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Synthesis of acyclic bis-vinyl pyrimidines: a general route to d4T via metathesis

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Abstract—Unsaturated acyclic pyrimidine analogues, 1-{1-[1-(hydroxymethyl)prop-2-enyloxy]prop-2-enyl}uracil, 1-{1-[1-(hydroxymethyl)prop-2-enyloxy]prop-2-enyl}thymine and 1-{1-[1-(hydroxymethyl)prop-2-enyloxy]prop-2-enyl}cytosine having two asymmetric carbon atoms have been prepared in good yield starting from uridine and 5-methyluridine. The bis-vinyl thymine derivative underwent ring closure metathesis to give d4T, thus providing a novel synthesis of this compound.

1. Introduction

Since the discovery of Human Immunodeficiency Virus (HIV) as the causative agent of AIDS, several nucleoside analogues have shown high effectiveness by inhibiting the HIV reverse transcriptase after their anabolic activation to 5′-triphosphate derivatives by cellular kinases.[1,2] In this regard, 2′,3′-dideoxy nucleoside analogues such as AZT,[3] DDC,[4] DDI,[5] 3TC,[6] ABC[7] and d4T[8] have been approved by the US Food and Drug Administration for treatment of HIV (Fig. 1).

The drug, d4T is a very potent and selective inhibitor of HIV.[9–12] Moreover, it has been found to be less cytotoxic than AZT in bone marrow progenitor cells[7,13] and less inhibitory to mitochondrial DNA replication.[14] In the course of the search for new antiviral agents with a higher therapeutic index the obvious emphasis is to design drugs with potent activity, low cytotoxicity and minimal side effects and which do not stimulate viral mutations. In an attempt to achieve these objectives our program was to synthesize novel nucleosides with modified glycone moieties such as benzo[*c*]furan nucleosides[15,16] as analogues of d4T and acyclic nucleosides which bear a relationship to both d4T[17] and acyclovir.[18] We describe herein a series of enantiomerically pure acyclic analogues of d4T and a novel route to d4T via ring closure metathesis; previously reported routes to d4T often start from nucleosides such as thymidine[19–23] and 5-methyluridine[24,25] and introduce the olefinic group in the glycone moiety via an elimination reaction.

Keywords: d4T; bis-vinyl nucleoside; double Wittig.

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2. Results and discussion

The thymine derivative **1** was obtained from 5-methyluridine (**4**), and the uracil and cytosine derivatives **2** and **3** were synthesized from uridine (**5**) as shown in Scheme 1.

5-Methyluridine (**4**) and uridine (**5**) were each treated in pyridine with an excess of trityl chloride and 4,4′-dimethoxytrityl chloride to give the corresponding trityl derivatives **6**[26] and **7**[27] in 72 and 69% yields, respectively. The oxidative cleavage of the *cis*-diol in the 2′,3′-position of compounds **6** and **7** was achieved with sodium periodate in a mixture of ethanol/water. The dialdehydes were unstable, hence after isolation they were directly subjected to a double Wittig olefination. The classical Wittig homologation using methyltriphenylphosphonium bromide and butyllithium in anhydrous THF afforded the acyclic nucleosides **8** and **9** each in ca. 25% yield. Modification of the temperature (room temperature to reflux) did not affect the yields (ca. 25%). On the other hand, the use of methyltriphenylphosphonium bromide and potassium *tert*-butoxide in a ratio 1:1 in refluxing toluene increased the yields of both bis-vinyl nucleosides **8** and **9** to ca. 50%. It was of particular note, that under such reaction conditions no diastereoisomeric by-products of either **8** or **9** were observed, by NMR spectroscopy, indicating that complete chiral integrity was retained at carbon atoms C1′ and C4′ of **8** and **9**. This observation was further supported by the subsequent conversion of **8** via ring closure metathesis and deprotection (described later and depicted in Scheme 2) to give only one enantiomeric form of d4T which had identical physical data ($[\alpha]_D^{20}=-46°$, *c* 0.7, water) with that of the authentic drug. However, it has been found by NMR spectroscopy, that treatment of **8** and **9** with an excess of base resulted in epimeristion at C1′ to give, in each case, a mixture of

