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SYNTHESIS OF 1'-PHENYL SUBSTITUTED NUCLEOSIDE ANALOGS

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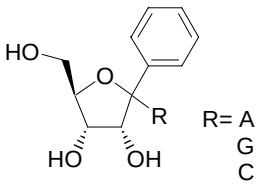
Abstract – 1'-Phenyl substituted ribonucleoside analogs with all four nucleobases have been synthesized by the conventional *N*-glycosidation method.

INTRODUCTION

Nucleoside analogs constitute an important class of compounds with a variety of biological activities such as antitumor, antiviral activity and so on. They have also attracted much attention as a useful component of synthetic oligonucleotides which are used in a variety of studies relating to gene expression. 1'-Aryl-*C*-nucleosides are employed to study hybridization behavior of nucleic acids or recognition properties in enzyme reaction due to their unique features in base stacking and shape-recognition ability.[1] We synthesized aryl-*C*-nucleoside analogs with a bicyclic sugar skeleton,[2] and showed that a phenyl part played an essential role for triplex DNA stabilization.[3] These studies with 1'-aryl-substituted nucleosides have led to interest in 1'-branched nucleosides[4] having both a phenyl and a nucleobase at the 1' position of the D-ribose skeleton (**1**). Although there are some naturally-occurring 1'-branched nucleosides (e.g. **2**, **3**),[5] only a limited number of studies have been reported on the synthesis.[6] Recently, Haraguchi et al reported the synthesis of 1'-carbon-substituted nucleoside analogs,[7] in which 1'-pheny substituted uridine was prepared by the reaction of triphenylaluminum with the corresponding uridine 1',2'-epoxide derivative. In this study, we applied the conventional *N*-glycosidation method to the 1'-phenyl-substituted D-ribose derivative to produce analogs with adenine, guanine, cytosine and thymine nucleobases.



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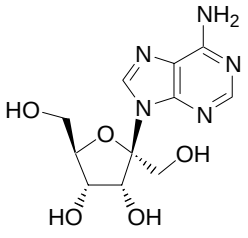

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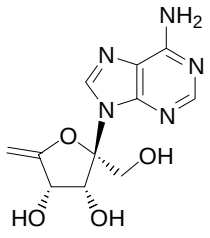

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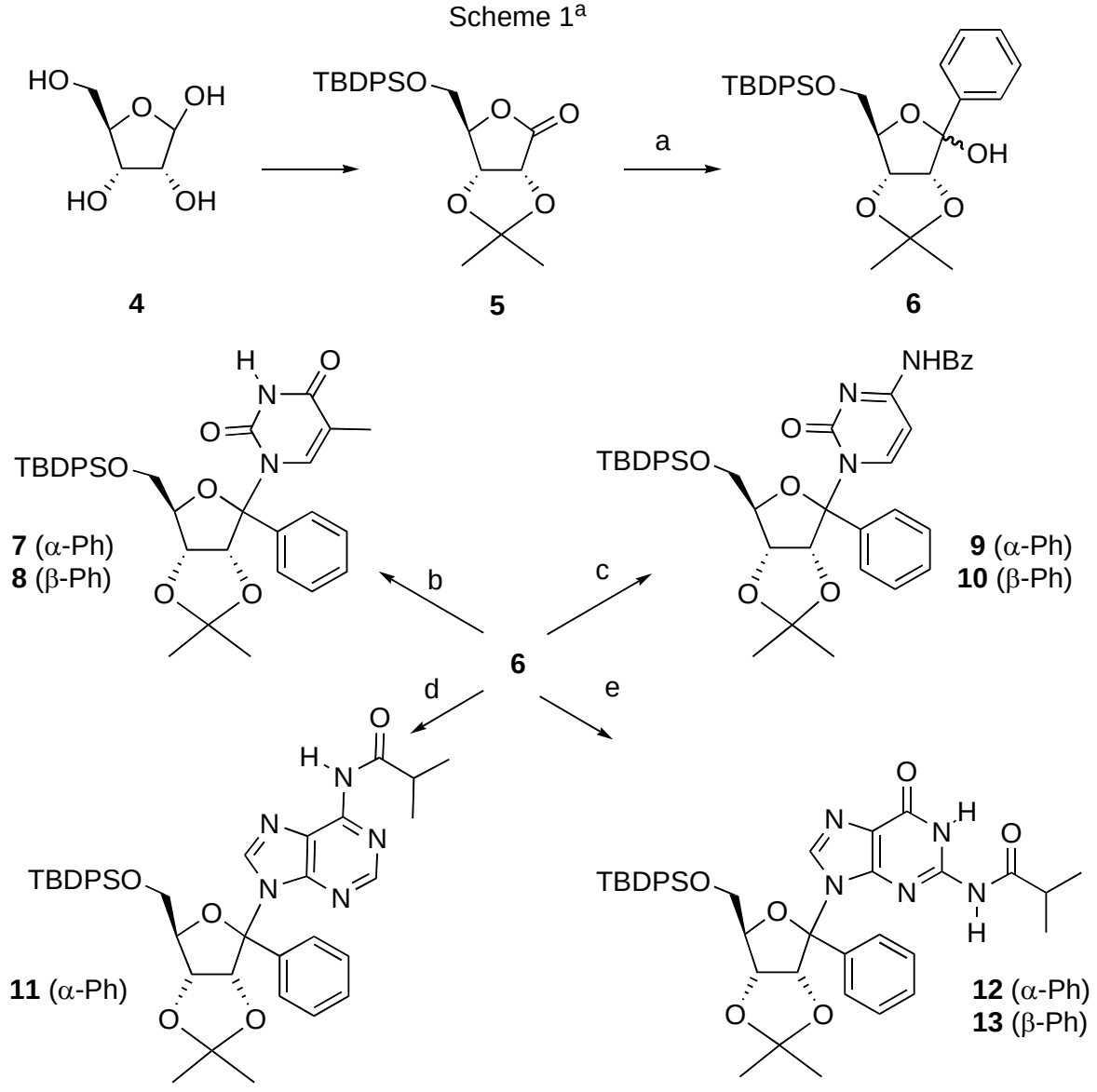
RESULTS AND DISCUSSION

