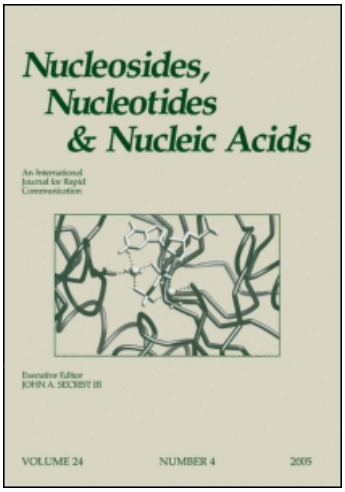


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Aldol Reaction of Nucleoside 5'-Carboxaldehydes with Acetone. Synthesis of 5'-*C*-Chain Extended Thymidine Derivatives

María-José Camarasa[a]; Federico G. De las Heras[a]; María Jesús Pérez-Pérez[a]
[a] Instituto de Química Médica, Madrid, Spain

To cite this Article Camarasa, María-José , Heras, Federico G. De las and Pérez-Pérez, María Jesús(1990) 'Aldol Reaction of Nucleoside 5'-Carboxaldehydes with Acetone. Synthesis of 5'-*C*-Chain Extended Thymidine Derivatives', Nucleosides, Nucleotides and Nucleic Acids, 9: 4, 533 — 546
To link to this Article: DOI: 10.1080/07328319008045185
URL: http://dx.doi.org/10.1080/07328319008045185

NUCLEOSIDES & NUCLEOTIDES, 9(4), 533-546 (1990)

ALDOL REACTION OF NUCLEOSIDE 5'-CARBOXALDEHYDES WITH ACETONE. SYNTHESIS OF 5'-C-CHAIN EXTENDED THYMIDINE DERIVATIVES

María-José Camarasa*, Federico G. De las Heras and
María Jesús Pérez-Pérez

Instituto de Química Médica, Juan de la Cierva 3,
28006 Madrid, Spain

ABSTRACT. Reaction of 3'-O-(t-butyldimethylsilyl)-2'-deoxythymidine-5'-carboxaldehyde and 2',3'-dideoxythymidine-5'-carboxaldehyde with acetone afforded a 3:2 mixture of the two (5'R)- and (5'S)-5'-acetonylthymidine derivatives.

A number of nucleoside derivatives, both synthetic, such as quantamycin,[1] and naturally occurring, such as griseolic acid,[2] liposidomycins,[3] octosyl acids,[4,5] ezomycins,[4,5] tunicamycin,[4-6] sinefungin,[4,5] polyoxins,[4,6] nikkomycins,[4-6] albomycins,[7] Capuramycin,[8] mildiomycin,[9], etc., having higher carbon sugar moieties, show important biological activities. One of the key steps for the total synthesis of these and related compounds is the stereocontrolled formation of a new C-C bond at the 5'-position. Some of the stereoselective methods used for the formation of such C-C bonds, involve the reaction of a nucleoside 5'-carboxaldehyde with cyanide ion,[10] nitromethane,[11] or a Grignard reagent[12]. Alternative methods for the stereocontrolled synthesis of 5'-C-chain extended nucleosides involve the reaction of ribofuranose-5-carboxaldehyde derivatives with dienes,[13] or the reaction of a 5-deoxy-5-nitroribose with chiral aldehydes,[14] followed by reaction with nucleic acid bases. A method for 5'-C-chain-extension, using free radical methodology, has recently been described[15]. The aldol reaction,

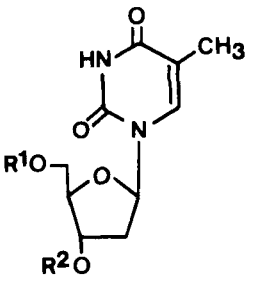
in spite of its well known utility for the stereocontrolled formation of new C-C bonds,[16] has not been applied to the preparation of 5'-C-chain-extended nucleosides. It has been used, however, for the synthesis of 4'-hydroxymethyl derivatives of nucleosides by reaction of nucleoside 5'-aldehydes with formaldehyde[17, 18, 19] and for the synthesis of 2'-and 3'-C-branched-chain sugars.[20]

In this paper we report the aldol reaction of thymidine-5'-carboxaldehyde derivatives with acetone, to afford stereoselectively 5'-C-acetonyl nucleosides.

Oxidation of 3'-O-t-butyldimethylsilylthymine (**1**)[21] with CrO_3/pyridine/Ac_2O[22] gave the thymidine-5'-aldehyde derivative **3**. This compound was unstable and, on standing in the open air, or by treatment in the NMR tube with water, was transformed to the 5'-aldehyde hydrate **4**. The similar behaviour of N^6-benzoyl-2',3'-O-isopropylideneadenosine-5'-aldehyde which tends to exist as the corresponding hydrate has been described.[12] The formation of aldehyde **3** was shown by IR and NMR spectroscopy, and was confirmed by acetylation of the hydrate **4** to afford the 5',5'-di-O-acetylderivative **5**, which was a stable product and was fully characterized.

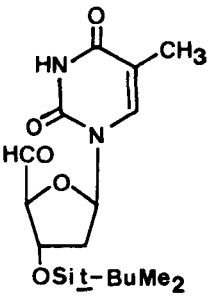
The aldol reaction of aldehyde **3** with acetone using as basic catalyst a 1M aqueous solution of K_2CO_3, was carried out by heating a pH 9 solution of the reagents. The aldol addition products 1-[1,4-anhydro-2,6,8-trideoxy-3-O-(t-butyldimethylsilyl)-α-L-lyxo and β-D-ribo-oct-7-ulosyl] thymines, **6** and **8**, were obtained in a 2:3 ratio. A very low yield (4%) of a third product, a (1:1) mixture of the two diastereoisomers **10**, was also obtained. The formation of **10** can be explained by elimination of the 3'-O-Sit-$BuMe_2$ group under the basic conditions used followed by aldol addition reaction of the α,β-unsaturated aldehyde. The elimination is favored by the acidity of H-4' alpha to the aldehyde group, and conjugation of the 3',4'-double bond with the aldehyde carbonyl group.

