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Reductive Cyclization of 6-Cyanomethyl-5-nitropyrimidines - an Efficient Route to 7-Alkyl-5*H*-pyrrolo[3,2-*d*]pyrimidines and 6-Amino-7,7-dialkyl--7*H*-pyrrolo[3,2-*d*]pyrimidines. Utilization in the Synthesis of 9-Deaza Analogues of DHPA[1].

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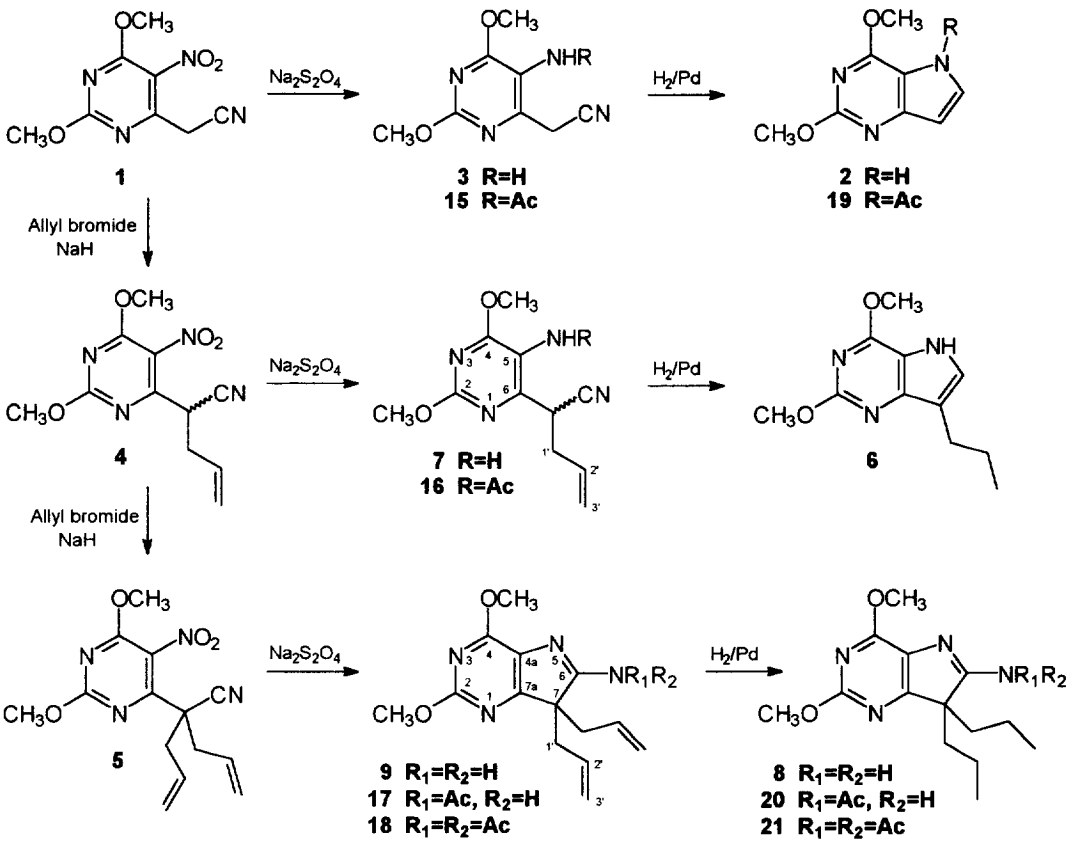
Abstract: Reductive cyclization of 6-(1-cyanoalkyl)-5-nitropyrimidines leads to 7-alkyl-5*H*-pyrrolo[3,2-*d*]pyrimidines. The presence of two alkyl substituents at the cyanomethyl group results in formation of 6-amino-7,7-dialkyl-7*H*-pyrrolo-[3,2-*d*]pyrimidines. By this method 7-(2,3-dihydroxypropyl)-2,4-dimethoxy-5*H*-pyrrolo[3,2-*d*]pyrimidine was prepared as an intermediate for the preparation of 9-deaza analogues of DHPA and related compounds.

INTRODUCTION

As part of our ongoing programme on the design, synthesis and biological evaluation of acyclic nucleoside analogues, we are interested in the preparation of the 9-deaza analogs of antiviral 9-(2,3-dihydroxypropyl)adenine (DHPA)[2]. Three main synthetic approaches for 7-C-substituted 5*H*-pyrrolo[3,2-*d*]pyrimidines are described in the literature:1) multistep procedure based on the synthesis of pyrrole nucleus from α-formylnitriles followed by ring-closure of condensed pyrimidine[3-6], 2) electrophilic substitution of preformed 5*H*-pyrrolo[3,2-*d*]pyrimidines at the position 7 (ref.[7]), 3) reductive cyclization of 6-cyanomethyl-5-nitropyrimidines substituted with alkyl group at their active methylene group[8-10]. The latter method was originally developed for the preparation of 3-alkylindoles by reductive cyclization of *o*-(alkylcyanomethyl)nitrobenzenes[11,12]. In the case of *o*-(dialkylcyanomethyl)nitrobenzenes 2-amino-3,3-dialkyl-3*H*-indole derivatives were isolated[9].

RESULTS AND DISCUSSION

According to the literature the cyanomethylpyrimidine[13] **1** provides by hydrogenation on palladium catalyst in ethyl acetate the 5*H*-pyrrolo[3,2-*d*]pyrimidine derivative **2**. The intermediary amino derivative **3** was prepared by reduction of compound **1** with sodium dithionite. Alkylation of sodium salt of compound **1** with allyl bromide gave racemic allyl derivative **4** besides a small amount of disubstituted product **5**. Compound **4** was then hydrogenated on palladium catalyst to give 2,4-dimethoxy-7-propyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (**6**) as the only product. On the other hand, reduction of compound **4** with sodium dithionite afforded only the intermediary amino derivative **7**. The presence of the intermediary amino derivatives **3** and **7** in the reaction mixture after hydrogenation can be avoided by performing it in acidic conditions. The hydrogenation of disubstituted derivative **5** resulted in the 6-amino-7*H*-pyrrolo[3,2-*d*]pyrimidine **8** as the only product. The intermediary amino derivative was not isolated. The reaction of compound **5** with sodium dithionite was accompanied by the ring closure providing the diallyl-7*H*-derivative **9**.



