# An Efficient Synthesis of 3′-Amino-3′-deoxyguanosine from Guanosine

by **Lei Zhang**, **Zhiyong Cui**, and **Biliang Zhang***

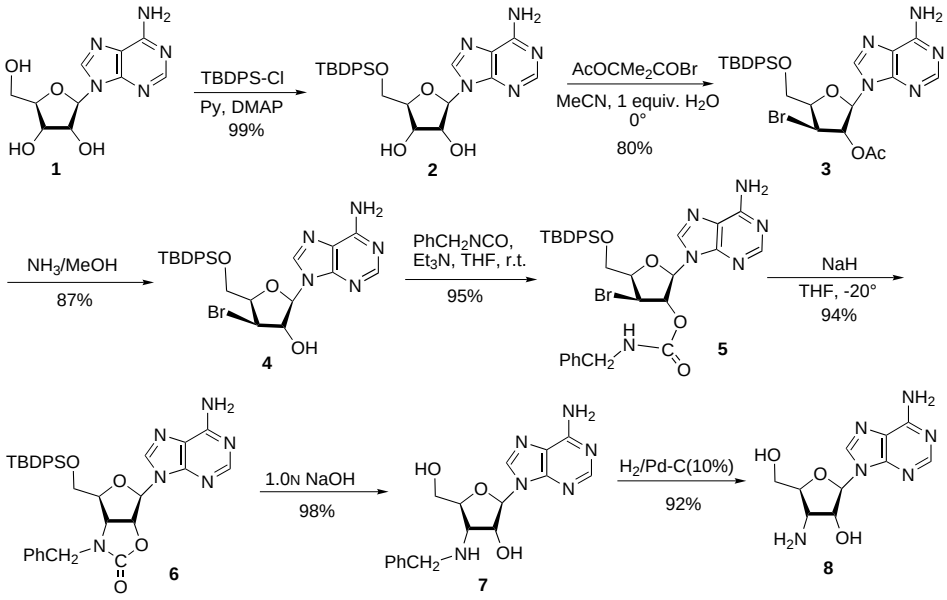
Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, MA 01605 USA (phone: (508) 856-6673; fax: (508) 856-4289; e-mail: biliang.zhang@umassmed.edu)

3′-Amino-3′-deoxyguanosine was synthesized from guanosine in eight steps and 58% overall yield. The 2′,3′-diol of 5′-*O*-[(*tert*-butyl)diphenylsilyl]-2-*N*-[(dimethylamino)methylidene]guanosine was reacted with α-acetoxyisobutyryl bromide and treated with 0.5N $NH_3$ in MeOH to yield 9-{2′-*O*-acetyl-3′-bromo-5′-*O*-[(*tert*-butyl)diphenylsilyl]-3′-deoxy-β-D-xylofuranosyl]-2-*N*-[(dimethylamino)methylidene]guanine, which was reacted with benzyl isocyanate, NaH, and then 3.0N NaOH, and finally with Pd/C (10%) and $HCO_2NH_4$ in EtOH/AcOH to afford 3′-amino-3′-deoxyguanosine.

**Introduction.** – Unnatural nucleotide derivatives have been shown to possess antibacterial, anticancer, and biosynthetic-inhibition activities [1–3]. 3′-Amino-3′-deoxynucleosides are very important bioactive molecules. 3′-Amino-3′-deoxyadenosine, known as puromycin, is an analogue of the 3′-terminus of aminoacyl charge-transfer RNA and a good acceptor in the peptidyl transferase reaction in the ribosome [4][5]. 3′-Amino-3′-deoxynucleosides are also the key intermediates in the synthesis of several backbone-modified oligonucleotides. For example, the phosphodiester in the natural oligonucleotides can be replaced by guanidine [6–9], amide [10][11], urea [12], carbamate [13], and aminoalkyl derivatives [14][15]. Such antisense oligonucleotides may have great potential as therapeutic and diagnostic agents. The oligonucleotide N(3′)–P(5′) phosphoramidates that can inhibit the telomerase have been shown to have potential therapeutic application [16][17], and they have been also used as substrate-analog inhibitors for ribozyme [18]. *Bruice* and co-workers have reported the synthesis of ribonucleic (A and U) guanidines for biological and biochemical studies [8][9]. Several synthetic routes have been suggested for the synthesis of 3′-amino-3′-deoxynucleosides. There are two major methods to approach the synthesis of sugar-modified nucleosides: *a*) modifications on the intact nucleosides [19–21]; *b*) attachment of the heterocyclic base to a modified glycosyl unit [22–26]. The coupling reactions of suitably protected purine bases with glucose or xylose derivatives usually gave low yields (overall yield < 20%). *Samano* and *Robins* [27] have reported a nine-step synthetic route to 3′-amino-3′-deoxyadenosine in 66% overall yield, and *Pfleiderer* and co-workers [28] have repeated the synthetic procedure of *Samano* and *Robins* to prepare 3′-amino-3′-deoxyadenosine. *Robins et al.* [29] have reported another improved method for the synthesis of 3′-amino-3′-deoxyadenosine. There were also several other reported methods to prepare 3′-amino-3′-deoxyguanosine by the attachment of the protecting guanine to 3′-azido-3′-deoxy-D-ribofuranose [30–33]. However, to our knowledge, there is so far no report on the preparation of the title compound directly from guanosine. In this paper, we report an efficient route for the synthesis of 3′-amino-3′-deoxyguanosine directly from guanosine.