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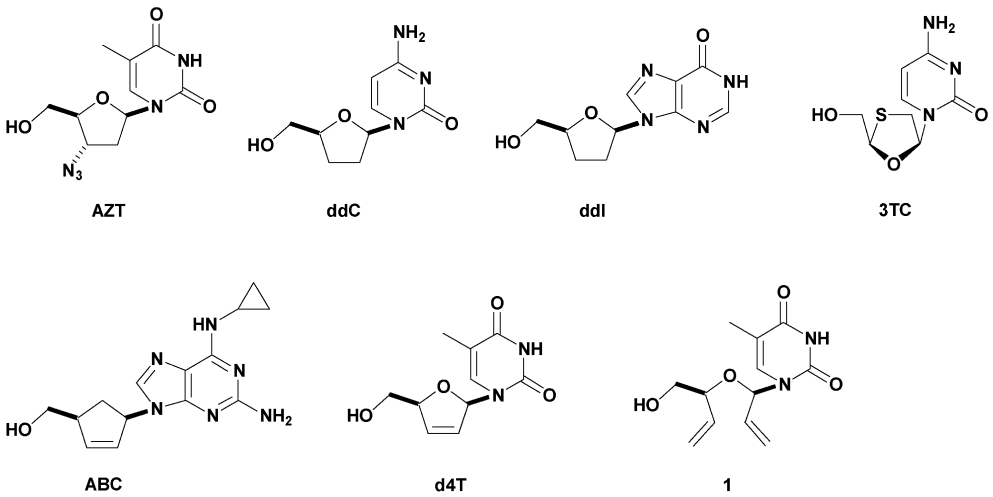
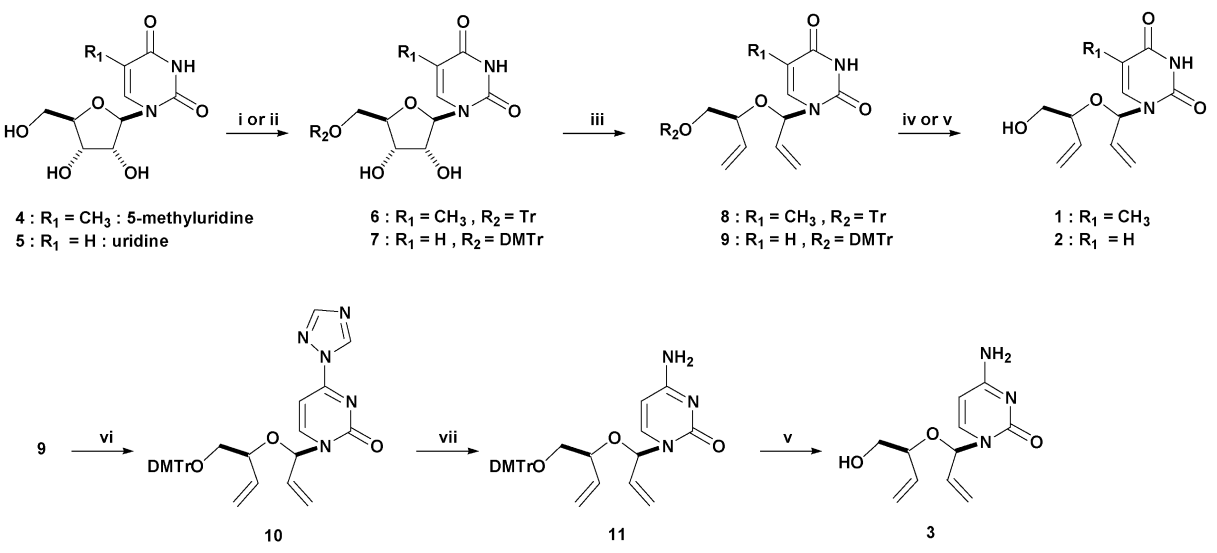


Figure 1.

