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Synthesis of 3′-Azolyl-2′,3′-dideoxyhexose Nucleosides

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1,8-Diazabicyclo[5.4.0]undec-7-ene salts of 2-methyl-4(5)-nitroimidazole or benzotriazole were obtained in crystalline form. Michael-type addition of these salts to (4*S*,5*R*)-(*E*)-4,6-di-*O*-acetyl-5-hydroxy-2-hexenal gave, after acetylation of the product, an isomeric mixture of acetylated 3-(azol-1-yl)-2,3-dideoxy-D-*arabino*-hexopyranosides and 3-(azol-1-yl)-2,3-dideoxy-D-*ribo*-hexofuranosides. Reaction of these peracetylated adducts with trimethylsilylated thymine in the presence of trimethylsilyl trifluoromethanesulfonate (TMS triflate) afforded the corresponding nucleosides which were deprotected by using methanolic ammonia. The nucleosides were found inactive against HIV-1 and HSV-1.

Since the time of isolation of azomycine (2-nitroimidazole),[1] the interest in nitroimidazoles has been increasing continuously. Antiprotozoal properties and radiosensitizing ability in respect to hypoxic tumor cells have been reported.[2] Some nitroimidazoles are also convenient starting materials for the synthesis of purine nucleobases and other heterocyclic systems.[3,4]

Azoles or their derivatives containing electron withdrawing groups (e.g., nitro) are usually converted into their corresponding anions by treatment with alkali metal hydroxides or alkoxides.[5,6] However, due to the instability of nitroimidazoles under these conditions, the alkali metal ion is often replaced by a heavy metal ion,[3,7] but these salts are rather insoluble in organic solvents and, additionally, they are very sensitive to traces of water. Such problems can be avoided by replacing the metal ion with an organic cation. Recently we have found a convenient method of preparation of azole salts using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a non-nucleophilic deprotonating reagent.[8] The salts with DBU are stable enough and fairly soluble in chlorinated solvents (e.g., dichloromethane, chloroform) and in *N*,*N*-dimethylformamide (DMF). Some of the salts have been used recently in the synthesis of reversed nucleosides with the nucleobase at the exocyclic carbon of the sugar moiety.[8] In the present work we report a new application of 2-methyl-4-nitroimidazole and benzotriazole salts with DBU in a Michael-type addition reaction to an α,β-unsaturated sugar aldehyde. This reaction provides glycosides modified at the 3-position of the sugar, which in turn are suitable reagents for the synthesis of nucleosides.

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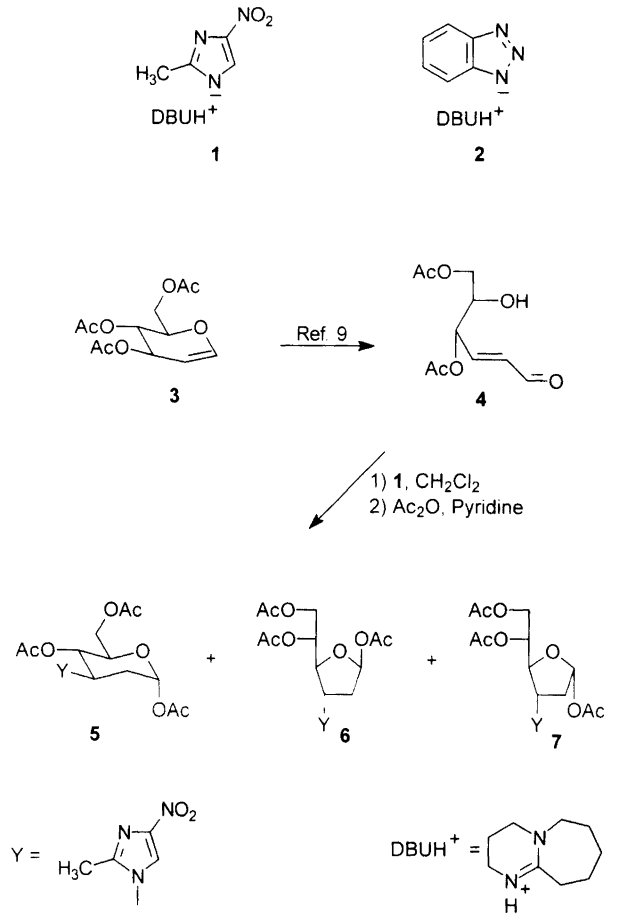
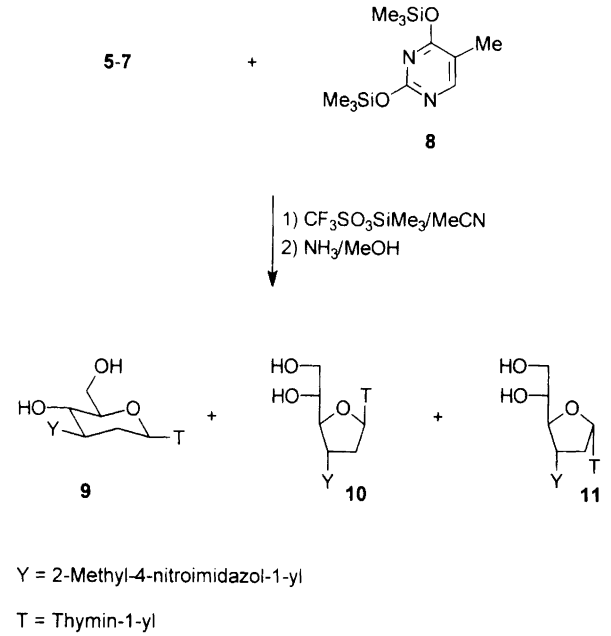
Results and discussion

