Studies on the Mechanism of Ribonucleotide Reductases

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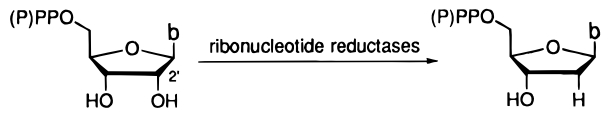
Abstract: Ribonucleotide reductases are enzymes that catalyze the conversion of ribonucleotides to 2′-deoxyribonucleotides. This important reaction is initiated by the generation of a C-3′ nucleotide radical and subsequent loss of the 2′-hydroxyl group. In order to model certain steps in this mechanism, selenol ester **23** was prepared and photolyzed providing the first selective chemical access to the 3′-adenosyl radical. From product analysis it could be shown that elimination of the 2′-OH function readily takes place under general base catalysis. The rate coefficient for this reaction was determined by competition kinetics to be $1.5 \cdot 10^6$ s^{-1} in the presence of 1 M triethylammonium acetate buffer at pH 7. Without catalyst the elimination rate is about 10^3 times slower. It can be concluded that a similar mechanism is also feasible for the key steps of the enzyme catalyzed reaction.

Ribonucleotide reductases are key enzymes in all living organisms. They catalyze the transformation of ribonucleotides **1** to the corresponding 2′-deoxyribonucleotides **2** providing the monomeric precursors required for DNA biosynthesis[1] (Scheme 1).

These enzymes, therefore, play a critical role in the regulation of cell growth and present a promising target for the design of chemotherapeutic agents in the field of antitumor and antiviral treatment.[2] Despite dramatic differences in structure and cofactor requirements[3] a common radical-based reaction mechanism has been postulated by Stubbe[1c,4] for all ribonucleotide reductases (Scheme 2).

The key steps involve formation of C-3′ nucleotide radical **3** via hydrogen atom abstraction by a cofactor induced sulfur based radical, protonation of the 2′-hydroxyl group of **3** by one of two redox-active cysteine residues, and elimination of water leading to the 2′-deoxy-3′-ketonucleotide radical **4**, which is subsequently reduced to the C-3′ radical **5** by the thiol/thiolate pair. In the final step, the initially abstracted hydrogen atom H_a is transferred back to the C-3′ position forming **2** with concomitant regeneration of the protein radical. Indirect evidence for the involvement of radical species in this enzymatic reaction has been obtained by numerous biological studies using isotopically labeled substrates,[5] mechanism-based inhibitors,[6] and site-directed mutants.[7] In spite of several attempts using modified substrates as radical traps for both enzyme[8] and substrate radicals,[9] direct observation of nucleotide radical intermediates was not possible until very recently.[10] It was the aim of our work to find an independent chemical access to C-3′ nucleoside radicals. In mechanistic studies of these radicals, especially with regard to a potential 2′-hydroxy elimination, important insight could be gained with respect to the key steps of the proposed mechanism.

Scheme 1



1 **2**

In the known studies concerning the dehydration of α,β-dihydroxyalkyl radicals, the radical generation took place via hydrogen atom abstraction by hydroxyl radicals. While this method was very successful with simple model systems such as ethylene glycol,[12] it proved to be less useful with more complex compounds like carbohydrates or nucleosides due to unselective hydrogen abstraction from all carbon atoms of the carbohydrate moiety[13] and preferred addition of hydroxyl radicals to nucleobases.[14] Hence, it was necessary to develop a method enabling us to selectively generate C-3′ nucleoside radicals. One possible way to achieve this task is to introduce a suitable functionality at C-3′ which is chemically stable but can be cleaved off homolytically under mild conditions. A

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(1) (a) Thelander, L.; Reichard, P. *Annu. Rev. Biochem.* **1979**, *48*, 133−158. (b) Eriksson, S.; Sjöberg, B. M. In *Allosteric Enzymes*; Hervé, G., Ed.; CRC Press: Boca Raton, 1990; pp 189−215. (c) Stubbe, J. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1990**, *63*, 349−417. (d) Thelander, L.; Gräslund, A. In *Metal Ions in Biological Systems*; Sigel, H., Sigel, A., Eds.; Marcel Dekker, Inc.: New York, 1994; pp 109−129.

(2) (a) Cory, J. G.; Chiba, P. In *Inhibitors of Ribonucleotide Diphosphate Reductase Activity*; Cory, J. G., Cory, A. H., Eds.; CRC Press: Boca Raton, FL, 1989; pp 245−264. (b) Robins, M. J.; Samano, M. C.; Samano, V. *Nucleotides Nucleosides* **1995**, *14*, 485−493.

(3) Reichard, P. *Science* **1993**, *260*, 1773−1777.

(4) (a) Ashley, G. W.; Stubbe, J. *Pharmac. Ther.* **1985**, *30*, 301−329. (b) Stubbe, J; van der Donk, W. A. *Chem. Biol.* **1995**, *2*, 793−801.

(5) (a) Stubbe, J. *Molec. Cell. Biochem.* **1983**, *50*, 25−45. (b) Ashley, G. W.; Harris, G.; Stubbe, J. *J. Biol. Chem.* **1986**, *261*, 3958−3964.

(6) (a) Thelander, L.; Larsson, A.; Hobbs, J.; Eckstein, F. *J. Biol. Chem.* **1976**, *251*, 1398−1405. (b) Harris, G.; Ator, M. A.; Stubbe, J. *Biochemistry* **1984**, *23*, 5214−5225. (c) Ator, M. A.; Stubbe, J. *Biochemistry* **1985**, *24*, 7214−7221. (d) Salowe, S. P.; Ator, M. A.; Stubbe, J. *Biochemistry* **1987**, *26*, 3408−3416. (e) Samano, V.; Robins, M. J. *J. Org. Chem.* **1991**, *56*, 7108−7113.

(7) (a) Mao, S. S.; Johnston, M. I.; Bollinger, J. M.; Stubbe, J. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 1485−1490. (b) Mao, S. S.; Holler, T. P.; Yu, G. X.; Bollinger, J. M.; Booker, S.; Johnston, M. I.; Stubbe, J. *Biochemistry* **1992**, *31*, 9733−9743. (c) Mao, S. S.; Holler, T. P.; Bollinger, J. M.; Yu, G. X.; Johnston, M. I.; Stubbe, J. *Biochemistry* **1992**, *31*, 9744−9751. (d) Mao, S. S.; Yu, G. X.; Chalfoun, D.; Stubbe, J. *Biochemistry* **1992**, *31*, 9752−9759.

(8) Auguste, S. P.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1995**, 395−404.

(9) Samano, V.; Robins, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 4007−4008.

(10) Preliminary EPR studies with a 2′-fluoromethylene substituted substrate analog suggest the presence of a nucleotide based radical.[11]

(11) van der Donk, W. A.; Yu, G.; Silva, D. J.; Stubbe, J.; McCarthy, J. R.; Jarvi, E. T.; Matthews, D. P.; Reswick, R. J.; Wagner, E. *Biochemistry* **1996**, *35*, 8381−8391.

(12) Steenken, S.; Davies, M. J.; Gilbert, B. C. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1003−1010 and references cited therein.

(13) von Sonntag, C.; Dizdaroglu, M. *Carbohydr. Res.* **1977**, *58*, 21−30.

(14) von Sonntag, C. *The Chemical Basis of Radiation Biology*; Taylor & Francis: London, 1987; pp 116−166.

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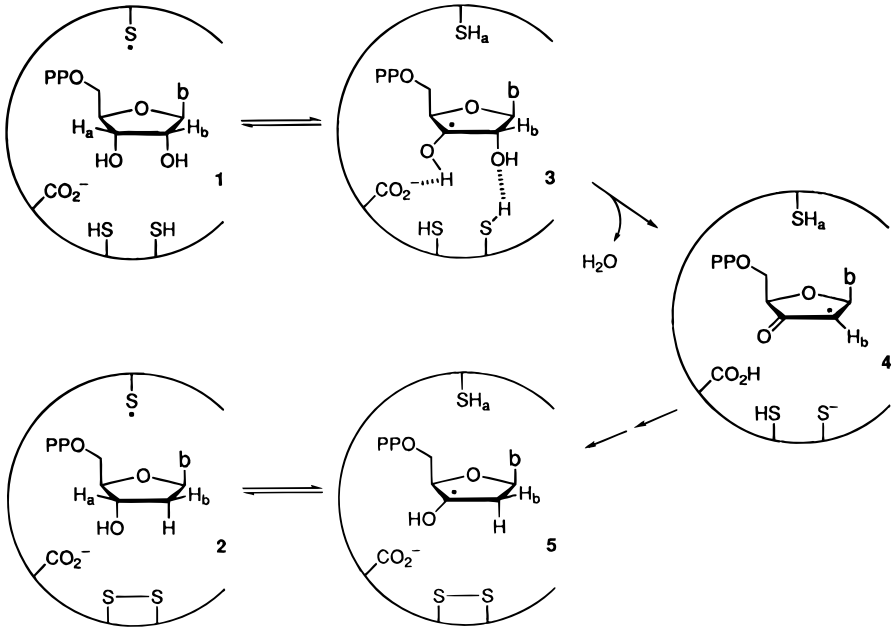
Scheme 2



functionality fulfilling these criteria is the selenol ester group. This group is usually easy to introduce[15] and stable under nonbasic conditions and in the absence of good nucleophiles. Due to its weak Se−C bond the selenol ester moiety is cleaved either by directly using UV light ($\lambda > 320$ nm) or in a photochemically induced radical chain process in the presence of a mediator such as Bu_3SnH.[15] The initially formed acyl radical readily decarbonylates[16] leading to the desired nucleoside radical.

In this paper we describe the synthesis of 3′-selenocarbonyl substituted nucleoside derivatives based on adenosine **6** and their application as precursors of C-3′ nucleoside radicals in studies to clarify the mechanism of the biosynthesis of 2′-deoxyribonucleotides.

Results and Discussion

Synthesis of the Radical Precursors. The first step on the way to 3′-phenylselenocarbonyl adenosine derivatives involved protection of the 2′- and 5′-hydroxyl groups. Silylation with *tert*-butyldimethylsilyl chloride in pyridine afforded the desired product **7** in 50% yield.[18] A three-step procedure allowed the protection of the nucleobase: silylation of the 3′-hydroxyl group was followed by dibenzoylation of the nucleobase in pyridine and final deprotection of the hydroxyl group under acidic conditions led to protected nucleoside **8** in quantitative yield. The free alcohol function of **8** was then oxidized with the Dess−Martin reagent[19,20] to the corresponding ketone **9** in 99% yield. The subsequent addition of a vinylcerium reagent,[21,22] generated *in situ* from vinylmagnesium bromide and cerium trichloride, led in 82% yield to allyl alcohol **10** having the *(S)*-configuration at the 3′-position (Scheme 3). This stereochemistry can be rationalized by an attack of the organometallic reagent from the α-face of the carbohydrate moiety due to the efficient shielding of the *β*-face by the nucleobase. This assumption is supported by results obtained when organometallic ethynyl derivatives were added to 3′-ketonucleosides.[23] In these cases, selectivities were found between 1.5:1 and 50:1 in favor of the α-attack depending on the reagent and the nucleobase.

The conversion of the vinyl grignard into the less basic cerium reagent is decisive for the addition reaction since it prevents the elimination of the nucleobase which occurs readily after deprotonation at the C−2′ position of the carbohydrate residue.[24] After silylation of the 3′-hydroxyl group in **10** with Horning's reagent,[25] compound **11** was readily ozonolyzed, and subsequent reductive workup with dimethyl sulfide[26] afforded aldehyde **12** in 68% yield. Further oxidation under mild conditions using potassium permanganate[27] led to carboxylic acid **13** in 77% yield (Scheme 3).

The coupling constant $J_{1',2'}$ of less than 0.5 Hz in the NMR spectrum of aldehyde **12** refers to a dihedral angle between C-1′−H-1′ and C-2′−H-2′ of nearly 90° which is characteristic for a 3′-*endo* conformation ($^3T_2$ conformation) of the carbohydrate residue (Figure 1). Additional NOE experiments were carried out on aldehyde **12** to ensure the proposed configuration at C−3′. Indeed, a strong NOE effect (22% and 14%) was observed between H−4′ and the hydrogen of the aldehyde function which indicates a *cis*-arrangement of these two substituents and therefore a D-xylose configuration of the carbohydrate moiety.

(15) For a recent overview of methods for the preparation of selenol ester, see: Ogawa, A.; Sonoda, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 6, pp 461−468.

(16) For examples of the use of acyl selenides in radical chemistry, see references cited in Crich, D.; Yao, Q. *J. Org. Chem.* **1996**, *61*, 3566−3570.

(17) In the case of the pivaloyl radical the rate of decarbonylation is $1.2 \cdot 10^5$ s^{-1} at 25 °C, see: Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317−323.

(18) Ogilvie, K. K.; Beaucage, S. L.; Schifman, A. L.; Theriault, N. Y.; Sadana, K. L. *Can. J. Chem.* **1978**, *56*, 2768−2780.

