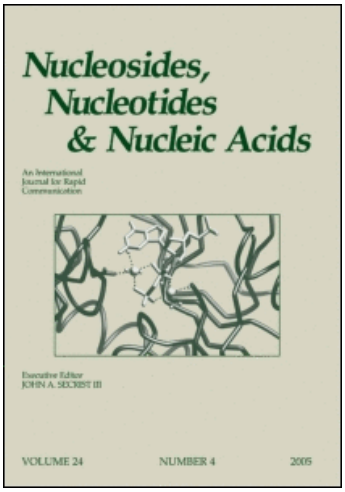

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Covalent Nucleoside Adducts of Aspidosperma Alkaloids

B. Danieli[a]; G. Lesma[a]; G. Palmisano[a]; D. Passarella[a]; B. Pyuskyulev[b]
[a] Dipartimento di Chimica Organica, e Industriale - Universita' degli Studi di Milano Centro CNR di Studio per le Sostanze Organiche Naturali Via Venezian, Milano, Italy [b] Institute of Organic Chemistry with Centre of Phytochemistry Bulgarian Academy of Sciences, Sofia, Bulgaria

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COVALENT NUCLEOSIDE ADDUCTS OF ASPIDOSPERMA ALKALOIDS

B. Danieli, G. Lesma,* G. Palmisano and D. Passarella

Dipartimento di Chimica Organica e Industriale - Universita' degli Studi di Milano
Centro CNR di Studio per le Sostanze Organiche Naturali
Via Venezian, 21 - 20133 Milano - Italy

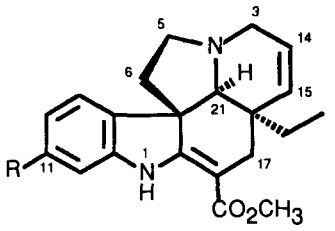
B. Pyuskyulev

Institute of Organic Chemistry with Centre of Phytochemistry
Bulgarian Academy of Sciences - Sofia - Bulgaria

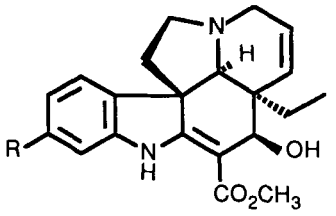
Abstract. In vitro *reaction of 17-OH tabersonine* **2a** *and its 11-OMe analogue* **2b** *with adenine, tri-O-acetyl adenosine, -guanosine and -cytidine under mild conditions, results in covalent adducts by electrophilic attack of reactive C-17 position of the alkaloids on the exocyclic nitrogen.*

Covalent modification of nucleic acid bases of DNA is receiving great attention[1] because it constitutes an important step in the tumorgenic and mutagenic processes initiated by carcinogens like alkylating agents and arene oxides, and in the development of biological activity displayed by some therapeutical agents such as antitumor antibiotics. Therefore a great number of investigations has been elicited on the *in vitro* reaction between nucleosides and nucleotides and a variety of organic compounds with the result that many derivatives with synthetic and natural products have been prepared.[2] Despite this, no mention on the reaction between nucleosides or nucleotides and indole alkaloids was previously reported. We have had the opportunity to synthesize some of these derivatives, which may have interesting and improved biological effects.

In the course of our studies on the modification of naturally available alkaloids, we have described[3] an efficient methodology for the regio- and stereospecific hydroxylation of tabersonine (TBS) **1a** and 11-methoxy TBS **1b** to the corresponding 17-β-hydroxyderivatives **2a,b**. These served as key intermediates for the first preparation of (-)-vindorosine and, more notably, (-)-vindoline, which is the indoline half (lower half) of the therapeutically valuable antitumor bisindole alkaloids vinblastine (vincaleukoblastine) and vincristine (leurocristine).[4]

