Palladium-Catalyzed Cross Coupling of 7-Iodo-2′-deoxytubercidin with Terminal Alkynes

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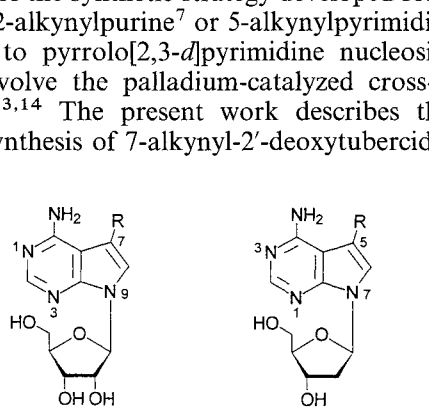
The 7-alkynyl-2′-deoxytubercidins (7-deaza-2′-deoxyadenosines) **7–17** have been prepared by the Pd(0)/Cu(I)-catalyzed cross coupling of 7-iodo-2′-deoxytubercidin (**2d**) with terminal alkynes. The coupling products include 17α-ethynyltestosterone and 17α-ethynylestradiol derivatives (**16**, **17**).

Tubercidin (**1a**) as well as 7-substituted derivatives – toyocamycin (**1b**); sangivamycin (**1c**) – (purine numbering is used throughout the general section) are naturally occurring antibiotics which exhibit antitumor activity.[1] Moreover, 7-iodotubercidin (**1d**) is a potent inhibitor of adenosine kinase.[2] Both the ribonucleoside **1a** and the 2′-deoxyribonucleoside **2a** have been incorporated into oligonucleotides.[3,4] It was shown that the 7-halogeno derivatives **2b, c** can stabilize the DNA duplex structure.[5] Also the enzymatic degradation of oligonucleotides with exo- and endonucleases is reduced making these compounds useful for antisense purposes.[6] The efficacy with regard to these properties should be increased when the electron-withdrawing character of 7-substituents is combined with the hydrophobicity of 7-alkynyl residues. Application of the synthetic strategy developed for the synthesis of 2-alkynylpurine[7] or 5-alkynylpyrimidine[8,9] nucleosides to pyrrolo[2,3-*d*]pyrimidine nucleosides[10–12] would involve the palladium-catalyzed cross-coupling reaction.[13,14] The present work describes the regiospecific synthesis of 7-alkynyl-2′-deoxytubercidins.

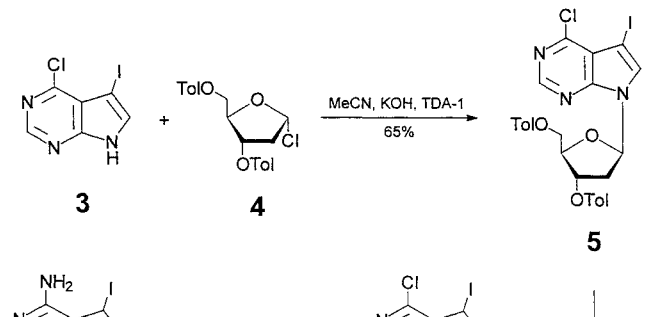


1a R = H
b R = CN
c R = $CONH_2$
d R = I

2a R = H
b R = Cl
c R = Br
d R = I

Scheme 1

7-Iodo-2′-deoxytubercidin (**2d**) served as precursor for the synthesis of the target compounds. It was prepared from 6-chloro-7-iodo-7-deazapurine (**3**)[15] which was obtained by regiospecific iodination of 6-chloro-7-deazapurine[16] with *N*-iodosuccinimide.[15] Stereoselective glycosylation of the 7-deazapurine anion of **3** with the halogenose **4** (MeCN, TDA-1, powdered KOH)[17,18,19] furnished the protected chloro nucleoside **5** in 65% yield. It was deblocked with methanolic ammonia (room temperature) on the sugar moiety to give the halogeno nucleoside **6**. Subsequently, the 6-chloro substituent of **6** was displaced with aqueous ammonia in an autoclave furnishing crystalline 7-iodo-2′-deoxytubercidin (**2d**).