The DBU salts **1** and **2** precipitated on mixing DBU and the azoles in tetrahydrofuran (THF). The (4*S*,5*R*)-(*E*)-4,6-diacetoxy-5-hydroxy-2-hexenal **4** was prepared by a one-pot procedure[9] from commercially available 3,4,6-tri-*O*-acetyl-D-glucal (**3**) and used as the substrate in a Michael-type reaction with 2-methyl-4-nitroimidazole · DBU salt **1**. Acetylation of the crude mixture with acetic anhydride in dry pyridine afforded an isomeric mixture of 1,4,6-tri-*O*-acetyl-3-(2-methyl-4-nitroimidazol-1-yl)-2,3-dideoxy-D-*arabino*-hexopyranoside (**5**) and 1,5,6-tri-*O*-acetyl-3-(2-methyl-4-nitroimidazol-1-yl)-D-*ribo*-hexofuranosides **6** and **7** in 65% yield. Preparative HPLC separation of the isomer mixture gave the ratio **5**:**6**:**7** as 6:7:8. Formation of the anomeric mixture of the furanoses **6** and **7** could be attributed to a base promoted acetyl shift from 4-*O* to 5-*O* in the sugar aldehyde **4**. A similar reaction has been observed before on addition of 1,2,4-triazole to **4** in the presence of DBU.[10] The glycosides **5**–**7** were separated for identification purposes only. The *ribo* configuration of the furanosides **6** and **7** was determined from 2D-COSY and NOE experiments. Irradiation of H-4′ in the furanoside **6** generated a 4% NOE of H-5 in the imidazole ring of **6** whereas irradiation of H-5 in the imidazole ring of **7** generated a 5% NOE of H-4′. The α anomeric configuration of **7** was deduced from the 6% NOE of H-1′ and 5% NOE of H-3′ on irradiation of H-2′β.

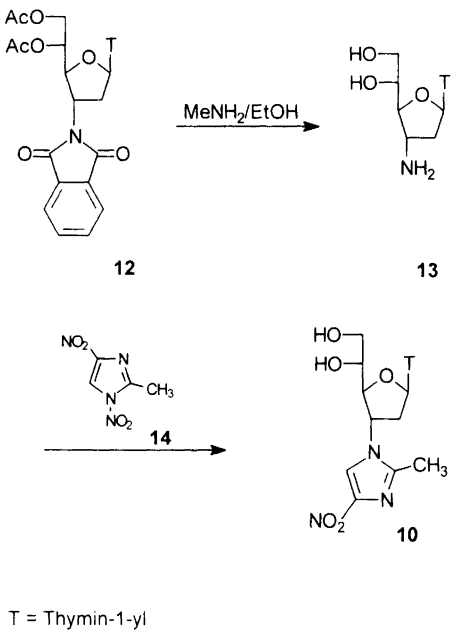
The isomer mixture of glycosides **5**–**7** was used without separation of the isomers in the subsequent synthesis of nucleosides because both α and β glycosides were expected to produce nearly identical mixtures of α and β nucleosides. The mixture was coupled with silylated



Scheme 1.



Scheme 2.

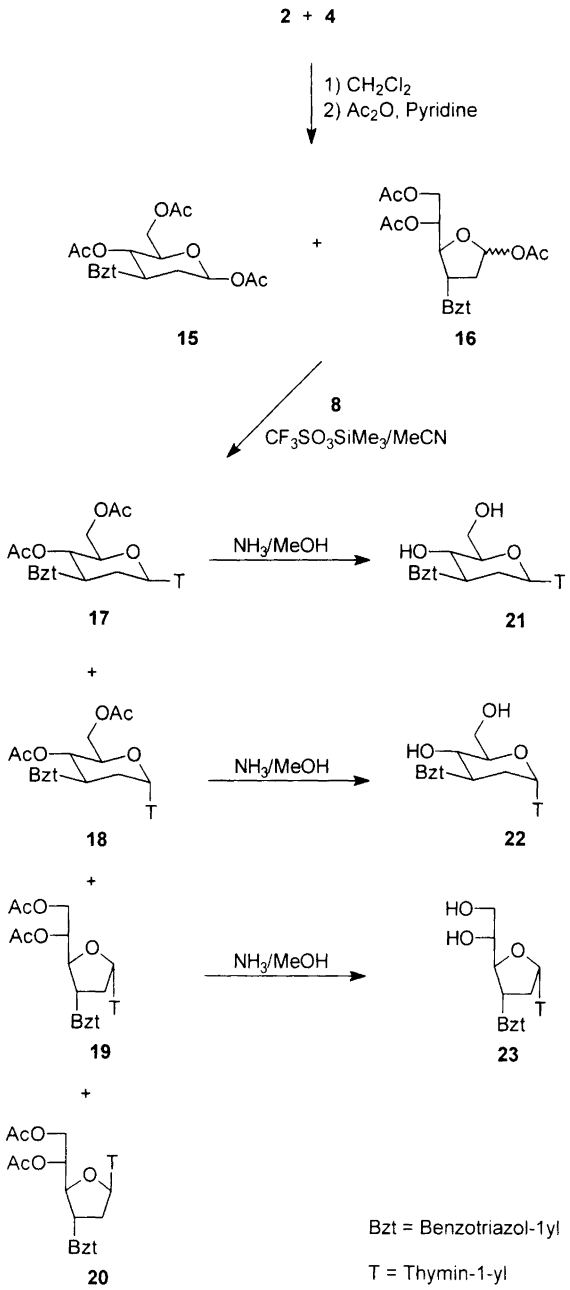


Scheme 3.

thymine **8** in anhydrous acetonitrile using TMS triflate as the catalyst according to the procedure described by Vorbrüggen[11,12] (Scheme 2). After silica gel column chromatography (CH_2Cl_2–MeOH, 97:3 v/v), a mixture of nucleosides was obtained in 65% yield and directly deprotected with methanolic ammonia to give the nucleosides **9–11** in 85% yield.

