Oligonucleotide Analogues with Integrated Bases and Backbone

Part 20[1])

Hydrazide- and Amide-Linked Analogues. 1. Design and Synthesis of Monomeric Building Blocks

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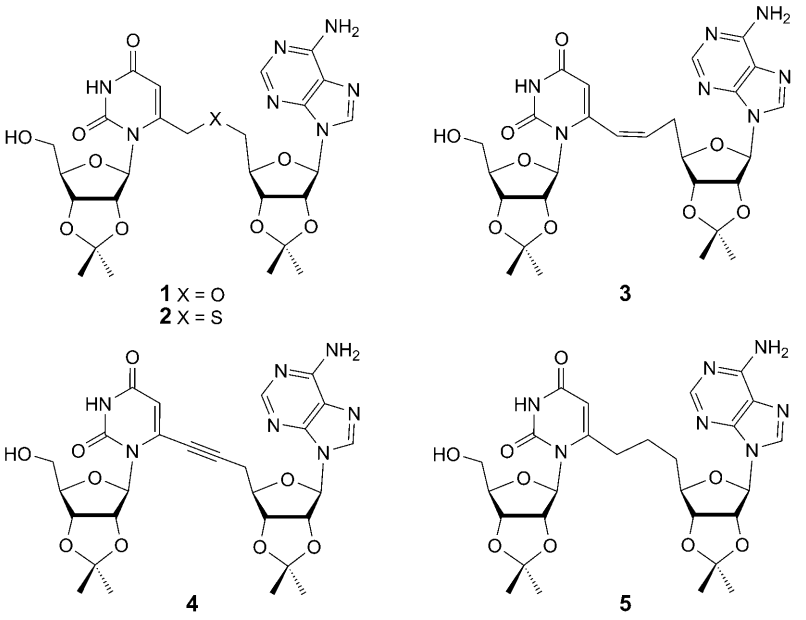
Hydrazide- and amide-linked oligonucleoside analogues with integrated bases and backbone were designed to allow for a rapid synthesis of long and water-soluble oligomers. The uracil-, cytosine-, and adenine-derived hydrazide building blocks **13**–**15** were synthesized by nucleophilic substitution with the hydrazine **23** of the halides **19**, **28**, and **34**, derived from the alcohols **18**, **27**, and **33**, respectively, while the uracil-, cytosine-, and adenine-derived amide building blocks **45**–**47** were synthesized by a *Curtius* degradation of the carboxylic acids **51**, **56**, and **61**. These acids were obtained by *Wittig* reaction of the aldehydes **49**, **53**, and **58**. The guanine-derived monomers **44** and **48** were synthesized by reductive cyclisation of the nitroso amides **38** and **63**, respectively, resulting from acylation of the known 2,6-diamino-4-(benzyloxy)-5-nitrosopyrimidine (**37**).

Introduction. – Nucleic acids, oligonucleotides, and their analogues are characterized by a contiguous backbone. The only exception are oligonucleotide analogues with integrated bases and backbone (ONIBs) that replace the backbone by a linker between C(5′) of the monoribonucleoside building blocks, and either C(6) of an adjacent pyrimidine or C(8) of an adjacent purine base [2]. Several partially protected, self-complementary adenosine- and uridine-derived dinucleosides of this type pair in $CHCl_3$ solution, *i.e.*, form cyclic duplexes, as shown for dinucleosides **1**–**4** possessing an oxymethylene- [3], thiomethylene- [4], (*Z*)-ethenylene [5], or ethynylene linker [6]. A detailed conformational analysis rationalized the formation of cyclic duplexes by self-complementary oxymethylene- and thiomethylene-, but not by ethylene-linked dinucleotides **5** [7], and predicted the structure of the energetically feasible cyclic duplexes [4]. The result of this analysis has been confirmed by the conformational analysis of thiomethylene-linked tetramers, evidencing the formation of an incipient A-type helix, characterised by a *syn*-conformation of the nucleobases, *Watson*–*Crick* or reverse-*Hoogsteen* base pairing, and a large twist angle [8].

A priori, it should be possible to vary the structure of the linker between the nucleobases within broad limits, provided that the resulting di- and oligonucleoside monoplexes adopt an energetically not disfavoured conformation that allows duplex

[1]) Part 19 [1].
[2]) Taken in part from the projected Ph.D. thesis of *M. P.* and *F. D. G.*
[3]) Taken from the diploma thesis of *M. S.*



formation by base pairing and base stacking. This implies that ONIBs are not restricted to ribonucleosides, and that the ribosyl units may be replaced by other structural elements. We intended to design ONIBs that are devoid of a carbohydrate moiety to evaluate the scope within which the architecture of ONIBs can be realised. Association of ONIBs in aqueous solution, and their interaction with DNA and RNA will require longer oligonucleotide analogues. The linker should thus allow for an efficient synthesis of such analogues, and ensure that their monoplexes and duplexes are water-soluble. These requirements suggested an amide bond as central connecting element between monomeric units. Similarly as for PNAs [9][10], this choice should allow assembling oligonucleotide analogues by one of the numerous methods for peptide coupling in solution and on a solid support. To attain a sufficient water-solubility of the analogues, we planned to introduce a side chain terminating with a carboxylate group. We thought to attach this side chain to a second N-atom of the linker, thus avoiding elements of chirality. To test if these precautions are indeed necessary, we planned to also synthesize oligonucleotide analogues where the substituted second N-atom is replaced by a CH_2 group. We describe the design of the new analogues and the synthesis of the monomeric building blocks required for their preparation in solution and on a solid support.

Results and Discussion. – 1. *Design of Peptide-Linked ONIBs.* For the design of peptide-linked ONIBs, we considered coupling amino and carboxy fragments derived from purine bases substituted at C(8) and N(9), and from pyrimidine bases substituted at C(6) and N(1). The above mentioned aim of introducing a second N-atom substituted by a carboxyalkyl group suggested to synthesize analogues linked by *N*-

acyl-*N*′-(carboxyalkyl)hydrazines. With the help of *Maruzen* models, we examined a range of analogues possessing such linkers differing in length and in the position of the *N*-acylhydrazine moiety. Among the analogues examined, those represented by a UA dimer (*Fig. 1,a*), in which the hydrazide moiety is separated on each side by a CH_2 group from the nucleobase, appeared to readily form cyclic duplexes *via Watson–Crick*-type base pairing and base stacking at distances of 3.6–4 Å, somewhat larger than those in A-, B- and Z-DNA (3.3–3.4 Å) [11]. These oligonucleotide analogues were studied in more detail by evaluating the energetically most favourable torsion angles of the monoplex (*Fig. 1,b*), and comparing them to the torsion angles required to form a cyclic duplex, as shown by the conformer in *Fig. 1,c*[4]). Whenever possible, we referred to experimental data, and calculated the energy change resulting from a larger deviation of a torsion angle from its energetically preferred value.

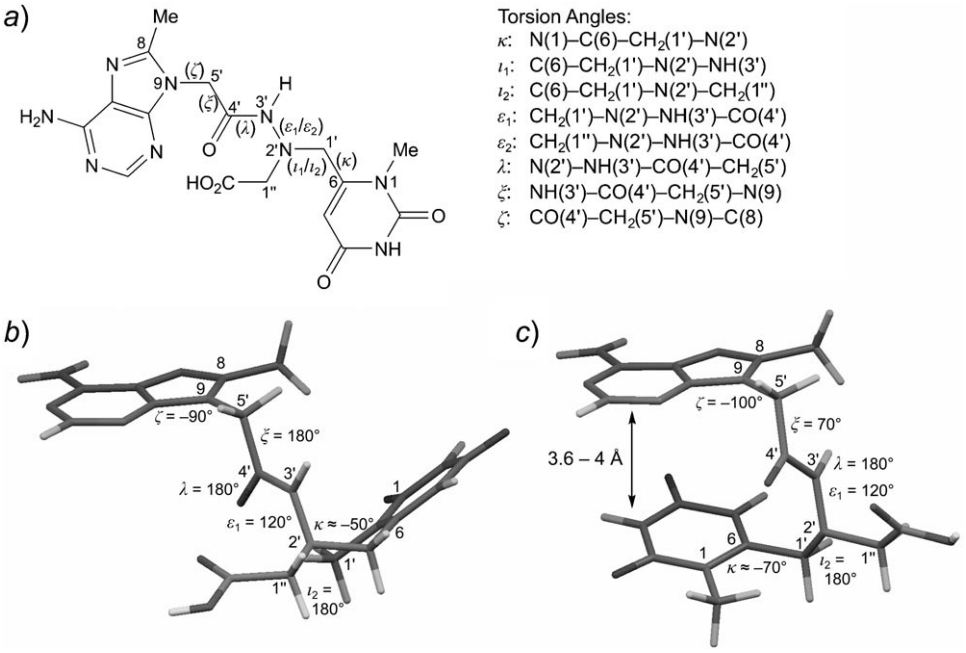


Fig. 1. a) *Definition of the torsion angles and numbering*[4]) *of a hydrazide-linked pyrimidine-purine (UA) dimer.* b) *Conformation of the UA dimer with energetically preferred torsion angles* κ–ζ. c) *Conformation of the UA dimer with torsion angles* κ–ζ, *required for pairing.*

The lone pairs of the tetrahedral and trigonal *N*-atoms of hydrazides prefer to be orthogonal to each other [12–14], resulting in the four energetically preferred conformers **6**–**9** (*Fig. 2*) with an (*E*)- or (*Z*)-configuration of the N–C(O) moiety, and a *syn*- or *anti*-orientation of the nonbonding, doubly occupied orbital of the tetrahedral *N*-atom relative to the acyl moiety. The (*Z*)-configuration is favoured in polar solvents

[4]) An arbitrary numbering of the linker is used to simplify the discussion within the conformational analysis.

and with increasing size of R^3 [12][15][5]), while the *syn*-conformation is favoured with increasing size of R^1 and R^2. A crystal structure search in the *Cambridge Structural Database* (CSD) for disubstituted hydrazides (R^1 = any C-substituent possessing at least one α-H-atom; R^2 = H; R^3 = any C-substituent) resulted in seven structures with one (*E*)-*syn* , three (*Z*)-*syn* , and three (*Z*)-*anti* conformers. The search for trisubstituted hydrazides (R^1, R^2 = any C-substituent possessing at least one α-H-atom; R^3 = any C-substituent) resulted in 14 structures with 13 (*Z*)-*syn*- and one (*E*)-*syn*-conformer. The data show the preference of the trisubstituted hydrazide linker for the (*Z*)-*syn*-conformation, with an average value for the torsion angles λ and $\varepsilon_1/\varepsilon_1$ of $\pm 172 \pm 5^\circ$ and $\pm 117 \pm 11^\circ$, respectively.

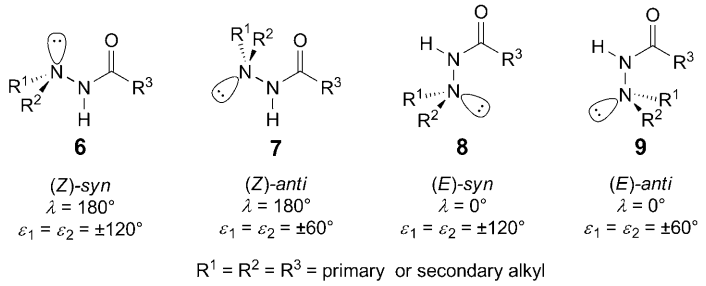


Fig. 2. *The four energetically preferred conformers of substituted hydrazides*

An antiperiplanar orientation of C(6) and either N(3′) or CH_2(1″) of the UA dimer (*Fig. 1*) results in two energetically preferred conformations around the CH_2(1′)–N(2′) bond; one with $\iota_2 = 60^\circ$ and the other with $\iota_2 = 180^\circ$. From the twelve crystal structures of trisubstituted hydrazides (R^1 = any substituted-phenyl substituent; R^2 = any C-substituent possessing at least one α-H-atom; R^3 = any C-substituent) in the *CSD*, three adopt $\iota_2 = \pm 75 \pm 1$ and 9 show $\iota_2 = \pm 171 \pm 5^\circ$. The preference for the larger value can be explained by a less destabilising synclinal interaction between C(6) and the sp^2-hybridised N(3′), as compared to a synclinal interaction between C(6) and the sp^3-hybridised CH_2(1′). The average value for κ, as defined in *Fig. 1*,*a*, is $\pm 44 \pm 13^\circ$, but conformational changes by rotation about the C(6)–CH_2(1′) bond are expected to be readily allowed [4].

To find the energetically most favoured torsion angles ξ and ζ, we referred to eight PNA structures possessing an acetamido group on N(1/9)[6]) as determined by 2D-NMR [17][18] and by crystal-diffraction [19–24] (*Protein Data Bank* (*PDB*)). We found average values of *ca.* 180° and $\pm 90^\circ$, respectively. An average value of $\pm 90 \pm 25^\circ$ for ζ was found for 36 crystal structures of *N(1/9)*-(carbonylmethyl)-substituted nucleobases in the *CSD*, while twelve of the 36 crystal structures possessing an acetamido substituent showed average values for $\xi = \pm 162 \pm 18^\circ$, corresponding to an antiperiplanar conformation of NH(3′) and N(9).

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[5]) If R^3 = H, there are usually (*E*)/(*Z*) mixtures observed [14][16].

[6]) N(1/9) and C(6/8) denotes N(1) and C(6) of a pyrimidine and N(9) and C(8) of a purine base, resp.

Stacking of the nucleobases and the right geometry for *Watson–Crick* base pairing required adjusting the torsion angles κ, ξ, and ζ from -50, 180, and -90 to -70, $+70$, and $-100°$, respectively (*Fig. 1*, $b \rightarrow c$). We assumed that changing κ and ζ from their energetically ideal values will result in only little torsional strain, and that the energy to be paid would be overcompensated by the H-bonds between the nucleobases [11][25], and by base stacking [26]. However, calculations[7]) to evaluate the energy to be paid for the adjustment of the torsion angle ξ from 180° to $+70°$ gave contradictory results[8]). It is thus not possible to specify an overall energy value to be paid for the conformational transition from conformer *b* to *c* in *Fig. 1*.

Modelling studies of various dimers suggested that stacking interactions depend on the sequence, and decrease in the order UA ≈ UU ≈ AA > AU. To evaluate the formation of duplexes between longer oligonucleotide analogues, we minimised the conformational energy of the octamer U_4A_4 (*Fig. 3*)[9]). The model suggested *Watson–Crick*-type base pairing and base stacking, with the hydrazide linker adopting a conformation with torsion angles $\kappa - \zeta$ as deduced for the cyclic duplex (*Fig. 1*, *c*). The

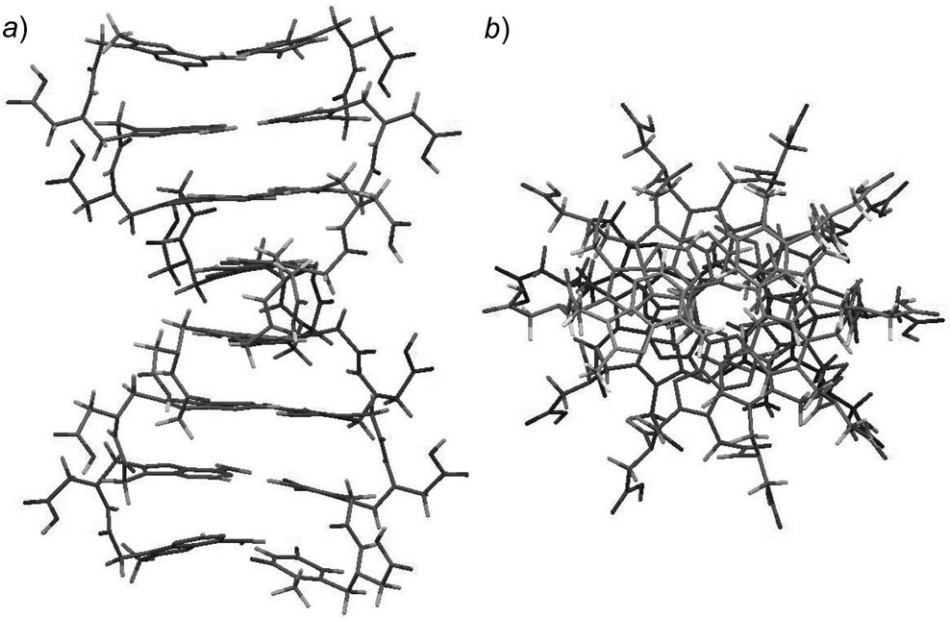

Fig. 3. *Model of the hydrazide-linked octamer U_4A_4. a*) Side view. *b*) Top view.

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7) *Ab initio* calculations using Spartan '06 and the 6-31G* basis set.

8) The conformational energies of *N*-methyl-2-(6-methyluracil-1-yl-)acetamide and *N*-methyl-2-(8-methyladenine-9-yl-)acetamide were minimised, resulting in an energy minimum of $\xi = -70°$ (*cf.* experimentally favoured: $\xi = 180°$). The value of $\xi = 70°$, required for duplex formation, corresponds to a calculated energy maximum.

9) *Amber** force-field calculation using *Macromodel 7.0*, with the H-bonds between the nucleobases constrained.

resulting double helix (racemic mixture of right- and left-handed helices) is characterised by a rise of 3.6–4 Å per base pair (*cf.* A- and B-DNA: 2.8 and 3.3–3.4 Å), a pitch of *ca.* 39 Å (*cf.* A- and B-DNA: 34 Å), and a twist angle of *ca.* 28° (*cf.* A-DNA: 31°; B-DNA: 36°).

The results of the conformational analysis encouraged us to synthesize hydrazide-linked base-backbone integrating analogues.

We also considered it instructive to evaluate analogues that are devoid of the carboxymethyl side chain and replace the *N*-unsubstituted hydrazide in the linker by an isosteric peptide moiety. We assumed the energetically preferred torsion angles κ, λ, ξ, and ζ to be about the same as for a de(carboxymethyl)-hydrazide linker, and restricted the conformational analysis of the amide linker to evaluating the torsion angles ι and ε (*Fig. 4*).

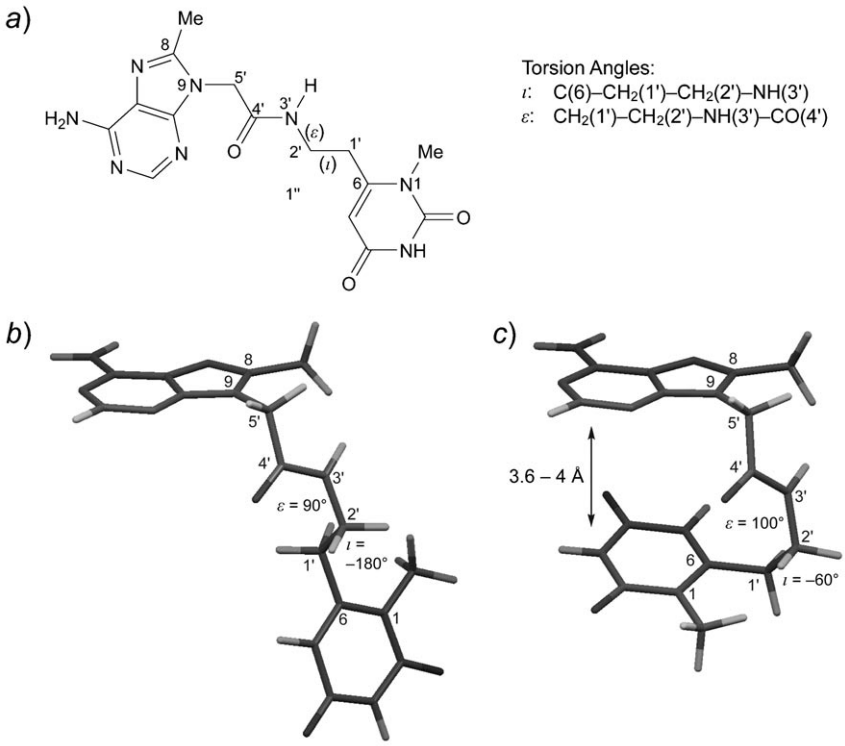
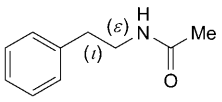


Fig. 4. a) *Definition of the torsion angles and numbering*[4]*) of an amide-linked pyrimidine-purine (UA) dinucleoside.* b) *Conformation of the UA dinucleoside with the energetically preferred torsion angles* ε *and* ι. c) *Conformation of the UA dinucleoside with torsion angles* ε *and* ι*, required for pairing.*

We expected the fragment C(6)–CH_2(1′)–CH_2(2′)–NH(3′) to adopt an energetically preferred antiperiplanar arrangement ($\iota = 180°$). To find the energetically most favoured torsion angle ε, we again referred to the eight PNA structures resolved by 2D-NMR and crystal diffraction [17–24], and calculated the preferred conformation of *N*-ethylacetamide[7]). We obtained an average value of $\varepsilon = \pm 90°$ from inspecting the *PDB*

data and from the calculations. The resulting conformation of the amide-linked UA dimer monoplex is shown in (*Fig. 4*, *b*).

Formation of a cyclic duplex requires a synclinal conformation of C(6) and NH(3′) ($\iota = -60°$), and a conformational adjustment from $\varepsilon = +90°$ to $\varepsilon = +100°$. The required deviation of the other torsion angles from their energetically preferred values appeared to be very similar to the hydrazide linker (*Fig. 1*, $b \rightarrow c$). The energy difference between the antiperiplanar and synclinal conformers appeared to be low, as estimated from a calculation for *N*-(2-phenethyl)acetamide **10** (0.25 kcal/mol). Similarly, the calculated energy difference between the antiperiplanar and synclinal conformations of the acetamides **11** and **12**, derived from uracil and adenine, amounts to 1.1 and 0.23 kcal/mol, respectively.



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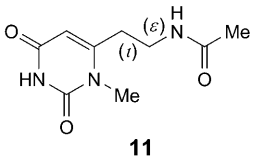

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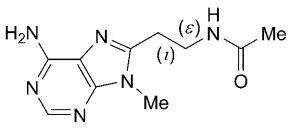

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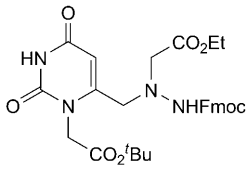
We considered the stabilisation by base pairing and base stacking in a cyclic duplex to well overcompensate the destabilisation of the synclinal conformer, and thus decided to also synthesize such amide-linked base-backbone integrating analogues, and to analyse their association[10]).

2. *Synthesis of the Monomeric Building Blocks for the Hydrazide-Linked Oligonucleotide Analogues.* We chose to synthesize the envisaged hydrazide-linked oligonucleosides by *N*-acylation of a hydrazine, deriving the required hydrazines and carboxylates from the fully protected monomeric building blocks **13**, **14**, **15**, and **16**. We temporarily protected the C- and the N-terminus as *tert*-butyl ester and (9*H*-fluoren-9-yl)methyl carbazate (Fmoc), respectively. The guanine-derived monomer was temporarily protected by *O*-benzylation. The side chain was permanently protected as ethyl ester, and the exocyclic amino group of the cytosine and adenine nucleobases as benzyloxy carbamates (Cbz). The exocyclic amino group of **16** did not require protection (see below).

The carboxylic acids **21**, **29**, **36**, and **44** were to be obtained by cleaving the *tert*-butyl esters, and the amines **20** and **35** by cleaving the *N*-Fmoc groups. At this stage, we did not yet remove the Fmoc group from **14** and **16**, as we began our investigations by synthesising di- and tetramers derived from uracil and adenine.

To prepare the fully protected uracil-derived building block **13** (*Scheme 1*), we hydroxymethylated the *tert*-butyl uracil-1-acetate (**17**) [28] by deprotonation at C(6) with lithium diisopropylamide (LDA), formylation with DMF, hydrolysis, and reduction of the resulting aldehyde with $NaBH_4$, to provide alcohol **18** in 45% yield along with 43% of starting material **17**. Attempts to optimise the *C(6)*-hydroxymethylation by deprotonating **17** with lithium 2,2,6,6-tetramethylpiperidide, lithium hexa-

[10]) To enhance the water-solubility of the amide-linked analogues, we envisaged attaching lysine residues to the C-terminus, considering the known effect of such a modification on the water-solubility of PNA oligomers [9][27].



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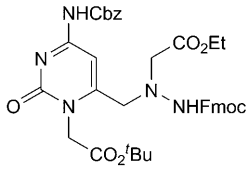

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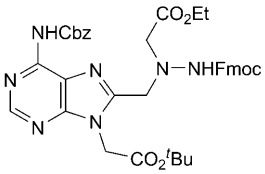

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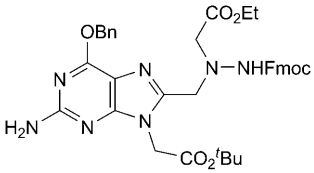

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methyldisilazide, or triphenylmethyl lithium, and by replacing DMF by *N*-methylformanilide or *N*-formylmorpholine did not increase the yield of **18**. The alcohol **18** was converted in 73% yield into the alkyl bromide **19** by mesylation with methanesulfonic anhydride in THF, followed by addition of a solution of LiBr in DMF. The bromomethyl derivative **19** was best substituted by treatment with a twofold excess of the Fmoc-protected ethyl hydrazinoacetate **23**[11]) in DMF, in the absence of base. This provided the fully protected uracil-derived **13** in a yield of 88%. Substitution of **19** in the presence of *Hünig*'s base, pyridine, 2,6-di(*tert*-butyl)-4-methylpyridine, or K_2CO_3 resulted in a less clean reaction, entailing partial loss of the Fmoc group. The desired monomers **20** and **21** were obtained in high yields by removing the Fmoc group with piperidine in THF, and by cleaving the *tert*-butyl ester with TFA in the presence of Et_3SiH.

The fully protected cytosine-derived building block **14** was synthesized in a similar way as **13** (*Scheme 1*). To prepare the Cbz-protected cytosine **25**, we modified the published procedure [30][31] by deprotonating a suspension of cytosine in DMF with NaH instead of using pyridine, and adding a slight excess of ClCOOBn. This raised the yield of **25** from 43–56% to 82% (batch size of 4 to 40 g). The Cbz-protected *tert*-butyl cytosine-1-acetate **26** was obtained in 68% yield by alkylation of **25** with $ClCH_2COO$-(*t*-Bu) [30]. Hydroxymethylation of **26** at C(6), similarly as described for **17**, gave the alcohol **27** in 51% yield besides 27% of starting material **26**. Mesylation of **27**, followed by addition of LiBr in DMF, provided the bromo derivative **28** that was directly treated with the Fmoc-protected ethyl hydrazinoacetate **23** to yield 57% of the fully protected cytosine-derived building block **14**. Cleavage of the *tert*-butyl ester with TFA in the presence of a large excess of Et_3SiH to avoid partial loss of the Cbz group [30] afforded 82% of the carboxylic acid **29**.

