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C5′-Adenosinyl Radical Cyclization. A Stereochemical Investigation

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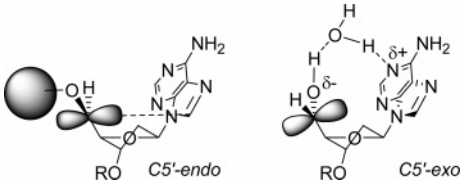

A variety of substituted 2′-deoxyadenosin-5′-yl radicals **3** were generated under different reaction conditions. Radicals **3** underwent intramolecular cyclization onto the C8−N7 double bond of the adenine moiety leading to aminyl radicals (5′*S*,8*R*)-**4** and (5′*R*,8*R*)-**4** and, eventually, to the corresponding cyclonucleosides **5** and **6**. The effect of the solvent, the nature of the substituents, and the generation method of radicals **3** on the stereoselectivity of the C5′-radical cyclization have been considered. The observed increase of the (5′*S*)/(5′*R*) ratio by increasing the bulkiness of the R_1 group is explained in terms of steric repulsion between R_1 and the purine moiety which favors the C5′-*endo* conformation, whereas the effect of the water solvent in promoting the (5′*R*)-stereoselective cyclization is ascribed to intermolecular hydrogen bonding stabilizing the C5′-*exo* confomation.

Introduction

Both exogenous agents, i.e., ionizing radiations, UV-rays and mutagenic chemical agents, and endogenous agents, as reactive oxygen species (ROS), can be responsible for the radical damage of DNA. Among ROS, highly diffusible hydroxyl radicals (•OH) can cause chemical modification to DNA either by radical addition to the base or hydrogen abstraction from one of the five positions of the sugar unit. For steric reasons, the H5′ hydrogen atom appears to be the most accessible one. The resulting C5′ radical can repair itself by hydrogen abstraction from glutathione, or can lead to DNA chemical modification or strand breakage.[1]

Among decomposition products of DNA exposed to ionising radiations, Dizdaroglu and co-workers reported the formation of cyclonucleotides characterized by an additional bond between the sugar unit and the base moiety.[2] These lesions are due to the intermediacy of C5′ radicals through intramolecular cyclization onto the C8 position of the adenine unit. It has been reported that the radical cyclization is (5′*R*)-stereoselective, with a (5′*S*)/(5′*R*) = 35:65 ratio.

The same (5′*R*)-stereoselectivity was found in model studies concerning the fate of C5′-radical of 2′-deoxyadenosine (**3a**) generated by 1,6-radical translocation (1,6-RT) from the C8 position. C8-Radicals were in turn produced from the corresponding 8-bromo derivative **1a** by γ-radiolysis[3] (Scheme 1, method A) or photolysis (Scheme 1, method B).[4,5] Thus, radicals **3a** generated in water under γ-radiolysis conditions gave the two diasteromeric isomers (5′*R*)-**6a** and (5′*S*)-**6a** in a (5′*S*)/(5′*R*) = 15:85 ratio (Table 1, entry 1).[3] A similar (5′*S*)/(5′*R*) = 18:82

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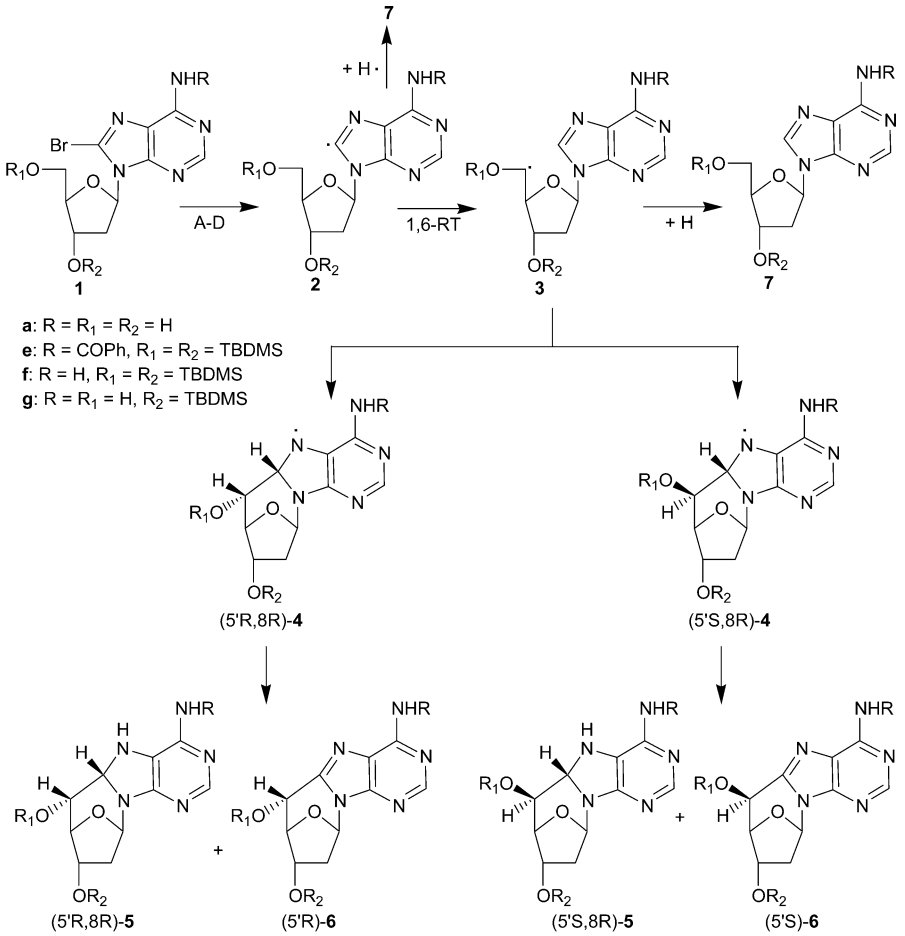
SCHEME 1. Chemical Studies on the Fate of 2′-Deoxyadenosin-5′-yl Radicals 3 Generated by 1,6-Radical Translocation (1,6-RT) under a Variety of Experimental Conditions[a]



[a] Method: (A) γ-rays, water; (B) $h\nu$, water or acetonitrile; (C) $(Me_3Si)_3SiH$, AIBN, fluorobenzene or acetonitrile, sealed tube, 85 °C; (D) $(Me_3Si)_3SiH$, AIBN, refluxing fluorobenzene.

ratio was found when **1a** was photolyzed in water solution (Table 1, entry 11), while a (5′*S*)/(5′*R*) = 37:63 ratio has been reported in acetonitrile solvent (Table 1, entry 12).[4]

In sharp contrast with the above results, indicating a large preference for the (5′*R*) configuration, we have recently reported[6] that radicals **3b** generated by tris(trimethylsilyl)silyl radical addition to the 2′-deoxyadenosine-5′-carbaldehyde **9** (Scheme 2, method E), led to a mixture of products (5′*S*,8*R*)-**5b** and (5′*S*)-**6b** in a completely (5′*S*)-stereoselective manner (Table 1, entry 2).

The discrepancy in results prompted us to investigate the factors affecting the stereoselectivity of the C5′-radical cyclization. The effect of the R, R_1, and R_2 substituents, the nature of the solvent, and the generation method of C5′-radicals **3** have been considered. As reported here, we found that the stereoselectivity only depends on the C5′-substituent hindrance and the nature of the solvent.

Results and Discussion

The origins of the observed stereoselectivity of C5′-radical cyclization were extrapolated from the behavior exhibited by radicals **3** generated both by tributyltin radical addition to the 2′-deoxyadenosine-5′-carbaldehyde **9** (Scheme 2, method F) and by 1,6-RT from the corresponding 2′-deoxyadenosin-8-yl radicals **2** (Scheme 1). These latter were in turn obtained from the 8-bromo derivatives **1** both by photolysis of the C8−Br bond (Scheme 1, method B) and by bromine atom abstraction by silyl radicals (Scheme 1, methods C and D).

