Free-Radical Synthesis of 3-(2-Cyanoethyl)- and 3-(2-Methoxycarbonylethyl)-2,3-dideoxy-α-D-*erythro*-pentofuranoside and Their Application in the Synthesis of Potential Antiviral Nucleosides

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Free-radical reaction of different carbohydrate educts **2**, **5**, and **7** with acrylonitrile in the presence of tributyltin hydride and a radical initiator (AIBN) gave the methyl 3-(2-cyanoethyl)-2,3-dideoxypentofuranosides **3a** and **6**. Similar reaction of **2** with methyl acrylate gave 3-(2-methoxycarbonylethyl)-2,3-dideoxypentofuranose **3b**. Nucleoside coupling of **3a** with silylated uracil gave an anomeric mixture of β- and α-nucleoside **8** and **9** which were deprotected to give **10** and **11**, respectively. Similar reaction of **3b** with silylated N^4-isobutyrylcytosine gave **12** and **13** which were deprotected to give the final nucleosides **16** and **17**, respectively. None of the compounds **10a**, **11**, **14-17** showed significant activity against HIV.

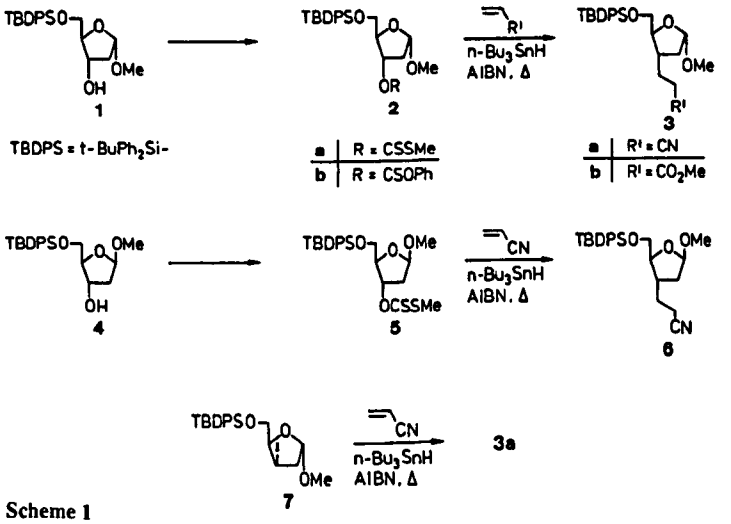
Radikalsynthese von 3-(2-Cyanethyl)- und 3-(2-Methoxycarbonylethyl)-2,3-didesoxy-α-D-*erythro*-pentofuranosid und ihre Anwendung zur Synthese potentiell antiviraler Nucleoside

Die Radikalreaktion der Zuckerderivate **2**, **5** und **7** mit Acrylnitril in Gegenwart von Tributylzinnhydrid und dem Radikalstarter AIBN führte zu den Methyl-3-(2-cyanethyl)-2,3-didesoxypentofuranosiden **3a** und **6**. Die analoge Reaktion von **2** mit Methylacrylat ergab die 3-(2-Methoxycarbonylethyl)-2,3-didesoxypentofuranose **3b**. Die Nucleosidverknüpfung von **3a** mit silyliertem Urazil lieferte das Anomerengemisch der β- und α-Nucleoside **8** und **9**, die zu **10** bzw. **11** entsilyliert wurden. Analog dazu wurden aus **3b** und silyliertem N^4-Isobutyrylcytosin **12** und **13** und durch Entfernen der Schutzgruppen **16** bzw. **17** erhalten. Keine der Verbindungen **10a**, **11**, **14-17** zeigte nennenswerte Aktivität gegen HIV.

The interest in modification of the carbohydrate moiety of nucleosides has tremendously increased since 3'-azido-2',3'-dideoxythymidine (AZT) was reported as a potent antiviral agent against human immunodeficiency virus (HIV)[1]. From the great number of modified nucleosides synthesized, it has been tried to determine structure activity relationships[2]. From these studies, the best suggestion is to modify the natural nucleosides at C-2' and C-3', but there seems to be very few structural possibilities. Carbon branched substituents have been introduced at C-3', but no appreciable activity against HIV has been reported for these compounds. Even non-polar groups with similar or less steric requirements than the azido group are almost inactive. Thus, a 3'-cyano group with very similar inductive effect F values and low steric requirements compared to hydroxyl and azide was reported to be almost inactive[3-7]. Also, longer chains of 2',3'-dideoxynucleosides like 3'-cyanomethyl[8,9,10], 3'-hydroxymethyl[11,12], 3'-phosphonomethyl[13,14], allyl and alkyl[12,15,16] have been introduced, but no activity against HIV has been reported.

Pyranosyl and furanosyl radicals are known to react with acrylonitrile in the presence of tributyltin hydride to give *C*-glycosyl compounds[17,18]. Besides, similar methods have been used to generate C-C bonds at carbon C-6 of hexofuranoses[19] and to introduce alkyl and allyl groups at carbon C'-3 in 2'-deoxynucleosides[12,15,16].

In this paper we want to extent this area with the free-radical synthesis of the methyl glycosides of 3-(2-cyanoethyl)-2,3-dideoxyfuranose **3a** and 3-(2-methoxycarbonylethyl)-



Scheme 1

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2,3-dideoxyfuranose **3b**. These two new carbohydrates are used for the preparation of some new nucleosides in order to evaluate the antiviral activities of this kind of compounds.

Chemistry

Xanthate **2a** was prepared in 96% yield from methyl 5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-α-D-*erythro*-pentofuranoside **1**[20] by treatment with NaH, CS_2, and CH_3I. A 3-ribosyl radical was thermally generated from **2a** in the presence of the radical initiator α,α'-azoisobutyronitrile (AIBN) together with tributyltin hydride and subsequent reaction with acrylonitrile gave **3a** in 26% yield after purification. When methyl acrylate was used as radical acceptor, **3b** was isolated in 23% yield.

The 3-ribosyl radical also initiated polymerization of the acrylonitrile and small fractions containing branched alkyl groups at C-3 according to ^{13}C-NMR were isolated as well, but they were not further identified. The relative reactivities of the different intermediate radicals in the reaction cycle are of great importance for a successful application of this method as observed by other groups[15-19].