**Results and Discussion.** – *Synthesis of 3′-Amino-3′-deoxyadenosine* (**8**). We have modified the nine-step route of *Samone* and *Robins* for synthesis of 3′-amino-3′-deoxyadenosine to a seven-step route with 55% overall yield (*Scheme 1*). Briefly, adenosine (**1**) was first protected with (*t*-Bu)$Ph_2$Si (TBDPS) at C(5′), to avoid formation of 5′-dioxolone, when treated with 2-acetoxyisobutyryl bromide to yield 2′-*O*-acetyl-3′-bromo-5′-*O*-[(*tert*-butyl)diphenylsilyl]-3′-deoxyadenosine (**3**). The *Moffatt* reaction [13] of adenosine with 2-acetoxyisobutyryl bromide ($AcOCMe_2COBr$) produced 2′-*O*-acetyl-3′-bromo-3′-deoxyadenosine. To avoid the formation of the 5′-dioxolone product, the 5′-OH group of adenosine was selectively protected by the acid-stable TBDPS group. The reaction of adenosine with slight excess of (*t*-Bu)$Ph_2$SiCl was carried out in dry pyridine for 40 h at room temperature in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP). The reaction of 5′-*O*-TBDPS-adenosine with 2-acetoxyisobutyryl bromide was performed in MeCN and 1.0 equiv. of $H_2O$ to give 2′-*O*-acetyl-3′-bromo-5′-*O*-[(*tert*-butyl)diphenylsilyl]-3′-deoxyadenosine (**3**). Deprotection of 2′-*O*-Ac group of 2′-*O*-acetyl-3′-bromo-5′-*O*-[(*tert*-butyl)diphenylsilyl]-3′-deoxyadenosine in dilute $NH_3$/MeOH solution led to the formation of 3′-bromo-5′-*O*-[(*tert*-butyl)diphenylsilyl]-3′-deoxyadenosine (**4**). The addition of $NH_3$/MeOH solution to a solution of 2′-*O*-acetyl-3′-bromo-3′-deoxyadenosine in MeOH was controlled at 0°, and the final concentration of $NH_3$ in MeOH was *ca.* 0.5 – 1.0N. No 2′,3′-anhydroadenosine was formed under these reaction conditions, but it was formed when the reaction was run in concentrated $NH_3$ in MeOH or aqueous solution for a longer time. Compound **3** was treated with 0.5N $NH_3$ in MeOH and then reacted with $PhCH_2NCO$ to yield **5**, which was reacted with NaH and then 1.0N NaOH, and, finally

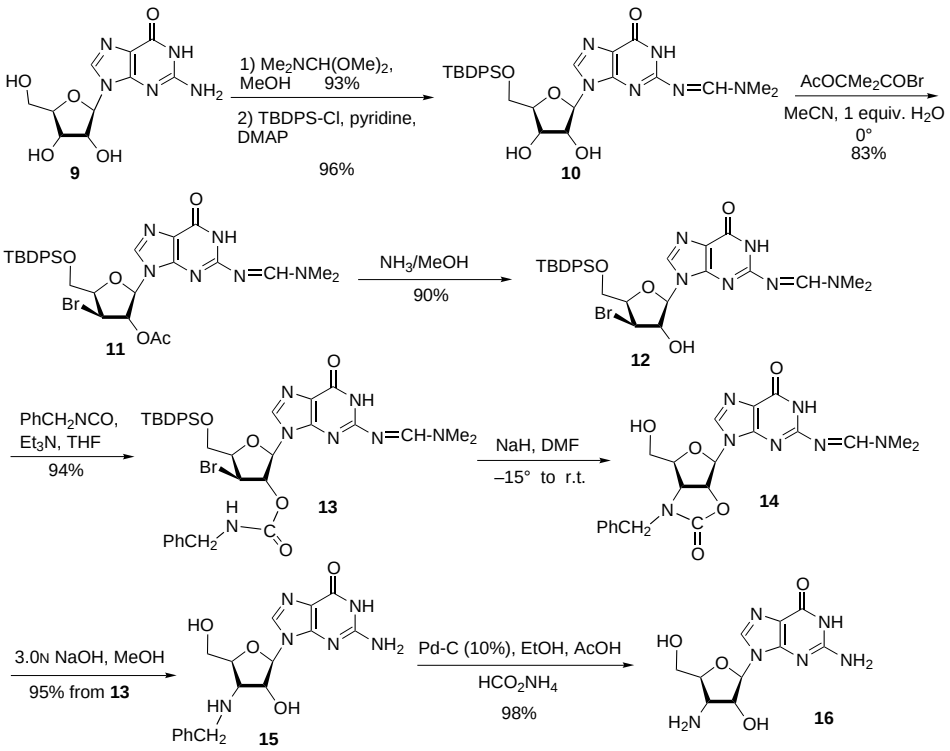
Scheme 1. *Synthesis of 3′-Amino-3′-deoxyadenosine* (**8**)



deprotected by hydrogenation with Pd–C (10%) in EtOH to afford 3′-amino-3′-deoxyadenosine (**8**).