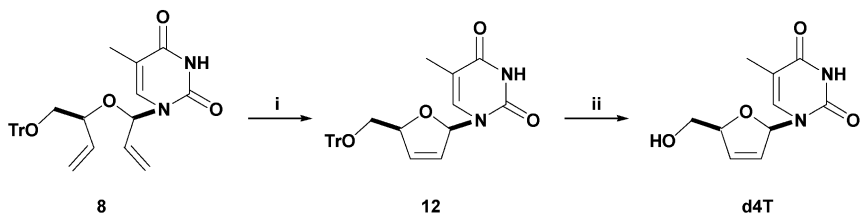
diastereoisomers, as determined by NMR spectroscopy, indicating the loss of chiral integrity. During the oxidation step in which **7** was treated with $NaIO_4$ in presence of ethanol and water, some deprotection of the primary hydroxyl group occurred to give the consequential by-product bis-(4-methoxyphenyl)phenylmethanol (10%); however, the trityl protecting group of **6** was fully retained during similar oxidation with no triphenylmethanol formation being observed by TLC. Recently, Rosenberg et al.[28] described this method using $NaIO_4$ in a mixture of acetone and water for the cleavage of the 4,4′-dimethoxytrityl group of nucleosides. The acyclic cytosine derivative **11** was obtained in 89% yield from **2** by Reese's method[29] via the 4-triazolo-uridine intermediate **10**. Deprotection of the 5′-*O*-trityl **8** by treatment with acetic acid 80% at 50°C gave the bis-vinyl acyclic nucleoside **1** in 88% yield. Compounds **9** and **11** were deprotected by hydrolysis with acetic acid–water (4:1) at room temperature to give the desired nucleosides **2** and **3** in 89 and 95% yields, respectively. The acyclic nucleosides **1**–**3** can be regarded as the first direct acyclic analogues of d4T.

During the last decade, convenience to use catalysts have greatly increased interest in the field of ring-closure metathesis.[30,31] Treatment of **8** with the first generation Grubbs reagent, benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium, resulted in a clean ring-closure metathesis to afford the d4T analogue **12** in 70% yield. The nucleoside **12** had identical physical data with those previously described by Cosford[23] and was readily deprotected by treatment with acetic acid–water (4:1) at 50°C to give d4T in quantitative yield.

In conclusion, we have developed a synthesis of a new class of acyclic enantiomerically pure nucleosides as potential anti-HIV agents in four steps in 30% overall yield. The new nucleoside derivatives are direct precursors of 2′,3′-didehydro-2′,3′-dideoxynucleosides which could be obtained via ring closing metathesis as has been demonstrated by our synthesis of d4T herein. This strategy could provide a new opening to a large variety of 2′,3′-didehydro-2′,3′-dideoxynucleosides and the corresponding carbanucleosides.



Scheme 1. (i) TrCl, pyr.; (ii) DMTrCl, pyr.; (iii) (a) $NaIO_4$, EtOH/H_2O, (b) Ph_3PCH_3Br, *t*-BuOK, toluene; (iv) AcOH–H_2O (4:1), 50°C; (v) AcOH–H_2O (4:1), room temperature; (vi) 1,2,4-triazole, $POCl_3$, CH_3CN, Et_3N; (vii) H_2O–NH_3 (7:3), 1,4-dioxane.



Scheme 2. (i) Benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium, CH_2Cl_2; (ii) AcOH–H_2O (4:1).

3. Experimental

3.1. General procedure

NMR spectra were recorded with a Lambda 400 spectrometer using standard conditions with a data point resolution of ca. 0.1 Hz. ^{1}H Chemical shifts were measured relative to Me_4Si and ^{13}C chemical shifts relative to $CDCl_3$ (77.0 ppm). All coupling constants are given in Hertz. Assignments of the ^{1}H spectra were made by detailed analysis using decoupling or correlation techniques where appropriate. Diastereoisomer ratios were determined from the integration of suitable peaks. Column chromatography was performed on silica gel (230–400 mesh; Prolabo) and TLC on silica gel 60, F_{254} (Merck) with detection by UV absorbance or phosphomolybdic acid. Optical rotation values are given in 10^{-1} deg cm^2 g^{-1}. High resolution ESI mass spectra were obtained on a LCT instrument (Micromass-Waters, UK) filled with a lockspray probe. NaI cluster ions were used as the lock mass for accurate mass measurements (resolution FWMH-5000).