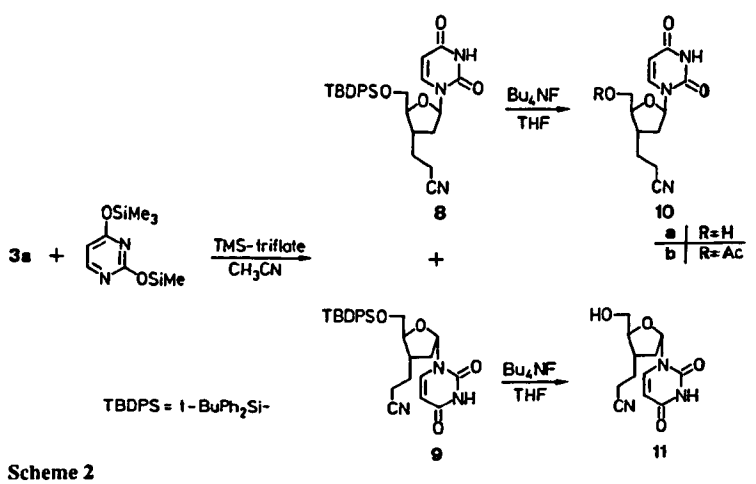
In order to increase the yield, three other radical precursors **2b**, **5**, and **7** were used. Phenoxythiocarbonate **2b** was prepared from **1** using phenyl chlorothioformate, pyridine, and 4-dimethylaminopyridine (DMAP). Large scale (24 mmol) free-radical reaction of **2b** with arylonitrile as radical acceptor gave only 23% isolated yield of **3a**. Reaction of **2b** with methyl acrylate also gave a disappointing low yield of **3b** (25%). The iodo compound **7**[20] was also reacted with acrylonitrile to give 24% yield of **3a** after purification.

Despite the low yield of products, high selectivity of *erythro* configuration of **3** and **6** was obtained. The corresponding *threo* isomers were not detected. This is consistent with the review by *Giese*[18]. A β-substituent of a cyclopentyl radical promotes a high degree of *anti* attack by the radical acceptor. In this case the bulky substituent at C-4 of the furanose ring protects the β-face of the ring resulting in *erythro* configuration as the major product. In order to see if the absence of the steric effect of the α-face of the ring from the anomeric methoxy substituent had any effect on the reaction, the xanthate **5** was used as substrate. Using the same method as for the preparation of **2a**, xanthate **5** was obtained from **4**[20] in 81% yield. Reaction of **5** with acrylonitrile gave compound **6** in only 19% yield after purification and the corresponding *threo* isomer of **6** was not detected. Thus, the steric hindrance of the α-face from the methoxy group in xanthate **2a** seems to be of minor importance in this free-radical reaction.

Nucleoside coupling of **3a** with silylated uracil and trimethylsilyl trifluoromethanesulfonate (TMS-triflate) as *Friedel-Crafts* catalyst[21,22] gave an anomeric mixture of β- and α-nucleoside **8** and **9** in 60% total yield. Removal of the silyl protecting group with tetrabutylammonium fluoride gave the final nucleosides **10a** and **11**. Similar reaction of **3b** with silylated N^4-isobutyrylcytosine gave a mixture of β- and α-nucleoside **12** and **13** in 59% total yield after separation. Desilylation with tetrabutylammonium fluoride resulted in the N^4-protected nucleosides **14** and **15** which were converted to **16** and **17**, respectively, by treatment with methylamine in absol. ethanol. The amide functionality at the alkyl chain at C'-3 in compound **16** and **17** gives a potential possibility of extra hydrogen bonding to the complimentary DNA-chain of a nucleotide.

The structural assignment of the nucleosides was mainly based on NMR studies. 2D-NOSY experiments on compound **10b** and compound **13** gave an unambiguous configurational assignment. Thus, in compound **10b** the β-configuration of the pyrimidine ring was confirmed by the 5% n.O.e. in H-6, when Ha-5' was irradiated. Besides, irradiation of H-1' gave a 3% n.O.e. in H-4'. Irradiation of CH_2 (Ha-1'' and Hb-1'') attached to C-3' proton by proton generated a 4% n.O.e. of H-4' in both cases which strongly proves *erythro* configuration. The acetyl derivative **10b** was selected for the n.O.e. experiment instead of **10a** and **11** because the latter compounds showed overlapping protons in their ^{1}H-NMR spectra.

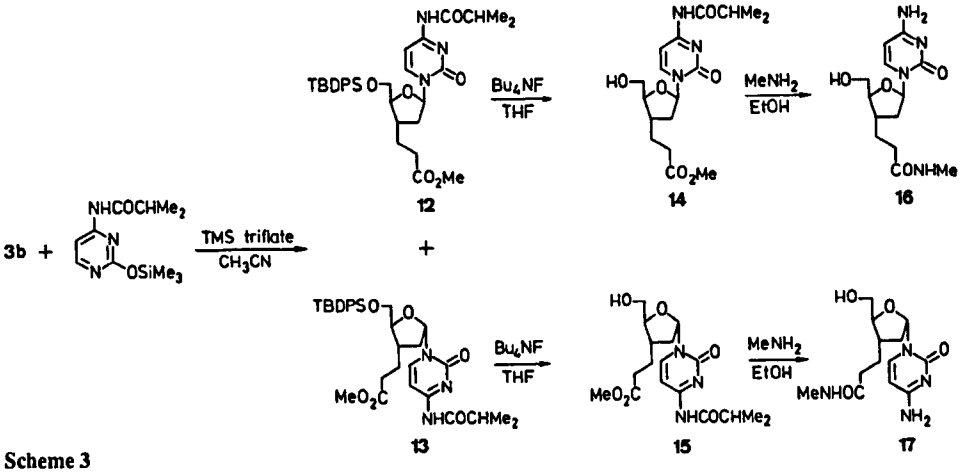
In compound **13** irradiation of H-4' generated a 8% n.O.e. in H-6 which was confirmed by a 6% n.O.e. in H-4' when H-6 was irradiated. The *erythro* configuration was assigned by irradiating one of the protons of CH_2 (Ha-1'') attached to C-3', generating a 4% n.O.e. in H-4' and a 3% n.O.e. in H-6 of the pyrimidine ring.



