Synthesis of Acyclic Carba-Nucleoside Phosphonates, Structural Analogues to Natural Deoxyribonucleotides

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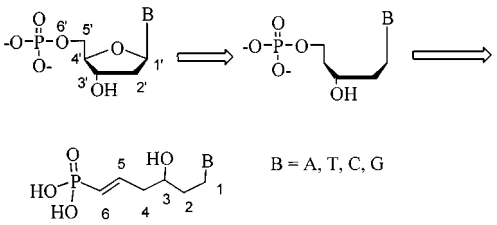
Acyclic carba-nucleoside phosphonates, modelled on natural deoxyribonucleotides have been prepared starting from DNA nucleobases and *tert*-butyl acrylate. The products obtained from a Michael-type reaction were elongated to β-oxo esters that were first reduced to β-hydroxy esters and then transformed into protected β-hydroxy aldehydes. Wittig–Horner–Emmons reaction with the anion of tetraisopropyl methylenebisphosphonate gave, after deprotection, the desired 4-hydroxy-6-purinyl- or -6-pyrimidinyl-1-hexenylphosphonic acids. A dimer, potential precursor of acyclic polynucleotides (APN), homomorphous with DNA, was also prepared.

Since the discovery of Acyclovir (ACV), the synthesis of acyclic nucleosides has attracted the interest of several organic and medicinal chemists.[1] The extensive work of Holy and De Clercq has demonstrated that, amongst the large number of molecules proposed as potentially active, the most promising structure for the discovery of effective antiviral agents should present a purine ring linked to an aliphatic chain bearing one OH and/or one phosphonate group as possible site of triphosphorylation.[2][3]

Following our interest in the synthesis of DNA chimerae,[4] we considered the possibility of preparing acyclic carba analogues of nucleosides homomorphous with the natural system.[5]



Scheme 1. B = A, T, C, G

Our idea was to remove the ribose oxygen atom, maintain the phosphorus atom in the molecule as a phosphonic acid and to introduce a double bond to give a certain level of conformational rigidity to the molecule.[6]

We report here a general synthesis of compounds of type **1** carrying adenine, cytosine, and thymine as nucleobases and a model oligomerisation reaction of **1** that could be employed for the preparation of acyclic polynucleotides (APN) homomorphous with DNA.[7]

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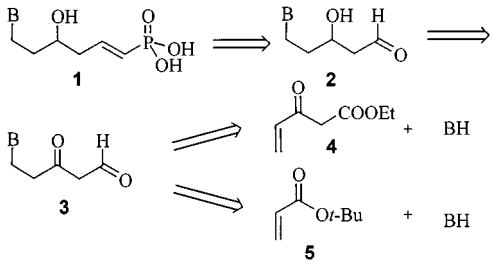
The retrosynthetic scheme proposed for the preparation of compounds of type **1** is shown in Scheme 2.



Scheme 2. B = adenine, cytosine, thymine

The vinyl phosphonic acid **1** can be prepared from a Wittig−Horner−Emmons reaction starting from the β-aldehyde **2** that can be related, through a simple series of chemoselective reductions, with β-oxo ester **3**. As several methods are reported the enantioselective reduction of the carbonyl group of a β-oxo ester, we decided to use this reaction for control of the stereochemistry of the products.

Compound **3** could be prepared according to a common strategy based on the introduction of the nucleobase on the carbon skeleton with a Michael-type reaction. Two sequences of events are possible: addition of the nucleobase to the unsaturated β-oxo ester **4** or Michael reaction of a nucleobase with an acrylate followed by a Claisen-type reaction.

As the first approach appeared more convergent, we decided to prepare compound **4** by reaction of the ethyl lithioacetate with acrolein followed by oxidation of the allylic alcohol **6** with the Jones reagent.[8] Product **4** was isolated by vacuum distillation in good yield and was immediately submitted to Michael reaction with adenine (Scheme 3).

The addition of nucleobases to α,β-unsaturated carbonyl compounds has been described to take place under basic conditions[9] that partially deprotonated the acidic methylene group of **4**. The desired addition product **3** could be obtained albeit in 12% yield only in case when Cs_2CO_3 in

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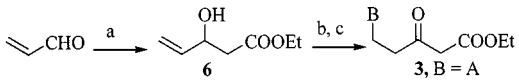
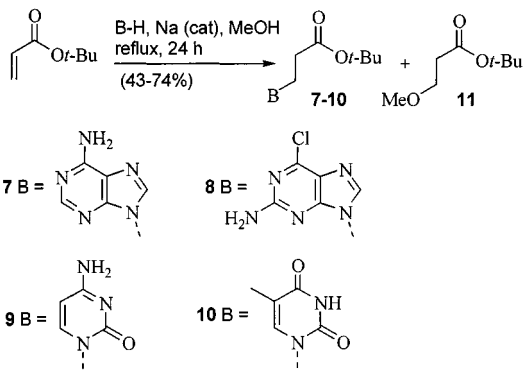
DMSO at room temperature for 28 h was employed (Scheme 3).



