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Nucleic Acid Related Compounds. 91. Biomimetic Reactions Are in Harmony with Loss of 2′-Substituents as Free Radicals (Not Anions) during Mechanism-Based Inactivation of Ribonucleotide Reductases. Differential Interactions of Azide, Halogen, and Alkylthio Groups with Tributylstannane and Triphenylsilane[1]

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Abstract: The initial step in the mechanism-based inactivation of ribonucleotide reductases by 2′-chloro-2′-deoxynucleotides is abstraction of H3′ by a proximal free radical on the enzyme. The C3′ radical is postulated to undergo spontaneous loss of chloride, and the resulting cationic radical loses a proton to give a 3′-keto intermediate. Successive β-eliminations produce a Michael acceptor which causes inactivation. This hypothesis would predict rapid loss of mesylate or tosylate anions from C2′, but sluggish loss of azide or thiomethoxide. In contrast, loss of azido and methylthio radicals from C2′ should occur readily whereas homolysis to give (methyl or tolylsulfonyl)oxy and fluoro radicals should be energetically prohibitive. Protected 3′-*O*-(phenoxythiocarbonyl)-2′-substituted nucleosides were treated with tributylstannane/AIBN or triphenylsilane/dibenzoyl peroxide in refluxing toluene. The 2′-*O*-(mesyl and tosyl) and 2′-fluoro compounds underwent direct radical-mediated hydrogenolysis of the thionocarbonate group to give 3′-deoxy-2′-substituted products, whereas 2′-(azido, bromo, chloro, iodo, and methylthio)-3′-thionocarbonates gave 2′,3′-didehydro-2′,3′-dideoxy derivatives via loss of 2′-substituents from an incipient C3′ radical. These results are in harmony with loss of radicals, but not anions, from C2′. The well-known radical-mediated hydrogenolytic cleavage of halogen and methylthio (slow) groups from C2′ of the 3′-hydroxy (unprotected) precursors and reduction of 2′-azides to amines occurred with tributylstannane/AIBN. Triphenylsilane/dibenzoyl peroxide gave parallel (but slower) hydrogenolysis with the 2′-(iodo, bromo, and methylthio) compounds, but cleavage of the 2′-chloro group was very slow and no reduction of 2′-azides to amines was detected. Rather, the latter system effected slow hydrogenolytic removal of the 2′-azido group. Thus, chemoselective differentiation of certain functional groups is possible with triphenylsilane and tributylstannane. Reduction of azides to amines with tributylstannane is known, but hydrogenolytic deazidation (slow) with triphenylsilane in the absence of amine formation appears to be novel.

Introduction

Ribonucleotide reductases execute 2′-deoxygenation of ribonucleoside 5′-di- and triphosphates in unique de novo biosyn-

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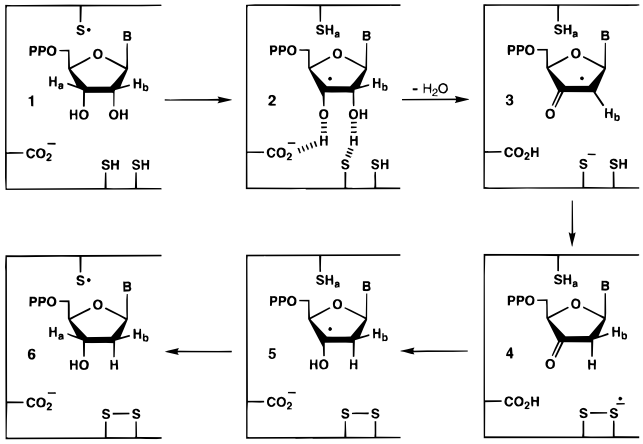
thetic pathways to DNA monomers.[2] The mammalian reductases are tightly controlled and present attractive chemotherapeutic targets for intervention with neoplastic replication of cells and proliferation of viruses.[2,3] Structural and mechanistic studies by the Swedish group demonstrated the function of allosteric control sites and redox dithiol/disulfide pairs on the R1 subunit and a tyrosine-centered free radical associated with a μ-oxo-bridged iron complex in the R2 subunit.[4,5] Rationalization of reduction of substrates and inactivation with 2′-substituted nucleotide analogues was clarified and refined by the elegant molecular mechanistic investigations of Stubbe and co-workers,[6−9] and reviews are available.[2,9g] New inhibitors of ribonucleotide reductases have been designed and synthesized.[3,10]

Stubbe's hypotheses for radical-mediated 2′-deoxygenation of the glycol[2c,d,6,9g] (Scheme 1) and inactivation of ribonucleotide reductases by 2′-chloro-2′-deoxynucleotides[2c,d,7,8,9g] (Scheme 2) were based on mechanisms proposed for conversions of ethylene glycol and chloroethanol to acetaldehyde with Fenton's reagent. That chemistry was predicated on generation of hydroxyl radicals with iron(II)/hydrogen peroxide and abstraction of carbinol hydrogen by a hydroxyl radical. However, Sawyer has recently challenged the generality of the Fenton mechanisms and showed that different iron chelate species gave different product distributions with model substrates.[11] Noteworthy was the observation that *none* of the results with iron(II) reagents paralleled product distributions with "authentic" hydroxyl radicals generated by radiolysis of water. This also might argue for more participation by protein prosthetic groups (Scheme 1)[9g] in mammalian and *Escherichia coli* ribonucleotide reductases than indicated in the original intuitively elegant mechanism for 2′-deoxygenation of substrates.[6] Abstraction of H3′ (H_a) from substrate nucleotide **1** gives 3′-radical **2**, which is proposed to be activated to give **3** by hydrogen bonding of OH3′ to a carboxylate and hydrogen bonding/protonation of O2′ by a cysteine pair. Such removal of the OH3′ proton by carboxylate[9g] with loss of O2′ as water constitutes a more plausible[12] anionic radical-mediated process than the original cation radical hypothesis.[6] The ketone radical **3** gains a hydrogen atom equivalent from the thiol/thiolate pair to give 3′-ketone **4**. Electron transfer reduction of **4** gives radical **5** with overall oxidation of two cysteines to a disulfide. Return of H_a to **5** completes the synthesis of 2′-deoxynucleotide **6** with regeneration of the initiating S• radical. Dissociation of **6** and reduction of the disulfide by a complex electron transfer pathway completes the enzyme turnover in preparation for another conversion of **1** → **6**.

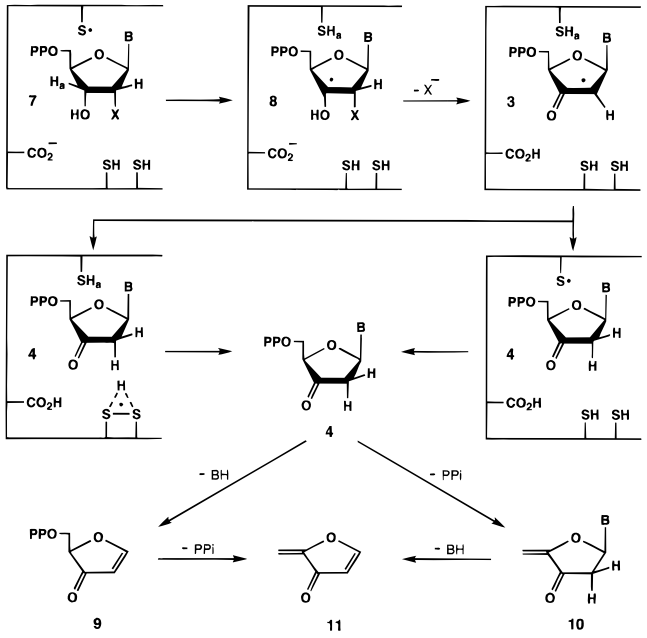
Scheme 2 illustrates Stubbe's most recent hypothesis for the mechanism-based inactivation of these reductases by 2′-chloro-2′-deoxynucleotides.[9g] Analogous abstraction of H3′ (H_a) from the alternative substrate/inactivator **7** gives 3′-radical **8**. Spontaneous loss of chloride from **8** and acceptance of the OH3′ proton by carboxylate is proposed to give the identical ketone

Scheme 1[a]



[a] Proposed[9g] substrate mechanism for ribonucleoside diphosphate reductase.

Scheme 2[a]



[a] Propsed[9g] anionic mechanism for inactivation in RDPR by 2′-chloro-2′-deoxyNDPs.

