptide coupling. A potential impact of the dipeptide motif on the bioactivity will also be studied with the synthesis of compounds comprising L-serine instead of D-serine or a modified peptide.

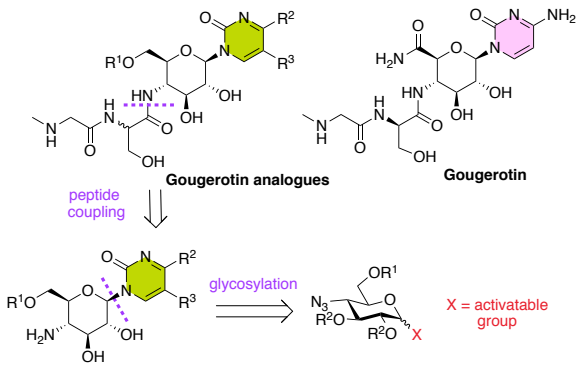
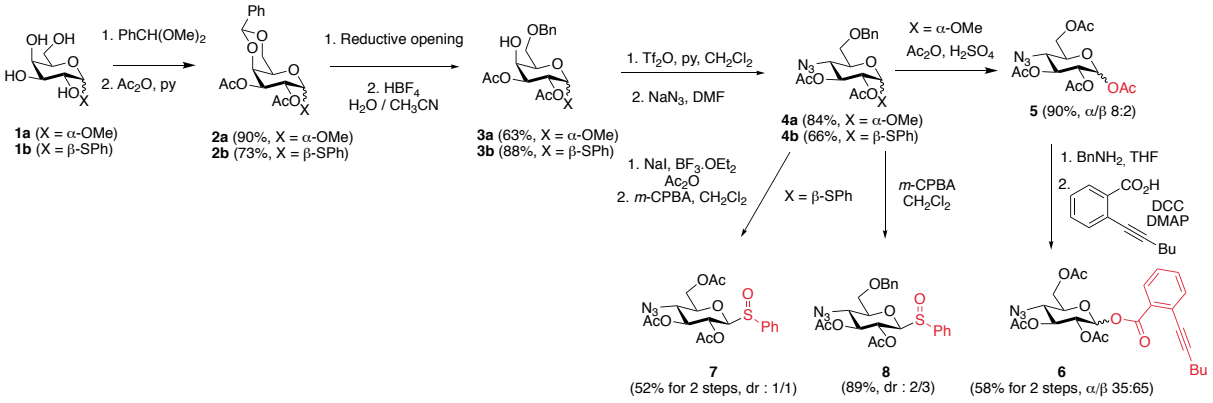


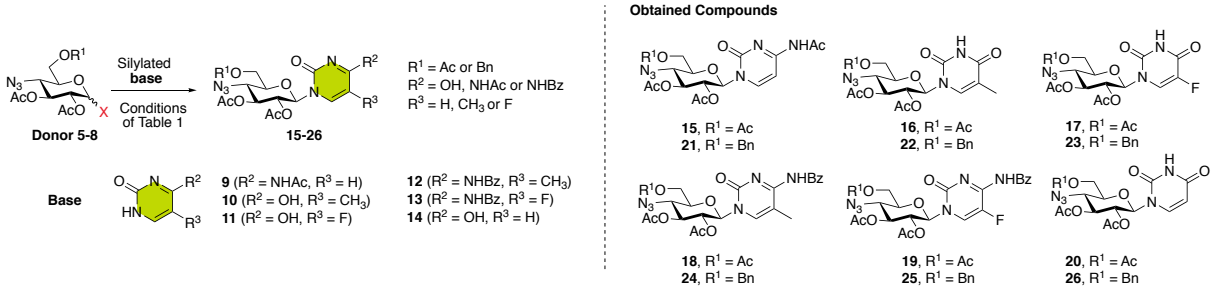
Figure 1. Retrosynthetic scheme of gougerotin analogues

First of all, we prepared anomeric acetate donor **5**, which is the most conventionally activatable donor used to synthesize nucleoside derivatives under Vorbrüggen glycosylation conditions (Scheme 1).[11] Methyl α-D-galactopyranoside **1a** was first protected as a 4,6-benzylidene acetal to yield the corresponding product, which was esterified with acetic anhydride in pyridine. Compound **2a** was then engaged in a reductive opening reaction of the 4,6-*O*-benzylidene acetal to lead to galactopyranoside **3a** having a free hydroxyl at position 4. Best results for this step were obtained using triethylsilane (2.5 eq.) in combination with triflic acid (2 eq.) as described by Sakagami and Hamana.[12] Since we also observed the formation of the corresponding 4-*O*-triethylsilyl ether adduct, the reaction mixture was further treated with tetrafluoroboric acid to furnish the desired alcohol **3a** in 63% yield. The latter was then reacted with Tf_2O in the presence of pyridine to form the triflate in the 4-position, that was displaced by NaN_3 with inversion of configuration leading to the glucopyranoside adduct **4a**. A final acetolysis step led to donor **5** as a mixture of anomers (α/β = 8:2).



Scheme 1. Preparation of different donors **5**-**8**. Conditions for the reductive opening: with **2a** (X = α-OMe) Et_3SiH (2.5 eq.), TfOH (2 eq.) in CH_3CN, with **2b** (X = β-SPh) Et_3SiH (1 eq.), cat. $Cu(OTf)_2$ in CH_3CN

With this donor in hand, we first performed the glycosylation of N^4-Ac-cytosine **9**, the nucleic base naturally present in the gougerotin. Reaction with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in MeCN gave the corresponding silylated cytosine, which was subsequently treated with **5** in the presence of trimethylsilyl triflate (TMSOTf, 1.5 eq.) for 12 h at 55 °C.[13] After workup and purification, the nucleoside **15** was isolated in 36% yield (Scheme 2, Table 1, entry 1) and as a single β-anomer due to the anchimeric assistance of the 2-OAc group. This was confirmed by the ^1H NMR spectrum showing a large coupling constant between protons H-1 and H-2 ($^3J_{1,2}$ = 9.5 Hz) indicating an axial orientation of both protons. The yield could be increased to 69% by using the Vorbrüggen method with $SnCl_4$ (3 eq.) in MeCN at 55°C for 12 h (Table 1, entry 2).[14] The glycosylation of other pyrimidine bases was then tested and for each base, the reaction conditions had to be readjusted accordingly. The results are summarized in Table 1. Similar yields were obtained with thymine **10** (entry 3) and 5-F-uracil **11** (entry 4), which led respectively to the β-glycosylated adducts **16** and **17** in 74 and 71% yield respectively. Note that 5-F-uracil **11** was silylated in the presence of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in combination with saccharin (5 mol%) as catalyst.[15] With 5-Me-N^4-obtained with silylated uracil **14**, which led to the corresponding β-nucleoside **20** (entry 7). This disappointing result led us to consider the use of other donors for these glycosylations. We started our investigations with the preparation of glycosyl *ortho*-hexynyl benzoate **6**, readily accessible from **5** after selective deacetylation at the anomeric position and subsequent esterification of the corresponding hemiacetal (Scheme 1). Recently, these donors have been shown to be superior donors for the *N*-glycosylation of nucleobases using gold catalysis under very mild conditions.[16] Donor **6** was then subjected to glycosylation with silylated pyrimidine bases under the catalysis of $Ph_3PAuNTf_2$ (10 mol%) Bz-cytosine **12** (entry 5) and 5-F-N^4-Bz-cytosine **13** (entry 6), which are rarely glycosylated with pyranosyl donors, moderate yields of 45 and 51% were achieved respectively for **18** and **19**. A much lower yield of 25% was also at room temperature in MeCN. In all cases the corresponding nucleosides were isolated with an excellent β-selectivity but with variable yields depending on the acceptor. For example, a good 78% yield was obtained with uracil **14** (entry 13). Moderate results (30 to 49%) were achieved with other bases (entries 8-11) and, with 5-F-N^4-Bz cytosine **13**, the



Scheme 2. Glycosylation of different pyrimidine bases **9-14** using donors **5-8**

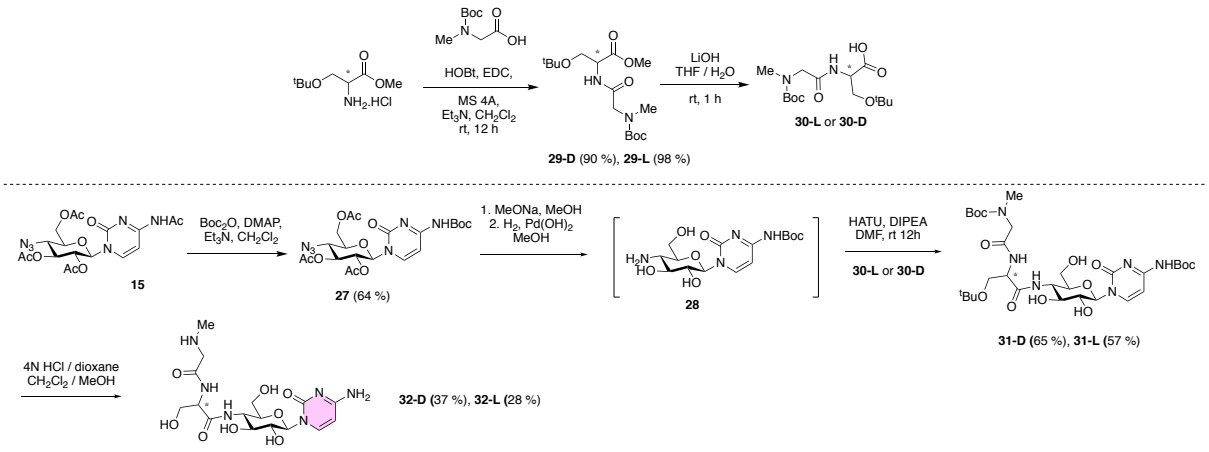
Table 1. *N*-Glycosylation conditions of different pyrimidine bases

entry	Donor	Base[a]	Conditions[b]	Compound, Yield (%)
1	**5**	**9**	TMSOTf (1.5 eq.)	**15**, 36
2	**5**	**9**	$SnCl_4$ (3 eq.)[c]	**15**, 69
3	**5**	**10**	$SnCl_4$ (3 eq.)	**16**, 74
4	**5**	**11**[d]	TMSOTf (1.5 eq.)	**17**, 71
5	**5**	**12**	$SnCl_4$ (3 eq.)	**18**, 45
6	**5**	**13**	$SnCl_4$ (3 eq.)	**19**, 51
7	**5**	**14**[d]	TMSOTf (1.5 eq.)	**20**, 25
8	**6**	**9**[e,f]	$Ph_3PAuNTf_2$ (10 mol%)	**15**, 49
9	**6**	**10**[e,f]	$Ph_3PAuNTf_2$ (10 mol%)	**16**, 48
10	**6**	**11**[f]	$Ph_3PAuNTf_2$ (10 mol%)	**17**, 40
11	**6**	**12**[e,f]	$Ph_3PAuNTf_2$ (10 mol%)	**18**, 30
12	**6**	**13**[f]	$Ph_3PAuNTf_2$ (10 mol%)	**19**, 9
13	**6**	**14**[e,f]	$Ph_3PAuNTf_2$ (10 mol%)	**20**, 78
14	**7**	**9**	TMSOTf (1.5 eq.)	**15**, 95
15	**7**	**10**	TMSOTf (1.5 eq.)	**16**, 89
16	**7**	**11**	TMSOTf (1.5 eq.)	**17**, 71
17	**7**	**12**	TMSOTf (1.5 eq.)	**18**, 88
18	**7**	**13**	TMSOTf (1.5 eq.)	**19**, 75
19	**7**	**14**	TMSOTf (1.5 eq.)	**20**, 94
20	**8**	**9**	TMSOTf (1.5 eq.)	**21**, 54
21	**8**	**10**	TMSOTf (1.5 eq.)	**22**, 77
22	**8**	**11**[d]	TMSOTf (1.5 eq.)	**23**, 76
23	**8**	**12**	TMSOTf (1.5 eq.)	**24**, 66
24	**8**	**13**	TMSOTf (1.5 eq.)	**25**, 50
25	**8**	**14**	TMSOTf (1.5 eq.)	**26**, 81

a) BSA (4 eq.) was used as silylating agent unless otherwise stated. b) the reaction mixture was heated for 12 h at 55 °C in MeCN unless otherwise stated c) the reaction was carried out in DCE. d) HMDS (1.8 eq.), saccharine (5 mol.%) e) with BSTFA (*N*,*O*-bis(trimethylsilyl)trifluoroacetamide). f) the reaction was carried out for 48 h at r.t.

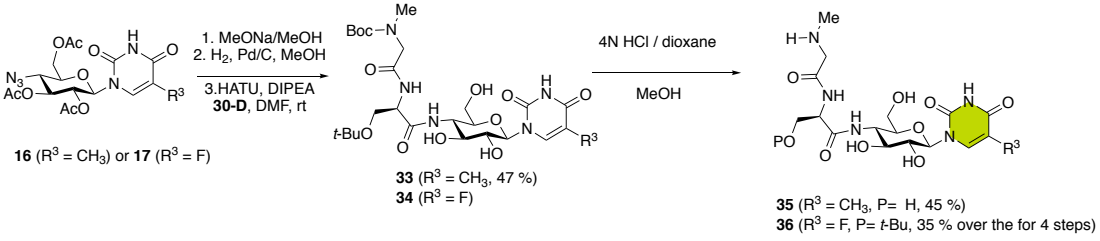
reaction led to a low conversion with the desired β-glycosylated adduct **19** been isolated in only 9% yield (entry 12). We then turned our attention to the use of sulfoxide donors[17] that we recently exploited with success in problematic glycosylations[18] and which have been very rarely used for the *N*-glycosylation with furanosyl or pyranosyl derivatives.[19] Donor **7** was prepared from phenyl β-D-thiogalactoside **1b**, following the same strategy as for **5**, *i.e.* 4,6-*O*-benzylidene acetal formation, *O*-2/*O*-3 acetylation (to **2b**), reductive opening of the acetal (Et_3SiH with cat. $Cu(OTf)_2$ to **3b**)[20] and introduction of the azide at C-4 through triflate displacement to afford **4b** (Scheme 1). The obtained **4b** was further treated by $NaI/BF_3{\bullet}OEt_2$ in acetic anhydride leading to the acetolysis of the 6-*O*Bn position.[21] Thioether oxidation was carried out under common conditions (*m*-CPBA) smoothly giving sulfoxides **7** as a mixture of two diastereomers (dr of 1:1). Donor **7** was then subjected to glycosylation after prior silylation of the pyrimidine bases with BSA in MeCN. In all cases, TMSOTf (1.5 eq.) was used as promoter and after 12 h at 55 °C, we were pleased to obtain the corresponding β-nucleosides in good to excellent yields ranging from 71 to 95% (entries 14-19). We also prepared 6-*O*Bn sulfoxide derivatives **8** (dr of 2:3) by direct oxidation of **4b**. *N*-glycosylation with this donor **8** efficiently led to 6-*O*Bn β-nucleosides in comparable yields (50-81%, entries 20-25).

