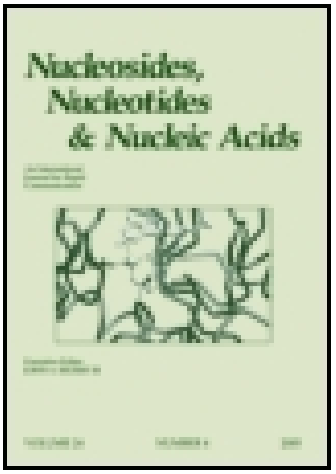

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Regioselective N^1-Alkylation of Guanosine Derivatives Protected at N^2 by an N,N-Dialkyl Amidine Group

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REGIOSELECTIVE N^1-ALKYLATION OF GUANOSINE DERIVATIVES PROTECTED AT N^2 BY AN *N,N*-DIALKYL AMIDINE GROUP

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ABSTRACT. Under Mitsunobu reaction conditions or in the presence of electrophilic alkylating reagents, alkylation of guanosine derivatives protected by an *N,N*-dialkyl amidine at the exocyclic amino group occurs selectively on nitrogen N^1 of the purine base.

Anchoring biologically relevant organic compounds to a support has become important for many applications such as liposome preparation[1], electrode functionali-zation[2], protein two-dimensional crystallization[3], catalytic antibody production[4], and of course solid phase chemistry and combinatorial chemistry. In the course of our development of GDP analogues anchored to a lipid support[5] or a protein carrier[6], we needed an efficient preparation of guanosine derivatives bearing aliphatic linkers on the purine base. For this purpose we examined the alkylation reaction of guanosine derivatives protected at the exocyclic primary amine by different *N,N*-dialkyl amidine groups. Using previously described procedures, we carried out alkylations either under Mitsunobu conditions or in the presence of electrophilic alkylating agents (Fig. 1). Herein we present some typical results of efficient and regioselective functionalization of guanosine derivatives at the N^1 position.

The alkylation of guanosine derivatives (unprotected at N^2 [7-13], acylated[14-22] or alkylated at N^2 [23-25]) *via* the Mitsunobu reaction has been extensively described in the literature to give selectively O^6-alkylation products. The literature concerning the direct alkylation reaction of guanine derivatives (either with the exocyclic amine free[12], acylated[26,27], or alkylated[27-31]) with electrophilic reagents indicates the formation of complex mixtures of products modified on the N^1, N^2, N^7, or O^6 positions. However, we found that when the exocyclic amine of the purine is protected as an *N,N*-dialkyl amidine, the

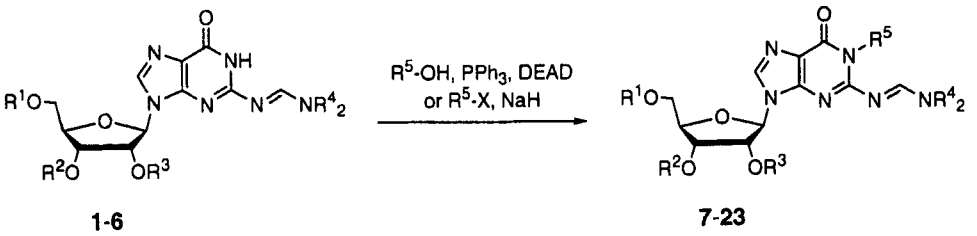


Figure 1

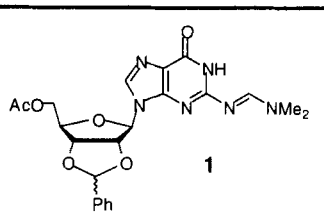
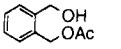
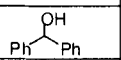
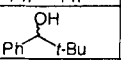
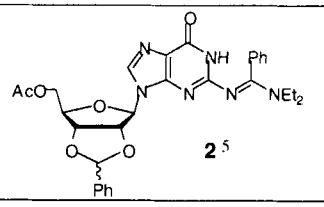
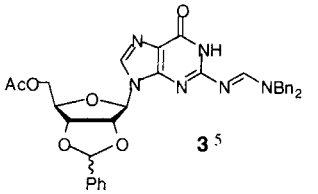
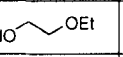
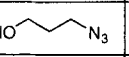
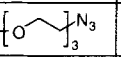
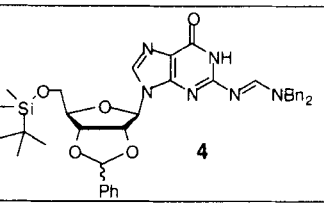
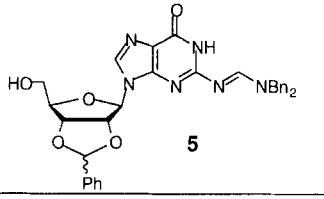
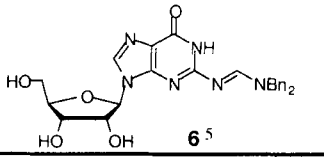
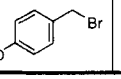
alkylation reaction becomes regioselective favoring compounds alkylated at N^1 (Table 1). These results indicate that the formamidine protective group is responsible for the unusual orientation of the alkylation reactions at N^1. Both the Mitsunobu and the direct alkylation reactions provide high yields and tolerate various protective groups such as acetals, esters and silyl ethers. A significant difference between the two procedures resides in that full protection of the ribose is required when using the Mitsunobu reaction pathway in order to avoid the formation of different alkoxyphosphonium species at the sugar moiety. That is not necessary when performing the direct alkylation reaction with an electrophile, provided the reagent is used in stoichiometric amount (Entries 12 to 16).

Considering that some examples of nucleophilic displacements by nitrogen atoms N^3 and N^7 in guanine derivatives have been reported in the literature under the conditions of the Mitsunobu reaction[32-34] or under basic conditions[29,35-42], the alkylation site had to be unambiguously assigned in our experiments. UV and NMR (^{13}C, ^{1}H-^{13}C correlations or NOE experiments) analyses allowed us to definitely rule out the N^7 and O^6 positions[43]. The collected data however did not allow distinction between N^1 and N^3 alkylations. The general structure assignment was ultimately achieved by radiocrystallography performed on one compound of the series. Removal of the formamidine protective group in compound **18** with potassium *t*-butoxide in *t*-butanol afforded compound **24** (Fig. 2) which structure could be established by X-rays analysis (Fig. 3)[44].