Scheme 3. a) EtOAc, LDA, THF, −78°C, 73%; b) Jones oxidation, 61%; c) adenine, Cs_2CO_3, DMSO, 12%

The preparation of **3** was then attempted according to the second approach. *tert*-Butyl acrylate was chosen as the Michael acceptor and several different reaction conditions were tested to obtain good yields of products **7−10**. The protocol proposed by Pandit,[10] who described the use of a molar excess of the heterocyclic compound in refluxing methanol in the presence of 10 mol-% of sodium, proved quite general and gave modest to good yields of the desired products **7−10** together with minor amounts (10−25%) of compound **11**, obtained by addition of methanol to the acrylate.

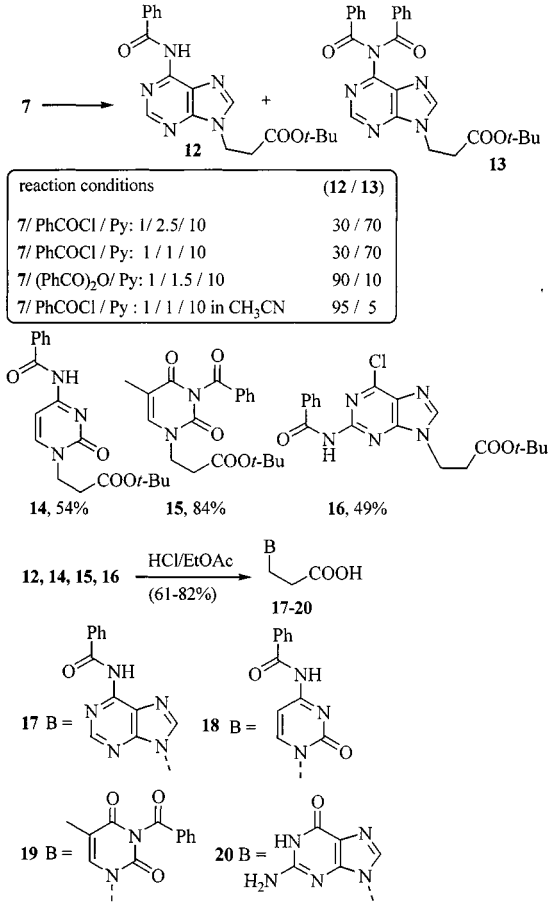


Scheme 4

Compounds **7−10**, after purification by crystallisation from water, require protection at the exocyclic NH_2 group (**7**, **8**, and **9**) or at the acidic NH thymine ring (**10**).

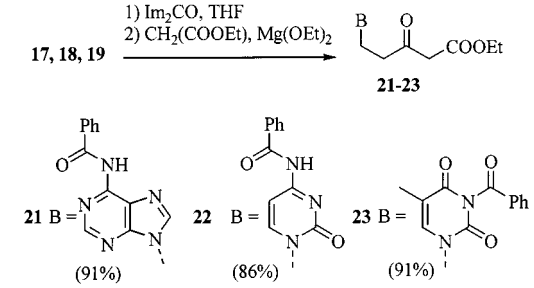
Using the adenyl derivative as the model compound, we decided to prepare the corresponding N^6-benzoyl derivative. According to a literature procedure,[11] reaction with benzoyl chloride (2.5 equiv.) in pyridine unexpectedly gave a mixture of the monobenzoyl compound **12** and the dibenzoyl derivative **13** in a 70:30 ratio. Use of 1 equiv. of benzoyl chloride also gave the same product ratio (obviously with lower chemical yields). Better results were obtained using benzoic anhydride in pyridine or benzoyl chloride/pyridine in acetonitrile with a catalytic amount of DMAP. The purification of **12** was straightforward using the second procedure; hence this was applied to the preparation of compounds **14−16** (62−79%).

Hydrolysis of esters **12**, **14**, and **15** was achieved by stirring in dry 3 M HCl in EtOAc at room temperature for 12 h to give the corresponding carboxylic acids **17−19** (61−82%). In this transformation the concentration of the acid had a crucial role as, at higher concentrations, the nitrogen atom was deprotected. However under these conditions, compound **16** was hydrolysed to give the guanylpropanoic acid **20**.