3.2. Syntheses

3.2.1. 5′-*O*-Trityl-5-methyluridine (6). A solution of trityl chloride (2.8 g, 9.90 mmol) in anhydrous dichloromethane (19 mL) was added dropwise to a solution of **4** (2.0 g, 8.26 mmol) in anhydrous pyridine (35 mL) at 0°C. Following the addition, the mixture was allowed to warm slowly to room temperature and set aside for 12 h. Methanol (7 mL) and ethyl acetate (50 mL) were added and the mixture was washed successively with saturated aqueous $NaHCO_3$ (200 mL) and H_2O (100 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The resulting residue was crystallized from chloroform to give **6** (2.3 g; 60%). Anal. calcd for $C_{29}H_{28}O_6N_2$: C, 69.59; H, 5.64; N, 5.60. Found: C, 69.55; H, 5.70; N, 5.65. The physical data were in accordance with those previously described by Matsuda.[26]

3.2.2. 5′-*O*-(4,4′-Dimethoxytrityl)uridine (7). A solution of 4,4′-dimethoxytrityl chloride (11.5 g, 3.4×10^{-2} mol) in anhydrous dichloromethane (60 mL) was added dropwise to a solution of **5** (5.0 g, 20.5×10^{-2} mol) in anhydrous pyridine (88 mL) at 0°C. The mixture was subsequently allowed to warm slowly to room temperature. After 12 h, methanol (7 mL) and ethyl acetate (50 mL) were added. The resulting mixture was washed successively with saturated aqueous $NaHCO_3$ (35 mL) and H_2O (100 mL). The organic phase was dried over $MgSO_4$, evaporated under reduced pressure and purified by column chromatography (hexane–ethyl acetate, 3:7) to afford the protected nucleoside **7** (8.4 g; 75%) as a foam. Anal. calcd for $C_{30}H_{30}O_8N_2$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.90; H, 5.49; N, 5.18. The physical data were in accordance with those previously described by Smith.[27]

3.2.3. 1-{1-[1-(Trityloxymethyl)prop-2-enyloxy]prop-2-enyl}thymine (8). A solution of sodium periodate (0.23 g, 1.09 mmol) in water (5 mL) was slowly added to a cooled stirred solution of the protected nucleoside **6** (0.5 g, 9.99×10^{-4} mol) in ethanol (10 mL). The reaction mixture was stirred at room temperature for 2 h and then filtered to remove the salts. The solution was diluted with ethyl acetate (15 mL), washed with a saturated solution of NaCl (2×15 mL) and dried over $MgSO_4$. The solvent was removed by evaporation under reduced pressure to yield a white powder of the corresponding dialdehyde derivative. The crude dialdehyde was dissolved in freshly distilled tetrahydrofuran (5 mL) and added without purification to a yellow solution of methyltriphenylphosphine bromide (1.3 g, 3.66 mmol) and potassium *tert*-butoxide (0.41 g, 3.66 mmol) in toluene (50 mL) at 60°C under argon. The reaction mixture was subsequently allowed to cool to room temperature over 1 h, washed twice with a saturated solution of ammonium chloride (2×30 mL), dried over $MgSO_4$, evaporated to a yellow syrup and purified by column chromatography (hexane–ethyl acetate, 3:2) to afford the protected nucleoside **8** (0.25 g; 50%) as a foam; R_f 0.4 (hexane–ethyl acetate, 13:7); ^{1}H NMR ($CDCl_3$) δ 1.84 (3H, s, CH_3), 3.08 (1H, dd, J=3.2, 10.5 Hz, H-5′a), 3.39 (1H, dd, J=7.9, 10.5 Hz, H-5′b), 3.90 (1H, m, H-4′), 5.31 (1H, dd, J=0.8, 4.4 Hz, H-3′–CH_2), 5.35 (1H, d, J=10.8 Hz, H-3′–CH_2), 5.46 (1H, dt, J=1.5, 10.4 Hz, H-2′–CH_2), 5.63 (1H, m, H-3′), 5.64 (1H, dt, J=1.5, 17.2 Hz, H-2′–CH_2), 5.85 (1H, qd, J=3.4, 10.4, 17.2 Hz, H-2′), 6.32 (1H, dt, J=1.7, 3.4 Hz, H-1′), 7.46–7.25 (15 H, m, trityl), 7.32 (1H, d, J=8.1 Hz, H-6), 9.73 (1H, bs, NH); ^{13}C NMR ($CDCl_3$) δ 13.0 (CH_3), 66.7 (C-5′), 78.7 (C-4′), 80.3 (C-1′), 112.1 (C-5), 119.6 (C-2′–CH_2), 121.1 (C-3′–CH_2), 133.4 (C-3′), 134.2 (C-2′), 136.6 (C-6), 151.7 (C-2), 164.7 (C-4), 87.2, 127.5, 128.2, 129.1, 144.3 (19C, trityl). Anal. calcd for $C_{31}H_{30}O_4N_2$: C, 75.28; H, 6.11; N, 5.66. Found: C, 75.25; H, 6.15; N, 5.71. HRMS (ESI) (M+Na^+) calcd for $C_{31}H_{30}O_4N_2Na$: 517.2144, found 517.2103.

