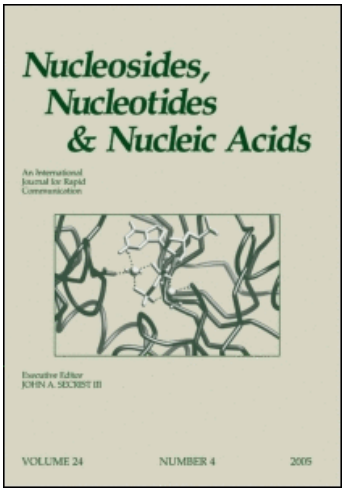


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of Ansa[1]-Cytidines

Konrad Krolikiewicz[a]; Martina Schäfer[a]; Helmut Vorbrüggen[a]
[a] Medicinal Chemistry, The former Schering AG, now Bayer Schering Pharma AG, Berlin, Germany

To cite this Article Krolikiewicz, Konrad , Schäfer, Martina and Vorbrüggen, Helmut(2009) 'Synthesis of Ansa[1]-Cytidines', Nucleosides, Nucleotides and Nucleic Acids, 28: 5, 695 — 712
To link to this Article: DOI: 10.1080/15257770903109896
URL: http://dx.doi.org/10.1080/15257770903109896

Nucleosides, Nucleotides and Nucleic Acids, 28:695–712, 2009

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770903109896

Taylor & Francis
Taylor & Francis Group

SYNTHESIS OF ANSA[1]-CYTIDINES

Konrad Krolikiewicz, Martina Schäfer, and Helmut Vorbrüggen

Medicinal Chemistry, The former Schering AG, now Bayer Schering Pharma AG, Berlin, Germany

□ *The synthesis of new ansa[1]-N[4]5-ethylene cytidines such as 3-β-D-ribofuranosyl-3,5,6,7-tetrahydro-2H-pyrrolo[2,3-d]pyrimidin-2-one is described and the problems connected with the ring closure to the desired tetrahydro-2H-pyrrolo[2,3-d]pyrimidine base discussed. The lack of biological activities of the new ansa[1]– cytidines is furthermore commented on.*

Keywords Synthesis of bicyclic ansa[1]-cytidines; stereochemistry; cytidine-deaminases

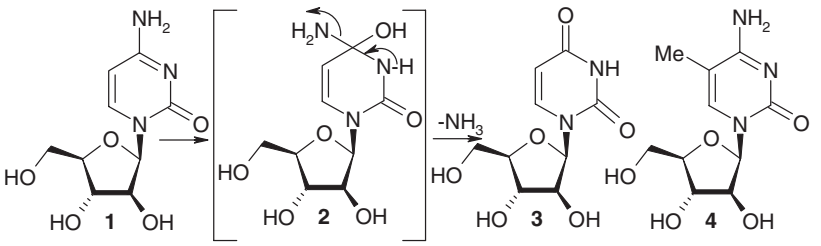
INTRODUCTION

This work on the synthesis of the new ansa[1]-ara-cytidine **23** was patented in 1995[2] and first presented at the 4th Swedish-German Nucleoside Meeting, Reisensburg Castle, Germany, November 23–26 (1996).[3]

Ara-cytidine **1** is an important cytostatic drug for the therapy of acute myeloid leukemia.[4] But its therapeutic application is hampered by its rather rapid enzymatic deamination in vivo by ubiquitous cytidine deaminases, which react via addition of the deaminases to the 6-position of **1** to give via **2** the biologically inactive ara-uridine **3**.[5] Consequently, substituents in 5-position such as in 5-methyl-ara cytidine **4** decrease the rate of deamination by monkey plasma and mouse kidney cytidine deaminase

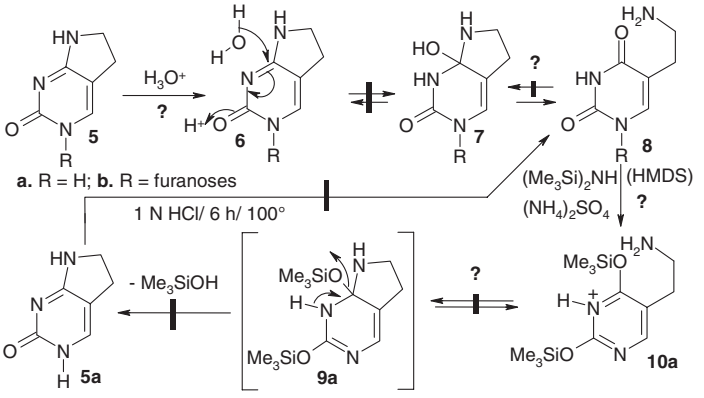
Received 20 May 2009; accepted 10 June 2009.
Dedicated to Professor Morris Robins on the occasion of his 70th birthday.
The authors are indebted to Professor M. Schneider and Drs. M. Schirner and H. Wiesinger for the biological data as well as to Dr. G. Michl for the spectroscopic data. The authors thank furthermore Professor K.A. Watanabe (formerly Sloan-Kettering-Institute, New York, USA) for a gift of 2-fluoro sugar **31** and in particular Professor J. Mulzer and Dr. M. Czibowski (University of Vienna, Austria) for the preparation of 2,2-difluoro sugar **35**.
Present address for H.V.: Institut für Chemie und Biochemie, Freie Universität, Berlin, Germany.
Address correspondence to Helmut Vorbruggen, Institut für Chemie und Biochemie, Freie Universität, Takustr.314195, Berlin, Germany. E-mail: helvor@chemie.fu-berlin.de

from a relative value (cytidine = 1) of ara-C **1** = 0.7 to a value for 5-methyl-ara-cytidine 4 = 0.10[6] (Scheme 1).



SCHEME 1 Deamination of ara-cytidine.

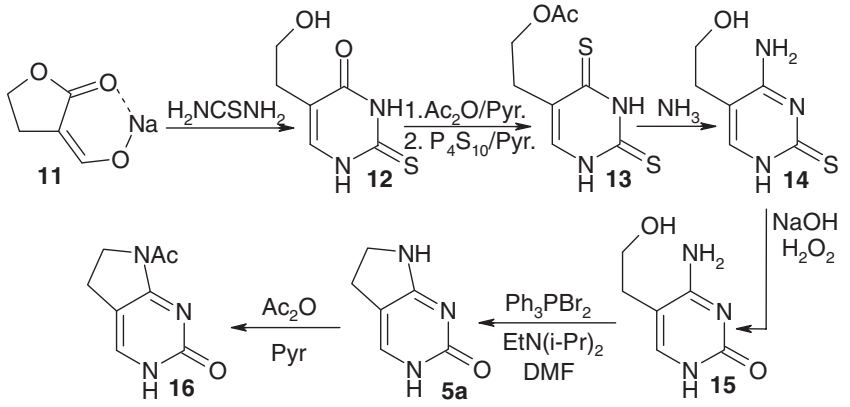
We thus wondered, whether a five membered ansa[1]-ring connecting the 5-position with the 4-amino group such as in ansa[1]-cytosine **5a** or in ansa[1]-ara-cytidine **23**, which induces a minimal steric distortion of the cytosine-ring, might not prevent all degradations by cytidine deaminases as well as by acids. In contrast to cytosine or cytidine the acid catalyzed addition of the elements of water to ansa[1]-cytosine **5a** or ansa[1]-cytidines **5b** would lead to a rather strained, high energy bicyclic intermediates, **7**, whose subsequent ring opening would afford **8**. We thus assumed that the known 5-aminoethyl-uracil **8a**[7] would vice versa not be cyclized by acid catalyzed silylation-amination[8] via **10** and **9** into ansa[1]-cytosine **5a**, because the 5-aminoethyl group cannot attack the 4-position of the aromatic silylated uracil **10a** from above (or below) the aromatic plane to the strained intermediate **9a**. The intermediate **9a** would supposedly lose trimethylsilanol as the leaving group to form the desired ansa[1]-cytosine **5a**. Most importantly, ansa[1]-cytosine **5a**, prepared by a subsequently discussed different route, remained unchanged on 6 hours heating with 1 N HCl to 100° and could thus not be hydrolyzed under mild acidic reaction conditions to 5-aminoethyl-uracil **8a**! (Scheme 2).