*Synthesis of 3′-Amino-3′-deoxyguanosine.* Adenosine could react with 2-acetoxyisobutyryl bromide to give 3′-bromo-2′-deoxyadenosine; however, guanosine yielded a mixture, presumably because of the 2-$NH_2$ group of purine. After the protection of 2-$NH_2$ group, guanosine can react with 2-acetoxyisobutyryl bromide to yield the desired product [34][35]. The synthesis of 3′-amino-3′-deoxyguanosine is outlined in *Scheme 2*. Guanosine **9** (2.0 g, 7.06 mmol) was reacted with *N*,*N*-dimethylformamide dimethyl acetal in MeOH to give 2-*N*-[(dimethylamino)methylidene]guanosine (2.22 g, 93%) [36], which was then treated with (*t*-Bu)$Ph_2SiCl$ in pyridine to yield **10** (3.3 g, 96%) [35]. To a suspension of **10** (2.3 g, 4.0 mmol) in MeCN (80 ml) containing a trace amount of $H_2O$ (64 µl, 3.6 mmol), 2-acetoxyisobutyryl bromide (2.2 ml, 15.2 mmol) was slowly added under Ar at 0°. The mixture was stirred at 0° for 2 h. After stirring at room temperature for an additional 4 h, the mixture was concentrated

Scheme 2. *Synthesis of 3′-Amino-3′-deoxyguanosine* (**16**)




Exact Mass: 372.1546
Mol. Wt.: 372.3787
C 54.83, H 5.41, N 22.57, O 17.19

Exact Mass: 282.1077
Mol. Wt.: 282.2562
C 42.55, H 5.00, N 29.77, O 22.67

under reduced pressure. The residue was dissolved in $CH_2Cl_2$ and washed with saturated $NaHCO_3$ ($2 \times 50$ ml) and brine ($2 \times 50$ ml). The organic layer was dried (anh. $Na_2SO_4$). After evaporating the solvent, the crude product was purified with a flash silica-gel column, eluting with a gradient from $CH_2Cl_2$ to MeOH/$CH_2Cl_2$ 95 : 5 to give **11** as a white solid (2.3 g, 83%). Reaction of **11** (820 mg, 1.2 mmol) in MeOH (30 ml) with 7.0N $NH_3$ in MeOH (0.85 ml) for 1.5 h at room temperature yielded 9-{3′-bromo-5′-*O*-[(*tert*-butyl)diphenylsilyl]-3′-deoxy-*β*-D-xylofuranosyl}-2-*N*-[(dimethylamino)methylene]guanine (**12**; 690 mg, 90%). Compound **12** (487 mg, 0.76 mmol) was dissolved in 5 ml of anhydrous THF and $Et_3N$ (318 µl, 2.28 mmol), and $PhCH_2NCO$ (282 µl, 2.28 mmol) was added under Ar. The mixture was stirred at room temperature for 2.5 d. MeOH (5 ml) was added, and the mixture was stirred for additional 2 h. After removing the solvent, the solid residue was purified with a silica-gel column eluted with a gradient of $CHCl_3$ and $CHCl_3$/MeOH 95 : 5 to give the desired compound **13** as a white solid (550 mg, 94%).

When **13** was reacted with NaH in anhydrous THF at $-20°$ and room temperature for 2 d, as described for adenosine, no reaction was observed. We repeated the reaction once more, but no ring-closing reaction had been observed. However, when the ring-closing reaction was performed in anhydrous DMF, the desired product **14** was obtained in very high yield. A solution of **13** (355 mg, 0.46 mmol) in 15 ml of anhydrous DMF was cooled with an ice/EtOH bath ($-15°$), and NaH (36 mg, 1.48 mmol) was added. The mixture was stirred for 4 h between $-15°$ and 0°, and for 24 h at room temperature. The reaction was monitored by TLC ($CHCl_3$/MeOH 9 : 1). After the disappearance of the starting material, the mixture was filtered, and the solution was evaporated under reduced pressure. The residue was dissolved in AcOEt (200 ml) and washed with $H_2O$ (20 ml), saturated $NaHCO_3$ ($2 \times 25$ ml), and brine (50 ml). The organic layer was dried ($Na_2SO_4$). By evaporation of the solvent, compound **14** was obtained and used for the next step of reaction without further purification. Compound **14** was treated with a solution of 3.0N NaOH (aq.) MeOH 1 : 1 to yield 3′-(benzylamino)-3′-deoxyguanosine (**15**). The pure compound **15** (207 mg, 95% from **13**) was obtained by the *C18* reversed-phase chromatography eluted with a gradient from $H_2O$ to MeOH/$H_2O$ 1 : 1. Compound **15** was dissolved in MeOH. The mixture with Pd/C (10%) catalyst was sealed in a stainless steel reaction vessel under 50 psi $H_2$ pressure and shaken at room temperature for a week. The mixture was filtered through *Celite*, and the filtrate was evaporated to dryness and worked up as usual to give 3′-amino-3′-deoxyguanosine (**16**) in very low yield because of the poor solubility of **15** in EtOH. Other deprotection methods to remove $PhCH_2$ group have also been tested. According to one of the successful methods compound **15** was dissolved in a mixture of EtOH and AcOH, and a catalytic amount of 10% Pd/C and an excess of ammonium formate were added. The suspension was stirred for 24 h at room temperature. The reaction was monitored by TLC. After removing the solid materials, the solvents were evaporated under reduced pressure. The residue was purified with a *C18* reversed-phase column eluted with a gradient of $H_2O$ and MeOH to give a white solid **16** (98%). The final product was confirmed by $^1$H- and $^{13}$C-NMR spectroscopy, and mass spectrometry. This synthetic route can be scaled up for a large-scale synthesis of 3′-amino-3′-deoxyguanosine (**16**). We are currently using these 3′-amino-3′-deoxy-nucleosides as building blocks to prepare backbone-modified oligonucleotides for biological studies.