3.2.4. 1-{1-[1-(4,4′-Dimethoxytrityloxymethyl)prop-2-enyloxy]prop-2-enyl}uracil (9). A solution of sodium periodate (0.23 g, 1.09 mmol) in water (5 mL) was slowly added to a cooled stirred solution of the protected nucleoside **7** (0.5 g, 9.15×10^{-4} mol) in ethanol (10 mL). The reaction mixture was stirred at room temperature for 2 h and then filtered to remove salts. The solution was treated with ethyl acetate (15 mL), washed with a saturated solution of NaCl (2×15 mL) and dried over $MgSO_4$. The solvent was removed by evaporation under reduced pressure to yield a

white powder of the corresponding dialdehyde. Without further purification the dialdehyde was dissolved in freshly distilled tetrahydrofuran (5 mL), and treated with a yellow solution of methyltriphenylphosphine bromide (1.3 g, 3.66 mmol) and potassium *tert*-butoxide (0.41 g, 3.66 mmol) in toluene (50 mL) at 60°C under argon. After 1 h, the mixture was cooled at room temperature, washed with a saturated solution of ammonium chloride (2×30 mL), dried over $MgSO_4$, evaporated to a yellow syrup and purified by column chromatography (hexane–ethyl acetate, 9:1) to afford bis-(4-methoxyphenyl)phenylmethanol (29.3 mg, 10%) and the protected nucleoside **9** (0.25 g; 51%) as a foam; R_f 0.5 (hexane–ethyl acetate, 1:1); ^{1}H NMR ($CDCl_3$) δ 3.07 (1H, dd, J=3.2, 10.4 Hz, H-5′a), 3.35 (1H, dd, J=8.2, 10.4 Hz, H-5′b), 3.91 (1H, m, H-4′), 5.30 (1H, s, H-3′–CH_2), 5.35 (1H, d, J=5.6 Hz, H-3′–CH_2), 5.44 (1H, dt, J=1.4, 10.4 Hz, H-2′–CH_2), 5.61 (1H, dt, J=1.4, 17.1 Hz, H-2′–CH_2), 5.74 (1H, d, J=7.9 Hz, H-5), 5.75 (1H, m, H-3′), 5.84 (1H, qd, J=3.6, 10.5, 17.1 Hz, H-2′), 6.26 (1H, dt, J=1.5, 3.6 Hz, H-1′), 7.53–7.25, 3.81 (21H, m, trityl), 7.43 (1H, d, J=7.9 Hz, H-6), 8.64 (1H, bs, NH); ^{13}C NMR ($CDCl_3$) δ 66.3 (C-5′), 78.8 (C-4′), 80.7 (C-1′), 103.5 (C-5), 119.6 (C-2′–CH_2), 121.2 (C-3′–CH_2), 133.2 (C-3′), 133.9 (C-2′), 141.2 (C-6), 151.5 (C-2), 164.0 (C-4), 55.6, 86.7, 113.5, 127.3, 128.2, 128.6, 130.5, 136.2, 136.4, 145.1, 158.9 (21C, trityl). Anal. calcd for $C_{32}H_{32}O_6N_2$: C, 71.09; H, 5.97; N, 5.18. Found: C, 71.05; H, 5.95; N, 5.22. HRMS (ESI) (M+Na^+) calcd for $C_{32}H_{32}O_6N_2Na$: 563.2140, found 563.2158.

