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$SnCl_4$ Versus $TiCl_4$-Mediated Coupling between N-6-Benzoyladenine and Perbenzoylated 2-Deoxypyranose: Application to the Synthesis of Certain Homochiral Acyclo and Carboacyclonucleosides

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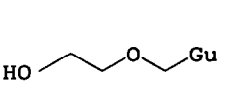
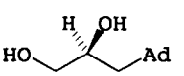
Abstract - 1,3,4-tri-O-benzoyl 2-deoxyribopyranose and persilylated N-6-benzoyladenine react in two different and regioselective ways according to the nature of the coupling reagent $SnCl_4$ or $TiCl_4$. The former Lewis acid gives rise to the anomeric mixture of N-9 nucleosides and the latter affords mainly 3'-deoxy 3'-(N-6-benzoyl-9-adenyl) glycals. These two series of derivatives constitute useful synthons for the preparation of homochiral acyclo and carboacyclonucleosides.

Introduction

Some acyclonucleosides[1,2] such as acyclovir[3] 1 or (S)-DHPA[4] 2 exhibit well established antiviral activities. Such compounds lacking chirality at the carbon bearing the nucleobase (C-1') are synthesized by means of a nucleophilic displacement reaction between activated or unactivated nucleobase and the desired functionalized side chain synthon.[5,6]

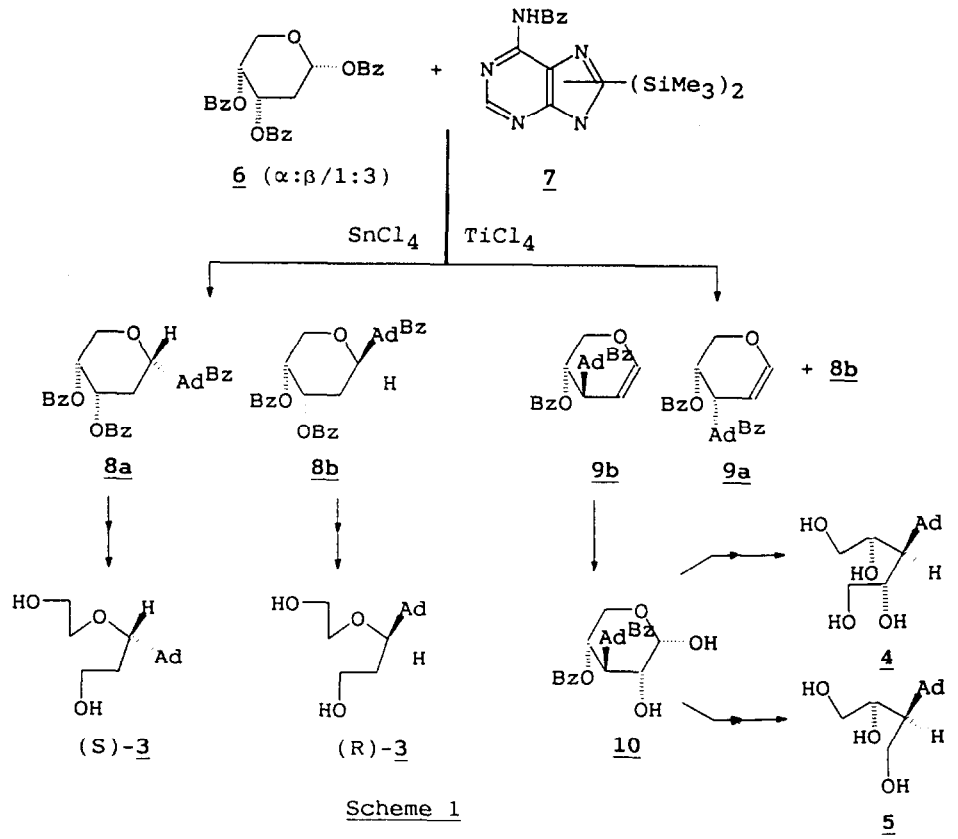


Acyclovir 1



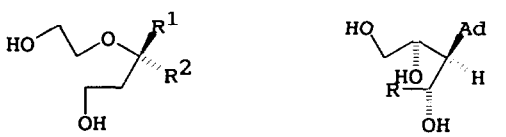
(S)-DHPA 2

In the search for new antiviral acyclonucleosides series, this procedure is of limited use when the C-1' is chiral as long as racemic or diastereomeric mixtures can be obtained. However, in some cases acyclonucleosides are synthesized through the ring opening of the carbohydrate moiety of a furano or a pyranonucleoside.[7] One of the advantages of this



Scheme 1

later procedure is to produce acyclonucleosides of defined chirality. In fact this strategy implies two essential steps *i.e.* nucleoside formation and sugar ring opening. The first one is crucial as long as it determines both the chirality at the newly created center (by formation of diastereomers and their subsequent separation) and the structure of the nucleosidic product (by a convenient condensation reaction which allow the specific substitution of a particular ring carbon sugar by the nucleobase).



