New 2′-*C*-Branched-Chain Sugar Nucleoside Analogs with Potential Antiviral or Antitumor Activity

Junior Wolf,[a] Jean-Marc Jarrige,[a] Jean-Claude Florent,[a] David S. Grierson,[b] Claude Monneret*[a]

[a] Service de Chimie, CNRS, URA 1387, Institut Curie, Section de Biologie, 26 rue d'Ulm, F-75231 Paris Cedex 05, France
[b] Institut de Chimie des Substances Naturelles CNRS, F-91198 Gif-sur-Yvette, France

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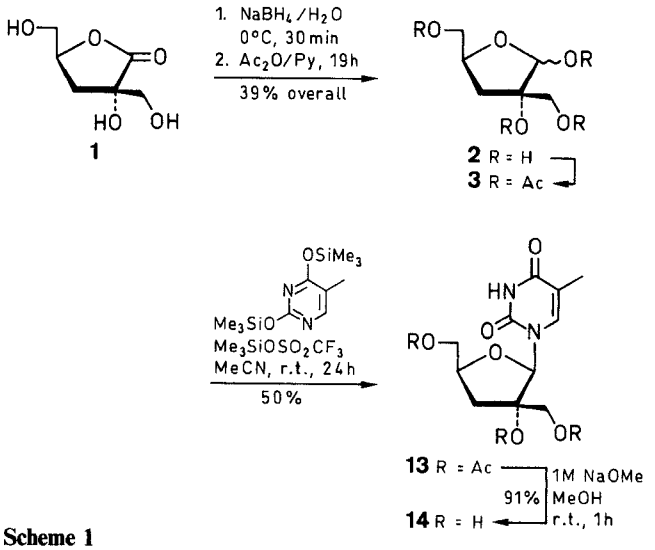
The synthesis of 2′-*C*-hydroxymethyl and 2′-*C*-methyl nucleoside analogs [1-(3-deoxy-2-hydroxymethyl-D-*erythro*-pentofuranosyl)-thymine **(14)**, the corresponding adenine derivative. **17**, 1-(2-methyl-β-D-ribofuranosyl)thymine **(20)** and 2′-methyladenosine **(23)**] by coupling of sugar moieties, easily prepared from α-D-isosaccharino- and α-D-glucosaccharino-1,4-lactone derivatives, respectively, with silylated thymine or 6-chloropurine is reported.

Since the first report of Walton et al.[1] that 2′-C- and 3′-C-methyladenosine were resistant to adenosine deaminase and that they exhibit inhibitory activity against KB cells in culture, a number of papers appeared concerning the synthesis of branched-chain sugars nucleosides.[2] A direct result of this work has been the discovery that molecules such as 2′-alkyl-2′-deoxycytidine display antitumor activity [potent inhibition of murine leukemia cell (L1210) comparable to Ara-C[3]] whereas others such as Oxetanocin A show promising in vitro activity against HIV.[4a] Furthermore, the Oxetanocine analog, Oxetanocin G produced by chemical and biological transformations,[4b] is a very potent and selective inhibitor of replication of human cytomegalovirus (HCMV)[4c] and the ring enlarged Oxetanocin A analog [6-amino-9-(2,3-dideoxy-3-hydroxymethyl-β-D-ribofuranosyl)-9*H*-purine] is an inhibitor of HIV-1.[5] In conjunction with an ongoing program in the nucleoside area these findings prompted us to undertake the preparation of new, structurally related branched-chain nucleosides in order to evaluate their biological activities.[6]

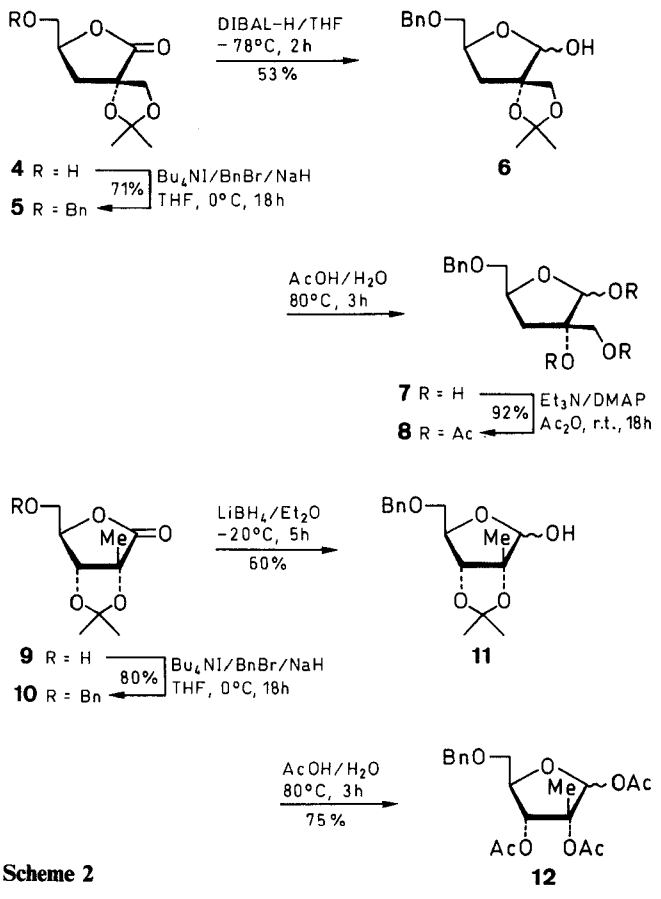
The starting branched-chain sugars α-D-isosaccharino-1,4-lactone **1** and 2,3-*O*-isopropylidene-α-D-glucosaccharino-1,4-lactone **9** were readily obtained from lactose[7] and fructose, respectively,[8] and transformed into the 1-*O*-acetyl derivatives **3** and **12** in preparation for coupling to a silylated base. In the first series, lactone **1** was reduced with sodium borohydride in water at 0 °C for 30 minutes[9] (Scheme 1). Compound **2** was immediately acetylated using acetic anhydride in pyridine at reflux to give the 1-*O*-acetylfuranosyl sugar **3** (39 % yield from **1**). Intermediate **3** was condensed with the disilylated derivative of thymine according to the Vorbrüggen protocol (trimethylsilyl triflate, acetonitrile).[10] Nucleoside **13** isolated in 48 % yield (based on **2**) was subsequently deacetylated using sodium methoxide in methanol furnishing **14** in 91 % yield. Although the desired nucleoside analog **14** was obtained in this manner, the low yield encountered during the borohydride reduction step led us to explore an alternative route to a suitably protected form of the pentofuranoside **2**.