SCHEME 2 Potential mechanisms of deaminations.

SYNTHESIS OF ANSA[1]-CYTOSINE

It was thus obvious that only cyclization of a cytosine with a leaving group connected to a 5-ethyl group would afford ansa[1]-cytosine **5a**. A suitable starting material for such a cyclization is the known 5-hydroxyethyl-cytosine **15**,[9,10] which we prepared, however, by a slightly modified route: Condensation of the sodium salt of 2-formyl-butyrolactone **11** with thiourea afforded 5-hydroxyethyl-2-thiouracil **12**, which was O-acetylated and subsequently transformed by heating with P_4S_{10} in pyridine into 5-acetoxyethyl-2,4-dithio-uracil **13**. Heating of **13** with ammonia under pressure afforded 5-hydroxyethyl-2-thio-cytosine **14**, which gave on desulfurization with alkaline H_2O_2 5-hydroxyethyl-cytosine **15** albeit in only moderate yield. Yet heating of **14** with chloroacetic acid furnished **15** likewise in only moderate yield. Cyclization[11] of **15** with in situ generated $Ph_3PBr_2/EtN(i\text{-}Pr)_2$ in DMF afforded the desired ansa[1]-cytosine **5a** in 77% yield, part of which was N-acetylated to **16** (Scheme 3).



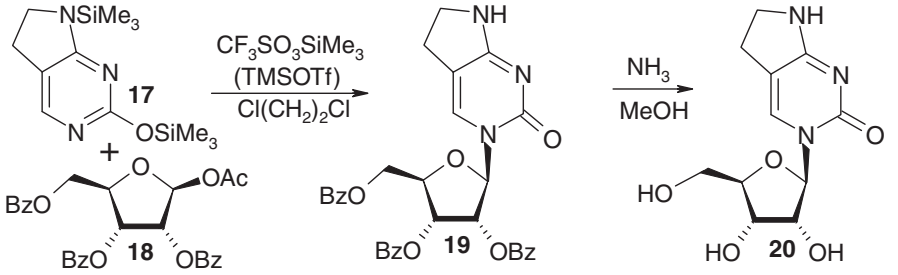
SCHEME 3 Synthesis of ansa[1]-cytosine.

An alternative approach to ansa[1]-cytosine **5a** starting with 3-formylation of N-Boc-butyrolactam and subsequent ring-closure with thiourea was abandoned after the biological investigation of ansa[1]-ara-cytidine **23**, of ansa[1]-ara-cytidine-hydrochloride **24** and other ansa[1]-cytidines demonstrated that none of these ansa[1]-cytidines showed any cytostatic or cytotoxic activity.

SYNTHESIS OF ANSA-CYTIDINES

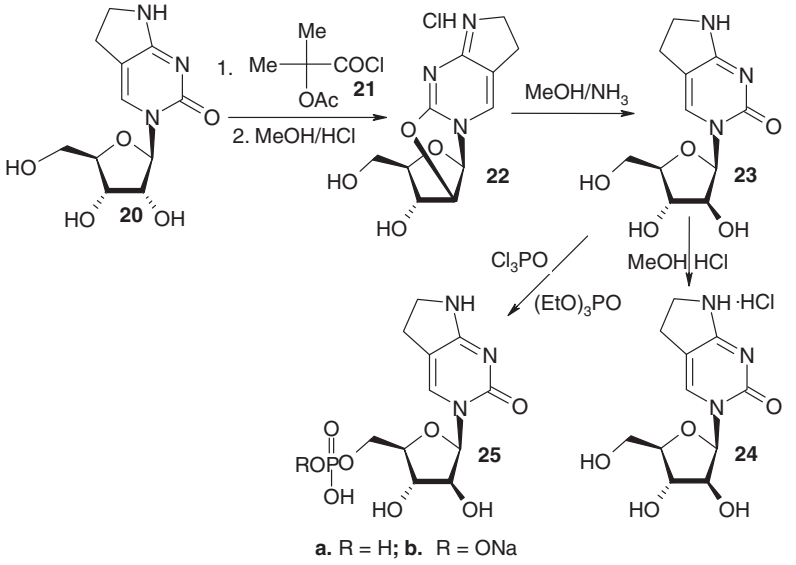
Silylation of ansa[1]-cytosine **5a** with hexamethyldisilazane (HMDS)/pyridine to **17** followed by reaction with the standard sugar 1-O-acetyl-2,3,5-tri-O-benzoyl-ß-D-ribofuranose **18** in 1,2-dichloroethane in the presence of trimethylsilyl triflate (TMSOTf)[12] afforded the protected crystalline ansa[1]-

cytidine **19** in 80% yield, which gave on saponification with methanolic ammonia the free crystalline ansa[1]-cytidine **20** in 89% yield (Scheme 4).



SCHEME 4 Synthesis of ansa[1]-uridine **20.**

Reaction of free ansa[1]-cytidine **20** with 2-acetoxy-isobutyryl chloride **21**[13] in acetonitrile provided in 79% yield the crystalline hydrochloride of the corresponding 2,2′-anhydro-nucleoside **22**. Subsequent conversion of the crude hydrochloride **22** with methanolic ammonia gave crystalline ansa[1]-ara-cytidine **23** in 64% yield, whose structural assignment was confirmed by x-ray structure analysis. (Figure 1) Treatment of **23** with methanolic HCl afforded crystalline ansa[1]-ara cytidine hydrochloride **24**. Phosphorylation of **23** with $POCl_3$ in triethylphosphate[14] provided the 5′-O-phosphate **25a** in 92% yield, which gave with NaOH the corresponding sodium salt **25b** (Scheme 5).



SCHEME 5 Syntheses of ansa[1]-ara-cytidines.

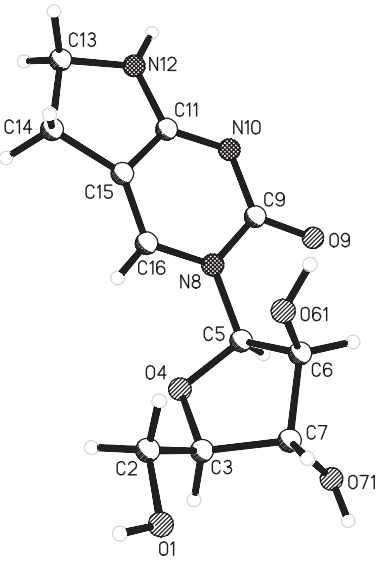
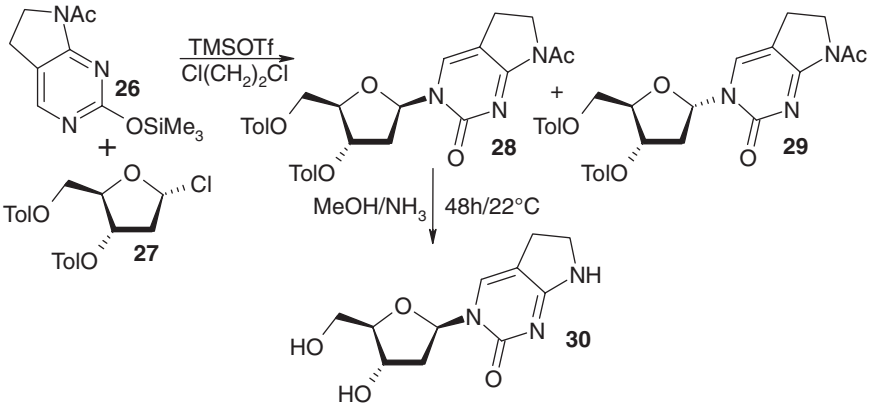


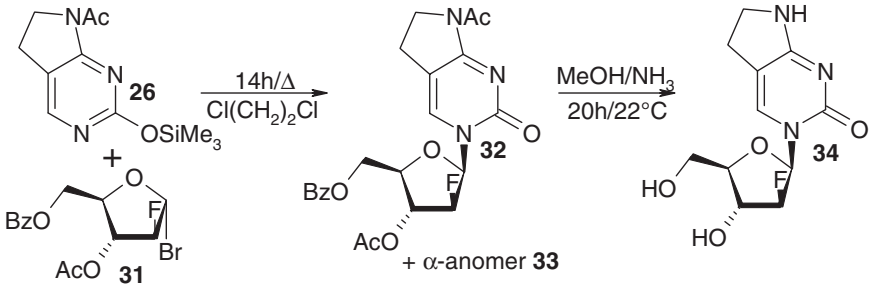
FIGURE 1 X-ray structure of ansa[1]-ara-cytidine **23**.

