Synthesis of 2-Substituted Adenine-arabinosides and Related Compounds[1] from 5-Amino-4-cyano-1-(β-D-ribofuranosyl)imidazole

Yoshiko SATO, Tokumi MARUYAMA and Mikio HONJO*

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770, Japan. *Received September 13, 1988*

Triflation of the N^5-benzylidene-3′,5′-*O*-silyl protected 5-amino-4-cyano-1-(β-D-ribofuranosyl)imidazole (AICN-riboside) (IIb), followed by nucleophilic displacement with OAc^- and N_3^- provided the corresponding 2′(*S*)-substituted derivatives (VIIa, VIIb). Deprotection of the silyl and benzylidene groups of VIIa, followed by hydrolysis of the acetyl group gave AICN-arabinoside (IXc). Reaction of IXc with alkyl, aryl and aralkyl nitriles afforded the corresponding 2-substituted adenine-arabinosides (XIa—e). The 2′-azido (Xa) and 2′-amino (Xb) analogs of XIa were similarly prepared.

Keywords imidazole-riboside; imidazole-arabinoside; triflation; nucleophilic displacement; 2-substituted adenine-arabinoside

The antiviral activity of 9-β-D-arabinofuranosyladenine (adenine-arabinoside) against deoxyribonucleic acid (DNA) viruses *in vitro* and *in vivo* is well documented.[2] The synthesis of several 2-substituted (*e.g.* halogeno, amino, hydroxy, methoxy, benzyloxy, ethylthio and methyl) adenine-arabinosides has been reported by employing a