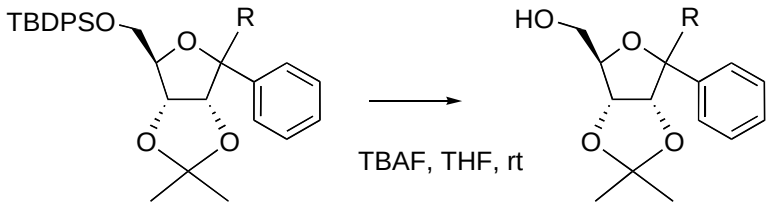
Synthetic route to 1'-phenyl-substituted nucleoside analogs is summarized in Scheme 1. Phenyllithium was added to the protected ribonolactone derivative **5**[8] as previously described to produce **6** as a mixture of stereoisomers (α-Ph/β-Ph 1:1).[9] As it was reported that acetylation of **6** caused ring opening to yield the acyclic acetate,[10] the alcohol **6** was directly used for *N*-glycosylation. Thus, thymine was reacted with **6** in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA) and TMSOTf in dry CH_3CN at 0 °C to afford the target nucleoside **8** (β-Ph) as a single isomer in 37 % yield together with 18 % recovered **6** and unidentified by-products.

Scheme 1[a]



[a]a) PhLi, THF, -78 °C, b) thymine, c) *N*-benzoylcytosine, d) *N*-isobutyryladenine, e) *N*-isobutyrylguanine in the presense of BSA, TMSOTf in dry MeCN at 50 °C.

Scheme 2

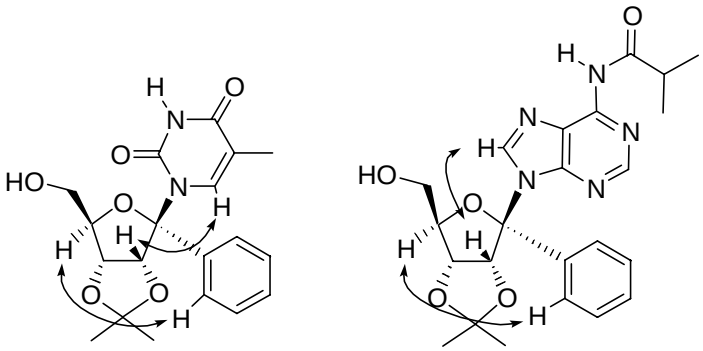


7 ,8, 11, 12

R =
14: thymine (α-Ph)
15: thymine (β-Ph)
16: *N*-isobutyryladenine (α-Ph)
17: *N*-isobutyrylguanine (α-Ph)