Reaction of silylated 7-N-acetyl-ansa[1]-cytosine **26** with crystalline 1-α-chloro-2-deoxy-3,5-di-O-toluoyl-ribofuranose **27**[15] in the presence of TMSOTf in 1,2-dichloroethane afforded 28% of the desired protected crystalline ß-anomer **28** as well as the protected crystalline α-anomer **29**. Saponification of the protected ß-anomer **28** gave 63% of the crystalline free ß-anomer **30** (Scheme 6).

Reaction of silylated 7-N-acetyl-ansa[1]-cytosine **26** with 3-O-acetyl-5-O-benzoyl-2-ß-fluoro-α-D-furanosyl chloride **31**[16] afforded ca. 36% of the corresponding protected ß-anomer **32** as well as some α-anomer **33**. The



SCHEME 6 Synthesis of 2′-deoxy-ansa[1]-cytidine **30**.

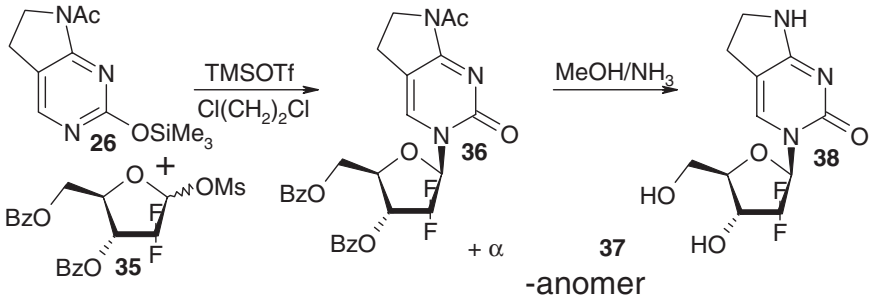


SCHEME 7 Synthesis of 2′-deoxy-2′-*β*-fluoro-ansa[1]-cytidine **34**.

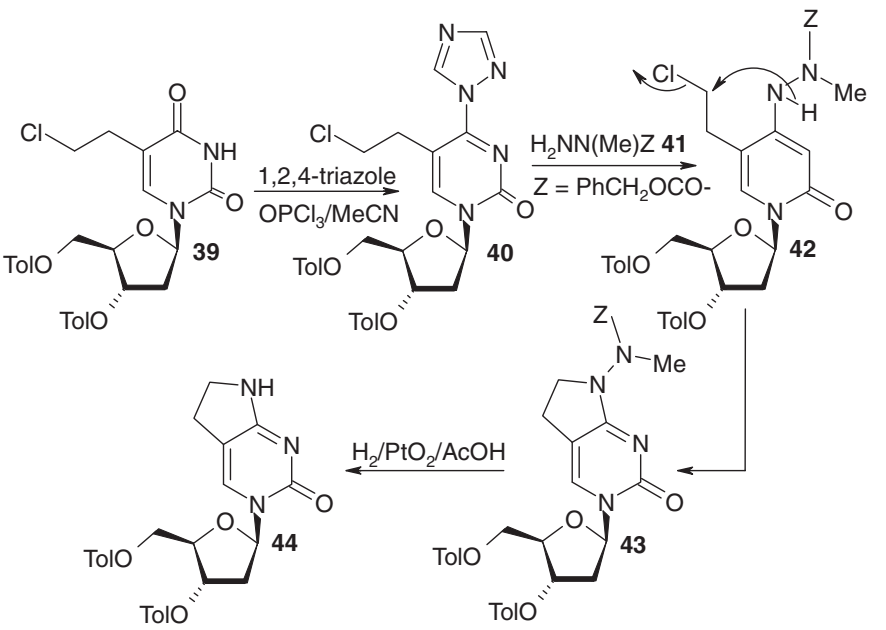
ß-anomer **32** gave on saponification the free crystalline ß-anomer **34** in 72% yield (Scheme 7).

Finally, treatment of silylated 7-N-acetyl-ansa[1]-cytosine **26** with the mixture of anomeric protected 1-O-mesyl-2-deoxy-2,2-difluoro-D-ribofuranose-3,5-di-O-benzoates **35**[17] in the presence of TMSOTf in boiling 1,2-dichloroethane gave rise to 20% of the *α*-anomer **37** as well as to 21% of the desired crystalline ß-anomer **36**, which furnished on saponification the free crystalline ß-anomer of 2′-deoxy-2′,2′-difluoro-ansa[1]-cytidine **38** in 63% yield (Scheme 8).

Starting from 5-(2-chloroethyl)-3′,5′-di(O-p-toluoyl)-2′-deoxyuridine[18] **39**, D.M.Brown et al.[19] described in 1999 an alternative synthesis of protected 2′-deoxy-ansa[1]-cytidine. Reaction of **39** with 1,2,4-triazole/$OPCl_3$ to **40**, followed by treatment with 1-N-methyl-1-N-carbo-benzyloxy-hydrazine **41** gave via **42** the protected N-substituted ansa[1]-cytidine **43**, which afforded on hydrogenation 2′-deoxy-3′,5′-di(O-p-toluoyl)-ansa[1]-cytidine **44** (Scheme 9).



SCHEME 8 Synthesis of 2′-deoxy-2′,2′-difluoro-ansa[1]-cytidine **38**.



SCHEME 9 Alternative synthesis of protected 2′-deoxy-ansa[1]-cytidine **44**.

BIOLOGICAL SCREENING

In the biological studies, in particular compounds **20** (ZK 182306), **22** (ZK 182308), and **24** (ZK 182307) were investigated in detail:

1. In vitro studies: All tested ansa-cytidines were inactive in cell lines of human prostate carcinoma as well as in cell lines of human large cell lung cancer.
2. In vivo studies: Likewise all tested ansa-cytidines were inactive in L 1210 mouse leukemia. The mean survival time (MST) of ca. 11 days was *not* enhancedby any of the tested compounds. In comparison, fludara (2-fluoro-ara-C-5′-O-phosphate) in doses of 5·250 mg/Kg as well as ara-C enhanced MST for up to 22–23 days.

Final Remarks

Due to the lack of any biological activity, the syntheses of the different ansa[1]−cytidines were not optimized. The described yields can thus certainly be improved. Unfortunately, we do not know as yet, why the investigated ansa[1]-cytidines are biologically inactive. My mandatory retirement from the former Schering AG (now Bayer Schering Pharma AG) in summer

1995 resulted in the termination of all further chemical and biological investigations.

EXPERIMENTAL

Melting points were determined using a Kofler block instrument and are uncorrected. TLC was performed on Silicagel plates (Merck, layer thickness 0.2 mm). SiO_2 with particle size = 0.04–0.063 mm was used for column chromatography. ^{1}H-NMR-spectra were recorded on a Bruker AC 250 FT NMR-spectrometer at 250 MHz with TMS as an internal standard. Although satisfactory combustion analytical data were obtained for all of the compounds described, some of these combustion data are unfortunately not anymore available.

