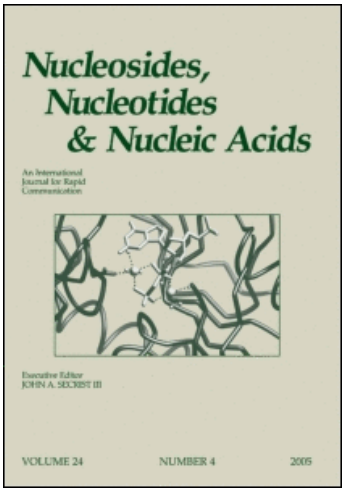

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Heterocyclic Nucleosede Analogues by Cycloaddition Reactions of 1-Vinylthymine with 1,3-Depoles

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HETEROCYCLIC NUCLEOSIDE ANALOGUES BY CYCLOADDITION REACTIONS OF 1-VINYLTHYMINE WITH 1,3-DIPOLES

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ABSTRACT: 1,3-Dipolar cycloaddition of 1-vinylthymine to azides, nitrile oxides, nitrones and nitronates has been investigated as a route to heterocyclic nucleoside analogues in which the nucleoside ribose moiety has been replaced by an alternative heterocycle. Reaction of 1-vinylthymine with highly reactive nitrile oxides affords 1-(isoxazolin-5-yl)thymine products in excellent yield at room temperature. The less reactive nitrone dipoles undergo cycloaddition to 1-vinylthymine at elevated temperature to afford 1-(isoxazolidin-5-yl)thymine cycloadducts in good-to-moderate yields, but show a tendency to eliminate thymine from the cycloaddition products over long reaction times. Azide cycloadditions to 1-vinylthymine proceed only under forcing conditions to which the fragile triazoline products are unstable.

INTRODUCTION

Considerable attention has been focused on the synthesis of 2',3'-dideoxy-, acyclo- and carbocyclic nucleoside analogues in the search for compounds with antiviral and anticancer activity.[1-5] More recently replacement of the ribose moiety with alternative heterocyclic rings has also received attention. For instance, reports of antiviral activity associated with "heterocyclic" nucleoside analogues possessing dioxolane and oxathiolane rings (*eg.* dioxolane-T and 3TC)[6-9] as surrogates for

deoxyribose have brought to prominence the potential of this class of compounds and stimulated growing interest in this area. However, in general the area remains a comparatively poorly exploited means of modifying the nucleoside structure.

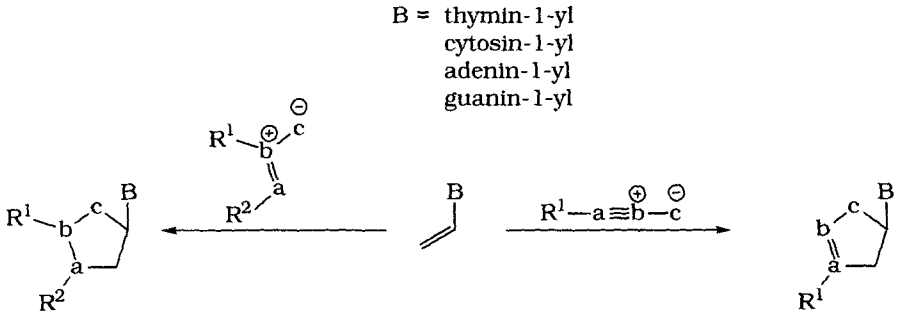
We were attracted by the potential of the 1,3-dipolar cycloaddition reaction for synthesis of novel heterocyclic nucleoside analogues. The 1,3-dipolar cycloaddition reaction is both synthetically economical, with the formation of two σ–bonds in a single process, and versatile, enabling access to five–membered heterocyclic rings possessing diverse patterns of heteroatom substitution and variable saturation. Thus, in principle any single dipolarophile embodying the nucleoside base component, 1-vinylpyrimidines or 9-vinylpurines for example, would enable synthesis of an array of different nucleoside analogues, *Scheme 1*. In this paper we report our investigations in this field, carried out over a number of years, which have been made in the thymine series.[10,11]

RESULTS AND DISCUSSION

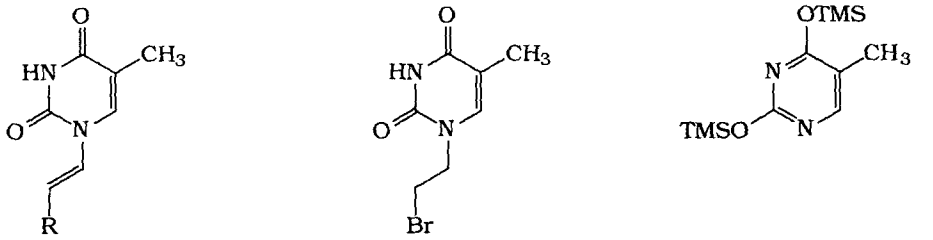
Attempts to prepare 1-vinylthymine (**1**), the key dipolarophile required for our cycloaddition studies, by direct vinylation of thymine or its silylated derivative **4** with vinyl acetate proved troublesome. Transvinylation proceeded only reluctantly under catalysis by fuming sulphuric acid and mercuric acetate[12,13] or sodium tetrachloropalladate[14] to afford the target compound with low conversion of the starting material (5–10%). This problem was compounded by difficulty in separating the product from unconverted thymine. A more practicable route to the target dipolarophile was found in the dehydrobromination[12] of bromide **3** which was prepared in 44% yield by alkylation[15] of the 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine (**4**)[16] with 1,2-dibromoethane. Base–induced elimination of hydrogen bromide from **3** proceeded smoothly upon treatment with potassium *tert*-butoxide in tetrahydrofuran to afford 1-vinylthymine in 77% yield.[17]

The cycloaddition reaction between 1-vinylthymine and ω-hydroxyalkyl azides such as **9** was first examined because this was expected to lead in the first instance to nucleoside analogues of type **5**, comprising a triazoline ring with thymine and hydroxyalkyl substituents, and because further transformation of **5** into aziridines of type **8** might be possible through expulsion of nitrogen. Moreover, at the outset of our work, cycloaddition reactions of *N*-vinylamides or lactams with azides were unstudied, and consequently an investigation of the dipolarophilic activity of 1-vinylthymine with respect to azides was of interest.

3-Azidopropanol (**9**), was readily prepared in 85% yield by treatment of 3-bromopropanol with Amberlite IR 400 (N_3^-) resin[18] in dichloromethane. Its reaction with 1-vinylthymine, which proceeded only slowly in boiling toluene and was incomplete after one week, led to precipitation of thymine from the reaction medium rather than formation of triazoline **6**. The thermal lability of triazolines is well documented, with decomposition occurring by a number of pathways, frequently involving heterolysis or homolysis of the N–N bond followed by expulsion of N_2 leading to aziridine or imine formation.[19] In the case of triazolines substituted with a nucleofugal group in the 5-position elimination of the nucleofuge rather than expulsion of nitrogen may occur to afford a triazole.[20-22]



Scheme 1

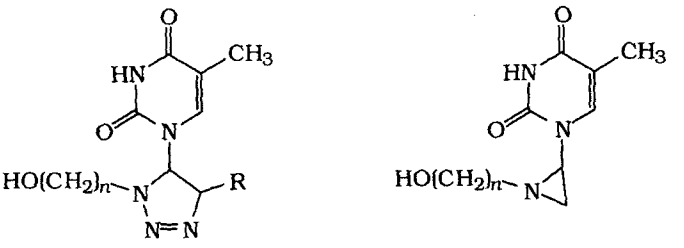


1 R = H
2 R = CO_2Et

3

4

Figure 1



5 R = H
6 R = H n = 3
7 R = CO_2Et

8

9

10 R = H n = 3
11 R = CO_2Et

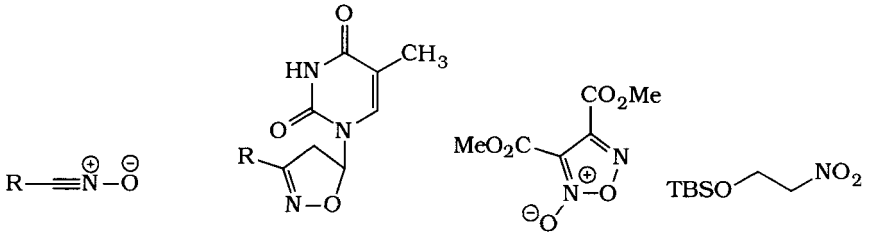
Figure 2

It seemed probable, therefore, that the reaction between azide **9** and 1-vinylthymine gives rise to the desired triazoline cycloadduct **6** as an intermediate which aromatises to triazole **10** by elimination of thymine under the reaction conditions. Indeed, we have noted elsewhere the propensity of the thymine nucleus to act as a leaving group in a variety of fragmentation reactions of thymine–containing bisheterocycles.[23] When the reaction progress was monitored by ^{1}H NMR spectroscopy formation of a trace component in the reaction mixture consistent with the putative triazole (**10**) was observed after two days at 110 °C. This constituent exhibited two broad singlet resonances at δ_H 7.67 and 7.77 consonant with the H-4 and H-5 signals expected for **10**.[24] The occurrence of two triplets at δ_H 3.66 and 4.60 (*J* 7 Hz) together with a further multiplet at δ_H 2.10 are also consistent with the structure of triazole **10**. At no point were signals from the intermediate triazoline cycloadduct (**6**) detected, underlining the fragility of this compound at elevated temperature. Prolonged heating of the reaction mixture eventually led to formation of thymine and polar intractable material from which isolation of the triazole was not accomplished.

During the course of these investigations Kadaba described the reaction of aryl azides with other *N*-vinylamides (*N*-vinylpyrrolidin-2-one and *N*-methyl-*N*-vinylacetamide).[25] In this work, moderate yields of triazoline cycloadducts were obtained when the reactions were conducted at room temperature over periods varying from a week to a year depending on the reactivities of the azide and dipolarophile. When carried out in refluxing ethanol, however, cycloaddition proceeded with concomitant elimination of pyrrolidinone or *N*-methylacetamide to afford the corresponding triazoles. The slow reaction of 1-vinylthymine with 3-azidopropanol indicates that the dipolarophile resembles an unactivated olefin in its activity towards azide cycloadditions. However, we also found that the behaviour of acrylate derivative **2**[26] towards cycloaddition with azide **9** was not significantly different from that of 1-vinylthymine itself, despite the presence of a potentially activating electron withdrawing ester group in the dipolarophile.

