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Improved and Reliable Synthesis of 3'-Azido-2', 3'-dideoxyguanosine Derivatives

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Improved and Reliable Synthesis of 3'-Azido-2',3'-dideoxyguanosine Derivatives[†]

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ABSTRACT

An improved synthesis of N²-protected-3'-azido-2',3'-dideoxyguanosine <u>20</u> and <u>23</u> is described. Deoxygenation of 2'-O-alkyl (and/or aryl) sulfonyl-5'-dimethoxytritylguanosine coupled with [1,2]-hydride shift rearrangement gave protected 9-(2-deoxy-threo-pentofuranosyl)guanines (<u>10</u>, <u>12</u> and <u>16</u>). This rearrangement was accomplished in high yield with a high degree of stereoselectivity using lithium triisobutylborohydride (L-Selectride[®]). Compounds <u>10</u>, <u>12</u> and <u>16</u> were transformed into 3'-O-mesylates (<u>18</u> and <u>21</u>), which can be used for 3'-substitution. The 3'-azido nucleosides were obtained by treatment of <u>18</u> and <u>21</u> with lithium azide. This procedure is reproducible with a good overall yield.

Key Words: Rearrangement; L-Selectride[®]; Reduction; Stereoselectivity; 3'-Azido-2'; 3'-dideoxyguanosine.

Since the discovery of the human immunodeficiency virus (HIV), there has been a growing interest in compounds that can block the replication of retroviruses. The activity of 3'-azido-3'-deoxythymidine (AZT), an approved drug for the treatment of AIDS patients, is partly attributed to an inhibition of the reverse transcriptase by the 5'-triphosphate metabolite of AZT.

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[†]In honor and celebration of the 70th birthday of Professor Leroy B. Townsend. *Correspondence: Morteza M. Vaghefi, TriLink BioTechnologies Inc., 9955 Mesa Rim Road, San

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Because of the efficacy of AZT as an antiretroviral agent, the synthesis and biological activity of other 3'-azido-2',3'-dideoxynucleosides is of great interest. Most of the efforts to date are focused on 3'-azido-2',3'-dideoxypyrimidine nucleoside derivatives for which a relatively convenient chemistry is well developed.

On the other hand, the methodology used to prepare the 3'-azido guanosine analog is not as well developed.^[1-6] Furthermore, in our hands the methods used to produce the 3'-azido adenosine analogs did not work with guanosine. We wish to describe an improved procedure that not only overcomes some of the difficulties encountered with earlier methods, but also can be scaled-up without difficulty.

RESULTS

 N^2 -Isobutyrylguanosine (2) was synthesized by treatment of guanosine (1) first with an excess of trimethylsilyl chloride in pyridine, and then with isobutyryl chloride. Silyl groups were then removed by treatment with water and dilute ammonia to yield 2. Nucleoside 2 was converted to its 3',5'-O-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl) derivative 3 which was then tosylated to give fully protected compound 4. Mesylation of 3 gave nucleoside 5. Removal of the silyl protective group from 4 and 5 with TBAF in THF proceeded without difficulties to give N^2 -isobutyryl-2'-O-tosyl-guanosine 6 and mesylate 7 in > 85% yield. Protection of the 5'-position with DMT-Cl in pyridine gave nucleoside 8 and mesylate 9. The overall yield of 8 from compound 1 was 37% (Scheme 1).

The next step in the synthesis of 3'-azido-2',3'-dideoxyguanosine is the elimination of the 2'-O-tosyl or mesyl group ($\underline{6}, \underline{7}, \underline{8}$ and $\underline{9}$) coupled with hydride rearrangement^[2] to yield compounds $\underline{10}$ and $\underline{12}$ (Scheme 2). Attempts to use the route described for the



Scheme 1. Synthesis of the 2'-O-mesyl-and tosyl derivatives of guanosine.

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Scheme 2. [1,2]-Hydride shift rearrangement of 2'-O-mesyl and tosyl derivatives of guanosine with Super-Hydride[®] or L-Selectride[®].

production of the three analog of deoxyadenosine,^[2] treatment with 10 eq. of lithium triethylborohydride (Super-Hydride^(R)) in THF, gave less than desirable results due to the lack of selectivity. Equal amounts of both the desired (<u>10</u> and <u>12</u>) and undesired (<u>11</u> and <u>13</u>) isomers were formed from the tosyl derivatives (<u>6</u> and <u>8</u>) (Scheme 2), whereas the mesyl analog (<u>9</u>) gave only traces of the desired compound (<u>10</u>).

The reactions were repeated without the protecting group (<u>14</u> and <u>15</u>) on the exocyclic amine to see if the isobutyryl group affected selectivity. Selectivity was improved somewhat (75% of <u>16</u> and 20% of <u>17</u>) (Scheme 3) but we felt that there was still considerable room for improvement.

We decided to investigate a bulkier lithium borohydride reagent (L-Selectride[®]; lithium triisobutyl-borohydride), which has been reported to perform stereoselective reductions. Originally L-Selectride[®] was developed as a selective hydride donator, and thus seemed to be a very practical choice for our purposes. The use of L-Selectride[®] on compounds <u>8</u> and <u>9</u> resulted in the formation of only the desired isomer, <u>10</u> (Scheme 2). This conversion not only occurred with absolute selectivity, but also in near quantitative yield.