Reversed-phase HPLC separation gave the pure nucleosides **9–11**. The *arabino* and β configuration of **9** is supported by the quartet ($J = 12$ Hz) of H-2′β in the ^{1}H NMR spectrum, due to axial–axial couplings to H-1′ and H-3′ and to a geminal coupling to H-2′α. Compounds **10** and **11** both have C-1′ and C-4′ ^{13}C NMR signals above 80 ppm as typically found for furanoside nucleosides. For compound **10** the configuration at the anomeric carbon was confirmed by comparison of the NMR spectra with those of compound **10** obtained in an independent synthesis by the following route. Compound **12**[13] was deprotected with 33% methylamine in absolute ethanol to afford 1-(3-amino-2,3-dideoxy-β-D-*ribo*-hexofuranosyl)thymine (**13**) (Scheme 3). The crude amino compound **13** was reacted without further purification with 2-methyl-1,4-dinitroimidazole **14**[14] in aqueous methanol as a suspension at 25 °C to afford the desired nucleoside **10** in 83% yield. It has previously been shown that an amino group can replace the N^1-NO_2 moiety of the imidazole ring in 1,4-dinitroimidazoles with retention of configuration of the carbon atom connected to the amino group.[15,16]

The sugar aldehyde **4** was reacted with the benzotriazole · DBU salt **2** under the same conditions as for the reaction of the sugar aldehyde with **1**, and this reaction was also followed by acetylation with acetic anhydride in pyridine. Column purification afforded an isomer mixture of the acetylated glycosides **15** and **16** in 89% yield. (Scheme 4).



Scheme 4.

Reaction of the mixture of glycoside isomers **15** and **16** with silylated thymine **8** in the presence of TMS triflate gave, after silica gel chromatographic purification, the corresponding nucleosides **17–20** in 65% yield. The isomers were separated by preparative reversed phase HPLC. The pure isomers **17**, **18**, **19** and **20** were obtained in the ratio 7:10:9:1 and were deprotected using methanolic ammonia. The structural assignment of the nucleosides **17** and **18** was based on the coupling constants of protons between 1' and 2' (2.1, 12.3 Hz, for **17** and 3.0, 6.2 Hz for **18**). The observed triplet for H-4' (J= 8.9–9.8 Hz) in **17** and **18** suggested that the benzotriazole substituent is in an equatorial position. The *arabino* and β configuration of **17** was also deduced from H-2'β which gave rise to a quartet in the ^{1}H NMR spectrum with J= 12.3 Hz due to large axial–axial and geminal couplings. 2D-COSY and NOE experiments on **23** gave an unambiguous configurational assignment. In **23** the α configuration of the thymine ring was confirmed by the 3% NOE of the H-6 signal when H-4' was irradiated. In addition, irradiation of H-5' gave a 2% NOE of H-1' and a 3% NOE in H-3' which supports a *ribo* and α configuration of the sugar moiety. It should be noted that in the isolated **17–20** nucleosides, the benzotriazole ring is linked to the sugar ring at *N*-1. Four signals in the aromatic part of the ^{1}H NMR spectra are observed instead of the expected two signals if addition had occurred at *N*-2. We have observed formation of both products in the synthesis of a reversed benzotriazole nucleoside under Mitsunobu reaction conditions.[17] Reaction of benzotriazole with methyl α-D-glucopyranoside gave methyl 6-deoxy-6-(benzotriazol-1-yl)- and methyl 6-deoxy-6-(benzotriazol-2-yl)-α-D-glucopyranosides in the ratio 2:1.

Test for antiviral activity. Compounds **9–11** and **21–23** did not show any significant activity at 100 μM against HIV-1 in MT-4 cells. Expression of HIV in culture medium was quantified by HIV antigen detection ELISA. The same compounds were also devoid of any activity at 100 μM against herpes simplex virus, type 1 (HSV-1), strain McIntyre when tested in African green monkey kidney cell line Vero.

Experimental

NMR spectra were recorded at 300 MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR on a Varian Gemini 2000 300 MHz spectrometer; δ-values are in ppm relative to tetramethylsilane as an internal standard. EI mass spectra were recorded on a Varian MAT 311 A spectrometer. Plasma desorption mass spectra (PDMS) were carried out on a BIOION 20R mass spectrometer with a radioactive ^{252}Cf source. Analytical silica gel TLC was performed on Merck precoated 60 F_{254} plates. The silica gel (0.040–0.063) used for column chromatography was purchased from Merck. Microanalyses were performed by the Microanalytical Laboratory of the Research Institute for Pharmacy and Biochemistry in Prague, Czech Republic.

The isomeric mixtures **5–7** and **17–20** were separated by reversed phase HPLC (Waters Delta Pak 300 A, 15m, RP 18, 57 × 300 mm column) with an isocratic EtOH–H_2O mixture.

Azole salts with 1,8-diazabicyclo[5.4.0]undec-7-ene **1** *and* **2** *(general procedure).* To a solution or suspension of the azole (10 mmol) in tetrahydrofuran (THF) (25 ml) cooled to 0 °C, was added dropwise DBU (10 mmol) with stirring. The mixture was then stirred for a few minutes, and the precipitate was filtered off and dried in a vacuum desiccator over solid NaOH.

Compound **1**: Yield 77%, m.p. 103–104 °C. ^{1}H NMR ($CDCl_3$): δ 7.88 (s, 1 H, H-imidazole), 3.5–3.38 (m, 6 H), 2.72–2.71 (m, 2 H), 2.34 (s, 3 H, CH_3), 2.05–1.75 (m, 9 H). ^{13}C NMR ($CDCl_3$): δ 166.60, 153.97, 147.47, 131.24, 77.26, 54.03, 48.46, 38.31, 32.30, 28.91, 26.77, 24.14, 19.71, 16.83 (CH_3). Anal. $C_{13}H_{21}N_5O_2$: C, N, H.

Compound **2**: Yield 95%, m.p. 126–127 °C. ^{1}H NMR ($CDCl_3$): δ 7.85–7.82 (m, 2 H, benzotriazole), 7.13–7.10 (m, 2 H, benzotriazole), 3.32–3.28 (m, 2 H), 3.08–3.00 (m, 4 H), 2.69- 2.67 (m, 2 H), 1.76–1.41 (m, 9 H). ^{13}C NMR ($CDCl_3$): δ 165.11, 144.31, 120.85 (2 C), 115.76 (2 C), 77.25, 53.13, 47.49, 37.46, 31.57, 28.20, 25.99, 23.46, 18.86. Anal. $C_{15}H_{21}N_5$: C, H, N.