Tributyltin Radical Addition to the 2′-Deoxyadenosine-5′-carbaldehyde 9. According with the methodology of Ueda[7] for the cyclization of adenosine-5′-carbaldehyde and Cadet[8] for the cyclization of thymidine-5′-carbaldehyde, radicals **3c** were generated by addition of tributyltin radicals to the carbonyl oxygen atom of the 5′-carbaldehyde **9**. The reaction was carried out in refluxing fluorobenzene under argon atmosphere for 2 h (Scheme 2, method F). The reaction mixture was filtered on silica gel column and analyzed by HPLC−MS and ^{1}H NMR. Cyclonucleosides (5′*S*,8*R*)-**5d** and (5′*S*)-**6d** and the 2′-deoxyadenosine derivative **7d** were found as the exclusive reaction

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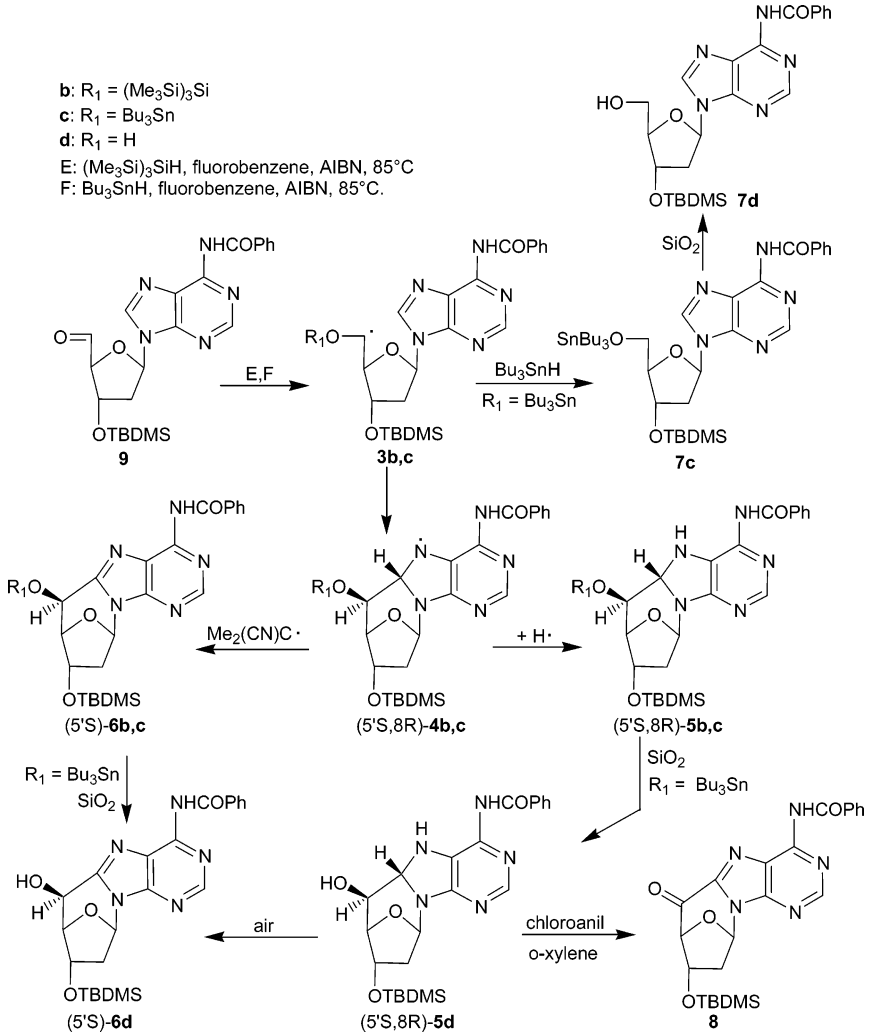
TABLE 1. Stereochemical outcome of the Cyclization of 2′-Deoxyadenosin-5′-yl Radicals 3

entry	substituents	radical **3**	method[a]	solvent	products, relative yields (%) (5′*S*)-**6**	(5′*S*)-**5**	(5′*R*)-**6**	(5′*R*)-**5**	**7**	5′*S*/5′*R* ratio
1	R = R_1 = R_2 = H	**3a**	A	H_2O	15	*b*	85	*b*	*b*	15:85[c]
2	R = COPh, R_1 = $(Me_3Si)_3Si$, R_2 = TBDMS	**3b**	E	PhF	52	48	*b*	*b*	*b*	100:0[d]
3	R = COPh, R_1 = Bu_3Sn, R_2 = TBDMS	**3c**	F	PhF	32	60	*b*	*b*	8	100:0[e]
4	R = COPh, R_1 = R_2 = TBDMS	**3e**	D	PhF	39	39	4	4	14	90:10[e]
5	R = COPh, R_1 = R_2 = TBDMS	**3e**	C	PhF	60	*b*	7	*b*	33	90:10[e]
6	R = COPh, R_1 = R_2 = TBDMS	**3e**	C	MeCN	65	*b*	8	*b*	27	90:10[e]
7	R = H, R_1 = R_2 = TBDMS	**3f**	C	PhF	55	*b*	7	*b*	38	90:10[e]
8	R = H, R_1 = R_2 = TBDMS	**3f**	C	MeCN	70	*b*	8	*b*	22	90:10[e]
9	R = R_1 = H, R_2 = TBDMS	**3g**	C	MeCN	38	*b*	32	*b*	30	55:45[e]
10	R = R_1 = R_2 = H	**3a**	C	MeCN	47	*b*	38	*b*	15	55:45[e]
11	R = R_1 = R_2 = H	**3a**	B	H_2O	7	*b*	31	*b*	*b*	18:82[f]
12	R = R_1 = R_2 = H	**3a**	B	MeCN	24	*b*	41	*b*	17	37:63[f]
13	R = R_1 = R_2 = H	**3a**	B	MeCN	*h*	*b*	g	*b*	30	50:50[e,g]
14	R = R_1 = H, R_2 = TBDMS	**3g**	B	MeCN	*h*	*b*	g	*b*	30	50:50[e,g]
15	R = H, R_1 = R_2 = TBDMS	**3f**	B	MeCN	52	*b*	18	*b*	30	75:25[e]
16	R = R_1 = R_2 = H	**3a**	B	MeCN/H_2O	25	*b*	60	*b*	15	30:70[e]
17	R = R_1 = H, R_2 = TBDMS	**3g**	B	MeCN/H_2O	25	*b*	60	*b*	15	30:70[e]

[a] A: 8-bromo-2′-deoxyadenosine **1**, γ-radiolysis. B: 8-bromo-2′-deoxyadenosine **1**, photolysis. C: 8-bromo-2′-deoxyadenosine **1**, $(Me_3Si)_3SiH$, AIBN, 85 °C, sealed tube. D: 8-bromo-2′-deoxyadenosine **1,** $(Me_3Si)_3SiH$, AIBN, refluxing solvent. E: aldehyde **9**, $(Me_3Si)_3SiH$, AIBN, 85 °C. F: aldehyde **9**, Bu_3SnH, AIBN, 85 °C. [b] Not detected. [c] Reference 3. [d] Reference 6. [e] Present work. [f] Reference 4. [g] Calculated by extrapolation at zero time. [h] Time dependent yield.

SCHEME 2. Products from Tributyltin-Promoted Reaction of Aldehyde 9



products in 60:32:8 ratio (Table 1, entry 3). Their formation can be easily explained through the intermediacy of the tributyltin hydride-promoted radicals **3c** as outlined in Scheme 2. Hydrogen atom abstraction from Bu_3SnH led to **7c**, whereas cyclization onto the C8−N7 double bond gave the radical **4c**, leading in turn to **5c** by H-atom abstraction and **6c** by oxidation,

possibly through a 2-cyanoisopropyl radical-mediated reaction.[9] Hydrolysis of the labile O−Sn bond during the workup eventually afforded compounds **5d**, **6d**, and **7d**.

