Radical Cyclization Approach to Cyclonucleosides

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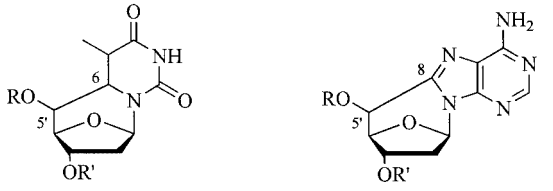
Efficient methodologies based on consecutive radical reactions for the preparation of cyclonucleosides **5** and **13** are reported. The reactions were performed on modified thymidine and 2′-deoxyadenosine substrates using $(TMS)_3SiH$ as the reducing agent. The protected 5′-carbaldehyde **3** afforded the cyclonucleoside **4** in 85% yield and in a diastereoisomeric ratio **4a**/**4b** = 3:7. The mono-desilylation at the 5′-*O* position of these cyclonucleosides has been successfully achieved by UV irradiation affording quantitatively derivatives **5a** and **5b**. The protected 5′-carbaldehyde **10** afforded the cyclonucleoside **12** in 70–75% yield as a single diastereoisomer (5′*R*) either in deoxygenated solution, followed by in situ oxidation of the reaction mixture by chloranil, or in aerobic conditions. The photochemical 5′-*O*-desilylation of **12** has been obtained in 56% yield affording the cyclopurine **13**. The reaction mechanisms have been studied in some detail using a variant of the radical clock methodology. The C5′ radical **6** or **15**, generated by addition of the $(TMS)_3Si^{\cdot}$ radical to the corresponding aldehyde, undergoes a 6-*exo-trig* cyclization on the base moiety prior to termination. The rate constants for both 6-*exo-trig* radical cyclizations have been estimated to be close to $10^5\ s^{-1}$ at 86 °C, the cyclization on the purine moiety being 4–5 times faster than that on the pyrimidine group.

Introduction

Cyclopurine and cyclopyrimidine lesions are observed among the decomposition products of DNA, when exposed to ionising radiations or to some antitumor agents.[1,2] Two examples of interest to us are 5′,6-cyclo-5,6-dihydrothymidine (**1**) and 5′,8-cyclo-2′-deoxyadenosine (**2**). Apart from the usual glycosidic bond in these moieties there is an additional base-sugar linkage between the C6 position of pyrimidine or C8 position of purine and the C5′ position of the 2′-deoxyribose. Lesions **1** and **2** may be formed in different diastereoisomeric forms, differing in the configuration at the C5′ position in both cases, as well as in the configuration of C5 and C6 in the pyrimidine derivative. From a mechanistic point of view, it has been verified that the C5′ radical, initially generated by hydrogen abstraction, intramolecularly attacks the double bond of the base moiety to form a cyclonucleotide as the final product, after oxidation or reduction (Scheme 1).[3,4]



1 **2**

Scheme 1. Examples of 5′,6-cyclopyrimidines and 5′,8-cyclopurine lesions.

The synthesis of **1** in a diastereoisomeric ratio (5′*S*,6*S*,5*R*)/(5′*S*,6*S*,5*S*) = 1:2.7 and in 61% yield was accomplished by $Bu_3Sn^{\cdot}$-mediated intramolecular cyclization of the corresponding 5′-carbaldehyde.[5] The (5′*S*)-isomer of **2** was prepared by the same research group in seven steps starting from N^6-benzoyl-2′-deoxyadenosine in an overall yield of <10%.[6] The preparation of the (5′*R*)-isomer of **2** was achieved by two additional steps, involving inversion of configuration at the C5′ position.[7]

Synthesis of modified 2′-deoxynucleosides containing specific DNA lesions and their incorporation into a defined sequence of oligonucleotides has been an outstanding approach to investigate the biological consequences. Synthetic oligonucleotides that contain the modified nucleosides **1**[5] or **2**[6,7] as well as similar cyclopurine[7] and cyclopyrimidine[8] moieties were also prepared. Recent studies have shown that the chemical synthesis of these lesions and their incorporation on specific sites of DNA are of considerable importance in order to investigate, in detail, the biochemical and biophysical features of the double helix damage.[9,10]

In our laboratory, a synthetically useful radical cascade process has been developed that allows the conversion of 8-bromo-2′-deoxyadenosine to **2** in a one-pot procedure. Using γ irradiation as a source of solvated electrons in

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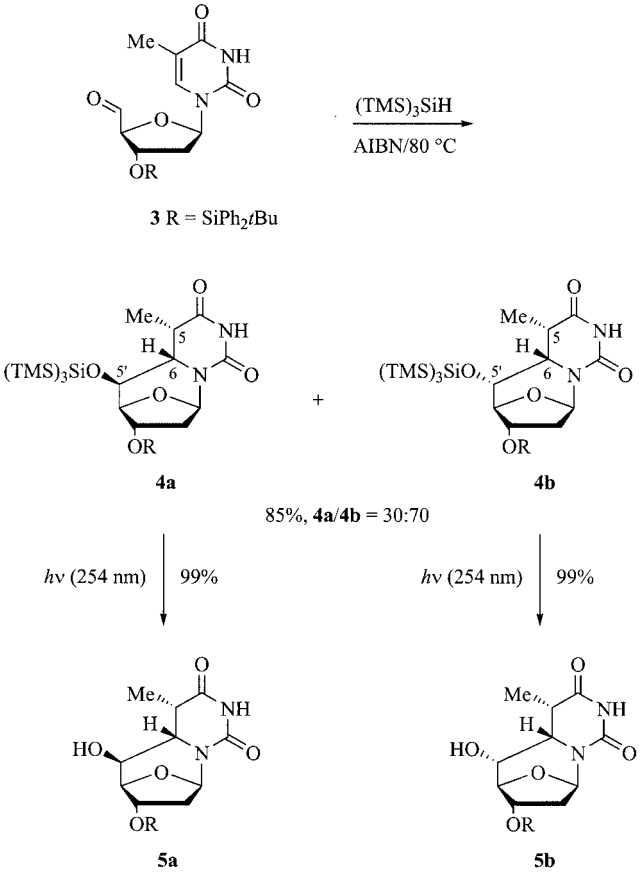
water, a diastereoisomeric ratio (5′*R*)/(5′*S*) = 6:1 in 70% overall yield (based on the recovered starting bromide) was obtained,[3] whereas UV irradiation in acetonitrile afforded a ratio (5′*R*)/(5′*S*) = 1.7:1 in 65% overall yield.[4] However, attempts to obtain the targeted phosphoramidite required for the synthesis of oligonucleotides failed due to the difficulties in differentiating the two secondary hydroxyl groups by the appropriate protective group. In this paper, we describe the cyclization of 5′-carbaldehydes **3** and **10** using $(TMS)_3SiH$ as the mediator[11] under a variety of conditions. Our main objective was to obtain a procedure for the preparation of some of the diastereoisomers of **1** and **2**, which overcomes the limitations of the existing approaches, mainly due to low yield multiple-step synthesis, or to diastereomeric mixtures that are difficult to separate, or to difficulties in differentiating the two secondary hydroxyl groups by appropriate protective groups. We also report kinetic studies of C5′ radical cyclizations using free-radical clock methodology.[12]

Results and Discussion

Reaction of $(TMS)_3SiH$ with 5′-Carbaldehyde 3: Aldehyde **3** is easily obtained from 3′-*O*-(*tert*-butyldiphenylsilyl)-thymidine using Dess–Martin periodinane in anhydrous CH_2Cl_2 as described previously.[5,8a] The key cyclization reactions were tested employing $(TMS)_3SiH$ and AIBN as the radical initiator. In a typical experiment, a deoxygenated solution of **3** in benzene (0.01 M) was treated with 5 equiv. of $(TMS)_3SiH$ and 0.2 equiv. AIBN, and the resulting mixture was stirred at 80 °C until the starting aldehyde was consumed. After evaporation of the solvent, ^1H NMR spectroscopic analysis showed two diastereoisomers of cyclonucleoside **4a** and **4b** as the only products (Scheme 2). These compounds were isolated by flash chromatography in a 25 and 60% yield, respectively, and fully characterized. Subsequently, a 20 mM solution of each of them in an 8:3 CH_2Cl_2/CH_3OH mixture was exposed to UV irradiation for 30 min at room temperature using a low-pressure mercury lamp (5.5 W).[13] The quantitative formation of the monodesilylated products **5a** and **5b** was obtained.



