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The effect of the base in the fragmentation of nucleotide C4′ radicals

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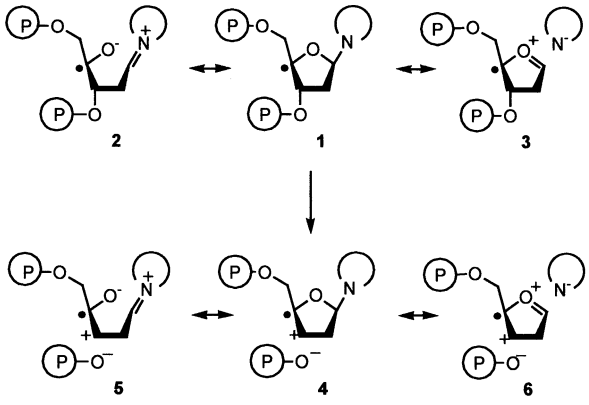
Abstract—A series of 3′-*O*-diethylphosphoryl-4′-α-[(2-halophenylethylthio)carbonyl] substituted esters of thymidine, cytidine, adenosine and guanosine are prepared by total synthesis and used as C4′-radical precursors in a competition kinetic method using tributyltin hydride as the reductant. The pseudo-first order rate constants for the C4′-radicals so generated decrease in the order guansoine>cytidine>adenosine>thymidine with that for guanosine being too rapid for determination by the present competition kinetic method. A ^{119}Sn NMR method is presented for estimation of the purity of tin hydride solutions.

1. Introduction

The chemistry of nucleotide C4′ radicals is an area that continues to attract much attention. This is because of (i) the central importance of these radicals in the degradation of DNA by antitumor antibiotics such as the bleomycins[1–7] and the enediynes,[8–10] and (ii) the use of such radicals as precursors to C3′,C4′ radical cations,[11,12] 'hole' generators[13,14] for the study of electron transfer in DNA. Strong evidence has been provided for the fragmentation of nucleotide C4′ radicals, with the expulsion of the C3′ phosphate, into C3′,C4′ radical cations even in non-polar solvents.[15] One area of particular interest to this laboratory has been the effect of substituents, notably the 2′-C–O bond in the ribonucleotides[15,16] and the base in general,[17] on the rate of fragmentation of C4′ radicals. Here we report on the effect of the base on the kinetics of fragmentation as determined by competition methods.

The substituent at the C1′ position of nucleotide C4′ radicals is conjugated to that radical via the ring oxygen and similarly, after fragmentation, to the radical cation as illustrated in Scheme 1. Any substituent at the C1′ position therefore affects the stability of both the radical and the radical cation, not necessarily in the same extent or even direction, and consequently has an effect on the rate of fragmentation.

Previously we attempted a qualitative interpretation of this effect through a method for C4′ radical generation involving thiyl radical addition to exocyclic 4′,5′ glycals,[17] an instrument first applied by the Giese group in their initial studies on nucleotide C4′ radical generation.[18] Later work[15] demonstrating the sensitivity of this method to multiple factors including the choice of thiol and initiator, as well as the concentrations of both, has led us to revisit this area using more quantitative, less fickle methods. Specifically, we intended to use the decarbonylation of nucleotide C4′ acyl radicals, generated from thiol esters as a means of entry into the C4′ radical suitable for use in standard competition kinetic methods. The application of such chemistry was hindered by the lack of methods for the preparation of nucleotide C4′ carboxylate derivatives compatible with the sensitive purine bases, with the existing routes involving functionalization of nucleosides at the C4′ position being limited to the more robust thymidine.[19–24] This problem was solved through the development of an efficient asymmetric synthesis of a C4′ carboxyl system, from tartaric acid, that permits the introduction of any requisite base at the end of the sequence.[25,26] 2-(2-Halophenyl)ethylthiol esters[27] were



Scheme 1. Resonance forms of C4′ radicals and the derived radical cations.

Keywords: radicals and radical reactions; kinetics; nucleotides; tin and compounds.

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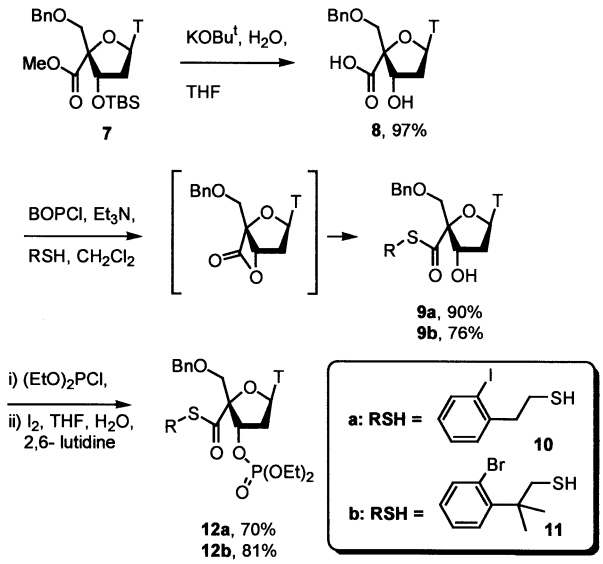
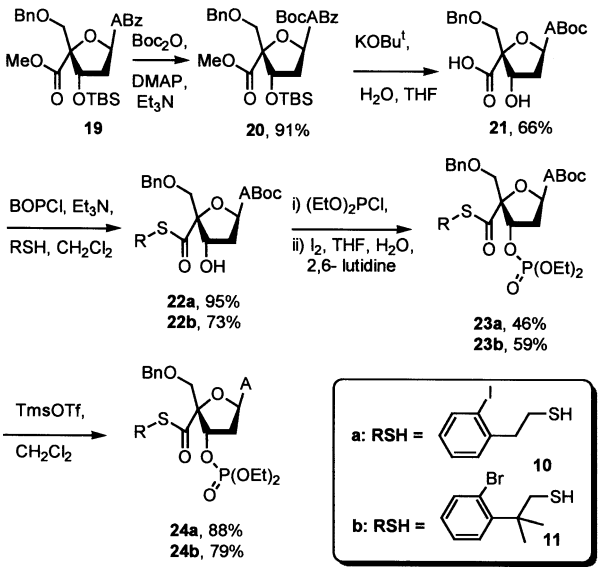


Scheme 2. Preparation of thymidine radical precursors.

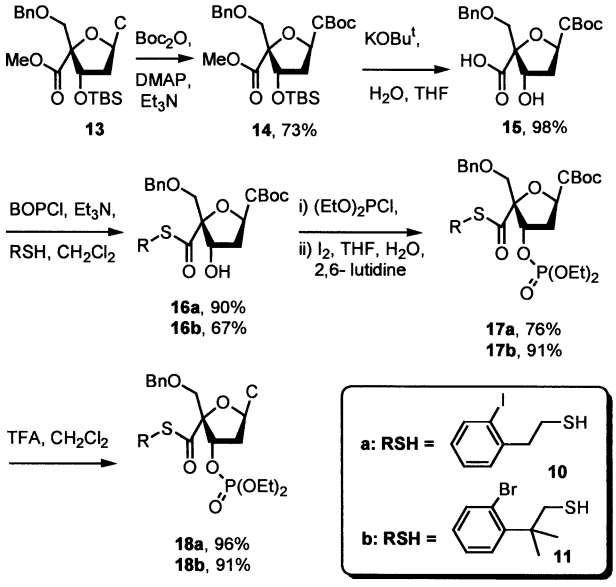


Scheme 4. Preparation of adenosine radical precursors.

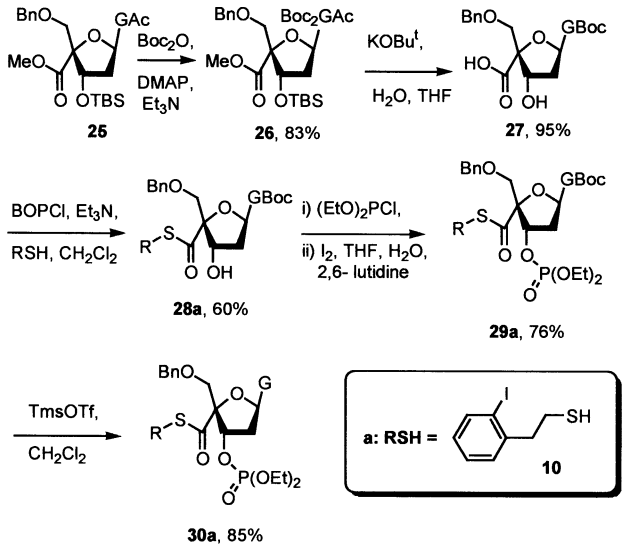
chosen as the precursors of choice for the acyl radical as they had been previously shown[20] to be compatible with the oxidizing conditions of the phosphoramidite method for introduction of the phosphate group and, unlike simple thiol esters, cleanly provide acyl radicals on treatment with tributyltin hydride and AIBN.[27] The decarbonylation of acyl radicals to give α-alkoxy-tertiary radicals was judged to be sufficiently rapid[28] as not to be a complicating factor in the kinetics of the heterolytic fragmentation of the C4′ radicals.

2. Synthesis of precursors

We began with the synthesis of the four systems in Schemes 2–5. The thymidine series (Scheme 2) was most straightforward and began with **7**, itself obtained by synthesis from tartaric acid.[26] Exposure to potassium *tert*-butoxide in aqueous THF brought about saponification of the hindered ester and concomitant removal of the silyl protecting group to give **8**. This was converted to the thiol esters **9a** and **b** by treatment with BOPCl and 2-(2-iodophenyl)ethyl thiol (**10**) or 2-(2-bromophenyl)-2-methylpropyl thiol (**11**), respectively. These esterifications proceed via the β-lactone, which may be isolated when the coupling is conducted at room temperature. However, for convenience sake, they were normally conducted in dichloromethane at reflux; then the lactone is opened smoothly by the thiol to give the anticipated esters. Finally, phosphorylation was achieved with diethylchlorophosphite followed by iodine oxidation. In the more sensitive cytidine, adenosine and guanosine series the basic nitrogen was protected in the form of the *tert*-butyloxycarbonyl derivative, which demanded an extra deprotection at the end of the series, with either trifluoroacetic acid or trimethylsilyl triflate. In the adenosine and guanosine series, because the synthetic material (**19** and **25**) was obtained with amide protection of



Scheme 3. Preparation of cytidine radical precursors.



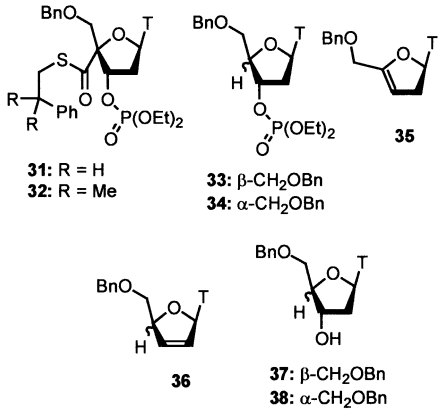
Scheme 5. Preparation of a guanosine radical precursor.

the base, treatment with Boc_2O afforded imides (**20** and **26**) which were selectively cleaved to the carbamates (**21** and **27**) in the course of the ester hydrolysis. In the thymidine, cytidine and adenosine series both 2-(2-iodophenyl)ethyl thiol and 2-(2-bromophenyl)-2-methylpropyl thiol were employed in the synthesis of thiol esters but only the former was used in the guanosine series. 2-(2-Iodophenyl)ethyl thiol (**10**) was prepared as previously described,[27] whereas 2-(2-bromophenyl)-2-methylpropylthiol (**11**) was obtained from 2-(2-bromophenyl)-2-methylpropanol[27] by Mitsunobu reaction with thiolacetic acid followed by DIBALH reduction. In the case of **11** the bromide was preferred over the corresponding iodide, a known compound,[27] because of the simpler preparation it afforded.

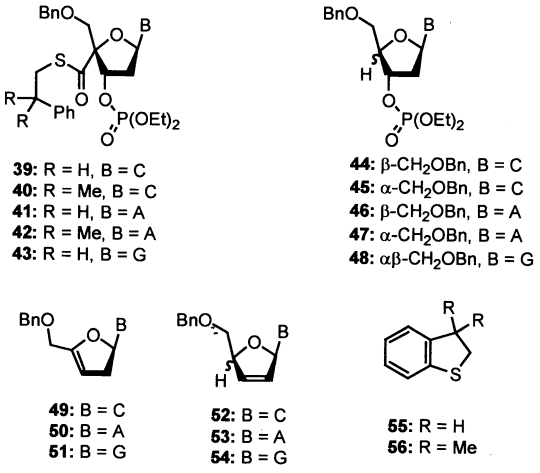
3. Product identification

In view of the small scale on which the kinetic runs were conducted and the complexity of some of the reaction mixtures, no attempt was made to quantify the various products other than the phosphates. However, at the end of a series of kinetic runs, all reaction mixtures for a particular base were combined and the products isolated by silica gel chromatography and their structures elucidated.