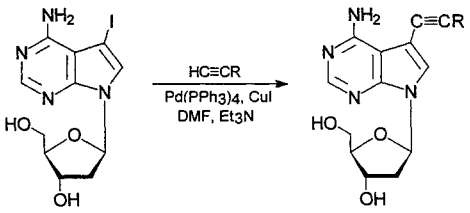


3 **4** **5** **2d** **6**

Scheme 2

On the basis of the studies of Heck,[13] various purine and pyrimidine nucleosides were subjected to the Pd-catalyzed cross-coupling reaction with terminal alkynes.[7–9] Terminator molecules for the Sanger dideoxy sequencing have also been prepared.[20] In our experiments the pyrrolo[2,3-*d*]pyrimidine nucleoside **2d** was coupled with various terminal alkynes. Protection of the sugar hydroxyl groups was not required. The coupling reaction was performed in DMF with tetrakis(triphenylphosphine)palladium(0), copper(I) iodide, and triethylamine under argon. The reaction was allowed to proceed until TLC indicated that the starting material was completely consumed. After quenching and flash chromatography, the desired 7-alkynyl-2′-deoxytubercidins **7–17** were isolated and characterized (Table 1). A 2:1 ratio of copper(I) vs. palladium(0) was found to be successful for the reaction. The average yield of alkynyl compounds was 50%. Lower copper(I)–palladium(0) ratios decreased the yields. In all cases the reaction mixture remained homogeneous and a single nucleoside was generated.

Terminal alkynes with no other functionality were used in most cases. We have also employed bulky alkynyl compounds, namely the steroids 17α-ethynylestradiol and 17α-ethynyltestosterone. Even in these cases a smooth reaction was observed and the crystalline nucleosides **16** and **17** were obtained. Among the terminal



2d **7–17**

Compnd.	R
7	C_3H_7
8	C_4H_9
9	C_5H_{11}
10	Ph
11	Cyclohexyl
12	CH_2CH_2OTHP
13	$Si(CH_3)_3$
14	$CH_2Si(CH_3)_3$
15	C_6H_9
16	17α-Estradiol
17	17α-Testosterone

THP =

Scheme 3

Table 1. Compounds **7–18** Prepared

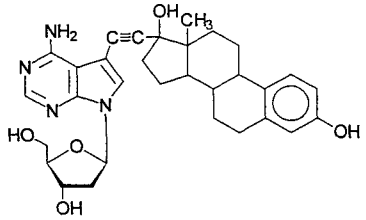
Product	Reaction Time (h)	Yield mg	Yield (%)	mp (°C) (MeOH)	UV (MeOH) λ_{max}(nm) (ε)
7	6	66	39	foam	240 (13800), 280 (10600)
8	7	84	48	147	239 (15000), 280 (11100)
9	7	72	39	oil	239 (14300), 280 (10700)
10	5	93	50	203	257 (13800), 296 (24300)
11	11	103	55	oil	239 (15900), 280 (11200)
12	3	126	59	foam	239 (13600), 280 (10900)
13	3	99	54	foam	248 (12300), 281 (12200)
14	4	93	49	foam	240 (16200), 280 (10700)
15	7	109	58	foam	239 (15700), 281 (10600)
16	7	180	62	262	281 (13800)
17	13	172	58	179	240 (30800), 280 (13000)
18	65	71	40	foam	268 (13500), 325 (11900)

[a] Satisfactory microanalyses obtained: C ± 0.33, H ± 0.34, N ± 0.20.

alkynes a diyne (octa-1,7-diyne) was used. In this case, only one alkyne group reacted under the conditions described for the other alkynes to give **15**. The reaction was also performed with alkenes, e. g. methyl acrylate. Similar to other compounds,[21] only one stereoisomer was formed. The *trans*-stereochemistry of **18** was deduced from the coupling constants (16 Hz) of the olefinic protons. The acetylene derivative **19** was prepared from **13** by treatment with K_2CO_3/MeOH.[22]

The structure of the nucleosides **2d**, **5–19** were confirmed by microanalyses, ^{1}H NMR and ^{13}C NMR spectra (Table 2, 3). For the assignment gated-decoupled as well as correlation spectra were used.