Following the sequence outlined in Scheme 2, benzylation of the isopropylidene derivative of α-D-isosaccharino-1,4-lactone **4** afforded **5** (71 %) which was reduced with



Scheme 1

diisobutylaluminum hydride (DIBAL-H) at −78 °C in tetrahydrofuran giving exclusively the aldose **6**. The target pentofuranosyl derivative **8** was obtained after



Scheme 2

hydrolysis of **6** and acetylation of **7** using standard procedures (92% overall yield). The corresponding conversion of the isopropylidene derivative of glucosaccharino-1,4-lactone **9** to the peracetylated sugar **12** involved: i) protection of the primary alcohol giving **10**, ii) reduction of lactone carbonyl in **10** with lithium borohydride in diethyl ether at −20°C providing aldose **11**, and iii) hydrolysis of the 2,3-isopropylidene function in **11** and acetylation.

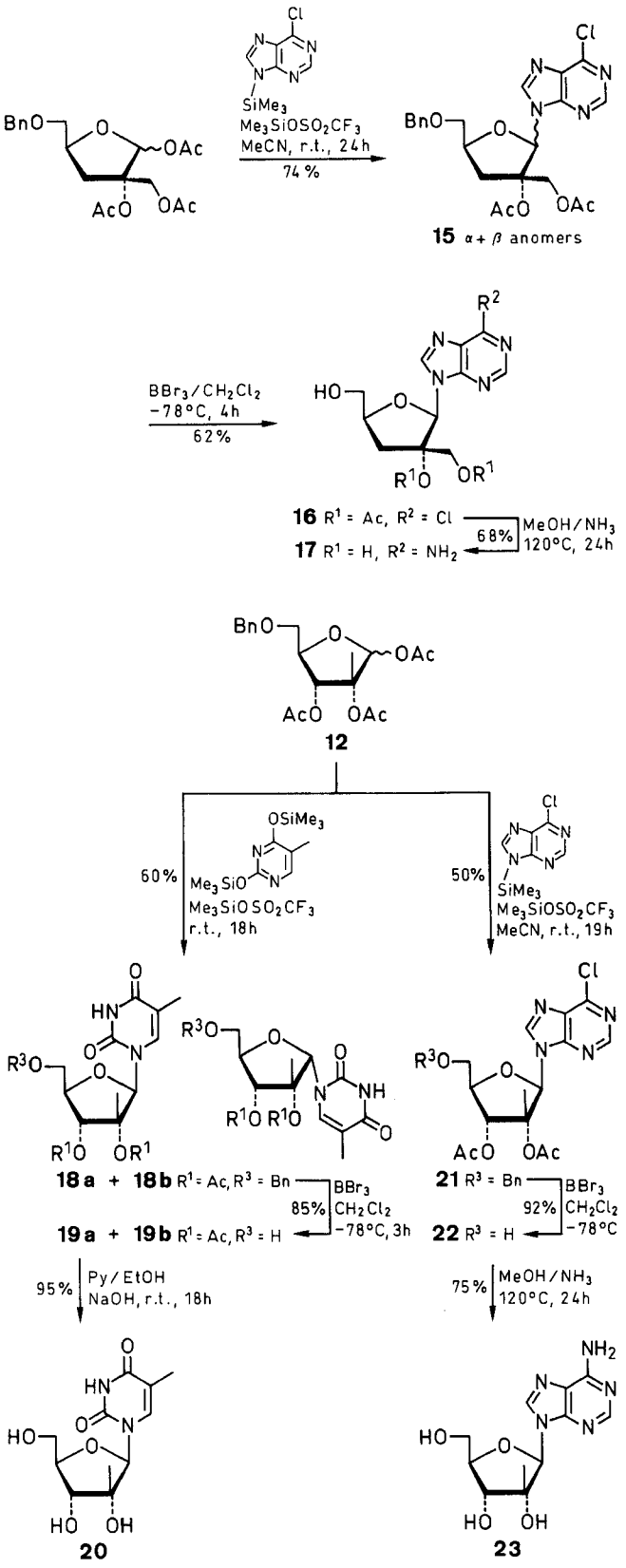
The purine analogs **17** and **23** were prepared by coupling the branched-chain sugars **8** and **12**, respectively, with the *N*-silylated derivative of 6-chloropurine. For compound **8**, the coupling reaction was moderately stereoselective producing a 4:1 mixture of anomers **15**β and **15**α, which we were unable to separate chromatographically. However, β-nucleoside **16** resulting from reaction of the mixture of **15**α and **15**β with boron tribromide at −78°C in toluene could be isolated as a pure compound after flash chromatography (62%). Subsequent treatment of **16** with methanolic ammonia afforded in 68% yield the desired 6-amino-9-(3-deoxy-2-*C*-hydroxymethyl-β-D-*erythro*-pentofuranosyl) nucleoside **17**. Compound **17** can be considered to be a 2′-*C*-hydroxymethyl analog of Cordycepin.[11]