The origin of the regioselectivity observed in the alkylation of guanosine derivatives protected at the primary amino group by an *N,N*-dialkyl amidine is not very well understood. It is likely that the regioselectivity of the reaction that was observed in the sulfonylation of compound **5** with triisopropylbenzenesulfonyl chloride (Entry 14) results from some steric hindrance between the dibenzyl formamidine moiety and the isopropyl groups, preventing the positioning of the chlorosulfonate reagent close enough to N^1. Steric hindrance occurs in some other examples in Table 1 (consider the alkoxyphosphonium intermediate species at entries 2 and 3 for example) and the reactions however do not result in O^6-alkylation products. This may indicate that some electronic effects play a key role in these alkylation reactions and additional work is required for full understanding of their regioselectivity.

In conclusion, we have found that the presence of the *N,N*-dialkyl amidine protective group on guanosine very efficiently directs the alkylation of the guanine moiety on the N^1

- Table 1 -

Entry	Substrate	Reagent	Reaction conditions	Product (Yield %)[a]
1	 **1**		PPh_3/DEAD	**7** (63)[b,c]
2			PPh_3/DEAD	**9** (51)[c]
3			PPh_3/DEAD	**10** (60)[c]
4		BnOH	PPh_3/DEAD	**11** (90)
5	 **2**[5]	BnOH	PPh_3/DEAD	**12** (91)
6	 **3**[5]	BnOH	PPh_3/DEAD	**13** (76)
7		BnBr	NaH	**13** (79)
8			PPh_3/DEAD	**14** (63)
9			PPh_3/DEAD	**15** (91)
10			PPh_3/DEAD	**16** (73)[d]
11	 **4**	BnOH	PPh_3/DEAD	**18** (84)
12	 **5**	MeI	NaH	**19** (82)
13		$Et_3O^+BF_4^-$	NaH	**20** (77)
14		TPSCl	NaH	**21** (56) O^6-derivative[e]
15	 **6**[5]	BnBr	NaH	**22** (80)
16			NaH	**23** (52)

[a]Based on isolated compounds. [b]Compound **8** resulting from O^6-alkylation was obtained in 27 % yield. [c]The compound was obtained after removal of the acetyl and formamidine protective groups by treatment with methanolic ammonia. [d]Compound **17** resulting from O^6-alkylation was obtained in 8 % yield. [e]Compound **21** resulted from O^6-sulfonylation as established through further sulfonate displacements[5].

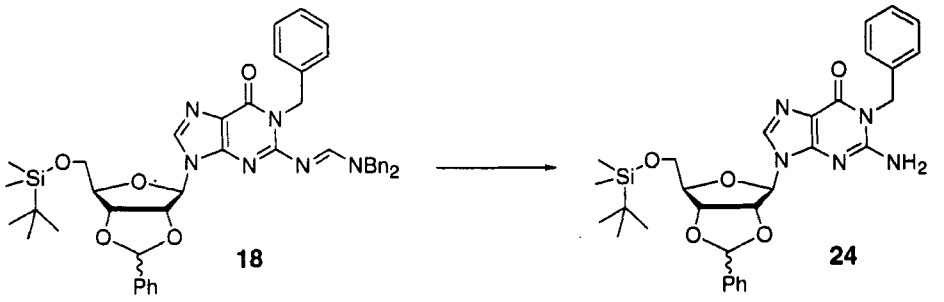


Figure 2

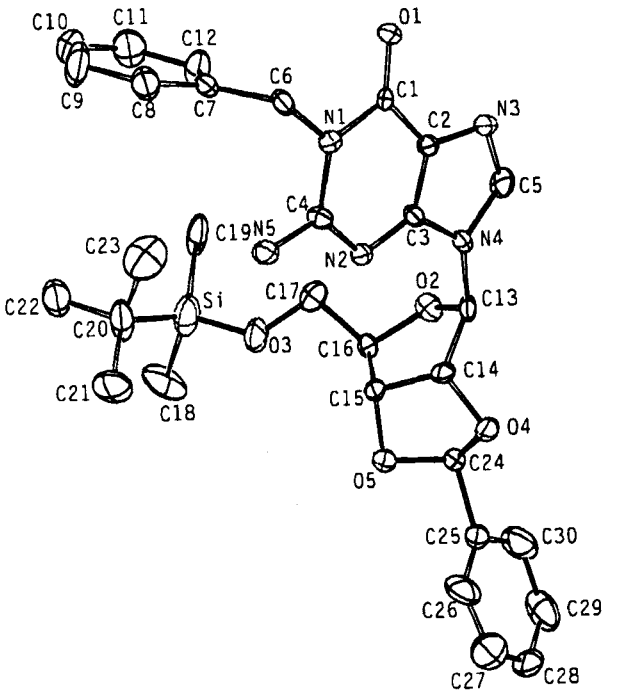


Figure 3

position, either through the Mitsunobu reaction or standard alkylation procedure. The regioselectivity observed is excellent and different from that previously reported with other protective groups at the N^2 position on the guanine moiety.

EXPERIMENTAL SECTION

General procedures.

-Alkylation via the Mitsunobu reaction : Diethyl azodicarboxylate (1.2 equiv.) is added

dropwise to a solution of the N^2-protected guanosine derivative (1.0 equiv.), the alcohol (1.1 equiv.) and triphenylphosphine (1.2 equiv.) in anhydrous THF. The reaction mixture is stirred at room temperature until total disappearance of the starting nucleoside. Then it is concentrated, and chromatographed over silica gel.

-Direct alkylation : To a suspension of NaH (1.1 equiv.) in anhydrous DMF at 0 °C is added the N^2-protected guanosine derivative (1.0 equiv.). The mixture is stirred for 1 hour before the electrophilic agent (1.1 equiv.) in DMF is added dropwise. The resulting solution is stirred at 0 °C till the reaction is complete (checked by TLC). A saturated ammonium chloride solution is added and the mixture is extracted with chloroform. The organic layer is dried over magnesium sulfate, evaporated under vacuum and the residue is purified by chromatography.

2-*N*-(*N,N*-Dimethylformamidino)-9-(5-*O*-acetyl-2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**1**, mixture of two diastereomers, white powder).