The title compound, 20, was thus readily obtained from this intermediate first by mesylation of the 3'-inverted hydroxyl. Subsequent treatment of 18 with lithium azide



Scheme 3. Rearrangement of 2'-O-mesyl and tosyl derivatives of guanosine without the protecting group on the exocyclic amine.

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Scheme 4. Conversion of N²-isobutyryl-9-(5-*O*-dimethoxytrityl-2-deoxy- β -D-threo-pentofurano-syl)guanine into N²-isobutyryl-9-(3-azido-2,3-dideoxy- β -D-erythro-pentofuranosyl)guanine.

in DMF at 100°C for two hours gave <u>19</u>, which was then deprotected with 80% AcOH/ H_2O giving a 15% overall yield of <u>20</u> from compound <u>1</u> (Scheme 4).

Mesylation of the unprotected nucleosides <u>16</u> was also possible but side reactions occurred. Although the N^2 -dimethylformamidine protection of <u>16</u> improved the mesylation reaction (<u>21</u>), the overall yield of 3'-azido <u>22</u> and <u>23</u> were not improved over the isobutyryl route (Scheme 5).

MATERIALS AND METHODS

Melting Points Are Uncorrected. ¹H NMR spectra were obtained at 500 MHz. Low-resolution ES mass spectra (LRMS) were recorded with an ionization voltage of



Scheme 5. Conversion of 9-(5-O-dimethoxytrityl- β -D-thereo-pentofuranosyl)guanine to N²-(dimethylaminomethylene)-9-(3-azido-2,3-dideoxy, β -D-erythro-pentofuranosyl)guanine.





90 eV. Reaction monitoring and compound purity determinations were performed with Beckman HPLC (System Gold, 126 Solvent Module with Beckman 168 detector) using mainly a reverse phase column. TLC was performed with Merck 60 F254 silica, and flash column chromatography with Silica Gel 60 Geduran[®] (40–63 μ m, Merck). Aldrich chemicals were used without purification. Solvents were purified, dried, and distilled before use. Super-Hydride[®] and L-Selectride[®] were from Aldrich Chemicals (Milwaukeee, WI).

 N^2 -Isobutyryl-3',5'-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)guanosine (3). To guanosine 1 (35 g, 124 mmol) dried by coevaporation with pyridine (2×200 mL) and suspended in anhydrous pyridine (500 mL) was added over 5 min trimethylchlorosilane (100 mL, 1075 mmol). This solution was stirred for 1 h at room temperature and then mixed with isobutyryl chloride (26 mL, 248 mmol). After 20 h, water (50 mL) was added, concentrated, and the residue was co-evaporated with water (2 \times 50 mL). Crude N^2 -isobutyrylguanosine (2) was dissolved in pyridine (100 mL) and ammonium hydroxide (20 mL), and the solution was concentrated to dryness. The residue was redissolved in pyridine (200 mL) and treated with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (38 mL, 132 mmol) overnight at room temperature. The volatiles were evaporated and the residue was dissolved in DCM (300 mL), washed with water, aqueous NaHCO₃, dried (MgSO₄) and evaporated to give crude product, which was purified by column chromatography (2.0 L SiO₂, in CH₂Cl₂:MeOH 98:2), to give 61 g of product 3 (102 mmol, 83% yield). ¹H NMR (500 MHz, Me₂SO-d₆): δ 12.8 (s, 1H, NH), 9.06 (s, 1H, NH), 7.90 (s, 1H, H-8), 5.86 (s, 1H, H-1'), 4.54 (dd, 1H, H-2'), 4.30 (d, 1H, H-3', J = 5.0 Hz), 4.14 (dd, 1H, H-5'a), 4.09 (ddd, 1H, H-4'), 4.04 (dd, 1H, H-4')H-5'b) 2.70 (m, 1H, HCMe₂), 1.27-1.00 m, (34 H, TPDS, CMe₂). C₂₆H₄₅N₅O₇Si₂. M = 595.84, LRMS m/z = 596 [100, M + H]⁺, 594 (100, M - H)⁻.

*N*²-Isobutyryl-2'-*O*-methanesulfonyl-3',5'-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)guanosine (<u>5</u>). Compound <u>3</u> (61 g, 102 mmol) was dissolved in anhydrous DCM (400 mL) and treated with DMAP (15 g, 124 mmol) and mesyl chloride (10 mL, 136 mmol, 1.3 eq). The reaction mixture was stirred for 1 h at room temperature, treated with MeOH (30 mL) and concentrated in vacuo. The residue was dissolved in DCM (400 mL) washed with aq. NaHCO₃, dried (MgSO₄), evaporated and purified by column chromatography (2.0 L SiO₂, in CH₂Cl₂:MeOH 98:2) to give 43 g (64 mmol, 63%) of <u>5</u> as a foam. ¹H NMR(500 MHz, CDCl₃): δ 12.07 (s, 1H, NH), 9.17 (s, 1H, NH), 7.99 (s, 1H, H-8), 6.05(s, 1H, H-1'), 5.24(d, 1H, H-2', J_{2',3'} = 4.3 Hz), 4.58 (dd, 1H, H-3', J_{3',4'} = 9.4 Hz), 4.28 (dd, 1H, H-5'a), 4.10 (d, 1H, H-4', J_{3',4'} = 9.4 Hz), 4.01 (dd, 1H, H-5'b), 3.20 (s, 3H, SO₂ CH₃) 2.67(m, 1H, <u>H</u>C Me₂), 1.24–1.04 (m, 34H, TPDS, Cme₂). C₂₇H₄₇N₅O₉SSi₂. M = 673.86, LRMS m/z = 674 [100, M + H]⁺, 672 [100, M - H]⁻.