Scheme 5

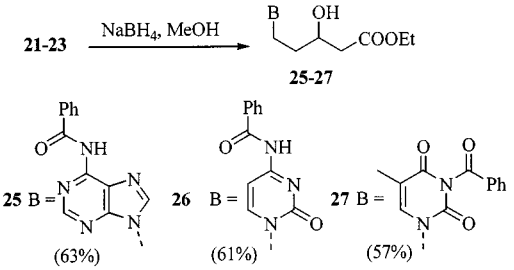
C-Alkylation of carboxylic acids **17−19** was carried out under neutral conditions converting the acid into the corresponding acylimidazole with carbonyldiimidazole (CDI) in THF followed by in situ treatment with the magnesium salt of monomethyl malonate.[12] The product β-oxo esters **21−23** were obtained decomplexed with magnesium and could therefore be isolated by column chromatography on silica gel in excellent yields.



Scheme 6

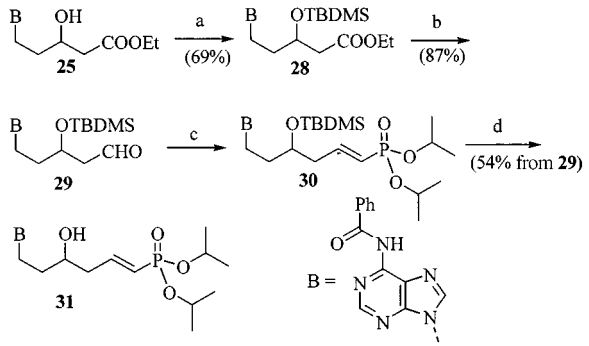
Unfortunately, the carboxylic derivative **20** did not react as it was completely insoluble in THF or in other aprotic solvents. Attempts to carry out the alkylation in DMF, where **20** was soluble, also failed.

Compound **21** was used once again as the model for enantioselective reduction of the carbonyl group. The enantioselective reduction of differently functionalized β-oxo esters has been successfully achieved with high *ee* using homogeneous transition metal catalyst hydrogenation in the presence of (binap)Ru or by applying reduction mediated by Baker's yeast.[13] As the second approach appeared simple, attempts were made to reduce compound **21** using dry yeast in an organic solvent,[14] in an aqueous medium after previous fermentation[15] or without fermentation.[16] However, under none of the attempted conditions was the formation of the alcohol **25** observed. The application of (binap)Ru-catalysed hydrogenation did not give better results.[17]. Reduction of **21** took place only with $NaBH_4$ in MeOH/THF to give product **25** (as a racemate) in 63% yield. The same procedure applied to oxo esters **22** and **23** gave alcohols **26** and **27** in 61 and 57% yields, respectively.



Scheme 7

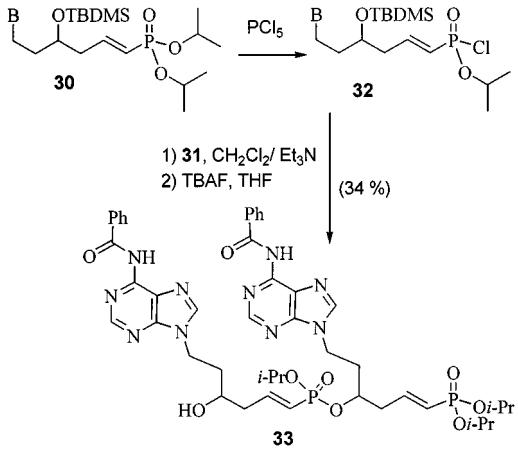
Although the formation of a racemic mixture cannot be considered a satisfactory result, we decided to undertake the synthetic sequence with the adenyl derivative **25**, as a model study. Alcohol **25** was protected as *tert*-butyldimethylsilyl ether with TBDMSCl/imidazole/DMF at 60°C and the corresponding product **28** was reduced to the aldehyde **29** with DIBAL-H at −78°C. The reduction proceeded smoothly at low temperature going to completion after 4 h at −78°C. The excess of DIBAL-H was destroyed at −78°C with MeOH and product **29** isolated, after the usual aqueous workup, by column chromatography. Although aldehyde **29** was sufficiently stable and could be stored at 0°C for several weeks, we used it immediately for the Wittig−Horner−Emmons reaction with tetraisopropyl methylenebisphosphonate with LDA (0°C to room temperature, 3 h) to give product **30**.



Scheme 8. a) TBDMSCl, imidazole, DMF, 60°C; b) DIBALH, toluene, −78°C; c) $CH_2[PO(OiPr)_2]_2$, LDA, THF, 0°C; d) TBAF, THF, room temp.

The deprotection of **30** with TBAF gave compound **31**, which was purified by column chromatography on silica gel and fully characterised. The stereochemistry of the double bond was confirmed by the *trans*-alkene coupling constant (14 Hz, determined after decoupling the CH_2 at δ = 2.2).

Compounds **30** and **31** were employed to prepare the dimer **33**. Compound **30** was refluxed in THF with 1 equiv. of PCl_5 for 3 h.[18] The solvent was removed under vacuum and crude **32** was treated with a solution of **31** in the presence of 5 equiv. of triethylamine to give **33**. After aqueous workup, the reaction producut was desilylated with TBAF to give compound **31** in 34% yield (as a mixture of diastereoisomers).



