Pergamon

Tetrahedron Vol. 50, No. 4, pp. 1189-1198, 1994

0040-4020/94 $6.00+0.00

0040-4020(93)E0091-S

Synthesis of a New Branched Chain Hexopyranosyl Nucleoside : 1-[2',3'-Dideoxy-3'-C-(hydroxymethyl)-α-D-erythro-pentopyranosyl]-thymine

K. Augustyns, J. Rozenski, A. Van Aerschot, R. Busson, P. Claes and P. Herdewijn*

Laboratory of Medicinal Chemistry, Rega Institute, Minderbroedersstraat 10, B-3000 Leuven, Belgium

Abstract: A straightforward synthesis of the branched chain nucleoside **7** is described. This synthesis involves two stereoselective steps : introduction of the hydroxymethyl group on the sugar is achieved by radical cyclization of the (bromomethyl)dimethylsilyl ether of the allylic alcohol **8**; the condensation reaction with thymine as base moiety resulted exclusively in the formation of the α-anomer.

INTRODUCTION

Recently we became interested in the synthesis of oligonucleotides containing hexopyranosyl nucleosides (fig. I), which might be useful as antisense oligonucleotides. We reported the synthesis and properties of oligonucleotides containing 2,3-dideoxy-β-D-*erythro*-hexopyranosyl nucleosides[1] **1**. These oligonucleotides were also synthesized by Eschenmoser et al[2] in an attempt to answer the question why nature choose pentose and not hexose nucleic acids. We also reported the synthesis and properties of oligonucleotides containing 3,4-dideoxy[3] (**2**) and 2,4-dideoxy-β-D-*erythro*-hexopyranosyl nucleosides[3,4] (**3**). Based on modeling studies[5], with pyranosyl nucleosides where the hydroxymethyl function and the secondary hydroxyl functions were moved around the different positions of the hexopyranose sugar, we became interested in the synthesis of the α and ß anomers of 2,3-dideoxy-3-*C*-(hydroxymethyl)-L-*threo*-pentopyranosyl nucleosides (**4,5**) and 2,3-dideoxy-3-*C*-(hydroxymethyl)-D-*erythro*-pentopyranosyl nucleosides (**6,7**).

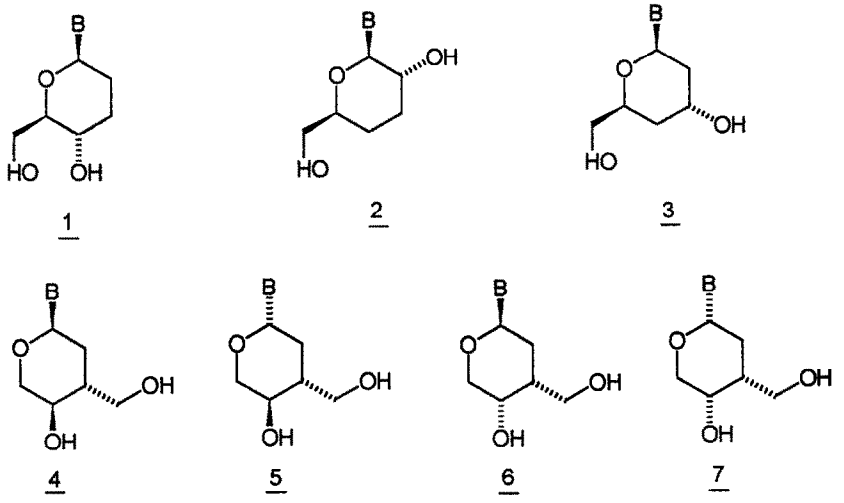
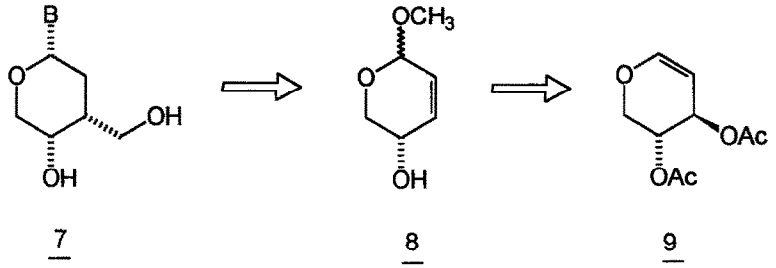


figure 1

The synthesis of such branched chain nucleoside analogues was hitherto unknown. As a first part on the synthetic studies of anomalous branched chain pyranosyl nucleosides, we describe here a straightforward synthesis of the α-isomer **7**. Retrosynthetic analysis of this molecule (scheme I) learned that **7** should be available from **9**. Introduction of the hydroxymethyl function can be achieved by radical cyclization of the (bromomethyl)dimethylsilyl ether of the allylic alcohol **8**. Compound **8** can be obtained from 3,4-di-*O*-acetyl-D-xylal (**9**) by an allylic rearrangement in the presence of MeOH and a Lewis acid catalyst.