The hydrophobicity of the 7-alkynyl derivatives is demonstrated by their long HPLC-retention time compared to that of 2′-deoxytubercidin. Also the pK_a-values are



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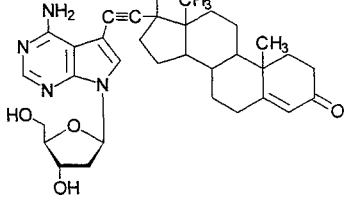
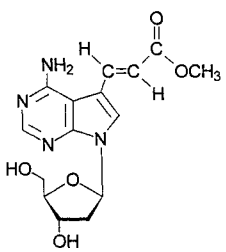
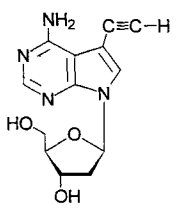


17



18



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Scheme 4

Table 2. ^{1}H NMR Chemical Shifts of 7-Substituted 2′-Deoxytubercidin Derivatives (Cross-Coupling Products)

Product	^{1}H NMR (DMSO-d_6)/TMS δ, J (Hz)
7	1.00 (t, J = 7.4, 3 H, CH_3), 1.59 (sextet, J = 7.1, 2 H, CH_2CH_3), 2.18 (m, 1 H, H_α-2′), 2.45 (t, J = 7.0, 2 H, C≡CCH_2, superimposed by H_β-2′), 2.47 (m, 1 H, H_β-2′, superimposed by DMSO and CH_2), 3.56 (m, 2 H, H-5′), 3.83 (m, 1 H, H-4′), 4.35 (m, 1 H, H-3′), 5.05 (t, J = 5.3, 1 H, 5′-OH), 5.24 (d, J = 3.8, 1 H, 3′-OH), 6.48 ("t", J = 6.9, 1 H, H-1′), 6.65 (br, 2 H, NH_2), 7.65 (s, 1 H, H-6), 8.11 (s, 1 H, H-2)
8	0.92 (t, J = 7.3, 3 H, CH_3), 1.47 (sextet, J = 7.2, 2 H, CH_2CH_3), 1.56 (quintet, J = 7.3, 2 H, $CH_2CH_2CH_3$), 2.18 (m, 1 H, H_α-2′), 2.48 (m, 3 H, H_β-2′, C≡CCH_2, superimposed by DMSO), 3.56 (m, 2 H, H-5′), 3.84 (m, 1 H, H-4′), 4.35 (m, 1 H, H-3′), 5.05 (t, J = 5.5, 1 H, 5′-OH), 5.24 (d, J = 3.9, 1 H, 3′-OH), 6.49 ("t", J = 7.0, 1 H, H-1′), 6.65 (br, 2 H, NH_2), 7.65 (s, 1 H, H-6), 8.11 (s, 1 H, H-2)
9	0.86 (t, J = 7.1, 3 H, CH_3), 1.30 (m, 2 H, CH_2CH_3), 1.35 (m, 2 H, $CH_2CH_2CH_3$), 1.50 (quintet, J = 7.1, 2 H, C≡CCH_2CH_2), 2.14 (m, 1 H, H_α-2′), 2.44 (m, 3 H, H_β-2, C≡CCH_2, superimposed by DMSO), 3.62 (m, 2 H, H-5′), 3.78 (m, 1 H, H-4′), 4.30 (m, 1 H, H-3′), 4.99 (t, J = 5.5, 1 H, 5′-OH), 5.19 (d, J = 3.9, 1 H, 3′-OH), 6.43 ("t", J = 6.9, 1 H, H-1′), 6.61 (br, 2 H, NH_2), 7.60 (s, 1 H, H-6), 8.06 (s, 1 H, H-2)
10	2.22 (m, 1 H, H_α-2′), 2.47 (m, 1 H, H_β-2′, superimposed by DMSO), 3.57 (m, 2 H, H-5′), 3.84 (m, 1 H, H-4′), 4.36 (m, 1 H, H-3′), 5.07 (t, J = 5.4, 1 H, 5′-OH), 5.28 (d, J = 3.6, 1 H, 3′-OH), 6.51 ("t", J = 6.7, 1 H, H-1′), 6.71 (br, 2 H, NH_2), 7.40, 7.56 (2 m, 5 H, 5 H_{arom}, 7.88 (s, 1 H, H-6), 8.15 (s, 1 H, H-2)
11	1.30–1.82 (several m, 10 H, $H_{cyclohexyl}$), 2.18 (m, 1 H, H_α-2′), 2.46 (m, 1 H, H_β-2′, superimposed by DMSO), 2.70 (m, 1 H, CH), 3.54 (m, 2 H, H-5′), 3.80 (m, 1 H, H-4′), 4.32 (m, 1 H, H-3′), 5.02 (t, J = 5.2, 1 H, 5′-OH), 5.23 (d, J = 3.4, 1 H, 3′-OH), 6.46 ("t", J = 7.0, 1 H, H-1′), 6.58 (br, 2 H, NH_2), 7.62 (s, 1 H, H-6), 8.09 (s, 1 H, H-2)