3.2.5. 1-{1-[1-(4,4′-Dimethoxytrityloxymethyl)prop-2-enyloxy]prop-2-enyl}cytosine (11). A solution of 1,2,4-1-*H*-triazole (0.57 g, 9.66 mmol) and $POCl_3$ (0.17 mL, 2.02 mmol) in acetonitrile (6 mL) was cooled at 0°C. Et_3N (1.1 mL, 9.24 mmol) was then added and the mixture stirred for 30 min at room temperature. A solution of **9** (0.5 g, 9.25×10^{-4} mol) in acetonitrile (3 mL) was added and the resulting heterogeneous mixture stirred overnight at room temperature. Et_3N (0.9 mL) and H_2O (0.4 mL) were added to give a homogeneous solution which was stirred for 15 min, dissolved in dichloromethane (15 mL), washed with a saturated solution of Na_2CO_3 (2×15 mL), dried over $MgSO_4$ and evaporated to give a yellow powder of the 1,2,4-triazolyl derivative **10**. Without further purification **10** was dissolved in dioxane (6.5 mL) and added to an aqueous solution of ammonia (30%) (2.15 mL) and set aside overnight at room temperature. The subsequent mixture was evaporated under reduced pressure and purified by column chromatography (ethyl acetate–methanol, 13:1) to afford **11** (0.44 g; 88%) as a white powder; mp 104°C; R_f 0.3 (dichloromethane–methanol, 95:5); ^{1}H NMR ($CDCl_3$) δ 3.02 (1H, dd, J=3.0, 10.3 Hz, H-5′a), 3.31 (1H, dd, J=8.2, 10.3 Hz, H-5′b), 3.94 (1H, m, H-4′), 5.26 (1H, dt, J=0.8, 10.2 Hz, H-3′–CH_2), 5.32 (1H, dt, J=0.8, 17.2 Hz, H-3′–CH_2), 5.35 (1H, dt, J=1.5, 10.5 Hz, H-2′–CH_2), 5.54 (1H, dt, J=1.5, 17.1 Hz, H-2′–CH_2), 5.60 (1H, m, H-3′), 5.63 (1H, d, J=7.3 Hz, H-5), 5.86 (1H, qd, J=3.6, 10.5, 17.1 Hz, H-2′), 6.41 (1H, dt, J=1.8, 3.6 Hz, H-1′), 7.63 (1H, J=7.3 Hz, H-6), 7.45–7.22, 3.81 (21H, m, trityl); ^{13}C NMR ($CDCl_3$) δ 66.5 (C-5′), 78.5 (C-4′), 81.3 (C-1′), 96.2 (C-5), 118.6 (C-2′–CH_2), 120.5 (C-3′–CH_2), 133.7 (C-3′), 134.9 (C-2′), 142.3 (C-6), 157.3 (C-2), 166.3 (C-4), 55.6, 86.6, 113.5, 127.2, 128.6, 128.6, 130.5, 136.3, 136.5, 145.3, 158.9 (21C, trityl). Anal. calcd for $C_{32}H_{33}O_5N_3$: C, 77.22; H, 6.16; N, 7.79. Found: C, 71.25; H, 6.19; N, 7.82. HRMS (ESI) (M+Na^+) calcd for $C_{32}H_{33}O_5N_3Na$: 562.2333, found 562.2318.

