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The Synthesis and Conformation of Dihydroxypiperidinyl Derivates of Nucleobases as Novel Iminosugar Nucleoside Analogs

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An optimized method for the synthesis of an important chiral scaffold, (3*S*,4*R*,5*R*)-1-*N*-Boc-3,4-isopropylidene-3,4,5-trihydroxypiperidine, was developed. Using this intermediate, the preparation of various chiral aminodihydroxypiperidines and their transformation into a series of non-glycosidic, six-membered azanucleosides was accomplished. NMR conformation analysis of the prepared piperidine azanucleosides revealed a preference for the chair conformation, with the nucleobase fixed in the equatorial position in all cases.

Introduction

The azanucleosides represent an important group of antimetabolites that exhibit a variety of biological effects. In these nucleoside analogs, the furanose sugar is replaced by a nitrogen heterocycle. Modifications of the nucleobase have also been introduced, as well as altering its position of attachment to the ring. Incorporation of *N*-acetylazathymidine **1** (Figure 1) into oligonucleotides resulted in strong inhibition of their degradation by 3′-exonucleases.[1] A one-step method for the transformation of amino acid derivatives into *N*-azasugar nucleosides was described by Boto et al.[2] Compound **2** was found to inhibit vaccinia virus.[3] The

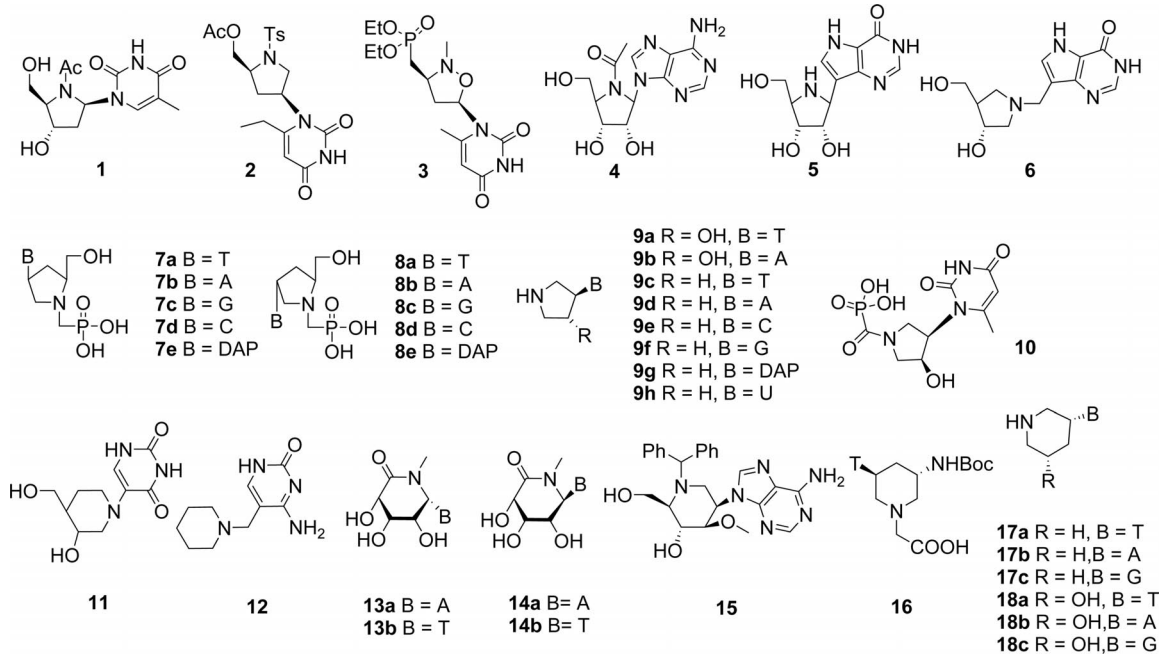

Figure 1. Iminosugar nucleoside and nucleotide analogues.

isoxazolidine derivative **3** was claimed to be an efficient inhibitor of HIV reverse transcriptase with low levels of cytotoxicity.[4]

To the best of our knowledge, synthesis of the first azasugar nucleoside analog **4** was reported by Reist et al.[5] The

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ring nitrogen atom of this compound was acylated to prevent it from spontaneous hydrolysis. Owing to the instability of iminonucleosides, most of the research has been focused on non-glycosidic or aza-*C*-nucleosides. Aza-*C*-nucleosides **5** and **6** (D-immucillin-H and D-DADMe-immucillin-H) have been shown to be potent inhibitors of human purine nucleoside phosphorylase, with K_i values of 56 and 16 pM, respectively.[6] These compounds are currently in clinical trials for the treatment of T- and B-cell cancers, as well as for a variety of autoimmune diseases.[7] Vaněk et al. described a synthesis of the nonglycosidic pyrrolidine nucleoside phosphonic acids **7a**–**e** and **8a**–**e**, but no antiviral or cytostatic activity was observed.[8] The synthesis of pyrrolidine nucleosides **9a**–**h** has been reported by our group.[9–10] Although no antibacterial, antiviral, or cytostatic activities were found, the compounds offered an additional site for further modification of the pyrrolidine nitrogen atom. Therefore, we prepared a series of nucleoside phosphonate analogs,[11] and introduced this motif successfully into an oligonucleotide.[12] The phosphonate derivative **10** was found to be a potent inhibitor of thymidine phosphorylase from spontaneous SD-rat lymphoma cells, exhibiting an IC_{50} value of 11 nM.[13] Pedersen et al. published the synthesis of piperidine nucleoside analog **11**, in which the nucleobase was attached to the piperidine nitrogen atom.[14] Prukala et al. reported the synthesis of the piperidine derivative of cytosine **12**, where the cyclic amine was introduced through a methylene bridge at position 5 of the cytosine, by using a Mannich-type reaction.[15] *N*-Methyl-D-ribopyranuronamide nucleosides **13a**–**b** and **14a**–**b** were synthesized and evaluated in antiviral and cytotoxic assays, however, no activity was found.[16–17] Piperidine nucleoside **15** was prepared by Kim et al.,[18] and it seemed that oligonucleotides containing this modification exhibited a strong hybridization with RNA counterparts, depending on the location and number of substitutions. Furthermore, it was suggested that the increase of hydrophobicity in these modified oligonucleotides can be advantageous for cellular uptake. Lonkar et al. incorporated the piperidine nucleoside analog **16** into the PNA mixmer, and these PNAs formed stable PNA:DNA complexes.[19] Synthesis of the piperidinyl- and hydroxypiperidinyl derivatives of nucleobases **17a**–**c** and **18a**–**c** was recently described by our group. On testing, none of these compounds exhibited either antibacterial or cytostatic activity.[20]

Based on this short survey, it can be concluded that the azanucleosides have recently been receiving steady attention and, in several cases, certain biological activities were recognized, as well as favorable effects on the oligonucleotide properties upon incorporation of the respective azanucleoside-modified units into the chains.

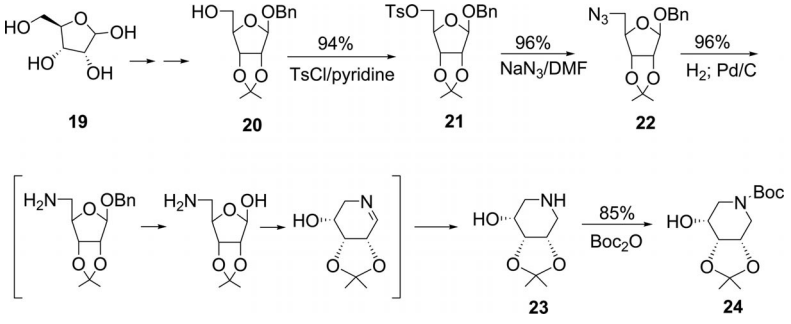
In this contribution, we present synthetic transformations leading to the formation of dihydroxypiperidinyl derivatives of nucleobases as a novel group of compounds. In addition to the synthetic efforts, our aim was to investigate in more detail the structure of the new compounds by means of conformational analyses. Finally, we wanted to perform basic tests to determine the biological activities of these compounds.

Results and Discussion

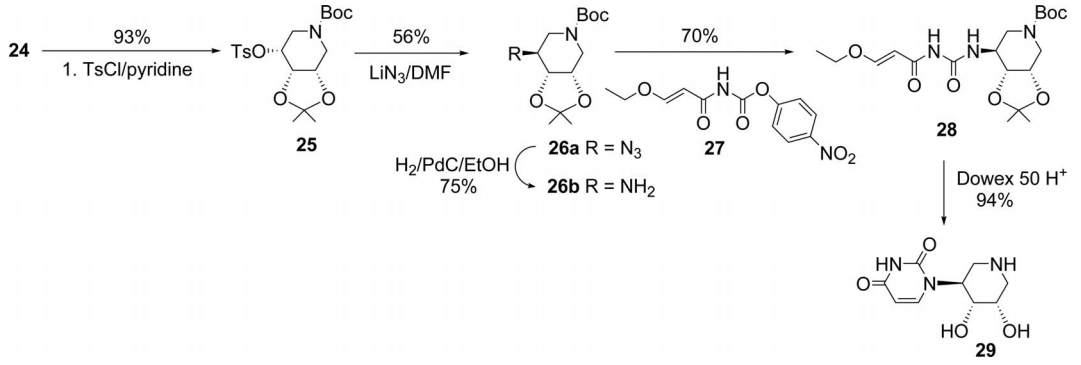
Chemistry

On the path to the target compounds, we wanted to first develop a synthesis of the piperidine precursor starting from an available and inexpensive starting material. Thus, the synthesis of conveniently protected trihydroxypiperidine **24** was accomplished by modifying the method developed by Igarashi and Ichikawa.[21] Specifically, benzyl 2,3-isopropylidene-riboside (**20**), prepared according to the literature procedure[22] from ribose (**19**), was used instead of 1-benzoyl 2,3-isopropylidene-riboside (Scheme 1). The advantage of using a benzyl protecting group was that a convenient, one-pot, four-step conversion of the azido derivative **22** (obtained in high yield via mesyl derivative **21**) into the piperidine derivative **23** was possible. In the process, the azido moiety of compound **22** was first reduced to an amine (which can be isolated, if the hydrogenation is monitored carefully) followed by hydrogenolytic removal of the benzyl group. The ribose ring was then opened and the formed six-membered iminosugar was reduced to afford the isopropylidenepiperidine derivative **23**. Using a standard procedure (Boc_2O, $NaHCO_3$, H_2O, EtOH), compound **23** was converted into the Boc derivative **24** in an excellent overall yield of 74%.

All attempts to introduce the nucleobase, either by substitution of the free hydroxyl group of product **24** using a Mitsunobu reaction, or by *N*-alkylation of the nucleobase



Scheme 1. Synthesis of conveniently protected trihydroxypiperidine **24**.



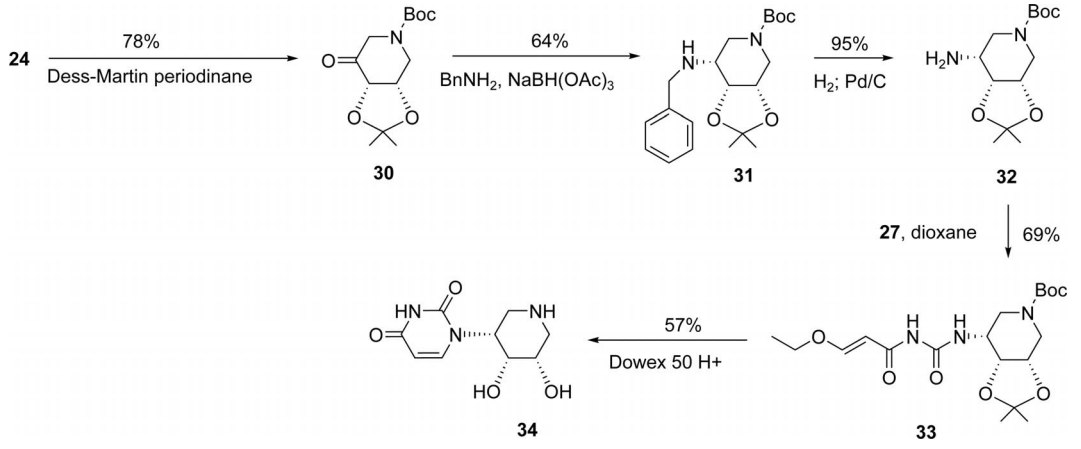
Scheme 2. Synthesis of the dihydroxypiperidinyl derivative of uracil **29**.

with the tosyl derivative **25**, failed. Only complex mixtures containing mainly elimination products were observed (data not shown). The reaction of tosyl derivative **25** with sodium azide afforded an unresolvable mixture of the expected azido derivative and elimination products (not fully characterized) (Scheme 2). The use of lithium azide improved the outcome of the reaction significantly, affording 56% isolated yield of the azido derivative **26a**; subsequent catalytic hydrogenation gave amino derivative **26b** in 75% yield.

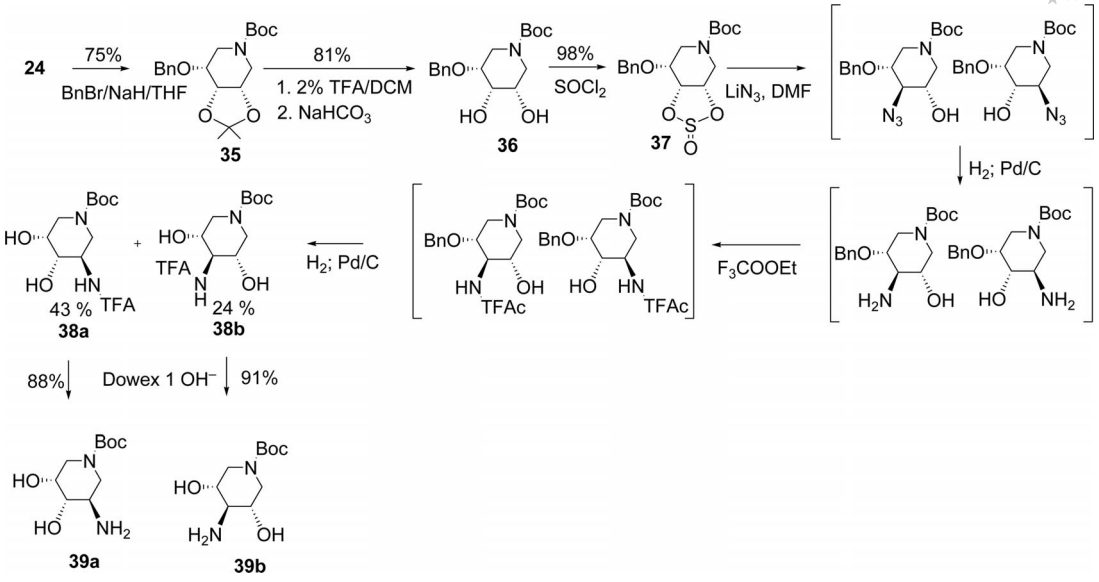
The reaction of amine **26b** with 4-nitrophenyl (3-ethoxyacryloyl)carbamate (**27**), recently developed in our laboratory,[23] yielded the urea derivative **28**, which afforded the uracil derivative **29** on treatment with Dowex 50 (H^+) in dioxane at 90 °C in a 66% overall yield.

To avoid alkylation reactions, we evaluated a different route for the preparation of the amino derivative. The intermediate **24** was first oxidized with Dess–Martin periodinate to afford ketone **30** a 78% yield, which underwent reductive amination with benzylamine using sodium triacetoxyborohydride[24] to afford the benzylamino derivative **31** (Scheme 3) in 64% yield. The benzyl group was subsequently removed by catalytic hydrogenation over Pd/C catalyst to afford the amino derivative **32**. The reductive amination proceeded with retention of configuration. The configuration of **31** was determined from the NMR spectra and was based on a comparison of the $^3J_{H,H}$ values of its piperidine ring with those of the benzyloxy derivative **36**. The coupling constants were essentially the same, which suggested that the same configuration and conformation existed in the piperidine ring. Additional proof that the configuration had been retained during the reductive amination were obtained from the differing NMR spectra of **26b** and **32**, whereby **26b** was prepared from the azido derivative **26a** formed stereoselectively by an S_N2 reaction that is known to take place through complete inversion of configuration. The amine **32** was then converted into the corresponding uracil derivative **34** in a 40% yield (over two steps) via urea intermediate **33** using the reagent **27**.

To obtain analogs of nucleosides resembling the natural ribo configuration, we elaborated the reaction sequence depicted in Scheme 4. The free hydroxyl group of **24** was benzylated (75% yield) and the isopropylidene protecting group was selectively removed by stirring with 2% trifluoroacetic acid (TFA) in dichloromethane at room temperature (81% yield). The reaction was followed by TLC and, after all the starting material was consumed, solid $NaHCO_3$ was immediately added to neutralize the TFA. The suspension was stirred until neutral pH. After filtration and evaporation of the solvent, the deprotected compound **36** was obtained by flash chromatography on silica gel. This procedure could be of general use for selective removal of the isopropylidene or DMTr protecting group in the presence of other acid-labile protecting groups, for example *N*-Boc. Selective removal of the 5,6-isopropylidene group from



Scheme 3. Synthesis of the dihydroxypiperidinyl derivative of uracil **34**.



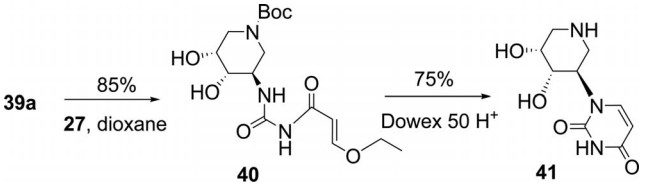
Scheme 4. Synthesis of aminodihydroxypiperidines **39a** and **39b**.

1,2;5,6-diisopropylideneglucose could be also achieved using this method (data not shown).

The *cis*-diol **36** reacted with thionyl chloride to provide the intermediate **37** in almost quantitative yield. It should be noted here that the cyclic sulfite **37** was formed as a mixture of diastereoisomers (isomerism at the sulfur atom), showing two spots on TLC. Compound **37**, after purification on silica gel, was treated with lithium azide in *N*,*N*-dimethylformamide (DMF) at elevated temperature. The unresolvable mixture of the 4- and 5-azido derivatives obtained after rapid silica gel purification, was hydrogenated over palladium catalyst. The mixture of the formed regioisomeric amines was protected with the trifluoroacetyl group by reaction with ethyl trifluoroacetate in ethanol, and the 3-*O*-benzyl protecting group was removed by catalytic hydrogenation. The obtained compounds **38a** and **38b** were easily separated by using flash chromatography on silica gel in 43 and 24% yield, respectively (calculated over four reaction steps). Finally, the trifluoroacetyl protecting groups of **38a** and **38b** were removed by treatment with Dowex 1 in OH^- form (88 and 91% yield, respectively). All the reaction steps proceeded in high yields and provided access to the piperidine nitrogen-protected azasugars **39a** and **39b**.

