

Synthesis of Prodrugs as Bridged Nucleosides

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Methods for the preparation of *N,N'*-connected bisnucleosides have been developed. The bridge is formally a carbonate ester of *N*-hydroxymethyl nucleosides. Both symmetrical and non-symmetrical bridged bisnucleosides are available.

A variety of drug delivery modifications has been proposed to enhance CNS (central nervous system) delivery of nucleosides, which as a class penetrate the blood-brain barrier poorly.¹ These include prodrug approaches with simple esters.^{2,3} We have reported on ether, carbonate and urethane deoxynucleoside derivatives as lipophilic prodrugs to enhance passive passage across the blood-brain barrier.⁴ After passage through the blood-brain barrier the lipophilic moiety was designed to be cleaved off from the nucleoside by enzymatic action, thereby liberating the parent nucleoside for subsequent phosphorylation to a nucleotide which presumably is the bioactive species.

The nucleosides **A** in Fig. 1 represent a group of lipophilic prodrugs taken from our series of *N*3-hydroxymethylated nucleosides.⁴ The lipophilic *N*3-hydroxyethyl carbonate **A** can be cleaved by esterases to a half ester of carbonic acid. The half ester is subsequently decarboxylated to a chemically unstable hydroxyethyl derivative which dissociates into the corresponding aldehyde and the parent nucleoside. In a further search for nucleosides with biocompatible physical properties we herein report on our efforts to develop methods for bridging nucleosides between annular nitrogen atoms. Group **B** structures in Fig. 1 demonstrate this principle. Methods for

the preparation of both symmetrical and non-symmetrical bridged compounds **B** were sought. The carbonate ester bridge is expected to be cleaved *in vivo* by esterases (*vide supra*).

Scheme 1 shows the construction of a symmetrical bridge structure **2**. The reaction **1** → **2** involves a dialkylation in a one-pot reaction with protected thymidine as the substrate, bis(chloromethyl) carbonate as the alkylating agent, and potassium carbonate as the base. The product **2** was isolated in 50% yield. The first alkylation step seems to be the faster reaction since under slightly modified conditions with 1,8-diazabicyclo-[5,4,0]undec-7-ene (DBU) as base, the monoalkylated product **3** was isolated in 51% yield. The latter is a key intermediate for further symmetrical or non-symmetrical alkylations (*vide infra*). In the alkylation with another molecule of the thymidine **1** the bridged structure **2** was isolated in 71% yield.

The dichloromethyl carbonate reagent used was available in a highly pure form by our general method for the preparation of α -chloroalkyl esters by the cleavage of α -thioalkyl carbonates with sulfur chloride.⁵

In a similar way Scheme 2 shows that two ribosyl nucleosides can be bridged as a carbonate. When 2',3'-di-*O*-isopropylideneuridine (**4**) was the substrate, the

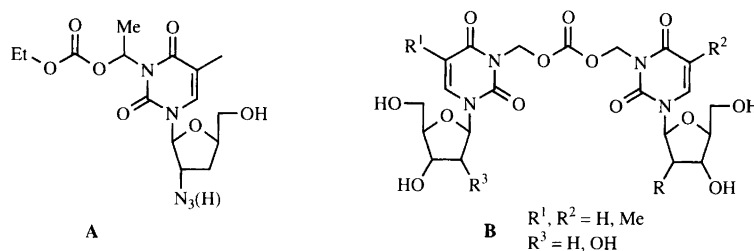
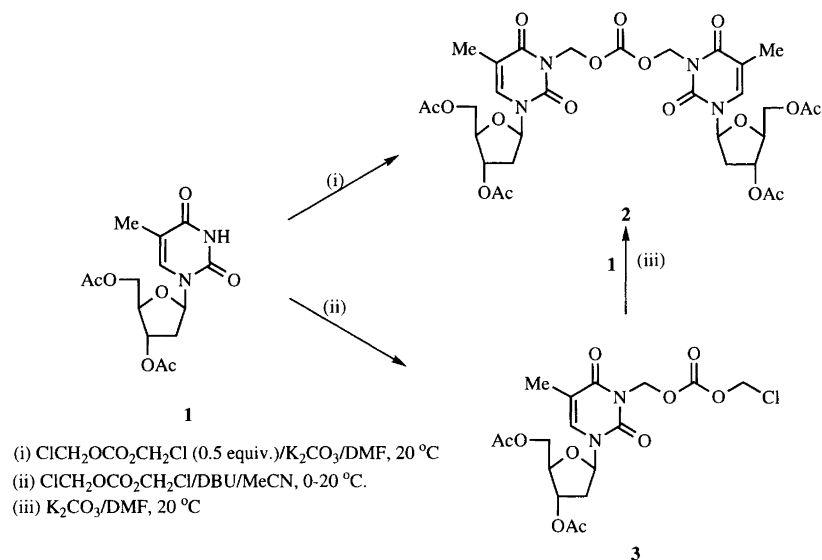


Fig. 1.