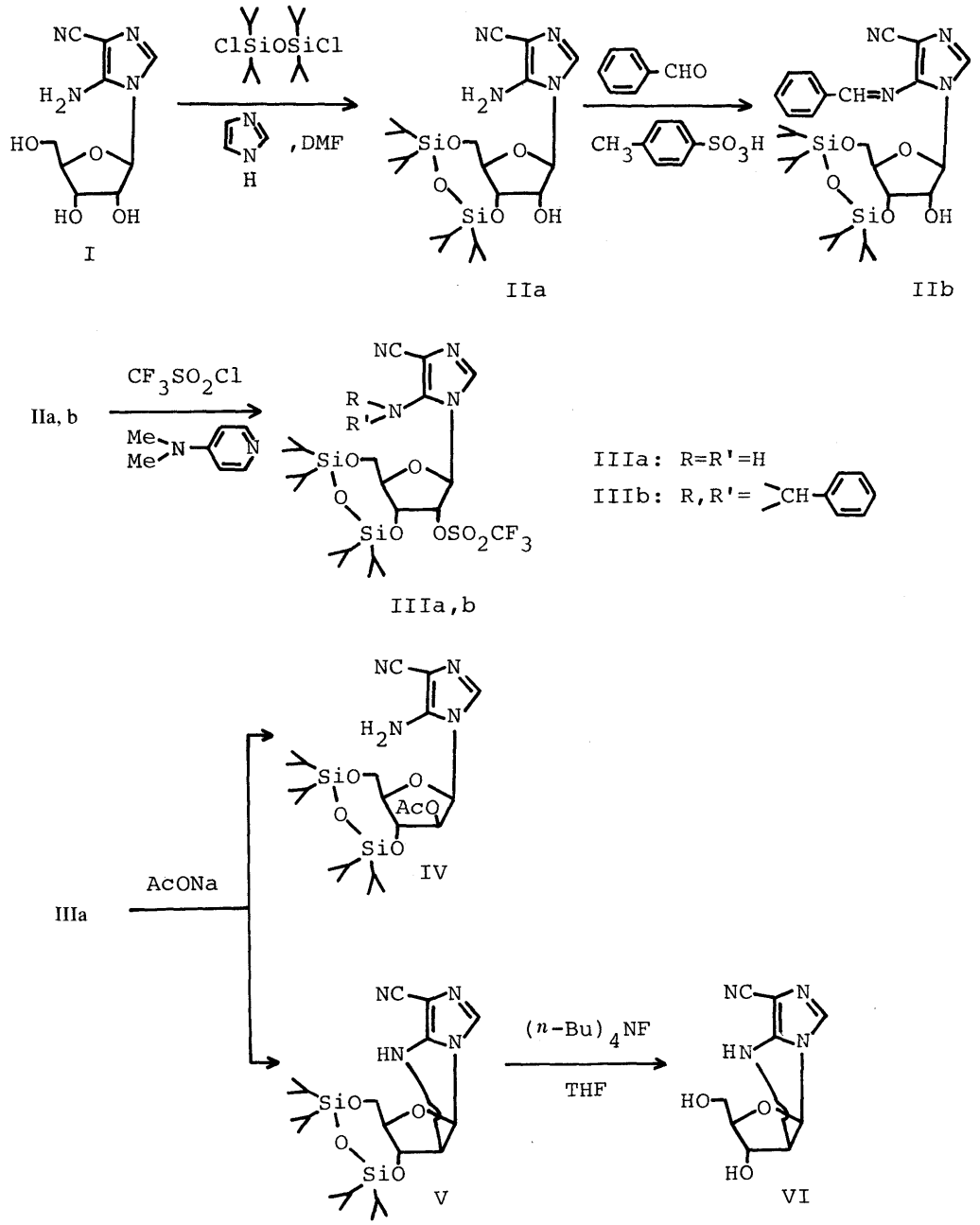

Chart 1

sugar-base coupling reaction,[3] a transformation of the base or sugar moiety of an appropriate nucleoside,[4] or an enzymatic arabinose-transfer reaction.[5] This paper describes a general method for the synthesis of 2-substituted, especially 2-alkyl, -aryl or -aralkyl, adenine-arabinosides, starting from 5-amino-4-cyano-1-(β-D-ribofuranosyl)imidazole (AICN-riboside) (I).[6]

An attempt at conversion of I to 5-amino-1-(β-D-arabinofuranosyl)-4-cyanoimidazole (AICN-arabinoside) (IXc) has been made by application of the method of Fukukawa *et al.*[7] Thus, treatment of I with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane afforded the corresponding 3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl) derivative (IIa). Compound IIa was allowed to react in pyridine with trifluoromethanesulfonyl chloride in the presence of 4-dimethylaminopyridine to give the 2′-*O*-triflate (IIIa) in high yield. A trial of S_N2 displacement with acetate anion at the 2′-position of IIIa was made to obtain the 2′(*S*)(ara)-*O*-acetate (IV). An intramolecular cyclization proceeded more smoothly than the displacement to afford the N^5,2′-anhydro compound (V) and IV in 69.0 and 8.9% yields, respectively. The structure of IV was confirmed by the mass (MS) and proton nuclear magnetic resonance (^{1}H-NMR) spectra: the configuration of the 2′(*S*)-acetoxy group was verified by an upfield shift[7] of the acetoxy proton signals (1.87 ppm), as compared with those (2.23 ppm) of the 2′(*R*)(ribo)-derivative. The structure of V was ascertained from the MS and ^{1}H-NMR spectra as well as elemental analysis: decoupling of the peak corresponding to H_2, caused the doublet of N^5-H (1H, J=3.67 Hz) to collapse into a singlet. Desilylation of V with tetra-*n*-butylammonium fluoride provided N^5,2′-anhydro-AICN-arabinoside (VI) in high yield.

