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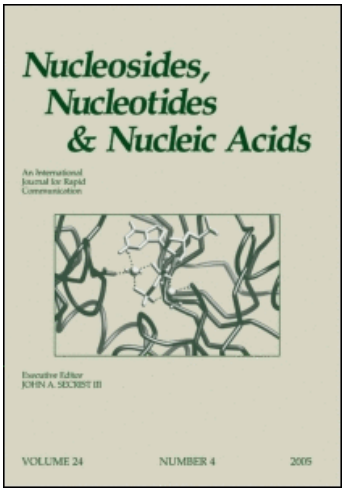

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Convenient Intermediates for the Preparation of *C*-4 Modified Derivatives of Pyrimidine Nucleosides

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NUCLEOSIDES & NUCLEOTIDES, 16(1&2), 53-65 (1997)

CONVENIENT INTERMEDIATES FOR THE PREPARATION OF *C*-4 MODIFIED DERIVATIVES OF PYRIMIDINE NUCLEOSIDES

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Abstract: 4-(4-Nitrophenoxy)-1-(β-D-ribofuranosyl)pyrimidin-2(1*H*)-one **15**, 5-methyl-4-(1,2,4-triazol-1-yl)-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1*H*)-one **7a** and 4-(4-nitrophenoxy)-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1*H*)-one **17a**, respectively, have been prepared and are recommended as reactive intermediates for the preparation of derivatives of uridine, thymidine and 2'-deoxyuridine which are modified at *C*-4.

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In recent years, considerable attention has been directed towards the synthesis of nucleoside analogues in the hope of discovering new and more effective antiviral and especially anti-HIV agents. A particularly convenient general approach to the preparation of nucleoside analogues involves the modification of the base and/or sugar residues of the principal nucleoside building blocks of deoxyribonucleic and ribonucleic acids (DNA and RNA, respectively). Where applicable, this approach has a considerable advantage over *ab initio* nucleoside synthesis in that much greater control can be exercised over both the stereochemistry and regiochemistry of the reactions involved. With regard to the synthesis of analogues of naturally-occurring pyrimidine nucleosides, modification reactions of uridine **1a** and thymidine **2a** at *C*-4 are of particular interest. Originally, such transformations were effected following an initial chlorination or thiation step[1]. However, studies directed towards the suppression of side-reactions in the phosphotriester approach to oligonucleotide synthesis led[2,3] to the development of more efficient *C*-4 modification reactions which take place under very mild conditions indeed. Thus it was found[2,3] that when 2',3',5'-tri-*O*-acetyluridine **1b** was treated with 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-1*H*-triazole (MSNT)[4] **3** in the presence of a catalytic amount of diphenyl phosphate in pyridine solution, 4-(3-nitro-1,2,4-triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)-pyrimidin-2(1*H*)-one **4a** was obtained and isolated as a crystalline solid in good yield. It was soon found[5] that this nitrotriazolation reaction was much more readily effected by

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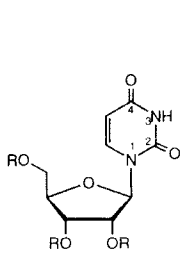
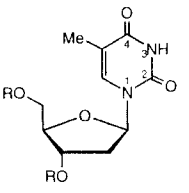
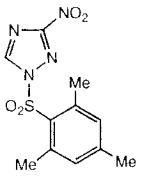
treating the substrate with 3-nitro-1,2,4-1*H*-triazole **5a** and diphenyl phosphorochloridate in pyridine solution. When the nitrotriazolo-derivative **4a** was treated[2,3] with concentrated aqueous ammonia, cytidine **6** was obtained as the only detectable nucleoside product, thereby indicating a very convenient approach to the modification of uridine at *C*-4.



1 a; R = H
b; R = Ac



2 a; R = H
b; R = Ac



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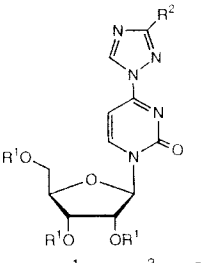
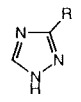
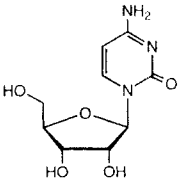


4 a; R^1 = Ac, R^2 = NO_2
b; R^1 = R^2 = H



5 a; R = NO_2
b; R = H



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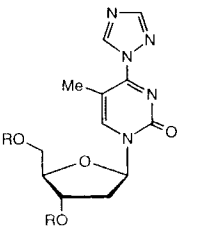
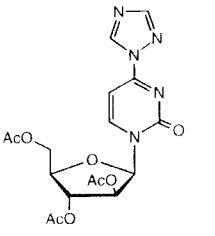


7 a; R = H



8

Following our initial study, it was reported[6] that 3',5'-di-*O*-acetyl- and 3',5'-di-*O*-(*tert*-butyldimethylsilyl)-thymidines (**2b** and **2**, R = $Me_2Si(Bu^t)$-, respectively) reacted with 1,2,4-1*H*-triazole **5b** and 4-chlorophenyl phosphorodichloridate in pyridine solution to give the corresponding triazolo-derivatives (**7**; R = Ac and $Me_2Si(Bu^t)$-, respectively). However, these reactions proceeded rather slowly[6], and we found[5] that triazolation was more readily effected by treatment with phosphorus oxychloride, 1,2,4-1*H*-triazole **5b** and triethylamine in acetonitrile. Our study was concerned mainly with the conversion of 1-(β-D-2,3,5-tri-*O*-acetyl-arabinofuranosyl)uracil into the corresponding triazolo-compound **8**. Under our reaction conditions[5], this transformation was completed in 90 min at room temperature. The product **8**, which was isolated as a crystalline solid in 80% yield, proved[5] to be a valuable intermediate in the preparation of 1-(β-D-arabino-furanosyl)cytosine (ara-C) and a number of its 4-*N*-alkyl (aryl) derivatives, all of which were obtained in high isolated yields. The phosphorus oxychloride - promoted triazolation reaction has since become very widely used[1].