This compound was obtained following a similar procedure to that described for the preparation of **3**[5]. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.52 and 8.51 (2s, 1H, N=C<u>H</u>-NMe$_2$); 7.68 (s, 1H, H_8); 7.54-7.34 (m, 5H, C_6H_5); 6.16 and 6.10 (2d, J = 2.5 Hz, 1H, $H_{1'}$); 6.15 and 6.01 (2s, 1H, PhC<u>H</u>O); 5.41-5.36 (m, 1H, $H_{2'}$); 5.09-5.00 (m, 1H, $H_{3'}$); 4.57-4.47 (m, 1H, $H_{4'}$); 4.49-4.13 (m, 2H, $H_{5'}$); 3.14 and 3.13 (2s, 3H, 1NCH$_3$); 3.06 and 3.05 (2s, 3H, 1NCH$_3$); 2.00 and 1.99 (2s, 3H, CH_3CO). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 170.1; 158.0; 157.6; 156.8; 149.4; 136.5; 135.3; 129.5 and 129.4; 128.1; 126.3; 126.2; 120.3; 107.3 and 103.9; 89.1 and 88.9; 84.7 and 83.5; 83.4 and 82.0; 81.7 and 80.0; 63.4; 41.1; 34.8; 20.3. MS (CI/NH_3): 469 $[M+H]^+$. IR (neat) ν 3111; 2933; 1743; 1683; 1633; 1538; 1243.

2-*N*-(*N,N*-Dibenzylformamidino)-9-(5-*O*-*t*-butyldimethylsilyl-2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**4**, mixture of two diastereomers, white powder).

Compound **4** was prepared according to the procedure described by Vincent *et al.*[45]. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.97 and 8.95 (2s, 1H, N=C<u>H</u>NBn$_2$); 8.88 and 8.84 (2s, 1H, O^6H); 7.90 and 7.85 (2s, 1H, H_8); 7.60-7.15 (m, 15H, 3C_6H_5); 6.31 (d, J = 3.0 Hz, 0.5H, $H_{1'}$); 6.25 (d, J = 2.6 Hz, 0.5H, $H_{1'}$); 6.21 and 6.06 (2s, 1H, PhC<u>H</u>O); 5.29 and 5.18 (2dd, J = 2.6, 3.0 Hz, 1H, $H_{2'}$); 5.11 and 5.03 (2dd, J = 2.3, 3.4 Hz, 1H, $H_{3'}$); 4.68 and 4.67 (2s, 2H, PhC<u>H$_2$</u>); 4.56 and 4.49 (2m, 1H, $H_{4'}$); 4.43 and 4.39 (2s, 2H, PhC<u>H$_2$</u>N); 3.88 (m, 2H, $H_{5'}$); 0.91 and 0.89 (2s, 9H, 3CCH_3); 0.10, 0.09, 0.07 and 0.06 (4s, 6H, 2SiCH_3). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 158.4 and 158.3; 157.9; 156.8 and 156.7; 149.6; 136.3; 136.1 and 135.8; 135.0 and 134.6; 129.8-126.4 (m); 120.7; 107.3 and 104.0; 89.5 and 88.8; 85.9 and 85.5; 85.0 and 84.5; 82.4 and 81.5; 63.3 and 63.1; 54.7; 48.1; 25.7; 18.2; -5.5 and -5.6. MS (CI/NH_3) m/z 693 $[M+H]^+$. IR (neat) ν 3032; 2928; 1685; 1615; 1535.

2-*N*-(*N,N*-Dibenzylformamidino)-9-(2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**5**, mixture of two diastereomers, white powder).

Compound **5** was prepared according to the procedure described by Vincent *et al.*[45].

^{1}H-NMR (CD_3SOCD_3, 200 MHz) δ 8.89 and 8.87 (2s, 1H, N=C<u>H</u>NBn$_2$); 7.81 and 7.76 (2s, 1H, H_8); 7.60-7.25 (m, 15H, $3C_6H_5$); 6.02 (d, J = 5.8 Hz, 1H, $H_{1'}$); 6.22 and 6.04 (2s, 1H, PhC<u>H</u>O); 5.37 (m, 1H, $H_{2'}$); 5.17 (m, 1H, $H_{3'}$); 4.75-4.40 (m, 5H, $H_{4'}$, 2PhC<u>H$_2$</u>N); 3.97-3.85 (m, 2H, $H_{5'}$). ^{13}C-NMR (CD_3SOCD_3/$CDCl_3$ 1/2, 50 MHz) δ 158.7; 157.8; 157.2; 149.2; 137.9 and 137.8; 136.1 and 135.8; 135.0 and 134.6; 129.8-126.0 (m); 121.4 and 121.3; 107.4 and 104.1; 91.6 and 90.3; 85.3 and 84.9; 83.8 and 83.5; 83.1 and 80.2; 62.5 and 62.2; 54.8; 47.8. MS (CI/NH_3) m/z 579 $[M+H]^+$. IR (neat) ν 3350; 3110; 3029; 2926; 1685; 1615; 1215.

1-(2-Hydroxymethyl-benzyl)-2-*N*-(*N,N*-dimethylformamidino)-9-(2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**7**, mixture of two diastereomers, glassy solid).
^{1}H-NMR ($CDCl_3$, 200 MHz) δ. 7.67 and 7.56 (2m, 1H, H_8); 7.54-7.33 (m, 5H, C_6H_5); 7.10-7.01 (m, 4H, C_6H_4); 6.15 and 5.96 (2m, 1H, PhC<u>H</u>O); 5.90 (d, J = 3.8 Hz, 0.5H, $H_{1'}$); 5.85 (d, J = 4.3 Hz, 0.5H, $H_{1'}$); 5.41 (s, 2H, N^{1}C<u>H$_2$</u>Ar); 5.28-5.21 (m, 1H, $H_{2'}$); 5.07-5.03 (m, 1H, $H_{3'}$); 4.79 (s, 2H, ArC<u>H$_2$</u>O); 4.55 and 4.40 (2m, 1H, $H_{4'}$); 3.94-3.86 (m, 1H, $1H_{5'}$); 3.76-3.64 (m, 1H, $1H_{5'}$). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 157.5; 153.5; 148.4 and 148.2; 137.3 and 137.0; 136.2 and 135.8; 134.3; 129.8 and 129.5; 128.5 and 128.4; 127.5; 126.5-126.3 (m); 117.2 and 117.0; 107.4 and 104.2; 92.2 and 90.5; 85.5 and 85.4; 83.8 and 83.1; 80.4; 63.3; 62.8 and 62.5; 41.1 and 40.1. MS (CI/NH_3) m/z 492 $[M+H]^+$. IR (neat) ν 3442; 3219; 2926; 2358; 1682; 1538; 1070.