 N^2 -Isobutyryl-2'-O-p-toluenesulfonyl-3',5'-O-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)guanosine (4). Compound 1 (35 g, 124 mmol) was coevaporated from pyridine (2 × 200 mL), suspended in pyridine (600 mL) and treated with trimethylchlorosilane (100 mL). After 1 h isobutyryl chloride (26 mL, 244 mmol, 2 eq) was added with cooling and the reaction mixture was stirred at room temperature for 24 h. The volatiles were evaporated and the residue was coevaporated with water (2 × 100 mL),



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ammonium hydroxide (20 mL), and pyridine (2 × 300 mL). The residue was redissolved in pyridine (600 mL) and treated with TPDS–Cl₂ (38 mL, 1 eq). After 3 h the volatiles were evaporated, the residue dissolved in CH₂Cl₂ (500 mL) and washed with water, aq. NaHCO₃, dried (MgSO₄) and evaporated to give the residue which was dissolved in CH₂Cl₂ (500 mL) and treated with DMAP (30 g, 246 mmol, 2 eq) and tosyl chloride (30 g, 157 mmol, 1.5 eq). After 3 h the reaction mixture was washed with 5% HCl, then with water, aq. NaHCO₃, dried (MgSO₄) and evaporated. Crude product was purified by column chromatography (3.0 L SiO₂, in CH₂Cl₂:MeOH 98:2) to afford 40 g of <u>5</u> (59 mmol, 48% from guanosine). ¹H NMR (500 MHz, CDCl₃): δ 12.07 (s, 1H, NH), 8.92 (s, 1H, NH), 7.85 (s, 1H, H-8), 7.74 (d, 2H, Ph, J = 8.0 Hz), 7.26 (d, 2H, Ph) 6.03 (s, 1H, H-1'), (s, 1H, H-2') J_{2',3'} = 4.5 Hz), 4.58 (dd, 1H, H-3', J_{3',4'} = 9.0 Hz), 4.16 (d, 1H, H-5'a, J = 13.0 Hz) 4.05 (d, 1H, H-4', J = 9.0 Hz), 3.95 (dd, 1H, H-5'b), 2.67 (m, 1H, <u>H</u>CMe₂), 2.40 (s, 3H, PhCH₃), 1.27–0.85 (m, 34H, TPDS, CMe₂). C₃₃H₅₁N₅O₉SSi₂. M = 749.95, LRMS m/z = 750 [100, M + H]⁺, 748 [100, M – H]⁻.

 N^2 -Isobutyryl-2'-*O*-p-toluenesulfonylguanosine (<u>6</u>). Compound <u>4</u> (40.0 g, 53.3 mol) was dissolved in anhydrous THF (400 mL) and treated with TBAF (1 M in THF, 110 mL) at room temperature for 2 h. The volatiles were evaporated to dryness and the residue was purified by column chromatography (2.0 L SiO₂, in CH₂Cl₂:MeOH 95:5) to give 23 g (45 mmol, 85%) of <u>6</u> as a white foam. ¹H NMR (500 MHz, Me₂SO-d₆): δ 12.01 (s, 1H, NH), 11.53 (s, 1H, NH), 7.43 (d, 2H, Ph, J = 8.0 Hz), 6.02 (d, 1H, 3'-OH, J = 5.0 Hz), 5.94 (d, 1H, H-1', J_{1',2'} = 7.5 Hz), 5.39 (dd, 1H, H-2', J_{2',3'} = 2.5 Hz), 5.20 (t, 1H, H-5'–OH, J = 5.0 Hz), 4.30 (m, 1H, H-3'), 4.00 (m, 1H, H-4'), 3.64 (m, 1H, H-5'a), 3.55 (m, 1H, H-5'b), 2.79 (m, 1H, HCMe₂), 2.26 (s, 3H, Ph CH₃), 1.17 (d, 6H, CMe₂, J = 6.8 Hz). C₂₁H₂₅N₅O₈S. M = 507.44, LRMS m/z = 336 [100, loss of tosyl]⁻.