In contrast to azides, nitrile oxides are particularly reactive 1,3-dipoles which readily undergo cycloaddition reaction with unactivated dipolarophiles. The reaction of 1-vinylthymine with nitrile oxides was expected to proceed with very high regioselectivity to afford 3-substituted 5-(thymin-1-yl)isoxazolines in accord with the strong regiochemical preference exhibited by this class of 1,3-dipoles in their reactions with monosubstituted alkenes.[27] Thus the reaction between 1-vinylthymine and nitrile oxide **12**, generated in the reaction medium by dropwise addition of excess methyl chlorooximidoacetate[28] to a solution of the dipolarophile and triethylamine in tetrahydrofuran, afforded a single cycloadduct (**14**) in 86% yield after chromatographic separation of furoxan **17**, the by–product arising from dimerisation of the nitrile oxide.

For our purposes it was desirable to have a hydroxymethylene substituent in the 3-position of the isoxazoline ring as this would provide nucleoside analogue **15** in which the thymidine deoxyribose moiety is replaced by an isoxazoline ring possessing the interesting geometrical feature of a planar junction between the ring and the 3-substituent. Some adenosine analogues with this feature function as transition state inhibitors of S-adenosylhomocysteine hydrolase and exhibit antiviral activity.[29] In



12 R = CO_2Me
13 R = CH_2OTBS

14 R = CO_2Me
15 R = CH_2OH
16 R = CH_2OTBS

17

18

Figure 3

principle, compound **15** should be readily accessible by selective reduction of the ester function in cycloadduct **14**, but in practice this process was invariably attended by elimination of thymine despite various attempts with different hydride reducing agents [$LiAlH_4$, $NaBH_4$, $Ca(BH_4)_2$ and $Zn(BH_4)_2$] at low temperature. Satisfactory separation of the polar product **15** from thymine could be achieved neither by recrystallisation nor by column chromatography. However, the corresponding *tert*-butyldimethylsilyl ether **16**, obtained by silylation of the crude alcohol under standard conditions, was readily separated from thymine by flash column chromatography and, after deprotection, gave the pure alcohol in 40% overall yield from ester **14**. A more efficient route to the same compound was found in the direct preparation of silyl ether **16** by reaction of 1-vinylthymine with nitrile oxide **13**. The nitrile oxide in this case was generated *in situ* by dehydration of the 2-nitroethanol derivative **18** with phenyl isocyanate. Thus, cycloadduct **16** was obtained in 87% yield after purification by flash column chromatography; deprotection with hydrofluoric acid in acetonitrile then furnished the target isoxazoline **15** in 78% yield. In independent studies Zhao *et al* have also recently reported the application of similar 1,3-dipolar cycloaddition methodology for the synthesis of dihydroisoxazolyl nucleoside analogues including compound **15**.[30-32] Zhao's group found compounds in the purine series to exhibit moderate anti HIV-1 activity.[32]

Silyl nitronates are also versatile reagents for the synthesis of isoxazolines, but are notably less reactive than nitrile oxides and undergo cycloaddition rather slowly with monosubstituted dipolarophiles unless activated by an electron withdrawing group.[33,34] The somewhat unstable primary cycloaddition products of such reactions, 5-substituted *N*-silyloxyisoxazolidines, are commonly not isolated but undergo further transformation in the presence of acid or fluoride ion either to afford the corresponding 2-isoxazoline (by elimination of silanol) or products arising from cleavage of the isoxazolidine ring. The reaction of 1-vinylthymine with nitronate **19** was, therefore, expected to provide an alternative route to isoxazoline **15** *via* the *N*-silyloxyisoxazolidine intermediate **20**. Nitronate **19** was readily generated in the presence of 1-vinylthymine

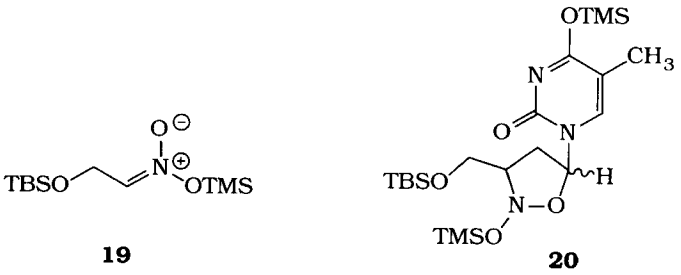
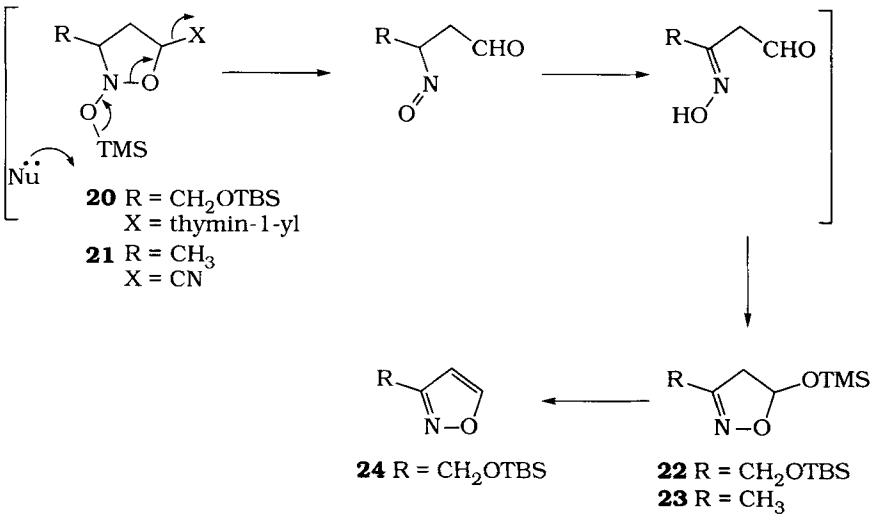


Figure 4

by reaction of nitro compound **18** with trimethylsilyl trifluoromethanesulphonate or *N,O*-bis(trimethylsilyl)acetamide (BSA).[35] The use of such silylating agents also conveniently rendered the polar dipolarophile soluble in non-polar solvents such as dichloromethane or benzene by simultaneous silylation of the thymine ring. Carrying out the reaction of 1-vinylthymine and nitro compound **18** in the presence of excess BSA in boiling benzene revealed complete consumption of the dipolarophile within 24h, monitoring the reaction progress by TLC. After cooling and quenching the reaction mixture with a little methanol thymine was obtained in quantitative yield together with a complex mixture of non-polar products containing the *tert*-butyldimethylsilyl moiety. At room temperature the reaction between 1-vinylthymine and nitronate **19** was exceedingly slow. Thus, the dipolarophile and nitro compound **18** were returned essentially unreacted when the reaction mixture was quenched with methanol after 3 weeks. Interestingly, however, a trace (< 5%) of isoxazoline **16** was detected in the ^{1}H NMR spectrum of the material recovered.

Thermal cleavage of the isoxazolidine ring in similar compounds has been reported previously and for this reason nitronate cycloaddition reactions are frequently conducted below 80 °C.[34] In the case of nitronate additions to acrylonitrile the reaction has been observed to proceed with concomitant expulsion of cyanide from the intermediate 5-cyano-*N*-trimethylsilyloxyisoxazolidines **21** leading to formation of isoxazolines **23**.[33] The displacement of the pyrimidine ring from intermediate isoxazolidine **20** by a similar mechanism involving cleavage of the endocyclic N–O bond, as shown in *Scheme 2*, might be invoked to explain the observed evolution of thymine in the reaction of 1-vinylthymine with nitronate **19**. The expected by-product **22** [or the corresponding isoxazole (**24**)] from this process could not, however, be isolated and the reaction gave rise to a number of unidentified compounds.

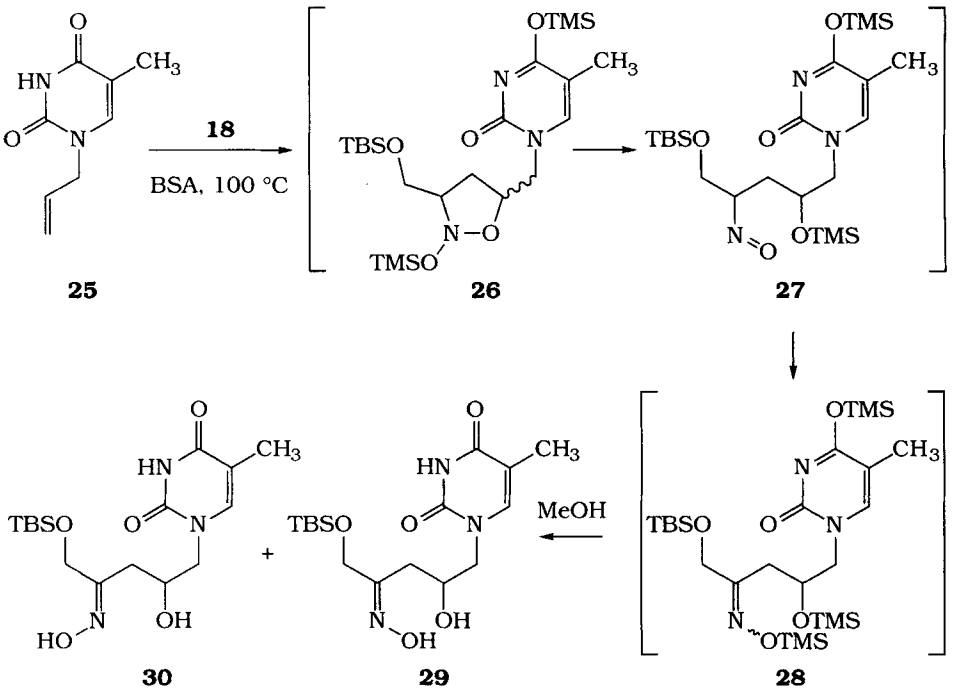
Insertion of a methylene group between the isoxazolidine and thymine rings of adduct **20** would interrupt the fragmentation process. Thus, in order to substantiate the proposed mechanism leading to expulsion of thymine, the cycloaddition of 1-allylthymine (**25**) to nitronate **19** was examined. Dipolarophile **25**, readily prepared by alkylation of pyrimidine **4** with allyl bromide, underwent cycloaddition upon heating



Scheme 2

with nitro compound **18** in neat BSA at 100 °C to afford a mixture of three components which were separated by flash column chromatography. The two faster running constituents, isolated in 58% and 19% yields, were shown to be isomeric on the basis of common parent ion peaks at *m/z* 372 in their CI mass spectra. These compounds exhibited similar ^{1}H and ^{13}C NMR spectra consistent with the structures of oximes **29** and **30** formed by isoxazolidine ring cleavage (Scheme 3). In the ^{1}H NMR spectrum of the minor product **30** the methylene *cis* to the oxime OH comes to resonance at δ_H 4.56, downfield from the corresponding methylene in **29** (δ_H 4.24).[36] The methylene *cis* to the oxime OH in the major isomer **29** (δ_H 2.52–2.74) shows a similar downfield displacement with respect to the corresponding group in **30** (δ_H 2.37–2.56).