3.2.6. 1-{1-[1-(Hydroxymethyl)prop-2-enyloxy]prop-2-enyl}thymine (1). An aqueous solution of acetic acid (80%, 65 mL) was added to **8** (0.5 g, 1.01×10^{-3} mol). After 1 h at 50°C, the mixture was co-evaporated with methanol and purified by column chromatography (ethyl acetate–methanol, 49:1) to afford **1** (0.22 g., 86%) as an oil; R_f 0.4 (dichloromethane–methanol, 95:5); ^{1}H NMR ($CDCl_3$) δ 1.90 (3H, s, CH_3), 3.62 (2H, m, H-5′a, H-5′b), 4.06 (1H, m, H-4′), 5.38 (1H, d, J=10.5 Hz, H-3′-CH_2), 5.44 (1H, d, J=1.4 Hz, J=10.5 Hz, H-3′-CH_2), 5.45 (1H, d, J=17.2 Hz, H-3′-CH_2), 5.57 (1H, dt, J=1.4, 17.2 Hz, H-2′–CH_2), 5.73 (1H, m, H-3′), 5.82 (1H, dq, J=3.5, 10.5, 17.2 Hz, H-2′–CH_2), 6.31 (1H, dt, J=1.7, 3.6 Hz, H-1′), 7.21 (1H, d, J=1.2 Hz, H-6), 9.70 (1H, bs, NH); ^{13}C NMR ($CDCl_3$) δ 12.5 (CH_3), 64.9 (C-5′), 79.7 (C-4′), 81.5 (C-1′), 111.8 (C-5), 120.0 (C-2′–CH_2), 121.2 (C-3′–CH_2), 132.8 (C-3′), 133.2 (C-2′), 136.0 (C-6), 151.2 (C-2), 163.7 (C-4). Anal. calcd for $C_{12}H_{16}O_4N_2$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.12; H, 6.43; N, 11.15. HRMS (ESI) (M+Na^+) calcd for $C_{12}H_{16}O_4N_2Na$: 275.1012, found 275.1008.

3.2.7. 1-{1-[1-(Hydroxymethyl)prop-2-enyloxy]prop-2-enyl}uracil (2). An aqueous solution of acetic acid (80%, 65 mL) was added to **9** (0.5 g, 9.15×10^{-4} mol). After 1 h at room temperature, the mixture was co-evaporated with methanol and purified by column chromatography (ethyl acetate–methanol, 49:1) to afford **2** (0.21 g., 95%) as a solid; mp 112°C; R_f 0.6 (dichloromethane–methanol, 95:5); ^{1}H NMR ($CDCl_3$) δ 3.59 (1H, dd, J=7.7, 12.0 Hz, H-5′a), 3.67 (1H, dd, J=3.6, 12.0 Hz, H-5′b), 4.09 (1H, m, H-4′), 5.38 (1H, d, J=10.4 Hz, H-3′–CH_2), 5.44 (1H, dt, J=1.2, 10.4 Hz, H-3′–CH_2), 5.46 (1H, d, J=17.4 Hz, H-3′–CH_2), 5.58 (1H, dt, J=1.2, 17.2 Hz, H-2′–CH_2), 5.74 (1H, m, H-3′), 5.75 (1H, d, J=8.1 Hz, H-5), 5.83 (1H, dq, J=3.7, 10.5, 17.1 Hz, H-2′–CH_2), 6.32 (1H, dt, J=1.6, 3.7 Hz, H-1′), 7.44 (1H, d, J=8.1 Hz, H-6), 9.91 (1H, bs, NH); ^{13}C NMR ($CDCl_3$) δ 65.3 (C-5′), 80.6 (C-4′), 81.3 (C-1′), 103.3 (C-5), 120.3 (C-2′–CH_2), 121.0 (C-3′–CH_2), 133.3 (C-3′), 133.5 (C-2′), 141.4 (C-6), 151.6 (C-2), 164.5 (C-4). Anal. calcd for $C_{11}H_{14}O_4N_2$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.43; H, 5.95; N, 11.78. HRMS (ESI) (M+Na^+) calcd for $C_{11}H_{14}O_4N_2Na$: 261.0864, found 261.0851.