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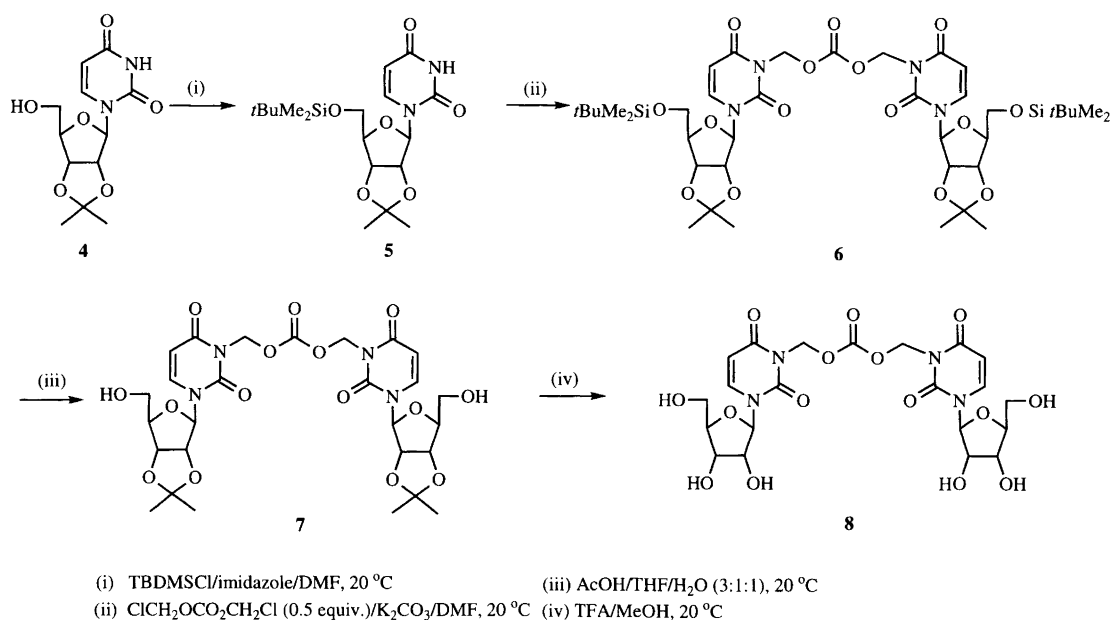
Scheme 1.

symmetrically bridged carbonate **6** was isolated in 73% yield after prior protection of the 5'-OH group as a silyl ether **5**. Inferior yields were obtained without 5'-OH protection. The two alkylation steps were run as a one-pot reaction with potassium carbonate as the base. Removal of the protecting groups was effected in a two-step process. The silyl groups were cleaved under mild acidic conditions using acetic acid in aqueous THF (75%). The isopropylidene group in the desilylated product **7** was cleaved by TFA in methanol which furnished the carbonate-bridged bisuridine **8** in 80% yield.

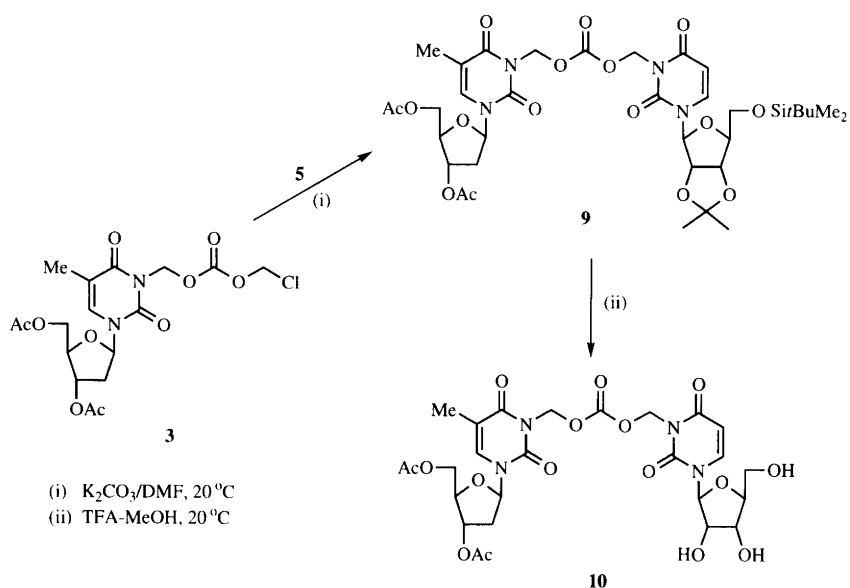
Non-symmetrical bridging is shown in Scheme 3 where a ribosyl and a 2'-deoxyribosyl nucleoside are joined