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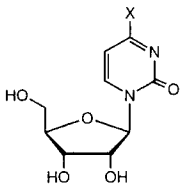

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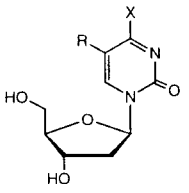
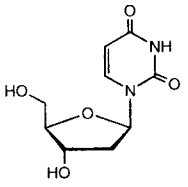


10 a; R = Me
b; R = H



11

The main purpose of the present investigation was to prepare a group of three reactive intermediates **9**, **10a** and **10b** (X = suitable leaving group) which were unprotected on their sugar hydroxy functions and which were readily susceptible to nucleophilic substitution at *C*-4 to give nucleoside analogues derived from uridine **1a**, thymidine **2a** and 2'-deoxyuridine **11**, respectively. Further essential requirements for the selected intermediates were that they should be easy to prepare and that they should be readily isolable as stable crystalline solids in good yields. Intermediates with unprotected sugar hydroxy functions were required for two reasons. First, it was considered desirable to minimize contamination with by-products in the nucleophilic substitution reactions. Secondly and more importantly, it was envisaged that such intermediates could readily be converted into suitably-protected 3'-phosphoramidites (or other such mononucleotide building blocks), and then incorporated into RNA and DNA molecules containing specific sites for subsequent base-modifications.

As a number of 4-(1,2,4-triazol-1-yl) intermediates had been used successfully in nucleoside modification reactions, it was decided to attempt first to convert uridine **1a** and thymidine **2a** into the corresponding unprotected triazolo-compounds **4b** and **7a**, respectively. Following Jones's temporary trimethylsilyl protection procedure[7], uridine **1a** was first allowed to react with chlorotrimethylsilane and triethylamine in acetonitrile (Scheme 1a). Triazolation was then effected in the usual way[5] with phosphorus oxychloride, 1,2,4-1*H*-triazole **5b** and triethylamine, and the trimethylsilyl protecting groups were removed by treatment with acetic acid in the methanol solution. In this way, the uridine derivative **4b** was obtained as a colourless crystalline solid in 89% isolated yield. No chromatographic purification step was required. However, the triazolo compound **4b** was very sensitive to base, and it was necessary to work-up the products with considerable care. Thymidine **2a** was similarly converted (Scheme 1b) into the corresponding triazolo compound **7a** which was also isolated as a crystalline solid in very good (88%) yield. Again no chromatographic purification step was required, and the product **7a** was found to be much more stable under the work-up conditions that the corresponding uridine derivative **4b**. Kimura *et al.*[8] previously reported that they had converted uridine **1a** into its triazolo-derivative **4b**, but these workers provided no

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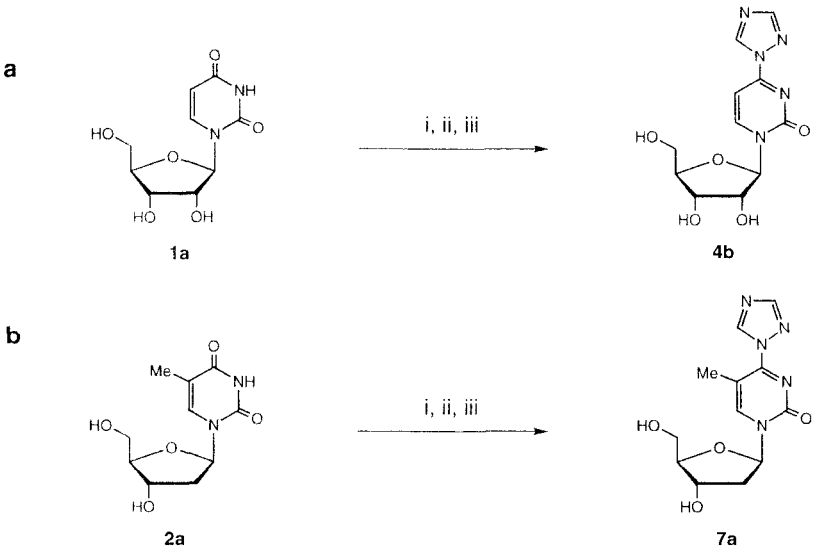

Scheme 1 *Reagents and conditions*: i, Me_3SiCl, Et_3N, MeCN, room temp.; ii, 1,2,4-1*H*-triazole **5b**, $POCl_3$, 0°C, 5h; iii, AcOH - MeOH (1:4 v/v), room temp.

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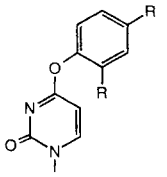
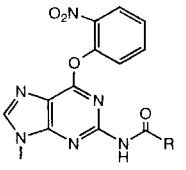
experimental evidence whatsoever in support of this claim; furthermore, they did not indicate the yield of product that they obtained. Other workers[9] had previously used essentially the same procedure (trimethylsilylation, followed by treatment with phosphorus oxychloride and 1,2,4-1*H*-triazole **5b**) to convert thymidine **2a** into its unprotected triazolo-derivative **7a** which they obtained in only 37% yield.