Scheme 2. Product studies of aldehyde **3** with $(TMS)_3SiH$ under free radical conditions and subsequent photochemical deprotection.

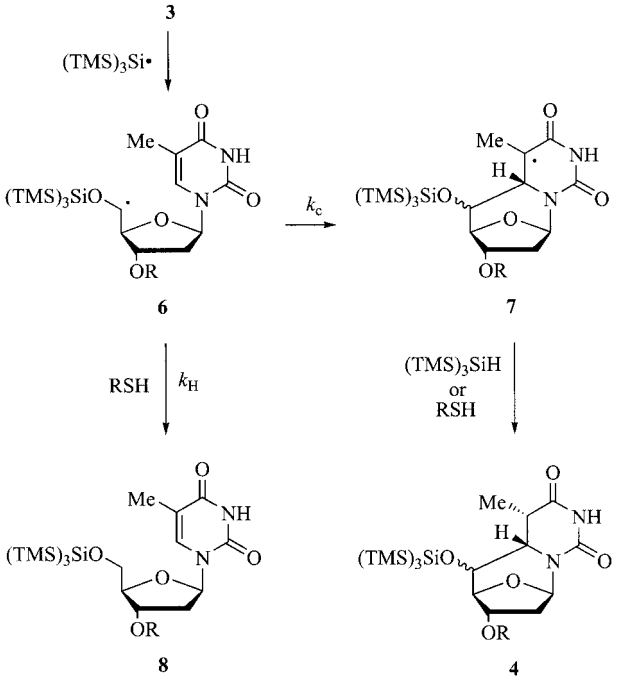
The stereochemistry of the two isomers was deduced from NMR spectroscopic analysis. The assignment of the (5′*S*,6*S*,5*S*) configuration to the isomer **4a** came from (i) the large $J_{5',6}$ = 9.2 Hz indicating that H5′ and H6 are in a *trans*-diaxial arrangement, (ii) NOE on H2′ (2%) and H3′ (6%) upon irradiation of H6, and (iii) NOE on H4′ (8%) observed only upon irradiation of H5. The assignment of the (5′*R*,6*S*,5*S*) configuration to the isomer **4b** came from (i) the small $J_{5',6}$ = 2.0 Hz indicating that H5′ and H6 are in an equatorial/axial arrangement, (ii) NOEs on H2′ (2%), H5′ (5%) and H6 (4%) upon irradiation of H3′, and (iii) irradiation of H5 caused an enhancement on H6 (4%), indicating that H5 and H6 are in an equatorial/axial and not in a *trans*-diaxial arrangement, which could be deduced by the $J_{5,6}$ value of 7.6 Hz.

From a mechanistic point of view, the addition of the $(TMS)_3Si^{\cdot}$ radical to aldehyde **3** affords the C5′ radical **6** that attacks intramolecularly the double bond of the thymine moiety to give radical **7** (6-*exo*-*trig* cyclization). Hydrogen abstraction from the silane gives product **4** and $(TMS)_3Si^{\cdot}$ radical, thus completing the cycle of this chain reaction (Scheme 3). Attempts to obtain the hydrosilylated product **8**, using high concentrations of $(TMS)_3SiH$, did not work, suggesting that the hydrogen abstraction step is very slow. Indeed, when the above-described typical experiment was carried out in the presence of 0.1 M PhSH, the ^1H NMR spectrum showed a quantitative formation of the reduction product **8**, which was isolated by flash chromatography in 95% yield.

Under these conditions, thiol acts as an effective hydrogen donor and the resulting thiyl radical is able to abstract hydrogen from the silane thus completing the cycle of this chain reaction [Equation (1)].[14]

$$RS^{\cdot} + (TMS)_3SiH \rightarrow RSH + (TMS)_3Si^{\cdot} \quad (1)$$

A rate constant k_c for the 6-*exo*-*trig* cyclization can be obtained, provided that conditions can be found in which the intermediate radical **6** is partitioned between the two reaction channels (Scheme 3), that is, the reaction with a hydrogen atom donor and the 6-*exo*-*trig* cyclization.[12] This scenario can be achieved by replacing PhSH with BuSH, which is a weaker hydrogen donor. A series of experiments



Scheme 3. Chemical studies on the fate of C5′ radical **6** under a variety of experimental conditions.

was conducted in which the aldehyde **3** was treated with a mixture of $(TMS)_3SiH$/BuSH in known concentrations at various temperatures in the presence of a radical initiator. ^1H NMR spectroscopy and LC/MS were used to analyze the reaction mixtures. The concentration of BuSH in the range 0.6–40 mM was chosen so that the ratio [**8**]/[**4**] ranged between 1:1 and 5:1. The ratio [**8**]/[**4**] varied in the manner expected with a change in the BuSH concentration, whereas the diastereoisomeric ratio **4a**/**4b** = 30:70 was nearly constant. Since the thiol concentration during the reaction remained essentially constant under our experimental conditions (pseudo-first-order conditions),[15] the relation [Equation (2)] is obeyed.[12]

$$[\mathbf{8}]/[\mathbf{4}] = (k_H/k_c)[\text{BuSH}] \quad (2)$$

The k_H/k_c values reported in Table 1 were obtained as the average of different experiments. Linear regression analysis of a log (k_H/k_c) vs. $1/T$ plot yields the relative Arrhenius parameters given by Equation (3) where $\theta = 2.3RT$ kcal mol^{-1} and the errors represent the standard deviation.

The rate constant k_H for the reaction of the α-silyloxyl secondary carbon-centered radical **6** with BuSH and its temperature dependence are unknown, although they are needed in order to obtain the Arrhenius expression for k_c from Equation (3). However, Newcomb and co-workers have determined rate constants very close to 2.0×10^7 M^{-1} s^{-1} for the reactions between octadecanethiol and primary alkyl or α-methoxyl secondary alkyl radicals in THF at 30 °C.[16] The Arrhenius parameters for the reaction of primary alkyl radicals with *t*BuSH are $\log(A/M^{-1}s^{-1}) = 8.15$ and $E_a = 1.86$ kcal/mol.[17] The combination of this data

Table 1. Kinetic data for the reaction of aldehyde **3** with $(TMS)_3$-SiH/BuSH in benzene.[a]

T [°C]	Initiator	k_H/k_c [M^{-1}][b]
25	Et_3B	853 ± 160 (3)
55	*t*BuONNO*t*Bu	330 ± 29 (4)
80	AIBN	152 ± 14 (5)
111	PhC(O)OO*t*Bu[c]	91 ± 5 (4)
142	*t*BuOO*t*Bu[d]	35 ± 4 (3)

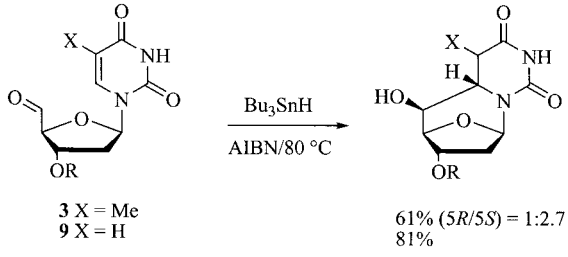
[a] Conditions: Aldehyde **3** 0.01 M, $(TMS)_3SiH$ 0.05 M, BuSH concentration in the range 0.6–40 mM and initiator 0.2 equiv. [b] Errors correspond to the standard deviation; the number of experiments performed for each temperature are given in parentheses. [c] In toluene. [d] In *o*-xylene.