together as a carbonate ester. The key reactant for this process was a chloromethyl monoalkylated nucleoside carbonate such as the chloromethyl ester **3**. The latter was used for alkylation of the uridine **5** with potassium carbonate as the base. The carbonate-bridged compound **9** was isolated in 87% yield. The silyl and isopropylidene protecting functions were removed in the uridine moiety by TFA in methanol to furnish the unsymmetrical carbonate **10** in 74% yield. As a prodrug, the acetyl groups in the carbonate **10** will be cleaved off by esterases and were therefore not removed. The carbonate **10** may also serve as a substrate for further chemical manipulations.

In conclusion we have developed methodology for



Scheme 2.



Scheme 3.

the preparation of symmetrical or non-symmetrical *N,N'*-nucleosylmethyl carbonates, which are potential prodrugs.

Experimental

The NMR spectra were recorded in CDCl_3 at 500 MHz (^1H) and at 125 MHz (^{13}C) unless otherwise stated. The mass spectra under electron impact conditions were recorded at 70 eV ionizing energy, and isobutane was used for chemical ionization (CI). Electrospray ionisation (ESI) was also used. The MS spectra are presented as m/z (% rel. int.).

Bis(chloromethyl) carbonate was prepared from chloromethyl phenylthiomethyl carbonate by sulfur chloride cleavage of the thio function.⁵

3',5'-di-O-acetylthymidine (1).⁶ Thymidine (4.87 g, 20.1 mmol) was suspended in acetic anhydride (50 ml) and DMAP (127 mg, 1.04 mmol) added. The mixture was stirred for 6.5 h and the resulting solution added in portions to sodium bicarbonate (100 g) in water (500 ml) with stirring. The mixture was stirred for 4.5 h and extracted with chloroform. The organic layer was washed with 1 M HCl and saturated sodium bicarbonate, dried (MgSO_4) and evaporated. The residue was triturated with diethyl ether and recrystallized from ethanol; yield 6.03 g (92%), m.p. 128°C . Anal.: $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_7$: C, H. ^1H NMR: δ 1.90 (3 H, s, 5-Me), 2.11 (7 H, m, $\text{MeCO} \times 2$ and H_A in H-2'), 2.43 (1 H, m, H_B in H-2'), 4.20 (1 H, m, H-4'), 4.31 (2 H, dd $\times 2$, H-5'), 5.17 (1 H, m, H-3'), 6.30 (1 H, dd, H-1'), 7.24 (1 H, s, H-6), 9.70 (1 H, s, NH). ^{13}C NMR: δ 12.66 (Me-5), 20.77 and 20.85 (MeCO), 37.41 (C-2'), 63.85 (C-5'), 74.07 (C-3'), 81.99 (C-4'), 84.66 (C-1'), 111.54 (C-5), 134.40 (C-6), 150.47 (C-2), 163.73 (C-4), 170.15 and 170.40 (MeCO).