Scheme 2

Besides, the deshielding effect of the nucleobase generates a considerable downfield shift of Ha-5' and Hb-5' when the nucleobase is changed from the α- to the β-side of the furanose ring in compound **13** and **12**. Similarly, H-4', Ha-1'', and Hb-1'' are shifted downfield when the nucleobase is changed from the β- to the α-side of the furanose ring. Such downfield shifts have previously been observed for 2-deoxy nucleosides[7].

In preliminary results the compounds **10a, 11, 14-17** did not show any significant activity against human immunodeficiency virus (HIV) strain HTLV-IIIB in MT-4 cells at 100 μM.



Scheme 3

Experimental Part

NMR experiments: Bruker AC250 FT NMR.- Microanalyses: NOVO NORDISK Microanalytical Laboratory A/S, Novo Allé, DK-2880 Bagsvaerd.- EI mass spectra: Varian MAT 311 A.

Methyl 5-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(methylthio)thiocarbonyl-α-D-erythro-pentofuranoside (**2a**)

A solution of **1**[20] (1.53 g, 3.96 mmol) and CS_2 (0.6 ml, 10 mmol) in dry THF was dropwise added to a suspension of NaH (50%, dispersion, 350 mg, 7.3 mmol) in dry tetrahydrofuran (10 ml) under N_2. After stirring for 1 h at room temp. CH_3I (0.5 ml, 8 mmol) was added in one portion. After additional 0.5 h the reaction was quenched with acetic acid (0.2 ml). After 10 min the reaction mixture was diluted with diethyl ether (25 ml) and extracted with a saturated solution of $NaHCO_3$ (2 x 25 ml) and a saturated solution of NaCl (25 ml). The ether phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give chromatographically pure xanthate **2a** as a yellow oil. Yield 1.82 g (96%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.70-7.34 (m, 10 H, aryl), 5.99-6.04 (m, H-3), 5.18 (d, 5.0 Hz, H-1), 4.34 (dd, 3.8 Hz, 3.2 Hz, H-4), 3.95 (dd, 11.0 Hz, 3.2 Hz, Ha-5), 3.79 (dd, 11.0 Hz, 3.8 Hz, Hb-5), 3.39 (s, OMe), 2.44-2.48 (m, H-2α, H-2β, SMe), 1.05 (s, 9H, CMe_3).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 135.53, 133.06, 129.65, 129.60, 127.63, 127.60 (aryl), 105.11 (C-1), 83.57, 83.49 (C-3, C-4), 64.18 (C-5), 57.75 (OMe), 39.29 (C-2), 26.71 ($CHMe_3$), 19.13 ($\underline{C}Me_3$), 18.69 (SMe).

Methyl 5-O-tert-butyldiphenylsilyl-2-deoxy-3-O-phenoxythiocarbonyl-α-D-erythro-pentofuranoside (**2b**)

Phenyl chlorothioformate (28.0 g, 0.162 mol) was added to a solution of **1**[20] (25.0 g, 0.065 mol) and 4-dimethylaminopyridine (20.0 g, 0.164 mol) in dichloromethane (250 ml) and pyridine (100 ml) at 0°C. The mixture was left overnight at 5°C. The solvent was removed *in vacuo* and the residue dissolved in benzene (200 ml) and washed with aqueous HCl (0.5 M, 2 x 50 ml) and a saturated solution of $NaHCO_3$ (50 ml). After drying over anhydrous $MgSO_4$ the benzene was removed at reduced pressure. The crude product (39.3 g) was purified by flash chromatography (Merck silica, 230-400 mesh, 5 x 40 cm, benzene and cyclohexane, gradient v:v 1:3 → 1:1) to give pure **2b**. Yield 28.0 g (82%), m.p. 77-78°C.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.72-7.07 (m, 15 H, aryl), 5.85 (dd, 7.2 Hz, 2.2 Hz, H-3), 5.20 (d, 4.6 Hz, H-1), 4.42 (dd, 3.7 Hz, 3.1 Hz, H-4), 3.98 (dd, 11.0 Hz, 3.1 Hz, Ha-5), 3.83 (dd, 11.0 Hz, 3.7 Hz, Hb-5), 3.41 (s, OMe), 2.58-2.47 (m, H-2α, H-2β), 1.07 (s, 9H, CMe_3).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 194.65 (C=S), 153.37, 135.58, 133.01, 132.99, 129.77, 129.73, 129.41, 127.74, 127.72, 126.45, 121.93 (aryl), 105.23 (C-1), 84.18, 83.69 (C-3, C-4), 64.40 (C-5), 55.02 (OMe), 39.42 (C-2), 26.78 (Me), 19.21 ($\underline{C}Me_3$).

Methyl 5-O-tert-butyldiphenylsilyl-3-(2-cyanoethyl)-2,3-dideoxy-α-D-erythro-pentofuranoside (**3a**)

From **2a**: A solution of xanthate **2a** (640 mg, 1.34 mmol) and freshly distilled acrylonitrile (0.90 ml, 13.5 mmol) in dry xylene (30 ml) was heated to 100°C under N_2. A solution of tributyltin hydride (0.70 ml, 2.68 mmol) and AIBN (90 mg, 0.55 mmol) in dry xylene (5 ml) was added dropwise within 2 h at 100°C. The mixture was heated further for 1 h and the solvent was then removed under reduced pressure. The residue was purified by flash chromatography (Merck silica, 230-400 mesh, 2 x 30 cm, cyclohexane and ethyl acetate, v:v = 12:1) to give pure **3a** as the main product. Yield 150 mg (26%).

From **2b**: A solution of **2b** (12.5 g, 24 mmol) and freshly distilled acrylonitrile (16.0 ml, 240 mmol) in dry toluene (300 ml) was heated to 80°C under N_2. A solution of tributyltin hydride (12.6 ml, 48 mmol) and AIBN (1.3 g, 8 mmol) in dry toluene (100 ml) was added dropwise during 1 h at 80°C. The mixture was heated further for 6 h and the solvent was then removed under reduced pressure. Chromatographic purification (Merck silica, 230-400 mesh, 5 x 60 cm, elution with cyclohexane (1 L) and then cyclohexane and ethyl acetate, v:v = 5:1) gave **3a** as the main product. Yield 2.42 g (24%).

