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Efficient diastereoselective synthesis of a new class of azanucleosides: 2′-homoazanucleosides

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ABSTRACT

Azanucleosides, sugar-modified nucleoside analogues containing a 4′ nitrogen atom, have shown a lot of therapeutic potential, e.g. as anti-cancer and antiviral agents. We report the synthesis of a series of 2′-homoazanucleosides, in which the nucleobase is attached to the 2′-position of the pyrrolidine ring via a methylene linker. A suitable orthogonally protected iminosugar was synthesized by ring closing metathesis and dihydroxylation as key steps and further converted to a series of 8 nucleoside analogues through Mitsunobu reaction with suitably protected nucleobases. The 5′ position of the adenine analogue was then further derivatized with thiols to afford 2 additional compounds. The final compounds were evaluated for biological activity.

1. Introduction

Azanucleosides, a class of sugar-modified nucleoside analogues in which the 4′-oxygen of the ribose is replaced by a nitrogen atom, have recently attracted considerable attention.[1,2] The Immucillins, a series of aza-sugar-*C*-nucleosides, show potential for the treatment of leukemia, auto-immune disorders, bacterial infections, etc.[3] The pyrrolidine nitrogen atom allows these nucleosides to function as transition state analogue inhibitors of several nucleoside-processing enzymes such as human purine nucleoside phosphorylase (PNP),[4] 5′-methylthioadenosine nucleosidase (MTAN) & 5′-methylthioadenosine phosphorylase (MTAP).[5] Due to the diverse essential functions of these enzymes among several organisms and species, inhibitors may exhibit various biological activities. The most notable are inhibition of quorum sensing (through MTAN) and anticancer activity (through MTAP and PNP).[4,6,7] Other noteworthy effects include antiparasitic and antibacterial activity.[8–10] Immucillin A (**1**), also shows broad-spectrum antiviral activity (Fig. 1). It is an RNA polymerase inhibitor and functions as a non-obligate chain terminator. It is currently in clinical trials for the treatment of Ebola virus infection under the name galidesivir®.[11–13]

The synthesis of azanucleosides is not trivial. The core iminosugar often requires a long multi-step synthesis, and attachment of the nucleobase poses a second challenge, due to the unstable hemiaminal linkage that would hydrolyze spontaneously upon contact with water. Several strategies have been investigated to overcome this liability. Apart from synthesizing C-nucleosides, where most of the research has been focusing on, enhanced stability can also be obtained by substituting the nitrogen. Chiacchio et al., for example, reported an N-Boc-protected 3′-deoxyazaribonucleoside that displays highly potent anti-HCV activity in a replicon assay.[14] A third strategy is the synthesis of *N*-homoazanucleosides, in which a methylene linker is inserted between the carbohydrate mimic and the base. Although this formal insertion of a CH_2 unit in the glycosidic bond lengthens the separation between the base and the pyrrolidine ring relative to that in the natural substrate, this bond is likewise elongated in transition states. 1′-homoaza-adenosine **3** is an inhibitor of protozoan nucleoside hydrolases, although less potent than the corresponding C-nucleoside.[15,16] Furthermore, several second-generation Immucillins, for example the femtomolar MTAP/MTAN inhibitor **2**, also possess an extra methylene linker between the pyrrolidine and the surrogate nucleobase.[17–19] In addition, homonucleosides are resistant towards nucleases, may still be phosphorylated by cellular enzymes and are able to pair with natural nucleosides through Watson-Crick interactions.[20] 1′-Homonucleosides were recently reviewed by Wróblewski et al.[21]

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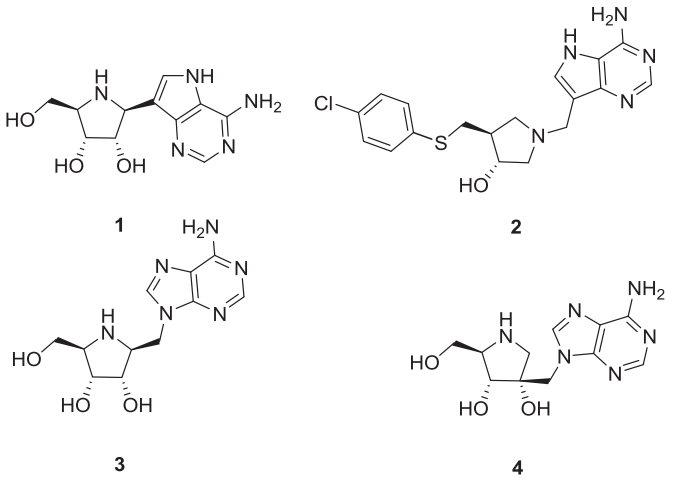


Fig. 1. Immucillin A (**1**), DADMe-Immucillin A (**2**), 1′-*N*-homoazanucleoside (**3**), 2′-*N*-homoazanucleoside (**4**).

In this work we report the synthesis of a series of 2'-homo-azanucleosides, regioisomers of the 1'-homoazanucleosides (e.g. **3**), in which the nucleobase is attached to the 2'-position of the pyrrolidine ring via a methylene linker. This transposition of the nucleobase affords analogues with the same number of bonds between the nucleobase and carbons 2′, 3′ and 4′ of the pyrrolidine ring as in the natural nucleosides and therefore might more closely mimic the spatial arrangements of natural nucleosides. A series of 2'-homo-azanucleosides was synthesized containing the natural and some closely related nucleobases, as well as two 5'-thio analogues, inspired by the potent methylthioadenosine-mimicking aza-C-nucleosides (e.g. **2**).

2. Results and discussion

2.1. Scaffold synthesis

We envisioned a convergent synthetic approach wherein the protected polyhydroxylated pyrrolidine scaffold is synthesized first, subsequently coupled with a variety of nucleobases. The desired 2′-*C*-hydroxymethyl iminosugar has, contrary to several of its stereoisomers,[22] not been reported yet. Its retrosynthesis comprises ring-closing metathesis and subsequent dihyroxylation as key steps (Fig. 2), based on the observation that this strategy has already been successfully applied in the synthesis of a number of analogous iminosugars.[23]

Several syntheses for the vinylglycinol precursor of **10** have been reported,[24,25] but we opted for the method of Van den Nieuwendijk et al. using an Ellman tert-butylsulfinamide because of its 100% enantiopurity.[26,27] *Rac*-Solketal **12** was first protected as benzyl ether, after which the isopropylidene acetal was hydrolyzed (Scheme 1). Oxidative cleavage of the resulting diol and condensation with (S)-*tert*-butanesulfinamide led to sulfinimine **14**. Addition of vinylmagnesium bromide resulted in a mixture of diastereoisomers in a 9:1 ratio in favor of the desired diastereoisomer **15,** as determined by 1H NMR. We found that the addition of hazardous $AlMe_3$, as described by Van den Nieuwendijk et al., could be omitted without a significant drop in diastereoselectivity. The two diastereoisomers could be separated by column chromatography, affording enantiopure **15**. Removal of the sulfinamine chiral auxiliary with HCl in MeOH and subsequent Boc-protection of the resulting amine furnished **10** in 45% yield over 6 steps.

The second building block was synthesized from commercially available 2-methylene-1,3-propanediol **17** (Scheme 2). Selective monoprotection as TBS-ether and subsequent iodination yielded **11**, which required purification prior to use in the alkylation reaction with **10** in order to get reproducible results.

Carbamate **10** was alkylated with 1.1 eq. of iodide **11** using sodium hydride as base (Scheme 3). Product **19** was then cyclized by ring closing metathesis, which proceeded smoothly with only 1.5 mol% Grubbs II catalyst. Ring-closed product **20** was then dihydroxylated with OsO_4 to yield diastereomerically pure **21**. The stereocenter already present apparently provides enough stereoinduction to have dihydroxylation selectively on the opposite face, rendering the reaction stereospecific. The stereochemistry was proven by X-ray analysis of compound **21** (see Supporting Information), which shows the product to be the expected diastereoisomer (Fig. 3). Isopropylidene protection of **21** was first tried with 2,2-dimethoxypropane and catalytic TsOH, but resulted in significant amounts of TBS-deprotected compound. This could be