Bis[(3',5'-di-O-acetylthymidin-3-yl)methyl] carbonate (2). *Method A (One-pot dialkylation)*. Potassium carbonate (76 mg, 0.55 mmol) was added to a solution of 3',5'-di-O-acetylthymidine (163 mg, 0.500 mmol) in DMF (1.5 ml) and the mixture stirred under N_2 for 1 h before bis(chloromethyl) carbonate (40 mg, 0.25 mmol) in DMF (1 ml) was added. The mixture was stirred for 3 d before the solvent was evaporated off. The residue was partitioned between chloroform and aqueous 10% ammonium chloride solution. The layers were separated, the aqueous phase was extracted with chloroform, the combined organic solutions were dried (MgSO_4) and evaporated and the residual material was subjected to flash chromatography on silica gel using chloroform-methanol 96:4. Evaporation of the collected eluates and trituration of the residual material with diethyl ether gave a white waxy material; yield 92 mg (50%). Anal. $\text{C}_{31}\text{H}_{38}\text{N}_4\text{O}_{17}$: C, H. ^1H NMR: δ 1.89 (6 H, s, 5-Me $\times 2$), 2.08 (14 H, m, $\text{MeCO} \times 4$ and HA in H-2' $\times 2$), 2.44 (2 H, m, HB in H-2' $\times 2$), 4.21 (2 H, m, H-4' $\times 2$) 4.31 (4 H, dd $\times 2$, H-5' $\times 2$), 5.16 (2 H, m, H-3' $\times 2$), 6.01 and 6.02 (4 H, AB, J 9.2 Hz, $\text{NCH}_2\text{O} \times 2$), 6.26 (2 H, dd, H-1' $\times 2$), 7.25 (2 H, s, H-6 $\times 2$). ^{13}C NMR: δ 13.19 (5-Me), 20.76 and 20.82 (MeCO), 37.51 (C-2'), 63.73 (C-5'), 66.87 (NCH_2O), 74.00 (C-3'), 82.14 (C-4'), 85.50 (C-1'), 110.57 (C-5), 133.52 (C-6), 149.95 (C-2), 152.05 (OCO_2), 161.93 (C-4), 170.08 and 170.31 (MeCO). MS (CI- NH_3): 738 (0, M), 463 (3), 446 (2), 389 (8), 372 (36), 98 (54), 88 (100).

Method B (two-step alkylation). Potassium carbonate (39 mg, 0.28 mmol) was added to a solution of 3',5'-di-O-acetylthymidine (83 mg, 0.25 mmol) in DMF (1 ml) and the mixture stirred under N_2 for 1 h before 3-chloromethoxycarbonyloxymethyl-3',5'-di-O-acetylthymidine (138 mg, 0.31 mmol) in DMF (1 ml) was

added. The resultant mixture was stirred for 3 d at ambient temperature and the product isolated as described above; yield 148 mg (79%).

3-Chloromethoxycarbonyloxymethyl-3',5'-di-O-acetylthymidine (3). DBU (163 μ l, 1.10 mmol) was added to 3',5'-di-O-acetylthymidine (326 mg, 1.00 mmol) in acetonitrile (5 ml) under N₂ and the solution cooled to 0 °C. Bis(chloromethyl) carbonate (204 mg, 1.28 mmol) in acetonitrile (5 ml) was added dropwise and the mixture stirred overnight while being allowed to reach ambient temperature. The solvent was evaporated off and the residue partitioned between chloroform and aqueous 10% ammonium chloride solution. The layers were separated, the aqueous phase extracted with chloroform, the combined organic solution dried (MgSO₄) and evaporated and the residual material was subjected to flash chromatography on silica gel using EtOAc–hexane (6:4). The oily material after chromatography was triturated with diethyl ether; yield 230 mg (51%) of a white solid, m.p. 124 °C. Anal.: C₁₇H₂₁ClN₂O₁₀: C, H. ¹H NMR: δ 1.94 (3 H, s, 5-Me), 2.12 (7 H, m, MeCO \times 2 and H_A in H-2'), 2.47 (1 H, m, H_B in H-2'), 4.23 (1 H, m, H-4'), 4.33 (2 H, dd \times 2, H-5'), 5.19 (1 H, m, H-3'), 5.71 (2 H, s, OCH₂Cl), 6.08 (2 H, s, NCH₂O), 6.29 (1 H, dd, H-1'), 7.29 (1 H, s, H-6). ¹³C NMR: δ 13.25 (5-Me), 20.83 and 20.88 (MeCO), 37.58 (C-2'), 63.77 (C-5'), 67.49 (NCH₂O), 72.24 (OCH₂Cl), 73.98 (C-3'), 82.23 (C-4'), 85.58 (C-1'), 110.73 (C-5), 133.76 (C-6), 150.02 (C-2), 152.00 (OCO₂), 161.99 (C-4), 170.14 and 170.38 (MeCO). MS: 450/448 (0.06/0.17, *M*), 339 (3), 201 (10), 140 (5), 110 (7), 98 (7), 81 (100).

