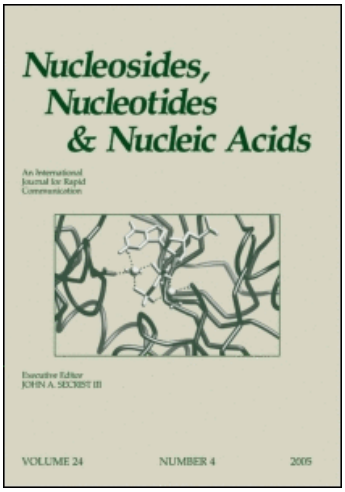

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SYNTHESIS OF RACEMIC CARBOACYCLONUCLEOSIDES DERIVED FROM BUTANE-1, 4-DIOL AND HEXANE-1, 6-DIOL

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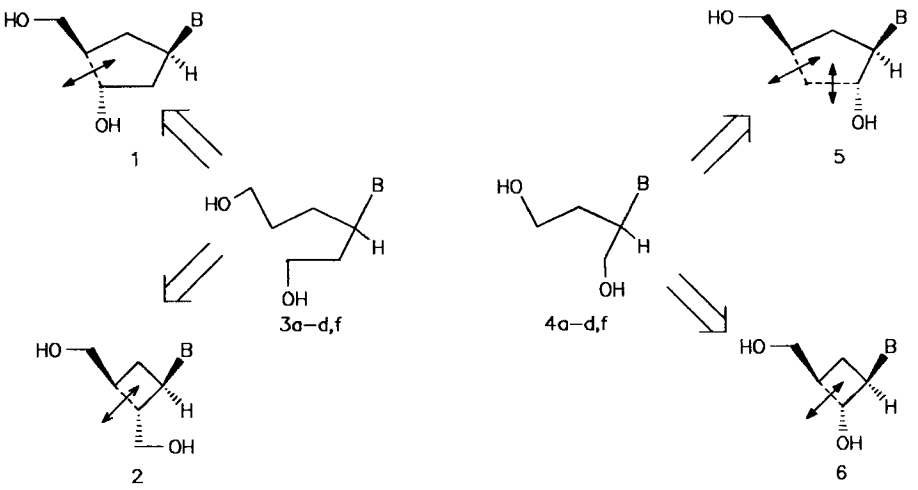
Abstract: The synthesis of racemic diethyl succinate and dimethyl adipate substituted in their 2 and 3 position respectively by usual heterocyclic bases are described *via* the Michael addition of nucleobases on diethyl maleate and dimethyl (E)-3-hexene-1, 6-dioate. The Michael adducts are further reduced to afford the corresponding carboacyclonucleosides.

The chemistry and biology of carbocyclic nucleoside analogues have been the subject of intense research during the past decades.[1-4] To date, most of the serious candidates or already approved antiviral drugs belong to the nucleoside family. In this field, a special mention must be devoted to the carbocyclic[5-12] nucleosides or their corresponding dideoxy didehydro derivatives[13-14] or the carbocyclic analogues[15-17] of oxetanocin. Research of new antiviral drugs which exhibit high therapeutic indexes must be worth pursuing for their clinical potential.

In this respect, we wish to report herewith the synthesis and the biological evaluation of racemic carboacyclic nucleosides **3** and **4** derived from hexane-1, 6-diol and butane-1, 4-diol respectively (scheme 1). Formally, the first ones (C6 series) can be considered as structural acyclic isomers of 2'-deoxycarbanucleosides **1** and carbaoxetanocin analogues **2**, while the second ones (C4 series) are related to 3'-deoxycarbanucleosides[18] **5** and carbocyclic *nor*oxetanocin[19] **6** after cleavage of the appropriate C-C bonds and deletion of *exo* methylene as figured on scheme 1. It is worth noting that the carboacyclonucleosides **3** and **4** are mainly characterized by a nucleobase linked to a secondary chiral center and that they are not directly attainable from the above cited biologically active parent molecules. Despite the large number[20] of carboacyclic nucleosides synthesized, a few related structures have been reported to our knowledge: *i.e.* threitol and xylitol containing theophylline[21-22] or adenine[22], or

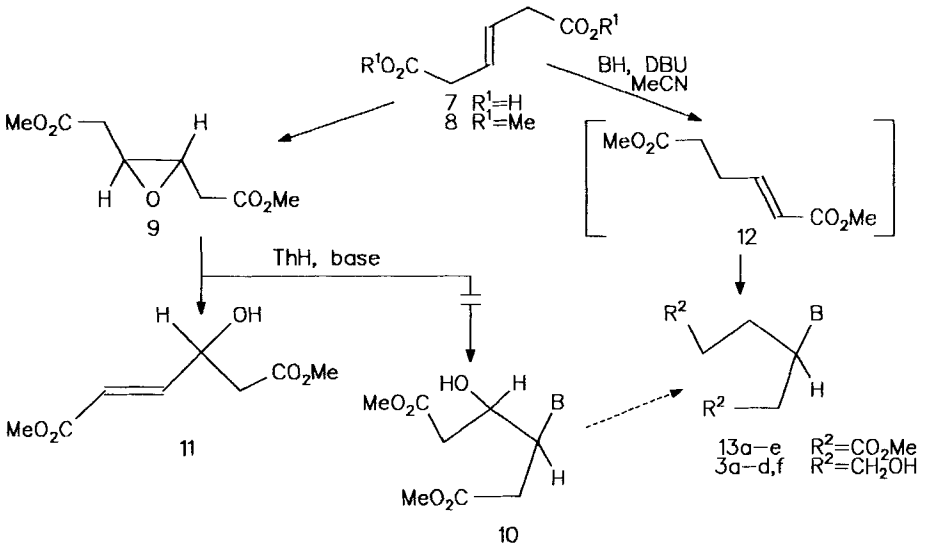


Scheme 1. a: B=Ad; b: B=Cy; c: B=Th; d: B=Ur; f: B=Gu

some EHNA analogues.[23] The major problem we are faced with the synthesis of trifunctional molecules as **3** and **4** is the introduction of the nucleobase (B) in the desired position. Essentially two strategies were envisioned to reach the compounds **3** of the C6 series: the first one focused on the nucleophilic opening of epoxide **9** by nucleobases and the second one was concerned by the conjugate addition of heterocyclic bases on α, ß-unsaturated ester **12**. The later approach was used to obtain the derivatives **4** belonging to the C4 series.

We took advantage of the easy availability of racemic and homochiral *trans* epoxide[24-25] **9** from ß-hydromuconic acid **7** which could provide after a three-step sequence (epoxide opening, deoxygenation and reduction) the expected carboacyclic nucleosides **3** (scheme 2). Concerning the crucial ring opening step of **9**, several attempts were performed using sodium salt of thymine in various conditions of solvent and temperature. In all cases, the epoxydiester **9** was readily rearranged into the known[25] ethylenic hydroxydiester **11** without any trace of the substitution derivative **10**.

