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Direct Synthesis of 8-Fluoro Purine Nucleosides via Metalation−Fluorination

Arun K. Ghosh, Pallavi Lagisetty, and Barbara Zajc*

Department of Chemistry, The City College and The City University of New York, 160 Convent Avenue, New York, New York 10031

barbaraz@sci.ccny.cuny.edu

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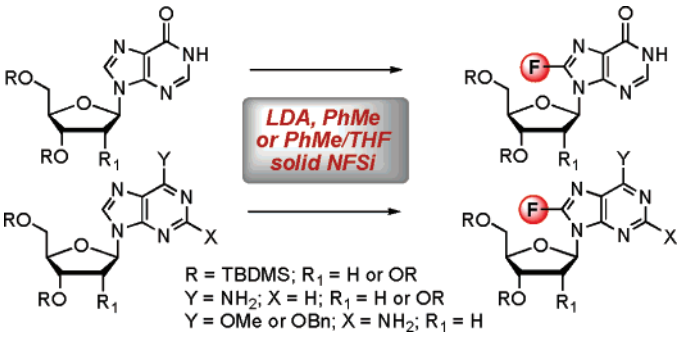

A straightforward access to protected 8-fluoro nucleosides via metalation−electrophilic fluorination under heterogeneous reaction conditions is reported. This is the first synthesis of 8-fluoro-2′-deoxyribonucleoside derivatives. Phenylsulfonyl substituted nucleosides are accompanying byproducts, possibly indicating a competing radical process. Higher yields of 8-fluoro derivatives were obtained with 2′-deoxyribonucleosides, as compared to ribonucleosides. Deprotection of the hydroxyl groups leading to 8-fluoro-2′-deoxyadenosine using TASF in methylene chloride demonstrates the compatibility of desilylation with 8-fluoro substituted nucleosides. NMR data indicate a syn conformation of the 8-fluoro derivatives.

Introduction

Fluorinated nucleosides and their analogues are of interest for their biological activity, and several methods have been reported for the introduction of fluorine either into the sugar moiety or into the nucleobase.[1] Among the latter, substitution at the C8 position of the purine base has received much less attention. The few methods that report the synthesis of 8-fluoro purine nucleosides utilize reaction of nucleosides with F_2/N_2,[2] the halex reaction with C8 bromo[3] or chloro[4] substituted nucleosides, and electrochemical oxidation in $CH_3CN/Et_3N\cdot 3HF$.[5] To the best of our knowledge, there are no reports on the synthesis of C8 fluoro substituted deoxynucleosides. Herein, we report the first synthesis of protected 8-fluoro derivatives of deoxyinosine, deoxyadenosine, and deoxyguanosine. Furthermore, to our knowledge, this study constitutes the first synthesis of 8-fluoro purine nucleosides via direct metalation−fluorination.

Recently, Roy and Schneller[6] reported that upon attempted fluorination of the C8 carbanion of a protected 5′-noraristeromycin with *N*-fluorobenzenesulfonimide (NFSi), no fluorination was observed, but the 8-phenylsulfonyl derivative was formed.[6] A single electron-transfer mechanism (SET) was suggested to lead to the 8-phenylsulfonyl product. In our recent work, we

* Corresponding author. Tel: (212) 650-8926; fax: (212) 650-6107.

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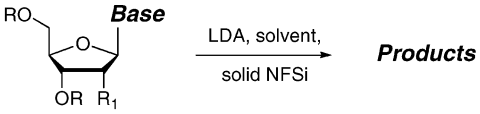
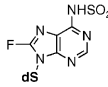
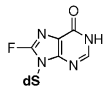
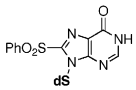
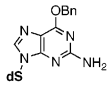
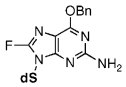
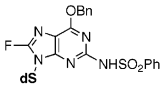
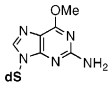
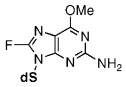
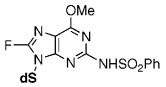
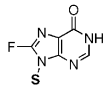
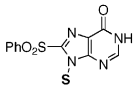
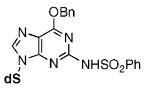
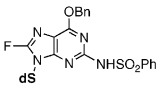
TABLE 1. Fluorination of Nucleosides



