Liquid–Liquid and Solid–Liquid Phase-transfer Glycosylation of Pyrrolo[2,3-*d*]-pyrimidines: Stereospecific Synthesis of 2-Deoxy-β-D-ribofuranosides related to 2'-Deoxy-7-carbaguanosine

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The yield of phase-transfer glycosylation of 2-amino-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (**3b**) with 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**4**) is limited under liquid–liquid conditions (50% aq. NaOH, CH_2Cl_2, Bu_4NHSO_4) due to deprotection of alkali-labile protecting groups in the halogenose (**4**). Application of more lipophilic 2-amino-4-alkoxypyrrolo[2,3-*d*]pyrimidines such as compounds (**3d**) or (**3e**) decreases side reactions to some extent. To overcome these difficulties solid–liquid phase-transfer glycosylation employing an aprotic solvent, solid KOH, and the cryptand tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) has been developed. The new glycosylation method leads stereospecifically in high yield to 2-amino-4-alkoxy- (**7a—c**) or 2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine 2-deoxy-β-D-*erythro*-pentofuranosides (**8b**) which can be converted into 2'-deoxy-7-carbaguanosine (**1**) or other 7-carbapurine 2'-deoxy-*erythro*-pentofuranosides ('2'-deoxyribonucleosides').

Compared with the glycosylation of purines glycosylation of pyrrolo[2,3-*d*]pyrimidines is rather difficult.[1] As the electron pair of the pyrrole nitrogen is part of the aromatic π-system, glycosylation at this position is only effective if the nucleobase anion is generated. The latter is a strong nucleophile, whereas the neutral base is not. Glycosylation of pyrrolo[2,3-*d*]-pyrimidines *via* pyrrolyl anions was first accomplished with NaH in dimethylformamide (DMF)[2] and was applied to the synthesis of D-ribonucleosides such as queuosine.[3] We we able to show that D-arabinonucleosides such as (**2b**)[4] and D-ribonucleosides such as (**2a**)[5,6] can be prepared if the nucleobase anion was generated under phase-transfer conditions employing a biphasic mixture of 50% aqueous NaOH and CH_2Cl_2 in the presence of a quaternary ammonium salt (liquid–liquid phase-transfer glycosylation). From configuration studies on these nucleosides it was found that glycosylation occurred stereoselectively or stereospecifically by inversion of configuration of the halogenose (**4**).[4,7]

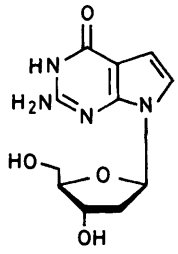
The same methodology was then applied to the synthesis of 2-deoxy-β-D-*erythro*-pentofuranosides (2'-deoxy-β-D-ribonucleosides)[8] employing the toluoyl-protected halogenase (**4**) instead of benzyl-protected D-ribo-or D-arabinofuranosyl halides. Comparison of glycosylation yields obtained from experiments with the halogenose (**4**) with those with benzyl-protected sugars showed that reaction yields were limited if the halogenose carried an alkali-labile protecting group. However, some glycosylation experiments gave rise to very high yields.[9] Correlation of nucleobase structures with glycosylation yields showed that two nucleobase properties are particularly important for high reaction yields and stereospecificity under liquid–liquid phase-transfer conditions: (i) solubility of the nucleobase in dichloromethane, the organic solvent used for the liquid–liquid reaction, and (ii) the hardness of the pyrrolyl nucleophile.

Recently we have reported on the synthesis of 2'-deoxy-7-carbaguanosine (**1**),[8] a pyrrolo[2,3-*d*]pyrimidine nucleoside which is isosteric with the naturally occurring DNA constituent 2'-deoxyguanosine. As a 7-carbapurine nucleoside, compound (**1**) exhibits extraordinary properties from the chemical,[10,11] and the biochemical points of view[12,13] but its synthetic availability was restricted by the moderate yield obtained during the glycosylation step. Therefore we have looked for improved procedures for its synthesis and also for the preparation of related 4-alkoxy and 4-chloro derivatives.[7]

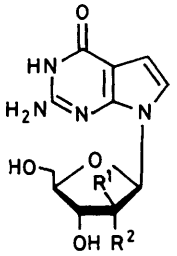
The nucleobase (**3b**), a synthetic intermediate towards (**1**), is only weakly soluble in small amounts of dichloromethane, which is employed as the organic phase during our liquid–liquid phase-transfer glycosylation. As a result the dissolution velocity of (**3b**) during the glycosylation reaction limits the reaction velocity. Accordingly, side reaction in the halogenose (**4**) became important. The most serious side reaction which occurs in the biphasic system dichloromethane–50% aqueous NaOH is the deprotection of the halogenose and the displacement of the anomeric halogen by hydroxyl ions. As 4-methylbenzoate—a strong nucleophile—is formed during deprotection the nucleobase anion has to compete with the carboxylate anion formed during phase-transfer glycosylation. As a result increased amounts of 2-deoxy-1,3,5,-tri-*O*-(*p*-toluoyl)-D-*erythro*-pentofuranoses are formed.[14] This reaction cycle is difficult to overcome even with an excess of the halogenose (**4**). With regard to these difficulties we have increased the lipophilicity of the nucleobase. As a consequence the partition of nucleobase anion between the organic and aqueous phase should be in favour of the organic phase. This process should speed up glycosylation and reduce side reactions occurring in the halogenose (**4**).