along with Equation (3) yields $\log(A/M^{-1}s^{-1}) = 10.0$ and $E_a = 8.4$ kcal mol^{-1} for the cyclization reaction in Scheme 3. The value of k_c can be calculated as 7×10^3 s^{-1} at 25 °C.[18]

$$\log k_H/k_c(M^{-1}) = -(1.82 \pm 0.23) + (6.50 \pm 0.37)/\theta \quad (3)$$

Radical **6** should be nearly planar in the two possible conformers that give rise to the (5′*S*)- and (5′*R*)-isomers. We suggest that the two conformers around the C4′–C5′ bond have similar stabilities with a low interconversion barrier. Therefore, the **4a**/**4b** = 30:70 ratio reflects that of the rate constants for the cyclization reaction of the two conformers. Both cyclizations occur with defined stereochemistry affording exclusively the chair conformation of the ring formed (**6**→**7**). The pre-exponential factor is within the expected range. The stereoselectivity observed for the transfer of hydrogen atom to radical **7** by both silicon hydride and thiols could be due to preference of attack from the less hindered side of the ring. Indeed, the *anti* rule has been successfully applied to many cases of cyclic radicals.[19]

It is also interesting to compare the present results with the findings of Cadet and co-workers from similar reactions using Bu_3SnH as the reducing agent.[5,8a] They reported that both aldehydes **3** and **9** afford analogous cyclonucleosides exclusively having *S*-configuration at the C5′ position and that aldehyde **3** affords two diastereoisomers (5*R*/5*S* = 1:2.7) (Scheme 4). The difference in chemical behavior exhibited by $(TMS)_3SiH$ and Bu_3SnH prompted us to re-investigate the reaction of aldehyde **3** with Bu_3SnH under the previously reported conditions. ^1H NMR spectroscopic analyses on the reaction mixture revealed the presence of three cyclonucleosides in a ratio of 15:65:20. Two diastereoisomers having *S*-configuration at the C5′ position and differing in the configuration C5 (5*R*/5*S* = 1:4.3) are the reported ones,[5] whereas the third one is the diastereoisomer



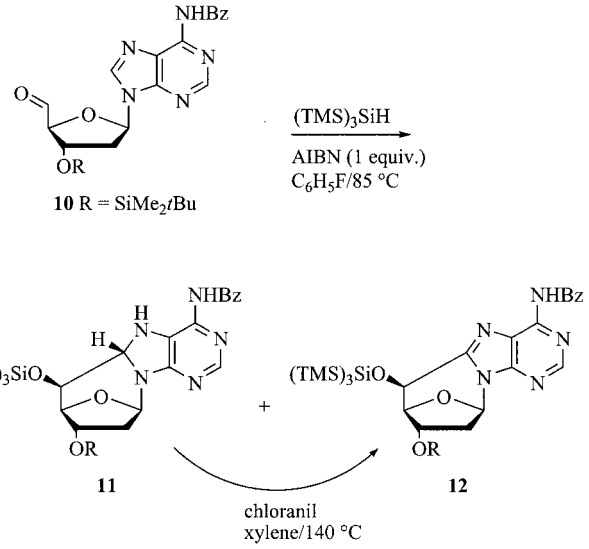
Scheme 4. Product studies reported by Cadet and co-workers.[5,8a]

5b having *R*-configuration at the C5′ position. Therefore, the cyclization of the Bu_3Sn adduct radical occurred with a diastereoisomeric ratio (5′*S*)/(5′*R*) = 80:20 whereas the cyclization of the corresponding silyl-substituted radical **6** occurred with a ratio (5′*S*)/(5′*R*) = 30:70, The inverted diastereoselectivity observed for the two reducing agents is probably due to the different spatial shapes of the $(TMS)_3$-Si and Bu_3Sn groups.[11]

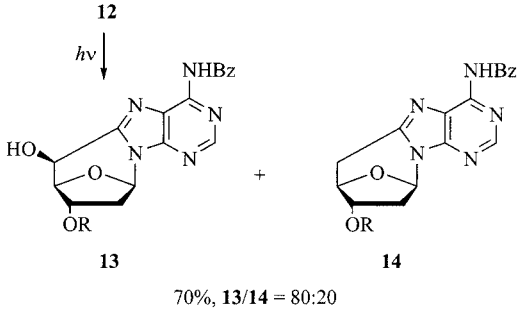
The photochemical deprotection of tris(trimethylsilyl)silyl ethers is also worth a comment. It has been reported that $(TMS)_3SiCl$ can be used for the protection of primary and secondary alcohols.[13] These silyl ethers are stable under the usual conditions employed in organic synthesis for the deprotection of other silyl groups and can be deprotected using photolysis at 254 nm, in yields ranging from 62 to 95%. Our findings point out the potentiality of this method if combined with radical reactions. Although a simple hydrosilylation/deprotection combination is formally equivalent to the ionic reduction of carbonyl moieties, the use of an aldehydic function in consecutive radical reactions followed by deprotection could be a new approach for the formation of new stereogenic centers based on the hindered properties of the $(TMS)_3Si$-group.[11]

Reaction of $(TMS)_3SiH$ with Aldehyde 10: Aldehyde **10** is prepared from DMSO-based oxidation of the 3′-*O*-protected derivative of *N*-benzoyl-2′-deoxyadenosine according to the Moffatt method.[20] The cyclization reaction was initially tested using the same conditions reported above for aldehyde **3**, i.e., a deoxygenated solution of **10** in fluorobenzene (0.01 M) was treated with 5 equiv. of $(TMS)_3SiH$ and 0.2 equiv. AIBN at 85 °C. After 2 h a low conversion of the starting aldehyde was observed. However, when the AIBN was used in stoichiometric amounts all the aldehyde was consumed.[21] ^1H NMR spectroscopic and LC/MS analysis of the crude reaction mixture showed the formation of cyclonucleosides **11** and **12** in a 1:1 ratio and in 70% overall yield together with some minor unidentified products (Scheme 5). Attempts to separate the cyclonucleosides **11** and **12** by flash chromatography were unsuccessful. However, when the mixture of **11** and **12** was treated by tetrachloro-1,4-benzoquinone (chloranil) in refluxing xylene,[22] compound **11** was quantitatively oxidized to **12**, which can be isolated and fully characterized. The stereochemistry of the above-mentioned cyclonucleosides was deduced from NMR analysis. The assignment of the (5′*S*,8*R*) configuration to isomer **11** came from NOEs on H2′ (2%) and H3′ (5%) upon irradiation of H8. The assignment of the 5′*S* configuration to isomer **12** came from the large $J_{4',5'}$ coupling of 6.0 Hz ($J_{4',5'}$ = 6.0 Hz and $J_{4',5'}$ = 0.0 Hz are reported for the 5′*S*- and 5′*R*-isomers of 5′,8-cyclo-2′-deoxyadenosine, respectively)[3] and the absence of NOEs on H3′ upon irradiation of H5′ and vice versa.

Photolysis with 254 nm light of a 20 mM solution of **12** in an 8:3 CH_2Cl_2/CH_3OH mixture afforded the 5′-*O*-desilylated compound **13** and the 2′,5′-dideoxy cyclic derivative **14** in 56% and 14% yields, respectively (Scheme 6). Prolonged photolysis of the reaction mixture did not show any changes, suggesting that compound **14** is a direct photoproduct. Further support for the assigned stereochemistry of the above-mentioned cyclonucleosides can be obtained by the excellent agreement of ^1H NMR spectroscopic data with those reported by Cadet and co-workers for compounds **13** and **14**.[6] In their synthetic approach, compound **13** was obtained by the sequential treatment of **14** with selenium oxide in refluxing 1,4-dioxane and $NaBH_4$ in methanol.