12	1.45–1.65 (several m, 6 H, 4 THP-H, CH_2C≡C), 2.18 (m, 1 H, H_α-2′), 2.48 (m, 1 H, H_β-2′, superimposed by DMSO), 2.72 (m, 2 H, CH_2CH), 3.50 (m, 2 H, C≡CCH_2CH_2O), 3.55 (m, 2 H, H-5′), 3.76 (m, 2 H, CH_2O of THP), 3.81 (m, 1 H, H-4′), 4.82 (m, 1 H, CH), 5.07 (t, J = 5.2, 1 H, 5′-OH), 5.25 (d, J = 3.4, 1 H, 3′-OH), 6.46 ("t", J = 6.4, 1 H, H-1′), 6.73 (br, 2 H, NH_2), 7.84 (s, 1 H, H-6), 8.09 (s, 1 H, H-2)
13	0.23 (s, 9 H, 3 CH_3), 2.17 (m, 1 H, H_α-2′, 2.46 (m, 1 H, H_β-2′, superimposed by DMSO), 3.54 (m, 2 H, H-5′), 3.82 (m, 1 H, H-4′), 4.33 (m, 1 H, H-3′), 5.02 (t, J = 5.4, 1 H, 5′-OH), 5.23 (d, J = 3.3, 1 H, 3′-OH), 6.47 ("t", J = 6.7, 1 H, H-1′), 6.76 (br, 2 H, NH_2), 7.80 (s, 1 H, H-6), 8.12 (s, 1 H, H-2)
14	0.12 (s, 9 H, 3 CH_3), 1.83 (s, 2 H, CH_2C≡C), 2.16 (m, 1 H, H_α-2′), 2.46 (m, 1 H, H_β-2′, superimposed by DMSO), 3.51 (m, 2 H, H-5′), 3.80 (m, 1 H, H-4′), 4.31 (m, 1 H, H-3′), 5.02 (t, J = 5.3, 1 H, 5′-OH), 5.21 (d, J = 3.8, 1 H, 3′-OH), 6.45 ("t", J = 6.9, 1 H, H-1′), 6.62 (br, 2 H, NH_2), 7.57 (s, 1 H, H-6), 8.08 (s, 1 H, H-2)
15	1.61 (m, 4 H, $CH_2CH_2CH_2$C≡CH), 2.20 (m, 3 H, H_α-2′, CH_2C≡CH), 2.48 (m, 3 H, H_β-2′, C≡CCH_2, superimposed by DMSO), 2.76 (s, 1 H, C≡CH), 3.54 (m, 2 H, H-5′), 3.81 (m, 1 H, H-4′), 4.32 (m, 1 H, H-3′), 5.04 (t, J = 5.4, 1 H, 5′-OH), 5.24 (d, J = 3.7, 1 H, 3′-OH), 6.46 ("t", J = 7.0, 1 H, H-1′), 6.63 (br, 2 H, NH_2), 7.64 (s, 1 H, H-6), 8.08 (s, 1 H, H-2)
16[a]	0.84 (s, 3 H, CH_3), 1.28–2.75 [several m, 17 H, H_α-2′, H_β-2′, H-C_S (6,7,8,9,11,12,14,15,16)], 3.55 (m, 2 H, H-5′), 3.83 (m, 1 H, H-4′), 4.34 (m, 1 H, H-3′), 5.04 (t, J = 5.2, 1 H, 5′-OH), 5.23 (d, J = 3.5, 1 H, 3′-OH), 5.64 [s, 1 H, OH(C_S17)], 6.45 (s, 1 H, H-C_S2), 6.49 (m, 2 H, H-1′, H-C_S4), 6.68 (br, 2 H, NH_2), 7.06 (d, J = 8.3, 1 H, H-C_S1), 7.69 (s, 1 H, H-6), 8.12 (s, 1 H, H-2), 8.95 [s, 1 H, OH(C_S3)]
17[a]	0.83 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 0.92–2.48 [several m, 21 H, H_α-2′, H_β-2′, H-C_S (1,2,6,7,8,9,11,12,14,15,16)], 3.54 (m, 2 H, H-5′), 3.80 (m, 1 H, H-4′), 4.31 (m, 1 H, H-3′), 5.02 (t, J = 5.4, 1 H, 5′-OH), 5.21 (d, J = 4.0, 1 H, 3′-OH), 5.60 [2 s, 2 H, H-C_S4, OH(C_S17)], 6.45 ("t", J = 6.9, 1 H, H-1′), 6.70 (br, 2 H, NH_2), 7.65 (s, 1 H, H-6), 8.09 (s, 1 H, H-2)
18	2.22 (m, 1 H, H_α-2′), 2.45 (m, 1 H, H_β-2′, superimposed by DMSO), 3.55 (m, 2 H, H-5′), 3.70 (s, 3 H, OCH_3), 3.83 (m, 1 H, H-4′), 4.36 (m, 1 H, H-3′), 5.04 (t, J = 5.1, 1 H, 5′-OH), 5.26 (d, J = 3.6, 1 H, 3′-OH), 6.41 (d, J = 15.6, 1 H, $H_{olefinic}$), 6.51 ("t", J = 6.6, 1 H, H-1′), 6.86 (s, 2 H, NH_2), 7.94 (d, J = 15.6, 1 H, $H_{olefinic}$), 8.11 (2 s, 2 H, H-2, H-6)

