Synthesis of analogues of nucleotides with all-carbon backbones: synthesis of *N*-protected *C*-linked dinucleotides

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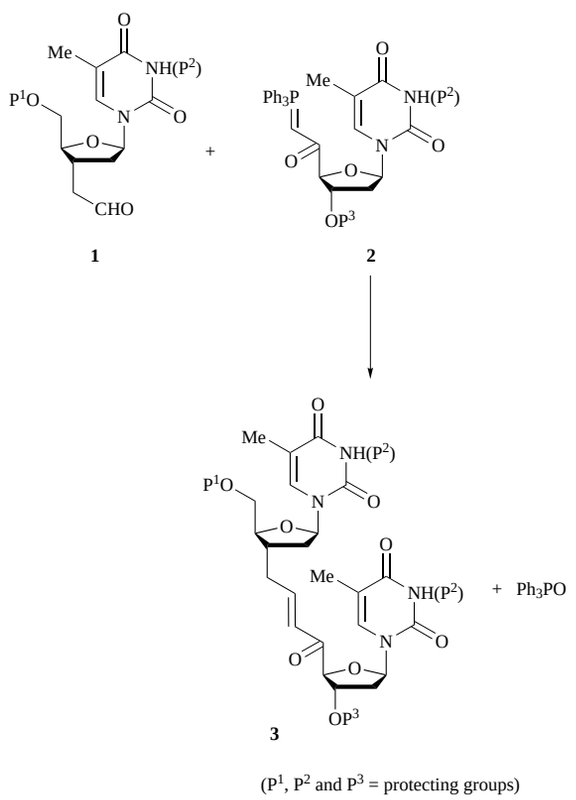
Oxidative cleavage of the protected 3′-propenyl-3′-deoxythymidine 28 using osmium tetraoxide and sodium periodate gives the aldehyde 29 which is converted *via* the acid 30 and imidazolide 31 into the stabilized ylide 32. This is condensed with the thymidine derived aldehyde hydrate 24 to give the dinucleotide analogue 34. Hydrogenation and desilylation give the saturated dinucleotide analogues 36 and 37.

One problem in the development of oligonucleotides as drugs is their instability towards nuclease enzymes.[1] The synthesis of nucleotide analogues which are stable to enzymic degradation has therefore been of considerable interest, *e.g.* for the development of antisense oligonucleotides.[2] Amongst the many oligonucleotide analogues which have been prepared and evaluated are those in which the polar phosphate groups have been replaced by functionality with increased stability towards enzymic cleavage, *e.g.* thiophosphates and phosphonates.[3] We now report full details of a synthesis of analogues of a dinucleotide in which the phosphate has been replaced by a three-carbon chain.[4] This substitute for the phosphate was selected for study since it should be completely stable towards nuclease enzymes. Moreover it is non-polar, achiral, so avoiding the introduction of additional stereogenic centres and the consequent proliferation of distereoisomers,[5] and provides options for the introduction of additional functionality for interaction with a specific site in a complementary nucleic acid strand. During the course of our work other approaches to *C*-linked oligonucleotides were reported.[6]

The Wittig reaction between a nucleoside derived aldehyde **1** and a stabilized ylide **2** was identified as a possible synthesis of the *C*-linked dinucleotide **3**. Stabilized ylides are not affected by aqueous and alcoholic conditions and strongly basic conditions are not required for their condensation with aldehydes. It was felt that these factors could be beneficial during the syntheses of *C*-linked oligonucleotides. At the onset of our work, the aldehydes **1** were known,[7,8] having been prepared by oxidative cleavage of the corresponding 3′-propenyl nucleosides. However, the level of protection that would be necessary for the thymine during the *C*-linked nucleotide synthesis was not clear.



1 **2** **3**

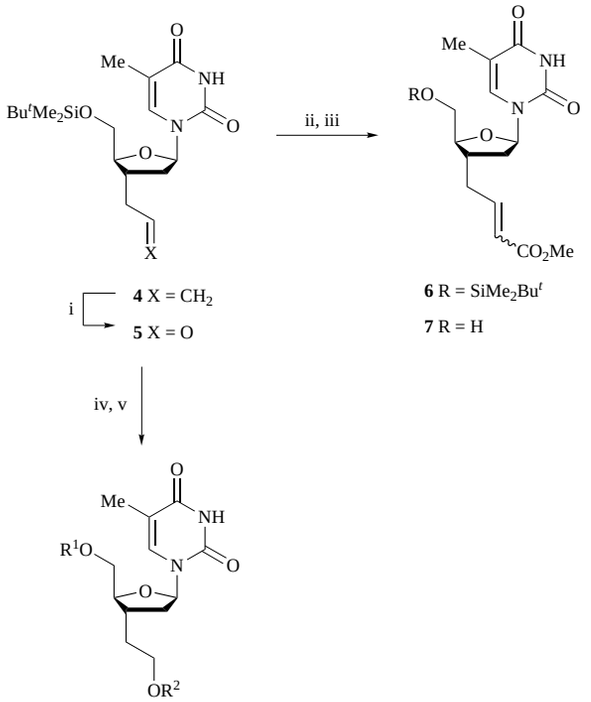
(P^1, P^2 and P^3 = protecting groups)

Results and discussion

The 3′-propenyl-3′-deoxythymidine **4**[7] was oxidized using osmium tetraoxide in aqueous dioxane followed by periodate cleavage of the diol so formed to give the aldehyde **5** (55%) (Scheme 1).[8] Treatment of this aldehyde with (methoxycarbonylmethylidene)(triphenyl)phosphorane at room temperature for 44 h gave the (*E*)-alkene (*E*)-**6** containing *ca.* 10% of its (*Z*)-isomer in good yield (89%), so confirming that Wittig reactions of the aldehyde could be carried out uneventfully with stabilized ylides. Desilylation of the Wittig product gave the hydroxy ester **7**. As an aside, the aldehyde was reduced using sodium borohydride[9] to the alcohol **8** which was deprotected[10] to give the thymidine homologue **9**. It now remained to prepare a ketophosphorane analogous to **2** for the crucial Wittig reaction.

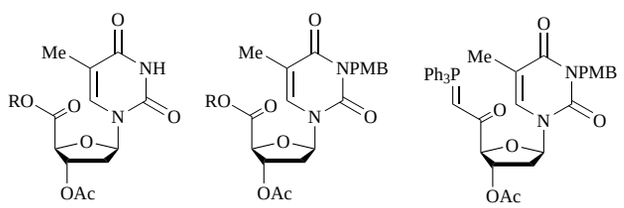
Oxidation of 3′-acetylthymidine[11] using pyridinium dichromate in the presence of acetic anhydride and *tert*-butyl alcohol[12,13] gave the *tert*-butyl ester **10**[14] which was hydrolysed to give the acid **11** using aqueous trifluoroacetic acid. However, attempts to convert this acid into a ketophosphorane *via* its 2-mercaptopyridine thioester were unsuccessful.

To check whether the free thymine *N*-H was responsible for this difficulty, the *tert*-butyl ester **11** was converted into its 3-(*p*-methoxybenzyl) derivative **12**, better yields for this protection being obtained using Mitsunobu conditions[15] rather than base-induced alkylation.[16] Acid-catalysed hydrolysis gave the carboxylic acid **13** but attempts to convert this into the ketophosphorane **14** by generation and trapping of its 2-mercaptopyridine thioester or acyl imidazolide were also unsuccessful. It would appear that the synthesis of phosphoranes analogous to **2** is not straightforward, perhaps because of interaction between activated 5′-carboxy groups and the thymine ring, and so it was decided to look for alternative procedures for the synthesis of the *C*-linked dinucleotides **3** rather than pursue a synthesis of the phosphorane **14**. Since aldol reactions followed by dehydration provide access to α,β-unsaturated carbonyl compounds, it was decided to examine aldol chemistry as an alternative route to *C*-linked dinucleotides.



4 X = CH_2
5 X = O
6 R = $SiMe_2Bu^t$
7 R = H
8 R^1 = $SiMe_2Bu^t$, R^2 = H
9 R^1 = R^2 = H

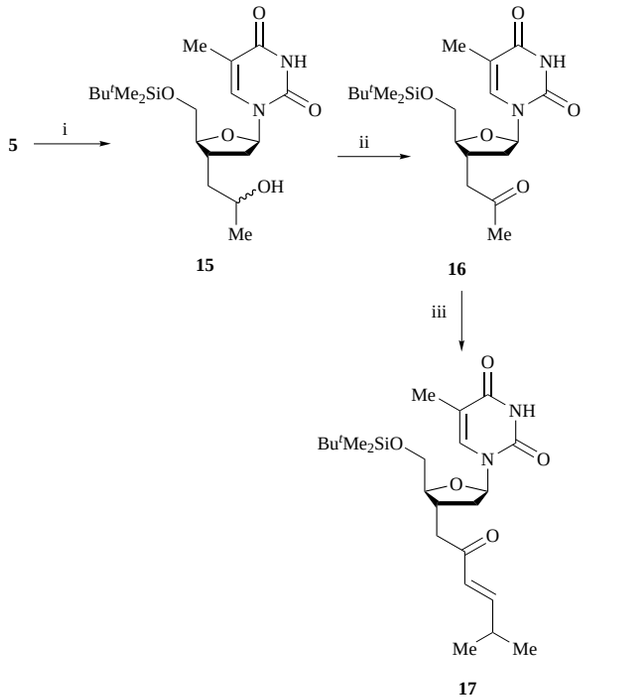
Scheme 1 *Reagents and conditions*: i, OsO_4, $NaIO_4$, aq. dioxane (55%); ii, $Ph_3P{=}CHCO_2Me$, chloroform, rt, 44 h [89%; (*E*):(*Z*) = 10:1]; iii, 80% aq. acetic acid, 70 °C, 3 h (88%); iv, sodium borohydride, methanol (76%); v, 80% aq. acetic acid, 70 °C, 5 h (90% conversion)



10 R = Bu^t
11 R = H
12 R = Bu^t
13 R = H
14
(PMB = *p*-methoxybenzyl)

The aldehyde **5** reacted with methylmagnesium bromide to give the alcohol **15** (63%) as a 50:50 mixture of epimers which were oxidized[17] to the ketone **16** (Scheme 2). Deprotonation of the ketone with lithium hexamethyldisilazide followed by addition of the enolate so formed to 2-methylpropanal gave the dehydrated aldol product **17** (41%) if the reaction mixture was stirred at room temperature before work-up together with unchanged ketone **16** (30%). Under milder reaction conditions only the unchanged ketone was obtained. The isolation of the unsaturated ketone **17** provided a precedent for a possible synthesis of *C*-linked dinucleotides using aldol reactions between the methyl ketone **16** and nucleoside 5′-aldehydes. The latter compounds are known to be available by oxidation of the corresponding nucleosides.