In the thymidine series the only substances isolated were the dehalogenated products **31** and **32**, and the stereoisomers **33** and **34** arising from radical decarbonylation. Neither the 3′,4′-(**35**) nor the 2′,3′-glycal (**36**) were isolated from this series. The stereochemistry of the reduced products (**33**) and (**34**) was assigned by NOESY correlations: in particular between the thymine vinylic hydrogen and H3′ and H5′ in **33** and between the same vinylic hydrogen and H4′ in **34**. A further NOESY correlation between H's 1′ and 4′ in **33** supported these assignments. Further confirmation of these structures was obtained by treatment of compound **9a** with tributyltin hydride and AIBN leading to a separable 1/2 mixture of the nucleosides **37** and **38**. Compound **37** obtained in this manner was identical to an authentic sample,[29] while **37** and **38** provided the anticipated phosphate, **33** or **34**, respectively, on treatment with butyllithium and then diethylphosphoryl chloride. As the ^1H NMR spectra of **37** and **38** were quite distinct and as a clear trend emerged in the ^1H NMR spectra, the stereochemistry of the corresponding products in subsequent series was assigned by analogy and occasional confirmatory NOESY measurements.



In the cytidine series both dehalogenated products (**39**) and (**40**), both reduction products (**44**) and (**45**) and both glycals (**49**) and (**52**) were isolated and characterized. In the adenosine series the product spectrum was comparable to that in the thymidine series with dehalogenation products (**41**) and (**42**) as well as reduction products (**46**) and (**47**) being isolated and identified while the glycals **50** and **53** were not found. Finally, the guanosine **30a** provided the dehalogenation product (**43**), and the glycal **51**, but neither the reduction products (**48**), nor the isomeric glycal **54**. Depending on the thiol ester employed, one or the other of the known[27] dihydrobenzothiophenes **55** and **56** was evident in the crude reaction mixtures from all kinetic runs, however in view of the relatively high volatility of these products no attempt was made at their isolation or quantification.

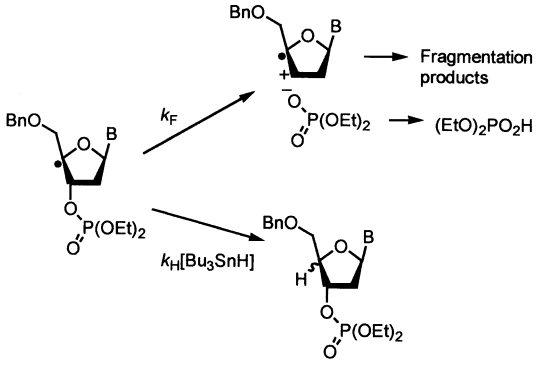


4. Kinetic method and analysis

It was anticipated that the standard tributyltin hydride competition method[30,31] for the determination of the kinetics of radical rearrangements could be adapted to the fragmentations of interest (Scheme 6).

Thus, the rate constant for fragmentation k_F was expected to be available from Eq. (1) provided that pseudo first order conditions in tin hydride are maintained.

$$\frac{\sum(\text{Fragmentation products})}{\sum(\text{Reduction products})} = \frac{k_F}{k_H[Bu_3SnH]} \quad (1)$$



Scheme 6. Competition kinetics.

However, it soon became apparent that the ^{1}H NMR spectra of the crude reaction mixtures were too complex to permit the accurate determination of product ratios by integration. Moreover, the anticipated primary fragmentation products, the 3′,4′-unsaturated-3′-deoxynucleosides, could not be isolated in all cases and were not immediately obvious in the product mixtures. Attention was therefore focused on the less convoluted ^{31}P NMR spectra and the use of Eq. (2) for the extraction of k_F in which protocol the sum of all fragmentation products is simply assayed as diethylphosphoric acid.

$$\frac{[(EtO)_2PO_2H)]}{\sum(\text{Reduced phosphates})} = \frac{k_F}{k_H[Bu_3SnH]} \quad (2)$$

As the project progressed, it became apparent that large excesses of tributyltin hydride, necessary for the uncritical application of pseudo-first order kinetic analyses, such as in Eqs. (1) and (2), could not be employed owing to the deleterious competing reaction of quenching of the initial aryl radical, particularly with the precursors derived from the simple, as opposed to *gem*-dimethylated, thiol esters. We therefore required a method of checking both the purity of the initial tin hydride employed and the extent of its consumption in the course of the reaction. The purity of tributyltin hydride can be crudely assayed from the relative intensity of the Sn–H resonance in the ^{1}H NMR spectrum or that of the Sn–H stretch in the IR spectrum. However, these approaches were considered to be neither sufficiently accurate for our purposes nor suitable to dosage of the residual tin hydride in the final reaction mixtures. Similarly, the protonolysis of tin hydrides with dichloroacetic acid, with measurement of the evolved hydrogen,[32] a method used even relatively recently,[33] was considered insufficient also on the grounds of accuracy on a small scale and incompatibility with reaction mixtures. We therefore turned to ^{119}Sn NMR spectroscopy[34,35] and the use of an internal standard. Trimethylphenyltin (Me_3SnPh, δ −29.2), for which we determined T_1 to be 1.2 s by the inversion recovery method, was selected for this purpose. Tributyltin hydride itself (δ −88.2) has a T_1 of 1.8 s, thus it was determined that the integration of ^{119}Sn NMR spectra recorded with a relaxation delay of 6 s should be sufficient for quantification of the Me_3SnPh/Bu_3SnH ratio in any given sample before and after the radical reaction. In the event a 4/1 (mol/mol) mixture of a fresh commercial sample of Bu_3SnH and Me_3SnPh was prepared, stored under Ar, and used for all kinetic analyses. ^{119}Sn NMR of the freshly prepared mixture showed an initial ratio of 3.69/1 Bu_3SnH/Me_3SnPh as well as several other peaks consistent with up to 10% contamination of the initial tin hydride, perhaps by Bu_3SnOH and $(Bu_3Sn)_2O$. A correction factor of 0.92, which takes into account the added Me_3SnPh and the impurities, was therefore applied when calculating tin hydride concentrations.

Initial experiments were carried out with the esters **12a**, **18a**, **24a**, and **30a**. Ideally, the kinetic runs should be carried out in water, or at least a mixed aqueous solvent, to best approximate the conditions pertaining in nature. However, in methanol, and in THF, it was found that the fragmentation was so rapid as to preclude the formation of the reduction production. When the Bu_3SnH concentration was raised to a level appropriate for trapping the C4′ radical in these solvents the only products obtained were those of simple dehalogenation of the substrates, namely **31**, **39**, **41** and **43**. It was necessary therefore to go to a less polar solvent to retard the fragmentations and permit the competitive trapping of the C4′ radicals by a lower concentration of stannane. Benzene was not suitable for solubility reasons and dichloromethane, which dissolved all the substrates, was inappropriate because of its reaction with tin hydrides. Eventually, a series of reactions were conducted in 1,2-dichloroethane as it not only dissolved all the substrates but was also shown in control experiments not to react with Bu_3SnH under the reaction conditions. Unfortunately, even under these conditons, although fragmentation and trapping of C4′ radicals were both evident, the simple dehalogenation products were still formed to a high degree and put us in the undesirable position of attempting to quantify several minor peaks against a background of the major resonance from the dehalogenation product, even in the ^{31}P NMR spectrum. Nevertheless, it was qualitatively evident that the fragmentation of the cytidine radical was somewhat faster than that of the adenosine and thymidine radicals, which had comparable speeds. Fragmentation of the guanosine C4′ radical was significantly faster to the extent that the reduction product(s) **48** was still not formed in anything but trace quantities. In view of the multiple imperfections with this system esters **12a**, **18a**, **24a**, and **30a** were not pursued further. Rather attention was focused on the *gem*-dimethyl series **12b**, **18b**, and **24b** in the hope that the accelerated closure of the aryl radical onto the thiol ester[27] would permit the use of higher concentrations of stannane while minimizing the problematic dehalogenation products and at the same time enabling the use of more polar solvents. The inability to locate a significant amount of **48** from **30a** even in non-polar dichloroethane, however, discouraged us from further work in the G series, especially in more polar solvents. Kinetic studies were eventually carried out with tributyltin hydride under pseudo-first order conditions in THF as solvent at 25°C with initiation by photolysis. Five runs were conducted for each of the esters **12b**, **18b**, and **24b** with incremental increases in the amount of stannane employed from 8 to 16 equiv. Inspection of the ^{119}Sn NMR spectra before and after the irradiation, with the help of the aforementioned Me_3SnPh internal standard, revealed that 3 equiv. of stannane were consumed typically and therefore that pseudo-first order analysis was appropriate. The three molar equivalents of stannane consumed in these reactions presumably arise one each from the radical process, the neutralization of the diethylphosphate produced, and interaction with an N–H bond of the base. The plots of stannane concentration versus the ratio of total reduced produced product/fragmentation product, as derived from the ^{31}P NMR spectra, are given for all three substrates in Fig. 1. The linear nature of these plots confirms the validity of the pseudo first order assumption and therefore the rate constants for fragmentation were extracted using Eq. (2) and a value of $3.5\times10^5\ M^{-1}\ s^{-1}$ (25°C) as the rate constant for the trapping reaction by tributyltin hydride. This number is the literature value[36] for the trapping of α-alkoxyalkyl radicals by tin hydride in THF: the reasonable assumption is that the presence of the base will not have a significant effect on this trapping reaction.

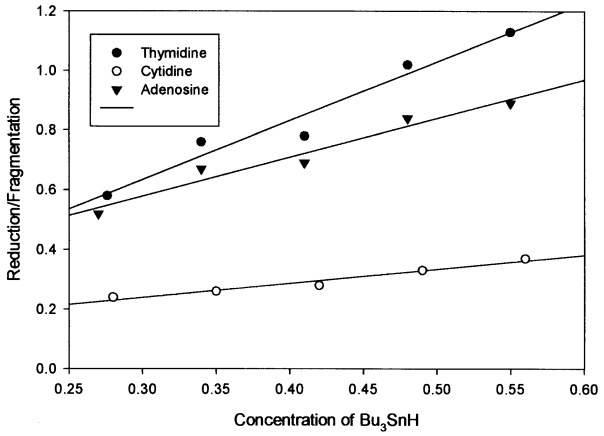


Figure 1. Plot of the reduction/fragmentation ratio against tin hydride concentration for the three bases.