(R)-**3** R^1=Ad R^2=H

(S)-**3** R^1=H R^2=Ad

4 R=CH_2OH

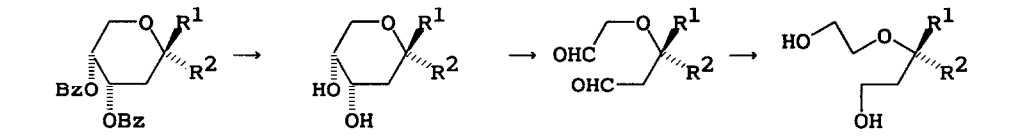
5 R=H

Therefore when starting from the same suitably protected sugar, various homochiral acyclo and carboacyclonucleosides series can be obtained. As an example we described herewith the synthesis of four

series (R)-3, (S)-3 and 4, 5 (scheme 1) of such acyclic derivatives using N-6-benzoyladenine and the easily available perbenzoylated 2-deoxy-D-ribopyranose.

SYTHESIS OF CHIRAL 3',4'-*SECO* ADENINE NUCLEOSIDES (SCHEME 2)

Deoxypyranonucleosides have been previously synthesized by means of an acid-catalyzed fusion,[5,8] between 6-chloropurine and either peracetylated D-arabinal or 2-deoxypyranose or by the reaction between the heavy metal salt of a purine and a 1-halogeno 2-deoxypyranose. The yields so far reported were from moderate to low and illustrate the difficulties



	R^1	R^2		R^1	R^2		R^1	R^2
8a	H	Ad^{Bz}	11a	H	Ad	(S)-3	H	Ad
8b	Ad^{Bz}	H	11b	Ad	H	(R)-3	Ad	H

Scheme 2

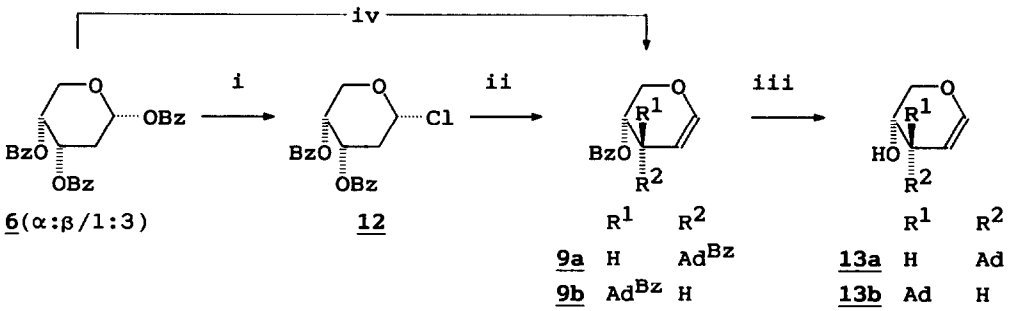
encountered during the N-glycosylation of nucleobases by 2-deoxy sugar derivatives by comparison with the sugars bearing a participating group at their C-2 position.[9] Among the usual nucleosidic condensation procedures, we used the modified Hilbert-Johnson reaction [10] between the readily available sugar 6 (1 step, 70% yield from 2-deoxy-D-ribose) and silylated N-6-benzoyladenine 7 in 1,2-dichloroethane at reflux with one equivalent of $SnCl_4$. The reaction mixture was analyzed by TLC and showed the formation of two new compounds and the reaction was stopped after 6 hours. After usual work-up, a column chromatography on silica gel gave 24% and 28% of pure 8a and 8b respectively. The UV spectra of these two products established they were N-9 anomers of N-6-benzoyladenine. The study of their NMR spectra allowed the assignment of an equatorial configuration of the aglycon for both of them and suggested a $^1C_4$ and $^4C_1$ conformation for 8a and 8b respectively.

Debenzoylation of 8a and 8b by methanolic ammonia gave the expected free nucleosides 11a and 11b in a quantitative yield (scheme 2). Each of these compounds was separately oxidized by sodium metaperiodate[11] into dialdehydo derivative which was without any purification reduced by sodium borohydride to give (S)-3 and (R)-3 in 85 and 80% yield respectively. The opposite value of their optical rotation ascertained these later compounds to be pure enantiomers.

SYNTHESIS OF CARBOACYCLO ADENYLYL DERIVATIVES (SCHEMES 3 AND 4)