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## Experimental Part

1. *General.* All solvents, org. and inorg. chemicals were purchased from *ACROS* or *Aldrich*. Solvents were dried according to standard methods. $CH_2Cl_2$, MeCN, and pyridine were refluxed over $CaH_2$ and freshly distilled before use. Reactions were run under Ar. TLC: pre-coated silica-gel thin-layer sheets *60 F254* from *Merck*; Flash chromatography (FC): silica gel *60*, 180–240 mesh from *Merck*. $^1$H-NMR: *Varian VNMR 400* spectrometer, with $CDCl_3$ or ($D_6$)DMSO as solvents and trace solvent peak as reference, data were recorded as $\delta$ in ppm. ESI-MS: *Finnigan LCQ$^{DUO}$* spectrometry.

2. *5′-*O*-[(*tert*-Butyl)diphenylsilyl]adenosine* (**2**). To a suspension of *adenosine* (**1**; 13.4 g, 50 mmol) in 250 ml of dry pyridine were added 4-(dimethylamino)pyridine (0.3 g, 2.5 mmol) and (*t*-Bu)$Ph_2SiCl$ (15.6 ml, 60 mmol) under Ar. The mixture was stirred at r.t. for 40 h. After the disappearance of the starting material (TLC), 10 ml of MeOH was added to the mixture, and the mixture was stirred at r.t. for 0.5 h. After removing the solvent, the residue was dissolved in $CHCl_3$ (50 ml) and precipitated with $Et_2O$ (200 ml) to form a white solid. After filtration, the solid was washed with $Et_2O$ and $H_2O$, and dried ($P_2O_5$) to give **2** (25.0 g, 98.8%). White solid. TLC ($CHCl_3$/MeOH 85:15): $R_f$ 0.43. $^1$H-NMR (($D_6$)DMSO): 8.46 (*s*, 1 H); 8.31 (*s*, 1 H); 7.61–7.33 (*m*, 10 H); 5.96 (*d*, $J$ = 4.58, 1 H); 4.59 (*t*, $J$ = 4.85, 1 H); 4.32 (*t*, $J$ = 4.94, 1 H); 4.06 (*dt*, $J$ = 3.85, 4.40, 1 H); 3.85 (*m*, 2 H); 0.97 (*s*, 9 H).

3. *2′-*O*-Acetyl-3′-bromo-5′-*O*-[(*tert*-butyl)diphenylsilyl]-3′-deoxyadenosine* (**3**). To a suspension of **2** (20 g, 40 mmol) in MeCN (400 ml) containing a trace amount of $H_2O$ (0.65 ml, 3.6 mmol) was added a soln. of 2-acetoxyisobutyryl bromide (17.5 ml, 0.12 mol) in dry MeCN (100 ml) at 0° over 1 h. A clear soln. was formed first after 2.5 h, and, then, a solid precipitate was formed when the reaction progressed. The mixture was stirred at 0° for 5 h. Sat. $NaHCO_3$ soln. was added dropwise at 0° until the pH of the soln. reached 8, and, then, the soln. was neutralized with AcOH to pH 5. The solid was filtered and washed with cold $H_2O$ (150 ml), MeCN (50 ml), and $Et_2O$ (50 ml). The solid product was dried ($P_2O_5$) to yield 11.56 g of **3**. The mother liquor was concentrated to a small volume and extracted with $CHCl_3$ (600 ml). The org. layer was washed with sat. $NaHCO_3$ soln. (2 × 50 ml) and brine (200 ml) and dried ($Na_2SO_4$). After evaporation, the residue was submitted to FC (silica gel; hexane/$CHCl_3$) 1:1 to 1:3 and $CHCl_3$/MeOH (0–5%)) to yield pure **3** (total 19.2 g, 79.5%), and a mixture of **3** and the 3′-acetyl-2′-bromo-2′-deoxy isomer. TLC ($CHCl_3$/MeOH 85:15): $R_f$ 0.61. TLC ($CHCl_3$/MeOH 9:1): $R_f$ 0.52. $^1$H-NMR ($CDCl_3$): 8.34 (*s*, 1 H); 8.15 (*s*, 1 H); 7.71–7.37 (*m*, 10 H); 6.21 (*d*, $J$ = 2.0, 1 H); 5.74 (*t*, $J$ = 2.0, 1 H); 5.62 (br., 2 H); 4.44 (*dd*, $J$ = 1.6, 4.0, 1 H); 4.36 (*m*, 1 H); 4.02 (*m*, 1 H); 2.20 (*s*, 3 H); 1.08 (*s*, 9 H).