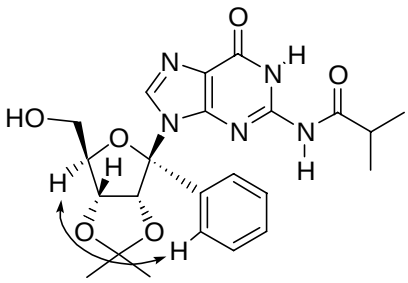
When this glycosidation was performed at 50 °C, two isomers (**7:** α-Ph, 31 % and **8:** β-Ph**,** 6 %) were obtained in 37 % yield. The fact that the β-Ph isomer became a minor product at 50 °C suggests that the β-Ph isomer is a kinetic product and the α-Ph isomer is formed by thermodynamic process. The 5' O-TBDPS group of **7** was deprotected with TBAF[11] to give **14** (α-Ph isomer) (Scheme 2) and its stereochemistry was determined by ^{1}H-COSY and ^{1}H-NOESY measurements (Figure 1). Similarly, *N*-benzoylcytosine was reacted with **6** in the presence of BSA, TMSOTf in dry CH_3CN at 50 °C to produce **9** (α-Ph, 29%) and **10** (β-Ph, 17%) in 46 % total yield. *N*-Isobutyryl derivatives of adenine[12] and guanine[13] were also similarly glycosylated with **6** in the presence of BSA, TMSOTf in dry CH_3CN at 50 °C. The adenine derivative gave a single isomer **11** (α-Ph) in low yield (9 %), and the guanine derivative produced the α-Ph isomer **12** (21 %) and the β-Ph isomer **13** (10 %) in 31 % total yield. Stereochemistry of these compounds was determined by ^{1}H-COSY and ^{1}H NOESY measurements as illustrated in Figure 1.

We attempted different reaction conditions to improve the yield of *N*-glycosidated compounds, such as at higher or lower reaction temperatures, or the use of large excess of reagents and so on, however, all conditions were not successful. It turned out that all nucleoside analogs synthesized in this study were labile even under mild acidic conditions,[14] and acetonide protecting groups was not removed. Stabilization of anomeric cation by the phenyl group may be responsible to instability of 1'-pheyl substituted nucleoside analogs. Treatment of the *N*-glycosidated compound (**16**) with ammonia in methanol also caused decomposition without cleavage of the isobutyryl protecting group, suggesting that 1'-phenyl substituted ribonucleoside analogs are also unstable in strong alkaline solution.



14 (α-Ph)

16 (α-Ph)



17 (α-Ph)

Figure 1. NOE Correlations for determination of the stereochemistry.

CONCLUSION

In summary, we synthesized 1'-phenyl branched nucleoside analogs with all four nucleobases. As this study has shown that nucleoside analogs become labile by introduction of 1'-phenyl group, structural modification of the ribose part such as changing to 4'-C analog will be needed to construct 1'-phenyl branched nucleoside analogs. Further study is now ongoing along this line.

EXPERIMENTAL

General: Melting points are uncorrected. ^{1}H-NMR spectra were measured at 400 MHz with Me_4Si as the internal standard. ESI-Mass spectra (ESI-MS) were taken in either positive or negative mode using methanol and formic acid or methanol only as a solvent respectively. Ultraviolet spectra (UV) were recorded on a Beckman Coulter DU 800 spectrophotometer. Column chromatography was carried out on 60N or FL60D silica gel. Thin layer chromatography (TLC) was performed on Merck Ltd. (precoated silica gel $60F_{245}$ plates).

5–*O*-(*tert*-Butyldiphenylsilyl)-2,3–*O*-isopropylidene-1–phenyl-D–ribofuranose (6). In very dry conditions and under argon pressure compound **5** (16.09 g, 37.78 mmol) was disolved in dry THF (235 mL), then phenyllithium 1.14 mol/L (49.52 mL, 56.68 mmol) was added dropwise at -78 ^{o}C then the reaction mixture was stirred at rt. After 4 h the reaction was quenched by saturated aqueous NH_4Cl (300