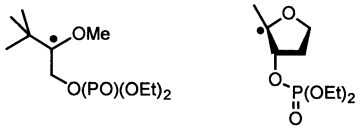
Table 1. Rate constants for the cleavage of C4′ radicals in THF solution

Substrate	Base	k_{Frag} (s^{-1})[a]
12b	T	$1.79\pm0.46\times10^5$ s^{-1}
18b	C	$7.29\pm1.89\times10^5$ s^{-1}
24b	A	$2.65\pm0.67\times10^5$ s^{-1}
57[b]	–	$2.0\pm0.2\times10^6$ s^{-1}
58[c]	–	$>3\times10^9$ s^{-1}

[a] Errors are at the 95% confidence interval (2.8σ).
[b] Acetonitrile plus 4.5% trifluoroethanol at 23°C.[11]
[c] Methanol at 25°C.[12]

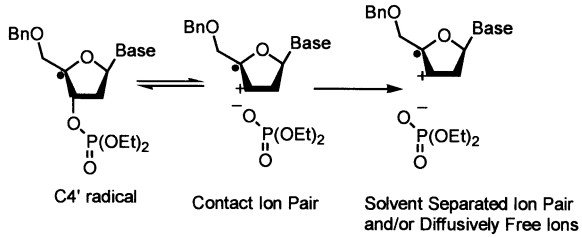
5. Discussion

As is evident from Fig. 1 and Table 1, the base does indeed have an effect on the observed rate of fragmentation of nucleotide C4′ radicals, with the fragmentation of the cytidine-based system being approximately four fold more efficient than that of the thymidine one, with adenosine fragmentation being marginally faster than that of thymidine. Although we have not been able to quantify it the fragmentation of the guanosine, as noted from the preliminary screening studies, is significantly faster than all of these three. For the purposes of comparison and discussion Table 1 also includes the literature values for the fragmentations of two model radicals **57** and **58**.[11,12]



57 **58**

We began with the premise that the conjugation of the C4′ radical to the base (Scheme 1) must lead to a dependence of the rate of fragmentation on the nature of the base. While this remains true, rationalization of the experimental results must now take into account the far more complex picture of C4′ radical fragmentation that has emerged since this work was initiated. Specifically, we have recently shown that (i) the C4′ radical is in equilibrium with the contact ion pair derived by fragmentation; (ii) the recombination of the contact ion pair is so rapid as to preclude scrambling of the non-esterified oxygens in the phosphate; (iii) that the



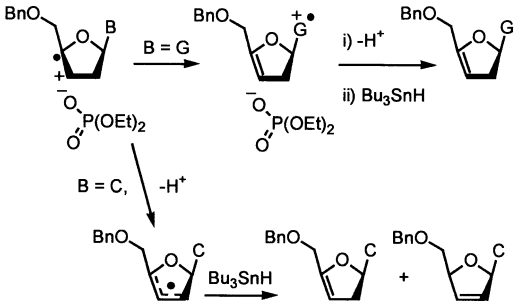
Scheme 7. Relationships between C4′ radicals, contact ion pairs and solvent-separated ion pairs.

contact ion pair may be trapped, even in benzene, with a suitably placed internal nucleophile; and (iv) escape from the contact ion pair is irreversible (Scheme 7).[15]

The very large difference in rates of fragmentation of the model radicals **57** and **58**, in spite of their very similar structures and the close concordance of solvents employed on the E_T30 scale was interpreted in terms of the different kinetic methods used and, more especially, the point in the reaction scheme at which those methods acted. In effect, radical **57** was generated in a time-resolved laser flash photolysis experiment and the fragmentation determined by diffusion controlled oxidation of a triarylamine reporter by the product radical cation. Importantly, this method detects the diffusively free radical cations and the measured rate constant therefore contains both the equilibrium constant for contact ion pair generation and the rate constant for cage escape.[12] On the other hand the rate constant for fragmentation of **58** was determined[11] by classical tin hydride competition kinetics with, as we have suggested,[12] the radical cation being removed from the contact ion pair by nucleophilic trapping by the methanol solvent. The observed rate constant for the fragmentation of **58** therefore does not contain a component from cage escape and is more likely a true measure of the actual initial rate of fragmentation.

With this in mind, it is evident that the much more rapid observed fragmentation in the guanosine series is likely the result of interception of the C3′C4′ radical cation within the contact ion pair. The mechanism of this interception evidently involves intramolecular oxidation of the guanine residue by the enol ether radical cation. This provides a base radical cation, likely to undergo deprotonation to the base radical and then reduction by the stannane to give the ultimate observed product (**51**). This explanation is fully in accord with the rate constant of $>1\times10^9$ M^{-1} s^{-1} for the *intermolecular* oxidation of dG by various enol ether radical cations,[14] and with Giese's elegant use of C3′C4′ radical cations as hole injection points for DNA electron transfer studies.[13]

Following a similar logic it is evident that the rate constants measured for the thymidine, cytidine, and adenosine series here do not involve rapid trapping reactions on or within the contact ion pair and therefore presumably do represent to some extent the influence of the base on the C4′ radical and on the derived radical cation (Scheme 1). The three plots in Fig. 1 pass close to but not through the origin. This implies[31] reversibility of the rate determining first order process, namely fragementation of the C4′ radical to the contact

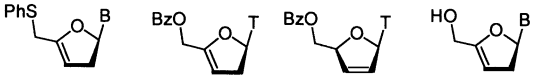


Scheme 8. Base dependent modes of glycal formation.

ion pair. Such a result is fully consistent with our earlier demonstration[15] of the rapid reversibility of this fragmentation.

It is of some interest that the glycal products are only observed in the G and C series. For G, as noted above, the enol ether results directly from oxidation of the base by the enol ether radical cation. For C such oxidation is unlikely and would not account for the mixture of regioisomers (**49** and **52**) formed. Most likely deprotonation of the enol ether radical cation, by either the heterocycle or the expelled diethyl phosphate, to give an allyl radical followed by trapping by the stannane is the answer here (Scheme 8).

The failure to isolate the glycal in the T series is in accord with earlier work by Giese when it was attributed to instability.[37] Presumably, the same logic pertains to our inability to isolate the A-derived glycals **50** and/or **53**. This apparent effect of the base on the stability of the glycals is not surprising when interpreted in terms of the conjugation of the base to the enol ether itself, similar to Scheme 1, and its consequent effect on protonation. Subtle effects of substituents on the stability of related glycals have previously been observed. Thus, although able to detect **59**–**63** in crude reaction mixtures, we were previously only able to isolate **63** and, whereas **35** and **36** have so far eluded us we previously experienced no difficulty in isolating and characterizing[20] the analogs **64** and **65** in which the 'arming'[38] 5′-*O*-benzyl ether is replaced by a 'disarming'[38] 5′-*O*-benzoate. The unprotected thymidine and guanosine glycals **66** and **67** have been prepared by an unambiguous routes.[39]



59: B = C
60: B = A
61: B = G
62: B = T
63: B = ABz

64 **65**

66: B = T
67: B = G

6. Experimental[40]

6.1. General protocols

6.1.1. *S*-2-(2-Bromophenyl)-2-methylpropyl thioacetate. To a solution of 2-(2-bromophenyl)-2-methylpropanol[27] (5.1 g, 22.3 mmol) and PPh_3 (11.7 g, 44.6 mmol) in THF (200 mL) was added dropwise DEAD (7.0 mL, 44.6 mmol). After the addition was complete, the reaction mixture was stirred for 2 h before thioacetic acid (6.4 mL, 89.2 mmol) was slowly introduced. After 16 h stirring, the reaction mixture was concentrated under reduced pressure and hexane (600 mL) was added, and the resulting precipitate was removed by filtration. The filtrate was kept in a refrigerator overnight and the resulting precipitate was removed by filtration. Removal of solvent followed by column chromatography on silica gel (eluent: hexane/CH_2Cl_2, 2:1) gave the title thiol ester (4.2 g, 77%) as an oil. ^{1}H NMR δ: 1.55 (s, 6H), 2.28 (s, 3H), 3.72 (s, 2H), 7.05–7.61 (m, 4H); ^{13}C NMR δ: 28.1, 31.0, 39.2, 40.8, 122.8, 127.7, 128.6, 129.6, 136.3, 144.6, 196.0. Anal. calcd for $C_{12}H_{15}BrOS$: C, 50.18; H, 5.26. Found: C, 50.43; H, 5.22.

6.1.2. 2-(2-Bromophenyl)-2-methylpropanethiol (11). To a solution of *S*-2-(2-bromophenyl)-2-methylpropylthiolacetate (4.1 g, 14.3 mmol) in Et_2O (200 mL) cooled to −78°C under Ar was slowly added DIBALH (23.8 mL, 35.7 mmol, 1.5 M in toluene). After the addition was complete, the reaction mixture was slowly warmed to 0°C over 0.5 h and then quenched with 3N HCl. The organic layer was separated, washed with water and brine and dried ($MgSO_4$). Removal of solvent followed by column chromatography on silica gel (eluent: hexane/CH_2Cl_2, 9:1) gave **11** (3.3 g, 96%) as a colorless oil. ^{1}H NMR δ: 0.97 (t, J=8.8 Hz, 1H), 1.57 (s, 6H), 3.25 (d, J=8.8 Hz, 2H), 7.05–7.62 (m, 4H); ^{13}C NMR δ: 28.0, 35.0, 42.1, 122.6, 127.7, 128.5, 130.4, 136.1, 144.3. Anal. calcd for $C_{10}H_{13}BrS$: C, 48.99; H, 5.34. Found: C, 49.12; H, 5.38.

6.2. General procedure for the preparation of thiolesters

To a mixture of the acid (0.62 mmol), Et_3N (0.36 mL, 2.6 mmol) and thiol **10**[27] or **11** (2–10 equiv.) in THF (10 mL) was added BOP–Cl (396 mg, 0.64 mmol). The reaction mixture was heated to reflux under Ar for 2 h before removal of the solvent. Column chromatography on silica gel gave the product as white foam.

6.3. General procedure for the preparation of diethyl phosphates

To a solution of substrate (0.24 mmol) and DMAP (250 mg, 2.2 mmol) in CH_2Cl_2 (5 mL) at 0°C was added $(EtO)_2PCl$ (188 μL, 1.3 mmol). The reaction mixture was stirred at 0°C until TLC showed the disappearance of the starting material. Then a solution of I_2 (0.5 M) in THF/H_2O/2,6-lutidine (4:1:1) was added dropwise until the brown color persisted. Stirring was continued for another 20 min before the reaction was quenched with $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). Removal of solvent followed by column chromatography on silica gel gave the product as white foam.

6.4. General procedure for the saponification of 4′-esters in the presence of *N*-Boc groups

To a solution of substrate (1.1 mmol) and water (0.13 mL, 7.2 mmol) in THF (25 mL) at room temperature was added $KOBu^t$ (2.29 g, 20.4 mmol) in one portion after which the reaction mixture was stirred at room temperature overnight.

Then water (10 mL) was added and the mixture was further stirred for 2 h. The reaction mixture was neutralized to pH 7 and the solvent was removed under reduced pressure. The residue was extracted with EtOAc (3×50 mL) and the combined organic layers were washed with water, then brine and dried (Na_2SO_4). Column chromatography on silica gel gave the product as white solid.

6.5. Preparation of thymidine radical precursors

6.5.1. 5′-*O*-Benzyl-4′α-carboxyl-2′-deoxythymidine (8). To a solution of **7**[26] (470 mg, 0.93 mmol) in THF (10 mL) containing water (21 μL, 1.2 mmol) was added $KOBu^t$ powder (464 mg, 4.1 mmol). After stirring overnight, the solvent was removed under reduced pressure and the residue was diluted with water (5 mL) and extracted with ether (3×2 mL). The water layer was neutralized with 3N HCl to Congo red and the resulting white solid was filtered, washed with cold water and dried under vacuum (326 mg, 93%). Mp 247–250°C; $[\alpha]_D^{20}$=+13.6 (*c*, 1.0, DMSO); ^{1}H NMR δ: 1.47 (s, 3H), 2.23 (t, *J*=6.9 Hz, 2H), 3.84 (d, *J*=10.4 Hz, 1H), 3.89 (d, *J*=10.5 Hz, 1H), 4.51–4.63 (m, 3H), 6.39 (t, *J*=6.5 Hz, 1H), 7.31–7.35 (m, 5H), 7.50 (s, 1H), 11.34 (s, 1H); ^{13}C NMR (DMSO) δ: 11.9, 71.4, 71.7, 72.8, 84.3, 90.1, 109.7, 127.5 (2×C), 127.7, 128.4 (2×C), 136.0, 138.1, 150.4, 163.7, 171.2. Anal. calcd for $C_{18}H_{20}N_2O_7{\cdot}0.5H_2O$: C, 56.76, H, 5.42. Found: C, 56.69, H, 5.39.

6.5.2. 5′-*O*-Benzyl-2′-deoxy-4′α-[(2-iodophenylethylthio)-carbonyl]thymidine (9a). It was prepared from acid **8** and **10** in 90% yield. $[\alpha]_D^{20}$=+12.8 (*c*, 1.2, $CHCl_3$); ^{1}H NMR δ: 1.63 (s, 3H), 2.32–2.40 (m, 2H), 2.94–3.00 (m, 2H), 3.09–3.13 (m, 2H), 3.71 (d, *J*=10.0 Hz, 1H), 3.86 (d, *J*=10.0 Hz, 1H), 4.57 (d, *J*=11.7 Hz, 1H), 4.62 (d, *J*=11.7 Hz, 1H), 4.67–4.74 (m, 1H), 6.70 (dd, *J*=8.7, 5.9 Hz, 1H), 6.88–6.93 (m, 1H), 7.23–7.38 (m, 7H), 7.58 (s, 1H), 7.80 (d, *J*=7.7 Hz, 1H), 8.35 (br, s, 1H); ^{13}C NMR δ: 12.2, 28.3, 40.0, 40.3, 52.1, 72.6, 73.9, 74.9, 86.0, 96.3, 100.3, 111.5, 127.6, 128.2, 128.7, 130.1, 135.8, 136.8, 139.4, 142.2, 150.5, 164.1. Anal. calcd for $C_{26}H_{27}IN_2O_6S$: C, 50.17, H, 4.37. Found: C, 50.32, H, 4.44.