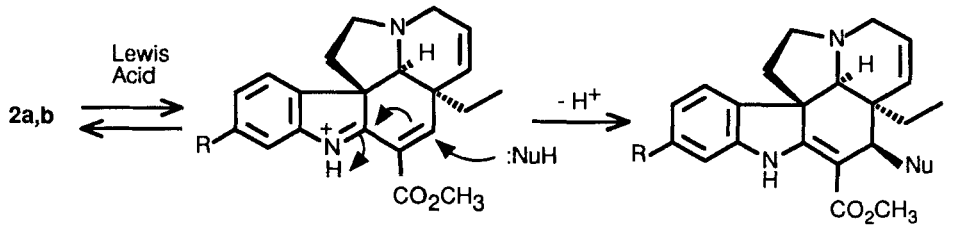


1a R = H; **1b** R = OCH_3



2a R = H; **2b** R = OCH_3

The 17-OH derivatives **2a,b** showed a great propensity to behave as vinylogous α-amino cation equivalent in the presence of Lewis acid and the combination of imine moiety and methoxycarbonyl substituent in the intermediate azadiene compound **3** would provide a synergism for electrophilic character of C-17 (Scheme 1).



3a R = H; **3b** R = OCH_3

4a R = H; **4b** R = OCH_3

Nu = aliphatic, aromatic, heterocyclic S- and N- nucleophiles

Scheme 1

Exploiting this reactivity we obtained a series of new Aspidosperma alkaloids substituted at position 17β with aliphatic, aromatic and heterocyclic S- and N-nucleophiles as depicted in formula **4** which represents potential precursors of C-17 modified vindolines.[5] As an extention of these findings, we report here on the reaction of **2a,b** with some representative nucleosides or nucleic acid bases to afford the corresponding 17-substituted indolenines **5**, **6**, **7** and **8**.

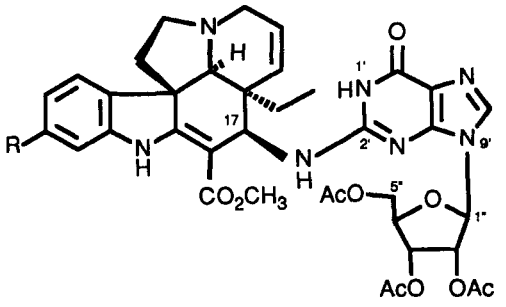
To assess the feasibility of our project, we first examined the reaction with adenine as a model compound. When t-butyl-dimethylsilyl chloride (TBDMSCl, 0.2 mmol) was added to a mixture of **2a** (0.1 mmol) and adenine (0.15 mmol) in dry dichloromethane in the presence of *N,N*-diisopropyl ethylamine (DIPEA, 0.2 mmol) at 0°C, a reaction proceeded smoothly to give the 17-β-adenyl derivative **5a** in 66% yield.

The elemental analysis of **5a** confirmed the empirical formula, $C_{26}H_{27}N_7O_2$, and the mass spectrum (FAB^+) had a MH^+ ion at *m/z* 470 corresponding to this composition. In addition, the FAB^+ spectrum showed intense peaks due to unimolecular fragmentation in the gas phase (B/E analysis) corresponding to protonated azadiene **3a** at *m/z* 335 and to protonated adenine at *m/z* 136. The infrared spectrum had a strong carbonyl band at 1665 cm^{-1} and two NH bands at 3430 and 3360 cm^{-1}. The presence of a β-anilino acrylic and adenine systems was supported by the UV absorptions at λ_{max} 232(sh), 288 and 325 nm (MeOH). The ^1H NMR spectra (200 MHz) further supported the proposed structure. H-1(s, δ 9.15), H-3*S*(brdd, δ 3.63, $J_{3S,3R}$ = 15.5 Hz, $J_{3S,14}$ = 4.5 Hz), H-3*R*(brd, δ 3.11), H-14(brdd, δ 5.74, $J_{14,15}$ = 11.5 Hz), H-15(brd, δ 5.63), CO_2CH_3(s, δ 3.82) and 19-CH_3(t, δ 0.74, $J_{18,19}$ = 7.2 Hz) corresponded to those protons in **2a**. The H-2' and H-8' protons of adenine appeared as two singlets at δ 8.41 and δ 7.87, respectively. The attachment of the adenyl moiety to the TBS C-17 carbon was demonstrated by the presence of a broad doublet (δ 8.91, $J_{17,6'\text{-NH}}$ = 8.5 Hz), assigned to 6'-NH proton, clearly coupled with H-17 which appeared as a broad multiplet at δ 5.64. Moreover, the assignment of the *S* configuration at C-17 was made on the basis of the coupling constant value $J_{17,21}$ = 1.5 Hz (W path), which indicates the α-equatorial arrangement of H-17. Additional evidence of this attachment was the downfield chemical shift of the H-5*R* (Δδ ≅ 0.4 ppm) and H-6*R* (Δδ ≅ 0.4 ppm) protons as compared to those of TBS **1a**, due to the anisotropy of the 17β -adenyl substituent.

