Aza-*C*-nucleosides as a New Class of Nucleosides

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Abstract: The synthesis of a new type of nucleoside analogue, aza-*C*-nucleosides, has been accomplished by the reaction of a number of hydroxylated piperidine and pyrrolidine derivatives with 5-bromouracil in pyridine. The conversion of the aza sugar (±)-*cis*-*N*-benzyl-4-hydroxymethylpiperidin-3-ol ((±)-**5a**) into (±)-**5b** with *trans*-configuration was accomplished in five steps by successive tritylation, mesylation, S_N2 reaction with sodium acetate, deacetylation by treatment with sodium methoxide to give (±)-**9** and finally detritylation with 80% acetic acid to give (±)-**5b**.

Key words: aza-*C*-nucleosides, aza sugars, nucleoside synthesis, piperidine sugar analogues, pyrollidine sugar analogues

The synthesis of sugar modified nucleoside analogues has been an active research area for many years. An interesting class of nucleosides is *C*-nucleosides in which the sugar part is linked to a heterocyclic base through a carbon-to-carbon bond instead of a carbon-to-nitrogen bond as in the most common nucleosides. Several *C*-nucleosides have been found in nature, and the first example was pseudouridine **1** (Ψ-uridine) which was isolated in 1957.[1] Many of the naturally occurring *C*-nucleosides are antibiotics and exhibit anticancer and/or antiviral activity.[2] In another class of nucleosides, one has replaced the natural glycons with aza sugars, which are polyhydroxylated cyclic amines. Due to their structural relationship to sugars polyhydroxylated piperidines, e.g. isofagomine[3] (3,4-dihydroxy-5-hydroxymethylpiperidine analogue of glucose), are interesting candidates for the inhibition of various glycosidases. Carbocyclic nucleoside analogues have been synthesized where one of the carbon atoms in a carbocyclic ring is replaced by a nitrogen atom (e.g. the 3′-aza-3′-deoxythymidine carboanalogue[4] or the pyrrolidinyl analogues of 2′,3′-dideoxycytidine **2**[5]).

This paper represents a new type of nucleoside analogue which is a hybrid of some of the characteristic elements outlined above. The nucleoside consists of an aza sugar linked from the nitrogen atom to the nucleobase at a carbon atom (e.g. **3**). This new type of nucleoside is called an aza-*C*-nucleoside.

Phillips[6] discovered in 1951 that 5-bromouracil reacts with amines to give 5-substituted aminouracils. When two to five equivalents of the amine were refluxed for a brief interval with 5-bromouracil, it gave the respective 5-substituted aminouracil in excellent yield. The fact that 5-substituted aminouracils can be synthesized in this manner led to the idea that different aza sugars could react with 5-bromouracil to produce the new aza-*C*-nucleosides.

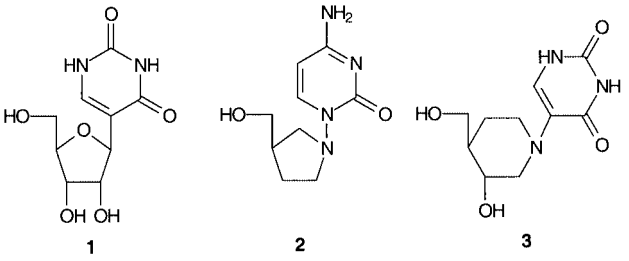
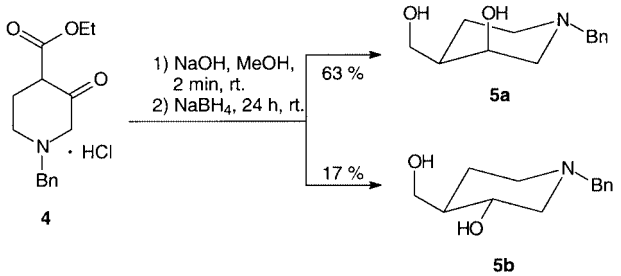


Figure 1

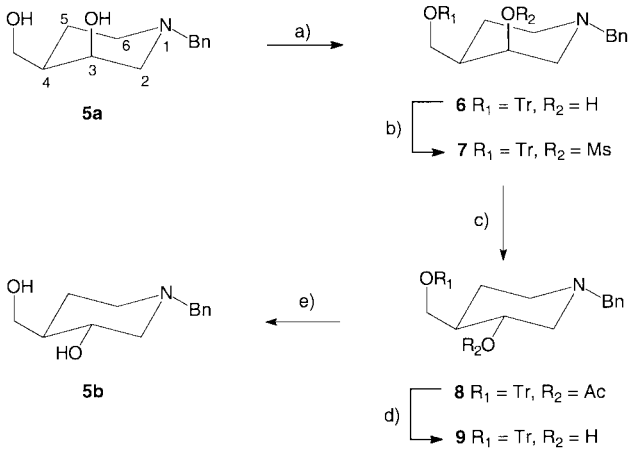
The conversion of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate hydrochloride (**4**) to the diastereomeric mixture of (±)-*cis*-1-benzyl-4-(hydroxymethyl)piperidin-3-ol ((±)-**5a**) and (±)-*trans*-1-benzyl-4-(hydroxymethyl)piperidin-3-ol ((±)-**5b**) has been accomplished according to a slightly modified literature procedure.[7] The commercially available **4** was treated with sodium hydroxide in methanol to liberate it from the hydrogen chloride. Subsequently the mixture was treated with 12 equivalents of sodium borohydride to obtain a diastereomeric mixture of (±)-**5a** and (±)-**5b** (Scheme 1). All attempts to achieve a satisfying separation of (±)-**5a** and (±)-**5b** by silica gel chromatography failed, and it turned out that laborious column chromatography on alumina or preparative high-pressure liquid chromatography (HPLC) were the only useful methods for separation. The reduction products (±)-**5a** and (±)-**5b** were formed in the ratio of 3.7:1.



Scheme 1

It was possible to convert the *cis*-isomer ((±)-**5a**) into the *trans*-isomer ((±)-**5b**) in five steps. Compound (±)-**5a** was tritylated with an excess of trityl chloride in pyridine in the presence of 4-dimethylaminopyridine (DMAP) and (±)-*cis*-1-benzyl-4-[(trityloxy)methyl]piperidin-3-ol ((±)-**6**) was obtained in a crystalline form in 73% yield after 6

days of reaction. Mesylation of (±)-**6** with methanesulfonyl chloride in pyridine gave the 3-*O*-mesyl derivative ((±)-**7**) as a crystalline compound in 86% yield. NMR spectroscopy verified the mesylation of the 3-OH group. The ^{1}H NMR spectrum showed the appearance of a singlet at δ 2.64 (CH_3SO_2) and a downfield shift for H-3 at δ 5.02 (compared to δ 3.96 for H-3 in (±)-**6**). The ^{13}C NMR spectrum showed a strong downfield shift for C-3 at 77.31 ppm (compared to 64.87 ppm for **(**±**)-6**) and the appearance of the methylsulfonyl group at 38.49 ppm. Inversion of configuration at C-3 caused by a S_N2 reaction was accomplished by heating a solution of (±)-**7** in DMF at 100 °C in the presence of a large excess of sodium acetate for 3 days. The ^{13}C NMR data for a sample of the crude product confirmed the synthesis of the acetylated compound (±)-**8**. The significant shift of the methylsulfonyl group at 38.49 ppm had disappeared. Furthermore the ^{13}C NMR spectrum showed an upfield shift for C-3 at 64.34 ppm (compared to 77.31 ppm for (±)-**7**). Without purification, (±)-**8** was deacetylated by treatment with a catalytic amount of sodium methoxide in methanol to give (±)-*trans*-1-benzyl-4-[(trityloxy)methyl]piperidin-3-ol ((±)-**9**) in 70% overall yield after column chromatography from **(**±**)-7**. After detritylation of (±)-**9** with 80% acetic acid, (±)-**5b** was obtained in 89% yield after column chromatography (Scheme 2).

