Synthesis of 6-*C*-Substituted Purine Nucleosides: α-(Aminomethylene)-9-β-D-ribofuranosylpurine-6-acetic Acid Derivatives

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α-(Aminomethylene)-β-D-ribofuranosylpurine-6-acetamide (4) and the ethyl acetate (9) have been synthesized by catalytic hydrogenation of 6-cyanomethylenepurine derivatives (3 and 7). 6-Cyanomethylenepurines were obtained by substitution of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (1) with α-cyanoacetamide and ethyl cyanoacetate, followed by deprotection of the isopropylidene group. Substitution of 4 and 9 with benzylamine and aniline gave the corresponding *N*-benzyl- and *N*-phenyl-substituted α-(aminomethylene)-β-D-ribofuranosylpurine-6-acetamides (5) and the ethyl acetate (10), respectively.

Keywords purine; enamino-amide; enamino-ethyl ester; catalytic hydrogenation; ribofuranose

N^6-Alkyladenosines are important intermediates in the study of the A_1 and A_2 adenosine receptors.[2] 6-*C*-Alkylpurine ribonucleosides are also useful as biological probes in studies of the mechanism of adenylosuccinate synthetase.[3] It is known that enamino-acetic acid derivatives are versatile starting materials for the synthesis of *N*-alkyl side chains by the substitution of amines.[4] However, there is only one report of a method for the introduction of an enamine moiety into purine at position 6.[5] Although 6-cyanomethylene purine derivatives can be prepared in high yield by reaction of the sodium salt of an activated cyanomethylene such as α-cyanoacetamide or ethyl cyanoacetate with 6-chlorinated or methylsulfonated purine derivatives,[6] the conversion of the cyano group to an enamine has not been described.

In a previous publication, we described[7] the synthesis of α-(aminomethylene)purine-6-acetonitrile *via* 6-dicyanomethylenepurine derivatives, which exist as an equilibrium mixture of the enamino-nitrile isomers.[8] However, α-(aminomethylene)-9*H*-purine-6-acetamides are only found in the *Z* form.[7c,d] Also, it was found that an *N*,*N*-dimethylformamide (DMF)–benzene solvent system was most successful for the catalytic hydrogenation of 6-dicyanomethylenepurine derivatives. In the present paper, we have extended our work to the synthesis of α-(aminomethylene)-9-β-D-ribofuranosylpurine-6-acetamide (**4**) and the ethyl acetate (**9**) and their *N*-substituted purine derivatives (**5** and **10**) *via* 6-cyanomethylene derivatives (**2** and **6**).

The syntheses of (*Z*)-α-(aminomethylene)-9-β-D-ribofuranosylpurine-6-acetamide (**4**) and its amino-substituted derivatives **5** are summarized in Chart 1. Initial attempts to substitute 6-chloro-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)purine with α-cyanoacetamide using sodium hydride were unsuccessful. Reaction of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (**1**)[9] with α-cyanoacetamide in the presence of sodium hydride in DMF gave α-cyano-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine-6-acetamide (**2**) in 71% yield, and this product was treated

