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Biomimetic Simulation of Free Radical-Initiated Cascade Reactions Postulated To Occur at the Active Site of Ribonucleotide Reductases[1]

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Abstract: Treatment of 5′-*O*-nitro esters of nucleosides with tributylstannane and AIBN at elevated temperatures caused β-scission of the resulting 5′-oxygen radical to give formaldehyde and dehomologated erythrofuranosyl nucleosides. Analogous treatment of 6′-*O*-nitro esters of homonucleosides [(5-deoxy-β-D-*ribo*-hexofuranosyl)-adenine or uracil nucleosides derived from D-glucose] resulted in generation of a 6′-oxygen radical followed by abstraction of H3′ by a [1,5]-hydrogen shift. Radical quenching with tributyltin deuteride gave 3′-[^{2}H]-homonucleosides. This deuterium transfer, and inversion of configuration at C3′ with unprotected homonucleosides, confirmed the relay-generation of C3′ free radicals. Analogous treatment of 6′-*O*-nitro esters of homonucleosides containing a 2′-chloro (**30**) or 2′-*O*-tosyl (**40**) substituent resulted in complete disappearance of starting material and generation of (*R*)-2-(2-hydroxyethyl)-3(2*H*)-furanone (**33**). Generation of a 6′-oxygen radical, [1,5]-hydrogen shift of H3′ to give a C3′ radical, and loss of the 2′-substituent would give unstable intermediates that could lose the heterocyclic base from C1′ to give **33**. This radical-initiated cascade simulates reactions postulated to occur at the active site of ribonucleotide reductases. Generation of a C3′ radical from **40** and loss of toluenesulfonic acid via a [1,2]-electron shift would generate a radical intermediate that could undergo deuterium transfer followed by β-elimination of the base to give the deuterated furanone **33**, as observed. This is in harmony with a new mechanism for substrate reduction of nucleotides to give 2′-deoxy products. Generation of a C3′ radical from **30** and loss of a chlorine atom by β-radical elimination would result in conjugate elimination of base and generation of **33** *without* incorporation of deuterium, as observed. Thus, one-electron elimination processes (as well as the previously postulated two-electron loss with groups from C2′) must be considered with mechanism-based inactivators of ribonucleotide reductases. Biomimetic reactions and new mechanistic considerations are discussed.

Introduction

Ribonucleotide reductases (RNRs) are the crucial enzymes that execute the only *de novo* biosynthesis of DNA monomers. Reichard and other investigators[2] defined basic functional and structural features of RNRs, and Stubbe and co-workers[3] performed elegant molecular mechanistic studies that clarified the role of free radical initiators and the resulting reaction cascade that results in reduction of substrate ribonucleotides to 2′-deoxy analogues. This field has been reviewed frequently.[2−4] The ribonucleoside diphosphate reductase (RDPR) from *Es-*

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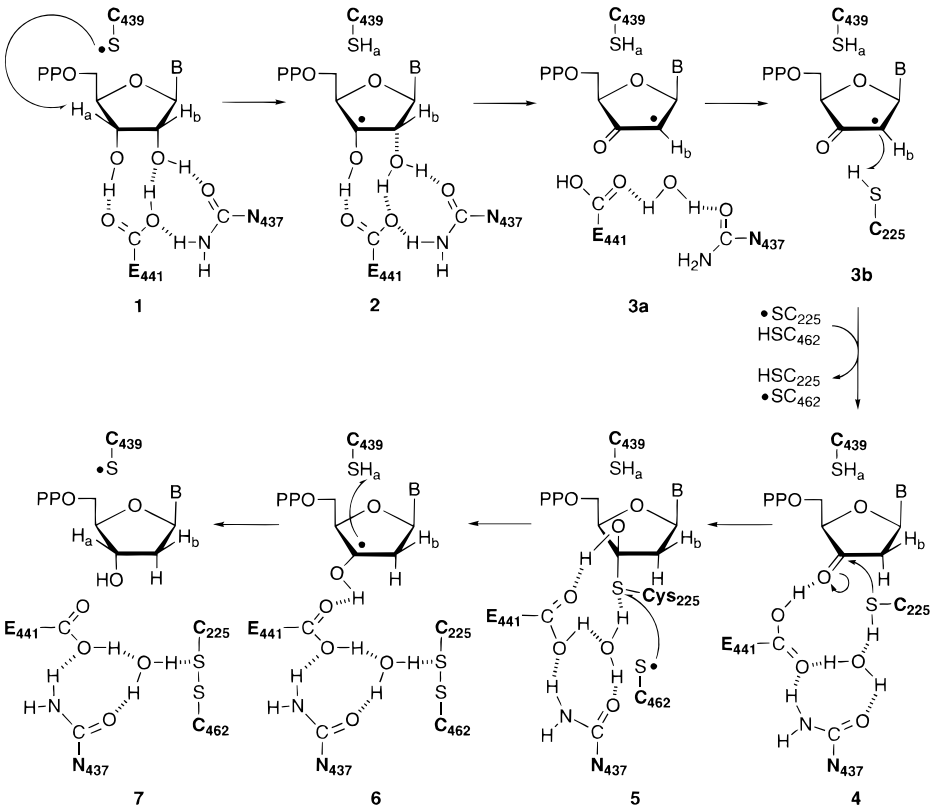
Scheme 1[a]



[a] Proposed mechanism for reduction of nucleoside diphosphate substrates with RDPR.[8]

cherichia coli (EC 1.17.4.1) has been studied most extensively and consists of two homodimeric subunits (R1 and R2). R1 contains cysteine residues that are involved in redox chemistry, binding sites for substrates and allosteric nucleotides that control the enzyme velocity and substrate selection, and a cysteine residue postulated to be the proximal radical initiator. R2 contains a diferric iron cluster associated with a tyrosyl free radical, which constitutes the "stable" radical system postulated to initiate an intriguing reaction cascade during each enzyme turnover. Mammalian and certain viral RDPRs have structural organization similar to that of *E. coli*.[2−4]

Stubbe's[3,5] original mechanistic rationalization for radical-mediated 2′-deoxygenation of ribonucleotides by RDPR was based[5a−d] on a mechanism proposed for conversion of ethylene glycol to acetaldehyde with acidic Fenton's reagent[6a] (hydroxyl radical initiation[6]). The enzymatic process was considered to be initiated by abstraction of H3′ from the substrate by the tyrosyl radical,[5c] or a protein residue,[5d] to give a C3′ radical. Protonation of the 2′-hydroxyl by a cysteine thiol was invoked to assist heterolytic departure of a water molecule (H_2O-2′) to produce a cation radical. Transfer of a hydride equivalent (from a dithiol pair) to the α-face of C2′ and return of H3′ to C3′ would produce the 2′-deoxynucleotide.[5d] Recent refinements of this hypothesis invoked a thiyl radical[3c,d,5e−h] (Cys439, generated by long-range electron transfer from Tyr222) as the proximal initiator for abstraction of H3′ from the substrate. Base-promoted heterolytic cleavage of C2′−O2′ (hydrogen bonding of OH3′ with the carboxylate of Glu441) was proposed to assist loss of water from C2′.[3c,d] Hydrogen transfer from the dithiol pair (Cys 225/462) at the α-face of C2′ and electron transfer from the resulting disulfide radical anion to C3′ would give the C3′ radical that would regain hydrogen from Cys439 to produce the 2′-deoxynucleotide and regenerate the thiyl radical.[3c,d] Additional evidence for C3′ radical initiation as the first step in the reduction of substrates, and also in mechanism-based inactivation of RNRs, has been reported.[7]

Siegbahn's very recent theoretical analysis of the substrate reaction cascade[8] correlated mechanistic processes with amino acid residues identified in X-ray crystal structures of the subunits.[9] Scheme 1 illustrates this analysis,[8] which is based on the Stubbe mechanism but adds new considerations and clarifies postulates[3,5] that were inconsistent with chemical properties. Abstraction of H3′ from substrate **1** by Cys439 is assisted by hydrogen bonding with Glu441 and Asn437, which promotes loss of water (H_2O-2′) from the resulting C3′ radical **2** by a [1,2]-electron shift to C2′ with concomitant net transfer