As lipophilic intermediates the alkoxy derivatives (**3c—e**) were synthesized. They were obtained from the chloro compound (**3a**)[14] which was subjected to nucleophilic displacement reaction of the halogen by different alkoxide ions in alcoholic solution. As one would expect, nucleophilic displacement reaction in compound (**3a**) was more difficult with branched-chain alkoxides than with regular ones. The reaction with sodium isopropoxide was most difficult and required vigorous heating under reflux for several days, instead of a few hours as in other cases. A tertiary butoxy residue could not be introduced by this displacement procedure. Compounds (**3c—e**) were characterized by ^1H n.m.r. spectroscopy. ^{13}C N.m.r. data are shown in Table 1 and were compared with those of the parent compound (**3b**).

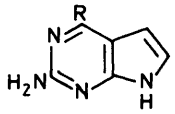
The butoxy derivatives (**3d**) and (**3e**) were then employed in liquid–liquid phase-transfer glycosylation under the same conditions already described for compound (**3b**).[8] The reaction



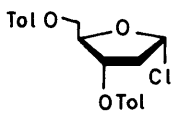
(1)



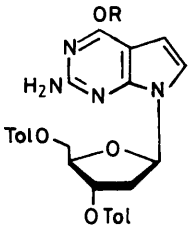
(2) a; R^1 = H, R^2 = OH
b; R^1 = OH, R^2 = H



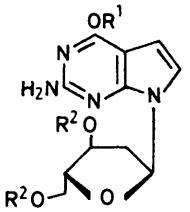
(3) a; R = Cl
b; R = OMe
c; R = OPr^i
d; R = OBu
e; R = OBu^i



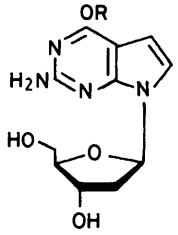
(4)
Tol = Me  CO-



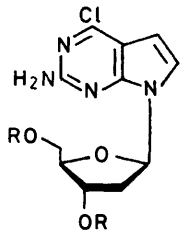
(5) a; R = Me
b; R = Bu
c; R = Bu^i



(6) a; R^1 = Bu, R^2 = Tol
b; R^1 = Me, R^2 = OH



(7) a; R = Me
b; R = Bu
c; R = Bu^i



(8) a; R = Tol
b; R = H

products (**5b**) or (**5c**) were isolated from the organic phase and purified by flash chromatography. Both compounds crystallized from methanolic solution. Table 2 shows that the application of highly lipophilic pyrrolo[2,3-*d*]pyrimidines such as compound (**3d**) or (**3e**) increased the yield of glycosylation from 48% (**5a**) to 58% (**5b**).

The assignment of glycosylation products with respect to the position of glycosylation as well as to the anomeric configuration was made on the basis of ^{1}H and ^{13}C n.m.r. spectroscopy. According to already published methods the position of glycosylation was derived from gated-decoupled ^{13}C n.m.r. spectra by observing the coupling pattern of the signal of C-6 with that of the anomeric proton.[15] Differences in the chemical shifts of 4′-H and 5′-$H_{a,b}$ of the sugar moiety of the protected glycosylation products[16] (**5b** and **c**) and the shape of the anomeric signal of the deprotected compounds (**7b** and **c**)[17] have been used to determine the configuration at the anomeric centre.

As has been shown earlier the halogenose (**4**) equilibrates in the presence of different catalysts.[18,19] According to ^{1}H and ^{13}C n.m.r. spectra the equilibration process was minimal if small amounts of catalyst (0.1 mol equiv.) were used. Larger amounts (0.5 mol equiv.), however, led to significant equilibration. As a consequence α- and β-nucleosides were formed. Compound (**6a**) was isolated from experiments if the amount of Bu_4NHSO_4 *vs.* nucleobase was 0.5 mol. equiv. α-Anomers, such as (**6b**), may be also formed during large-scale experiments as the formation of the hydrophobic nucleobase anion is limited by the transport of organic and inorganic ions through the phase boundary.

Two mechanisms can explain α-nucleoside formation: (i) equilibration of the α-halogenose[18,19] to an α/β-mixture which is then attacked by the nucleobase anion *via* an S_N2 mechanism, and (ii) a change of the reaction mechanism from S_N2 to S_N1. This reaction should be favoured by polar solvents or large amounts of ionic species. Glycosylation reactions carried out in DMF[20] or in the presence of large amounts of Bu_4NHSO_4[21] support this explanation.

