# A Surprising Ring Opening Mechanism in the Formation of α-D-Arabinofuranosyl Nucleosides from 5-Substituted Uracils

Per Trolle Jørgensen,[a] Erik B. Pedersen,*[a] Claus Nielsen[b]

[a] Department of Chemistry, Odense University, DK-5230 Odense M, Denmark
[b] Retrovirus Laboratory, Department of Virology, Statens Seruminstitut, Artillerivej 5, DK-2300 Copenhagen, Denmark

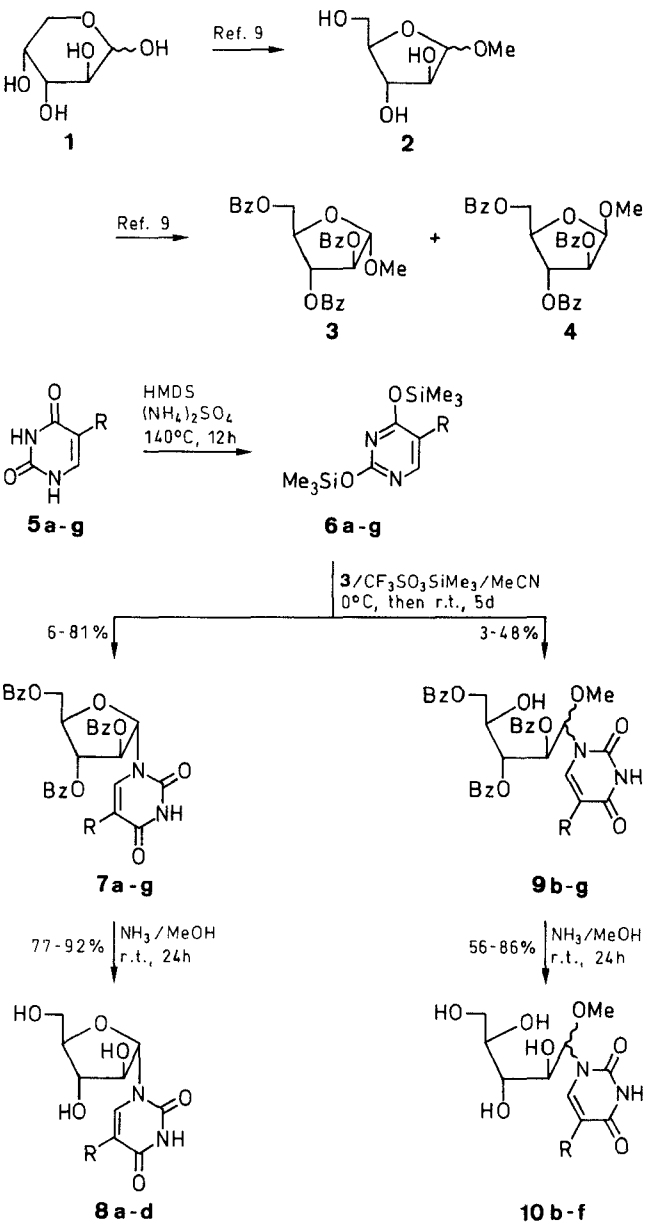
*Received 13 March 1992*

Reaction of silylated 5-substituted uracil derivatives **6** with methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside (**3**) in the presence of trimethylsilyl trifluoromethanesulfonate afforded a mixture of the corresponding 5-substituted 1-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)uracils **7** and the acyclo 2,3,5-tri-*O*-benzoyl-1-*O*-methyl-1-(uracil-1-yl)-D-arabinitols **9** with the methoxy group intact at C-1. Compound **7** was deprotected with methanolic ammonia to give **8**. Compound **7** was also reacted with Lawesson's Reagent to generate the corresponding 4-thio-α-D-arabinofuranoside nucleoside **14** which was deprotected by treatment with methanolic ammonia to give the nucleosides **15**. Deprotected acyclo nucleosides **10** were likewise obtained from compounds **9**. The mechanism for formation of the nucleosides **7** is discussed and the acyclo nucleosides **9** are believed to be intermediates.

Although a few α-nucleosides and nucleotides have been found to occur naturally,[1] all nucleotides found in nucleic acids and all essential nucleosides and nucleotides occurring elsewhere are in the β-configuration. For this reason α-anomers have been assumed by most investigators to be biologically inert, and few have been examined for biological activity. The latter concept, however, may require reconsideration since several α-nucleosides are now known to exhibit significant antimetabolic properties,[2] (antitumor and antiviral properties). Among the D-arabinofuranosyl nucleosides, the β-anomers of which are potent and clinically employed therapeutic agents, the α-anomer of 9-D-arabinofuranosyladenine has been shown to exhibit appreciable antiviral activity.[3]

Since little synthetic work on α-arabinonucleosides of pyrimidine has been reported,[4-8] it led us to undertake the synthesis of additional α-D-arabinofuranosyl nucleosides from 5-substituted uracils.

The conversion of D-(−)-arabinose (**1**) to methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside (**3**) has been described in the literature.[9] Following a glycosidation with hydrochloric acid in methanol with concomitant ring contraction to the pentofuranoside **2**, the hydroxy groups were protected upon treatment with benzoyl chloride in dry pyridine to afford **3** and **4**. Pure **3** was obtained as a white solid by crystallization from ethanol in 50% yield based on **1**. The 5-substituted uracils **5** were prepared as previously described[10] and silylated in order to obtain **6** according to standard procedures by refluxing the nucleobase in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of catalytic amounts of ammonium sulfate.[11,12] Condensation of the methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside (**3**) and the silylated nucleobase **6** was carried out according to the Friedel–Crafts catalyzed[13] silyl Hilbert–Johnson reaction modified by Vorbrüggen et al.[12] The reaction was performed in dry acetonitrile in the presence of trimethylsilyl trifluoromethanesulfonate producing **7** in 6–81% yield, in accordance with the *trans* rule of Baker,[14] exclusively as α-nucleosides. The protected nucleosides **7** were deblocked by treatment with methanolic ammonia and separated by silica column chromatography to give **8** in 77–92% yield. Besides **7** we obtained nucleoside analogues **9** in 3–48% yield having an acyclic sugar chain with the methoxy group intact.




| 5-10 | R | 5-10 | R |
|---|---|---|---|
| a | Cl | | |
| b | Me | e | Me–N N– |
| c | –N5 | f | HO–CH2–CH2–N N– |
| d | Bn–N N– | g | Bn–N N– |

**Scheme 1**

This is the first known example of a coupling directly with a protected pentofuranoside and a silylated nucleobase to generate an acyclo nucleoside of type **9**. Treatment of the protected nucleoside **9** with methanolic ammonia at room temperature gave 56–86% yield of pure acyclic nucleoside **10** (Scheme 1).

The compounds **7e–f** were isolated in low yields contaminated with the corresponding acyclic nucleosides **9e–f**. Since complete purification was not possible, **8e–f** could not be isolated in the subsequent deprotection reaction. For **7g** and **9g** it was only possible to obtain pure samples in small amounts because of very complex reaction mixtures.

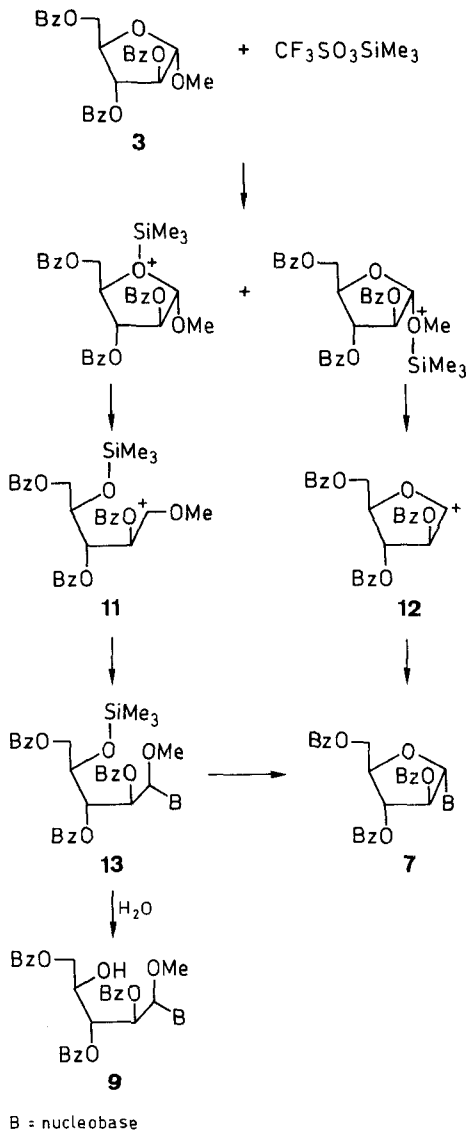
The α-configurations of **7** and **8** were supported by their NMR data (see Experimental). The chemical shifts and coupling constants of anomeric protons (1′-H) in **7** and **8** were in accordance with the reported values for α-arabinosides.[3] Smaller coupling constants of the anomeric protons in protected arabinosides, in general, were found than those for the corresponding deblocked arabinosides, in conformity with the literature observations.[3] According to the 2D $^1$H NMR spectra the following order was established. The 2′-OH group of **8** appears at lower field than the 3′-OH. Furthermore, the chemical shift difference between the signals for the 2′-OH and 3′-OH is in the range of 0.21–0.27 ppm in conformity with the literature observations of the α-anomer.[15]

In the first synthesis of acyclic sugar nucleosides related to compounds **10b–f**, Wolfrom and co-workers[16] started with D-galactose and obtained, by way of the acetylated diethyl dithioacetal, two different crystalline products from coupling with adenine. These products were considered to be C-1 epimers, one was dextrorotatory and the other levorotatory, but the configuration at C-1′ was not determined. The NMR spectra of the ring opened products **9** showed only one set of signals for **9b,d**, whereas for **9c,e,f** two acyclic nucleosides were obtained, a major and a very minor product, with nearly uniform $^{13}$C NMR spectra indicating that they are C-1′ epimers. Compounds **9** were deprotected with ammonia in methanol to give the corresponding debenzoylated compounds **10**, as their corresponding pure epimers.