 N^2 -Isobutyryl-2'-*O*-methanesulfonylguanosine (7). Nucleoside <u>5</u> (43 g, 64 mmol) was dissolved in THF (400 mL) and treated with TBAF (1M in THF, 128 mL). The reaction mixture was stirred at room temperature for 1 h, concentrated in vacuo and purified by column chromatography (2.0 L SiO₂, in CH₂Cl₂:MeOH 95:5) to afford 23.7 g (55 mmol, 86%) of <u>7</u> as a white foam. ¹H NMR (500 MHz, Me₂SO-d₆): δ 12.10 (s, 1H, NH), 11.65 (s, 1H, NH), 8.27 (s, 1H, H-8), 6.10 (d, 1H, H-1', J_{1',2'} = 5.9 Hz), 5.91 (d, 1H, 3'-OH, J = 5.0 Hz), 5.44 (t, 1H, 5'-OH, J = 5.0 Hz), 5.20 (t, 1H, H-2', J = 5.0 Hz), 4.47 (dd, 1H, H-3'), 4.00 (m, 1H, H-4',) 3.66 (m, 1H, H-5'a), 3.59 (m, 1H, H-5'b), 3.18 (s, 3H, SO₂ CH₃), 2.77 (m, 1H, <u>H</u>CMe₂), 1.12 (d, 6H, CMe₂. J = 6.8 Hz). C₁₅H₂₁N₅O₈S. M = 431.36, LRMS m/z = 430 [100, M − H][−].

 N^2 -Isobutyryl-2'-O-methanesulfonyl-5'-O-dimethoxytritylguanosine (9). Nucleoside 7 (26.8 g, 62 mmol) was dissolved in pyridine then evaporated to dryness, redissolved in pyridine (500 mL) and treated with DMTCl, (25 g, 1.2 eq., 73.8 mmol). After 3 h the pyridine was evaporated together with toluene (500 mL), the residue was dissolved in CH₂Cl₂ (500 mL), washed with saturated aq. NaHCO₃, dried (Mg SO₄), evaporated and purified by column chromatography (2.0 L SiO₂, in CH₂Cl₂:MeOH 97:3, then 95:5) to yield compound 9 as a white foam (36 g, 49 mmol, 79%). ¹H NMR (500 MHz, Me₂SO-d₆): δ 12.12 (s, 1H, NH), 11.59 (s, 1H, NH), 8.16 (s, 1H, H-8), 7.33–6.80

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(m, 13h, Ph), 6.18 (d, 1H, H-1' $J_{1',2'}$ = 4.3 Hz), 5.87 (d, 1H, 3'-OH, J = 6.0 Hz), 5.59 (dd, 1H, H-2', $J_{2',3'}$ = 4.7 Hz), 4.60 (k, 1H, H-3') 4.10 (m, 1H, H-4'), 3.72 (s, 6H, OMe), 3.35 (m, 1H, H-5'a), 3.22 (s, 3H, SO₂CH₃), 3.20 (m, 1H, H-5'b), 2.73 (m, 1H, <u>H</u>CMe₂), 1.12 (2d, 6H, CMe₂, J = 6.8 Hz). C₃₆H₃₉N₅O₁₀S. M = 733.7, LRMS m/z = 734 [100, M + H]⁺, 732 [100, M - H]⁻.

*N*²-Isobutyryl-2'-*O*-p-toluenesulfonyl-5'-*O*-dimethoxytritylguanosine (§). Nucleoside <u>6</u> (23 g, 45 mmol) was mixed with DMTCl (23 g, 68 mmol, 1.5 eq) in anhydrous pyridine (300 mL) and stirred at room temperature for 3 h. The solution was diluted with toluene (300 mL) and evaporated to dryness. The residue was treated with EtOAc and saturated solution of NaHCO₃; organic layer was washed with water, dried (MgSO₄) and evaporated to give a yellow foam. Crude <u>8</u> was purified by column chromatography (2.0 L SiO₂, in CH₂Cl₂:MeOH 95:5) to afford pure <u>8</u> (33 g, 40.8 mmol, 91%) as a yellow foam. ¹H NMR (500 MHz, Me₂SO-d₆): δ 11.99 (s, 1H, NH), 11.34 (s, 1H, NH), 7.93 (s, 1H, H-8) 7.22-6.79 (m, 17H, Ph), 5.99 (d, 1H, 3'-OH, J = 6.0 Hz), 5.97 (d, 1H, H-1, J_{1',2'} = 6.4 Hz), 5.54 (t, 1H, H-2', J_{2',3'} = 6.0 Hz), 4.30 (dd, 1H, H-3'), 4.07 (m, 1H, H-4'), 3.71 (s, 6H, OMe), 3.34 (m, 1H, H-5'a), 3.15 (m, 1H, H-5'b), 2.73 (m, 1H, <u>H</u>CMe₂), 2.26 (s, 3H, PhCH₃) 1.15 (2d, 6H, CMe₂, J = 6.8 Hz). C₄₂H₄₃N₅O₁₀S. M = 809.76, LRMS m/z = 810 [100, M + H]⁺, 808 [100, M - H]⁻.