The aldol addition reaction of 3'-deoxythymidine-5'-aldehyde **13** with acetone in the presence of aqueous K_2CO_3 afforded very low yields of the two 1- 1,4-anhydro-2,3,6,8-tetradeoxy-α-L-threo and β-D-erythro-oct-7-ulosyl)thymines **14** (4%) and **15** (6%).

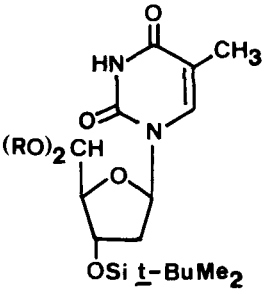


1 , $R^1 = H$, $R^2 = t\text{-}BuMe_2Si$

2 , $R^1 = t\text{-}BuMe_2Si$; $R^2 = H$

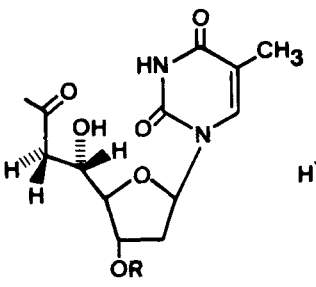


3



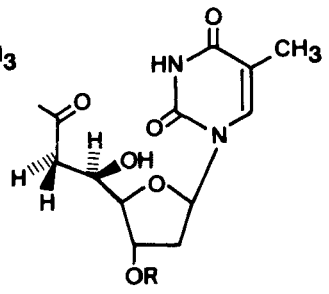
4 , R = H

5 , $R = CH_3CO$



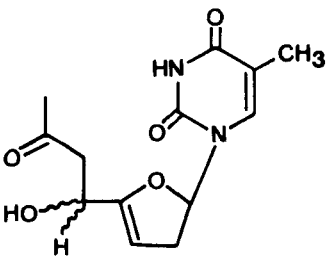
6 , $R = t\text{-}BuMe_2Si$

7 , R = H

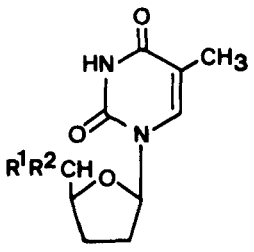


8 , $R = t\text{-}BuMe_2Si$

9 , R = H



10

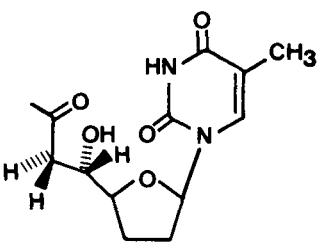


11 , $R^1 = t\text{-}BuMe_2SiO$

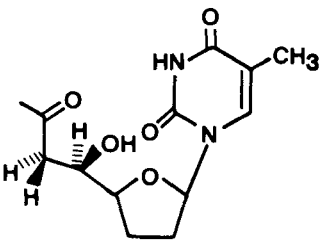
$R^2 = H$

12 , $R^1 = OH$, $R^2 = H$

13 , R^1 , $R^2 = O$



14



15

Fig 1

TABLE 1. Coupling Constants of 1-(1,4-Anhydrooct-7-ulosyl)thymine Derivatives **6** and **8**

Compound	Solvent	$J_{5',OH}$	$J_{4',5'}$	$J_{5',6'a}$	$J_{5',6'b}$	$J_{6'a,6'b}$
6	$CDCl_3$	3.7	1.8	2.6	9.8	18.2
	$(CD_3)_2SO$	5.4	1.9	5.9	7.0	16.6
8	$CDCl_3$	3.6	3.95	10.0	2.6	17.8
	$(CD_3)_2SO$	6.0	5.5	8.6	3.7	15.8

Aldehyde **13** was prepared as follows. Free radical 3'-deoxygenation[23] of 5'-O-(t-butyldimethylsilyl)-thymidine, **2**, by reaction with N,N'-thiocarbonyldiimidazole and with tributyltin hydride afforded 5'-O-(t-butyldimethylsilyl)-3'-deoxythymidine **11** in 84% yield. In spite of the reported instability of 2',3'-dideoxynucleosides[24] to acidic conditions, **11** was readily desilylated by treatment with a 0.1 N solution of HCl in MeOH to give 3'-deoxythymidine, **12**, in 93% yield. Oxidation of **12** with CrO_3/pyridine/Ac_2O gave the aldehyde **13** which, like **3**, was unstable.