[a] C_S-refers to carbon atoms of steroid skeleton.

decreased from 2′-deoxytubercidin (**2a**, pK_a = 5.3[23]) to the 7-alkynyl derivatives (**8**, pK_a = 4.3). As the alkyne residue is planar with respect to the pyrrolo[2,3-*d*]pyrimidine heterocycle stacking interactions between the bases are expected to increase. These properties should stabilize the DNA-structure, when 7-alkynyl-2′-deoxytubercidins replace 2′-deoxyadenosine residues in double helical nucleic acids.

TLC: glass plates coated with a 0.25 mm layer of silica gel Sil G-25 with fluorescence indicator UV_{254} (Merck, Darmstadt, Germany). Column flash chromatography (FC): silica gel 60 (Merck, Darmstadt) at 0.5 bar. Solvent system: CH_2Cl_2/MeOH, 9:1 (A). Mp: SMP-20 apparatus (Büchi, Switzerland). NMR spectra: AC-250 and AC-500 spectrophotometer (Bruker, Rheinstetten, Germany). UV spectra: 150–20 spectrophotometer (Hitachi, Japan). Elemental analyses were performed by Mikroanalytisches Laboratorium Beller, Göttingen, Germany. Petroleum ether used had boiling range 40–65 °C.

4-Chloro-7-[2-deoxy-3,5-di-*O*-(4-toluoyl)-β-D-*erythro*-pentofuranosyl]-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (5):

To a solution of compound **3**[15] (1.0 g, 3.6 mmol) in MeCN (60 mL) were added KOH (0.50 g, 8.9 mmol) and TDA-1 (tris[2-(2-methoxyethoxy)ethyl]amine; 75 μL, 0.24 mmol). After stirring at r.t. for 10 min, 2-deoxy-3,5-di-*O*-(4-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**4**;[24] 1.7 g, 4.4 mmol) was added and stirring continued for another 10 min. Insoluble material was filtered and washed several times with hot acetone. The combined filtrates were evaporated to dryness and the residue was subjected to FC (column: 15 × 5 cm, petroleum ether/EtOAc, 4:1). Crystallization from *i*-PrOH yielded colourless needles (1.5 g, 65%); mp 138 °C; TLC (silica gel, petroleum ether/EtOAc, 4:1): R_f 0.50.