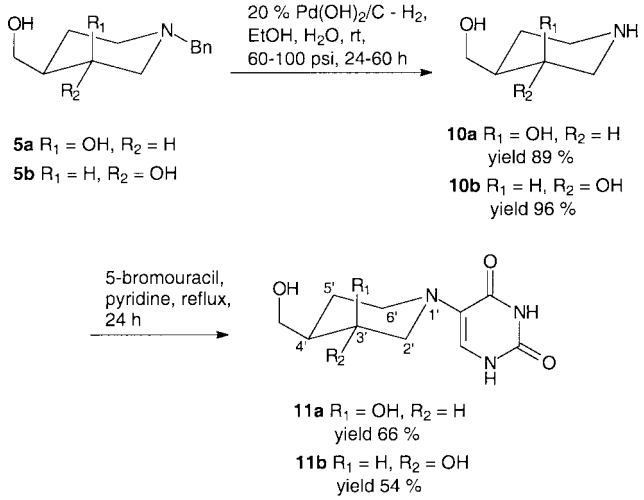


Reaction conditions: a) TrCl, pyridine, DMAP, r.t., 6 d, 73%; b) MsCl, pyridine, 0 °C for 10 min then 4 h at r.t., 86%; c) NaOAc, DMF, 100 °C, 3 d; d) NaOMe, MeOH, r.t., 2 d, 70%; e) 80% AcOH, reflux, 10 min, 89%.

Scheme 2

Debenzylation of (±)-**5a** and (±)-**5b** by catalytic hydrogenolysis was attempted with palladium-on-carbon as the catalyst. It turned out to be a poor choice of catalyst, and therefore Pearlman catalyst (20% palladium hydroxide-on-carbon) was used instead. Treatment of (±)-**5a** and (±)-**5b** with this catalyst in the presence of hydrogen under pressure gave the free amines (±)-*cis*-4-(hydroxymethyl)piperidin-3-ol **((**±**)-10a)** and (±)-*trans*-4-(hydroxymethyl)piperidin-3-ol **((**±**)-10b),** respectively, in excellent yields (Scheme 3).

The amines used by Phillips[6] in the synthesis of 5-substituted aminouracils were not only reagents but acted also as solvents. Some of the aza sugars that were used in the present work are solids. Therefore a suitable solvent had to be found for the reaction between 5-bromouracil and the aza sugars used. DMF was tested for this purpose, but it turned out that a small amount of 5-(dimethylamino)uracil was formed as a byproduct due to the presence of dimethylamine as an impurity in DMF. Pyridine on the other hand was a suitable solvent, and in addition this solvent also acts as an acid acceptor. (±)-5-[*cis*-3-Hydroxy-4-(hydroxymethyl)piperidin-1-yl]uracil ((±)-**11a**) and (±)-5-[*trans*-3-hydroxy-4-(hydroxymethyl)piperidin-1-yl]uracil ((±)-**11b**) were synthesized by refluxing a mixture of 5-bromouracil and three equivalents of the appropriate aza sugar, (±)-**10a** and (±)-**10b** respectively, in pyridine for 24 h (Scheme 3). Using less than three equivalents of the aza sugar made it very difficult to get rid of unreacted 5-bromouracil.



Scheme 3

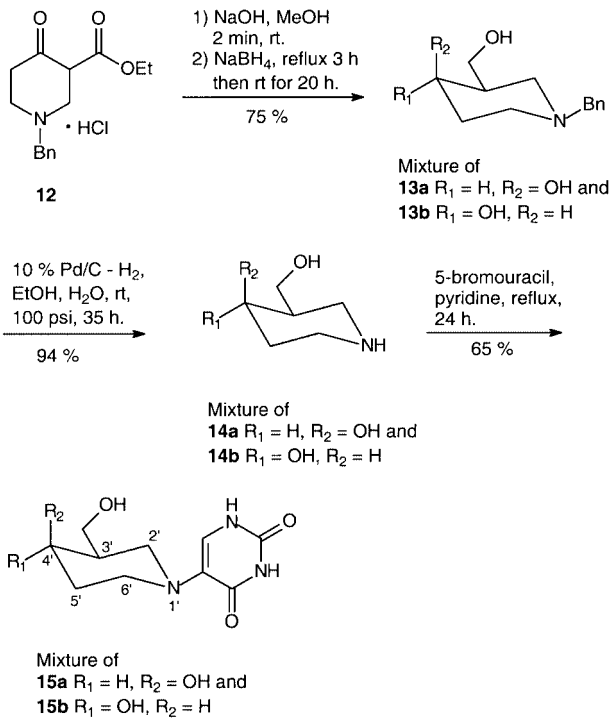
NMR evidence for the assignment of the structures is based on 2D NMR experiments, the position of 3′-H and its coupling with the protons in the 2′-position. In the ^{1}H NMR spectrum for the *cis*-isomer ((±)-**11a**) the signal for the equatorial proton in the 3′-position (3′-H_e) appeared at 3.80 ppm. The axial proton (3′-H_a) for the *trans*-isomer ((±)-**11b**) showed an upfield absorption at 3.29–3.45 ppm. The coupling pattern of 2′-H_a for **(**±**)-11a** appeared as a doublet-doublet originating from a large geminal coupling to 2′-H_e and a small vicinal coupling to 3′-H_e. For **(**±**)-11b** the coupling pattern of 2′-H_a appeared as a triplet originating from a large geminal coupling to 2′-H_e and a large vicinal coupling to 3′-H_a.

A similar synthetic pathway as the one described for (±)-**11a** and (±)-**11b** has been performed in the synthesis of a mixture of the structural isomers (±)-5-[*cis*-4-hydroxy-3-