4. *3′-Bromo-5′-*O*-[(*tert*-butyl)diphenylsilyl]-3′-deoxyadenosine* (**4**). A suspension of **3** (10.6 g, 17.3 mmol) in 750 ml of MeOH was cooled to 0° in an ice-bath, and 7.0N $NH_3$/MeOH soln. (5 ml, 35 mmol) was added dropwise. The mixture was stirred overnight at 4°, and then at room temperature for 3 h. The white precipitate was filtered and washed with cold MeOH (50 ml). The solid product was dried ($P_2O_5$) to yield 7.0 g of pure **4**. The mother liquor was neutralized with AcOH (2 ml) to pH 5 and evaporated to dryness. The solid was washed with cold $H_2O$, dried ($P_2O_5$), and submitted to FC (silica gel; $CH_2Cl_2$/MeOH (0–5%)). The collected fractions were evaporated to give 1.5 g of **4** (total 8.6 g, 87.4%) and a mixture of **4** and the 2′,3′-epoxide compound (0.5 g).

5. *2′-*O*-[(Benzylamino)carbonyl]-3′-bromo-5′-*O*-[(*tert*-butyl)diphenylsilyl]-3′-deoxyadenosine* (**5**). To a soln. of **4** (6.82 g, 12 mmol) in 150 ml of anh. THF were added $Et_2O$ (3.75 ml, 27 mmol) and $PhCH_2NCO$ (4.5 ml, 36 mmol). The mixture was stirred at r.t. until the disappearance of the starting material for 3 d. MeOH (10 ml) was added, and the mixture was stirred for 0.5 h. After evaporating the solvent, the residue was submitted to FC (silica gel; $CH_2Cl_2$, $CHCl_3$, and $CHCl_3$/MeOH 95:5). The desired fractions were collected and evaporated to yield **5** (8.0 g, 95.0%). White foam. TLC (AcOEt/MeOH 95:5): $R_f$ 0.68. $^1$H-NMR ($CDCl_3$): 8.27 (*s*, 1 H); 8.14 (*s*, 1 H); 7.71–7.27 (*m*, 15 H); 6.23 (*d*, $J$ = 2.4, 1 H); 6.10 (br., 2 H); 5.71 (*s*, 1 H); 5.67 (*t*, $J$ = 6.0, 1 H); 4.53 (*dd*, $J$ = 4.0, 1.2, 1 H); 4.37 (*m*, 3 H); 4.01 (*m*, 1 H); 1.07 (*s*, 9 H).

6. *3′-(Benzylamino)-5′-*O*-[(*tert*-butyl)diphenylsilyl]-3′-*N*,2′-*O*-carbonyl-3′-deoxyadenosine* (**6**). To a soln. of **5** (8.0 g, 11.4 mmol) in 225 ml of anh. THF was added NaH powder (547 mg, 22.4 mmol) at −15° (ice/EtOH bath). The suspension was stirred at −15 to −10° for 1 h. When the reaction took place at −15°, $H_2$ bubbles were observed. The reaction was completed after 1 h at −10°. After filtering through *Celite*, the filtrate was neutralized with AcOH (*ca.* 1 ml) and evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (500 ml) and washed with $H_2O$ (50 ml), sat. $NaHCO_3$ soln. (3 × 50 ml), and brine (2 × 50 ml). The combined aq. layers were re-extracted with $CHCl_3$ (2 × 50 ml), and the combined org. layers were dried ($Na_2SO_4$). After

evaporation, the residue was submitted to FC (silica gel; MeOH/$CHCl_3$ 2:98) to yield **6** (6.67 g, 94.3%). White foam. TLC (AcOEt/MeOH 95:5): $R_f$ 0.64. $^1$H-NMR ($CDCl_3$): 8.07 (*s*, 1 H); 7.86 (*s*, 1 H); 7.52–7.18 (*m*, 15 H); 6.14 (*d*, *J* = 2.8, 1 H); 5.92 (*dd*, *J* = 8.4, 2.8, 1 H); 5.68 (*s*, 2 H); 4.70 (*d*, *J* = 15.2, 1 H); 4.57 (*dd*, *J* = 8.4, 2.8, 1 H); 4.28 (*m*, 3 H); 3.60 (*m*, 2 H); 0.97 (*s*, 9 H).

7. *3′-(Benzylamino)-3′-deoxyadenosine* (**7**). To a soln. of **6** (6.2 g, 10 mmol) in MeOH (200 ml) was added an aq. NaOH soln. (2.0N, 200 ml) in five portions. Each addition was stopped, when the soln. became cloudy, and then more NaOH (aq.) was added after the soln. became clear. The reaction was complete after 3 d. The mixture was neutralized with AcOH to pH 6. The soln. was filtered through *Celite*, and the filtrate was evaporated under reduced pressure. The residue was co-evaporated with EtOH to afford a white solid. The crude product was purified by FC (silica gel; MeOH/$CHCl_3$ (0–10%)). The collected fractions were evaporated to give **7** (3.45 g, 96.7%). White solid. TLC ($CHCl_3$/MeOH 9:1): $R_f$ 0.37. TLC (i-PrOH/aq. $NH_3$/$H_2O$ 8:1:1): $R_f$ 0.83. $^1$H-NMR ((D$_6$)DMSO): 8.36 (*s*, 1 H); 8.12 (*s*, 1 H); 7.36–7.19 (*m*, 8 H); 5.96 (*d*, *J* = 3.8, 1 H); 4.57 (*dd*, *J* = 5.1, 3.8, 1 H); 3.92 (*m*, 1 H); 3.80–3.70 (*m*, 3 H); 3.56–3.33 (*m*, 2 H).