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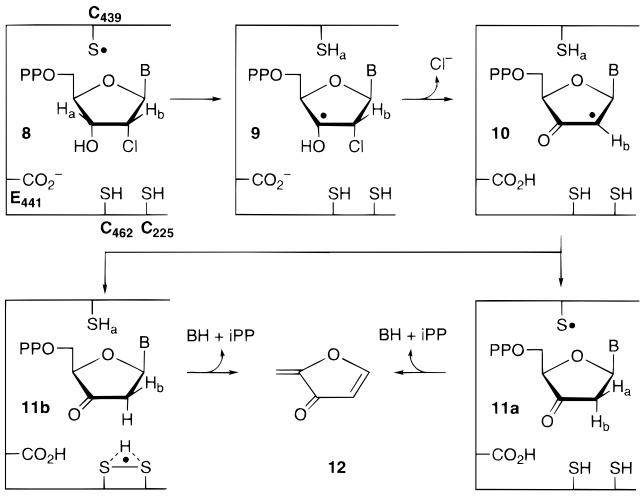
of the 3′-hydroxyl hydrogen to O2′.[8] The hydrogen-bonded transition state for **2** → **3a** has *minimal* charge separation in harmony with chemical reactions at C2′. We had demonstrated that free radical reactions proceed readily at C2′,[10] whereas generation of cationic character[3,5] is energetically prohibitive (C2′ is bonded to the electron-deficient anomeric center).[10a] Hydrogen transfer from Cys225 to C2′ of the ketone radical **3b** is exothermic to produce the most stable intermediate in the sequence, the 2′-deoxy-3′-ketone **4**.[8] Stubbe's mechanism is vague regarding electron/proton transfer to **4** from a disulfide anion radical,[3,5] and a recent alternative pathway was suggested without theoretical support.[9f] A chemically plausible postulate, with a kinetically competent activation energy barrier, invokes a protein residue-assisted addition of the thiol moiety of Cys225 (generated by hydrogen transfer from the proximal HSCys462 to •SCys225) to the ketone function in the hydrogen-bonded complex **4**.[8] Attack of the •SCys462 radical at the hydrogen-bonded sulfur of the resulting thiohemiacetal complex **5** then generates the C3′ radical **6** and a hydrogen-bonded cystine disulfide complex. Hydrogen transfer from Cys439 to C3′ is exothermic to give the 2′-deoxynucleotide product **7** and regenerate •SCys439. Reduction of the disulfide to the HSCys225/HSCys462 dithiol pair is then required for the next catalytic cycle. This elegant theoretical analysis[8] preserves the fundamental concepts of the Stubbe mechanism,[3,5] corrects[10] the postulated[3a,b,5a−d] generation of cation radical character at C2′, and offers for the first time a chemically and theoretically plausible route for the overall rate-limiting reduction of the 2′-deoxy-3′-ketone intermediate **4**.

Lenz and Giese performed photochemical studies with selenoester models that fragment to generate nucleoside mimics of the natural nucleotide C3′ radical **2**.[11] Photolysis rates were pH dependent, and addition of acetate buffer enhanced rates in harmony with base-promoted assistance of the cleavage of water from C2′ (**2** → **3a**, Scheme 1), rather than acid-catalyzed generation of a radical cation.[3a,b,5a−d] The photolysis results[11] are compatible with studies of Schulte-Frohlinde and co-workers on radiolytic generation and decomposition of oxygen-containing radicals.[12]

Mechanism-based inactivation of RDPR with 2′-(azido and chloro)-2′-deoxynucleoside 5′-diphosphates was discovered by

Scheme 2[a]



[a] Proposed mechanism for inactivation of RDPR by 2′-chloro-2′-deoxy-NDPs.[3c]

Thelander et al.[13] Inhibition of RNRs with 2′-chloro analogues was proposed to involve analogous initiation by abstraction of H3′[3,14] followed by spontaneous heterolytic cleavage of the C2′−Cl bond to release chloride and produce a cation radical.[14] Abstraction of hydrogen from a Cys by C2′[14b] and β-elimination of H2′/base and H4′/inorganic pyrophosphate from the 2′-deoxy-3′-ketonucleotide were postulated to produce the 2-methylene-3(2*H*)-furanone Michael acceptor, which effected covalent alkylation/inactivation of the enzyme.

Scheme 2 illustrates Stubbe's recent hypothesis for this mechanism-based inactivation.[3c] Abstraction of H3′ from **8** gives C3′ radical **9**. Loss of chloride and the 3′-hydroxyl proton gives ketone radical **10**. Hydrogen transfer from Cys439 to **10** at the β-face gives **11a** (with regeneration of •SCys439) and that from Cys225/462 to the α-face gives **11b** (without regeneration of •SCys439). Dissociation of **11** from the enzyme active site followed by H2′/base and H4′/iPP β-eliminations would produce the Michael inactivator,[3c,14] 2-methylene-3(2*H*)-furanone (**12**).

Over a decade ago, we[15] began biomimetic studies to simulate the initiation/elimination cascade that occurs during reductions and mechanism-based inactivations mediated by RNRs. Our rudimentary models generated 3′-deoxy C3′ radicals with substitutents at C2′.[16] Treatment of 2′-(azido, bromo, chloro, iodo, and methylthio)nucleoside 3′-thionocarbonates with Bu_3SnH/AIBN produced 3′-deoxy C3′ radicals that underwent loss of the 2′-substitutent to give 2′,3′-didehydro-2′,3′-dideoxynucleosides. In contrast, analogous 3′-thionocarbonates with 2′-fluoro or 2′-*O*-(mesyl or tosyl) substituents (anionic leaving groups) underwent hydrogen transfer to the C3′ radical to give the 3′-deoxy-2′-[fluoro or *O*-(mesyl or tosyl)] derivatives.[16] A radical relay system has now been constructed[17] with homologated nucleoside analogues to allow generation of 6′-oxyl radicals [from 6′-*O*-nitro-2′-(substituted)homonucleosides] that are positioned to abstract H3′ and produce 3′-hydroxyl-containing C3′ radicals. Chlorine atom[17a] or toluenesulfonic acid[17b] loss from

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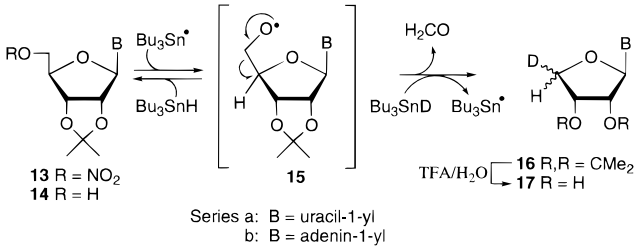
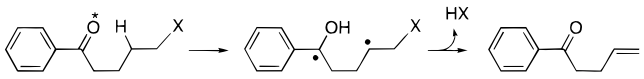
Scheme 3



Scheme 4[a]



[a] Substituents included X = Cl, Br, I, SR, SOR, and SO_2R.[22]

these α-hydroxy radicals provided the first simulation of the radical cascade processes postulated to occur at the active site of RNRs.

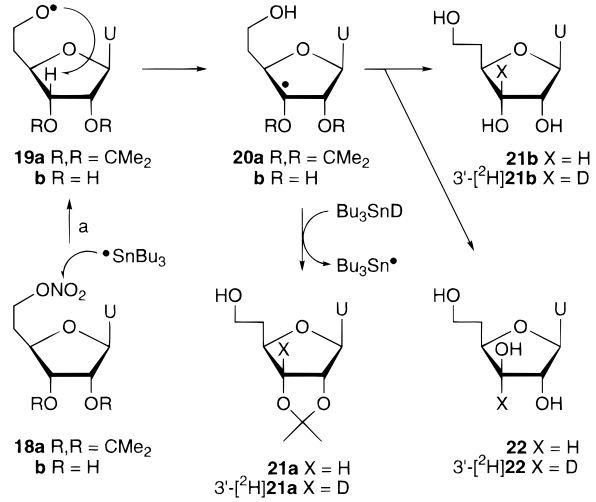
Results and Discussion

An initial approach[15] involved generation of 5′-oxyl radicals from readily available 5′-*O*-nitro esters of protected ribonucleosides.[18] However, treatment of 5′-*O*-nitro-2′,3′-*O*-isopropylideneuridine[18] (**13a**) with Bu_3SnD/AIBN/benzene/Δ[19] resulted in *β*-scission (loss of formaldehyde from **15a**) to give the 4′-glycosyl radical (Scheme 3). Deuterium transfer occurred stereoselectively at the *β*-face to give the dehomologated erythrose derivative **16a** (*R/S*, ∼7:3). Deuterium transfer to the 5′-oxyl radical **15a** also occurred (to give **14a**, after aqueous workup), but no deuterium exchange was detected at C3′ (^{1}H NMR). Treatment of **13a** with Bu_3SnD/AIBN/xylenes/Δ gave a higher ratio of **16a**/**14a** (∼1:1). Deprotection of **16a** gave 9-(*β*-D-erythrofuranosyl)uracil[20] (**17a**). Similar treatment of the adenine analogue **13b** gave **17b**, and analogous dehomologation was observed with 2′-*O*-(*tert*-butyldimethylsilyl)-3′-deoxy-5′-*O*-nitroadenosine.[15] This provides a convenient new route to tetrofuranosyl nucleosides.

