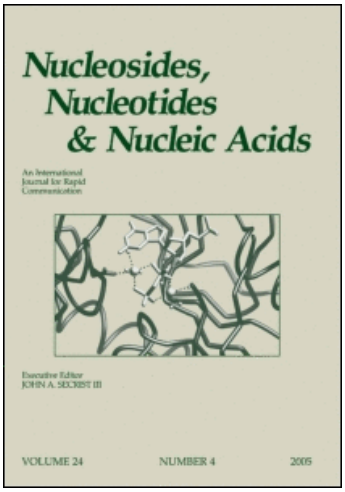

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Studies on the Chemical Synthesis of Potential Antimetabolites. 32.[1] Synthesis of β-D-Pentofuranosyldeazaadenines as Candidate Inhibitors for S-Adenosylhomocysteinases and Methyltransferases

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STUDIES ON THE CHEMICAL SYNTHESIS OF POTENTIAL ANTIMETABOLITES. 32.[1] SYNTHESIS OF β-D-PENTOFURANOSYLDEAZAADENINES AS CANDIDATE INHIBITORS FOR S-ADENOSYLHOMOCYSTEINASES AND METHYLTRANSFERASES

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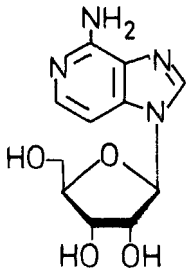
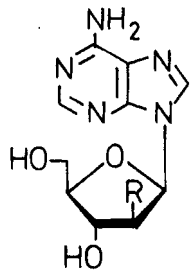
Abstract 9-β-D-Arabinofuranosyldeazaadenines [1-deaza-araA (4a) and 3-deaza-araA (4b)] were prepared from 6-chloro-β-D-ribofuranosyl-1- (6a) and -3-deazapurine (6b), respectively. Synthesis of 2'-deoxy-1-deaza-adenosine (5a) from 1-deazaadenosine (6c) is also described.

S-Adenosylhomocysteine (SAH), which is one of the products of biological methylation catalyzed by S-adenosyl-L-methionine (SAM)-dependent methyltransferases, is an extraordinarily potent inhibitor against the enzymes. In addition, SAH is reversibly synthesized by S-adenosyl-homocysteinase (SAHase, EC 3.3.1.1). The remarkable SAHase-catalyzed hydrolysis can be observed only when adenosine, one of the hydrolysis products, is removable from the system, for example, in the presence of adenosine deaminase, kinase, or phosphorylase. These properties of SAH and SAHase indicate that SAH may be a crucial endogeneous regulator of biological methylation.[2]

3-Deazaadenosine (1) was found to be an excellent substrate as well as a potent inhibitor of the SAHase.[3] The nucleoside has been shown to possess inhibitory activity against herpes simplex type 1 and some oncogenic viruses.[4]



1

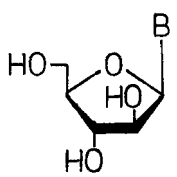


2: R = OH
3: R = H

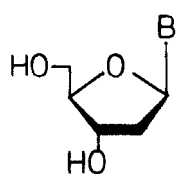
In previous communications, we have described the synthesis of deazaadenosines (1[5] and 6c[6]) and 2'-deoxy-3-deazaadenosine (5b),[7] which have inhibitory activities against SAHase.[8] These findings, coupled with the fact that some nucleosides including arabinofuranosyladenine (araA, 2) and 2'-deoxyadenosine (3) act as irreversible inhibitors of the SAHase-catalyzed reaction[9] prompted us to prepare some additional derivatives of deazapurine nucleosides.

In this paper we describe new and efficient syntheses of 9-β-D-arabinofuranosyldeazaadenines [1-deaza-araA (4a) and 3-deaza-araA (4b)] and 2'-deoxy-1-deazaadenosine (5a).