In order to carry out the peptide coupling and access analogues, we first examined azide reduction directly on compound **15**. However, while using Staudinger conditions[22] or different hydrogenation conditions to reduce the azide



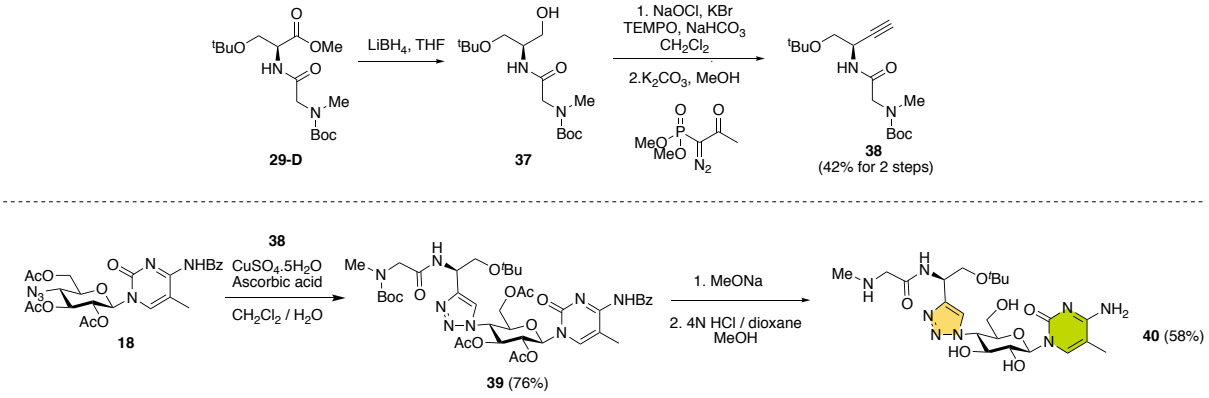
Scheme 3. Preparation of analogues **32-D** and **32-L**

to amine, we obtained complex mixtures that probably result from deacetylation and acetate migration. To solve this problem, we decided to protect first the N^4-cytosine with a *tert*-butylcarbamate group and remove all the acetyl groups before hydrogenation (Scheme 3). Therefore, compound **15** was treated with Boc_2O in the presence of NEt_3 and 4-dimethylaminopyridine (DMAP) to provide the corresponding derivative **27** by concomitant deprotection of N^4-Ac-cytosine. Zemplén deacetylation was carried out followed by hydrogenation with palladium hydroxide in methanol. This sequence led to the corresponding amine **28** that was used without purification in the following peptide coupling. The synthesis of the dipeptide fragment **30-D**, naturally present in the gougerotin, started with the coupling of the methyl ester of D-*O*-*tert*-butyl-serine with Boc-sarcosine using hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in the presence of triethylamine in CH_2Cl_2. The obtained dipeptide **29-D** was then saponified with lithium hydroxide to carboxylic acid **30-D**. The same sequence was also performed with the methyl ester of L-*O*-*tert*-butyl-serine providing the corresponding dipeptide fragment **30-L**. The peptide coupling of amine **28** was then carried out with both dipeptides **30-D** and **30-L** using the coupling agent HATU[23] in the presence of Hünig's base in DMF to furnish **31-D** and **31-L** in 65 and 57% yield respectively. Both compounds were then treated with 4N HCl in MeOH/CH_2Cl_2 to remove the Boc and *t*-butyl groups allowing the preparation of analogues **32-D** and **32-L**. Due of the high polarity of these products and associated difficulties to their purification, these compounds were obtained in 37 and 28% yields respectively.



Scheme 4. Preparation of analogues **35**-**36**

To access other compounds, the two uracil derivatives **16** and **17**, were subjected to a similar reaction sequence, namely Zemplén deacetylation, hydrogenation followed by dipeptide coupling with carboxylic acid **30-D**, affording the corresponding peptidonucleosides **33** and **34** (Scheme 4). Further deprotection with HCl 4N allowed us to obtain analogues **35** and **36**. For **34**, a partial deprotection was obtained leading to **36** as the major adduct still having the *t*-butyl group on the serine. Attempts to further deprotect led to a very low yield of desired product due to degradation. Taking advantage of the presence of the azide in position C-4 of pyranosyl compound **18**, we also prepared compound **40** containing a triazole unit (Scheme 5). To this end we synthesized alkyne **38** from **29-D** after its reduction to alcohol **37**, oxidation to the aldehyde[24] and treatment with dimethyl (1-diazo-2-oxopropyl)phosphonate[25] in the presence of potassium carbonate in MeOH. The CuAAC reaction[26] between alkyne **38** and azide **18** was carried out in a water/dichloromethane mixture with $CuSO_4 \cdot 5H_2O$ and ascorbic acid to smoothly give the triazole derivative **39** in 76% yield. Final removal of the acyl groups with MeONa in methanol followed by treatment with 4N HCl at room temperature gave, as for **36**, a partial deprotection leading to **40** having the *t*-butyl group on the serine as the major adduct in 58% yield.



Scheme 5. Preparation of analogue **40**

Conclusion

In this article, we have successfully prepared a series of peptidonucleosides, analogues of gougerotin. The main modifications relate to the replacement of the natural nucleic base by other pyrimidine bases and the replacement of the carboxamide function at C5 by an hydroxymethyl group. For the glycosylation stage, a methodological study involving different anomeric leaving groups (acetate, phenylsulfoxide and *ortho*-hexynylbenzoate) was carried out. Using six different pyrimidines, the sulfoxide donor in combination with TMSOTf as a promoter most generally led to the best yields. The antifungal activities of the synthesized analogues were evaluated in preventive tests against a panel of different pathogens such as *Podosphaera fuliginea, Uromyces appendiculatus, Puccinia triticina, Alternaria brassicae Botryotiniacinereal, Zymoseptoria tritici*. Although some of the analogs were found to have good bioactivities, none of them showed superior activity to gougerotin itself.

Experimental

General remarks

All non-aqueous reactions were run under an inert atmosphere (argon), by using standard techniques for manipulating air-sensitive compounds and the glassware was stored in the oven prior to use. All reagents and solvents were commercially available and were used without further purification. Molecular sieves 4 Å were used as a powder and were activated overnight at 250 °C and under reduced pressure, in a Kugelrohr apparatus or with a micro-wave for 45 seconds. Reactions were monitored with analytical Merck TLC silica gel 60 F254 plates and visualized under UV (254 nm) and stained with $KMNO_4$ or vanillin. Column chromatography was done with Merck Geduran silical gel Si 60 (40-63 µm) and Redisep Rf columns (silica gel Si 60 , 40-63 µm) on an Interchim puriFlash® apparatus and on a Teledyne Isco combiflash Rf. Preparative thin-layer chromatography was performed on silica gel 60 F254 0.5 mm 20×20 cm plates and visualised under UV (254 nm). Deuterated chloroform used for NMR analyses was generally neutralized by addition of anhydrous and granular K_2CO_3. NMR spectra were recorded with AM 300, AVANCE 300 and AVANCE 500 Brüker spectrometers. Chemical shifts are given in parts per million, referenced to the solvent peak of $CDCl_3$, defined at 77.2 ppm (^{13}C NMR) and 7.26 ppm (^{1}H NMR) or to the solvent peak of CD_3OD, defined at 49.9 ppm (^{13}C NMR) and 3.34 ppm (^{1}H NMR) or to the solvent peak of D_2O, defined at 4.79 ppm (^{1}H NMR) or to the solvent peak of DMSO-d_6, defined at 39.5 ppm (^{13}C NMR) and 2.50 ppm (^{1}H NMR). Data are reported as follow: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, bs = broad singlet), coupling constant (in Hz) and integration. IR spectra were recorded on a Perkin-Elmer Spectrum BX instrument with an FT-IR system. Optical rotation were measured on an Anton Paar MCP300 polarimeter using a cell of 1-dm-length path. Mass spectra were recorded with Waters Micromass LCT Premier mass spectrometer.

Methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-galactopyranoside 2a. To a suspension of methyl α-D-galactopyranoside (5.0 g, 25.75 mmol, 1.0 eq.) and camphor-10-sulfonic acid (119.6 mg, 0.52 mmol, 0.02 eq.) in dry chloroform (400 mL) under argon atmosphere was added dropwise benzaldehyde dimethyl acetal (5.4 mL, 36.05 mmol, 1.4 eq.). The resulting mixture was stirred for 24 h at 80 °C. Solvent was then removed and the residue was diluted in EtOAc (75 mL), neutralized with triethylamine then washed with water (75 mL). Aqueous phase was extracted with EtOAc (10 x 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the pure 4,6-*O*-benzylidene acetal intermediate (6.52 g, 23.12 mmol, 90%) as a white

powder (Experimental data are in agreement with those reported in the literature).[27] To a stirred solution of the 4,6-*O*-benzylidene acetal (2.47 g, 8.76 mmol, 1 eq.) in pyridine (14 mL) was added acetic anhydride (6.62 mL, 70.1 mmol, 8 eq.). The resulting mixture was stirred at room temperature for 12 h. Solvent was then removed and the residue was co-evaporated with toluene (3 x 20 mL). The crude product was purified by flash chromatography on silica gel (Heptane/EtOAc 70:30 to 60:40) to afford product **2a** (3.20 g, 8.74 mmol, quantitative) as a white powder. $[\alpha]_D^{25}$ + 202.3 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.46 (m, 2H, H_{Ar}), 7.41-7.31 (m, 3H, H_{Ar}), 5.50 (s, 1H, *H*7), 5.35 (dd, 1H, $J_{2,1}$= 3.0 Hz, $J_{2,3}$= 10.5 Hz, *H*2), 5.30 (dd, 1H, $J_{3,4}$= 2.5 Hz, $J_{3,2}$= 10.5 Hz, *H*3), 5.07 (d, 1H, $J_{1,2}$= 3.0 Hz, *H*1), 4.45 (d, 1H, $J_{4,3}$= 2.5 Hz, *H*4), 4.27 (dd, 1H, $J_{6,5}$= 1.5 Hz, $J_{6,6'}$= 12.5 Hz, *H*6), 4.05 (dd, 1H, $J_{6',5}$= 1.5 Hz, $J_{6',6}$= 12.5 Hz, *H*6'), 3.74 (m, 1H, *H*5), 3.40 (s, 3H, OCH_3), 2.07 (s, 3H, OCOCH_3), 2.06 (s, 3H, OCOCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (*C*=O), 170.4 (*C*=O), 137.7 (*C*q_{Ar}) 129.2 (*C*H_{Ar}), 128.4 (*C*H_{Ar}), 126.4 (*C*H_{Ar}), 101.1 (*C*7), 98.0 (*C*1), 74.1 (*C*4), 69.3 (*C*6), 68.8 (*C*3), 68.3 (*C*2), 62.2 (*C*5), 55.7 (O*C*H_3), 21.2 (OCO*C*H_3), 21.1 (OCO*C*H_3). IR ν (film, cm^{-1}) 2914 (=C-H), 2866 (CH_3), 1746 (C=O); ESIHRMS *m/z* = 389.1214 $[M+Na]^+$. $C_{18}H_{22}O_8Na$ requires 389.1212.

Methyl 2,3-di-*O*-acetyl-6-*O*-benzyl-α-D-galactopyranoside 3a. A solution of **2a** (2.72 g, 7.4 mmol, 1 eq.) and 4Å molecular sieves (5 g) in dry CH_2Cl_2 (50 mL) was stirred for 1 h at room temperature under argon atmosphere. The mixture was cooled to –78 °C and Et_3SiH (1.18 mL, 7.4 mmol, 1 eq.) and TfOH (330 µL, 3.7 mmol, 0.5 eq.) were added successively. After being stirred for 15 min at –78 °C, Et_3SiH (1eq.) and TfOH (0.5 eq) were added again. After 15 min on same conditions, new additions of Et_3SiH (0.5 eq.) and TfOH (0.5 eq.) were done. Finally, after again 15 min, a final addition of TfOH (0.5 eq.) was realized. The resulting mixture was stirred at –78°C for 30 min then diluted with $CHCl_3$ (20 mL) and poured in saturated aqueous solution of sodium bicarbonate (40 mL). The organic layer was extract with $CHCl_3$ (3 x 25 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was directly dissolved in MeCN (25 mL) and treated with a diluted aqueous solution of HBF_4 (0.25 M, 25 mL). The resulting solution was stirred at room temperature for 1h30 and then quenched with saturated solution of $NaHCO_3$ until neutralization. Aqueous layer was extracted with EtOAc (3 x 15 mL). Organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (Heptane/EtOAc 90:10 to 60:40) to afford the clean product **3a** (1.52 g, 4.1 mmol, 63%) as a colorless oil. $[\alpha]_D^{25}$ +119.6 (*c* = 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H, H_{Ar}), 5.30 (dd, 1H, $J_{2,1}$ = 3.0 Hz, $J_{2,3}$= 10.5 Hz, *H*2), 5.24 (dd, 1H, $J_{3,4}$ = 2.5 Hz, $J_{3,2}$ = 10.5 Hz, *H*3), 5.00 (d, 1H, $J_{1,2}$ = 3.0 Hz, *H*1), 4.60 (d, 1H, $J_{H,H}$ = 12.0 Hz, CH_2Ph) 4.54 (d, 1H, $J_{H,H}$ = 12.0 Hz, CH_2Ph), 4.24 (m, 1H, *H*4), 3.97 (t, 1H, $J_{5,4}$ = $J_{5,6}$ = 4.5 Hz, *H*5), 3.78 (dd, 1H, $J_{6,5}$ = 4.5 Hz, $J_{6,6'}$ = 10.0 Hz, *H*6), 3.73 (dd, 1H, $J_{6',5}$ = 4.5 Hz, $J_{6',6}$ = 10.0 Hz, *H*6'), 3.38 (s, 3H, OCH_3), 3.01 (bs, 1H, O*H*), 2.08 (s, 3H, OCOCH_3), 2.06 (s, 3H, OCOCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (*C*=O), 170.3 (*C*=O), 137.5 (*C*q_{Ar}), 128.7 (*C*H_{Ar}), 128.1 (*C*H_{Ar}), 127.9 (*C*H_{Ar}), 97.6 (*C*1), 74.1 (*C*H_2Ph), 70.4 (*C*2), 70.4 (*C*6), 69.4 (*C*4), 68.5 (*C*3), 68.1 (*C*5), 55.6 (O*C*H_3), 21.2 (OCO*C*H_3), 21.1 (OCO*C*H_3); IR ν (film, cm^{-1}) 3466 (O-H), 2934 (=C-H), 1738 (C=O); ESIHRMS *m/z* = 391.1369 $[M+Na]^+$. $C_{18}H_{24}O_8Na$ requires 391.1369.

Methyl 2,3-di-*O*-acetyl-4-azido-6-*O*-benzyl-α-D-glucopyranoside 4a. Galactopyranose **3a** (77 mg, 0.209 mmol, 1 eq.) was co-evaporated 2 times with toluene (5 mL) and then diluted in dry CH_2Cl_2 (C = 0.1 M, 2 mL) under argon atmosphere. Pyridine (0.18 mL, 2.29 mmol, 11 eq.) was added and the mixture was cooled to 0 °C. Triflic anhydride (70 µL, 0.418 mmol, 2 eq.) was added and the mixture stirred for 90 min at 0 °C. The mixture was quenched by addition of 10% aqueous $NaHCO_3$ solution (20 mL), the phases were separated and the organic layer was extracted with 3% hydrochloric acid (3 x 10 mL), with water (10 mL), dried over Na_2SO_4 and was concentrated under vacuum. The resulting crude product was co-evaporated with toluene (3 x) to remove all traces of pyridine and dried for 1 h under vacuum. The yellow residue was dissolved in dry DMF (2.4 mL), sodium azide (332 mg, 5.12 mmol, 12 eq.) was added, and the reaction mixture was stirred overnight. The mixture was diluted with water and EtOAc (15 mL) and the phases were separated. The organic phase was washed with brine (3 x 15 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (Heptane/EtOAc 90:10 to 80:20) to afford **4a** (69 mg, 0.175 mmol, 84%) as a colorless oil. $[\alpha]_D^{25}$ + 136.2 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H, H_{Ar}), 5.41 (t, 1H, $J_{3,2}$ = 10.0 Hz, *H*3), 4.91 (d, 1H, $J_{1,2}$ = 4.0 Hz, *H*1), 4.85 (dd, 1H, $J_{2,1}$ = 4.0 Hz, $J_{2,3}$ = 10.0 Hz, *H*2), 4.65 (d, 1H, $J_{H,H}$= 12.0 Hz, CH_2Ph) 4.54 (d, 1H, $J_{H,H}$= 12.0 Hz, CH_2Ph), 3.79 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 10.0 Hz, *H*4), 3.74-3.41 (m, 3H, *H*5, *H*6, *H*6'), 3.36 (s, 3H, OCH_3), 2.08 (s, 3H, OCOCH_3), 2.05 (s, 3H, OCOCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5 (*C*=O), 170.0 (*C*=O), 137.8 (*C*q_{Ar}), 128.7 (*C*H_{Ar}), 128.0 (*C*H_{Ar}), 128.0 (*C*H_{Ar}), 97.3 (*C*1), 73.8 (*C*H_2Ph), 71.2 (*C*2), 70.9 (*C*3), 69.3 (*C*5), 68.5 (*C*6), 60.2 (*C*4), 55.6 (O-*C*H_3), 21.0 (OCO*C*H_3), 21.0 (OCO*C*H_3); IR ν (film, cm^{-1}) 2935 (CH_2), 2106 (N_3), 1746 (C=O); ESIHRMS *m/z* = 457.1712 [M+ CH_3CN +Na]$^+$. $C_{20}H_{26}N_4O_7Na$ requires 457.1699.