The reaction of aminopiperidine **39a** with reagent **27**[23] proceeded smoothly to afford, after flash chromatography, intermediate **40** in 85% yield (Scheme 5). After cyclization and Boc group removal by heating with Dowex 50 (H^+) in dioxane at 80 °C, followed by preparative HPLC purification, uracil derivative **41** was obtained in 75% yield.

Derivatives of the purine nucleobases were synthesized using the established procedures of nucleobase assembly.[25–26] Thus, the reaction of **39a** with 5-amino-4,6-dichloropyrimidine (**42**) afforded compound **43** in 57% yield (Scheme 6). Subsequent reaction with diethoxymethyl acetate in DMF provided 6-chloropurine **44** in 49% yield. Final treatment of compound **44** with concentrated aqueous ammonia, followed by Boc group removal with TFA, afforded the desired adenine derivative **45** in 75% yield, whereas treatment of **44** with aqueous 1 M HCl at 75 °C afforded the hypoxanthine derivative **46** (in the same yield).

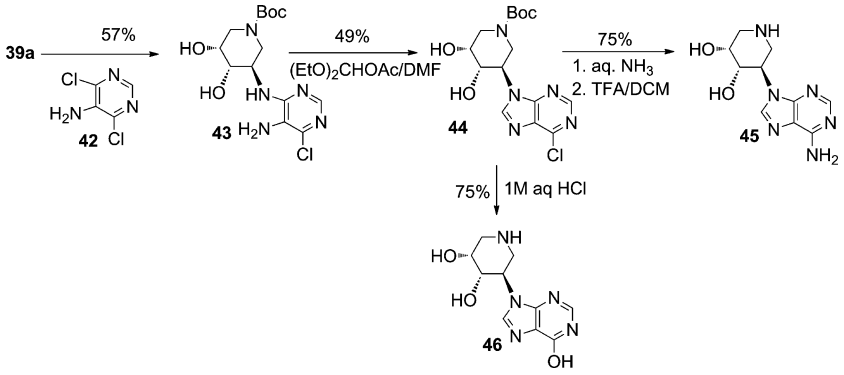


Scheme 5. Synthesis of dihydroxypiperidinyl derivative of uracil **41**.

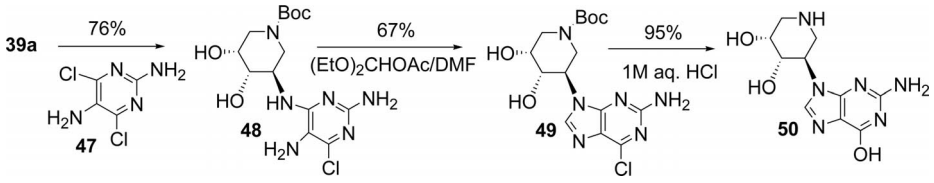
The reaction of **39a** with 2,5-diamino-4,6-dichloropyrimidine (**47**) afforded compound **48** in 76% yield (Scheme 7). The reaction of **48** with diethoxymethyl acetate in DMF provided the chlorpurine derivative **49** in 67% yield, which was then treated with 1 M HCl at 75 °C to afford guanine derivative **50** in 95% yield.

The reaction of aminopiperidine **39b** with 4-nitrophenyl (3-ethoxyacryloyl)carbamate (**27**),[23] followed by cyclization and Boc group removal by heating with Dowex 50 (H^+) in dioxane at 80 °C, and then by preparative HPLC purification, afforded uracil derivative **52** in 58% overall yield (Scheme 8). Adenine derivative **54** was prepared in 30% overall yield by reaction of **39b** with 5-amino-4,6-dichloropyrimidine (**42**), followed by reaction with diethoxymethyl acetate in DMF, treatment with concentrated aqueous ammonia, and Boc group removal with TFA. Guanine derivative **56** was obtained in 33% overall yield starting from compound **39b** by employing, first, treatment with reagent **47**, followed by diethoxymethyl acetate cyclization and subsequently by aqueous 1 M HCl treatment.

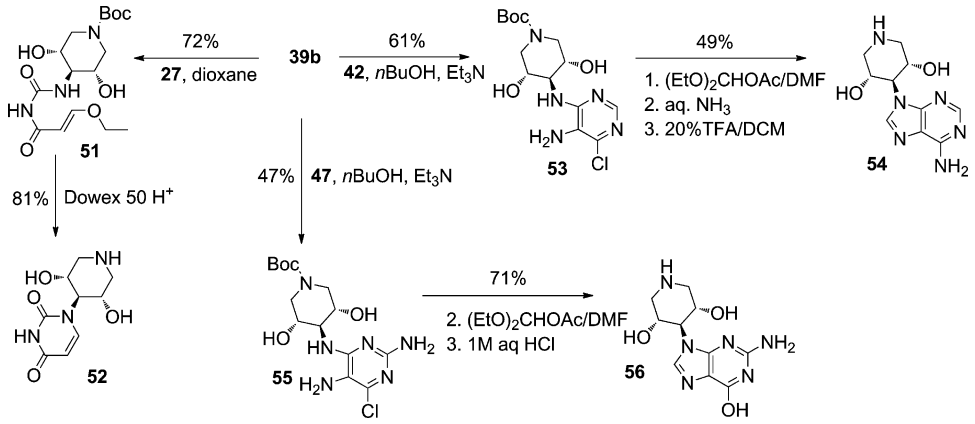
Finally, to demonstrate the general usefulness of the iminosugar chemistry presented here, amines **26**, **39a**, and **39b** were converted into the respective *N*-acetyl derivatives **57**–



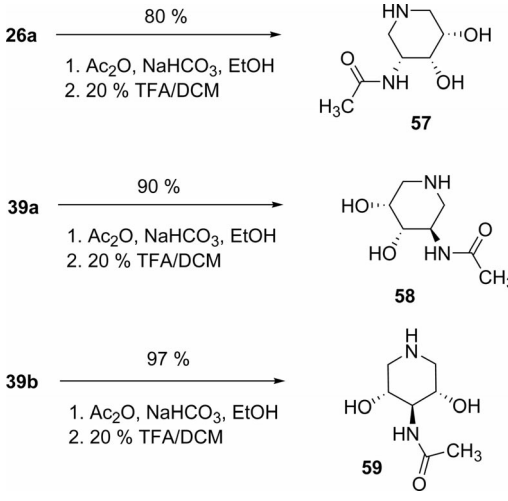
Scheme 6. Synthesis of the dihydroxypiperidinyl derivative of adenine **45** and hypoxanthine **46**.



Scheme 7. Synthesis of the dihydroxypiperidinyl derivative of guanine **50**.



Scheme 8. Synthesis of dihydroxypiperidinyl derivative of uracil **52**, adenine **54**, and guanine **56**.



Scheme 9. Synthesis of *N*-acetylpiperidine azasugars **57**–**59**.

59, as potential inhibitors of glycosidases,[27] by reaction with acetic anhydride followed by treatment with TFA to remove the isopropylidene (**57**) or Boc (**58**–**59**) protecting groups (Scheme 9). The *N*-acetyl derivative **59** could be used as starting material for the synthesis of inhibitors of sialidases.[28]

Biological Activity Testing

In keeping with the aims set for this work, we submitted compounds **29**, **34**, **41**, **45**–**46**, **50**, **52**, **54**, and **56**–**59** for biological activity screening. However, no significant cytostatic (L1210, HL60, HeLa S3, CCRF-CEM), antibacterial (*Enterococcus faecalis* CCM 4224, *Staphylococcus aureus* CCM 4223, *Escherichia coli* CCM 3954, *Pseudomonas aeruginosa* CCM 3955 *Bacillus subtilis*, *Streptococcus agalactiae*), or antiviral (HIV, HCV, RSV) activities of the prepared compounds were observed. Further tests of the pre-

pared *N*-acetylazasugars **57**–**59**, considered as potential inhibitors of several glycosidases, are underway.

Conformation Analysis of Piperidine Nucleosides

^{1}H NMR spectra of the final azanucleosides were used to determine the piperidine ring conformation. Structural information is encoded in the vicinal H,H coupling constants of the piperidine ring, which can be extracted from ^{1}H NMR spectra (see Table 1). Characteristic coupling values for the axial–axial interaction (J = 10.0–12.1 Hz) could thus be used to predict the spatial arrangement of protons in the ring. For example, the 4′-proton (for numbering, see Figure 2) is in an axial position in derivatives **41**, **45**, **46**, **50**, **54**, and **56**, whereas in compound **34** it occupies an equatorial position. We observed a preferred chair conformation, with the nucleobase fixed in the equatorial position, for all target azanucleosides (Figure 2).

Table 1. Vicinal coupling constants of the piperidine ring protons (for numbering see Figure 2).

	J(2′a,3′)	J(2′b,3′)	J(3′,4′)	J(4′,5′)	J(5′,6′ax)	J(5′,6′eq)
34[a]	5.1	11.4	2.9	1.7	12.1	4.3
41[b]	2.9	1.6	3.0	10.7	11.2	4.7
45[a]	3.2	1.4	2.9	10.7	12.1	5.4
46[a]	3.5	0.9	2.9	10.7	10.7	6.5
50[a]	3.3	1.5	2.9	10.6	10.6	6.1
52[c]	5.3	10.2	10.3	10.3	10.2	5.3
54[a]	4.8	10.3	10.0	10.0	10.3	4.8
56[a]	4.8	10.7	10.3	10.3	10.7	4.8

[a] In D_2O, 25–28 °C. [b] In [D_6]DMSO, 60 °C. [c] In CD_3OD, –80 °C.

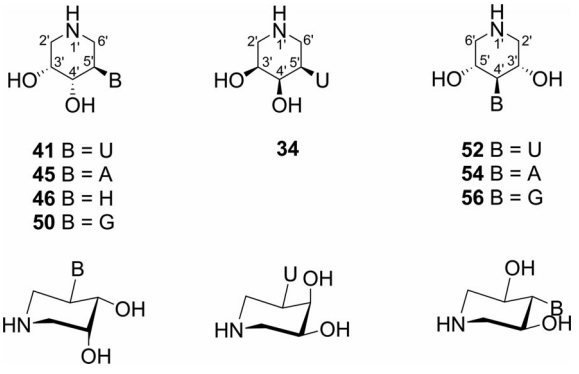


Figure 2. Preferred conformation of the piperidine ring in target azanucleosides.

In the ^{1}H NMR spectra of piperidine derivatives protected with the Boc group, all signals appeared as broad lines; this is not surprising because it is well-known that rotation around the C–N bonds in amides is restricted by the partial double character of this bond. The slow interconversion between the two rotamers at room temperature causes the broadening of NMR signals. At higher temperatures, the rotation around the partial double bond is faster and the NMR signals become sharper. We were surprised to observe significant line broadening also in the NMR spectra of some of the deprotected derivatives, namely, the uracil nucleosides **41** and **52**, where the pyrimidine base is attached *trans* to a neighboring hydroxyl group. When the ^{1}H NMR spectra of these pyrimidine derivatives were measured at higher temperature (100 °C, [D_6]DMSO), one set of sharp signals was present; at low-temperature, the spectra (–80 °C, CD_3OD) consisted of two sets of sharp signals with different intensities. These observations indicate a slow exchange between the two conformers of the nucleosides. The most important differences in the chemical shifts between the two conformers were observed for C-6, C-4′, H-3′, and H-4′ signals (see Table 2). Initially, we believed that the conformational change of the six-membered piperidine ring could be responsible for the line broadening of the signals (exchange between two chairs, or between chair and boat conformations). However, from the coupling pattern observed in the ^{1}H NMR spectra at low temperature, it became clear that both conformers have identical chair conformations. For example, the signal arising from the hydrogen atom H-4′ (attached to the carbon atom bearing the uracil part of the molecule) appeared as a triplet with a large coupling constant (J = 10.3 Hz), which indicates *axial* positions for all three hydrogen atoms in the 4′ and 5′ positions in compound **52**.

Table 2. Experimental ^{13}C and ^{1}H NMR chemical shifts of conformers C1 and C2 of compound **52** measured in CD_3OD at –80 °C. Experimental and calculated (B3LYP/6-311+G(d,p)/PCM) chemical shift differences (C1–C2).

	δexp(C1)	δexp(C2)	$\Delta\delta$exp(C1–C2)	$\Delta\delta$calc(C1–C2)
C-2	154.06	152.33	1.7	2.0
C-4	166.58	167.44	–0.9	–0.7
C-5	102.83	100.94	1.9	1.8
C-6	142.99	151.19	–8.2	–9.4
C-2′	52.06	51.84	0.2	–0.4
C-3′	69.13	66.27	2.9	3.6
C-4′	65.70	79.11	–13.4	–15.0
H-5	5.82	5.63	0.2	0.2
H-6	7.88	7.50	0.4	0.1
H-2′ax	2.50	2.40	0.1	0.2
H-2′eq	3.16	3.16	0.0	0.0
H-3′	3.64	4.51	–0.9	–0.8
H-4′	4.44	3.24	1.2	1.5

The results of selective 1D-NOE measurements showed that the two conformations are rotamers around the C4′–N1 bond (see Figure 3). Spatial proximity between H-6, H-3′, and H-5′ atoms was observed in one conformer, and between the H-6 and H-4′ atoms in the second. To further support these findings, we optimized the geometries of the two conformers in silico at the DFT level and then calculated the ^{1}H and ^{13}C chemical shifts. The experimental and calculated chemical shifts of the two conformers agreed very well (see Table 2).

It is interesting that the slow interconversion between the two conformers was observed only in uracil nucleosides **41** and **52**, for which both the uracil part and the neighboring hydroxyl group were equatorial. We did not observe similar behavior for the purine derivatives **45**, **46**, **50**, **54**, and **56** or for uracil derivative **34**, where the neighboring hydroxyl group was axial. The barrier for rotation around the C4′–

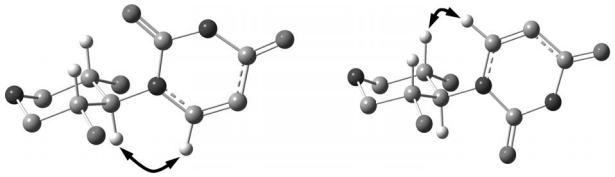


Figure 3. Conformer C1 (left) and C2 (right) of compound **52**. Geometries were optimized at the B3LYP/6-31+G(d,p)/PCM level. Experimentally observed NOE contacts are shown. Hydrogen atoms not important for the conformational analysis were omitted for clarity.

N1 bond is probably higher in the uracil derivatives because of higher steric demands of the six-membered uracil ring in comparison with the purine molecule (see Figure 4).

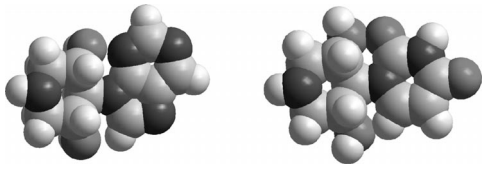


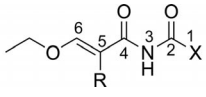
Figure 4. Proposed transition states for rotamer interconversion of purine (left) and uracil (right) nucleosides.

Conclusions

This work is a new contribution to the chemistry of azasugars and the azasugar nucleosides. We present convenient synthetic methods for the preparation of the protected chiral aminodihydroxypiperidines **26b**, **32**, **39a**, and **39b**, which are useful intermediates for broader synthetic exploitation, and subsequent utilization of these chiral scaffolds in the synthesis of a series of novel azanucleosides **29**, **34**, **41**, **45**, **46**, **52**, **54**, and **56**. Knowledge gained from developing the synthetic transformations may be of general usefulness for further work in areas related to modified nucleosides. The conformations of the novel compounds were evaluated by using NMR and computational approaches, and we were able to determine a preference for the chair conformations for the piperidine ring in the compounds investigated. Prepared piperidine azanucleosides **29**, **34**, **41**, **45**, **46**, **52**, **54**, and **56** offer further possibilities for derivatization at the piperidine nitrogen atom, thereby providing the chance to prepare yet more types of structurally diverse compounds, for example, phosphonate piperidine nucleotides, and, consequently, extend the range of potentially available biologically active compounds. Such possibilities make these compounds interesting, although no significant biological effects have been observed so far. Tests on the prepared *N*-acetylazasugars **57**–**59** as potential inhibitors of certain glycosidases, are underway.