Barton's nitrite[21] and Wagner's *δ*-substituted aryl ketone[22] (Scheme 4) photolysis studies had shown that a six-membered transition state is favorable for abstraction of hydrogen by an oxyl radical. A [1,5]-hydrogen shift was observed with oxyl radicals generated from nitrate esters with Bu_3SnH.[19b] Carbohydrates with benzoyl groups tethered at C4′ were recently synthesized for proposed generation of C3′ radicals,[23] but irridiation would generate oxygen radicals with *ϵ* (rather than the favored *δ*) separation from H3′. Wagner demonstrated that photoactivated elimination (even with iodine) proceeded poorly if a seven-membered transition state was required.[22b]

Our syntheses of 6′-*O*-nitrohomonucleosides utilized sugar precursors[15,17,24] (full experimental details are in the Supporting Information), because 5′-homologations of nucleosides require multistep procedures (for each base) and often give low overall yields.[25] Deprotection of 2′,3′-*O*-isopropylidene-6′-*O*-nitrohomouridine[17a] (**18a**) gave 6′-*O*-nitrohomouridine (**18b**). Homoadenosine[17b] (**28b**) and 6′-*O*-nitrohomoadenosine[17b] (**27b**) were converted into their 2′,3′-*O*-isopropylidene derivatives **28a** and **27a**, respectively, by standard procedures. Regioselective tosylation[26] of 6′-*O*-nitrohomoadenosine (**27b**) gave 6′-*O*-nitro-2′-*O*-tosylhomoadenosine[17b] (**40**). Nitration[18] of 3′-*O*-TBDMS-2′-*O*-tosylhomoadenosine (prepared by bis-silylation of 2′-*O*-tosylhomoadenosine[17b] and selective primary desilylation[27]) and deprotection also gave **40**, whereas attempted nitration of **28a** resulted in glycosyl cleavage. The stabilizing effect of a 2′-*O*-tosyl ester against acid-catalyzed hydrolysis of the glycosyl bond of adenosine was known.[28]

Scheme 5[a]



[a] (a) Bu_3SnD/AIBN/benzene (or benzene/DMAC)/Δ.

Treatment of **18a** (Scheme 5) with Bu_3SnD/AIBN/benzene/Δ gave **21a** and 3′-[^{2}H]**21a** (86%, ∼1:4; ^{1}H NMR, HRMS). The decrease (∼80%) in the ^{1}H NMR signal at *δ* 4.76 (H3′) is consistent with generation of 6′-oxyl radical **19a**, [1,5]-shift[19b,21,22] of H3′ (**19a** → **20a**), and quenching of the C3′ radical by deuterium transfer from the stannane (**20a** → 3′-[^{2}H]-**21a**), in competition with deuterium transfer to the 6′-oxyl

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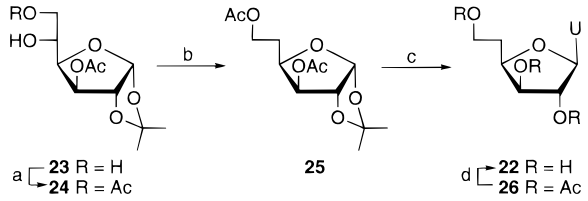
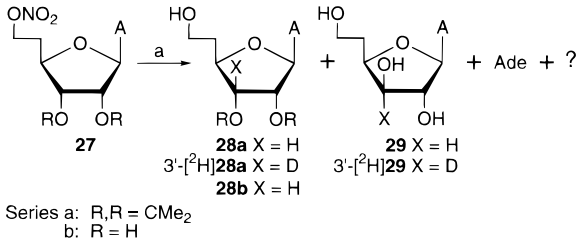
(29) (a) Quantitative *estimations* of unimolecular rate constants for the C4′−C5′ *β*-scission to release formaldehyde from **15** (Scheme 3, $k_1 \approx 10^7$ s^{-1}), for [1, 5]-hydrogen shifts from C3′ to O6′ (**19** → **20**, Scheme 5, $k_1 \approx 10^7-10^8$ s^{-1}), (**41** → **42**, Scheme 9, $k_1 \approx 10^7$ s^{-1}), and for the corresponding [1, 5]-hydrogen shifts that result in generation of C3′ radicals in Schemes 7 ($k_1 \approx 10^6$ s^{-1}) and 8 ($k_1 \approx 10^8$ s^{-1}) (in competition with deuterium transfer from Bu_3SnD to nucleoside oxyl radicals) were calculated with a rate constant ($k_2 = 2 \times 10^8$ M^{-1} s^{-1})[29b] for the reaction *t*-BuO• + Bu_3SnH → *t*-BuOH + Bu_3Sn•. Major assumptions include using a "constant" concentration for Bu_3SnD (used in 5−40 molar excess), using the known rate constant[29b] for our "related" deuterium transfer to primary oxyl radicals, ignoring competing processes that generate minor byproducts, and using our detection limit (∼2%)[29c] for the nucleoside bimolecular deuterium transfer byproduct. (b) Scaiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 5399−5400. (c) Robins, M. J.; Sarker, S.; Wnuk, S. F. *Nucleosides Nucleotides* **1998**, *17*, 785−790.

Scheme 6[a]



[a] (a) AcCl/collidine/CH_2Cl_2/−78 °C. (b) (i) PTCCl/DMAP/CH_3CN; (ii) Bu_3SnH/AIBN/toluene/Δ. (c) (i) TFA/H_2O; (ii) Ac_2O/pyridine; (iii) (persilylated)uracil/$SnCl_4$/CH_3CN. (d) NH_3/MeOH.

Scheme 7[a]



[a] (a) Bu_3SnD/AIBN/benzene/DMAC/Δ.

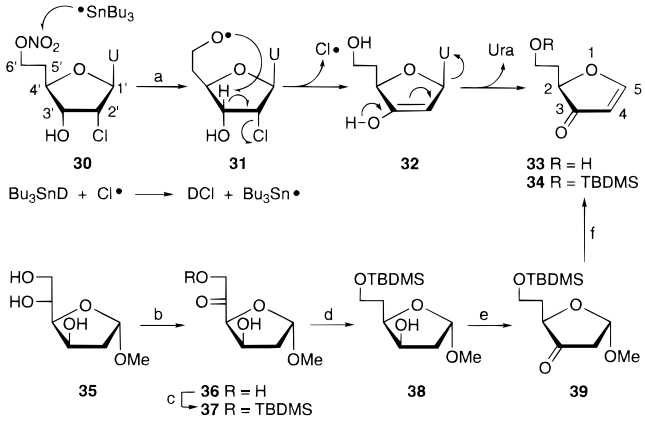
radical (∼20%) (and exchange during workup). Analogous treatment [Bu_3SnD/AIBN/benzene/*N*,*N*-dimethylacetamide (DMAC)/Δ)] of 6′-*O*-nitrohomouridine (**18b**), with a more conformationally flexible sugar ring, gave 3′-[^{2}H]**21b** and its xylo epimer 3′-[^{2}H]**22** (87%, ∼1.3:1) with >98% deuterium incorporation at C3′ (^{1}H NMR) of both compounds.[29] Formation of the ribo and xylo C3′ epimers, as well as the complete 3′-deuteration, confirmed the intermediacy of a 3′-radical. The xylo epimer, **22**, of homouridine was synthesized independently from 3-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose[30] (**23**) by a route (Scheme 6) parallel to that used[17a] for **21b**.

Treatment of **27a** (Scheme 7) with Bu_3SnD/AIBN/benzene/Δ gave **28a** and 3′-[^{2}H]**28a** (83%, ∼1:1; ^{1}H NMR, HRMS). The unprotected **27b** (more conformationally flexible sugar ring) was converted into a mixture of homoadenosine (**28b**, no ^{2}H exchange at C3′) and the completely deuterated xylo epimer 3′-[^{2}H]**29** (∼81%, ∼1.3:1). Adenine (∼5%) and an unidentified product (∼10%, possibly a 3′-ketone) also were isolated. Nucleoside 3′-ketones decompose readily by β-elimination (H2′/base), especially in the presence of bases. Addition of tetrabutylammonium fluoride (TBAF) to a solution of the unidentified product resulted in its immediate decomposition with release of adenine. Repetition of parallel treatments of **18b**, and HPLC of the reaction mixture, indicated a correspondingly unstable compound plus uracil.

Deuterium transfer from the stannane to the 6′-oxyl radical (to give **28b**, after workup) competes successfully with intramolecular [1,5]-abstraction of H3′ with adenine homonucleoside **27b**. When a C3′ radical is generated, it is quenched by deuterium transfer at the α-face to produce 3′-[^{2}H]**29** (more hindered β-face than uracil analogues[31]). Parallel treatment of **27b** with Bu_3SnH gave a similar product distribution. The ^{1}H NMR signal at δ 3.87 (H3′) in the spectrum of 9-(5-deoxy-β-D-*xylo*-hexofuranosyl)adenine[32] (**29**) was absent in the spectrum of 3′-[^{2}H]**29**.