The identities of the products **9** and **10** were fully established by NMR spectroscopy.

The benzoylated acyclic sugar nucleosides **9** generally show weak $M + H^+$ peaks in their FAB mass spectra together with more intensive peaks for the ions resulting from splitting off methanol from the parent ions.

Formation of the acyclic nucleoside **9** is easily explained by a mechanism in which the ring oxygen of the sugar is silylated making ring opening possible with formation of the acyclic carbonium ion **11** which, in turn, can condense with the silylated nucleobase to give **13**; an intermediate that produces the acyclic nucleoside **9** by hydrolysis. More intriguing, the same intermediate may represent an important route for formation of the nucleosides **7**. This is in contrast with the generally accepted idea that such nucleosides should be formed from the cyclic carbonium ion **12** generated via exocyclic silylation of the glycoside **3**.



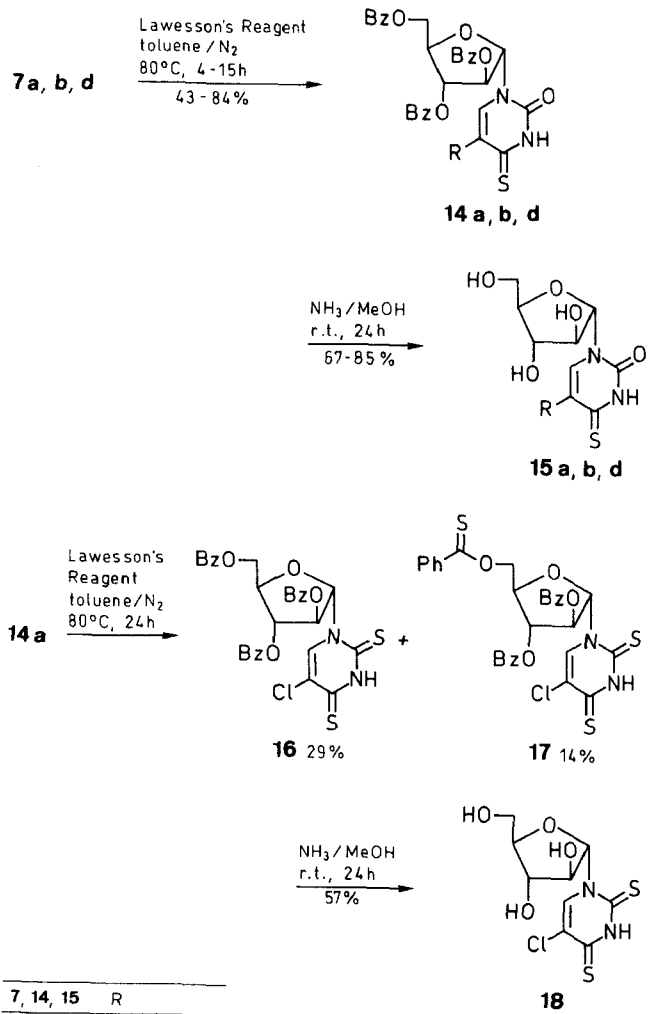

**Scheme 2**

An isolated yield around 50% of the acyclic nucleoside **9f** shows formation of the acyclic carbonium ion **11** to be strongly favored and this should be the case for all the reactions in the present investigation since it is hard to believe that the 5-substituent of the nucleobase should determine which carbonium ion **11** or **12** that is preferentially formed. This is particularly the case for reactions with **6b** (5-methyl) and **6c** (5-hexyl) even though they result in completely different product distributions with a high yield of the α-nucleoside **7b** by reaction of the former and with the acyclic nucleoside **9c** was the major product by reaction of the latter. Another indication about **13** as an intermediate in the formation of the α-nucleosides **7** came from TLC analysis during the reaction. For reactions with preferential formation of the α-nucleoside **7**, close inspection of the TLC plates in the beginning of the reactions revealed that **7** and the acyclic nucleoside **9** were formed in equal amounts. As expected for an intermediate, the spot of compound **9** did not increase in intensity during the reaction whereas that of the α-nucleoside **7** was strongly intensified. In one case extra TMS triflate was added and disappearance of the acyclic nucleoside **9** was observed. In summary, from the above observations we

conclude that a substantial amount or maybe all the α-nucleoside **7** is formed via the acyclic nucleoside **9**.

Since the introduction of a sulfur-containing group into an organic compound increases its lipophilicity as well as its ability to cross the blood-brain barrier (a prerequisite for an efficient anti-HIV drug) different 4-substituted sulfur-containing nucleosides were also synthesized.

Thiation of 5-substituted 1-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)uracils **7a,b,d** was carried out with the Lawesson's Reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide][17,18] to give **14a,b,d** in 43–84% yield. The compounds **14a,b,d** were then deprotected in a saturated solution of ammonia in methanol and separated by column chromatography on silica gel to give **15a,b,d** in 67–85% yield. $^{13}C$ NMR spectrum showed a characteristic downfield shift of C-4 from $\delta$ = 164 to 190 upon introduction of the sulfur atom. In contrast to the 4-thiopyrimidine nucleosides readily available from the corresponding 4-oxopyrimidine nucleosides by thiation with phosphorus pentasulfide[19] or Lawesson's Reagent,[17,18] no formation of 2,4-dithio or 2-thio derivatives was observed. Ueda and coworkers[20] have reported the preparation of 2,4-dithiouridine by direct thiation with phosphorus pentasulfide of 2',3',5'-tri-*O*-benzoyl-4-thiouridine under forcing conditions.




| 7, 14, 15 | R |
|---|---|
| a | Cl |
| b | Me |
| d | Bn–N N– |

**Scheme 3**

Pure **14a** was treated with Lawesson's Reagent under the same condition as for the formation of **14a** to obtain 1-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-5-chloro-2,4-dithiouracil **(16)** in 29% yield and **17** in 14% yield. Compounds **16** and **17** were deprotected and the product separated by silica gel column chromatography to give **18** in 57% yield (Scheme 3).

The thiation reaction of **14a** was followed by thin-layer chromatography and showed two main spots during 24 hours. The slower eluting component **16** afforded 1-(α-D-arabinofuranosyl)-5-chloro-2,4-dithiouracil **(18)** on debenzoylation. The compound eluting ahead of **16**, also gave **18** on deblocking, indicating that the difference between **16** and **17** exists in the blocking group, i.e. thiation of one benzoyl group of **16**. $^{13}C$ NMR showed that C-5' for **17** resonates at lower field than for **16** corresponding to thiation of carbonyl in benzoyl group at C-5'. The identities of the products **15** and **18** were also established by NMR spectroscopy.

The compounds **8a–d**, **10b,c** and **15a,b** did not show any significant activity at 100 μM against Herpes Simplex Virus type 1 (HSV-1), strain McIntyre, when propagated in a continuous cell line from rabbit cornea (SIRC) which was maintained in Eagle's MEM containing 1% fetal calf serum and test compounds. The same compounds were also devoid of activity at 100 μM against HIV-1 (strain HTLV-IIIB) in MT-4 cells, when MT-4 cells were incubated with virus, washed and added in a proportion of 1:10 to uninfected MT-4 cells which had been preincubated in test compound containing growth medium for 2 hours. The MT-4 cells were maintained with the culture medium likewise containing the test compound and expression of HIV in culture medium was quantitated by HIV antigene detection ELISA. The compounds **9b**, **9c** and **9d** were toxic against MT-4 cells at 100, 10 and 10 μM, respectively, but at 10 fold lower concentrations no activity against HIV-1 was observed. The same compounds showed no activity against HSV-1 at non-cytotoxic concentrations at 10, 10 and 100 μM, respectively.

NMR spectra were recorded on a Bruker 250 FT NMR spectrometer, TMS as internal standard. Mass spectra were recorded on a Varian Mat 311A spectrometer. FAB mass spectra were recorded on a Kratos MS-50 spectrometer. The silica gel (0.040–0.063 mm) used for column chromatography was purchased from Merck.

**5-Substituted 1-(2,3,5-Tri-*O*-benzoyl-α-D-arabinofuranosyl)uracils 7a–g and 5'-Substituted 2,3,5-Tri-*O*-benzoyl-1-*O*-methyl-1-(uracil-1-yl)-D-arabinitol 9b–g; General Procedure:**

A mixture of 5-substituted uracil **5a–g** (15 mmol), $(NH_4)_2SO_4$ (50 mg) and HMDS (40 mL) was refluxed (140°C) overnight. The solvent was removed under reduced pressure. The resulting oily residue of **6a–g** was dissolved in dry MeCN (50 mL), cooled to 0°C and a solution of methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside (**3**; 5 g, 10.5 mmol) in dry MeCN (30 mL) was added at 0°C. A solution of $CF_3SO_3SiMe_3$ (2.85 mL, 15.75 mmol) in dry MeCN (20 mL) was added dropwise and the mixture was stirred at r.t. for

5 d. The mixture was diluted with $CH_2Cl_2$ (200 mL), washed with a cold sat. aq $NaHCO_3$ (150 mL), cold $H_2O$ (3 × 150 mL) and dried ($Na_2SO_4$). The solvent was removed in vacuo and the residue was chromatographed on silica gel (100 g) with $CHCl_3$ to obtain the compounds **7a–g** and **9b–g**.

