690 cm^{-1}. After 3 months at 25 °C, **12** showed a slight new TLC spot at the origin.

Anal. Calcd for $C_{44}H_{58}S_7$: C, 65.12; H, 7.21; S, 27.66. Found: C, 65.26; H, 7.24; S, 27.85.

On a larger scale (19.3 g of **15**), the yields of **14**, **13** (n^{25}_D 1.5979), and **12** (n^{25}_D 1.6090) were 103%, 62% and 87%, respectively.

2-[3-(Trimethylammonio)propyl]-5-(trimethylammonio)-pentanol Salts (16). Me_3N (16 mL, 10.7 g, 181 mmol) was allowed to vaporize, and the vapor was passed into a flask equipped with a dry ice condenser and containing a solution of the carbinol **5** (9.0 g, 45.2 mmol) and NaI (0.68 g, 4.5 mmol) in DMF (120 mL). When vaporization was complete, the flask was cooled in a dry ice–acetone bath, the dry ice condenser was removed, and the flask was stoppered tightly. The reaction mixture was stirred magnetically at ca. 25 °C for 4 days, and then additional Me_3N (16 mL, 181 mmol) was added as above. After 6 more days of stirring at ca. 25 °C, the reaction mixture (containing considerable solid) was transferred to two 250-mL centrifuge bottles, along with Et_2O rinses (total ca. 300 mL) of the reaction flask. The white solid that was collected in each centrifuge tube was washed with Et_2O (3 × 100 mL). Removal of Et_2O at reduced pressure in a vacuum desiccator over P_2O_5 left 15.0 g (100% when the weight of NaI is subtracted) of the **dichloride 16** (X = Cl) as a hygroscopic solid: NMR (D_2O) δ 3.58 (d, 2 H), 3.34 (t, 4 H), 3.13 (s, 18 H), 2.01–1.24 (m, 9 H).

A mixture of **16** (X = Cl; 0.54 g, 1.7 mmol) and KI (0.6 g, 3.6 mmol) in EtOH was warmed on a steam bath. Insoluble KCl was removed by hot filtration, and the solid that precipitated from the filtrate upon cooling was recrystallized from EtOH to give 0.47 g (55%) of the diiodide **16** (X = I): mp 180–184 °C dec; this diiodide was only slightly hygroscopic; NMR (D_2O) δ 3.55 (d, 2 H), 3.32 (t, 4 H), 3.10 (s, 18 H), 2.01–1.27 (m, 9 H).

The addition of a solution of KPF_6 (1.16 g, 6.3 mmol) in H_2O to one of the carbinol **16** (X = Cl; 1.00 g, 3.2 mmol) in H_2O caused precipitation of a white solid that was collected by filtration to give 0.70 g (41%) of the bis(hexafluorophosphate) **16** (X = PF_6); this product did not appear to be hygroscopic: mp 208–210 °C dec; NMR (Me_2SO-d_6) δ 3.40 (d, 2 H), 3.24 (t, 4 H), 3.04 (s, 18 H), 1.88–1.11 (m, 9 H); IR (KBr) 3640, 2960, 2880, 2640, 1480, 1410, 1390, 1090, 1050, 1030, 970, 840, 830, 740 cm^{-1}.

In another quaternization of the carbinol **5**, the product was isolated as a dipicrate [**16**, X = $(NO_2)_3PhO$]. Thus a mixture of the carbinol **5** (510 mg, 2.56 mmol), Me_3N (1.5 mL, 1.0 g, 16.9 mmol), and NaI (40 mg, 0.27 mmol) in DMF (10 mL) was stirred at ca. 25 °C for 8 days. After the addition of enough H_2O to effect solution, the solution was washed with Et_2O, and the solvent was evaporated to give 0.77 g (95% of **16**, X = Cl) of a pasty solid. A solution of this solid (2.4 mmol, assuming it to be **16**, X = Cl) in EtOH (10 mL) was mixed with a solution of picric acid (1.2 g, 1.1 g assuming 10% H_2O, 4.8 mmol) in 0.75 N NaOH (10 mL) to give 1.82 g of yellow solid that was collected and recrystallized from EtOH to give 0.47 g (26%, based on **5**) of analytically pure **16** [X = $(NO_2)_3PhO$]: mp 160–162 °C dec.; NMR (Me_2SO-d_6) δ 8.73 (s, 4 H), 3.13 (s, 18 H), 1.92–1.08 (m, 9 H); IR (KBr) 3410, 3370, 3090, 3040, 2960, 2930, 2870, 2650, 1640, 1610, 1560, 1550, 1475, 1435, 1370–1240, 1160, 1075, 905, 780, 740, 705 cm^{-1}.