3,5,6,7-Tetrahydro-2H-pyrrolo[2,3d]pyrimidin-2-one 5a

To a suspension of 5-(2-hydroxyethyl)cytosine[9] **15** (7.55 g = 50 mmol) and triphenylphosphine (15.73 g = 60 mmol) in dry N,N-dimethylformamide (DMF) (75 mL) a solution of 1,2-dibromotetrachloroethane (17.91 g = 55mol) was added at ca 5°C with stirring within 1 hour and the reaction mixture stirred for 18 hours at 21°C. Ethyldisopropylamine (25.85 g = 200 mmol) was added and the reaction mixture stirred for 2 hours at 82–84°C oil bath temperature, whereupon initially everything passed into solution followed after ca. 45 minutes by precipitation of crystals. After cooling to 65°C the crystals were filtered and washed with DMF (35 mL), whereupon crude **5a** (2.51 g) was obtained. The filtrate was evaporated in vacuo and the residue stirred with ethyldiisopropylamine (20 mL) in CH_2Cl_2 (500 mL). The precipitate was filtered and washed with ethyldiisopropylamine (10 ml) in CH_2Cl_2 (10 mL), whereupon a further crop of crude **5a** (5.03 g) was obtained. The combined batches of crude **5a** were suspended in H_2O (150 mL) and a saturated solution of aqueous $NaHCO_3$ added drop wise with stirring until a p_H = 8–9 was reached. After 1 hour stirring the aqueous solution was evaporated in vacuo and the residue recrystallized from H_2O (50 mL) with addition of charcoal to give after filtration pure **5a**, (4.8 g), m.p 310°C (dec.), which starts subliming at 260°C. The mother liquor was evaporated (2 g) and silylated with HMDS/TCS and the residue submitted to short path vacuum distillation. The distillate (1.28 g) was recrystallized from H_2O (20 mL) with charcoal (0.3 g) to give after filtration an additional amount of **5a** (0.48 g). Combined yield of **5a** = 5.28 g (77%). **^{1}H-NMR (DMSO-D_6)** δ: 2.68–2.73 (tr, CH_2—C), 3.56–3.63 (tr, CH_2—N), 7.18 (s, H—C=C)

Analysis calcd.for $C_6H_7N_3O$ (137.15): C52.54, H5.15, N30.64 Found: C52.38, H4.97, N30.99.

7-Acetyl-3,5,6,7-tetrahydro-2H-pyrrolo[2,3d]pyrimidin-2-one 16

To a suspension of 3,5,6,7-tetrahydro-2H-pyrrolo[2,3d]pyrimidin-2-one **5a** (3.7 g, 30 mmol) in abs. pyridine (50 mL) acetic anhydride (8 ml) was added with stirring, whereupon the reaction mixture warmed up to 28°C. After 1 hour stirring the starting material had dissolved and stirring was continued for further 18 hours. The solution was evaporated *in vacuo* and evapo-ration was repeated three times after addition of 30 ml portions of abs. xylene and the residue dried in vacuo. Recrystallization from methanol (50 mL) and H_2O (2 mL) gave a first crop (1.58 g) m.p. 274–279°C of the N-acetyl compound **16**. Concentration of the mother liquor to 25 mL afforded a second crop of **16** (0.68 g). The mother liquor was evaporated and the residue stirred with pyridine (25 mL) and acetic anhydride (5 mL) for 20 hours. After repeated evaporation with xylene a further amount (2.1 g) of nearly pure **16** was isolated m.p. = 274–279°C. Combined yield of **16** = 4.36 g (81.1%).

^{1}H-NMR (DMSO-D_6) δ: 2–56 (s, CH_3—CO), 2.72–2.78 (m, CH_2—C=C), 3.88–3.92 (m, CH_2N), 7.56 (s, H—C=C), 11.05 (br, HN) Analysis calcd.for $C_6H_7N_3O$ (137.15) Analysis calcd. for $C_8H_9N_3O_2$ (179.18): C53.62, H5.06, N23.45; Found: C53.19, H5.21, N23.15.

3-(2′,3′,5′-Tri-O-benzoyl-ß-D-ribofuranosyl)-3,5,6,7-tetrahydro-2H-pyrrolo[2.3d]-pyrimidin-2-one 19

3,5,6,7,-Tetrahydro-2H-pyrrolo[2,3d]pyrimidin-2-on **5a** (4.11 g = 30 mmol) was heated for 1 hour with hexamethyldisilazane (HMDS) (30 ml) in abs. pyridine (30 ml), whereupon some substance had not dissolved as yet. Thus TCS (1 ml) was added and boiling continued for further 2.5 hours. The excess of HMDS and pyridine was evaporated *in vacuo* and the residue dried at 0.1 mm vacuum, whereupon crystalline bis-trimethylsilyl compound **17** was obtained. The silyl compound **17** and 1-O-acetyl-2,3,5-tri-O-benzoyl-ß-D-ribofuranose **18** (15.14 g = 30 mmol) were dissolved in abs. 1,2-dichloroethane (150 mL), a solution of trimethylsilyl triflate (TMSOTf) (6.6 mL = 36 mmol) in abs. 1,2-dichloroethane (30 mL) added within 0,5 hours with stirring at 22°C and the reaction mixture kept for 16 hours at 22°C. After dilution with CH_2Cl_2 (150 mL) the reaction mixture was shaken with ice-cold sat. $NaHCO_3$-solution (250 mL), the layers separated and the aqueous phase re-extracted with two portions of CH_2Cl_2 (75 mL). The combined organic phase was dried (Na_2SO_4) and evaporated. The residue (18.64 g) was chromatographed in EtOAc on a column of silicagel (150 g). Elution with EtOAc (1.5 L) gave only traces of side products. Subsequent elution with EtOAc-ethanol (9:1) (500 mL) afforded yellowish **19** (0.31 g). Continued elution with EtOAc-ethanol (9:1) (500 mL) gave rise to pure ho-

mogenous protected nucleoside **19** (13.42 g = 76.82%), which crystallized from a small volume of methanol. m.p. = 224–226°C.

^{1}NMR (DMSO-D_6): δ: 2.99 (tr,2H; CH_2-C = C)), 3.74 (tr, 2H; CH_2-N), 3.79–3.92 (m, 2H; H_5'), 4.13 (m, 4.13 (m, 1H, H_4'), 4.21 (m, 1H, H_3'), 4.28–4.32 (m, 1 h, H_2'), 7.48 (s, 1 H H-C = C).

3-ß-D-Ribofuranosyl-3,5,6,7-tetrahydro-2H-pyrrolo [2,3-d]pyrimidin-2-one 20

2′,3′,5′-Tri-O-benzoate **19** (16.15 g = 27.8 mmol) was kept for 72 hours in sat. methanolic ammonia (250 mL), whereupon t.l.c. (upper phase of n-BuOH : AcOH : H_2O = 4:1:5) indicated that no starting material **19** was anymore present. On evaporation *in vacuo* the nucleoside **20** started to crystallize. The crystalline residue was dissolved in a mixture of water (300 ml) and methyl-t-butylether (200 mL) and shaken. After separation of the phases, the aqueous phase was re-extracted with methyl-t-butylether (200 mL). After concentrating the aqueous phase to 150 ml, the hot yellowish solution was decolorized with charcoal (2 g), the charcoal washed with hot H_2O (75 mL) and the combined aqueous filtrates evaporated to give crude crystalline free nucleoside **20** (7.8 g). Recrystallization from a mixture of ethanol (175 mL) and H_2O (40 mL) afforded pure **20** (4.8 g), m.p. = 224–226°C. On concentration of the mother liquor a second crop of pure **20** (1.84 g) was obtained. Combined yield of **20** = 6.64 g = 88.8%.