5′-(4,4′-Dimethoxytrityl)thymidine **18** was acetylated, the acetate **19** converted into its 3-(*p*-methoxybenzyl) derivative **20**, and the dimethoxytrityl protecting group removed[18] to give the 5′-alcohol **21** (Scheme 3). Oxidation to the aldehyde **22** was carried out under Pfitzner–Moffatt[19] conditions and the aldehyde purified by chromatography of its dianilinoethane derivative **23**.[20] However hydrolysis back to the aldehyde using an acidic Dowex resin in aqueous tetrahydrofuran[21] gave the aldehyde hydrate **24** and attempts to convert this into the free aldehyde by azeotropic distillation with benzene in a Dean–Stark apparatus resulted in significant decomposition of the product. Moreover, attempts to carry out aldol reactions of the aldehyde

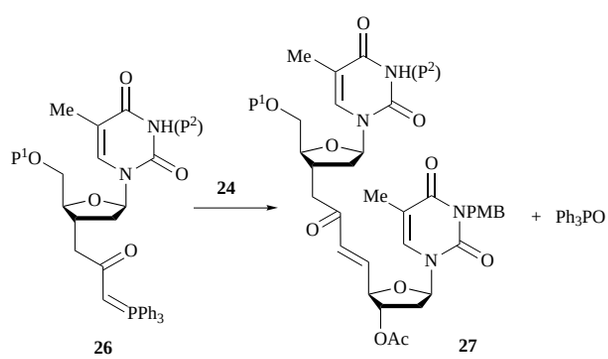


15
16
17

Scheme 2 *Reagents and conditions*: i, methylmagnesium bromide, diethyl ether (63%); ii, dimethyl sulfoxide, oxalyl chloride, dichloromethane, then triethylamine (82%); iii, lithium hexamethyldisilazide, tetrahydrofuran, 0 °C, 2-methylpropanal, rt, 16 h (**17**, 41%; recovered **16**, 30%)

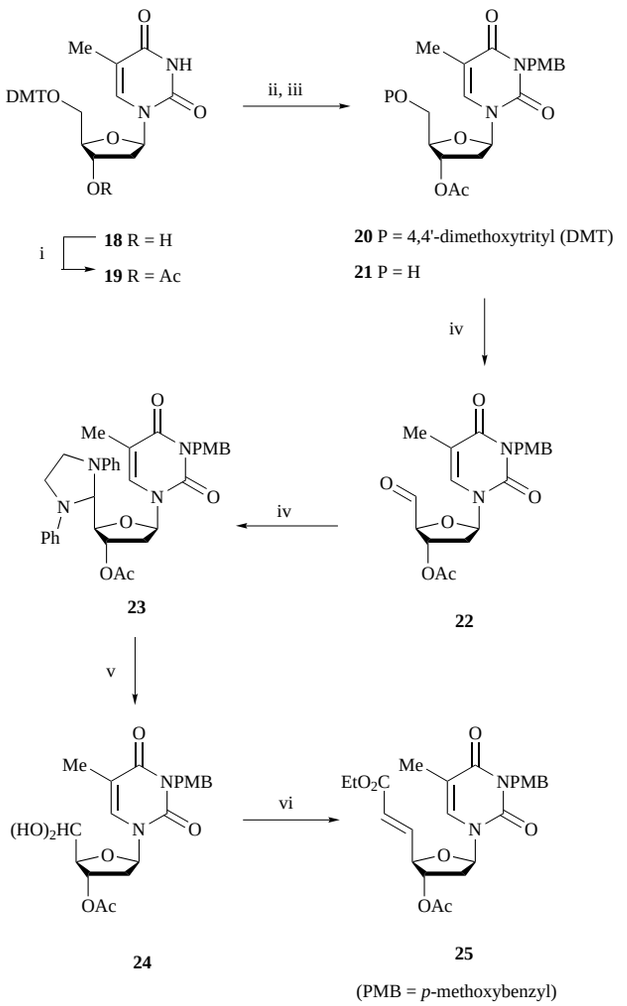
22 either before purification of its dianilinoethane derivative, or as its hydrate **24**, with either acetophenone or the ketone **16** were unsuccessful.

5′-Nucleoside-derived aldehydes are known to undergo Wittig reactions with stabilized ylides,[20] and following literature precedent the aldehyde hydrate **24** was found to react cleanly with (ethoxycarbonylmethylidene)(triphenyl)phosphorane in dichloromethane at room temperature to give the (*E*)-alkene **25**. An alternative strategy for the synthesis of the *C*-linked nucleotides **27** involving the condensation of the 3′-oxoalkylphosphorane **26** with the 5′-nucleoside aldehyde hydrate **24** was therefore investigated.



26
27
(P[1], P[2] = protecting groups
PMB = *p*-methoxybenzyl)

Using the Mitsunobu procedure, the 3′-propenyl-3′-deoxy nucleoside **4** was converted into its 3-(*p*-methoxybenzyl) derivative **28** (Scheme 4). This was oxidized using osmium tetraoxide and sodium periodate to give the aldehyde **29** and further oxidation using buffered sodium chlorite gave the carboxylic acid **30** which was converted into its acyl imidazolide **31**. Reaction of this imidazolide with an excess of methylene(triphenyl)-phosphorane gave the ketophosphorane **32** which was isolated in a yield of 57%, based on the acid **30**, after chromatography on silica. The structure of the ylide was consistent with its



Scheme 3 *Reagents and conditions*: i, acetic anhydride, pyridine (87%); ii, *p*-methoxybenzyl alcohol, triphenylphosphine, diethyl azocarboxylate (98%); iii, 90% aq. acetic acid, 50 °C, 1 h (65%); iv, *N*,*N*′-dicyclohexylcarbodiimide, dimethyl sulfoxide, dichloroacetic acid, rt, 2 h, oxalic acid, methanol, 30 min followed by the addition 1,2-dianilinoethane (**23**, 91% based on **21**); v, Dowex, tetrahydrofuran (96%); vi, (ethoxycarbonylmethylidene)(triphenyl)phosphorane, dichloromethane, rt, 96 h (48%)

spectroscopic data. Reaction with 2-methylpropanal gave the α,β-unsaturated ketone **33**.

Condensation of the aldehyde hydrate **24** with the ketophosphorane **32** was carried out at room temperature in dichloromethane and gave the Wittig product **34** in a yield of 78%. A small excess of the phosphorane was used in these reactions to ensure complete conversion of the aldehyde since unchanged aldehyde was very difficult to separate from the product. The structure of the product was confirmed spectroscopically. For example, an ion at 901 mu corresponding to $M^+ + 1$ was observed in its FAB mass spectrum and a signal at δ 6.89 (1 H, dd, *J* 4, 16) in its ^{1}H NMR spectrum was assigned to 5′-H, the vinylic coupling of 16 Hz confirming the (*E*)-geometry of the double bond.†

Hydrogenation of the Wittig product **34** gave the saturated *C*-dinucleotide **36** but did not result in deprotection of the pyrimidine rings. Attempts to remove the *N*-(*p*-methoxybenzyl) protecting groups from the *C*-linked dinucleotide **34** using dichlorodicyanoquinone[22] were not successful and resulted instead in loss of the *tert*-butyldimethylsilyl group to give the 5′-hydroxy-*C*-linked dinucleotide **35**. Attempts at the oxidative removal of the *N*-(*p*-methoxybenzyl) groups from the hydrogenated product **36** gave the desilylated product **37** which was also prepared by treatment of **36** with tetrabutylammonium fluoride (78%). Attempts to remove the *p*-methoxybenzyl groups from the saturated *C*-linked nucleotide **36** using lithium in liquid ammonia,[23] and from the desilylated product **37** oxidatively using cerric ammonium nitrate[24] or dichlorodicyanoquinone,[22] or under acidic conditions using aluminium(III) chloride–anisole or trimethylsilyl iodide–pyridine,[25] were also unsuccessful.

Conclusions

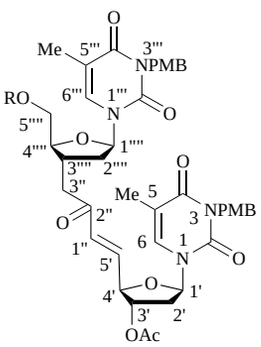
Reactions of stabilized ylides with nucleoside derived 5′-aldehydes are useful for the preparation of *C*-linked dinucleotides, *e.g.* **34**–**37**. As ketophosphoranes are stable to water, it is possible to use aldehyde hydrates in these reactions and so avoid the purification of anhydrous nucleoside 5′-aldehydes which can be difficult to handle. The work outlined in this paper was carried out using intermediates prepared from thymidine in which the pyrimidine rings were *N*-protected using *p*-methoxybenzyl groups. Removal of the *p*-methoxybenzyl groups from the final *C*-linked dinucleotides was not achieved and so unprotected *C*-linked dinucleotides required for binding studies were not prepared. The use of other protecting groups which could be removed from the final products together with the synthesis of unprotected *C*-linked di- and tri-nucleotides is discussed in the accompanying paper.[26]

Experimental

All non-aqueous reactions were performed under an atmosphere of dry argon or nitrogen. Proton nuclear magnetic resonance spectra were recorded on Varian Unity 500 (500 MHz), Varian XL 300 (300 MHz), Bruker AC 300 (300 MHz) and Varian Gemini 200 (200 MHz) spectrometers in [^{2}H]chloroform unless otherwise stated. Carbon nuclear magnetic resonance spectra were recorded on a Bruker AC 300 M spectrometer operating at 75 MHz. Infrared spectra were recorded on a Perkin-Elmer 1710 FT spectrometer as evaporated films unless otherwise stated. Mass spectra were recorded on Kratos MS 25 (low resolution) and Kratos Concept-1S (high resolution) spectrometers using electron impact (EI), chemical ionization (CI) or fast atom bombardment (FAB) modes of ionization. Optical rotations were measured using an Optical Activity AA 100 polarimeter with specific rotations determined at 20 °C and given in units of 10^{-1} deg cm^2 g^{-1}.

Chromatography refers to flash column chromatography and was carried out using May and Baker Sorbsil C60 silica gel (40–60 μm) as a stationary phase. Analytical high performance liquid chromatography was carried out using a Waters Z Module with Novapak ODS 4 m as stationary phase and detection by ultraviolet absorption at 254 nm. Preparative high performance liquid chromatography (HPLC) was carried out using an automated Gilson apparatus on a Rainin ODS

† The *C*-linked dinucleotides described in this paper are named as substituted thymidines. The numbering scheme used is illustrated in **i** below.