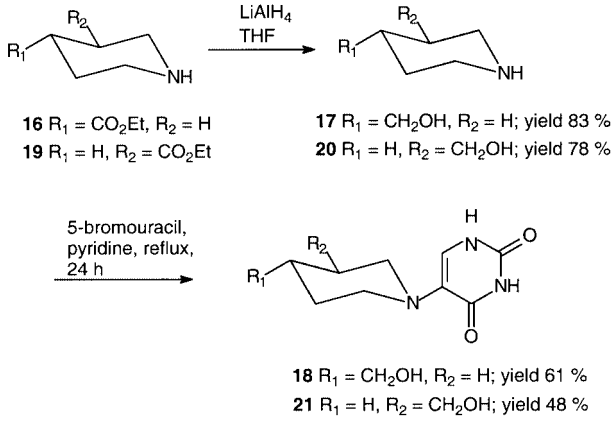
(hydroxymethyl)piperidin-1-yl]uracil ((±)-**15a**) and (±)-5-[*trans*-4-hydroxy-3-(hydroxymethyl)piperidin-1-yl]-uracil((±)-**15b**) (Scheme 4). The commercially available starting material ethyl 1-benzyl-4-oxopiperidine-3-carboxylate hydrochloride (**12**) was reduced with sodium borohydride under almost the same conditions as described earlier[8] and as described for the reduction of **4**, to yield a mixture of (±)-*cis*-, and (±)-*trans*-1-benzyl-3-(hydroxymethyl)piperidin-4-ol ((±)-**13a**/(±)-**13b**). Refluxing of the reaction mixture for 3 h before it was left standing overnight gave an improved yield. No problems with the purification of the product was stated in the literature, but in the present work, it was discovered that some rather stable boron complexes were formed, according to mass spectrometry experiments. In order to liberate (±)-**13a**/(±)-**13b** from these boron complexes it was found necessary to repeat refluxing of the reaction mixture with methanol and evaporating the methanol several times. A diastereomeric mixture of (±)-**13a**/(±)-**13b** (1.5:1) in 75% yield was obtained after silica gel chromatography. Debenzylation of (±)-**13a**/(±)-**13b** with 10% palladium-on-carbon in the presence of hydrogen under pressure gave a mixture of (±) *cis*-, and (±) *trans*-3-(hydroxymethyl)piperidin-4-ol ((±)-**14a**/(±)-**14b**) in 94% yield. Refluxing a mixture of 5-bromouracil and three equivalents of (±)-**14a**/(±)-**14b** in pyridine for 24 h gave a mixture of (±)-5-[*cis*-4-hydroxy-3-(hydroxymethyl)piperidin-1-yl]uracil ((±)-**15a**) and (±)-5-[*trans*-4-hydroxy-3-(hydroxymethyl)piperidin-1-yl]uracil ((±)-**15b**) in 65% yield. A satisfying separation of the diastereomeric mixture was not possible by silica gel chromatography. Also an attempt to separate the corresponding acetylated diastereomers of **13** failed. The separations of the intermediate stereoisomers were rather difficult. Small samples of (±)-**13a** and (±)-**13b** were separated and used for spectroscopy. The *trans* configuration of (±)-**13b** was deduced from 2D COSY and ^{1}H NMR coupling constants. Large H-H axial-axial couplings to 2-H_a and 5-H_a proved the hydroxymethyl group and hydroxy group, respectively, to be equatorial. Only compound (±)-**13b** was available in a sufficient amount for debenzylation to (±)-**14b** which again was used for the spectral assignment. In this case the *trans* configuration was proved by two large ^{1}H NMR axial-axial couplings to 4-H_a.

Reduction of commercially available ethyl isonipecotate (**16**) with $LiAlH_4$ in THF gave piperidin-4-ylmethanol (**17**) in 83% yield.[9-11] Three equivalents of **17** was reacted with 5-bromouracil in pyridine to give 5-[4-(hydroxymethyl)piperidin-1-yl]uracil (**18**) in 61% yield (Scheme 5). The structural isomer (±)-5-[3-(hydroxymethyl)piperidin-1-yl]uracil ((±)-**21**) was synthesized in a similar manner starting from commercially available ethyl nipecotate (**19**) (Scheme 5).

For the synthesis of the pyrrolidino aza-*C*-nucleoside **25** we started from ethyl *N*-benzyl-*N*-(2-carbethoxyethyl)glycinate[12] **22** which in a Dieckmann condensation was cyclized to 1-benzyl-4-(hydroxymethyl)pyrrolidin-3-ol.

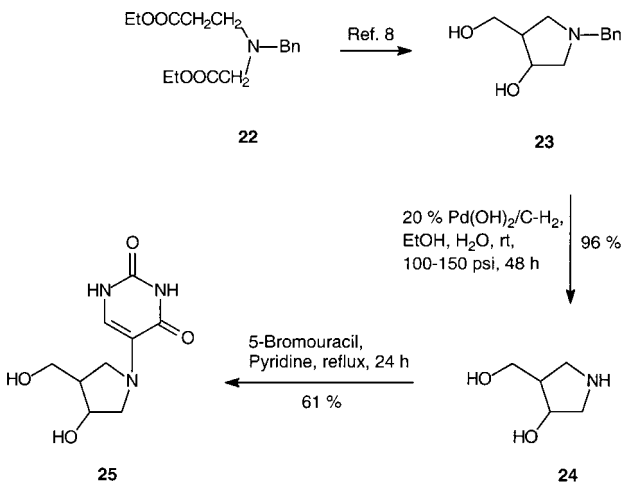


Scheme 4



Scheme 5

A five molar excess of sodium borohydride was capable of reducing the ß-oxo ester in methanol to the diol[8] **23**. Debenzylation was done using 20% palladium hydroxide-on-carbon in the presence of hydrogen under pressure to give 4-(hydroxymethyl)pyrrolidin-3-ol **24** as a diastereomeric mixture in 96% yield. The target compound 5-[3-hydroxy-4-(hydroxymethyl)pyrrolidin-1-yl]uracil **25** was obtained as a 4:1 *cis/trans* diastereomeric mixture in 61% yield by refluxing a mixture of 5-bromouracil and three equivalents of the aza sugar in pyridine for 24 h. All attempts to separate the diastereomeric mixture **25** by chromatography on alumina oxide or silica gel were unsuccessful (Scheme 6).



Scheme 6

NMR spectra were recorded on a Bruker AC-300 FT NMR spectrometer at 300 MHz for ^{1}H NMR and at 62.9 MHz for ^{13}C NMR with TMS as an internal standard. EI mass spectra were recorded on a Finnigan MAT SSQ 710. FAB mass spectra were recorded on a Kratos MS 50 RF. Thin layer chromatography (TLC) analyses were carried out with use of TLC plates 60 F_{254} purchased from Merck and were visualized in an iodine chamber and/or with a ninhydrin spray reagent (0.3 g ninhydrin in 100 ml butan-1-ol and 3 ml HOAc). The silica gel (0.040−0.063 mm) and aluminium oxide (0.063−0.200 mm) used for column chromatography were purchased from Merck. Microanalysis were carried out at the H. C. Ørsted Institute, Universitetparken 5, DK-2100 Copenhagen. Preparative HPLC was performed on a Waters Delta Pak 300 A, 15m, RP 18, 57 × 300 mm column. Ethyl 1-benzyl-3-oxopiperidine-4-carboxylate hydrochloride, ethyl isonipecotate, ethyl nipecotate, and ethyl *N*-benzyl-*N*-(2-carbetoxyethyl)glycinate were purchased from Aldrich. Ethyl 1-benzyl-4-oxopiperidine-3-carboxylate hydrochloride was purchased from Acros. 5-Bromouracil was purchased from Sigma.

(±) *cis*-, and (±) *trans*-1-Benzyl-4-(hydroxymethyl)piperidin-3-ol ((±)-5a, (±)-5b)

$NaBH_4$ (9.53 g, 252 mmol) was added in small portions to a stirred mixture of NaOH (0.84 g, 21 mmol) and **4** (6.25 g, 21 mmol) in anhyd MeOH (100 mL) at r.t. The addition was continued over 2 h to avoid vigorous reflux and foaming of the mixture. After stirring for 24 h, H_2O (125 mL) was added dropwise over 30 min and stirring was continued for 24 h. The MeOH was distilled off in vacuo and the remaining aqueous residue was extracted with $CHCl_3$ (3 × 250 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The highly viscous oil was chromatographed on a 35 × 6 cm column of alumina (Merck II) (1% MeOH in $CHCl_3$). The *cis*-isomer (±)-**5a** was the first compound eluated from the column and was isolated as white crystals. The *trans*-isomer (±)-**5b** was isolated from the second fraction as a white powder. The diastereomeric mixture could also be separated by preparative HPLC on a RP 18 column with 96% EtOH/H_2O (20:80) at 50 ml/min to give (±)-**5b** t_R (HPLC) 55 min, and (±)-**5a** t_R (HPLC) 78 min.