(19) For the preparation of the Dess−Martin reagent, see: (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.

(20) (a) Samano, V.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 410−412. (b) Samano, V.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 5186−5188.

(21) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamija, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.

(22) Bender, S. L.; Moffett, K. K. *J. Org. Chem.* **1992**, *57*, 1646−1647.

(23) (a) Huss, S.; De las Heras, F. G.; Camarasa, M. J. *Tetrahedron* **1991**, *47*, 1727−1736. (b) Jung, P. M. J.; Burger, A.; Bielmann, J.-F. *Tetrahedron Lett.* **1995**, *36*, 1031−1034.

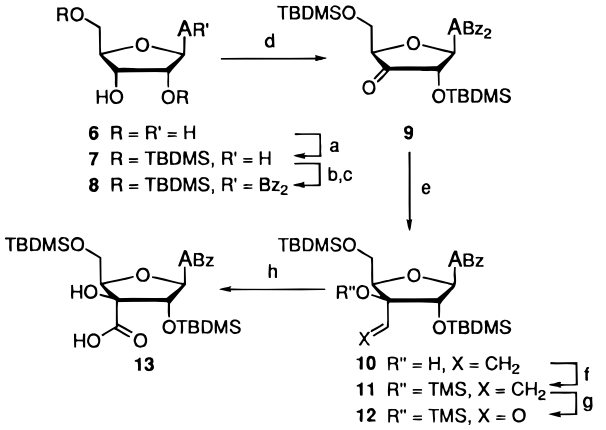
(24) For addition reactions of alkylcerium reagents to easily enolizable ketones, see: Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233−4236.

(25) TMSCl/TMSimidazole/*N*,*O*-bisTMSacetamide (2:3:3), commercially available: Fluka Product No. 85432. See: Chambaz, E. M.; Horning, E. C. *Anal. Biochem.* **1969**, *30*, 7−24.

(26) Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273−4278.

(27) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537−4540.

Scheme 3[a]



[a] (a) TBDMSCl, pyr, room temperature, 50%. (b) TMSCl, pyr, 0 °C → room temperature, then BzCl, 0 °C → room temperature. (c) cat. TsOH, EtOH, room temperature, quantitative (from **7**). (d) Dess−Martin periodinane,[19] CH_2Cl_2, room temperature, 99%. (e) $H_2C{=}CHMgBr$, $CeCl_3$, THF, −78 °C, then **9**, −78 °C, 82%. (f) Horning's reagent,[25] CH_2Cl_2, room temperature (g) O_3, CH_2Cl_2, −78 °C, then Me_2S, −78 °C → room temperature, 68% (from **10**). (h) 1 M $KMnO_4$, ^{t}BuOH, phosphate buffer, room temperature, then saturated Na_2SO_3, HCl (→ pH 3), 0 °C, 77%.

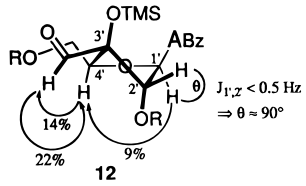
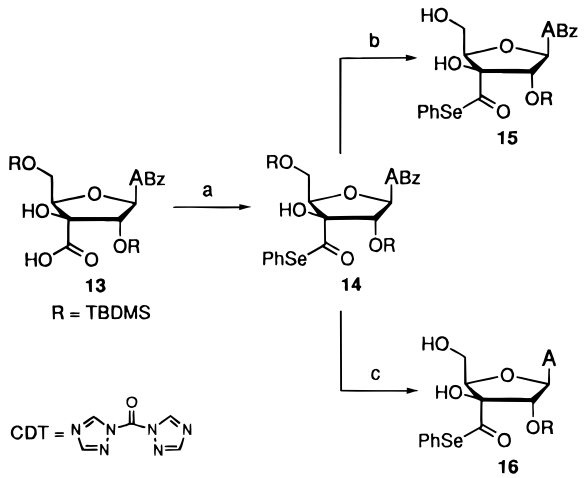


Figure 1. NOE effects and coupling constant $J_{1',2'}$ in nucleoside **12** in agreement with a xylo configuration and a 3′-*endo* conformation.

Activation of the carboxylic acid function in **13** to the corresponding acid chloride by reaction with either dichloromethyl methyl ether[28] or an α-chloroenamine[29] was unsuccessful. We then turned our attention to a method leading directly from **13** to the protected selenol ester **14** using acyl 1,2,4-triazolides as reactive intermediates.[30] These activated acyl compounds can be produced *in situ* and react with selenols to give the corresponding selenol esters under mild conditions and in good yields. Thus, compound **13** was treated with carbonyldi-1,2,4-triazole (CDT) at room temperature to form the triazolide which reacted subsequently with benzeneselenol to give **14** in 79% yield. The deprotection of the carbohydrate moiety in **14** was challenging since selenol esters react easily with nucleophiles, and consequently the choice of the reaction conditions was limited. Thus, treatment of **14** with fluoride in aprotic medium[31] led only to decomposition products. On the other hand, the use of trifluoroboron etherate[32] in dichloromethane allowed solely for the obtaining of the 5′-deprotected compound **15** in 98% yield. Other methods allowing for hydrolysis of silyl ethers (TBAF/AcOH/THF, $HF_{aqueous}/CH_3CN$,[33] NH_4F/CH_3OH,[34] Dowex 50W-X8/CH_3OH[35]) resulted also in sole deprotection at the 5′-position. Additional cleavage of the benzoyl group at the nucleobase was achieved by using stronger acidic conditions. Thus, treatment of compound **14** with 5% HCl in ethanol at 50 °C gave **16** in 79% yield (Scheme 4). Interestingly, the selenol ester function was stable under these conditions.

Scheme 4[a]

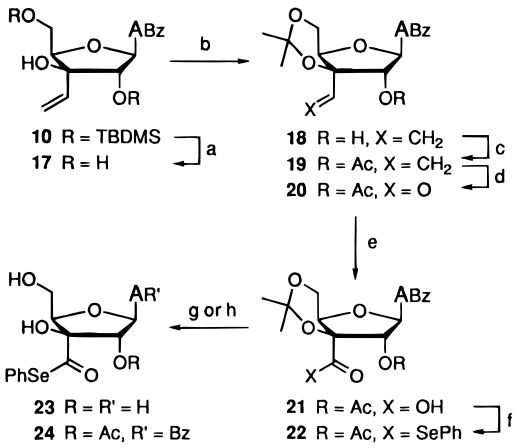


[a] (a) CDT, DMF, 0 °C → room temperature, then PhSeH, 0 °C, 79%. (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, reflux, 98%. (c) 5% HCl in EtOH, 50 °C, 79%.

With regard to our planned model studies on the 2′-deoxygenation of ribonucleotides, we needed to synthesize a 3′-selenocarbonyl nucleoside bearing a free 2′-hydroxyl function. Therefore, we decided to replace the *tert*-butyldimethylsilyl residues by protecting groups which would be less stable toward acidic hydrolysis, prior to the introduction of the selenol ester function. Starting from **10**, reaction with tetrabutylammonium fluoride in THF[31] at 0 °C led to the deprotected vinyl nucleoside **17** in good yield. Standard conditions (acetone/camphorsulfonic acid (CSA)[36] or 2,2-dimethoxypropane/CSA/DMF[37]) for acetonide formation did not lead to product **18**. However, the use of the strong Lewis acid aluminum trichloride[38] in the presence of acetone gave rise to a quick reaction, and the acetonide **18** was obtained in almost quantitative yield. Consecutive treatment with acetic anhydride in pyridine[39] afforded the 2′-*O*-acetyl derivative **19** in 97% yield. The conversion of **19** into the corresponding carboxylic acid **21** was carried out following the two-step procedure described earlier (ozonolysis under reductive conditions to **20** and subsequent permanganate oxidation). The selenol ester **22** was obtained in 72% yield by reaction of acid **21** with phenyl dichlorophosphate to the mixed anhydride which was treated *in situ* with benzeneselenol.[40] Complete deprotection of the carbohydrate moiety and the nucleobase took place in 78% yield in the presence of 5% HCl in ethanol. Radical precursor **23** was obtained as crystalline hydrochloride and could be easily separated from side products by filtration. On the other hand, treatment of **22** with 80% trifluoroacetic acid[41] at room temperature led only to the hydrolysis of the acetonide and afforded **24** in 86% yield (Scheme 5).

(28) Ottenheijm, H. C. J.; DeMan J. H. M. *Synthesis* **1975**, 163−164.
(29) Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180−1181.
(30) Gais, H.-J. *Angew. Chem.* **1977**, *89*, 251−252.
(31) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190−6191.
(32) Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.* **1979**, *9*, 295−299.
(33) (a) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981−3984. (b) Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron* **1985**, *26*, 681−684.
(34) (a) White, J. D.; Amedio, J. C., Jr.; Gut, S.; Jayasinghe, L. *J. Org. Chem.* **1989**, *54*, 4268−4271. (b) Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177−1180.
(35) Corey, E. J.; Ponder, J. W.; Ulrich, P. *Tetrahedron Lett.* **1980**, *21*, 137−140.
(36) (a) Schmidt, O. Th. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolfrom, M. L., Eds.; Academic Press Inc.: New York, 1963; Vol. 2, pp 318−325. (b) de Belder, A. N. *Adv. Carbohydr. Chem.* **1965**, *20*, 219−302.
(37) Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495−4499.
(38) Lal, B.; Gidwani, R. M.; Rupp, R. H. *Synthesis* **1989**, 711−713.
(39) (a) Weber, H.; Khorana, H. G. *J. Mol. Biol.* **1972**, *72*, 219−249. (b) Zhdanov, R. I.; Zhenodarova, S. *Synthesis* **1975**, 222−245.
(40) Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285−3294.
(41) Leblanc, Y.; Fitzsimmons, B. J.; Adams, J; Perez, F.; Rokash, J. *J. Org. Chem.* **1986**, *51*, 789−793.

Scheme 5[a]



[a] (a) TBAF, THF, 0 °C, 82%. (b) $AlCl_3$, acetone/Et_2O 2:1, 0 °C, 99%. (c) Ac_2O, pyr, 0 °C → room temperature, 97%. (d) O_3, CH_2Cl_2, −78 °C, then Me_2S, −78 °C → room temperature, 69%. (e) 1 M $KMnO_4$, ^{t}BuOH, phosphate buffer, room temperature, then saturated Na_2SO_3, HCl (→ pH 3), 0 °C, 91%. (f) $PhOP(O)Cl_2$, NEt_3, THF, 0 °C, then PhSeH, NEt_3, 0 °C, 72%. (g) 5% HCl in EtOH, 50 °C, 78%. (h) 80% CF_3COOH, room temperature, 86%.

Photolysis of the Radical Precursors. All irradiation experiments were carried out at 20 °C in methanol or acetonitrile/water (1:1) and, in most cases, in the presence of an H-donor such as Bu_3SnH or ^{t}BuSH as radical scavenger. The composition of the crude product mixture was quantitatively analyzed by ^{1}H-NMR spectroscopy using either pentachloroethane or the total integral of the two adenine protons as internal standards.

Photolysis reactions of radical precursor **23** in methanol in the presence of Bu_3SnH and ^{t}BuSH led exclusively to the formation of the direct reduction products **6** in good yields (Scheme 6 and Table 1, entries 1 and 2). The preferred attack of the H-donor from the α-face of the C-3′ nucleoside radical **25** is due to the efficient *β*-face shielding by the nucleobase. Through H/D exchange between the deuterated solvent and the thiol, a selective deuteration at C-3′ (>80% as estimated by ^{1}H-NMR) could be observed (entry 2). These results clearly indicate that the selenol ester **23** is an excellent radical precursor and that the selective C-3′ radical generation can either be achieved by a photoinduced chain reaction (entry 1) or direct photolysis (entry 2). The fact that in the presence of efficient radical traps like Bu_3SnH or ^{t}BuSH the formation of 2′-deoxygenated products could not compete with direct reduction led to the use of Bu_6Sn_2 as radical mediator (entry 3). In this case due to the much slower radical trapping reaction by H abstraction from the solvent, 57% of adenine (**32**), 10% of 2,3-dihydro-2-hydroxymethylfuran-3-one (**34**), and only 35% of the reduction products **6** were formed.

Although the appearance of the free nucleobase in nucleoside reactions is often indicative for unspecific degradation, the presence of enolone **34** suggests that adenine (**32**) might be formed from 2′-deoxy-3′-ketoadenosine (**30**) by an elimination reaction. The elimination of the nucleobase from 2′-deoxy-3′-ketonucleosides is a well-known reaction[42,43] and is also discussed by Stubbe as an important step in the ribonucleotide reductase mechanism when substrate-based inhibitors[6c,44] or site-directed mutated enzymes[7c] were employed. The absence of free nucleobase **32** under the conditions of entry 1 shows that adenine (**32**) is not formed directly from the radical **25** or the radical precursor **23**.