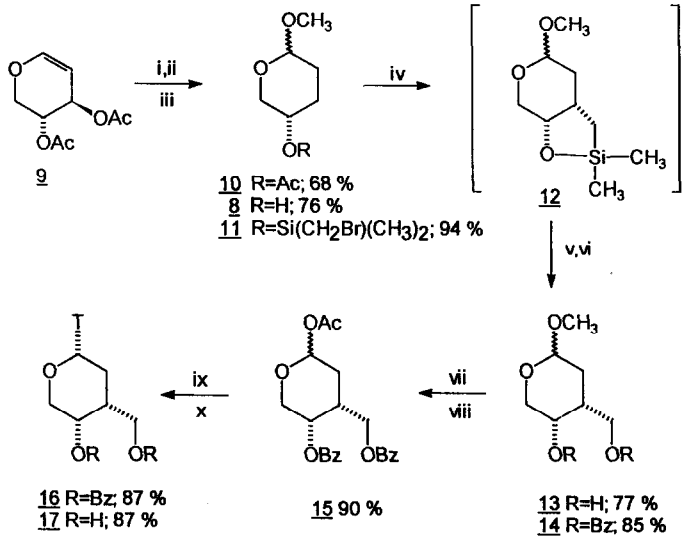


scheme I

CHEMISTRY

3,4-Di-*O*-acetyl-D-xylal (**9**) was synthesized according to a published procedure[6] from D-xylose. The 2,3-dideoxy-2,3-unsaturated methylpyranoside (**10**) (scheme II) was obtained from **9** by an allylic rearrangement in the presence of MeOH and boron trifluoride etherate as a catalyst (Ferrier rearrangement[7]). Deprotection of **10**, followed by reaction with (bromomethyl)dimethylsilylchloride yielded the (bromomethyl)dimethylsilyl ether **11**. Radical cyclizations of (bromomethyl)dimethylsilyl allyl ethers have been used[8] to provide 1,3-diols after a Tamao oxidation[9]. So, treatment of **11** with Bu_3SnH provided the cyclic intermediate **12**, which after oxidative cleavage resulted in the erythro-1,3-diol **13**. Protection of the two hydroxyl functions with a benzoyl group and conversion of the anomeric methoxy to an acetoxy function resulted in a sugar (**15**), which was a suitable derivative for Vorbrüggen sugar-base condensation[10]. Reaction of **15** with silylated thymine and trimethylsilyl trifluoromethanesulfonate as a catalyst afforded exclusively the α-anomer (**16**) in 87% yield suggesting that the 3'-benzoyloxymethyl group is not participating in the condensation reaction. Otherwise also some of the ß-anomers should be formed. Deprotection of **16** resulted in the branched chain nucleoside **17**.

Scheme II

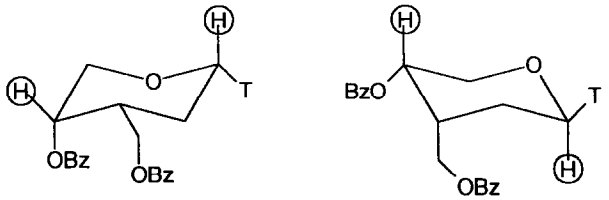


Ac = acetyl, Bz = benzoyl, Me = methyl, T = thymin-1-yl

i : MeOH, $BF_3.Et_2O$; ii : NaOMe; iii : $ClSi(CH_2Br)Me_2$, DMAP, Et_3N, CH_2Cl_2; iv : Bu_3SnH, AIBN; v : KF, $KHCO_3$, H_2O_2; vi : BzCl; vii : HOAc, 80%; viii : Ac_2O; ix : thymine, BSA, $CF_3SO_3SiMe_3$; x : NaOMe