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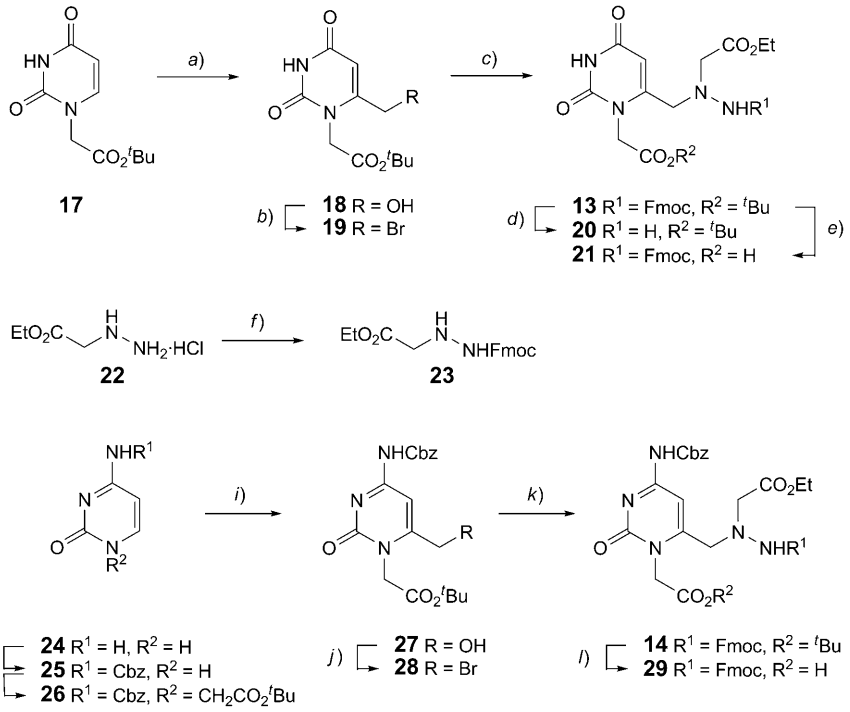
[11]) We obtained **23** in 78% yield by treating ethyl hydrazinoacetate hydrochloride (**22**) [29] with *N*-succinimidoyl (9*H*-fluoren-9-yl)methylcarbonate (Fmoc-OSu) and *N*-methylmorpholine (NMM) in THF.

Scheme 1



a) 1. LDA (= lithium diisopropylamide), THF, −70°, 2 h; 2. DMF, −70°; 3. AcOH, EtOH; 4. $NaBH_4$; 45% of **18**; 43% of **17**. *b*) 1. Ms_2O, $EtN(i\text{-}Pr)_2$, THF; 2. LiBr, DMF; 73%. *c*) **23**, DMF; 88%. *d*) Piperidine, THF; 96%. *e*) TFA (= CF_3COOH), Et_3SiH, CH_2Cl_2; 99%. *f*) Fmoc-OSu (Fmoc = (9*H*-fluoren-9-yl)methoxycarbonyl), NMM (= *N*-methylmorpholine), THF; 78%. *g*) 1. NaH, DMF; 2. $ClCO_2Bn$; 82%. *h*) $ClCH_2CO_2(t\text{-}Bu)$, K_2CO_3, Cs_2CO_3, DMF; 68%. *i*) 1. LDA, THF, −70°; 2. DMF, −70°; 3. AcOH, EtOH; 4. $NaBH_4$; 51% of **27**; 27% of **26**. *j*) 1. Ms_2O (Ms = mesyl = methanesulfonyl), THF; 2. LiBr, DMF. *k*) **23**, DMF; 57% from **27**. *l*) TFA, Et_3SiH, CH_2Cl_2; 82%. Cbz = (Benzyloxy)carbonyl.

Crystallisation of the fully protected building block **13** from MeOH afforded crystals suitable for X-ray analysis. *Fig. 5* shows capped sticks representations of the crystal structure.

A comparison of the torsion angles of crystalline **13** with those predicted is not straightforward, as two molecules of crystalline **13** are linked by four intermolecular H-bonds (two H-bonds each between the carbazate NH and C=O groups of one molecule with the C(4)=O and N(3)−H groups of the second one) with a stacking distance of 3.3 Å between the uracil planes. Even so, the torsion angles κ, ι_1, ι_2, ξ, and ζ of crystalline **13** deviate by less than $\pm 6°$ from those derived by conformational analysis of the hydrazide linker in the monoplex (*Table*).

The largest deviations from the values predicted for the monoplex were found for the torsion angles λ, ε_1, and ε_2 ($\Delta\lambda = 166°$, $\Delta\varepsilon_1 = 186°$, and $\Delta\varepsilon_2 = 183°$), corresponding to an (*E*)-*anti*-conformation of **13**. This conformation appears to be favoured by the

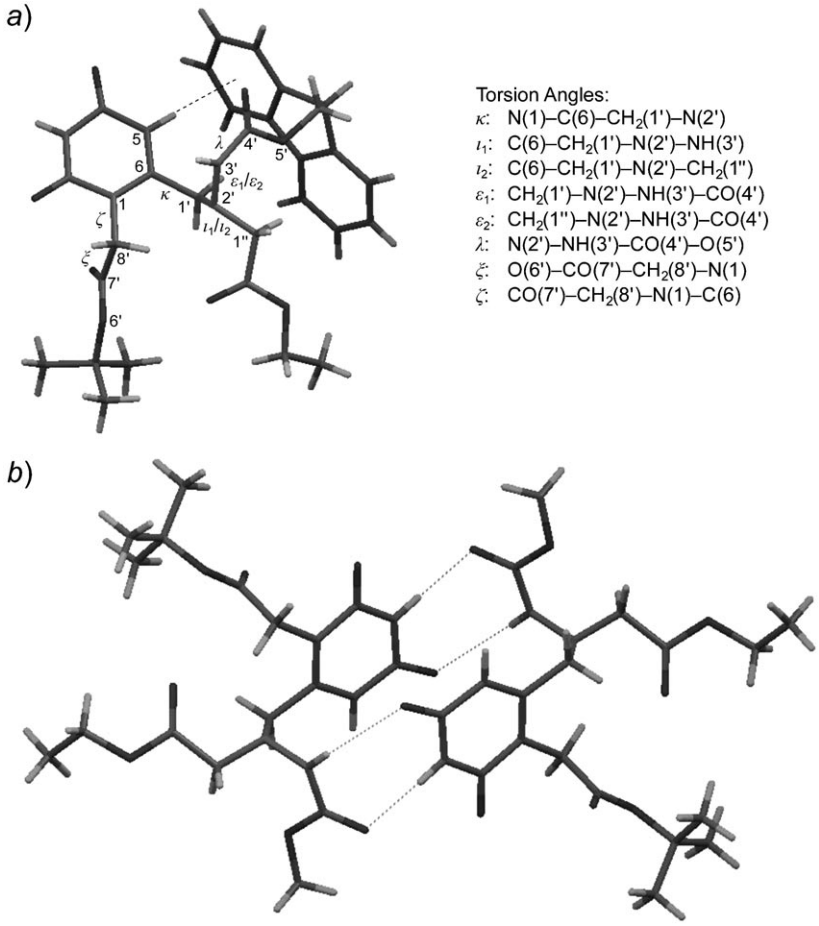


Fig. 5. *Crystal structure of* **13**. *a*) Capped sticks representation indicating the torsion angles $\kappa-\zeta$. *b*) Intermolecular H-bonding between two molecules (the 9*H*-fluorene-9-yl groups are deleted for the sake of clarity).

intermolecular H-bonds and by a stabilising face-to-edge-type interaction between H–C(5) of the uracil moiety and one aromatic ring of the fluorenyl group. The distance of 2.65 Å between H–C(5) and the σ-plane of a fluorenyl benzene group, and their almost orthogonal arrangement are in agreement with such an interaction that may stabilise the conformation by *ca.* 2.5 kcal/mol (*cf.* [32]).

To prepare the Cbz-protected adenine **31**, we modified the published procedure [30] (*Scheme 2*), deprotonating adenine with NaH and adding 1.1 instead of 2.2 equiv. of ClCOOBn. This raised the yield from 44 to 76% (batch size of 5–80 g). Alkylation of **31** with $ClCH_2COO(t\text{-Bu})$ [30] yielded 78% of **32**. Hydroxymethylation of **32** at C(8) yielded 76% of the 8-hydroxymethyl derivative **33**, besides small amounts of starting material. Mesylation of **33**, followed by addition of LiBr in DMF provided 85% of the bromo derivative **34** that was treated with hydrazinoacetate **23** in DMF to

Table. *Torsion Angles of the Crystal Structure of* **13** *and Comparison with the Torsion Angles Derived for the Hydrazide Linker*

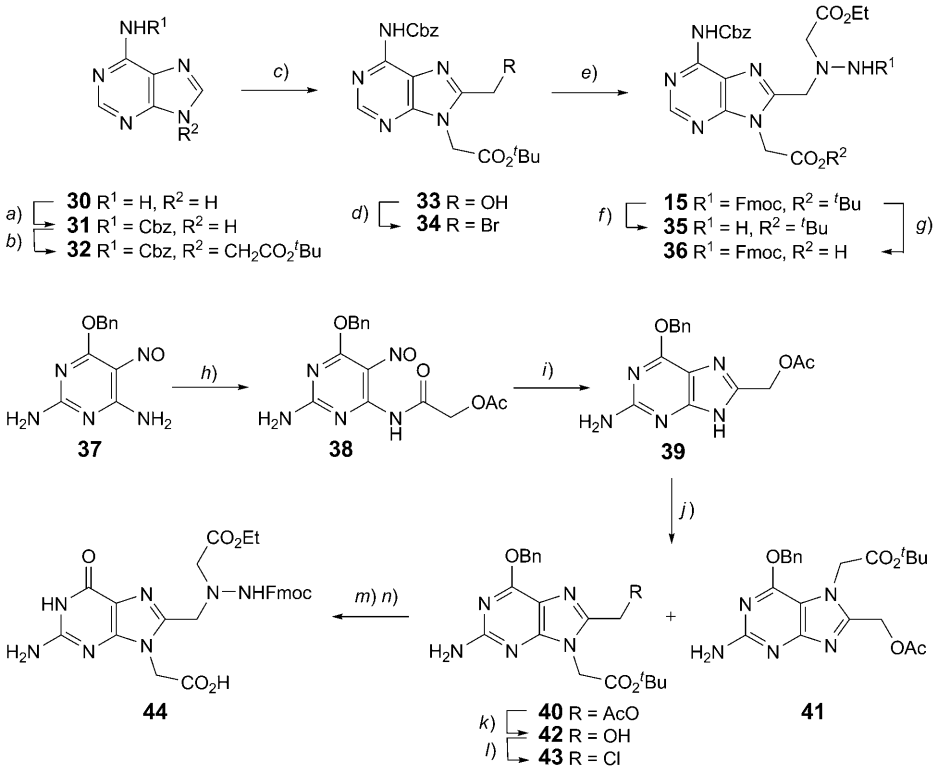
Torsion angles	Observed in the crystal Structure of **13**[a]) [°]	Evaluated by conformational analysis of the hydrazide linker	
		Monoplex[b]) [°]	Duplex[b]) [°]
κ	−65	−50	−70
ι_1	−59	−60	−60
ι_2	+173	180	180
ε_1	−66	+120	+120
ε_2	+63	−120	−120
λ	−14	180	180
ξ	−178	180	+70
ζ	−95	−90	−100

[a]) Torsion angles according to definition in *Fig. 5*. [b]) Torsion angles according to definition in *Fig. 1*.

yield 85% of the fully protected adenine-derived building block **15**. The hydrazine **35** was prepared in 85% yield by removing the Fmoc group of **15** with piperidine, and the carboxylic acid **36** was obtained in a yield of 98% by cleaving the *tert*-butyl ester with TFA, similarly as described above for **29**.

For the synthesis of the guanine-derived carboxylic acid **44** (*Scheme 2*), we acylated the NH_2 group at C(6) of 2,6-diamino-4-(benzyloxy)-5-nitrosopyrimidine (**37**) [33], with acetoxyacetyl chloride in THF to obtain the 6-(acylamino)-5-nitrosopyrimidine **38** (84%). Reductive cyclisation of **38** with Ph_3P in *o*-xylene [34] yielded almost quantitatively the 8-(acetoxymethyl)purine **39**. Alkylation of **39** with $ClCH_2COO(t\text{-Bu})$ gave **40** and **41** in a ratio of 3:1, the regioselectivity being very similar to the one of the alkylation of 2-amino-6-chloropurine [30][31]. The desired regioisomer **40** was isolated in 69% yield by silica-gel chromatography, and its structure was assigned on the basis of the cross-peak between C(8) and CH_2–N(9) in the HMBC spectrum. Deacetylation of **40** led in 94% to the alcohol **42** that was treated with MsCl/LiCl to provide the chloromethyl derivative **43**. The yield was 76% on a 0.6 g scale, and 47% on a 16 g scale. On the large scale, the reaction was somewhat less clean, and, more significantly, purification of **43** by silica-gel chromatography proved difficult due to the low solubility of **43** in organic solvents and its progressive decomposition on silica gel when MeOH was used as an eluent. Attempts to prepare **43** or the analogous bromo derivative by mesylating **42** with Ms_2O, followed by treatment with LiCl or LiBr, as for the synthesis of **19**, **28**, and **34**, did not meet with success. Alkylation of the protected ethyl hydrazinoacetate **23** with **43** under the conditions used for the preparation of **13**, **14**, and **15** failed, as **43** did not react with **23** in the absence of a base. Addition of *Hünig*'s base induced partial cleavage of the Fmoc group over longer reaction times. However, coupling the chloro compound **43** with **23** in the presence of Bu_4NBr and 2,6-lutidine in DMSO was successful if slow, requiring 3 d for complete consumption of starting materials. The resulting fully protected guanine-derived building block was directly treated with TFA, similarly as described above for the other monomers, to cleave both the *tert*-butyl ester and the benzyl ether groups [31]. The carboxylic acid **44** was obtained in a yield of 91% from **43**.

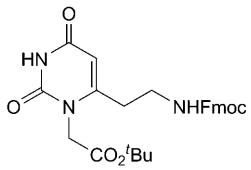
Scheme 2



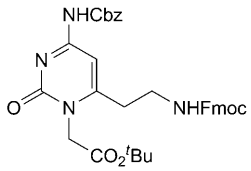
a) 1. NaH, DMF; 2. $ClCO_2Bn$; 76%. *b*) $ClCH_2CO_2(t\text{-Bu})$, K_2CO_3, Cs_2CO_3, DMF; 78%. *c*) 1. LDA, THF, −76°; 2. DMF, −76°; 3. AcOH, EtOH; 4. $NaBH_4$; 76%. *d*) 1. Ms_2O, $EtN(i\text{-Pr})_2$, CH_2Cl_2; 2. LiBr, DMF; 85%. *e*) **23**, DMF; 85%. *f*) Piperidine, THF; 86%. *g*) TFA, Et_3SiH, CH_2Cl_2; 98%. *h*) $ClCOCH_2OAc$, THF; 84%. *i*) Ph_3P, *o*-Xylene, 120°; 99%. *j*) $ClCH_2CO_2(t\text{-Bu})$, K_2CO_3, DMF; 69% of **40**. *k*) K_2CO_3, $MeOH/H_2O$; 94%. *l*) 1. MsCl, $EtN(i\text{-Pr})_2$, DMF; 2. LiCl; 47%. *m*) **23**, Bu_4NBr, 2,6-lutidine, DMSO. *n*) TFA, Et_3SiH, CH_2Cl_2; 91% from **43**.

We originally intended to protect the NH_2 group at C(2) of the guanine-derived monomer by benzyloxycarbonylation to avoid acylating this amino group during formation of the hydrazide bond. However, attempts at introducing the Cbz group in **38**, **40**, and **44** failed under a variety of conditions, such as those applied for the protection of adenine and cytosine, the use of *Rapoport*'s reagent (1-[(benzyloxy)-carbonyl]-2-ethylimidazolium tetrafluoroborate) [35], or of ClCOOBn in the presence of KH and 18-crown-6 [30][36]. Fortunately, it turned out that this amino group did not require protection, as **40** did neither react with Ac_2O, nor with **21** and **36** using HATU in the presence of *Hünig*'s base, similarly as it was reported for some guanine-derived monomers in the synthesis of PNA [31][37].

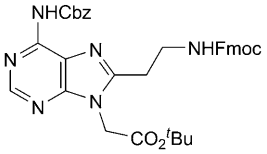
3. *Synthesis of the Building Blocks Required for the Preparation of Amide-Linked Oligonucleotide Analogues.* We chose the same protecting groups for the fully protected building blocks **45**, **46**, **47**, and **48** as for the hydrazide building blocks.



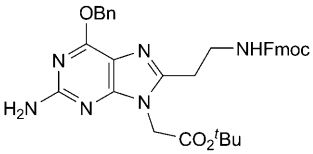
45



46



47



48

Formylation of the *tert*-butyl acetate **17** provided 37% of **49** (*Scheme 3*). *Wittig* reaction of **49** with benzyl (triphenylphosphoranylidene)acetate in THF yielded 76% of the acrylate **50**. Hydrogenation in the presence of Pd/C in THF/MeOH reduced the olefinic C=C bond and cleaved the benzyl ester of **50** to give the carboxylic acid **51** in practically quantitative yield. The acyl azide was generated from **51** *via* the mixed anhydride with ClCOOEt in THF. The crude acyl azide obtained upon aqueous workup was heated in dry dioxane in the presence of 9*H*-fluorene-9-methanol to give the fully protected uracil-derived building block **45** (90% from **51**). Treatment of **45** with TFA cleaved the *tert*-butyl ester, and yielded 72% of the carboxylic acid **52**.

The fully protected cytosine-derived building block **46** was similarly synthesized (*Scheme 3*). Aldehyde **53** was obtained in 64% yield by formylating the Cbz-protected *tert*-butyl cytosine-1-acetate **26**. *Wittig* reaction gave the methyl acrylate **54**[12]) that could not be completely separated from Ph_3PO when the reaction was performed on a scale of 7 g (97% of **54**/Ph_3PO). Reduction of the olefinic C=C bond of **54** · Ph_3PO with $NaBH_4$ in MeOH gave 98% of **55**/Ph_3PO, and saponification with LiOH in H_2O/THF afforded 83% of the carboxylic acid **56** that was separated from Ph_3PO by chromatography. The fully protected cytosine-derived building block **46** was obtained in 57% yield by *Curtius* degradation and interception of the isocyanate with 9*H*-fluorene-9-methanol, besides 29% of starting material **56**. The *tert*-butyl ester was again cleaved by the action of TFA in the presence of a large excess of Et_3SiH to provide the carboxylic acid **57** in almost quantitative yield.

Preparation of the fully protected adenine-derived building block **47** (*Scheme 4*) began by formylating the Cbz-protected *tert*-butyl adenine-9-acetate **32**, similarly as described above, to give aldehyde **58** (58%). The *Wittig* reaction to provide methyl acrylate **59** (90%) was performed similarly as described for **54**. The olefinic C=C bond of **59** was reduced with $NaBH_4$ in MeOH, and the methyl ester was saponified with

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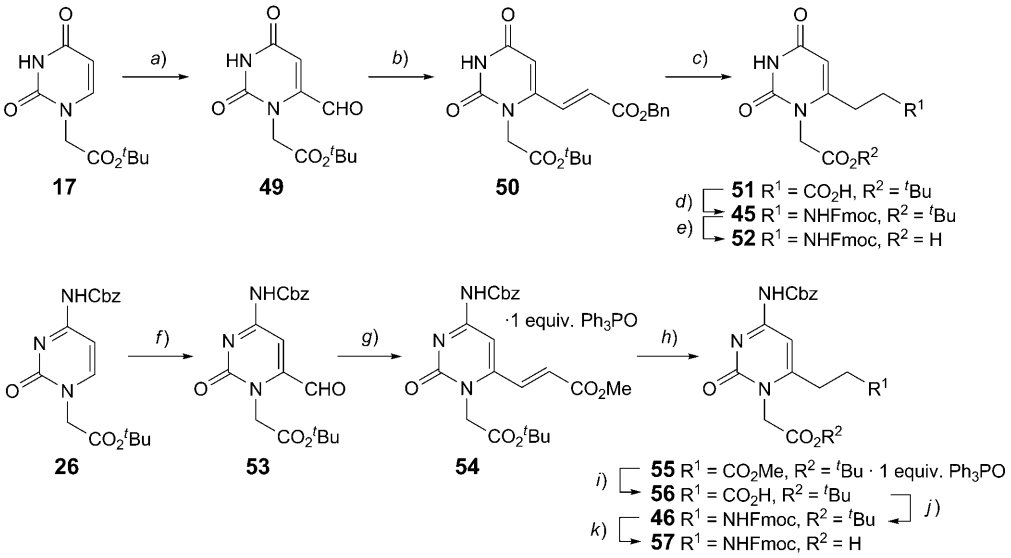
[12]) The methyl ester was chosen, as hydrogenolytic cleavage of the benzyl ester was expected to cleave also the NCbz group.

Scheme 3

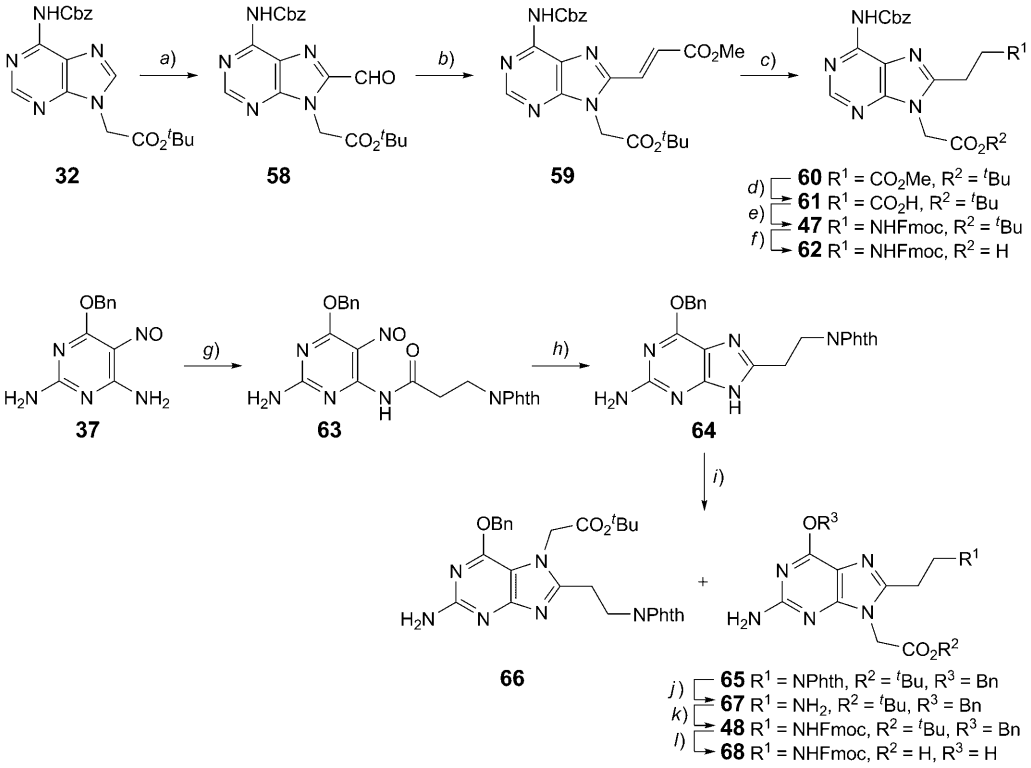


a) 1. LDA, THF, −76°; 2. DMF, −76°; 3. AcOH; 37%. *b*) Ph_3PCHCO_2Bn, THF; 76%. *c*) H_2, $Pd(OAc)_2$, MeOH/THF; 100%. *d*) 1. $ClCO_2Et$, $EtN(i\text{-}Pr)_2$, THF; 2. NaN_3, H_2O; 3. 9*H*-fluorene-9-methanol, dioxane, 100°; 90%. *e*) TFA, Et_3SiH, CH_2Cl_2; 72%. *f*) 1. LDA, THF, −76°; 2. DMF, −76°; 3. AcOH, EtOH; 64%. *g*) Ph_3PCHCO_2Me, THF; 97%. *h*) $NaBH_4$, MeOH; 98%. *i*) LiOH, THF/H_2O; 83%. *j*) 1. $ClCO_2Et$, $EtN(i\text{-}Pr)_2$, THF/acetone; 2. NaN_3, H_2O; 3. 9*H*-fluorene-9-methanol, dioxane, 80°; 57%. *k*) TFA, Et_3SiH, CH_2Cl_2; 98%.

LiOH in H_2O/THF 4:1 to yield 73% of **60** and 81% of **61**. The resulting carboxylic acid **61** was converted to the acyl azide that was subjected to a *Curtius* degradation, intercepting the resulting isocyanate with 9*H*-fluorene-9-methanol. This provided 52% of the fully protected adenine-derived building block **47**, besides 13% of starting material **61** resulting from hydrolysis of the acyl azide during aqueous workup. Cleaving the *tert*-butyl ester with TFA in the presence of a large excess of Et_3SiH afforded the carboxylic acid **62** in 98% yield.

To prepare the fully protected guanine-derived building block **48**, we acylated 2,6-diamino-4-(benzyloxy)-5-nitrosopyrimidine (**37**) [33] with *N*-phthaloyl-*β*-alanyl chloride (**69**) [38] to obtain the nitrosoamide **63** in 94% yield (*Scheme 4*). Its reductive cyclisation to the 8-(phthalimidoethyl)purine **64** using Me_3P proceeded at a lower temperature (60° instead of 120°) and more cleanly than the cyclisation of **63** using Ph_3P. The crude *C(8)*-substituted guanine **64** was alkylated with $ClCH_2COO(t\text{-}Bu)$, to provide a *ca.* 3:1 mixture of the *N(9)*- and *N(7)*-substituted regioisomers **65** and **66**, respectively. Their structure was assigned on the basis of the cross-peak between C(8) and CH_2–N(9) in the HMBC spectrum. The desired **65** was obtained pure by chromatography (51% from **63**). Hydrazinolytic dephthaloylation in EtOH yielded 86% of **67**, and Fmoc protection gave the fully protected guanine-derived building block **48** in 86% yield. The *tert*-butyl ester and the benzyl ether groups of **48** were cleaved by treatment with TFA/Et_3SiH to yield 98% of the carboxylic acid **68**.