Anal. Calcd for $C_{26}H_{38}N_8O_{15}$: C, 44.44; H, 5.45; N, 15.95. Found: C, 44.42; H, 5.65; N, 15.76.

Acknowledgment. This investigation was supported by the U.S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DAMD17-79-C-9039; this paper has been designated as Contribution No. 1628 to the Army Research Program on Antiparasitic Drugs. For support in early related phases, we also thank the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIH Research Grant AM11685) and the Research Council of Vanderbilt University.

Registry No. **2**, 79899-30-2; **3**, 79899-31-3; **4**, 79899-32-4; **5**, 79899-33-5; **6**, 79899-34-6; **7**, 79899-35-7; **8**, 79899-36-8; **9**, 3753-27-3; **10**, 79899-37-9; **11**, 79899-38-0; **12**, 79899-39-1; **13**, 79899-40-4; **14**, 79899-41-5; **15**, 79899-42-6; **16** (X = Cl), 79899-43-7; **16** (X = I), 79899-44-8; **16** (X = PF_6), 79899-46-0; **16** (X = $(NO_2)_3PhO$), 79899-47-1; 2-(3-mercaptopropyl)-5-mercaptopentanol, 79899-48-2.

2-Amino-7-(β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one. Synthesis of *ara*-7-Deazaguanosine via Phase-Transfer Glycosylation

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2-Amino-7-(β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**2**), the 7-deaza analogue of 9-(β-D-arabinofuranosyl)guanine (ara-G, **1**) has been synthesized via phase-transfer glycosylation of 4-methoxy-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4**) with 2,3,5-tri-*O*-benzyl-1-bromo-D-arabinofuranose (**5**). The reaction was performed in a biphasic mixture of methylene chloride/50% aqueous NaOH in the presence of benzyltriethylammonium chloride as a catalyst. A regioselective N-7 glycosylation occurred to give a mixture of the anomers **6** and **7** in 84% yield. Chromatographic separation of the mixture afforded the pure β anomer **7** in 63% yield. The formation of **7** and the total yield decreased if lower NaOH concentrations were used. Treatment with acid resulted in ether cleavage of **7**, yielding **8a**, and subsequent methoxymethylation gave **8b**. The latter was converted to the protected nucleoside **8c** by nucleophilic displacement of the 2-methylthio group with acetamide/sodium hydride. After deacetylation of **8c**, the amino compound **8d** was formed. Its benzyl and methoxymethyl protecting groups were simultaneously removed by the action of boron trichloride to give crystalline 7-deaza ara-G (**2**).

The 9-β-D-arabinofuranosyl nucleosides of the naturally occurring purine and pyrimidine bases of nucleic acids have been synthesized and shown to have interesting biological activities.[1] They act as inhibitors of several enzymes such as ribonucleotide reductase or DNA polymerase.[2] Inhibitory specificity exists toward virus-induced enzymes. 9-(β-D-Arabinofuranosyl)adenine (ara-A)[3] possesses a broad spectrum of activity against herpes viruses[4] but is unfortunately deactivated by the action of adenosine deaminase.[5] The deamination can be avoided by replace-

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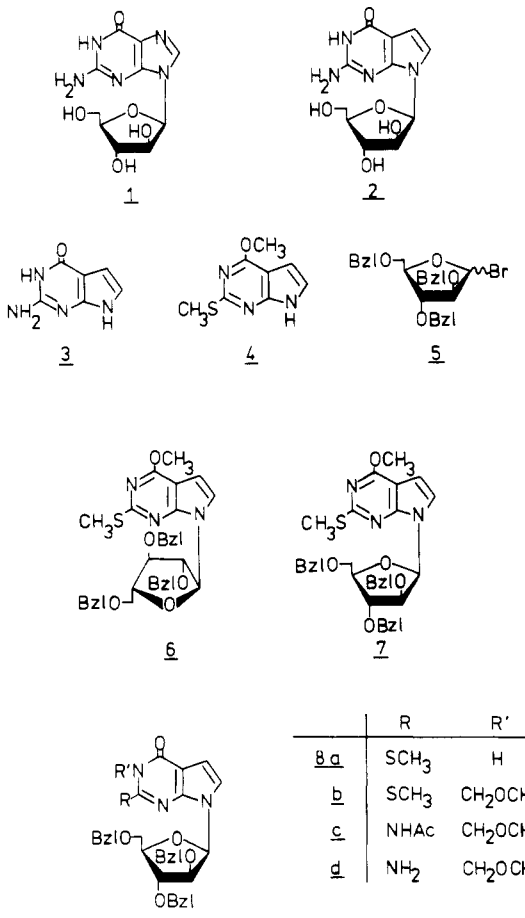
0022-3263/82/1947-0226$01.25/0

Chart I



ment of the purine aglycon of ara-A by a pyrrolo[2,3-*d*]-pyrimidine heterocycle. Thus, 4-amino-7-(β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidine (ara-tubercidin) which has recently been synthesized[6,7] cannot be deaminated by the enzyme but still shows antiviral activity.