Deprotection of diesters (**5b**) and (**5c**) was accomplished with sodium methoxide in methanol. The alkoxynucleosides (**7b**) and (**7c**) were isolated after flash chromatography in more than 85% yield. ^{13}C N.m.r. data of nucleobases and nucleosides are summarized in Table 1. The chemical shifts of nucleobases are only slightly influenced by *N*-7 glycosylation.

Treatment of compound (**7b**) and (**7c**) with aqueous NaOH resulted in formation of compound (**1**) with yields ~90%. Similar results have been reported for methoxy analogue (**7a**).[22] It was expected that the butoxy group would decrease the reaction velocity in nucleophilic displacement reactions. Quantitative data were obtained in 2M-KOH at 80 °C. The reaction of compounds (**7a**) and (**7b**) was monitored u.v. spectrophotometrically at 260 nm. The decrease of absorbance was used to determine kinetic data according to the equation $k = 1/t \ln (E_0 - E_\infty)/(E_t - E_\infty)$. Values of $k = 4.18 \times 10^{-3}$ min^{-1} were found for (**7a**) and $k = 1.64 \times 10^{-3}$ min^{-1} for (**7b**). These data correspond to half-lives of 166 min (**7a**) and 423 min (**7b**). Although nucleophilic displacement in (**7b**) was decreased compared with (**7a**) the butoxy group did not affect the high yields obtained in the preparative-scale experiments of alkaline treatment. Moreover, it was apparent that strongly alkaline reaction conditions and elevated temperatures did not degrade the nucleoside molecules, a process which occurs rapidly with the parent purines.

The better yields obtained during liquid–liquid phase-transfer glycosylation of (**3d**) [58% of (**5b**)] compared with 48% in the case of (**5a**) demonstrate that lipophilic nucleobases increase glycosylation yields to some extent. However, these results were still not sufficiently good for our purposes. The application of NaH in acetonitrile[23] was even less satisfactory, probably due to reactions occurring at the 2-amino group of the nucleobase moiety.

Table 1. ^{13}C N.m.r. data of pyrrolo[2,3-*d*]pyrimidines and their 2′-deoxy-D-*erythro*-pentofuranosides in $(CD_3)_2SO$

Compd.	C-2	C-4	C-4a	C-5	C-6	C-7a	OCH_x	CH_x	CH_2	Me
(1)	152.5	158.5	100.1	102.1	116.7	150.5				
(3a)	159.4	151.0	108.7	98.8	123.2	154.7				
(3b)	159.6	163.1	97.1	98.1	119.1	155.2	52.6			
(3c)	159.4	162.2	97.3	98.8	119.1	155.2	67.1			22.1
(3d)	159.4	162.6	96.9	98.0	119.1	155.0	64.6	30.6	18.8	13.7
(3e)	159.3	162.7	96.9	97.9	119.1	155.0	70.9	27.4		19.0
(5a)	159.5	162.9	97.3	99.6	119.0	154.5	52.7			
(5b)	159.6	162.4	97.3	99.7	118.9	154.5	64.8	30.5	18.7	13.6
(5c)	159.6	162.9	97.3	99.7	118.9	154.6	71.2	27.5		19.0
(6a)	159.5	162.7	97.3	99.1	119.0	154.1	64.8	30.5	18.7	13.6
(6b)	159.5	163.0	97.1	98.9	120.5	154.3	52.9			
(7a)	159.4	163.0	97.3	98.9	119.5	154.2	52.5			
(7b)	159.4	162.7	97.2	99.1	119.3	154.3	64.8	30.6	18.7	13.7
(7c)	159.4	162.8	97.2	99.0	119.3	154.3	71.0	27.5		19.0
(8a)	159.2	151.2	108.9	100.0	122.6	153.7				
(8b)	159.2	151.0	108.9	99.6	122.9	153.6				

Compd.	C-1′	C-2′	C-3′	C-4′	C-5′
(1)	82.2	39.5	70.8	86.9	61.9
(5a)	80.8	35.8	75.1	82.7	64.2
(5b)	80.8	35.8	75.2	82.6	64.3
(5c)	80.8	35.8	75.3	82.6	64.3
(6a)	81.8	37.0	74.9	83.2	64.2
(6b)	82.2	*b*	70.8	87.3	61.9
(7a)	82.4	*b*	70.9	86.9	62.0
(7b)	82.2	*b*	71.0	86.0	62.1
(7c)	82.3	*b*	71.0	86.9	62.1
(8a)	80.9	35.7	74.9	82.8	64.0
(8b)	82.4	39.2	70.8	87.1	61.8

[a] Chemical shifts are given in δ-values relative to $SiMe_4$ as internal standard. [b] Superimposed by Me_2SO.