From **7**: A solution of iodide **7**[20] (0.50 g, 1.0 mmol) and freshly distilled acrylonitrile (0.90 ml, 13.5 mmol) in dry xylene (25 ml) was heated to 90°C under N_2. A solution of tributyltin hydride (0.53 ml, 2.0 mmol) and AIBN (35 mg, 0.21 mmol) in dry xylene (10 ml) was added dropwise within 1 h. The mixture was heated further for 1 h and the solvent was then removed under reduced pressure. The semisolid residue was dissolved in

acetonitrile (25 ml) and filtered through celite. After extraction with pentane (3 x 25 ml) the acetonitrile was evaporated to give crude **3a** as a yellow oil. Flash chromatographic purification (Merck silica, 230-400 mesh, 2 x 40 cm, cyclohexane and ethyl acetate v:v = 5:1) gave pure **3a** as an oil. Yield 100 mg (24%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.72-7.35 (m, 10 H, aryl), 5.00 (dd, 5.0 Hz, 1.7 Hz, H-1), 3.79 (dd, 7.9 Hz, 4.3 Hz, Ha-5), 3.71 (dd, 7.9 Hz, 4.3 Hz, Hb-5), 3.67 (t, 4.3 Hz, H-4), 3.32 (s, OMe), 2.30-1.55 (m, H-2α, H-2β, H-3, Ha-1', Hb-1', Ha-2', Hb-2'), 1.07 (s, CMe_3).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 135.55, 135.52, 133.22, 129.67, 127.15 (aryl), 119.15 (CN), 105.03 (C-1), 83.21 (C-4), 65.38 (C-5), 54.59 (OMe), 38.85 (C-3), 37.79 (C-2), 29.70 (C-2'), 26.77 (Me), 19.12 ($\underline{C}Me_3$), 15.83 (C-1').- MS E.I.: m/z (%) = 392 (M - OMe, 6%)$^+$, 366 (22), 336 (11), 335 (27), 334 (100), 213 (40), 199 (48), 197 (10), 183 (10), 135 (19), 124 (36).

Methyl 5-O-tert-butyldiphenylsilyl-3-(2-methoxycarbonylethyl)-2,3-dideoxy-α-D-erythro-pentofuranoside (**3b**)

From **2a**: A solution of xanthate **2a** (1.46 g, 3.07 mmol) and freshly distilled methyl acrylate (2.6 ml, 30.0 mmol) in dry xylene (20 ml) was heated to 90°C under N_2. A solution of tributyltin hydride (1.2 ml, 5.2 mmol) and AIBN (50 mg, 0.31 mmol) in dry xylene (10 ml) was added dropwise during 1 h at 90°C. The mixture was heated further for 1 h and the solvent was then removed under reduced pressure. The crude product was purified by flash chromatography (Merck silica, 230-400 mesh, 3 x 50 cm, hexane and ethyl acetate v:v = 5:1) to give pure **3b**. Yield 302 mg (23%).

From **2b**: A solution of **2b** (12.5 g, 24 mmol) and freshly distilled methyl acrylate (24 ml, 267 mmol) in dry toluene (500 ml) was heated to 80°C under N_2. A solution of tributyltin hydride (10.6 ml, 40 mmol) and AIBN (1.3 g, 8 mmol) in dry toluene (60 ml) was added dropwise during 1 h at 80°C. The mixture was heated further for 6 h at 80°C and the solvent was then removed under reduced pressure. The crude product was purified by flash chromatography (Merck silica, 230-400 mesh, 5 x 60 cm, elution with hexane (1.5 L) and then with hexane and ethyl acetate, v:v = 15:1) to give pure **3b** as the main product as an oil. Yield 2.57 g (25%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.71-7.25 (m, 10 H, aryl), 5.00 (dd, 5.3 Hz, 2.0 Hz, H-1), 3.80 (dt, 8.9 Hz, 4.6 Hz, H-4), 3.72-3.66 (m, Ha-5, Hb-5), 3.64 (s, OMe), 3.34 (s, OMe), 2.31-2.17 (m, H-2β, Ha-2', Hb-2'), 2.10-1.95 (m, H-3), 1.91-1.63 (m, Ha-1', Hb-1'), 1.57 (ddd, 13.0 Hz, 5.2 Hz, 2.0 Hz, H-2α), 1.06 (s, 9H, CMe_3).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 173.45 (C=O), 135.55, 135.52, 133.44, 129.52, 127.53 (aryl), 105.10 (C-1), 83.54 (C-4), 65.32 (C-5), 54.62 (OMe), 51.32 (OMe), 38.96 (C-3), 38.30 (C-2), 32.72 (C-2'), 28.89 (C-1'), 26.71 (CH_3), 19.13 ($\underline{C}Me_3$).- $C_{26}H_{36}O_5Si \cdot 1/2\ H_2O$ Calc. C 67.1 H 8.01 Found C 66.8 H 8.04.

Methyl 5-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(methylthio)thiocarbonyl-β-D-erythro-pentofuranoside (**5**)

NaH (50% dispersion, 0.81 g, 16.8 mmol) was added in several portions to a solution of **4**[20] (4.5 g, 11.7 mmol) and CS_2 (2.2 ml, 36.5 mmol) in dry THF (40 ml) under N_2. After 1 h at room temp. CH_3I (1.4 ml, 22.6 mmol) was added in one portion and the mixture was stirred for 0.5 h. The mixture was quenched by dropwise addition of acetic acid (0.6 ml) and after 10 min diluted with diethyl ether (100 ml) and washed with a saturated solution of $NaHCO_3$ (2 x 25 ml) and a saturated solution of NaCl (2 x 50 ml), dried over anhydrous $MgSO_4$ and evaporated and dried over P_2O_5 to give xanthate **5** as an oil. Yield 4.8 g (81%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.71-7.35 (m, 10 H, aryl), 6.05 (ddd, 7.4 Hz, 3.7 Hz, 2.4 Hz, H-3), 5.17 (dd, 5.4 Hz, 3.4 Hz, H-1), 4.33 (ddd, 6.7 Hz, 5.4 Hz, 2.4 Hz, H-4), 3.81 (dd, 10.6 Hz, 5.4 Hz, Ha-5), 3.72 (dd, 10.6 Hz, 6.7 Hz, Hb-5), 3.32 (s, OMe), 2.54 (s, SMe), 2.44 (ddd, 14.5 Hz, 7.4 Hz, 3.4 Hz, H-2β), 2.25 (ddd, 14.5 Hz, 5.4 Hz, 3.7 Hz, H-2α), 1.06 (s, 9H, $C(CH_3)_3$).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 135.51, 133.18, 129.59, 127.58 (aryl), 105.53 (C-1), 84.34, 83.69 (C-3, C-4), 64.44 (C-5), 55.23 (OMe), 38.77 (C-2), 26.66 (Me), 19.05 ($\underline{C}Me_3$), 18.98 (SMe).

