One-step Synthesis of 5′-Azido-nucleosides †

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Regioselective azidation of unprotected or appropriately protected nucleosides was conducted by means of the reagent triphenylphosphine–carbon tetrabromide–lithium azide. By use of this reagent, 5′-azido-5′-deoxy-nucleosides were prepared conveniently in one step from nucleosides in high yields. Secondary hydroxy-groups of appropriately 5′-protected nucleosides were also converted by the reagent to azido-functions with complete inversion.

AMINO-NUCLEOSIDES have been increasing in importance since their derivatives such as polyoxin,[1] puromycin,[2] and tubercidin [3] have been shown to have potential bio-activity. Amino-nucleosides have been conventionally synthesised *via* azido-nucleosides as the synthetic intermediates. The azido-nucleosides were often prepared *via* the sulphonylation reaction of appropriately protected nucleosides followed by nucleophilic displacement of the sulphonates with metal azide,[4] or by the ring opening reaction of cyclo-nucleosides with metal azide.[5]

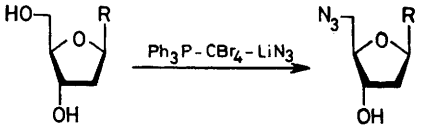
On the other hand, Moffatt [6] has reported regio-selective one-step halogenation of the 5′-hydroxy-group of unprotected nucleosides by means of a combination of tervalent phosphorus compounds and carbon tetra-halides. Mitsunobu [7] reported the use of triphenyl-phosphine–diethyl azodicarboxylate as a reagent for the synthesis of amino-nucleoside derivatives. Castro [8] also reported the preparation of azido-sugars by the reaction of unprotected sugars with carbon tetrachloride and hexamethylphosphoric triamide, followed by the treatment of the resulting alkoxyphosphonium salt with sodium azide. Recently, we reported [9] that 5′-(alkyl or aryl)thio-5′-deoxynucleosides were obtained selectively by the reaction of unprotected nucleosides with dialkyl (or diaryl) disulphides and tervalent phosphorus compounds such as triphenylphosphine or tri-n-butyl-phosphine under very mild conditions. These reactions were thought to proceed *via* nucleophilic attack of thiolate ions, formed from the combined reagents, on the activated 5′-carbons of nucleoside derivatives.

In connection with synthetic studies of nucleotide derivatives [10] having a P–N bond including amino-nucleosides, our interest was focused on the selective synthesis of 5′-azidonucleosides from unprotected nucleosides by a one-step procedure. Therefore, the reaction of nucleosides with phosphonium salts in the presence of metal azides was studied since the azide ion behaves as a strong nucleophile.

RESULTS AND DISCUSSION

First, direct conversion of unprotected thymidine (1a) to 5′-azido-5′-deoxythymidine (2a) was examined by means of the following reagents in the presence of an excess of metal azide: methyltriphenoxyphosphonium iodide, triphenylphosphine–diethyl azodicarboxylate, triphenylphosphine–carbon tetrahalides, and tri-n-butylphosphine–carbon tetrahalides. In order to find optimum conditions for the direct 5′-azidation of thymidine, the order of mixing of reagents, metal azides, and solvents was varied, and the reaction conditions and results are summarized in Table 1

We found that the most effective combination was triphenylphosphine–carbon tetrabromide–lithium azide, which gave the best yield (90%) of (2a). Lithium azide



(1) (2)

a; R = thymine
b; R = N^6-benzoyladenine
c; R = N^4-benzoylcytosine

has the advantage of being easily soluble in dry DMF compared with sodium azide, so that the reaction can be conducted in homogeneous solution. If the reaction system contains even a small amount of water, the reaction does not proceed satisfactorily. Dryness of lithium azide and nucleoside derivatives was most important in the azidation reactions. It should be noted that under the reaction conditions by-products such as 5′-bromo-5′-deoxythymidine and cyclothymidine were not detected. A plausible explanation for the superiority of carbon tetrabromide over carbon tetrachloride may be that the nucleophilicity of Br^- ion in DMF may be poorer than that of Cl^- ion [11] so that the N_3^- ion attacks more effectively the 5′-carbon atom of the sugar moiety.

There is an alternative route whereby unprotected nucleosides are initially converted to the 5′-halogeno-5′-deoxy-nucleosides by treatment with triphenylphosphine and carbon tetrahalides, and then the halogeno-nucleosides formed were further treated with lithium azide (without isolating them) to give the 5′-azido-5′-deoxy-nucleosides.