The α-anomeric configuration of this nucleoside analogue was based on the 500MHz ^1H NMR spectrum of **17**. Assignments of shifts and coupling constants for all hydrogens is straightforward in this case, and easily follows from expanded spectra and the use of homo- and heterocorrelated spectroscopy. The hydrogen at C-1' is clearly an axial hydrogen on account of its large coupling constant (J = 10.73Hz) with the axial C-2' hydrogen. This means that the thymine is equatorially oriented, as is seemingly normal for pyranosyl nucleosides[2c,4b,11,12]. Thus, the ß-anomers of pyranosyl nucleosides crystallize in a slightly flattened $^4c_1$ chain conformation, allowing the base to come in an equatorial conformation[11,12]. The α-nucleosides, on the other hand, then adopt a $^1C_4$ conformation again with the base moiety in the equatorial position (fig. II). Differentiation between α or ß is easily based in this case on the coupling constants of the hydrogen on C-4'. This H-4' signal appears as a broad singlet with a half-band width of 2.5Hz, inferring only small couplings. The exact values, which could be extracted from the other multiplets ($J_{4',5'a}$ = 1.08Hz, $J_{4',5'e}$ = 1.61Hz and $J_{4',3'}$ = 2.81Hz) all point to an equatorial H-4' and therefore the α-configuration is retained for **17**.

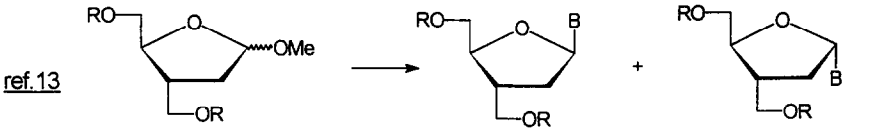
FIGURE II



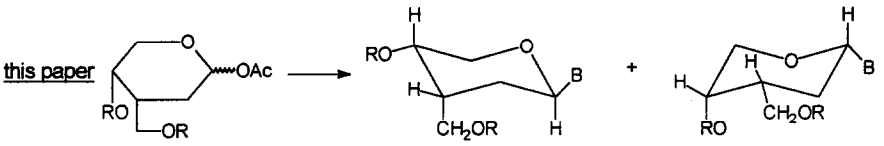
$^1C_4$ α $^4C_1$ β

The exclusive formation of the α-nucleoside is in contrast with the 1:1 ratio for the α/ß anomer normally obtained with the branched chain furanosyl analogue[13] (**18**) (scheme III). We noticed this remarkable preponderance of one anomer also with the 2,4-dideoxy-*β*-D-*erythro*-hexopyranosyl nucleosides (**19a-e**)[4b]. However, in this case it is the ß-anomer which seems to be favoured. Extension of the reaction time from 6 h (**19a**) to 16 h (**19b**) at room temperature turned the ß/α ratio from 2.5/1 to 8/1 with the same total isolated yield. The α-anomer is thus gradually converted to the thermodynamically favoured ß-anomer. After 16 h at room temperature an equilibrium is reached. Also the sugar-base condensation of other hexopyranosyl nucleosides (**20** and **21**)[2c,12] lead to preponderant formation of the ß-anomer under thermodynamic conditions. The only exception (**21e**) is the condensation with the α-hexopyranosyl bromide which results in the formation of the α-anomer. However, a reaction time of 2 h at room temperature is probably not sufficient to obtain the equilibrium necessary for isolating the thermodynamically favoured ß-anomer. The conclusion which can be drawn from these experiments is that (1) conformations are preferred where the base moiety has an equatorial orientation, and (2) in the cases studied, the

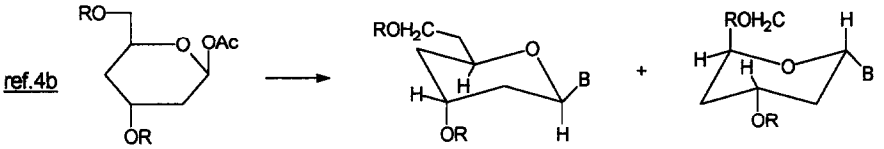
anomer which has a conformation with the CH_2OR placed equatorial is highly favoured over the anomer where the CH_2OR is axially oriented. This is in agreement with the theoretical calculation of the conformation of pyranose rings in monosaccharides, where an axial CH_2OH is twice as destabilizing as an axial OH, whereas an equatorial CH_2OH and an equatorial OH give an almost equal destabilization[14].