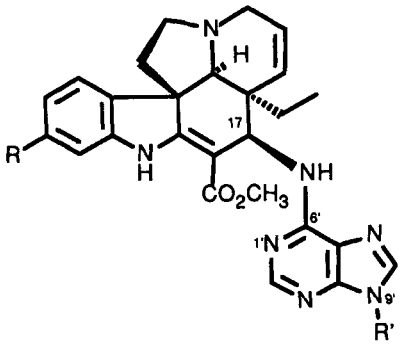
With the above information in hand, we turned our attention to the reaction of **2a** with tri-O-acetyl adenosine,[6] tri-O-acetyl guanosine[7] and tri-O-acetyl cytidine.[8,9]

The reaction of **2a** with tri-O-acetyl adenosine, as described above, gave the adduct **6a** [MS (FAB^+): *m/z* 728 (MH^+)]in 86% yield. The spectral data for **6a** were more complex because of the presence of the D-ribofuranosyl group; however, excellent correlation was clearly evident between **6a** and **5a**. In particular, in the ^1H NMR spectrum (300 MHz) of **6a** the 6'-NH signal appears as a doublet at δ 8.87 ($J_{17,6'\text{-NH}}$ = 8.7 Hz), while H-21 appears as a broad singlet at δ 2.99.

With the highly nucleophilic tri-O-acetyl guanosine, the conversion of **2a** to the adduct **7a** (95%) progressed rapidly and was complete after 2 h (compared with 7-8 h required for the reaction with tri-O-acetyl adenosine under the same conditions). The structure of the adduct **7a** [MS (FAB^+): *m/z* 744 (MH^+)] was confirmed by careful analysis of its ^1H- (300 MHz) and ^{13}C NMR (50.2 MHz, APT pulse sequence) spectra. Appropriate resonances of N(1')-H (s, δ 11.25), H-8' (s, δ 7.88) and ribose protons (see Experimental) were observed. The joining of the guanosine moiety to the C-17 carbon atom, as indicated in formula **7a**, was confirmed, as before, by the appearance in the ^1H NMR spectra of two broad one proton doublet absorptions at δ 8.15 and δ 5.25 coupled