The third and more polar of the reaction products, isolated in 18% yield, also contained the thymine ring and acyclic chain arising from N–O bond scission of the intermediate isoxazolidine **26**. Curiously, however, the compound exhibited a number of additional features in its NMR spectra. In particular, two *tert*-butyldimethylsilyl ether groups were evident together with a doublet at δ_H 4.56 (2 H, *J* 3.6 Hz) in the ^{1}H spectrum which was coupled to a downfield triplet at δ_H 6.99 (1 H, *J* 3.6 Hz). These signals, which correlated respectively with resonances at δ_C 60 (CH_2) and δ_C 144 (CH) in the ^{13}C spectrum, suggested the structure of an azomethine oxide, nitrone **33**, substituted with a (*tert*-butyldimethylsilyloxy)methylene group at the α carbon. The FAB mass spectrum of **33** corroborated this assignment and exhibited a strong molecular ion at *m/z* 529 (100%) and the diagnostically valuable M-16 peak (*m/z* 513; 50%) which is characteristic of nitrones and other *N*-oxides.[37] It is significant that **33** embodies the thermodynamically less stable aldonitrone structure rather than the

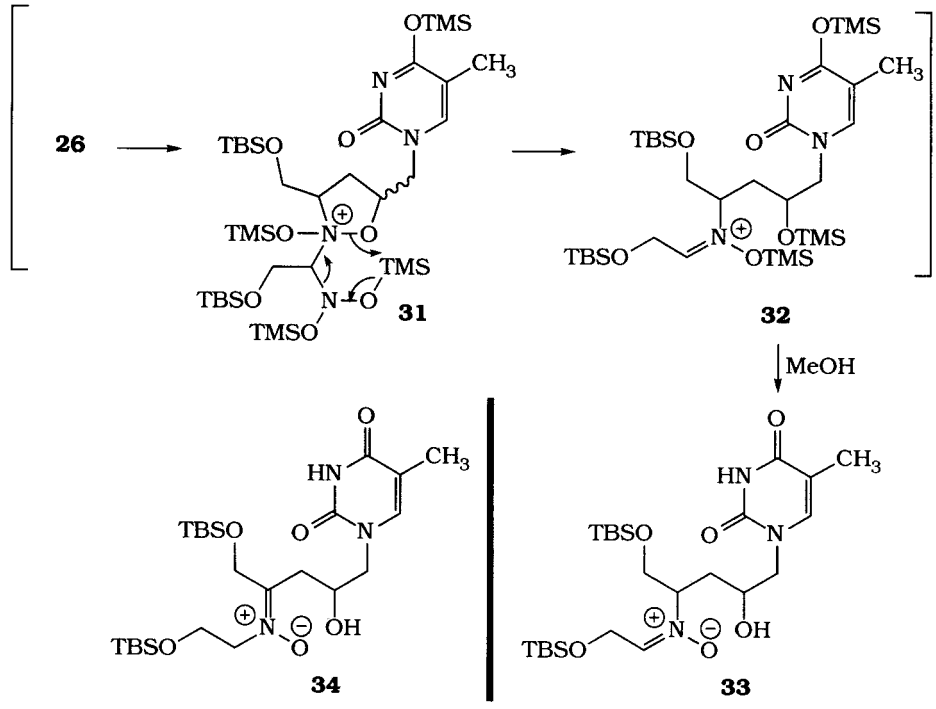


Scheme 3

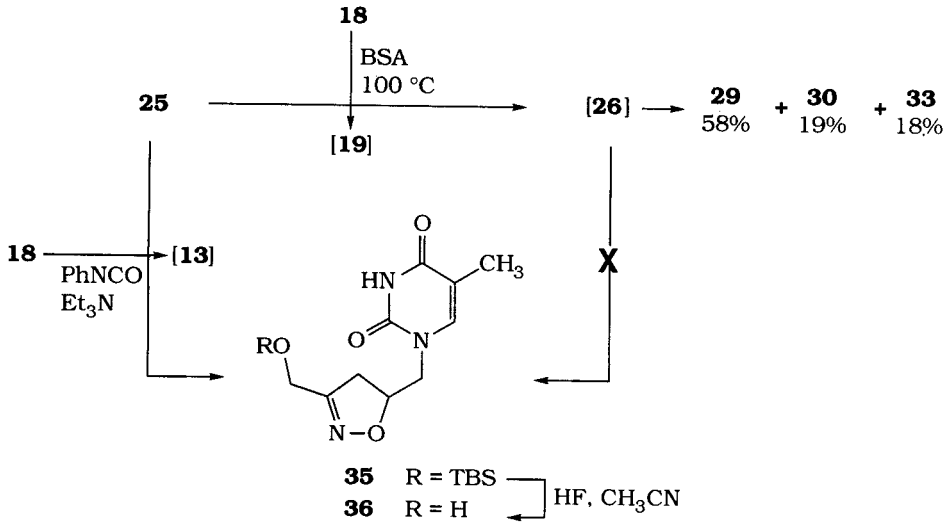
corresponding ketonitrone (**34**) and this indicates that its formation does not involve alkylation of oximes **29** and **30**. Its formation may involve nucleophilic attack by isoxazolidine **26** on a second molecule of nitronate **19** after the initial cycloaddition reaction; elimination of a nitrite species and desilylation by methanol would afford nitrone **33** by an overall process depicted in Scheme 4.

The total material accumulating in the isolated compounds **29**, **30** and **33** upon reaction of nitronate **19** with 1-allylthymine accounts for 95% of the starting material; formation of isoxazoline **35** by elimination of trimethylsilanol from isoxazolidine **26**, as opposed to ring scission, was not observed, Scheme 5. The additional conformational flexibility associated with insertion of the methylene between the heterocyclic rings of this nucleoside analogue prompted us to undertake its synthesis by reaction of 1-allylthymine with nitrile oxide **13** under similar conditions used for the preparation of isoxazoline **16**. Compound **35** was isolated in 84% yield and desilylated with hydrofluoric acid in acetonitrile to afford **36** (91%).[38]

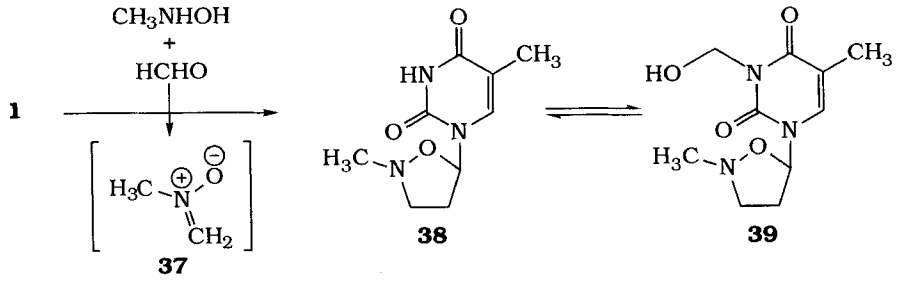
The reaction of 1-vinylthymine with nitrones was expected to afford more stable adducts than **26** bearing an alkyl side chain attached to the isoxazolidine ring N atom instead of the silyloxy group. These nucleoside analogues possess a pseudo sugar ring in which the asymmetric 4' centre has been replaced by a centre of inversion. We



Scheme 4



Scheme 5



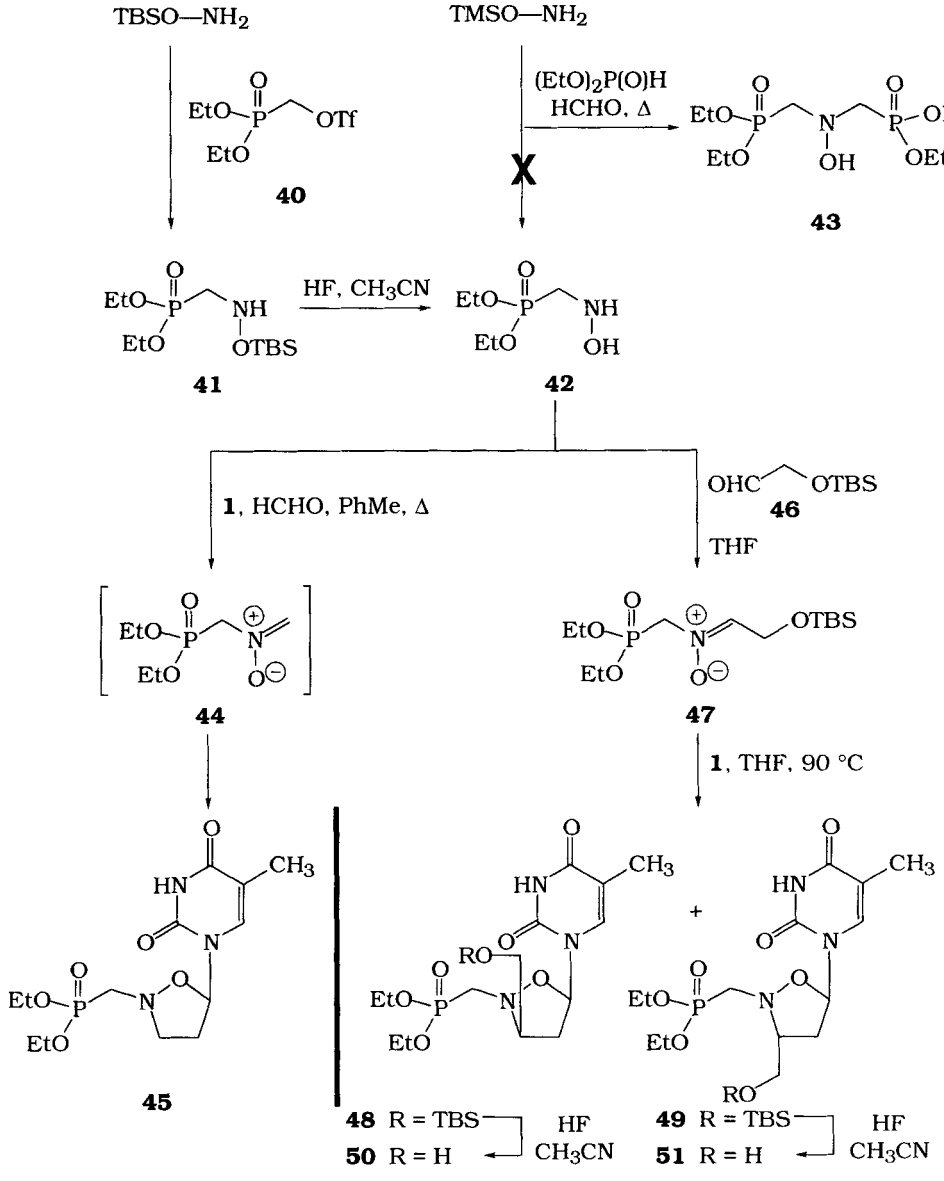
Scheme 6

chose, in the first instance, to test the methodology by reaction 1-vinylthymine with the simple *N*-methyl nitrone **37** generated *in situ* during the one-pot reaction of the dipolarophile with *N*-methylhydroxylamine hydrochloride, sodium acetate and excess paraformaldehyde in boiling toluene, Scheme 6. Isoxazolidine **38** was isolated in 48% yield by flash column chromatographic purification of the crude reaction product which also contained variable amounts of thymine (presumably formed by decomposition of the product) and occasionally the formaldehyde modified product **39**, as evidenced by an additional set of product signals including a singlet resonance at δ_H 5.5 for the N-3 methylene. Removal of the excess formaldehyde by codistillation with toluene at the end of the reaction resolved the latter problem.