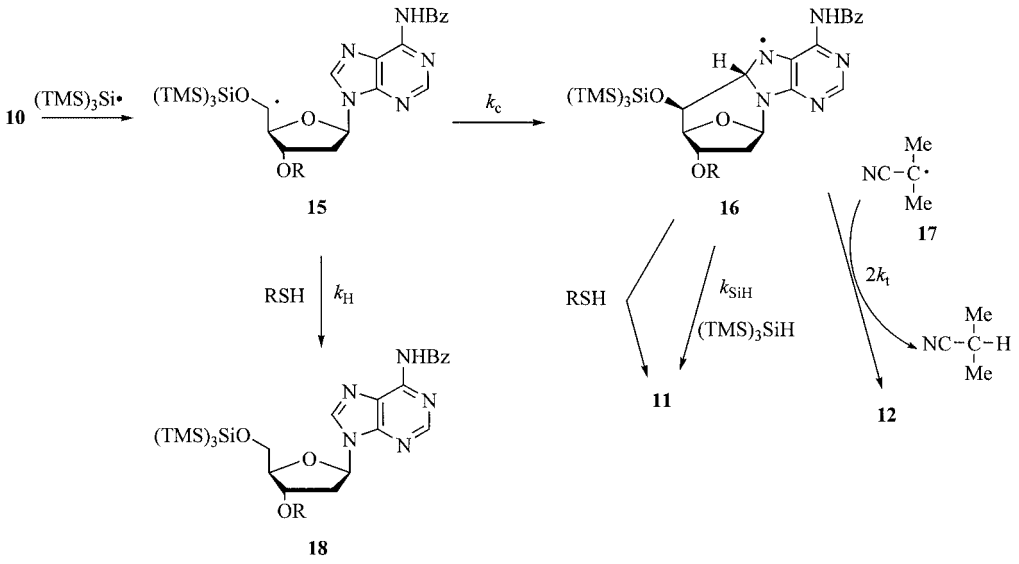


Scheme 5. Product studies of the reaction of aldehyde **10** with $(TMS)_3SiH$ using 1 equiv. of AIBN in reflux fluorobenzene and subsequent oxidation by chloranil in reflux xylene.



Scheme 6. Photolysis of **12** by 254 nm light in CH_2Cl_2/MeOH for 90 min.

From a mechanistic point of view, the addition of the $(TMS)_3Si^{\cdot}$ radical to aldehyde **10** affords the C5′ radical **15** that attacks the adenine moiety intramolecularly to give the aminyl radical **16** (Scheme 7).[3] Radical **15** should be nearly planar and the two possible conformers give rise to the (5′*R*)- and (5′*S*)-isomers. The steric hindrance between the adenine and $OSi(TMS)_3$ moieties favors one of these conformers. The cyclization occurs with defined stereochemistry, affording exclusively the chair conformation in the rings formed (**15**→**16**). Hydrogen abstraction from the silane gives product **11** and $(TMS)_3Si^{\cdot}$ radical. However, the large quantity of oxidized **12** is not straightforward. Beckwith el al.[21] recently reported that the Bu_3SnH-mediated intramolecular-homolytic substitution requires large amounts of initiator, as in the present work. Based on their investiga-

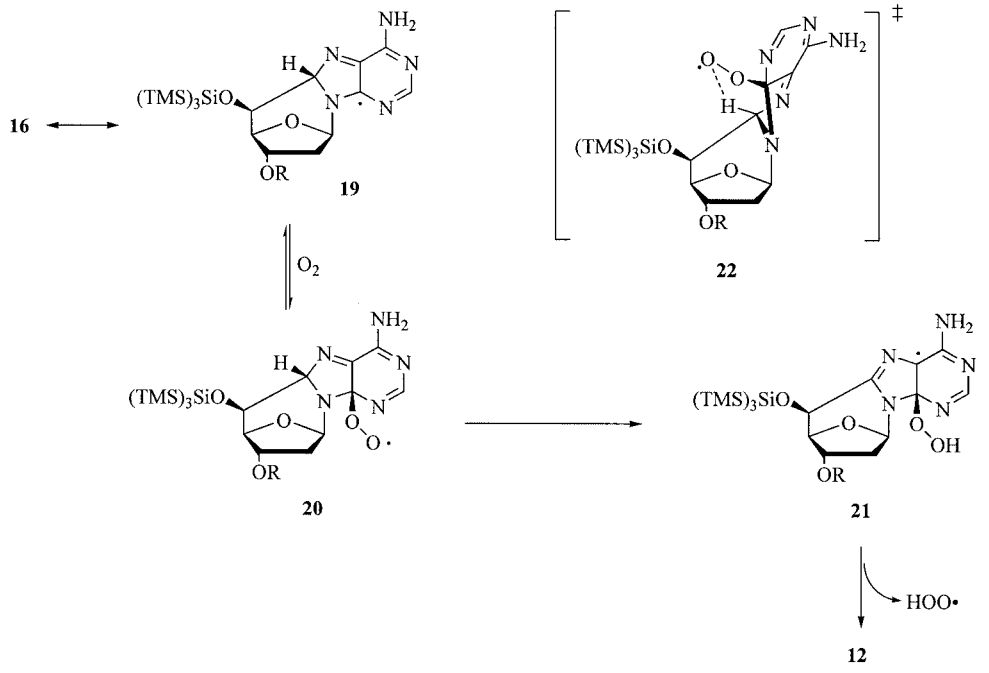


Scheme 7. Chemical studies on the fate of C5′ radical **15** under a variety of experimental conditions.

tion, we suggest that the oxidized product **12** derives from the reaction of radical **16** with radical **17**, which was generated from the decomposition of AIBN. Assuming that $2k_t \approx 10^9\ M^{-1}\,s^{-1}$ and $[R^{\cdot}] \approx 10^{-8}\ M$, we calculated, from the distribution of the products, $k_{SiH} \approx 2\times10^2\ s^{-1}$, which is in excellent agreement with the reported rate constants of $Ar_2N^{\cdot}$ radicals with $(TMS)_3SiH$.[23]

When the above-described experiment was carried out in the presence of PhSH (0.1 M) and a small amount of AIBN, the ^1H NMR spectrum showed a quantitative formation of the reduction product **18** that was isolated by flash chromatography in a 95% yield (Scheme 7). Under these conditions, the hydrogen donor is the thiol that is able to intercept the C5′ radical prior to cyclization. As shown in Equation (1), the resulting thiyl radical abstracts hydrogen from the silane, thus completing this chain reaction.

A series of experiments was also conducted in which aldehyde **10** was treated with $(TMS)_3SiH$/BuSH in order to provide the conditions in which the rate constant k_c for the 6-*exo-trig* cyclization could be obtained (Scheme 7). In particular, deoxygenated fluorobenzene 0.01 M solutions of **10** containing 0.05 M $(TMS)_3SiH$, 0.02–0.1 M BuSH and 0.2 equiv. AIBN were refluxed at 86 °C. ^1H NMR spectroscopy and LC/MS were used to analyze the reaction mixtures. The relative concentrations of **18**, **11**, and **12** varied in the expected manner as the concentration of BuSH was changed.



Scheme 8. Proposed mechanism for the reaction of aminyl radical **16** with molecular oxygen. Structure **22** represents a transition state.

Analysis of the data in the usual manner [cf. Equation (2) in the previous section] allowed a $k_H/k_c = 28.6 \pm 2.4$ M^{-1} to be obtained, as an average of three independent experiments (errors corresponds to the standard deviation).

A rate constant $k_c = 3.5 \times 10^5$ s^{-1} at 86 °C is calculated by taking $k_H = 1.0 \times 10^7$ M^{-1} s^{-1}.[17] For comparison, an absolute rate constant $k_c = 1.6 \times 10^5$ s^{-1} at 22 °C is obtained by pulse radiolysis for the corresponding unprotected radical in water.[3] Moreover, a $k_c = 7.7 \times 10^4$ s^{-1} at 86 °C is calculated for the cyclization of radical **6**, which is nearly five times slower than the cyclization of radical **15**.

