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Generation of C-1' Radicals through a β-(Acyloxy)alkyl Rearrangement in Modified Purine and Pyrimidine Nucleosides

Thanasis Gimisis, Giuseppina Ialongo and Chryssostomos Chatgilialoglu*

I.Co.C.E.A., Consiglio Nazionale delle Ricerche, Via P. Gobetti 101, 40129 Bologna, Italy

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Abstract: The synthesis of protected 1',2'-didehydro-2'-deoxyadenosines has been optimized by incorporating a phosphoranylidene protection of the adenine amino function. These unsaturated adenosines have served as substrates for the electrophilic iodopivaloyloxylation leading to new nucleosides modified at the anomeric position. Reaction of halopivaloates **10**, **11** and **12** with tributyltin hydride generates indirectly C-1' radicals through a β-(acyloxy)alkyl rearrangement. Rate constants for these rearrangements have been measured by using free-radical clock methodology and comparison of these data with previous reported results provides structural information about the nature of this important class of radicals. © 1997 Elsevier Science Ltd. All rights reserved.

Functionalization of the C-1′ position in nucleosides has recently emerged as a useful methodology not only for accessing pharmacologically important modified nucleosides but also for studying biological processes related to DNA damage.[1-3] Specifically, there is a number of natural products reminiscent of nucleosides which contain modifications at the C-1' position. Examples can be found in angustamycin C[3a] which has interesting antiviral and antitumor properties and in hydantocidin,[4a] a natural spironucleoside with herbicidal and plant growth regulatory activities. Modification of the C-1' position has been effected synthetically by *N*-glycosylation of suitable sugar precursors,[4b-d] building-up of the base moiety on a suitable sugar substrate,[2,4e] or by chemical transformation of natural nucleosides.[1b,3a]

In our laboratory, we have undertaken a systematic investigation of the radical chemistry associated with the C-1′ position.[1] In a preliminary communication[1c] we reported a β-(acyloxy)alkyl radical rearrangement which leads to the generation of a ribofuranosyl C-1′ radical in a protected uridine (equation 1). H. Tanaka and coworkers[3b,d] also reported similar results and centered their efforts on the synthetic applications of this new migration reaction, whereas we focused our interest on its mechanistic implications. We initially ascribed the driving force for this rearrangement to the delocalization of the unpaired electron onto the uridine moiety. In order to better understand the role of a particular base in the formation and stability of C-1′ radicals, we have now extended this rearrangement in protected adenosine substrates. We report here our results on the synthesis of the radical precursor 2′-deoxy-2′-halogeno-1′-esters of the required protected adenosines together with a kinetic study of the radical rearrangement reaction.

(1)

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RESULTS AND DISCUSSION

Synthesis of Protected 1',2'-Didehydro-2'-deoxyadenosines. The first 1′,2′-unsaturated purine nucleoside was reported by M. J. Robins *et al.* in 1974.[5] The initial low yielding synthetic procedure has recently been ameliorated by Sanghvi and coworkers[6] by utilizing the commercially available but expensive 9-(β-D-arabinofuranosyl)adenine. We decided to use the relatively inexpensive (-)-adenosine (**1**) as our starting material and attempt to bypass the triflate intermediate for economical reasons.

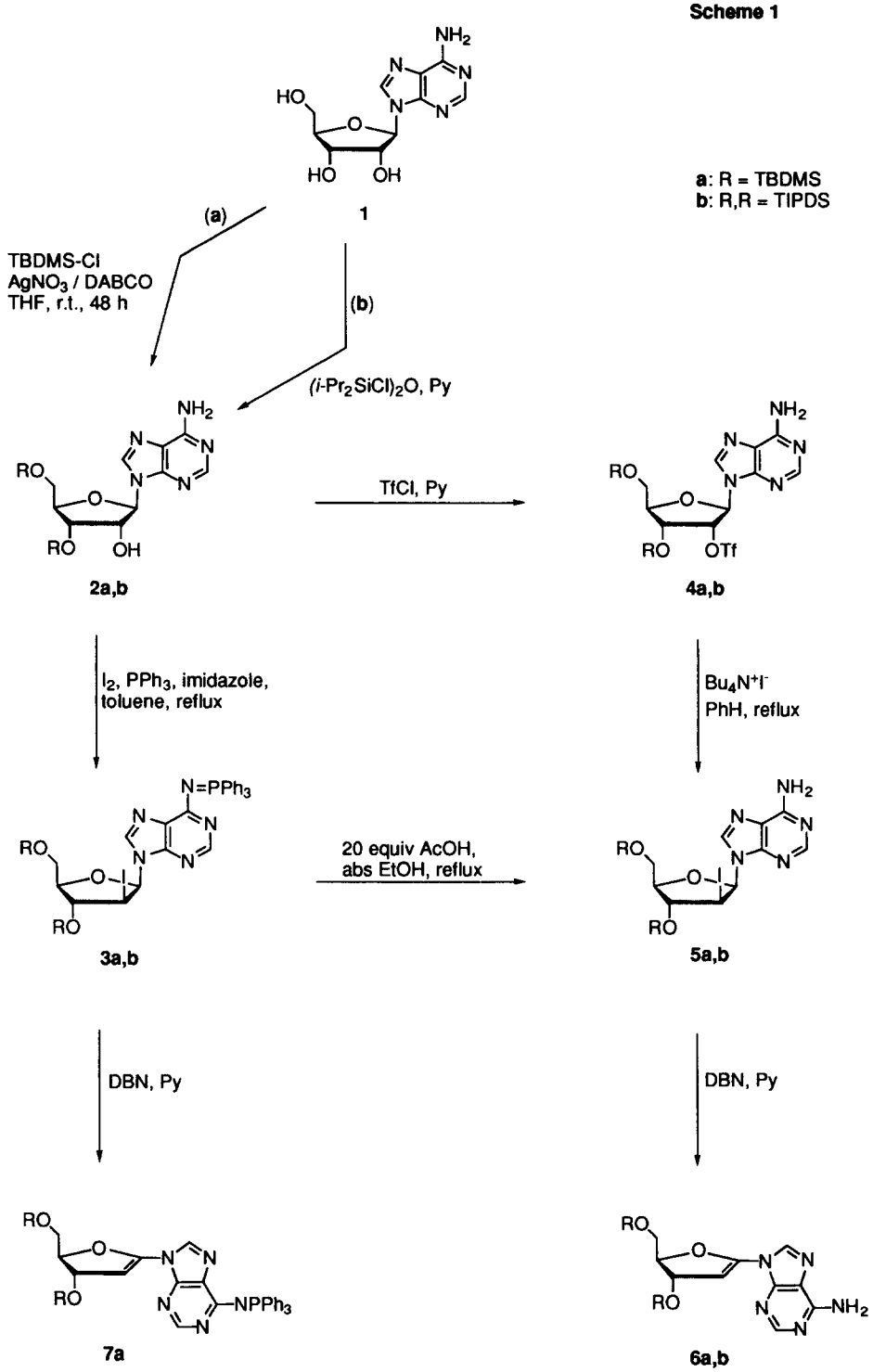
Application of the conditions developed by Ogilvie and coworkers[7] for the regioselective 3′,5′-disilylation of adenosine in the presence of silver perchlorate and *p*-nitropyridine oxide gave mainly the 5′-monoprotected adenosine in a relatively slow reaction. On the other hand, in the presence of silver nitrate and DABCO regioselective 3′,5′-diprotection did occur as reported (compound **2a**), albeit in a slower reaction (48 h). Regiospecific 3′,5′-protection was also achieved by using 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane under the standard conditions (compound **2b**).[8]

Transformation of the 2′α-hydroxyl group to the corresponding β-iodide has been previously effected in the case of 3′, 5′-*O*-TIPDS-adenosine (**2b**) in a two step procedure *via* the corresponding 2′-*O*-triflate (**4b**).[9] This procedure was repeated successfully and was also applied in the case of 3′,5′-di-*O*-TBDMS-adenosine **2a** to yield the corresponding iodide **5a** in a 35 % combined yield. We were able to improve the yield of the product **5a** to 65 % by modifying the iodination step (tetrabutylammonium iodide in refluxing benzene).[10]

We sought an alternative one-step iodination procedure and attempted to apply the conditions developed by Garegg *et al.* for converting a hydroxy- into an iodo-group in carbohydrates.[11] In the case of 3′,5′-*O*-TIPDS-adenosine (**2b**) we obtained a single product in good yield (59 % after purification) which was similar but not identical to the expected 2′-iodo-3′,5′-*O*-TIPDS-adenosine (**5b**). The presence of aromatic proton signals in the ^{1}H NMR spectrum along with the recent report of the preparation of *N*-triphenylphosphoranylidene nucleosides through a Mitsunobu-type reaction[12] led to the conclusion that iodination was accompanied by protection of the free amino group of the adenine to the corresponding *N*-triphenylphosphoranylidene **3b**. Further corroboration came from the full characterization of the new compound along with the chemical transformation to the known 2′-iodo-3′,5′-*O*-TPDS-adenosine (**5b**), in high yield (96 %), through deprotection of the triphenylphosphoranylidene protecting group. In this respect, the reported methodology does not allow for the deprotection of triphenylphosphoranylidene group selectively.[12] We found that significantly milder conditions (20 equiv. of glacial acetic acid in absolute ethanol) than the published ones were adequate for this deprotection reaction. Our conditions did not affect the 3′,5′-disilyl protection.