Scheme 4



a) 1. LDA, THF, −76°; 2. DMF, −76°; 3. AcOH, EtOH; 58%. *b*) Ph_3PCHCO_2Me, THF; 90%. *c*) $NaBH_4$, MeOH; 73%. *d*) LiOH, THF/H_2O; 81%. *e*) 1. $ClCO_2Et$, $EtN(i\text{-}Pr)_2$, THF/acetone; 2. NaN_3, H_2O; 3. 9*H*-fluorene-9-methanol, dioxane, 80°; 52%. *f*) TFA, Et_3SiH, CH_2Cl_2; 98%. *g*) Phth-*β*-Ala-Cl (Phth = phthaloyl; **69**), THF; 94%. *h*) Me_3P, toluene, 60°. *i*) $ClCH_2CO_2(t\text{-}Bu)$, K_2CO_3, Cs_2CO_3, DMF; 51% of **65**. *j*) N_2H_4, EtOH; 86%. *k*) Fmoc-OSu, THF; 86%. *l*) TFA, Et_3SiH, CH_2Cl_2; 98%.

We thank Dr. *B. Bernet* for his contribution to the conformational analyses and for checking the manuscript, and the ETH-Zürich and *Syngenta*, Basel, for generous support.

Experimental Part

General. THF was distilled from Na/benzophenone, CH_2Cl_2, MeOH, DMF, pyridine, $EtN(i\text{-}Pr)_2$, and $(i\text{-}Pr)_2NH$ from CaH_2. Reactions were run under N_2. Qual. TLC: precoated silica-gel plates (*Merck* silica gel *60 F254*); detection by UV light at 254 nm wavelength and by spraying with 'mostain' and heating. Flash chromatography (FC): silica gel *Fluka 60* or *Merck 60* (0.04–0.063 mm). UV Spectra: 10^{-5} M solns. in $CHCl_3$ or MeOH at 20° in a 1-cm *Suprasil* cell. FT-IR: solid state (ATR). ^{1}H- and ^{13}C-NMR: at 300 or 400 MHz and 75 or 100 MHz, resp. MS: matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF) with 0.05M indol-3-acrylic acid (IAA) in THF, or with 0.05M *α*-cyano-4-hydroxycinnamic acid (CCA) in MeCN/EtOH/H_2O, and high-resolution (HR) MALDI-TOF with 0.05M 2,5-dihydrobenzoic acid (DHB) in THF.

tert-*Butyl 6-[(1-(2-Ethoxy-2-oxoethyl)-2-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}hydrazino)methyl]-uracil-1-acetate* (**13**). A soln. of **23** (19.6 g, 58 mmol) in DMF (150 ml) was treated dropwise with a soln. of **19** (11.7 g, 37 mmol) in DMF (100 ml), stirred at r.t. for 2 d, treated with sat. $NaHCO_3$ soln. (300 ml), and extracted with AcOEt (5×200 ml). Drying of the combined org. layers ($MgSO_4$), filtration, evaporation, and FC (AcOEt/cyclohexane 1:1 → 4:1) gave **13** (18.6 g, 88%). White powder. R_f (AcOEt/cyclohexane 1:1) 0.21. M.p. 196–199°. UV ($CHCl_3$): 267 (28700), 302 (5700). IR (ATR): 3270*w*, 3151*w*, 3094*w*, 2980*w*, 1740*s*, 1702*s*, 1677*s*, 1466*m*, 1448*m*, 1409*m*, 1391*m*, 1365*m*, 1326*m*, 1232*s*, 1207*s*, 1159*s*, 1126*m*, 1102*w*, 1065*m*, 1028*w*, 1001*w*, 979*w*, 933*w*, 870*w*, 846*w*, 830*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 11.44 (*s*, H–N(3)); 8.91 (br. *s*, $NHCO_2$); 7.89–7.29 (*m*, 8 arom. H); 5.60 (br. *s*, H–C(5)); 4.91 (br. *s*, CH_2–N(1)); 4.27 (br. *s*, CH_2–C(9′)); 4.18 (br. *s*, H–C(9′)); 4.09 (*q*, $J = 7.0$, MeCH_2O); 3.72 (br. *s*, CH_2–C(6), NCH_2CO_2Et); 1.40 (*s*, ^{t}Bu); 1.19 (*t*, $J = 7.2$, *Me*CH_2O). ^{1}H-NMR (300 MHz, (D_6)DMSO, 100°): 11.00 (*s*, H–N(3)); 8.38 (*s*, $NHCO_2$); 7.85–7.29 (*m*, 8 arom. H); 5.55 (*s*, H–C(5)); 4.81 (*s*, CH_2–N(1)); 4.37 (*d*, $J = 6.3$, CH_2–C(9′)); 4.21 (*t*, $J = 6.5$, H–C(9′)); 4.13 (*q*, $J = 6.9$, MeCH_2O); 3.72, 3.60 (2*s*, CH_2–C(6), NCH_2CO_2Et); 1.43 (*s*, ^{t}Bu); 1.23 (*t*, $J = 6.9$, *Me*CH_2O). ^{13}C-NMR (75 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 168.88 (*s*, *C*O_2Et); 167.87 (*s*, *C*$O_2{}^t$Bu); 162.23 (*s*, C(4)); 154.98, 150.71 (2*s*, C(2), $NHCO_2$); 151.46 (*s*, C(6)); 143.43 (2*s*); 140.56 (2*s*); 127.54 (2*d*); 126.99 (2*d*); 124.90 (2*d*); 119.99 (2*d*); 103.79 (*d*, C(5)); 81.54 (*s*, Me_3C); 65.61 (*t*, *C*H_2–C(9′)); 60.38 (*t*, Me*C*H_2O); 57.57 (*t*, *C*H_2–C(6)); 56.61 (*t*, N*C*H_2CO_2Et); 46.59 (*d*, C(9′)); 45.26 (*t*, CH_2–N(1)); 27.65 (*q*, *Me*$_3$C); 14.07 (*q*, *Me*CH_2O). ESI-MS: 601 (100, $[M + Na]^+$), 545 (23, $[M - {}^t\text{Bu} + H + Na]^+$), 523 (11, $[M - {}^t\text{Bu} + 2\,H]^+$). Anal. calc. for $C_{30}H_{34}N_4O_8$ (578.61): C 62.27, H 5.92, N 9.68; found: C 62.32, H 6.15, N 9.91.

X-Ray Analysis of **13**. Crystals of **13** were obtained by slow evaporation of a soln. of **13** in MeOH (dimensions of the analysed crystal: cube $0.4 \times 0.22 \times 0.04$ mm). $C_{30}H_{34}N_4O_8$, $M_r = 578.62$, triclinic *P*1, $a = 10.7336(7)$, $b = 11.0417(9)$, $c = 13.1991(9)$ Å, $\alpha = 75.096(4)$, $\beta = 74.695(4)$, $\gamma = 84.237(4)°$, $V = 1457.2(2)$ Å^3, $Z = 2$, $D_x = 1.319$ Mg·m^{-3}. The reflections were measured on a *KappaCCD* diffractometer, with MoK_α radiation $\lambda = 0.71073$ Å. Cell parameters from 9199 refl., $\theta = 0.998–24.108°$, $\mu = 0.097$ mm^{-1}, $T = 223$ K. 6105 Measured reflections, 4217 independent reflections, 2837 observed reflections ($> 2\sigma(I)$). Refinement on F^2: full-matrix least-squares refinement, R(all) = 0.1095, R(gt) = 0.0700. All diagrams and calculations were performed using *maXus* (*Bruker Nonius*, Delft and *MacScience*, Japan). The program SIR97 was used to solve the structure and the program SHELXL-97 to refine it.

tert-*Butyl* N^4-*[(Benzyloxy)carbonyl]-6-[(1-(2-ethoxy-2-oxoethyl)-2-{[(9*H*-fluoren-9-yl)methoxy]-carbonyl}hydrazino)methyl]cytosine-1-acetate* (**14**). A soln. of **27** (8.5 g, 22 mmol) in THF (85 ml) was cooled to 0°, treated with EtN^iPr$_2$ (11.4 ml, 65 mmol), stirred for 30 min, treated dropwise with a soln. of Ms_2O (11.4 g, 65 mmol) in THF (50 ml), and stirred for 2.5 h while being allowed to reach r.t. The soln. was cooled to 0°, treated dropwise with a soln. of LiBr (9.5 g, 109 mmol) in DMF (85 ml), stirred for 3 h while being allowed to reach r.t., cooled to 0°, treated with sat. $NaHCO_3$ soln. (100 ml), and extracted with AcOEt (3×300 ml). The combined org. layers were dried ($MgSO_4$), filtered, and evaporated. A soln. of the residue in DMF (60 ml) was treated portionwise with **23** (18.6 g, 55 mmol), stirred for 12 h at r.t., and diluted with AcOEt (100 ml) and sat. $NaHCO_3$ soln. (100 ml). After separation of the layers, the aq. layer was extracted with AcOEt (3×200 ml). Drying of the combined org. layers ($MgSO_4$), filtration, evaporation, and FC (AcOEt/cyclohexane 1:2 → 4:1) gave **14** (8.8 g, 57%). White powder. R_f (AcOEt/cyclohexane 2:1) 0.48. UV (MeOH): 254 (24400), 300 (13600). IR (ATR): 3217*w* (br.), 2979*w*, 1736*s*, 1704*m*, 1668*m*, 1616*m*, 1567*m*, 1498*m*, 1450*m*, 1415*m*, 1389*s*, 1369*m*, 1324*w*, 1192*s*, 1152*s*, 1077*m*, 1052*m*, 1028*m*, 971*w*, 862*w*, 817*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.71 (*s*, NH–C(4)); 8.94 (*s*, NH–N); 7.86–7.24 (*m*, 13 arom. H); 7.04 (*s*, H–C(5)); 5.09 (*s*, CH_2–N(1)); 4.97 (*s*, PhCH_2); 4.21 (br. *s*, CH_2–C(9′)); 4.14–4.07 (*m*, MeCH_2O, H–C(9′)); 3.90 (*s*, CH_2–C(6)); 3.79 (*s*, NCH_2CO_2Et); 1.41 (*s*, Me_3C); 1.20 (*t*, $J = 7.2$, *Me*CH_2O). ^{13}C-NMR (100 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 169.08 (*s*, *C*O_2Et); 167.81 (*s*, *C*$O_2{}^t$Bu); 162.35 (*s*, C(4)); 155.93 (*s*, C(2)); 155.14 (*s*, N–NCO_2, C(6)); 152.87 (*s*, C(4)N*C*O_2); 143.57 (2*s*); 140.64 (2*s*); 135.76 (*s*); 128.37 (2*d*); 128.08 (2*d*); 127.89 (2*d*); 127.57 (2*d*); 126.98 (*d*); 124.90 (2*d*); 119.99 (2*d*); 96.97 (*d*, C(5)); 81.39 (*s*, Me_3C); 66.39 (*t*, PhCH_2); 65.69 (*t*, *C*H_2–C(9)); 60.38 (*t*, Me*C*H_2O); 57.78, 56.63 (2*t*, CH_2–C(6), N*C*H_2CO_2Et); 46.70 (*t*, CH_2–N(1)); 46.48 (*d*, C(9′)); 27.60 (*q*, *Me*$_3$C); 13.94 (*q*, *Me*CH_2O). HR-MALDI-MS: 750.2524 (12, $[M + K]^+$, $C_{38}H_{41}KN_5O_9^+$; calc. 750.2536), 734.2770 (10, $[M + Na]^+$, $C_{38}H_{41}N_5NaO_9^+$; calc. 734.2796),

712.2976 (100, $[M+H]^+$, $C_{38}H_{42}N_5O_9^+$; calc. 712.2977), 656.2324 (21, $[M-{}^t\mathrm{Bu}+2\,H]^+$, $C_{34}H_{34}N_5O_9^+$; calc. 656.2351).

tert-*Butyl* N^6-*[(Benzyloxy)carbonyl]-8-[(1-(2-ethoxy-2-oxoethyl)-2-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}hydrazino)methyl]adenine-9-acetate* (**15**). A soln. of **23** (7.15 g, 21.0 mmol) in DMF (200 ml) was treated dropwise with a soln. of **34** (9.1 g, 21.0 mmol) in DMF (70 ml) and stirred for 16 h at r.t. The soln. was poured on sat. $NaHCO_3$ soln. and extracted with AcOEt (5 ×). The combined org. fractions were washed with brine (5 ×), dried ($MgSO_4$), and evaporated. FC (AcOEt/cyclohexane 1:1) gave **15** (12.0 g, 85%). White foam. R_f (CH_2Cl_2/MeOH 19:1) 0.38. UV (MeOH): 230 (5740), 266 (37620), 212 (54720). IR (ATR): 3191*w*, 3063*w*, 3033*w*, 2979*w*, 2942*w*, 2903*w*, 1733*m*, 1613*m*, 1590*m*, 1538*w*, 1497*w*, 1477*w*, 1450*m*, 1392*w*, 1368*m*, 1321*w*, 1299*w*, 1237*m*, 1201*s*, 1151*s*, 1102*m*, 1041*m*, 1029*m*, 1006*w*, 972*w*, 847*w*, 758*m*, 739*s*, 697*m*. ^{1}H-NMR (400 MHz, (D_6)DMSO): 10.65 (br. *s*, NH–C(6)); 8.83 (br. *s*, N*H*Fmoc); 8.59 (*s*, H–C(2)); 7.85–7.15 (*m*, 13 arom. H); 5.48 (br. *s*, CH_2–N(9)); 5.20 (*s*, PhCH_2); 4.31 (br. *s*, CH_2–C(8)); 4.22 (*d*, *J* = 6.5, CH_2–C(9′)); 4.15–4.05 (*m*, MeCH_2O, H–C(9′)); 3.73 (br. *s*, NCH_2CO_2Et); 1.41 (*s*, Me_3C); 1.19 (*t*, *J* = 7.1, *Me*CH_2O). ^{13}C-NMR (100 MHz, (D_6)DMSO): 168.97 (*s*, *C*O_2Et); 167.05 (*s*, *C*$O_2{}^t$Bu); 154.97 (*s*, NNHCO_2); 153.67 (*s*, NH*C*O_2Bn); 151.96 (*s*, C(4)); 151.48 (*s*, C(8)); 150.50 (*d*, C(2)); 148.81 (*s*, C(6)); 143.48 (2*s*); 140.60 (2*s*); 136.30 (*s*); 128.28–124.90 (11*d*); 121.92 (*s*, C(5)); 119.96 (2*d*); 82.10 (*s*, Me_3C); 66.17 (*t*, Ph*C*H_2); 65.49 (*t*, CH_2–C(9′)); 60.27 (*t*, Me*C*H_2O); 57.52, 53.79 (2*t*, *C*H_2–C(8), N*C*H_2CO_2Et); 46.49 (*d*, C(9′)); 44.42 (*t*, *C*H_2–N(9)); 27.55 (*q*, *Me*$_3$C); 13.91 (*q*, *Me*CH_2O). HR-MALDI-MS: 774.2650 (8, $[M+K]^+$, $C_{39}H_{41}KN_7O_8^+$; calc. 774.2654), 758.2927 (61, $[M+Na]^+$, $C_{39}H_{41}N_7NaO_8^+$; calc. 758.2914), 736.3075 (100, $[M+H]^+$, $C_{39}H_{42}N_7O_8^+$; calc. 736.3095), 702.2270 (18, $[M-{}^t\mathrm{Bu}+H+Na]^+$, $C_{35}H_{33}N_7NaO_8^+$; calc. 702.2288), 680.2442 (22, $[M-{}^t\mathrm{Bu}+2\,H]^+$, $C_{35}H_{34}N_7O_8^+$; calc. 680.2469), 628.2511 (14, $[M-BnOH+H]^+$, $C_{32}H_{34}N_7O_7^+$; calc. 628.2520), 594.1703 (2, $[M-BnOH-{}^t\mathrm{Bu}+H+Na]^+$, $C_{28}H_{25}N_7NaO_7^+$; calc. 594.1713), 572.1875 (9, $[M-BnOH-{}^t\mathrm{Bu}+2\,H]^+$, $C_{28}H_{26}N_7O_7^+$; calc. 572.1894). Anal. calc. for $C_{39}H_{41}N_7O_8$ (735.78): C 63.66, H 5.62, N 13.33; found: C 63.43, H 5.67, N 13.16.

tert-*Butyl 6-(Hydroxymethyl)uracil-1-acetate* (**18**). A soln. of ^{i}Pr$_2$NH (29.7 ml, 210 mmol) in THF (200 ml) was cooled to −67°, treated dropwise with 1.6M BuLi in hexane (131 ml, 210 mmol), stirred for 20 min, warmed to 0°, stirred for 20 min, cooled to −68°, and treated dropwise with a soln. of **17** (9.5 g, 42 mmol) in THF (225 ml). After stirring for 2 h at −70°, the soln. was treated dropwise with DMF (65 ml, 840 mmol), stirred for another 1.5 h at −70°, treated dropwise with AcOH (24 ml, 420 mmol), diluted with EtOH (200 ml), allowed to reach 0°, treated portionwise with $NaBH_4$ (4.8 g, 126 mmol), stirred for 30 min, treated with sat. NH_4Cl soln. (500 ml), allowed to reach r.t., and extracted with CH_2Cl_2 (3 × 300 ml). Drying of the combined org. layers ($MgSO_4$), filtration, evaporation, and FC (CH_2Cl_2/MeOH 97:3 → 92:8) gave **17** (4.1 g, 43%) and **18** (4.8 g, 45%).

Data of **18**. White powder. R_f (CH_2Cl_2/MeOH 9:1) 0.40. M.p. 174–175°. UV ($CHCl_3$): 264 (9500). IR (ATR): 3461*w*, 3142*w*, 3090*w*, 3006*w*, 2978*w*, 2927*w*, 2874*w*, 2808*w*, 1745*m*, 1689*s*, 1656*m*, 1617*w*, 1476*m*, 1427*m*, 1397*m*, 1378*m*, 1367*m*, 1232*m*, 1206*m*, 1158*s*, 1078*w*, 1044*m*, 994*m*, 980*w*, 930*w*, 871*m*, 851*m*, 823*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 11.36 (*s*, NH); 5.77 (*t*, *J* = 5.6, OH); 5.65 (*s*, H–C(5)); 4.44 (*s*, NCH_2); 4.21 (*d*, *J* = 5.1, CH_2–C(6)); 1.41 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, (D_6)DMSO): 167.29 (*s*, CO_2); 162.84 (*s*, C(4)); 156.39 (*s*, C(2)); 151.65 (*s*, C(6)); 98.89 (*d*, C(5)); 81.86 (*s*, Me_3C); 59.00 (*t*, CH_2OH); 44.54 (*t*, NCH_2); 27.63 (*q*, *Me*$_3$C). HR-EI-MS: 256.1055 (3, M^+, $C_{11}H_{16}N_2O_5^+$; calc. 256.1059), 200.0430 (2, $[M-{}^t\mathrm{Bu}+H]^+$, $C_7H_8N_2O_5^+$; calc. 200.0433), 183.0399 (15, $[M-{}^t\mathrm{BuO}]^+$, $C_7H_7N_2O_4^+$; calc. 183.0400), 156.0530 (34, $[M-CO_2{}^t\mathrm{Bu}+H]^+$, $C_6H_8N_2O_3^+$; calc. 156.0535), 57.0719 (100, ^{t}Bu$^+$, $C_4H_9^+$; calc. 57.0699). Anal. calc. for $C_{11}H_{16}N_2O_5$ (256.26): C 51.56, H 6.29, N 10.93; found: C 51.66, H 6.30, N 10.80.

tert-*Butyl 6-(Bromomethyl)uracil-1-acetate* (**19**). A soln. of **18** (12.6 g, 49 mmol) and Et^{i}Pr$_2$ (17.1 ml, 98 mmol) in THF (320 ml) was cooled to 0°, treated dropwise with a soln. of Ms_2O (12.9 g, 74 mmol) in THF (30 ml), and stirred for 2 h. The soln. was allowed to reach r.t., treated dropwise with a soln. of LiBr (8.5 g, 98 mmol) in DMF (120 ml), stirred for 4 h, treated with brine (300 ml), and extracted with AcOEt (3 × 300 ml). Drying of the combined org. layers ($MgSO_4$), filtration, evaporation, and crystallisation from MeOH gave **19** (11.5 g, 73%). White crystals. R_f (CH_2Cl_2/MeOH 95:5) 0.40. M.p. 232–240°. UV ($CHCl_3$): 277 (12270). IR (ATR): 3003*w*, 2815*w*, 1737*s*, 1720*s*, 1697*s*, 1607*w*, 1471*m*, 1459*w*, 1414*s*, 1385*m*, 1372*m*, 1234*m*, 1198*w*, 1167*m*, 1140*m*, 992*w*, 923*w*, 883*m*, 866*m*, 821*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.59 (br. *s*, NH); 5.81 (*d*, *J* = 2.1, H–C(5)); 4.65 (*s*, NCH_2); 4.02 (*s*, CH_2–C(6)); 1.49 (*s*, ^{t}Bu).

^{13}C-NMR (75 MHz, (D_6)DMSO): 166.28 (*s*, CO_2); 162.10 (*s*, C(4)); 151.34, 151.24 (2*s*, C(2), C(6)); 103.13 (*d*, C(5)); 81.72 (*s*, Me_3C); 45.63 (*t*, NCH_2); 28.10 (*t*, CH_2Br); 27.67 (*q*, Me_3C). HR-EI-MS: 320.0186 (2, M^+, $C_{11}H_{15}{}^{81}BrN_2O_4^+$; calc. 320.0195), 318.0210 (2, M^+, $C_{11}H_{15}{}^{79}BrN_2O_4^+$; calc. 318.0215), 219.9657 (14, $[M-CO_2{}^t\text{Bu}+H]^+$, $C_6H_7{}^{81}BrN_2O_2^+$; calc. 219.9670), 217.9675 (14, $[M-CO_2{}^t\text{Bu}+H]^+$, $C_6H_7{}^{79}BrN_2O_2^+$; calc. 217.9691), 57.0711 (100, $^t\text{Bu}^+$, $C_4H_9^+$; calc. 57.0699). Anal. calc. for $C_{11}H_{15}BrN_2O_4$ (319.15): C 41.40, H 4.74, N 8.78; found: C 41.69, H 4.82, N 8.72.

tert-*Butyl 6-{[1-(2-Ethoxy-2-oxoethyl)hydrazino]methyl}uracil-1-acetate* (**20**). A soln. of **13** (5 g, 8.6 mmol) in THF (150 ml) was treated dropwise with piperidine (1.3 ml, 13.1 mmol), stirred for 8 h at r.t., and evaporated. The solid residue was washed with Et_2O (5 × 50 ml). The solid was suspended in CH_2Cl_2 (200 ml) and filtered. Evaporation of the filtrate gave **20** (3.0 g, 96%). White powder. R_f (CH_2Cl_2/MeOH 95 :5) 0.23. M.p. 133–134°. UV ($CHCl_3$): 267 (8300). IR (ATR): 3178*w* (br.), 2980*w*, 1730*s*, 1687*s*, 1624*w*, 1458*m*, 1419*m*, 1390*m*, 1370*m*, 1235*m*, 1199*m*, 1156*s*, 1103*w*, 1026*w*, 926*w*, 865*w*, 819*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 11.37 (*s*, H–N(3)); 5.60 (*s*, H–C(5)); 4.65 (*s*, CH_2–N(1)); 4.10 (*q*, J = 7.2, MeCH_2O); 3.68 (*s*, NH_2); 3.63 (*s*, CH_2–C(6)); 3.49 (*s*, NCH_2CO_2Et); 1.41 (*s*, ^{t}Bu); 1.21 (*t*, J = 6.9, *Me*CH_2O). ^{13}C-NMR (75 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 169.76 (*s*, CO_2Et); 167.31 (*s*, $CO_2{}^t$Bu); 162.39 (*s*, C(4)); 151.65 (*s*, C(6)); 151.59 (*s*, C(2)); 103.70 (*d*, C(5)); 81.31 (*s*, Me_3C); 60.10 (*t*, CH_2–C(6)); 60.00 (*t*, MeCH_2O); 59.84 (*t*, NCH_2CO_2Et); 45.32 (*t*, CH_2–N(1)); 27.68 (*q*, Me_3C); 14.12 (*q*, *Me*CH_2O). HR-ESI-MS: 379.1589 (82, $[M+Na]^+$, $C_{15}H_{24}N_4NaO_6^+$; calc. 379.1588), 323.0962 (100, $[M-{}^t\text{Bu}+H+Na]^+$, $C_{11}H_{16}N_4NaO_6^+$; calc. 323.0962), 301.1151 (18, $[M-{}^t\text{Bu}+2H]^+$, $C_{11}H_{17}N_4O_6^+$; calc. 301.1143). Anal. calc. for $C_{15}H_{24}N_4O_6$ (356.37): C 50.55, H 6.79, N 15.72; found: C 50.71, H 6.71, N 15.70.

tert-*Butyl 6-[(1-(2-Ethoxy-2-oxoethyl)-2-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}hydrazino)methyl]-uracil-1-acetic Acid* (**21**). A suspension of **13** (3.2 g, 5.5 mmol) in CH_2Cl_2 (50 ml) was treated dropwise with Et_3SiH (1.1 ml, 6.9 mmol) and TFA (12.3 ml, 166 mmol) and stirred for 4.5 h at r.t. After evaporation, the solid residue was washed with Et_2O (10 × 50 ml). Filtration gave **21** (2.9 g, 99%). White powder. R_f (AcOEt/MeOH/H_2O 80 :15 :5) 0.27. M.p. 234–236°. UV (MeOH): 264 (32400), 299 (9400). IR (ATR): 3383*w*, 3270–2410*w* (br.), 3021*w*, 1734*m*, 1710*s*, 1665*s*, 1469*m*, 1448*w*, 1417*s*, 1390*m*, 1333*m*, 1300*w*, 1270*w*, 1211*s*, 1176*m*, 1141*m*, 1064*m*, 1016*m*, 984*w*, 957*w*, 933*w*, 886*m*, 858*m*, 832*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 12.97 (br. *s*, CO_2H); 11.42 (*d*, J = 2.1, H–N(3)); 8.89 (br. *s*, $NHCO_2$); 7.89–7.29 (*m*, 8 arom. H); 5.59 (br. *s*, H–C(5)); 4.89 (br. *s*, CH_2–N(1)); 4.27 (br. *s*, CH_2–C(9′)); 4.17 (br. *s*, H–C(9′)); 4.09 (*q*, J = 7.1, MeCH_2O); 3.78, 3.73 (2 br. *s*, CH_2–C(6), NCH_2CO_2Et); 1.18 (*t*, J = 7.1, *Me*CH_2O). ^{1}H-NMR (300 MHz, (D_6)DMSO, 80°): 11.10 (*s*, H–N(3)); 8.48 (br. *s*, $NHCO_2$); 7.86–7.29 (*m*, 8 arom. H); 5.53 (*s*, H–C(5)); 4.82 (*s*, CH_2–N(1)); 4.34 (*d*, J = 6.6, CH_2–C(9′)); 4.20 (*t*, J = 6.5, H–C(9′)); 4.12 (*q*, J = 7.0, MeCH_2O); 3.72, 3.61 (2*s*, CH_2–C(6), NCH_2CO_2Et); 1.21 (*t*, J = 7.2, *Me*CH_2O). ^{13}C-NMR (75 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 170.08 (*s*, CO_2H); 168.87 (*s*, CO_2Et); 162.23 (*s*, C(4)); 154.96 (*s*, $NHCO_2$); 151.50, 150.82 (2*s*, C(2), C(6)); 143.42 (2*s*); 140.54 (2*s*); 127.51 (2*d*); 126.96 (2*d*); 124.93 (2*d*); 119.97 (2*d*); 103.66 (*d*, C(5)); 65.57 (*t*, CH_2–C(9′)); 60.37 (*t*, MeCH_2O); 57.50, 56.55 (2*t*, CH_2–C(6), NCH_2CO_2Et); 46.56 (*d*, C(9′)); 44.70 (*t*, CH_2–N(1)); 14.06 (*q*, *Me*CH_2O). HR-MALDI-MS: 545.1646 (100, $[M+Na]^+$, $C_{26}H_{26}N_4NaO_8^+$; calc. 545.1643). Anal. calc. for $C_{26}H_{26}N_4O_8$ (522.51): C 59.77, H 5.02, N 10.72; found: C 59.49, H 5.03, N 10.65.