1,4,6-Tri-O-*acetyl-2,3-dideoxy-3-(2-methyl-4-nitroimidazol-1-yl)*-α-D-arabino-*hexopyranoside* (**5**) and *1,5,6-tri*-O-*acetyl-2,3-dideoxy-3-(2-methyl-4-nitroimidazol-1-yl)*-α,β-D-ribo-*hexofuranosides* **6**, **7**. A solution of **4** (7.37 g, 32 mmol) in anhydrous CH_2Cl_2 (50 ml) was added to a solution of 2-methyl-4-nitroimidazole DBU salt **1** (7.26 g, 26 mmol) in CH_2Cl_2 (100 ml) at 0 °C with stirring. The temperature was allowed to rise 25 °C and stirring was continued for 24 h. The solvent was evaporated off under reduced pressure and the residue was mixed with pyridine (8.5 ml, 105 mmol), and acetic anhydride (16.5 ml, 175 mmol) and stirred at 25 °C overnight. The solvents were removed under reduced pressure followed by co-evaporation twice with toluene (2 × 20 ml). The residual oil was purified on a silica gel column using a mixture of CH_2Cl_2–MeOH (99:1 v/v) as the eluent to give a mixture of **5**–**7** in 65% yield (6.75 g). The isomers (0.5 g sample) were separated by HPLC (EtOH–H_2O, 12:88 v/v).

1,4,6-Tri-O-*acetyl-2,3-dideoxy-3-(2-methyl-4-nitroimidazol-1-yl)*-α-D-arabino-*hexopyranoside* (**5**). Yield 0.17 g (34%); m.p. 136–137 °C; t_R = 62 min. ^{1}H NMR ($CDCl_3$): δ 7.85 (s, 1 H, H-5 Im), 6.41 (d, 1 H, J = 2.0 Hz, H-1′), 5.24 (t, 1 H, J = 10 Hz, H-4′), 4.59 (ddd, 1 H, J = 5.3, 10.1, 11.6 Hz, H-3′), 4.32 (dd, 1 H, J = 4.0, 12.3 Hz, H-6′), 4.19 (ddd, 1 H, J = 2.3, 4.0, 10.1 Hz, H-5′), 4.10 (dd, 1 H, J = 2.3, 12.3 Hz, H-6″), 2.52 (s, 3 H, CH_3), 2.48–2.37 (m, 2 H, H-2′$_e$, H-2′$_a$), 2.21 (s, 3 H, CH_3CO), 2.11 (s, 3 H, CH_3CO), 1.95 (s, 3 H, CH_3CO). ^{13}C NMR ($CDCl_3$): δ 170.73 (CO), 168.62 (CO), 168.59 (CO), 147.32 (C-4 Im), 145.07 (C-2 Im), 116.60 (C-5 Im), 89.86 (C-1′), 70.76 (C-4′), 68.86 (C-5′), 61.51 (C-6′), 53.33 (C-3′), 35.16 (C-2′), 20.84 (CH_3CO), 20.54 (CH_3CO), 20.03 (CH_3CO), 13.21 (CH_3). Anal. $C_{16}H_{21}N_3O_9$: C, H, N.

1,5,6-Tri-O-*acetyl-2,3-dideoxy-3-(2-methyl-4-nitroimidazol-1-yl)*-β-D-ribo-*hexofuranoside* (**6**). Yield 0.12 g (24%), glass, t_R = 130 min. ^{1}H NMR ($CDCl_3$): δ 7.81 (s, 1 H, H-5 Im), 6.63 (dd, 1 H, J = 2.0, 5.7 Hz, H-1′), 5.20 (ddd, 1 H, J = 3.0, 6.0, 8.9 Hz, H-5′), 4.88 (m, 1 H, H-3′), 4.57 (dd, 1 H, J = 3.0, 12.2 Hz, H-6′), 4.37 (dd, 1 H, J = 3.9, 8.9 Hz, H-4′), 4.07 (dd, 1 H, J = 6.0, 12.2 Hz, H-6″), 2.77 (ddd, 1 H, J = 2.0, 8.0, 14.6 Hz, H-2′β), 2.55 (dt, 1 H, J = 6.0, 14.6 Hz, H-2′α), 2.55 (s, 3 H, CH_3 Im), 2.17 (s, 3 H, CH_3CO), 2.09 (s, 3 H, CH_3CO), 2.09 (s, 3 H, CH_3CO). ^{13}C NMR ($CDCl_3$): δ 170.49 (CO), 170.19 (CO), 169.54 (CO), 147.25 (C-4 Im), 144.47 (C-2 Im), 116.20 (C-5 Im), 97.44 (C-1′), 83.10 (C-4′), 71.60 (C-5′), 61.99 (C-6′), 57.85 (C-3′), 40.04 (C-2′), 20.93 (CH_3CO), 20.62 (CH_3CO), 20.51 (CH_3CO), 13.08 (CH_3 Im).

1,5,6-Tri-O-*acetyl-2,3-dideoxy-3-(2-methyl-4-nitroimidazol-1-yl)*-α-D-ribo-*hexofuranoside* (**7**). Yield 0.06 g (12%), glass, t_R = 175 min. ^{1}H NMR ($CDCl_3$): δ 8.13 (s, 1 H, H-5 Im), 6.55 (d, 1 H, J = 5.5 Hz, H-1′), 5.15 (ddd, 1 H, J = 3.0, 5.4, 6.8 Hz, H-5′), 4.80 (ddd, 1 H, J = 2.6, 4.5, 9.9 Hz, H-3′), 4.53 (dd, 1 H, J = 2.6, 6.8 Hz, H-4′), 4.51 (dd, 1 H, J = 3.0, 12.4 Hz, H-6′), 4.11 (dd, 1 H, J = 5.4, 12.4 Hz, H-6″), 2.94 (ddd, 1 H, J = 5.5, 9.9, 15.0 Hz, H-2′β), 2.50 (s, 3 H, CH_3 Im), 2.24–2.20 (m, 1 H, H-2′α), 2.20 (s, 3 H, CH_3CO), 2.07 (s, 6 H, 2 × CH_3CO). ^{13}C NMR ($CDCl_3$): δ 170.58 (CO), 170.01 (CO), 169.24 (CO), 147.52 (C-4 Im), 144.86 (C-2 Im), 117.45 (C-5 Im), 97.21 (C-1′), 83.37 (C-4′), 71.15 (C-5′), 61.90 (C-6′), 56.76 (C-3′), 39.47 (C-2′), 21.04 (CH_3CO), 20.62 (CH_3CO), 20.48 (CH_3CO), 13.20 (CH_3 Im).