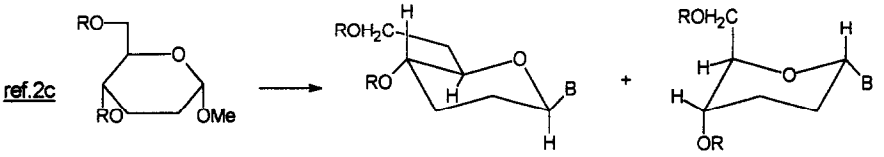
18	B=Si-C, TBDMSTf, CH_2Cl_2, R=Bz, RT, 24h, 54 %	1	:	1



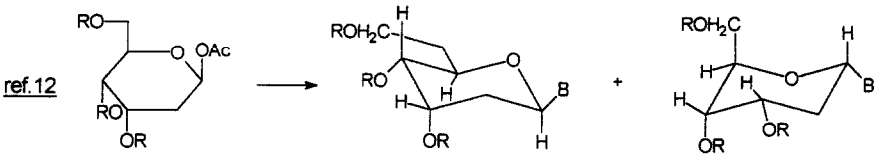
16	B=T, BSA, TMSTf, CH_2Cl_2, R=Bz, RT, 18h, 87 %	0	:	1



19a	B=T, BSA, TMSTf, $ClCH_2CH_2Cl$, R=Bz, RT, 6h, 77 %	2.5	:	1
19b	B=T, BSA, TMSTf, $ClCH_2CH_2Cl$, R=Bz, RT, 16h, 80 %	8	:	1
19c	B=C^{Bz}, BSA, TMSTf, $ClCH_2CH_2Cl$, R=Bz, RT, 16h, 64 %	7	:	1
19d	B=G^{Ac}, DPC, BSA, TMSTf, CH_3CN, R=Bz, RT, 17h, 41 %	5	:	1
19e	B=A^{Bz}, BSA, TMSTf, CH_3CN, R=Bz, 50°C, 54h, 30 %	8		



20a	B=U, HMDS, TMSCl, $SnCl_4$, CH_3CN, R=Ac, 45°C, 20h, 78 %	3	:	1
20b	B=U, HMDS, TMSCl, $SnCl_4$, CH_3CN, R=Ac, 45°C, 20h, 83 %	7	:	2
20c	B=C^{Bz}, BSA, $SnCl_4$, CH_3CN, R=Ac, 45°C, 2h, 70 %	5	:	2
20d	B=A^{Bz}, HMDS, TMSCl, $SnCl_4$, CH_3CN, R=Bz, RT, 20h, 71 %	4	:	3
20e	B=G^{iBu}, BSA, TMSTf, CH_3CN, R=Bz, 80°C, 16h, 32 %	6	:	2



21a	B=Si-U, TMSTf, CH_3CN, R=NBz, reflux, 2h, HPLC	9	:	1
21b	B=Si-C^{AC}, TMSTf, CH_3CN, R=NBz, RT, 10 days, 82 %	β		
21c	B=SiClP, TMSTf, CH_3CN, R=NBz, RT, 12h, 62 %	β		
21d	B=SiCl_2P, TMSTf, CH_3CN, R=NBz, RT, 16h, 1H NMR	8	:	2
21e	B=Si-U, a), CH_3CN, R=NBz, RT, 2h, 57 %			α

a) starting sugar : α-bromo derivative

Si-B = silylated base, C = cytosine, T = thymine, C^{Bz} = N^4-benzoylcytosine, $G^{AC,DPC}$ = N^2-acetyl-O^6-diphenylcarbamoylguanine, A^{Bz} = N^6-benzoyladenine, U = uracil, G^{iBu} = N^2-isobutyrylguanine, C^{AC} = N^4-acetylcytosine, ClP = 6-chloropurine, Cl_2P = 2,6-dichloropurine, BSA = bis(trimethylsilyl)acetamide, HMDS = hexamethyldisilazane, TMSCl = trimethylsilyl chloride, TBDMSTf = tert-butyldimethylsilyl trifluoromethanesulfonate, TMSTf = trimethylsilyl trifluoromethanesulfonate, Bz = benzoyl, Ac = acetyl, NBz = 4-nitrobenzoyl, RT = room temperature

CONCLUSION

The synthesis of 3'-branched pyranosyl nucleosides can easily be accomplished by radical cyclisation of a (bromomethyl)dimethylsilyl allyl ether. Sugar base condensation reactions yields predominantly the pyranosyl nucleosides where both the base moiety and the benzoyloxymethyl group are oriented equatorially. This means that in the case of condensation reactions with 1-O-acetyl-4-O-benzoyl-3-C-[(benzoyloxy)methyl]-2,3-dideoxy-D-*erythro*-pentopyranose exclusively the α-anomer is formed.

EXPERIMENTAL SECTION

Melting points were determined with a Büchi-Tottoli apparatus and are uncorrected.