In order to exclude the intramolecular cyclization, another trial was made after protection of the amino group of IIIa with benzylidene group. Reaction of IIa with benzaldehyde in the presence of *p*-toluenesulfonic acid gave the N^5-benzylidene derivative (IIb)[8] (Chart 1). Triflation of IIb, followed by nucleophilic attack on the 2′-*O*-triflate (IIIb) with sodium acetate in dimethylformamide (DMF) afforded the 2′(*S*)-*O*-acetate derivative (VIIa) as a caramel in 83% yield. The structure of VIIa was confirmed by the ^{1}H-NMR and MS spectra. Nucleophilic displacement of IIIb with sodium azide also gave the corresponding derivative (VIIb) in high yield. Desilylation of VIIa and VIIb to VIIIa and VIIIb, followed by removal of the benzylidene group with acetic acid provided the corresponding AICN-arabinoside derivatives (IXa, IXb). Hydrolysis of IXa with methanolic ammonia or reduction of IXb with triphenylphosphine yielded the 2′(*S*)-hydroxy (IXc) or 2′(*S*)-amino compound (IXd), respectively. The 2′(*S*)-configuration of IXc was confirmed by a downfield shift of the H-1′ proton signal.[10]

Reaction of IXb and IXc with alkyl, aryl and aralkyl nitriles in methanolic ammonia[11] gave the corresponding 2-substituted adenine-arabinosides (Xa and XIa—e). Reduction of Xa yielded the 2′(*S*)-amino derivative (Xb) (Chart 2). The structures of these 2-substituted adenine-arabinosides were confirmed by the MS and ^{1}H-NMR spectra and elemental analyses. The ultraviolet (UV) spectra of Xa, Xb, XIa, XIb and XId were similar to that of 2-methyladenosine,[11a] but a bathochromic shift was observ-

