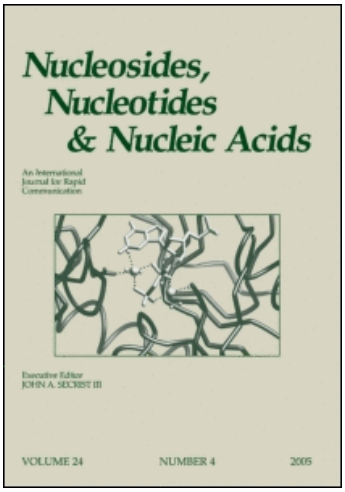

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A STEREOSPECIFIC SYNTHESIS OF PYRIMIDINE β-D-2'-DEOXYRIBONUCLEOSIDES§1

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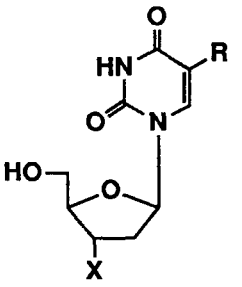
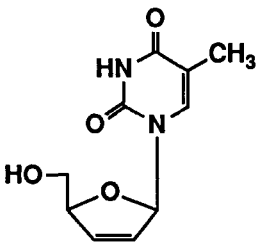
Abstract: *A stereospecific route for the synthesis of pyrimidine 2'-β-D-deoxyribonucleosides has been developed using suitably modified methyl 2-deoxy-D-ribofuranosides. The stereochemistry of the nucleoside bond is dictated by the chirality at C-4 of the pentofuranose. A novel palladium hydroxide catalyzed alcholysis of a nucleoside bond has been discovered. Preliminary studies of the mechanism and limitations of this reaction are described.*

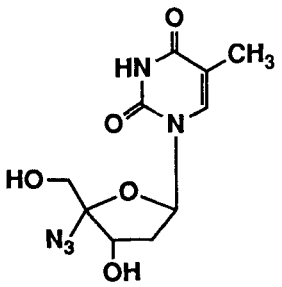
The introduction of AZT as a clinically useful anti HIV drug[2-4] has spurred interest in discovering other sugar-modified deoxynucleosides. 3'-Deoxythymidine (d_2T)[5], 3'-deoxy-2'3'-didehydrothymidine (d_4T)[6], 2',2'-dideoxy-3'-azidouridine (ddAZU)[7], 2',3'-dideoxycytidine (ddC)[8], and more recently, 4'-azidothymidine (ADRT)[9] are examples of such pyrimidine nucleosides with potential clinical utility.



X = N_3, R = CH_3, AZT
X = N_3, R = H, AZU
X = H , R = CH_3, d_2T



d_4T



ADRT

§ This paper is dedicated to the memory of Professor Tohru Ueda

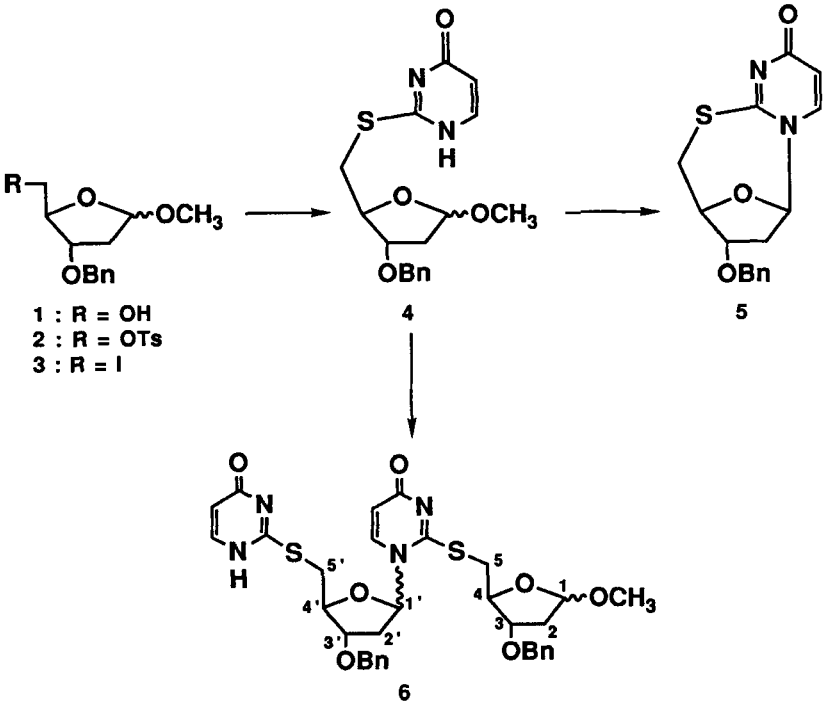
The relative inaccessibility of 2-deoxypentofuranoses and the formation of α, β-mixtures during glycosylation[10] have resulted in dependence on naturally occurring deoxynucleosides as starting materials. Consequently, efforts have been directed at developing alternate synthetic routes to prepare these compounds. There are literature reports using 2-deoxypentofuranoses where formation of β–over α-anomers is preferred. The use of copper iodide, for example, resulted in β/α ratios of 9:1[11]. More recently, a 3 α-*O*-2-methyl-sulfinylethyl group was shown to participate in a glycosylation reaction favoring β–attack by the base resulting in predominant formation of the β–anomer[12]. However, a regiospecific synthesis using 2-deoxy-pentofuranosides does not appear to have been reported.