With the aim of optimizing the yield of cyclonucleoside **12**, we performed the reaction in the presence of oxygen. A solution of **10** in fluorobenzene (0.01 M) was treated with 5 equiv. of $(TMS)_3SiH$ and stoichiometric amounts of AIBN at 85 °C under air. Complete conversion of the starting aldehyde was observed within 2 h with the formation of cyclonucleoside **12** as the sole product in 75% yield. The mechanism that we conceived for the reaction is outlined in Scheme 8. We have previously shown by kinetic studies using pulse radiolysis techniques that the unprotected aminyl radical **16** reacts reversibly with oxygen.[3] Aminyl radical **16** is in resonance with the structure **19**, where the unpaired electron is placed at the C4 position, and addition to molecular oxygen can afford peroxyl radical **20**. This radical should undergo a facile hydrogen migration via the chair-type transition state **22** to generate the C6 radical **21**, which eliminates the HOO$^{\cdot}$ radical, thus affording product **12**. Hydrogen abstraction from silane by the HOO$^{\cdot}$ radical should regenerate the $(TMS)_3Si^{\cdot}$ radical, thus completing this chain reaction.[24]

Conclusions

We have disclosed two short and efficient synthetic sequences, based on consecutive radical reactions followed by photochemical desilylation, for the preparation of cyclonucleosides **5** and **13**. The C5′ radicals, generated by addition of the $(TMS)_3Si^{\cdot}$ radical to the corresponding 5′-carbaldehyde, are the key intermediates in these transformations. The 6-*exo*-*trig* cyclization is effective with both pyrimidine and purine derivatives, although the nature of the base plays an important role in the stereochemical outcome. Our findings can furnish a molecular basis for forthcoming experiments involving the role of these conformationally restricted structures in DNA damage.

The research described in this article has demonstrated the feasibility of radical reactions for the preparation of 5′,6-cyclopyrimidine and 5′,8-cyclopurine nucleosides starting from easily available modified derivatives. We envisage that this approach can be extended to other pyrimidine and purine nucleosides.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a Varian Mercury 400 spectrometer at 400 MHz and 100.6 MHz, respectively. Chemical shifts are expressed in ppm (δ) and coupling constants in Hertz (Hz). LC/MS analyses were performed with an Agilent 1100 HPLC system and an Esquire 3000 Plus Bruker mass spectromer. LC analyses were performed with a Zorbax C8 column (4.6 × 150 mm, 5 μM) with a linear gradient acetonitrile/water from 50:50 to 95:5 in 20 min at a flow rate 0.6 mL/min, detection at λ = 260 nm. Column chromatography was performed by the method of Still using Merck 230–400 mesh ASTM silica gel 60. Analytical thin-layer chromatography (TLC) was performed using Merck 60 F_{254} 0.2 precoated silica gel plates. Compounds were visualized using ultraviolet light or by heating plates previously immersed in an ammonium molybdate/ceric ammonium sulfate/sulfuric acid mixture. Solvents were freshly distilled prior to use. All other reagents were used as received.

Reaction of 5′-Carbaldehyde 3 with $(TMS)_3SiH$: AIBN (3 mg, 0.02 mmol) and $(TMS)_3SiH$ (0.175 mL, 0.5 mmol) were added to a 0.01 M solution of aldehyde **3**[5] (48 mg, 0.1 mmol) in C_6H_5 (10 mL). The solution was refluxed under argon for 1 h. Analysis by LC/MS and ^{1}H NMR spectroscopy of the crude reaction mixture after evaporation of the solvent showed the formation of compounds **4a** and **4b** in 30:70 ratio and in 85% overall yield. Column chromatography on silica gel by gradient elution with *n*-hexane/ethyl acetate led to separation of the two compounds.

(5′*S*,6*S*,5*S*)-3′-*O*-(*tert*-Butyldiphenylsilyl)-5′-*O*-[tris(trimethylsilyl)silyl]-5′,6-cyclo-5,6-dihydrothymidine (4a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.80 (m, 10 H, Ph), 7.2 (s, 1 H, NH), 5.91 (d, $J_{1',2'}$ = 6.0 Hz, 1 H, H-1′), 4.67 (dd, $J_{2',3'}$ = 2, $J_{2'',3'}$ = 7.0 Hz, 1 H, H-3′), 4.47 (d, $J_{4',5'}$ = 5.0 Hz, 1 H, H-4′), 3.58 (dd, $J_{4',5'}$ = 5.0, $J_{5',6}$ = 9.2 Hz, 1 H, H-5′), 3.00 (dd, $J_{5,6}$ = 3.2, $J_{5',6}$ = 9.2 Hz, 1 H, H-6), 2.73 (dq, $J_{5,6}$ = 3.2, $J_{5,Me}$ = 7.2 Hz, 1 H, H-5), 2.27 (ddd, $J_{2',2''}$ = 14, $J_{1',2'}$ = 6.0, $J_{2',3'}$ = 2 Hz, 1 H, H-2′), 1.46 (dd, $J_{2',2''}$ = 14, $J_{2'',3'}$ = 7.0 Hz, 1 H, H-2′′), 1.22 (d, J = 7.2 Hz, 3 H, Me), 1.05 (s, 9 H, *t*BuSi), 0.15 (s, 27 H, MeSi) ppm; NOE experiments: irradiation at δ = 3.00 (H-6) ppm caused enhancements of signals at δ = 1.46 (H-2′′, 2%), 2.73 (H-5, 9%) ppm and 4.67 (H-3′, 6%) ppm whereas no enhancement of the signal at δ = 3.58 (H-5′) ppm was found; irradiation at δ = 3.58 (H-5′) ppm caused enhancements of signals at δ = 4.47 (H-4′, 8%) ppm whereas no enhancement of the signal at δ = 2.73 (H-5) ppm was found. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.86 (Me), 11.68 (Me), 19.34 (q), 26.89 (Me), 36.25 (CH), 42.17 (CH_2), 54.79 (CH), 68.53 (CH), 71.64 (CH), 84.35 (CH), 86.65 (CH), 127.88 (CH), 128.16 (CH), 129.91 (CH), 130.15 (CH), 133.40 (q), 134.65 (q), 135.82 (CH), 135.91 (CH), 150.59 (CO), 172.43 (CO) ppm. MS (ESI): 749 [M + Na$^+$].

(5′*R*,6*S*,5*S*)-3′-*O*-(*tert*-Butyldiphenylsilyl)-5′-*O*-[tris(trimethylsilyl)silyl]-5′,6-cyclo-5,6-dihydrothymidine (4b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.4–7.70 (m, 10 H, Ph), 7.1 (s, 1 H, NH), 6.30 (d, $J_{1',2'}$ = 7.0 Hz, 1 H, H-1′), 4.55 (d, $J_{4',5'}$ = 2.0 Hz, 1 H, H-4′), 4.38 (dd, $J_{2',3'}$ = 2.5, $J_{2'',3'}$ = 7.0 Hz, 1 H, H-3′), 3.18 (t, $J_{4',5'} = J_{5',6}$ = 2 Hz, 1 H, H-5′), 3.14 (dd, $J_{5,6}$ = 7.5, $J_{5',6}$ = 2.0 Hz, 1 H, H-6), 2.64 (quintuplet, $J_{5,6} = J_{5,Me}$ = 7.5 Hz, 1 H, H-5), 2.07 (ABXY, $J_{A,B}$ = 14, $J_{1',2'}$ = 7.0, $J_{2',3'}$ = 2.5 Hz, 1 H, H-2′), 1.95 (ABX, $J_{A,B}$ = 14, $J_{2'',3'}$ = 7.0 Hz, 1 H, H-2′′), 1.14 (d, J = 7.5 Hz, 3 H, Me), 1.05 (s, 9 H, *t*BuSi). 0.15 (s, 27 H, MeSi) ppm; NOE experiments: irradiation at δ = 2.64 (H-5) ppm caused enhancements of signals at δ = 3.14 (H-6, 4%) and 1.14 (Me, 1.5%) ppm whereas no enhancement of the signal at δ = 3.18 (H-5′) ppm; Irradiation at δ = 4.38 (H-3′) ppm caused enhancements of signals at δ = 1.95 (H-2′′, 2%), 3.18 (H-5′, 5%), 3.14 (H-6, 6%), and 4.55 (H-4′, 4%) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.94 (Me), 9.30 (Me), 19.28 (q), 26.92 (Me), 35.05 (CH), 40.14 (CH_2), 54.99 (CH), 69.40 (CH), 73.74 (CH), 85.22 (CH), 85.96 (CH), 128.07 (CH), 130.20 (CH),

133.33 (q), 133.86 (q), 136.04 (CH), 136.08 (CH), 154.05 (CO), 170.48 (CO) ppm. MS (ESI): 749 [M + Na^+].