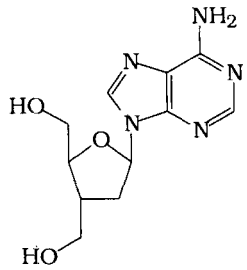
The methodology was extended by examination of the reaction of a second α-unsubstituted nitrone (**44**) derived from hydroxylamine **42** and formaldehyde, Scheme 7. Initial attempts to prepare the requisite hydroxylamine by direct condensation of hydroxylamine *O*-trimethylsilyl ether[39] with formaldehyde and diethyl phosphite failed to stop at the monoalkylated stage and afforded *N,N*-disubstituted hydroxylamine **43** instead.[40] Monoalkylation was, however, successfully accomplished by reaction of diethyl phosphonomethyl triflate (**40**)[41] with two equivalents of hydroxylamine *O*-*tert*-butyldimethylsilyl ether[39] and afforded the protected hydroxylamine (**41**) in 67% yield. Desilylation with hydrofluoric acid in acetonitrile then furnished the desired hydroxylamine (**42**) in 96% yield.

The reaction of hydroxylamine **42** with formaldehyde and 1-vinylthymine in boiling toluene afforded the target isoxazolidine **45** along with small quantities of thymine, the latter again presumably formed by decomposition of the cycloadduct. Indeed, the isolated adduct was found to be unstable to prolonged heating at 60 °C and completely decomposed to thymine and an unidentified mixture of polar, intractable products during the course of 5 days. The cycloaddition was, therefore, best conducted with excess dipolarophile avoiding excessively long reaction times; in this way **45** was obtained in 75% yield after purification by flash column chromatography.

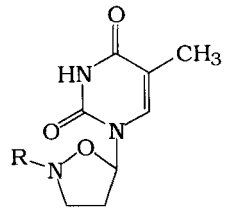
Attention was next turned to the reaction of 1-vinylthymine with nitrone **47** as a means of introducing an additional hydroxymethylene chain into the product structure.



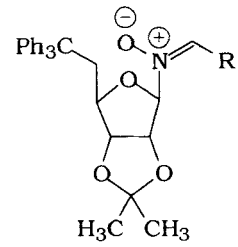
Scheme 7



52



53 R = THP
54 R = H



55

Figure 5

Interest in the synthesis of nucleoside analogues branched at C-3' with a hydroxymethylene chain has been stimulated by the antiviral activity of compounds such as **52** and the oxetanocins.[42] The nitrone, prepared by condensation of hydroxyacetaldehyde derivative **46**[43-48] with hydroxylamine **44** in tetrahydrofuran over activated 4 Å molecular sieves, was reacted with excess 1-vinylthymine in a sealed tube at 90 °C for 24 h. An inseparable 1.7:1 mixture of adducts **48** and **49** (72%) was obtained and deprotected with hydrofluoric acid in acetonitrile. Compounds **50** and **51** were partially separated by repeated flash column chromatography and isolated in yields of 19% and 25% respectively. These branched chain isoxazolidines, like compound **45**, were found to be moderately unstable towards elimination of thymine. Thus isoxazolidine **51** in CD_3OD solution substantially decomposed to thymine and a complex unidentifiable mixture of components after a period of 1 month at room temperature.

Peak assignments in the ^1H NMR spectrum of isoxazolidine **50** were made from a COSY experiment. The relative stereochemistry of this compound was deduced from cross-peaks observed in a 2D NOESY spectrum recorded using a TPPI phase-sensitive NOESY sequence with a 1.1 second mixing time. Contacts, classified as strong (solid curve) or weak (dashed curve), are presented in Figure 6. Of particular interest is the strong contact between the thymine ring H-6 and isoxazolidine H-4'b. This implies that the thymine ring is on the same side of the five-membered ring as H-4'b and is confirmed by the strong contact between H-5' and H-4'a. The contact of H-3' with H-4'a is very close to the diagonal and hence likely to have an unreliable intensity, however, its contact with H-4'b is weak. In addition there is a weak contact between H-4'b and both CH_2-7' hydrogens, but no contact at all between the latter methylene and H-4'a. This requires H-3' to be on the opposite side of the isoxazolidine ring to H-4'b and hence the thymine ring. H-3' also shows a weak contact with H-5' and clear contacts with all 4 hydrogens of CH_2-6' and CH_2-7'; this leads to the conclusion that the *N*-substituent lies on the lower face of the isoxazolidine ring. The ^1H NMR spectrum of the isomeric

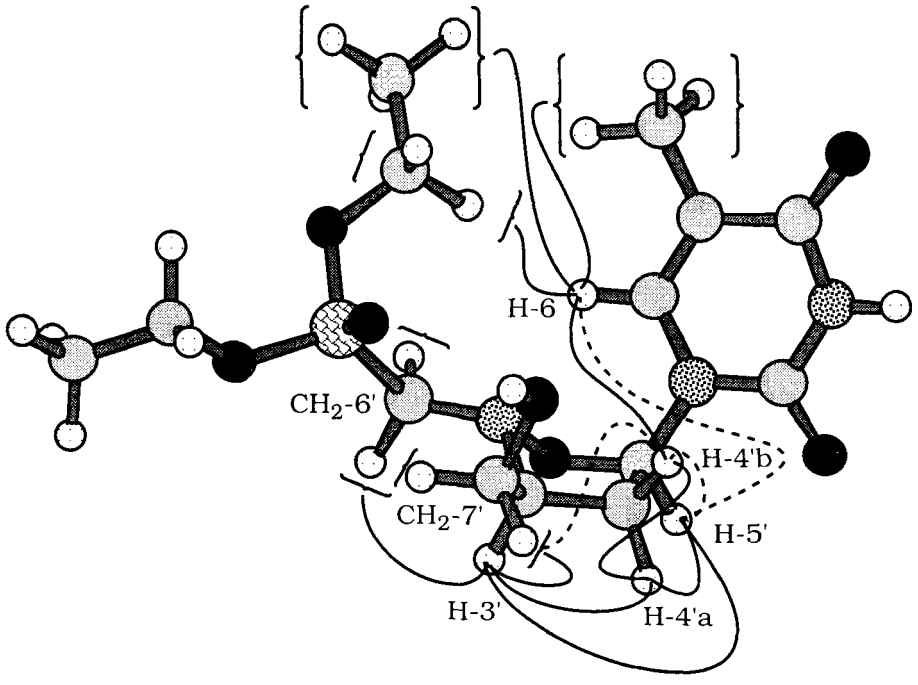


Figure 6: Schematic representation of the structure of compound **50** illustrating observed nuclear Overhauser enhancements.

isoxazolidine (**51**) exhibited less well resolved resonances and did not lend itself to NOESY studies. This compound was ascribed *trans* stereochemistry across C-3' and C-5' by virtue of the assignment given to **50**.

Compounds **15**, **36**, **45**, **50** and **51** were tested for anti-HIV-1 activity and found to be inactive. Since commencing these studies several other reports have appeared describing the synthesis isoxazolidine nucleoside analogues. In the main these have involved nucleosidation of 5-acetoxyisoxazolidine derivatives by persilylated nucleobases.[49-52] In one instance the nucleosidation route has been applied in an enantioselective synthesis.[52] Tronchet[50], Sindona[53] and their co-workers, however, have also explored the reaction of 1-vinylthymine with nitrones. In the latter work an *N*-tetrahydropyranyl nitrone was reacted with 1-vinylthymine to afford isoxazolidine derivative **53**, Figure 5, which was subsequently deprotected under acidic conditions to furnish the parent *N*-unsubstituted compound (**54**). Adaptation of this methodology using nitrones carrying the carbohydrate-derived chiral auxiliaries developed by Vasella[54-58] (*e.g.* **55**) instead of the tetrahydropyranyl group should provide the basis for an enantioselective synthesis of these nucleoside analogues using the cycloaddition methodology. In contrast to the isoxazolines none of the isoxazolidine nucleoside analogues so far reported have shown significant antiviral activity.

In summary, we have studied the scope of the 1,3-dipolar cycloaddition reaction of nitrile oxides, nitronates, nitrones and azides with 1-vinylthymine and found the latter to resemble an unactivated alkene in terms of its dipolarophilic activity. The reaction provides a concise route into diverse heterocyclic nucleoside analogues from a single dipolarophile embodying the nucleobase. Highly reactive 1,3-dipoles (nitrile oxides) afford good yields of cycloadduct under mild conditions. Product yields with less reactive dipoles (nitrones) maybe somewhat compromised by the fragility of the cycloadducts to prolonged periods at elevated temperature. For the least reactive 1,3-dipole studied (3-azidopropanol) complete decomposition of the cycloadduct occurred under the conditions required for its preparation. The scope of the reaction is, therefore, limited by the reactivity of the 1,3-dipoles and the stability of the resulting cycloadducts which show a propensity to eliminate thymine.