Scheme 9

Product **33** is formally an acyclic dinucleotide (in protected form) which is topologically related to DNA and to PNA as it presents two atoms between the nucleobase and the chain and six atoms between the carbon atoms that carry the pendant nucleobases.[19]

Compounds **25**−**33** are currently subjected to antiviral activity tests. As the synthetic strategy has proved to be successful, we are currently persuing the synthesis of the asymmetric analogue of **33**.

Experimental Section

9-(2-*tert*-Butoxycarbonylethyl)adenine (7). − General Procedure: To a solution of adenine (4.0 g, 29.6 mmol), dissolved in dry MeOH (100 mL), sodium (0.15 g, 6.5 mmol) was added and the mixture refluxed for 2 h under nitrogen. *tert*-Butyl acrylate (9.2 g, 71.6 mmol) was added and the mixture refluxed for additional 18 h. The solvent was evaporated and the crude residue dissolved in water. Product **7** separated as a fine precipitate that was filtered and crystallised from hot water to give 5.6 g of **7** (74% yield), m.p. 183−185°C. − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.40 (s, 9 H), 2.83 (t, *J* = 6 Hz, 2 H), 4.45 (t, *J* = 6 Hz, 2 H), 5.64 (br. s, 2 H), 7.90 (s, 1 H), 8.36 (s, 1 H). − $C_{12}H_{17}N_5O_2$ (263.30): calcd. C 54.74, H 6.51, N 26.60; found C 54.47, H 6.43, N 26.35.

2-Amino-9-(2-*tert*-butoxycarbonylethyl)-6-chloropurine (8): 43% yield, m.p. 163−165°C. − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.42 (s, 9 H), 2.75 (t, *J* = 6 Hz, 2 H), 4.35 (t, *J* = 6 Hz, 2 H), 5.90 (br. s, 2 H), 8.41 (s, 1 H). − $C_{12}H_{16}ClN_5O_2$ (297.74): calcd. C 48.41, H 5.42, N 23.52; found C 48.30, H 5.42, N 23.40.

1-(2-*tert*-Butoxycarbonylethyl)cytosine (9): 63% yield, m.p. 185−188°C. − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.35 (s, 9 H), 2.55 (t, *J* = 6 Hz, 2 H), 3.76 (t, *J* = 6 Hz, 2 H), 5.58 (d, *J* = 7 Hz, 1 H), 7.00 (s, 2 H), 7.51 (d, *J* = 7 Hz, 1 H). − $C_{11}H_{17}N_3O_3$ (239.27): calcd. C 55.22, H 7.16, N 17.56; found C 55.10, H 7.11, N 17.66.

1-(2-*tert*-Butoxycarbonylethyl)thymine (10): 65% yield m.p. 190−191°C. − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.40 (s, 9 H), 2.00 (s, 3 H), 2.80 (t, *J* = 6 Hz, 2 H), 4.12 (t, *J* = 6 Hz, 2 H), 7.35 (s, 1 H), 8.27 (br. s, 1 H). − $C_{12}H_{18}N_2O_4$ (254.29): calcd. C 56.68, H 7.13, N 11.02; found C 56.43, H 7.06, N 11.12.

***N*^{6}-Benzoyl-9-(2-*tert*-butoxycarbonylethyl)adenine (12). − General Procedure:** To a solution of **7** (5.6 g, 21.2 mmol) in dry MeCN (22 mL) at 0°C, dry pyridine (9 mL) was added followed by freshly distilled benzoyl chloride (7.53 g, 54.8 mmol). The mixture was refluxed for 12 h, then cooled to room temp. and poured into a flask containing melting ice and conc. HCl (5 mL). The formed precipitate was filtered, washed with water and crystallised from hot water to give 7.2 g of **12** (88% yield), m.p. 127−128°C. − IR (KBr): ṽ = 3450, 1740, 1670, 1610 cm^{-1}. − ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.39 (s, 9 H), 2.83 (t, *J* = 6 Hz, 2 H), 4.47 (t, *J* = 6 Hz, 2 H), 7.45, 7.55, and 8.11 (m, 5 H), 8.00 (s, 1 H), 8.33 (s, 1 H), 9.3 (br. s, 1 H). − $C_{19}H_{21}N_5O_3$ (367.41): calcd. C 62.11, H 5.36, N 19.06; found C 62.33, H 6.26, N 19.22.