Application of the above methodology to 3′,5′-di-*O*-TBDMS-adenosine (**2a**), led to the formation of the intermediate *N*-triphenylphosphoranylidene iodide **3a** in 85% yield, whose amino function was also successfully deprotected in 95% yield. In summary, 2′-iodo-3′,5′-di-*O*-TBDMS-adenosine (**5a**) could be obtained through treatment of 3′,5′-di-*O*-TBDMS-adenosine with triphenylphosphine, imidazole, and iodine in refluxing toluene, followed by refluxing in absolute ethanol in the presence of excess of glacial acetic acid in 81% combined yield.

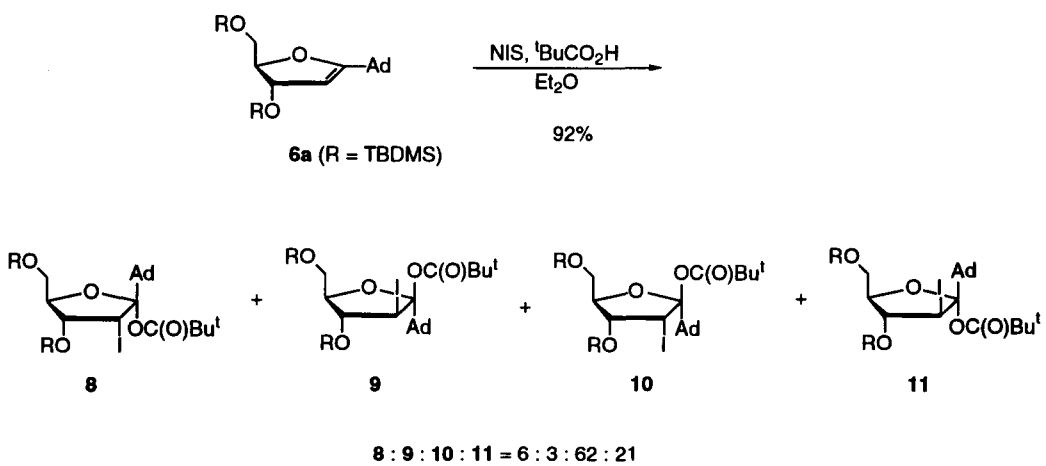
Scheme 1


NH2
HO
HO OH
1
(a)
TBDMS-Cl
AgNO3 / DABCO
THF, r.t., 48 h
(b)
(i-Pr2SiCl)2O, Py
a: R = TBDMS
b: R,R = TIPDS
RO
RO OH
2a,b
TfCl, Py
RO OTf
4a,b
I2, PPh3, imidazole,
toluene, reflux
Bu4N+I-
PhH, reflux
N=PPh3
3a,b
20 equiv AcOH,
abs EtOH, reflux
5a,b
DBN, Py
DBN, Py
NPPh3
7a
6a,b

The elimination of HI from the 2′-iodides **5a** and **5b** occurred smoothly under the originally published conditions[5b] (DBN in pyridine), to yield the corresponding **6a** and **6b**[6] in 85 and 90% yield, respectively, after crystallization. Similarly, compound **3a** was transformed to **7a** in 66% yield.

Electrophilic Haloacyloxylation Reactions. The electrophilic iodo-pivaloyloxylation reaction was carried out using **6a** in order to provide a protected adenine system comparable to the previously reported uridine analog.[1e] The optimized conditions for the synthesis of the protected 2'-deoxy-1'-C-pivaloyloxy-2'-iodoadenosines are outlined scheme 2. The structure assignment for the resulting products (Figure 1) was based on the previous findings by the Tanaka group which established some empirical rules corroborated by X-ray data.[3a] In our case, the H-2' protons of the four possible diastereomers appeared as doublets at 5.06 ($J_{2',3'}$ = 1.6 Hz), 5.37 ($J_{2',3'}$ = 4.9 Hz), 5.53 ($J_{2',3'}$ = 2.2 Hz), and 6.26 ppm ($J_{2',3'}$ = 5.3 Hz). The two signals with the smaller coupling constants were assigned to the diastereomers possessing a β-iodo group, since the dihedral angle between H-2' and H-3' is close to 90° in this case. Other similarities in the spectra of the β-iodo diastereomers included similarly small $J_{3',4'}$, and chemically equivalent 5'-Hs which appeared as doublets or poorly resolved AB quartets. Further corroboration of the above assignments came from NOE experiments which gave large (~12 %) negative NOEs on H-3' upon irradiation of the corresponding H-2' in the presumed α-iodo diastereomers (large $J_{2',3'}$) and low or unobserved (<4 %) NOEs for the β-iodo ones. On the other hand, the products of *syn* addition could be distinguished from those *anti*, since they corresponded to the minor products of the reaction[3a] and also contained in their ^{1}H NMR spectra well separated signals for the two *tert*-butyl groups of TBDMS present in the molecules. In contrast, the signals of the *tert*-butyl groups in the ^{1}H NMR spectra of the *anti* products were coincident. Therefore, we could easily assign the four doublets which appeared in the ^{1}H NMR spectra of the diastereomeric mixtures to α-*syn*, β-*syn*, α-*anti*, and β-*anti* in order of appearance (downfield to upfield) in the spectra of iodo-pivaloates.

Scheme 2



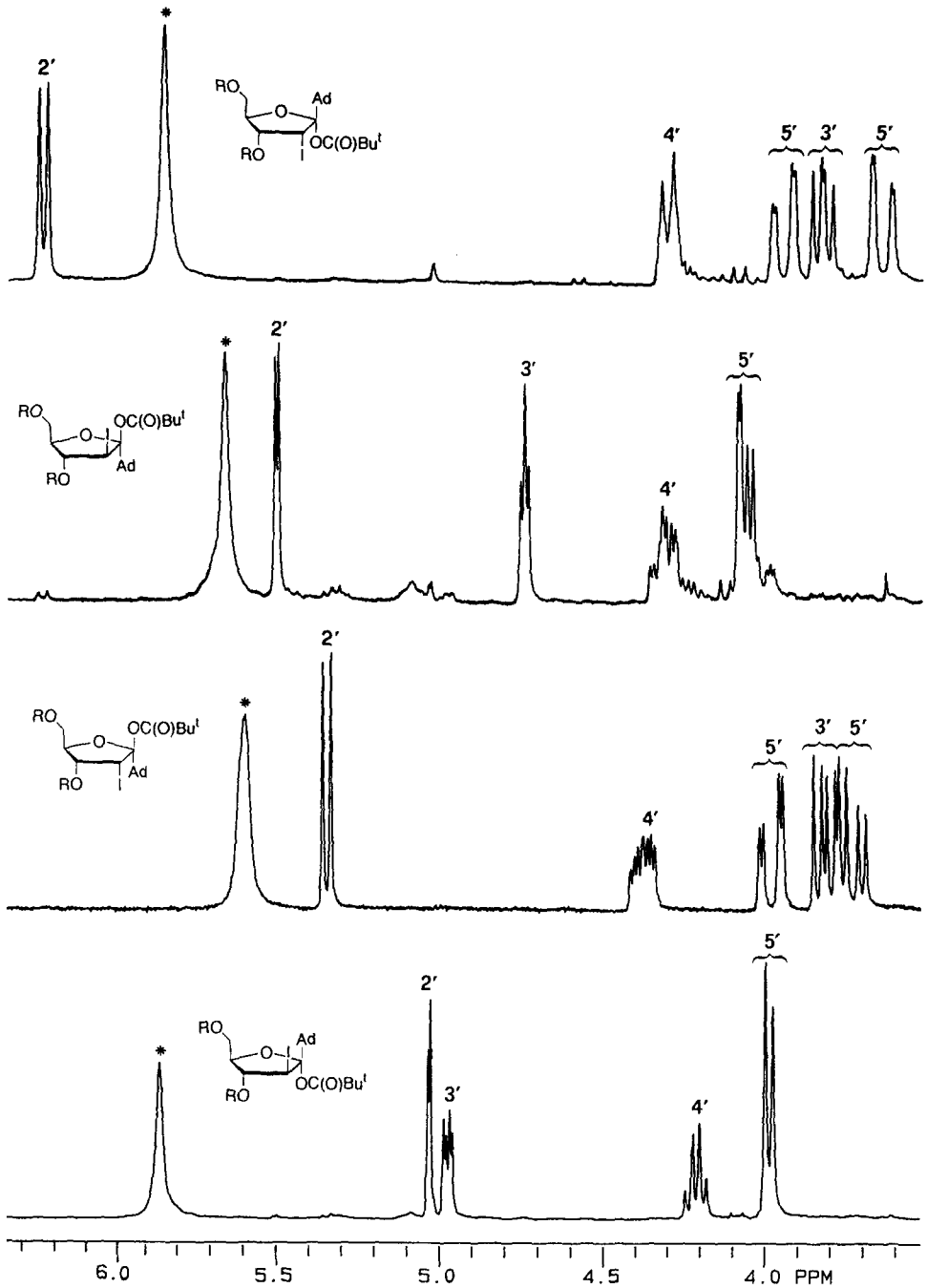


Figure 1. ^{1}H NMR spectra of the nucleosides (R = TBDMS) in the region of sugar resonances. (*) Resonance signal from NH_2 group of adenine.