Using the same coupling conditions, reaction of *N*-silyl-6-chloropurine with the 2-methylribose intermediate **12** produced the β-nucleoside **21** stereoselectively (50% yield). Deprotection of the 5′-hydroxyl group (92% yield) of **21** followed by ammonolysis of **22** with saturated ammonia in methanol afforded 2′-*C*-methyladenosine **23** previously described by Walton et al.[1]

The pyrimidine analogue **20** was obtained from **12** by coupling with bis(trimethylsilyl)thymine under the conditions described for the preparation of **14**. An unexpected mixture[2d] of α and β isomers **18a** and **18b** (60% overall yield) was obtained under these conditions. Structure of N_1-nucleosides was unambiguously established for both compounds by examination of the chemical shift in NMR of the H-1′ proton (δ = 6.36 and 6.26) since it is well known that N_3-β-D-nucleosides show a characteristic shift of the H-1′ proton up to 1 ppm.[12] By deprotection at the 5′ position using boron tribromide (53%), intermediate **19** was isolated as a pure product by column chromatography and subsequently deacetylated (95% yield) by treatment with ethanol/sodium hydroxide. Analog **20** was purified by flash chromatography on silica gel (53% yield).

It should be remarked that in general the coupling reactions of our branched-chain sugars with the silylated bases were considerably slower than the corresponding reactions with 2-deoxyribose derivatives, probably due to steric hindrance by the bulky C-2 alkyl group. This problem plus the possibility for formation of a carbocation at the C-2 center may be reasons for the numerous side products which are formed during the couplings.

The structures of the nucleoside analogs **14**, **17**, **20** and **23** were determined from an analysis of the ^{1}H NMR data. Furthermore, the CD spectra of **14** and **20** show a positive cotton effect at 260–280 nm in agreement with a β-pyrimidine nucleoside structure.[13a] A negative cotton effect characteristic for β-purine nucleosides[13b] was also observed for **17** and **23**.



Melting points were determined using a Reichert Thermovar apparatus and are uncorrected. Microanalysis were performed by the "Laboratoire de Microanalyse du CNRS" Lyon. IR spectra were determined on a Perkin-Elmer Model 1710 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker apparatus (270 MHz), using TMS as an internal standard. Mass spectra were

recorded on a Nermag R10-10C (DCI/NH_3) spectrometer. Optical rotations were measured at 20 °C with a Perkin-Elmer Model 241 polarimeter. Flash chromatographies[14] were performed on Merck silica gel 60 (Art. 9385) and chromatography on Merck silica gel n°7736. In all cases, the solvent system used for the chromatographic separations was chosen such that, on TLC, an R_f of 0.25–0.30 was observed for the compound to be isolated.

2-*C*-Acetoxymethyl-1,2,5-tri-*O*-acetyl-3-deoxy-D-*erythro*-pentofuranose (3):
In a 250 mL flask was dissolved 5 g (30 mmol) of **1** in H_2O (50 mL). Then, a 1 M solution of $NaBH_4$ in H_2O (7.5 mL) was added at 0 °C. After being stirred for 0.5 h, a TLC indicated that the reaction was complete. The mixture was deionized with IRC 50 (H^+) amberlyst resin, and co-evaporated with MeOH (4 × 50 mL). After purification by flash column chromatography with a gradient of solvent (from CH_2Cl_2/MeOH, 9:1 to 5:1, v/v), 2 g of a sirup containing crude compound **2** was directly treated with pyridine (20 mL) and Ac_2O (6 mL) at reflux for 19 h. After cooling, MeOH was added and the solvent evaporated under reduced pressure. Co-evaporation of the residue with toluene followed by flash chromatography (cyclohexane/acetone, 1:1) gave 4 g of **3** (39% from **1**).

$C_{14}H_{20}O_9$ (332.2) calc. C 50.58 H 6.06 found 50.70 5.95

MS (DCI/NH_3): m/z = 350 $(M + 18)^+$; 306, 273.

^{1}H NMR (90 MHz, $CDCl_3$): δ = 6.39 (s, 0.3 H, 1-H), 6.36 (s, 0.7, 1-H), 4.78–3.96 (m, 5 H, 2'-H, 4-H, 5-H), 2.73 (m, 1 H, 3-Ha), 2.21 (m, 1 H, 3-Hb), 2.01 (s, 12 H, OAc).

5-*O*-Benzyl-2-*C*-hydroxymethyl-2,2'-*O*-isopropylidene-α-D-isosaccharino-1,4-lactone (5):
To a cooled (0 °C) solution of **4**[7] (8 g, 39 mmol) in THF (80 mL) was added, portionwise, NaH (1.44 g, 60 mmol), followed by Bu_4NI (2.54 g, 8 mmol) and BnBr (14.4 mL). The suspension was stirred overnight (18 h) and neutralized by addition of 50% aq AcOH at 0 °C. Then, the mixture was extracted with EtOAc and the combined organic layers were washed with aq. $NaHCO_3$, with H_2O, with brine and dried (Na_2SO_4). After concentration, the oily residue was purified by flash chromatography (hexane/acetone, 3:1) affording 8.13 g of **5** (71%); syrup, $[\alpha]_D^{20}$ + 33° (c = 1, $CHCl_3$).