 N^2 -Isobutyryl-9-(5-*O*-dimethoxytrityl-2-deoxy-β-D-threo-pentofuranosyl)guanine (<u>10</u>). To a solution of nucleoside <u>8</u> (4.2 g, 5 mmol) in anhydrous THF (50 mL), cooled in an ice bath, was added lithium triethylborohydride (Super-Hydride[®], 1M in THF, 50 mL, 10 eq.). After 16 hours, water (10 mL) was added to the reaction mixture, and the volatiles were evaporated. The residue was dissolved in DCM, washed with water, dried and purified by column chromatography (400 mL of SiO₂, CH₂Cl₂:MeOH 95:5). Compound <u>10</u> was obtained (0.87 g, 1.4 mmol, 26%) as white crystals with mp 178–183°C. ¹H NMR (500 MHz, CDCl₃) δ 12.08 (S, 1H, NH), 8.92 (s, 1H, NH), 7.93 (s, 1H, H-8), 7.42–6.79 (m, 13H, Ph), 6.07 (dd, 1H, H-1', J = 2.0 Hz), 4.88 (d, 1H, 3'-OH, J = 5.5 Hz), 4.49 (1m, 1H, H-3'), 4.07 (m, 1H, H-4'), 3.54 (m, 1H, H-5'a, J = 8.5 Hz), 3.45 (m, 1H, H-5'b), 2.72 (m, 1H, H-2'a), 2.58 (m, 1H, CH Me₂), 2.50 (m, 1H, H-2'b), 1 22 (d, 3, HC<u>M</u>e, J = 6.8 Hz), 1.21 (d, 3H, HC<u>M</u>e, J = 6.8 Hz). C₃₅H₃₇N₅O₇. M = 639.7, LRMS m/z = 640 [100, M + H]⁺ · 638 [100, M - H]⁻.

2'-O-Methanesulfonyl-5'-O-dimethoxytritylguanosine (<u>15</u>). Nucleoside <u>9</u> (31 g, 42 mmol) was dissolved in saturated solution of ammonia in methanol (300 mL) and stirred at room temperature overnight. The volatiles were evaporated to give compound <u>15</u> (27 g, 40.7 mmol, 96%) as white crystals with mp 160–163°C (with decomp.). ¹H NMR (500 MHz, Me₂SO–d₆): δ 8.60 (s, 1H, NH), 7.83 (s, 1H, H-8) 7.35–7.20 and 6.86–6.83 (m, 13H, Ph), 6.50 (s, 2H, NH₂), 6.05 (d, 1H, H-1', J_{1',2'} = 4.0 Hz), 5.84 (s, 1H, 3'-OH), 5.53 (t, 1H, H-2', J = 4.7 Hz), 4.57 (m, 1H, H-3'), 4.05 (m, 1H, H-4'), 3.73 (s, 6H, OMe), 3.33 (m, 1H, H-5'a), 3.24 (m, 1H, H-5'b), 3.24 (s, 3H, SO₂Me). C₃₂H₃₃N₅O₉S. M = 663.6, LRMS m/z = 664 [100, M + H]⁺, 662 [100, M – H]⁻.

2'-O-p-Toluenesulfonyl-5'-O-dimethoxytritylguanosine (<u>14</u>). Nucleoside <u>8</u>(3.3 g, 4 mmol) was dissolved in saturated solution of ammonia in methanol (20 mL) and stirred overnight. The solution was evaporated to dryness, the crystalline residue was



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diluted with methanol and filtered to give compound <u>14</u> (2.3 g, 3.1 mmol, 77%) as white crystals, mp 198–202°C (with decomp.); ¹H NMR (500 MHz, Me₂SO–d₆): δ 10.61 (s, 1H, NH), 7.62 (s, 1H, H-8), 7.54–6.84 (m, 17H, Ph), 6.25 (s, 2 H, NH₂), 5.90 (d, 1H, H-1', J_{1',2'} = 6.0 Hz), 5.84 (d, 1H, 3'-OH, J = 6.0 Hz), 4.32 (m, 1H, H-3'), 4.03–3.99 (m, 2H, H-4', H-5'a), 3.73 (s, 6H, 2 OMe), 2.31 (s, 3H, Ph–Me). C₃₈H₃₇N₅O₉S. M = 739.72, LRMS m/z = 740 [100, M + H]⁺, 738 [100, M – H]⁻.

9-(5-*O***-Dimethoxytrityl-2-deoxy-β-D-threo-pentofuranosyl)guanine** (<u>16</u>). Nucleoside <u>15</u> (30 g, 45 mmol) was dissolved in hot THF (300 mL) and evaporated to dryness. The residue again was dissolved in THF (500 mL) cooled to 5°C (ice-water bath) and stirred under argon atmosphere for 30 min. L-Selectride[®] (1 M in THF, 450 mL) was added dropwise over 30 min and the reaction mixture was stirred for 3 h. The water (20 mL) was added very carefully and the solution was evaporated to dryness. The residue was dissolved in CH₂Cl₂ (600 mL) and washed with sat. aq. NaHCO₃. During washing, <u>16</u> precipitated. The precipitate was filtered off, washed with water and dried under vacuum to give compound <u>16</u> (23 g, 40.4 mmol, 90%), mp 178–183°C; ¹H NMR (500 MHz, Me₂SO–d₆); δ 10.61 (s, 1H, NH), 7.79 (s, 1H, H-8), 7.28–6.80 (m, 13H, Ph), 6.47 (s, 2H, NH₂), 6.10 (dd, 1H, H-1', J_{1',2'} = 6.0 Hz), 5.38 (d, 1H, 3'-OH, J = 4.0 Hz), 4.30 (m, 1H, H-3'), 4.15 (m, 1H, H-4'), 3.32 (m, 1H, H-5'a), 3.18 (m, 1H, H-5'b), 2.66 (m, 1H, H-2'a), 2.17 (m, 1H, H-2'b). C₃₁H₃₁N₅O₆. M = 569.5, LRMS m/z = 570 [100, M + H]⁺, 568 [100, M – H]⁻.