1-[2,3-Dideoxy-3-(2-methyl-4-nitroimidazol-1-yl)-β-D-arabino-*hexopyranosyl]thymine* (**9**) *and 1-[2,3-dideoxy-3-(2-methyl-4-nitroimidazol-1-yl)*-α,β-D-ribo-*hexofuranosyl]thymine* (**10**, **11**). Thymine (1.0 g, 8 mmol), $(NH_4)_2SO_4$ (0.02 g, 0.15 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (20 ml, 97 mmol) were refluxed for 12 h. The excess of HMDS was removed *in vacuo* at 25 °C. The residue was dissolved in anhydrous CH_3CN (20 ml) and a mixture of **5**–**7** (1.6 g, 4 mmol) was added. The resulting solution was cooled to −20 °C and trimethylsilyl trifluoromethanesulfonate (TMS triflate) (0.9 ml, 5 mmol) was added dropwise with stirring. The temperature was allowed to increase to 25 °C and stirring was continued for 24 h. The mixture was diluted with CH_2Cl_2 (100 ml) and quenched with a sat. aq. solution of $NaHCO_3$ (25 ml). The organic layer was washed with water (2 × 10 ml) and dried (Na_2SO_4). The solvents were evaporated off under reduced pressure, the residual oil was filtered through a silica gel column (MeOH–CH_2Cl_2, 3:97 v/v). Fractions containing nucleosides were collected, evaporated to a syrup (1.2 g, 65%) and dissolved in sat. methanolic ammonia (100 ml). After 24 h of stirring, the solvent was removed under reduced pressure. Column chromatographic purification of the residue on a silica gel column using CH_2Cl_2–MeOH (90:10 v/v) gave an isomeric mixture of nucleosides (0.88 g, 85%). HPLC separation of the mixture **10**–**12** (sample 0.35 g) (EtOH–H_2O, 4:96 v/v) gave the pure isomers.

1-[2,3-Dideoxy-3-(2-methyl-4-nitroimidazol-1-yl)-β-D-arabino-*hexopyranosyl]thymine* (**9**). Yield 0.09 g (26%), m.p. 187–188 °C, t_R = 100 min. ^{1}H NMR (DMSO-d_6): δ

8.61 (s, 1 H, H-5 Im), 7.73 (s, 1 H, H-6), 5.96 (dd, 1 H, J=3.0, 11.0 Hz, H-1'), 5.52 (br s, 1 H, OH), 3.98 (t, 1 H, J=5.8 Hz, H-4'), 3.65–3.85 (m, 2 H, H-3', H-5'), 3.60–3.51 (m, 2 H, H-6'), 2.62 (q, 1 H, J=12.0 Hz, H-2'β), 2.44 (s, 3 H, CH_3 Im), 2.14 (dd, 1 H, J=3.0, 12.0 Hz, H-2'α), 1.84 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6): δ 163.84 (C-4), 150.33 (C-2), 146.46 (C-4 Im), 146.26 (C-2 Im), 136.69 (C-6), 119.52 (C-5 Im), 109.65 (C-5), 80.31 (C-1'), 78.51 (C-5'), 69.12 (C-4'), 60.53 (C-6'), 58.00 (C-3'), 34.38 (C-2'), 13.11 (CH_3 Im), 12.17 (CH_3). Anal. C_{15} H_{19} N_5 $O_7 \cdot 0.5$ H_2O: C, H, N.

*1-[2,3-Dideoxy-3-(2-methyl-4-nitroimidazol-1-yl)-β-*D-ribo-*hexofuranosyl]thymine* (**10**). Yield: 0.06 g (17%), glass; t_R =153 min. ^{1}H NMR (DMSO-d_6): δ 11.50 (s, 1 H, NH), 8.74 (s, 1 H, H-5 Im), 7.72 (s, 1 H, H-6), 6.37 (dd, 1 H, J=5.2, 7.8 Hz, H-1'), 5.27 (br s, 1 H, OH), 5.10 (q, 1 H, J=8.1 Hz, H-3'), 4.36 (br s, 1 H, OH), 4.17 (dd, 1 H, J=5.3, 8.1 Hz, H-4'), 3.75 (m, 1 H, H-5'), 3.36–3.28 (m, 2 H, H-6'), 2.72–2.58 (m, 2 H, H-2'), 2.45 (s, 3 H, CH_3 Im), 1.83 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6): δ 164.18 (C-4), 150.76 (C-2), 146.62 (C-4 Im), 146.00 (C-2 Im), 137.06 (C-6), 120.24 (C-5 Im), 110.03 (C-5), 83.47 (C-1'), 83.37 (C-4'), 72.14 (C-5'), 63.01 (C-6'), 55.53 (C-3'), 38.52 (C-2'), 13.29 (CH_3 Im), 12.36 (CH_3).

*1-[2,3-Dideoxy-3-(2-methyl-4-nitroimidazol-1-yl)-α-*D-ribo-*hexofuranosyl]thymine* (**11**). Yield 0.09 g (26%), m.p. 193–194 °C, t_R=130 min. ^{1}H NMR (DMSO-d_6): δ 11.39 (s, 1 H, NH), 8.90 (s, 1 H, H-5 Im), 7.94 (s, 1 H, H-6), 6.21 (dd, 1 H, J=5.5, 9.0 Hz, H-1'), 5.15–5.06 (m, 2 H, H-3', 4'-OH), 4.66–4.58 (m, 1 H, H-4'), 4.45 (dd, 1 H, J=5.5, 8.1 Hz, H-5'), 3.65 (t, 1 H, J=5.0 Hz, 6'-OH), 3.27–3.15 (m, 2 H, H-6'), 2.89–2.81 (m, 2 H, H-2'), 2.45 (s, 3 H, CH_3 Im), 1.87 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6): δ 163.91 (C-4), 150.64 (C-2), 146.30 (C-4 Im), 145.87 (C-2 Im), 136.99 (C-6), 120.05 (C-5 Im), 109.87 (C-5), 83.41 (C-1'), 81.76 (C-5'), 72.28 (C-4'), 62.55 (C-6'), 55.71 (C-3'), 37.95 (C-2'), 12.91 (CH_3 Im), 11.98 (CH_3).