6.5.3. 5′-*O*-Benzyl-4′α-[(2-(2-bromophenyl)-2-methyl-propylthio)carbonyl]-2′-deoxythymidine (9b). It was prepared from acid **8** and **11** in 76% yield. $[\alpha]_D^{20}$=+15.1 (*c*, 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.56 (s, 6H), 1.61 (s, 3H), 2.28–2.42 (m, 2H), 3.07 (b, 1H), 3.63–3.75 (m, 3H), 3.88 (d, *J*=10.1 Hz, 1H), 4.54 (d, *J*=11.6 Hz, 1H), 4.60 (d, *J*=11.6 Hz, 1H), 4.67–4.69 (m, 1H), 6.62–6.67 (m, 1H), 7.01–7.06 (m, 1H), 7.21–7.37 (m, 7H), 7.55–7.59 (m, 2H), 9.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 12.3, 27.8, 28.0, 38.4, 40.4, 40.5, 73.0, 74.1, 75.0, 86.3, 96.7, 111.5, 122.6, 127.6, 127.8, 128.45, 128.51, 128.9, 129.4, 136.0, 137.1, 144.0, 150.6, 164.2; HRMS calcd for $C_{28}H_{31}BrNaN_2O_6S$: 625.0984. Found: 625.0994 $[M+Na]^+$.

6.5.4. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-[(2-iodophenylethylthio)carbonyl]thymidine (12a). It was prepared by the general phosphorylation method in 70% yield. $[\alpha]_D^{20}$=+7.5 (*c*, 1.2, $CHCl_3$); ^{1}H NMR δ: 1.25–1.36 (m, 6H), 1.58 (s, 3H), 2.34–2.46 (m, 1H), 2.61–2.67 (m, 1H), 2.94–3.06 (m, 4H), 3.74 (d, *J*=10.2 Hz, 1H), 4.01–4.16 (m, 5H), 4.54 (d, *J*=11.3 Hz, 1H), 4.67 (d, *J*=11.3 Hz, 1H), 5.29 (t, *J*=5.6 Hz, 1H), 6.72 (q, *J*=5.3 Hz, 1H), 6.89–6.93 (m, 1H), 7.26–7.38 (m, 7H), 7.53 (s, 1H), 7.81 (d, *J*=7.8 Hz, 1H), 8.33 (s, 1H); ^{13}C NMR δ: 12.3, 16.2, 16.3, 28.6, 39.6, 40.3, 64.5, 64.6, 72.7, 74.3, 78.9, 79.9, 85.6, 94.4, 94.5, 101.0, 111.9, 127.9, 128.7, 129.0, 130.2, 135.4, 136.7, 139.8, 142.5, 150.5, 163.8; ^{31}P NMR δ: −4.17; ESIMS, *m/z*: 781 $[M+Na]^+$.

6.5.5. 5′-*O*-Benzyl-4′α-[(2-(2-bromophenyl)-2-methyl-propylthio)carbonyl]-2′-deoxy-3′-*O*-diethylphosphoryl-thymidine (12b). It was prepared by the general phosphorylation method in 81% yield. $[\alpha]_D^{20}$=+2.0 (*c*, 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.31–1.38 (m, 6H), 1.52 (s, 9H), 2.30–2.39 (m, 1H), 2.57–2.64 (m, 1H), 3.55 (d, *J*=13.4 Hz, 1H), 3.68–3.73 (m, 2H), 3.98 (d, *J*=10.2 Hz, 1H), 4.03–4.15 (m, 4H), 4.49 (d, *J*=11.4, 1H), 4.62 (d, *J*=11.4, 1H), 5.22–5.27 (m, 1H), 6.58–6.62 (m, 1H), 7.01–7.06 (m, 1H), 7.20–7.35 (m, 7H), 7.51 (s, 1H), 7.55 (d, *J*=7.8 Hz, 1H), 9.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 12.2, 16.3, 27.7, 27.9, 38.5, 39.6, 40.2, 64.4, 72.9, 74.3, 79.8, 85.7, 94.6, 94.7, 111.8, 122.4, 127.6, 127.9, 128.5, 128.9, 129.2, 135.4, 136.1, 136.8, 144.0, 150.5, 164.0, 198.5; ^{31}P NMR ($CDCl_3$) δ: −4.29; HRMS calcd for $C_{32}H_{41}BrN_2O_9PS$: 739.1454. Found: 739.1453 $[M+H]^+$.

6.6. Preparation of cytidine radical precursors

6.6.1. 5′-*O*-Benzyl-3′-*O*-(*tert*-butyldimethylsilyl)-4-*N*-(*tert*-butyloxycarbonyl)-2′-deoxy-4′α-methoxycarbonyl-cytidine (14). To a solution of **13**[26] (226 mg, 0.46 mmol), Et_3N (62 μL, 0.46 mmol) and DMAP (57 mg, 0.46 mmol) in CH_2Cl_2 (3.5 mL), was added Boc_2O (102 mg, 0.66 mmol) at room temperature, after which the reaction mixture was stirred for 5 h before removal of the solvent. Column chromatography (eluent: EtOAc/hexane, 1:1–3:1) then gave a white solid (210 mg, 77%). Mp 70–72°C; $[\alpha]_D^{20}$=+48.0 (*c*, 1.1, $CHCl_3$); ^{1}H NMR δ: 0.01 (s, 3H), 0.02 (s, 3H), 0.83 (s, 9H), 1.52 (s, 9H), 2.12–2.22 (m, 1H), 2.65–2.75 (m, 1H), 3.74 (s, 3H), 3.88 (d, *J*=10.6 Hz, 1H), 3.98 (d, *J*=10.6 Hz, 1H), 4.55–4.65 (m, 3H), 6.48 (q, *J*=4.4 Hz, 1H), 6.97 (d, *J*=7.5 Hz, 1H), 7.22–7.41 (m, 5H), 8.33 (d, *J*=7.5 Hz, 1H); ^{13}C NMR δ: −5.4, −5.0, 17.6, 25.4 (3×C), 27.9 (3×C), 41.3, 52.1, 69.1, 72.0, 73.7, 82.3, 87.5, 90.7, 94.3, 128.0 (2×C), 128.2, 128.6 (2×C), 136.8, 144.2, 151.2, 162.5, 169.7. Anal. calcd for $C_{29}H_{43}N_3O_8Si$: C, 59.06, H, 7.35. Found: C, 58.84, H, 7.60.

6.6.2. 5′-*O*-Benzyl-4-*N*-(*tert*-butyloxycarbonyl)-4′α-carboxyl-2′-deoxycytidine (15). It was prepared from **14** in 98% yield. Mp 188–190°C; $[\alpha]_D^{20}$=+31.1 (*c*, 1.3, $CHCl_3$); ^{1}H NMR δ: 1.53 (s, 9H), 2.17–2.26 (m, 1H), 2.57–2.66 (m, 1H), 3.92 (d, *J*=10.4 Hz, 1H), 4.01 (d, *J*=10.4 Hz, 1H), 4.57–4.59 (m, 3H), 6.38 (t, *J*=6.0 Hz, 1H), 6.99 (d, *J*=7.5 Hz, 1H), 7.29–7.40 (m, 5H), 8.31 (d, *J*=7.6 Hz, 1H); ^{13}C NMR δ: 18.8 (3×C), 32.5, 62.5, 63.6, 65.3, 73.6, 79.5, 83.5, 87.1, 119.7, 119.8 (2×C), 120.1 (2×C), 129.5, 136.1, 143.9, 148.1, 155.4, 163.7. Anal. calcd for $C_{22}H_{27}N_3O_8{\cdot}2.5H_2O$: C, 52.17, H, 6.37. Found: C, 51.78, H, 5.71.

6.6.3. 5′-*O*-Benzyl-4-*N*-(*tert*-butyloxycarbonyl)-2′-deoxy-4′α-[(2-iodophenylethylthio)carbonyl]cytidine (16a). It

was prepared from **15** and **10** in 90% yield. $[\alpha]_D^{20}=+29.6$ (*c*, 1.1, $CHCl_3$); ^1H NMR δ: 1.52 (s, 9H), 2.18–2.23 (m, 1H), 2.63–2.70 (m, 1H), 2.83 (br, s, 1H), 2.95–2.99 (m, 2H), 3.08–3.14 (m, 2H), 3.74 (d, *J*=10.1 Hz, 1H), 3.83 (d, *J*=10.2 Hz, 1H), 4.55 (s, 2H), 4.64 (br, s, 1H), 6.67 (t, *J*=6.2 Hz, 1H), 6.87–6.92 (m, 1H), 7.07 (d, *J*=7.5 Hz, 1H), 7.25–7.45 (m, 7H), 7.80 (d, *J*=7.6 Hz, 1H), 8.19 (d, *J*=7.6 Hz, 1H); ^{13}C NMR δ: 28.0, 28.3, 40.0, 41.5, 52.1, 71.9, 73.9, 74.3, 76.6, 77.1, 77.5, 82.5, 88.1, 95.1, 96.5, 100.3, 128.0, 128.2, 128.3, 128.6, 130.1, 136.7, 139.4, 142.3, 144.1, 151.2, 155.1, 162.6. Anal. calcd for $C_{30}H_{34}IN_3O_7S$: C, 50.92, H, 4.84. Found: C, 51.04, H, 5.28.

6.6.4. 5′-*O*-Benzyl-4′α-[(2-(2-bromophenyl)-2-methylpropylthio)carbonyl]-4-*N*-(*tert*-butyloxycarbonyl)-2′-deoxycytidine (16b). It was prepared from **13** and **11** in 67% yield. $[\alpha]_D^{20}=+3.8$ (*c*, 2.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.53 (s, 6H), 2.08–2.20 (m, 1H), 2.55–2.65 (m, 1H), 3.24–3.36 (b, 1H), 3.66 (s, 2H), 3.70 (d, *J*=10.2 Hz, 1H), 3.82 (d, *J*=10.2 Hz, 1H), 4.51 (s, 2H), 4.58–4.63 (m, 1H), 6.50–6.56 (m, 1H), 7.00–7.06 (m, 2H), 7.18–7.39 (m, 7H), 7.54–7.57 (m, 1H), 7.65 (b, 1H), 8.16 (d, *J*=7.6 Hz, 1H); ^{13}C ($CDCl_3$) δ: 27.8 27.9, 28.2, 38.3, 40.4, 41.4, 72.0, 74.10, 74.13, 82.8, 88.1, 95.1, 96.5, 122.5, 127.6, 128.2, 128.41, 128.43, 128.9, 129.4, 136.0, 136.9, 143.9, 144.2, 151.3, 155.1, 162.6, 201.7; HRMS calcd for $C_{32}H_{39}BrN_3O_7S$: 688.1692. Found: 688.1693 $[M+H]^+$.

6.6.5. 5′-*O*-Benzyl-4-*N*-(*tert*-butyloxycarbonyl)-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-[(2-iodophenylethylthio)-carbonyl]cytidine (17a). It was prepared by the general phosphorylation procedure in 76% yield. $[\alpha]_D^{20}=+16.6$ (*c*, 1.6, $CHCl_3$); ^1H NMR δ: 1.28–1.39 (m, 6H), 1.53 (s, 9H), 2.26–2.33 (m, 1H), 2.83–3.08 (m, 5H), 3.75 (d, *J*=10.1 Hz, 1H), 3.99 (d, *J*=10.3 Hz, 1H), 4.07–4.15 (m, 4H), 4.51 (d, *J*=11.4 Hz, 1H), 4.61 (d, *J*=11.3 Hz, 1H), 5.24 (t, *J*=5.4 Hz, 1H), 6.70 (t, *J*=5.5 Hz, 1H), 6.89–6.94 (m, 1H), 7.05 (d, *J*=7.6 Hz, 1H), 7.22–7.43 (m, 7H), 7.81 (d, *J*=7.9 Hz, 1H), 8.13 (d, *J*=7.6 Hz, 1H); ^{13}C NMR δ: 16.0, 16.1, 28.0, 28.4, 29.6, 40.0, 40.6, 64.3, 71.8, 74.1, 79.1, 82.8, 87.4, 94.7, 95.1, 100.1, 128.2, 128.4, 128.7, 129.9, 136.3, 139.5, 142.2, 143.8, 150.9, 154.8, 162.5; ^{31}P NMR δ: −4.09. Anal. calcd for $C_{34}H_{43}IN_3O_{10}PS$: C, 48.40, H, 5.14. Found: C, 48.63, H, 5.26.