$C_{16}H_{20}O_5$ (292.3) calc. C 67.74 H 7.53 found 67.91 7.55

IR (film): ν = 1725 cm^{-1} (CO lactone).

MS (DCI/NH_3): m/z = 310 $(M + 18)^+$, 277, 220.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.30 (s, 5 H_{arom}), 4.70 (m, 1 H, 4-H), 4.52 (s, 2 H, CH_2Ph), 4.22 (d, 1 H, J = 9 Hz) and 4.00 (d, 1 H, J = 9 Hz) (AB syst., 2'-H), 3.70 (dd, 1 H, J = 12, 3 Hz) and 3.50 (dd, 1 H, J = 12, 3 Hz) (ABX, 5'-H), 2.38 (m, 2 H, 3-H), 1.48 (s, 3 H) and 1.42 (s, 3 H) (CMe_2).

5-*O*-Benzyl-3-deoxy-2-*C*-hydroxymethyl-2,2'-*O*-isopropylidene-D-*erythro*-pentofuranose (6):
DIBAL-H (43 mL of a 1 M solution in THF) was added to a cooled solution (−78 °C) of **5** (5 g, 17.1 mmol) in THF (150 mL) under Ar. After stirring for 2 h until the temperature rose to −40 °C, the reaction was stopped by dropwise addition of MeOH. The mixture was acidified by addition of cold 10% aq H_2SO_4 and extracted with EtOAc. The organic layers were washed with cold H_2O, brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded a syrup. Flash chromatography with hexane/acetone (3:1) gave 2.8 g (53%) of **6**, as an anomeric mixture.

$C_{16}H_{22}O_5$ (294.3) calc. C 65.29 H 7.53 found 65.32 7.48

MS (DCI/NH_3): m/z = 312 $(M + 18)^+$, 294 $(M + H)^+$, 277 $(M + H-17)^+$.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.23 (m, 5 H_{arom}), 5.07 (s, 0.3 H) and 5.00 (s, 0.7 H), (1-H), 4.62 (d, J = 6 Hz) and 4.50 (d, J = 6 Hz) (AB syst., CH_2Ph), 4.50 (m, 1 H, 4-H), 4.33–3.86 (m, 1 H, 5-H), 3.87–3.67 (m, 2'-H), 2.33–1.87 (m, 2 H, 3-H), 1.40 (s), 1.39 (s) and 1.40 (s) (CMe_2).

2-*C*-Acetoxymethyl-1,2-di-*O*-acetyl-5-*O*-benzyl-3-deoxy-D-ribofuranose (8):
Lactol **6** (1.3 g, 4.5 mmol) was dissolved in a mixture of AcOH (15 mL) and H_2O (10 mL), and stirred at 80 °C for 3 h. Evaporation of the solution under reduced pressure followed by co-evaporations with toluene (2 × 10 mL) gave **7** as a residue which was immediately dissolved in anhydr. CH_2Cl_2 and cooled to 0 °C. After addition of Et_3N (2.43 mL, 18 mmol), DMAP (313 mg, 2.5 mmol) and Ac_2O (1.5 mL, 15 mmol), the mixture was stirred overnight (18 h) at r.t. Extraction with EtOAc with usual workup led after evaporation under reduced pressure to a residue which was purified by flash chromatography (hexane/acetone 3:1). This afforded 1.75 g (92%) of **8**.

$C_{19}H_{24}O_8$ (380.4) calc. C 59.99 H 6.36 found 59.88 6.40

IR (film): ν = 1746 cm^{-1} (CO ester).

MS (DCI/NH_3): m/z = 398 $(M + NH_4)^+$, 350, 321 $(M + H - OAc)^+$.

^{1}H NMR (270 MHz, $CDCl_3$, mixture of anomers): δ = 7.21 (m, 5 H_{arom}), 6.45 (s) and 6.31 (s, 1-H), 4.73–4.38 (m, 3 H, 4-H, 2'-H), 3.52 (m, 2 H, 5-H), 2.75–2.10 (m, 2 H, 3-H), 2.05 (s), 2.03 (s) and 2.01 (s) (OAc).

5-*O*-Benzyl-2,3-*O*-isopropylidene-2-*C*-methyl-D-ribono-1,4-lactone (10):
NaH (264 mg, 17 mmol) was added to a cooled solution (0 °C) of compound **9**[8] (2 g, 10 mmol) in anhydr. THF (80 mL). After stirring for 0.5 h at 0 °C, Bu_4NI (369.35 mg) and BnBr (2.4 mL, 20 mmol) were added and the reaction was stirred overnight (18 h) at r.t. Addition of AcOH (0.5 mL) and H_2O (100 mL) was followed by extraction with Et_2O. The organic phases were washed with H_2O, dried (Na_2SO_4) and evaporated to dryness. The residue gave after flash chromatography (hexane/acetone, 8:1) 2.2 g (80%) of compound **10** as a syrup; $[\alpha]_D^{20}$ − 25° (c = 0.9, $CHCl_3$).