On the basis of these initial studies, we concluded that, while compound **7a** was a suitable intermediate for the preparation of modified thymidine derivatives, the corresponding uridine derivative **4b** was perhaps too reactive to meet the present requirements (see below). A number of years ago, in connection with some studies that were directed towards the synthesis of oligonucleotides by the phosphotriester approach, we introduced[10] the use of aryl groups for the protection of the lactam functions of uracil (as in **12a** and **12b**) and guanine (as in **13**) residues. These aryl protecting groups were selected to ensure that they would withstand all the reactions and operations involved in the assembly and purification of fully-protected oligonucleotides, and would then be easily removable by nucleophilic displacement with the conjugate base of an appropriate oxime (e.g. *E*-2-nitrobenzaldoxime[11]). Clearly, the susceptibility of 4-*O*-aryloxy groups to nucleophilic displacement can easily be increased by the introduction of appropriate electron-withdrawing aromatic substituents. This was first demonstrated by Nyilas and

Chattopadhyaya[12] who showed that 4-(2-nitrophenoxy)-1-(β-D-2-*O*-methylribofuranosyl)pyrimidin-2(1*H*)-one **14** could readily be converted into 2'-*O*-methylcytidine and other modified nucleosides.



12 a; R = H
b; R = Ac



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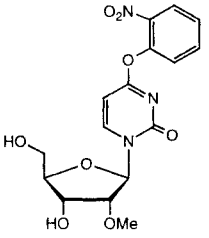

14

After some preliminary studies, the 4-nitro group was selected as the aromatic substituent. Uridine **1a** was again first trimethylsilylated (Scheme 2a) but 1-methylpyrrolidine was used as the base instead of triethylamine. A twofold excess of phosphorus oxychloride was then added to the cooled reaction mixture and, after 15 min, a large excess of 4-nitrophenol was added. When the reaction was complete, the products were worked-up and the trimethylsilyl protecting groups were removed as above in preparation of the corresponding triazolo-compound **4b**. In this way, 4-(4-nitrophenoxy)-1-(β-D-ribofuranosyl)pyrimidin-2(1*H*)-one **15** was obtained and isolated as a colourless crystalline solid in 88% yield. The latter 4-nitrophenyl derivative **15** was found to be more stable under the work-up conditions and thus easier to prepare than the corresponding triazolo-derivative **4b**. We had previously recommended the use of 1-methylpyrrolidine[13] as an alternative catalyst to trimethylamine[14] in nucleophilic substitution reactions by aryloxide ions at the 6-position of activated 2-*N*-acylguanine residues. In the same way, 2'-deoxyuridine **16a** (≡ **11**) and thymidine **16b** (≡ **2a**) were converted (Scheme 2b) into the corresponding 4-*O*-(4-nitrophenyl) derivatives. The latter compounds **17a** and **17b** were isolated as relatively stable colourless crystalline solids in 83 and 81% yields, respectively. In our original approach[10] to the synthesis of 4-*O*-aryl derivatives of uridine, we first prepared an intermediate 4-(3-nitro-1,2,4-triazol-1-yl) derivative (related to compound **4a**) and then allowed it to react with the appropriate phenol and triethylamine. Similarly, the 4-*O*-phenyl derivative of thymidine **10a** (X = OPh) was originally prepared[13] from the 4-(1,2,4-triazol-1-yl) compound **7** (R = $MeOCH_2CO$). We believe that the present procedure involving the use of phosphorus oxychloride as activating agent and 1-methylpyrrolidine as a catalyst in both the ribo- and deoxyribo- series (Scheme **2a** and **2b**, respectively) is not only more convenient but also leads to improved yields of the desired products.

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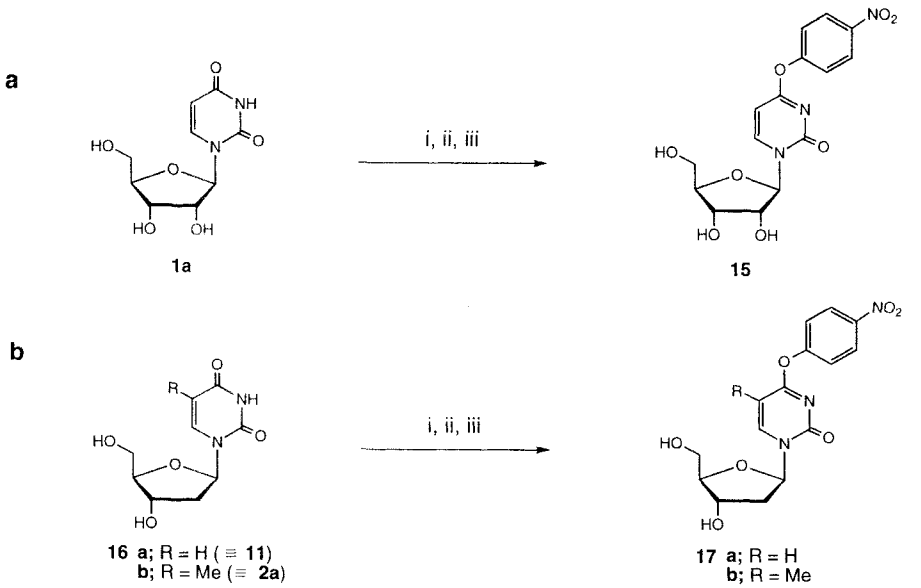

Scheme 2 *Reagents and conditions*: i, Me_3SiCl, 1-methylpyrrolidine, MeCN, room temp., 5h; ii, a, $POCl_3$, 0°C, 15 - 20 min, b, 4-nitrophenol, 0°C, 3 - 5.5 h; iii, AcOH - MeOH (1:4 v/v), room temp., 5 h.