*Ethyl 2-(2-{[(9*H*-Fluoren-9-yl)methoxy]carbonyl}hydrazine)acetate* (**23**). A suspension of **22** (30.0 g, 194 mmol) in THF (1 l) was cooled to 0°, treated with 4-methylmorpholine (NMM; 21.3 ml, 194 mmol), then dropwise within 2.5 h with a soln. of Fmoc-OSu (59.5 g, 176 mmol) in THF (500 ml) at 0°, and stirred for 3 h. The precipitate was filtered off and washed with THF. After evaporation of the filtrate, the residue was poured on H_2O. Extraction with AcOEt (3×), washing of the combined org. layers with brine (3×), drying ($MgSO_4$), evaporation, and crystallisation from AcOEt/cyclohexane gave **23** (46.7 g, 78%). Colourless needles. R_f (CH_2Cl_2/MeOH 98 :2) 0.40. M.p. 112–113°. UV ($CHCl_3$): 268 (19231), 290 (5154), 301 (5923). IR (ATR): 3392*m*, 3229*w*, 3037*w*, 2981*w*, 2893*w*, 1733*s*, 1709*s*, 1552*w*, 1487*m*, 1463*m*, 1449*m*, 1398*w*, 1371*m*, 1350*w*, 1279*m*, 1210*s*, 1178*m*, 1127*m*, 1104*m*, 1079*m*, 1048*m*, 1031*m*, 995*w*, 954*w*, 938*w*, 892*w*, 861*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.78–7.29 (*m*, 8 arom. H); 6.66 (br. *s*, NHC=O); 4.45 (*d*, J = 6.9, CH_2–C(9)); 4.26–4.19 (*m*, MeCH_2O, NHCH_2, H–C(9)); 3.65 (br. *s*, NHCH_2); 1.30 (*t*, J = 7.1, *Me*CH_2O). ^{1}H-NMR (400 MHz, (D_6)DMSO): 8.75 (br. *s*, NHC=O); 7.90–7.30

(*m*, 8 arom. H); 4.88 (br. *s*, NH*C*H_2); 4.30 (*d*, *J* = 7.0, CH_2–C(9)); 4.22 (*t*, *J* = 6.9, H–C(9)); 4.11 (*q*, *J* = 7.1, MeCH_2O); 3.50 (br. *s*, NHCH_2); 1.20 (*t*, *J* = 7.1, *Me*CH_2O). ^{13}C-NMR (100 MHz, (D_6)DMSO; assignments based on a HSQC spectrum): 170.27 (*s*, *C*O_2Et); 156.64 (*s*, NHC=O); 143.67 (2*s*); 140.63 (2*s*); 127.56 (2*d*); 126.96 (2*d*); 125.18 (2*d*); 120.01 (2*d*); 65.61 (*t*, *C*H_2–C(9)); 59.97 (*t*, MeCH_2O); 52.00 (*t*, NHCH_2); 46.57 (*d*, C(9)); 13.99 (*q*, *Me*CH_2O). HR-ESI-MS: 363.1330 (100, $[M+Na]^+$, $C_{19}H_{20}N_2NaO_4^+$; calc. 363.1315). Anal. calc. for $C_{19}H_{20}N_2O_4$ (340.37): C 67.05, H 5.92, N 8.23; found: C 66.78, H 5.90, N 8.22.

N^4-*[(Benzyloxy)carbonyl]cytosine* (**25**). A suspension of NaH (60% in mineral oil, washed with 5 × 100 ml of pentane, 14.4 g, 360 mmol) in DMF (150 ml) was cooled to 0°, treated with cytosine (10 g, 90 mmol), stirred for 1 h, treated with ClCOOBn (13.5 ml, 95 mmol), allowed to reach r.t., stirred for 14 h, and treated carefully with H_2O and ice (200 ml). After neutralisation of the resulting soln. with 5M HCl, a precipitate was formed, which was filtered off, washed with H_2O (5 × 50 ml) and dried to give **25** (18.1 g, 82%). White powder. Spectroscopic data were in agreement with those in [30].

tert-*Butyl* N^4-*[(Benzyloxy)carbonyl]cytosine-1-acetate* (**26**) [30]. A suspension of **25** (18 g, 73 mmol), K_2CO_3 (10.1 g, 73 mmol), and Cs_2CO_3 (2.4 g, 7.4 mmol) in DMF (250 ml) was cooled to 0°, treated dropwise with $ClCH_2COO^tBu$ (10.5 ml, 73 mmol), allowed to reach r.t., stirred for 22 h, and filtered. The combined filtrates were evaporated, and the residue was dissolved in AcOEt (500 ml) and H_2O (100 ml). The layers were separated, and the aq. layer was extracted with AcOEt (2 × 100 ml). Drying of the combined org. layers ($MgSO_4$), filtration, evaporation, and crystallisation from toluene gave **26** (17.9 g, 68%). White crystals. M.p. 169–171° (*cf.* 168–169° [30]). Spectroscopic data were in agreement with those in [30].

tert-*Butyl* N^4-*[(Benzyloxy)carbonyl]-6-(hydroxymethyl)cytosine-1-acetate* (**27**). A soln. of $^iPr_2NH$ (32 ml, 244 mmol) in THF (200 ml) was cooled to −72°, treated dropwise with 1.6M BuLi in hexane (152 ml, 244 mmol), stirred for 30 min, warmed to 0°, stirred for 20 min, cooled to −72°, and treated dropwise with a soln. of **26** (17.5 g, 49 mmol) in THF (350 ml). After stirring for 2 h at −70°, the soln. was treated dropwise with DMF (75 ml, 969 mmol) and stirred for another 2 h at −70°. The soln. was allowed to reach r.t., treated with AcOH (33 ml), diluted with EtOH (300 ml), treated portionwise with $NaBH_4$ (5.5 g, 145 mmol), stirred for 3.5 h, treated with sat. NH_4Cl soln. (500 ml), and extracted with AcOEt (3 × 400 ml). The combined org. layers were washed with brine (3 × 250 ml), dried ($MgSO_4$), filtered, and evaporated. FC ($CHCl_3$/MeOH 98:2 → 95:5) gave **26** (4.75 g, 27%) and **27** (9.7 g, 51%).

Data of **27**. White powder. R_f (CH_2Cl_2/MeOH 95:5) 0.33. UV (MeOH): 242 (14200), 295 (7100). IR (ATR): 3253*w* (br.), 2978*w*, 1738*m*, 1645*m*, 1610*m*, 1567*m*, 1497*m*, 1455*m*, 1414*m*, 1384*s*, 1368*s*, 1193*s*, 1150*s*, 1105*m*, 1061*m*, 1035*m*, 971*w*, 912*w*, 860*w*, 836*w*, 818*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.76 (*s*, NH–C(4)); 7.41–7.33 (*m*, 5 arom. H); 7.23 (*s*, H–C(5)); 5.89 (*t*, *J* = 4.8, OH); 5.19 (*s*, PhCH_2); 4.53 (*s*, CH_2–N(1)); 4.35 (*d*, *J* = 5.1, CH_2–C(6)); 1.41 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 166.72 (*s*, *C*$O_2{}^t$Bu); 162.43 (*s*, C(4)); 161.84 (*s*, C(6)); 155.59 (*s*, C(2)); 152.89 (*s*, $NHCO_2$); 135.82 (*s*); 128.31 (2*d*); 127.98 (*d*); 127.80 (2*d*); 91.67 (*d*, C(5)); 81.72 (*s*, Me_3C); 66.42 (*t*, Ph*C*H_2); 59.18 (*t*, CH_2OH); 45.78 (*t*, CH_2–N(1)); 27.65 (*q*, *Me*$_3$C). HR-MALDI-MS: 428.1224 (10, $[M+K]^+$, $C_{19}H_{23}KN_3O_6^+$; calc. 428.1218), 412.1478 (18, $[M+Na]^+$, $C_{19}H_{23}N_3NaO_6^+$; calc. 412.1479), 390.1660 (100, $[M+H]^+$, $C_{19}H_{24}N_3O_6^+$; calc. 390.1660), 334.1035 (21, $[M-{}^t\text{Bu}+2\,H]^+$, $C_{15}H_{16}N_3O_6^+$; calc. 334.1034).

N^4-*[(Benzyloxy)carbonyl]-6-[(1-(2-ethoxy-2-oxoethyl)-2-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}hydrazino)methyl]cytosine-1-acetic Acid* (**29**). A soln. of **14** (4.5 g, 6.3 mmol) and Et_3SiH (10 ml, 63 mmol) in CH_2Cl_2 (60 ml) was cooled to 0°, treated dropwise with TFA (18.7 ml, 252 mmol), allowed to reach r.t., stirred for 17 h, and evaporated at r.t. The residue was suspended in Et_2O (50 ml). Filtration (washing with 4 × 50 ml of Et_2O) gave **29** (3.4 g, 82%). White powder. R_f (CH_2Cl_2/MeOH 9:1) 0.11. UV (MeOH): 255 (21800), 300 (13300). IR (ATR): 3448–2170*w* (br.), 3217*w*, 2929*w*, 1726*m*, 1677*m*, 1614*m*, 1568*m*, 1497*m*, 1450*m*, 1415*m*, 1388*m*, 1191*s*, 1082*m*, 1053*m*, 1027*m*, 969*w*, 930*w*, 910*w*, 826*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.68 (br. *s*, NH–C(4)); 8.94 (*s*, NH–N); 7.86–7.24 (*m*, 13 arom. H); 7.04 (*s*, H–C(5)); 5.07 (*s*, CH_2–N(1)); 4.96 (*s*, PhCH_2); 4.20 (br. *s*, CH_2–C(9)); 4.14–4.06 (*m*, MeCH_2O, H–C(9′)); 3.94 (*s*, CH_2–C(6)); 3.81 (*s*, NCH_2CO_2Et); 1.19 (*t*, *J* = 6.8, *Me*CH_2O). ^{13}C-NMR (100 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 169.95 (*s*, CO_2H); 169.01 (*s*, *C*O_2Et); 162.22 (*s*, C(4)); 155.90 (*s*, C(2)); 155.18 (*s*, N–*C*O_2); 155.09 (*s*, C(6)); 152.84 (*s*, C(4)N*C*O_2);

143.51 (2*s*); 140.57 (2*s*); 135.71 (*s*); 128.32 (2*d*); 128.02 (2*d*); 127.81 (2*d*); 127.51 (2*d*); 126.92 (*d*); 124.88 (2*d*); 119.93 (2*d*); 96.86 (*d*, C(5)); 66.29 (*t*, Ph*C*H$_2$); 65.63 (*t*, *C*H$_2$–C(9)); 60.34 (*t*, Me*C*H$_2$O); 57.67 (*t*, N*C*H$_2$CO$_2$Et); 56.59 (*t*, *C*H$_2$–C(6)); 46.40 (*d*, C(9′)); 46.12 (*t*, CH$_2$–N(1)); 13.89 (*q*, *Me*CH$_2$O). HR-MALDI-MS: 678.2185 (22, $[M+Na]^+$, $C_{34}H_{33}N_5NaO_9^+$; calc. 678.2170), 656.2346 (100, $[M+H]^+$, $C_{34}H_{34}N_5O_9^+$; calc. 656.2351).

N^6-*[(Benzyloxy)carbonyl]adenine* (**31**). NaH (60% dispersion in oil, 94.7 g, 2.37 mol) was washed with dry Et$_2$O (3×), dried and cooled to 0°. After the addition of DMF (1.5 l), adenine (80 g, 592 mmol) was added as a solid in several small portions. The suspension was stirred at 0° for 45 min, treated dropwise with ClCOOBn (88.7 ml, 622 mmol) over 1 h, warmed to r.t., and stirred for 16 h. The yellow soln. was poured on ice water (2 l), neutralized with conc. HCl (145 ml), and filtered. The white solid was washed with H$_2$O and Et$_2$O and dried (75°, oil pump vacuum) affording **31** (121 g, 76%). White powder. Spectroscopic data were in agreement with those in [30].

tert-*Butyl* N^6-*[(Benzyloxy)carbonyl]adenine-9-acetate* (**32**) [30]. A suspension of **31** (62.3 g, 231 mmol), K$_2$CO$_3$ (40.0 g, 231 mmol) and Cs$_2$CO$_3$ (7.54 g, 23.1 mmol) in DMF (500 ml) was treated dropwise with ClCH$_2$COO^{t}Bu (36.4 ml, 255 mmol) and stirred for 14 h at r.t. The yellow suspension was poured on H$_2$O and extracted with AcOEt (4×). The combined org. fractions were washed with brine (4×), dried (MgSO$_4$), and filtered. Evaporation of the filtrate and crystallisation from AcOEt/cyclohexane gave **32** (59.0 g, 78%). Colourless crystals. Spectroscopic data were in agreement with those in [30].

tert-*Butyl* N^4-*[(Benzyloxy)carbonyl]-8-(hydroxymethyl)adenine-9-acetate* (**33**). A soln. of ^{i}Pr$_2$NH (119 ml, 908 mmol) in THF (750 ml) was cooled to −76°, treated dropwise with 1.6M BuLi in hexane (567 ml, 908 mmol), warmed to 0°, stirred for 1 h and stored at 4° for 13 h. The soln. was cooled to −76° and treated dropwise with a soln. of **32** (58.0 g, 151 mmol) in THF (500 ml) over 1 h. After stirring for 2 h at −76°, the soln. was treated dropwise with DMF (567 ml, 3.03 mol) over 30 min and stirred for another 2 h at −76°. The soln. was treated with AcOH (113 ml, 1.97 mol), allowed to reach r.t., diluted with EtOH (1.5 l), treated with NaBH$_4$ (22.9 g, 605 mmol) in several small portions, and stirred for 1.5 h. The suspension was filtered, and the filtrate was evaporated. A suspension of the residue in H$_2$O was extracted with AcOEt (4×). The combined org. fractions were washed with brine (5×), dried (MgSO$_4$), filtered, and evaporated. FC (AcOEt/cyclohexane 3:1) gave **33** (49 g, 78%). Yellow foam. R_f (CH$_2$Cl$_2$/MeOH 19:1) 0.20. UV (MeOH): 269 (21000), 212 (34080). IR (ATR): 3195*w*, 2979*w*, 2937*w*, 1740*s*, 1614*m*, 1590*m*, 1538*w*, 1498*w*, 1453*m*, 1391*w*, 1367*m*, 1322*w*, 1303*w*, 1281*w*, 1208*s*, 1159*s*, 1104*m*, 1039*m*, 971*w*, 859*w*, 844*w*, 799*w*, 764*w*, 743*m*, 696*m*, 667*m*. ^{1}H-NMR (300 MHz, CDCl$_3$; assignments based on a HSQC and a HMBC spectrum): 9.66 (*s*, NH); 8.60 (*s*, H–C(2)); 7.29–7.24 (*m*, 5 arom. H); 5.24 (br. *s*, OH); 5.13 (*s*, PhC*H*$_2$); 4.91 (*s*, CH$_2$–N(9)); 4.74 (*s*, CH$_2$–C(8)); 1.40 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, CDCl$_3$; assignments based on a HSQC and a HMBC spectrum): 166.02 (*s*, *C*O$_2$^{t}Bu); 153.90 (*s*, C(8)); 152.47 (*s*, C(4)); 152.30 (*d*, C(2)); 151.32 (*s*, NH*C*O$_2$Bn); 148.59 (*s*, C(6)); 135.25 (*s*); 128.38 (2*d*), 128.27 (3*d*); 120.11 (*s*, C(5)); 83.57 (*s*, Me$_3$*C*); 67.56 (*t*, Ph*C*H$_2$); 57.74 (*t*, CH$_2$–C(8)); 44.31 (*t*, CH$_2$–N(9)); 27.98 (*q*, *Me*$_3$C). HR-MALDI-MS: 452.1329 (4, $[M+K]^+$, $C_{20}H_{23}KN_5O_5^+$; calc. 452.1336), 436.1589 (16, $[M+Na]^+$, $C_{20}H_{23}N_5NaO_5^+$; calc. 436.1597), 414.1766 (100, $[M+H]^+$, $C_{20}H_{24}N_5O_5^+$; calc. 414.1777), 396.0702 (2, $[M-{}^t\text{Bu}+H+K]^+$, $C_{16}H_{15}KN_5O_5^+$; calc. 396.0710), 380.0963 (5, $[M-{}^t\text{Bu}+H+Na]^+$, $C_{16}H_{15}N_5NaO_5^+$; calc. 380.0971), 358.1143 (79, $[M-{}^t\text{Bu}+2H]^+$, $C_{16}H_{16}N_5O_5^+$; calc. 358.1151). Anal. calc. for $C_{20}H_{23}N_5O_5$ (413.43): C 58.10, H 5.61, N 16.94; found: C 58.09, H 5.52, N 16.73.

tert-*Butyl* N^6-*[(Benzyloxy)carbonyl]-8-(bromomethyl)adenine-9-acetate* (**34**). A soln. of **33** (13.5 g, 32.7 mmol) in CH$_2$Cl$_2$ (100 ml) was cooled to 0°, treated dropwise with a soln. of Ms$_2$O (8.54 g, 49 mmol) in CH$_2$Cl$_2$ (40 ml), stirred for 1.5 h, treated with a soln. of LiBr (14.2 g, 163 mmol) in DMF (70 ml), and stirred for another h. The suspension was allowed to reach r.t., stirred for 2 h, and diluted with sat. NH$_4$Cl soln. The aq. layer was extracted with AcOEt (3×). The combined org. fractions were washed with brine (3×), dried (MgSO$_4$), and evaporated. FC (AcOEt/cyclohexane 2:1) gave **34** (13.3 g, 85%). White powder. R_f (CH$_2$Cl$_2$/MeOH 19:1) 0.33. M.p. 135.6–136.5°. UV (MeOH): 278 (23540), 212 (28940). IR (ATR): 3180*w*, 3117*w*, 2978*w*, 2935*w*, 1772*m*, 1732*s*, 1599*m*, 1581*m*, 1542*m*, 1463*w*, 1455*w*, 1391*w*, 1367*m*, 1335*w*, 1299*w*, 1258*m*, 1240*m*, 1198*s*, 1152*s*, 1102*m*, 1046*m*, 1028*m*, 973*w*, 940*w*, 905*w*, 892*w*, 860*w*, 840*w*, 799*m*, 743*m*, 696*m*, 661*w*, 613*w*. ^{1}H-NMR (300 MHz, CDCl$_3$; assignments based on a HSQC and a HMBC spectrum): 9.28 (br. *s*, NH); 8.70 (*s*, H–C(2)); 7.33–7.31 (*m*, 5 arom. H); 5.23 (*s*, PhC*H*$_2$); 4.97 (*s*,

CH_2–N(9)); 4.56 (*s*, CH_2–C(8)); 1.43 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, $CDCl_3$; assignments based on a HSQC and a HMBC spectrum): 165.32 (*s*, $CO_2{}^t$Bu); 153.05 (*d*, C(2)); 152.78 (*s*, C(4)); 151.00 (*s*, NH*C*O_2Bn); 149.34 (*s*, C(8)); 149.20 (*s*, C(6)); 135.20 (*s*); 128.42 (3*d*); 128.30 (2*d*); 120.98 (*s*, C(5)); 83.89 (*s*, Me_3C); 67.75 (*t*, Ph*C*H_2); 44.63 (*t*, CH_2–N(9)); 28.01 (*q*, *Me*$_3$C); 21.68 (*t*, CH_2–C(8)). HR-MALDI-MS: 498.0769 (6, $[M+Na]^+$, $C_{20}H_{22}{}^{79}BrN_5NaO_4^+$; calc. 498.0753), 500.0753 (6, $[M+Na]^+$, $C_{20}H_{22}{}^{81}BrN_5NaO_4^+$; calc. 500.0732), 476.0931 (86, $[M+H]^+$, $C_{20}H_{23}{}^{79}BrN_5O_4^+$; calc. 476.0933), 478.0915 (100, $[M+H]^+$, $C_{20}H_{23}{}^{81}BrN_5O_4^+$; calc. 478.0913), 420.0302 (35, $[M-{}^t\text{Bu}+2\,H]^+$, $C_{16}H_{15}{}^{79}BrN_5O_4^+$; calc. 420.0307), 422.0287 (33, $[M-{}^t\text{Bu}+2\,H]^+$, $C_{16}H_{15}{}^{81}BrN_5O_4^+$; calc. 422.0287), 398.1823 (23, $[M-Br+H]^+$, $C_{20}H_{24}N_5O_4^+$; calc. 398.1828), 342.1210 (6, $[M-Br-{}^t\text{Bu}+2\,H]^+$, $C_{16}H_{16}N_5O_4^+$; calc. 342.1202). Anal. calc. for $C_{20}H_{22}BrN_5O_4$ (476.32): C 50.43, H 4.66, N 14.70; found: C 50.52, H 4.75, N 14.53.

tert-*Butyl* N^6-*[(Benzyloxy)carbonyl]-8-{[1-(2-ethoxy-2-oxoethyl)hydrazino]methyl}adenine-9-acetate* (**35**). A soln. of **15** (50.0 mg, 68.0 μmol) in DMF (450 μl) was cooled to 0°, treated with piperidine (67.2 μl, 680 μmol), and stirred for 1 h at 0°. Evaporation and FC (CH_2Cl_2/MeOH 98 : 2) gave **35** (30.4 mg, 87%). Yellow foam. R_f (CH_2Cl_2/MeOH 9 : 1) 0.47. UV (MeOH): 270 (23760), 211 (37080). IR (ATR): 3317*w*, 3182*w*, 2979*w*, 1737*m*, 1614*m*, 1540*w*, 1500*w*, 1453*m*, 1368*m*, 1302*m*, 1200*s*, 1153*s*, 1101*m*, 1031*m*, 971*m*, 850*m*, 742*w*, 698*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO; assignments based on a HMBC spectrum): 10.61 (br. *s*, NH–C(6)); 8.59 (*s*, H–C(2)); 7.50–7.30 (*m*, 5 arom. H); 5.22 (*s*, PhCH_2); 5.17 (*s*, CH_2–N(9)); 4.20 (*s*, CH_2–C(8)); 4.13 (*q*, *J* = 7.1, MeCH_2O); 3.73 (br. *s*, NH_2); 3.57 (*s*, NCH_2CO_2Et); 1.42 (*s*, ^{t}Bu); 1.22 (*t*, *J* = 7.1, *Me*CH_2O). ^{13}C-NMR (100 MHz, (D_6)DMSO): 169.98 (*s*, *C*O_2Et); 166.74 (*s*, *C*$O_2{}^t$Bu); 153.53 (*s*, C(4)); 152.09 (*s*, NH*C*O_2Bn); 151.91 (*s*, C(8)); 151.36 (*d*, C(2)); 148.63 (*s*, C(6)); 136.30 (*s*); 128.31 (2*d*); 127.87 (*d*); 127.73 (2*d*); 122.23 (*s*, C(5)); 82.00 (*s*, Me_3C); 66.16 (*t*, Ph*C*H_2); 59.96, 59.90 (2*t*, Me*C*H_2O, NCH_2CO_2Et); 56.50 (*t*, *C*H_2–C(8)); 44.47 (*t*, CH_2–N(9)); 27.59 (*q*, *Me*$_3$C); 14.04 (*q*, *Me*CH_2O). HR-MALDI-MS: 552.1988 (3, $[M+K]^+$, $C_{24}H_{31}KN_7O_6^+$; calc. 552.1973), 536.2244 (23, $[M+Na]^+$, $C_{24}H_{31}N_7NaO_6^+$; calc. 536.2234), 514.2418 (100, $[M+H]^+$, $C_{24}H_{32}N_7O_6^+$; calc. 514.2414), 480.1614 (6, $[M-{}^t\text{Bu}+H+Na]^+$, $C_{20}H_{23}N_7NaO_6^+$; calc. 480.1608), 458.1779 (52, $[M-{}^t\text{Bu}+2\,H]^+$, $C_{20}H_{24}N_7O_6^+$; calc. 458.1788).