The R or S absolute configuration of the new chiral center at C-5' of the aldol addition products **6/8**, **14/15**, as well as the conformation of the C-5'—C-8' chain, were assigned by ^1H NMR spectroscopy as indicated below for compounds **6** (5'-S) and **8** (5'-R) (Table 1). Fig. 2 shows the three main rotamers around C-5'--C-6' for compounds **6** and **8**. The participation of rotamers **6**-I and **8**-III should be very low because H-5' is gauche to both H-6' protons. According to the high values of $J_{5',6'b}$ for **6** and $J_{5',6'a}$ for **8**, H-5' is in the anti disposition with respect to one of H-6'. The contribution of rotamers **6**-III and **8**-I should be low because C-4' and $COCH_3$, the bulkiest of groups attached to C-5' and C-6' respectively, are gauche. The main contribution should be

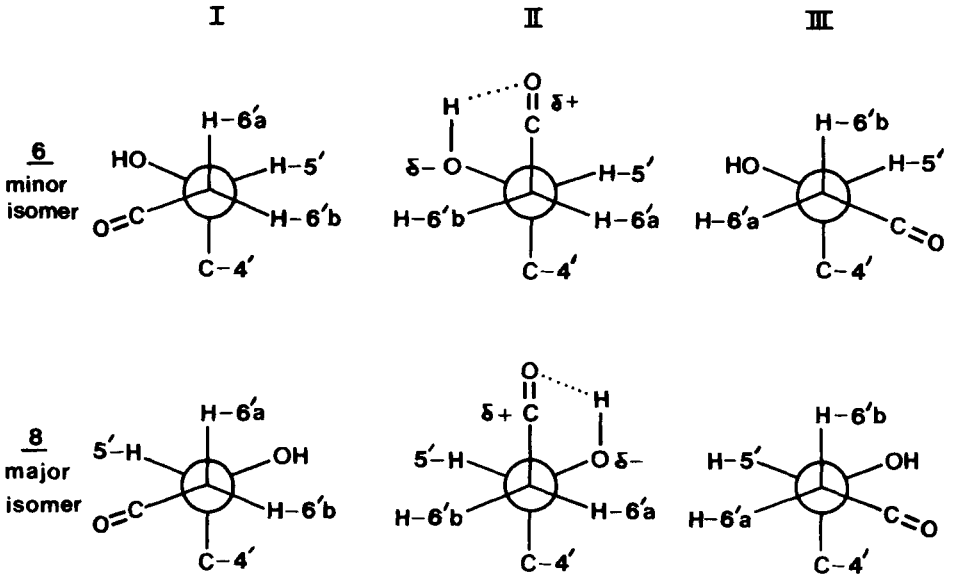


Fig. 2. Rotamers around the C-5'--C-6' bond of **6** and **8**

that of rotamers **6**-II and **8**-II because C-4' and $COCH_3$ are in an antiperiplanar orientation, and H-5' and one of H-6' also have an anti relationship, according to the observed coupling constants. The participation of these rotamers **6**-II and **8**-II should be even higher in chloroform solution, due to the stabilizing polar and/or hydrogen bond effects shown in Fig. 2. These effects disappear in $(CD_3)_2SO$ solution.

Fig. 3 shows the three main rotamers around the C-4'—C-5' bond for compounds **6** and **8**. Rotamers **6**-V and **8**-VI are most strained from the steric point of view since $COCH_3$, the bulkiest of the groups attached to C-5' is gauche to C-3' and 5'-O, the bulkiest groups attached to C-4'. Thus, their contribution to the rotational equilibrium should be very low. According to the observed low $J_{4',5'}$ values, the main contribution should be that of rotamers **6**-VI and **8**-V in which H-4' and H-5' are gauche. However,rotamer **6**-VI should be more stable than **8**-V because CH_2COCH_3 and C-3' the bulkiest of groups have an antiperiplanar disposition in the former and gauche in the latter. According to the observed $J_{4',5'}$ values, the participation of rotamers **6**-IV and **8**-IV, in

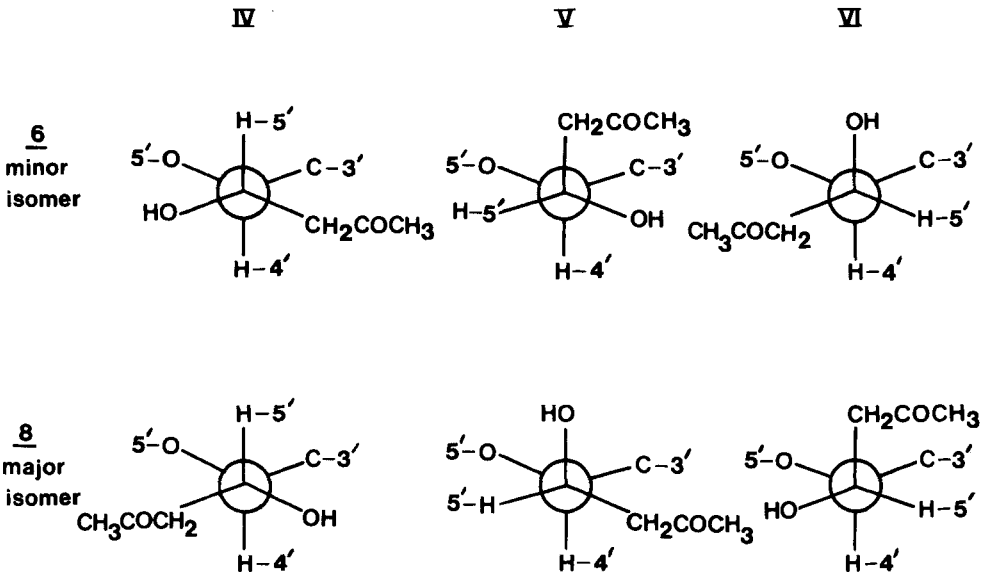


Fig. 3. Rotamers around the C-4'--C-5' bond **6** and **8**

which H-4' and H-5' have an anti relationship should be lower. However, the stability of **8**-IV should be higher than that of **6**-IV because CH_2COCH_3 and C-3' are anti in the former and gauche in the latter. Taking into account that **6**-VI is more stable than **8**-V and **8**-IV more stable than **6**-IV, the minor diastereoisomer **6**, which shows the lowest $J_{4',5'}$ coupling constant and, thus highest preference for the rotamer in which H-4' and H-5' are gauche, should have an S absolute configuration (L series). Similarly, the major compound **8** having a bigger value of $J_{4',5'}$, which indicates a higher participation of the rotamer in which H-4' and H-5' are anti disposition, should have an R configuration at C-5' (D series)

This assignment of configuration to the major and minor diastereoisomer is in agreement with the Cram's Rule[25] according to which the acetone would add to the carbonyl aldehyde group from the less hindered "a" face to afford the major diastereoisomer having a R absolute configuration (D series) (Fig. 4).