The encouraging properties of ara-tubercidin[8] have prompted us to synthesize the 7-deaza analogue of ara-G.[9] N-7 glycosylation of the aglycon **3** in a direct manner has not been possible since the pyrimidine moiety is more nucleophilic than the pyrrole. Because of the low N-7 nucleophilicity of pyrrolo[2,3-*d*]pyrimidines the synthetic methods developed for ara-G[10] cannot be adapted for the synthesis of 7-deaza ara-G (**2**). A regioselective method of 7-glycosylation of pyrrolo[2,3-*d*]pyrimidines has been developed[11,12] to overcome these difficulties by using phase-transfer conditions.[13-15] In the following paper we present the synthesis of *ara*-7-deazaguanosine (**2**) and investigate the influence of the NaOH concentration on phase-transfer glycosylation reaction.

Table I. Amount of Anomers (6 and 7) Formed during Phase-Transfer Glycosylation of 4 (100 mg, 0.51 mmol) with the Halogenose 5 (350 mg, 0.72 mmol)[a]

	[aqueous NaOH], %				
	10	20	30	40	50
nonreacted chromophore 4, %	57	36	18	19	3
yield of α anomer 6 %	18	22	21	19	17
yield of β anomer 7, %	25	42	61	62	80
total yield of 6 and 7, %	43	64	82	81	97
anomeric ratio of β to α	~1.5	~2	~3	~3.5	~5

[a] In the presence of benzyl triethylammonium chloride (10 mg) as a catalyst. The reactions were performed in a biphasic mixture of methylene chloride (15 mL) and aqueous NaOH at different concentrations at room temperature. Vigorous mixing (15 min) was achieved with a vibromixer. The reaction products were separated by TLC (silica gel, solvent A) and quantified with a TLC scanner at 282 nm.

Results and Discussion

As a common intermediate for the synthesis of ara 7-deaza ara-G (**2**) we chose 2-(methylthio)-4-methoxypyrrolo[2,3-*d*]pyrimidine (**4**)[16] which is appropriately protected. It contains a bulky substituent at C-2, and its 4-methoxy group avoids keto–enol tautomerism at N-3/O-4. These precautions diminish the electrophilic attack of N-1 or N-3 during glycosylation and increase the solubility of the aglycon in organic solvents which is an important factor for a successful glycosylation under phase-transfer conditions. The N-7 nucleophilicity was increased by anion formation. 2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl bromide (**5**) was freshly prepared from 2,3,5-tri-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-D-arabinofuranose according to the method of Fletcher.[17a]

Phase-transfer glycosylation was carried out in a biphasic reaction mixture of methylene chloride and 50% aqueous sodium hydroxide. The organic layer contained the chromophore **4**, the halogenose **5**, and benzyltriethylammonium chloride as catalyst. Glycosylation took place after thorough mixing with a vibromixer and was complete after only 15 min with formation of the anomers **6** and **7** in 84% yield. Chromatographic separation of the anomers was achieved on silica gel with chloroform/methanol as solvents. The β anomer **7**, which was isolated from the slower migrating zone, was formed in 63% yield and the α anomer **6**, which migrated more rapidly, in 21% yield. The structural assignment of the separated anomers was achieved by rigorous comparison with intermediates already used for the synthesis of 7-(β-D-arabinofuranosyl)-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one.[16]

During elucidation of the appropriate reaction conditions the concentration of NaOH in the inorganic phase was varied between 10% and 50%. In these experiments all other parameters were held constant. As shown in Table I a low concentration of sodium hydroxide resulted in a low yield of the glycosylation products **6**/**7** and a large amount of unreacted chromophore **4**. This decrease can be explained by solvation phenomena of the ion pair formed between the anion of compound **4** and the benzyltrietylammonium counterion. If the NaOH concentration is low, the amount of "free" water is high. It is then likely that the anion of the aglycon **4** is encumbered by water molecules and that its reactivity is correspondingly reduced. In contrast, a relatively solvation-free anion