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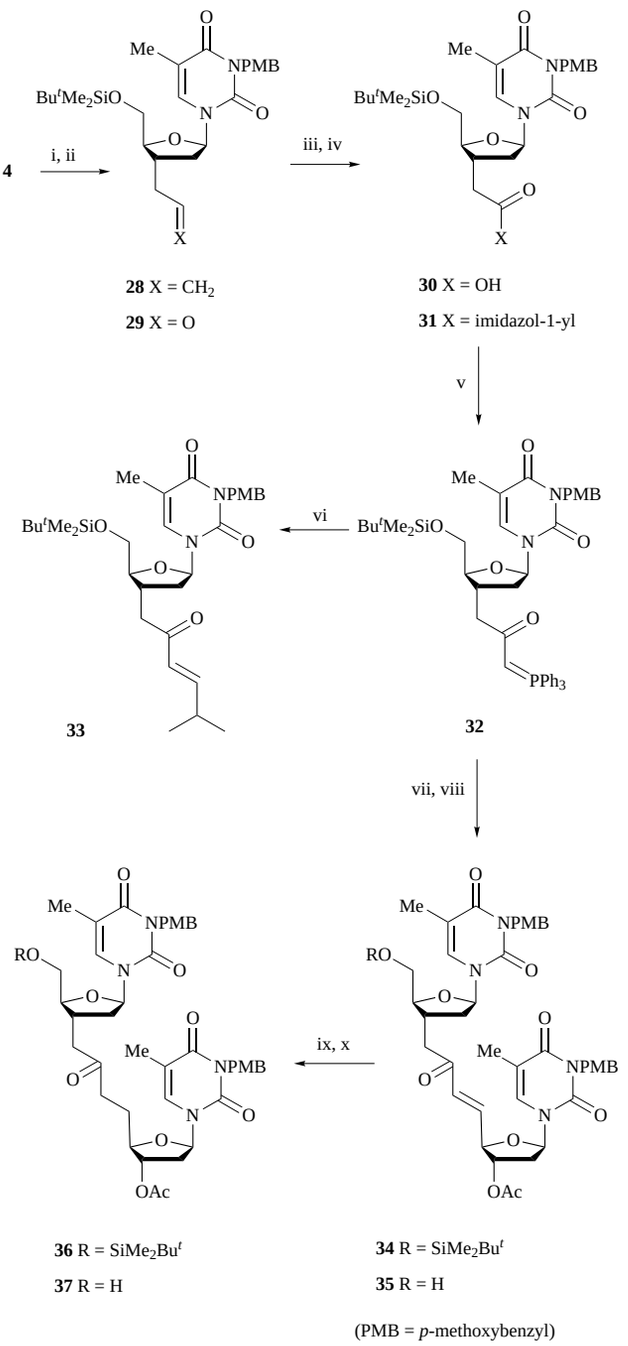

Scheme 4 *Reagents and conditions*: i, *p*-methoxybenzyl alcohol, triphenylphosphine, diethyl azodicarboxylate, dioxane (88%); ii, osmium tetraoxide, aq. dioxane, sodium periodate (51%); iii, sodium chlorite, *tert*-butyl alcohol, 2-methylbut-2-ene, sodium dihydrogen phosphate, rt, 2 h (100%); iv, 1,1′-carbonyldiimidazole, tetrahydrofuran, rt, 16 h (96%); v, *n*-butyllithium, methyl(triphenyl)phosphonium bromide, tetrahydrofuran, rt, 20 min, then add **31**, rt, 4 h (59%); vi, 2-methylpropanal, benzene, heat under reflux, 4.5 h (32%); vii, **24**, dichloromethane, rt, 50 h (78%); viii, dichlorodicyanoquinone, dichloromethane–water, rt, 24 h (56%); ix, 10% palladium on charcoal, methanol, hydrogen, rt, 16 h (95%); x, tetrabutylammonium fluoride, tetrahydrofuran, rt, 25 min (78%)

column, 8 μm, 21.4 internal diameter, length 25 cm, with UV detection at 254 nm. Mobile phases are quoted for individual compounds.

Light petroleum refers to the fraction which distils between 40 and 60 °C and ether refers to diethyl ether. All solvents were dried and distilled before use. (3′*S*)-5′-*O*-(*tert*-Butyldimethylsilyl)-3′-(prop-2-enyl)-3′-deoxythymidine **4** was prepared following the literature procedure[7] and had mp 110–112 °C (hexane–ether) (lit.,[7] 114–115 °C), $[a]_D$ +120 (*c* 0.98 in chloroform).

(3′*R*)-5′-*O*-(*tert*-Butyldimethylsilyl)-3′-(formylmethyl)-3′-deoxythymidine 5

Osmium tetraoxide (0.8 cm^3, 1% in water, 0.1 mmol) was added to a solution of the 5′-*O*-(*tert*-butyldimethylsilyl)-3′-(prop-2-enyl)-3′-deoxythymidine **4** (1.197 g, 3.15 mmol) in aqueous dioxane (75%, 14 cm^3) and the mixture stirred at room temperature for 10 min. Sodium periodate (1.42 g, 6.62 mmol) was added portionwise over 20 min, keeping the temperature between 20–25 °C with vigorous stirring. The reaction mixture was stirred at ambient temperature for 5 h and then diluted with ethyl acetate and stirred for a further 30 min. The residue was filtered off and washed with ethyl acetate. The organic solution was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–hexane (2:1) as eluent gave the title compound **5**[8] as a foam (668 mg, 55%); $[a]_D$ +19.25 (*c* 0.41 in methanol); ν_{max}([$^2H_6$]-dimethyl sulfoxide)/cm^{-1} 3491, 1699, 1683, 1471 and 1270; δ_H([$^2H_6$]dimethyl sulfoxide) 0.0 (6 H, s, Me_2Si), 0.8 (9 H, s, Me_3CSi), 1.7 (3 H, s, 5-Me), 2.0 and 2.14 (each 1 H, m, 2′-H), 2.45–2.75 (3 H, m, 3′-H and 3′-CH_2), 3.6–3.85 (3 H, m, 4′-H and 5′-H_2), 5.95 (1 H, dd, *J* 5, 6.5, 1′-H), 7.45 (1 H, s, 6-H), 9.6 (1 H, s, CHO) and 11.2 (1 H, s, NH); *m*/*z* (FAB) 383 (M^+ + 1, 9%), 325 (5), 273 (15), 257 (100) and 213 (30).

(3′*S*)-5′-*O*-(*tert*-Butyldimethylsilyl)-3′-(3-methoxycarbonylprop-2-enyl)-3′-deoxythymidine 6

(Methoxycarbonylmethylidene)(triphenyl)phosphorane (1.7 g, 5.1 mmol) was added to the aldehyde **5** (394 mg, 1.02 mmol) in chloroform (50 cm^3) and the mixture stirred at ambient temperature for 44 h. After concentration under reduced pressure, the residue was absorbed onto silica and eluted with ethyl acetate–cyclohexane (1:1) to give the (*E*)-alkene (*E*)-**6** containing 10% of its (*Z*)-isomer (*Z*)-**6** (398 mg, 89%). These isomers were separated by preparative HPLC (flow 15 cm^3 min^{-1}; mobile phase: 60:40 acetonitrile–water). The (*E*)-isomer of the *title compound* (*E*)-**6** was an oil (Found: M^+ + H, 439.2267. $C_{21}H_{35}N_2O_6Si$ requires *M*, 439.2264); $[a]_D$ +18.3 (*c* 0.94 in chloroform); ν_{max}($CHBr_3$)/cm^{-1} 1700, 1680, 1470, 1436, 1264, 838 and 768; δ_H 0.13 (6 H, s, Me_2Si), 0.95 (9 H, s, Me_3CSi), 1.91 (3 H, s, 5-Me), 2.05–2.35 (3 H, m, 2′-H_2, 3′-H), 2.35–2.55 (2 H, m, 1″-H_2), 3.6–3.85 (2 H, m, 5′-H and 4′-H), 3.75 (3 H, s, CO_2Me), 4.0 (1 H, dd, *J* 2.5, 11.5, 5′-H′), 5.9 (1 H, d, *J* 15.5, 3″-H), 6.1 (1 H, dd, *J* 4.5, 6.5, 1′-H), 6.88 (1 H, dt, *J* 15.5, 7, 2″-H), 7.55 (1 H, s, 6-H) and 8.4 (1 H, br s, NH); *m*/*z* (FAB) 439 (M^+ + 1, 12%), 381 (4) and 313 (90). The (*Z*)-isomer of the *title compound* (*Z*)-**6** was an oil; δ_H 0.1 (6 H, s, Me_2Si), 0.93 (9 H, s, Me_3CSi), 1.91 (3 H, s, 5-Me), 2.15 (2 H, m, 2′-H_2), 2.38 (1 H, m, 3′-H), 2.65–2.9 (2 H, m, 1″-H_2), 3.6–3.85 (2 H, m, 4′-H and 5′-H), 3.7 (3 H, s, CO_2Me), 3.98 (1 H, d, *J* 9, 5′-H′), 5.85 (1 H, d, *J* 11, 3″-H), 6.09 (1 H, dd, *J* 4.5, 6.5, 1′-H), 6.19 (1 H, dt, *J* 11, 8, 2″-H) and 7.45 (1 H, s, 6-H).

(3′*S*,1″*E*)-3′-(1-Methoxycarbonylprop-1-en-3-yl)-3′-deoxythymidine 7

The silyl ether **6** (34.2 mg, 0.078 mmol) was dissolved in acetic acid (80%, 0.5 cm^3) and the solution heated on a water bath (70 °C) for 2 h. After concentration under reduced pressure, chromatography of the residue using light petroleum–ethyl acetate (1:1) as eluent gave the *title compound* **7** (22 mg, 88%) as a foam (Found: M^+ + H, 325.1418. $C_{15}H_{21}N_2O_6$ requires *M*, 325.1400); $[a]_D$ +7.4 (*c* 0.58 in ethanol); ν_{max}/cm^{-1} 3440, 3200, 1700, 1474, 1274, 1213, 1112, 1050, 917 and 731; δ_H 1.85 (3 H, s, 5-Me), 2.05–2.75 (6 H, overlapping m, OH, 2′-H_2, 3′-H and 3″-H_2), 3.7 (2 H, m, 4′-H and 5′-H), 3.7 (3 H, s, CO_2Me), 4.0 (1 H, d, *J* 10, 5′-H′), 5.88 (1 H, d, *J* 15, 1″-H), 6.1 (1 H, dd, *J* 3, 7, 1′-H), 6.88 (1 H, dt, *J* 15, 7, 2″-H), 7.6 (1 H, s, 6-H) and 9.25 (1 H, s, NH); *m*/*z* (FAB) 325 (M^+ + 1, 11%), 199 (18) and 186 (100).