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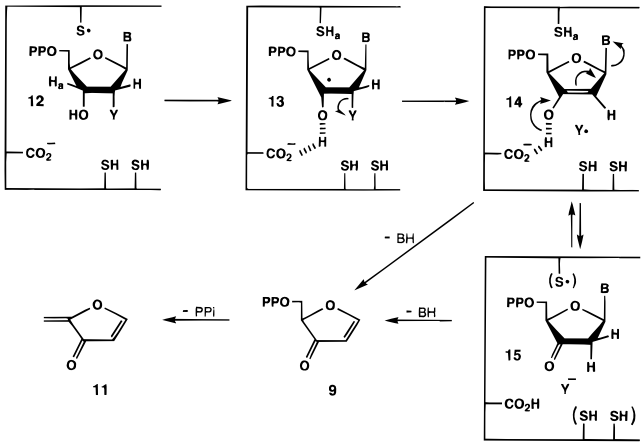
Scheme 3[a]



[a] Radical elimination mechanism for inactivation of RDPR by 2′-Y-2′-deoxyNDPs.

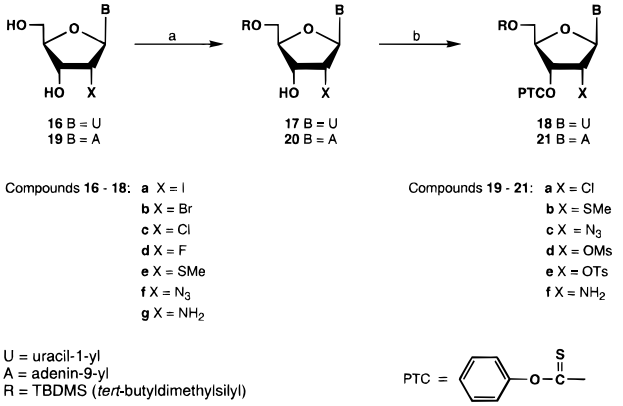
radical species **3** *without* involvement of the cysteine pair on R1. Return of H_a (from SH_a) to C2′ of **3** gives the same 2′-deoxy 3′-ketone **4** with regeneration of S•, whereas transfer of a hydrogen atom equivalent from the cysteine pair generates **4** with loss of S• (retention of SH results in loss of the primary initiating tyrosyl radical). Dissociation of **4** from the enzyme and successive β-eliminations (H2′/base → **9**; H4′/inorganic pyrophosphate → **10**) generate the electrophilic 2(*H*)-methylene-3-furanone (**11**) which inactivates the enzyme by Michael addition/alkylation.

Results and Discussion

We now propose a fundamental mechanistic alternative for inactivation with certain 2′-substituted nucleotides which involves loss of radical rather than anionic[7,9g] species from C2′. As illustrated in Scheme 3, abstraction of H3′ from **12** and loss of radical Y• from C2′ of **13** would give enol **14**. Conjugate elimination of the base from **14**, or tautomerization to the 3′-ketone [and reduction of Y• → Y^- (**15**)], followed by dissociation from the enzyme and β-elimination(s), would give the 2(*H*)-methylene-3-furanone (**11**) postulated to be the Michael acceptor that causes mechanism-based inactivation.[9g] This is a more plausible alternative than loss of an anion from C2′ of **13** with incipient generation of cationic radical character.[7,9g] Generation of cationic character is unfavorable since C2′ is bonded to the electron-deficient anomeric carbon.[12]

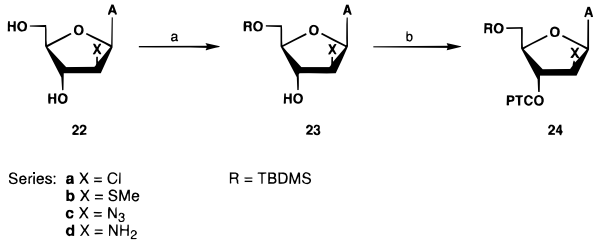
Bond dissociation energies and known radical elimination reactions[13,14] are in harmony with loss of azido, bromo, chloro, iodo, and methylthio radicals from C2′ upon generation of a C3′ radical, whereas spontaneous loss of mesylate, tosylate, and fluoride anions would be consistent with expulsion of chloride from a 3′-radical species. Since the glycosyl-base moieties of nucleoside systems might present unexpected stereoelectronic effects, we prepared a consistent series of 3′-*O*-(phenoxythiocarbonyl)-2′-substituted nucleoside analogues and exposed them to both tributylstannane/AIBN and triphenylsilane/dibenzoyl peroxide in toluene at reflux. The 2′-substituted uridine derivatives **16a**−**f** (ribo configuration, Scheme 4) were prepared

Scheme 4[a]



[a] (a) TBDMSCl/imidazole/DMF or TBDMSCl/pyridine; (b) PTCCl/DMAP/CH_3CN.

Scheme 5[a]



[a] (a) TBDMSCl/pyridine; (b) PTCCl/DMAP/CH_3CN.

by nucleophilic ring openings with 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil. The 2′-substituted derivatives **19a**−**e** (ribo) and **22a**−**c** (arabino, Scheme 5) were obtained by triflate displacements from 9-{3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxane-1,3-diyl)-2-*O*-[(trifluoromethyl)sulfonyl]-β-D-arabinofuranosyl}adenine and 3′,5′-*O*-TIPDS-2′-*O*-Tf-adenosine, respectively, or by mesylation/tosylation of 3′,5′-*O*-TIPDS-adenosine (see the Experimental Section).

Unprotected 2′-substituted nucleosides were converted into 5′-*O*-(*tert*-butyldimethylsilyl) derivatives **17a**−**f**, **20a**−**e**, and **23a**−**c** with known procedures.[15] These compounds were treated with phenyl thionochlorocarbonate/DMAP[16] to give the 5′-*O*-TBDMS-3′-*O*-(phenoxythiocarbonyl)-2′-substituted products **18a**−**f**, **21a**−**e**, and **24a**−**c**, respectively (Table 1). These paired 5′-*O*-TBDMS (Table 2) and 5′-*O*-TBDMS-3′-*O*-PTC (Table 3) derivatives were subjected to simultaneous, parallel treatment with tributylstannane/AIBN/toluene/Δ[16] and also with triphenylsilane/BzOOBz/toluene/Δ.[17,18] The known stannyl radical mediated hydrogenolysis[19] of iodo, bromo, chloro, and methylthio (slow[20]) groups from **17a**−**c**,**e**, and **20a**,**b**/**23a**,**b** gave identical 5′-*O*-TBDMS-2′-deoxyuridine (**28a**) or -adenosine (**28b**) (Figure 1) derivatives in the control series. The control 2′-azido **17f** and **20c**/**23c** compounds were reduced[19,21] to their 2′-amino derivatives **17g** and **20f**/**23d**.

Triphenylsilyl radical mediated hydrogenolysis of the iodo **17a** and bromo **17b** compounds proceeded much more slowly

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to yield **28a**, and small quantities of the 2′-deoxy derivatives **28a**,**b** were obtained with the chloro, **17c** and **20a**/**23a**, and methylthio, **17e** and **20b**/**23b**, compounds. Triphenylsilane/BzOOBz/toluene/Δ had virtually no effect on the 2′-azido, **17f** and **20c**/**23c**, controls under our standard conditions, and starting materials were recovered almost quantitatively. However, excess Ph_3SiH/BzOOBz and prolonged reaction times (5 equiv, 6 h/Δ) gave small quantities of the 2′-deoxy derivatives **28a** (7% from **17f**, plus traces of uracil) and **28b** (8% from **20c**) [plus the recovered 2′-azido substrates (∼85%)]. Computer searches failed to retrieve examples of radical-mediated cleavage of the carbon−nitrogen bond with azides.[18,19] A related cleavage with isocyanides and tris(trimethylsilyl)silane has been reported,[18a] and addition of organosilyl radicals to organic azides to form 1,3- or 3,3-triazenyl radical species is known.[22] As expected, the control 2′-fluoro **17d** and 2′-*O*-(mesyl **20d** and tosyl **20e**) compounds were inert in both the stannyl and silyl reagent systems.