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Table II. Proton NMR Spectral Data of Pyrrolo[2,3-*d*]pyrimidine Nucleosides[a]

compd	chemical shift							
	2-H	5-H	6-H	1'-H	2'-H	3'-H	4'-H	5'-H
2-amino-7-(β-D-arabinofuranosyl)-pyrrolo[2,3-*d*]pyrimidin-4-one (2)		6.50 (d, 3.9)	7.04 (d, 3.9)	6.30 (d, 6.0)	4.48 (t, 6.0)	~3.9 (m)	4.30 (dd, 6.4, 6.4)	~3.9 (m)
4-amino-7-(β-D-arabinosuranosyl)-pyrrolo[2,3-*d*]pyrimidine[7]	7.98 (s)	6.56 (d, 3.91)	7.34 (d, 3.9)	6.45 (d, 5.9)	4.51 (t, 5.9)	3.9 (m)	4.31 (m, 6.4)	3.9 (m)
7-(β-D-arabinofuranosyl)-pyrrolo[2,3-*d*]pyrimidin-4-one[16]	8.80 (s)	6.70 (d, 3.7)	7.40 (d, 3.7)	6.48 (d, 5.9)	4.54 (t, 6.2)	4.0 (m)	4.24 (dd)	4.0 (m)
2-amino-7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidin-4-one[19]		6.56 (d, 3.7)	7.04 (d, 3.7)	6.00 (d, 6.7)	4.61 (t, 5.5)	4.36 (t, 3.6)	4.18 (q, 4.0)	3.82 (m)

[a] All spectra were recorded in D_2O with HOD (4.80 ppm) as an internal standard. Chemical shifts are given in δ values, while the values in parentheses are coupling constants given in hertz.

accompanied by a highly lipophilic solvated benzyltriethylammonium cation is generated at a NaOH concentration of 50%, and therefore its reactivity is relatively high. A highly reactive aglycon is a basic requirement for an effective glycosylation since the halogenose **5** gradually decomposes under the strongly alkaline reaction conditions of phase-transfer glycosylation.

The ratio of the anomers **7**/**6** was also influenced by a concentration change of sodium hydroxide (Table I). Their formation can be explained by an S_N2 displacement of the anomeric bromine substituents of the halogenoses **5** by the anion of the aglycon **4**. Since the α anomer of the halogenose is the dominating isomer[17b] the preferred formation of the β nucleoside **7** agrees with this mechanism. The change in the ratio of the anomers on decreasing the concentration of NaOH in the inorganic phase was unexpected. This may be due to a competition between the glycosylation reaction and the decay of the halogenose **5**. If the rate of decomposition of the anomeric halogenoses depends on their structure, the ratio of the anomeric nucleosides will necessarily be affected, resulting in this case in a final ratio of 1:1.5. High yields of the β anomer **7** are therefore only obtained at the highest possible NaOH concentration in the inorganic phase. Although aqueous conditions can be used during phase-transfer glycosylation, the amount of "free" water available in the inorganic phase should be as low as possible.

The conversion of the 2-methylthio group of **7** into an amino group was carried out under conditions which have already been used for the synthesis of the rare nucleoside Q[18] and its parent compound 7-deazaguanosine.[19] The 4-methoxy group of **7** was first cleaved by refluxing the material in a mixture of hydrochloric acid/dioxane containing trace amounts of a radical inhibitor. This afforded the deazainosine derivative **8a** in 82% yield. Nucleophilic displacement could then performed selectively at C-2 without affecting C-4. In order to avoid anion formation at N-3 or O-4 under the alkaline conditions necessary for this displacement reaction, the nitrogen at position 3 was protected with a methoxymethyl residue. Compound **8a** was methoxymethylated under anhydrous conditions with chloromethyl methyl ether in the presence of sodium hydride, yielding the *N*-methoxymethyl derivative **8b**. After chromatographic separation and exhaustive drying, the viscous material was treated with a mixture of molten acetamide and sodium hydride. After careful neutralization of the cold melt, compound **8c** was isolated by extraction and column chromatography. The acetyl group of **8c** was then cleaved by the action of concentrated ammonia in methanol. Since we were unable to separate compound **8c** from **8b** chromatographically and as their UV spectra did not differ significantly, we checked the completeness of the reaction by ^1H NMR. Complete deprotection of the acetyl residue was accomplished after 12 h at room temperature. The isolated material showed an unusual ^1H NMR spectrum in deuteriochloroform. Besides the expected coupling pattern of the N-3 side chain, a nonequivalence of the methyl signals and the methylene protons was observed. This may be due to an immobilization of the N-3 protecting group by an intramolecular hydrogen bond between the 2-amino group and the ether oxygen of the methoxymethyl residue.