8. *3′-Amino-3′-deoxyadenosine* (**8**). A mixture of **7** (3.0 g, 8.4 mmol) and 10% Pd/C (0.3 g) in EtOH/$H_2O$ (150 ml/150 ml) was sealed in a stainless steel reactor and shaken under $H_2$ (30 psi) at r.t. for 5 d. The mixture was filtered through *Celite* and washed with hot DMSO. The combined soln. was evaporated under reduced pressure to yield white crystals, which were washed with $Et_2O$. The solid product was dried ($P_2O_5$) to yield **8** (2.05 g, 91.8%). White solid. TLC (i-PrOH/aq. $NH_3$/$H_2O$ 8:1:1): $R_f$ 0.52. $^1$H-NMR ($D_2O$): 8.16 (*s*, 1 H); 8.06 (*s*, 1 H); 5.97 (*d*, *J* = 4.7, 1 H); 4.83 (*dd*, *J* = 6.6, 4.7, 1 H); 4.29 (*m*, 1 H); 3.96 (*t*, *J* = 6.0, 1 H); 3.82–3.65 (*m*, 2 H).

9. *2-[(Dimethylamino)methylidene]guanosine.* To a suspension of guanosine **9** (2.0 g, 7.06 mmol) in 20 ml of abs. MeOH was added *N*,*N*-(dimethylamino)formamide dimethyl acetal (3.4 ml, 25.2 mmol). The mixture was stirred at r.t. for 5 d. The solid precipitate was filtered off and washed with cold MeOH and $Et_2O$, and dried to yield the product (2.22 g, 93.3%). White solid. $^1$H-NMR ((D$_6$)DMSO): 3.01 (*s*, 1 H); 3.13 (*s*, 1 H); 3.56 (*m*, 2 H); 3.88 (*q*, *J* = 6.8, 4.0, 1 H); 4.09 (*q*, *J* = 8.0, 4.8, 1 H); 4.46 (*q*, *J* = 11.2, 6.0, 1 H); 5.01 (*t*, *J* = 5.6, 1 H); 5.17 (*d*, *J* = 3.6, 1 H); 5.40 (*d*, *J* = 6.4, 1 H); 5.78 (*d*, *J* = 6.4, 1 H); 8.02 (*s*, 1 H); 8.51 (*s*, 1 H); 11.33 (br., 1 H). ESI-MS: 361.3 ([*M* + Na]$^+$); calc. for *M*$^+$: 338.1).

10. *5′-O-[(*tert*-Butyl)diphenylsilyl]-2-[(dimethylamino)methyledene)guanosine* (**10**). A suspension of 2-[(dimethylamino)methylidene]guanosine (2.2 g, 6.5 mmol) in 80 ml of dry pyridine was stirred with (*t*-Bu)$Ph_2SiCl$ (1.9 ml, 7.1 mmol) and DMAP (45 mg, 0.37 mmol) for 3 d to give a clear soln. A MeOH (10 ml) was added, and the mixture was stirred for an additional 0.5 h and evaporated under reduced pressure. The residue was washed with cold $H_2O$ and dried under vacuum. The solid was stirred with $Et_2O$, filtered, and washed with $Et_2O$. The solid product was dried in vacuum to give **10** (3.3 g, 96.2%). White solid. TLC ($CHCl_3$/MeOH 9:1): $R_f$ 0.28. ESI-MS: 599.4 ([*M* + Na]$^+$); calc. for *M*$^+$: 576.3).