Treatment of the 5′-*O*-TBDMS-3′-*O*-PTC-2′-(iodo, bromo, chloro, and methylthio) derivatives **18a**−**c**,**e**, and **21a**,**b**/**24a**,**b** with Bu_3SnH/AIBN/toluene/Δ resulted in radical-mediated elimination to give 5′-*O*-TBDMS-2′,3′-didehydro-2′,3′-dideoxyuridine (**29a**) and -adenosine (**29b**) (Figure 1) as major products. The ribo azido derivatives **18f** and **21c** gave **29a** and **29b**, respectively, in moderate yields under these conditions, but reduction of the azido group and other byproduct formation[23] was observed. The arabino epimer **24c** underwent stannyl-mediated elimination to give **29b**, but competing reduction of the azido group and hydrogenolysis of the thionocarbonate function also produced 9-(2-amino- 5-*O*-TBDMS-2,3-dideoxy-*β*-D-*threo*-pentofuranosyl)adenine (**38b**). The 2′,3′-didehydro-2′,3′-dideoxy compounds **29a**,**b** were produced with Ph_3SiH/BzOOBz, but at much lower conversion levels. Byproduct formation again occurred with the ribo 2′-azido-3′-*O*-PTC epimers **18f** and **21c** (presumed silyl radical attack on the PTC function and interaction with the cis-vicinal azido group), but the elimination product **29b** was formed almost exclusively with the arabino (trans) epimer **24c** (with major recovery of starting material).

Treatment of the 5′-*O*-TBDMS-3′-*O*-PTC-2′-(fluoro, mesyloxy, and tosyloxy) derivatives **18d** and **21d**,**e** with Bu_3SnH/AIBN or Ph_3SiH/BzOOBz resulted in radical-mediated hydrogenolysis of the thionocarbonate function to give the 5′-*O*-TBDMS-3′-deoxy-2′-(fluoro, mesyloxy, and tosyloxy) compounds **33a**, **34b**, and **36b** (lower conversions with Ph_3SiH). No formation of the 2′,3′-unsaturated **29a**,**b** was observed. Others have reported[24,25] synthetic deoxygenations with vicinal fluorothionocarbonates, but we analyzed our reduction mixtures with 500-MHz ^{1}H NMR and mass spectrometry for trace quantities of elimination products.

Our results clearly demonstrate that generation of a free radical at C3′ of 2′-substituted nucleoside derivatives can cause loss of radical species from C2′ (with both ribo and arabino epimers) to give 2′,3′-didehydro-2′,3′-dideoxy products **29a**,**b**. In contrast, no loss of mesylate, tosylate, or fluoride anions from C2′ was detected. In an intramolecular competition experiment, 5′-*O*-TBDMS-2′-deoxy-2′-fluoro-2′-(methylsulfonyl)-3′-*O*-PTC-uridine (**27**, Scheme 6) was treated with Bu_3SnH/AIBN/toluene/Δ. Sulfonyl (radical) elimination occurred smoothly to give the 2′-fluoro-2′,3′-unsaturated product **31a** which was deprotected (NH_4F/MeOH)[26] to give the known **32a**.[24a] The control 2′-fluoro-2′-(methylsulfonyl) derivative **26** was inert in the Bu_3SnH/AIBN system. The latter results might have relevance to mechanism-based inactivation of ribonucleotide reductases by 5′-phosphate esters of the anticancer agent gemcytabine (2′-deoxy-2′,2′-difluorocytidine).[27,28] If spontaneous loss of fluoride from a C3′ radical of the geminal difluoride is impeded, homolysis of other bond(s) or interactions of the initial 3′-radical with functional groups on the enzymes might occur.

In summary, we have demonstrated that treatment of the 5′-*O*-TBDMS-2′-(azido, bromo, chloro, iodo, and methylthio) nucleoside 3′-thionocarbonates **18a**−**c**,**e**,**f** and **21a**−**c**/**24a**−**c** with Bu_3SnH/AIBN or Ph_3SiH/BzOOBz in refluxing toluene resulted in elimination to give the 2′,3′-didehydro-2′,3′-dideoxy derivatives **29a**,**b**. The stannyl radical system is more robust and gives higher conversions, but suffers from competing hydrogenolysis of halo substituents and reduction of azido groups. The silyl radical system requires larger excesses of reagent/initiator and extended reaction times, but reduction of azido groups was not detected and minimal hydrogenolysis of methylthio and chloro groups was observed. Large excesses of Ph_3SiH/BzOOBz and extended reflux in toluene caused some hydrogenolytic deazidation to give the 2′-deoxy analogues. No elimination of vicinal fluoride, mesylate, or tosylate from C2′ occurred with **18d** or **21d**,**e** upon generation of a free radical at C3′. Instead, intermolecular hydrogen transfer occurred with overall hydrogenolysis of the 3′-thionocarbonate group to give the 3′-deoxy products **33a**, **34b**, and **36b**. These results are in harmony with loss of radical (but not anionic) species during the mechanism-based inactivation of ribonucleotide reductases with several 2′-substituted nucleoside 5′-phosphates. However, alternative mechanistic possibilities might be available within enzyme active sites, especially if base-catalyzed deprotonation of OH3′ by a proximal carboxylate occurs. Stubbe's original hypotheses for 2′-deoxygenation of natural substrates[6] and analogous 2′-defluorinations to give 2′-deoxynucleotides are intuitively elegant. Homolyses of C2′−O2′ and C2′−F bonds are energetically prohibitive, but additional contributions by protein prosthetic groups such as the proximal carboxylate could be crucial. We recently have generated novel C3′ free radical analogues containing O3′ which provide the first chemical models for simulation of the initiation/elimination cascade proposed (Scheme 3) to occur during mechanism-based inactivation of ribonucleotide reductases by 2′-substituted nucleoside 5′-phosphates.[29]

Experimental Section

Uncorrected melting points were determined with a capillary apparatus. UV spectra were measured with solutions in MeOH. NMR spectra were obtained with solutions in $CDCl_3$; ^{1}H (Me_4Si) at 200 or 500 MHz, ^{13}C (Me_4Si) at 50 MHz (Table 4), and ^{19}F (CCl_3F) at 470.3

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Table 1. Preparation and Characterization of Substrates for Model Free Radical Reactions[a]

