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Synthesis of 8,6′-Cyclo-6′-deoxyhexofuranosyladenines: Adenosines Fixed in an Anti-conformation (Nucleosides and Nucleotides. LXVI[1])

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For studies of the conformation of nucleosides around the glycosyl linkages, the carbon-bridged cycloadenosines, 8,6′-cyclo-6′-deoxyallofuranosyladenine and its 5′-epimer, were synthesized by the following route. Treatment of N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine 5′-aldehyde (**1**) with dimethyloxosulfonium methylide afforded the 5′,6′-anhydrohexofuranosyladenine (**2**), which was treated with thiophenoxide to give the diastereomeric 6′-phenylthio derivatives (**4**). Photoirradiation of **4** followed by 5′-*O*-acetylation afforded 5′-*O*-acetyl-8,6′-cyclo-6′-deoxy-hexofuranosyladenine derivatives (**6b**, **7b**). Attempted synthesis of a 8,7′-cyclo-heptofuranosyl derivative by way of photolysis of a 7′-phenylthio-heptofuranosyladenine resulted in the formation of 5′,6′,7′-trideoxy-2′,3′-*O*-isopropylidene-β-D-ribo-heptofuranosyladenine (**11**). The nature of the circular dichroism spectra of **6** and **7** is discussed.

Keywords——adenosine; nucleoside conformation; *C*-cycloadenosine; 8,6′-cyclo-6′-dexoy-β-D-allofuranosyladenine; 8,6′-cyclo-6′-deoxy-α-D-talofuranosyladenine; heptofuranosyladenine; photocyclization; CD; NMR

In our series of studies on the synthesis of carbon-bridged cyclonucleosides, we have obtained 8,5′-,[2-5] 8,2′-,[1,6,7] and 8,3′-[1,6] cyclo derivatives of adenosine or 2′-deoxyadenosine. In addition, we have demonstrated that the sign of the circular dichroism (CD) spectra of nucleosides is a function of the glycosyl torsion angles as well as the nature of the nucleobases.[1] For example, 5′-deoxy-8,5′-cycloadenosines and 3′-deoxy-8,3′-ethanoadenosine showed strong negative CD bands, whereas the 8,2′-methano- and 8,2′-ethanoadenosines showed positive bands. Therefore, it follows that there is a transitional glycosyl torsion angle for the reversal of the sign of CD spectra within the anti-range. To confirm this point, additional models having glycosyl torsion angles (χ) around 50—80° are required.

This paper describes a synthesis of 8,5′-cyclo derivatives connected by one methylene group, *i.e.*, 8,6′-cyclo-hexofuranosyladenine derivatives, from 6′-deoxy-6′-phenylthiohexofuranosyladenines.[8]

In order to obtain the precursor hexofuranosyl derivatives from adenosine, adenosine 5′-aldehyde derivatives would be useful. Among various procedures for chain elongation from the 5′-aldehyde functions of nucleosides,[9] the pathway invovlving the use of the nitromethane adduct of 2′,3′-*O*-isopropylideneadenosine 5′-aldehyde[10] or N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine 5′-aldehyde (**1**)[11] has not been satisfactory.

Therefore, the other route from **1** was investigated. Treatment of **1** with dimethyloxosulfonium methylide afforded the expected 5′,6′-anhydro-β-D-allo- and α-L-talofuranosides (**2**) in 32% yield. The structure of **2** was confirmed by measurement of the nuclear magnetic resonance (NMR) spectrum, in which a signal at δ 2.76 ppm due to the methylene protons in the epoxide was observed. The main by-product in this reaction was assumed to be the adduct

(**3**) of dimsyl carbanion. The use of tetrahydrofuran (THF) in the above condensation resulted in a small increase of the yield of **2** to 40%. Heating of **2** with sodium thiophenoxide in dimethylformamide (DMF) followed by debenzoylation afforded the 6′-phenylthio derivative (**4**) in 70% yield. The proton signals at δ 8.36 and 8.33 (H-8, 1 : 1) in **4** correspond to those of the β-D-allo- and α-L-talofuranosides. The 6′-methylene signals were also shifted downfield to 3.2 ppm as a result of the epoxide ring-opening.

