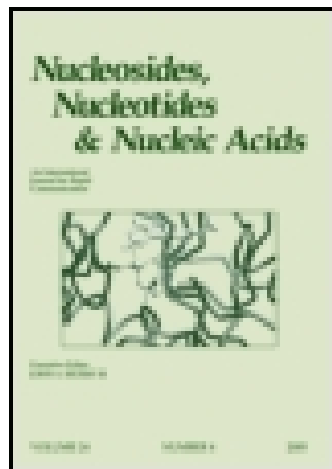


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Nucleosides. LIV¹ Synthesis and Properties of 3'-Azido- and 2',3'-Dideoxy-6,7-diphenyllumazine Nucleosides

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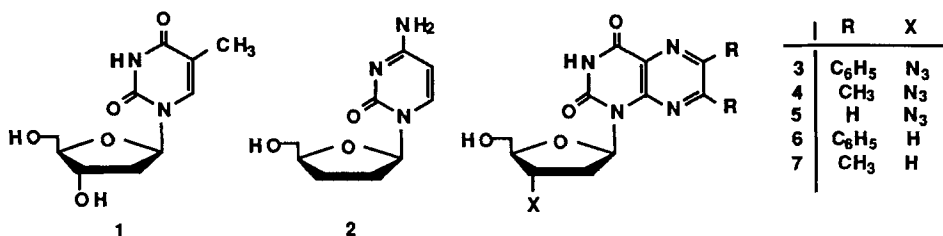
NUCLEOSIDES. LIV¹
**SYNTHESIS AND PROPERTIES OF 3'-AZIDO- AND 2',3'-DIDEOXY-
6,7-DIPHENYLLUMAZINE NUCLEOSIDES**

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Abstract. The best approach for the synthesis of 1-(3-azido-2,3-dideoxy- β -D-erythro-pentofuranosyl)lumazine (5) and its 6,7-dimethyl- (4) and 6,7-diphenyl derivatives (3) has been found in the interconversion of the corresponding 1-(2-deoxy- β -D-threo-pentofuranosyl)-lumazines. Monomethoxytritylation at the 5'-position (1 7, 3 4, 4 9) followed by mesylation at the 3'-OH group and subsequent nucleophilic displacement by lithium azide afforded 1 9, 2 9 and 4 7 which were deprotected by acid treatment to give 3-5 in good yields. The syntheses of 1-(2,3-dideoxy- β -D-glycero-pentofuranosyl)- 6,7-diphenyllumazine (6) and its 6,7-dimethyl derivative (7) were achieved from 1-(2-deoxy- β -D-erythro-pentofuranosyl)- 6,7-diphenyllumazine and the corresponding 6,7-dimethylumazine (2 6) via their 5'-O-p-toluoyl- (2 0, 3 0), and 3'-deoxy-3'-iodo derivatives (2 4, 3 1) to form, after radical dehalogenation and final deprotection, 6 and 7. The newly synthesized lumazine nucleosides have been characterized by elemental analyses, UV- and NMR spectra.

The rapid spread of AIDS has led to massive efforts to cure this disease. A number of nucleoside analogues has been found to show potent antiretroviral activity in vitro and some of these compounds, such as 3'-azido-3'-deoxythymidine (AZT) (1) and 2',3'-dideoxycytidine (2) have shown clinical benefit in AIDS patients^{2,3}.

In memory of Roland K. Robins and in admiration of his most valuable contributions to nucleoside, nucleotide and nucleic acid chemistry.



Since lumazine nucleosides possess similar structural features as the thymidine derivative potential antiviral activity was also assumed for the 3'-azido (**3-5**) as well as the 2',3'-dideoxynucleoside derivatives (**6,7**) of this series. In order to investigate such biological activities firstly 3'-azido- (**3**) as well as 1-(2,3-dideoxy-β-D-ribofuranosyl)-6,7-diphenyllumazine (**6**) have been synthesized.

The sugar component for the glycosylation reactions 1,2-di-O-acetyl-3,5-di-O-pivaloyl-D-xylofuranose (**10**) was prepared by an alternative and effective approach to the method of Horwitz et al.⁴ starting from 1,2-O-isopropylidene-α-D-xylofuranose (**8**) via its 3,5-di-O-pivaloyl derivative **9** to give **10** in good yield⁵. Silylated 6,7-diphenyllumazine (**11**)⁶ was then glycosylated with **10** using BF₃·OEt₂ in ethyl acetate⁷ to yield, after silica gel chromatography, **12** in 72 % yield. The 2'-O-acetyl group was selectively removed by treatment with pyridine /acetic acid (4:1)⁸ to give 80 % of 6,7-diphenyl-1-(3,5-di-O-pivaloyl-β-D-xylofuranosyl)lumazine (**13**). Treatment of **13** with phenoxythiocarbonyl chloride in CH₃CN in presence of 4-dimethylaminopyridine (DMAP) afforded in 92 % the 3'-O-phenoxythiocarbonyl derivative **14**. Its reduction with n-Bu₃SnH⁹ yielded 72 % of 1-(2-deoxy-3,5-di-O-pivaloyl-β-D-threo-pentofuranosyl)-6,7-diphenyllumazine (**15**), from which the pivaloyl groups were cleaved by sodium methoxide to give **16**. The monomethoxytrityl group was then introduced into the 5'-OH-position to form **17** in 69 % yield followed subsequently by 3'-OH mesylation to **18** in 84 % yield and nucleophilic displacement of this function by sodium azide¹⁰ in DMF at 80°C overnight. Work-up and silica gel column chromatography afforded 64 % of **19** which on further deblocking by acid treatment using p-toluenesulfonic acid in dichloromethane / MeOH 4:1 gave the desired 1-(3-azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-6,7-diphenyllumazine (**3**) in 74 % yield.

2',3'-Dideoxynucleosides are typically synthesized from 2'-deoxynucleosides via Barton-type deoxygenation reactions, or from intact nucleosides by

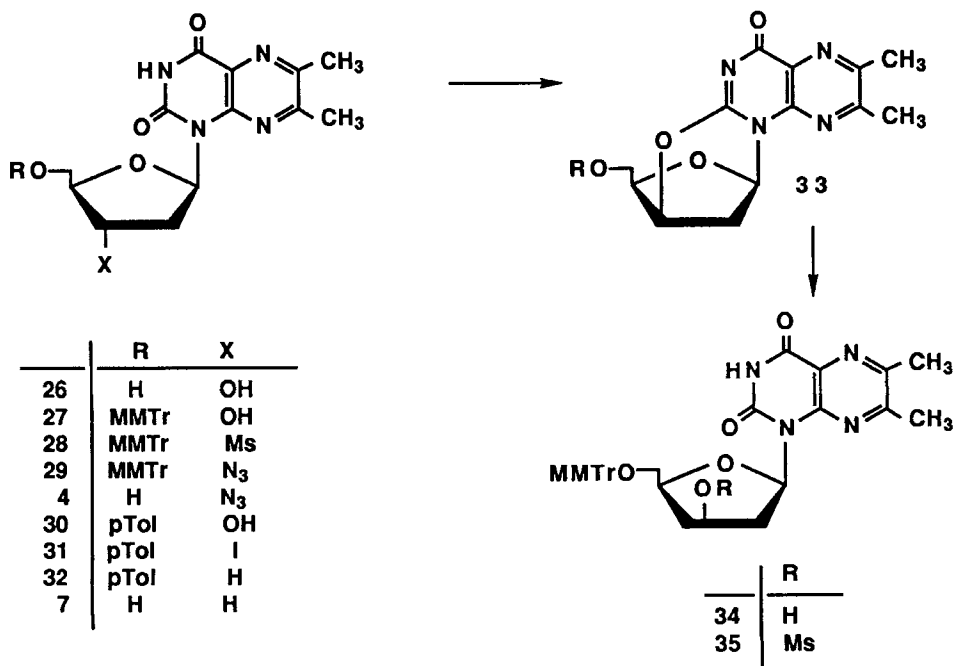


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toluene using azodiisobutyronitrile (AIBN) as a catalyst afforded the protected 2',3'-dideoxy nucleoside **25** in 77 % yield and the final deacylation by 0.01 N NaOMe at room temperature for 15 h resulted in 88 % yield of 1-(2,3-dideoxy- β -D-glycero-pentofuranosyl)-6,7-diphenyllumazine (**6**).