			selected ^{1}H NMR data[c,d]					
compd	procedure	yield[b] (%)	H1′[g] ($J_{1'-2'}$)	H2′[h] ($J_{2'-3'}$)	H3′[h] ($J_{3'-4'}$)	H2[i] (5)[g] (J_{5-6})	UV[e] [nm (ϵ)]	HRMS[f] *m/z* (%; dev; MH^+ formula)
17b	A	85	6.34 (5.6)	4.40 (4.2)	4.21−4.27[j]	5.73[h] (8.1, 2.0[k])	260 (9600)	423.0764 (100; −1.0; $C_{15}H_{26}{}^{81}BrN_2O_5Si$)[l]
17c	A	82	6.22 (4.5)	4.34−4.39[j]	4.34−4.39[j]	5.72[h] (8.1, 1.8[k])	260 (9400)	377.1291 (100; −0.9; $C_{15}H_{26}{}^{35}ClN_2O_5Si$)[m]
17d[n]	A	90	6.13[h] (2.0, 14.5[o])	4.96[p] (4.0, 52.3[q])	4.28−4.46[j]	5.69 (8.1)	260 (9800)	361.1586 (100; −0.9; $C_{15}H_{26}FN_2O_5Si$)
17e	A	91	6.09 (8.1)	3.34 (4.8)	4.27 (2.0)	5.73[h] (8.1, 2.2[k])	262 (9800)	389.1578 (100; 1.1; $C_{16}H_{29}N_2O_5SSi$)
17f	A	94	6.04 (3.7)	4.04−4.11[j]	4.32−4.39[j]	5.71 (8.1)	261 (10 000)	384.1692 (100; −1.1; $C_{15}H_{26}N_5O_5Si$)
18b	B	87	6.47 (6.7)	4.55 (1.5)	5.63−5.69[j]	5.76 (8.2)	253 (11 100)	559.0751 (100; −0.6; $C_{22}H_{30}{}^{81}BrN_2O_6SSi$)[r]
18c	B	91	6.37 (6.5)	4.51−4.60[j]	5.71−5.80[j]	5.71−5.80[j]	252 (11 200)	513.1272 (100; −1.0; $C_{22}H_{30}{}^{35}ClN_2O_6SSi$)[s]
18d[t]	B	91	6.27[h] (3.2, 14.8[o])	5.33[p] (4.6, 51.6[q])	5.65−5.77[j]	5.65−5.77[j]	253 (11 500)	497.1584 (100; 0.4; $C_{22}H_{30}FN_2O_6SSi$)
18e	B	65	6.36 (8.6)	3.47 (5.4)	5.74−5.82[j]	5.74−5.82[j]	251 (11 000)	525.1531 (100; −1.9; $C_{23}H_{33}N_2O_6S_2Si$)
18f	B	85	6.24 (5.9)	4.27 (5.7)	5.72−5.79[j]	5.72−5.79[j]	257 (11 500)	520.1674 (74; −1.2; $C_{22}H_{30}N_5O_6SSi$)
20b[u]	E	88	6.14 (8.3)	4.09 (5.2)	4.30−4.39[j]	8.17	259 (15 000)	412.1843 (100; 0.4; $C_{17}H_{30}N_5O_3SSi$)
21b	G	40	6.34 (8.9)	4.12 (5.3)	5.97[g]	8.29	258 (14 800)	548.1815 (81; −0.7; $C_{24}H_{34}N_5O_4S_2Si$)
21c	F	79	6.24 (6.5)	4.95 (5.1)	6.01 (3.2)	8.22	258 (17 300)	543.1853 (100; −0.5; $C_{23}H_{31}N_8O_4SSi$)
21d	F	60	6.45 (5.2)	5.85 (5.3)	6.05 (3.9)	8.24	257 (16 400)	596.1666 (100; −0.3; $C_{24}H_{34}N_5O_7S_2Si$)
21e	F	85	6.34 (6.9)	5.68 (5.3)	5.93 (1.8)	8.03	259 (14 900)	672.1988 (100; 0.6; $C_{30}H_{38}N_5O_7S_2Si$)
23a	D	56[v]	6.57 (4.5)	4.60−4.75[j]	3.98−4.12[j]	8.34	259 (15 900)	400.1561 (100; −1.1; $C_{16}H_{27}{}^{35}ClN_5O_3Si$)[w]
23b	C	96[x]	6.58 (6.6)	3.62 (9.9)	4.39 (7.3)	8.31	261 (16 000)	412.1848 (100; 0.9; $C_{17}H_{30}N_5O_3SSi$)
23c[u]	D	92[y]	6.42 (6.9)	4.64 (8.1)	4.38[p] (8.3)	8.17	260 (14 600)	407.1984 (100; 0.9; $C_{16}H_{27}N_8O_3Si$)
24a	F	65	6.63 (4.0)	4.80−4.91[j]	5.97−6.03[j]	8.25	257 (16 000)	536.1553 (100; −0.2; $C_{23}H_{31}{}^{35}ClN_5O_4SSi$)[z]
24c	F	63	6.54 (4.4)	4.69 (1.6)	5.91 (3.2)	8.19	258 (17 400)	543.1953 (100; −0.5; $C_{23}H_{31}N_8O_4SSi$)
26 (2′*S*)[aa]	A	92	6.46 (18.4[o])		4.89 (8.7, 23.0[bb])	5.71 (8.2)	256 (9900)	439.1379 (100; 0.9; $C_{16}H_{28}FN_2O_7SSi$)
27 (2′*S*)[cc]	B	75	6.65 (19.1[o])		6.90 (8.9, 22.1[bb])	5.78 (8.3)	255 (12 000)	575.1347 (80; −0.7; $C_{23}H_{32}FN_2O_8S_2Si$)

[a] See the Experimental Section for synthetic procedures and complete data for representative compounds. [b] Yields are for amorphous solids after silica chromatography (>95%; NMR, TLC) unless otherwise noted. [c] δ ($CDCl_3$) at 200 MHz unless otherwise noted; "apparent" first-order coupling constants (Hz, in parentheses). [d] Complete NMR data are given for representative compounds in the Experimental Section. [e] MeOH. [f] Chemical ionization (CH_4); deviations (dev) from calculated MH^+ ions are in milimass units; all *m/z* values were within ±3.7 ppm of theory. [g] Doublet unless otherwise noted. [h] Doublet of doublets unless otherwise noted. [i] Singlet. [j] Multiplet. [k] (J_{5-NH}). [l] 421.0794 (99; −1.5; $C_{15}H_{26}{}^{79}BrN_2O_5Si$). [m] 379.1271 (39; 0.1; $C_{15}H_{26}{}^{37}ClN_2O_5Si$). [n] ^{19}F NMR δ −205.0 (dt, $J_{F-2'}$ = 52.2 Hz, $J_{F-1',3'}$ = 16.8 Hz). [o] ($J_{1'-F}$). [p] Doublet of doublet of doublets. [q] ($J_{2'-F}$). [r] 557.0770 (90; −0.8; $C_{22}H_{30}{}^{79}BrN_2O_6SSi$). [s] 515.1261 (40; 0.8; $C_{22}H_{30}{}^{37}ClN_2O_6SSi$). [t] ^{19}F NMR δ −205.0 (dt, $J_{F-2'}$ = 52.5 Hz, $J_{F-1',3'}$ = 14.1 Hz). [u] DMSO-d_6. [v] mp 201−203 °C. [w] 402.1542 (38; 0.9; $C_{16}H_{27}{}^{37}ClN_5O_3Si$). [x] mp 192−193 °C. [y] mp 190−191 °C. [z] 538.1522 (42; −0.3; $C_{23}H_{31}{}^{37}ClN_5O_4SSi$). [aa] Data from *R*/*S* mixture: δ 6.65 (d, $J_{1'-F}$ = 7.0 Hz, 0.2, *R*-H1′); ^{19}F NMR δ −161.0 (br d, $J_{F-3'}$ = 23.6 Hz, 0.2, *R*-F2′), −167.2 (br t, $J_{F-1',3'}$ = 20.7 Hz, 0.8, *S*-F2′). [bb] ($J_{3'-F}$). [cc] Data from *R*/*S* mixture: ^{19}F NMR δ −159.6 (br d, $J_{F-3'}$ = 19.2 Hz, 0.13, *R*-F2′), −160.2 (br t, $J_{F-1',3'}$ = 19.5 Hz, 0.87, *S*-F2′).

MHz unless otherwise noted. Mass spectra were determined at 20 eV (EI) or with chemical ionization (CI, CH_4). Merck kieselgel 60F_{254} sheets were used for TLC: S_1 (EtOAc/*i*-PrOH/H_2O, 4:1:2; upper layer), S_2 (MeOH/$CHCl_3$, 1:9), S_3 (MeOH/EtOAc, 1:12), S_4 (Me_2CO/$CHCl_3$, 1:3), S_5 (cyclohexane/EtOAc, 1:3), and observation under 254 nm light. Merck kieselgel 60 (230−400 mesh; difficult separations) or (60−200 mesh) was used for silica column chromatography. Dowex 1 × 2 (OH^-) resin was used for ion exchange chromatography. Chemicals were reagent grade, and solvents were distilled. Pyridine, benzene, and toluene were dried by reflux over and distillation from CaH_2. Elemental analyses were determined by M-H-W Laboratories, Phoenix, AZ.

The 2′-substituted pyrimidine nucleosides were prepared by ring-opening reactions with 2,2′-anhydro-araU by literature procedures (with modifications noted) for **16a**, **16b**,[30] **16c**,[30] **16d**[30] (pyridinium hydrofluoride instead of anhydrous liquid HF, 50% yield), **16e**,[31] and **16f**.[32] The 2′-substituted purine ribo and arabino nucleosides were obtained by displacement of triflate from 3′,5′-*O*-TIPDS-adenosine and its arabino epimer as previously described for **19b**,[33] **19c**,[34] **22c**;[34] compounds **19a**,[35] **22a**,[36] and **22b**[37] were prepared analogously (data as reported and in Table 4). Compounds **19d** and **19e**[38] were prepared by mesylation or tosylation of 3′,5′-*O*-TIPDS-adenosine and deprotection as illustrated with **19d**. Compound **25** [2′(*R*/*S*), ~1:6] was prepared as reported.[31]

2′-Deoxy-2′-iodouridine (16a). Trifluoroacetic acid (0.39 mL, 570

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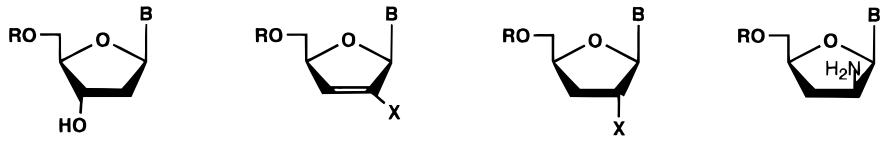


28 R = TBDMS

29 R = TBDMS, X = H
30 R = X = H
31 R = TBDMS, X = F
32 R = H, X = F

33 R = TBDMS, X = F
34 R = TBDMS, X = OMs
35 R = H, X = OMs
36 R = TBDMS, X = OTs
37 R = H, X = OTs

38 R = TBDMS
39 R = H

Series: **a** B = U
b B = A

Figure 1. Products from model radical reactions with (Bu_3SnH/AIBN or Ph_3SiH/BzOOBz)/toluene/Δ.