Experimental Section

Compounds **20**, **23**, and **24** have been reported in literature[21] but were not fully characterized, therefore, we provide full characterization here. Unless stated otherwise, all solvents were anhydrous. Reagent **27** was prepared according to literature procedures,[23] whereas 1-benzyl-2,3-isopropylidenglucose (**20**) was prepared according to the procedure described by Watanabe et al.[22] TLC was performed on silica gel pre-coated aluminum plates (Silica gel/TLC-cards), UV 254 (Fluka), and the compounds were detected by UV light (254 nm), by heating (detection of dimethoxytrityl group; orange color), by spraying with 1% ethanolic solution of ninhydrine (to visualize amines), or by spraying with 1% solution of 4-(4-nitrobenzyl)pyridine in ethanol followed by heating and treating with gaseous ammonia (blue color: detection of alkylating agents, e.g., the tosyl derivatives). Preparative column chromatography was carried out on silica gel (40–60 μm; Fluka), and elution was performed at the flow rate of 40 mL/min. Analytical RP HPLC was performed with an LC5000 Liquid Chromatograph (INGOS-PIKRON, Czech Rep.) using a Luna C18 (2) column (4.6 × 150 mm) at a flow rate of 1 mL/min with a gradient elution of methanol in 0.1 M TEAA, pH 7.5 (A = 0.1 M TEAB; B = 0.1 M TEAB in 50% aqueous methanol; C = methanol). Preparative RP HPLC was performed with an LC5000 Liquid Chromatograph (INGOS-PIKRON, CR) using a Luna C18 (2) column (250 × 21.2 mm) at the flow rate of 10 mL/min by a gradient elution of methanol in 0.1 M TEAB, pH 7.5 (A = 0.1 M TEAB; B = 0.1 M TEAB in 50% aqueous methanol; C = methanol). All final compounds were lyophilized from water. Melting points were determined wirth a Stuart SMP model 30 instrument. Optical rotation values were measured with an AUTOPOL IV polarimeter (Rudolph Research Analytical, USA) at the sodium D line at 20 °C. Mass spectra were recorded with a ZAB-EQ (VG Analytical) instrument, using FAB (ionization with Xe, accelerating voltage 8 kV; glycerol and thioglycerol were used as matrices) and with an LTQ Orbitrap XL (Thermo Fisher Scientific) instrument using ESI ionization. NMR spectra were measured with Bruker AVANCE 400 (^{1}H at 400 MHz, ^{13}C at 100.6 MHz), Bruker AVANCE 500 (^{1}H at 500 MHz, ^{13}C at 125.7 MHz), and/or Bruker AVANCE 600 (^{1}H at 600.1 MHz, ^{13}C at 150.9 MHz) spectrometers. Chemical shifts (ppm, δ scale) were referenced to TMS or 1,4-dioxane [δ(^{1}H) = 3.75 ppm, δ(^{13}C) = 69.3 ppm; when D_2O was used as solvent] as internal standard, or to residual solvent signal [(D_6)DMSO: δ(^{1}H) = 2.50 ppm, δ(^{13}C) = 39.7 ppm; CD_3OD: δ(^{1}H) = 3.31 ppm, δ(^{13}C) = 49.0 ppm]; coupling constants (J) are given in Hz. Complete assignment of protons and carbons was achieved by analysis of the correlated homonuclear 2D-COSY and heteronuclear ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC spectra. Relative configuration was checked using DPFGSE-NOE and 2D-ROESY techniques. The nucleobase atom numbering was also adopted for use in the case of linear intermediates:



1-*O*-Benzyl-2,3-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-β-D-ribofuranose (21):[29] Tosyl chloride (19 g, 100 mmol) was added to a solution of 1-*O*-benzyl-2,3-*O*-isopropylidene-β-D-ribofuranose (prepared according to Watanabe et al.;[22] 19 g, 67.78 mmol) in pyridine (400 mL). The reaction mixture was stirred at r.t. for 30 d. Water (3 mL) was added and the mixture was concentrated in vacuo. The residue was co-evaporated with toluene (2 × 100 mL) and the desired product was obtained by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene; yield 94% (27.59 g, 63.5 mmol). ^{1}H NMR (500.0 MHz, $CDCl_3$, 28 °C): δ = 1.28, 1.44 [2 × q, ^4J = 0.8 Hz, 2 × 3 H, $(CH_3)_2C$], 2.42 (s, 3 H, CH_3-Ts), 4.03 (dd, J_{gem} = 10.0, $J_{5b,4}$ = 6.8 Hz, 1 H, 5b-H), 4.06 (dd, J_{gem} = 10.0, $J_{5a,4}$ = 7.7 Hz, 1 H, 5a-H), 4.36 (ddd, $J_{4,5}$ = 7.7,

6.8, $J_{4,3}$ = 0.7 Hz, 1 H, 4-H), 4.39, 4.58 (2×d, J_{gem} = 11.8 Hz, 2×1 H, CH_2Ph), 4.62 (d, $J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 4.63 (br. d, $J_{3,2}$ = 6.0 Hz, 1 H, 3-H), 5.12 (s, 1 H, 1-H), 7.25 (m, 2 H, *o*-Bn-H), 7.27–7.36 (m, 5 H, *m*,*p*-Bn-H, *m*-Ts-H), 7.76 (m, 2 H, *o*-Ts-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$, 28 °C): δ = 21.57 (CH_3-Ts), 24.72, 26.23 [(**C**H_3)$_2$C], 69.27 (CH_2-5, CH_2Ph), 81.34 (CH-3), 83.71 (CH-4), 84.93 (CH-2), 107.24 (CH-1), 112.64 [**C**(CH_3)$_2$], 127.88 (CH-*o*-Bn, CH-*o*-Ts), 128.00 (CH-*p*-Bn), 128.43 (CH-*m*-Ts), 129.86 (CH-*m*Bn), 132.55 (C-*i*-Ts), 136.66 (C-*i*-Bn), 145.00 (C-*p*Ts) ppm. IR: $\tilde{\nu}_{max}$ ($CHCl_3$), 3090 (w), 3067 (w), 1599 (m), 1497 (m), 1455 (m), 1400 (m), 1383 (s), 1373 (vs), 1308 (m), 1292 (m), 1190 (vs), 1177 (vs), 1161 (s), 1096 (vs), 1079 (vs), 1059 (s), 1027 (m, sh), 1018 (s), 984 (vs), 920 (m), 815 (s), 399 (s), 577 (m), 555 (s), 533 (m), 518 (m) cm^{-1}. HRMS-FAB: calcd. for $C_{22}H_{27}O_7S$ [M + H]$^+$ 435.14775; found 435.14661.

5-Azido-1-*O*-benzyl-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranose (22): Sodium azide (12 g, 175 mmol) was added to a solution of **21** (15.21 g, 35 mmol) in DMF (200 mL), and the reaction mixture was stirred at 80 °C overnight. The mixture was filtered through Celite, the filtrate was concentrated in vacuo, and the desired product was obtained by flash chromatography of the residue on silica gel using a linear gradient of ethyl acetate in toluene; yield 96% (10.26 g, 33.59 mmol). ^{1}H NMR (600.1 MHz, $CDCl_3$, 28 °C): δ = 1.31, 1.48 [2×quint, ^4J = 0.6, ^5J = 0.6 Hz, 2×3 H, (CH_3)$_2$C], 3.30 (dd, J_{gem} = 12.4, $J_{5b,4}$ = 6.8 Hz, 1 H, 5b-H), 3.49 (dd, J_{gem} = 12.4, $J_{5a,4}$ = 7.9 Hz, 1 H, 5a-H), 4.34 (dddq, $J_{4,5}$ = 7.9, 6.8, $J_{4,3}$ = 1.2, ^5J = 0.6 Hz, 1 H, 4-H), 4.50 (d, J_{gem} = 11.7 Hz, 1 H, CH_aH_bPh), 4.62 (ddq, $J_{3,2}$ = 6.0, $J_{3,4}$ = 1.2, ^5J = 0.6 Hz, 1 H, 3-H), 4.70 (dd, $J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 4.75 (d, J_{gem} = 11.7 Hz, 1 H, CH_aH_bPh), 5.19 (s, 1 H, 1-H), 7.30 (m, 1 H, *p*-Ph-H), 7.32 (m, 2 H, *o*-Ph-H), 7.35 (m, 2 H, *m*-Ph-H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 28 °C): δ = 24.83, 26.34 [(CH_3)$_2$C], 53.64 (CH_2-5), 69.49 (CH_2Ph), 82.06 (CH-3), 85.21 (CH-2), 85.55 (CH-4), 107.63 (CH-1), 112.68 [C(CH_3)$_2$], 127.96 (CH-*p*-Ph), 128.03 (CH-*o*-Ph), 128.50 (CH-*m*Ph), 136.79 (C-*i*-Ph) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3091 (vw), 3068 (w), 3030 (w), 2107 (vs), 1607 (vw), 1588 (vw), 1498 (w), 1456 (m), 1384 (m), 1376 (m), 1358 (m), 1307 (m, sh), 1273 (s), 1160 (m), 1099 (s), 1077 (s), 1043 (s), 1029 (m), 1011 (m), 915 (w), 699 (m), 551 (w), 514 (w) cm^{-1}. HRMS-FAB: calcd. for $C_{15}H_{20}O_4N_3$ [M + H]$^+$ 306.1454; found 306.1462.

(3*S*,4*R*,5*R*)-3,4-*O*-Isopropylidene-3,4,5-trihydroxypiperidine (23): A solution of **22** (10.26 g, 33.58 mmol) in ethanol (400 mL) was hydrogenated in the presence of Pd/C catalyst (1 g) overnight. The catalyst was filtered off through Celite and the filtrate was evaporated to afford the desired product in a 96% yield (6.12 g, 32.36 mmol) as a white solid. M.p. 96–97 °C. ^{1}H NMR (600.1 MHz, [D$_6$]DMSO, 28 °C): δ = 1.25, 1.42 [2×s, 2×3 H, (CH_3)$_2$C], 2.37 (dd, J_{gem} = 12.6, $J_{2b,3}$ = 8.3 Hz, 1 H, 2b-H), 2.43 (dd, J_{gem} = 11.8, $J_{6b,5}$ = 10.3 Hz, 1 H, 6b-H), 2.64 (dddd, J_{gem} = 11.8, $J_{6a,5}$ = 5.1, $J_{6a,2a}$ = 1.0, $J_{6a,4}$ = 0.7 Hz, 1 H, 6a-H), 2.79 (ddd, J_{gem} = 12.6, $J_{2a,3}$ = 6.2, $J_{2a,6a}$ = 1.0 Hz, 1 H, 2a-H), 3.62 (ddd, $J_{5,6}$ = 10.3, 5.1, $J_{5,4}$ = 3.8 Hz, 1 H, 5-H), 3.99 (ddd, $J_{3,2}$ = 8.3, 6.2, $J_{3,4}$ = 4.9 Hz, 1 H, 3-H), 4.20 (dd, $J_{4,5}$ = 4.9, $J_{4,3}$ = 3.8 Hz, 1 H, 4-H) ppm. ^{13}C NMR (150.9 MHz, [D$_6$]DMSO, 28 °C): δ = 26.51, 28.32 [(CH_3)$_2$C], 46.89 (CH_2-6), 47.23 (CH_2-2), 66.35 (CH-5), 72.86 (CH-3), 75.78 (CH-4), 108.30 [C(CH_3)$_2$] ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3427 (v br., sh), 3266 (m), 3090 (m, v br.), 2987 (s), 2937 (s), 2869 (s), 2836 (m), 1456 (m), 1382 (s), 1371 (s), 1339 (w), 1245 (s), 1219 (s), 1171 (m), 1093 (s), 1076 (vs), 1045 (vs), 1003 (m), 858 (s), 700 (w), 514 (m) cm^{-1}. HRMS-FAB: calcd. for $C_8H_{16}O_3N$ [M + H]$^+$ 174.11247; found 174.11245.

(3*S*,4*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3,4-*O*-isopropylidene-3,4,5-trihydroxypiperidine (24): A mixture of compound **23** (3.1 g, 17.9 mmol), $NaHCO_3$ (8.4 g, 100 mmol), and Boc_2O (6 g, 20 mmol) in 50% aqueous ethanol (200 mL) was stirred at r.t. for 1 h. The mixture was filtered, concentrated in vacuo, and the desired product was obtained by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene, followed by a linear gradient of ethanol in ethyl acetate; yield 85% (4.13 g, 15.11 mmol); white crystals; m.p. 88.5–89.5 °C. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 28 °C; a mixture of amidic rotamers ca. 4:3): δ = 1.25, 1.33 [2×s, 2×6 H, (CH_3)$_2$C], 1.38 {br. s, 18 H, [(CH_3)$_3$C]}, 3.03 (br. d, J_{gem} = 14.5 Hz, 1 H, 2b-H), 3.05–3.16 (m, 3 H, 2×H-6b, 2b-H), 3.17–3.25 (m, 2 H, 6a-H), 3.48, 3.55 (2×br. d, J_{gem} = 14.5 Hz, 2×1 H, 2a-H), 3.77, 3.88 (2×dt, $J_{5,6}$ = 11.2, $J_{5,4}$ = $J_{3,OH}$ = 5.9 Hz, 2×1 H, 5-H), 4.22–4.31 (m, 4 H, 4,3-H), 5.11 (d, $J_{OH,5}$ = 5.9 Hz, 1 H, OH-5) ppm. ^{13}C NMR (150.9 MHz, [D$_6$]DMSO, 28 °C; a mixture of amidic rotamers ca. 4:3): δ = 24.84, 26.68 [(CH_3)$_2$C], 28.31 [(CH_3)$_3$C], 41.46, 42.83 (CH_2-2), 43.20, 43.74 (CH_2-6), 64.35 (CH-5), 72.52 (CH-3), 74.20 (CH-4), 78.70 [C(CH_3)$_3$], 108.12 [C(CH_3)$_2$], 154.69 (CO) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3573 (w), 3445 (w), 2983 (s), 1688 (vs, br.), 1473 (m), 1465 (m, sh), 1456 (s), 1413 (vs), 1394 (s), 1384 (s), 1378 (s), 1368 (s), 1260 (s, sh), 1248 (s), 1163 (vs), 1139 (s), 1075 (s), 1044 (s), 1001 (s), 855 (m), 514 (m) cm^{-1}. HRMS-FAB: calcd. for $C_{13}H_{24}O_5N$ [M + H]$^+$ 274.1655; found 274.1649.

(3*R*,4*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-4,5-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-3,4,5-trihydroxypiperidine (25): Tosyl chloride (7.5 g, 39.14 mmol) was added to a solution of **24** (7.13 g, 26.09 mmol), triethylamine (11 mL, 78.27 mmol), and 4-(dimethylamino)pyridine (DMAP; 0.32 g, 2.6 mmol) in CH_2Cl_2 (260 mL), and the reaction mixture was stirred at r.t. overnight. The mixture was washed with saturated aq. $NaHCO_3$, and the title product was obtained by flash chromatography on silica gel using linear gradient of ethyl acetate in toluene; yield 93% (10.38 g, 24.27 mmol); white solid; m.p. 133–135 °C. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.25, 1.36 [2×s, 2×3 H, (CH_3)$_2$C], 1.39 {s, 9 H, [(CH_3)$_3$C]}, 2.44 (s, 3 H, CH_3-Ts), 3.31 (br. dd, J_{gem} = 14.3, $J_{6b,5}$ = 3.0 Hz, 1 H, 6b-H), 3.33 (m, 2 H, 2-H), 3.50 (dd, J_{gem} = 14.3, $J_{6a,5}$ = 3.7 Hz, 1 H, 6a-H), 4.33 (m, 1 H, 5-H), 4.35 (m, 1 H, 4-H), 4.81 (ddd, $J_{3,2}$ = 8.6, 6.7, $J_{3,4}$ = 3.0 Hz, 1 H, 3-H), 7.48 (m, 2 H, *m*-Ts-H), 7.82 (m, 2 H, *o*-Ts-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 20.63 (CH_3-Ts), 24.40, 25.92 [(CH_3)$_2$C], 27.70 [(CH_3)$_3$C], 40.93 (CH_2-2), 41.92 (CH_2-6), 71.48 (CH-4), 72.00 (CH-5), 74.00 (CH-3), 78.95 [C(CH_3)$_3$], 108.78 [C(CH_3)$_2$], 127.11 (CH-*o*-Ts), 129.72 (CH-*m*-Ts), 133.39 (C-*i*-Ts), 144.67 (C-*p*Ts), 153.79 (CO) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2983 (s), 1693 (vs, br.), 1599 (m), 1495 (m), 1475 (m), 1456 (s), 1414 (vs), 1395 (s), 1384 (s), 1376 (vs, sh), 1368 (vs), 1309 (m), 1292 (m), 1260 (s), 1246 (s), 1190 (vs), 1178 (vs), 1163 (vs, sh), 1121 (m, sh), 1057 (m), 1035 (w), 1020 (m), 1001 (s), 988 (s), 855 (s), 815 (s), 704 (w), 571 (m), 554 (s), 513 (m) cm^{-1}. HRMS-ESI: calcd. for $C_{20}H_{29}O_7NNaS$ [M + Na]$^+$ 450.15569; found 450.15567.

(3*S*,4*R*,5*S*)-5-Azido-1-(*tert*-butoxycarbonyl)-3,4-*O*-isopropylidene-3,4-dihydroxypiperidine (26a): A mixture of compound **25** (8.58 g, 20.07 mmol) and lithium azide (2.95 g, 60 mmol) in DMF (200 mL) was stirred at 120 °C for 3 d. The solvent was removed in vacuo and the residue was applied onto a column of silica gel. Using a linear gradient of ethyl acetate in toluene, the desired product was obtained in 56% yield (3.35 g, 11.22 mmol) as a yellowish oil. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.32, 1.42 [2×s, 2×3 H, (CH_3)$_2$C], 1.44 {s, 9 H, [(CH_3)$_3$C]}, 3.10 (dd, J_{gem} = 13.4, $J_{6b,5}$ = 7.9 Hz, 1 H, 6b-H), 3.34 (dd, J_{gem} = 14.5, $J_{2b,3}$ = 3.5 Hz, 1 H, 2b-H), 3.64 (ddd, J_{gem} = 13.4, $J_{6a,5}$ = 4.1, $J_{6a,2a}$ = 0.9 Hz, 1 H, 6a-H), 3.76 (ddd, $J_{5,6}$ = 7.9, 4.1, $J_{5,4}$ = 5.7 Hz, 1 H, 5-H), 3.85 (ddd, J_{gem} = 14.5, $J_{2a,3}$ = 3.5, $J_{2a,6a}$ = 0.9 Hz, 1 H, 2a-H), 4.12 (t, $J_{4,3}$ =

$J_{4,5}$ = 5.7 Hz, 1 H, 4-H), 4.29 (dt, $J_{3,4}$ = 5.7, $J_{3,2}$ = 3.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 25.08, 27.09 [$(CH_3)_2C$], 27.73 [$(CH_3)_3C$], 41.97 (CH_2-6), 42.41 (CH_2-2), 58.56 (CH-5), 71.47 (CH-3), 74.51 (CH-4), 79.06 [$C(CH_3)_3$], 108.47 [$C(CH_3)_2$], 154.18 (CO) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2985 (s), 2109 (vs), 1691 (vs, br.), 1477 (s), 1456 (s), 1413 (vs), 1394 (s), 1385 (vs), 1375 (vs), 1368 (vs), 1247 (vs), 1160 (vs), 1055 (s, sh), 1039 (m), 857 (m, sh), 556 (w), 514 (w, sh) cm^{-1}. HRMS-ESI: calcd. for $C_{13}H_{22}O_4N_4Na$ [M + Na]$^+$ 321.15333; found 321.15333.