With relay generation of C3′ radicals clearly established, we proceeded with biomimetic modeling of radical cascade decomposition reactions.[17,33] Treatment of 2′-chloro-2′-deoxy-6′-*O*-nitrohomouridine (**30**) (Scheme 8) with Bu_3SnD/AIBN/benzene/Δ resulted in decomposition of **30** with concomitant generation of uracil and (*R*)-2-(2-hydroxyethyl)-3(2*H*)-furanone (**33**). NMR and HRMS spectra, and an independent synthesis of the silyl ether **34**, confirmed the structure of the rather unstable enone **33**. Incubation of 2′-chloro-2′-deoxynucleotides with RNRs is known to produce the 2-methylene-3(2*H*)-furanone[14] (**12**) analogue of **33**.

Scheme 8[a]



[a] (a) Bu_3SnD/AIBN/benzene/Δ. (b) (i) $(Bu_3Sn)_2O$/$CHCl_3$/Δ; (ii) Br_2. (c) TBDMSCl/pyridine. (d) (i) $TsNHNH_2$/MeOH; (ii) $NaBH_4$/MeOH/Δ. (e) CrO_3/pyridine/Ac_2O. (f) TEA/MeOH.

A plausible mechanism for conversion of **30** into **33** involves generation of the 6′-oxyl radical **31** and relay [1,5]-H3′ abstraction. Loss of a chlorine atom,[17] but not a chloride anion,[14] would produce enol **32**. Radical chains would be propagated by deuterium transfer from Bu_3SnD to chlorine atoms. Conjugate elimination (or tautomerization of **32** into the 2′-deoxy-3′-ketone and β-elimination) of uracil would give **33**. During in vivo inactivation of RNRs by 2′-chloro-2′-deoxynucleotides, released chlorine atoms might be reduced to chloride by proximal thiol groups. Hydrogen bonding of the 3′-hydroxyl proton to Glu441 would enhance negative character at C2′. The incipient enolate could remove the proton (H_a) from Cys439 to give **11a** (some migration of [^{3}H]3′ to C2′ at the β-face is observed[3b,14b]), or accept a proton at the α-face to produce **11b** (Scheme 2), with a one-electron alteration in the oxidation state(s) of the thiol(s).

Methyl 2-deoxy-α-D-*arabino*-hexofuranoside[35] (**35**) was prepared from 2-deoxyglucose. Oxidation[36] of **35**, silylation of the 5-oxo derivative **36**, and deoxygenation[37] of **37** gave the 2,5-dideoxy sugar **38**. Oxidation[31] of **38** gave the 3-ketone **39** which underwent β-elimination to give the TBDMS-protected 3(2*H*)-furanone derivative **34** upon treatment with triethylamine (TEA)/MeOH. Formation of **34** is in harmony with results on C3′ oxidations of 5′-*O*-tritylthymidine, during which the 3′-ketone

(30) Gramera, R. E.; Ingle, T. R.; Whistler, R. L. *J. Org. Chem.* **1964**, *29*, 2074−2075.

(31) Hansske, F.; Madej, D.; Robins, M. J. *Tetrahedron* **1984**, *40*, 125−135.

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(33) The 2′-chloro-2′-deoxy-6′-*O*-nitrohomouridine model was chosen to mimic inactivation of RNRs by 2′-chloro-2′-deoxyuridine 5′-phosphates.[13,14] Our first studies[15] with 2′-(azido and chloro)-5′-*O*-nitrouridine derivatives had shown that generation of a 5′-oxyl radical was faster than cleavage of the C2′-chlorine bond, but reduction of an azido group to amino[34] was competitive with generation of a 5′-oxyl radical.

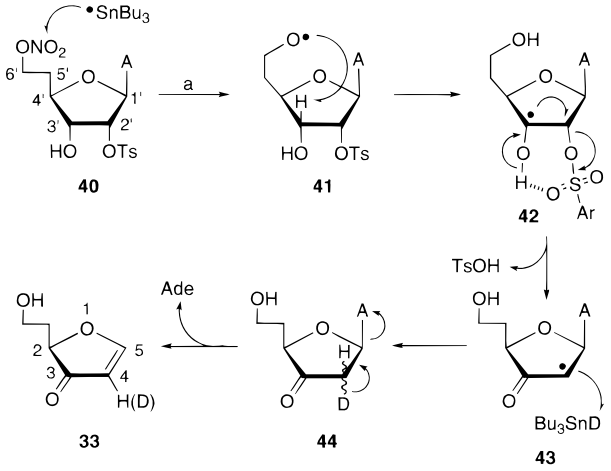
(34) (a) Samano, M. C.; Robins, M. J. *Tetrahedron Lett.* **1991**, *44*, 6293−6296. (b) Poopeiko, N. E.; Pricota, T. I.; Mikhailopulo, I. A. *Synlett* **1991**, 342−342.

(35) Walker, T. E.; Ehler, D. S.; Unkefer, C. J. *Carbohydr. Res.* **1988**, *181*, 125−134.

(36) Tsuda, Y.; Hanajima, M.; Matsuhira, N.; Okuno, Y.; Kanemitsu, K. *Chem. Pharm. Bull.* **1989**, *37*, 2344−2350.

(37) Caglioti, L. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 62−63.

Scheme 9[a]



[a] (a) Bu_3SnD/AIBN/benzene/Δ.

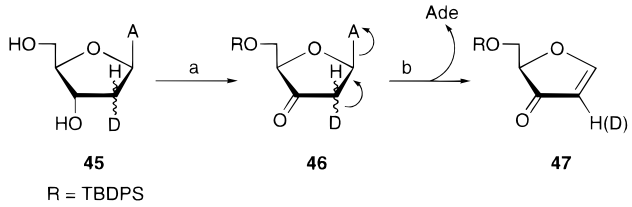
derivative undergoes β-elimination under mild conditions to give (*R*)-2-[(trityloxy)methyl]-3(2*H*)-furanone.[31,38] Such β-eliminations with other nucleoside[39,40] and 2′-deoxy-3′-oxopentofuranose[38a] derivatives have been reported. Spectral data for **34** were compatible with those for the radical cascade product **33**.

Treatment of **40** (Scheme 9) with Bu_3SnD/AIBN/benzene/Δ resulted in its decomposition into 2′-*O*-tosylhomoadenosine [28%, no ^2H at C3′ (^1H NMR)] plus adenine and (*R*)-2-(2-hydroxyethyl)-3(2*H*)-furanone (**33**, 62%). ^1H NMR spectra of this **33** had ∼30% reduction in the signal at δ 5.71 (H4) (corresponds to H2′ of **40**). HRMS peaks at *m*/*z* 129.0545 (100, MH^+ [$C_6H_9O_3$] = 129.0552) and 130.0619 (41, MH^+ [$C_6H_8DO_3$] = 130.0614) confirmed the incorporation of deuterium. Thus, radical-induced decompositions of these 2′-chloro **30** and 2′-tosylate **40** analogues proceed by different mechanisms (Schemes 8 and 9, respectively).

Generation of the 6′-oxyl radical (**40** → **41**) (Scheme 9) followed by [1,5]-shift of H3′ would give the C3′ radical (**41** → **42**). Loss of toluenesulfonic acid from **42**, with a concerted [1,2]-electron shift, would produce the C2′-radical intermediate **43**. Deuterium transfer from the stannane to **43** would occur selectively at the less hindered α face[10b] to give the 2′-deoxy-2′-deuterio-3′-oxohomoadenosines [**44**; C2′(*R*/*S*), ∼30:70] which would undergo anti β-elimination to give **33** (with ∼30% deuterium remaining at C4). Deuterium transfer from Bu_3SnD to **43** would propagate radical chains (**40** → **43**). In contrast, the decomposition of 2′-chloro analogue **30** (Scheme 8) (with no deuterium incorporation into **33**) is analogous to our elimination reactions in which generation of a 3′-deoxy C3′ radical was followed by loss of (azido, bromo, chloro, iodo, or methylthio) radicals from C2′ to give the 2′,3′-olefin.[16] In that series, generation of the 3′-deoxy C3′ radical with 2′-(fluoro, mesylate, or tosylate) substituents resulted in hydrogen transfer from the stannane to C3′ and retention of the 2′-substituent.