7a R = H; **7b** R = OCH_3

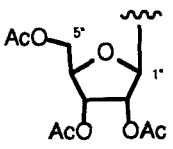


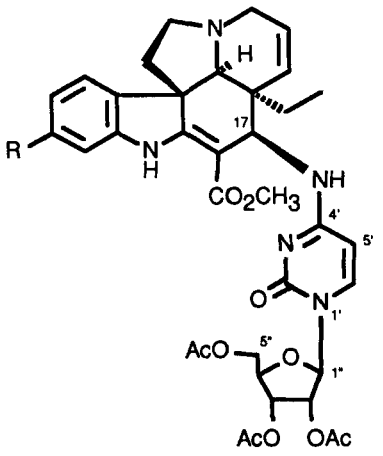
5a R = R' = H

6a R = H

6b R = OCH_3

R' =





8a R = H; **8b** R = OCH_3

to each other (7.9 Hz) corresponding to 2'-NH and H-17 respectively. Further, the downfield chemical shift of H-5*R* (δ 3.23) and H-6*R* (δ 2.21), that corresponded closely to those protons in **5a**, and the small coupling ($J_{17,21} \cong 1$ Hz, W path) between H-17 and H-21 (δ 2.96) also supported this assignment. The ^{13}C NMR spectral data for **7a** are consistent with the assigned structure. Importantly, the signal for carbon 17 (δ 51.5) occurs in an upfield position, characteristic of a secondary amine, with respect to the same carbon in the starting 17-hydroxy TBS **2a** (δ 70.0).[3]

Reaction of tri-O-acetyl cytidine with **2a** provided the adduct **8a** in 88% yield after chromatography. The structure of **8a** [MS (FAB$^+$): *m/z* 704 (MH$^+$)], which showed the typical IR and UV absorptions for TBS **1a** and cytidine chromophores, was confirmed by comparing the ^1H NMR absorptions (supported by decoupling) and ^{13}C resonances with analogous ones in compounds **5a-7a**. Interestingly, both ^{13}C- (75.4 MHz) and ^1H

NMR (300 MHz) spectra of **8a** showed, at 25°C in DMSO-d_6, two sets of non-equivalent resonances which coalesced at about 100°C suggesting the presence of two conformational isomers (see Experimental) in a 7:3 ratio. The observed couplings between the protons 4'-NH (δ 8.15 and δ 8.88) and H-17 (δ 5.38 and δ 4.65) (7.8 Hz in both conformers) might provide evidence for the proposed structure of **8a**, as well as the long-range coupling (W path, $J_{17,21} \cong 1$ Hz) between H-21 (δ 2.90 and δ 2.95) and H-17 protons confirmed the configuration at C-17. These features suggest two conformations probably resulting from restricted rotation about the C-4', 4'-N bond.[10] The ^{13}C NMR spectrum also supported such a mixture with the relevant C-17 peaks at δ 50.2 for the major isomer and δ 52.9 for the other.

Finally, the related adducts **5-8b** were cleanly prepared as described above, in good yield, starting from 11-methoxy-17-hydroxy TBS **2b**. Due to the paucity of 11-methoxy TBS **1b**, these transformations were carried out on a micromole scale and the reaction products thus obtained were recognized by FAB^+ mass spectra and ^1H NMR analysis in comparison with the corresponding TBS derivatives. In particular, in the ^1H NMR spectrum of **5-8b** the only detectable differences were the presence of a singlet at δ 3.71-3.75 for 11-methoxy group and the ABX system for the aromatic protons at δ 7.15 (d, 1H, $J_{9,10}$ = 7.8 Hz , H-9), 6.35-6.38 (brd, 1H, H-10) and 6.40-6.43 (brs, 1H, H-12).

When the coupling between **2a,b** and nucleosides or nucleic acid bases was performed in buffered aqueous ethanol (pH 6.8-7.4), only trace amounts of the adducts **5, 6, 7** and **8** were detected by HPLC analysis.

In summary, aspidospermidine alkaloids are ubiquitous in nature, but no studies have been reported on the reactivity of such compounds with nucleic acid bases. We have found that the highly reactive 17-hydroxy aspidospermidines **2a,b** are able to modify both purine and pyrimidine bases to give extended systems not previously described. Although under physiological conditions compounds **5, 6, 7, 8** were formed in trace amounts, this challenging reactivity turns the attention to biological testing of the compounds **1a,b** and of the modified nucleosides here synthesized.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 681 spectrometer for chloroform solutions. UV spectra on a Perkin-Elmer model 554 for solutions in methanol. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian XL-200 (^1H, 200 MHz; ^{13}C, 50.2 MHz) and Bruker AC-300 (^1H, 300MHz; ^{13}C, 75.4 MHz) spectrometers using $CDCl_3$ as solvent unless otherwise stated. FAB^+ mass spectra were determined on a VG 70-70 EQ-HF instrument equipped with its standard