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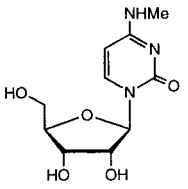
4-(4-Nitrophenoxy)-1-(β-D-ribofuranosyl)pyrimidin-2(1*H*)-one **15**, 5-methyl-4-(1,2,4-triazol-1-yl)-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1*H*)-one **7a** and 4-(4-nitrophenoxy)-1-(β-D-2-deoxyribofuranosyl)-pyrimidin-2(1*H*)-one **17a** were selected as the three intermediates of choice, represented above in an abbreviated form as **9**, **10a** and **10b**, respectively. All three of these compounds were treated first with a nitrogen nucleophile, viz. methylamine. Thus, when the uridine intermediate **15** was allowed to react with a large excess of *ca.* 8.0 M ethanolic methylamine for 1.5 hr at room temperature, it was quantitatively converted into the 4-*N*-methyl derivative **18** of cytidine. The latter compound was isolated as a colourless crystalline solid in 97% yield. No chromatographic purification step was needed. In the same way, the thymidine and 2'-deoxyuridine derivatives **7a** and **17a** were converted into 4-methylamino-5-methyl- and 4-methylamino-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1*H*)-ones **19a** and **19b**, respectively. These two compounds were isolated as colourless crystalline solids in very high (93 and 95%, respectively) yields.



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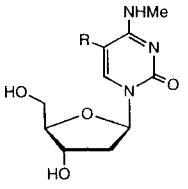
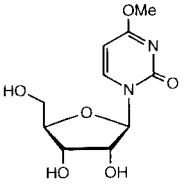


19 a; R = Me
b; R = H



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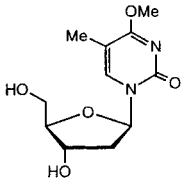

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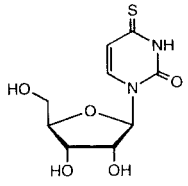

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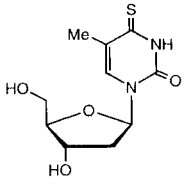

23

Finally, the reactions between the uridine and thymidine intermediates **15** and **7a** and (a) an oxygen nucleophile and (b) a sulfur nucleophile were investigated. When the uridine intermediate **15** was treated with an excess of sodium methoxide in anhydrous methanol at room temperature, it was readily converted into 4-methoxy-1-(β-D-ribofuranosyl)pyrimidin-2(1*H*)-one **20** which, following purification by chromatography on silica gel, was isolated as a colourless crystalline solid in 87% yield; when thymidine intermediate **7a** was heated, under reflux, with an excess of triethylamine in anhydrous methanol solution, 4-methoxy-5-methyl-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1*H*)-one **21** was obtained and isolated as a colourless crystalline solid in 97% yield. No chromatographic purification step was required. Putative triethylammonium hydrogen sulfide, prepared by bubbling hydrogen sulfide gas into a solution of triethylamine in anhydrous methanol solution at room temperature, was selected as the sulfur nucleophile. The uridine and thymidine intermediates **15** and **7a** were treated with this reagent at room temperature and, in both cases, the products were purified by chromatography on silica gel. In this way, 4-thiouridine **22** and 4-thiothymidine **23** were obtained as yellow crystalline solids in 83 and 97% isolated yields, respectively. The present procedures for converting uridine **1a** and thymidine **2a** into their 4-thio-derivatives involve very mild reaction conditions and are, in our opinion, particularly convenient.

From the results of the present study, we believe that 4-(4-nitrophenoxy)-1-(β-D-ribofuranosyl)pyrimidin-2(1*H*)-one **15**, 5-methyl-4-(1,2,4-triazol-1-yl)-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1*H*)-one **7a** and 4-(4-nitrophenoxy)-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1*H*)-one **17a** are suitable intermediates for the preparation of *C*-4 modified derivatives of uridine, thymidine and 2'-deoxyuridine, respectively. We have not so far incorporated any of these intermediates into oligonucleotides.

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EXPERIMENTAL

Melting points were measured with a Büchi melting point apparatus and were uncorrected. ^{1}H NMR spectra were measured at 360 MHz with a Bruker AM360 spectrometer; ^{13}C NMR spectra were measured at 90.6 MHz with the same spectrometer. *J* values are given in Hz. Merck silica gel 60 F_{254} TLC plates were developed in solvent system A [dichloromethane - methanol (85 : 15 v/v)]. Merck silica gel 60 was used for short column chromatography. Acetonitrile, 1-methylpyrrolidine and triethylamine were dried by heating with calcium hydride, under reflux, and were then distilled. Acetonitrile and triethylamine were stirred over no. 4A molecular sieves.