mL), extracted with AcOEt (200 mL), washed with water (200 mL), saturated aqueous sodium chloride solution (200 mL), dried over anhydrous sodium sulfate and evaporated to afford a crude yellowish brown oil (21.98 g).Column chromatography (60N silica gel, hexane/AcOEt 20:1) afforded the desired compound (an anomeric mixture α-Ph/β-Ph 1:1 with total yield 71%) as an yellow oil. IR 3392, 3070, 2934, 2858 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.11 (9H, s), 1.23 (3H, s), 1.36 (3H, s), 3.77 (1H, dd, *J* = 11.05, 3.75 Hz), 3.95 (1H, dd, *J* = 11.05, 3.93 Hz), 4.43-4.45 (1H, m), 4.48 (1H, s), 4.67 (1H, d, *J* =5.81Hz), 4.92 (1H, dd, *J* =5.81, 1.94Hz), 7.29-7.46 (9H, m), 7.60-7.72 (6H, m). ESI-MS calcd for $C_{30}H_{36}O_5Si$ $[M+Na]^+$ 527.31, found 527.31.

1-[5–*O*-(*tert*-Butyldiphenylsilyl)-2,3–*O*-isopropylidene-1–phenyl–*α,β*-D–ribofuranosyl]thymine (8, 7). To a suspension of thymine (34.5 mg, 0.273 mmol) in dry MeCN (0.5 mL) and under argon pressure was added a solution of compound **6** (116 mg, 0.228 mmol) in MeCN (0.5 mL), compound **6** was freshly dried by azeotrope method in dry acetonitril two times. BSA (224.08 μL, 0.912 mmol) was added and the reaction mixture was stirred at rt where it became clear solution after 10 minutes. After 1.5 h TMSOTf (45.42 μL, 0.25 mmol) was added drop wise then the reaction mixture was heated up immediately to 50°C and after 4.5 h the reaction was quenched by saturated aqueous sodium bicarbonate (6 mL), extracted with AcOEt (30 mL x 2), washed with water (30 mL), saturated aqueous sodium chloride (30 mL), dried over anhydrous sodium sulfate and evaporated to afford a crude yellow oil 150 mg. Flash chromatography (FL 60 D silica gel, hexane/ AcOEt 8:1) afforded 24 mg recovered start and the target compounds **7** and **8** as a pure two isomers, α and β-phenyl respectively. The α-phenyl isomer **7** as white crystals (crystallized from hexane) in 31 % yield and the β-phenyl isomer **8** as colorless oil in 6 % yield, (the total yield is 37 %). The α-phenyl isomer was further more purified by another column chromatography (normal silica gel, hexane/AcOEt 4:1 HPLC grade):

Physical data for 7 (α-phenyl)**:** IR 3300, 3070, 2932, 1666 cm^{-1}. ^{1}H-NMR (400 MHz, CD_3COCD_3) δ 0.96 (9H, s, SiBu-*t*), 0.98 (3H, s), 1.06 (3H, s) 1.68 (3H, s), 3.76 (1H, dd, H-5', *J* = 7.2 Hz and 6.4 Hz), 3.84 (1H, dd, H-5', *J* = 7.2Hz and 6.4 Hz), 4.23-4.27 (1H, m, H-4'), 4.91 (1H, dd, H-3', *J* = 3.2 Hz), 5.28 (1H, d, H-2', *J* = 6.0 Hz), 7.10-7.19 (3H, m, aromatic), 7.31-7.38 (8H, m, aromatic), 7.47 (1H, m, aromatic), 7.64-7.66 (4H, m, aromatic and H-6). UV absorption in methanol: λ_{max} 259 nm. ESI-MS calcd for $C_{35}H_{40}N_2O_6Si$ $[M+Na]^+$ 635.25, found 635.40.

Physical data for 8 (β-phenyl)**:** IR, 3386, 3080, 2929, 2856, 1742, 1674, 1596, 1478. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.96 (9H, s, SiBu-*t*), 1.37 (3H, s, isop.-Me), 1.40 (3H, s, isop.-Me), 1.99 (3H, d, 5-Me, *J* =11.6 Hz), 3.35-3.38 (1H, m, H-5'), 3.44-3.46 (1H, m, H-5'), 4.30-4.38 (1H, m, H-4'), 4.84-4.98 (1H, m, H-3'), 5.65 (1H, d, H-2', *J* =5.6 Hz), 7.27-7.49 (15H, m, aromatic), 7.76 (1H, bs, NH), 7.82 (1H, d, H-6, *J* =13.2 Hz). ESI-MS calcd for $C_{35}H_{40}N_2O_6Si$ $[M+Na]^+$ 635.25, found 635.42.