5'-O-tert-Butyldimethylsilyl-2',3'-di-O-isopropylideneuridine (5).⁷ *tert*-Butyldimethylsilyl chloride (1.72 g, 11.4 mmol) and imidazole (1.58 g, 23.2 mmol) were added to a solution of 2',3'-di-O-isopropylideneuridine (2.82 g, 9.93 mmol) in DMF (10 ml) and the mixture was stirred under N₂ at ambient temperature overnight. Diethyl ether was added and the mixture washed with water (\times 4), the ether solution dried (MgSO₄) and evaporated, and the residual material triturated with diisopropyl ether and pentane; yield 3.18 g (80%) of a white powder, m.p. 136 °C. An analytical sample was recrystallized from dilute ethanol; m.p. 137 °C. Anal. C₁₈H₃₀N₂O₆Si: C, H. ¹³C NMR: δ -5.60 and -5.50 (SiMe), 18.29 (C in *t*-Bu), 25.30 (Me in isopropylidene), 25.79 (Me in *t*-Bu), 27.22 (Me in isopropylidene), 63.30 (C-5'), 80.20 (C-3'), 85.32 (C-2'), 86.62 (C-4'), 91.84 (C-1'), 102.16 (C-5), 114.05 (C in isopropylidene), 140.56 (C-6), 150.15 (C-2), 163.41 (C-4). MS (CI): 399 (36, *M*⁺ + H), 383 (3), 341 (30), 287 (42), 229 (22), 173 (41), 133 (47), 113 (100).

Bis[(5'-O-tert-Butyldimethylsilyl-2',3'-di-O-isopropylideneuridin-3-yl)methyl] carbonate (6). Potassium carbonate (153 mg, 1.11 mmol) was added to a solution of 5'-O-*tert*-butyldimethylsilyl-2',3'-di-O-isopropylidene-

uridine (399 mg, 1.00 mmol) in DMF (3 ml) and the mixture stirred under N₂ for 1 h before bis(chloromethyl) carbonate (78 mg, 0.49 mmol) in DMF (2 ml) was added. The mixture was stirred at ambient temperature for 3 d before the solvent was evaporated off. The residue was partitioned between chloroform and 10% ammonium chloride and the aqueous phase extracted with chloroform. The organic phase was dried (MgSO₄) and evaporated, and the product isolated after flash chromatography on silica gel using chloroform and chloroform–methanol (99:1) for elution; yield 317 mg (73 %) of a white foam. Anal. C₃₉H₆₂N₄O₁₅Si₂: C, H. ¹H NMR: δ 0.04 and 0.05 (12 H, s \times 2, SiMe₂ \times 2), 0.85 (18 H, s, *t*-Bu \times 2), 1.32 and 1.54 (12 H, s \times 2, isopropylidene \times 2), 3.74 (2 H, dd, H_A in H-5' \times 2), 3.88 (2 H, dd, H_B in H-5' \times 2), 4.30 (2 H, m, H-4' \times 2), 4.64 (2 H, dd, H-2' \times 2), 4.70 (2 H, dd, H-3' \times 2), 5.67 (2 H, d, *J* 8.2 Hz, H-5 \times 2), 5.90 (2 H, d, *J* 2.5 Hz, H-1' \times 2), 5.98 (4 H, s, NCH₂O \times 2), 7.67 (2 H, d, *J* 8.2, H-6 \times 2). ¹³C NMR: δ -5.62 and -5.52 (SiMe), 18.24 (C in *t*-Bu), 25.27 (Me in isopropylidene), 25.76 (Me in *t*-Bu), 27.19 (Me in isopropylidene), 63.24 (C-5'), 66.52 (NCH₂O), 80.18 (C-3'), 85.59 (C-2'), 86.92 (C-4'), 92.87 (C-1'), 101.27 (C-5), 113.95 (C in isopropylidene), 139.39 (C-6), 150.06 (C-2), 151.99 (CO), 161.22 (C-4). MS (CI-CH₄): 882 (0, *M*), 413 (5), 355 (3), 341 (3), 287 (9), 229 (12), 201 (16), 133 (34), 115 (79), 75 (100).