UV (MeOH): λ_{max} = 235 nm (ε = 25600).

^{1}H NMR (DMSO-d_6): δ = 2.39, 2.41 (2 s, 6 H, 2 CH_3), 2.78 (m, 1 H, H_α-2′), 3.11 (m, 1 H, H_β-2′), 4.56 (m, 2 H, H-5′), 4.66 (m, 1 H, H-4′), 5.77 (m, 1 H, H-3′), 6.77 (dd, 1 H, J = 7.0 Hz, H-1′), 7.34, 7.90 (2 dd, 8 H, J = 7.8, 7.9 Hz, 2 C_6H_4), 8.18 (s, 1 H, H-6), 8.66 (s, 1 H, H-2).

Table 3. ^{13}C NMR Data of 7-Substituted 2′-Deoxytubercidin Derivatives in DMSO-d_6/TMS, δ[a,b]

Product	C-2 C-2	C-4 C-6	C-4a C-5	C-5 C-7	C-6 C-8	C-7a C-4	Acetylenic Carbons		C-1′	C-3′	C-4′	C-5′
2d	152.0	157.3	103.2	51.9	126.9	149.8			83.0	71.0	87.5	62.0
5	150.7	151.2	116.7	53.9	133.3	150.5			83.7	74.7	81.5	63.9
6	151.1	151.4	116.7	53.3	133.5	150.5			85.5	70.8	87.8	61.7
7	152.5	157.5	102.3	95.5	125.4	149.0	92.3	73.8	83.1	70.9	87.4	61.9
8	152.5	157.5	102.3	95.5	125.4	149.0	92.4	73.6	83.1	70.9	87.4	61.9
9	152.5	157.5	102.3	95.5	125.3	149.0	92.5	73.6	83.1	70.9	87.4	61.8
10	152.9	153.7	102.4	94.8	126.9	149.5	91.2	83.2	83.3	71.0	87.7	62.0
11	152.7	157.7	102.5	95.5	125.4	149.1	96.4	73.9	83.2	71.1	87.6	62.0
12	152.7	157.7	102.5	95.4	125.1	149.1	90.3	74.4	83.3	71.1	87.6	61.8
13	152.8	157.6	102.3	94.6	127.0	149.1	96.7	99.2	83.2	70.9	87.5	61.8
14	152.6	157.7	102.6	96.4	125.1	149.0	90.7	72.2	83.2	71.1	87.5	62.0
15	152.5	157.4	102.3	95.4	125.4	149.0	95.4	71.3	83.0	70.9	87.4	61.8
16	152.6	157.5	102.3	95.0	125.5	149.1	96.5	77.7	83.1	70.9	87.4	61.8
17	152.7	157.7	102.3	95.1	125.6	149.1	96.5	77.8	83.2	71.1	87.6	62.0
18	152.1	158.0	101.0	111.5	123.7	151.2	137.4[c]	115.5[c]	83.2	70.9	87.6	62.0
19	152.7	157.5	102.3	93.9	127.0	149.1	77.3	82.9	83.2	70.9	87.5	61.8

[a] Only for compound **5**, C-2′ was detected at $\delta = 36.2$. For all other compounds, the signal corresponding to C-2′ was superimposed by DMSO.
[b] The assignments C-2/C-2, C-4/C-6, C-4a/C-5, C-5/C-7, C-6/C-8 and C-7a/C-4 refer to systematic and purine numbering, respectively (see structures **1** and **2**).
[c] C-olefinic.

$C_{27}H_{23}ClIN_3O_5$ (631.9) calc. C 51.33 H 3.67 N 6.65 found 51.55 3.78 6.80

4-Chloro-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (6):
Compound **5** (2.0 g, 3.2 mmol) was stirred for 24 h at r.t. in MeOH (160 mL, sat. with NH_3 at 0 °C) and the solvent was evaporated. FC (column: 20 × 3 cm, A) and crystallization from *i*-PrOH gave colourless crystals (0.79 g, 63 %); mp 151 °C; TLC (silica gel, A): R_f 0.45.