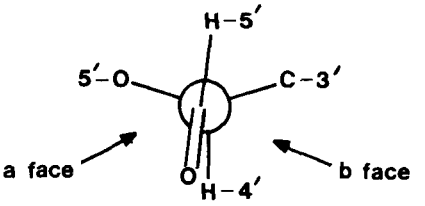


Fig. 4

The stereochemistry at C-4' of **14** and **15** was inferred from nuclear Overhauser effect (n.O.e.) experiments.[26] The signals of H-1' and H-4' of compounds **14** and **15** were irradiated and the magnitudes of n.O.e. at H-4' and H-1' protons respectively were observed. Thus in compound **14** irradiation of H-1' induced a n.O.e. value in H-4' of ≃ 3% on the other hand irradiation of H-4' induced a n.O.e. value in H-1' of ≃ 2%. Similarly irradiation of H-4' and H-1' in compound **15** induced a n.O.e.s of ≃ 2% in H-1' and ≃ 2% in H-4' respectively. The n.O.e.s values indicated that in both nucleosides **14** and **15** protons H-1' and H-4' are "down".

EXPERIMENTAL

Melting points were determined on a Reichert-Jung Thermovar, microscope apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded with Varian EM-390 (^{1}H, 90 MHz), Bruker AM-200 (^{1}H, 200 MHz; ^{13}C, 50 MHz), and Varian XL-300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) spectrometers using Me_4Si as internal standard. IR spectra were recorded with a Shimadzu IR-435 spectrophotometer. UV spectra were taken on a Perkin-Elmer 550 SE spectrophotometer. Mass spectra were obtained with a Vacuum Generators VG 12-250 spectrophotometer. Analytical tlc plates were purchased from Merck. Flash column chromatography was performed with silica gel 60 230-400 mesh (Merck). Compounds were detected by UV light (254 nm) or by spraying the plates with 30% H_2SO_4 in ethanol, and heating.

3'-O-(tert-Butyldimethylsilyl)thymidine-5'-aldehyde (3). A mixture of CrO_3 (1.12 g, 11.2 mmol), methylene chloride (8 mL), N,N-dimethyl-

formamide (2 mL), and pyridine (1.8 mL, 22.4 mmol) was stirred at room temperature for 20 min. To this mixture acetic anhydride (1.06 mL, 11.2 mmol) and a solution of **1** (1 g, 2.8 mmol) in methylene chloride (8 mL) and N,N-dimethylformamide (2 mL) were added. The resulting mixture was stirred at room temperature for 15 min. Ethanol (0.5 mL) was added and the mixture was poured on ethyl acetate and filtered through silica gel (30 g) wet with ethyl acetate. The solution was concentrated under reduced pressure to leave **3** (0.7 g) as an unstable syrup which decomposed on standing and was used as such for the next step. IR (film) 1705 cm^{-1} (CHO); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.86 (s, 9H $(CH_3)_3$ CSi), 1.90 (s, 3H, 5-CH_3), 2.2 (m, 2H, H-2'), 3.8-4.8 (m, 4H, H-3', H-4', H-5'), 6.30 (t, 1H, H-1'), 7.55 (s, 1H, H-6), 8.82 (bs, 1H, 3-NH), 9.75 (s, 1H, CHO)

5',5'-Di-O-acetyl-3'-O-t-butyldimethylsilylthymidine-5'-aldehyde hydrate (5). A mixture of **3** (0.5 g), pyridine (5 mL) and acetic anhydride (1 mL) was stirred at room temperature for 24 h. The solution was concentrated under reduced pressure and the residue was purified by column chromatography using ethyl acetate/hexane (1:2) as eluent to give **5** (0.215 g) as a syrup: ^1H NMR ($CDCl_3$, 90 MHz) δ 0.84 (s, 9H, $(CH_3)_3CSi$), 1.87 (s, 3H, 5-CH_3), 2.0-2.4 (m, 2H, H-2'), 2.07-2.08 (2s, 6H, 5'-CH_3CO), 4.09 (dd, 1H, $J_{3',4'}$ = 1.4, $J_{4',5'}$ = 5.1 Hz, H-4'), 4.43 (m, 1H, H-3'), 6.38 (dd, 1H, $J_{1',2'a}$ = 9, $J_{1',2'b}$ = 5Hz, H-1'), 6.88 (d, 1H, H-5'), 7.27 (s, 1H, H-6), 8.79 (bs, 1H, 3-NH); ^{13}C NMR [$CDCl_3$, 50 MHz] δ 12.37 (5-CH_3), 17.87 ($\underline{C}$ Me_3), 20.67 (CH_3CO), 25.60 [$(CH_3)_3$], 40.61 (C-2'), 71.92, 85.49, 86.06, 87.29 (C-1', C-3', C-4', C-5'), 111.25 (C-5), 134.87 (C-6), 150.29 (C-2), 163.75 (C-4), 168.40, 168.47 ($CH_3\underline{C}O$); MS, $\underline{m/z}$: 457 (M^+ + 1, 1.6%), 399 (M^+ - Me_3C, 32), 357 (45), 341 (33), 339 (71), 297 (100).