source, using Xe as gas and glycerol as matrix. Analytical tlc plates were purchased from Merck. Compounds were detected on developed chromatograms by fluorescence quenching (λ 254 nm) and visualized with cerium (IV) ammonium sulphate (CAS) (1% in 85% phosphoric acid); R_F and colours (CAS spray on tlc) of products are given. Flash Chromatography (FC) was performed with Silica gel S (230-400 mesh, Merck). Preparative tlc (plc) was performed on 0.25 thick layers of Merck silica gel HF_{254} coated on 20 x 20 cm glass plates.

General procedure for the reaction of 2a with nucleosides or nucleic acid bases. To a solution of the 17-hydroxy TBS **2a** (0.1 mmol) in dry dichloromethane (5 mL) under a nitrogen atmosphere, the appropriate nucleoside or nucleic acid base (0.15 mmol) was added. The mixture was cooled (0°C) and DIPEA (0.2 mmol) followed by TBDMSCl (0.2 mmol) in dichloromethane (1 mL) were added dropwise. Stirring was continued (2-8 h) while the reaction reached room temperature. In all cases, when product formation had reached a maximum, as evidenced by tlc, the reaction mixture was neutralized and the solvent removed *in vacuo*. The residue was purified as specified in each case.

Reaction of 17-hydroxy-TBS 2a with adenine. 2a and adenine were reacted as described above. The residue was purified by FC using chloroform/methanol (19:1) as the eluent to give **5a** (66%) as white crystals from methanol: mp 125°C (dec.); R_F 0.40 [chloroform/methanol (9:1); pale yellow]; IR ν_{max} ($CHCl_3$) 3430, 3360, 1665 and 1595 cm^{-1}; UV λ_{max} (MeOH) 232(sh), 288 and 325 nm; ^1H NMR (200 MHz) δ 0.74 (t, 1H, $J_{18,19}$ = 7.2 Hz, 19-CH_3), 1.16 (m, 2H, H-19), 1.85 (brdd, 1H, $J_{6S,6R}$ = 11.8Hz, $J_{6S,5S}$ = 4.0 Hz, H-6*S*), 2.50 (ddd, 1H, $J_{6R,5S}$ = 10 Hz, $J_{6R,5R}$ = 5.5 Hz, H-6*R*), 2.71 (brddd, 1H, $J_{5S,5R}$ = 8.5 Hz, H-5*S*), 2.99 (1H, d, $J_{17,21}$ =1.5 Hz, H-21), 3.11 (brd, 1H, $J_{3S,3R}$ = 15.5 Hz, H-3*R*), 3.42 (brdd, 1H, H-5*R*), 3.63 (brdd, 1H, $J_{3S,14}$ = 4.5, H-3*S*), 3.82 (s, 3H, CO_2CH_3), 5.63 (brd, 1H, $J_{14,15}$ = 11.5 Hz, H-15), 5.64 (m, 1H, H-17), 5.74 (brdd, 1H, H-14), 6.85 (brd, 1H, $J_{11,12}$ =7.5 Hz, H-12), 6.89 (brt, 1H, $J_{9,10} \cong J_{10,11}$ = 7.5 Hz, H-10), 7.17 (brt, 1H, H-11), 7.22 (brd, 1H, H-9), 7.87 (s, 1H, H-8'), 8.41 (s, 1H, H-2'), 8.91 (brd, 1H, $J_{17,6'\text{-NH}}$ = 8.5 Hz, 17-NH), 9.15 (s, 1H, N(1)-H); MS (FAB^+), *m/z* 470 (MH^+), 335 (protonated azadiene **3a**), 136 (protonated adenine).