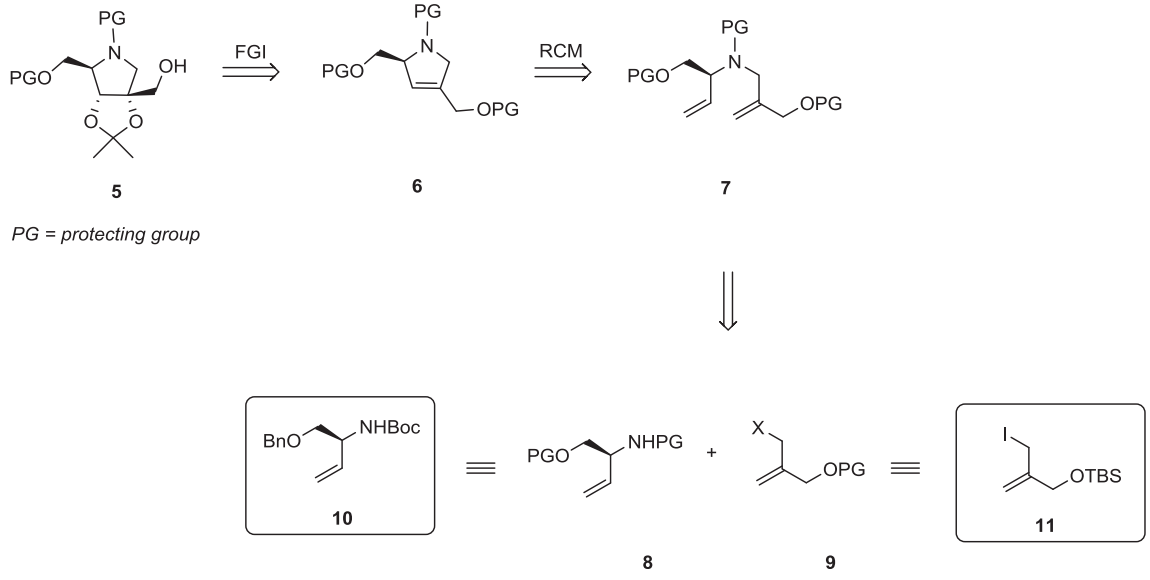
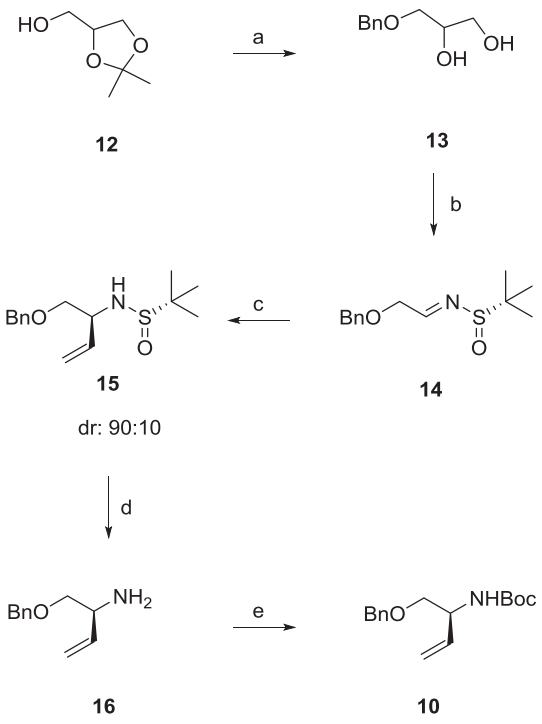
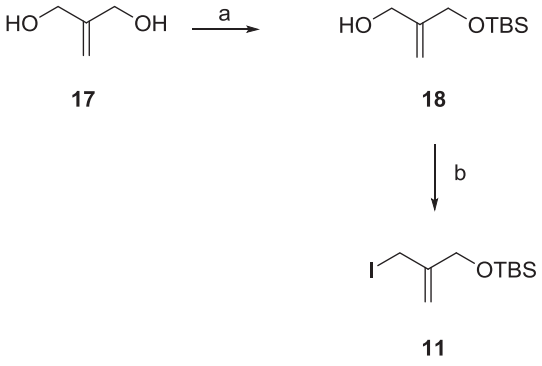


Fig. 2. Retrosynthesis of the 2′-*N*-homoazanucleoside scaffold. (FGI = functional group interconversion, RCM = ring closing metathesis).



Scheme 1. Synthesis of *(S)*-*O*-benzyl-*N*-Boc-vinylglycinol **10**. Reagents and conditions: a) (i) BnBr, NaH, THF/DMF, 0 °C to rt, 3 h; (ii) AcOH/H_2O, rt, 24 h, 97% (2 steps); b) (i) $NaIO_4$, CH_2Cl_2/H_2O, 0 °C, 6 h; (ii) (*S*)-*tert*-butylsulfinamide, $CuSO_4$, CH_2Cl_2, rt, overnight, 77% (2 steps); c) vinylMgBr, toluene, −78 °C, 3 h, 71%; d) (i) HCl, MeOH, rt, 1.5 h; (ii) aq. NaOH, rt, 94% (2 steps); e) Boc_2O, Et_3N, CH_2Cl_2, rt, 4 h, 90%.



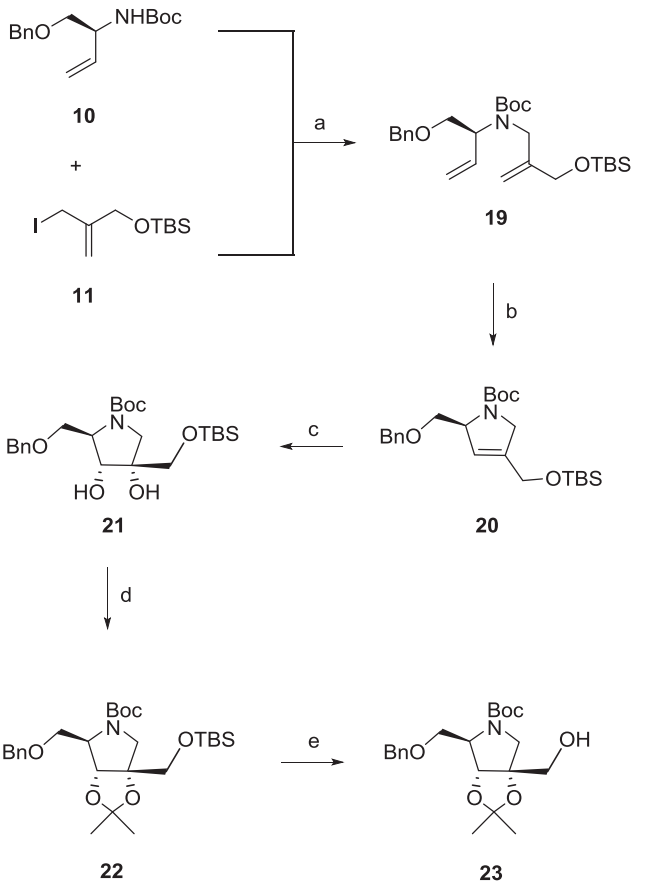
Scheme 2. Synthesis of 1-iodo-2-methylenepropanol **11**. a) TBS-Cl, NaH, THF, rt, 2 h, 85%; b) I_2, imidazole, PPh_3, Et_2O/MeCN, rt, 30 min, 48%.

circumvented by using 2-methoxypropene and 2 mol% camphersulphonic acid (CSA), affording **22** in almost quantitative yield. Final TBS-deprotection with TBAF provided the orthogonally protected central scaffold **23** in 43% yield over 5 steps from **10**.

2.2. Nucleobase coupling and deprotection

Introduction of the desired nucleobase in **23** was accomplished by a Mitsunobu reaction. Two possible issues (i.e. the solubility of the nucleobases in organic solvents and the alkylation site selectivity) were avoided by prior protection of the nucleobases.[28]

We chose protecting groups that are cleavable under the same conditions as the protecting groups on the pyrrolidine scaffold. Adenine was protected as its N-6-Boc_2 derivative, and almost exclusively yielded the desired coupling product **24** (Scheme 4).[29]



Scheme 3. Synthesis of protected iminosugar scaffold **23**. Reagents and conditions: a) NaH, DMF, rt, 1 h, rt, 80%; b) 1.5 mol% Grubbs II, DCE, 50 °C, 4 h; c) OsO_4, NMO, acetone/H_2O, rt, overnight, 92%; d) 2-methoxypropene, CSA (cat.), THF, rt, 24 h, 98%; e) TBAF, THF, rt, 1 h, 98%.