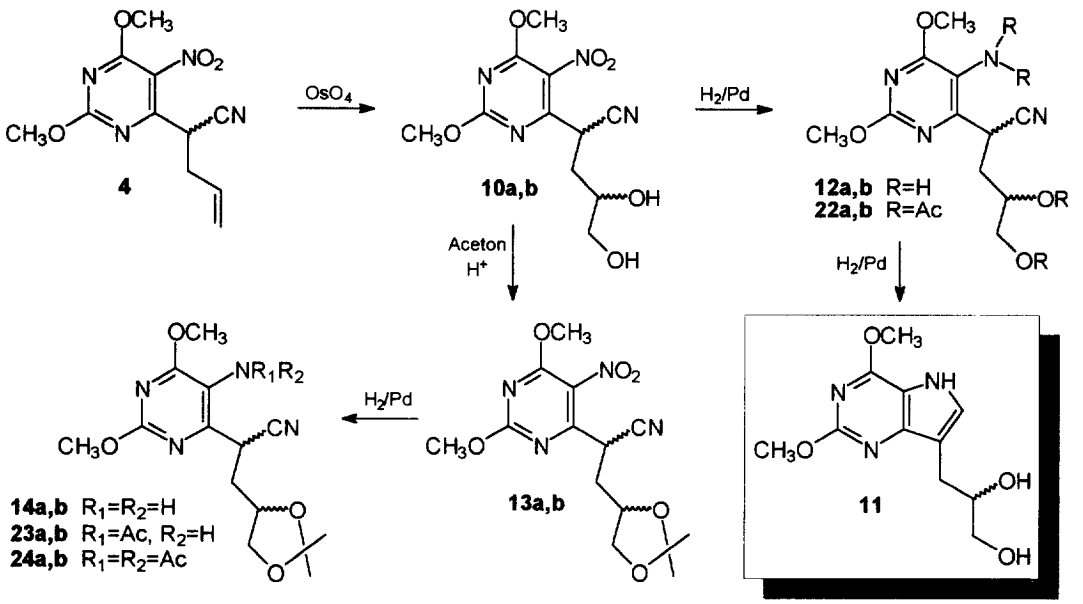
Scheme 1.

The formation of 6-amino-7*H*-derivatives **8** and **9** is analogous to the formation of 2-amino-3,3-dialkyl-3*H*-indole derivatives by reductive cyclization of 2-nitrophenylacetonitriles bearing two alkyl substituents at the methylene group[11].

In order to obtain the desired 7-dihydroxypropyl derivative **11**, the allyl derivative **4** was hydroxylated with osmium tetroxide to afford the diol **10a,b** (unseparable mixture of diastereomers 2:1; determined by ^{1}H NMR without distinguishing the configuration). The catalytic hydrogenation of compound **10a,b** in ethyl acetate - acetic acid 2:1 mixture gave the desired 5*H*-pyrrolo[3,2-*d*]pyrimidine **11**. However, the hydrogenation of the compound **10a,b** in ethyl acetate in the absence of acid afforded the amine **12a,b** as the only product. Also the isopropylidene derivative **13a,b** gave the amine **14a,b** on hydrogenation in the absence of acid.

To enable an unequivocal structural elucidation, the above compounds were converted into their acetates **15**, **16**, **17**, **19**, **20**, **23a,b** (diacetates **18**, **21**, and **24a,b** were isolated as byproducts) and tetraacetate **22a,b** by treatment with acetic anhydride in pyridine under usual conditions.

The structural assignment of the pyrimidine derivatives is based on proton-coupled ^{13}C NMR spectra (Figure 1). The carbon C-2 and C-4 signals were distinguished by their interaction with protons of the methoxy groups [J(C,H)=3.9]. In the monoacetyl derivatives **15**, **16**, and **23** interactions of NH proton: J(C-5,NH) = 2.0-3.0, J(C-6,



Scheme 2.

NH) = 3.0-5.0, J(C=O, NH) = 3.0-4.0 [at compound **15** also J(C-4, NH) = 1.5] were observed. These interactions and others, which are depicted on Fig. 1, confirm the allocation of the other quaternary carbons. The values in Tab. 1-6 show significant upfield shifts of carbons C-2, C-4, C-5, and C-6 approx. 3, 8, 6, and 18 ppm in the 5-amino derivatives **3**, **7**, **12a,b**, and **14a,b** compared to the starting nitro derivatives **1**, **4**, **10a,b**, and **13a,b**. The mono-acetylation of the 5-aminopyrimidines **3**, **7**, and **14a,b** causes a 10 ppm upfield shift of carbon C-5 and downfield shifts of carbons C-4 and C-6 (approx. 11 and 18-20 ppm) in the corresponding acetates **15**, **16**, and **23a,b**. The presence of cyano group, which resisted the reduction by sodium dithionite, was also confirmed by IR spectra at 2250 cm^{-1}.