The radical-induced loss of toluenesulfonic acid (**42** → **43**) (Scheme 9) is analogous to the [1,2]-hydride shift rearrangement,[40−42] which converts 2′-*O*-tosyladenosine into 9-(2-deoxy-β-D-*threo*-pentofuranosyl)adenine ($LiEt_3BH$/THF/DMSO).[41] In

Scheme 10[a]



[a] (a) (i) TBDPSCl/pyridine; (ii) Dess−Martin periodinane/CH_2Cl_2. (b) Bu_3SnD/AIBN/benzene/Δ.

that case, a 2′-deoxy-3′-ketone intermediate is formed by a [1,2]-hydride shift (H3′ from C3′ to C2′) with loss of tosylate.[41] The present concerted [1,2]-electron shift with generation of a carbonyl group at C3′ would provide the driving force for expulsion of toluenesulfonic acid (**42** → **43**). Zipse performed a theoretical study on a C3′ radical species in which a seven-membered ring (connecting OH3′ and OH2′ by hydrogen bonding with an "XH" species) intermediate was found to undergo concerted loss of water from C2′.[43] Formation of the seven-membered hydrogen-bonded intermediate **42** and concerted elimination of toluenesulfonic acid are not unreasonable in benzene solution. The calculations of Siegbahn assumed an average dielectric constant of $\epsilon = 4$ for the aqueous-surrounded protein environment of the active site of RDPR.[8] His study indicated that transition state energies were affected to a very minor extent by changing parameters for the dielectric constant (vacuum versus $\epsilon = 4$). Therefore, benzene ($\epsilon = 2.3$) should be a better model for the RDPR active site environment than polar media.[11] Model reactions in more polar, especially aqueous, media would favor more polarized transition states, which Nature apparently has selected against in protein environments at the active sites in which nonpolarized, concerted processes are energetically favored.[8]

Additional evidence for the mechanism in Scheme 9 was obtained by parallel treatment of 2′-deoxy-3′-ketone[44] derivatives **46** (Scheme 10). Silylation of 2′-deoxy-2′-deuterioadenosine[10b] [**45**; C2′(*R*/*S*), ∼85:15) and Dess−Martin oxidation[45] gave **46**. Downfield shifts of H2′,2″ peaks, reduction in their intensities, and splitting simplifications[44] in the ^1H NMR spectra were consistent with **46**. Treatment of **46** with Bu_3SnD/AIBN/benzene/Δ (*identical* control reaction mixture; however, the thermal β-elimination is not dependent on Bu_3SnD/AIBN) gave (*R*)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-3(2*H*)-furanone (**47**), a dehomologated analogue of **33**. Reduction (∼15%) of the ^1H NMR signal at δ 5.75 (H4) is in harmony with an antistereospecific β-elimination (^2H_S/adenine) from **46** (∼85% (*S*)-[^2H]). Such decompositions of 2′-deoxy-3′-ketonucleosides with elimination of the base are well-known.[31,38−40]

The mechanism illustrated in Scheme 9 simulates substrate reactions postulated to occur at the active site of *E. coli* RDPR (Scheme 1), except for reduction of the 3′-ketone **44** and return of a hydrogen atom to C3′. The external tributylstannyl radical generates internal 6′-oxyl radical **41** analogous to generation of the proximal •SCys439 by long-range electron transfer from •OTyr122 in RDPR. The [1,5]-shift of H3′ to O6′ generates the C3′ radical **42** analogous to the conversion of **1** → **2** by RDPR. The [1,2]-electron shift with loss of toluenesulfonic acid converts

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(39) Sugiyama, H.; Fujimoto, K.; Saito, I. *J. Am. Chem. Soc.* **1995**, *117*, 2945−2946.
(40) Kawana, M.; Takeuchi, K.; Ohba, T.; Kuzuhara, H. *Nucleic Acids Res., Symp. Ser. No. 17*, **1986**, 37−40.
(41) Hansske, F.; Robins, M. J. *J. Am. Chem. Soc.* **1983**, *105*, 6736−6737.
(42) (a) Kawana, M.; Kuzuhara, H. *Tetrahedron Lett.* **1987**, *28*, 4075−4078. (b) Kawana, M.; Kuzuhara, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 469−478.
(43) Zipse, H. *J. Am. Chem. Soc.* **1995**, *117*, 11798−11806.
(44) Samano, V.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 5186−5188.
(45) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

42 → **43** analogous to the conversion of **2** → **3a** by RDPR. Stereoselective (~70%) transfer of deuterium at the α-face of **43** gives **44**, whereas analogous transfer of hydrogen occurs with complete stereoselectivity at the α-face of **3b** to give **4** with RDPR. It is remarkable that our biomimetic system fully simulates reactions performed by an *E. coli* RDPR Glu441 → Gln441 site-directed mutant.[7c] The mutant enzyme also was unable to perform the final reduction step (Gln441 lacks the acidic hydrogen-bonding capability of Glu441), and the 3′-ketonucleotide (analogous to our **44**) was the end product of that mutant enzyme sequence.[7c]

Summary and Conclusions

Treatment of 5′-*O*-nitropentofuranosyl nucleosides with Bu_3SnD/AIBN/benzene/Δ resulted in *β*-scission of the C4′−C5′ bond of the O5′ radical intermediate, rather than [1,4]-abstraction of H3′ (five-membered transition state). This provides access to tetrofuranosyl homologues (Scheme 3). We have constructed 6′-*O*-nitrohomonucleosides and demonstrated free radical relay exchange of H3′ for D3′ with Bu_3SnD. Treatment of 2′-chloro-2′-deoxy-6′-*O*-nitrohomouridine (**30**) under analogous conditions resulted in decomposition of **30** to give uracil plus (*R*)-2-(2-hydroxyethyl)-3(2*H*)-furanone (**33**) with no incorporation of deuterium into **33** (Scheme 8). In contrast, analogous treatment of 6′-*O*-nitro-2′-*O*-tosylhomoadenosine (**40**) resulted in decomposition of **40** to give adenine and **33** with ~30% deuterium incorporation at C4 (Scheme 9). Thus, the results with **40** (Scheme 9) are in harmony with the Stubbe/Siegbahn mechanism (Scheme 1) for reduction of substrates, and provide a biomimetic model for free radical-induced relay reaction cascades postulated to occur at the active site of ribonucleotide reductases. However, the results with **30** (Scheme 8) are consistent with *β*-elimination of a chlorine atom in harmony with photochemical studies of Wagner (Scheme 4), and are incompatible with loss of chloride anion (Scheme 2). Our studies have provided experimental evidence for differentiation between one-electron (Scheme 8) and two-electron (Scheme 9) loss with 2′-substitutents upon generation of O3′-containing C3′ radicals. Studies are in progress to evaluate solvent (benzene is known to stabilize chlorine atoms[46]), ionic, and general base effects on such reactions.

Experimental Section

A capillary apparatus was used for uncorrected melting points. UV spectra are of solutions in MeOH. ^{1}H (200 or 500 MHz) and ^{13}C (50 or 125 MHz) NMR spectra are of solutions in $Me_4Si/CDCl_3$ unless otherwise specified. Mass spectra (MS and HRMS) were obtained by electron impact (20 eV), chemical ionization (CI; CH_4), or fast atom bombardment (FAB; thioglycerol matrix) techniques. Reagent grade chemicals were used, and solvents were dried by reflux and distillation from CaH_2 (except acetone/P_2O_5) under an argon atmosphere. TLC was performed with Merck kieselgel 60-F_{254} sheets, and products were detected with 254 nm light or by color development (I_2 or 10% H_2SO_4/MeOH). Merck kieselgel 60 (230−400 mesh) was used for column chromatography. RP-HPLC was performed with a SpectraPhysics P200 pump system with an Apex Prepsil column (25 cm). NH_3/MeOH was saturated at −10 °C. Elemental analyses were by M-H-W Laboratories, Phoenix, AZ. Only key experiments are described in this paper. Full experimental details, spectral data, and characterization for all compounds are available in the Supporting Information.

1-(4-Deuterio-*β*-D-erythrofuranosyl)uracil (17a). A solution of **13a**[18] (25 mg, 0.076 mmol), AIBN (5 mg, 0.03 mmol), and Bu_3SnD (0.103 mL, 111 mg, 0.38 mmol) in dried xylene (5 mL) was deoxygenated (Ar, 45 min) and refluxed for 1 h. Volatiles were evaporated, and the residue was chromatographed ($CHCl_3$ → 1.5% MeOH/$CHCl_3$) to give **16a** (8 mg, 41%; 4′*R*/*S*, ~7:3): ^{1}H NMR *δ* 1.30, 1.44 (2s, 2 × 3H), 4.17 (s, 0.7H), 4.33 (d, *J* = 3.8 Hz, 0.3H), 5.04−5.08 (m, 1H), 5.17 (d, *J* = 5.8 Hz, 1H), 5.38 (s, 1H), 5.71 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 8.71 (br s, 1H, ex); HRMS (CI) *m*/*z* 256.1043 (100, MH^+ [$C_{11}H_{14}DN_2O_5$] = 256.1044). Further elution gave 2′,3′-*O*-isopropylideneuridine (10 mg; 46%).

Procedure A. A solution of **16a** (8 mg, 0.031 mmol) in TFA/H_2O (9:1, 1 mL) was stirred at 0 °C for 1 h. Volatiles were evaporated, EtOH was added and evaporated, and the residue was chromatographed ($CHCl_3$ → 7% MeOH/$CHCl_3$) to give **17a** (5 mg, 75%; 4′*R*/*S*, ~7:3) with data as reported[20] except for ^{2}H effects: ^{1}H NMR (Me_2SO-d_6) *δ* 3.65 (d, *J* = 2.2 Hz, 0.7H), 4.14−4.22 (m, 1.3H); HRMS (CI) *m*/*z* 216.0738 (45, MH^+ [$C_8H_{10}DN_2O_5$] = 216.0731).