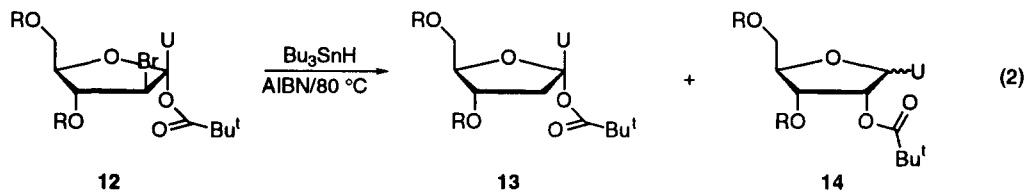
The preparation of the above iodopivaloates was preceded by an optimization process which involved preparation of the corresponding bromo- and iodoacetates, and bromopivaloates of adenosine. Since these intermediates were not used further in the radical rearrangement reactions, we did not attempt to fully characterize them and therefore the following discussion is based mainly on the ^{1}H NMR analysis of the crude mixtures.[13] During optimization, we examined, apart from the effect of temperature and base (triethylamine), the product distribution when the reaction was carried out with combinations of *N*-iodosuccinimide or *N*-bromosuccinimide with acetic or pivalic acid. When 1',2'-didehydro-2'-deoxy-3',5'-di-TBDMS-adenosine was subjected to the previously reported optimized conditions (1 equiv NBS, 5 equiv PvOH, 5 equiv Et_3N),[3a] no reaction was observed. Upon replacement of pivalic with acetic acid, a slow reaction ensued that could be brought to completion by addition of up to 15 equiv of acetic acid/triethylamine, 3 equiv. of NBS, and 24 h reaction to yield a mixture of diastereomeric bromopivaloates characterized by a β/α = 1/1 selectivity for the initial approach of NBS and an anti/syn = 16/1 selectivity for the approach of the pivaloate in respect to the 2'-halide. Elimination of triethylamine from the above mixture (1 equiv NBS, 5 equiv AcOH) resulted in a fast reaction (2 h) and an improvement of the β/α face selectivity (2.3/1) with concurrent elimination of the anti/syn selectivity (1.1/1). The product distribution remained relatively constant over a range of temperatures (-78 °C, r.t.) although a considerable slowing down of the reaction was observed at lower temperatures. Similarly, there was not a significant change of the distribution upon exchanging acetic for pivalic acid. An improvement of both anti/syn (~10/1) and β/α face (1/2.5) selectivities was observed upon replacement of NBS with NIS (1 equiv NIS, 5 equiv PvOH). Finally, a further enhancement of both reaction time (15 min) and selectivity (β/α = 1/4.4; anti/syn = 13.7/1) was achieved by performing the reaction in dichloromethane. In these cases, however, the major diastereomer isolated from the reaction was the 2'α-iodo-*trans*-pivaloate, indicating an α-face preference for the initial approach of the bulky NIS to the 1', 2'-didehydro-2'-deoxyadenosine.

A number of conclusions can be drawn from the above experiments, in comparison with the previously studied pyrimidine system and adenine bromopivaloates.[3a,c,d] The starting 1',2'-didehydro-2'-deoxyadenosines exhibited an enhanced stability when compared with the corresponding 1',2'-didehydro-2'-deoxyuridines. As a result, the electrophilic addition reactions were slow and in the presence of triethylamine could be hardly brought to completion only in the presence of large excess of acid, in agreement with the previous report.[3e] As a positive result, the bromo or iodo acetates were stable products which could be purified *via* flash column chromatography without any decomposition, contrary to the reported instability of the corresponding bromoacetates of uridine.[3d] The loss of *anti/syn* stereoselectivity observed upon exclusion of triethylamine from the reaction mixture was regained by utilizing the bulkier *N*-iodosuccinimide. Nevertheless, a reversal of β/α face selectivity accompanied the use of NIS and a preferential approach of NIS from the α-face was observed in the purine system, rendering the 2'-deoxy-2'-iodo-1'-pivaloate ester of α-D-adenosine as the major product of the reaction, isolated in 62 % yield.

Radical-Based Reductions of Halopivaloates. The nucleoside derivatives **10**, **11** and **12**[3a] were reduced with Bu_3SnH under standard free-radical conditions [AIBN (10 mol %) benzene, 80 °C]. The results are outlined in Table 1 and eqs 2-4.

In particular, with uridine bromopivaloate **12** after 30 min reaction a mixture of the direct reduction product **13** and a 6:1 anomeric mixture of the rearranged products **14** (eq. 2) were obtained. With higher

concentrations of Bu_3SnH, there was an increase of the direct reduction product (cf. entries 1 and 2 in Table 1). The major configurational isomer of **14** was determined as the α-anomer through 1-D NOE experiments[14a] which showed characteristic NOEs between the C-1' hydrogen and those hydrogens in positions C-2' (12 %), C-3' (2.0 %) and C-6' (2.3 %). To further corroborate the structure of compounds **14**, we undertook their synthesis by an alternative route. 3',5'-Di(*t*-butyldimethylsilyl)-β-uridine prepared according to the published procedure[7] was further bis-acylated at positions 2 and 2' with trimethylacetyl chloride in pyridine in the presence of a catalytic amount of DMAP. Selective hydrolysis (0.1 M KOH in ethanol) of the 2-trimethylacetyl group furnished the β-anomer of **14** in 30 % yield. Lewis acid promoted isomerization of the anomeric configuration[14b] provided an inseparable (~1:1) mixture of α- and β-anomers, whose ^1H NMR spectrum was completely assigned.



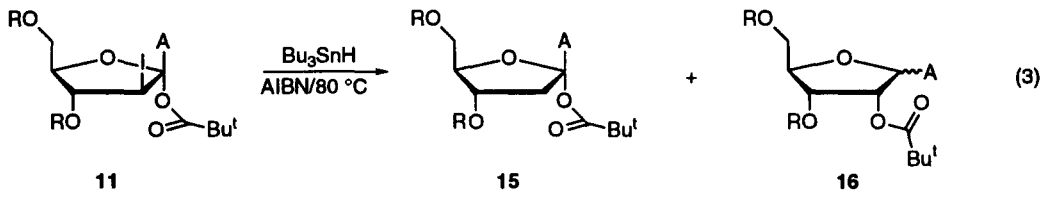
12 **13** **14** (2)

When the purine iodide **11**, bearing the same diastereomeric composition as **12**, was subjected to the above standard free radical conditions a fast reaction ensued that produced **15** accompanied by a mixture (7:1) of the two anomeric riboadenosines **16** with the α-anomer predominating (eq. 3). Again, in higher concentrations of Bu_3SnH, there was an increase of the direct reduction product (cf. entries 3 and 4 in Table 1). However, the direct reduction product **15** proved to be unstable and decomposed upon attempted purification to give 1',2'-didehydroadenosine (**6a**). Therefore, it was characterized by ^1H NMR of the crude reaction mixture which contained characteristic 2'-H signals as doublets of doublets centered at 3.37 and 3.51 ppm, respectively. The rearranged product **16** was isolated as a mixture and was hydrolyzed to the corresponding mixture of α- and β-D-adenosine in order to establish unequivocally their assignment by comparison of the ^1H NMR spectra with those of commercially available samples.

Table 1. Product studies for the reduction of halopivaloates 10, 11 and 12[a]

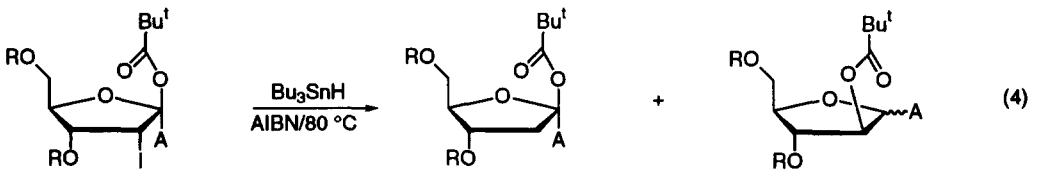
Entry	Substrate[b]	Bu_3SnH,[c] M	Product (Yield,[d] %)	Reduced:Rearranged[e]	α:β[f]
1	**12**	0.120	**13+14** (99)	4.3:1	6:1
2	**12**	0.060	**13+14** (97)	2.0:1	6:1
3	**11**	0.112	**15+16** (93)	6.9:1	7:1
4	**11**	0.032	**15+16** (90)	1.6:1	7:1
5	**10**	0.103	**17+18** (97)	2.1:1	1:12
6	**10**	0.052	**17+18** (95)	0.9:1	1:12

[a] At 80 °C in benzene. [b] Starting concentration of substrate was 0.05 M. [c] 1.2 equiv of Bu_3SnH. [d] ^1H NMR yields, toluene used as an internal standard. [e] Direct reduction product for the starting compound **10** refers to the sum of **17** and **6a** (see text). [f] α- and β-anomers of the rearranged products.



11 **15** **16**

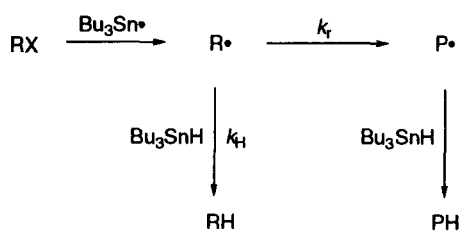
Finally, reduction of the α-purine iodide **10** led similarly to a mixture of the direct reduction product **17** and an anomeric mixture of **18** with the β-anomer predominating in this case. Again, with higher concentrations of Bu_3SnH, there was an increase of the direct reduction product (cf. entries 5 and 6 in Table 1). Compound **17** proved to be even more unstable than isomer **15** and decomposed slowly during the course of the reaction (20 min at 80 °C) to give quantitatively 1',2'-unsaturated purine nucleoside **6a**. The anomers **18** were in turn hydrolyzed as a mixture to the corresponding triols, and ^1H NMR established their assignments to the known α- and β-D-arabinosyladenosine.[15,16]



10 **17** **18**

β-(Acyloxy)alkyl Radical Rearrangement. We sought to provide rate constants for the radical migration of the pivaloate group in the reactions 2-4. An indirect procedure for measuring the rate constant of a unimolecular path involves competition between this process and a radical-molecule reaction of the radical (*free-radical clock* methodology[17]). For example, the rate constants k_r of the rearrangement R• → P• can be obtained (scheme 3), providing that conditions can be found in which radical R• is partitioned between the two reaction channels, that is, reaction with the Bu_3SnH and rearrangement to P• radical.