Anal. Calcd. for $C_{20}H_{32}N_2O_8Si$: C, 52.62; H, 7.02; N, 6.14. Found: C, 52.62; H, 7.24; N, 6.44.

Aldol Reaction of 3 with Acetone. To a solution of aldehyde **3** (0.7 g), in acetone (15 mL), a 1 M aqueous solution of K_2CO_3 was added until the pH was 9. The resulting mixture was refluxed for 5 h and evaporated to dryness at reduced pressure. The residue was dissolved in chloroform (100 mL) and washed with water (50 mL). The aqueous layer was treated with chloroform (2 x 50 mL). The combined organic layers were washed

with a saturated aqueous solution of NaCl (75 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography using chloroform/acetone (100:5). The fastest running product was identified as **1-(1,4-anhydro-2,6,8-trideoxy-3-O-(t-butyldimethylsilyl)-α-L-lyxo-oct-7-ulosyl) thymine (6)** (0.18 g, 16.5% from **1**) as a syrup: IR (film) 3400 (OH), 3180 (NH), 1700 cm^{-1} (7'-CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.89 (s, 9H, $(CH_3)_3C$), 1.90 (d, 3H, J = 1.0 Hz, 5-CH_3), 2.14-2.25 (m, 2H, H-2'), 2.22 (s, 3H, 8'-CH_3), 2.68 (dd, 1H, $J_{5',6a'}$ = 2.6, $J_{6'a,6'b}$ = 18.2 Hz, H-6'a), 2.88 (dd, 1H, $J_{5',6'b}$ = 9.8 Hz, H-6'b), 3.62 (d, 1H, $J_{5',OH}$ = 3.7 Hz, 5-OH), 3.73 (dd, $J_{3',4'}$ = 3.0; $J_{4',5'}$ = 1.8 Hz; H-4'), 4.23 (m, 1H, H-5'), 4.52 (m, 1H, H-3'), 6.30 (dd, 1H, $J_{1',2'a}$ = 6.5; $J_{1',2'b}$ = 7.0 Hz, H-1'), 7.69 (q, 1H, J = 1.2 Hz, H-6), 8.46 (bs, 1H, 3-NH); ^1H NMR [$(CD_3)_2SO$, 200 MHz] δ 0.87 (s, 9H, $(CH_3)_3C$), 1.76 (s, 3H, 5-CH_3), 1.98-2.14 (m, 2H, H-2'), 2.10 (s, 3H, 8'-CH_3), 2.60 (dd, 1H, $J_{5',6'a}$ = 5.9, $J_{6'a,6'b}$ = 16.63 Hz, H-6'a), 2.65 (dd, 1H, $J_{5',6'b}$ = 7.0 Hz, H-6'b), 3.69 (dd, 1H, $J_{3',4'}$ = 2.6, $J_{4',5'}$ = 2.0 Hz, H-4'), 4.08 (dt, 1H, H-5'), 4.43 (m, 1H, H-3'), 5.25 (d, 1H, $J_{5',OH}$ = 5.4 Hz, 5'-OH), 6.15 (dd, 1H, $J_{1',2'a}$ = 6.1, $J_{1',2'b}$ = 7.8 Hz, H-1'), 7.80 (q, 1H, J = 1.1 Hz, H-6), 10.85 (bs, 1H, 3-NH); MS, m/z : 413 (M^+ + 1, 2.5%), 355 (M^++ 1 -Me_3C, 76%), 337 (69), 287 (M^+ - base, 13), 229 (100), 211 (76), 203 (28), 201 (87), 184 (10), 171 (27).

Anal. Calcd. for $C_{19}H_{32}N_2O_6Si$: C, 55.31; H, 7.82; N, 6.79. Found: C, 55.27; H, 7.62; N, 6.56.

The second product eluted was identified as **1-(1,4-anhydro-2,6,8-trideoxy-3-O-(t-butyldimethylsilyl)-β-D-ribo-oct-7-ulosyl)thymine (8)** (0.235 g, 21.5% from **1**) as a syrup: IR (film) 3400 (OH), 3180 (NH), 1705 cm^{-1} (7'-CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 9H, $(CH_3)_3C$), 1.92 (d, 3H, J = 1.2 Hz, 5-CH_3), 2.11-2.30 (m, 2H, H-2'), 2.22 (s, 3H, 8'-CH_3), 2.63 (dd, 1H, $J_{5',6'a}$ = 10.0, $J_{6'a,6'b}$ = 17.8 Hz, H-6'a), 2.72 (dd, 1H, $J_{5',6'b}$ = 2.6 Hz H-6'b), 3.51 (d, 1H, $J_{5',OH}$ = 3.0 Hz, 5'-OH), 3.74 (dd, 1H, $J_{3',4'}$ = 2.8, $J_{4',5'}$ = 4.0 Hz, H-4'), 4.25 (m, 1H, H-5'), 4.54 (m, 1H, H-3'), 6.22 (dd, 1H, $J_{1',2'a}$ = 6.5; $J_{1',2'b}$ = 7.2 Hz, H-1'), 7.46 (q, 1H, J = 1.3 Hz, H-6), 8.45 (bs, 1H, 3-NH); ^1H NMR [$(CD_3)_2SO$, 200 MHz] δ 0.87 (m, 9H $(CH_3)_3C$), 1.78 (d, 3H, J = 0.5 Hz, 5-CH_3), 1.97 (ddd, 1H, $J_{1',2'a}$ = 5.7, $J_{2'a,2'b}$ = 13.2, $J_{2'a,3'}$ = 2.0, H-2'a), 2.12 (s, 3H, 8'-CH_3), 2.19 (ddd, 1H, $J_{1',2'b}$ = 8.4, $J_{2'b,3'}$ = 5.1 Hz, H-2'b), 2.52