 N^2 -[(Dimethylamino)methylene]-9-(3-O-methanesulfonyl-5-O-dimethoxytrityl-2'-deoxy-BD-threo-pentofuranosyl)guanine (21). Nucleoside 16 (5.0 g, 8.8 mmol) was dissolved in hot pyridine and evaporated to dryness. The residue was suspended in pyridine (100 mL) and treated with N,N-dimethylformamide dimethyl acetal (3.0 mL, 28 mmol, 2 eq.) at room temperature overnight. The volatiles were evaporated in vacuo and the residue was coevaporated from xylenes, then dissolved in pyridine (100 mL) and cooled to 4°C (ice-water bath). Methanesulfonyl chloride (1.2 mL, 15.5 mmol, 1.5 eq.) in pyridine (2 mL) was added dropwise at stirring then DMAP (100 mg) was added. After 20 h the volatiles were evaporated, the residue was dissolved in CH₂Cl₂, washed with aq. NaHCO₃, dried (MgSO₄), evaporated and purified on the silica gel (500 mL) column (CH₂Cl₂:MeOH 97:3) to give compound **21** (2.6 g, 3.7 mmol, 42%) as a brown foam. ¹H NMR (500 MHz, Me₂SO- d_6): δ 11.36 (s, 1H, NH), 8.58 (s, 1H, HC=N), 7.71 (s, 1H, H-8), 7.40–6.84 (m, 13H, Ph), 6.30 (dd, 1H, H-1'), 5.43 (m, 1H, H-3'), 4.40 (m, 1H, H-4'), 3.73 (s, 6H, OMe), 3.13 (s, 3H, SO₂Me), 3.08 (s, 3H, NMe). 3.03 (s, 3H, NMe), 2.71 (m, 1H, H-2'a), 2.50 (m, 1H, H-2'b). C₃₅H₃₈N₆O₈S. M = 702.69, LRMS $m/z = 703 [100, M + H]^+$, 701 [100, $M - H]^-$.

 N^2 -[(Dimethylamino)methylene]-9-(3-azido-5-*O*-dimethoxytrityl-2,3-dideoxy-β-D-erythro-pentofuranosyl)guanine (<u>22</u>). Nucleoside <u>21</u> (2.6 g, 3.7 mmol) was dissolved in DMF (50 mL) and treated with LiN₃ (0.9 g, 18.5 mmol, 5 eq.) at room temperature for 3 h. The volatiles were evaporated to dryness. The residue was dissolved in CH₂Cl₂, washed with water and purified by column chromatography (400 mL SiO₂, in CH₂Cl₂:MeOH 98:2) to give compound <u>22</u> (1.8 g, 75%). ¹H NMR (500 MHz, Me₂SO-d₆): δ 11.37 (s, 1H, NH), 8.53 (s, 1H, HC=N), 8.02 (s, 1H, H-8), 7.31-6.80 (m, 13H, Ph) 6.23 (dd, 1H, H-1', J_{1',2'a} = 7.0 Hz, J_{1',2'b} = 2.5 Hz), 4.73 (dd,

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1H, H-3'), 3.89 (m, 1H, H-4'), 3.72 (s, 6H, 2 OMe), 3.10 (s, 3H, N Me), 3.02 (s, 3H, N Me), 2.52 (m, 1H, H-2'a), other protons overlapped the signals associated with H₂O and N-me. $C_{34}H_{35}N_9O_5$. M = 649.68, LRMS m/z = 650 [100, M + H]⁺, 648 [50, M - H]⁻.

*N*²-(Dimethylaminomethylene)-9-(3-azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)guanine (23). Nucleoside 22 (1.8 g, 2.8 mmol) was dissolved in 80% AcOH/H₂O (50 mL) and stirred at room temperature for 1 h. The volatiles were evaporated and the residue was purified by column chromatography (400 mL SiO₂, in CH₂Cl₂:MeOH 95:5) to give compound 23 (0.63 g, 1.8 mmol, 66%) as white crystals, mp 193–195°C. ¹H NMR (500 MHz), Me₂SO-d₆): δ 11.35 (s, 1H, NH), 8.58 (s, 1H, HC=N), 8.04 (s, 1H, H-8), 6.20 (t, 1H, H-1', J = 6.6 Hz), 5.13 (m, 1H, 5'-OH), 4.62 (m, 1H, H-3'), 3.90 (m, 1H, H-4'), 3.58 (m, 2H, H-5'a, H-5'b), 3.16 (s, 3H, NMe), 3.03 (s, 3H, NMe), 2.85 (m, 1H, H-2'a), 2.46 (m, 1H, H-2'b). C₁₃H₁₇N₉O₃. M = 347.33, LRMS m/z = 348 [50, M + H]⁺, 346 [100, M - H]⁻, HPLC purity: 99%.