EXPERIMENTAL

General Procedure. Melting points were determined using a Reichert Thermovar apparatus and are uncorrected. Mass spectra were obtained on MS-50 AEI (EI, 70 eV) and MS-9 AEI (CI, isobutane) spectrometers. ^{1}H NMR spectra were recorded at 200, 250 and 400 MHz on Bruker AC200, AC250 and DPX400 spectrometers, using tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 50, 63 and 100 MHz on the same instruments. Chemical shift data are reported in parts per million (δ in ppm) where s, d, dd, t, q and m designate singlet, doublet, doublet of doublets, triplet, quartet and multiplet respectively. *J* Values are given in Hz. IR spectra were recorded on a Perkin Elmer 1600 FT IR spectrometer. Flash column chromatography was performed using Merck silica gel 60 (Art. 9385). In all cases the solvent system used for the chromatographic separations was chosen such that on TLC an R_f of 0.25-0.30 was observed for the compound to be isolated. TLC was performed on Merck silica gel 60 F_{254} precoated sheets (1.05554) with detection by UV light and iodine or alkaline potassium permanganate reagents. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl under argon and all other solvents were purified by distillation prior to use. Reactions were routinely carried out under an inert atmosphere of argon.

Antiviral Assay on CEM-c113 Cells and RT Dosage. Following the protocols used earlier by us to evaluate the anti-HIV activity of a series of N^3-substituted AZT derivatives,[59] the heterocyclic nucleoside analogues prepared in this work were tested for their ability to inhibit HIV replication in CEM-c113 cells (LAI strain[60]). The HIV-1 induced cytopathic effect (CPE) was monitored by the MTT viability assay to determine EC_{50MTT} and CC_{50} as previously described.[61] HIV replication was also followed by measurement of the reverse transcriptase activity in the culture supernatant (EC_{50RT}). Briefly, antiviral assays were performed as follows: 1 x 10^4 cells/wells were incubated in microtitration plates for 1 h with 10-fold diluted concentrations of the compound, then infected by HIV-1 LAI strain. Cultures were incubated for 7 days at 37 °C in a CO_2 incubator (5%). At day 7 the supernatant was removed for reverse transcriptase (RT) assay to determine inhibition of viral production (EC_{50RT}) and 3-(4,5-dimethylthiazol-2-

yl)-2,5-diphenyltetrazolium bromide was added in cell suspension to determine cell viability (CC_{50} and EC_{50MTT}) by the MTT assay. The toxicity of the products (CC_{50}) was defined in relation to the viability of uninfected, untreated control cells. The inhibition of CPE (EC_{50MTT}) of the products was defined in relation to the infected untreated cells.

1-Ethenyl-5-methyl-2,4-pyrimidinedione (**1**).—To a stirred solution of bromide **3** (500 mg, 2.15 mmol) in dry THF (50 ml) was added a suspension of potassium *tert*-butoxide (850 mg, 6.95 mmol) in THF (5 ml). After 2 h the excess base was neutralised with methanolic hydrogen chloride and the reaction mixture filtered through a short plug of silica gel, washing well with THF, to remove the salts. The filtrate was evaporated and the resulting solid residue recrystallised from ethanol to afford the product as a colourless solid (251 mg; 77%), m.p. 205-206 °C (EtOH); υ_{max} (nujol)/cm^{-1} 3180, 3051, 1699, 1417, 1343, 1277, 1182, 1129, 975, 909, 845, 692; δ_H(200 MHz; DMSO-d_6) 1.84 (3 H, s, CH_3), 4.85 (1 H, d, *J* 9, CH=CH_2), 5.34 (1 H, *J* 16, CH=C*H*2), 7.13 (1 H, dd, *J* 9 and 16, CH=CH_2), 7.92 (1 H, s, H-6), 11.42 (1 H, br s, NH); δ_C(50 MHz; DMSO-d_6) 11.86 (CH_3), 99.73 (CH=*C*H_2), 110.64 (C-5), 129.14 (*C*H=CH_2), 134.88 (C-6), 149.28 (C-2), 163.52 (C-4); *m/z* (EI) 152 (M^+) (Found: C, 55.21; H, 5.49; N, 18.15. $C_7H_8N_2O_2$ requires C, 55.26; H, 5.30; N, 18.41%).

1-(2-Bromoethyl)-5-methyl-2,4-pyriminidinedione (**3**).—Sodium iodide (1.00 g, 6.67 mmol) was added to a stirred solution of 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine[16] (**4**; 59.6 g, 220 mmol) in 1,2-dibromoethane (300 ml) at 100 °C. After 24 h the reaction mixture was cooled and decanted into water (500 ml). The resulting slurry was filtered, washing the residue well with boiling $CHCl_3$, and the filtrate separated. The aqueous phase was further extracted with $CHCl_3$ and the combined extract dried (sodium sulphate) and evaporated to a solid residue which upon recrystallisation from ethanol afforded the product as a colourless solid (22.5 g; 44%), m.p. 199-200 °C (EtOH); υ_{max} (nujol)/cm^{-1} 3160, 3100, 1714, 1668, 1456, 1432, 1386, 1354, 1342, 1276, 1225, 943, 908, 758, 687; δ_H(200 MHz; DMSO-d_6) 1.76 (1 H, d, *J* 0.8, CH_3), 3.73 (2 H, t, *J* 6.5, CH_2Br), 4.03 (2 H, t, *J* 6.5, NCH_2), 7.56 (1 H, d, *J* 0.8, H-6), 11.34 (1 H, br s, NH); δ_C(50 MHz; DMSO-d_6) 11.82 (CH_3), 30.47 (CH_2Br), 48.50 (NCH_2), 108.22 (C-5), 141.33 (C-6), 150.70 (C-2), 164.12 (C-4); *m/z* (CI) 233 and 235 (MH^+) (Found: C, 36.09; H, 3.84; N, 11.73. $C_7H_9N_2O_2Br$ requires C, 36.07; H, 3.89; N, 12.02%).

3-Azido-1-propanol (**9**).—To a stirred solution of 3-bromo-1-propanol (0.50 ml, 5.30 mmol) in dichloromethane (10 ml) was added Amberlite IR 400(N_3^-) resin (3.50 g; ca. 8.9 mmol N_3^-). After 24 h the reaction mixture was filtered, washing well with dichloromethane, and the filtrate evaporated to afford azide **9** as a colourless oil (455 mg; 85%) in greater than 95% purity; υ_{max} (neat)/cm^{-1} 3363 (br), 2949, 2883, 2100, 1456, 1428, 1370, 1344, 1297, 1262, 1059, 957, 902; δ_H(200 MHz; $CDCl_3$) 1.83 (2 H, p, *J* 5, CH_2-2), 2.45 (1 H, br m, OH), 3.44 (2 H, t, *J* 5, CH_2-3), 3.73 (2 H, t, *J* 5, CH_2-1); δ_C(50 MHz; $CDCl_3$) 31.48 (C-2), 48.48 (C-3), 59.77 (C-1); *m/z* (CI) 102 (MH^+). (Found: C, 34.41; H, 6.51; N, 39.37. $C_3H_7N_3O{\bullet}CH_2Cl_2$ (0.073 equiv.) requires C, 34.40; H, 6.72; N, 39.17%).[62]

Reaction of 1-Vinylthymine (**1**) *with Azide* **9**.—A solution of 1-vinylthymine (340 mg, 2.24 mmol) and azide **9** (226 mg, 2.24 mmol) in dry toluene (7.5 ml) was boiled. After 7 d the slovent was evaporated and the residue subjected to dry flash column chrmoatography (silica gel; THF) to recover unreacted 1-vinylthymine and a more polar product shown by ^{1}H NMR spectroscopy to be identical to thymine (30 mg; 11%); δ_H(200 MHz; DMSO-d_6) 1.73 (3 H, s, CH_3), 7.26 (1 H, s, H-6), 10.60 (1 H, br s, NH), 11.00 (1 H, br s, NH).

1-[3-(Methoxycarbonyl)-4,5-dihydroisoxazol-5-yl]thymine (**14**).—To a stirred solution of 1-vinylthymine (**1**; 331 mg, 2.18 mmol) and triethylamine (2.38 ml, 16.9 mmol) in dry THF (30 ml) was added dropwise over 9 h a solution of methyl chlorooximidoacetate[28] (1.71 g, 16.9 mmol) in THF (120 ml). The reaction mixture was filtered (to remove the precipitated amine hydrochloride) and evaporated. The resulting residue was purified by flash column chromatography (silica gel; 25% heptane/EtOAc) and recrystallised from ethanol to afford cycloadduct **14** as a colourless solid (473 mg; 86%), m.p. 222-223 °C (EtOH); υ_{max} (nujol)/cm^{-1} 3180, 3100, 3030, 1734, 1721, 1684, 1436, 1362, 1352, 1285, 1256, 1219, 910; δ_H(200 MHz; DMSO-d_6) 1.77 (3 H, s, 5-CH_3), 3.37 (1 H, dd, *J* 5.5 and 19, N=CCH_2), 3.69 (1 H, dd, *J* 11 and 19, N=CCH_2), 3.83 (3 H, s, OCH_3), 6.77 (1 H, dd, *J* 5.5 and 11, OCH), 7.46 (1 H, s, H-6), 11.49 (1 H, br s, NH); δ_C(50 MHz; DMSO-d_6) 11.75 (5-CH_3), 37.56 (NC=CH_2), 52.48 (OCH_3), 87.43 (OCH), 110.56 (C-5), 136.73 (C-6), 150.04 (C-2), 152.16 (**C**O_2Me), 159.82 (C=N), 163.58 (C-4); *m/z* (CI) 254 (MH^+) (Found: C, 47.17; H, 4.14; N, 16.30. $C_{10}H_{11}N_3O_5$ requires C, 47.43; H, 4.38; N, 16.59%).

1-[3-(Hydroxymethyl)-4,5-dihydroisoxazol-5-yl]thymine (**15**).—To a solution of isoxazoline **16** (164 mg, 0.482 mmol) in CH_3CN (3 ml) was added a solution of hydrofluoric acid in CH_3CN (1:9 v/v 40% HF(aq)-CH_3CN; 1.5 ml). After 1 h the reaction mixture was evaporated *in vacuo*, pumped and the resulting residue recrystallised from methanol to afford the product as a colouless solid (80 mg; 74%), m.p. 178-179 °C (MeOH); υ_{max} (nujol)/cm^{-1} 3442, 3170, 3100, 3060, 2925, 2854, 1706, 1662, 1457, 1429, 1383, 1345, 1290, 1260, 1168, 1071, 1030, 1019, 976, 902, 758, 679; δ_H(200 MHz; DMSO-d_6) 1.78 (3 H, s, 5-CH_3), 3.20 (1 H, dd, *J* 4 and 19, N=CCH_2), 3.20 (1 H, dd, *J* 4 and 19, N=CCH_2), 4.27 (2 H, m, CH_2OH), 5.43 (1 H, t, *J* 6, OH), 6.61 (1 H, dd, *J* 4 and 10, OCHN), 7.11 (1 H, s, H-6), 11.39 (1 H, br s, NH); δ_C(50 MHz; DMSO-d_6) 11.96 (5-CH_3), 40.22 (N=CCH_2), 55.71 (CH_2OH), 83.83 (OCHN), 110.26 (C-5), 135.45 (C-6), 150.05 (C-2), 160.17 (N=C), 163.51 (C-4); *m/z* (CI) 226 (MH^+) (Found: C, 47.97; H, 4.96; N, 18.44. $C_9H_{11}N_3O_4$ requires C, 48.00; H, 4.92; N, 18.66%).