2-*N*-(*N,N*-Dimethylformamidino)-6-*O*-(2-hydroxymethyl-benzyl)-9-(2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**8**, mixture of two diastereomers, glassy solid).
^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.65 and 7.56 (2s, 1H, H_8); 7.53-7.29 (m, 9H, C_6H_5, C_6H_4); 6.25 and 6.03 (2s, 1H, PhC<u>H</u>O); 5.92 (d, J = 4.2 Hz, 0.5H, $H_{1'}$); 5.87 (d, J = 4.7 Hz, 0.5H, $H_{1'}$); 5.63 (s, 2H, O^{6}C<u>H$_2$</u>Ar); 5.32-5.10 (m, 4H, $H_{2'}$, $H_{3'}$, NH_2); 4.79 (s, 2H, ArC<u>H$_2$</u>OH); 4.63 and 4.49 (2m, 1H, $H_{4'}$); 4.00 and 3.94 (2m, 2H, $H_{5'}$). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 160.7; 158.9 and 158.8; 152.2 and 152.0; 139.3; 138.7 and 138.5; 136.1 and 135.6; 133.6; 129.4; 129.0; 128.8; 127.7; 127.4; 126.3 and 126.1; 115.9 and 115.6; 107.2 and 104.1; 92.5 and 90.6; 85.3; 83.5 and 83.1; 82.8 and 80.2; 65.8; 63.0 and 62.7; 62.1. MS (CI/NH_3) m/z 492 $[M+H]^+$. IR (neat) ν 3340; 2938; 1614; 1587; 1462; 1416; 1252.

1-(Diphenyl-methyl)-2-*N*-(*N,N*-dimethylformamidino)-9-(5-*O*-acetyl-2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**9**, mixture of two diastereomers, glassy solid).
^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.75 and 7.65 (2s, 1H, H_8); 7.53-7.25 (m, 16H, $3C_6H_5$, N^{1}C<u>H</u>Ph$_2$); 6.27 and 6.03 (2s, 1H, PhC<u>H</u>O); 5.96 (d, J = 4.1 Hz, 0.5H, $H_{1'}$); 5.92 (d, J = 4.8 Hz, 0.5H, $H_{1'}$); 5.34-5.26 (m, 1H, $H_{2'}$); 5.18-5.15 (m, 1H, $H_{3'}$); 4.64 and 4.50 (2m, 1H, $H_{4'}$); 4.02-3.92 and 3.82-3.70 (2m, 2H, $H_{5'}$). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 160.7; 158.7 and 158.6; 152.5 and 152.3; 140.2; 138.8 and 138.6; 136.4 and 135.8; 131.8; 129.7 and 129.4; 128.4; 128.2; 127.6; 127.1; 127.0; 126.3; 126.1; 107.3 and 104.4; 92.9 and 91.1; 85.5 and 83.6; 83.3 and 82.7; 80.3 and 78.4; 63.0 and 62.7; 60.2. MS (CI/NH_3) m/z 538 $[M+H]^+$. IR (neat) ν 3332; 3202; 2927; 1614; 1882; 1247; 1093.

1-(*t*-Butylphenyl-methyl)-2-*N*-(*N,N*-dimethylformamidino)-9-(5-*O*-acetyl-2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**10**, mixture of four diastereomers, glassy solid). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.70 and 7.61 (2s, 1H, H_8); 7.54-7.24 (m, 10H, $2C_6H_5$); 6.27 and 6.05 (2m, 1H, PhC<u>H</u>O); 6.03 (m, 1H, N^1C<u>H</u>Ph); 5.93 (d, J = 4.3 Hz, 0.5H, $H_{1'}$); 5.88 (d, J = 4.0 Hz, 0.5H, $H_{1'}$); 5.35-5.12 (m, 2H, $H_{2'}$, $H_{3'}$); 4.63 and 5.50 (2m, 1H, $H_{4'}$); 4.04-3.78 (m, 2H, $H_{5'}$); 1.06 (s, 9H, $3CCH_3$). MS (CI/NH_3) m/z 518 $[M+H]^+$. IR (neat) ν 3331; 3202; 2956; 1613; 1582; 1461; 1410; 1251; 1094.

1-Benzyl-2-*N*-(*N,N*-dimethylformamidino)-9-(5-*O*-acetyl-2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**11**, mixture of two diastereomers, white powder). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.48 and 8.46 (2s, 1H, N=C<u>H</u>NMe_2); 7.70 and 7.51 (2s, 1H, H_8); 7.56-7.19 (m, 10H, $2C_6H_5$); 6.19 (d, J = 3.6 Hz, 0.5H, $H_{1'}$); 6.18 and 6.04 (2s, 1H, PhC<u>H</u>O); 6.12 (d, J = 2.5 Hz, 0.5H, $H_{1'}$); 5.54 (s, 2H, N^1C<u>H_2</u>Ph); 5.45 and 5.38 (2dd, J = 2.4, 6.5 Hz, 1H, $H_{2'}$); 5.08 and 5.03 (2dd, J = 3.2, 6.4 Hz, 1H, $H_{3'}$); 4.63-4.51 (m, 1H, $H_{4'}$); 4.48-4.06 (m, 2H, $H_{5'}$); 3.15 (s, 3H, $1NCH_3$); 3.09 (s, 3H, $1NCH_3$); 2.04 (s, 3H, CH_3CO). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 170.0; 157.7; 157.0; 156.9; 156.6; 147.2; 138.1; 136.3 and 136.1; 135.3; 131.5; 129.5 and 129.4; 128.0; 127.6; 126.3; 126.1; 120.0 and 119.9; 107.4 and 103.9; 88.8; 84.7 and 83.4; 83.3 and 82.0; 81.6 and 81.0; 63.4; 45.0; 40.8; 34.9; 20.2. MS (CI/NH_3) m/z 559 $[M+H]^+$. IR (neat) ν 32935; 1743; 1686; 1629; 1494; 1243.