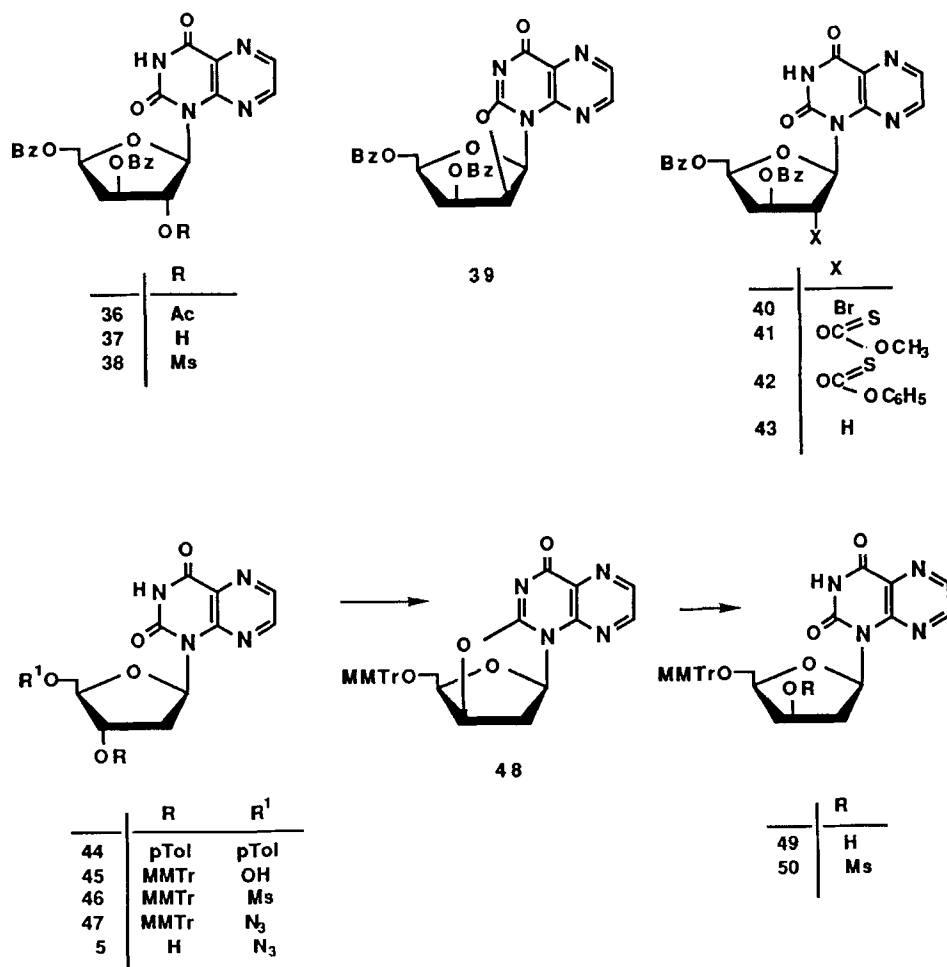
The syntheses of 3'-azido- (**4**) and 1-(2,3-dideoxy- β -D-glyceropento-furanosyl)-6,7-dimethylumazine (**7**) were performed starting from 1-(2-deoxy- β -D-erythro-pentofuranosyl)-6,7-dimethylumazine (**26**)^{6,12}. The 5'-O-monomethoxytrityl derivative **27**¹⁴ was first converted into 1-(2-deoxy- 5-O-monomethoxytrityl-3-O-mesyl- β -D-erythro-pentofuranosyl)-6,7-dimethyl-lumazine (**28**) which on treatment with DBU gave 2,3'-anhydro-1-(2-deoxy-5-O-monomethoxytrityl- β -D-threo-pentofuranosyl)-6,7-dimethylumazine (**33**). Base hydrolysis opened the anhydro ring to afford **34**, subsequent mesylation gave **35** which reacted with lithium azide in DMF to give **29** in 77% yield. Acid deprotection of **29** finally furnished 1-(3-azido-2,3-dideoxy- β -D-erythro-pentofuranosyl)- 6,7-dimethylumazine (**5**).

In another series of reactions compound **26** was firstly selectively acylated at the 5'-position to 1-(2-deoxy-5-O-toluoyl-1- β -D-erythro-pentofuranosyl)-



6,7-dimethylumazine (**30**), followed by displacement of the 3'-OH group by iodine using methyltriphenoxyphosphonium iodide¹³ to **31**, dehalogenation by $n\text{-Bu}_3\text{SnH}$ in a radical chain reaction to **32** which provided 1-(2,3-dideoxy- β -D-glycero-pentofuranosyl)-6,7-dimethylumazine (**7**) in good overall yield after deprotection.

The first attempt to synthesize 1-(3-azido-2-deoxy- β -D-erythro-pentofuranosyl)-lumazine (**5**) was undertaken from 1-(2-O-acetyl-3,5-di-O-benzoyl- β -D-threo-pentofuranosyl)-lumazine (**36**) which resulted from a glycosylation reaction of lumazine with 1,2-O-diacetyl-3,5-di-O-benzoylxylofuranose¹⁵ via the



"silyl"-method in presence of trimethylsilyl triflate as catalyst. Selective deacetylation of **3 6** and led to **3 7** which was mesylated to **3 8** and finally cyclized by 1.8-diaza-bicyclo(5.4.0)-undec-7-ene (DBU) to 2,2'-anhydro-1-(3,5-di-O-benzoyl- β -D-lyxofuranosyl)-lumazine (**3 9**). Treatment of **3 9** with 8% HBr in DMF afforded 1-(2-bromo-3,5-di-O-benzoyl- β -D-xylofuranosyl)-lumazine (**4 0**) which turned out to be relatively unstable in cyclizing back to the 2,2'-anhydronucleoside **3 9**. This instability seems to be also responsible for the fact that all attempts to reduce **4 0** to **4 3** failed by forming more easily **3 9** under the applied reaction conditions. Finally we converted **3 7** into the corresponding 2'-O-methoxythiocarbonyl- (**4 1**) and 2'-O-phenoxy-thiocarbonyl derivative (**4 2**), respectively, in order to perform the Barton reduction with azodiisobutyronitrile / $n\text{-Bu}_3\text{SnH}$ to **4 3**. Only **4 2** could be transformed into **4 3** in 48% yield whereas the analogous reaction with **4 1** failed completely.

The low overall yield in the interconversion of **3 6** into **4 3** forced us to try the synthesis of **5** from 1-(2-deoxy- β -D-erythro-pentofuranosyl)-lumazine^{6,12} for which, however, the glycosylation of lumazine to **4 4** had to be improved over the reported syntheses. Based upon the results of Freskos¹⁶ we found that treatment of 2,4-bis-trimethylsiloxypteridine⁶ by subsequent addition of 1 equivalent CuI and 3,5-di-O-p-toluoyl-2-deoxy-erythro-pentofuranosyl chloride led to a 79% yield of a 1-(2-deoxy-3,5-di-O-p-toluoyl- α,β -D-erythro-pentofuranosyl)-lumazine mixture in a 1 / 10 ratio from which **4 4** was obtained in 72%. Deacylation⁶ and monomethoxytritylation¹⁴ to **4 5** was achieved by known methods. In a sequence of reactions **4 5** was first mesylated to **4 6**, this compound then cyclized by DBU treatment to the 2,3'-anhydro nucleoside **4 8** which gave **4 9** after base hydrolysis, and subsequent mesylation afforded **5 0**. Nucleophilic displacement of the 3'-mesyl group by lithium azide in DMF resulted in a 75% yield of **4 7** which led on detritylation by p-toluenesulfonic acid in CH_2Cl_2 / MeOH to 1-(3-azido-2-deoxy- β -D-erythro-pentofuranosyl)-lumazine (**5**).

Physical Properties

The newly synthesized compounds were characterized by elemental analyses, UV and ¹H-NMR spectra. The azido group was detected by IR spec-

troscopy. The UV data and the R_f -values in various chromatographical systems taken from precoated silica-gel thin layer sheets are listed in table 1.

It can be seen from the UV data that structurally related compounds show in general very similar spectra what the UV maxima and the extinction coefficients are concerned. Formation of an anhydro-nucleoside structure (**33,39**) is reflected in a small hypsochromic shift of the longest transition.

The ^1H -NMR data are reported in the experimental part and do not show any peculiarities in comparison to the common types of nucleosides. It should be mentioned that the N-1-(2-deoxy- β -D-erythro-pentofuranosyl)-lumazines show in CDCl_3 a large chemical shift difference between the H-2' α and the H-2' β signals characteristic for the β -anomer whereas the same protons resonate in the α -anomer more closely or even coincide with each other.

Experimental Section

General. - TLC: Precoated silica-gel thin layer sheets F 1500 LS 254 from Schleicher & Schüll. - Prep. TLC: Silica-gel 60 PF₂₅₄ (Merck). - Prep. column chromatography: Silica-gel (Merck 60, 0.063-0.2 mesh). - M.p.: Büchi apparatus, model Dr. Tottoli; no corrections. - UV/VIS: Uvikon 820, Kontron and Perkin Elmer, Lambda 5; λ_{max} in nm (log ϵ). - ^1H -NMR: Bruker WM-250; in δ (ppm) relative to TMS. - IR: PolarisTM, Mattson FTIR in cm^{-1} .

1-(3-Azido-2,3-dideoxy- β -D-erythro-pentofuranosyl)-6,7-diphenyllumazine (3). A solution of **19** (0.54 g, 0.74 mmole) in 25 ml of 2 % p-toluenesulfonic acid in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ - (4:1) was stirred at 0°C for 20 min and neutralized with saturated sodium bicarbonate. The aqueous solution was dried over sodium sulfate. Yield: 0.26 g (77 %), m.p.: 152-155°C. IR (KBr): 2103 cm^{-1} . ^1H -NMR (CDCl_3): 9.31 (s, 1H, NH); 7.29-7.52 (m, 11H, H-C(1') and Ar-H); 4.89 (t, 1H, 5'-OH); 4.70 (q, 1H, H-C(3')); 3.76-4.03 (m, 3H, H-C(4') and H-C(5')); 2.36-3.19 (m, 2H, H-C(2')).

Anal. calc. for $\text{C}_{23}\text{H}_{19}\text{N}_7\text{O}_4 \cdot 1/2 \text{H}_2\text{O}$ (466.5): C, 59.71; H, 4.32; N, 21.00. Found: C, 59.85; H, 4.44; N, 21.12.

