ARTICLE

OBC
www.rsc.org/obc

Synthesis and molecular structure of new acyclic analogues of nucleotides with a 1,2-alkadienic skeleton

Valery K. Brel,*[a] Vitaly K. Belsky,[b] Adam I. Stash,[b] Valery E. Zavodnik[b] and Peter J. Stang[c]

[a] *Institute of Physiologically Active Compounds, Russian Academy of Sciences, Chernogolovka, Moscow Region, 142432, Russian Federation. E-mail: brel@ipac.ac.ru; Fax: 7(095)7857024*

[b] *L. Karpov of Institute of Physical-Chemistry, Moscow, 105064, Russian Federation*

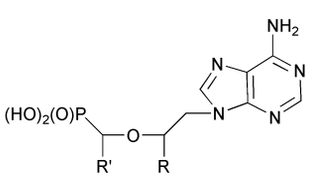
[c] *Department of Chemistry, University of Utah, Salt Lake City, UT 84112, USA*

Received 15th August 2003, Accepted 6th October 2003
First published as an Advance Article on the web 27th October 2003

Reaction of 1-chloro-4-(diethoxyphosphonyl)alka-2,3-dienes **14**,**15** with purine and pyrimidine heterocyclic bases in the presence of cesium carbonate afforded new acyclic analogues of nucleotides containing a 1,2-alkadienic skeleton **18**–**23**. Dealkylation of **18**–**23** furnished phosphonic acids **2a**–**f**. In contrast, alkylation reaction with 1-chloro-4-(diethoxyphosphonyl)octa-2,3-diene **16** led to *Z*- and *E*- 1,3-alkadienic phosphonates **25a**,**b** and **26a**,**b**. A similar reaction with 1-chloro-4-(diethoxyphosphonyl)-2-methylbuta-2,3-diene **17** led to the elimination of hydrochloride and formation of 4-(diethylphosphonyl)-2-methylbut-1-en-3-yne **24**. Molecular structures of new acyclic nucleotides **18** and **2f** are determined by X-ray crystallographic analysis.

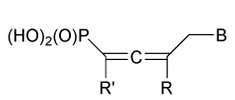
Introduction

Acyclic analogues of nucleotides are at the center of current interest as potential antiviral and anticancer agents.[1] These are the analogues of natural nucleotides where pentafuranosyl sugar ring has been replaced with an acyclic moiety that mimics the natural sugar or sugar phosphate. The area of acyclic nucleotides has been widely explored due to their broad-spectrum antiviral activity against several DNA and RNA viruses.[1a] A large number of interesting acyclic nucleotides targeted as antiviral and anticancer agents have been synthesized.[2–4] For example, 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA **1a**, Fig. 1) effectively inhibits a wide array of DNA viruses (herpes, adeno, irido, and poxviruses)[2] and retroviruses (Moloney murine sarcoma virus (MSV),[3] murine acquired immunodeficiency disease,[4] hepatitis B[5] and for clinical studies against AIDS[6]).



1a-e

R, R' = H (a); R =CH_2OH, R' = H (b); R = CH_3, R' = H (c); R = CH_2F, R' = H (d); R = H, R' = F (e),



2

B = adenin-9-yl; uracil-1-yl; thymin-1-yl.

Fig. 1

Modification of the side-chain of PMEA-derivatives strongly influences the antiviral selectivity of the compounds.[7,8] For example, *N*-(3-hydroxy-2-phosphonomethoxypropyl)purine **1b** acts solely on DNA viruses,[2b] while *N*-(2-phosphonomethoxypropyl)purine **1c**[7] and *N*-(3-fluoro-2-phosphonomethoxypropyl)purine **1d** exclusively affect retroviruses.[7,9] 9-[2-(Phosphonofluoromethoxy)ethyl]adenine **1e** and its monoester were inactive against HIV-1, but exhibited potent activity against both human cytomegalovirus (HCMV) and Epstein Barr virus (EBV).[8]

Our previous work[10] focused on the applications of phosphorylated allenes for the construction of unsaturated organophosphorus compounds. It is necessary to note, that unsaturated analogues of nucleosides, cyclic and acyclic, are currently the focus of much attention as antiviral and antitumor agents. For example, Zemlicka[11] has demonstrated that a group of allenic analogues of nucleosides (B–CH=C=CR–CH_2–OH, where: B = adenin-N^9-yl or cytosin-N^1-yl; R = H, CH_2OH) exhibits a high and selective anti-HIV effect *in vitro*.

In order to better understand the role of the carbon skeleton in acyclic analogues of nucleotides **1** (Fig. 1), we designed an efficient methodology for the preparation of a new type of phosphonate analogues of nucleotides **2a**–**f**. The goal of our current research is the synthesis of new acyclic analogues of nucleotides, which will be useful for further biological studies. The target compounds were prepared, in which the pentafuranosyl sugar ring has been replaced by a –C=C=C–CH_2– skeleton.

Results and discussion

In a preliminary publication, we have reported the synthesis of the new nucleotide analogues **2**.[10f] Now we provide details of our methods for the construction of unsaturated nucleotide analogues.

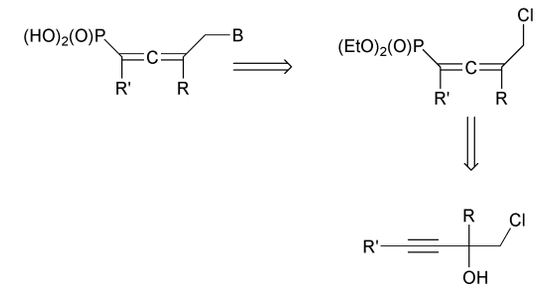
Retrosynthetic analysis of the target compounds revealed that the acyclic analogues of nucleotides with the –C=C=C–CH_2– skeleton can be constructed by coupling 1-chloro-4-(diethoxyphosphonyl)alka-2,3-diene with the corresponding purine and pyrimidine heterocyclic bases (Scheme 1).

Our synthetic strategy, (illustrated in Scheme 3) was centered on the phosphorylated allenes.[12] They were synthesized in good yield from acetylenic alcohols **6**–**9** by Horner–Mark [2,3]-sigmatropic rearrangement[13] of the unstable phosphites **10**–**13**, which were generated *in situ* by reaction with diethyl chlorophosphite in the presence of triethylamine in diethyl ether at −15 °C. As a rule the acetylene-allene rearrangement was complete after 24 h at room temperature (Scheme 2). ^{31}P NMR spectrum of the reaction mixture showed the near quantitative conversion of phosphites **10**–**13** to the phosphorylated allenes **14**–**17**.

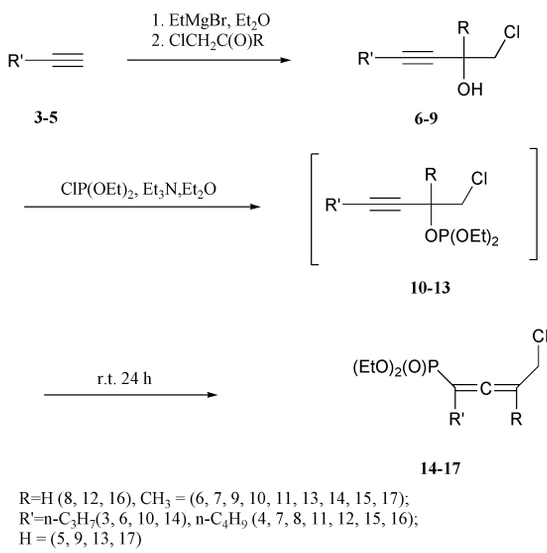
Compounds **14**–**17** are stable enough to be handled at ambient temperature. Analytically pure phosphorylated allenes

DOI: 10.1039/b309684j

 This journal is © The Royal Society of Chemistry 2003

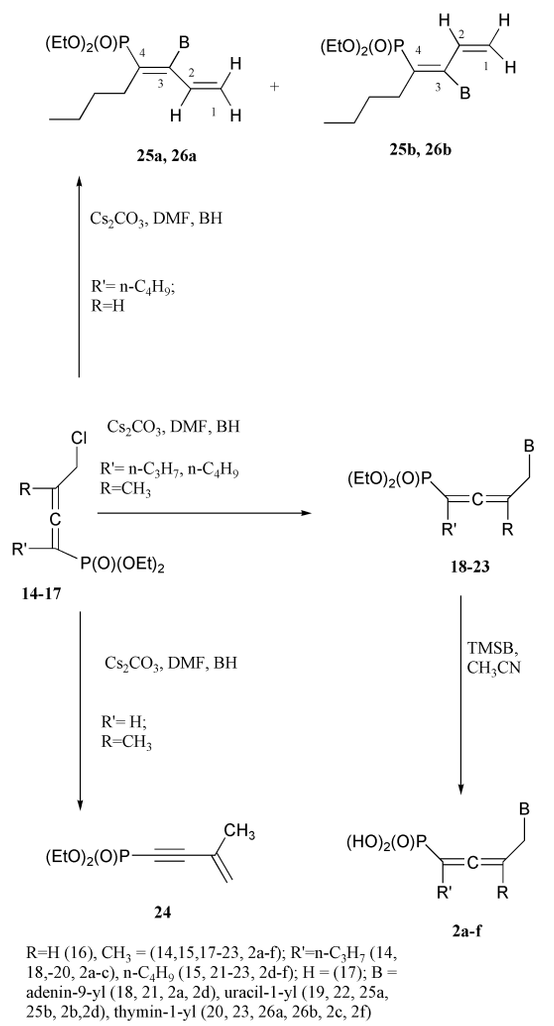


Scheme 1



R=H (8, 12, 16), CH_3 = (6, 7, 9, 10, 11, 13, 14, 15, 17); R'=n-C_3H_7(3, 6, 10, 14), n-C_4H_9 (4, 7, 8, 11, 12, 15, 16); H = (5, 9, 13, 17)

Scheme 2



R=H (16), CH_3 = (14,15,17-23, 2a-f); R'=n-C_3H_7 (14, 18,-20, 2a-c), n-C_4H_9 (15, 21-23, 2d-f); H = (17); B = adenin-9-yl (18, 21, 2a, 2d), uracil-1-yl (19, 22, 25a, 25b, 2b,2d), thymin-1-yl (20, 23, 26a, 26b, 2c, 2f)

Scheme 3

14–**17** were isolated as a colorless or pale yellow oil by column chromatography on silica gel.