1-[5–*O*-(*tert*-Butyldiphenylsilyl)-2,3–*O*-isopropylidene-1–phenyl–α-β-D–ribofuranosyl]-*N*-benzoyl-

cytosine (10, 9). To a suspension of *N*-benzoylcytosine (56.76 mg, 0.264 mmol) in dry MeCN (0.7 mL) and under argon pressure, was added a solution of **6** (111mg, 0.22 mmol) in dry MeCN (0.5 mL) to afford a white suspension, BSA (215.60 µl, 0.88 mmol) was carefully added to afford a clear colorless solution that was stirred at rt for 1.5 h. TMSOTf (43.79 µL, 0.242 mmol) was added and immediately the reaction mixture was heated up to 50°C to afford an yellow solution. After 6 h the reaction was quenched by saturated aqueous $NaHCO_3$ (20 mL), and was extracted by $CHCl_3$ (60 mL), then was washed with water (60 mL), saturated aqueous sodium chloride (30 mL) and the organic layer was dried over anhydrous sodium sulfate and was evaporated to afford crude yellowish oil (105 mg). The crude was purified by column chromatography (60 N silica gel, HPLC grade hexane/AcOEt 15:1), where the starting material was recovered in 19 % and the target compounds **9** and **10** were obtained in (29 %, 17 %) respectively (total yield 46 %):

Physical data for 9 (α-phenyl**):** IR 3301, 3070, 2933, 1671, 1541 cm^{-1}. ^{1}H-NMR (400 MHz, C_3D_6O) δ 0.97 (9H, s), 1.06 (3H, s), 1.69 (3H, s), 3.80 (1H, dd, H-5', *J* = 8.8 Hz, 6.4 Hz), 3.87 (1H, dd, H-5', *J* = 9.2 Hz, 7.2 Hz), 4.41-4.26 (1H, m, H-4'), 4.91-4.95 (1H, m, H-3'), 5.28 (1H, d, H-2', *J* = 6.0 Hz), 7.12-7.19 (4H, m, aromatic), 7.31-7.42 (13H, m, aromatic), 7.64-7.65 (5H, m, aromatic). ESI-MS calcd for $C_{41}H_{43}N_3O_6Si$ $[M+K]^+$ 740.25, found 740.39.

Physical data for 10 (β-phenyl**):** IR 3391, 3070, 2931, 2859, 1676 cm^{-1}. ^{1}H-NMR (400 MHz, C_3D_6O) δ 0.95 (9H, s), 1.25 (3H, s), 1.56 (3H, s), 1.82 (1H, s), 3.82-4.18 (3H, m, H-5', H-4'), 4.39-4.46 (1H, m, H-3'), 4.78-4.84 (1H, m, H-2'), 7.04-7.14 (3H, m, aromatic), 7.26-7.41 (13H, m, aromatic), 7.61-7.70 (6H, m, aromatic). ESI-MS calcd for $C_{41}H_{43}N_3O_6Si$ $[M+K]^+$ 740.25, found 740.39.

***N*^{6}-Isobutyryladenine.** To a suspension of adenine (2 g, 0.0148 mol) in dry DMF (25 mL) was carefully added isobutyric anhydride (5.64 mL, 0.034 mol) to afford a white suspension. The reaction mixture was refluxed at 155°C to afford a clear solution after 30 min. After 3 h the reaction was quenched by saturated aqueous $NaHCO_3$ (60 mL), and was extracted by $CHCl_3$ (160 mL), then was washed with water (100 mL), saturated aqueous sodium chloride (100 mL) and the organic layer was dried over anhydrous sodium sulfate and was evaporated to afford crude white solid. The crude was washed by a mixture of water and EtOH (1:1) to afford a pure white solid in 64 % yield. IR 3250, 2977, 1690 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.29-1.36 (6H, m), 3.15-3.25 (1H, m), 8.38 (1H, br. s), 8.66 (1H, s), 8.78 (1H, s). ESI-MS calcd for $C_9H_{11}N_5O$ $[M+H]^+$ 206.10, found 206.07.