1-Benzyl-2-*N*-(*N,N*-diethylbenzamidino)-9-(5-*O*-acetyl-2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**12**, mixture of two diastereomers, white powder). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.80-7.15 (m, 16H, H_8, $3C_6H_5$); 6.05 and 5.85 (2s, 1H, PhC<u>H</u>O); 6.00 and 5.85 (2d, J = 4.4 Hz, 1H, $H_{1'}$); 5.83 and 5.32 (2m, 2H, N^1C<u>H_2</u>Ph); 4.92 (m, 1H, $H_{2'}$); 4.75-3.80 (m, 5H, $H_{3'}$, $H_{4'}$, $2H_{5'}$, 1NC<u>H</u>Me); 3.55 (m, 1H, 1NC<u>H</u>Me); 3.14 (m, 2H, 1NC<u>H_2</u>Me); 1.98 and 1.97 (2s, 3H, CH_3CO); 1.31 and 1.06 (2m, 6H, NCH_2C<u>H_3</u>). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 169.9 and 169.8; 163.2 and 163.1; 157.9; 155.9; 146.9 and 146.8; 135.5; 138.2; 137.1 and 136.8; 135.5; 133.2; 132.9; 132.8; 131.8; 131.6; 131.1; 129.6; 129.5; 128.8; 128.2; 128.0; 127.9; 127.3; 127.0; 126.8; 126.3; 126.1; 119.6 and 119.5; 107.2 and 103.6; 89.8 and 89.7; 84.3 and 83.9; 82.6 and 82.4; 81.7; 63.6 and 63.4; 45.3; 43.8; 41.8; 20.2; 14.0; 12.6. MS (CI/NH_3) m/z 693 $[M+H]^+$. IR (neat) ν 2980; 1743; 1689; 1552; 1521; 1491. Anal. Calcd for $C_{37}H_{38}N_6O_6$: C 67.05; H 5.78; N 12.68. Found: C 66.82; H 5.70; N 12.51.

1-Benzyl-2-*N*-(*N,N*-dibenzylformamidino)-9-(5-*O*-acetyl-2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**13**, mixture of two diastereomers, white powder). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.84 and 8.81 (2s, 1H, N=C<u>H</u>NBn_2); 7.73 and 7.72 (2s, 1H, $1H_8$); 7.60-7.15 (m, 20H, $4C_6H_5$); 6.23 and 6.17 (2d, J = 2.3 Hz, 1H, $H_{1'}$); 6.19 and 6.03 (2s, 1H, PhC<u>H</u>O); 5.57 (AB syst., Δδ = 9.0 Hz, J_{AB} = 14.3 Hz, 2H, N^1C<u>H_2</u>Ph); 5.48 and 5.42 (2dd, J = 2.3, 6.4 Hz, 1H, $H_{2'}$); 5.03 and 4.98 (2dd, J = 4.8, 6.4 Hz, 1H, $H_{3'}$); 4.66 (s, 2H, 1PhC<u>H_2</u>NCH); 4.62 and 4.53 (2q, J = 4.5 Hz, 1H, $H_{4'}$); 4.43-4.37 (m, 3H, $1H_{5'}$, 1PhC<u>H_2</u>NCH);

4.25 (dd, J = 6.0, 11.7 Hz, 1H, $1H_{5'}$); 2.00 (s, 3H, CH_3CO). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 170.4; 158.0; 157.8 and 157.7; 157.1; 147.3; 138.1; 136.8 and 136.6; 135.5; 135.5 and 134.9; 134.8 and 134.7; 132.1 and 131.9; 123.0 and 129.8; 129.1; 128.8; 128.5; 128.2; 128.1; 127.9; 127.6; 127.6; 126.7; 126.6; 126.4; 120.8; 107.8; 104.4; 89.5; 85.3 and 83.8; 83.7 and 82.3; 82.2 and 81.3; 63.9 and 63.8; 54.2; 48.5; 45.4; 20.6. MS (CI/NH_3) m/z 711 $[M+H]^+$. IR ($CHCl_3$) ν 2929; 1743; 1689; 1611; 1220; 1093. Anal. Calcd for $C_{41}H_{38}N_6O_6$: C, 69.28; H, 5.39; N, 11.82. Found: C, 69.38; H, 5.44; N, 12.01.

1-(2-Ethoxy-ethyl)-2-*N*-(*N,N*-dibenzylformamidino)-9-(5-*O*-acetyl-2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**14**, mixture of two diastereomers, white powder).
^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.89 and 8.87 (2s, 1H, N=C<u>H</u>NBn$_2$); 7.69 (s, 1H, H_8); 7.60-7.15 (m, 15H, $3C_6H_5$); 6.21 and 6.14 (2d, J = 2.2 Hz, 1H, $H_{1'}$); 6.18 and 6.03 (2s, 1H, PhC<u>H</u>O); 5.48 and 5.44 (2dd, J = 2.2, 6.4 Hz, 1H, $H_{2'}$); 5.03 (m, 1H, $H_{3'}$); 4.71 (s, 2H, PhC<u>H$_2$</u>N); 4.56 (t, J = 6.6 Hz, 2H, NC<u>H$_2$</u>CH$_2$O); 4.51-4.05 (m, 5H, $H_{4'}$, $2H_{5'}$, PhC<u>H$_2$</u>N); 3.66 (t, J = 6.6 Hz, 2H, NCH$_2$C<u>H$_2$</u>O); 3.45 (q, J = 6.9 Hz, 2H, CH_3C<u>H$_2$</u>O); 1.98 (s, 3H, CH_3CO); 1.09 (t, J = 6.9 Hz, 3H, C<u>H$_3$</u>CH$_2$O). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 170.3; 157.7; 157.6; 157.1; 147.1; 136.7 and 136.5; 135.5; 135.1; 134.7; 130.1-126.3 (m); 120.7; 107.7 and 104.2; 89.5; 85.1; 83.7 and 82.3; 82.2 and 81.4; 67.6; 66.1; 63.9 and 63.8; 54.8; 48.5; 41.1; 20.5; 15.0. MS (CI/NH_3) m/z 693 $[M+H]^+$. IR (neat) ν 3031; 2974; 2870; 1743; 1687; 1613.