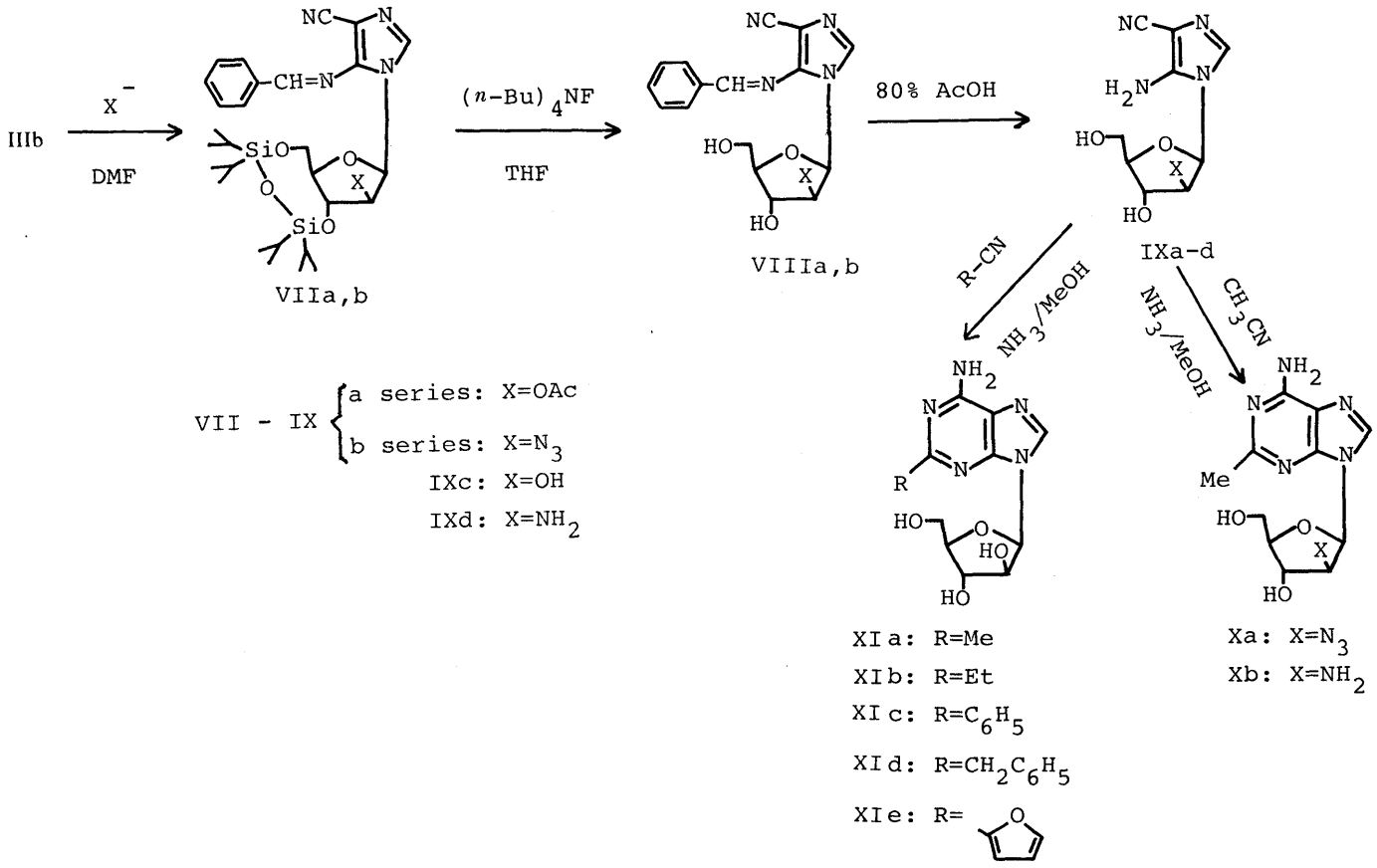

Chart 2

ed in those of XIc and XIe.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus (hot stage type) and are uncorrected. The UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. MS were measured with a Shimadzu LKB 9000B spectrometer. The ^{1}H-NMR spectra were recorded with a JEOL GX-400 (400 MHz) spectrometer in $CDCl_3$ or dimethyl sulfoxide (DMSO-d_6) with tetramethylsilane as an internal standard. Circular dichroism (CD) spectra were recorded with a JASCO J500C spectropolarometer at 25 °C. Thin-layer chromatography (TLC) was carried out on plates (2 × 10 cm) coated with Wakogel B-5 including fluorescent indicator F_{254} (Merck) and developped with $CHCl_3$–EtOH (10 : 1).

The physical properties and ^{1}H-NMR parameters of all compounds prepared in this study are summarized in Tables I and II, respectively.

5-Amino-4-cyano-1-(3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl)imidazole (IIa) I (960 mg, 4 mmol) and imidazole (1.20 g, 17.6 mmol) were dissolved in DMF (10 ml), and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (1.40 g, 4.4 mmol) was added to the solution. The mixture was stirred at room temperature for 40 min, then water was added to quench the reaction. The solvent was removed *in vacuo*, and the residue was dissolved in $CHCl_3$ (50 ml). The organic layer was washed with water (30 ml), dried over $MgSO_4$, and concentrated to a small volume to give a white crystalline material (1.61 g, 84%).