6.6.6. 5′-*O*-Benzyl-4′α-[(2-(2-bromophenyl)-2-methylpropylthio)carbonyl]-4-*N*-(*tert*-butyloxycarbonyl)-2′-deoxy-3′-*O*-diethylphosphorylcytidine (17b). It was prepared by the general phosphorylation procedure in 91% yield. $[\alpha]_D^{20}=+9.0$ (*c*, 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 1.25–1.30 (m, 6H), 1.43 (s, 9H), 1.49 (s, 6H), 2.18–2.28 (m, 1H), 2.74–2.77 (m, 1H), 3.54 (d, *J*=13.4 Hz, 1H), 3.64–3.68 (m, 2H), 3.92 (d, *J*=10.1 Hz, 1H), 4.00–4.10 (m, 4H), 4.43 (d, *J*=11.2 Hz, 1H), 4.53 (d, *J*=11.2 Hz, 1H), 5.11–5.19 (m, 1H), 6.50–6.57 (m, 1H), 6.92–7.02 (m, 2H), 7.16–7.35 (m, 7H), 7.50 (d, *J*=7.8 Hz, 1H), 7.98 (b, 1H), 8.05 (d, *J*=7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 16.3, 27.7, 27.9, 28.1, 38.5, 40.2, 40.7, 64.4, 72.1, 74.3, 79.1, 82.6, 87.5, 95.0, 95.1, 95.2, 122.3, 127.6, 128.3, 128.5, 128.6, 128.9, 129.2, 136.0, 136.6, 144.0, 151.4, 154.8, 162.9, 198.3; ^{31}P NMR ($CDCl_3$) δ: −4.12; HRMS calcd for $C_{36}H_{48}BrN_3O_{10}PS$: 824.1981. Found: 824.1976 $[M+H]^+$.

6.6.7. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-[(2-iodophenylethylthio)carbonyl]cytidine (18a). To a solution of **17a** (107 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) at 0°C was added TFA (1 mL). After stirring at 0°C for 5 min, the ice bath was removed and the reaction mixture maintained at room temperature for 2 h. The solvent was the removed under reduced pressure and the residue was redissolved in EtOAc (30 mL) and washed with $NaHCO_3$, brine and dried over Na_2SO_4. Removal of the solvent followed by column chromatography on silica gel (eluent: $CHCl_3$/MeOH: 10:1–5:1) then gave a white foam (91 mg, 96%). $[\alpha]_D^{20}=+10.5$ (*c*, 1.0, $CHCl_3$); ^1H NMR δ: 1.25–1.35 (m, 6H), 2.25–2.32 (m, 1H), 2.71–2.77 (m, 1H), 2.91–3.07 (m, 4H), 3.75 (d, *J*=10.2 Hz, 1H), 4.00–4.14 (m, 5H), 4.49 (d, *J*=11.2 Hz, 1H), 4.63 (d, *J*=11.2 Hz, 1H), 5.25 (t, *J*=5.2 Hz, 1H), 5.43 (d, *J*=7.4 Hz, 1H), 6.76 (dd, *J*=8.2, 5.5 Hz, 1H), 6.88–6.94 (m, 1H), 7.26–7.38 (m, 7H), 7.79–7.84 (m, 2H); ^{13}C NMR δ: 16.3, 16.4, 28.7, 29.9, 40.3, 64.6, 72.4, 74.4, 79.5, 87.3, 94.3, 94.5, 100.4, 128.4, 128.6, 128.7, 128.9, 130.2, 137.0, 139.8, 141.9, 142.6, 155.6, 165.4; ^{31}P NMR δ: −4.09. Anal. calcd for $C_{29}H_{35}IN_3O_8PS$: C, 46.85, H, 4.74. Found: C, 47.11, H, 4.88.

6.6.8. 5′-*O*-Benzyl-4′α-[(2-(2-bromophenyl)-2-methylpropylthio)carbonyl]-2′-deoxy-3′-*O*-diethylphosphorylcytidine (18b). It was prepared analogously to **18a** in 91% yield. $[\alpha]_D^{20}=-2.0$ (*c*, 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 1.22–1.35 (m, 6H), 1.49 (s, 6H), 2.22–2.34 (m, 1H), 2.58–2.68 (m, 1H), 3.55 (d, *J*=13.4 Hz, 1H), 3.66 (d, *J*=13.4 Hz, 1H), 3.70 (d, *J*=10.0 Hz, 1H), 3.89 (d, *J*=10.0 Hz, 1H), 3.96–4.10 (m, 4H), 4.44 (d, *J*=11.4 Hz, 1H), 4.52 (d, *J*=11.4 Hz, 1H), 5.14–5.21 (m, 1H), 5.71 (d, *J*=7.5 Hz, 1H), 6.51 (t, *J*=6.8 Hz, 1H), 7.00 (t, *J*=7.5 Hz, 1H), 7.15–7.35 (m, 7H), 7.52 (d, *J*=7.5 Hz, 1H), 7.60 (d, *J*=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 16.2, 16.3, 27.7, 27.9, 38.4, 39.9, 40.3, 64.4, 64.5, 72.5, 74.2, 79.4, 87.6, 94.5, 94.6, 95.8, 122.4, 127.6, 128.2, 128.4, 128.5, 128.8, 129.3, 136.0, 136.9, 141.0, 144.1, 155.9, 166.2, 198.8; ^{31}P NMR ($CDCl_3$) δ: −4.15; HRMS calcd for $C_{31}H_{40}BrN_3O_8PS$: 724.1457. Found: 724.1442 $[M+H]^+$.

6.7. Preparation of adenosine radical precursors

6.7.1. 6-*N*-Benzoyl-5′-*O*-benzyl-3′-*O*-(*tert*-butyl-dimethylsilyl)-6-*N*-(*tert*-butyloxycarbonyl)-2′-deoxy-4′α-methoxycarbonyladenosine (20). A solution of **19**[26] (135 mg, 0.22 mmol), Et_3N (33 μL, 0.25 mmol) and DMAP (29 mg, 0.23 mmol) in CH_2Cl_2 (1.5 mL), was treated with Boc_2O (101 mg, 0.64 mmol) at room temperature followed by stirring for 1 h. Removal of the solvent followed by column chromatography (eluent: EtOAc/hexane, 1:2–1:1) then gave a white foam (160 mg, 100%). $[\alpha]_D^{20}=-2.4$ (*c*, 1.4, $CHCl_3$); ^1H NMR δ: 0.04 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.32 (s, 9H), 2.61–2.74 (m, 1H), 3.76 (s, 3H), 3.84 (d, *J*=10.5 Hz, 1H), 3.95 (d, *J*=10.5 Hz, 1H),4.53 (d, *J*=12.2 Hz, 1H), 4.59 (d, *J*=12.3 Hz, 1H), 4.89 (t, *J*=6.3 Hz, 1H), 6.74 (t, *J*=5.0 Hz, 1H), 7.22–7.55 (m, 8H), 7.89 (d, *J*=7.1 Hz, 1H), 8.44 (s, 1H), 8.80 (s, 1H); ^{13}C NMR δ: −5.2, −4.8, 17.8, 25.6 (3×C), 27.5 (3×C), 40.7, 52.3, 69.8, 73.2, 73.8, 84.5, 85.1, 91.2, 128.0, 128.5, 128.6, 128.7,128.9, 132.6, 135.6, 137.2, 143.9, 150.7, 151.7,

152.1, 152.6, 170.1, 171.5. Anal. calcd for $C_{37}H_{47}N_5O_8Si$: C, 61.90, H, 6.60. Found: C, 61.94, H, 6.73.

6.7.2. 5′-*O*-Benzyl-6-*N*-(*tert*-butyloxycarbonyl)-4′α-carboxyl-2′-deoxyadenosine (21). It was prepared from **20** in 66% yield. Mp 242–243°C; $[\alpha]_D^{20}=+10.2$ (*c*, 1.3, $CHCl_3$); ^{1}H NMR δ: 1.56 (s, 9H), 2.55–2.70 (m, 1H), 2.75–2.90 (m, 1H), 3.78–4.00 (m, 2H), 4.38 (s, 2H), 4.72 (br, s, 1H), 6.70 (br, s, 1H), 7.00–7.20 (m, 5H), 8.40 (s, 1H), 8.51 (s, 1H); ^{13}C NMR δ: 37.6, 41.0, 80.5, 81.7, 82.3, 89.9, 92.4, 99.2, 133.2, 137.1, 138.0, 148.1, 152.0, 159.6, 160.8, 160.9, 161.3. Anal. calcd for $C_{23}H_{27}N_5O_7\cdot 3H_2O$: C, 51.20, H, 6.16. Found: C, 50.78, H, 5.58.

6.7.3. 5′-*O*-Benzyl-6-*N*-(*tert*-butyloxycarbonyl)-2′-deoxy-4′α-[(2-iodophenylethylthio)carbonyl]adenosine (22a). It was prepared from **21** in 95% yield. $[\alpha]_D^{20}=+15.2$ (*c*, 1.3, $CHCl_3$); ^{1}H NMR δ: 1.57 (s, 9H), 2.39 (br, s, 1H), 2.55–2.64 (m, 1H), 2.90–3.02 (m, 3H), 3.12–3.17 (m, 2H), 3.77 (d, *J*=10.0 Hz, 1H), 3.87 (d, *J*=10.1 Hz, 1H), 4.57 (s, 2H), 4.82 (br, s, 1H), 6.78 (t, *J*=6.0 Hz, 1H), 6.88–6.94 (m, 1H), 7.25–7.36 (m, 7H), 7.81 (d, *J*=7.6 Hz, 1H), 7.91 (s, 1H), 8.22 (s, 1H); ^{13}C NMR δ: 28.1, 28.4, 40.0, 72.5, 74.1, 82.5, 85.4, 96.7, 100.5, 122.0, 127.9, 128.2, 128.4, 128.7, 130.1, 137.0, 139.6, 141.2, 142.3, 149.7, 150.0, 153.1. Anal. calcd for $C_{31}H_{34}IN_5O_6S.H_2O$: C, 49.67, H, 4.84. Found: C, 49.27, H, 4.62.

6.7.4. 5′-*O*-Benzyl-4′α-[(2-(2-bromophenyl)-2-methylpropylthio)carbonyl]-6-*N*-(*tert*-butyloxycarbonyl)-2′-deoxyadenosine (22b). It was prepared from **21** in 73% yield. $[\alpha]_D^{20}=+15.1$ (*c*, 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 15H), 2.53–2.60 (m, 1H), 2.83–2.92 (m, 1H), 3.61 (d, *J*=14.0 Hz, 1H), 3.68 (d, *J*=14.0 Hz, 1H), 3.73 (d, *J*=10.1 Hz, 1H), 3.85 (d, *J*=10.1 Hz, 1H), 4.22 (b, 1H), 4.46 (d, *J*=11.9 Hz, 1H), 4.53 (d, *J*=11.9 Hz, 1H), 4.75–4.82 (m, 1H), 6.70 (t, *J*=7.1 Hz, 1H), 6.98 (t, *J*=8.1 Hz, 1H), 7.14–7.30 (m, 7H), 7.50 (d, *J*=7.8 Hz, 1H), 8.26 (s, 1H), 8.69 (s, 1H), 8.70 (b, 1H); ^{13}C NMR ($CDCl_3$) δ: 27.8, 28.3, 36.1, 38.2, 40.4, 40.6, 72.6, 74.1, 74.6, 82.3, 85.8, 97.1, 122.5, 127.5, 128.0, 128.2, 128.4, 128.7, 129.3, 136.0, 137.1, 141.5, 144.0, 150.0, 150.1, 153.0, 172.2, 201.8; HRMS calcd for $C_{33}H_{39}BrN_5O_6S$: 712.1804. Found: 712.1801 $[M+H]^+$.

6.7.5. 5′-*O*-Benzyl-6-*N*-(*tert*-butyloxycarbonyl)-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-[(2-iodophenylethylthio)-carbonyl]adenosine (23a). It was prepared from **22a** in 46% yield. $[\alpha]_D^{20}=+3.5$ (*c*, 2.6, $CHCl_3$); ^{1}H NMR δ: 1.28–1.37 (m, 6H), 1.57 (s, 9H), 2.90–3.12 (m, 6H), 3.77 (d, *J*=10.1 Hz, 1H), 4.04 (d, *J*=10.1 Hz, 1H), 4.08–4.18 (m, 4H), 4.55 (d, *J*=11.7 Hz, 1H), 4.61 (d, *J*=11.6 Hz, 1H), 5.36 (t, *J*=5.0 Hz, 1H), 6.83 (dd, *J*=8.6, 5.9 Hz, 1H), 6.89–6.94 (m, 1H), 7.24–7.38 (m, 7H), 7.81 (d, *J*=7.6 Hz, 1H), 7.96 (s, 1H), 8.20 (s, 1H), 8.75 (s, 1H); ^{13}C NMR δ: 16.1, 28.0, 28.4, 40.1, 64.3, 72.1, 74.2, 79.4, 82.2, 84.7, 94.8, 100.1, 121.6, 128.0, 128.3, 128.4, 128.7, 129.9, 136.5, 139.5, 140.7, 142.3, 149.5, 149.8, 150.6, 153.1; ^{31}P NMR δ: −4.06; ESIMS, *m*/*z*: 868 $[M+1]^+$.