However, in this manner, (2a) was obtained in an unsatisfactory yield (50%), using methyltriphenoxyphosphonium iodide at the first stage.

† Preliminary report, T. Hata, I. Yamamoto, and M. Sekine, *Chemistry Letters*, 1975, 977.

TABLE 1

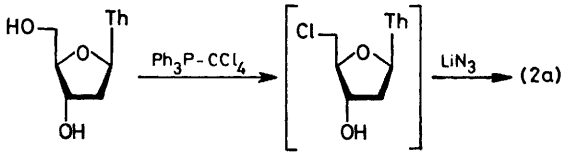
Preparation of 5′-azido-5′-deoxythymidine

Reagent(s) (mmol) (A)	(B)	LiN_3 (mmol)	(1a) (mmol)	Mixing order and temperature [a]	Solvent	Time/h	Yield (%)
[$(PhO)_3PMe$][I] (3.2)		5.4 [b]	2.67	(1a) $\xrightarrow[\text{r.t.}]{(A)}$ $\xrightarrow[57\ °C]{NaN_3}$	DMF	0.16 + 3	50
Ph_3P (0.5)	$EtO_2CN{=}NCO_2Et$ (0.5)	0.5	0.4	A + B + LiN_3 $\xrightarrow[\text{r.t.}]{(1a)}$	DMF	21	46
Ph_3P (0.7)	$EtO_2CN{=}NCO_2Et$ (1.5)	1.5	0.5	(1a) + LiN_3 $\xrightarrow[\text{r.t.}]{(B)}$	DMF	4.5	36
Ph_3P (2.0)	CCl_4 (6.0)	6.0	2.0	(1a) + (A) + LiN_3 $\xrightarrow[\text{r.t.}]{(B)}$	DMF	21	86
Ph_3P (2.7)	CCl_4 (10.0)	4.0	2.0	(1a) + A $\xrightarrow[\text{r.t.}]{(B)}$ $\xrightarrow{\text{dist.}}$ $\xrightarrow[80\ °C]{LiN_3}$	DMF	21 + 2.5	78
Ph_3P (0.7)	CCl_4 (0.5)	1.5	0.5	(1a) + (A) + LiN $\xrightarrow[\text{r.t.}]{(B)}$	Pyridine	27	36
Ph_3P (2.04)	CBr_4 (2.04)	10.0	2.0	(1a) + (A) + LiN_3 $\xrightarrow[\text{r.t.}]{(B)}$	DMF	24	90
Ph_3P (2.04)	CI_4 (2.04)	10.0	2.0	(1a) + (A) + LiN_3 $\xrightarrow[\text{r.t.}]{(B)}$	DMF	17	68
Bu_3P (1.02)	CCl_4 (1.02)	5.0 [b]	1.0	(1a) + (A) + NaN_3 $\xrightarrow[\text{r.t. } 85\ °C]{(B)}$	DMF	3 + 15	56

[a] r.t. = Room temperature. [b] Sodium azide was used in place of lithium azide.

Moffatt [6] reported that a combination of triphenylphosphine and carbon tetrachloride was the most successful halogenating reagent compared with other combinations, such as triphenylphosphine–carbon tetraiodide or triphenylphosphine–carbon tetrabromide, as far as the yields of 5′-halogeno-5′-deoxynucleosides were concerned.

We tried the reaction of thymidine with triphenylphosphine–carbon tetrachloride followed by successive treatment with lithium azide at room temperature for 25 h; (2a) was obtained in 78% yield through the two-step reaction.

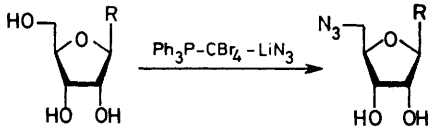


(1a)

The above two experiments indicate that the stepwise method *via* halogeno-nucleosides gave more difficult separation of the desired products from the by-products, and gave relatively lower yields, as compared with the one-step procedure with triphenylphosphine–carbon tetrabromide (or carbon tetrachloride)–lithium azide.

This method using triphenylphosphine–carbon tetrabromide—lithium azide was also applicable to the synthesis of 5′-azido-5′-deoxynucleosides: N^6-benzoyldeoxyadenosine and N^4-benzoyldeoxycytidine were successfully converted to the corresponding azido-nucleosides (2b) and (2c) in 66% and 71% yields, respectively. In these cases, by-products such as 5′-halogeno-2′,5′-dideoxynucleosides and cyclonucleosides were not detected at all.