We have recently introduced synthetic methodologies to prepare all four 2-deoxypentofuranoses from readily available *D*-isoascorbic and *L*-ascorbic acids[13]. In the present study use is made of the chirality at C-4 in these furanosides to stereospecifically prepare the title compounds.

Our work was patterned after that of Mizuno and co-workers[14], who used the 5'-thioether functionality to deliver adenine from the β–face of arabinose. In a model study 2*S*-(1-methyl-3-*O*-benzyl-2-deoxy-*D*-erythro-pentofuranos-5-yl)thiouracil (**4**) was prepared to study its intramolecular cyclization to 2*S*,5'-anhydro-3'-*O*-benzyl-2'-deoxy-β-*D*-erythro-pentofuranosyl uridine (**5**). The synthesis is outlined in **Scheme 1**. Treatment of methyl 3-*O*-benzyl-2-deoxy-*D*-erythropentofuranoside (**1**)[13] with p-toluenesulfonyl chloride furnished the corresponding tosylate **2**. Direct displacement of the tosyl group with 2-thiouracil, using a variety of organic bases[15,16] failed to give the desired thioether **4**. However, the unstable iodo compound **3** proved to be amenable to such a displacement to yield product **4** in 85% yield.

Intramolecular glycosylation was then pursued. When thioether **4** was persilylated and then treated with one equivalent of TMS-triflate in acetonitrile, the anhydronucleoside **5** was obtained in 65% yield. The use of more than one equivalent of TMS-triflate resulted in discoloration and decomposition of the starting material. However, when one half an equivalent was used, nucleoside bond formation took place inter-, rather than, intramolecularly to give a product whose structure was tentatively assigned as **6**. This was based on elemental and mass spectral analyses as well as extensive ^{1}H and ^{13}C NMR studies.

The ^{1}H NMR spectrum of **6** was expectedly complicated since this structure represents a mixture of two pairs of diastereomers. However several significant features could be analyzed and assigned. There are two sets of pairs of anomeric protons, the more shielded pair consisted of a major and a minor (3:1) doublet of doublets at δ 5.1 and 5.03 ppm respectively. By analogy with earlier work[13], they



Scheme 1

represent the β- and α- protons at position 1[§]. The deshielded pair similarly consisted of a major and minor (3:1) doublet at 6.17 and 6.15 ppm respectively. These represented a mixture of anomers at position 1'. Having assigned the anomeric protons, COSY studies helped analyze and assign pairs of protons at positions 2 (2.14 and 2.04 ppm), 3 (4.19 and 3.91 ppm) and 4 (4.3 ppm). Similarly, assignments were made at positions 2' (2.7 and2.3 ppm), 3' (4.1 ppm) and 4' (4.74 ppm). Pairs of doublets were also found for the pyrimidine protons at positions 5 and 6. Duplicity of peaks was also found in the ^{13}C NMR spectrum. HETCOR studies correlated protons with carbons. However, exact assignment of the stereochemistry of the nucleoside bond was not possible.

The exact mechanism by which this reaction proceeds is not completely understood. It appears that partial activation of the sugar and differentiation of the

[§] The simple numbering system was adopted to avoid complexities encountered when traditional numbering was used.