Carboacyclonucleosides [12] can be synthesized by the ring opening of

pseudonucleosides. These later compounds can be defined as nucleosides isomers in which the nucleobase is linked to a carbon atom of the sugar ring different from the anomeric position. Such unusual nucleosides have been scarcely described in the literature;[13-15] for example some 3'-purinyl derivatives of 2-deoxy-D-ribose were obtained by a Michael addition of a nucleobase on an unprotected sugar under various experimental conditions (solvent, pH, catalyst). Moreover certain 3'-adenylyl 3'-deoxyribopyranosyl glycals have been reported to appear during the acid catalyzed condensation of a peracetylated glycal and a purine.[16] As pyranoid glycals [17] are usually prepared from the corresponding 2-deoxyglycosyl halides we explored the reaction of 1-chloro 2-deoxy 3,4-di-O-benzoyl-D-ribopyranose **12** with N-6-benzoyl bistrimethylsilyladenine **7** in 1, 2-dichloromethane and molecular sieves 4Å as an acid scavenger (scheme 3). The extreme reactivity of the chloro sugar could result in a facile elimination of hydrogen chloride under the mild conditions of heating and of basicity. After six hours the reaction was stopped and TLC analysis revealed the presence of a new compound together with unreacted starting material. Chromatography on silica gel afforded 30% yield of a product **9b** having a UV spectrum consistent with a N-9 regioisomer of adenine. Structural analysis by NMR spectroscopy is in accordance with the presence of an unsaturation on the sugar moiety; a full assignment of all coupling constants gave the following assessments: $J_{1',2'}$ = 6 Hz agrees with the literature[18] data for an 1'-2' unsaturation; the high value of $J_{3',4'}$ = 10 Hz implies a trans diaxial relationship between hydrogens $H_{3'}$ and $H_{4'}$ and then a 3'-β configuration of the base; a $^4H_5$ conformation[19] is attributed to the glycal part of the molecule.



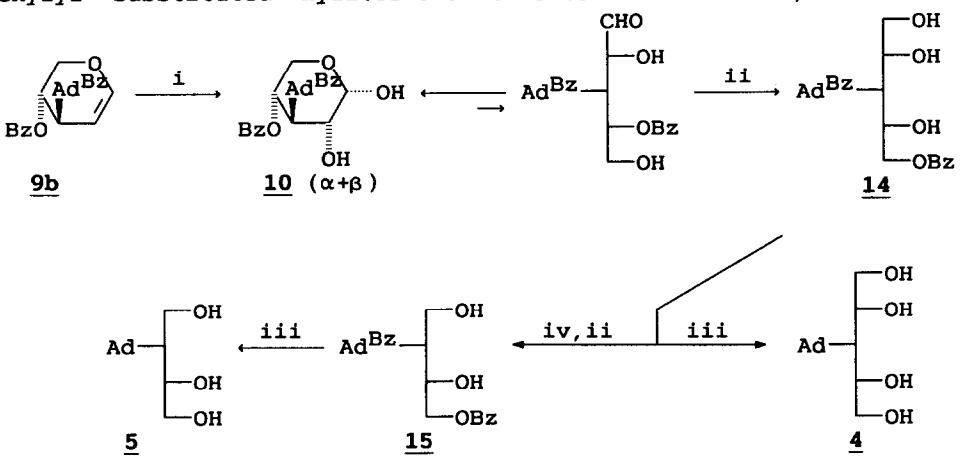
Scheme 3-i:HClg/CH_2Cl_2,0°C,1hr,94% yield;ii:$Ad^{Bz}(-SiMe_3)_2$,molecular sieves 4 Å,CH_2ClCH_2Cl;iii:NH_3/MeOH,30% yield;iv:$Ad^{Bz}(-SiMe_3)_2$,$TiCl_4$ (1 equiv.),CH_2ClCH_2Cl,reflux,12hrs.

This interesting result prompted us to investigate the way to circumvent the preparation of the chloro derivative **12**. This was done by the use of $TiCl_4$ [20] since this Lewis acid is also known to be a powerful chlorinating agent[21] at the anomeric position of polyacetylated sugars. For this purpose the reaction was conducted in the same conditions which afforded the nucleosides **8a** and **8b** but $SnCl_4$ was changed for 1.2 equivalents of $TiCl_4$. TLC monitoring showed the appearance of essentially three

new products after 12 hours; besides the formerly described compound **9b**, a second slightly less polar product **9a** and traces of the nucleoside **8b** were formed. Preparative HPLC separation gave 24, 26 and 5% of **9a**, **9b** and **8b** respectively. Spectral data (UV and NMR) of **9a** are consistent with the 3'-α epimer of **9b** in a $^5H_4$ conformation.

Having two unsaturated derivatives in reasonable yields, we undertook the synthesis of compounds **4** and **5** starting from the 3'-β epimer **9b** to which was applied the following sequence of reactions (scheme 4): a catalyzed cis-dihydroxylation by osmium tetroxide[22] and N-methylmorpholine N-oxide gave two compounds **10**α and **10**β in 93% yield which were analyzed as an anomeric mixture (α:β/65:35) of xylopyranose-like compounds in a $^4C_1$ conformation[23] by a careful study of the following ^{1}H-NMR coupling constants[24] $J_{1',2'}$, $J_{2',3'}$ and $J_{3',4'}$ (see experimental section). Then it appeared that cis-hydroxylation of **9b** occured specifically from the α-side. $NaBH_4$ reduction of **10** (α+β) in ethanol gave exclusively **14** with 80% yield. The ^{1}H-NMR spectrum of this product points out an obvious migration of the 4'-benzoate group to the 5'-terminal position; three exchangeable OH protons appear as two doublets and one triplet *versus* one doublet and two triplets for the expected untransposed structure. Full deprotection of **14** afforded the final tetrol **4** in 90% yield as an expected optically inactive (meso) compound. At last, the vic-diol of **14** was cleaved by sodium periodate and the resulting dialdehydo functions were reduced by sodium borohydride in order to give **15**, which was finally deprotected to the optically active triol **5** (scheme 4).