Anal. Calcd. for $C_{26}H_{27}N_7O_2$: C, 66.51; H, 5.80; N, 20.88. Found: C, 65.8; H, 5.74; N, 21.10.

Reaction of 17-hydroxy-TBS 2a with tri-O-acetyl adenosine. 2a and tri-O-acetyl adenosine were allowed to react for 8 h as described above. The residue was purified

by FC using chloroform/methanol (4:1) as eluent to give **6a** (86%) as a white foam: R_F 0.32 [chloroform/methanol (4:1), yellow]; IR ν_{max} ($CHCl_3$) 3550, 1735 and 1665 cm^{-1}; UV λ_{max} (MeOH) 230 (sh), 284 and 323 nm; ^1H NMR (300 MHz) δ 0.76 (t,1H, $J_{18,19}$ = 7.5 Hz, 19-CH_3), 1.15 (m, 2H, H-19), 1.85 (brdd, 1H, $J_{6R,6S}$ = 11.5 Hz, $J_{5S,6S}$ = 4.0 Hz, H-6*S*), 2.05 (s, 3H, $OCOCH_3$), 2.15 (s,6H, two $OCOCH_3$), 2.48 (ddd, 1H, $J_{5S,6R}$ = 10.0 Hz, $J_{5R,6R}$ = 5.5 Hz, H-6*R*), 2.72 (ddd, 1H, $J_{5S,5R}$ = 8.5 Hz, H-5*S*), 2.99(brs, 1H, H-21), 3.11 (brd, 1H, $J_{3R,3S}$ = 16.0 Hz, H-3*R*), 3.41 (brdd, 1H, H-5*R*), 3.60 (brdd, 1H, $J_{3S,14}$ = 4.4 Hz, H3*S*), 3.82 (s, 3H, CO_2CH_3), 4.38 (m, 3H, H-4" + H-5"), 5.65 (m, 2H, H-15 + H-17), 5.68 (brdd, 1H, $J_{2",3"}$ = 5.5 Hz, $J_{3",4"}$ = 5.0 Hz, H-3"), 5.78 (br dd, 1H, $J_{14,15}$ = 9.8 Hz, H-14), 5.95 (t, 1H, $J_{1",2"}$ = 5.5 Hz, H-2"), 6.12 (d, 1H, H-1"), 6.84 (brd, 1H, $J_{11,12}$ = 7.5 Hz, H-12), 6.88 (brt, 1H, $J_{10,11} \cong J_{9,10}$ = 7.5 Hz, H-10), 7.17 (brt, 1H, H-11), 7.22 (brd, 1H, H-9), 7.78 (s, 1H, H-8'), 8.36 (s, 1H, H-2'), 8.87 (d, 1H, $J_{17,6'\text{-NH}}$ = 8.7 Hz, 17-NH), 9.14 (s, 1H, N(1)-H); MS (FAB^+) *m/z* 728 (MH^+).