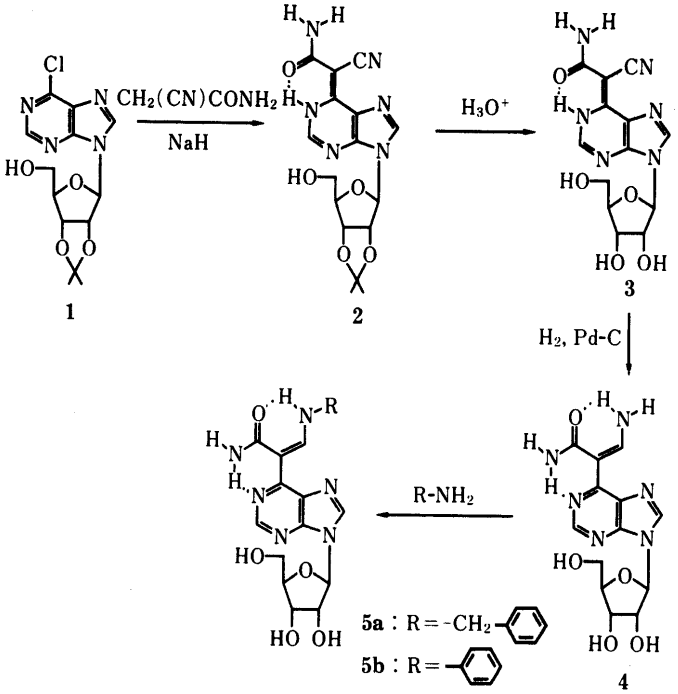

Chart 1

TABLE I. ^{1}H-NMR Data for **4** and **5** in DMSO-d_6

Compd. No.	Chemical shifts of aglycone moiety (ppm) (*J* in Hz)						Others and H-1′ of ribofuranosyl
	H-2 (s)	H-8 (s)	C=CH (d)	CONH (br s)	CONH (br s)	C=CNH (m)	
4	8.61	8.59	9.61[a]	6.96	9.94—10.15[b]		8.30 (br s, NH), 5.98 (1H, d, *J*=5 Hz, H-1′)
5a	8.63	8.60	9.73 (*J*=13)	7.06	10.09	11.11	4.48—4.64 (2H, m, CH_2), 7.36 (5H, s, Ph-H), 6.00 (1H, d, *J*=5 Hz, H-1′)
5b	8.80	8.74	10.26 (*J*=13)	7.13	10.16	12.71[c] (*J*=12)	7.07—7.45 (5H, m, Ph-H), 6.00 (1H, d, *J*=5 Hz, H-1′)

a) dd, *J*=16 Hz, *J*=8 Hz. *b*) m. *c*) d.

with 40% aqueous trifluoroacetic acid to give α-cyano-9-β-D-ribofuranosylpurine-6-acetamide (**3**) in 84% yield. Catalytic hydrogenation of **3** over 5% Pd-C in DMF–benzene under medium pressure (4 atm) gave **4** in 75% yield. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum the vinyl proton was found at δ 9.61 as a doublet of doublets which collapsed to a singlet on adding deuterium oxide (Table I). Although the signal of the vinyl proton of an enamine moiety generally appears at δ 7—8,[4] in this case the large downfield shift of the vinyl proton is due to the anisotropic effect of the purine ring.[7c,d] From this, the configuration of the vinyl proton was concluded to be *Z*. Interestingly, although α-(aminomethylene)-9-(methoxymethyl)-9*H*-purine-6-acetonitrile exists in an enamino-nitrile tautomeric equilibrium (*E*/*Z*),[8] the enamino-amide moiety of **4** is only found in the *Z* form.

Substitution of **4** with benzylamine or aniline under heating gave the corresponding *N*-substituted enamines **5a** and **5b** in 95% yield and 66% yield, respectively. In the ^{1}H-NMR spectra the vinyl protons of **5a** and **b** were found at δ 9.73 (1H, d) and δ 10.26 (1H, d), respectively, indicating that both **5a** and **5b** are in the *Z* form.

Substitution of **1** with ethyl cyanoacetate in the presence of sodium hydride in DMF gave ethyl α-cyano-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine-6-acetate (**6**) in 81% yield. Its isopropylidene group was removed with acid to give **7** in 81% yield. Catalytic hydrogenation of **7** over 5% Pd–C in DMF–benzene under medium pressure (4 atm) gave ethyl 2-(9-β-D-ribofuranosylpurin-6-yl)propionate (**8**) in 21% yield as an over-reduced by-product and ethyl α-(aminomethylene)-9-β-D-ribofuranosylpurine-6-acetate (**9**) in 75% yield (Chart 2). In the ^{1}H-NMR spectrum the vinyl protons of **9** exhibited two sets of signals at δ 7.67 (m, *E*) as the minor signal and at δ 7.99 (br s, *Z*) as the major signal which collapsed to a singlet on adding deuterium oxide.[7c,d] On the basis of the chemical shift of the vinyl proton, **9** seems to exist in an enamino ester tautomeric equilibrium.[7c,d] The ratio of geometrical isomers (*E*/*Z*) in deuteriodimethyl sulfoxide (DMSO-d_6) is 38 : 62 based on the integration ratios of the H-2 and vinyl proton signals of the isomers in the ^{1}H-NMR spectrum.