Similarly, from appropriately protected ribonucleosides (3a—c), several 5′-azido-5′-deoxyribonucleosides (4a—c) could be obtained in satisfactory yields as shown in Table 2.



(3) (4)

a; R = uracil
b; R = N^6-benzoyladenine
c; R = N^4-benzoylcytosine

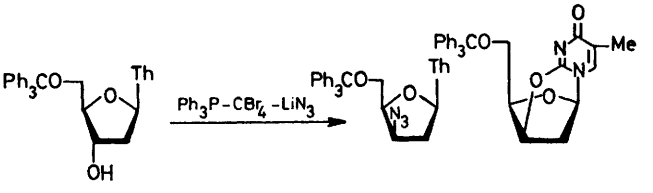
Next, the direct conversion of secondary hydroxy-groups of nucleosides to the azido-group was examined. 5′-*O*-Tritylthymidine (5) treated with triphenylphosphine–carbon tetrabromide–lithium azide (1 : 1 : 5 equiv.) in DMF for 17 h gave a *threo*-isomer, 1-(3-azido-3-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (6), in 45% yield. In this reaction, the *erythro*-isomer, 3′-azido-3′-deoxy-5′-*O*-tritylthymidine (7), could not be detected and 5′-*O*-trityl-2,3′-anhydrothymidine (8) was formed to some extent (t.l.c.). When the reaction was performed with a small excess of triphenylphosphine–carbon

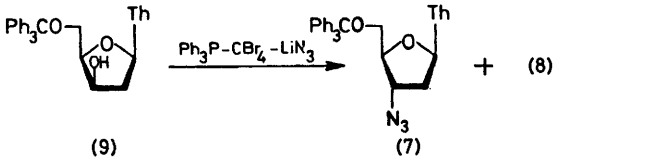
TABLE 2

Preparation of 5′-azido-5′-deoxynucleosides

Nucleoside	Ph_3P (equiv.)	CBr_4 (equiv.)	LiN_3 (equiv.)	Time/h	Yield (%)
Thymidine (1a)	1.02	1.02	5	24	90
N^6-Benzoyl-deoxyadenosine (1b)	1.02	1.02	5	27	66
N^4-Benzoyl-deoxycytidine (1c)	1.02	1.02	5	27	71
Uridine (3a)	1.30	1.50	3	24	92
N^6-Benzoyladenosine (3b)	1.02	1.02	5	24	56
N^4-Benzoylcytidine (3c)	1.00	1.00	5	18	46

tetrabromide and a large excess of lithium azide, (6) and (8) were obtained in 69 and 20% yields, respectively. In the above reactions, when hexamethylphosphoric triamide (HMPA) was chosen as the solvent, compound (8) could not be detected but the yield of compound (6) decreased to 38%. 5′-*O*-Trityluridine and 2′,5′-di-*O*-trityluridine did not react with triphenylphosphine–carbon tetrabromide–lithium azide under the conditions described above.





Next, a stereoisomer of (5), 1-(2-deoxy-5-*O*-trityl-β-D-xylofuranosyl)thymine (9), having the *threo* configuration, was allowed to react with triphenylphosphine–carbon tetrabromide–lithium azide in DMF. This reaction gave predominantly the *erythro* isomer (7) in 67% yield, and a trace amount of (6) was detected (t.l.c.). The configuration of (6) and (7) was determined on the basis of n.m.r. spectral considerations. It has been recognised [6] that the C-2′ protons in 3′-halogeno-2′,3′-deoxynucleosides with the *threo* configuration have markedly different chemical shifts, and are separated from each other by 0.5—1.0 p.p.m.; and also that, in compounds with the *erythro* configuration, the coupling constants between the C-1′ and the two C-2′ protons $J_{1',2a}$ and $J_{1',2b}$) are very similar and C-1′-H appears as a triplet, while in the *threo* compounds, the coupling constants between the C-1′ and the two C-2′ protons are different and C-1′-H appears as a quartet.