TABLE 1 - Physical Data of 6,7-Diphenyllumazine Nucleosides

Compound	UV-Absorption Spectra in MeOH						R _f
	λ_{\max} (nm)			log ϵ			
3	223	274	359	4.45	4.26	4.16	0.15 ^a
6	231	273	359	4.35	4.17	4.11	0.17 ^a
12	222	272	358	4.46	4.44	4.36	0.51 ^a
13	225	272	359	4.67	4.59	4.36	0.38 ^a
14	225	275	359	4.45	4.18	4.13	0.53 ^d
15	225	275	359	4.46	4.25	4.14	0.38 ^d
16	225	274	358	4.25	4.05	4.00	0.15 ^b
17	227	274	358	4.58	4.23	4.12	0.48 ^b
18	227	274	358	4.57	4.20	4.13	0.34 ^a
19	223	273	358	4.70	4.42	4.24	0.67 ^a
23	231	273	358	4.47	4.08	4.04	0.21 ^c
24	231	273	359	4.49	4.16	4.08	0.51 ^c
25	231	273	359	4.50	4.17	4.09	0.44 ^a
4	229		323	4.10		3.98	0.32 ^b
7	236		324	4.30		3.81	0.34 ^b
28	230		323	4.25		3.79	0.53 ^b

1-(3-Azido-2,3-dideoxy- β -D-erythro-pentofuranosyl)-6,7-dimethylumazine (4). Detritylation of **29** (0.83 g, 1.37 mmole) was achieved at 0°C with a 1% solution of p-toluenesulfonic acid in CH₂Cl₂/MeOH (4:1) (25 ml) and stirring for 20 min. The solution was diluted with H₂O (2 ml) and then neutralized with sodium bicarbonate. It was extracted several times with CHCl₃, the organic layer dried over sodium sulfate and after concentration to a smaller volume purified by column chromatography (3,5 x 7 cm) on silica gel with CHCl₃/MeOH (98:2). The main fraction gave an amorphous solid on evaporation. Yield: 0.36 g (75 %), m.p. 97-99°C. IR(KBr): 2103 cm⁻¹. ¹H-NMR (CDCl₃): 9.30 (bs, 1H, NH); 7.24 (dd, 1H, H-C(1'')); 4.72 (m, 1H, H-C(3')); 3.82-

TABLE 1 - Continued

Compound	UV-Absorption Spectra in MeOH						R _f
	λ _{max} (nm)			log ε			
29	231		324	4.33		3.80	0.54 ^b
30	236		323	4.48		3.89	0.31 ^b
31	236		323	4.48		3.89	0.42 ^b
32	236		324	4.28		3.82	0.35 ^a
33	231	313	[327]	4.34	3.95	[3.76]	0.27 ^b
34	[227]	278	328	[4.40]	3.53	3.93	0.36 ^b
35	230		322	4.32		3.88	0.41 ^b
5	231		314	4.18		3.84	0.32 ^b
36	230		315	4.51		3.78	0.33 ^e
37	230		316	4.54		3.81	0.10 ^e
38	230		312	4.61		3.87	0.51 ^b
39	229		311	4.85		4.18	0.22 ^b
40	229		312	4.66		3.86	0.50 ^b
41	230		316	4.63		3.81	0.51 ^e
42	229		314	4.61		3.75	0.43 ^a
43	230		315	4.62		3.86	0.28 ^a
44	238		315	4.61		3.79	0.68 ^b
46	231		314	4.59		3.98	0.46 ^b
47	231		316	4.37		3.77	0.59 ^b
48	231	[260[314	4.34	[3.63]	3.80	0.36 ^b
49	231	279	315	4.40	3.46	3.78	0.43 ^b
50	230		314	4.57		3.97	0.48 ^b

a: CHCl₃/Acetone (9:1); b: CHCl₃/MeOH (95:5); c: CHCl₃/THF (14:1);
d: n-Hexane/Et₂O (1:2); e: Toluene/AcOEt (1:2).

3.99 (m, 3H, H-C(4'), H-C(5')); 3.80 (bs, 1H, H-O(5')); 3.07 (m, 1H, H-C(2'α)); 2.68 (s, 6H, 6,7 CH₃); 2.38 (m, 1H, H-C(2'α)).

Anal. calc. for C₁₃H₁₅N₇O₄ (342.5): C, 45.59; H, 4.71; N, 28.62.
Found: C, 45.83; H, 4.66; N, 28.21.

1-(3-Azido-2,3-dideoxy-β-D-erythro-pentofuranosyl)-lumazine

(5). Detritylation of **47** (0.91 g, 1.58 mmole) was achieved in a 1% solution of p-TsOH in CH₂Cl₂/MeOH (4:1) at 0°C with stirring. After 2 h H₂O (2 ml) was added dropwise and then neutralized by a saturated solution of sodium bicarbonate. The reaction solution was extracted several times with CHCl₃, the organic phase dried over sodium sulfate, concentrated to a small volume and then purified by column chromatography (3 x 7 cm) on silica gel with CHCl₃/MeOH (98:2). An amorphous solid was obtained on evaporation. Yield: 0.37 g (76 %), m.p. 88-91°C. IR(KBr): 2103 cm⁻¹. ¹H-NMR (CDCl₃): 9.76 (bs, 1H, NH); 8.68 (s, 2H, 6,7-H); 7.21 (dd, 1H, H-C(1')); 4.71 (m, 1H, H-C(3')); 3.83-4.05 (m, 3H, H-C(4'), H-C(5')); 3.37 (bs, 1H, 5'-OH); 3.08 (m, 1H, H-C(2'α)); 2.38 (m, 1H, H-C(2'α)).

Anal. calc. for C₁₁H₁₁N₇O₄ · 1/2 H₂O (314.3): C, 42.04; H, 3.85; N, 31.19. Found: C, 42.43; H, 3.78; N, 30.96.

1-(2,3-Dideoxy-β-D-glycero-pentofuranosyl)-6,7-diphenyl-

lumazine (6). In 0.01 N sodium methoxide (20 ml) was suspended **27** (0.30 g (0.56 mmole) which dissolved gradually at room temperature. After 15 h H₂O (10 ml) was added and the mixture was neutralized with saturated sodium bicarbonate. On evaporation the product **6** crystallized and was washed after filtration with cold water and n-pentane and dried. Yield: 0.19 g (82 %), m.p.: 165-166°C. ¹H-NMR (CDCl₃): 9.76 (s, 1H, NH); 7.19-7.50 (m, 11H, Ar-H and H-C(1')); 4.25-4.29 (q, 1H, H-C(4')); 3.66-3.94 (ddd, 2H, H-C(5')); 3.38 (t, 1H, 5'-OH); 2.02-2.78 (m, 4H, H-C(2') and H-C(3')).

Anal. calc. for C₂₃H₂₀N₄O₄ (416.4): C, 66.34; H, 4.84; N, 13.45. Found: C, 66.07; H, 4.85; N, 13.21.

1-(2,3-Dideoxy-β-D-glycero-pentofuranosyl)-6,7-dimethyl-

lumazine (7). A suspension of **32** (0.33 g, 0.75 mmole) in 0.01 N sodium methoxide in MeOH (20 ml) was stirred at room temperature for 2 h to give a

clear solution. After addition of H₂O (10 ml) and neutralization by dilute acetic acid to pH 7 was evaporated to dryness. The residue was purified by column chromatography (3 x 7 cm) on silica gel with CHCl₃/MeOH (98:2). The main fraction was evaporated to give a colourless solid. Yield: 0.20 g (90 %), m.p. 107-109°C. ¹H-NMR (DMSO-d₆): 11.78 (s, 1H, NH); 6.80 (dd, 1H, H-C(1')); 3.96 (dd, 1H, H-C(4')); 3.51 (d, 2H, H-C(5')); 2.56 (s, 6H, 6,7-CH₃); 2.17-2.26 (m, 4H, H-C(2'α), H-C(2'β), H-C(3'α), H-C(3'β)).

Anal. calc. for C₁₃H₁₆N₄O₄ · 1/2 H₂O (301.3): C, 51.82; H, 5.69; N, 18.59. Found: C, 51.39; H, 5.38; N, 18.22.

1,2-O-Isopropylidene-3,5-di-O-pivaloyl-α-D-xylofuranose (9).

A solution of 1,2-O-isopropylidene-α-D-xylofuranose (8) (18.8 g, 0.1 mole) in dry pyridine (100 ml) was cooled in an ice-bath. Pivaloyl chloride (25.2 ml, 0.2 mole) was then added dropwise with stirring. The mixture was allowed to stand at room temperature protected from moisture for 5 h, then MeOH (5 ml) was added slowly into the solution and after 10 min. the solution was concentrated to dryness. The oil was extracted with CHCl₃ (50 ml) and H₂O (30 ml). The organic phase was dried over sodium sulfate and evaporated to dryness to give a colorless solid. Yield: 31.2 g (87 %). ¹H-NMR (CDCl₃): 5.94 (d, 1H, H-C(1)); 5.26 (d, 1H, H-C(2)); 4.55 (m, 1H, H-C(4)); 4.46 (d, 1H, H-C(3)); 4.22 (m, 2H, H-C(5)); 1.34-1.56 (2s, 6H, isopropyl); 1.18-1.23 (2s, 18H, 2 x pivaloyl).

Anal. calc. for C₁₈H₃₀O₇ (358.4): C, 60.32; H, 8.44. Found: C, 60.13; H, 8.39.

1,2-Di-O-acetyl-3,5-di-O-pivaloyl-D-xylofuranose (10). In 75% formic acid (300 ml) 1,2-O-isopropylidene-3,5-di-O-pivaloyl-α-D-xylofuranose (9) (17.9 g, 50 mmole) was heated to 50°C for 2 h. It was evaporated to dryness, coevaporated with n-butanol (2 x 50 ml) followed by toluene (2 x 50 ml) and dry pyridine (20 ml). Treatment with acetic anhydride (40 ml) in dry pyridine (100 ml) for 2 h afforded acetylation. The reaction mixture was evaporated to a smaller volume, then poured into ice water and extracted with CHCl₃ (3x 50 ml). The organic phase was washed with H₂O, dried over sodium sulfate and evaporated after filtration to give a solid. Yield: 14.5 g (95 %). ¹H-NMR (CDCl₃): 6.14-6.43 (2d, 1H, H_α-C(1) and H_β-C(1)); 5.36-5.57 (m, 2H, H-C(2) and H-C(3));

4.68 (m, 1H, H-C(4)); 4.02-4.31 (m, 2H, H-C(5)); 2.15 (2s, 6H, 2 x COMe); 1.18-1.24 (2s, 18H, 2 x pivaloyl).