6.7.6. 5′-*O*-Benzyl-4′α-[(2-(2-bromophenyl)-2-methylpropylthio)carbonyl]-6-*N*-(*tert*-butyloxycarbonyl)-2′-deoxy-3′-*O*-diethylphosphoryladenosine (23b). It was prepared from **22b** by the general phosphorylation protocol in 59% yield. $[\alpha]_D^{20}=+2.5$ (*c*, 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, *J*=7.2 Hz, 6H), 1.95–2.07 (m, 15H), 2.79–2.94 (m, 2H), 3.58 (d, *J*=13.1 Hz, 1H), 3.67 (d, *J*=13.1 Hz, 1H), 3.70 (d, *J*=10.5 Hz, 1H), 3.94 (d, *J*=10.5 Hz, 1H), 4.00–4.12 (m, 4H), 4.46 (d, *J*=12.2 Hz, 1H), 4.50 (d, *J*=12.2 Hz, 1H), 5.22–5.31 (m, 1H), 6.67 (t, *J*=7.1 Hz, 1H), 6.98 (t, *J*=7.7 Hz, 1H), 7.12–7.33 (m, 7H), 7.50 (d, *J*=7.8 Hz, 1H), 8.18 (s, 1H), 8.63 (s, 1H), 8.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 16.2, 16.3, 27.7, 27.8, 28.2, 38.3, 40.1, 40.3, 64.4, 64.5, 72.3, 74.2, 79.2, 79.3, 82.2, 85.1, 95.1, 95.3, 122.4, 127.5, 128.1, 128.3, 128.4, 128.7, 129.2, 136.0, 136.7, 141.1, 144.0, 150.0, 150.2, 153.1, 198.2; ^{31}P NMR ($CDCl_3$) δ: −4.18; HRMS calcd for $C_{37}H_{48}BrN_5O_9PS$: 848.2094. Found: 848.2133 $[M+H]^+$.

6.7.7. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-[(2-iodophenylethylthio)carbonyl]adenosine (24a). It was prepared from **23a** in 88% yield by the same method as described below for the preparation of **30a**. $[\alpha]_D^{20}=+8.5$ (*c*, 0.9, $CHCl_3$); ^{1}H NMR δ: 1.31–1.35 (m, 6H), 2.83–3.11 (m, 6H), 3.77 (d, *J*=10.1 Hz, 1H), 4.03 (d, *J*=10.2 Hz, 1H), 4.07–4.17 (m, 4H), 4.55 (d, *J*=11.7 Hz, 1H), 4.60 (d, *J*=11.7 Hz, 1H), 5.36 (t, *J*=5.0 Hz, 1H), 5.91 (s, 2H), 6.78 (dd, *J*=8.4, 5.8 Hz, 1H), 6.87–6.93 (m, 1H), 7.25–7.37 (m, 7H), 7.80 (d, *J*=8.0 Hz, 1H), 8.08 (s, 1H), 8.34 (s, 1H); ^{13}C NMR δ: 16.3, 16.4, 28.7, 29.9, 40.2, 40.4, 64.5, 72.4, 74.4, 79.7, 84.9, 95.0, 95.1, 100.1, 128.2, 128.5, 128.7, 128.9, 130.2, 136.9, 139.1, 139.8, 142.6, 150.0, 153.4, 155.7; ^{31}P NMR δ: −4.06; ESIMS, *m*/*z*: 768 $[M+1]^+$.

6.7.8. 5′-*O*-Benzyl-4′α-[(2-(2-bromophenyl)-2-methylpropylthio)carbonyl]-2′-deoxy-3′-*O*-diethylphosphoryladenosine (24b). It was prepared from **23b** in 79% yield. $[\alpha]_D^{20}=+1.8$ (*c*, 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.33 (m, 6H), 1.52 (s, 3H), 1.53 (s, 3H), 2.76–3.01 (m, 2H), 3.62 (d, *J*=13.7 Hz, 1H), 3.70 (d, *J*=13.7 Hz, 1H), 3.75 (d, *J*=9.6 Hz, 1H), 3.99 (d, *J*=9.6 Hz, 1H), 4.03–4.18 (m, 4H), 4.50 (d, *J*=11.7 Hz, 1H), 4.55 (d, *J*=11.7 Hz, 1H), 5.27–5.37 (m, 1H), 6.21 (s, 2H), 6.62–6.72 (m, 1H), 6.98–7.08 (m, 1H), 7.17–7.38 (m, 7H), 7.53–7.59 (m, 1H), 8.05 (s, 1H), 8.28 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 16.2, 16.3, 27.7, 27.8, 38.4, 40.0, 40.3, 64.4, 64.5, 72.5, 74.2, 79.29, 79.35, 84.9, 95.1, 95.2, 122.4, 127.6, 128.1, 128.35, 128.42, 128.8, 129.3, 136.0, 136.9, 139.2, 144.1, 153.1, 155.7, 198.5; ^{31}P NMR ($CDCl_3$) δ: −4.17; HRMS calcd for $C_{32}H_{39}BrNaN_5O_7PS$: 770.1389. Found: 770.1364 $[M+Na]^+$.

6.8. Preparation of a guanosine radical precursor

6.8.1. 2-*N*-Acetyl-5′-*O*-benzyl-3′-*O*-(*tert*-butyldimethylsilyl)-2-*N*,3-*N*-bis(*tert*-butyloxycarbonyl)-2′-deoxy-4′α-methoxycarbonylguanosine (26). To a solution of **25** (428 mg, 0.78 mmol),[26] Et_3N (465 μL, 3.5 mmol) and DMAP (403 mg, 3.2 mmol) in CH_2Cl_2 (10 mL), was added Boc_2O (1.44 g, 9.1 mmol) at room temperature, after which the reaction mixture was refluxed for 2 h. Removal of the solvent followed by column chromatography (eluent: EtOAc/Hexane, 1:2–1:0) then gave a white foam (484 mg, 83%). $[\alpha]_D^{20}=+24.7$ (*c*, 1.1, $CHCl_3$); ^{1}H NMR δ: 0.02 (s, 3H), 0.03 (s, 3H), 0.84 (s, 9H), 1.39 (s, 9H), 1.71 (s, 9H), 2.58–2.64 (m, 5H), 3.74 (s, 3H), 3.87 (s, 2H), 4.57 (s, 2H), 4.89 (t, *J*=6.7 Hz, 1H),

6.64 (t, J=5.9 Hz, 1H), 7.26–7.33 (m, 5H), 8.30 (s, 1H); ^{13}C NMR δ: −5.0, −4.7, 18.0, 25.7 (3×C), 26.2, 28.1 (3×C), 28.6 (3×C), 41.1, 52.4, 70.2, 73.2, 74.0, 83.6, 85.1, 91.0, 121.9, 128.2, 128.8, 137.4, 141.8, 150.9, 151.9, 161.5, 170.4, 172.8.

6.8.2. 5′-*O*-Benzyl-2-*N*-(*tert*-butyloxycarbonyl)-4′α-carboxyl-2′-deoxyguanosine (27). It was prepared from **26** in 95% yield. Mp 270°C (decomp.); $[\alpha]_D^{20}$=+12.2 (*c*, 0.9, $CHCl_3$); ^{1}H NMR δ: 1.56 (s, 9H), 2.47–2.51 (m, 1H), 2.73–2.80 (m, 1H), 3.89 (d, J=10.4 Hz, 1H), 3.97 (d, J=10.4 Hz, 1H), 4.50–4.60 (m, 2H), 4.71 (t, J=5.1 Hz, 1H), 6.49 (d, J=6.3 Hz, 1H), 7.18–7.30 (m, 5H), 8.10 (s, 1H); ^{13}C NMR δ: 28.5 (3×C), 41.2, 73.4, 74.0, 74.7, 84.8, 86.2, 93.6, 120.9, 128.9, 129.0 (2×C), 129.5 (2×C), 139.4, 139.9, 149.5, 150.7, 155.6, 157.8. Anal. calcd for $C_{23}H_{27}N_5O_8.2H_2O$: C, 51.39, H, 5.81. Found: C, 51.62, H, 5.20.

6.8.3. 5′-*O*-Benzyl-2-*N*-(*tert*-butyloxycarbonyl)-2′-deoxy-4′α-[(2-iodophenylethylthio)carbonyl]guanosine (28a). It was prepared from **27** and **10** in 60% yield. $[\alpha]_D^{20}$=+17.4 (*c*, 1.0, $CHCl_3$); ^{1}H NMR δ: 1.55 (s, 9H), 2.45–2.55 (m, 1H), 2.71–2.80 (m, 3H), 2.97–3.05 (m, 2H), 3.11–3.15 (m, 2H), 3.69 (d, J=10.1 Hz, 1H), 3.79 (d, J=10.1 Hz, 1H), 4.51 (d, J=11.9 Hz, 1H), 4.59 (d, J=12.0 Hz, 1H), 4.84 (br, s, 1H), 6.49 (t, J=5.9 Hz, 1H), 6.88–6.94 (m, 1H), 7.20–7.35 (m, 7H), 7.48 (br, s, 1H), 7.81 (d, J=7.6 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR δ: 28.2, 28.6, 40.3, 40.5, 72.4, 74.2, 74.8, 84.7, 84.8, 96.6, 100.6, 107.0, 120.9, 128.1, 128.6, 128.8, 130.3, 137.0, 137.2, 139.8, 142.4, 147.2, 148.5, 152.8, 155.7. Anal. calcd for $C_{31}H_{34}IN_5O_7S$: C, 49.80, H, 4.58. Found: C, 50.29, H, 4.83.

6.8.4. 5′-*O*-Benzyl-2-*N*-(*tert*-butyloxycarbonyl)-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-[(2-iodophenylethylthio)-carbonyl]guanosine (29a). This was prepared from **28a** in 76% yield. $[\alpha]_D^{20}$=+9.0 (*c*, 1.0, $CHCl_3$); ^{1}H NMR δ: 1.32–1.36 (m, 6H), 1.54 (s, 9H), 2.75–2.82 (m, 1H), 2.87–3.15 (m, 5H), 3.72 (d, J=10.6 Hz, 1H), 3.92 (d, J=10.4 Hz, 1H), 4.06–4.16 (m, 4H), 4.51 (s, 2H), 5.56–5.65 (m, 1H), 6.44 (t, J=6.7 Hz, 1H), 6.90–6.98 (m, 1H), 7.21–7.34 (m, 7H), 7.77–7.85 (m, 2H); ^{13}C NMR δ: 16.3, 16.4, 28.2, 28.7, 38.8, 40.3, 64.6 (m), 71.7, 74.2, 78.7, 84.4, 84.5, 94.3, 94.4, 100.4, 121.1, 128.0, 128.4, 128.7, 130.2, 136.8, 137.5, 139.8, 142.5, 147.4, 148.3, 152.7, 155.7; ^{31}P NMR δ: −4.03. Anal. calcd for $C_{35}H_{43}IN_5O_{10}PS$: C, 47.57, H, 4.90. Found: C, 48.13, H, 5.19.

6.8.5. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-[(2-iodophenylethylthio)carbonyl]guanosine (30a). To a solution of **29a** (97 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) at 0°C was added TmsOTf (194 μL, 1.1 mmol) dropwise. After stirring at 0°C for 30 min, another portion of TmsOTf (80 μL, 0.55 mmol) was added. After a further 20 min at this temperature, the reaction was quenched with $NaHCO_3$, washed with brine and dried. Removal of the solvent followed by column chromatography on silica gel (eluent: $CHCl_3$/MeOH: 20:1 to 10:1) gave a white solid (72 mg, 85%). Mp 176–178°C; $[\alpha]_D^{20}$=−1.7 (*c*, 1.5, $CHCl_3$); ^{1}H NMR δ: 1.31–1.36 (m, 6H), 2.02 (br, s, 1H), 2.76–3.09 (m, 5H), 3.77 (d, J=10.0 Hz, 1H), 3.97 (d, J=10.2 Hz, 1H), 4.08–4.17 (m, 4H), 4.58 (s, 2H), 5.41 (br, s, 1H), 6.27 (br, s, 1H), 6.54 (t, J=5.5 Hz, 1H), 6.88–6.93 (m, 1H), 7.20–7.34 (m, 7H), 7.79–7.81 (m, 2H); ^{13}C NMR δ: 16.3, 16.4, 28.7, 39.7, 40.4, 64.6, 72.3, 74.3, 79.5, 84.6, 94.6, 100.4, 117.2, 128.2, 128.4, 128.7, 130.2, 136.0, 137.0, 139.8, 142.6, 151.6, 154.0, 159.2; ^{31}P NMR δ: −4.03; ESIMS, *m/z*: 784 $[M+1]^+$.