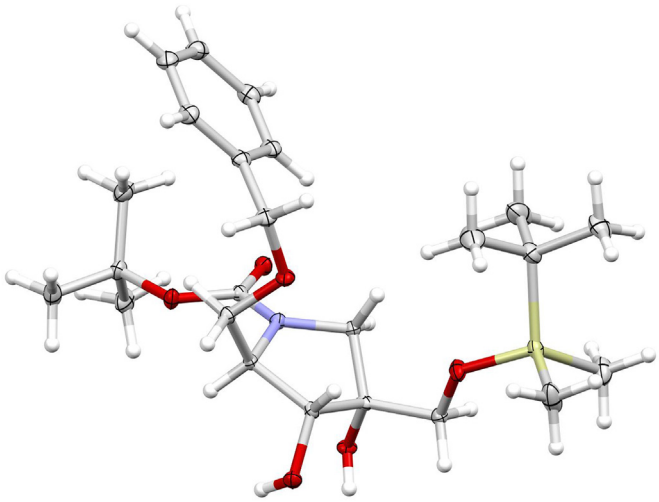
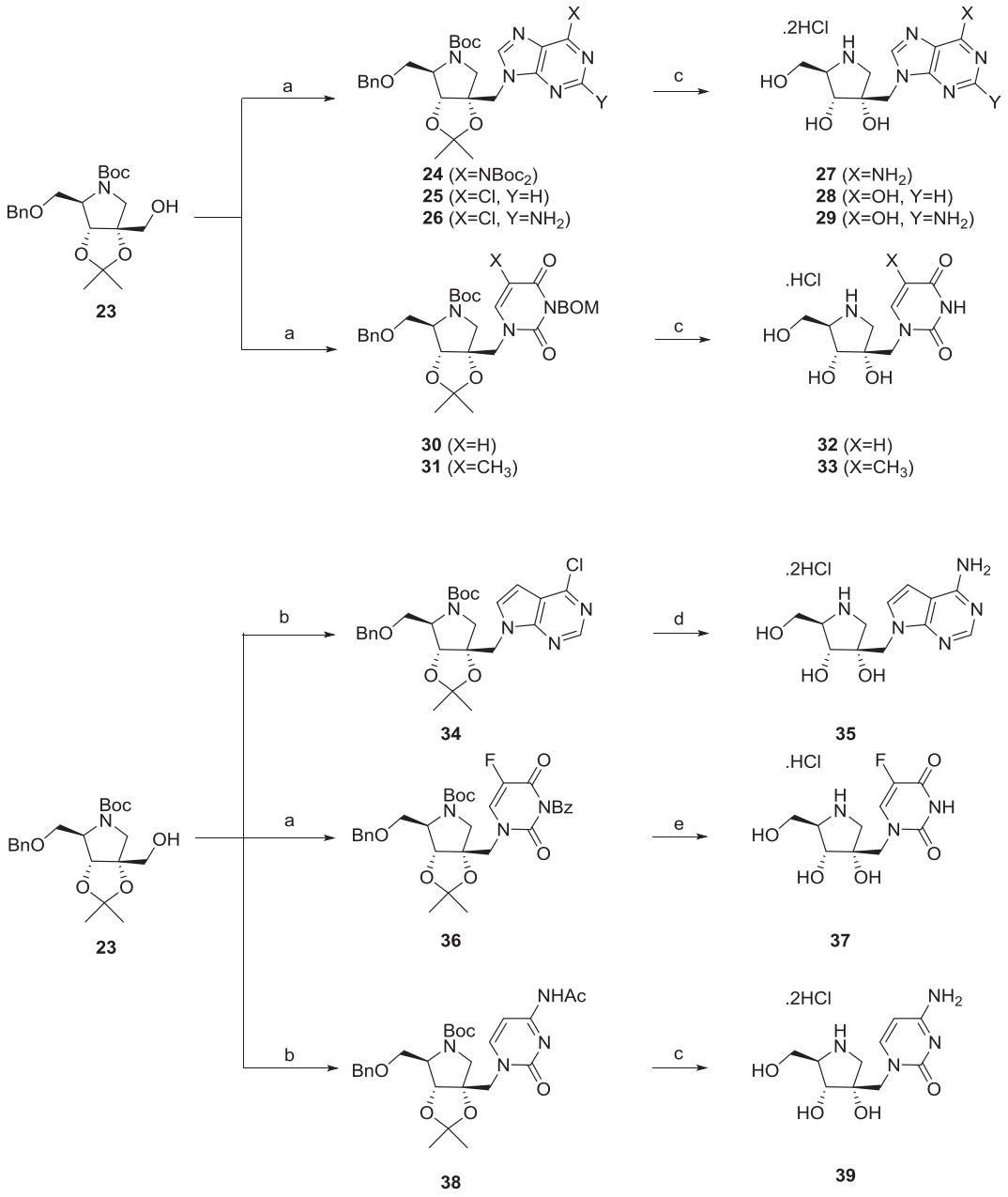


Fig. 3. Molecular X-ray structure of **21**, showing thermal displacement ellipsoids at the 50% probability level.

N-3-BOM-protected uracil and thymine readily afforded **30** and **31**.[30] We first tried to deprotect the resulting nucleosides in 2 steps using hydrogenolysis with Pd/C and subsequent acidic hydrolysis. However, hydrogenolysis proved to be difficult and afforded only small amounts of debenzylated product, presumably due to the



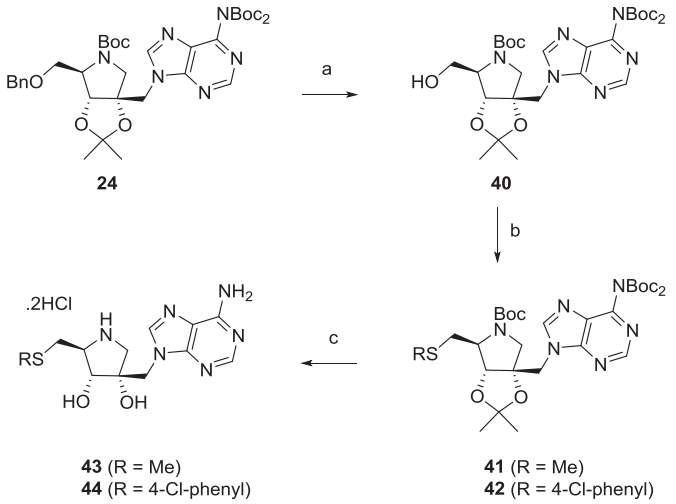
Scheme 4. Nucleobase alkylation and deprotection. Reagents and conditions: a) protected nucleobase, PPh_3, DIAD, THF, dioxane or acetonitrile, 0 °C to rt, overnight; b) i) Ms-Cl, Et_3N, CH_2Cl_2, 2 h, 0 °C to rt; ii) protected nucleobase, K_2CO_3, 18-crown-6, DMF, Δ, overnight; c) i) BCl_3, CH_2Cl_2, -78 °C, 2 h; ii) MeOH, 5 min, −78 °C to rt; iii) HCl, H_2O; d) i) NaN_3, DMF, 60 °C, overnight; ii) $Pd(OH)_2$, H_2, EtOH, rt, 24 h, 74%; iii) conc. HCl, THF/H_2O, reflux, 1 h; e) i) 7 N NH_3 in MeOH, MeOH, rt, overnight, 98%; ii) BCl_3, CH_2Cl_2, -78 °C, 2 h, 53%; iii) HCl, H_2O.

coordinating effects of the different nitrogen atoms of the nucleobase to the palladium.[31] Fortunately, deprotection with the Lewis acid BCl_3, provided the completely deprotected nucleosides in one step.[32] Purification by column chromatography and acidification yielded the desired nucleoside analogues as their HCl salts.

The guanine and hypoxanthine analogues **28** and **29** were synthesized from the corresponding 6-chloropurines. The chloride was substituted for a hydroxy function during the BCl_3-mediated deprotection, by dropwise quenching with MeOH at low temperature. Substitution can be avoided by adding Et_3N prior to quenching with MeOH.[33]

Mitsunobu reaction of **23** with 7-deaza-6-chloropurine to synthesize **34** was not possible due to the less acidic pyrrole NH. Hence, **23** was first mesylated and then substituted in a classical S_N2 fashion, to afford **34**. The chloride was then substituted with NaN_3. Reduction of the azide and simultaneous removal of the 5′-O-benzyl with $Pd(OH)_2$ and H_2, followed by acidic hydrolysis of the remaining protecting groups afforded 7-deazadenine analogue **35**. 5-Fluorouracil was introduced as its N-3-benzoyl protected derivative.[34] Deprotection of **36** was realized in 2 steps: first basic removal of the benzoyl group, then treatment with BCl_3. Lastly, substitution of the mesylate of **23** with N-4-acetylcytosine, afforded an acceptable amount of N-1-alkylated **38**.

The regiochemistry of the nucleobase alkylation reactions was verified on the final compounds via NMR data, which were in agreement with those found in literature.[20,35–37] The deprotected compounds were purified by column chromatography and converted to the corresponding mono- or bis-HCl salts.[38]



Scheme 5. 5'-derivatization of **24**. Reagents and conditions: a) $Pd(OH)_2$, H_2, MeOH, 40 °C, overnight, 56%; b) Ms-Cl, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h; c) 4-chloro-thiophenol, NaH, DMF, 50 °C, 4 h, 97% or NaSMe, DMSO, 50 °C, overnight; d) i) BCl_3, CH_2Cl_2, -78 °C, 2 h, ii) HCl, H_2O.

2.3. 5'-derivatization

$Pd(OH)_2$-catalyzed hydrogenolysis of **24** yielded alcohol **40**, which was then converted to the mesylate and subsequently substituted with sodium thiomethoxide or 4-chlorothiophenol to yield **41** and **42,** respectively (Scheme 5). Deprotection with BCl_3 and HCl-salt formation yielded **43** and **44**.

2.4. Biological evaluation

The synthesized nucleosides were screened against a panel of viruses (HSV-1, HSV-2, Vaccinia virus, Adenovirus-2, Human Coronavirus) and microorganisms (*Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, *Trypanosoma brucei*) in cell cultures, but no activity was found in concentrations up to 64 μM. The effect on signaling molecule (AI-2, AHL/CAI-1) production in *Vibrio harveyi* was also investigated, but no activity was found in concentrations up to 100 μM.

3. Conclusions

A convenient synthetic approach was developed to prepare a series of 2'-homoazanucleosides. The unprecedented orthogonally protected iminosugar scaffold was synthesized first, involving a ring closing metathesis and dihyroxylation as key steps. All steps proceeded in high yield, highlighting the practical use of this synthesis. From this scaffold a series of 9 nucleoside analogues with different nucleobases, as well as two 5'-thio modified adenine analogues was synthesized. The nucleoside analogues were evaluated broadly for antiviral, antibacterial, and antiprotozoal activity, but failed to show activity.