4-(1,2,4-Triazol-1-yl)-1-(β-D-ribofuranosyl)pyrimidin-2(1H)-one **4b**. - Triethylamine (10.5 mL, 75.3 mmol) and chlorotrimethylsilane (3.2 mL, 25.2 mmol) were added to a stirred suspension of uridine (1.23 g, 5.04 mmol) in dry acetonitrile (40 mL) at room temperature. After 1 h, the reaction mixture was cooled (ice-water bath) and 1,2,4-1*H*-triazole (3.45 g, 50.0 mmol) and phosphorus oxychloride (0.93 mL, 10.0 mmol) were added with continuing stirring. After a further period of 5 h, the products were poured into 0.5 M triethylammonium phosphate buffer (pH 7.0, 150 mL), and the resulting mixture was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Acetic acid - methanol (1 : 4 v/v, 15 mL) was added to the residue and the resulting solution was allowed to stand at room temperature. After 5 h, diethyl ether (30 mL) was added dropwise, with stirring, to this solution over a period of 30 min. After a further period of 2 h, colourless crystals of the *title compound* **4b** (1.32 g, 89%) were collected by filtration (Found, in material recrystallized from methanol - acetic acid (99.5 : 0.5 v/v) : C, 44.55; H, 4.18; N, 23.45. $C_{11}H_{13}N_5O_5$ requires : C, 44.75; H, 4.44; N, 23.72%); m.p. 198 - 200°C dec; R_f 0.32 (system A); δ_H [$(CD_3)_2SO$] 3.64 (1 H, m), 3.81 (1 H, m), 3.98 (2 H, m), 4.04 (1 H, m), 5.07 (1 H, d, *J* 6.0), 5.27 (1 H, t, *J* 4.9), 5.66 (1 H, d *J* 4.9), 5.79 (1 H, d, *J* 2.2), 6.97 (1 H, d, *J* 7.2), 8.40 (1 H, s), 8.84 (1 H, d, *J* 7.2), 9.44 (1 H, s); δ_C [$(CD_3)_2SO$] 59.4, 68.1, 74.6, 84.1, 91.2, 93.7, 143.7, 148.4, 153.8, 154.1, 158.6.

5-Methyl-4-(1,2,4-triazol-1-yl)-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1H)-one **7a**. - Triethylamine (10.5 mL, 75.3 mmol) and chlorotrimethylsilane (3.2 mL, 25.2 mmol) were added to a stirred suspension of thymidine (1.22 g, 5.04 mmol) in dry acetonitrile (40 mL) at room temperature. After 1.5 h, the reaction mixture was cooled (ice-water bath), and 1,2,4-1*H*-triazole (3.12 g, 45.2 mmol) and phosphorus oxychloride (0.95 mL, 10.2 mmol) were added with continued stirring. After a further period of 5 h, the products were poured into saturated aqueous sodium hydrogen carbonate (250 mL), and the resulting mixture was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Acetic acid - methanol (1:4 v/v, 15 mL) was added to the residue, and the resulting solution was allowed to stand at room temperature. After 4.5 h, diethyl ether (30 mL) was added dropwise, with stirring, to this solution over a period of 30 min. After a further period of 2 h, colourless crystals of the *title compound* **7a** (1.30 g, 88%) were collected by filtration (Found, in material recrystallized from methanol - acetic acid (99.5 : 0.5 v/v) : C, 49.08; H, 5.11; N, 23.94. Calc. for $C_{12}H_{15}N_5O_4$: C, 49.14; H, 5.16; N 23.88%) ; m.p. 175°C dec.; R_f 0.42 (system A); δ_H [$(CD_3)_2SO$] 2.15 (1 H, m), 2.30 (3 H, s), 2.38 (1 H, m), 3.63 (1 H, m), 3.72 (1 H, m), 3.91 (1 H, m), 4.27 (1 H, m), 5.22 (1 H, t, *J* 5.0), 5.31 (1 H, t, *J* 6.0), 8.37 (1 H, s), 8.60 (1 H, s), 9.31 (1 H, s); δ_C [$(CD_3)_2SO$] 16.2, 40.9, 60.4, 69.2, 86.9, 88.1, 104.4, 145.2, 147.9, 153.1, 153.4, 157.7.

4-(4-Nitrophenoxy)-1-(β-D-ribofuranosyl)pyrimidin-2(1H)-one **15**. - 1-Methylpyrrolidine (7.5 mL, 72 mmol) followed by chlorotrimethylsilane (3.9 mL, 30.7 mmol)

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was added to a suspension of uridine (1.23 g, 5.0 mmol) in dry acetonitrile (40 mL), and the reaction mixture was stirred at room temperature for 1 h and then cooled (ice-water bath). After 10 min, phosphorus oxychloride (0.93 mL, 10.0 mmol) was added, and then after a further period of 15 min, 4-nitrophenol (4.88 g, 35.0 mmol) was added. After 3 h, the products were extracted with 0.5 M triethylammonium phosphate buffer (pH 7.0, 150 mL), and the aqueous layer was back extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Acetic acid - methanol (1 : 4 v/v, 15 mL) was added to the residue and the resulting solution was allowed to stand at room temperature. After 5 h, diethyl ether (30 mL) was added dropwise over a period of 30 min to the stirred solution. After a further period of 3 h, colourless crystals of the *title compound* **15** (1.62 g, 88%) were collected by filtration (Found, in material recrystallized from ethanol - acetic acid (99.5 : 0.5 v/v) : C, 49.04; H, 4.10; N, 11.21. $C_{15}H_{15}N_3O_8$ requires : C, 49.32; H, 4.14; N, 11.50%) m.p. 204-206°C dec; R_f 0.52 (system A); δ_H [$(CD_3)_2SO$] 3.62 (1 H, m), 3.77 (1 H, m), 3.93 (1 H, m), 3.99 (2 H, m), 5.06 (1 H, d, *J* 5.7), 5.25 (1 H, t, *J* 4.9), 5.54 (1 H, d, *J* 4.8), 5.75 (1 H, d, *J* 2.3), 6.41 (1 H, d, *J* 7.4), 7.52 (2 H, m), 8.33 (2 H, m), 8.61 (1 H, d, *J* 7.4); δ_C [$(CD_3)_2SO$] 59.7, 68.5, 74.6, 84.2, 90.4, 94.3, 123.4, 125.4, 145.0, 146.5, 154.2, 156.5, 170.3.