So, we investigated the second route involving the Michael addition of nitrogen nucleophiles to α, ß-unsaturated carbonyl compounds, for it constitutes a very convenient procedure to introduce amino functionality to the ß-position of carbonyl compounds.[26] Purines and pyrimidines have been sparingly[27-34] reported in Michael-



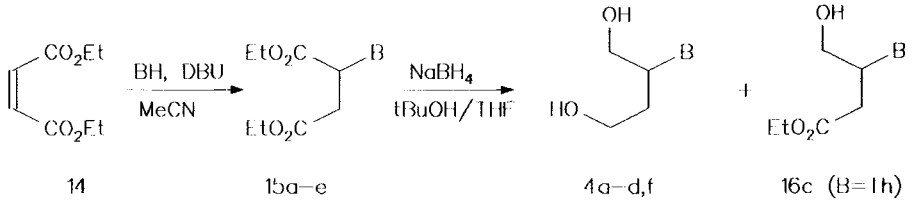
Scheme 2. a: B=Ad; b: B=Cy; c: B=Th; d: B=Ur; e: B=Gu^{dpc}_{Ac}; f: B=Gu

type reactions. Unlike secondary amines, heterocyclic bases considered as weak nucleophiles need a prior activation step either by trimethylsilylation or by a base (EtONa, K_2CO_3, Et_3N, DBU). Moreover, Michael acceptors involved in these reactions were essentially constituted by acrylonitrile, propynal, ethyl acrylate, unsaturated lactone or unsaturated sugar aldehyde.

Recently, a procedure[34] has been developed for the synthesis of acyclonucleosides using α, ß-unsaturated esters with a catalytic amount of DBU in acetonitrile. We chose this process and investigated the nucleophilic conjugate addition of nucleobases on two elected unsaturated diesters such as dimethyl (E)-2-hexene-1, 6-dioate **12** and diethyl maleate **14**, in order to obtain the adducts **13** and **15** precursors of the desired carboacyclic nucleosides **3** and **4**.

Conjugate addition of nucleobases to diethyl maleate 14.

Preliminary experiments were performed on C4 series (scheme 3) in order to optimize the chemical yields. The diethyl maleate **14** (4.5 equiv.) dissolved in dry acetonitrile (5 ml/mmol) was reacted with the unprotected nucleobase (1 equiv.), DBU (0.05 equiv.) and stirred at room temperature. The reaction was stopped after 1-6 days when no more evolution was observed on tlc. The solvent was removed under reduced pressure and the crude residue chromatographed on silica gel. The N-1 pyrimidyl and



Scheme 3. a: B=Ad; b: B=Cy; c: B=Th; d: B=Ur; e: B=Gu^{dpc}_{Ac}; f: B=Gu

N-9 purinyl adducts **15a-e** were obtained regiospecifically with good yields (Table 1) for cytosine (**15b**, 88%) and thymine (**15c**, 95%) whereas they were lower for uracil (**15d**, 40%) and adenine (**15a**, 5%). No reaction occurred with guanine probably due partly to its poor solubility in acetonitrile which constitutes a major drawback in this type of reaction. We enhanced significantly the yields by using a larger amount of DBU (1.5 equiv.) in the same conditions as before (**15a**, 41%; **15b**, 93%; **15c**, 98%; **15d**, 80%). The regioisomerism was ascertained by U.V. spectroscopy in three different media by comparison with maxima absorptions reported[35-36] for known monosubstituted nucleobases.

Concerning the case of guanine or its $\underline{N}^2$-isobutyryl derivative, we obtained in both cases, because of the complete *in situ* removal of the isobutyryl group by DBU, the same complex mixture (comparison on tlc) without addition product. By using $\underline{N}^2$-acetyl $\underline{O}^6$-diphenylcarbamoylguanine[37] instead of guanine, the expected adduct **15e** was isolated but in a low yield. Whatever the amount of DBU (0.05 or 1.5 equiv.), the yields in **15e** were comparable (31-34%). It is worth noting that while Gu^{dpc}_{Ac} is completely soluble when using an excess of DBU the yield is not increased accordingly. The chemical yield in **15e** was improved from 34 to 77% by performing the reaction without solvent (31 equiv. of **14** and 1.5 equiv. of DBU). Some additional experiments have been made on **15c** in particular scaling up (8 to 50 mmol of thymine) and use of different ratios of Michael acceptor (7.5, 4.5 and 1.5 equiv.) to afford similar and reproductible results.

In the course of these 1, 4-additions we observed the expected partial isomerization of diethyl maleate into diethyl fumarate which could be rationalized by the assumed[38] reversibility of the Michael addition reaction. In fact, the sole DBU (0.05 or 1.5 equiv.) in acetonitrile is able to isomerize diethyl maleate to give after 5h at room temperature a mixture maleate/fumarate (55/45 or 5/95), which parallels a

Table 1. Yields of Michael Addition of Nucleobases on Unsaturated Diesters 14 and 8.

		a	b	c	d	e	f
	DBU equiv.	Ad	Cy	Th	Ur	Gu^{dpc}_{Ac}	Gu
Diesters 15 from 14 C4 series	0.05	5	88	95	40	31	(a)
	1.5	41	93	98	80	34	(a)
		98(b)	–	–	–	77(b)	–
Diesters 13 from 8 C6 series	1.5	60	34	91	64	29	–
		–	98(b)	–	–	78(b)	–

a-The formation of the adduct is not observed; b-Reactions performed with 30 equiv. of diester without acetonitrile.

recent finding[39] on the dimethyl maleate-fumarate isomerization (THF, RT, 4.5 h) in the presence of LiBr/DBU (1.1:1 equiv./equiv.) (4:5 mixture maleate/fumarate) whose mechanism is not clear so far.

Michael addition of nucleobases on unconjugated dimethyl (E)-3-hexene-1, 6-dioate 8.

The procedure used for the C4 series was extended to the C6 series by using 1.5 equiv. of DBU. This allowed us to isolate from unsaturated diester **8** the expected N-1 pyrimidyl and N-9 purinyl adducts **13a-e** with moderate to fair yields (scheme 2, Table 1). It is worth mentioning that dimethyl (E)-3-hexene-1, 6-dioate[40] **8** resulting from Fischer esterification of commercially available (E)-ß-hydromuconic acid **7** was conjugated[41] *in situ* with DBU to afford dimethyl (E)-2-hexene-1, 6-dioate **12** avoiding its cumbersome preparation.[42]

Reduction of the C6 and C4 diesters 13a-e and 15a-e.