4. Experimental section

4.1. General

All reactions described were performed under argon atmosphere and at ambient temperature unless stated otherwise. All reagents and solvents were purchased from Sigma–Aldrich (Diegem, Belgium), Acros Organics (Geel Belgium), TCI Europe (Zwijndrecht, Belgium) or Carbosynth Ltd (Compton Berkshire, United Kingdom) and used as received. NMR solvents were purchased from Eurisotop (Saint-Aubin, France). Reactions were monitored by TLC analysis using TLC aluminium sheets (Macherey–Nagel, Alugram Sil G/UV254) with detection by UV or by spraying with a solution of $(NH_4)_6Mo_7O_{24} \times 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4 \times 2H_2O$ (10 g/L) in H_2SO_4 (10%) followed by charring or an aqueous solution of $KMnO_7$ (20 g/L) and K_2CO_3 (10 g/L) followed by charring. Silica gel column chromatography was performed manually using Grace Davisil 60 Å silica gel (40–63 lm) or automated using a Grace Reveleris X2 system and the corresponding flash cartridges. High resolution spectra were recorded with a Waters LCT Premier XE Mass spectrometer. ^1H and ^{13}C NMR spectra were recorded with a Varian Mercury-300BB (300/75 MHz) spectrometer. Chemical shifts are given in ppm (d) relative to tetramethylsilane as an internal standard (^1H NMR) or the NMR solvent (^{13}C NMR). In ^{19}F NMR, signals have been referred to $CDCl_3$ or DMSO-d_6 lock resonance frequency according to IUPAC referencing with $CFCl_3$ set to 0 ppm. Coupling constants are given in Hz. The correct regiochemistry of the nucleobase alkylation reactions was verified via HMBC NMR experiments of the final compounds. Optical rotations were recorded on a PerkinElmer 241 polarimeter, using a sodium-vapor lamp (D-line; $\lambda = 589.3$ nm).

4.2. Synthesis

4.2.1. General procedure 1: mitsunobu reaction

Diisopropylazodicarboxylate (2.3 eq.) was added dropwise to a solution of triphenylphosphine (2.3 eq.) in THF, dioxane or acetonitrile (indicated in individual procedures) at 0 °C. After 15 min, alcohol **23** was added and the reaction was allowed to warm to room temperature. The appropriate protected nucleobase was added and the reaction mixture stirred overnight. When TLC indicated the disappearance of the starting material, the mixture was concentrated *in vacuo*, absorbed onto celite® and purified by flash column chromatography to afford the protected nucleoside analogue.

4.2.2. General procedure 2: BCl_3-mediated deprotection

BCl_3 (1.0 M in CH_2Cl_2, 10 eq.) was added to a solution of protected nucleoside (0.1 M) in CH_2Cl_2 at −78 °C. When TLC analysis indicated disappearance of the starting material and the presence of a single lower-running spot, MeOH (5 mL) was added dropwise and the mixture warmed to room temperature. Then it was concentrated *in vacuo* and co-evaporated with MeOH 3 times. The residue was dissolved in MeOH, absorbed onto celite® and purified by flash column chromatography ($MeOH/NH_4OH/CH_2Cl_2$ 20:1:79 and then 45:5:50).

4.2.3. General procedure 3: HCl-salt formation

The purified compound was dried under high vacuum overnight, and dissolved in MeOH (10 mL). Concentrated HCl (0.5 mL) was added, and the mixture concentrated *in vacuo*. The residue was dissolved in 10 mL H_2O, transferred to a separation funnel, and washed with 2×5 mL $CHCl_3$. The water phase was then lyophilized overnight to afford the final nucleoside as its HCl salt.

4.2.4. 3-(benzyloxy)propane-1,2-diol (***13***)

Sodium hydride (60% wt. in mineral oil, 15.4 g, 117 mmol, 1.3 eq.) was added portionwise to a solution of *rac*-solketal in a mixture of DMF (50 mL) and THF (150 mL) at 0 °C. When gas evolution had ceased, benzyl bromide (23.9 g, 140 mmol, 1.2 eq.) was added dropwise. After 3 h, TLC analysis (Hexanes/EtOAc 1:1) indicated disappearance of the starting material. 150 mL water was added and the mixture was extracted with 3×200 mL Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4

and concentrated *in vacuo*. The residue was dissolved in AcOH/H_2O 4:1 and stirred 24 h at room temperature. The mixture was concentrated *in vacuo*, and purified by flash column chromatography (hexanes/EtOAc, 7:3 and 0:10). The product was obtained as a transparent oil in 97% yield (2 steps). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.30–3.42 (3 H, m), 3.47 (1 H, s), 3.64 (1 H, dt, J = 16.1, 5.6 Hz), 4.49 (2 H, s), 4.52 (1 H, t, J = 5.9 Hz), 4.69 (1 H, d, J = 5.0 Hz), 7.21–7.42 (5 H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 62.9, 70.3, 71.7, 72.0, 127.0, 127.1, 127.9, 138.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{10}H_{15}O_3^+$: 183.10212; found 183.10184.

4.2.5. (S,E)-N-(2-(benzyloxy)ethylidene)-2-methylpropane-2-sulfinamide (**14**)

3-(benzyloxy)propane-1,2-diol **13** (8.70 g, 47.7 mmol) was dissolved in CH_2Cl_2 (90 mL) and cooled to 0 °C. A solution of $NaIO_4$ (15.3 g, 71.6 mmol, 1.5 eq.) in H_2O (90 mL) was added and the reaction mixture was stirred for 6 h. The mixture was then transferred to a separation funnel and extracted with 3 × 150 mL CH_2Cl_2. The organic phases were dried over Na_2SO_4 and concentrated *in vacuo* under medium pressure at 35 °C. The residue was dissolved in CH_2Cl_2 after which anhydrous $CuSO_4$ (15.2 g, 95.4 mmol, 2.0 eq.) was added, followed by (*S*)-2-methyl-2-propane-sulfinamide (6.94 g, 57.3 mmol, 1.2 eq). The reaction mixture was stirred overnight, filtered over celite® and concentrated *in vacuo*. The residue was purified by flash column chromatography (Hexanes/EtOAc 9:1 to 7:3) to afford **14** as a yellow oil in 77% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.13 (9 H, s), 4.32 (2 H, dd, J = 3.4, 1.0 Hz), 4.55 (2 H, s), 7.26–7.38 (5 H, m), 8.05 (1H, t, J = 3.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 22.4, 56.9, 71.2, 73.3, 127.8, 128.0, 128.5, 137.2, 166.7. HRMS (ESI-TOF) *m/z*: [M+H]+ Calculated for $C_{13}H_{20}O_2S$+: 254.12148; found 254.1209.

4.2.6. (S)-N-((S)-1-(benzyloxy)but-3-en-2-yl)-2-methylpropane-2-sulfinamide (**15**)

Compound **14** (9.28 g, 36.6 mmol, 1.0 eq.) was dissolved in dry toluene and cooled to −78 °C. Vinylmagnesium bromide (1.0 M in THF, 54.9 mL, 54.9 mmol, 1.5 eq.) was added dropwise (0.5 mL/min). After 3 h, 7 mL of a saturated solution of Na_2SO_4 in H_2O was added slowly and the mixture was warmed to room temperature. The mixture was further dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified twice by column chromatography (5–25% EtOAc in hexanes) to afford diastereomerically pure **15** as a yellow oil in 71% yield.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.07–1.20 (9 H, m), 3.46 (1 H, dd, J = 9.7, 6.4 Hz), 3.50 (1 H, dd, J = 9.7, 6.4 Hz), 3.79–3.97 (1 H, m), 4.51 (2 H, s), 4.92 (1 H, d, J = 6.2 Hz), 5.14 (2 H, dt, J = 10.5, 1.2 Hz), 5.28 (2 H, dt, J = 17.3, 1.8 Hz), 5.78 (1 H, ddd, J = 17.0, 10.5, 7.0 Hz), 7.24–7.46 (5 H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 22.4, 55.0, 57.1, 72.0, 72.5, 116.9, 127.4, 127.5, 128.2, 137.2, 138.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{15}H_{24}O_2S^+$: 282.15278; found 282.1521.

4.2.7. (S)-1-(benzyloxy)but-3-en-2-amine (**16**)

10 mL concentrated HCl was added to a solution of **15** (18.7 g, 66.4 mmol) in MeOH at room temperature. After 90 min, TLC analysis indicated completion of the reaction and the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (Hexanes/EtOAc 1:1 to remove a higher-running impurity and then CH_2Cl_2/MeOH 9:1 to elute the title compound as its HCl salt). The purified HCl salt was then dissolved in 200 mL 0.5 M NaOH solution and extracted with 3 × 100 mL CH_2Cl_2. The organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a yellow oil in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.48 (2 H, br. s), 3.31 (1 H, dd, J = 9.1, 7.9 Hz), 3.51 (1 H, dd, J = 9.1, 4.1 Hz), 3.63 (1 H, br. s.), 4.56 (2 H, s), 5.11 (1 H, dt, J = 10.4, 1.2 Hz), 5.24 (1 H, dt, J = 17.3, 1.5 Hz), 5.84 (1 H, ddd, J = 17.1, 10.6, 6.0 Hz), 7.24–7.43 (5 H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 53.8, 73.3, 75.1, 115.2, 127.7, 128.4, 137.9138.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{11}H_{16}NO^+$: 178.12319; found 178.1211.