*1-(3-Amino-2,3-dideoxy-β-*D-ribo-*hexofuranosyl) thymine* (**13**). Compound **12**[13] (0.24 g, 0.5 mmol) was dissolved in 33% $MeNH_2$ in absolute EtOH (10 ml). The solution was stirred at 25 °C overnight. The solvent was evaporated off at reduced pressure, and the residue was purified on a silica gel column using CH_2Cl_2–MeOH (80:20 v/v) as the eluent. The oily product (0.12 g, 88%) was used for the next step without further purification.

*1-[2,3-Dideoxy-3-(2-methyl-4-nitroimidazol-1-yl)-β-*D-ribo-*hexofuranosyl]thymine* (**10**). Compound **13** (0.12 g, 0.44 mmol) was added to a solution of 2-methyl-1,4-dinitroimidazole (**14**) (0.076 g, 0.44 mmol) in a MeOH–H_2O mixture (5 ml, 1:1 v/v) with stirring. After 24 h, the solvent was evaporated off and the residue was purified on a silica gel column using CH_2Cl_2–MeOH (90:10) as the eluent. Compound **10** was obtained as white foam. Yield 0.14 g (83%). This compound showed ^{1}H NMR and ^{13}C NMR spectra identical with those of compound **10**. EI MS: m/z (%)=381 (M^+, 5), 161 (40), 126 (90), 97 (45), 55 (100). Anal. $C_{15}H_{19}N_5O_7 \cdot 0.25$ H_2O: C, H, N.

*1-[4,6-Di-*O*-acetyl-3-(benzotriazol-1-yl)-2,3-dideoxy-(α,β)-*D-arabino-*hexopyranosyl]thymines* (**17**, **18**) *and 1-[5,6-di-*O*-acetyl-3-(benzotriazol-1-yl)-2,3-dideoxy-(α,β)-*D-ribo-*hexofuranosyl]thymines* (**19**, **20**). A solution of **4** (7.4 g, 32 mmol) in anhydrous CH_2Cl_2 (50 ml) was added dropwise to a solution of benzotriazole DBU salt **2** (7.1 g, 26 mmol) in anhydrous CH_2Cl_2 (100 ml) at 0 °C with stirring. The temperature was allowed to rise to 25 °C and stirring was continued for 24 h. After evaporation of solvent, the residual oil was dissolved in pyridine (8.5 ml, 105 mmol), acetic anhydride (10.5 ml, 111 mmol) was added and stirring was continued for 18 h. The solvents were evaporated off under reduced pressure followed by co-evaporation with toluene (2 × 20 ml). The residue was purified on a silica gel column using CH_2Cl_2–MeOH (97:3 v/v) as the eluent. Compounds **15** and **16** were obtained as a mixture in 89% yield (9.1 g). The isomeric mixture **15**, **16** (3.91 g 10 mmol) was added to a solution of trimethylsilylated thymine (2.52 g, 20 mmol) (see synthesis of **9**–**11**) in anhydrous MeCN (40 ml) and cooled to −20 °C. TMS triflate (2.2 ml, 12.2 mmol) was added with stirring. After 24 h the mixture was diluted with CH_2Cl_2 (100 ml) and quenched with sat. aq. $NaHCO_3$ (25 ml). The organic layer was washed with water (2 × 15 ml), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Column chromatographic purification of the residue gave a pure isomer mixture of nucleosides **17**–**20** in total yield 65% (2.97 g). A sample of **17**–**20** (0.3 g) was separated by reverse HPLC with EtOH–H_2O (15:85 v/v) as the eluent.

*1-[4,6-Di-*O*-acetyl-3-(benzotriazol-1-yl)-2,3-dideoxy-β-(α, β)-*D-arabino-*hexopyranosyl]thymine* (**17**). Yield 0.07 g (23%), m.p. 132–133 °C, t_R=110 min. ^{1}H NMR ($CDCl_3$): δ 9.37 (s, 1 H, NH), 8.09 (d, 1 H, J=8.3 Hz, H-Bzt), 7.61 (t, 1 H, J=8.3 Hz, H-Bzt), 7.54 (d, 1 H, J=8.3 Hz, H-Bzt), 7.43 (t, 1 H, J=8.3 Hz, H-Bzt), 7.40 (d, 1 H, J=0.9 Hz, H-6), 6.19 (dd, 1 H, J=2.1, 12.3 Hz, H-1'), 5.45 (t, 1 H, J=9.8 Hz, H-4'), 5.14 (ddd, 1 H, J= 4.5, 9.8, 12.3 Hz, H-3'), 4.32 (dd, 1 H, J=5.2, 12.6 Hz, H-6'), 4.19 (dd, 1 H, J=2.0, 12.6 Hz, H-6''), 4.10 (ddd, 1 H, J=2.0, 5.2, 9.8 Hz, H-5'), 3.15 (q, 1 H, J=12.3 Hz, H-2'β), 2.66 (ddd, 1 H, J=2.1, 4.5, 12.3 Hz, H-2'α), 2.09 (s, 3 H, CH_3CO), 2.00 (s, 3 H, CH_3CO), 1.57 (d, 3 H, J=0.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 170.84 (CO), 168.55 (CO), 163.52 (C-4), 150.36 (C-2), 145.82 (C-9 Bzt), 134.68 (C-6), 133.52 (C-8 Bzt), 127.96 (C-5 Bzt), 124.50 (C-6 Bzt), 120.60 (C-4 Bzt), 112.42 (C-5), 108.98 (C-7 Bzt), 79.94 (C-1'), 76.20 (C-4'), 69.69 (C-5'), 62.14 (C-6'), 57.53 (C-3'), 34.85 (C-2'), 20.71 (CH_3CO), 19.93 (CH_3CO), 12.56 (CH_3). PDMS: m/z=458 (M^+ +1).