TABLE 1: ^{1}H and ^{13}C -NMR data for Compound **5**

	δ (ppm)	J (Hz)		δ (ppm)
H6	7.57	*d*, $J_{6,5}$=7.5	C5'	36.34
Ph	7.38-7.28	*m*	C2'	40.12
H5	6.02	*d*, $J_{5,6}$=7.5	CH_2-Ph	71.32
H1'	5.96	*dd*, $J_{1',2'\alpha}$=9; $J_{1',2'\beta}$=2.7	C3'	82.16
H4'	4.76	*dd*, $J_{4',5'a}$=2.1; $J_{4',5'b}$=3.3	C4'	83.76
CH_2-Ph	4.53	q_{AB}, J=11.7	C1'	96.96
H3'	4.35	*dd*, $J_{3',2'\beta}$=6; $J_{3',2'\alpha}$=1	C5	109.87
H5'a	3.47	*dq*, J_{AB}=14.7; $J_{5'a,4'}$=2.1	Ph(C2,C6)	127.82
H2'β	2.90	*dq*, $J_{2'\beta,2'\alpha}$=15; $J_{2'\beta,1'}$=2.7; $J_{2'\beta,3'}$=6	Ph(C4)	128.10
			Ph(C3,C5)	128.61
H2'α	2.79	*dq*, $J_{2'\alpha,2'\beta}$=15; $J_{2'\alpha,1'}$=9; $J_{2'\alpha,3'}$=1	Ph(C1)	137.14
			C6	144.69
H5'b	2.70	*dq*, J_{AB}=14.7; $J_{5'b,4'}$=3.3	C4	160.40
			C2	167.58

nucleophilicity of the heterocycle, offer a reasonable explanation of what was observed.

The structure of compound **5** was assigned using spectroscopic and chemical methods. The chemical shifts and the corresponding coupling constants were obtained from homo- and heteronuclear COSY experiments, and are presented in **Table 1**. It is worth mentioning that the proton at δ 2.90 (H–2'β) is weakly coupled (J = 2.7 Hz), while H-2'α (δ 2.79) is strongly coupled (J = 9 Hz) to the anomeric proton (H-1'). The respective dihedral angles at H1'-C1'C2'-H2'α (Ø = 0°) and H1'-C1'-C2'-H2'β (Ø = 90°) are responsible for the observed differences in the coupling constants[17]. In addition, the dihedral angle between H-3' and H-4' is almost 90° which explains the $J_{3',4'}$ value of zero. Another unusual feature in the ^{1}H NMR spectrum of **5** is the high shielding of H-5'b (δ 2.7) compared to that of the same proton in **4**. Examination of Dreiding models clearly showed this proton, unlike H-5'a, to fall in the shielding cone of the π system between C-2 and N-3.

Although the ^{1}H and ^{13}C NMR data obtained provided most of the necessary structural information, it was insufficient for definitively assigning the glycosylation site (N1 versus N3). This may be obtained either by an unambiguous synthesis of **5**, its conversion to a well characterized compound, or by ^{1}H-coupled-^{13}C NMR spectroscopic methods. Thus, the conversion of **5** to a known derivative by established

TABLE 2: Comparison of the ^{13}C NMR chemical shifts for **7** with literature values

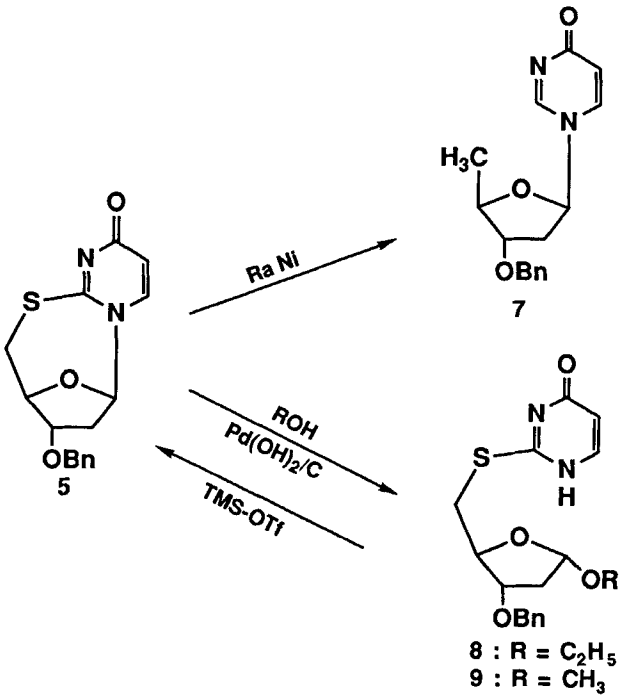
	3-methyl-4-oxo-pyrimidine[a]	1-methyl-4-oxo-pyrimidine[a]	7
C2	151.50	152.45	150.14
C4	161.44	169.76	170.63
C5	115.66	112.82	112.85
C6	153.58	142.04	137.52

