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Direct C-8 Lithiation of Naturally-Occurring Purine Nucleosides. A Simple Method for the Synthesis of 8-Carbon-Substituted Purine Nucleosides[1)]

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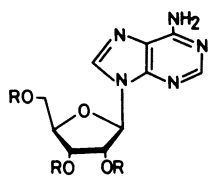
The sugar moiety of adenosine, inosine, or guanosine was protected with a *tert*-butyldimethylsilyl group. The C-8 lithiation of these protected nucleosides was carried out with lithium diisopropylamide in tetrahydrofuran at below −70 °C. The reactions of the C-8-lithiated species with MeI, HCO_2Me, and $ClCO_2Me$ were examined. The resulting products having a carbon substituent at the C-8 position were converted to the corresponding 8-carbon-substituted purine nucleosides by treatment with tetrabutylammonium fluoride. The whole sequence constitutes a simple method for the preparation of 8-carbon-substituted purine nucleosides from intact purine nucleosides.

Keywords——lithiation; purine nucleoside; LDA; 8-carbon-substituted purine nucleoside; *tert*-butyldimethylsilyl group

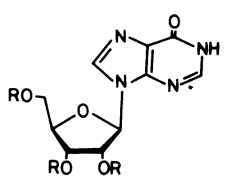
Our recent studies on the lithiation of nucleosides[2)] have demonstrated the effectiveness of this approach for the introduction of a variety of functionalities into the base moiety. In an earlier paper, we reported the use of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine as a starting material in the lithiation approach to the synthesis of 8-carbon-substituted adenosines, 6-thioinosines, and nebularines.[3,4)]

In connection with our continuing studies on the lithiation chemistry of nucleosides, we would like to report here the direct C-8 metallation of naturally-occurring purine nucleosides—adenosine (**1**), inosine (**2**), and guanosine (**3**)—which provides a simple method for the preparation of their 8-carbon-substituted derivatives.

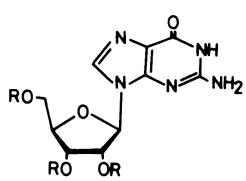
Although the preparation of purine nucleosides having carbon substituent at the C-8 position has ample precedent in the literature, most methods are based on either radical reaction, which suffers from the problem of regiospecificity,[5)] or nucleophilic displacement, in which only cyanide ion or ethyl sodioacetoacetate can be used as a nucleophile.[6)] An alternative method, palladium-catalyzed condensation of Grignard reagents with trimethyl-



1: R=H
4: R=TBDMS
Fig. 1



2: R=H
5: R=TBDMS
Fig. 2



3: R=H
6: R=TBDMS
Fig. 3

silyl derivatives of 8-bromopurine nucleosides,[7] is far from satisfactory in synthesis due to its poor yields.

The above facts prompted us to carry out the present work. There have been two reports on the lithiation of purine nucleosides other than those cited in references 3 and 4. Barton and his co-workers described, for the first time in studies on the lithiation of purine nucleosides, the C-8 metallation and successive methylation of N^6-methyl-2′,3′-*O*-isopropylideneadenosine to obtain N^6,N^6-dimethyl-8-methyl-2′,3′-*O*-isopropylideneadenosine in 35% yield.[8] Halogen–lithium exchange reaction of 8-bromopurine nucleosides has also been used for the modification of the C-8 position.[9] However, the direct C-8 lithiation of "intact purine nucleosides" is unprecedented to our knowledge.

A major concern in the lithiation of nucleosides is the problem of protection of hydroxyl groups and selection of a suitable lithiating agent. In our previous studies, the use of a combination of acid-labile protecting groups such as 5′-*O*-methoxymethyl/2′,3′-*O*-isopropylidene and 5′-*O*-*tert*-butyldimethylsilyl (TBDMS)/2′,3′-*O*-methoxymethylidene was successful in effecting lithiation of uridine[2a] and an imidazole nucleoside.[2g] However, these are not suitable for purine nucleosides, since their glycosidic bonds undergo acid-catalyzed hydrolysis.[10] The TBDMS group would meet our requirements because of its stability under strongly basic conditions and its easy cleavage under neutral conditions with fluoride anion.[11]

When adenosine (**1**), inosine (**2**), and guanosine (**3**) were treated with TBDMSCl (3.5, 5.0, and 6.0 eq, respectively) in *N*,*N*-dimethylformamide (DMF) containing imidazole (7—10 eq) at room temperature overnight, the corresponding 2′,3′,5′-tris-*O*-TBDMS derivatives (**4**,[12] **5**, and **6**[13]) were obtained as crystals in high yields. We then examined the C-8 lithiation of these protected nucleosides (**4**—**6**). As purine nucleosides are known to undergo hydrogen exchange at the C-8 position[14] and as the C-8 hydrogen was considered to be rather acidic, lithium diisopropylamide (LDA)[15] was used in the present investigation.

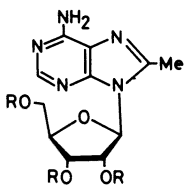
When **4** in tetrahydrofuran (THF) was added to a THF solution of LDA (3 eq) at below −70 °C, a clear solution of the lithiated species resulted. After keeping the mixture below −70 °C for 1.5 h, CD_3OD was added to the solution and the resulting deuterated product was isolated by short-column chromatography on silica gel. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the deuterated **4** in $CDCl_3$ showed, by comparison of the integrals of the H-2 (δ 8.33 ppm) and H-8 (δ 8.15 ppm) signals with that of the H-1′ signal (δ 6.02 ppm), that the metallation took place at the C-8 position in a regiospecific manner in 68% yield. As can be seen from Table I, a higher deuterium incorporation was observed when the above reaction was performed by using 5 eq of LDA. In a similar manner, LDA lithiation of **5** and **6** was examined by deuteration and the results are summarized in Table I. In an attempt to increase the lithiation levels, lithium 2,2,6,6-tetramethylpiperidide (LTMP), which is a more basic lithiating agent than LDA,[16] was also examined but no practical advantage could be found in the use of this expensive reagent. Thus, throughout this study, 5 eq of LDA was used for the C-8 lithiation of **4**—**6**.