*1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-5-chlorouracil* (**7a**): Yield: 5.12 g (80.5%); mp 102–104°C.

| | | | | |
|---|---|---|---|---|
| $C_{30}H_{23}ClN_2O_9 \cdot 1.5H_2O$ | calc. | C 58.31 | H 4.24 | N 4.53 |
| (618.0) | found | 58.05 | 3.89 | 4.40 |

$^1$H NMR (DMSO-$d_6$/TMS): $\delta$ = 4.68 (2H, d, $J$ = 4.8 Hz, 5′-H), 5.19 (1H, m, 4′-H), 5.91 (1H, t, $J$ = 4.3 Hz, 3′-H), 6.12 (1H, t, $J$ = 4.0 Hz, 2′-H), 6.30 (1H, d, $J$ = 3.9 Hz, 1′-H), 7.45–8.05 (15H, m, $H_{arom}$), 8.37 (1H, s, 6-H), 11.89 (1H, s, NH).

$^{13}$C NMR (DMSO-$d_6$/TMS): $\delta$ = 63.88 (C-5′), 76.24 (C-3′), 79.38 (C-2′), 81.48 (C-4′), 90.19 (C-1′), 107.52 (C-5), 128.45, 128.50, 128.61, 129.06, 129.11, 129.37, 133.30, 133.60, 133.70 ($C_{arom}$), 138.80 (C-6), 149.48 (C-2), 158.87 (C-4), 164.60, 164.70, 165.24 (3 × C=O).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 591 ($M + H^+$, 8).

*1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-5-methyluracil* (**7b**): Yield: 3.75 g (63%); mp 94–96°C.

$^1$H NMR (DMSO-$d_6$/TMS): $\delta$ = 1.84 (3H, s, $CH_3$), 4.70 (2H, d, $J$ = 4.8 Hz, 5′-H), 5.16 (1H, m, 4′-H), 5.92 (1H, t, $J$ = 4.5 Hz, 3′-H), 6.08 (1H, t, $J$ = 4.0 Hz, 2′-H), 6.33 (1H, d, $J$ = 4.0 Hz, 1′-H), 7.45–8.05 (15H, m, $H_{arom}$), 7.83 (1H, s, 6-H), 11.48 (1H, s, NH).

$^{13}$C NMR (DMSO-$d_6$/TMS): $\delta$ = 11.90 ($CH_3$), 64.02 (C-5′), 76.46 (C-3′), 79.35 (C-2′), 81.23 (C-4′), 89.45 (C-1′), 109.54 (C-5), 128.44, 128.55, 128.65, 129.12, 129.38, 129.41, 133.35, 135.68, 133.76 ($C_{arom}$), 137.07 (C-6), 150.39 (C-2), 163.68 (C-4), 164.63, 164.78, 165.30 (3 × C=O).

FAB MS (glycerol): $m/z$ (%) = 571 ($M + H^+$, 1.5).

*1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-5-hexyluracil* (**7c**): Yield: 0.43 g (6.4%).

$^1$H NMR ($CDCl_3$/TMS): $\delta$ = 0.85 (3H, t, $J$ = 6.4 Hz, $CH_3$), 1.23–1.46 (8H, m, $CH_2$), 2.25–2.33 (2H, m, $CH_2$), 4.72 (2H, m, 5′-H), 4.99 (1H, m, 4′-H), 5.76 (1H, t, $J$ = 3.2 Hz, 3′-H), 5.96 (1H, t, $J$ = 2.9 Hz, 2′-H), 6.23 (1H, $J$ = 3.1 Hz, 1′-H), 7.20–8.04 (16H, m, 6-H, $H_{arom}$), 9.30 (1H, s, NH).

$^{13}$C NMR ($CDCl_3$/TMS): $\delta$ = 13.90 ($CH_3$), 22.40, 26.85, 28.23, 28.78, 31.34 ($CH_2$), 63.66 (C-5′), 77.41 (C-3′), 80.42 (C-2′), 83.36 (C-4′), 91.25 (C-1′), 115.65 (C-5), 128.26, 128.32, 128.39, 128.49, 128.51, 128.80, 129.71, 129.88, 133.16, 133.48, 133.72, 133.78 ($C_{arom}$), 135.56 (C-6), 150.04 (C-2), 163.32 (C-4), 165.08, 165.23, 165.98 (3 × C=O).

FAB MS (glycerol): $m/z$ (%) = 641 ($M + H^+$, 1.5).

*1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-5-(4-benzylpiperazino)uracil* (**7d**): Yield: 5.21 g (68%); mp 109–111°C.

$^1$H NMR (DMSO-$d_6$/TMS): $\delta$ = 2.41 (4H, m, $CH_2$), 2.87 (4H, m, $CH_2$), 3.43 (1H, d, $J$ = 9.3 Hz, $CH_2Ph$), 3.50 (1H, d, $J$ = 9.3 Hz, $CH_2Ph$), 3.67 (2H, d, $J$ = 4.6 Hz, 5′-H), 5.10 (1H, m, 4′-H), 5.87 (1H, t, $J$ = 3.8 Hz, 3′-H), 6.09 (1H, t, $J$ = 3.6 Hz, 2′-H), 6.30 (1H, d, $J$ = 3.7 Hz, 1′-H), 7.07 (1H, s, 6-H), 7.27–8.03 (20H, m, $H_{arom}$), 11.48 (1H, s, NH).

$^{13}$C NMR (DMSO-$d_6$/TMS): $\delta$ = 49.34 ($CH_2$), 52.10 ($CH_2$), 61.78 ($NCH_2Ph$), 63.58 (C-5′), 77.15 (C-3′), 79.90 (C-2′), 81.27 (C-4′), 90.20 (C-1′), 125.05 (C-5), 126.67, 127.34, 127.90, 128.42, 128.44, 128.57, 128.60, 129.02, 129.10, 129.27, 129.31, 133.25, 133.51, 133.64 ($C_{arom}$), 137.95 (C-6), 149.15 (C-2), 160.24 (C-4), 164.62, 164.88, 165.23 (3 × C=O).

FAB MS (glycerol): $m/z$ (%) = 731 ($M + H^+$, 72).

*1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-5-(4-methylpiperazinomethyl)uracil (7e)*: Yield: 6% (from $^1$H NMR of **7e** + **9e**).

$^1$H NMR ($CDCl_3$/TMS): $\delta$ = 2.21 (3H, s, $CH_3$), 2.36–2.47 (8H, m, $CH_2$), 3.30 (2H, d, $J$ = 2.0 Hz, $CH_2$), 4.71–4.74 (2H, m, 5′-H), 4.97–4.99 (1H, m, 4′-H), 5.78 (1H, t, $J$ = 3.8 Hz, 3′-H), 5.99 (1H, t, $J$ = 3.2 Hz, 2′-H), 6.18 (1H, d, $J$ = 3.4 Hz, 1′H), 7.26–8.10 (16H, m, 6-H, $H_{arom}$).

$^{13}$C NMR ($CDCl_3$/TMS): $\delta$ = 45.61 ($CH_3$), 52.59 (2 × $CH_2$), 52.92 ($CH_2$), 54.79 (2 × $CH_2$), 63.88 (C-5′), 77.41 (C-3′), 80.48 (C-2′), 83.31 (C-4′), 91.75 (C-1′), 111.11 (C-5), 128.35, 128.54, 129.36, 129.61, 129.70, 129.78, 129.90, 133.17, 133.41, 133.79 ($C_{arom}$), 138.51 (C-6), 149.96 (C-2), 163.07 (C-4), 165.25, 165.37, 165.97 (3 × C=O).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 669 ($M + H^+$, 16).

*1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-5-[4-(2-hydroxyethyl)piperazinomethyl]uracil* (**7f**): Yield: 0.8% (from $^1$H NMR of **7f** + **9f**).

$^1$H NMR ($CDCl_3$/TMS): $\delta$ = 2.28–2.48 (10H, m, $CH_2$), 3.25 (2H, br s, $CH_2$), 3.57 (2H, t, $J$ = 5.7 Hz, $CH_2OH$), 4.71–4.75 (2H, m, 5′-H), 4.95–5.0 (1H, m, 4′-H), 5.78 (1H, t, $J$ = 4.1 Hz, 3′-H), 5.98 (1H, t, $J$ = 3.2 Hz, 2′-H), 6.18 (1H, d, $J$ = 3.2 Hz, 1′-H), 7.26–8.10 (16H, m, 6-H, $H_{arom}$).

$^{13}$C NMR ($CDCl_3$/TMS): $\delta$ = 52.43 (4 × $CH_2$), 52.60 ($CH_2N$), 57.24, 59.06 ($CH_2CH_2OH$), 63.84 (C-5′), 77.42 (C-3′), 80.48 (C-2′), 83.29 (C-4′), 91.81 (C-1′), 110.77 (C-5), 128.28, 128.49, 128.84, 129.61, 129.69, 129.75, 129.89, 132.99, 133.19, 133.44 ($C_{arom}$), 136.78 (C-6), 149.89 (C-2), 163.04 (C-4), 165.08, 165.37, 166.22 (3 × C=O).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 699 ($M + H^+$, 3).

*1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-5-(4-benzylpiperazinomethyl)uracil* (**7g**): Yield: 33 mg (0.4%).

$^1$H NMR ($CDCl_3$/TMS): $\delta$ = 2.38–2.51 (8H, m, $CH_2$), 3.20–3.35 (2H, m, $CH_2N$), 3.42 (2H, s, $NCH_2Ph$), 4.70–4.73 (2H, m, 5′-H), 4.96–5.01 (1H, m, 4′-H), 5.78 (1H, t, $J$ = 3.8 Hz, 3′-H), 6.00 (1H, t, $J$ = 3.4 Hz, 2′-H), 6.16 (1H, d, $J$ = 3.3 Hz, 1′-H), 7.22–8.11 (21H, m, 6-H, $H_{arom}$).