(±) *cis*-1-Benzyl-4-(hydroxymethyl)piperidin-3-ol ((±)-5a)

Yield 2.91 g (63%); mp 76-77 °C (Lit.[7] 77–78 °C, Lit.[13] 78 °C).

^{1}H NMR (DMSO-d_6): δ = 1.33−1.59 (m, 3H, 4-H_a, 5-H_e, 5-H_a), 1.94 (td, 1H, *J* = 10.2, 2.5 Hz, 6-H_a), 2.04 (dd, 1H, *J* = 11.6, 1.8 Hz, 2-H_a), 2.65−2.76 (m, 2H, 2-H_e, 6-H_e), 3.27 (m, 1H, C*H*$_2$OH), 3.42 (s, 2H, C*H*$_2$Ph), 3.47 (m, 1H, C*H*$_2$OH), 3.72 (m, 1H, 3-H_e), 3.94 (d, 1H, *J* = 6.9 Hz, 3-OH), 4.30 (t, 1H, *J* = 5.1 Hz, CH$_2$O*H*), 7.32 (m, 5H, H_{arom}).

^{13}C NMR (DMSO-d_6): δ = 23.15 (C-5), 42.16 (C-4), 52.25 (C-6), 59.25 (C-2), 62.05, 62.13 (CH$_2$OH, *C*H$_2$Ph), 64.93 (C-3), 126.80, 128.12, 128.84, 138.66 ($C_{arom.}$).

EI-MS: *m/z* = 221 (M^+).

(±) *trans*-1-Benzyl-4-(hydroxymethyl)piperidin-3-ol ((±)-5b)

Yield 0.79 g (17%); mp 102−105 °C (Lit.[7] 104−104.5 °C, Lit.[13] 104 °C).

^{1}H NMR (DMSO-d_6): δ = 1.17−1.28 (m, 2H, 4-H_a, 5-H_a), 1.65 (t, 1H, *J* = 10.3 Hz, 2-H_a), 1.67 (m, 1H, 5-H_e), 1.83 (td, 1H, *J* = 11.2, 1.8 Hz, 6-H_a), 2.73 (dt, 1H, *J* = 10.4, 3.5 Hz, 6-H_e), 2.85 (dd, 1H, *J* = 10.4, 4.5 Hz, 2-H_e), 3.21−3.34 (m, 2H, 3-H_a, C*H*$_2$OH), 3.36 (d, 1H, *J* = 13.4 Hz, C*H*$_2$Ph), 3.47 (d, 1H, *J* = 13.2 Hz, C*H*$_2$Ph), 3.63 (dt, 1H, *J* = 10.3, 3.8 Hz, C*H*$_2$OH), 4.35 (t, 1H, *J* = 5.1 Hz, CH$_2$O*H*), 4.58 (d, 1H, *J* = 5.3 Hz, 3-OH), 7.29 (m, 5H, H_{arom}).

^{13}C NMR (DMSO-d_6): δ = 26.93 (C-5), 45.54 (C-4), 52.90 (C-6), 60.60 (C-2), 62.04 (*C*H$_2$Ph), 62.72 (CH$_2$OH), 67.72 (C-3), 126.89, 128.18, 128.83, 138.69 (C_{arom}).

EI-MS: *m/z* = 221 (M^+).

(±) *cis*-1-Benzyl-4-[(trityloxy)methyl]piperidin-3-ol ((±)-6)

Compound (±)-**5a** (3.20 g, 14.46 mmol) was coevaporated with anhyd pyridine (2 × 15 mL) to remove traces of H_2O, and was then dissolved in anhyd pyridine (50 mL) under Ar. Triphenylmethyl chloride (TrCl) (6.05 g, 21.69 mmol) and a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) was added. The reaction was monitored by TLC and after 3 d at r.t. the mixture was heated for 3 h at 50 °C. The heating had no effect and an additional amount of TrCl (1.20 g) was added after 4 and 5 days of reaction, respectively. After a total of 6 days of reaction, the mixture was poured into ice-water (100 mL) and stirred for 1 h. The mixture was extracted with CH_2Cl_2 (2 × 150 mL) and the combined organic fractions were washed with sat. aq $NaHCO_3$ (2 × 50 mL). The organic phase was dried ($MgSO_4$), filtered and coevaporated with anhyd toluene in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2) to give the title compound (±)-**6** as white crystals; yield 4.89 g (73%); mp 178−179 °C.

^{1}H NMR ($CDCl_3$): δ = 1.37−1.55 (m, 2H, 5-H_e, 5-H_a), 1.65 (m, 1H, 4-H_a), 1.97 (td, 1H, *J* = 11.8, 4.0 Hz, 6-H_a), 2.14 (d, 1H, *J* = 11.4 Hz, 2-H_a), 2.67 (m, 1H, 6-H_e), 2.81 (m, 1H, 2-H_e), 2.91−3.03 (m, 2H, C*H*$_2$OTr, 3-OH), 3.22 (dd, 1H, *J* = 7.7, 8.8 Hz, C*H*$_2$OTr), 3.49 (s, 2H, C*H*$_2$Ph), 3.96 (m, 1H, 3-H_e), 7.16−7.33 (m, 15H, H_{arom}), 7.41−7.48 (m, 5H, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 23.76 (C-5), 40.74 (C-4), 52.89 (C-6), 59.62 (C-2), 62.57 (*C*H$_2$Ph), 64.87 (*C*H$_2$OTr), 65.84 (C-3), 86.29 (*C*(Ph)$_3$), 127.15, 128.31, 128.99, 138.26 ($C_{arom\text{-}benzyl}$), 126.89, 127.74, 128.80, 144.40 ($C_{arom\text{-}trityl}$).

$C_{32}H_{33}NO_2 \cdot 0.2\ H_2O$ calc.	C	82.26	H	7.21	N	3.00
(463.6) found	C	82.12	H	7.11	N	3.03

FAB-MS (3-nitrobenzylalcohol): *m/z* = 464 (M^++1).

(±) *cis*-1-Benzyl-3-(methylsulfonyl)-4-[(trityloxy)methyl]piperidine ((±)-7)

Compound (±)-**6** (2.20 g, 4.75 mmol) was coevaporated with anhyd pyridine (2 × 15 mL) to remove traces of H_2O and dissolved in anhyd pyridine (40 mL) under Ar. To this stirred solution at 0 °C methanesulfonyl chloride (1.10 mL, 14.25 mmol) was added via a syringe and the mixture was then stirred first at 0 °C for 10 min and then at r.t. for 4 h. The mixture was again cooled to 0 °C and 50% aq pyridine (30 mL) was added. The mixture was diluted with $CHCl_3$ (200 mL), washed successively with H_2O (100 mL), sat. aq $NaHCO_3$ (100 mL), and H_2O (100 mL). The organic phase was

dried ($MgSO_4$), filtered and coevaporated with anhyd toluene in vacuo. The residue was purified by silica gel column chromatography (1% MeOH in CH_2Cl_2) to give the title compound (±)-**7** as white fluffy crystals; yield 2.22 g (86%); mp 54 °C.