(5′*S*,6*S*,5*S*)-3′-*O*-(*tert*-Butyldiphenylsilyl)-5′,6-cyclo-5,6-dihydrothymidine (5a): A 20 mM solution of **4a** (10 mg, 0.02 mmol) in an 8:3 CH_2Cl_2/MeOH mixture (25 mL) was photolysed at λ = 254 nm for 30 min to give quantitatively the 5′-*O*-desilylated compound **5a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.0 (s, 1 H, NH), 7.25–7.80 (m, 10 H, Ph), 6.2 (d, $J_{1',2'}$ = 6.0 Hz, 1 H, H-1′), 4.55 (dd, $J_{2',3'}$ = 3.0, $J_{2'',3'}$ = 7.0 Hz, 1 H, H-3′), 4.18 (d, $J_{4',5'}$ = 4.4 Hz, 1 H, H-4′), 3.67 (dd, $J_{4',5'}$ = 4.4, $J_{5',6}$ = 9.3 Hz, 1 H, H-5′), 3.01 (dd, $J_{5,6}$ = 3.6, $J_{5',6}$ = 9.3 Hz, 1 H, H-6), 2.75 (m, 1 H, H-5), 2.31 (ddd, $J_{2',2''}$ = 14.4, $J_{1',2'}$ = 6.0, $J_{2',3'}$ = 3.0 Hz, 1 H, H-2′), 2.12 (dd, $J_{2',2''}$ = 14.4, $J_{2'',3'}$ = 7.0 Hz, 1 H, H-2′′), 1.18 (d, J = 7.2 Hz, 3 H, Me), 1.05 (s, 9 H, *t*BuSi) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 11.24 (Me), 19.25 (q), 27.06 (Me), 36.00 (CH), 43.42 (CH_2), 53.75 (CH), 62.90 (CH), 69.97 (CH), 84.25 (CH), 86.20 (CH), 127.99 (CH), 128.05 (CH), 130.17 (CH), 130.19 (CH), 133.25 (q), 133.61 (q), 135.93 (CH), 151.18 (CO), 173.33 (CO) ppm. MS (ESI): 503 (M + 23).

(5′*R*,6*S*,5*S*)-3′-*O*-(*tert*-Butyldiphenylsilyl)-5′,6-cyclo-5,6-dihydrothymidine (5b): A 20 mM solution of **4b** (10 mg, 0.02 mmol) in an 8:3 CH_2Cl_2/MeOH mixture (25 mL) was photolysed at λ = 254 nm for 30 min to give quantitatively the 5′-*O*-desilylated compound **5b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.6 (s, 1 H, NH), 7.4–7.8 (m, 10 H, Ph), 6.42 (d, $J_{1',2'}$ = 6.0 Hz, 1 H, H-1′), 4.26 (dd, $J_{2',3'}$ = 3.0, $J_{2'',3'}$ = 6.5 Hz, 1 H, H-3′), 4.24 (d, $J_{4',5'}$ = 2.4 Hz, 1 H, H-4′), 3.20 (dd, $J_{5',6}$ = 1.5, $J_{5,6}$ = 7.5 Hz, 1 H, H-6), 2.96 (br. s, collapsing to a doublet upon irradiation at δ = 3.2, $J_{4',5'}$ = 2.4 Hz, 1 H, H-5′), 2.88 (br. s, 1 H, OH), 2.70 (quintuplet, $J_{5,6}$ = $J_{5,\ CH3}$ = 7.5 Hz, 1 H, H-5), 2.34 (A part of an ABXY system, J_{AB} = 14.5, $J_{1',2'}$ = 6.0, $J_{2',3'}$ = 3.0 Hz, 1 H, H-2′), 2.30 (B part of an ABX system, J_{AB} = 14.5, $J_{2'',3'}$ = 6.5 Hz, 1 H, H-2′′), 1.18 (d, J = 7.2 Hz, 3 H, Me), 1.05 (s, 9 H, *t*BuSi) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 9.16 (Me), 19.25 (q), 27.04 (Me), 34.99 (CH), 39.78 (CH_2), 54.80 (CH), 65.56 (CH), 73.22 (CH), 85.52 (CH), 87.52 (CH), 128.12 (CH), 128.18 (CH), 128.21 (CH), 130.31 (CH), 133.52 (q), 136.12 (CH), 154.95 (CO), 171.51 (CO) ppm. MS (ESI): 503 [M + 23].

3′-*O*-(*tert*-Butyldiphenylsilyl)-5′-*O*-[tris(trimethylsilyl)silyl]thymidine (8): AIBN (3 mg, 0.02 mmol), $(TMS)_3SiH$ (0.175 mL, 0.5 mmol) and thiophenol (0.1 mL, 1.0 mmol) were added to a 0.01 M solution of the aldehyde **3** (48 mg, 0.1 mmol) in C_6H_5 (10 mL). The solution was refluxed under argon for 1 h. ^{1}H NMR spectroscopic analysis of the reaction mixture showed the presence of compound **8** in 95% yield. Column chromatography led to separation of a pure sample. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.0 (s, 1 H, H-6), 7.3–7.70 (m, 10 H, Ph), 7.2 (s, 1 H, NH), 6.38 (dd, $J_{1',2'}$ = 5.2, $J_{1',2''}$ = 9 Hz, 1 H, H-1′), 4.35 (d, $J_{2'',3'}$ = 5.0, 1 H, H-3′), 4.08 (br. s, 1 H, H-4′), 3.63 (dd, $J_{5',5''}$ = 11, $J_{4',5'}$ = 2 Hz, 1 H, H-5′), 3.32 (dd, $J_{5',5''}$ = 11, $J_{4',5''}$ = 2 Hz, 1 H, H-5′′), 2.16 (dd, $J_{2',2''}$ = 14, $J_{1',2'}$ = 5.2 Hz, 1 H, H-2′), 1.68 (ddd, $J_{2',2''}$ = 14, $J_{1',2''}$ = 9, $J_{2'',3'}$ = 5.0 Hz, 1 H, H-2′′), 1.87 (s, 3 H, Me), 1.05 (s, 9 H, *t*BuSi), 0.15 (s, 27 H, MeSi) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 0.39 [3(CH_3)$_3$Si], 0,65 (q), 12.62 (CH_3), 26.89 [(CH_3)$_3$CSi], 41.16 (C2′), 68.01 (C5′), 74.05 (C3′), 84.90 (C1′), 87.90 (C4′), 110.64 (C5), 127.91 (CH), 133.19 (q), 133.31 (q), 135.19 (C6), 135.66 (CH), 135.70 (CH), 150.01 (q), 163.53 (q) ppm. MS (ESI): 749 [M + Na^+].