$C_{16}H_{20}O_5$ (292.3) calc. C 67.74 H 7.53 found 65.82 6.80

IR (film): ν = 1720 cm^{-1} (CO, lactone).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.30–7.15 (m, 5 H, H_{arom}), 4.68–4.37 (m, 4 H, 3-H, 4-H, CH_2Ph), 3.73 (d, 2 H, J = 2 Hz, 5-H), 1.58 (s, 3 H, Me), 1.44 (s, 3 H and 1.41 (s, 3 H) (CMe_2).

5-*O*-Benzyl-2,3-*O*-isopropylidene-2-*C*-methyl-D-ribofuranose (11):
Lactone **10** (2.2 g, 7.5 mmol) was dissolved in anhydr. Et_2O (80 mL) under Ar and $LiBH_4$ (166 mg, 7.5 mmol) was added after cooling to −20 °C. After 5 h, the reaction was quenched by addition of MeOH and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated to dryness. Flash chromatography (hexane/acetone, 4:1) of the residue afforded 1.30 g of lactol **11** (60%) as a mixture of anomers.

$C_{16}H_{22}O_5$ 294.35 calc. C 65.29 H 7.53 found 65.19 7.60

$[\alpha]_D^{20}$ − 2° (c = 0.9, $CHCl_3$, equil.).

IR (film): ν = 3400 cm^{-1} (OH).

MS (DCI/NH_3): m/z = 293, 277 $(M^+ - 17)$.

^{1}H NMR (270 MHz, $CDCl_3$ mixture of anomers): δ = 7.33–7.17 (m, 5 H, H_{arom}), 4.80–4.40 (m, 4 H, CH_2Ph, 3-H, 4-H), 4.26 (s) and 4.17 (s, 1-H), 3.81–3.57 (m, 2 H, 5-H), 1.54 (s) and 1.50 (s, 2-C-Me), 1.50–1.43 (m, 6 H, CMe_2).

1,2,3-tri-*O*-Acetyl-5-*O*-benzyl-2-*C*-methyl-D-ribofuranose (12):
A solution **11** (500 mg, 1.7 mmol) in H_2O (2 mL) and AcOH (3 mL) was stirred for 3 h at 80 °C. The residue obtained after co-evaporations under reduced pressure with toluene (2 × 10 mL) was treated as in the case of preparation of **8** [anhydr. CH_2Cl_2, DMAP (93 mg, 0.76 mmol), Et_3N (1.4 mL, 1.8 mmol) and Ac_2O (0.6 mL)] to afford **12** (538 mg, 75%).

$C_{19}H_{24}O_8$ (380.4) calc. C 59.99 H 6.36 found 60.05 6.40

IR (film): ν = 1745 cm^{-1} (C=O, ester).

MS (DCI/NH_3): m/z = 398 $(M + NH_4)^+$, 322 $(M - OAc)^+$, 321 $(M - AcOH)^+$.

^1H NMR (270 MHz, $CDCl_3$, mixture of anomers): δ = 7.26–7.15 (m, 5H, H_{arom}), 6.44 (s) and 6.35 (s, 1-H), 5.41 (d, J = 9, 3-H), 5.06 (d, J = 4, 3-H), 4.57 (d, 2H, CH_2Ph), 4.18 (m, 1H, 4-H), 3.77–3.62 (m, 5-H), 2.15–1.93 (5 s, OAc), 1.62 (s) and 1.56 (s, Me).

1-(2-*C*-Acetoxymethyl-2,5-Di-*O*-acetyl-3-deoxy-D-*erythro*-pentofuranosyl)thymine (13):

A suspension of dry thymine (504 mg, 4 mmol) in hexamethyldisilazane (HMDS, 10 mL) and dry pyridine (5 mL) was refluxed in the absence of moisture until dissolution was complete (4 h). The mixture was concentrated in vacuo to dryness and co-evaporated with dry toluene (3 × 30 mL) to afford a crude residue. Then a solution of **3** (0.5 g, 1.5 mmol) in MeCN (5 mL) was added to this residue followed by addition of trimethylsilyl triflate in MeCN (8 mL of a 1 M solution). The reaction was stirred for 24 h at r.t., and then poured into cold sat. aq $NaHCO_3$. The resulting mixture was extracted with EtOAc, washed with H_2O, dried (Na_2SO_4) and evaporated giving a crude product which was purified by flash chromatography (cyclohexane/acetone, 2:1) furnishing 300 mg (50%) of **13**; $[\alpha]_D^{20}$ + 7° (c = 0.5, EtOH).

$C_{17}H_{22}O_9N_2$	calc.	C 51.25	H 5.56	N 7.03
(398.36)	found	51.07	5.62	6.98

MS (DCI/NH_3): m/z = 416 $(M + NH_4)^+$, 399 $(M + H)^+$, 273.

IR (film): ν = 1740 (CO ester), 1700, 1240 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 10.00 (s, 1H, NH), 7.20 (s, 1H, 5-H), 6.20 (s, 1H, 1-H), 4.60 (d, 2H, J = 12 Hz, 2'-H), 4.50 (m, 1H, 4-H), 4.37 (dd, 1H, J = 12, 2.5 Hz, 3'-H), 2.10 (s, 3H), 2.06 (s, 3H), 1.93 (s, 3H), and 1.78 (s, 3H) (OAc, Me-5).