Methylation at the C-8 position of **4** was first carried out. When the lithiated **4** prepared by using 5 eq of LDA as mentioned above was reacted with MeI (3 eq) for 2 h at below −70 °C, 2′,3′,5′-tris-*O*-TBDMS-8-methyladenosine (**7**) was isolated in 45% yield and most of the starting material (**4**) was left unchanged after quenching with AcOH. Although Barton *et al.*[8] have reported the simultaneous methylation at the N-6 and C-8 positions in the reaction of lithiated N^6-methyl-2′,3′-*O*-isopropylideneadenosine, the N^6-methylated product of **7** was not detected even in a trace amount in our reaction. The absence of such an undesired product could be attributed to the lower reaction temperature, which decreases the nucleophilicity of the N^6-anion. Treatment of **7** with tetrabutylammonium fluoride (TBAF) in THF for 2 h at room temperature gave 8-methyladenosine (**8**)[5d] in 85% yield.

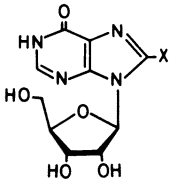
A similar methylation of the lithiated **5** (5 eq of MeI, 3 h), on the other hand, gave a

TABLE I. Deuterium Incorporation (%) at the C-8 Position of **4**—**6**

Compd.	LDA			LTMP
	3 eq	4 eq	5 eq	5 eq
4	68	67	77	83
5	75	89	91	87
6	42	45	66	57



7: R=TBDMS
8: R=H
Fig. 4

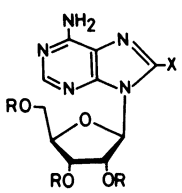


9: X=Me
10: X=Et
11: X=$CHMe_2$
Fig. 5

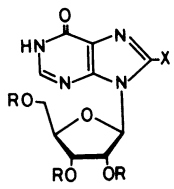
mixture of products which could not be separated at this stage. After removal of the TBDMS groups, 8-methyl- (**9**),[5d] 8-ethyl- (**10**), and 8-isopropylinosines (**11**) were obtained by preparative thin layer chromatography (TLC) in 21%, 16%, and 15% yields, respectively. The formation of **10** and **11** apparently results from further methylation of the initially formed 8-methyl derivative and this is in accord with our earlier observation in the case of 6-chloropurine nucleoside.[3]

A functionalized alkyl group, the hydroxymethyl group, can be introduced by electrophilic reaction of HCO_2Me followed by reduction of the resulting formyl derivative with $NaBH_4$. Thus, when HCO_2Me (5 eq, 3 h) was added to the lithiated **4**, the 8-formyladenosine derivative (**12**) was produced. Subsequent reduction of **12** with $NaBH_4$ in MeOH gave the 8-hydroxymethyladenosine derivative (**13**) in 62% yield from **4**. Deprotection of **13** gave 8-hydroxymethyladenosine (**14**) in 87% yield as crystals (mp 209—210 °C). This compound has been reported recently but not in a crystalline form.[6c] The lithiated **5** also followed the above reaction sequence, giving the 8-formylinosine derivative (**15**) in 71% yield and then its 8-hydroxymethyl derivative (**16**) in 92% yield. 8-Hydroxymethylinosine (**17**) was obtained as crystals (mp >290 °C) upon TBAF treatment of **16**. Similarly, the 8-formyl derivative (**18**) of guanosine was prepared in 41% yield. Although the yield of **18** was not quite satisfactory, it is noteworthy that the lithiation reaction could work with such a polar substrate as **6**. Reduction of **18** followed by deprotection gave 8-hydroxymethylguanosine (**19**: 86% from **18**, mp 212—214 °C).

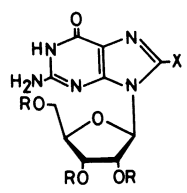
The reactions with $ClCO_2Me$ were next examined. Treatment of the lithiated **4** with 5 eq of $ClCO_2Me$ (3 h, below −70 °C) gave two products. Both products, isolated by column chromatography, had one D_2O-exchangeable proton and one aromatic proton in their ^1H-NMR spectra measured in $CDCl_3$, indicating that one amino proton and a proton at the C-8



12: R=TBDMS, X=CHO
13: R=TBDMS, X=CH_2OH
14: R=H, X=CH_2OH
Fig. 6



15: R=TBDMS, X=CHO
16: R=TBDMS, X=CH_2OH
17: R=H, X=CH_2OH
Fig. 7



18: R=TBDMS, X=CHO
19: R=H, X=CH_2OH
Fig. 8

position had been displaced during this reaction. The ^{1}H-NMR spectrum of the slower-moving product showed two CO_2Me signals at 3.88 and 4.07 ppm, which was suggestive of the structure **20**, while that of the faster-moving one indicated the presence of two fixed isopropyl groups (1.24 and 1.57 ppm, each as a double doublet) and one CO_2Me group (3.89 ppm, singlet).

Since LDA was apparently the origin of the two isopropyl groups and since such nucleophilic attack of diisopropylamide anion was considered to be less favored at N^6-CO_2Me than at C^8-CO_2Me, the structure **21** was assigned to the latter product. The yield of **20** and **21** were 27% and 50%, respectively.

From the result of methylation of the lithiated **4**, we assumed that regioselective reaction at the C-8 position might be possible by using a limited amount of $ClCO_2Me$. However, when this reaction was conducted with 1 eq of the electrophile, **21** was the sole product (20% yield). The structures of **20** and **21** were eventually further confirmed by NH_3/MeOH treatment (at room temperature, overnight) which gave **22** (24%) plus **23** (46%) and **24** (79%), respectively, as shown in Chart 1.