Because of the stability of the N-glycosylic bond in pyrrolo[2,3-*d*]pyrimidine nucleosides the cleavage of the N-3 methoxymethyl group of **8d** was attempted in hydrochloric acid. However, all efforts to obtain the N-3 deprotected compound by refluxing **8d** in dioxane/hydrochloric acid failed. After evaporation of the solvent, at least four reaction products could be detected. None of these products showed the typical UV spectrum of the aglycon **3** with an absorption maximum at 259 nm and a shoulder around 280 nm. Although the shape of the spectra were similar to that of the chromophore, the maxima were always shifted to higher wavelength.

Because of these difficulties we then gave preference to debenzylation of the O-protecting groups of **8d** by catalytic hydrogenation with Pd/charcoal as the catalyst. Deprotection was effected during 24 h under normal pressure. The isolated material was not homogeneous, and the compound isolated from the main zone gave an unusual UV spectrum with a maximum at 290 nm. We have evidence that in this case the pyrrolo[2,3-*d*]pyrimidine moiety was partially hydrogenated. We therefore decided to remove both the N-3 and the O-protecting groups by the action of boron trichloride in methylene chloride at −78 °C.[20] In contrast to the previous methods only one reaction product was detected by TLC during analytical testing. By use of preparative-scale synthesis, crystalline *ara*-7-deazaguanosine (**2**) was obtained. It showed a UV maximum at 259 nm in methanol, similar to that of the aglycon **3** (257 nm) and coinciding with the pH-dependent spectra (Figure 1) of 7-deazaguanosine.[19]

The structure of the nucleoside **2** was assigned from its NMR data. The ^{13}C signals of the chromophore moiety of **2** appeared at 99.72 (C-4a), 100.96 (C-5), 119.99 (C-6), 150.79 (C-7a), 152.79 (C-2), and 158.86 ppm (C-4). Except for C-6 they coincide with those of the aglycon **3** with signals at 99.93 (C-4a), 101.56 (C-5), 116.56 (C-6), 151.14 (C-7a), 152.21 (C-2), and 158.89 ppm (C-4),[16] thus confirming that the nucleoside **2** contains the chromophore **3** as a nucleobase. The downfield shift of the C-6 signal

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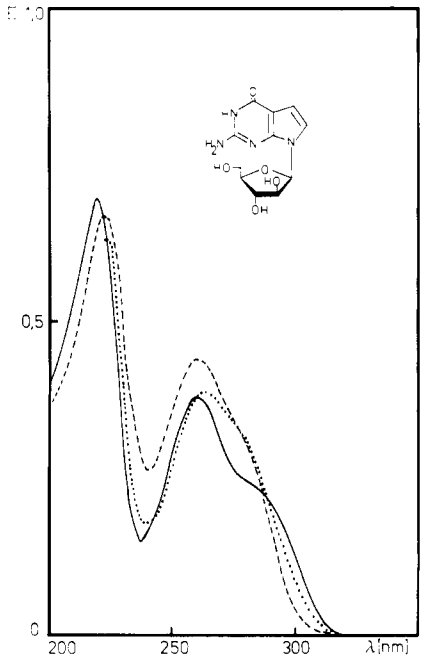

Figure 1. UV spectra of *ara*-7-deazaguanosine (2) in 0.1 M sodium phosphate, pH 7.0 (–); 0.1 N HCl (- -); 0.1 N NaOH (···).

Table III. Chromatographic and Electrophoretic Mobilities of Pyrrolo[2,3-*d*]pyrimidine and Guanine Derivatives

	R_f (silica gel, solvent F)	R_e[a] cellulose (solvent G)	R_e[a] silica gel (solvent H)
ara-7-deaza-guanosine (2)	0.3	2.1 (–)	1.3 (–)
7-deaza-guanosine[16]	0.3	0	0.6 (–)
7-deaza-guanine	0.5	1.0 (–)	1.0 (–)
guanosine	0.2	0	0.5 (–)
guanine	0	0	0

[a] (–) toward cathode, (+) toward anode.

by about 3.5 ppm indicates N-7 glycosylation. The arabino structure of the sugar moiety of **2** can be derived by comparing its ^{1}H NMR signals with other arabinonucleosides.

As can be seen from Table II, all sugar protons appear at similar values, whereas β-ribonucleosides such as 7-deaza G[19,21] show a different pattern. Finally, the anomeric configuration could be assigned on the basis of the chemical shift of its anomeric proton. This is located at about 6.3 ppm, similar to those of β ara nucleosides shown in Table II, whereas α-arabinonucleosides are shifted upfield to around 6.0 ppm. The latter results from the shielding of the 2-hydroxyl group.

The homogeneity of **2** was tested first by TLC. Since we were not able to separate ribo- and arabinoisomers by this method, we developed the material by electrophoresis (Table III). Excellent separation was achieved in this case, especially if sodium tetraborate was used as solvent due to complex formation of ribonucleosides with the borate anion.