(dd, 1H, $J_{5',6'a}$ = 8.6, $J_{6'a,6'b}$ = 15.8 Hz, H-6'a), 2.60 (dd, 1H, $J_{5',6'b}$ = 3.7 Hz, H-6'b), 3.59 (dd, 1H, $J_{3',4'}$ = 1.7, $J_{4',5'}$ = 5.5 Hz, H-4'), 4.03 (m, 1H, H-5'), 4.50 (m, 1H, H-3'), 5.30 (d, 1H, $J_{5',OH}$ = 6.0 Hz, 5'-OH), 6.14 (dd, 1H, H-1'), 7.54 (q, 1H, H-6), 10.91 (bs, 1H, 3-NH); MS, m/z: 413 (M^+ + 1, 10.5%), 355 (M^+ + 1-(Me_3C, 13%), 337 (8), 295 (11), 287 (4), 269 (7), 229 (33), 211 (39)

Anal. Calcd. for $C_{19}H_{32}N_2O_6Si$: C, 55.31; H, 7.82; N, 6.79. Found: C, 55.18; H, 7.88; N, 7.04.

The third band gave the starting product **1** (0.054 g).

The slowest running product was identified by ^1H NMR as a (1:1) mixture of **1-(1,4-anhydro-2,3,6,8-tetradeoxy-β-D- and α-L-glycero-oct-3-en-7-ulosyl)thymine (10)** (0.035 g, 4%) as a syrup; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.93, 1.94 (2d, 6H, 5-CH_3), 2.20, 2.23 (2s, 6H, 8'-CH_3), 2.64 (m, 2H, $J_{2'a,2'b}$ = 17.4 Hz, H-2'a), 2.88 (m, 4H, H-6'), 3.24, 3.27 (2m, 2H, $J_{1',2'b}$ = 1.7, $J_{2'b,3'}$ = 1.7, $J_{2'b,5'}$ = 0.6 Hz, H-2'b), 4.71 (m, 2H, H-5'), 5.09 (m, 2H, H-3'), 6.72, 6.76 (2dd, 2H, $J_{1',2'a}$ = 2.0, $J_{1',2'b}$ = 4.2 Hz, H-1'), 7.10, 7.13 (2q, 2H, J = 1.3Hz, H-6), 8.70 (bs, 2H, 3-NH).

1-(1,4-Anhydro-2,6,8-trideoxy-α-L-lyxo-oct-7-ulosyl)thymine (7). A mixture of **6** (0.25 g, 0.606 mmol), tetrahydrofuran (12 mL), and tetrabutylammonium fluoride trihydrate (0.174 g, 0.666 mmol) was stirred for 30 min at room temperature. The mixture was passed through a short column of silica gel, which was eluted with tetrahydrofuran and then with acetone. The eluted solution was concentrated and purified by column chromatography using chloroform/acetone (2:1) as eluent to give **7** (0.172 g, 95%) as a solid: mp 103-106°C; UV λ_{max} (MeOH) 262 nm (ε 10390); IR (KBr) 3480 (OH), 1700 cm^{-1} (C=O); ^1H NMR [CD_3COCD_3, 300 MHz] δ 1.80 (d, 3H, J = 1.3 Hz, 5-CH_3), 2.14 (s, 3H, 8'-CH_3), 2.17 (ddd, 1H, $J_{1',2'a}$ = 6.0, $J_{2'a,2'b}$ = 13.4, $J_{2'a,3'}$ = 2.8 Hz, H-2'), 2.25 (ddd, 1H, $J_{1',2'b}$ = 8.2, $J_{2'b,3'}$ = 5.7 Hz, H-2'b), 2.69 (dd, 1H, $J_{5',6'a}$ = 8.7, $J_{6'a,6'b}$ = 16.8 Hz, H-6'a), 2.75 (dd, 1H, $J_{5',6'b}$ = 3.8 Hz, H-6'b), 3.75 (dd, 1H, $J_{3',4'}$ = 2.4, $J_{4',5'}$ = 4.4 Hz, H-4'), 4.25 (m, 1H, H-5'), 4.42 (2d, 2H, 3'-OH, 5'-OH), 4.56 (m, 1H, H-3'), 6.30 (dd, 1H, H-1'), 7.68 (q, 1H, H-6), 10.01 (bs, 1H, 3-NH); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 12.44 (5-CH_3), 30.65 (C-8'), 40.59 (C-2'), 47.60 (C-6'), 68.48, 71.16, 85.52 (C-3', C-4', C-5'), 90.23 (C-1'), 110.82 (C-5), 137.18 (C-6), 151.43 (C-2), 164.34 (C-4), 207.58 (C-7').

Anal. Cald. for $C_{13}H_{18}N_2O_6$: C, 52.35; H, 6.04; N, 9.39. Found: C, 52.00; H, 6.27; N, 9.02.