(3′*S*)-5′-*O*-(*tert*-Butyldimethylsilyl)-3′-(2-hydroxyethyl)-3′-deoxythymidine 8

Sodium borohydride (51 mg, 1.35 mmol) was added portionwise to an ice-cooled solution of the aldehyde **5** (258 mg, 0.67 mmol) in methanol (4 cm^3). The reaction mixture was stirred for 16 h and then poured onto water (20 cm^3) and dichloromethane (40 cm^3). The organic layer was washed with water and brine. The combined aqueous layers were back-extracted with dichloromethane and the organic extracts were dried ($NaSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate as eluent gave the *title compound* **8** (195 mg, 76%) as a foam (Found: $M^+ + H$, 385.2154. $C_{18}H_{33}N_2O_5Si$ requires *M*, 385.2159); $[a]_D$ +33.9 (*c* 1.29 in chloroform); $\nu_{max}(CHBr_3)/cm^{-1}$ 1680, 1470, 1260, 1060, 837, 782 and 768; δ_H 0.15 (6 H, s, Me_2Si), 0.95 (9 H, s, Me_3CSi), 1.53 (1 H, m, 1″-H), 1.7–1.85 (2 H, m, OH and 1″-H′), 1.9 (3 H, s, 5-Me), 2.15 and 2.25 (each 1 H, m, 2′-H), 2.43 (1 H, m, 3′-H), 3.65–3.8 (4 H, m, 4′-H, 5′-H and 2″-H_2), 4.0 (1 H, dd, *J* 4, 13, 5′-H′), 6.1 (1 H, dd, *J* 3, 6, 1′-H), 7.58 (1 H, s, 6-H) and 8.75 (1 H, br s, NH); δ_C −5.3, 12.6, 18.5, 26.0, 34.5, 34.9, 39.3, 61.1, 63.1, 85.0, 86.4, 110.2, 135.7, 150.3 and 163.7; *m*/*z* (FAB) 385 ($M^+ + 1$, 8%), 327 (6), 281 (4), 259 (48) and 201 (31).

(3′*S*)-3′-(2-Hydroxyethyl)-3′-deoxythymidine 9

The silyl ether **8** (81 mg, 2.1 mmol) was dissolved in 80% aqueous acetic acid (1.5 cm^3) and the solution stirred over a water bath at 70 °C for 5 h when TLC indicated 90% completion. The solvent was removed under reduced pressure and preparative HPLC (flow: 12 $cm^3\ min^{-1}$; mobile phase: 50:50 methanol–water) gave the *title compound* **9** as a foam (Found: $M^+ + H$, 271.1297. $C_{12}H_{19}N_2O_5$ requires *M*, 271.1294); $[a]_D$ +65.4 (*c* 0.7 in ethanol); ν_{max}/cm^{-1} 3414, 1667, 1477, 1274 and 1059; $\delta_H([^2H_6]$dimethyl sulfoxide) 1.48 (1 H, m, 1″-H), 1.78 (1 H, m, 1″-H′), 1.9 (3 H, s, 5-Me), 2.05–2.45 (3 H, m, 2′-H_2 and 3′-H), 3.55 (2 H, m, 2″-H_2), 3.73 (2 H, m, 5′-H and 4′-H), 3.85 (1 H, m, 5′-H′), 4.55 (1 H, exch. D_2O, t, *J* 5, 2″-OH), 5.15 (1 H, exch. D_2O, t, *J* 5, 5′-OH), 6.05 (1 H, dd, *J* 2.5, 7, 1′-H), 8.0 (1 H, s, 6-H) and 11.3 (1 H, s, NH); *m*/*z* (FAB) 271 ($M^+ + 1$, 52%) and 127 (100).

3′-*O*-Acetyl-5′-*O*-*tert*-butyl-5′-oxothymidine 10

Pyridinium dichromate (266 mg, 0.707 mmol), acetic anhydride (0.33 cm^3, 3.46 mmol) and *tert*-butyl alcohol (0.65 cm^3, 6.92 mmol) were added to a solution of 3′-*O*-acetylthymidine (98 mg, 0.35 mmol) in dichloromethane (2 cm^3) rinsing with further dichloromethane (0.5 cm^3) to complete the addition. After 1 h at ambient temperature, the reaction mixture was transferred to a silica gel column (1 × 3 cm) in ethyl acetate. After 15 min, the column was eluted with ethyl acetate and the filtrate concentrated under reduced pressure. Chromatography of the residue using toluene–ethyl acetate (2:1) as eluent gave the *title compound* **10** (85 mg, 70%) as a solid, mp 158–159 °C, $[a]_D$ +36.16 (*c* 0.56 in $CHCl_3$) (Found: C, 54.45; H, 6.7; N, 8.1. $C_{16}H_{22}N_2O_7$ requires C, 54.25; H, 6.25; N, 7.9%; Found: $M^+ + H$, 355.1507. $C_{16}H_{23}N_2O_7$ requires *M*, 355.1505); ν_{max}/cm^{-1} 3194, 1742, 1698, 1470, 1371, 1334, 1280, 1224, 1193, 1161, 1132, 1100, 1072, 842 and 776; $\delta_H([^2H_6]$dimethyl sulfoxide) 1.55 (9 H, s, Me_3C), 1.9 (3 H, s, 5-Me), 2.2 (3 H, s, $MeCO_2$), 2.45 (2 H, m, 2′-H_2), 4.58 (1 H, d, *J* 2, 4′-H), 5.58 (1 H, m, 3′-H), 6.38 (1 H, t, *J* 7, 1′-H), 7.38 (1 H, s, 6-H) and 11.5 (1 H, s, NH); $\delta_C([^2H_6]$dimethyl sulfoxide) 12.3, 20.7, 27.5, 35.3, 75.6, 81.8, 82.3, 85.5, 109.6, 136.1, 150.5, 163.6, 168.7 and 169.5; *m*/*z* (FAB) 355 ($M^+ + 1$, 29%), 299 (70), 173 (18) and 127 (100).

3′-*O*-Acetyl-5′-oxothymidine 11

The *tert*-butyl ester **10** (265 mg, 0.75 mmol) was stirred in aqueous trifluoroacetic acid (80%, 3 cm^3) at ambient temperature for 4 h. After concentration under reduced pressure, water was added to the residue, and the mixture concentrated under reduced pressure. The residue was then azeotroped with toluene to yield the *title compound* **11** (Found: M^+, 298.0799. $C_{12}H_{14}N_2O_7$ requires *M*, 298.0801); ν_{max}(KBr disc)/cm^{-1} 3537, 3600–2400, 3016, 2627, 1740, 1481, 1375, 1282, 1126, 1102, 1053, 950, 796 and 710; $\delta_H([^2H_4]$methanol) 2.0 (3 H, s, 5-Me), 2.2 (3 H, s, $MeCO_2$), 2.35 and 2.5 (each 1 H, m, 2′-H), 4.7 (1 H, m, 4′-H), 5.65 (1 H, m, 3′-H), 6.55 (1 H, m, 1′-H) and 8.3 (1 H, s, 6-H); *m*/*z* (CI) 316 ($M^+ + 18$, 9%), 299 ($M^+ + 1$, 35) and 127 (100).

3′-*O*-Acetyl-5′-*O*-*tert*-butyl-3-(4-methoxybenzyl)-5′-oxothymidine 12

The *tert*-butyl ester **10** (418 mg, 1.18 mmol) in tetrahydrofuran (4 cm^3) was added to an ice-cold mixture of sodium hydride (52 mg, 60% w/w in mineral oil, 1.3 mmol) in tetrahydrofuran (2.5 cm^3) and the mixture warmed to room temperature. After 40 min the mixture was cooled to 0 °C, tetrabutylammonium iodide (44 mg, 0.12 mmol) was added followed by 4-methoxybenzyl chloride (176 mg, 1.2 mmol), and the mixture was stirred for 16 h at ambient temperature. Water was added and the mixture extracted with ethyl acetate, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using hexane–ethyl acetate (2:1) as eluent gave the *title compound* **12** (209 mg, 37%) as a foam, $[a]_D$ +25.01 (*c* 2.215 in $CHCl_3$) (Found: M^+, 474.2010. $C_{24}H_{30}N_2O_8$ requires *M*, 474.2002); ν_{max}/cm^{-1} 1747, 1704, 1672, 1646, 1513, 1465, 1371, 1301, 1247, 1226, 1180, 1105, 1076, 987, 908, 842, 778 and 733; δ_H 1.53 (9 H, s, Me_3C), 2.0 (3 H, s, 5-Me), 2.09 (1 H, s, 2′-H), 2.13 (3 H, s, $MeCO_2$), 2.48 (1 H, dd, *J* 5, 14, 2′-H′), 3.8 (3 H, s, MeO), 4.45 (1 H, s, 4′-H), 5.08 (2 H, s, 3-CH_2), 5.4 (1 H, d, *J* 5, 3′-H), 6.5 (1 H, dd, *J* 5, 9.5, 1′-H), 6.85 and 7.45 (each 2 H, d, *J* 8.5, ArH) and 8.0 (1 H, s, 6-H); *m*/*z* (CI) 492 ($M^+ + 18$, 2%), 475 ($M^+ + 1$, 38), 419 (35), 293 (13), 276 (52) and 247 (64), together with unreacted ester **10** (235 mg, 44%).

4-Methoxybenzyl alcohol (585 mg, 4.24 mmol) in dioxane (1 cm^3), triphenylphosphine (1.11 g, 4.24 mmol) and diethyl azodicarboxylate (0.67 cm^3, 4.24 mmol) were added to a solution of the *tert*-butyl ester **10** (1.0 g, 2.8 mmol) in dioxane (14 cm^3) and the mixture stirred at room temperature. After 8 h, concentration and chromatography of the residue using cyclohexane–ethyl acetate (9:1) as eluent gave the *title compound* **12** (1.25 g, 94%) with spectroscopic data identical to samples prepared as outlined above.

3′-*O*-Acetyl-3-(4-methoxybenzyl)-5′-oxothymidine 13

A solution of the *tert*-butyl ester **12** (546 mg, 1.15 mmol) in aqueous trifluoroacetic acid (80%, 10 cm^3) was stirred at ambient temperature for 2 h then concentrated under reduced pressure. Water was added and the mixture concentrated under reduced pressure. The residue was azeotroped with benzene to give the *title compound* **13** (Found: $M^+ + H$, 419.1445. $C_{20}H_{23}N_2O_8$ requires *M*, 419.1454); ν_{max}/cm^{-1} 3460, 3600–2200, 1747, 1701, 1670, 1636, 1513, 1469, 1378, 1247, 1182, 1076, 1035, 986 and 820; $\delta_H([^2H_6]$dimethyl sulfoxide) 1.95 (3 H, s, 5-Me), 2.15 (3 H, s, $MeCO_2$), 2.42 (2 H, m, 2′-H_2), 3.8 (3 H, s, OMe), 4.65 (1 H, s, 4′-H), 5.05 (2 H, s, 3-CH_2), 5.6 (1 H, m, 3′-H), 6.45 (1 H, t, *J* 7.5, 1′-H), 6.84 and 7.38 (each 2 H, d, *J* 8.5, ArH), 8.15 (1 H, s, 6-H) and 13.6 (1 H, br s, CO_2H); δ_C 13.4, 14.4, 14.5, 20.9, 36.3, 44.1, 55.3, 88.1, 111.1, 113.8, 114.1, 128.3, 128.9, 129.7, 130.8, 134.5, 151.2, 159.2, 163.5 and 170.2; *m*/*z* (FAB) 441 ($M^+ + 23$, 7%) and 419 ($M^+ + 1$, 26).