9-(*β*-D-Erythrofuranosyl)adenine (17b). Treatment of **13b**[18] [60 mg, 0.17 mmol; prepared (20%) by nitration of 2′,3′-*O*-isopropylideneadenosine with *N*-nitropyrazole/triflic acid/CH_3CN[47]] with Bu_3SnH (1.05 mL, 1.14 g, 3.9 mmol) as described for **17a** [with chromatography (EtOAc → 20% Me_2CO/EtOAc)] gave **16b** (24 mg, 50%): MS *m*/*z* 277 (38, M^+), 164 (100), 136 (61). Deprotection of **16b** (30 mg, 0.1 mmol) by procedure A, chromatography [Dowex 1 × 2 (OH^-), MeOH/H_2O (1:1)], and crystallization (MeOH/Et_2O) gave **17b** (19 mg, 75%): mp 235−237 °C (lit.[20] mp 230−232 °C dec).

1-(5-Deoxy-*β*-D-*ribo*-hexofuranosyl)uracil (21b). A solution of 1-(2,6-di-*O*-acetyl-3-*O*-benzoyl-5-deoxy-*β*-D-*ribo*-hexofuranosyl)-uracil[17a] (446 mg, 1 mmol) in NH_3/MeOH (10 mL) was stirred in a sealed flask for 18 h at ambient temperature. Volatiles were evaporated, and the residue was chromatographed (10% MeOH/CH_2Cl_2) and recrystallized (EtOH) to give **21b** (211 mg, 82%): mp 151−152 °C (lit.[25b] 154−157 °C); UV max 262 nm (*ϵ* 10 100); ^{1}H NMR (Me_2SO-d_6) *δ* 1.76 (2 × dd, *J* = 13.6, 7.0 Hz, 2H), 3.42−3.52 (m, 2H), 3.79 ("q", *J* = 5.0 Hz, 1H), 3.86 (dd, *J* = 7.0, 5.0 Hz, 1H), 4.05 ("q", *J* = 5.0 Hz, 1H), 4.51 (t, *J* = 5.0 Hz, 1H, ex), 5.08 (d, *J* = 5.0 Hz, 1H, ex), 5.32 (d, *J* = 5.0 Hz, 1H, ex), 5.63 (d, *J* = 8.1 Hz, 1H), 5.69 (d, *J* = 5.0 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 11.30 (br s, 1H, ex); ^{13}C NMR (Me_2SO-d_6) *δ* 36.61, 57.75, 72.93, 73.33, 80.67, 88.77, 102.27, 141.39, 150.92, 163.30; MS (CI) *m*/*z* 259 (12, MH^+), 129 (25), 113 (100).

1-(5-Deoxy-2,3-*O*-isopropylidene-*β*-D-*ribo*-hexofuranosyl)uracil (21a). $TsOH·H_2O$ (19 mg, 0.1 mmol) and triethyl orthoformate (0.498 mL, 444 mg, 3 mmol) were added to a suspension of **21b** (258 mg, 1 mmol) in dried Me_2CO (10 mL), and stirring was continued for 3 h at ambient temperature. $NaHCO_3$ (84 mg, 1 mmol) was added, and stirring was continued for 30 min. The mixture was diluted (EtOAc) and filtered, and the filtrate was evaporated. The residue was chromatographed (5% MeOH/CH_2Cl_2) to give **21a** as a white foam (244 mg, 82%): UV max 259 nm; ^{1}H NMR *δ* 1.35, 1.57 (2s, 2 × 3H), 2.00 (dd, *J* = 12.0, 6.5 Hz, 2H), 2.70 (br s, 1H, ex), 3.73−3.85 (m, 2H), 4.20 (td, *J* = 6.5, 5.0 Hz, 1H), 4.76 ("t", *J* = 6.5, 5.0 Hz, 1H), 4.99 (dd, *J* = 6.5, 2.0 Hz, 1H), 5.59 (d, *J* = 2.0 Hz, 1H), 5.75 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 9.83 (br s, 1H, ex); ^{13}C NMR *δ* 25.88, 27.72, 35.92, 60.22, 84.11, 84.64, 85.91, 94.70, 103.27, 115.37, 142.92, 150.41, 163.52; MS *m*/*z* 298 (1, M^+), 283 (40, M − Me). Anal. Calcd for $C_{13}H_{18}N_2O_6$ (298.3): C, 49.81; H, 5.70; N, 26.40. Found: C, 49.76; H, 5.81; N, 26.20.

1-(5-Deoxy-2,3-*O*-isopropylidene-6-*O*-nitro-*β*-D-*ribo*-hexofuranosyl)uracil (18a). Procedure B. Cold fuming nitric acid (3 mL; *d* = 1.5 g/mL) in Ac_2O (3 mL) was added to **21a** (60 mg, 0.2 mmol) in Ac_2O (5 mL) at −60 °C, stirring was continued for 20 min, and the solution was poured into ice-cold saturated $NaHCO_3/H_2O$. The mixture was extracted (EtOAc), and the combined organic phase was washed (brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (3% MeOH/CH_2Cl_2) and recrystallized (EtOH) to give **18a** (63 mg, 92%): mp 146−147 °C; UV max 260 nm; ^{1}H NMR *δ* 1.35, 1.58 (2 × s, 2 × 3H), 2.18 (dd, *J* = 13.0, 6.6 Hz, 2H), 4.15 (td, *J* = 6.6, 4.8 Hz, 1H), 4.56 ("td", *J* = 6.5, 2.5 Hz, 2H), 4.73 (dd, *J* = 6.5, 4.8 Hz, 1H), 5.09 (dd, *J* = 6.5, 1.8 Hz, 1H), 5.47 (d, *J* = 1.8 Hz, 1H), 5.75 (dd, *J* = 8.0 Hz, 2.2 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 8.75 (br s 1H, ex); ^{13}C NMR *δ* 25.30, 27.15, 30.60, 69.67, 83.85,

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84.15, 84.28, 95.77, 102.70, 114.83, 143.10, 149.59, 162.71; HRMS (FAB) *m/z* 344.1097 (48, MH^+ = 344.1094). Anal. Calcd for $C_{13}H_{17}N_3O_8$ (343.3): C, 45.48; H, 4.99; N, 12.24. Found: C, 45.64; H, 5.06; N, 12.15.

1-(5-Deoxy-3-deuterio-2,3-*O*-isopropylidene-*β*-D-*ribo*-hexofuranosyl)uracil (3′-[^{2}H]21a). Procedure C. A solution of **18a** (10 mg, 0.03 mmol), Bu_3SnD (40 μL, 44 mg, 0.15 mmol), and AIBN (~2 mg) in dried benzene (5 mL) was deoxygenated (Ar, 20 min) and then heated for 1 h at reflux. Volatiles were evaporated, and the residue was chromatographed (5% MeOH/CH_2Cl_2) to give **21a**/3′-[^{2}H]**21a** (~1:4; 7.5 mg, 86%): UV max 259 nm; ^{1}H NMR δ 4.20 (t, J = 6.5 Hz, 1, H4′), 4.76 ("t", J = 6.5, 5.0 Hz, ~0.2, H3′), 4.99 (d, J = 2.0 Hz, 1, H2′), other peaks same as for **21a**; MS (CI) *m/z* 300 (100, MH^+ [3′-[^{2}H]**21a**]), 299 (22, MH^+ [**21a**]).

1-(5-Deoxy-6-*O*-nitro-*β*-D-*ribo*-hexofuranosyl)uracil (18b). A solution of the residue (EtOAc) from deprotection of **18a** (68 mg, 0.2 mmol) by procedure A was washed (saturated $NaHCO_3/H_2O$, brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (7% MeOH/CH_2Cl_2) to give **18b** (55 mg, 90%) as a white solid: mp 161−162.5 °C; UV (MeOH) max 261 nm; ^{1}H NMR (Me_2SO-d_6) δ 2.06−2.14 (m, 2H), 3.82−3.88 (m, 2H), 4.12 ("q", $J \cong$ 5.0 Hz, 1H), 4.62 (dd, J = 10.6, 6.4 Hz, 2H), 5.23 (d, J = 5.2 Hz, 1H, ex), 5.45 (d, J = 5.5 Hz, 1H, ex), 5.64 (d, J = 8.0 Hz, 1H), 5.72 (d, J = 4.9 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 11.38 (br s, 1H, ex); ^{13}C NMR (Me_2SO-d_6) δ 30.00, 70.78, 72.43, 72.86, 79.68, 89.24, 102.03, 141.44, 150.62, 163.05; HMRS (CI) *m/z* 304.0789 (6, MH^+ [$C_{10}H_{14}N_3O_8$] = 304.0781).