This sequence of reactions affords an interesting entry to new adenylyl substituted xylitol and threitol derivatives, which are not



Scheme 4: i: OsO_4/tBuOH, acetone-water, NMO; ii: $NaBH_4$, EtOH; iii:NH_3, MeOH; iv: $NaIO_4$, water, dioxane, RT.

readily accessible *via* a direct substitution by adenine of one internal hydroxyl function of acyclic polyhydroxylated derivatives. Change in reaction conditions *i.e.* temperature and amount of Lewis acid did not

improve the yield of compounds 8 and 9.

EXPERIMENTAL SECTION

Melting points were obtained with a Büchi (capillary) apparatus and were uncorrected. UV spectra were determined on a Cary 1186 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the "Service de Microanalyse du CNRS, Division de Vernaison". Fast Atom bombardment mass spectra were recorded on a Jeol JMS-DX 300 apparatus. ^{1}H-NMR spectra were determined on a Brüker AC 250, Brüker WM 360 WB or Varian EM 360 spectrometer and were recorded in DMSO-d_6; 1,3,4-tri-O-benzoyl-2-deoxy-α,β-D-ribopyranose (6) was prepared according to the procedure of Zinner.[25] N-6-benzoyladenine was obtained as described by Kohn.[26] The silylation of N-6-benzoyladenine was performed according to Winkley.[27]

N-6- Benzoyl-9-(2'-deoxy-3',4'-di-O-benzoyl-D-ribopyranosyl) adenine α and β (8a) and (8b).

Silylated N-6-benzoyladenine 7 (from N-6-benzoyladenine, 11.5 g, 48 mmol) in 1,2-dichloroethane (50 mL) was added to the sugar 6 (20 g, 44 mmol) dissolved in 1,2-dichloroethane (250 mL) under an argon atmosphere. After addition of $SnCl_4$ (1 equiv., 5 mL), the resulting solution was refluxed 6 hrs and then maintained at room temperature overnight. The reaction mixture was poured into a cooled aqueous sodium hydrogen carbonate solution and filtered on celite. The organic phase was washed with water, dried and concentrated under vacuum and chromatographed on silica gel; elution with ethyl acetate (0 to 100%) in cyclohexane gave in the elution order the two anomers 8b and 8a.

The β anomer 8b crystallized from dichloromethane/cyclohexane (98/2) (6.94 g, 28% yield); R_f 0.44 (dichloromethane: methanol 95:5 v/v); m.p. 242°C, λ_{max} (EtOH 95) 227, 276 nm; MS : (m/z) 564 (MH^+), 136 (BH_2^+); ^{1}H-NMR (DMSO-d_6) δ 11.0 (s, 1H, NH); 8.90 (s, 1H, H-2); 8.85 (s, 1H, H-8); 8.2-7.4 (m, 15H, aromatics); 6.37 (dd, 1H, $J_{1',2'a}$= 11 Hz, $J_{1',2'e}$= 2.3 Hz, H-1'); 5.98 (t, 1H, $J_{3',4'}$= 3 Hz, H-3'); 5.44 (t, 1H, $J_{4',5'e}$= 4 Hz, $J_{4',5'a}$= 10 Hz, H-4'); 4.24 (q, 2H, $J_{5'a,5'e}$= 13.3 Hz, H-5', H-5"); 3.33 (q, 1H, $J_{2'a,3'}$= 4.05 Hz, $J_{2'a,2'e}$= 13 Hz, H-2'a); 2.60 (m, 1H, H-2'e).

The α anomer 8a crystallized in ethyl acetate (5.9 g, 24% yield); R_f 0.30 (dichloromethane: methanol 95:5 v/v); m.p. 245°C, λ_{max} (EtOH 95) 227, 276 nm; MS: (m/z) 564 (MH^+), 136 (BH_2^+); ^{1}H-NMR (DMSO-d_6) δ 11.0 (s, 1H, NH); 8.90 (s, 1H, H-2); 8.85 (s, 1H, H-8); 8.25-7.45 (m, 15H, aromatics); 6.23 (dd, 1H, $J_{1',2'a}$= 11.25 Hz, $J_{1',2'e}$= 2.01 Hz, H-1'); 5.76 (t, 1H, $J_{3',4'}$= 4.8 Hz, H-3'); 5.62 (t, 1H, $J_{4',5'e}$= 4.05 Hz, $J_{4',5'a}$= 3.7 Hz, H-4'); 4.25 (m, 2H, $J_{5'a,5'e}$= 13 Hz, H-5', H-5"); 3.33 (q, 1H, $J_{2'a,2'e}$= 11 Hz, $J_{2'a,3'}$= 9.16 Hz, H-2'a); 2.55 (m, 1H, H-2'e).

