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3'-Deoxy-3'-Hydroxymethyl-aldopentopyranosyl Nucleoside Synthesis. Part I.

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Abstract : A straightforward synthesis of 3'-deoxy-3'-hydroxymethyl-aldopentopyranosyl nucleosides is described starting from β-D-xylopyranosyl nucleosides. β-D-xylopyranosyl thymine **17a,b,c** and uracil **17d** are converted into the 4'-benzoylated derivatives **18a,b** and further into the 2',3'-enepyranosyl compounds **19b,c**. A 3'-hydroxymethyl appendix has been introduced using a free-radical methodology to furnish **20a,b**. Inversion of configuration of the 4'-position yielded the target nucleosides **22a,b**. X-ray and ^{1}H NMR conformation analysis prove the equatorial orientation of the base moiety in the target compounds.

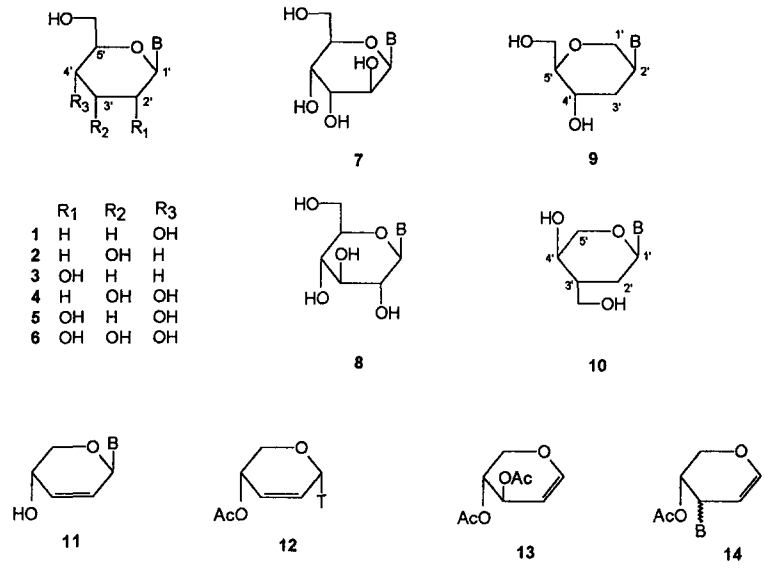
INTRODUCTION

The interest in methodologies to synthesize nucleosides with a six membered carbohydrate moiety has increased during the last years. This is due to recent developments in the antiviral field and to their use as building blocks for oligonucleotide synthesis. Pyranosyl-oligonucleotides have been synthesized with the aim of obtaining antisense molecules with potential antitumoral activity[1] or in a search after the chemical etiology of the natural nucleic acids[2]. Pyranosyl-like nucleosides have been found to possess potent antiherpes activity[3].

The pyranosyl nucleosides which have been used as building blocks for oligonucleotide synthesis [2',3'-dideoxy-D-*erythro*hexopyranosyl[1,2] (**1**), 2',4'-dideoxy-D-*erythro*hexopyranosyl[1] (**2**), 3',4'-dideoxy-D-*erythro*hexopyranosyl[1] (**3**), 2'-deoxy-D-*ribo*hexopyranosyl[2] (**4**), 3'-deoxy-D-*ribo*hexopyranosyl[2] (**5**), D-allopyranosyl[2] (**6**), D-altropyranosyl[2] (**7**), D-glucopyranosyl[2] (**8**)] all have an anomeric centre, a base moiety in the 1'-position and the hydroxymethyl group in the 5'-position (Scheme 1).

This is not so, however, with the antiviral compounds, where the substitution pattern differs from the natural carbohydrate structure. These compounds (**9**) have a 2',5'-substitution pattern between the base moiety and the hydroxymethyl group and no anomeric centre. The removal of the anomeric center in **9** resulted in a conformational change which places the base part in the axial orientation[4] instead of the usual equatorial conformation. The question about the reason for the biological activity is, most probably, related to the problem of the conformational preference of **9**, which could be due to the presence of repulsion forces between the secondary hydroxyl group and the lone pairs of the ring oxygen atom of **9**. These structural characteristics could be important for selective recognition of the molecules by the thymidine kinase of herpes viruses[5]. In an effort to find the reason for the biological activity of **9**, we started the synthesis of several pyranosyl-like nucleosides (**10**) with one hydroxymethyl group and one hydroxyl group in positions 3' and 4' with respect to the pyrimidine base moiety (uracil, cytosine, thymine in the 1' position). In the structures (**10**) presented here, the anomeric centre is conserved while the hydroxymethyl group and the secondary hydroxyl group are interconversed with respect to **9**.

Scheme 1



	R_1	R_2	R_3
1	H	H	OH
2	H	OH	H
3	OH	H	H
4	H	OH	OH
5	OH	H	OH
6	OH	OH	OH

SYNTHESIS

The synthesis of the branched pyranosyl nucleosides of type **10** starts with the synthesis of β-D-glycero-pent-2'-eno-pyranosyl nucleosides **11** (B = T,U) (Scheme 1). Compounds of this structure can be considered to be the products of a Ferrier rearrangement[6,7]. A well known propensity of this reaction to furnish the most thermodynamically stable products is a discouraging factor and, in fact, attempted condensation of trimethylsilylated thymine with di-O-acetyl-D-xylal (**13**) under the influence of tritylium perchlorate and lithium perchlorate has furnished exclusively the α anomer **12**[8] (Scheme 1). Moreover, the carbon atom C3 in glycal **13** can also act as an electrophile to furnish compounds of a type **14**[9,10] (Scheme 1). Finally, acid catalyzed 1,2 addition of 6-chloropurine to a double bond in 3,4,6-tri-O-acetyl-D-glucal[11] and 3,4-di-O-acetyl-D-arabinal[12] has been recorded*. It should be noted that β-D-glycero-2',3'-dideoxypent-2'-enopyranosyl thymine **11** (B = T) has been obtained in small yield during Lewis acid catalyzed reaction of 1,3,4-tri-O-benzoyl-2-deoxy-β-D-ribo-pyranose with trimethylsilylated thymine, along with the expected anomeric mixture at 3',4'-di-O-benzoyl-2'-deoxy-D-erythro-pentapyranosyl thymine[13].

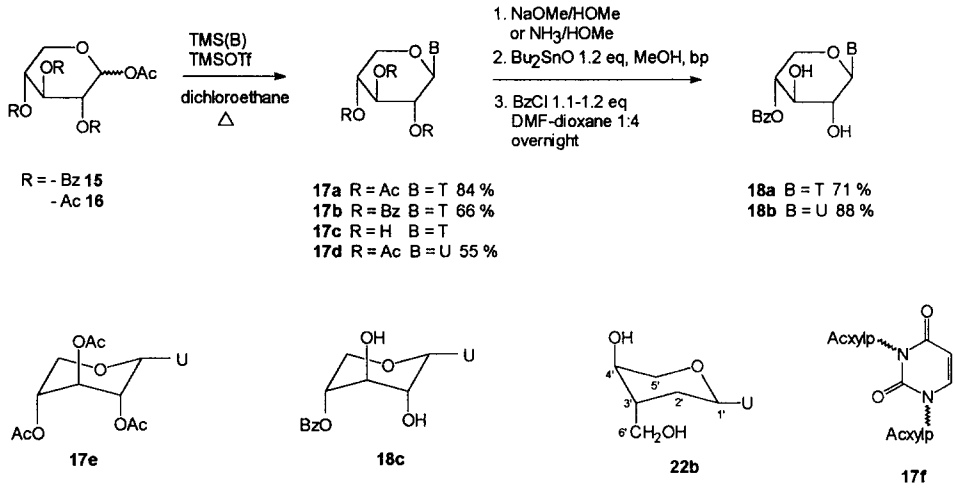
In view of these facts we have planned our synthesis of olefins **11** (B = T,U) in a stepwise way which involves (i) sugar-base condensation; (ii) selective 4'-O-protection and (iii) conversion of the resulting vicinal diol into an olefin.

Using either 1-O-acetyl-2,3,4-tri-O-benzoylxylopyranose[14] (**15**) or 1,2,3,4-tetra-O-acetylxylopyranose[15] (**16**) and trimethylsilylated thymine under the influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane (Vorbrüggen conditions), good yields of the coupled products **17a** and **17b** have been obtained (Scheme 2). The compound **17b** has previously been obtained but has not been characterized[16]. The nucleoside **17a** has been accompanied by small amount of the corresponding α anomer (5 %). Deprotection of the acyl

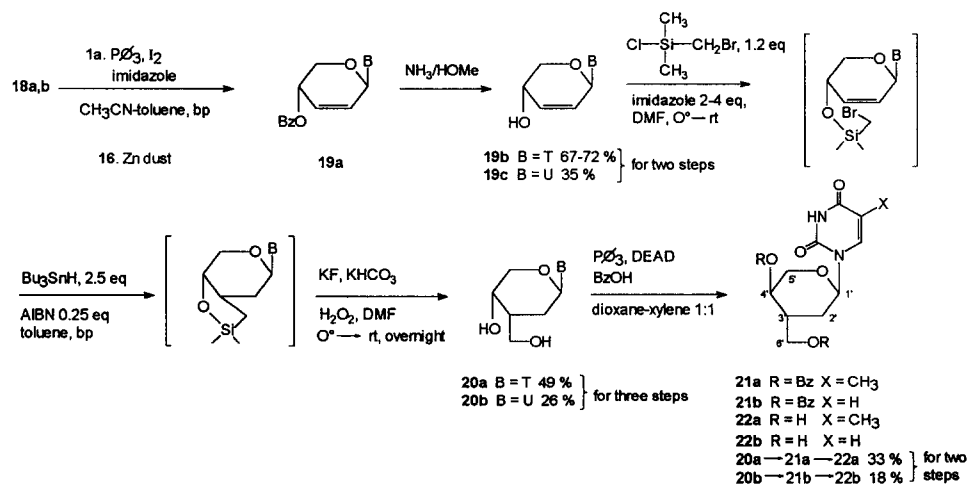
* Yet, a series of β configured pent-2'-enopyranosyl nucleosides of a type **11** (B = A,C,G) can be easily prepared using modification of the known procedures; manuscript in preparation.