^1H NMR Spectra of 5*H*-pyrrolo[3,2-*d*]pyrimidines **6** and **11** are characterized by the presence of doublet of NH (δ = 11.50-11.80 ppm) and by doublet of H-6 (δ = 7.30-7.50 ppm). 7*H*-Pyrrolo[3,2-*d*]pyrimidines **8** and **9** show two-proton signal of NH_2 group (δ = 7.10 ppm) and their acetyl derivatives **17** and **20** show signal NH (δ = 10.50 ppm). The signals of C-2 and C-4 carbons in 7*H*-derivatives **8**, **9**, **17**, **18**, **20**, and **21** were assigned by proton-coupled ^{13}C NMR [J(C,H) = 3.9]. In monoacetyl derivatives **17** and **20** the carbon C-6 and C-7, in contrast of the C-4 atom, interact with proton NH-Ac [J(C,NHAc) ~ 2.0; Fig.1]. This interaction, the substitution effects observed in the mono- and diacetyl derivatives (Tab. 1-6), as well as the absence of the cyano group in the IR spectra confirm the 7*H*-structure of these compounds.

The three types of studied compounds exhibit characteristic UV spectra (in methanol): the 5-amino-6-(1-cyanoalkyl)pyrimidines **3**, **7**, **12a,b**, **14a,b**: λ_{max} = 303 nm (ε = 6000), λ_{max} = 237 nm (ε = 8500); 5*H*-pyrrolo[3,2-*d*]pyrimidines **6**, **11**: λ_{max} = 268 nm (ε = 10000), λ_{max} = 224 nm (ε = 15000); 7*H*-pyrrolo[3,2-*d*]pyrimidines **8**, **9** give only one maximum: λ_{max} = 268 nm (ε =19000).

Table 1. ^{1}H NMR (Chemical Shifts and Interaction Constants).

δ (ppm)	2	3	4	5	6	7	8	9	10a	10b
CH_3O	3.86 s 4.01 s	3.80 s 3.92 s	4.13 s 4.135 s	4.09 s 4.11 s	3.86 s 4.00 s	3.80 s 3.92 s	3.83 s 3.91 s	3.81 s 3.87 s	4.03 s 4.06 s	4.03 s 4.065 s
H-6	7.52 dd				7.30 d					
H-7	6.36 d									
NH_2		4.62 s				4.74 s	7.08 s	7.15 s		
NH	11.77 d				11.41 d					
CH-CN		3.98 s	4.28 dd			4.53 t			4.58 dd	4.55 dd
H-1'a			2.79 m	2.99 dd	2.58 t	2.61 m	1.73 m	2.51 br d	2.18 ddd	2.25 ddd
H-1'b				2.74 dd			1.68 m		1.80 ddd	1.97 ddd
H-2'a			5.83 ddt	5.79 ddt	1.66 m	5.80 ddt	0.91 m	5.16 ddt	3.66 m	3.32 m
H-2'b							0.54 m			
H-3'a			5.24 dq	5.24 dq	0.90 t	5.19 dq	0.70 t	4.88 ddt	3.88 dt	3.31 dt
H-3'b			5.22 dq	5.23 dq		5.12 ddt		4.80 ddt	3.25 dt	3.23 dt
OH									4.71 t 5.04 d	4.65 t 4.79 d
J (Hz)	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10a**	**10b**
6, 7	2.9									
6, NH	1.5				2.4					
CHCN, 1'a			6.8			7.1			11.0	7.8
CHCN, 1'b			7.8			7.1			4.9	6.4
1'a, 1'b			a	13.9		a		a	13.4	13.4
1'a, 2'			7.1	7.1	7.4	6.8	a	6.8	2.7	3.9
1'b, 2'									10.5	8.8
2', 3'a			17.1	17.3	7.3	17.1	7.3	17.1	5.1	5.1
2', 3'b			10.0	10.3		10.3		10.0	6.1	6.1
3'a, 3'b			1.5	1.5		1.7		2.2	11.0	11.0
1', 3'a			1.2	1.2		1.5		1.2		
1', 3'b			1.0	1.0		1.0		1.0		
2', OH									5.1	5.1
3', OH									5.7	5.6

a - Unresolved multiplet, the value of the interaction constant (J) cannot be estimated.

Table 2. ^{13}C NMR Spectra (Chemical Shifts).

δ (ppm)	1	2	3	4	5	6	7	8	9	10a	10b
C-2	163.30	156.98	160.31	163.75	162.57	156.77	160.79	157.24	157.48	163.85	163.92
C-4	163.97	159.54	155.74	164.10	164.30	159.03	155.79	159.99	159.82	164.14	164.14
C-4a		111.19				111.29		129.42	129.79		
C-5	128.10		122.52	128.71	127.20		122.27			128.44	129.00
C-6	158.29	130.53	139.15	159.06	157.24	128.15	141.74	175.13	173.89	160.76	160.16
C-7		100.89				114.60		57.59	56.89		
C-7a		151.22				149.96		169.86	168.78		
CN	115.97		117.43	116.86	117.95		119.63			118.42	119.08
OCH_3	56.18 56.21	53.39 54.06	54.13 54.24	55.96 56.31	55.83 56.00	53.26 53.92	54.11 54.31	53.30 54.40	53.28 54.42	56.28 56.33	56.28 56.33
C-CN	24.87		21.55	35.71	48.72		32.50			36.88	36.44
C-1'				36.76	41.91 41.94	25.79	35.04	37.92	39.53	36.85	36.41
C-2'				131.36	130.45 130.49	22.85	133.81	17.01	132.66	69.01	68.57
C-3'				120.31	121.22 121.25	14.06	118.76	14.19	118.36	65.75	65.62

Table 3. ^{1}H NMR (Chemical Shifts and Interaction Constants, Cont.).