[a] Cited from ref. 23.

synthetic routes was attempted. Following literature procedures[18,19], base hydrolysis of **5** failed to proceed as expected. The corresponding 5'-mercaptouridine was not obtained. The decomposition of **5** under these conditions could be due to base catalyzed hydration at the 5,6- positions followed by fragmentation. 5'-Thiouridines are known to undergo an intramolecular Michael addition reaction to form 5',6-cyclonucleosides[20,21]. Therefore, an alternate route was sought for the conversion of **5** to a known compound.

Desulfurization of **5** with excess Raney nickel for l5 h in a mixture of isopropanol and benzene gave nucleoside **7** in 32% yield (**Scheme 2**). The structure of **7** was proved by the magnitude of $J_{2,6}$ (2.5 Hz) which was comparable to that found in 1-alkyl-4-pyrimidinones.[22] Similarly, ^{13}C chemical shifts of the pyrimidine carbons were closer in value to those of 1-methyl-4-oxo but not 3-methyl-4-oxo- pyrimidine[23], as shown in **Table 2**. Conclusive evidence for the site of glycosylation was derived from ^{1}H-coupled ^{13}C NMR spectroscopy of **5**. In this structure C-6 was found to be coupled to H-1' (J = 4.5Hz); a finding that cannot be explained had glycosylation taken place at N-3.

Attempts to debenzylate **7** to compare the UV data of the product with that of a known compound[24] failed to give the desired derivative. Thus the desulfurization -debenzylation sequence was reversed. When **5** was subjected to transfer hydrogenation (20% $Pd(OH)_2/C$) in a mixture of ethanol and cyclohexene, an unexpected less polar compound was isolated from the reaction mixture in reasonable yield. Elemental analysis as well as ^{1}H NMR data showed the presence of the benzyl group and the addition of one mole of ethanol to the starting material. The chemical shift of the anomeric proton at δ 5.02 ppm ruled out ethanolysis at C-5' and strongly suggested stereospecific cleavage of the glycosidic bond to form **8**. Indeed, when the reaction was carried out in methanol, compound **9** was obtained whose ^{1}H NMR spectrum was identical to that of one diastereomer of **4**. Assignment of the α-stereochemistry at the anomeric position was based on ^{1}H NMR analysis. The



Scheme 2

difference in chemical shifts of the 2'- protons (0.25 ppm) and the $H_{1',2'}$ coupling constants (1.5 and 5.4 Hz) were closer to those of methyl 3-*O*-benzyl-α-*D*-erythro-pentofuranoside (0.25 ppm; 1.5 and 6.0 Hz) than the β-anomer (0.07 ppm; 2.1 and 5.3 Hz)[13]. Also, stereochemical considrations dictate α- rather than β- approach of the alkoxide ion. Final confirmation of the structure was obtained when **9** was recyclized to **5** under reaction conditions described earlier.

Attempts to explain this unusual reaction were then undertaken. Elimination of cyclohexene had no effect on the outcome of the reaction. However, removal of palladium hydroxide, or the use of palladium on carbon instead, resulted in isolation of the starting material. Similar results were obtained when a catalytic amount of sodium methoxide was used. However, when palladium on carbon was added to this reaction, methanolysis did take place to form **9**.

Although this reaction does not appear to have been previously described in the nucleoside literature, it seems to proceed via a known mechanism of palladium catalyzed reactions[25]. Oxidative metal addition to the enaminone system in the heterocycle weakens the nucleoside bond making it susceptible to nucleophilic

attack by the alkoxide ion. Reductive elimination of the metal generates the observed product. The scope and utility of this reaction are currently under investigation.

EXPERIMENTAL

Melting points were determined on a Buchi 535 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on either a Varian EM 390 or a Bruker AM-300 spectrometer, as indicated, using Me_4Si (TMS) as an internal standard. Optical rotations were measured on a Perkin-Elmer Model 141 automatic digital readout polarimeter. Anhydrous acetonitrile and dimethyl-formamide (DMF) were obtained by distillation from CaH_2 and P_2O_5, respectively. Solvent evaporations were performed under diminished pressure using a Buchi Rotary Evaporator unless otherwise stated. Davison silica gel (grade H, 60-200 mesh), purchased from Fisher Scientific, was used for all column chromatography. A Chromatotron Model 7924T was used to complete various separations as indicated. The 2.0 or 4.0 mm plates used were coated with silica gel PF254 containing $CaSO_4$. Thin-layer chromatography was performed on precoated silica gel plates (60-F254, 0.2 mm) manufactured by E.M. Science, Inc. and short-wave ultraviolet light (254 nm) was used to detect the UV absorbing compounds. All solvent proportions are by volume unless otherwise indicated. Elemental analyses were performed by MHW Laboratories, Phoenix, AR.