In most syntheses of β-D-pentofuranosylpurines, condensation of a suitably protected heterocycle with a blocked 1-acyloxy- or 1-halogeno-sugar constitutes the method of choice. However, in the case of the preparation of β-D-arabinofuranosides and 2'-deoxy-β-D-ribofuranosides this approach occasionally fails to give satisfactory results, owing to the formation of the α-anomer or an anomeric mixture of products. We utilized some recent advances in the transformation of ribofuranosides to arabinofuranosides[10] and 2'-deoxyribofuranosides[11] for the preparation of the title compounds (4a, 4b, and 5a), because the synthesis of 6-chloro-1- and 3-deazapurine ribofuranosides as well as deazaadenosines has been already developed by us and others.[5,6,12]

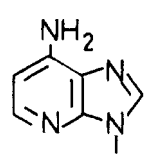


4a
4b

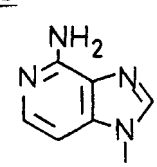


5a
5b

B =



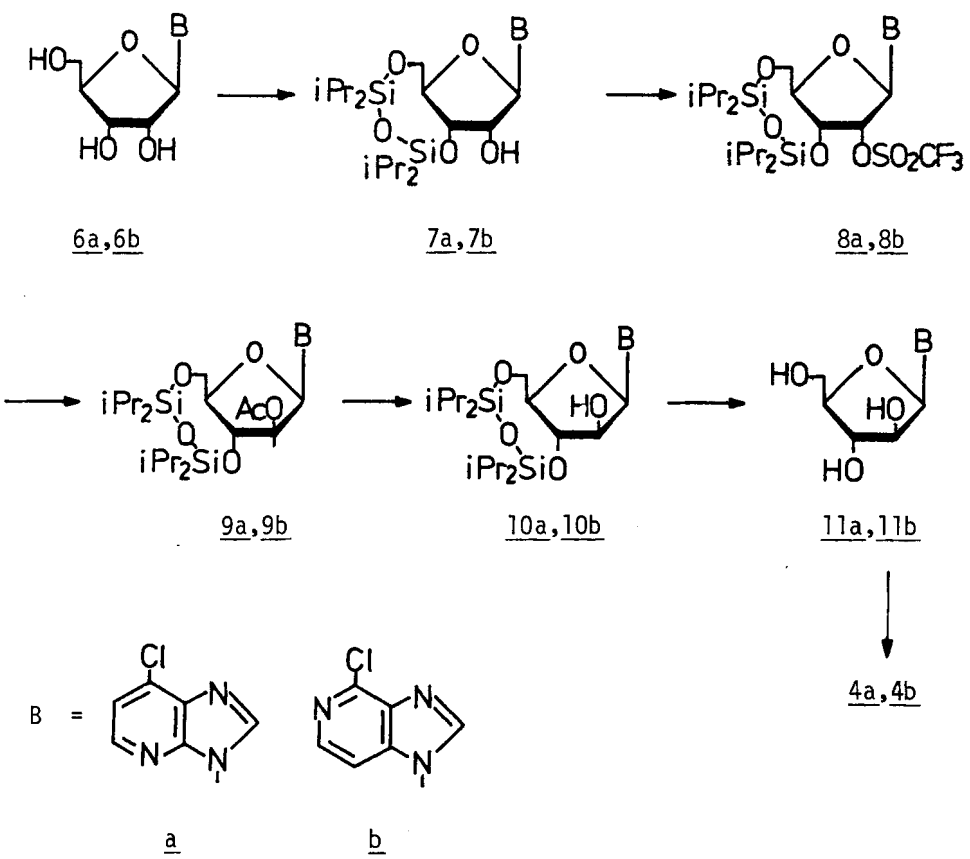
a



b

Synthesis of β-D-Arabinofuranosyldeazaadenines (4a and 4b)

A procedure developed by Fukukawa et al.[10] was successfully applied to the preparation of 4a and 4b. Thus, 3',5'-O-silylated ribonucleoside (7a or 7b), prepared from 6-chlorodeazapurine ribofuranoside (6a or 6b) and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane,[13] was converted into the corresponding trifluoromethanesulfonyl derivative (8a or 8b). Pmr signals due to H-2' of both 8a and 8b appeared at much lower field compared with those of the corresponding 2'-O-unprotected nucleosides. Nucleophilic displacement of the triflyloxy group with sodium acetate in hexamethylphosphoramide (HMPA) gave rise to 2'-O-acetyl-arabinofurano-