(3*S*,4*R*,5*S*)-5-Amino-1-(*tert*-butoxycarbonyl)-3,4-*O*-isopropylidene-3,4-dihydroxypiperidine (26b): Compound **26a** (3.35 g, 11.22 mmol) in ethanol (150 mL) was hydrogenated using Pd/C catalyst (0.4 g) overnight. The catalyst was filtered off through Celite and the solvent was removed in vacuo. The title compound was obtained by flash chromatography on silica gel using a linear gradient of ethanol in chloroform, as a colorless oil; yield 75% (2.3 g, 8.45 mmol). ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.29, 1.37 [2 × q, ^4J = 0.7 Hz, 2 × 3 H, $(CH_3)_2C$], 1.42 {s, 9 H, [$(CH_3)_3C$]}, 2.88 (dd, J_{gem} = 12.7, $J_{6b,5}$ = 7.2 Hz, 1 H, 6b-H), 3.95 (ddd, $J_{5,6}$ = 7.2, 3.8, $J_{5,4}$ = 5.3 Hz, 1 H, 5-H), 3.44 (dd, J_{gem} = 14.1, $J_{2b,3}$ = 3.8 Hz, 1 H, 2b-H), 3.46 (ddd, J_{gem} = 12.7, $J_{6a,5}$ = 4.0, $J_{6a,2a}$ = 0.9 Hz, 1 H, 6a-H), 3.67 (dd, J_{gem} = 14.1, $J_{2a,3}$ = 3.8 Hz, 1 H, 2a-H), 3.86 (dd, $J_{4,3}$ = 6.4, $J_{4,5}$ = 5.3 Hz, 1 H, 4-H), 4.21 (dt, $J_{3,4}$ = 6.4, $J_{3,2}$ = 3.8 Hz, 1 H, 3-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 25.03, 27.15 [$(CH_3)_2C$], 27.86 [$(CH_3)_3C$], 42.41 (CH_2-2), 45.36 (CH_2-6), 49.09 (CH-5), 71.37 (CH-3), 77.51 (CH-4), 78.29 [$C(CH_3)_3$], 107.49 [$C(CH_3)_2$], 154.48 (CO) ppm. HRMS-ESI: calcd. for $C_{13}H_{25}O_4N_2$ [M + H]$^+$ 273.18088; found 273.18089.

(3*S*,4*R*,5*S*)-5-[3-(3-Ethoxyacryloyl)ureido]-1-(*tert*-butoxycarbonyl)-3,4-*O*-isopropylidene-3,4-dihydroxypiperidine (28): 2-Nitrophenyl (3-ethoxyacryloyl)carbamate (0.56 g, 2 mmol) was added to a solution of amine **26b** (0.5 g, 1.84 mmol) in dioxane (20 mL). The reaction mixture was stirred at r.t. overnight, then the solvent was removed in vacuo and the title compound was purified by chromatography on silica gel using a linear gradient of ethyl acetate in toluene; yield 70% (0.55 g, 1.29 mmol); yellowish foam. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.28 (t, J_{vic} = 7.0 Hz, 3 H, CH_3CH_2O), 1.30, 1.42 [2 × s, ^4J = 0.6 Hz, 2 × 3 H, $(CH_3)_2C$], 1.43 [s, 9 H, $(CH_3)_3C$], 3.15 (dd, J_{gem} = 13.1, $J_{6'b,5'}$ = 7.3 Hz, 1 H, 6′b-H), 3.56 (dd, J_{gem} = 14.5, $J_{2'b,3'}$ = 3.7 Hz, 1 H, 2′b-H), 3.60 (ddd, J_{gem} = 13.1, $J_{6'a,5'}$ = 4.0, $J_{6'a,2'a}$ = 0.8 Hz, 1 H, 6′a-H), 3.79 (dd, J_{gem} = 14.5, $J_{2'a,3'}$ = 3.7 Hz, 1 H, 2′a-H), 3.88 (dddd, $J_{5',NH}$ = 7.8, $J_{5',6'}$ = 7.3, 4.0, $J_{5',4'}$ = 5.5 Hz, 1 H, 5′-H), 3.99 (q, J_{vic} = 7.0 Hz, 2 H, CH_3CH_2O), 4.13 (dd, $J_{4',3'}$ = 6.1, $J_{4',5'}$ = 5.5 Hz, 1 H, 4′-H), 4.27 (dt, $J_{3',4'}$ = 6.1, $J_{3',2'}$ = 3.7 Hz, 1 H, 3′-H), 5.57 (d, J_{vic} = 12.3 Hz, 1 H, 5-H), 7.54 (d, J_{vic} = 12.3 Hz, 1 H, 6-H), 8.57 (d, $J_{NH,5'}$ = 7.8 Hz, 1 H, NH-1), 9.74 (br. s, 1 H, NH-3) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 13.91 (CH_3CH_2O), 25.12, 27.06 [$(CH_3)_2C$], 27.75 [$(CH_3)_3C$], 42.46 (CH_2-6′), 42.74 (CH_2-2′), 47.93 (CH-3′), 67.11 (CH_3CH_2O), 71.12 (CH-5′), 74.23 (CH-4′), 78.81 [$C(CH_3)_3$], 98.43 (CH-5), 107.99 [$C(CH_3)_2$], 153.09 (C-2), 154.26 (CO), 161.64 (CH-6), 167.60 (C-4) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3429 (w), 3238 (w, br.), 3135 (w, sh), 3105 (w), 2985 (m), 1704 (s, sh), 1687 (vs, sh), 1679 (vs), 1626 (s, sh), 1614 (s), 1548 (s), 1494 (m), 1475 (m), 1458 (m), 1408 (m), 1396 (m), 1384 (m), 1376 (m, sh), 1369 (m), 1245 (s), 1166 (s), 1109 (m), 1075 (m, sh), 1064 (m), 1016 (w), 962 (vw), 859 (w, sh), 512 (w) cm^{-1}. HRMS-ESI: calcd. for $C_{19}H_{31}N_3O_7Na$ [M + Na]$^+$ 436.20542; found 436.20527.

(3*S*,4*R*,5*S*)-1-(4,5-Dihydroxypiperidin-5-yl)uracil (29): A mixture of **28** (0.45 g, 1.05 mmol), dioxane (15 mL), and 1 M aq. H_2SO_4 was stirred at 90 °C overnight. The mixture was diluted with water (40 mL) and applied onto a column of Dowex 50 (H$^+$) ion exchanger. The resin was washed consecutively with 50% aq. ethanol (200 mL) and water (100 mL), and the title compound was eluted with 3% aq. ammonia. The pure compound **29** was then obtained by preparative reverse-phase HPLC; yield 94% (0.24 g, 0.99 mmol); white amorphous solid; $[\alpha]^{20}$ = +96 (c = 0.329, H_2O). ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 60 °C): δ = 2.56 (br. t, J_{gem} = $J_{6'b,5'}$ = 11.9 Hz, 1 H, 6′b-H), 2.59 (dd, J_{gem} = 13.9, $J_{2'b,3'}$ = 1.6 Hz, 1 H, 2′b-H), 2.81–2.87 (m, 2 H, 2′a, 6′a-H), 3.76 (m, 1 H, 3′-H), 3.79 (dd, $J_{4',5'}$ = 10.7, $J_{4',3'}$ = 3.0 Hz, 1 H, 4′-H), 4.40 (ddd, $J_{5',6'b}$ = 11.9, $J_{5',4'}$ = 10.7, $J_{5',6'a}$ = 4.7 Hz, 1 H, 5′-H), 4.48 (br. s, 1 H, OH), 4.58 (br. s, 1 H, OH), 5.51 (d, $J_{5,6}$ = 7.9 Hz, 1 H, 5-H), 7.62 (d, $J_{6,5}$ = 8.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 48.05 (CH_2-6′), 50.30 (CH_2-2′), 56.79 (CH-5′), 69.26 (CH-3′), 69.68 (CH-4′), 100.66 (CH-5), 142.96 (CH-6), 151.49 (C-2), 163.11 (C-4) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3480 (w, br., sh), 3288 (m, v br.), 3190 (br. m, sh), 2901 (m, v br.), 1686 (vs, br.), 1625 (m, sh), 1463 (m), 1385 (m), 1257 (m), 1101 (m), 1066 (m), 990 (w, br.), 811 (w), 766 (w), 719 (w) cm^{-1}. HRMS-ESI: calcd. for $C_9H_{14}O_4N_3$ [M + H]$^+$ 228.0979; found 228.0978.

(4*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-4,5-*O*-isopropylidene-4,5-dihydroxypiperidin-3-one (30): Dess–Martin periodinate (12.1 g, 28.5 mmol) was added to a solution of **24** (5.18 g, 19 mmol) in CH_2Cl_2 (200 mL) at r.t. The reaction mixture was stirred for 2 h then washed with sat. $NaHCO_3$. The title compound was purified by chromatography on silica gel using a linear gradient of ethyl acetate in toluene; yield 78% (4 g, 14.74 mmol); thick yellowish oil that solidified on standing in a refrigerator. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.32, 1.33 [2 × s, 2 × 3 H, $(CH_3)_2C$], 1.43 {s, 9 H, [$(CH_3)_3C$]}, 3.52 (dd, J_{gem} = 14.6, $J_{6b,5}$ = 3.2 Hz, 1 H, 6b-H), 3.82 (dd, J_{gem} = 17.4, $J_{2b,4}$ = 0.7 Hz, 1 H, 2b-H), 3.88 (ddd, J_{gem} = 14.6, $J_{6a,5}$ = 3.6, $J_{6a,2a}$ = 1.7 Hz, 1 H, 6a-H), 4.21 (ddd, J_{gem} = 17.4, $J_{2a,6a}$ = 1.7, $J_{2a,4}$ = 0.7 Hz, 1 H, 2a-H), 4.46 (dt, $J_{4,5}$ = 7.5, $J_{4,2}$ = 0.7 Hz, 1 H, 4-H), 4.58 (ddd, $J_{5,4}$ = 6.8, $J_{5,6}$ = 3.6, 3.2 Hz, 1 H, 5-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 25.01, 26.40 [$(CH_3)_2C$], 27.70 [$(CH_3)_3C$], 44.21 (CH_2-6), 52.80 (CH_2-2), 74.55 (CH-5), 76.57 (CH-4), 79.36 [$C(CH_3)_3$], 109.72 [$C(CH_3)_2$], 153.78 (CO), 202.07 (C-3) ppm. IR ([D$_6$]DMSO): $\tilde{\nu}_{max}$ = 2981 (m), 2935 (m), 1737 (m), 1694 (vs), 1478 (w), 1456 (m), 1416 (m), 1393 (m), 1383 (m), 1372 (m, sh), 1368 (s), 1265 (m, sh), 1247 (s), 1158 (vs), 1122 (m), 1085 (m) cm^{-1}. HRMS-ESI: calcd. for $C_{13}H_{21}O_5NNa$ [M + Na]$^+$ 294.1312; found 294.1309.

(3*S*,4*R*,5*R*)-5-(Benzylamino)-1-(*tert*-butoxycarbonyl)-3,4-*O*-isopropylidene-3,4-dihydroxypiperidine (31): Sodium triacetoxyborohydride (3 g, 14 mmol) was added to a mixture of compound **30** (2.54 g, 9.36 mmol) and benzylamine (2 mL, 18.72 mmol) in CH_2Cl_2 (100 mL), and the mixture was stirred at r.t. under an argon atmosphere for 5 h. The solvents were removed in vacuo and the title compound was obtained by chromatography on silica gel using a linear gradient of ethanol in chloroform; yield 64% (2.16 g, 5.96 mmol); yellowish oil. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.30, 1.38 [2 × quint, ^4J = ^5J = 0.6 Hz, 2 × 3 H, $(CH_3)_2C$], 1.40 {s, 9 H, [$(CH_3)_3C$]}, 2.85 (dddd, $J_{5,6}$ = 11.7, 5.1, $J_{5,4}$ = 3.0, $J_{5,3}$ = 0.6 Hz, 1 H, 5-H), 2.97 (t, J_{gem} = $J_{6b,5}$ = 11.7 Hz, 1 H, 6b-H), 3.16 (dd, J_{gem} = 14.1, $J_{2b,3}$ = 3.4 Hz, 1 H, 2b-H), 3.46 (dd, J_{gem} = 11.7, $J_{6a,5}$ = 5.1 Hz, 1 H, 6a-H), 3.53 (dd, J_{gem} = 14.1, $J_{2a,3}$ = 4.0 Hz, 1 H, 2a-H), 3.84 (s, 2 H, CH_2Ph), 4.27 (ddd, $J_{3,4}$ = 7.2, $J_{3,2}$ = 4.0, 3.4 Hz, 1 H, 3-H), 4.44 (ddd, $J_{4,3}$ = 7.2, $J_{4,5}$ = 3.0, $J_{4,6a}$ = 1.0 Hz, 1 H, 4-H), 7.22 (m, 1 H, *p*-Ph-H), 7.30 (m, 2 H, *m*-Ph-H), 7.35 (m, 2 H, *o*-Ph-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]-DMSO, 100 °C): δ = 24.48, 26.28 [$(CH_3)_2C$], 27.88 [$(CH_3)_3C$], 41.99 (CH_2-2), 42.35 (CH_2-6), 49.75 (CH_2Ph); 51.98 (CH-5), 71.91 (CH-3), 72.03 (CH-4), 78.25 [$C(CH_3)_3$], 107.56 [$C(CH_3)_2$], 126.20 (CH-*p*-Ph), 127.41 (CH-*o*-Ph), 127.75 (CH-*m*Ph), 140.73 (C-*i*-Ph), 154.24

(CO) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3345 (vw, br.), 3088 (vw), 3066 (vw), 2983 (m), 2935 (m), 1686 (vs), 1604 (vw), 1586 (vw), 1495 (w), 1476 (m, sh), 1465 (m, sh), 1455 (m), 1413 (s), 1393 (m), 1384 (m), 1375 (m, sh), 1368 (s), 1355 (w, sh), 1316 (w), 1260 (m, sh), 1245 (s), 1163 (s), 1145 (m, sh), 1070 (m), 1053 (m), 1028 (w), 1000 (m), 855 (w), 700 (m), 513 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{31}O_4N_2$ $[M + H]^+$ 363.2278; found 363.2277.

(3*S*,4*R*,5*R*)-5-Amino-1-(*tert*-butoxycarbonyl)-3,4-*O*-isopropylidene-3,4-dihydroxypiperidine (32): Compound **31** (2.16 g, 5.96 mmol) in methanol (200 mL) was hydrogenated in the presence of Pd/C catalyst (0.6 g) overnight. The catalyst was removed by filtration through Celite and the solvent was removed in vacuo. The title compound was obtained in 95% yield (1.38 g, 5.066 mmol) as a colorless oil. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.30, 1.36 [2 × s, 2 × 3 H, $(CH_3)_2C$], 1.41 {s, 9 H, $[(CH_3)_3C]$}, 2.92 (m, 6b,5-H), 3.14 (dd, J_{gem} = 14.2, $J_{2b,3}$ = 3.1 Hz, 1 H, 2b-H), 3.28 (m, 1 H, 6a-H), 3.57 (dd, J_{gem} = 14.2, $J_{2a,3}$ = 3.6 Hz, 1 H, 2a-H), 4.24 (m, 1 H, 4-H), 4.29 (ddd, $J_{3,4}$ = 7.3, $J_{3,2}$ = 3.6, 3.1 Hz, 1 H, 3-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 24.43, 26.21 $[(CH_3)_2C]$, 27.92 $[(CH_3)_3C]$, 41.69 (CH_2-2), 44.85 (CH_2-6), 46.63 (CH-5), 72.05 (CH-3), 74.71 (CH-4), 78.18 $[C(CH_3)_3]$, 107.41 $[C(CH_3)_2]$, 154.29 (CO) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3385 (w), 3321 (vw, br.), 2983 (m), 1687 (vs), 1583 (w, br.), 1475 (m), 1465 (m, sh), 1415 (s), 1394 (m), 1383 (m), 1376 (m, sh), 1368 (s), 1246 (s), 1172 (s, sh), 1162 (s), 1140 (m), 1051 (m), 1005 (w, sh), 854 (m), 513 (w) cm^{-1}. HRMS-ESI: calcd. for $C_{13}H_{25}O_4N_2$ $[M + H]^+$ 273.18088; found 273.18087.

(3*S*,4*R*,5*R*)-5-[3-(3-Ethoxyacryloyl)ureido]-1-(*tert*-butoxycarbonyl)-3,4-*O*-isopropylidene-3,4-dihydroxypiperidine (33): 2-Nitrophenyl (3-ethoxyacryloyl)carbamate (0.84 g, 3 mmol) was added to a solution of the amine **32** (0.7 g, 2.57 mmol) in dioxane (25 mL), and the reaction mixture was stirred at r.t. for 4 h. The solvent was removed in vacuo and the title compound was obtained by chromatography on silica gel using a linear gradient of ethyl acetate in toluene in 69% yield (0.73 g, 1.77 mmol) as a yellowish foam. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 80 °C): δ = 1.27 (t, J_{vic} = 7.1 Hz, 3 H, CH_3CH_2O), 1.31, 1.39 [2 × s, 2 × 3 H, $(CH_3)_2C$], 1.41 {s, 9 H, $[(CH_3)_3C]$}, 3.00 (t, J_{gem} = $J_{6'b,5'}$ = 11.6 Hz, 6′b-H), 3.25 (br. d, J_{gem} = 14.4 Hz, 1 H, 2′b-H), 3.64 (dd, J_{gem} = 11.6, $J_{6'a,5'}$ = 5.2 Hz, 1 H, 6′a-H), 3.64 (dd, J_{gem} = 14.4, $J_{2'a,3'}$ = 2.6 Hz, 1 H, 2′a-H), 3.98 (q, J_{vic} = 7.1 Hz, 2 H, CH_3CH_2O), 4.09 (m, 1 H, 3′-H), 4.37 (m, 1 H, 4′-H), 4.39 (m, 1 H, 5′-H), 5.54 (d, J_{vic} = 12.3 Hz, 1 H, 5-H), 7.57 (d, J_{vic} = 12.3 Hz, 1 H, 6-H), 8.87 (d, $J_{NH,3'}$ = 8.4 Hz, 1 H, NH-1), 9.94 (br. s, 1 H, NH-3) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 80 °C): δ = 14.17 (CH_3CH_2O), 24.45, 26.24 $[(CH_3)_2C]$, 27.99 $[(CH_3)_3C]$, 41.26 (CH_2-6′), 41.45 (CH_2-2′), 45.09 (CH-5′), 67.31 (CH_3CH_2O), 71.94 (CH-3′), 72.12 (CH-4′), 78.74 $[C(CH_3)_3]$, 98.38 (CH-5), 108.14 $[C(CH_3)_2]$, 153.14 (C-2), 154.33 (CO), 162.10 (CH-6), 167.67 (C-4) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3428 (w), 3270 (br. m, sh), 3238 (m, br.), 3133 (w, br., sh), 3106 (w, br.), 2984 (s), 1704 (vs, sh), 1686 (vs), 1677 (vs, sh), 1626 (s), 1614 (s), 1542 (vs), 1495 (m), 1474 (s), 1458 (s), 1411 (s), 1394 (s), 1384 (s), 1376 (m, sh), 1368 (s), 1242 (s), 1172 (vs, sh), 1163 (vs), 1137 (s), 1075 (m), 1052 (m), 1004 (m), 977 (w), 962 (w), 850 (m), 512 (m) cm^{-1}. HRMS-ESI: calcd. for $C_{19}H_{31}O_7N_3Na$ $[M + Na]^+$ 436.2054; found 436.2052.