Experimental Section

Melting points were determined on a Berl apparatus (Wagner & Munz) and were not corrected. Elemental analysis were performed by Mikroanalytisches Labor Beller. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian EM 390, Bruker WM 250, or Bruker HX-60 spectrometers; δ values are in parts per million relative to tetramethyl silane as an internal standard. UV spectra were measured on a Uvicon 810 spectrometer (Kontron); TLC scanning was performed with a CS-920 high-speed TLC scanner (Shimadzu). Thin-layer chromatography (TLC) and thin-layer electrophoresis (TLE) were carried out on silica gel F 254 plates (Woelm), or cellulose plates (Merck); visualization was achieved by 254-nm irradiation. Column chromatography was performed on silica gel 60 (230–400-mesh ASTM; Merck) and Lobar prepacked columns (LiChroprep Si 60, size C; Merck). Electrophoresis was carried out in a TLE double chamber (Desaga). Solvent systems: A, $CHCl_3$; B, $CHCl_3$–MeOH (98.5:1.5); C, $CHCl_3$–MeOH (97.5:2.5); D, $CHCl_3$–MeOH (95:5); E, $CHCl_3$–MeOH (8:2); F, $CHCl_3$–MeOH (7:3); G, 0.1 M sodium tetraborate (pH 9.0); H, 0.1 M sodium citrate (pH 6.5).

Phase-Transfer Glycosylation of 4-Methoxy-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidine (4) with 2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl Bromide (5). Dry hydrogen bromide was bubbled into a solution of 2,3,5-tri-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-D-arabinofuranose[17] (3.5 g, 6.15 mmol) in dichloromethane (15 mL) until no further *p*-nitrobenzoic acid precipitated. The acid was filtered off and washed with a small volume of dichloromethane. The combined filtrates were evaporated to give the viscous halogenose **5**. This was dissolved in dichloromethane (20 mL) and poured into a suspension of **4** (1.0 g, 5.1 mmol) in dichloromethane (10 mL). After benzyltriethylammonium chloride (0.3 g, 1.1 mmol) and an equal volume of 50% aqueous sodium hydroxide were added, the mixture was stirred for 15 min with a vibromixer. The organic layer was separated, washed with water, dried with sodium sulfate, and filtered, and the solvent was removed in vacuo. The remaining viscous residue was dissolved in chloroform (20 mL) applied to a column of silica gel (70 × 5 cm) and chromatographed with chloroform. Two main zones were separated.

4-Methoxy-2-(methylthio)-7-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidine (6). From the more rapidly migrating zone was isolated the viscous α anomer **6** (0.63 g, 21%) which was then crystallized from methanol as colorless needles: mp 62–63 °C; ^{1}H NMR ($CDCl_3$) δ 6.47 (d, H-1′, $J_{1'2'}$ = 2.5 Hz), 6.47 (d, H-1′, $J_{1'2'}$ = 3 Hz).[16]

4-Methoxy-2-(methylthio)-7-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidine (7). The slower migrating zone contained the viscous β anomer **7**: 1.94 g (63%); ^{1}H NMR ($CDCl_3$) δ 6.73 (d, H-1′, $J_{1'2'}$ = 5 Hz), 6.72 (d, H-1′, $J_{1'2'}$ = 4.5 Hz).[16]

2-(Methylthio)-7-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4-one (8a). A solution of 1.0 g (1.67 mmol) of **7** in dioxane (50 mL) containing 50 mg of 4′4′-thiobis(2-*tert*-butyl-5-methylphenol) and 0.5 N HCl (20 mL) was refluxed for 16 h. The resulting solution was concentrated (20 mL), diluted with chloroform (100 mL), and washed with water. The organic layer was separated and dried with sodium sulfate, and the solvent was evaporated. The remaining oil was dissolved in chloroform and chromatographed on a Lobar silica gel column. Elution with the same solvent afforded a light yellow syrup (0.8 g, 82%) of **8a**: homogeneous on TLC (solvent C) R_f 0.32; UV (methanol) λ_{max} 268 nm (ε 11 600), 286 (11900); ^{1}H NMR ($CDCl_3$) δ 2.53 (s, SCH_3), 3.68 (d, H-5′, J = 4.5 Hz), 4.00–4.70 (m, H-4′,3′,2′), 4.15, 4.53, 4.60 (s, 13 benzyl CH_2), 6.60 (d, H-1′, J = 5.0 Hz), 6.67 (d, H-5, J = 3.5 Hz), 7.18 (d, H-6, J = 3.5 Hz), 6.85–7.47 (m, 15 aromatic H), 12.45 (s, NH); ^{13}C NMR (Me_2SO-d_6) δ 12.82 (SCH_3), 69.22 (C-5′), 71.30, 71.68, 72.34 (3 benzyl CH_2), 79.27 (C-2′), 80.75 (C-3′), 81.99 (C-1′, C-4′), 101.80 (C-5), 104.89 (C-4a), 121.42 (C-6), 127.51, 128.16 (15 aromatic C), 137.22, 137.87, 138.00 (3 aromatic C), 147.56 (C-7a), 155.0 (C-2), 158.59 (C-4).