Ultraviolet spectra were recorded with a Philips PU8740 UV/VIS scanning spectrophotometer. The NMR spectra were determined with a JEOL FX 90Q spectrometer or a Varian Unity 500MHz (for compound **17**) spectrometer. Chemical ionization mass spectra (CIMS) and liquid secondary ion mass spectra (LSIMS) were obtained using a Kratos Concept 1H mass spectrometer. Column chromatography was performed on silica gel (0.060-0.200 mm). Pyridine was dried by distillation after refluxing on KOH. Dichloromethane was refluxed on calcium hydride and distilled. Toluene (Na), and methanol (Mg,I_2) were refluxed on a drying agent prior to distillation.

Methyl-4-O-Acetyl-2,3-dideoxy-α/ß-D-pent-2-enopyranoside (10)

A solution of 1 g (5 mmol) of 3,4-di-*O*-acetyl-D-xylal[6] in 20 mL of toluene was treated with 260 µL (6.42 mmol) of methanol and with 180 µL (1.46 mmol) of boron trifluoride etherate at 0°C under nitrogen. After 1 h, the mixture was diluted with CH_2Cl_2 (100 mL) and washed twice with a $NaHCO_3$ solution (7%, 100 mL). The organic layer was dried, evaporated and purified by column chromatography (hexane - EtOAc 85:15) affording 585 mg (3.40 mmol, 68%) of the title compound as a mixture of two anomers. Separated fractions of both anomers were isolated for characterization of the compounds.

HRMS (LSIMS) m/z: ($C_8H_{12}O_4$ + H^+). Calcd. 173.0813. Found 173.0813.

Faster eluting compound

^1H NMR ($CDCl_3$) δ 2.07 (s, 3H, CH_3CO), 3.45 (s, 3H, CH_3O), 3.78 (d, 1H, J=2.5Hz) and 3.86 (d, 1H, J=0.9Hz) (H-5), 4.84 (m, 1H, H-1), 5.28 (m, 1H, H-4), 5.90 (m, 2H, H-2, H-3)ppm.

^{13}C NMR ($CDCl_3$) δ 20.8 ($\underline{CH_3}CO$), 55.7 (CH_3O), 60.1 (C-5), 64.8 (C-4), 95.2 (C-1), 128.7 and 129.0 (C-2, C-3), 170.3 (C=O)ppm.

$C_8H_{12}O_4$: Calcd C, 55.81; H, 7.02; N, 37.17. Found C, 55.62; H, 6.83; N, 36.96.

Slower eluting compound

^1H NMR ($CDCl_3$) δ 2.09 (s, 3H, CH_3CO), 3.44 (s, 3H, CH_3O), 3.89 (dd, 1H, J=0.9 and 12.7 Hz) and 4.15 (dd, 1H, J=2.8 and 12.7 Hz) (H-5), 4.85-5.00 (m, 2H, H-1, H-4), 6.03 (m, 2H, H-2, H-3)ppm.

^{13}C NMR ($CDCl_3$) δ 20.9 ($\underline{CH_3}CO$), 55.5 (CH_3O), 61.1 (C-5), 63.2 (C-4), 93.9 (C-1), 124.9 and 130.6 (C-2, C-3), 170.4 (C=O)ppm.

$C_8H_{12}O_4$: Calcd. C, 55.81; H; 7.02; N, 37.17. Found C, 55.72; H, 6.94; N, 37.11.

Methyl 4-O-(Bromomethyl)dimethylsilyl-2,3-dideoxy-α/β-D-pent-2-enopyranoside (11)

A solution of 530 mg (3.08 mmol) of **10** was treated with a 0.1 M solution of NaOMe in methanol (20 mL) for 16 h at room temperature. After adding acetic acid (1.7 mL), evaporation and coevaporation with toluene, the mixture was purified by column chromatography (hexane-EtOAc 50:50) affording 305 mg (2.35 mmol, 76%) of **8**. To a solution of 305 mg of **8** and 29 mg (0.24 mmol) of 4-dimethylaminopyridine in CH_2Cl_2 dry (15 mL) was added at 0°C under nitrogen, 400µL (2.88 mmol) of Et_3N and 360 µL (2.55 mmol) of (bromomethyl)chlorodimethylsilane. The mixture was stirred for 30 min at room temperature. The organic phase was washed twice with

brine, dried, evaporated and purified by flash column chromatography (hexane-EtOAc 80:20) yielding 620 mg of the title compound as a mixture of two anomers (2.21 mmol, 94% from **8**).
^{1}H NMR ($CDCl_3$) δ 0.30 (s, 6H, CH_3Si), 2.50 (s, 2H, CH_2Br), 3.42 (s, 3H, CH_3O), 3.60-4.20 (m, 3H, H-4, H-5), 4.70-4.90 (m, 1H, H-1), 5.90-6.15 (m, 2H, H-2, H-3)ppm.
^{13}C NMR ($CDCl_3$) δ -2.6, -2.4, -1.0, 0.1 (CH_3Si), 16.1 (CH_2Br), 55.4 and 55.5 (CH_3O), 62.3, 62.6, 64.2, 64.5 (C-4, C-5), 94.3 and 94.8 (C-1), 126.2, 128.2, 129.0, 133.7 (C-2, C-3)ppm.