$^{13}$C NMR ($CDCl_3$/TMS): $\delta$ = 52.66, 52.81 ($CH_2$), 62.71 ($NCH_2Ph$), 63.86 (C-5′), 77.11 (C-3′), 80.51 (C-2′), 83.33 (C-4′), 91.89 (C-1′), 111.00 (C-5), 126.88, 128.04, 128.34, 128.51, 129.00, 129.36, 129.69, 129.78, 129.89, 133.15, 133.75, 137.89 ($C_{arom}$), 138.63 (C-6), 149.93 (C-2), 163.15 (C-4), 165.23, 165.37, 165.97 (3 × C=O).

FAB MS (3-Nitrobenzyl alcohol): $m/z$ (%) = 745 ($M + H^+$, 48).

*2,3,5-Tri-O-benzoyl-1-O-methyl-1-(5-methyluracil-1-yl)-D-arabinitol* (**9b**): Yield: 0.42 g (3.3%); mp 97°C.

| | | | | |
|---|---|---|---|---|
| $C_{32}H_{30}N_2O_{10} \cdot 0.5H_2O$ | calc. | C 62.84 | H 5.11 | N 4.58 |
| (611.6) | found | 62.90 | 5.26 | 4.34 |

$^1$H NMR (DMSO-$d_6$/TMS): $\delta$ = 1.78 (1H, s, $CH_3$), 3.34 (3H, s, $OCH_3$), 3.08–4.13 (1H, m, 4′-H), 4.27 (1H, dd, $J$ = 11.7, 5.2 Hz, 5′-H), 4.40 (1H, dd, $J$ = 11.5, 3.5 Hz, 5′-H), 5.69–5.91 (4H, m, 1′-H, 2′-H, 3′-H, 4′-OH), 7.45–8.1 (16H, m, 6-H, $H_{arom}$), 11.17 (1H, s, NH).

$^{13}$C NMR ($CDCl_3$/TMS): $\delta$ = 12.30 (q, $CH_3$), 57.1 (q, $OCH_3$), 65.53 (t, C-5′), 68.18, 70.79, 71.10 (3 × d, C-2′, C-3′, C-4′), 83.65 (d, C-1′), 111.76 (s, C-5), 128.08, 128.21, 128.59, 128.61, 128.77, 129.49, 129.65, 129.84, 129.94, 133.02, 133.92, 134.41 ($C_{arom}$), 133.61 (ddq, C-6), 151.08 (s, C-2), 163.23 (s, C-4), 165.34, 165.89, 166.60 (3 × C=O).

FAB MS (glycerol): $m/z$ (%) = 603 ($M + H^+$,1)

*2,3,5-Tri-O-benzoyl-(5-hexyluracil-1-yl)-1-O-methyl-D-arabinitol* (**9c**): The more polar compound; yield: 0.193 g (2.7%); mp 123–124°C.

| | | | | |
|---|---|---|---|---|
| $C_{37}H_{40}N_2O_{10}$ | calc. | C 66.06 | H 5.99 | N 4.16 |
| (672.7) | found | 65.92 | 5.99 | 4.17 |

$^1$H NMR ($CDCl_3$/TMS): $\delta$ = 0.81 (3H, t, $J$ = 6.8 Hz, $CH_3$), 1.03–1.24 (8H, m, $CH_2$), 1.95–2.00 (2H, m, $CH_2$), 3.29 (3H, s, $OCH_3$), 3.97 (1H, d, $J$ = 5.5 Hz, 4′-OH), 4.27 (1H, m, 4′-H), 4.37 (1H, dd, $J$ = 11.7, 5.4 Hz, 5′-H), 4.60 (1H, dd, $J$ = 11.6, 2.7 Hz, 5′-H), 5.81 (1H, dd, $J$ = 8.8, 4 Hz, 3′-H), 5.94 (1H, t, $J$ = 3.9 Hz, 2′-H), 6.10 (1H, d, $J$ = 3.2 Hz, 1′-H), 7.08 (1H, s, 6-H), 7.38–8.04 (15H, m, $H_{arom}$), 9.28 (1H, s, NH).

$^{13}$C NMR ($CDCl_3$/TMS): $\delta$ = 13.89 ($CH_3$), 22.32, 26.45, 27.84, 28.68, 31.24 ($CH_2$), 57.25 ($OCH_3$), 65.62 (C-5′), 68.53, 70.51, 71.76 (C-2′, C-3′, C-4′), 85.65 (C-1′), 115.74 (C-5), 128.21, 128.31, 128.46, 129.26, 129.45, 129.66, 129.83, 132.99, 133.20, 133.63 ($C_{arom}$), 133.93 (C-6), 150.75 (C-2), 163.12 (C-4), 165.38, 165.63, 166.56 (3 × C=O).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 673 ($M + H^+$, 11).

The less polar compound, yield: 2.34 g (33%); mp 140–142°C.

$C_{37}H_{40}N_2O_{10}$ (672.7) calc. C 66.06 H 5.99 N 4.16 found 66.10 5.79 4.14

$^1H$ NMR ($CDCl_3$/TMS): $\delta$ = 0.88 (3H, t, $J$ = 6.3 Hz, $CH_3$), 1.26–1.45 [8H, m, $(CH_2)_4$], 2.21–2.28 (2H, m, $CH_2$), 3.33 (3H, s, $OCH_3$), 3.58 (1H, s, 4′-OH), 4.37 (1H, dd, $J$ = 11.9, 5.6 Hz, 5′-H), 4.55 (1H, dd, $J$ = 11.9, 2.9 Hz, 5′-H), 5.78–5.94 (3H, m, 1′-H, 2′-H, 3′-H), 7.18 (1H, s, 6-H), 7.36–8.11 (15H, m, $H_{arom}$), 8.50 (1H, s, NH).

$^{13}C$ NMR ($CDCl_3$/TMS): $\delta$ = 13.96 ($CH_3$), 22.45, 26.68, 28.10, 28.65, 31.44 ($CH_2$), 57.08($OCH_3$), 65.48 (C-5′), 68.13, 70.72, 71.00 (C-2′, C-3′, C-4′), 83.52 (C-1′), 116.23 (C-5), 128.0, 128.23, 128.60, 128.62, 128.73, 129.46, 129.65, 129.86, 129.94, 133.05, 133.64, 133.98 ($C_{arom}$), 134.14 (C-6), 150.98 (C-2), 162.78 (C-4), 165.36, 166.91, 166.62 (3 × C=O).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 673 ($M + H^+$, 7).

*2,3,5-Tri-O-benzoyl-1-[5-(4-benzylpiperazino)uracil-1-yl]-1-O-methyl-*D*-arabinitol* (**9d**): Yield: 0.19 g (2.4%); mp 103–107°C.

$C_{42}H_{42}N_4O_{10} \cdot 0.5H_2O$ (771.8) calc. C 65.36 H 5.62 N 7.26 found 65.49 5.61 6.99

$^1H$ NMR ($CDCl_3$/TMS): $\delta$ = 2.56 (4H, s, $CH_2$), 2.84–3.00 (4H, m, $CH_2$), 3.30 (3H, s, $OCH_3$), 3.53 (3H, s, 4′-OH, $CH_2Ph$), 4.12 (1H, m, 4′-H), 4.35 (1H, dd, $J$ = 11.9, 5.6 Hz, 5′-H), 4.54 (1H, dd, $J$ = 11.9, 3.0 Hz, 5′-H), 5.77–5.94 (3H, m, 1′-H, 2′-H, 3′-H), 7.25 (1H, s, 6-H), 7.24–8.07 (20H, m, $H_{arom}$), 8.10 (1H, s, NH).

$^{13}C$ NMR ($CDCl_3$/TMS): $\delta$ = 49.81 ($CH_2$), 52.33 ($CH_2$), 57.00 ($OCH_3$), 62.62 ($NCH_2Ph$), 65.45 (C-5′), 68.05, 70.66, 70.80 (C-2′, C-3′, C-4′), 83.66 (C-1′), 122.09 (C-5), 126.98, 128.01, 128.08, 128.18, 128.55, 128.71, 128.74, 129.08, 129.43, 129.60, 129.82, 129.91, 132.97, 133.55, 133.85 ($C_{arom}$), 137.54 (C-5), 149.98 (C-2), 160.02 (C-4), 165.33, 165.75, 166.55 (3 × C=O).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 763 ($M + H^+$, 48).

*2,3,5-Tri-O-benzoyl-1-O-methyl-1-[5-(4-methylpiperazinomethyl)-uracil-1-yl]-*D*-arabinitol* (**9e**): The more polar compound; yield: 3.4% (from $^1H$ NMR of **7e** + **9e**).

$^1H$ NMR ($CDCl_3$/TMS): $\delta$ = 2.19 (3H, s, $CH_3$), 2.38–2.48 (8H, m, $CH_2$), 3.33 (3H, s, $OCH_3$), 4.31–4.37 (2H, m, 5′-H), 4.51–4.56 (1H, m, 4′-H), 5.74–6.01 (3H, m, 1′-H, 2′-H, 3′-H), 7.31 (1H, s, 6-H), 7.35–8.11 (16H, m, $H_{arom}$).