By using radical precursor **24** with acetate at C-2′ as a better leaving group, it was possible to demonstrate that the formation of free nucleobase is fully related to the 2′-deoxygenation (Scheme 6 and Table 2). The first irradiation experiments in the presence of Bu_3SnH lead to *N*-benzoyladenine (**33**), enolone **34**, and acetic acid in high yields. The 2′-deoxy-3′-ketonucleoside **31** was only detected in 0 and 15% yields, respectively (entry 1 and 2). The amount of **31** could be increased to 52% under milder conditions avoiding the workup step (evaporation of the solvent for subsequent NMR analysis) by using CD_3OD as solvent (entry 3). Due to the use of Bu_3SnD as trapping reagent a selective deuteration at C-2′ of **31** (>90% as estimated by NMR) and at C-3 of **34** (52% by GC/MS) could be observed. Only in the presence of the more reactive radical scavenger ^{t}BuSH was it possible to detect the formation of the direct reduction product **27**, exclusively in the xylo configuration (entry 4). Through H/D exchange betweeen CD_3OD and ^{t}BuSH a selective deuteration at C-3′ of **27** (>80% by NMR) took place.

The results in Table 2 clearly indicate that the free nucleobase **33** is quantitatively formed from the 2′-deoxy-3′-ketonucleoside **31**, since the decrease in the yield of nucleobase **33** (57 and 40%) parallels an increase in the yield of ketone **31** by 52 and 37%, respectively (entry 1−3). In addition, the free nucleobase **33** and enolone **34**, are detected in nearly the same yield under mild conditions (entry 3). This leads to further support of the assumption that the nucleobase **33** is entirely formed from ketone **31**. The somewhat lower yields of enolone **34** in comparison to free nucleobase **32** or **33** in the other experiments are probably due to further reactions of **34** acting as a Michael acceptor.[43]

The results listed in Tables 1 (entry 1−3) and 2 moreover indicate that the elimination of acetic acid from the initially formed C-3′ radical is a fast process (compared to the elimination of water) which competes successfully with the direct trapping reaction to **27**. This observation is in agreement with pulse radiolytic studies of ethylene glycol derivatives by Schulte-Frohlinde. He could show that elimination of acetic acid[45] occurs in neutral aqueous solution about 10^3 times faster than elimination of water[46] (Scheme 7).

All irradiation experiments discussed so far were conducted in methanol. In order to simulate the reaction conditions found in an enzyme pocket more accurately, mixtures of acetonitrile and aqueous buffer solutions were employed. We chose the triethylammonium acetate buffer (TEAA buffer, pH 7) which is volatile and therefore easy to remove. Since Bu_3SnH is not soluble under these conditions, it had to be replaced by the water soluble tris[3-(2-methoxyethoxy)propyl]stannane (**35**) described by Breslow.[47] The irradiation of selenol ester **23** using tin hydride **35** and 0.1 M TEAA buffer led to an astonishing result (Table 1, entry 4). Despite the presence of the efficient H-donor **35** mainly the products following the 2′-OH elimination were formed.[49] This indicates that the use of a buffered aqueous solution strongly accelerates the elimination of the 2′-hydroxy group from the C-3′ nucleoside radical.

Competition Kinetic Studies. To gain a better understanding of the factors controlling the radical induced dehydration,

(42) (a) Sugiyama, H.; Fujimoto, K.; Saito, I. *J. Am. Chem. Soc.* **1995**, *117*, 2945−2946. (b) Hansske, F.; Madej, D.; Robins, M. J. *Tetrahedron* **1984**, *40*, 125−135. (c) Binkley, R. W.; Hehemann, D. G.; Binkley, W. W. *J. Org. Chem.* **1978**, *43*, 2573−2576.

(43) Schreiber, S. L.; Ikemoto, N. *Tetrahedron Lett.* **1988**, *29*, 3211−3214.

(44) Ator, M. A.; Stubbe, J. *J. Biol. Chem.* **1986**, *261*, 3595−3599.

(45) Matsushige, T.; Koltzenburg, G.; Schulte-Frohlinde, D. *Ber. Bunsenges. Phys. Chem.* **1975**, *79*, 657−661.

(46) Burchill, C. E.; Perron, K. M. *Can. J. Chem.* **1971**, *49*, 2382−2389.

(47) (a) Light, J.; Breslow, R. *Tetrahedron Lett.* **1990**, *31*, 2957−2958. (b) Light, J.; Breslow, R. *Org. Synth.* **1995**, *72*, 199−207.[48]

(48) The boiling point of the tin bromide is not given correctly in this reference. In order to purify this compound, we applied Kugelrohr destillation at 240−250 °C and 0.05 mbar.

(49) In addition, the irratiation time could be reduced from over 2 h (Table 1, entry 1−3) to less than 5 min (entry 4).

Scheme 6

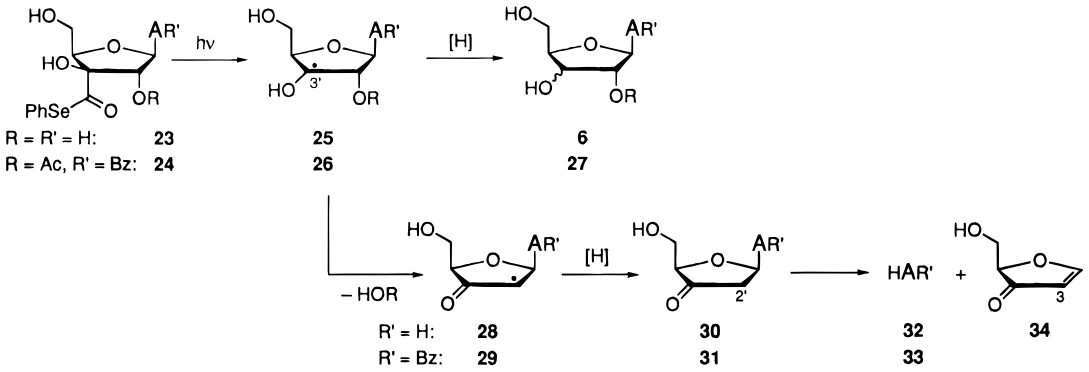


Table 1. Results of Irradiation Reactions with Radical Precursor **23**

entry	reaction conditions	**6** (xylo/ribo)	**32** (%)	**34** (%)
1	Bu_3SnH, CH_3OH, 2.5 h	94% (3:1)		
2	^tBuSH, CD_3OD, 2.5 h	78%[a] (4:1)		
3	Bu_6Sn_2, CH_3OH, 2.5 h	35% (3:1)	57	10
4	R_3SnH (**35**)[b], 0.1 M TEAA[c] CH_3CN/H_2O 1:1, 5 min	14% (4:1)	80	50

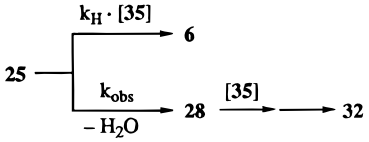
[a] >80% deuteration at C-3′ (NMR). [b] R = 3-(2-methoxyethoxy)-propyl. [c] Triethylammonium acetate.

Table 2. Results of Irradiation Reactions with Radical Precursor **24**

entry	reaction conditions	**27** (%)	**31** (%)	**33** (%)	**34** (%)	AcOH (%)
1	Bu_3SnH, CH_3OH, 3 h[a]			84	78	90
2	Bu_3SnH, CH_3OH, 3 h[a]		15	67	41	88
3	Bu_3SnD, CD_3OD, 3 h		52[b]	27	25[c]	92
4	^tBuSH, CD_3OD, 3 h	9[d,e]		70	54[f]	50

[a] Workup: evaporation of solvent (reduced pressure, 40 °C). [b] >90% deuterated at C-2′ (NMR). [c] 52% deuterated at C-3 (GC/MS). [d] Exclusively with xylo configuration. [e] >80% deuterated at C-3′ (NMR). [f] ~40% deuterated at C-3 (NMR).

competition kinetic experiments were accomplished. As illustrated below, the unimolecular dehydration process (**25** → **28**, with rate coefficient k_{obs}) competes with the bimolecular direct reduction (**25** → **6**, with rate coefficient k_H).

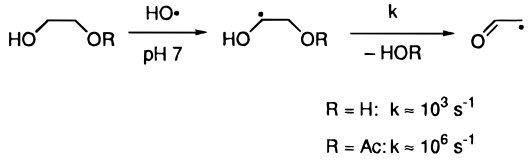


When the tin hydride **35** involved in the reduction step is used in large excess with respect to the radical precursor, this second-order reaction can be treated as a pseudo-first-order process. Under this constraint and provided that the competing reactions are irreversible and the products observed are stable under the reaction conditions, the ratio of the rate coefficients can be calculated directly from the product distribution and the initial radical trap concentration according to eq 1. Since ketone **30** was not detected by NMR, the concentration of adenine (**32**), being the only stable product of the dehydration sequence, was used as a measure for the amount of originally formed **28**.[50] The product ratio [**32**]/[**6**] was determined using reversed-phase HPLC.

$$\frac{[\mathbf{32}]}{[\mathbf{6}]} = \frac{k_{obs}}{k_H} \cdot \frac{1}{[\mathbf{35}]} \qquad (1)$$

In order to come to an absolute value of k_{obs} the rate coefficient k_H for the H-atom transfer from tin hydride **35** to the C-3′ nucleoside radical **25** has to be accurately determined. Using a calibrated radical clock,[51] k_H for the H-transfer from **35** to a tertiary alkyl radical at 20 °C in acetonitrile was measured to be $1.2 \cdot 10^6$ M^{-1} s^{-1} in good accord to the corresponding value[52] for Bu_3SnH ($k_H = 1.6 \cdot 10^6$ M^{-1} s^{-1}). Changing the solvent to acetonitrile/water 1:1 led to an acceleration of the reaction by a factor of 5, probably due to stabilization of the polar transition state.[53] Moreover, results of Beckwith[54] and Newcomb[55,56] show that k_H decreases by about the same amount on going from alkyl to α-methoxyalkyl and α,β-dimethoxyalkyl radicals, the latter being more accurate models for the C-3′ nucleoside radical **25**. This behavior is rationalized by the higher stability of α-oxyalkyl and especially α,β-dioxyalkyl radicals and by the unfavorable transition state between the electron rich radical and the nucleophilic H-atom donor. A combination of both solvent and substituent effect allowed us to set k_H in the present case to approximately $1 \cdot 10^6$ M^{-1} s^{-1}.[57]

Scheme 7



The results of a series of competition reactions with radical precursor **23** (3 mM in acetonitrile/water 1:1) in the presence of 0.1 M TEAA buffer (pH 7) and various concentration of tin hydride **35** (17−155 mM) are shown in Figure 2.

The excellent linear dependence of the product ratio [**32**]/[**6**] on the reciprocal tin hydride concentration 1/[**35**] provides support for the applicability of eq 1. From the slope a ratio of $k_{obs}/k_H = 0.142$ M is obtained, which leads to a rate coefficient k_{obs} for the elimination of water from radical **25** of $1.4 \cdot 10^5$ s^{-1} at 20 °C. In the absence of buffer or in the presence of 0.5 M sodium chloride, values for k_{obs} of only $2 \cdot 10^3$ s^{-1} were measured in single kinetic determinations. These results clearly show that

(50) This assumption is further supported by the fact that the combined yield of **6** and **32** (as judged by HPLC) exceeded 80% in every kinetic experiment.

(51) Tronche, Ch.; Martinez, F. N.; Horner, J. H.; Newcomb, M.; Senn, M.; Giese, B. *Tetrahedron Lett.* **1996**, *37*, 5845−5848.

(52) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739−7742.

(53) For an analogous explanation using thiols as H-donors see ref 51.

(54) Beckwith, A. L. J.; Glover, S. A. *Aust. J. Chem.* **1987**, *40*, 157−173.

(55) Johnson, C. C.; Horner, J. H.; Tronche, Ch.; Newcomb, M. *J. Am. Chem. Soc.* **1995**, *117*, 1684−1687.

(56) Dhanabalasingham, B.; Martinez, F. N.; Simakov, P. A.; Newcomb, M. Unpublished results.

(57) Recent results by Newcomb[56] support this value. He determined a preliminary value of $1.3 \cdot 10^6$ M^{-1} s^{-1} for the H-atom transfer from the tin hydride **35** to a secondary α,β-dimethoxyalkyl radical in acetonitrile/water (1:1) at 34 °C.

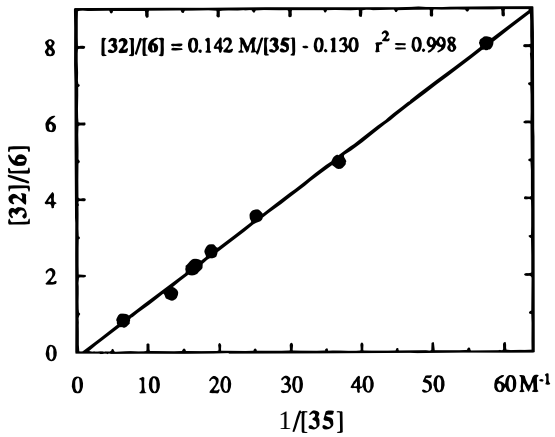


Figure 2. Ratios of [**32**] to [**6**] formed from reactions of radical **25** in acetonitrile/water (1:1) in the presence of 0.1 M triethylammonium acetate and various concentrations of tin hydride **35**.