(3*S*,4*R*,5*R*)-1-(4,5-Dihydroxypiperidin-5-yl)uracil (34): A mixture of compound **33** (0.73 g, 1.77 mmol) and Dowex 50 H^+ (10 g) in dioxane (40 mL) was stirred at 90 °C for 3 h. The reaction mixture was then poured into an empty column. The resin was washed consecutively with 50% aq. ethanol (100 mL) and water (100 mL), and the title compound was eluted with 3% aq. ammonia (250 mL). The title compound was obtained by preparative reverse-phase HPLC in 57% yield (0.33 g, 1.45 mmol) as a white amorphous solid. $[\alpha]^{20}$ = +111.5 (*c* = 0.695, H_2O). ^{1}H NMR (500.0 MHz, D_2O, 25 °C): δ = 2.68 (dd, J_{gem} = 12.8, $J_{2'b,3'}$ = 11.4 Hz, 1 H, 2′b-H), 2.90 (dd, J_{gem} = 12.1, $J_{6'b,5'}$ = 4.3 Hz, 1 H, 6′b-H), 2.92 (dd, J_{gem} = 12.8, $J_{2'a,3'}$ = 5.1 Hz, 1 H, 2′a-H), 3.07 (t, J_{gem} = $J_{6'a,5'}$ = 12.1 Hz, 1 H, 6′a-H), 3.82 (ddd, $J_{3',2'}$ = 11.4, 5.1, $J_{3',4'}$ = 2.9 Hz, 1 H, 3′-H), 4.15 (dd, $J_{4',3'}$ = 2.9, $J_{4',5'}$ = 1.7 Hz, 1 H, 4′-H), 4.56 (td, $J_{5',6'}$ = 12.1, 4.3, $J_{5',4'}$ = 1.7 Hz, 1 H, 5′-H), 5.80 (d, $J_{5,6}$ = 8.1 Hz, 1 H, 5-H), 7.72 (d, $J_{6,5}$ = 8.1 Hz, 1 H, 6-H) ppm. ^{13}C NMR (125.7 MHz, D_2O, 25 °C): δ = 43.20 (CH_2-6′), 46.47 (CH_2-2′), 57.19 (CH-5′), 70.67 (CH-3′), 71.85 (CH-4′), 103.62 (CH-5), 147.43 (CH-6), 155.01 (C-2), 169.14 (C-4) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3400 (m, v br., sh), 3298 (m, br.), 3190 (br. m, sh), 1687 (vs, br.), 1618 (m, sh), 1463 (m), 1384 (m), 1263 (m), 1078 (m), 1060 (w, sh), 1016 (w), 994 (w), 810 (w), 765 (w), 719 (w) cm^{-1}. HRMS-ESI: calcd. for $C_9H_{14}O_4N_3$ $[M + H]^+$ 228.0979; found 228.0978.

(3*S*,4*R*,5*R*)-5-*O*-Benzyl-1-(*tert*-butoxycarbonyl)-3,4-*O*-isopropylidene-3,4,5-trihydroxypiperidine (35): Sodium hydride (6.9 g, 172.2 mmol) was added to a solution of **24** (15.69 g, 57.4 mmol) and benzyl bromide (10 mL, 86.1 mmol) in THF (600 mL) at room temp. The reaction mixture was heated to reflux for 5 h, then cooled to 0 °C, and acetic acid (10 mL, 172.2 mmol) was slowly added (*CAUTION!* hydrogen evolution!). The solvents were then removed in vacuo and the desired product was obtained by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene; yield 75% (15.7 g, 43.23 mmol). ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 80 °C): δ = 1.29, 1.36 [2 × s, 2 × 3 H, $(CH_3)_2C$], 1.40 {s, 9 H, $[(CH_3)_3C]$}, 3.16 (br. dd, J_{gem} = 14.3, $J_{2b,3}$ = 3.4 Hz, 1 H, 2b-H), 3.21 (dd, J_{gem} = 11.6, $J_{6b,5}$ = 10.6 Hz, 1 H, 6b-H), 3.41 (ddd, J_{gem} = 11.6, $J_{6a,5}$ = 5.4, $J_{6a,4}$ = 1.0 Hz, 1 H, 6a-H), 3.54 (dd, J_{gem} = 14.3, $J_{2a,3}$ = 3.8 Hz, 1 H, 2a-H), 3.78 (ddd, $J_{5,6}$ = 10.6, 5.4, $J_{5,4}$ = 2.9 Hz, 1 H, 5-H), 4.29 (ddd, $J_{3,4}$ = 7.3, $J_{3,2}$ = 3.8, 3.4 Hz, 1 H, 3-H), 4.53 (ddd, $J_{4,3}$ = 7.3, $J_{4,5}$ = 2.9, $J_{4,6a}$ = 1.0 Hz, 1 H, 4-H), 4.58, 4.64 (2 × d, J_{gem} = 12.0 Hz, 2 × 1 H, CH_2Ph), 7.29 (m, 1 H, *p*-Ph-H), 7.35 (m, 4 H, *o*,*m*-Ph-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 80 °C): δ = 24.63, 26.30 $[(CH_3)_2C]$, 27.97 $[(CH_3)_3C]$, 41.28 (CH_2-6), 42.21 (CH_2-2), 70.26 (CH_2Ph), 71.43 (CH-4), 72.09 (CH-5), 72.21 (CH-3), 78.58 $[C(CH_3)_3]$, 108.18 $[C(CH_3)_2]$, 127.26 (CH-*p*-Ph), 127.32 (CH-*o*-Ph), 128.02 (CH-*m*Ph), 138.33 (C-*i*-Ph), 154.30 (CO) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3082 (w), 3067 (w), 2983 (s), 1688 (vs, br.), 1606 (vw), 1586 (vw), 1496 (m), 1474 (s), 1464 (s, sh), 1455 (s), 1415 (vs, br.), 1394 (s), 1384 (vs), 1374 (s, sh), 1368 (vs), 1314 (m), 1260 (s, sh), 1245 (vs), 1239 (vs), 1172 (vs, sh), 1164 (vs, br.), 1148 (s, sh), 1092 (vs), 1070 (s), 1052 (s, sh), 1028 (m, sh), 1010 (s, sh), 912 (w), 855 (s), 699 (s), 513 (m), 461 (vw) cm^{-1}. HRMS-ESI: calcd. for $C_{20}H_{29}O_5NNa$ $[M + Na]^+$ 386.1938; found 386.1937.

(3*R*,4*S*,5*S*)-3-*O*-Benzyl-1-(*tert*-butoxycarbonyl)-3,4,5-trihydroxypiperidine (36): Compound **35** (33 g, 91 mmol) was dissolved in 1.5% TFA/CH_2Cl_2 (600 mL) containing water (4 mL). The reaction mixture was vigorously stirred and monitored by TLC (EtOH/$CHCl_3$, 10%). Upon completion, $NaHCO_3$ (20 g) was added and the suspension was vigorously stirred until a neutral pH value was reached. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. Preparative chromatography on silica gel using a linear gradient of ethanol in chloroform provided the desired product in 81% yield (23.82 g, 73.71 mmol). ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 80 °C): δ = 1.39 (s, 9 H, $[(CH_3)_3C]$), 2.96 (br. dd, J_{gem} = 12.6, $J_{6b,5}$ = 9.9 Hz, 1 H, 6b-H), 3.07 (dd, J_{gem} = 12.6, $J_{2b,3}$ = 9.8 Hz, 1 H, 2b-H), 3.35 (ddd, $J_{3,2}$ = 9.8, 4.5, $J_{3,4}$ = 2.5 Hz, 1 H, 3-H), 3.39 (dddd, $J_{5,6}$ = 9.9, 4.7, $J_{5,OH}$ = 6.9, $J_{5,4}$ = 2.5 Hz, 1 H, 5-H), 3.57 (dddd, J_{gem} = 12.6, $J_{6a,5}$ = 4.7, ^4J = 1.4, 0.7 Hz, 1 H, 6a-

H), 3.66 (br. dd, J_{gem} = 12.6, $J_{2a,3}$ = 4.5 Hz, 1 H, 2a-H), 3.99 (br. dt, $J_{4,OH}$ = 3.6, $J_{4,3}$ = $J_{4,5}$ = 2.5 Hz, 1 H, 4-H), 4.33 (br. d, $J_{OH,4}$ = 3.6 Hz, 1 H, OH-4), 4.36 (br. d, $J_{OH,5}$ = 6.9 Hz, 1 H, OH-5), 3.54, 3.61 (2×d, J_{gem} = 12.1 Hz, 2×1 H, CH_2Ph), 7.28 (m, 1 H, *p*-Ph-H), 7.34 (m, 2 H, *m*-Ph-H), 7.36 (m, 2 H, *o*-Ph-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 80 °C): δ = 27.87 [(**C**H$_3$)$_3$C], 41.26 (CH_2-2), 44.16 (CH_2-6), 67.24 (CH-5), 68.20 (CH-4), 69.57 (CH_2Ph), 74.98 (CH-3), 78.70 [**C**(CH$_3$)$_3$], 127.11 (CH-*p*-Ph), 127.24 (CH-*o*-Ph), 128.91 (CH-*m*Ph), 138.48 (C-*i*-Ph), 154.11 (CO) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3570 (s), 3495 (s, br.), 3090 (w), 3067 (m), 2981 (s), 1686 (vs, v br.), 1610 (w, sh), 1587 (w), 1496 (m), 1475 (s), 1464 (s, sh), 1455 (vs), 1428 (vs, br.), 1394 (vs), 1368 (vs), 1312 (s, sh), 1236 (vs, br.), 1167 (vs, br.), 1135 (vs), 1093 (vs), 1076 (vs), 1054 (vs), 1029 (s), 1003 (m), 913 (w), 699 (s) cm^{-1}. HRMS-ESI: calcd. for $C_{17}H_{25}O_5NNa$ [M + Na]$^+$ 346.1625; found 346.1625.

(3*R*,4*R*,5*S*)-3-*O*-Benzyl-1-(*tert*-butoxycarbonyl)-3,4,5-trihydroxypiperidin-3,4-yl Sulfite (37): Thionyl chloride (5.32 mL, 73.15 mmol) was added dropwise to a solution of **36** (19.7 g, 60.96 mmol), and triethylamine (21.24 mL, 152.4 mmol) in CH_2Cl_2 (600 mL) at 0 °C. After 1 h, the temperature was increased to r.t. and the reaction mixture was extracted with saturated aq. $NaHCO_3$ (300 mL). The organic phase was dried with sodium sulfate and concentrated in vacuo. The title product was obtained as a mixture of two diastereoisomers (due to chiral S atom), after purification by chromatography on silica gel using a linear gradient of ethanol in chloroform; yield 98% (22.07 g, 59.74 mmol). ^1H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.39, 1.40 {2×s, 2×9 H, [(CH$_3$)$_3$C]}, 3.16 (dd, J_{gem} = 12.1, $J_{2b,3}$ = 10.6 Hz, 1 H, 2b-H), 3.22 (dd, J_{gem} = 13.3, $J_{2b,3}$ = 3.1 Hz, 1 H, 2b-H), 3.49 (dd, J_{gem} = 15.1, $J_{6b,5}$ = 3.7 Hz, 1 H, 6b-H), 3.63 (dd, J_{gem} = 14.4, $J_{6b,5}$ = 6.0 Hz, 1 H, 6b-H), 3.68–3.75 (m, 3 H, 2×H-2a, 6a-H), 3.89 (dt, $J_{3,4}$ = 6.7, $J_{3,2}$ = 3.1 Hz, 1 H, 3-H), 3.96 (ddd, $J_{3,2}$ = 10.6, 5.3, $J_{3,4}$ = 3.3 Hz, 1 H, 3-H), 3.98 (br. dd, J_{gem} = 15.1, $J_{6a,5}$ = 3.5 Hz, 1 H, 6a-H), 4.57, 4.63, 4.67, 4.70 (4×d, J_{gem} = 12.1 Hz, CH_2Ph), 4.94–5.00 (m, 2 H, 5-H), 5.11, 5.26 (2×m, 2×1 H, 4-H), 7.26–7.38 (m, 10 H, *o*,*m*,*p*-Ph-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 27.72, 27.75 [(CH$_3$)$_3$C], 41.50, 41.59, 41.79, 42.76 (6, CH_2-2), 70.37 (CH_2Ph); 70.39 (CH-3), 70.76 (CH_2Ph), 71.04 (CH-3), 75.60, 77.62 (CH-5), 77.96 (CH-4), 79.10, 79.12 [C(CH$_3$)$_3$], 80.22 (CH-4), 126.96, 127.07 (CH-*p*-Ph), 127.22, 127.25 (CH-*o*-Ph), 127.80, 127.91 (CH-*m*Ph), 137.76, 137.83 (C-*i*-Ph), 153.52, 153.95 (CO) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3092 (w), 3071 (w), 3026 (w), 3007 (w), 2977 (m), 1693 (vs), 1609 (w), 1586 (w), 1499 (w), 1478 (m), 1464 (m, sh), 1454 (s), 1428 (s), 1391 (w), 1365 (m), 1316 (w), 1306 (w), 1281 (m), 1275 (m), 1240 (s), 1205 (s), 1171 (s), 1095 (m), 1075 (m), 1031 (w), 1012 (s), 998 (m, sh), 763 (s), 732 (s), 695 (m), 674 (m), 460 (w) cm^{-1}. HRMS-ESI: calcd. for $C_{17}H_{23}O_6NSNa$ [M + Na]$^+$ 392.1138; found 392.1137.

(3*R*,4*S*,5*R*)-1-(*tert*-Butoxycarbonyl)-3,4-dihydroxy-5-(trifluoroacetamido)piperidine (38a), (3*S*,4*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3,5-dihydroxy-4-(trifluoroacetamido)piperidine (38b): A mixture of compound **37** (9 g, 24.36 mmol) and LiN_3 (5 g, 100 mmol) in DMF (140 mL) was stirred at 90 °C for 3 d. The solvent was removed in vacuo and the crude material was purified by chromatography on silica gel using a linear gradient of ethyl acetate in toluene to provide a mixture of isomeric azido derivatives (ratio, 1:2) in 92% yield (7.78 g, 22.33 mmol) as a yellowish thick oil. This mixture of isomers was then dissolved in ethanol (400 mL) and subjected to hydrogenation in the presence of Pd/C catalyst (1 g) overnight. The catalyst was removed by filtration through Celite, then ethyl trifluoroacetate (3.6 mL, 30 mmol) was added and the mixture was stirred at r.t. overnight. The solvent was removed in vacuo and the expected mixture of isomeric trifluoroacetamides was obtained by chromatography on silica gel using a linear gradient of ethyl acetate in toluene. The mixture was dissolved in ethanol (300 mL) and subjected to hydrogenation in the presence of Pd/C catalyst (2 g) overnight. The title trifluoroacetamide isomers were finally separated by chromatography on silica gel using a linear gradient of ethyl acetate in toluene to provide **38b** (24%, 5.79 mmol) and **38a** (43%, 10.54 mmol) as white amorphous solids (yields calculated over four reaction steps).

Compound 38a: ^1H NMR (500.0 MHz, [D$_6$]DMSO, 80 °C): δ = 1.40 {s, 9 H, [(CH$_3$)$_3$C]}, 2.77 (m, 1 H, 6b-H), 2.95 (dd, J_{gem} = 12.9, $J_{2b,3}$ = 1.5 Hz, 1 H, 2b-H), 3.57 (br. d, $J_{4,5}$ = 9.4 Hz, 1 H, 4-H), 3.78 (br. m, 1 H, 3-H), 3.82 (br. m, 1 H, 2a-H), 3.85 (br. m, 1 H, 6a-H), 3.90 (td, $J_{5,4}$ = 9.4, $J_{5,6}$ = 9.4, 4.7 Hz, 1 H, 5-H), 4.49 (br. d, $J_{OH,3}$ = 3.3 Hz, 1 H, OH-3), 4.56 (br. d, $J_{OH,4}$ = 4.3 Hz, 1 H, OH-4), 8.94 (br. s, 1 H, NH) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 80 °C): δ = 27.96 [(CH$_3$)$_3$C], 44.54 (CH_2-6), 47.49 (CH_2-2), 48.66 (CH-5), 66.85 (CH-3), 70.66 (CH-4), 78.70 [C(CH$_3$)$_3$], 115.83 (q, $J_{C,F}$ = 288.6 Hz, CF_3), 154.51 (CO), 156.40 (q, $J_{C,F}$ = 36.1 Hz, $COCF_3$) ppm. ^{19}F NMR (470.3 MHz, [D$_6$]-DMSO, 80 °C): δ = –70.76 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3433 (m, br.), 3325 (br. m, sh), 2982 (m), 1708 (vs), 1674 (s), 1558 (m), 1479 (m), 1464 (m, sh), 1434 (s), 1396 (m), 1369 (s), 1305 (m), 1247 (s), 1212 (s), 1187 (vs, sh), 1165 (vs), 1140 (s), 1081 (m), 727 (m), 519 (w) cm^{-1}. HRMS-ESI: calcd. for $C_{12}H_{18}O_5N_2F_3$ (M – H)$^-$ 327.1173; found 327.1175.