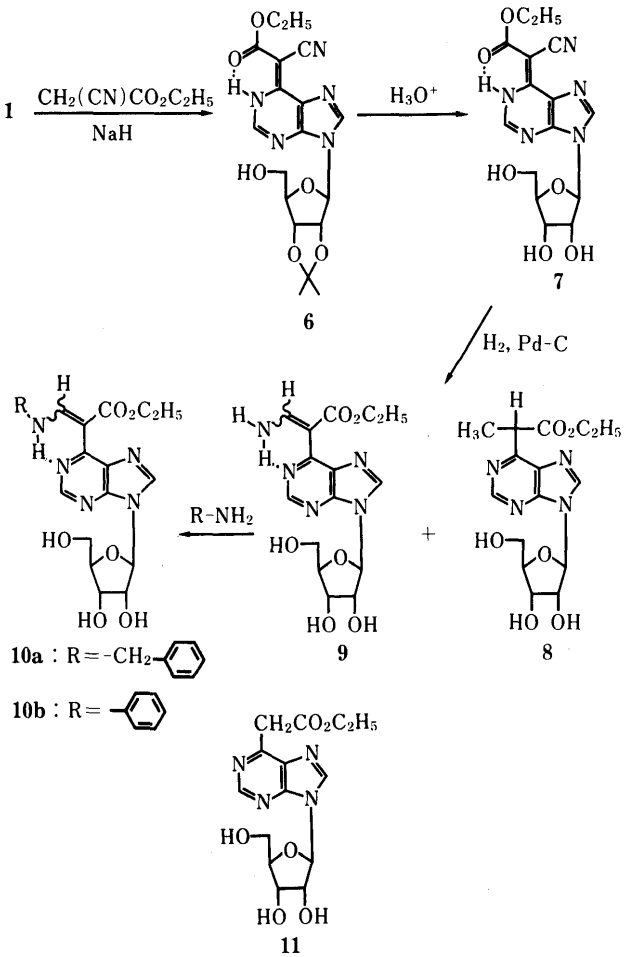

Chart 2

Substitution of **9** with benzylamine under heating for 5 h gave ethyl α-(*N*-benzylaminomethylene)-9-β-D-ribofuranosylpurine-6-acetate (**10a**) in 89% yield. In the ^{1}H-NMR spectrum (DMSO-d_6) the vinyl proton signal was found at δ 7.84 (*E*) and δ 8.01 (*Z*).[7c,d] The amino proton signal was found at δ 9.36 (*E*) and δ 8.98 (*Z*). On the basis of the chemical shifts of the amino and vinyl protons, the geometrical isomers (*E*/*Z*) of *N*-substituted **10a** seem to exist in an enamino ester tautomeric equilibrium. The ratio of geometrical isomers was 47 : 53 based on the integration ratios of signals due to the two isomers in the ^{1}H-NMR spectrum. Similarly, after reaction of **9** with aniline, the *N*-substituted phenylamine **10b** was obtained in 55% yield. The ratio of geometrical isomers (*E*/*Z*) in DMSO-d_6 was 48 : 52. In this reaction ethyl 9-β-D-ribofuranosylpurine-6-acetate (**11**) was obtained in 21% yield as a by-product by addition of aniline at the α-position of the enamine, followed by cleavage of the carbon–carbon bond of the enamine moiety, with concomitant formation of the amidine fragment.[10]

In conclusion, the present work demonstrates that catalytic hydrogenation of 6-cyanomethylene purine derivatives (**3** and **7**) to the corresponding α-(aminomethylene)-9-β-D-ribofuranosylpurine-6-acetamide (**4**) and the ethyl acetate (**9**) in DMF–benzene is highly chemoselective, because the enamine moiety and purine ring are unaffected. Compounds **4** and **9** are versatile intermediates for the preparation of 6-enaminopurine ribonucleosides having alkyl or aryl substituents.