Table 3. Catalytic Effect of Various Buffers on the Dehydration Reaction (**25** → **28**)

buffer	pH	k_{obs}/k_H	acceleration rate[a]
10 mM phosphate	8	0.244 M	162
10 mM phosphate	7	0.082 M	55
25 mM imidazole	7	0.024 M	16
100 mM piperazine	6	0.023 M	16
100 mM TEAF[b]	6	0.016 M	11
20 mM citrate	5	0.006 M	4

[a] Compared with the reaction in the absence of buffer. [b] Triethylammonium formate.

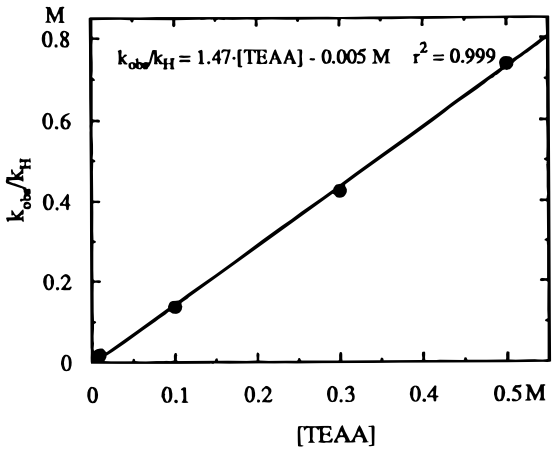


Figure 3. Relative rate coefficients k_{obs}/k_H from reactions of radical **25** in acetonitrile/water (1:1) in the presence of tin hydride **35** and various concentrations of triethylammonium acetate (TEAA).

the acceleration of the elimination reaction is due to the TEAA buffer and that its influence is not a salt effect. As the results in Table 3 illustrate, the catalytic effect on the dehydration is not restricted to TEAA. The acceleration factor in the last column refers to the competition kinetic in the absence of buffer ($k_{obs}/k_H = 1.5 \cdot 10^{-3}$ M).

In order to obtain a better understanding of the dependence of the elimination step on the TEAA buffer, the ratio of k_{obs}/k_H was measured by single kinetic determination for buffer concentrations ranging from 10 to 500 mM.

From the plot in Figure 3 it is evident that the rate of the elimination reaction is linearly dependent on the buffer concentration according to the relation $k_{obs} = 1.47 \cdot k_H \cdot$[TEAA] or $k_{obs} = 1.5 \cdot 10^6$ M^{-1} s$^{-1} \cdot$[TEAA], respectively. Such a linear rate dependence on the buffer concentration is characteristic of reactions following general acid or base catalysis.[58] Studying the pH dependence of the dehydration reaction should allow us to specify the general catalysis. Therefore, the ratio of k_{obs}/k_H

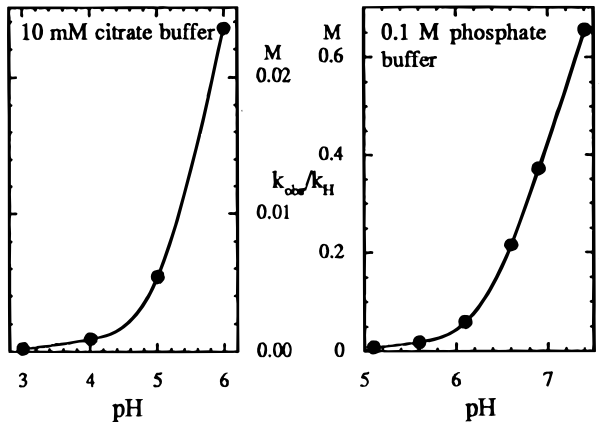
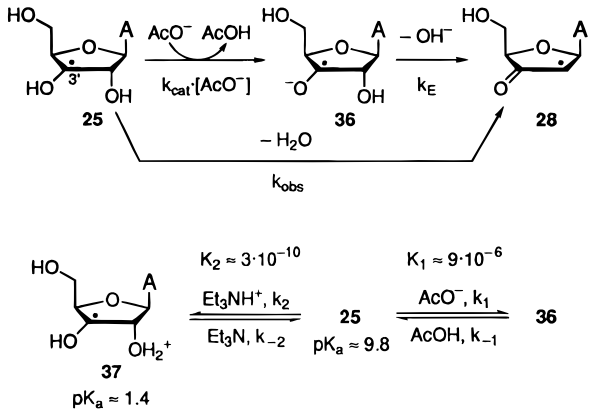


Figure 4. pH dependence of the relative rate coefficients k_{obs}/k_H from reactions of radical **25** in acetonitrile/water (1:1) in the presence of tin hydride **35**.

Scheme 8



was determined in the range from pH 3−6 (10 mM citrate buffer) and from pH 5−7.5 (0.1 M phosphate buffer).

The two plots in Figure 4 clearly indicate that with increasing proton concentration the rate of elimination steadily decreases. Over the whole pH range studied, the elimination of water from the C-3′ nucleoside radical **25** is therefore subject to general base catalysis.[59] Consequently in the case of the TEAA buffer the catalytically active species is acetate. For the observed rate coefficient we can therefore write $k_{obs} = 1.5 \cdot 10^6$ M^{-1} s$^{-1} \cdot$[AcO$^-$].

General Base Catalysis in the Enzyme Reaction Mechanism. In general base catalyzed reactions the rate determining step is a proton transfer from the substrate to the base which is followed by a rapid transformation of the intermediate to the product. That means for the reaction investigated in this study that the C-3′ nucleoside radical **25** is deprotonated by acetate to the ketyl **36**. In a subsequent, faster step the 2′-hydroxy group of **36** is eliminated as OH$^-$, leading to the carbonyl conjugated radical **28** (Scheme 8, top). The rate of the overall reaction is solely dependent on the first step and is thus directly proportional to the acetate concentration (with $k_{obs} = k_{cat} \cdot$[AcO$^-$] and $k_{cat} = 1.5 \cdot 10^6$ M^{-1} s^{-1}).

Although an analogous base catalyzed mechanism has already been suggested[1c,4a] for the dehydration step in the ribonucleotide reductase mediated reaction based on model studies using simple α,β-dihydroxyalkyl radicals under specific hydroxide catalysis,[60] it never became as popular as the alternative acid catalyzed

(58) (a) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705−718. (b) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425−432. (c) Hoffmann, R. W. *Aufklärung von Reaktionsmechanismen*; Thieme Verlag: Stuttgart, 1976; pp 231−243.

(59) General base catalysis has also been observed in the radical-induced dehydration reaction of carbohydrates, see: (a) Tamba, M.; Quintiliani, M. *Radiat. Phys. Chem.* **1984**, *23*, 259−263. (b) Akhlaq, M. S.; Al-Baghdadi, S.; von Sonntag, C. *Carbohydr. Res.* **1987**, *16*, 71−83.

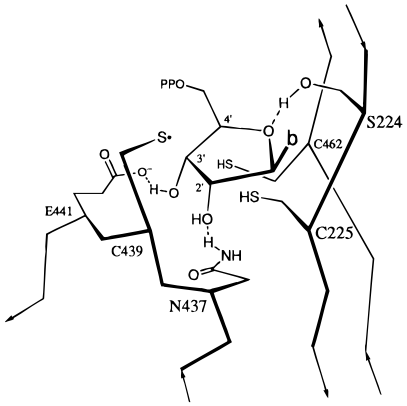


Figure 5. Schematic drawing of the active-site region of the *E. coli* ribonucleotide reductase with a plausible position for a model-built substrate molecule.

mechanism shown in Scheme 2. According to our findings, this acid catalyzed mechanism, however, seems not to be operative under reaction conditions where weak acids are used. This can be rationalized by a much more unfavored equilibrium in the case of the general acid catalyzed reaction compared with the corresponding general base catalysis (Scheme 8, bottom).

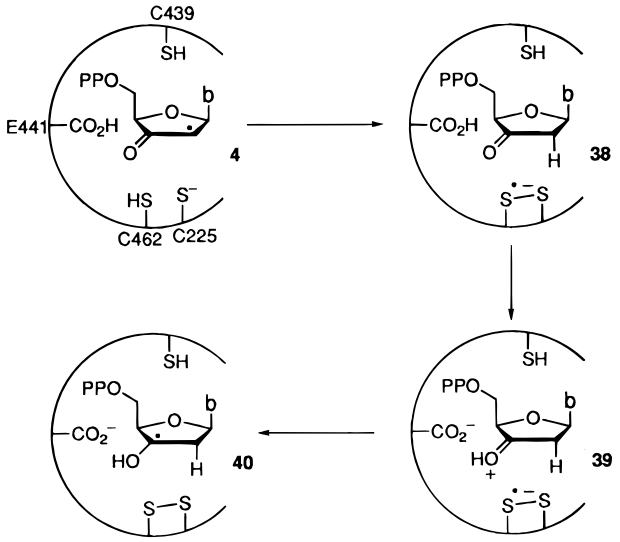
Using the known values for 2-deoxyribose radicals[12,61] the pK_a value for the 3′-hydroxy group of radical **25** and the protonated 2′-hydroxy group of radical **37** can be estimated to 9.8[61] and 1.4,[12] respectively.[62] Thus, under neutral conditions using triethylammonium acetate as buffer this leads to a more advantageous equilibrium for the general base catalyzed process ($K_1 \approx 10^{-5}$) than for the reaction under general acid catalysis ($K_2 \approx 3 \cdot 10^{-10}$). Because the difference of the pK_a values is large, one can assume for both reactions that the faster proton transfer steps are diffusion-controlled[63] ($k_{-1} \approx k_{-2} \approx 10^{10}$ M^{-1} s^{-1}). The rate coefficients k_1 and k_2 therefore become 10^5 and 3 M^{-1} s^{-1}, respectively. This estimation leads to the conclusion that the deprotonation step **25** → **36** is much faster than the protonation step **25** → **37**. The fair agreement between the measured value for k_{cat} ($\approx 10^6$ M^{-1} s^{-1}) and k_1 supports this interpretation.

For a general base catalysis to appear in the ribonucleotide reductase mediated process, an appropriate basic functionality has to be present at a suitable position in the active cavity of the enzyme. That this is indeed the case has been shown only recently by Uhlin and Eklund.[64] They crystallized the R1 subunit of the *E. coli* reductase thus providing the first detailed structure of the active center of a ribonucleotide reductase (Figure 5).

In this model the three polar amino acid side chains from serine (S224), asparagine (N437), and glutamate (E441), all of them highly conserved in other reductases, are forming hydrogen bonds with O-4′, O-2′, and O-3′, respectively. Supposing this model to be correct, E441 would thus be perfectly positioned to act as a general base able to deprotonate the 3′-hydroxy group after generation of the C-3′ nucleotide radical.

The question now arises to what extent the results of the general catalysis by acetate in solution can be compared with an enzymatic catalysis by glutamate. As to the chemical

Scheme 9



reactivity, the acetate group and the glutamate side chain behave very similarly having pK_a values of 4.76 and 4.4, respectively. There is, however, a fundamental difference between enzyme and solution chemistry. While catalysis in solution is intermolecular showing second-order kinetics, reactions in an enzyme−substrate complex are better described as intramolecular processes with first-order kinetics. An appropriate model for an enzyme reaction is therefore the corresponding reaction in solution where the catalyst is an integral part of the molecule.[65] Furthermore, it is well-known that in the case of general acid−base catalysis intramolecularly catalyzed processes are about as efficient as their intermolecular counterparts at concentrations for the general catalyst of 1−10 M.[66] Using such a value for the acetate concentration in the present study, the rate coefficient for the elimination of water in the ribonucleotide reductase mediated process can be estimated to 10^6−10^7 s^{-1}, which signifies a rate enhancement of at least 10^3 as compared to the uncatalyzed dehydration reaction. Such a strongly accelerated deoxygenation step is absolutely essential for the enzyme mechanism.

Since it is known from model studies by von Sonntag[67] and Asmus[68] that hydrogen atom abstraction from hydroxyalkyl compounds by thiyl radicals ($k_H \approx 10^3$−10^4 M^{-1} s^{-1}) is 10^4−10^5 times slower than the reverse reaction, an unfavorable equilibrium for the corresponding enzyme reaction (**1** ⇀↽ **3**, Scheme 2) can be expected. In order to drive this equilibrium to the products, it has to be followed by a fast and irreversible step such as the proposed general base catalyzed β-elimination, which is able to compete successfully with the hydrogen atom transfer from cysteine 439 to the C-3′ radical **3**.

The analogy between our model reaction and the enzyme mechanism ends with the reduction of **4** to the 2′-deoxy-3′-ketonucleotide **38** (Scheme 9). To prevent elimination of the nucleobase from **38**, as observed in the present study, a rapid reduction of the carbonyl group by a disulfide radical anion has been postulated.[1c,4] This reaction is thermodynamically not feasible in the absence of acid, since the reduction of a ketone to the corresponding ketyl ($E_0 = -2.1$ V for the isopropyl ketyl[69]) by a disulfide radical anion ($E_0 = -1.6$ V for the

(60) (a) Bansal, K. M.; Grätzel, M.; Henglein, A.; Janata, E. *J. Phys. Chem.* **1973**, *77*, 16−19. (b) Steenken, S. *J. Phys. Chem.* **1979**, *83*, 595−599.