1-[3-(tert-Butyldimethylsilyloxymethyl)-4,5-dihydroisoxazol-5-yl]thymine (**16**).—To a stirred solution of 1-vinylthymine (**1**; 377mg, 2.47 mmol) and triethylamine (75 µl, 0.53 mmol) in dry benzene (75 ml) under reflux was added nitro compound **18** (552 mg, 2.69 mmol) and phenyl isocyanate (600 µl, 5.52 mmol). After 3 d further nitro compound (276 mg, 1.34 mmol) and phenyl isocyanate (300 µl, 2.76 mmol) were added. The reaction mixture was cooled after a further 2 d, filtered (to remove precipitated diphenyl urea) and evaporated. The residue was purified by flash column chromatography (silica

gel; 25% EtOAc/heptane) to obtain the product as a colourless, crystalline solid (749 mg; 89%), m.p. 117-118 °C (Et_2O-hexane); υ_{max} (nujol)/cm^{-1} 3182, 3056, 3019, 2956, 2930, 2859, 1695, 1464, 1391, 1361, 1341, 1289, 1260, 1216, 1098, 839; δ_H(200 MHz; $CDCl_3$) 0.11 (6 H, s, $(CH_3)_2Si$), 0.89 (9 H, s, $(CH_3)_3C$), 1.91 (3 H, s, 5-CH_3), 3.12 (1 H, dd, *J* 3 and 19, N=CCH_2), 3.59 (1 H, dd, *J* 9 and 19, N=CCH_2), 4.46 (1 H, d, *J* 13, $SiOCH_2$), 4.54 (1 H, d, *J* 13, $SiOCH_2$), 6.68 (1 H, dd, *J* 3 and 9, OCHN), 6.97 (1 H, s, H-6), 9.10 (1 H, br s, NH); δ_C(50 MHz; $CDCl_3$) -5.39 ($(CH_3)_2Si$), 12.52 (5-CH_3), 18.22 (CSi), 25.72 ($(CH_3)_3C$), 42.55 (N=CCH_2), 57.85 ($SiOCH_2$), 84.76 (OCHN), 112.00 (C-5), 134.51 (C-6), 150.32 (C-2), 159.68 (N=C), 163.93 (C-4); *m/z* (CI) 340 (MH^+) (Found: C, 52.85; H, 7.39; N, 12.33. $C_{15}H_{25}N_3O_4Si$ requires C, 53.07; H, 7.42; N, 12.38%).

Reaction of 1-Vinylthymine (**1**) *with Nitronate* **19**.—To a stirred solution of 1-vinylthymine (20.0 mg, 0.131 mmol) and nitro compound **18** (80.1 mg, 0.390 mmol) in dry benzene (4 ml) was added *N,O*-bis(trimethylsilyl)acetamide (300 µl, 1.21 mmol). The reaction mixture was then heated at reflux under nitrogen for 24 h, cooled, quenched with methanol (5 ml) and evaporated *in vacuo* to afford a solid residue. The residue was taken up in $CHCl_3$ and filtered to obtain a colourless solid which was shown by TLC and ^1H NMR spectroscopy to be identical to thymine (16.3 mg; 99%); δ_H(200 MHz; DMSO-d_6) 1.73 (3 H, s, CH_3), 7.26 (1 H, s, H-6), 10.65 (1 H, br s, NH), 10.97 (1 H, br s, NH).

5-Methyl-1-(2-propenyl)-2,4-pyrimidindione (**25**).—Allyl bromide (50 ml, 590 mmol) and 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine[16] (**4**; 36.8 g, 136 mmol) were heated at reflux under nitrogen. After 7 h the reaction mixture was cooled and quenched by cautious addition of methanol (12.0 ml, 296 mmol) and powdered anhydrous sodium carbonate (30.0 g, 283 mmol). After the effervesence had subsided the reaction mixture was filtered, washing well with THF. The filtrate was evaporated *in vacuo* and the solid residue obtained recrystallised from EtOH-heaxane to afford the product as a colourless solid (15.56 g; 69%), m.p. 112-113 °C (EtOH-hexane); υ_{max} ($CHCl_3$)/cm^{-1} 3175, 3018, 2933, 2897, 2830, 1690, 1468, 1433, 1425, 1375, 1345, 1245, 1218, 769, 755, 668; δ_H(200 MHz; $CDCl_3$) 1.64 (3 H, s, CH_3), 4.33 (2 H, d, *J* 5, NCH_2), 5.24 (1 H, d, *J* 17, CH=CH_2), 5.28 (1 H, d, *J* 9, CH=CH_2), 5.86 (1 H, ddt, *J* 17, 10 and 5, C*H*=CH_2), 6.98 (1 H, s, H-6), 9.90 (1 H, br s, NH); δ_C(50 MHz; $CDCl_3$) 12.11 (CH_3), 49.62 (NCH_2), 110.75 (C-5), 118.84 (CH=CH_2), 131.82 (*C*H=CH_2), 139.80 (C-6), 151.14 (C-2), 164.63 (C-4); *m/z* (EI) 166 (M^+) (Found: C, 57.68; H, 5.95; N, 16.93. $C_8H_{10}N_2O_2$ requires C, 57.82; H, 6.07; N, 16.86%).

Reaction of 1-Allylthymine (**25**) *with Nitronate* **19**.—1-Allylthymine (210 mg, 1.26 mmol) was stirred with *N,O*-bis(trimethylsilyl)acetamide (3.50 ml, 14.2 mmol) under nitrogen until a clear solution had formed. Nitro compound **18** (956 mg, 4.66 mmol) was added and the reaction mixture heated to 100 °C. After 2 h the reaction mixture was cooled to room temperature and the light fractions and excess silylating agent removed rapidly *in vacuo* (20 to 120 °C at 0.5 mmHg). The residual oil was taken up in absolute methanol (20 ml) and stirred over sodium carbonate (1 g). After 1 h the

reaction mixture was diluted with ether (20 ml), filtered through a short plug of silica gel and the filtrate evaporated. TLC analysis (silica gel, EtOAc) revealed the formation of three components which were separated by flash column chromatography (silica gel; 50%EtOAc/heptane → 2% MeOH/EtOAc gradient) to afford successively oxime **29** (274 mg; 58%), oxime **30** (89 mg; 19 %) and nitrone **33** (121 mg; 18%) as colourless solids.

Oxime 29, m.p. 119-121 °C ($CHCl_3$); υ_{max} (nujol)/cm^{-1} 3282, 3061, 2924, 2854, 1699, 1662, 1250, 1084, 854, 836; δ_H(200 MHz; CD_3OD) 0.09 (6 H, s, $(CH_3)_2Si$), 0.90 (9 H, s, $(CH_3)_3C$), 1.85 (3 H, s, 5-CH_3), 2.57 (1 H, dd, *J* 8 and 13, N=CC***H***$_2$CH), 2.69 (1 H, dd, *J* 5 and 13, N=CC***H***$_2$CH), 3.49 (1 H, dd, *J* 9 and 14, NC***H***$_2$CH), 3.96 (1 H, dd, *J* 3 and 14, NC***H***$_2$CH), 4.18-4.31 (1 H, m, C***H***(OH)), 4.24 (2 H, s, $SiOCH_2$), 7.37 (1 H, s, H-6); δ_C(50 MHz; CD_3OD) 12.13 (5-CH_3), 19.06 (CSi), 26.31 ((*C*H_3)$_3$C), 31.56 (N=C***C***H_2CH), 55.16 (N***C***H_2CH), 65.55 ($SiOCH_2$), 67.91 (CH(OH)), 110.21 (C-5), 144.31 (C-6), 152.99 (C-2), 157.56 (N=C), 166.88 (C-4); *m/z* (CI) 372 (MH^+) (Found: C, 51.88; H, 7.69; N, 11.26. $C_{16}H_{29}N_3O_5Si$ requires C, 51.73; H, 7.87; N, 11.31%).

Oxime 30, m.p. 204-206 °C (MeOH); υ_{max} (nujol)/cm^{-1} 3425, 3275, 2925, 2855, 1700, 1676, 1115, 849, 774; δ_H(200 MHz; CD_3OD) 0.10 (6 H, s, $(CH_3)_2Si$), 0.92 (9 H, s, $(CH_3)_3C$), 1.85 (3 H, d, *J* 0.8, d, 5-CH_3), 2.43 (1 H, dd, *J* 7 and 14, N=CC***H***$_2$CH), 2.52 (1 H, dd, *J* 5 and 14, N=CC***H***$_2$CH), 3.51 (1 H, dd, *J* 8 and 14, NC***H***$_2$CH), 3.95 (1 H, dd, *J* 4 and 14, NC***H***$_2$CH), 4.14-4.24 (1 H, m, C***H***(OH)), 4.56 (2 H, AB q, $SiOCH_2$), 7.38 (1 H, d, *J* 0.8, H-6); δ_C(50 MHz; CD_3OD) 12.16 (5-CH_3), 19.07 (CSi), 26.34 ((*C*H_3)$_3$C), 36.56 (N=C***C***H_2CH), 54.74 (N***C***H_2CH), 59.22 ($SiOCH_2$), 68.21 (CH(OH)), 110.24 (C-5), 144.37 (C-6), 152.99 (C-2), 159.24 (N=C), 166.94 (C-4); *m/z* (CI) 372 (MH^+) (Found: C, 51.63; H, 7.63; N, 11.22. $C_{16}H_{29}N_3O_5Si$ requires C, 51.73; H, 7.87; N, 11.31%).