The cyclonucleoside (5′*S*)-**6d** has been previously reported.[6] Compound **5d** was isolated by silica gel column chromatography and fully characterized by spectral analysis and chemical evidences. The (5′*S*,8*R*) configuration was easily assigned on the basis of the ^{1}H NMR spectrum. The value of $J_{4',5'} = 4.5$ Hz coupling constant is typical for the (5′S)-configuration, whereas a coupling constant $J_{4',5'} = 0-1.0$ Hz value would have been expected for the (5′*R*)-isomer.[10] On the other hand, the large $J_{5',8} = 7.5$ coupling constant is indicative for protons in a *trans* diaxial orientation, in agreement with the (8*R*)-configuration. NOE experiments supported the (5′*S*,8*R*) configuration. Irradiation on the H8 signal caused a significant NOE enhancement of the H3′ signal (3%), besides smaller enhancements of H2′ (1%) and H5′ (1%) signals. Moreover, irradiation on the H5′ signal caused an enhancement of H8 (1%) and H4′ (3.5%), but not H3′. A further support to the structure of **5d** came from air oxidation in chloroform solution which led quantitatively to **6d**. Attempts to aromatize the five-membered ring of the purine unit of **5d** with chloroanil, a chemoselective oxidizing agent for hydroaromatic rings, unexpectedly led to the ketone **8**.

Thermal Reaction of the 8-Bromo-2′-deoxyadenosine 1 with Silyl Radicals. Reactions of the 8-bromo derivatives **1** with silyl radicals were generally carried out at 85 °C in a sealed tube in air-saturated fluorobenzene or acetonitrile solutions in the presence of a 5-fold excess of tris(trimethylsilyl)silane [$(Me_3Si)_3SiH$] and equimolar amounts of AIBN (Scheme 1, method C).

The reaction of **1e** gave a 60:7:33 mixture of cyclonucleosides (5′*S*)-**6e** and (5′*R*)-**6e** and the 2′-deoxyadenosine derivative **7e** (Table 1, entry 5), as determined by ^{1}H NMR and HPLC−MS analysis of the reaction mixture. The (5′*S*)-configuration of the major isomer was assigned on the basis of the $J_{4',5'} = 6.5$ Hz value, whereas the (5′*R*) configuration of the minor isomer was assigned on the basis of $J_{4',5'} = 0$ Hz.[10] Subsequent silica gel column chromatography allowed us to separate a pure sample of (5′*S*)-**6e**, which was fully characterized. The formation of reaction products can be easily explained as follows: AIBN-promoted tris(trimethylsilyl)silyl radicals[11] abstract the bromine atom from **1e**; the resulting C8-radicals **2e** can undergo hydrogen abstraction, leading to the 2′-deoxyadenosine derivative **7e**, or 1,6-RT to C5′-radicals **3e**. Radicals **3e** can cyclize onto the C8−N7 double bond leading to aminyl radicals **4e**, then to cyclonucleosides **6e** by dioxygen-promoted oxidation. The cyclization was found to be strongly (5′*S*)-stereoselective, with a (5′*S*)/(5′*R*) = 90:10 ratio (Scheme 1).

In principle, the 2′-deoxyadenosine derivative **7e** could be also derived from radicals **3e** by H-atom abstraction, but this possibility seems to be unlikely. In fact, we have reported[6] that analogous radicals **3b** are incapable of abstracting a hydrogen atom under the reaction conditions employed (see Table 1, entry 2).

The role of dioxygen in promoting the formation of **6e** was highlighted when the reaction of **1e** was repeated in refluxing fluorobenzene under argon atmosphere (Scheme 1, method D), conditions that ensured the absence of air. Under these non-oxidative conditions aminyl radicals **4e** led to both cyclonucleosides **6e** and **5e**, the first one possibly through the above-mentioned 2-cyanoisopropyl radical promoted reaction,[9] the second one by H-atom abstraction from [$(Me_3Si)_3SiH$].

^{1}H NMR and HPLC−MS analyses of the reaction mixture showed the cyclonucleosides (5′*S*,8*R*)-**5e**, (5′*S*)-**6e**, (5′*R*,8*R*)-**5e**, and (5′*R*)-**6e** and the 2′-deoxyadenosine derivative **7e** in a 39:39:4:4:14 ratio (Table 1, entry 4), this suggesting that the cyclization is (5′*S*,8*R*)-stereoselective.

Compound (5′*S*,8*R*)-**5e** could be separated by column chromatography and characterized by spectral analysis. The structure of the minor isomer (5′*R*,8*R*)-**5e** was assigned on the basis of the HPLC−MS spectrum and the ^{1}H NMR analysis which indicated the specific H1′ signal at δ 6.10.

A further support to the structure of the above compounds (5′*S*,8*R*)-**5e** and (5′*R*,8*R*)-**5e** came from the oxidation of the reaction mixture with chloroanil, leading to the disappearance of **5e** and the formation of a mixture of (5′*S*)-**6e**, (5′*R*)-**6e** and **7e** in the expected 78:8:14 ratio, as determined by ^{1}H NMR analysis.

Similar results were obtained from the reaction of **1f** carried out in fluorobenzene. HPLC−MS and ^{1}H NMR analysis showed the presence of (5′*S*)-**6f**, (5′*R*)-**6f**, and **7f** as the exclusive products in 55:7:38 ratio (Table 1, entry 7). Also in this case the cyclization was found to be (5′*S*)-stereoselective with a (5′*S*)/(5′*R*) = 90:10 ratio. Structural assignment arose from HPLC-MS and ^{1}H NMR analysis. The (5′*S*) and (5′*R*) configurations of the chiral center were assigned based on the values of coupling constant $J_{4',5'} = 6.0$ and 0 Hz, respectively. Unfortunately, compounds (5′*S*)-**6f** and (5′*R*)-**6f** were not fully characterized due to the impossibility of obtaining pure samples by column chromatography.

As suggested by results, the stereochemistry of the cyclization of radicals **3** does not depend on their generation method, since radicals **3b** and **3c**, directly generated by addition to the aldehyde **9** of silyl and stannyl radicals, respectively, and radicals **3e** and **3f**, indirectly generated by 1,6-RT, cyclize in the same 5′*S*-stereoselective manner (Table 1, entries 2−5, 7).

Also the polarity of the solvent does not play any role, as shown by the results obtained from the reaction of **1e** and **1f** carried out in acetonitrile. Compounds (5′*S*)-**6e**,**f**, (5′*R*)-**6e**,**f**, and **7e**,**f** were found as the exclusive reaction products, with the same (5′*S*)/(5′*R*) = 90:10 ratio (Table 1, entries 6 and 8).

On the contrary, the reaction of both **1a** and **1g** carried out in acetonitrile led to a mixture of cyclized products (5′*S*)-**6a**,**g** and (5′*R*)-**6a**,**g** in an almost nonstereoselective manner, irrespective of the steric hindrance of the C3′-OR_2 substituent (Table 1, entries 8 and 9). The overall results led us to the conclusion that the stereoselectivity is determined by the bulkiness of the C5′-OR_1 substituent, since the (5′*S*)/(5′*R*) ratio passed from 100:0 to 90:10 and 55:45 by decreasing the steric demand of the R_1 substituent from Bu_3Sn or $(Me_3Si)_3Si$ to TBDMS and H (Table 1, entries 2−10).

Photolysis of the 8-Bromo-2′-deoxyadenosine 1. As mentioned above, some of us have recently reported the photolysis of **1a** carried out in acetonitrile.[4] HPLC−MS analysis of the reaction mixture detected the cyclonucleosides **6a** in a (5′*R*)-stereoselective mode with a (5′*S*)/(5′*R*) = 37:63 ratio (Table 1, entry 12).