Anal. calc. for $C_{19}H_{30}O_9$ (402.4): C, 56.71; H, 7.51. Found: C, 56.58; H, 7.53.

1-(2-O-Acetyl-3,5-di-O-pivaloyl- β -D-xylofuranosyl)-6,7-diphenyllumazine (12). A mixture of 6,7-diphenyllumazine (3.16 g, 10 mmole) and hexamethyldisilazane (100 ml) was refluxed overnight in the presence of a few crystals of ammonium sulfate. The clear solution was concentrated in va-cuum, the resulting syrup dissolved in ethyl acetate (150 ml) and then 1,2-di-O-acetyl-3,5-di-O-pivaloyl-D-xylofuranose (**10**) (4.02 g, 10 mmol) and $BF_3 \cdot OEt_2$ (7 ml) added. The mixture was stirred at room temperature for 2 h and then neutralized with saturated sodium bicarbonate. The organic layer was washed with H_2O and dried over sodium sulfate. The crude product was purified by column chromatography (220 g of silica gel, eluted with $CHCl_3$) to give on evaporation of the main fraction a colorless solid. Yield: 4.73 g (72 %), m.p.: 130-132°C. 1H -NMR ($CDCl_3$): 8.45 (s, 1H, NH); 7.30-7.47 (m, 10H, Ar-H); 6.82 (d, 1H, H-C(1')); 6.01 (t, 1H, H-C(2')); 5.47 (t, 1H, H-C(3')); 4.51 (t, 1H, H-C(4')); 4.37 (d, 2H, H-C(5')); 2.05 (s, 3H, -OAc); 1.12-1.27 (2s, 18H, 2 x pivaloyl).

Anal. calc. for $C_{35}H_{38}N_4O_9$ (658.7): C, 63.82; H, 5.81; N, 8.51. Found: C, 63.37; H, 5.71; N, 8.50.

1-(3,5-Di-O-pivaloyl- β -D-xylofuranosyl)-6,7-diphenyllumazine (13). In a mixture of pyridine/acetic acid (4:1, 75 ml) 1-(2-O-acetyl-3,5-di-O-pivaloyl- β -D-xylofuranosyl)-6,7-diphenyllumazine (**12**) (4.73 g, 7.4 mmole) was dissolved at room temperature and then hydrazine monohydrate (1.3 ml) added and stirred for 22 h. It was evaporated, extracted with $CHCl_3$ and washed with H_2O . The organic layer was dried over sodium sulfate, then concentrated to a small volume and put onto a short silica gel column for chromatography with $CHCl_3$ / MeOH (99:1) to give a solid on evaporation of the main fraction. Yield: 3.21 g (72 %), m.p.: 141-143°C. 1H -NMR ($CDCl_3$): 8.84 (brs, 1H, NH); 7.28-7.52 (m, 10H, Ar-H); 6.91 (d, 1H, H-C(1')); 5.25 (d, 1H, H-C(2')); 5.08 (t, 1H, H-C(3'));

4.39-4.58 (m, 3H, H-C(4') and H-C(5')); 3.46 (s, 1H, 2'-OH); 1.18-1.24 (2s, 18H dipivaloyl).

Anal. calc. for $C_{33}H_{36}N_4O_8 \cdot H_2O$ (634.7): C, 62.44; H, 6.03; N, 8.82.

Found: C, 62.52; H, 5.88; N, 8.61.

1-(3,5-Di-O-pivaloyl-2-O-phenoxythiocarbonyl- β -D-xylofuranosyl)-6,7-diphenylumazine (14). To a solution of **13** (1.86 g, 3 mmole) in dry CH_3CN was added 4-N,N-dimethylaminopyridine (DMAP) (1.08 g, 15.7 mmole) and phenoxythiocarbonyl chloride (PTC-Cl) (0.54 g, 3.6 mmole). The mixture was stirred for 10 min. and then poured into ice-water (30 ml). It was extracted with ethyl acetate (3 x 20 ml), dried over sodium sulfate and evaporated in vacuo. The residue was dissolved in $CHCl_3$ and chromatographed on silica gel with $CHCl_3$ to give a solid. Yield: 2.07 g (92 %), m.p.: 130-131°C. 1H -NMR ($CDCl_3$): 8.50 (s, 1H, NH); 7.18-7.54 (m, 15H, Ar-H); 7.05 (d, 1H, H-C(1')); 6.56 (d, 1H, H-C(2')); 5.65 (t, 1H, H-3'); 4.61 (t, 1H, H-C(4')); 4.41 (d, 2H, H-C(5')); 1.19-1.31 (2s, 18H, dipivaloyl).

Anal. calc. for $C_{40}H_{40}N_4O_9$ (752.8): C, 63.82; H, 5.30; N, 7.44. Found:

C, 63.39; H, 5.30; N, 7.44.

1-(2-Deoxy-3,5-di-O-pivaloyl- β -D-threo-pentofuranosyl)-6,7-diphenylumazine (15). To a solution of **14** (1.85 g, 3 mmole) in toluene (60 ml) was added under nitrogen atmosphere azodiisobutyronitrile (AIBN) (2 g, 12 mmole) and $n\text{-Bu}_3SnH$ (4.8 ml, 18 mmole). It was heated under reflux for 1.5 h and then evaporated. The residue was purified by silica gel column chromatography (4 x 15 cm) by elution with 1) 500 ml of n -hexane, 2) 700 ml of n -hexane/diethylether (1:2) to give a solid. Yield: 1.31 g (73 %), m.p.: 139 - 142°C. 1H -NMR ($CDCl_3$): 8.58 (s, 1H, NH); 7.30-7.50 (m, 10H, Ar-H); 7.12 (t, 1H, H-C(1')); 5.45 (m, 1H, H-C(3')); 4.26-4.44 (m, 3H, H-C(4') and H-C(5')); 2.71-3.04 (m, 2H, H-C(2')); 1.18-1.25 (2s, 18H, dipivaloyl).

Anal. calc. for $C_{35}H_{36}N_4O_7 \cdot 1/2 H_2O$ (609.7): C, 65.01; H, 6.11; N,

9.19. Found: C, 64.70; H, 6.09; N, 9.29.

6,7-Diphenyl-1-(2-deoxy- β -D-threo-pentofuranosyl)umazine (16). A solution of **15** (1.31 g, 2.2 mmole) in 0.05 N sodium methoxide (100 ml) was stirred over night and then neutralized with 10% acetic acid. A solid

crystallized on evaporation and gave after filtration and washing with cold H₂O and diethylether yellowish crystals. Yield: 0.79 g (84 %), m.p.: 142-143°C.

¹H-NMR (DMSO-d₆): 12.21 (s, 1H, NH); 7.34-8.30 (m, 10H, Ar-H); 6.99 (dd, 1H, H-C(1')); 5.02 (d, 1H, 3'-OH); 4.61 (t, 1H, 5'-OH); 4.18 (brs, 1H, H-C(3')); 3.46-3.75 (m, 3H, H-C(4') and H-C(5')); 2.35-2.64 (m, 2H, H-C(2')).

Anal. calc. for C₂₃H₂₀N₄O₅ (450.4): C, 61.33; H, 4.92; N, 12.44. Found: C, 61.78; H, 4.89; N, 12.35.

1-(2-Deoxy-5-O-p-monomethoxytrityl-β-D-threo-pentofuranosyl)-6,7-diphenylumazine (17). To a solution of **16** (1.4 g, 3.2 mmole) in dry pyridine (15 ml) was added p-monomethoxytrityl chloride (1.2 g, 3.6 mmole) and stirred over night. The reaction mixture was poured into ice-water (25 ml), the solid collected, dissolved in CHCl₃, washed with H₂O and dried over sodium sulfate. The crude product was purified by a silica gel column chromatography (2 x 15 cm, CHCl₃/MeOH 98:2) to give a colorless solid. Yield: 1.5 g (69 %), m.p.: 161-162°C. ¹H-NMR (CDCl₃): 9.66 (s, 1H, NH); 6.77-7.57 (m, 25H, H-C(1') and Ar-H); 4.88 (d, 1H, 3'-OH); 4.31 (m, 1H, H-C(3')); 3.37 (s, 3H, -OMe); 3.54 (d, 2H, H-C(5')); 2.38-2.83 (m, 2H, H-C(2')).

Anal. calc. for C₄₃H₃₆N₄O₆ · 1/2 H₂O (713.8): C, 72.35; H, 5.22; N, 7.85. Found: C, 72.39; H, 5.29; N, 7.80.

1-(2-Deoxy-3-O-mesyl-5-O-p-monomethoxytrityl-β-D-threo-pentofuranosyl)-6,7-diphenylumazine (18). To a cold solution (0°C) of **17** (1.4 g, 2 mmole) in dry pyridine (30 ml) was added slowly methanesulfonyl chloride (0.4 ml, 5.2 mmole) and then the reaction mixture stirred at room temperature for 2 h. The mixture was slowly poured into ice-water (50 ml). The solid was collected, washed well with H₂O and dried in a desiccator. Recrystallization from EtOH (20 ml) afforded colorless crystals. Yield: 1.1 g (84 %), m.p.: 152-156°C. ¹H-NMR (CDCl₃): 8.75 (s, 1H, NH); 6.77-7.50 (m, 24H, Ar-H); 6.99 (t, 1H, H-C(1')); 5.42 (m, 1H, H-C(3')); 4.26 (8q, 1H, H-C(4')); 3.76 (s, 3H, -OMe); 2.74-3.66 (m, 4H, H-C(2') and H-C(5')); 2.65 (s, 3H, -Me).