In order to prevent from a retro-Michael reaction, the reduction of diesters functionalized by an heterocyclic base had to be performed carefully. First assays were done on diethyl 2-(1-thymyl) succinate **15c**. $NaBH_4$ (1.82 mol/mol of **15c**) in THF/*t*BuOH (2:1) afforded (from 0°C to RT) a mixture (3:1) of diol **4c** and monoester **16c** with a 77% overall yield. The observed selective reduction at C-1' is coherent

Table 2. Yields of Reduction Reactions of Michael Adducts by $NaBH_4$ in THF/tBuOH.

DIESTERS	a	b	c	d	e
	Ad	Cy	Th	Ur	Gu^{dpc}_{Ac}
DIOLS	a	b	c	d	f
	Ad	Cy	Th	Ur	Gu
Diols 4 C4 series	55	22(a,b)	85	83	93(d)
Diols 3 C6 series	38	25(c) 23(b)	87	98(a)	82(c)

a-$CaBH_4$ in THF/tBuOH; b-Reductions by $NaBH_4$, acetylation then deacetylation; c-$LiAlH_4$/THF; d-Reduction by $NaBH_4$ followed by a treatment with methanolic ammonia.

with regioselectivities reported on closely related structures[43-46] (substituted or unsubstituted malate and aspartate derivatives).

The complete reduction of the two esters functions was achieved by using a larger excess of $NaBH_4$ (5.66 mol/mol of **15c**) and the expected diol **4c** was isolated with a 85% yield. The reductions were mainly performed according to these last experimental conditions (table 2). The extent of retro-Michael reaction was minimized in some cases by using $CaBH_4$ or $LiAlH_4$ in place of $NaBH_4$.

Concerning the diols **3b** and **4b** derived of cytosine, difficulties arose during the purification step due to their proximity (tlc) with the liberated cytosine. So the crude reduction mixtures were acetylated (Ac_2O, pyridine) and the resulting acetylated cytosine more easily separated at this stage. Further deacylation (methanolic ammonia) afforded the expected diols **3b** and **4b**.

For guanine derivatives **13e** and **15e**, the reductions were done either by $LiAlH_4$ which simultaneously reduced ester functions and removed the acetyl and diphenycarbamoyl protecting groups, or by $NaBH_4$ followed by a methanolic ammonia treatment.

Compounds **3a-f** and **4a-f** were tested *in vitro* against HIV and several other virus strains. Only the C4 diol **4d** derived from uracil exhibited a marginal activity against HIV.

In conclusion, this work deals with efficient experimental conditions in order to perform successfully the conjugate addition of usual heterocyclic bases on α, ß-unsaturated esters. The corresponding reduced Michael adducts containing the five common nucleobases are described.

Experimental

M.p.s were obtained with a Büchi (capillary) apparatus and were uncorrected. UV spectra were determined on a Uvikon-810 spectrophotometer. Elemental analyses were performed by the 'Service de Microanalyse du CNRS, Division de Vernaison'. ^{1}H NMR spectra were determined on a Brüker AC250, or a Varian EM390 spectrometer. *J* Values are given in Hz. Mass spectra were obtained with a Jeol JMS-DX300 by the FAB ionization method.

Michael Additions. General Procedure for the Preparation of Diesters **13a**-f *and* **15a**-f. Diethyl maleate **14** or dimethyl (E)-3-hexene-1, 6-dioate **8** (4.5 mmol) in acetonitrile (20 cm^3) was reacted with nucleobase (Ad, Cy, Th, $Gu^{dpc}{}_{Ac}$, Ur) (1 mmol) with a variable amount of DBU (0.05 or 1.5 mmol). The heterogeneous solution was stirred at room temp. 1 to 6 d. The solvent was removed under reduced pressure to give an oil which was chromatographed on a silica gel column using methanol-dichloromethane as the eluting system. Chemical yields are reported in the table 1.

Diethyl 2-(9-adenyl)succinate **15a**. The *title compound* was obtained as a solid following the aforementioned procedure (6 d). After chromatography with methanol (0 to 2%) in dichloromethane as the eluent **15a** was isolated; R_f 0.17 (methanol-dichloromethane 5:95), m.p. 116-119°C, λ_{max}(EtOH, 95%)/nm 259.5, λ_{max}(0.1 mol dm^{-3} HCl)/nm 258, λ_{max}(0.1 mol dm^{-3} KOH)/nm 259.5, δ_H(250 MHz; $CDCl_3$) 1.20 (3 H, t, $J_{CH_2CH_3}$ 7.21, CH_3CH_2O), 1.21 (3 H, t, $J_{CH_2CH_3}$ 7.21, CH_3CH_2O), 3.25 (1 H, dd, $J_{3'-3''}$ 17.44, $J_{2'-3''}$ 5.09, 3"-H), 3.38 (1 H, dd, $J_{2'-3'}$ 7.4, 3'-H), 4.12 (1 H, q, $J_{CH_2CH_3}$ 7.11, CH_3CH_2O-C1), 4.127 (1 H, q, $J_{CH_2CH_3}$ 7.11, CH_3CH_2O-C1), 4.28 (2 H, q, $J_{CH_2CH_3}$ 7.14, CH_3CH_2O-C4), 5.65 (1 H, dd, 2'-H), 5.9 (2 H, s, NH_2), 8.02 (1 H, s, 2-H) and 8.34 (1 H, s, 8-H); m/z 308 $[MH]^+$ and 136 $[BH_2]^+$; (Found: C, 50.64; H, 5.59; N, 22.41. $C_{13}H_{17}N_5O_4$ requires C, 50.80; H, 5.57; N, 22.78%).

Diethyl 2-(1-cytosyl)succinate **15b**. The *title compound* was obtained as a solid following the aforementioned procedure (4 d). After chromatography with methanol (0 to 4%) in dichloromethane as the eluent **15b** was isolated; R_f 0.07 (methanol-dichloromethane 5:95), m.p. 176-179°C, λ_{max}(EtOH, 95%)/nm 270,

λ_{max}(0.1 mol dm^{-3} HCl)/nm 278, λ_{max}(0.1 mol dm^{-3} KOH)/nm 276, δ_H(250 MHz; $CDCl_3$) 1.13 (3 H, t, $J_{CH_2CH_3}$ 7.03, CH_3CH_2O), 1.16 (3 H, t, $J_{CH_2CH_3}$ 7.03, CH_3CH_2O), 2.98 (1 H, dd, $J_{3'-3''}$ 16.7, $J_{2'-3''}$ 7.96, 3"-H), 3.15 (1 H, dd, $J_{2'-3'}$ 6.15, 3'-H), 4.10 (2 H, m, CH_3CH_2O), 5.02 (1 H, dd, 2'-H), 5.67 (1 H, d, J_{5-6} 7.31, 5-H), 7.2 (2 H, s, NH_2), 7.63 (1 H, d, 6-H) and 10.4 (1 H, s, 3-NH); m/z 284 $[MH]^+$ and 112 $[BH_2]^+$; (Found: C, 51.06; H, 5.98; N, 14.48. $C_{12}H_{17}N_3O_5$ requires C, 50.87; H, 6.04; N, 14.83%).