1,2,3,6-Tetra-*O*-acetyl-4-azido-α-D-glucopyranose 5. To a stirred solution of **4a** (57 mg, 0.16 mmol, 1 eq.) in acetic anhydride (0.5 mL) was added dropwise at 0 °C H_2SO_4 (10 µL). The resulting mixture was stirred overnight at room

temperature and then diluted by cold water. After being stirred for 1 h, the phases were separated and the aqueous phase was extracted with EtOAc (3 x 2 mL). Organic layers were combined, neutralized with aqueous $NaHCO_3$ (4 mL), then washed with brine (2 x 3 mL), dried over Na_2SO_4 and evaporated under vacuum. The residue was then purified by flash chromatography on silica gel (Heptane/EtOAc 70:30 to 60:40) to afford clean product **5** (α/β 8:2) (43 mg, 0.12 mmol, 73%) as a colorless oil (Experimental data agree with those reported in the literature).[28]

2,3,6-Tri-*O*-acetyl-4-azido-D-glucopyranose 5-OH. To a stirred solution of **5** (1 eq., 50 mg, 0.13 mmol) in THF (1.3 mL) was added benzylamine (1.5 eq., 22 µL, 0.20 mmol) and the resulting mixture was stirred at room temperature for 14 h under inert atmosphere. After addition of 1 N HCl (0.1 mL), the reaction mixture was stirred for one more hour. The reaction mixture was diluted with 1 N HCl (6 mL) and extracted with CH_2Cl_2 (3 x 8 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduce pressure. The residue was purified by flash chromatography on silica gel (Heptane/EtOAc 70:30 to 40:60) to give the corresponding hemiacetal **5-OH** (28 mg, 0.085 mmol, 63%, α/β = 70:30) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51 (t, 0.7H, $J_{3,2} = J_{3,4} = 10.0$ Hz, *H*3α), 5,38 (bs, 0.7H, *H*1α), 5.19 (t, 0.3H, $J_{3,2} = J_{3,4} = 9.5$ Hz, *H*3β), 4.82 (dd, 0.7H, $J_{2,3} = 10.0$ Hz, $J_{2,1} = 3.5$ Hz, *H*2α), 4.80 (dd, 0.3H, $J_{2,3} = 9.5$ Hz, $J_{2,1} = 8.0$ Hz, *H*2β), 4.70 (t, 0.3H, $J_{1,2} = 7.0$ Hz, *H*1β), 4.39 (dd, 0.3H, $J_{6,6'} = 12.0$ Hz, $J_{6,5} = 2.5$ Hz, *H*6β), 4.37 (dd, 0.7H, $J_{6,6'} = 12.0$ Hz, $J_{6,5} = 2.5$ Hz, *H*6α), 4.22 (dd, 1H, $J_{6',6} = 12.0$ Hz, $J_{6',5} = 4.0$ Hz, *H*6'β, *H*6'α), 4.02 (ddd, 0.7H, $J_{5,4} = 10.0$ Hz, $J_{5,6'} = 4.0$ Hz, $J_{5,6} = 2.5$ Hz, *H*5α), 3.63 (t, 0.3H, $J_{4,3} = J_{4,5} = 10$ Hz, *H*4β), 3.58 (t, 0.7H, $J_{4,3} = J_{4,5} = 10.0$ Hz, *H*4α), 3.48 (ddd, 0.3H, $J_{5,4} = 10.0$ Hz, $J_{5,6'} = 4.0$ Hz, $J_{5,6} = 2.5$ Hz, *H*5β), 2.10 (s, 3H, OCOCH_3), 2.09 (s, 3H, OCOCH_3), 2.06 (s, 3H, OCOCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (*C*=O), 170.8 (*C*=O), 170.7 (*C*=O), 170.4 (*C*=O), 169.9 (*C*=O), 95.5 (*C*1β), 90.6 (*C*1α), 73.5 (*C*2β), 73.2 (*C*3β), 72.5 (*C*5β), 71.5 (*C*2α), 70.6 (C3α), 67.8 (*C*5α), 63.0 (*C*6β), 62.8 (*C*6α), 60.4 (*C*4β), 60.3 (*C*4α), 21.0 (CO*C*H$_3$) 20.9 (CO*C*H$_3$), 20.8 (CO*C*H$_3$); IR ν (film, cm^{-1}) 3458 (O-H), 2960 (CH_3), 2108 (N_3), 1739 (C=O); ESIHRMS *m/z* = 354.0903 $[M+Na]^+$. $C_{12}H_{17}N_3O_8Na$ requires 354.0913.

1-*O*-(*ortho*-Hexynylbenzoyl)-2,3,4-tri-*O*-acetyl-4-azido-D-glucopyranose 6. To a stirred solution of **5-OH** (1 eq., 28 mg, 0.08 mmol) and *ortho*-(hex-1-yn-1-yl)benzoic acid (1.2 eq., 20 mg, 0.10 mmol), in CH_2Cl_2 (0.3 mL) were added DCC (1.5 eq., 26 mg, 0.13 mmol) and DMAP (1.5 eq., 15 mg, 0.13 mmol) under inert atmosphere. After being stirred for 3 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (1 mL) and washed with saturated aqueous $NaHCO_3$ (1 mL) and brine (1 mL). The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Heptane/EtOAc 90:10 to 70:30) to provide **6** (36 mg, 84%; α/β = 3:6) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93-7.79 (m, 1H, H_{Ar}α, H_{Ar}β), 7.53-7.21 (m, 3H, H_{Ar}α, H_{Ar}β), 6.51 (d, 0.4H, $J_{1,2} = 3.5$ Hz, *H*1α), 5.86 (d, 0.6H, $J_{1,2} = 8.0$ Hz, *H*1β), 5.55 (t, 0.4H, $J_{3,2} = J_{3,4} = 10.0$ Hz, *H*3α), 5.23 (t, 0.6H, $J_{3,2} = J_{3,4} = 9.0$ Hz, *H*3β), 5.16 (dd, 0.6H, $J_{2,1} = 8.0$ Hz, $J_{2,3} = 9.0$ Hz, *H*2β), 5.09 (dd, 0.4H, $J_{2,1} = 3.5$ Hz, $J_{2,3} = 10.0$ Hz, *H*2α), 4.37-4.20 (m, 2H, *H*6α, *H*6'α, *H*6β, *H*6'β), 4.03-3.94 (m, 0.4H, *H*5α), 3.72 (t, 0.6H, $J_{4,3} = J_{4,5} = 9.0$ Hz, *H*4β), 3.69 (t, 0.4H, $J_{4,3} = J_{4,5} = 10.0$ Hz, *H*4α), 3.65-3.58 (m, 0.6H, *H*5β), 2.50-2.36 (m, 2H, *H*7), 2.07 (s, 3H, COCH_3), 2.04 (s, 3H, COCH_3), 1.93 (s, 1.2H, COCH_3α), 1.92 (s, 1.8H, COCH_3β), 1.64-1.49 (m, 2H, *H*8), 1.49-1.34 (m, 2H, *H*9), 0.88 (t, 3H, $J_{CH3,9} = 7.0$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 (*C*=O), 170.2 (*C*=O), 170.0 (*C*=O), 169.9 (*C*=O), 164.2 (*C*q), 163.3 (*C*q), 135.4 (*C*H$_{Ar}$), 135.0 (*C*H$_{Ar}$), 132.8 (*C*H$_{Ar}$), 132.7 (*C*H$_{Ar}$), 130.9 (*C*H$_{Ar}$), 129.8 (Cq$_{Ar}$), 129.2 (*C*q$_{Ar}$), 127.6 (*C*H$_{Ar}$), 127.4 (*C*H$_{Ar}$), 126.1 (*C*q$_{Ar}$), 125.5 (*C*q$_{Ar}$), 97.7 (*C*q$_{alkyne}$), 97.5 (*C*q$_{alkyne}$), 92.1 (*C*1β), 90.1 (*C*1α), 79.8 (*C*q$_{alkyne}$), 79.1 (*C*q$_{alkyne}$), 73.7 (*C*3β), 73.1 (*C*5β), 70.8 (*C*3α), 70.6 (*C*2β, C5α), 69.7 (*C*2α), 62.7 (*C*6β), 62.5 (*C*6α), 60.2 (*C*4β), 60.0 (*C*4α), 30.9 (*C*8β), 30.8 (*C*8α), 22.3 (*C*9β, *C*9α), 20.9 (CO*C*H$_3$), 20.9 (CO*C*H$_3$), 20.8 (CO*C*H$_3$), 20.7 (CO*C*H$_3$), 20.7 (CO*C*H$_3$), 19.8 (*C*7β), 19.7 (*C*7α), 13.9 (*C*H$_3$β), 13.8 (*C*H$_3$α); IR ν (film, cm^{-1}) 2959 (CH_3), 2935 (CH_2), 2229 (alkyne), 2110 (N_3), 1745 (C=O); ESIHRMS *m/z* = 538.1804 $[M+Na]^+$. $C_{25}H_{29}N_3O_9Na$ requires 538.1801.

Phenyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-thio-β-D-galactopyranoside 2b. To a stirred solution of Na (52 mg, 20 mol%) in dry MeOH (113 mL) was added phenyl 2,3,4,6-tetra-*O*-acetyl-thio-β-D-galactoside (5 g, 11.35 mmol, 1 eq.) under argon atmosphere. The resulting mixture was stirred at room temperature for 2 h and then neutralized with Dowex® H^+, filtered on celite®, concentrated under reduced pressure and co-evaporated with toluene to afford the deprotected adduct **1b**. This latter (3.03 g, 11.3 mmol, 1 eq.) was then dissolved in dry MeCN (24 mL) then benzaldehyde dimethyl acetal (2.7 mL, 17.8 mmol, 1.6 eq.) and p-TsOH (15 mol%, 300 mg) were added. The mixture was stirred at room temperature for 2 h under argon atmosphere and then neutralized with Et_3N (2 mL). Water (30 mL) and EtOAc (50 mL) were added and the aqueous layer was extracted with EtOAc (2 x 50 mL). Organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was recrystallized with heptane/EtOAc 70:30 to afford the desired compound (3.3 g, 82%) as a white solid (experimental data agree with those reported in the literature).[29] The obtained product (3.27 g, 11.1 mmol, 1 eq.) was dissolved in pyridine (12 mL). Ac_2O (6 mL) was added and the mixture was stirred at room temperature overnight. Pyridine was co-evaporated with

toluene. The crude product was recrystallized with Heptane/EtOAc 55/45 to afford **2b** (3.61 g, 73%) as a white solid (experimental data agree with those reported in the literature).[Erreur ! Signet non défini.]

Phenyl 2,3-di-*O*-acetyl-6-*O*-benzyl-thio-β-D-galactopyranoside 3b. A solution of **2b** (5.0 g, 11.2 mmol, 1 eq.) in dry MeCN (110 mL) was cooled to 0 °C and Et_3SiH (10.8 mL, 67.4 mmol, 1 eq.) was added, followed by the addition of $Cu(OTf)_2$ (200 mg, 0.56 mmol, 0.05 eq.). The resulting mixture was stirred at 0 °C for 1 h and then hydrolysed with a saturated solution of $NaHCO_3$ (60 mL). The phases were separated and organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The desired product was obtained in mixture with the silylated one (6.28 g, ratio 30:70). The crude mixture was directly dissolved in MeCN (20 mL) and treated with a diluted aqueous solution of HBF_4 (C = 0.25 M, 20 mL). The resulting solution was stirred at room temperature for 1.5 h and then quenched with saturated solution of $NaHCO_3$ until neutralization. Aqueous layer was extracted with EtOAc (3 x 15 mL). Organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (Heptane/EtOAc 90:10 to 40:60) to afford product **3b** (4.43 g, 9.93 mmol, 88%) as a colorless oil. (Experimental data agree with those reported in the literature).[30]

Phenyl 2,3-di-*O*-acetyl-4-azido-6-*O*-benzyl-thio-β-D-glucopyranoside 4b. **3b** (500 mg, 1.12 mmol, 1 eq.) was co-evaporated 2 times with toluene (5 mL) and then diluted in dry CH_2Cl_2 (C = 0.1 M, 11.2 mL) under argon atmosphere. Pyridine (1.0 mL, 12.32 mmol, 11 eq.) was added and the mixture was cooled to 0 °C. Triflic anhydride (280 µL, 1.68 mmol, 2 eq.) was added and the mixture stirred for 90 min at 0 °C. The mixture was quenched by addition of 10% aqueous $NaHCO_3$ solution (50 mL), the phases were separated and the organic layer was extracted with 3% hydrochloric acid (3 x 20 mL), with water (20 mL), dried over Na_2SO_4 and was concentrated under vacuum. The resulting crude product was co-evaporated with toluene (3 x) to remove all traces of pyridine and dried for 1 h under vacuum. The yellow residue was dissolved in dry DMF (10 mL), sodium azide (1.6 g, 25.0 mmol, 12 eq.) was added, and the reaction mixture was stirred overnight. The mixture was diluted with water and EtOAc (20 mL) and the phases were separated. The organic phase was washed with brine (3 x 30 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (Heptane/EtOAc 90:10 to 80:20) to afford product **4b** (347 mg, 0.736 mmol, 66%) as a colorless oil. $[\alpha]_D^{25}$ – 4.4 (*c* =1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.34 (m, 2H, H_{Ar}), 7.30-7.09 (m, 8H, H_{Ar}), 5.04 (dd, 1H, $J_{3,2}$ = 9.5 Hz and $J_{3,4}$ = 10.0 Hz, *H*3), 4.79 (dd, 1H, $J_{2,1}$ = 10.0 Hz and $J_{2,3}$ = 9.5 Hz, *H*2), 4.56 (d, 1H, $J_{1,2}$ = 10.0 Hz, *H*1), 4.52 (d, 1H, $J_{H,H}$ = 12.0 Hz, CH_2Ph), 4.45 (d, 1H, $J_{H,H}$ = 12.0 Hz, CH_2Ph), 3.69 (dd, 1H, $J_{6,6'}$ = 11.0 Hz and $J_{6,5}$ = 2.0 Hz, *H*6), 3.64 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 10.0 Hz, *H*4) 3.62 (dd, 1H, $J_{6',6}$ = 11.0 Hz, $J_{6',5}$ = 4.0 Hz, *H*6'), 3.31 (ddd, 1H, $J_{5,4}$ = 10.0 Hz, $J_{5,6'}$ = 4.0 Hz and $J_{5,6}$ = 2.0 Hz, *H*5), 1.96 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (*C*=O), 169.7 (*C*=O), 138.0 (*C*q_{Ar}), 133.3 (*C*H$_{Ar}$), 132.0 (*C*q_{Ar}), 129.2 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 128.5 (*C*H$_{Ar}$), 128.0 (CH*C*$_{Ar}$), 127.9 (*CH$_{Ar}$*), 85.9 (*C*1), 78.4 (*C*5) 75.0 (*C*3), 73.8 (*C*H_2Ph), 70.4 (*C*2), 69.0 (*C*6), 60.0 (*C*4), 21.0 (CO*C*H_3), 20.9 (CO*C*H_3); IR ν (film, cm^{-1}) 3122 (=C-H), 2926 (-CH_2), 2110 (N_3), 1752 (C=O); ESIHRMS *m/z* = 494.1360 $[M+Na]^+$. $C_{23}H_{25}N_3O_6SNa$ requires 494.1362.

Phenyl 2,3,6-tri-*O*-acetyl-4-azido-thio-β-D-glucopyranoside. To a stirred solution of **4b** (1.48g, 3.14 mmol, 1 eq.) in dry acetic anhydride (5.6 mL) at 0 °C was added dropwise a solution of NaI (471 mg, 3.14 mmol, 1 eq) in MeCN (1.9 mL) followed by BF_3•OEt_2 (1.16 mL, 4.71 mmol, 1.5 eq). After completion of the reaction, the reaction mixture was quenched with aqueous $Na_2S_2O_3$ until neutralization and extracted with EtOAc (15 mL). The organic layer was washed with water (3 x 15 mL), brine (3 x 15 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography (Heptane/EtOAc 90:10 to 75:25) to afford the desired clean product (0.8242 g, 62%) as a colorless oil. $[\alpha]_D^{25}$ – 2.80 (*c*=1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) : 7.56-7.44 (m, 2H, H_{Ar}), 7.37-7.28 (m, 3H, H_{Ar}), 5.21 (t, 1H, $J_{2,3}$=$J_{3,4}$=10.5 Hz, *H*3), 4.91 (t, 1H, $J_{1,2}$=$J_{2,3}$= 10.5 Hz, *H*2), 4.68 (d, 1H, $J_{1,2}$= 10.5 Hz, *H*1), 4.52-4.45 (dd, 1H, $J_{6,6'}$=12.5 Hz and $J_{6,5}$= 2.0 Hz, *H*6), 4.30-4.21 (dd, 1H, $J_{6,6'}$=12.5 Hz and $J_{6',5}$= 5.0 Hz, H$_{6'}$) 3.64 (t, 1H, $J_{4,5}$=$J_{3,4}$=10.0 Hz, *H*4), 3.54-3.46 (ddd, 1H, $J_{4,5}$=10.2 Hz, $J_{6',5}$=5.0 Hz and $J_{6,5}$=2.0 Hz, *H*5), 2.13 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.11 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) : 170.38 (*C*=O), 169.87 (*C*=O), 169.48 (*C*=O), 133.4 (2**C*H$_{Ar}$), 128.9 (2**C*H$_{Ar}$), 128.5 (*C*q_{Ar}), 85.6 (*C*1), 75.9 (*C*5), 74.7 (*C*3), 69.8 (*C*2), 62.8 (*C*6), 59.9 (*C*4), 20.8 (CO*C*H_3), 20.6 (CO*C*H_3); IR ν (film, cm^{-1}) : 2952 (-CH2), 2109 (N3), 1745 (C=O); ESIHRMS *m/z* = 446.1004 $[M+Na]^+$. $C_{18}H_{21}N_3O_7SNa$ requires 446.0998.