Although we have no clear explanation for the attack of diisopropylamide anion in the above methoxycarbonylation of **4**, the acylation at the N-6 position should be responsible for this result, since LDA (5 eq) treatment of **22** under similar conditions did not furnish **24**. Compounds **22**—**24** were converted to the corresponding free nucleosides (**25**—**27**) in high yields by TBAF treatment.

Finally, the reaction of the lithiated **5** with $ClCO_2Me$ (3 eq, 2 h, below -70 °C) was carried out. The corresponding 8-methoxycarbonyl derivative (**28**) was isolated in 61% yield as the sole product. In contrast to the case of adenosine, it is interesting that the 8-CO_2Me group survived completely during this reaction. Deprotection of **28** gave 8-methoxycarbonyl-

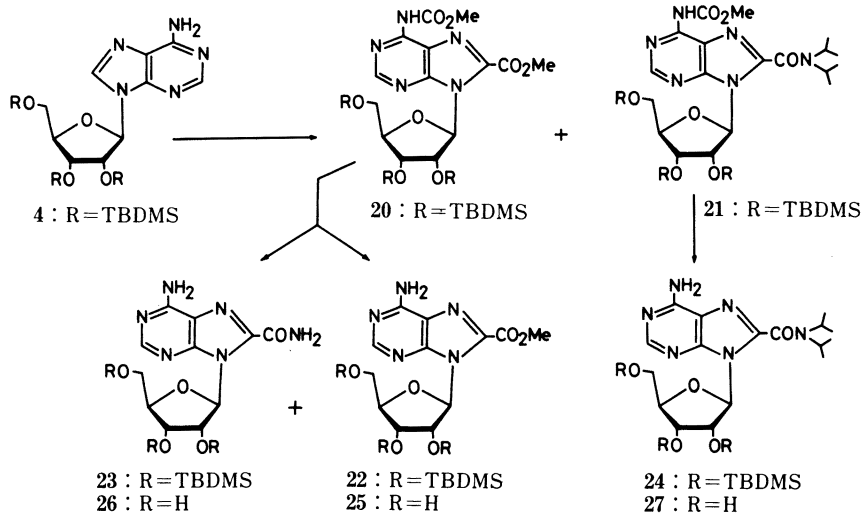
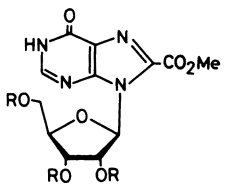


Chart 1



28: R=TBDMS
29: R=H

Fig. 9

inosine (**29**) in 73% yield.

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured with tetramethylsilane (TMS) as an internal standard, with a JEOL JNM-FX 100 NMR spectrometer. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. Ultraviolet (UV) spectra were recorded on a Shimadzu UV-240 spectrophotometer. Reactions at low temperature were performed using a CryoCool CC-100 (NESLAB Instrument, Inc.). Butyllithium in hexane was titrated before use by using diphenylacetic acid in THF. THF was distilled from sodium benzophenone ketyl. Column chromatography was carried out either on silica gel (Wakogel® C-200) or on magnesium silicate (Florisil®). TLC was performed on silica gel (precoated Silica gel plates 60 F_{254}, Merck).

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)adenosine (4)——Compound **1** (267 mg, 1.0 mmol) was added to a mixture of TBDMSCl (528 mg 3.5 mmol) and imidazole (340 mg, 5.0 mmol) in DMF (2 ml), and the resulting solution was stirred at room temperature overnight. The mixture was poured into EtOAc–H_2O and the organic layer was separated, dried (Na_2SO_4) and evaporated to dryness. Column chromatographic purification (benzene : EtOAc = 4 : 1) of the residue gave **4** (532 mg, 86%). Crystallization from MeOH–H_2O gave an analytical sample (mp 143—144 °C, lit.[12] mp 142—144 °C). *Anal.* Calcd for $C_{28}H_{55}N_5O_4Si_3$: C, 55.16; H, 9.09; N, 11.49. Found: C, 55.10; H, 9.15; N, 11.41. MS *m/z*: 594 (M − Me), 552 (M − Bu-*tert*), 135 (B + 1). UV λ_{max}^{MeOH} nm (ε): 260 (15600), λ_{min}^{MeOH} nm (ε): 229 (2900). ^{1}H-NMR ($CDCl_3$) δ: 0.10—0.13 (18H, m, SiMe), 0.79—0.95 (27H, m, SiBu-*tert*), 3.80 (1H, m, H-4′), 3.96—4.18 (2H, m, CH_2-5′), 4.32 (1H, dd, H-3′), 4.69 (1H, dd, H-2′), 5.80 (2H, br, NH_2), 6.02 (1H, d, H-1′), 8.15 (1H, s, H-8), 8.33 (1H, s, H-2).

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)inosine (5)——This compound was prepared from **2** (1.07 g, 4.0 mmol), TBDMSCl (3.02 g, 20 mmol), and imidazole (1.91 g, 28 mmol) in DMF (5 ml) by the same procedure as used for the preparation of **4**. Silica gel column chromatography (benzene : EtOAc = 2 : 1) gave **5** (2.21 g, 91%). Crystallization from MeOH gave an analytical sample (mp 248—249 °C). *Anal.* Calcd for $C_{28}H_{54}N_4O_5Si_3$: C, 55.07; H, 8.91; N, 9.17. Found: C, 55.29; H, 9.15 N, 9.40. MS *m/z*: 595 (M − Me), 553 (M − Bu-*tert*), 136 (B + 1). UV λ_{max}^{MeOH} nm (ε): 247 (11300), $\lambda_{shoulder}^{MeOH}$ nm (ε): 260 (6500), λ_{min}^{MeOH} nm (ε): 225 (4500). ^{1}H-NMR ($CDCl_3$) δ: 0.10—0.15 (18H, m, SiMe), 0.82—0.97 (27H, m, SiBu-*tert*), 3.74—4.56 (5H, m, H-2′, H-3′, H-4′, CH_2-5′), 6.02 (1H, d, J = 4.9 Hz, H-1′), 8.17 (1H, s, H-2), 8.24 (1H, s, H-8), 13.21 (1H, br, NH).