Methyl 5-O-tert-butyldiphenylsilyl-3-(2-cyanoethyl)-2,3-dideoxy-β-D-erythro-pentofuranoside (**6**)

A solution of xanthate **5** (0.48 g, 1.0 mmol) and freshly distilled acrylonitrile (0.33 ml, 5.0 mmol) in dry xylene (20 ml) was heated to 90°C under N_2. A solution of tributyltin hydride (0.30 ml, 1.13 mmol) and AIBN (20 mg, 0.12 mmol) in dry xylene (2 ml) was added dropwise during 1 h at 90°C. The mixture was heated for further 2 h and the solvent was then removed under reduced pressure. The crude product was purified by flash chromatography (Merck silica, 2 x 40 cm, cyclohexane and ethyl acetate v:v = 7:1) to give pure oily **6** as the main product. Yield 82 mg (19%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.70-7.36 (m, 10 H, aryl), 4.94 (d, 4.9 Hz, H-1), 3.80-3.66 (m, H-4, Ha-5, Hb-5), 3.23 (s, OMe), 2.56-1.26 (m, H-2α, H-2β, H-3, Ha-1', Hb-1', Ha-2', Hb-2'), 1.08 (s, 9H, CMe_3).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 135.48, 133.22, 129.67, 127.63 (aryl), 119.10 (CN), 104.55 (C-1), 84.78 (C-4), 66.79 (C-5), 54.28 (OMe), 39.26 (C-3), 38.94 (C-2), 29.41 (C-2'), 26.74 (Me), 19.09 ($\underline{C}Me_3$), 16.02 (C-1').

1-(5-O-tert-butyldiphenylsilyl-3-(2-cyanoethyl)-2,3-dideoxy-β-D-erythro-pentofuranosyl)uracil (**8**) *and*
1-(5-O-tert-butyldiphenylsilyl-3-(2-cyanoethyl)-2,3-dideoxy-α-D-erythro-pentofuranosyl)uracil (**9**)

A solution of nitrile **3a** (1.0 g, 2.4 mmol) and silylated uracil (1.3 g, 4.8 mmol) in dry acetonitrile (20 ml) was cooled to -30°C. Trimethylsilyl trifluoromethanesulfonate (0.87 ml, 4.8 mmol) in dry acetonitrile (4 ml) was added dropwise. After 30 min at -30°C, the temp. was increassed to 20°C. After 2 h analytical silica TLC (methanol and dichloromethane, v:v = 3:97) showed no more starting material. The mixture was diluted with dichloromethane (50 ml) and quenched with a saturated solution of $NaHCO_3$ (2 x 10 ml). After washing with water (2 x 20 ml) the org. phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual syrup was purified by flash chromatography (Merck silica, 230-400 mesh, 3 x 40 cm, chloroform, cyclohexane and isopropanol v:v:v = 46:46:8) to give **8** (400 mg, 33%) as the major product and **9** (180 mg, 15%) as minor product, both as oils. A mixed interfraction of both anomers (150 mg, 12%) was obtained as well. Total yield 730 mg (60%).

8: ^{1}H-NMR ($CDCl_3$): δ (ppm) = 10.02 (broad, NH), 8.01 (d, 8.1 Hz, H-6), 7.72-7.70 (m, 10 H, aryl), 6.11 (d, 5.1 Hz, H-1'), 5.47 (d, 8.1 Hz, H-5), 4.14 (d, 11.0 Hz, Ha-5'), 3.73-3.68 (m, H-4', Hb-5'), 2.41-2.07 (m, H-2'α, H-2'β, H-3', Ha-2'', Hb-2''), 1.62-1.36 (m, Ha-1'', Hb-1''), 1.11 (s, 9H, CMe_3).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 163.54 (C-4), 150.34 (C-2), 139.72 (C-6), 135.45, 135.24, 132.33, 132.02, 130.12, 129.95, 127.85, 127.77 (aryl), 118.43 (CN), 101.78 (C-5), 85.88 (C-4'), 84.91 (C-1'), 62.20 (C-5'), 38.83 (C-3'), 35.55 (C-2'), 27.00 (C-2''), 26.78 (Me), 19.02 (CMe_3), 15.75 (C-1'').

9: ^{1}H-NMR ($CDCl_3$): δ (ppm) = 9.86 (broad, NH), 7.68-7.34 (m, 11 H, aryl, H-6), 5.96 (t, 6.4 Hz, H-1'), 5.73 (d, 8.1 Hz, 5-H), 3.96-3.92 (m, H-4'), 3.83 (dd, 11.3 Hz, 3.3 Hz, Ha-5'), 3.73 (dd, 11.3 Hz, 3.8 Hz, Hb-5'), 2.80 (ddd, 13.1 Hz, 7.0 Hz, 6.4 H, H-2'β), 2.42-2.20 (m, H-3', Ha-2'', Hb-2''), 1.83-1.56 (m, H-2'α, Ha-1'', Hb-1''), 1.08 (s, 9H, CMe_3).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 163.53 (C-4), 150.19 (C-2), 139.21 (C-6), 135.42, 132.76, 129.80, 127.70, 127.66 (aryl), 118.55 (CN), 102.08 (C-5), 87.05 (C-1'), 85.21 (C-4'), 64.35 (C-5'), 39.16 (C-3'), 38.57 (C-2'), 27.83 (C-2''), 26.69 (Me), 19.03 (CMe_3), 15.87 (C-1'').