(61) Hayon, E.; Simic, M. *Acc. Chem. Res.* **1974**, *7*, 114−121.

(62) Compared with alcohols (pK_a(ROH) ≈ 17, pK_a(ROH_2^+) ≈ −2), the presence of the carbon-centered radical in **25** therefore increases the aciditiy of the α-hydroxy group by more than 7 orders of magnitude, while the basicity of the β-hydroxy group is only enhanced by 3−4 orders of magnitude.

(63) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1−19.

(64) Uhlin, U.; Eklund, H. *Nature* **1994**, *370*, 533−539.

(65) (a) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969. (b) Page, M. I. In *The Chemistry of Enzyme Action*; Page, M. I., Ed.; Elsevier: Amsterdam, 1984, pp 229−269.

(66) Page, M. I. *Chem. Soc. Rev.* **1973**, *2*, 295−323.

(67) Akhlaq, M. S.; Schuchmann, H.-P.; von Sonntag, C. *Int. J. Radiat. Biol.* **1987**, *51*, 91−102.

(68) Schöneich, C.; Bonifacic, M.; Asmus, K.-D. *Free Rad. Res. Commun.* **1989**, *6*, 393−405.

disulfide radical anion from alkyl thiols[70]) is highly endothermic. In the presence of an acid catalyst (such as the protonated glutamate residue), however, the reduction leads via the protonated ketone **39** to the α-hydroxy radical **40** which has a much less negative reduction potential ($E_0 = -1.4$ V for 2-hydroxy-2-propyl radical[69]). According to this suggestion, the glutamate residue, therefore, not only acts as a base in the elimination step but also as an acid in the reduction sequence (**38** → **40**).

Conclusions

The synthesis of a novel 3′-selenocarbonyl nucleoside allows for the first time a selective generation of the 3′-adenosyl radical.[71] Using competition kinetic methods we could show that these radicals give rise to a rapid elimination of the 2′-hydroxy group. This observation lends additional support to the mechanism for the important enzymatic 2′-deoxygenation reaction of ribonucleotides proposed by Stubbe[1c,4] in which C-3′ nucleotide radicals represents key intermediates. However, in contrast to this mechanism where acid catalysis by a cysteine residue is postulated, the observed elimination reaction in solution is exclusively subject to general base catalysis. This finding, together with the recent discovery of a glutamate residue in the active site of the *E. coli* reductase,[64] favors general base catalysis in the enzyme mediated reaction.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer (^{1}H at 300 MHz, ^{13}C at 75.5 MHz). Ultraviolet spectra were recorded on a Perkin-Elmer Lambda 2 spectrometer. Combustion analyses were performed at the Microanalytical Laboratory at the University of Basel. Mass spectra were obtained on a VG 70−250 spectrometer. Analytical and preparative TLC were performed on E. Merck silica gel 60 F_{254} plates. Unless otherwise indicated, all separations were carried out under flash chromatography (FC) conditions on silica gel (Chemische Fabrik Uetikon, 230−400 mesh, particle size 35−70 μm). Analytical HPLC was performed on Hewlett Packard 1050 series chromatographs. All solvents were predried by standard methods. All other commercially obtained reagents were used as received.

Synthesis of the Radical Precursors. 6-*N*,*N*-Dibenzoyl-2′,5′-di-*O*-(*tert*-butyldimethylsilyl)adenosine (8). Disilylated nucleoside **7**[18] (9.60 g, 19.4 mmol) was coevaporated twice with anhydrous pyridine (50 mL each) and then dissolved in anhydrous pyridine (150 mL), and the solution was cooled to 0 °C. Trimethylsilyl chloride (4.9 mL, 38.7 mmol) was added under stirring, and the mixture was allowed to warm to room temperature. After 1 h, benzoyl chloride (11.2 mL, 96.8 mmol) was slowly added dropwise at 0 °C, and the reaction mixture was again brought to room temperature. After 2 additional h, it was carefully hydrolyzed at 0 °C with saturated aqueous $NaHCO_3$ (250 mL) and extracted three times with EtOAc (400 mL, 200 mL, 100 mL). The combined organic phases were washed with 2 N HCl and with H_2O and then dried over Na_2SO_4. After evaporation of the solvent in vacuo and coevaporation with toluene, the residue was dissolved in anhydrous EtOH (150 mL), cooled to 0 °C, and treated under stirring with *p*-toluenesulfonic acid (150 mg). The reaction was complete after 1 h (TLC control, eluent: EtOAc/pentane 1:3). Two spatulas of solid $NaHCO_3$ were added, the solvent was evaporated under reduced pressure, and the residue was dissolved in EtOAc (250 mL). The organic phase was washed with H_2O (2 × 150 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo to give 13.6 g (100%) of nucleoside **8** as a white foam: $R_f = 0.28$ (EtOAc/pentane 1:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.39 (s, 1H), 7.87−7.84 (m, 4H), 7.51−7.45 (m, 2H), 7.37−7.32 (m, 4H), 6.15 (d, $J = 5.3$ Hz, 1H), 4.65 (t, $J = 5.1$ Hz, 1H), 4.26 (m, 1H), 4.23 (m, 1H), 3.99 (dd, $J = 12.5$, 2.6 Hz, 1H), 3.86 (dd, $J = 12.5$, 2.7 Hz, 1H), 2.70 (d, $J = 3.8$ Hz, 1H), 0.93 (s, 9H), 0.82 (s, 9H), 0.12 (s, 3H), 0.115 (s, 3H), −0.08 (s, 3H), −0.22 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.1, 153.0, 152.2, 151.8, 143.1, 134.5, 134.1, 132.8, 130.5, 129.4, 128.8, 128.6, 127.9, 88.0, 85.4, 76.6, 71.3, 63.1, 26.0, 25.5, 18.5, 17.8, −5.10, −5.30, −5.66, −5.75; FAB−MS (NBA) *m/z* 706 $[M + 3]^+$, 705 $[M + 2]^+$, 704 $[M + 1]^+$, 600 $[M + 1 - Bz]^+$, 344 $[ABz_2 + 1]^+$, 240 $[ABz + 1]^+$, 136 $[A + 1]^+$, 105 Bz^+; FAB−MS (NBA + KCl) *m/z* 743 $[M + 1 + K]^+$, 742 $[M + K]^+$. Anal. Calcd for $C_{36}H_{49}N_5O_6Si_2$ [703.99]: C, 61.42; H, 7.02; N, 9.95. Found: C, 61.66; H, 6.81; N, 9.59.

6-*N*,*N*-Dibenzoyl-9-(2,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuran-3-ulosyl)adenine (9). A sample of Dess−Martin periodinane reagent[19] (17.0 g, 40.0 mmol) was dissolved under argon in anhydrous CH_2Cl_2 (200 mL) at 0 °C. Then, a solution of nucleoside **8** (14.1 g, 20.0 mmol) in anhydrous CH_2Cl_2 (100 mL) was added under stirring. The yellowish mixture was allowed to warm up slowly to room temperature and was stirred in the dark. The reaction was complete after 3 days (TLC control, eluent: CH_2Cl_2/acetone 40:1). The mixture was treated with saturated aqueous $NaHCO_3$ (300 mL) containing $Na_2S_2O_3$ (30 g), stirred for 15 min, and extracted with Et_2O (500 mL). The organic phase was then washed with saturated aqueous $NaHCO_3$ (2 × 200 mL), H_2O (200 mL), and brine (100 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, 13.8 g (99%) of ketone **9** were obtained as a pale yellow foam: $R_f = 0.45$ (CH_2Cl_2/acetone 40:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.37 (s, 1H), 7.88−7.85 (m, 4H), 7.52−7.46 (m, 2H), 7.38−7.33 (m, 4H), 6.20 (d, $J = 8.3$ Hz, 1H), 4.91 (dd, $J = 8.3$, 0.8 Hz, 1H), 4.32 (dd, $J = 2.1$, 1.3 Hz, 1H), 3.98−3.97 (m, 2H), 0.90 (s, 9H), 0.70 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), −0.03 (s, 3H), −0.27 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 208.0, 172.1, 153.2, 152.5, 152.1, 142.7, 134.0, 132.9, 129.4, 128.7, 127.6, 85.2, 82.6, 77.8, 62.3, 25.8, 25.2, 18.2, 17.9, −4.85, −5.47, −5.66, −5.75; FAB−MS (NBA) *m/z* 703 $[M + 2]^+$, 702 $[M + 1]^+$, 344 $[ABz_2 + 1]^+$, 240 $[ABz + 1]^+$, 105 Bz^+; FAB−MS (NBA + KCl) *m/z* 741 $[M + 1 + K]^+$, 740 $[M + K]^+$. Anal. Calcd for $C_{36}H_{47}N_5O_6Si_2$ [701.98]: C, 61.60; H, 6.75; N, 9.98. Found: C, 61.46; H, 6.75; N, 9.98.

6-*N*-Benzoyl-9-(2,5-di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-vinyl-β-D-xylofuranosyl)adenine (10). $CeCl_3 \cdot 7H_2O$ (18.5 g, 49.6 mmol) was dried at 140 °C (oil bath temperature) in vacuo ($4 \cdot 10^{-2}$ mbar) for 8 h. The resulting white powder was then cooled under argon to 0 °C (ice bath) and treated under vigorous stirring with cold anhydrous THF (100 mL), and the mixture was stirred overnight at room temperature. The suspension was cooled to −78 °C, and vinylmagnesium bromide (50 mL, 1 M solution in THF) was added. After stirring for 4 h at −78 °C, a solution of ketone **9** (5.61 g, 7.99 mmol) in anhydrous THF (20 mL) was added slowly with a motor-driven syringe pump for 1 h. After 2 additional h, the orange suspension was treated with AcOH (6 mL) and allowed to warm up to room temperature. The reaction mixture was partitioned between diluted aqueous $NaHCO_3$ (300 mL) and EtOAc (300 mL), the phases were separated, and the aqueous phase was extracted twice with EtOAc (2 × 150 mL). The combined organic phases were washed with diluted aqueous $NaHCO_3$ (200 mL), H_2O (150 mL), and brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. FC (eluent: EtOAc/CH_2Cl_2/pentane 1:1:2) afforded 4.10 g (82%) of nucleoside **10** as a yellowish foam: $R_f = 0.27$ (EtOAc/CH_2Cl_2/pentane 1:1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (broad s, 1H), 8.83 (s, 1H), 8.55 (s, 1H), 8.05−8.01 (m, 2H), 7.65−7.57 (m, 1H), 7.57−7.52 (m, 2H), 6.16 (s, 1H), 6.08 (dd, $J = 17.2$, 10.8 Hz, 1H), 5.78 (s, 1H), 5.68 (dd, $J = 17.3$, 1.7 Hz, 1H), 5.44 (dd, $J = 10.8$, 1.7 Hz, 1H), 4.25 (s, 1H), 4.19−4.11 (m, 2H), 4.03 (dd, $J = 11.7$, 2.8 Hz, 1H), 0.92 (s, 9H), 0.91 (s, 9H), 0.09 (s, 6H), 0.08 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.6, 152.4, 151.3, 149.4, 142.6, 135.1, 133.7, 132.6, 128.9, 127.8, 123.0, 117.3, 91.3, 85.2, 82.7, 82.5, 61.6, 25.7, 18.1, 17.9, −4.6, −4.9, −5.5, −5.8; FAB−MS (NBA) *m/z* 627 $[M + 2]^+$, 626 $[M + 1]^+$, 240 $[ABz + 1]^+$, 136 $[A + 1]^+$, 105 Bz^+; FAB−MS (NBA + KCl) *m/z* 665 $[M + 1 + K]^+$, 664 $[M + K]^+$. Anal. Calcd for $C_{31}H_{47}N_5O_5Si_2$ [625.92]: C, 59.49; H, 7.57; N, 11.19. Found: C, 59.32; H, 7.41; N, 11.01.

(69) Schwarz, H. A.; Dodson, R. W. *J. Phys. Chem.* **1989**, *93*, 409−414.

(70) Surdhar, P. S.; Armstrong, D. A. *J. Phys. Chem.* **1986**, *90*, 5915−5917.

(71) For the generation of unnatural derivatives, see: (a) Robins, M. J.; Guo, Z.; Samano, M. C.; Wnuk, S. F. *J. Am. Chem. Soc.* **1996**, *118*, 11317−11318. (b) Lehmann, T. E.; Berkessel, A. *J. Org. Chem.* **1997**, *62*, 302−309.

(72) Xi, C.; Jun-Dong, Z.; Li-He, Z. *Synthesis* **1989**, 383−384.

(73) Newcomb, M. *Tetrahedron* **1991**, *49*, 1151−1176.

