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Towards the synthesis of sulfonamide-based RNA mimetics

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ABSTRACT

The scalable, divergent synthesis of all four monomers required for the preparation of sulfonamide-based RNA mimetics is described. Such mimetics may combine excellent mimicry of the parent RNA with enhanced (bio)chemical robustness and convenient oligomerization. As a proof of principle, a dimer resulting from the monomers is described.

1. Introduction

In recent years short regulatory RNAs have come to the forefront of biological research, for example, as mediators in the important RNA interference technology.[1] Since such RNA molecules are able to selectively and effectively inhibit individual genes, they have great potential in combating diseases in which the expression level of a certain gene is deregulated.

However, the direct application of RNAs as therapeutics is hampered by a number of serious drawbacks: (i) they are negatively charged which makes cellular uptake difficult and often necessitates complex transfection techniques; (ii) they are still complex and delicate synthetic targets and (iii) they are degraded by extra- and intracellular nucleases. In order to remedy such drawbacks, nucleic acid mimetics may be used, arguably the most successful of which have been the peptide nucleic acids (PNAs),[2] locked nucleic acids (LNAs)[3] and morpholinos.[4] However, such mimetics often lack the 2′-OH group which distinguishes RNA from DNA and may be of importance in certain biological interactions. Furthermore, in particular for PNAs and morpholinos, although they have found many successful biological applications, the chemical backbone structure is very different from natural nucleic acids which may also be of importance in certain biological settings.

Herein we report an RNA mimetic in which the phosphate is replaced by the semi-isosteric sulfonamide moiety (sRNAs, Fig. 1). The sulfonamide moiety has a similar charge distribution as the phosphates found in RNA, albeit not negatively charged. In addition, they are (bio)chemically stable and can be introduced in a stepwise solid phase oligomerization procedure analogous to the preparation of oligosulfonamide peptidomimetics.[5] Their closest relatives are the DNA sulfonamide mimetics,[6] however the syntheses described for these structures would not allow the introduction of a 2′-OH group necessary for true RNA mimicry and would not be suitable for the stepwise incorporation into any RNA nucleotide sequence. Studies on sulfamoyl-based DNA dimers, which are structurally similar to the mimics described here, have shown that such compounds have structural properties similar to natural DNA.[7]

Apart from oligomerization into small RNA mimetics, a number of different applications of the monomers described here can be envisaged. For instance, a similar adenine monomer may function as an ATP analogue and be conveniently conjugated to a peptide leading to potential bisubstrate-based inhibitors.[8] Furthermore, the primer essential for the replication of many viruses consists of a peptide functionalized with one or more uridine groups and

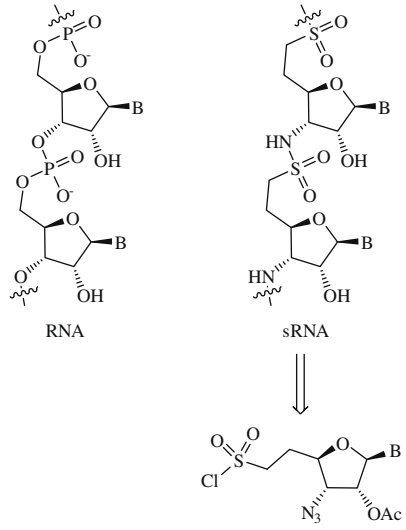

Figure 1. Sulfonamide-based RNA mimetics (sRNAs).

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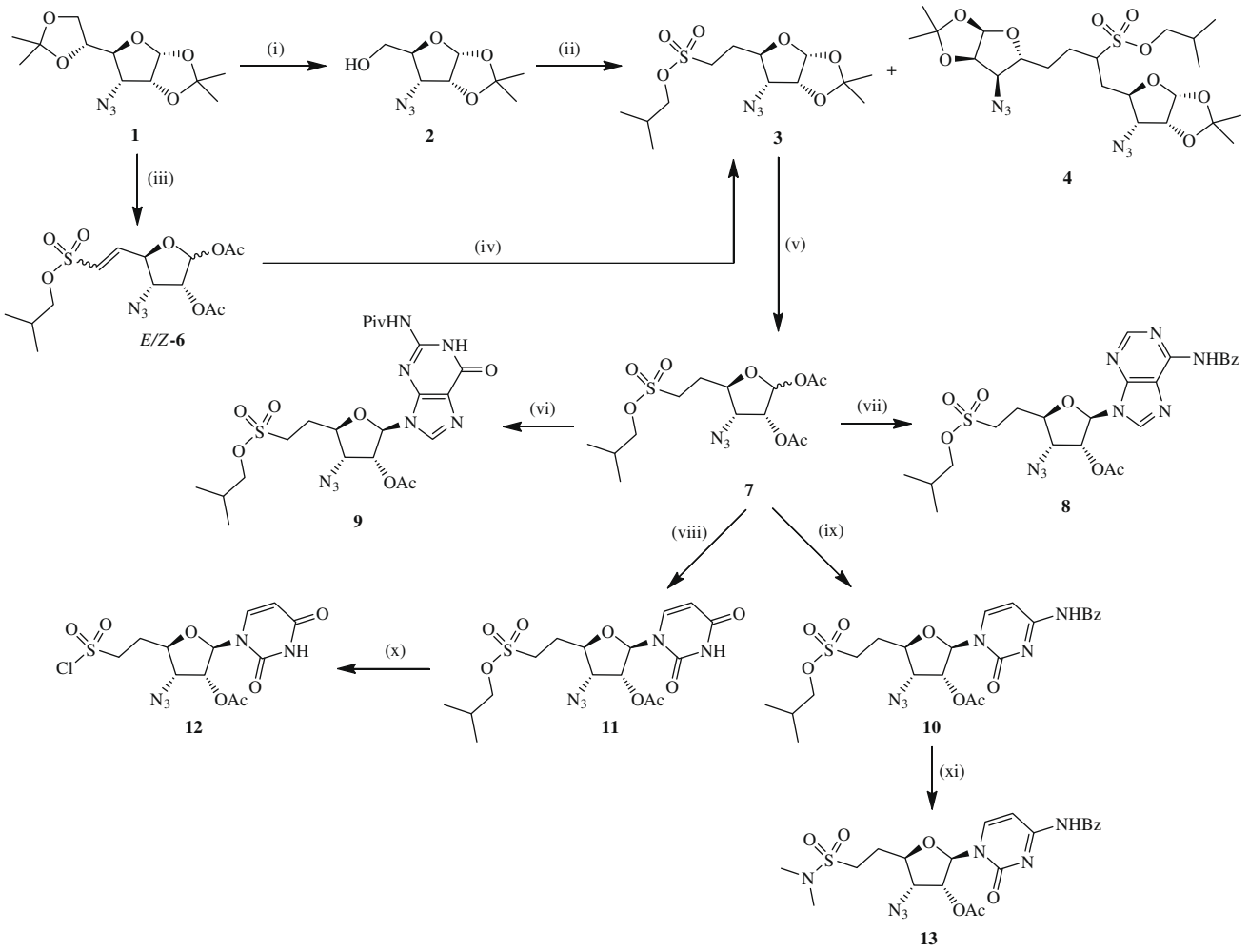
constructs containing the sulfonamide moieties may function as potential anti-virals.[9]

The synthesis of such oligomers requires a complete and suitable set of monomers (Fig. 1). The azido moiety will be used as a protected amine which can then be released under mild conditions such as catalytic hydrogenation and the Staudinger reaction. In addition, a sulfonyl chloride moiety is introduced which can react rapidly with the liberated amine at the 'N-terminus' of the growing oligomer.