Preparation of 1',2'-unsaturated nucleosides 9a and 9b from 6 : General procedure.

To the silylated N-6-benzoyladenine 7 (from N-6-benzoyladenine, 6.45 g, 27 mmol) was added perbenzoylated sugar 6 (12.2 g, 27 mmol) dissolved in dry 1,2-dichloroethane (175 mL) under an argon atmosphere. After addition of titanium tetrachloride (1.2 equiv.), the solution was refluxed under stirring four hours and left at room temperature overnight. The solution was poured into a cold aqueous solution of sodium hydrogen carbonate, filtered on celite and washed several times with hot 1,2-dichloroethane. The organic phase was extracted with water, dried on sodium sulfate and evaporated. The crude residue was chromatographed by preparative HPLC on silica gel (elution with ethyl acetate-dichloromethane (4:6 v/v)). The nucleosides 8b, 9b and 9a were collected in the elution order with respective yields of 5% (0.6 g), 26% (3.12 g) and 24%

(2.88 g).

1',2',3'-Trideoxy-4'-O-benzoyl-3'-(N-6-benzoyl-9-adenyl)-D-*threo*-pent-1'-enopyranose (9b).

The nucleoside **9b** was crystallized in ethyl acetate-cyclohexane (99:1 v/v); R_f 0.51 (dichloromethane:methanol 95:5 v/v); m.p. 140-141 °C, λ_{max} (EtOH 95) 229, 277 nm; MS: (m/z) 442 (MH^+), 136 (BH_2^+); ^{1}H-NMR (DMSO-d_6) δ 11.18 (s, 1H, NH); 8.73 (s, 1H, H-2); 8.57 (s, 1H, H-8); 8.04-7.51 (m, 10H, aromatics); 6.95 (dd, 1H, $J_{1',2'}$= 6.3 Hz, $J_{1',3'}$= 1.7 Hz, H-1'); 5.61 (d, 1H, $J_{4',5'a}$= 7.8 Hz, $J_{4',5'e}$= 3.1 Hz, H-4'); 5.46 (m, 1H, $J_{3',4'}$= 8.2 Hz, H-3'); 5.11 (dd, 1H, $J_{2',3'}$= 3.8 Hz, H-2'); 4.27 (m, 2H, H-5', H-5"). Anal. Calcd for $C_{24}H_{19}N_5O_4$: C, 65.30; H, 4.34; N, 15.86. Found: C, 65.97; H, 4.96; N, 15.80.

1',2',3'-Trideoxy-4'-O-benzoyl-3'-(N-6-benzoyl-9-adenyl)-D-*erythro*-pent-1'-enopyranose (9a).

The nucleoside **9a** was crystallized in ethyl acetate-cyclohexane (99:1 v/v); R_f 0.48 (dichloromethane: methanol 95:5 v/v); m.p. 135-137 °C, λ_{max} (EtOH 95) 229, 277 nm; MS: (m/z) 442 (MH^+), 136 (BH_2^+); ^{1}H-NMR (DMSO-d_6) δ 11.16 (s, 1H, NH); 8.62 (s, 1H, H-2); 8.56 (s, 1H, H-8); 8.1-7.4 (m, 10H, aromatics); 6.98 (dd, 1H, $J_{1',2'}$= 6.2 Hz, $J_{1',3'}$= 2 Hz, H-1'); 5.86 (m, 1H, $J_{3',4'}$= 4.7 Hz, H-3'); 5.64 (m, 1H, $J_{4',5'a}$= 3.2 Hz, $J_{4',5'e}$= 3.5 Hz, H-4'); 5.16 (dd, 1H, $J_{2',3'}$= 2.6 Hz, H-2'); 4.48-4.18 (m, 2H, H-5', H-5"). Anal. Calcd for $C_{24}H_{19}N_5O_4$: C, 65.30; H, 4.34; N, 15.86. Found: C, 65.23; H, 4.60; N, 15.71.

9-(2'-Deoxy-β-D-ribopyranosyl)adenine (11b).

Benzoylated nucleoside **8b** was dissolved in methanolic ammonia at 0°C and stirred two days at room temperature. The solution was evaporated to give a residue, which was chromatographed on silica gel. Elution with dichloromethane-methanol (8:2 v/v) gave **11b** which crystallized in water: methanol (90% yield); R_f 0.43 (dichloromethane: methanol 7:3 v/v); m.p. 262-264 °C, λ_{max} (water) 258 nm (ε 16337), $[\alpha]_D^{21}$ -17.64° (c 1.02, water), ^{1}H-NMR (DMSO-d_6) δ 8.32 (s, 1H, H-2); 8.10 (s, 1H, H-8); 7.25 (s, 2H, NH_2); 5.93 (dd, 1H, $J_{1',2'a}$= 11.3 Hz, $J_{1',2'e}$= 2.12 Hz, H-1'); 4.96 (d, 1H, $J_{3',OH}$= 2.85 Hz, OH-3'); 4.86 (d, 1H, $J_{4',OH}$= 5.28 Hz, OH-4'); 4.08 (m, 1H, H-3'); 3.8-3.6 (m, 3H, $H_{4'}$, $H_{5'}$, $H_{5"}$); 2.64 (td, 1H, $J_{2'a,2'e}$= 13.4 Hz, $J_{2'a,3'}$= 2.3 Hz, H-2'a); 2.01 (m, 1H, $J_{2'e,3'}$= 4.01 Hz, H-2'e). Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.21; N, 27.88. Found; C, 47.82; H, 5.11; N, 27.76.