Table 2. Yields (%) of pyrrolo[2,3-*d*]pyrimidine 2′-deoxy-β-D-*erythro*-pentofuranosides obtained by liquid–liquid and solid–liquid phase-transfer glycosylation

		solid–liquid[a]	
Compd.	liquid–liquid[a] (Bu_4NHSO_4)	(Bu_4NHSO_4)	(TDA-1)
(5a)	48[8]	57	61
(5b)	58	66	73
(5c)	54		
(8a)	45[14]	54	70

[a] For details see Experimental section.

In order to increase yields further we turned from liquid–liquid phase-transfer glycosylation to solid–liquid reaction conditions. As a result we have set up a solid–liquid system containing solid KOH, a cryptand, and an aprotic solvent. As cryptand, tris-[2-(2-methoxyethoxy)ethyl]amine (TDA-1)[24] was selected as catalyst; this compound is an aminopolyether and combines properties of an amine with those of crown ether. It is able to form cavities in anhydrous aprotic solvents. Thereby it chelates monovalent and divalent cations as well as transition metal salts. TDA-1 shows great complexing affinity for ionic compounds containing large polarizable anions, *e.g.*, nucleobase anions. An excess of KOH was used in solid–liquid phase-transfer glycosylation to ensure that traces of water and hydrochloric acid, formed during the reaction, were removed. Otherwise the cryptand will be protonated at its nitrogen and will lose its ability to bind cations. The nucleobase anion, made hydrophobic by TDA-1, is now soluble in acetonitrile and as highly reactive as a naked anion.

Phase-transfer glycosylation of the nucleobases (**3b**, **d**, and **e**) with the halogenose (**4**) occurred rapidly under solid–liquid conditions and was complete within a few minutes at room temperature. Separation of a precipitate and purification by flash chromatography yielded anomerically pure β-glycosylation products. Table 2 summarizes glycosylation yields obtained under different conditions. It is apparent that the solid–liquid method gave much better yields than experiments carried out in liquid–liquid systems. The experiments carried out in acetonitrile with solid KOH and TDA-1 as catalyst were superior to those in dichloromethane, solid KOH, and Bu_4NHSO_4. Larger-scale experiments should be even more efficient due to smaller losses of glycosylation products during work-up.

As we have shown earlier, compound (**8a**) is a useful intermediate for the synthesis of 7-carbapurine '2′-deoxyribonucleosides'[14] since nucleophilic displacement of the 4-chloro group opens up a route for the synthesis of 4-oxonucleosides, such as compound (**1**). Other substituents (NH_2, SH) can also be introduced by nucleophilic displacement reaction of the 4-halogen. Original experiments carried out under liquid–liquid conditions and employing the nucleobase (**3a**) and the halogenose (**4**) led to yields of only 45% of the glycosylation product (**8a**)[14] We have now employed solid–liquid conditions for the synthesis of (**8a**) and were able to isolate this compound in 70% yield as crystalline material. Deprotection of (**8a**) with sodium methoxide gave the deoxynucleoside (**8b**) in 68% yield.[14]

The 4-chloro group of pyrrolo[2,3-*d*]pyrimidine nucleosides is not as reactive as the corresponding substituent in purines. As a consequence much more vigorous reaction conditions are necessary to convert (**8b**)[14] into (**1**). Direct displacement with NaOH gave (**1**) in 85% yield. However, the reaction did not work well with the protected form (**8a**). Therefore it is advisable to convert (**8a**) first into (**7a**)[25] with sodium methoxide. Compound (**7a**) could be then effectively converted into (**1**).[22] The conversion of (**8b**) into other useful nucleosides by nucleophilic displacement has already been reported.[14]

In conclusion the synthesis of pyrrolo[2,3-*d*]pyrimidine '2'-deoxy-β-D-ribonucleosides' under solid–liquid conditions (aprotic solvent, TDA-1, solid KOH) is a stereospecific reation giving rise to high yields of 2'-deoxy-β-D-nucleosides. In many cases it is superior to liquid–liquid phase-transfer glycosylation or methods employing sodium hydride[23] as reagent for nucleobase anion formation.

Experimental

Elemental analyses were performed by Mikroanalytisches Labor Beller (Göttingen, W. Germany) and the Institut für Organische Chemie, Biochemie und Isotopenforschung der Universität Stuttgart (W. Germany). U.v. spectra were measured on a Uvikon 810 spectrophotometer (Kontron, Switzerland) and a U-3200 spectrophotometer (Hitachi, Japan). ^{1}H N.m.r. spectra were recorded at 250.0 MHz and ^{13}C n.m.r. spectra at 62.9 MHz on a Bruker AC 250 spectrometer. Chemical shifts are in p.p.m. relative to Me_4Si. T.l.c. was carried out on silica gel SIL G-25 UV_{254} plates (Machery & Nagel, W. Germany). Quantitative t.l.c. data were obtained with a Chromato-Scanner CS 950 (Shimadzu, Japan).