UV (MeOH): $\lambda_{max} = 234$ nm ($\varepsilon = 25200$).

^{1}H NMR (DMSO-d_6): $\delta = 2.27$ (m, 1 H, H_α-2′), 2.48 (m, 1 H, H_β-2′, superimposed by DMSO), 3.56 (m, 2 H, H-5′), 3.85 (m, 1 H, H-4′), 4.36 (m, 1 H, H-3′), 4.98 (t, $J = 4.9$ Hz, 1 H, 5′-OH), 5.31 (d, $J = 3.6$ Hz, 1 H, 3′-OH), 6.61 ("t", $J = 6.6$ Hz, 1 H, H-1′), 8.19 (s, 1 H, H-6), 8.63 (s, 1 H, H-2).

$C_{11}H_{11}ClIN_3O_3$ (395.6) calc. C 33.40 H 2.80 N 10.62 found 33.64 3.01 10.78

4-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (2d):
A suspension of compound **6** (1.0 g, 2.5 mmol) in 25 % aq NH_3/1,4-dioxane (1:1, 160 mL) was stirred for 15 h at 110 °C under pressure in an autoclave. After evaporation, the residue was submitted to FC (column: 20 × 5 cm, A); colourless needles from MeOH (0.66 g, 70 %); mp 194 °C; TLC (silica gel, A): R_f 0.40.

UV (MeOH): $\lambda_{max} = 283$ nm ($\varepsilon = 8500$).

^{1}H NMR (DMSO-d_6): $\delta = 2.16$ (m, 1 H, H_α-2′), 2.46 (m, 1 H, H_β-2′, superimposed by DMSO), 3.54 (m, 2 H, H-5′), 3.81 (m, 1 H, H-4′), 4.33 (m, 1 H, H-3′), 5.00 (t, $J = 5.4$ Hz, 1 H, 5′-OH), 5.23 (d, $J = 3.9$ Hz, 1 H, 3′-OH), 6.49 ("t", $J = 7.0$ Hz, 1 H, H-1′), 6.65 (br, 2 H, NH_2), 7.65 (s, 1 H, H-6), 8.10 (s, 1 H, H-2).

$C_{11}H_{13}IN_4O_3$ (376.2) calc. C 35.13 H 3.48 N 14.90 found 35.33 3.60 15.01

Pd-Catalyzed Cross Coupling of 4-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (2d) with Terminal Alkynes and Alkenes; General Procedure:
A suspension of **2d** (200 mg, 0.53 mmol) and CuI (20.2 mg, 0.106 mmol) in anhydr. DMF (3 mL) was treated with the alkyne (10 equiv) or the alkene (15 equiv), anhydr. Et_3N (108 mg, 1.06 mmol), and $Pd(PPh_3)_4$ (62 mg, 0.054 mmol). The mixture was stirred under Ar forming a clear yellow solution. The reaction was allowed to proceed until the starting material disappeared (TLC-monitoring). The mixture was diluted with MeOH/CH_2Cl_2 (5 mL, 1:1) and Dowex 1X8 (100–200 mesh; 500 mg, bicarbonate form) was introduced. After stirring for 15 min, the evolution of gas ceased. Stirring was continued for another 30 min, the mixture was filtered and the resin was washed with MeOH/CH_2Cl_2 (30 mL, 1:1). The combined filtrates were evaporated to dryness. The residue was chromatographed on a silica gel column (10 × 5 cm) using CH_2Cl_2 with an increasing amount of MeOH (10, 15, 20 %). The main zone afforded the nucleoside derivative upon evaporation (Tables 1–3).

4-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-(ethynyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (19):
A solution of compound **13** (100 mg, 0.29 mmol) and anhydr. K_2CO_3 (8 mg) in MeOH (10 mL) was stirred for 1 h at r.t. After evaporation the residue was subjected to FC (column: 10 × 3 cm, A). The isolated product was recrystallized from MeOH; colourless crystals (58 mg, 73 %); mp 223 °C; TLC (silica gel, A): R_f 0.34.