The structural identity of allenes **14**–**17** was established by their ^{13}P and ^{13}C NMR spectra. The ^{31}P chemical shift is characteristic of compounds with a four-coordinate phosphorus atom linked to an *sp*^{2}-hybridized carbon.[10] The extreme low field position of the central allenic carbon atom resonance (211.94 ppm) allows the immediate identification of the allenic moiety by ^{13}C NMR spectroscopy.[14]

With these compounds in hand, we wished to study the condensation of 1-chloro-4-(diethoxyphosphonyl)alka-2,3-diene with some purine and pyrimidine heterocyclic bases. Several kinds of alkylation of the alkyl halides by purine and pyrimidine heterocyclic bases have been described earlier; among them alkylation in the presence of sodium hydride, potassium carbonate and cesium carbonate. However, the use of sodium or potassium salts of purine and pyrimidine is restricted by their limited solubility in DMF, therefore we used cesium carbonate. Condensation using the standard conditions (1 equivalent of chloroallene and 2 equivalents each of heterocyclic base and cesium carbonate in DMF at 75 °C for 2 h) afforded the target compounds **18**–**23**. The progress of condensation was monitored by TLC on SiO_2. Diesters **18**–**23** were isolated by column chromatography on silica gel in good yield.

Unlike compounds **14** and **15**, 1-chloro-4-(diethoxyphosphonyl)-2-methylbuta-2,3-diene **17**, with a hydrogen on C4, does not react with heterocyclic bases under the same conditions. The reaction of allene **17** with the adenine and Cs_2CO_3 in DMF at 75 °C led to the 1-4 elimination of hydrogen chloride providing 4-(diethylphosphonyl)-2-methylbut-1-en-3-yne **24** in 85% isolated yield. The 1-4 elimination of HCl from **17** was readily confirmed by the absence of the signal of the CH_2Cl group at 4.12 ppm and the signal of the C4 proton at 5.42 ppm in the ^{1}H NMR spectrum, which were present in the starting compound **17**.

In contrast to the alkylation observed for allenes **14** and **15**, 1-chloro-4-(diethoxyphosphonyl)octa-2,3-diene **16** (with a proton on C2), behaved in a different fashion. The interaction of phosphonate **16** with uracil or thymine in the presence of Cs_2CO_3 at 75 °C leads to formation of 1,3-alkadienes **25** and **26**, as *Z* and *E* isomers. The structural identity of 1,3-alkadienes **25a**,**25b** and **26a**,**26b** was established by their ^{1}H and ^{13}C NMR spectra. The CH_2 signals in **25a**,**25b** and **26a**,**26b** appear at the lowest field of the 1,3-alkadiene portion as a doublet, of doublet, of doublets at 6.77 ppm for **25a** and **26a** (*Z* isomers) and at 7.44 ppm for **25b** and **26b** (*E* isomers), coupled to phosphorus ($J_{2,P}$ = 1.5–2.0 Hz) as well as H_{cis} ($J_{2,cis}$ = 10.7 Hz) and H_{trans} ($J_{2,trans}$ = 16.9 Hz). The protons of the $=CH_2$ exhibit a pattern typical for a vinyl group.

The ^{13}C NMR spectra and, particularly, the DEPT experiment further corroborated the proposed structure. Compounds **25a**,**25b** and **26a**,**26b** contain two (in **25a**,**25b**) or three (in **26a**,**26b**) different kinds of methyl groups, four different kinds of methylene moieties (including $=CH_2$) group and three (in **25a**,**25b**) or two (in **26a**,**26b**) different kinds of CH groups. C2 forms a split doublet which is coupled to phosphorus ($J_{C2,P}$ = 15.6 or 15.9 Hz for **25a**,**26a**) and ($J_{C2,P}$ = 4.6 or 4.8 Hz for **25b**,**26b**). The $J_{C2,P}$ value of 15.6 or 15.9 Hz (for **25a**,**26a**) is in agreement with *trans* arrangement of the phosphonate group and C2.[11b] The quarternary C4 which carries the phosphonate moiety, has the largest coupling constant ($J_{C4,P}$ = 168.6–174.5 Hz).

Next we have turned our attention to the deesterification of the phosphonate group. For this purpose we have chosen bromotrimethylsilane (TMS-Br) (an efficient reagent for dealkylation of phosphonate dialkyl ester) to generate the

Table 1 Selected significant bond distances (Å) and bond angles (deg) for compounds **18** and **2f**

Compound	**18**	**2f**
Bond distances		
P–C(1)	1.766 (13)	1.782 (3)
N(1)–C(4)	1.460 (10)	1.463 (3)
C(1)–C(2)	1.285 (15)	1.305 (3)
C(1)–C(6)	1.650 (3)	1.513 (4)
C(2)–C(3)	1.288 (15)	1.301 (3)
C(3)–C(4)	1.491 (13)	1.503 (4)
C(3)–C(5)	1.518 (13)	1.500 (3)
Bond angles		
C(2)–C(1)–P	118.1 (9)	118.8 (2)
C(6)–C(1)–P	114.6 (11)	116.6 (19)
C(1)–C(2)–C(3)	177.5 (12)	177.1 (3)
C(2)–C(3)–C(4)	124.0 (9)	120.9 (2)
C(2)–C(3)–C(5)	122.3 (12)	124.0 (2)
C(4)–C(3)–C(5)	113.6 (11)	115.2 (2)
N(1)–C(4)–C(3)	112.1 (8)	112.9 (2)

corresponding phosphonic acid. Treating the diethyl esters **18**–**23** with 5 eq. of the TMS-Br in acetonitrile at room temperature for 12 h under a nitrogen atmosphere furnished the phosphonic acids **2a**–**f** in good yield. The high purity free phosphonic acids **2b**,**2c**,**2e**,**2f** were obtained by the simple recrystallization from dry methanol (or hexane, for acids **2a**,**2d**). Some phosphonic acids, for example **2a**,**2d**, have been shown to be very hydroscopic.

X-Ray crystallography study of 18 and 2f†

The structures of both **18** and **2f** were provided by the X-ray diffraction analysis.[15] Only a few X-ray crystallography studies of phosphorylated allenes without purine or pyrimidine heterocyclic substituents have been reported before.[16–18]

Colorless crystals of 1-(adenin-9-yl)-4-(diethylphosphonyl)-2-methylhepta-2,3-diene **18** and 2-methyl-4-(phosphonyl)-1-(thymin-1-yl)octa-2,3-diene **2f** used for the X-ray diffraction analysis were grown by slow cooling of saturated solutions of the compounds in $CHCl_3$ (for compound **18**) or MeOH (for compound **2f**). Geometrical parameters for diester **18** and acid **2f** are given in Table 1.

In the structure of **18** (Fig. 2) the geometrical parameters of the adenine moiety are in good agreement with those of the "free" molecule[19,20] the other bond lengths correspond to the mean values for the similar structures.[21] The system of cumulative double bonds in **18** is linear and has an orthogonal configuration of the substituents at C1 and C3. The angle between the adenine moiety plane (max. deviation 0.02 Å) and the C6–C10 plane (max. deviation 0.01 Å) is 83.5°, and the angle between the latter and the P–C10–C11 plane is 83.3°. The distances in the allene system are consistent with those found in ref. 16. The molecular packing is also governed by the intermolecular hydrogen bonds NH ··· N with parameters: N5–H51$_n$ 1.03 Å, H51$_n$ ··· N4 2.09 Å, N5 ··· N4 2.990 Å (, 1 − y, ½ + z), angle NHN 145°; N5–H52$_n$ 1.10 Å, H52$_n$ ··· N3 2.04 Å, N5 ··· N3 3.073 Å (1 − x, y, ½ − z), angle NHN 155°. These bonds unite molecules into parallel layers.

The peculiarity in the X-ray crystallographic structure of **2f** consists of the statistic disorder associated with the phosphonate group which rotates around the C1–P bond (Fig. 3). Therefore it is not possible to distinguish the P=O bond from the P–OH bond. The rest of the geometrical parameters are in normal range. The planar fragment N1–C4–C3–C2–C1 is at an 89.5° angle with the planar thymine ring.

† CCDC reference numbers 218714 and 218715. See http://www.rsc.org/suppdata/ob/b3/b309684j/ for crystallographic data in .cif or other electronic format.

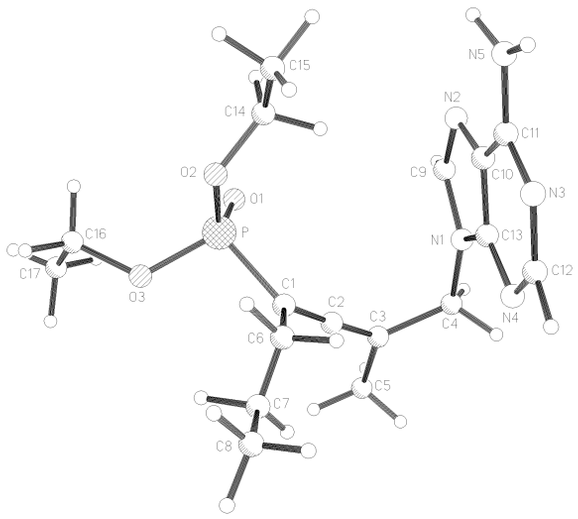


Fig. 2 Molecular structure of 1-(aden-9-yl)-4-(diethylphosphonyl)-2-methylhepta-2,3-diene **18** as obtained by X-ray crystallography.