Methyl 3-*O*-benzyl-2-deoxy-5-*O*-(*p*-toluenesulfonyl)-D-*erythro*-pentofuranoside (2). *p*-Toluenesulfonyl chloride (0.44 g, 2.30 mmol) was added to a solution of **1**[12] (0.50 g, 2.10 mmol) in dry pyridine (5 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 12 h and then poured into CH_2Cl_2 (300 mL). This organic solution was washed with cold 1 N HCl (4 x 100 mL), dried over $MgSO_4$, and concentrated. Purification of the crude product by column chromatography using hexanes/EtOAc (4:1) as the eluant afforded **2** (0.75 g, 91% yield, anomeric mixture) as a gum: ^1H NMR (90 MHz, $CDCl_3$) δ 1.90-2.20 (*m*, 2H, H-2), 2.36 (*s*, 3H, PhC*H*$_3$), 3.09, 3.23 (2*s*, 3H, β- & α-OC*H*$_3$), 3.77-4.20 (*m*, 4H, H-3, H-4, and H-5), 4.30-4.47 (*s*, 2H, C*H*$_2$-Ph), 4.77-5.07 (*m*, 1H, H-1), 6.90-7.30 (*s*, 7H, Ph and tosyl), 7.50-7.80 (m, 2H, tosyl). Anal. Calcd for $C_{20}H_{24}O_6S$: C, 61.21; H, 6.16; S, 8.17. Found: C, 61.48; H, 6.26; S, 8.01.

Methyl 3-*O*-Benzyl-2,5-dideoxy-5-iodo-D-*erythro*-pentofurano-side (3). Potassium iodide (6.0 g, 37.20 mmol) was added to a solution of **2** (7.28 g, 18.60 mmol) in anhydrous DMF (120 mL) and the resulting mixture was stirred at 85 °C for 4 h. After the solvent was removed under high vacuum, H_2O (100 mL) was added and the aqueous solution was extracted with Et_2O (4 x 100 mL). The organic layers were

combined, washed with 10% $Na_2S_2O_3$ solution (200 mL), dried over $MgSO_4$ and concentrated. Purification of the crude product by column chromatography using hexanes/EtOAc (6:1) as the eluant gave **3** (6.23 g, 94% yield, anomeric mixture) as a gum: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.97-2.27 (*m*, 2H, H-2), 1.97-3.33 (*m*, 5H, H-5 and OCH_3), 3.73-4.23 (*m*, 2H, H-3, and H-4), 4.43-4.53 (*s*, 2H, CH_2Ph), 4.90-5.13 (*m*, 1H, H-1), 7.17-7.43 (*s*, 5H, Ph).

2*S*-(1-Methyl-3-*O*-benzyl-2-deoxy-D-*erythro*-pentofuranos-5-yl)thiouracil (4). To a cooled (0 °C) suspension of sodium hydride (60% dispersion in mineral oil, 0.26 g, 6.4 mmol), previously washed with hexanes (3 x 10 mL), in dry DMF (5 mL) was added dropwise a solution of 2-thiouracil (0.74 g, 5.80 mmol) in dry DMF (25 mL). After the reaction mixture was stirred at room temperature for 1 h, a solution containing compound **3** (2.02 g, 5.80 mmol) in dry DMF (25 mL) was added dropwise. The resulting mixture was stirred at room temperature for 1 h, heated at 80 °C for 5 h and then cooled to room temperature. Following concentration, the residue was diluted with water (30 mL) and then extracted with CH_2Cl_2 (3 x 150 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography using hexanes/EtOAc (3:2) as the eluant to give **4** (1.69 g, 83% yield, anomeric mixture) as a gum: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.93-2.33 (*m*, 2H, H-2'), 3.27-3.50 (*m*, 5H, H-5' and OCH_3), 3.76-4.37 (*m*, 2H, H-3' and H-4'), 4.40-4.57 (*s*, 2H, CH_2Ph), 4.90-5.13 (*m*, 1H, H-1'), 6.11 (*d*, J = 7.5 Hz, 1H, H-5), 7.37-7.17 (*m*, 5H, Ph), 7.71 (*m*, 1H, H-6), 11.8-12.5 (*br.s*, 1H, N*H*). Anal. Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04; S, 9.20. Found: C, 58.80; H, 5.81; N, 7.84; S, 8.96.