^{1}H-NMR (D_2O): δ = 3.7–3.9 (m), 4.07–4.12 (m, H_4'), 4.17–4.22 (m, H_3'), 4.27–4.30 (m, H_2'), 5.92–5.95 (m, H_1'), 7.47 (s, H–C=C), Analysis calcd. for $C_{11}H_{15}N_3O_5$ (269.25) C49.07, H5.61, N15.61, Found: C49.13, H5.35, N15.54.

2,2′-Anhydro-3-(ß-D-arabinofuranosyl)-3,5,6,7-tetrahydro-2H-pyrrolo[2,3d]-pyrimidin-2-one hydrochloride 22

To a stirred suspension of 3-ß-D-ribofuranosyl-3,4,6,7-tetrahydro-2H-pyrrolo[2,3-d]pyri-midin-2-one **20** (1,35 g = 5 mmol) in abs. acetonitrile (50 mL) α-acetoxyisobutyric acid chloride **21** (3,29 g = 20 mmol) was added and the reaction stirred for 4 hours at 21°C, whereupon a clear colourless solution had formed, which did not contain any more starting material **20** acc to t.l.c. (upper phase of n-BuOH : AcOH : H_2O = 4:1:5). After evaporation *in vacuo* the colourless viscous residue was stirred three times with diethylether (100 mL each) and the residue taken up in a 1 molar solution of HCl in abs. methanol (75 mL). After stirring for 18 hours at 21°C colourless crystals had precipitated, which were filtered and washed with abs. methanol (40 mL) and dried to give pure crystalline **22** (1.14 g = 79%), m.p. = 226–230-235°C (dec.) Evaporation of the mother liquor afforded only a small amount of residue (0.16 g).

^{1}H-NMR (DMSO-D_6): δ: 3.03–3.07 (tr, CH_2-CH_2N), 3.4–3.43 (m, CH_2OH), 3.82–3.86 (m, N-CH_2), 4.22 (s, H_4'), 4.48 (s, H_3'), 5.04 (m, 5-OH), 5.4 (d, H_2'), 6.5 (d, H_1'), 7.96 (s, H–C=C).

3-(ß-D-Arabinofuranosyl)-3,5,6,7-tetrahydro-2H-pyrrolo [2,3-d]pyrimidine-2-one 23

To a suspension of D-ribofuranoside **20** (2.69 g = 10 mmol) in abs. acetonitrile (150 mL) α-acetoxyisobutyric chloride (6.58 g = 5.7 ml = 40 mmol) was added under nitrogen and stirred for 5 hours at 23°C to give after evaporation *in vacuo* and stirring of the residue for 15 minutes with methyl-t-butyl ether (250 mL) a fine colourless precipitate. After filtration the residue was washed with methyl-tert.butyl ether (300 mL) and dissolved in 10% aqueous ammonia (25 mL) and stirred for 2 days at 22°C. After removal of the solvents *in vacuo*, the residue was twice evaporated after addition of H_2O (30 mL). The oily residue was suspended in methanol (50 mL), the colourless precipitate filtered, washed with methanol (10 mL) and dried to give a first crop of **23** (0.268 g). The mother liquor was evaporated and suspended in methanol (30 mL) and kept for 16 hours at 23°C to give on filtration and washing with of methanol (10 ml) a second crop of **23** (0.743 g). Because the mother liquor refused to crystallize, the substance was twice co-distilled with toluene (50 mL) and stirred for 16 hours with acetic anhydride (15 mL) and pyridine (30 mL), whereupon the mixture warmed slightly and the residue passed into solution. The brown-yellow reaction mixture was co-distilled twice with xylene (40 mL) *in vacuo* and the residue dissolved in methylene chloride (100 mL). After extraction with ice cold sat $NaHCO_3$-solution (60 mL) and water (40 mL) the methylene chloride solution was dried (Na_2SO_4) and the filtrate evaporated. The residue (2.4 g) was dissolved in ethyl acetate (35 mL) and chromatographed in ethyl acetate on a column of SiO_2 (100 g). The first eluate (700 mL) was discarded, whereas the subsequent fraction (800 mL) afforded a colourless foam (1.9 g), which was kept for 16 hours in methanolic ammonia (50 mL). After evaporation *in vacuo* the residue crystallized slowly from methanol (50 mL) to give in two crops further amounts (0.7 g) of crystalline **23**. m.p. = 225°/232–236°C. Combined yield of **23** = 1.71 g = 63.5%.

H^1-NMR (DMSO-D_6): δ = 2.82 (tr. J = 7.8 Hz; $\underline{CH_2}$-CH_2N), 3.53 (tr. J = 7.8 Hz; CH_2-N), 3.59 (m. H_5'), 3.71 (dtr. J = 3, 4.9 Hz; H_4'), 3.87 (m, H_3'), 3.92 (m, H_2'), 6.03 (d, H1′), 7.37 (s, H–C=C), 7.78 (s, NH)

MS (EI): m/z = 269 (M^+), 251, 238, 208, 177, 166, 138, 121, 110, 70, Analysis calcd. for $C_{11}H_{15}N_3O_5$ (269.25) C49.06, H5.62, N15.61. Found: 48.76, H5.44, N15.12

MS (CI): m/z = 270 (M+1) 168, 138;

Crystal data for 23: $C_{11}H_{15}N_3O_5$,. M_r = 296.26, orthorhombic, space group C222(1), crystal dimensions 0.5 × 0.15 × 0.05 mm^3, unit cell

dimensions $a = 6.9089(2)$, $b = 18.5962(5)$, $c = 18.0369(5)$Å, $\alpha = 90.0^\circ$, $\beta = 90.0^\circ$, $\gamma = 90.0^\circ$, $V = 2317.37(11)$ Å ^{3}, $Z = 8$, $\rho_{calcd} = 1.544$ Mgm^{-3}, $F(000) = 1136$, $\mu(Mo_{K\alpha}) = 1.049$ mm^{-1}, $T = 100K$, $\lambda = 1.54178$Å, $4.76^\circ \leq \Theta \leq 69.50^\circ$, max. Resolution = 0.82Å, 8936 reflections collected of which 2117 are independent [$R_{int} = 0.0369$, Friedel mates are not merged]. R indices (all data) $R_1 = \Sigma| F_o\text{-}F_c| / \Sigma F_o = 0.0270$ for $I > 2\sigma(I)$ and $wR_2 = \Sigma[w(F_o^2\text{-}F_c^2)^2/\Sigma wF_o^4]^{1/2} = 0.0681$ for all data; min./max. electron density: 0.298/–0.204 $eÅ^{-3}$. Intensity data for **23** was recorded for a shock-cooled crystal mounted in an oil drop on a three circle diffractometer with a Smart6000 CCD area detector using ω scans. Data was integrated using the program SAINT. All data was corrected semi-empirical for systematic errors such as absorption using the program SADABS. The structures were solved by Direct Methods using the program SHELXS 96 and refined against F^2 by least squares. All non-hydrogen atoms could be refined anisotropically. All hydrogen atoms were placed in geometrical ideal positions and refined using the riding model, in which the methyl groups could rotate about their local threefold axes. The isotropic temperature factors of all hydrogen atoms are 1.2 and 1.5 times the size of the temperature factors of the corresponding heavy atoms. The absolute structure could be determined. The Flack Parameter refined to -0.0088(0.0610).

The crystallographic data for the structure have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC.

3-(ß-D-Arabinofuranosyl)-3,5,6,7-tetrahydro-2H-pyrrolo [2,3-d]pyrimidine-2-one hydro chloride 24

To a stirred solution of crude ansa-ara-C **23** (3.1 g = 11 mmol) in methanol (120 mL) 2N NaOH (30 ml = 60 mmol) was added, whereupon a distinct smell of NH_3 could be recognized. After evaporation *in vacuo*, the residue was taken up in methanol (100 mL) and stirred for 0.25 hours. The insoluble part was filtered and washed with methanol (30 mL). To the combined filtrate methanolic HCl was added carefully until the solution had reached a pH = 3, whereupon NaCl was precipitated. After continued stirring for 30 minutes the precipitated NaCl was filtered and washed with methanol (30 mL). The filtrate was evaporated and the residue extracted with abs. ethanol (75 mL), whereupon pure crystalline **24** (3.28 g) was obtained, which was washed with methanol (30 mL). After evaporation of the mother liquor, the residue was dissolved in boiling methanol (30 mL) to give on cooling a further amount of **24** (0.23 g). Combined yield of **24** = 3.51 g (76.5%), m.p. = 204–207°C (dec).