(3′*S*)-5′-*O*-(*tert*-Butyldimethylsilyl)-3′-(2-hydroxypropyl)-3′-deoxythymidine 15

Methylmagnesium bromide in ether (3 M, 3 cm^3, 9 mmol) was added to a solution of the aldehyde **5** (1.11 g, 2.9 mmol) in ether (56 cm^3) at room temperature and the mixture stirred vigorously. After 4 h, saturated aqueous ammonium chloride and saturated aqueous ethylenediaminetetraacetic acid were

added. The resulting emulsion was extracted with ether, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–light petroleum (3:2) as eluent gave recovered aldehyde **5** (64 mg, 6%) followed by the *title compound* **15** (730 mg, 63%) as a 50:50 mixture of epimers at C(2″) (Found: $M^+ + H$, 399.2312. $C_{19}H_{35}N_2O_5Si$ requires *M*, 399.2315); ν_{max}/cm^{-1} 3425, 3200, 3025, 1700, 1472, 1271, 1125, 1007, 837 and 780; δ_H 0.1 (6 H, s, Me_2Si), 0.9 (9 H, s, Me_3CSi), 1.23 (3 H, m, 3″-H_3), 1.3–1.7 (3 H, m, 1″-H_2 and OH), 1.94 and 1.95 (each 1.5 H, s, 5-Me), 2.0–2.6 (3 H, m, 2′-H_2 and 3′-H), 3.6–3.95 (3 H, m, 4′-H, 5′-H and 2″-H), 4.03 (1 H, d, *J* 9, 5′-H′), 6.05 (1 H, m, 1′-H), 7.55 and 7.6 (each 0.5 H, s, 6-H), 8.9 (0.5 H, br s, NH) and 9.0 (0.5 H, br s, NH); *m*/*z* (FAB) 399 ($M^+ + 1$, 24%), 273 (100), 257 (40) and 215 (47).

(3′*R*)-5′-*O*-(*tert*-Butyldimethylsilyl)-3′-(2-oxopropyl)-3′-deoxythymidine 16

Dimethyl sulfoxide (0.29 cm^3, 4.04 mmol) in dichloromethane (35 cm^3) was added dropwise to a solution of oxalyl chloride (0.23 cm^3, 2.57 mmol) in dichloromethane (35 cm^3) at −50 °C and the mixture stirred for 10 min. A cooled solution of the alcohol **15** (735 mg, 1.84 mmol) in dichloromethane (48 cm^3) was added and the mixture stirred for 20 min. Triethylamine (1.3 cm^3) was added and the mixture allowed to warm to room temperature before being diluted with water and extracted with dichloromethane. The extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate–light petroleum (3:2) as eluent gave the *title compound* **16** (598 mg, 82%) as a white solid, mp 142–143 °C, $[\alpha]_D$ +11.33 (*c* 0.3 in $CHCl_3$) (Found: C, 57.1; H, 8.3; N, 7.1. $C_{19}H_{32}N_2O_5Si$ requires C, 57.5; H, 8.1; N, 7.0%; Found: $M^+ + H$, 397.2159. $C_{19}H_{33}N_2O_5Si$ requires *M*, 397.2159); ν_{max}/cm^{-1} 3150, 3050, 1700, 1471, 1362, 1270, 1125, 1007, 837 and 780; δ_H 0.1 (6 H, s, Me_2Si), 0.95 (9 H, s, Me_3CSi), 1.92 (3 H, s, 5-Me), 2.01 (1 H, m, 2′-H), 2.15 (3 H, s, 3″-H_3), 2.25 (1 H, m, 2′-H′), 2.52 (1 H, m, 1″-H), 2.72 (2 H, m, 3′-H and 1″-H′), 3.73 (1 H, m, 4′-H), 3.78 and 3.95 (each 1 H, dd, *J* 2, 11.5, 5′-H), 6.15 (1 H, t, *J* 6.5, 1′-H), 7.55 (1 H, s, 6-H) and 9.0 (1 H, s, NH); δ_C −5.3, 12.6, 18.5, 26.0, 30.2, 33.8, 38.6, 46.6, 63.8, 84.7, 85.5, 110.7, 135.5, 150.5, 163.8 and 206.4; *m*/*z* (FAB) 397 ($M^+ + 1$, 10%), 339 (7) and 271 (70).

(3′*R*,3″*E*)-5′-*O*-(*tert*-Butyldimethylsilyl)-3′-(5-methyl-2-oxohex-3-en-1-yl)-3′-deoxythymidine 17

n-Butyllithium in hexane (1.6 M, 0.2 cm^3, 0.32 mmol) was added dropwise to a cooled (0 °C) solution of hexamethyldisilazane (0.66 cm^3, 0.32 mmol) in tetrahydrofuran (0.25 cm^3), the mixture was stirred for 20 min, then the ketone **16** (46.6 mg, 0.13 mmol) was added in tetrahydrofuran (0.25 cm^3). After 20 min, 2-methylpropanal (0.011 cm^3, 0.15 mmol) in tetrahydrofuran (0.1 cm^3) was added, and the reaction mixture allowed to warm to room temperature and stirred for 16 h. Water was added and the mixture extracted with ethyl acetate, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (1:1) as eluent gave the *title compound* **17** (24 mg, 41%) as an oil, $[\alpha]_D$ +3.73 (*c* 0.63 in $CHCl_3$) (Found: $M^+ + H$, 451.2616. $C_{23}H_{39}N_2O_5Si$ requires *M*, 451.2628); ν_{max}/cm^{-1} 3200, 3050, 1689, 1470, 1269, 1124, 837 and 780; δ_H 0.1 (6 H, s, Me_2Si), 0.95 (9 H, s, Me_3CSi), 1.1 (6 H, d, *J* 6, 2 × Me), 1.95 (3 H, s, 5-Me), 2.05 (1 H, m, 2′-H), 2.28 (1 H, m, 2′-H′), 2.48 (1 H, m, 5″-H), 2.65 (1 H, dd, *J* 6.5, 16, 1″-H), 2.7–2.95 (2 H, m, 3′-H and 1″-H′), 3.78 (2 H, m, 4′-H and 5′-H), 3.95 (1 H, dd, *J* 2.5, 11, 5′-H′), 6.05 (1 H, dd, *J* 1.5, 16, 3″-H), 6.18 (1 H, t, *J* 7, 1′-H), 6.82 (1 H, dd, *J* 7, 16, 4″-H), 7.55 (1 H, s, 6-H) and 8.8 (1 H, br s, NH); δ_C −5.3, 12.6, 18.5, 21.3, 26.0, 31.2, 34.2, 38.7, 43.0, 64.0, 85.0, 85.7, 110.7, 127.4, 135.6, 150.4, 154.5, 163.7 and 198.4; *m*/*z* (FAB) 451 ($M^+ + 1$, 4%), 415 (17), 379 (6) and 325 (78) together with recovered ketone **16** (15 mg, 30%).

3′-*O*-Acetyl-5′-*O*-(4,4′-dimethoxytrityl)thymidine 19

5′-*O*-(4,4′-Dimethoxytrityl)thymidine **18** (15 g, 27.5 mmol) was dissolved in a mixture of pyridine (25 cm^3) and acetic anhydride (25 cm^3) and the solution stirred at room temperature for 16 h. The mixture was then poured onto ice–water and extracted with chloroform. The organic extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using dichloromethane–pyridine (99:1) as eluent gave the *title compound* **19** (14 g, 87%) as a foam, $[\alpha]_D$ +11.4 (*c* 1.115 in $CHCl_3$) (Found: $M^+ + H$, 587.2396. $C_{33}H_{35}N_2O_8$ requires *M*, 587.2393); ν_{max}/cm^{-1} 3065, 1692, 1608, 1510, 1466, 1367, 1251, 1177, 1107, 1076, 1032 and 830; δ_H 1.58 (3 H, s, 5-Me), 2.1 (3 H, s, $MeCO_2$), 2.45 (2 H, m, 2′-H_2), 3.45 and 3.49 (each 1 H, dd, *J* 2.5, 10, 5′-H), 3.8 (6 H, s, 2 × OMe), 4.15 (1 H, m, 4′-H), 5.45 (1 H, m, 3′-H), 6.45 (1 H, t, *J* 7.5, 1′-H), 6.85 (4 H, d, *J* 9, ArH), 7.13–7.43 (9 H, m, ArH), 7.64 (1 H, s, 6-H) and 8.08 (1 H, br s, NH); *m*/*z* (FAB) 586 (M^+, 8%) and 303 (100).

3′-*O*-Acetyl-3-(4-methoxybenzyl)-5′-*O*-(4,4′-dimethoxytrityl)-thymidine 20

4-Methoxybenzyl alcohol (742 mg, 5.37 mmol) in dioxane (1 cm^3) was added to a solution of the protected thymidine **19** (2.1 g, 3.58 mmol) in dioxane (16 cm^3), followed by triphenylphosphine (1.4 g, 5.37 mmol). Diethyl azodicarboxylate (0.85 cm^3, 5.37 mmol) was then added dropwise and the reaction mixture was stirred at ambient temperature for 16 h before being concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (4:1) containing triethylamine (1%) as eluent gave the *title compound* **20** (2.49 g, 98%) as a foam, $[\alpha]_D$ +11.75 (*c* 0.57 in $CHCl_3$) (Found: $M^+ + H$, 707.2985. $C_{41}H_{43}N_2O_9$ requires *M*, 707.2968); ν_{max}/cm^{-1} 3583, 3312, 1738, 1669, 1641, 1609, 1512, 1466, 1301, 1247, 1178, 1065 and 1034; δ_H 1.45 (3 H, s, 5-Me), 2.08 (3 H, s, $MeCO_2$), 2.45 (2 H, m, 2′-H_2), 3.42 and 3.48 (each 1 H, dd, *J* 2.5, 10, 5′-H), 3.8 (9 H, s, 3 × OMe), 4.15 (1 H, m, 4′-H), 5.08 (2 H, s, 3-CH_2), 5.43 (1 H, m, 3′-H), 6.49 (1 H, dd, *J* 6, 8.5, 1′-H), 6.85 (4 H, d, *J* 9, ArH), 7.28 (6 H, m, ArH), 7.35 (5 H, m, ArH), 7.5 (2 H, d, *J* 9, ArH) and 7.6 (1 H, s, 6-H); *m*/*z* (FAB) 707 ($M^+ + 1$, 5%) and 303 (100).