1-[4,6-Di-O-acetyl-3-(benzotriazol-1-yl)-2,3-dideoxy-α-D-arabino-hexopyranosyl]thymine (**18**). Yield 0.1 g (33%), m.p. 154–155 °C, $t_R = 140$ min. ^{1}H NMR ($CDCl_3$): δ 9.53 (s, 1 H, NH), 8.05 (d, 1 H, $J = 8.2$ Hz, H-Bzt), 7.72 (d, 1 H, $J = 8.2$ Hz, H-Bzt), 7.51 (td, 1 H, $J = 1.0$, 7.1, 8.2 Hz, H-Bzt), 7.36 (td, 1 H, $J = 1.0$, 7.1, 8.2 Hz, H-Bzt), 7.30 (d, 1 H, $J = 1.0$ Hz, H-6), 5.82 (dd, 1 H, $J = 3.0$, 6.2 Hz, H-1′), 5.72 (ddd, 1 H, $J = 5.8$, 8.9, 9.5 Hz, H-3′), 5.61 (t, 1 H, $J = 8.9$ Hz, H-4′), 4.32 (dd, 1 H, $J = 5.2$, 12.1 Hz, H-6′), 4.21 (ddd, 1 H, $J = 2.5$, 5.2, 8.9 Hz, H-5′), 4.12 (dd, 1 H, $J = 2.5$, 12.1 Hz, H-6″), 3.31 (ddd, 1 H, $J = 6.2$, 9.5, 14.6 Hz, H-2′β), 3.18 (ddd, 1 H, $J = 3.0$, 5.8, 14.6 Hz, H-2′α), 2.06 (s, 3 H, CH_3CO), 2.01 (d, 3 H, $J = 1.0$ Hz, CH_3), 1.71 (s, 3 H, CH_3CO). ^{13}C NMR ($CDCl_3$): δ 170.65 (CO), 168.90 (CO), 163.92 (C-4), 150.81 (C-2), 145.88 (C-9 Bzt), 139.08 (C-6), 133.65 (C-8 Bzt), 127.76 (C-5 Bzt), 124.32 (C-6 Bzt), 120.82 (C-4 Bzt), 112.32 (C-5), 109.40 (C-7 Bzt), 84.10 (C-1′), 72.25 (C-5′), 68.99 (C-4′), 61.85 (C-6′), 56.14 (C-3′), 31.78 (C-2′), 20.55 (CH_3CO), 20.11 (CH_3CO), 12.32 (CH_3). Anal. $C_{21}H_{23}N_5O_7 \cdot 0.5\ H_2O$: C, N, H.

1-[5,6-Di-O-acetyl-3-(benzotriazol-1-yl)-2,3-dideoxy-α-D-ribo-hexofuranosyl]thymine (**19**). Yield 0.09 g (30%), m.p. 144–145 °C, $t_R = 150$ min. ^{1}H NMR ($CDCl_3$): δ 9.57 (s, 1 H, NH), 8.12 (d, 1 H, $J = 8.4$ Hz, H-Bzt), 7.63 (s, 1 H, H-6), 7.60 (d, 1 H, $J = 8.4$ Hz, H-Bzt), 7.45 (m, 2 H, H-Bzt), 6.53 (t, 1 H, $J = 7.0$ Hz, H-1′), 5.51 (q, 1 H, $J = 7.5$ Hz, H-3′), 5.36 (ddd, 1 H, $J = 3.1$, 6.1, 8.1 Hz, H-5′), 5.11 (dd, 1 H, $J = 6.1$, 8.1 Hz, H-4′), 4.46 (dd, 1 H, $J = 3.1$, 12.3 Hz, H-6′), 4.12 (dd, 1 H, $J = 6.1$, 12.3 Hz, H-6″), 3.25 (ddd, 1 H, $J = 7.0$, 8.1, 14.3 Hz, H-2′β), 2.97 (td, 1 H, $J = 7.0$, 14.3 Hz, H-2′α), 2.01 (s, 3 H, CH_3CO), 1.96 (s, 3 H, CH_3CO), 1.73 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 170.46 (CO), 170.12 (CO), 163.84 (C-4), 150.73 (C-2), 145.91 (C-9 Bzt), 135.02 (C-6), 132.81 (C-8 Bzt), 128.26 (C-5 Bzt), 124.58 (C-6 Bzt), 120.49 (C-4 Bzt), 111.93 (C-5), 108.84 (C-7 Bzt), 84.95 (C-1′), 80.52 (C-4′), 71.30 (C-5′), 62.10 (C-6′), 58.80 (C-3′), 37.72 (C-2′), 20.39 ($2 \times CH_3CO$), 12.51 (CH_3). PDMS: $m/z = 458$ ($M^+ + 1$).

1-[5,6-Di-O-acetyl-3-(benzotriazol-1-yl)-2,3-dideoxy-β-D-ribo-hexofuranosyl]thymine (**20**). Yield 0.01 g (3.3%), glass, $t_R = 205$ min. ^{1}H NMR ($CDCl_3$): δ 8.99 (s, 1 H, NH), 8.12 (d, 1 H, $J = 8.3$ Hz, H-Bzt), 7.85 (d, 1 H, $J = 8.3$ Hz, H-Bzt), 7.58 (m, 2 H, H-6, H-Bzt), 7.25 (m, 1 H, H-Bzt), 6.27 (t, 1 H, $J = 6.3$ Hz, H-1′), 5.67 (m, 1 H, H-3′), 5.46 (m, 1 H, H-5′), 4.77 (t, 1 H, $J = 6.7$ Hz, H-4′), 4.50 (d, 1 H, $J = 12.5$ Hz, H-6′), 4.06 (dd, 1 H, $J = 5.0$, 12.5 Hz, H-6″), 3.16–3.07 (m, 2 H, H-2′), 2.00 (s, 3 H, CH_3CO), 1.97 (s, 3 H, CH_3CO), 1.70 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 170.40 (CO), 170.08 (CO), 163.75 (C-4), 150.25 (C-2), 145.80 (C-9 Bzt), 137.83 (C-6), 132.78 (C-8 Bzt), 128.30 (C-5 Bzt), 124.75 (C-6 Bzt), 120.68 (C-4 Bzt), 111.80 (C-5), 109.14 (C-7 Bzt), 89.45 (C-1′), 81.75 (C-4′), 71.82 (C-5′), 62.64 (C-6′), 59.15 (C-3′), 37.51 (C-2′), 20.69 (CH_3CO), 20.63 (CH_3CO), 12.48 (CH_3).