9-(2'-Deoxy-α-D-ribopyranosyl)adenine (11a).

Compound **11a** was prepared in the same manner as **11b** with **8a** as starting material: yield 98%; R_f 0.35 (dichloromethane: methanol 7:3 v/v); m.p. 235°C (methanol), λ_{max} (water) 258 nm (ε 15731), $[\alpha]_D^{21}$ +5.66° (c 1.06, water), ^{1}H-NMR (DMSO-d_6) δ 8.32 (s, 1H, H-2); 8.14 (s, 1H, H-8); 7.3 (s, 2H, NH_2); 5.66 (dd, 1H, $J_{1',2'a}$= 11 Hz, $J_{1',2'e}$= 2.09 Hz, H-1'); 4.93 (d, 1H, $J_{3',OH}$= 5.75 Hz, OH-3'); 4.70 (d, 1H, $J_{4',OH}$= 4.85 Hz, OH-4'); 3.9-3.6 (m, 4H, H-3', H-4', H-5', H-5"); 2.50 (td, 1H, $J_{2'a,2'e}$= 13.4 Hz, $J_{2'a,3'}$= 10.98 Hz, H-2'a); 1.9 (m, 1H, $J_{2'e,3'}$= 2 Hz, H-2'e). Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.21; N, 27.88. Found: C, 47.94; H, 5.24; N, 27.68.

1-Chloro 3,4-di-O-benzoyl 2-deoxy-α,β-D-ribopyranose (12).

Through a cooled (0°C) solution of perbenzoylated sugar **6** (1 g, 2.2 mmol) in dry dichloromethane (30 mL) was bubbled HCl gaz during one hour. The solution was then diluted with dichloromethane, washed with a saturated aqueous solution of sodium hydrogenocarbonate and water, dried over sodium sulfate, and evaporated under vacuum. The crude oil was chromato-

graphed on silica gel (elution with ethyl acetate (0 to 5%) in dichloromethane) to give 12 as an oil in 94% yield (0.74 g). ^{1}H-NMR (DMSO-d_6) δ 8.08-7.16 (m, 10H, aromatics); 6.66 (m, 1H, H-1); 6.1 (pt, 1H, $J_{3,4}$= 4 Hz, $J_{3,2a}$= 7 Hz, H-3); 5.75 (m, 1H, H-4); 4.50-4.28 (m, 2H, H-5', H-5"); 2.8-2.2 (m, 2H, H-2', H-2").

Preparation of 1',2'-unsaturated nucleosides 9a,b and 13a,b from 12.

To a mixture of chlorosugar 12 (0.211 g, 0.58 mmmol) and molecular sieves 4 Å in dry 1,2-dichloromethane (5 mL) was added silylated N-6-benzoyladenine 7 (from N-6-benzoyladenine, 0.134 g, 0.56 mmol) in dichloromethane (15 mL). The homogeneous solution was refluxed 3 hours, then cooled at 0°C, neutralized with saturated aqueous $NaHCO_3$ (20 mL) and extracted with dichloromethane. The organic phase was dried over sodium sulfate, concentrated under vacuum to give the crude mixture of 9a and 9b (0.13 g). This later was reacted immediately with methanolic ammonia (30 mL) at 0°C overnight and gave after concentration and purification on silica gel (methanol(0 to 10%) in dichloromethane) the deprotected glycal derivatives 13a, 13b with a 30% yield (0.040 g).

Preparation of 3',4'-seco 2'-deoxynucleosides of adenine (R)-3 and (S)-3: General procedure.

Sodium periodate (1.3 mmol) dissolved in a minimum of water was added to the deprotected nucleoside (1 mmol) 11a (or 11b) in the mixture dioxane-water (8:7 v/v, 15 mL). The reaction was left four hours at room temperature and the excess of sodium periodate neutralized with ethylene glycol (2 mL). The resulting precipitate was filtered and washed with dioxane. The filtrate was evaporated to give an oil which was immediately dissolved in absolute ethanol (5 mL) and reduced by sodium borohydride (4 mmol) at 0°C. After one hour, the solution was hydrolyzed with acetone (1 mL) and water (0.5 mL), evaporated and chromatographed on silica gel.

9-[1'-(2'-Hydroxyethoxy)-3'-hydroxypropyl]adenine ((R)-3).