4.2.8. tert-butyl (S)-(1-(benzyloxy)but-3-en-2-yl)carbamate (**10**)

Et_3N (6.01 mL, 43.1 mmol, 2.0 eq.) and Boc_2O (6.44 mL, 28.0 mmol, 1.5 eq.) were added to a solution of **16** (3.82 g, 21.6 mmol) in CH_2Cl_2 (150 mL) at room temperature. After 4 h of stirring, the mixture was transferred to a separation funnel. 70 mL saturated NH_4Cl solution was added and the mixture was extracted with 3 × 100 mL CH_2Cl_2. The organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (Hexanes/Et_2O 9:1) to afford **10** as a colourless oil in 90% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.36–1.44 (9 H, m), 3.46 (2 H, d, J = 6.4 Hz), 4.13–4.28 (1 H, m), 4.50 (2 H, s), 5.09 (1 H, dt, J = 10.5, 1.5 Hz), 5.18 (1 H, dt, J = 17.6, 1.8 Hz), 5.74–5.91 (1 H, m), 6.48 (1 H, d, J = 7.6 Hz), 7.19–7.42 (5 H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 27.8, 52.1, 71.5, 71.7, 77.4, 114.7, 126.8, 126.9, 127.6, 136.6, 138.1, 154.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{16}H_{24}NO_3^+$: 278.17517; found 278.1750.

4.2.9. 2-(((tert-butyldimethylsilyl)oxy)methyl)prop-2-en-1-ol (**18**)

Sodium hydride (60% wt. in mineral oil, 0.800 g, 20.0 mmol, 1.0 eq.) was dispersed in dry THF (70 mL). 2-methylene-1,3-propanediol (1.67 mL, 20.0 mmol, 1.0 eq.) in dry THF (10 mL) was added dropwise. A precipitate was formed. After 45 min, TBS-Cl (3.01 g, 20.0 mmol, 1.0 eq.) was added. After 2 h of stirring, 100 mL H_2O was added and the mixture was extracted with 3 × 100 mL EtOAc. The combined organic fractions were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (0–15% EtOAc in hexanes) yielded **18** as a colourless oil in 85%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.05–0.12 (6 H, m), 0.87–0.96 (9 H, m), 2.08 (1 H, br. s.), 4.17 (2 H, s), 4.21–4.27 (2 H, m), 5.05–5.15 (2 H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm −5.5, 18.3, 25.6, 25.8, 64.6, 65.1, 111.1, 147.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{11}H_{16}NO^+$: 203.14629; found 203.1462.

4.2.10. tert-butyl((2-(iodomethyl)allyl)oxy)dimethylsilane (**11**)

Compound **18** (3.456 g, 17.08 mmol) was dissolved in Et_2O/MeCN 4:1 (200 mL). PPh_3 (6.27 g, 23.9 mmol, 1.4 eq.), and imidazole (1.63 g, 23.9 mmol, 1.4 eq.) were added, followed by I_2 (6.07 g, 23.9 mmol, 1.4 eq.). A white precipitate started to form. After 30 min, TLC analysis indicated completion of the reaction, and 100 mL 2 M $Na_2S_2O_3$ solution was added. The mixture was extracted 3 times with 100 mL Et_2O, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (100% hexanes and 10% EtOAc in hexanes) to afford **11** as an orange oil in 48% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.07–0.16 (6 H, m), 0.93 (9 H, s), 3.96 (2 H, s), 4.31 (2 H, s), 5.20 (1 H, d, J = 1.5 Hz), 5.32 (1 H, d, J = 0.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm −5.4, 5.7, 18.3, 25.9, 63.9, 113.3, 145.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{10}H_{22}IOSi^+$: 313.04791; found 313.0478.

4.2.11. tert-butyl (S)-(1-(benzyloxy)but-3-en-2-yl)(2-(((tert-butyldimethylsilyl)oxy)methyl)allyl)carbamate (**19**)

NaH (60% in mineral oil, 0.309 g, 7.74 mmol, 1.3 eq.) was added to an ice-cold solution of compound **10** (1.65 g, 5.95 mmol) in DMF (25 mL). After 30 min, a solution of compound **11** (2.60 g, 8.33 mmol, 1.4 eq.) in DMF (5 mL) was added and the mixture warmed to room temperature. After 1 h, TLC analysis (Hexanes/EtOAc 8:2) indicated completion of the reaction. 50 mL water was

added and the mixture was extracted with 3 × 50 mL Et_2O. The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (0–10% Et_2O in hexanes). The product was retrieved in 80% yield as a colourless oil. ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C) δ ppm 0.05 (6 H, s), 0.89 (9 H, s), 1.39 (9 H, s), 3.65 (2 H, ddd, J = 29.9, 9.7, 7.0 Hz), 3.79 (2 H, dd, J = 16.7, 6.7 Hz), 4.08 (2 H, s), 4.41 (1 H, d, J = 6.7 Hz), 4.48 (2 H, dd, J = 11.7, 3.5 Hz), 4.99 (2 H, s), 5.11–5.19 (2 H, m), 5.82–6.00 (1 H, m), 7.22–7.42 (5 H, m). ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ ppm −5.9, 17.5, 25.3, 27.6, 47.2, 58.2, 63.5, 70.0, 71.7, 78.6, 108.9, 116.4, 126.8, 127.6, 134.8, 137.9, 145.4, 154.3. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{26}H_{44}NO_4Si^+$: 462.30342; found 462.3055.

4.2.12. tert-butyl (S)-2-((benzyloxy)methyl)-4-(((tert-butyldimethylsilyl)oxy)methyl)-2,5-dihydro-1H-pyrrole-1-carboxylate (**20**)

Compound **19** (6.60 g, 14.3 mmol) was dissolved in dry degassed 1,2-dichloroethane (10 mL). The reaction was warmed to 50 °C and Grubbs II catalyst (0.121 g, 0.143 mmol, 1 mol%) in 2 mL DCE was added. After 1 h of stirring, a second portion of Grubbs II catalyst (0.060 g, 0.071 mmol, 0.5 mol%) in 2 mL DCE was added. After 3 more hours, TLC analysis indicated that most of the starting material reacted and further progression of the reaction had ceased. The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (0–10% Et_2O in hexanes). The obtained material was not pure enough for NMR analysis and was used as such in the next reaction. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{24}H_{40}NO_4Si^+$: 434,27012; found 434.2725.

4.2.13. tert-butyl (2R,3R,4R)-2-((benzyloxy)methyl)-4-(((tert-butyldimethylsilyl)oxy)methyl)-3,4-dihydroxypyrrolidine-1-carboxylate (**21**)

To a stirred solution of **20** (4.70 g, 10.8 mmol, 1.0 eq.) in acetone/water (3:1, 100 mL was added $K_2OsO_4 \cdot 2H_2O$ (0.041 g, 0.11 mmol, 0.01 eq.), followed by NMO monohydrate (2.13 g, 15.7 mmol, 1.5 eq.). The mixture was stirred overnight, after which Na_2SO_3 (3.96 g, 31.4 mmol, 3.0 eq.) was added and the mixture stirred for another hour. The mixture was concentrated *in vacuo* to remove the acetone, diluted with water (50 mL) and extracted with 3 × 100 mL EtOAc. The organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (0–40% EtOAc in hexanes) to afford **21** in 70% yield as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C). δ ppm 0.05 (6 H, s), 0.87 (9 H, s), 1.39 (9 H, s), 3.24 (1 H, d, J = 12.3 Hz), 3.40 (1 H, d, J = 11.4 Hz), 3.43–3.57 (3 H, m), 3.65 (1 H, dd, J = 10.0, 1.8 Hz), 3.90 (1 H, dd, J = 9.8, 4.0 Hz), 4.20 (2 H, br. s.), 4.50 (2 H, s), 4.68 (1 H, br. s.), 7.17–7.39 (5 H, m). ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C). δ ppm −6.0, 17.4, 25.3, 27.8, 52.9, 61.9, 63.0, 67.6, 71.1, 72.2, 76.0, 77.9, 126.6, 126.7, 127.6, 138.3, 153.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{24}H_{40}NO_4Si^+$: 468.27759; found 468.2796.

4.2.14. tert-butyl (2R,3R,4R)-2-((benzyloxy)methyl)-4-(((tert-butyldimethylsilyl)oxy)methyl)-3,4-isopropylidene-pyrrolidine-1-carboxylate (**22**)

Camphersulphonic acid (0.029 g, 0.125 mmol, 0.02 eq.) was added to a solution of **21** (2.94 g, 6.28 mmol, 1.0 eq.) in THF (180 mL). 2-methoxypropene (5.80 mL, 62.8 mmol, 10.0 eq.) was added and the mixture was stirred for 24 h 200 μL Et_3N was added and the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (0–20% EtOAc in hexanes) to afford **22** as a colourless oil in 98% yield. ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C) δ ppm 0.04 (6 H, s), 0.88 (9 H, s), 1.33 (3 H, s), 1.34 (3 H, s), 1.39 (9 H, s), 3.31 (1 H, d, J = 12.3 Hz), 3.46–3.61 (3 H, m), 3.70 (2 H, s), 4.04 (1 H, dd, J = 6.4, 4.4 Hz), 4.48 (1 H, s), 4.50 (2 H, s), 7.20–7.43 (5 H, m). ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ ppm −5.9, 17.5, 25.3, 26.9, 27.6, 27.6, 54.1, 64.3, 68.3, 72.1, 78.5, 111.0, 126.9, 127.0, 127.8, 137.7, 152.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{27}H_{45}NO_6Si^+$: 508.30889; found 508.3120.