5-Benzylideneamino-4-cyano-1-(3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl)imidazole (IIb) A solution of IIa (4.82 g, 10 mmol), benzaldehyde (2 ml) and *p*-toluenesulfonic acid (0.2 g, 1.2 mmol) in benzene (200 ml) was heated under reflux for 3 h, then cooled. After removal of the solvent, the syrup was dissolved in $CHCl_3$ (50 ml). The organic layer was washed successively with 5% $NaHCO_3$ (5 ml) and water (5 ml), dried over $MgSO_4$, and concentrated to a small volume (10 ml). The solution was chromatographed over a column of Silica gel G (3.2 × 32 cm) with a gradient of 0—3% EtOH in $CHCl_3$ to afford a pale-yellowish caramel (5.35 g, 94%).

5-Amino-4-cyano-1-(2-*O*-triflyl-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl)imidazole (IIIa) IIa (2.4 g, 5 mmol) and 4-dimethylaminopyridine (1.00 g, 8.2 mmol) were dissolved in a mixture of triethylamine (1.2 ml) and pyridine (50 ml), then ice-cooled. Trifluoromethanesulfonyl chloride (1.0 ml, 9.39 mmol) was added to the solution and the mixture was stirred at room temperature for 30 min. The reaction was quenched by the addition of water (1 ml) and the solution was evaporated to dryness. The residue was partitioned between $CHCl_3$ (50 ml) and water (50 ml). The organic layer was washed with water (20 ml), dried over $MgSO_4$ and chromatographed over a column of Silica gel G (2.6 × 33 cm) with a gradient of 0—2% EtOH in $CHCl_3$ (1.5 l) to give a caramel (2.42 g, 79%).

5-Benzylideneamino-4-cyano-1-(2-*O*-triflyl-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl)imidazole (IIIb) IIb (7.5 g, 13.2 mmol) in pyridine (130 ml) was treated with trifluoromethanesulfonyl chloride (2.64 ml, 24.8 mmol) in the presence of 4-dimethylaminopyridine

TABLE I. Physical Properties of AICN-Riboside Related Compounds

Compd. No.	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	MS (*m/z*)	UV $\lambda_{max}^{0.1\,N\,HCl}$ nm (ε)	$\lambda_{max}^{neutral}$ nm (ε)	$\lambda_{max}^{0.1\,N\,NaOH}$ nm (ε)
IIa	162—164	$C_{21}H_{38}N_4O_5Si_2$	52.25 (52.16)	7.93 8.22	11.61 10.97)	482 (M^+) 439 ($M^+-C_3H_7$)	241	246[a]	247
IIb	—	$C_{28}H_{42}N_4O_5Si_2$	58.91 (58.55)	7.42 7.48	9.81 9.72)	570 (M^+) 527 ($M^+-C_3H_7$)	—	274[a] (11100) 342 (12000)	—
IIIa	—			—		615 (M^+)	242	244[a]	245
IIIb	—	$C_{29}H_{41}F_3N_4O_7SSi_2$	49.55 (49.68	5.88 5.98	7.97 7.77)	703 (M^+) 660 ($M^+-C_3H_7$)	—	274[a] (11300) 341 (11500)	—
IV	—			—		524 (M^+)	242	246[a]	246
V	156—157	$C_{21}H_{36}N_4O_4Si_2$	54.28 (53.85	7.81 8.22	12.06 11.62)	464 (M^+) 421 ($M^+-C_3H_7$)	241	246[a]	246
VI	236—238	$C_9H_{10}N_4O_3 \cdot 1/5\,H_2O$	47.87 (47.95	4.64 4.51	24.81 24.53)	222 (M^+)	239 (14000)	246[b] (15200)	246 (14700)
VIIa	—	$C_{30}H_{44}N_4O_6Si_2$	58.79 (58.79	7.24 7.29	9.14 8.99)	612 (M^+) 569 ($M^+-C_3H_7$)	—	274[a] (11000) 341 (11900)	—
VIIb	—			—		595 (M^+)	—	274, 341[a]	—
VIIIa	—	$C_{18}H_{18}N_4O_5 \cdot H_2O$	55.67 (55.49	5.19 5.03	14.43 14.40)	370 (M^+)	—	274[a] (10700) 341 (11000)	—
VIIIb	284—286	$C_{16}H_{15}N_7O_3$	54.39 (54.33	4.28 4.31	17.75 27.34)	353 (M^+)	—	274, 341[a]	—
IXa	—			—		—	242	247[a]	247
IXb	178—181	$C_9H_{11}N_7O_3 \cdot 0.3H_2O$	39.94 (40.37	4.32 4.27	36.23 35.99)	265 (M^+)	239 (11500)	246[b] (12300)	246 (12600)
IXc	157—158 151—152[c]	$C_9H_{12}N_4O_4$	45.00 (45.00	5.04 5.40	23.33 23.08)	—	239 (10800)	245[b] (12000)	245 (12000)
IXd	183—184	$C_9H_{13}N_5O_3 \cdot 0.7H_2O$	42.92 (43.18	5.76 5.73	27.81 27.57)	239 (M^+)	241 (11100)	245[b] (11400)	245 (11500)
Xa	104—110	$C_{11}H_{14}N_8O_3 \cdot 4/5\,H_2O$	41.20 (41.13	4.90 4.86	34.94 34.89)	306 (M^+)	258 (13100)	262[b] (13800)	262 (14100)
Xb	248—250	$C_{11}H_{16}N_6O_3 \cdot 0.3H_2O$	46.25 (46.15	5.86 5.81	29.42 29.21)	280 (M^+)	256 (13200)	262[b] (13700)	262 (13900)
XIa	248—249	$C_{11}H_{15}N_5O_4 \cdot H_2O$	44.14 (43.83	5.73 5.75	23.40 23.66)	281 (M^+)	257 (13300)	261.5[a] (13900)	262 (14100)
XIb	142—144	$C_{12}H_{17}N_5O_4 \cdot 1/5\,H_2O$	48.22 (48.18	5.87 5.84	23.43 23.75)	295 (M^+)	258 (14500)	261[a] (15100)	261 (15700)
XIc	230—234	$C_{16}H_{17}N_5O_4$	55.97 (55.96	4.99 5.07	20.40 20.28)	343 (M^+)	271 (16300)	269[a] (14400) 239 (23800)	270 (14400) 239 (24500)
XId	—			—		357 (M^+)	260	261[a]	261
XIe	272—277	$C_{14}H_{15}N_5O_5 \cdot 1/5\,H_2O$	49.91 (50.07	4.61 4.59	20.79 20.64)	333 (M^+)	316 (20000) 284 (14400)	299[a] (19100) 286 (17600) 258 (19000)	299 (19000) 286 (17400)