The nucleoside 11b (40 mg, 0.16 mmol) was successively reacted with sodium periodate (44 mg, 0.2 mmol) and sodium borohydride (24 mg, 0.64 mmol). Chromatography on silica gel with methanol (0 to 15%) in dichloromethane afforded acyclonucleoside (R)-3 which was recrystallized from water (32 mg, 80% yield), R_f 0.54 (dichloromethane: methanol 7:3 v/v), m.p. 138°C, λ_{max} (water) 257 nm (ε 26046), $[\alpha]_D^{20}$ +10.14° (c 0.69, water); MS: (m/z) 254 (MH^+), 136 (BH_2^+); ^{1}H-NMR (DMSO-d_6) δ 8.33 (s, 1H, H-2); 8.12 (s, 1H, H-8); 7.30 (s, 2H, NH_2); 5.86 (t, 1H, $J_{1',2'}$= 6.68 Hz, H-1'); 4.67 (t, 2H, $J_{OH,CH}$= 6.68 Hz, OH-3', OH-5'); 3.61-3.06 (m, 6H, CH_2O); 2.40 (td, 1H, H-2'); 2.20 (td, 1H, H-2"). Anal. Calcd for $C_{10}H_{15}N_5O_3$: C, 47.42; H, 5.97; N, 27.66. Found: C, 47.35; H, 5.98; N, 27.81.

9-[1'-(2'-Hydroxyethoxy)-3'-hydroxypropyl]adenine ((S)-3).

The nucleoside 11a (1 g, 4 mmol) was treated with sodium periodate (1.1 g, 5.2 mmol) and then with sodium borohydride (0.6 g, 16 mmol.). After chromatography on silical gel (same eluent as for (R)-3) acyclonucleoside (S)-3 was obtained by recrystallization in water (34 mg, 85% yield). $[\alpha]_D^{20}$ -9.67° (c 0.62 water). All others physical properties and spectroscopic data were similar to those reported for (R)-3.

3'-Deoxy-4'-O-benzoyl-3'-(N-6-benzoyl-9-adenyl)-D-*threo*-pentopyranose (10α,β).

To the 1',2'-unsaturated nucleoside 9b (0.13 g, 0.3 mmol) dissolved in acetone (1.8 mL) and water (0.3 mL) was added a solution 0.02 M of osmium tetroxide in tert-butyl alcohol (1.92 mL) and 4-methylmorpholine N-oxide (90 mg, 0.6 mmol). After six hours at room temperature, the solution was diluted with dichloromethane, washed with HCl 5 M (0.7 mL),

$Na_2S_2O_5$ 45% (1.1 mL) and water. The organic phase was dried on sodium sulfate and concentrated. After a chromatography on silica gel with methanol (0 to 10%) in dichloromethane as eluent, the mixture of anomers **10** (α:β 65/35) was isolated with a 93% yield (0.132 g) as a foam.

R_f 0.50 (dichloromethane:methanol 88:12 v/v); λ_{max} (EtOH 95) 229, 277 nm; MS: (m/z) 476 (MH^+), 136 (BH_2^+); ^{1}H-NMR (DMSO-d_6) δ 11.06 (s, 1H, NH); 8.73 (s, 1H, H-2); 8.08 (s, 1H, H-8); 8-7.39 (m, 10H, aromatics); 7.19 (d, 1H, $J_{1',OH}$= 6.2 Hz, OH-1'β); 7.02 (d, 1H, $J_{1',OH}$= 4.32 Hz, OH-1'α); 5.74 (d, 1H, $J_{2',OH}$= 5.63 Hz, OH-2'β); 5.65 (m, 2H, H-4'); 5.37 (d, 1H, $J_{2',OH}$= 7.25 Hz, OH-2'α); 5.17 (t, 1H, $J_{1',2'}$= 3.87 Hz, H-1'α); 5.04 (t, 1H, $J_{3',4'}$= $J_{3',2'}$= 10.45 Hz, H-3'α); 4.84 (t, 1H, $J_{3',2'}$= $J_{3',4'}$= 9.45 Hz, H-3'β); 4.66 (t, 1H, $J_{1',2'}$= 7.12 Hz, H-1'β); 4.58 (m, 1H, H-2'α); 4.18 (m, 1H, H-2'β); 3.92-3.60 (m, 2H, H-5', H-5").

1'-O-Benzoyl-3'-deoxy-3'-(N-6-benzoyl-9-adenyl)-D-*threo*-pentitol (14).