4.2.15. tert-butyl (2R,3R,4R)-2-((benzyloxy)methyl)-4-hydroxymethyl-3,4-isopropylidene-pyrrolidine-1-carboxylate (**23**)

TBAF (1.0 M in THF, 10.8 mL, 10.77 mmol, 1.2 eq.) was added to a solution of **22** (4.56 g, 8.98 mmol, 1.0 eq.) in THF. After 1 h, TLC analysis showed completion of the reaction. The mixture was concentrated *in vacuo*, and the residue purified by flash column chromatography (0–30% EtOAc in hexanes) to afford **23** in 98% yield as a colourless oil. ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C) δ ppm 1.33 (3 H, s), 1.34 (3 H, s), 1.39 (9 H, s), 3.33 (1 H, d, J = 12.3 Hz), 3.49–3.61 (6 H, m), 4.04 (1 H, t, J = 5.8 Hz), 4.48 (1 H, s), 4.51 (2 H, s), 4.84 (1 H, t, J = 5.8 Hz), 7.23–7.42 (5 H, m). ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ ppm 27.0, 27.6, 27.7, 54.0, 62.8, 63.2, 67.9, 72.0, 78.4, 83.9, 110.8, 126.9, 127.7, 137.8, 153.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{21}H_{32}NO_6^+$: 394.22242; found 394.2132.

4.2.16. tert-butyl (2R,3R,4R)-2-((benzyloxy)methyl)-4-(N-9-methyl-N-6-bis-tert-butyloxycarbonyl-adenine)-3,4-isopropylidene-pyrrolidine-1-carboxylate (**24**)

Compound **23** (0.596 g, 1.51 mmol) was subjected to general procedure 1, using N-6-Boc_2-adenine as nucleobase and THF as solvent. The residue was purified by flash column chromatography (5 → 40% EtOAc in hexanes) to afford **24** as a white foam in 65% yield. ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C) δ ppm 1.00 (3 H, s), 1.30 (3 H, s), 1.37 (9 H, s), 1.38 (18 H, s), 3.58 (2 H, dd, J = 12.6, 2.9 Hz), 3.62–3.70 (2 H, m), 4.61 (2 H, dd, J = 12.0, 2.9 Hz), 4.69 (2 H, s), 4.75 (1 H, s), 7.21–7.46 (5 H, m), 8.47 (1 H, s), 8.82 (1 H, s). ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ ppm 21.1, 26.5, 26.9, 27.3, 27.6, 46.6, 55.6, 63.5, 69.0, 72.4, 78.8, 82.7, 111.7, 127.1, 127.2, 127.8, 137.7, 147.2, 149.0, 149.4, 151.1, 152.7, 153.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{36}H_{51}N_6O_9^+$: 711,37121; found 711.3737.

4.2.17. tert-butyl (2R,3R,4R)-2-((benzyloxy)methyl)-4-(N-9-methyl-6-chloropurine)-3,4-isopropylidene-pyrrolidine-1-carboxylate (**25**)

Compound **23** (0.261 g, 0.66 mmol) was subjected to general procedure 1, using 6-chloropurine as nucleobase and THF as solvent. The residue was purified by flash column chromatography (10–40% EtOAc in hexanes) to afford **25** as a white powder in 58% yield. ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C) δ ppm 1.03 (3 H, s), 1.31 (3 H, s), 1.37 (9 H, s), 3.52–3.68 (4 H, m), 4.03 (1 H, t, J = 3.8 Hz), 4.58 (2 H, dd, J = 12.3, 3.8 Hz), 4.69 (2 H, s), 4.74 (1 H, s), 7.23–7.42 (5 H, m), 8.55 (1 H, s), 8.77 (1 H, s). ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ ppm 27.4, 28.1, 28.5, 47.8, 56.4, 64.4, 69.9, 73.2, 79.7, 110.0, 112.7, 127.9, 128.0, 128.0, 128.7, 138.5, 152.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{26}H_{33}ClN_5O_5^+$: 530.21648; found 530.2158.

4.2.18. tert-butyl (2R,3R,4R)-2-((benzyloxy)methyl)-4-(N-9-methyl-2-amino-6-chloropurine)-3,4-isopropylidene-pyrrolidine-1-carboxylate (**26**)

Compound **23** (0.300 g, 0.76 mmol) was subjected to general procedure 1, using 2-amino-6-chloropurine as base and 1,4-dioxane as solvent. The residue was purified by flash column chromatography (10–45% EtOAc in hexanes), but **26** could not be separated from Mitsunobu byproducts. The residue was used as such in the next reaction. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{26}H_{34}N_6O_5^+$: 545.22738; found 545.2316.

4.2.19. (2R,3R,4R)-2-((hydroxy)methyl)-4-(N-9-methyladenine)-3,4-dihydroxy-pyrrolidine (**27**)

Compound **24** (0.143 g, 0.20 mmol) was subjected to general

procedure 2 and general procedure 3. white powder, 85% yield (2 steps). ^{1}H NMR (300 MHz, D_2O) δ ppm 3.28 (1 H, d, J = 12.9 Hz), 3.55 (1 H, d, J = 12.9 Hz), 3.69 (1 H, ddd, J = 9.1, 5.6, 3.5 Hz), 3.86 (1 H, dd, J = 12.6, 5.6 Hz), 3.98 (1 H, dd, J = 12.7, 3.4 Hz), 4.26 (1 H, d, J = 9.1 Hz), 4.46 (2 H, s), 8.08 (1 H, s), 8.09 (1 H, s). ^{13}C NMR (75 MHz, D_2O) δ ppm 47.3, 51.5, 57.7, 62.3, 72.2, 77.0, 117.7, 142.9, 148.9, 151.7, 154.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{11}H_{17}N_6O_3^+$: 281.13567; found 281.1374. $[\alpha]_D^{21}$: +28.9° (c = 0.18, H_2O).

4.2.20. (2R,3R,4R)-2-(hydroxymethyl)-4-(N-9-methylhypoxanthine)-3,4-dihydroxy-pyrrolidine (**28**)

Compound **25** (0.094 g, 0.177 mmol) was subjected to general procedure 2 and general procedure 3. White powder, 44% yield. ^{1}H NMR (300 MHz, D_2O) δ ppm 3.33 (1 H, d, J = 12.9 Hz), 3.54–3.72 (2 H, m), 3.83 (1 H, dd, J = 12.9, 5.6 Hz), 3.95 (1 H, dd, J = 12.6, 3.2 Hz), 4.30 (1 H, d, J = 9.1 Hz), 4.66 (2 H, m, J = 1.0 Hz), 8.28 (1 H, s), 8.81 (1 H, br. s.). ^{13}C NMR (75 MHz, D_2O) δ ppm 48.7, 51.4, 57.6, 62.3, 72.3, 76.3, 148.0, 155.9. (3 quaternary carbons missing). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{11}H_{16}N_5O_4^+$: 282.11968; found 282.1188. $[\alpha]_D^{21}$: +27.2° (c = 0.31, H_2O) .

4.2.21. (2R,3R,4R)-2-(hydroxymethyl)-4-(N-9-methylguanine)-3,4-dihydroxy-pyrrolidine (**29**)

Compound **26** was subjected to general procedure 2 and general procedure 3. White solid, 11% yield (3 steps). ^{1}H NMR (300 MHz, D_2O) δ ppm 3.36 (1 H, d, J = 13.2 Hz), 3.58–3.71 (2 H, m), 3.84 (1 H, dd, J = 12.9, 5.6 Hz), 3.96 (1 H, dd, J = 12.6, 3.5 Hz), 4.29 (1 H, d, J = 9.1 Hz), 4.52 (2 H, d, J = 2.6 Hz), 8.88 (1 H, br. s.). ^{13}C NMR (75 MHz, D_2O) δ ppm 48.6, 51.5, 57.6, 62.2, 72.2, 76.1, 155.2, 155.4. (3 quaternary carbons missing). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{11}H_{17}N_6O_4^+$: 297.13058; found 297.1295. $[\alpha]_D^{21}$: +64.3° (c = 0.25, H_2O).

4.2.22. tert-butyl (2R,3R,4R)-2-((benzyloxy)methyl)-4-(N-3-benzyloxymethyluracil)-3,4-isopropylidene-pyrrolidine-1-carboxylate (**30**)

Compound **23** (0.253 g, 0.64 mmol) was subjected to general procedure 1, using in N-3-BOM-uracil as nucleobase and THF as solvent. The residue was purified by flash column chromatography (10–45% EtOAc in hexanes), affording **30** as a colourless oil in 52% yield. ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C) δ ppm 1.25 (3 H, s), 1.32 (3 H, s), 1.38 (9 H, s), 3.44 (1 H, d, J = 12.3 Hz), 3.59 (2 H, d, J = 4.7 Hz), 3.66 (1 H, d, J = 12.6 Hz), 3.97–4.26 (4 H, m), 4.55 (2 H, s), 4.61 (2 H, s), 4.68 (1 H, s), 5.39 (2 H, s), 5.71 (1 H, d, J = 8.0 Hz), 7.20–7.38 (10 H, m), 7.54 (1 H, d, J = 8.0 Hz). ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ ppm 22.5, 27.6, 28.3, 28.5, 51.6, 56.2, 64.2, 69.6, 70.7, 71.7, 73.1, 79.6, 100.6, 112.5, 127.7, 127.8, 127.9, 127.9, 128.6, 128.6, 138.6, 146.6, 152.4, 153.6, 162.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{33}H_{42}N_3O_8^+$: 608.29665; found 608.2994.