Reaction of 17-hydroxy-TBS 2a with tri-O-acetyl guanosine. 2a and tri-O-acetyl guanosine were allowed to react for 2 h as described above. The residue was purified by FC using chloroform/methanol (19:1) as eluent to give **7a** (95%) as a glass : R_F 0.30 [chloroform/methanol (19:1), yellow]; IR ν_{max} ($CHCl_3$) 3555, 1740, 1668 cm^{-1}; UV λ_{max} (MeOH) 254, 287, 325 nm; ^1H NMR (300 MHz, DMSO-d_6) δ 0.66 (t, 3H, $J_{18,19}$ = 7.4 Hz, 19-CH_3), 1.05 (m, 2H, H-19), 1.67 (brdd, 1H, $J_{6S,6R}$ = 11.2 Hz, $J_{5S,6S}$ = 3.9 Hz, H-6*S*), 2.02 (s, 3H, $OCOCH_3$), 2.08 (s, 3H, $OCOCH_3$), 2.09 (s, 3H, $OCOCH_3$), 2.21 (ddd, 1H, $J_{5S,6R}$ = 11.5 Hz, $J_{5R,6R}$ = 5.5 Hz, H-6*R*), 2.69 (ddd, 1H, $J_{5R,5S}$ = 8.5 Hz, H-5*S*), 2.96 (brs, 1H, H-21), 3.15 (brd, 1H, $J_{3S,3R}$ = 16.0 Hz, H-3*R*), 3.23 (brdd, 1H, H-5*R*), 3.55 (brdd, 1H, $J_{3S,14}$ = 4.5 Hz, H-3*S*), 3.75 (s, 3H, CO_2CH_3), 4.25-4.45 (m, 3H, H-4" + H-5"), 5.25 (brd, 1H, $J_{17,N(2')\text{-H}}$ = 7.9 Hz, H-17), 5.60 (m, 1H, H-15 + H-3"), 5.92 (t, 1H, $J_{2",3"} \cong J_{2",1"}$ =5.5 Hz, H-2"), 5.93 (m, 1H, H-14), 6.08 (d, 1H, H-1"), 6.88 (brt, 1H, $J_{9,10} \cong J_{10,11}$ = 7.2 Hz, H-10), 7.11 (brd, 1H, $J_{11,12}$ = 7.2 Hz, H-12), 7.18 (brt, 1H, H-11), 7.35 (brd, 1H, H-9), 7.88 (s, 1H, H-8'), 8.15 (brd, 1H, 2'-NH), 9.75 (s, 1H, N(1)-H), 11.25 (brs, 1H, N(1')-H); ^{13}C-NMR (50.2 MHz, DMSO-d_6) δ 7.5 (C-18), 20.2 and 20.3 (3 CH_3-CO_2), 28.4 (C-19), 43.9 (C-20), 45.6 (C-6), 49.8 (C-5), 50.1 (C-3), 50.8 (OCH_3), 51.5 (C-17), 54.1 (C-7), 63.5 (C-5"), 67.3 (C-21), 70.2 (C-2"), 72.4 (C-3"), 79.2 (C-4"), 85.4 (C-1"), 94.1 (C-16), 110.4 (C-12), 116.8 (C-3'), 120.5 (C-9), 120.6 (C-10), 127.7 (C-12 + C-14), 129.5 (C-15), 137.2 (C-8 + C-8'), 143.1 (C-13), 150.7 (C-6'), 152.5 (C-4'), 157.3 (C-2'), 166.3 (C-2), 167.1 (CO_2CH_3), 169.2, 169.3 and 170.0 (3 acetate carbonyl); MS (FAB^+), *m/z* 744 (MH^+).

Reaction of 17-hydroxy-TBS 2a with tri-O-acetyl cytidine. 2a and tri-O-acetyl cytidine were allowed to react for 2 h as described above. The residue was purified by