^{1}H-NMR (D_2O): δ: 2.95 (m, 2H, CH_2-CH_2N), 3.6 (m, 2 H, H_5'), 3.78, (m, 1H, H_4'), 3.88 (m, 2H, CH_2-N), 3.92 (m, 1H, H_3'), 4.04 (1 H, H_2'), 6.0 (m, 1H, $H_{1'}$), 7.72 (s, 1 H, H–C=C)

Analysis calcd. for $C_{11}H_{16}N_3O_5Cl$ (305.73) C43.21, H5.28, N13.74, Cl11.60. Found: C43.09, H5.35, N13.50, Cl11.50.

3-(ß-D-Arabinofuranosyl)-3,5,6,7-tetrahydro-2-H-pyrrolo [2,3-d]pyrimidin-2-one-5′-O-phosphate 25a

To a stirred suspension of 3-(ß-D-arabinofuranosyl)-3,5,6,7-tetrahydro-2-H-pyrrolo[2,3-d]-pyrimidin-2-one **23** (0.404 g = 1.5 mmol) in triethyl phosphate (7.5 mL) phosphorous oxychloride (0.173 ml = 1.88 mmol) was added slowly within one hour with a syringe at −25°C. The reaction mixture was stirred for another hour at −20° and then for two further hours in an ice bath at + 2°C. After addition with stirring to ice water (25 mL) the mixture was kept for two further hours at + 22°C. The triethyl phosphate was removed by extraction with six 25 ml portions of CH_2Cl_2. The remaining aqueous phase was then gradually added to a solution of 1,2-butyleneoxide (1 mL) in ethanol (180 mL). After 5 hours stirring at 22°C, the precipitated colourless substance was filtered and washed with ethanol (25 mL), whereupon pure 5′-O-phosphate **25a** (0.39 g) was obtained. After evaporation of the mother liquor, the residue was taken up in H_2O (5 mL) and the aqueous solution added to ethanol (75 ml), whereupon another crop (0.093 g) of **25a** was obtained. Combined yield of **25a** = 0.483 g = 92.4%.

MS (FAB): m/z = 372 ($M{\cdot}H^+$).

Sodium 3-(ß-D-arabinofuranosyl)-3,5,6,7-tetrahydro-2H-pyrrolo[2,3d]pyrimidim-2-one-5′-O-phosphate 25b

3-(ß-D-Arabinofuranosyl)-3,5,6,7-tetrahydro-2-H-pyrrolo[2,3-d]pyrimidin-2-one-5′-O-phosphate **25a** (0.2 g = 0.57 mmol) was suspended in H_2O (10 ml) and titrated with 1 N NaOH until the solution reached a p_H = 7. The clear solution was slowly added within 2 hours with stirring to ethanol (70 mL), the crystals filtered and washed with ethanol (15 mL) to give after drying *in vacuo* pure sodium 3-(ß-D-arabinofuranosyl)-3,5,6,7-tetrahydro-2H-pyrrolo-[2,3d]pyrimidim-2-one-5′-O-phosphate **25b** (0.196 g = 92.9%).

MS (FAB): M/z = 394 (M+Na) 372 (M-H^+) 273, 133

3-(2′-Deoxy-3′,5′-di-O-toluoyl-ß-D-ribofuranosyl)-3,5,6,7-tetrahydro-2H-pyrrolo[2,3-d]-pyrimidin-2-one 28

7-Acetyl-3,5,6,7-tetrahydro-2H-pyrrolo[2,3-d]-pyrimidin-2-one **16** (1.79 g = 10 mmol) was boiled for 2 hours with hexamethyldisilazane (HMDS) (2.1

mL = 10 mmol) and trimethyl-chlorosilane (TCS) (1.27 mL = 10 mmol) in acetonitrile (45 mL), whereupon a clear solution of **26** formed and NH_4Cl had sublimed into the reflux condenser. After evaporation the residue was boiled and evaporated with three 15 ml portions of abs. xylene. The crystalline residue of **26** was suspended in 1,2-dichloroethane (120 mL) and 3,5-di-O-toluoyl-2-deoxy-α-D-ribofuranosyl chloride **27** (3.86 g = 10 mmol) added. At + 5°C a solution of trimethylsilyl triflate (TMSOTf) (1.99 mL = 11 mmol) was added slowly with stirring within 45 minutes and the reaction mixture stirred for 4 hours at 21°C and kept for 18 hours at + 4°C. After addition of an ice cold saturated aqueous solution of $NaHCO_3$ (120 mL) some red-brown substance was precipitated and an emulsion formed. After filtration over a G 4 glass filter funnel and washing the filter with CH_2Cl_2, the phases of the filtrate were separated and the aqueous phase extracted twice with CH_2Cl_2 (60 mL). The combined organic phase gave after drying (Na_2SO_4) and evaporation crude amorphous brownish product (4.75 g), which was dissolved in EtOAc–CH_2Cl_2 (1:1) (40 mL) and chromatographed over a column of silica gel (180 g). Elution with EtOAc–CH_2Cl_2 (1:1) (0.5 L) provided some unidentified material, which was discarded, whereas the next fraction (0.5 L) afforded on evaporation some red-brown product (0.15 g). The next 0.5 L eluate furnished nearly colourless, partially crystalline mixture (3.4 g) of the protected ß-anomer **28** and α- anomer **29**. Further elution with 1 L of EtOAc–CH_2Cl_2 (1:1) afforded nearly pure α-anomer **29** (0.4 g), which crystallized from a small amount of acetone. m.p. = 148–150°C.

The mayor eluate fraction (3.4 g) crystallized from acetone-CH_2Cl_2 (ca.100 mL) to give pure protected ß-anomer **28** (1.5 g = 28.2%), m.p. 203–205°C. The mother liquors contained acc. to t.l.c. (upper phase of toluene-AcOH-H_2O = 5:5:1) mainly the α-anomer **29** and was therefore seeded with crystalline **29**, whereupon a further amount of crystalline **29** was obtained. Combined yield of **28** and **29** = 4 g (75.3%).

^{1}H-NMR ($CDCl_3$): 28 δ: 2.23–2.26 (m, 1 H, CH_2-N), 2.42 + 2.44 (s, 2x Me-Aryl), 2.40–2.50 (m, 1 H, CH_2-N), 2.69 (s, MeCO), 3.07 (d,d,d, J = 15 Hz 1 H, $H_{2'}$), 3.83–3.90 + 3.94–4.02 (m, 2x 1 H, CH_2-N), 4.60 (dd, J = 3 Hz and 11 Hz, 1 H, $H_{5'}$), 4.63 (dd; J = 2 + 3 Hz, 1 H, $H_{4'}$), 5.62 (d, J = 7 Hz, 1 H, $H_{3'}$); 6.39 (dd, J = 6 Hz and 8 Hz, 1 H, $H_{1'}$); 7.24 (d, J = 8 Hz, H-Ar); 7.28 (d, J = 8 Hz, H-Ar), 7.64 (s, 1 H, H-C = C), 7.85 (d, J = 8 Hz, H-Ar), 7.97 (d, J = 8 Hz, H-Ar) Analysis calcd for $C_{29}H_{29}N_3O_4$ (531.55) C65.52, H5.5, N7.91 Found C 65.56, H5.29, N7.93.