*N*²-Isobutyryl-9-(5-*O*-dimethoxytrityl-2-deoxy-β-D-threo-pentofuranosyl)guanine (<u>10</u>). Nucleoside <u>8</u> (31.6 g, 39 mmol) in anhydrous THF (400 mL) was cooled to 5°C (ice-water bath) and stirred for 30 min under argon atmosphere. L-Selectride[®] (1M in THF, 390 mL, 10 eq.) was added dropwise and the reaction mixture was stirred for 2 h, then quenched with water (20 mL, dropwise). The volatiles were evaporated and the residue was purified by column chromatography (2.0 L SiO₂, in CH₂Cl₂:MeOH 95:5) to give compound <u>10</u> (22.5 g, 35.2 mmol, 90%) as a light yellow foam. ¹H NMR (500 MHz, Me₂SO-d₆): δ 12.10 (s, 1H, NH), 11.74 (s, 1H, NH), 8.01 (s, 1H, H-8), 7.40–6.79 (m, 13H, Ph), 6.21 (d, 1H, H-1', J = 7.8 Hz), 5.29 (d, 1H, 3'-OH, J = 4.0 Hz), 4.33 (m, 1H, H-3'), 4.21 (m, 1H, H-4'), 3.72 (s, 6H, 2-OMe), 3.33 (m, 1H, H-5'a, overlapped by H₂O), 3.17 (m, 1H, H-5'b), 2.77 (m, 1H, H-2'a), 2.69 (m, 1H, HCMe₂), 2.27 (m, 1H, H-2'b), 1.12 (d, 3H, CH₃, J = 6.8 Hz), 1.11 (d, 3H, CMe₂, J = 6.8 Hz). C₃₅H₃₇N₅O₇. M = 639.70, LRMS m/z = 640 [100, M + H]⁺, 638 [100, M - H]⁻.

*N*²-Isobutyryl-9-(3-*O*-methanesulfonyl-5-*O*-dimethoxytrityl-2-deoxy-β-D-threopentofuranosyl)guanine (<u>18</u>). Nucleoside <u>10</u> (0.32 g, 0.54 mmol) was evaporated from anhydrous pyridine, then redissolved in pyridine (5 mL) and treated with mesylchloride (80 µl, 1 mmol, 2 eq) at room temperature overnight. The volatiles were evaporated to dryness and the residue was chromatographed on silica gel column (80 mL, CH₂Cl₂:MeOH 98:2) to give compound <u>18</u> (0.284 g, 0.4 mmol, 73%). ¹H NMR (500 MHz, Me₂SO-d₆): δ 12.12 (s, 1H, NH), 11.75 (S, 1H, NH), 7.83 (s, 1H, H-8), 7.40-6.83 (m, 13H, Ph), 6.27 (dd, 1H, H-1', J = 8.0 Hz, J = 2.0 Hz), 5.43 (t, 1H, H-3', J = 4.0 Hz), 4.44 (m, 1H, H-4'), 3.73 (s, 6H, 2-OMe), 3.35 (m, 1H, H-5'a), 3.21 (m, 1H, H-5'b), 3.07 (s, 3H, SO₂Me), 3.02 (m, 1H, H-2'a), 2.79 (m, 1H, CHMe₂), 2.71 (m, 1H, H-2'b), 1.12 (d, 3H, <u>H</u>CMe, J = 6.8 Hz), 1.11 (d, 3H, CMe₂, J = 6.8 Hz). C₃₆H₃₉N₅O₉S. M = 717.71, LRMS m/z = 718 [100, M + H]⁺, 716 [100, M - H]⁻.

 N^2 -Isobutyryl-9-(3-azido-5-*O*-dimethoxytrityl-2,3-dideoxy- β -D-erythro-pentofuranosyl)guanine (<u>19</u>). Nucleoside <u>18</u> (22.5 g, 31 mmol) was dissolved in pyridine (200 mL) and concentrated, then redissolved in pyridine (400 mL) and treated with mesylchloride (MsCl) (3.0 mL, 38 mmol, 1.1 eq) at room temperature for 4 h.