6-*N*-Benzoyl-9-(2,5-di-*O*-(*tert*-butyldimethylsilyl)-3-*O*-(trimethylsilyl)-3-*C*-vinyl-β-D-xylofuranosyl)adenine (11). Nucleoside **10** (4.10 g, 6.55 mmol) was dissolved under argon in anhydrous CH_2Cl_2 (50 mL), treated with Horning's silylation reagent[25] (6 mL), and stirred for 72 h at room temperature. The reaction mixture was partitioned between H_2O (150 mL) and Et_2O (150 mL), the phases were separated, and the organic phase was washed with H_2O (2 × 150 mL) and brine (100 mL). After drying over Na_2SO_4 and concentration in vacuo, 4.66 g (6.68 mmol) of crude silyl ether **11** was obtained as a white foam which was employed directly in the next step without further purification: $R_f = 0.32$ (EtOAc/pentane 1:2), $R_f = 0.46$ (EtOAc/CH_2Cl_2/pentane 1:1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (broad s, 1H), 8.82 (s, 1H), 8.36 (s, 1H), 8.05−8.02 (m, 2H), 7.64−7.51 (m, 3H), 6.07 (dd, J = 17.7, 11.3 Hz, 1H), 6.01 (d, J = 1.7 Hz, 1H), 5.44 (d, J = 11.3 Hz, 1H), 5.41 (d, J = 17.8 Hz, 1H), 4.54 (d, J = 1.7 Hz, 1H), 4.51 (t, J = 5.3 Hz, 1H), 4.03 (d, J = 5.3 Hz, 2H), 0.95 (s, 9H), 0.90 (s, 9H), 0.155 (s, 3H), 0.145 (s, 3H), 0.12 (s, 3H), −0.04 (s, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.7, 152.7, 152.4, 149.2, 142.0, 134.9, 133.8, 132.6, 128.7, 127.9, 122.9, 119.0, 90.8, 85.3, 83.9, 82.7, 62.9, 26.0, 25.7, 18.5, 17.9, 2.14, −4.47, −4.75, −5.21, −5.28.

6-*N*-Benzoyl-9-(2,5-di-*O*-(*tert*-butyldimethylsilyl)-3-*O*-(trimethylsilyl)-3-*C*-formyl-β-D-xylofuranosyl)adenine (12). Crude nucleoside **11** (4.66 g, 6.68 mmol) was dissolved in CH_2Cl_2 (70 mL) and the solution was cooled to −78 °C. The reaction flask was then connected to an ozonolysis apparatus, and ozone (3% O_3 in O_2, flow 15 mL/min) was passed through the solution for 1 h. The reaction mixture was then treated with Me_2S (1.47 mL, 20 mmol) and stirred for 2 h at room temperature. After removal of the solvent in vacuo, the crude product was purified by FC (eluent: pentane/CH_2Cl_2/^{t}BuOMe 3:1:1), and 3.10 g (68% from **10**) of aldehyde **12** were obtained as a yellowish foam: $R_f = 0.25$ (pentane/CH_2Cl_2/^{t}BuOMe 3:1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.93 (broad s, 1H), 8.80 (s, 1H), 8.23 (s, 1H), 8.03−8.00 (m, 2H), 7.62−7.50 (m, 3H), 6.16 (s, 1H), 4.98 (dd, J = 5.3, 8.1 Hz, 1H), 4.67 (s, 1H), 3.93 (m, 2H), 0.945 (s, 9H), 0.87 (s, 9H), 0.27 (s, 3H), 0.105 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.003 (s, 9H).

6-*N*-Benzoyl-9-(2,5-di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-carboxy-β-D-xylofuranosyl)adenine (13). Aldehyde **12** (75 mg, 107 μmol) was dissolved in a mixture of ^{t}BuOH (1.5 mL) and phosphate buffer (pH 7, 1 mL). The solution was then stirred with $KMnO_4$ (1 mL of 1 M aqueous solution) at room temperature. After 2 h, the excess of permanganate was reduced by addition of saturated aqueous Na_2SO_3 (2 mL). The reaction mixture was then cooled to 0 °C, carefully acidified to pH 3 with diluted HCl and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, treated with silica gel (0.5 g), and concentrated in vacuo. The residue was purified by FC (eluent: CH_2Cl_2/CH_3OH/AcOH 100:10:1), and 53 mg (77%) of carboxylic acid **13** were obtained as a fine white precipitate: R_f = 0.30 (CH_2Cl_2/CH_3OH/AcOH 100:10:1); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.70 (s, 1H), 8.68 (s, 1H), 8.15−8.12 (m, 2H), 7.67−7.53 (m, 3H), 6.30 (d, J = 3.4 Hz, 1H), 4.87 (d, J = 3.4 Hz, 1H), 4.69 (t, J = 4.5 Hz, 1H), 4.11 (d, J = 4.4 Hz, 2H), 0.92 (s, 9H), 0.83 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.04 (s, 3H), −0.04 (s, 3H); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.2 (s, 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.05−8.03 (m, 2H), 7.67−7.61 (m, 1H), 7.57−7.52 (m, 2H), 6.15 (d, J = 3.5 Hz, 1H), 6.12−5.92 (broad s, 1H), 4.69 (d, J = 3.5 Hz, 1H), 4.50 (t, J = 4.8 Hz, 1H), 3.94 (d, J = 4.7 Hz, 2H), 0.86 (s, 9H), 0.77 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H), −0.02 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 172.1, 166.2, 152.8, 152.5, 151.1, 143.3, 134.9, 133.2, 129.3, 129.2, 125.4, 89.9, 84.2, 83.9, 83.3, 63.3, 26.3, 25.9, 19.0, 18.3, −4.67, −4.94, −5.05, −5.29.

6-*N*-Benzoyl-9-(2,5-di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-phenylselenocarbonyl-β-D-xylofuranosyl)adenine (14). A sample of carboxylic acid **13** (230 mg, 357 μmol) was dissolved in anhydrous DMF (3 mL) under argon and cooled to 0 °C. 1,1′-Carbonyldi-1,2,4-triazole (147 mg, 893 μmol) was added, and the solution was stirred overnight at room temperature. The reaction mixture was then cooled to 0 °C and treated with PhSeH (96.0 μL, 893 μmol). After stirring for 1 h at 0 °C, EtOAc (50 mL) was added, and the mixture was washed with brine (4 × 30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by FC (eluent: EtOAc/CH_2Cl_2/pentane 1:1:3), and 220 mg (79%) of selenol ester **14** were obtained as a fine white precipitate: R_f = 0.38 (EtOAc/CH_2Cl_2/pentane 1:1:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (broad s, 1H), 8.78 (s, 1H), 8.37 (s, 1H), 8.02−8.00 (m, 2H), 7.59−7.54 (m, 1H), 7.50−7.44 (m, 2H), 7.38−7.34 (m, 5H), 6.99 (s, 1H), 6.06 (d, J = 2.2 Hz, 1H), 4.72 (d, J = 2.2 Hz, 1H), 4.55 (t, J = 3.7 Hz, 1H), 4.20 (dd, J = 11.8, 3.7 Hz, 1H), 4.04 (dd, J = 11.8, 3.6 Hz, 1H), 0.92 (s, 9H), 0.80 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.04 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.2, 164.7, 152.4, 149.7, 149.2, 142.2, 135.7, 133.4, 132.6, 129.0, 128.6, 128.6, 127.8, 126.1, 123.3, 90.6, 90.0, 83.6, 80.9, 62.0, 25.7, 25.4, 18.0, 17.6, −4.78, −5.00, −5.59, −5.82; FAB−MS (NBA) *m/z* 787 [M + 4]$^+$, 786 [M + 3]$^+$, 785 [M + 2]$^+$, 784 [M + 1]$^+$, 783 M$^+$, 782 [M − 1]$^+$, 781 [M − 2]$^+$, 780 [M − 3]$^+$ 599 [M + 1 − PhSeCO]$^+$, 598 [M − PhSeCO]$^+$, 240 [ABz + 1]$^+$, 136 [A + 1]$^+$, 105 Bz$^+$; FAB−MS (NBA + KCl) *m/z* 825 [M + 3 + K]$^+$, 824 [M + 2 + K]$^+$, 823 [M + 1 + K]$^+$, 822 [M + K]$^+$, 821 [M − 1 + K]$^+$, 820 [M − 2 + K]$^+$, 819 [M − 3 + K]$^+$, 818 [M − 4 + K]$^+$.

6-*N*-Benzoyl-9-(2-O-(*tert*-butyldimethylsilyl)-3-*C*-phenylselenocarbonyl-β-D-xylofuranosyl)adenine (15). A solution of selenol ester **14** (50 mg, 64 μmol) and BF_3·Et_2O (0.24 mL, 1.92 mmol) in anhydrous CH_2Cl_2 (3 mL) was heated under reflux. After 2 h, the mixture was treated with EtOAc (20 mL) and washed with H_2O (3 × 20 mL) and brine (2 × 10 mL). After removal of the solvent in vacuo, 42 mg (98%) of selenol ester **15** were obtained as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (broad s, 1H), 8.81 (s, 1H), 8.01 (s, 1H), 8.04−8.00 (m, 2H), 7.65−7.50 (m, 1H), 7.48−7.39 (m, 7H), 6.66−6.62 (m, 1H), 5.94 (d, J = 6.8 Hz, 1H), 5.21 (d, J = 2.2 Hz, 1H), 5.04 (d, J = 6.7 Hz, 1H), 4.38 (broad s, 1H), 4.10−4.06 (m, 1H), 3.99−3.94 (m, 1H), 0.77 (s, 9H), 0.05 (s, 3H), −0.47 (s, 3H).

9-(2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-phenylselenocarbonyl-β-D-xylofuranosyl)adenine (16). Nucleoside **14** (160 mg, 204 μmol) was treated with 5% HCl in EtOH (6 mL) for 5 h at 50 °C, then EtOAc (60 mL) was added, and the reaction mixture was washed with H_2O (4 × 30 mL). The combined aqueous phases were extracted with EtOAc (20 mL), and the organic phases were washed with brine (2 × 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by FC (eluent: CH_2Cl_2/EtOH 15:1) and 91 mg (79%) of selenol ester **16** were obtained as a white precipitate: R_f = 0.27 (CH_2Cl_2/EtOH 15:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.74 (s, 1H), 7.54−7.50 (m, 2H), 7.44−7.39 (m, 3H), 7.24 (dd, J = 10.8, 3.0 Hz, 1H), 5.83 (d, J = 7.1 Hz, 1H), 5.71 (broad s, 2H), 5.23 (s, 1H), 5.07 (d, J = 7.1 Hz, 1H), 4.34 (t, J = 1.6 Hz, 1H), 4.33 (ddd, J = 13.4, 2.9, 1.5 Hz, 1H), 3.93 (ddd, J = 13.3, 11.1, 2.0 Hz, 1H), 0.77 (s, 9H), 0.04 (s, 3H), −0.49 (s, 3H);); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.17 (s, 1H), 7.80 (s, 1H), 7.47 (broad s, 2H), 7.44−7.40 (m, 5H), 5.88 (d, J = 5.3 Hz, 1H), 5.44 (dd, J = 6.5, 5.0 Hz, 1H), 4.98 (d, J = 5.3 Hz, 1H), 4.22 (dd, J = 4.7, 3.8 Hz, 1H), 3.73−3.68 (m, 2H), 0.71 (s, 9H), −0.02 (s, 3H), −0.35 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 204.6, 156.0, 148.2, 152.5, 140.8, 136.0, 129.3, 129.0, 128.2, 125.8, 89.0, 88.5, 82.7, 80.9, 62.7, 25.7, 17.7, −4.47, −5.71; FAB−MS (NBA) *m/z* 569 [M + 4]$^+$, 568 [M + 3]$^+$, 567 [M + 2]$^+$, 566 [M + 1]$^+$, 565 M$^+$, 564 [M − 1]$^+$, 563 [M − 2]$^+$, 562 [M − 3]$^+$, 381 [M + 1 − PhSeCO]$^+$, 380 [M − PhSeCO]$^+$, 136 [A + 1]$^+$; FAB−MS (NBA + KCl) *m/z* 607 [M + 3 + K]$^+$, 606 [M + 2 + K]$^+$, 605 [M + 1 + K]$^+$, 604 [M + K]$^+$, 603 [M − 1 + K]$^+$, 602 [M − 2 + K]$^+$, 601 [M − 3 + K]$^+$, 600 [M − 4 + K]$^+$.