1-(3-Deoxy-2-*C*-hydroxymethyl-D-*erythro*-pentofuranosyl)thymine (14):

To a stirred solution of **13** (126 mg, 0.3 mmol) in MeOH (2 mL) was added 0.5 mL of a 1 M solution of NaOMe in MeOH. After 1 h, the mixture was neutralized by addition of Amberlite IRC 50 (H^+), filtered and evaporated under reduced pressure. Purification by flash chromatography (CH_2Cl_2/MeOH, 80:20) gave 80 mg (91%) of **14** as a syrup; $[\alpha]_D^{20}$ + 30° (c = 0.5, EtOH).

$C_{11}H_{16}O_6N_2$	calc.	C 48.53	H 5.92	N 10.29
(272.2)	found	48.78	5.88	10.35

MS (DCI/NH_3): m/z = 290 $(M + NH_4)^+$, 273 $(M + H)^+$, 164, 127.

^1H NMR (270 MHz, $CDCl_3$): δ = 8.59 (s, 1H, NH), 7.84 (s, 1H, 5-H), 6.42 (s, 1H, 1-H), 4.28 (dd, 1H, J = 12, 2 Hz, 4-H), 3.86 (dd, 1H, J = 11, 2 Hz) and 3.79 (d, 1H, J = 11 Hz, 2'-H), 2.49 (dd, 1H, J = 2, 13 Hz) and 2.06 (dd, 1H, J = 13, 5 Hz, 3'-H), 1.83 (s, 3H, Me-5).

9-(2-Acetoxymethyl-2-*O*-acetyl-5-*O*-benzyl-α- and β-D-*erythro*-pentofuranosyl)-6-chloro-9*H*-purine (15):

To a mixture of 9-trimethylsilyl-6-chloropurine [prepared by refluxing 6-chloropurine (250 mg, 1.65 mmol) in HMDS (7 mL, 33 mmol) during 18 h followed by evaporation to dryness and two co-evaporations with toluene (2 × 25 mL)] and sugar **8** (520 mg, 1.37 mmol) in dry MeCN (30 mL) was added trimethylsilyl triflate (1.65 mL of a 1 N solution in MeCN). The mixture was stirred for 24 h at r.t. and quenched by pouring into ice-cold sat. aq $NaHCO_3$ (20 mL). Extraction with EtOAc with washing with H_2O, brine and drying (Na_2SO_4) gave, after evaporation under reduced pressure, a residue which was purified by flash chromatography (hexane/acetone 4:1). This afforded **15** (480 mg, 74%) as a crystalline mixture of anomers (4:1, β/α ratio from NMR data), which could not be separated.

$C_{22}H_{22}ClN_4O_6$	calc.	C 55.76	H 4.67	N 11.82
(473.8)	found	55.80	4.79	11.70

IR (film): ν = 1752 cm^{-1} (CO ester).

MS (DCI/NH_3): m/z = 475 $(M + H)^+$, 321 (oxonium), 155 (base).

^1H NMR (270 MHz, $CDCl_3$): δ = 8.60 (s, 1H, 2-H), 8.57 (s, 1H, 8-H), 7.17 (br s, 5H, $PhCH_2$), 6.46 (s, 1'-H, β-anomer), 6.40 (s, 1'-H, α-anomer), 4.75–4.38 (m, 4H, CH_2Ph, 2'-H), 3.98 (d, 1H, J = 15 Hz) and 3.85 (dd, 1H, J = 15, 3 Hz) (ABX syst., 5'-H), 3.60 (dd, 1H, J = 11, 3 Hz, 4'-H), 2.75–2.39 (m, 2H, 3'-H), 2.12 (s, 3H, OAc), 1.78 (s, 3H, OAc).

9-(2-Acetoxymethyl-2-*O*-acetyl-3-deoxy-β-D-*erythro*-pentofuranosyl-6-chloro-9*H*-purine (16):

A solution of compound **15** (200 mg, 0.42 mmol) in anhydr. toluene at − 78°C was treated with a 1 M solution of BBr_3 in CH_2Cl_2 (4 mL). After 4 h, ice-cold sat. aq. $NaHCO_3$ was added and the mixture was extracted with EtOAc. Usual workup afforded after flash chromatography (hexane/acetone, 3:2), 180 mg (62%) of **16** as a foam; $[\alpha]_D^{20}$ − 52° (c = 1, $CHCl_3$).

$C_{15}H_{17}ClN_4O_6$	calc.	C 46.92	H 4.45	N 14.56
(384.8)	found	46.97	4.39	14.70

MS (DCI/NH_3): m/z = 385 $(M + H)^+$, 266, 155 (base).

IR (film): ν = 1747 cm^{-1} (CO ester).

^1H NMR (270 MHz, $CDCl_3$): δ = 8.55 (s, 1H, 8-H), 8.49 (s, 1H, 2-H), 6.42 (s, 1'-H), 4.69 (d, 1H, J = 12 Hz) and 4.47 (d, 1H, J = 12 Hz) (AB syst, 2''-H), 4.64 (m, 1H, 4'-H), 3.96–3.52 (m, 3H, 5'-H, OH), 2.97 (dd, 1H, J = 15, 9 Hz, 3'-H_a), 2.50 (dd, 1H, J = 15, 6 Hz, 3'-H_b), 2.15 (s, 6H, OAc).

9-(3-Deoxy-2-*C*-hydroxymethyl-β-D-*erythro*-pentofuranosyl)adenine (17):

A solution of **16** (40 mg, 0.1 mmol) in MeOH saturated with NH_3 (12.5 mL) was heated at 120°C in an autoclave for 24 h, and then concentrated in vacuo to dryness. The residue was purified by flash chromatography (EtOAc/MeOH, 5:1), to give **17** as a solid which was recrystallized from MeOH (20 mg, 68%); mp 252°C; $[\alpha]_D^{20}$ − 18° (c = 1, H_2O).