dS: R = TBDMS, R_1 = H
S: R = TBDMS, R_1 = OTBDMS

rxn	substrate	solvent	products, isolated yields (%)		
1	 **1**	PhMe **1**: 0.06 M	 **8**	 **9**	**8** 27 (39)[a] **9** 11 **1**[b] 30
2	 **2**	PhMe THF 1:3.5 **2**: 0.033 M	 **10**	 **11**	**10** 34 (52)[a] **11** 14 **2**[b] 33
3	 **3**	PhMe **3**: 0.068 M	 **12**	 **13**	**12** 14 (32)[a] **13** 11 **3**[b] 56
4	 **4**	PhMe **4**: 0.077 M	 **14**	 **15**	**14** 15 (28)[a] **15** 6 **4**[b] 48
5	 **5**	PhMe **5**: 0.066 M	 **16**		**16** 18[c] (25)[a,c] **5**[b] 28[c]
6	 **6**	PhMe THF 1:3 **6**: 0.041 M	 **17**	 **18**	**17** 16[d] (25)[a,d] **18** 21[d] **6**[b] 38[d]
7	 **7**	PhMe **7**: 0.058 M	 **13**		**13** 20 (34)[a] **7**[b] 40

[a] Yield based on recovered starting material. [b] Recovered starting material. [c] Prolonged reaction times: after addition of NFSi: −78 °C for 90 min, 0 °C for 2 h, rt for 1 h. [d] Prolonged reaction times: after addition of NFSi: −78 °C for 90 min, −10 to 0 °C for 90 min.

have discovered that fluorination of carbanions by NFSi resulted in only recovered starting material when reactions were performed under homogeneous conditions. However, under heterogeneous conditions, high yields of fluorinated products were obtained.[7] In this context, the recovery of unfluorinated derivatives in the fluorination of carbanions has also been suggested to occur via a SET mechanism.[8] This prompted our interest in reinvestigating the metalation-fluorination of nucleosides. We reasoned that metalation−fluorination under heterogeneous conditions might yield the desired C8 fluoro derivatives.

Results and Discussion

To test our hypothesis, the fluorination of di-TBDMS protected 2′-deoxyadenosine was undertaken. Variation of reaction conditions with regard to base (LDA and *n*-BuLi), solvent (toluene and THF), temperature (−78 °C, 0 °C, and room temperature), and reaction time as well as the stoichiometry of reagents resulted in the following optimized reaction procedure. The nucleoside was dissolved in toluene (or a mixture of toluene and THF to ensure solubility) and cooled to −78 °C. LDA (5 equiv) was added, and the mixture was allowed to stir at −78 °C for 2 h (90 min for **1**, Table 1). Solid NFSi (3 equiv) was then added, and the stirring continued for 90 min at −78 °C (75 min for **1**) and at 0 °C for 30 min, followed by standard isolation (see the Supporting Information). The outcome of the reaction depends highly on the solvent used, and for each substrate, the solvent system was optimized. Table 1 shows the product distributions for a series of deoxyribonucleosides and ribonucleosides, along with the solvent system used in each case.[9]

Fluorination of protected 2′-deoxyadenosine **1** resulted in a reaction mixture that contained two fluorinated products and the starting material.[10a] The mixture was separated by column chromatography to give a major product, 8-fluoro-2′-deoxyad-

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(8) (a) Differding, E.; Rüegg, G. M. *Tetrahedron Lett.* **1991**, *32*, 3815−3818. (b) Differding, E.; Wehrli, M. *Tetrahedron Lett.* **1991**, *32*, 3819−3822. (c) Barnes, K. D.; Hu, Y.; Hunt, D. A. *Synth. Commun.* **1994**, *24*, 1749−1755.

(9) In some cases, the formation of other very minor byproducts was observed that we were unable to isolate.