M.p.s were determined on a Linström apparatus, (Wagner & Munz, W. Germany) and are not corrected. Column and flash chromatography (0.5 bar) was carried out on silica gel 60 H (Merck, W. Germany). The columns were connected to a Uvicord S detector and an UltroRac fraction collector (LKB Instruments, Sweden). Solvent systems used were: A ($CHCl_3$–MeOH, 9:1), B (CH_2Cl_2–EtOAc, 95:5), C ($CHCl_3$–MeOH, 98:2), D (CH_2Cl_2), E (CH_2Cl_2–MeOH, 95:5), F ($CHCl_3$–MeOH, 95:5). Butan-1-ol, 2-methylpropan-1-ol, and propan-1-ol were distilled over K_2CO_3, and acetonitrile over CaH_2. Tris-[2-(2-methoxyethoxy)ethyl]amine (TDA-1) was a trade product of Aldrich Chemicals (USA).

2-*Amino*-4-*isopropoxy*-7H-*pyrrolo*[2,3-d]*pyrimidine* (**3c**).—2-Amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**3a**)[14] (1.0 g, 6.0 mmol) was dissolved in 1M-sodium isopropoxide in propan-2-ol [Na (2.3 g) in anhydrous 2-propan-2-ol (100 ml)]. The solution was refluxed for 7 days. The cooled solution was neutralized with glacial acetic acid, the inorganic salt was removed by filtration, and the solvent was evaporated off. Chromatography of the residue on silica gel 60 (column 7 × 5 cm, solvent F) yielded a main zone which gave a solid after evaporation. Recrystallization from MeOH yielded the *title compound* as crystals (370 mg, 32%), m.p. 134 °C (Found: C, 56.6; H, 5.95; N, 29.2. $C_9H_{12}N_4O$ requires C, 56.24; H, 6.29; N, 29.15%); R_F (solvent A) 0.7; $\lambda_{max.}$ (MeOH) 256 and 286 nm (ε 7 000 and 6 800); $\delta_H([^2H_6]Me_2SO)$ 1.31 (d, *J* 6.00 Hz, 2 Me), 5.43 (m, CH), 5.92 (br s, NH_2), 6.14 (m, 5-H), 6.79 (m, 6-H), and 11.0 (s, 7-H).

2-*Amino*-4-*butoxy*-7H-*pyrrolo*[2,3-d]*pyrimidine* (**3d**).—A solution of compound (**3a**) (2.0 g, 11.9 mmol) in 1M-sodium butoxide [Na (2.3 g) in anhydrous butan-1-ol (100 ml)] was refluxed for 3 h. Excess of solvent was removed by evaporation and the oily residue was dissolved in ether. The solution was neutralized with glacial acetic acid, the inorganic salt was removed by filtration, and the filtrate was dried over Na_2SO_4. Upon filtration and evaporation a solid was obtained which was crystallized from MeOH–water (9:1) to afford the *title compound* as needles (1.6 g, 66%), m.p. 130 °C (Found: C, 58.4; H, 6.8; N, 26.85. $C_{10}H_{14}N_4O$ requires C, 58.24; H, 6.84; N, 27.14%); R_F (solvent A) 0.7; $\lambda_{max.}$(MeOH) 258 and 286 nm (7 500 and 7 700); $\delta_H([^2H_6]Me_2SO)$ 1.01 (t, *J* 8 Hz, Me), 1.51 (m, CH_2Me), 1.79 (m, OCH_2CH_2), 4.42 (t, *J* 8 Hz, OCH_2), 6.01 (br s, NH_2), 6.24 (m, 5-H), 6.88 (m, 6-H), and 11.07 (s, 7-H).

2-*Amino*-4-*isobutoxy*-7H-*pyrrolo*[2,3-d]*pyrimidine* (**3e**).—Compound (**3e**) was prepared as described for (**3d**) except that the chloride (**3a**) (4.0 g, 23.7 mmol) was heated under reflux with 1M-sodium isobutoxide [Na (5.75 g) in anhydrous 2-methylpropan-1-ol (250 ml)]. The ice-cold solution was neutralized with glacial acetic acid, and evaporated under reduced pressure, and the residue was extracted with ether. The combined extracts were dried over sodium sulphate, and filtered, and the solvent was evaporated off. Crystallization from water–MeOH (1:9) yielded the *title compound* as needles (3.2 g, 65%), m.p. 143 °C (Found: C, 58.3; H, 6.9; N, 27.25. $C_{10}H_{14}N_4O$ requires C, 58.24; H, 6.84; N, 27.14%); R_F (solvent A) 0.7; $\lambda_{max.}$ 258 and 286 nm (7 500 and 7 800); $\delta_H([^2H_6]Me_2SO)$ 0.96 (d, *J* 7 Hz, 2 Me), 2.04 (m, CH), 4.11 (d, *J* 7 Hz, OCH_2), 5.97 (br s, NH_2), 6.17 (m, 5-H), 6.81 (m, 6-H), and 11.0 (s, 7-H).