N^6-*[(Benzyloxy)carbonyl]-8-[(1-(2-ethoxy-2-oxoethyl)-2-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}hydrazino)methyl]adenine-9-acetic Acid* (**36**). A soln. of **15** (10.0 g, 13.6 mmol) in CH_2Cl_2 (140 ml) was treated with Et_3SiH (21.7 ml, 136 mmol) and TFA (41.9 ml, 544 mmol) and stirred for 20 h at r.t. After evaporation at 30°, the residue was treated with $^i Pr_2O$ (250 ml). The precipitate was filtered off, ground, and washed several times with $^i Pr_2O$. Drying of the solid gave **36** (9.05 g, 98%). White powder. R_f (CH_2Cl_2/MeOH 3 : 2) 0.54. M.p. 117.1–118.3°. UV (MeOH): 230 (4740), 266 (31100), 211 (50020). IR (ATR): 3123*w*, 3065*w*, 3036*w*, 2975*w*, 2902*w*, 1733*s*, 1716*s*, 1647*m*, 1619*m*, 1585*m*, 1551*w*, 1479*w*, 1398*w*, 1377*m*, 1288*m*, 1255*m*, 1200*s*, 1162*s*, 1082*m*, 1043*m*, 1030*m*, 981*w*, 962*w*, 797*w*, 785*w*, 758*m*, 742*s*, 719*m*, 698*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 10.80 (br. *s*, NH–C(6)); 8.85 (br. *s*, NNH); 8.61 (*s*, H–C(2)); 7.85–7.18 (*m*, 13 arom. H); 5.48 (br. *s*, CH_2–N(9)); 5.21 (*s*, PhCH_2); 4.35 (br. *s*, CH_2–C(8)); 4.21 (*d*, *J* = 6.9, CH_2–C(9′)); 4.13–4.06 (*m*, MeCH_2O, H–C(9′)); 3.77 (br. *s*, NCH_2CO_2Et); 1.18 (*t*, *J* = 7.2, *Me*CH_2O). ^{13}C-NMR (75 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 169.09 (*s*, CO_2H); 168.81 (*s*, *C*O_2Et); 155.03 (br. *s*, $NNHCO_2$); 154.81 (*s*, C(4)); 153.16 (*s*, NH*C*O_2Bn); 151.87 (*s*, C(8)); 150.69 (*d*, C(2)); 148.25 (*s*, C(6)); 143.30 (2*s*); 140.43 (2*s*); 136.01 (*s*); 128.16–124.81 (11*d*); 121.43 (*s*, C(5)); 119.84 (2*d*); 66.31 (*t*, Ph*C*H_2); 65.42 (*t*, *C*H_2–C(9′)); 60.32 (*t*, Me*C*H_2O); 57.46, 53.50 (2*t*, *C*H_2–C(8), N*C*H_2CO_2Et); 46.47 (*d*, C(9′)); 44.01 (*t*, *C*H_2–N(9)); 14.00 (*q*, *Me*CH_2O). HR-MALDI-MS: 702.2240 (37, $[M+Na]^+$, $C_{35}H_{33}N_7NaO_8^+$; calc. 702.2288), 680.2452 (100, $[M+H]^+$, $C_{35}H_{34}N_7O_8^+$; calc. 680.2469), 572.1867 (19, $[M-BnOH+H]^+$, $C_{28}H_{26}N_7O_7^+$; calc. 572.1894).

2-{[2-Amino-6-(benzyloxy)-5-nitrosopyrimidin-4-yl]amino}-2-oxoethyl Acetate (**38**). A suspension of **37** (21.2 g, 86.6 mmol) in THF (430 ml) was cooled to 0°, treated with $AcOCH_2COCl$ (11.2 ml, 104 mmol) over 30 min, stirred for 3 h, and evaporated. The residue was treated with H_2O. The solid was filtered off, washed with H_2O and Et_2O, and dried to give **38** (25.1 g, 84%). Blue powder. R_f (CH_2Cl_2/MeOH 19 : 1) 0.35. M.p. 177.4–178.5°. UV ($CHCl_3$): 349 (26420), 255 (19120). IR (ATR): 3437*m*, 3291*w*, 3198*w*, 3143*w*, 2960*w*, 1746*m*, 1718*m*, 1640*m*, 1584*s*, 1546*s*, 1520*m*, 1500*m*, 1469*s*, 1448*s*, 1387*s*, 1336*s*, 1293*s*, 1276*m*, 1243*m*, 1207*s*, 1155*s*, 1083*m*, 1065*s*, 1048*s*, 942*m*, 912*m*, 857*m*, 846*m*, 827*m*, 792*w*, 763*m*,

748*w*, 728*s*, 695*s*. ^{1}H-NMR (300 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 12.33 (*s*, NH); 8.82–8.80 (*m*, NH_2); 7.60–7.37 (*m*, 5 arom. H); 5.65 (*s*, PhCH_2); 5.09 (*s*, AcOCH_2); 2.18 (*s*, AcO). ^{13}C-NMR (125 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 169.88, 169.82 (2*s*, Me*C*=O, NHC=O); 163.30 (*s*, C(6)); 138.70 (*s*, C(4)); 135.60 (*s*); 128.51 (2*d*); 128.49 (2*d*); 128.33 (*d*); 68.64 (*t*, Ph*C*H_2); 65.08 (*t*, AcO*C*H_2); 20.34 (*q*, *Me*C=O). HR-MALDI-MS: 384.0697 (12, $[M+K]^+$, $C_{15}H_{15}KN_5O_5^+$; calc. 384.0710), 368.0959 (100, $[M+Na]^+$, $C_{15}H_{15}N_5NaO_5^+$; calc. 368.0971). Anal. calc. for $C_{15}H_{15}N_5O_5$ (345.31): C 52.17, H 4.38, N 20.28; found: C 52.08, H 4.35, N 20.09.

*8-(Acetoxymethyl)-6-*O*-benzylguanine* (**39**). A suspension of **38** (30.2 g, 87.5 mmol) and Ph_3P (55.0 g, 210 mmol) in *o*-xylene (580 ml) was heated to reflux for 4 h, while the colour changed from blue to yellow. After cooling the soln. to 4°, the resulting suspension was kept at 4° for 36 h and filtered. The solid was ground and washed with toluene. Crystallisation from MeOH gave **39** (27.1 g, 99%). Colourless needles. R_f (CH_2Cl_2/MeOH 19:1) 0.15. M.p. 193.1–194.2°. UV (MeOH): 286 (10280), 246 (7700), 209 (31780). IR (ATR): 3485*w*, 3387*m*, 3277*w*, 3089*w*, 3009*w*, 3000*w*, 2932*w*, 2809*w*, 2690*w*, 1739*s*, 1640*m*, 1624*m*, 1592*s*, 1537*w*, 1486*m*, 1450*m*, 1417*s*, 1373*m*, 1352*s*, 1336*m*, 1264*s*, 1224*s*, 1203*m*, 1167*m*, 1100*m*, 1036*s*, 1022*m*, 995*s*, 973*m*, 836*m*, 789*m*, 762*w*, 731*s*, 693*m*, 670*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 12.60 (*s*, NH); 7.51–7.31 (*m*, 5 arom. H); 6.37 (*s*, NH_2); 5.47 (*s*, PhCH_2); 5.08 (*s*, CH_2–C(8)); 2.08 (*s*, AcO). ^{13}C-NMR (100 MHz, (D_6)DMSO): 169.67 (*s*, Me*C*=O); 159.52 (*s*, C(6), C(2)); 155.77 (*s*, C(4)); 144.49 (*s*, C(8)); 136.48 (*s*); 128.21 (2*d*); 127.83 (3*d*); 113.33 (*s*, C((5)); 66.68 (*t*, Ph*C*H_2); 59.22 (*t*, *C*H_2–C(8)); 20.59 (*q*, *Me*C=O). HR-MALDI-MS: 352.0809 (12, $[M+K]^+$, $C_{15}H_{15}KN_5O_3^+$; calc. 352.0812), 336.1062 (32, $[M+Na]^+$, $C_{15}H_{15}N_5NaO_3^+$; calc. 336.1073), 314.1244 (100, $[M+H]^+$, $C_{15}H_{16}N_5O_3^+$; calc. 314.1253), 254.1029 (38, $[M-AcO]^+$, $C_{13}H_{12}N_5O^+$; calc. 254.1036). Anal. calc. for $C_{15}H_{15}N_5O_3$ (313.31): C 57.50, H 4.83, N 22.35; found: C 57.23, H 4.88, N 22.20.

Alkylation of **39**. A suspension of **39** (27.2 g, 86.9 mmol) and K_2CO_3 (36.0 g, 261 mmol) in DMF (175 ml) was treated dropwise with $ClCH_2COO^tBu$ (18.6 ml, 130 mmol) over 5 min. The suspension was stirred for 8 h, diluted with AcOEt (300 ml), and filtered. The filtrate was diluted with sat. NH_4Cl soln. and H_2O, and extracted with AcOEt (4×). The combined org. fractions were washed with brine (5×), dried ($MgSO_4$), and filtered. Evaporation and FC (CH_2Cl_2/MeOH 98:2 → 9:1) gave **40** (25.8 g, 69%) along with **41**.

tert-*Butyl 8-(Acetoxymethyl)-6-*O*-benzylguanine-9-acetate* (**40**). White powder. R_f (CH_2Cl_2/MeOH 19:1) 0.35. M.p. 148.0–148.5°. UV (MeOH): 261 (29760), 209 (48400). IR (ATR): 3486*m*, 3292*w*, 3178*w*, 3119*w*, 3011*w*, 2981*w*, 2937*w*, 1740*s*, 1627*m*, 1615*s*, 1583*s*, 1530*m*, 1494*m*, 1467*m*, 1454*m*, 1438*m*, 1413*m*, 1384*m*, 1368*m*, 1350*s*, 1317*m*, 1260*s*, 1235*s*, 1222*s*, 1212*s*, 1162*s*, 1154*s*, 1112*m*, 1069*m*, 1021*s*, 1005*w*, 967*m*, 947*m*, 916*m*, 861*m*, 854*m*, 842*w*, 790*m*, 771*w*, 752*s*, 708*m*, 700*m*, 676*w*. ^{1}H-NMR (400 MHz, $CDCl_3$; assignments based on a HSQC and a HMBC spectrum): 7.81–7.27 (*m*, 5 arom. H); 5.55 (*s*, PhCH_2); 5.22 (*s*, CH_2–C(8)); 4.89 (*s*, NH_2); 4.80 (CH_2–N(9)); 2.09 (*s*, AcO); 1.46 (*s*, ^{t}Bu). ^{13}C-NMR (100 MHz, $CDCl_3$; assignments based on a HSQC and a HMBC spectrum): 170.24 (*s*, Me*C*=O); 166.38 (*s*, *C*$O_2{}^t$Bu); 161.04 (*s*, C(6)); 159.47 (*s*, C(2)); 155.34 (*s*, C(4)); 145.12 (*s*, C(8)); 136.35 (*s*); 128.46 (2*d*); 128.38 (2*d*); 128.03 (*d*); 114.60 (*s*, C(5)); 83.23 (*s*, Me_3C); 68.19 (*t*, Ph*C*H_2); 58.66 (*t*, *C*H_2–C(8)); 44.29 (*t*, CH_2–N(9)); 28.00 (*q*, *Me*$_3$C); 20.65 (*q*, *Me*C=O). HR-MALDI-MS: 466.1492 (2, $[M+K]^+$, $C_{21}H_{25}KN_5O_5^+$; calc. 466.1493), 450.1754 (12, $[M+Na]^+$, $C_{21}H_{25}N_5NaO_5^+$; calc. 450.1753), 428.1931 (100, $[M+H]^+$, $C_{21}H_{26}N_5O_5^+$; calc. 428.1934), 394.1119 (5, $[M-{}^t\text{Bu}+H+Na]^+$, $C_{17}H_{17}N_5NaO_5^+$; calc. 394.1127), 372.1293 (93, $[M-{}^t\text{Bu}+2H]^+$, $C_{17}H_{18}N_5O_5^+$; calc. 372.1308), 312.1083 (52, $[M-{}^t\text{Bu}-AcO+H]^+$, $C_{15}H_{14}N_5O_3^+$; calc. 312.1091). Anal. calc. for $C_{21}H_{25}N_5O_5$ (427.45): C, 59.01, H 5.90, N 16.38; found: C 58.81, H 5.93, N 16.09.

tert-*Butyl 8-(Acetoxymethyl)-6-*O*-benzylguanine-7-acetate* (**41**). Yellow powder. R_f (CH_2Cl_2/MeOH 19:1) 0.05. M.p. 149.4–152.6°. UV (MeOH): 301 (8640), 213 (38220). IR (ATR): 3482*w*, 3296*w*, 3172*w*, 2979*w*, 1740*s*, 1632*s*, 1572*s*, 1511*w*, 1482*m*, 1454*m*, 1432*m*, 1390*m*, 1369*m*, 1326*s*, 1305*w*, 1226*s*, 1175*s*, 1150*s*, 1084*w*, 1065*m*, 1032*m*, 970*w*, 955*w*, 919*w*, 895*w*, 849*m*, 790*m*, 743*m*, 698*m*, 680*w*, 655*w*, 629*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 7.52–7.32 (*m*, 5 arom. H); 6.27 (*s*, NH_2); 5.43 (*s*, PhCH_2); 5.23 (*s*, CH_2–C(8)); 5.00 (CH_2–N(9)); 2.01 (*s*, AcO); 1.24 (*s*, ^{t}Bu). ^{13}C-NMR (100 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 169.53 (*s*, Me*C*=O); 166.70 (*s*, *C*$O_2{}^t$Bu); 162.08 (*s*, C(2)); 159.74 (*s*, C(4)); 156.37 (*s*, C(6)); 150.56 (*s*, C(8));

136.20 (*s*); 128.34 (2*d*); 127.96 (*d*); 127.83 (2*d*); 107.40 (*s*, C(5)); 81.80 (*s*, Me_3C); 67.17 (*t*, Ph*C*H_2); 57.31 (*t*, *C*H_2–C(8)); 47.38 (*t*, CH_2–N(7)); 27.35 (*q*, *Me*$_3$C); 20.34 (*q*, *Me*C=O). HR-MALDI-MS: 466.1494 (12, $[M+K]^+$, $C_{21}H_{25}KN_5O_5^+$; calc. 466.1493), 450.1752 (11, $[M+Na]^+$, $C_{21}H_{25}N_5NaO_5^+$; calc. 450.1753), 428.1933 (100, $[M+H]^+$, $C_{21}H_{26}N_5O_5^+$; calc. 428.1934), 394.1127 (2, $[M-{}^t\text{Bu}+H+Na]^+$, $C_{17}H_{17}N_5NaO_5^+$; calc. 394.1127), 372.1305 (31, $[M-{}^t\text{Bu}+2H]^+$, $C_{17}H_{18}N_5O_5^+$; calc. 372.1308).

tert-*Butyl 6*-O-*Benzyl-8-(hydroxymethyl)guanine-9-acetate* (**42**). A suspension of **40** (14.1 g, 33 mmol) and K_2CO_3 (4.79 g, 34.7 mmol) in MeOH/H_2O 3:1 (330 ml) was stirred for 5 h at r.t. After evaporation of MeOH and dilution with sat. NH_4Cl soln., the solid was filtered off, washed with H_2O, and dried to give **42** (12.0 g, 94%). White powder. R_f (CH_2Cl_2/MeOH 19:1) 0.26. M.p. 216.2° (dec.). UV (MeOH): 285 (13380), 252 (10780), 211 (32360). IR (ATR): 3482*w*, 3287*w*, 3160*w*, 3110*w*, 3060*w*, 2981*w*, 2931*w*, 1746*s*, 1624*s*, 1587*s*, 1490*m*, 1471*m*, 1445*s*, 1406*m*, 1390*m*, 1363*m*, 1346*m*, 1315*m*, 1253*s*, 1223*s*, 1152*s*, 1115*m*, 1070*s*, 1030*m*, 982*m*, 937*m*, 915*w*, 874*m*, 841*m*, 785*m*, 757*m*, 749*m*, 739*w*, 705*s*, 666*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 7.51–7.34 (*m*, 5 arom. H); 6.52 (*s*, NH_2); 5.60 (*t*, *J* = 5.3, OH); 5.50 (*s*, PhCH_2); 4.82 (*s*, CH_2–N(9)); 4.54 (*d*, *J* = 4.7, CH_2–C(8)); 1.41 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, (D_6)DMSO): 166.61 (*s*, *C*$O_2{}^t$Bu); 159.52, 159.45 (2*s*, C(2), C(6)); 155.67 (*s*, C(4)); 149.35 (*s*, C(8)); 136.52 (*s*); 128.21 (2*d*); 128.10 (2*d*); 127.81 (*d*); 111.85 (*s*, C((5)); 81.78 (*s*, Me_3C); 66.77 (*t*, Ph*C*H_2); 56.92 (*t*, *C*H_2–C(8)); 43.83 (*t*, CH_2–N(9)); 27.64 (*q*, *Me*$_3$C). HR-MALDI-MS: 424.1386 (3, $[M+K]^+$, $C_{19}H_{23}KN_5O_4^+$; calc. 424.1387), 408.1654 (5, $[M+Na]^+$, $C_{19}H_{23}N_5NaO_4^+$; calc. 408.1648), 386.1827 (100, $[M+H]^+$, $C_{19}H_{24}N_5O_4^+$; calc. 386.1828), 352.1022 (1, $[M-{}^t\text{Bu}+H+Na]^+$, $C_{15}H_{15}N_5NaO_4^+$; calc. 352.1022), 330.1192 (54, $[M-{}^t\text{Bu}+2H]^+$, $C_{15}H_{16}N_5O_4^+$; calc. 330.1202). Anal. calc. for $C_{19}H_{23}N_5O_4$ (385.42): C, 59.21, H 6.01, N 18.17; found: C 59.28, H 6.07, N 18.18.

tert-*Butyl 6*-O-*Benzyl-8-(chloromethyl)guanine-9-acetate* (**43**). A soln. of **42** (16 g, 41.5 mmol) in DMF (400 ml) was cooled to 0°, treated with EtN^iPr_2 (10.9 ml, 62.3 mmol), followed by MsCl (4.82 ml, 62.3 mmol) within 10 min, stirred for 1 h at 0°, treated with LiCl (8.80 g, 208 mmol), stirred for 30 min, and poured on H_2O. The suspension was extracted with $CHCl_3$/MeOH 95:5 (1×), and the aq. suspension was filtered. The filtrate was extracted with $CHCl_3$/MeOH 95:5 (4×). The combined org. fractions were washed with brine (3×), dried ($MgSO_4$), and evaporated. The residue was combined with the solid obtained by the filtration of the aq. suspension, washed with H_2O, and dried. FC (CH_2Cl_2/MeOH 99.75:0.25 → 99.5:0.5) gave **43** (7.90 g, 47%). White powder. R_f (CH_2Cl_2/MeOH 19:1) 0.41. M.p. 210° (dec.). UV (MeOH): 291 (15600), 255 (10020), 211 (32640). IR (ATR): 3479*w*, 3279*w*, 3161*w*, 3109*w*, 3058*w*, 3033*w*, 2975*w*, 2938*w*, 1753*s*, 1621*s*, 1586*s*, 1518*m*, 1493*m*, 1471*m*, 1452*m*, 1439*m*, 1407*w*, 1379*m*, 1367*m*, 1357*m*, 1344*m*, 1318*m*, 1258*s*, 1225*s*, 1151*s*, 1108*m*, 1066*m*, 1030*w*, 987*w*, 965*w*, 937*m*, 913*w*, 866*m*, 858*m*, 839*m*, 788*m*, 771*m*, 758*m*, 747*m*, 732*m*, 718*m*, 699*s*, 684*m*, 629*m*. ^{1}H-NMR (300 MHz, $CHCl_3$/CD_3OD): 7.45–7.25 (*m*, 5 arom. H); 5.48 (*s*, PhCH_2); 5.17 (*s*, NH_2); 4.80 (*s*, CH_2–N(9)); 4.67 (*s*, CH_2–C(8)); 1.43 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, $CDCl_3$/CD_3OD): 166.04 (*s*, $CO_2{}^t$Bu); 160.87 (*s*, C(6)); 159.54 (*s*, C(2)); 155.06 (*s*, C(4)); 145.27 (*s*, C(8)); 135.94 (*s*); 128.30 (2*d*); 128.19 (2*d*); 128.00 (*d*); 113.85 (*s*, C(5)); 83.58 (*s*, Me_3C); 68.31 (*t*, Ph*C*H_2); 44.35 (*t*, CH_2–N(9)); 37.25 (*t*, *C*H_2–C(8)); 27.97 (*q*, *Me*$_3$C). HR-MALDI-MS: 426.1332 (3, $[M+Na]^+$, $C_{19}H_{22}ClN_5NaO_3^+$; calc. 426.1309), 404.1491 (100, $[M+H]^+$, $C_{19}H_{23}ClN_5O_3^+$; calc. 404.1489), 370.1884 (21, $[M-{}^t\text{Bu}+H+Na]^+$, $C_{15}H_{14}ClN_5NaO_3^+$; calc. 370.0683), 348.0860 (76, $[M-{}^t\text{Bu}+2H]^+$, $C_{15}H_{15}ClN_5O_3^+$; calc. 348.0863). Anal. calc. for $C_{19}H_{22}ClN_5O_3$ (403.86): C, 56.51, H 5.49, N 17.34; found: C 56.75, H 5.62, N 17.26.

*8-[(1-(2-Ethoxy-2-oxoethyl)-2-{[(9*H*-fluoren-9-yl)methoxy]carbonyl}hydrazino)methyl]guanine-9-acetic Acid* (**44**). A soln. of **43** (7.50 g, 18.5 mmol), **23** (12.6 g, 37.0 mmol), and Bu_4NBr (17.9 g, 55.4 mmol) in DMSO (92 ml) was treated with lutidine (6.46 ml, 55.4 mmol), stirred for 72 h at r.t., and poured on H_2O. After extraction with AcOEt (5×), the combined org. fractions were washed with brine (5×), dried ($MgSO_4$), filtered, and evaporated. FC (AcOEt) gave a crude product (*tert*-butyl acetate) contaminated with **23**, that was used for the next reaction. A soln. of the crude *tert*-butyl acetate in CH_2Cl_2 (180 ml) was treated with Et_3SiH (14.8 ml, 92.4 mmol) and TFA (137 ml, 1.85 mmol), and stirred for 16 h at r.t. After evaporation at 30°, the residue was treated with Et_2O (200 ml). The precipitate was filtered off, ground, and washed several times with Et_2O. Drying of the solid gave **44** (9.45 g, 91% from **43**). White solid. R_f (CH_2Cl_2/MeOH 3:2) 0.54. M.p. 186.3–192.5°. UV (MeOH): 299 (6120), 262 (35920), 210 (51200). IR (ATR): 3318*w*, 3215*w*, 3165*w*, 3066*w*, 2983*w*, 2942*w*, 1724*m*, 1688*s*, 1641*s*, 1582*s*, 1511*w*, 1494*w*, 1478*w*, 1450*m*, 1394*w*, 1373*m*, 1357*m*, 1288*w*, 1203*s*, 1159*m*, 1054*w*, 1025*m*, 976*w*, 961*w*,

894*w*, 854*w*, 782*w*, 759*m*, 739*s*, 695*w*, 659*w*, 620*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 13.10 (br. *s*, CO_2H); 10.60 (br. *s*, H–N(1)); 8.76 (*s*, NNH); 7.88–7.18 (*m*, 8 arom. H); 6.53 (br. *s*, NH_2); 5.14 (br. *s*, CH_2–N(9)); 5.23–3.99 (*m*, *C*H_2–C(8), MeCH_2O, *C*H_2–C(9′), H–C(9′)); 3.64 (br. *s*, NCH_2CO_2Et); 1.17 (*t*, *J* = 7.2, *Me*CH_2O). ^{13}C-NMR (75 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 169.47, 168.85 (2*s*, CO_2H, *C*O_2Et); 156.16 (*s*, C(6)); 154.82 (*s*, $NNHCO_2$); 153.57, 152.46 (2*s*, C(2), C(4)); 143.42 (2*s*); 142.94 (*s*, C(8)); 140.47 (2*s*); 127.43–119.91 (8*d*); 114.59 (*s*, C(5)); 65.42 (*t*, *C*H_2–C(9′)); 60.23 (*t*, Me*C*H_2O); 57.13 (*t*, N*C*H_2CO_2Et); 53.60 (*t*, *C*H_2–C(8)); 46.54 (*d*, C(9′)); 43.52 (*t*, CH_2–N(9)); 14.03 (*q*, *Me*CH_2O). HR-MALDI-MS: 584.1869 (44, $[M+Na]^+$, $C_{27}H_{27}N_7NaO_7^+$; calc. 584.1870), 562.2050 (100, $[M+H]^+$, $C_{27}H_{28}N_7O_7^+$; calc. 562.2050).