4-(4-Nitrophenoxy)-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1H)-one **17a**. - 1-Methylpyrrolidine (7.5 mL, 72 mmol) followed by chlorotrimethylsilane (3.2 mL, 25.2 mmol) was added to a suspension of 2'-deoxyuridine (1.141 g, 5.0 mmol) in dry acetonitrile (40 mL), and the reaction mixture was stirred at room temperature for 1 h and then cooled (ice-water bath). After 10 min, phosphorus oxychloride (0.93 mL, 10.0 mmol) was added, followed after a further period of 20 min by 4-nitrophenol (4.88 g, 35 mmol). After 5.5 h, the products were extracted with 0.5 mol dm^{-3} triethylammonium phosphate buffer (pH 7.0, 150 mL), and the aqueous layer was back extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Acetic acid - methanol (1 : 4 v/v, 15 mL) was added to the residue and the resulting solution was allowed to stand at room temperature. After 5 h, diethyl ether (30 mL) was added dropwise over a period of 30 min to the stirred solution. After stirring for a further period of 3 h, colourless crystals of the *title compound* **17a** (1.45 g, 83%) were collected by filtration (Found, in material recrystallized from methanol - acetic acid (99.5 : 0.5 v/v) : C, 51.47; H, 4.26; N, 11.89. $C_{15}H_{15}N_3O_7$ requires: C, 51.58; H, 4.33; N, 12.03%), m.p. 177°C dec; R_f 0.53 (system A); δ_H [$(CD_3)_2SO$] 2.03 (1 H, m), 2.29 (1 H, m), 3.62 (2 H, m), 3.87 (1 H, m), 4.23 (1 H, m), 5.11 (1 H, t, *J* 5.1), 5.26 (1 H, d, *J* 4.3), 6.08 (1 H, t, *J* 6.2), 6.39 (1 H, d, *J* 7.3), 7.51 (2 H, m), 8.32 (2 H, m), 8.48 (1 H, d, *J* 7.4); δ_C [$(CD_3)_2SO$] 40.9, 60.8, 69.8, 86.4, 87.9, 94.2, 123.4, 125.3, 145.0, 146.2, 154.0, 156.5, 170.2.

5-Methyl-4-(4-nitrophenoxy)-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1H)-one **17b**. - 1-Methylpyrrolidine (7.5 mL, 72 mmol) followed by chlorotrimethylsilane (3.2 mL, 25.2 mmol) was added to a suspension of thymidine (1.22 g, 5.0 mmol) in dry acetonitrile (40 mL), and the reaction mixture was stirred at room temperature for 1 h and then cooled (ice-water bath). After 10 min, phosphorus oxychloride (0.93 mL, 10.0 mmol) was added, followed after a further period of 20 min by 4-nitrophenol (4.88 g, 35 mmol). After 5.5 h, the products were extracted with 0.5 M triethylammonium phosphate buffer (pH 7.0, 150 mL) and the aqueous layer was back extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Acetic acid - methanol (1 : 4 v/v, 15 mL) was added to the residue and the resulting solution was allowed to stand at room temperature. After 5 h, diethyl ether (30 mL) was added dropwise over a period of 30 min to the stirred solution. After stirring for a further period of 1 h, colourless crystals of the *title compound* **17b** (1.48 g, 81%) were collected by filtration (Found, in material recrystallized from methanol - acetic acid

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(99.5 : 0.5 v/v) : C, 52.58; H, 4.61; N, 11.42. $C_{16}H_{17}N_3O_7$ requires : C, 52.89; H, 4.72; N, 11.57%), m.p. 171-173°C; R_f 0.56 (system A); δ_H [$(CD_3)_2SO$] 2.06 (1 H, m), 2.09 (3 H, s), 2.25 (1 H, m), 3.65 (2 H, m), 3.85 (1 H, m), 4.25 (1 H, m), 5.14 (1 H, t, *J* 5.1), 5.26 (1 H, d, *J* 4.3), 6.10 (1 H, t, *J* 6.3), 7.51 (2 H, d, *J* 9.0), 8.31 (3 H, m); δ_C [$(CD_3)_2SO$] 11.9, 40.7, 60.8, 69.8, 86.0, 87.8, 102.8, 123.6. 125.3, 143.3, 144.9, 153.9, 156.9, 169.3.