2*S*,5'-Anhydro-1-(3-*O*-benzyl-2,5-dideoxy-β-D-*erythro*-pentofuranosyl)-2-thiouracil (5). Compound **4** (0.25 g, 0.72 mmol) was refluxed in a solution of hexamethyldisilazane (HMDS, 10 mL) containing catalytic $(NH_4)_2SO_4$ (*ca.* 25 mg) until the solution turned clear (10 h). The reaction mixture was then cooled to room temperature and the excess HMDS was removed by high vacuum distillation. The residue was dissolved in dry CH_3CN (5 mL), the resulting solution cooled to -20 °C, and trimethylsilyl-trifluoromethanesulfonate (TMS-OTf, 0.14 mL, 0.73 mmol) was added. After stirring at -20 °C for 2 h, the reaction mixture was warmed to room temperature and stirred for an additional 4 h. Following dilution with CH_2Cl_2 (60 mL), the organic mixture was extracted with cold sat'd $NaHCO_3$ (50 mL), dried over Na_2SO_4, and concentrated. Purification of the crude mixture on a Chromatotron [4.0 mm plate, gradient elution as follows: CH_2Cl_2 (50 mL); CH_2Cl_2/EtOAc (5:1, 200 mL); CH_2Cl_2/EtOAc/MeOH (20:5:1, 400 mL)] yielded compound **5** (0.10 g, 65% yield) as a white solid and the starting material **4** (82 mg). Physical data for compound **5** follow: mp 150-152 °C; $[\alpha]_D^{26}$ = -79.90° (c = 0.97, EtOH); Anal. Calcd for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85; S, 10.13. Found: C, 60.48, H, 5.32; N, 8.63; S, 10.16.

2-(3-*O*-Benzyl-2,5-dideoxy-1-methyl-ribofuranos-5-yl)-5'-(4-pyrimidon-2-yl)-3'-*O*-Benzyl-2',5'-dideoxy-2,5'-dithiouridine (6). Compound **4** (1.47 g, 4.2 mmol) was treated as described under **5** using 0.5 equivalent of trimethylsilyl-trifluoromethanesulfonate (TMS-OTf, 0.4 mL, 2.1 mmol). Purification of the crude mixture yielded compound **5** (0.10 g, 16.9% yield), the starting material **4** (0.82 mg) and **6** (0.32g, 25.8% yield). Anal. Calcd for $C_{33}H_{36}N_4O_7S_2$: C, 59.62; H, 5.46; N, 8.43. Found: C, 59.68, H, 5.42; N, 8.26. MS. m/e 664.1.

1-(3-*O*-Benzyl-2',5'-dideoxy-β-D-*erythro*-pentofuranosyl)-4-pyrimidin-one (7). Raney nickel-2800 (Ra-Ni, 50% in water, 6.0 g), previously washed with 2-propanol (3 x 5 mL), was added to a solution of **5** (0.54 g, 1.71 mmol) in 2-propanol (25 mL) and benzene (10 mL). The solution was heated at 90 °C with vigorous stirring for 3.5 h. The reaction mixture was cooled to room temperature and then filtered through a celite pad which was subsequently washed with absolute EtOH (100 ml). The filtrate was concentrated to give the crude product which was purified by column chromatography using EtOAc/MeOH (130:1) as the eluant to give **7** (0.17 g, 34.7% yield) as a gum: $[\alpha]_D^{26}$ = +2.97° (c = 1.045, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (*d*, 3H, CH_3, $J_{CH3,4'}$ = 6.30 Hz), 2.15 (*ddd*, 1H, H-2'β, $J_{2'\alpha,2'\beta}$ = 13.98 Hz, $J_{2'\beta,1'}$ = 7.60 Hz, $J_{2'\beta,3'}$ = 6.00 Hz), 2.49 (*ddd*, 1H, H-2'α, $J_{2'\alpha,2'\beta}$ = 13.98 Hz, $J_{2'\alpha,1'}$ = 7.50 Hz, $J_{2'\alpha,3'}$ = 2.70 Hz), 3.92 (*ddd*, 1H, H-3', $J_{3',2'\beta}$ = 6.00 Hz, $J_{3',4'}$ = 2.80 Hz, $J_{3',2'\alpha}$ = 2.70 Hz), 4.30 (*dq*, 1H, H-4', $J_{4',3'}$ = 2.80 Hz, $J_{4',CH3}$ = 6.30 Hz), 4.55 (s, 2H, CH_2Ph), 5.70 (*dd*, 1H, H-1', $J_{1',2'\beta}$ = 7.50 Hz, $J_{1',2'\alpha}$ = 7.50 Hz), 6.27 (*d*, 1H, H-5, $J_{5,6}$ = 7.82 Hz), 7.30 (*m*, 5H, Ph), 7.41 (*dd*, 1H, H-6, $J_{6,2}$ = 2.78 Hz, $J_{6,5}$ = 7.82 Hz), 8.23 (*d*, 1H, H-2, $J_{2,6}$ = 2.78 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.87 (*C*H_3), 38.33 (C2'), 71.70 (*C*H_2Ph), 81.33 (C4'), 82.44 (C3'), 91.26 (C1'), 112.85 (C5), 127.71 (Ph (C2, C6)), 128.08 (Ph (C4)), 128.59 (Ph (C3, C5)), 137.29 (Ph (C1)), 137.52 (C6), 150.14 (C2), 170.63 (C4). Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.33; N, 9.79. Found: C, 67.38; H, 6.38; N, 9.56.