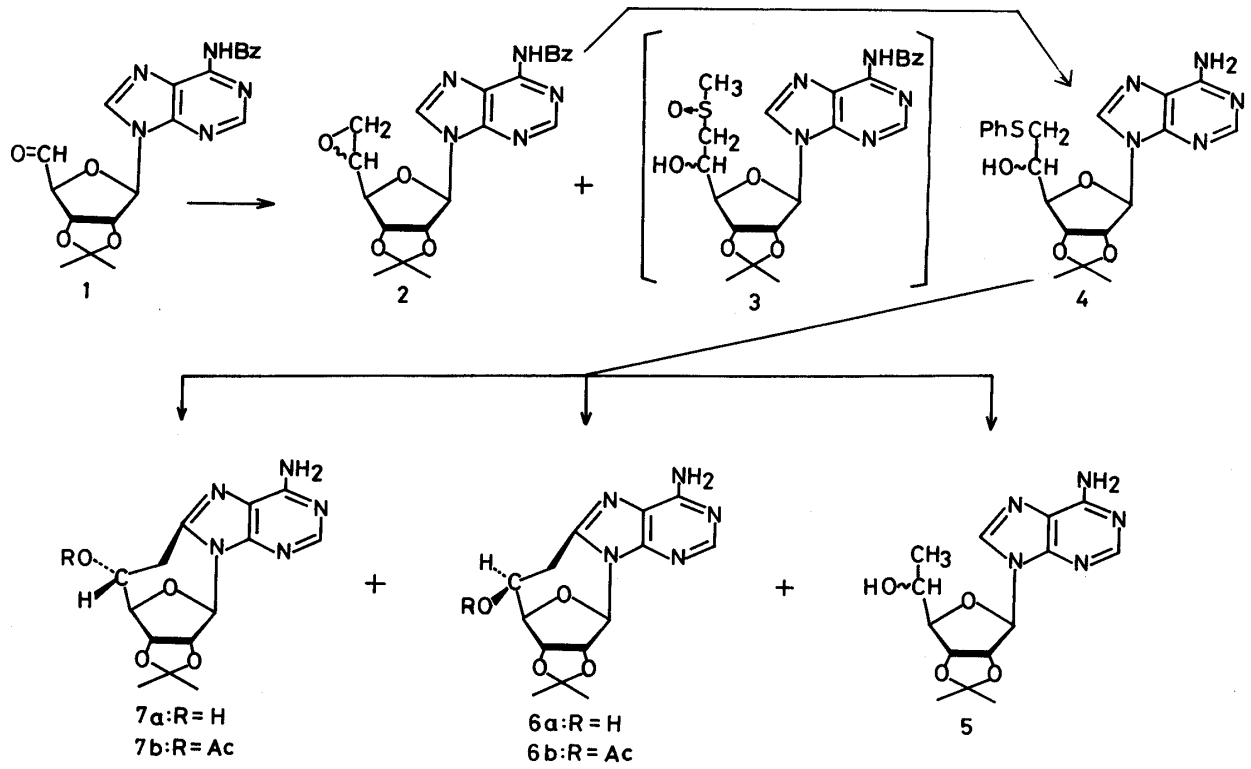

Chart 1

Irradiation of **4** in acetonitrile in the presence of trimethyl phosphite[2] followed by separation of the products by preparative thin layer chromatography (PTLC) gave the 6′-deoxy derivative (**5**, 46%), 5′(*S*)-8,6′-cyclo derivative (**6a**, 20%), and 5′(*R*)-8,6′-cyclo derivative (**7a**, 17%). The **5** was confirmed by the mass spectrum (*m/z* 321, M^+) and by comparison of the NMR spectrum with that of the known N^6-benzoyl derivative of **5**, prepared by the Grignard reaction of **1** with methylmagnesium chloride,[11] to be a mixture of 6′-deoxy-β-D-allo- and 6′-deoxy-α-L-talofuranosyladenines. Compound **6a** (and **7a**) gave a molecular ion peak at *m/z* 319. In the NMR spectra of their 5′-*O*-acetylated derivatives (**6b** and **7b**), the protons at the 8-positions were absent. Although the configuration at the 5′-position of **6b** and **7b** cannot be determined from the NMR measurements, it was tentatively assigned based on comparisons of the relative mobilities of the 5′-*S* and *R* diasteromers of 8,5′-cycloadenosines[3] and 8,5′-cyclo-5′-deoxy-5′-hydroxyalkyladenosines[5] on silica gel thin layer chromatography (TLC) (the *S*-diastereomers travel faster).

Both **6b** and **7b** showed intense positive bands around their major absorption regions in the CD spectra. This is in contrast with the spectra of 5′-deoxy-8,5′-cycloadenosines which showed rather strong negative CD bands. In the present case there is a possibility of *endo–exo* puckering at the ring involving the 5′,6′-linkage. It is known that 8,5′-anhydro-8-mercaptoadenosine (a 5′-deoxy sulfur isostere of **6** or **7** at the 6′-carbon) shows $S^{5'}$-*endo*-puckering[12] so that the staggered conformation at the 4′,5′-linkage will be possible. In the present case, it can also be expected that the preferred conformation for **6b** and **7b** should

be the 6′-*endo* form in which the 4′,5′ and 6′-substitutents are in the staggered form. A molecular model investigation based on this assumption indicated that the glycosyl torsion angles of **6** and **7** would be about 60° in the anti region. Thus, it follows that there is a transitional torsion angle between *ca.* 30° (for 8,5′(*R* and *S*)-cycloadenosines)[13,14] and *ca.* 60° for the inversion of the sign of CD spectra of adenosine. Further discussion on the transitional torsion angles will be possible after determination of the precise torsion angles of **6** and **7** by X-ray diffraction analysis.