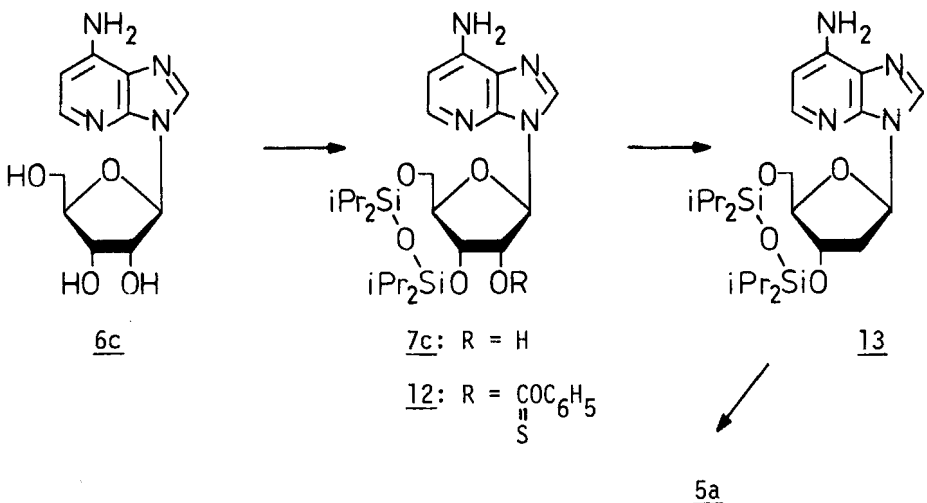
sides (9a and 9b) in 84 and 87 % yields, respectively. Treatment of 9a or 9b with methanolic ammonia or triethylamine followed by tetrabutylammonium fluoride afforded β-D-arabinofuranosyl-6-chlorodeazapurine (11a or 11b). Deaza-araA (4a or 4b) was obtained by treatment of 11a or 11b with hydrazine hydrate followed by Raney nickel reduction.[12c] In the

pmr spectra signals due to the anomeric proton of the resulting nucleosides (11a, 11b, 4a, and 4b) appeared at lower field by ca. 0.4 ppm compared with that of the corresponding ribofuranosides (see TABLE 1), showing that the formers are desired β-D-arabinofuranosides. These facts are in keeping with the empirical rule[15] which states that H-1' resonates at lower field when the 1',2'-substituents are cis than they are trans. Overall yields of 4a and 4b were about 35 and 18 %, respectively.

After the completion of the preparation of 4b, Montgomery et al. reported the synthesis of the same nucleoside by a condensation method.[15] Physical properties including spectral data of 4b were virtually identical with the reported values.

Synthesis of 2'-Deoxy-1-deazaadenosine (5a)

3',5'-O-Silylated 1-deazaadenosine (7c), prepared from 1-deazaadenosine (6c)[5] and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, was converted into 2'-O-phenoxythiocarbonyl derivative (12), which was reduced with tributyltin hydride to afford a 2'-deoxynucleoside (13).[10,11] Treatment of 13 with tetrabutylammonium fluoride gave rise to 5a in 31.8 % yield, based on 6c.



6c 7c: R = H 13

12: R = COC_6H_5 (S)

5a

Biological Evaluation

Compounds 4a, 4b, 5a, and 6c were tested for their effects on the yellow lupin SAHase and were found to inhibit the SAHase irrevers-

TABLE 1 Pmr Chemical Shifts and Coupling Constants of Prepared Nucleosides (DMSO-d_6)*

Compd.	H-1	H-2	H-3	H-8	NH_2	H-1'	H-2'	H-3'	H-4'	H-5'
6c	6.36d ($J_{1,2}$=5.4 Hz)	7.75d	-	8.22s	6.47s	5.84d ($J_{1',2'}$=6.3 Hz)	4.68t	4.11q	3.96q	3.63q 3.53q
4a	6.37d ($J_{1,2}$=5.4 Hz)	7.77d	-	8.09s	6.30s	6.27d ($J_{1',2'}$=3.9 Hz)	— 4.10m —		3.74m	3.62m
5a	6.34d ($J_{1,2}$=5.5 Hz)	7.75d	-	8.23s	6.42s	6.34q ($J_{1',2'}$=8.5, 5.9 Hz)	2.18m 2.77m	4.38m	3.88m	3.56m
6a	7.48d ($J_{1,2}$=5.4 Hz)	8.32d	-	8.79s	-	6.04d ($J_{1',2'}$=5.9 Hz)	4.60q	4.16q	3.96m	3.64m
11a	7.44d ($J_{1,2}$=5.4 Hz)	8.29d	-	8.59s	-	6.42d ($J_{1',2'}$=4.4 Hz)	— 4.15m —		3.81q	3.66m
1	-	7.64d ($J_{2,3}$=5.9 Hz)	6.89d	8.27s	6.15s	5.73d ($J_{1',2'}$=5.7 Hz)	4.30q	4.07q	3.93q	3.61m
4b	-	7.62d ($J_{2,3}$=5.9 Hz)	6.80d	8.16s	6.08s	6.10d ($J_{1',2'}$=4.9 Hz)	4.13q	4.06q	3.73m	3.61m
6b	--	8.15d ($J_{2,3}$=5.6 Hz)	7.89d	8.68s	-	5.91d ($J_{1',2'}$=6.1 Hz)	4.32m	4.11m	4.03m	3.65m
11b	-	8.11d ($J_{2,3}$=5.9 Hz)	7.74d	8.60s	-	6.31d ($J_{1',2'}$=5.4 Hz)	4.21q	4.08q	3.79m	3.69m