The 100-MHz n.m.r. spectrum of (6) revealed that C-1′-H appears as a triplet with a coupling constant of 6.4 Hz and the two C-2′ protons have the same chemical shift and are coupled equally with both C-1′-H and C-3′-H (J 6.4 Hz). On the other hand, the n.m.r. spectrum of (7) showed that C-1′-H appears as a double doublet at δ 6.11 and has different coupling constants with the two C-2′ protons ($J_{1',2'a}$ 3.1, $J_{1',2'b}$ 7.5 Hz). Moreover, the two C-2′ protons of (7) appear at δ 2.06 and 2.66 and a large *gem*-coupling between them (J_{gem} 14.8 Hz) was observed, while, in the n.m.r. spectrum of (7), such *gem*-coupling was not observed at all. Such a phenomenon has also been reported in the case of 3′-substituted-halogenonucleosides.[6] The configuration of (7) was also confirmed by direct comparison with an authentic sample prepared by the ring-opening reaction of (8) with sodium azide.[12] The reagent of triphenylphosphine–carbon tetrabromide–lithium azide proved to be useful because the reagent converted the secondary hydroxy-groups of thymidine derivatives stereospecifically into azido-groups with almost complete inversion. The utility of this reagent might be emphasised by comparison with the azidation of 3′-iodo-3′-deoxy-5′-*O*-tritylthymidine (10) with sodium azide in DMF at 100 °C for 30 min, which gave a mixture of (6) and (7) in the ratio of 43 : 57.

It is concluded that the present method provides a practical and convenient synthesis of azido-nucleosides, which useful synthetic intermediates of amino-nucleosides, by a one-step procedure under very mild conditions, and that the reactions proceed regioselectivity and stereospecifically.

EXPERIMENTAL

I.r. spectra were recorded on a Hitachi 124 spectrophotometer, and n.m.r. spectra on a JEOL JNM-4H-100 spectrometer. In all experiments atmospheric moisture was carefully excluded (P_4O_{10}, argon atmosphere, serum caps). Lithium azide was prepared from sodium azide and lithium sulphate according to the literature procedure,[13] and was exhaustively dried under reduced pressure before use. Dimethylformamide was distilled after being dried over P_4O_{10} and stored over molecular sieves. Pyridine was distilled over toluene-*p*-sulphonyl chloride and stored over calcium hydride. Triphenylphosphine as purchased was recrystallised from benzene. Carbon tetrachloride was distilled after being dried over P_4O_{10}, and stored over P_4O_{10}. Carbon tetrabromide was purchased and dried *in vacuo* before use. Carbon tetraiodide was prepared by the procedure given in the literature.[14] Methyltriphenoxyphosphonium iodide and diethyl azodicarboxylate were prepared according to the literature procedures.[6,15] n-Butylphosphine was freshly distilled before use. Silica gel (Wakogel (C-200) was purchased from the Wako Chemical Co. All nucleosides derivatives for azidation were dried over P_4O_{10} at 100 °C *in vacuo* overnight before use. 1-(2-Deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine (10) was prepared by the ring-opening reaction from 5′-*O*-trityl-2,3′-anhydrothymidine [16] according to the literature procedure.[17]

5′-Azido-5′-deoxythymidine (2).—*Method using carbon tetrabromide–triphenylphosphine.* To a mixture of thymidine (484 mg, 2.0 mmol), triphenylphosphine (535 mg, 2.04 mmol), and lithium azide (490 mg 10 mmol) in dry DMF (10 ml) was added carbon tetrabromide (677 mg, 2.04 mmol) at room temperature, with vigorous stirring to make a homogeneous solution. The mixture was stirred for a further 24 h and then methanol (1 ml) was added. After the usual work-up, column chromatography on silica gel (80 g) eluted a crude product with $CHCl_3$–MeOH (9 : 1, v/v) which was purified by recrystallisation from methanol to give (2a) (489 mg, 90%), m.p. 164—166.5 °C; $\nu_{max.}$ (KBr) 2 100 cm^{-1}; δ ($CDCl_3$–DMSO, 1 : 1 v/v) 1.88 (3 H, s, Me), 2.22 (2 H, dd, $J_{2',3'}$ 5 Hz, C-2′-H), 3.57 (1 H, d, $J_{4',5'a}$ 5.3 Hz, C-5′a-H), 3.57 (1 H, d, $J_{4',5'b}$ 3.8 Hz, C-5′b-H), 3.92 (1 H, m, C-4′-H), 4.25 (1 H, m, C-3′-H), 5.23 (1 H, m, OH), 6.24 (1 H, t, $J_{1',2'}$ 7 Hz, C-1′-H), 7.33 (1 H, s, C-5-H), and 11.06 (1 H, br s, NH) (Found: C, 44.85; H, 4.85; N, 26.5. $C_{10}H_{13}N_5O_4$ requires C, 44.95; H, 4.90; N, 26.21%).