2,3,6-Tri-*O*-acetyl-4-azido-β-D-glucopyranosyl phenyl sulfoxide 7. To a stirred solution the previous described sulfide compound (1.4 g, 3.27 mmol, 1 eq.) in CH_2Cl_2 (31 mL) was added *m*-CPBA (75%, 0.85 g, 3.92 mmol, 1.2 eq.) at -78 °C under argon atmosphere. The resulting mixture was stirred at -30 °C overnight and a solution of aqueous $Na_2S_2O_3$/$NaHCO_3$ 50:50 (20/20 mL) was then added. The solution was allowed to warm at room temperature, extracted with EtOAc (2 x 30 mL). Organics layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (Heptane/EtOAc 80:20 to 50:50) to afford the clean product **7** as a mixture of two diastereoisomers (dr = 1:1, 1.2 g, 84%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) : 7.71-

7.50 (m, 10H, H_{Ar}), 5.40-5.14 (m, 4H, H_2, H_3), 4.51-4.44 (m, 2H, H_6), 4.31 (dd, 1H, $J_{6,6}$=12.0 Hz and $J_{6,5}$=1.5 Hz, H_6), 4.24 (d, 1H, $J_{2,1}$=9.5 Hz, H_1), 4.22-4.09 (m, 2H, H_1, H_6), 3.70-3.56 (m, 2H, H_4), 3.52-3.47 (m, 1H, H_5), 3.43-3.33 (m, 1H, H_5), 2.14 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.86 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) : 170.2 (*C*=O), 170.1 (*C*=O), 169.9 (*C*=O), 169.5 (*C*=O), 169.2 (*C*=O), 131.7 (C_{Ar}), 131.5 (C_{Ar}), 129.0 (C_{Ar}), 128.9 (C_{Ar}), 125.7 (C_{Ar}), 125.4 (C_{Ar}), 92.4 (*C*1), 90.1 (*C*1), 77.5 (*C*5), 77.0 (*C*5), 74.9 (*C*3), 74.6 (*C*3), 67.5 (*C*2), 67.1 (*C*2), 62.4 (*C*6), 62.2 (*C*6), 59.6 (*C*4), 59.3 (*C*4), 20.7 (CO*C*H$_3$), 20.6 (CO*C*H$_3$), 20.5 (CO*C*H$_3$); IR ν (film, cm^{-1}) : 2942 (-CH2), 2110 (N3), 1741 (C=O); ESIHRMS *m/z* = 901.2006 [2M+Na]$^+$. $C_{36}H_{42}N_6O_{16}S_2Na$ requires 901.2006.

2,3-Di-*O*-acetyl-4-azido-6-*O*-benzyl-β-D-glucopyranosyl phenyl sulfoxide 8. To a stirred solution of **4b** (1.0 g, 2.12 mmol, 1 eq.) in CH_2Cl_2 (21 mL) was added *m*-CPBA (above 75%, 550 mg, 3.18 mmol, 1.5 eq.) at –78 °C under argon atmosphere. The resulting mixture was stirred at –30 °C overnight and dimethylsulfide (0.2 mL) was then added. The solution was allowed to warm at room temperature, diluted with CH_2Cl_2 (10 mL), washed with water (8 mL), with a saturated aqueous solution of $NaHCO_3$ (8 mL), with water again (8 mL) and finally with brine (8 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (Heptane/EtOAc 80:20 to 60:40) to afford product **8** (914 mg, 1.875 mmol, 89%) as a colorless oil and as a mixture of two diastereoisomers (dr = 2:3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.59 (m, 2H, H_{Ar}), 7.55-7.42 (m, 3H, H_{Ar}), 7.42-7.21 (m, 5H, H_{Ar}), 5.29 (t, 0.4H, $J_{2x,1x} = J_{2x,3x}$ = 9.5 Hz, *H*2x), 5.24 (t, 0.6H, $J_{2y,1y} = J_{2y,3y}$ = 9.0 Hz *H*2y), 5.19 (t, 0.4H, $J_{3x,2x} = J_{3x,4x}$ = 9.5 Hz, *H*3x), 5.16 (t, 0.6H, $J_{3y,2y} = J_{3y,4y}$ = 9.0 Hz, *H*3y), 4.56-4.36 (m, 2.6H, CH_2Ph, *H*1y), 4.25 (d, 0.4H, $J_{1x,2x}$ = 9.5 Hz, *H*1x), 3.82-3.69 (m, 2.2H, *H*6, *H*6'), 3.69-3.56 (m, 1H, *H*4), 3.48-3.38 (dt, 0.6H, $Jb_{5y,4y}$ = 10.0 Hz, $J_{5y,6'y}$ = 5.0 Hz and $J_{5y,6y}$ = 2.5 Hz, *H*5y), 3.36-3.24 (ddd, 0.4H, $Jb_{5x,4x}$ = 10.0 Hz, $J_{5x,6'x}$ = 6.0 Hz and $J_{5x,6x}$ = 4.0 Hz, *H*5x), 2.10 (s, 1.2H, OCOCH_3x), 2.08 (s, 1.8H, OCOCH_3y), 2.06 (s, 1.2H, OCOCH_3x), 1.83 (s, 1.8H, OCOCH_3y); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (*C*=O), 170.3 (*C*=O), 169.7 (*C*=O), 169.4 (*C*=O), 139.6 (*C*q$_{Ar}$), 139.0 (*C*q$_{Ar}$), 137.8 (*C*q$_{Ar}$), 137.7 (*C*q$_{Ar}$), 131.8 (*C*H$_{Ar}$), 131.7 (*C*H$_{Ar}$), 129.2 (*C*H$_{Ar}$), 129.1 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 128.5 (*C*H$_{Ar}$), 128.1 (*C*H$_{Ar}$), 128.0 (*C*H$_{Ar}$), 127.9 (*C*H$_{Ar}$), 127.9 (*C*H$_{Ar}$), 125.8 (*C*H$_{Ar}$), 125.6 (*C*H$_{Ar}$), 93.0 (*C*1y), 90.5 (*C*1x), 79.3 (*C*5x), 79.0 (*C*5y), 75.1 (*C*2y), 74.8 (*C*3y), 73.8 (*C*H$_2$Ph), 68.6 (*C*6x), 68.4 (*C*6y), 67.8 (*C*2x), 67.4 (*C*3x), 59.4 (*C*4y), 59.2 (*C*4x), 20.9 (CO*C*H$_3$), 20.8 (CO*C*H$_3$), 20.7 (CO*C*H$_3$); IR ν (film, cm^{-1}) 2988 (=C-H), 2901 (-CH$_2$), 2110 (N$_3$), 1755 (C=O); ESIHRMS *m/z* = 510.1312 [M+Na]$^+$. $C_{23}H_{25}N_3O_7SNa$ requires 510.1311.

***N*-Acetyl-cytosine 9**. To a stirred solution of cytosine (500 mg, 4.5 mmol, 1eq.) in pyridine (2.5 mL) was added acetic anhydride (2.1 mL, 22.05 mmol, 5 eq.). The resulting mixture was stirred overnight at room temperature then diluted with EtOAc (2.0 mL) and stirred again for 30 min at room temperature. The resulting white solid was filtered, washed with EtOAc, co-evaporated with toluene and dried under vacuum to afford clean product **9** (0.6521 g, 95%) as a white solid (experimental data agree with those reported in the literature).[31]

***N*-Benzoyl-5-methyl-cytosine 10**. To a suspension of 5-methyl-cytosine (1.5 g, 12 mmol, 1eq.) in dry MeCN (40 mL) was added benzoic anhydride (3.25 g, 14.4 mmol, 1.2 eq.) followed by DMAP (293 mg, 2.4 mmol, 0.2 eq.) under argon atmosphere. The resulting mixture was refluxed for 24 h then EtOH (25 mL) was added to the hot solution. The solution was cooled to room temperature and the resulting solid was filtered, washed with EtOH (15 mL) and Et_2O (15 mL) and dried under vacuum to afford clean product **10** (1.913 g, 70%) as a white solid (experimental data agree with those reported in the literature).[32]

***N*-Benzoyl-5-fluoro-cytosine 13**. To a suspension of 5-fluoro-cytosine (1.5 g, 11.6 mmol, 1 eq.) in dry MeCN (15 mL) was added benzoic anhydride (3.15g, 13.9 mmol, 1.2 eq.) followed by DMAP (283 mg, 2.32 mmol, 0.2 eq.) under argon atmosphere. The resulting mixture was refluxed for 24 h then EtOH (2 mL) was added to the hot solution. The solution was cooled to room temperature and the resulting solid was filtered, washed with EtOH (15 mL) and Et_2O (15 mL) and dried under vacuum to afford clean product **13** (1.9 g, 70%) as a white solid (experimental data agree with those reported in the literature).[33]

General Procedure for the glycosylation of sulfoxide donors. To a stirred solution of the nitrogen base (1.6 eq.) in dry MeCN (2/3 V_{tot}) under argon atmosphere was added BSA (4 eq.). The resulting mixture was heated at 60 °C for 1h and then cooled to room temperature. The donor (1 eq.) is stirred with 4 Å molecular sieves in dry MeCN (1/3 V_{tot}) under argon for 1 h. The solution of the nitrogen base was added to the donor and then TMSOTf (1.5 eq.). The resulting mixture was heated at 55 °C overnight and then quenched with aqueous $NaHCO_3$. The reaction mixture was filtered and the aqueous phase was extracted with EtOAc (5x). The organic layers were combined, washed with NaCl, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel to afford the clean product.

2,3,6-Tri-*O*-acetyl-4-azido-1-*N*-(*N*-acetyl-cytosine)-β-D-glucopyranoside 15. The General Procedure was followed using **7** (300 mg, 0.68 mmol), **9** (184 mg, 1.09 mmol), BSA (0.67 mL, 2.72 mmol), TMSOTf (0.18 mL, 1.02 mmol), 4 Å molecular sieves (200 mg) in dry MeCN (13.6 mL). The residue was purified by flash chromatography on silica gel (EtOAc) to afford product **15** (304 mg, 0.65 mmol, 95%) as a colorless oil. $[\alpha]_D^{25}$ + 56.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 8.14 (d, 1H, $J_{HAr,HAr}$ = 7.5 Hz, H_{Ar}), 7.49 (d, 1H, $J_{HAr,HAr}$ = 7.5 Hz, H_{Ar}), 6.12 (d, 1H, $J_{1,2}$ = 9.0 Hz, *H*1), 5.54 (t, 1H, $J_{3,2} = J_{3,4}$ = 9.5 Hz, *H*3), 5.32 (t, 1H, $J_{2,3} = J_{2,1}$ = 9.5 Hz, *H*2), 4.47 (dd, 1H, $J_{6,6'}$ = 13.0 Hz and $J_{6,5}$ = 1.0 Hz, *H*6), 4.31 (dd, 1H, $J_{6',6}$ = 13.0 Hz and $J_{6',5}$ = 4.5 Hz, *H*6'), 4.00-3.93 (m, 2H, *H*4, *H*5), 2.21 (s, 3H, NHCOCH_3), 2.14 (s, 3H, OCOCH_3), 2.12 (s, 3H, OCOCH_3), 1.94 (s, 3H, OCOCH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 173.9 (*C*=O), 173.1 (*C*=O), 172.0 (*C*=O), 172.0 (*C*=O), 165.5 (*C*q_{Ar}), 158.6 (Cq_{Ar}), 147.5 (CH_{Ar}), 99.8 (CH_{Ar}), 83.6 (*C*1), 77.1 (*C*4), 75.4 (*C*3), 73.2 (*C*2), 64.8 (*C*6), 61.9 (*C*5), 25.4 (CO*C*H_3), 21.4 (CO*C*H_3), 21.1 (CO*C*H_3); IR ν (film, cm^{-1}) 3239 (=C-H), 2112 (N_3), 1747 (C=O), 1663 (NH-C=O); ESIHRMS *m/z* = 467.1486 $[M+H]^+$. $C_{18}H_{23}N_6O_9$ requires 467.1527.

2,3,6-Tri-*O*-acetyl-4-azido-1-*N*-thymine-β-D-glucopyranoside 16. The general procedure was followed using **7** (70 mg, 0.16 mmol), **10** (32 mg, 0.256 mmol), BSA (0.16 mL, 0.64 mmol), TMSOTf (43 µL, 0.24 mmol, 1.5 eq.), 4 Å molecular sieves (150 mg) in dry MeCN (3mL). The residue was purified by preparative TLC (Hept/EtOAc 20:80) to afford product **16** (63 mg, 89%) as a white powder. $[\alpha]_D^{25}$ + 8.7 (*c* = 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H, N*H*), 7.05 (d, 1H, $J_{HAr,CH3}$= 1.3 Hz, H_{Ar}), 5.82 (d, 1H, $J_{1,2}$= 9.5 Hz, *H*1), 5.35 (t, 1H, $J_{3,2} = J_{3,4}$= 9.5 Hz, *H*3), 5.10 (t, 1H, $J_{2,1} = J_{2,3}$= 9.5 Hz, *H*2), 4.37 (dd, 1H, $J_{6,6'}$= 12.5 Hz and $J_{6,5}$= 1.5 Hz, *H*6), 4.25 (dd, 1H, $J_{6',6}$= 12.5 Hz, $J_{6',5}$ = 4.5 Hz, *H*6'), 3.71-3.64 (m, 2H, *H*4, *H*5), 2.11 (s, 3H, C(O)CH_3), 2.10 (s, 3H, C(O)CH_3), 1.97 (s, 3H, C(O)CH_3), 1.92 (d, 3H, $J_{CH3,HAr}$= 1.0 Hz, $C_{Ar}CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (*C*=O), 169.7 (*C*=O), 169.4 (*C*=O), 162.9 (*C*q_{Ar}), 150.2 (*C*q_{Ar}), 134.3 (*C*H_{Ar}), 112.3 (*C*q_{Ar}, 80.2 (*C*1), 75.1 (*C*5), 73.5 (*C*3), 69.3 (*C*2), 62.6 (*C*6), 59.9 (*C*4), 20.8 (C(O)*C*H_3), 20.6 (C(O)*C*H_3), 20.4 (C(O)*C*H_3), 12.6 (CAr*C*H_3); IR ν (film, cm^{-1}) 3220 (N-H), 3075 (=C-H), 2931 (CH_3), 2111 (N_3), 1748 (C=O), 1690 (NH-C=O); ESIHRMS *m/z* = 440.1418 $[M+H]^+$. $C_{17}H_{22}N_5O_9$ requires 440.1409.