^{1}H NMR ($CDCl_3$): δ = 1.43 (m, 1H, 5-H_e), 1.57 (qd, 1H, *J* = 12.3, 4.0 Hz, 5-H_a), 1.83 (m, 1H, 4-H_a), 2.06 (td, 1H, *J* = 11.5, 3.0 Hz, 6-H_a), 2.20 (d, 1H, *J* = 13.0 Hz, 2-H_a), 2.64 (s, 3H, Ms), 2.89 (m, 1H, 6-H_e), 3.05−3.17 (m, 2H, C*H*$_2$OTr), 3.30 (m, 1H, 2-H_e), 3.49 (d, 1H, *J* = 13.4 Hz, C*H*$_2$Ph), 3.57 (d, 1H, *J* = 13.4 Hz, C*H*$_2$Ph), 5.02 (m, 1H, 3-H_e), 7.19−7.34 (m, 15H, H_{arom}), 7.38−7.44 (m, 5H, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 23.62 (C-5), 38.49 (CH_3SO_2), 40.14 (C-4), 52.28 (C-6), 56.53 (C-2), 62,40 (*C*H$_2$Ph), 63.51 (*C*H$_2$OTr), 77.31 (C-3), 86.79 (*C*(Ph)$_3$), 127.23, 128.26, 129.13, 137.67 ($C_{arom-benzyl}$), 127.17, 127.90, 128.69, 143.87 ($C_{arom-trityl}$).

$C_{33}H_{35}NO_4S$	calc.	C	73.17	H	6.51	N	2.59
(541.7)	found	C	73.11	H	6.48	N	2.60

FAB-MS (3-nitrobenzyl alcohol): *m/z* = 542 (M^++1).

(±) *trans*-1-Benzyl-4-[(trityloxy)methyl]piperidin-3-ol ((±)-9)

A mixture of (±)-**7** (500 mg, 0.92 mmol) and NaOAc (0.76 g, 9.2 mmol) in anhyd DMF (10 mL) was stirred at 100 °C until TLC (5% MeOH in CH_2Cl_2) showed the absence of starting material (3 days). The mixture was cooled to r.t. and evaporated in vacuo. The residue was dissolved in $CHCl_3$ (50 mL) and washed successively with sat. aq $NaHCO_3$ (20 mL) and H_2O (2 × 20 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated in vacuo. This gave crude (±)-**8** as a brown viscous oil. The product was dissolved in MeOH (10 mL) and a mixture of NaOMe (17 mg, 0.31 mmol) in MeOH (3 mL) was added. The mixture was stirred at r.t. for 48 h. The MeOH was distilled off in vacuo and H_2O (25 mL) was added. The mixture was extracted with $CHCl_3$ (3 × 50 mL) and the combined organic fractions were dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was purified by silica gel column chromatography (1% MeOH in CH_2Cl_2) to give the title compound (±)-**9** as a very viscous oil; yield 298 mg (70% overall yield calculated from (±)-**7**).

^{1}H NMR ($CDCl_3$): δ = 1.27−1.43 (m, 1H), 1.81−1.93 (m, 1H), 2.27−2.38 (m, 1H), 2.57−2.73 (m, 1H), 2.87−3.01 (m, 2H), 3.18 (t, 1H, *J* = 9.1 Hz, 3-H_a), 3.34 (dd, 1H, *J* = 5.7, 9.5 Hz), 3.41 (d, 2H, *J* = 4.6 Hz), 3.50 (d, 1H, *J* = 13.2, C*H*$_2$Ph), 3.96 (d, 1H, *J* = 13.2, C*H*$_2$Ph), 7.21−7.37 (m, 15H, H_{arom}), 7.44−7.49 (m, 5H, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 28.56 (C-5), 40.93 (C-4), 52.62 (C-6), 59.34 (C-2), 59.92 (*C*H$_2$Ph), 64.22 (*C*H$_2$OTr), 65.63 (C-3), 87.04 (*C*(Ph)$_3$), 127.74, 128.34, 128.78 ($C_{arom-benzyl}$), 127.09, 127.92, 128.58, 144.02 ($C_{arom-trityl}$).

Deprotection of (±)-9 to give (±)-5b

Compound (±)-**9** (200 mg, 0.43 mmol) was refluxed with 80% HOAc (10 mL) for 10 min. After cooling to r.t. the mixture was evaporated in vacuo and the residue was made alkaline with slow addition of sat. aq $NaHCO_3$ at r.t. After stirring for 30 min, the mixture was extracted with $CHCl_3$ (3 × 50 mL), and the combined organic fractions were dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was purified by silica gel column chromatography (0−10% MeOH in CH_2Cl_2) to give (±)-**5b**; yield 85 mg (89%). The spectroscopical data were identical with those earlier stated for (±)-**5b** in this work.

(±) *cis*-4-(Hydroxymethyl)piperidin-3-ol ((±)-10a)

20% $Pd(OH)_2$-C (462 mg) was mixed with a solution of (±)-**5a** (3.10 g, 14.00 mmol) in EtOH−H_2O 1:1 (50 mL). The mixture was hydrogenated at r.t. under pressure (100 psi). After 60 h the mixture was filtered through Celite and the solvent evaporated in vacuo. The residue was purified by recrystallization from EtOAc (70 mL) to give the title compound (±)-**10a** as a white powder; yield 1.64 g (89%); mp 122−126 (Lit.[14] 129−130 °C, Lit.[15] 126−127 °C). NMR was in agreement with previously reported results.[14]

(±)-5-[*cis*-3-Hydroxy-4-(hydroxymethyl)piperidin-1-yl]uracil((±)-11a)

A mixture of (±)-**10a** (1.37 g, 10.42 mmol) and 5-bromouracil (0.66 g, 3.47 mmol) in anhyd pyridine (10 mL) was refluxed for 24 h, cooled to r.t. and evaporated in vacuo. Traces of pyridine were coevaporated with toluene. The residue was dissolved in MeOH (50 mL) under heating, and the hot solution was filtered. After cooling to 0 °C the precipitate was isolated by filtration and purified by recrystallization from MeOH (40 mL) to give the title compound (±)-**11a** as a white powder; yield 556 mg (66%); mp 260−264 °C.

^{1}H NMR (DMSO-d_6): δ = 1.37−1.45 (m, 1H, 5′-H_e), 1.45−1.67 (m, 2H, 4′-H_a, 5′-H_a), 2.39 (td, 1H, *J* = 10.6, 2.5 Hz, 6′-H_a), 2.58 (dd, 1H, *J* = 11.9, 1.8 Hz, 2′-H_a), 3.07 (dd, 1H, *J* = 11.7, 3.3 Hz, 2′-H_e), 3.21 (m, 1H, 6′-H_e), 3.30 (dd, 1H, *J* = 10.4, 6.4 Hz, C*H*$_2$OH), 3.49 (dd, 1H, *J* = 10.4, 6.5 Hz, C*H*$_2$OH), 3.80 (m, 1H, 3′-H_e), 4.12 (br s, 1H, 3′-OH), 4.34 (br s, 1H, CH$_2$O*H*), 6.78 (s, 1H, 6-H), 10.42 (br s, 1H, NH), 11.02 (br s, 1H, NH).