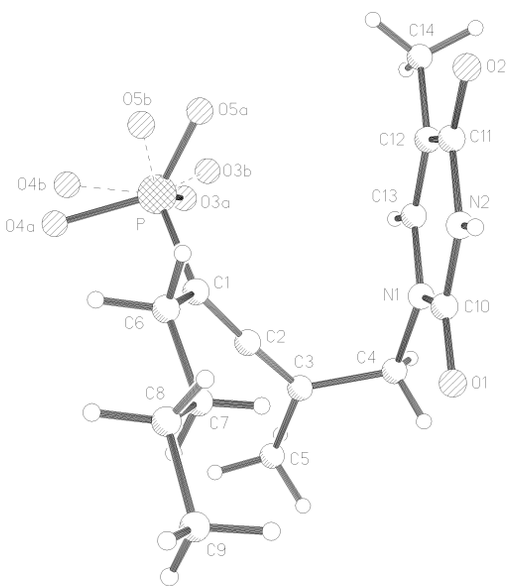


Fig. 3 Molecular structure of 2-methyl-4-(phosphonyl)-1-(thymin-1-yl)octa-2,3-diene **2f** as obtained by X-ray crystallography.

Conclusion

In summary, a convenient and efficient synthesis of a series of new purine and pyrimidine-containing acyclic analogues of nucleotides with a 1,2-alkadienic skeleton, starting from readily available 1-chloro-4-(diethoxyphosphonyl)alka-2,3-dienes, has been described. Further studies on this potentially important synthetic methodology are currently in progress. The detailed biological evaluation of these analogues and applications of phosphorylated allenes to the synthesis of interesting phosphonic acid derivatives will be reported in due course.

Experimental

^{1}H NMR spectra were recorded at 200 MHz. Chemical shifts for ^{1}H NMR are reported in ppm relative to tetramethylsilane as internal standard or to residual solvent signals. ^{31}P NMR spectra were recorded at 81.01 MHz using an external capillary containing 85% H_3PO_4in H_2O as reference. ^{13}C NMR spectra were recorded at 50.3 MHz. Signal multiplicities were determined with DEPT techniques. Chemical shifts refer to tetramethylsilane or to residual solvent signals. Column chromatography on silica gel was performed with Fluka Silica

gel 100 (0.035–0.070 mm). All reactions were monitored by thin-layer chromatography on Fluka Silica Gel 60 F-254/TLC-cards (20 × 20 × 0.2 cm) with detection by spraying with $KMnO_4$ solution.

All reagents were of commercial quality or were purified before use. Organic solvents were purified and dried according to established procedures by distillation under argon atmosphere from an appropriate drying agent. Reagents and organic solvents were procured from Aldrich Chemical Co and Fluka.

1-Chloro-2-methylhept-3-yn-2-ol 6

To a solution of EtMgBr (prepared from 1.2 g, 0.05 g-atom of magnesium turnings, and 6.5 g, 0.06 mol of ethyl bromide in 50 cm^3 of Et_2O), 1-pentyne (4.6 g, 0.065 mol) was added dropwise over 30 min at 0 °C. The mixture was stirred at rt for 0.5 h, at 34 °C for 2 h and then cooled in an ice bath. Chloroacetone (4.6 g, 0.05 mol) in Et_2O (10 cm^3) was added dropwise over 15 min and the mixture was heated to reflux for an additional 15–20 min. The mixture was cooled and sat. aq NH_4Cl was added carefully to dissolve the solid components. The two layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 cm^3). The combined organic fractions were dried (Na_2SO_4) and solvent was evaporated *in vacuo* and then distilled at reduced pressure. Yield: 71%. Bp 83–85 °C/1–1.5 mm Hg (Found: C, 59.73; H, 8.14. $C_8H_{13}ClO$ (160.644) requires C, 59.81; H, 8.16%); δ_H(200 MHz, $CDCl_3$) 3.65 and 3.59 (2 H, AB, *J* 10.9, CH_2Cl), 2.89 (1 H, br s, OH), 2.19 (2 H, t, *J* 7.1, CH_2), 1.55 (3 H, s, CH_3), 1.53 (2 H, sext, *J* 7.1, CH_2), 0.98 (3 H, t, *J* 7.1, CH_3); δ_C(50.3 MHz, $CDCl_3$) 84.97 (C≡), 80.99 (C≡), 67.36 (COH), 54.10 (CH_2Cl), 26.95 (CH_3), 21.69 (CH_2), 20.29 (CH_2), 13.16 (CH_3).

1-Chloro-2-methyloct-3-yn-2-ol 7

Compound **7** was prepared in the same manner described for **6**. Yield: 71%. Bp 98–99 °C/1–1.5 mm Hg (Found: C, 61.80; H, 8.58. $C_9H_{15}ClO$ (174.671) requires C, 61.89; H, 8.66%); δ_H(200 MHz, $CDCl_3$) 3.68 and 3.60 (2 H, AB, *J* 10.8, CH_2Cl), 2.90 (1 H, br s, OH), 2.12 (2 H, t, *J* 7.2, CH_2), 1.53 (3H, s, CH_3), 1.48 (4 H, m, 2 × CH_2), 0.90 (3 H, t, *J* 7.2, CH_3); δ_C(50.3 MHz, $CDCl_3$) 84.83 (C≡), 80.93 (C≡), 67.19 (COH), 54.42 (CH_2Cl), 26.93 (CH_2), 21.54 (CH_2), 20.16 (CH_2), 20.09 (CH_2), 13.16 (CH_3).

1-Chlorooct-3-yn-2-ol 8

Compound **8** was prepared from 1-hexyne and chloroacetaldehyde[22] by the method described for **6**. Yield: 68%. Bp 94 °C/1–1.5 mm Hg (Found: C, 59.91; H, 8.19. $C_8H_{13}ClO$ (160.644) requires C, 59.81; H, 8.16%); δ_H(200 MHz, $CDCl_3$) 4.58 (1 H, ddt, *J* 4.3, *J* 6.6, *J* 2.0, C*H*OH), 3.68 (1 H, dd, *J* 4.3, *J* 11.1, C*H*HCl), 3.62 (1 H, dd, *J* 6.6, *J* 11.1, C*H*HCl), 2.70 (1 H, br s, OH), 2.23 (3 H dt, *J* 2.0, *J* 6.9, ≡C–CH_2), 1.45 (4 H, m, 2 × CH_2), 0.83 (3 H, t, *J* 6.9, CH_3); δ_C(50.3 MHz, $CDCl_3$) 87.32 (C≡), 77.20 (C≡), 62.55 (CHOH), 49.24 (CH_2Cl), 30.27 (CH_2), 21.73 (CH_2), 18.15 (CH_2), 13.40 (CH_3).

1-Chloro-2-methylbut-3-yn-2-ol 9

Compound **9** was synthesized starting from chloroacetone according to the described procedure.[23] Yield: 69%. Bp 54–55 °C/15 mm Hg. (lit.[24] 44–46 °C/15 mm Hg).

General procedure for preparation of the phosphorylated allenes 14–17. 1-Chloro-4-(diethoxyphosphonyl)-2-methylhepta-2,3-diene 14

NEt_3 (1.62 g, 0.016 mol) was added to solution of acetylenic alcohol **6** (2.24 g, 0.014 mol) in Et_2O (100 cm^3) under N_2 and the mixture was cooled to −15 °C. A solution of diethyl chlorophosphite (2.22 g, 0.0142 mol) in Et_2O (10 cm^3) was added dropwise and the mixture was stirred at −15 °C for 1 h and at room temperature for 24 h. The solid was removed by filtration and the solvent was evaporated under reduced pressure. The crude product was chromatographed ($CHCl_3$/MeOH = 10 : 0.3) to give **14** (3.1 g, 78%) as a colorless oil. TLC: R_f = 0.28 ($CHCl_3$/MeOH, 10 : 0.1) (Found: C, 51.42; H, 7.86; P, 10.97. $C_{12}H_{22}ClO_3P$ (280.732) requires C, 51.34; H, 7.90; P, 11.03%); ν_{max}(film)/cm^{-1} 1972 (C=C=C); δ_H(200 MHz, $CDCl_3$) 4.08 (6H, m, 2 × CH_3CH_2O + CH_2Cl), 2.17 (2 H, dt, *J* 7.2, $J_{H,P}$ 10.6, CH_2), 1.88 (3 H, d, $J_{H,P}$ 6.6, =C=CCH_3), 1.51 (2 H, sext, *J* 7.2, CH_2), 1.33 (6 H, t, *J* 7.0, 2 × OCH_2CH_3), 0.95 (3 H, t, *J* 7.2, CH_3); δ_C(50.3 MHz, $CDCl_3$) 206.21 (d, $J_{C,P}$ 5.3, =C=), 99.37 (d, $J_{C,P}$ 16.3, =*C*(CH_3)CH_2Cl), 95.50 (d, $J_{C,P}$ 186.1, PC=), 62.20 (d, $J_{C,P}$ 6.2, CH_2OP), 62.14 (d, $J_{C,P}$ 6.2, CH_2OP), 46.64 (d, $J_{C,P}$ 7.0, CH_2Cl), 30.45 (d, $J_{C,P}$ 6.6, CH_2), 21.07 (d, $J_{C,P}$ 6.9, CH_2), 16.14 (d, $J_{C,P}$ 6.5, 2 × *C*H_3CH_2OP), 15.66 (d, $J_{C,P}$ 6.4, =C*C*H_3), 13.43 (s, CH_3); δ_P(81.01 MHz, $CDCl_3$) 18.40 (s).

1-Chloro-4-(diethoxyphosphonyl)-2-methylocta-2,3-diene 15

Compound **15** was synthesized according to the described procedure.[23] Yield: 75%.