functions (NaOMe/HOMe or NH_3/HOMe) has furnished a deprotected pentopyranosyl nucleoside **17c**. Selective 4'-O-benzoylation has been performed by analogy[17] to the procedure described for methyl β-D-xylopyranoside to give **18a** in 71 % yield. This vicinal diol has been subjected to several olefination conditions[18] (I a. MsCl, Py, b. NaI, Zn; II a. $HC(OMe)_2NMe_2$, b. Ac_2O, Δ; III a. ClCS(OPh), Py, b. Bu_3SnH, AIBN). These methods did not give satisfactory results and only a combination of two other procedures[19,20] has been successful. Boiling of the diol **18a** in acetonitrile-toluene in the presence of triphenylphosphine and imidazole and portionwise addition of iodine, followed by addition of zinc powder (to facilitate collapse of the intermediate iodo triphenylphosphonium complex), has furnished the olefin **19a** (B = T), which co-migrates on TLC with triphenylphosphine oxide (Scheme 3). Therefore a mixture of both has been treated with NH_3/HOMe to remove the 4'-protecting group. The product **19b** (much more polar than **19a**, B = T) has been isolated in 67-72 % yield for two steps.

Scheme 2



Scheme 3

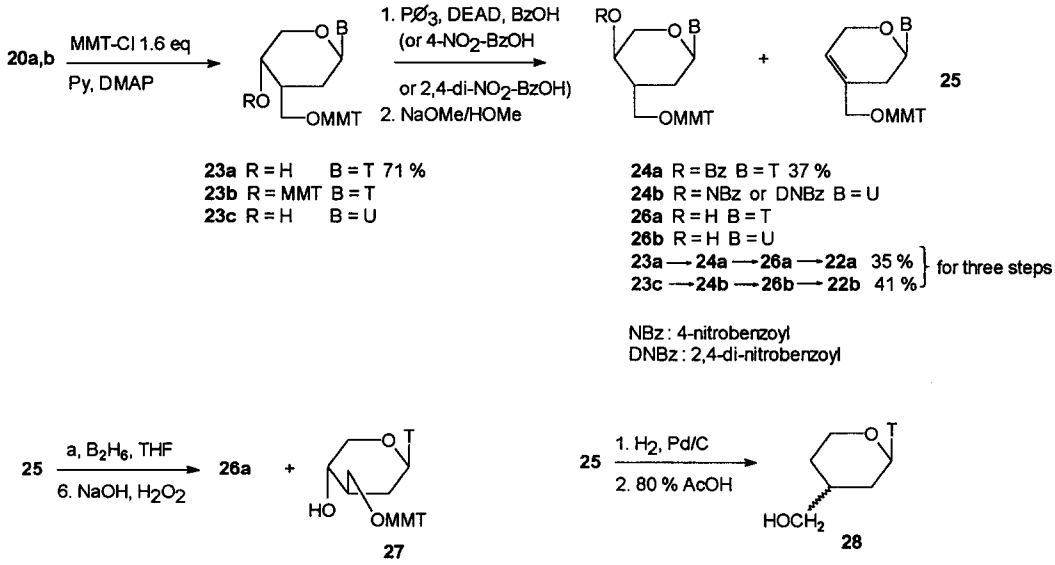


The 3'-hydroxymethyl appendix has been introduced in a syn manner with respect to the 4'-OH group by way of a known procedure[21,22], which has already been applied in carbohydrates[23,24] and nucleosides[25]. The branched nucleoside **20a** has been obtained in 49 % yield for three consecutive steps. NMR data of **20a** (D_2O, 500 MHz) : H1' δ 5.89, $J_{1',2'ax}$ = 7.1 Hz, $J_{1',2'eq}$ = 4.8 Hz; H4' δ 4.10, $J_{4',5'ax}$ = 8.1 Hz, $J_{4',5'eq}$ = $J_{4',3'}$ = 4.1 Hz, suggests either a flattened $^4C_1$ conformation of the pyranosyl ring (with equatorial thymine and axial 3'-hydroxymethyl appendix) or an equilibrium $^4C_1 \rightleftharpoons {}^1C_4$, the former conformer being predominant. This is in accordance with a previously noticed tendency for pyranosyl nucleosides to locate a heterocyclic base in an equatorial position[25].

Inversion of configuration at the carbon atom 4' has been achieved by a Mitsunobu reaction[26]. Treatment of the diol **20a** with triphenyl phosphine-diethyl azodicarboxylate-benzoic acid has furnished an intermediate dibenzoate **21a** accompanied by elimination product(s). Without characterization, this mixture has been O-deprotected. The most polar compound formed has been shown to be the target **22a**. Alternatively, the primary OH group in **20a** has been reacted with methoxyphenyl diphenylmethyl chloride to furnish **23a** (small amount of bis-protected derivative **23b** has also been formed) (Scheme 4). Mitsunobu inversion of configuration yielded a benzoate **24a** (formed in 37 % yield) and an elimination product **25**. The exact yield of **25** is not known due to difficulties of its purification by chromatography (interference with benzoic acid).

Methanolic ammonia treatment of **24a** has furnished **26a**, a building block for antisense constructs[1]. Acid treatment of **26a** yielded a deprotected compound **22a**, identical with the one obtained via the di-O-benzoate **21a**. The signal of the 4' proton in **22a** is a singlet (half-width 3H, δ 3.78, D_2O). This, together with a coupling pattern of the anomeric proton ($J_{1'2'ax}$ 10.8 Hz, $J_{1'2'eq}$ 2.8 Hz, δ 5.56) again favours $^4C_1$ conformation with C3',4' functionalities disposed axially. This finding is confirmed by X-ray study of **22b** (see below). The elimination product **25** has been subjected to a hydroboration-oxidation procedure to furnish **26a** and (formed in equal amounts) the less polar diastereomeric product **27**. Finally, reduction of the double bond in **25**, followed by de-methoxytritylation has furnished an unseparable 1:1 mixture of the product **28**.

Scheme 4



Repitition of the above scheme with uracil has furnished a compound **22b** (Scheme 3) (which also adopts a $^4C_1$ conformation in D_2O solution and in a crystalline form). Our initial plan to convert it to a cytidine analogue has been impeded by a low yield of the olefination step (**18b→19c**) (Scheme 3) and the 3' branching step (**19c→20b**)

(Scheme 3). In both cases the yields with the uracil base were half lower than for the thymine counterpart. Also, the glycosylation step has to be precisely controlled to avoid N1,N3-bis glycosylation and extensive β→α anomerization (see Experimental). Two compounds, identified by mass spectrometry as **17f**, have been isolated. However, we were unable to establish their anomeric configurations on the bases of a 200 MHz spectrum. The α-D anomer **17e** can be separated by chromatography after the glycosylation step (it is slightly more polar than the β-D anomer **17d**), or (much easier) after 4'-benzoylation step (compound **18c** is less polar than **18a**). Both α -D derivatives **17e** and **18c** adapt exclusively a $^1C_4$ conformation in DMSO-d_6 solution as evidenced by the shapes of the H1',2',3',4' resonance lines. All four appear as broadened singlets excluding any diaxial couplings. It is clear that the functionalities at the carbon atoms C2',3',4' are oriented axially and that the driving force for this is a pronounced tendency for a uracil to adapt the equatorial position (the same applies to **20b**, **22b** and to thymine in **20a** and **22a**). Anomeric effect does not favour an axially oriented uracil or thymine, since it is considered to be weak[29]. Moreover, electron withdrawing properties of the two oxygen atoms at C2,4 decrease the electron density at N1 imparting a partial positive character to it, favouring therfore an equatorial orientation of a pyrimidine via reversed anomeric effect[29]. This, in conjunction with a steric bulk of both pyrimidines, may explain the conformational features of the products **17e**, **18c**, **20a,b** and **22a,b**, although it is intriging that the tendency of a pyrimidine to adopt equatorial orientation overrides all syn-diaxial interactions of the substituents at the carbon atoms C2',3',4'. Similar behaviour has already been recorded for 2,3,4-tri-O-acetyl-α-D-xylopyranosyl imidazole[30]. An interesting manifestation of an axial orientation of the 4'-OH group is its deshielding influence on the axial proton 2', which is located ca 0.4 ppm downfield in relation to the equatorial one in both compounds **22a,b**.

In order to assign the configuration of **22b** we have completely analyzed its ^1H NMR spectrum. In the COSY experiment the connectivities between the resonance of H-1' and those of H-2A' and H-2B', as well as between the latter and the resonances for H-3' can be identified. The assignment of the resonances of the other protons by a COSY experiment is uncertain (some coupling constants smaller than the resolution, they can be identified from the shape of the patterns in the 1D NMR spectrum). Taking into consideration the small values for the vicinal coupling constants in the AB part of an ABX spin system (H-5A', H-5B' and H-4') with A at δ 4.01 and B at δ 3.92 (typical values for the coupling constants between H-5' and H6' in the D-*galacto* configuration in the $^4C_1$ form of aldohexopyranoses), we ascribe these resonances to the protons C-5' of the present compound. The AB resonances of the other ABX spin system (H-6A', H-6B' and H-3') at δ 3.80 and δ 3.76 are ascribed to H-4'. Although the resonance for H-3' can be assigned from the COSY experiment, the resonances for H-3' and H-4' can be discriminated by considering the chemical shifts. It is indeed expected that a proton in α place of an electronegative group is expected at a lower field, than in the case that it is sandwiched between two α-carbon protons.