This finding seems to be in contrast with our suggestion about the role of the C5′-OR_1 substituent, since in the case of R_1 =

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(10) For $J_{4',5'}$ values of 5′,8-cyclo-2′-deoxyadenosines see refs 3, 4, 15, and 16.

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TABLE 2. Product Relative Yields (%) from Photolysis of 1a and 1g in Acetonitrile at Different Irradiation Times

time (min)	(5′*R*)-**6a**	(5′*S*)-**6a**	**A**	*R*/*S* ratio	(5′*R*)-**6g**	(5′*S*)-**6g**	**B**	*R*/*S* ratio
15	48	30	22	1.6				
30	48	25	26	2.0	49	41	9	1.2
50	47	20	33	2.4	50	38	12	1.3
100	29	7	64	3.9	48	34	18	1,4
140	25	5	70	5.0	48	27	25	1.8
180	13	2	85	6.5	44	21	35	2.1

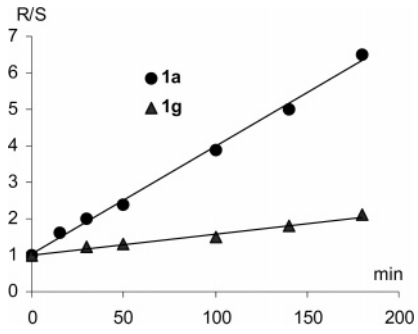

FIGURE 1. (5′*R*)/(5′*S*) ratio vs time from photolysis of 1.0 mM acetonitrile solutions of **1a** and **1g**.

H a lack of stereoselectivity should be expected. This disagreement prompted us to reinvestigate this reaction.

Photolyses of 1.0 mM deaerated acetonitrile solutions of **1a** were carried out using a 125 W medium-pressure mercury lamp. The reaction mixtures were monitored at different irradiation times by both HPLC−MS and ^{1}H NMR. In all cases ^{1}H NMR analysis showed the presence of the cyclonucleosides (5′*R*)-**6a** and (5′*S*)-**6a**, 2′-deoxyadenosine **7a**, and an unknown compound (**A**) as the exclusive reaction products in time-depending relative yields. In particular, the (5′*R*)/(5′*S*) ratio (Table 2 and Figure 1) increased with the irradiation time from 1.6 at 15 min to 6.5 at 180 min. Obviously, none of these values can be representative of the authentic (5′*S*)/(5′*R*) stereoselectivity. We reasoned that the correct stereoselectivity must be evaluated from the linear relationship (*R*/*S*) vs time by extrapolation at zero time. As a result, we calculated a (5′*S*)/(5′*R*) = 50:50 ratio (Figure 1 and Table 1, entry 13). This value strengthens our suggestion that in the absence of steric effects played by the C5′-OR$_1$ substituent the cyclization is nonstereoselective. Also, ^{1}H NMR analysis showed the relative yield of compound **A** to increase with the irradiation time at the expense of the cyclized products (5′*S*)-**6a** and (5′*R*)-**6a** (Table 2). We concluded that the cyclized products (5′*S*)-**6a** and (5′*R*)-**6a** are not stable under the reaction conditions, both leading to **A**, but at different rates.

A brief investigation about the formation of **A** was carried out. Unexpectedly, photolysis of a 1.0 mM acetonitrile solution of a 1:1 mixture of (5′*S*)-**6a** and (5′*R*)-**6a** did not lead to compound **A** at all. In the presence of 0.2 mM bromine, the above solution was found to be stable in the dark within 2 h, whereas under photolytic conditions almost complete decomposition occurred within 1 h with formation of compound **A** as the major product. Attempts to obtain a pure sample of **A** by either silica gel or C-18 reversed-phase column chromatography failed. Even though the analysis of a ca. 80% purity sample allowed us to obtain a confident ^{1}H NMR spectrum (see Experimental Section), an unambiguous mass spectrum could not be obtained by HPLC−MS analysis. Therefore, the structure of compound **A** and its formation mechanism remain unknown.

Similar results were obtained by photolysis of **1g** in acetonitrile. ^{1}H NMR analyses at different irradiation times showed the presence of the cyclonucleosides (5′*R*)-**6g** and (5′*S*)-**6g**, the 2′-deoxyadenosine derivative **7g**, and an unknown compound **B** in different relative yields. Also in this case, the (5′*R*)/(5′*S*) ratio was found to increase with the irradiation time (Table 2). Extrapolation at zero time of the linear relationship (*R*/*S*) vs time gave a (5′*S*)/(5′*R*) = 50:50 ratio (Figure 1 and Table 1, entry 14). As for compound **A**, compound **B** could not be isolated from the reaction mixture and it remains uncharacterized. However, ^{1}H NMR spectral analysis allowed to establish a structural similarity between **A** and **B** (see the Experimental Section).

The effect of the bulkiness of the C5′-OR$_1$ substituent in favoring the (5′*S*)-cyclization was definitively proved by the photolysis of **1f** in acetonitrile, which led to a mixture of the cyclized products (5′*S*)-**6f** and (5′*R*)-**6f** and the 2′-deoxyadenosine derivative **7f** in a 52:18:30 ratio (Table 1, entry 15). It is noteworthy that the relative yields of the cyclized products (5′*S*)-**6f** and (5′*R*)-**6f** were found unchanged with the irradiation time up to 90 min, in contrast with the behavior exhibited by the cyclonucleosides **6a** and **6g** which lead to compounds **A** and **B**, respectively, under the reaction conditions. As a matter of fact, we can infer that the presence of the hydroxy group in the C5′-position is essential for the bromine-promoted decomposition of the cyclonucleosides **6a** and **6g**.

Effect of the Bulkiness of the C5′-OR$_1$ Substituent. The observed effect of the bulkiness of the C5′-OR$_1$ substituent can be explained in terms of steric and stereoelectronic factors. The formation of the C5′−C8 bond occurs when the orbital containing the unpaired electron and the purine moiety form an angle of 109°.[12] This situation is achieved when the C5′ radical and the purine base are in a pseudo-diaxial orientation[3a] (Scheme 3).

In this conformation, the purine base can be *syn* (a) or *anti* (b) with respect to the sugar ring. The cyclization in the *anti* conformation is expected to lead to the (8*R*)-configuration through a chair transition state: this would be preferred with respect to the *syn* cyclization, leading to the (8*S*)-configuration through a boat transition state.[3] In agreement, we always found the cyclized products **5** in the (8*R*)-configuration. Therefore, we can confidently assume that the cyclization occurs in the *anti* conformation.

Analogously, the C5′−OR$_1$ group can be inside (C5′-*endo* conformation) (c) or outside (C5′-*exo* conformation) (d) with respect to the sugar unit. In the absence of steric effects, the cyclization can occur in both C5′-*endo* and C5′-*exo* conformations, leading to radicals (5′*S*,8*R*)-**4** and (5′*R*,8*R*)-**4**, respectively, in a nonstereoselective mode. In contrast, steric effects due to the steric repulsion between bulky R$_1$ substituents and the purine moiety should favor the C5′-*endo* conformation, from which the (5′*S*,8*R*)-**4** radical is formed.