1-Chloro-4-(diethoxyphosphonyl)octa-2,3-diene 16

Obtained as oil after column chromatography on silica gel ($CHCl_3$/MeOH = 10 : 0.3) in 64% yield. TLC: R_f = 0.21 ($CHCl_3$/MeOH = 10 : 0.1) (Found: C, 51.28; H, 7.96; P, 11.10. $C_{12}H_{22}ClO_3P$ (280.732) requires C, 51.34; H, 7.90; P, 11.03%); ν_{max}(film)/cm^{-1} 1971 (C=C=C); δ_H(200 MHz, $CDCl_3$) 5.62 (1 H, dtt, $J_{H,P}$ 12.5, *J* 7.5, *J* 3.0, =CH), 4.20–4.05 (6 H, m, 2 × OCH_2CH_3 + CH_2Cl), 2.28–2.14 (2 H, m, =CCH_2), 1.44 (4 H, m, 2 × CH_2), 1.34 (6 H, t, *J* 7.0, 2 × OCH_2CH_3), 0.92 (3 H, t, *J* 7.2 Hz, CH_3); δ_C(50.3 MHz, $CDCl_3$) 207.94 (d, $J_{C,P}$ 5.7, =C=), 97.34 (d, $J_{C,P}$ 184.9, PC=), 91.42 (d, $J_{C,P}$ 15.8, HC=), 62.43 (d, $J_{C,P}$ 6.1, OCH_2CH_3), 62.30 (d, $J_{C,P}$ 6.1, OCH_2CH_3), 41.19 (d, $J_{C,P}$ 7.4, CH_2Cl), 29.78 (d, $J_{C,P}$ 6.7, CH_2), 27.93 (d, $J_{C,P}$ 5.5, CH_2), 21.92 (s, CH_2), 14.64 (d, *J* 6.8, 2 × CH_3CH_2O), 13.62 (s, CH_3); δ_P(81.01 MHz, $CDCl_3$) 17.62 (s).

1-Chloro-4-(diethoxyphosphonyl)-2-methylbuta-2,3-diene 17

Compound **17** was synthesized according to the described procedure.[23] Yield: 68%.

General procedure for preparation of the allenes 18–23. 1-(Adenin-9-yl)-4-(diethylphosphonyl)-2-methylhepta-2,3-diene 18

The mixture of adenine (0.54 g, 0.004 mol) and cesium carbonate (1.3 g, 0.004 mol) in DMF (30 cm^3) was stirred at 75 °C for 0.5 h with exclusion of moisture. After the addition of 1-chloro-2-methyl-4-(diethylphosphonyl)hepta-2,3-diene **14** (0.56 g, 0.002 mol) the mixture was heated under stirring at 75 °C for an additional 2 h, until the starting compound **14** disappeared (TLC). The suspension was filtered and the filtrate taken down to dryness *in vacuo*. The residue was extracted with a boiling mixture of $CHCl_3$/MeOH (10 : 2) (3 × 30 cm^3 portion) and filtered. Solvents were evaporated *in vacuo* and the residue was chromatographed on a silica gel column ($CHCl_3$/MeOH, 10 : 0.4⟶10 : 1.5) to give product **18** (0.36 g, 48 %) as solid. TLC: R_f = 0.58 ($CHCl_3$/MeOH = 10 : 1.5). An analytical sample was obtained by recrystallizing twice from hexane to afford the product as a white solid. Mp 102–106 °C (Found: C, 53.86; H, 6.94; N, 18.54, P, 8.20. $C_{17}H_{26}N_5O_3P$ (379.400) requires C, 53.82; H, 6.91; N, 18.46; P, 8.16%); ν_{max}(KBr)/cm^{-1} 1970 (C=C=C); δ_H(200 MHz, $CDCl_3$) 8.36 (1 H, s) and 8.00 (1 H, s, H_8 and H_2adenine), 5.95 (2 H, s, NH_2), 4.80 (2 H, d, $J_{H,P}$ 6.5, CH_2N), 4.08–3.94 (4 H, m, 2 × CH_3CH_2O), 2.1–1.89 (2 H, m, CH_2–C=), 1.81 (3 H, d, $J_{H,P}$ 6.8, CH_3–C=), 1.39–1.25 (8 H, m, CH_2 + 2 × CH_3CH_2O), 0.84 (3H, t, *J* 7.4 Hz, CH_3); δ_C(50.3 MHz, $CDCl_3$) 206.00 (d, $J_{C,P}$ 5.7, =C=), 155.51 (s, =C, adenine), 152.92 (s, =CH, adenine), 149.96 (s, =C, adenine), 140.86 (s, =CH,

adenine), 119.05 (s, =C, adenine), 99.14 (d, $J_{C,P}$ 16.5, C=C=*C*–CH_3), 97.18 (d, $J_{C,P}$ 185.3, P–C=), 62.13 (d, $J_{C,P}$ 5.9, 2 × CH_3CH_2O), 45.22 (d, $J_{C,P}$ 6.9, CH_2N), 30.37 (d, $J_{C,P}$ 6.5, CH_2), 21.17 (d, $J_{C,P}$ 6.6, CH_2), 16.23 (d, $J_{C,P}$ 6.4, 2 × CH_3CH_2O), 15.87 (d, $J_{C,P}$ 6.6, CH_3C=C=), 13.38 (s, CH_3); δ_P(81.01 MHz, $CDCl_3$) 18.60 (s).

4-(Diethylphosphonyl)-2-methyl-1-(uracil-1-yl)hepta-2,3-diene 19

Compound **19** was prepared in the same manner described for **18**. 63% (0.45 g) yield. TLC: R_f = 0.51 ($CHCl_3$/MeOH = 10 : 1.0) (Found: C, 53.87; H, 7.03; N, 7.81; P, 8.61. $C_{16}H_{25}N_2O_5P$ (356.360) requires C, 53.93; H, 7.07; N, 7.86; P, 8.69%); ν_{max}(KBr)/cm^{-1} 1967 (C=C=C); δ_H(200 MHz, $CDCl_3$) 9.65 (1 H, br s, NH), 7.53 (1 H, d, *J* 7.8, =CH uracil), 5.74 (1 H, dd, *J* 7.8, $J_{H,P}$ 2.0 Hz, =CH uracil), 4.39 (2 H, d, $J_{H,P}$ 6.8, CH_2N), 4.18–3.96 (4 H, m, 2 × CH_3CH_2O), 2.15–2.01 (2 H, m, CH_2–C=), 1.78 (3 H, d, $J_{H,P}$ 6.8, CH_3–C=), 1.45 (2 H, sext, $J_{H,P}$ 7.2, CH_2), 1.33 (3 H, t with small splits, *J* 7.2, CH_3CH_2O), 1.32 (3 H, t, *J* 7.2, CH_3CH_2O), 0.91 (3 H, t, *J* 7.2, CH_3); δ_C(50.3 MHz, $CDCl_3$) 206.18 (d, $J_{C,P}$ 6.0, =C=), 163.91 (s, C=O), 150.89 (s, C=O), 144.14 (s, =CH uracil), 102.03 (s, =CH uracil), 98.66 (d, $J_{C,P}$ 16.7, C=C=*C*–CH_3), 96.85 (d, $J_{C,P}$ 185.8, P–C=), 61.86 (d, $J_{C,P}$ 6.0, CH_3CH_2O), 61.76 (d, $J_{C,P}$ 5.9, CH_3CH_2O), 48.35 (d, $J_{C,P}$ 6.7, CH_2N), 30.02 (d, $J_{C,P}$ 6.2, CH_2), 20.88 (d, $J_{C,P}$ 6.6, CH_2), 15.96 (d, $J_{C,P}$ 6.4, CH_3CH_2O), 15.22 (d, $J_{C,P}$ 6.3, CH_3CH_2O), 15.22 (d, $J_{C,P}$ 6.7, CH_3 C=C=), 13.16 (s, CH_3); δ_P(81.01 MHz, $CDCl_3$) 18.74 (s).

4-(Diethylphosphonyl)-2-methyl-1-(thymin-1-yl)hepta-2,3-diene 20

Compound **20** was prepared in the same manner described for **18**. 70% (0.52 g) yield. TLC: R_f = 0.56 ($CHCl_3$/MeOH = 10 : 1.0) (Found: C, 55.8; H, 7.31; N, 7.50; P, 8.32. $C_{17}H_{27}N_2O_5P$ (370.387) requires C, 55.13; H, 7.35; N, 7.56; P, 8.36%); ν_{max}(KBr)/cm^{-1} 1967 (C=C=C); δ_H(200 MHz, $CDCl_3$) 10.25 (1 H, br s, NH), 7.31 (1 H, q, *J* 1.2, =CH thymine), 4.35 (2 H, d, $J_{H,P}$ 6.4, CH_2N), 4.17–4.08 (4 H, m, 2 × CH_3CH_2O), 2.15–2.01 (2 H, m, CH_2–C=), 1.93 (3 H, d, *J* 1.2, H_3C thymine), 1.78 (3 H, d, $J_{H,P}$ 6.8, CH_3–C=), 1.45 (2 H, sext, *J* 7.2, CH_2), 1.33 (3 H, t with small splits, *J* 7.2, CH_3CH_2O), 1.32 (3 H, t, *J* 7.2, CH_3CH_2O), 0.91 (3 H, t, *J* 7.2, CH_3); δ_C(50.3 MHz, $CDCl_3$) 206.23 (d, $J_{C,P}$ 6.0, =C=), 164.36 (s, C=O), 151.03 (s, C=O), 140.03 (s, =CH thymine), 110. 56 (s, CH_3–*C*= thymine), 98.66 (d, $J_{C,P}$ 16.7, C=C=*C*–CH_3), 96.78 (d, $J_{C,P}$ 186.0, P–C=), 61.89 (d, $J_{C,P}$ 6.1, CH_3CH_2O), 61.83 (d, $J_{C,P}$ 6.0, CH_3CH_2O), 48.32 (d, $J_{C,P}$ 6.7, CH_2N), 30.20 (d, $J_{C,P}$ 6.4, CH_2), 21.04 (d, $J_{C,P}$ 6.6, CH_2), 16.08 (d, $J_{C,P}$ 6.3, 2 × CH_3CH_2O), 15.39 (d, $J_{C,P}$ 6.6, CH_3C=C=), 13.28 (s, CH_3), 12.01 (s, CH_3 thymine); δ_P(81.01 MHz, $CDCl_3$) 18.83 (s).