3′-*O*-Acetyl-3-(4-methoxybenzyl)thymidine 21

The dimethoxytrityl ether **20** (725 mg, 1.03 mmol) was dissolved in aqueous acetic acid (90%, 8 cm^3) and the solution heated to 50 °C for 1 h before being cooled, diluted with dichloromethane and washed with saturated aqueous sodium hydrogen carbonate and water. The aqueous layer was extracted with dichloromethane and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (2:1) as eluent gave the *title compound* **21** (268 mg, 65%) as a solid, mp 113–114 °C, $[\alpha]_D$ +3.49 (*c* 0.315 in $CHCl_3$) (Found: C, 59.4; H, 6.1; N, 6.8. $C_{20}H_{24}N_2O_7$ requires C, 59.4; H, 6.0; N, 6.9%); ν_{max}/cm^{-1} 3441, 1740, 1701, 1668, 1639, 1513, 1468, 1404, 1245, 1197, 1106, 1066, 1032, 993, 917, 852 and 780; δ_H 1.95 (3 H, s, 5-Me), 2.1 (3 H, s, $MeCO_2$), 2.37 (2 H, m, 2′-H_2), 3.75 (3 H, s, OMe), 3.9 (2 H, m, 5′-H_2), 4.1 (1 H, dd, *J* 2, 5, 4′-H), 4.7 (1 H, br s, OH), 5.05 (2 H, s, 3-CH_2), 5.34 (1 H, m, 3′-H), 6.28 (1 H, t, *J* 7, 1′-H), 6.85 (2 H, d, *J* 9, ArH) and 7.47 (3 H, m, 6-H and ArH); *m*/*z* (CI) 422 ($M^+ + 18$, 1%), 405 ($M^+ + 1$, 35) and 243 (100).

3′-*O*-Acetyl-5′,5′-(*N*,*N*′-diphenylethylenediamino)-3-(4-methoxybenzyl)-5′-deoxythymidine 23

Dichloroacetic acid (0.03 cm^3) was added to a solution of the alcohol **22** (264 mg, 0.65 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (540 mg, 2.6 mmol) in dimethyl sulfoxide (2.5 cm^3) and the mixture was stirred at room temperature for 2 h. Oxalic acid (250 mg, 2 mmol) in methanol (1.25 cm^3) was added carefully to the resultant solution. After 30 min, the mixture was filtered,

and the precipitate washed with cold methanol. Dianilinoethane (208 mg, 0.948 mmol) was added to the organic extracts and the mixture stirred in the dark at ambient temperature for 24 h before being poured onto aqueous sodium hydrogen carbonate (2%) and extracted with chloroform (×3). The organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was triturated with light petroleum–ethyl acetate (3:1), filtered and the filtrate concentrated under reduced pressure. Chromatography using light petroleum–ethyl acetate (3:1) as eluent gave the *title compound* **23** (354 mg, 91%), as a foam, $[\alpha]_D$ +20.5 (*c* 0.95 in $CHCl_3$) (Found: $M^+ + H$, 597.2705. $C_{34}H_{37}N_4O_6$ requires *M*, 597.2713); ν_{max}/cm^{-1} 1740, 1704, 1671, 1644, 1598, 1502, 1465, 1368, 1299, 1245, 1194, 1034, 911, 820, 778, 750, 732 and 694; δ_H 1.5 (3 H, s, 5-Me), 1.85 (3 H, s, $MeCO_2$), 1.75–2.05 (2 H, m, 2′-H_2), 3.43–3.88 (4 H, m, 2 × CH_2N), 3.65 (3 H, s, OMe), 4.34 (1 H, dd, *J* 4, 1.5, 4′-H), 4.86 and 4.92 (each 1 H, d, *J* 13.5, 3-CH), 5.28 (1 H, dt, *J* 3.5, 4, 3′-H), 5.73 (1 H, m, 5′-H), 6.2 (1 H, dd, *J* 5.5, 8.5, 1′-H), 6.55 (1 H, s, 6-H), 6.65–6.78 (8 H, m, ArH), 7.12 (4 H, m, ArH) and 7.32 (2 H, d, *J* 8.5, ArH); *m*/*z* (FAB) 597 ($M^+ + 1$, 5%) and 223 (100).

3′-*O*-Acetyl-5′-hydroxy-3-(4-methoxybenzyl)thymidine 24

Dowex resin (1.0 g, H^+) was added to a solution of the amino acetal **23** (79 mg, 0.133 mmol) in aqueous tetrahydrofuran (50%, 6 cm^3) and the suspension was stirred at room temperature for 8 h. The resin was then filtered off and washed with tetrahydrofuran. The organic extracts were concentrated under reduced pressure to approximately half their volume and washed with water. Benzene was added and the mixture concentrated under reduced pressure. This process was repeated three times and the residue was dried overnight under vacuum to give the *title compound* **24** (54 mg, 96%) (Found: $M^+ - OH$, 403.1495. $C_{20}H_{23}N_2O_7$ requires *M*, 403.1505); ν_{max}/cm^{-1} 3400, 1742, 1703, 1669, 1641, 1513, 1466, 1300, 1246, 1035 and 778; δ_H([$^2H_6$]dimethyl sulfoxide) 1.95 (3 H, s, 5-Me), 2.18 (3 H, s, $MeCO_2$), 2.35 (2 H, m, 2′-H_2), 3.8 (3 H, s, OMe), 3.95 (1 H, d, *J* 3, 4′-H), 4.45–4.6 (3 H, m, 5′-H, 3-CH_2), 5.45 (1 H, m, 3′-H), 6.35 (1 H, t, *J* 7.5, 1′-H), 6.4 and 6.5 (each 1 H, exch. D_2O, d, *J* 5, OH), 6.95 and 7.35 (each 2 H, d, *J* 8.5, ArH) and 8.0 (1 H, s, 6-H); *m*/*z* (FAB) 421 ($M^+ + 1$, 6%), 403 ($M^+ - OH$, 20) and 391 (24).

(*E*)-3′-*O*-Acetyl-5′-(ethoxycarbonylmethylidene)-3-(4-methoxybenzyl)-5′-deoxythymidine 25

(Ethoxycarbonylmethylidene)(triphenyl)phosphorane (75 mg, 0.213 mmol) was added to a solution of the aldehyde hydrate **24** (86 mg, 0.2 mmol) in dichloromethane (2 cm^3) at ambient temperature. The mixture was stirred for 96 h then concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (1:1) as eluent gave the *title compound* **25** (47 mg, 48%) as an oil, $[\alpha]_D$ +13.27 (*c* 1.04 in $CHCl_3$) (Found: $M^+ + H$, 473.1943. $C_{24}H_{29}N_2O_8$ requires *M*, 473.1924); ν_{max}/cm^{-1} 1760, 1707, 1671, 1646, 1513, 1466, 1372, 1305, 1245, 1179 and 1036; δ_H 1.3 (3 H, t, *J* 7, CH_2CH_3), 1.95 (3 H, s, 5-Me), 2.13 (3 H, s, $MeCO_2$), 2.16 (1 H, m, 2′-H), 2.43 (1 H, ddd, *J* 2.5, 5.5, 14, 2′-H′), 3.75 (3 H, s, OMe), 4.25 (2 H, q, *J* 7, CH_2CH_3), 4.6 (1 H, m, 4′-H), 5.05 (2 H, s, 3-CH_2), 5.15 (1 H, m, 3′-H), 6.15 (1 H, dd, *J* 2, 16, 1″-H), 6.42 (1 H, dd, *J* 5.5, 8.5, 1′-H), 6.83 (2 H, d, *J* 8.5, ArH), 7.0 (1 H, dd, *J* 5, 16, 5′-H), 7.09 (1 H, s, 6-H) and 7.45 (2 H, d, *J* 8.5, ArH); δ_C 13.4, 14.2, 20.8, 24.8, 29.3, 33.5, 36.4, 44.1, 55.2, 60.9, 82.5, 85.4, 111.3, 113.7, 123.3, 129.0, 130.9, 132.5, 142.5, 151.0, 159.2, 163.0, 165.6 and 170.2; *m*/*z* (FAB) 473 ($M^+ + 1$, 12%) and 247 (30).

(3′*S*)-5′-*O*-(*tert*-Butyldimethylsilyl)-3-(4-methoxybenzyl)-3′-(prop-2-enyl)-3′-deoxythymidine 28

Following the procedure outlined for the synthesis of the *p*-methoxybenzyl derivative **12**, the 3′-deoxythymidine derivative **4** (496 mg, 1.3 mmol) gave, after chromatography using light petroleum–ethyl acetate (4:1) as eluent, the *title compound* **28** (573 mg, 88%) as an oil, $[\alpha]_D$ +22.6 (*c* 4.6 in $CHCl_3$) (Found: $M^+ + H$, 501.2783. $C_{27}H_{41}N_2O_5Si$ requires *M*, 501.2785); ν_{max}/cm^{-1} 1700, 1664, 1642, 1513, 1465, 1349, 1299, 1248, 1178, 1130, 1036, 1003, 918, 837, 779 and 749; δ_H 0.12 (6 H, s, Me_2Si), 0.95 (9 H, s, Me_3CSi), 1.95 (3 H, s, 5-Me), 2.0–2.45 (5 H, overlapping m, 2′-H_2, 3′-H and 1″-H_2), 3.75 (2 H, m, 4′-H and 5′-H), 3.78 (3 H, s, OMe), 4.0 (1 H, br d, *J* 9, 5′-H′), 4.95–5.15 (4 H, overlapping m, 3-CH_2 and 3″-H_2), 5.74 (1 H, m, 2″-H), 6.1 (1 H, t, *J* 5.5, 1′-H), 6.83 and 7.45 (each 2 H, d, *J* 8.5, ArH) and 7.58 (1 H, s, 6-H); *m*/*z* (FAB) 501 ($M^+ + 1$, 17%) and 443 (20).