1-(1,4-Anhydro-2,6,8-trideoxy-β-D-ribo-oct-7-ulosyl)thymine (9). A mixture of **8** (0.25 g. 0.606 mmol), tetrahydrofuran (12 mL) and tetrabutylammonium fluoride trihydrate (0.174 g, 0.666 mmol) reacted and was worked up as indicated before for the preparation of **7**, to afford **9** (0.174 g, 96%) as a solid: mp 161-163°C; UV λ_{max} (MeOH) 264 nm (ε 10500); IR (KBr) 3450 (OH), 1700 cm^{-1} (C=O); ^1H NMR (CD_3COCD_3, 300 MHz) δ 1.79 (d, 3H, J = 1.2, 5-CH_3), 2.13 (s, 3H, 8'-CH_3), 2.18 (ddd, 1H, $J_{1',2'a}$ = 6.1, $J_{2'a,2'b}$ = 13.3, $J_{2'a,3'}$ = 2.8 Hz, H-2'a), 2.27 (ddd, 1H, $J_{1',2'a}$ = 7.9, $J_{2'a,3'}$ = 5.8, H-2'b), 2.72 (dd, 1H, $J_{5',6'a}$ = 4.9, $J_{6'a,6'b}$ = 17.0 Hz, H-6'a), 2.79 (dd, 1H, $J_{5',6'b}$ = 8.0 Hz, H-6'b), 3.83 (t, 1H, $J_{3',4'} = J_{4',5'}$ = 2.4 Hz, H-4'), 4.28 (m, 1H, H-5'), 4.43 (m, 2H, 3'-OH, 5'-OH), 4.46 (m, 1H, H-3'), 6.29 (dd, 1H, H-1'), 7.94 (q, 1H, H-6), ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 12.56 (5-CH_3), 30.61 (C-8'), 40.75, 47,93 (C-2', C-6'), 68.09, 72.99, 85.69 (C-3', C-4', C-5'), 90.14 (C-1'), 110.65 (C-5), 137.47 (C-6), 151.44 (C-2), 164.38 (C-4), 207.89 (C-7').

Anal. Cald. for $C_{13}H_{18}N_2O_6$: C, 52.35; H, 6.04; N, 9.39. Found: C, 52.60; H, 6.32; N, 9.65.

3'-Deoxy-5'-O-(t-butyldimethylsilyl)-thymidine (11). A solution of **2** (1 g, 2.9 mmol) in toluene (12 mL)) was treated with N,N'-thiocarbonyldiimidazole (0.65 g, 3.6 mmol). The mixture was heated at 80°C for 30 min and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (50 mL), washed with a 5% aqueous solution of HCl (30 mL) and with water (30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was dissolved in toluene (20 mL) and tranferred to a three necked flask. α,α'-Azobis(isobutyronitrile) (90 mg, 0.56 mmol) was added, argon was bubbled through the suspension for 15 min, and then tributyltin hydride (1.1 mL, 4.2 mmol) was added through a septum. The reaction flask was heated in an oil bath at 80°C for 4 h under argon atmosphere. The reaction was allowed to reach room temperature, washed with water (20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography using EtOAc/hexane (1:2) as eluent to give **11** (0.80 g, 84%) as a solid: mp 125-128°C; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.96 (s,

9H, $(CH_3)_3C$), 1.94 (s, 3H, 5-CH_3), 1.9-2.5 (m, 4H, H-2', H-3'), 3.63-4.25 (m, 3H, H-4', H-5'), 6.10 (dd, 1H, $J_{1',2'a}$ = 6, $J_{1',2'b}$ = 5 Hz, H-1'), 7.57 (s, 1H, H-6), 9.43 (bs, 1H, 3-NH).

Anal. Calcd. for $C_{16}H_{28}N_2O_4Si$: C, 56.45; H, 8.23; N, 8.23. Found: C, 56.83; H, 8.31; N, 8.57.

3'-Deoxythymidine (12). Compound **11** (0.68 g, 2 mmol), was treated with a 0.1 N solution of HCl in MeOH (50 mL). The resulting mixture was stirred at room temperature for 30 min, neutralized with a 1N solution of NaOH in MeOH and evaporated to dryness. The residue was purified by column chromatography using chloroform:acetone (2:1) as the eluent to give **12** (0.42 g, 93%) mp 150-152°C; mp lit[23] 150-152°C; mp lit[27] 147-149° C.

Aldol Reaction of 3'-deoxythymidine-5'-aldehyde (13) with acetone. Following the same procedure described before for the preparation of **3**, CrO_3 (1.12 g, 11.2 mmol) and pyridine (1.8 mL, 22.4 mmol) reacted with **12** (0.63 g, 2.8 mmol) to give **13** (0.47 g) as a syrup which decomposed on standing. The syrup was dissolved in acetone (8 mL), and a 1M aqueous solution of K_2CO_3 was added until the pH was 9. The mixture was reacted and worked up as indicated before for the preparation of **6** and **8**, to give a residue which was chromatographed by column chromatography using chloroform: ethanol (100: 3). The fastest running product was identified as **1-(1,4-anhydro-2,3,6,8-tetradeoxy-α-L-threo-oct-7-ulosyl)thymine** (**14**) (31 mg, 4% from **12**), as a syrup; ^1H NMR (CD_3COCD_3, 300 MHz) δ 1.82 (d, 3H, J = 1.2 Hz, 5-CH_3), 1.98-2.16 (m, 3H, H-2'a, H-3'a, H-3'b), 2.18 (s, 3H, 8'-CH_3), 2.33 (m, 1H, H-2'b), 2.74 (dd, 1H, $J_{5',6'a}$ = 8.7, $J_{6'a,6'b}$ = 16.68 Hz, H-6'a), 2.86 (dd, 1H, $J_{5',6'b}$ = 3.9 Hz, H-6'b), 4.05 (dt, 1H, $J_{3'a,4'} \approx J_{3'b,4'}$ = 7.0, $J_{4',5'}$ = 2.9 Hz, H-4'), 4.26 (m, 1H, H-5'), 4.45 (d, 1H, $J_{5',OH}$ = 4.8 Hz, 5'-OH), 6.09 (dd, 1H, $J_{1',2'a}$ = 3.8, $J_{1',2'b}$ = 6.7 Hz, H-1'), 8.02 (q, 1H, H-6), 9.98 (bs, 1H, 3-NH).