(10) (a) Minor quantity (approximately 5%) of the 8-phenylsulfonyl derivative of **1** was also observed in the crude reaction mixture. (b) For byproduct **9**, the H-2 proton was not clearly discernable in the ^{1}H NMR ($CDCl_3$ or C_6D_6), due to other aromatic resonances from the phenylsulfonyl

enosine **8** (entry 1, 27% isolated yield, 39% based on recovered starting material), and a minor product, 8-fluoro-N^6-phenylsulfonyl-2′-deoxyadenosine **9** (entry 1, 11% isolated yield).[10b] The total yield of the 8-fluoro derivatives (combined **8** and **9**) was consistently around 40%, but in several repetitions, the ratio of **8** to **9** varied when THF−toluene was used as the solvent, indicating that subtle factors could influence the reaction. More consistent yields of **8** and **9** were obtained in toluene, when fresh LDA and freshly prepared **1** were used. Both products showed fluorine resonances at δ −102.1 ppm (**8**) and δ −99.1 ppm (**9**) in ^{19}F NMR. The purine C8 proton resonance (δ 8.14 ppm) was no longer present in the ^{1}H NMR of **8** and **9**. This and the ^{19}F resonances are indicative of C8 fluorine substitution. Also, ^{19}F chemical shifts of **8** and **9** were consistent with that reported in the literature for protected 8-fluoro adenosine.[11] Fluorination of protected 2′-deoxyinosine **2** (entry 2) resulted in 8-fluoro-2′-deoxyinosine as the major product (**10**, 34% isolated yield, 52% based on recovered starting material), which showed a fluorine resonance at δ −101.8 ppm. A minor product (**11**, 14% isolated yield) on the other hand, did not show any fluorine resonance. The ^{1}H NMR of **11** showed a disappearance of the purine C8 proton resonance (δ 8.15 ppm) with the concomitant appearance of new phenyl resonances in the aromatic region. On the basis of the NMR data, as well as a comparison to the data of the N^1-arylsulfonyl and O^6-arylsulfonyl derivatives, the structure of **11** was assigned as 8-phenylsulfonyl-2′-deoxyinosine. Next, fluorination of the protected O^6-benzyl 2′-deoxyguanosine derivative was performed (**3**, entry 3). The 8-fluoro derivative **12** was isolated in a lower yield (14%), along with the 8-fluoro-N^2-phenylsulfonyl derivative (**13**, 11%) and the recovered starting material (56%). Similar results were obtained for the O^6-methyl derivative **4** (entry 4). Finally, the reactivity of ribonucleosides was tested as well. The same reactivity pattern as in the 2′-deoxyribonucleoside series was observed. However, yields of the 8-fluoro products in the ribonucleosides were lower. Protected adenosine **5** gave 14% of the 8-fluoro derivative, and inosine **6** gave only 5% of the desired 8-fluoro product, along with 8-phenylsulfonyl derivative as the major product (20%). However, upon prolonged reaction times, the yield of the 8-fluoro derivative in the case of **5** (entry 5) increased to 18%, and in the case of **6** (entry 6), the yield of the 8-fluoro derivative increased to 16%, while that of the 8-phenylsulfonyl derivative **18** remained nearly the same (21%).

Fluorinated nucleosides, presumably formed through a S_N process, were obtained with all substrates studied, along with recovered starting materials and phenylsulfonyl derivatives. The presence of the latter two suggests a parallel SET mechanism.[6−8] It is therefore likely that under heterogeneous metalation−fluorination conditions, a competing nucleophilic substitution reaction and SET process resulted in the mixtures of products observed. On the other hand, under homogeneous reaction conditions, SET possibly becomes the major process leading only to recovered starting materials and phenylsulfonyl-derived products.[6] In the case of ribonucleosides, it is possible that the S_N reaction is slower due to steric reasons since higher conversions were achieved upon prolonged reaction times. Furthermore, due to solubility constraints, as in the case of deoxyinosine **2**, a mixture of toluene−THF was used in the case of protected inosine **6** as well. However, this also increases the solubility of NFSi (added as solid). Both the increased solubility of NFSi as well as the increased steric bulk of the ribose derivative **6** may have contributed to the lower yield of the 8-fluoro product **17** and the higher yield of the 8-phenylsulfonyl derivative **18**.