(3′*R*)-5′-*O*-(*tert*-Butyldimethylsilyl)-3-(4-methoxybenzyl)-3′-(formylmethyl)-3′-deoxythymidine 29

Osmium tetraoxide (1% in water, 0.54 cm^3) was added to a solution of the alkene **28** (434 mg, 0.87 mmol) in aqueous dioxane (75%, 5.35 cm^3) and the mixture stirred at room temperature for 15 min, until it turned black. Sodium periodate (390 mg, 1.81 mmol) was then added portionwise over 20 min with vigorous stirring keeping the temperature between 20–25 °C. After 24 h ethyl acetate was added and the mixture stirred for a further 30 min. The precipitate was filtered off and washed with ethyl acetate. The organic solution was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (2:1) as eluent gave the *title compound* **29** (221 mg, 51%) as a foam, $[\alpha]_D$ +15.46 (*c* 4.5 in $CHCl_3$) (Found: $M^+ + 1$, 503.2566. $C_{26}H_{39}N_2O_6Si$ requires *M*, 503.2577); ν_{max}/cm^{-1} 3426, 1699, 1670, 1640, 1513, 1466, 1248, 1178, 1107, 837 and 779; δ_H 0.125 (6 H, s, Me_2Si), 0.9 (9 H, s, Me_3CSi), 1.95 (3 H, s, 5-Me), 2.05 and 2.3 (each 1 H, m, 2′-H), 2.6 (1 H, m, 1″-H), 2.75 (2 H, m, 3′-H and 1″-H′), 3.78 (2 H, m, 4′-H and 5′-H), 3.8 (3 H, s, OMe), 3.95 (1 H, dd, *J* 2.5, 11, 5′-H′), 5.02 and 5.08 (each 1 H, d, *J* 13.5, 3-CH), 6.15 (1 H, dd, *J* 5, 6.5, 1′-H), 6.85 and 7.45 (each 2 H, d, *J* 9, ArH), 7.55 (1 H, s, 6-H) and 9.8 (1 H, s, CHO); *m*/*z* (FAB) 503 ($M^+ + 1$, 5%) and 445 (5).

(3′*R*)-5′-*O*-(*tert*-Butyldimethylsilyl)-3′-(carboxymethyl)-3-(4-methoxybenzyl)-3′-deoxythymidine 30

A solution of the aldehyde **29** (727 mg, 1.44 mmol) in *tert*-butyl alcohol (19 cm^3) was charged with an excess of 2-methylbut-2-ene (8.5 cm^3) followed by the addition of a solution of sodium chlorite (1.3 g, 14 mmol) and sodium dihydrogen phosphate (1.8 g, 11.5 mmol) in water (8.5 cm^3). The mixture was stirred at room temperature for 2.5 h then concentrated under reduced pressure. The residue was dissolved in water and extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give the *title compound* **30** (750 mg, 100%) as a foam (Found: $M^+ + H$, 519.2528. $C_{26}H_{39}N_2O_7Si$ requires *M*, 519.2526); ν_{max}/cm^{-1} 3500–2400, 1700, 1670, 1639, 1513, 1468, 1350, 1299, 1249, 1178, 1131, 837 and 780; δ_H([$^2H_6$]benzene) 0.08 (6 H, s, Me_2Si), 0.95 (9 H, s, Me_3CSi), 1.75–2.15 (3 H, overlapping m, 2′-H_2, 1″-H), 2.0 (3 H, s, 5-Me), 2.25 (1 H, dd, *J* 6, 16.5, 1″-H′), 2.55 (1 H, m, 3′-H), 3.34 (3 H, s, OMe), 3.4 (1 H, m, 4′-H), 3.5 and 3.75 (each 1 H, dd, *J* 3, 11, 5′-H), 5.23 (2 H, s, 3-CH_2), 6.2 (1 H, dd, *J* 4.5, 6.5, 1′-H), 6.85 (2 H, d, *J* 8.5, ArH), 7.35 (1 H, s, 6-H) and 7.85 (2 H, d, *J* 8.5, ArH); *m*/*z* (FAB) 519 ($M^+ + 1$, 45%) and 461 (23).

(3′*R*)-5′-*O*-(*tert*-Butyldimethylsilyl)-3′-[2-(imidazol-1-yl)-2-oxoethyl]-3-(4-methoxybenzyl)-3′-deoxythymidine 31

1,1′-Carbonyldiimidazole (750 mg, 4.7 mmol) was added to a solution of the acid **30** (750 mg, 1.44 mmol) in tetrahydrofuran (5 cm^3) and the mixture stirred at ambient temperature for 16 h. The reaction mixture was then dissolved in ice-cold ether and washed with ice-cold water. The organic layer was washed with ice-cold brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was diluted with benzene, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Azeotropic

drying of the resultant oil with benzene gave the *title compound* **31** (788 mg, 96%) as a foam (Found: $M^+ + H$, 569.2790. $C_{29}H_{41}N_4O_6Si$ requires *M*, 569.2795); ν_{max}/cm^{-1} 3434, 1737, 1699, 1670, 1640, 1513, 1468, 1387, 1247, 1178, 1123, 1036, 837 and 779; $\delta_H([^2H_6]benzene)$ 0.02 (6 H, s, Me_2Si), 0.9 (9 H, s, Me_3CSi), 1.47 (1 H, ddd, *J* 4.5, 6, 13.5, 2′-H), 1.62 (1 H, dd, *J* 6, 17.5, 1″-H), 1.9 (2 H, m, 2′-H′, 1″-H′), 1.95 (3 H, s, 5-Me), 2.44 (1 H, m, 3′-H), 3.22 (3 H, s, OMe), 3.3 (1 H, dt, *J* 2.5, 5, 4′-H), 3.55 and 3.68 (each 1 H, dd, *J* 3, 11, 5′-H), 5.15 and 5.25 (each 1 H, d, *J* 13, 3-CH), 6.2 (1 H, t, *J* 6.5, 1′-H), 6.75 (2 H, d, *J* 9, ArH), 6.98 (2 H, m, imid. H), 7.32 (1 H, d, *J* 1, imid. H), 7.65 (1 H, s, 6-H) and 7.8 (2 H, d, *J* 9, ArH); *m*/*z* (FAB) 569 ($M^+ + 1$, 45%), 533 (22), 519 (11) and 475 (22).

(3′*R*)-5′-*O*-(*tert*-Butyldimethylsilyl)-3-(4-methoxybenzyl)-3′-[3-(triphenylphosphoranylidene)-2-oxopropyl]-3′-deoxythymidine 32

n-Butyllithium in hexane (1.5 M, 2.2 cm^3, 3.18 mmol) was added dropwise to methyl(triphenyl)phosphonium bromide (1.14 g, 3.18 mmol) suspended in tetrahydrofuran (18 cm^3) and the resultant mixture was stirred at room temperature for 20 min. The imidazolide **31** (740 mg, 1.30 mmol) in tetrahydrofuran (19 cm^3) was added dropwise and the solution stirred for 4 h before being filtered through Celite and the precipitate washed with ethyl acetate. The organic extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate as eluent gave the *title compound* **32** (595 mg, 59%) as a foam, $[a]_D$ +21.77 (*c* 0.31 in $CHCl_3$) (Found: $M^+ + H$, 777.3494. $C_{45}H_{54}N_2O_6PSi$ requires *M*, 777.3489); ν_{max}/cm^{-1} 1699, 1664, 1641, 1513, 1466, 1438, 1400, 1248, 1178, 1108, 838 and 779; $\delta_H([^2H_6]benzene)$ 0.07 (6 H, s, Me_2Si), 1.00 (9 H, s, Me_3CSi), 2.03 (3 H, s, 5-Me), 2.26 (2 H, m, 2′-H_2), 2.4 and 2.63 (each 1 H, dd, *J* 8, 14, 1″-H), 2.95 (1 H, m, 3′-H), 3.33 (3 H, s, OMe), 3.72 (1 H, dd, *J* 4, 11, 5′-H), 3.8 (1 H, m, $Ph_3P{=}CH$), 3.95 (2 H, m, 4′-H and 5′-H), 5.28 and 5.33 (each 1 H, d, *J* 12.5, 3-CH), 6.52 (1 H, t, *J* 5.5, 1′-H), 6.85 (2 H, d, *J* 9, ArH), 7.06–7.18 (9 H, m, ArH), 7.62 (1 H, s, 6-H), 7.5–7.87 (6 H, m, ArH) and 7.91 (2 H, d, *J* 9, ArH); δ_P 15.93; *m*/*z* (FAB) 777 ($M^+ + 1$, 68%) and 531 (48).

(3′*R*,3″*E*)-5′-*O*-(*tert*-Butyldimethylsilyl)-3-(4-methoxybenzyl)-3′-(5-methyl-2-oxohex-3-enyl)-3′-deoxythymidine 33

2-Methylpropanal (0.01 cm^3, 0.11 mmol) was added to a solution of the ylide **32** (27 mg, 0.035 mmol) in benzene (0.4 cm^3) and the mixture was heated under reflux for 4.5 h. After concentration under reduced pressure, chromatography of the residue using light petroleum–ethyl acetate (3:1) as eluent gave the *title compound* **33** (6 mg, 32%) as an oil, $[a]_D$ +6.0 (*c* 0.3 in $CHCl_3$) (Found: $M^+ + H$, 571.3205. $C_{31}H_{47}N_2O_6Si$ requires *M*, 571.3203); ν_{max}/cm^{-1} 1700, 1666, 1642, 1513, 1465, 1349, 1249, 1178, 1124, 837 and 779; δ_H 0.15 (6 H, s, Me_2Si), 0.95 (9 H, s, Me_3CSi), 1.14 (6 H, d, *J* 6.5, 2 × Me), 1.98 (3 H, s, 5-Me), 2.1 and 2.27 (each 1 H, m, 2′-H), 2.53 (1 H, m, 5″-H), 2.66 (1 H, dd, *J* 6.5, 16, 1″-H), 2.85 (2 H, m, 3′-H and 1″-H′), 3.75–3.9 (2 H, overlapping m, 4′-H and 5′-H), 3.82 (3 H, s, OMe), 3.98 (1 H, dd, *J* 2.5, 11, 5′-H′), 5.05 and 5.12 (each 1 H, d, *J* 14, 3-CH), 6.06 (1 H, dd, *J* 1.5, 15.5, 3″-H), 6.22 (1 H, t, *J* 6, 1′-H), 6.8–6.9 (3 H, m, 4″-H and ArH), 7.5 (2 H, d, *J* 8.5, ArH) and 7.55 (1 H, s, 6-H); *m*/*z* (FAB) 571 ($M^+ + 1$, 23%), 513 (17) and 325 (100).