^{13}C NMR (DMSO-d_6): δ = 23.01 (C-5′), 41.89 (C-4′), 49.46 (C-6′), 56.19 (C-2′), 62.04 (*C*H$_2$OH), 64.65 (C-3′), 126.90, 126.94 (C-5, C-6), 150.46 (C-2), 161.91 (C-4).

$C_{10}H_{15}N_3O_4$	calc.	C	49.79	H	6.27	N	17.42
(241.3)	found	C	49.82	H	6.22	N	17.22

EI-MS: *m/z* = 241 (M^+).

(±) *trans*-4-(Hydroxymethyl)piperidin-3-ol ((±)-10b)

20% $Pd(OH)_2$-C (116 mg) was mixed with a solution of (±)-**5b** (777 mg, 3.51 mmol) in EtOH−H_2O 1:1 (15 mL). The mixture was hydrogenated at r.t. under pressure (60 psi). After 24 h the mixture was filtered through Celite and the solvent evaporated in vacuo. The title compound (±)-**10b** was isolated as a brown oil, and the bulk of the product was carried on to the next step without further purification; yield 444 mg (96%). A small portion was triturated in EtOAc to give a light brown oil used for characterization.

^{1}H NMR (DMSO-d_6): δ = 1.32−1.50 (m, 2H, 4-H_a, 5-H_a), 1.80 (m, 1H, 5-H_e), 2.46 (t, 1H, *J* = 11.2 Hz, 2-H_a), 2.66 (m, 1H, 6-H_a), 3.04−3.12 (m, 2H, 6-H_e, 2-H_e), 3.34 (dd, 1H, *J* = 10.8, 5.5 Hz, C*H*$_2$OH), 3.50 (m, 1H, 3-H_a), 3.56 (dd, 1H, *J* = 11.0, 2.4 Hz, C*H*$_2$OH).

^{13}C NMR (DMSO-d_6): δ = 24.01 (C-5), 42.70 (C-4), 43.80 (C-6), 48.28 (C-2), 61.34 (*C*H$_2$OH), 64.36 (C-3).

EI-MS: *m/z* = 131 (M^+).

(±)-5-[*trans*-3-Hydroxy-4-(hydroxymethyl)piperidin-1-yl]uracil ((±)-11b)

The title compound was synthesized from (±)-**10b** (400 mg, 3.05 mmol) and 5-bromouracil (194 mg, 1.02 mmol) in anhyd pyridine (5 mL) in the same way as compound (±)-**11a**. Yield 132 mg (54%) as a brown powder; mp 277−280 °C.

^{1}H NMR (DMSO-d_6): δ = 1.19−1.39 (m, 2H, 4′-H_a, 5′-H_a), 1.74 (m, 1H, 5′-H_e), 2.05 (t, 1H, *J* = 11.4 Hz, 2′-H_a), 2.26 (m, 1H, 6′-H_a), 3.16 (m, 1H, 6′-H_e), 3.29−3.45 (m, 4H, C*H*$_2$OH, 2′-H_e, 3′-H_a, H_2O), 3.66 (dd, 1H, *J* = 10.3, 2.4 Hz, C*H*$_2$OH), 4.39 (br s, 1H, CH$_2$O*H*), 4.73 (br s, 1H, 3′-OH), 6.72 (s, 1H, 6-H), 10.42 (br s, 1H, NH), 11.00 (br s, 1H, NH).

^{13}C NMR (DMSO-d_6): δ = 26.82 (C-5′), 45.30 (C-4′), 49.77 (C-6′), 57.26 (C-2′), 62.56 (CH_2OH), 67.31 (C-3′), 126.37, 126.53 (C-5, C-6), 150.43 (C-2), 161.73 (C-4).

$C_{10}H_{15}N_3O_4 \cdot 0.4\ H_2O$	calc.	C	48.34	H	6.41	N	16.91
(241.3)	found	C	48.60	H	6.43	N	16.85

EI-MS: *m/z* = 241 (M^+).

(±) *cis*-, and (±) *trans*-1-Benzyl-3-(hydroxymethyl)piperidin-4-ol ((±)-13a/(±)-13b)

$NaBH_4$ (4.54 g, 120 mmol) was added in small portions to a stirred mixture of NaOH (0.40 g, 10 mmol) and **12** (2.98 g, 10 mmol) in anhyd MeOH (30 mL) at r.t. Addition was continued over 30 min to avoid vigorous reflux and foaming of the mixture. After stirring for an additional 30 min at r.t. the mixture was refluxed for 3 h and then left standing for 20 h at r.t. H_2O (50 mL) was added dropwise over 30 min and stirring was continued for 24 h. The MeOH was distilled in vacuo and the remaining residue was added a new portion of MeOH (20 mL). The mixture was refluxed for 10 min, cooled to r.t. and again the MeOH was distilled in vacuo. This process was repeated five times, and the remaining H_2O solution was extracted with $CHCl_3$ (4 × 50 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The higly viscous yellow oil was passed through a short column of silica gel, eluting with 0-50% MeOH in CH_2Cl_2. When the less polar starting material was eluted the polarity of the eluent was increased and the more polar diastereomeric mixture of (±)-**13a** and (±)-**13b** was obtained as a viscous oil; yield 1.66 g (75%). According to NMR integrals (±)-**13a** and (±)-**13b** were formed in the ratio of 1.5:1.

Tedious column chromatography on silica gel (50% MeOH in CH_2Cl_2) gave first a small sample of the pure diastereomer **13b** and then **13a** which were used for characterization.

(±) *cis*-1-Benzyl-3-(hydroxymethyl)piperidin-4-ol ((±)-13a)

^{1}H NMR (DMSO-d_6): δ = 1.57 (m, 2H, H-5_a, 5-H_e), 1.69 (m, 1H, 3-H_a), 2.16 (t, 1H, *J* = 10.4 Hz, 2-H_a), 2.36 (m, 2H, 6-H_a, 6-H_e), 2.45 (dd, 1H, *J* = 3.5, 10.4 Hz, 2-H_e), 3.28−3.52 (m, 2H, C*H*$_2$OH), 3.40 (d, 1H, *J* = 13.4 Hz, C*H*$_2$Ph), 3.46 (d, 1H, *J* = 13.4 Hz, C*H*$_2$Ph), 3.79 (m, 1H, 4-H_e), 4.28 (s, 1H, CH$_2$O*H*), 4.33 (d, 1H, *J* = 3.3 Hz, 4-OH), 7.18−7.35 (m, 5H, H_{arom}).

^{13}C NMR (DMSO-d_6): δ = 32.68 (C-5), 43.33 (C-3), 48.26 (C-6), 51.12 (C-2), 61.16 (*C*H$_2$OH), 62.56 (*C*H$_2$Ph), 64.24 (C-4), 126.79, 128.16, 128.80, 138.93 (C_{arom}).

EI-MS: *m/z* = 221 (M^+).