Scheme 3

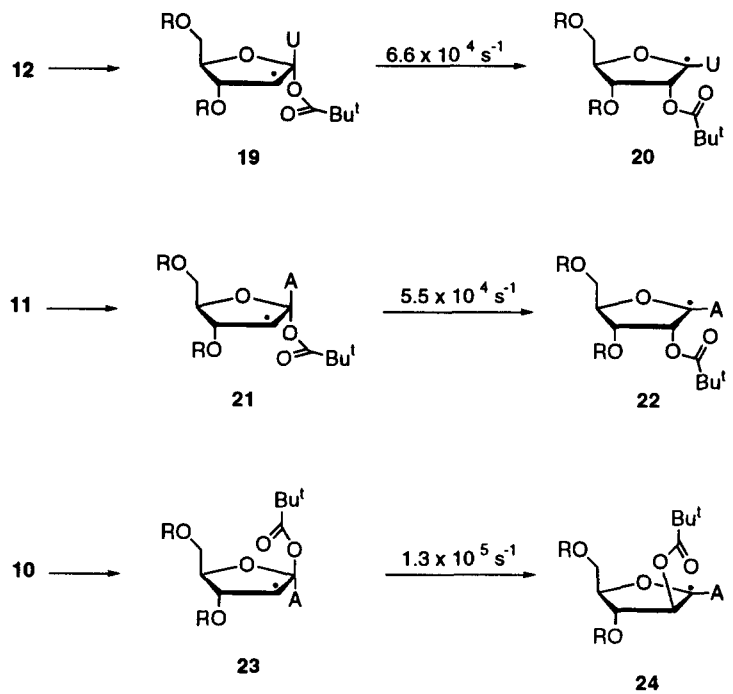


Inspection of Table 1 reveals that this scenario can be achieved if the hydride concentration changes appreciably during the course of the reaction (bimolecular process under second order conditions). Under these conditions the following relation holds:[18]

$$[RH]/[PH] = 1/[PH]\{[Bu_3SnH]_0 + k_r/k_H\}\{1 - e^{-k_H/k_r[PH]}\} - 1 \qquad (5)$$

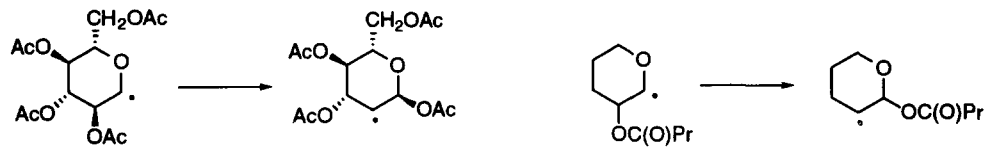
where [RH] is the direct reduction product, [PH] the rearranged reaction product(s) and $[Bu_3SnH]_0$ is the initial tin hydride concentration. When eq. 5 was applied to the experimental data of Table 1, the average k_r/k_H values of 0.018, 0.015 and 0.035 M were obtained for the starting nucleosides **12**, **11** and **10**, respectively. Taking $k_H = 3.65 \times 10^6\ M^{-1}\ s^{-1}$ for the reaction of Bu_3SnH with a secondary alkyl radical at 80 °C,[19] we calculated the k_r values to be 6.6×10^4, 5.5×10^4 and $1.3 \times 10^5\ s^{-1}$ for reactions **19** → **20**, **21** → **22**, and **23** → **24**, respectively (Scheme 4).[20] It can be seen in scheme 4 that (i) the rate constants are the same within experimental errors upon substitution of uracil by adenine in the same diastereotopic configuration and (ii) there is a small increase of the rate constants of the radical rearrangement going from α to β configuration of the bulky pivaloate within the adenine system.

Scheme 4



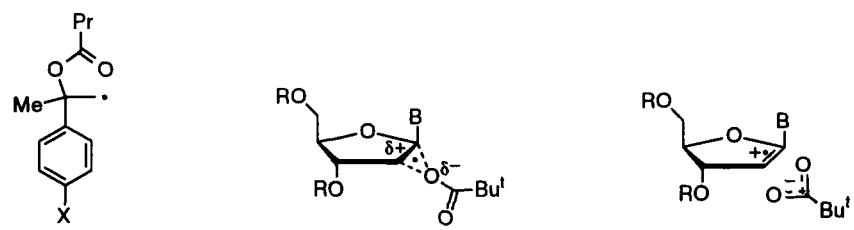
It should also be noted that the stereochemical β/α distribution depends on the nature of the cyclic radicals and follows the rule proposed by Giese, i.e., the preferred reaction occurs *anti* to the substituent adjacent to the radical center.[21] Thus, β/α ratios of 1:6 and 1:7 are observed for **20** and **22**, respectively, whereas a 12:1 β/α ratio is obtained for radical **24** (cf. Scheme 4).

This 1,2-migration of an acyloxy group to a free radical terminus was first reported thirty years ago[22] and has attracted considerable attention both from a synthetic and a mechanistic point of view.[23] Of interest to us are the reports of Giese[24] and Beckwith[25] on the rearrangement of glucosyl radical **25** into **26** and of β-(acyloxy)tetrahydropyranyl radical **27** into **28**. At first sight the fact that these rearrangements proceed to the less electronically stabilized radical **26** and **28** seems surprising. However, it was shown that in the absence of significant driving force, the β-(acyloxy)alkyl rearrangement does not occur readily (thermodynamic control).[26] Giese and coworkers[24] pointed out that the anomeric stabilization in the radical products is the driving force for these reactions. Conversely, in our systems a carbon-oxygen anomeric bond was cleaved in the course of the reaction, and therefore the stabilization of radicals **20**, **22** and **24** due to the uridine or adenine moieties must be at least as large as the anomeric stabilization.



25 **26** **27** **28**

On the other hand, Beckwith and Duggan have recently determined the rates of rearrangements of three *p*-substituted phenyl derivatives **29** by means of similar clock methodology.[27] The rate constants for X= CN, H and OMe are found to be 1.6×10^4, 6.2×10^4 and 1.7×10^5 s^{-1}, respectively, at 75 °C. A Hammett correlation indicates a polarized transition state which is further evidenced by the dependence of the rate constant of the unsubstituted derivative **29** on solvent polarity. Thus, it is now well established that there is a relationship between electronic environment (solvent or substituent effects) and rearrangement rate. The fact that the rate constants measured in the present work are of the same order of magnitude with those of Beckwith and Duggan, although the exothermicities are expected to be much lower, suggests that charge separation in the course of the reactions is an important issue for the pivaloate shift in nucleosides **10-12**. The transition state for these rearrangements is expected to be either like **30** or **31**, the three-center-five-electron mechanism (**30**) being less polarized than that of the five-center-five electron shift (**31**).[23]



29 **30** **31**

CONCLUSIONS

In summary we have disclosed two short and economical synthetic sequences for the preparation of protected 1',2'-didehydro-2'-deoxyadenosines, which involved in one case *N*-triphenylphosphoranylidene protection. These adenosines were used for the preparation of 2'-deoxy-2'-halogeno-1'-esters of adenosine through an electrophilic addition reaction. The scope and stereoselectivity of this reaction was studied and the conditions were optimized in order to maximize the yield of 2'-deoxy-2'-iodo-1'-pivaloate ester of α-D-adenosine.

Radical-based reductions of halopivaloates **10**, **11** and **12** afford C-1' radicals via a β-(acyloxy)alkyl rearrangement. By applying free-radical clock methodology the rate constant for these rearrangements is found to be 5-10x10^4 s^{-1} at 80 °C and is independent of the nature of base (uracil or adenine). Comparison with literature data led us to suggest that these rearrangements are mainly thermodynamically controlled, although polar effects should play a very important role in enhancing the rates. To our knowledge this is the first experimental evidence that in C-1' radicals are stabilized substantially by the presence of the base and the degree of stabilization is similar for purine and pyrimidine moieties.

EXPERIMENTAL PART

General. Unless otherwise stated, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on a Varian model VXR-200 FT-NMR spectrometer at 200 MHz and 50 MHz, respectively. Chemical shifts are expressed in ppm (δ) and coupling constants in Hertz (Hz). Infrared (IR) spectra were recorded on a Nicolet model 205 FT-IR spectrometer using KBr pellets. Melting points (m.p.) were determined on a Büchi model 510 or SMP-20 apparatus and are uncorrected. Column chromatography was performed by the method of Still using Merck 230-400 mesh ASTM silica gel 60. Analytical (TLC) and preparative (PLC) thin layer chromatography was performed using Merck 60 F_{254} 0.2 and 1 mm precoated silica gel plates, respectively. Compounds were visualized using ultraviolet light, iodine vapor, or by heating plates previously immersed in ammonium molybdate / ceric ammonium sulfate / sulfuric acid mixture. Solvents were freshly distilled prior to use. Diethyl ether (Et_2O) was distilled from $LiAlH_4$. Triethylamine (Et_3N) was distilled from calcium hydride. Benzene and toluene were distilled from sodium metal. Water content in organic solvents was measured by a Prolabo model Hydromat 2 coulorimetric Karl Fisher titration apparatus. All other reagents were used as received. All air- or moisture-sensitive reactions were conducted in oven or flame-dried glassware, and under an atmosphere of house nitrogen or argon. Moisture sensitive reagents were transferred through rubber septa using syringes or cannulas.