TABLE 2. Spectroscopic Data of Starting and C8 Fluoro-Derived Ribonucleosides, 2′-Deoxyribonucleosides, and 2-F-dI[a]

	^{19}F		^{1}H			^{13}C
compound	C(8)-F	H-8	H-2	H-2′α	H-2′β	C8 ($^2J_{CF}$)
1		8.14	8.36	2.43	2.64	139.0
8	−102.1		8.30	2.26	3.18	149.7 (215.6)
5		8.15	8.33		4.69	139.7
16	−103.3		8.30		5.17	151.8 (253.6)
2		8.15	8.11[b]	2.45	2.56	138.5
10	−101.8		8.04[b]	2.30	3.01	150.8 (252.6)
2FdI[c]	−61.0	8.12		2.44	2.52	139.1
6		8.23	8.09[b]		4.51	139.1
17	−102.2		8.11[b]		4.95	151.1 (254.0)
3		7.90		2.34	2.57	137.6
12	−103.6			2.21	3.02	150.6 (250.8)
7		8.07		2.33−2.45 (2H2′)		139.4
13	−100.1			2.19	2.86	151.6 (252.8)
4		7.91		2.35	2.57	137.6
14	−103.5			2.22	3.02	150.5 (250.8)

[a] Solvent: $CDCl_3$; referenced to $CFCl_3$ (^{19}F), $CHCl_3$ in $CDCl_3$ (^{1}H), and $CDCl_3$ (^{13}C). [b] Sample concentration not determined; chemical shifts are concentration dependent (see Table 3). [c] 2-Fluoro-3′,5′-bis-*O*-(*t*-butyldimethylsilyl)-2′-deoxyinosine.

Since the fluorination of O^6-benzyl 2′-deoxyguanosine derivative (**3**) gave nearly equal amounts of the 8-fluoro (**12**) and 8-fluoro-N^2-phenylsulfonyl (**13**) products, we were curious as to whether a better yield could be obtained in the fluorination of the N^2-phenylsulfonyl-derivative of **3**. Furthermore, this would allow us to unequivocally confirm the structure of **13**. Therefore, **7** was synthesized via phenylsulfonylation of **3** and subjected to fluorination. In this case, a 20% yield of the 8-fluoro product **13** was obtained (Table 1, entry 7). This is roughly similar to the overall fluorination efficiency of **3** (Table 1, entry 3, 25% combined yield of products **12** and **13)**.

We also made an attempt at decreasing the amount of radical-derived products by performing the fluorination reaction of protected 2′-deoxyinosine (**2**) in the presence of the radical scavenger TEMPO. TEMPO appeared to be the best choice that would be unreactive toward the fluorinating agent and to the basic reaction conditions used. Substrate **2** was chosen since its fluorination also yielded 14% of the 8-phenylsulfonyl side product **11** (Table 1, entry 2). The fluorination of **2** in the presence of TEMPO gave no yield improvement of the desired 8-fluoro derivative **10**, but the formation of additional byproducts, possibly resulting from reaction between TEMPO and radical intermediates, was observed.

Further, NMR spectra of the C8 fluoro purine of ribo and 2′-deoxyribonucleosides were compared, along with the starting substrates (Table 2). Initially, the H-2 (where present) and H-8 protons of purine and H-2′α and H-2′β protons of the sugar moiety were assigned via NOESY. Purine H-2 in protected dA (**1**) and A (**5**) was more downfield shifted than H-8. By contrast, in protected dI (**2**) and I (**6**), H-8 was more downfield shifted than H-2. For example, in dI, the resonance at 8.15 ppm showed NOE with H-1′ at 6.41 ppm, whereas the H-2 resonance at 8.11 showed NOE with the NH resonance at 12.92 ppm. Upon

moiety. However, HRMS supports structure **9**. Further, low resolution MS showed besides a molecular ion peak at *m*/*z* 638 ($M^+ + 1$) a base peak at *m*/*z* 294, which was consistent with this structure and would be produced by loss of the saccharide unit.

(11) ^{19}F resonance in $CDCl_3$ of 8-fluoro-2′,3′,5′-tris-*O*-(acetyl)-adenosine is at −102.9 ppm.[2a]

TABLE 3. Effect of Concentration on ^{1}H Chemical Shifts of H-2, H-8, and NH[a]

compound	concn (M)	H-2[b]	H-8[b]	NH[b]
1	0.02	8.35	8.13	
	0.09	8.34	8.13	
8	0.02	8.31		
	0.09	8.30		
2	0.02	8.09	8.14	12.74
	0.09	8.14	8.15	13.03
10	0.02	8.10		13.05
	0.09	8.15		13.22
6	0.02	8.09	8.23	12.89
	0.09	8.14	8.23	13.16
17	0.02	8.10		13.05
	0.09	8.16		13.24

[a] Solvent: $CDCl_3$; referenced to $CHCl_3$ in $CDCl_3$. [b] ^{1}H chemical shifts.