Diethyl 2-(1-thymyl)succinate **15c**. The *title compound* was obtained as a solid following the aforementioned procedure (1 d). After chromatography with methanol (0 to 5%) in dichloromethane as the eluent **15c** was isolated; R_f 0.46 (methanol-dichloromethane 5:95), m.p. 102-104°C, λ_{max}(EtOH, 95%)/nm 265, λ_{max}(0.1 mol dm^{-3} HCl)/nm 265, λ_{max}(0.1 mol dm^{-3} KOH)/nm 265, δ_H(250 MHz; $CDCl_3$) 1.248 (3 H, t, $J_{CH_2CH_3}$ 7.13, CH_3CH_2O), 1.252 (3 H, t, $J_{CH_2CH_3}$ 7.13, CH_3CH_2O), 1.92 (3 H, d, $J_{6\text{-Me}}$ 1.21, 5-Me), 3.12 (1 H, dd, $J_{3'-3''}$ 17.72, $J_{2'-3''}$ 8.52, 3"-H), 3.25 (1 H, dd, $J_{2'-3'}$ 4.76, 3'-H), 4.15 (2 H, m, CH_3CH_2O), 4.25 (2 H, m, CH_3CH_2O), 4.98 (1 H, dd, 2'-H), 7.1 (1 H, s, 3-NH) and 7.16 (1 H, d, 6-H); m/z 299 $[MH]^+$ and 127 $[BH_2]^+$; (Found: C, 52.57; H, 6.08; N, 9.37. $C_{13}H_{18}N_2O_6$ requires C, 52.34; H, 6.08; N, 9.39%).

Diethyl 2-(9-uracyl)succinate **15d**. The *title compound* was obtained as a solid following the aforementioned procedure (3 d). After chromatography with methanol (0 to 2%) in dichloromethane as the eluent **15d** was isolated; R_f 0.41 (methanol-dichloromethane 5:95), m.p. 111-114°C, λ_{max}(EtOH, 95%)/nm 260, λ_{max}(0.1 mol dm^{-3} HCl)/nm 260, λ_{max}(0.1 mol dm^{-3} KOH)/nm 260, δ_H(250 MHz; $CDCl_3$) 1.239 (3 H, t, $J_{CH_2CH_3}$ 7.21, CH_3CH_2O), 1.247 (3 H, t, $J_{CH_2CH_3}$ 7.21, CH_3CH_2O), 3.11 (1 H, dd, $J_{3'-3''}$ 16.3, $J_{2'-3''}$ 8.55, 3"-H), 3.22 (1 H, dd, $J_{2'-3'}$ 4.54, 3'-H), 4.14 (2 H, m, CH_3CH_2O-C1), 4.22 (2 H, m, CH_3CH_2O-C4), 5.02 (1 H, dd, 2'-H), 5.69 (1 H, d, J_{5-6} 8.05, 5-H), 7.34 (1 H, d, 6-H) and 8.93 (1 H, s, 3-NH); m/z 285 $[MH]^+$ and 113 $[BH_2]^+$; (Found: C, 50.58; H, 5.90; N, 9.87. $C_{12}H_{16}N_2O_6$ requires C, 50.70; H, 5.67; N, 9.85%).

Diethyl 2-[9-(N^2-acetyl-O^6-diphenylcarbamoyl)guanyl]succinate **15e**. The *title compound* was obtained as a solid following the aforementioned procedure (6 d). After chromatography with methanol (0 to 2%) in dichloromethane as the eluent **15e** was isolated; R_f 0.61 (methanol-dichloromethane 5:95), (hygroscopic foam), λ_{max}(EtOH, 95%)/nm 278, 227, λ_{max}(0.1 mol dm^{-3} HCl)/nm 278, 227, λ_{max}(0.1 mol dm^{-3} KOH)/nm 278, δ_H(250 MHz; $CDCl_3$) 1.21 (3 H, t, $J_{CH_2CH_3}$ 7.14, CH_3CH_2O), 1.22 (3 H, t, $J_{CH_2CH_3}$ 7.14, CH_3CH_2O), 2.53 (3 H, s, MeCO), 3.24 (1 H, dd, $J_{3'-3''}$ 17.46, $J_{2'-3''}$ 7.4, 3"-H), 3.32 (1 H, dd, $J_{2'-3'}$ 5.09, 3'-H),

4.12 (2 H, m, CH_3CH_2O), 4.25 (2 H, m, CH_3CH_2O), 5.65 (1 H, dd, 2'-H), 7.3 (10 H, m, aromatic), 7.96 (1 H, s, 2-H) and 8.12 (1 H, s, 8-H); m/z 308 $[MH]^+$, 196 $[BH_2]^+$ and 366 $[(M+H\text{-}DPC)]^+$; (Found: C, 60.22; H, 5.29; N, 14.80. $C_{28}H_{28}N_6O_7$ requires C, 59.99; H, 5.03; N, 14.99%).

Dimethyl 3-(9-adenyl)adipate **13a**. The *title compound* was obtained as a solid following the aforementioned procedure (6 d). After chromatography with methanol (0 to 7%) in dichloromethane as the eluent **13a** was isolated; R_f 0.13 (methanol-dichloromethane 5:95), m.p. 146-148°C, λ_{max}(EtOH, 95%)/nm 260, λ_{max}(0.1 mol dm^{-3} HCl)/nm 259, λ_{max}(0.1 mol dm^{-3} KOH)/nm 260.5, δ_H(250 MHz; $CDCl_3$) 2.19 (2 H, m, 5'-H, 5"-H), 2.25 (1 H, m, 4"-H), 2.64 (1 H, m, 4'-H), 2.92 (1 H, dd, $J_{2'-3'}$ 4.76, $J_{2'-2"}$ 16.86, 2'-H), 3.35 (1 H, dd, $J_{2"-3'}$ 9.14, 2"-H), 3.59 (3 H, s, MeO), 3.61 (3H, s, MeO), 4.92 (1 H, m, 3'-H), 5.95 (2 H, s, NH_2), 7.8 (1 H, s, 2-H) and 8.3 (1 H, s, 8-H); m/z 308 $[MH]^+$ and 136 $[BH_2]^+$; (Found: C, 51.12; H, 5.71; N, 22.52. $C_{13}H_{17}N_5O_4$ requires C, 50.80; H, 5.57; N, 22.78%).