2. Results and discussion

From the outset we decided to prepare the required azido sulfonyl chloride monomers in a divergent manner by introducing the nucleosidic base late in the synthesis, after the introduction of the azido and sulfonate moieties (Scheme 1). Thus, the commercially available diacetone-D-glucose was converted into azido compound **1** in two steps using a literature procedure.[10] The more labile 5,6-*O*-isopropylidene was removed by mild acidolysis after which oxidative diol cleavage and reduction with lithium borohydride afforded compound **2** which has the desired D-*ribo* stereochemistry.[11]

At this point the sulfonyl moiety was introduced by first converting the remaining free hydroxyl group into the corresponding triflate, which was subsequently subjected to nucleophilic substitution with the anion derived from isobutyl mesylate.[6] Various conditions were evaluated for this reaction, such as using *n*BuLi, *t*BuLi or LDA to generate the anion, adding HMPA, TMEDA or a crown ether to solubilize the anion, carrying out the reaction at −78 °C throughout or allowing the reaction mixture to slowly heat to temperatures up to −20 °C or even room temperature. However, the best yield obtained was 51%. This relatively low yield can be explained by the formation of significant amounts of dimer **4** resulting from the deprotonation of **3** upon formation followed by reaction with a further triflate starting compound. In spite of its relatively low yield, since this procedure could be carried out on a sizeable scale (2 g), sufficient material for further synthesis was obtained. However, we have found an alternative route which leads to a better overall yield for the transformation of **1** into **3** (Scheme 1). In this synthesis, after selective deprotection of the terminal acetonide and subsequent oxidative cleavage as before, the resulting aldehyde was treated with Horner–Wadsworth–Emmons (HWE) reagent **5**, which is itself accessible using a literature procedure.[12] Using



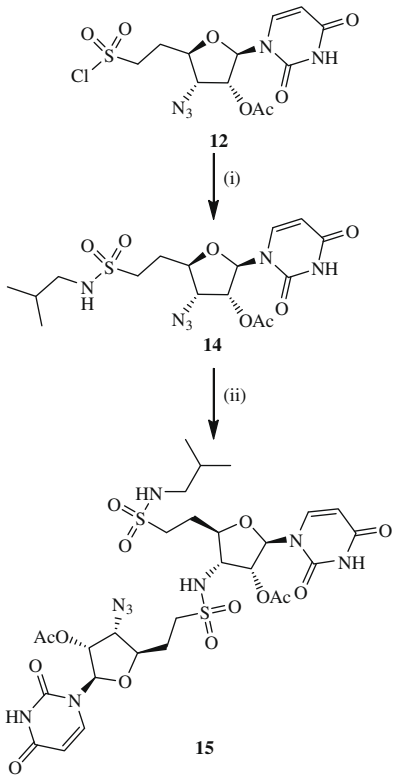
Scheme 1. Monomer synthesis. Reagents and conditions: *Method A*: (i) (1) 50% HOAc (aq), 50 °C; (2) $NaIO_4$, MeOH; (3) $LiBH_4$, THF, −20 °C (77%); (ii) (1) Tf_2O, pyr., −20 °C; (2) isobutyl sulfonate, *n*BuLi, HMPA, −78 °C, THF (51%); *Method B*: (iii) (1) 50% HOAc (aq), 50 °C; (2) $NaIO_4$, MeOH; (3) NaH, **5**, −20 °C THF; (iv) $NaBH_4$, −20 °C to rt, THF (67%); (v) (1) 90% TFA (aq); (2) Ac_2O, pyr (80%); (vi) N^2-pivaloylguanine, bis-TMS-acetamide, $SnCl_4$, CH_3CN (58%); (vii) N^6-benzoyladenine, bis-TMS-acetamide, $SnCl_4$, CH_3CN (51%); (viii) uracil, bis-TMS-acetamide, $SnCl_4$, CH_3CN (71%); (ix) N^2-benzoylcytosine, bis-TMS-acetamide, $SnCl_4$, CH_3CN (63%); (x) (1) KI, acetone, Δ; (2) 20% $COCl_2$ in toluene, DMF, DCM (61%); (xi) (1) KI, acetone, Δ; (2) 20% $COCl_2$ in toluene, DMF, DCM; (3) dimethylamine·HCl, NMM, DCM (72%).

sodium hydride as the base, the smooth formation of a 1:1 mixture of two isomeric products was observed, one of which could clearly be identified as the desired *E*-unsaturated product *E*-**6** from coupling constants in the ^{1}H NMR spectrum ($^3J_{H\text{-}5,H\text{-}6}$ 15.2 Hz). The identity of the other product *Z*-**6** could not be unambiguously established at this point since it has an intermediate coupling constant ($^3J_{H\text{-}5,H\text{-}6}$ 11.4 Hz), and might therefore also be the result of epimerization of the aldehyde at C-4 under the basic reaction conditions employed. At this point we decided to carry out the subsequent reduction of the conjugated double bond using sodium borohydride on the mixture even though chromatographic separation was possible. This led to the formation of a single product **3** demonstrating that **6Z** was indeed the *Z*-unsaturated HWE-product, which was identical in all respects to the material resulting from the substitution strategy described above. The yield for this synthesis was 67%, which is a clear improvement over the substitution route described above (yield for the same overall transformation 39%).

In order to convert **3** towards the introduction of the nucleoside base, the remaining isopropylidene-protecting group was removed by acidolysis and the resulting free hydroxyl moieties were acetylated using a mixture of acetic anhydride and pyridine, yielding bis-acetate **7** as a 1:4 mixture of anomers in 80% yield. The stage was now set for the introduction of suitably protected silylated bases using $SnCl_4$ as a Lewis acid catalyst.[13] Four bases were used: N^6-benzoyladenosine,[14] N^2-pivaloylguanidine,[15] N^4-benzoylcytosine[16] and uracil afforded fully protected monomer **8, 9**, **10** and **11** as single anomers in 51%, 58%, 63% and 71% yields, respectively. These building blocks are stable and can be kept for months at ambient temperature.

In order for oligomerization to occur, the sulfonate ester present in the monomers has to be deprotected and converted into the corresponding sulfonyl chloride. This was demonstrated using the uridine building block **11**. Deprotection using potassium iodide at an elevated temperature followed by treatment with phosgene in the presence of DMF afforded sulfonyl chloride **12** in 61% yield over two steps. Compound **12** is relatively stable and can be purified by column chromatography after which it can be stored for several months at −20 °C. As an alternative, we attempted to transform stable sulfonate ester **10** into a sulfonamide coupling product without intermediate purification of the sulfonyl chloride. Thus, cytidine monomer **10** was deprotected using potassium iodide and was converted into a sulfonyl chloride using phosgene and DMF as described above. Then, the crude sulfonyl chloride was treated with the hydrochloric acid salt of dimethyl amine in the presence of NMM as a base and smooth conversion into sulfonamide **13** was observed (72% yield after purification by column chromatography).

Next, we decided to demonstrate the principle of oligomerization by the preparation of a uridine–uridine dimer as shown in Scheme 2. First, uridine mimic **12** was coupled to isobutylamine using NMM as a base, yielding isobutyl sulfonamide **14** in 91% yield after purification by column chromatography. Interestingly, this reaction demonstrates the potential for the sulfonyl chloride monomers to be conjugated to any amine-containing molecule. The subsequent formation of the dimer **15** was carried out by the reduction of the azido moiety in **14** to the corresponding amine using catalytic hydrogenolysis. During the hydrogenation reaction, 1 equiv of acetic acid was added in order to protect the resulting amino moiety by protonation. This was deemed necessary because upon prolonged standing, migration of the 2′-acetyl-protecting group to the liberated amine occurs to a sizeable degree obviously leading to lower yields. The crude amine was immediately treated with a further equivalent of sulfonyl chloride **9** again using NMM as a base. After purification, the dimer **15** was obtained in 67% yield.