2,3,6-Tri-*O*-acetyl-4-azido-1-*N*-(5-fluoro-uracil)-β-D-glucopyranoside 17. The general procedure was followed using **7** (70 mg, 0.16 mmol), **11** (33 mg, 0.256 mmol), BSA (0.16 mL, 0.64 mmol), TMSOTf (43 µL, 0.24 mmol, 1.5 eq.), 4 Å molecular sieves (150 mg) in dry MeCN (3 mL). The residue was purified by preparative TLC (Hept/EtOAc 30:70) to afford product **17** (49 mg, 68%) as a yellow powder. $[\alpha]_D^{25}$ + 23.0 (*c* =1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, 1H, $J_{NH,F}$= 4.5 Hz, N*H*), 7.34 (d, 1H, $J_{HAr,F}$= 5.5 Hz, H_{Ar}), 5.84 (d, 1H, $J_{1,2}$= 9.5 Hz, *H*1), 5.39 (t, 1H, $J_{3,2}$= $J_{3,4}$= 9.5 Hz, *H*3), 5.03 (t, 1H, $J_{2,3} = J_{2,1}$= 9.5 Hz, *H*2), 4.39 (dd, 1H, $J_{6,6}$ = 12.5 Hz and $J_{6,5}$= 1.5 Hz, *H*6), 4.25 (dd, 1H, $J_{6',6}$ = 12.5 Hz and $J_{6',5}$ = 4.5 Hz, *H*6'), 3.80-3.71 (m, 1H, *H*5), 3.66 (dd, 1H, $J_{4,5}$ = 10.5 Hz and $J_{4,3}$ = 9.5 Hz, *H*4), 2.11 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 1.98 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (*C*=O), 169.9 (*C*=O), 169.5 (*C*=O), 156.4 (d, $J_{C\text{-}F}$ = 27 Hz, *C*q_{Ar}), 142.4 (*C*q_{Ar}), 139.3 (*C*q_{Ar}), 123.3 (d, $J_{C\text{-}F}$ = 34 Hz, *C*H_{Ar}), 80.5 (*C*1), 75.0 (*C*5), 73.1 (*C*3), 69.5 (*C*2), 62.4 (*C*6), 59.7 (*C*4), 20.8 (C(O)*C*H_3), 20.6 (C(O)*C*H_3), 20.4 (C(O)*C*H_3); IR ν (film, cm^{-1}) 3222 (N-H), 3096 (=C-H), 2116 (N_3), 1712 (C=O), 1673 (NH-C=O); ESIHRMS *m/z* = 444.1167 $[M+H]^+$. $C_{16}H_{19}N_5O_9F$ requires 444.1180.

2,3,6-Tri-*O*-acetyl-4-azido-1-*N*-(4-*N*-benzoyl-5-methyl-cytosine)-β-D-glucopyranoside 18. The general procedure was followed using **7** (70 mg, 0.16 mmol), **12** (59 mg, 0.256 mmol), BSA (0.16 mL, 0.64 mmol), TMSOTf (43 µL, 0.24 mmol, 1.5 eq.), 4 Å molecular sieves (150 mg) in dry MeCN (3 mL). The residue was purified by preparative TLC (Hept/EtOAc 30:70) to afford product **18** (76 mg, 88%) as a white powder. $[\alpha]_D^{25}$ + 4.1 (*c* = 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39-8.19 (m, 2H, H_{Ar}), 7.59-7.36 (m, 3H, H_{Ar}), 7.20 (d, 1H, $J_{HAr,CH3}$ = 1.5 Hz, H_{Ar}), 5.85 (d, 1H, $J_{1,2}$ = 9.5 Hz, *H*1), 5.35 (m, 1H, *H*3), 5.12 (t, 1H, $J_{2,1} = J_{2,3}$ = 9.5 Hz, *H*2), 4.38 (d, 1H, $J_{6,6'}$ = 12.5 Hz, *H*6), 4.27 (dd, 1H, $J_{6',6}$ = 12.5 Hz and $J_{6',5}$ = 3.5 Hz, *H*6'), 3.79-3,61 (m, 2H, *H*4, *H*5), 2.12 (s, 3H, CH_3), 2.11 (s, 3H, COCH_3), 1.98 (s, 3H, COCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0 (*C*=O), 170.5 (*C*=O), 170.0 (*C*=O), 169.6 (*C*=O), 159.0 (*C*q_{Ar}), 148.2 (*C*q_{Ar}), 136.9 (Cq_{Ar}), 135.5 (*C*H_{Ar}), 133.0 (*C*H_{Ar}), 130.2 (*C*H_{Ar}), 128.4 (*C*H_{Ar}), 113.3 (*C*q_{Ar}), 80.6 (*C*1), 75.4 (*C*5), 73.8 (*C*3), 69.8 (*C*2), 62.9 (*C*6), 60.1 (*C*4), 20.8 (C(O)*C*H_3), 20.6 (C(O)*C*H_3), 14.0 (*C*H_3); IR ν (film, cm^{-1}) 3072 (=C-H), 2959 (C-H), 2110 (N_3), 1740 (C=O), 1707 (C=O), 1656 (NH-C=O); ESIHRMS *m/z* = 543.1835 $[M+H]^+$. $C_{24}H_{27}N_6O_9$ requires 543.1840.

2,3,6-Tri-*O*-acetyl-4-azido-1-*N*-(4-*N*-benzoyl-5-fluoro-cytosine)-β-D-glucopyranoside 19. The general procedure was followed using **7** (70 mg, 0.16 mmol), **13** (56 mg, 0.256 mmol), BSA (0.16 mL, 0.64 mmol), TMSOTf (43 µL, 0.24 mmol, 1.5 eq.), 4 Å molecular sieves (150 mg) in dry MeCN (3 mL). The residue was purified by preparative TLC (Hept/EtOAc 20:80) to afford product **19** (75 mg, 75%) as a white powder. $[\alpha]_D^{20}$ = + 37.4 (c = 0.5, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, 2H, $J_{HAr,HAr}$ = 7.5 Hz, H_{Ar}), 7.55 (t, 1H, $J_{HAr,HAr}$ = 7.5 Hz H_{Ar}), 7.47-7.39 (m, 3H,

H_{Ar}), 5.82 (d, 1H, $J_{1,2}$= 9.5 Hz, *H*1), 5.37 (t, 1H, $J_{3,2}$= $J_{3,4}$= 9.5 Hz, *H*3), 5.03 (t, 1H, $J_{2,3}$ = $J_{2,1}$= 9.5 Hz, *H*2), 4.39 (d, 1H, $J_{H6,H6'}$ = 12.5 Hz, *H*6), 4.27 (dd, 1H, $J_{H6',H6}$ = 12.5 Hz and $J_{H6',H5}$ = 4.0 Hz, H6'), 3.72-3.63 (m, 2H, *H*4, *H*5), 2.12 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 1.99 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5 (*C*=O), 170.1 (*C*=O), 169.5 (*C*=O), 151.8 (d, $J_{C\text{-}F}$ = 19 Hz, *C*q$_{Ar}$), 146.8 (*C*q$_{Ar}$), 141.8 (*C*q$_{Ar}$), 138.7 (*C*H$_{Ar}$), 135.7 (*C*H$_{Ar}$), 133.7 (*C*H$_{Ar}$), 130.4 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 124.0 (d, $J_{C\text{-}F}$ = 35 Hz, *C*H$_{Ar}$), 81.1 (*C*1), 75.5 (*C*5), 73.4 (*C*3), 69.8 (*C*2), 62.7 (*C*6), 60.0 (*C*4), 21.0 (C(O)*C*H$_3$), 20.7 (C(O)*C*H$_3$), 20.6 (C(O)*C*H$_3$); IR ν (film, cm^{-1}) 3100 (=C-H), 2113 (N_3), 1754 (C=O), 1674 (NH-C=O) ESIHRMS *m/z* = 547.1589 $[M+H]^+$. $C_{23}H_{24}N_6O_9F$ requires 547.1589.

2,3,6-Tri-*O*-acetyl-4-azido-1-*N*-uracil-β-D-glucopyranoside 20. The general procedure was followed using **7** (70 mg, 0.16 mmol), **14** (29 mg, 0.256 mmol), BSA (0.16 mL, 0.64 mmol), TMSOTf (43 µL, 0.24 mmol, 1.5 eq.), 4 Å molecular sieves (150 mg) in dry MeCN (3 mL). The residue was purified by preparative TLC (Hept/EtOAc 20:80) to afford product **20** (63 mg, 94%) as a white powder. $[\alpha]_D^{25}$ + 24.1 (*c* =1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (bs, 1H, N*H*), 7.21 (d, 1H, $J_{HAr,HAr}$ = 8.5 Hz, H_{Ar}), 5.77 (d, 1H, $J_{1,2}$ = 9.5 Hz, *H*1), 5.74 (d, 1H, $J_{HAr,HAr}$ = 8.5 Hz, H_{Ar}), 5.32 (t, 1H, $J_{3,2}$ = $J_{3,4}$ = 9.0 Hz, *H*3), 5.03 (dd, 1H, $J_{2,1}$ = 9.5 Hz, $J_{2,3}$ = 9.0 Hz, *H*2), 4.33 (d, 1H, $J_{6,6'}$ = 12.5 Hz, *H*6), 4.20 (dd, 1H, $J_{6',6}$ = 12.5 Hz and $J_{6',5}$ = 3.0 Hz, *H*6'), 3.72-3.53 (m, 2H, *H*4, *H*5), 2.05 (s, 6H, 2 CH_3), 1.93 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5 (*C*=O), 169.9 (*C*=O), 169.6 (*C*=O), 162.4 (*C*q$_{Ar}$), 150.3 (*C*q$_{Ar}$), 139.1 (*C*H$_{Ar}$), 104.0 (*C*H$_{Ar}$), 80.5 (*C*1), 75.4 (*C*5), 73.6 (*C*3), 69.6 (*C*2), 62.7 (*C*6), 60.1 (*C*4), 21.0 (*C*H$_3$), 20.8 (*C*H$_3$), 20.5 (*C*H$_3$); IR ν (film, cm^{-1}) 2960 (=C-H), 2111 (N_3), 1748 (C=O), 1689 (NH-C=O); ESIHRMS *m/z* = 426.1260 $[M+H]^+$. $C_{16}H_{19}N_5O_9F$ requires 426.1261.

2,3-Di-*O*-acetyl-4-azido-6-*O*-benzyl-1-*N*-(*N*-acetyl-cytosine)-β-D-glucopyranoside 21. The General Procedure was followed using **8** (50 mg, 0.10 mmol), **9** (25 mg, 0.16 mmol), BSA (0.1 mL, 0.41 mmol), TMSOTf (22 µL, 0.12 mmol), 4 Å molecular sieves (50 mg) in dry MeCN (1 mL). The residue was purified by preparative TLC (Heptane/EtOAc 1:1) to afford product **21** (28 mg, 0.05 mmol, 54%) as a colorless oil. $[\alpha]_D^{25}$ + 47.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7,67 (d, 1H, $J_{HAr,HAr}$ = 7.5 Hz, H_{Ar}), 7.47 (d, 1H, $J_{HAr,HAr}$ = 7.5 Hz, H_{Ar}) 7.36-7.27 (m, 5H, H_{Ar}), 5.99 (d, 1H, $J_{1,2}$ = 9.5 Hz, *H*1), 5.32 (dd, 1H, $J_{3,2}$ = 9.5 Hz and $J_{3,4}$ = 10.0 Hz, *H*3), 5.03 (t, 1H, $J_{2,3}$ = $J_{2,1}$ = 9.5 Hz, *H*2), 4.57 (d, 1H, $J_{H,H}$ = 12.0 Hz, CH_2Ph), 4.52 (d, 1H, $J_{H,H}$ = 12.0 Hz, CH_2Ph), 3.94 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 10.0 Hz, *H*6), 3.80-3.67 (m, 2H, *H*6), 3.60 (ddd, 1H, $J_{5,4}$ = 10.0 Hz and $J_{5,6}$ = 3.5 Hz, $J_{5,6'}$ = 2.0 Hz, *H*5), 2.23 (s, 3H, NHCOCH_3), 2.08 (s, 3H, OCOCH_3), 1.92 (s, 3H, OCOCH_3); ^{13}C NMR (75 MHz, MeOD) δ 170.0 (*C*=O), 169.7 (*C*=O), 163.1 (*C*q$_{Ar}$), 155.3 (*C*q$_{Ar}$), 144.5 (*C*H$_{Ar}$), 137.6 (*C*q$_{Ar}$), 128.7 (*C*H$_{Ar}$), 128.2 (*C*H$_{Ar}$), 128.1 (*C*H$_{Ar}$), 98.0 (*C*H$_{Ar}$), 81.5 (*C*1), 77.3 (*C*5), 73.9 (*C*H$_2$Ph), 73.5 (*C*2), 71.0 (*C*3), 68.2 (*C*6), 59.7 (*C*4), 25.2 (CO*C*H$_3$), 20.8 (CO*C*H$_3$), 20.6 (CO*C*H$_3$); IR ν (film, cm^{-1}) 3148 (=C-H), 2110 (N_3), 1754 (C=O), 1667 (NH-C=O); ESIHRMS *m/z* = 515.1878 $[M+H]^+$. $C_{23}H_{27}N_6O_8$ requires 515.1890.

2,3-Di-*O*-acetyl-4-azido-6-*O*-benzyl-1-*N*-thymine-β-D-glucopyranoside 22. The General Procedure was followed using **8** (581 mg, 1.2 mmol), Thymine **10** (267 mg, 2.1 mmol), BSA (1.3 mL, 5.29 mmol), TMSOTf (1.6 mL, 1.9 mmol) in dry MeCN (25 mL). The residue was purified by flash chromatography on silica gel (Heptane/EtOAc 70:30 to 60:40) to afford product **22** (496 mg, 77%) as a white powder. $[\alpha]_D^{25}$ + 11.1 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.25 (m, 5H, H_{Ar}), 7.11 (d, 1H, $J_{HAr,CH3}$= 1.0 Hz, H_{Ar}), 5.79 (d, 1H, $J_{1,2}$= 9.5 Hz, *H*1), 5.29 (dd, 1H, $J_{3,2}$= 9.5 Hz and $J_{3,4}$= 10.0 Hz, *H*3), 5.07 (t, 1H, $J_{2,1}$ = $J_{2,3}$= 9.5 Hz, *H*2), 4.59 (d, 1H, $J_{H,H}$ = 12.0 Hz, CH_2Ph), 4.52 (d, 1H, $J_{H,H}$ = 12.0 Hz, CH_2Ph), 3.90 (t, 1H, $J_{4,3}$ = $J_{4,5}$ = 10.0 Hz, *H*4), 3.79-3.66 (m, 2H, *H*6, *H*6'), 2.08 (s, 3H, C(O)CH_3), 1.95 (s, 3H, C(O)CH_3), 1.91 (d, 3H, $J_{CH3,HAr}$= 1.0 Hz, C$_{Ar}$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (*C*=O), 169.8 (*C*=O), 163.5 (*C*q$_{Ar}$), 150.6 (*C*q$_{Ar}$), 137.6 (*C*q$_{Ar}$), 134.6 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 128.2 (*C*H$_{Ar}$), 128.0 (*C*H$_{Ar}$), 112.3 (*C*q$_{Ar}$), 80.2 (*C*1), 76.9 (*C*5), 73.8 (*C*H$_2$Ph), 73.7 (*C*3), 69.8 (*C*2), 68.2 (*C*6), 59.7 (*C*4), 20.8 (C(O)*C*H$_3$), 20.6 (C(O)*C*H$_3$), 12.6 (CAr*C*H$_3$); IR ν (film, cm^{-1}) 3675 (N-H), 2988 (=C-H), 2901 (CH_2), 2111 (N_3), 1754 (C=O), 1697 (NH-C=O); ESIHRMS *m/z* = 487.1783 $[M+H]^+$. $C_{22}H_{26}N_5O_8$ requires 487.1781.

2,3-Di-*O*-acetyl-4-azido-6-*O*-benzyl-1-*N*-(5-fluoro-uracil)-β-D-glucopyranoside 23. A mixture of 5-fluoro-uracil **11** (42 mg, 0.31 mmol, 1.5 eq.), hexamethyldisilazane (77 µL, 0.37 mmol, 1.8 eq.) and saccharine (3 mg, 0.01 mmol, 6.5 mol%) in anhydrous MeCN (1.5 mL) was refluxed for 30 min under inert atmosphere. **8** (100 mg, 0.21 mmol, 1 eq.) and TMSOTf (56 µL, 0.37 mmol, 1.5 eq.) were then added and the resulting mixture was refluxed for 6 h, cooled to room temperature, neutralized with saturated aqueous sodium bicarbonate (3 mL) and extracted with CH_2Cl_2 (8 mL). The organic extract was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Heptane/EtOAc 90:10 to 50:50) to afford the clean product **23** (80 mg, 0.16 mmol, 76%) as a yellow powder. $[\alpha]_D^{25}$ + 25.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.26 (m, 6H, H_{Ar}), 5.75 (dd, 1H, $J_{1,2}$= 9.5 Hz and $J_{1,HAr}$ = 1.5 Hz, *H*1), 5.30 (t, 1H, $J_{3,2}$ = $J_{3,4}$ = 9.5 Hz, *H*3), 4.97 (t, 1H, $J_{2,3}$= $J_{2,1}$= 9.5 Hz, *H*2), 4.58 (d, 1H, $J_{H,H}$ = 12.0 Hz, CH_2Ph), 4.53 (d, 1H, $J_{H,H}$ = 12.0 Hz, CH_2Ph), 3.89 (t, 1H, $J_{4,3}$= $J_{4,5}$ = 10.0 Hz, *H*4), 3.80-3.66 (m, 2H, *H*6, *H*6'), 3.59 (dt, 1H, $J_{5,4}$ = 10.0 Hz, $J_{5,6}$ = 5.0 Hz, $J_{5,6'}$ = 2.0 Hz, *H*5),

2.09 (s, 3H, CH_3), 1.97 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 (*C*=O), 169.7 (*C*=O), 156.5 (d, $J_{C\text{-}F}$ = 27 Hz, *C*q$_{Ar}$), 149.1 (*C*q$_{Ar}$), 142.6 (*C*q$_{Ar}$), 139.4 (*C*q$_{Ar}$), 137.4 (*C*q$_{Ar}$), 128.7 (*C*H$_{Ar}$), 128.3 (*C*H$_{Ar}$), 123.5 (d, $J_{C\text{-}F}$ = 34 Hz, *C*H$_{Ar}$), 80.9 (*C*1), 77.0 (*C*5), 73.8 (*C*H$_2$Ph), 73.3 (*C*3), 69.9 (*C*2), 68.1 (*C*6), 59.5 (*C*4), 20.8 (C(O)*C*H$_3$), 20.5 (C(O)*C*H$_3$); IR ν (film, cm^{-1}) 3089 (NH), 2112 (N$_3$), 1710 (C=O), 1670 (NH-C=O); ESIHRMS *m/z* = 514.1348 [M+Na]$^+$. $C_{21}H_{22}N_5O_8FNa$ requires 514.1350.