Dimethyl 3-(1-cytosyl)adipate **13b**. The *title compound* was obtained as a solid following the aforementioned procedure (6 d). After chromatography with methanol (0 to 10%) in dichloromethane as the eluent **13b** was isolated; R_f 0.05 (methanol-dichloromethane 5:95), m.p. 83-85°C, λ_{max}(EtOH, 95%)/nm 273, 239, λ_{max}(0.1 mol dm^{-3} HCl)/nm 282, λ_{max}(0.1 mol dm^{-3} KOH)/nm 274.5, δ_H(250 MHz; $CDCl_3$) 2.04 (1 H, m, 4'-H), 2.38 (2 H, m, 5'-H, 5"-H), 2.38 (1 H, m, 4"-H), 2.67 (1 H, dd, $J_{2'-3'}$ 5.05, $J_{2'-2"}$ 16.79, 2'-H), 3.15 (1 H, dd, $J_{2"-3'}$ 8.09, 2"-H), 3.63 (3H, s, MeO), 3.64 (3H, s, MeO), 4.55 (1 H, m, 3'-H), 5.79 (1 H, d, J_{5-6} 7.32, 5-H), 6.12 (1 H, s, 4-H), 7.27 (1 H, d, 6-H) and 7.55 (1 H, s, 4-H); m/z 284 $[MH]^+$ and 112 $[BH_2]^+$; (Found: C, 50.77; H, 5.97; N, 14.66. $C_{12}H_{17}N_3O_5$ requires C, 50.87; H, 6.04; N, 14.83%).

Dimethyl 3-(1-thymyl)adipate **13c**. The *title compound* was obtained as a solid following the aforementioned procedure (1 d). After chromatography with methanol (0 to 1%) in dichloromethane as the eluent **13c** was isolated; R_f 0.35 (methanol-dichloromethane 5:95), m.p. 115-117°C, λ_{max}(EtOH, 95%)/nm 269, λ_{max}(0.1 mol dm^{-3} HCl)/nm 268, λ_{max}(0.1 mol dm^{-3} KOH)/nm 268, δ_H(250 MHz; $CDCl_3$) 1.92 (3 H, d, $J_{6\text{-}Me}$ 1.07, 5-Me), 2.06 (1 H, m, 4'-H), 2.28 (1 H, m, 4"-H), 2.31 (2 H, m, 5'-H, 5"-H), 2.68 (1 H, dd, $J_{2"-3'}$ 5.06, $J_{2'-2"}$ 16.76, 2"-H), 3.04 (1 H, dd, $J_{2'-3'}$ 9, 2'-H), 3.66 (3 H, s, MeO), 3.67 (3 H, s, MeO), 4.61 (1 H, m, 3'-H), 7,00 (1 H, d, $J_{6\text{-}Me}$ 1.07, 6-H) and 9.01 (1 H, s, 3-H); m/z 299 $[MH]^+$ and 127 $[BH_2]^+$; (Found: C, 52.29; H, 6.19; N, 9.20. $C_{13}H_{18}N_2O_6$ requires C, 52.34; H, 6.08; N, 9.39%).

Dimethyl 3-(1-uracyl)adipate **13d**. The *title compound* was obtained as a solid following the aforementioned procedure (6 d). After chromatography with methanol (0 to 4%) in dichloromethane as the eluent **13d** was isolated; R_f 0.37 (methanol-dichloromethane 5:95), m.p. 88-89°C, λ_{max}(EtOH, 95%)/nm 264, λ_{max}(0.1 mol dm^{-3} HCl)/nm 267, λ_{max}(0.1 mol dm^{-3} KOH)/nm 266.5, δ_H(250 MHz; $CDCl_3$) 2.07 (1 H, m, 4'-H), 2.32 (3 H, m, 5'-H, 5"-H, 4'-H), 2.69 (1 H, dd, $J_{2"-3'}$ 4.86, $J_{2'-2"}$ 16.88, 2"-H), 3.06 (1 H, dd, $J_{2'-3'}$ 9,08, 2'-H), 3.661 (3 H, s, MeO), 3.666 (3 H, s, MeO), 4.6 (1 H, m, 3'-H), 5.7 (1 H, d, J_{5-6} 8, 5-H), 7.19 (1 H, d, 6-H) and 9.31 (1 H, s, 3-NH); m/z 285 $[MH]^+$ and 113 $[BH_2]^+$; (Found: C, 50.47; H, 5.52; N, 9.93. $C_{12}H_{16}N_2O_6$ requires C, 50.7; H, 5.67; N, 9.85%).

Dimethyl 2-[9-(N²-acetyl-O⁶-diphenylcarbamoyl)guanyl]adipate **13e**. The *title compound* was obtained as a solid following the aforementioned procedure (6 d). After chromatography with methanol (0 to 2%) in dichloromethane as the eluent **13e** was isolated; R_f 0.55 (methanol-dichloromethane 5:95), hygroscopic foam, λ_{max}(EtOH, 95%)/nm 280, λ_{max}(0.1 mol dm^{-3} HCl)/nm 280, λ_{max}(0.1 mol dm^{-3} KOH)/nm 277.5, δ_H(250 MHz; $CDCl_3$) 2.08 (2 H, m, 5'-H, 5"-H), 2.18 (1 H, m, 4'-H), 2.49 (4 H, m, 4"-H, MeCO), 2.83 (1 H, dd, $J_{2'-3'}$ 4.54, $J_{2'-2"}$ 17.04, 2'-H), 3.21 (1 H, dd, $J_{2"-3'}$ 9,35, 2"-H), 3.53 (6 H, s, 2MeO), 4.84 (1 H, m, 3'-H), 7.22 (10 H, m, aromatic), 7.84 (1 H, s, 8-H) and 7.9 (1 H, s, 2-NH); m/z 561 $[MH]^+$, 196 $[BH_2]^+$ and 366 $[(M+H\text{-}DPC)^+]$; (Found: C, 59.73; H, 5.22; N, 14.79. $C_{28}H_{28}N_6O_7$ requires C, 59.99; H, 5.03; N, 14.99%).

General Procedure for the Reduction of Diesters **13a-e** *and* **15a-e**. *Preparation of diols* ***3a-d,f*** *and* ***4a-d,f***.

The diesters ***13a-e*** and ***15a-e*** (1.63 mmol) dissolved in THF (15 ml) and *t*BuOH (7 ml) were reacted with sodium borohydride (9.22 mmol). The heterogeneous solution was stirred at room temperature 2-5 d. After a neutralization by HCl 0,1 N, the solvents were removed under reduced pressure and the resulting residue chromatographed on a silica gel column using methanol-dichloromethane as the eluting system. Chemical yields are reported in the table 2.