Scheme 2. Synthesis of UU-dimer **15**. Reagents and conditions: (i) isobutyl amine, NMM, DCM (91%); (ii) (1) H_2, 10% Pd/C, HOAc, THF; (2) **12**, NMM, DMF (67%).

3. Conclusions

A divergent synthesis of azido sulfonate building blocks suitable for RNA mimicry was developed, and was carried out successfully for all four RNA bases. The uracil monomer was subsequently transformed into the corresponding 'activated' sulfonyl chloride and subjected to a dimerization procedure resulting in a dimeric compound. The cytidine monomer was converted into a sulfonamide coupling product without isolation of the intermediate sulfonyl chloride demonstrating the usefulness of the sulfonate monomers as stable building blocks for the preparation of sulfonamide RNA mimetics.

4. Experimental

4.1. General procedures

Reactions were carried out at ambient temperature unless stated otherwise. All reagents were used as supplied from commercial sources unless stated otherwise. DCM and CH_3CN were stored on molecular sieves (4 Å) prior to use. R_f values were determined by thin layer chromatography (TLC) on Merck precoated Silica Gel $60F_{254}$ plates. Spots were visualized by UV-quenching, ninhydrin or Hanessian's stain (cerium molybdate). Column chromatography was carried out using Silicycle UltraPure silica gel (40–63 μm). ^{1}H NMR spectra were recorded on a Varian G-300 (300 MHz) spectrometer and chemical shifts are given in ppm relative to TMS (0.00 ppm). ^{13}C NMR spectra were recorded using the attached proton test (APT) sequence on a Varian G-300 (75.5 MHz) spectrometer and chemical shifts are given in ppm relative to $CDCl_3$ (77.0 ppm). Electrospray ionization mass spectrometry was performed on a Shimadzu LCMS-QP8000 single quadrupole benchtop mass spectrometer in positive ionization mode.

4.2. 3-Azido-3-deoxy-1,2-*O*-isopropylidene-β-D-ribose 2[11]

3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-β-D-allofuranose **1**[10] (4.31 g, 15.1 mmol) was dissolved in a mixture of acetic acid (20 mL), water (10 mL) and MeOH (10 mL), and then stirred overnight at 50 °C. The reaction mixture was then evaporated and co-evaporated twice with toluene. The residue was redissolved in MeOH (40 mL) and a solution of $NaIO_4$ (3.89 g, 18.2 mmol) in water (8 mL) was added. The resulting mixture was stirred for 15 min at room temperature, after which the volatiles were evaporated. The crude material was triturated with $CHCl_3$ (50 mL) and after evaporation the resulting oil was redissolved in dry THF (20 mL). After cooling to −20 °C, a 2 M solution of $LiBH_4$ in THF (7.55 mL) was added, and this solution was stirred for 1 h at −20 °C. Then, brine (20 mL) was added and the product was extracted with DCM (2 × 50 mL). After drying on Na_2SO_4 and column chromatography (EtOAc/hexanes, 2/1 v/v), **2** (2.89 g, 77%) was obtained as a white solid. R_f (EtOAc/hexanes, 1/1 v/v) = 0.36; $[\alpha]_D^{23} = +124.4$ (*c* 0.85, $CHCl_3$) {lit.[11e] $[\alpha]_D^{20} = +130.4$ (*c* 0.97)}; δ_H (300 MHz, $CDCl_3$) 1.37, 1.57 (6H, 2 × s, C(CH_3)$_2$), 3.24 (1H, q, O*H*, *J* 4.1 Hz), 3.58 (1H, dd, H-3, *J* 4.7 Hz, *J* 9.6 Hz), 3.69 (1H, m, H-5a), 3.95 (1H, m, H-5b), 4.11 (1H, m, H-4), 4.76 (1H, t, H-2, *J* 4.1 Hz), 5.81 (1H, d, H-1, *J* 3.6 Hz); δ_C (75.5 MHz, $CDCl_3$) 25.9 (C(CH_3)$_3$), 58.9 (C-3), 59.6 (C-5), 77.9, 79.8 (C-2, C-4), 103.8 (C-1), 112.7 (*C*(CH_3)$_2$); for $C_8H_{13}N_3O_4$ calcd C, 44.65; H, 6.09; N, 19.53; found C, 44.42; H, 5.91; N, 19.27.

4.3. 3-Azido-3,5,6-trideoxy-6-(isobutyloxysulfon)-1,2-*O*-isopropylidene-β-D-ribo-hexofuranose 3

Method A: 3-Azido-3-deoxy-1,2-*O*-isopropylidene-β-D-ribose **2** (2.32 g, 11.6 mmol) was dissolved in dry DCM (30 mL) and pyridine (1.42 mL, 17.4 mmol) was added. After cooling to −20 °C, trifluoromethanesulfonic anhydride (2.15 mL, 12.8 mmol) was added in portions. The mixture was stirred for 30 min at −20 °C, after which it was washed with 1 M HCl (30 mL) and water (30 mL). After drying on Na_2SO_4, the crude triflate was obtained as an off-white crystalline solid which was used without further purification. Isobutyl methylsulfonate (1.95 g, 12.8 mmol) and HMPA (2.0 mL) were dissolved in dry THF (20 mL) under a nitrogen atmosphere and cooled to −78 °C. Then, a 2.5 M solution of *n*BuLi in hexanes (5.12 mL) was added dropwise. The resulting yellow solution was stirred at −78 °C for 1 h, after which a solution of the triflate in dry THF (5 mL) was added and the resulting mixture was stirred for 2 h at −78 °C. The reaction was quenched with acetic acid (4.0 mL) and after heating to room temperature, saturated aqueous $NaHCO_3$ (20 mL) was added. The crude product was extracted with DCM (2 × 30 mL) and dried on Na_2SO_4. Column chromatography (EtOAc/hexanes, 1/4 v/v) yielded **3** (2.07 g, 51%) as a clear, colourless oil.

Method B: 3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-β-D-allofuranose **1** (622 mg, 2.89 mmol) was dissolved in a mixture of acetic acid (5.0 mL), H_2O (2.5 mL) and MeOH (2.5 mL) and stirred at 50 °C overnight. After evaporation of the solvents and co-evaporation with toluene, the crude diol was redissolved in a mixture of MeOH (10 mL) and water (2.0 mL), and sodium periodate (742 mg, 3.47 mmol) was added. The resulting mixture was stirred at room temperature for 20 min after which all volatiles were evaporated. Trituration with $CHCl_3$ afforded the crude aldehyde. THF (10 mL) was cooled to −20 °C, 60% NaH in mineral oil (127 mg, 3.17 mmol) and isobutyl (diphenoxyphosphoryl) methanesulfonate **5** (1.10 g, 2.89 mmol) were added, and the resulting mixture was stirred at −20 °C for 15 min, after which the crude aldehyde was added in THF (5.0 mL). After stirring for three hours at −20 °C, $CHCl_3$ (25 mL) and water (10 mL) were added and the layers separated. The organic layer was dried on Na_2SO_4 affording isomers *E*-**6** and *Z*-**6** as a 1:1 mixture as judged by ^{1}H NMR integration. R_f (EtOAc/hexanes, 1/2 v/v) = 0.26 and 0.50; δ_H (300 MHz, $CDCl_3$) 0.96 (2 × 6H, 2 × d, *E*-*i*Bu-CH_3, *Z*-*i*Bu-CH_3, *J* 6.6 Hz), 1.37, 1.38, 1.58, 1.60 (4 × 3H, 4 × s, *E*-C(CH_3)$_2$, *Z*-C(CH_3)$_3$), 2.01 (2 × 1H, m, *E*-*i*Bu-CH, *Z*-*i*Bu-CH), 3.14 (1H, dd, *Z*-H-3, *J* 4.4 Hz, *J* 9.6 Hz), 3.33 (1H, dd, *E*-H-3, *J* 4.5 Hz, 9.6 Hz), 3.89 (2H, m, *E*-*i*Bu-CH_2), 3.98 (2H, d, *Z*-*i*Bu-CH_2, *J* 6.6 Hz), 4.68 (1H, ddd, *E*-H-4, *J* 1.7 Hz, *J* 4.4 Hz, *J* 9.9 Hz), 4.82 (2 × 1H, m, *E*-H-2, *Z*-H-2), 5.68 (1H, t, *Z*-H-4, *J* 9.5 Hz), 5.86, 5.88 (2 × 1H, 2 × d, *E*-H-1, *Z*-H-1, *J* 3.6 Hz), 6.25 (1H, dd, *Z*-H-5, *J* 9.2 Hz, *J* 11.4 Hz), 6.46 (1H, d, *Z*-H-6, *J* 11.4 Hz), 6.60 (1H, dd, *E*-H-6, *J* 1.7 Hz, *J* 15.1 Hz), 6.94 (1H, dd, *E*-H-5, *J* 4.2 Hz, *J* 11.5 Hz).