$^{13}C$ NMR ($CDCl_3$/TMS): $\delta$ = 45.60 ($CH_3$), 52.33 (2 × $CH_2$), 52.82 ($CH_2$), 54.46 (2 × $CH_2$), 57.12 ($OCH_3$), 65.34 (C-5′), 69.80, 70.85, 71.46 (C-2′, C-3′, C-4′), 85.66 (C-1′), 110.88 (C-5), 128.28, 128.36, 128.54, 129.36, 129.47, 129.71, 129.91, 132.99, 133.44 ($C_{arom}$), 136.72 (C-6), 150.37 (C-2), 162.78 (C-4), 165.09, 165.98, 166.23 (3 × C=O).

The less polar compound; yield: 2.7 g (37%); mp 110–112.5°C.

$C_{37}H_{40}N_4O_{10} \cdot 0.5H_2O$ (709.8) calc. C 62.61 H 5.82 N 7.89 found 62.48 5.69 7.40

$^1H$ NMR ($CDCl_3$/TMS): $\delta$ = 2.25 (3H, s, $CH_3$), 2.47 (8H, s, $CH_2$), 3.17–3.28 (6H, m, 4′-OH, $OCH_3$, $CH_2$), 4.24–4.46 (3H, m, 4′-H, 5′-H), 5.80–5.86 (3H, m, 1′-H, 2′-H, 3′-H), 7.37–8.13 (16H, m, 6-H, $H_{arom}$).

$^{13}C$ NMR ($CDCl_3$/TMS): $\delta$ = 45.46 ($CH_3$), 52.55 (2 × $CH_2$), 53.06 ($CH_2$), 54.71 (2 × $CH_2$), 56.99 ($OCH_3$), 65.58 (C-5′), 69.12, 69.90, 71.27 (C-2′, C-3′, C-4′), 83.73 (C-1′), 111.50 (C-5), 127.03, 128.21, 128.51, 128.55, 128.99, 129.56, 129.73, 129.83, 132.91, 133.49 ($C_{arom}$), 136.98 (C-6), 150.96 (C-2), 163.01 (C-4), 164.68, 165.37, 166.10 (3 × C=O).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 701 ($M + H^+$, 100).

*2,3,5-Tri-O-benzoyl-1-(5-[4-(2-hydroxyethyl)piperazinomethyl]uracil-1-yl)-1-O-methyl-*D*-arabinitol* (**9f**): The more polar compound; yield: 0.7% (from $^1H$ NMR of **7e** + **9f**).

$^1H$ NMR ($CDCl_3$/TMS): $\delta$ = 2.28–2.48 (10H, m, $CH_2$), 3.30–3.37 (6H, m, 4′-OH, $CH_2$, $OCH_3$), 3.52–3.59 (3H, m, $CH_2OH$), 4.31–4.57 (3H, m, 4′-H, 5′-H), 5.77–5.79 (1H, m, 3′-H), 6.02 (1H, t, $J$ = 3.5 Hz, 2′-H), 6.18 (1H, d, $J$ = 3.4 Hz, 1′-H), 7.31–8.10 (16H, m, 6-H, $H_{arom}$).

$^{13}C$ NMR ($CDCl_3$/TMS): $\delta$ = 52.60 (4 × $CH_2$), 52.90 ($CH_2N$), 57.56, 57.62, 58.99 ($CH_2CH_2OH$, $OCH_3$), 65.32 (C-5′), 69.79, 70.88, 71.46 (C-2′, C-3′, C-4′), 85.72 (C-1′), 110.92 (C-5), 128.35, 128.54, 128.84, 129.43, 129.69, 129.75, 129.89, 132.99, 133.14, 133.8 ($C_{arom}$), 136.78 (C-6), 150.32 (C-2), 162.75 (C-4), 165.10, 165.37, 166.21 (3 × C=O).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 731 ($M + H^+$, 1.3).

The less polar compound; yield: 3.7 g (48%); mp 127–129°C.

$C_{38}H_{42}N_4O_{11} \cdot 0.25H_2O$ (735.3) calc. C 62.07 H 5.76 N 7.62 found 62.55 5.91 7.08

$^1H$ NMR ($CDCl_3$/TMS): $\delta$ = 2.04–2.56 (10H, m, $CH_2$), 3.20–3.33 (6H, m, 4′-OH, $CH_2$, $OCH_3$), 3.61 (3H, t, $J$ = 5.2 Hz, $CH_2OH$), 4.09–4.15 (1H, m, 4′-H), 4.36 (1H, dd, $J$ = 11.7, 5.7 Hz, 5′-H), 4.54 (1H, dd, $J$ = 11.8, 2.8 Hz, 5′-H), 5.80–5.94 (3H, m, 1′-H, 2′-H, 3′-H), 7.33–8.12 (16H, m, 6-H, $H_{arom}$).

$^{13}C$ NMR ($CDCl_3$/TMS): $\delta$ = 52.43 (4 × $CH_2$), 52.75 ($CH_2N$), 57.14, 57.56, 58.98 ($CH_2CH_2OH$, $OCH_3$), 65.48 (C-5′), 67.85, 70.77, 70.90 (C-2′, C-3′, C-4′), 83.55 (C-1′), 111.51 (C-5), 127.89, 128.21, 128.60, 128.67, 129.39, 129.61, 129.84, 129.88, 133.18, 133.66, 134.03 ($C_{arom}$), 137.04 (C-6), 150.85 (C-2), 162.73 (C-4), 165.34, 165.84, 166.57 (3 × C=O).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 731 ($M + H^+$, 68).

*2,3,5-Tri-O-benzoyl-1-[5-(4-benzylpiperazinyl)methyluracil-1-yl]-1-O-methyl-*D*-arabinitol* (**9g**): Yield: 27 mg (0.3%).

$^1H$ NMR ($CDCl_3$/TMS): $\delta$ = 2.47 (8H, s, $CH_2$), 3.22–3.51 (8H, m, 4′-OH, $NCH_2$, $OCH_3$, $CH_2Ph$), 4.10–4.15 (1H, m, 4′-H), 4.37 (1H, dd, $J$ = 11.9, 5.7 Hz, 5′-H), 5.54 (1H, dd, $J$ = 11.9, 2.9 Hz, 5′-H), 5.79–5.94 (3H, m, 1′-H, 2′-H, 3′-H), 7.25–8.11 (21H, 6-H, $H_{arom}$).

$^{13}C$ NMR ($CDCl_3$/TMS): $\delta$ = 52.58 ($NCH_2$), 52.80 ($CH_2N$), 57.14 ($OCH_3$), 62.72 ($NCH_2Ph$), 65.51 (C-5′), 68.06, 70.84, 71.04 (C-2′, C-3′, C-4′), 83.68 (C-1′), 111.75 (C-5), 126.90, 127.97, 128.07, 128.22, 128.60, 128.64, 128.78, 129.00, 129.50, 129.65, 129.86, 130.73, 133.03, 133.18, 133.98, 137.01 ($C_{arom}$), 137.98 (C-6), 150.87 (C-2), 162.62 (C-4), 165.37, 165.89, 166.58 (3 × C=O).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 777 ($M + H^+$, 100).

**1-(α-*D*-Arabinofuranosyl)-5-chlorouracil (8a); Typical Procedure for Deprotection of 7a–d:**

Compound **7a** (4 g, 6.78 mmol) was dissolved in a sat. solution of $NH_3$ in MeOH (100 mL) and stirred at r.t. for 24 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel with $CH_2Cl_2$/MeOH (95:5, v/v) to obtain compound **8a** as a hygroscopic foam; yield: 1.73 g (92%).

$C_9H_{11}ClN_2O_6 \cdot 0.5H_2O$ (287.7) calc. C 37.58 H 4.20 N 9.20 found 37.81 4.45 9.70

$^1H$ NMR (DMSO-$d_6$/TMS): $\delta$ = 3.47–3.59 (2H, m, 5′-H), 3.95 (1H, s, 3′-H), 4.12–4.22 (2H, m, 2′-H, 4′-H), 4.94 (1H, br s, 5′-OH), 5.45 (1H, br s, 3′-OH), 5.72 (2H, 2 × d, $J$ = 4.8, 1.9 Hz, 1′-H, 2′-OH), 8.03 (1H, s, 6-H), 11.85 (1H, s, NH).

$^{13}C$ NMR (DMSO-$d_6$/TMS): $\delta$ = 61.12 (C-5′), 74.98 (C-3′), 79.52 (C-2′), 87.55 (C-4′), 91.18 (C-1′), 106.63 (C-5), 138.53 (C-6), 149.51 (C-2), 158.93 (C-4).

EI MS: $m/z$ (%) = 278 ($M^+$, 2.5).

*1-(α-*D*-Arabinofuranosyl)-5-methyluracil* (**8b**): Compound **7b** (5.34 g, 9.37 mmol) yielded compound **8b** as a hygroscopic foam; yield: 1.86 g (77%).

$^1H$ NMR ($CD_3OD$/TMS) data were identical with those previously reported.[8,21]

$^{13}C$ NMR (DMSO-$d_6$/TMS): $\delta$ = 11.99 ($CH_3$), 61.13 (C-5′), 74.72 (C-3′), 79.15 (C-2′), 85.77 (C-4′), 89.31 (C-1′), 109.00 (C-5), 136.92 (C-6), 150.59 (C-2), 163.75 (C-4).

EI MS: $m/z$ (%) = 258 ($M^+$, 10.5).

*1-(α-*D*-Arabinofuranosyl)-5-hexyluracil* (**8c**): Compound **7c** (0.33 g, 0.516 mmol) afforded **8c**; yield: 0.130 g (77%).