11. *2′-O-Acetyl-3′-bromo-5′-O-[(*tert*-butyl)diphenylsilyl]-3′-deoxy-2-[(dimethylamino)methylidene]guanosine* (**11**). To a suspension of **10** (2.3 g, 4.0 mmol) in 80 ml of MeCN was added 64 µl of $H_2O$. The mixture was cooled to 0° in an ice-$H_2O$ bath, and 1-(bromocarbonyl)-1-methyl acetate (2.2 ml, 15.2 mmol) was added dropwise under Ar. The mixture was stirred at 0° for 2 h to give a clear soln. After stirring for an additional 4 h at r.t., the mixture was evaporated to dryness. The residue was dissolved in $CHCl_3$ (150 ml) and washed carefully with cold $H_2O$ (20 ml), $NaHCO_3$ soln. (3 × 30 ml), and brine (50 ml). The aq. layers were re-extracted with $CHCl_3$ (3 × 30 ml), and the combined org. layers were dried ($Na_2SO_4$) and evaporated under reduced pressure. The residue was submitted to FC (silica gel; MeOH/$CHCl_3$ (0–5%)) to afford **11** (2.3 g, 82.8%). White foam. TLC ($CHCl_3$/MeOH 9:1): $R_f$ 0.52. $^1$H-NMR ($CDCl_3$, 400 MHz): 1.08 (*s*, 9 H); 2.21 (*s*, 3 H); 3.06 (*s*, 3 H); 3.18 (*s*, 3 H); 4.02 (*m*, 2 H); 4.38 (*d*, 4.4, 1 H); 4.43 (*m*, 1 H); 5.95 (*d*, *J* = 1.8, 1 H); 6.07 (*s*, 1 H); 7.38–7.71 (*m*, 10 H); 7.84 (*s*, 1 H); 8.61 (*s*, 1 H); 9.71 (br., 1 H). $^{13}$C-NMR ($CDCl_3$): 19.4; 21.1; 27.0; 35.4; 41.6; 50.3; 64.8; 81.9; 82.2; 88.8; 120.6; 128.1; 130.2; 132.9; 133.0; 135.8; 136.4; 150.0; 157.4; 158.3; 159.0; 169.1. ESI-MS: 703.3 ([*M* + Na]$^+$), 705.3 ([*M* + Na + 2]$^+$); calc. for *M*$^+$: 680.2.

12. *3′-Bromo-5′-O-[(*tert*-butyl)diphenylsilyl]-3′-deoxy-2-[(dimethylamino)methylidene]guanosine* (**12**). To a soln. of **11** (820 mg, 1.2 mmol) in 30 ml of MeOH was added dropwise a 7.0N soln. of $NH_3$ in MeOH (0.85 ml, 6 mmol). The mixture was stirred at r.t. for 1.5 h. AcOH (1 ml) was added, and the solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (100 ml) and washed with $H_2O$ (20 ml), $NaHCO_3$ soln. (2 × 20 ml), and brine (2 × 20 ml). The aq. layers were extracted with $CHCl_3$ (2 × 20 ml), and the combined org. layers were dried ($Na_2SO_4$). After evaporation, the residue was submitted to FC to yield **12** (690 mg, 89.7%). White solid. TLC ($CHCl_3$/MeOH 9:1): $R_f$ 0.42. $^1$H-NMR ($CDCl_3$): 1.03 (*s*, 9 H); 3.06 (*s*, 3 H); 3.17 (*s*, 3 H); 3.97 (*m*, 2 H); 4.44 (*q*, *J* = 9.9, 5.1, 1 H); 4.54 (*dd*, *J* = 5.1, 3.7, 1 H); 5.17 (br., 1 H); 5.78 (br., 1 H); 5.85 (*d*, *J* = 3.3, 1 H); 7.35–7.69 (*m*, 10 H); 7.79 (*s*, 1 H); 8.51 (*s*, 1 H); 8.82 (br., 1 H). $^{13}$C-NMR ($CDCl_3$): 19.5;

27.1; 30.0; 35.4; 41.8; 54.5; 65.0; 81.0; 82.7; 90.7; 119.2; 128.0; 130.1; 133.2; 135.8; 137.6; 150.6; 157.0; 158.7. ESI-MS: 661.3 ($[M+Na]^+$), 663.3 ($[M+Na+2]^+$); calc. for $M^+$: 638.2.

13. *2′-*O*-[(Benzylamino)carbonyl]-3′-bromo-5′-*O*-[(*tert*-butyl)diphenylsilyl]-3′-deoxy-2-[(dimethylamino)methylidene]guanosine* (**13**). A soln. of **12** (487 mg, 0.76 mmol), $Et_3N$ (318 µl, 2.28 mmol), and $PhCH_2NCO$ (282 µl, 2.28 mmol) in 8 ml of anh. THF was stirred at r.t. for 2.5 d. MeOH (5 ml) was added and the mixture was stirred for 2 h. After removal of solvent, the residue was submitted to FC (silica gel; MeOH/$CHCl_3$) (0–5%)) to give **13** (550 mg, 93.7%). White solid. TLC (AcOEt/MeOH 9:1): $R_f$ 0.30. $^1$H-NMR ($CDCl_3$): 1.08 (*s*, 9 H); 3.01 (*s*, 3 H); 3.04 (*s*, 3 H); 3.02 (*m*, 2 H); 4.43 (*m*, 4 H); 5.45 (*t*, *J* = 5.9, 1 H); 5.96 (*d*, *J* = 1.5, 1 H); 6.11 (*s*, 1 H); 7.29–7.47 (*m*, 15 H); 7.81 (*s*, 1 H); 8.65 (*s*, 1 H); 8.95 (*s*, 1 H). $^{13}$C-NMR ($CDCl_3$): 19.4; 27.0; 35.2; 41.4; 45.5; 51.0; 64.8; 81.7; 83.3; 88.7; 120.5; 127.7; 127.9; 128.1; 128.9; 133.0; 133.1; 135.7; 135.8; 136.3; 138.1; 150.2; 154.7; 157.4; 158.4; 159.0. ESI-MS: 794.2 ($[M+Na]^+$), 796.2 ($[M+Na+2]^+$); calc. for $M^+$: 771.2.