Anal. calc. for C₄₄H₃₈N₄O₈S · 1/2 H₂O (791.8): C, 66.74; H, 4.96; N, 7.07. Found: C, 66.39; H, 5.00; N, 7.02.

1-(3-Azido-2,3-dideoxy-5-O-p-monomethoxy-trityl-β-D-erthro-pentofuranosyl)-6,7-diphenylumazine (19). A mixture of **18** (1.0 g, 1.27 mmole) and sodium azide (0.1 g) in DMF (15 ml) was heated to 80°C over night. The DMF was evaporated, the residue dissolved in CHCl₃ (30 ml), washed with H₂O and purified after drying over sodium sulfate by column chromatography (3 x 15 cm, CHCl₃) to give a colorless solid. Yield: 0.65 g (70 %), m.p.: 129-131°C. IR(KBr): 2103 cm⁻¹. ¹H-NMR (CDCl₃): 8.82 (s, 1H, NH); 6.73-7.47 (m, 25H, H-C(1') and Ar-H); 4.68-4.71 (q, 1H, H-C(3')); 3.73-4.02 (m, 3H, H-C(4') and H-C(5')); 3.80 (s, 3H, -OMe); 2.36-3.15 (m, 2H, H-C(2')).

Anal. calc. for C₄₃H₃₅N₇O₅ · 1/2 H₂O (738.8): C, 69.91; H, 4.91; N, 13.27. Found: C, 69.94; H, 4.84; N, 13.06.

1-(2-Deoxy-5-O-p-toluoyl-β-D-threo-pentofuranosyl)-6,7-diphenylumazine (23). A solution of p-toluoyl chloride (0.42 ml, 3 mmole) in 1,2-dichloroethane (5 ml) was added dropwise to a stirred solution of **16** (1.29 g, 3 mmole) in dry pyridine (40 ml) at -5°C. Stirring was continued for 30 min at 0°C. The reaction mixture was poured into ice-water (100 ml) and extracted with CHCl₃. The combined extracts were washed with saturated sodium bicarbonate and water, dried over sodium sulfate and evaporated to dryness. The crude product was purified through a silica gel column (3 x 15 cm, CHCl₃/MeOH (98:2), 400 ml) to give a colorless solid. Yield: 1.27 g (77 %). ¹H-NMR (DMSO-d₆): 12.21 (s, 1H, NH); 7.27-7.84 (m, 14H, phenyl); 7.08 (t, 1H, H-C(1')); 5.33 (d, 1H, 3'-OH); 4.16-4.61 (m, 4H, H-C(3'), H-C(4') and H-C(5')); 2.68-2.72 (m, 2H, H-C(2')); 2.34 (s, 3H, CH₃).

Anal. calc. for C₃₁H₂₆N₄O₆ · 1/2 H₂O (559.6): C, 66.54; H, 4.86; N, 10.01. Found: C, 66.68; H, 4.88; N, 10.21.

1-(2,3-Dideoxy-3-iodo-5-O-p-toluoyl-β-D-erythro-pentofuranosyl)-6,7-diphenylumazine (24). A mixture of **23** (1.1 g, 2 mmole) and methyltriphenoxyposphonium iodide (2 g, 4 mmole) in dry DMF (5 ml) was stirred for 2 h. The mixture was poured into H₂O (50 ml), the solid dissolved in CHCl₃ and washed well with H₂O. The crude product was purified through a silica gel column (3 x 12 cm, CHCl₃ 350 ml) to give a yellowish solid. Yield: 1 g (75 %), m.p.: 124-126°C. ¹H-NMR (CDCl₃): 8.94 (s, 1H, NH); 7.18-7.95 (m, 14H,

Ar-H and H-C(1')); 4.55 (t, 1H, H-C(3')); 4.43-4.50 (m, 3H, H-C(4') and H-C(5')); 2.85-3.35 (m, 2H, H-C(2') and H-(2'')); 2.37 (s, 3H, -Me).

Anal. calc. for $C_{31}H_{25}N_4O_5 \cdot 1/2 H_2O$ (669.5): C, 55.61; H, 3.91; N, 8.37. Found: C, 55.64; H, 3.97; N, 8.37.

1-(2,3-dideoxy-5-O-p-toluoyl- β -D-glycero-pentofuranosyl)-6,7-diphenylumazine (25). A solution of **24** (0.66 g, 1 mmole) in dry toluene (20 ml) was treated under dry nitrogen atmosphere with $n\text{-Bu}_3\text{SnH}$ (1.2 ml) and azodiisobutyronitrile (AIBN) (0.4 g). The stirred mixture was then heated to 85°C for 2 h and after cooling dropwise added to n -hexane (150 ml). The resulting precipitate was collected by filtration, washed with n -hexane and dried in a desiccator. Yield: 0.43 g (81 %), m.p.: 128-130°C. $^1\text{H-NMR}$ (CDCl_3): 9.10 (s, 1H, NH); 7.17-7.94 (m, 15H H-C(1') and Ar-H); 4.51-4.60 (m, 1H, H-C(4')); 4.36-4.47 (m, 2H, H-C(5')); 2.36 (s, 3H, -Me); 2.06-2.73 (m, 4H, H-C(2') and H-C(3')).

Anal. calc. for $C_{31}H_{26}N_4O_5 \cdot 1/2 H_2O$ (543.6): C, 68.62; H, 5.01; N, 10.33. Found: C, 68.90; H, 5.05; N, 10.69.

1-(2-Deoxy- β -D-erythro-pentofuranosyl)-6,7-dimethylumazine (26). A mixture of 6,7-dimethylumazine¹⁷ (3.84 g) and a few crystals of ammonium sulfate in hexamethyldisilazane (HMDS) (25 ml) was heated under reflux for 4 h. The clear solution was evaporated to dryness, the residue dissolved in dry benzene (100 ml), then 3,5-di-O-p-toluoyl-2-deoxy-D-erythro-pentofuranosyl chloride (8.0 g) added and stirred for 2 days at room temperature. The reaction solution was evaporated to dryness, and the residue recrystallized from MeOH (100 ml) to give colourless crystals of 6,7-dimethyl-1-(2-deoxy-3,5-di-O-p-toluoyl- β -D-erythro-pentofuranosyl)-lumazine. Yield : 4.68 g (46 %), m.p.: 152-155°C. Lit.⁶ m.p. 154-155°C.

The reaction product (4.36 g, 4.0 mmole) was stirred in 0.1 N NaOCH_3 (100 ml) for 2 h at room temperature. The precipitate was dissolved by addition of H_2O (50 ml), then the solution neutralized by Dowex-50 (H^+ -form) to pH 5. After evaporation the residue was recrystallized from n -propanol (800 ml) by addition of ether (120 ml) to give colourless crystals. Yield: 1.89 g (77 %), m.p. 175°C (decomp.). Lit.⁶: 180°C (decomp.). The material was chromatographically and spectrophotometrically identical with an authentic sample.

1-(2-Deoxy-3-O-mesyl-5-O-p-monomethoxytrityl-β-D-erythro-pentofuranosyl)-6,7-dimethylumazine (28). A solution of 1-(2-deoxy-5-O-p-monomethoxytrityl-β-D-erythro-pentofuranosyl)-6,7-dimethylumazine (**27**) (2.32 g, 4.0 mmole) in dry pyridine (20 ml) was treated by slow addition of methanesulfonyl chloride (0.5 ml, 6.5 mmole) at room temperature for 2 h with stirring. The reaction mixture was diluted with ice-water (100 ml), the product extracted by CH₂Cl₂ (30 ml) and then the organic layer dried over sodium sulfate. After evaporation crystallization from EtOH (10 ml) gave colourless crystals. Yield: 2.38 g (91 %), m.p. 113-115°C. ¹H-NMR (DMSO-d₆): 11.90 (s, 1H, NH); 6.78-7.42 (m, 14H, Ar-H); 7.03 (dd, 1H, H-C(1')); 5.42 (q, 1H, H-C(3')); 4.19 (dd, 1H, H-C(4')); 3.70 (s, 3H, OMe); 3.15 (s, 3H, SO₂CH₃); 3.02-3.40 (m, 2H, H-C(5')); 2.33-2.64 (m, 8H, 6,7-CH₃, H-C(2'α), H-C(2'β)).

Anal. calc. for C₃₄H₃₄N₄O₈S (658.7): C, 61.99; H, 5.20; N, 8.50. Found: C, 61.71; H, 5.34; N, 8.32.

1-(3-Azido-2,3-dideoxy-5-O-p-monomethoxytrityl-β-D-erythro-pentofuranosyl)-6,7-dimethylumazine (29). A solution of **28** (0.5 g, 0.76 mmole) in dry DMF (3 ml) was treated with lithium azide (0.1 g, 1.6 mmole) with stirring at 80°C over night under anhydrous conditions. The DMF was removed in high vacuum, the residue dissolved in CH₂Cl₂ (10 ml), then washed with H₂O and the organic layer dried over sodium sulfate. The product was purified by silica gel column chromatography (3 x 5 cm) with CHCl₃/MeOH (99:1). The main fraction was evaporated to a colourless solid foam. Yield: 0.3 g (77 %), m.p. 121-124°C. IR (KBr): 2103 cm⁻¹. ¹H-NMR (CDCl₃): 8.58 (bs, 1H, NH); 6.76-7.44 (m, 15H, H-C(1'), Ar-H); 4.50 (q, 1H, H-C(3')); 3.98 (q, 1H, H-C(4')); 3.77 (s, 3H, OCH₃); 3.42 (dq, 2H, H-C(5')); 3.02 (m, 1H, H-C(2'β)); 2.49-2.63 (2s, 6H, 6,7 CH₃); 2.40 (m, 1H, H-C(2'α)).