Nitrone 33; υ_{max} ($CHCl_3$)/cm^{-1} 3365, 3140, 2957, 2931, 2858, 1707, 1667, 1473, 1438, 1385, 1362, 1254, 1153, 1113, 902, 837; δ_H(200 MHz; $CDCl_3$) 0.01-0.03 (12 H, m, 2 x $(CH_3)_2Si$), 0.84-0.86 (18 H, m, 2 x $(CH_3)_3C$), 1.56 (1 H, br t, J 12, CHC***H***$_2$CH(OH)), 1.82 (3 H, s, 5-CH_3), 2.00-2.19 (1 H, br m, CHC***H***$_2$CH(OH)), 3.45-4.25 (6 H, m, NC***H***$_2$C***H***(OH) and SiOC***H***$_2$C***H***), 4.55 (2 H ,d, *J* 3.6, OC***H***$_2$CH=N), 5.54 (1 H, br m, OH), 6.99 (1 H, t, *J* 3.6, OCH_2C***H***=N), 7.38 (1 H, s, H-6), 10.20 (1 H, br s, NH); δ_C(50 MHz; $CDCl_3$) 12.17 (5-CH_3), 18.16 (CSi), 25.80 ((***C***H_3)$_3$C), 33.42 (CH***C***H_2CH), 54.05 (NCH_2), 59.75 (***C***H_2C=N), 62.40 (SiO***C***H_2CH), 65.88 (CH), 73.34 (CH), 109.94 (C-5), 142.12 (CH), 143.90 (CH), 151.95 (C-2), 164.77 (C-4); *m/z* (FAB) 529 (M^+; 100%), 513 ($(M-O)^+$; 50%).[63]

1-[[3-(tert-Butyldimethylsilyloxymethyl)-4,5-dihydroisoxazol-5-yl]methyl]thymine (**35**).—To a stirred solution of 1-allylthymine (**25**; 1.00 g, 6.03 mmol) in dry toluene (75 ml) at 60 °C under nitrogen was added nitro compound **18** (1.45 g, 7.04 mmol), phenyl isocyanate (1.50 ml, 13.8 mmol) and triethylamine (100 µl, 0.72 mmol). After 1 d further nitro compound (1.45 g, 7.04 mmol) and phenyl isocyanate (1.50 ml, 13.8 mmol) were added. The reaction mixture was cooled after 4 d and filtered (to remove precipitated diphenyl urea), washing well with 50% EtOAc/heptane. The filtrate was evaporated *in vacuo* to a residue which was subjected to flash column chromatography (silica gel; 25% heptane/EtOAc) to obtain cycloadduct **35** as a colourless oil which slowly solidified on standing (1.79 g; 84%), m.p. 109-110 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3188,

2955, 2931, 2858, 1683, 472, I465, 1253, 1098, 839; δ_H(250 MHz; $CDCl_3$) 0.07 (6 H, s, $Si(CH_3)_2$), 0.88 (9 H, s, $C(CH_3)_3$), 1.90 (3 H, s, 5-CH_3), 2.83 (1 H, dd, *J* 7 and 18, N=CCH_2), 3.19 (1 H, dd, *J* 11 and 18, N=CCH_2), 3.61 (1 H, dd, *J* 8 and 14, NCH_2), 4.07 (1 H, dd, *J* 2 and 14, NCH_2), 4.39 (2 H, s, OCH_2), 4.81-4.92 (1 H, m, OCH), 7.15 (1 H, s, H-6), 9.81 (1 H, br s, NH); δ_C(63 MHz; $CDCl_3$) -5.53 ($Si(CH_3)_2$), 12.16 (5-CH_3), 18.07 ($\mathbf{C}(CH_3)_3$), 25.61 ($C(\mathbf{C}H_3)_3$), 37.87 (N=$C\mathbf{C}H_2$), 50.51 (NCH_2), 58.09 (OCH_2), 78.02 (OCH), 110.53 (C-5), 141.32 (C-6), 151.57 (C-2), 159.02 (C=N), 164.59 (C-4); *m/z* (CI) 354 (MH^+) (Found: C, 54.37; H, 7.41; N, 11.83. $C_{16}H_{27}N_3O_4Si$ requires C, 54.36; H, 7.70; N, 11.89%).

1-[(3-(Hydroxymethyl)-4,5-dihydroisoxazol-5-yl)methyl]thymine (**36**).—To a stirred solution of isoxazoline **35** (340 mg, 0.962 mmol) in CH_3CN (2.5 ml) at 0 °C was added a solution of hydrofluoric acid in CH_3CN (1:9 v/v 40% HF (aq)-CH_3CN; 2 ml). After 1 h the reaction mixture was evaporated *in vacuo*, pumped and the resulting residue recrystallised from EtOAc-MeOH to afford **36** as a colourless solid (209 mg; 91%), m.p. 178-179 °C (EtOAc-MeOH); υ_{max} (Nujol)/cm^{-1} 3435, 3165, 3036, 2953, 2854, 1682-1665, 1472, 1423, 1348, 1253, 1226, 1070, 870, 763, 715; δ_H(200 MHz; DMSO-d_6) 1.78 (3 H, s, 5-CH_3), 2.85 (1 H, dd, *J* 7 and 18, N=CCH_2), 3.18 (1 H, dd, *J* 11 and 18, N=CCH_2), 3.70 (1 H, dd, *J* 7 and 14, NCH_2), 3.85 (1 H, dd, *J* 4 and 14, NCH_2), 4.19 (2 H, d, *J* 3, $HOC\mathbf{H}_2$), 4.72-4.87 (1 H, m, OCH), 5.33 (1 H, t, *J* 3, HO), 7.45 (1 H, s, H-6), 11.32 (1 H, br s, NH); δ_C(50 MHz; DMSO-d_6) 11.99 (5-CH_3), 37.98 (N=$C\mathbf{C}H_2$), 50.53 (NCH_2), 56.12 ($HOCH_2$), 77.17 (OCH), 108.40 (C-5), 141.95 (br, C-6), 151.18 (C-2), 159.76 (C=N), 164.32 (C-4); *m/z* (CI) 240 (MH^+) (Found: C, 50.13; H, 5.63; N, 17.38. $C_{10}H_{13}N_3O_4$ requires C, 50.21; H, 5.48; N, 17.56%).

1-(2-Methylisoxazolidin-5-yl)thymine (**38**).—Paraformaldehyde (1.23 g, 41.0 mmol), *N*-methylhydroxylamine hydrochloride (1.55 g, 18.5 mmol), sodium acetate (2.48 g, 30.2 mmol) and 1-vinylthymine (**1**; 528 mg, 3.47 mmol) were boiled in dry toluene (50 ml). After 9 h the reaction mixture was partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic layer was further washed with brine, dried ($MgSO_4$) and evaporated. The residue was taken up in toluene (20 ml), treated with triethylamine (30 μl) and the solvent slowly distilled out at atmospheric pressure (to decompose the formaldehyde modified derivative **39** and remove excess paraformaldehyde). Compound **38** (354 mg, 48%) was isolated by flash column chromatography (silica gel; 2% MeOH/EtOAc), m.p. 141-143 °C (CH_2Cl_2-light petroleum); δ_H(200 MHz; $CDCl_3$) 1.95 (3 H, s, 5-Me), 2.34 (1 H, m, *J* 13.0, 9.7, 7.3, and 3.8, H-4a'), 2.55 (1 H, br m, H-3a'), 2.81 (3 H, s, NMe), 2.94 (1 H, m, *J* 13.0, 7.5, 7.5 and 1.9, H-4b'), 3.40 (1 H, br m, H-3b'), 6.21 (1 H, dd, *J* 3.8 and 7.5, H-5'), 7.63 (1 H, s, H-6), 9.19 (1 H, br s, NH); δ_C(50 MHz; $CDCl_3$) 12.55 (5-Me), 38.00 (C-4'), 45.15 (2'-Me), 56.57 (C-3'), 83.53 (C-5'), 110.51 (C-5), 135.99 (C-6), 150.79 (C-2), 164.49 (C-4); *m/z* (EI) 211 (M^+), 86 (M^+-B) (Found (EI) *M* 211.0944. $C_9H_{13}N_3O_3$ requires 211.0957).[63]

Diethyl N-(tert-butyldimethylsilyloxy)aminomethylphosphonate (**41**).—To a stirred solution of *tert*-butyldimethylsilyloxyamine[39] (9.00 g, 61.1 mmol) and triethylamine (4.50 ml, 32.3 mmol) in dry CH_2Cl_2 (60 ml) at 0 °C under nitrogen was added diethyl

phosphonomethyl triflate[41] (9.00 g, 30.0 mmol). The reaction mixture was allowed to warm slowly to room temperature and the solvent was then evaporated to afford a residual oil which was purified by flushing *rapidly* through a column of flash chromatography silica gel (ϕ = 40 mm x l = 150 mm; 5-50% EtOAc/heptane gradient) to obtain compound **41** (6.00 g, 67%) as a clourless oil; υ_{max} (neat)/cm^{-1} 3460, 3240, 2958, 2930, 2857, 1249, 1055, 1026, 781; δ_H(200 MHz; $CDCl_3$) 0.09 (6 H, s, $(CH_3)_2Si$), 0.90 (9 H, s, $(CH_3)_3C$), 1.32 (6 H, t, *J* 7, $(CH_3CH_2O)_2$), 3.29 (2 H, d, $^2J_{HP}$ 12, CH_2P), 4.06-4.20 (4 H, m, $(CH_3CH_2O)_2$); δ_C(50 MHz; $CDCl_3$) 16.41 (d, $^3J_{CP}$ 5.9, $(CH_3CH_2O)_2$), 17.95 ($(CH_3)_3C$), 26.20 ($(CH_3)_3C$), 50.44 (d, $^1J_{CP}$ 141, CH_2P), 62.04 (d, $^2J_{CP}$ 6, $(CH_3CH_2O)_2$).

Diethyl N-hydroxyaminomethylphosphonate (**42**).—To a stirred solution of silyl ether **41** (254 mg, 0.854 mmol) in CH_3CN (0.5 ml) was added a solution of hydrofluoric acid in acetonitrile (1:9 v/v 40% HF (aq) - CH_3CN; 1 ml). After 1 h the reaction mixture was partitioned between $CHCl_3$ (20 ml) and saturated aqueous sodium chloride solution (10 ml) containing sodium carbonate (0.3 g). The organic phase was separated and the aqueous phase further extracted with $CHCl_3$ (5 x 20 ml). The combined extract was dried (sodium sulphate), filtered and evaporated to afford the hydroxylamine as a wax (151 mg; 96%) in greater than 95% purity by NMR spectroscopy; m.p ca. 35 °C; υ_{max} (neat)/cm^{-1} 3280, 2985, 2934, 2910, 1444, 1395, 1290, 1229, 1165, 1098, 1052, 1025, 971, 783; δ_H(200 MHz; $CDCl_3$) 1.29 (6 H, t, *J* 7, $(CH_3CH_2O)_2$), 3.33 (2 H, d, *J* 12, PCH_2), 4.03-4.18 (4 H, m, $(CH_3CH_2O)_2$), 5.00 (2 H, br m, NHOH); δ_C(50 MHz; $CDCl_3$) 16.40 (d, $^3J_{CP}$ 6, $(CH_3CH_2O)_2$), 49.92 (d, $^1J_{CP}$ 149, PCH_2), 62.25 (d, $^2J_{CP}$ 6, $(CH_3CH_2O)_2$); *m/z* (EI) 183 (M^+). An analytical sample was prepared by derivitisation with picric acid, m.p. (picrate) 112-113 °C (EtOH-Et_2O). (Found: C, 32.11; H, 4.27; N, 13.33. picrate $C_5H_{14}NO_4P.C_6H_3N_3O_7$ requires C, 32.05; H, 4.16; N, 13.59%).