1-(3-Azido-propyl)-2-*N*-(*N,N*-dibenzylformamidine)-9-(5-*O*-acetyl-2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**15**, mixture of two diastereomers, white powder).
^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.95 and 8.92 (2s, 1H, N=C<u>H</u>NBn$_2$); 7.72 and7.71 (2s, 1H, H_8); 7.60-7.15 (m, 15H, $3C_6H_5$); 6.23 and 6.15 (2d, J = 2.6 Hz, 1H, $H_{1'}$); 6.and 6.04 (2s, 1H, PhC<u>H</u>O); 5.49 and 5.44 (2dd, J = 2.6, 6.2 Hz, 1H, $H_{2'}$); 5.01 (m, 1H, $H_{3'}$); 4.77 (s, 2H, 1PhC<u>H$_2$</u>N); 4.70-4.25 (m, 7H, $H_{4'}$, $2H_{5'}$, 1PhC<u>H$_2$</u>N, N^{1}CH$_2$); 3.29 (t, J = 6.6 Hz, 2H, CH_2N_3); 1.98 (m, 5H, N^{1}CH$_2$C<u>H$_2$</u>). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 170.3; 157.8; 157.7; 156.8; 147.2 and 147.1; 136.7; 135.7-135.1 (m); 129.8-126.1 (m); 120.8 and 120.7; 107.9 and 104.4; 89.6 and 89.5; 85.3 and 84.8; 83.8 and 82.8; 82.5 and 81.4; 63.9 and 63.8; 54.9; 49.2; 48.5; 40.3; 30.0; 20.6. MS (CI/NH_3) m/z 705 $[M+H]^+$. IR (neat) ν 3031; 2929; 2096; 1743; 1687; 1612.

1-{2-[2-(2-Azido-ethoxy)-ethoxy]-ethyl}-2-*N*-(*N,N*-dibenzylformamidino)-9-(5-*O*-acetyl-2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**16**, mixture of two diastereomers, white powder).
^{1}H-NMR ($CDCl_3$, 200 MHz) δ 8.91 and 8.88 (2s, 1H, N=C<u>H</u>NBn$_2$); 7.70 (s, 1H, H_8); 7.60-7.15 (m, 15H, $3C_6H_5$); 6.23 and 6.14 (2d, J = 6.4 Hz, 1H, $H_{1'}$); 6.19 and 6.03 (2s, 1H, PhC<u>H</u>O); 5.47 and 5.42 (2dd, J = 2.3, 6.4 Hz, 1H, $H_{2'}$); 5.03 (2dd, J = 3.2, 6.4 Hz, 1H, $H_{3'}$); 4.71 (s, 2H, 1PhC<u>H$_2$</u>N); 4.60 (t, J = 6.3 Hz, 2H, N^{1}CH$_2$); 4.62-4.36 (m, 2H, $H_{4'}$, $1H_{5'}$); 4.48 (s, 2H, PhC<u>H$_2$</u>N); 4.28-4.19 (m, 1H, $1H_{5'}$); 3.74 (t, J = 6.3 Hz, 2H, N^{1}CH$_2$C<u>H$_2$</u>O); 3.69-3.54 (m, 6H, N$_3$CH$_2$C<u>H$_2$</u>OC<u>H$_2$</u>C<u>H$_2$</u>); 3.28 (t, J = 5.2 Hz, 2H, N_3CH_2); 2.00 (s, 3H, CH_3CO). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 170.3; 157.7; 157.6; 157.0; 147.0; 136.7 and 136.5; 135.5 and

135.4; 135.1; 134.7; 129.9; 129.7; 129.0; 128.8; 128.4; 128.1; 127.9; 127.7; 126.5; 126.4; 120.7; 107.7 and 104.3; 89.5; 85.2; 83.7; 82.3; 82.2 and 81.4; 70.4; 70.0; 69.7; 68.3; 63.9; 54.8; 50.4; 48.6; 41.2; 20.5. MS (CI/NH_3) m/z 779 $[M+H]^+$. IR ($CHCl_3$) ν 2923; 2106; 1743; 1690; 1613; 1493; 1223; 1097. Anal. Calcd for $C_{40}H_{43}N_9O_8$: C 61.77; H 5.58; N 16.21. Found: C 61.29; H 5.31; N 15.84.

2-*N*-(*N,N*-Dibenzylformamidino)-6-*O*-{2-[2-(2-azido-ethoxy)-ethoxy]-ethyl}-9-(5-*O*-acetyl-2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**17**, mixture of two diastereomers, white powder).

^{1}H-NMR ($CDCl_3$, 200 MHz) δ 9.04 s, 1H, N=C<u>H</u>NBn$_2$); 7.86 and 7.85 (2s, 1H, H_8); 7.60-7.15 (m, 15H, $3C_6H_5$); 6.33 and 6.29 (2d, J = 2.6 Hz, 1H, $H_{1'}$); 6.16 and 6.01 (2s, 1H, PhC<u>H</u>O); 5.61 and 5.50 (2dd, J = 2.6, 4.8 Hz, 1H, $H_{2'}$); 5.17 (m, 1H, $H_{3'}$); 4.91-4.04 (m, 9H, $H_{4'}$, $2H_{5'}$, O^6CH_2, 2PhC<u>H</u>$_2$N); 3.91 (t, J = 4.9 Hz, 2H, $O^6CH_2C\underline{H}_2$); 3.71 (m, 6H, $N_3CH_2C\underline{H}_2OC\underline{H}_2C\underline{H}_2$); 3.36 (t, J = 5.0 Hz, 2H, CH_2N_3); 1.99 and 1.97 (2s, 3H, CH_3CO). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 170.3; 162.3; 160.5; 158.9; 153.1; 139.3 and 139.0; 135.8-135.5 (m); 129.0-122.7 (m); 118.0; 107.7 and104.2; 89.4 and 88.8; 84.9 and 83.5; 84.1 and 82.1; 81.9 and 81.1; 70.7; 70.5; 69.9; 69.1; 65.7; 63.8; 54.2; 50.5; 47.9; 20.5. MS (CI/NH_3) m/z 779 $[M+H]^+$. IR (neat) ν 3064; 2919; 2872; 2108; 1743; 1619; 1591.