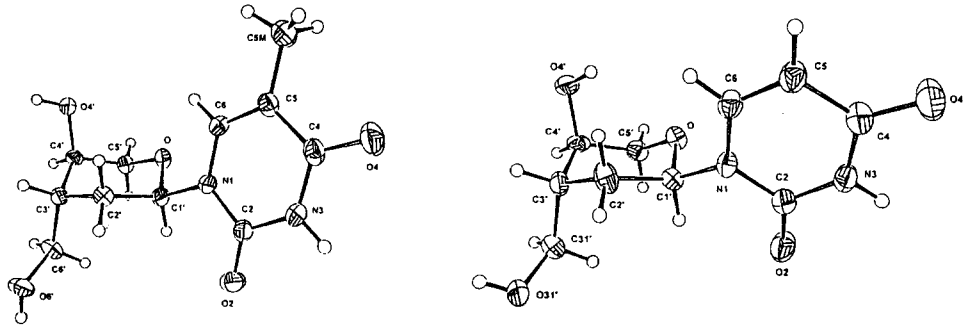
From the patterns for H-1', H-2B' and H-2B' we measure : $^3J(1',2A') = 10.9$ Hz, $^3J(1',2B') = 2.8$ Hz, $^3J(2A',3') = 5.7$ Hz and $^1J(2B',3') = 2.5$ Hz. We have compared these values with those measured in 2-deoxy-α,β-D-*arabino*hexopyranose and 2-deoxy-α,β-D-*lyxo*hexopyranose[27]. For the α-D form in the $^4C_1$ configuration it was reported : $^3J(1,2ax) = 3.2/3.6$ Hz, $^3J(1,2eq) = 1.2/1.3$ Hz, $^3J(2ax,3) = 11.8/12.0$ Hz and $^3J(2eq,3) = 5.1/5.6$ Hz. For the α-D form it was reported : $^3J(1,2ax) = 9.6/9.8$ Hz, $^1J(1,2eq) = 2.1$ Hz, $^3J(2ax,3) = 12.0$ Hz and $^3J(2eq,3) = 4.9$ Hz. The values found for the vicinal coupling constants between H-1' and H-2ax' (= H-2A') on one hand and H-2eq' (= H-2B') on the other point to the β-D form in the $^4C_1$ configuration. The values found for the coupling constants between H-2eq' and H-2ax' point to an axial position of the substituent on C-3' in this configuration. It is not possible to unravel the pattern for H-3', because it is the som of $^3J(2ax',3')$, $^3J(2eq',3')$, $^3J(3',4')$, $^3J(3',6A')$, $^3J(3',6-B')$ and a long-range coupling constant between H-3' and H-5'.

From the patterns for H-5A' and H-5B' it follows that $^3J(4',5A') \approx 1.6$ Hz and that also $^3J(4',5B')$ is small. H-5B' even has a long-range coupling constant with H-3'. From the bandwith of H-4' it follows that $^3J(3',4')$ is very small (1 Hz). These values are in agreement with the data found for such coupling constant in α- and β-L-arabinopyranose and α- and β-D-galactopyranose[28] where $^3J(3,4) = 3.2/3.7$ Hz, $^3J(4,5ax) = 1.5$ Hz and $^3J(4,5eq) = 2.4/2.5$ Hz. The values for $^3J(4,5Hz)$ and $^3J(4,5B)$ point to a $^4C_1$ configuration for **22b**. Indeed, in

the $^1C_4$ configuration the coupling constants between H-4 and H-5ax should be ≃ 11 Hz. Since $^3J(3,4)$ for a D-*galacto* configuration in the $^4C_1$ configuration is expected to be ≈3.5 Hz, the small value for $^3J(3',4')$ found for the present compound here point again to the axial disposition. The values for the coupling constants $^3J(3',6A')$ and $^3J(3',6B')$ are averaged values and point to free rotation of the CH_2OH-6' group.

The extensive elimination during inversion of configuration at the position 4' during Mitsunobu reaction has been tried to overcome by using p-nitrobenzoic acid or 2,4-di-nitrobenzoic acid instead of benzoic acid. It has been reported[31] that application of a more acidic nucleophilic components (i.e. whose conjugated bases are weaker) increases the yield of inverted products. Using the three acids mentioned above, however, we have not noticed a substantial change in the substitution/elimination ratio.

Both compounds **22a,b** have also been examined by X-ray (Scheme 5A and 5B). Crystals were obtained by slow evaporation methods. Application of the monomer **26a** for oligomer synthesis, hybridization properties and results of biological studies will be published later.



Scheme 5 : ORTEP drawing of the thymine compound 22A and the uracil compound 22B

TABLE 1

Identification code	22a	22b	Identification code	22a	22b
Empirical formula	$C_{11}H_{16}N_2O_5$	$C_{10}H_{14}N_2O_5$	$F(000)$	544	256
Formula weight	256.26	242.23	Crystal size	0.3 x 0.2 x 0.2 mm	0.4 x 0.2 x 0.2 mm
Temperature	293(2) K	293(2) K	Theta range	2.01 to 24.95°	2.22 to 24.97°
Wavelength	0.71069 A	0.71069 A	Scan mode	ω	ω
Crystal system	orthorhombic	monoclinic	Index ranges	$-6\le h\le 6$, $-14\le k\le 14$,	$-10\le h\le 10$, $0\le k\le 7$,
Space group	$P2_1\,2_1\,2_1$	$P2_1$		$-22\le l\le 22$	$-11\le l\le 6$
Unit cell dimensions	a = 5.207(3) Å	a = 8.875(7) Å	Reflections collected	5483	1977
	b = 11.918(7) Å	b = 6.596(5) Å	Independent reflections	2099 [R(int) = 0.0533]	1033 [R(int) = 0.0334]
	c = 19.168(10) Å	c = 9.656(7) Å	Observed reflections	1612	639
	α = 90.00(4) °	α = 90.00(6) °	Refinement method	Full-matrix least-sq.	Full-matrixleast-sq.
	β = 90.00(4) °	ß = 108.34(6) °		on F^2	on F^2
	γ = 90.00(4) °	γ = 90.00(6) °	Data/parameters	2099/167	1033/159
Volume	1189.5(11) Å^3	536.6(7) Å^3	Goodness-of-fit on F^2	1.026	0.993
Z	4	2	Weighting scheme	a = 0.0333, b = 0.0044	a = 0.0449, b = 0.00
Density (calculated)	1.431 Mg m^{-3}	1.499 Mg m^{-3}	$w=1/(\sigma^2(F_o^2)+(aP)^2+bP$ with $P=(\mathrm{Max}(F_o^2,F_o)+2F_c^2)/3$		
Absorption coeff.	0.114 mm^{-1}	0.121 mm^{-1}	Final R indices	R_1 = 0.0299,	R_1 = 0.0345,
			$[F_o>4\sigma(F_o)]$	wR_2 = 0.0650	wR_2 = 0.0726
			R indices (all data)	R_1 = 0.0547,	R_1 = 0.0889,
				wR_2 = 0.0717	wR_2 = 0.0865
			Extinction coefficient	0.024(2)	0.053(9)
			Largest diff. peak and hole	0.156 and -0.119 e.A^{-3}	0.182 and -0.182 e.A^{-3}

GENERAL

Silylations of thymine and uracil have been performed in boiling hexamethyldisilazane (HMDS; ca 2 ml per 1 mmol of a pyrimidine) in the presence of a catalytic amount of $(NH_4)_2SO_4$, with exclusion of moisture, until reaction mixtures become homogenous. The solutions have been cooled down to room temperature, evaporated and co-evaporated with p-xylene using an oil pump. Vaccum has been broken using dry nitrogen. Sugar-base couplings, 4'-O-benzoylations and Mitsunobu reactions have been performed under a blanket of dry nitrogen.
NMR spectra have been recorded on a Bruker AM-360 spectrometer or a Varian 200 or 500 spectrometers in DMSO-d_6 solutions unless otherwise stated. The symbols H6',6" refer to the protons of the 3'-hydroxymethyl appendix. The ^1H NMR spectra of **20b** (20 mg compound in 0.4 ml DMSO-d_6 solutions) at 20°C were obtained with a BRUKER AM500 spectrometer operating at 500.12 MHz, using a pulse angle of 19° and a resolution of 0.33 Hz/point. The methyl resonance of DMSO (= δ 2.5) was used as secundary reference.
The COSY 45 experiment was recorded in absolute value mode using a 90° (^1H)-t_1-45°(^1H)-t_2 sequence[32]. A 0.5 K x 1 K data matrix was obtained with 16 scans. No zero filling was performed. Resolution enhancements in ω_1 and ω_2 were obtained by a 2-shifted sine-bell function in t_2 and t_1.
UV absorptions have been recorded in MeOH solutions with Philips PU 8740 UV/Vis spectrophotometer. Exact mass measurements (HRMS) have been performed on a Kratos Concept 1H mass spectrometer (Kratos, Manchester, U.K.). Conditions for the liquid secondary ion mass spectra (LSIMS) with Cs^+ as primary ion beam, chemical ionisation (CI) and electron impact (EI) mass spectra are given further.
X-ray diffraction intensities were measured on a Stoe STADI4 diffractometer using graphite-monochromated Mo Kα radiation. Crystal data collection and refinement parameters are listed in Table 1.
The atomic coordinates and other data for **22a** and **22b** is deposited in the Cambridge Crystallographic Data Centre. This data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