Anal. calc. for C₃₃H₃₇N₇O₅ (605.7): C, 65.44; H, 5.16; N, 16.19. Found: C, 65.01; H, 5.33; N, 16.01.

1-(2-Deoxy-5-O-p-toluoyl-β-D-erythro-pentofuranosyl)-6,7-dimethylumazine (30). A solution of p-toluoyl chloride (1.1 ml, 8.33 mmole) in 1,2-dichloroethane (15 ml) was added slowly to **26** (2.5 g, 8.1 mmole) in dry pyridine (30 ml). The solution was stirred over night, then diluted with ice-water (50 ml) to get a precipitate. After filtration the solid was dissolved

in CHCl_3 (30 ml), washed with H_2O and then the organic layer dried over sodium sulfate. After evaporation the residue was dissolved in CH_2Cl_2 (5 ml) and added dropwise with vigorous stirring into n-hexane (100 ml) forming a colourless solid. Yield: 3.1 g (73 %), m.p. 152-154°C. $^1\text{H-NMR}(\text{DMSO-}d_6)$: 11.82 (s, 1H, NH); 7.28-7.84 (2d, 4H, Ar-H); 7.02 (dd, 1H, H-C(1')); 5.36 (d, 1H, H-O(3')); 4.29-4.66 (m, 3H, H-C(4'), H-C(5')); 3.99 (m, 1H, H-C(3')); 2.89 (m, 1H, H-C(2'α)); 2.51-2.57 (2s, 6H, 6,7 CH_3); 2.36 (s, 3H, C- CH_3); 2.15 (m, 1H, H-C(2'α)).

Anal. calc. for $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_6$ (426.4): C, 59.15; H, 5.20; N, 13.14.

Found: C, 59.58; H, 5.37; N, 13.15.

1-(2,3-Dideoxy-3-iodo-5-O-p-toluoyl-β-D-erythro-pentofuranosyl)-6,7-dimethylumazine (31). In dry DMF (5 ml) was dissolved **30** (0.86 g, 2.0 mmole) and methyltriphenoxyphosphonium iodide (1.9 g, 4.0 mmole) and then the mixture stirred at room temperature for 2 h. It was evaporated in high vacuum, the residue in CHCl_3 (15 ml) and washed subsequently with a solution of sodium thiosulfate and H_2O . The organic layer was dried over sodium sulfate and purified after evaporation to a smaller volume by column chromatography (3 x 12 cm) on silica gel with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (99:1). The main fraction gave on evaporation a colourless amorphous solid. Yield: 0.77 g (72 %), m.p. 116°C (decomp.). $^1\text{H-NMR}(\text{CDCl}_3)$: 8.80 (s, 1H, NH); 7.22-7.95 (m, 5H, H-C(1'), Ar-H); 4.85 (q, 1H, H-C(3')); 4.50-4.76 (m, 3H, H-C(4'), H-C(5')); 3.24 (dq, 1H, H-C(2')); 2.88 (m, 1H, H-C(2'α)); 2.61, 2.64 (2s, 6H, 6,7 CH_3); 2.39 (s, 3H, C- CH_3).

Anal. calc. for $\text{C}_{21}\text{H}_{21}\text{IN}_4\text{O}_4$ (536.3): C, 47.03; H, 3.95; N, 10.45.

Found: C, 47.06; H, 3.87; N, 10.45.

1-(2,3-Dideoxy-5-O-p-toluoyl-β-D-glycero-pentofuranosyl)-6,7-dimethylumazine (32). In dry toluene (20 ml) was dissolved **31** (0.64 g, 1.2 mmole) under N_2 -atmosphere. It was heated to 85°C in an oil-bath and then azodiisobutyronitrile (0.4 g) and n- Bu_3SnH (1.2 ml) added with stirring. After heating for 2 h was evaporated to dryness. The residue was put onto a silica gel column for chromatography with n-hexane (300 ml) followed by $\text{CHCl}_3/\text{MeOH}$ (99:1, 400 ml). The main fraction was evaporated to an amorphous solid. Yield: 0.40 g (82 %), m.p. 99-101°C. $^1\text{H-NMR}(\text{CDCl}_3)$: 8.71

(bs, 1H, NH); 7.18-7.93 (m, 4H, Ar-H); 7.11 (dd, 1H, H-C(1')); 4.40-4.62 (m, 3H, H-C(4'), H-C(5')); 2.60 (s, 6H, 6,7 CH₃); 2.44-2.60 (m, 3H, H-C(2'_α), H-C(2'_β), H-C(3'_β)); 2.39 (s, 3H, C-CH₃); 2.14 (m, 1H, H-C(3'_α)).

Anal. calc. for C₂₁H₂₂N₄O₅ · 1/2 H₂O (419.4): C, 60.14; H, 5.52; N, 13.35. Found: C, 59.70; H, 5.37; N, 13.29.

2,3'-Anhydro-1-(2-deoxy-5-O-p-monomethoxytrityl-β-D-threo-pentofuranosyl)-6,7-dimethylumazine (33). To a solution of **28** (2.3 g, 3.5 mmole) in dry CH₂Cl₂ (35 ml) was added 1.8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.76 ml, 5.0 mmole) and then heated 1 h under reflux. After cooling it was washed with H₂O (2 x 10 ml), the organic layer dried over sodium sulfate and then evaporated to dryness to give a chromatographically pure material. Yield: 1.75 g (89 %), m.p. 142-145°C. ¹H-NMR (DMSO-d₆): 6.68-7.34 (m, 14H, Ar-H); 6.99 (d, 1H, H-C(1')); 5.48 (s, 1H, H-C(3')); 4.50 m, 1H, H-C(4')); 3.66 (s, 3H, O-CH₃); 3.14 (m, 2H, H-C(5')); 2.34-2.70 (m, 8H, 6,7 CH₃, H-C(2'_α), H-C(2'_β)).

Anal. calc. for C₃₃H₃₀N₄O₅ · 1/2 H₂O (571.7): C, 69.33; H, 5.46; N, 9.80. Found: C, 69.76; H, 5.54; N, 9.88.

1-(2-Deoxy-5-O-p-monomethoxytrityl-β-D-threo-pentofuranosyl)-6,7-dimethylumazine (34). A solution of **33** (1.68 g, 3.0 mmole) in EtOH (30 ml) was treated with 1N sodium hydroxide (3 ml) for 1 h under reflux. After cooling it was neutralized with dilute acetic acid, then evaporated to dryness and the residue dissolved in CH₂Cl₂ (30 ml). After washing with H₂O, drying of the organic layer over sodium sulfate was evaporated to a colourless solid, which was used without further purification. Yield: 1.56 g (90 %), m.p. 175 °C ¹H-NMR (DMSO-d₆): 12.0 (s, 1H, NH); 6.81-7.39 (m, 1H, Ar-H); 6.89 (dd, 1H, H-C(1')); 5.24 (d, 1H, H-O(3')); 4.23 (s, 1H, H-C(3')); 4.04 (s, 1H, H-C(4')); 3.72 (s, 3H, O-CH₃); 3.22 (m, 2H, H-C(5')); 2.59 (m, 1H, H-C(2'_β)); 2.53 (2s, 6H, 6,7-CH₃); 2.30 (dd, 1H, H-C(2'_α)).

Anal. calc. for C₃₂H₃₂N₄O₆ (580.7): C, 68.28; H, 5.56; N, 9.65. Found: C, 68.39; H, 5.75; N, 9.49.

1-(2-Deoxy-3-O-mesyl-5-O-p-monomethoxytrityl-β-D-threo-pentofuranosyl)-6,7-dimethylumazine (35). A solution of **34** (0.58 g, 1.0 mmole) in dry pyridine (5 ml) was treated with methanesulfonyl chloride (0.5

ml, 6.5 mmole) by dropwise addition and subsequent stirring for 2 h at room temperature. It was diluted with ice-water (100 ml), then extracted with CH_2Cl_2 (2 x 20 ml), the organic layer washed with H_2O (3 x 10 ml) and then dried over sodium sulfate. Purification was achieved by column chromatography (3 x 10 cm) on silica gel with $\text{CHCl}_3/\text{MeOH}$ (99:1) to give a colourless solid on evaporation of the main fraction. Yield: 0.6 g (91 %), m.p. 132-134°C. $^1\text{H-NMR}$ (CDCl_3): 9.00 (s, 1H, NH); 6.75-7.42 (m, 14H, Ar-H); 6.87 (dd, 1H, H-C(1')); 5.36-5.41 (m, 1H, H-C(3')); 4.30 (q, 1H, H-C(4')); 3.77 (s, 3H, OCH_3); 3.50 (m, 2H, H-C(5')); 3.21 (m, 1H, H-C(2'β)); 2.85 (s, 3H, SO_2CH_3); 2.79 (m, 1H, H-C(2'α)); 2.46, 2.60 (2s, 6H, 6,7 CH_3).

Anal. calc. for $\text{C}_{34}\text{H}_{34}\text{N}_4\text{O}_8$ (658.7): C, 61.99; H, 5.20; N, 8.50. Found: C, 61.96; H, 5.10; N, 8.60.