***N*^{4}-Benzoyl-1-[(2-*tert*-butoxycarbonyl)ethyl]cytosine (14):** 54% yield, m.p. 175−179°C. − IR (KBr): ṽ 3440, 1720, 1660, 1600 cm^{-1}. − ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.41(s, 9 H), 2.29 (t, *J* = 6 Hz, 2 H), 4.11 (t, *J* = 6 Hz, 2 H), 7.42 (d, *J* = 8 Hz, 1 H), 8.03 (d, *J* = 8 Hz, 1 H), 7.51, 7.66, and 8.14 (m, 5 H), 8.98 (br. s, 1 H). − $C_{18}H_{21}N_3O_4$ (343.38): calcd. C 62.96, H 6.16, N 12.24; found C 62.77, H 6.06, N 12.18.

***N*^{3}-Benzoyl-1-(2-*tert*-butoxycarbonylethyl)thymine (15):** 84% yield, m.p. 168−169°C. − IR (KBr): ṽ = 3450, 1730, 1660, 1610 cm^{-1}. − ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.40 (s, 9 H), 1.92 (s, 3 H), 2.70 (t, *J* = 6 Hz, 2 H), 3.95 (t, *J* = 6 Hz, 2 H), 7.20 (s, 1 H), 7.46, 7.59, and 8.11 (m, 5 H). − $C_{19}H_{22}N_2O_5$ (358.39): calcd. C 63.67, H 6.19, N 7.82; found C 63.77, H 6.26, N 7.78.

2-Benzoylamino-9-(2-*tert*-butoxycarbonylethyl)-6-chloropurine (16): 49% yield, m.p. 113−115°C. − IR (KBr): ṽ = 3450, 1730, 1660, 1610 cm^{-1}. − ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.39 (s, 9 H), 2.70 (t, *J* = 6 Hz, 2 H), 4.58 (t, *J* = 6 Hz, 2 H), 7.49, 7.55, and 8.18 (m, 5 H), 8.31 (s, 1 H), 9.19 (br. s, 1 H). − $C_{19}H_{20}ClN_5O_3$ (401.85): calcd. C 56.79, H 5.02, Cl 8.82, N 7.82; found C 56.77, H 5.10, Cl 8.90, N 7.79.

***N*^{6}-Benzoyl-9-(2-carboxyethyl)adenine (17). − General Procedure:** Compound **12** (3.7 g, 10.1 mmol) was dissolved in a solution of dry HCl in EtOAc (67 mL of a 3.5 M solution) and stirred at room temp. for 24 h. A white solid was separated and filtered. The filtrate was diluted with ether (50 mL) to precipitate additional product which was collected, mixed with the first crop and crystallised from water. Obtained 1.9 g of **17** (61% yield), m.p. 198−200°C. − IR (KBr): ṽ = 3450−2700, 1710, 1660, 1610 cm^{-1}. − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.96 (t, *J* = 6 Hz, 2 H), 4.50 (t, *J* = 6 Hz, 2 H), 7.54, 7.65, and 8.01 (m, 5 H), 8.75 (s, 1 H), 8.85 (s, 1 H), 9−10 (br. s, 2 H). − ^{13}C NMR (75 MHz, [D$_6$]DMSO) δ 34.9, 47.2, 127.0, 128.4, 129.0, 131.9, 133.5, 144.8, 148.9, 152.0, 155.0, 168.3, 177.0. − $C_{15}H_{13}N_5O_3$ (311.90): calcd. C 57.87, H 4.21, N 22.50; found C 57.74, H 4.16, N 22.37.

***N*^{4}-Benzoyl-1-(2-carboxyethyl)cytosine (18):** 82% yield, m.p. 213−215°C. − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.70 (t, *J* = 6 Hz, 2 H), 4.00 (t, *J* = 6 Hz, 2 H), 7.25 (d, *J* = 7 Hz, 1 H), 8.15 (d, *J* = 8 Hz, 1 H), 7.50, 7.61 and 8.10 (m, 5 H), 9−10 (br. s, 2 H). − ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 35.8, 45.9, 98.7, 121.6, 127.0, 128.4, 129.0, 131.9, 158.6, 161.6, 171.7, 177.9 − $C_{14}H_{13}N_3O_4$ (287.27): calcd. C 58.53, H 4.56, N 14.63; found C 58.64, H 4.66, N 14.73.

***N*^{3}-Benzoyl-1-(2-carboxyethyl)thymine (19):** 79% yield, m.p. 165−167°C. − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.94 (s, 3 H), 2.70 (t, *J* = 6 Hz, 2 H), 3.91 (t, *J* = 6 Hz, 2 H), 7.75 (s, 1 H), 7.6, 7.8, and 7.90 (m, 5 H), 10 (br. s, 1 H). − ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 15.9, 31.6, 43.8, 109.7, 121.6, 127.0, 128.4, 129.0, 134.8, 155.5, 165.7, 169.7, 177.0. − $C_{15}H_{14}N_2O_5$ (302.29): calcd. C 59.60, H 4.67, N 9.27 Found C 59.70, H 4,46, N 9.73.