2-*Amino*-4-*butoxy*-7-[2-*deoxy*-3,5-*di*-O-(p-*toluoyl*)-β-D-erythro-*pentofuranosyl*]-7H-*pyrrolo*[2,3-d]*pyrimidine* (**5b**).—*Method A* [*liquid–liquid phase-transfer glycosylation* (*PTG*)]. A solution of compound (**3d**) (506 mg, 2.5 mmol) and Bu_4NHSO_4 (85 mg, 0.25 mmol) in a mixture of dichloromethane (5 ml)–50% aqueous NaOH (10 ml) was thoroughly stirred with a vibromixer for 30 s at room temperature. A solution of 2-deoxy-3,5-di-O-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride (**4**) (1.46 g, 3.6 mmol)[26] in a small volume of dichloromethane was added to the stirred mixture, which was stirred for another 3 min. The mixture was then diluted with dichloromethane (100 ml) and washed with water (100 ml). The aqueous phase was extracted twice with dichloromethane (2 × 100 ml) and the combined organic phases were dried over sodium sulphate. The filtrate was evaporated to dryness and the residue was chromatographed on a silica gel column (15 × 5 cm) with solvent B. Evaporation of the main zone yielded a foam (795 mg, 58%), which gave crystals from MeOH, m.p. 122 °C.

Method B (*solid–liquid PTG, TDA-1*). A suspension of powdered KOH (336 mg, 6.0 mmol) in anhydrous acetonitrile (25 ml) was stirred at room temperature under nitrogen and TDA-1 (95%; 39 mg, 0.12 mmol) was added. After 15 min, compound (**3d**) (250 mg, 1.2 mmol) was dissolved in the reaction mixture and the mixture was stirred for 10 min. Then the halogenose (**4**) (530 mg, 1.3 mmol) was added. After the mixture had been stirred for another 5 min, insoluble material was removed by filtration. The filtrate was evaporated to dryness and the residue was chromatographed on a silica gel column (10 × 5 cm; solvent B). Evaporation of the eluate yielded a solid (490 mg, 73%), which crystallized from ethanol as needles, m.p. 122 °C.

Method C (*solid–liquid PTG*, Bu_4NHSO_4). A suspension of powdered KOH (543 mg, 10 mmol) and Bu_4NHSO_4 (68 mg, 0.2 mmol) in anhydrous dichloromethane (30 ml) was stirred for 15 min under nitrogen. Compound (**3d**) (400 mg, 2.0 mmol) was added and the mixture was stirred for another 30 min. After addition of the solid halogenose (**4**) (884 mg, 2.2 mmol), the mixture was stirred for 3 min, solid material was removed by filtration, and the filtrate was evaporated to dryness. The residue was chromatographed on a silica gel column (15 × 5 cm; solvent B) to yield the *title compound* as a solid (710 mg, 66%) (Found: C, 66.85; H, 6.2; N, 9.9. $C_{31}H_{34}N_4O_6$ requires C, 66.65; H, 6.13; N, 10.03%); R_F (solvent A) 0.8; $\lambda_{max.}$(MeOH) 240 and 283 nm (36 300 and 9 300); $\delta_H([^2H_6]Me_2SO)$ 0.92 (t, *J* 8 Hz, aliph. Me), 1.41 (m, CH_2Me), 1.70 (m, OCH_2CH_2), 2.57 (m, 2'-H_a), 2.60 (s, 2 Ar*Me*), 2.91 (m, 2'-H_b), 4.32 (t, *J* 7 Hz, OCH_2), 4.52 (m, 4'-H and 5'-H_2), 5.66 (m, 3'-H), 6.24 (br s, NH_2), 6.27 (d, *J* 4 Hz, 5-H), 6.54 (m, 1'-H), 7.06 (d, *J* 4 Hz, 6-H), and 7.35 and 7.91 (m, 8 ArH).

2-*Amino*-4-*butoxy*-7-[2-*deoxy*-3,5-*di*-O-(p-*toluoyl*)-α-D-erythro-*pentofuranosyl*]-7H-*pyrrolo*[2,3-d]*pyrimidine* (**6a**).—Compound (**6a**) was isolated in small amounts from glycosylation experiments carried out, according to method A, on

compound (**5b**) but using 0.5 mol equiv. of Bu_4NHSO_4 instead of 0.1 mol equiv. Compound (**6a**) was obtained as a solid, $\delta_H([^2H_6]Me_2SO)$ 0.92 (t, *J* 7 Hz, aliph. Me), 1.41 (m, CH_2), 1.71 (m, CH_2), 2.62 (m, 2′-H_b), 3.10 (m, 2′-H_a), 4.35 (t, *J* 7 Hz, OCH_2), 4.47 (m, 5′-H_2), 4.78 (m, 4′-H), 5.62 (m, 3′-H), 6.20 (br s, NH_2), 6.27 (d, *J* 4 Hz, 5-H), 6.55 (dd, *J* 3 and 8 Hz, 1′-H), 7.15 (d, *J* 4 Hz, 6-H), and 7.33 and 7.87 (m, ArH).