Methyl 2,3-Dideoxy-3-C-(hydroxymethyl)-α/β-D-*erythro*-pentopyranoside (13)

A toluene solution (15 mL) of Bu_3SnH (630 μl, 2.27 mmol) containing AIBN (34 mg, 0.21 mmol) was added dropwise over 6 h to a solution of **11** (582 mg, 2.07 mmol) in refluxing toluene (50 mL) under nitrogen. After completion of the addition, the mixture was allowed to reflux for 2 additional hours. The solvent was evaporated and the cyclic intermediate (**12**) was dissolved in a 1:1 mixture of MeOH-THF (20 mL). This solution was treated with KF (481 mg, 8.28 mmol), $KHCO_3$ (415 mg, 4.14 mmol) and H_2O_2 (35%, 1.8 mL, 20.7 mmol) for 16 h at room temperature. The volatiles were removed by evaporation and the resulting mixture was purified by column chromatography (CH_2Cl_2-MeOH 95:5) affording 259 mg (1.60 mmol, 77%) of the title compound as a 7:3 mixture of two anomers, as shown by ^{1}H NMR.
HRMS (LSIMS) m/z: ($C_7H_{14}O_4$ + Na^+). Calcd. 185.079. Found 185.074.
^{1}H NMR (DMSO-d_6) δ 1.00-2.00 (m, 3H, H-2, H-3), 3.24 (s, CH_3O), 3.30-3.75 (m, 5H, H-4, H-5, $\underline{CH_2}OH$), 4.15-4.50 (m, 2H, 4-OH, $CH_2\underline{OH}$), 4.29 (dd, 0.3H, J=3.2 and 8.0 Hz, H-1_{ax}), 4.64 (br s, 0.7H, H-1_{eq})ppm.
^{13}C NMR (DMSO-d_6) δ 27.2 and 29.0 (C-2), 35.6 and 40.9 (C-3), 54.0 and 55.2 (CH_3O), 62.4, 62.8, 64.5, 69.8 (C-5, CH_2OH), 63.4 and 63.7 (C-4), 97.4 and 102.3 (C-1)ppm.
$C_7H_{14}O_4$: Calcd. C, 51.84; H, 8.70; N, 39.46. Found: C, 51.57; H, 8.52; N, 39.27.

1-O-Acetyl-4-O-benzoyl-3-C-[(benzoyloxy)methyl]-2,3-dideoxy-α/β-D-*erythro*-pentopyranose (15)

A solution of 192 mg (1.19 mmol) of **13** in pyridine (10 mL) was treated with 0.7 mL (6.03 mmol) benzoyl chloride for 16 h at room temperature. The excess reagent was destroyed with water, and the mixture was concentrated by evaporation, followed by extraction [CH_2Cl_2 - $NaHCO_3$ solution (7%)]. The organic layer was dried, evaporated and purified by column chromatography (CH_2Cl_2-MeOH 99.5:0.5) affording 376 mg (1.02 mmol, 85%) of **14**. This material was dissolved in 80% aqueous acetic acid (50 mL) and kept for 10 h at 80°C. After evaporation and coevaporation with toluene (2 x), the mixture was dissolved in pyridine/acetic anhydride (30 mL, 2/1) and stirred for 17 h at room temperature. Evaporation, coevaporation with toluene and purification by column chromatography (CH_2Cl_2-MeOH 99.5:0.5) afforded 367 mg (0.92 mmol, 90% from **14** of the title compound as a 3:2 mixture of two anomers.
^{1}H NMR ($CDCl_3$) δ 1.70-2.30 (m, 2H, H-2), 2.13 (s, 3H, CH_3), 2.50-2.90 (m, 1H, H-3), 3.80-4.75 (m, 4H, H-5, $\underline{CH_2}OBz$), 5.20-5.45 (m, 1H, H-4), 5.81 (t, 0.4H) and 6.33 (br s, 0.6H) (H-1), 7.30-7.60 (m, 6H, aromatic H), 7.90-8.15 (m, 4H, aromatic H)ppm.