Anal. Calcd for $C_{33}H_{33}N_3O_5S$: C, 67.90; H, 5.70; N, 7.20; S, 5.49. Found: C, 68.02; H, 5.69; N, 7.04; S, 5.51.

3-(Methoxymethyl)-2-(methylthio)-7-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4-one (8b). A suspension of **8a** (1.0 g, 1.71 mmol) in 100 mL of dry dimethoxyethane and sodium hydride (0.7 g, 23 mmol, 20% paraffin) was stirred for 10 min at 0 °C. After addition of chloromethyl methyl ether (1.75 mL, 23 mmol) the stirring was continued for another 50 min at room temperature. The mixture was filtered

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and the solvent evaporated. The viscous residue was applied to a Lobar silica gel column, and compound **8b** was eluted with solvent A. After evaporation, viscous **8b** was isolated: 0.84 g (78.5%); TLC (solvent C) R_f 0.38; UV (methanol) λ_{max} 270 nm (ϵ 7200), 301 (8300); ^{1}H NMR ($CDCl_3$) δ 2.53 (s, SCH_3), 3.45 (s, OCH_3), 3.70 (d, H-5', J = 5.0 Hz), 4.0–4.83 (m, H-4',3',2'), 4.17, 4.53, 4.63 (s, 3 benzyl CH_2), 5.62 (s, NCH_2), 6.58 (d, H-1', J = 4.0 Hz), 6.60 (d, H-5, J = 3.5 Hz), 7.15 (d, H-6, J = 3.5 Hz), 6.83–7.40 (m, 15 aromatic H); ^{13}C NMR (Me_2SO-d_6) δ 14.57 (SCH_3), 56.21 (OCH_3), 69.22 (C-5'), 71.30, 71.75, 72.33 (3 CH_2), 73.24 (NCH_2O), 79.33 (C-2'), 80.63 (C-3'), 82.05 (C-4', C-1'), 102.38 (C-5), 102.90 (C-4a), 122.07 (C-6), 127.57, 128.22 (15 aromatic C), 138.06, 137.93, 137.16 (3 aromatic C), 145.72 (C-7a), 157.23 (C-2), 158.14 (C-4).

Anal. Calcd for $C_{35}H_{37}N_3O_6S$: C, 66.97; H, 5.94; N, 6.69; S, 5.11. Found: C, 67.14; H, 5.94; N, 6.60; S, 5.08.

2-(Acetylamino)-3-(methoxymethyl)-7-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidine (8c). A mixture of sodium hydride (0.48 g, 16 mmol, 20% in paraffin) and freshly sublimized acetamide (5.0 g) was heated to a clear melt at 100 °C in an oil bath under nitrogen. After the mixture cooled, the nucleoside **8b** (1.0 g, 1.6 mmol) was added to the molten material, and the resulting mixture was heated for another 40 min at 100 °C. The cooled mixture was then carefully neutralized with glacial acetic acid at 0 °C, diluted with water, and extracted with benzene. The organic layer was separated, dried over sodium sulfate, filtered, and evaporated. The remaining residue was dissolved in chloroform and applied to a Lobar silica gel column (solvent B). From the main zone compound **8c** (0.87 g, 86%) was obtained as a colorless syrup after evaporation: TLC (solvent C) R_f 0.38; UV (methanol) λ_{max} 265 nm (ϵ 7700), 295 (8500); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, $NHCOCH_3$), 3.38 (s, OCH_3), 3.68 (d, H-5', J = 5.0 Hz), 3.90–4.67 (m, H-4',3',2'), 4.27, 4.51, 4.60 (s, 3 benzyl CH_2), 5.52 (s, NCH_2O), 6.46 (d, H-1', J = 5.0 Hz), 6.62 (d, H-5, J = 3.5 Hz), 7.21 (d, H-6, J = 3.5 Hz), 6.83–7.45 (m, 15 aromatic H), 8.45 (br s, NHAc); ^{13}C NMR (Me_2SO-d_6) δ 22.99 ($COCH_3$), 56.27 (OCH_3), 69.55 (C-5'), 71.29, 71.75, 72.33 (3 CH_2), 72.33 (OCH_2N), 79.39 (C-2'), 81.33 (C-3'), 82.05 (C-1', C-4'), 103.33 (C-4a), 104.65 (C-5), 124.60 (C-6), 127.57, 128.22 (15 aromatic C), 137.28, 137.93, 138.06 (3 aromatic C), 145.32, 144.73 (C-2, C-7a), 158.33 (C-4), 170.25 (CO).