2-*Amino*-7-[2-*deoxy*-3,5-*di*-O-(p-*toluoyl*)-β-D-erythro-*pentofuranosyl*]-4-*isobutoxy*-7H-*pyrrolo*[2,3-d]*pyrimidine* (**5c**).—Compound (**5c**) was prepared from (**3e**) (513 mg, 2.5 mmol) according to method A, described for compound (**5b**). Chromatography was carried out on a 15 × 5 cm silica gel column with solvent E, to yield the *title compound* as a solid (752 mg, 54%), which crystallized from 2-methylpropan-1-ol as needles, m.p. 139 °C (Found: C, 66.5; H, 6.0; N, 9.8. $C_{31}H_{34}N_4O_6$ requires C, 66.65; H, 6.13; N, 10.03%); R_F (solvent C) 0.6; $\lambda_{max.}$(MeOH) 246 and 283 nm (34 600 and 9 300); $\delta_H([^2H_6]Me_2SO)$ 1.04 (d, *J* 7 Hz, 2 Me), 2.13 (m, CH), 2.46 and 2.48 (s, 2 Ar*Me*), 2.67 (2′-H_b), 3.03 (m, 2′-H_a), 4.21 (d, *J* 7 Hz, OCH_2), 4.60 (m, 4′-H and 5′-H_2), 5.75 (m, 3′-H), 6.32 (br s, NH_2), 6.37 (d, *J* 4 Hz, 5-H), 6.62 (m, 1′-H), 7.15 (d, *J* 4 Hz, 6-H), and 7.44 and 7.94 (m, 8 ArH).

2-*Amino*-7-[2-*deoxy*-3,5-*di*-O-(p-*toluoyl*)-β-D-erythro-*pentofuranosyl*]-4-*methoxy*-7H-*pyrrolo*[2,3-d]*pyrimidine* (**5a**).—Compound (**5a**) was prepared from (**3b**) (500 mg, 3.0 mmol) according to method B, described for (**5b**), except that KOH (700 mg, 12.5 mmol), TDA-1 (100 mg, 0.31 mmol), and the halogenose (**4**) (1.2 g, 3.1 mmol) were used. Chromatographic purification (solvent B) afforded the *title compound* as foam (955 mg, 61%), which crystallized from methanol as needles, m.p. 147 °C (lit.,[25] 149 °C).

The reaction carried out analogously to method C, described for the preparation of (**5b**) using (**3b**) (400 mg, 2.4 mmol), (**4**) (884 mg, 2.2 mmol), and Bu_4NHSO_4 (68 mg, 0.2 mmol) gave, after chromatography (solvent B), compound (**5a**) as crystals (710 mg, 57%) from methanol, m.p. 149 °C (lit.,[25] 149 °C).

2-*Amino*-4-*chloro*-7-[2-*deoxy*-3,5-*di*-O-(p-*toluoyl*)-β-erythro-*pentofuranosyl*]-7H-*pyrrolo*[2,3-d]*pyrimidine* (**8a**).—Compound (**8a**) was prepared as described for compound (**5b**) method B except that acetonitrile (40 ml), powdered KOH (1.2 g, 21.4 mmol), TDA-1 (100 mg, 0.31 mmol), 2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**3a**) (1.05 g, 6.23 mmol), and the halogenose (**4**) (2.45 g, 6.31 mmol) were used. The reaction time after addition of the halogenose was 30 min. Solvent D followed by solvent B was used for column chromatography. Recrystallization from propan-2-ol–methanol yielded the title compound as crystals (2.27 g, 70%), m.p. 168 °C. Compound (**8a**) was identical with that described according to ref. 14.

2-*Amino*-4-*butoxy*-7-(2-*deoxy*-β-D-erythro-*pentofuranosyl*)-7H-*pyrrolo*[2,3-d]*pyrimidine* (**7b**).—Compound (**5b**) (670 mg, 1.2 mmol) in 1.0M-sodium methoxide–methanol (25 ml) was stirred for 12 h at room temperature. The reaction mixture was neutralized with glacial acetic acid and evaporated to dryness. The residue was suspended in solvent E, the suspension was filtered, and the filtrate was subjected to flash chromatography (solvent E). From the main zone, *title compound* (**7b**) (336 mg, 87%) was isolated as a solid (Found: C, 56.1; H, 7.0; N, 17.5. $C_{15}H_{22}N_4O_4$ requires C, 55.89; H, 6.88; N, 17.38%); R_F (solvent A) 0.4; $\lambda_{max.}$(MeOH) 260 and 286 nm (9 200 and 7 500); $\delta_H([^2H_6]Me_2SO)$ 1.01 (t, *J* 7 Hz, Me), 1.50 (m, CH_2Me), 1.79 (m, OCH_2CH_2), 2.18 (m, 2′-H_b), 2.45 (m, 2′-H_a), 3.58 (m, 5′-H_2), 3.84 (m, 4′-H), 4.39 (m, 3′-H), 4.43 (t, *J* 7 Hz, OCH_2), 5.01 (t, *J* 6 Hz, 5′-OH), 5.28 (d, *J* 4 Hz, 3′-OH), 6.21 (br s, NH_2), 6.33 (d, *J* 4 Hz, 5-H), 6.47 (m, 1′-H), and 7.16 (d, *J* 4 Hz, 6-H).