To the anomeric mixture of **10** (α:β 65/35) (142 mg, 0.3 mmol) dissolved in ethanol 95 (2 mL) was added sodium borohydride (45 mg, 1.2 mmol) at 0°C in five minutes. After two hours, the solution was neutralized by acetone-water and evaporated. A purification by chromatography on silica gel using methanol (0 to 10%) in dichloromethane as eluent gave the compound **14** which crystallized in the mixture dichloromethane-cyclohexane (7:3 v/v) (114 mg, 80% yield); R_f 0.31 (dichloromethane:methanol 88:12 v/v); m.p. 123-126°C, λ_{max} (EtOH 95) 229, 276 nm; ^{1}H-NMR (DMSO-d_6) δ 11.13 (s, 1H, NH); 8.65 (s, 1H, H-2); 8.46 (s, 1H, H-8); 8.15-7.46 (m, 10H, aromatics); 5.76 (d, 1H, $J_{2',OH}$= 8.9 Hz, OH-2'); 5.30 (d, 1H, $J_{4',OH}$= 8.9 Hz, OH-4'); 5.03 (t, 1H, $J_{3',2'}$= $J_{3',4'}$= 8.8 Hz, H-3'); 4.83 (t, 1H, $J_{5',OH}$= 6 Hz, OH-5'); 4.50 (m, 1H, H-2'); 4.13 (m, 3H, CH_2OBz, H-4'); 3.6-3.0 (m, 2H, CH_2OH).

3'-Deoxy-3'-(9-adenyl)-D-*threo*-pentitol (4).

The compound **14** (100 mg, 0.2 mmol) was reacted with a solution of methanolic ammonia (8 mL) at room temperature during 48 hours. The solvent was removed and the residue dissolved in water. After an extraction with diethyl ether, the tetrol **4** crystallized in water (48 mg, 90% yield). R_f 0.60 (isopropanol:ammonia:water 7:1:2 v/v/v); m.p. 235°C (dec), λ_{max} (water) 258 nm (ε 20300); MS:(m/z) 270 (MH^+), 136 (BH_2^+); ^{1}H-NMR (DMSO-d_6) δ 8.12 (s, 1H, H-2); 8.03 (s, 1H, H-8); 7.24 (s, 2H, NH_2); 5.25 (m, 2H, 2OH); 4.72 (m, 2H, 2OH); 4.68 (t, 1H, $J_{2',3'}$= $J_{3',4'}$= 5.64 Hz, H-3'); 4.06 (q, 2H, H-2', H-4'); 3.31 (d, 4H, $J_{1',2'}$= $J_{4',5'}$= 5.12 Hz, 2 CH_2OH). Anal. Calcd for $C_{10}H_{15}N_5O_4$: C, 44.60; H, 5.61; N, 26.01. Found: C, 44.48; H, 5.59; N, 25.93.

N-6-Benzoyl-9-(1'-O-benzoyl-2',4'-dihydroxy-2'S,3'R-butyl)adenine (15).

To the protected tetrol **14** (95 mg, 0.2 mmol) in dioxane (2 mL) and water (1 mL) was added sodium periodate (55 mg, 0.26 mmol). After six hours at 25°C, excess of sodium periodate was precipitated by addition of dioxane (5 mL), and the precipitate washed carefully with dioxane. The filtrate was concentrated to a residue which was dissolved in ethanol 95 (5 mL). Sodium borohydride (30 mg, 0.8 mmol) in ethanol 95 (2 mL) was then added. After one hour at 0°C, the solution was neutralized by addition of water (1 mL) and acetone (1 mL) and evaporated. Purification by chromatography on silica gel with methanol (0 to 15%) in dichloromethane as eluent afforded the triol **15** (62 mg, 68% yield) which crystallized in the mixture dichloromethane-cyclohexane (8:2 v/v). R_f 0.25 (dichloromethane:methanol 88:12 v/v); m.p. 133-135 °C, λ_{max} (EtOH 95) 229, 276 nm; MS:(m/z) 448 (MH^+), 136 (BH_2^+); ^{1}H-NMR (DMSO-d_6) δ 11.16 (s, 1H, NH); 8.70 (s, 1H, H-2); 8.50 (s, 1H, H-8); 8.20-7.44 (m, 10H, aromatics); 5.84 (d, 1H, $J_{2',OH}$= 5.4 Hz, OH-2'); 5.18 (t, 1H, $J_{4',OH}$= 5.46 Hz, OH-4'); 4.92 (m, 2H, CH_2OBz); 4.48 (m, 1H, H-3'); 4.15-3.9 (m, 3H, H-2', CH_2OH).

9-(1',3',4'-Trihydroxy-2'R,3'S-butyl)adenine (5).
This compound was prepared in the same manner as **4** with **15** as starting material: 80% yield after crystallization in water; R_f 0.14 (dichloromethane:methanol 7:3 v/v); m.p. 280°C (dec), λ_{max} (water) 258 nm (ϵ 25100); MS:(m/z) 240 (MH^+), 136 (BH_2^+); $[\alpha]_D^{20}$ +13.3° (c 1.02, water); ^{1}H-NMR (DMSO-d_6) δ 8.12 (s, 1H, H-2); 8.03 (s, 1H, H-8); 7.24 (s, 2H, NH_2); 4.67 (td, 1H, J = 5.5 Hz, H-2'); 4.08-4.01 (m, 3H, 2OH, H-3'); 3.42-3.24 (m, 5H, CH_2OH, OH). Anal. Calcd for $C_9H_{13}N_5O_3$: C, 45.18; H, 5.47; N, 29.27. Found: C, 45.30; H, 5.17; N, 28.98.

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