$C_{15}H_{24}N_2O_6 \cdot 1.5H_2O$ (355.4) calc. C 50.70 H 6.81 N 7.88 found 50.48 7.03 7.65

$^1H$ NMR (DMSO-$d_6$/TMS): $\delta$ = 0.86 (3H, t, $J$ = 6.3 Hz, $CH_3$), 1.26–1.41 (8H, m, $CH_2$), 2.20 (2H, t, $J$ = 6.9 Hz, $CH_2$), 3.44–3.58

(2H, m, 5′-H), 3.92 (1H, s, 3′-H), 4.07–4.12 (2H, m, 2′-H, 4′-H), 4.92 (1H, s, 5′-OH), 5.45 (1H, s, 3′-OH), 5.66 (1H, d, $J$ = 4.9 Hz, 2′-OH), 5.73 (1H, d, $J$ = 4.5 Hz, 1′-H), 7.53 (1H, s, 6-H), 11.18 (1H, s, NH).

$^{13}$C NMR (DMSO-$d_6$/TMS): $\delta$ = 13.86 ($CH_3$), 21.96, 26.15, 28.09, 28.15, 30.96 ($CH_2$), 61.21 (C-5′), 75.02 (C-3′), 79.37 (C-2′), 86.31 (C-4′), 89.80 (C-1′), 113.27 (C-5), 137.04 (C-6), 150.47 (C-2), 163.40 (C-4).

EI MS: $m/z$ (%) = 328 ($M^+$, 8).

*1-(α-D-Arabinofuranosyl)-5-(4-benzylpiperazino)uracil* (**8d**): Compound **7d** (2.26 g, 3.09 mmol) afforded the title compound **8d** as a white solid; yield: 1.08 g (83%), mp 94.3–96.6°C.

| $C_{20}H_{26}N_4O_6 \cdot 2H_2O$ (454.5) | calc. | C 52.86 | H 6.65 | N 12.33 |
|---|---|---|---|---|
| | found | 53.27 | 6.30 | 12.47 |

$^1$H NMR (DMSO-$d_6$/TMS): $\delta$ = 2.46 (4H, s, $CH_2$), 2.85 (4H, s, $CH_2$), 3.50 (4H, s, 5′-H, $C\underline{H}_2Ph$), 4.10 (1H, s, 3′-H), 4.12 (2H, m, 2′H, 4′-H), 4.97 (1H, s, 5′-OH), 5.53 (1H, s, 3′-OH), 5.75 (1H, d, $J$ = 4.5 Hz, 2′-OH), 5.80 (1H, d, $J$ = 4.3 Hz, 1′-H), 7.11 (1H, s, 6-H), 7.25–7.33 (5H, m, $H_{arom}$), 11.34 (1H, s, NH).

$^{13}$C NMR (DMSO-$d_6$/TMS): $\delta$ = 49.62 ($CH_2$), 52.32 ($CH_2$), 61.29, 61.94 (C-5′, $\underline{C}H_2Ph$), 75.59 (C-3′), 79.77 (C-2′), 87.10 (C-4′), 90.58 (C-1′), 125.42 (C-5), 125.42, 126.93, 128.15, 128.80, 138.1 (C-6, $C_{arom}$), 149.41 (C-2), 160.44 (C-4).

EI MS: $m/z$ (%) = 418 ($M^+$, 12).

**1-*O*-Methyl-1-(5-methyluracil-1-yl)-D-arabinitol (10b); Typical Procedure for Preparation of 10b–f:**

Compound **9b** (0.15 g, 0.25 mmol) was dissolved in a sat. solution of $NH_3$ in MeOH (10 mL) and stirred at r.t. for 24 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel with $CH_2Cl_2$/MeOH (95:5, v/v) to obtain the pure compound **10b**; yield: 60 mg (82%).

$^1$H NMR (DMSO-$d_6$/TMS): $\delta$ = 1.79 (3H, s, $CH_3$), 3.16–3.57 (7H, m, 3′-H, 4′-H, 5′-H, $OCH_3$), 3.81–3.86 (1H, m, 2′-H), 4.27–4.35 (2H, m, 3′-OH, 5′-OH), 4.51 (1H, d, $J$ = 5.4 Hz, 4′-OH), 4.92 (1H, d, $J$ = 6.9 Hz, 2′-OH), 5.47 (1H, d, $J$ = 6.2 Hz, 1′-H), 7.35 (1H, s, 6-H), 11.30 (1H, s, NH).

$^{13}$C NMR (DMSO-$d_6$/TMS): $\delta$ = 12.20 ($CH_3$), 56.18 ($OCH_3$), 63.17 (C-5′), 69.94, 70.43, 70.98 (C-2′, C-3′, C-4′), 86.5 (C-1′), 109.18 (C-5), 135.57 (C-6), 151.12 (C-2), 163.84 (C-4).

EI MS: $m/z$ (%) = 290 ($M^+$, 0.8).

HRMS: $m/z$, $C_9H_{11}N_2O_6$, calc.: 290.1114; found: 290.1107.

*1-(5-Hexyluracil-1-yl)-1-O-methyl-D-arabinitol* (**10c**): **9c** (the less polar compound) (2 g, 2.98 mmol) afforded **10c** as a white solid; yield: 0.92 g (86%); mp 108–110°C.

| $C_{16}H_{28}N_2O_7$ (360.4) | calc. | C 53.32 | H 7.83 | N 7.77 |
|---|---|---|---|---|
| | found | 53.33 | 7.80 | 7.40 |

$^1$H NMR (DMSO-$d_6$/TMS): $\delta$ = 0.86 (3H, t, $J$ = 6.3 Hz, $CH_3$), 1.25–1.41 (8H, m, $CH_2$), 2.17–2.23 (2H, m, $CH_2$), 3.18–3.55 (7H, m, 3′-H, 4′-H, 5′-H, $OCH_3$), 3.82–3.87 (1H, m, 2′-H), 4.23–4.30 (2H, m, 3′-OH, 5′-OH), 4.45 (1H, d, $J$ = 5.4 Hz, 4′-OH), 4.87 (1H, d, $J$ = 7.0 Hz, 2′-OH), 5.48 (1H, d, $J$ = 6.0 Hz, 1′-H), 7.25 (1H, s, 6-H), 11.23 (1H, s, NH).

$^{13}$C NMR (DMSO-$d_6$/TMS): $\delta$ = 13.78 ($CH_3$), 21.89, 26.09, 27.82, 27.96, 30.89 ($CH_2$), 56.03 ($OCH_3$), 63.16 (C-5′), 70.06, 70.47, 71.00 (C-2′, C-3′, C-4′), 86.44 (C-1′), 113.17 (C-5), 136.44 (C-6), 150.88 (C-2), 163.23 (C-4).

EI MS: $m/z$ (%) = 360 ($M^+$, 0.7).

*1-[5-(4-Benzylpiperazino)uracil-1-yl]-1-O-methyl-*D-arabinitol (**10d**): Yield: 20 mg (56%).

$^1$H NMR ($CD_3OD$/TMS): $\delta$ = 2.71 (4H, br s, $CH_2$), 3.08 (4H, br s, $CH_2$), 3.39–3.41 (1H, m, 3′-H), 3.45 (3H, s, $OCH_3$), 3.68–3.91 (5H, m, 4′-H, 5′-H, $C\underline{H}_2Ph$), 4.10 (1H, d, $J$ = 8.5 Hz, 2′-H), 5.76 (1H, d, $J$ = 8.5 Hz, 1′-H), 7.03 (1H, s, 6-H), 7.35–7.40 (5H, m, $H_{arom}$).

$^{13}$C NMR ($CD_3OD$/TMS): $\delta$ = 51.19 ($CH_2$), 54.05 ($CH_2$), 57.38 ($OCH_3$), 64.14 ($\underline{C}H_2Ph$), 65.01 (C-5′), 71.30, 71.51, 72.93 (C-2′, C-3′, C-4′), 88.03 (C-1′), 125.86 (C-5), 128.79, 129.64, 130.03, 131.01 ($C_{arom}$), 138.43 (C-6), 153.66 (C-2), 163.5 (C-4).

EI MS: $m/z$ (%) = 450 ($M^+$, 0.3).

*1-O-Methyl-1-[5-(4-methylpiperazinomethyl)uracil-1-yl]-D-arabinitol* (**10e**): **9e** (the less polar compound) (2 g, 2.85 mmol) afforded **10e**; yield: 0.87 g (79%).

$^1$H NMR ($CD_3OD$/TMS): $\delta$ = 2.33 (3H, s, $CH_3$), 2.60 (8H, br s, $CH_2$), 3.37–3.45 (6H, m, 3′-H, $CH_2$, $OCH_3$), 3.71–3.90 (3H, m, 4′-H, 5′-H), 4.08 (1H, d, $J$ = 8.3 Hz, 2′-H), 5.80 (1H, d, $J$ = 8.3 Hz, 1′-H), 7.65 (1H, s, 6-H).

$^{13}$C NMR ($CD_3OD$/TMS): $\delta$ = 46.23 ($CH_3$); 53.27 ($CH_2$), 54.15 ($CH_2N$), 55.87 ($CH_2$), 57.29 ($OCH_3$), 65.26 (C-5′), 71.43, 71.61, 72.69 (C-2′, C-3′, C-4′), 87.85 (C-1′), 111.25 (C-5), 141.58 (C-6), 154.80 (C-2), 166.91 (C-4).

EI MS: $m/z$ (%) = 388 ($M^+$, 0.4).

HRMS: $m/z$, $C_{16}H_{28}N_4O_7$, calc.: 388.1958; found: 388.1963.

*1-(5-[4-(2-Hydroxyethyl)piperazinomethyl]uracil-1-yl)-1-O-methyl-*D-*arabinitol* (**10f**): **9f** (the less polar compound) (2 g, 2.74 mmol) afforded **10f**; yield: 0.95 g (83%).