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)guanosine (6)——This compound was prepared from **3** (1.13 g, 4.0 mmol), TBDMSCl (3.62 g, 24 mmol), and imidazole (2.72 g, 40 mmol) in DMF (20 ml) by the procedure as used for the preparation of **4**. Silica gel column chromatography (6% EtOH in $CHCl_3$) gave **6** (2.10 g, 86%). Crystallization from MeOH–H_2O gave an analytical sample (mp 255—257 °C, lit.[13] mp > 245 °C, dec.). *Anal.* Calcd for $C_{28}H_{55}N_5O_5Si_3 \cdot 1/2H_2O$: C, 52.97; H, 8.89; N, 11.03. Found: C, 53.09; H, 8.97; N, 11.13. MS *m/z*: 568 (M − Bu-*tert*), 151 (B + 1). UV λ_{max}^{MeOH} nm (ε): 256 (20000), $\lambda_{shoulder}^{MeOH}$ nm (ε): 266 (16200), λ_{min}^{MeOH} nm (ε): 223 (1900). ^{1}H-NMR ($CDCl_3$) δ: 0.02—0.14 (18H, m, SiMe), 0.87—0.96 (27H, m, SiBu-*tert*), 3.74—4.49 (5H, m, H-2′, H-3′, H-4′, CH_2-5′), 5.83 (1H, d, J = 3.9 Hz, H-1′), 6.29 (2H, br, NH_2), 7.90 (1H, s, H-8), 12.03 (1H, br, NH).

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-8-methyladenosine (7)——LDA (7.5 mmol) in THF (15 ml) was placed in a three-necked flask equipped with a gas-inlet adaptor, thermometer, and rubber septum. To this, a solution of **4** (915 mg, 1.5 mmol) in THF (15 ml) was added, under positive pressure of dry argon, at such a rate that the temperature did not exceed −70 °C. The mixture was stirred for 1.5 h at below −70 °C, MeI (0.28 ml, 4.5 mmol) was added and the whole was stirred for a further 3 h. The reaction was then quenched by adding AcOH (0.43 ml, 7.5 mmol). Evaporation of the solvent followed by chromatography on a silica gel column (0.5% EtOH in $CHCl_3$) gave **7** (417 mg, 45%). Crystallization from EtOH gave an analytical sample (mp 170—172 °C). *Anal.* Calcd for $C_{29}H_{57}N_5O_4Si_3$: C, 55.85; H, 9.21; N, 11.23. Found: C, 55.80; H, 9.33; N, 11.10. MS *m/z*: 567 (M − Bu-*tert*), 149 (B + 1). UV λ_{max}^{MeOH} nm (ε): 260 (17100), λ_{min}^{MeOH} nm (ε): 229 (4100). ^{1}H-NMR ($CDCl_3$) δ: 0.04—0.16 (18H, m, SiMe), 0.77—0.97 (27H, m, SiBu-*tert*), 2.62 (3H, s, 8-Me), 3.76 (1H, m, H-4′), 3.98—4.12 (2H, m, CH_2-5′), 4.51 (1H, dd, H-3′), 5.43—5.53 (3H, m, H-2′, NH_2), 5.79 (1H, d, J = 6.3 Hz, H-1′), 8.24 (1H, s, H-2).

8-Methyladenosine (8)——TBAF · $3H_2O$ (265 mg, 0.84 mmol) was added to a solution of **7** (150 mg, 0.24 mmol) in THF (7 ml) and the mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the resulting residue was chromatographed on a Florisil column (15% EtOH in $CHCl_3$). This afforded **8** (58 mg, 86%), which was crystallized from MeOH–H_2O to give an analytical sample (mp 199—202 °C, sintering at 132 °C; lit.[5d] mp 130—133 °C). *Anal.* Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.37; N, 24.90. Found: C, 46.91; H, 5.38; N, 24.63. MS *m/z*: 149 (B + 1). UV $\lambda_{max}^{H_2O}$ nm (ε): 261 (14500), $\lambda_{min}^{H_2O}$ nm (ε): 227 (800). ^{1}H-NMR (CD_3OD) δ: 2.64 (3H, s, 8-Me), 3.75—3.85 (2H, m, CH_2-5′), 4.18 (1H, m, H-4′), 4.31 (1H, m, H-3′), 4.92 (1H, dd, H-2′), 5.90 (1H, d, J = 3.9 Hz, H-1′), 8.10 (1H, s, H-2).

8-Alkylinosines (9, 10, and 11)——The C-8 alkylation of **5** (916 mg, 1.5 mmol) with MeI (0.47 ml, 7.5 mmol) was carried out for 3 h by the same procedure as used for the preparation of **7**. Silica gel column chromatography (2%

EtOH in $CHCl_3$) gave a mixture of products, which was treated with TBAF·$3H_2O$ (1.66 g, 5.3 mmol) in THF (15 ml) for 2 h. Column chromatography on Florisil (40% EtOH in $CHCl_3$) gave a mixture of **9**, **10**, and **11**. Purification by preparative TLC (silica gel, 6% EtOH in $CHCl_3$) gave **9** (91 mg, 21%), **10** (72 mg, 16%), and **11** (71 mg, 15%).

Physical data for **9** are as follows. mp 163—165 °C (MeOH–H_2O). *Anal.* Calcd for $C_{11}H_{14}N_4O_5 \cdot H_2O$: C, 44.00; H, 5.37; N, 18.66. Found: C, 43.98; H, 5.18; N, 18.52. MS *m/z*: 150 (B+1). UV $\lambda_{max}^{H_2O}$ nm (ε): 251 (12400), $\lambda_{min}^{H_2O}$ nm (ε): 226 (4600). ^{1}H-NMR (DMSO-d_6) δ: 2.51 (overlapped with DMSO, 8-Me), 3.58—3.62 (2H, m, CH_2-5′), 3.91—3.94 (1H, m, H-4′), 4.13 (1H, m, H-3′), 4.65—4.84 (1H, m, H-2′), 5.04—5.42 (3H, m, 2′-OH, 3′-OH, 5′-OH), 5.78 (1H, d, *J*=6.8 Hz, H-1′), 8.01 (1H, s, H-2), 12.37 (1H, br, NH).