Experimental

All melting points were determined on a Yamato capillary melting point apparatus, MP-21, and are uncorrected. Infrared (IR) spectra were taken on a JASCO A-102 spectrophotometer. Ultraviolet (UV) spectra were measured using a Hitachi EPS-3T spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-FX 100 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were measured on a JEOL JMS-D300 spectrometer. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; sh, shoulder; and dd, doublet of doublets.

α-Cyano-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine-6-acetamide (2) A solution of α-cyanoacetamide (4.290 g, 0.05 mol) in dry DMF (30 ml) was added to a cold (0—5 °C) stirred suspension of 60% sodium hydride (2.0 g, 0.05 mol) in dry DMF (60 ml) over a period of 30 min under argon, and stirring was continued for 20 min at room temperature. At this time a solution of **1** (3.267 g, 0.01 mol) in DMF (30 ml) was added and the solution was stirred for 7 h at room temperature. The solvent was evaporated *in vacuo*, and the residue was adjusted to pH 7 with 3% hydrochloric acid. The solution was allowed to stand overnight, and the resulting precipitate was collected by filtration, and washed with water. Recrystallization from DMF–MeOH gave **2** (2.671 g, 71%) as colorless needles, mp 221—224 °C. IR (KBr): 3480, 3400, 2195 (CN), 1645 cm^{-1}. UV λ_{max}^{MeOH} nm (ε); 329 (33000 sh), 338 (37000). ^{1}H-NMR (DMSO-d_6) δ: 1.33 (3H, s, Me), 1.54 (3H, s, Me), 6.13 (1H, d, *J*=2 Hz, H-1'), 7.01

(2H, br s, NH_2), 8.46 (2H, s, H-2, H-8), 14.98 (1H, br s, NH). MS *m/z*: 374 (M^+), 332. *Anal.* Calcd for $C_{16}H_{18}N_6O_5$: C, 51.33; H, 4.85; N, 22.45. Found: C, 51.05; H, 4.96; N, 22.32.

α-Cyano-9-β-D-ribofuranosylpurine-6-acetamide (3) A solution of **2** (1.872 g, 5 mmol) in 40% aqueous trifluoroacetic acid (60 ml) was stirred for 1.5 h at room temperature. The resulting precipitate was collected by filtration, and recrystallized from DMSO–MeOH to give **3** (1.409 g, 84%) as colorless needles, mp 202—205 °C (dec.). IR (KBr): 2180 (CN) cm^{-1}. UV λ_{max}^{MeOH} nm (ε): 329 (33000 sh), 338 (36300). ^{1}H-NMR (DMSO-d_6) δ: 5.91 (1H, d, J=5 Hz, H-1'), 7.00 (2H, br s, NH_2), 8.44 (1H, br s, H-2), 8.54 (1H, s, H-8), 14.96 (1H, br s, NH). MS *m/z*: 334 (M^+), 261, 202 (B+1). *Anal.* Calcd for $C_{13}H_{14}N_6O_5$: C, 46.70; H, 4.22; N, 25.14. Found: C, 46.75; H, 4.29; N, 24.80.