Table 2. Control Free Radical Reactions with 5′-*O*-TBDMS-2′-substituted Nucleosides[a]

	procedure H		procedure I	
substrate	product(s)[b]	yields[c] (%)	product(s)[b]	yields[c] (%)
17a	**28a**	92	**17a**/**28a**	65:30
17b	**28a**	88	**17b**/**28a**	75:20
17c	**28a**	82	**17c**/**28a**	88[c]:5[d]
17d	**17d**	90	**17d**	93
17e[e]	**17e**/**28a**	75:25	**17e**/**28a**	77:15
17f	**17g**[f]	90	**17f**/**28a**[g]	90:3
20a	**28b**	90	**20a**/**28b**	85:10
20b	**20b**/**28b**	65:28	**20b**/**28b**	75:18
20c	**20f**[h]	94	**20c**/**28b**[i]	90:3
20d	**20d**	93	**20d**	92
20e	**20e**	91	**20e**	90
23a	**28b**	92	**23a**/**28b**	90[c]:5[d]
23b	**23b**[j]	87	**23b**[j]	91
23c	**23d**[k]	92	**23c**	93
26	**26**	91	**26**	93

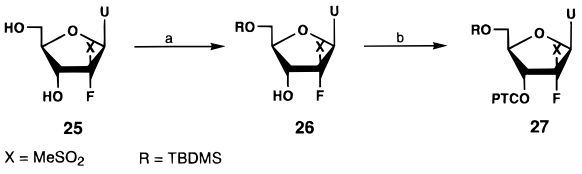
[a] See the Experimental Section for procedure H (Bu_3SnH/AIBN/toluene/Δ/2 h) and procedure I (Ph_3SiH/BzOOBz/toluene/Δ/4 h). [b] The **17d**,[42] **20e**,[43] **28a**,[44] and **28b**[15a,43] products had physical and spectroscopic properties as reported. [c] Yields are for amorphous solids after chromatography (silica). [d] TLC. [e] Excess Bu_3SnH (6 equiv) and extended reflux (6 h) gave **17e**/**28a** (∼1:1, 90%). [f] Deprotection (TBAF/THF) and purification[21a] gave **16g** (80% from **17f**) with data as reported.[21a,32] [g] Excess Ph_3SiH (5 equiv) and extended reflux (7 h) gave **17f**/**28a**/uracil (∼85:7:3). [h] Deprotection (TBAF/THF) and chromatography [Dowex 1 × 2 (OH^-); H_2O → 30% MeOH/H_2O] gave **19f** (89% from **20c**) with data as reported.[34] [i] Excess Ph_3SiH (5 equiv) and extended reflux (7 h) gave **20c**/**28b** (84:8). [j] Traces (TLC) of **28b**. [k] Deprotection (TBAF/THF) and chromatography [Dowex 1 × 2 (OH^-); H_2O → 70% MeOH/H_2O] gave **22d** (86% from **23c**) with data as reported.[34]

Table 3. Model Free Radical Reactions with 5′-*O*-TBDMS-3′-*O*-PTC-2′-substituted Nucleosides[a]

	procedure H		procedure I	
substrate	product(s)[b]	yields[c] (%)	product(s)[b]	yields[c] (%)
18a	**29a**	91	**18a**/**29a**	20:70
18b	**29a**	89	**18b**/**29a**	48:36
18c	**29a**	93	**18c**/**29a**	46:35
18d	**33a**[d]	88	**18d**/**33a**[d]	55:35
18e	**29a**	87	**18e**/**29a**	42:37
18f	**29a**	41	**18f**/**29a**	28:32
21a	**29b**	76	**21a**/**29b**	63:26
21b	**29b**	82	**21b**/**29b**	35:35
21c	**29b**	45	**29b**	30
21d	**34b**[e]	95	**21d**/**34b**[e]	45:40
21e	**36b**[f]	88	**21d**/**36b**[f]	70:20
24a	**29b**[g]	85	**24a**/**29b**	70:12
24b	**29b**	80	**24b**/**29b**	50:35
24c	**29b**/**38b**[h]	35:45	**24c**/**29b**	45:45
27	**31a**[i]	80	**27**/**31a**[i]	70:18

[a] See the Experimental Section for procedure H (Bu_3SnH/AIBN/toluene/Δ/2 h) and procedure I (Ph_3SiH/BzOOBz/toluene/Δ/4 h). [b] The **29a**,[45] **29b**,[45] and **33a**[24c] products had physical and spectroscopical properties as reported. [c] Yields are for amorphous solids after chromatography (silica). [d] ^{19}F NMR δ −180.0 (dddd, $J_{F-2'}$ = 51.2 Hz, $J_{F-1'}$ = 16.4 Hz, $J_{F-3'}$ = 19.3 Hz, $J_{F-3''}$ = 42.5 Hz). [e] Deprotection of **34b** (TBAF/THF) gave **35b** (86% from **21d**) with data as reported.[25] [f] Deprotection of **36b** (TBAF/THF) gave **37b** (82% from **21e**; see Experimental Section). [g] Deprotection of **29b** (TBAF/THF) gave **30b**[45] (81% from **24a**). [h] Deprotection of **38b** (NH_4F/MeOH/Δ/2 h) and chromatography [RP-HPLC (C_{18}; 10 → 30% CH_3CN/H_2O; 2.8 mL/min, 70 min)] gave **39b** (32% from **24c**) with data as reported.[46] [i] Deprotection of **31a** (NH_4F/MeOH/Δ/2 h) gave **32a** with data as reported[24a] and ^{19}F NMR (DMSO-d_6) δ −138.8 (br t, J = 4.5 Hz).

Scheme 6[a]



25 X = $MeSO_2$ R = TBDMS **26** **27**

[a] (a) TBDMSCl/imidazole/DMF; (b) PTCCl/DMAP/CH_3CN.

mg, 5.0 mmoL) was added to a stirred solution of 2,2′-anhydro-1-(β-D-arabinofuranosyl) uracil[39] (840 mg, 3.71 mmoL) and dried NaI (1.66g, 11.0 mmoL) in dried DMF (25 mL) under N_2. The solution was heated at ∼85 °C for 45 min and cooled to ambient temperature. Saturated $Na_2S_2O_3/H_2O$ (∼1.0 mL) was added to the mixture, and an amber-colored solution was obtained. Volatiles were evaporated in vacuo, and the residue was chromatographed [EtOAc → 3% MeOH/EtOAc → MeOH/S_1/EtOAc (1:3:20)] and "diffusion crystallized"[40] (MeOH/EtOAc) to give **16a** (946 mg, 72%) as white needles: mp 147−151 °C dec (lit.[41] mp 80−100 °C); UV max 260 nm (ε 10 000), min 228 nm (ε 2000); ^1H NMR (DMSO-d_6) δ 3.59 (m, 2, H5′,5″), 3.83 (m, 1, H3′), 3.97 (m, 1, H4′), 4.51 (dd, $J_{2'-1'}$ = 7.7 Hz, $J_{2'-3'}$ = 4.8 Hz, 1, H2′), 5.21 (br s, 1, OH5′), 5.72 (d, J_{5-6} = 8.1 Hz, H5), 6.01 (br s, 1, OH3′), 6.22 (d, 1, H1′), 7.85 (d, 1, H6), 11.39 (br s, 1, NH); MS (CI) *m/z* 355 (40, MH^+), 225 (100).