2-(9-Adenyl)butane-1, 4-diol **4a**. The *title compound* was obtained as a solid following the general procedure (2 d). After chromatography with methanol (0 to 20%) in dichloromethane as the eluent **4a** was isolated and crystallized in methanol; R_f 0.31 (isopropanol/ammonia/water 10:2:1), m.p. 187-188°C, λ_{max} (EtOH, 95%)/nm 260, λ_{max}(0.1 mol. dm^{-3} KOH)/nm 260, λ_{max}(0.1 mol. dm^{-3} HCl)/nm 260, δ_H (250 MHz; DMSO-d_6) 2.08 (2H, m, 3'-H, 3"-H), 3.21 (1H, m, 4"-H), 3.32 (1H, m, 4'-H), 3.7 (1H, m, 1"-H), 3.86 (1H, m, 1'-H), 4.57 (1H, t, $J_{HO\text{-}CH_2}$ 4.93, OH), 4.6

(1H, m, 2'-H), 5.03 (1H, t, $J_{HO\text{-}CH_2}$ 5.17, OH), 7.18 (2H, s, NH_2) and 8.1 (2H, s, 2-H, 8-H); m/z 224 $[MH]^+$ and 136 $[BH_2]^+$; (Found: C, 48.57; H, 6.13; N, 31.14. $C_9H_{13}N_5O_2$ requires C, 48.42; H, 5.86; N, 31.37%).

2-(1-Cytosyl)butane-1, 4-diol **4b**. The *title compound* was obtained as a solid following the general procedure (3 d) with a slight modification: after 2 d, calcium chloride (0.51 g, 4.61 mmol) was added to the solution. After chromatography with methanol (0 to 20%) in dichloromethane as the eluent a mixture of **4b** and cytosine was isolated. This mixture was then acetylated by acetic anhydride (42 mmol) in pyridine (50 ml) overnight at room temp, and the pyridine was removed under reduced pressure. The residue was extracted with dichloromethane, the organic phase washed with an aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution and dried on sodium sulfate. After removal of the solvents the triacetylated derivative of **4b** was isolated (72%) after chromatography on silica gel using methanol (0 to 4%) in dichloromethane. R_f 0.39 (methanol-dichloromethane 5:95), λ_{max} (EtOH, 95%)/nm 274.5, 224, λ_{max}(0.1 mol. dm^{-3} HCl)/nm 274, 224, λ_{max}(0.1 mol. dm^{-3} KOH)/nm 274 , δ_H(250 MHz, $CDCl_3$) 2.015 (3H, s, OAc), 2.039 (3H, s, OAc), 2.13 (2H, m, 3"-H, 3'-H), 2.27 (3H, s, NAc), 4.1 (2H, m, 4'-H, 4"-H), 4.31 (1H, dd, $J_{1"\text{-}2'}$ 3.89, $J_{1'\text{-}1"}$ 11.86, 1"H), 4.46 (1H, dd, $J_{1'\text{-}2'}$ 6.78, $J_{1'\text{-}1"}$ 11.86, 1'H), 4.9 (1H, m, 2'-H), 7.43 (1H, d, $J_{5\text{-}6}$ 7.4, 5-H), 7.59 (1H, d, $J_{5\text{-}6}$ 7.4, 6-H) and 9.71 (1H, s, 4-NH); m/z 326 $[MH]^+$

The triacetylated compound was then reacted with methanolic ammonia overnight at room temp. and the solvents removed under reduced pressure. After a chromatography on silica gel using methanol (0 to 50%) in dichloromethane **4b** was isolated. R_f 0.44 (isopropanol/ammonia/water 10:2:1), m.p. 137-140°C, λ_{max} (EtOH, 95%)/nm 275, λ_{max}(0.1 mol. dm^{-3} HCl)/nm 286.5, λ_{max}(0.1 mol. dm^{-3} KOH)/nm 275, δ_H(250 MHz, DMSO-d_6) 1.74 (2H, m, 3'-H, 3"-H), 3.36 (2H, m, 4'-H, 4"-H), 3.49 (1H, dd, $J_{1"\text{-}2'}$ 4.48, $J_{1'\text{-}1"}$ 11.5, 1"H), 3.6 (1H, dd, $J_{1'\text{-}2'}$ 6.6, $J_{1'\text{-}1"}$ 11.5, 1'H), 4.56 (1H, t, $J_{HO\text{-}CH_2}$ 5.13, 4'-OH), 4.56 (1H, s, 2'-H), 4.94 (1H, t, $J_{HO\text{-}CH_2}$ 5.31, 1'-OH), 5.69 (1H, d, $J_{5\text{-}6}$ 7.28, 5-H), 7.02 (1H, d, 3-NH), 7.55 (1H, d, $J_{5\text{-}6}$ 7.28, 6-H) and 10.39 (2H, s, 4-NH_2); m/z 200 $[MH]^+$ and 112 $[BH_2]^+$; (Found: C, 48.02; H, 6.43; N, 20.91. $C_8H_{13}N_3O_3$ requires C, 48.23; H, 6.57; N, 21.09%).

2-(1-Thymyl)butane-1, 4-diol **4c**. The *title compound* was obtained as a solid following the general procedure (4 d). After chromatography with methanol (5 to 20%) in dichloromethane as the eluent **4c** was isolated; R_f 0.5 (isopropanol/ammonia/water 10:2:1), m.p. 173-176°C, λ_{max} (EtOH, 95%)/nm 271,

λ_{max}(0.1 mol. dm^{-3} HCl)/nm 272, λ_{max}(0.1 mol. dm^{-3} KOH)/nm 271.5, δ_H(250 MHz, DMSO-d_6) 1.79 (5H, m, 3'-H, 3"-H, 5-Me), 3.36 (2H, m, 4'-H, 4"-H), 3.55 (2H, m, 1"-H, 1'-H), 4.52 (2H, m, 4'-OH, 2'-H), 4.94 (1H, s, 1'-OH), 7.5 (1H, s, 6-H) and 11.15 (1H, s, 3-NH); m/z 215 $[MH]^+$ and 127 $[BH_2]^+$; (Found: C, 50.34; H, 6.51; N, 12.90. $C_9H_{14}N_2O_4$ requires C, 50.46; H, 6.58; N, 13.07%).