4-Methylamino-1-(β-D-ribofuranosyl)pyrimidin-2(1H)-one **18**. - A solution of 4-(4-nitrophenoxy)-1-(β-D-ribofuranosyl)pyrimidin-2(1*H*)-one **15** (0.73 g, 2.0 mmol) in ethanolic methylamine (*ca.* 8.0 M, 5 mL, *ca.* 40 mmol) was stirred at room temperature. After 1.5 h, the products were evaporated under reduced pressure and the residue was redissolved in methanol (4 mL). Diethyl ether (12 mL) was added dropwise to the stirred solution over a period of 30 min. After a further period of 4 h, colourless crystals of the *title compound* **18** (0.50 g, 97%) were collected by filtration (Found : C, 46.58; H, 5.85; N, 16.21. Calc. for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88; N, 16.33%), m.p. 191-192°C (lit.[15] 202-203°C); R_f 0.10 (system A); δ_H [$(CD_3)_2SO$] 2.75 (3 H, d, *J* 4.7), 3.53 (1 H, m), 3.64 (1 H, m), 3.81 (1 H, m). 3.92 (2 H, m), 4.97 (1 H, d, *J* 4.9), 5.03 (1 H, t, *J* 5.2), 5.28 (1 H, d, *J* 4.9), 5.71 (1 H, d, *J* 7.5), 5.76 (1 H, d, *J* 3.6), 7.66 (1 H, quart, *J* 4.7), 7.78 (1 H, d, *J* 7.5); δ_C [$(CD_3)_2SO$] 27.0, 60.7, 69.5, 74.0, 84.1, 89.1, 94.6, 140.1, 155.5, 163.8.

4-Methylamino-5-methyl-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1H)-one **19a**. - A solution of 5-methyl-4-(1,2,4-triazol-1-yl)-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1*H*)-one **7a** (0.59g, 2.0 mmol) in ethanolic methylamine (*ca.* 8.0 M, 5 mL, *ca.* 40 mmol) was stirred at room temperature. After 1 h, the products were evaporated under reduced pressure and the residue was redissolved in methanol (0.5 mL). Diethyl ether (10 mL) was added dropwise over a period of 10 min to the stirred solution. After a further period of 2 h, colourless crystals of the *title compound* **19a** (0.48 g, 93%) were collected (Found, in material recrystallized from methanol : C, 51.67; H, 6.67; N, 16.13. Calc. for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46%); m.p. 226-228°C (lit.[15] 225-227°C); R_f 0.15 (system A); δ_H [$(CD_3)_2SO$] 1.83 (3 H, s), 1.94 (1 H, m), 2.05 (1 H, m) 2.78 (3 H, d, *J* 4.3), 3.56 (2 H, m), 3.74 (1 H, m), 4.20 (1 H, m), 5.00 (1 H, t, *J* 5.2), 5.19 (1 H, d, *J* 4.1), 6.18 (1 H, t, *J* 6.7), 7.17 (1 H, quart., *J* 4.4), 7.56 (1 H, s); δ_C [$(CD_3)_2SO$] 13.1, 27.6, 40.2, 61.4, 70.5, 84.5, 87.1, 101.7, 136.9, 155.1, 163.2.

4-Methylamino-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1H)-one **19b**. - A solution of 4-(4-nitrophenoxy)-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1*H*)-one **17a** (0.70g, 2.0 mmol) in ethanolic methylamine (*ca.* 8.0 M, 5 mL, *ca.* 40 mmol) was stirred at room temperature. After 1.5 h, the products were evaporated under reduced pressure and the residue was redissolved in methanol (4 mL). Diethyl ether (12 mL) was added dropwise over a period of 30 min to the stirred solution. After a further period of 4 h, colourless crystals of the *title compound* **19b** (0.46 g, 95%) were collected by filtration (Found: C, 49.61; H, 6.23; N, 17.39. Calc. for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42%), m.p. 188-190°C (lit.[16] 191-193°C); R_f 0.14 (system A); δ_H [$(CD_3)_2SO$] 1.95 (1 H, m), 2.09 (1 H, m), 2.74 (3 H, d, *J* 4.7), 3.54 (2 H, m), 3.75 (1 H, m), 4.19 (1 H, m), 4.97 (1 H, t, *J* 5.3), 5.20 (1 H, d, *J* 4.2), 5.73 (1 H, d, *J* 7.5), 6.16 (1 H, dd, *J* 6.3 and 7.1), 7.67 (1 H, quart., *J* 4.4), 7.72 (1 H, d, *J* 7.5); δ_C [$(CD_3)_2SO$] 26.9, 40.3, 61.4, 70.5, 84.8, 87.1, 94.6, 139.6, 155.2, 163.8.

4-Methoxy-1-(β-D-ribofuranosyl)pyrimidin-2(1H)-one **20**. - Methanolic sodium methoxide (*ca.* 4.4 M, 1.0 mL, *ca.* 4.4 mmol) was added to a stirred solution of 4-(4-nitrophenoxy)-1-(β-D-ribo-furanosyl)pyrimidin-2(1*H*)-one **15** (0.73 g, 2.0 mmol) in anhydrous methanol (10 mL) at room temperature. After 1 h, glacial acetic acid (0.25 mL,

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4.4 mmol) was added and the products were evaporated under reduced pressure. The residual glass was fractionated by short column chromatography on silica gel. The column was eluted with dichloromethane - methanol mixtures (100 : 0 to 90 : 10 v/v), and the appropriate fractions were combined and evaporated under reduced pressure to give the *title compound* **20** (0.45 g, 87%) (Found, in material recrystallized from acetonitrile : C, 46.25; H, 5.35; N, 10.85. Calc. for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.46; N, 10.85%), m.p. 138-140°C (lit.[17] 141-142°C); R_f 0.40 (system A); δ_H [$(CD_3)_2SO$] 3.58 (1 H, m), 3.71 (1 H, m), 3.81 (3 H, s), 3.88 (1 H, m), 3.95 (2 H, m), 5.04 (1 H, d, *J* 4.4), 5.16 (1 H, t, *J* 4.9), 5.47 (1 H, d, *J* 3.5), 5.78 (1 H, d, *J* 2.7), 6.05 (1 H, d, *J* 7.4), 8.32 (1 H, d, *J* 7.4); δ_C [$(CD_3)_2SO$] 53.9, 60.0, 68.8, 74.5, 84.2, 89.9, 94.6, 144.3, 155.0, 171.1.