a) MeOH. *b*) H_2O. *c*) K. Kadir, G. Mackenzie and G. Shaw, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 2304.

TABLE II. Proton Chemical Shifts in the 400 MHz Spectra of AICN-Riboside Related Compounds and 2-Substituted Adenine-arabinosides in $CDCl_3$ (x) or DMSO-d_6 (y)

Compd. No.	H-2	N–H (or NH_2)	H-1′	H-2′	H-3′	H-4′	H-5′	H-2′OH	H-3′OH	H-5′OH	Others
IIa	7.16	4.42	5.55	4.16	4.10	4.06	4.16				4.64 (2′-OH, dd)
x	(s)	(br s)	(d)	(m)	(m)	(m)	(m)				1.1 ((iso-Pr)$_2$Si, m)
IIb	7.77		6.01	4.29	4.50	4.12	4.14 (m)				9.08 ($C_6H_5C\underline{H}$=N–, s)
x	(s)		(s)	(d)	(dd)	(m)	4.04 (m)				7.5—8.0 (C_6H_5–, m)
											2.92 (2′-OH, s)
											1.1 ((iso-Pr)$_2$Si, m)
IIIa	7.20	4.5	5.8	5.15	4.85	(4.1—4.3)					1.1 ((iso-Pr)$_2$Si, m)
x	(s)	(br s)	(d)	(m)	(m)	(d-like)					
IIIb	7.85		6.2	5.3	4.64	(3.9—4.43)					9.05 ($C_6H_5C\underline{H}$=N–, s)
x	(s)		(s)	(d)	(dd)	(m)					7.3—8.0 (C_6H_5–, m)
											1.1 ((iso-Pr)$_2$Si, m)
IV	7.00	4.42	5.98	5.26	4.81	3.76	4.14 (d)				1.87 (2′-O-Ac, s)
x	(s)	(s)	(d)	(dd)	(dd)	(dd)	4.02 (dd)				1.1 ((iso-Pr)$_2$Si, m)
V	7.22	5.42	6.11	4.85	4.44	4.00 (H-5′a)					1.1 ((iso-Pr)$_2$Si, m)
x	(s)	(d)	(d)	(m)	(dd)	3.9 (H-4′,H5′b)					
VI	7.73	7.43	6.33	4.71	4.18	4.01	3.15		5.58	4.87	
y	(s)	(d)	(d)	(dd)	(d)	(dd)	(m)		(d)	(dd)	
VIIa	7.84		6.25	5.58	4.55	3.88	4.08				8.98 ($C_6H_5C\underline{H}$=N–, s)
x	(s)		(d)	(dd)	(dd)	(m)	(m)				7.3—8.0 (C_6H_5–, m)
											1.81 (2′-O-Ac, s)
											1.1 ((iso-Pr)$_2$Si, m)
VIIb	7.80		6.35	4.3—4.4		(3.8—4.2)					9.06 ($C_6H_5C\underline{H}$=N–, s)
x	(s)		(dd)	(m)		(m)					7.3—8.0 (C_6H_5–, m)
											1.1 ((iso-Pr)$_2$Si, m)
VIIIa	8.11		6.38	5.41	4.52	(3.98—4.01)					8.97 ($C_6H_5C\underline{H}$=N–, s)
x	(s)		(d)	(dd)	(dd)	(H-4′,H-5′a, m)					7.5—7.9 (C_6H_5–, m)
						3.87 (H-5′b, m)					1.86 (2′-O-Ac, s)
VIIIb	8.24		6.32	4.58	4.22	(3.65—3.85)			6.11	5.35	9.04 ($C_6H_5C\underline{H}$=N–, s)
x	(s)		(d)	(dd)	(dd)	(m)			(d)	(dd)	7.5—8.1 (C_6H_5–, m)
IXa	7.29	6.27	6.06	5.20	4.33	(3.5—3.85)			5.81	5.21	1.92 (2′-O-Ac, s)
x	(s)	(s)	(d)	(dd)	(m)	(m)			(d)	(dd)	
IXb	7.49	6.35	5.92	4.37	4.18	(3.62—3.80)			6.17	5.40	
y	(s)	(s)	(d)	(dd)	(dd)	(m)			(br s)	(br s)	
IXc	7.35	6.13	5.75	4.09	4.00	(3.40—3.70)		5.64	5.54	5.16	
y	(s)	(s)	(d)	(m)	(m)	(m)		(br s)	(br s)	(br s)	
IXd	7.51	6.11	5.68	3.71	3.85	(3.40—3.65)			5.42	5.22	1.5 (2′-NH_2, br s)
y	(s)	(s)	(d)	(dd)	(m)	(m)			(d)	(br s)	
Xa	8.24	7.19	6.38	4.57	4.42	(3.5—3.85)			6.08	5.33	2.41 (–CH_3, s)
y	(s)	(s)	(d)	(dd)	(dd)	(m)			(d)	(dd)	
Xb	8.18	7.11	6.19	4.08 (m, H-3′)					5.43	5.23	2.38 (–CH_3, s)
y	(s)	(s)	(d)	(3.45—3.8) (H-2′, H-4′, H-5′)					(d)	(br s)	1.50 (2′-NH_2, br s)
XIa	8.08	7.10	6.22	(4.10—4.15)		3.77	3.65	5.60	5.50	5.14	2.39 (–CH_3, s)
y	(s)	(s)	(d)	(m)		(m)	(m)	(d)	(d)	(dd)	
XIb	8.08	7.10	6.24	(4.1—4.2)		3.78	3.67	5.61	5.51	5.10	2.66 (–CH_2–, m)
y	(s)	(s)	(d)	(m)		(m)	(m)	(d)	(d)	(br s)	1.23 (–CH_3, dd)
XIc	8.19	7.27	6.39	(4.18—4.23)		3.81	3.70	5.66	5.56	5.03	7.43—8.37 (–C_6H_5, m)
y	(s)	(s)	(d)	(m)		(m)	(m)	(d)	(d)	(dd)	
XId	8.10	7.17	6.25	(4.13—4.17)		3.78	3.63	5.62	5.52	5.12	7.15—7.31 (–$CH_2C_6\underline{H}_5$, m)
y	(s)	(s)	(d)	(m)		(m)	(m)	(d)	(d)	(dd)	3.97 (–$C\underline{H}_2C_6H_5$, s)
XIe	8.18	7.32	6.30	(4.15—4.21)		3.80	3.68	5.66	5.56	5.05	7.79 (furanyl H-5, s)
y	(s)	(s)	(d)	(m)		(m)	(m)	(d)	(d)	(dd)	7.07 (furanyl H-3, d)

(2.64 g, 21.6 mmol) and triethylamine (3.3 ml) as described above to afford a caramel (7.0 g, 75%).

Reaction of IIIa and NaOAc A solution of IIIa (923 mg, 1.5 mmol) and NaOAc (615 mg, 7.5 mmol) in DMF (10 ml) was stirred at room temperature overnight and filtered to remove insoluble materials. The filtrate was evaporated to dryness *in vacuo* and the resulting syrup was partitioned between $CHCl_3$ (30 ml) and water (20 ml). The organic layer was washed with water (20 ml), dried over $MgSO_4$ and concentrated to a small volume. The solution was chromatographed over a column of Silica gel G (2.2 × 20 cm) with 5% EtOH in $CHCl_3$ (2 l). The first fraction was evaporated to dryness, giving 5-amino-1-(2-*O*-acetyl-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl)-4-cyanoimidazole (IV) as a caramel (70 mg, 9%).