(*Z*)-α-(Aminomethylene)-9-β-D-ribofuranosylpurine-6-acetamide (4) A solution of **3** (1.003 g, 3 mmol) in DMF–benzene (1:1 v/v, 200 ml) was hydrogenated over 5% Pd–C (900 mg) for 24 h at room temperature under 4 atm pressure. The catalyst was filtered off, and the filtrate was evaporated *in vacuo*. The residue was recrystallized from MeOH to give **4** (0.752 g, 75%) as yellow needles, mp 167—168 °C. IR (KBr): 3370, 3220, 3170, 1638 (CO) cm^{-1}. UV λ_{max}^{MeOH} nm (ε): 237 (14400), 265 (10500), 332 (26300). MS *m/z*: 336 (M^+), 224, 204 (B+1). *Anal.* Calcd for $C_{13}H_{16}N_6O_5$: C, 46.42; H, 4.80; N, 24.99. Found: C, 46.05; H, 4.76; N, 24.60.

(*Z*)-α-(*N*-Benzylaminomethylene)-9-β-D-ribofuranosylpurine-6-acetamide (5a) A solution of **4** (0.336 g, 1 mmol) and benzylamine (0.297 g, 3 mmol) in ethanol (15 ml) was refluxed with stirring for 24 h. After cooling, the resulting precipitate was collected by filtration and recrystallized from MeOH to give **5a** (0.399 g, 95%) as colorless needles, mp 116—117 °C. IR (KBr): 3350, 1635 (CO) cm^{-1}. UV λ_{max}^{MeOH} nm (ε): 240 (15800), 274 (10700), 343 (27500), 351 (26900 sh). MS *m/z*: 426 (M^+), 294 (B+1). *Anal.* Calcd for $C_{20}H_{22}N_6O_5$: C, 56.33; H, 5.20; N, 19.71. Found: C, 56.23; H, 5.11; N, 19.53.

(*Z*)-α-(*N*-Phenylaminomethylene)-9-β-D-ribofuranosylpurine-6-acetamide (5b) A solution of **4** (0.336 g, 1 mmol) and aniline (0.279 g, 3 mmol) in ethanol (15 ml) was refluxed with stirring for 14 d. After cooling, the resulting precipitate was recrystallized from tetrahydrofuran–MeOH to give **5b** (0.272 g, 66%) as yellow needles, mp 120—121 °C. IR (KBr): 3350, 1640 (CO) cm^{-1}. UV λ_{max}^{MeOH} nm (ε): 241 (17000), 281 (16200), 371 (36300). MS *m/z*: 412 (M^+), 280 (B+1). *Anal.* Calcd for $C_{19}H_{20}N_6O_5$: C, 55.33; H, 4.89; N, 20.38. Found: C, 55.03; H, 4.94; N, 20.64.

Ethyl α-Cyano-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine-6-acetate (6) A solution of ethyl cyanoacetate (1.018 g, 9 mmol) in dry DMF (5 ml) was added dropwise to a cold (0—5 °C) stirred suspension of 60% sodium hydride (0.264 g, 6.6 mmol) in dry DMF (15 ml) over a period of 15 min, and the solution was stirred for 5 min at room temperature under argon. A solution of **1** (0.980 g, 3 mmol) in dry DMF (10 ml) was added, and the mixture was stirred for 15 h at 80 °C. After cooling, the solvent was evaporated *in vacuo* and the residue was acidified to pH 4 with 10% acetic acid. The resulting precipitate was collected by filtration and recrystallized from ethanol to give **6** (0.987 g, 81%) as colorless needles, mp 223—225 °C (dec.). IR (KBr); 3270, 3125, 2200 (CN), 1650 (CO) cm^{-1}. UV λ_{max}^{MeOH} nm (ε): 338 (37100), 328 (32300). ^{1}H-NMR (DMSO-d_6) δ: 1.28 (3H, t, J=7 Hz, Me), 1.33 (3H, s, Me), 1.54 (3H, s, Me), 4.23 (2H, q, CH_2), 6.16 (1H, d, J=2 Hz, H-1'), 8.51 (1H, s, H-2), 8.48 (1H, s, H-8). MS *m/z*: 403 (M^+), 314, 231 (B+1). *Anal.* Calcd for $C_{18}H_{21}N_5O_6$: C, 53.59; H, 5.24; N, 17.36. Found: C, 53.57; H, 5.28; N, 17.66.