2',3',4'-Tri-O-acetyl-β-D-xylopyranosylthymine 17a
To a trimethylsilylated thymine (prepared from 8.8 g, 75 mmol of a base) has been added a solution of 20 g (75 mmol) of per-O-acetylated xylopyranose **16**[15] in 240 ml of dichloroethane via a canula, followed by TMSOTf, 50 mmol, 9.6 ml. This clear solution has been kept on an oil bath at 58° overnight, followed by 70° for 24 more hours. TLC (in CH_2Cl_2-MeOH 20:0.5) clearly shows the main β product, and a very small amount of a more polar α anomer, which has not been analyzed. Extractive work-up and chromatography in CH_2Cl_2-MeOH 1000:25 gave 16.59 g of pure **6a**, and 5.5 g of contaminated fractions. Re-purification has furnished 2.72 g of **17a**. Total yield : 19.31 g (84 %). This mixture consists of 95 % of the β anomer by integration of H-1' signals.
^1H (360 MHz) δ : 11.38 (s, 1H, H-3); 7.85 (s, 1H, H-6); 5.88 (d, 1H, $J_{1'2'}$ = 8.9 Hz, H-1'); 5.46 (t, 1H, J 9.4 and 9.4 Hz, H2'(3'); 5.38 (t, 1H, J 9.1 and 9.3 Hz, H3'(2'); 5.12 (dt, 1H, $J_{4'5'eq}$ = 5.4 Hz, $J_{4'5'ax}$ = $J_{4'3'}$ = 10.2 Hz, H-4'); 3.97 (dd, 1H, $J_{5'eq4'}$ = 5.5 Hz, $J_{5'eq5'ax}$ = - 11.1 Hz, H 5'eq); 3.74 (t, 1H, $J_{5'ax5'eq}$ = - 10.8 Hz, $J_{5'ax4'}$ = 10.8 Hz, H5'ax); 2.01, 1.98 and 1.82 (three s, 3H each OAc); 1.76 (s, 3H, CH_3).
α anomer : 5.94 (d, 1H, $J_{1'2'}$ = 3.5 H); it was impossible to extract other signals pertaining to this compound; HRMS (EI) calc. for $C_{16}H_{20}N_2O_9$: 384.1168, found 284.1172.

2',3',4'-Tri-O-benzoyl-β-D-xylopyranosyl-thymine 17b
The anomeric mixture of 1-O-acetyl-2,3,4-tri-O-benzoyl-D-xylopyranose 15 (3.3 g; 6.5 mmol) has been added to trimethylsilylated thymine [prepared from 1.86 g (14.8 mmol) of thymine] in dry dichloromethane (50 ml). This solution has been treated with 1.5 ml (7.8 mmol) of TMSOTf at 0°. The reaction mixture has been left overnight at room temperature. More catalyst has been added (1.4 ml, 7.2 mmol) and reflux has been maintained during 10 h. Extractive work-up followed by chromatography (CH_2Cl_2-MeOH 1000:7.5) furnished 2.48 g (66 % counted on a carbohydrate) of **17b** as a glassy material.

^{1}H (360 MHz) δ : 11.35 (s, 1H, H-3); 8.05 (2, 1H, J_{6,CH_3} = 1.0 Hz, H-6); 7.89 - 7.39 (m, 15H, H aromatic); 6.26 (d, 1H, $J_{1'2'}$ = 9.1 Hz, H-1'); 6.14 (t, 1H, $J_{3'4'} = J_{3'2'}$ = 9.5 Hz, H-3'); 5.91 (t, 1H, $J_{2'1'}$ and $J_{2'3'}$ = 9.2 and 9.3 Hz, H-2'); 5.64 (dt, 1H, $J_{4'5'eq}$ = 5.5 Hz, $J_{4'3'}$ and $J_{4'5'ax}$ = 10.0 Hz, H-4'); 4.29 (dd, 1H, $J_{5'eq4'}$ = 5.5 Hz, $J_{5'eq5'ax}$ = - 11.1 Hz, H-5'eq); 4.11 (t, 1H, $J_{5'ax4'}$ = 10.8 Hz, $J_{5'ax5'eq}$ = - 10.9 Hz, H-5'ax); 1.82 (d, 3H, J_{6,CH_3} = 1.0 Hz, CH3).
HRMS (CI, i-butane) : calc. for $[M+H]^+$ $C_{31}H_{27}N_2O_9$ 571.1717, found 571.1747.

β-D-xylopyranosyl thymine 17c

A. From **17a**

To a solution of the triacetate **17a** (19.31 g) in 600 ml of absolute MeOH has been added a small piece of metallic sodium. After two days the solution has been neutralized with Dowex WX-8 $H^{\oplus}$ resin. The resin has been filtered and washed with MeoH. The combined solution has been evaporated and dried on an oil pump to furnish 12.63 g (97 %) of the deprotected compound **17c** which has not been characterized.

B. From **17b**

Compound **17b** (2.48 g) in 60 ml of methanol saturated with ammonia (at 0°) has been left overnight. The solvent has been evaporated. The residual oily material has been passed through a short bed of silica gel in CH_2Cl_2-MeOH 5:1 containing a few ml of Et_3N. Fractions containing the product (R_f 0.24) have been evaporated and dried to yield 0.82 g (73 %) of **17c**.

4'-O-benzoyl-β-D-xylopyranosyl thymine 18a

The triol **17c** 1.01 g (3.91 mmol) and 1.13 g of Bu_2SnO (98 % pure, 4.45 mmol) in 50 ml of MeOH has been boiled during 2.5 hours. The nearly clear solution has been evaporated to dryness and co-evaporated with dioxane. Vacuum has been broken with dry N_2. The glassy residue has been solubilized in DMF (4.5 ml) and dioxane (35 ml) under N_2. This solution has been chilled in an ice-bath and benzoyl chloride 0.53 ml (4.6 mmol) has been injected. After the solution has been kept overnight at room temperature the solvent has been evaporated. Co-evaporation with p-xylene has removed the residual DMF. The product spontaneously crystallized after addition of 8 ml of ethyl acetate, to furnish 1.01 g (71 %) of **18a**.
mp 226-233 dec (cryst. CH_2Cl_2-MeOH)
^{1}H (360 MHz) : 11.32 (s, 1H, H-3); 8.06-7.52 (m, 6H, H aromatic, H-6); 5.69 (d, 1H, J = 4.5 Hz, OH); 5.60 (d, 1H, J = 5.1 Hz, OH); 5.43 (d, 1H, $J_{1'2'}$ = 8.8 Hz, H-1'); 4.94 (dt, 1H, $J_{4'5'eq}$ = 5.5 Hz, $J_{4'5'ax}$ = 10.4 Hz, $J_{4'3'}$ = 10.4 Hz, H-4'); 4.02 (dd, 1H, $J_{5'eq4'}$ = 5.5 Hz, $J_{5'eq5'ax}$ = - 11.1 Hz, H5'eq); 3.75 (dt, 1H J = 4.9, 8.8 and 8.8 Hz, H2'(3')); 3.70 (dt, 1H, J = 5.4, 8.8 and 8.8 Hz, H3'(2')); 3.51 (t, 1H, $J_{5'ax4'}$ = 10.9 Hz, $J_{5'ax5'eq}$ = - 11.0 Hz, H5'ax); 1.79 (d, 3H, J_{CH_36} = 1.0 Hz, CH_3).
HRMS (CI, i-butane) calc. for $[M+H]^+$ $C_{17}H_{19}N_2O_7$ 363.1192, found 363.1218.

2',3'-Dideoxy-β-D-glyceropent-2'-enopyranosyl thymine 19b

Compound **18a** 0.23 g (0.63 mmol) in acetonitrile (8 ml) has been warmed up to boiling. Some undissolved material has still been present. Addition of imizaole 0.17 g (2.5 mmol) has resulted in complete solubilization. Toluene 15 ml has been added followed by triphenylphosphine 0.365 g (1.4 mmol) and iodine 0.35 g (1.4 mmol) portionwise. The yellow-brown solution has been boiled for 2 hours. Zinc powder 0.33 g has been added portionwise and the discolorated solution has been maintained at boiling temperature for 2.5 hours. At this stage TLC has shown a product **19a** (B = T) which comigrates with triphenyl phosphine oxide, together with a marginal amount of a more polar compound which is located near the start spot. The mixture has been filtered through a sintered glass, evaporated and passed through a silica gel column in CH_2Cl_2-MeOH 700:25 to harvest a mixture of the olefin and triphenylphosphine mixture (0.56 g). Overnight treatment with NH_3/MeOH has resulted in formation of a more polar deprotected olefin **19b**. Chromatography in CH_2Cl_2-MeOH 15:1 has furnished 0.102 g of **8a** (72 % for two consecutive reactions) as a glassy compound.

Larger scale preparation of 19b

Triol **17c** (10.89 g, 42.2 mmol) has been stannylated with 12.33 g of dibutyltin oxide (98 % pure, 48.5 mmol) in 600 ml of methanol during 3 h and 4' benzoylated using 42 ml of DMF, 290 ml of dioxane and 5.4 ml (46.4 mmol) of benzoyl chloride. Dioxane and DMF have been evaporated. Addition of EtOAc and hexane to turbidity resulted in deposition of 18.2 g of the crude 4'-benzoate **18a** evidently contaminated with tin compounds (theoretically yield is 14.69 g). This impure material has been used for the olefination step without adversely affecting the yield. This impure **18a** (6.2 g), 4.7 g of imidazol, 9.9 g of triphenylphosphine in 140 ml of CH_3CN and 250 ml of toluene, 9.5 g of iodine and 8.9 g of zinc have been reacted together. A second portion of 12 g of impure **18a** has also been reacted using proportional amounts of the reagents. Care should be taken during additions of iodine and zinc, since vigorous effervescence takes place after addition of each portion of the reagents. The combined reaction mixture has been worked-up as described above to furnish 4.9 g of **19b** (52 % for three consecutive steps **17c** → **18a** → **19b**).