Effect of the Water Solvent. Despite our considerations, radicals **3a** generated from the 8-bromo derivative **1a** both by γ-radiolisys[3] and photolysis[4,5] in water have been reported to cyclize in a (5′*R*)-stereoselective mode (Table 1, entries 1 and 10). Moreover, in an earlier work, (5′*R*)-5′,8-cyclo-2′-deoxyadenosine **6a** was identified as one of the principal products of γ-radiolysis in water of 2′-deoxyadenosine **7a**.[13] In this case,

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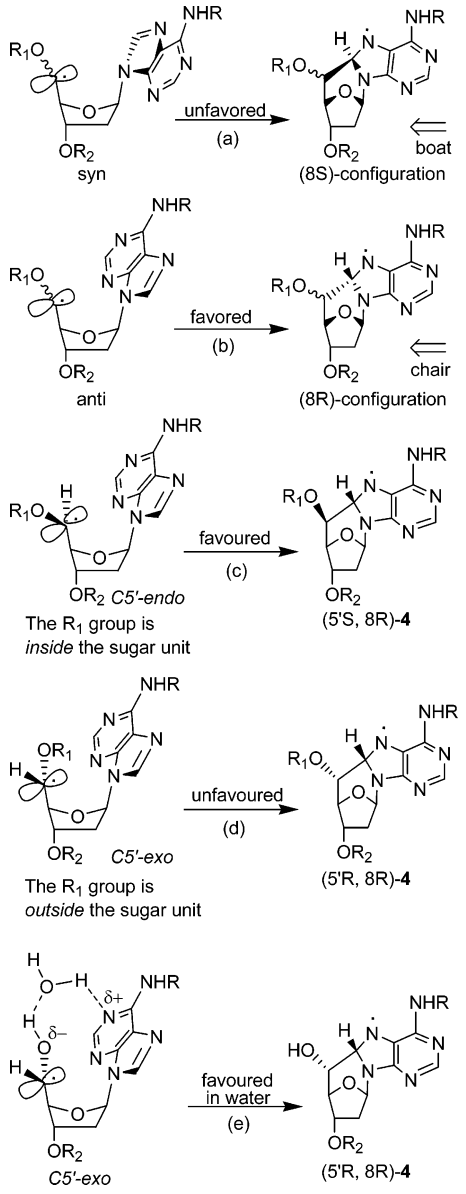
SCHEME 3. Conformational Effects on the Stereochemistry of the 2′-Deoxyadenosin-5′-yl Radical Cyclization



radicals **3a** were directly generated by H5′-atom abstraction by hydroxyl radicals.

Since the (5′*S*)/(5′*R*) ratio was found to be independent of the irradiation time, it represents the real (5′*S*)/(5′*R*) cyclization ratio. In this light, it might be concluded that the observed (5′*R*)-stereoselectivity should be actually due to some effect played by the water solvent.

A further support to the water effect came from the photolysis of **1a** carried out in a 1:1 acetonitrile/water mixture. ^{1}H NMR analysis showed the formation of the cyclonucleosides **6a** in a (5′*S*)/(5′*R*) = 30:70 ratio (Table 1, entry 16), which is between the 50:50 ratio found in neat acetonitrile and 18:82 ratio in neat water (Table 1, entries 12 and 10). As in the reaction carried out in neat water, the (5′*S*)/(5′*R*) ratio was found independent of the irradiation time, and no compound **A** was formed at all.

Similarly, the photolysis of **1g** in a 1:1 acetonitrile/water mixture gave the cyclonucleosides **6g** in the same (5′*S*)/(5′*R*) = 30:70 time-independent ratio (Table 1, entry 17).

To explain the role of water in favoring the (5′*R*)-cyclization, it might be suggested that in this protic solvent the C5′-*exo* conformation of radicals **3a**,**g** is preferred due to the formation of intermolecular hydrogen bonds between the C5′-OH hydrogen atom and the oxygen atom of the sugar ring and/or the N1 nitrogen atom (Scheme 3e).

The Case of the C5′-Radical of Adenosine (Ribo Form). In light of our suggestion on the role of the water solvent and the steric demand of the C5′-substituent, the hitherto unrationalized results reported in the literature about the stereoselectivity of the adenosin-5′-yl radical cyclization can be explained. Ueda and co-workers[7] reported that C5′ radicals directly generated in benzene solvent from the C5′-aldehyde through a tributyltin hydride mediated reaction led to the corresponding cyclonucleoside in a (5′*S*)-stereoselective mode with a (5′*S*)/(5′*R*) = 100:0 ratio. Based on our theory, this can be explained in terms of steric effects played by the bulky tributyltin group which favors the C5′-*endo* conformation. On the other hand, an opposite (5′*R*)-stereoselectivity was found in water by generating C5′-radicals from both adenosine[14] and 8-bromoadenosine[15] under γ-radiolysis conditions. In both cases we can suggest that the water solvent stabilizes the C5′-*exo* conformation through intermolecular hydrogen bonding.

Conclusions

2′-Deoxyadenosin-5′-yl radicals **3** were generated both directly by tributyltin radical addition to the carbonyl oxygen atom of the aldehyde **9** and by 1,6-RT from the corresponding C8-radicals. These latter were in turn generated starting from the corresponding 8-bromo derivatives **1** both under thermal conditions through bromine atom abstraction by silyl radicals and by photolysis of the C8−Br bond. In all cases radicals **3** underwent intramolecular cyclization onto the C8−N7 double bond to aminyl radicals (5′*S*,8*R*)-**4** and (5′*R*,8*R*)-**4**, finally leading to the cyclonucleosides (5′*S*)-**6** and (5′*R*)-**6** and, under anaerobic conditions, (5′*S*,8*R*)-**5** and (5′*R*,8*R*)-**5** (Scheme 1 and Table 1). The (5′*S*)/(5′*R*) ratio was found independent of the polarity of the solvent (fluorobenzene or acetonitrile), the method of generation of radicals **3**, and the nature of the C3′-OR_2 substituent (R_2 = H or TBDMS). Instead, it strongly depends on the steric hindrance of the C5′-OR_1 substituent (R_1 = H, TBDMS, or Bu_3Sn). The increase of the (5′*S*)/(5′*R*) ratio by increasing the bulkiness of the R_1 group is explained in terms of steric repulsion between the R_1 group and the purine moiety which disfavors the C5′-*exo* conformation of the radical **3** (Scheme 3).

On the contrary, radicals **3** generated by photolysis in water solvent cyclized in a (5′*R*)-stereoselective manner. The effect of the water is explained assuming that intermolecular hydrogen bonding between a water molecule, the C5′-OH and the oxygen atom of the sugar ring, or the N1 atom of the purine unit, stabilizes the C5′-*exo* confomation (Scheme 3).

Experimental Section

General Methods. HPLC analyses were performed on a C18 and C8 column (4.6 × 150 mm, 5 μm) with a linear gradient water/acetonitrile at a 0.6 mL/min flow rate, detection at λ 260 nm.

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Starting Materials. 8-Bromo-2′-deoxyadenosine (**1a**) was bought and used as it was. *N*-Benzoyl-O3′-(*tert*-butyldimethylsilyl)-5′-oxo-2′-deoxyadenosine (**9**) was synthesized as we previously reported in the literature.[6]

Synthesis of 8-Bromo-O3′,O5′-bis(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (1f). Commercial 8-bromo-2′-deoxyadenosine (330 mg, 1.0 mmol) was dissolved in dry DMF (10 mL). Imidazole (200 mg, 3.0 mmol), (dimethylamino)pyridine (30 mg, 0.25 mmol), and *tert*-butyldimethylsilyl chloride (TBDMSCl) (375 mg, 2.5 mmol) were added to the solution. The reaction mixture was allowed to stir at room temperature for 3 h, and then water was added (10 mL). The resulting mixture was extracted with ethyl acetate (2 × 10 mL). The organic layer was dried (Na_2SO_4), the solvent evaporated under reduced pressure, and the residue purified on silica gel column. The elution with ethyl acetate/hexane 80:20 yielded the desired product as a yellow foam (530 mg, 0.95 mmol, 95% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s; 1H); 6.34 (t, $J_{1',2'} = J_{1',2''} = 7.0$ Hz; 1H), 6.14 (br s; 2H), 4.86 (ddd; $J_{2',3'} = 4.0$ Hz; $J_{2'',3'} = 5.2$ Hz; $J_{3',4'} = 3.6$ Hz; collapsing to dd upon irradiation at δ 2.22; $J_{3',4'} = 3.6$ Hz, $J_{2'',3'} = 5.2$ Hz; collapsing to dd upon irradiation at δ 3.94, $J_{2',3'} = 4.0$ Hz; $J_{2'',3'} = 5.2$ Hz; 1H), 3.90−3.95 (m; 2H), 3.63−3.69 (m; 2H), 2.22 (ddd, $J_{2',2''} = 12.0$ Hz, $J_{2',3'} = 4.0$ Hz, $J_{1',2'} = 7.0$ Hz; 1H), 0.95 (s; 9H), 0.90 (s; 9H), 0,00 (s; 6H), −0,05 (s; 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ − 5.3, −5.2, −4.5, −4.45, 18.3, 18.6, 26.1, 37.0, 62.8, 72.5, 86.5, 88.0, 120.7, 128.5, 151.1, 152.3, 154.4; MS (ES+) *m*/*z* 560 (M + 1), 582 (M + 23); MS^2 (560) 216; MS (ES−) 558 (M − 1). Anal. Calcd for $C_{22}H_{40}BrN_5O_3Si_2$: C, 47.30; H, 7.22; Br, 14.30; N, 12.54. Found: C, 47.45; H, 7.20; Br, 14.35; N, 12.50.