Ethyl α-Cyano-9-β-D-ribofuranosylpurine-6-acetate (7) A solution of **6** (4.034 g, 1 mmol) in 40% aqueous trifluoroacetic acid (70 ml) was stirred for 4 h at room temperature. The resulting precipitate was collected by filtration and recrystallized from DMF–chloroform to give **7** (2.935 g, 81%) as colorless needles, mp 218—221 °C (dec.). (lit.[6c] mp 230—233 °C (dec.)). IR (KBr): 3375, 3225, 2200 (CN), 1650 (CO) cm^{-1}. UV λ_{max}^{MeOH} nm (ε): 338 (38000), 328 (33000). ^{1}H-NMR (DMSO-d_6) δ: 1.28 (3H, t, J=7 Hz, Me), 4.23 (2H, q, CH_2), 5.94 (1H, d, J=5 Hz, H-1'), 8.50 (1H, s, H-2), 8.62 (1H, s, H-8), 13.58 (1H, br s, NH). MS *m/z*: 363 (M^+), 231 (B+1).

Catalytic Hydrogenation of 7 A solution of **7** (0.726 g, 0.002 mol) in DMF–benzene (1:1 v/v, 80 ml) was hydrogenated over 5% Pd–C (0.5 g) for 48 h at room temperature under 4 atm pressure. The catalyst was filtered off, and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on Florisil (60 g) using 9% ethanol in dichloromethane as eluent and the eluate was evaporated *in vacuo* to give ethyl 2-(9-β-D-ribofuranosylpurin-6-yl)propionate (**8**) (0.150 g, 21%) as a foam (lit.[6c] foamy). IR (KBr): 3375, 1730 (CO), 1595 cm^{-1}. UV λ_{max}^{MeOH} nm (ε): 262 (8710). ^{1}H-NMR (DMSO-d_6) δ: 1.09 (3H, t, J=7 Hz, Me), 1.53 (3H, d, J=7 Hz, Me), 4.08 (2H, q, CH_2), 4.51 (1H, q, J=7 Hz, CH), 6.04 (1H, d, J=6 Hz, H-1'), 8.81 (1H, s, H-8), 8.88 (1H, d, J=6 Hz, H-2). MS *m/z*: 352 (M^+), 249 (B+30), 221 (B+2). High-resolution MS *m/z*: 352.1360 (M^+, Calcd for $C_{15}H_{20}N_4O_6$: 352.1385).

Further elution with the same solvent gave ethyl α-(aminomethylene)-9-β-D-ribofuranosylpurine-6-acetate (**9**) (0.551 g, 75%), which was recrystallized from acetone–hexane to give colorless prisms, mp 100—101 °C. IR (KBr): 3325, 1665 (CO), 1635, 1580 cm^{-1}. UV λ_{max}^{MeOH} nm (ε): 323 (186000), 263 (11700), 236 (11700). ^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, t, J=7 Hz, Me), 3.95—4.23 (2H, m, CH_2), 5.98 (1H, d, J=5 Hz, H-1'), 7.70 (0.38H, m, C=CH, *E*), 7.99 (1.62H, br s, NH, C=CH, *Z*), 8.59 (1H, s, H-8), 8.66 (0.62H, s, H-2, *Z*), 8.74 (0.38H, s, H-2, *E*). MS *m/z*: 365 (M^+), 306, 233 (B+1). High-resolution MS *m/z*: 365.1336 (M^+, Calcd for $C_{15}H_{19}N_5O_6$: 365.1337).