UV (MeOH) λ_{max} : 263.6 nm (ε = 8674)

^1H (300 MHz) δ : 11.37 (s, 1H, H-3); 7.24 (q, 1H, J_{6CH_3} = 1.0 Hz, H-6); 6.22 (dt, 1H, $J_{3'3'}$ = 10.2 Hz, $J_{3'1'}$ and $J_{3'4'}$ = 1.8 and 2.2 Hz, H-3'); 6.16 (q, 1H, $J_{1'2'} = J_{1'3'} = J_{1'4'}$ = 1.9 Hz, H-1'); 5.70 (dt, 1H, $J_{2'3'}$ = 10.2 Hz, $J_{2'1'} = J_{2'4'}$ = 1.6 Hz, H-2'); 5.24 (d, 1H, J = 6.1 Hz, OH); 4.15 (bs, 1H, H-4'); 3.90 (dd, 1H, $J_{5'eq5'ax}$ = - 11.4 Hz, $J_{5'eq4'}$ = 6.5 Hz, H5'eq); 3.46 (dd, 1H, $J_{5'ax5'eq}$ = -11.3 Hz, $J_{5'ax4'}$ =6.9 Hz, H5'ax); 1.75 (d, 3H, J_{CH_36} = 1.0 Hz, CH_3).

^{13}C (75.5 MHz) : 163.98, 150.74, C2,C4; 136.99, 136.68, C6,C2'(3'); 124.75, C3'(2'); 109.59, C5; 77.07, C1'; 68.30, C5'; 60.41, C4'; 12.07, CH_3.

HRMS (EI) calc. for $C_{10}H_{12}N_2O_4$ 224.0797, found 224.0805.

2',3'-Dideoxy-3'-C-hydroxymethyl-β-D-erythro-pentopyransoyl thymine 20a

To a chilled (ice-bath) solution of **19b** 0.369 g, 1.65 mmol and imidazol 0.27 g, 4 mmol in 20 ml of DMF has been added bromomethylchlorodimethylsilane 0.27 ml (2 mmol). After 1 h at room temperature the mixture has been transfered to a separatory funnel charged with ice-cold water and rapidly extracted with dichloromethane (2 x). The combined organic layer has been dried ($MgSO_4$) and evaporated. Total work-up time was ca 15 minutes. The silyl compound has been dried on an oil pump, dissolved in toluene 50 ml, and treated at boiling point with Bu_3SnH 0.55 ml and AIBN 0.030 g in 50 ml of toluene dropwise. Addition time was ca 30 minutes. After a total of 3 h of boiling, the mixture has been evaporated and DMF 15 ml has been added. After being chilled in ice-bath, KF 0.375 g, $KHCO_3$ 0.300 g and 1.35 ml of 35 % H_2O_2 have been consecutively added with stirring. After an overnight reaction at room temperature, the heterogenous mixture has been filtered through sintered glass and evaporated. The resulting slurry has been directly applied on a top of a silica gel column prepared in CH_2Cl_2-MeOH 10:1. Elution with the same solvent system has furnished **20a** as a glassy material, 0.21 g or 49 % for three consecutive reactions.

^1H (500 MHz, D_2O) δ : 7.607 (q, 1H, H_{6CH_3} = 1.0 Hz, H-6); 5.891 (dd, 1H, $J_{1'2'eq}$ = 4.8 Hz, $J_{1',2'ax}$ = 7.1 Hz, H-1'); 4.102 (dt, 1H, $J_{4'5'ax}$ = 8.1 Hz, $J_{4'5'eq}$ = 4.1 Hz, $J_{4'3'}$ = 4.1 Hz, H-4'); 3.924 (dd, 1H, $J_{6'6"}$ = - 11.3 Hz, $J_{6'3'}$ = 5.8 Hz, H-6'); 3.835 (dd, 1H, $J_{5'eq5'ax}$ = - 12.3 Hz, $J_{5'eq4'}$ = 4.4 Hz, H5'eq); 3.814 (dd, 1H, $J_{6"6'}$ = - 11.3 Hz, $J_{6"3'}$ = 8.1 Hz, H-6"); 3.727 (dd, 1H, $J_{5'ax5'eq}$ = - 12.1 Hz, $J_{5'ax4'}$ = 8.0 Hz, H5'ax); 2.426 - 2.366 (m, 1H, H-3'); 2.133 - 2.033 (m, 2H, H2'ax,2'eq); 1.893 (d, 3H, J_{CH_36} = 1.0 Hz, CH_3).

HRMS (LSIMS, thioglycerol) calc. for $[M+H]^+$ $C_{11}H_{17}N_2O_5$ 257.1137, found 257.1152.

2',3'-Dideoxy-3'-C-hydroxymethyl-α-L-threopentopyranosyl thymine 22a

A. To a mixture of 0.013 g (0.051 mmol) of **20a** in dioxane-m-xylene (1:1, 4 m) has been consecutively added benzoic acid 0.025 g (0.20 mmol), triphenylphosphine 0.053 g (0.20 mmol) and diethyl azadicarboxylate 0.03 ml (0.2 mmol) under nitrogen. After 4 days at room temperature the mixture has been evaporated and (without isolation of the intermediate dibenzoate **21a**) treated with 8 ml of ammonia in MeOH. The most

polar compound formed has been isolated by chromatography (CH_2Cl_2-MeOH 10:1) to furnish 0.003 g of **22a** (23 % for two reactions).

B. Compound **26a**, 0.072 g was been treated with 8 ml of 80 % AcOH for 20 min. After evaporation of the acid at ~ 30°, the treatment has been repeated. After evaporation and co-evaporation with DMF, chromatography (CH_2Cl_2-MeOH 10:1) has been furnished 0.024 g, 69 % of **22a**.

C. In order to avoid separation of **24a** and **25** (see below), this mixture can be stepwise deprotected to give **22a**. Thus, Mitsunobu inversion of configuration has been performed with 0.90 g (1.70 mmol) of **23a**, 0.89 g 3.3 mmol of triphenylphosphine, 0.41 g (6.8 mmol) of BzOH and 0.53 ml (6.8 mmol) of DEAD in dioxane, 40 ml, at bp during 1.5 h. After evaporation of the solvent, chromatography (CH_2Cl_2-MeOH 20:0.25) has furnished a mixture of **24a** and **25**. This has been treated with NH_3/MeOH overnight. After evaporation of methanol, detritylation with AcOH as bove, and chromatography, 0.154 g (35 % for three consecutive steps) of **22a** has been isolated.

mp. 193-4° (cryst. from MeOH-CH_2Cl_2); λ_{max} (MeOH) 266.4 nm (ε 9856); Exact mass : (CI, i-butane) calc. for $[M+H]^+$ $C_{11}H_{16}N_2O_5$ 256.1059, found 256.1056; Combustion analysis : calc. C : 51.56, H : 6.29, N : 10.93; found C : 51.40, H : 6.32, N : 10.80.

^1H NMR (500 MHz, D_2O) : 7.70 (q, 1H, $J_{5\text{-}CH_3}$ = 1.2 Hz, H-6), 5.76 (dd, 1H, $J_{1'2'ax}$ = 10.8 Hz, $J_{1'2'eq}$ = 2.8 Hz, H-1'), 4.00 (dd, 1H, $J_{5'ax5'eq}$ = - 13.2 Hz, $J_{5'eq4'}$ = 1.8 Hz, $H_{5'eq}$), 3.92 (dt, 1H, $J_{5'ax5'eq}$ = - 13.2 Hz, $J_{5'ax4'}$ and $J_{5'ax3'}$ = 1.8 Hz and 1.9 Hz, $H_{5'ax}$), 3.81 (dd, 1H, $J_{6'6''}$ = - 11.5 Hz, $J_{6'3'}$ = 7.6 Hz, H6'), 3.78 (s, 1H, half-width 3Hz, H4'), 3.76 (dd, 1H, $J_{6''6'}$ = - 11.5 Hz, $J_{6''3'}$ = 7.1 Hz, H6''), 2.29 - 2.23 (m, 1H, H3'), 2.23 (ddd, 1H, $J_{2'ax1'}$ = 11.0 Hz, $J_{2'ax2'eq}$ = - 13.5 Hz, $J_{2'ax3'}$ = 5.6 Hz, $H_{2'ax}$), 1.88 (d, 3H, J_{CH_36} = 1.2 Hz, CH_3), 1.76 (dt, 1H, $J_{2'eq2'ax}$ = - 14.3 Hz, $J_{2'eq1'}$ = $J_{2'eq3'}$ = 3.1 Hz, $H_{2'eq}$).

2',3'-Dideoxy-3'-C-[p-methoxyphenyldiphenylmethyloxy-methyl]-β-D-erythropentopyranosyl thymine 23a

Conventional methoxyltritylation of 2.13 g (8.32 mmol) of **20a** using 1.6 mol eq of p-methoxyphenyldiphenyl-methylchloride in pyridine and a catalytic amount of p-dimethylaminopyridine at 80° has furnished **23a** as a glassy solid, 3.26 g (71 %) after chromatography in CH_2Cl_2-MeOH (20:0.5). Di-protected derivative **23b** 0.346 g isolated as a forerunner has not been further characterized.

^1H (200 MHz) δ : 11.27 (s, 1H, H3); 7.59 (s, 1H, H6); 7.42 - 7.18 and 6.91 - 6.87 (m, 14H, H aromatic); 5.75 (dd, 1H, $J_{1'2'ax}$ = 10.6 Hz, $J_{1'2'eq}$ = 3.0 Hz, H1'); 4.99 (d, 1H, $J_{OH4'}$ = 2.9 Hz, OH); 3.90 - 3.80 (m, 1H, H4'); 3.73 (s, 3H, OMe); 3.63 (dd, 1H, J = 5.2 and 11.8 Hz, downfield part of the AB pattern of H5' or 6'); 3.39 - 3.20 (partly superimposed on the residual H_2O, 3H, H5',6'); 2.42 - 2.33 (unresolved, 1H, H3'); 2.14 - 2.00 (m, 2H, 2 x H2'); 1.79 (s, 3H, CH_3).

^{13}C (50 MHz) : 163.18, 150.29 (C2,4); 158.17, 111.56, 135.44; 130.12, 128.11, 127.98, 126.83, 113.31, 85.95, 55.11, (MMT); 136.36, 109.50 (C5,6); 77.21 (C1'); 67.84, 59.21 (C5'6'); 64.72 (C4'); 37.60 (C3'); 29.56 (C2'); 12.12 (CH_3).