1-(Adenin-9-yl)-4-(diethylphosphonyl)-2-methylocta-2,3-diene 21

Compound **21** was prepared in the same manner described for **18**. 58% (0.46 g). TLC: R_f = 0.55 ($CHCl_3$/MeOH = 10 : 1.5). Mp 92–96 °C. (Found: C, 54.90; H, 7.13; N, 17.70; P, 7.76. $C_{18}H_{28}N_5O_3P$ (393.427) requires C, 54.95; H, 7.17; N, 17.80; P, 7.87%); ν_{max}(KBr)/cm^{-1} 1970 (C=C=C); δ_H(200 MHz, $CDCl_3$) 8.31 (1 H, s) and 7.96 (1 H, s, H_8 and H_2 adenine), 6.48 (2 H, br s, NH_2), 4.76 and 4.72 (2 H, ABX, *J* 15.8, $J_{H,P}$ 7.0, $J_{H,P}$ 5.9, CH_2N), 4.12–3.89 (4 H, m, 2 × CH_3CH_2O), 2.1–1.83 (2 H, m, CH_2–C=), 1.81 (3 H, d, $J_{H,P}$ 7.0, CH_3–C=), 1.34–1.12 (10 H, m, 2 × CH_2, 2 × CH_3CH_2O), 0.80 (3 H, t, *J* 7.1, CH_3); δ_C(50.3 MHz, $CDCl_3$) 205.85 (d, $J_{C,P}$ 5.9, =C=), 155.60 (s, =C adenine), 152.85 (s, =CH adenine), 149.79 (s, =C adenine), 140.77 (s, =CH adenine), 118.88 (s, =C adenine), 99.34 (d, $J_{C,P}$ 16.8, C=C=*C*–CH_3), 97.33 (d, $J_{C,P}$ 185.6, P–C=), 62.08 (d, $J_{C,P}$ 5.9, CH_3CH_2O), 61.85 (d, $J_{C,P}$ 6.1, CH_3CH_2O), 45.06 (d, $J_{C,P}$ 7.2, CH_2N), 29.91 (d, $J_{C,P}$ 6.5, CH_2), 27.93 (d, $J_{C,P}$ 6.1, CH_2), 21.86 (s, CH_2), 16.16 (d, $J_{C,P}$ 6.4, 2 × CH_3CH_2O), 15.83 (d, $J_{C,P}$ 6.6, CH_3C=C=), 13.61 (s, CH_3); δ_P(81.01 MHz, $CDCl_3$) 18.68 (s).

4-(Diethylphosphonyl)-2-methyl-1-(uracil-1-yl)octa-2,3-diene 22

Compound **22** was prepared in the same manner described for **18**. 72% (0.53 g) yield. TLC: R_f = 0.48 ($CHCl_3$/MeOH = 10 : 1.0) (Found: C, 55.04; H, 7.31; N, 7.52; P, 8.42. $C_{17}H_{27}N_2O_5P$ (370.387) requires: C, 55.13; H, 7.35; N, 7.56; P, 8.36%); ν_{max}(KBr)/cm^{-1} 1967 (C=C=C); δ_H(200 MHz, $CDCl_3$) 10.28 (1 H, br s, NH), 7.43 (1 H, d, *J* 7.9, =CH uracil), 5.67 (1 H, dd, *J* 7.9, $J_{H,P}$ 2.0, =CH uracil), 4.33 and 4.28 (2 H, ABX, *J* 16.0, $J_{H,P}$ 7.1, $J_{H,P}$ 5.9, CH_2N), 4.11–3.91 (4 H, m, 2 × CH_3CH_2O), 2.09–1.96 (2 H, m, CH_2–C=), 1.70 (3 H, d, $J_{H,P}$ 6.9, CH_3–C=), 1.41–1.21 (10 H, m, 2 × CH_2, 2 × CH_3CH_2O), 0.82 (3 H, t, *J* 7.2, CH_3); δ_C(50.3 MHz, $CDCl_3$) 206.5 (d, $J_{C,P}$ 6.1, =C=), 163.80 (s, C=O), 150.96 (s, C=O), 144.25 (s, =CH uracil), 102. 31 (s, =CH uracil), 98.78 (d, $J_{C,P}$ 16.7, C=C=*C*–CH_3), 97.30 (d, $J_{C,P}$ 185.8, P–C=), 62.01 (d, $J_{C,P}$ 5.9, CH_3CH_2O), 62.13 (d, $J_{C,P}$ 6.1, CH_3CH_2O), 48.73 (d, $J_{C,P}$ 6.6, CH_2N), 29.98 (d, $J_{C,P}$ 6.4, CH_2), 27.93 (d, $J_{C,P}$ 6.3, CH_2), 21.90 (s, CH_2), 16.22 (d, $J_{C,P}$ 6.3, CH_3CH_2O), 16.19 (d, $J_{C,P}$ 6.2, CH_3CH_2O), 15.47 (d, $J_{C,P}$ 6.7, CH_3C=C=), 13.63 (s, CH_3); δ_P(81.01 MHz, $CDCl_3$) 18.85 (s).

4-(Diethylphosphonyl)-2-methyl-1-(thymin-1-yl)octa-2,3-diene 23

Compound **23** was prepared in the same manner described for **18**. 68% (0.52 g) yield. TLC: R_f = 0.51 ($CHCl_3$/MeOH = 10 : 1.0) (Found: C, 56.18; H, 7.70; N, 7.34; P, 8.17. $C_{18}H_{29}N_2O_5P$ (384.414) requires C, 56.24; H, 7.60; N, 7.29; P, 8.06); ν_{max}(KBr)/cm^{-1} 1967 (C=C=C); δ_H(200 MHz, $CDCl_3$) 9.57 (1 H, s, NH), 7.13 (1 H, q, *J* 1.2, =CH), 4.29 (2 H, d, $J_{H,P}$ 6.4, CH_2N), 4.10–3.94 (4 H, m, 2 × CH_3CH_2O), 2.11–1.98 (2 H, m, CH_2–C=), 1.87 (3 H, d, *J* 1.2, H_3C thymine), 1.71 (3 H, d, $J_{H,P}$ 6.9, CH_3–C=), 1.41–1.22 (10 H, m, 2 × CH_2 + 2 × CH_3CH_2O), 0.83 (3 H, t, *J* 7.2, CH_3); δ_C(200 MHz, $CDCl_3$) 206.4 (d, $J_{C,P}$ 6.1, =C=), 164.26 (s, C=O), 150.98 (s, C=O), 140.10 (s, =CH thymine), 110.77 (s, CH_3–*C*= thymine), 98.86 (d, $J_{C,P}$ 16.6, C=C=*C*–CH_3), 97.05 (d, $J_{C,P}$ 185.9, P–C=), 62.06 (d, $J_{C,P}$ 6.0, CH_3CH_2O), 61.98 (d, $J_{C,P}$ 6.0, CH_3CH_2O), 48.54 (d, $J_{C,P}$ 6.7, CH_2N), 30.03 (d, $J_{C,P}$ 6.5, CH_2), 27.98 (d, $J_{C,P}$ 6.4, CH_2), 21.95 (s, CH_2), 16.24 (d, $J_{C,P}$ 6.3, 2 × CH_3CH_2O), 15.55 (d, $J_{C,P}$ 6.6, CH_3C=C=), 13.94 (s, CH_3), 12.18 (s, CH_3 thymine); δ_P(81.01 MHz, $CDCl_3$) 18.93 (s).

General procedure for preparation of the compounds 2a–2f. 1-(Adenin-9-yl)-2-methyl-4-(phosphonyl)hepta-2,3-diene 2a

Bromotrimethylsilane (0.77 g, 0.005 mol) was added dropwise, *via* syringe, at room temperature, to the diester **18** (0.379 g, 0.001 mol) in 10 cm^3 of alcohol-free chloroform and the reaction mixture was stirred in a closed flask overnight. The solvents were removed under diminished pressure and the residual oil was dissolved in CH_3CN (40 cm^3), treated with water (0.5 cm^3) and the solution stirred at 40–50 °C for 1 h. The reaction mixture was evaporated *in vacuo*, and the product was crystallized from hexane: yield 0.22 g (68%) of compound **2a**. Mp 144–146 °C (Found: C, 48.37; H, 5.64; N, 21.60; P, 9.47. $C_{13}H_{18}N_5O_3P$ (323.293) requires C, 48.30; H, 5.61; N, 21.66; P, 9.58%); ν_{max}(KBr)/cm^{-1} 1965 (C=C=C); δ_H(200 MHz, $CDCl_3$) 8.45 (1 H, s) and 8.42 (1 H, s, H_8 and H_2adenine), 5.27 (s, $(HO)_2P(O)$, NH_2 and $OHCD_3$), 4.97 (2 H, d, $J_{H,P}$ 6.9, CH_2N), 2.00–1.83 (2 H, m, CH_2–C=), 1.84 (3 H, d, $J_{H,P}$ 6.8, CH_3C=C=), 1.34 (2 H, sext, *J* 7.4, CH_2), 0.85 (3 H, t, $J_{H,H}$ 7.4, CH_3); δ_C (50.3 MHz, CD_3OD) 203.42 (d, $J_{C,P}$ 5.5, =C=), 149.55 (s, =C, adenine), 148.28 (s, =CH, adenine), 143.97 (s, =C, adenine), 143.29 (s, =CH, adenine), 117.40 (s, =C, adenine), 99.11 (d, $J_{C,P}$ 16.2, C=C=*C*–CH_3), 99.25 (d, $J_{C,P}$ 184.7, P–C=), 44.93 (d, $J_{C,P}$ 6.9, CH_2N), 29.62 (d, $J_{C,P}$ 7.2, CH_2), 20.47 (d, $J_{C,P}$ 6.4, CH_2), 14.12 (d, $J_{C,P}$ 6.5, CH_3C=C=), 12.00 (s, CH_3); δ_P(81.01 MHz, $CDCl_3$) 15.89 (s).