$C_{11}H_{15}N_5O_4$	calc.	C 46.97	H 5.38	N 24.90
(281.3)	found	46.80	5.29	24.80

MS (DCI/NH_3): m/z = 282 (M + H) +, 156 (base); 136.

IR (film): ν = 1752 cm^{-1} (CO ester).

^1H NMR (270 MHz, $CDCl_3$): δ = 8.03 (s, 1H, 8-H), 7.92 (s, 1H, 2-H), 7.10 (br s, 2H, NH_2), 6.03 (s, 1-H), 5.22 (s, 1H, OH), 4.96 (s, 1H, OH), 4.76 (s, 1H, OH), 4.42 (br s, 4'-H), 2.14 (dd, 1H, J = 10, 3 Hz, 3'a-H), 1.98 (dd, 1H, J = 14, 6 Hz, 3'b-H).

1-(2,3-di-*O*-Acetyl-5-*O*-benzyl-2-*C*-methyl-α and β-D-ribo furanosyl)thymine (18a) and (18b):

To a mixture of bis(trimethylsilyl)thymine, prepared by treating overnight 1.12 g (9 mmol) of thymine as described for compound **14**, in MeCN (5 mL) were added **12** (2.5 g, 6.7 mmol) and then trimethylsilyl triflate (8 mL of a 1 N stock solution in MeCN). The reaction was stirred for 18 h at r.t., then sat. aq $NaHCO_3$ was added (5 mL) and the mixture extracted with CH_2Cl_2. The organic layers were washed with H_2O with brine and dried (Na_2SO_4) and evaporated to afford a residue purified by flash chromatography (hexane/acetone, 2:1) giving **18** (1.8 g, 60%) as a mixture of anomers (β/α = 70:30 from NMR data).

$C_{22}H_{26}N_2O_8$	calc.	C 59.19	H 5.87	N 6.27
(446.5)	found	59.23	5.60	6.19

IR (film): ν = 1680 cm^{-1} (C=O).

MS (DCI/NH_3). m/z = 464 (M+ 18), 447 $(M + H)^+$, 321 (sugar); 127 (base).

^1H NMR (270 MHz, $CDCl_3$): δ = 8.66 (s, NH), 8.62 (s, NH), 6.37 (s, 0.7H, 1'-H β), 6.26 (s, 0.3H, 1'-H α), 5.44 (d, 1H, J = 7.5, 3'-H), 4.36–4.20 (m, 1H, 4'-H), 3.87 (d, 1H), and 3.63 (d, 1H) (AB syst., J = 10, 5'-H).

1-(2,3-Di-*O*-acetyl-2-*C*-methyl-α- and β-D-ribofuranosyl)thymine (19a) and (19b):

To a solution of **18** (400 mg, 0.9 mmol) in anhydr. CH_2Cl_2 at − 78°C was added a 1 M solution of BBr_3 (11 mL). After 3 h, ice cold aq. $NaHCO_3$ was added and the mixture extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4) and evaporated. The residue obtained was purified by column chromatography on silica gel 60 H (hexane/acetone, 2.5:1) to give 144 mg of the β-anomer **19a** and 60 mg of the α-anomer **19b** (85% overall yield).

β-Anomer **19a**: syrup; $[\alpha]_D^{20}$ + 55° (*c* = 1.2, $CHCl_3$).

$C_{15}H_{20}O_8N_2$	calc.	C 50.56	H 5.66	N 7.86
(356.3)	found	50.47	5.72	7.91

MS (DCI/NH_3): *m/z* = 374 (+18), 357 $(M+H)^+$, 232, 224.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.60 (br s, NH), 7.44 (s, 1 H, 6-H), 6.17 (s, 1 H, 1′-H), 5.31 (d, 1 H, *J* = 7 Hz, 3′-H), 4.10 (m, 1 H, 4′-H), 3.99 (dd, 1 H, *J* = 12, 2 Hz), 3.79 (d, 1 H, *J* = 12, 2 Hz) (ABX syst., 5′-H), 2.13 (s, 6 H, OAc), 1.94 (s, 3 H, Me), 1.59 (s, 3 H, Me).

α-Anomer **19b**: syrup; $[\alpha]_D^{20}$ + 26° (*c* = 0.95, $CHCl_3$).

$C_{15}H_{20}O_8N_2$	calc.	C 50.56	H 5.66	N 7.86
(356.3)	found	50.61	5.55	7.90

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.97 (br s, NH), 7.44 (s, 1 H, 6-H), 6.20 (s, 1 H, 1′-H), 5.38 (d, 1 H, *J* = 8 Hz, 3′-H), 4.09 (dd, 1 H, *J* = 8, 3 Hz, 4′-H), 3.98 (d, 1 H, *J* = 12 Hz), and 3.78 (d, 1 H, *J* = 12 Hz) (ABX syst., 5′-H), 2.32, 2.14 (2 s, 2 × 3 H, OAc), 1.63 (s, 3 H, MeC_2).

1-[2-*C*-methyl-β-D-ribofuranosyl]thymine (20):

To a solution of **19a** (120 mg, 0.34 mmol) in pyridine (0.5 mL) and EtOH (3 mL), 2 mL of a 1 M NaOH solution were added. After being stirred overnight, the solution was neutralized with IR50 (H^+) Amberlyst ion-exchange resin.