2-(Ethyl-3-*O*-benzyl-2-deoxy-α-D-*erythro*-pentofurano-5-yl)thiouracil (8). Cyclohexene (14 mL) and $Pd(OH)_2$/C (20%, 0.14 g) were added to a solution of **5** (0.14 g, 0.44 mmol) in absolute EtOH (28 mL) and the reaction mixture was heated at 85 °C for 24 h. The solution was filtered through a celite pad, which was subsequently washed with hot MeOH (150 ml). Following concentration of the filtrate, the residue was purified by column chromatography using of hexanes/EtOAc (4:1) as the eluant to give **8** (0.12 g, 74.8% yield) as a gum: $[\alpha]_D^{26}$ = +73.43° (c = 0.99, EtOH); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.00-1.03 (*t*, 3H, CH_2CH_3), 1.77-2.40 (*m*, 2H, H-2'), 3.03-4.00 (*m*, 5H, H-4', H-5' and C$H_2$$CH_3$), 4.17-4.40 (*m*, 1H, H-3'), 4.40-4.73 (*s*, 2H, CH_2Ph), 4.90-5.20 (*m*, 1H, H-1'), 6.13 (*d*, 1H, H-5, $J_{5,6}$ = 7.50 Hz), 6.73-7.53 (*s*, 5H, Ph), 7.63 (*d*, 1H, H-6, $J_{5,6}$ = 7.50 Hz), 12.86 (*s*, 1H, N*H*). Anal. Calcd for $C_{18}H_{22}N_2O_4S$: C, 59.64; H, 6.12; N, 7.73; S, 8.85. Found: C, 59.74; H, 6.25; N, 7.56; S, 8.64.

2-(Methyl-3-*O*-benzyl-2-deoxy-α-D-*erythro*-pentofurano-5-yl)thiouracil (9). The same procedure followed for **8** using MeOH gave **9** in 58.1% yield as white powder: mp 80-82 °C; $[\alpha]_D^{26}$ = +90.21° (c = 2.9, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (*ddd*, 1H, H-2'β, $J_{2'\beta,1'}$ = 1.5 Hz, $J_{2'\beta,3'}$ = 3.3 Hz, $J_{2'\beta,2'\alpha}$ = 15.00 Hz), 2.29 (*ddd*, 1H, H-2'α, $J_{2'\alpha,1'}$ = 5.4 Hz, $J_{2'\alpha,3'}$ = 8.00 Hz, $J_{2'\alpha,2'\beta}$ = 15.00 Hz), 3.4 (*s*, 3H, OCH_3), 3.43-3.51 (*m*, 2H, H-5'), 3.91 (*ddd*, 1H, H-3', $J_{3',2'\beta}$ = 3.3 Hz, $J_{3',4'}$ = 4.5 Hz, $J_{3',2'\alpha}$ = 8.00 Hz), 4.38 (*ddd*, 1H, H-4', $J_{4',3'}$ = 4.5 Hz, $J_{4'\alpha,5'\alpha}$ = 4.9 Hz, $J_{4',5'}$ = 5.5 Hz), 4.56 (q_{AB}, 2H, CH_2Ph, J = 12 Hz), 5.06 (*dd*, 1H, H-1', $J_{1',2'\beta}$ = 1.5 Hz, $J_{1',2'\alpha}$ = 5.4 Hz), 6.21 (*d*, 1H, H-5, $J_{5,6}$ = 6.6 Hz), 7.2-7.3 (*m*, 5H, Ph), 7.8 (*d*, 1H, H-6, $J_{5,6}$ = 6.6 Hz), 13.2 (*br s*, 1H, N*H*). Anal. Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04; S, 9.20. Found: C, 58.76; H, 5.79; N, 7.89; S, 8.98.