δ (ppm)	11[b]	12a	12b	13a	13b	14a	14b	15	16	17
CH_3O	3.86 s 4.01 s	3.80 s 3.925 s	3.795 s 3.93 s	4.03 s 4.07 s	4.03 s 4.07 s	3.80 s 3.92 s	3.79 s 3.93 s	3.90 s 3.90 s	3.92 s 3.93 s	3.90 s 3.97 s
NH_2		4.56 s	4.65 s			4.68 s	4.72 s			
NH	11.51 d							9.35 s	9.35 s	10.53 s
CH-CN		4.48 dd	4.44 dd	4.58 dd	4.57 dd	4.51 dd	4.47 dd	3.65 s	4.26 dd	
H-1'a	2.82 dd	2.12 ddd	2.20 ddd	2.19 ddd	2.25 ddd	2.20 m	2.20 m		2.62 ddd	2.89 dd
H-1'b	2.62 dd	1.65 ddd	1.87 ddd	2.09 ddd	2.20 ddd	1.96 ddd	2.10 m		2.58 ddd	2.58 dd
H-2'	3.74 m	3.64 m	3.26 m	4.27 m	4.25 m	4.18 m	3.98 m		5.78 ddt	5.11 ddt
H-3'a	3.29 ddd	3.38 dt	3.35 dt	4.08 dd	3.99 dd	4.05 dd	3.96 dd		5.15 dq	4.88 ddt
H-3'b	3.26 ddd	3.26 dt	3.25 dt	3.63 dd	3.59 dd	3.57 dd	3.56 dd		5.11 dq	4.81 ddt
OH	4.59 t 4.87 d	4.68 t 4.89 d	4.60 t 4.85 d							
$(CH_3)_2C$				1.26 s 1.31 s	1.21 s 1.30 s	1.28 s 1.33 s	1.23 s 1.34 s			
N-Ac								2.01 s	2.04 s	2.30 s
J (Hz)	**11[b]**	**12a**	**12b**	**13a**	**13b**	**14a**	**14b**	**15**	**16**	**17**
CHCN, 1'a		10.8	9.0	10.0	6.5	9.6	7.6		6.6	
CHCN, 1'b		4.9	5.6	5.2	7.0	5.6	7.0		8.1	
1'a, 1'b	14.7	13.7	13.4	13.4	13.7	13.8	a		14.2	13.7
1'a, 2'	5.1	2.7	3.4	2.8	5.2	a	a		7.1	7.3
1'b, 2'	7.1	10.3	8.8	9.6	7.5	7.3	a		7.1	7.1
2', 3'a	5.3	5.1	5.0	6.1	6.0	6.8	6.0		17.1	17.1
2', 3'b	5.3	6.0	6.0	5.2	5.7	6.2	6.0		10.3	10.0
3'a ,3'b	11.0	11.0	11.0	8.3	8.3	8.3	8.3		1.5	2.2
2', OH	4.9	5.6	5.1							
3', OH	5.8	5.6	5.4							
1', 3'a									1.5	1.2
1', 3'b									1.2	1.0

a - Unresolved multiplet, the value of the interaction constant (J) cannot be estimated.
b - δ(H-6) = 7.35 d; J(6,NH) = 2.9.

Table 4. ^{13}C NMR (Chemical Shifts, Cont.).

δ (ppm)	11	12a	12b	13a	13b	14a[c]	14b[c]	15	16	17
C-2	156.88	161.03	160.99	163.51	163.57	161.00	160.88	162.18	162.55	159.57
C-4	159.02	156.02	156.16	164.02	163.96	156.02	155.87	166.81	167.40	162.14
C-4a	111.12									126.83
C-5		121.71	122.83	128.28	128.68	122.66	122.10	111.84	111.63	
C-6	129.45	143.62	142.42	160.31	159.55	142.28	141.19	157.76	161.03	167.72
C-7	111.62									59.84
C-7a	149.89									170.50
CN		120.01	120.77	118.00	118.37	119.97	119.61	116.92	119.07	
C-CN		30.43	29.13	33.38	32.26	30.13	29.46	22.83	33.94	
OCH_3	53.40 54.01	54.26 54.47	54.26 54.47	56.18 56.24	56.18 56.24	54.14 54.38	54.14 54.38	54.68 55.03	54.77 55.08	53.73 54.84
C-1'	28.61	35.60	35.85	36.90	36.09	35.09	35.20		35.98	37.56
C-2'	71.77	69.21	68.76	72.98	72.63	73.19	73.11		133.54	131.95
C-3'	65.46	65.86	65.72	68.92	68.18	68.44	68.39		118.96	118.84
C=O								169.15	169.69	170.35
$CO-CH_3$								22.70	22.73	25.23

c - δ(isopropylidene): 25.75; 27.03; 108.65.

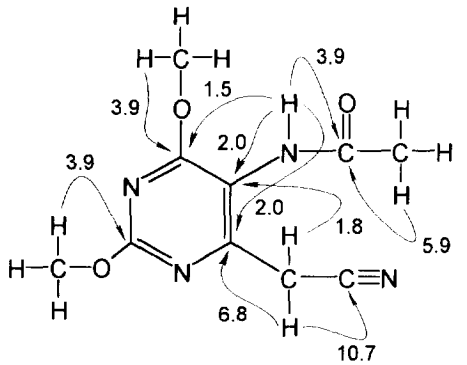
Table 5. ^{1}H NMR (Chemical Shifts and Interaction Constants, Cont.).