HRMS (LSIMS, thioglycerol doped with NaCl) calc. for $[M+Na]^+$ $C_{31}H_{32}N_2O_6Na$ 551.2158, found 551.2169.

23b : glassy solid

HRMS (conditions as for **23a**) calc. for $[M+Na]^+$ $C_{51}H_{48}N_2O_7Na$ 823.3359, found 823.3364.

4'-O-Benzoyl-2',3'-dideoxy-3'-C(p-methoxyphenyldiphenylmethyloxy-methyl)-α-L-threo-pentopyranosyl thymine 24a and elimination product 25

The alcohol **23a** 0.198 g, 0.36 mmol in dioxane (8 ml) and m-xylene (8 ml) has been treated with triphenylphosphine (0.19 g, 0.72 mmol), benzoic acid (0.09 g, 0.72 mmol), and DEAD (0.11 ml, 0.72 mmol). After an overnight reaction, TLC has shown two principal products **24a** (less polar) and **25** accompanied by triphenylphosphine (migrating with solvent-front) and BzOH and triphenylphosphine oxide. Chromatography

(CH_2Cl_2-MEOH 10:0.25) has furnished **24a** 0.082 g, 37 % and 0.072 g of impure fractions contaminated with **25**. Exact yield of **25** has not been evaluated due to difficulties of its purification.

24a : glassy compound

^1H (200 MHz) : 11.37 s, 1H, H3), 8.12 - 6.87 (m, 15H, H aromatic, H6); 5.71 (dd, 1H, $J_{1'2'ax}$ = 9.2 Hz, $J_{1'2'eq}$ = 1 Hz, H1'); 4.96 (6s, 1H, H4'); 4.10 - 3.72 (m, 7H, 2 x H5', 2 x H6', OMe); 1.61 (s, 3H, CH_3); signals of protons 2' and 3' coincide with the DMSO signal.

^{13}C : 165.31; 133.74; 130.00, 129.75 and 129.02 (OBr); 158.47, 144.43, 135.12, 130.30, 128.23, 127.17, 113.56, 86.41, 55.28 (MMT); 163.90, 150.46 (C2,4); 136.05 (C6); 109.81 (C5); 77.76 (C1'), 68.03, 66.60, 62.46 (C4',5',6'); 36.96 (C3'); 27.23 (C2'), 12.49 (CH_3).

HRMS (LSIMS, thioglycerol doped with NaCl) calcd. for $[M+Na]^+$ $C_{38}H_{36}N_2O_7Na$ 655.2420, found 655.2432.

25 : glassy compound

^1H (200 MHz) : 11.38 (6S, 1H, H-3); 7.62 - 6.87 (m, 15H, H-6, H aromatic); 5.89 (bs, half-width 7 Hz, 1H, H4'); 5.69 (dd, 1H, $J_{1'2'ax}$ = 9.5 Hz, $J_{1'2'eq}$ = 3.0 Hz, H1'); 4.36 (bs, half-width 10 Hz, 2H, 2 x H5'); 3.75 (s, 3H, OMe); 3.49 (bs, half-width 6Hz, 2H, 2 x H6'); 2.09 (a pair of broad singlets, half-width 11 Hz, $J_{2'ax2'eq}$ = -14 Hz, H2'ax); signal of H2'eq coincides with residual DMSO multiplet; 1.78 (s, 3H, CH_3).

^{13}C (50 MHz) : 158.49, 144.59, 135.26, 130.19, 128.24, 128.10, 127.20, 113.56, 86.10, 55.31 (MMT); 164.01 and 150.58 (C2,4); 136.69 (C6); 131.94 (C3'); 120.28 (C4'); 109.79 (C5); 78.06 (C1'); 65.94 (C5',6'); 29.45 (C2'); 12.28 (CH_3).

HRMS (LSIMS, thioglycerol doped with NaCl) calc. for $[M+Na]^+$ $C_{31}H_{30}N_2O_5Na$ 533.2053, found 533.2054.

2',3'-Dideoxy-3'-C-[p-methoxyphenyldiphenylmethyloxy-methyl]-α-L-threo-pento-pyranosylthymine 26a

A. Conventional 4'-O-debenzoylation of **24a**, 0.50 g with NH_3/MeOH has furnished 0.37 g (88 %) of **26a**, after chromatography in CH_2Cl_2-MeOH 20:0.6.

B. Olefin **25** (0.035 g) in THF, (8 ml) has been hydroborated with 0.8 ml 2M diborane in THF, at ice-bath temperature. After 3h 3N aqueous NaOH 1 ml and 35 % H_2O_2 1 ml have been added. TLC after 3 h has shown two principal compounds : R_f 0.36 (in CH_2Cl_2-MEOH 20:0.7) identical with **24a** described above, and R_f 0.54 having a tentative structure **27**. Compound **27** has not been isolated. Chromatography has furnished 0.010 g (28 %) of **26a**.

26a : amorphous compound

HRMS (thioglycerol-doped with NaCl) calc. for $[M+Na]^+$ $C_{31}H_{32}N_2O_6Na$ 551.2158, found 551.2169.

^1H (200 MHz) δ : 11.31 (bs, 1H, H3); 8.09 - 6.86 (three groups of multiplets, 15H, H aromatic, H6); 5.58 (d, 1H, $J_{1'2'ax}$ = 9.9 Hz, H1'); 5.05 (bs, 1H, OH); 3.79 (s, 3H, OMe); 3.73 - 3.11 (m, 5H, H4', 2 x H5', 2 x H6'); 2.60 - 2.10 (m, 3H, 2 x H2', H3', superimposed on the residual DMSO signal); 1.81 (s, 3H, CH_3).

^{13}C (50 MHz) : 158.29, 144.40, 135.17, 131.32, 130.13, 128.32, 128.09, 127.57, 126.99, 113.42, 86.02, 55.18 (MMT); 163.85, 150.27 (C2,4); 136.29 (C6), 109.43 (C5), 77.50 (C1'); 69.08, 62.63 (C5',6'); 63.66 (C4'), 38.09 (C3'); 26.90 (C2'), 12.20 (CH_3).

4'-(R,S)Hydroxymethyl-2'-(R)-thymin-1-yl-tetrahydropyrane 28

Olefin **25** (0.22 g) in 30 ml of EtOH and 0.043 g of 10 % Pd/C catalyst has been hydrogenated in a Parr apparatus at 30 psi for 10 h. The catalyst has been filtered off and a solvent has been evaporated. The residue has been deprotected with 80 % AcOH (twice). After evaporation of an acid and chromatography (in CH_2Cl_2-MeOH 20:0.4) 0.069 g of **28** (thick syrup) as a 1:1 mixture of epimers has been isolated.

28

UV (MeOH) λ_{max} 250.3 nm (ε 15729).

^1H (200 MHz, CD_3OD) : 7.57 (q, 1H, J_{6,CH_3} = 1.2 Hz) and 7.53 (q, 1H, J_{6,CH_3} = 1.1 Hz) H-6s; 5.76 (dd, 1H, $J_{1'2'eq}$ = 6.6 Hz, $J_{1'2'ax}$ = 10.3 Hz) and 5.59 (dd, 1H, $J_{1'2'eq}$ = 2.2 Hz, $J_{1'2'ax}$ = 10.9 Hz, H-1's) 4.20 - 3.31

(four groups of multiplets, 8H, 2 x 5's, 2 x 6's); 2.30 - 1.30 (four groups of multiplets; 16H, 2 x 2's, 2 x 3's, 2 x 4's, 2 x CH_3).
^{13}C (50 MHz, CD_3OD) : 166.30, 152.15 (C2,4); 137.94 (C6); 111.62 (C5); 83.20, 79.80 (C1's); 68.95, 67.29 [C6s(5s)]; 65.37, 63.06 [C5's(6's)]; 39.02, 35.24 (C3's); 34.58, 32.08 [C2's(4's)]; 29.28, 26.67 [C4's(2's)]; 12.38 (CH_3).
HRMS (LSIMS, thioglycerol) calc. for $[M+H]^+$ $C_{11}H_{17}N_2O_6$ 241.1189, found 241.1186.

2',3',4'-Tri-O-acetyl-β-D-xylopyranosyl uracil 17d, 2',3',4'-tri-O-acetyl-α-D-xylopyranosyl uracil 17e and N1,N3-bis(2',3'4'-tri-O-acetyl-D-xylopyranosyl)uracil 17f.

A. Uracil (2.22 g, 19.8 mmol) has been trimethylsilylated. To this has been added a solution of tetra-O-acetyl-D-xylopyranose (7.4 g, 21.9 mmol), **16**, in 80 ml of dichloroethane, followed by 3.8 ml (19.8 mmol) of TMSOTf. After an overnight reaction at external temperature of 65°, TLC has shown (in the order of increasing polarity) and unreacted carbohydrate, an N1,N3-bis-glycosylated product **17f** and the spot corresponding to **17d** and an α anomer **17e**. After extractive work-up and chromatography in CH_2Cl_2-MeOH 20:0.2, 1.93 g (14 %) of **17f** and 1.61 g (20.7 %) of **17d** has been obtained, together with small amount of the marginally more polar α anomer **17e**.
B. Condensation of 8.0 g, 23.8 mmol of per-O-acetylated xylopyranose **16** with uracil 6.67 g (59.5 mmol) in the presence of 7.7 ml (40 mmol), of TMSOTf at 64° overnight (oil bath temperature), followed by 8 h at bp, has furnished 5.1 g (55 %) of **17d**, slightly contaminated with **17e**. Compound **17f** also formed in this reaction in much smaller amount, has not been isolated.
C. Repetition of the above condensation with 12.0 g (35.7 mmol) of xylopyranose peracetate (**16**) 12.0 g (107.1 mmol) of uracil (trimethylsilylated) and TMSOTf 20.7 ml (107 mmol) in 200 ml of dichloroethane at 77° (oil bath) overnight, after usual work-up and chromatography, has furnished 5.18 g of the β anomer **17d**, 5 g of the mixed fraction **17d** and **17e**, and 1.45 g of pure α anomer **17e**.