Reaction of 5′-Carbaldehyde 3 with Bu_3SnH:[5] AIBN (0.06 mmol) and Bu_3SnH (0.6 mmol) were added to a 0.01 M solution of aldehyde **3** (150 mg, 0.3 mmol) in C_6H_5 (30 mL). The solution was refluxed under argon for 2 h. After evaporation the crude reaction mixture was eluted on a silica gel column by *n*-hexane/ethyl acetate from 90:10 to 0:100 to eliminate tin byproducts. ^{1}H NMR analysis of the residue, after evaporation of the solvent, showed the formation of three diastereoisomeric cyclization products in a ratio **5a**/**5b**/(5′*S*,5*R*,6*S*)[5] = 65:20:15 and in 80% overall yield.

Preparation of 5′-Carbaldehyde 10: N^5-Benzoyl-3′-*O*-(*tert*-butyldimetylsilyl)-2′-deoxyadenosine[25] (470 mg, 1 mmol) was dissolved in dry DMSO (5 mL). Dicyclohexylcarbodiimide (820 mg, 4 mmol) and dichloroacetic acid (0.041 mL, 0.5 mmol) in dry DMSO (1.4 mL) were added to the solution. The mixture was stirred at room temperature for 1 h and then ethyl acetate (4 mL) was added. Oxalic acid (250 mg, 2 mmol) was added portionwise followed by ethyl acetate (4 mL). The solution was left whilst stirring for 1 h at room temp. The mixture was filtered through celite and the filtrate was washed with water and extracted with ethyl acetate (3 × 5 mL). The organic layer was dried, the solvent evaporated under reduced pressure and the residue purified on a silica gel column. The elution with 80:20 diethyl ether: pentane gave the 5′-carbaldehyde **10** as a yellow foam (380 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.8 (s, 1 H, CHO), 9.10 (br. s, 1 H, NH), 8.74 (s, 1 H, H-2′), 8.30 (s, 1 H, H-8), 7.4–8.0 (m, 5 H, Ph), 6.58 (dd, $J_{1',2'}$ = 8.0, $J_{1',2''}$ = 6.4 Hz, 1 H, H–1′), 4.90 (m, 1 H, H-3′), 4.45 (d, $J_{3',4'}$ = 1.2 Hz, 1 H, H-4′), 2.90 (ddd, $J_{2',2''}$ = 14.0, $J_{2',1'}$ = 8.0, $J_{2',3'}$ = 2.0 Hz, 1 H, H-2′), 2.48 (ddd, $J_{2',2''}$ = 14.0, $J_{2'',1'}$ = 6.4, $J_{2'',3'}$ = 3 Hz, 1 H, H-2′′), 0.95 (s, 9 H, *t*BuSi), 0.18 (s, 6 H, MeSi) ppm. MS (ESI): 468 (M + 1). MS^2 (468) 239. The aldehyde **10** contained its hydrated form **10′** (**10**/**10′** ratio 80:20). The ratio **10**/**10′** changed by adding a drop of D_2O in the NMR tube, going from an 80:20 to 30:70 ratio within 50 min, then it remained constant over 20 h. The 30:70 ratio should be considered the equilibrium ratio in $CDCl_3$:D_2O (v/v 7:1).

Hydrated 5′-Carbaldehyde 10′: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.20 (br. s, 1 H, NH), 8.70 (s, 1 H, H-2), 8.18 (s, 1 H, H-8), 7.4–8.0 (m, 5 H, Ph), 6.42 (dd, $J_{1',2'}$ = 10.0, $J_{1',2''}$ = 5.0 Hz, 1 H, H-1′), 5.16 (d, $J_{4',5'}$ = 2 Hz, 1 H, H-5′), 4.57 (d, $J_{2',3'}$ = 4.8 Hz, 1 H, H-3′), 4.15 (d, $J_{4',5'}$ = 2 Hz, 1 H, H-4′), 2.91 (m, 1 H, H-2′), 2.22 (dd, $J_{1',2''}$ = 5.0, $J_{2',2''}$ = 13.5 Hz, 1 H, H-2′′), 0.95 (s, 9 H, *t*BuSi), 0.18 (s, 6 H, MeSi) ppm. MS (ESI): 486 [M + 1].

Reaction of 5′-Carbaldehyde 10 with $(TMS)_3SiH$: AIBN (15 mg, 0.1 mmol) and $(TMS)_3SiH$ (0.175 mL, 0.5 mmol) were added to a 0.01 M solution of the aldehyde **10** (50 mg, 0.1 mmol) in C_6H_5F (10 mL). The solution was refluxed under argon for 2 h. Analysis by LC/MS and ^{1}H NMR of the crude reaction mixture after evaporation of the solvent showed the formation of compounds **11** and **12** in a 1:1 ratio and in overall yields of 70%. Attempts to separate the cyclonucleosides **11** and **12** by flash chromatography were unsuccessful. When the mixture was treated by chloranil in refluxing xylene the compound **11** was quantitatively oxidized to **12**.

(5′*S*,8*R*)-N^5-Benzoyl-3′-*O*-(*tert*-butyldimethylsilyl)-5′-*O*-[tris(trimethylsilyl)silyl]-5′,8-cyclo-7,8-dihydro-2′-deoxyadenosine (11): ^{1}H NMR (400 **MHz**, $CDCl_3$): δ = 9.6 (s, 1 H, NH), 7.9 (s, 1 H, H-2), 7.4–7.8 (m, 5 H, Ph), 6.13 (d, $J_{1',2'}$ = 6.0 Hz, 1 H, H-1′), 5.20 (d, $J_{NH,8}$ = 6.0 Hz, 1 H, NH), 4.82 (dd, $J_{5',8}$ = 7.0, $J_{NH,8}$ = 6.0 Hz, 1 H, H-8), 4.58 (dd, $J_{2'',3'}$ = 7.0, $J_{2',3'}$ = 2.0 Hz, 1 H, H-3′), 4.18 (d, $J_{4',5'}$ = 4.5 Hz, 1 H, H-4′), 3.35 (dd, $J_{4',5'}$ = 4.5, $J_{5',8}$ = 7.0 Hz, 1 H, H-5′), 2.31 (ABX system, $J_{2',2''}$ = 13.5, $J_{2'',3'}$ = 7.0 Hz, 1 H, H-2′′), 2.14 (ABXY system, $J_{2',2''}$ = 13.5, $J_{1',2'}$ = 6.0, $J_{2',3'}$ = 2.0 Hz, 1 H, H-2′), 0.9 (s, 9 H, *t*BuSi), 0.3 (s, 3 H, MeSi), 0.13 (s, 27 H, Me_3Si), 0.1 (s, 3 H, MeSi) ppm; NOE experiments: irradiation at δ = 4.82 (H-8) ppm caused enhancements at δ = 2.31 (H-2′, 2%), 3.35 (H-5′, 2%), and 4.58 (H3′, 5%) ppm; irradiation at δ = 3.35 (H5′) ppm caused enhancements at δ = 4.82 (H-8, 2%), 4.18 (H4′, 4.5%) ppm; LC/MS (ESI): 738 [M + Na^+], 716 [M + 1]. MS^2 (716) 698, 584.

(5′*S*)-N^5-Benzoyl-3′-*O*-(*tert*-butyldimethylsilyl)-5′-*O*-[tris(trimethylsilyl)silyl]-5′,8-cyclo-2′-deoxyadenosine (12): ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 9.0 (s, 1 H, NH), 7.9 (s, 1 H, H-2), 7.4–7.8 (m, 5 H, Ph), 6.46 (d, $J_{1',2'}$ = 4.5 Hz, 1 H, H-1′), 4.94 (d, $J_{4',5'}$ = 6.0 Hz, 1 H, H-5′), 4.70 (dd, $J_{2'',3'}$ = 7.0, $J_{2',3'}$ = 4.5 Hz, 1 H, H-3′), 4.62 (d, $J_{4',5'}$ = 6.0 Hz, 1 H, H-4′), 2.53 (dd, $J_{2',2''}$ = 13.0, $J_{2'',3'}$ = 7.0 Hz, 1 H, H-2′′), 2.20 (ddd, $J_{2',2''}$ = 13.0, $J_{1',2'}$ = $J_{2',3'}$ = 4.5 Hz, 1 H, H-2′), 0.90 (s, 9 H, *t*BuSi), 0.30 (s, 3 H, MeSi), 0.13 (s, 27 H, Me_3Si), 0.10 (s, 3 H, MeSi) ppm; NOE experiments: irradiation at δ = 4.94 (H-5′) ppm causes an enhancement at δ = 4.62 (H-4′, 6%) ppm but none at δ = 4.70 (H-3′) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –4.58 (Me), –3.95 (Me), 0.78 (Me), 17.93 (q), 25.92 (Me), 46.83 (CH_2), 69.63 (CH), 71.08 (CH), 85.68 (CH), 87.16 (CH), 122.53 (q), 127.85 (CH), 129.10 (CH), 132.96 (CH), 134.11 (q), 149.12 (q), 149.28 (q), 151.09 (q), 152.96 (CH), 164.28 (CO) ppm. MS (ESI): 736 [M + 23], 714 [M + 1]. MS^2 (714) 514.