(*E*)-3′-*O*-Acetyl-3-(4-methoxybenzyl)-5′-{3-[(3′*R*)-5′-*O*-(*tert*-butyldimethylsilyl)-3-(4-methoxybenzyl)-3′-deoxythymidin-3′-yl]-2-oxopropylidene}-5′-deoxythymidine 34

The ylide **32** (203 mg, 0.262 mmol) was added to a solution of the aldehyde hydrate **24** (99 mg, 0.238 mmol) in dichloromethane (2 cm^3) and the mixture was stirred at ambient temperature for 50 h. After concentration under reduced pressure, the residue was diluted with ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using hexane–ethyl acetate (2:1) as eluent gave the *title compound* **34** (166 mg, 78%) as a foam, $[a]_D$ +5.64 (*c* 1.4 in $CHCl_3$) (Found: $M^+ + H$, 901.4053. $C_{47}H_{61}N_4O_{12}Si$ requires *M*, 901.4055); ν_{max}/cm^{-1} 1702, 1669, 1642, 1513, 1465, 1351, 1247, 1178, 1036, 838 and 778; $\delta_H([^2H_6]benzene)$ 0.10 and 0.11 (each 3 H, s, MeSi), 1.0 (9 H, s, Me_3CSi), 1.67 (3 H, s, 5-Me), 1.69–1.83 (2 H, overlapping m, 2′-H and 2″″-H), 1.85 (3 H, s, 5‴-Me), 1.92 (1 H, ddd, *J* 2, 6, 14, 2″″-H′), 2.02 (3 H, s, $MeCO_2$), 2.05 (1 H, dd, *J* 7, 18, 3″-H), 2.12 (1 H, ddd, *J* 6, 8, 14, 2′-H′), 2.33 (1 H, dd, *J* 7, 18, 3″-H′), 2.7 (1 H, m, 3″″-H), 3.3 (6 H, s, 2 × OMe), 3.51 (1 H, dt, *J* 5, 2, 4″″-H), 3.68 and 3.83 (each 1 H, dd, *J* 1.5, 7, 5″″-H), 4.34 (1 H, m, 4′-H), 4.97 (1 H, m, 3′-H), 5.19 (1 H, d, *J* 11, HC*H*Ph), 5.22–5.31 (3 H, m, *H*CHPh and CH_2Ph), 6.28–6.37 (3 H, overlapping m, 1′-H, 1″-H and 1″″-H), 6.58 (1 H, s, 6-H), 6.85 (4 H, m, ArH), 6.89 (1 H, dd, *J* 4, 16, 5′-H), 7.47 (1 H, s, 6‴-H) and 7.88 (4 H, m, ArH); $\delta_C([^2H_6]benzene)$ −5.4, 13.4, 13.6, 18.5, 20.2, 26.0, 30.1, 34.1, 35.8, 38.6, 44.0, 44.1, 44.2, 54.7, 64.3, 76.8, 83.0, 85.5, 85.7, 86.5, 109.9, 111.0, 114.0, 114.1, 129.9, 130.3, 131.4, 131.5, 132.8, 133.2, 141.0, 151.1, 151.3, 159.7, 159.8, 162.6, 163.1, 169.8 and 196.8; *m*/*z* (FAB) 901 ($M^+ + 1$, 2%), 803 (8), 655 (4) and 413 (47).

(*E*)-3′-*O*-Acetyl-3-(4-methoxybenzyl)-5′-{3-[(3′*R*)-3-(4-methoxybenzyl)-3′-deoxythymidin-3′-yl]-2-oxopropylidene}-5′-deoxythymidine 35

Dichlorodicyanoquinone (9 mg, 0.04 mmol) was added to the silyl ether **34** (16.5 mg, 0.018 mmol) in dichloromethane–water (9:1, 0.1 cm^3) and the mixture was stirred at ambient temperature for 24 h during which time further dichloromethane (2 × 0.5 cm^3) and dichlorodicyanoquinone (2 mg, 0.5 equiv.) were added. The reaction mixture was then diluted with water and extracted with ethyl acetate, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (1:1) as eluent gave the *title compound* **35** (8 mg, 56%) as a foam, $[a]_D$ +5.13 (*c* 1.15 in $CHCl_3$) (Found: $M^+ + H$, 787.3171. $C_{41}H_{47}N_4O_{12}$ requires *M*, 787.3190); ν_{max}/cm^{-1} 3500, 1742, 1701, 1669, 1640, 1513, 1467, 1351, 1246, 1178, 1107, 1035, 779 and 731; $\delta_H([^2H_6]benzene)$ 1.54–1.72 (2 H, m), 1.62 and 1.78 (each 3 H, s, Me), 1.75–1.9 (2 H, m), 1.95 (3 H, s, Me), 2.0 (2 H, m), 2.49 (1 H, m, 3″″-H), 2.8 (1 H, br s, OH), 3.16 (1 H, d, *J* 8.5, 4″″-H), 3.25 and 3.26 (each 3 H, s, OMe), 3.38 (1 H, dd, *J* 3, 13, 5″″-H), 3.8 (1 H, d, *J* 13, 5″″-H′), 4.27 (1 H, m, 4′-H), 4.94 (1 H, dt, *J* 3, 8, 3′-H), 5.13, 5.18, 5.2 and 5.25 (each 1 H, d, *J* 13, HC*H*Ph), 6.06 (1 H, dd, *J* 2.5, 6.5, 1″″-H), 6.15 (1 H, t, *J* 6.5, 1′-H), 6.25 (1 H, dd, *J* 1.5, 16, 1″-H), 6.49 (1 H, s, 6-H), 6.79 (4 H, d, *J* 9, ArH), 6.86 (1 H, dd, *J* 5, 16, 5′-H), 7.72 (1 H, s, 6‴-H) and 7.77 and 7.82 (each 2 H, d, *J* 9, ArH); *m*/*z* (FAB) 787 ($M^+ + 1$, 1%), 541 (1) and 391 (70).

3′-*O*-Acetyl-3-(4-methoxybenzyl)-5′-{3-[(3′*R*)-5′-*O*-(*tert*-butyldimethylsilyl)-3-(4-methoxybenzyl)-3′-deoxythymidin-3′-yl]-2-oxopropyl}-5′-deoxythymidine 36

Palladium on charcoal (10%, 44 mg) was added to a solution of the *C*-linked dinucleotide **34** (40 mg, 0.044 mmol) in methanol (2 cm^3) and the suspension was stirred at ambient temperature under an atmosphere of H_2 for 16 h. The mixture was filtered through Celite which was washed with ethyl acetate. The organic extracts were concentrated under reduced pressure and chromatography of the residue using light petroleum–ethyl acetate (1:1) as eluent gave the *title compound* **36** (38 mg, 95%) as a foam, $[a]_D$ +50.83 (*c* 0.12 in $CHCl_3$) (Found: $M^+ + H$, 903.4219. $C_{47}H_{63}N_4O_{12}Si$ requires *M*, 903.4212); ν_{max}/cm^{-1} 1702, 1668, 1643, 1513, 1465, 1351, 1246, 1178, 1035, 838 and 779; $\delta_H([^2H_6]benzene)$ 0.04 (6 H, s, Me_2Si), 0.92 (9 H, s, Me_3CSi), 1.6 (3 H, s, 5-Me), 1.56–2.2 (10 H, overlapping m, 2′-H_2, 2″″-H_2, 5′-H_2, 1″-H_2, 3″-H_2), 1.88 and 1.97 (each 3 H, s, Me), 2.56 (1 H, m, 3″″-H), 3.26 (6 H, s, 2 × OMe), 3.42 (1 H, m,

4‴″-H), 3.59 (1 H, dd, *J* 5, 18, 5‴″-H), 3.78 (2 H, overlapping m, 4′-H, 5‴″-H′), 4.74 (1 H, m, 3′-H), 5.14 (1 H, d, *J* 13, HC*H*Ph), 5.2 (2 H, m, CH_2Ph), 5.24 (1 H, d, *J* 13, *H*CHPh), 6.26 (1 H, t, *J* 6, 1‴″-H), 6.31 (1 H, dd, *J* 6, 9, 1′-H), 6.68 (1 H, s, 6-H), 6.78 (4 H, m, ArH), 7.42 (1 H, s, 6‴-H) and 7.78 and 7.82 (each 2 H, d, *J* 9, ArH); δ_C([$^2H_6$]benzene) −5.4, 13.5, 13.6, 14.3, 18.5, 20.3, 26.0, 27.5, 29.8, 30.1, 33.6, 36.1, 36.6, 44.0, 44.1, 45.6, 54.7, 64.2, 76.7, 83.9, 85.4, 85.7, 85.8, 109.9, 110.7, 114.1, 130.0, 130.3, 131.4, 131.5, 132.7, 133.2, 151.1, 151.3, 159.7, 159.8, 162.8, 163.1, 170.0 and 206.9; *m*/*z* (FAB) 903 (M^+ + 1, 5%) and 657 (17).

3′-*O*-Acetyl-3-(4-methoxybenzyl)-5′-{3-[(3′*R*)-3-(4-methoxybenzyl)-3′-deoxythymidin-3′-yl]-2-oxopropyl}-5′-deoxythymidine 37

Tetrabutylammonium fluoride in tetrahydrofuran (1 M, 0.16 cm^3, 0.16 mmol) was added to the *C*-linked dinucleotide **36** (49 mg, 0.054 mmol) in tetrahydrofuran (0.5 cm^3) at 0 °C and the solution was stirred for 25 min. Water was added, the mixture was extracted with ethyl acetate and the extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (1:9) as eluent gave the *title compound* **37** (33 mg, 78%) as a foam, $[\alpha]_D$ +31.66 (*c* 0.15 in $CHCl_3$) (Found: M^+ + H, 789.3327. $C_{41}H_{49}N_4O_{12}$ requires *M*, 789.3347); ν_{max}/cm^{-1} 3496, 1738, 1700, 1667, 1639, 1513, 1467, 1352, 1299, 1246, 1178, 1104, 1034, 820 and 779; δ_H([$^2H_6$]benzene) 1.48–2.18 (10 H, overlapping m, 2′-H_2, 2‴″-H_2, 5′-H_2, 1″-H_2, 3″-H_2), 1.6 (3 H, s, 5-Me), 1.88 and 1.98 (each 3 H, s, Me), 2.41 (1 H, m, 3‴″-H), 2.6 (1 H, br s, OH), 3.14 (1 H, m, 4‴″-H), 3.27 (6 H, s, 2 × OMe), 3.35 (1 H, dd, *J* 2.5, 12.5, 5‴″-H), 3.75 (2 H, m, 4′-H, 5‴″-H′), 4.74 (1 H, m, 3′-H), 5.12, 5.19, 5.21 and 5.26 (each 1 H, d, *J* 13.5, HC*H*Ph), 6.06 (1 H, dd, *J* 3.5, 6.5, 1‴″-H), 6.24 (1 H, dd, *J* 6.5, 9, 1′-H), 6.61 (1 H, s, 6-H), 6.77 and 6.79 (each 2 H, d, *J* 9, ArH), 7.67 (1 H, s, 6‴-H) and 7.77 and 7.83 (each 2 H, d, *J* 9, ArH); δ_C([$^2H_6$]benzene) 13.5, 13.6, 20.3, 27.5, 31.6, 35.9, 38.4, 39.2, 43.9, 44.1, 44.3, 54.7, 62.0, 76.7, 83.9, 85.8, 86.0, 86.5, 109.5, 110.7, 114.1, 129.9, 130.3, 131.5, 132.9, 134.0, 151.1, 151.2, 159.7, 159.8, 162.8, 163.2, 170.1 and 206.2; *m*/*z* (FAB) 789 (M^+ + 1, 10%) and 525 (14).

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