1-(3-(2-Cyanoethyl)-2,3-dideoxy-β-D-erythro-pentofuranosyl)uracil (**10a**)

Tetrabutylammonium fluoride (1.9 ml, 1 M solution in THF) was added to a solution of **8** (400 mg, 0.79 mmol) in THF (3 ml). The mixture was stirred 1 h at room temp. The solvent was removed under reduced pressure and the residue purified by flash chromatography (Merck silica, 230-400

mesh, 2 x 30 cm, chloroform and methanol v:v = 99:1) to give pure β-nucleoside **10a**. Yield 200 mg (95%), m.p. 132-133°C.- ^{1}H-NMR (DMSO-d_6): δ (ppm) = 11.27 (broad, NH), 8.01 (d, 8.0 Hz, H-6), 5.94 (d, 5.8 Hz, H-1'), 5.58 (d, 8.0 Hz, 5-H), 3.73-3.55 (m, H-4', Ha-5', Hb-5'), 3.35 (s, OH), 2.54 (t, 7.3 Hz, Ha-2'', Hb-2''), 2.47-2.06 (m, H-2'α, H-2'β, H-3'), 1.86-1.77 (m, Ha-1''), 1.60-1.46 (m, Hb-1'').- ^{13}C-NMR (DMSO-d_6): δ (ppm) = 163.20 (C-4), 150.30 (C-2), 140.47 (C-6), 120.49 (CN), 100.82 (C-5), 85.76 (C-4'), 84.31 (C-1'), 60.25 (C-5'), 37.78 (C-3'), 36.06 (C-2'), 26.81 (C-2''), 14.90 (C-1').- MS E.I.: m/z (%) = 265 (M^+, 3), 154 (84), 136 (14), 113 (44), 112 (48), 110 (100), 108 (13).- $C_{12}H_{15}N_3O_4$ Calc. C 54.3 H 5.70 N 15.8 Found C 54.3 H 5.88 N 15.1. Peak matching on M^+: $C_{12}H_{15}N_3O_4$ Calc. 265.1063 Found 265.1061.

1-(5-O-Acetyl-3-(2-cyanoethyl)-2,3-dideoxy-β-D-erythro-pentofuranosyl) uracil (**10b**)

10a (26 mg, 0.1 mmol) was dissolved in dichloromethane (5 ml). Acetic anhydride (0.2 ml, 0.2 mmol), pyridine (0.16 ml, 0.2 mmol) and DMAP (20 mg, 0.2 mmol) were added at 20°C. After 1 h the mixture was washed with a 0°C cold aqueous N-HCl (2 x 2 ml) and water (5 ml). After drying over anhydrous $MgSO_4$ the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (Merck silica, 230-400 mesh, 1 x 25 cm, dichloromethane and methanol, v:v = 99:1) to give pure **10b**. Yield 28 mg (93%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.65 (d, 8.1 Hz, H-6), 6.05 (dd, 6.4 Hz, 2.7 Hz, H-1'), 5.76 (d, 8.1 Hz, H-5), 4.43-4.31 (m, Ha-5', Hb-5'), 3.95 (dt, 7.6 Hz, 4.2 Hz, H-4'), 2.54-2.30 (m, H-2'α, Ha-2'', Hb-2''), 2.29-2.17 (m, H-2'β, H-3'), 2.14 (s, Me), 2.03-1.88 (m, Ha-1''), 1.76-1.61 (m, Hb-1'').

1-(3-(2-Cyanoethyl)-2,3-dideoxy-α-D-erythro-pentofuranosyl)uracil (**11**)

Tetrabutylammonium fluoride (0.82 ml, 1 M in THF) was added to a solution of **9** (180 mg, 0.36 mmol) in THF (2 ml). The mixture was stirred for 1 h at room temp. The solvent was removed under reduced pressure and the residue purified by flash chromatography (Merck silica, 230-400 mesh, chloroform and methanol 99:1) to give pure α-nucleoside **11** as an oil. Yield 70 mg (73%).- ^{1}H-NMR (DMSO-d_6): δ (ppm) = 11.28 (broad, NH), 7.73 (d, 8.0 Hz, H-6), 5.99 (t, 6.6 Hz, H-1'), 5.63 (d, 8.0 Hz, H-5), 3.94 (ddd, 8.0 Hz, 4.5 Hz, 3.2 Hz, H-4'), 3.53 (dd, 11.9 Hz, 3.2 Hz, Ha-5'), 3.41 (dd, 11.9 Hz, 4.5 Hz, Hb-5'), 3.38 (broad, OH), 2.56-2.45 (m, H-2'β, H-3', Ha-2''), 2.30-2.10 (m, Hb-2''), 1.90-1.58 (m, H-2'α, Ha-1', Hb-1').- ^{13}C-NMR (DMSO-d_6): δ (ppm) = 163.35 (C-4), 150.48 (C-2), 140.74 (C-6), 120.45 (CN), 101.61 (C-5), 85.04 (C-1'), 84.81 (C-4'), 61.95 (C-5'), 38.93 (C-3'), 37.08 (C-2'), 26.92 (C-2''), 15.05 (C-1'').- MS E.I.: m/z (%) = 265 (M^+, 2), 154 (80), 136 (12), 113 (34), 112 (33), 110 (100), 108 (13). Peak matching on M^+: $C_{12}H_{15}N_3O_4$ Calc. 265.1063 Found 265.1060.

1-(5-O-tert-Butyldiphenyl-silyl-3-(2-methoxycarbonylethyl)-2,3-dideoxy-β-D-erythro-pentofuranosyl)-N^4-isobutyrylcytosine (**12**) *and*
1-(5-O-tert-Butyldiphenyl-silyl-3-(2-methoxycarbonylethyl)-2,3-dideoxy-α-D-erythro-pentofuranosyl)-N^4-isobutyrylcytosine (**13**)

A solution of **3b** (900 mg, 1.95 mmol) and silylated N^4-isobutyrylcytosine (560 mg, 2.21 mmol) in dry acetonitrile (20 ml) was cooled to -35°C. Trimethylsilyl trifluoromethanesulfonate (0.53 ml, 2.92 mmol) was added dropwise. After 1.5 h at -35°C analytical silica TLC (dichloromethane and methanol, v:v = 95:5) showed no more **3b**. The mixture was diluted with dichloromethane (50 ml) and quenched with a saturated solution of $NaHCO_3$ (25 ml). After washing with water (2 x 25 ml) the org. phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (Merck silica, 230-400 mesh, 2 x 40 cm, dichloromethane and methanol, v:v = 97:3) to give the β-anomer **12** (220 mg, 19%) as the most polar isomer and the α-anomer **13** (400 mg, 34%) as the less polar isomer. Besides, a mixed interfraction (70 mg, 6%) was obtained. Total yield of **12** and **13**: 690 mg (59%).