Physical data for **10** (obtained as a foam) are as follows. MS *m/z*: 164 (B+1). UV $\lambda_{max}^{H_2O}$ nm: 250, $\lambda_{min}^{H_2O}$ nm: 232. ^{1}H-NMR (DMSO-d_6) δ: 1.28 (3H, t, $CH_2\underline{CH_3}$), 2.86 (2H, q, $\underline{CH_2}CH_3$), 3.58—3.62 (2H, m, CH_2-5′), 3.94 (1H, m, H-4′), 4.15 (1H, dd, H-3′), 4.82 (1H, dd, H-2′), 5.11 (3H, br, 2′-OH, 3′-OH, 5′-OH), 5.78 (1H, d, *J*=6.8 Hz, H-1′), 8.01 (1H, s, H-2). Compound **10** was converted to its triacetate, whose high-resolution MS was measured. High-resolution MS *m/z*: 422.1436 (M^+) Calcd for $C_{18}H_{22}N_4O_8$ 422.1436. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, t, 8-$CH_2\underline{CH_3}$), 2.06, 2.09, and 2.16 (9H, each as s, Ac), 2.91 (2H, q, 8-$\underline{CH_2}CH_3$), 4.30—4.39 (2H, m, CH_2-5′), 4.49 (1H, m, H-4′), 5.79 (1H, dd, H-3′), 5.96 (1H, d, *J*=5.1 Hz, H-1′), 6.19 (1H, dd, H-2′), 8.03 (1H, s, H-2), 12.80 (1H, br, NH).

Physical data for **11** are as follows. mp 143—145 °C (MeOH–H_2O). *Anal.* Calcd for $C_{13}H_{18}N_4O_5 \cdot 1/2H_2O$: C, 48.89; H, 5.99; N, 17.55. Found: C, 48.63; H, 6.07; N, 17.31. MS *m/z*: 178 (B+1), 163 (B+1−Me). UV $\lambda_{max}^{H_2O}$ nm (ε): 252 (14000), $\lambda_{min}^{H_2O}$ nm (ε): 224 (3800). ^{1}H-NMR (DMSO-d_6, after addition of D_2O) δ: 1.30 (6H, d, $CH\underline{Me_2}$), 3.14—3.48 (2H, m, CH_2-5′), 3.63 (1H, q, $C\underline{H}Me_2$), 3.95 (1H, m, H-4′), 4.17 (1H, dd, H-3′), 4.90 (1H, dd, H-2′), 5.82 (1H, d, *J*=6.8 Hz, H-1′), 8.02 (1H, s, H-2).

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-8-hydroxymethyladenosine (13)——The C-8 formylation of **4** (766 mg, 1.26 mmol) with HCO_2Me (0.46 ml, 7.5 mmol) was carried out for 3 h by the same procedure as used for the preparation of **7**. The reaction mixture containing **12** was diluted with MeOH and treated with $NaBH_4$. After being quenched with AcOH, the mixture was evaporated to dryness. The resulting mixture was taken up into $CHCl_3$–H_2O. The organic layer was separated, dried (Na_2SO_4), and chromatographed on a silica gel column (4% EtOH in $CHCl_3$) to give **13** (245 mg, 61%) as a foam. *Anal.* calcd for $C_{29}H_{57}N_5O_7Si_3$: C, 54.45; H, 8.98; N, 10.95. Found: C, 54.74; H, 9.20; N, 10.75. MS *m/z*: 583 (M−Bu-*tert*), 165 (B+1). UV λ_{max}^{MeOH} nm (ε): 262 (15900), λ_{min}^{MeOH} nm (ε): 231 (4100). ^{1}H-NMR ($CDCl_3$) δ: 0.02—0.16 (18H, m, SiMe), 0.75—0.83 (27H, m, SiBu-*tert*), 3.57—3.80 (1H, m, H-4′), 3.94—4.07 (2H, m, CH_2-5′), 4.50 (1H, dd, H-3′), 4.91 (2H, s, 8-$C\underline{H_2}OH$), 5.34 (1H, dd, H-2′), 5.92 (1H, d, *J*=5.9 Hz, H-1′), 8.27 (1H, s, H-2).

8-Hydroxymethyladenosine (14)——Compound **13** (176 mg, 0.28 mmol) was deprotected with TBAF·$3H_2O$ (309 mg, 0.96 mmol) in THF (15 ml) as described for the preparation of **8**. Florisil column chromatography (30% EtOH in $CHCl_3$) gave **14** (72 mg, 87%). Crystallization from EtOH–H_2O gave an analytical sample (mp 209—210 °C). *Anal.* Calcd for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56. Found: C, 44.56; H, 5.11; N, 23.30. MS *m/z*: 166 (B+2). UV $\lambda_{max}^{H_2O}$ nm (ε): 263 (15000), $\lambda_{min}^{H_2O}$ nm (ε): 230 (2500). ^{1}H-NMR (DMSO-d_6, after addition of D_2O) δ: 3.58 (2H, m, CH_2-5′), 4.01 (1H, m, H-4′), 4.18 (1H, dd, H-3′), 4.61, 4.72 (2H, each as d, 8-$C\underline{H_2}OH$), 4.82 (1H, dd, H-2′), 6.02 (1H, d, *J*=7.3 Hz, H-1′), 8.10 (1H, s, H-2).