Bis[(2',3'-di-O-isopropylideneuridin-3-yl)methyl] carbonate (7). A solution of bis[(5'-O-*tert*-butyldimethylsilyl-2',3'-di-O-isopropylideneuridin-3-yl)methyl] carbonate (442 mg, 0.501 mmol) in acetic acid–THF–water (3:1:1; 5 ml) was stirred at ambient temperature for 22 h and diluted with water. NaHCO₃ (5 g) was added in portions and the mixture was stirred until the bubbling ceased and then extracted with chloroform. The organic phase was dried (MgSO₄) and evaporated. Flash chromatography of the residue on silica gel using EtOAc–methanol (95:5) for elution gave 265 mg of a white foamy material after drying at ambient temperature/0.05 mmHg for 8 h. NMR showed the foamy solid to be the title compound together with ethyl acetate, ratio 5:3; calculated yield 245 mg (75%). ¹H NMR (200 MHz): δ 1.33 and 1.54 (12 H, s \times 2, isopropylidene \times 2), 2.25 (2 H, br s, OH \times 2), 3.77 (2 H, dd, H_A in H-5' \times 2), 3.89 (2 H, dd, H_B in H-5' \times 2), 4.28 (2 H, m, H-4' \times 2), 4.90 (2 H, dd, H-3' \times 2), 4.98 (2 H, dd, H-2' \times 2), 5.56 (2 H, d, *J* 2.6 Hz, H-1' \times 2), 5.74 (2 H, d, *J* 8.2 Hz, H-5 \times 2), 5.99 (4 H, s, NCH₂O \times 2), 7.39 (2 H, d, *J* 8.2, H-6 \times 2). ¹³C NMR (50 MHz): δ 25.84 and 27.78 (Me), 62.84 (C-5'), 66.69 (NCH₂O), 80.39 (C-3'), 84.01 (C-2'), 87.13 (C-4'), 96.24 (C-1'), 101.38 (C-5), 113.83 (C in isopropylidene), 140.94 (C-6), 149.37 (C-2), 151.10 (CO), 160.28 (C-4). MS (ESI): 1331 (30, 2*M* + Na), 677 (100, *M* + Na), 655 (12, *M* + H).

Bis[(uridin-3-yl)methyl] carbonate (8). Trifluoroacetic acid (3 ml) was added to bis[(2',3'-di-O-isopropylidene-

uridin-3-yl)methyl] carbonate (196 mg, 0.299 mmol) in methanol (3 ml) at 0°C. The mixture was stirred at ambient temperature for 4 h, cooled to 0°C and more trifluoroacetic acid (3 ml) was added. The mixture was stirred at ambient temperature for another 5 h and evaporated. Methanol was added and evaporated off ($\times 3$). Flash chromatography of the residual material on silica gel using methanol–chloroform (35:65) where the chloroform contained 1% ethanol gave 144 mg of white waxy material after drying at ambient temperature/0.05 mmHg for 17 h. NMR showed the title compound obtained under these conditions to have bound ethanol, ratio 2:1; calculated yield 138 mg (80%). ^1H NMR (CD_3CN): δ 3.25 (2 H, br s, OH $\times 2$), 3.69 (2 H, dd, H_A in H-5' $\times 2$), 3.72–4.20 [m, (H-2', H-3', H-4', OH and H_B in H-5') $\times 2$], 5.72 (2 H, d, J 8.2 Hz, H-5 $\times 2$), 5.79 (2 H, d, J 3.9 Hz, H-1' $\times 2$), 5.91 (4 H, s, NCH_2O $\times 2$), 7.87 (2 H, d, J 8.2 Hz, H-6 $\times 2$). MS (ESI): 1171 (40, $2M + \text{Na}$), 597 (100, $M + \text{Na}$), 575 (38, $M + \text{H}$).