6-*N*-Benzoyl-9-(3-*C*-vinyl-β-D-xylofuranosyl)adenine (17). Nucleoside **10** (5.11 g, 8.16 mmol) was dissolved in anhydrous THF (100 mL) under argon and cooled to 0 °C. The solution was then treated with TBAF (20.4 mL, 1 M solution in THF) and stirred for 3 h. The solvent was removed in vacuo, and the residue was purified by FC (short column with large diameter, eluent: CH_2Cl_2/MeOH gradient 9:1 → 2:1). A brown oil (3.0 g) was obtained which still contained TBA salts and which crystallized on standing. Dissolving this mixture in EtOH and precipitating the product with a 1:1 Et_2O/CH_2Cl_2 mixture afforded after filtration 2.78 g (82%) of deprotected nucleoside **17** as a white precipitate: $R_f = 0.41$ (CH_2Cl_2/EtOH 8:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.2 (broad s, 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.06−8.03 (m, 2H), 7.67−7.61 (m, 1H), 7.57−7.52 (m, 2H), 6.23 (d, J = 5.4 Hz, 1H), 6.14 (dd, J = 17.5, 10.9 Hz, 1H), 6.11 (broad s, 1H), 5.51 (s, 1H), 5.43 (dd, J = 17.5, 1.9 Hz, 1H), 5.31 (dd, J = 10.9, 1.9 Hz, 1H), 4.81 (t, J = 5.6 Hz, 1H), 4.18 (dd, J = 5.4, 1.0 Hz, 1H), 4.12 (dd, J = 6.8, 2.7 Hz, 1H), 3.75−3.58 (m, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 165.6, 151.8, 150.2, 151.5, 143.0, 136.6, 133.4, 132.4, 128.5, 125.6, 115.9, 90.6, 86.0, 82.9, 80.8, 59.5; FAB−MS (NBA) *m/z* 399

$[M + 2]^+$, 398 $[M + 1]^+$, 282 $[M - Bz]^+$, 240 $[ABz + 1]^+$, 136 $[A + 1]^+$, 105 Bz^+, 77 Ph^+; FAB−MS (NBA + KCl) *m/z* 437 $[M + 1 + K]^+$, 436 $[M + K]^+$. Anal. Calcd for $C_{19}H_{19}N_5O_5$ [397.40]: C, 57.43; H, 4.82; N, 17.62. Found: C, 57.09; H, 4.86; N, 17.40.

6-*N*-Benzoyl-9-(3,5-*O*-isopropylidene-3-*C*-vinyl-β-D-xylofuranosyl)adenine (18). A suspension of nucleoside **17** (737 mg, 1.85 mmol) in dry acetone (20 mL) was prepared under argon and cooled to 0 °C. It dissolved instantaneously upon addition of a solution of $AlCl_3$ (740 mg, 5.56 mmol) in dry Et_2O (11 mL). After stirring for 1 h at room temperature, the reaction mixture was treated with diluted aqueous $NaHCO_3$ (20 mL) and extracted with $CHCl_3$ (40 mL) and CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Acetonide **18** (800 mg, 99%) was obtained as a white foam: $R_f = 0.40$ (CH_2Cl_2/EtOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (broad s, 1H), 8.82 (s, 1H), 8.77 (s, 1H), 8.04−8.01 (m, 2H), 7.61−7.50 (m, 3H), 6.27 (s, 1H), 6.03 (dd, J = 18.1, 11.4 Hz, 1H), 5.58 (d, J = 11.3 Hz, 1H), 5.39 (d, J = 18.1 Hz, 1H), 4.37 (broad s, 1H), 4.34 (broad s, 1H), 4.24 (dd, J = 13.5, 0.8 Hz, 1H), 4.16 (dd, J = 13.5, 1.5 Hz, 1H), 3.04 (broad s, 1H), 1.44 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.6, 152.4, 150.8, 149.2, 142.3, 136.7, 133.8, 132.7, 128.8, 127.8, 123.2, 119.7, 99.1, 91.5, 82.4, 81.7, 75.8, 58.9, 29.8, 23.2; FAB−MS (NBA) *m/z* 439 $[M + 2]^+$, 438 $[M + 1]^+$, 240 $[ABz + 1]^+$, 105 Bz^+; FAB−MS (NBA + KCl) *m/z* 477 $[M + 1 + K]^+$, 476 $[M + K]^+$. Anal. Calcd for $C_{22}H_{23}N_5O_5$ [437.46]: C, 60.40; H, 5.30; N 16.01. Found: C, 59.94; H, 5.53; N 15.02.

6-*N*-Benzoyl-9-(2-*O*-acetyl-3,5-*O*-isopropylidene-3-*C*-vinyl-β-D-xylofuranosyl)adenine (19). Acetonide **18** (1.87 g, 3.85 mmol) was coevaporated twice with anhydrous pyridine (10 mL each), then dissolved in anhydrous pyridine (25 mL) under argon, and cooled to 0 °C. AcOH (400 μL, 4.24 mmol) was added, and the reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo, and the residue was coevaporated twice with toluene (10 mL each). The crude product was purified by FC (eluent: CH_2Cl_2/acetone 2:1) yielding 1.79 g (97%) of acetate **19** as a white foam: $R_f = 0.34$ (CH_2Cl_2/acetone 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (broad s, 1H), 8.82 (s, 1H), 8.76 (s, 1H), 8.04−8.02 (m, 2H), 7.61−7.50 (m, 3H), 6.33 (s, 1H), 5.96 (dd, J = 18.1, 11.4 Hz, 1H), 5.51 (s, 1H), 5.41 (d, J = 11.4 Hz, 1H), 5.25 (d, J = 18.1 Hz, 1H), 4.34 (broad s, 1H), 4.23−4.12 (m, 2H), 2.12 (s, 3H), 1.47 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.5, 164.5, 152.7, 151.3, 149.2, 142.0, 136.5, 133.7, 132.6, 128.8, 127.8, 123.2, 118.1, 99.4, 88.4, 82.2, 81.0, 75.4, 58.4, 29.8, 22.9, 21.1; FAB−MS (NBA) *m/z* 481 $[M + 2]^+$, 480 $[M + 1]^+$, 479 M^+, 242 $[M + 2 - ABz]^+$, 241 $[M + 1 - ABz]^+$, 240 $[M - ABz]^+$ and $[ABz + 1]^+$, 136 $[A + 1]^+$, 105 Bz^+, 77 Ph^+; FAB−MS (NBA + KCl) *m/z* 520 $[M + 1 + K]^+$, 519 $[M + K]^+$. Anal. Calcd for $C_{24}H_{25}N_5O_6$ [479.50] C, 60.12; H, 5.26; N 14.61. Found: C, 59.87; H, 5.37; N 13.91.

6-*N*-Benzoyl-9-(2-*O*-acetyl-3-*C*-formyl-3,5-*O*-isopropylidene-β-D-xylofuranosyl)adenine (20). Nucleoside **19** (1.78 g, 3.71 mmol) was dissolved in CH_2Cl_2 (30 mL), and the solution was cooled to −78 °C. The reaction flask was then connected to an ozonolysis apparatus and ozone (3% O_3 in O_2, flow 15 mL/min) was passed through the solution for 1 h. The reaction mixture was then treated with Me_2S (816 μL, 11.1 mmol) and stirred for 1 h at room temperature. The solvent was removed in vacuo, and the residue was purified by FC (eluent: CH_2Cl_2/acetone 3:1) to yield 1.23 g (69%) of aldehyde **20** as a yellowish precipitate: $R_f = 0.32$ (CH_2Cl_2/acetone 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.96 (broad s, 1H), 8.81 (s, 1H), 8.71 (s, 1H), 8.05−8.02 (m, 2H), 7.62−7.51 (m, 3H), 6.39 (s, 1H), 5.52 (s, 1H), 4.67 (broad s, 1H), 4.22 (d, J = 14.0 Hz, 1H), 4.06 (dd, J = 14.0, 1.9 Hz, 1H), 2.15 (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 198.0, 169.5, 164.8, 152.8, 151.3, 149.4, 141.6, 133.6, 132.8, 128.8, 127.9, 123.3, 99.7, 88.5, 84.6, 82.3, 73.8, 58.9, 29.1, 22.0, 20.7; FAB−MS (NBA) *m/z* 483 $[M + 2]^+$, 482 $[M + 1]^+$, 243 $[M + 1 - ABz]^+$, 240 $[ABz + 1]^+$, 136 $[A + 1]^+$, 105 Bz^+, 77 Ph^+; FAB−MS (NBA + KCl) *m/z* 521 $[M + 1 + K]^+$, 520 $[M + K]^+$. Anal. Calcd for $C_{23}H_{23}N_5O_7$ [481.47]: C, 57.38; H, 4.82; N 14.55. Found: C, 57.42; H, 5.24; N 13.25.

6-*N*-Benzoyl-9-(2-*O*-acetyl-3-*C*-carboxy-3,5-*O*-isopropylidene-β-D-xylofuranosyl)adenine (21). A solution of aldehyde **20** (1.23 g, 2.55 mmol) in ^{t}BuOH (30 mL) and phosphate buffer (pH 7, 15 mL) was treated with $KMnO_4$ (10 mL, 1 M aqueous solution) under stirring at room temperature. After 30 min the excess of oxidant was reduced by adding saturated aqueous Na_2SO_3 (10 mL). The reaction mixture was cooled to 0 °C, carefully acidified with HCl to pH 3, and extracted with CH_2Cl_2 (4 × 30 mL) whereby the aqueous phase was gradually brought to pH 2 by addition of HCl. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo, and the residue was coevaporated consecutively with toluene, $CHCl_3$, and CH_2Cl_2 yielding 1.16 g (91%) of carboxylic acid **21** as a fine white precipitate: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.25 (s, 1H), 8.77 (s, 1H), 8.63 (s, 1H), 8.07−8.05 (m, 2H), 7.68−7.53 (m, 3H), 6.32 (s, 1H), 5.59 (s, 1H), 4.63 (broad s, 1H), 4.20 (broad d, J = 13.9 Hz, 1H), 4.06 (d, J = 13.8 Hz, 1H), 2.12 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 169.9, 168.4, 165.6, 151.9, 151.7, 150.4, 141.9, 133.2, 132.4, 128.5, 125.2, 99.1, 87.0, 81.7, 79.9, 73.8, 58.4, 28.8, 20.4.

6-*N*-Benzoyl-9-(2-*O*-acetyl-3,5-*O*-isopropylidene-3-*C*-phenylselenocarbonyl-β-D-xylofuranosyl)adenine (22). A solution of carboxylic acid **21** (805 mg, 1.62 mmol) in anhydrous THF (30 mL) was cooled to 0 °C under argon. NEt_3 (680 μL, 4.85 mmol) and $PhOPOCl_2$ (480 μL, 3.24 mmol) were added under stirring, the mixture was agitated for 1 h, and then addition of NEt_3 (1.16 mL, 7.90 mmol) and PhSeH (520 μL, 4.90 mmol) was followed by stirring for 30 min at 0 °C and subsequent treatment with H_2O and EtOAc (50 mL each). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with brine (2 × 30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by FC (eluent: CH_2Cl_2/acetone 5:1) afforded 739 mg (72%) of selenol ester **22** as a white precipitate: $R_f = 0.22$ (CH_2Cl_2/acetone 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (broad s, 1H), 8.84 (s, 1H), 8.72 (s, 1H), 8.05−8.03 (m, 2H), 7.64−7.50 (m, 3H), 7.45−7.39 (m, 5H), 6.25 (d, J = 1.3 Hz, 1H), 5.83 (d, J = 1.3 Hz, 1H), 4.70 (t, J = 1.6 Hz, 1H), 4.19 (m, 2H), 2.13 (s, 3H), 1.63 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 200.6, 168.1, 164.5, 152.9, 151.5, 149.4, 141.6, 135.9, 133.7, 132.7, 129.5, 129.4, 128.8, 127.8, 124.7, 123.1, 101.2, 87.8, 87.5, 82.5, 73.1, 59.2, 29.2, 22.8, 20.5; FAB−MS (NBA) *m/z* 640 $[M + 3]^+$, 639 $[M + 2]^+$, 638 $[M + 1]^+$, 637 M^+, 636 $[M - 1]^+$, 635 $[M - 2]^+$, 394 $[M - 3]^+$, 240 $[ABz + 1]^+$, 105 Bz^+; FAB−MS (NBA + KCl) *m/z* 678 $[M + 2 + K]^+$, 677 $[M + 1 + K]^+$, 676 $[M + K]^+$, 675 $[M - 1 + K]^+$, 674 $[M - 2 + K]^+$, 673 $[M - 3 + K]^+$, 672 $[M - 4 + K]^+$. Anal. Calcd for $C_{29}H_{27}N_5O_7Se$ [636.47]: C, 54.73; H, 4.28; N 11.00. Found: C, 55.20; H, 4.42; N 10.43.