3.2.8. 1-{1-[1-(Hydroxymethyl)prop-2-enyloxy]prop-2-enyl}cytosine (3). An aqueous solution of acetic acid (80%, 65 mL) was added to **9** (0.5 g, 9.27×10^{-4} mol). After 1 h at room temperature, the mixture was co-evaporated with methanol and purified by column chromatography (ethyl acetate–methanol, 3:1) to afford **3** (0.20 g, 91%) as a white powder; mp 48°C, R_f 0.3 (dichloromethane–methanol, 80:20); ^{1}H NMR ($CDCl_3$) δ 3.54 (1H, dd, J=8.0, 12.0 Hz, H-5′a), 3.66 (1H, dd, J=3.2, 12.0 Hz, H-5′b), 4.06 (1H, m, H-4′), 5.31 (1H, d, J=10.5 Hz, H-3′–CH_2), 5.35 (1H, dt, J=1.3, 10.5 Hz, H-3′–CH_2), 5.41 (1H, d, J=17.2 Hz, H-3′–CH_2), 5.48 (1H, dt, J=1.3, 17.2 Hz, H-2′–CH_2), 5.73 (1H, m, H-3′), 5.81 (1H, dq, J=3.8, 10.5, 17.2 Hz, H-2′-CH_2), 5.88 (1H, d, J=7.1 Hz, H-5), 6.38 (1H, dt, J=1.6, 3.7 Hz, H-1′), 7.48 (1H, d, J=8.1 Hz, H-6); ^{13}C

NMR ($CDCl_3$) δ 64.4 (C-5′), 80.2 (C-4′), 81.8 (C-1′), 95.5 (C-5), 118.2 (C-2′–CH_2), 119.7 (C-3′–CH_2), 134.0 (C-3′), 134.7 (C-2′), 142.2 (C-6), 157.8 (C-2), 166.5 (C-4). Anal. calcd for $C_{11}H_{15}O_3N_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.73; H, 6.38; N, 17.81. HRMS (ESI) ($M+Na^+$) calcd for $C_{11}H_{15}O_3N_3Na$: 260.1023, found 260.1011.

3.2.9. 1-(2,3-Dideoxy-β-D-glycero-pent-2-enofuranosyl-5-*O*-trityl)thymine (12). The Grubbs reagent (20 mg) was added to a solution of **8** (0.1 g, 2.02×10^{-4} mol) in freshly distilled dichloromethane (15 mL) and reacted overnight, under nitrogen, at 35°C. The reaction produced a precipitate which was removed by filtration. The filtrate was evaporated under reduced pressure and purified by column chromatography (hexane–ethyl acetate, 7:3) to afford **12** (75 mg, 79%) as a white powder. Anal. calcd for $C_{29}H_{26}O_4N_2$: C, 74.66; H, 5.62; N, 6.00. Found: C, 74.70; H, 5.59; N, 6.05. The physical data were in accordance with those previously described by Cosford.[23]

3.2.10. 1-(2,3-Dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine (d4T). A solution of **12** (0.1 g, 2.14×10^{-4} mol) in water (1 mL) and glacial acetic acid (4 mL) was heated at 50°C for 1 h. After cooling, the solvents were removed under reduced pressure to give a residue which was purified by column chromatography (ethyl acetate) to afford d4T (34 mg, 71%) as a white powder. Anal. calcd for $C_{10}H_{12}O_4N_2$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.71; H, 5.42; N, 12.52. The physical data ($[\alpha]_D^{20}=-46°$, *c* 0.7, water) were in accordance with those previously described by Cosford[23] and Mansuri.[20]

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