*Pmr spectra were taken using about 3 % solution at ordinary probe temperature (25°). Signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet).

ibly.[8a] These compounds as well as other deazapurine nucleosides also possess inhibitory activities against bovine SAHase.[8b] Details of the results will be the subject of a forthcoming paper.

EXPERIMENTAL

Melting points were determinied on a Yamato melting point apparatus, Type MP-1, and are uncorrected. Ultraviolet absorption spectra were taken on a Hitachi Recording Spectrophotometer 323. Proton magnetic resonance spectra were recorded on a JEOL FX-200 Spectrometer. Mass spectra as well as high resolution mass spectra were taken on a JMS D-300 JEOL Mass Spectrometer. Circular dichroism spectra were taken on a JASCO J-40 Spectropolarimeter.

6-Chloro-9-(3,5-O-tetraisopropyldisiloxanyl-β-D-ribofuranosyl)-9H-1-deazapurine (7a)

To a solution of 6-chloro-9-β-D-ribofuranosyl-9H-1-deazapurine (6a, 1.0 g, 3.5 mmol) in pyridine (10 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSCl_2$, 1.19 g, 3.8 mmol) and the mixture was stirred at room temperature for 3 h. Water (30 mL) was added to the solution and the mixture was extracted with three 50-mL portions of chloroform. Concentration of the dried (Na_2SO_4) solution gave a syrup, which was purified over a silica-gel column (φ1.4 cm x 41 cm). Evaporation of the chloroform fraction containing desired product gave 7a (1.66 g, 89.8 %) as a white foam. MS: m/e 528/530 (M + 1), 527/529 (M^+), 485/487 (M + 1 - iPr), 484/486 (M - iPr). Pmr in chloroform-d: δ 8.24 (s, 1H, H-8), 8.23 (d, 1H, H-2, $J_{1,2}$= 5.4 Hz), 7.30 (d, 1H, H-1, $J_{1,2}$= 5.4 Hz), 6.09 (d, 1H, H-1', $J_{1',2'}$= 1.0 Hz), 5.04 (dd, 1H, H-3'), 4.59 (dd, 1H, H-2'), 4.0 ∿ 4.2 (m, 3H, H-4' and H-5'), 1.0 ∿ 1.2 (m, 28H, iPr).

6-Chloro-9-(3,5-O-tetraisopropyldisiloxanyl-β-D-ribofuranosyl)-9H-3-deazapurine (7b)

6-Chloro-9-β-D-ribofuranosyl-9H-3-deazapurine (6b, 1.97 g, 6.9 mmol) was converted to a 3',5'-O-protected derivative (7b) with $TIPDSCl_2$ (2.27 g, 7.2 mmol) by a procedure similar to that used to prepare 7a. 7b

(2.90 g, 79.6 %) was obtained as a colorless foam. MS: m/e 528/530 (M + 1), 527/529 (M^+), 485/487 (M + 1 - iPr), 484/486 (M - iPr), 154/156 (B + 2H). Pmr in chloroform-d: δ 8.25 (s, 1H, H-8), 8.23 (d, 1H, H-2, $J_{2,3}$= 5.6 Hz), 7.46 (d, 1H, H-3, $J_{2,3}$= 5.6 Hz), 5.95 (d, 1H, H-1', $J_{1',2'}$= 1.4 Hz), 4.56 (q, 1H, H-3'), 4.05 ∿ 4.25 (m, 4H, H-2', H-4', and H-5'), 1.0 ∿ 1.2 (m, 28H, iPr).