17d : syrup;
^1H (360 MHz) δ : 11.40 (s, 1H, H3); 7.95 (d, 1H, $J_{6,5}$ = 8.1 Hz, H6); 5.91 (d, 1H, $J_{1'2'}$ = 9.0 Hz, H1'); 5.67 (d, 1H, $J_{5,6}$ = 8.1 Hz, H5); 5.46 (t, 1H, $J_{3'4'}$ = 9.4 and $J_{3'2'}$ = 9.4 Hz, H3'); 5.39 (t, 1H, $J_{2',1'}$ = 9.1 Hz, $J_{2',3'}$ = 9.2 Hz, H2'); 5.13 (dt, 1H, $J_{4'5'eq}$ = 5.5 Hz, $J_{4'5'ax}$ and $J_{4'3'}$ = 10.2 and 10.1 Hz, H4'); 3.98 (dd, 1H, $J_{5'eq4'}$ = 5.5 Hz, $J_{5'eq5'ax}$ = - 11.0 Hz, H5'eq); 3.74 (t, 1H, $J_{5'ax4'}$ = 10.8 Hz, $J_{5'ax5'eq}$ = - 10.8 Hz, H5'ax).
^{13}C (50 MHz) δ : 169.74, 169.61, 169.29 ($\underline{C}OCH_3$); 162.94, 150.53 (C2,4); 141.33 (C6); 102.48 (C5); 80.12 (C1'); 71.95, 69.61, 68.03 (C2',3',4'); 64.03 (C5'); 20.59, 20.47, 20.21 ($COCH_3$).
HRMS (CI, i-butane) calc. for $[M+H]^+$ $C_{15}H_{19}N_2O_9$ 371.1091, found 371.1093.
17e : mp 157-158° (EtOH)
^1H (200 MHz) δ : 11.42 (s, 1H, H3); 7.53 (d, 1H, $J_{6,5}$ = 7.9 Hz, H6); 5.86 (s, 1H, H1'); 5.62 (d, 1H, $J_{5',6'}$ = 8.1 Hz, H5); 5.02 (s, 1H, H3'); 4.85 (s, 1H, H2'); 4.70 (s, 1H, H4'); 4.20 (1H, AB, J = 13.8 and 19.7 Hz, 2 x H5'); 2.17, 2.11 and 2.04 (three s, 3H each, 3 x OAc).
^{13}C (50MHz) : 169.62, 169.40 and 168.66 ($\underline{C}OCH_3$); 162.95, 149.71 (C2,4); 140.48, 101.38 (C5,6); 78.54 (C1'); 67.04 (C5'); 66.00, 65.55 and 65.07 (C2',3',4'); 20.83 and 20.50 ($CO\underline{C}H_3$).
HRMS (LSIMS, thioglycerol) calc. for $[M+H]^+$ $C_{15}H_{19}N_2O_9$ 371.1090, found 371.1106.
17f : glassy material;
^{13}C (50 MHz) 169.86, 169.73, 169.64 ($\underline{C}OCH_3$); 161.52, 149.13 (C2,4); 141.84, 100.74 (C5,6); 80.30, 78.88 (C1's); 72.35, 72.19, 68.82, 68.46, 68.06, 64.10 (C2's,3's,4's,5's); 20.72, 20.62, 20.37, 20.23 ($CO\underline{C}H_3$).
HRMS (CI, i-butane) calc. for $[M+H]^+$ $C_{26}H_{33}N_2O_{16}$ 629.1830, found 629.1806.

4'-O-Benzoyl-β-D-xylopyranosyl-uracil 18b and 4'-O-benzoyl-α-D-xylopyranosyl-uracil 18c

A. Compound **17d** 5.18 g has been deacetylated in MeOH 250 ml with a catalytic amount of NaOMe overnight. The solution has been nuetralized with Dowex 50 WX-8, filtered and evaporated to furnishe 3.04 g of a deprotected β-xylopyranosyl-uracil. This compound has been stannylated with 3.41 g, 13.7

mmol, of dibutyltin oxide in MeOH (70 ml) at bp during 3 h, and 4'-O-benzoylated using 1.59 ml (13.7 mmol) of benzoyl chloride in a mixture of DMF 15 ml and dioxane 60 ml, as described for thymidine counterpart **18a**. After crystallization from EtOAc hexane, 3.8 g (88 %) of **18b** has been obtained.

B. A mixture of the α and β anomers **17d,e** from exp. C above (5 g) has been deacetylated with NaOMe in HOMe. TLC (CH_2Cl_2-MeOH 5:1, developed twice) has shown two compounds, the upper one being α anomer. Neutralization and evaporation has furnished 2.46 g of the amorphous material which has been 4' benzoylated using 1.29 ml (11.1 mmol) of benzoyl chloride, in DMF (13 ml) and dioxane (50 ml). TLC (CH_2Cl_2-MeOH 10:1.25) has shown two principal products, R_f 0.27 being **18c** and R_f 0.18 being **18b**. Chromatography (CH_2Cl_2-MeOH 10:0.8) has furnised 0.72 g of **18c** (less polar) and 1.46 g of **18b** (more polar).

18b : mp 218-236 (dec., cryst. from EtOH-EtOAc)

^1H (200 MHz) 11.39 (s, 1H, H3); 8.04-8.00 and 7.73-7.51 (m, 5H, COPh); 7.84 (d, 1H, $J_{6,5}$ = 8.0 Hz, H6); 5.66 (d, 1H, J = 8.3 Hz, OH); 5.64 (d, 1H, J = 8.0 Hz, H5); 5.63 (d, 1H, J = 7.0 Hz, OH); 5.74 (d, 1H, $J_{1',2'}$ = 8.8 Hz, H1'); 4.93 (dt, 1H, $J_{4'5'eq}$ = 5.7 Hz, $J_{4,5'ax}$, $J_{4'3'}$ = 8.6 and 9.0 Hz, H4'); 4.05 (dd, 1H, $J_{5'eq4'}$ = 5.2 Hz, $J_{5'eq5'ax}$ = -11.0 Hz, H5'); 3.80-3.61 (m, 2H, H2',3') [after exchange with D_2O 3.73 (t, 1H, J = 8.9 Hz, and 9.8 Hz, H2'(3'); 3.64 (t, 1H, J = 11.0 and 10.9 Hz, H3'(2')].

^{13}C (50 MHz) 165.63 (COPh); 163.25, 151.15 (C2,4); 141.66 (C6); 133.78, 129.69, 128.95 (COPh); 102.31 (C5); 83.38 (C1'), 74.03, 71.82, 70.94 (C2',3',4'); 64.82 (C5').

HRMS (CI, i-butane) calc. for $[M+H]^+$ $C_{16}H_{17}N_2O_7$ 349.1036, found 349.1063.

18c : mp 232-233° (cryst. from CH_2Cl_2-HOMe);

^1H (200 MHz) 11.36 (s, 1H, H3); 8.09-8.06 and 7.69-7.53 (m, 5H, COPh); 7.75 (d, 1H, $J_{6,5}$ = 8.1 Hz, H6); 5.69 (d, 1H, J = 3.8 Hz, OH); 5.84 (d, 1H, H1'); 5.63 (d, 1H, $J_{5,6}$ = 8.1 Hz, H5); 5.40 (d, 1H, J = 5.1 Hz, OH); 4.80 (bs,half-width 6 Hz, 1H, H4'); 4.17 (AB, 2H, J = 12.8 and 22.0 Hz, 2 x H5'); 4.02 (bs, half-width 9 Hz, 1H, H2'(3')); 3.65 (bs, half-width 11 Hz, 1H, H3'(2')).

^{13}C (50 MHz) 165.50 (COPh); 163.46, 150.29 (C2,4); 143.15 (C6); 133.61, 130.27, 129.67, 128.91 (COPh); 100.44 (C5); 79.60 (C1'), 69.56, 68.07, 67.86, 66.59 (C2',3',4').

HRMS (CI, i-butane) calc. for $[M+H]^+$ $C_{16}H_{17}N_2O_7$ 349.1036, found 349.1063.

2',3'-Dideoxy-β-D-glyceropent-2'-enopyranosyl uracil 19c

Diol **18b** (3.8 g, 10.9 mmol) has been converted into the 2',3'-olefin by analogy to the thymine counterpart **18a**, using triphenylphosphine (6.2 g, 23.6 mmol) imidazol (2.94 g, 43.2 mmol) I_2 (ca 6 g, 24 mmol) in a mixture of 130 ml of acetonitrile and 170 ml of toluene. After 2 h at bp, Zn dust 5.7 g has been added and boiling has been continued for 1 h. TLC (CH_2Cl_2-MeOH 20:1) has shown a triphenylphosphine spot partly overlapping with the more polar 4' benzoylated olefin **19a** (B = U) and an unidentified spot located near the start.

The mixture has been filtered and evaporated. The residueal material has been passed through a silica gel column (in CH_2Cl_2-MeOH 20:0.5) to get a mixture of triphenylphosphine and the benzoylated olefin **19a** B = U. After debenzoylation in NH_3/HOMe overnight and chromatography in CH_2Cl_2-MeOH (10:1) 0.69 g (30 %) of the **19c** has been isolated.

The same reaction performed on 0.21 g of **18b** has furnished the olefin **19c** in a slightly better yield of 0.044 g (35 %).