Compound 38b: ^1H NMR (500.0 MHz, [D$_6$]DMSO, 80 °C): δ = 1.42 {s, 9 H, [(CH$_3$)$_3$C]}, 2.96 (br. dd, J_{gem} = 13.5, $J_{2b,3\&6b,5}$ = 10.5 Hz, 2 H, 2b,6b-H), 3.42 (ddt, $J_{3,2\&5,6}$ = 10.5, 5.2, $J_{3,4\&5,4}$ = 9.6, $J_{3,OH\&5,OH}$ = 5.2 Hz, 2 H, 3,5-H), 3.49 (br. t, $J_{4,3}$ = $J_{4,5}$ = 9.6 Hz, 1 H, 4-H), 4.39 (ddd, J_{gem} = 13.5, $J_{2a,3\&6a,5}$ = 5.2, $J_{2a,4\&6a,4}$ = 2.0 Hz, 2 H, 2a,6a-H), 4.95 (br. d, $J_{OH,3\&OH,5}$ = 5.2 Hz, 2 H, OH-3,5), 8.74 (br. s, 1 H, NH) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 80 °C): δ = 27.93 [(CH$_3$)$_3$C], 49.02 (CH_2-2,6), 61.04 (CH-4), 66.60 (CH-3,5), 79.02 [C(CH$_3$)$_3$], 116.08 (q, $J_{C,F}$ = 288.9 Hz, CF_3), 153.76 (CO), 156.54 (q, $J_{C,F}$ = 35.5 Hz, $COCF_3$) ppm. ^{19}F NMR (470.3 MHz, [D$_6$]DMSO, 80 °C): δ = –70.81 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3419 (m, br.), 3340 (m, sh), 3275 (m, sh), 2982 (w), 1726 (s, sh), 1707 (vs), 1672 (vs), 1567 (m, br.), 1480 (m), 1466 (m), 1436 (s), 1396 (m), 1370 (m), 1309 (m), 1254 (m, sh), 1215 (s), 1184 (vs), 1165 (vs), 1149 (vs, sh), 1095 (m), 1068 (m), 1023 (m), 728 (w), 518 (vw) cm^{-1}. HRMS-ESI: calcd. for $C_{12}H_{18}O_5N_2F_3$ (M – H)$^-$ 327.1173; found 327.1169.

(3*R*,4*S*,5*R*)-5-Amino-1-(*tert*-butoxycarbonyl)-3,4-dihydroxypiperidine (39a): Dowex 1 (OH$^-$ form; 8 g) was added to a solution of **38a** (6.73 mmol) in a mixture of ethanol (25 mL) and water (10 mL). The reaction mixture was stirred at r.t. for 30 min, then the resin was filtered off and the filtrate was concentrated in vacuo to provide the desired product **39a** in 88% yield (1.38 g, 5.94 mmol) as a white amorphous solid. ^1H NMR (500.0 MHz, [D$_6$]DMSO, 80 °C): δ = 1.42 {s, 9 H, [(CH$_3$)$_3$C]}, 2.68 (dd, J_{gem} = 12.8, $J_{6b,5}$ = 8.1 Hz, 1 H, 6b-H), 2.84 (ddd, $J_{5,6}$ = 8.1, 4.3, $J_{5,4}$ = 7.7 Hz, 1 H, 5-H), 3.08 (dd, J_{gem} = 13.3, $J_{2b,3}$ = 2.9 Hz, 1 H, 2b-H), 3.19 (dd, $J_{4,5}$ = 7.7, $J_{4,3}$ = 3.2 Hz, 1 H, 4-H), 3.63 (ddd, J_{gem} = 13.3, $J_{2a,3}$ = 2.9, $J_{2a,6a}$ = 1.7 Hz, 1 H, 2a-H), 3.69 (ddd, J_{gem} = 12.8, $J_{6a,5}$ = 4.3, $J_{6a,2a}$ = 1.7 Hz, 1 H, 6a-H), 3.72 (ddd, $J_{3,2}$ = 5.4, 2.9, $J_{3,4}$ = 3.2 Hz, 1 H, 3-H), 3.95, 4.02 (2 br. d, 2×1 H, 2×OH) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 80 °C): δ = 27.88 [(**C**H$_3$)$_3$C], 47.04 (CH_2-2), 47.54 (CH_2-6), 49.13 (CH-5), 66.27 (CH-3), 74.66 (CH-4), 78.05 [**C**(CH$_3$)$_3$], 154.50 (CO) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3499 (m), 3456 (s), 3359 (s), 3345 (s), 3333 (s), 3288 (m), 2977 (s), 1683 (vs), 1665 (vs), 1609 (m), 1593 (m), 1481 (s), 1457 (s), 1439 (vs), 1428 (s, sh), 1390 (s), 1366 (s), 1247 (s), 1202 (s), 1174 (vs), 1145 (vs), 1089 (s, sh),

1076 (s, sh), 1056 (m, sh) cm^{-1}. HRMS-ESI: calcd. for $C_{10}H_{20}O_4N_2Na$ $[M + Na]^+$ 255.1315; found 255.1316.

(3*S*,4*R*,5*R*)-4-Amino-1-(*tert*-butoxycarbonyl)-3,5-dihydroxypiperidine (39b): Dowex 1 anion exchanger (OH^- form; 8 g) was added to a solution of **38b** (1.47 g, 4.48 mmol) in a solvent mixture of ethanol (20 mL) and water (10 mL). The reaction mixture was stirred at r.t. for 2 h, then the resin was filtered off and the filtrate was concentrated in vacuo to provide the desired product in 91% yield (0.95 g, 4.09 mmol) as a white foam. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.41 {s, 9 H, [$(CH_3)_3C$]}, 2.35 (br. t, $J_{4,3} = J_{4,5}$ = 8.9 Hz, 1 H, 4-H), 2.47 (br. dd, J_{gem} = 13.1, $J_{2b,3\&6b,5}$ = 10.4 Hz, 2 H, 2b,6b-H), 3.04 (ddd, $J_{3,2\&5,6}$ = 10.4, 5.3, $J_{3,4\&5,4}$ = 8.9 Hz, 2 H, 3,5-H), 3.92, 3.93 (2 × dd, J_{gem} = 13.1, $J_{2a,3\&6a,5}$ = 5.3 Hz, 2 × 1 H, 2a,6a-H), 4.65 (br. s, 2 H, OH-3,5) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 27.81 [$(CH_3)_3C$], 48.43 (CH_2-2,6), 61.85 (CH-4), 69.75 (CH-3,5), 78.58 [$C(CH_3)_3$], 153.76 (CO) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3562 (m), 3491 (m), 3413 (br. m, sh), 3373 (s), 3341 (s, br.), 3313 (s, sh), 3085 (w, v br.), 3000–2400 (m, v br.), 2996 (m), 2974 (m), 1691 (vs), 1667 (s), 1632 (w), 1563 (w), 1485 (s), 1465 (m), 1425 (vs), 1393 (m), 1367 (s), 1258 (s), 1236 (s), 1173 (vs), 1152 (m, sh), 1138 (m), 1074 (s), 1050 (vs), 1014 (m, br.) cm^{-1}. HRMS-ESI: calcd. for $C_{10}H_{20}O_4N_2Na$ $[M + Na]^+$ 255.1315; found 255.1313.

(3*R*,4*S*,5*R*)-1-(*tert*-Butoxycarbonyl)-3,4-dihydroxy-5-[3-(3-ethoxyacryloyl)ureido]piperidine (40): 4-Nitrophenyl (3-ethoxyacryloyl)-carbamate (1 g, 3.5 mmol) was added to a solution of amine **39a** (0.44 g, 1.89 mmol) in dioxane (40 mL). The reaction mixture was stirred at r.t. for 4 h, then the solvent was removed in vacuo and the title compound was purified by chromatography on silica gel using a linear gradient of ethanol in chloroform, as a yellowish foam in 79% yield (0.56 g, 1.5 mmol). ^{1}H NMR (500.0 MHz, [D$_6$]-DMSO, 100 °C): δ = 1.27 (t, J_{vic} = 7.0 Hz, 3 H, CH_3CH_2O), 1.40 {s, 9 H, [$(CH_3)_3C$]}, 3.19 (dd, J_{gem} = 13.2, $J_{6'b,5'}$ = 6.3 Hz, 1 H, 6′b-H), 3.34 (dd, J_{gem} = 13.0, $J_{2'b,3'}$ = 6.6 Hz, 1 H, 2′b-H), 3.38 (dd, J_{gem} = 13.0, $J_{2'a,3'}$ = 4.1 Hz, 1 H, 2′a-H), 3.57–3.65 (m, 3 H, 6′a,3′,4′-H), 3.81 (dtd, $J_{5',NH}$ = 7.8, $J_{5',4'}$ = 6.3, $J_{5',6'}$ = 6.3, 3.7 Hz, 1 H, 5′-H), 3.98 (q, J_{vic} = 7.0 Hz, 2 H, CH_3CH_2O), 4.38 (br. s, 1 H, OH-3′), 4.49 (br. s, 1 H, OH-4′), 5.56 (d, J_{vic} = 12.3 Hz, 1 H, 5-H), 7.52 (d, J_{vic} = 12.3 Hz, 1 H, 6-H), 8.51 (d, $J_{NH,5'}$ = 7.8 Hz, 1 H, NH-1), 9.68 (br. s, 1 H, NH-3) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 13.95 (CH_3CH_2O), 27.79 [$(CH_3)_3C$], 43.74 (CH_2-6′), 45.61 (CH_2-2′), 48.97 (CH-5′), 65.88 (CH-3′), 67.07 (CH_3CH_2O), 70.19 (CH-4′), 78.48 [$C(CH_3)_3$], 98.52 (CH-5), 153.25 (C-2), 154.17 (CO), 161.46 (CH-6), 167.49 (C-4) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3500 (br. m, sh), 3418 (m, v br.), 3272 (m, br.), 3143 (w, br.), 2982 (m), 1698 (vs, sh), 1692 (vs), 1678 (vs), 1613 (s), 1556 (s, sh), 1545 (s), 1500 (w, sh), 1426 (m), 1396 (w), 1368 (m), 1480 (m), 1473 (m, sh), 1246 (s), 1211 (m), 1171 (s, br.), 1143 (s), 1063 (m), 985 (w), 978 (w, sh) cm^{-1}. HRMS-ESI: calcd. for $C_{16}H_{27}O_7N_3Na$ $[M + Na]^+$ 396.1741; found 396.1742.

(3*R*,4*S*,5*R*)-1-(3,4-Dihydroxypiperidin-5-yl)uracil (41): A mixture of **40** (0.84 g, 2.25 mmol) and Dowex 50 (H^+) ion exchange resin (9 g) in dioxane (30 mL) was stirred at 90 °C for 3 h. The reaction mixture was then poured into an empty column. The resin was washed consecutively with 50% aq. ethanol (150 mL) and water (150 mL), and the title compound was eluted with 3% aq. ammonia (250 mL). The title compound was obtained by reverse-phase preparative HPLC as a white amorphous solid in a 64% yield (0.33 g, 1.44 mmol). ^{1}H NMR, ^{13}C NMR, IR, and HRMS-ESI data were identical to those of enantiomeric compound **29**. $[\alpha]^{20}$ = –85 (*c* = 0.247, H_2O).

(3*R*,4*S*,5*R*)-5-[(5-Amino-6-chloropyrimidin-4-yl)amino]-1-(*tert*-butoxycarbonyl)-3,4-dihydroxypiperidine (43): A mixture of amine **39a** (2 g, 8.61 mmol), 3-amino-4,6-dichloropyrimidine (2.8 g, 17.22 mmol), and triethylamine (5.1 mL, 37 mmol) in *n*-butanol (80 mL) was stirred in a pressure vessel at 130 °C for 3 d. The solvent was removed in vacuo and the title compound was purified by chromatography on silica gel using a linear gradient of ethanol in chloroform; yield 57% (1.76 g, 4.89 mmol); brown foam. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.35 [s, 9 H, $(CH_3)_3C$], 3.07 (m, 1 H, 6′b-H), 3.23 (br. dd, J_{gem} = 13.3, $J_{2'b,3'}$ = 3.1 Hz, 1 H, 2′b-H), 3.57 (br. dd, J_{gem} = 13.3, $J_{2'a,3'}$ = 5.8 Hz, 1 H, 2′a-H), 3.67 (dd, $J_{4',5'}$ = 7.7, $J_{4',3'}$ = 3.0 Hz, 1 H, 4′-H), 3.81 (m, 1 H, 6′a-H), 3.88 (dt, $J_{3',2'a}$ = 6.0, $J_{3',2'b} = J_{3',4'}$ = 3.0 Hz, 1 H, 3′-H), 4.22 (m, 1 H, 5′-H), 4.88 (br. s, 2 H, NH_2), 6.25 (br. d, $J_{NH,5'}$ = 6.9 Hz, 1 H, NH), 7.76 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 27.79 [$(CH_3)_3C$], 44.18 (CH_2-6′), 46.08 (CH_2-2′), 50.32 (CH-5′), 66.14 (CH-3′), 70.94 (CH-4′), 78.25 [$C(CH_3)_3$], 123.47 (C-5), 137.66 (C-6), 145.38 (CH-2), 152.07 (C-4), 155.35 (CO) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3417 (s, br.), 3255 (br. m, sh), 2976 (m), 2685 (w, v br., sh), 1693 (s, br.), 1660 (s, br.), 1633 (m, sh), 1578 (vs), 1495 (m, sh), 1476 (m, sh), 1462 (m), 1423 (s), 1394 (m), 1367 (m), 1338 (w), 1244 (m), 1212 (m), 1166 (s), 1137 (m), 1053 (m), 848 (w), 769 (w) cm^{-1}. HRMS-ESI: calcd. for $C_{14}H_{23}O_4N_5Cl$ $[M + H]^+$ 360.1433; found 360.1436.

(3*R*,4*S*,5*R*)-6-Chloro-9-[1(-*tert*-butoxycarbonyl)-3,4-dihydroxypiperidin-5-yl]purine (44): Compound **43** (1.08 g, 3 mmol) was dissolved in diethoxymethyl acetate (30 mL, 180 mmol) and the solution was stirred under an argon atmosphere at r.t. for 3 h. The reaction mixture was stirred at 80 °C for 2 d, then the excess diethoxymethyl acetate was removed in vacuo and the title compound was obtained by flash chromatography on silica gel using a linear gradient of ethyl acetate in toluene; yield 49% (0.54 g, 1.46 mmol); brownish foam. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.42 [s, 9 H, $(CH_3)_3C$], 3.53 (dd, J_{gem} = 13.2, $J_{6'b,5'}$ = 11.1 Hz, 1 H, 6′b-H), 3.53 (dd, J_{gem} = 14.9, $J_{2'b,3'}$ = 3.4 Hz, 1 H, 2′b-H), 4.08 (ddd, J_{gem} = 13.2, $J_{6'a,5'}$ = 4.8, $J_{6'a,2'a}$ = 1.6 Hz, 1 H, 6′a-H), 4.22 (ddd, J_{gem} = 14.9, $J_{2'a,3'}$ = 3.4, $J_{2'a,6'a}$ = 1.6 Hz, 1 H, 2′a-H), 4.44 (dt, $J_{3',4'}$ = 5.6, $J_{3',2'}$ = 3.4 Hz, 1 H, 3′-H), 4.89 (dd, $J_{4',5'}$ = 8.3, $J_{4',3'}$ = 5.6 Hz, 1 H, 4′-H), 5.04 (ddd, $J_{5',6'}$ = 11.1, 4.8, $J_{5',4'}$ = 8.3 Hz, 1 H, 5′-H), 8.71 (s, 1 H, 8-H), 8.76 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 27.69 [$(CH_3)_3C$], 43.44 (CH_2-2′), 43.95 (CH_2-6′), 54.71 (CH-5′), 73.22 (CH-3′), 73.56 (CH-4′), 79.51 [$C(CH_3)_3$], 131.00 (C-5), 145.61 (CH-8), 149.34 (C-6), 151.10 (CH-2), 151.81 (C-4), 153.83 (CO) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3422 (w, v br.), 2979 (m), 1700 (vs), 1592 (s), 1561 (s), 1489 (m), 1478 (m), 1436 (s, sh), 1418 (s, br.), 1400 (s, sh), 1367 (m), 1337 (s), 1230 (m), 1200 (s), 1166 (vs), 1149 (s, sh), 1090 (s), 1017 (m), 935 (s), 793 (w), 649 (w), 637 (m) cm^{-1}. HRMS-ESI: calcd. for $C_{15}H_{21}O_4N_5Cl$ $[M + H]^+$ 370.1282; found 370.1284.

(3*R*,4*S*,5*R*)-9-(3,4-Dihydroxypiperidin-5-yl)adenine (45): Concentrated aq. ammonia (20 mL) was added to chloropurine derivative **44** (0.31 g, 0.84 mmol) and the reaction mixture was stirred at r.t. for 3 d. The reaction mixture was concentrated in vacuo, 3 M HCl (30 mL) was added, and the reaction mixture was stirred at 80 °C overnight. The reaction mixture was diluted with water (40 mL) and applied onto a column of Dowex 50 H^+ ion exchanger. The resin was then washed consecutively with 50% aq. ethanol (200 mL) and water (100 mL), and the title compound was eluted with 3% aq. ammonia. The product was finally purified by reverse-phase preparative HPLC to provide **45** in 50% yield (0.104 g, 0.416 mmol) as a white amorphous solid; $[\alpha]^{20}$ = +80 (*c* = 0.236, H_2O).^{1}H NMR (500.0 MHz, D_2O, 25 °C): δ = 3.46 (dd, J_{gem} = 13.6, $J_{2'b,3'}$ = 1.4 Hz, 1 H, 2′b-H), 3.61 (ddd, J_{gem} = 13.6, $J_{2'a,3'}$ =

3.2, $J_{2'a,6'b}$ = 1.9 Hz, 1 H, 2′a-H), 3.78 (ddd, J_{gem} = 12.8, $J_{6'b,5'}$ = 5.4, $J_{6'b,2'a}$ = 1.9 Hz, 1 H, 6′b-H), 3.84 (dd, J_{gem} = 12.8, $J_{6'a,5'}$ = 12.1 Hz, 1 H, 6′a-H), 4.44 (ddd, $J_{3',2'a}$ = 3.2, 1.4, $J_{3',4'}$ = 2.9 Hz, 1 H, 3′-H), 4.60 (dd, $J_{4',5'}$ = 10.7, $J_{4',3'}$ = 2.9 Hz, 1 H, 4′-H), 5.15 (td, $J_{5',6'}$ = 12.1, 5.4, $J_{5',4'}$ = 10.7 Hz, 1 H, 5′-H), 8.45 (s, 2 H, 2,8-H) ppm. ^{13}C NMR (125.7 MHz, D_2O, 25 °C): δ = 47.05 (CH_2-6′), 51.06 (CH_2-2′), 54.96 (CH-5′), 68.43 (CH-3′), 71.60 (CH-4′), 121.49 (C-5), 146.63 (CH-8), 147.00 (CH-2), 151.68 (C-4), 152.69 (C-6) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3401 (s, br.), 3333 (s, br.), 3210 (s, br.), 2935 (m, br.), 2700 (w, br., sh), 1642.9 (vs), 1600 (s), 1574 (m), 1505 (w), 1476 (m), 1415 (m), 1371 (w), 1330 (m), 1304 (m), 1207 (w), 1091 (m), 798 (w), 727 (w), 705 (w), 650 (m) cm^{-1}. HRMS-FAB: calcd. for $C_{10}H_{15}O_2N_6$ $[M + H]^+$ 251.12510; found 251.12519.