Anal. Calcd. for $C_{23}H_{38}O_5N_3ClSi_2 \cdot 1/6CHCl_3$: C, 50.77; H, 7.02; N, 7.67; Cl, 9.70. Found: C, 50.56; H, 7.14; N, 7.55, Cl, 9.43.

3',5'-O-Tetraisopropyldisiloxanyl-1-deazaadenosine (7c)

1-Deazaadenosine (6c, 500 mg, 1.88 mmol) was treated with $TIPDSCl_2$ (0.65 g, 2.07 mmol) under the same conditions used to prepare 7a to give 7c (888 mg, 93 %) as a white foam. MS: m/e 508 (M^+), 465 (M - iPr), 163 (B + 30), 135 (B + 2H). Pmr in chloroform-d: δ 7.98 (s, 1H, H-8), 7.97 (d, 1H, H-2, $J_{1,2}$= 5.4 Hz), 6.43 (d, 1H, H-1, $J_{1,2}$= 5.4 Hz), 6.03 (d, 1H, H-1', $J_{1',2'}$= 1.5 Hz), 5.10 (dd, 1H, H-3'), 4.85 (s, 2H, NH_2), 4.58 (dd, 1H, H-2'), 4.13 (m, 3H, H-4' and H-5'), 1.0 ∿ 1.2 (m, 28H, iPr).

6-Chloro-9-(3,5-O-tetraisopropyldisiloxanyl-2-O-trifluoromethanesulfonyl-β-D-ribofuranosyl)-9H-1-deazapurine (8a)

To a mixture of 7a (1.55 g, 2.94 mmol), N,N-dimethylaminopyridine (39.5 mg), and triethylamine (0.45 mL) in methylene chloride (14 mL) was added trifluoromethanesulfonyl chloride (0.35 mL, 3.29 mmol) under ice cooling. The mixture was stirred at room temperature for 1 h, poured onto ice-water(ca. 20g), and extracted with three 100-mL portions of chloroform. Concentration of the dried (Na_2SO_4) organic layer gave a syrup, which was chromatographed over a silica-gel column (φ1.4 cm x 42 cm) with chloroform as the eluent to give 1.64 g(84.4 %) of 8a as a colorless syrup. MS: m/e 617/619 (M + 1 -iPr), 616/618 (M - iPr), 484/486 (M + 1 - iPr - CF_3SO_2). Pmr in chloroform-d: δ 8.27 (s, 1H, H-8), 8.22 (d, 1H, H-2, $J_{1,2}$= 5.4 Hz), 7.34 (d, 1H, H-1, $J_{1,2}$= 5.4 Hz), 6.22 (s, 1H, H-1'), 5.79 (d, 1H, H-2'), 5.23 (d, 1H, H-3'), 4.0 ∿ 4.3 (m, 3H, H-4' and H-5'), 1.0 ∿ 1.2 (m, 28H, iPr).

6-Chloro-9-(3,5-O-tetraisopropyldisiloxanyl-2-O-trifluoromethanesulfonyl-β-D-ribofuranosyl)-9H-3-deazapurine (8b)

Compound 7b (6.81 g, 12.9 mmol) was triflated under similar conditions as described above to give a triflate 8b (7.39 g, 86.7 %) as a color-

less foam. MS: m/e 660/662 (M + 1), 659/661 (M^+), 617/619 (M + 1 - iPr), 616/618 (M - iPr). Pmr in chloroform-d: δ 8.36 (s, 1H, H-8), 8.26 (d, 1H, H-2, $J_{2,3}$= 5.4 Hz), 7.43 (d, 1H, H-3, $J_{2,3}$= 5.4 Hz), 6.21 (s, 1H, H-1'), 5.10 (d, 1H, H-2'), 4.72 (dd, 1H, H-3'), 4.36 (d, 1H, H-5'a), 4.21 (dd, 1H, H-4'), 4.11 (dd, 1H, H-5'b), 1.0 ∿ 1.2 (m, 28H, iPr).

Anal. Calcd. for $C_{24}H_{37}O_7N_3F_3ClSSi_2 \cdot 1/7CHCl_3$: C, 42.81; H, 5.53; N, 6.20; Cl, 7.48. Found: C, 42.64; H, 5.45; N, 6.30; Cl, 7.32.