Method using methyltriphenoxyphosphonium iodide. Thymidine (646 mg, 2.67 mmol) and freshly prepared methyltri-

phenoxyphosphonium iodide (1.424 g, 3.2 mmol) were dissolved in dry DMF (10 ml). After stirring the mixture at room temperature for 10 min, lithium azide (352 mg, 5.4 mmol) was added and the mixture was heated at 57 °C for 3 h, then methanol (1 ml) was added. After cooling to room temperature, sodium thiosulphate was added until the brown colour disappeared. The solvent was removed *in vacuo*, and chromatography on a column of silica gel (75 g) [$CHCl_3$–MeOH (9 : 1, v/v)] gave (2a) (356 mg, 50%); $\nu_{max.}$ (KBr) 2 100 cm^{-1}.

Method via *5'-chloro-5'-deoxythymidine*. To a mixture of thymidine (484 mg, 2.0 mmol) and triphenylphosphine (750 mg, 2.7 mmol) in dry DMF (10 ml) was added carbon tetrachloride (1.0 ml, 10 mmol), and the mixture was stirred at room temperature for 21 h. After reaction was complete, excess of carbon tetrachloride was removed *in vacuo*, lithium azide (196 mg, 4 mmol) was added, the resulting mixture was stirred at 80 °C for 2.5 h, and then methanol (1 ml) was added. The solvent was removed and chromatography on a column of silica gel (75 g) [$CHCl_3$–MeOH (9 : 1, v/v)] gave compound (2a) (415 mg, 78%), m.p. 163—167 °C; $\nu_{max.}$ (KBr) 2 100 cm^{-1}.

5'-Azido-2',5'-dideoxy-N⁶-benzoyladenosine (2b).—To a mixture of N^6-benzoyl-2'-deoxyadenosine (850 mg, 2.15 mmol), triphenylphosphine (574 mg, 2.19 mmol), and lithium azide (526 mg, 10.74 mmol) in dry DMF (10 ml) was added carbon tetrabromide (727 mg, 2.19 mmol). The mixture was stirred at room temperature for 27 h, then methanol (1 ml) was added, and the solvent was removed *in vacuo*; chromatography on a column of silica gel (60 g) (eluant $CHCl_3$–MeOH, 9 : 1 v/v) eluted first triphenylphosphine oxide and then fractions containing (2b). Solvent was removed and the residual syrup was dissolved in tetrahydrofuran and poured into an excess of light petroleum. The precipitate was collected by filtration and dried over P_4O_{10}; (2b) (594 mg, 66%), m.p. 102 °C (decomp.); $\nu_{max.}$ (KBr) 2 100 cm^{-1}; δ ($CDCl_3$–DMSO, 1 : 1 v/v) 2.80 (2 H, t, $J_{2',3'}$ 7.5 Hz, C-2'-H), 3.58 (1 H, d, $J_{4',5'a}$ 3.5 Hz, C-5'a-H), 3.67 (1 H, d, $J_{4',5'b}$ 5.0 Hz, C-5'b-H), 4.07 (1 H, m, C-4'-H), 4.52 (1 H, m, C-3'-H), 5.38 (1 H, br d, J 4 Hz, OH), 6.50 (1 H, t, $J_{1',2'}$ 7.5 Hz, C-1'H), 7.30—7.67 (3 H, m, Ar), 7.88—8.18 (2 H, m, Ar), 8.38 and 8.65 (2 H, s, C-2-H and C-8-H), and 10.61 (1 H, br s, NH) (Found: C, 53.75; H, 4.4; N, 27.85. $C_{17}H_{16}N_8O_3$ requires C, 53.66; H, 4.51; N, 27.68%).