Evaporation of the second fraction gave 5,2′-anhydro-5-amino-1-(3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl)-4-cyanoimidazole (V) as a white powder (480 mg, 69%).

5,2′-Anhydro-5-amino-1-(β-D-arabinofuranosyl)-4-cyanoimidazole (VI) Tetra-*n*-butylammonium fluoride (0.5 ml of 1 M solution in tetrahydrofuran (THF), 0.5 mmol) was added to a solution of Va (120 mg, 0.25 mmol) in THF (5 ml) and the solution was kept at room temperature for 10 min, then acetic acid (0.1 ml) was dropped into the mixture. The solution was evaporated to dryness and the residue was dissolved in water (5 ml). The aqueous solution was applied to a column of Amberlite IR 120B (1.5 × 10 cm), which was washed with water (50 ml) and eluted with 10% NH_4OH. The eluate was concentrated to a small volume to give a white crystalline material (35.8 mg, 60%). CD[θ]^{25} nm: +21500 (245) and +21200 (238) (positive maximum), +20200 (241.5) positive minimum).

1-(2-*O*-Acetyl-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl)-5-benzylideneamino-4-cyanoimidazole (VIIa) A solution of IIIb (4.4 g, 6.3 mmol) and NaOAc (2.6 g, 31.5 mmol) in DMF (100 ml) was stirred at room temperature for 2 d, resulting in the disappearance of UV-absorbing spot of IIIa on TLC. After removal of inorganic substances by

filtration, the solution was evaporated *in vacuo* and the residue was partitioned between benzene (100 ml) and water (50 ml). The organic layer was washed with water (50 ml), dried over $MgSO_4$ and chromatographed over a column of Silica gel G (3.0 × 40 cm) with a gradient of 0—2% EtOH in $CHCl_3$ (2 l) to give a caramel (3.2 g, 83%).

1-(2-Azido-2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl)-5-benzylideneamino-4-cyanoimidazole (VIIb) A solution of IIIb (17.0 g, 24.2 mmol) and NaN_3 (7.86 g, 121 mmol) in DMF (250 ml) was stirred at room temperature for 1 d and treated in a manner similar to that described above to afford a pale-yellowish caramel (11.9 g, 83%).

Desilylation of 3',5'-*O*-Tetraisopropyldisiloxane-1,3-diyl Group VIIa (2.32 g, 3.79 mmol) was dissolved in ice-cooled THF (10 ml) and tetra-*n*-butylammonium fluoride (7.6 ml of 1.0 M solution in THF, 2 eq) was added to the solution. The mixture was left at room temperature for 5 min, then the reaction was quenched with acetic acid (0.6 ml) and the resulting mixture was chromatographed over a column of Silica gel G (2.4 × 22 cm) with a gradient of 6—12.5% EtOH in $CHCl_3$ (1 l) to afford 1-(2-*O*-acetyl-β-D-arabinofuranosyl)-5-benzylideneamino-4-cyanoimidazole (VIIIa) as a pale-yellowish caramel (1.02 g, 73%). VIIb was desilylated in a manner similar to that described above to afford 1-(2-azido-2-deoxy-β-D-arabinofuranosyl)-5-benzylideneamino-4-cyanoimidazole (VIIIb, 70%).

Deprotection of Benzylidene Group A solution of VIIIa (890 mg, 2.4 mmol) in 80% acetic acid (30 ml) was kept at room temperature for 2 h; it showed a single UV-absorbing spot which migrated a shorter distance compared with that of VIIIa on TLC. The mixture was evaporated to dryness and the residue was dissolved in a small amount of EtOH and chromatographed over a column of Silica gel G (2.4 × 18 cm) with a gradient of 5—17% EtOH in $CHCl_3$ (0.8 l). Evaporation of the desired fraction gave 1-(2-*O*-acetyl-β-D-arabinofuranosyl)-5-amino-4-cyanoimidazole (IXa) as a caramel (540 mg, 80%). VIIIb was deprotected in a manner similar to that described above, giving 5-amino-1-(2-azido-2-deoxy-β-D-arabinofuranosyl)-4-cyanoimidazole (IXb, quantitative).

5-Amino-1-(β-D-arabinofuranosyl)-4-cyanoimidazole (IXc)[4h] IXa (622 mg, 2.2 mmol) was dissolved in methanolic ammonia (saturated at 0 °C, 35 ml). The mixture was kept at room temperature for 3 h and concentrated carefully to a small volume, then chromatographed over a column of Silica gel G (2.4 × 20 cm) with a gradient of 17—33% EtOH in $CHCl_3$ (1 l). The solid obtained after evaporation of the desired fraction was recrystallized from EtOH to give colorless needles (431 mg, 81%).