6-Chloro-9-(3,5-O-tetraisopropyldisiloxanyl-2-O-acetyl-β-D-arabinofuranosyl)-9H-1-deazapurine (9a)

A mixture of 8a (1.27 g, 1.93 mmol) and sodium acetate (0.32 g, 3.86 mmol) in hexamethylphosphoramide (HMPA, 3 mL) was stirred for 6 h at room temperature. The reaction mixture was applied to silica gel plates, which were developed with benzene-ethyl acetate (1 : 1). Eluate of a main zone was concentrated in vacuo to give 9a (852 mg, 77.7 %) as a clear syrup. MS: m/e 570/572 (M + 1), 569/571 (M^+), 527/529 (M + 1 - iPr), 526/528 (M - iPr). Pmr in chloroform-d: δ 8.50 (s, 1H, H-8), 8.25 (d, 1H, H-2, $J_{1,2}$= 5.4 Hz), 7.29 (d, 1H, H-1, $J_{1,2}$= 5.4 Hz), 6.59 (d, 1H, H-1', $J_{1',2'}$= 6.4 Hz), 5.60 (dd, 1H, H-2'), 4.91 (t, 1H, H-3'), 4.14 (t, 2H, H-5'), 3.97 (m, 1H, H-4'), 1.64 (s, 3H, CH_3CO), 1.0 ∿ 1.2 (m, 28H, iPr).

6-Chloro-9-(3,5-O-tetraisopropyldisiloxanyl-2-O-acetyl-β-D-arabinofuranosyl)-9H-3-deazapurine (9b)

To a solution of 8b (4.31 g, 6.53 mmol) in HMPA (40 mL) was added sodium acetate (0.82 g, 10 mmol) and the mixture was stirred at room temperature for 3.5 h. The reaction mixture was poured onto ice-water (100 g) to afford a gummy substance, which was dissolved in chloroform (100 mL). The solution was washed with water several times to remove HMPA. The dried (Na_2SO_4) chloroform solution was concentrated in vacuo to give 9b as a colorless foam. Pmr in chloroform-d: δ 8.20 (s, 1H, H-8), 8.19 (d, 1H, H-2, $J_{2,3}$= 5.9 Hz), 7.41 (d, 1H, H-3, $J_{2,3}$= 5.9 Hz), 6.33 (d, 1H, H-1', $J_{1',2'}$= 6.6 Hz), 5.47 (dd, 1H, H-2'), 4.73 (t, 1H, H-3'), 4.23 (dd, 1H, H-5'a), 4.09 (dd, 1H, H-5'b), 3.93 (m, 1H, H-4'), 1.61 (s, 3H, CH_3CO), 1.0 ∿ 1.2 (m, 28H, iPr).

6-Chloro-9-β-D-arabinofuranosyl-9H-1-deazapurine (11a)

A solution of 9a (852 mg, 1.5 mmol) and triethylamine (10 mL) in methanol (50 mL) was allowed to stand overnight at room temperature. The

mixture was concentrated *in vacuo* to leave a crude sample of 3',5'-*O*-silylated arabinoside (*10a*). To a solution of *10a* in THF (10 mL) was added n-Bu_4NF (814 mg, 3.3 mmol) and the mixture was stirred for 20 min at room temperature. To the mixture was added water (30 mL) and the solution was washed with three 50-mL portions of chloroform. Concentration of the aqueous layer gave a white solid, which was purified with preparative silica gel plates. The eluent of a main band was concentrated *in vacuo* to give a crude sample of *11a*, which was crystallized from ethanol: 390 mg (91.7 %), mp 196 ∿ 197°. MS: m/e 285/287 (M^+), 254/256 (M - 31), 212/214 (M - 73), 182/184 (B + 30), 153/155 (B + H), 152/154 (B). High resolution MS: Calcd. for $C_{11}H_{12}O_4N_3Cl$; 285.0514. Observed; 285.0517. Uv λmax: nm (*p*H 11) 256, 280 (pH 1) 249, 274, 281.

Anal. Calcd. for $C_{11}H_{12}O_4N_3Cl$: C, 46.25; H, 4.23; N, 14.71; Cl, 12.41. Found: C, 46.09; H, 4.38; N, 14.79; Cl, 12.29.