14. *3′-(Benzylamino)-2′-*O*,3′-*N*-carbonyl-3′-deoxy-2-[(dimethylamino)methylidene]guanosine* (**14**). A soln. of **13** (355 mg, 0.46 mmol) in 15 ml of anh. DMF was cooled to −15° in an ice-EtOH bath. NaH (36 mg, 1.48 mmol) was added under Ar. The suspension was stirred at −15 to 0° for 4 h, and at r.t. for 24 h, leading to disappearance of starting material. The solution was filtered and evaporated to dryness. The residue was dissolved in AcOEt (150 ml) and washed with $H_2O$ (20 ml), $NaHCO_3$ soln. (2 × 25 ml), and brine (50 ml). The aq. layers were extracted with $CHCl_3$ (3 × 20 ml), and the combined org. layers were dried ($Na_2SO_4$). After removing the solvent, the residue was used directly for the next step without further purification. In another reaction with 100 mg (0.13 mmol) of **6**, 53 mg (91.4%) of **14** was isolated by FC (silica gel). TLC ($CHCl_3$/MeOH 9:1): $R_f$ 0.32. $^1$H-NMR ($CDCl_3$): 3.00 (*s*, 3 H); 3.07 (*s*, 3 H); 3.51 (*m*, 1 H); 3.85 (*m*, 1 H); 4.29 (*d*, *J* = 6.2, 1 H); 4.31 (*s*, 1 H); 4.52 (*dd*, *J* = 8.4, 2.5, 1 H); 4.75 (*d*, *J* = 6.2, 1 H); 5.35 (br., 1 H); 5.45 (*dd*, *J* = 8.2, 3.9, 1 H); 6.07 (*d*, *J* = 3.9, 1 H); 7.28–7.34 (*m*, 5 H); 7.86 (*s*, 1 H); 8.45 (*s*, 1 H); 9.80 (br., 1 H). $^{13}$C-NMR ($CDCl_3$): 35.4; 41.7; 47.6; 60.7; 62.5; 80.2; 85.5; 91.3; 120.7; 128.6; 128.7; 129.3; 135.1; 137.8; 150.0; 157.0; 157.5; 158.2; 158.8. ESI-MS: 476.3 ($[M+Na]^+$); calc. for $M^+$: 453.2.

15. *3′-(Benzylamino)-3′-deoxyguanosine* (**15**). To a soln. of **14** (crude product without purification) in 20 ml of MeOH was added 20 ml of 3.0N NaOH soln. The mixture was stirred at r.t. for 3 d. The mixture was neutralized with AcOH to pH 5. After evaporating the solvent, a white solid was obtained and washed with $Et_2O$. The solid was dried ($P_2O_5$) to yield 133 mg of **15**. The aq. soln. was concentrated to a small volume and was loaded on a *C18* reversed-phase column and eluted with $H_2O$/MeOH. After evaporation, a total amount of 207 mg (95% from **13**) of **15** was obtained. TLC (i-PrOH/$NH_3$/$H_2O$ 8:1:1). $R_f$ 0.60. $^1$H-NMR ($(D_6)$DMSO): 3.29 (*m*, 1 H); 3.50 (*dd*, *J* = 3.5, 11.6, 1 H); 3.65 (*m*, 1 H); 3.73 (*d*, *J* = 7.7, 2 H); 3.82 (*m*, 1 H); 4.39 (*t*, *J* = 4.6, 1 H); 5.08 (br., 1 H); 5.75 (*d*, *J* = 3.7, 1 H); 5.85 (br., 1 H); 7.03 (br., 2 H); 7.19–7.35 (*m*, 5 H); 7.86 (*s*, 1 H). $^{13}$C-NMR ($(D_6)$DMSO): 51.7; 59.5; 62.2; 73.1; 84.3; 88.8; 117.3; 127.3; 135.6; 141.4; 151.7; 155.4; 158.4. ESI-MS: 395.3 ($[M+Na]^+$); calc. for $M^+$: 372.2.

16. *3′-Amino-3′-deoxyguanosine* (**16**). To a soln. of **15** (60 mg, 0.16 mmol) in 10 ml of EtOH and 2 ml of AcOH were added 10% Pd/C (140 mg, 50% wet) and ammonium formate (760 mg). The suspension was stirred overnight at r.t. The reaction was monitored by TLC. After filtration, the solvents were removed by evaporation under reduced pressure. The residue was purified by a *C18* reversed-phase column with $H_2O$/MeOH. After evaporation, **16** (45 mg, 98%) was obtained. White solid. $^1$H-NMR (400 MHz, $(D_6)$DMSO): 1.82 (br., 2 H); 3.40 (*dd*, *J* = 5.2, 5.6, 1 H); 3.54 (*dd*, *J* = 3.3, 3.6, 1 H); 3.64 (*m*, 1 H); 3.68 (*m*, 1 H); 4.10 (*dd*, *J* = 3.2, 2.4, 1 H); 5.71 (*d*, *J* = 2.4, 1 H); 6.66 (br., 2 H); 7.93 (*s*, 1 H). $^{13}$C-NMR (100 MHz, $(D_6)$DMSO): 52.5; 60.9; 75.0; 85.1; 88.0; 116.6; 135.2; 150.8; 153.9; 156.9. ESI-MS: 283.1 ($[M+H]^+$); calc. for $M^+$: 282.1.

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