After filtration, evaporation under reduced pressure, then co-evaporation with toluene, **20** was obtained as a crystalline compound (86 mg, 95%); mp 201 °C, $[\alpha]_D^{20}$ + 69° (*c* = 0.8, H_2O).

$C_{11}H_{16}N_2O_6$	calc.	C 48.53	H 5.92	N 10.29
(272.3)	found	48.62	5.88	10.35

MS (DCI/NH_3): *m/z* = 290 $(M+18)^+$, 273 $(M+H)^+$, 182, 164, 124.

UV (MeOH): λ = 257 nm (ε = 372).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.07 (s, 1 H, 6-H), 5.97 (s, 1 H, 1′-H), 4.02 (d, 1 H, *J* = 12 Hz, 4-H), 3.94 (s, 2 H, 5′-H), 3.84 (d, 1 H, *J* = 12 Hz, 3-H), 1.88 (s, 3 H, Me-base), 1.17 (s, 3 H, Me sugar).

6-Chloro-9-(2,3-di-*O*-acetyl-5-*O*-benzyl-2-*C*-methyl-β-D-ribofuranosyl)-9*H*-purine (21):

To a solution of 6-chloropurine [(460 mg, 3 mmol) silylated following the same procedure as for the preparation of **15**] in MeCN (5 mL) under Ar was added a solution of compound **12** (1 g, 2.63 mmol) in MeCN (50 mL) followed by addition of trimethylsilyl triflate (6 mL of a 0.5 N stock solution in MeCN). The resulting mixture was stirred for 19 h at r.t. and quenched by addition of aq $NaHCO_3$. Extraction with CH_2Cl_2 with usual workup followed by purification by flash chromatography (hexane/acetone, 4:1) led to 520 mg (50%) of **21**; $[\alpha]_D^{20}$ − 1° (*c* = 1, $CHCl_3$).

$C_{22}H_{24}ClO_6N_4$	calc.	C 55.76	H 4.68	N 11.82
(473.9)	found	55.82	4.59	11.75

MS ((DCI/NH_3): *m/z* = 475 (M + 1), 321 (M + − base).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.77 (s, 1 H, 2-H), 8.56 (s, 1 H, 8-H), 6.60 (s, 1 H, 1′-H), 5.87 (s, 5 H_{arom}), 5.71 (d, 2 H, $J_{3,4}$ = 6 Hz, 3′-H), 4.63 (s, 2 H, CH_2Ph), 4.35 (m, 1 H, 4′-H), 3.89 (d, 1 H) and 2.35 (dd, 1 H, *J* = 10, 3 Hz, 5′-H).

6-Chloro-9-(2,3-di-*O*-acetyl-2-*C*-methyl-β-D-ribofuranosyl)-9*H*-purine (22):

A solution of compound **21** (120 mg, 0.25 mmol) in anhydr. CH_2Cl_2 was treated at − 78 °C for 3 h with a solution of BBr_3 in CH_2Cl_2 (2 mL of a 1 M stock solution). Addition of sat. aq $NaHCO_3$ and extraction with CH_2Cl_2 with washings with H_2O, brine gave after drying (Na_2SO_4) and concentration under reduced pressure a crude residue. Compound **22** was isolated (90 mg, 92%) as a pure compound after purification by flash chromatography (hexane/acetone, 4:1); syrup, $[\alpha]_D^{20}$ − 6° (*c* = 1, $CHCl_3$).

$C_{15}H_{17}ClO_6N_4$	calc.	C 46.82	H 4.45	N 14.56
(384.8)	found	46.95	4.53	14.49

MS (DCI/NH_3): *m/z* = 385 (M + 1), 351, 264, 231 (M + − base), 155 (base).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.81 (s, 1 H, 2-H), 8.51 (s, 1 H, 8-H), 8.61 (d, 1 H, *J* = 15, 3 Hz), 6.60 (s, 1 H, 1′-H), 4.24 (m, 1 H, 4′-H), 4.07 (dd, 1 H, *J* = 15, 3 Hz), 3.80 (dd, *J* = 15, 3 Hz) (ABX syst., 5′H), 2.14 (s, 6 H, OAc), 1.32 (s, 3 H, Me).

2′-*C*-Methyladenosine (23):

A solution of **22** (37 mg, 0.1 mmol) in MeOH (12.5 mL) saturated with NH_3 at 0 °C was kept for 24 h at 120 °C in an autoclave and then concentrated in vacuo to dryness. The residue was purified by flash chromatography (EtOAc/MeOH, 5:1), to give **23** (20 mg, 75%) as a crystalline compound; mp 256 °C; $[\alpha]_D^{20}$ − 20° (*c* = 1, H_2O). [Lit.[1] mp 257–258 °C; $[\alpha]_D^{20}$ − 21° (H_2O)].

$C_{11}H_{15}ClO_5N_4$	calc.	C 46.97	H 5.38	N 24.90
(281.2)	found	46.78	5.30	25.50

MS (DCI/NH_3): *m/z* = 297, 282 $(M+H)^+$, 266, 236, 136.

UV (MeOH): λ = 259 nm (ε = 16.000).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.44 (s, 1 H, 8-H), 8.10 (s, 1 H, 2-H), 5.98 (s, 1 H, 1′-H), 4.18 (d, 1 H, *J* = 9 Hz, 3′-H), 4.20–3.80 (m, 4 H, 5′H, 4′-H, OH), 1.21 (s, 3 H, Me-2′).

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