^{13}C NMR ($CDCl_3$) δ 20.9 ($\underline{CH_3}CO$), 26.9 and 28.5 (C-2), 31.8 and 36.6 (C-3), 63.2, 64.2, 64.4, 66.3, 66.7, 67.3 (C-4, C-5, $\underline{CH_2}OBz$), 90.5 and 93.0 (C-1), 128.2, 129.4, 129.5, 132.9, 133.1 (aromatic), 165.6 and 166.0 ($\underline{CO}C_6H_5$), 168.9 and 169.3 ($\underline{CO}CH_3$)ppm.
$C_{22}H_{22}O_7$: Calcd. C, 66.32; H, 5.57; N, 28.11. Found C, 66.12; H, 5.71; N, 28.04.

1-[4'-O-Benzoyl-3'-C-[(benzoyloxy)methyl]-2',3'-dideoxy-α-D-*erythro*-pentopyranosyl]thymine (16)

A mixture of 367 mg (0.92 mmol) of **15**, 232 mg (1.84 mmol) of thymine and 1.38 mL (5.52 mmol) of bis(trimethylsilyl)acetamide in CH_2Cl_2 (10 mL) was refluxed for 3 h. Trimethylsilyl trifluoromethane sulfonate (230 μL, 1.18 mmol) was added to the clear solution at room temperature under nitrogen. The solution was kept for 18 h at room temperature, followed by dilution with CH_2Cl_2 and washing with a 7% aqueous $NaHCO_3$ solution. The organic layer was dried, evaporated and purified by column chromatography [(1) hexane -EtOAc 70:30, (2) hexane - EtOAc 50:50] affording 373 mg (0.80 mmol, 87%) of the title compound.
HRMS (LSIMS) m/z : ($C_{25}H_{24}O_7N_2 + H^+$). Calcd. 465.166. Found 465.167.
^1H NMR ($CDCl_3$) δ 1.80-2.20 (m, 2H, H-2'), 1.94 (s, 3H, CH_3), 2.50-2.90 (m, 1H, H-3'), 3.80-4.55 (m, 4H, H-5', $\underline{CH_2}OBz$), 5.30 (br s, 1H, H-4'), 5.86 (dd, 1H, J=4.1 and 9.0 Hz, H-1'), 7.20-7.70 (m, 7H, H-6, aromatic H), 7.90-8.20 (m, 4H, aromatic H), 9.70 (br s, 1H, NH)ppm.
^{13}C NMR ($CDCl_3$) δ 12.5 (q, CH_3), 29.0 (t, C-2'), 37.4 (d, C-3'), 64.2 (t, $\underline{CH_2}OBz$), 66.3 (d, C-4'), 69.5 (t, C-5'), 80.7 (d, C-1'), 111.3 (s, C-5), 128.2, 128.4, 129.4, 133.0, 133.3 (aromatic), 134.7 (d, C-6), 150.0 (s, C-2), 163.6 (s, C-4), 165.4 and 166.0 (CO)ppm.
$C_{25}H_{24}O_7N_2$: Calcd. C, 64.55; H, 5.21; N, 6.03. Found C, 64.83; H, 5.04; N, 5.87.

1-[2',3'-Dideoxy-3'-C-(hydroxymethyl)-α-D-*erythro*-pentopyranosyl]-thymine (17)