The mixture was dissolved in THF (10 mL), cooled to −20 °C after which sodium borohydride (131 mg, 3.47 mmol) was added. The resulting suspension was allowed to slowly heat to room temperature over 6 h. $CHCl_3$ (25 mL) and water (10 mL) were added and the layers separated. The organic layer was dried on Na_2SO_4 after which column chromatography (EtOAc/hexanes, 1/4 v/v) afforded **3** (679 mg, 67%) as a clear colourless oil. R_f (EtOAc/hexanes, 1/3 v/v) = 0.29; $[\alpha]_D^{23} = +97.1$ (*c* 0.69, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz) 0.87 (6H, d, *i*Bu-C*H*$_3$, *J* 6.3 Hz), 1.24, 1.44 (6H, 2 × s, C(C*H*$_3$)$_2$), 1.90 (2H, m, H-5a, H-5b), 2.19 (1H, m, *i*Bu-C*H*), 3.04 (1H, dd, H-3, *J* 4.6 Hz, *J* 9.7 Hz), 3.16 (2H, m, H-6a, H-6b), 3.87 (2H, d, *i*Bu-C*H*$_2$, *J* 6.3 Hz), 3.99 (1H, m, H-4), 4.65 (1H, t, H-2, *J* 4.1 Hz), 5.68 (1H, d, H-1, *J* 3.6 Hz); δ_C (75.5 MHz, $CDCl_3$) 18.2, 27.9 (2 × *i*Bu-CH_3), 25.8, 25.9 (C(CH_3)$_2$), 26.1 (C-5), 36.6 (*i*Bu-*C*H), 46.0 (C-6), 63.8, 74.8, 79.7 (C-2, C-3, C-4), 75.5 (*i*Bu-CH_2), 103.7 (C-1), 112.7 (*C*(CH_3)$_2$); for $C_{13}H_{23}N_3O_6S$ calcd C, 44.69; H, 6.63; N, 12.03; found C, 44.56; H, 6.88; N, 12.15.

4.4. 1,2-Di-*O*-acetyl-3-azido-3,5,6-trideoxy-6-(isobutyloxysulfon)-α/β-D-ribo-hexofuranose 7

3-Azido-3,5,6-trideoxy-6-(isobutyloxysulfon)-1,2-*O*-isopropylidene-β-D-*ribo*-hexofuranose **3** (1.25 g, 3.58 mmol) was dissolved in a mixture of TFA (2.7 mL) and water (0.3 mL) and stirred for 30 min at room temperature, after which the volatiles were evaporated and the residue co-evaporated twice with toluene. Pyridine (5.0 mL) and acetic anhydride (5.0 mL) were added and the resulting mixture was stirred overnight at room temperature. The solvents were evaporated and the residue was co-evaporated twice with toluene. Column chromatography (EtOAc/hexanes, 1/2 v/v) afforded a mixture of anomers **7** (1.12 g, 80%) as a clear, colourless oil. R_f (EtOAc/hexanes, 1/2 v/v) = 0.40; $[\alpha]_D^{23} = +23.9$ (*c* 0.81, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 0.99 (6H, d, α-*i*Bu-C*H*$_3$, β-*i*Bu-C*H*$_3$, *J* 6.6 Hz), 2.01–2.39 (2H, m, α-H-5a, β-H-5a, α-H-5b, β-H-5b), 2.08 (2.4H, s, α-Ac-C*H*$_3$), 2.12 (0.6H, s, β-Ac-C*H*$_3$), 3.24 (2H, m, α-H-6a, β-H-6a, α-H-6b, β-H-6b), 3.85 (0.2H, dd, α-H-3, *J* 4.9 Hz, *J* 7.7 Hz), 3.94 (0.8H, dd, β-H-3, *J* 4.8 Hz, *J* 7.5 Hz), 4.00 (0.4H, d, α-*i*Bu-C*H*$_2$, *J* 6.6 Hz), 4.01 (1.6H, d, β-*i*Bu-C*H*$_2$, *J* 6.6 Hz), 4.12 (0.8H, m, β-H-4), 4.19 (0.2H, m, α-H-4), 5.26 (0.2H, dd, α-H-2, *J* 4.6 Hz, *J* 7.5 Hz), 5.35 (0.8H, d, β-H-2, *J* 4.7 Hz), 6.11 (0.8H, s, β-H-1), 6.38 (0.2H, d, α-H-1, *J* 4.6 Hz); δ_C (75.5 MHz, $CDCl_3$) 18.2, 19.8, 2.1, 20.6 (α-*i*Bu-*C*H$_3$, β-*i*Bu-*C*H3, α-*i*Bu-*C*H, β-*i*Bu-*C*H), 27.6 (α-C-5), 27.8, 27.9 (αβ-Ac-*C*H$_3$), 28.4 (β-C-5), 45.8 (β-C-6), 46.0 (α-C-6), 61.0, 71.4, 80.1 (α-C-2, α-C-3, α-C-4), 62.9, 75.6, 79.4 (β-C-2, β-C-3, β-C-4), 75.5 (αβ-*i*Bu-*C*H$_2$), 93.3 (α-C-1), 97.8 (β-C-1), 168.5, 169.1, 169.2, 169.3 (2 × αβ-C=O); for $C_{14}H_{23}N_3O_8S$ calcd C, 42.74; H, 5.89; N, 10.68; found C, 42.45; H, 5.81; N, 10.91.