UV (MeOH): $\lambda_{max} = 237, 279$ nm ($\varepsilon = 11200, 11100$).

^{1}H NMR (DMSO-d_6): $\delta = 2.21$ (m, 1 H, H_α-2′), 2.47 (m, 1 H, H_β-2′, superimposed by DMSO), 3.56 (m, 2 H, H-5′), 3.84 (m, 1 H, H-4′), 4.26 (s, 1 H, C≡CH), 4.36 (m, 1 H, H-3′), 5.05 (t, $J = 5.3$ Hz, 1 H, 5′-OH), 5.25 (d, $J = 3.8$ Hz, 1 H, 3′-OH), 6.49 ("t", $J = 6.9$ Hz, 1 H, H-1′), 6.65 (br, 2 H, NH_2), 7.81 (s, 1 H, H-6), 8.13 (s, 1 H, H-2).

$C_{13}H_{14}N_4O_3$ (274.3) calc. C 56.93 H 5.15 N 20.43 found 56.77 5.21 20.42

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(1) Suhadolnik, R.J. *Nucleosides as Biological Probes;* Wiley-Interscience: New York, 1979; pp 158–169.
(2) Cottam, H.J. *Drugs of the Future* **1994**, *19*, 485.
(3) Seela, F.; Kehne, A. *Biochemistry* **1985**, *24*, 7556.

(4) Seela, F.; Mersmann, K.; Grasby, J.A.; Gait, M.J. *Helv. Chim. Acta* **1993**, *76*, 1809.
(5) Seela, F.; Thomas, H. *Helv. Chim. Acta* **1995**, *78*, 94.
(6) Seela, F.; Ramzaeva, N., unpublished.
(7) Matsuda, A.; Shinozaki, M.; Miyasaka, T.; Machida, H.; Abiru, T. *Chem. Pharm. Bull.* **1985**, *33*, 1766.
(8) Robins, M.J., Barr, P.J. *J. Org. Chem.* **1983**, *48*, 1854.
(9) Gutierrez, A.J.; Terhorst, T.J.; Matteucci, M.D.; Froehler, B.C. *J. Am. Chem. Soc.* **1994**, *116*, 5540.
(10) Hobbs, F.W. *J. Org. Chem.* **1989**, *54*, 3420.
(11) Cocuzza, A.J. *Tetrahedron Lett.* **1988**, *29*, 4061.
(12) Taylor, E.C.; Kuhnt, D. *J. Med. Chem.* **1992**, *35*, 4450.
(13) Heck, R.F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.
(14) de Meijere, A.; Meyer, F.E. *Angew. Chem.* **1994**, *106*, 2473; *Angew. Chem. Intl. Ed. Engl.* **1994**, *33*, 2379.
(15) Pudlo, J.S.; Nassiri, M.R.; Kern, E.R.; Wotring, L.L.; Drach, J.C.; Townsend, L.B. *J. Med. Chem.* **1990**, *33*, 1984.
(16) Seela, F.; Muth, H.-P.; Bindig, U. *Synthesis* **1988**, 670.
(17) Thomas, H. *Thesis*, University of Osnabrueck, 1995.
(18) Seela, F.; Winkeler, D. *J. Org. Chem.* **1983**, *48*, 3119.
(19) Seela, F.; Westermann, B.; Bindig, U. *J. Chem. Soc., Perkin Trans. 1* **1988**, 697.
(20) Prober, J.M.; Trainor, G.L.; Dam, R.J.; Hobbs, F.W.; Robertson, C.W.; Zagursky, R.J.; Cocuzza, A.J.; Jensen, M.A.; Baumeister, K. *Sciece* **1987**, *238*, 336.
(21) Bergstrom, D.E.; Brattesani, A.J.; Ogawa, M.K.; Schweickert, M.J. *J. Org. Chem.* **1981**, *46*, 1423.
(22) Austin, W.B.; Bilow, N.; Kelleghan, W.J.; Lau, S.Y. *J. Org. Chem.* **1981**, *46*, 2280.
(23) Seela, F.; Grein, T. *Nucleic Acids Res.* **1992**, *20*, 2297.
(24) Hoffer, M. *Chem. Ber.* **1960**, *93*, 2777.