(±) *trans*-1-Benzyl-3-(hydroxymethyl)piperidin-4-ol ((±)-13b)

^{1}H NMR (DMSO-d_6): δ = 1.40 (qd, 1H, *J* = 11.5, 4.0 Hz, 5-H_a), 1.49 (m, 1H, 3-H_a), 1.68 (t, 1H, *J* = 11.0 Hz, 2-H_a), 1.73 (m, 1H, 5-H_e), 1.86 (td, 1H, *J* = 11.9, 2.4 Hz, 6-H_a), 2.70 (m, 1H, 2-H_e), 2.87 (m, 1H, 6-H_e), 3.11 (m, 1H, C*H*$_2$OH), 3.22 (m, 1H, 4-H_a), 3.41 (m, 2H, C*H*$_2$Ph), 3.61 (dd, 1H, *J* = 10.6, 4.0 Hz, C*H*$_2$OH), 4.32 (br s, 1H, CH$_2$O*H*), 4.54 (d, 1H, *J* = 5.1 Hz, 4-OH), 7.18−7.33 (m, 5H, H_{arom}).

^{13}C NMR (DMSO-d_6): δ = 34.32 (C-5), 45.95 (C-3), 51.74 (C-6), 55.03 (C-2), 61.35 (*C*H$_2$OH), 62.19 (*C*H$_2$Ph), 68.53 (C-4), 126.91, 128.23, 128.48, 138.76 (C_{arom}).

EI-MS: *m/z* = 221 (M^+).

(±) *cis*-, and (±) *trans*-3-(Hydroxymethyl)piperidin-4-ol ((±)-14a/(±)-14b)

10% Pd-C (864 mg) was mixed with a solution of (±)-**13a**/(±)-**13b** (5.80 g, 26.2 mmol) in EtOH−H_2O 1:1 (110 mL). The mixture was hydrogenated at r.t. under pressure (100 psi). After 35 h the mixture was filtered through Celite and the solvent evaporated in vacuo. The mixture of (±)-**14a**/(±)-**14b** was isolated as a very viscous oil; yield 3.23 g (94%). A small sample of the pure diastereomer (±)-**13b** was debenzylated in a similar manner and used for spectral assignment.

(±) *cis*-3-(Hydroxymethyl)piperidin-4-ol ((±)-14a)

^{1}H NMR (DMSO-d_6): δ = 1.48 (m, 2H, 5-H_a, 5-H_e), 1.57 (m, 1H, 3-H_a), 2.53−2.68+2.79 (m+m, 3H+1H, 2-H_a, 2-H_e, 6-H_a, 6-H_e), 3.35 (m, 1H, C*H*$_2$OH), 3.44 (dd, 1H, *J* = 6.0, 10.4 Hz, C*H*$_2$OH), 3.82 (m, 1H, 4-H).

^{13}C NMR (DMSO-d_6): δ = 33.36 (C-5), 41.31 (C-3), 43.69 (C-6), 43.94 (C-2), 60.71 (*C*H$_2$OH), 65.37 (C-4).

EI-MS: *m/z* = 131 (M^+).

(±) *trans*-3-(Hydroxymethyl)piperidin-4-ol ((±)-14b)

^{1}H NMR (DMSO-d_6): δ = 1.25 (dq, 1H, *J* = 4.0, 11.4 Hz, 5-H_a), 1.34 (m, 1H, 3-H_a), 1.71 (m, 1H, 5-H_e), 2.16 (t, 1H, *J* = 11.4 Hz, 2-H_a), 2.40 (m, 1H, 6-H_a), 2.88 (m, 1H, 2-H_e), 3.00 (m, 1H, 6-H_e), 3.21 (dt, 1H, *J* = 4.4, 10.1 Hz, 4-H_a), 3.28 (dd, 1H, *J* = 7.5, 10.6 Hz, C*H*$_2$OH), 3.62 (dd, 1H, *J* = 7.3, 10.4 Hz, C*H*$_2$OH).

^{13}C NMR (DMSO-d_6): δ = 35.35 (C-5), 44.46 (C-3), 46.99 (C-6), 47.55 (C-2), 61.31 (CH$_2$OH), 68.93 (C-4).

EI-MS: *m/z* = 131 (M^+).

(±) 5-[*cis/trans*-4-Hydroxy-3-(hydroxymethyl)piperidin-1-yl]uracil ((±)-15a/(±)-15b)

The title compound was synthesized in the same way as (±)-**11a** from (±)-**14a**/(±)-**14b** (2.75 g, 21 mmol) and 5-bromouracil (1.34 g, 7 mmol) in anhyd pyridine (25 mL). Yield 1.09 g (65%) as a light brown powder; mp 261—264 °C. According to NMR integrals (±)-**15a** and (±)-**15b** were formed in the ratio of 1.2:1.

^{1}H NMR (DMSO-d_6): δ = 1.48 (dq, 1H, *J* = 4.0, 11.5 Hz, 5′-$H_{a,\ 15b}$), 1.55−1.69 (m, 3H, 3′-$H_{a,\ 15b}$, 5′-$H_{a,\ 15a}$, 5′-$H_{e,\ 15a}$), 1.73−1.84 (m, 2H, 3′-$H_{a,\ 15a}$, 5′-$H_{e,\ 15b}$), 2.16 (t, 1H, *J* = 11.0 Hz, 2′-$H_{a,\ 15b}$), 2.34 (m, 1H, 6′-$H_{a,\ 15b}$), 2.56 (t, 1H, *J* = 11.4 Hz, 2′-$H_{a,\ 15a}$), 2.75 (m, 1H, 6′-$H_{a,\ 15a}$), 2.82−2.93 (m, 2H, 2′-$H_{e,\ 15a}$, 6′-$H_{e,\ 15a}$), 3.14−3.36 (m, 4H, 2′-$H_{e,\ 15b}$, 6′-$H_{e,\ 15b}$, 4′-$H_{a,\ 15b}$, C*H*$_2$OH$_{15b}$), 3.35−3.54 (m, 2H, C*H*$_2$OH$_{15a}$), 3.67 (m, 1H, C*H*$_2$OH$_{15b}$), 3.85 (m, 1H, 4′-$H_{e,\ 15a}$), 4.31−4.47 (m, 3H, OH), 4.62 (d, 1H, *J* = 4.2 Hz, 4′-OH), 6.71 (s, 1H, 6-H_{15b}), 6.73 (s, 1H, 6-H_{15a}), 10.41 (br s, 2H, 2 × NH), 11.02 (br s, 2H, 2 × NH).

^{13}C NMR (DMSO-d_6): δ = 32.40 (C-5′$_{15a}$), 34.11 (C-5′$_{15b}$), 43.17 (C-3′$_{15a}$), 45.44 (C-6′$_{15a}$), 45.88 (C-3′$_{15b}$), 48.14 (C-2′$_{15a}$), 48.63 (C-6′$_{15b}$), 51.88 (C-2′$_{15b}$), 60.75 (*C*H$_2$OH$_{15a}$), 61.13 (CH$_2$OH$_{15b}$), 64.06 (C-4′$_{15a}$), 68.06 (C-4′$_{15b}$), 125.98 (C-5_{15a}), 126.20 (C-5_{15b}), 126.87 (C-6_{15b}), 127.29 (C-6_{15a}), 150.44 (C-2_{15b}), 150.47 (C-2_{15a}), 161.78 (C-4_{15b}), 161.90 (C-4_{15a}).

$C_{10}H_{15}N_3O_4$	calc.	C	49.79	H	6.27	N	17.42
(241.3)	found	C	49.65	H	6.21	N	17.30

EI-MS: *m/z* = 241(M^+).