1-[3-(Benzotriazol-1-yl)-2,3-dideoxy-β-D-arabino-hexopyranosyl]thymine (**21**) *(general procedure for deprotection of* **17**–**19***).* Compound **17** (0.06 g, 0.1 mmol) was dissolved in sat. methanolic ammonia (10 ml) and stirred overnight at 25 °C. The solvent was evaporated off under reduced pressure. The residue was purified on a silica gel column using MeOH–CH_2Cl_2 (10:90 v/v) as the eluent. Yield 0.04 g (82%), m.p. 180–181 °C. ^{1}H NMR (DMSO-d_6): δ 11.36 (s, 1 H, NH), 8.04 (d, 1 H, $J = 8.3$ Hz, H-Bzt), 7.98 (d, 1 H, $J = 8.3$ Hz, H-Bzt), 7.85 (s, 1 H, H-6), 7.56 (t, 1 H, $J = 8.3$ Hz, H-Bzt), 7.41 (t, 1 H, $J = 8.3$ Hz, H-Bzt), 6.03 (d, 1 H, $J = 10.0$ Hz, H-1′), 5.38 (d, 1 H, $J = 6.5$ Hz, 4′-OH), 5.29 (m, 1 H, H-3′), 4.73 (t, 1 H, $J = 6.0$ Hz, 6′-OH), 4.10 (q, 1 H, $J = 7.1$ Hz, H-4′), 4.01 (m, 1 H, H-5′), 3.76 (m, 1 H, H-6′), 3.62 (m, 1 H, H-6′), 2.79 (q, 1 H, $J = 12.1$ Hz, H-2′β), 2.28 (dd, 1 H, $J = 2.0$, 12.1 Hz, H-2′α), 1.83 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6): δ 163.83 (C-4), 150.29 (C-2), 145.08 (C-9 Bzt), 136.65 (C-6), 133.81 (C-8 Bzt), 127.05 (C-5 Bzt), 123.97 (C-6 Bzt), 119.04 (C-4 Bzt), 111.25 (C-5), 109.74 (C-7 Bzt), 80.91 (C-1′), 78.97 (C-5′), 68.04 (C-4′), 60.61 (C-6′), 59.85 (C-3′), 38.60 (C-2′), 11.81 (CH_3).

1-[3-(Benzotriazol-1-yl)-2,3-dideoxy-α-D-arabino-hexopyranosyl]thymine (**22**). Yield 0.04 g (69%), m.p. 145–146 °C. ^{1}H NMR (DMSO-d_6): δ 11.35 (s, 1 H, NH), 8.07 (d, 1 H, $J = 8.4$ Hz, H-Bzt), 7.92 (d, 1 H, $J = 8.4$ Hz, H-Bzt), 7.74 (s, 1 H, H-6), 7.59 (t, 1 H, $J = 8.4$ Hz, H-Bzt), 7.43 (t, 1 H, $J = 8.4$ Hz, H-Bzt), 6.05 (dd, 1 H, $J = 3.8$, 5.7 Hz, H-1′), 5.51 (d, 1 H, $J = 7.2$ Hz, 4′-OH), 5.41 (td, 1 H, $J = 5.6$, 9.3 Hz, H-3′), 4.71 (t, 1 H, $J = 5.6$ Hz, 6′-OH), 4.11 (q, 1 H, $J = 8.0$ Hz, H-4′), 3.75–3.57 (m, 3 H, H-5′, H-6′), 2.96 (ddd, 1 H, $J = 3.8$, 9.3, 12.6 Hz, H-2′α), 2.80 (ddd, 1 H, $J = 5.7$, 9.3, 12.6 Hz, H-2′β), 1.87 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6): δ 164.32 (C-4), 151.11 (C-2), 145.36 (C-9 Bzt), 138.60 (C-6), 133.89 (C-8 Bzt), 127.30 (C-5 Bzt), 124.26 (C-6 Bzt), 119.32 (C-4 Bzt), 111.37 (C-5), 109.52 (C-7 Bzt), 80.48 (C-1′), 76.88 (C-5′), 68.37 (C-4′), 60.65 (C-6′), 58.78 (C-3′), 32.19 (C-2′), 12.25 (CH_3).

1-[3-(Benzotriazol-1-yl)-2,3-dideoxy-α-D-ribo-hexofuranosyl]thymine (**23**). Yield 0.06 g (80%), m.p. 152–153 °C. ^{1}H NMR (DMSO-d_6): δ 11.34 (s, 1 H, NH), 8.09 (d, 1 H, $J = 8.3$ Hz, H-Bzt), 7.98 (d, 1 H, $J = 8.3$ Hz, H-Bzt), 7.77 (d, 1 H, $J = 1.2$ Hz, H-6), 7.61 (t, 1 H, $J = 8.3$ Hz, H-Bzt), 7.45 (t, 1 H, $J = 8.3$ Hz, H Bzt), 6.38 (t, 1 H, $J = 6.7$ Hz, H-1′), 5.84 (m, 1 H, H-3′), 5.35 (d, 1 H, $J = 5.3$ Hz, 5′-OH), 4.84 (t, 1 H, $J = 5.0$ Hz, H-4′), 4.63 (t, 1 H, $J = 5.3$ Hz, 6′-OH), 3.77 (quintet, 1 H, $J = 5.0$ Hz, H-5′), 3.36–3.20 (m, 2 H, H-6′), 3.13 (m, 1 H, H-2′β), 2.83 (dt, 1 H, $J = 6.3$, 13.9 Hz, H-2′α), 1.81 (d, 3 H, $J = 1.2$ Hz, CH_3). ^{13}C NMR (DMSO-d_6): δ 163.91 (C-4), 150.60 (C-2), 145.40 (C-9 Bzt), 136.20 (C-6), 132.83 (C-8 Bzt), 127.50 (C-5 Bzt), 124.31 (C-6 Bzt), 119.30 (C-4

Bzt), 110.97 (C-5), 109.39 (C-7 Bzt), 84.94 (C-1′), 83.88 (C-4′), 72.06 (C-5′), 62.33 (C-6′), 57.49 (C-3′), 38.59 (C-2′), 12.10 (CH_3).

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