Synthesis of 8-Bromo-N5-benzoyl-O3′,O5′-bis(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (1e). 8-Bromo-O3′,O5′-bis(*tert*-butyldimethylsilyl)-2′-deoxyadenosine **1f** (400 mg, 0.70 mmol) was dissolved in dry pyridine (7 mL). Benzoyl chloride (92 μL, 0.77 mmol) was added, and the solution was allowed to stir at room temperature overnight. The reaction mixture was treated with water (7 mL) and extracted with ethyl acetate (2 × 7 mL). The solvent was evaporated under reduced pressure and the residue purified on silica gel column by gradual elution with ethyl acetate/hexane. The pure product was obtained as a white foam (170 mg, 0.26 mmol, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (br s; 1H), 8.02 (s; 1H); 8.00−7.50 (m; 5H), 6.41 (d, $J_{1',2'} = 7.0$ Hz, 1H), 4.87 (m; 1H), 3.97 (m; collapsing to t upon irradiation at δ 4.87, $J_{4',5'} = J_{4',5''} = 6.0$ Hz; 1H), 3.90 (m; 1H), 3.90 (dd, $J_{5',5''} = 11.2$ Hz; $J_{4',5'} = 6.0$ Hz; 1H), 3.71 (dd; $J_{5',5''} = 11.2$ Hz; $J_{4',5''} = 6.0$ Hz; 1H), 3.52 (dd; $J_{2',2''} = 13.0$ Hz; $J_{2',3'} = 6.0$ Hz; 1H), 2.30 (ddd, collapsing to dd upon irradiation at δ 6.41 $J_{2',2''} = 13.0$ Hz, $J_{2',3'} = 4.0$ Hz, $J_{1',2'} = 7.0$ Hz; 1H), 0.95 (s; 9H), 0.90 (s; 9H), 0.00 (s; 6H), −0,05 (s; 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.2, −4.3, 18.3, 18.6, 26.0, 37.2, 62.8, 72.3, 88.2, 88.2, 128.0, 129.1, 129.1, 130.8, 134.1, 152.4, 162.6, 164.7; MS (ES+) 664 (M + 1); MS^2 (664) 320. Anal. Calcd for $C_{29}H_{44}BrN_5O_4Si_2$: C, 52.55; H, 6.69; Br, 12.06; N, 10.57. Found: C, 52.70; H, 6.65; Br, 12.10; N, 10.60.

Synthesis of 8-Bromo-O3′-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (1g). 8-Bromo-O3′,O5′-bis(*tert*-butyldimethylsilyl)-2′-deoxyadenosine **1f** (560 mg, 1.0 mmol) was dissolved in dry THF dry (20 mL). Trifluoroacetic acid/water 1:1 mixture (10 mL) was added dropwise at 0 °C to the solution. The mixture was allowed to stir at 0 °C for 1 h. The reaction mixture was then neutralized by the addition of $NaHCO_3$ (saturated solution). The resulting mixture was extracted with ethyl acetate (2 × 50 mL). The solvent was evaporated under reduced pressure/ and the residue was purified on silica gel column. The target compound was obtained as a white foam (310 mg, 0.7 mmol, 70% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (br s; 1H), 8.26 (s; 1H); 6.49 (br s; 2H), 6.42 (dd, $J_{1',2'} = 9.5$ Hz, $J_{1',2''} = 5.6$ Hz; 1H), 4.71 (d, $J_{2',3'} = 5.0$ Hz; 1H), 4.14 (br s; 1H), 3.93 (part A of a ABX system, $J_{AB} = 12.8$ Hz, $J_{AX} = 1.5$ Hz; 1H), 3.74 (part B of a ABX system $J_{AB} = 12.8$ Hz, $J_{BX} = 2.0$ Hz; 1H), 3.0 (ddd; $J_{2'',2'} = 13.0$ Hz, $J_{1',2'} = 9.5$ Hz, $J_{2',3'} = 5.0$, Hz; 1H), 2.18 (dd, $J_{2'',2'} = 13.0$ Hz, $J_{1',2''} = 5.6$,Hz, 1H), 0.95 (s; 9H), 0.10 (s; 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.5, −4.45, 18.3, 26.0, 40.9, 63.4, 74.0, 88.9, 90.7, 121.0, 127.5, 150.0, 151.4, 154.4; MS (ES+) 444 (M + 1); MS^2 (444) 214. Anal. Calcd for $C_{16}H_{26}BrN_5O_3Si$: C, 43.24; H, 5.90; Br, 17.98; N, 15.76. Found: C, 43.10; H, 5.90; Br, 18.00; N, 15.70.

Reaction of *N*-Benzoyl-O3′-(*tert*-butyldimethylsilyl)-5′-oxo-2′-deoxyadenosine (9) with Bu_3SnH. The aldehyde **9** (250 mg, 0.5 mmol) was dissolved in fluorobenzene (25 mL). AIBN (0.25 mmol, 40 mg) and Bu_3SnH (0.27 mL, 1.0 mmol) were added, and the solution was refluxed under argon atmosphere for 2 h. The solvent was removed under reduced pressure and the crude mixture analyzed by HPLC−MS and ^{1}H NMR. ^{1}H NMR showed the exclusive presence of the cyclized products (5′*S*)-**6d**[5] and (5′*S*,8*R*)-**5d** and 2′-deoxyadenosine **7d**[16] in 32:60:8 ratio. Silica gel column chromatography provided a pure sample of (5′*S*,8*R*)-**5d** as a pale yellow foam.

(5′*S*,8*R*)-*N*-Benzoyl-O3′-(*tert*-butyldimethylsilyl)-5′,8-cyclo-7,8-dihydro-2′-deoxyadenosine [(5′*S*,8*R*)-5d]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.2 (br s, disappeared on D_2O shake; 1H), 7.9 (s; 1H), 7.4−8.0 (m; 5H), 6.10 (d, $J_{1',2'} = 6.0$ Hz; 1H), 5.49 (d, disappeared on D_2O shake, $J_{NH,8} = 4.0$ Hz; 1H), 4.89 (dd, $J_{5',8} = 7.5$ Hz, $J_{NH,8} = 4.0$ Hz; collapsed to doublet on D_2O shake; 1H), 4.67 (dd, $J_{2'',3'} = 7.0$, $J_{2',3'} = 2.0$ Hz; 1H), 4.20 (d, $J_{4',5'} = 4.5$ Hz; 1H), 3.73 (dd, $J_{4',5'} = 4.5$, $J_{5',8} = 7.5$ Hz; 1H), 2.35 (1H, $J_{2',2''} = 14.0$, $J_{2'',3'} = 7.0$ Hz; 1H), 2.18 (ddd, $J_{2',2''} = 14.0$, $J_{1',2'} = 6.0$, $J_{2',3'} = 2.0$ Hz; 1H), 0.9 (s; 9H), 0.3 (s; 3H), 0.1 (s; 3H); irradiation at δ 3.73 caused an enhancement of the signal at δ 4.20 (3.5%) at δ 4.89 (1%); irradiation at δ 5.49 caused an enhancement of the signal at δ 4.67 (3%), δ 3.73 (1%), δ 2.35 (1%); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.6, −4.5, 18.3, 26.0, 42.0, 69.7, 71.1, 81.9, 86.1, 122.1, 127.9, 128.2, 128.9, 132.8, 133.0, 135.2, 149.6, 160.6, 166.1; MS (ES+) 470 (M + 1); MS^2 (470) 338, MS^3 (338) 320. Anal. Calcd for $C_{23}H_{31}N_5O_4Si$: C, 58.82; H, 6.65; N, 14.91. Found: C.58.9; H, 6.60; N, 14.95.