9-[3,5-bis-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-2-trifluoromethylsulfonyloxy-β-D-arabinofuranosyl]-9H-purin-6-amine (4a). To a stirred solution of **2a** (550 mg, 1 mmol) in dry pyridine (12.5 mL), under a nitrogen atmosphere, were added triethylamine (153 μL, 1.1 mmol) and 4-(dimethylamino)pyridine (122 mg, 1 mmol) and the solution was cooled to 0 °C. To the above solution was added trifluoromethanesulfonyl chloride (125 μL, 1.17 mmol) , at 0 °C, and the resulting mixture was stirred for 3 h at r.t.. It was then poured into ice (20 mL) and diluted with ethyl acetate (20 mL). The phases were separated, the organic phase was

washed with sat. aq. $NaHCO_3$ (10 mL x 2), and brine (10 mL x 2), and dried over $MgSO_4$, then filtered and evaporated under reduced pressure to yield 630 mg (100%) of **4a** as a yellow solid, which was further purified by recrystallization from hexane. R_f (ethyl acetate): 0.77. m.p. (hexane): 105-106 °C. ^1H NMR δ 0.01, 0.06, 0.17, 0.19 (s, 3H each, $SiCH_3$), 0.85, 0.95 (s, 9H each, $SiC(CH_3)_3$), 3.76 (dd, 1H, $J_{5\alpha',5\beta'}$ = 11.8 Hz, $J_{5\alpha',4}$ = 2.6, 5α'-H), 4.00 (dd, 1H, $J_{5'\beta,4}$ = 2.9 Hz, 5'β-H), 4.01 (ddd, 1H, 4'-H), 4.86 (dd, 1H, $J_{3',4'}$ = 4.7 Hz, 3'-H), 5.84 (dd, 1H, $J_{2',3'}$ = 4.4 Hz, 2'-H), 6.03 (bs, 2H, NH_2), 6.28 (d, 1H, $J_{1',2'}$ = 4.2 Hz, 1'-H), 8.06 (s, 1H, 2-H), 8.33 (s, 1H, 8-H). ^{13}C NMR δ -5.7, -5.0 (2 x $SiCH_3$), 17.8, 18.2 (SiC), 25.6, 25.7 ($SiC(CH_3)_3$), 61.4 (CH_2), 70.1 (CH), 84.9 (CH), 85.3 (CH), 86.4 (CH), 118.3 (q, J_{CF} = 320 Hz, CF_3), 119.9 (C), 139.1 (CH), 149.5 (C), 153.2 (CH), 155.8 (C). IR ν 2930, 2958, 1667, 1603, 1473, 1424, 1248, 1211, 1154, 1117, 842 cm^{-1}. Anal. Calcd for $C_{23}H_{40}F_3N_5O_6SSi_2$: C, 44.00; H, 6.42; N, 11.15; Found: C, 43.84; H, 6.40; N, 11.17.

9-[2-Deoxy-2-iodo-3,5-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]-β-D-arabinofuranosyl]-9H-purin-6-amine (5a). To a stirred solution of **4a** (1.5 g, 2.4 mmol) in dry benzene (6 mL) was added tetrabutylammonium iodide (2.3 g, 6.24 mmol) and the resulting mixture was refluxed for 4 h, under a nitrogen atmosphere. After cooling, the solution was treated with sat. aq. $NaHCO_3$ (10 mL) and after stirring for 30 min, it was diluted with ethyl acetate (10 mL), the phases were separated and the organic phase was washed with sat. aq. $Na_2S_2O_3$ and then dried over $MgSO_4$. Filtration and evaporation under reduced pressure yielded the crude product as a colored foam, which was purified via flash column chromatography (ethyl acetate: hexane 1:1) to render 945 mg (65%) of **5a** as a colorless foam. R_f (ethyl acetate): 0.54. m.p. (hexane): 167-168 °C. ^1H NMR δ 0.14 (s, 6H, $SiCH_3$), 0.16, 0.22 (s, 3H each, $SiCH_3$), 0.96 (s, 18H, $SiC(CH_3)_3$), 3.86-4.08 (m, 3H, 4'&5'-H), 4.62 (dd, 1H, $J_{2',3'}$ = 6.4 Hz, $J_{2',1'}$ = 6.1 Hz, 2'-H), 4.83 (dd, 1H, $J_{3',4'}$ = 6.4 Hz, 3'-H), 5.70 (bs, 2H, NH_2), 6.20 (d, 1H, 1'-H), 8.24 (s, 1H, 2-H), 8.36 (s, 1H, 8-H). ^{13}C NMR δ -5.3, -5.2, -4.7, -3.6 (CH_3), 17.8, 18.5 (C), 25.8 (3xCH_3), 26.0 (3xCH_3), 33.4 (CH), 62.2 (CH_2), 78.3 (CH), 84.2 (CH), 86.0 (CH), 119.5 (C), 138.4 (CH), 149.5 (C), 153.0 (CH), 155.7 (CH). IR ν 3313, 3163, 1676, 1604, 1252, 1101, 834 cm^{-1}. Anal. Calcd for $C_{22}H_{40}IN_5O_3Si_2$: C, 43.63; H, 6.66; N, 11.56; Found: C, 43.56; H, 6.73; N, 11.66.

9-[2-Deoxy-2-iodo-3,5-*O*-[(1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-D-arabinofuranosyl]-9H-purin-6-amine (5b). To a stirred solution of **4b**[9] (1.3 g, 2.0 mmol) in dry benzene (5 mL) was added tetrabutylammonium iodide (2.3 g, 6.24 mmol) and the resulting mixture was refluxed for 6 h, under a nitrogen atmosphere. After cooling, the solution was treated with sat. aq. $NaHCO_3$ (10 mL) and after stirring for 30 min, it was diluted with ethyl acetate (10 mL), the phases were separated, and the organic phase was washed with aq. $Na_2S_2O_3$ (10 mL x 2) and then dried over $MgSO_4$. Filtration and evaporation under reduced pressure yielded the crude product as a colored foam, which was purified via flash column chromatography (ethyl acetate: hexane, 1:1) to render 855 mg (69%) of **5b** as a colorless foam. R_f (ethyl acetate): 0.42. m.p. (EtOH): 164-166 °C (lit.[9] 165-168 °C). The spectroscopic data of the product were in complete agreement with the reported ones.[9]

9-[2-Deoxy-2-iodo-3,5-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]-β-D-arabinofuranosyl]-9H-purin-6-*N*-triphenylphosphoranylideneamine (3a). To a stirred solution of **2a** (440 mg, 0.88 mmol), triphenylphosphine (923 mg, 3.42 mmol), and imidazole (239 mg, 3.42 mmol) in dry toluene (44 mL) was

added iodine (335 mg, 2.61 mmol) and the resulting mixture was refluxed for 3 h under nitrogen atmosphere. After cooling, the solution was treated with sat. aq. $NaHCO_3$ (10 mL) and after stirring 30 min, it was diluted with ethyl acetate (10 mL), the phases were separated and the organic phase was washed with a sat. aq. $Na_2S_2O_3$ (10 mL x 2) and dried over $MgSO_4$. Filtration and evaporation under reduced pressure yielded the crude product as a colored foam which was purified via column chromatography (ethyl acetate: hexane 1: 1) to render 453 mg (59%) of **3a** as a colorless foam. R_f(ethyl acetate:hexane; 1:1): 0.26. m.p. (hexane): 151-152 °C. ^{1}H NMR δ 0.12 (s, 3H, $SiCH_3$), 0.14 (s, 6H, $SiCH_3$), 0.19 (s, 3H, $SiCH_3$), 0.81, 0.86 (s, 9H each, $SiC(CH_3)_3$), 3.92-4.06 (m, 3H, 4'&5'-H), 4.58 (dd, 1H, $J_{2',1'}$ = 5.9, $J_{2',3'}$ = 5.6 Hz, 2'-H), 4.82 (dd, 1H, $J_{3',4'}$, = 5.4 Hz, 3'-H), 6.11 (d, 1H, 1'-H), 7.42-7.53 (m, 9H, Ph), 7.90 (m, 6H, *o*-Ph), 8.07 (s, 1H, 2-H), 8.18 (s, 1H, 8-H). ^{13}C NMR δ -5.4, -5.3, -4.8, -3.8 (CH_3), 17.8 (C), 18.4 (C), 25.7 (3xCH_3), 26.0 (3xCH_3), 34.1 (CH), 62.3 (CH_2), 78.7 (CH), 84.0 (CH), 85.8 (CH), 128.0 (C), 128.1 (3xCH), 128.3 (3xCH), 130.0 (3xC), 131.7 (3xCH), 133.2 (3xCH), 133.4 (3xCH), 137.0 (C), 149.3 (C), 151.8 (CH), 160.8 (C). IR ν 2929, 1579, 1437, 1112, 838 cm^{-1}. Anal. Calcd for $C_{40}H_{53}IN_5O_3PSi_2$: C, 55.48; H, 6.17; N, 8.09; Found: C, 54.81; H, 6.20; N, 8.16.