5-Amino-1-(2-amino-2-deoxy-β-D-arabinofuranosyl)-4-cyanoimidazole (IXd) Triphenylphosphine (150 mg, 0.57 mmol) was added to a solution of IXb (100 mg, 0.38 mmol) in pyridine (2 ml) and the mixture was kept at room temperature for 1 h, then concentrated NH_4OH (1 ml) was added. The solution was allowed to stand for 2 h, and evaporated to dryness. The residual syrup was triturated with water (20 ml) and filtered to remove insoluble materials. The aqueous solution was washed twice with benzene (5 ml) and concentrated to a small volume to give a white crystalline material (58.2 mg, 65%).

9-(2-Azido-2-deoxy-β-D-arabinofuranosyl)-2-methyladenine (Xa) IXc (500 mg, 1.9 mmol) was dissolved in a mixture of acetonitrile (2 ml) and methanolic ammonia (saturated at 0 °C, 15 ml) and heated in a steel bomb at 140 °C overnight, then cooled in ice-water. The solution was concentrated carefully and chromatographed over a column of Silica gel G (2.7 × 25 cm) with a gradient of 0—18% EtOH solution in $CHCl_3$ (800 ml). The residue obtained after evaporation of the desired fraction was crystallized from water to give a white crystalline meterial (242 mg, 42%).

9-(2-Amino-2-deoxy-β-D-arabinofuranosyl)-2-methyladenine (Xb) A solution of Xa (80 mg, 0.26 mmol) in pyridine (2 ml) was treated with triphenylphosphine (125 mg, 0.48 mmol) in a manner similar to that described for IXd to give needles (70 mg, 96%).

Other 2-substituted adenine-arabinoside (XIa[5]—e) were prepared by treatment of IXc with acetonitrile, propionitrile, benzonitrile, benzyl cyanide, or furonitrile in a manner similar to that described in the case of Xa in 65, 55, 62, 44 and 83% yields, respectively.

References and Notes

1) Part of this work was presented at the 106th Annual Meeting of the Pharmaceutical Society of Japan in Chiba, April 1986.
2) T. W. North and S. S. Cohen, *Pharmacol. Ther.*, **4**, 81 (1979).
3) *a*) F. Keller, I. J. Botvinick and J. E. Bunker, *J. Org. Chem.*, **32**, 1644 (1967); *b*) D. S. Bhakuni and P. K. Gupta, *Indian J. Chem.*, **22B**, 508 (1983).
4) *a*) E. J. Reist and L. Goodman, *Biochemistry*, **3**, 15 (1964); *b*) J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **12**, 498 (1969); *c*) G. B. Elion and R. A. Strelitz, Ger. Offen. 2056327 (1968) [*Chem. Abstr.*, **75**, 64224*g* (1971)]; *d*) G. B. Elion, J. E. Lister and L. M. Beachamp III, Ger. Offen. 2156637 (1972) [*Chem. Abstr.*, **77**, 75424*q* (1972)]; *e*) K. Miyai, L. B. Allen, J. H. Huffman, R. W. Sidwell and R. L. Tolman, *J. Med. Chem.*, **17**, 242 (1974); *f*) Wellcome Foundation Ltd., Burrough Wellcome Co., Brit. Patent 1386584 (1975) [*Chem. Abstr.*, **84**, 59944*v* (1976)]; *g*) J. A. Montgomery, S. D. Clayton and A. T. Shortnacy, *J. Heterocycl. Chem.*, **16**, 157 (1979); *h*) K. Kadir, G. Mackenzie and G. Shaw, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 2304; *i*) J. A. Secrist III, A. T. Shortnacy and J. A. Montgomery, *J. Med. Chem.*, **31**, 405 (1988).
5) T. Utagawa, H. Morisawa, S. Yamanaka, A. Yamazaki, F. Yoshinaga and Y. Hirose, *Agric. Biol. Chem.*, **49**, 2167 (1985).
6) K. Suzuki and I. Kumashiro, Japan. Patent 5225 (1969) [*Chem Abstr.*, **71**, 12561*n* (1969)].
7) K. Fukukawa, T. Ueda and T. Hirano, *Chem. Pharm. Bull.*, **31**, 1582 (1983).
8) An N^5-benzylidene derivative of 2',3'-*O*-isopropylidene-AICN-riboside has already been prepared.[9]
9) Personal communication from Dr. R. Marumoto, Takeda Chem. Ind., Ltd.
10) L. B. Townsend, "Synthetic Procedures in Nucleic Acids Chemistry," Vol. 2, ed. by W. W. Zorbach and R. S. Tipson, John Wiley and Sons, Inc., New York, 1973, p. 333.
11) *a*) A. Yamazaki, I. Kumashiro and T. Takenishi, *J. Org. Chem.*, **33**, 2583 (1968); *b*) R. Marumoto, Y. Yoshioka, O. Miyashita, S. Shima, K. Imai, K. Kawazoe and M. Honjo, *Chem. Pharm. Bull.*, **23**, 759 (1975).