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Additional MsCl (3.0 m L, 1.1 eq) was added and reaction mixture was stirred overnight. The dark solution was diluted with saturated solution of aq. NaHCO₃ (1.0 L) and extracted with CH₂Cl₂. The combined extracts (500 mL) were washed with water, dried (MgSO₄) and evaporated. LiN₃ (45 mL, 20% in water, 5 eq) was evaporated three times from dimethylformamide and redissolved in DMF (100 mL). This solution was added to a solution of mesylate in DMF (150 mL) and the reaction mixture was heated at 100° C for 2 h. The volatiles were evaporated and the residue was coevaporated from xylenes and dissolved in CH_2Cl_2 , washed with brine, dried (MgSO₄) and the solvents removed. The crude material was purified by column chromatography (2.0 L SiO₂, in CH₂Cl₂:MeOH 98:2) to give a compound **19** (16.7 g, 25 mmol, 81%). ¹H NMR (500 MHz, Me₂SO-d₆): δ 12.08 (s, 1H, NH), 11.62 (s, 1H, NH), 8.23 (s, 1H, H-8), 7.29–6.77 (m, 13H, Ph), 6.22 (dd, 1H, H-1', J = 7.0 Hz), 4.71 (m, 1H, H-3') 3.95 (m, 1H, H-4'), 3.71 (s, 6H, 2 OMe), 3.17 (m, 2H, H-5'a, H-5'b), 2.98 (m, 1H, H-2'a), 2.77 $(m, 1H, CHMe_2)$, 2.56 (m, 1H, H-2'b), 1.12 $(d, 3H, CMe_2, J = 6.8 Hz)$, 1.11 $(d, 3H, CMe_2)$ $CMe_2 J = 6.8 Hz$). $C_{35}H_{36}N_8O_6$. M = 664.71, LRMS m/z = 665 [100, M + H]⁺, 663 $[100, M - H]^{-}$.

*N*²-Isobutyryl-9-(3-azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)guanine (<u>20</u>). Nucleoside <u>19</u> (16.7 g, 25 mmol) was dissolved in 80% AcOH/H₂O (200 mL) and the reaction mixture was stirred at room temperature for 2 h. The volatiles were evaporated to dryness and the residue was purified by column chromatography (2.0 L, SiO₂) (CH₂Cl₂:MeOH 97:3, then 95:5), to give compound <u>20</u> (6.4 g, 17.7 mmol, 70%) as a white foam. ¹H NMR (500 MHz, Me₂SO-d₆): δ 12.08 (s, 1H, NH), 11.66 (s, 1H, NH), 8.26 (s, 1H, H-8), 6.17 (t, 1H, H-1', J = 6.5 Hz) 5.13 (t, 1H, 5'-OH, J = 5.5 Hz), 4.58 (m, 1H, H-3') 3.91 (m, 1H, H-4') 3.57 (m, 2H, H-5'a, H-5'b), 2.84 (m, 1H, H-2'a), 2.76 (m, 1H, H-2'b), 2.50 (m, 1H, CHMe₂), 1.12 (d, 6H, CMe₂, J = 6.8 Hz). C₁₄H₁₈N₈O₄. M = 362.3, LRMS m/z = 363 [45, M + H]⁺, 361 [100, M – H]⁻. HPLC purity: 98%.

CONCLUSION

Deoxygenative [1,2]-hydride shift rearrangement^[2] of 2'-O-mesyl and 2'-O-tosylguanosine derivatives was achieved in a stereoselective manner using lithiumtriisobutylborohydride (L-Selectride[®]) in THF. The previously described lithium triethylborohydride (Super-Hydride[®]) in a similar reaction^[2] gives a mixture of erythro and threo isomers. This improvement allows large scale preparation of 3'-azido-2',3'-dideoxyguanosine in 15% overall yield. Optimization of each step is still being investigated.

REFERENCES

- Imazawa, M.; Eckstein, F. Synthesis of 3'-Azido-2',3'-dideoxyribofuranosylpurines. J. Org. Chem. 1978, 43, 3044–3048.
- Hansske, F.; Robins, M.J. A Deoxygenative [1,2]-Hydride Shift Rearrangement Converting Cyclic cis-Diol Monotosylates to Inverted Secondary Alcohols. J. Am. Chem. Soc. 1983, 106, 6736–6737.





- Herdewijn, P.A.M. Anchimeric Assistance of a 5'-O-Carbonyl Function for Inversion of Configuration at the 3'-Carbon Atom of a 2'-Deoxyadenosine. Synthesis of 3'-Azido-2',3'-dideoxyadenosine and 3'-Azido-2'-3-dideoxyinosine. J. Org. Chem. 1988, 53, 5050-5053.
- 4. Herdewijn, P.A.M.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S.; Vanderhaeghe, H. 3'-Substituted 2',3'-dideoxynucleoside Analogues as Potential Anti-HIV (HTLV-III/LAV) Agents. J. Med. Chem. **1987**, *30*, 1270–1278.
- Robins, M.J.; Wood, S.G.; Dalley, N.K.; Herdewijn, P.A.M.; Balzarini, J.; De Clercq, E. Nucleic Acid Related Compounds. 57. Synthesis, X-Ray Crystal Structure, Lipophilic Partition Properties, and Antiretroviral Activities of Anomeric 3'-Azido-2',3'-dideoxy-2,6-diaminopurine Ribosides. J. Med. Chem. 1989, 32, 1763–1768.
- Herdewijn, P.A.M.; Balzarini, J.; Baba, M.; Pauwels, R.; Van Aerschot, A.; Janssen, G.; De Clercq, E. Synthesis and Anti-HIV Activity of Different Sugar-Modified Pyrimidine and Purine Nucleosides. J. Med. Chem. **1988**, *31*, 2040–2048.

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