2-Methyl-4-(phosphonyl)-1-(uracil-1-yl)hepta-2,3-diene 2b

Compound **2b** was prepared in the same manner described for **2a**. Yield 0.24 g (80%). Mp 184–186 °C (Found: C, 48.07; H, 5.74; N, 9.36; P, 10.40. $C_{12}H_{17}N_2O_5P$ (300.252) requires C, 48.00; H, 5.71; N, 9.33; P, 10.32%); ν_{max}(KBr)/cm^{-1} 1965 (C=C=C); δ_H (200 MHz, CD_3OD) 7.43 (1 H, d, *J* 8.0, =CH uracil), 5.55 (1 H, d, *J* 8.0, =CH uracil), 5.00 (s, $(HO)_2P(O)$, NH and $OHCD_3$), 4.32 and 4.16 (2 H, ABX, *J* 15.6, $J_{H,P}$ 6.4, $J_{H,P}$ 7.6, CH_2N), 2.2–1.93 (2 H, m, CH_2–C=), 1.66 (3 H, d, $J_{H,P}$ 6.6, CH_3–C=), 1.34 (2 H, sext, *J* 7.4, CH_2), 0.81 (3 H, t, $J_{H,H}$ 7.4, CH_3); δ_C (50.3 MHz, CD_3OD) 203.75 (d, $J_{C,P}$ 5.7, =C=), 164.74 (s, C=O), 150.70 (s, C=O), 145.21 (s, =CH uracil), 100.53 (s, =CH uracil), 99.10 (d, $J_{C,P}$ 184.9, P–C=), 98.65 (d, $J_{C,P}$ 16.2, C=C=*C*–CH_3), 48.20 (d, $J_{C,P}$ 6.9, CH_2N), 29.78 (d, $J_{C,P}$ 6.5, CH_2), 20.58 (d, $J_{C,P}$ 6.6, CH_2), 13.94 (d, $J_{C,P}$ 6.5, *C*H_3C=C=), 12.11 (s, CH_3); δ_P (81.01 MHz, CD_3OD) 16.18 (s).

2-Methyl-4-(phosphonyl)-1-(thymin-1-yl)hepta-2,3-diene 2c

Compound **2c** was prepared in the same manner described for **2a**. Yield 0.25 g (79%). Mp 204–206 °C (Found: C, 49.62; H, 6.14; N, 8.97; P, 9.81. $C_{13}H_{19}N_2O_5P$ (314.279) requires C, 49.68; H, 6.09; N, 8.91; P, 9.86%); ν_{max}(KBr)/cm^{-1} 1961 (C=C=C); δ_H (200 MHz, CD_3OD) 7.38 (1 H, q, *J* 1.2, =CH thymine), 5.13 (s, $(HO)_2P(O)$, NH and CD_3OH), 4.38 and 4.22 (2 H, ABX, *J* 15.6, $J_{H,P}$ 6.2, $J_{H,P}$ 7.8, CH_2N), 2.15–2.02 (2 H, m, CH_2–C=), 1.86 (3 H, d, $J_{H,H}$ 1.2, H_3C thymine), 1.76 (3 H, d, $J_{H,P}$ 6.6, CH_3–C=), 1.46 (2 H, sext, *J* 7.2, CH_2), 0.92 (3 H, t, *J* 7.2, CH_3); δ_C (50.3 MHz, CD_3OD) 203.75 (d, $J_{C,P}$ 5.5, =C=), 164.92 (s, C=O), 150.93 (s, C=O), 141.05 (s, =CH thymine), 109.45 (s, CH_3–*C*= thymine), 99.01 (d, $J_{C,P}$ 185.0, P–C=), 99.73 (d, $J_{C,P}$ 16.2, C=C=*C*–CH_3), 47.91 (d, $J_{C,P}$ 6.5, CH_2N), 29.80 (d, $J_{C,P}$ 7.4, CH_2), 20.60 (d, $J_{C,P}$ 6.7, CH_2), 13.87 (d, $J_{C,P}$ 6.6, *C*H_3C=C=), 12.13 (s,CH_3), 10.41 (s, CH_3 thymine); δ_P (81.01 MHz, CD_3OD) 16.36 (s).

1-(Adenin-9-yl)-2-methyl-4-(phosphonyl)octa-2,3-diene 2d

Compound **2d** was prepared in the same manner described for **2a**. Yield 0.17 g (51%). Mp 122 –126 °C (Found: C, 49.74; H, 5.93; N, 20.72; P, 9.23. $C_{14}H_{20}N_5O_3P$ (337.319) requires C, 49.85; H, 5.98; N, 20.76; P, 9.18); ν_{max}(KBr)/cm^{-1} 1965 (C=C=C); δ_H (200 MHz, CD_3OD) 8.48 (1 H, s) and 8.47 (1 H, s, H_8 and H_2adenine), 5.7 (s, $(HO)_2P(O)$, NH_2 and CD_3OH), 5.00 (2 H, d, $J_{H,P}$ 7.1, CH_2N), 2.02–1.84 (2 H, m, CH_2–C=), 1.86 (3 H, d, $J_{H,P}$ 7.0, CH_3–C=), 1.30–1.12 (4 H, m, 2 × CH_2), 0.80 (3 H, t, $J_{H,P}$ 7.2, CH_3); δ_C (50.3 MHz, CD_3OD) 203.30 (d, $J_{C,P}$ 5.6, =C=), 149.40 (s, =C, adenine), 148.21 (s, =CH, adenine), 143.99 (s, =C, adenine), 143.34 (s, =CH, adenine), 117.19 (s, =C, adenine), 99.53 (d, $J_{C,P}$ 16.3, C=C=*C*–CH_3), 99.26 (d, $J_{C,P}$ 185.3, P–C=), 44.88 (d, $J_{C,P}$ 6.9, CH_2N), 29.36 (d, $J_{C,P}$ 6.5, CH_2), 27.16 (d, $J_{C,P}$ 7.4, CH_2), 21.12 (s, CH_2), 14.21 (d, $J_{C,P}$ 6.4, *C*H_3C=C=), 12.73 (s, CH_3); δ_P (81.01 MHz, CD_3OD) 16.05 (s).

2-Methyl-4-(phosphonyl)-1-(uracil-1-yl)octa-2,3-diene 2e

Compound **2e** was prepared in the same manner described for **2a**. Yield 0.24 g (75%). Mp 158–162 °C (Found: C, 49.66; H, 6.13; N, 8.89; P, 9.90. $C_{13}H_{19}N_2O_5P$ (314.279) requires C, 49.68; H, 6.09; N, 8.91; P, 9.86%); ν_{max}(KBr)/cm^{-1} 1965 (C=C=C); δ_H (200 MHz, CD_3OD) 7.54 (1 H, d, *J* 7.9, =CH uracil), 5.66 (1 H, d, *J* 7.9, =CH uracil), 5.00 (s, $(HO)_2P(O)$, NH and CD_3OH), 4.34 and 4.30 (2 H, ABX, *J* 15.6, $J_{H,P}$ 6.4, $J_{H,P}$ 7.6, CH_2N), 2.18–2.06 (2 H, m, CH_2–C=), 1.78 (3 H, d, $J_{H,P}$ 6.6, CH_3–C=), 1.49–1.24 (4 H, m, 2 × CH_2), 0.91 (3 H, t, *J* 7.3, CH_3); δ_C (50.3 MHz, CD_3OD) 203.66 (d, $J_{C,P}$ 5.7, =C=), 164.76 (s, C=O), 150.75 (s, C=O), 145.20 (s, =CH uracil), 100.53 (s, HC= uracil), 99.45 (d, $J_{C,P}$ 184.6, P–C=), 98.70 (d, $J_{C,P}$ 16.2, C=C=*C*–CH_3), 48.67 (d, $J_{C,P}$ 6.7, CH_2N), 29.52 (d, $J_{C,P}$ 6.5, CH_2), 27.42 (d, $J_{C,P}$ 7.3, CH_2), 21.33 (s, CH_3), 13.98 (d, $J_{C,P}$ 6.5, *C*H_3C=C=), 12.27 (s, CH_3); δ_P (81.01 MHz, CD_3OD) 16.18 (s).

2-Methyl-4-(phosphonyl)-1-(thymin-1-yl)octa-2,3-diene 2f

Compound **2f** was prepared in the same manner described for **2a**. Yield 0.25 g (76%). Mp 214–216 °C (Found: C, 51.20; H, 6.43; N, 8.62; P, 9.51. $C_{14}H_{21}N_2O_5P$ (328.306) C, 51.22; H, 6.45; N, 8.53; P, 9.43%); ν_{max}(KBr)/cm^{-1} 1961 (C=C=C); δ_H (200 MHz, CD_3OD) 7.38 (1 H, q, *J* 1.0 Hz, =CH thymine), 5.00 (s, $(HO)_2P(O)$, NH and CD_3OH), 4.30 and 4.24 (2 H, ABX, *J* 15.5, $J_{H,P}$ 6.2, $J_{H,P}$ 7.6, CH_2N), 2.17–2.04 (2 H, m, CH_2–C=), 1.86 (3 H, d, *J* 1.0, H_3C thymine), 1.76 (3 H, d, $J_{H,P}$ 6.6, CH_3–C=), 1.44–1.27 (4 H, m, 2 × CH_2), 0.91 (3 H, t, *J* 7.3, CH_3); δ_C (50.3 MHz, CD_3OD) 204.63 (d, $J_{C,P}$ 5.6, =C=), 165.89 (s, C=O), 151.90 (s, C=O), 142.02 (s, =CH thymine), 110.41 (s, CH_3–*C*= thymine), 100.22 (d, $J_{C,P}$ 184.8, P–C=), 99.75 (d, $J_{C,P}$ 16.2, C=C=*C*–CH_3), 48.85 (d, $J_{C,P}$ 6.8, CH_2N), 30.52 (d, $J_{C,P}$ 6.5, CH_2), 28.37 (d, $J_{C,P}$ 7.5, CH_2), 22.32 (s, CH_2), 14.89 (d, $J_{C,P}$ 6.6, *C*H_3C=C=), 13.27 (s, CH_3), 11.40 (s, CH_3 thymine); δ_P (81.01 MHz, CD_3OD) 16.31 (s).