5'-Azido-2',5'-dideoxy-N⁴-benzoylcytidine (2c).—To a mixture of N^4-benzoyl-2'-deoxycytidine (994 mg, 3 mmol), triphenylphosphine (803 mg, 3.06 mmol), and lithium azide (735 mg, 5 mmol) in dry DMF (15 ml) was added carbon tetrabromide (1.015 g, 3.06 mmol). The mixture was stirred at room temperature for 27 h, methanol (1 ml) was added, solvent was removed *in vacuo*, and chromatography on a column of silica gel (80 g) [eluant $CHCl_3$–MeOH (95 : 5, v/v)] gave a syrup which was crystallised from methanol to give (2c) (772 mg, 72%), m.p. 147 °C; $\nu_{max.}$ (KBr) 2 100 cm^{-1}; δ ($CHCl_3$–DMSO, 1 : 1 v/v) 2.25 (2 H, t, $J_{2',3'}$ 6.5 Hz, C-2'-H), 3.64 (1 H, d, $J_{4',5'a}$ 5 Hz, C-5'a-H), 3.65 (1 H, d, $J_{4',5'b}$ 4.5 Hz), 4.00 (1 H, m, C-4'-H), 4.18 (1 H, m, C-3'-H), 5.32 (1 H, br d, J 4.2 Hz, OH), 6.19 (1 H, t, $J_{1',2'}$ 6.5 Hz, C-1'-H), 7.30—7.63 (4 H, m, Ar and C-5-H), 7.88—8.18 (3 H, m, Ar and C-5-H), 10.95 (1 H, br s, NH) (Found: C, 53.65; H, 4.45; N, 23.2. $C_{16}H_{16}N_6O_4$ requires C, 53.93; H, 4.53; N, 23.58%).

5'-Azido-5'-deoxyuridine (4a).—To a mixture of uridine (488 mg, 2 mmol), triphenylphosphine (750 mg, 2.9 mmol), and lithium azide (294 mg, 6 mmol) in dry DMF (10 ml) was added carbon tetrabromide (995 mg, 3 mmol). The mixture was stirred at room temperature for 4 h, the solvent was removed *in vacuo*, and chromatography on a column of silica gel (75 g) [eluant $CHCl_3$–MeOH (5 : 1, v/v)] gave compound (4a) (500 mg, 92%), m.p. 150—150.5 °C (decomp.); $\nu_{max.}$ (KBr) 2 100 cm^{-1}; δ ($CDCl_3$–DMSO, 1 : 1 v/v) 3.59 (2 H, m, C-5'-H), 3.80—4.33 (3 H, m, C-2', -3', and -4'-H), 5.61 (1 H, d, $J_{5,6}$ 7.6 Hz, C-6-H), 5.77 (1 H, d, $J_{1',2'}$ 3.7 Hz, C-1'-H), 7.10 (3 H, br, NH and OH), and 7.53 (1 H, d, $J_{5,6}$ 7.6 Hz, C-5-H) (Found: C, 40.15; H, 4.05; N, 25.8. $C_9H_{11}N_5O_5$ requires C, 40.15; H, 4.12; N, 26.01%).

5'-Azido-5'-deoxy-N⁶-benzoyladenosine (4b).—To a mixture of N^6-benzoyladenosine [17] (557 mg, 1.5 mmol), triphenylphosphine (469 mg, 1.56 mmol), and lithium azide (367 mg, 7.5 mmol) in dry DMF (7.5 ml) was added carbon tetrabromide (517 mg, 1.56 mmol). The mixture was stirred at room temperature for 24 h, methanol (1 ml) was added, the reaction was left at room temperature for 30 min, and then solvent was removed *in vacuo*. Chromatography of the residue on a column of silica gel (80 g) eluted first triphenylphosphine oxide [$CHCl_3$–MeOH (95 : 5, v/v)] and then (4b) (337 mg, 56%) ($CHCl_3$–MeOH (9:1, v/v)], m.p. 171 °C (decomp.); $\nu_{max.}$ (KBr) 2 100 cm^{-1}; δ ($CDCl_3$–DMSO, 1 : 1 v/v) 3.64 (1 H, d, $J_{4',5'a}$ 4.2 Hz, C-5'a-H), 3.72 (1 H, d, $J_{4',5'b}$ 6.4 Hz, C-5'b-H), 4.03—4.50 (2 H, m, C-3'- and -4'-H), 4.78 (1 H, m, C-2'-H), 5.24 and 5.53 (2 H, d, J 5.0 Hz, OH), 6.10 (1 H, d, $J_{1',2'}$ 4.9 Hz, C-1'-H), 7.30—7.63 (3 H, m, Ar), 7.90—8.20 (2 H, m, Ar), 8.53 and 8.68 (2 H, s, C-2-H and C-8-H), and 10.96 (1 H, br s, NH) (Found: C, 51.1; H, 4.25; N, 27.85. $C_{17}H_{16}N_8O_4$ requires C, 51.03; H, 4.23; N, 27.75%).