6.9. Kinetics and product isolation

General procedure for competition kinetic radical reactions. Standard solutions of each radical precursor (55 mg) were prepared in THF (1 mL) and used to dispense 0.2 mL aliquots into NMR tubes, which were then sealed and purged with Ar. A stock mixture of Bu_3SnH (5.927 mL, 22.04 mmol) and Me_3SnPh (1.00 mL, 5.54 mmol) was prepared and its denisty determined to be 1.16 g mL^{-1} from which it was calculated that 1 mL of this solution contains 3.29 mmol of Bu_3SnH. This mixture was further examined by ^{119}Sn NMR resulting in the application of a correction factor of 0.92 to give an effective concentration of Bu_3SnH of 3.03 mmol mL^{-1}. Aliquots of this mixture (36.4, 45.5, 54.6, 63.6 or 72.7 μL) were then added to the reaction vessels and the total volume made up to 0.4 mL. The tubes were irradiated in a rotating carousel in a Rayonet photoreactor (254 nm) for 5 h at room temperature then the solvent was removed under reduced pressure and the crude reaction mixtures were analyzed by ^{1}H and ^{31}P NMR spectroscopy resulting in the experimental data recorded in Tables 2–4. The reaction mixtures for a set precursor were then combined and concentrated under reduced pressure. The residue was dissolved in MeCN (10 mL) and extracted with hexane until no tin residue remained in the acetonitrile layer. Concentration of the acetonitrile layer and purification by preparative TLC then gave the various reaction products as characterzed below.

6.9.1. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-(2-phenylethylthiocarbonyl)thymidine (31). ^{1}H NMR δ: 1.32–1.37 (m, 6H), 1.61 (s, 3H), 2.41–2.46 (m, 1H), 2.63–2.68 (m, 1H), 2.81–2.92 (m, 2H), 3.03–3.12 (m, 2H), 3.76

Table 2. Experimental data for thymidine

Vol. of stock soln (μL)	Bu_3SnH (μmol)	[Bu_3SnH] (M)	Molar equiv. Bu_3SnH	Ratio reduction/fragmention[a]
36.4	110.2	0.276	8.15	0.576
45.5	137.8	0.343	10.19	0.764
54.6	165.2	0.413	12.22	0.779
63.6	192.8	0.482	14.26	1.007
72.7	220.4	0.551	16.30	1.129

$\sum$([**33**] + [**34**])/[$(EtO)_2PO_2H$] = 0.04 + 1.96[Bu_3SnH] (r^2=0.96).

[a] Reduction/fragmentation = $\sum$([**33**] + [**34**])/[$(EtO)_2PO_2H$] as determined by ^{31}P NMR spectroscopy.

Table 3. Experimental data for cytidine

Vol. of stock soln (μL)	Bu_3SnH (μmol)	[Bu_3SnH] (M)	Molar equiv Bu_3SnH	Ratio reduction/fragmentation[a]
37.1	112.4	0.281	8.14	0.235
46.4	140.6	0.352	10.17	0.262
55.7	168.8	0.422	12.21	0.278
65.0	197.0	0.493	14.24	0.325
74.2	224.8	0.562	16.27	0.372

$\sum([\mathbf{44}] + [\mathbf{45}])/[(EtO)_2PO_2H] = 0.09 + 0.48[Bu_3SnH]$ (r^2=0.96).
[a] Reduction/fragmentation = $\sum([\mathbf{44}] + [\mathbf{45}])/[(EtO)_2PO_2H]$ as determined by ^{31}P NMR spectroscopy.

(d, *J*=10.2 Hz, 1H), 4.06 (d, *J*=10.1 Hz, 1H), 4.12–4.15 (m, 4H), 4.56 (d, *J*=11.4 Hz, 1H), 4.69 (d, *J*=11.4 Hz, 1H), 5.32 (t, *J*=5.9 Hz, 1H), 6.74 (dd, *J*=9.6, 5.3 Hz, 1H), 7.26–7.40 (m, 10H), 7.56 (s, 1H), 8.55 (s, 1H); ^{13}C NMR δ: 12.5, 16.5, 30.4, 35.9, 39.8, 64.8, 73.0, 74.6, 80.2, 85.9, 94.3, 94.7, 99.6, 112.2, 127.0, 128.2, 128.9, 129.0, 129.2, 135.6, 137.0, 140.2, 150.5, 163.8; ^{31}P NMR δ: −4.17; ESIMS, *m/z*: 656 $[M+Na]^+$.

6.9.2. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-(2-phenyl-2-methylpropylthiocarbonyl)thymidine (32). ^1H NMR ($CDCl_3$) δ: 1.34–1.37 (m, 6H), 1.39 (s, 3H), 2.35–2.42 (m, 1H), 2.60–2.66 (m, 1H), 3.09 (d, *J*=13.3 Hz, 1H), 3.32 (d, *J*=13.3 Hz, 1H), 3.65 (d, *J*=10.0 Hz, 1H), 3.98 (d, *J*=10.0 Hz, 1H), 4.05–4.15 (m, 4H), 4.53 (d, *J*=11.3 Hz, 1H), 4.66 (d, *J*=11.3 Hz, 1H), 5.27 (t, *J*=10.5 Hz, 1H), 6.65–6.67 (m, 1H), 7.19–7.23 (m, 1H), 7.27–7.40 (m, 8H), 7.55 (s, 1H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 12.5, 16.48, 16.53, 28.2, 28.6, 38.7, 39.9, 42.3, 64.7, 73.2, 73.4, 74.6, 80.0, 85.8, 94.9, 95.0, 122.1, 126.1, 126.7, 128.1, 128.3, 128.7, 128.9, 129.2, 135.7, 137.0, 147.6, 150.3, 163.5, 198.6; ^{31}P NMR ($CDCl_3$) δ: −4.23; HRMS calcd for $C_{32}H_{41}NaN_2O_9PS$: 683.2168. Found: 683.2174 $[M+Na]^+$.

6.9.3. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphorylthymidine (33 and 34). For **33**: ^1H NMR δ: 1.36–1.39 (m, 6H), 1.62 (s, 3H), 2.25–2.33 (m, 1H), 2.51–2.56 (m, 1H), 3.78 (dd, *J*=8.5, 2.0 Hz, 1H), 3.85 (dd, *J*=8.5, 2.3 Hz, 1H), 4.13–4.18 (m, 4H), 4.38 (d, *J*=1.8 Hz, 1H), 4.61 (d, *J*=11.5 Hz, 1H), 5.13 (t, *J*=6.1 Hz, 1H), 6.47 (dd, *J*=8.7, 5.6 Hz, 1H), 7.28–7.39 (m, 5H), 7.56 (s, 1H), 8.15 (s, 1H); ^{13}C NMR δ for **33**: 12.6, 16.5, 16.6, 39.5, 64.7, 70.7, 70.9, 74.2, 78.9, 79.0. 85.0, 111.7, 128.1, 128.6, 129.1, 135.9, 137.6, 150.6, 163.6; ^{31}P NMR δ: −3.30; ESIHRMS, calcd for $C_{21}H_{29}NaN_2O_8P$: 491.1559. Found: 491.1578 $[M+Na]^+$. For **34**: ^1H NMR δ: 1.26–1.37 (m, 6H), 1.96 (s, 3H), 2.25–2.45 (m, 1H), 2.80–2.90 (m, 1H), 3.72 (dd, *J*=10.3, 6.8 Hz, 1H), 3.79 (dd, *J*=10.4, 4.2 Hz, 1H), 4.08–4.20 (m, 4H), 4.58–4.65 (m, 2H), 4.65 (d, *J*=12.0 Hz, 1H), 5.14–5.16 (m, 1H), 6.23 (t, *J*=6.8 Hz, 1H), 7.12 (s, 1H), 7.33–7.38 (m, 5H), 8.32 (s, 1H); ^{13}C NMR δ: 12.8, 16.3, 29.9, 40.0, 64.5, 68.6, 73.9, 82.6, 87.1, 111.4, 128.0, 128.1, 128.7, 135.8, 137.8, 150.1, 163.6; ^{31}P NMR δ: −3.24; ESIHRMS, calcd for $C_{21}H_{29}NaN_2O_8P$: 491.1559. Found: 491.1548 $[M+Na]^+$.

6.9.4. Preparation of authentic samples of 33 and 34. To a solution of **9a** (27.5 mg, 0.044 mmol) and AIBN (10 mmol%) in benzene (0.5 mL) was added Bu_3SnH (15 μL, 0.055 mmol) and the reaction mixture was heated to reflux for 2 h. Removal of the solvent followed by column chromatography then gave **38** (6 mg, 41%) and **37** (4 mg, 27%) as colorless oils. For **38**: ^1H NMR δ: 1.92 (s, 3H), 2.21–2.28 (m, 1H), 2.48–2.58 (m, 1H), 3.0 (br s, 1H), 3.80–3.90 (m, 2H), 4.40–4.47 (m, 1H), 4.57–4.65 (m, 3H), 6.22 (t, *J*=6.6 Hz, 1H), 7.08 (s, 1H), 7.26–7.42 (m, 5H), 8.55 (br s, 1H). For **37**: ^1H NMR δ: 1.58 (s, 3H), 2.08 (br s, 1H), 2.15–2.38 (m, 2H), 3.65–3.85 (m, 2H), 4.08–4.12 (m, 1H), 4.52–4.62 (m, 3H), 6.40 (t, *J*=6.6 Hz, 1H), 7.25–7.41 (m, 5H), 7.56 (s, 1H), 8.25 (br s, 1H). To a solution of **37** or **38** (3.3 mg, 0.01 mmol) in THF (0.5 mL) at 0°C was added BuLi (20 μL, 0.05 mmol) followed with diethyl chlorophosphate (7.3 μL, 0.05 mmol) and the reaction mixture was stirred at room temperature for 2 h. Preparative TLC on silica gel (eluent: EtOAc/hexane, 4/1) then gave **34** or **33** (2.3 mg, 50%) as colorless oils identical in all respects to the above isolated samples.

6.9.5. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-(2-phenylethylthiocarbonyl)cytidine (39). ^1H NMR δ: 1.28–1.38 (m, 6H), 2.20–2.30 (m, 1H), 2.70–2.80 (m, 1H), 2.85–2.95 (m, 2H), 3.06–3.09 (m, 2H), 3.76 (d, *J*=10.1 Hz, 1H), 4.03 (d, *J*=10.1 Hz, 1H), 4.05–4.15 (m, 4H), 4.52 (d, *J*=11.3 Hz, 1H), 4.64 (d, *J*=11.3 Hz, 1H), 5.25–5.30 (m, 1H), 5.55 (d, *J*=7.4 Hz, 1H), 6.70–6.75 (m, 1H), 7.23–7.41 (m, 10H), 7.82 (d, *J*=7.5 Hz, 1H); ^{13}C NMR δ: 16.3, 28.1, 30.2, 40.4, 64.5, 72.5, 74.4, 79.6, 87.2, 94.5, 94.9,

Table 4. Experimental data for adenosine

Vol. of stock soln (μL)	Bu_3SnH (μmol)	[Bu_3SnH] (M)	Molar equiv Bu_3SnH	Ratio reduction/fragmentation[a]
35.9	108.8	0.272	8.13	0.520
44.9	136.0	0.340	10.17	0.669
53.9	163.3	0.410	12.20	0.692
62.9	190.6	0.477	14.23	0.838
71.9	217.9	0.545	16.27	0.887

$\sum([\mathbf{46}] + [\mathbf{47}])/[(EtO)_2PO_2H] = 0.18 + 1.32[Bu_3SnH]$ (r^2=0.96).
[a] Reduction/fragmentation = $\sum([\mathbf{46}] + [\mathbf{47}])/[(EtO)_2PO_2H]$ as determined by ^{31}P NMR spectroscopy.

126.8, 128.4, 128.6, 128.7, 128.9, 136.9, 140.0, 141.7, 155.3, 165.5; ^{31}P NMR δ: −4.09; ESIMS, *m/z*: 618 $[M+1]^+$.