TABLE 4. Selected ^{13}C Chemical Shifts of Starting and C8 Fluoro dA, A, dI, and dG[a]

compound	C4′	Δδ[b]	C1′	Δδ[b]	C3′	Δδ[b]	C2′	Δδ[b]
1	87.9		84.3		71.9		41.3	
8	87.8	−0.1	83.0	−1.3	72.0	+0.1	37.5	−3.8
5	85.5		88.3		72.0		75.7	
16	86.0	+0.5	87.3	−1.0	72.3	+0.3	72.5	−3.2
2	88.0		84.5		71.7		41.6	
10	87.9	−0.1	83.2	−1.3	71.9	+0.2	37.9	−3.7
2FdI[c]	88.2	+0.2	84.7	+0.2	71.7	0.0	41.5	−0.1
3	87.7		83.7		72.0		40.9	
12	87.5	−0.2	82.5	−1.2	72.0	0.0	37.4	−3.5

[a] Nucleosides: 0.047 M in $CDCl_3$; referenced to $CDCl_3$. [b] Chemical shift difference observed upon substitution: − for upfield shift and + for downfield shift. [c] 2-Fluoro-3′,5′-bis-*O*-(*t*-butyldimethylsilyl)-2′-deoxyinosine.

fluorination, the resonance at 8.04 in 8-F-dI (**10**) showed a strong NOE with the NH proton at 12.54 ppm, supportive of fluorination at the 8-position. In the case of sugar H-2′ protons, H-2′β showed NOE with H-8, which was not the case with H-2′α. Furthermore, H-2′β showed a stronger NOE with H-3′, whereas H-2′α showed a stronger NOE with H-1′.

Each C-8 fluoro derivative showed a ^{19}F resonance at about −100 ppm, and the C8 resonance at ∼138 ppm disappeared and was replaced by a doublet at ∼150 ppm (Table 2). A common feature in the ^{1}H NMR spectra of all 8-fluoro deoxyribonucleosides was an approximately 0.5 ppm downfield shift of the H-2′β and a small upfield shift for H-2′α proton on the sugar moiety. Similarly, 8-F substituted ribonucleosides showed a ∼0.5 ppm downfield shift of H-2′. Such a downfield shift in deoxyribo and ribonucleosides has been reported upon C8 substitution by other substituents, including halogens.[12−14] Whereas most literature data are reported for unprotected nucleosides in polar solvents, Gannett and Sura have shown the same trend for downfield shifted H-2′ with silylated nucleosides in $CDCl_3$.[13]

In interpreting the NMR spectra of 8-fluoro-dI (**10**), we observed that chemical shifts of the H-2 and NH protons were concentration dependent, whereas H-8 and other protons in the compound were not. Upon further analysis, a similar behavior was observed in the ^{1}H NMR spectra of dI (**2**), as well as I (**6**) and 8-F-I (**17**). These concentration dependent chemical shifts would be consistent with intermolecular H-bonding where the NH proton and the C(O) of the purine are involved. In such an event, not only would the NH proton be affected but also H-2 that is proximal to the H-bonded site. H-8 and other protons can be expected to be largely unchanged. In contrast, the H-2 chemical shift in dA (**1**) and 8-F-dA (**8**) did not show any concentration dependence. Table 3 shows chemical shifts of NH (where present), H-2, and H-8 at two different concentrations for dA, dI, I, and their 8-fluoro derivatives. Other substrates were not subjected to this analysis. As is clear from Table 3, upon increasing the concentration, a downfield shift of NH and H-2 protons occurs in I and dI series consistent with increased intermolecular associations.

Next, ^{13}C resonances of the saccharide moiety in the fluoro derivatives were compared to those of the starting nucleosides. The most distinctive feature upon C8 substitution is a ∼3.5 ppm upfield shift of C2′ (Table 4). A smaller upfield shift of ∼1 ppm was also observed for C1′ upon 8-F substitution (Table 4).[15]

In assessing syn and anti conformations of nucleosides, a dramatic downfield shift of H-2′ and an upfield shift of C2′ are reported in the literature for the syn conformation.[12−14,16] Both these features were observed in the NMR spectra of silyl protected 8-fluoro nucleosides described here, suggesting that the 8-fluoro derivatives adopt a syn conformation.