(3*R*,4*S*,5*R*)-9-(3,4-Dihydroxypiperidin-5-yl)-6-oxopurine (46): Chloropurine derivative **44** (0.28 g, 0.76 mmol) in 3 M HCl (10 mL) was stirred at 90 °C overnight. The reaction mixture was then diluted with water (40 mL) and applied onto a column of Dowex 50 H^+ ion exchange resin, which was washed consecutively with 50% aq. ethanol (200 mL) and water (100 mL), and the title compound was eluted with 3% aq. ammonia. After solvent evaporation, **46** (78%, 0.15 g, 0.593 mmol) was obtained as a white amorphous solid. $[\alpha]^{20}$ = –54 (*c* = 0.165, H_2O). ^{1}H NMR (500.0 MHz, D_2O, 25 °C): δ = 3.37 (dd, J_{gem} = 14.2, $J_{2'b,3'}$ = 0.9 Hz, 1 H, 2′b-H), 3.53 (dd, J_{gem} = 14.2, $J_{2'a,3'}$ = 3.5 Hz, 1 H, 2′a-H), 3.78 (m, 2 H, 6′-H), 4.39 (br. dd, $J_{3',2'a}$ = 3.5, $J_{3',4'}$ = 2.9 Hz, 1 H, 3′-H), 4.54 (dd, $J_{4',5'}$ = 10.7, $J_{4',3'}$ = 2.9 Hz, 1 H, 4′-H), 5.02 (td, $J_{5',6'}$ = 10.7, 6.5, $J_{5',4'}$ = 10.7 Hz, 1 H, 5′-H), 8.19 (s, 1 H, 2-H), 8.22 (s, 1 H, 8-H) ppm. ^{13}C NMR (125.7 MHz, D_2O, 25 °C): δ = 47.70 (CH_2-6′), 51.10 (CH_2-2′), 55.06 (CH-5′), 68.89 (CH-3′), 71.98 (CH-4′), 126.56 (C-5), 143.80 (CH-8), 148.47 (CH-2), 151.94 (C-4), 161.34 (C-6) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3424 (vs, br.), 1694 (s), 1637 (m, br.), 1587 (m), 1517 (w), 1418 (w), 1346 (w), 1216 (w), 1150 (w), 1093 (w), 1010 (w), 788 (w), 647 (w) cm^{-1}. HRMS-ESI: calcd. for $C_{10}H_{14}O_3N_5$ $[M + H]^+$ 252.10912; found 252.10911.

(3*R*,4*S*,5*R*)-5-[(2,5-Diamino-6-chloropyrimidin-4-yl)amino]-1-(*tert*-butoxycarbonyl)-3,4-dihydroxypiperidine (48): A mixture of amine **39a** (2.44 g, 10.5 mmol), 2,5-diamino-4,6-dichloropyrimidine (3.76 g, 21 mmol), and triethylamine (7.3 mL, 52.5 mmol) in *n*-butanol (80 mL) was stirred in a pressure vessel at 135 °C overnight. The solvent was removed in vacuo and the title compound was recovered by chromatography on silica gel using a linear gradient of ethanol in chloroform; yield 76% (2.99 g, 7.98 mmol); light-brown foam. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 80 °C): δ = 1.37 [s, 9 H, $(CH_3)_3$C], 3.05 (br. m, 1 H, 6′b-H), 3.21 (br. d, J_{gem} = 12.6 Hz, 1 H, 2′b-H), 3.53 (m, 1 H, 2′a-H), 3.64 (dd, $J_{4',5'}$ = 8.1, $J_{4',3'}$ = 2.9 Hz, 1 H, 4′-H), 3.74 (br. d, J_{gem} = 13.3 Hz, 1 H, 6′a-H), 3.82 (dt, $J_{3',2'}$ = 6.1, 2.9, $J_{3',4'}$ = 2.9 Hz, 1 H, 3′-H), 4.13 (m, $J_{5',4'}$ = 8.1, $J_{5',NH}$ = 7.6, $J_{5',6'}$ = 6.8, 4.3 Hz, 1 H, 5′-H), 4.43, 5.37 (2 ×br. s, 2×2 H, NH_2), 6.03 (br. d, $J_{NH,5'}$ = 7.6 Hz, 1 H, NH-5′) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 80 °C): δ = 27.92 [$(CH_3)_3$C], 45.75 (CH_2-6′), 46.46 (CH_2-2′), 49.89 (CH-5′), 66.16 (CH-3′), 70.98 (CH-4′), 78.37 [$C(CH_3)_3$], 113.38 (C-5), 141.72 (C-6), 154.38 (CO), 155.45, 155.51 (C-2,4) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3532 (w, sh), 3501 (w), 3420 (m, sh), 3395 (m), 3330 (br. m, sh), 3220 (w, br., sh), 2980 (s), 2574 (w, br.), 2453 (w, br.), 1686 (s), 1610 (s), 1570 (vs), 1504 (m), 1473 (s, sh), 1455 (s), 1431 (s), 1393 (m), 1368 (m), 1347 (w, sh), 1248 (s), 1164 (s), 1111 (m), 1092 (m) cm^{-1}. HRMS-ESI: calcd. for $C_{14}H_{24}O_4N_6Cl$ $[M + H]^+$ 375.15421; found 375.15430.

(3*R*,4*S*,5*R*)-1-(*tert*-Butoxycarbonyl)-6-chloro-9-(3,4-dihydroxypiperidin-5-yl)purine (49): Diethoxymethyl acetate (1.43 mL, 8.78 mmol) was added to a solution of **48** (2.99 g, 7.98 mmol) in DMF (80 mL) and the reaction mixture was stirred first at r.t. for 4 h and then at 120 °C overnight. The solvent was removed in vacuo and the chloroguanine intermediate **49** was obtained by chromatography on silica gel using a linear gradient of ethanol in chloroform; yield 67% (2.06 g, 5.35 mmol); brownish amorphous solid. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.43 [s, 9 H, $(CH_3)_3$C], 3.32 (dd, J_{gem} = 12.9, $J_{6'b,5'}$ = 11.1 Hz, 1 H, 6′b-H), 3.06 (dd, J_{gem} = 13.8, $J_{2'b,3'}$ = 1.7 Hz, 1 H, 2′b-H), 4.44 (ddd, $J_{3',4'}$ = 3.0, $J_{3',2'}$ = 3.5, 1.7 Hz, 1 H, 3′-H), 4.22 (ddd, J_{gem} = 13.8, $J_{2'a,3'}$ = 3.5, $J_{2'a,6'a}$ = 2.2 Hz, 1 H, 2′a-H), 4.13 (ddd, J_{gem} = 12.9, $J_{6'a,5'}$ = 4.8, $J_{6'a,2'a}$ = 2.2 Hz, 1 H, 6′a-H), 4.18 (dd, $J_{4',5'}$ = 10.7, $J_{4',3'}$ = 3.0 Hz, 1 H, 4′-H), 4.56 (ddd, $J_{5',6'}$ = 11.1, 4.8, $J_{5',4'}$ = 10.7 Hz, 1 H, 5′-H), 4.60 (br. s, 2 H, OH-3′,5′), 6.43 (br. s, 2 H, NH_2), 8.10 (s, 1 H, 8-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 27.82 [$(CH_3)_3$C], 45.18 (CH_2-2′), 47.99 (CH_2-6′), 52.74 (CH-5′), 67.28 (CH-3′), 70.20 (CH-4′), 78.81 [$C(CH_3)_3$], 123.70 (C-5), 141.87 (CH-8), 149.20 (C-6), 154.33, 154.39 (C-4, CO), 159.25 (C-2) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3494 (br. m, sh), 3385 (s), 3219 (m), 2976 (m), 2931 (w), 1693 (s, sh), 1679 (s), 1612 (vs), 1566 (s), 1514 (m), 1467 (s), 1428 (s), 1407 (s), 1395 (s, sh), 1367 (s), 1319 (w, sh), 1280 (m, sh), 1263 (m), 1247 (m), 1199 (m), 1166 (s), 1001 (w), 863 (w), 784 (w), 764 (w), 640 (w) cm^{-1}. HRMS-ESI: calcd. for $C_{15}H_{22}O_4N_6Cl$ $[M + H]^+$ 385.13856; found 385.13860.

(3*R*,4*S*,5*R*)-9-(3,4-Dihydroxypiperidin-5-yl)guanine (50): Compound **49** (2.06 g, 5.35 mmol) was treated with 1.5 M HCl (40 mL) at 75 °C overnight. The reaction mixture was diluted with water (40 mL) and applied onto a column of Dowex 50 H^+ ion exchange resin (50 mL), which was washed consecutively with 50% aq. ethanol (200 mL) and water (300 mL), and the title compound was eluted with 3% aq. ammonia (400 mL). After evaporation of solvents, the obtained yellowish solid was suspended in a hot water/ethanol mixture (2:1, 50 mL), cooled down, and filtered. The desired compound was obtained in 95% yield (1.35 g, 5.08 mmol) as a beige amorphous powder. $[\alpha]^{20}$ = –43 (*c* = 0.309, H_2O). ^{1}H NMR (500.0 MHz, D_2O, 25 °C): δ = 3.42 (dd, J_{gem} = 13.6, $J_{2'b,3'}$ = 1.5 Hz, 1 H, 2′b-H), 3.59 (ddd, J_{gem} = 13.6, $J_{2'a,3'}$ = 3.3, $J_{2'a,6'}$ = 1.5 Hz, 1 H, 2′a-H), 3.79 (m, 2 H, 6′-H), 4.43 (m, 1 H, 3′-H), 4.58 (dd, $J_{4',5'}$ = 10.6, $J_{4',3'}$ = 2.9 Hz, 1 H, 4′-H), 5.02 (td, $J_{5',6'}$ = 10.6, 6.1, $J_{5',4'}$ = 10.6 Hz, 1 H, 5′-H), 8.69 (s, 1 H, 8-H) ppm. ^{13}C NMR (125.7 MHz, D_2O, 25 °C): δ = 46.60 (CH_2-6′), 50.97 (CH_2-2′), 55.50 (CH-5′), 68.34 (CH-3′), 71.03 (CH-4′), 113.38 (C-5), 140.34 (CH-8), 153.69 (C-4), 157.51 (C-2), 159.03 (C-6) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3394 (m), 3287 (m), 3241 (m), 3183 (m), 3003 (m), 2831 (m), 2793 (m), 2735 (m), 2684 (m), 2625 (w), 2552 (w), 1716 (vs), 1685 (w, sh), 1643 (vs), 1603 (m), 1560 (w), 1537 (w), 1400 (m), 1380 (m), 1091 (w), 1073 (w), 793 (w), 689 (w) cm^{-1}. HRMS-ESI: calcd. for $C_{10}H_{15}O_3N_6$ $[M + H]^+$ 267.12001; found 267.12004.

(3*S*,4*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-3,5-dihydroxy-4-[3-(3-ethoxyacryloyl)ureido]piperidine (51): 4-Nitrophenyl (3-ethoxyacryloyl)-carbamate (0.58 g, 2.1 mmol) was added to a solution of amino derivative **39b** (0.73 g, 3.14 mmol) in dioxane (40 mL). The reaction mixture was stirred at r.t. for 4 h, and the solvent was removed in vacuo. The title compound was obtained by chromatography on silica gel using a linear gradient of ethanol in chloroform; yield 72% (0.84 g, 2.25 mmol); yellowish foam. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.28 (t, J_{vic} = 7.0 Hz, 3 H, CH_3CH_2O), 1.42 {s, 9 H, [$(CH_3)_3$C]}, 2.58 (dd, J_{gem} = 12.6, $J_{2'b,3'\&6'b,5'}$ = 9.4 Hz, 2 H, 2′b,6′b-H), 3.31–3.41 (m, 3 H, 3′,4′,5′-H), 3.96 (m, 2 H, 2′a,6′a-H), 3.99 (q, J_{vic} = 7.0 Hz, 2 H, CH_3CH_2O), 4.93 (br. d, $J_{OH,3'\&OH,5'}$ = 4.3 Hz, 2 H, OH-3′,5′), 5.58 (d, J_{vic} = 12.3 Hz, 1 H, 5-H), 7.55 (d, J_{vic} = 12.3 Hz, 1 H, 6-H), 8.53 (d, $J_{NH,4'}$ = 6.3 Hz, 1 H, NH-1), 9.68 (br. s, 1 H, NH-3) ppm. ^{13}C NMR (125.7 MHz,

[D$_6$]DMSO, 100 °C): δ = 13.96 (CH_3CH_2O), 27.80 [$(CH_3)_3C$], 48.78 (CH_2-2′,6′), 60.91 (CH-4′), 67.06 (CH_3CH_2O), 67.72 (CH-3′,5′), 78.82 [$C(CH_3)_3$], 98.68 (CH-5), 153.65 (CO), 154.59 (C-2), 161.44 (CH-6), 167.42 (C-4) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3404 (m, v br.), 3333 (br. m, sh), 3259 (m, br.), 3220 (br. m, sh), 3112 (m, br.), 3095 (w, br., sh), 2982 (m), 1698 (vs), 1676 (vs), 1632 (m, sh), 1605 (s), 1562 (s), 1498 (w), 1478 (m), 1466 (m), 1420 (m), 1394 (m), 1366 (m), 1247 (s), 1183 (s), 1150 (s), 1135 (s), 1072 (m), 1055 (m), 1014 (m), 984 (w), 957 (w) cm^{-1}. HRMS-ESI: calcd. for $C_{16}H_{27}O_7N_3Na$ [M + Na]$^+$ 396.1741; found 396.1743.

(3*S*,4*R*,5*R*)-1-(3,5-Dihydroxypiperidin-4-yl)uracil (52): A mixture of compound **51** (0.56 g, 1.5 mmol) and Dowex 50 (H$^+$) ion exchange resin (7 g) in dioxane (25 mL) was stirred at 90 °C for 3 h. The resin was washed consecutively with 50% aq. ethanol (150 mL) and water (150 mL), and the title compound was eluted with 3% aq. ammonia (250 mL). The title compound was obtained by reverse-phase preparative HPLC in a yield of 81% (276 mg, 1.21 mmol) as a white amorphous solid. $[a]^{20}$ = 0 (c = 0.217, H_2O). ^{1}H NMR (500.0 MHz, MeOD, –80 °C): δ (conformation A) = 2.50 (dd, J_{gem} = 11.5, $J_{2'ax,3'} = J_{6'ax,5'}$ = 10.2 Hz, 2 H, 2′ax,6′ax-H), 3.16 (m, 2 H, 2′eq,6′eq-H), 3.64 (ddd, $J_{3',4'} = J_{5',4'}$ = 10.3, $J_{3',2'ax} = J_{5',6'ax}$ = 10.2, $J_{3',2'eq} = J_{5',6'eq}$ = 5.3 Hz, 2 H, 3′-H, 5′-H), 4.44 (t, $J_{4',3'} = J_{4',5'}$ = 10.3 Hz, 1 H, 4′-H), 5.82 (d, $J_{5,6}$ = 8.2 Hz, 1 H, 5-H), 7.88 (d, $J_{6,5}$ = 8.2 Hz, 1 H, 6-H) ppm; δ (conformation B) = 2.40 (dd, J_{gem} = 11.4, $J_{2'ax,3'} = J_{6'ax,5'}$ = 10.0, 2 H, H-2′ax,6′ax), 3.16 (m, 2 H, H-2′$_{eq}$,6′$_{eq}$), 3.24 (t, $J_{4',3'} = J_{4',5'}$ = 10.0, 1 H, H-4′), 4.51 (td, $J_{3',4'} = J_{5',4'} = J_{3',2'ax} = J_{5',6'ax}$ = 10.0, $J_{3',2'eq} = J_{5',6'eq}$ = 5.3, 2 H, H-3′, H-5′), 5.63 (d, $J_{5,6}$ = 8.0, 1 H, H-5), 7.50 (d, $J_{6,5}$ = 8.1, 1 H, H-6) ppm. ^{13}C NMR (125.7 MHz, MeOD, –80 °C): δ (conformation A) = 52.06 (CH_2-2′,6′), 65.70 (CH_2-4′), 69.13 (CH-3′,5′), 102.83 (CH-5), 142.99 (CH-6), 154.06 (C-2), 166.58 (C-4) ppm; δ (conformation B) = 51.84 (CH_2-2′,6′), 66.27 (CH_2-3′,5′), 79.11 (CH-4′), 100.94 (CH-5), 151.19 (CH-6), 152.33 (C-2), 167.44 (C-4) ppm. IR (KBr):$\tilde{\nu}_{max}$ = 3396 (m, br.), 3313 (br. m, sh), 3187 (br. m, sh), 2826 (w, v br.), 1682 (vs, br.), 1630 (m, sh), 1463 (m), 1385 (m), 1262 (m), 1083 (w), 1052 (m), 1017 (w), 811 (w), 766 (w), 719 (vw) cm^{-1}. HRMS-ESI: calcd. for $C_9H_{14}O_4N_3$ [M + H]$^+$ 228.0979; found 228.0978.