(5'-*O*-*tert*-Butyldimethylsilyl-2',3'-*di*-*O*-isopropylidene-uridin-3-yl)methyl (3',5'-*di*-*O*-acetylthymidin-3-yl)methyl carbonate (9). Potassium carbonate (38 mg, 0.28 mmol) was added to a solution of 5'-*O*-*tert*-butyldimethylsilyl-2',3'-*di*-*O*-isopropylideneuridine (100 mg, 0.251 mmol) in DMF (1 ml) and the mixture stirred under N_2 for 1 h before 3-chloromethoxycarbonyloxymethyl-3',5'-*di*-*O*-acetylthymidine (136 mg, 0.303 mmol) in DMF (1 ml) was added. The mixture was stirred at ambient temperature for 3 d before the solvent was evaporated off. The residue was partitioned between chloroform and 10% ammonium chloride and the aqueous phase extracted with chloroform. The organic phase was dried (MgSO_4), evaporated and the product isolated after flash chromatography on silica gel using EtOAc–hexane (6:4). The product after chromatography was an oily material which was extracted into diethyl ether, and the ether solution evaporated; yield 177 mg (87%) of a white foamy solid. Anal. for $\text{C}_{35}\text{H}_{50}\text{N}_4\text{O}_{16}\text{Si}$: C, H. ^1H NMR: δ 0.04 and 0.05 (6 H, s $\times 2$, SiMe_2), 0.85 (9 H, s, *t*-Bu), 1.32 and 1.54 (6 H, s $\times 2$, isopropylidene), 1.90 (3 H, d, J 1.2 Hz, Me-5T), 2.09 (7 H, m, MeCO $\times 2$ and H_A in H-2'T), 2.46 (1 H, m, H_B in H-2'T), 3.75 (1 H, dd, H_A in H-5'U), 3.88 (1 H, dd, H_B in H-5'U), 4.21 (1 H, m, H-4'T), 4.32 (3 H, m, H-4'U and H-5'T), 4.63 (1 H, dd, H-2'U), 4.70 (1 H, dd, H-3'U), 5.17 (1 H, m, H-3'T), 5.68 (1 H, d, J 8.2 Hz, H-5U), 5.90 (1 H, d, J 2.6 Hz, H-1'U), 5.98 and 5.99 (2 H, AB, J 9.1 Hz, CH_2 -3U), 6.02 (2 H, s, CH_2 -3T) 6.27 (1 H, dd, H-1'T), 7.25 (1 H, d, J 1.2 Hz, H-6T), 7.68 (1 H, d, J 8.2 Hz, H-6U). ^{13}C NMR: δ -5.61 and 5.51 (SiMe), 13.19 (Me-5T), 18.25 (C in *t*-Bu), 20.76

and 20.82 (MeCO), 25.27 (Me in isopropylidene), 25.77 (Me in *t*-Bu), 27.19 (Me in isopropylidene), 37.58 (C-2T), 63.25 (C-5'U), 63.76 (C-5'T), 66.60 and 66.84 (CH_2 -3U and CH_2 -3T), 74.05 (C-3T), 80.21 (C-3'U), 82.21 (C-4T), 85.57 and 85.61 (C-1'T and C-2'U), 86.90 (C-4'U), 92.85 (C-1'U), 101.28 (C-5U), 110.60 (C-5T), 113.98 (C in isopropylidene), 133.49 (C-6T), 139.39 (C-6U), 149.98 and 150.10 (C-2U and C-2T), 152.05 (OCO_2), 161.26 (C-4U), 161.93 (C-4T), 170.08 and 170.31 (MeCO).

(3',5'-*Di*-*O*-acetylthymidin-3-yl)methyl (uridin-3-yl)methyl carbonate (10). (5'-*O*-*tert*-Butyldimethylsilyl-2',3'-*di*-*O*-isopropylideneuridin-3-yl)methyl (3',5'-*di*-*O*-acetylthymidin-3-yl)methyl carbonate (40.9 mg, 0.0504 mmol) in trifluoroacetic acid–methanol (2:1; 2 ml) was stirred at ambient temperature for 1 h and evaporated. Methanol was added and evaporated off again ($\times 3$). Flash chromatography of the residue on silica gel using chloroform–methanol (9:1) gave 26.8 mg of a white material after drying at ambient temperature/0.05 mmHg for 12 h. NMR showed that the product dried under these conditions contained some chloroform, ratio 2:1; calculated yield 24.6 mg (74%). ^1H NMR (200 MHz): δ 1.91 (3 H, s), 2.05–2.3 (7 H, m), 2.5 (1 H, m), 3.48 (1 H, br s), 3.7–4.0 (3 H, m), 4.09 (1 H, br s), 4.2–4.45 (5 H, m), 4.50 (1 H, br s), 5.20 (1 H, m), 5.65–5.85 (2 H, m), 5.93 and 5.99 (4 H, s $\times 2$), 6.25 (1 H, m), 7.33 (1 H, s), 7.85 (1 H, d, J 8.3 Hz). MS (ESI): 1335 (100, $2M + \text{Na}$), 679 (93, $M + \text{Na}$), 657 (55, $M + \text{H}$).

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