1-Benzyl-2-*N*-(*N,N*-dibenzylformamidino)-9-(5-*O*-*t*-butyldimethylsilyl-2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**18**, mixture of two diastereomers, white powder).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.87 and 8.86 (2s, 1H, N=C<u>H</u>NBn$_2$); 7.89 and 7.83 (2s, 1H, H_8); 7.60-7.15 (m, 20H, $4C_6H_5$); 6.28 and 6.21 (2d, J = 4.1 Hz, 1H, $H_{1'}$); 6.18 and 6.02 (2s, 1H, PhC<u>H</u>O); 5.57 (s, 2H, N^1CH_2); 5.32 and 5.20 (2dd, J = 4.1, 9.5 Hz, 1H, $H_{2'}$); 5.08 and 4.99 (2dd, J = 4.0, 9.5 Hz, 1H, $H_{3'}$); 4.63 and 4.61, (2s, 2H, 1PhC<u>H</u>$_2$NCH); 4.54 and 4.39 (2m, 1H, $H_{4'}$); 4.35 and 4.30 (2s, 2H, 1PhC<u>H</u>$_2$NCH); 3.85 (m, 2H, $2H_{5'}$); 0.88 and 0.86 (2s, 9H, $3CCH_3$); 0.07, 0.06, 0.04 and 0.02 (4s, 6H, $2SiCH_3$). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 158.1; 158.0; 157.0; 147.5 and 147.4; 138.3; 136.9-134.2 (m); 130.1-126.5 (m); 120.4 and 120.3; 107.5 and 104.2; 89.7 and 89.1; 86.0 and 85.7; 85.3 and 84.7; 82.7 and 81.8; 63.5 and 63.2; 54.8; 48.3 and 48.2; 45.3; 25.9; 18.3; -5.4; -5.5. MS (CI/NH_3) m/z 783 $[M+H]^+$. IR (neat) ν 3031; 2928; 1688; 1612; 1492.

1-Methyl-2-*N*-(*N,N*-dibenzylformamidino)-9-(2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**19**, mixture of two diastereomers, white powder).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.80 and 8.78 (2s, 1H, N=C<u>H</u>NBn$_2$); 7.74 and 7.68 (2s, 1H, H_8); 7.60-7.15 (m, 15H, $3C_6H_5$); 6.26 and 6.08 (2s, 1H, PhC<u>H</u>O); 6.00 and 5.97 (2d, J = 6.6 Hz, 1H, $H_{1'}$); 5.43 (m, 1H, $H_{2'}$); 5.19 (m, 1H, $H_{3'}$); 4.75-4.55 (m, 3H, $H_{4'}$, 1PhC<u>H</u>$_2$N); 4.50 and 4.49 (2s, 2H, 1PhC<u>H</u>$_2$N); 4.03 and 3.66 (2m, 2H, $H_{5'}$); 3.63 (s, 3H, N^1CH_3). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 158.1; 158.0 and 157.9; 157.7; 146.8; 137.9; 136.0-134.3 (m); 130.0-126.3 (m); 121.9; 107.7 and 104.3; 92.4 and 91.0; 85.0 and 84.0; 83.8 and 83.3; 83.1 and 80.3; 62.9 and 62.6; 55.0; 48.2 and 48.1; 30.2. MS (CI/NH_3) m/z 593 $[M+H]^+$. IR (neat) ν 3271; 3031; 2928; 1687; 1613; 1094.

1-Ethyl-2-*N*-(*N,N*-dibenzylformamidino)-9-(2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**20**, mixture of two diastereomers, white powder).
^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.86 and 8.83 (2s, 1H, N=C<u>H</u>NBn$_2$); 7.79 and 7.75 (s, 1H, H_8); 7.60-7.15 (m, 15H, $3C_6H_5$); 6.26 and 6.07 (2s, 1H, PhC<u>H</u>O); 6.04 and 6.01 (2d, J = 2.4 Hz, 1H, $H_{1'}$); 5.41 (m, 1H, $H_{2'}$); 5.19 (m, 1H, $H_{3'}$); 4.80-4.41 (m, 5H, $H_{4'}$, 2PhC<u>H$_2$</u>N); 4.49 (q, J = 6.9 Hz, 2H, N^{1}C<u>H$_2$</u>CH$_3$); 4.05 and 3.84 (2m, 2H, $H_{5'}$); 1.22 (t, J = 6.9 Hz, 3H, N^{1}CH$_2$C<u>H$_3$</u>). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 158.1; 157.6; 157.2; 146.9; 137.7; 135.9-134.2 (m); 130.1-126.3 (m); 121.2; 107.5 and 104.3; 92.0 and 90.7; 85.2 and 85.1; 83.9 and 83.5; 80.4; 62.7 and 62.4; 55.1; 48.1; 38.0; 13.8. MS (CI/NH_3) m/z 607 $[M+H]^+$. IR (neat) ν 3306; 3028; 2928; 1684; 1613; 1090.

2-*N*-(*N,N*-Dibenzylformamidino)-6-*O*-(2,4,6-triisopropylbenzenesulfonyl)-9-(2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**21**, mixture of two diastereomers, white powder).
^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H, N=C<u>H</u>NBn$_2$); 8.17 and 8.01 (2s, 1H, H_8); 7.65-7.20 (m, 17H, $3C_6H_5$, $2SO_2$Ar<u>H</u>), 6.23 and 6.11 (2d, J = 6.0 Hz, 1H, $H_{1'}$); 6.36 and 6.11 (2s, 1H, PhC<u>H</u>O); 5.47 (m, 1H, $H_{2'}$); 5.27 (m, 1H, $H_{3'}$); 4.90-4.43 (m, 3H, $H_{4'}$, 1PhC<u>H$_2$</u>N); 4.39-4.05 (m, 4H, 1PhC<u>H$_2$</u>N, 2ArC<u>H</u>Me$_2$); 4.05 and 3.86 (2m, 2H, $H_{5'}$); 2.82 (h, J = 6.8 Hz, 1H, 1ArC<u>H</u>Me$_2$); 1.27 (d, J = 6.8 Hz, 12H, 4ArCHC<u>H$_3$</u>); 1.18 (d, J = 6.8 Hz, 6H, 2ArCHC<u>H$_3$</u>). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 162.1 and 162.0; 159.7; 155.0; 154.8 and 154.6; 154.5; 154.0; 150.6; 142.5 and 142.2; 136.5; 135.85 and 135.6; 135.1; 130.0-123.7 (m); 120.3 and 120.0; 107.4 and 104.6; 93.1 and 90.9; 85.9 and 84.0; 85.7 and 83.5; 83.0 and 80.4; 63.2 and 62.8; 54.4; 47.7; 34.0; 29.8; 24.6; 23.3. MS (CI/NH_3) m/z 845 $[M+H]^+$. IR (neat) ν 3291; 2960; 2928; 2870; 1595; 1560.