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-8-formylinosine (15)——The C-8 formylation of **5** (916 mg, 1.5 mmol) with HCO_2Me (0.46 ml, 7.5 mmol) was carried out for 3 h by the same procedure as used for the preparation of **7**. Silica gel column chromatography (benzene : EtOAc=4 : 1) gave **15** (680 mg, 71%), which was crystallized from MeOH (mp 210—212 °C). *Anal.* Calcd for $C_{29}H_{54}N_4O_6Si_3$: C, 54.53; H, 8.52; N, 8.77. Found: C, 54.84; H, 8.85; N, 8.49. MS *m/z*: 581 (M−Bu-*tert*), 164 (B+1). IR ($CHCl_3$) cm^{-1}: 1690 (CHO). UV λ_{max}^{MeOH} nm (ε): 251 (8600), $\lambda_{shoulder}^{MeOH}$ nm (ε): 263 (6900), λ_{min}^{MeOH} nm (ε): 226 (5100). ^{1}H-NMR ($CDCl_3$) δ: 0.04—0.16 (18H, m, SiMe), 0.76—0.98 (27H, m, SiBu-*tert*), 3.69—4.06 (3H, m, H-4′, CH_2-5′), 4.51 (1H, m, H-3′), 5.20 (1H, dd, H-2′), 6.86 (1H, d, *J*=6.1 Hz, H-1′), 8.28 (1H, s, H-2), 9.99 (1H, s, 8-CHO), 12.95 (1H, br, NH).

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-8-hydroxymethylinosine (16)——Compound **15** (639 mg, 1.0 mmol) in MeOH (20 ml) was treated with $NaBH_4$ (82 mg, 2.2 mmol) at room temperature for 15 min. After being quenched with AcOH, the mixture was evaporated to dryness. Chromatographic purification of the residue (2% EtOH in $CHCl_3$) gave **16** (589 mg, 92%), which was crystallized from MeOH (mp 250—251 °C). *Anal.* Calcd for $C_{29}H_{56}N_4O_6Si_3$: C, 54.36; H, 8.81; N, 8.74. Found: C, 54.48; H, 8.99; N, 8.74. MS *m/z*: 584 (M−Bu-*tert*), 166 (B+1). UV λ_{max}^{MeOH} nm (ε): 252 (13400), $\lambda_{shoulder}^{MeOH}$ nm (ε): 264 (7700), λ_{min}^{MeOH} nm (ε): 227 (6000). ^{1}H-NMR ($CDCl_3$) δ: 0.06—0.15 (18H, m, SiMe), 0.76—0.96 (27H, m, SiBu-*tert*), 3.69—3.94 (3H, m, CH_2-5′, 8-$CH_2\underline{OH}$), 4.11 (1H, m, H-4′), 4.40 (1H, dd, H-3′), 4.91—5.04 (3H, m, H-2′, 8-$C\underline{H_2}OH$), 6.00 (1H, d, *J*=6.4 Hz, H-1′), 8.15 (1H, s, H-2), 13.06 (1H, br, NH).

8-Hydroxymethylinosine (17)——Compound **16** (322 mg, 0.5 mmol) was deprotected with TBAF·$3H_2O$ (552 mg, 1.75 mmol) in THF (15 ml) as described for the preparation of **8**. Florisil column chromatography (50% EtOH in $CHCl_3$) gave **17** (122 mg, 82%), which was crystallized from MeOH (mp >290 °C). *Anal.* calcd for $C_{11}H_{14}N_4O_6 \cdot 2/3H_2O$: C, 42.58; H, 4.98; N, 18.05. Found: C, 42.60; H, 4.68; N, 17.78. MS *m/z*: 152 (B+1). UV $\lambda_{max}^{H_2O}$ nm (ε): 252 (12000), $\lambda_{min}^{H_2O}$ nm (ε): 225 (3400). ^{1}H-NMR (DMSO-d_6, after addition of D_2O) δ: 3.46—3.50 (2H, m, CH_2-5′), 3.94 (1H, m, H-4′), 4.16 (1H, m, H-3′), 4.59, 4.67 (2H, each as d, 8-$C\underline{H_2}OH$), 4.74 (1H, dd, H-2′), 5.99 (1H,

d, J=6.3 Hz, H-1′), 8.05 (1H, s, H-2).

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-8-formylguanosine (18)——The C-8 formylation of **6** (614 mg, 1.0 mmol) with HCO_2Me (0.3 ml, 5.0 mmol) was carried out for 2 h by the same procedure as used for the preparation of **7**. Silica gel column chromatography (3% EtOH in $CHCl_3$) gave **18** (262 mg, 41%). MS m/z: 596 (M−Bu-*tert*), 179 (B+1). UV λ_{max}^{MeOH} nm: 337, 258, $\lambda_{shoulder}^{MeOH}$ nm: 266, λ_{min}^{MeOH} nm: 291, 231. ^{1}H-NMR ($CDCl_3$) δ: 0.04—0.16 (18H, m, SiMe), 0.78—0.98 (27H, m, SiBu-*tert*), 3.71—3.94 (2H, m, CH_2-5′), 4.05 (1H, m, H-4′), 4.46 (1H, m, H-3′), 5.09 (1H, t, H-2′), 6.64 (1H, d, J=5.6 Hz, H-1′), 6.79 (2H, br, NH_2), 9.98 (1H, s, 8-CHO), 12.15 (1H, s, NH).

8-Hydroxymethylguanosine (19)——Compound **18** (134 mg, 0.21 mmol) in MeOH (4 ml) and THF (1 ml) was treated with $NaBH_4$ (22 mg, 0.6 mmol) at room temperature for 15 min. After being quenched with AcOH, the mixture was evaporated to dryness. The resulting residue was dissolved in $CHCl_3$ and the solution was washed with H_2O. The organic layer was separated, dried (Na_2SO_4), filtered, and evaporated. The residue thus obtained was treated with TBAF·$3H_2O$ (231 mg, 0.73 mmol) in THF (5 ml) as described for the preparation of **8**. Florisil column chromatography (40% EtOH in $CHCl_3$) gave **19** (57 mg, 86%), which was crystallized from MeOH–H_2O (mp 212—214 °C). *Anal.* Calcd for $C_{11}H_{15}N_5O_6 \cdot 1/2H_2O$: C, 40.99; H, 5.17; N, 21.73. Found: C, 41.22; H, 5.39; N, 21.43. MS m/z: 181 (B+1). UV $\lambda_{max}^{H_2O}$ nm (ε): 259 (7200), $\lambda_{shoulder}^{H_2O}$ nm (ε): 270 (5900), $\lambda_{min}^{H_2O}$ nm (ε): 226 (2300). ^{1}H-NMR (DMSO-d_6, after addition of D_2O) δ: 2.53—2.57 (2H, m, CH_2-5′), 3.89 (1H, m, H-4′), 4.13 (1H, dd, H-3′), 4.43, 4.61 (2H, each as d, 8-C<u>H</u>$_2$OH), 5.84 (1H, d, J=6.8 Hz, H-1′).