5'-Azido-5'-deoxy-N⁴-benzoylcytidine (4c).—N^4-Benzoylcytidine (868 mg, 2.5 mmol), triphenylphosphine (656 mg, 2.5 mmol), and lithium azide (613 mg, 12.5 mmol) were suspended in dry DMF (10 ml), and to the suspension was added carbon tetrabromide (829 mg, 2.5 mmol). After a few minutes, the reaction mixture became clear; it was stirred at room temperature for 18 h, methanol (1 ml) was added, the mixture was left at room temperature for 30 min, and the solvent was then removed *in vacuo*. Chromatography on a column of silica gel (150 g) gave first triphenylphosphine oxide [$CHCl_3$–MeOH (95 : 5, v/v)] and then (4c) [$CHCl_3$–MeOH (9 : 1, v/v)] (430 mg, 46%), m.p. 175—178 °C (decomp.); $\nu_{max.}$ (KBr) 2 100 cm^{-1}; δ($CDCl_3$–DMSO, 1 : 1 v/v) 3.70 (2 H, m, C-5'-H), 3.90—4.28 (3 H, m, C-2',-3'-, and -4'-H), 5.08 and 5.45 (2 H, br d, J 5.0 Hz, OH), 5.83 (1 H, d, $J_{1',2'}$ 2.2 Hz, C-1'-H), 7.28—7.65 (4 H, m, Ar and C-5-H), 7.85—8.20 (3 H, m, Ar and C-6-H), and 11.05 (1 H, br s, NH) (Found: C, 51.35; H, 4.4; N, 22.6. $C_{16}H_{16}N_6O_6$ requires C, 51.61; H, 4.33; N, 22.57%).

1-(3-Azido-2,3-dideoxy-5-O-trityl-β-D-threo-pentofuranosyl)-thymine (6).—(*A*) To a mixture of 5'-tritylthymidine (563 mg, 1 mmol), triphenylphosphine (262 mg, 1 mmol), and lithium azide (245 mg, 5 mmol) in dry DMF (5 ml) was added carbon tetrabromide (563 mg, 1 mmol). The mixture was stirred at room temperature for 17 h, methanol (1 ml) was added, and after continuous stirring for an additional 30 min, chloroform was added, and the white precipitate of unreacted lithium azide was filtered off. The filtrate was concentrated and DMF was completely removed *in vacuo*. Chromatography on a column of silica gel (20 g) eluted first [$CHCl_3$–MeOH (95 : 5, v/v)] triphenylphosphine oxide, then (6) contaminated with triphenylphosphine oxide in the second fraction, and finally a mixture of 5'-*O*-tritylthymidine and 5'-*O*-trityl-2,3'-anhydrothymidine. Compound (6) was

purified from triphenylphosphine oxide by repeated chromatography on silica gel (15 g) eluting with CH_2Cl_2–EtOAc (6 : 1, v/v). The product eluted was homogeneous on t.l.c. and was recrystallised from PriOH to give (6) (231 mg, 45%), which softened at 85 and decomposed at 105 °C; $\nu_{max.}$ (*KBr*) 2 100 cm^{-1}, $\delta(CDCl_3)$ 1.81 (3 H, s, Me), 2.06 (1 H, ddd, $J_{gem\text{-}2'a,2'b}$ 14.8 Hz, $J_{1',2'a}$ 3.1 Hz, $J_{2'a\ 3'}$ 1 Hz, C-2'a-H), 2.66 (1 H, ddd, $J_{gem\text{-}2'a\ 2'b}$ 14.8 Hz, $J_{1',2'b}$ 7.6 Hz, $J_{2'b,3'}$ 5.5 Hz, C-2'b-H), 3.29 (1 H, dd, $J_{gem\text{-}5'a,5'b}$ 10 Hz, $J_{5'a,4'}$ 5.4 Hz, C-5'a-H), 3.59 (1 H, dd, $J_{gem\text{-}5'a,5'b}$ 10 Hz, $J_{5'b,4'}$ 5.6 Hz, C-5'b-H), 3.91—4.28 (2 H, m, C-3'- and -4'-H), 6.11 (1 H, dd, $J_{1',2'a}$ 3.1 Hz, $J_{1',2'b}$ 7.5 Hz, C-1'-H), 7.08—7.62 (16 H, m, ArH and C-6-H), and 9.71 (1 H, br s, NH) (Found: C, 67.4; H, 5.55; N, 13.2. $C_{29}H_{27}N_5O_4$ requires C, 67.63; H, 5.47; N, 13.42%).