9-[2-Deoxy-2-iodo-3,5-*O*-[(1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-β-D-arabinofuranosyl]-9H-purin-6-*N*-triphenylphosphoranylideneamine (3b). To a stirred solution of **2b** (510 mg, 2 mmol), triphenylphosphine (525 mg, 2 mmol), and imidazole (108 mg, 1.5 mmol) in dry toluene (25 mL) was added iodine (381 mg, 1.5 mmol) and the resulting mixture was refluxed for 6 h, under a nitrogen atmosphere. After cooling, the solution was treated with sat. aq. $NaHCO_3$ (10 mL), and after stirring for 30 min it was diluted with ethyl acetate (10 mL), the phases were separated and the organic phase was washed with sat. aq. $Na_2S_2O_3$ (20 mL x 2), H_20 (20 mL x 2), and then dried over $MgSO_4$. Filtration and evaporation under reduced pressure yielded the crude product as a colored foam, which was further purified via flash column chromatography (ethyl acetate:hexane; 1:1) to render 211 mg (58%) of **3b** as a colorless foam. R_f(ethyl acetate): 0.70. m.p. (hexane) 95-96 °C. ^{1}H NMR δ 0.10 (28H, 4x*i*-Pr), 3.84 (ddd, 1H, 4'-H), 4.11 (dd, 1H, $J_{5'\alpha,5'\beta}$ = 13.8, $J_{5'\alpha,4'}$ = 3.0 Hz, 5'α-H), 4.24 (dd, 1H, $J_{5'\beta,4'}$ = 4.4 Hz, 5'β-H), 4.68 (dd, 1H, $J_{3',4'}$ = 6.7 Hz, 3'-H), 4.98 (dd, 1H, $J_{2',3'}$ = 7.8 Hz, 2'-H), 6.2 (d, 1H, $J_{1',2'}$ = 6.6 Hz, 1'-H), 7.44-7.48 (m, 9H, Ph), 7.90 (m, 6H, *o*-Ph), 8.06 (s, 1H, 2-H), 8.09 (s, 1H, 8-H). ^{13}C NMR (C_6D_6) δ 13.1, 13.2, 13.5 & 14.0 (CH), 17.3, 17.6 (CH_3), 17.7 (2xCH_3), 31.5 (CH), 63.3 (CH_2), 79.3 (CH), 84.4 (CH), 85.0 (CH), 129.2 (C), 131.2 (3xC), 131.7 (3xCH), 132.6 (6xCH), 132.8 (6x CH), 138.2 (CH), 150.2 (C), 152.0 (CH), 161.8 (C). IR ν 2945, 1580, 1449, 1138, 1111, 1166, 1036 cm^{-1}. Anal. Calcd for $C_{40}H_{51}IN_5O_4PSi_2$: C, 54.60; H, 5.84; N, 7.96; Found: C, 54.48; H, 5.90; N, 7.94.

1',2'-Didehydro-2'-deoxy-3',5'-bis-*O*-[(1,1,dimethylethyl)dimethylsilyl]adenosine (6a). To a stirred solution of **5a** (1.0 g, 1.65 mmol) in dry pyridine (16.5 mL) was added dropwise 1,5-diazobicyclo[4.3.0]non-5-ene (815 μL, 6.6 mmol) and the resulting mixture was stirred for 3 hours at r.t.. The solution was partitioned between ethyl acetate (20 mL) and H_2O (10 mL), the phases were separated and the organic phase was washed with 5 mL of aq. HCl (1%), aq. $NaHCO_3$ (20 mL x 2), brine (20 mL x 2) and was then dried over $MgSO_4$. Filtration and evaporation under reduced pressure yielded the crude product as a yellow solid which was further purified by recrystallization from hexane to yield 670 mg (85 %) of **6a** as white flakes. R_f(hexane: ethyl acetate; 1:1): 0.54. m.p. (hexane): 164-165 °C. ^{1}H NMR (C_6D_6) δ 0.00, 0.03 (s, 3H each,

$SiCH_3$), 0.16 (s, 6H, SiCH3), 0.91, 1.00 (s, 9H each, $SiC(CH_3)_3$), 3.55 (dd, 1H, $J_{5'a,5'\beta}$ = 11.0, $J_{5'\alpha,4'}$ = 5.7 Hz, 5'α-H), 3.66 (dd, 1H, $J_{5'\beta,4'}$ = 5.4 Hz, 5'β-H), 4.61 (ddd, 1H, $J_{4',3'}$ = 2.6 Hz, 4'-H), 5.21 (dd, 1H, $J_{3',2'}$ = 2.7 Hz, 3'-H), 5.31 (bs, 2H, NH_2), 6.30 (d, 1H, H-2'), 7.96 (s, 1H, 2-H), 8.60 (s, 1H, 8-H). ^{13}C NMR (C_6D_6) δ -5.4, -5.3, -4.3, -4.0 (CH_3), 18.2 (C), 18.4 (C), 25.9 (3xCH_3), 26.0 (3xCH_3), 63.0 (CH_2), 76.8 (CH), 88.2 (CH), 89.8 (CH), 120.6 (C), 136.6 (CH), 147.3 (C), 149.5 (C), 154.3 (CH), 156.5 (C). IR ν 1678, 1603, 1472, 835 cm^{-1}. Anal. Calcd for $C_{22}H_{39}N_5O_3Si_2$: C, 55.31; H, 8.23; N, 14.66; Found: C, 55.42; H, 8.40; N, 14.30.

1',2'-Didehydro-2'-deoxy-3,5-*O*-[(1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]adenosine (6b). To a stirred solution of **5b** (1.0 g, 1.65 mmol) in dry pyridine (16.5 mL) was added dropwise 1,5-diazobicyclo[4.3.0]non-5-ene (815 μL, 6.6 mmol), the resulting mixture was stirred for 4 h at r.t.. The solution was diluted with 20 mL of ethyl acetate and 10 mL of H_2O, the phases were separated and the organic phase was washed with 5 mL of aq. HCl (1%), sat. aq. $NaHCO_3$ (20 mL x 2), brine (20 mL x 2) and was then dried over $MgSO_4$. Filtration and evaporation under reduced pressure yielded the crude product as a yellow solid which was further purified by recrystallization from hexane to yield 730 mg (90 %) of **6b** as white crystals. R_f(hexane: ethyl acetate; 1:1): 0.54. The spectroscopic data of the product were in complete agreement with the reported ones.[6]

1',2'-Didehydro-2'-deoxy-3',5'-bis-*O*-[(1,1,-dimethylethyl)dimethylsilyl]-N^7-triphenylphosphoranylideneadenosine (7a). To a stirred solution of **3a** (200 mg, 0.23 mmol) in dry pyridine (2.3 mL) was added dropwise 1,5-diazobicyclo[4.3.0]non-ene (113 μL, 0.92 mmol) and the resulting mixture was stirred for 24 h at r.t. under a nitrogen atmosphere. The solution was diluted with 10 mL of ethyl acetate and 5 mL of H_2O, the phases were separated and the organic phase was washed with aq. HCl (5 mL, 1%), sat. aq. $NaHCO_3$ (10 mL x 2), brine (10 mL x 2) and then dried over $MgSO_4$. Filtration and evaporation under reduced pressure yielded the crude product as a yellow solid, which was further purified by crystallization from hexane to furnish 112 mg (66 %) as white crystals. R_f(hexane: ethyl acetate; 1:1): 0.45. m.p. (hexane): 146-147 °C. ^1H NMR δ 0.03, 0.06, 0.10, 0.12 (s, 3H each, $SiCH_3$), 0.87, 0.89 (s, 9H each, $SiC(CH_3)_3$), 3.68 (dd, 1H, $J_{5'\alpha,5'\beta}$ = 16.8, $J_{5'\alpha,4}$ = 5.9 Hz, 5'α-H), 3.80 (dd, 1H, $J_{5'\beta,4}$ = 5.9 Hz, 5'β-H), 4.52 (ddd, 1H, $J_{4',3'}$ = 2.6 Hz, 4'-H), 5.08 (dd, 1H, $J_{3',2'}$ = 2.6 Hz, 3'-H), 5.72 (d, 1H, 2'-H), 7.49-7.59 (m, 9H, Ph), 7.89 (m, 6H, *o*-Ph), 8.10 (s, 1H, 2-H), 8.15 ppm (s, 1H, 8-H). ^{13}C NMR δ -5.4 (2xCH_3), -4.8 (CH_3), -4.2 (CH_3), 18.0 (C), 18.3 (C), 25.8 (3xCH_3), 25.9 (3xCH_3), 62.9 (CH_2), 76.3 (CH), 87.1 (CH), 89.2 (CH), 128.0 (C), 128.2 (CH), 128.5 (CH), 130.0, 131.8, 131.9, 133.2 (CH), 133.4 (CH), 136.0 (CH), 147.1 (C), 152.8 (CH). IR ν 1583, 1553, 1452, 1116, 837 cm^{-1}. Anal. Calcd for $C_{40}H_{52}N_5O_3PSi_2$: C, 65.10; H, 7.10; N, 9.49; Found: C, 65.50; H, 7.11; N, 9.44.

Iodopivaloxylation of 6a. To a stirred solution of **6a** (1.00 g, 2.1 mmol) in dry ethyl ether (25 mL), was added pivalic acid (1.07 g, 10.5 mmol), and, after cooling at 0 °C, N-iodosuccinimide (567 mg, 2.52 mmol). The resulting mixture was stirred for 4.5 h under a nitrogen atmosphere. The resulting solution was treated with sat. aq. NaS_2O_3 (20 mL) and after stirring for 30 min it was diluted with ethyl acetate (20 mL), the phases were separated and the organic phase was washed with sat. aq. $NaHCO_3$ (20 mL x 2), brine (20 mL x 2) and then dried over Na_2SO_4. Filtration and evaporation under reduced pressure yielded the crude product as a foam (1.55 g) which was purified via flash column chromatography (ethyl ether), to render 1.41 g (2.0 mmol, 95 %) of a diastereomeric mixture of **8-11** which was analyzed by ^1H NMR spectroscopy.