tert-*Butyl 6-[2-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)ethyl]uracil-1-acetate* (**45**). A soln. of **51** (2.2 g, 7.48 mmol) in THF (60 ml) was cooled to $-2°$, treated dropwise with EtN^iPr_2 (1.43 ml, 8.23 mmol), stirred for 30 min, treated dropwise with $ClCO_2$Et (1.1 ml, 11.23 mmol), stirred for 1 h, treated with a soln. of NaN_3 (983 mg, 14.97 mmol) in H_2O (3 ml), and stirred for another hour at $-2°$. The soln. was treated with ice (50 ml) and extracted with CH_2Cl_2 (5 × 50 ml). After drying ($MgSO_4$) of the combined org. layers and evaporation at r.t., the residue was added to a soln. of 9*H*-fluorene-9-methanol (7.35 g, 37.43 mmol) in dioxane (30 ml). Stirring for 1.5 h at 100°, evaporation, and FC ($CHCl_3$/MeOH 99:1) gave **45** (3.31 g, 90%). White powder. R_f ($CHCl_3$/MeOH 9:1) 0.58. M.p. 90–93°. UV ($CHCl_3$): 267 (30627), 301 (5577). IR (ATR): 2979*w* (br.), 1674*s* (br.), 1619*m*, 1521*w*, 1449*m*, 1414*m*, 1392*m*, 1368*m*, 1235*s*, 1200*w*, 1151*s*, 1085*w*, 996*w*, 944*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO, 80°): 11.05 (br. *s*, H–N(3)); 7.84–7.30 (*m*, 8 arom. H); 7.23 (br. *s*, N*H*Fmoc); 5.47 (*s*, H–C(5)); 4.46 (*s*, CH_2–N(1)); 4.34 (*d*, *J* = 6.6, CH_2–C(9″)); 4.19 (*t*, *J* = 6.6, H–C(9″)); 3.22 (*q*, *J* = 6.9, 2 H–C(2′)); 2.53 (*t*, *J* = 6.9, 2 H–C(1′)); 1.41 (*s*, ^{t}Bu). ^{1}H-NMR (400 MHz, $CDCl_3$; assignment based on a HSQC and a HMBC spectrum): 9.69 (br. *s*, H–N(3)); 7.76–7.29 (*m*, 8 arom. H); 5.62 (*s*, H–C(5)); 5.53 (*t*, *J* = 5.9, N*H*Fmoc); 4.54 (*s*, CH_2–N(1)); 4.40 (*d*, *J* = 6.8, CH_2–C(9″)); 4.19 (*t*, *J* = 6.8, H–C(9″)); 3.37 (*q*, *J* = 6.3, 2 H–C(2′)); 2.60 (*t*, *J* = 6.7, 2 H–C(1′)); 1.46 (*s*, Me_3C). ^{13}C-NMR (100 MHz, $CDCl_3$; assignment based on a HSQC and a HMBC spectrum): 167.03 (*s*, *C*$O_2{}^t$Bu); 162.87 (*s*, C(4)); 156.46 (*s*, $NHCO_2$); 154.07 (*s*, C(6)); 151.66 (*s*, C(2)); 143.76 (2*s*); 141.32 (2*s*); 127.75–120.00 (8*d*); 101.99 (*d*, C(5)); 83.44 (*s*, Me_3C); 66.89 (*t*, *C*H_2–C(9″)); 47.18 (*d*, C(9″)); 45.48 (*t*, CH_2–N(1)); 38.54 (*t*, C(2′)); 32.62 (*t*, C(1′)); 27.97 (*q*, *Me*$_3$C). HR-MALDI-MS: 530.1695 (51, $[M+K]^+$, $C_{27}H_{29}N_3KO_3^+$; calc. 530.1688), 514.1952 (100, $[M+Na]^+$, $C_{27}H_{29}N_3NaO_3^+$; calc. 514.1949), 492.2134 (14, $[M+H]^+$, $C_{27}H_{30}N_3O_3^+$; calc. 492.2129). Anal. calc. for $C_{27}H_{29}N_3O_6$ (491.54): C 65.97, H 5.95, N 8.55; found: C 65.56, H 5.95, N 8.42.

tert-*Butyl* N^4*-[(Benzyloxy)carbonyl]-6-[2-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)ethyl]cytosine-1-acetate* (**46**). A suspension of **56** (1.80 g, 4.17 mmol) in THF/acetone 1:1 (83 ml) was cooled to $-10°$, treated dropwise with EtN^iPr_2 (800 µl, 4.59 mmol) and ClCOOEt (599 µl, 6.26 mmol), and stirred for 1 h. The resulting orange soln. was treated with a soln. of NaN_3 (553 mg, 8.35 mmol) in H_2O (17 ml) and stirred for 1 h at $-10°$. The red soln. was treated with ice/brine and extracted with CH_2Cl_2 (5×). The combined org. fractions were dried ($MgSO_4$) and evaporated at r.t. A soln. of the residue in dioxane (17 ml) was treated with 9*H*-fluorene-9-methanol (8.19 g, 41.8 mmol) and heated to 80° for 1 h. Evaporation and FC (CH_2Cl_2/MeOH 99:1 → 98:2) gave **46** (2.37 g, 57%). Yellow foam. The aq. soln. from the workup was acidified with 1M HCl and extracted with $CHCl_3$ (5×). Drying ($MgSO_4$), filtration, and evaporation gave **56** (528 mg, 29%). R_f (CH_2Cl_2/MeOH 19:1) 0.24. UV (MeOH): 299 (15300), 247 (24300), 208 (71100). IR (ATR): 3229*w*, 2972*w*, 1739*m*, 1707*m*, 1665*m*, 1607*m*, 1566*m*, 1497*m*, 1450*m*, 1412*m*, 1389*m*, 1368*m*, 1210*s*, 1194*s*, 1151*s*, 1082*m*, 1061*m*, 1003*w*, 946*w*, 916*w*, 858*w*, 820*w*, 788*w*, 758*m*, 739*s*, 696*m*, 620*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO, 80°): 10.38 (br. *s*, NH–C(4)); 7.87–7.29 (*m*, 13 arom. H); 7.18 (br. *s*, N*H*Fmoc); 6.92 (*s*, H–C(5)); 5.16 (*s*, PhCH_2); 4.61 (*s*, CH_2–N(1)); 4.35 (*d*, *J* = 6.5, CH_2–C(9″)); 4.22 (*t*, *J* = 6.5, H–C(9″)); 3.25 (*q*, *J* = 6.5, 2 H–C(2′)); 2.73 (*t*, *J* = 6.2, 2 H–C(1′)), 1.42 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, (D_6)DMSO): 166.88 (*s*, *C*$O_2{}^t$Bu); 161.94 (*s*, C(4)); 159.00 (*s*, C(6)); 155.92 (*s*, NH*C*O_2Fm); 155.66 (*s*, C(2)); 152.82 (*s*, NH*C*O_2Bn); 143.63 (2*s*); 140.53 (2*s*); 135.70 (*s*); 128.26–119.96 (13*d*); 94.41 (*d*, C(5)); 81.67 (*s*, Me_3C); 66.36 (*t*, PhCH_2); 65.38 (*t*, CH_2–C(9″)); 46.68 (*d* and *t*, C(9″) and C(2′)); 38.49 (*t*, CH_2–N(1)); 32.88 (*t*, C(1′)); 27.62 (*q*, *Me*$_3$C). HR-MALDI-MS: 663.2217 (12, $[M+K]^+$, $C_{35}H_{36}KN_4O_7^+$; calc. 663.2221), 647.2487 (21, $[M+Na]^+$, $C_{35}H_{36}N_4NaO_7^+$; calc. 647.2482), 625.2661 (100, $[M+H]^+$, $C_{35}H_{37}N_4O_7^+$; calc. 625.2662), 607.1611 (3, $[M-{}^t\text{Bu}+H+K]^+$, $C_{31}H_{28}KN_4O_7^+$; calc. 607.1595),

591.1850 (9, $[M-{}^t\mathrm{Bu}+\mathrm{H}+\mathrm{Na}]^+$, $C_{31}H_{28}N_4NaO_7^+$; calc. 591.1856), 569.2030 (39, $[M-{}^t\mathrm{Bu}+2\,\mathrm{H}]^+$, $C_{31}H_{29}N_4O_7^+$; calc. 569.2036).

tert-*Butyl* N^6-*[(Benzyloxy)carbonyl]-8-[2-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)ethyl]adenine-9-acetate* (**47**). A suspension of **61** (2.50 g, 5.49 mmol) in THF/acetone 1:1 (110 ml) was cooled to $-10°$, treated dropwise with EtN^iPr_2 (1.05 ml, 6.04 mmol) and ClCOOEt (787 µl, 8.23 mmol), and stirred for 1 h. The resulting yellow soln. was treated with a soln. of NaN_3 (714 mg, 10.98 mmol) in H_2O (22 ml) and stirred for another h at $-10°$. The greenish soln. was treated with ice/brine and extracted with CH_2Cl_2 (5×). The combined org. fractions were dried ($MgSO_4$) and evaporated at r.t. A soln. of the residue in dioxane (22 ml) was treated with 9*H*-fluorene-9-methanol (10.8 g, 45.9 mmol), heated to 80°, stirred for 1 h, and evaporated. FC (CH_2Cl_2/MeOH 99:1 → 98:2) gave **47** (2.87 g, 52%). White powder. The aq. layer from the workup was acidified with 1M HCl and extracted with $CHCl_3$ (5×). The combined org. fractions were dried ($MgSO_4$), and filtered. Evaporation gave **61** (344 mg, 13%).

Data of **47**. R_f (CH_2Cl_2/MeOH 95:5) 0.29. M.p. 94.2–95.5°. UV (CH_3OH): 211 (55740), 266 (38540), 300 (6120). IR (ATR): 3338*w* (br.), 3064*w*, 3037*w*, 2980*w*, 1757*m*, 1739*m*, 1713*s*, 1616*s*, 1524*m*, 1491*m*, 1479*m*, 1452*s*, 1426*w*, 1391*m*, 1367*m*, 1322*m*, 1264*m*, 1236*s*, 1206*s*, 1151*s*, 1101*m*, 1070*w*, 1035*m*, 987*w*, 969*m*, 939*w*, 896*w*, 858*w*, 796*w*, 741*s*, 699*m*, 653*w*, 630*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 10.57 (*s*, NH–C(6)); 8.57 (*s*, H–C(2)); 7.88–7.28 (*m*, 13 arom. H, N*H*Fmoc); 5.22 (*s*, PhCH_2); 5.02 (*s*, CH_2–N(9)); 4.33 (*d*, *J* = 6.8, CH_2–C(9″)); 4.21 (*t*, *J* = 6.6, H–C(9″)); 3.47 (*q*, *J* = 6.4, 2 H–C(2′)); 2.99 (*t*, *J* = 7.1, 2 H–C(1′)); 1.40 (*s*, ^{t}Bu). ^{13}C-NMR (400 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 166.56 (*s*, $CO_2{}^t$Bu); 156.05 (*s*, NHCO_2Fm); 153.67 (*s*, C(8)); 153.07 (*s*, C(4)); 152.07 (*s*, NHCO_2Bn); 151.10 (*d*, C(2)); 148.21 (*s*, C(6)); 143.82 (2*s*); 140.71 (2*s*); 136.34 (*s*); 128.35–125.05 (11*d*); 122.38 (*s*, C(5)); 120.08 (2*d*); 82.52 (*s*, Me_3C); 66.22 (*t*, PhCH_2); 65.35 (*t*, CH_2–C(9″)); 46.69 (*d*, C(9″)); 43.82 (*t*, CH_2–N(9)); 37.94 (*t*, C(2′)); 27.54 (*q*, Me_3C); 27.29 (*t*, C(1′)). HR-MALDI-MS: 687.2337 (9, $[M+\mathrm{K}]^+$, $C_{36}H_{36}KN_6O_6^+$; calc. 687.2333), 671.2588 (58, $[M+\mathrm{Na}]^+$, $C_{36}H_{36}N_6NaO_6^+$; calc. 671.2594), 649.2774 (100, $[M+\mathrm{H}]^+$, $C_{36}H_{37}N_6O_6^+$; calc. 649.2775), 615.1965 (9, $[M-{}^t\mathrm{Bu}+\mathrm{H}+\mathrm{Na}]^+$, $C_{32}H_{28}N_6NaO_6^+$; calc. 615.1968), 593.2142 (16, $[M-{}^t\mathrm{Bu}+2\,\mathrm{H}]^+$, $C_{32}H_{29}N_6O_6^+$; calc. 593.2149), 541.2192 (15, $[M-\mathrm{BnO}]^+$, $C_{29}H_{29}N_6O_5^+$; calc. 541.2199). Anal. calc. for $C_{36}H_{36}N_6O_6$ (648.71): C 66.65, H 5.59, N 12.95; found C 66.36, H 5.57, N 12.80.

tert-*Butyl 6-*O*-Benzyl-8-[2-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)ethyl]guanine-9-acetate* (**48**). A soln. of **67** (6.20 g, 15.6 mmol) in THF (100 ml) was cooled to 0°, treated dropwise with a cold (0°) soln. of Fmoc-OSu (5.77 g, 17.1 mmol) in THF (60 ml) over 10 min and stirred for 30 min. Evaporation and FC (AcOEt/cyclohexane 1:1) gave **48** (8.35 g, 86%). White powder. R_f (CH_2Cl_2/MeOH 19:1) 0.39. M.p. 139.2–141.1°. UV (MeOH): 255 (27140), 211 (54660). IR (ATR): 3483*w*, 3411*w*, 3312*w*, 3184*w*, 2971*w*, 2943*w*, 1745*m*, 1729*s*, 1635*m*, 1593*s*, 1530*m*, 1489*m*, 1470*m*, 1449*m*, 1436*m*, 1426*m*, 1392*m*, 1377*m*, 1367*m*, 1351*m*, 1331*m*, 1297*m*, 1233*s*, 1195*m*, 1157*m*, 1144*s*, 1098*w*, 1078*m*, 1064*m*, 1042*m*, 1006*m*, 980*m*, 935*w*, 913*w*, 878*w*, 867*w*, 846*m*, 832*w*, 792*m*, 756*s*, 738*s*, 727*m*, 700*m*, 669*w*, 620*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO, 100°): 7.85–7.26 (*m*, 13 arom. H); 6.97 (*s*, N*H*Fmoc); 6.02 (*s*, NH_2); 5.53 (*s*, PhCH_2); 4.74 (*s*, CH_2–N(9)); 4.32 (*d*, *J* = 6.5, CH_2–C(9″)); 4.21 (*t*, *J* = 6.7, H–C(9″)); 3.43 (*q*, *J* = 6.2, 2 H–C(2′)); 2.84 (*t*, *J* = 7.3, 2 H–C(1′)); 1.42 (*s*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.28 (*s*, $CO_2{}^t$Bu); 159.96 (*s*, C(6)); 158.69 (*s*, C(2)); 156.39 (*s*, NHCO_2); 155.32 (*s*, C(4)); 149.30 (*s*, C(8)); 143.86 (2*s*); 141.14 (2*s*); 136.53 (*s*); 128.34–119.85 (13*d*); 114.14 (*s*, C(5)); 83.36 (*s*, Me_3C); 68.10 (*t*, CH_2–C(9″)); 66.83 (*t*, PhCH_2); 47.25 (*d*, C(9″)); 43.79 (*t*, CH_2–N(9)); 37.76 (*t*, C(2′)); 28.11 (*q*, Me_3C); 27.69 (*t*, C(1′)). HR-MALDI-MS: 659.2344 (7, $[M+\mathrm{K}]^+$, $C_{35}H_{36}KN_6O_5^+$; calc. 659.2384), 643.2633 (14, $[M+\mathrm{Na}]^+$, $C_{35}H_{36}N_6NaO_5^+$; calc. 643.2645), 621.2817 (100, $[M+\mathrm{H}]^+$, $C_{35}H_{37}N_6O_5^+$; calc. 621.2825), 603.1751 (1, $[M-{}^t\mathrm{Bu}+\mathrm{H}+\mathrm{K}]^+$, $C_{31}H_{28}KN_6O_5^+$; calc. 603.1758), 587.1990 (2, $[M-{}^t\mathrm{Bu}+\mathrm{H}+\mathrm{Na}]^+$, $C_{31}H_{28}N_6NaO_5^+$; calc. 587.2019), 565.2167 (30, $[M-{}^t\mathrm{Bu}+2\,\mathrm{H}]^+$, $C_{31}H_{29}N_6O_5^+$; calc. 565.2199). Anal. calc. for $C_{35}H_{36}N_6O_5$ (620.70): C, 67.73, H 5.85, N 13.54; found: C 67.91, H 5.69, N 13.44.

tert-*Butyl 6-Formyluracil-1-acetate* (**49**). A soln. of $^iPr_2NH$ (35 ml, 265 mmol) in THF (150 ml) was cooled to $-76°$, treated dropwise with 1.6M BuLi in hexane (166 ml, 265 mmol), stirred for 20 min, warmed to 0°, stirred for 15 min, cooled to $-76°$, treated dropwise with a soln. of **17** (10 g, 44.2 mmol) in THF (200 ml), and stirred for 2 h at $-76°$. The soln. was treated dropwise with DMF (68 ml, 884 mmol), stirred for another 2.5 h at $-76°$, allowed to reach r.t., treated with AcOH (32 ml) and sat. NH_4Cl soln. (150 ml), and extracted with $CHCl_3$ (4 × 50 ml). Drying of the combined org. fractions ($MgSO_4$),

evaporation, and FC (CH_2Cl_2/MeOH 99:1 → 9:1) gave **49** (4.15 g, 37%) and **17**. White powder. R_f (CH_2Cl_2/MeOH 19:1) 0.18. M.p. 182.5–183.5°. UV ($CHCl_3$): 306 (68800). IR (ATR): 3196*w*, 3066*w*, 2982*w*, 1736*m*, 1697*s*, 1674*s*, 1615*m*, 1467*m*, 1418*m*, 1384*s*, 1367*s*, 1291*w*, 1232*s*, 1156*s*, 1076*m*, 973*m*, 920*m*, 867*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.48 (*s*, CHO); 8.69 (br. *s*, NH); 6.29 (*d*, *J* = 2.1, H–C(5)); 4.94 (*s*, CH_2–N(1)); 1.47 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, (D_6)DMSO): 188.13 (*d*, CHO); 167.09 (*s*, $CO_2{}^t$Bu); 162.43 (*s*, C(4)); 150.94 (*s*, C(2)); 146.19 (*s*, C(6)); 113.39 (*d*, C(5)); 81.62 (*s*, Me_3C); 44.44 (*t*, CH_2–N(1)); 27.44 (*q*, Me_3C). HR-EI-MS: 254.0899 (0.6, M^+, $C_{11}H_{14}N_2O_5^+$; calc. 254.0903), 181.0253 (14, $[M-{}^t\text{BuO}]^+$, $C_7H_5N_2O_4^+$; calc. 181.0249), 57.0697 (100, ^{t}Bu$^+$). Anal. calc. for $C_{11}H_{14}N_2O_5$ (254.09): C 51.97, H 5.55, N 11.02; found: C 51.89, H 5.56, N 10.85.

*Benzyl (*E*)-3-(1-{[(*tert*-Butoxy)carbonyl]methyl}uracil-6-yl)prop-2-enoate* (**50**). A soln. of **49** (3.10 g, 12.19 mmol) and benzyl (triphenylphosphoranylidene)acetate (5.51 g, 13.41 mmol) in THF (32 ml) was stirred for 5 h at r.t., diluted with H_2O (80 ml), and extracted with $CHCl_3$ (4 × 25 ml). Drying of the combined organic layers ($MgSO_4$), evaporation, and FC (AcOEt/cyclohexane 1:1) gave **50** (3.58 g, 76%). White powder. R_f (cyclohexane/AcOEt 1:2) 0.58. M.p. 176–177°. UV ($CHCl_3$): 241 (8790), 304 (6370). IR (ATR): 3182*w*, 3058*w*, 2985*w*, 2815*w*, 1740*m*, 1720*m*, 1681*s*, 1611*s*, 1496*w*, 1450*m*, 1412*m*, 1393*m*, 1367*m*, 1311*m*, 1281*m*, 1236*s*, 1202*m*, 1168*s*, 1152*s*, 1041*w*, 1007*m*, 995*m*, 972*m*, 944*w*, 922*w*. ^{1}H-NMR (400 MHz, $CDCl_3$; assignment based on a HSQC and a HMBC spectrum): 9.72 (br. *s*, NH); 7.37 (br. *s*, 5 arom. H); 7.26 (*dd*, *J* = 11.6, 0.5, H–C(3)); 6.48 (*d*, *J* = 11.6, H–C(2)); 5.87 (*d*, *J* = 0.5, H–C(5′)); 5.24 (*s*, PhCH_2); 4.50 (*s*, CH_2–N(1′)); 1.43 (*s*, ^{t}Bu). ^{13}C-NMR (100 MHz, $CDCl_3$; assignment based on a HSQC and a HMBC spectrum): 166.32 (*s*, $CO_2{}^t$Bu); 164.31 (*s*, CO_2Bn); 162.42 (*s*, C(4′)); 151.12 (*d*, C(2′)); 150.72 (*s*, C(6′)); 135.03 (*s*); 134.34 (*d*, C(3)); 128.71 (2*d*); 128.67 (*d*, C(2)); 128.51 (2*d*); 128.40 (*d*); 102.08 (*d*, C(5′)); 83.66 (*s*, Me_3C); 67.38 (*t*, PhCH_2); 45.98 (*t*, CH_2–N(1)); 27.88 (*q*, Me_3C). HR-EI-MS: 386.1476 (15, M^+, $C_{20}H_{22}N_2O_6^+$; calc. 386.1478), 330.0843 (47, $[M-{}^t\text{Bu}+\text{H}]^+$, $C_{16}H_{14}N_2O_6^+$; calc. 330.0846), 313.0819 (56, $[M-{}^t\text{BuO}]^+$, $C_{16}H_{13}N_2O_5^+$; calc. 313.0824), 285.0870 (21, $[M-CO_2{}^t\text{Bu}]^+$, $C_{15}H_{13}N_2O_4^+$; calc. 285.0875), 224.0428 (34, $[M-{}^t\text{Bu}-\text{OBn}+2\text{ H}]^+$, $C_9H_8N_2O_5^+$; calc. 224.0422), 195.0404 (40, $[M-{}^t\text{Bu}-CO_2\text{Bn}+\text{H}]^+$, $C_8H_7N_2O_4^+$; calc. 195.0400), 180.0502 (19, $[M-\text{O}^t\text{Bu}-CO_2\text{Bn}+2\text{ H}]^+$, $C_8H_8N_2O_3^+$; calc. 180.0524), 151.0507 (25, $[M-CO_2{}^t\text{Bu}-CO_2\text{Bn}+\text{H}]^+$, $C_7H_7N_2O_2^+$; calc. 151.0502), 91.0538 (48, $C_7H_7^+$), 57.0715 (100, ^{t}Bu$^+$), 41.0452 (12, $[H_2C{=}CH{-}CH_2]^+$). Anal. calc. for $C_{20}H_{22}N_2O_6$ (386.40): C 62.17, H 5.74, N 7.25; found: C 62.04, H 5.75, N 7.13.

*3-(1-{[*tert*-Butoxy)carbonyl]methyl}uracil-6-yl)propanoic Acid* (**51**). A suspension of $Pd(OAc)_2$ (173 mg, 0.77 mmol) in MeOH (30 ml) was stirred for 1 h at r.t. under H_2, treated with a soln. of **50** (2.98 g, 7.73 mmol) in THF (50 ml), and stirred for 14 h. Filtration through *Celite* and evaporation gave **51** (2.30 g, 100%). White powder. R_f ($CHCl_3$/MeOH 3:1) 0.26. M.p. 169–170°. UV ($CHCl_3$): 265 (9587). IR (ATR): 3116*w*, 2982*w*, 2931*w*, 2870*w*, 2694*w*, 2550*w*, 1745*m*, 1697*s*, 1635*s*, 1472*m*, 1443*m*, 1421*s*, 1393*m*, 1368*s*, 1314*w*, 1288*w*, 1237*s*, 1217*s*, 1191*m*, 1155*s*, 1064*w*, 1037*w*, 1022*w*, 1006*w*, 927*m*, 862*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2CO$, spectrum of higher order): 10.11 (br. *s*, NH); 5.53 (*s*, H–C(5′)); 4.62 (*s*, CH_2–N(1′)); 2.84–2.76 (*m*, 2 H–C(2)); 2.72–2.65 (*m*, 2 H–C(3)); 1.46 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, (D_6)DMSO): 172.57 (*s*, CO_2H); 167.18 (*s*, $CO_2{}^t$Bu); 162.21 (*s*, C(4′)); 155.74 (*s*, C(6′)); 151.41 (*s*, C(2′)); 99.72 (*d*, C(5′)); 81.92 (*s*, Me_3C); 45.16 (*t*, CH_2–N(1′)); 30.95 (*t*, C(2)); 27.62 (*q*, Me_3C); 26.65 (*t*, C(3)). HR-EI-MS: 298.1160 (3, M^+, $C_{13}H_{18}N_2O_6^+$; calc. 298.1165), 225.0501 (11, $[M-{}^t\text{BuO}]^+$, $C_9H_9N_2O_5^+$; calc. 225.0511), 198.0638 (21, $[M-CO_2{}^t\text{Bu}+\text{H}]^+$, $C_8H_{10}N_2O_4^+$; calc. 198.0635), 153.0661 (24, $[M-CO_2{}^t\text{Bu}-CO_2]^+$, $C_7H_9N_2O_2^+$; calc. 153.0659), 57.0715 (100, ^{t}Bu$^+$, $C_4H_9^+$).