Ethyl 3-(1-thymyl)-4-hydroxy butanoate **16c**. To the diester **15c** (20.5 g, 68.76 mmol) dissolved in a mixture of THF (200 ml) and *t*BuOH (100ml), was added sodium borohydride (4.75 g, 0.125 mol) and the solution was stirred at room temp. 1 d. After usual treatment and chromatography on silica gel using methanol (5 to 20%) in dichloromethane the diol **4c** (8.73 g) and the monoester **16c** (3.23 g) were separated. **16c**: R_f 0.37 (methanol-dichloromethane 10:90), m.p. 142-144°C, λ_{max} (EtOH, 95%)/nm 269, λ_{max}(0.1 mol. dm^{-3} KOH)/nm 274, λ_{max}(0.1 mol. dm^{-3} HCl)/nm 269, δ_H(250 MHz, DMSO-d_6) 1.13 (3H, t, $J_{CH_2\text{-}CH_3}$ 7.11, OCH_2CH_3), 1.77 (3H, d, $J_{5\text{-}6}$ 0.61, 5-Me), 2.73 (1H, d, $J_{3"\text{-}2'}$ 8.93, 3"-H), 2.77 (1H, d, $J_{3'\text{-}2'}$ 6.48, 3'-H), 3.6 (2H, m, 1"-H, 1'-H), 4.04 (2H, q, $J_{CH_2\text{-}CH_3}$ 7.11, OCH_2CH_3), 4.7 (1H, m, 2'-H), 5.1 (1H, t, $J_{HO\text{-}CH_2}$ 5.59, 1'-OH), 7.55 (1H, d, $J_{5\text{-}6}$ 0.61, 6-H) and 11.2 (1H, s, 3-NH); m/z 513 $[2MH]^+$, 257 $[MH]^+$ and 127 $[BH_2]^+$

2-(1-Uracyl)butane-1, 4-diol **4d**. The *title compound* was obtained as an oil following the general procedure (2 d). After chromatography with methanol (0 to 20%) in dichloromethane as the eluent **4d** was isolated; R_f 0.41 (isopropanol/ammonia/water 10:2:1), λ_{max} (EtOH, 95%)/nm 265, λ_{max}(0.1 mol. dm^{-3} HCl)/nm 267, λ_{max}(0.1 mol. dm^{-3} KOH)/nm 266, δ_H(250 MHz; DMSO-d_6) 1.79 (2H, m, 3'-H, 3"-H), 3.36 (2H, m, 4"-H, 4'-H), 3.51 (1H, dd, $J_{1"\text{-}2'}$ 4.65, $J_{1'\text{-}1"}$ 11.71, 1"-H), 3.58 (1H, dd, $J_{1'\text{-}2'}$ 7.17, $J_{1'\text{-}1"}$ 11.71, 1'-H), 4.49 (1H, m, 2'-H), 4.56 (1H, t, $J_{HO\text{-}CH_2}$ 5.2, OH), 4.97 (1H, t, $J_{HO\text{-}CH_2}$ 5.2, OH), 5.54 (1H, d, $J_{5\text{-}6}$ 7.92, 5-H), 7.6 (1H, d, $J_{5\text{-}6}$ 7.92, 6-H) et 8.9 (1H, s, 3-NH); m/z 201 $[MH]^+$ and 113 $[BH_2]^+$; (Found: C, 47.82; H, 5.85; N, 13.82. $C_8H_{12}N_2O_4$ requires C, 47.99; H, 6.04; N, 13.99%).

2-(9-Guanyl)butane-1, 4-diol **4f**. The *title compound* was obtained as an oil following the general procedure (6 d). After neutralization and removal of the solvents, the resulting crude compound was treated with methanolic ammonia (5 ml) at room temp. overnight. The solvent was evaporated under reduced pressure and the residue chromatographed on silica gel (reverse phase C2) with water as the eluent to give **4f**. R_f 0.31 (isopropanol/ammonia/water 10:2:1), λ_{max} (EtOH, 95%)/nm 251.7, 256, λ_{max}(0.1 mol. dm^{-3} HCl)/nm 256, λ_{max}(0.1 mol. dm^{-3} KOH)/nm 257, δ_H(300 MHz; DMSO-d_6) 1.96 (2H, m, 3'-H, 3"-H), 3.18 (1H, m, 4"-H), 3.31 (1H, m, 4'-H), 3.6 (1H, dd, $J_{1"\text{-}2'}$ 4.35, $J_{1'\text{-}1"}$ 11.33, 1"-H), 3.75 (1H, dd, $J_{1'\text{-}2'}$ 7,

$J_{1'-1''}$ 11.33, 1'-H), 4.41 (1H, m, OH), 4.53 (1H, m, 2'-H), 4.99 (1H, m, OH), 6.43 (2H, s, 2-NH_2), 7.65 (1H, s, 8-H) and 10.62 (1H, s, 1-NH); m/z 240 $[MH]^+$ and 136 $[BH_2]^+$; (Found: C, 44.98; H, 5.37; N, 29.02. $C_9H_{13}N_5O_3$ requires C, 45.2; H, 5.48; N, 29.29%).

3-(9-Adenyl)hexane-1, 6-diol **3a**. The *title compound* was obtained as a solid following the general procedure (5 d). After chromatography with methanol (10 to 15%) in dichloromethane as the eluent **3a** was isolated; R_f 0.64 (isopropanol/ammonia/water 10:2:1), m.p. 130-132°C, λ_{max} (EtOH, 95%)/nm 261, λ_{max}(0.1 mol. dm^{-3} HCl)/nm 261, λ_{max}(0.1 mol. dm^{-3} KOH)/nm 261, δ_H(300 MHz; DMSO-d_6) 1.1 (1H, m, 4"-H), 1.25 (1H, m, 4'-H), 1.87 (1H, m, 2"-H), 1.97 (2H, m, 5"-H, 5'-H), 2.15 (1H, m, 2'-H), 3.14 (2H, m, 6"-H, 6'-H), 3.29 (2H, m, 1"-H, 1'-H), 4.42 (1H, t, J_{HO-CH_2} 5.16, OH), 4.56 (1H, t, J_{HO-CH_2} 4.85, OH), 4.58 (1H, m, 3'-H), 7.16 (2H, s, 6-NH_2), 8.1 (1H, s, 2-H) and 8.17 (1H, s, 8-H); m/z 252 $[MH]^+$ and 136 $[BH_2]^+$; (Found: C, 52.69; H, 6.90; N, 27.72. $C_{11}H_{17}N_5O_2$ requires C, 52.57; H, 6.81; N, 27.86%).

3-(1-Cytosyl)hexane-1, 6-diol **3b**. The *title compound* was obtained as an oil according to the general procedure, followed by subsequent acetylation and deacetylation reactions in the same experimental conditions as for the diol **4b**.

Triacetylated derivative of ***3b***: R_f 0.37 (methanol-dichloromethane 5:95), δ_H(250 MHz; $CDCl_3$) 1.55 (2H, m, 2"-H, 2'-H), 1.74 (4H, m, 5"-H, 5'-H, 4"-H, 4'-H), 1.91 (3H, s, OAc), 2 (3H, s, OAc), 2.18 (3H, s, N-Ac), 3.96 (4H, m, 6"-H, 6'-H, 1"-H, 1'-H), 4.73 (1H, s, 3'-H), 7.37 (1H, d, J_{5-6} 7.42, 5-H), 7.43 (1H, d, J_{5-6} 7.42, 6-H) and 9.69 (1H, s, 4-NH); m/z 234 $[MH]^+$, 312 $[M\text{-}Ac+H]^+$ and 112 $[BH_2]^+$.