6.9.6. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-(2-phenyl-2-methylpropylthiocarbonyl)cytidine (40). ^{1}H NMR ($CDCl_3$) δ: 1.33–1.36 (m, 6H), 1.62 (s, 6H), 2.24–2.33 (m, 1H), 2.73–2.79 (m, 1H), 3.13 (d, *J*=13.5 Hz, 1H), 3.29 (d, *J*=13.5 Hz, 1H), 3.69 (d, *J*=10.0 Hz, 1H), 3.99 (d, *J*=10.0 Hz, 1H), 4.04–4.16 (m, 4H), 4.49 (d, *J*=11.0 Hz, 1H), 4.63 (d, *J*=11.0 Hz, 1H), 5.22–5.28 (m, 1H), 5.39 (d, *J*=7.5 Hz, 1H), 6.71–6.76 (m, 1H), 7.21–7.42 (m, 10H), 7.88 (d, *J*=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 16.5, 28.2, 28.6, 30.1, 38.7, 40.6, 42.4, 64.7, 72.6, 74.5, 79.2, 87.3, 94.2, 126.1, 126.7, 128.4, 128.5, 128.7, 129.0, 129.1, 137.2, 142.3, 147.7, 165.9, 198.8; ^{31}P NMR ($CDCl_3$) δ: −4.06; HRMS calcd for $C_{31}H_{41}N_3O_8PS$: 646.2352. Found: 646.2353 $[M+H]^+$.

6.9.7. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-(2-phenylethylthiocarbonyl)adenosine (41). ^{1}H NMR δ: 1.34–1.37 (m, 6H), 2.87–2.90 (m, 3H), 2.95–3.05 (m, 1H), 3.01–3.13 (m, 2H), 3.79 (d, *J*=10.1 Hz, 1H), 4.05 (d, *J*=10.1 Hz, 1H), 4.12–4.16 (m, 4H), 4.59 (d, *J*=11.7 Hz, 1H), 4.62 (d, *J*=11.7 Hz, 1H), 5.37–5.40 (m, 1H), 5.85 (br, s, 2H), 6.80 (dd, *J*=8.6, 5.8 Hz, 1H), 7.23–7.39 (m, 10H), 8.11 (s, 1H), 8.36 (s, 1H); ^{13}C NMR δ: 16.6, 30.4, 37.4, 40.4, 64.8, 72.6, 74.6, 79.9, 85.1, 95.2, 95.3, 127.0, 128.0, 128.2, 128.5, 128.7, 128.8, 128.9, 129.0, 129.1, 137.1, 139.4, 140.3, 150.2, 153.6, 155.8; ^{31}P NMR δ: −4.06; ESIMS, *m/z*: 642 $[M+1]^+$.

6.9.8. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-(2-phenyl-2-methylpropylthiocarbonyl)adenosine (42). ^{1}H NMR ($CDCl_3$) δ: 1.34–1.38 (m, 6H), 1.40 (s, 6H), 2.82–2.87 (m, 1H), 2.93–3.01 (m, 1H), 3.13 (d, *J*=13.5 Hz, 1H), 3.34 (d, *J*=13.5 Hz, 1H), 3.72 (d, *J*=10.3 Hz, 1H), 3.99 (d, *J*=10.3 Hz, 1H), 4.09–4.16 (m, 4H), 4.56 (d, *J*=11.8 Hz, 1H), 4.60 (d, *J*=11.8 Hz, 1H), 5.33–5.36 (m, 1H), 5.64 (s, 2H), 6.72–6.75 (m, 1H), 7.20–7.23 (m, 1H), 7.29–7.39 (m, 9H), 8.10 (s, 1H), 8.35 (s, 1H); ^{13}CNMR ($CDCl_3$) δ: 16.5, 16.6, 28.2, 28.5, 30.1, 31.3, 38.8, 40.3, 42.4, 51.3, 64.7, 72.7, 74.6, 79.6, 85.1, 95.4, 120.1, 126.1, 126.7, 128.2, 128.4, 128.7, 129.1, 137.1, 139.5, 147.7, 150.1, 153.6, 155.7, 198.7; ^{31}P NMR ($CDCl_3$) δ: −4.11; HRMS calcd for $C_{32}H_{41}N_5O_7PS$: 670.2464. Found: 670.2485 $[M+H]^+$.

6.9.9. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphoryl-4′α-(phenylethylthiocarbonyl)guanosine (43). ^{1}H NMR δ: 1.28–1.40 (m, 6H), 2.07 (br, s, 2H), 2.84–3.12 (m, 4H), 3.80 (br, s, 1H), 4.00 (d, *J*=10.1 Hz, 1H), 4.13–4.18 (m, 4H), 4.61 (s, 2H), 5.44 (s, 1H), 6.15 (br, s, 2H), 6.55–6.57 (m, 1H), 7.23–7.37 (m, 10H), 7.82 (s, 1H); ^{13}C NMR δ: 16.6, 36.0, 40.6, 64.8, 72.5, 74.5, 79.8, 84.9, 95.0, 100.6, 117.5, 127.0, 128.4, 128.6, 128.9, 129.0, 130.5, 136.3, 137.2, 140.0, 142.8, 151.9, 154.2, 159.5; ^{31}P NMR δ: −4.03; ESIMS, *m/z*: 680 $[M+Na]^+$.

6.9.10. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphoryl-cytidine (44 and 45). For **44**: ^{1}H NMR δ: 1.29–1.42 (m, 6H), 2.19–2.23 (m, 1H), 2.68–2.71 (m, 1H), 3.77 (dd, *J*=10.5, 2.2 Hz, 1H), 3.85 (dd, *J*=10.5, 2.2 Hz, 1H), 4.11–4.17 (m, 4H), 4.38 (d, *J*=2.3 Hz, 1H), 4.54 (d, *J*=11.4 Hz, 1H), 5.07–5.10 (m, 1H), 5.47 (d, *J*=7.2 Hz, 1H), 6.45 (t, *J*=6.5 Hz, 1H), 7.29–7.40 (m, 5H), 7.83 (d, *J*=7.2 Hz, 1H); ^{13}C NMR δ: 16.5, 30.1, 40.6, 64.6, 70.2, 74.2, 85.0, 86.6, 94.0, 128.3, 128.5, 129.0, 137.7, 142.2, 155.8, 165.8; ^{31}P NMR δ: −3.37; ESIHRMS, calcd for $C_{20}H_{28}NaN_3O_7P$: 476.1563. Found: 476.1549 $[M+Na]^+$. For **45**: ^{1}H NMR δ: 1.28–1.36 (m, 6H), 2.28–2.35 (m, 1H), 3.02–3.06 (m, 1H), 3.76 (dd, *J*=10.5, 7.0 Hz, 1H), 3.83 (dd, *J*=10.5, 3.5 Hz, 1H), 4.07–4.14 (m, 4H), 4.49–4.52 (m, 1H), 4.59 (d, *J*=12.0 Hz, 1H), 4.65 (d, *J*=11.9 Hz, 1H), 5.10–5.15 (m, 1H), 5.72 (d, *J*=7.4 Hz, 1H), 6.18 (t, *J*=6.5 Hz, 1H), 7.32–7.38 (m, 5H), 7.53 (d, *J*=7.4 Hz, 1H); ^{13}C NMR δ: 16.5, 30.1, 41.6, 64.6, 69.0, 74.1, 82.9, 92.6, 94.0, 128.2, 138.1, 141.5, 155.8, 165.8; ^{31}P NMR δ: −3.18; ESIHRMS, calcd for $C_{20}H_{28}NaN_3O_7P$: 476.1563. Found: 476.1559 $[M+Na]^+$.

6.9.11. 5′-*O*-Benzyl-2′-deoxy-3′-*O*-diethylphosphoryl-adenosine (46 and 47). For **46**: ^{1}H NMR δ: 1.36–1.39 (m, 6H), 2.74–2.76 (m, 1H), 2.86–2.90 (m, 1H), 3.76 (dd, *J*=10.5, 3.1 Hz, 1H), 3.80 (dd, *J*=10.5, 3.2 Hz, 1H), 4.14–4.20 (m, 4H), 4.46–4.48 (m, 1H), 4.59 (s, 2H), 5.20–5.23 (m, 1H), 5.66 (br, s, 2H), 6.57 (dd, *J*=8.2, 5.9 Hz, 1H), 7.33–7.39 (m, 5H), 8.10 (s, 1H), 8.36 (s, 1H); ^{13}C NMR δ: 16.6, 30.1, 40.1, 64.6, 70.4, 74.2, 79.1, 84.5, 85.3, 128.3, 128.5, 129.0, 137.7, 139.3, 150.2, 153.5, 155.7; ^{31}P NMR δ: −3.36; ESIHRMS, calcd for $C_{21}H_{29}N_5O_6P$: 478.1855. Found: 478.1852 $[M+H]^+$. **47**: ^{1}H NMR δ: 1.33–1.38 (m, 6H), 2.92–2.95 (m, 1H), 3.30–3.33 (m, 1H), 3.75 (dd, *J*=10.3, 6.8 Hz, 1H), 3.83 (dd, *J*=10.3, 4.5 Hz, 1H), 4.12–4.17 (m, 4H), 4.57 (d, *J*=12.0 Hz, 1H), 4.63 (d, *J*=12.0 Hz, 1H), 4.87–4.88 (m, 1H), 5.34–5.36 (m, 1H), 5.70 (br, s, 2H), 6.40 (t, *J*=6.8 Hz, ^{1}H), 7.29–7.36 (m, 5H), 7.89 (s, 1H), 8.33 (s, 1H); ^{13}C NMR δ: 16.6, 30.1, 39.4, 64.6, 68.6, 74.1, 78.5, 82.6, 85.4, 121.0, 128.2, 128.8, 138.1, 140.3, 149.9, 153.4, 155.8; ^{31}P NMR δ: −3.15; ESIHRMS, calcd for $C_{21}H_{28}NaN_5O_6P$: 500.1675. Found: 500.1668 $[M+Na]^+$.

6.9.12. 5′-*O*-Benzyl-3′,4′-didehydro-2′,3′-dideoxycytidine (49). ^{1}H NMR δ: 2.52–2.56 (m, 1H), 3.15–3.20 (m, 1H), 4.15 (s, 2H), 4.64 (s, 2H), 5.10 (s, 1H), 5.65 (d, *J*=7.4 Hz, 1H), 6.67 (dd, *J*=9.0, 3.4 Hz, 1H), 7.34–7.51 (m, 5H), 7.52 (d, *J*=7.4 Hz, 1H); ^{13}C NMR δ: 29.9, 38.1, 64.5, 73.2, 87.0, 94.2, 99.3, 127.9, 128.2, 128.7, 137.8, 141.0, 155.4, 165.3; ESIHRMS, calcd for $C_{16}H_{17}NaN_3O_3$: 322.1168. Found: 322.1162 $[M+Na]^+$.

6.9.13. 5′-*O*-Benzyl-3′,4′-didehydro-2′,3′-dideoxyguanosine (51). ^{1}H NMR (CD_3OD) δ: 3.04–3.07 (m, 1H), 3.30–3.36 (m, 1H), 4.14 (s, 2H), 4.52 (d, *J*=11.6 Hz, 1H), 4.56 (d, *J*=11.8 Hz, 1H), 5.28 (s, 1H), 6.67 (dd, *J*=9.3, 3.4 Hz, 1H), 7.27–7.35 (m, 5H), 7.85 (s, 1H); ^{13}C NMR (d^6-DMSO) δ: 64.6, 72.1, 76.3, 80.8, 83.4, 99.5, 117.3, 128.4, 128.6, 129.1, 135.0, 138.8, 151.7, 153.6, 155.1, 158.0, 159.3; ESIMS, *m/z*: 340 $[M+1]^+$.

6.9.14. 5′-*O*-Benzyl-2′,3′-didehydro-2′,3′-dideoxycytidine (52). ^{1}H NMR δ: 4.11 (s, 2H), 4.65 (s, 2H), 4.91 (s, 1H), 5.30 (s, 1H), 5.65 (d, *J*=7.4 Hz, 1H), 6.18 (s, 1H), 7.35–7.49 (m, 6H), 7.49 (d, *J*=7.3 Hz, 1H); ^{13}C NMR δ: 64.8, 73.5, 75.8, 81.1, 91.6, 93.9, 96.0, 102.7, 117.8, 128.1, 129.0, 140.6, 155.4, 165.3; ESIMS, *m/z*: 300 $[M+1]^+$.

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