4-(Diethylphosphonyl)-2-methylbut-1-en-3-yne 24

Compound **24** was prepared in the same manner described for **18**. 84% (0.34 g) yield. TLC: R_f = 0.74 ($CHCl_3$/MeOH = 10 : 0.3) (Found: C, 53.50; H, 7.53; P, 15.20. $C_9H_{15}O_3P$ (202.191) requires C, 53.46; H, 7.48; P, 15.32%); ν_{max}(film)/cm^{-1} 1614, 1676, 2183 and 2990; δ_H (200 MHz, $CDCl_3$) 5.61 (1 H, ddq, *J* 1.0, *J* 1.3, $J_{H,P}$ 1.2, *H*HC=), 5.53 (1 H, ddq, *J* 1.6, *J* 1.3, $J_{H,P}$ 1.1, H*H*C=), 4.18 (4 H, m, *J* 7.1, $J_{H,P}$ 8.5, 2 × CH_3CH_2O), 1.94 (3 H, m, CH_3–C=), 1.37 (6 H, t, *J* 7.1, 2 × C*H*$_3$$CH_2$O); δ_C(50.3 MHz, $CDCl_3$) 127.70 (d, $J_{C,P}$ 3.3, =CH_2), 124.14 (d, $J_{C,P}$ 5.8, =C), 99.96 (d, $J_{C,P}$ 52.0, ≡C), 77.05 (d, $J_{C,P}$ 299.6, ≡C–P), 63.00 (d, $J_{C,P}$ 5.6, 2 × CH_3CH_2O), 22.02 (d, $J_{C,P}$ 1.7, =C*CH*$_3$), 15.95 (d, $J_{C,P}$ 7.0, 2C*H*$_3$$CH_2$O); δ_P(81.01 MHz, $CDCl_3$) 5.78 (s).

***Z*-4-(Diethylphosphonyl)-3-(uracil-1-yl)octa-2,3-diene 25a and *E*-4-(diethylphosphonyl)-3-(uracil-1-yl)octa-2,3-diene 25b**

The procedure for compound **18** was followed using compound **16** (0.32 g, 0.002 mol), uracil (0.45 g, 0.004 mol), and Cs_2CO_3 (1.3 g, 0.004 mol) in DMF (30 ml) to give *Z* and *E* isomers **25a** and **25b**. The *Z*/*E* ratio was 1 : 1. The mixture of *Z* and *E* isomers was chromatographed on a silica gel column ($CHCl_3$/MeOH, 10 : 0.4⟶10 : 1.0) to give the *Z* isomer (0.15 g, 20%) and *E* isomer (0.17 g, 23%) as an oil.

***Z* Isomer 25a.** TLC: R_f = 0.39 ($CHCl_3$/MeOH = 10 : 0.8) (Found: C, 55.01; H, 7.27; N, 7.50; P, 8.43. $C_{17}H_{27}N_2O_5P$ (370.387) requires C, 55.13; H, 7.35; N, 7.56; P, 8.36%); ν_{max}(film)/cm^{-1} 1996, 1701 (C=C); δ_H(200 MHz, $CDCl_3$) 8.92 (1 H, br s, NH), 7.00 (1 H, d, *J* 7.8, =CH uracil), 6.77 (1 H, ddd, *J* 16.8, *J* 10.4, $J_{H,P}$ 2.0, –*HC*=CH_2), 5.74 (1 H, dd, *J* 7.8, $J_{H,P}$ 2.2, =CH uracil), 5.51 (1 H, dd, *J* 10.4, $J_{H,P}$ 3.6, =CH*H*,), 5.30 (1 H, dd, *J* 16.8, *J* 1.6, =C*H*H), 4.14–3.98 (4 H, m, 2 × CH_3CH_2O), 2.37 (2 H, dt, *J* 7.2, $J_{H,P}$ 18.8, CH_2C=), 1.60–1.35 (4 H, m, 2 × CH_2), 1.30 (3 H, t, *J* 6.6, C*H*$_3$$CH_2$O), 1.26 (3 H, t, *J* 6.8, C*H*$_3$$CH_2$O), 0.92 (3 H, t, *J* 7.2, CH_3); δ_C(50.3 MHz, $CDCl_3$) 163.68 (s, C=O), 149.70 (s, C=O), 145.53 (s, =CH uracil), 143.25 (d, $J_{C,P}$ 2.1, N–C=), 134.01 (d, $J_{C,P}$ 174.5, P–C=), 129.02 (d, $J_{C,P}$ 15.6, –*C*H=CH_2), 121.14 (s, =CH_2), 101.06 (s, =CH uracil), 62.44 (d, $J_{C,P}$ 6.0, 2 × CH_3CH_2O), 31.80 (d, $J_{C,P}$ 1.9, CH_2), 29.42 (d, $J_{C,P}$ 6.6, CH_2), 22.67 (s, CH_2), 16.17 (d, $J_{C,P}$ 6.7, 2 × *C*$H_3$$CH_2$O), 13.72 (s, CH_3); δ_P(81.01 MHz, $CDCl_3$) 16.45 (s).

***E* Isomer 25b.** TLC: R_f = 0.47 ($CHCl_3$/MeOH = 10 : 0.8) (Found: C, 55.21; H, 7.39; N, 7.48; P, 8.30. $C_{17}H_{27}N_2O_5P$ (370.387) requires C, 55.13; H, 7.35; N, 7.56; P, 8.36%); ν_{max}(film)/cm^{-1} 1994, 1700 (C=C); δ_P(200 MHz, $CDCl_3$) 9.63 (1 H, br s, NH), 7.55 (1 H, ddd, *J* 16.8, *J* 10.8, $J_{H,P}$ 1.4, *HC*=CH_2), 7.0 (1 H, d, *J* 8.0, CH= uracil), 5.83 (1 H, dd, *J* 8.0, $J_{H,P}$ 2.0, CH= uracil), 5.42 (1 H, dd, *J* 10.8, *J* 1.2, =CH*H*), 5.14 (1 H, d, *J* 16.8, =C*H*H), 4.27–4.08 (4 H, m, 2 × CH_3CH_2O), 2.28–2.13 (2 H, m,

CH_2C=), 1.49–1.24 (10 H, m, 2 × CH_2+ 2 × CH_3CH_2), 0.86 (3 H, t, J 7.2, CH_3); δ_C(50.3 MHz, $CDCl_3$) 163.63 (s, C=O), 148.99 (s, C=O), 144.81 (s, =CH uracil), 144.34 (d, $J_{C,P}$ 3.4, N–C=), 133.95 (d, $J_{C,P}$ 168.7, P–C=), 131.26 (d, $J_{C,P}$ 4.6, –*C*H=CH_2), 119.84 (s, =CH_2), 102.14 (s, =CH uracil), 62.46 (d, $J_{C,P}$ 5.5, CH_3CH_2O), 62.21 (d, $J_{C,P}$ 5.6, CH_3CH_2O), 30.78 (d, $J_{C,P}$ 6.6, CH_2), 30.65 (s, CH_2), 22.84 (s, CH_2), 16.19 (d, $J_{C,P}$ 6.4, CH_3CH_2O), 16.11 (d, $J_{C,P}$ 6.6, CH_3CH_2O), 13.51 (s, CH_3); δ_P(81.01 MHz, $CDCl_3$) 17.22 (s).

Z-4-(Diethylphosphonyl)-3-(thymin-1-yl)octa-2,3-diene 26a and *E*-4-(diethylphosphonyl)-3-(thymin-1-yl)octa-2,3-diene 26b

Compounds **26a** and **26b** prepared in the same manner described for **25a** and **25b**. The mixture of *Z* and *E* isomers was chromatographed on a silica gel column ($CHCl_3$/MeOH, 10 : 0.4⟶10 : 1.0) to give the *Z* isomer (0.14 g, 18%) and *E* isomer (0.16 g, 21%) as an oil.

***Z* Isomer 26a.** TLC: R_f = 0.42 ($CHCl_3$/MeOH = 10 : 0.8) (Found: C, 56.29; H, 7.61; N, 7.32; P, 8.00. $C_{18}H_{29}N_2O_5P$ (384.414) requires C, 56.24; H, 7.60; N, 7.29; P, 8.06%); ν_{max}(film)/cm^{-1} 1995, 1700 (C=C); δ_H(200 MHz, $CDCl_3$) 9.10 (1 H, br s, NH), 6.84 (1 H, q, J 1.2, =CH thymine), 6.77 (1 H, ddd, J 16.9, J 10.7, $J_{H,P}$ 2.0, –*HC*=CH_2), 5.50 (1 H, dd, J 10.7, $J_{H,P}$ 4.5, =CH*H*,), 5.28 (1 H, dd, J 16.9, J 1.5, =C*H*H), 4.14–3.99 (4 H, m, 2 × CH_3CH_2O), 2.52 (2 H, dt, J 7.2, $J_{H,P}$ 19.0, CH_2C=), 1.94 (3 H, d, J 1.2, CH_3–C= thymine), 1.65–1.40 (4 H, m, 2 × CH_2), 1.30 (3 H, t, J 6.6, CH_3CH_2O), 1.26 (3 H, t, J 6.8, CH_3CH_2O), 0.96 (3 H, t, J 7.2, CH_3); δ_C(50.3 MHz, $CDCl_3$) 164.39 (s, C=O), 149.82 (d, $J_{C,P}$ 1.2, C=O), 143.43 (d, $J_{C,P}$ 2.0, N–C=), 141.48 (d, $J_{C,P}$ 1.5, =CH thymine), 133.73 (d, $J_{C,P}$ 174.5, P–C=), 129.00 (d, $J_{C,P}$ 15.9, –*C*H=CH_2), 121.09 (s, =CH_2), 109.18 (s, CH_3–*C*= thymine), 62.40 (d, $J_{C,P}$ 5.8, CH_3CH_2O), 62.25 (d, $J_{C,P}$ 6.1, CH_3CH_2O), 31.81 (d, $J_{C,P}$ 1.9, CH_2), 29.44 (d, $J_{C,P}$ 6.9, CH_2), 22.64 (s, CH_2), 16.10 (d, $J_{C,P}$ 6.8, 2 × CH_3CH_2O), 13.69 (s, CH_3), 12.16 (s, CH_3 thymine); δ_P(81.01 MHz, $CDCl_3$) 16.70 (s).