2,3-Di-*O*-acetyl-4-azido-6-*O*-benzyl-1-*N*-(4-*N*-benzoyl5-methyl-cytosine)-β-D-glucopyranoside 24. The General Procedure was followed using **8** (45 mg, 0.092 mmol), **12** (34 mg, 0.148 mmol), BSA (90 µL, 0.37 mmol), TMSOTf (20 µL, 0.11 mmol), 4 Å molecular sieves (50 mg) in dry MeCN (0.9 mL). The residue was purified by preparative TLC (Heptane/EtOAc 1:1) to afford product **24** (36 mg, 66%) as a yellow powder. $[\alpha]_D^{25}$ – 12.7 (*c* =1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33-8.25 (m, 2H, *H*$_{Ar}$), 7.57-7.26 (m, 9H, *H*$_{Ar}$), 5.82 (d, 1H, $J_{1,2}$ = 9.5 Hz, *H*1), 5.30 (dd, 1H, $J_{3,2}$ = 9.5 Hz, $J_{3,4}$ = 10.0 Hz, *H*3), 5.10 (t, 1H, $J_{2,1} = J_{2,3}$ = 9.5 Hz, *H*2), 4.60 (d, 1H, $J_{H,H}$ = 12.0 Hz, C*H*$_2$Ph), 4.53 (d, 1H, $J_{H,H}$ = 12.0 Hz, C*H*$_2$Ph), 3.95 (t, 1H, $J_{4,3} = J_{4,5}$ = 10.0 Hz, *H*4), 3.81-3.68 (m, 2H, *H*6, *H*6'), 3.50 (ddd, 1H, $J_{5,4}$ = 10.0 Hz, $J_{5,6}$ = 4.5 Hz, $J_{5,6'}$ = 2.0 Hz, *H*5), 2.10 (s, 3H, C*H*$_3$), 2.09 (s, 3H, COC*H*$_3$), 1.96 (s, 3H, COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0 (*C*=O), 170.0 (*C*=O), 169.7 (*C*=O), 159.2 (*C*q$_{Ar}$), 148.2 (*C*q$_{Ar}$), 137.6 (*C*q$_{Ar}$), 137.0 (*C*q$_{Ar}$), 135.9 (*C*H$_{Ar}$), 132.9 (*C*H$_{Ar}$), 130.2 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 128.4 (*C*H$_{Ar}$), 128.2 (*C*H$_{Ar}$), 128.0 (*C*H$_{Ar}$), 113.1 (*C*qAr), 80.7 (*C*1), 77.0 (*C*5), 73.8 (*C*H$_2$Ph), 73.7 (*C*3), 69.9 (*C*2), 68.2 (*C*6), 59.6 (*C*4), 20.8 (C(O)*C*H$_3$), 20.6 (C(O)*C*H$_3$), 13.9 (*C*H$_3$); IR ν (film, cm^{-1}) 2109 (N$_3$), 1753 (C=O), 1709 (C=O) 1656 (NH-C=O); ESIHRMS *m/z* = 591.2208 [M+H]$^+$. $C_{29}H_{31}N_6O_8$ requires 591.2203.

2,3-Di-*O*-acetyl-4-azido-6-*O*-benzyl-1-*N*-(4-*N*-benzoyl-5-fluoro-cytosine)-β-D-glucopyranoside 25. The General Procedure was followed using **8** (1.49 g, 3.05 mmol), **13** (1.14 g, 4.89 mmol), BSA (2.27 mL, 9.16 mmol), TMSOTf (0.66 mL, 3.66 mmol) in dry MeCN (30 mL). The residue was purified by preparative HPLC, gradient from 30 to 100% MeCN in 15 min, to afford product **25** (918 mg, 1.54 mmol, 50%) as a yellow powder. $[\alpha]_D^{20}$ + 22.9 (*c* =0.84, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, 2H, $J_{HAr,HAr}$ = 7.0 Hz, *H*$_{Ar}$), 7.57-7.43 (m, 4H, *H*$_{Ar}$), 7.42-7.30 (m, 5H, *H*$_{Ar}$), 5.79 (d, 1H, $J_{1,2}$= 9.0 Hz, *H*1), 5.32 (t, 1H, $J_{3,2}$= $J_{3,4}$= 9.5 Hz, *H*3), 5.00 (t, 1H, $J_{2,3}$= $J_{2,1}$= 9.5 Hz, *H*2), 4.61 (d, 1H, $J_{H,H}$ = 12.0 Hz, C*H*$_2$Ph), 4.56 (d, 1H, $J_{H,H}$ = 12.0 Hz, C*H*$_2$Ph), 3.94 (t, 1H, $J_{4,3}$= $J_{4,5}$= 10.0 Hz, *H*4), 3.81-3.71 (m, 2H, *H*6, *H*6'), 3.59 (d, 1H, $J_{5,4}$ = 10.0 Hz, *H*5), 2.12 (s, 3H, C*H*$_3$), 2.00 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (*C*=O), 169.7 (*C*=O), 152.2 (*C*q$_{Ar}$), 147.0 (*C*q$_{Ar}$), 141.5 (*C*q$_{Ar}$), 139.5 (*C*q$_{Ar}$), 137.5 (*C*q$_{Ar}$), 133.5 (*C*H$_{Ar}$), 130.4 (*C*H$_{Ar}$), 128.8 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 128.3 (*C*H$_{Ar}$), 128.1 (*C*H$_{Ar}$), 81.1 (*C*1), 77.1 (*C*5), 73.9 (*C*H$_2$Ph), 73.3 (*C*3), 70.1 (*C*2), 68.1 (*C*6), 59.5 (*C*4), 20.8 (C(O)*C*H$_3$), 20.6 (C(O)*C*H$_3$); IR ν (film, cm^{-1}) 3089 (=C-H), 2111 (N$_3$), 1753 (C=O), 1672 (NH-C=O); ESIHRMS *m/z* = 595.1951 [M+H]$^+$. $C_{28}H_{28}N_6O_8F$ requires 595.1953.

2,3-Di-*O*-acetyl-4-azido-6-*O*-benzyl-1-*N*-uracil-β-D-glucopyranoside 26. The General Procedure was followed using **8** (400 mg, 0.82 mmol), **14** (147 mg, 1.31 mmol), BSA (0.80 mL, 3.28 mmol), TMSOTf (0.18 mL, 0.98 mmol) in dry MeCN (8.2 mL). The residue was purified by flash chromatography (Heptane/EtOAc 90:10 to 50:50) to afford product **26** (314 mg, 0.66 mmol, 81%) as a yellow powder. $[\alpha]_D^{25}$ + 20.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (bs, 1H, N*H*), 7.43-7.29 (m, 6H, *H*$_{Ar}$), 5.81 (d, 1H, $J_{1,2}$ = 9.0 Hz, *H*1), 5.80 (d, 1H, $J_{HAr,HAr}$ = 8.0 Hz, *H*$_{Ar}$), 5.33 (t, 1H, $J_{3,2} = J_{3,4}$ = 9.5 Hz, *H*3), 5.07 (dd, 1H, $J_{2,1}$ = 9.0 Hz, $J_{2,3}$ = 9.5 Hz, *H*2), 4.62 (d, 1H, $J_{H,H}$ = 12.0 Hz, C*H*$_2$Ph), 4.55 (d, 1H, $J_{H,H}$ = 12.0 Hz, C*H*$_2$Ph), 3.94 (dd, 1H, $J_{4,3}$ = 9.5 Hz, $J_{4,5}$ = 10.0 Hz, *H*4), 3.82-3.70 (m, 2H, *H*6, *H*6'), 3.61 (ddd, 1H, $J_{5,4}$ = 10.0 Hz, $J_{5,6}$ = 3.0 Hz, $J_{5,6'}$ = 2.0 Hz, *H*5), 2.13 (s, 3H, C*H*$_3$), 1.99 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (*C*=O), 169.7 (*C*=O), 162.5 (*C*q$_{Ar}$), 150.3 (*C*q$_{Ar}$), 139.4 (*C*H$_{Ar}$), 137.5 (*C*q$_{Ar}$), 128.7 (*C*H$_{Ar}$), 128.3 (*C*H$_{Ar}$), 128.0 (*C*H$_{Ar}$), 103.8 (*C*H$_{Ar}$), 80.6 (*C*1), 77.0 (*C*5), 73.9 (*C*H$_2$Ph), 73.5 (*C*3), 69.8 (*C*2), 68.2 (*C*6), 59.6 (*C*4), 20.8 (*C*H$_3$), 20.6 (*C*H$_3$); IR ν (film, cm^{-1}) 2109 (N$_3$), 1752 (C=O), 1688 (NH-C=O); ESIHRMS *m/z* = 474.1626 [M+H]$^+$. $C_{21}H_{24}N_5O_8$ requires 474.1625.

2,3,6-Tri-*O*-acetyl-4-azido-1-*N*-(*N*-*tert*-butyloxycarbonyl--cytosine)-β-D-glucopyranoside 27. To a stirred solution of **15** (40 mg, 0.09 mmol) in CH_2Cl_2 (1 mL) was added di-*tert*-butyl-dicarbonate (40 µL, 0.17 mmol, 2 eq.), triethylamine (12 µL, 0.09 mmol, 1 eq.) and 4-dimethylaminopyridine (10.5 mg, 0.09 mmol, 1 eq.). The resulting mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 99:1 to 98:2) to afford product **27** (29 mg, 0.06 mmol, 64%) as a yellow powder. $[\alpha]_D^{25}$ + 41.7 (*c* = 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 1H, $J_{HAr,HAr}$ = 7.5 Hz, *H*$_{Ar}$), 7.30 (d, 1H, $J_{HAr,HAr}$ = 7.5 Hz, *H*$_{Ar}$), 6.05 (d, 1H, $J_{1,2}$ = 9.5 Hz, *H*1), 5.40 (t, 1H, $J_{2,1} = J_{2,3}$ = 9.5 Hz, *H*2), 5.07 (t, 1H, $J_{3,2} = J_{3,4}$ = 9.5 Hz, *H*3), 4.39 (d, 1H, $J_{6,6'}$ = 12.5 Hz, *H*6), 4.27 (dd, 1H, $J_{6',6}$ = 12.5 Hz, $J_{6',5}$ = 4.0 Hz, *H*6'), 3.76-3.67 (m, 2H, *H*4, *H*5), 2.11 (s, 6H, OCOC*H*$_3$), 1.97 (s, 3H, OCOC*H*$_3$), 1.51 (s, 9H, OC(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5 (*C*=O), 170.2 (*C*=O), 169.5 (*C*=O), 143.8 (*C*H$_{Ar}$), 96.3 (*C*H$_{Ar}$), 83.7 (*C*q), 81.3 (*C*1), 75.5 (*C*4), 73.5 (*C*3), 70.7 (*C*2), 62.7 (*C*6), 60.2 (*C*5), 28.2 (C(*C*H$_3$)$_3$), 20.9 (CO*C*H$_3$), 20.8 (CO*C*H$_3$), 20.6 (CO*C*H$_3$); IR ν (film,

cm^{-1}) 2987 (C-H), 2109 (N_3), 1751 (C=O), 1731 (C=O), 1667 (NH-C=O), 1626 (NH-C=O); ESIHRMS *m/z* = 525.1945 $[M+H]^+$. $C_{21}H_{29}N_6O_{10}$ requires 525.1953.

Methyl Boc-sarcosinyl-*O-tert*-butyl-D-serinate 29-D. To a stirred solution of *O-tert*-butyl-D-serine methyl ester (250 mg, 1.18 mmol, 1 eq.) and Boc-sarcosine (290 mg, 1.54 mmol, 1.3 eq.) in dry CH_2Cl_2 (9.8 mL) were added 4Å molecular sieves (400 mg), hydroxybenzotriazole (239 mg, 1.77 mmol, 1.5 eq.) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (452 mg, 2.36 mmol, 2 eq.). The resulting mixture was cooled to 0 °C and Et_3N (0.49 mL, 3.54 mmol, 3 eq.) was added. After being stirred overnight at room temperature, the mixture was diluted with aqueous saturated $NaHCO_3$ (8 mL). The aqueous phase was then extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (Heptane/EtOAc 80:20 to 60:40) to afford product **29-D** (367 g, 90%) as a colorless oil. $[\alpha]_D^{25}$ – 26.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (m, 1H, *H*2), 4.17-3.81 (m, 2H, *H*3), 3.80 (dd, 1H, $J_{1,1'}$ = 9.0 Hz, $J_{1',1}$ = 3.0 Hz, *H*1), 3.72 (s, 3H, OCH_3), 3.53 (dd, 1H, $J_{1,1'}$ = 9.0 Hz, $J_{1',1}$ = 3.0 Hz, *H*1), 2.93 (s, 3H, NCH_3), 1.46 (s, 9H, $CO_2C(CH_3)_3$), 1.10 (s, 9H, $OC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.1 (*C*1), 53.4 (*C*3), 52.8 (*C*2), 52.6 (O*C*H_3), 35.7 (N*C*H_3), 28.5 ($CO_2C(CH_3)_3$), 27.5 ($OC(CH_3)_3$); IR ν (film, cm^{-1}) 3314 (N-H), 2975 (CH_3), 2935 (CH_2), 1751 (C=O), 1684 (NH-C=O); ESIHRMS *m/z* = 347.2182 $[M+H]^+$. $C_{16}H_{31}N_2O_6$ requires 347.2191.

Boc-sarcosinyl-*O-tert*-butyl-D-serine 30-D. To a stirred solution of **29-D** (367 mg, 1.06 mmol, 1 eq.) in THF/H_2O mixture (8.8 mL/1.8 mL 5:1), was added lithium hydroxide (33 mg, 1.38 mmol, 1.3 eq.). The resulting mixture was stirred for 1 h at room temperature and then concentrated under vacuum until THF was evaporated. HCl 1 N was then added until the pH 2. The aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum to afford the clean product **30-D** (351 mg, 1.06 mmol, quantitative). The product is used without further purification. $[\alpha]_D^{25}$ – 32.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, 1H, $J_{NH,H2}$ = 8.0 Hz, *N*H), 4.68 (m, 1H, *H*2), 4.07-3.64 (m, 2H, *H*3, *H*3'), 3.85 (dd, 1H, $J_{1,1'}$ = 9.0 Hz, $J_{1,2}$ = 3.0 Hz, *H*1), 3.55 (dd, 1H, $J_{1,1'}$ = 9.0 Hz, $J_{1',2}$ = 4.0 Hz, *H*1'), 2.92 (s, 3H, NCH_3), 1.44 (s, 9H, $CO_2C(CH_3)_3$), 1.12 (s, 9H, $OC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7 (*C*=O), 169.9 (*C*=O), 81.2 ($CqCO_2C(CH_3)_3$), 74.1 ($CqOC(CH_3)_3$), 61.7 (*C*1), 53.3 (*C*3), 52.7 (*C*2), 35.8 (N*C*H_3), 28.5 ($CO_2C(CH_3)_3$), 27.5 ($OC(CH_3)_3$); IR ν (film, cm^{-1}) 3320 (O-H), 2975 (CH_3), 2935 (CH_2), 1739 (C=O), 1670 (NH-C=O); ESIHRMS *m/z* = 355.1842 $[M+Na]^+$. $C_{15}H_{28}N_2O_6Na$ requires 355.1845.