4.5. 3-Azido-3,5-dideoxy-5-(isobutyloxysulfonmethyl)-N^6-benzoyl-adenosine 8

To a suspension of N^6-benzoyladenine (589 mg, 2.46 mmol) in CH_3CN (5.0 mL) *N*,*O*-bis(trimethylsilyl)acetamide (1.80 mL, 7.38 mmol) was added and this mixture was stirred at room temperature for 30 min. The resulting clear solution was cooled to −20 °C after which 1,2-di-*O*-acetyl-3-azido-3,5,6-trideoxy-6-(isobutyloxy-

sulfon)-α/β-D-*ribo*-hexofuranose **7** (484 mg, 1.23 mmol) and $SnCl_4$ (722 μL, 6.15 mmol) were added. After stirring at −20 °C to room temperature for 72 h, water (10 mL) was added and the crude product was quickly extracted with $CHCl_3$ (20 mL). After drying on Na_2SO_4 and column chromatography (MeOH/DCM, 3/97 v/v), **8** (292 mg, 51%) was obtained as a clear colourless oil. R_f (MeOH/DCM, 1/9 v/v) = 0.66; $[\alpha]_D^{23} = +6.6$ (*c* 2.20, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 0.94 (6H, d, *i*Bu-CH_3, *J* 6.6 Hz), 2.00 (1H, m, *i*Bu-CH), 2.18 (3H, s, C(O)CH_3), 2.43 (2H, m, H-5′a, H-5′b), 3.26 (2H, m, H-6′a, H-6′b), 3.96 (2H, d, *i*Bu-CH_2, *J* 6.6 Hz), 4.21 (1H, m, H-4′), 4.72 (1H, dd, H-3′, *J* 5.8 Hz, 7.4 Hz), 6.00 (1H, dd, H-2′, *J* 3.3 Hz, 5.8 Hz), 6.03 (1H, d, H-1′, *J* 3.3 Hz), 7.54 (3H, m, ArH), 8.02 (2H, d, ArH, *J* 7.2 Hz), 8.11 (1H, s, H-2/8), 8.74 (1H, s, H-2/8), 9.39 (1H, br s, NH); δ_C (75.5 MHz, $CDCl_3$) 18.3 (*i*Bu-CH_3), 20.2 (*i*Bu-CH), 26.9 (C-5′), 28.0 (C(O)CH_3), 45.9 (C-6′), 62.6, 75.1, 79.5 (C-2′, C-3′, C-4′), 75.6 (*i*Bu-CH_2), 87.9 (C-1′), 123.9, 127.8, 128.5, 132.6, 133.1, 149.9, 151.0, 164.9, 169.6 (2 × C=O, C-2, C-4, C-5, C-6, C-8); for $C_{24}H_{28}N_8O_7$ calcd C, 50.34; H, 4.93; N, 19.57; found C, 50.05; H, 4.86; N, 19.37.

4.6. 3-Azido-3,5-dideoxy-5-(isobutyloxysulfonmethyl)-N^2-pivaloyl-guanosine 9

To a suspension of N^2-pivaloylguanine (385 mg, 1.64 mmol) in CH_3CN (5.0 mL), *N*,*O*-bis(trimethylsilyl)acetamide (1.21 mL, 4.91 mmol) was added and this mixture was stirred at room temperature for 30 min. The resulting clear solution was cooled to −20 °C after which 1,2-di-*O*-acetyl-3-azido-3,5,6-trideoxy-6-(isobutyloxysulfon)-α/β-D-*ribo*-hexofuranose **7** (428 mg, 1.09 mmol) and $SnCl_4$ (512 μL, 4.36 mmol) were added. After stirring at −20 °C to room temperature for 24 h, water (10 mL) was added and the crude product was quickly extracted with $CHCl_3$ (20 mL). After drying on Na_2SO_4 and column chromatography (EtOAc/hexanes, 3/1 v/v), **9** (358 mg, 58%) was obtained as a white solid. R_f (EtOAc/hexanes, 3/1 v/v) = 0.22; $[\alpha]_D^{23} = +47.7$ (*c* 0.21, DMF); δ_H (300 MHz, $CDCl_3$) 0.99 (6H, d, *i*Bu-CH_3, *J* 6.8 Hz), 1.39 (6H, s, C(CH_3)$_2$), 2.05 (1H, m, *i*Bu-CH), 2.27 (3H, s, Ac-CH_3), 2.47 (2H, m, H-5′a, H-5′b), 3.36 (1H, m, H-6′a), 3.54 (1H, m, H-6′b), 4.04 (2H, d, *i*Bu-CH_2, *J* 6.7 Hz), 4.15 (1H, m, H-4′), 4.85 (1H, dd, H-3′, *J* 6.0 Hz, *J* 8.2 Hz), 6.07 (1H, d, H-1′, *J* 2.8 Hz), 6.34 (1H, dd, H-2′, *J* 2.7 Hz, *J* 5.8 Hz), 7.81 (1H, s, H-8), 8.98 (1H, s, H-1), 12.3 (1H, s, 6-NH); δ_C (75.5 MHz, $CDCl_3$) 18.5 (*i*Bu-CH_3), 20.6 (*i*Bu-CH), 26.6 (C(CH_3)$_3$), 26.9 (C-5′), 28.1 (Ac-CH_3), 40.2 (C(CH_3)$_3$), 46.1 (C-6′), 62.0, 77.4, 79.8 (C-2′, C-3′, C-4′), 75.8 (*i*Bu-CH_2), 90.0 (C-1′), 110.4, 147.5, 152.1, 157.8, 170.4, 181.1 (3 × C=O, C-2, C-4, C-5, C-6, C-8); for $C_{22}H_{32}N_8O_8S$ calcd C, 46.47; H, 5.67; N 19.71; found C, 46.20; H, 5.62; N, 19.84.

4.7. 3-Azido-3,5-dideoxy-5-(isobutyloxysulfonmethyl)-N^4-benzoyl-cytidine 10

To a suspension of N^4-benzoylcytosine (123 mg, 0.57 mmol) in CH_3CN (2.0 mL), *N*,*O*-bis(trimethylsilyl)acetamide (418 μL, 1.71 mmol) was added and stirred at room temperature for 30 min. The resulting clear solution was cooled to −20 °C after which 1,2-di-*O*-acetyl-3-azido-3,5,6-trideoxy-6-(isobutyloxysulfon)-α/β-D-*ribo*-hexofuranose **7** (223 mg, 0.57 mmol) and $SnCl_4$ (201 μL, 1.71 mmol) were added. The mixture was allowed to slowly heat to room temperature and stirred overnight, after which water (10 mL) was added and the product was extracted quickly with $CHCl_3$ (10 mL). After drying on Na_2SO_4 and column chromatography (EtOAc/hexanes, 1/1 v/v), **10** (198 mg, 63%) was obtained as a white foam. R_f (EtOAc/hexanes, 1/1 v/v) = 0.14; $[\alpha]_D^{23} = +42.3$ (*c* 0.26, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 0.98 (6H, d, CH(CH_3)$_2$, *J* 6.9 Hz), 2.04 (1H, m, CH(CH_3)$_2$), 2.18 (3H, s, C(O)CH_3), 2.36 (2H, m, H-5′a, H-5′b), 3.34 (2H, m, H-6′a, H-6′b), 4.01 (2H, d, OCH_2, *J* 6.6 Hz), 4.08 (1H, m, H-4′), 4.33 (1H, dd, H-3′, *J* 6.2 Hz, *J* 8.9 Hz), 5.61 (1H, d, H-1′, *J* 2.2 Hz), 5.76 (1H, dd, H-2′, *J* 2.2 Hz, *J* 6.2 Hz), 7.49 (4H, m, ArH, H-5), 7.71 (1H, d, H-6, *J* 7.5 Hz), 7.91 (2H, m, ArH), 9.24 (1H, br s, NH); δ_C (75.5 MHz, $CDCl_3$) 18.5 (*i*Bu-CH_3), 20.6 (*i*Bu-CH), 26.7 (C-5′), 28.2 (C(O)CH_3), 46.1 (C-6′), 62.5, 75.5, 79.4 (C-2′, C-3′, C-4′), 75.8 (*i*Bu-CH_2), 94.0 (C-1′), 97.1 (C-5), 127.7, 128.8, 132.8, 133.2 (ArC), 146.3 (C-6), 154.3, 163.1, 166.7, 170.0 (C=O, C=N); for $C_{23}H_{28}N_6O_8S$ calcd C, 50.36; H, 5.14; N, 15.32; found C, 50.41; H, 5.38; N, 15.07.