4.2.23. tert-butyl (2R,3R,4R)-2-((benzyloxy)methyl)-4-(N-3-benzyloxymethylthymine)-3,4-isopropylidene-pyrrolidine-1-carboxylate (**31**)

Compound **23** (0.275 g, 0.70 mmol) was subjected to general procedure 1, using N-3-BOM-thymine as nucleobase and THF as solvent. The residue was purified by flash column chromatography (10–45% EtOAc in hexanes), but **31** could not be separated from Mitsunobu byproducts. The residue was used as such in the next reaction. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{34}H_{44}N_3O_8^+$: 622.31230; found 622.3138.

4.2.24. (2R,3R,4R)-2-((hydroxy)methyl)-4-(N-1-methyluracil)-3,4-dihydroxy-pyrrolidine (**32**)

Compound **30** (0.177 g, 0.29 mmol) was subjected to general procedure 2 and general procedure 3. white powder, 32% yield (3 steps). ^{1}H NMR (300 MHz, D_2O) δ ppm 3.39 (1 H, d, J = 13.2 Hz), 3.50 (1 H, d, J = 13.2 Hz), 3.67 (1 H, ddd, J = 9.1, 5.9, 2.8 Hz), 3.80–4.01 (3 H, m), 4.14 (1 H, d, J = 14.9 Hz), 4.19 (1 H, d, J = 9.1 Hz), 5.81 (1 H, d, J = 7.9 Hz), 7.59 (1 H, d, J = 7.9 Hz). ^{13}C NMR (75 MHz, D_2O) δ ppm 51.6, 51.7, 57.8, 61.9, 72.2, 77.3, 101.4, 147.9, 152.5, 166.7. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{33}H_{42}N_3O_8^+$: 258,10845; found 258.1086. $[\alpha]_D^{21}$: +68.9° (c = 0.10, H_2O).

4.2.25. (2R,3R,4R)-2-((hydroxy)methyl)-4-(N-1-methylthymine)-3,4-dihydroxy-pyrrolidine (**33**)

Compound **31** was subjected to general procedure 2 and general procedure 3. light yellow powder, 37% yield (3 steps). ^{1}H NMR (300 MHz, D_2O) δ ppm 1.85 (3 H, s), 3.39 (1 H, d, J = 12.9 Hz), 3.49 (1 H, d, J = 13.2 Hz), 3.67 (1 H, ddd, J = 9.0, 5.6, 3.5 Hz), 3.81–4.14 (4 H, m), 4.18 (1 H, d, J = 9.1 Hz), 7.44 (1 H, d, J = 1.0 Hz). ^{13}C NMR (75 MHz, D_2O) δ ppm 11.3, 51.3, 51.6, 57.8, 61.9, 72.1, 77.3, 110.5, 143.7, 152.5, 166.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{11}H_{18}N_3O_5^+$: 272,12410; found 272.1245. $[\alpha]_D^{21}$: +64.6° (c = 0.43, H_2O).

4.2.26. tert-butyl (2R,3R,4R)-2-((benzyloxy)methyl)-4-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)-3,4-isopropylidene-pyrrolidine-1-carboxylate (**34**)

Compound **23** (0.524 g, 1.33 mmol, 1.0 eq.) and DMAP (0.024 g, 0.2 mmol, 0.1 eq.) were dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. Et_3N (0.279 mL, 2.00 mmol, 1.5 eq.) and Ms-Cl (0.155 mL, 2.0 mmol, 1.5 eq.) were added and the mixture was stirred for 2 h 25 mL saturated $NaHCO_3$ solution was added, and the mixture was extracted with 3 × 50 mL CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in 7 mL DMF and added to a previously stirred (30 min) mixture of 6-chloro-7-deazapurine (0.511 g, 3.33 mmol, 2.5 eq.) and NaH (60% wt. in mineral oil, 0.106 g, 2.66 mmol, 2.0 eq.). The temperature was raised to 85 °C and the mixture stirred overnight. The mixture was filtered over celite®, rinsed with EtOAc and transferred to a separation funnel. 30 mL saturated $NaHCO_3$ solution was added and the mixture was extracted with 3 × 50 mL EtOAc. The organic phases were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography (10–50% EtOAc in hexanes) to yield **34** as a colourless oil in 14% yield (2 steps). ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C) δ ppm 1.08 (3 H, s), 1.31 (3 H, s), 1.36 (9 H, s), 3.45–3.67 (4 H, m), 3.98–4.06 (1 H, m), 4.50–4.75 (5 H, m), 6.66 (1 H, d, J = 3.5 Hz), 7.25–7.39 (4 H, m), 7.65 (1 H, d, J = 3.5 Hz), 8.62 (1 H, s). ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ ppm 27.4, 28.2, 28.5, 48.8, 56.3, 64.3, 69.7, 73.1, 79.6, 85.7, 99.1, 112.6, 117.1, 127.9, 128.0, 128.7, 133.0, 138.5, 150.8, 151.3, 151.8, 153.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{27}H_{33}ClN_4O_5^+$: 529.22123; found 529.2209.

4.2.27. (2R,3R,4R)-2-((hydroxy)methyl)-4-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)-3,4-dihydroxy-pyrrolidine (**35**)

NaN_3 (0.029 g, 0.45 mmol, 3.0 eq.) was added to a solution of compound **34** (0.080 g, 0.15 mmol, 1.0 eq.) in 5 mL DMF. The solution was warmed to 85 °C and stirred for 24 h 10 mL water was added, and the mixture was extracted with 3 × 25 mL EtOAc. The organic phases were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography (5–40% EtOAc in hexanes). The residue was dissolved in 5 mL EtOH, $Pd(OH)_2$ (0.016 g, 20% wt.) was added and the reaction mixture was stirred under H_2 atmosphere for 24 h. The mixture was filtered over celite®, concentrated *in vacuo*, and used crude in the next reaction. The residue was dissolved in a mixture of THF & H_2O (1:1, 4 mL) and 1 mL concentrated HCl was added. After 1 h of stirring, the mixture was concentrated *in vacuo* and purified by flash column chromatography ($MeOH/NH_4OH/CH_2Cl_2$ 20:1:9 and 45:5:55). The residue

was then subjected to general procedure 3 to afford **35** in 54% yield (3 steps) as a white solid. ^{1}H NMR (300 MHz, D2O) δ ppm 3.23 (1 H, d, J = 12.9 Hz), 3.54 (1 H, d, J = 13.2 Hz), 3.67 (1 H, ddd, J = 9.0, 5.6, 3.2 Hz), 3.83 (1 H, dd, J = 12.9, 5.6 Hz), 3.95 (1 H, dd, J = 12.6, 3.2 Hz), 4.22 (1 H, d, J = 9.1 Hz), 4.52 (2 H, d, J = 3.2 Hz), 6.81 (1 H, d, J = 3.8 Hz), 7.37 (1 H, d, J = 3.5 Hz), 8.23 (1 H, s). ^{13}C NMR (75 MHz, D_2O) δ ppm 48.4, 51.5, 57.7, 62.1, 72.0, 77.6, 101.5, 101.8, 129.3, 141.7, 147.2, 150.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{12}H_{18}N_5O_3^+$: 280.14042; found 280.1403. $[\alpha]_D^{21}$: +36.0° (c = 0.10, H_2O).

4.2.28. tert-butyl (2R,3R,4R)-2-((benzyloxy)methyl)-4-(N-3-benzoyl-5-fluorouracil)-3,4-isopropylidene-pyrrolidine-1-carboxylate (**36**)

Compound **23** (0.281 g, 0.71 mmol) was subjected to general procedure 1, using N-3-benzoyl-5-fluorouracil as nucleobase and MeCN as solvent. The residue was purified by flash column chromatography (5–40% EtOAc in hexanes), but **36** could not be separated from Mitsunobu byproducts. The residue was used as such in the next reaction. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{32}H_{37}FN_3O_8^+$: 610.22592; found 610.2605.

4.2.29. (2R,3R,4R)-2-((hydroxy)methyl)-4-(N-1-methyl-5-fluorouracil)-3,4-dihydroxy-pyrrolidine (**37**)

Compound **36** (0.075 g, 0.12 mmol) was dissolved in 3 mL MeOH. A 7 N solution of NH_3 in MeOH (2 mL) was added and the mixture was stirred overnight. The mixture was concentrated *in vacuo* and purified by flash column chromatography (10–40% EtOAc in hexanes). The residue was subjected to general procedure 2 and general procedure 3. White powder, 52% yield. ^{1}H NMR (300 MHz, D_2O) δ ppm 3.39 (1 H, d, J = 13.2 Hz), 3.49 (1 H, d, J = 12.9 Hz), 3.67 (1 H, ddd, J = 8.9, 5.6, 3.1 Hz), 3.80–4.16 (5 H, m), 4.19 (1 H, d, J = 9.1 Hz), 7.80 (1 H, d, J = 5.9 Hz). ^{13}C NMR (75 MHz, D_2O) δ ppm 51.6, 51.8, 57.8, 61.9, 72.1, 77.2, 131.6, 132.0, 138.6, 141.7, 151.0, 159.9. ^{19}F NMR (282 MHz, D_2O) δ ppm −168.09. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{10}H_{15}FN_3O_5^+$: 276.09903; found 276.0985. $[\alpha]_D^{21}$: +77.9° (c = 0.12, H_2O).