As a comparison, di-TBDMS protected 2-fluoro-2′-deoxyinosine (2FdI) was synthesized,[17] and its data are also included in Tables 2 and 4. In the 2FdI case, its ^{19}F signal appears at −61.0 ppm, whereas the chemical shifts of the H-2′ protons and C2′ carbon resemble those of protected dI (**2**).

Finally, we were interested in assessing whether hydroxyl group deprotection could be achieved. Removal of hydroxyl protecting groups in 8-fluoro substituted nucleosides has proven to be a nontrivial process. An enzymatic method for the removal of acetate protecting groups has been reported.[2c] More recently, due to the difficulties associated with basic deprotection, acid-labile (2′,3′-acetonide 5′-THP) protection has been implemented.[3b] This, however, is not as readily applicable to the more acid-sensitive purine deoxyribonucleosides. We therefore tested the feasibility of the removal of the TBDMS groups on the silylated 8-fluoro-2′-deoxyadenosine (**8**). Various conditions were tested (e.g., CsF/MeCN, CsF/18-Cr-6/MeCN, 1% I_2/MeOH, DDQ/MeCN:H_2O 9:1, tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)/MeCN, and TASF/DME) with little success. Using TASF in CH_2Cl_2, deprotection of **8** could be accomplished in 26% yield (29% based on recovered **8**; see Supporting Information for details). In our experience, it appears that the deprotection and decomposition are concomitant processes. However, the silyl protected fluoro nucleosides are generally stable in solution and to chromatography conditions. Comparably, for the 2′,3′-acetonide 5′-THP protected adenosine, it has been reported that hydroxyl group deprotection using formic or acetic acid led to the displacement of fluorine, and this took place only after complete deprotection of OH groups.[3b]

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(15) Weaker downfield shifts have been reported for C3′ and C4′. The extent to which C1′ was downfield shifted depended on the substituent: 1.38 for 8-Cl adenosine and 2.45 for the 8-Br analogue[12] and 1.4 for 8-Cl dG, 2.5 for 8-Br dG, and 4.8 for 8-I dG.[14] An upfield shift of 1.50 was reported for C1′ of 8-fluoroadenosine, as compared to adenosine.[2c]
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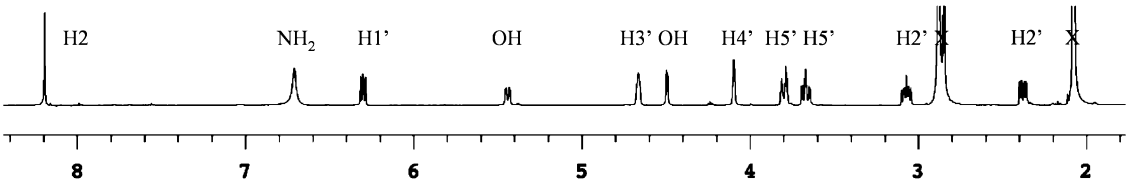

FIGURE 1. ^{1}H NMR spectrum of 8-fluoro-2′-deoxyadenosine in acetone-d_6.