FC using chloroform/methanol (19:1) as eluent to give **8a** (88%) as a white foam. R_F 0.30 [chloroform/methanol (9:1); yellow]; IR ν_{max} ($CHCl_3$) 3550, 3470, 1735, 1665 cm^{-1}; UV λ_{max} (MeOH) 230, 254 (sh), 284, 320 nm; ^1H NMR (300 MHz, DMSO-d_6) δ (major isomer): 0.70 (t, 3H, $J_{18,19}$ = 7.4 Hz, 19-CH_3), 1.64 (dd, 1H, $J_{6S,6R}$ = 11.8 Hz, $J_{6S,5S}$ = 4.2 Hz, H-6*S*), 2.33 (ddd, 1H, $J_{6R,5S}$ = 11.0 Hz, $J_{6R,5R}$ = 5.5 Hz, H-6*R*), 2.66 (ddd, 1H, $J_{5R,5S}$ = 8.5 Hz, H-5*S*), 2.90 (brs, 1H, H-21), 3.15 (brd, 1H, $J_{3S,3R}$ = 16.2 Hz, H-3*R*), 3.20 (m, 1H, H-5*R*), 3.48 (brdd, $J_{3S,14}$ = 4.8 Hz, H-3*S*), 2.71 (s, 3H, CO_2CH_3), 5.38 (m, 2H, H-2" + H-17), 5.84 (d, 1H, $J_{1",2"}$ = 5.2 Hz, H-1"), 5.85 (d, 1H, $J_{5',6'}$ = 7.4 Hz, H-5'), 7.51 (d, 1H, H-6'), 8.15 (brd, 1H, $J_{17,4'\text{-NH}}$ = 7.8 Hz, 4'-NH); δ (minor isomer): 1.68 (brdd, 1H, $J_{6S,6R}$ = 11.8 Hz, $J_{6S,5S}$ = 4.2 Hz, H-6*S*), 2.18 (ddd, 1H, $J_{6R,5S}$ = 11.0 Hz, $J_{6R,5R}$ = 5.5 Hz, H-6*R*), 2.79 (ddd, 1H, $J_{5R,5S}$ = 8.5 Hz, H-5*S*), 2.95 (brd, $J_{17,21}$ = 1.2 Hz, H-21), 3.59 (brdd, $J_{3S,14}$ = 4.2 Hz, H-3*S*), 3.80 (s, 3H, CO_2CH_3), 4.65 (brdd, $J_{17,4'\text{-NH}}$ = 7.8 Hz, H-17), 5.90 (d, $J_{1",2"}$ = 4.2 Hz, H-1"), 6.37 (d, 1H, $J_{5',6'}$ = 7.5 Hz, H-5'), 7.80 (d, 1H, H-6'), 8.88 (brd, 1H, 4'-NH), 9.90 (s, 1H, N(1)-H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ (major isomer) 7.7 (C-18), 28.7 (C-19), 45.7 (C-6), 50.2 (C-17), 54.1 (C-7), 68.2 (C-21), 93.9 (C-16), 90.1 (C-5'), 141.3 (c-6'), 169.5 (CO_2CH_3), δ (minor isomer) 7.5 (C-18), 28.7 (C-19), 45.4 (C-6), 52.9 (C-17), 54.5 (C-7), 68.2 (C-21), 91.6 (C-5'), 143.4 (C-6'), 170.1 (CO_2CH_3); MS (FAB^+) *m/z* 704 (MH^+).

General procedure for the reaction of 2b with nucleosides or nucleic acid bases. **2b** (0.01 mmol) in 0.5 mL of dry dichloromethane was reacted with a 2-fold molar excess of the appropriate nucleoside or nucleic acid base in the presence of DIPEA (0.02 mmol) amd TBDMSCl (0.02 mmol) as described for **2a**. After elimination of the solvent, the reaction products were purified by tlc using chloroform/methanol (19:1) as eluent.

Adduct 5b. White solid; R_F 0.38 [chloroform/methanol (9:1), pale yellow]; MS (FAB^+) *m/z* 500 (MH^+).

Adduct 6b. White foam; R_F 0.22 [chloroform/methanol (19:1), yellow]; MS (FAB^+) *m/z* 758 (MH^+).

Adduct 7b. White foam; R_F 0.26 [chloroform/methanol (19:1), yellow]; MS (FAB^+) *m/z* 774 (MH^+).

Adduct 8b. White solid; R_F 0.28 [chloroform/methanol (19:1), yellow]; MS (FAB^+) *m/z* 734 (MH^+).

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9) The tri-O-acetylated nucleosides were employed in order to increase the solubility of both reagents and products.
10) It must be noted that NMR spectra of **5a, 6a** and **7a** showed an unique set of signals. Presumably the greater steric demainds of the purine nucleus over the pyrimidine one, would greatly favor one rotamer over the other. A detailed conformational study by dynamic NMR about this problem will be reported elsewhere.

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