9-(5-Deoxy-*β*-D-*ribo*-hexofuranosyl)adenine (28b). A solution of 9-(2-*O*-acetyl-3,6-di-*O*-benzoyl-5-deoxy-*β*-D-*ribo*-hexofuranosyl)-adenine[17b] (531 mg, 1 mmol) in NH_3/MeOH (10 mL) was stirred in a sealed flask overnight at ambient temperature. Volatiles were evaporated, and the residue was dissolved (H_2O) and washed (CH_2Cl_2, 3×). The aqueous phase was evaporated, and the residue was recrystallized (H_2O) to give **28b** (234 mg, 83%): mp 230−232 °C (lit.[48] mp 231.5−232.5 °C); UV max 260 (ϵ 15 200); ^{1}H NMR (Me_2SO-d_6) δ 1.79 (dd, J = 12.2, 7.1 Hz, 2H), 3.45 (dd, J = 10.8, 5.4 Hz, 2H), 4.00 (td, J = 7.1, 4.8 Hz, 1H), 4.09 ("q", $J \cong$ 4.8 Hz, 1H), 4.48 (t, J = 5.0 Hz, 1H, ex), 4.66 (q, J = 5.2 Hz, 1H), 5.17 (d, J = 4.8 Hz, 1H, ex), 5.41 (d, J = 5.2 Hz, 1H, ex), 5.82 (d, J = 5.2 Hz, 1H), 7.28 (br s, 2H, ex), 8.12 (s, 1H), 8.30 (s, 1H); ^{13}C NMR (Me_2SO-d_6) δ 36.57, 57.57, 72.98, 73.48, 81.08, 87.50, 119.28, 140.03, 149.59, 152.81, 156.22; MS (CI) *m/z* 282 (42, MH^+), 136 (100).

9-(5-Deoxy-2,3-*O*-isopropylidene-*β*-D-*ribo*-hexofuranosyl)adenine (28a). Treatment of **28b** (100 mg, 0.35 mmol) as described for **21b** → **21a** [with concentrated NH_3/H_2O (2 mL) in place of $NaHCO_3$] and evaporation of volatiles gave a residue that was slurried with EtOAc/acetone (1:1). Filtration of the suspension, evaporation of the filtrate, and chromatography (8% MeOH/CH_2Cl_2) and recrystallization (MeOH) of the residue gave **28a** (94 mg, 82%): mp 269−271 °C dec (lit.[25d] 265−268 °C dec); UV max 259 nm; ^{1}H NMR (Me_2SO-d_6) δ 1.29, 1.50 (2 × s, 2 × 3H), 1.61−1.70 (dd, J = 13.7, 6.0 Hz, 1H), 1.72−1.81 (dd, J = 13.7, 7.1 Hz, 1H), 3.38 (dd, J = 11.2, 5.6 Hz, 2H), 4.20 (td, J = 7.1, 3.3 Hz, 1H), 4.50 (t, J = 5.0 Hz, 1H, ex), 4.87 (dd, J = 6.2, 3.3 Hz, 1H), 5.47 (dd, J = 6.2, 2.7 Hz, 1H), 6.07 (d, J = 2.7 Hz, 1H), 7.32 (br s, 2H, ex), 8.14 (s, 1H), 8.30 (s, 1H); ^{13}C NMR (Me_2SO-d_6) δ 25.27, 27.03, 36.26, 57.14, 82.95, 83.03, 83.71, 88.46, 113.36, 119.07, 139.92, 148.94, 152.76, 156.12; HRMS (FAB) *m/z* 322.1512 (17, MH^+ [$C_{14}H_{20}N_5O_4$] = 322.1515).

9-(5-Deoxy-2,3-*O*-isopropylidene-6-*O*-nitro-*β*-D-*ribo*-hexofuranosyl)adenine (27a). Protection of **27b**[17b] (326 mg, 1 mmol) (as described for **28b** → **28a**) [with chromatography (5% MeOH/CH_2Cl_2)] gave **27a** (293 mg, 80%): UV max 259 nm; ^{1}H NMR δ 1.37, 1.60 (2 × s, 2 × 3H), 2.15−2.24 (dd, J = 11.7, 6.0 Hz, 2H), 4.26−4.35 (m, 1H), 4.42−4.52 (m, 2H), 5.01 (dd, J = 6.3, 3.9 Hz, 1H), 5.53 (dd, J = 6.3, 2.2 Hz, 1H), 5.83 (br s, 2H, ex), 6.01 (d, J = 2.2 Hz, 1H), 7.87 (s, 1H), 8.32 (s, 1H); ^{13}C NMR δ 25.36, 27.15, 30.79, 69.55, 83.44, 83.85, 84.12, 90.52, 114.73, 118.82, 140.25, 149.57, 153.11, 155.60; HRMS (FAB) *m/z* 367.1381 (27, MH^+ [$C_{14}H_{19}N_6O_6$] = 367.1366).

9-(5-Deoxy-3-deuterio-2,3-*O*-isopropylidene-*β*-D-*ribo*-hexofuranosyl)adenine (3′-[^{2}H]28a). Treatment of **27a** (0.03 mmol, 11 mg) by procedure C [with chromatography (8% MeOH/CH_2Cl_2)] gave **28a**/3′-[^{2}H]**28a** (~1:1; 8 mg, 83%): UV max 259 nm; ^{1}H NMR (Me_2SO-d_6) δ 4.20 (t, J = 7.1 Hz, 1, H4′), 4.87 (dd, J = 6.2, 3.3 Hz, 0.50, H3′), 5.47 (d, J = 2.7 Hz, 1, H2′), other peaks same as in the spectrum of **28a**; the ^{13}C NMR (Me_2SO-d_6) peak at δ 83.71 (C3′) was reduced to ~50% intensity; HRMS (FAB) *m/z* 322.1511 (100, MH^+ [$C_{14}H_{20}N_5O_4$] = 322.1515), 323.1583 (98, MH^+ [$C_{14}H_{19}DN_5O_4$] = 323.1578).

1-(5-Deoxy-3-deuterio-*β*-D-*ribo*-hexofuranosyl)uracil (3′-[^{2}H]21b) and 1-(5-Deoxy-3-deuterio-*β*-D-*xylo*-hexofuranosyl)uracil (3′-[^{2}H]22). Treatment of **18b** (12 mg, 0.04 mmol) by procedure C [DMAC (1 mL) added for solubility] [with chromatography (15% MeOH/CH_2Cl_2)] followed by RP-HPLC (15 → 40% CH_3CN/H_2O; 2.8 mL/min, 60 min) gave 3′-[^{2}H]**21b** and 3′-[^{2}H]**22** (9 mg, 87%; ~1.3:1). Data for 3′-[^{2}H]-**21b**: UV max 261 nm; ^{1}H NMR (Me_2SO-d_6) no peak at δ 3.79 (H3′ → ^{2}H3′), 3.86 (dd, J = 7.0, 5.0 Hz, 1, H4′), 4.05 (t, J = 5.0 Hz, 1, H2′), other peaks same as those for **21b**; ^{13}C NMR (Me_2SO-d_6) peaks same as those for **21b** except no peak at δ 72.93 (C3′); HRMS (FAB) *m/z* 259.0900 (23, M^+ [$C_{10}H_{13}DN_2O_6$] = 259.0915). Data for 3′-[^{2}H]-**22**: UV max 260 nm; ^{1}H NMR (Me_2SO-d_6) no peak at δ 3.79 (H3′ → ^{2}H3′), 3.96 (t, J = 4.0 Hz, 1, H2′), 4.24 (t, J = 6.6 Hz, 1, H4′), other peaks same as those for **22**; ^{13}C NMR (Me_2SO-d_6) peaks same as those for **22** except no peak at δ 75.44 (C3′); HRMS (FAB) *m/z* 259.0933 (10, M^+ [$C_{10}H_{13}DN_2O_6$] = 259.0915).

A sample of **18b** (17 mg) was treated as described, except the first evaporation residue was partitioned (CH_2Cl_2/H_2O). The aqueous phase was evaporated, and the residue was subjected to RP-HPLC as described to give uracil (~5%; t_R = 24.4 min), 3′-[^{2}H]**21b** (~50%; t_R = 27.7 min), 3′-[^{2}H]**22** (~36%; t_R = 31.4 min), and an unidentified product (~7%; t_R = 34.3 min). This unidentified product decomposed immediately to give uracil upon addition of TBAF/THF.