3-(2′-Deoxy-ß-D-ribofuranosyl)-3,5,6,7-tetrahydro-2H-pyrrolo [2,3-d]pyrimidin-2-one 30

A suspension of 3-(2′-deoxy-3′,5′-di-O-toluoyl-ß-D-ribofuranosyl)-3,5,6,7-tetrahydro-2H-pyrrolo[2,3-d]-pyrimidin-2-one **28** (1.3 g = 2.45 mmol) in

methanolic ammonia (150 mL) was stirred for 48 hours at 22°C, whereupon a clear yellowish solution had formed. After evaporation *in vacuo*, the residue was taken up in H_2O (150 mL) and methyl-t-butylether (100 mL). After separation, the aqueous phase was evaporated *in vacuo* and the colourless crystalline residue (0.68 g) recrystallized from H_2O (5 mL) to give pure **30** (0.22 g), m.p. = 135–140°–223–226°C. The mother liquor afforded on evaporation and recrystallization from ethanol-H_2O = 9 : 1 (8 mL) a second crop of **30** (0.17 g) m.p. = 134–150–224–228°C. Combined yield of **30** = 0.39 g = 62.9%.

H^1-NMR (D_2O): δ: 2.24 (m, 2H, H_2'), 3.75 (m, J = 8 Hz, CH_2-CH_2N), 3.75 (m, CH_2-N), 3.82 (m, 2H, H_5'), H_4'), 4.43 (m, J = 2 +3Hz, H_3'), 6.33 (tr. J = 6Hz, H_1'), 7.5 (s, H–C=C).

MS (CI): 254 ($M + H^+$) 164, 138, Analysis calcd. for $C_{11}H_{15}N_3O_4$ (253.25) C52.17, H5.97, N16.59, Found: C48.79, H6.00, N15.48, calcd. for $C_{11}H_{15}N_3O_4$ H_2O (271.25) C48.7, H6.32, N15.49.

3-(3-O-Acetyl-5-O-benzoyl-2-deoxy-2-fluoro-ß-D-arabinofuranosyl)-N^7-acetyl-3,5,6,7-tetrahydro-2H-pyrrolo [2,3-d]pyrimidin-2-one 32

N-Acetyl-ansa-cytosine **16** (0.896 g = 5 mmol) was silylated with HMDS-TCS (cf. prepa-ration of **23**) for 30 minutes in boiling acetonitrile (40 mL), whereupon a clear solution of **26** had formed and NH_4Cl had sublimed into the reflux condenser. After evaporation *in vacuo* with careful exclusion of humidity, followed twice by evaporation with abs. xylene (15 mL). the residue was dissolved in abs. 1,2-dichloroethane (20 mL). A solution of 3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide **31** (1.206 g = 5 mmol) was added and the reaction mixture refluxed for 14 hours under nitrogen. After dilution with CH_2Cl_2 (50 mL) an ice cold saturated solution of $NaHCO_3$ (75 mL) was added and the mixture shaken. The phases were separated and the aqueous phase re-extracted with two 30 mL portions of CH_2Cl_2. The combined organic phase was dried (Na_2SO_4) and evaporated. The crude product (2.53 g) was dissolved in the upper phase (20 ml) of toluene : AcOH : H_2O = 5:5:1 and chromatographed with the same solvent mixture on a column of silicagel (120 g). After a fore run of 500 ml, the subsequent 150 mL eluted pure ß-anomer **32** (0.812 g = 35.4%), whereas the subsequent 150 mL eluted a ß/α-mixture (0.21 g). The last 150 mL solvent mixture eluted pure α-anomer **33** (0.04 g = 1.7%).

^{1}H-NMR ($CDCl_3$): ß-Anomer **32** δ: 2.18,(s, 3H,$COCH_3$), 2.7 (s,3H, N-$COCH_3$), 2.68 (m, 2H, CH_2CH_2N) 4.05 (tr.2H, J = 8 Hz, CH_2N), 4.4 (tr, 2H, H_4'), 4.68 (dd,2H, J = 4 +12 Hz, H_4'), 4.76 (dd, 2H, J = 3 +12Hz, H_5') 5.30 (dd,1 H, J = 1 + 7 Hz, H_2'), 5.25–5.45 (m, H_2'), 6.28 + 6.34 (dd, 1 H, J = 2 +17Hz, H_1'), 7.2–8.8 (m, H-ar), 7.58 (s, 1H, H-C = C),

MS (EI): m/z = 459 (M^+), 439 (M-1 +F) 380, 338,318, 281, 219, 180, 137, 105

MS (CI) = 460, ($M + H^+$)

3-(2-Deoxy-2-fluoro-ß-D-arabinofuranosyl)-3,5,6,7-tetrahydro-2H-pyrrolo[2,3d]-pyrimidin-2-one 34

Pure N^7-acetyl-3-(3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-ß-D-arabinofuranosyl)- 3,5,6,7- tetrahydro-2H-pyrrolo[2,3-d]pyrimidin-2-one **32** (0.77 g = 0.168 mmol) was stirred for 20 hours at 22°C in methanolic ammonia and the reaction mixture evaporated *in vacuo*. The residue was taken up in H_2O (150 mL) and methyl-t-butyl ether (75 ml), the aqueous phase re-extracted twice with methyl-tert-butyl ether (50 mL) and once with CH_2Cl_2 (75 mL). On evaporation of the aqueous phase *in vacuo*, the residue was dissolved in H_2O (10 mL), char-coal (0.2 g) added and filtered, whereupon the char coal was washed with H_2O (10 mL). After evaporation of the aqueous filtrate the residue (0.54 g) was dissolved in boiling ethanol (30 mL) to give on cooling pure free nucleoside **34** (0.290 g), m.p. = 219–221°C. Concentration of the mother liquor gave a second crop of **34** (0.038 g). Combined yield of **34** = 0.328g = 71.9%.

^{1}H-NMR (DMSO): δ 2.85 (tr. 2H, J = 8Hz, CH_2CH_2N), 3.5–3.6 (m, 3H, CH_2N), 3.78 (m,1H, H_4'), 4.12–4.21(m, 1H, H_3'), 4.83 (dd, J = 2 + 3Hz, H_2'), 6.08–6.13(dd, J = 3 + 17 Hz, H_1'). 7.4 (s,1H,H-C = C)

MS (EI) m/z = 271 (M^+), 251 (M-H_2O), 204, 177, 137, 121, 110, 93, 82;

MS (CI) m/z = 272 (M+1) 252, 177, 138 Analysis cald. for $C_{11}H_{14}N_3FO_4$ (271.26) C48.71, H5.2, N14.49, F7.0, Found: C48.62, H5.21, N15.31, F6.73

3-(3,5-Di-O-benzoyl-2-deoxy-2,2-difluoro-ß-D-ribofuranosyl)-N^7-acetyl-3,5,6,7-tetrahydro-2H-pyrrolo[2,3d]pyrimidin-2-one 36

A suspension of **16** (0.896 g = 5 mmol) in abs. acetonitrile (50 mL) was heated with hexamethyldisilazane (HMDS) (0.63 mL) and trimethylchlorosilane (TCS) = 38 mL) (cf. preparation of **27**) for 90 minutes at reflux, whereupon **26** was formed and NH_4Cl sublimed into the reflux condenser. After evaporation, the residue was dried *in vacuo* for 4h at 40–50°C and dissolved in dry 1,2-dichloroethane. The anomeric mixture of 3,5-di-O-benzoyl-2-deoxy-2,2-difluoro-ribofuranosyl-1-O-mesylates **35** (0.896g = 5 mmol) was added as well as subsequently a solution of trimethylsilyl triflate (TMSOTf) (0.93 mL = 5 mmol) with stirring at 22°C. After heating to reflux for 19 hours, the mixture was cooled, a further amount of TMSOTf (0.37 mL = 2 mmol) added and the reaction mixture heated again for 19 hours at reflux. Because the reaction was still not complete, a final amount of TMSOTf (0.37 mL = 2 mmol) was added and the reaction mixture refluxed again for further 5h, whereupon tlc.