4.8. 3-Azido-3,5-dideoxy-5-(isobutyloxysulfonmethyl)-uridine 11

To a suspension of uracil (479 mg, 4.27 mmol) in CH_3CN (5.0 mL), *N*,*O*-bis(trimethylsilyl)acetamide (3.17 mL, 12.8 mmol) was added and this mixture was stirred at room temperature for 30 min. The resulting clear solution was cooled to −20 °C after which 1,2-di-*O*-acetyl-3-azido-3,5,6-trideoxy-6-(isobutyloxysulfon)-α/β-D-*ribo*-hexofuranose **7** (1.11 g, 2.28 mmol) and $SnCl_4$ (1.32 mL, 11.3 mmol) were added. After stirring at −20 °C to room temperature for 24 h, water (10 mL) was added and the crude product was quickly extracted with $CHCl_3$ (20 mL). After drying on Na_2SO_4 and column chromatography (EtOAc/hexanes, 2/1 v/v), **11** (888 mg, 71%) was obtained as a clear, colourless oil. R_f (EtOAc/hexanes, 3/1 v/v) = 0.30; $[\alpha]_D^{23} = +31.5$ (*c* 1.38, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 0.98 (6H, d, *i*Bu-CH_3, *J* 6.9 Hz), 2.04 (1H, m, *i*Bu-CH), 2.19 (3H, s, Ac-CH_3), 2.31 (2H, m, H-5′a, H-5′b), 3.31 (2H, m, H-6′a, H-6′b), 4.01 (3H, m, *i*Bu-CH_2, H-4′), 4.27 (1H, dd, H-3′, *J* 6.5 Hz, *J* 8.2 Hz), 5.54 (1H, d, H-1′, *J* 2.8 Hz), 5.62 (1H, dd, H-2′, *J* 2.8 Hz, *J* 6.5 Hz), 5.79 (1H, d, H-5, *J* 8.1 Hz), 7.31 (1H, d, H-6, *J* 8.1 Hz), 10.3 (1H, s, H-3); δ_C (75.5 MHz, $CDCl_3$) 18.3 (*i*Bu-CH_3), 20.2 (*i*Bu-CH), 26.5 (C-5′), 28.0 (Ac-CH_3), 45.7 (C-6′), 62.2, 75.0, 78.8 (C-2′, C-3′, C-4′), 75.7 (*i*Bu-CH_2), 92.4 (C-1′), 102.6 (C-5), 142.3 (C-6), 149.9, 163.6, 169.7 (3 × C=O); for $C_{16}H_{23}N_5O_8S$ calcd C, 43.14; H, 5.20; N, 15.72; found C, 42.88; H, 5.15; N, 15.59.

4.9. 3-Azido-3,5-dideoxy-5-(chlorosulfonmethyl)-uridine 12

To a solution of 3-azido-3,5-dideoxy-5-(isobutyloxysulfon)-uridine **11** (861 mg, 1.93 mmol) in acetone (10 mL), sodium iodide (579 mg, 3.86 mmol) was added, and the resulting mixture was stirred at reflux for 48 h. The resulting white precipitate was removed by filtration and suspended in DCM (10 mL), after which DMF (300 μL) and a 20% solution of phosgene in toluene (3.0 mL) were added. This mixture was stirred for 5 h at room temperature after which the solids were removed by filtration. The filtrate was evaporated and subjected to column chromatography (EtOAc/hexanes, 2/1 v/v), after which **12** (480 mg, 61%) was obtained as a white foam. R_f (EtOAc/hexanes, 1/1 v/v) = 0.19; $[\alpha]_D^{23} = +42.1$ (*c* 0.21, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 2.21 (3H, s, Ac-CH_3), 2.44 (1H, m, H-5′a), 2.55 (1H, m, H-5′b), 3.85 (2H, m, H-6′a, H-6′b), 4.04 (2H, m, H-3′, H-4′), 4.37 (1H, dd, H-2′, *J* 6.3 Hz, *J* 8.5 Hz), 5.65 (1H, d, H-1′, *J* 6.3 Hz), 5.78 (1H, d, H-5, *J* 8.0 Hz), 7.13 (1H, d, H-6, *J* 8.0 Hz), 9.61 (1H, s, H-3); δ_C (75.5 MHz, $CDCl_3$) 20.4 (Ac-CH_3), 27.1 (C-5′), 60.8 (C-6′), 62.2, 75.2, 78.6 (C-2′, C-3′, C-4′), 94.3 (C-1′), 102.9 (C-5), 143.2 (C-6), 150.0, 163.8, 170.1 (3 × C=O); for $C_{12}H_{14}ClN_5O_7S$ calcd C, 35.34; H, 3.46; N, 17.17; found C, 35.49; H, 3.25; N, 16.92.

4.10. 3-Azido-3,5-dideoxy-5-(dimethylaminosulfonmethyl)-N^4-benzoyl-cytidine 13

3-Azido-3,5-dideoxy-5-(isobutyloxysulfonmethyl)-N^4-benzoyl-cytidine **10** (66 mg, 0.12 mmol) and potassium iodide (20 mg, 0.12 mmol) were added to acetone (3.0 mL) and stirred at reflux temperature for 48 h, after which the volatiles were evaporated. The residue was suspended in DCM (2.5 mL) and a 20% solution of phosgene in toluene (1.0 mL) was added. DMF (0.5 mL) was added dropwise followed by stirring for 3 h at room temperature,

after which a clear, light brown solution was obtained. The solvents were evaporated and dimethylamine·HCl (9.8 mg, 0.12 mmol) and NMM (33 μL, 0.30 mmol) were added. After stirring for 1 h at room temperature, TLC analysis indicated complete transformation into a new product and the reaction mixture was washed with 1 M HCl (aq) and brine. After drying on Na_2SO_4 and column chromatography (EtOAc/hexanes, 3/1 v/v), **13** (45 mg, 72%) was obtained as an off-white foam. R_f (EtOAc/hexanes, 3/1 v/v) = 0.18; $[\alpha]_D^{23} = +38.7$ (*c* 0.61, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 2.20 (3H, s, C(O)CH_3), 2.33 (2H, m, H-5′a, H-5′b), 2.90 (6H, s, N(CH_3)$_2$), 3.09 (2H, m, H-6′a, H-6′b), 4.10 (1H, m, H-4′), 4.33 (1H, dd, H-3′, *J* 6.2 Hz, *J* 8.8 Hz), 5.55 (1H, d, H-1′, *J* 2.2 Hz), 5.72 (1H, dd, H-2′, *J* 2.2 Hz, *J* 6.2 Hz), 7.59 (5H, m, ArH, H-5, H-6), 7.93 (2H, m, ArH), 9.63 (1H, br s, NH); δ_C (75.5 MHz, $CDCl_3$) 20.6 (C(O)CH_3), 26.3 (C-5′), 37.5, 37.6 (N(CH_3)$_2$), 54.8 (C-6′), 62.7, 75.7, 79.9 (C-2′, C-3′, C-4′), 94.8 (C-1′), 97.4 (C-5), 127.8, 129.0, 132.7, 133.4 (ArC), 156.8 (C-6), 154.1, 163.2, 169.9 (3 × C=O); for $C_{21}H_{27}N_7O_7S$ calcd C, 48.36; H, 5.22; N, 18.80; found C, 48.61; H, 5.02; N, 18.69; *m/z* (ESI +ve) 522.2 $[M+H]^+$, $C_{21}H_{28}N_7O_7S$ requires 522.2.