Diastereomerically pure products were isolated through careful flash column chromatography of the crude mixtures (40 % ethyl acetate in hexanes) which yielded 89 mg of **8** (6.3 %), 44 mg of **9** (3.2 %), 920 mg of **10** (66 %), and 348 mg of **11** (25 %):

2'-Deoxy-3',5'-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]-1'-C-(2,2-dimethyl-1-oxopropoxy)-2'-iodoadenosine (8). m.p. (hexane): 139-140 °C ^{1}H NMR δ 0.06 (s, 6H, $SiCH_3$), 0.08, 0.20 (s, 3H, $SiCH_3$), 0.74 (s, 9H, $SiC(CH_3)_3$), 0.92 (s, 9H, $SiC(CH_3)_3$, 1.21 (s, 9H, $COC(CH_3)_3$) 3.67 (dd, 1H, $J_{5'\alpha,5'\beta}$ = 12.0, $J_{5'\alpha,4'}$ = 1.9 Hz, 5'α–H), 3.86 (dd, 1H, $J_{3',2'}$ = 5.3 Hz, 3'-H), 3.98 (dd, 1H, $J_{5'\beta,4'}$ = 2.2 Hz, 5'β-H), 4.33 (ddd, 1H, 4'-H), 5.71 (bs, 2H, NH_2), 6.26 (d, 1H, 2'-H), 8.15 (s, 1H, 2-H), 8.33 ppm (s, 1H, 8-H). NOE: irradiation of H-3' resulted in a 12% NOE on H-2' and a 4.6% on H-4'. ^{13}C NMR δ -5.7 (2xCH_3), -4.8, -4.3 (CH_3), 18.0, 18.2 (C), 25.8, 26.8 (CH_3), 29.6 (C), 46.3 (CH_2), 59.9, 68.9, 85.7 (CH), 109.7, 119.4 (C), 139.6 (CH), 148.9 (C), 152.9 (CH), 155.6, 174.9 (C). IR ν 1767, 1687, 1608, 1470, 1119, 1087, 837 cm^{-1}. Anal. Calcd for $C_{27}H_{48}IN_5O_5Si_2$: C, 45.95; H, 6.85; N, 9.92 ; Found: C, 45.65; H, 6.79; N, 9.88.

9-[2-Deoxy-3,5-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]-1-C-(2,2-dimethyl-1-oxopropoxy)-2-iodo-α-D-arabinofuranosyl]-9H-purin-6-amine (9). m.p. (hexane): 99-100 °C. ^{1}H NMR δ 0.03, 0.10, 0.11 (s, 3H each, $SiCH_3$), 0.56, 0.92 (s, 9H each, t-BuSi), 1.18 (s, 9H, t-BuCO_2), 4.09 (m, 2H, 5'-H), 4.35 (ddd, 1H, $J_{4',5'\alpha}$ = 7.5, $J_{4',5'\beta}$ = 5.9 Hz, $J_{4',3'}$ = 2.6 Hz 4'-H), 4.77 (dd, 1H, $J_{3,2'}$ = 2.2 Hz, 3'-H), 5.53 (d, 1H, 2'-H), 5.69 (bs, 2H, NH_2), 8.18 (s, 1H, 2-H), 8.34 (s, 1H, 8-H). NOE: irradiation of H-3' resulted in a 4.9% NOE on H-2'. ^{13}C NMR δ -5.2 (2xCH_3), -5.16, -4.70 (CH_3), 17.4, 18.4 (C), 25.2, 26.0, 26.8 (CH_3), 29.7 (C), 39.8 (CH_2), 64.3, 79.8, 90.2 (CH), 109.2, 120.2 (C), 140.0 (CH), 149.0 (C), 153.0 (CH), 155.3, 174.3 (C). IR ν 1763, 1680, 1604, 1253, 1131 cm^{-1}. Anal. Calcd for $C_{27}H_{48}IN_5O_5Si_2$: C, 45.95; H, 6.85; N, 9.92 ; Found: C, 45.75; H, 6.83; N, 9.95.

9-[2-Deoxy-3,5-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]-1-*C*-(2,2-dimethyl-1-oxopropoxy)-2-iodo-α-D-ribofuranosyl]-9H-purin-6-amine (10). m.p. (hexane): 142-143 °C. ^{1}H NMR δ 0.09, 0.10, 0.16, 0.19 (s, 3H each, $SiCH_3$), 0.92, 0.94 (s, 9H each, Si $C(CH_3)_3$), 1.10 (s, 9H, $COC(CH_3)_3$), 3.76 (dd, 1-H, $J_{5'\alpha,5'\beta}$ = 12.0, $J_{5\alpha',4'}$ = 4.6 Hz, 5'α-H), 3.85 (dd, 1H, $J_{3',4'}$ = 8.2, $J_{3',2'}$ = 4.9 Hz, 3'-H), 4.01 (dd, 1H, $J_{5'\beta,4'}$ =2.2 Hz, 5'β-H), 4.40 (ddd, 1H, 4'-H), 5.37 (d, 1H, 2'-H), 5.62 (bs, 2H, NH_2), 8.20 (s, 1H, 2-H), 8.32 (s, 1H, 8-H). ^{13}C NMR (50 MHz; $CDCl_3$) δ -5.2, -5.1, -4.7, -4.4 (CH_3), 18.1, 18.6 (C), 25.8, 26.1, 26.8 (CH_3), 39.4 (C), 44.3 (CH_2), 62.1, 69.8, 86.4 (CH), 110.8, 120.3 (C), 139.7 (CH), 148.5 (C), 153.0 (CH), 155.4, 174.3 (C). IR ν 2496, 1769, 1673, 1606, 1473 cm^{-1}. Anal. Calcd for $C_{27}H_{48}IN_5O_5Si_2$: C, 45.95; H, 6.85; N, 9.92; Found: C, 45.79; H, 6.86; N, 9.94.

9-[2-Deoxy-3,5-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]-1-*C*-(2,2-dimethyl-1-oxopropoxy)-2-iodo-β-D-arabinofuranosyl]-9H-purin-6-amine (11). m.p. (hexane): 150-152 °C. ^{1}H NMR δ 0.12 (s, 3H, $SiCH_3$), 0.13 (s, 6H, $SiCH_3$), 0.20 (s, 3H, $SiCH_3$), 0.93 (s, 18H, t-BuSi), 1.15 (s, 9H, t-BuCO_2), 4.01 (d, 2H, $J_{5',4'}$ = 4.6 Hz, 5'-H), 4.23 (td, 1H, $J_{4',3'}$ = 3.8 Hz, 4'-H), 5.00 (dd, 1H, $J_{3',2'}$ = 1.6 Hz, 3'-H), 5.06 (d, 1H, 2'-H), 5.93 (bs, 2H, NH_2), 8.17 (s, 1H, 2-H), 8.32 (s, 1H, 8-H). ^{13}C NMR δ -5.3, -5.2, -4.9, -4.0 (CH_3), 17.9, 18.5 (C), 25.8, 26.0, 26.8 (CH_3), 36.7 (CH_2), 39.7 (C), 62.6, 81.8, 89.1 (CH), 111.1, 120.0 (C), 139.3 (CH), 148.5 (C), 153.0

(CH), 155.4, 175.3 (C). IR ν 1759, 1670, 1260, 1255, 1119, 1107, 839 cm^{-1}. Anal. Calcd for $C_{27}H_{48}IN_5O_5Si_2$: C, 45.95; H, 6.85; N, 9.92; Found: C, 45.85; H, 6.80; N, 9.88.

Reduction of compound 12; Representative procedure. A solution of **12**[3a] (63.6 mg, 0.1 mmol) in C_6D_6 (2 mL), containing AIBN (1.6 mg, 0.01 mmol) as the radical initiator and toluene (10 μL) as an internal standard, in a 5-mL Wheaton® conical reaction vial, was carefully deoxygenated by repeated freeze-vacuum-thaw-nitrogen-gas cycles. The solution was then brought to 80 °C and immediately treated with a single injection of Bu_3SnH (35 mg, 0.12 mmol). The progress of the reaction was monitored after 7, 17 and 30 min reaction by fast cooling of the reaction vials in an acetone/dry ice bath, allowing them to warm to room temperature and obtaining ~0.6 mL aliquots for ^1H NMR analysis. The product distribution was calculated by careful integration of the H-6 signals for the uridine base (8.06, 7.42, and 7.62 ppm for **13**, **14** (α-anomer), and **14** (β-anomer), respectively) and by using the integral of the toluene methyl group (at 2.10 ppm) as the internal standard (see Table I). After 30 min at 80 °C, the reaction mixture was concentrated and was purified by flash column chromatography (40 % ethyl acetate/hexanes) to yield **14** (15 mg, 27 % as a 6:1 anomeric mixture). Due to decomposition of **13** during column chromatography, it was characterized from the ^1H NMR of the crude product:

2'-Deoxy-3',5'-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]-1'-*C*-(2,2-dimethyl-1-oxopropoxy)-uridine (13). ^1H NMR (C_6D_6) δ -0.09, -0.08, 0.25, 0.34 (s, 3H each, $SiCH_3$), 0.81, 0.95 (s, 9H each, $SiC(CH_3)_3$), 1.19 (s, 9H, $COC(CH_3)_3$), 2.82 (dd, 1H, $J_{2'\alpha,2'\beta}$ = 14.1, $J_{2'\alpha,3'}$ = 5.7 Hz, 2'α–H), 3.32 (dd, 1H, $J_{2'\beta,3'}$ = 3.5 Hz, 2'β-H) 3.42 (m, 2H, 5'–H), 4.34 (m, 2H, 3'&4'-H), 5.55 (d, 1H, $J_{5,6}$ = 8.2 Hz, 5-H), 8.06 (d, 1H, 6-H), 9.63 (bs, 1H, NH).