δ (ppm)	18	19[d]	20	21	22a	22b	23a[e]	23b[e]	24a[e]	24b[e]
CH_3O	3.95 s 4.01 s	3.90 s 3.98 s	3.89 s 3.98 s	3.93 s 4.01 s	3.96 s 3.98 s	3.96 s 3.98 s	3.92 s 3.925 s	3.92 s 3.925 s	3.96 s 3.98 s	3.955 s 3.98 s
NH-Ac			10.38 s				9.40 s	9.37 s		
CH-CN					4.43 dd	4.50 dd	4.25 dd	4.22 dd	4.30 dd	4.35 dd
H-1'a	2.63 dd		2.04 m	1.83 m	2.25 m	2.25 m	2.10 m	2.10 m	2.15 m	2.15 m
H-1'b	2.57 dd		1.76 m	1.74 m	1.90 m	2.05 m	1.85 ddd	2.00 m	1.85 ddd	2.12 m
H-2'a	5.41 ddt		0.81 m	1.09 m	5.08 m	5.08 m	4.19 m	4.00 m	4.20 m	3.92 m
H-2'b			0.49 m	0.75 m						
H-3'a	5.03 ddt		0.68 t	0.76 t	4.24 dd	4.21 dd	4.05 dd	3.94 dd	4.05 dd	3.98 dd
H-3'b	4.92 ddt				4.06 dd	4.03 dd	3.58 dd	3.49 dd	3.60 dd	3.52 dd
N-Ac	2.21 s 2.32 s	2.66 s	2.33 s	2.21 s 2.43 s	2.10 s 2.39 s	2.18 s 2.30 s	2.01 s	2.02 s	2.16 s 2.33 s	2.20 s 2.29 s
O-Ac					1.99 s 2.01 s	1.98 s 2.01 s				
J (Hz)	**18[c]**	**19**	**20**	**21**	**22a**	**22b**	**23a**	**23b**	**24a**	**24b**
CHCN, 1'a					9.5	9.5	6.1	6.5	5.0	7.0
CHCN, 1'b					3.6	5.1	9.3	7.0	9.3	7.5
1'a, 1'b	13.7				a	a	13.4	a	13.7	a
1'a, 2'	7.3		a	a	a	a	a	a	a	a
1'b, 2'	7.3				a	a	5.1	a	5.1	a
2', 3'a	17.1		7.1	7.1	3.6	3.6	6.3	6.0	6.1	6.1
2', 3'b	10.0				5.6	5.4	5.4	6.0	5.4	5.6
3'a, 3'b	2.2				12.0	12.0	8.3	8.3	8.3	8.3

a - Unresolved multiplet, the value of the interaction constant (J) cannot be estimated.
c - J(1,3'a) = 1.2; J(1,3'b) = 1.0.
d - δ(H-6) = 8.12 d; δ(H-7) = 6.64 d; J(6,7) = 3.7.
e - δ(isopropylidene) = 1.25-1.35 s.

Table 6. ^{13}C NMR Spectra (Chemical Shifts, Cont.).

δ (ppm)	18	19	20	21	22a	22b	23a	23b	24a	24b
C-2	158.26	157.10	159.43	158.07	164.04	164.05	161.37	160.72	162.22	161.84
C-4	163.85	161.45	162.13	163.05	167.41	167.41	167.43	167.43	167.35	167.46
C-4a	116.19	110.28	127.06	116.03						
C-5					113.30	113.62	111.22	111.87	113.35	114.04
C-6	154.15	133.82	168.90	155.63	162.02	161.85	162.70	162.64	164.14	164.08
C-7	56.05	106.80	60.26	56.84						
C-7a	162.99	158.03	171.59	164.70						
OCH_3	54.58 54.70	54.11 54.58	53.72 54.81	54.54 55.13	55.49 55.52	55.49 55.52	54.80 55.09	54.79 55.09	55.49 55.52	55.49 55.52
CN					118.67	118.52	118.78	119.52	118.54	119.02
C-CN					30.08	30.15	31.78	30.87	30.91	31.33
C-1'	41.05		36.23	39.84	32.50	31.92	36.54	36.35	36.46	35.87
C-2'	131.50		16.99	17.27	68.46	69.22	72.88	72.85	72.86	72.53
C-3'	120.04		14.08	13.99	64.00	63.82	68.27	68.18	68.28	68.34
C=O	169.09 179.28	167.67	170.52	168.93 179.19	170.19 170.30 172.00 172.52	170.03 170.30 171.98 172.41	169.64	169.46	172.19 172.47	172.04 172.37
CO-CH_3	25.09 26.48	24.25	25.39	25.53 26.17	20.62 21.05 25.79 26.18	20.65 20.88 25.92 26.09	22.63	22.69	25.83 26.07	25.95 26.00
$C(CH_3)_2$							108.83	108.58	108.85	108.82
$C(CH_3)_2$							25.50 27.02	25.58 26.94	25.46 26.92	25.47 26.96



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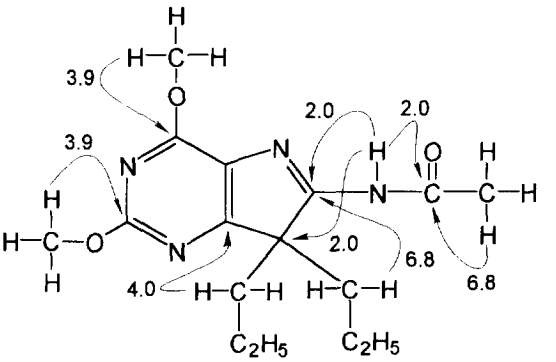

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Figure 1. ^{13}C NMR Spectra: Long-range coupling constants J (Hz).

EXPERIMENTAL SECTION

General: The melting points were determined on Kofler block and are uncorrected. TLC was performed on silica gel with fluorescent indicator on aluminum plates (Silufol UV 254, Kavalier, Czech). Column chromatography was carried out on silica gel (Sigma, 40-63 μm) or on neutral aluminium oxide (Woelm). Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer, using the EI (electron energy 70 eV), FAB (ionization by Xe, accelerating voltage 8 kV), matrices are glycerol and thioglycerol or 2-hydroxyethyl disulfide. NMR spectra were measured on Varian Unity 500 instrument (^1H NMR at 500 MHz, ^{13}C at 125.7 MHz) in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. In the case of ^{13}C NMR the APT as well as proton-coupled spectra were measured, signals were referenced to the solvent (δ = 39.7 ppm). IR spectra were measured on FT IR Bruker IFS 88 spectrometer in chloroform at concentration approx. 3%. UV spectra were measured on Beckman DU-65 spectrophotometer in methanol solutions.