9-(2-Carboxyethyl)guanine (20): 78% yield, m.p. 235−238°C (dec.). − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.80 (t, *J* = 7 Hz, 2 H), 4.17 (t, *J* = 7 Hz, 2 H), 7.10 (br. s, 2 H), 7.88 (s, 1 H), 10 (br. s, 1 H). − $C_8H_9N_5O_3$ (223.19): calcd. C 43.05, H 4.06, N 31.38; found C 43.11, H 4.09, N 31.45.

***N*^{6}-Benzoyl-9-(4-ethoxycarbonyl-3-oxobutyl)adenine (21). − General Procedure:** To a solution of acid **17** (2.0 g, 6.36 mmol) in dry THF (32 mL) under nitrogen and magnetic stirring CDI (1.09 g, 6.7 mmol) was added and the mixture stirred at room temperature for 6 h. Magnesium ethyl malonate, prepared from monoethyl malonate[20] (5.83 g, 44.2 mmol) and magnesium ethoxide (2.52 g, 22.0 mmol) in THF (110 mL), was added and the mixture stirred for additional 20 h. The solvent was evaporated under vacuum and the crude residue purified by column chromatography on silica gel (eluent CHCl$_3$ followed by CHCl$_3$/EtOH, 10:1). Obtained 2.22 g of **21** (91% yield), m.p. 85−86°C. − IR (KBr): ṽ = 3400, 1730, 1710, 1660, 1610 cm^{-1}. − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.21 (t, *J* = 7 Hz, 3 H), 3.27 (t, *J* = 6 Hz, 2 H), 3.44 (s, 2 H), 4.13 (q, *J* = 7 Hz, 2 H), 4.57 (t, *J* = 6 Hz, 2 H), 7.5, 7.6, and 8.00 (m, 5 H), 8.14 (s, 1 H), 8.78 (s, 1 H), 9.1 (br. s, 1 H). − ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 14.9, 39.7, 41.8, 48.9, 59.8, 127.6, 128.7, 129.7, 131.6, 133.8, 144.6, 147.3, 152.6, 154.7, 167.8, 171.7, 202.2. − $C_{19}H_{19}N_5O_4$ (381.39): calcd. C 59.84, H 5.02, N 18.36; found C 59.75, H 5,06, N 18.43.

***N*^{4}-Benzoyl-1-(4-ethoxycarbonyl-3-oxobutyl)cytosine (22):** 86% yield, m.p. 149−150°C. − IR (KBr): ṽ = 3430, 1730, 1705, 1650, 1640, 1610 cm^{-1}. − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.27 (t, *J* = 7 Hz, 3 H), 3.20 (t, *J* = 7 Hz, 2 H), 3.48 (s, 2 H), 4.10 (t, *J* = 7 Hz, 2 H), 4.20 (q, *J* = 7 H, 2 H), 7.51 (d, *J* = 8 Hz, 1 H), 7.7, 7.8, and 7.9 (m, 5 H), 7.95 (d, *J* = 8 Hz, 1 H), 8.7 (s, 1 H). − ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 14.9, 38.9, 40.8, 47.8, 58.1, 99.7, 121.3, 126.5, 127.8, 130.1, 133.7, 138.9, 161.7, 166.1, 174.3, 201.1. − $C_{18}H_{19}N_3O_5$ (357.37): calcd. C 60.50, H 5.36, N 11.76; found C 60.55, H 5,46, N 11.43.

***N*^{3}Benzoyl-1-(4-ethoxycarbonyl-3-oxobutyl)thymine (23):** 91% yield, m.p. 122−123°C. − IR (KBr): ṽ = 1740, 1710, 1650−1640, 1610 cm^{-1}. − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.26 (t, *J* = 7 Hz, 3 H), 1.93 (s, 3 H), 3.07 (t, *J* = 6 Hz, 2 H), 3.46 (s, 2 H), 3.98 (t, *J* = 6 Hz, 2 H), 4.18 (q, *J* = 7 Hz, 2 H), 7.33 (s, 1 H), 7.4, 7.6, and 7.9 (m, 5 H). − ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 13.9, 19.7, 36.9, 42.8, 44.8, 55.1, 101.7, 121.3, 125.5, 127.8, 130.1, 133.7, 155.7, 159.7, 164.1, 173.3, 203.1. − $C_{19}H_{20}N_2O_6$ (383.41): calcd. C 61.28, H 5.41, N 7.52; found C 61.10, H 5,52, N 7.27.