2-*Amino*-7-(2-*deoxy*-β-D-erythro-*pentofuranosyl*)-4-*isobutoxy*-7H-*pyrrolo*[2,3-d]*pyrimidine* (**7c**).—Compound (**7c**) was prepared in a similar manner to that described for (**7b**). From the ditoluate (**5c**) (540 mg, 0.97 mmol) was obtained amorphous product (**7c**) (268 mg, 86%) after flash-chromatography (solvent F) (Found: C, 55.7; H, 7.0; N, 17.3. $C_{15}H_{22}N_4O_4$ requires C, 55.89; N, 6.88; N, 17.38%); R_F (solvent A) 0.3; $\lambda_{max.}$(MeOH) 260 and 286 nm (9 400 and 7 700); $\delta_H([^2H_6]Me_2SO)$ 1.04 (d, *J* 7 Hz, 2 Me), 2.13 (m, CH), 2.18 (m, 2′-H_b), 2.47 (m, 2′-H_a), 3.56 (m, 5′-H_2), 3.85 (m, 4′-H), 4.21 (d, *J* 7 Hz, OCH_2), 4.38 (m, 3′-H), 5.02 (t, *J* 6 Hz, 5′-OH), 5.29 (d, *J* 4 Hz, 3′-OH), 6.23 (br s, NH_2), 6.35 (d, *J* 4 Hz, 5-H), 6.49 (m, 1′-H), and 7.17 (d, *J* 4 Hz, 6-H).

2-*Amino*-7-(2-*deoxy*-α-D-erythro-*pentofuranosyl*)-4-*methoxy*-7H-*pyrrolo*[2,3-d]*pyrimidine* (**6b**).—Compound (**6b**) was isolated in small amounts from large-scale experiments carried out under liquid–liquid conditions.[8] It was purified on a silica gel column (solvent F), where it migrated more slowly than the corresponding β-anomer (**7a**), and was obtained as a solid (Found: C, 51.0; H, 5.8; N, 19.75. $C_{12}H_{16}N_4O_4$ requires C, 51.42; H, 5.75; N, 19.99%); R_F (solvent A) 0.4; $\lambda_{max.}$(MeOH) 260 and 286 nm (10 300 and 7 800); $\delta_H([^2H_6]Me_2SO)$ 2.10 (m, 2′-H_b), 2.70 (m, 2′-H_a), 3.43 (m, 5′-H_2), 3.92 (s, OMe), 3.98 (m, 4′-H), 4.26 (m, 3′-H), 4.81 (t, *J* 6 Hz, 5′-OH), 5.47 (d, *J* 4 Hz, 3′-OH), 6.19 (br s, NH_2), 6.27 (d, *J* 4 Hz, 5-H), 6.39 (dd, *J* 4 and 8 Hz, 1′-H), and 7.30 (d, *J* 4 Hz, 6-H).

2-*Amino*-7-(2-*deoxy*-β-D-erythro-*pentofuranosyl*)-3,7-*dihydropyrrolo*[2,3-d]*pyrimidin*-4-*one* (**1**).—(i) *From* (**7b**). Compound (**7b**) (139 mg, 0.43 mmol) was heated in 2M-aqueous NaOH under reflux for 4 h. The cooled solution was neutralized with glacial acetic acid and the precipitate was filtered off and recrystallized from water to form needles (103 mg, 90%), m.p. 245 °C (lit.,[8] 249 °C).

(ii) *From* (**7c**). Compound (**7c**) (630 mg, 1.96 mmol) in 2M-NaOH (40 ml) was treated as described for compound (**7b**). Work-up gave needles (450 mg, 86%), m.p. 248 °C (decomp.) (lit.,[8] 249 °C).

(iii) *From* (**8b**). Compound (**8b**)[14] (100 mg, 0.35 mmol) was heated in 0.2M-NaOH (10 ml) under reflux for 3 h. The solution was cooled, neutralized with acetic acid, and filtered. The filtrate was applied to an Amberlite XAD-4 column. Elution with water and recrystallization (water) yielded crystalline (**1**) (79 mg, 85%), identical with the compound obtained by method (i) or (ii).

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