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Table 4. ^{13}C NMR Spectral Data[a,b]

compd	C2	C4	C5	C6	C8	C1′	C2′	C3′	C4′	C5′
16a	150.79	163.61	102.56	140.23		89.44	31.84	70.37	85.78	60.87
16b	150.73	163.72	102.37	140.32		88.27	53.75	69.26	85.40	60.33
16c	150.74	163.51	102.34	140.26		88.14	60.24	69.32	85.15	61.94
16d	150.48	163.90	101.80	140.92		87.49[c]	93.60[d]	67.57[e]	83.28	59.52
16e[f]	150.95	163.20	102.63	140.67		87.56	53.28	72.13	86.76	61.60
16f	150.62	163.70	102.23	140.49		85.34[g]	64.82	70.55	85.91[g]	60.34
19a	152.98	149.33	119.48	156.48	139.86	88.06[g]	61.23[g]	70.55	86.61[g]	61.42[g]
19b[f]	152.90	149.31	119.32	156.20	140.21	87.69	53.31	72.53	88.80	62.01
19c	152.98	149.27	119.42	156.44	139.72	85.50[g]	64.46	71.41	86.38[g]	61.33
19d[h]	152.93	149.03	119.14	156.08	140.15	85.67	80.16	68.89	86.01	61.05
19e[i]	152.19	147.96	119.53	156.04	140.17	85.14	79.04	69.95	87.56	61.71
22a	152.96	149.38	117.95	156.01	139.59	82.79[g]	63.87	74.09	83.55[g]	59.94
22b[j]	152.74	149.51	118.38	156.05	139.84	84.62	56.15	72.53	83.98	59.79
22c	152.92	149.29	118.48	155.91	139.66	81.98[g]	67.55	71.55	83.13[g]	59.65
25(2′*S*)[k]	150.13	163.24	101.48	141.44		85.75[l]	107.67[m]	68.62[n]	80.77	57.95

[a] δ (Me_2SO-d_6) at 50.0 MHz. [b] Proton-decoupled singlets unless otherwise noted. [c] (d, $J_{C1'-F}$ = 34.4 Hz). [d] (d, $J_{C2'-F}$ = 184.7 Hz). [e] (d, $J_{C3'-F}$ = 16.1 Hz). [f] δ 13.96 (MeS). [g] Assignments might be reversed. [h] CH_3 signal overlapped by DMSO peaks. [i] δ 21.31 (CH_3) 126.89, 129.62, 131.24, 145.40 (Aryl). [j] δ 15.04 (MeS). [k] δ 38.31 ($MeSO_2$). [l] (d, $J_{C1'-F}$ = 38.4 Hz). [m] (d, $J_{C2'-F}$ = 229.0 Hz). [n] (d, $J_{C3'-F}$ = 15.7 Hz).

The bromo **16b** (71%; 3 h, ∼l05 °C) and chloro **16c** (76%; 4 h, ∼105 °C) compounds were prepared analogously with LiBr and LiCl, respectively.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-2′-iodouridine (17a). Procedure A. TBDMSCl (136 mg, 0.9 mmoL) and imidazole (129 mg, 1.9 mmoL) were added to a solution of **16a** (270 mg, 0.76 mmoL) in dried DMF (8 mL), and stirring was continued overnight at ambient temperature. The solution was evaporated, and the residue was chromatographed [EtOAc → 3% MeOH/EtOAc (or $CHCl_3$ → 2% MeOH/$CHCl_3$)] to give **17a** (330 mg, 93%) as a white foam: UV max 260 nm (ϵ 9700); ^1H NMR δ 0.12 (s, 6, Me_2Si), 0.92 (s, 9, *t*-Bu), 2.42 (d, $J_{OH3'-3'}$ = 4.5 Hz, 1, OH3′), 3.81−4.01 (m, 3, H3′,5′,5″), 4.23−4.28 (m, 1, H4′), 4.39 (dd, $J_{2'-3'}$ = 4.7 Hz, $J_{2'-1'}$ = 6.8 Hz, 1, H2′), 5.73 (d, J_{5-6} = 8.1 Hz, 1, H5), 6.43 (d, 1, H1′), 7.87 (d, 1, H6), 8.71 (br s, 1, NH); MS (CI) *m/z* 469.0649 (100, MH^+ [$C_{15}H_{26}IN_2O_5Si$] = 469.0656).

Treatment of **16b**−**f** and **25** by procedure A gave **17b** (85%), **17c** (82%), **17d** (90%), **17e** (91%), **17f** (94%), and **26** (92%), respectively.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-2′-iodo-3′-*O*-(phenoxythiocarbonyl)uridine (18a). Procedure B. PTCCl (76 μL, 95 mg, 0.55 mmol) was added to a solution of **17a** (234 mg, 0.5 mmol) and DMAP (126 mg, 1.03 mmol) in dried MeCN (7 mL), and stirring was continued overnight at ambient temperature. Volatiles were evaporated, and the residue was partitioned (HCl/H_2O//$CHCl_3$). The organic layer was washed ($NaHCO_3/H_2O$, brine), dried ($MgSO_4$), evaporated, and chromatographed [$CHCl_3$ → 1% MeOH/$CHCl_3$ (or EtOAc → 2% MeOH/EtOAc)] to give **18a** (296 mg, 95%) as a white foam: UV max 254 nm (ϵ 11 500); ^1H NMR δ 0.17 (s, 6, Me_2Si), 0.95 (s, 9, *t*-Bu), 4.01 (s, 2, H5′,5″), 4.47−4.54 (m, 2, H2′,4′), 5.48−5.53 (m, 1, H3′), 5.77 (d, J_{5-6} = 8.1 Hz, 1, H5), 6.54 (d, $J_{1'-2'}$ = 8.1 Hz, 1, H1′), 7.15−7.51 (m, 5, Ph), 7.82 (d, 1, H6), 8.56 (br s, 1, NH); MS (CI) *m/z* 605.0636 (100, MH^+ [$C_{22}H_{30}IN_2O_6SSi$] = 605.0639).

Treatment of **17b**−**f** and **26** by procedure B gave **18b** (87%), **18c** (91%), **18d** (91%), **18e** (65%), **18f** (85%), and **27** (75%), respectively.

2′-*O*-(Methylsulfonyl)adenosine (19d). (a) Mesylation. Mesyl chloride (0.255 mL, 378 mg, 3.3 mmol) was added to a suspension of dried 3′,5′-*O*-TIPDS-adenosine[16] (1.40 g, 2.7 mmol) in dried pyridine (15 mL), and stirring was continued overnight at ambient temperature. Saturated $NaHCO_3/H_2O$ was added, the mixture was evaporated, and the residue was partitioned (cold 1 M HCl/H_2O//$CHCl_3$). The organic phase was washed ($NaHCO_3/H_2O$, H_2O, brine), dried (Na_2SO_4), evaporated, and chromatographed ($CHCl_3$ → 2% MeOH/$CHCl_3$) to give 3′,5′-*O*-TIPDS-2′-*O*-(methylsulfonyl)adenosine (1.43 g, 90%): ^1H NMR δ 0.99−1.21 (m, 28, 4 × *i*-Pr), 3.27 (s, 3, SO_2CH_3), 3.97−4.35 (m, 3, H4′,5′,5″), 5.08 (dd, $J_{3'-4'}$ = 9.2 Hz, $J_{3'-2'}$ = 4.9 Hz, 1, H3′), 5.53 (d, 1, H2′), 5.64 (br s, 2, NH_2), 6.15 (s, 1, H1′), 8.01 (s, 1, H2), 8.27 (s, 1, H8). **(b) Deprotection.** NH_4F (1.48 g, 40.0 mmol) was added to a suspension of this material (1.43 g, 2.43 mmol) in MeOH (60 mL), and stirring was continued overnight at ambient temperature. Volatiles were evaporated, and the residue was chromatographed ($CHCl_3$ → 6% MeOH/$CHCl_3$) and crystallized (MeOH/EtOAc) to give **19d** (673 mg, 81%): mp 178−180 °C; UV max 258 nm (ϵ 14 400), min 239 nm (ϵ 9300); ^1H NMR (DMSO-d_6) δ 3.21 (s, 3, SO_2CH_3), 3.53−3.80 (m, 2, H5′,5″), 4.05 (m, 1, H4′), 4.54 (q, J = 4.9 Hz, 1, H3′), 5.48 (t, J = 5.5 Hz, 1, OH5′), 5.59 (dd, $J_{2'-1'}$ = 5.9 Hz, $J_{2'-3'}$ = 5.2 Hz, 1, H2′), 5.94 (d, $J_{OH3'-3'}$ = 5.4 Hz, 1, OH3′), 6.24 (d, 1, H1′), 7.44 (br s, 2, NH_2), 8.18 (s, 1, H2), 8.40 (s, 1, H8); MS (CI) *m/z* 346 (100, MH^+). Anal. Calcd for $C_{11}H_{15}N_5O_6S$ (345.3): C, 38.26; H, 4.38; N, 20.28. Found: C, 38.49; H, 4.50; N, 20.27.