***N*^{6}-Benzoyl-9-(4-ethoxycarbonyl-3-hydroxybutyl)adenine (25). − General Procedure:** To a solution of NaBH$_4$ (0.1 g, 2.6 mmol), in EtOH (15 mmol), compound **21** (1.0 g, 2.6 mmol) in THF (5 mL) was added. The mixture was stirred for 2 h, the solvent evaporated, and the crude residue purified by flash chromatography (eluent: CHCl$_3$). Obtained 0.62 g of a waxy material (62% yield). − IR

(KBr): $\tilde{\nu}$ = 3400−3200, 1725, 1650, 1610 cm^{-1}. − ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.4 (m, 3 H), 2.2 (m, 2 H), 2.5 (m, 1 H), 2.8 (br. s, 1 H), 3.2 (m, 1 H), 4.02 (t-like, 3 H), 4.2 (m, 1 H) 4.4 (m, 2 H), 7.5, 7.6, and 8.0 (m, 5 H), 8.03 (s, 1 H), 8.81 (s, 1 H), 9.12 (s, 1 H). − ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 14.9, 39.7, 41.8, 48.9, 59.8, 61.6, 127.6, 128.7, 129.7, 132.6, 133.1, 144.9, 149.0, 152.8, 155.7, 166.6, 173.3. − $C_{19}H_{21}N_5O_4$ (383.41): calcd. C 59.52, H 5.52, N 18.27; found C 60.00, H 5,42, N 18.47.

***N*⁴-Benzoyl-1-(4-ethoxycarbonyl-3-hydroxybutyl)cytosine (26):** 61% yield. − IR (KBr): $\tilde{\nu}$ = 3400−3100, 1715, 1650, 1640, 1610 cm^{-1}. − ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.2 (m, 3 H), 2.2−2.4 (m, 2 H), 3.2−3.5 (m, 3 H), 3.9−4.1 (m, 2 H), 4.10 (t-like, 2 H), 7.50 (d, *J* = 8 Hz, 1 H), 7.7, 7.8, and 7.9 (m, 5 H), 7.85 (d, *J* = 8 Hz, 1 H), 8.3(s, 1 H). − ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 12.9, 32.9, 40.0, 45.8, 57.1, 63.3, 99.0, 121.3, 126.5, 127.8, 130.1, 137.7, 157.7, 166.9, 175.7. − $C_{18}H_{21}N_3O_5$ (359.38): calcd. C 60.16, H 5.89, N 11.69; found C 60.01, H 5.96, N 11.73.

***N*³-Benzoyl-1-(4-ethoxycarbonyl-3-hydroxybutyl)thymine (27):** 57% yield. − IR (KBr): $\tilde{\nu}$ = 3200, 1710, 1650−1640, 1610 cm^{-1}. − ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.2 (m, 3 H), 1.96 (s, 3 H), 1.9−2.4 (m, 5 H), 3.3 (m, 2 H), 3.9 (m, 1 H), 4.14(m, 2 H), 7.19 (s, 1 H), 7.4, 7.6, and 7.9 (m, 5 H). − ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 14.9, 18.7, 36.0, 42.0, 43.8, 50.1, 68.9, 101.7, 121.3, 125.5, 127.8, 130.1, 138.7, 155.7, 159.7, 164.1, 173.3. − $C_{19}H_{22}N_2O_6$ (374.39): calcd. C 60.95, H 5.92, N 7.48; found C 61.01, H 5.92, N 7.47.

***N*⁶-Benzoyl-9-[3-(*tert*-butyldimethylsilyloxy)-4-ethoxycarbonyl-butyl]adenine (28):** To a solution of **25** (0.360 g, 0.94 mmol) in dry DMF (0.7 mL) imidazole (0.18 g, 2.6 mmol) was added followed by TBDMSCl (0.17 g, 1.13 mmol). The vial was sealed and the mixture stirred for 72 h at 70°C (oil bath). The solvent was evaporated and the product purified by column chromatography on silica gel (eluent: $CHCl_3$). Obtained 0.32 g (69% yield). − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 3 H), 0.11 (s, 3 H), 0.92 (s, 9 H), 1.22 (t, *J* = 7 Hz, 3 H), 2.1−2.3 (m, 2 H), 2.5 (m, 2 H), 4.10 (q, *J* = 7 Hz, 2 H), 4.25 (m, 1 H), 4.35 (m, 2 H), 7.4, 7.6, and 8.0 (m, 5 H), 8.76 (s, 1 H), 8.86 (s, 1 H), 9.02 (s, 1 H). − $C_{25}H_{35}N_5O_4Si$ (497.67): calcd. C 60.34, H 7.09, N 14.07; found C 60.44, H 7.06, N 14.19.