19c : syrup; ^1H (360 MHz) : 11.40 (bs, 1H, H3); 7.41 (d, 1H, $J_{6,5}$ = 8.1 Hz, H6); 6.24 (dt, 1H, $J_{3'2'}$ = 10.2 Hz, $J_{4'3'}$ = $J_{3'1'}$ = 2.3 Hz, H3'); 6.17 (q, 1H, $J_{1'2'}$ = $J_{1'3'}$ = $J_{1'4'}$ = 2.0 Hz, H1'); 5.73 (dt, 1H, $J_{2'3'}$ = 10.3 Hz, $J_{2'1'}$ = $J_{2'4'}$ = 1.9 Hz, H2'); 5.58 (d, 1H, $J_{5,6}$ = 8.0 Hz, H5); 5.24 (d, 1H, J = 6.0 Hz, OH); 4.17-4.08 (m, 1H, H4'); 3.88 (dd, 1H, $J_{5'eq4'}$ = 4.7 Hz, $J_{5'eq5'ax}$ = - 11.5 Hz, H5'eq); 3.49 (dd, 1H, $J_{5'ax4'}$ = 6.6 Hz, $J_{5'ax5'eq}$ = - 11.4 Hz, H5'ax).

^{13}C (50 MHz) : 163.42, 150.83 (C2,4); 141.84 (C6); 136.71, 124.62 (C2',3'); 101.94 (C5); 77.13 (C1'), 68.18 (C4'); 60.39 (C5').

UV (MeOH) : λ_{max} 259.4, ε 8605.

HRMS (EI) calc. for $C_9H_{10}N_2O_4$ 210.0641, found 210.0648.

2',3'-Dideoxy-3'-hydroxymethyl-β-D-erythro-pentopyranosyl uracil 20b

This compound has been prepared as described for the thymine counterpart **20a**. Silylation : 0.894 g (4.3 mmol) of **19c** in DMF (1.5 ml); 0.72 ml (5.3 mmol) of bromomethylchlorodimethylsilane; imidazol 0.72 (10.6 mmol).
Cyclisation : Bu_3SnH 2.0 ml (7.4 mmol) AIBN 0.12 g (0.73 mmol) in toluene (50 ml); the substrate in 130 ml of toluene.
Oxidation : the substrate in DMF (30 ml); KF 0.98 g; $KHCO_3$ 0.79 g, 35 % H_2O_2 3.5 ml, overnight. Flash chromatography in CH_2Cl_2-MeOH 10:1 has furnished 0.271 g of **20b**, 26 % for three steps.
20b : glassy solid
^1H (200 MHz) : 11.34 (bs, 1H, H3); 7.74 (d, 1H, $J_{6,5}$ = 8.1 Hz, H6); 5.84 (dd, 1H, $J_{1'2'ax}$ = 8.8 Hz, $J_{1'2'eq}$ = 4.8 Hz, H1'); 5.62 (d, 1H, $J_{5,6}$ = 8.1 Hz, H5); 5.05 (d, 1H, $J_{OH,4'}$ = 4.4 Hz, 4'OH); 4.56 (t, 1H, $J_{OH,6'}$ = 5.1 and 4.7 Hz, OH6'); 3.88 (sextette, 1H, $J_{4'5'ax'}$ = 9.8 Hz, $J_{4'OH}$ = $J_{4'3'}$ = $J_{4'5'eq}$ = 4.9 Hz, H4'); 3.78-3.41 (m, 4H, 2 x H5', 2 x H6'); 2.23-1.86 (two groups of multiplets, 3H, H3', 2 x H2').
^{13}C (50 MHz) : 163.23, 150.50 (C2,4); 141.18 (C6); 101.95 (C5); 77.53 (C1'), 67.99, 65.32, 57.79 (C4'5,6'); 29.34 (C2'); the C3' signal is hidden under the DMSO signal.
HRMS (LSIMS, thioglycerol) calc. for $[M+H]^+$ $C_{10}H_{15}N_2O_5$ 243.0981, found 243.0986.

2',3'-Dideoxy-3'-C'-(p-methoxyphenyldiphenylmethyloxy-methyl)-β-D-erythropentopyranosyl uracil 23c

Diol **20b** 0.239 g in pyridine 10 ml and a catalytic amount of DMAP has been reacted with 0.37 g (1.19 mmol) of p-methoxyphenyldiphenylmethyl chloride overnight at room temperature. More reagent (0.07 g) has been added and the reaction has been continued for 6 h. Extractive work-up and chromatography (CH_2Cl_2-MeOH 20:0.5) has furnished 0.30 g (59 %) of **23c**. A small amount of a less polar product, presumably the bis-protected derivative, has not been isolated.
23c : glassy solid
^1H (200 MHz) : 11.35 (s, 1H, H3); 7.73 (d, 1H, $J_{6,5}$ = 8.1 Hz, H6); 7.44-6.89 (two groups of multiplets, 14H, H aromatic); 5.76 (apparent dd, 1H, $J_{1'2'ax}$ = 8.4 Hz, $J_{1'2'eq}$ = 2.7 Hz, H1'); 5.63 (d, 1H, $J_{5,6}$ = 8.1 Hz); 5.02 (d, 1H, $J_{OH,4'}$ = 4.0 Hz, OH); 3.88 (sextette, 1H, $J_{4'5'ax'}$ = 9.9 Hz, $J_{4'OH}$ = $J_{4'3'}$ = $J_{4'5'eq}$ = 4.9 Hz, H4'); 3.75 (s, 3H, OMe); 3.64 (dd, 1H, J = 4.8 and 11.0 Hz, downfield part of AB system of H5'(6'); 3.41-3.22 (superimposed on the residual H_2O signal 3H, H5',6'); 2.42-2.32 (m, 1H, H3'); 2.20-1.85 (unresolved, 2H, 2 x 2').
^{13}C (50 MHz) : 163.27, 150.45 (C2,4); 158.31, 144.80, 135.58, 130.28, 128.26, 129.15, 126.99, 113.49, 86.11, 55.26 (MMT); 141.06 (C6); 102.01 (C5); 77.56 (C1'), 67.98, 64.75, 59.47 (C4'5',6'); 37.49 (C3'); 29.57 (C2').
HRMS (LSIMS, thioglycerol doped with NaCl) calc. for $[M+Na]^+$ $C_{30}H_{30}N_2NaO_6$ 537.2002, found 537.1966.

2',3'-Dideoxy-3'-C-hydroxymethyl-α-L-threopentopyranosyl uracil 22b

A. The compound **23c** (0.182 g, 0.35 mmol) in a mixture of dioxane-p-xylene 24 ml, has been treated with triphenylphosphine (0.24 g, 0.9 mmol) 2,4-di-nitro-p-benzoic acid (0.19 g, 0.9 mmol) and DEAD (0.14 ml, 0.9 mmol) added in this order. After an overnight reaction TLC has shown two compounds (besides triphenylphosphine, triphenylphosphine oxide and DNBzOH), the upper one being the substitution product **24b** and the slightly more polar being the elimination product by analogy to thymine counterparts **24a** and **25**. Both compounds have been isolated (as a mixture) by flash chromatography (CH_2Cl_2-MeOH 20:0.3) and treated with a catalytic amount of NaOMe/HOMe. TLC at this step has shown the product **26b** being the most polar one. This has been isolated by flash chromatography (CH_2Cl_2-MeOH 20:0.9) and without characterization subjected to 80 % AcOH (30 ml) treatment during 30 min (two times). After evaporation of the acid and flash chromatography (CH_2Cl_2-MeOH 10:1.25) 0.035 g of **22b** (41 % for three steps) has been isolated.

B. Diol **20b** (0.017 g, 0.07 mmol) in a dioxane : m-xylene mixture (1:1, 8 ml) has been treated with triphenylphosphine (0.053 g, 0.2 mmol) BzOH (0.025 g, 0.2 mmol) and DEAD (0.03 ml, 0.2 mmol) at room temperature during 3 days. The mainly formed compound is **21b** and, besides, elimination products have been isolated by flash chromatography (CH_2Cl_2-MeOH 20:0.5). After NH_3/HOMe treatment overnight and chromatography (as above) 0.003 g (18 % for two steps) of **22b** has been retained.

mp 185.5-186° (cryst. from MeOH); λ_{max} 260.5 (MeOH), ε 10390; HRMS (LSIMS, thioglycerol) calc. for $[M+H]^+$ $C_{10}H_{15}N_2O_5$ 243.0981, found 243.0992; combustion analysis : calc. C : 49.58, H : 5.83, N : 11.56; found C : 49.81, H : 5.91, N : 11.60.

^1H NMR (500 MHz, D_2O) : 7.84 (d, 1H, $J_{5,6}$ = 8.1 Hz, H6); 5.88 (d, 1H, $J_{5,6}$ = 8.1 Hz, H5); 5.78 (dd, 1H, $J_{1'2'ax}$ = 10.9 Hz, $J_{1'2'eq}$ = 2.8 Hz, H1'); 4.01 (dd, 1H, $J_{5'eq5'ax}$ = - 13.2 Hz, $J_{5'eq4'}$ = 1.6 Hz, $H_{5'eq}$); 3.91 (dt, 1H, $J_{5'ax5'eq}$ = - 13.1 Hz, $J_{5'ax4'}$ = $J_{5'ax3'}$ = 1.5 Hz, $H_{5'ax}$); 3.81 (dd, 1H, $J_{6'6''}$ = - 11.6 Hz, $J_{6'3'}$ = 7.6 Hz, H6'); 3.78 (bs, 1H, half width 5 Hz, H4'); 3.76 (dd, 1H, $J_{6'6''}$ = - 11.6 Hz, $J_{6''3'}$ = 5.2 Hz, H6''); 2.28-2.23 (m, 1H, H3'); 2.21 (ddd, 1H, $J_{2'ax2'eq}$ = - 13.8 Hz, $J_{2'ax1'}$ = 11.1 Hz, $J_{2'ax3'}$ = 5.7 Hz, $H_{2'ax}$); 1.80 (dt, 1H, $J_{2'eq2'ax}$ = - 13.6 Hz, $J_{2'eq1'}$ = $J_{2'eq3'}$ = 2.5 Hz, $H_{2'eq}$).

^{13}C (50 MHz) 166.64, 151.90 (C2,4); 142.27, 102.80 (C5,6); 79.20 (C1'); 69.05, 61.44 (C5',6'); 64.43 (C4'); 41.05 (C3'); 26.42 (C2').

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