Known compound **19e**[38] was obtained analogously with tosyl chloride (1.5 equiv; 66% overall yield, data as reported).

5′-*O*-(*tert*-Butyldimethylsilyl)-2′-chloro-2′-deoxyadenosine (20a). Procedure C. TBDMSCl (78 mg, 0.50 mmol) was added to a solution of dried **19a** (98 mg, 0.34 mmol) in dried pyridine (4 mL), and stirring was continued overnight at ambient temperature. Dried Et_3N (0.8 mL) was added, stirring was continued for 1 h at ambient temperature, volatiles were evaporated, and the residue was chromatographed (hexanes/EtOAc, 2:3) to give **20a** (76 mg, 56%): mp 192−193 °C; UV max 259 nm (ϵ 14 200), min 226 nm (ϵ 1000); ^1H NMR (DMSO-d_6) δ 0.06 (s, 6, Me_2Si), 0.88 (s, 9, *t*-Bu), 3.80 (dd, $J_{5''-5'}$ = 11.3 Hz, $J_{5''-4'}$ = 4.3 Hz, 1, H5″), 3.92 (dd, $J_{5'-4'}$ = 4.0 Hz, 1, H5′), 4.01−4.13 (m, 1, H4′), 4.40−4.52 (m, 1, H3′), 5.20 (dd, $J_{2'-1'}$ = 5.7 Hz, $J_{2'-3'}$ = 5.0 Hz, 1, H2′), 6.02 (d, $J_{OH3'-3'}$ = 4.8 Hz, 1, OH3′), 6.20 (d, 1, H1′), 7.40 (br s, 2, NH_2), 8.17 (s, 1, H2), 8.36 (s, 1, H8); ^{13}C NMR (DMSO-d_6) δ [−5.17, 18.27, 26.02 (TBDMS)], 61.72 (C5′), 62.49 (C2′), 69.37 (C3′), 84.95 (C4′), 87.95 (C1′), 119.00 (C5), 139.34 (C8), 149.38 (C4), 153.16 (C2), 156.04 (C6); MS (CI) *m/z* 402.1537 {45, MH^+ ($C_{16}H_{27}$[^{37}Cl]N_5O_3Si) = 402.1542}, 400.1557 {100, MH^+ ($C_{16}H_{27}$[^{35}Cl]N_5O_3Si) = 400.1572}.

2′-Azido-5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (20c). Procedure D. TBDMSCl (80 mg, 0.51 mmol) was added to a solution of dried **19c** (102 mg, 0.35 mmol) in dried pyridine (4 mL), and stirring was continued overnight at ambient temperature. Dried Et_3N (1.5 mL) was added, and the solution was stirred for 30 min and evaporated. The residue was partitioned (EtOAc//cold dilute HCl/H_2O), and the organic phase was washed ($NaHCO_3/H_2O$, brine), dried ($MgSO_4$), evaporated, and recrystallized (EtOAc/MeOH) to give **20c** (132 mg, 93%): mp 152−154 °C dec; UV max 259 nm (ϵ 15 300), min 227 nm (ϵ 2000); ^1H NMR (DMSO-d_6) δ 0.02 (s, 6, Me_2Si), 0.88 (s, 9, *t*-Bu), 3.72−4.06 (m, 3, H4′,5′,5″), 4.63 (q, J = 5.1 Hz, 1, H3′), 4.73 (t, J = 4.7 Hz, 1, H2′), 6.02 (d, $J_{1'-2'}$ = 4.7 Hz, 1, H1′), 6.08 (d, $J_{OH3'-3'}$ = 5.1 Hz, OH3′), 7.38 (br s, 2, NH_2), 8.17 (s, 1, H2), 8.31 (s, 1, H8); MS (CI) *m/z* 407.1976 (78, MH^+ [$C_{16}H_{27}N_8O_3Si$] = 407.1975).

5′-*O*-(*tert*-Butyldimethylsilyl)-2′-*O*-(methylsulfonyl)adenosine (20d). Dried Et_3N (0.14 mL) was added to a suspension of dried **19d** (210 mg, 0.6 mmol) and a catalytic amount (∼5 mg) of DMAP in dried CH_2Cl_2 (5 mL). TBDMSCl (150 mg, 0.97 mmol) was added in three portions, and the suspension was stirred overnight at ambient temperature. Pyridine (1 mL) was added, and stirring was continued for 2 h. Volatiles were evaporated, and the residue was partitioned (NH_4Cl/H_2O//$CHCl_3$). The organic phase was washed (H_2O, brine), dried ($MgSO_4$), and evaporated and the residue was chromatographed (30

→ 95% EtOAc/hexanes) to give **20d** (221 mg, 80%) as a slightly yellow glass: UV max 259 nm (ϵ 13 200), min 225 nm (ϵ 1300); ^{1}H NMR (DMSO-d_6) δ 0.02 and 0.04 (s and s, 3 and 3, Me_2Si), 0.86 (s, 9, *t*-Bu), 3.25 (s, 3, CH_3), 3.79 (dd, $J_{5''-5'} = 11.5$ Hz, $J_{5''-4'} = 3.9$ Hz, 1, H5″) 3.90−4.05 (m, 2, H4′,5′), 4.61 (q, $J = 5.5$ Hz, 1, H3′), 5.61 (dd, $J_{2'-1'} = 3.9$ Hz, $J_{2'-3'} = 5.1$ Hz, 1, H2′), 5.95 (d, $J_{OH3'-3'} = 5.7$ Hz, 1, OH3′), 6.25 (d, Hz, 1, H1′), 7.39 (br s, 2, NH_2), 8.17 (s, 1, H2), 8.31 (s, 1, H8); MS (CI) *m/z* 460.1689 (100, MH^+ [$C_{17}H_{30}N_5O_6SSi$] = 460.1686).

5′-*O*-(*tert*-Butyldimethylsilyl)-2′-*O*-(*p*-tolylsulfonyl)adenosine (20e). Procedure E. TBDMSCl (447 mg, 2.9 mmol) was added to a suspension of dried **19e** (672 mg, 1.6 mmol) in dried pyridine (12 mL), and stirring was continued overnight at ambient temperature. Volatiles were evaporated, and the residue was partitioned (HCl/H_2O//EtOAc). The organic phase was washed ($NaHCO_3/H_2O$, brine), dried (Na_2SO_4), and evaporated, and the residue was chromatographed (CH_2Cl_2 → 3.5% MeOH/CH_2Cl_2) to give **20e** (566 mg, 66%) as a white glass: UV max 261 nm (ϵ 13 100), min 242 nm (ϵ 7100); ^{1}H NMR (DMSO-d_6) δ 0.04 (s, 6, $SiMe_2$), 0.88 (s, 9, *t*-Bu), 2.29 (s, 3, CH_3), 3.74 (dd, $J_{5''-5'} = 11.3$ Hz, $J_{5''-4'} = 4.3$ Hz, 1, H5″), 3.90 (dd, $J_{5'-4'} = 4.4$ Hz, 1, H5′), 4.02−4.08 (m, 1, H4′), 4.32−4.38 (m, 1, H3′), 5.51 (dd, $J_{2'-1'} = 6.6$ Hz, $J_{2'-3'} = 5.4$ Hz, 1, H2′), 6.04 (d, 1, H1′), 6.07 (d, $J_{OH3'-3'} = 5.5$ Hz, 1, OH3′), 7.05 (d, $J = 8.2$ Hz, 2, H_{arom}), 7.34 (br s, 2, NH_2), 7.43 (d, 2, H_{arom}), 8.02 (s, 1, H2), 8.07 (s, 1, H8); MS (CI) *m/z* 536.1986 (100, MH^+ [$C_{23}H_{34}N_5O_6SSi$] = 536.1999).