Photolysis of 12: A 20 mM solution of **12** (10 mg, 0.02 mmol) in an 8:3 CH_2Cl_2/MeOH mixture (25 mL) was photolysed at λ = 254 nm for 90 min to give the 5′-*O*-desilylated compound **13** and dideoxyadenosine **14** in 56% and 14% yields, respectively.

(5′*S*)-*N*^{5}-Benzoyl-3′-*O*-(*tert*-butyldimethylsilyl)-5′,8-cyclo-2′-deoxyadenosine (13): ^1H NMR (400 MHz, $CDCl_3$): δ = 9.2 (s, 1 H, NH), 8.6 (s, 1 H, H-2), 7.4–8.0 (m, 5 H, Ph), 6.46 (d, $J_{1',2'}$ = 4.8 Hz, 1 H, H-1′), 5.46 (d, $J_{4',5'}$ = 6.0 Hz, 1 H, H-5′), 4.77 (dd, $J_{2'',3'}$ = 7.0, $J_{2',3'}$ = 4.0 Hz, 1 H, H-3′), 4.33 (d, $J_{4',5'}$ = 6.0 Hz, 1 H, H-4′), 2.47 (dd, $J_{2',2''}$ = 13.0, $J_{2'',3'}$ = 7.0 Hz, 1 H, H-2′′), 2.21 (ddd, $J_{2',2''}$ = 13.0, $J_{1',2'}$ = $J_{2',3'}$ = 4.0 Hz, 1 H, H-2′), 0.90 (s, 9 H, *t*BuSi), 0.30 (s, 3 H, MeSi), 0.10 (s, 3 H, MeSi) ppm; NOE experiments: irradiation at δ = 5.46 (H-5′) ppm causes an enhancement of the signal at δ = 4.33 (H4′, 2.5%) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –4.77 (Me), –4.59 (Me), 18.07 (q), 25.92 (Me), 46.55 (CH_2), 64.76 (CH), 69.37 (CH), 85.60 (CH), 86.36 (CH), 85.96 (CH), 122.62 (q), 128.20 (CH), 129.09 (CH), 133.15 (CH), 133.59 (q), 148.79 (q), 150.03 (q), 152.55 (CH), 165.49 (CO) ppm. MS (ESI): 468 [M + 1]. MS^2 (468) 336, 268.

***N*^{5}-Benzoyl-3′-*O*-(*tert*-butyldimethylsilyl)-5′,8-cyclo-2′,5′-dideoxyadenosine (14):** ^1H NMR (400 MHz, $CDCl_3$): 9.2 (s, 1 H, NH), 8.65 (s, 1 H, H-2), 7.4–8.0 (m, 5 H, Ph), 6.58 (d, $J_{1',2'}$ = 4.8 Hz, 1 H, H-1′), 4.76 (d, $J_{4',5'}$ = 4.8 Hz, 1 H, H-4′), 4.43 (dd, $J_{2'',3'}$ = 7.0, $J_{2',3'}$ = 4.0 Hz, 1 H, H-3′), 3.58 (part A of a ABX system, $J_{4',5'\ (AX)}$ = 4.8, J_{AB} = 18 Hz, 1 H, H-5′), 3.10 (part B of a ABX system, $J_{4',5'\ (AX)}$ = 0, J_{AB} = 18 Hz; 1 H, H-5′), 2.63 (dd, $J_{2',2''}$ = 14.0, $J_{2'',3'}$ = 7.0 Hz, 1 H, H-2′′), 2.31 (ddd, $J_{2',2''}$ = 14.0, $J_{1',2'}$ = $J_{2',3'}$ = 4.0 Hz, 1 H, H2′), 0.90 (s, 9 H, *t*BuSi), 0.30 (s, 3 H, MeSi), 0.10 (s, 3 H, MeSi) ppm. MS (ESI): 452 [M + 1]. MS^2 (452) 320. MS^3 (320) 302.

***N*^{5}-Benzoyl-3′-*O*-(*tert*-butyldimethylsilyl)-5′-*O*-[tris(trimethylsilyl)silyl]-2′-deoxyadenosine (18):** AIBN (3 mg, 0.02 mmol), $(TMS)_3SiH$ (0.175 mL, 0.5 mmol)and thiophenol (0.1 mL, 1.0 mmol) were added to a 0.01 M solution of the aldehyde **10** (50 mg, 0.1 mmol) in C_6H_5F (10 mL). The solution was refluxed under argon for 1 h. ^1H NMR analysis of the reaction mixture showed the presence of compound **18** in 85% yield. Column chromatography led to separation of a pure sample. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.10 (s, 1H, NH), 8.8 (s, 1 H, H8), 8.20 (s, 1 H, H-2), 7.5–8.0 (m, 5 H, Ph), 6.47 (dd, $J_{1',2'}$ = 7.5, $J_{1',2''}$ = 6.0 Hz, 1 H, H-1′), 4.58 (m, 1 H, H-3′), 4.0 (ddd, $J_{4',5''}$ = 3.0, $J_{4',5'}$ = 5.0, $J_{4',3'}$ = 3.0 Hz; 1 H, H-4′), 3.76 (ABX, J_{AB} = 11.0, $J_{4',5'}$ = 5.0 Hz, 1 H, H-5′), 3.62 (ABX, J_{AB} = 11.0, $J_{4',5''}$ = 3.0 Hz, 1 H, H-5′′), 2.75 (ddd, $J_{2',2''}$ = 13.0, $J_{2',1'}$ = $J_{2',3'}$ = 7.5 Hz, 1 H, H-2′), 2.40 (ddd, $J_{2',2''}$ = 13.0, $J_{2'',1'}$ = 6.0, $J_{2'',3'}$ = 2.8 Hz, 1 H, H-2′′), 0.9 (s, 9 H, tBuSi), 0.13 (s, 27 H, Me_3Si), 0.1 (s, 6 H, MeSi) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –4.43 (CH), 0.64 (CH_3), 18.25 (q), 26.01 (CH_3), 41.00 (CH_2), 67.70 (CH_2), 72.50 (CH), 85.17 (CH), 88.48 (CH), 128.10 (CH), 129.10 (CH), 132.94 (CH), 141.87 (q), 149.71 (q), 152.89 (CH), 164.84 (CO) ppm. MS (ESI): 738 [M + 23], 716 [M + 1]. MS^2 (716) 240.

Kinetic Experiments: A solution containing aldehyde **3** or **10** (0.1 mmol), and $(TMS)_3SiH$ (0.17 mL, 0.5 mmol) and the appropriate amount of BuSH in a particular solvent was deoxygenated with argon (30 min). Reactions were initiated either by Et_3B at 25 °C or thermally (AIBN, *tert*-butyl hyponitrite, *tert*-butyl perbenzoate or di-*tert*-butyl peroxide). Solutions were refluxed for 1 h and analyzed by ^1H NMR spectroscopy and/or LC/MS.

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