9-[2-*O*-Trimethylacetyl-3,5-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]-α-D-ribofuranosyl]-9H-purin-6-amine (14, α-anomer). ^1H NMR (C_6D_6) δ 0.00, 0.01, 0.07, 0.09 (s, 3H each), 0.89, 0.97, 1.10 (s, 9H each), 3.56 (dABq, 2H, *J* = 11.6, 0.8 Hz), 3.98 (dt, 1H, *J* = 5.3, 0.8 Hz), 4.41 (t, 1H, *J* = 5.3 Hz), 5.57 (d, 1H, *J* = 8.1 Hz), 5.60 (t, 1H, *J* = 5.3 Hz), 6.46 (d, 1H, *J* = 5.3 Hz), 7.42 (d, 1H, *J* = 8.1 Hz). ^{13}C NMR (C_6D_6) δ -5.44, -5.29, -5.20, -4.78 (CH_3), 18.0, 18.5 (C), 25.8, 26.0, 27.2 (CH_3), 38.9 (C), 62.5 (CH_2), 71.1, 72.3, 84.8, 86.1, 101.2, 141.1 (CH), 150.7, 163.3, 176.3 (C).

2'-*O*-Trimethylacetyl-3',5'-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]- adenosine (14, β-anomer). ^1H NMR (C_6D_6) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.07 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 0.94 (s, 9H), 1.24 (s, 9H), 3.65 (dABq, 2H, J = 11.7, 2.0 Hz), 3.97 (dt, 1H, J = 4.6, 2.0 Hz), 4.50 (t, 1H, J = 4.6 Hz),5.45 (t, 1H, J = 4.6 Hz), 5.58 (d, 1H, J = 8.2 Hz), 6.28 (d, 1H, J = 4.6 Hz), 7.62 (d, 1H, J = 8.2 Hz), 9.40 (bs, 1H). ^{13}C NMR (C_6D_6) δ -5.58, -5.46, -5.02, -4.54 (CH_3), 18.2, 18.5 (C), 25.9, 26.0, 27.2 (CH_3), 38.9 (C), 61.9 (CH_2), 70.0, 75.8, 85.3, 88.0, 102.7, 139.4 (CH), 150.5, 163.2, 176.9 (C).

Independent synthesis of anomeric mixture 14. To a stirred solution of 3',5'-di(*t*-butyldimethylsilyl)-β-uridine[7] (672 mg, 1.42 mmol) in dry pyridine (8 mL), were added trimethylacetyl chloride (0.70 mL, 5.7 mmol) followed by DMAP (140 mg, 1.14 mmol) and the resulting mixture was stirred for 1 h at 25 °C. The solution was partitioned between ethyl acetate (20 mL) and H_2O (10 mL), the phases were separated and the

organic phase was washed with 5 mL of aq. HCl (1%), aq. $NaHCO_3$ (20 mL x 2), brine (20 mL x 2) and was then dried over $MgSO_4$. Filtration and evaporation under reduced pressure yielded the crude product as a yellow foam (900 mg, 99%). ^{13}C NMR demonstrated that it corresponded to a 2',4-*O*-dipivaloate : ^{13}C NMR (C_6D_6) -5.10, -5.05, -4.86, -4.54 ($SiCH_3$), 18.2, 18.5 (SiC), 26.0, 26.1 ($SiC(\underline{C}H_3)_3$), 27.3, 27.4 (C(O) $C(\underline{C}H_3)_3$), 38.9, 43.9 (C(O) $\underline{C}(CH_3)_3$), 62.7 (CH_2), 70.8, 75.7, 86.5, 87.0, 102.5, 139.4 (CH), 149.5 (C), 161.9, 177.0, 183.2 (CO). This product was then dissolved in ethanolic KOH (0.1 N, 15 mL) and stirred at r.t., overnight. Column chromatography (40 % ethyl acetate/hexanes) yielded 240 mg (30%) of the pure β-anomer of **14** as a white foam. This material was subsequently dissolved in 1,2-dichloroethane (5 mL) and treated with bis(trimethylsilyl)acetamide (0.21 mL, 1.3 mmol) and uracil (93 mg, 0.83 mmol) and the resulting mixture was refluxed for 30 min. After cooling to r.t., the reaction mixture was treated with trimethylsilyl triflate (98 μL, 0.54 mmol) and was further refluxed for 4 h. It was then cooled to r.t., partitioned between CH_2Cl_2 (20 mL), and sat. aq. $NaHCO_3$ and stirred vigorously for 30 min. The resulting precipitate was filtered, the filtrate was washed with H_2O (10 mL), and dried over Na_2SO_4. Filtration and evaporation under reduced pressure gave the crude product which was purified with flash column chromatography (40% ethyl acetate/hexanes) to give 122 mg (51%) of a 1.2:1 (α:β) anomeric mixture **14**, the ^1H NMR spectrum of which was in agreement with that reported in the reduction of **12**.

Reduction of compound 11. The same procedure, as described for compound **12** above, was used. The reaction between **11** (70 mg, 0.1 mmol) and Bu_3SnH (19 mg, 0.032 M) was completed within 30 min. The product distribution was calculated by integration of the H-2 signals for the adenine base (8.56, 8.32, and 7.94 ppm for **15**, **16** (α-anomer), and **16** (β-anomer), respectively). The unstable orthoamide **15** decomposed upon attempted purification and it was therefore characterized from the crude mixture:

2'-Deoxy-3',5'-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]-1'-*C*-(2,2-dimethyl-1-oxopropoxy)-adenosine (15). ^1H NMR (C_6D_6) δ 0.00, 0.02, 0.13, 0.15 (s, 3H each, $SiCH_3$), 0.90 (s, 18H, $SiC(CH_3)_3$), 1.12 (s, 9H, $COC(CH_3)_3$), 3.37 (dd, 1H, $J_{2'\alpha,2'\beta}$ = 14.0, $J_{2'\alpha,3'}$ = 5.5 Hz, 2'α–H), 3.51 (dd, 1H, $J_{2'\beta,3'}$ = 6.8 Hz, 2'β-H) 3.56 (dd, 1H, $J_{5'\alpha,5'\beta}$ = 11.6, $J_{5'\alpha,4'}$ = 2.7 Hz, 5'α–H), 3.67 (dd, 1H, $J_{5'\beta,4'}$ = 3.0 Hz, 5'β-H), 4.45 (ddd, 1H, $J_{4',3'}$ = 5.2 Hz, 4'-H), 4.66 (ddd, 1H, 3'-H), 5.71 (bs, 2H, NH_2), 8.57 (s, 1H, 2-H), 8.61 (s, 1H, 8-H).
The crude concentrate (52 mg) was dissolved in ethanolic KOH (1 N, 2 mL) and refluxed for 1 h or until TLC (10 % MeOH/EtOAc) showed complete deprotection. Flash column chromatography (10 % MeOH/EtOAc) yielded a white powder (9 mg, 34% from **11**) which was characterized by ^1H NMR through comparison with commercially available samples.

Adenosine ^1H NMR (D_2O) δ 6.06 (d, 1H, J = 6.0 Hz, 1'-H) [ref (28) δ 6.06 (J = 6.0 Hz)].

α-Adenosine ^1H NMR (D_2O) δ 6.32 (d, 1H, J = 4.6 Hz, 1'-H). [ref (16) δ 6.30 (J = 4.5 Hz)].

Reduction of compound 10. The same procedure, as described for compound **12** above, was used. The reaction between **10** (70 mg, 0.1 mmol) and $BuSn_3H$ (30 mg, 0.052 M) was completed within 15 min. The product distribution was calculated by integration of the H-2 signals for the adenine base (8.47, 8.07, 8.13, and 7.96 ppm for **17**, **18** (α-anomer), **18** (β-anomer), and **6a**, respectively). The unstable orthoamide **17**

decomposed slowly during the reaction and it was therefore characterized from the ^{1}H NMR spectra of the reaction mixture:

9-[2-Deoxy-3,5-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]-1-C-(2,2-dimethyl-1-oxopropoxy)-α-D-ribofuranosyl]-9H-purin-6-amine (17). ^{1}H NMR (200 MHz; C_6D_6) δ -0.18, -0.06, 0.07, 0.08 (s, 3H each, $SiCH_3$), 0.71, 0.97 (s, 9H each, Si $C(CH_3)_3$), 1.08 (s, 9H, $COC(CH_3)_3$), 3.19 (dd, 1H, $J_{2'\alpha,2'\beta}$ = 14.2, $J_{2\alpha',3'}$ = 5.9 Hz, 2'α-H), 3.48 (dd, 1H, $J_{2'\beta,3'}$ = 3.4 Hz, 2'β-H),), 3.76 (dd, 2H, $J_{5',4'}$ = 5.1 Hz, 5'-H), 4.22 (td, 1H, $J_{4',3'}$ = 5.0 Hz, 4'-H), 4.56 (ddd, 1H, 3'-H), 5.83 (bs, 2H, NH_2), 8.47 (s, 1H, 2-H), 8.61 ppm (s, 1H, 8-H).
The crude concentrate (54 mg) was deprotected as described above for **11**. The product (12 mg, 45% from **10**) was characterized by ^{1}H NMR through comparison with literature data:

9-(α-D-Arabinofuranosyl)adenine ^{1}H NMR (200 MHz; dmso-d_6) δ 5.92 (d, 1H, J = 5.3 Hz, 1'-H), 8.25 (s, 1H), 8.40 ppm (s, 1H). [ref (17)) δ 5.95 (J = 5.5 Hz), 8.26 (s, 1H), 8.40 ppm (s, 1H)].

9-(β-D-Arabinofuranosyl)adenine ^{1}H NMR (200 MHz; dmso-d_6) δ 6.26 (d, 1H, J = 4.8 Hz, 1'-H), 8.14 (s, 1H), 8.19 ppm (s, 1H). [ref (18)) δ 6.26 (d, 1H), 8.13 (s, 1H), 8.18 ppm (s, 1H)].

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