*6-[2-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)ethyl]uracil-1-acetic Acid* (**52**). A soln. of **45** (3.4 g, 6.91 mmol) in CH_2Cl_2 (30 ml) was treated with ^{i}Pr$_3$SiH (7.1 ml, 34.55 mmol) and TFA (15.4 ml, 6.91 mmol), and stirred for 8 h at r.t. After evaporation, the residue was suspended in Et_2O (30 ml). The solid was filtered off, washed with Et_2O, and dried to give **52** (2.35 g, 78%). White powder. R_f ($CHCl_3$/MeOH 3:2) 0.31. M.p. 147–151°. UV (MeOH): 265 (24000), 300 (5000). IR (ATR): 2973*w* (br.), 1672*s* (br.), 1524*m*, 1449*m*, 1412*m*, 1396*m*, 1335*w*, 1246*m*, 1199*m*, 1148*m*, 1101*w*, 1086*w*, 995*w*, 931*w*, 880*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 13.19 (br. *s*, CO_2H); 11.35 (*s*, H–N(3)); 7.92–7.65 (*m*, 4 arom. H); 7.48 (*t*, *J* = 5.7, N*H*Fmoc); 7.42–7.31 (*m*, 4 arom. H); 5.50 (*s*, H–C(5)); 4.51 (*s*, CH_2–N(1)); 4.32 (*d*, *J* = 6.9, CH_2–C(9″)); 4.21 (*t*, *J* = 6.9, H–C(9″)); 3.18 (*q*, *J* = 6.0, 2 H–C(2′)); 2.55 (*t*, *J* = 6.0, 2 H–C(1′)). ^{13}C-NMR (75 MHz, (D_6)DMSO): 169.82 (*s*, CO_2H); 162.49 (*s*, C(4)); 156.19 (*s*, NHCO_2Fm); 154.30 (*s*, C(6)); 151.75 (*s*, C(2)); 143.86 (2*s*); 140.77 (2*s*); 127.62–120.13 (8*d*); 100.87 (*d*, C(5)); 65.54 (*t*,

*C*H$_2$–C(9″)); 46.73 (*d*, C(9″)); 44.67 (*t*, CH$_2$–N(1)); 38.03 (*t*, C(2′)); 31.79 (*t*, C(1′)). HR-MALDI-MS: 474.1091 (5, $[M + K]^+$, $C_{23}H_{21}KN_3O_6^+$; calc. 474.1067), 458.1319 (100, $[M + Na]^+$, $C_{23}H_{21}N_3NaO_6^+$; calc. 458.1323), 436.1509 (*17*, $[M + H]^+$, $C_{23}H_{22}N_3O_6^+$; calc. 436.1509).

tert-*Butyl* N^4-*[(Benzyloxy)carbonyl]-6-formylcytosine-1-acetate* (**53**). A soln. of ^{i}Pr$_2$NH (24.1 ml, 184 mmol) in THF (100 ml) was cooled to −76°, treated dropwise with 1.6M BuLi in hexane (115 ml, 184 mmol), warmed to 0°, stirred for 30 min, cooled to −76°, treated dropwise with a soln. of **26** (11.0 g, 30.6 mmol) in THF (50 ml) over 30 min, and stirred for 2 h. The soln. was treated dropwise with DMF (47.4 ml, 612 mmol) over 30 min and stirred for another 2 h at −76°. The soln. was treated with AcOH (22.8 ml, 398 mmol), allowed to reach r.t., and evaporated. The residue was diluted with H_2O and extracted with AcOEt (4×). The combined org. layers were washed with brine (5×), dried ($MgSO_4$), and evaporated. FC (CH_2Cl_2/MeOH 97:3 → 9:1) gave **53** (7.60 g, 64%). Yellow foam. R_f (CH_2Cl_2/MeOH 19:1) 0.21. UV (MeOH): 297 (8560), 244 (16320), 209 (26880). IR (ATR): 3115*w*, 2997*w*, 2976*w*, 2937*w*, 1740*s*, 1706*m*, 1657*s*, 1612*s*, 1563*m*, 1511*m*, 1455*w*, 1417*m*, 1407*w*, 1379*s*, 1369*m*, 1290*w*, 1226*s*, 1151*s*, 1084*w*, 1064*m*, 1028*w*, 994*w*, 968*w*, 947*w*, 927*m*, 867*w*, 840*m*, 781*m*, 769*w*, 740*s*, 715*m*, 697*m*, 664*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 11.27 (*s*, NH); 9.68 (*s*, H–C(5)); 7.70–7.34 (*m*, 5 arom. H); 5.24 (*s*, PhC*H*$_2$); 4.85 (*s*, CH$_2$–N(1)); 1.41 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, (D_6)DMSO): 187.67 (*d*, CHO); 166.94 (*s*, *C*O$_2{}^t$Bu); 163.19 (*s*, C(4)); 155.01 (*s*, C(6)); 152.93 (*s*, NH*C*O$_2$Bn); 148.91 (*s*, C(2)); 135.56 (*s*); 128.33 (2*d*); 128.09 (2*d*); 127.90 (*d*); 102.81 (*d*, C(5)); 81.69 (*s*, Me$_3$*C*); 66.72 (*t*, PhC*H*$_2$); 45.55 (*t*, CH$_2$–N(1)); 27.44 (*q*, *Me*$_3$C). HR-MALDI-MS: 458.1346 (6, $[M + MeOH + K]^+$, $C_{20}H_{25}KN_3O_7^+$; calc. 458.1330), 444.1184 (7, $[M + H_2O + K]^+$, $C_{19}H_{23}KN_3O_7^+$; calc. 444.1173), 442.1599 (14, $[M + MeOH + Na]^+$, $C_{20}H_{25}N_3NaO_7^+$; calc. 442.1590), 428.1440 (15, $[M + H_2O + Na]^+$, $C_{19}H_{23}N_3NaO_7^+$; calc. 428.1434), 420.1778 (96, $[M + MeOH + H]^+$, $C_{20}H_{26}N_3O_7^+$; calc. 420.1771), 410.1345 (9, $[M + Na]^+$, $C_{19}H_{21}N_3NaO_6^+$; calc. 410.1328), 406.1614 (100, $[M + H_2O + H]^+$, $C_{19}H_{24}N_3O_7^+$; calc. 406.1614), 388.1508 (34, $[M + H]^+$, $C_{19}H_{22}N_3O_6^+$; calc. 388.1509), 386.0974 (7, $[M + MeOH - {}^t\!Bu + H + Na]^+$, $C_{16}H_{17}N_3NaO_7^+$; calc. 386.0964), 372.0814 (7, $[M + H_2O - {}^t\!Bu + H + Na]^+$, $C_{15}H_{15}N_3NaO_7^+$; calc. 372.0808), 364.1142 (53, $[M + MeOH - {}^t\!Bu + 2\,H]^+$, $C_{16}H_{18}N_3O_7^+$; calc. 364.1145), 354.0708 (8, $[M - {}^t\!Bu + H + Na]^+$, $C_{15}H_{13}N_3NaO_6^+$; calc. 354.0702), 350.0982 (74, $[M + H_2O - {}^t\!Bu + 2\,H]^+$, $C_{15}H_{16}N_3O_7^+$; calc. 350.0988), 332.0882 (31, $[M - {}^t\!Bu + 2\,H]^+$, $C_{15}H_{14}N_3O_6^+$; calc. 332.0883). Anal. calc. for $C_{19}H_{21}N_3O_6$ (387.39): C 58.91, H 5.46, N 10.85; found: C 58.63, H 5.53, N 10.55.

Methyl (E)*-3-(*N^4*-[(Benzyloxy)carbonyl]-1-{[(*tert*-butoxy)carbonyl]methyl}cytosin-6-yl)prop-2-enoate* (**54**). A soln. of **53** (6.80 g, 17.6 mmol) and methyl (triphenylphosphoranylidene)acetate (6.16 g, 18.4 mmol) in THF (88 ml) was stirred for 3 h at r.t. and evaporated to give a 1:1 mixture **54**/Ph_3PO (12.5 g, 97%). A small sample was ground and suspended in ^{i}Pr$_2$O. Filtration and washing with ^{i}Pr$_2$O gave pure **54**. Yellow powder. R_f (CH_2Cl_2/MeOH 19:1) 0.28. M.p. 71.1–76.1°. UV (MeOH): 314 (6960), 239 (13760), 207 (37740). IR (ATR): 2978*w*, 2954*w*, 1736*m*, 1729*m*, 1669*m*, 1602*m*, 1562*m*, 1496*m*, 1454*w*, 1432*w*, 1423*m*, 1387*m*, 1369*m*, 1311*m*, 1276*m*, 1259*m*, 1197*s*, 1175*s*, 1149*s*, 1052*m*, 971*w*, 947*w*, 911*w*, 858*w*, 819*w*, 785*m*, 744*m*, 696*m*. ^{1}H-NMR (300 MHz, $CDCl_3$; assignments based on a HSQC and a HMBC spectrum): 7.93 (br. *s*, NH); 7.39–7.26 (*m*, 5 arom. H, H–C(3), H–C(5′)); 6.58 (*d*, *J* = 15.7, H–C(2)); 5.20 (*s*, PhC*H*$_2$); 4.67 (*s*, CH$_2$–N(1′)); 3.82 (*s*, MeO); 1.45 (*s*, Me$_3$C). ^{13}C-NMR (75 MHz, $CDCl_3$; assignments based on a HSQC and a HMBC spectrum): 166.13 (*s*, *C*O$_2{}^t$Bu); 164.91 (*s*, CO$_2$Me); 161.79 (*s*, C(4′)); 155.74 (*s*, C(2′)); 154.48 (*s*, C(6′)); 152.21 (*s*, NH*C*O$_2$Bn); 134.81 (*s*); 134.09 (*d*, C(3)); 128.83 (*d*); 128.61 (2*d*); 128.27 (2*d*); 93.93 (2*d*, C(2), C(5′)); 83.39 (*s*, Me$_3$*C*); 67.98 (*t*, PhC*H*$_2$); 52.40 (*q*, MeO); 47.02 (*t*, *C*H$_2$–N(1′)); 27.81 (*q*, *Me*$_3$C). HR-MALDI-MS: 482.1327 (24, $[M + K]^+$, $C_{22}H_{25}KN_3O_7^+$; calc. 482.1330), 466.1484 (64, $[M + Na]^+$, $C_{22}H_{25}N_3NaO_7^+$; calc. 466.1590), 444.1758 (100, $[M + H]^+$, $C_{22}H_{26}N_3O_7^+$; calc. 444.1771), 426.0699 (10, $[M - {}^t\!Bu + H + K]^+$, $C_{18}H_{17}KN_3O_7^+$; calc. 426.0704), 410.0955 (46, $[M - {}^t\!Bu + H + Na]^+$, $C_{18}H_{17}N_3NaO_7^+$; calc. 410.0964), 388.1127 (82, $[M - {}^t\!Bu + 2\,H]^+$, $C_{18}H_{18}N_3O_7^+$; calc. 388.1145).

*Methyl 3-(*N^4*-[(Benzyloxy)carbonyl]-1-{[(*tert*-butoxy)carbonyl]methyl}cytosine-6-yl)propanoate* (**55**). A soln. of **54**/Ph_3PO 1:1 (7.60 g, 17.1 mmol of **54**) in MeOH (115 ml) was cooled to 0°, treated with $NaBH_4$ (973 mg, 25.7 mmol) in several portions over 20 min and stirred for 1.5 h at 0°. The soln. was poured on H_2O and extracted with CH_2Cl_2 (5×). The combined org. fractions were washed with brine (3×), dried ($MgSO_4$), filtered, and evaporated. Drying of the residue gave a 1:1 mixture **55**/Ph_3PO (12.3 g, 98%). A small sample was ground and suspended in ^{i}Pr$_2$O. Filtration and washing with ^{i}Pr$_2$O gave

pure **55**. Yellow powder. R_f (CH_2Cl_2/MeOH 19:1) 0.25. M.p. 55.3–56.1°. UV (MeOH): 296 (9460), 241 (16500), 211 (28640). IR (ATR): 2978*w*, 2953*w*, 1733*s*, 1665*m*, 1607*m*, 1564*m*, 1498*m*, 1453*w*, 1437*w*, 1411*m*, 1389*m*, 1368*s*, 1291*w*, 1207*s*, 1192*s*, 1149*s*, 1061*m*, 1029*w*, 984*w*, 949*w*, 923*w*, 896*w*, 856*w*, 821*w*, 787*m*, 770*w*, 744*m*, 735*m*, 695*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.05 (*s*, NH); 7.35–7.26 (*m*, 5 arom. H); 7.09 (*s*, H–C(5′)); 5.17 (*s*, PhCH_2); 4.67 (*s*, CH_2–N(1′)); 3.69 (*s*, MeO); 2.82 (*t*, *J* = 7.7, 2 H–C(3)); 2.68 (*t*, *J* = 7.7, 2 H–C(2)); 1.43 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.55 (*s*, *C*O_2Et); 166.52 (*s*, *C*$O_2{}^t$Bu); 161.67 (*s*, C(4′)); 160.27 (*s*, C(6′)); 156.31 (*s*, C(2′)); 152.32 (*s*, NH*C*O_2Bn); 135.00 (*s*); 128.53 (2*d*); 128.47 (*d*); 128.16 (2*d*); 93.51 (*d*, C(5′)); 83.07 (*s*, Me_3C); 67.69 (*t*, Ph*C*H_2); 52.10 (*q*, MeO); 46.45 (*t*, *C*H_2–N(1)); 31.07 (*t*, C(2′)), 27.82 (*q*, *Me*$_3$C); 27.66 (*t*, C(3′)). HR-MALDI-MS: 484.1498 (8, $[M+K]^+$, $C_{22}H_{27}KN_3O_7^+$; calc. 484.1486), 468.1748 (32, $[M+Na]^+$, $C_{22}H_{27}N_3NaO_7^+$; calc. 468.1747), 446.1928 (100, $[M+H]^+$, $C_{22}H_{28}N_3O_7^+$; calc. 446.1927), 412.1119 (6, $[M-{}^t\text{Bu}+H+Na]^+$, $C_{18}H_{19}N_3NaO_7^+$; calc. 412.1121), 390.1291 (45, $[M-{}^t\text{Bu}+2H]^+$, $C_{18}H_{20}N_3O_7^+$; calc. 390.1301).

*3-(*N^4*-[(Benzyloxy)carbonyl]-1-{[(*tert*-butoxy)carbonyl]methyl}cytosin-6-yl)propanoic Acid* (**56**). *a*) A soln. of **55** (156 mg, 350 μmol) in THF/H_2O 4:1 (3.5 ml) was cooled to 0°, treated with LiOH · H_2O (147 mg, 3.5 mmol) in one portion and stirred for 2 h. Neutralisation with *Amberlite IR-120* (prewashed with MeOH and THF), filtration, evaporation, and FC (CH_2Cl_2/MeOH 99:1 → 9:1) gave **56** (125 mg, 83%). White powder.

b) A soln. of **55**/Ph_3PO 1:1 (7.41 g, 16.6 mmol of **55**) in THF/H_2O 4:1 (130 ml) was cooled to 0°, treated with LiOH · H_2O (6.98 g, 166 mmol) in one portion, and stirred for 3.5 h. Neutralisation with *Amberlite IR-120* (prewashed with MeOH and THF), filtration, evaporation, FC (CH_2Cl_2/MeOH 99:1 → 9:1), and washing of the residue after evaporation of the fractions containing **56** with AcOEt gave **56** (2.15 g, 30%). White powder. R_f (CH_2Cl_2/MeOH 4:1) 0.56. M.p. 155.6–163.1°. UV (MeOH): 297 (9200), 240 (14960), 211 (24000). IR (ATR): 2980*w*, 2933*w*, 1754*m*, 1744*m*, 1698*m*, 1602*m*, 1587*m*, 1511*m*, 1412*m*, 1391*m*, 1373*m*, 1367*m*, 1298*w*, 1213*s*, 1193*s*, 1151*s*, 1067*m*, 1035*w*, 982*w*, 970*w*, 906*w*, 862*w*, 821*m*, 776*m*, 768*m*, 746*m*, 728*m*, 697*m*, 672*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 10.90 (br. *s*, NH); 7.41–7.36 (*m*, 5 arom. H); 6.99 (*s*, H–C(5′)), 5.18 (*s*, PhCH_2); 4.64 (*s*, CH_2–N(1′)); 2.81 (*t*, *J* = 6.9, 2 H–C(3)); 2.55 (*t*, *J* = 6.9, 2 H–C(2)); 1.41 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 172.60 (*s*, CO_2H); 166.96 (*s*, *C*$O_2{}^t$Bu); 162.077 (*s*, C(4′)); 161.08 (*s*, C(6′)); 155.68 (*s*, C(2′)); 152.92 (*s*, NH*C*O_2Bn); 135.79 (*s*); 128.30 (2*d*); 127.97 (*d*); 127.75 (2*d*); 92.95 (*d*, C(5′)); 81.65 (*s*, Me_3C); 66.29 (*t*, Ph*C*H_2); 46.38 (*t*, CH_2–N(1′)); 30.98 (*t*, C(2)); 27.41 (*q* and *t*, *Me*$_3$C and C(3)). HR-MALDI-MS: 470.1334 (11, $[M+K]^+$, $C_{21}H_{25}KN_3O_7^+$; calc. 470.1330), 454.1592 (25, $[M+Na]^+$, $C_{21}H_{25}N_3NaO_7^+$; calc. 454.1590), 432.1769 (100, $[M+H]^+$, $C_{21}H_{26}N_3O_7^+$; calc. 432.1771), 414.0701 (2, $[M-{}^t\text{Bu}+H+K]^+$, $C_{17}H_{17}KN_3O_7^+$; calc. 414.0704), 398.0955 (6, $[M-{}^t\text{Bu}+H+Na]^+$, $C_{17}H_{17}N_3NaO_7^+$; calc. 398.0964), 376.1131 (46, $[M-{}^t\text{Bu}+2H]^+$, $C_{17}H_{18}N_3O_7^+$; calc. 376.1145).

N^4*-[(Benzyloxy)carbonyl]-6-[2-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)ethyl]cytosine-1-acetic Acid* (**57**). A soln. of **46** (4.38 g, 7.01 mmol) in CH_2Cl_2 (70 ml) was treated with Et_3SiH (11.2 ml, 70.1 mmol) and TFA (21.6 ml, 280 mmol), and stirred for 16 h at r.t. After evaporation at 30°, the residue was treated with $^i Pr_2O$ (80 ml). The resulting precipitate was filtered off, ground, and washed several times with $^i Pr_2O$. Drying of the solid gave **57** (3.91 g, 98%). White powder. R_f (CH_2Cl_2/MeOH 3:2) 0.37. M.p. 121.7–122.3°. UV (MeOH): 230 (12700), 265 (17500), 209 (50400). IR (ATR): 2953*w*, 1719*m*, 1666*m*, 1602*m*, 1569*m*, 1507*m*, 1449*m*, 1414*m*, 1391*m*, 1209*s*, 1191*s*, 1139*m*, 1087*m*, 1066*m*, 1002*m*, 908*w*, 826*w*, 758*m*, 739*s*, 695*m*, 620*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 11.20 (br. *s*, NH–C(4)); 7.89–7.28 (*m*, 13 arom. H, N*H*Fmoc); 6.97 (*s*, H–C(5)); 5.10 (*s*, PhCH_2); 4.65 (*s*, CH_2–N(1)); 4.31 (*d*, *J* = 6.9, CH_2–C(9″)); 4.20 (*t*, *J* = 6.5, H–C(9″)); 3.23 (*q*, *J* = 6.2, 2 H–C(2′)); 2.75 (*t*, *J* = 6.5, 2 H–C(1′)). ^{13}C-NMR (75 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 169.19 (*s*, CO_2H); 161.84 (*s*, C(4)); 159.06 (*s*, C(6)); 155.92 (*s*, NH*C*O_2Fm); 155.63 (*s*, C(2)); 152.81 (*s*, NH*C*O_2Bn); 143.61 (2*s*); 140.51 (2*s*); 135.68 (*s*); 128.23–119.92 (13*d*); 94.38 (*d*, C(5)); 66.33 (*t*, Ph*C*H_2); 65.39 (*t*, *C*H_2–C(9″)); 46.66 (*d*, C(9″)); 46.06 (*t*, C(2′)); 38.44 (*t*, CH_2–N(1)); 32.83 (*t*, C(1′)). HR-MALDI-MS: 607.1608 (8, $[M+K]^+$, $C_{31}H_{28}KN_4O_7^+$; calc. 607.1595), 591.1861 (27, $[M+Na]^+$, $C_{31}H_{28}N_4NaO_7^+$; calc. 591.1856), 569.2036 (100, $[M+H]^+$, $C_{31}H_{29}N_4O_7^+$; calc. 569.2036).

tert-*Butyl* N^6-*[(Benzyloxy)carbonyl]-8-formyladenine-9-acetate* (**58**). A soln. of ^{i}Pr$_2$NH (14.77 ml, 113 mmol) in THF (80 ml) was cooled to $-76°$, treated dropwise with 1.6M BuLi in hexane (70.42 ml, 113 mmol), stirred for 20 min, warmed to 0°, stirred for 1 h, and left at 4° for 16 h. The soln. was cooled to $-76°$, treated dropwise with a soln. of **32** (7.20 g, 18.8 mmol) in THF (30 ml), stirred for 2 h, treated dropwise with DMF (29.08 ml, 376 mmol), and stirred for another 2 h. The soln. was treated with AcOH (6.45 ml) and allowed to warm to r.t. After evaporation, the residue was diluted with H_2O and extracted with AcOEt (4×). The combined org. layers were washed with H_2O and brine (3×), dried ($MgSO_4$), filtered, and evaporated. FC (AcOEt/cyclohexane 3:1) gave **58** (4.50 g, 58%). Yellow foam. R_f (CH_2Cl_2/MeOH 95:5) 0.28. UV (MeOH): 212 (33160), 269 (21080). IR (ATR): 3239*w* (br.), 3189*w* (br.), 2979*w*, 1742*s*, 1697*m* (br.), 1604*s*, 1583*m*, 1522*w*, 1499*w*, 1454*s*, 1414*w*, 1391*m*, 1367*m*, 1322*w*, 1290*m*, 1282*m*, 1249*m*, 1229*m*, 1198*s*, 1150*s*, 1106*m*, 1029*m*, 973*w*, 943*w*, 897*w*, 850 *m*, 801 *w*, 743*m*, 696*m*, 664*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.97 (*s*, CHO); 8.84 (*s*, H–C(2)); 8.78 (*s*, NH); 7.44–7.34 (*m*, 5 arom. H); 5.30 (*s*, PhCH_2); 5.23 (*s*, CH_2–N(9)); 1.46 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 183.68 (*d*, CHO); 165.58 (*s*, *C*O$_2^t$Bu); 155.70 (*d*, C(2)); 152.03 (*s*, C(4)); 151.63 (*s*, NH*C*O$_2$Bn); 150.40 (*s*, C(6)); 145.43 (*s*, C(8)); 134.95 (*s*); 128.67 (3*d*); 128.60 (2*d*); 121.78 (*s*, C(5)); 83.68 (*s*, Me$_3$*C*); 68.23 (*t*, Ph*C*H$_2$); 45.51 (*t*, CH_2–N(9)); 28.07 (*q*, *Me*$_3$C). HR-MALDI-MS: 434.1428 (22, $[M+Na]^+$, $C_{20}H_{21}N_5NaO_5^+$; calc. 434.1440), 412.1609 (100, $[M+H]^+$, $C_{20}H_{22}N_5O_5^+$; calc. 412.1621), 384.1660 (14, $[M-CHO+2H]^+$, $C_{19}H_{22}N_5O_4^+$; calc. 384.1672), 378.0807 (9, $[M-{}^t\text{Bu}+Na+H]^+$, $C_{16}H_{13}N_5NaO_5^+$; calc. 378.0814), 356.0980 (57, $[M-{}^t\text{Bu}+2H]^+$, $C_{16}H_{14}N_5O_5^+$; calc. 356.0995).

*Methyl (*E*)-3-(*N^6*-[(Benzyloxy)carbonyl]-9-{[(*tert*-butoxy)carbonyl]methyl}adenine-8-yl)prop-2-enoate* (**59**). A soln. of **58** (7.50 g, 18.2 mmol) and methyl (triphenylphosphoranylidene)acetate (6.40 g, 19.1 mmol) in THF (90 ml) was stirred for 3 h at r.t. and evaporated. The residue was washed repetitively with hot cyclohexane to give **59** (7.70 g, 90%). Yellow foam. R_f (CH_2Cl_2/MeOH 95:5) 0.38. UV (MeOH): 205 (26480), 238 (22280), 318 (21760). IR (ATR): 3245*w* (br.), 3181*w* (br.), 2980*w*, 2951*w*, 1740*m*, 1719*s* (br.), 1648*w*, 1606*m*, 1586*m*, 1519*w*, 1449*m*, 1437*m*, 1388*w*, 1367*m*, 1295*m*, 1272*m*, 1207*s*, 1150*s*, 1103*m*, 1037*m*, 967*m*, 951*w*, 897*w*, 848*w*, 800*w*, 746*m*, 696*m*, 617*w*. ^{1}H-NMR (300 MHz, $CDCl_3$; assignments based on a HSQC and a HMBC spectrum): 8.72 (*s*, H–C(2′)); 8.62 (*s*, NH); 7.43 (*d*, J = 15.4, H–C(3)); 7.45–7.31 (*m*, 5 arom. H); 7.06 (*d*, J = 15.7, H–C(2)); 5.23 (*s*, PhCH_2); 4.93 (*s*, CH_2–N(9′)); 3.79 (*s*, MeO); 1.43 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, $CDCl_3$; assignments based on a HSQC and a HMBC spectrum): 165.80 (*s*, *C*O$_2$Me); 165.37 (*s*, *C*O$_2^t$Bu); 153.32 (*d*, C(2′)); 152.08 (*s*, C(4′)); 150.53 (*s*, NH*C*O$_2$Bn); 149.27 (*s*, C(6′)); 148.00 (*s*, C(8′)); 135.19 (*s*); 128.54 (2*d*); 128.49 (2*d*); 128.43 (*d*); 127.84 (*d*, C(3)); 126.80 (*d*, C(2)); 121.79 (*s*, C(5′)); 84.04 (*s*, Me$_3$*C*); 67.69 (*t*, Ph*C*H$_2$); 52.16 (*q*, MeO); 43.94 (*t*, CH_2–N(9′)); 27.78 (*q*, *Me*$_3$C). HR-MALDI-MS: 506.1459 (4, $[M+K]^+$, $C_{23}H_{25}KN_5O_6^+$; calc. 506.1442), 490.1716 (13, $[M+Na]^+$, $C_{23}H_{25}N_5NaO_6^+$; calc. 490.1703), 468.1881 (100, $[M+H]^+$, $C_{23}H_{26}N_5O_6^+$; calc. 468.1883), 434.1072 (5, $[M-{}^t\text{Bu}+Na+H]^+$, $C_{19}H_{17}N_5NaO_6^+$; calc. 434.1077), 412.1246 (96, $[M-{}^t\text{Bu}+2H]^+$, $C_{19}H_{18}N_5O_6^+$; calc. 412.1257), 368. 1344 (13, $[M-CO_2{}^t\text{Bu}+2H]^+$, $C_{18}H_{18}N_5O_4^+$; calc. 368.1359).