4.2.30. tert-butyl (2R,3R,4R)-2-((benzyloxy)methyl)-4-(N-1-methyl-N-4-acetylytosine)-3,4-isopropylidene-pyrrolidine-1-carboxylate (**38**)

Compound **23** (0.275 g, 0.70 mmol, 1.0 eq.) and DMAP (0.08 g, 0.07 mmol, 0.1 eq.) were dissolved in CH_2Cl_2 (8 mL) and cooled to 0 °C. Et_3N (0.146 mL, 1.05 mmol, 1.5 eq.) and Ms-Cl (0.081 mL, 1.05 mmol, 1.5 eq.) were added and the mixture was stirred for 1 h 25 mL saturated $NaHCO_3$ solution was added, and the mixture was extracted with 3 × 50 mL CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in 6 mL DMF. N-4-acetylcytosine (0.129 g, 0.84 mmol, 1.2 eq.), K_2CO_3 (0.145 g, 1.05 mmol, 1.5 eq.) and 18-crown-6 (0.030 mL, 0.14 mmol, 0.2 eq.) were added and the mixture was warmed to 75 °C. After 18 h, the mixture was filtered over celite® and purified by flash column chromatography (0–5% MeOH in CH_2Cl_2) to afford **38**. **38** could not be obtained pure enough for NMR analysis and was used as such in the next reactions. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{27}H_{37}N_5O_7^+$: 529.26568; found 529.2678.

4.2.31. (2R,3R,4R)-2-((hydroxy)methyl)-4-(N-1-methylcytosine)-3,4-dihydroxy-pyrrolidine (**39**)

Compound **38** (0.098 g, 0.185 mmol) was subjected to general procedure 2 and general procedure 3. Off-white solid, 15% (2 steps). ^{1}H NMR (300 MHz, D_2O) δ ppm 3.39 (1 H, d, J = 13.2 Hz), 3.50 (1 H, d, J = 13.2 Hz), 3.65 (1 H, ddd, J = 11.8, 5.6, 3.1 Hz), 3.83 (1 H, dd, J = 12.7, 5.7 Hz), 3.96 (1 H, dd, J = 12.7, 3.4 Hz), 4.03 (1 H, d, J = 15.5 Hz), 4.16–4.25 (2 H, m), 6.16 (1 H, d, J = 7.6 Hz), 7.79 (1 H, d, J = 7.9 Hz). ^{13}C NMR (75 MHz, D_2O) δ ppm 51.6, 52.4, 57.7, 61.9, 72.2, 76.9, 94.3, 149.3, 150.3, 159.5. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{10}H_{17}N_4O_4^+$: 257,12444; found 257.1256. $[\alpha]_D^{21}$: +50.8° (c = 0.21, H_2O).

4.2.32. tert-butyl (2R,3R,4R)-2-((hydroxy)methyl)-4-(N-9-methyl-N-6- bis-tert-butyloxycarbonyl -adenine)-3,4-isopropylidene-pyrrolidine-1-carboxylate (**40**)

$Pd(OH)_2$ (0.107 g, 20% wt.) was added to a solution of compound **24** (0.537 g, 0.76 mmol) in MeOH. The reaction mixture was warmed to 40 °C and stirred under H_2 atmosphere for 3 days. The mixture was filtered over celite®, concentrated *in vacuo*, and purified by flash column chromatography (10–50% EtOAc in hexanes) to afford **40** as a white foam in 56% yield. ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C) δ ppm 1.02 (3 H, s), 1.30 (3 H, s), 1.35–1.41 (27 H, m), 3.57 (2 H, s), 3.60–3.69 (2 H, m), 3.92 (1 H, t, J = 4.1 Hz), 4.67–4.81 (3 H, m), 4.93 (1 H, t, J = 5.0 Hz), 8.51 (1 H, s), 8.84 (1 H, s). ^{13}C NMR (75 MHz, DMSO-d_6, 80 °C) δ 26.6, 26.9, 27.3, 27.7, 46.9, 55.8, 60.5, 65.4, 78.6, 82.7, 111.6, 127.2, 147.1, 149.0, 149.4, 151.1, 152.8, 153.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{29}H_{45}N_6O_9^+$: 621,32426; found 621.3249.

4.2.33. tert-butyl (2R,3R,4R)-2-((methylthio)methyl)-4-(N-9-methyl-N-6-bis-tert-butyloxycarbonyl -adenine)-3,4-isopropylidene-pyrrolidine-1-carboxylate (**41**)

Compound **40** (0.119 g, 0.19 mmol, 1.0 eq.) and DMAP (0.002 g, 0.02 mmol, 0.1 eq.) were dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C. Et_3N (0.040 mL, 0.29 mmol, 1.5 eq.) and Ms-Cl (0.022 mL, 0.29 mmol, 1.5 eq.) were added and the mixture was stirred for 1 h 10 mL saturated $NaHCO_3$ solution was added, and the mixture was extracted with 3 × 25 mL CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in DMSO (4 mL), NaSMe (0.043 g, 0.61 mmol, 3.2 eq.) was added and the temperature was raised to 50 °C. After 5 h of stirring, TLC analysis indicated completion of the reaction. The reaction mixture was diluted with EtOAc (50 mL), washed with 2 × 15 mL saturated $NaHCO_3$ solution and 15 mL of brine, dried over Na_2SO4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (15–60% EtOAc in hexanes) to afford a mixture of 2 products, **41** and mono-Boc-protected **41**. The mixture of these two compounds was used in the next reactions. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{30}H_{47}N_6O_8S^+$: 651.31706; found 651.3173. Calculated for $C_{25}H_{39}N_6O_6S^+$: 551.26518; found 551.2678.

4.2.34. tert-butyl (2R,3R,4R)-2-(4-chloro-phenylthiomethyl)-4-(N-9-methyl-N-6- bis-tert-butyloxycarbonyl -adenine)-3,4-isopropylidene-pyrrolidine-1-carboxylate (**42**)

Compound **40** (0.120 g, 0.19 mmol, 1.0 eq.) and DMAP (0.002 g, 0.02 mmol, 0.1 eq.) were dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C. Et_3N (0.040 mL, 0.29 mmol, 1.5 eq.) and Ms-Cl (0.022 mL, 0.29 mmol, 1.5 eq.) were added and the mixture was stirred for 1 h 10 mL saturated $NaHCO_3$ solution was added, and the mixture was extracted with 3 × 25 mL CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was used crude in the next reaction. The residue was dissolved in 3 mL DMF and added to a previously stirred (30 min) mixture of 4-chloro-thiophenol (0.082 g, 0.57 mmol, 3.0 eq.) and NaH (60% wt. in mineral oil, 0.019 g, 0.48 mmol, 2.5 eq.) in 2 mL DMF. The mixture was stirred overnight and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL), washed with saturated Na_2CO_3 solution (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (10 → 50% EtOAc in hexanes) to afford **42**

as a colourless oil in 97% yield (2 steps). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{35}H_{48}ClN_6O_8S^+$: 747,29374; found 747.2935.

*4.2.35. (2R,3R,4R)-2-(methylthiomethyl)-4-(N-9-methyladenine)-3,4-dihydroxy-pyrrolidine (**43**)*

The mixture of compounds **41** and mono-Boc-deprotected **41**was dissolved in a mixture of THF and H_2O (1/1, 4 mL) and 1 mL concentrated HCl was added. After 2 h of stirring, the mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (). The residue was then subjected to general procedure 3 to afford **43** as an off-white solid in 29% yield (4 steps). ^{1}H NMR (300 MHz, D_2O) δ ppm 2.09 (3 H, s), 2.58–2.88 (3 H, m), 3.10–3.26 (2 H, m), 3.75 (1 H, d, $J = 8.8$ Hz), 4.30 (2 H, s), 8.04 (1 H, s), 8.06 (1 H, s). ^{13}C NMR (75 MHz, D_2O) δ ppm 14.9, 35.9, 49.1, 52.8, 60.6, 77.4, 78.2, 117.7, 142.8, 149.0, 152.2, 155.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{12}H_{19}N_6O_2S^+$: 311.12847; found 311.1281.

*4.2.36. (2R,3R,4R)-2-(4-chloro-phenylthiomethyl)-4-(N-9-methyladenine)-3,4-dihydroxy-pyrrolidine (**44**)*

Compound **42** was dissolved in a mixture of THF and H_2O (1/1, 4 mL) and 1 mL concentrated HCl was added. After 4 h of stirring, the mixture was concentrated *in vacuo* and the residue purified by flash column chromatography ($MeOH/NH_4OH/CH_2Cl_2$ 0:0:100 to 20:1:79). The residue was then subjected to general procedure 3 to afford **44** as a white solid in 66% yield (4 steps). ^{1}H NMR (300 MHz, D_2O) δ ppm 3.20–3.34 (2 H, m), 3.47–3.71 (3 H, m), 4.17 (1 H, d, $J = 9.1$ Hz), 4.55 (2 H, s), 7.30–7.41 (4 H, m), 8.30 (1 H, s), 8.39 (1 H, s). ^{13}C NMR (75 MHz, D_2O) δ ppm 33.0, 47.6, 51.2, 60.0, 75.2, 76.7, 117.8, 129.3, 131.6, 132.9, 144.5, 145.3, 149.7. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calculated for $C_{17}H_{20}ClN_6O_2S^+$: 407.10515; found 407.1063. $[\alpha]_D^{21}$: +75.1° (c = 0.28, H_2O).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.05.083.

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