12: Hygroscopic foam.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.81 (broad, NH), 8.49 (d, 7.4 Hz, H-6), 7.71-7.37 (m, 10 H, aryl), 7.26 (d, 7.4 Hz, H-5), 6.10 (d, 5.9 Hz, H-1'), 4.15 (d, 10.1 Hz, Ha-5'), 3.95-3.69 (m, H-4', Hb-5'), 3.66 (s, OMe), 2.67 (septet, 6.9 Hz, C<u>H</u>Me$_2$), 2.39-2.07 (m, H-2'α, H-2'β, H-3', Ha-2'', Hb-2''), 1.74-1.63 (m, Ha-1''), 1.51-1.37 (m, Hb-1''), 1.22 (d, 6.9 Hz, Me), 1.20 (d, 6.9 Hz, Me), 1.12 (s, 9H, CMe$_3$).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 176.70 (C=O), 172.82 (C=O), 162.20 (C-4), 155.07 (C-2), 144.55 (C-6), 135.50, 135.34, 132.46, 132.29, 130.01, 129.93, 127.83 (aryl), 95.76 (C-5), 87.08 (C-1'), 86.65 (C-4'), 62.26 (C-5'), 51.51 (OCH_3), 39.53 (C-3'), 36.49 (C-2'), 35.13 (C-2''), 32.27 (CHMe$_2$), 26.80 (CH_3), 25.94 (C-1''), 19.07 (<u>C</u>Me$_3$), 18.98 (Me), 18.89 (Me).- $C_{33}H_{43}N_3SiO_6$ Calc. C 65.4 H 7.15 N 6.9 Found C 65.4 H 7.31 N 6.6.- MS E.I.: m/z (%) = 549 (M^+ - C_4H_8, 28), 548 (73), 425 (13), 368 (19), 367 (100), 335 (14), 268 (41), 225 (15), 213 (29), 199 (86).

13: Hygroscopic foam.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.55 (broad, NH), 7.89 (d, 7.5 Hz, H-6), 7.69-7.36 (m, 11 H, aryl), 5.96 (t, 6.1 Hz, H-1'), 3.96 (ddd, 7.7 Hz, 4.5 Hz, 3.3 Hz, H-4'), 3.86 (dd, 11.4 Hz, 3.3 Hz, Ha-5'), 3.73 (dd, 11.4 Hz, 4.5 Hz, Hb-5'), 3.65 (s, OCH_3), 2.98 (ddd, 13.5 Hz, 7.5 Hz, 6.1 Hz, H-2'β), 2.63 (septet, 6.9 Hz, C<u>H</u>Me$_2$), 2.33-2.23 (m, H-3', Ha-2'', Hb-2''), 1.82-1.68 (m, Ha-1''), 1.62-1.41 (m, H-2'α, Hb-1''), 1.23 (d, 6.9 Hz, Me), 1.07 (s, 9H, CMe$_3$).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 176.76 (amide), 172.95 (ester), 162.17 (C-4), 155.03 (C-2), 143.08 (C-6), 135.51, 133.07, 132.99, 129.75, 127.68 (aryl), 95.84 (C-5), 88.31 (C-1'), 86.40 (C-4'), 64.55 (C-5') 51.55 (OMe), 39.96 (C-3'), 39.24 (C-2'), 36.67 (C-2''), 32.39 (CHMe$_2$), 27.48 (C-1''), 26.72 (Me), 19.12 (CMe$_3$), 18.98 (Me), 18.91 (Me).- $C_{33}H_{43}N_3SiO_6$ · 1/4 H_2O Calc. C 64.9 H 7.18 N 6.9 Found C 65.3 H 7.32 N 6.4.- MS E.I.: m/z (%) = 549 (M^+ - C_4H_8, 13), 548 (34), 368 (29), 367 (100), 335 (12), 268 (20), 253 (15), 225 (18), 213 (35), 199 (87).

1-(3-(2-Methoxycarbonylethyl)-2,3-dideoxy-β-D-erythro-pentofuranosyl)-N^4-isobutyrylcytosine (**14**)

Tetrabutylammonium fluoride (0.35 ml, 1 M in THF) was added to a 0°C cold solution of **12** (210 mg, 0.35 mmol) in THF (3 ml). After 2 h at 0°C the solvent was removed under reduced pressure and the residue purified by flash chromatography (Merck silica, 230-400 mesh, 1 x 20 cm, dichloromethane and methanol, v:v = 95:5) to give pure **14** as a hygroscopic foam. Yield 94 mg (77%), m.p. 67-69°C.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.57 (d, 7.5 Hz, H-6), 8.49 (broad, NH), 7.42 (d, 7.5 Hz, H-5), 6.07 (d, 6.0 Hz, H-1'), 4.10 (d, 11.0 Hz, Ha-5'), 3.87-3.82 (m, H-4', Hb-5'), 3.67 (s, OCH_3), 3.37 (broad, OH), 2.94 (septet, 6.9 Hz, C<u>H</u>Me$_2$), 2.48-2.13 (m, H-2'α, H-2'β, H-3', Ha-2'', Hb-2''), 1.61-15.0 (m, Ha-1''), 1.46-1.31 (m, Hb-1''), 1.22 (d, 6H, 6.9 Hz, 2 x CH_3).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 176.80 (amide), 173.51 (ester), 162.07 (C-4), 155.31 (C-2), 145.29 (C-6), 95.67 (C-5), 87.28 (C-4'), 87.13 (C-1'), 61.11 (C-5'), 51.71 (OMe), 39.63 (C-3'), 36.67 (C-2'), 34.95 (C-2''), 32.15 (<u>C</u>HMe$_2$), 26.03 (C-1''), 18.95 (Me).- $C_{17}H_{25}N_3O_5$ · 1 1/2 H_2O Calc. C 54.0 H 7.46 N 11.1 Found C 54.4 H 7.15 N 10.5.