***E* Isomer 26b.** TLC: R_f = 0.53 ($CHCl_3$/MeOH = 10 : 0.8) (Found: C, 56.30; H, 7.65; N, 7.38; P, 8.13. $C_{18}H_{29}N_2O_5P$ (384.414) requires C, 56.24; H, 7.60; N, 7.29; P, 8.06%); ν_{max}-(film)/cm^{-1} 1996, 1700 (C=C); δ_H(200 MHz, $CDCl_3$) 9.20 (1 H, br s, NH), 7.54 (1 H, ddd, J 16.9, J 10.8, $J_{H,P}$ 1.5, *HC*=CH_2), 6.84 (1 H, q, J 1.2, =CH thymine), 5.43 (1 H, dd, J 10.8, $J_{H,P}$ 1.4, =CH*H*), 5.15 (1 H, d, J 16.9, =C*H*H), 4.30–4.05 (4 H, m, 2 × CH_3CH_2O), 2.21 (2 H, dt, J 7.2, $J_{H,P}$ 18.3, CH_2C=), 1.98 (3 H, d, J 1.2, CH_3–C= thymine), 1.42–1.24 (10 H, m, 2 × CH_2+2 × CH_3CH_2), 0.86 (3H, t, J 7.2, CH_3); δ_C(50.3 MHz, $CDCl_3$) 164.15 (s, C=O), 149.00 (s, C=O), 144.78 (d, $J_{C,P}$ 25.3, N–C=), 140.08 (s, =CH thymine), 133.74 (d, $J_{C,P}$ 168.6, P–C=), 131.28 (d, $J_{C,P}$ 4.8, –*C*H=CH_2), 119.84 (s, =CH_2), 110.69 (s, CH_3–*C*= thymine), 62.41 (d, $J_{C,P}$= 5.5, CH_3CH_2O), 62.17 (d, $J_{C,P}$ 6.0, CH_3CH_2O), 30.72 (d, $J_{C,P}$ 6.8, CH_2), 30.72 (d, $J_{C,P}$ 1.8, CH_2), 22.84 (s, CH_2), 16.21 (d, $J_{C,P}$ 6.4, CH_3CH_2O), 16.14 (d, $J_{C,P}$ 6.5, CH_3CH_2O), 13.53 (s, CH_3), 12.19 (s, CH_3 thymine); δ_C(81.01 MHz, $CDCl_3$) 17.47 (s).

Crystal structure determination of 1-(adenin-9-yl)-4-(diethylphophonyl)-2-methylhepta-2,3-diene 18

Crystal data. $C_{17}H_{26}N_5O_3P$, M = 379.40, monoclinic, a = 28.047(6), b = 11.272(2), c = 13.562(3) Å, β = 103.05 (3), U = 4176.8(15) Å^3, T = 293(2) K, space group C_2/c, Z = 8, μ(Mo–K_α) = 0.157 mm^{-1}, 1018 reflections measured, 997 unique (R_{int} = 0.0186) which were used in all calculations. The final $wR(F^2)$ was 0.1621 (all data).

Crystal structure determination of 2-methyl-4-(phosphonyl)-1-(thymin-1-yl)octa-2,3-diene 2f

Crystal data. $C_{14}H_{20}N_2O_5P$, M = 327.29, monoclinic, a = 14.135(3), b = 8.272(2), c = 14.408(3) Å, β = 106.97 (3), U = 1611.3(15) Å^3, T = 293(2) K, space group $P2_1/n$, Z = 4, μ(Mo–K_α) = 0.195 mm^{-1}, 1890 reflections measured, 1810 unique (R_{int} = 0.02141) which were used in all calculations. The final $wR(F^2)$ was 0.1059 (all data).

Acknowledgements

This work was supported by grants from the National Institute of Health (FIRCA 2RO3TW000437) and International Science and Technology Center (project 1151B).

References

1 (*a*) *Nucleosides and Nucleotides as Antitumour and Antiviral Agents*, ed. C. K. Chu and D. C. Baker. Plenum Press, New York, 1993; (*b*) E. De Clercq and E. Clin, *Microbiol. Rev.*, 1997, **10**, 674–693; (*c*) A. Holy, H. Dvorakova, J. Jindrich, M. Masojidkova, M. Budesinsky, J. Balzarini, G. Andrei and E. De Clercq, *J. Med. Chem.*, 1996, **39**, 4073–4088; (*d*) A. Holy, J. Günter, H. Dvorakova, M. Masojidkova, G. Andrei, R. Snoeck, J. Balzarini and E. De Clercq, *J. Med. Chem.*, 1999, **42**, 2064–2086 (and references cited therein); (*e*) E. De Clercq, *Intervirology*, 1997, **40**, 295–303.

2 (*a*) E. De Clercq, A. Holy, I. Rosenberg, T. Sakuma, J. Balzarini and P. C. Maudgal, *Nature*, 1986, **323**, 464–467; (*b*) E. De Clercq, T. Sakuma, M. Baba, R. Pauwels, J. Balzarini, I. Rosenberg and A. Holy, *Antiviral Res.*, 1987, **8**, 261–272; (*c*) E. De Clercq, *J. Med. Microbiol.*, 1998, **47**, 1–3.

3 J. Balzarini, H. Sobis, L. Naesens, M. Vandeputte and E. De Clercq, *Int. J. Cancer*, 1990, **45**, 486–489.

4 J. D. Gangemi, R. M. Cozens, E. De Clercq, J. Balzarini and H. K. Hochkeppel, *Antimicrob. Agents Chemother.*, 1989, **33**, 1864–1868.

5 R. A. Heijtink, G. A. Dewilde, J. Kruining, L. Berk, J. Balzarini, E. De Clercq, A. Holy and S. W. Schalm, *Antiviral Res.*, 1993, **21**, 141–153.

6 K. C. Cundy, P. A. Barditch-Crovo, R. E. Walker, A. C. Collier, D. Ebeling, J. Toole and H. S. Jaffe, *Antimicrob. Agents Chemother.*, 1995, **39**, 2401–2405.

7 D. Rejman, M. Masojidkova, E. De Clercq and I. Rosenberg, *Nucleosides Nucleotides*, 2001, **20**, 1497–1522 (and references cited therein).

8 W. Chen, M. T. Flavin, R. Filler and Z.-Q. Xu, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3979–3988.

9 K. Hartmann, M. Kuffer, J. Balzarini, L. Naesens, M. Goldberg, V. Erfle, F. D. Goebel, E. De Clercq, J. Jindrich, A. Holy, N. Bischofberger and W. Kraft, *J. Acquired Immune Defic. Syndr. Hum. Retrovirol.*, 1998, **17**, 120–128.

10 (*a*) V. K. Brel, *Synth. Commun.*, 2002, **32**, 2855–2862; (*b*) V. K. Brel, *Synthesis*, 2001, 1539–1545; (*c*) V. K. Brel, *Synth. Commum.*, 1999, **29**, 3869–3880; (*d*) V. K. Brel, *Synthesis*, 1998, 710–712; (*e*) V. K. Brel and P. J. Stang, *Eur. J. Org. Chem.*, 2003, 224–229; (*f*) V. K. Brel and P. J. Stang, *225*th ACS National Meeting, 2003, Abstract 132, New Orleans, Division of Organic Chemistry.

11 (*a*) J. Zemlicka, in *Nucleosides and Nucleotides as Antitumour and Antiviral Agents*, ed. C. K. Chu and D. C. Baker, Plenum Press, New York, 1993, 73–100; (*b*) S. Megati, S. Phadtare and J. Zemlicka, *J. Org. Chem.*, 1992, **57**, 2320–2327.

12 I. V. Alabugin and V. K. Brel, *Usp. Khim.*, 1997, **66**, 225–245 (*Russ. Chem. Rev. (Engl. Trans.)*, 1997, **66**, 205–224); (Chem. Abs., 1998, **128**, 114977r).

13 V. Mark, *Tetrahedron Lett.*, 1962, 281–284.

14 R. Wolfgang, in *The Chemistry of Allenes*, ed. S. R. Landor, Academic, London, 1982, vol. 2.

15 X-Ray studies were executed in the L. Karpov of Institute of Physics-Chemistry, Moscow.

16 A. N. Chekhlov, V. K. Brel, E. V. Abramkin and N. S. Zefirov, *Dokl. Akad. Nauk SSSR*, 1991, **319**, 417–421.

17 A. M. Gazaliev, O. A. Nurkenov, R. Z. Kasenov, K. M. Turdybekov and Yu. T. Struchkov, *Zh. Obshch. Khim.*, 1992, **62**, 1522–1528.

18 V. Yu. Nesterov and V. A. Naumov, *Zh. Obshch. Khim.*, 1992, **62**, 2585–2597.

19 T. J. Kirstenmacher and T. Shigematsu, *Acta Crystallogr.*, 1974, **B30**, 1528–1543.

20 S. M. Tret'yak, V. V. Mitkevich and L. F. Sukhodub, *Kristallografiya*, 1987, **32**, 1268–1280.

21 F. H. Allen, O. Kennard and D. G. Watson, *J. Chem. Soc., Perkin Trans. 2*, 1987, **N12**, S1.

22 H. Gross, *J. Prakt. Chem.*, 1963, **21**, 99–106.

23 V. K. Brel, *Synthesis*, 2002, 1829–1832.

24 N. Gershtein, *Zh. Obshch. Khim.*, 1942, **12**, 124–129.