(*B*) To a mixture of 5'-*O*-tritylthymidine (1.689 g, 3 mmol), triphenylphosphine (835 mg, 3.2 mmol), and lithium azide (735 mg, 15 mmol) in dry DMF (10 ml) was added carbon tetrabromide (1.089 g, 3.25 mmol). The mixture was stirred at room temperature for 44 h. After the work-up described in (*A*) (6) (1.05 g, 69%) was obtained. It softened at 75 and decomposed at 105 °C. 5'-*O*-Trityl-2,3'-anhydrothymidine (293 mg, 20%) was also isolated (Found: C, 68.15; H, 5.8. $C_{29}H_{27}N_5O_4$ requires C, 68.36; H, 5.34).

(*C*) To a mixture of 5'-*O*-tritylthymidine (1.125 g, 2 mmol), triphenylphosphine (524 mg, 2 mmol), and lithium azide (490 mg, 10 mmol) in dry HMPA (10 ml) was added carbon tetrabromide (664 mg, 2 mmol), and the mixture was stirred at room temperature for 16 h. In this reaction, a considerable amount of nitrogen gas was evolved when carbon tetrabromide was added. Methanol (1 ml) was added to the mixture, it was stirred for 30 min, then poured into ice–water (500 ml) and the precipitate was collected and dried. Chromatography of the precipitate as described in (*A*) gave compound (6) (385 mg, 38%); compound (8) was not detected at all.

Azidation of 5'-O-Trityl-3'-iodo-3'-deoxythymidine (10).—5'-*O*-Trityl-3'-iodo-3'-deoxythymidine [6] (800 mg, 1.35 mmol) was mixed with sodium azide (880 mg, 13.5 mmol) in dry DMF (10 ml) and the mixture was heated at 100 °C for 30 min. After cooling the mixture, solvent was removed *in vacuo*, the residue was treated with water (50 ml), and the precipitate was collected and washed with water to give a crude mixture of (6) and (7) in the ratio of 43 : 57 (650 mg, 95%). It was purified by column chromatography on silica gel, eluting first with CH_2Cl_2 and then with CH_2Cl_2–EtOAc (6 : 1, v/v). The purified material softened at 75 and decomposed at 105 °C.

5'-O-Trityl-3'-azido-3'-deoxythymidine (7).—To a mixture of 1-(2-deoxy-5-*O*-trityl-β-D-xylofuranosyl)thymine (727 mg, 1.5 mmol) and triphenylphosphine (401 mg, 1.53 mmol) in dry DMF (5 ml) was added carbon tetrabromide (508 mg, 1.53 mmol), and the mixture was stirred at room temperature for 43 h. Then methanol (1 ml) was added, the reaction was set aside at room temperature for an additional 30 min, and the solvent was then removed *in vacuo*. Chloroform was added to the residue and the white precipitate was filtered off; the filtrate was concentrated and then chromatographed on a column of silica gel (40 g) [eluant $CHCl_3$–MeOH (95 : 5, v/v)] to yield fractions containing (7) contaminated with a small amount of triphenylphosphine oxide and a trace amount of (6). Further chromatography on silica gel (30 g) [eluant CH_2Cl_2–EtOAc (6 : 1 v/v)] gave (7) contaminated with a trace amount of (6), and a final chromatographic run on a column on silica gel (15 g) [eluant carbon tetrachloride–tetrahydrofuran (6 : 1 v/v] gave pure (7) (508 mg, 67%), which softened at *ca.* 60 and decomposed at 97 °C. An analytical sample was obtained by precipitation from tetrahydrofuran solution by addition of an excess of ether–light petroleum; $\nu_{max.}$ (KBr) 2 100 cm^{-1}; $\delta(CDCl_3)$ 1.53 (3 H, s, Me), 2.43 (2 H, t, $J_{1',2'}$ $J_{2',3'}$ = 6.4 Hz, C-2'-H), 3.30 (1 H, dd, $J_{5'a,4'}$ 3.0 Hz, $J_{5'a,5'b}$ 10.4 Hz, C-5'a-H), 3.56 (1 H, dd, $J_{5'b,4'}$ 2.8 Hz, $J_{5'a,5'b}$ 10.4 Hz, C-5'b-H), 3.95 (1 H, m, C-4'-H), 4.31 (1 H, m, C-3'-H), 6.22 (1 H, t, C-1'-H), 7.12—7.60 (16 H, m, Ar and C-6-H), 9.53 (1 H, br s, NH) (Found: C, 68.7; H, 5.85; N, 12.7. $C_{29}H_{27}N_5O_4$ requires C, 68.57; H, 5.73; N, 12.74%).

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