6-Chloro-9-(3,5-O-tetraisopropyldisiloxanyl-β-D-arabinofuranosyl)-9H-3-deazapurine (*10b*)

A solution of *9b*, prepared from *8b* (4.31 g), in methanolic ammonia (*ca.* 50 mL) was allowed to stand overnight at room temperature. The mixture was concentrated *in vacuo* to give a syrup, which was chromatographed over a silica gel column with chloroform-methanol (25 : 1) as the eluent to give *10b* (2.82 g, 81.8 % based on *8b*). MS: m/e 528/530 (M + 1), 527/529 (M^+), 485/487 (M + 1 -iPr), 484/486 (M - iPr). Pmr in chloroform-d: δ 8.32 (s, 1H, H-8), 8.12 (d, 1H, H-2, $J_{2,3}$= 5.9 Hz), 7.41 (d, 1H, H-3, $J_{2,3}$= 5.9 Hz), 6.08 (d, 1H, H-1', $J_{1',2'}$= 5.4 Hz), 4.67 (q, 1H, H-2'), 4.48 (t, 1H, H-3'), 4.09 (d, 2H, H-5'), 3.89 (m, 1H, H-4'), 1.0 ∿ 1.2 (m, 28H, iPr).

6-Chloro-9-β-D-arabinofuranosyl-9H-3-deazapurine (*11b*)

To a solution of *10b* (2.82 g, 5.34 mmol) in THF (50 mL) was added N-Bu_4NF (1.5g, 5.9 mmol) and the mixture was stirred for 15 min at room temperature. Water (50 mL) was added to the reaction mixture and the solution was extracted with four 50-mL portions of chloroform. *11b* (0.944 g, 61.8 %) crystallized from the aqueous layer as needles, mp 200 ∿ 201°. MS: m/e 285/287 (M^+), 182/184 (B + 30), 166/168 (B + 14), 154/156 (B + 2H), 153/155 (B + H). Uv λmax: nm (*p*H 11) 256.5, 265, 271.5sh; (*p*H 1) 256, 266, 272.

Anal. Calcd. for $C_{11}H_{12}O_4N_3Cl \cdot 1/3H_2O$: C, 45.29; H, 4.38; N, 14.41. Found: C, 45.54; H, 4.15; N, 14.46.

9-β-D-Arabinofuranosyl-9H-1-deazaadenine (1-deaza-araA, 4a)

A solution of 11a (380 mg, 1.33 mmol) in 80 % hydrazine hydrate (7 mL) was refluxed for 1 h under nitrogen atmosphere. The mixture was concentrated in vacuo to give 6-hydrazino-nucleoside as a colorless syrup [uv λmax: nm(pH 11) 265, 284; (pH 1) 271sh, 283], which was dissolved in oxygen-free water (7 mL). Raney nickel was added to the solution and the mixture was refluxed for 1 h under nitrogen atmosphere. The catalyst was filtered off and washed with water (10 mL). Combined filtrate and washing were concentrated in vacuo to afford a white solid, which was recrystallized from water, giving 4a (232 mg, 65.6 %), mp 261 ∿ 262°. MS: m/e 266 (M^+), 249 (M - 17), 236 (M - 30), 163 (B + 30), 134 (B + H). Uv λmax: nm (ε) (pH 12.5) 263 (11,900), 278 (8,850); (pH 1.21) 266sh, 283 (14,000). CD: nm ([θ]) (pH 12.3) 282 (-5,310), 273 (-4,060), 268 (-4,870), 236 (0), 225 (+9,850).

Anal. Calcd. for $C_{11}H_{14}O_4N_4 \cdot 1/6H_2O$: C, 49.11; H, 5.33; N, 20.80. Found: C, 49.07; H, 5.37; N, 20.80.

9-β-D-Arabinofuranosyl-9H-3-deazaadenine (3-deaza-araA, 4b)

The nucleoside 11b (58 mg, 0.2 mmol) was converted into 4b by a similar procedure described above. In this case, 4b was obtained as mono-HCl salt, which was chromatographed over a Dowex 1 x 2 (OH^-) column with 30 % methanol as the eluent to give a HCl-free sample of 4b (27.5 mg, 50.9 %) with undefinitive melting point. MS: m/e 266 (M^+), 176 (B + 43), 147 (B + 14), 135 (B + 2H), 134 (B + H). Uv λmax: nm (ε) (pH 11.3) 265 (9,820); (pH 1.20) 262 (9,790). CD: nm ([θ]) (pH 11.3) 258 (-4,380), 235sh (-1,750), 226 (0), 220 (+5,040).

Anal. Calcd. for $C_{11}H_{14}O_4N_4 \cdot 1/3H_2O$: C, 48.57; H, 5.43; N, 20.60. Found: C, 48.78; H, 5.33; N, 20.59.