1-(2-O-Acetyl-3,5-di-O-benzoyl-β-D-threo-pentofuranosyl)-lumazine (36). Silylation of lumazine (4.1 g, 25 mmole) was achieved by heating in hexamethyldisilazane (HMDS) (100 ml) in presence of a few crystals of ammonium sulfate under reflux for 6 h. The excess of HMDS was removed in high vacuum, the remaining oil dissolved in ethyl acetate (30 ml). A solution of 1,2-di-O-acetyl-3,5-di-O-benzoyl-D-xylofuranose¹⁷ in ethyl acetate (30 ml) was added followed by trimethylsilyl triflate (6). Stirring was continued for 2 h at room temperature and then MeOH (5 ml) and H_2O (30 ml) added and neutralized with a saturated solution of sodium bicarbonate. The organic layer was separated, dried over sodium sulfate and evaporated. The residue was purified by column chromatography (7 x 20 cm) on silica gel with toluene/ethyl acetate (9:1). The main fraction gave on evaporation a colourless solid. Yield: 9.43 g (69 %), m.p. 112-114°C. $^1\text{H-NMR}$ (CDCl_3): 8.78 (bs, 1H, NH); 8.44-8.61 (2d, 2H, 6,7 H); 7.36-8.16 (m, 10H, Ar-H); 6.72 (d, 1H, H-C(1')); 6.25 (dd, 1H, H-C(2')); 5.83 (dd, 1H, H-C(3')); 4.78 (m, 3H, H-C(4'), H-C(5')); 2.13 (s, 3H, OAc).

Anal. calc. for $\text{C}_{27}\text{H}_{22}\text{N}_4\text{O}_9$ (546.5): C, 59.34; H, 4.06; N, 10.25. Found: C, 59.31; H, 4.21; N, 10.11.

1-(3,5-Di-O-benzoyl-β-D-xylofuranosyl)-lumazine (37). To a solution of **36** (1.09 g, 2.0 mmole) in pyridine/acetic acid (4:1, 25 ml) was added hydrazine hydrate (1 ml) and then stirred at room temperature over night. It was evaporated to dryness, the residue treated with H_2O (30 ml) and CHCl_3 (30 ml).

The organic layer was dried over sodium sulfate, evaporated to a small volume and put onto a silica gel column (3 x 10 cm) for chromatography with toluene/ethyl acetate (9:1). The main fraction gave on evaporation a colourless solid.

Yield: 0.87 g (86 %), m.p. 136-138°C ¹H-NMR (CDCl₃): 9.85 (s, 1H, NH); 8.42-8.51 (2d, 2H, 6,7H); 7.30-8.05 (m, 10H, Ar-H); 6.79 (d, 1H, H-C(1')); 5.51 (d, 2H, H-C(2'), H-C(3')); 4.70-4.82 (m, 3H, H-C(4'), H-C(5')); 4.31 (bs, 1H, H-O(2')).

Anal. calc. for C₂₅H₂₀N₄O₈ (504.5): C, 59.52; H, 4.00; N, 11.11. Found: C, 59.47; H, 4.13; N, 11.17.

1-(3,5-Di-O-benzoyl-2-O-mesyl-β-D-xylofuranosyl)-lumazine

(38). A solution of **37** (4.03 g, 8.0 mmole) in dry pyridine (50 ml) was cooled to -10°C and then methanesulfonyl chloride (1 ml, 13 mmole) added dropwise with stirring. Stirring was continued for 2 h at 0°C, then ice-water (100 ml) added and the precipitate collected. It was dissolved in CH₂Cl₂ (50 ml), washed with H₂O (3 x 20 ml) and then the organic layer dried over sodium sulfate followed by evaporation to dryness. The residue was dissolved in little CH₂Cl₂ and then added dropwise with vigorous stirring into n-pentane (100 ml) to give an amorphous solid. Yield: 3.88 g (84 %), m.p. 128-130°C. ¹H-NMR (CDCl₃): 9.06 (s, 1H, NH); 8.49-8.62 (2d, 2H, 6,7H); 7.35-8.14 (m, 10H, Ar-H); 7.02 (d, 1H, H-C(1')); 6.23 (dd, 1H, H-C(2')); 5.71 (q, 1H, H-C(3')); 4.73-4.87 (m, 3H, H-C(4'), H-C(5')); 3.20 (s, 3H, SO₂CH₃).

Anal. calc. for C₂₆H₂₂N₄O₁₀S (582.5): C, 53.61; H, 3.81; N, 9.62. Found: C, 53.20; H, 3.94; N, 9.50.

2,2'-Anhydro-1-(3,5-di-O-benzoyl-β-D-lyxofuranosyl)-lumazine

(39). To a solution of **38** (2.91 g, 5 mmole) in dry CH₂Cl₂ (40 ml) was added DBU (1 ml, 6 mmole) and then the mixture heated under reflux for 15 min. After cooling the organic phase was washed with H₂O (3 x 20 ml), then dried over sodium sulfate and evaporated to dryness to give a chromatographically pure material. Yield: 2.24 g (93 %), m.p. 125-126°C. ¹H-NMR (CDCl₃): 8.52-8.76 (2d, 2H, 6,7-H); 7.27-8.05 (m, 10H, Ar-H); 6.87 (d, 1H, H-C(1')); 5.86-5.94 (m, 2H, H-C(2'), H-C(3')); 4.98 (m, 1H, H-C(4')); 4.55 (dq, 2H, H-C(5')).

Anal. calc. for C₂₅H₁₈N₄O₇ · 1/2 H₂O (495.5): C, 60.60; H, 3.86; N, 11.31. Found: C, 60.83; H, 3.84; N, 11.52.

1-(2-Bromo-2-deoxy-3,5-di-O-benzoyl- β -D-xylofuranosyl)-lumazine (40). A solution of **39** (1.94 g, 4 mmole) and lithium bromide (0.7 g, 8 mmole) in dry DMF (30 ml) was treated at room temperature with 33% HBr in acetic acid (10 ml) for 1 h. The mixture was poured into ice-water, the precipitate collected, then dissolved in CH_2Cl_2 , washed with water and finally dried over sodium sulfate. Purification was achieved by column chromatography (3 x 5 cm) on silica gel with $\text{CHCl}_3/\text{MeOH}$ (99:1). The main fraction gave on evaporation a colourless solid. Yield: 1.51 g (67 %), m.p. 117°C (decomp.). $^1\text{H-NMR}$ (CDCl_3): 8.90 (bs, 1H, NH); 8.56-8.68 (2d, 2H, 6,7H); 7.32-8.11 (m, 10H, Ar-H); 7.21 (d, 1H, H-C(1')); 5.93 (t, 1H, H-C(2')); 5.68 (q, 1H, H-C(3')); 4.87 (q, 1H, H-C(4')); 4.70 (m, 2H, H-C(5')).

Anal. calc. for $\text{C}_{25}\text{H}_{19}\text{BrN}_4\text{O}_7$ (567.4): C, 52.92; H, 3.38; N, 9.88.

Found: C, 52.76; H, 3.57; N, 9.73.

1-(3,5-Di-O-benzoyl-2-O-methoxythiocarbonyl- β -D-xylofuranosyl)-lumazine (41). A mixture of **37** (0.5 g, 1 mmole) and N,N'-thiocarbonyl-diimidazole (0.19 g, 1 mmole) in dry CHCl_3 (10 ml) was stirred at room temperature for 30 min. After evaporation, the residue was dissolved in MeOH (10 ml) and heated to 50°C for 2 h. It was again evaporated, then dissolved in little CHCl_3 and purified by column chromatography (1.5 x 10 cm) on silica gel with CHCl_3 . Yield: 0.34 g (59 %), m.p. 114-115°C. $^1\text{H-NMR}$ (CDCl_3): 8.92 (bs, 1H, NH); 8.46-8.62 (2d, 2H, 6,7H); 7.35-8.18 (m, 10H, Ar-H); 6.81 (d, 1H, H-C(1')); 6.77 (d, 1H, H-C(2')); 5.91 (d, 1H, H-C(3')); 4.78 (m, 3H, H-C(4'), H-C(5')); 4.02 (s, 3H, SO_2CH_3).

Anal. calc. for $\text{C}_{27}\text{H}_{22}\text{N}_4\text{O}_9\text{S}$ (578.6): C, 56.05; H, 3.83; N, 9.68.

Found: C, 55.77; H, 3.88; N, 9.45.

1-(3,5-Di-O-benzoyl-2-O-phenoxythiocarbonyl- β -D-xylofuranosyl)-lumazine (42). To a solution of **37** (0.252 g, 0.5 mmole) in dry CHCl_3 (5 ml) was added 4-(dimethylamino)-pyridine (DMAP) (0.05 g, 0.5 mmole) and phenoxythiocarbonyl chloride (0.09 ml, 0.6 mmole). After stirring for 10 min. the mixture was quenched with ice-water (10 ml) and extracted with ethyl acetate (2 x 20 ml). The organic layer was dried over sodium sulfate, then evaporated and the residue purified by column chromatography (1.5 x 7 cm) on silica gel with toluene/ ethyl acetate (2:1). Yield: 0.28 g (88 %), m.p. 116-117°C.

$^1\text{H-NMR}$ (CDCl_3): 8.90 (bs, 1H, NH); 8.47-8.62 (2d, 2H, 6,7H); 7.06-8.22 (m, 14H, ar-H); 6.93 (d, 1H, H-C(1')); 6.81 (d, 1H, H-C(2')). 6.00 (d, 1H, H-C(3')); 4.74-4.90 (m, 3H, H-C(4'), H-C(5')).

Anal. calc. for $\text{C}_{32}\text{H}_{24}\text{N}_4\text{O}_9\text{S}$ (640.6): C, 60.00; H, 3.78; N, 8.74.

Found: C, 60.04; H, 3.92; N, 8.36.