4.11. 3-Azido-3,5-dideoxy-5-(isobutylaminosulfonmethyl)-uridine 14

3-Azido-3,5-dideoxy-5-(chlorosulfon)-uridine **12** (25 mg, 61 μmol) was dissolved in DCM (1.0 mL) after which NMM (10.1 μL, 91 μmol) and isobutylamine (6.7 μL, 67 μmol) were added. The resulting mixture was stirred for 90 min at room temperature, after which it was washed with 1 M HCl (aq) and brine, dried on Na_2SO_4 and purified by column chromatography (EtOAc/hexanes, 3/1 v/v) yielding **14** (24.6 mg, 91%) as a white foam. (EtOAc/hexanes, 3/1 v/v) = 0.55; $[\alpha]_D^{23} = +48.8$ (*c* 0.32 g/100 mL, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 0.97 (6H, d, CH(C*H*$_3$)$_2$, *J* 6.6 Hz), 1.79 (1H, m, C*H*(CH_3)$_3$), 2.20 (3H, s, C(O)CH_3), 2.32 (2H, m, H-5′a, H-5′b), 2.93 (2H, m, NHC*H*$_2$), 3.18 (2H, m, H-6′a, H-6′b), 3.99 (1H, m, H-4′), 4.24 (1H, dd, H-3′, *J* 6.3 Hz, *J* 8.2 Hz), 4.84 (1H, br s, CH_2N*H*), 5.44 (1H, d, H-1′, *J* 2.8 Hz), 5.60 (1H, dd, H-2′, *J* 2.8 Hz, *J* 6.3 Hz), 5.78 (1H, d, H-5, *J* 8.2 Hz), 7.21 (1H, d, H-6, *J* 8.2 Hz), 9.62 (1H, br s, H-3); δ_C (75.5 MHz, $CDCl_3$) 19.8 (CH(*C*H$_3$)$_2$), 20.5 (C(O)*C*H$_3$), 27.1 (*C*H(CH_3)$_2$), 28.9 (C-5′), 48.4 (NH*C*H$_2$), 50.6 (C-6′), 62.6, 75.4, 79.6 (C-2′, C-3′, C-4′), 93.2 (C-1′), 103.0 (C-5), 142.5 (C-6), 149.9, 163.5, 170.1 (C=O); for $C_{16}H_{24}N_6O_7S$ calcd C, 43.24; H, 5.44; N, 18.91; found C, 43.28; H, 5.19; N, 18.73; *m/z* (ESI +ve) 444.9 $[M+H]^+$, $C_{16}H_{25}N_6O_7S$ requires 445.1.

4.12. UU-dimer 15

3-Azido-3,5-dideoxy-5-(isobutylaminosulfon)-uridine **14** (20.0 mg, 45 μmol) was dissolved in THF (1.0 mL) after which acetic acid (3.9 μL, 68 μmol) and 10% Pd/C (5.0 mg) were added. The resulting mixture was stirred under a H_2 atmosphere for 2 h when TLC indicated complete consumption of the starting material. The solvents were evaporated and co-evaporated twice with toluene. The residue was dissolved in DMF (1.0 mL) after which **12** (18.4 mg, 45 μmol) and NMM (14.8 μL, 135 μmol) were added. The reaction mixture was stirred overnight at room temperature, after which the volatiles were evaporated and the residue was purified by column chromatography (MeOH/DCM, 5/95 to 20/80 v/v), yielding **15** (23.8 mg, 67%) as a white foam. R_f (MeOH/DCM, 9/1 v/v) = 0.26; δ_H (300 MHz, $CDCl_3$) 0.98 (6H, d, CH(C*H*$_3$)$_2$, *J* 6.6 Hz), 1.81 (1H, m, C*H*(CH_3)$_2$), 2.15 (6H, s, 2 × C(O)CH_3), 2.31 (4H, m, 2 × H-5′a, 2 × H-5′b), 2.90 (2H, NHC*H*$_2$), 3.10 (4H, m, 2 × H-6′a, 2 × H-6′b), 3.99 (2H, m, 2 × H-4′), 4.30 (1H, dd, H-3′, *J* 6.4 Hz, *J* 8.0 Hz), 4.54 (1H, m, H-3′), 4.80 (1H, br s, N*H*CH_2), 5.45 (1H, d, H-1′, *J* 2.7 Hz), 5.58 (3H, m, H-1′, 2 × H-2′), 5.78 (2H, m, 2 × H-5), 7.19 (2H, m, 2 × H-6), 9.50 (2H, br s, 2 × H-3); for $C_{28}H_{39}N_9O_{14}S_2$ calcd C, 42.58; H, 4.98; N, 15.96; found C, 42.29; H, 5.20; N, 15.77; *m/z* (ESI +ve) 789.9 $[M+H]^+$, $C_{28}H_{40}N_9O_{14}S_2$ requires 790.2.