Ethyl α-(*N*-Benzylaminomethylene)-9-β-D-ribofuranosylpurine-6-acetate (10a) A solution of **9** (0.181 g, 0.5 mmol) and benzylamine (0.160 g, 1.50 mmol) in ethanol (7 ml) was refluxed with stirring for 5 h. After cooling, the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on Florisil (20 g) using 4% ethanol in dichloromethane as eluent and the eluate was evaporated *in vacuo* to give **10a** (0.201 g, 89%) as a foam. IR (KBr): 3400, 3300, 1665 (CO), 1620 cm^{-1}. UV λ_{max}^{MeOH} nm (ε): 238 (15000), 273 (17800), 333 (32300). ^{1}H-NMR (DMSO-d_6) δ: 1.13 (3H, t, J=7 Hz, Me), 3.95—4.23 (2H, m, CH_2), 4.53—4.71 (2H, m, CH_2), 5.98 (1H, d, J=5 Hz, H-1'), 7.34 (5H, br s, phenyl-H), 7.84 (0.47H, d, J=14 Hz, C=CH, *E*), 8.01 (0.53H, d, J=14 Hz, C=CH, *Z*), 8.60 (1H, s, H-8), 8.66 (0.53H, s, H-2, *Z*), 8.73 (0.47H, s, H-2, *E*), 8.98 (0.53H, br s, NH, *Z*), 9.36 (0.47H, br s, NH, *E*). MS *m/z*: 455 (M^+), 351, 323 (B+1). High-resolution MS *m/z*: 455.1796 (M^+, Calcd for $C_{22}H_{25}N_5O_6$: 455.1807).

Reaction of 9 with Aniline A solution of **9** (0.181 g, 0.5 mmol) and aniline (0.139 g, 1.5 mmol) was refluxed with stirring for 4 d, then allowed to cool. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (30 g) using 4% ethanol in dichloromethane as eluent and the eluate was evaporated *in vacuo* to give ethyl α-(*N*-phenylaminomethylene)-9-β-D-ribofuranosylpurine-6-acetate (**10b**) (0.120 g, 55%) as a foam. IR (KBr): 3375, 3300, 1665 (CO), 1625 cm^{-1}. UV λ_{max}^{MeOH} nm (ε): 232 (10500), 284 (10700), 353 (25700). ^{1}H-NMR (DMSO-d_6) δ: 1.19 (3H, t, J=7 Hz, Me), 4.13—4.34 (2H, m, CH_2), 6.03 (1H, d, J=5 Hz, H-1'), 7.04—7.33 (5H, m, phenyl-H), 8.20 (0.48H, d, J=13 Hz, C=CH, *E*), 8.53 (0.52H, d, J=13 Hz, C=CH, *Z*), 8.71 (1H, s, H-8), 8.77 (0.52H, s, H-2, *Z*), 8.91 (0.48H, s, H-2, *E*), 10.31 (0.52H, d, J=13 Hz, NH, *Z*), 10.52 (0.48H, d, J=13 Hz, NH, *E*). MS *m/z*: 441 (M^+), 309 (B+1). High-resolution MS *m/z*: 441.1643 (M^+, Calcd for $C_{21}H_{23}N_5O_6$: 441.1650).

Further elution with the same solvent gave ethyl 9-β-D-ribofuranosylpurine-6-acetate (**11**) (45 mg, 21%) as a foam (lit.[6c] glassy solid). IR (KBr): 3325, 1730 (CO), 1600 cm^{-1}. UV λ_{max}^{MeOH} nm (ε): 262 (7200), 334 (1660). ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7 Hz, Me), 3.96—4.25 (2H, m, CH_2), 4.17 (2H, s, CH_2), 6.03 (1H, d, J=6 Hz, H-1'), 8.81 (1H, s, H-8), 8.87 (1H, s, H-2). MS *m/z*: 338 (M^+), 249, 207 (B+2). High-resolution MS *m/z*: 338.1236 (M^+, Calcd for $C_{14}H_{18}N_4O_6$: 338.1228).

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