A solution of 360 mg (0.78 mmol) of **16** was dissolved in 0.1 M solution of NaOMe in methanol (10 mL) and kept at room temperature for 48 h. After adding acetic acid (1 mL), evaporation and coevaporation with toluene, the mixture was purified by column chromatography (CH_2Cl_2-MeOH 90:10) affording 173 mg (0.68 mmol, 87%) of the title compound as a white foam. An analytical pure sample was obtained after crystallization from MeOH-Et_2O.
UV (MeOH) λ_{max} = 266 nm ($\log\varepsilon$ = 4.00); (0.01 N NaOH) λ_{max} = 266 nm ($\log\varepsilon$ = 3.89)
HRMS (EI) m/z: ($C_{11}H_{16}N_2O_5$). Calcd. 256.1059. Found 256.1051.
^1H NMR (D_2O, 500MHz) δ 1.675 (dt, 1H, H-2'e), 1.726 (dt, 1H, H-2'a), 1.819 (d, 3H, CH_3), 2.081 (m, $\nu_{1/2}$=10Hz 1H, H-3'), 3.479 (dd, 1H, 3'-CH_{2B}), 3.634 (dd, 1H, 3'-CH_{2A}), 3.797 (dd, 1H, H-5'a), 3.840 (brs, $\nu_{1/2}$=2.5Hz, 1H, H-4'), 4.002 (dd, 1H, H-5'e), 5.618 (dd, 1H, H-1'), 7.613 (q, 1H, H-6)ppm. H-H couplings: $^3J_{1',2'e}$ = 2.82Hz, $^3J_{1',2'a}$ = 10.73Hz, $^2J_{2',2'}$ = 12.80Hz, $^3J_{2'e,3'}$ = 4.30Hz, $^3J_{2'a,3'}$ = 12.49Hz, $^3J_{3',CH2A}$ = 7.58Hz, $^3J_{3',CH2B}$ = 6.58Hz, $^3J_{3',4'}$=2.82Hz, $^2J_{CH2A,CH2B}$ = 11.01Hz, $^3J_{4',5'a}$ = 1.08Hz, $^3J_{4',5'e}$ = 1.61Hz, $^2J_{5',5'}$ = 12.62Hz, $^4J_{6,Me}$ = 1.07Hz.
^{13}C NMR (DMSO-d_6 + D_2O) δ 12.0 (CH_3), 27.5 (C-2'), 41.4 (C-3'), 62.3 and 62.8 (C-4', $\underline{CH_2}OH$), 72.7 (C-5'), 80.7 (C-1'), 109.3 (C-5), 136.5 (C-6), 150.2 (C-2), 163.7 (C-4)ppm.

El. Anal. $C_{11}H_{16}N_2O_5$ Calcd. C, 51.56; H, 6.29; N, 10.93. Found C, 51.23; H, 6.31; N, 10.65

ACKNOWLEDGEMENT

A. Van Aerschot is a research associate of the Belgian National Fund of Scientific Research. We thank Dr. G. Janssen for coordinating the mass spectrometry. This work has been supported by grants from the Belgian F.G.W.O. (Fonds voor Geneeskundig Wetenschappelijk Onderzoek, project 3.0076.92). We thank Dominique Brabants for editorial help.

REFERENCES

1. Augustyns, K.; Van Aerschot, A.; Urbanke, C.; Herdewijn, P. *Bull. Soc. Chim. Belg.* **1992**, *101*, 119-130.
2. (a) Eschenmoser, A. *Nachr. Chem. Tech. Lab.* **1992**, *75*, 218-259.
   (b) Eschenmoser, A.; Dobler, M. *Helv. Chim. Acta* **1992**, *75*, 218-259.
   (c) Böhringer, AM; Roth, H.-J.; Hunziker, J.; Göbel, M., Krishnan, R.; Giger, A.; Schweizer, B., Schreiber, J.; Leumann, C.; Eschenmoser, A. *Helv. Chim. Acta* **1992**, *75*, 1416-1477.
3. Augustyns, K.; Vandendriessche, F.; Van Aerschot, A.; Busson, R.; Urbanke, C.; Herdewijn, P. *Nucleic Acids Res.* **1992**, *20*, 4711-4716.
4. (a) Augustyns, K.; Van Aerschot, A.; Herdewijn, P. *Bioorg. Med. Chem. Letters* **1992**, *2*, 945-948.
   (b) Augustyns, K., Rozenski, J., Van Aerschot, A., Janssen, G., Herdewijn, P. *J. Org. Chem.* **1993**, 2977-2982.
   (c) Augustyns, K.; Godar, G., Hendrix, C., Van Aerschot, A., Rozenski, J., Saison-Behmoaras, T., Herdewijn, P. Nucleic Acids Res. **1993**, in press.
5. De Winter, H. et al., unpublished results.
6. Helferich, B.; Gindy, M. *Chem. Ber.* **1954**, 87, 1488-1491.
7. Ferrier, R.J.; Prasad, N. *J. Chem. Soc. (C)* **1969**, 570-575.
8. (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itah, K. *J. Org. Chem.* **1984**, *49*, 2298-2300.
   (b) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500-501.
9. Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120-2122.
10. Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234-1255.
11. De Winter, H.L.; De Ranter, C.J.; Blaton, N.M.; Peeters, O.M.; Van Aerschot, A.; Herdewijn, P. *Acta Cryst.* **1992**, *B48*, 95-103.
12. Nord, L.D.; Dalley, N.K.; McKernan, P.A.; Robins, R.K. *J. Med. Chem.* **1987**, *30*, 1044-1054.
13. Svansson, L.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1991**, *56*, 2993-2997.
14. El Khadem, H.S. in Carbohydrate Chemistry: monosaccharides and their oligomers. Academic Press. **1988**, 49-50.

(*Received in Belgium* 3 *September* 1993; *accepted* 21 *October* 1993)