4-Methoxy-5-methyl-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1H)-one **21**. - Triethylamine (1.0 mL, 7.2 mmol) was added to a stirred suspension of 5-methyl-4-(1,2,4-triazol-1-yl)-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1*H*)-one **7a** (0.59 g, 2.0 mmol) in anhydrous methanol, and the reaction mixture was then heated under reflux. After 30 min, the products were evaporated under reduced pressure and the residue was redissolved in methanol (0.5 mL). Diethyl ether (10 mL) was added dropwise over a period of 10 min to the stirred solution. After a further period of 1 h, colourless crystals of the *title compound* **21** (0.50 g, 97%) were collected by filtration (Found, in material recrystallized from methanol : C, 51.40; H, 6.05; N, 10.96. Calc. for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93%), m.p. 169-171°C (lit.[18] 170-172°C); R_f 0.46 (system A); δ_H [$(CD_3)_2SO$] 1.88 (3 H, s), 2.00 (1 H, m), 2.19 (1 H, m), 3.59 (2 H, m), 3.81 (1 H, m), 3.84 (3 H, s), 4.22 (1 H, m), 5.07 (1 H, t, *J* 5.0), 5.24 (1 H, d, *J* 4.1), 6.24 (1 H, t, *J* 6.4), 8.01 (1 H, s); δ_C [$(CD_3)_2SO$] 11.9, 40.6, 54.0, 61.0, 70.0, 85.4, 87.6, 102.9, 140.8, 154.7, 169.9.

4-Thiouridine **22**. - Hydrogen sulfide was bubbled into a stirred solution of triethylamine (0.77 mL, 5.5 mmol) in anhydrous methanol (10 mL) at room temperature. After 10 min, 4-(4-nitrophenoxy)-1-(β-D-ribofuranosyl)pyrimidin-2(1*H*)-one **15** (0.37 g, 1.0 mmol) was added and stirring was continued at room temperature. After 5 h, the products were evaporated under reduced pressure, and the residue was fractionated by short column chromatography on silica gel. The column was eluted with dichloromethane - methanol (100 : 0 to 85 : 15 v/v), and the appropriate fractions were combined and evaporated under reduced pressure to give the *title compound* **22** (0.22 g, 83%) as a yellow solid (Found, in material recrystallized from acetonitrile: C, 41.59; H, 4.73; N, 10.85. Calc. for $C_9H_{12}N_2O_5S$: C, 41.53; H, 4.65; N, 10.76%), m.p. 137-139°C (lit.[19] 135-138°C dec); R_f 0.36 (system A); δ_H [$(CD_3)_2SO$] 3.55 (1 H, m), 3.65 (1 H, m), 3.86 (1 H, m), 3.96 (1 H, m), 4.03 (1 H, m), 5.13 (2 H, m), 5.48 (1 H, d, *J* 5.4), 5.73 (1 H, d, *J* 4.8), 6.31 (1 H, d, *J* 7.5), 7.84 (1 H, d, *J* 7.6), 12.73 (1 H, br s); δ_C [$(CD_3)_2SO$] 60.5, 69.6, 74.0, 84.9, 88.5, 112.6, 136.0, 148.0, 190.2.

4-Thiothymidine **23**. - Hydrogen sulfide was bubbled into a stirred solution of triethylamine (0.29 mL, 2.0 mmol) in anhydrous methanol (10 mL) at room temperature. After 10 min, 5-methyl-4-(1,2,4-triazol-1-yl)-1-(β-D-2-deoxyribofuranosyl)pyrimidin-2(1*H*)-one **7a** (0.29 g, 1.0 mmol) was added and stirring was continued at room temperature. After 1 h, the products were evaporated under reduced pressure, and the residue was fractionated by short column chromatography on silica gel. The column was eluted with dichloromethane - methanol mixtures (100 : 0 to 85 : 15 v/v), and the appropriate fractions were combined and evaporated under reduced pressure to give the *title compound* **23** (0.25 g, 97%) as a yellow solid (Found, in material recrystallized from acetonitrile : C, 46.68; H, 5.36; N, 11.15. Calc. for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 4.46; N, 10.85%), m.p. 122-124°C (lit.[20] 125-127°C); R_f 0.51 (system A); δ_H [$(CD_3)_2SO$] 1.96 (3, H, s), 2.14 (2 H, dd, *J* 5.0 and 6.5), 3.59 (2 H, m), 3.79 (1 H, m), 4.24 (1 H,

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m), 5.10 (1 H, t, *J* 5.1), 5.27 (1 H, d, *J* 4.3), 6.10 (1 H, t, *J* 6.6), 7.89 (1 H, s), 12.69 (1 H, br s); δ_C [$(CD_3)_2SO$] 17.0, 39.9, 61.0, 70.1, 84.7, 87.7, 117.7, 133.5, 147.8, 190.7.

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