1-[5–*O*-(*tert*-Butyldiphenylsilyl)-2,3–*O*-isopropylidene-1–phenyl–*β*-D–ribofuranosyl]-*N*^{6}-isobutyryl-adenine (11). To a suspension of isobutyryladenine (63.96 mg, 0.312 mmol) in dry MeCN (0.7 mL) and under argon pressure, was added a solution of **6** (142 mg, 0.281 mmol) in dry MeCN (0.8 mL) to afford a white suspension, then BSA (467.95 µL, 1.91 mmol) was carefully added to afford a clear colorless solution that was stirred at rt for 1.5 h. TMSOTf (30.39 µL, 0.168 mmol) was added and

immediately the reaction mixture was heated up to 50°C to afford an yellow solution. After 14 h the reaction was quenched by saturated aqueous $NaHCO_3$ (20 mL), and was extracted by AcOEt (60 mL), then was washed with water (60 mL), saturated aqueous sodium chloride (60 mL) and the organic layer was dried over anhydrous sodium sulfate and was evaporated to afford crude yellowish semisolid (175 mg). The crude was purified by column chromatography (60 N silica gel, hexane/AcOEt 10:1), where the starting material was recovered in 20 % and the target compound was obtained in 9 % yield as a white solid single isomer. IR 3288, 3070, 2931, 1668, 1545 cm^{-1}. ^{1}H-NMR (400 MHz, C_3D_6O) δ 0.97 (9H, s), 0.98 (3H, s), 1.06 (3H, s), 1.17 (3H, s), 1.69 (3H, s), 2.63 (1H, s), 3.78 (1H, dd, H-5', *J* = 6.0 Hz, 6.4 Hz), 3.89 (1H, dd, H-5', *J* =7.2 Hz, 6.8 Hz), 4.23-4.27 (1H, m, H-4'), 4.90-4.94 (1H, m, H-3'), 5.28 (1H, d, H-2', *J* = 6 Hz), 7.12-7.19 (3H, m, aromatic), 7.30-7.41 (9H, m, aromatic), 7.64-7.66 (5H, m, aromatic). ESI-MS calcd for $C_{39}H_{45}N_5O_5Si$ $[M+K]^+$ 730.28, found 730.29.

***N*^{2}-Isobutyrylguanine.** To a suspension of guanine (2 g, 13.25 mmol) in dry DMF (25 mL) and under argon, isobutyric anhydride (5 mL, 30.15 mmol) was added dropwise and the reaction mixture was refluxed at 155°C for 3 h. The reaction mixture changed to clear solution after 1 h and after cooling down a white solid appeared. The reaction mixture was filtered and the precipitate was washed by a mixture of water and EtOH (1:1) to afford a white solid, and the filtrate was extracted by $CHCl_3$ (2 x 50 mL) and evaporated to afford white crystals: mp > 300 °C (combined yield 98 %). IR 3486, 3373, 3124, 2975, 2936, 1670, 1647 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO) δ 1.10 (6H, d, *J* = 6.8 Hz), 2.70-2.82 (1H, m), 8.01 (1H, s). ESI-MS calcd for $C_9H_{11}N_5O_2$ $[M+Na]^+$ 244.22, found 244.12.

1-[5–*O*-(*tert*-Butyldiphenylsilyl)-2,3–*O*-isopropylidene-1–phenyl–*α,β*-D–ribofuranosyl]-*N*^{2}-isobutyrylguanine (13, 12). To a solution of **6** (210 mg, 0.415 mmol) in dry MeCN (4 mL) and under argon N^2-isobutyrylguanine (359 mg, 1.663 mmol) was added at rt followed by the addition of BSA (711.72 μL, 2.905 mmol) and stirred at rt for 1 h. TMSOTf (45.04 μL, 0.249 mmol) was added dropwise and the reaction mixture was stirred at 50 °C under argon pressure for 5 h. The reaction mixture was quenched by saturated aqueous $NaHCO_3$ (30 mL) and extracted by AcOEt (2 x 40 mL), then washed with water and brine (each 50 mL), dried over anhydrous sodium sulfate and evaporated under vacum to afford a crude white solid (224 mg). The crude solid contained some insoluble salts that could not be dissolved in AcOEt so filtered out and the filtrate was evaporated under reduced pressure to afford crude white solid that was purified by flash chromatography (60 N silica gel, hexane/AcOEt 6:1) to afford compounds **12, 13** each as a white solid in 21, 10 % respectively (total yield 31 %) as well as 19 % of the starting compound was recovered. Compound **12** was further purified by another column chromatography (normal silica gel, HPLC grade hexane/AcOEt 4:1):