9-(3-*C*-Phenylselenocarbonyl-β-D-xylofuranosyl)adenine (23). Selenol ester **22** (366 mg, 575 μmol) was dissolved in a solution of 5% HCl in EtOH (10 mL) and stirred for 5 h at 50 °C. During this time, a white precipitate appeared. The solvent was removed under reduced pressure, and the residue was dissolved in MeOH (8 mL) and treated with Et_2O (20 mL). The white precipitate formed was filtered off and washed several times with cold Et_2O. The filtrate was concentrated under reduced pressure and treated under the same conditions to obtain more precipitate. On the whole, 218 mg (78%) of selenol ester **23** was obtained in its hydrochloride form: $R_f = 0.15$ (CH_2Cl_2/EtOH 8:1); ^{1}H NMR (300 MHz, CD_3OD) (free amine) δ 8.31 (s, 1H), 8.24 (s, 1H), 7.53−7.37 (m, 5H), 5.97 (d, J = 3.9 Hz, 1H), 4.79 (d, J = 3.9 Hz, 1H), 4.44 (t, J = 4.4 Hz, 1H), 3.88 (d, J = 4.4 Hz, 2H); ^{1}H NMR (300 MHz, CD_3OD) (hydrochloride) δ 8.65 (s, 1H), 8.43 (s, 1H), 7.53−7.37 (m, 5H), 6.16 (d, J = 3.6 Hz, 1H), 4.71 (d, J = 3.5 Hz, 1H), 4.51 (t, J = 4.1 Hz, 1H), 3.96 (d, J = 4.1 Hz, 2H); ^{13}C NMR (75.5 MHz, CD_3OD) (hydrochloride) δ 205.1, 152.0, 149.7, 145.7, 143.9, 137.2, 130.2, 129.8, 127.9, 120.3, 91.1, 90.7, 84.8, 83.5, 61.5; FAB−MS (NBA) (free amine with $M^+ = 451$) *m/z* 454 $[M + 3]^+$, 453 $[M + 2]^+$, 452 $[M + 1]^+$, 451 M^+, 450 $[M - 1]^+$, 449 $[M - 2]^+$, 448 $[M - 3]^+$, 266 $[M - PhSeCO]^+$, 137 $[A + 2]^+$, 136 $[A + 1]^+$; FAB−MS (NBA + KCl) *m/z* 492 $[M + 2 + K]^+$, 490 $[M + K]^+$, 488 $[M - 2 + K]^+$; UV(MeOH) λ (ε) 206 (44 000), 261 (25 000), 300 (1500). Anal. Calcd for $C_{17}H_{17}N_5O_5Se \cdot HCl \cdot H_2O$ [504.78]: C, 40.45; H, 4.00; N, 13.87. Found: C, 40.37; H, 4.03; N, 14.13.

6-*N*-Benzoyl-9-(2-*O*-acetyl-3-*C*-phenylselenocarbonyl-β-D-xylofuranosyl)-adenine (24). Selenol ester **22** (355 mg, 558 μmol) was dissolved in 80% aqueous trifluoroacetic acid (5 mL) and stirred for 30 min at room temperature. After evaporation of the solvent under reduced pressure, the residue was coevaporated with toluene (2 × 10 mL) and then purified by FC (eluent: CH_2Cl_2/EtOH 20:1) to give 286

mg (86%) of selenol ester **24** as a yellowish precipitate: $R_f = 0.17$ (CH_2Cl_2/EtOH 20:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (broad s, 1H), 8.80 (s, 1H), 8.10 (s, 1H), 8.06−8.02 (m, 2H), 7.65−7.40 (m, 8H), 6.69 (broad s, 1H), 6.11 (d, $J = 5.2$ Hz, 1H), 5.98 (d, $J = 5.2$ Hz, 1H), 5.70−5.55 (broad s, 1H), 4.41 (t, $J = 2.6$ Hz, 1H), 4.10 (dd, $J =$ 13.2, 2.5 Hz, 1H), 4.00 (dd, $J = 13.0$, 1.9 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 204.3, 169.6, 164.9, 152.2, 150.5, 150.0, 142.5, 135.9, 133.2, 132.9, 129.3, 129.1, 128.8, 128.0, 125.8, 123.4, 88.2, 87.0, 83.0, 80.9, 61.1, 20.5; FAB−MS (NBA) *m/z* 601 [M + 4]$^+$, 600 [M + 3]$^+$, 599 [M + 2]$^+$, 598 [M + 1]$^+$, 597 M$^+$, 596 [M − 1]$^+$, 595 [M − 2]$^+$, 594 [M − 3]$^+$, 412 [M − PhSeCO]$^+$, 240 [ABz + 1]$^+$, 136 [A + 1]$^+$, 105 Bz$^+$; FAB−MS (NBA + KCl) *m/z* 639 [M + 3 + K]$^+$, 638 [M + 2 + K]$^+$, 637 [M + 1 + K]$^+$, 636 [M + K]$^+$, 635 [M − 1 + K]$^+$, 634 [M − 2 + K]$^+$, 633 [M − 3 + K]$^+$, 632 [M − 4 + K]$^+$.

Photolyses of the Radical Precursors. Irradiation experiments were carried out at 20 °C using either a Heraeus TQ-150 (150 W) Hg high-pressure lamp with Pyrex coating (lamp A) or an Osram (500 W) Hg high-pressure lamp with 320 nm filter (lamp B). The reaction mixtures were analyzed by ^{1}H-NMR; products were identified by comparison with authentic material or the known data for analogous compounds (references cited). Yields were determined by product isolation or from NMR spectra using internal standards (pentachloroethane or total integral of adenine protons).

Photolyses of Radical Precursor 23. A solution of selenol ester **23** (14.1 mg, 29.0 μmol) and Bu_3SnH (17 μL, 64 μmol) in 4 mL of CH_3OH was purged with argon for 10 min and subsequently irradiated for 2.5 h with lamp A. The solvent was removed in vacuo, and the products were purified by preparative TLC (eluent: CH_2Cl_2/EtOH 4:1). 7.3 mg (94%) of the reduction products **6** (xylo/ribo 3:1) were obtained as a white precipitate: $R_f = 0.19$ (CH_2Cl_2/EtOH 4:1); ^{1}H NMR (300 MHz, CD_3OD) (xylo-isomer[71]) δ 8.33 (s, 1H), 8.20 (s, 1H), 5.96 (d, J = 1.9 Hz, 1H), 4.46 (t, $J = 1.9$ Hz, 1H), 4.36−4.31 (m, 1H), 4.20 (dd, $J = 3.8$, 1.6 Hz, 1H), 3.96 (dd, $J = 11.9$, 4.6 Hz, 1H), 3.90 (dd, $J =$ 11.9, 6.1 Hz, 1H); (ribo-isomer) δ 8.30 (s, 1H), 8.17 (s, 1H), 5.96 (d, $J = 6.4$ Hz, 1H), 4.73 (dd, $J = 6.4$, 5.1 Hz, 1H), 4.31 (dd, $J = 5.2$, 2.5 Hz, 1H), 4.16 (q, $J = 2.5$ Hz, 1H), 3.88 (dd, $J = 12.5$, 2.5 Hz, 1H), 3.73 (dd, $J = 12.5$, 2.8 Hz, 1H).

A solution of selenol ester **23** (8.3 mg, 17.1 μmol) in 0.7 mL of CD_3OD was purged for 10 min with argon. ^{t}BuSH (2.9 μL, 26 μmol) was added, and the mixture was irradiated for 2.5 h using lamp B. The yield of reduction products **6** (selectively deuterated at C-3′) determined by ^{1}H-NMR analysis was 78% (xylo/ribo 4:1).

A solution of selenolester **23** (11.6 mg, 23.8 μmol) and Bu_6Sn_2 (13 μL, 25 μmol) in 4 mL of CH_3OH was purged with argon for 5 min and then irradiated with lamp A for 3 h. The solvent was removed in vacuo, and the residue analyzed by ^{1}H-NMR. Thirty-five percent of the reduction products **6** (xylo/ribo 3:1), 55% of adenine (**32**), and 10% of enolone **34** could be detected. Preparative TLC (eluent: CH_2Cl_2/EtOH 4:1) yielded 1.8 mg (57%) of adenine (**32**) and 2.2 mg (35%) of reduction products **6**. Compound **32**: $R_f = 0.22$ (CH_2Cl_2/EtOH 4:1); ^{1}H NMR (300 MHz, CD_3OD) δ 8.13 (s, 1H), 8.04 (s, 1H). Compound **34**:[42a,c] $R_f = 0.41$ (CH_2Cl_2/EtOH 12:1); ^{1}H NMR (300 MHz, CD_3OD) δ 8.54 (d, $J = 2.5$ Hz, 1H), 5.71 (d, $J = 2.5$ Hz, 1H), 4.53 (ddd, $J =$ 4.6, 3.0, 0.8 Hz, 1H), 3.97 (dd, $J = 12.5$, 2.9 Hz, 1H), 3.83 (dd, $J =$ 12.5, 4.5 Hz, 1H).

A solution of selenol ester **23** (8.0 mg, 16.4 μmol) and tin hydride **35** (40 μL, 85 μmol) in 5 mL of CH_3CN/H_2O (1:1) containing 0.1 M triethylammonium acetate buffer (TEAA buffer) was purged with argon for 10 min and irradiated for 5 min using lamp A. The solvent was evaporated in vacuo, and the residue was coevaporated with 5 mL of toluene. NMR analysis showed the formation of 14% of **6** (xylo/ribo 4:1), 80% of adenine (**32**), and 50% of enolone **34**.

Photolyses of Radical Precursor 24. A solution of selenol ester **24** (11.2 mg, 18.8 μmol) and Bu_3SnH (12.5 μL, 47.2 μmol) in 3 mL of CH_3OH was purged with argon for 10 min and irradiated with lamp A for 3 h. After evaporation of the solvent in vacuo, the crude reaction mixture was analyzed by ^{1}H-NMR. Besides 7% of the starting material, 84% of 6-*N*-benzoyladenine (**33**), 78% of enolone **34**, and 90% of AcOH could be detected. A second NMR spectrum, recorded after 2 h, revealed only 40% of **34**; the yields of the other products were unchanged. Compound **33**: $R_f = 0.31$ (CH_2Cl_2/EtOH 12:1); ^{1}H NMR (300 MHz, CD_3OD) δ 8.70 (s, 1H), 8.46 (s, 1H), 8.12−8.09 (m, 2H), 7.69−7.64 (m, 1H), 7.60−7.54 (m, 2H).

A repetition of the photolysis under the same conditions led to the formation of 67% of **33**, 41% of **34**, 88% of AcOH, and 15% of the 2′-deoxy-3′-ketonucleoside **31**. Compound **31**:[20b] ^{1}H NMR (300 MHz, CD_3OD) δ 8.70 (s, 1H), 8.66 (s, 1H), 8.11−8.06 (m, 2H), 7.67−7.51 (m, 3H), 6.81 (t, $J = 7.0$ Hz, 1H), 4.29 (t, $J = 3.0$ Hz, 1H), 3.89−3.86 (m, 2H), 3.30 (m, 2H).

A solution of **24** (10.0 mg, 16.7 μmol) and Bu_3SnD (11.1 μL, 41.9 μmol) in 0.7 mL of CD_3OD was purged with argon for 10 min and irradiated with lamp A for 3 h. The following products could be detected by ^{1}H-NMR: 27% of 6-*N*-benzoyladenine (**33**), 25% of enolone **34** (52% deuterated at C-3 as judged by GC/MS), 92% of AcOH, and 52% of the 2′-deoxy-3′-ketonucleoside **31** (>90% mono-deuterated at C-2′).

A solution of **24** (13.2 mg, 22.1 μmol) in 0.7 mL of CD_3OD was purged for 10 min with argon. ^{t}BuSH (5.0 μL, 45 μmol) was added, and the mixture was irradiated for 3 h using lamp B. The NMR analysis showed the formation of 70% of 6-*N*-benzoyladenine (**33**), 54% of enolone **34** (ca. 40% deuterated at C-3), 50% AcOH, and 9% of direct reduction product **27**, exclusively with xylo configuration and > 80% deuterated at C-3′. Compound **27**: ^{1}H NMR (300 MHz, CD_3OD) δ 8.68 (s, 1H), 8.66 (s, 1H), 8.09−8.06 (m, 2H), 7.67−7.51 (m, 3H), 6.29 (d, $J = 1.7$ Hz, 1H), 5.39 (t, $J = 1.8$ Hz, 1H), 4.32 (dd, $J = 5.9$, 4.8 Hz, 1H), 3.99 (dd, $J = 11.8$, 4.9 Hz, 1H), 3,94 (dd, $J = 11.9$, 5.9 Hz, 1H), 2.15 (s, 3H).

Competition Kinetic Experiments with Radical Precursor 23. Indirect kinetic studies involved conventional competition experiments.[72] They were performed at 20 °C with CH_3CN/H_2O 1:1 as solvent and with tin hydride **35** as radical trap. The product ratio [**32**]/[**6**] was determined by analytical HPLC (Merck Lichrospher 100, RP 18 (5 μm), 250 mm × 4 mm, 25 °C) at 254 nm. Solvents: A: 20 mM TEAA buffer, B: CH_3CN. Gradient: A/B: 98/2(2 min)−13 min−85/15−10 min−0/100(10 min). Retention times: 9.2 min (**32**, correspondence factor: 13.32 mM/AU), 11.3 min (**6** ribo isomer, correspondence factor: 14.62 mM/AU), 10.5 min (**6** xylo isomer).

In a typical experiment, selenol ester **23** (3 mM) and an excess of tin hydride **35** (20−150 mM, freshly prepared from the corresponding tin bromide[47]) were dissolved under argon in 1.0 mL of degassed CH_3CN/H_2O 1:1, containing the buffer stated, and subsequently irradiated for 5 min with lamp A (see photolyses). The reaction mixture (0.1 mL) was diluted with 0.9 mL of H_2O and directly analyzed by HPLC.

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