(3*S*,4*R*,5*R*)-4-[(5-Amino-6-chloropyrimidin-4-yl)amino]-1-(*tert*-butoxycarbonyl)-3,5-dihydroxypiperidine (53): A mixture of amine **39b** (0.35 g, 1.5 mmol), 3-amino-4,6-dichloropyrimidine (0.5 g, 3 mmol), and triethylamine (0.9 mL, 6.45 mmol) in *n*-butanol (15 mL) was stirred in a pressure vessel at 130 °C for 3 d. The solvent was removed in vacuo, and purified by preparative chromatography on silica gel using a linear gradient of ethanol in chloroform to provide the title compound in 61% yield (330 mg, 0.917 mmol) as a brown foam. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.44 {s, 9 H, [$(CH_3)_3C$]}, 2.68 (dd, J_{gem} = 13.0, $J_{2'b,3'\&6'b,5'}$ = 10.2 Hz, 2 H, 2′b,6′b-H), 3.52 (ddd, $J_{3',2'\&5',6'}$ = 10.2, 5.3, $J_{3',4'\&5',4'}$ = 9.3 Hz, 2 H, 3′,5′-H), 3.92 (td, $J_{4',3'} = J_{4',5'}$ = 9.3, $J_{4',NH}$ = 7.6 Hz, 1 H, 4′-H), 4.01 (dd, J_{gem} = 13.0, $J_{2'a,3'\&6'a,5'}$ = 5.3 Hz, 2 H, 2′a,6′a-H), 4.73 (br. s, 4 H, OH-3′,5′, NH_2), 6.38 (br. d, $J_{NH,4'}$ = 7.6 Hz, 1 H, NH), 7.71 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 27.81 [$(CH_3)_3C$], 48.85 (CH_2-2′,6′), 61.75 (CH-4′), 68.12 (CH-3′,5′), 78.77 [$C(CH_3)_3$], 123.16 (C-5), 137.57 (C-6), 145.16 (CH-2), 153.50 (C-4), 153.77 (CO) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3420 (br. s, sh), 3369 (s, br.), 3262 (m, br.), 2977 (m), 2710 (w, br., sh), 1697 (s), 1668 (s), 1584 (vs), 1496 (m, sh), 1479 (m, sh), 1466 (s), 1423 (s), 1395 (m), 1368 (m), 1340 (m), 1240 (m), 1217 (m), 1165 (s), 1138 (m), 1072 (m, sh), 1050 (m, sh), 1016 (m), 850 (w), 768 (w) cm^{-1}. HRMS-FAB: calcd. for $C_{14}H_{23}O_4N_5Cl$ [M + H]$^+$ 360.1433; found 360.1428.

(3*S*,4*R*,5*R*)-9-(3,5-Dihydroxypiperidin-4-yl)adenine (54): Diethoxymethyl acetate (0.2 mL, 1.3 mmol) was added to a solution of **53** (0.33 g, 0.92 mmol) in DMF (12 mL). The reaction mixture was stirred at r.t. for 2 h and then at 110 °C overnight. The solvent was removed in vacuo and the chloroguanine intermediate was purified by chromatography on silica gel using a linear gradient of ethanol in chloroform. Concentrated aq. ammonia (20 mL) was added and the reaction mixture was stirred at room temp. for 3 d. The reaction mixture was concentrated in vacuo, then 3 M HCl (30 mL) was added and the reaction mixture was stirred at 80 °C overnight. The reaction mixture was diluted with water (40 mL) and applied onto a column of Dowex 50 (H$^+$) ion exchange resin, which was washed consecutively with 50% aq. ethanol (200 mL) and water (100 mL), and the title compound was eluted with 3% aq. ammonia. The pure substance was purified by reverse-phase preparative HPLC as a white amorphous solid in a yield of 49% (113 mg, 0.45 mmol). $[a]^{20}$ = 0 (c = 0.279, H_2O). ^{1}H NMR (600.1 MHz, D_2O, 28 °C): δ = 2.62 (dd, J_{gem} = 12.8, $J_{2'b,3'\&6'b,5'}$ = 10.3 Hz, 2 H, 2′b,6′b-H), 3.32 (dd, J_{gem} = 12.8, $J_{2'a,3'\&6'a,5'}$ = 4.8 Hz, 2 H, 2′a,6′a-H), 4.22 (t, $J_{4',3'} = J_{4',5'}$ = 10.0 Hz, 1 H, 4′-H), 4.27 (ddd, $J_{3',2'b\&5',6'b}$ = 10.3, $J_{3'\&5',4'}$ = 10.0, $J_{3',2'a\&5',6'a}$ = 4.8 Hz, 2 H, 3′,5′-H), 8.21 (s, 1 H, 2-H), 8.26 (s, 1 H, 8-H) ppm. ^{13}C NMR (150.9 MHz, D_2O, 28 °C): δ = 52.69 (CH_2-2′,6′), 69.26 (CH-4′), 71.07 (CH-3′,5′), 121.63 (C-5), 144.21 (CH-8), 152.46 (C-4), 155.23 (CH-2), 158.40 (C-6) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3345 (s, br.), 2981 (m), 1751 (w), 1770 (w, sh), 1697 (vs), 1646 (m), 1608 (m), 1571 (m), 1550 (w), 1515 (w), 1479 (m), 1468 (m), 1424 (s), 1390 (m, sh), 1367 (s), 1340 (m, sh), 1308 (m), 1259 (s), 1235 (s), 1220 (s, sh), 1173 (s), 1162 (s), 1083 (m), 1072 (m), 1023 (m), 856 (w), 794 (w), 787 (w), 765 (w), 650 (m) cm^{-1}. HRMS-ESI: calcd. for $C_{10}H_{13}O_3N_6$ (M – H)$^-$ 249.1100; found 249.1097.

(3*S*,4*R*,5*R*)-4-[(2,5-Diamino-6-chloropyrimidin-4-yl)amino]-1-(*tert*-butoxycarbonyl)-3,5-dihydroxypiperidine (55): A mixture of amine **39b** (0.57 g, 2.45 mmol), 2,5-diamino-4,6-dichloropyrimidine (0.88 g, 4.9 mmol), and triethylamine (1.7 mL, 12.25 mmol) in *n*-butanol (25 mL) was stirred in a pressure vessel at 135 °C overnight. The solvent was removed in vacuo and the title compound was purified by chromatography on silica gel using a linear gradient of ethanol in chloroform; yield 47% (0.43 g, 1.15 mmol); brown foam. ^{1}H NMR (500.0 MHz, [D$_6$]DMSO, 100 °C): δ = 1.44 {s, 9 H, [$(CH_3)_3C$]}, 2.68 (dd, J_{gem} = 13.0, $J_{2'b,3'\&6'b,5'}$ = 10.3 Hz, 2 H, 2′b,6′b-H), 3.47 (ddd, $J_{3',2'\&5',6'}$ = 10.3, 5.0, $J_{3',4'\&5',4'}$ = 9.1 Hz, 2 H, 3′,5′-H), 3.76 (td, $J_{4',3'} = J_{4',5'}$ = 9.1, $J_{4',NH}$ = 6.8 Hz, 1 H, 4′-H), 4.00 (m, 2 H, 2′a,6′a-H), 4.88, 4.99, 5.33 (3 ×br. s, 3 × H, OH-3′,5′, NH_2), 6.17 (br. d, $J_{NH,4'}$ = 6.8 Hz, 1 H, NH) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO, 100 °C): δ = 27.82 [$(CH_3)_3C$], 48.81 (CH_2-2′,6′), 61.70 (CH-4′), 68.46 (CH-3′,5′), 78.78 [$C(CH_3)_3$], 113.10 (C-5), 140.07 (C-6), 153.71 (CO), 155.06, 156.80 (C-2,4) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3419 (vs, br.), 2977 (w), 1697 (s), 1642 (s, sh), 1635 (s, sh), 1623 (s), 1575 (s), 1501 (m), 1475 (m, sh), 1464 (m), 1455 (m, sh), 1425 (s), 1393 (m, sh), 1367 (m), 1346 (w), 1306 (w), 1257 (m), 1235 (m), 1165 (m), 1151 (m), 1102 (w, sh), 1092 (w), 869 (vw), 771 (w) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{24}O_4N_6Cl$ [M + H]$^+$ 375.15421; found 375.15428.

(3*S*,4*R*,5*R*)-9-(3,5-Dihydroxypiperidin-4-yl)guanine (56): Diethoxymethyl acetate (0.2 mL, 1.3 mmol) was added to a solution of **55** (0.43 g, 1.15 mmol) in DMF (12 mL). The reaction mixture was stirred at r.t. for 2 h and then at 110 °C overnight. The solvent was removed in vacuo and the chloroguanine intermediate was purified by chromatography on silica gel using a linear gradient of ethanol in chloroform. Without further characterization, at this point, it was treated with 1.5 M HCl (20 mL) at 75 °C overnight. The reaction mixture was diluted with water (40 mL) and applied onto a

column of Dowex 50 (H^+) ion exchange resin (40 mL), which was washed consecutively with 50% aq. ethanol (100 mL) and water (200 mL), and the title compound was eluted with 3% aq. ammonia (200 mL). The obtained yellowish solid was suspended in a hot water/ethanol mixture (2:1), which was then cooled and filtered. The desired compound was obtained in 71% (220 mg, 0.826 mmol) overall yield as a beige amorphous powder. $[a]^{20} = 0$ (c = 0.071, H_2O). ^1H NMR (500.0 MHz, D_2O, 25 °C): δ = 2.61 (dd, J_{gem} = 12.6, $J_{2'b,3'\&6'b,5'}$ = 10.7 Hz, 2 H, 2′b,6′b-H), 3.31 (dd, J_{gem} = 12.6, $J_{2'a,3'\&6'a,5'}$ = 4.8 Hz, 2 H, 2′a,6′a-H), 4.07 (t, $J_{4',3'} = J_{4',5'}$ = 10.3 Hz, 1 H, 4′-H), 4.21 (ddd, $J_{3',2'b\&5',6'b}$ = 10.7, $J_{3'\&5',4'}$ = 10.3, $J_{3',2'a\&5',6'a}$ = 4.8 Hz, 2 H, 3′,5′-H), 7.94 (s, 1 H, 8-H) ppm. ^{13}C NMR (125.7 MHz, D_2O, 25 °C): δ = 52.55 (CH_2-2′,6′), 68.41 (CH-4′), 70.89 (CH-3′,5′), 119.03 (C-5), 141.37 (CH-8), 155.46 (C-4), 156.37 (C-2), 161.90 (C-6) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3564 (w), 3460 (m, sh), 3411 (m), 3320 (s), 3292 (s, sh), 3133 (m, br.), 2779 (w, v br.), 1692 (vs), 1657 (m), 1622 (s), 1575 (m), 1535 (m), 1481 (m), 1416 (m), 1084 (m), 1045 (m), 779 (m), 643 (w) cm^{-1}. HRMS-ESI: calcd. for $C_{10}H_{15}O_3N_6$ $[M + H]^+$ 267.12001; found 267.12002.

(3*R*,4*R*,5*S*)-*N*-(4,5-Dihydroxypiperidin-3-yl)acetamide (57): Acetic anhydride (80 μL, 0.88 mmol) was added to a mixture of **26** (0.2 g, 0.73 mmol) and $NaHCO_3$ (70 mg, 0.88 mmol) in ethanol (10 mL). The reaction mixture was stirred at r.t. for 3 h, then the solvent was removed in vacuo and the acetylated intermediate was purified by chromatography on silica gel using a linear gradient of ethanol in chloroform. Without further characterization, the intermediate was dissolved in 20% TFA in CH_2Cl_2 (15 mL) and stirred at r.t. overnight. The solvent was removed in vacuo and the residue was co-evaporated with a 1:1 ethanol/toluene mixture (3 × 20 mL) to afford pure **57** in 80% (102 mg, 0.584 mmol) as a white amorphous solid. ^1H NMR (500.0 MHz, D_2O, 28 °C): δ = 2.04 (s, 3 H, CH_3), 3.17 (dd, J_{gem} = 12.7, $J_{2b,3}$ = 9.4 Hz, 1 H, 2b-H), 3.18 (dd, J_{gem} = 12.4, $J_{6b,5}$ = 9.0 Hz, 1 H, 6b-H), 3.25 (dd, J_{gem} = 12.7, $J_{2a,3}$ = 4.3 Hz, 1 H, 2a-H), 3.28 (dd, J_{gem} = 12.4, $J_{6a,5}$ = 4.2 Hz, 1 H, 6a-H), 4.08 (dd, $J_{4,3}$ = 3.1, $J_{4,5}$ = 2.6 Hz, 1 H, 4-H), 4.10 (ddd, $J_{5,6}$ = 9.0, 4.2, $J_{5,4}$ = 2.6 Hz, 1 H, 5-H), 4.25 (ddd, $J_{3,2}$ = 9.4, 4.3, $J_{3,4}$ = 3.1 Hz, 1 H, 3-H) ppm. ^{13}C NMR (125.7 MHz, D_2O, 28 °C): δ = 24.68 (CH_3), 44.32 (CH_2-2), 46.22 (CH_2-6), 49.12 (CH-3), 67.90 (CH-5), 69.57 (CH-4), 176.77 (CO) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3402 (vs, br.), 3280 (br. s, sh), 1648 (s, br.), 1542 (m, br.), 1376 (m), 1086 (w), 1071 (w), 993 (w) cm^{-1}. HRMS-ESI: calcd. for $C_7H_{15}O_3N_2$ $[M + H]^+$ 175.10772; found 175.10775.

(3*R*,4*S*,5*R*)-*N*-(4,5-Dihydroxypiperidin-3-yl)acetamide (58): Acetic anhydride (0.11 mL, 1.2 mmol) was added to a mixture of **39a** (0.22 g, 1 mmol) and $NaHCO_3$ (0.1 g, 1.2 mmol) in ethanol (10 mL). The reaction mixture was stirred at r.t. for 3 h, then the solvent was removed in vacuo and the acetylated intermediate was purified as a white foam by chromatography on silica gel using a linear gradient of ethanol in chloroform. Without further characterization, the intermediate was dissolved in 20% TFA in CH_2Cl_2 (15 mL) and stirred at r.t. overnight. The solvent was removed in vacuo and the residue was co-evaporated with a 1:1 ethanol/toluene mixture (3 × 20 mL) to afford the desired compound in 90% yield (190 mg, 0.9 mmol) as a white amorphous solid. ^1H NMR (500.0 MHz, D_2O, 28 °C): δ = 2.02 (s, 3 H, CH_3), 2.88 (dd, J_{gem} = 12.8, $J_{2b,3}$ = 12.0 Hz, 1 H, 2b-H), 3.21 (dd, J_{gem} = 13.7, $J_{6b,5}$ = 1.6 Hz, 1 H, 6b-H), 3.45 (m, 1 H, 6a-H), 3.46 (m, 1 H, 2a-H), 3.80 (dd, $J_{4,3}$ = 10.5, $J_{4,5}$ = 3.0 Hz, 1 H, 4-H), 4.27 (td, $J_{5,4}$ = 3.0, $J_{5,6}$ = 3.0, 1.6 Hz, 1 H, 5-H), 4.32 (ddd, $J_{3,2}$ = 12.0, 4.8, $J_{3,4}$ = 10.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR (125.7 MHz, D_2O, 28 °C): δ = 24.74 (CH_3), 47.44 (CH_2), 47.99 (CH-3), 50.63 (CH_2-6), 68.22 (CH-5), 72.48 (CH-4), 177.46 (CO) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3456 (s), 3322 (vs), 1659 (vs), 1640 (m, sh), 1564 (s, sh), 1546 (vs), 1377 (m), 1097 (m), 1005 (m) cm^{-1}. HRMS-ESI: calcd. for $C_7H_{15}O_3N_2$ $[M + H]^+$ 175.10772; found 175.10765.

(3*S*,4*R*,5*R*)-*N*-(3,5-Dihydroxypiperidin-4-yl)acetamide (59): Acetic anhydride (0.19 mL, 1.85 mmol) was added to a mixture of **39b** (0.43 g, 1.85 mmol) and $NaHCO_3$ (0.17 g, 2 mmol) in ethanol (20 mL). The reaction mixture was stirred at r.t. for 3 h, then the solvent was removed in vacuo and the acetylated intermediate was purified as a white foam by chromatography on silica gel using a linear gradient of ethanol in chloroform. Without further characterization, the intermediate was dissolved in 20% TFA in CH_2Cl_2 (25 mL) and stirred at r.t. overnight. The solvent was removed in vacuo and the residue was co-evaporated with a 1:1 ethanol/toluene mixture (3 × 20 mL). The residue was dissolved in water and passed through a column of Dowex 1 (Cl^-) ion exchange resin (50 mL). After removal of the solvents in vacuo, compound **59** was obtained in 97% yield (0.38 g, 1.8 mmol) as a white amorphous solid. ^1H NMR (500.0 MHz, [D_6]DMSO, 25 °C): δ = 1.84 (s, 3 H, CH_3), 2.66 (br. m, 2 H, 2b,6b-H), 3.15 (br. dd, J_{gem} = 12.3, $J_{2a,3\&6a,5}$ = 4.6 Hz, 2 H, 2a,6a-H), 3.55 (td, $J_{4,3} = J_{4,5}$ = 9.4, $J_{4,NH}$ = 8.4 Hz, 1 H, 4-H), 3.65 (ddd, $J_{3,2b\&5,6b}$ = 10.7, $J_{3\&5,4}$ = 9.4, $J_{3,2a\&5,6a}$ = 4.6 Hz, 2 H, 3,5-H), 8.02 (d, $J_{NH,4}$ = 8.4 Hz, 1 H, NH-4), 9.50 (br. d, J_{gem} = 10.0 Hz, 1 H, NHb-1), 9.58 (br. q, $J_{gem} = J_{NH,2b} = J_{NH,6b}$ = 10.0 Hz, 1 H, NHa-1) ppm. ^{13}C NMR (125.7 MHz, [D_6]DMSO, 25 °C): δ = 23.25 (CH_3), 47.16 (CH_2-2,6), 58.16 (CH-4), 65.46 (CH-3,5), 170.69 (CO) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3454 (s, br.), 3350 (s), 2968 (m, sh), 2939 (s), 2782 (s), 2725 (m), 2696 (m), 2675 (m), 2603 (w), 2566 (w), 2515 (w), 2475 (m), 2448 (w), 1617 (m), 1667 (vs), 1597 (w), 1567 (m, sh), 1549 (s), 1473 (w), 1459 (m), 1406 (w), 1365 (m), 1307 (m), 1091 (m), 1075 (w), 1042 (s), 632 (w), 599 (m), 588 (m) cm^{-1}. HRMS-ESI: calcd. for $C_7H_{15}O_3N_2$ $[M + H]^+$ 175.10772; found 175.10759.

Calculations: The geometry optimization of both conformers of compound **52** and the chemical shifts were calculated at the B3LYP/6-311+G**/PCM level, with methanol used as the implicit solvent as implemented in the Gaussian 09 program.[30]

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