1-[2-(Diethylphosphonomethyl)isoxazolidin-5-yl]thymine (**45**).—Paraformaldehyde (815 mg), hydroxylamine **42** (193 mg, 1.05 mmol) and 1-vinylthymine (**1**; 464 mg, 3.05 mmol) were boiled in dry toluene (50 ml). After 7 h the reaction mixture was concentrated by distillation at atmospheric pressure (to remove excess paraformaldehyde), the remainder of the solvent being removed *in vacuo*. The residue was taken up in dichloromethane, filtered (to remove excess 1-vinylthymine and traces of thymine), and flash column chromatographed (silica gel; 5% MeOH/EtOAc) to obtain cycloadduct **45** (276 mg, 75%); υ_{max} (neat)/cm^{-1} 3485, 3179, 3061, 2985, 2932, 2910, 2868, 2819, 1695, 1469, 1453, 1268, 1110, 1052, 1027, 969; δ_H(200 MHz; $CDCl_3$) 1.36 (6 H, t, *J* 7, $(CH_3CH_2O)_2$), 1.94 (3 H, s, 5-Me), 2.28-2.46 (1 H, m, H-4a'), 2.65-2.78 (1 H, m, H-3a'), 2.90-3.05 (1 H, m, H-4b'), 3.24-3.57 (2 H, m, CH_2P), 3.54-3.65 (1 H, m, H-3b'), 4.12-4.26 (4 H, m, $(CH_3CH_2O)_2$), 6.18 (1 H, dd, *J* 4 and 8, H-5'), 7.81 (1 H, s, H-6), 10.26 (1 H, br s, NH); δ_C(50 MHz; $CDCl_3$) 12.26 (5-Me), 16.17 ($^3J_{CP}$ 3, $(CH_3CH_2O)_2$), 37.69 (C-4'), 53.56 ($^1J_{CP}$ 163, CH_2P), 56.29 ($^3J_{CP}$ 12, C-3'), 62.09 ($^2J_{CP}$6, $(CH_3CH_2O)_2$), 62.35 ($^2J_{CP}$6, $(CH_3CH_2O)_2$), 83.25 (C-5'), 110.14 (C-5), 135.85 (C-6), 150.56 (C-2), 164.22 (C-4); *m/z* (CI) 348 (MH^+), 222 (M^+-B), 127 (BH_2^+) (Found: C, 38.54; H, 5.15; N, 9.84. $C_{13}H_{22}N_3O_6P$·0.66 eqiuv. $CHCl_3$ requires C, 38.51; H, 5.36; N, 9.86%) (Found (EI) *M* 347.1249. $C_{13}H_{22}N_3O_6P$ requires 347.1246).[64]

cis-1-[2-(Phosphonomethyl)-3-(hydroxymethyl)isoxazolidin-5-yl]thymine (**50**) *and trans-1-[2-(Phosphonomethyl)-3-(hydroxymethyl)isoxazolidin-5-yl]thymine* (**51**).—To a stirred solution of hydroxylamine **42** (518 mg, 2.83 mmol) in dry THF (10 ml) over activated 4 Å molecular sieves was added aldehyde **46**[43-48] (1.00 g, 5.75 mmol). After 1.5 h TLC (SiO_2, 5% MeOH/EtOAc) indicated complete conversion of the hydroxylamine to the UV active nitrone; δ_H(200 MHz; $CDCl_3$) 0.07 (6 H, s, $Si(CH_3)_2$), 0.88 (9 H, s, $C(CH_3)_3$), 1.36 (6 H, t, *J* 7, $(CH_3CH_2O)_2$), 4.10-4.31 (6 H, m, CH_2N and $(CH_3CH_2O)_2$), 4.60 (2 H, app t, *J* 5, CH_2O), 6.93 (1 H, app q, *J* 4, N=CH); δ_C(63 MHz; $CDCl_3$) -5.37 ($Si(CH_3)_2$), 16.44 ($^3J_{CP}$ 6, $(CH_3CH_2O)_2$), 18.28 ($C(CH_3)_3$), 25.89 ($C(CH_3)_3$), 37.69 (C-4'), 59.99 (OCH_2), 61.02 ($^1J_{CP}$ 151, CH_2P), 63.54 ($^2J_{CP}$ 6, $(CH_3CH_2O)_2$), 142.85 ($^3J_{CP}$ 7, CH=N). The reaction mixture was then transferred by cannula under nitrogen to a sealed tube containing 1-vinylthymine (**1**; 2.00 g, 13.14 mmol). The tube was closed and heated at 90 °C. After 24 h the reaction mixture was cooled and evaporated to afford a slurry which was thoroughly triturated with EtOAc to remove much of the excess dipolarophile. The solution containing the cycloadducts was evaporated and the resulting residue subjected to flash column chromatography (5% MeOH/EtOAc) in order to remove final traces of compound **1**. The inseparable mixture of isoxazolidines **48** and **49** (998 mg) obtained in this manner was taken up in a mixture of 40% hydrofluoric acid and acetonitrile (1:9 v/v; 5 ml) for 2 h. The reaction mixture was then diluted with $CHCl_3$ (10 ml) and powdered anhydrous sodium carbonate (2 g) was added. The reaction mixture was filtered and evaporated to afforded a yellow oil (767 mg) comprising a 1.7:1 mixture of **50** and **51**. The adducts were partially separated by repeated flash column chromatography (5-10% MeOH/EtOAc gradient) to afford the less polar adduct **50** as an oil (200 mg; 19%) and **51**, also an oil, (266 mg; 25%).

Isoxazolidine **50**; υ_{max} (neat)/cm^{-1} 3392, 3210, 3064, 2986, 2932, 1695, 1471 1393, 1273, 1238, 1216, 1108, 1027, 975, 755; δ_H(400 MHz; $CDCl_3$) 1.30-1.37 (6 H, m, $(CH_3CH_2O)_2$), 1.93 (3 H, s, 5-Me), 2.26 (1 H, ddd, *J* 3.6, 9.3 and 13.6, H-4'b), 2.75 (1 H, br s, OH), 2.97 (1 H, app dt, *J* 13.7 and 7.8, H-4'a), 3.04-3.09 (1 H, br m, H-3'), 3.44 (1 H, dd, *J* 11.6 and 15.8, CH_2P), 3.55 (1 H, dd, *J* 12.1 and 15.8, CH_2P), 3.70 (1 H, dd, *J* 5.4 and 12.5, CH_2O), 3.86 (1 H, dd, *J* 12.0 and 12.5, CH_2O), 4.00-4.25 (4 H, m, $(CH_3CH_2O)_2$), 6.14 (1 H, dd, *J* 3.6 and 7.5, H-5'), 7.95 (1 H, s, H-6), 8.70 (1 H, br s, NH); δ_C(101 MHz; $CDCl_3$) 12.64 (5-Me), 16.50 ($^3J_{CP}$ 6, CH_3CH_2O), 16.53 ($^3J_{CP}$ 6, CH_3CH_2O), 40.24 (C-4'), 52.72 ($^1J_{CP}$ 168, CH_2P), 60.99 (CH_2O), 62.52 ($^2J_{CP}$ 6, CH_3CH_2O), 63.07 ($^3J_{CP}$ 6, CH_3CH_2O), 69.56 ($^3J_{CP}$ 15, C-3'), 82.85 (C-5'), 110.52 (C-5), 136.60 (C-6), 150.75 (C-2), 164.20 (C-4); (Found (EI) weak *M* 377.1378. $C_{14}H_{24}N_3O_7P$ [M^+] requires 377.1352) (Found (EI) weak *M* 346.1161. $C_{13}H_{21}N_3O_6P$ [$M-CH_2OH]^+$ requires 346.1168).[63]

Isoxazolidine **51**; υ_{max} (neat)/cm^{-1} 3392, 3188, 2990, 2932, 1695, 1471, 1394, 1369, 1271, 1243, 1229, 1164, 1099, 1049, 1028, 973, 756; δ_H(400 MHz; $CDCl_3$) 1.30-1.37 (6 H, m, $(CH_3CH_2O)_2$), 1.94 (3 H, s, 5-Me), 2.42 (1 H, ddd, *J* 4.5, 7.6 and 12.2, H-4'a), 2.45 (1 H, br s, OH), 2.64 (1 H, app dt, *J* 12 and 7, H-4'b), 3.55-3.67 (3 H, br m, CH_2P and H-3'), 3.73-3.78 (2 H, m, CH_2O), 4.10-4.23 (4 H, m, $(CH_3CH_2O)_2$), 6.11 (1 H, dd, *J* 4.4 and 7.5, H-5'), 7.54 (1 H, s, H-6), 8.80 (1 H, br s, NH); δ_C(63 MHz; $CDCl_3$) 12.52 (5-Me), 16.42 ($^3J_{CP}$ 5, $(CH_3CH_2O)_2$), 38.59 (C-4'), 51.03 ($^1J_{CP}$ 164, CH_2P), 61.12 (CH_2O), 62.53

($^2J_{CP}$ 6, $CH_3\mathbf{C}H_2O$), 62.80 ($^2J_{CP}$ 6, $CH_3\mathbf{C}H_2O$), 66.61 ($^3J_{CP}$ 15, C-3'), 83.26 (C-5'), 111.10 (C-5), 136.13 (C-6), 150.66 (C-2), 164.21 (C-4); (Found (EI) weak *M* 377.1396. $C_{14}H_{24}N_3O_7P$ [M^+] requires 377.1352) (Found (EI) weak *M* 346.1158. $C_{13}H_{21}N_3O_6P$ [$M-CH_2OH]^+$ requires 346.1168).[63]

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62 In order to avoid excessive loss of azide **9** by evaporation dichloromethane was not exhaustively removed on pumping.
63 This compound was unstable to the prolonged drying conditions required to remove solvent traces for microanalysis; satisfactory microanalysis was, therefore, not possible.
64 A $CHCl_3$ solution of the purified isoxazolidine **45** was subjected to fine filtration; evaporation of the filtrate and brief pumping (30 min @ 0.01 mmHg) gave a viscous oil which analysed correctly, taking into account the presence of residual chloroform.