5-Amino-6-cyanomethyl-2,4-dimethoxypyrimidine (3)

A solution of sodium dithionite (1.7 g, 10 mmol) in water (20 ml) was added to compound **1** (224 mg, 1 mmol) in methanol (20 ml) and the reaction mixture was stirred 2 h at room temperature. The solvent was evaporated and the residue was taken into ethyl acetate and extracted three times with sodium chloride, the organic layer dried over magnesium sulfate and evaporated. Chromatography on silica gel column with toluene - ethyl acetate mixture (19:1) gave product **3** (98 mg, 50%) as yellow crystals: mp 130-132 °C; MS(FAB): 195 (MH^+); IR ($CHCl_3$, cm^{-1}): 3446 w, 3373 w (NH_2); 2253 vw (CN); 1588 s, 1484 m, 1405 s, 1380 vs (ring); 1469 s, 1460 m,sh, 1089 m, 1043 w (CH_3); Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.67; H, 5.30; N, 28.62.

6-(1-Cyano-3-buten-1-yl)-2,4-dimethoxy-5-nitropyrimidine (4) and
6-(4-Cyano-1,6-heptadien-4-yl)-2,4-dimethoxy-5-nitropyrimidine (5)

Sodium hydride (60% wt dispersion in mineral oil, 160 mg, 4 mmol) was added to a solution of compound **1** (897 mg, 4 mmol) in 1,2-dimethoxyethane (20 mL) and the red suspension was then stirred 30 min in room temperature. Solution of allyl bromide (520 μL, 6 mmol) in 1,2-dimethoxymethane (30 mL) was added and the reaction mixture was stirred two days at room temperature. The reaction mixture was taken into ethyl acetate and extracted twice with saturated ammonium chloride and once with saturated sodium chloride solution. Organic layer was dried over magnesium sulfate and evaporated under reduced pressure. Chromatography on silica gel column with toluene - ethyl acetate mixture (24:1) gave product **4** (910 mg, 86 %) as yellow oil: MS (FAB): 265 (MH^+); Anal. Calcd. for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N 21.20. Found: C, 49.78; H, 4.54; N 21.06; and product **5** (50 mg, 4%) as white crystals: mp 86-88 °C; MS (FAB): 305 (MH^+); IR ($CHCl_3$, cm^{-1}): 3086 vw, 2987 vw, 1642 vw, 990 w (double bond); 2245 vw (CN); 1574 m, 1493 m, 1395 w, 1378 w (ring); 1539 m, 1351 m, 841w (NO_2); 1464 m, 1456 w, 1067 w,br (CH_3); Anal. Calcd. for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.03; H, 5.41; N, 18.59.

With the use of excess allyl bromide (3.5 mL, 40 mmol) under above conditions, the compound **5** (970 mg, 80%) was obtained as the only product.

2,4-Dimethoxy-7-propyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (6)

10% Palladium on activated carbon (10 mg) was added under argon to a solution of compound **4** (264 mg, 1 mmol) in ethyl acetate (50 mL) and the reaction mixture was hydrogenated under slight overpressure of hydrogen overnight. Thereafter, the reaction mixture was filtered over Celite and the filtrate evaporated. Chromatography on silica gel column with toluene gave product **6** (189 mg, 85%) as white crystals: mp 103-105 °C; MS (FAB): 222 (MH^+); Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.59; H, 6.75; N, 19.06.

5-Amino-6-(1-cyano-3-buten-1-yl)-2,4-dimethoxypyrimidine (7)

To compound **4** (264 mg, 1 mmol) in methanol (20 mL) was added a solution of sodium dithionite (1.7 g, 10 mmol) in water (20 mL) and the reaction mixture was stirred 2 h at room temperature. The solvent was evaporated and the residue was taken into ethyl acetate, extracted three times with saturated sodium chloride solution, dried over magnesium sulfate and evaporated. Chromatography on silica gel column with toluene - ethyl acetate mixture (9:1) gave product **7** (150 mg, 64%) as yellow oil: MS (FAB): 235 (MH^+); IR ($CHCl_3$, cm^{-1}): 3447 w, 3370 w, 1620 w,sh; 3085w, 2990 w,sh, 1643 w,989 w, 929 m (vinyl); 2242 w (CN); 1587 s, 1484 s, 1405 s, 1380 vs (ring); 1468 s, 1460 s,sh, 1087 s, 1045 m (CH_3); Anal. Calcd. for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.21; H, 6.09; N, 23.77.

6-Amino-2,4-dimethoxy-7,7-dipropyl-7*H*-pyrrolo[3,2-*d*]pyrimidine (8)

10% Palladium on activated carbon (10 mg) was added under argon to a solution of compound **5** (304 mg, 1 mmol) in ethyl acetate (50 mL) and the reaction mixture was hydrogenated under slight overpressure of hydrogen overnight. Thereafter, the reaction mixture was filtered over Celite and the filtrate evaporated. Chromatography on silica gel column with chloroform - methanol mixture (99:1) gave product **8** (119 mg, 43%) as white powder: mp 252-254 °C; MS (FAB): 279 (MH^+); IR ($CHCl_3$, cm^{-1}): 3520 w, 3410 w, 1630 s (NH_2), 1581 m, 1556 w, 1473 m, 1466 m (OCH_3), 1457 m (OCH_3), 1381 m, 1366 vs, 1075 w (OCH_3), 1053 w (OCH_3); Anal. Calcd. for $C_{14}H_{22}N_4O_2$: C, 60.41; H, 7.97; N, 20.13. Found: C, 60.12; H, 8.06; N, 19.89.