Physical data for 12 (α-phenyl**):** IR, 3100-3600 (broad peak), 3274, 3069, 2928, 2855, 1665, 1551 cm^{-1}. ^{1}H-NMR (400 MHz, C_6D_6O) δ 0.97 (9H, s), 0.98 (3H, s), 1.06 (3H, s), 1.16 (3H, d, *J* =8.8 Hz), 1.69 (3H,

s), 2.63 (1H, s), 3.80 (1H, dd, H-5', *J* = 6.4, 6.4 Hz), 3.87 (1H, dd, H-5', *J* = 7.2 Hz), 4.23-4.26 (1H, m, H-4'), 4.92 (1H, dd, H-3', *J* = 3.2 Hz and 3.6Hz), 5.28 (1H, d, H-2', *J* = 5.6 Hz), 7.12-7.19 (3H, m, aromatic), 7.31-7.42 (9H, m, aromatic), 7.64-7.65 (4H, m, aromatic). ESI-MS calcd for $C_{39}H_{45}N_5O_6Si$ $[M+K]^+$ 746.28, found 746.46.

Physical data for 13 (*β*-phenyl): IR, 3100-3600 (broad peak), 3365, 2925, 2854, 1680, 1606, 1562 cm^{-1}. ^{1}H-NMR (400 MHz, C_6D_6O) δ 0.95 (9H, s), 1.17 (3H, s), 1.25 (3H, s), 1.56 (3H,d), 1.83 (1H, d), 2.63 (1H, s), 3.85-3.94 (2H, m, H-5'), 4.09-4.21 (1H, m, H-4'), 4.40-4.46 (1H, m, H-3'), 4.47-8.82 (1H, m, H-2'), 7.04-7.14 (2H, m, aromatic), 7.26-7.41 (10H, m, aromatic), 7.65-7.67 (4H, m, aromatic). ESI-MS calcd for $C_{39}H_{45}N_5O_6Si$ $[M+K]^+$ 746.28, found 745.97.

1-[2,3–*O*-Isopropylidene-1–phenyl–*β*-D–ribofuranosyl]thymine (14). To a solution of **7** (80 mg, 0.1307 mmol) in dry THF (4 mL) was added tetrabutylammonium fluoride (94 μL, 0.326 mmol), and the reaction mixture was stirred at rt for 2 h, where its color changed from pale yellow to dark reddish to orange. The reaction was quenched by water (20 mL), and was extracted by AcOEt (60 mL), then was washed with water (20 mL), saturated aqueous sodium chloride (20 mL) and the organic layer was dried over anhydrous sodium sulfate and was evaporated to afford crude colorless oil (68 mg). The crude was purified by flash chromatography (60 N silica gel, AcOEt/MeOH 30:1). The target was obtained in 49 % yield as a white solid. IR 3294, 3064, 2933, 1746, 1667, 1537 cm^{-1}. ^{1}H-NMR (400 MHz, C_3D_6O) δ 0.73 (3H, s, isop.-Me), 1.06 (3H, s, isop.-Me), 1.83 (3H, d, 5-Me, *J* = 2.4 Hz), 3.56-3.62 (1H, m, H-5'), 3.69-3.72 (1H, m, H-5'), 4.14 (1H, brs, NH), 4.19-4.28 (1H, m, H-4'), 4.87 (1H,dd, H-3', *J* = 2.8 Hz, 2.8 Hz), 5.35 (1H, d, H-2', *J* = 6.4 Hz), 7.14-7.27 (3H, m, aromatic), 7.37 (2H, d, aromatic, *J* = 7.2 Hz), 7.57 (1H, s, H-6). ESI-MS calcd for $C_{19}H_{22}N_2O_6$ $[M+Na]^+$ 397.13, found 397.14.