References

1. For recent reviews, see: (a) Carninci, P.; Yasuda, J.; Hayashizaki, Y. *Curr. Opin. Cell. Biol.* **2008**, *20*, 274; (b) Ventura, A.; Jacks, T. *Cell* **2009**, *136*, 586; (c) Dorokhov, Y. L. *Mol. Biol.* **2007**, *41*, 519; (d) Baulcombe, D. *Trends Biochem. Sci.* **2005**, *30*, 290.
2. (a) Nielsen, P. E.; Egholm, M.; Berg, R. H.; Buchardt, O. *Science* **1991**, *254*, 1497; (b) Egholm, M.; Buchardt, O.; Nielsen, P. E.; Berg, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 1895; (c) Egholm, M.; Nielsen, P. E.; Buchardt, O.; Berg, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 9677; (d) Düholm, K. L.; Egholm, M.; Behrens, C.; Christensen, L.; Hansen, H. F.; Vulpius, T.; Petersen, K. H.; Berg, R. H.; Nielsen, P. E.; Buchardt, O. *J. Org. Chem.* **1994**, *59*, 5767.
3. (a) Koshkin, A. A.; Singh, S. K.; Nielsen, P.; Rajwanshi, V. K.; Kumar, R.; Meldgaard, M.; Olsen, C. E.; Wengel, J. *Tetrahedron* **1998**, *54*, 3607; (b) Singh, S. K.; Nielsen, P.; Koshkin, A. A.; Wengel, J. *Chem. Commun.* **1998**, 455; (c) Koshkin, A. A.; Nielsen, P.; Meldgaard, M.; Rajwanshi, V. K.; Singh, S. K.; Wengel, J. *J. Am. Chem. Soc.* **1988**, *120*, 13252.
4. (a) Summerton, J. *Biochem. Biophys. Acta* **1999**, *1489*, 141; (b) Nasevicius, A.; Ekker, S. C. *Nat. Genet.* **2000**, *26*, 216.
5. (a) De Bont, D. B. A.; Moree, W. J.; Liskamp, R. M. J. *Bioorg. Med. Chem.* **1996**, *4*, 667; (b) De Bont, D. B. A.; Dijkstra, G. D. H.; Den Hartog, J. A. J.; Liskamp, R. M. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3035; (c) De Bont, D. B. A.; Sliedregt-Bol, K. M.; Hofmeyer, L. J. F.; Liskamp, R. M. J. *Bioorg. Med. Chem.* **1999**, *7*, 1043; (d) Monnee, M. C. F.; Marijne, M. F.; Brouwer, A. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **2000**, *41*, 7991; (e) Brouwer, A. J.; Monnee, M. C. F.; Liskamp, R. M. J. *Synthesis* **2000**, 1579; (f) De Jong, R.; Rijkers, D. T. S.; Liskamp, R. M. J. *Helv. Chim. Acta* **2002**, *85*, 4230; (g) Brouwer, A. J.; Liskamp, R. M. J. *J. Org. Chem.* **2004**, *69*, 3662.
6. (a) McElroy, E. B.; Bandaru, R.; Huang, J. X.; Widlanski, T. S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1071; (b) Reynolds, R. C.; Crooks, P. A.; Maddry, J. A.; Akhtar, M. S.; Montgomery, J. A.; Secrist, J. A. *J. Org. Chem.* **1992**, *57*, 2983; (c) Maddry, J. A.; Reynolds, R. C.; Secrist, J. A.; Montgomery, J. A.; Crooks, P. A. U.S. Patent 5561,225.; (d) Musicki, B.; Widlanski, T. S. *Tetrahedron Lett.* **1991**, *32*, 1267; (e) Crooks, P. A.; Reynolds, R. C.; Maddry, J. A.; Rathore, A.; Akhtar, M. S.; Montgomery, J. A.; Secrist, J. A. *J. Org. Chem.* **1992**, *57*, 2830.
7. (a) Fettes, K. J.; Howard, N.; Hickman, D. T.; Adah, S.; Player, M. R.; Torrence, P. F.; Micklefield, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 485; (b) Fettes, K. J.; Howard, N.; Hickman, D. T.; Adah, S. A.; Player, M. R.; Torrence, P. F.; Micklefield, J. *Chem. Commun.* **2000**, 765; (c) Moriou, C.; Thomas, M.; Adeline, M.-T.; Martin, M.-T.; Chiaroni, A.; Pochet, S.; Fourrey, J.-L.; Favre, A.; Clivio, P. *J. Org. Chem.* **2007**, *72*, 43.
8. (a) Poot, A. J.; Van Ameijde, J.; Slijper, M.; Van den Berg, A.; Hilhorst, R.; Ruijtenbeek, R.; Liskamp, R. M. J. *ChemBioChem* **2009**, *10*, 2042; (b) Broom, A. D. *J. Med. Chem.* **1989**, *32*, 2; (c) Radzicka, A.; Wolfenden, T. *Methods Enzymol.* **1995**, *249*, 284; (d) Parang, K.; Cole, P. A. *Pharmacol. Ther.* **2002**, *93*, 145; (e) Ricouart, A.; Gesquiere, J. C.; Tartar, A.; Sergheraert, C. *J. Med. Chem.* **1991**, *34*, 73; (f) Räägel, H.; Lust, M.; Uri, A.; Pooga, M. *FEBS J.* **2008**, *275*, 3608; (g) Enkvist, E.; Raidaru, G.; Vaasa, A.; Pehk, T.; Lavogina, D.; Uri, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5336; (h) Loog, M.; Uri, A.; Raidaru, G.; Järv, J.; Ek, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1447; (i) Hines, A. C.; Cole, P. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2951; (j) Parang, K.; Till, J. H.; Ablooglu, A. J.; Kohanski, R. A.; Hubbard, S. R.; Cole, P. A. *Nat. Struct. Biol.* **2001**, *8*, 37; (k) Hines, A. C.; Parang, K.; Kohanski, R. H.; Hubbard, S. R.; Cole, P. A. *Bioorg. Chem.* **2005**, *33*, 285; (l) Meyer, S. C.; Shomin, C. D.; Gaj, T.; Ghosh, I. *J. Am. Chem. Soc.* **2007**, *129*, 13812; (m) Lee, J. H.; Kumar, S.; Lawrence, D. S. *ChemBioChem* **2008**, *9*, 507; (n) Kumar, A.; Wang, Y.; Lin, X.; Sun, G.; Parang, K. *ChemMedChem* **2007**, *2*, 1346.
9. (a) Kriek, N. M. A. J.; Meeuwenoord, N. J.; Van den Elst, H.; Heus, H. A.; Van der Marel, G. A.; Filippov, D. V. *Org. Biomol. Chem.* **2006**, *4*, 3576; (b) Dreeftromp, C. M.; Van der Marel, J. C. M.; Van den Elst, H.; Van der Marel, G. A.; Van Boom, J. H. *Nucleic Acid Res.* **1992**, *20*, 4015; (c) Filippov, D. V.; Kuyl-Yeheskiely, E.; Van der Marel, G. A.; Tesser, G. I.; Van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 3597; (d) Lee, Y. F.; Nomoto, A.; Detjen, B. M.; Wimmer, E. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 59; (e) Salas, M. *Annu. Rev. Biochem.* **1991**, *160*, 39; (f) Blanco, L.; Lázaro, J. M.; De Vega, M.; Bonnin, A.; Salas, M. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 12198; (g) Wimmer, E. *Cell* **1982**, *28*, 199.
10. (a) Baer, H. H.; Gan, Y. *Carbohydr. Res.* **1991**, *210*, 233; (b) Garcia Fernandez, J. M.; Ortiz Mellet, C.; Jimenez Blanco, J. L.; Fuentes, J. *J. Org. Chem.* **1994**, *59*, 5565; (c) Gruner, S. A. W.; Truffault, V.; Voll, G.; Locardi, E.; Stockle, M.; Kessler, H. *Chem. Eur. J.* **2002**, *8*, 4365; Watterson, M. P.; Pickering, L.; Smith, M. D.; Hudson, S. J.; Marsh, P. R.; Mordaunt, J. E.; Watkin, D. J.; Newman, C. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1999**, *10*, 1855.
11. (a) Liang, C. W.; Kim, M. J.; Jeong, L. S.; Chun, M. W. *Nucleosides Nucleotides Nucleic Acids* **2003**, *22*, 2039; (b) Gao, Z.-G.; Duong, H. T.; Sonina, T.; Kim, S.-K.; Van Rompaey, P.; Van Calenbergh, S.; Mamedova, L.; Kim, H. O.; Myong, J.; Kim, A. Y.; Liang, B. T.; Jeong, L. S.; Jacobson, K. A. *J. Med. Chem.* **2006**, *49*, 2689; (c) Radatus, B. K.; Murthy, K. S. K.; Weeratunga, G.; Horne, S. E.; Kothakonda, K. K.; Wolf, E. C. G.; Wang, Z. U.S. Patent, US2,008,009,639.; (d) Van Rompaey, P.; Jacobsen, K. A.; Gross, A. S.; Gao, Z.-G.; Van Calenbergh, S. *Bioorg. Med. Chem.* **2005**, *13*, 973; (e) Elliot, R. P.; Fleet, G. W. J.; Vogt, K.; Wilson, F. X.; Wang, Y.; Witty, D. R.; Storer, R.; Myers, P. L.; Wallis, C. J. *Tetrahedron: Asymmetry* **1990**, *1*, 715; (f) Yamashita, M.; Kawai, Y.; Uchida, I.; Komori, T.; Kohosaka, M.; Imanaka, H.; Sakane, K.; Setoi, H.; Teraji, T. *J. Antibiot.* **1984**, *37*, 1284.
12. Carretero, J. C.; Demillequand, M.; Ghosez, L. *Tetrahedron* **1987**, *43*, 5125.

13. (a) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234; (b) Vorbrüggen, H.; Höfke, G. *Chem. Ber.* **1981**, *114*, 1256; (c) Vorbrüggen, H.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1279.
14. Bullock, M. W.; Hand, J. J.; Stokstad, E. L. R. *J. Org. Chem.* **1957**, *22*, 568.
15. Taylor, E. C.; Kuhnt, D.; Chang, Z. Y. *J. Org. Chem.* **1991**, *56*, 6937.
16. Lagoja, I. M.; Pochet, S.; Boudou, V.; Little, R.; Lescrinier, E.; Rozenski, J.; Herdewijn, P. *J. Org. Chem.* **2003**, *68*, 1867.