Although we have proposed a syn conformation of the protected derivatives based upon NMR analysis, there is clear evidence for this conformation in the deprotected 8-fluoro-2′-deoxyadenosine (8-F-dA). It has been shown for 2′-deoxyadenosine derivatives that the appearance of the H-5′ resonances is dependent upon two factors: the predominant purine conformation and an intramolecular hydrogen bond that is dependent upon that conformation. In nonpolar solvents, an intramolecular 5′-OH···N3 hydrogen bond has been proposed in a syn conformation.[18] In such a case, one H-5′ proton is strongly coupled with the 5′-OH resulting in the appearance of a pseudo-triplet for that proton, and the other geminal H-5′ appears only as a doublet.[18] A similar behavior has been reported for purine-like C-nucleosides even in the polar solvent DMSO.[19] Here, ^{1}H NMR spectra and resolution-enhanced spectra of 8-F-dA were obtained (the resolution-enhanced spectrum is shown in Figure 1). The previously described pattern was observed in the fairly polar acetone-d_6. One H-5′ appears as a broadened pseudo-triplet of doublets (3.64 ppm, J_{app} = ∼11.1, 2.1), whereas the other geminal H-5′ appears as a broadened doublet of multiplets (3.77 ppm, J = 12.2). Upon resolution enhancement, one H-5′ appeared as a ddd (J = 12.5, 9.8, 2.8) and the other as a ddd (J = 12.5, 5.8, 3.2). This clearly indicates different couplings of the C5′ protons (9.8 and 3.2 Hz) with the 5′-OH, which would be possible with a rigidly held structure resulting from an intramolecular 5′-OH···N3 hydrogen bond. In this case also, one H-2′ appears at 2.35 ppm and the other at 3.04 ppm, consistent with the typical downfield shift observed in TBDMS protected 8-fluoro substituted nucleosides.[20] The presence of the fluorine was confirmed by the resonance at δ −106.9 ppm in the ^{19}F NMR of 8-F-dA. Among ribonucleosides, a higher preference for a syn conformation has been suggested for unprotected 8-fluoroadenosine, as compared to adenosine.[2c]

We have shown for the first time that 8-fluoropurine ribo and 2′-deoxyribonucleosides can be synthesized via metalation−fluorination under heterogeneous fluorination conditions. Product distribution suggests competing ionic and radical processes. Since the outcome of the reaction depends strongly on the solubility of substrates, the choice of reaction solvent is highly substrate dependent. To the best of our knowledge, this is also the first synthesis of 8-fluoro-2′-deoxyribonucleosides. By deprotection of silyl protected 8-fluoro-2′-deoxyadenosine, we have also demonstrated that silyl removal is compatible with the presence of the 8-fluoro substituent. On the basis of NMR evidence, a syn conformation of the 8-fluoro derivatives is proposed.

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(20) For comparison, the ^{1}H NMR spectrum of 2′-deoxyadenosine in acetone-d_6 shows a similar pattern for H-5′ protons with the two H-2′ protons appearing at 2.32 and 2.92 ppm.

Experimental Section

General Procedure for Fluorination of 3′,5′-Bis-*O*-(*t*-butyldimethylsilyl) Protected 2′-Deoxyribonucleosides (1−4, 7) and 2′,3′,5′-Tris-*O*-(*t*-butyldimethylsilyl) Protected Ribonucleosides (5, 6). A stirring solution of protected ribonucleoside or 2′-deoxyribonucleoside (1 molar equiv) in dry solvent (toluene or toluene−THF mixture; the solvent and the amount of solvent per mmol of nucleoside depended on the solubility of the nucleoside), was cooled to −78 °C (dry ice/*i*-PrOH) under nitrogen. LDA (5 molar equiv of a 2.0 M solution in heptane/THF/EtPh) was added to the reaction mixture, and the mixture was allowed to stir at −78 °C for 2 h (1.5 h for **1**). After that time, solid NFSi (3 molar equiv) was added. The mixture was allowed to stir at −78 °C for 90 min (75 min for **1**), then warmed to 0 °C with continued stirring for an additional 30 min (**1**−**4** and **7**). In the case of **5**, the reaction mixture was allowed to stir at −78 °C for 90 min after the addition of NFSi, then at 0 °C for 2 h and at room temperature for 1.5 h. In the case of **6**, the reaction mixture was allowed to stir at −78 °C for 90 min after the addition of NFSi and then at −10 °C to 0 °C for 1.5 h. Sat aq NH_4Cl was added to the mixture, and the layers were separated. The aqueous layer was extracted with EtOAc (3×), and the combined organic layer was washed with sat aq $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude reaction mixtures were purified by column chromatography on silica gel. For each substrate, the amount of substrate and solvent used in the reaction, eluting solvent for chromatography, product yield, and spectroscopic data are given under the specific compound headings in the Supporting Information.

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Supporting Information Available: Experimental details; ^{1}H NMR spectra of **8**, **10**, **12**−**14**, **16**, **17**, and 8-F-dA; as well as ^{19}F NMR spectrum of 8-F-dA. This information is available free of charge via the Internet at http://pubs.acs.org.

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