The reduction of diester **13b** (0.91 g, 3.23 mmol) was also performed by $LiAlH_4$ (0.49 g, 13 mmol) in a mixture of diethyl ether (20 ml) and dichloromethane (5 ml). The reaction was stirred at room temp. 4 d and the excess of hydride destroyed with aqueous HCl 2N. The solvents were removed under reduced pressure and the residue chromatographed on silica gel using methanol (5 to 30%) in dichloromethane as the eluting system. **3b** was isolated as an oil: R_f 0.53 (isopropanol/ammonia/water 10:2:1), λ_{max} (EtOH, 95%)/nm 273, λ_{max}(0.1 mol. dm^{-3} HCl)/nm 284, λ_{max}(0.1 mol. dm^{-3} KOH)/nm 273, δ_H(250 MHz; DMSO-d_6) 1.22 (2H, m, 5"-H, 5'-H), 1.65 (2H, m, 4"-H, 4'-H), 1.73 (2H, m, 2"-H, 2'-H), 3.26 (2H, t, $J_{6'-5'}=J_{6''-5''}$ 6.6, 6"-H, 6'-H), 3.33 (2H, t, $J_{1'-2'}=J_{1''-2''}$ 6.54, 1"-H, 1'-H), 4.43 (1H, t, J 5.17, OH), 4.49 (1H, t, J 5.21, OH), 4.54 (1H, m, 3'-H), 5.7 (1H, d, J_{5-6} 7.26, 5-H), 7.00 (2H, s, 4-NH_2), and 7.59 (1H, d, J_{5-6} 7.26, 6-H); m/z 455 $[2M+H]^+$, 250

$[M+Na]^+$, 228 $[MH]^+$ and 112 $[BH_2]^+$; (Found: C, 52.72; H, 7.42; N, 18.32. $C_{10}H_{17}N_3O_3$ requires C, 52.85; H, 7.53; N, 18.48%).

3-(1-Thymyl)hexane-1, 6-diol **3c**. The *title compound* was obtained as a solid following the general procedure (2 d). After chromatography with methanol (0 to 20%) in dichloromethane as the eluent **3c** was isolated. R_f 0.59 (isopropanol/ammonia/water 10:2:1), m.p. 71-72°C, λ_{max} (EtOH, 95%)/nm 271, λ_{max}(0.1 mol. dm^{-3} HCl)/nm 272,5, λ_{max}(0.1 mol. dm^{-3} KOH)/nm 271; δ_H(250 MHz; DMSO-d_6) 1.27 (2H, m, 5"-H, 5'-H), 1.68 (2H, m, 4"-H, 4'-H), 1.77 (2H, m, 2"-H, 2'-H), 1.78 (3H, s, 5-Me), 3.32 (4H, m, 6"-H, 6'-H, 1"-H, 1'-H), 4.43 (1H, t, JHO-CH_2 5.17, OH), 4.49 (1H, t, JHO-CH_2 4.83, OH), 4.49 (1H, m, 3'-H), 7.53 (1H, s, 6-H) et 11.09 (1H, s, 3-NH); m/z 243 $[MH]^+$ and 127 $[BH_2]^+$; (Found: C, 54.35; H, 7.38; N, 11.38. $C_{11}H_{18}N_2O_4$ requires C, 54.53; H, 7.48; N, 11.56%).

3-(1-Uracyl)hexane-1, 6-diol **3d**. The *title compound* was obtained as an oil following the general procedure (3 d). After chromatography with methanol (0 to 15%) in dichloromethane as the eluent **3d** was isolated. R_f 0.53 (isopropanol/ammonia/water 10:2:1), λ_{max} (EtOH, 95%)/nm 266, λ_{max}(0.1 mol. dm^{-3} HCl)/nm 266.5, λ_{max}(0.1 mol. dm^{-3} KOH)/nm 264; δ_H(250 MHz; DMSO-d_6) 1.28 (2H, m, 4"-H, 4'-H), 1.63 (2H, m, 5"-H, 5'-H), 1.72 (2H, m, 2"-H, 2'-H), 3.36 (4H, m, 6"-H, 6'-H, 1"-H, 1'-H), 4.48 (1H, t, JHO-CH_2 5.4, OH), 4.55 (1H, t, JHO-CH_2 5.11, OH), 4.58 (1H, m, 3'-H), 5.58 (1H, d, $J_{5\text{-}6}$ 7.92, 5-H), 7.66 (1H, d, $J_{5\text{-}6}$ 7.92, 6-H) and 11.2 (1H, s, 3-NH); m/z 229 $[MH]^+$ and 113 $[BH_2]^+$; (Found: C, 52.51; H, 7.12; N, 12.15. $C_{10}H_{16}N_2O_6$ requires C, 52.62; H, 7.06; N, 12.27%).

3-(9-Guanyl)hexane-1, 6-diol **3f**. The reduction of diester **13e** (0.41 g, 0.73 mmol) was performed by $LiAlH_4$ (0.22 g, 5.88 mmol) in a mixture of diethyl ether (10 ml) and dichloromethane (2.5 ml). The reaction was stirred at room temp. 2 d and the excess of hydride destroyed with aqueous HCl 2N. The solvents were removed under reduced pressure and the residue chromatographed on silica gel (reverse phase C2) using water as the eluent. **3f** was isolated as a solid. R_f 0.42 (isopropanol/ammonia/water 10:2:1), m.p. 180°C decomp., λ_{max} (EtOH, 95%)/nm 253.5, λ_{max}(0.1 mol. dm^{-3} HCl)/nm 255, λ_{max}(0.1 mol. dm^{-3} KOH)/nm 269; δ_H(250 MHz; DMSO-d_6) 1.13 (1H, m, 4"-H), 1.25 (1H, m, 4'-H), 1.87 (3H, m, 2"-H, 5"-H, 5'-H), 2.03 (1H, m, 2'-H), 3.14 (1H, m, 6"-H), 3.29 (3H, m, 6'-H, 1"-H, 1'-H), 4.36 (1H, m, 3'-H), 4.44 (1H, t, JHO-CH_2 4.94, OH), 4.56 (1H, t, JHO-CH_2 4.59, OH), 6.68 (2H, s, 2-NH_2), 7.42 (1H, s, 1-NH) and 7.71 (1H, s, 8-H); m/z 290 $[M+Na]^+$, 268 $[MH]^+$ and 152 $[BH_2]^+$; (Found: C, 49.31; H, 6.35; N, 26.02. $C_{11}H_{17}N_5O_3$ requires C, 49.42; H, 6.41; N, 26.20%).

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