A solution of **5d** (47 mg, 0.10 mmol) and chloroanil (37 mg, 0.15 mmol) in *o*-xylene (3 mL) was refluxed for 20 min.[17] The solvent was eliminated under reduced pressure and the residue chromatographed on silica gel column. Gradual elution with pentane/ethyl acetate gave the ketone **8** (40 mg, 0.09 mmol, 90%).[5]

Reaction of 8-Bromo-2′-deoxyadenosine 1 with Tris(trimethylsilyl)silane [$(Me_3Si)_3SiH$]. General Procedure. A 10.0 mM solution of the appropriate 8-bromo-2′-deoxyadenosine **1** (0.30 mmol), $(Me_3Si)_3SiH$ (0.46 mL, 15 mmol), and AIBN (50 mg, 0.30 mmol) in fluorobenzene or acetonitrile (30 mL) was kept in a sealed tube in a thermostatic bath at 90 °C for 2 h. The solvent was removed under reduced pressure and the residue analyzed by HPLC−MS and ^{1}H NMR.

From 1e in Fluorobenzene. ^{1}H NMR and HPLC−MS analysis of the reaction mixture evidenced the presence of cyclonucleosides (5′*S*)-**6e** and (5′*R*)-**6e** and 2′-deoxyadenosine **7e**[16] as the only detectable compounds in 60:7:33 ratio. Silica gel column chromatography of the crude mixture led to the isolation of a pure sample of the major isomer (5′*S*)-**6e**.

(5′*S*)-N5-Benzoyl-O3′,O5′-bis(*tert*-butyldimethylsilyl)-5′,8-cyclo-2′-deoxyadenosine (5′*S*)-6e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (1H, s; 1H), 8.0 and 7.5−7.7 (m; 5H), 6.5 (d, $J = 4.5$ Hz; 1H), 5.28 (d, $J = 6.5$ Hz; 1H), 4.84 (dd, $J = 7.0$ and 4.5 Hz; 1H), 4.6 (d, $J_{4',5'} = 6.5$ Hz; 1H), 2.56 (dd, $J = 13.2$ and 7.0 Hz; 1H), 2.27 (dt, $J_d = 13.2$, 5.0, $J_t = 4.5$ Hz; 1H), 1.0 (s; 9H), 0.9 (s; 9H), 0.35 (s; 3H), 0.29 (s; 3H), 0.07 (s; 3H), 0.04 (3s; 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.6, −4.4, −4.3, 18.0, 18.9, 25.9, 26.1, 48.8, 66.3, 69.6, 85.9, 87.2, 128.2, 128.4, 129.2, 133.3, 133.3, 143.5, 148,6, 151,1, 154.2, 164.1; MS (ES+) 582 (M + 1), MS^2 (582)

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450(40), 382 (100), 318 (30). Anal. Calcd for $C_{29}H_{43}N_5O_4Si_2$: C, 59.86; H, 7.45; N, 12.04. Found: C, 59.90; H, 7.45; N, 12.00.

The minor isomer (5′*R*)-**6e** was characterized by HPLC−MS and ^{1}H NMR analysis of a (5′*S*)-**6e** and (5′*R*)-**6e** mixture.

(5′*R*)-N5-Benzoyl-O3′,O5′-bis(*tert*-butyldimethylsilyl)-5′,8-cyclo-2′-deoxyadenosine (5′*R*)-6e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s; 1H), 8.0 and 7.5−7.7 (m; 5H), 6.60 (1H, d, J = 5.0 Hz; 1H), 4.80 (s; 1H), 4.60 (s, 1H), 4.28 (dd, J = 7.0 e 4.0 Hz; 1H), 2.46 (dd, J = 13.2 and 7.0 Hz; 1H), 2.27 (m; superimposed to signals of the 5′*S*-isomer); HPLC−MS (ES+) 582 (M + 1), MS^2 (582) 450(100), 382 (30), 318 (80).

The reaction was repeated in refluxing fluorobenzene. ^{1}H NMR and HPLC−MS analysis of the reaction mixture evidenced the presence of cyclonucleosides (5′*S*,8*R*)-**5e**, (5′*R*,8*R*)-**5e**, (5′*S*)-**6e**, and (5′*R*)-**6e** and the 2′-deoxyadenosine derivative **7e** in 39:4:39:4:14 ratio. Column chromatography of the crude mixture led to the separation of a pure sample of (5′*S*,8*R*)-**5e**.

(5′*S*,8*R*)-*N*-Benzoyl-O3′,O5′-bis(*tert*-butyldimethylsilyl)-5′,8-cyclo-7,8-dihydro-2′-deoxyadenosine (5′*S*,8*R*)-5e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s; 1H), 8.20 (d; 2H), 7.4−7.6 (m; 3H), 6.17 (d, J = 6.5 Hz; 1H), 5.20 (dd, J = 7.8 and 6.0 Hz; 1H), 4.70 (dd, J = 7.0 and 2.0; 1H), 4.23 (d, $J_{4',5'}$ = 6.5 Hz; 1H), 3.90 (dd, J = 6.5 and 7.8 Hz; 1H), 2.7 (m; 1H), 2.2 (m; 1H),1.0 (s; 9H), 0.9 (s; 9H), 0.35 (s; 3H), 0.30 (s; 3H), 0.1 (s; 3H), 0.05 (3s; 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.5, −4.5, −4.3, −4.0, 18.1, 18.2, 25,7, 26.6, 42.1, 69.3, 72,8, 81.9, 86.8, 121.6, 127.9, 129.0, 129.2, 131.1, 133.2, 133.9, 143.9, 160.1, 166.1; MS (ES+) 584 (M + 1); MS^2 (584) 452 (50), 382 (30), 320 (100). Anal. Calcd for $C_{29}H_{45}N_5O_4Si_2$: C, 59.66; H, 7.77; N, 11.99. Found: C,59.75; H, 7.80; N, 11.95.

The minor isomer (5′*R*,8*R*)-**5e** showed a ^{1}H NMR signal at δ 6.10 (1H, d, J = 6.5 Hz) and a HPLC−MS signal at MS (ES+) 584 (M + 1).

The 39:4:39:4:14 mixture of compounds (5′*S*,8*R*)-**5e**, (5′*R*,8*R*)-**5e**, (5′*S*)-**6e**, (5′*R*)-**6e**, and **7e** obtained from a repeated reaction in boiling fluorobenzene was dissolved in *o*-xylene. Chloroanil (75 mg, 0.30 mmol) was added, the resulting mixture was refluxed for 20 min, and the solvent was eliminated under reduced pressure. ^{1}H NMR and HPLC−MS of the crude showed the exclusive presence of compounds (5′*S*)-**6e**, (5′*R*)-**6e**, and **7e** in a 78:8:14 ratio.

From 1e in Acetonitrile. ^{1}H NMR and HPLC-MS analysis of the reaction mixture showed the presence of cyclonucleosides (5′*S*)-**6e**, (5′*R*)-**6e,** and 2′-deoxyadenosine **7e** in 65:8:27 ratio as the only detectable compounds.