***N*⁶-Benzoyl-9-[3-(*tert*-butyldimethylsilyloxy)-5-oxopentyl]adenine (29):** Compound **28** (0.25 g, 0.5 mmol) was dissolved in dry CH_2Cl_2 (0.7 mL) and this solution cooled to −78°C. DIBAL-H in toluene (0.6 mL of a 1 M solution) was added and the mixture stirred at −78°C for 4 h. Methanol (0.5 mL) was added to destroy the excess of DIBAL-H than the mixture was warmed to room temp., diluted with additional CH_2Cl_2 and washed with a saturated solution of NH_4Cl. The organic phase was separated, dried with Na_2SO_4, and the solvent evaporated to give 0.2 g of the crude aldehyde as a waxy material that was immediately employed in the next step (87% yield). − IR (neat): $\tilde{\nu}$ = 3450, 2860, 2740, 1730, 1620 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 3 H), 0.09 (s, 3 H), 0.89 (s, 9 H), 1.2 (m, 2 H), 2.1−2.3 (m, 2 H), 2.6 (m, 1 H), 4.3 (m, 2 H), 7.4, 7.5, and 8.0 (m, 5 H), 8.7 (s, 1 H), 8.8 (s, 1 H), 9.3 (s, 1 H), 9.8 (s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.3, 13.9, 21.7, 37.7, 44.1, 52.2, 66.6, 127.3, 128.4, 128.9, 131.1, 133.5, 144.8, 147.9, 152.0, 154.9, 165.3, 199.9.

***N*⁶-Benzoyl-9-(3-hydroxy-6-diisopropylphosphono-5-hexenyl)-adenine (31):** To a solution of tetraisopropyl methylenediphosphonate (0.34 g, 1 mmol) in dry THF (1 mL), cooled to 0°C, LDA (1.1 mL of a 1 M solution in THF) was added and the mixture stirred at room temp. for 3 h. After cooling again to 0°C, **29** (0.2 g, 0.44 mmol), dissolved in THF (1 mL), was added and the mixture was stirred at room temperature for 5 h. A saturated solution of NH_4Cl was added and the product extracted with $CHCl_3$ (15 mL). The organic layer was separed, dried with anhydrous Na_2SO_4 and the solvent evaporated. The crude residue (0.52 g) was divided in two portions of 0.25 g each. One portion was washed several times with diethyl ether to give product **30** sufficiently pure to be used in the next step (FAB/MS; *m/z*: 615.3). The other portion was dissolved in THF (5 ml) and TBAF (0.17 g, 0.53 mmol) was added. The mixture was stirred at room temp. for 12 h, the solvent evaporated and the product **31** isolated by column chromatography on silica gel (eluent: $CHCl_3$/EtOH, 8:1). Obtained 0.06 g (54% yield, based on 0.22 mmol of starting compound **29**). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.3 (m, 12 H), 2.2 (m, 2 H), 2.3−2.5 (m, 3 H), 4.4 (m, 1 H), 4.5−4.8 (m, 4 H), 5.75, (dd, *J* = 18 and 14 Hz, 1 H), 6.6−6.8 (m, 1 H), 7.5, 7.6, and 8.0 (m, 5 H), 8.78 (s, 1 H), 9.12 (s, 1 H), 9.78 (s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9, 39.7 (d), 48.9, 59.8, 61.6, 71.6, 113.9 (d), 127.6, 128.7, 129.7, 132.6, 133.1 (d), 144.9, 149.0, 150.7, 152.8, 155.7, 166.6. − $C_{24}H_{32}N_5O_5P$ (501.52): calcd. C 57.48, H 6.43, N 13.96; found C 57.57, H 6.37, N 13.7.

Dimer 33 (Not Optimized Procedure): A solution of the crude phosphonate **30** (0.2 g, 0.32 mmol) in dry THF (0.7 mL), containing PCl_5 (0.1 g, 0.45 mmol), was heated in a sealed vial at 70°C for 5 h. After cooling to room temp., the solvent was removed at room temp. under vacuum and the remaining crude product was dissolved in 1 mL of dry THF and this solution added to a cooled (0°C) solution of alcohol **31** (0.16 g, 0.32 mmol) and Et_3N (0.5 g, 5 mmol) in dry THF (1 mL). The mixture was stirred for 12 h. The solid was filtered off and to the solution TBAF (0.31 g, 1 mmol) in THF (1 mL) was added and the mixture stirred for additional 3 h. The solvent was evaporated and the product **33** isolated by column chromatography on silica gel (eluent: $CHCl_3$). Obtained 0.21 g (34% yield). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.3−1.4 (m, 18 H), 2.1−2.6 (br. m, 9 H), 4.2−4.4 (m, 2 H), 4.6−4.8 (m, 7 H), 7.5−7.9 (m, 10 H), 8.6 (br. s, 1 H), 8.7 (br. s, 1 H), 8.9 (br. s, 1 H), 9.2 (br. s, 1 H), 9.4 (br. s 2 H). − HRMS: calcd. for $C_{45}H_{56}N_{10}O_9P_2$; *m/z*: 942.3707, found 942.3712.

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