1-(5-Deoxy-*β*-D-*xylo*-hexofuranosyl)uracil (22). A solution of 1-(2,3,6-tri-*O*-acetyl-5-deoxy-*β*-D-*xylo*-hexofuranosyl)uracil (**26**; 384 mg, 1 mmol) in NH_3/MeOH (10 mL) was stirred in a sealed flask overnight at ambient temperature. Volatiles were evaporated, and the residue was chromatographed (15% MeOH/CH_2Cl_2) and recrystallized (EtOH) to give **22** (215 mg, 83%): mp 159−160.5 °C; UV max 262 nm (ϵ 10 200); ^{1}H NMR (Me_2SO-d_6) δ 1.84 (dd, J = 13.2, 6.6 Hz, 2H), 3.53 (dd, J = 11.3, 5.1 Hz, 2H), 3.79 (dd, J = 3.4, 2.8 Hz, 1H), 3.96 (t, J = 4.0 Hz, 1H), 4.24 (td, J = 6.6, 2.8 Hz, 1H), 4.57 (t, J = 5.1 Hz, 1H, ex), 5.39 (d, J = 3.4 Hz, 1H, ex), 5.60 (d, J = 4.0 Hz, 1H, ex), 5.65 (d, J = 8.1 Hz, 1H), 5.78 (d, J = 4.0 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 11.29 (br s, 1H, ex); ^{13}C NMR (Me_2SO-d_6) δ 31.68, 58.11, 75.44, 80.56, 81.35, 91.19, 101.03, 141.69, 150.75, 163.54; HRMS (FAB) *m/z* 259.0935 (100, MH^+ [$C_{10}H_{15}N_2O_6$] = 259.0930). Anal. Calcd for $C_{10}H_{14}N_2O_6$ (258): C, 46.51; H, 5.46; N, 10.85. Found: C, 46.40; H, 5.69; N, 10.69.

9-(5-Deoxy-*β*-D-*xylo*-hexofuranosyl)adenine (29). Bu_3SnH (41 μL, 44.6 mg, 0.15 mmol) and AIBN (~2 mg) were added to **27b** (10 mg, 0.03 mmol) in DMAC (1 mL) and dried benzene (9 mL). The solution was deoxygenated (Ar, 20 min) and heated at reflux for 2 h [AIBN (~2 mg) was added after 1 h]. Volatiles were evaporated, the residue was dissolved (H_2O), and the aqueous solution was washed (CH_2Cl_2, 3×). The aqueous phase was evaporated, and the residue was subjected to RP-HPLC (10 → 40% CH_3CN/H_2O; 2.8 mL/min, 80 min) to give adenine (~4%, t_R = 38.0 min), homoadenosine (**28b**, ~47%; t_R = 40.3 min), **29** (~37%, t_R = 47.6 min), and an unidentified product (~12%, t_R = 61.8 min). Data for compound **29**:[32] UV 260 nm; ^{1}H NMR (Me_2SO-d_6) δ 1.82 (dd, J = 12.8, 6.4 Hz, 2H), 3.49 (m, t after D_2O ex, J = 6.4 Hz, 2H), 3.87 (m, 1H), 4.25 (m, 2H), 4.53 (t, J = 4.8 Hz, 1H, ex), 5.79 (d, J = 1.2 Hz, 1H), 5.88 (m, 2H, ex), 7.33 (br s, 2H, ex), 8.13 (s, 1H), 8.21 (s, 1H); ^{13}C NMR (Me_2SO-d_6) δ 31.73, 57.83, 75.89, 79.94, 81.46, 89.48, 118.73, 139.72, 148.58, 152.30, 156.01; HRMS (FAB) *m/z* 282.1201 (5, MH^+ [$C_{11}H_{16}N_5O_4$] = 282.1202).

9-(5-Deoxy-3-deuterio-*β*-D-*xylo*-hexofuranosyl)adenine (3′-[^{2}H]-29). Treatment of **27b** (10 mg, 0.03 mmol) with Bu_3SnD (as described for **29**) and RP-HPLC gave adenine, homoadenosine (**28b**), 3′-[^{2}H]**29**, and an unidentified product with yield ratios and retention times similar to those described for **29**. Data for 3′-[^{2}H]**29** (3 mg, 35%): UV max 260 nm; ^{1}H NMR (Me_2SO-d_6) all peaks such as those for **29** except no

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peak at δ 3.87 (H3′ → ^{2}H3′); ^{13}C NMR (Me_2SO-d_6) peaks same as those for **29** except no peak at δ 75.89 (C3′); HRMS (CI) *m*/*z* 283.1277 (4, MH^+ [$C_{11}H_{15}DN_5O_4$] = 283.1265).

(*R*)-2-(2-Hydroxyethyl)-3(2*H*)-furanone (33). Treatment of **30**[17a] (10 mg, 0.031 mmol) by procedure C (45 min) [with preparative HPLC (6 → 8% MeOH/CH_2Cl_2)] gave uracil and **33** (3 mg, 75%): UV max 259 nm; ^{1}H NMR (MeOH-d_4) δ 2.01−2.17 (m, 2H), 3.73 (dd, *J* = 7.5, 5.5 Hz, 2H), 4.63 (dd, *J* = 9.3, 4.0 Hz, 1H), 5.71 (d, *J* = 2.5 Hz, 1H), 8.50 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (MeOH-d_4) δ 35.48, 58.68, 83.67, 107.55, 181.25, 208.42; HRMS (CI) *m*/*z* 129.0555 (100, MH^+ [$C_6H_9O_3$] = 129.0552).

(*R*)-4-Deuterio-2-(2-hydroxyethyl)-3(2*H*)-furanone (4-[^{2}H]33) from 40. Treatment of **40**[17b] (12 mg, 0.025 mmol) by procedure C [2 h, AIBN (∼2 mg) added after 1 h] [with preparative HPLC (6 → 10% MeOH/CH_2Cl_2)] gave 2′-*O*-tosylhomoadenosine[17b] (∼3 mg, 28%; spectral data as listed[17b] with no ^{2}H exchange for H3′), adenine (∼2 mg, 62%), and 4-[^{2}H]**33** (∼2 mg, 62%; with ∼30% ^{2}H at C4): UV max 259 nm; ^{1}H NMR (MeOH-d_4) δ 5.71 (d, *J* = 2.5 Hz, ∼0.7H), all other peaks same as for **33**; ^{13}C NMR (MeOH-d_4) δ 107.55 (∼30% diminished), all other peaks same as for **33**; HRMS (CI) *m*/*z* 129.0545 (100, MH^+ [$C_6H_9O_3$] = 129.0552), 130.0619 (41, MH^+ [$C_6H_8DO_3$] = 130.0614).

(*R*)-2-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-3(2*H*)-furanone (34). Methyl 6-*O*-(*tert*-butyldimethylsilyl)-2,5-dideoxy-α-D-*glycero*-hexofuranosid-3-ulose (**39**; 137 mg, 0.5 mmol) in 20% Et_3N/MeOH (10 mL) was stirred for 2 h at ambient temperature. Volatiles were evaporated, and the residue was dissolved (EtOAc). The solution was washed (H_2O, brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (15% EtOAc/hexanes) to give **34** (42 mg, 34%): UV max 260 nm; ^{1}H NMR (MeOH-d_4) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.79 (ddd, *J* = 18.1, 8.9, 4.8 Hz, 1H), 2.09 (dtd, *J* = 18.1, 4.0, 7.1 Hz, 1H), 3.78−3.84 (m, 2H), 4.62 (dd, *J* = 8.9, 4.0 Hz, 1H), 5.70 (d, *J* = 2.5 Hz, 1H), 8.49 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (MeOH-d_4) δ −5.24, −5.16, 19.26, 26.49, 35.59, 59.74, 83.34, 107.65, 181.17, 208.46; HRMS (CI) *m*/*z* 243.1413 (100, MH^+ [$C_{12}H_{23}O_3Si$] = 243.1416).

(*R*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-4-deuterio-3(2*H*)-furanone (47). Treatment of 9-[5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-2-deuterio-β-D-*glycero*-pentofuranos-3-ulosyl]adenine (**46**; 49 mg, 0.1 mmol) by procedure C [with chromatography (15 → 30% EtOAc/hexanes)] gave **47** (26 mg, 74%; ∼15% ^{2}H4): ^{1}H NMR δ 0.99 (s, 9H), 4.02 (dd, *J* = 11.5, 4.0 Hz, 1H), 4.10 (dd, *J* = 11.5, 2.7 Hz, 1H), 4.45 (dd, *J* = 4.0, 2.7 Hz, 1H), 5.75 (d, *J* = 2.5 Hz, ∼0.85H), 7.39−7.70 (m, 10H), 8.31 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR δ (19.27, 26.61), 62.69, 85.34, 107.88, (127.74, 129.82, 132.68, 132.94, 135.57, 135.63), 178.77, 202.72; HRMS (FAB) *m*/*z* 375.1417 (100, MNa^+ [$C_{21}H_{24}O_3SiNa$] = 375.1392), 376.1437 (20, MNa^+ [$C_{21}H_{23}DO_3SiNa$] = 376.1455).

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Supporting Information Available: Full experimental details, spectral data, and characterization for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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