(system: upper phase of toluene-AcOH-H_2O = 5:5:1) indicated that no unreacted base **16** was anymore present. After workup with CH_2Cl_2 and ice cold sat. aqueous $NaHCO_3$-solution (150 mL), the CH_2Cl_2 phase was dried (Na_2SO_4), filtered and evaporated. The brownish oily crude protected nucleoside (2.64 g) was chromatographed with the upper phase of toluene-AcOH-H_2O = 5:5:1 on a column of silica gel (120 g). After a forerun of 475 ml, the next 600 ml eluted a mixture (0.73 g), whereas the subsequent 600 mL afforded pure α-anomer **37** (0.48 g). The mixture (0.73 g) was analogously re-chromatographed on a column of silica gel (120 g) to give after a forerun of 0.5 L in the subsequent 0.5 L fraction pure ß-anomer **36** (0.540 g) as well as finally some pure α-anomer **37** (0.05 g). Combined yield = 0.54 g = 20.9% of ß anomer **36** as well as 0.511 g = 19.7% of α-anomer **37**:

^{1}H-NMR ($CDCl_3$): ß-Anomer **37** δ = 2.67 (tr. 2H, J = 8 Hz, CH_2CH_2N), 2.73 (s, 3H; CH_3CO), 4.3 (tr. 2H, J = 8 Hz, CH_2N), 4.6 (m, 1H, H_4'), 4.58–4.9 (m, 2H, H_5'), 5.63–5.68 (m, 1H, H_3'), 6.58–6.63 (m, 1H, H_1'), 7.41 (s, 1H, H—C=C), 7.45–8.13 (m, arom.H),

MS (CI): m/z = 540 (M + H); 498, 478; 436;

MS (EI): m/z = 600, 573, 539 (M^+), 511, 497, 434, 399, 398, 390, 376, 361, 356

3-(2-Deoxy-2,2-difluoro-ß-D-ribofuranosyl)-3,5,6,7-tetrahydro-2H-pyrrolo[2,3-d]-pyrimidin-2-one 38

A suspension of the ß-anomer 3(3,5-di-O-benzoyl-2-deoxy-2,2-difluoro-ß-D-ribofurano-syl)-N^7-acetyl-3,5,6,7-tetrahydro-2H-pyrrolo[2,3-d]pyrimidin-2-one **36** (0.480 g = 0.89 mmol) in sat. methanolic ammonia (40 mL) was stirred for 18 hours at 22°C, whereupon a clear solution formed after 0.5 hours. After evaporation and workup with H_2O-CH_2Cl_2 followed by extraction of the aqueous phase with CH_2Cl_2 and ethyl acetate, the aqueous phase was evaporated and the yellowish crystalline residue (0.26 g) recrystallized from H_2O (5 mL), whereupon pure nucleoside **38** was obtained in two crops (0.161 g = 62.5%), mp. 167–170°C

^{1}H-NMR (DMSO-D_6): δ = 2.85 (m, 2H, CH_2CH_2N), 3.58 (tr, 3H, J = 8 Hz, $\underline{CH_2}CH_2N$), 3.63–3.65 (m, 1H, H_4'), 3.76 (m, 1H, H_5'), 4.13–4.18(m,1H, H_3'), 6.1–6.15 (m, 1H, H_1'), 7.43 (s, 1H, H-C = C)

MS (CI): m/z 290 ($M + H^+$) 138;

MS (EI): m/z = 290, 289 (M^+) 272, 215, 208, 195, 172, 164, 138, 137, 121, 110, 109, 93, 82, 60, 44

REFERENCES

1. The term ansa in combination with rings denotes a (looped) handle of a molecule like the looped handle of a tea cup. (cf. ansa rings under Google or Scifinder).

2. Vorbrüggen, H.; Krolikiewicz, K.; Schirner, M.; Schneider, M.; Wiesinger, H.; Neue Cytosin- und Cytidinderivate. Ger.Offen.(1996) DE 19514523; *Chem. Abstr.* **1996**, 125, 329288.
3. Krolikiewicz, K.; Mueller-Fahrnow, A.; Vorbrüggen, H.; Unpublished lecture.
4. Grant, S. Biochemical modulation of cytosine arabinoside. *Pharmacology&Therapeutics*, **1990**, 48, 29.
5. Watanabe, K.; Reichman, U.; Fox, J.J.; Chou, T-C. Nucleosides CXIX: Substrate specificity and mechanism of action of cytidine deaminases of monkey plasma and mouse kidney. *Chem. Biol. Interctions* **1981**, 37, 41.
6. Kreis, W.; Watanabe, K.A.; Fox, J.J. Structural requirements for the enzymatic deamination of cytosine nucleosides. *Helv. Chim. Acta* **1978**, 61, 1011.
7. Berlin, A. Ya.; Korbukh, I.A. *Khim. Geterosikl. Soedin* **1968**, 377; *Chem. Abstr.* **1968**, 69, 96670s.
8. Vorbrüggen, H.; Krolikiewicz, K.; Niedballa, U. Eine neue und einfache Synthese von Cytidinen. *Liebigs Ann.* **1975**, 988.
9. Fissekis, J.D.; Myles, A.; Brown, G.B. Synthesis of 5-hydroxyalkylpyrimidines From lactones. *J. Org. Chem.* **1964**, 29, 2670.
10. Fissekis, J.D.; Sweet, F. The Chemistry of some 5-(2-hydroxyalkyl)uracil derivatives and a synthesis of 5-vinyluracil. *J. Org. Chem.* **1973**, 28, 264.
11. Appel, R. Tert.phosphane/tetrachloromethane, a versatile reagent for chlorination, dehydration and P-N linkage. *Angew. Chem. Int. Ed. Engl.* **1975**, 14, 801.
12. Vorbrüggen, H.; Krolikiewicz, K.; Bennua-Skalmowski, B. Nucleoside synthesis with trimethylsilyl triflate and trimethylsilyl perchlorate. *Chem. Ber.* **1981**, 114, 1234.
13. Russel, A.F.; Prystsz, M.; Hamamura, K.; Verheyden, J.P.H.; Moffatt, J.G. Reaction of 2-acyloxyisobutyryl halides with nucleosides. V. Reaction with cytidine and its derivatives. *J. Org. Chem.* **1974**, 39, 2182.
14. Yoshikawa, M.; Kato, T.; Takenishi, T. A novel method for phosphorylation of nucleosides to 5′-nucleotides. *Tetrahedron Lett.* **1967**, 8, 5065.
15. Hoffer, M. α-Thymidin. *Chem. Ber.* **1960**, 93, 2777.
16. Watanabe, K.A.; Su, T.L.; Klein, R.S.; Chu, C.K.; Matsuda, A.; Chun, M.W.; Lopez, C.; Fox, J.J. Nucleosides 123. Synthesis of antiviral nucleosides. 5-Substituted 1-(2-deoxy-2-halogeno-ß-D-arabinofuranosyl)cytosines and–uracils. Some structure-activity relationships. *J. Med. Chem.* **1983**, 26, 152.
17. Chou, T.S., Heath, P.C.; Patterson, L.E.; Poteet, L.M.; Lakin, R.E.; Hunt, A.H. Stereospecific Synthesis of 2-deoxy-2,2-difluororibonolactone and its use in the preparation of 2′deoxy-2′,2′-difluoro-ß-D-ribofuranosyl pyrimidine nucleosides: The key role of selective crystallisation. *Synthesis* **1992**, 565.
18. Griengl, H.; Bodenteich, M.; Hayden, W.; Wanek, E.; Streicher, W.; Stuetz, P.; Bachmayer, H.; Ghazzouli, I.; Rosenwirth, B. 5-Haloalkyl-2′-deoxyuridines: A novel type of potent nucleoside analogue. *J. Med. Chem.* **1985**, 28, 1679.
19. Loukes, D.; Bazzanini, R.; Brown, D.M. The synthesis of cyclic N^4-amino-2′-deoxycytidine derivatives. *Helv. Chim. Acta* **1999**, 82, 2028.