5-[4-(Hydroxymethyl)piperidin-1-yl]uracil (18)

The title compound was synthesized from **17**[9] (1.20 g, 10.42 mmol) and 5-bromouracil (0.50 g, 2.62 mmol) in dry pyridine (10 mL) in the same way as compound (±)-**11a**. Yield 359 mg (61%) as an off-white powder; mp 278−280 °C.

^{1}H NMR (DMSO-d_6): δ = 1.20 (m, 2H, 3′-H_a, 5′-H_a), 1.41 (m, 1H, 4′-H), 1.66 (m, 2H, 3′-H_e, 5′-H_e), 2.29 (m, 2H, 2′-H_a, 6′-H_a), 3.16−3.33 (m, 4H, 2′-H_e, 6′-H_e, C*H*$_2$OH), 6.71 (s, 1H, 6-H), 10.62 (br s, 2H, 2 × NH).

^{13}C NMR (DMSO-d_6): δ = 28.56 (C-3′, C-5′), 38.01 (C-4′), 50.00 (C-2′, C-6′), 65.89 (CH$_2$OH), 126.07, 127.19 (C-6, C-5), 150.44 (C-2), 161.75 (C-4).

$C_{10}H_{15}N_3O_3 \cdot 0.3\ H_2O$	calc.	C	52.07	H	6.82	N	18.22
(225.3)	found	C	52.07	H	6.84	N	17.82

EI-MS: *m/z* = 225 (M^+).

(±) 3-(Hydroxymethyl)piperidine ((±)-20)
A solution of **19** (10.0 mL, 10.12 g, 64.37 mmol) in anhyd THF (100 mL) was slowly added to a ice-cooled suspension of $LiAlH_4$ (3.40 g, 90 mmol) in anhyd THF (300 mL). After the visibel gas evolution ceased, the mixture was left standing at r.t. for 20 h. The reaction was quenched with $MgSO_4 \cdot 7H_2O$ until all evolution of gas ceased, and the slurry was filtered and washed with anhyd THF. The THF fraction was evaporated in vacuo and the viscous product was purified by vacuum destillation to give the title compound (±)-**20** as a viscous oil; yield 5.79 g (78%); bp 90 °C/0.03 mbar.

^{1}H NMR (DMSO-d_6): δ = 0.96 (qd, 1H, *J* = 11.7, 4.0 Hz, 4-H_a), 1.30 (qt, 1H, *J* = 12.1, 3.8 Hz, 5-H_a), 1.39−1.57 (m, 2H, 5-H_e, 3-H_a), 1.67 (m, 1H, 4-H_e), 2.12 (t, 1H, *J* = 11.5 Hz, 2-H_a), 2.36 (td, 1H, *J* = 11.5, 2.7 Hz, 6-H_a), 2.81 (dt, 1H, *J* = 11.7, 3.5 Hz, 6-H_e), 2.94 (dd, 1H, *J* = 11.7, 3.5 Hz, 2-H_e), 3.19 (m, 2H, C*H*$_2$OH).

^{13}C NMR (DMSO-d_6): δ = 25.71 (C-5), 27.80 (C-4), 39.41 (C-3), 46.64 (C-6), 49.89 (C-2), 64.50 (CH_2OH).

EI-MS: *m/z* = 115 (M^+).

(±)-5-[3-(Hydroxymethyl)piperidin-1-yl]uracil ((±)-21)
The title compound was synthesized from (±)-**20** (1.20 g, 10.42 mmol) and 5-bromouracil (0.50 g, 2.62 mmol) in dry pyridine (10 mL) in the same way as compound (±)-**11a**. Yield 280 mg (48%) as a white powder; mp 244−246 °C.

^{1}H NMR (DMSO-d_6): δ = 0.97 (m, 1H, 4′-H_a), 1.50 (m, 1H, 5′-H_a), 1.59−1.73 (m, 3H, 5′-H_e, 4′-H_e, 3′-H_a), 2.08 (t, 1H, *J* = 10.4 Hz, 2′-H_a), 2.29 (td, 1H, *J* = 11.0, 2.5 Hz, 6′-H_a), 3.11−3.32 (m, 4H, 6′-H_e, 2′-H_e, C*H*$_2$OH), 4.44 (t, 1H, *J* = 5.1 Hz, CH_2O*H*), 6.68 (s, 1H, 6-H), 10.40 (br s, 1H, NH), 11.00 (br s, 1H, NH).

^{13}C NMR (DMSO-d_6): δ = 24.37 (C-5′), 26.64 (C-4′), 38.52 (C-3′), 50.76 (C-6′), 53.89 (C-2′), 64.08 (CH_2OH), 126.17 (C-6), 127.30 (C-5), 150.37 (C-2), 161.75 (C-4).

$C_{10}H_{15}N_3O_3$	calc.	C	53.32	H	6.71	N	18.65
(225.3)	found	C	52.93	H	6.68	N	18.35

EI-MS: *m/z* = 225 (M^+).

4-(Hydroxymethyl)pyrrolidin-3-ol (24)
20% $Pd(OH)_2$/C (1.1 g) was mixed with a solution of **23**[8] (5.0 g, 24 mmol) in EtOH/H_2O 1:1 (100 mL). The mixture was hydrogenated at r.t. under pressure (150 psi). After 48 h the mixture was filtered through Celite and the solvent evaporated in vacuo to give 2.7 g (96%) yield of the product as a colorless viscous oil which can be used without further purification.

5-[3-Hydroxy-4-(hydroxymethyl)pyrrolidin-1-yl]uracil (25)
A mixture of **24** (2.1 g, 18 mmol) and 5-bromouracil (1.15 g, 6 mmol) in anhyd pyridine (20 mL) was refluxed for 24 h, cooled to r.t. and evaporated in vacuo. Traces of pyridine were coevaporated with toluene. The residue was recrystallized from MeOH to give 830 mg (61%) yield in a 4:1 *cis*/*trans* diastereomeric mixture of the title compound **25** as a brownish powder; mp 273–275 °C.

^{1}H NMR (DMSO-d_6): δ = 2.0-2.3 (m, 1H, 4′-H), 2.75 (dd, 1H, *J* = 9.8, 5.9 Hz, 5′-H), 2.85 (dd, 1H, *J* = 9.8, 4.1 Hz, 5′-H), 3.13.7 (m, 4H, 2′-H, C*H*$_2$OH), 3.90 (q, 1H, *J* = 4.8 Hz, 3′-H), 4.7 (br s, 2H, 2 x OH), 6.35 (s, 1H, 6-H (*trans* isomer)), 6.41 (s, 1H, 6-H (*cis* isomer)), 10.3 (br s, 1H, NH), 10.9 (br s, 1H, NH).

^{13}C NMR (DMSO-d_6) *cis* isomer: δ = 48.96 (C-4′), 51.65 (C-5′), 57.73 (C-2′), 61.80 (CH_2OH), 71.06 (C-3′), 120.25 (C-5), 125.34 (C-6), 150.22 (C-2), 161.62 (C-4).

$C_9H_{13}N_3O_4 \cdot 0.4\ H_2O$	calc.	C	45.76	H	5.97	N	17.79
(236.23)	found	C	45.70	H	5.96	N	17.55

EI-MS: *m/z* = 227 (M^+).

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