Compounds **20b** (procedure E, 88%), **23a** (procedure D, 56%), **23b** (procedure C, 96%), and **23c** (procedure D, 92%) were prepared analogously to those described.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′-chloro-2′-deoxy-3′-*O*-(phenoxythiocarbonyl)adenosine (21a). Procedure F. DMAP (103 mg, 0.84 mmol) and PTCCl (70 μL, 86 mg, 0.50 mmol) were added to a suspension of dried **20a** (161 mg, 0.40 mmol) in dried MeCN (6 mL), and stirring of the yellow solution was continued for 6 h at ambient temperature. Volatiles were evaporated, and the residue was chromatographed [EtOAc/cyclohexanes (1:3) → MeOH/cyclohexane/EtOAc (1:25:75)] to give **21a** (206 mg, 95%) as an off-colored glass: mp 192−193 °C; UV max 257 nm (ϵ 15 100), min 224 nm (ϵ 5700); ^{1}H NMR δ 0.15 (s, 6, Me_2Si), 0.95 (s, 9, *t*-Bu), 4.03 (m, 2, H5′,5″), 4.58 (m, 1, H4′), 5.22 (dd, $J_{2'-1'} = 6.1$ Hz, $J_{2'-3'} = 5.9$ Hz, 1, H2′), 5.97 (m, 1, H3′), 6.32 (br s, 2, NH_2), 6.40 (d, 1, H1′), 7.08−7.55 (m, 5, Ph), 8.16 (s, 1, H2), 8.39 (s, 1, H8); ^{13}C NMR δ [−5.03, −4.81, 18.91, 26.45 (TBDMS)], 58.37 (C5′), 63.20 (C2′), 81.01 (C3′), 83.91 (C4′), 88.80 (C1′), 120.36 (C5), 139.04 (C8), 150.50 (C4), 153.43 (C2), 155.96 (C6), [122.16, 127.42, 130.19, 153.80, 194.34 (PTC)]; MS (CI) *m/z* 538.1511 {43, MH^+ ($C_{23}H_{31}[^{37}Cl]N_5O_4SSi$) = 538.1525}, 536.1538 {100, MH^+ ($C_{23}H_{31}[^{35}Cl]N_5O_4SSi$) = 536.1555}.

Analogous treatment of **20c**−**e** and **23a**,**c** by procedure F gave **21c** (79%), **21d** (60%), **21e** (85%), **24a** (65%), and **24c** (63%), respectively.

9-[5-*O*-(*tert*-Butyldimethylsilyl)-2-*S*-methyl-3-*O*-(phenoxythiocarbonyl)-2-thio-*β*-D-arabinofuranosyl]adenine (24b). Procedure G. DMAP (59 mg, 0.48 mmol) and PTCCl (42 μL, 54 mg, 0.31 mmol) were added to a suspension of dried **23b** (90 mg, 0.22 mmol) in cold (5 °C), dried MeCN (3 mL) and pyridine (0.1 mL). After ∼15 min, dried pyridine (0.5 mL), CH_2Cl_2 (1 mL), MeCN (10 mL), and PTCCl (42 μL, 54 mg, 0.31 mmol) were added, and the resulting yellow solution was stirred overnight at 5 °C. Volatiles were evaporated, the residue was partitioned ($NaHCO_3/H_2O$//$CHCl_3$), and the organic phase was washed (H_2O, brine), dried (Na_2SO_4), and evaporated. The residue was chromatographed ($CHCl_3$ → 3% MeOH/$CHCl_3$) to give **24b** (55 mg, 45%) as an off-white foam: UV max 259 nm (ϵ 14 500), min 228 nm (ϵ 7200); ^{1}H NMR δ 0.15 (s, 6, Me_2Si), 0.95 (s, 9, *t*-Bu), 1.90 (s, 3, SCH_3), 3.91 (dd, $J_{2'-1'} = 5.5$ Hz, $J_{2'-3'} = 3.8$ Hz, 1, H2′), 4.05 (m, 2, H5′,5″), 4.37 (m, 1, H4′), 6.07 (dd, $J_{3'-4'} = 3.7$ Hz, 1, H3′), 6.39 (br s, 2, NH_2), 6.69 (d, 1, H1′), 7.11−7.50 (m, 5, Ph), 8.32 (s, 1, H2), 8.36 (s, 1, H8); MS (CI) *m/z* 548.1830 (100, MH^+ [$C_{24}H_{34}N_5O_4S_2Si$] = 548.1822).

Analogous treatment (procedure G) of **20b** gave **21b** (40%).

Model Reactions with Bu_3SnH/AIBN/Toluene/Δ. Procedure H.[47−49] Individual samples (0.1 mmol) of nucleosides **17**, **18**, **20**, **21**, **23**, **24**, **26**, and **27** were dissolved in dried toluene (4 mL; ∼25 mM solutions) and deoxygenated (Ar, 45 min). Bu_3SnH (54 μL, 58 mg, 0.2 mmol) was injected through the septum, and deoxygenation was continued for 15 min. AIBN (5 mg, 0.03 mmol) was added, and the solution was heated at gentle reflux (∼115 °C, oil bath) for 2.5 h under Ar [some reactions were complete after ∼30 min (TLC)]. Volatiles were evaporated, and the residue was chromatographed {$CHCl_3$ → 5% MeOH/$CHCl_3$ [or EtOAc → 5% MeOH/EtOAc; or $CHCl_3$ → MeOH/Me_2CO/$CHCl_3$ (1:10:50); or EtOAc → 20% S_1/EtOAc]} to give the respective products (Tables 2 and 3).

Model Reactions with Ph_3SiH/BzOOBz/Toluene/Δ. Procedure I.[47,48] Individual samples (0.1 mmol) of nucleosides **17**, **18**, **20**, **21**, **23**, **24**, **26**, and **27** were dissolved in dried toluene (4 mL, ∼25 mM solutions) and deoxygenated (Ar, 45 min). Ph_3SiH (78 mg, 0.3 mmol) and BzOOBz (10 mg, 0.04 mmol) were added, and the solution was heated at gentle reflux (∼115 °C, oil bath) for 3 h. [Second portions of Ph_3SiH (52 mg, 0.2 mmol) and BzOOBz (5 mg, 0.02 mmol) were added and reflux was continued for 4 h in some cases.] Volatiles were evaporated, and the residue was chromatographed as described in procedure H to give the respective products (Tables 2 and 3).

3′-Deoxy-2′-*O*-(*p*-tolylsulfonyl)adenosine (37b). Compound **21e** (67 mg, 0.1 mmol) was treated by procedure H (1 h), the resulting **36b** (TLC, S_5; quantitative after evaporation) was dissolved in THF (5 mL), and TBAF/THF (1 M, 0.2 mL) was added. The solution was stirred for 3 h at ambient temperature, and volatiles were evaporated in vacuo. The residue was purified by preparative RP-HPLC (10 → 50% MeCN/H_2O; 2.8 mL/min, 100 min) to give white solid **37b** (33 mg, 81%; t_R = 81 min): mp 110−115 °C (softening), 225−230 °C dec; UV max 262, 228 nm (ϵ 17 600, 11 400), min 240 nm (ϵ 7700); ^{1}H NMR (DMSO-d_6/D_2O) δ 2.22−2.52 (m, 5, H3′,3″, CH_3), 3.44 (dd, $J_{5''-5'} = 12.3$ Hz, $J_{5''-4'} = 3.7$ Hz, 1, H5″), 3.63 (dd, $J_{5'-4'} = 3.0$ Hz, 1, H5′), 4.31−4.39 (m, 1, H4′), 5.56 (ddd, $J_{2'-3''} = 6.4$ Hz, $J_{2'-3'} = 4.7$ Hz, $J_{2'-1'} = 4.0$ Hz, 1, H2′), 6.02 (d, 1, H1′), 7.19 (d, $J = 8.5$ Hz, 2, H_{arom}), 7.55 (d, 2, H_{arom}), 8.1 (s, 1, H2), 8.27 (s, 1, H8); MS (FAB) *m/z* 406 (100, MH^+). Anal. Calcd for $C_{17}H_{19}N_5O_5S\cdot H_2O$ (423.4): C, 48.22; H, 5.00; N, 16.54. Found: C, 48.51; H, 5.26; N, 16.60.

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(47) Oven- or flame-dried glassware was flushed with argon prior to use.

(48) Crude 5′-*O*-TBDMS mixtures were (a) dissolved in THF (3 mL) and stirred for 6 h at ambient temperature with TBAF/THF (1 M; 0.25 mL) or (b) dissolved in MeOH (3 mL) and refluxed for 3 h with NH_4F (15 equiv). These deprotection mixtures were evaporated, and the residues were chromatographed [Dowex 1 × 2 (OH^-); H_2O → 40% MeOH/H_2O) for **30b** and **35b**; silica gel (EtOAc → 20% S_1/EtOAc) for **32a**] if necessary.

(49) Excess Bu_3SnH was removed from products by extensive washing of silica columns with EtOAc/pentane prior to elution of product(s) or by vigorously stirring the residue with EtOAc/KF/H_2O (5 mL/50 mg/0.5 mL) for 16 h at ambient temperature (no 5′-desilylation observed) followed by chromatography.