1-Benzyl-2-*N*-(*N,N*-dibenzylformamidino)-9-(β-D-ribofuranosyl)-guanine (**22**, white powder).
Mp 191-193°C. ^{1}H-NMR ($CDCl_3$,/CD_3OD : 1/3, 200 MHz) δ 8.81 (s, 1H, N=C<u>H</u>NBn$_2$); 7.94 (s, 1H, H_8); 7.40-7.10 (m, 15H, $3C_6H_5$); 5.91 (d, J = 6.4 Hz, 1H, $H_{1'}$); 5.47 (s, 2H, N^{1}C<u>H$_2$</u>Ph); 4.74 (dd, J = 5.3, 6.4 Hz, 1H, $H_{2'}$); 4.57 (s, 2H, 1PhC<u>H$_2$</u>NCH); 4.45 (s, 2H, 1PhC<u>H$_2$</u>NCH); 4.34 (dd, J = 3.0, 5.3 Hz, 1H, $H_{3'}$); 4.16 (m, 1H, $H_{4'}$); 3.79 (AB part of ABX syst., Δδ = 15.0 Hz, J_{AB} = 12.4 Hz, J_{AX} = 2.6 Hz, J_{BX} = 2.6 Hz, 2H, $H_{5'}$). ^{13}C-NMR (CD_3OD, 50 MHz) δ 159.1; 158.3; 148.7; 139.2; 138.4; 135.6; 135.5; 129.5; 129.3; 129.0; 128.8; 128.7; 128.4; 127.7; 127.5; 120.7; 90.0; 86.9; 74.8; 71.8; 62.7; 55.5; 48.5; 43.3. MS (CI/NH_3) m/z 581 $[M+H]^+$. IR (neat) ν 3384; 1674; 1611; 1492; 1118. Anal. Calcd for $C_{32}H_{33}N_6O_5$: C 66.08; H 5.72; N 14.45. Found: C 66.20; H 5.74; N 14.79.

1-(4-Methoxy-benzyl)-2-*N*-(*N,N*-dibenzylformamidino)-9-β-D-ribofuranosyl-guanine (**23**, white powder).
Mp 183-185°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.86 (s, 1H, N=C<u>H</u>NBn$_2$); 7.45 (s, 1H, H_8); 7.31-7.15 (m, 10H, $2C_6H_5$); 7.09 (d, J = 8.7 Hz, 2H, 2Ar<u>H</u>); 6.64 (d, J = 8.7 Hz, 2H, 2Ar<u>H</u>); 5.72 (d, J = 7.6 Hz, 1H, $H_{1'}$); 5.51 (m, 1H, $H_{2'}$); 5.16 (AB syst., J_{AB} = 13.6 Hz, Δν = 0.46, 2H,

$N^1C\underline{H}_2Ar$); 4.69-4.48 (m, 5H, $H_{3'}$, $2PhC\underline{H}_2N$; 4.34 (m, 1H, $H_{4'}$); 3.89-3.71 (m, 2H, $2H_{5'}$); 3.72 (s, 3H, CH_3O). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 159.2; 158.6; 157.2; 157.1; 146.8; 139.1; 134.7; 129.4-127.8 (m); 125.2; 120.2; 113.5; 91.6; 87.0; 72.9; 72.1; 63.1; 55.2; 47.9; 45.2. MS (NH_3) m/z 612 $[M+H]^+$. IR (neat) ν 3323; 2928; 1683; 1611; 1493.

1-Benzyl-9-(5-*O*-*t*-butyldimethylsilyl-2,3-*O*-benzylidene-β-D-ribofuranosyl)-guanine (**24**, white powder).

Compound **18** (77 mg, 0.98 μmol) and *t*-BuOK (31 mg, 2.7 μmol) are stirred for 6 h at 45 °C in *t*-BuOH/THF/water 10:3:2 (3 ml). Solvents are removed *in vacuo* and the crude residue is purified by chromatography over silica gel to yield **24** as a mixture of two diastereomers (55 mg, 97 %).^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.77 and 7.73 (2s, 1H, H_8); 7.60-7.15 (m, 10H, $2C_6H_5$); 6.12 and 5.98 (2s, 1H, $PhC\underline{H}O$); 6.11 and 6.05 (2d, J = 2.5 Hz, 1H, $H_{1'}$); 5.25 (m, 3H, $H_{2'}$, $N^1C\underline{H}_2Ph$); 5.11 (m, 3H, $H_{3'}$, NH_2); 4.49 and 4.36 (2m, 1H, $H_{4'}$); 3.81 (m, 2H, $H_{5'}$); 0.91 and 0.88 (2s, 9H, $3CCH_3$); 0.07, 0.06, 0.05 and 0.04 (4s, 6H, $2SiCH_3$). ^{13}C-NMR ($CD_3SOCD_3/CDCl_3$ 1:2, 75 MHz) δ 157.1; 153.3; 148.2; 136.0; 135.8; 134.9; 130.2-126.3 (m)118.0; 107.6 and 104.2; 89.8 and 89.1; 86.4 and 85.3; 84.3; 82.5 and 80.8; 63.4 and 63.2; 44.9; 25.9; 18.3; -5.4; -5.5. MS (CI/NH_3) m/z 576 $[M+H]^+$. IR (neat) ν 2951; 2927; 2854; 1690; 1630; 1535.

One of the two diastereomers selectively crystalizes in THF/benzene/toluene 1:5:5 as shown by the X-rays analysis.

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43. Data not shown.

44. Crystallographic data for compound **24** :

Formula	$C_{30}H_{37}N_5O_5Si \cdot C_6H_5CH_3$	Wavelength (Å)	0.71073
MW	667.89	Radiation	MoKα graphite monochrom.
Crystal system	orthorhombic	Diffractometer	Enraf. Nonius CA4D
Space group	P 2_1 2_1 2_1	Scan mode	θ/2θ
a (Å)	10.6097(6)	hkl limits	0,13/0,17/-30,0
b (Å)	14.2065(8)	Theta limits (deg)	2.5/26.30
c (Å)	24.166(2)	Number of data meas.	4164
V ($Å^3$)	3642.5 (7)	Nb data with I > 3σ(I)	1982
Z	4	Weighting scheme	$4Fo^2/(\sigma^2(Fo^2)+0.0004$ $Fo^2)+1.0$
Dcalc (gcm^{-3})	1.22	Number of variables	432
F000	1424	R	0.092
μ(mm^{-1})	0.107	Rw	0.099
Trans. min/max	0.9742/1.0000	GOF	1.246
Temp. (K)	294	Largest peak in final diff. ($eÅ^{-3}$)	1.072.

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