Boc-sarcosinyl-*O-tert*-butyl-L-serine methyl ester 29-L. To a stirred solution of *O-tert*-butyl-L-serine methyl ester hydrochloride (250 mg, 1.18 mmol, 1 eq.) and Boc-sarcosine (290 mg, 1,55 mmol, 1.3 eq.) in dry CH_2Cl_2 (10 mL) were added 4Å molecular sieves (335 mg), hydroxybenzotriazole (240 mg, 1.77 mmol, 1.5 eq.) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (453 mg, 0.47 mmol, 2 eq.). The resulting mixture was cooled to 0 °C and Et_3N (0.5 mL, 2.36 mmol, 3 eq.) was added. After being stirred overnight at room temperature, the mixture was diluted with aqueous saturated $NaHCO_3$ (6 mL). Aqueous phase was then extracted with EtOAc (3 x 5 mL). Organic layers were combined, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (Heptane/EtOAc 50:50 to 30:70) to afford product **29-L** (400 g, 1.16 mmol, 98%) as a colorless oil. $[\alpha]_D^{25}$ + 32.9 (*c* = 0.82, $CHCl_3$).

Boc-sarcosinyl-*O-tert*-butyl-L-serine 30-L. To a stirred solution of **29-L** (320 mg, 0.92 mmol, 1 eq.) in THF/H_2O mixture (7.7 mL/1.5 mL 5:1) was added lithium hydroxide (29 mg, 1.20 mmol, 1.3 eq.). The resulting mixture was stirred for 1 h at room temperature and then concentrated under vacuum until THF was evaporated. HCl 1 N was then added until pH 2. The aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum to afford the clean product **30-L** (305 mg, 0.92 mmol, quantitative). The product is used without further purification. $[\alpha]_D^{25}$ + 27.3 (*c* = 1.0, $CHCl_3$).

Peptidonucleoside 31-D. The solution **1** was prepared with Na (10 mg) in dry MeOH (2 mL, C = 0.22 M). To a stirred solution of the protected nucleoside **27** (147 mg, 0.28 mmol) in dry MeOH (5 mL) was added the solution **1** (0.26 mL, 20 mol%). The resulting mixture was stirred at room temperature for 1 h and then neutralized with Dowex® H^+, filtered on celite and concentrated under reduce pressure to afford clean product without further purification. The obtained product (105 mg) was then hydrogenated at atmospheric pressure in the presence of $Pd(OH)_2$ (40%w/w, 42 mg) in MeOH (2.6 mL) for 12 h. The resulting mixture was then filtered on celite® and concentrated under reduced pressure to afford the clean corresponding amine (94 mg). To a stirred solution of the latter in DMF (4 mL) was added the dipeptide (109 mg, 0.33 mmol, 1.3 eq.) and DIPEA (0.17 mL, 1.01 mmol, 4 eq.). After 1 min, HATU (144 mg, 0.32 mmol, 1.5 eq.) was added and the resulting mixture was stirred at room temperature for 18 h. Solvent was removed and the crude product was purified by flash chromatography on silica gel (EtOAc/EtOH 99:1 to 92:8) to afford product **31-D** (113 mg, 0.16 mmol, 65%) as a yellow powder; $[\alpha]_D^{25}$ + 14.6 (*c* = 1.1, MeOH). ^{1}H NMR (500

MHz, CD_3OD)[34] δ 8.11 (d, 1H, $J_{HAr,HAr}$ = 7.5 Hz, H_{Ar}), 7.33-7.26 (m, 1H, H_{Ar}), 5.77 (d, 1H, $J_{1,2}$ = 9.0 Hz, *H*1), 4.60-4.49 (m, 1H, *H*7), 4.10-3.53 (m, 10H, *H2*, *H*3, *H*4, *H5*, *H*6, *H*8, *H*9), 3.03-2.83 (m, 3H, NCH_3), 1.56 (s, 9H, $CO_2C(CH_3)_3$), 1.50-1.41 (m, 9H, $OC(CH_3)_3$), 1.20 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR (75 MHz, CD_3OD)[35] δ 172.1 (*C*=O), 163.7 (*C*q), 157.0 (*C*q), 156.9 (*C*q), 151.9 (*C*=O), 144.9 (CH, C_{Ar}), 96.1 (CH, C_{Ar}), 85.2 (*C*1), 83.4 ($C(CH_3)_3$), 80.2 (*C*H), 75.8 (*C*H), 74.4 (CH_2), 73.9 ($C(CH_3)_3$), 73.8 ($C(CH_3)_3$), 71.6 (CH_2), 62.8 (CH_2), 56.1 (*C*7), 53.4 (*C*H), 53.1 (CH_2), 36.8 (NCH_3), 28.9 ($C(CH_3)_3$), 28.5 ($C(CH_3)_3$), 27.8 ($C(CH_3)_3$); IR ν (film, cm^{-1}) 3264 (N-H), 2976 (CH), 2926 (CH), 1758 (C=O), 1656 (NH-C=O); ESIHRMS *m/z* = 687.3566 $[M+H]^+$. $C_{30}H_{51}N_6O_{12}$ requires 687.3565.

Peptidonucleoside 32-D. To a stirred solution of **31-D** (90 mg, 0.131 mmol, 1 eq.) in CH_2Cl_2/MeOH (2:1 v/v, 1.3 mL) was added a solution of 4M HCl in dioxane (0.23 mL, 0.92 mmol, 7 eq.). The resulting mixture was stirred at room temperature for 2 days and then diluted with H_2O and then neutralized with DOWEX® MONOSPHERE® 550A (OH) anion exchange resin. The mixture was filtered on celite and then concentrated under vaccum. The crude product was purified by preparative TLC (H_2O/EtOH/EtOAc 4:4:2, pH 9) to afford **32-D** as a white powder (21 mg, 0.05 mmol, 37%). $[\alpha]_D^{25}$ – 31.3 (*c* = 1.1, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 7.73 (d, 1H, $J_{HAr,HAr}$ = 7.5 Hz, H_{Ar}), 6.07 (bs, 1H, H_{Ar}), 5.64 (d, 1H, $J_{1,2}$ = 9.5 Hz, *H*1), 4.45 (t, 1H, $J_{7,8} = J_{7,8'}$ = 5.5 Hz, *H*7), 3.94 (s, 2H, *H*9), 3.91-3.80 (m, 1H, *H*4), 3.86 (d, 2H, $J_{8,7}$ = 5.5 Hz, *H*8), 3.80-3.71 (m, 3H, *H*2, *H*3, *H*5), 3.68 (dd, 1H, $J_{6,6'}$ = 12.5 Hz, $J_{6,5}$ = 1.5 Hz, *H*6), 3.57 (dd, 1H, $J_{6',6}$ = 12.5 Hz, $J_{6',5}$ = 5.5 Hz, *H*6'), 2.74 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, D_2O) δ 172.0 (*C*=O), 166.7 (*C*=O), 166.0 (*C*=O), 157.9 (Cq_{Ar}), 141.7 (CH_{Ar}), 97.0 (CH_{Ar}), 83.3 (*C*1), 77.5 (*C*5), 73.7 (*C*3), 71.7 (*C*2), 61.0 (*C*8), 60.6 (*C*6), 55.9 (*C*7), 51.3 (*C*4), 49.4 (*C*9), 32.8 (NCH_3); IR ν (film, cm^{-1}) 3310 (O-H), 3282 (N-H), 2976 (CH_3), 2933 (CH_2), 1744 (C=O), 1653 (NH-C=O); ESIHRMS *m/z* = 431.3424 $[M+H]^+$. $C_{16}H_{28}N_6O_8$ requires 431.1890.

Peptidonucleoside 31-L. The **solution 1** was prepared with Na (10 mg) in dry MeOH (2 mL, C = 0.22 M). To a stirred solution of the protected nucleoside **27** (503 mg, 0.96 mmol) in dry MeOH (16 mL) was added the **solution 1** (0.88 mL, 20 mol%). The resulting mixture was stirred at room temperature for 1 h and then neutralized with Dowex® H^+, filtered on celite and concentrated under reduce pressure to afford clean product without further purification. The obtained product (355 mg) was then hydrogenolysed at atmospheric pressure in the presence of $Pd(OH)_2$-C (40%w/w, 142 mg) in MeOH (8.9 mL) for 12 h. The resulting mixture was then filtered on celite® and concentrated under reduced pressure to afford the clean corresponding amine (318 mg). To a stirred solution of the latter (150 mg, 0.40 mmol) in DMF (6 mL) was added the dipeptide (174 mg, 0.52 mmol, 1.3 eq.) and DIPEA (0.28 mL, 1.61 mmol, 4 eq.). After 1 min, HATU (184 mg, 0.48 mmol, 1.5 eq.) was added and the resulting mixture was stirred at room temperature for 18 h. Solvent was removed and the crude product was purified by flash chromatography on silica gel (EtOAc/EtOH 99:1 to 92:8) to afford product **31-L** (158 mg, 0.23 mmol, 57%) as a yellow powder. $[\alpha]_D^{20}$ – 99.0 (*c* = 0.34, H_2O/MeOH 1:1); ^{1}H NMR (500 MHz, CD_3OD)[34] δ 8.15 (d, 1H, $J_{HAr,HAr}$ = 7.5 Hz, H_{Ar}), 7.37 (d, 1H, $J_{HAr,HAr}$ = 7.5 Hz, H_{Ar}), 5.81 (d, 1H, $J_{1,2}$ = 9.0 Hz, *H*1), 4.60-4.49 (m, 1H, *H*7), 4.10-3.97 (m, 2H, H9), 3.95 (t, 1H, $J_{4,3} = J_{4,5}$= 10.0 Hz, *H*4), 3.87-3.71 (m, 2H, *H*3, *H*6), 3.71-3.58 (m, 5H, *H2*, *H*5, *H*6', *H*8), 3.03-2.91 (bs, 3H, NCH_3), 1.58 (s, 9H, $CO_2C(CH_3)_3$), 1.55-1.47 (m, 9H, $OC(CH_3)_3$), 1.25 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR (75 MHz, CD_3OD)[35] δ 173.4 (*C*=O), 171.9 (*C*=O), 165.3 (*C*q), 158.6 (*C*q), 153.6 (*C*=O), 146.5 (CH_{Ar}), 97.7 (CH_{Ar}), 85.3 (*C*1), 83.4 ($C(CH_3)_3$), 81.8 ($C(CH_3)_3$), 80.2 (*C*5), 75.8 (*C*3), 75.0 ($C(CH_3)_3$), 74.5 (*C*2), 62.8 (*C*6), 58.6 (*C*8), 55.7 (*C*7), 53.2 (*C*4), 52.9 (*C*9), 36.4 (NCH_3), 28.8 ($C(CH_3)_3$), 28.5 ($C(CH_3)_3$), 27.8 ($C(CH_3)_3$); IR ν (film, cm^{-1}) 3310 (O-H), 3282 (N-H), 2976 (CH_3), 2933 (CH_2), 1744 (C=O), 1653 (NH-C=O); ESIHRMS *m/z* = 687.3566 $[M+H]^+$. $C_{30}H_{51}N_6O_{12}$ requires 687.3565.

Analogue 32-L. To a stirred solution of **31-L** (90 mg, 0.131 mmol, 1 eq.) in CH_2Cl_2/MeOH (2:1 v/v, 1.3 mL) was added a solution of 4M HCl in dioxane (0.23 mL, 0.92 mmol, 7 eq.). The resulting mixture was stirred at room temperature for 2 days and then diluted with H_2O and then neutralized with DOWEX® MONOSPHERE® 550A (OH) anion exchange resin. The mixture was filtered on celite and then concentrated under vaccum. The crude product was purified by preparative TLC (H_2O/EtOH/EtOAc 4:4:2, pH 9) to afford clean product **32-L** as a white powder (10.3 mg, 0.024 mmol, 28%). $[\alpha]_D^{25}$ + 278.3 (*c* = 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 7.80 (d, 1H, $J_{HAr,HAr}$ = 7.5 Hz, H_{Ar}), 6.14 (d, 1H, $J_{HAr,HAr}$ = 7.5 Hz, H_{Ar}), 5.71 (d, 1H, $J_{1,2}$ = 9.0 Hz, *H*1), 4.52 (t, 1H, $J_{7,8} = J_{7,8'}$ = 5.5 Hz, *H*7), 3.99 (t, 1H, $J_{4,3} = J_{4,5}$= 10.0 Hz, *H*4), 3.92 (d, 2H, $J_{8,7}$ = 5.5 Hz, *H*8), 3.85 (dd, 1H, $J_{3,2}$= 9.0 Hz and $J_{3,4}$ = 10.0 Hz, *H*3), 3.82 (t, 1H, $J_{2,3} = J_{2,1}$= 9.0 Hz, *H*2), 3.80-3.70 (m, 2H, *H*5, *H*6), 3.66-3.60 (m, 3H, *H*6, *H*9), 2.54 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, D_2O) δ 172.2 (*C*=O), 171.1 (*C*=O), 166.1 (*C*=O), 158.0 (Cq_{Ar}), 141.8 (CH_{Ar}), 97.1 (CH_{Ar}), 83.1 (*C*1), 77.5 (*C*5), 73.8 (*C*3), 71.7 (*C*2), 61.2 (*C*8), 60.7 (*C*6), 55.8 (*C*7), 51.4 (*C*4), 51.3 (*C*9), 33.8 (NCH_3); IR ν (film, cm^{-1}) 3310 (O-H), 3282 (N-H), 2976 (CH_3), 2933 (CH_2), 1744 (C=O), 1653 (NH-C=O); ESIHRMS *m/z* = 431.1890 $[M+H]^+$. $C_{16}H_{27}N_6O_8$ requires 431.1901.

Peptidonucleoside 33. The same Procedure as described for **31-D** was followed using **16** (315 mg, 0.72 mmol), **solution 1** (0.65 mL, C = 0.44 M, 40 mol%) in MeOH (10 mL) to obtain the deacetylated compound (227 mg). The

obtained product was hydrogenolysed with $Pd(OH)_2$-C (68 mg) in MeOH (3.8 mL) to give the corresponding amine (110 mg, 0.38 mmol). Then, the peptide coupling was carried out with the amine (110 mg), **30-D** (195 mg, 0.59 mmol), DIPEA (0.3 mL, 1.8 mmol) and HATU (206 mg, 0.54 mmol) in DMF (7.5 mL). The residue was purified by flash chromatography on silica gel (EtOAc/EtOH 99:1 to 92:8) to afford clean product **33** (204 mg, 0.34 mmol, 47%) as a yellow powder. $[\alpha]_D^{25}$ +24.4 (c = 0.55, MeOH). ^{1}H NMR (500 MHz, CD_3OD)[34] δ 7.60 (s, 1H, H_{Ar}), 5.55 (d, 1H, $J_{1,2}$ = 9.0 Hz, *H*1), 4. 45 (t, 1H, $J_{7,8} = J_{7,8'}$ = 5.0 Hz, *H*7), 4.01-3.91 (m, 2H, *H*9), 3.89-3.55 (m, 7H, *H2*, *H*3, *H*4, *H*5, *H*6, *H*8), 2.99-2.88 (m, 3H, NCH_3), 1.91 (s, 3H, CH_3), 1.57-1.35 (m, 9H, $OC(CH_3)_3$), 1.21 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR (75 MHz, CD_3OD)[35] δ 172.0 (*C*=O), 170.6 (*C*=O), 170.5 (*C*=O), 164.7 (*C*=O), 151.5 (*C*=O), 136.7 (CH_{Ar}), 110.5 (Cq_{Ar}), 85.5 (*C*1), 80.3 ($C(CH_3)_3$), 78.3 (*C*H), 74.0 (*C*H), 73.5 ($C(CH_3)_3$), 71.9 (*C*H), 61.4 (CH_2), 54.3 (*C*7), 51.7 (*C*H), 51.5 (CH_2), 35.1 (NCH_3), 27.2 ($C(CH_3)_3$), 26.2 ($C(CH_3)_3$), 10.8 (CH_3); IR ν (film, cm^{-1}) 3295 (N-H), 2974 (CH), 1654 (NH-C=O); ESIHRMS *m/z* = 602.4783 $[M+H]^+$. $C_{26}H_{44}N_5O_{11}$ requires 602.3037.