$^1$H NMR ($CD_3OD$/TMS): $\delta$ = 2.60–2.69 (10H, m, $CH_2$, $C\underline{H}_2CH_2OH$), 3.39–3.46 (6H, m, 3′-H, $NCH_2$, $OCH_3$), 3.72–3.93 (5H, m, 4′-H, 5′-H, $C\underline{H}_2OH$), 3.95 (1H, d, $J$ = 8.3 Hz, 2′-H), 5.70 (1H, d, $J$ = 8.4 Hz, 1′-H), 7.67 (1H, s, 6-H).

$^{13}$C NMR ($CD_3OD$/TMS): $\delta$ = 53.45 ($CH_2$), 54.15 ($NCH_2$), 54.51 ($CH_2$), 57.29 ($OCH_3$), 60.10, 61.52 ($CH_2$), 65.33 (C-5′), 71.45, 71.67, 72.77 (C-2′, C-3′, C-4′), 87.87 (C-1′), 111.23 (C-5), 141.79 (C-6), 154.08 (C-2), 166.08 (C-4).

**5-Substituted α-D-Arabinofuranosyl-4-thiouracils 14a,b,d; General Procedure:**

A mixture of **7a,b,d** (0.88 mmol) in dry toluene (30 mL) was treated with Lawesson's Reagent (0.18 g, 0.45 mmol) and the resulting solution was heated at 80°C with stirring for 4–15 h under $N_2$. The solvent was removed in vacuo and the residue purified by chromatography on silica gel with $CHCl_3$ to give the pure compounds **14a, b, d** as yellow solids.

*1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-5-chloro-4-thiouracil* (**14a**): Yield: 0.38 (74%); mp 113–115°C.

| $C_{30}H_{23}ClN_2O_8S$ (607.0) | calc. | C 59.36 | H 3.82 | N 4.61 |
|---|---|---|---|---|
| | found | 59.33 | 3.97 | 4.45 |

$^1$H NMR ($CDCl_3$/TMS): $\delta$ = 4.65 (1H, dd, $J$ = 11.9, 5.0 Hz, 5′-H), 4.79 (1H, dd, $J$ = 11.9, 6.3 Hz, 5′-H), 4.99–5.05 (1H, m, 4′-H), 5.76 (1H, t, $J$ = 2.5 Hz, 3′-H), 5.89 (1H, t, $J$ = 2.3 Hz, 2′-H), 6.23 (1H, d, $J$ = 2.5 Hz, 1′-H), 7.26 (1H, s, 6-H), 7.37–8.11 (16H, m, 6-H, $H_{arom}$), 9.75 (1H, s, NH).

$^{13}$C NMR ($CDCl_3$/TMS): $\delta$ = 63.50 (C-5′), 77.03 (C-3′), 80.54 (C-2′), 84.70 (C-4′), 91.94 (C-1′), 118.99 (C-5), 128.19, 128.25, 128.54, 128.77, 128.88, 129.34, 129.86, 130.17, 132.54, 133.44, 134.11, 134.15 (C-6, $C_{arom}$), 146.49 (C-6), 165.02, 165.20, 166.09 (3 × C=O), 184.60 (C-4).

IR (KBr): $\nu$ = 1178 $cm^{-1}$ (C=S).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 607 ($M + H^+$, 17).

*1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-5-methyl-4-thiouracil* (**14b**): Yield: 0.43 g (84%); mp 103–105°C.

$^1$H NMR ($CDCl_3$/TMS): $\delta$ = 2.07 (3H, s, $CH_3$), 4.67 (1H, dd, $J$ = 11.9, 4.9 Hz, 5′-H), 4.77 (1H, dd, $J$ = 11.9, 6.0 Hz, 5′-H), 4.98–5.04 (1H, m, 4′-H), 5.76 (1H, t, $J$ = 2.8 Hz, 3′-H), 5.95 (1H, t, $J$ = 2.6 Hz, 2′-H), 6.22 (1H, d, $J$ = 2.7 Hz, 1′-H), 7.39 (1H, s, 6-H), 7.41–8.11 (15H, m, $H_{arom}$), 9.91 (1H, s, NH).

$^{13}$C NMR ($CDCl_3$/TMS): $\delta$ = 17.12 ($CH_3$), 63.58 (C-5′), 77.14 (C-3′), 80.33 (C-2′), 83.97 (C-4′), 91.59 (C-1′), 119.36 (C-5), 128.21, 128.21, 128.35, 128.55, 128.60, 129.28, 129.70, 129.93, 131.79, 133.21, 133.86 (C-6, $C_{arom}$), 147.44 (C-2), 165.00, 165.07, 165.97 (3 × C=O), 190.44 (C-4).

IR (KBr): $\nu$ = 1179 $cm^{-1}$ (C=S).

EI MS: $m/z$ (%) = 586 ($M^+$, 0.3).

*1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-5-(4-benzylpiperazino)-4-thiouracil* (**14d**): Yield: 0.22 g (43%); mp 105–108°C.

$^1$H NMR ($CDCl_3$/TMS): $\delta$ = 2.52 (4H, br s, $CH_2$), 2.88–2.97 (4H, m, $CH_2$), 3.40 (1H, d, $J$ = 7.8 Hz, $CH_2Ph$), 3.51 (1H, d, $J$ = 7.8 Hz, $CH_2Ph$), 4.66 (1H, dd, $J$ = 11.9, 4.8 Hz, 5'-H), 4.75 (1H, dd, $J$ = 11.9, 5.7 Hz, 5'-H), 4.95–4.98 (1H, m, 4'-H), 5.72 (1H, t, $J$ = 2.9 Hz, 3'-H), 5.91 (1H, t, $J$ = 2.6 Hz, 2'-H), 6.20 (1H, d, $J$ = 2.9 Hz, 1'-H), 6.90 (1H, s, 6-H), 7.28–8.09 (20H, m, $H_{arom}$).

$^{13}$C NMR ($CDCl_3$/TMS): $\delta$ = 50.86 ($CH_2$), 52.66 ($CH_2$), 62.72 ($NCH_2Ph$), 63.49 (C-5'), 77.52 (C-3'), 80.54 (C-2'), 83.78 (C-4'), 91.79 (C-1'), 123.76 (C-5), 127.00, 128.11, 128.18, 128.29, 128.35, 128.52, 128.58, 129.17, 129.22, 129.70, 129.91, 133.121, 133.78, 133.82, 165.96 ($C_{arom}$), 137.81 (C-6), 146.28 (C-2), 165.05, 165.30, 165.96 (3 × C=O), 186.51 (C=S).

IR (KBr): $\nu$ = 1178 $cm^{-1}$ (C=S).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 747 ($M + H^+$, 20).

**1-(α-D-Arabinofuranosyl)-5-chloro-4-thiouracil (15a); Typical Procedure:**

The compound **14a** (0.18 g, 0.305 mmol) was dissolved in sat. solution of $NH_3$ in MeOH (10 mL) and stirred at r.t. for 24 h. The solvent was removed in vacuo and the residue chromatographed on silica gel with $CH_2Cl_2$/MeOH (95:5, v/v) to give the title compound **15a** as a yellow solid; yield: 0.06 g (67%); mp 122–124°C.

| | | | | |
|---|---|---|---|---|
| $C_9H_{11}ClN_2O_5S \cdot 1H_2O$ | calc. | C 34.57 | H 4.19 | N 8.96 |
| (312.73) | found | 34.41 | 3.73 | 8.50 |

$^1$H NMR (DMSO-$d_6$/TMS): $\delta$ = 3.54 (2H, s, 5'-H), 3.95 (1H, s, 3'-H), 4.16, 4.27 (2H, 2 × s, 2'-H, 4'-H), 5.03 (1H, s, 5'-OH), 5.47 (1H, s, 3'-OH), 5.67 (1H, s, 2'-OH), 5.80 (1H, s, 1'-H), 8.05 (1H, s, 6-H), 13.10 (1H, s, NH).

$^{13}$C NMR (DMSO-$d_6$/TMS): $\delta$ = 61.18 (C-5'), 75.04 (C-3'), 79.51 (C-2'), 88.78 (C-4'), 92.27 (C-1'), 116.37 (C-5), 135.45 (C-6), 147.03 (C-2), 185.30 (C=S).

IR (KBr): $\nu$ = 1200 $cm^{-1}$ (C=S).

EI MS: $m/z$ (%) = 294 ($M^+$, 0.9).

*1-(α-D-Arabinofuranosyl)-5-methyl-4-thiouracil* (**15b**): The compound **14b** (0.25 g, 0.427 mmol) was treated with $NH_3$ in MeOH (15 mL) as described for **15a** to afford the title compound **15b** as a yellow gum; yield: 0.10 g (85%).

| | | | | |
|---|---|---|---|---|
| $C_{10}H_{14}N_2O_5S \cdot 0.5H_2O$ | calc. | C 42.40 | H 5.34 | N 9.89 |
| (383.3) | found | 42.77 | 5.40 | 9.98 |

$^1$H NMR (DMSO-$d_6$/TMS): $\delta$ = 1.99 (3H, s, $CH_3$), 3.44–3.60 (2H, m, 5'-H), 3.92–3.97 (1H, m, 3'-H), 4.05–4.22 (2H, m, 2'-H, 4'-H), 4.92 (1H, t, $J$ = 5.4 Hz, 5'-OH), 5.40 (1H, d, $J$ = 4.0 Hz, 3'-OH), 5.69 (2H, m, 1'-H, 2'-OH), 7.7 (1H, s, 6-H), 12.65 (1H, s, NH).

$^{13}$C NMR (DMSO-$d_6$/TMS): $\delta$ = 16.63 ($CH_3$), 61.12 (C-5'), 74.76 (C-3'), 79.35 (C-2'), 86.93 (C-4'), 90.61 (C-1'), 117.21 (C-5), 134.11 (C-6), 147.84 (C-2), 190.64 (C=S).