Anal. Calcd for $C_{36}H_{38}O_7N_4$: C, 67.69; H, 6.00; N, 8.77. Found: C, 67.88; H, 6.04; N, 8.76.

4-Amino-3-(methoxymethyl)-7-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidine (8d). Compound **8c** (1.0 g, 1.6 mmol) in methanol/concentrated ammonia (50 mL, 10:1) was stirred for 12 h and then evaporated to dryness. The oily residue was applied to a Lobar silica gel column (solvent B) to afford a colorless syrup: 0.94 g (94%); TLC (solvent C) R_f 0.38); UV (methanol) λ_{max} 262 nm (ϵ 12700), 289 (7400); ^{1}H NMR ($CDCl_3$) δ 3.36 (s, OCH_3), 3.66 (d, H-5', J = 5.0 Hz), 4.00–4.30 (m, H-4',3',2'), 4.20, 4.53, 4.60 (s, 3 benzyl CH_2), 5.20 (s, NH_2), 5.45 and 5.57 (NCH_2O, J = 10.5 Hz), 6.43 (d, H-1', J = 5.0 Hz), 6.53 (d, H-5, J = 3.5 Hz), 7.00 (d, H-6, J = 3.5 Hz), 6.92–7.45 (m, 15 aromatic H); ^{13}C NMR (Me_2SO-d_6) δ 55.63 (OCH_3), 70.16 (C-5'), 71.19, 71.55, 72.33 (3 CH_2), 72.33 (OCH_2N), 79.46 (C-3'), 81.27 (C-2'), 81.79 (C-1', C-4'), 98.62 (C-5), 103.50 (C-4a), 121.36 (C-6), 127.51, 128.22 (15 aromatic C), 137.42, 137.97, 138.20 (3 aromatic C), 149.14 (C-7a), 153.03 (C-2), 158.27 (C-4).

Anal. Calcd for $C_{34}H_{36}O_6N_4$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.29; H, 6.18; N, 9.26.

4-Amino-7-(β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (2). To a solution of compound **8d** (355 mg, 0.59 mmol) in methylene chloride (30 mL) was added a solution of 1.2 M boron trichloride in methylene chloride (10 mL, 12 mmol) at −78 °C (dry ice–acetone). The mixture was kept for 4 h at the same temperature. It was then treated with methanol–methylene chloride (50 mL, 1:1) and stored at room temperature for another 30 min. The solvent was evaporated, the residue dissolved in ethanol (150 mL) and carefully neutralized with 1 N aqueous sodium hydroxide. Inorganic precipitate was filtered and the solution evaporated. The resultant was dissolved in methanol (50 mL), adsorbed on silica gel (10 g) and the solvent removed in vacuo. The suspension of this silica gel in solvent E was applied to the top of a silica gel column (30 × 2.5 cm). Elution with solvent E yielded a colorless syrup (97 mg, 58.0%) which could be crystallized from ethanol as colorless crystals which decompose at 210 °C; TLC (solvent E) R_f 0.2; UV (methanol) λ_{max} 218 nm (ϵ 19800), 259 (12500), 280 (7800); ^{1}H NMR, see Table II; ^{13}C NMR (Me_2SO-d_6) δ 61.54 (C-5'), 75.95 (C-3',2'), 83.16 (C-1'), 83.76 (C-4'), 99.64 (C-4a), 100.88 (C-5), 119.94 (C-6), 150.71 (C-7a), 152.71 (C-2), 158.78 (C-4).

Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.80; H, 5.00; N, 19.85. Found: C, 46.58; H, 5.28; N, 19.25.

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Syntheses of Isoretronecanol and Lupinine

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Syntheses of (±)-isoretronecanol and (±)-lupinine are described which employ the 1,3-dipolar additions of cyclic nitrones to dihydrofuran and dihydropyran. The reaction proceeded regio- and stereoselectively to afford the adducts, which were converted into the title compounds by two-step processes.

Alkaloids containing the nitrogen atom in bridgehead position of two rings, indolizidine, pyrrolizidine, and quinolizidine alkaloids, have a wide and varied distribution in the nature.[1] Some of these alkaloids demonstrate a broad range of pharmacological activities[2] and have generated substantial synthetic interest.[3] This report deals

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