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-N^6,8-bis(methoxycarbonyl)adenosine (20) and 2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-8-(*N*,*N*-diisopropylcarbamoyl)-N^6-methoxycarbonyladenosine (21)——The methoxycarbonylation of **4** (915 mg, 1.5 mmol) with $ClCO_2Me$ (0.58 ml, 7.5 mmol) was carried out for 3 h by the same procedure as used for the preparation of **7**. Silica gel column chromatography ($CHCl_3$) gave **20** (288 mg, a syrup, 27%) and **21** (503 mg, a foam, 50%).

Physical data for **20** are as follows. MS m/z: 670 (M+1−Bu-*tert*), 638 (M+1−Bu-*tert*−OMe), 220 (B+1−OMe). UV λ_{max}^{MeOH} nm: 280, λ_{min}^{MeOH} nm: 242. ^{1}H-NMR ($CDCl_3$) δ: 0.03—0.16 (18H, m, SiMe), 0.77—0.97 (27H, m, SiBu-*tert*), 3.67—4.19 (3H, m, H-4′, CH_2-5′), 3.88, 4.07 (6H, each as s, N^6-CO_2Me, 8-CO_2Me), 4.57 (1H, m, H-3′), 5.58 (1H, dd, H-2′), 6.83 (1H, d, H-1′), 8.24 (1H, br, NH), 8.79 (1H, s, H-2).

Physical data for **21** are as follows. MS m/z: 320 (B+1), 261 (B+1−CO_2Me). UV λ_{max}^{MeOH} nm: 270, λ_{min}^{MeOH} nm: 235. ^{1}H-NMR ($CDCl_3$) δ: 0.08—0.23 (18H, m, SiMe), 0.78—0.94 (27H, m, SiBu-*tert*), 1.24, 1.57 (12H, each as dd, CH<u>Me</u>$_2$), 3.53—4.07 (5H, m, H-4′, CH_2-5′, C<u>H</u>Me$_2$), 4.59 (1H, m, H-3′), 5.53 (1H, dd, H-2′), 5.85 (1H, d, J=5.9 Hz, H-1′), 8.01 (1H, br, NH), 8.73 (1H, s, H-2).

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-8-methoxycarbonyladenosine (22) and 2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)adenosine-8-carboxamide (23)——Compound **20** (288 mg, 0.4 mmol) was treated with NH_3/MeOH (15 ml) overnight. After evaporation of the solvent, the residue was chromatographed on a silica gel column (1—2% EtOH in $CHCl_3$). This afforded **22** (63 mg, a foam, 24%) and **23** (119 mg, a powder, 46%).

Physical data for **22** are as follows. MS m/z: 611 (M−Bu-*tert*), 162 (B+1−OMe). UV λ_{max}^{MeOH} nm: 278, λ_{min}^{MeOH} nm: 244. ^{1}H-NMR ($CDCl_3$) δ: 0.02—0.16 (18H, m, SiMe), 0.77—0.96 (27H, m, SiBu-*tert*), 3.61—4.09 (3H, m, H-4′, CH_2-5′), 3.91 (3H, s, 8-CO_2Me), 4.62 (1H, m, H-3′), 5.51 (1H, dd, H-2′), 5.76 (2H, br, NH_2), 7.16 (1H, d, J=5.4 Hz, H-1′), 8.76 (1H, s, H-2).

Physical data for **23** are as follows. MS m/z: 176 (B+1). UV λ_{max}^{MeOH} nm: 285, λ_{min}^{MeOH} nm: 246. ^{1}H-NMR ($CDCl_3$) δ: 0.02—0.16 (18H, m, SiMe), 0,79—0.97 (27H, m, SiBu-*tert*), 3.74 (1H, m, H-4′), 4.05 (2H, m, CH_2-5′), 4.67 (1H, dd, H-3′), 5.51 (1H, dd, H-2′), 5.78 (2H, br, NH_2), 7.13 (1H, d, J=4.9 Hz, H-1′), 8.34 (1H, s, H-2).

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-8-(*N*,*N*-diisopropylcarbamoyl)adenosine (24)——Compound **21** (503 mg, 0.68 mmol) was treated with NH_3/MeOH (20 ml) overnight. After evaporation of the solvent, the residue was chromatographed on a silica gel column (1% EtOH in $CHCl_3$). This afforded **24** (393 mg, 79%) as a foam. MS m/z: 680 (M+1−Bu-*tert*), 263 (B+2), 162 (B+1−NPr_2). UV λ_{max}^{MeOH} nm: 270, λ_{min}^{MeOH} nm: 235. ^{1}H-NMR ($CDCl_3$) δ: 0.08—0.23 (18H, m, SiMe), 0.89—1.02 (27H, m, SiBu-*tert*), 1.29, 1.65 (12H, each as dd, CH<u>Me</u>$_2$), 3.67—4.24 (5H, m, H-4′, CH_2-5′, C<u>H</u>Me$_2$), 4.72 (1H, m, H-3′), 5.62 (1H, dd, H-2′), 5.77 (2H, br, NH_2), 5.90 (1H, d, J=5.9 Hz, H-1′), 8.38 (1H, s, H-2).