Peptidonucleoside 35. To a stirred solution of **33** (30 mg, 0.05 mmol, 1 eq.) in CH_2Cl_2/MeOH (2:1 v/v, 0.6 mL) was added a solution of 4M HCl in dioxane (0.3 mL, 1.2 mmol, 25 eq.). The resulting mixture was stirred at room temperature for 2 days and then diluted with H_2O and then neutralized with NEt_3 (0.2 mL). The mixture was concentrated under vaccum and the crude product was purified by preparative TLC (H_2O/EtOH/EtOAc 2:2:1, with 1% of NH_4OH) to afford clean product **35** as a white powder (10 mg, 0.022 mmol, 45%); $[\alpha]_D^{20}$ + 8.9 (c = 1.0, MeOH); ^{1}H NMR (300 MHz, D_2O) δ 7.62 (s, 1H, H_{Ar}), 5.61-5.54 (m, 1H, *H*1), 4.44 (t, 1H, $J_{7,8} = J_{7,8'}$ = 5.5 Hz, *H*7), 3.92-3.79 (m, 4H, 1 x C*H and* CH_2), 3.79-3.64 (m, 5H, 3 x C*H and* CH_2), 3.63-3.54 (m, 1H, CH_2), 2.67 (s, 3H, NCH_3), 1.86 (s, 3H, CH_3); ^{13}C NMR (75 MHz, D_2O) δ 172.1 (*C*=O), 167.8 (*C*=O), 166.3 (*C*=O), 152.2 (*C*=O), 137.3 (CH_{Ar}), 111.1 ($CqAr$), 82.5 (*C*1), 77.5 (*C*H), 73.6 (*C*H), 71.6 (*C*H), 61.1 (CH_2), 60.7 (CH_2), 56.0 (*C*7), 51.4 (*C*H), 49.4 (CH_2), 33.1 (NCH_3), 11.4 (CH_3); IR ν (film, cm^{-1}) 3288 (N-H), 2923 (CH), 2854 (CH), 1664 (NH-C=O); ESIHRMS *m/z* = 446.1867 $[M+H]^+$. $C_{18}H_{27}N_5O_9$ requires 446.1887.

Peptidonucleoside 36. The same Procedure as described for **31-D** was followed using **17** (194 mg, 0.72 mmol), **solution 1** (1.2 mL, C=0.22 M, 40 mol% of Na) in MeOH (7 mL). The obtained product (125 mg) was hydrogenolysed with $Pd(OH)_2$-C (50 mg) in MeOH (4 mL) to give the corresponding amine (107 mg). Then, the peptide coupling was carried out using the amine (107 mg, 0.37 mmol), **30-D** (158 mg, 0.48 mmol), DIPEA (0.25 mL, 1.48 mmol) and HATU (167 mg, 0.44 mmol) in DMF (6 mL). The residue was purified by chromatography on silica gel (DCM/MeOH 96:4 to 92:8) to afford **34** (124 mg, 0.20 mmol, 56% over three steps). ESIHRMS *m/z* = 606.2786 $[M+H]^+$. $C_{25}H_{41}N_5O_{11}F$ requires 606.2787. As **34** was not very clean, it was not fully characterized and then engaged in the next step. To a stirred solution of **34** (124 mg, 0.2 mmol, 1 eq.) in CH_2Cl_2/MeOH (2:1 v/v, 2.3 mL) was added a solution of 4M HCl in dioxane (0.35 mL, 1.4 mmol, 6.8 eq.). The resulting mixture was stirred at room temperature for 3 days and then diluted with H_2O and then neutralized with NEt_3 (0.2 mL). The mixture was concentrated under vaccum and the crude product was purified by preparative TLC (H_2O/EtOH/EtOAc 3:1:1, with 1% of NH_4OH) to afford clean product **36** as a white powder (54 mg, 0.013 mmol, 63%). $[\alpha]_D^{20}$ – 73.3 (c = 0.15, H_2O/MeOH: 1:1); ^{1}H NMR (300 MHz, D_2O) δ 7.94 (d, 1H, $J_{HAr,F}$ = 6.0 Hz, H_{Ar}), 5.59 (d, 1H, $J_{1,2}$ = 9.0 Hz, *H*1), 4.51-4.38 (m, 1H, *H*7), 3.99-3.46 (m, 10H, *H*2, *H*3, *H*4, *H*5, *H*6, *H*8, *H*9), 2.72 (s, 3H, NCH_3), 2.72 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, D_2O) δ 181.4 (*C*=O), 172.3 (*C*=O), 166.7 (*C*=O), 161.2 (d, J = 23.6 Hz, CH_{Ar}), 152.2 (CO), 125.3 (d, J = 23.6 Hz, *C*qAr), 125.2 (*C*H), 82.9 (*C*1), 77.5 (*C*H), 75.0 ($C(CH_3)_3$), 73.3 (*C*H), 71.7 (*C*H), 61.0 (CH_2), 60.7 (CH_2), 56.0 (*C*7), 51.3 (*C*H), 49.4 (CH_2), 32.8 (NCH_3), 26.4 ($C(CH_3)_3$); IR ν (film, cm^{-1}) 3288 (N-H), 2923 (CH), 2854 (CH), 1664 (NH-C=O); ESIHRMS *m/z* = 506.2249 $[M+H]^+$. $C_{20}H_{33}N_5O_9F$ requires 506.2262.

***tert*-butyl (*R*)-(2-((1-(*tert*-butoxy)-3-hydroxypropan-2-yl)amino)-2-oxoethyl)(methyl)carbamate 37**. To a stirred solution of **29-D** (193 mg, 0.557 mmol, 1 eq.) in THF (2 mL) was added at 0 °C $LiBH_4$ (21 mg, 0.95 mmol, 1.7 eq.). The resulting mixture was stirred at room temperature for 4 h and then hydrolyzed with a saturated aqueous solution of NH_4Cl (10 mL). Water (10 mL) was added and the aqueous phase was extracted with EtOAc (3 x 15 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (Heptane/EtOAc 30:70 to 0:100) to afford product **37** (160 mg, 0.5 mmol, 90%) as a colorless oil. $[\alpha]_D^{20}$ – 5.4 (c = 0.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$)[34] δ 6.81-6.58 (bs, 1H, N*H*), 4.03-3.93 (m, 1H, C*H*N), 3.91-3.81 (m, 2H, $COCH_2N$), 3.80 (dd, 1H, J= 11.5 and 3.5 Hz, CH_2), 3.69-3.58 (m, 1H, CH_2), 3.57-3.50 (m, 2H, CH_2), 3.25-3.09 (m, 1H, O*H*), 2.91 (s, 3H, NCH_3), 1.43 (s, 9H, $C(CH_3)_3$), 1.15 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$)[35] δ 169.5 (*C*=O), 80.7 ($C(CH_3)_3$), 73.8 ($C(CH_3)_3$), 64.4 (CH_2), 63.0 (CH_2), 53.1 ($COCH_2N$), 50.5 (*C*HN), 35.6 (NCH_3), 28.3 ($C(CH_3)_3$), 27.3 ($C(CH_3)_3$); IR ν (film, cm^{-1}) 3217 (N-H), 2974 (CH), 2875 (CH), 1662 (NH-C=O); ESIHRMS *m/z* = 419.2219 $[M+H]^+$. $C_{15}H_{31}N_2O_5$ requires 419.2233.

***tert*-butyl (*R*)-(2-((1-(*tert*-butoxy)but-3-yn-2-yl)amino)-2-oxoethyl)(methyl)carbamate 38**. To a stirred solution of alcohol **37** (0.130 g, 0.408 mmol, 1.0 eq.) in CH_2Cl_2 (8 mL) at 0 °C was added saturated aqueous $NaHCO_3$ (4 mL),

KBr (49 mg, 0.408 mmol, 1.0 eq.) and TEMPO (3 mg, 0.02 mmol, 0.05 eq.). NaOCl (0.5 M, 1.6 mL, 2.0 eq.) was then added with a syringe pump over 30 min. Saturated aqueous $Na_2S_2O_3$ (4 mL) was added, the phases were separated and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the corresponding crude α-amino aldehyde (95 mg) which was used directly in the next step. To the latter (90 mg, 0.284 mmol, 1 eq.) and dimethyl (1-diazo-2-oxopropyl)phosphonate (96 mg, 0.498 mmol, 1.75 eq.) in MeOH (2 mL) at 0 °C was added K_2CO_3 (83 mg, 0.597 mmol, 2.1 eq.). The resulting mixture was stirred at 0 °C for 3 h and was hydrolyzed with a sat. aq. solution of NH_4Cl (10 mL). Water (10 mL) was added and the aqueous phase was extracted with EtOAc (3 x 15 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated under vacuum pressure. The crude product was purified by flash chromatography on silica gel (Heptane/EtOAc 70:30 to 50:50) to afford product **38** (51 mg, 0.163 mmol, 42% over the two steps) as a colorless oil. $[\alpha]_D^{20}$ + 2.5 (*c* = 0.32, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$)[34] δ 6.65-6.26 (bs, 1H, N*H*), 4.83-4.69 (m, 1H, C*H*N), 3.90-3.67 (m, 2H, COC*H*$_2$N), 3.50-3.37 (m, 2H, C*H*$_2$), 2.86 (s, 3H, C*H*$_3$), 2.17 (d, 1H, *J* = 2.5 Hz, C*H*$_{Alkyne}$), 1.41 (s, 9H, C(C*H*$_3$)$_3$), 1.09 s, 9H, (C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$)[35] δ 168.5 (*C*=O), 81.4 (Cq$_{Alkyne}$), 80.7 (*C*(CH$_3$)$_3$), 73.6 (*C*(CH$_3$)$_3$), 70.8 (*C*H$_{Alkyne}$), 63.5 (*C*H$_2$), 53.1 (*C*H$_2$), 41.6 (CO*C*H$_2$N), 35.6 (N*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$), 27.4 (C(*C*H$_3$)$_3$); IR ν (film, cm^{-1}) 3310 (N-H), 2975 (CH), 2873 (CH), 1666 (NH-C=O); ESIHRMS *m/z* = 335.1947 [M+Na]$^+$. $C_{16}H_{28}N_2O_4$ requires 335.1947.

Peptidonucleoside 39. To a stirred solution of azid **18** (78 mg, 0.144 mmol, 1.0 eq.) and alkyne **38** (45 mg, 0.144 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at r.t. was added $CuSO_4$•5H_2O (4 mg, 0.014 mmol, 0.1 eq.) in water (1 mL) followed by sodium ascorbate (3 mg, 0.014 mmol, 0.1 eq.) in water (1 mL). After stirring for 18 h, water (10 mL) and EtOAc (15 mL) were added. The phases were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Heptane/EtOAc 50:50 to 0:100) to afford product **39** (94 mg, 0.163 mmol, 76%) as a colorless oil. $[\alpha]_D^{20}$ – 26.9 (*c* = 0.58, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$)[34] δ 8.28 (d, 2H, *J* = 7.5 Hz, *H*$_{Ar}$), 7.57 (s, 1H, *H*$_{triazole}$), 7.54-7.46 (m, 1H, *H*$_{Ar}$), 7.42(t, 2H, *J* = 7.5 Hz, *H*$_{Ar}$), 7.27 (s, 1H, *H*$_{Ar}$), 6.94-6.77 (bs, 1H, N*H*), 6.09 (d, 1H, $J_{1,2}$ = 9.5 Hz, *H*1), 5.79 (t, 1H, $J_{3,4} = J_{3,2}$ = 9.5 Hz, *H*3), 5.27 (t, 1H, $J_{2,3} = J_{2,1}$ = 9.5 Hz, *H*2), 5.23-5.12 (m, 1H, C*H*N), 4.73 (t, 1H, $J_{4,5} = J_{4,3}$ = 9.5 Hz, *H*4), 4.62-4.61 (m, 1H, *H*5), 4.08 (dd, 1H, *J* = 2.0 and 12.0 Hz, C*H*$_2$), 3.94-3.73 (m, 4H, C*H*$_2$), 3.62-3.49 (m, 1H, C*H*$_2$), 2.92 (s, 3H, NC*H*$_3$), 2.12 (s, 3H, C*H*$_3$), 2.04 (s, 3H, COC*H*$_3$), 1.97 (s, 3H, COC*H*$_3$), 1.85 (s, 3H, COC*H*$_3$), 1.45 (s, 9H, C(C*H*$_3$)$_3$), 1.09 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$)[35] δ 179.9 (*C*=O), 169.9 (*C*=O), 169.7 (*C*=O), 169.0 (*C*=O), 168.5 (*C*=O), 158.8 (*C*=O), 148.0 (*C*q), 136.7 (*C*q), 135.1 (*C*H$_{Ar}$), 132.8 (*C*H$_{Ar}$), 130.0 (*C*H$_{Ar}$), 128.1 (*C*H$_{Ar}$), 122.6 (*C*H$_{Triazole}$), 113.2 (*C*H$_{Ar}$), 80.6 (*C*1), 77.2 (*C*q), 74.9 (*C*5), 73.5 (*C*q), 72.2 (*C*3), 69.7 (*C*2), 62.8 (CH$_2$), 61.8 (CH$_2$), 59.9 (*C*4), 53.0 (*C*H$_2$), 46.5 (*C*HN), 35.8 (N*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$), 27.4 (C(*C*H$_3$)$_3$), 20.6 (CO*C*H$_3$), 20.4 (CO*C*H$_3$), 20.1 (CO*C*H$_3$), 13.7 (*C*H$_3$); IR ν (film, cm^{-1}) 2973 (CH), 2854 (CH), 1750 (CO), 1704 (CO), 1659 (NH-C=O); ESIHRMS *m/z* = 855.3889 [M+H]$^+$. $C_{40}H_{55}N_8O_{13}$ requires 855.13889.

Peptidonucleoside 40. The solution **1** was prepared with Na (20 mg) in dry MeOH (2 mL). To a stirred solution of the protected nucleoside **39** (70 mg, 0.028 mmol) in dry MeOH (0.2 mL) was added the solution **1** (0.4 mL, 1 eq.). The resulting mixture was stirred at room temperature for 5 h and a solution of 4M HCl in dioxane (0.6 mL, 2.4 mmol, 30 eq.) was added. The resulting mixture was stirred at room temperature for 8 h and neutralized with NEt_3 (0.35 mL). The mixture was concentrated under vaccum and the crude product was purified by preparative TLC (H_2O/EtOH/EtOAc 1:2:2, with 1% of NH_4OH) to afford product **40** as a white powder, which was washed several times with $CHCl_3$ (25 mg, 0.047 mmol, 58%). $[\alpha]_D^{20}$ – 43.4 (*c* = 0.35, H_2O/MeOH: 1/1); ^{1}H NMR (300 MHz, CD_3OD) δ 8.15 (s, 1H, *H*$_{triazole}$), 7.91 (s, 1H, *H*$_{Ar}$), 7.62-7.24 (bs, 1H, N*H*), 5.89 (d, 1H, $J_{1,2}$ = 9.5 Hz, *H*1), 5.31 (t, 1H, *J* = 5.5 Hz, C*H*N), 4.74 (t, 1H, $J_{3,4} = J_{3,2}$ = 9.5 Hz, *H*3), 5.34-4.24 (m, 2H, *H*4 and *H*5), 3.97-3.88 (m, 2H, C*H*$_2$), 3.85 (t, 1H, $J_{2,1} = J_{2,3}$ = 9.5 Hz, *H*2), 3.82-3.71 (m, 2H, C*H*$_2$), 3.52 (dd, 1H, *J* = 1.5 and 12.0 Hz, *H*6), 3.52 (dd, 1H, *J* = 4.0 and 12.0 Hz, *H*6'), 2.78 (s, 3H, NC*H*$_3$), 2.10 (s, 3H, C*H*$_3$), 1.21 (s, 9H, C(C*H*$_3$)$_3$), 1.09 (C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, CD_3OD) δ 164.9 (*C*=O), 163.4 (*C*=O), 153.5 (*C*q), 145.8 (*C*q), 140.6 (*C*H$_{Ar}$), 124.0 (*C*H$_{Triazole}$), 100.7 (*C*q), 83.7 (*C*1), 77.5 and 74.4 (*C*4 and *C*5), 73.4 (*C*q), 72.4 (*C*2), 63.0 (*C*H$_2$), 61.7 (*C*3), 60.0 (*C*6), 49.4 (*C*H$_2$), 47.2 (*C*HN), 32.4 (N*C*H$_3$), 26.3 (C(*C*H$_3$)$_3$), 11.7 (*C*H$_3$); IR ν (film, cm^{-1}) 3056 (NH), 2921 (CH), 1666 (NH-C=O); ESIHRMS *m/z* = 525.2787 [M+H]$^+$. $C_{22}H_{37}N_8O_7$ requires 525.2785.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

We gratefully acknowledge financial supports from CNRS and from Bayer CropScience (PhD thesis of MB).

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34 Peaks in ^{1}H-NMR spectrum broad and split due to the presence of *N*-Boc rotamers
35 Peaks in ^{13}C-NMR spectrum broad and split due to the presence of *N*-Boc rotamers.