6-Amino-7,7-diallyl-2,4-dimethoxy-7*H*-pyrrolo[3,2-*d*]pyrimidine (9)

A solution of sodium dithionite (4.4 g, 26 mmol) in water (52 mL) was added to compound **5** (812 mg, 2.6 mmol) in methanol (52 mL) and the reaction mixture was stirred 2 h at room temperature. The solvent was evaporated and the residue was taken into ethyl acetate, extracted three times with saturated sodium chloride solution, dried over magnesium sulfate and evaporated. Chromatography on silica gel column with chloroform - methanol mixture (49:1) gave product **9** (303 mg, 42%) as white powder: mp 185-190 °C; MS (FAB): 275 (MH^+); Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.42. Found: C, 61.22; H, 6.73; N, 20.19.

6-(1-Cyano-3,4-dihydroxybutyl)-2,4-dimethoxy-5-nitropyrimidine (10a,b)

To the 1.3 M solution of hydrogen peroxide in *tert*-butanol (6.2 mL, 8 mmol), prepared from mixture of *tert*-butanol and 30% aqueous hydrogen peroxide (5:1) which was dried with several portions of magnesium sulfate and the concetration adjusted to 1.3 M, was added 0.5% solution of osmium tetroxide in *tert*-butanol (100 μL) followed by compound **4** (1.1 g, 4 mmol) in *tert*-butanol (10 mL). The reaction mixture was left to stand overnight at room temperature. The solvent was evaporated and the chromatography on silica gel column with chloroform - methanol mixture (49:1) gave product **10a,b** (966 mg, 81%, 2:1 mixture of diastereomers) as colorless oil: MS (FAB): 299 (MH^+); Anal. Calcd.for $C_{11}H_{14}N_4O_6$: C, 44.30; H, 4.73; N, 18.78. Found: C, 44.43; H, 4.87; N, 18.66.

7-(2,3-Dihydroxypropyl)-4,6-dimethoxy-5*H*-pyrrolo[3,2-*d*]pyrimidine (11)

10% Palladium on activated carbon (10 mg) was added under argon to compound **10a,b** (533 mg, 1.8 mmol) in ethyl acetate - acetic acid (2:1) mixture (150 mL) and the reaction mixture was hydrogenated under slight overpressure of hydrogen overnight. The catalyst was filtered off over Celite and the filtrate evaporated. Chromatography on silica gel column with chloroform - methanol mixture (24:1) gave product **11** (283 mg, 62%) as white crystals: mp 102-104 °C; MS (FAB): 254 (MH^+); Anal. Calcd. for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N,16.59. Found: C, 51.98; H, 5.91; N, 16.65.

5-Amino-6-(1-cyano-3,4-dihydroxybutyl)-2,4-dimethoxypyrimidine (12a,b)

10% Palladium on activated carbon (5 mg) was added under argon to compound **10a,b** (149 mg, 0.5 mmol) in ethyl acetate (25 mL) and the reaction mixture was hydrogenated with slight overpressure of hydrogen overnight. The catalyst was filtered off and the filtrate evaporated. Chromatography on silica gel column with chloroform - methanol mixture (24:1) gave product **12a,b** (95 mg, 71%) as a mixture of diastereomers (4:3); yellow oil: MS (FAB): 269 (MH^+); Anal. Calcd. for $C_{11}H_{16}N_4O_4$: C, 49.25; H, 6.01; N, 20.88. Found: C, 49.46; H, 6.15; N, 21.03.

6-[1-Cyano-2-[(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl]-2,4-dimethoxy-5-nitropyrimidine (13a,b)

A solution of compound **10a,b** (400 mg, 1.3 mmol) in acetone (20 mL) was acidified with p-toluenesulfonic acid monohydrate and the mixture kept overnight at room temperature. Excess triethylamine was added, the solvent evaporated, the residue taken into ethyl acetate, extracted with sodium bicarbonate and evaporated. Chromatography on silica gel column with toluene - ethyl acetate mixture (19:5) gave product **13a,b** (380 mg, 84%) as a mixture of diastereomers (2:1); white crystalline solid: MS (FAB): 339 (MH^+); IR ($CHCl_3$, cm^{-1}): 2990 w (isopropylidene); 2252 vw (CN); 1586 vs,sh, 1572 vs, 1495 s, 1396 m, 1380 s (ring); 1532 m, 1344 s, 843 m (NO_2); 1467 m, 1455 m, 1066 m, 1045 w,sh (CH_3); Anal. Calcd. for $C_{14}H_{18}N_4O_6$: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.93; H, 5.33; N, 16.55.

5-Amino-6-[1-cyano-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl]-2,4-dimethoxypyrimidine (14a,b)

10% Palladium on activated carbon (10 mg) was added under argon to compound **13a,b** (338 mg, 1 mmol) in ethyl acetate (50 ml) and the reaction mixture was hydrogenated with slight overpressure of hydrogen overnight. The reaction mixture was filtered over Celite and the filtrate evaporated. Chromatography on silica gel column with toluene - ethyl acetate mixture (19:1) gave product **14a,b** (271 mg, 88%) as a mixture of diastereomers (6:5); yellow oil: MS (FAB): 309 (MH^+); IR ($CHCl_3$, cm^{-1}): 3443 w,br, 3366 w,br, 1625 m, sh (NH_2); 2990 m (isopropropylidene); 2252 m (CN); 1587 s, 1484 s, 1405 s, 1380, 1361 m,sh (ring); 1468 s, 1458 s,sh, 1089 m, 1070 s, 1045 m,sh (CH_3); Anal. Calcd. for $C_{14}H_{20}N_4O_4$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.71; H, 6.59; N, 18.29.