8-Methoxycarbonyladenosine (25)——Compound **22** (39 mg, 0.06 mmol) was deprotected with TBAF·$3H_2O$ (66 mg, 0.21 mmol) in THF (4 ml) as described for the preparation of **8**. Florisil column chromatography (8% EtOH in $CHCl_3$) gave **25** (16 mg, 82%), which was crystallized from MeOH (mp 200—201 °C, lit.[6b] mp 199—200 °C). UV λ_{max}^{MeOH} nm: 278, λ_{min}^{MeOH} nm; 246. ^{1}H-NMR (DMSO-d_6, after addition of D_2O) δ: 2.54 (3H, s, 8-CO_2Me), 3.51—3.64 (2H, m, CH_2-5′), 4.00 (1H, m, H-4′), 4.14 (1H, m, H-3′), 4.83 (1H, dd, H-2′), 5.77 (1H, d, J=7.3 Hz, H-1′), 8.05 (1H, s, H-2).

Adenosine-8-carboxamide (26)——Compound **23** (93 mg, 0.14 mmol) was deprotected with TBAF·$3H_2O$ (155 mg, 0.49 mmol) in THF (5 ml) as described for the preparation of **8**. Florisil column chromatography (40% EtOH in $CHCl_3$) gave **26** (38 mg, 86%), which was crystallized from EtOH (mp 250—251 °C, lit.[6b] mp 249—251 °C). MS m/z: 181 (B+1). UV $\lambda_{max}^{H_2O}$ nm: 289, $\lambda_{min}^{H_2O}$ nm: 245. ^{1}H-NMR (DMSO-d_6) δ: 3.49—3.71 (2H, m, CH_2-5′), 3.94 (1H, m, H-4′), 4.17—4.20 (1H, m, H-3′), 4.94—4.98 (1H, m, H-2′), 5.08—5.60 (3H, m, 2′-OH, 3′-OH, 5′-OH), 6.77 (1H, d, J=6.6 Hz, H-1′), 7.58 (2H, br, NH_2), 8.00 (2H, br, 8-$CONH_2$), 8.18 (1H, s, H-2).

Adenosine-8-(*N,N*-diisopropyl)carboxamide (27)——Compound **24** (153 mg, 0.2 mmol) was deprotected with TBAF·$3H_2O$ (221 mg, 0.7 mmol) in THF (7 ml) as described for the preparation of **8**. Florisil column chromatography (8% EtOH in $CHCl_3$) gave **27** (64 mg, 81%), which was crystallized from EtOH–H_2O (mp 238—240 °C). *Anal.* Calcd for $C_{17}H_{26}N_6O_5$: C, 51.77; H, 6.64; N, 21.31. Found: C, 52.02; H, 6.83; N, 21.37. MS *m/z*: 263 (B+2), 262 (B+1), 162 (B+1−NPr_2). UV $\lambda_{max}^{H_2O}$ nm·(ε): 268 (15600), $\lambda_{min}^{H_2O}$ nm (ε): 239 (7400). ^{1}H-NMR (DMSO-d_6, after addition of D_2O) δ: 1.21, 1.49 (12H, each as dd, CH<u>Me</u>$_2$), 3.59—3.81 (4H, m, CH_2-5′, C<u>H</u>Me_2), 4.01 (1H, m, H-4′), 4.19 (1H, dd, H-3′), 4.97 (1H, dd, H-2′), 5.65 (1H, d, *J*=6.8 Hz, H-1′), 8.20 (1H, s, H-2).

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-8-methoxycarbonylinosine (28)——The methoxycarbonylation of **5** (611 mg, 1.0 mmol) with $ClCO_2Me$ (0.39 ml, 5.0 mmol) was carried out for 1 h by the same procedure as used for the preparation of **7**. Silica gel column chromatography (1% EtOH in $CHCl_3$) gave **28** (418 mg, 61%) as a syrup. MS *m/z*: 612 (M−Bu-*tert*), 208 (B+1). UV λ_{max}^{MeOH} nm: 287, λ_{min}^{MeOH} nm: 240. ^{1}H-NMR ($CDCl_3$) δ: 0.02—0.16 (18H, m, SiMe), 0.80—0.97 (27H, m, SiBu-*tert*), 3.78 (1H, m, H-4′), 4.01 (3H, s, 8-CO_2Me), 4.03 (2H, m, CH_2-5′), 4.51 (1H, m, H-3′), 5.38 (1H, dd, H-2′), 6.84 (1H, d, H-1′), 8.26 (1H, s, H-2), 12.89 (1H, br, NH).

8-Methoxycarbonylinosine (29)——Compound **28** (305 mg, 0.46 mmol) was deprotected with TBAF·$3H_2O$ (497 mg, 1.6 mmol) in THF (10 ml) as described for the preparation of **8**. Florisil column chromatography (15% EtOH in $CHCl_3$) gave **29** (109 mg, 73%), which was crystallized from EtOH (mp 189—190 °C, dec.). *Anal.* calcd for $C_{12}H_{14}N_4O_7$: C, 44.18; H, 4.32; N, 17.17. Found: C, 44.51; H, 4.50; N, 16.81. MS *m/z*: 194 (B+1), 134 (B+1−CO_2Me). UV $\lambda_{max}^{H_2O}$ nm (ε): 284 (13200), $\lambda_{min}^{H_2O}$ nm (ε): 240 (3500). ^{1}H-NMR (DMSO-d_6) δ: 3.50—3.63 (2H, m, CH_2-5′), 3.93 (3H, s, 8-CO_2Me), 4.19—4.27 (2H, m, H-3′, H-4′), 4.87—4.96 (2H, m, H-2′, 5′-OH), 5.13, 5.33 (2H, each as d, 2′-OH, 3′-OH), 6.58 (1H, d, *J*=5.9 Hz, H-1′), 8.20 (1H, s, H-2), 12.69 (1H, br, NH).

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References

1) This paper is dedicated to Professor Morio Ikehara on the occasion of his retirement from Osaka University in March, 1986.
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