1-(2-Deoxy-3,5-di-O-benzoyl- β -D-threo-pentofuranosyl)-lumazine (43). To a solution of **42** (0.64 g, 1 mmole) in dry toluene (10 ml) was added under N_2 -atmosphere azodiisobutyronitrile (0.06 g) and $n\text{-Bu}_3\text{SNH}$ (1.6 ml, 6 mmole) with stirring. After 15 min the mixture was heated to 80°C for 8 h. It was evaporated to dryness and the residue purified by column chromatography (1.5 x 10 cm) on silica gel with n -hexane (200 ml) followed by toluene/ethyl acetate (2:1, 600 ml). The main fraction gave on evaporation a colourless solid. Yield: 0.232 g (48 %), m.p. $116\text{--}117^\circ\text{C}$. $^1\text{H-NMR}$ (DMSO-d_6): 11.98 (s, 1H, NH); 8.59-8.63 (2d, 2H, 6,7H); 7.14-8.05 (m, 10H, Ar-H); 6.93 (t, 1H, H-C(1')); 5.76 (m, 1H, H-C(3')); 4.51-4.76 (m, 3H, H-C(4'), H-C(5')); 3.16 (m, 1H, H-C(2' β)); 2.71 (m, 1H, H-C(2' α)).

Anal. calc. for $\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_7$ (488.5): C, 61.47; H, 4.13; N, 11.47.

Found: C, 61.09; H, 4.25; N, 11.11.

1-(2-Deoxy-3,5-di-O-p-toluoyl- β -D-erythro-pentofuranosyl)-lumazine (44)⁷. A mixture of lumazine (8.2 g, 50 mmole) and a few crystals of ammonium sulfate in hexamethyldisilazane (HMDS) (100 ml) was refluxed for 2 days till a clear solution was obtained. The excess of HMDS was distilled off in vacuum, the residue dissolved in dry CHCl_3 (200 ml) and then cuprous iodide (9.5 g, 50 mmole) added. After stirring for 5 min at room temperature 2-deoxy-3,5-di-O-p-toluoyl- α -D-erythro-pentofuranosyl chloride (19.4 g, 50 mmole) was added. The mixture was stirred for 15 min, then a saturated solution of sodium bicarbonate added, the organic layer dried over sodium sulfate and then the filtrate evaporated to dryness. The residue was recrystallized from CHCl_3 / MeOH (1:2, 225 ml) to give a colourless precipitate. Yield: 18.7 g (72 %), m.p. $154\text{--}155^\circ\text{C}$. Lit⁶: m.p. $156\text{--}158^\circ\text{C}$.

The work-up of the filtrate by silica gel column chromatography (3 x 7 cm) with CHCl_3 /MeOH (98:2) yielded 1.7 g (6.6 %) of the α -anomer. The products were characterized by comparison with authentic samples.

1-(2-Deoxy-3-O-mesyl-5-O-p-monomethoxytrityl-β-D-erythro-pentofuranosyl)-lumazine (46). A solution of 1-(2-deoxy-5-O-p-monomethoxytrityl-β-D-erythro-pentofuranosyl)lumazine¹⁴ in dry pyridine (50 ml) was cooled to -10°C and then dropwise added methanesulfonyl chloride (1 ml) with stirring. The mixture was then stirred for 2 h at 0°C, treated with ice-water (100 ml) and the resulting precipitate collected. The solid was dissolved in CH₂Cl₂ (50 ml), washed with H₂O (3 x 20 ml) and then the organic layer dried over sodium sulfate and filtered. The filtrate was concentrated to a small volume, which was dropwise added with vigorous stirring to n-pentane (100 ml) forming an amorphous solid. Yield: 2.7 g (91 %), m.p. 217-218°C. ¹H-NMR (DMSO-d₆): 12.02 (s, 1H, NH); 8.55, 8.59 (2d, 2H, 6,7-H); 6.66-7.38 (m, 14H, Ar-H); 7.05 (dd, 1H, H-C(1')); 5.35 (m, 1H, H-C(3')); 4.18 (q, 1H, H-C(4')); 3.71 (s, 3H, OCH₃); 3.31 (m, 2H, H-C(5')); 3.16 (s, 3H, SO₂CH₃); 3.02 (m, 1H, H-C(2'β)); 2.77-2.53 (m, 1H, H-C(2'α)).

Anal. calc. for C₃₂H₃₀N₄O₈S (630.7): C, 60.94; H, 4.79; N, 8.88.
Found: C, 60.57; H, 4.84; N, 8.65.

1-(3-Azido-2,3-dideoxy-5-O-p-monomethoxytrityl-β-D-erythro-pentofuranosyl)-lumazine (47). A solution of **50** (0.46 g, 0.73 mmole) in dry DMF (3 ml) was treated with lithium azide (0.1 g, 1.6 mmole) at 80°C for 4 h under exclusion of moisture. It was evaporated to dryness in high vacuum, the residue dissolved in CH₂Cl₂ (10 ml), washed with H₂O (2 x 5 ml) and then the organic layer dried over sodium sulfate. After concentration to a small volume purification was achieved by silica gel chromatography (3 x 5 cm) with CHCl₃/MeOH (99:1). The main fraction gave on evaporation an amorphous solid. Yield: 0.32 g (75 %), m.p. 119-120°C. ¹H-NMR (CDCl₃): 8.90-9.10 (bs, 1H, NH); 8.44-8.61 (2d, 2H, 6,7-H); 6.77-7.45 (m, 14H, Ar-H); 7.10 (dd, 1H, H-C(1')); 4.53 (q, 1H, H-C(3')); 3.96 (q, 1H, H-C(4')); 3.77 (s, 3H, OCH₃); 3.41 (m, 2H, H-C(5')); 3.03 (m, 1H, H-C(2'β)); 2.35 (m, 1H, H-C(2'α)).

Anal. calc. for C₃₁H₂₇N₇O₃ (577.6): C, 64.46; H, 4.71; N, 16.97.
Found: C, 64.06; H, 4.88; N, 16.76.

2,3'-Anhydro-1-(2-deoxy-5-O-p-monomethoxytrityl-β-D-threo-pentofuranosyl)-lumazine (48). A solution of **46** (2.52 g, 4 mmole) in dry CH₂Cl₂ (40 ml) was treated with 1,8-diaza-bicyclo[5.4.0]-undec-7-ene (DBU)

(1 ml, 6 mmole) by boiling under reflux for 1 h. After cooling the reaction solution was washed with H₂O (3 x 20 ml), the organic phase dried over sodium sulfate and then evaporation to a small volume purified by column chromatography (3 x 5 cm) on silica gel with CHCl₃/MeOH (98:2). The main fraction was evaporated to give an amorphous solid. Yield: 1.8 g (84 %), m.p. 186-190°C. ¹H-NMR (DMSO-d₆): 8.91, 8.87 (2d, 2H, 6,7-H); 6.70-7.33 (m, 14H, Ar-H); 7.02 (d, 1H, H-C(1')); 5.52 (s, 1H, H-C(3')); 4.53 (bs, 1H, H-C(4')); 3.67 (s, 3H, OCH₃); 3.18 (m, 2H, H-C(5')); 2.60 (m, 2H, H-C(2'β), H-C(2'α)).

Anal. calc. for C₃₁H₂₆N₄O₅ (534.7): C, 69.64; H, 4.90; N, 10.49.

Found: C, 69.45; H, 4.93; N, 10.40.

1-(2-Deoxy-5-O-p-monomethoxytrityl-β-D-threo-pentofuranosyl)-lumazine (49). A solution of EtOH (30 ml) and 1 N sodium hydroxide (3 ml) containing **48** (1.6 g, 3 mmole) was heated under reflux for 1 h. After cooling the solution was neutralized with acetic acid to pH 7, evaporated to dryness and then the residue taken up in CH₂Cl₂ (30 ml). It was washed with H₂O, dried over sodium sulfate and then again evaporated to an amorphous solid. The material was chromatographically pure and was not further purified for the next step. Yield: 1.42 g (85 %), m.p. 127-129°C. ¹H-NMR (CDCl₃): 9.06 (s, 1H, NH); 8.60, 8.68 (2d, 2H, 6,7-H); 6.76-7.17 (m, 14H, Ar-H); 7.01 (dd, 1H, H-C(1')); 5.04 (d, 1H, 3'-OH); 4.35 (m, 1H, H-C(3')); 3.96 (m, 1H, H-C(4')); 3.77 (s, 3H, OCH₃); 3.54 (dq, 2H, H-C(5')); 2.77 (m, 1H, H-C(2'β); 2.42 (dd, 1H, H-C(2'α)).

Anal. calc. for C₃₁H₂₈N₄O₆ (552.6): C, 67.37; H, 5.11; N, 10.14.

Found: C, 67.62; H, 5.22, N, 9.90.

1-(2-Deoxy-3-O-mesyl-5-O-p-monomethoxytrityl-β-D-threo-pentofuranosyl)-lumazine (50). - A solution of **49** (0.55 g, 1 mmole) in dry pyridine (20 ml) was cooled to -10°C and then dropwise added methane-sulfonyl chloride (0.5 ml) with stirring. The reaction mixture was stirred for 2 h at 0°C, then diluted with H₂O (50 ml) and the precipitate filtered off. The solid was dissolved in CH₂Cl₂ (20 ml), washed with H₂O (3 x 10 ml) and then the organic layer dried over sodium sulfate. The filtrate was evaporated to a small volume and then added dropwise under vigorous stirring into n-pentane (50 ml) to give an amorphous solid. Yield: 0.54 g (86 %), m.p. 144-147°C. ¹H-NMR (CDCl₃):

9.12 (s, 1H, NH); 8.56, 8.61 (2d, 2H, 6,7-H); 6.77-7.43 (m, 14H, Ar-H); 5.37 (m, 1H, H-C(3')); 4.23 (q, 1H, H-C(4')); 3.77 (s, 3H, OCH₃); 3.50 (m, 2H, H-C(5')); 3.27 (m, 1H, H-C(2'β)); 2.88 (s, 3H, SO₂CH₃); 2.81 (m, 1H, H-C(2'α)).

Anal. calc. for C₃₂H₃₀N₄O₈ · 1/2 H₂O (639.7): C, 60.09; H, 4.57; N, 8.76. Found: C, 60.08; H, 4.66; N, 8.78.

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