From 1f in Fluorobenzene. ^{1}H NMR and HPLC−MS of the reaction mixture showed the formation of cyclized products (5′*S*)-**6f** and (5′*R*)-**6f** and 2′-deoxyadenosine **7f**[18] in a 55:7:38 ratio as the only detectable products. Silica gel column chromatography of the crude mixture led to separation of a fraction mainly containing cyclized products **6f**, which were identified on the basis of HPLC−MS and ^{1}H NMR signals.

(5′*S*)-O3′,O5′-Bis(*tert*-butyldimethylsilyl)-5′,8-cyclo-2′-deoxyadenosine (5′*S*)-6f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s; 1H), 6.40 (d, J = 4.5 Hz; 1H), 5.90 (br s; 2H), 5.20 (d, J = 6.0 Hz; 1H), 4.83 (dd, J = 7.0 and 4.5 Hz; 1H), 4.57 (d, $J_{4',5'}$ = 6.0 Hz; 1H), 2.53 (dd, J = 13.2 and 7.0 Hz; 1H), 2.20 (dt, J_d = 13.2, J_t = 4.5 Hz; 1H), 0.9 (s; 18 H), 0.1 (s; 12H); HPLC-MS (ES+) 478 (M + 1); MS^2 (478) 346 (40), 278 (100), 214 (80)].

(5′*R*)-O3′,O5′-Bis(*tert*-butyldimethylsilyl)-5′,8-cyclo-2′-deoxyadenosine (5′*R*)-6f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.3 (s; 1H), 6.50 (d, J = 4.8 Hz; 1H), 4.73 (s; 1H), 4.57 (s; 1H); MS (ES+) 478 (M + 1); MS^2 (578) 346 (20), 278 (100), 214 (70).

From 1f in Acetonitrile. ^{1}H NMR and HPLC−MS analysis of the reaction mixture showed the presence of cyclonucleosides (5′*S*)-**6f**, (5′*R*)-**6f,** and 2′-deoxyadenosine **7f** in a 70:8:22 ratio as the only detectable compounds.

From 1g in Acetonitrile. ^{1}H NMR and HPLC−MS analysis of the reaction mixture showed the presence of products (5′*S*)-**6g**, (5′*R*)-**6g**, and 2′-deoxyadenosine **7g**[18] in a 38:32:30 ratio as the only detectable compounds. Reaction products were not separable by column chromatography.

(5′*S*)-O3′-(*tert*-butyldimethylsilyl)-5′,8-cyclo-2′-deoxyadenosine (5′*S*)-6g: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s; 1H), 6.38 (d, $J_{1',2''}$ = 4.8 Hz; 1H), 5.1 (d, $J_{4',5'}$ = 6.4 Hz; 1H), 4.75 (dd, $J_{2',3'}$ = 7.2 Hz, $J_{2'',3'}$ = 4.0 Hz; 1H), 4.50 (d, $J_{4',5'}$ = 6.4 Hz; 1H), 2.46 (dd, $J_{2',2''}$ = 13.2, $J_{2',3'}$ 7.2 Hz; 1H), 2.06 (ddd,, $J_{2',2''}$ = 13.2, $J_{1',2''}$ = $J_{2',3'}$ = 4.8 Hz 1H), 0.85 (s, 9H), 0.02 (s; 6H); MS (ES+) 364 (M + 1); MS^2 (364), 164 (100), 136 (60).

(5′*R*)-O3′-(*tert*-butyldimethylsilyl)-5′,8-cyclo-2′-deoxyadenosine (5′*R*)-6g: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s; 1H), 6.44 (d, $J_{1',2''}$ = 5.0 Hz; 1H), 4.65 (s; 1H), 4.43 (s; 1H), 4.37 (m; 1H), 2.36 (dd, $J_{2',2''}$ = 13.2, $J_{2',3'}$ 7.0 Hz; 1H), 2.0 (ddd, $J_{2',2''}$ = 13.2, $J_{1',2''}$ = $J_{2',3'}$ = 5.0 Hz; 1H), 0.85 (s, 9H), 0.06 (s; 6H); MS (ES+) 364 (M + 1); MS^2 (364) 164 (100), 136 (10).

From 1a in Acetonitrile. ^{1}H NMR and HPLC−MS analysis of the reaction mixture showed the presence of products (5′*S*)-**6a**[5] and (5′*R*)-**6a**[5] and 2′-deoxyadenosine **7a** in a 47:38:15 ratio as the only detectable compounds.

Photolysis of 8-Bromo-2′-deoxyadenosine 1 in Acetonitrile. General Procedure. A 1.0 mM solution of the appropriate 8-bromo-2′-deoxyadenosine **1** in acetonitrile (10 mL) was irradiated under argon atmosphere for 30 min, unless otherwise stated, using a 125 W medium-pressure mercury lamp. The solvent was eliminated under reduced pressure and the residue analyzed by HPLC−MS and ^{1}H NMR.

From 1f. HPLC−MS and ^{1}H NMR analysis showed the presence of products (5′*S*)-**6f**, (5′*R*)-**6f**, and **7f** as the only detectable compounds in a 52:18:30 ratio.

From 1g. The reaction was monitored at different irradiation times by HPLC−MS and ^{1}H NMR. In all cases, compounds (5′*R*)-**6g**, (5′*S*)-**6g**, 2′-deoxyadenosine **7g**, and product **B** were detected as the only reaction products. Relative yields are reported in Table 2. The reaction mixture obtained at 3 h irradiation time was unsuccessfully chromatographed on silica gel column to obtain a pure sample of product **B** [^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (s; disappeared upon D_2O shake; 1H), 9.40 (s; disappeared upon D_2O shake; 1H), 8.78 (s; 1H), 7.0 (d, $J_{1',2'}$ = 6.0 Hz; collapsing to singlet upon irradiation at δ 2.30; 1H), 6.65 (s; 1H), 4.92 (dd, $J_{2',3'}$ = 4.5 Hz, $J_{2''3'}$ = 7.0 Hz; collapsing to doublet, J = 4.5 Hz, upon irradiation at δ 2.85, collapsing to doublet, J = 7.0 Hz, upon irradiation at δ 2.30; 1H), 2.85 (dd, $J_{2',2''}$ = 14.0, $J_{2''3'}$ = 7.0, 1H), 2.30 (1H, m; 1H), 0.9 (s; 9H), 0.1 (s; 6H)].

From 1a. The reaction was monitored at different irradiation times by HPLC−MS and ^{1}H NMR analysis. In all cases, compounds (5′*R*)-**6a**, (5′*S*)-**6a**, **7a**, and product **A** were detected as the only reaction products. Relative yields are reported in Table 2. The reaction mixture obtained at 3 h irradiation time was unsuccessfully chromatographed on silica gel and RP-C18 column to obtain a pure sample of product **A** [^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (s; disappeared upon D_2O shake; 1H), 9.38 (s; disappeared upon D_2O shake; 1H), 8.70 (s; 1H), 7.50 (br s; disappeared upon D_2O shake; 2H), 6.98 (d, $J_{1',2'}$ = 6.0 Hz; collapsing to singlet upon irradiation at δ 2.40; 1H), 6.57 (s; 1H), 6,00 (br d; disappeared upon D_2O shake; collapsing to singlet upon irradiation at δ 4.72; 1H), 4.72 (br dd, collapsing to dd upon D_2O shake; $J_{2',3'}$ = 2.4 Hz, $J_{2''3'}$ = 7.0 Hz; collapsing to doublet, J = 7.0 Hz, upon irradiation at δ 2.40 and to doublet, J = 2.4 Hz, upon irradiation at δ 2.80; 1H), 2.80 (dd, $J_{2',2''}$ = 15,0, $J_{2''3'}$ = 7.0; 1H), 2.40 (m; 1H)].

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