Preparation of Acetyl Derivatives 15-24 (General Procedure)

Compounds **2**, **3**, **7**, **8**, **9**, and **14a,b** (1 mmol) in pyridine (10 ml) were treated with acetic acid anhydride (1 ml) overnight and then methanol (2 ml) was added. The mixture was evaporated in vacuo, co-evaporated with toluene and the residue was purified by silica gel chromatography to provide corresponding monoacetate (50-85%) and diacetate (0-30%). In the case of compound **12a,b** the reaction time was prolonged for 10 days; the tetraacetate **20a,b** was isolated as the only product.

5-(N-Acetylamino)-6-cyanomethyl-2,4-dimethoxypyrimidine (15)

White crystals; mp 133-134°C; MS(FAB): 237(MH^+); IR ($CHCl_3$, cm^{-1}): 3419 m (NH); 2256 vw (CN); 1697 m, 1483 vs (amide); 1600 s, 1583 s, 1483 vs, 1412 m, 1396 m,sh, 1390 vs, 1378 vs (ring); 1470 s, 1457 m, 1095 m, 1079 m, 1065 m (CH_3); Anal. Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C,50.79; H, 5.04; N, 23.64.

5-(N-Acetylamino)-6-(1-cyano-3-buten-1-yl)-2,4-dimethoxypyrimidine (16)

Colorless oil; MS(FAB): 277(MH^+); IR ($CHCl_3$, cm^{-1}): 3417 m (NH_2); 3085 w, 1643 w, 1000 m, 929 m (double bond); 1699 s, 1483 vs (amide); 1596 s, 1573 s, 1489 vs, 1405 s, 1390 s, 1376 vs (ring); 1469s, 1458 s,sh, 1090 s, 1067 m (CH_3); Anal. Calcd. for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.75; H, 5.93; N, 19.99.

6-(N-Acetylamino)-7,7-diallyl-2,4-dimethoxy-7*H*-pyrrolo[3,2-*d*]pyrimidine (17)

White crystals; mp 177-180 °C; MS(FAB): 317(MH^+); Anal. Calcd. for $C_{16}H_{20}N_4O_3$: C, 60.75; H, 6.37; N,17.71. Found: C, 60.72, H, 6.19; N, 17.48.

6-(N,N-Diacetylamino)-7,7-diallyl-2,4-dimethoxy-7*H*-pyrrolo[3,2-*d*]pyrimidine (18)

Oil; MS(FAB): 359 (MH^+); Anal. Calcd. for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.07; H, 5.94; N, 15.66.

5-Acetyl-2,4-dimethoxy-5*H*-pyrrolo[3,2-*d*]pyrimidine (19)

White crystals; mp 109 °C, MS(FAB): 222(MH^+); Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.30; H, 5.01; N, 19.00. Found: C, 54.24; H, 4.91; N, 19.11.

6-(N-Acetylamino)-2,4-dimethoxy-7,7-dipropyl-7*H*-pyrrolo[3,2-*d*]pyrimidine (20)

White crystals; mp 204-205 °C, MS(FAB): 321(MH^+); IR ($CHCl_3$, cm^{-1}): 3391 w (NH_2); 1704 m, 1683 w (amid); 1635 m, 1612 m, 1587 m, 1564 m, 1477 m, 1403 w, 1387 m, 1367 vs (ring); 1467 s , 1457 m, 1078 m, 1052 m, 1019 w (CH_3); Anal. Calcd. for $C_{16}H_{24}N_4O_3$: C, 59.98; H, 7.55; N, 17.49. Found: C, 60.13; H, 7.32; N, 17.33.

6-(N,N-Diacetylamino)-2,4-dimethoxy-7,7-dipropyl-7*H*-pyrrolo[3,2-*d*]pyrimidine (21)

Colorless oil; MS(FAB): 363(MH^+); Anal. Calcd. for $C_{18}H_{26}N_4O_4$: C, 59.65; H, 7.23; N, 15.46. Found: C, 59.61; H, 7.40; N, 15.19.

6-(1-Cyano-3,4-diacetoxybutyl)-5-(N,N-diacetylamino)-2,4-dimethoxypyrimidine (22a,b)
Colorless glass; MS(FAB): 437(MH^+); IR ($CHCl_3$, cm^{-1}): 2247 vw (CN); 1742 vs,br (C=O); 1703 s,sh, 1490 s (amid); 1595 s, 1569 s, 1490 s, 1403 s,sh, 1390 s,sh, 1378 vs, 1370 s,sh (ring); 1469 s, 1457 s, 1085 m,br, 1048 m, 1017 m (CH_3); Anal. Calcd. for $C_{19}H_{24}N_4O_8$: C, 52.29; H, 5.54; N, 12.84. Found: C, 52.52; H, 5.68; N, 13.01.

6-[1-Cyano-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl]-5-(N-acetylamino)-2,4-dimethoxypyrimidine (23a,b)
Colorless glass; MS(FAB): 351 (MH^+); IR ($CHCl_3$, cm^{-1}): 3416 m, 3332 w,br (NH); 2992 m (isopropylidene); 2248 w (CN); 1699 s, 1483 s (amide); 1597 s, 1572 s, 1483 s, 1404 s, 1390 s, 1376 vs (ring); 1470 s, 1457 s, 1093 m, 1070 s, 1050 m,sh (CH_3); Anal. Calcd. for $C_{16}H_{22}N_4O_5$: C, 54.85; H, 6.33; N, 15.99. Found: C, 54.96; H, 6.21; N, 16.08.

6-[1-Cyano-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl]-5-(N,N-diacetylamino)-2,4-dimethoxypyrimidine (24a,b)
Colorless glass; MS(FAB): 393 (MH^+); Anal. Calcd. for $C_{18}H_{24}N_4O_6$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.86; H, 6.01; N, 14.00.

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