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References

1. Taken in part from a Masters of science thesis (L. J. Ping), Departement of Chemistry; University of Rhode Island, May 1991.
2. Horwitz, J. P.; Chua, J.; Noel, M. *J. Org. Chem.* **1964**, *29*, 2076.
3. Lin, T. S.; Prusoff, W. H. *J. Med. Chem.* **1978**, *21*, 109.
4. Fischl, M. A.; Richman, D. D.; Grieco, M. H.; Gottlieb, M. S.; Volberding, P. A.; Laskin, O. L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Schooley, R. T.; Jackson, G. G.; Durack, D. T.; King, D. *N. Engl. J. Med.* **1987**, *317*, 185.
5. Baba, M.; Pauwels, R.; Herdewijn, P.; De Clerq, E.; Desmyler, J.; Vendeputte, *M. Biochem. Biophys. Res. Commun.* **1987**, *142*, 128.
6. Lin, T. S.; Chen, M.S.; McLaren, C.; Gao, Y. S.; Ghazzouli, L.; Prusoff, W. H. *J. Med. Chem.* **1987**, *30*, 440.
7. Lin, T. S.; Guo, J.Y.; Schinazi, R.F.; Chu, C.K.; Xiang, J. N.; Prusoff, W. H. *J. Med. Chem.* **1988**, **31**, 336.
8. Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci.*, U.S.A. **1986**, *83*, 1911.
9. Prisbe, E.J.; Maag, H.; Verheyden, J. P. H. *ACS Natl. Meeting 201st*, Atlanta, GA, Carb 28, April 14-19, **1991**.
10. Jarvi, E. T.; Sunkara, P. S.; Bowlin, T. L. *Nucleosides & Nucleotides*, **1989**, *8*, 1111.
11. Freskos, J. N. *Nucleosides & Nucleotides* **1989**, *8*, 549.
12. Okauchi, T.; Kubota, H.; Narasaka, K. *Chem. Lett.* **1989**, 267.

13. Vargeese, C.; Abushanab, E. *J. Org. Chem.* **1990**, *55*, 4400.
14. Mizuno, Y.; Kaneko, C.; Oikawa, Y. *J. Org. Chem.* **1974**, *39*, 1440.
15. Lin, T. S.; Shen, Z.-Y.; August, E. M.; Brankovan, V.; Yang, H.; Chazzouli, I.; Prusoff, W. H. *J. Med. Chem.* **1989**, *32*, 1891.
16. Ueda, T. and Shibuya, S. *Chem. Pharm. Bull.* **1970**, *39*, 1440.
17. Abraham, R. J.; Fisher, J.; Loftus, P. "Introduction to NMR Spectroscopy," John Wiley & Sons, **1988**, p. 45.
18. Brown, D. M.; Parihar, D. B.; Todd, A.; Varadarajan, S. *J. Chem. Soc.* **1958**, 3028.
19. Fox, J. J. and Wempen, I. *J. Org. Chem.* **1969**, *34*, 1020.
20. Bannister, B. and Kagan, F. *J. Am. Chem. Soc.* **1960**, *82*, 3363.
21. Reist, E. J.; Benitez, A.; Goodman, L. *J. Org. Chem.* **1963**, *29*, 554.
22. Bauer, L.; Wright, G. E.; Mikrut, B. A.; Bell, C. L. *Heterocycles*, **1965**, 447.
23. Barlin, G. B.; Brown, D. J.; Fenn, M. D. Aust. *J. Chem.* **2984**, *37*, 2391.
24. Brown, D. J.; Hoerger, E.; Mason, S. F. *J. Chem. Soc.* **1955**, 211.
25. Heck, R.F. "Palladium Reagents in Organic Syntheses", Academic Press, New York **1985**, p.118.

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