*Methyl 3-(*N^6*-[(Benzyloxy)carbonyl]-9-{[(*tert*-butoxy)carbonyl]methyl}adenin-8-yl)propanoate* (**60**). A suspension of **58** (7.34 g, 15.7 mmol) in MeOH (105 ml) was treated with a minimum of THF to obtain a soln., cooled to 0°, treated with $NaBH_4$ (5.94 g, 157 mmol) in several portions over 20 min, and stirred for 3 h at 0°. The soln. was poured on H_2O and extracted with CH_2Cl_2 (5×). The combined org. fractions were washed with brine (3×), dried ($MgSO_4$), filtered, and evaporated. Drying of the residue gave **60** (5.41 g, 73%). White foam. R_f (CH_2Cl_2/MeOH 95:5) 0.31. UV (MeOH): 211 (35620), 270 (19820). IR (ATR): 3279*w* (br.), 2980*w*, 2952*w*, 1732*s*, 1609*m*, 1590*m*, 1520*w*, 1497*w*, 1451*m*, 1393*w*, 1366*m*, 1338*w*, 1321*w*, 1301*m*, 1204*s*, 1149*s*, 1102*m*, 1026*m*, 971*w*, 941*w*, 911*w*, 894*w*, 844*w*, 799*w*, 737*m*, 696*m*, 649*w*, 619*w*. ^{1}H-NMR (300 MHz, $CDCl_3$; assignments based on a HSQC and a HMBC spectrum): 8.69 (*s*, H–C(2′)); 8.41 (*s*, NH); 7.42–7.32 (*m*, 5 arom. H); 5.26 (*s*, PhCH_2); 4.90 (*s*, CH_2–N(9′)); 3.66 (*s*, MeO$_2$C); 3.06–3.01 (*m*, 2 H–C(3)); 2.98–2.93 (*m*, 2 H–C(2)); 1.45 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, $CDCl_3$; assignments based on a HSQC and a HMBC spectrum): 172.53 (*s*, *C*O$_2$Me); 165.80 (*s*, *C*O$_2^t$Bu); 154.09 (*d*, C(2′)); 152.36 (*s*, C(4′)); 152.14 (*s*, C(8′)); 150.70 (*s*, NH*C*O$_2$Bn); 147.97 (*s*, C(6′)); 135.37 (*s*); 128.57 (2*d*); 128.52 (2*d*); 128.41 (*d*); 120.76 (*s*, C(5′)); 83.74 (*s*, Me$_3$*C*); 67.67 (*t*, Ph*C*H$_2$); 52.07 (*q*, MeO); 43.99 (*t*, CH_2–N(9′)); 30.56 (*t*, C(2)); 28.06 (*q*, *Me*$_3$C); 22.54 (*t*, C(3)). HR-MALDI-MS: 508.1603 (6, $[M+K]^+$, $C_{23}H_{27}KN_5O_6^+$; calc. 508.1598), 492.1855 (37, $[M+Na]^+$, $C_{25}H_{27}N_5NaO_6^+$; calc. 492.1859), 470.2031 (100, $[M+H]^+$, $C_{23}H_{28}N_5O_6^+$; calc. 470.2040), 436.1225 (12, $[M-{}^t\text{Bu}+H+Na]^+$,

$C_{19}H_{19}N_5NaO_6^+$; calc. 436.1233), 414.1394 (98, $[M-{}^t\mathrm{Bu}+2\,H]^+$, $C_{19}H_{20}N_5O_6^+$; calc. 414.1414), 370.1503 (7, $[M-CO_2{}^t\mathrm{Bu}+2\,H]^+$, $C_{18}H_{20}N_5O_4^+$; calc. 370.1515). Anal. calc. for $C_{23}H_{27}N_5O_6$ (469.49): C 58.84, H 5.80, N 14.92; found C 58.55, H 5.71, N 14.75.

*3-(*N^6*-[(Benzyloxy)carbonyl]-9-{[(*tert*-butoxy)carbonyl]methyl}adenin-8-yl)propanoic Acid* (**61**). A soln. of **60** (5.05 g, 10.8 mmol) in THF/H_2O 4:1 (110 ml) was cooled to 0°, treated with LiOH·H_2O (1.35 g, 32.3 mmol) in one portion, and stirred for 2 h at 0°. The resulting white suspension was neutralized with *Amberlite IR-120* (prewashed with MeOH and THF) and filtered. Evaporation of the filtrate, FC (CH_2Cl_2/MeOH 97:3 → 80:20), and washing the yellow solid product with small amounts of AcOEt gave **61** (3.98 g, 81%). White foam. R_f (CH_2Cl_2/MeOH 4:1) 0.55. M.p. 64.3–66.7°. UV (MeOH): 212 (35740), 271 (21020). IR (ATR): 3394–2778*w* (br.), 3192*w* (br.), 2979*w*, 2938*w*, 1738*s* (br.), 1613*m*, 1595*m*, 1536*w*, 1496*w*, 1453*m*, 1392*w*, 1367*m*, 1323*w*, 1298*w*, 1279*w*, 1207*s*, 1149*s*, 1105*w*, 1022*m*, 970*w*, 943*w*, 848*w*, 798*w*, 744*m*, 696*m*, 619*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 12.35 (br. *s*, OH); 10.54 (br. *s*, NH); 8.57 (*s*, H–C(2′)); 7.47–7.33 (*m*, 5 arom. H), 5.22 (*s*, PhCH_2); 5.09 (*s*, CH_2–N(9)); 3.07 (*t*, *J* = 7.2, 2 H–C(3)); 2.82 (*t*, *J* = 7.2, 2 H–C(2)); 1.42 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 173.03 (*s*, CO_2H); 166.42 (*s*, $CO_2{}^t$Bu); 154.91 (*s*, C(8′)); 153.05 (*s*, C(4′)); 152.06 (*s*, NHCO_2Bn); 150.79 (*d*, C(2′)); 147.90 (*s*, C(6′)); 136.22 (*s*); 128.18 (2*d*); 127.76 (2*d*); 127.65 (*d*); 122.22 (*s*, C(5′)); 82.42 (*s*, Me_3C); 66.15 (*t*, PhCH_2); 43.78 (*t*, CH_2–N(9)); 38.65 (*t*, C(2)); 27.57 (*q*, Me_3C); 22.13 (*t*, C(3)). HR-MALDI-MS: 494.1450 (3, $[M+K]^+$, $C_{22}H_{25}KN_5O_6^+$; calc. 494.1442), 478.1700 (24, $[M+Na]^+$, $C_{22}H_{25}N_5NaO_6^+$; calc. 478.1703), 456.1880 (91, $[M+H]^+$, $C_{22}H_{26}N_5O_6^+$; calc. 456.1883), 422.1070 (10, $[M-{}^t\mathrm{Bu}+H+Na]^+$, $C_{18}H_{17}N_5NaO_6^+$; calc. 422.1077), 400.1252 (100, $[M-{}^t\mathrm{Bu}+2\,H]^+$, $C_{18}H_{18}N_5O_6^+$; calc. 400.1257). 356.1356 (13, $[M-CO_2{}^t\mathrm{Bu}+2\,H]^+$, $C_{17}H_{18}N_5O_4^+$; calc. 356.1359). Anal. calc. for $C_{22}H_{25}N_5O_6$ (455.46): C 58.02, H 5.53, N 15.38; found: C 57.99, H 5.45, N 15.15.

N^6*-[(Benzyloxy)carbonyl]-8-[2-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)ethyl]adenine-9-acetic Acid* (**62**). A soln. of **47** (1.50 g, 2.31 mmol) in CH_2Cl_2 (23 ml) was treated with $HSiEt_3$ (3.69 ml, 23.1 mmol) and TFA (7.13 ml, 10.6 mmol), and stirred for 16 h at r.t. After evaporation at 30°, the residue was treated with ^{i}Pr$_2$O (50 ml). The precipitate was filtered off, ground, and washed several times with ^{i}Pr$_2$O. Drying of the solid gave **62** (1.36 g, 98%). White solid. R_f (CH_2Cl_2/MeOH 3:2) 0.50. M.p. 110.8–115.1°. UV (MeOH): 210 (49340), 266 (26500), 300 (4240). IR (ATR): 3435–2765*w* (br.), 3036*w*, 3032*w*, 2950*w*, 1713*m* (br.), 1658*m*, 1615*m*, 1529*m*, 1498*w*, 1450*m*, 1414*w*, 1366*w*, 1322*w*, 1207*s*, 1171*s*, 1137*s*, 1106*m*, 1078*w*, 1034*w*, 968*w*, 900*w*, 796*w*, 758*m*, 739*s*, 696*m*, 663*w*, 620*w*. ^{1}H-NMR (400 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 13.48 (br. *s*, CO_2H); 10.64 (br. *s*, NH–C(6)); 8.58 (*s*, H–C(2)); 7.88–7.28 (*m*, 13 arom. H, N*H*Fmoc); 5.22 (*s*, PhCH_2); 5.04 (*s*, CH_2–N(9)); 4.32 (*d*, *J* = 6.8, CH_2–C(9″)); 4.21 (*t*, *J* = 6.6, H–C(9″)); 3.48 (*q*, *J* = 6.4, 2 H–C(2′)); 3.01 (*t*, *J* = 7.0, 2 H–C(1′)). ^{13}C-NMR (400 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 167.04 (*s*, CO_2H); 154.23 (*s*, NHCO_2Fm); 152.01 (*d*, C(2)); 151.22 (*s*, C(8)); 150.33 (*s*, C(4)); 149.08 (*s*, NHCO_2Bn); 146.23 (*s*, C(6)); 142.00 (2*s*); 138.89 (2*s*); 134.47 (*s*); 126.53–123.25 (11*d*); 120.40 (*s*, C(5)); 118.24 (2*d*); 64.45 (*t*, PhCH_2); 63.54 (*t*, CH_2–C(9″)); 44.87 (*d*, C(9″)); 41.43 (*t*, CH_2–N(9)); 36.09 (*t*, C(2′)); 25.45 (*t*, C(1′)). HR-MALDI-MS: 615.1972 (44, $[M+Na]^+$, $C_{32}H_{28}N_6NaO_6^+$; calc. 615.1968), 593.2143 (100, $[M+H]^+$, $C_{32}H_{29}N_6O_6^+$; calc. 593.2149), 549.2227 (14, $[M-CO_2+H]^+$, $C_{31}H_{29}N_6O_4^+$; calc. 549.2250), 485.1569 (30, $[M-BnO]^+$, $C_{25}H_{21}N_6O_5^+$; calc. 485.1573).

N-*[2-Amino-6-(benzyloxy)-5-nitrosopyrimidin-4-yl]-3-(phthalimido)propanamide* (**63**). A suspension of **37** (17.2 g, 70.2 mmol) in CH_2Cl_2 (700 ml) was cooled to 0°, treated with **69** (19.6 g, 77.2 mmol), stirred for 5 min, warmed to r.t., stirred for another 2 h, and filtered. The filtrate was washed with 0.1M NaOH (5×), dried ($MgSO_4$), filtered, and evaporated. The combined solids of the first filtration and of the evaporation were dried to afford **63** (29.3 g, 94%). Green powder. R_f (CH_2Cl_2/MeOH 19:1) 0.44. M.p. 170.0–175.1°. UV (MeOH): 348 (13060), 242 (12760). IR (ATR): 3326*w*, 3241*w*, 1771*w*, 1706*s*, 1643*m*, 1593*s*, 1544*s*, 1468*s*, 1449*m*, 1394*s*, 1344*s*, 1309*m*, 1267*m*, 1206*s*, 1190*s*, 1170*s*, 1152*s*, 1111*m*, 1073*m*, 1003*m*, 985*w*, 972*w*, 912*w*, 884*w*, 870*m*, 847*w*, 793*m*, 774*w*, 745*w*, 714*s*, 699*m*, 672*w*, 639*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO); assignments based on a HSQC and a HMBC spectrum): 12.19 (*s*, NH); 8.74, 8.65 (2*s*, NH_2); 7.88–7.80 (*m*, 4 arom. H); 7.56–7.36 (*m*, 5 arom. H); 5.61 (*s*, PhCH_2); 3.89 (*t*, *J* = 6.9, 2 H–C(3)); 3.24 (*t*, *J* = 6.9, 2 H–C(2)). ^{13}C-NMR (75 MHz, (D_6)DMSO); assignments based on a HSQC and a HMBC spectrum): 172.76 (*s*, C(1)); 167.38 (2*s*, 2 C=O); 163.13 (*s*, C(6′)); 138.40 (*s*, C(4′));

135.44 (*s*); 134.21 (2*d*); 131.41 (2*s*); 128.64–122.87 (7*d*); 68.52 (*t*, Ph*C*H$_2$); 37.59 (*t*, C(3)); 33.25 (*t*, C(2)); signals of C(2′) and C(5′) hidden due to coalescence. HR-MALDI-MS: 485.0961 (16, $[M+K]^+$, $C_{22}H_{18}KN_6O_5^+$; calc. 485.0976), 469.1211 (52, $[M+Na]^+$, $C_{22}H_{18}N_6NaO_5^+$; calc. 469.1236), 447.1403 (73, $[M+H]^+$, $C_{22}H_{19}N_6O_5^+$; calc. 447.1417), 433.1592 (100, $[M-O+3\,H]^+$, $C_{22}H_{21}N_6O_4^+$; calc. 433.1624), 416.1339 (100, $[M-NO]^+$, $C_{22}H_{18}N_5O_4^+$; calc. 416.1353), 379.0735 (8, $[M-Tol+H+Na]^+$, $C_{15}H_{12}N_6NaO_5^+$; calc. 379.0767), 357.0931 (55, $[M-Tol+2\,H]^+$, $C_{15}H_{13}N_6O_5^+$; calc. 357.0947).

Alkylation of **63**. A suspension of **63** (18.6 g, 41.7 mmol) and 1M Me_3P in THF (100 ml, 100 mmol) in toluene (280 ml) was subjected to a sonicator at 60° for 4 h, while the colour changed from blue over green to yellow. The suspension was cooled to 4°. The solid was filtered off, ground, and washed with toluene, H_2O, and Et_2O. Drying gave the crude 8-alkylated guanine (13.7 g, 33.0 mmol). A suspension of the 8-alkylated guanine (13 g, 31.4 mmol), K_2CO_3 (13.0 g, 94.1 mmol), and Cs_2CO_3 (1.02 g, 3.14 mmol) in DMF (63 ml) was treated dropwise with $ClCH_2COO^tBu$ (5.83 ml, 40.8 mmol) over 5 min, stirred for 14 h at r.t., and poured into H_2O. The mixture was neutralized with 1M HCl and extracted with AcOEt (5×). The combined org. fractions were washed with brine (5×), dried ($MgSO_4$), filtered, and evaporated. FC (AcOEt/cyclohexane 1:1) gave **65** (10.63 g, 51% from **63**) along with **66** eluted with CH_2Cl_2/MeOH 9:1.

tert-*Butyl 6*-O-*Benzyl-8-(2-phthalimidoethyl)guanine-9-acetate* (**65**). White powder. R_f (CH_2Cl_2/MeOH 19:1) 0.40. M.p. 176.7–176.9°. UV (MeOH): 286 (15280), 217 (59340). IR (ATR): 3490*w*, 3317*w*, 3189*w*, 2968*w*, 2942*w*, 1771*w*, 1744*m*, 1717*s*, 1635*m*, 1591*s*, 1527*w*, 1492*w*, 1470*m*, 1438*m*, 1396*s*, 1378*m*, 1363*s*, 1330*m*, 1288*w*, 1255*m*, 1235*s*, 1214*m*, 1188*w*, 1153*s*, 1084*w*, 1065*m*, 1000*m*, 863*m*, 791*m*, 777*w*, 736*m*, 718*s*, 692*m*, 669*m*, 607*w*. ^{1}H-NMR (400 MHz, (D$_6$)DMSO); assignments based on a HSQC and a HMBC spectrum): 7.89–7.80 (*m*, 4 arom. H); 7.48–7.31 (*m*, 5 arom. H); 6.46 (*s*, NH_2); 5.46 (*s*, PhCH_2); 4.80 (*s*, CH_2–N(9)); 3.98 (*t*, J = 7.7, 2 H–(2′)); 3.02 (*t*, J = 7.7, 2 H–(1′)); 1.41 (*s*, ^{t}Bu). ^{13}C-NMR (100 MHz, (D$_6$)DMSO); assignments based on a HSQC and a HMBC spectrum): 167.59 (*s*, 2 C=O); 166.85 (*s*, $CO_2{}^t$Bu); 159.42 (*s*, C(2)); 159.19 (*s*, C(6)); 155.45 (*s*, C(4)); 147.66 (*s*, C(8)); 136.62 (*s*); 134.30 (2*d*); 131.66 (2*s*); 128.33–122.97 (7*d*); 112.36 (*s*, C(5)); 82.28 (*s*, Me_3C); 66.82 (*t*, PhCH_2); 43.42 (*t*, CH_2–N(9)); 34.94 (*t*, C(2′)); 27.57 (*q*, Me_3C); 25.26 (*t*, C(1′)). HR-MALDI-MS: 567.1748 (7, $[M+K]^+$, $C_{28}H_{28}KN_6O_5^+$; calc. 567.1758), 551.2016 (16, $[M+Na]^+$, $C_{28}H_{28}N_6NaO_5^+$; calc. 551.2019), 529.2203 (100, $[M+H]^+$, $C_{28}H_{29}N_6O_5^+$; calc. 529.2199), 495.1390 (2, $[M-{}^t\text{Bu}+H+Na]^+$, $C_{24}H_{20}N_6NaO_5^+$; calc. 495.1393), 473.1560 (30, $[M-{}^t\text{Bu}+2\,H]^+$, $C_{24}H_{21}N_6O_5^+$; calc. 473.1573). Anal. calc. for $C_{28}H_{28}N_6O_5$ (528.56): C, 63.63, H 5.34, N 15.90; found: C 63.65, H 5.33, N 15.53.

tert-*Butyl 6*-O-*Benzyl-8-(2-phthalimidoethyl)guanine-7-acetate* (**66**). Yellow powder. R_f (CH_2Cl_2/MeOH 19:1) 0.16. M.p. 215.8–216.2°. UV (MeOH): 297 (11700), 219 (60360). IR (ATR): 3459*w*, 3293*w*, 3171*w*, 3066*w*, 2981*w*, 1768*w*, 1737*m*, 1704*s*, 1624*s*, 1582*s*, 1504*m*, 1482*m*, 1446*m*, 1424*m*, 1409*m*, 1394*s*, 1364*s*, 1337*m*, 1329*m*, 1289*w*, 1252*m*, 1240*s*, 1221*s*, 1173*s*, 1150*s*, 1100*m*, 1086*w*, 1063*m*, 1010*m*, 988*m*, 942*w*, 906*w*, 868*w*, 851*m*, 790*s*, 744*m*, 721*s*, 695*s*, 666*m*, 623*w*. ^{1}H-NMR (400 MHz, (D$_6$)DMSO); assignments based on a HSQC and a HMBC spectrum): 7.90–7.81 (*m*, 4 arom. H); 7.49–7.34 (*m*, 5 arom. H); 6.15 (*s*, NH_2); 5.43 (*s*, PhCH_2); 4.97 (*s*, CH_2–N(7)); 3.96 (*t*, J = 7.5, 2 H–C(2′)); 3.09 (*t*, J = 7.5, 2 H–C(1′)); 1.25 (*s*, ^{t}Bu). ^{13}C-NMR (100 MHz, (D$_6$)DMSO); assignments based on a HSQC and a HMBC spectrum): 167.54 (*s*, 2 C=O of Phth); 166.88 (*s*, $CO_2{}^t$Bu); 162.68 (*s*, C(4)); 159.41 (*s*, C(2)); 155.71 (*s*, C(6)); 154.15 (*s*, C(8)); 136.30 (*s*); 134.28 (2*d*); 131.62 (2*s*); 128.30–122.96 (7*d*); 106.59 (*s*, C(5)); 81.88 (*s*, Me_3C); 66.90 (*t*, PhCH_2); 46.80 (*t*, CH_2–N(7)); 35.24 (*t*, C(2′)); 27.32 (*q*, Me_3C); 24.79 (*t*, C(1′)). HR-MALDI-MS: 567.1745 (10, $[M+K]^+$, $C_{28}H_{28}KN_6O_5^+$; calc. 567.1758), 551.2010 (30, $[M+Na]^+$, $C_{28}H_{28}N_6NaO_5^+$; calc. 551.2019), 529.2185 (98, $[M+H]^+$, $C_{28}H_{29}N_6O_5^+$; calc. 529.2199), 511.1129 (6, $[M-{}^t\text{Bu}+H+K]^+$, $C_{24}H_{20}KN_6O_5^+$; calc. 511.1132), 495.1383 (9, $[M-{}^t\text{Bu}+H+Na]^+$, $C_{24}H_{20}N_6NaO_5^+$; calc. 495.1393), 473.1568 (100, $[M-{}^t\text{Bu}+2\,H]^+$, $C_{24}H_{21}N_6O_5^+$; calc. 473.1573).

tert-*Butyl 8-(2-Aminoethyl)-6*-O-*benzylguanine-9-acetate* (**67**). A suspension of **65** (10.0 g, 18.9 mmol) in EtOH (190 ml) was treated with $N_2H_4\cdot H_2O$ (18.4 ml, 378 mmol) and stirred for 3 h at r.t. The suspension turned to a soln. after 15 min and then to a viscous suspension. The suspension was filtered, the solid was washed with AcOEt, and the yellow filtrate was evaporated. The residue was diluted with H_2O and extracted with AcOEt (3×). The combined org. fractions were washed with 0.1M NaOH (3×) and brine (3×), dried ($MgSO_4$), filtered, and evaporated. Drying gave **67** (6.52 g, 86%). White powder. R_f (CH_2Cl_2/MeOH 3:2) 0.20. M.p. 120.1–121.5°. UV (MeOH): 285 (13160), 251 (11940), 210 (34560). IR (ATR): 3481*w*, 3316*w*, 3192*w*, 2976*w*, 2935*w*, 2876*w*, 1738*m*, 1612*s*, 1587*s*, 1483*m*, 1428*m*,

1355*m*, 1311*m*, 1232*s*, 1149*s*, 1082*m*, 1062*m*, 1029*w*, 988*w*, 941*w*, 910*w*, 861*w*, 844*w*, 789*m*, 737*m*, 697*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO); assignments based on a HSQC and a HMBC spectrum): 7.53–7.34 (*m*, 5 arom.); 6.43 (*s*, NH_2); 5.48 (*s*, PhCH_2); 4.79 (*s*, CH_2–N(9)); 2.89 (*t*, J = 6.6), 2.71 (*t*, J = 6.7) (2 H–C(1′), 2 H–C(2′)); 1.41 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 166.89 (*s*, $CO_2{}^t$Bu); 159.11 (*s*, C(6)); 158.90 (*s*, C(2)); 155.33 (*s*, C(4)); 149.73 (*s*, C(8)); 136.55 (*s*); 128.34 (2*d*); 128.22 (2*d*); 127.86 (*d*); 112.12 (*s*, C((5)); 81.97 (*s*, Me_3C); 66.63 (*t*, PhCH_2); 43.31 (*t*, CH_2–N(9)); 39.41 (*t*, C(2′)); 30.56 (*t*, C(1′)); 27.43 (*q*, Me_3C). HR-MALDI-MS: 437.1718 (4, $[M+K]^+$, $C_{20}H_{26}KN_6O_3^+$; calc. 437.1703), 421.1969 (11, $[M+Na]^+$, $C_{20}H_{26}N_6NaO_3^+$; calc. 421.1964), 399.2136 (100, $[M+H]^+$, $C_{20}H_{27}N_6O_3^+$; calc. 399.2145), 365.1330 (2, $[M-{}^t\text{Bu}+H+Na]^+$, $C_{16}H_{18}N_6NaO_3^+$; calc. 365.1338), 343.1505 (77, $[M-{}^t\text{Bu}+2H]^+$, $C_{16}H_{19}N_6O_3^+$; calc. 343.1519).

*8-[2-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)ethyl]guanine-9-acetic Acid* (**68**). A suspension of **48** (7.80 g, 12.6 mmol) in CH_2Cl_2 (130 ml) was treated with Et_3SiH (10.0 ml, 62.8 mmol) and TFA (93.3 ml, 1.26 mol). The resulting soln. was stirred for 18 h at r.t. and evaporated at 30°. The residue was suspended in Et_2O (200 ml). The solid was filtered off, ground, and washed several times with Et_2O. Drying of the solid gave **68** (5.84 g, 98%). White powder. R_f (CH_2Cl_2/MeOH 3:2) 0.14. M.p. 183.3–194.2°. UV (MeOH): 287 (14800), 254 (11580), 211 (35320). IR (ATR): 3324*w*, 3207*w*, 3162*w*, 3064*w*, 2945*w*, 2737*w*, 1692*s*, 1632*s*, 1592*s*, 1541*m*, 1449*m*, 1368*m*, 1248*m*, 1196*m*, 1186*m*, 1137*m*, 1075*w*, 1059*w*, 1005*w*, 862*w*, 828*w*, 797*w*, 772*w*, 759*m*, 739*s*, 698*w*, 647*w*, 620*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 13.35 (br. *s*, CO_2H); 10.82 (*s*, H–N(1)); 7.90–7.25 (*m*, 5 arom. H, N*H*Fmoc); 6.67 (*s*, NH_2); 4.77 (*s*, CH_2–N(9)); 4.32 (*d*, J = 6.5, CH_2–C(9″)); 4.22 (*t*, J = 6.4, H–C(9″)); 3.38 (*q*, J = 6.5, 2 H–C(2′)); 2.85 (*t*, J = 7.2, 2 H–C(1′)). ^{13}C-NMR (75 MHz, (D_6)DMSO; assignments based on a HSQC and a HMBC spectrum): 168.68 (*s*, CO_2H); 155.86 (*s*, NHCO_2Fm); 155.44, 153.71 (2*s*, C(2), C(6)); 151.52 (*s*, C(4)); 146.07 (*s*, C(8)); 143.66 (2*s*); 140.53 (2*s*); 128.49–119.95 (8*d*); 112.90 (*s*, C(5)); 65.35 (*t*, CH_2–C(9″)); 46.67 (*d*, C(9″)); 43.11 (*t*, CH_2–N(9)); 38.04 (*t*, C(2′)); 26.70 (*t*, C(1′)). HR-MALDI-MS: 513.1287 (14, $[M+K]^+$, $C_{24}H_{22}KN_6O_5^+$; calc. 513.1289), 497.1545 (29, $[M+Na]^+$, $C_{24}H_{22}N_6NaO_5^+$; calc. 497.1549), 475.1728 (100, $[M+H]^+$, $C_{24}H_{23}N_6O_5^+$; calc. 475.1730).

N-*Phthaloyl-β-alanyl Chloride* (**69**). A suspension of *N*-phthaloyl-β-alanine (20 g, 81.6 mmol) in CH_2Cl_2 (370 ml) was treated with 2M oxalyl chloride in CH_2Cl_2 (91.2 ml, 182 mmol) and stirred for 16 h at r.t. Evaporation of the colourless soln. gave **69** (22.7 g, 98%). Spectroscopic data were in agreement with [38].

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