1-(3-(2-Methoxycarbonylethyl)-2,3-dideoxy-α-D-erythro-pentofuranosyl)-N^4-isobutyrylcytosine (**15**)

Tetrabutylammonium fluoride (0.41 ml, 1 M in THF) was added to a 0°C cold solution of **13** (250 mg, 0.41 mmol) in THF (4 ml). After 1 h at 0°C the solvent was removed under reduced pressure and the residue purified by flash chromatography (Merck silica, 230-400 mesh, 1 x 20 cm, dichloromethane and methanol v:v = 95:5) to give pure nucleoside **15** as a hygroscopic foam. Yield 135 mg (93%).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.59 (broad, NH), 7.96 (d, 7.5 Hz, H-6), 7.48 (d, 7.5 Hz, H-5), 6.09 (t, 6.3 Hz, H-1'), 4.04 (ddd, 7.9 Hz, 4.7 Hz, 2.5 Hz, H-4'), 3.89 (dd, 12.2 Hz, 2.5 Hz, Ha-5'), 3.71-3.63 (m, Hb-5', OCH_3), 2.98 (ddd, 12.9 Hz, 7.5 Hz, 6.3 Hz, H-2'β), 2.65 (septet, 6.9 Hz, C<u>H</u>Me$_2$), 2.38-2.26 (m, H-3', Ha-2'', Hb-2''), 1.95-1.81 (m, Ha-1''), 1.66-1.51 (m, H-2'α, Hb-1''), 1.23 (d, 6H, 6.9 Hz, 2

x CH_3).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 176.91 (amide), 173.13 (ester), 162.27 (C-4), 155.15 (C-2), 143.15 (C-6), 96.18 (C-5), 88.08 (C-1'), 86.36 (C-4'), 63.00 (C-5'), 51.66 (OCH_3), 40.06 (C-3'), 38.83 (C-2'), 36.63 (C-2''), 32.30 ($CHMe_2$), 27.06 (C-1''), 18.93 (Me).- $C_{17}H_{25}N_3O_5 \cdot 1/2\ H_2O$ Calc. C 56.6 H 7.27 N 11.7 Found C 56.2 H 7.48 N 11.1.

1-(3-(2-Methylaminocarbonylethyl)-2,3-dideoxy-β-D-erythro-pentofuranosyl)cytosine (16)

14 (65 mg, 0.19 mmol) was dissolved in a solution of 33% methylamine in absol. ethanol (20 ml). After 24 h at 20°C the solvent was removed under reduced pressure and the product was purified by flash chromatography (Merck silica, 230-400 mesh, 1 x 20 cm, methanol) to give pure **16** as an oil which crystallized on standing in the refrigerator. Yield 47 mg (86%); m.p. 80-82°C. Hygroscopic.- ^{1}H-NMR (CD_3OD): δ (ppm) = 8.24 (d, 7.5 Hz, H-6), 6.05 (d, 5.6 Hz, H-1'), 5.90 (d, 7.5 Hz, H-5), 3.95 (dd, 13.3 Hz, 3.4 Hz, Ha-5'), 3.80-3.73 (m, H-4', Hb-5'), 2.73 (s, $NHCH_3$), 2.31-2.14 (m, H-2'α, H-2'β, H-3', Ha-2'', Hb-2''), 1.97-1.85 (m, Ha-1''), 1.63-1.33 (m, Hb-1'').- ^{13}C-NMR (CD_3OD): δ (ppm) = 175.94 (amide), 167.71 (C-4), 158.28 (C-2), 142.76 (C-6), 95.16 (C-5), 88.32 (C-4'), 87.45 (C-1'), 62.06 (C-5'), 40.53 (C-3'), 37.41 (C-2'), 35.25 (C-2''), 28.62 (CH_3), 26.32 (C-1'').- $C_{13}H_{20}N_4O_4 \cdot 1/2\ H_2O$ Calc. C 51.1 H 6.93 N 18.3 Found C 51.2 H 7.18 N 17.7.

1-(3-(2-Methylaminocarbonylethyl)-2',3'-dideoxy-α-D-erythro-pentofuranosyl)cytosine (17)

15 (110 mg, 0.31 mmol) was dissolved in a solution of 33% methylamine in absol. ethanol (20 ml). After 24 h at 20°C the solvent was removed under reduced pressure and the product was purified by flash chromatography (Merck silica, 230-400 mesh, 1 x 20 cm, methanol) to give pure **17** as an oil which crystallized on standing in the refrigerator. Yield 93 mg (100%); m.p. 58-60°C. Hygroscopic.- ^{1}H-NMR (CD_3OD): δ (ppm) = 7.79 (d, 7.5 Hz, H-6), 6.06 (dd, 7.0 Hz, 6.1 Hz, H-1'), 5.96 (d, 7.5 Hz, H-5), 4.03 (ddd, 8.0 Hz, 4.8 Hz, 2.8 Hz, H-4'), 3.79 (dd, 12.2 Hz, 2.8 Hz, Ha-5'), 3.61 (dd, 12.2 Hz, 4.8 Hz, Hb-5'), 2.81-2.70 (m, H-2'β, CH_3), 2.39-2.15 (m, H-3', Ha-2'', Hb-2''), 1.97-1.83 (m, Ha-1''), 1.73-1.55 (m, H-2'α, Hb-1'').- ^{13}C-NMR (CD_3OD): δ (ppm) = 175.89 (amide), 167.71 (C-4), 158.31 (C-2), 141.93 (C-6), 95.95 (C-5), 88.57 (C-1'), 87.50 (C-4'), 63.80 (C-5'), 40.61, 40.50 (C-2', C-3'), 35.45 (C-2''), 29.23 (CH_3), 26.34 (C-1'').- $C_{13}H_{20}N_4O_4 \cdot 1/2\ H_2O$ Calc. C 51.1 H 6.93 N 18.3 Found C 51.2 H 7.38 N 18.0.

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