9-(3,5-O-Tetraisopropyldisiloxanyl-2-O-phenoxythiocarbonyl-β-D-ribofuranosyl)-9H-1-deazaadenine (12)

Compound 7c (880 mg, 1.73 mmol), phenoxythiocarbonyl chloride (568 mg, 3.46 mmol), N,N-dimethylaminopyridine (211 mg, 1.73 mmol), and triethylamine (0.5 mL) were dissolved in acetonitrile (10 mL). The mixture was stirred for 3 h at room temperature under nitrogen atmosphere and

then poured onto ice-water (ca 20 g). The mixture was extracted with three 50-mL portions of chloroform. The organic layer was washed with water (50 mL), dried over Na_2SO_4, and concentrated in vacuo to give a crude sample of 12, which was chromatographed over a silica gel column (ϕ 1.6 cm x 34 cm) with chloroform as the eluent to give 12 (907 mg, 81.3 %) as a foam. MS: m/e 644 (M^+), 601 (M - iPr), 541 (M - 103), 163 (B + 30), 134 (B + H). Pmr in chloroform-d: δ 8.00 (s, 1H, H-8), 7.96 (d, 1H, H-2, $J_{1',2}$= 5.6 Hz), 7.1 ∿ 7.5 (m, 5H, Ph), 6.44 (d, 1H, H-1, $J_{1,2}$ = 5.6 Hz), 6.40 (dd, 1H, H-2'), 6.22 (d, 1H, H-1', $J_{1',2'}$= 1.0 Hz), 5.37 (dd, 1H, H-3'), 4.89 (s, 2H, NH_2), 4.03 ∿ 4.21 (m, H-4' and H-5'), 1.0 ∿ 1.2 (m, 28H, iPr).

9-(2-Deoxy-3,5-O-tetraisopropyldisiloxanyl-β-D-erythropentofuranosyl)-9H-1-deazaadenine (13)

To a refluxing solution of 12 (847 mg, 1.32 mmol) and a catalytic amount of 2,2'-azobis(2-methylpropionitrile) in toluene (20 mL) was added n-Bu_3SnH (3.0 mL) and the mixture was refluxed for 3 h under a nitrogen atmosphere. The solvent was evaporated in vacuo to give a yellow syrup, which was purified with silica gel plates to give 13 (652 mg, a quantitative yield) as a foam. MS: m/e 492 (M^+), 449 (M - iPr), 163 (B + 30), 134 (B + H). Pmr in chloroform-d: 8.07 (s, 1H, H-8), 8.01 (d, 1H, H-2, $J_{1,2}$= 5.4 Hz), 6.43 (d, 1H, H-1, $J_{1,2}$= 5.4 Hz), 6.37 (dd, 1H, H-1', $J_{1',2'}$=3.8 Hz), 5.02 (s, 2H, NH_2), 4.91 (q, 1H, H-3'), 4.05 (m, 2H, H-5'), 3.90 (m, 1H, H-4'), 2.65 (m, 2H, H-2'), 1.0 ∿ 1.1 (m, 28H, iPr).

9-(2-Deoxy-β-D-erythropentofuranosyl)-9H-1-deazaadenine (2'-deoxy-1-deazaadenosine, 5a)

To a solution of 13 (640 mg, 1.30 mmol) in THF (10 mL) was added n-Bu_4NF (640 mg, 2.6 mmol) and the mixture was stirred for 20 min at room temperature. Water (200 mL) was added and the solution was extracted with three 100-mL portions of chloroform. The aqueous layer was concentrated in vacuo to afford a pale foam, which was chromatographed over a Dowex 1 x 8 (OH^-) column (ϕ 2.2 cm x 41 cm) with 60 % methanol as the eluent to give 5a (136 mg, 42.0 % based on 12) as needles, mp 207∿208°. MS: m/e 251 (M^+), 220 (M - 31), 163 (B + 30), 134 (B + H). Uv λmax: nm (ε) (pH 12.4) 263 (10,800), 278 (8,530); (pH 1.43) 266sh, 283 (14,100). CD: nm ([θ]) (pH 12.7) 265 (-1,840), 236 (0), 233 (+370), 231 (0), 220 (-5,510).

Anal. Calcd. for $C_{11}H_{14}O_3N_4 \cdot 1/3H_2O$: C, 51.56; H, 5.77; N, 21.86. Found: C, 51.65; H, 5.58; N, 21.46.

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