IR (KBr): $\nu$ = 1205 $cm^{-1}$ (C=S).

EI MS: $m/z$ (%) = 274 ($M^+$, 1.4).

1-(α-D-*Arabinofuranosyl)-5-(4-benzylpiperazino)-4-thiouracil* (**15d**): In the same manner as described for the preparation of compound **15a**. The compound **14d** (0.10 g, 0.134 mmol) was treated with $NH_3$ in MeOH (15 mL) to afford the title compound **15d** as a yellow solid; yield: 43 mg (74%); mp 118–120°C.

| | | | | |
|---|---|---|---|---|
| $C_{20}H_{26}N_4O_5S$ | calc. | C 55.28 | H 6.03 | N 12.89 |
| (434.5) | found | 55.02 | 6.11 | 12.63 |

$^1$H NMR ($CD_3OD$/TMS): $\delta$ = 2.80–2.99 (8H, m, $CH_2$), 3.81–3.83 (4H, m, 5'-H, $CH_2Ph$), 4.17 (1H, t, $J$ = 2.8 Hz, 3'-H), 4.26 (1H, t, $J$ = 2.2 Hz, 2'-H or 4'-H), 4.42–4.47 (1H, m, 2'-H or 4'-H), 5.94 (1H, d, $J$ = 2.1 Hz, 1'-H), 7.39–7.50 (5H, m, $H_{arom}$), 7.70 (1H, s, 6-H).

$^{13}$C NMR ($CD_3OD$/TMS): $\delta$ = 52.64 ($CH_2$), 54.30 ($CH_2$), 63.53 (C-5', $CH_2Ph$), 78.15 (C-3'), 82.79 (C-2'), 90.80 (C-4'), 95.5 (C-1'), 129.28, 129.83, 131.34, 134.49 ($C_{arom}$).

IR (KBr): $\nu$ = 1269 $cm^{-1}$ (C=S).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 435 ($M + H^+$, 5).

**1-(2,3,5-Tri-O-benzoyl-α-D-arabinofuranosyl)-5-chloro-2,4-dithiouracil (16) and 1-(2,3-Di-O-benzoyl-5-O-thiobenzoyl-α-D-arabinofuranosyl)-5-chloro-2,4-dithiouracil (17):**

To a mixture of **14a** (0.20 g, 0.339 mmol) in dry toluene (30 mL) was added Lawesson's Reagent (0.18 g, 0.45 mmol),and the solution was heated with stirring under $N_2$ at 80°C for 24 h. The solvent was removed in vacuo and the residue purified by chromatography on silica gel with $CHCl_3$ to give **16** and **17**.

**16** (the less polar compound): Yield: 60 mg (29%) as a yellow solid; mp 118–119°C.

$^1$H NMR ($CDCl_3$/TMS): $\delta$ = 4.59 (1H, dd, $J$ = 11.7, 5.5 Hz, 5'-H), 4.87 (1H, dd, $J$ = 11.7, 7.2 Hz, 5'-H), 5.07–5.12 (1H, m, 4'-H), 5.64 (1H, s, 3'-H), 5.95 (1H, br s, 2'-H), 6.89 (1H, d, $J$ = 1.4 Hz, 1'-H), 7.39–8.11 (16H, m, 6-H, $H_{arom}$).

$^{13}$C NMR ($CDCl_3$/TMS): $\delta$ = 63.25 (C-5'), 76.51 (C-3'), 80.11 (C-2'), 86.39 (C-4'), 95.12 (C-1'), 123.61 (C-5), 127.93, 128.21, 128.41, 128.67, 128.83, 129.13, 129.65, 129.79, 130.00, 130.81, 133.36, 133.93, 134.12 (C-6, $C_{arom}$), 164.27, 164.59, 165.96 (3 × C=O), 170.00 (C-2), 180.79 (C-4).

IR (KBr): $\nu$ = 1178 $cm^{-1}$ (C=S).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 623 ($M + H^+$, 0.6).

**17** (the more polar compound): Yield: 30 mg (14%) as a yellow solid; mp 122–123°C.

$^1$H NMR ($CDCl_3$/TMS): $\delta$ = 4.96 (1H, dd, $J$ = 10.9, 4.4 Hz, 5'-H), 5.17–5.29 (2H, m, 4'-H, 5'-H), 5.66 (1H, s, 3'-H), 6.00 (1H, s, 2'-H), 6.90 (1H, s, 1'-H), 7.38 (1H, s, 6-H), 7.41–8.27 (15H, m, $H_{arom}$), 11.01 (1H, s, NH).

$^{13}$C NMR ($CDCl_3$/TMS): $\delta$ = 70.03 (C-5'), 76.48 (C-3'), 79.78 (C-2'), 86.12 (C-4'), 95.11 (C-1'), 123.59 (C-5), 128.02, 128.15, 128.49, 128.65, 128.86, 128.95, 129.79, 130.03, 130.84, 133.18, 133.99, 134.18 ($C_{arom}$), 137.54 (C-6), 164.12, 164.58 (2 × C=O), 169.93 (C-2), 180.80 (C-4), 210.53 (C=S).

IR (KBr): $\nu$ = 1179 $cm^{-1}$ (C=S).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 640 ($M + H^+$, 0.4).

**1-(α-D-Arabinofuranosyl)-5-chloro-2,4-dithiouracil (18):**

A mixture of **16** (60 mg, 0.081 mmol) and **17** (30 mg, 0.039 mmol) was dissolved in sat. solution of $NH_3$ in MeOH(10 mL) and stirred at r.t. for 24 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel with $CH_2Cl_2$/MeOH (95:5, v/v) to give the title compound **18** as a yellow gum; yield: 21 mg (57%).

$^1$H NMR (DMSO-$d_6$/TMS): $\delta$ = 3.54–3.59 (2H, m, 5'-H), 3.95–3.99 (1H, m, 3'-H), 4.21 (1H, m, 2'-H or 4'-H), 4.42–4.47 (1H, m, 2'-H or 4'-H), 5.12–5.15 (1H, m, 5'-OH), 5.44–5.45 (1H, d, $J$ = 4.9 Hz, 3'-OH), 5.89 (1H, d, $J$ = 5.2 Hz, 2'-OH), 6.21 (1H, s, 1'-H), 7.92 (1H, s, 6-H), 14.25 (1H, s, NH).

$^{13}$C NMR (DMSO-$d_6$/TMS): $\delta$ = 61.31 (C-5'), 75.42 (C-3'), 81.00 (C-2'), 91.31 (C-4'), 97.44 (C-1'), 121.93 (C-5), 134.07 (C-6), 170.00 (C-2).

FAB MS (3-nitrobenzyl alcohol): $m/z$ (%) = 311 ($M + H^+$, 2).

*The Danish Medical Research Council is gratefully acknowledged for their support.*

(1) Séquin, U. *Experientia* **1973**, *29*, 1059.
(2) Yamaguchi, T.; Saneyoshi, M. *Chem. Pharm. Bull.* **1984**, *32*, 1441.
(3) Bennett, L. L.; Shannon, W. M.; Allan, P. W.; Arnett, G. *Ann. N. Y. Acad. Sci.* **1975**, *225*, 342.
(4) Nishimura, T.; Shimizu, B. *Chem. Pharm. Bull.* **1965**, *13*, 803.
(5) Kulikowski, T.; Zawadzki, Z.; Shugar, D. *J. Med. Chem.* **1979**, *22*, 647.
(6) Montgomery, J. A.; Thomas, M. J. *J. Heterocycl. Chem.* **1979**, *16*, 353.
(7) Sharma, R. A.; Goodman, M. M.; Bobek, M. *J. Carbohydr. Nucleosides, Nucleotides* **1980**, *7*, 21.

(8) Chow, K.; Danishefsky, S. *J. Org. Chem.* **1990**, *55*, 4211.
(9) Fletcher, H.G. In *Methods in Carbohydrate Chemistry*; Whistler, R.L.; Wolfrom, M.L. Eds.; Academic Press: New York, 1963; Vol. 2, p. 228.
(10) Pedersen, H.; Pedersen, E.B.; Nielsen, C.M. *Heterocycles*, **1992**, *34*, 265.
Motawia, M.S.; Jørgensen, P.T.; Larnkjær, A.; Pedersen, E.B.; Nielsen, C. *Monatsh. Chem.*, in press.
Kjærsgaard, U.; Pedersen, E.B.; Nielsen, C. *Acta Chem. Scand.*, in press.
(11) Wittenburg, E. *Z. Chem.* **1964**, *4*, 303.
(12) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.
(13) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3654.
(14) Baker, B.R. *Ciba Found. Symp., Chem. Biol. Purines.* **1957**, 120.
(15) Bourgeois, W.; Seela, F. *J. Chem. Soc., Perkin Trans 1* **1991**, 279.
(16) Wolfrom, M.L.; Forster, A.B.; McWain, P.; Bebenbary, W.V.; Thompson, A. *J. Org. Chem.* **1961**, *26*, 3095.
(17) Pedersen, B.S.; Scheibye, S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223.
(18) Palomino, E.; Meltsner, B.R.; Kessel, D.; Horwitz, J.P. *J. Med. Chem.* **1990**, *33*, 258.
(19) Horwitz, J.P.; Chua, J.; DaRouge, M.A.; Noel, M.; Klundt, I.L. *J. Org. Chem.* **1966**, *31*, 205.
(20) Ueda, T.; Iida, Y.; Ikeda, K.; Mizuno, Y. *Chem. Pharm. Bull.* **1968**, *16*, 1788.
(21) Melnik, S.Y.; Miniker. T.D.; Yartseua, I.V. *Bioorg. Khim.* **1982**, *8*, 1094.