1-[2,3–*O*-Isopropylidene-1–phenyl–*α*-D–ribofuranosyl]thymine (15). To a solution of **8** (21 mg, 0.0343 mmol) in dry THF (2 mL) was added tetrabutylammonium fluoride (24.5 μL, 0.0857 mmol), and the reaction mixture was stirred at rt for 14 h, where its color changed from colorless to yellow. The reaction was quenched by water (4 mL), and was extracted by AcOEt (40 mL), then was washed with water (20 mL), saturated aqueous sodium chloride (20 mL) and the organic layer was dried over anhydrous sodium sulfate and was evaporated to afford crude yellowish oil (17 mg). The crude was purified by flash chromatography (60 N silica gel, AcOEt/MeOH 30:1). The target was obtained in 63 % yield as a white solid. IR 3392, 3062, 2933, 1661, 1492 cm^{-1}. ^{1}H-NMR (400 MHz, C_3D_6O) δ 1.25 (3H, s), 1.55 (3H, s), 1.84 (3H, d, 5-Me *J* = 5.2 Hz), 3.29 (1H, dd, H-5', *J* = 6.6 and 7.2 Hz), 3.64-3.70 (1H, m, H-5'), 4.00-4.14 (1H, m, H-4'), 4.37 (1H, d, H-5', *J* = 7.2 Hz), 4.68-4.74 (1H, m, H-2'), 7.02-7.47 (6H, m, aromatic and H-6). ESI-MS calcd for $C_{19}H_{22}N_2O_6$ $[M-H]^-$ 373.13, found 373.12.

1-[2,3–*O*-Isopropylidene-1–phenyl–*β*-D–ribofuranosyl]-N^6-isobutyryladenine (16). To a solution of **11** (20 mg, 0.0289 mmol) in dry THF (2 mL) was added tetrabutylammonium fluoride (21 μL, 0.0723

mmol), and the reaction mixture was stirred at rt for 1 h. The reaction was quenched by water (3 mL), and was extracted by AcOEt (40 mL), then was washed with water (20 mL), saturated aqueous sodium chloride (20 mL) and the organic layer was dried over anhydrous sodium sulfate and was evaporated to afford crude colorless oil (15 mg). The crude was purified by flash chromatography (60 N silica gel, HPLC grade AcOEt/MeOH 30:1). The target was obtained in 62 % yield as white solid. IR 3292, 3064, 2930, 1667, 1540 cm^{-1}. ^{1}H-NMR (400 MHz, C_3D_6O) δ 0.76 (3H, s), 1.07 (3H, s), 1.16 (3H, s), 1.83 (3H, s), 2.80-2.81 (1H, m), 3.57-3.72 (2H, m, H-5'), 4.18-4.21 (1H, m, H-4'), 4.21 (1H, br. s, NH), 4.85-4.88 (1H,dd, H-3', *J* = 2.8 Hz, 2.8 Hz), 5.31 (1H, d, H-2', *J* = 6.4 Hz), 7.12-7.20 (4H, m, phenyl and H-2), 7.36-7.37 (2H, m, phenyl), 7.64 (1H, s, H-8). ESI-MS calcd for $C_{23}H_{27}N_5O_5$ $[M+K]^+$ 492.16, found 492.21.

1-[2, 3–*O*-Isopropylidene-1–phenyl–*β*-D–ribofuranosyl]-N^2-isobutyrylguanine (17). To a solution of **12** (18 mg, 0.0254 mmol) in dry THF (2 mL) was added tetrabutylammonium fluoride (25 μl, 0.088 mmol), where the color of the reaction mixture changed from colorless to dark yellow then to pale yellow. After 1 h the reaction was quenched by water (3 mL), and was extracted by AcOEt (30 mL), then was washed with water (20 mL), saturated aqueous sodium chloride (20 mL) and the organic layer was dried over anhydrous sodium sulfate and was evaporated to afford crude yellow oil (15 mg). The crude was purified by flash chromatography (60 N silica gel, HPLC grade AcOEt/MeOH 30:1). The target was obtained in 60 % yield. IR 3299, 3063, 2987, 1664, 1541 cm^{-1}. ^{1}H-NMR (400 MHz, C_3D_6O) δ 0.73 (3H, s), 0.91 (1H, s, OH), 1.06 (3H, s), 1.82-1.84 (3H, m), 1.90-1.94 (3H, m), 2.64 (1H, s), 3.56-3.62 (1H, m, H-5'), 3.68-3.73 (1H, m, H-5'), 4.19 (1H, q, H-4', *J* = 4.4 Hz), 4.88 (1H,dd, H-3', *J* = 2.8 Hz, 2.8 Hz), 5.34 (1H, d, H-2', *J* = 6.4 Hz), 7.14-7.27 (3H, m, aromatic), 7.37 (2H, d, aromatic, *J* = 7.2 Hz), 7.57 (1H, s, H-8). ESI-MS calcd for $C_{23}H_{27}N_5O_6$ $[M+K]^+$ 508.15, found 508.12.

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