Anal. Calcd. for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.42; N, 9.93. Found: C, 55.08, H, 6.40; N, 10.05.

The slowest running product was identified as **1-(1,4-anhydro-2,3,6,8-tetradeoxy-β-D-erythro-oct-7-ulosyl)thymine (15)** (46 mg, 6% from **12**). as a syrup; ^1H NMR (CD_3COCD_3, 300 MHz) δ 1.79 (d, 3H, J = 1.2 Hz, 5-CH_3), 1.94-2.11 (m, 3H, H-2'a, H-3'a, H-3'b), 2.14 (s, 3H, 8'-CH_3), 2.31

(m, 1H, H-2'b), 2.60 (dd, 1H, $J_{5',6'a}$ = 8.5, $J_{6'a,6'b}$ = 16.5 Hz, H-6'), 2.67 (dd, 1H, $J_{5',6'b}$ = 3.47 Hz, H-6'b), 3.93 (m, 1H, $J_{3',4'}$ = 6.5, $J_{4',5'}$ = 4.2 Hz, H-4'), 4.34 (m, 1H, H-5'), 6.04 (dd, 1H, $J_{1',2'a}$ = 3.7, $J_{1',2'b}$ = 6.8 Hz, H-1'), 7.81 (q, 1H, H-6), 9.95 (bs, 1H, 3-NH).

Anal. Calcd. for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.42; N, 9.93. Found: C, 55.20; H, 6.59; N, 9.71.

REFERENCES

1. Hanessian, S.; Sato, K.; Liak, T.J.; Danh, N.; Cheney, B.V. J. Am. Chem. Soc. 1984, **106**, 6114.
2. Takahashi, S.; Nakagawa, F.; Kawazoe, K.; Furukawa, Y.; Sato, S.; Tamura, C.; Naito, T. J. Antibiot. 1985, **38**, 830.
3. Ubukata, M.; Isono, K.; Kimura, K.; Nelson, C.C.; McCloskey, J.A. J. Am. Chem. Soc. 1988, **110**, 4416.
4. Suhadolnik, R.J. "Nucleosides as Biological Probes", Wiley Interscience, New York, 1979.
5. Buchanan, J.G.; Wightman, R.M. Topics Antibiot. Chem. 1982, **6**, 231.
6. Carrasco, L.; Vázquez, D. Med. Res. Rew. 1984, **4**, 471.
7. Maehr, H.; Pitcher, R.G. J. Antibiot. 1971, **24**, 830.
8. Yamaguchi, H.; Sato, S.; Yoshida, S.; Takada, K.; Itoh, M.; Seto, H.; Otake, N. J. Antibiot. 1986, **39**, 1047.
9. Harada, S.; Mizuta, E.; Kishi, T. Tetrahedron 1981, **37**, 1317.
10. Damodaran, N.P.; Jones, G.H.; Moffatt, J.G. J. Am. Chem. Soc. 1971, **93**, 3812.
11. Mizuno, Y.; Tsuchida, K.; Tampo, H. Chem. Pharm. Bull. 1984, **82**, 2915.
12. Ranganathan, R.S.; Jones, G.H.; Moffatt, J.G. J. Org. Chem. 1974, **39**, 290.
13. Danishefsky, S.; Hungate, R. J. Am. Chem. Soc. 1986, **108**, 2486.
14. a) Suami, T.; Sasai, H.; Matsuno, K. Chem. Lett. 1983, 819. b) Kozaki, S.; Sakanaka, O.; Yasuda, T.; Shimizu, T.; Ogawa, S.; Suami, T. J. Org. Chem. 1988, **53**, 281.
15. Barton, D.H.R.; Gero, S.D.; Quiclet-Sire, B.; Samadi, M. J. Chem. Soc. Chem. Commum. 1988, 1372.

16. Heathcock, C.H., in "Asymmetric Synthesis"; Morrison, J.D., Ed., Academic Press: Orlando, 1984; Vol. 3, p. 111.
17. Leland, D.L.; Kotick, M.P. Carbohydr. Res. 1974, **38**, C9.
18. Verheyden, J.P.H.; Moffatt, J.G. J. Am. Chem. Soc. 1975, **97**, 4386.
19. Jones, G.H.; Taniguchi, M.; Tegg. D.; Moffatt, J.G. J. Org. Chem. 1979, **44**, 1309.
20. Yoshimura, J. Adv. Carbohydr. Chem. Biochem. 1984, **42**, 69.
21. Ogilvie, K.K.; Iwacha, D.J. Tetrahedron Lett. 1973, 317.
22. Hansske, F.; Madej, D.; Robins, M.J. Tetrahedron 1984, **40**, 125.
23. Prisbe, E.J.; Martin, J.C. Synthetic Communications 1985, **15**, 401.
24. York, J.L. J. Org. Chem. 1981, **46**, 2171.
25. Cram. J.D.; Abd Elhafez, F.A. J. Am. Chem. Soc. 1952, **74**, 5828.
26. Berstein, M.A.; Morton, H.E.; Guindon, Y. J. Chem. Soc. Perkin 2, 1986, 1156.
27. Pfitzner, K.E.; Moffatt, J.G. J. Org. Chem. 1964, **29**, 1508.

Received September 13, 1989.