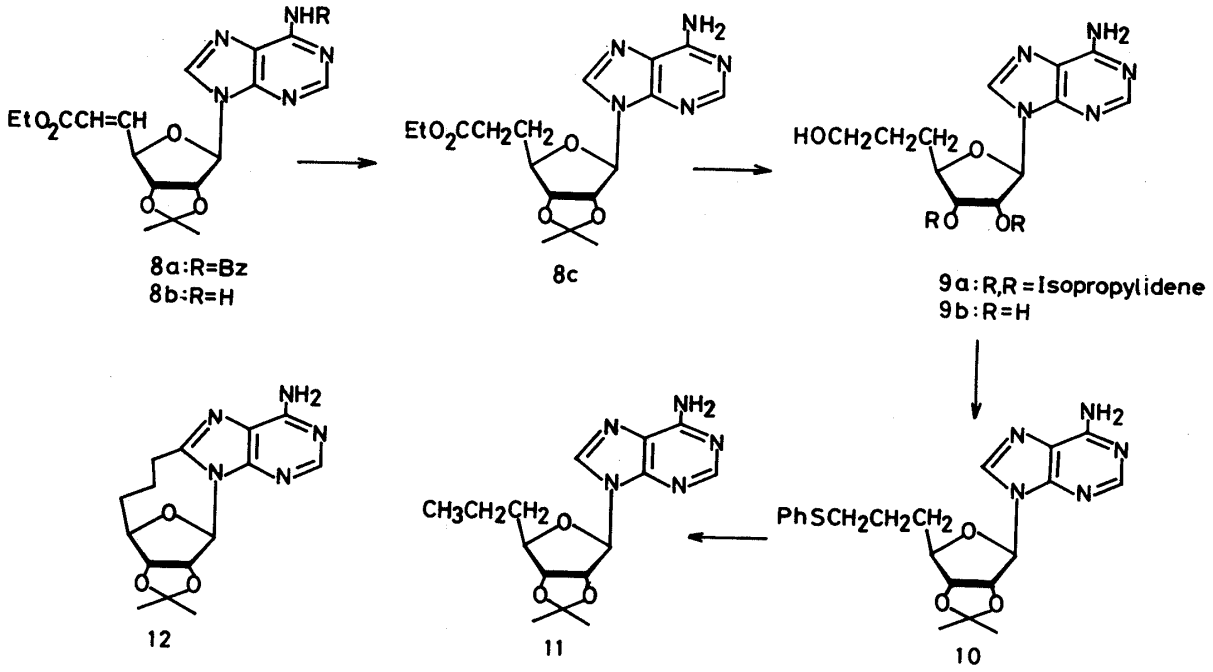

Chart 2

To obtain elongated methylene-bridged cycloadenosines, 9-(5,6-dideoxy-β-D-ribo-heptofuranosyl)adenine (**9**) was expected to be useful. Walker *et al.*[10] and Montgomery *et al.*[15] have already reported the Wittig reaction of **1** with ethoxycarbonylmethylenetriphenylphosphorane to give the product **8a**, from which **9b** was obtained[10] in low yield by subsequent conversions. 2′,3′-*O*-Isopropylideneadenosine 5′-aldehyde has been likewise converted to amorphous **8b**.[15] In our hands, **8b** was obtained in a yield of 58% as a crystalline form. Treatment of **8b** with lithium borohydride afforded amorphous **9a** in high yield *via* a saturated ester intermediate **8c**. Compound **9a** was deprotected to **9b** by treatment with 80% trifluoroacetic acid, the physical data of which were identical with those reported.[10] Compound **9a** was treated with tosyl chloride followed by thiophenoxide to furnish the 7′-phenylthio derivative (**10**). Irradiation of **10** in the presence of trimethyl phosphite in acetonitrile, however, resulted in a reduction to give 9-(5,6,7-trideoxy-2,3-*O*-isopropylidene-β-D-ribo-heptofuranosyl)adenine (**11**). The ultraviolet (UV) spectra of **11** showed an absorption maximum at 258 nm, which is diagnostic for 8-unsubstituted adenosines, since the 8-*C*-cycloadenosines so far synthesized[1-8] exhibit absorption maxima at wavelengths longer than 260 nm, in general. The NMR spectrum of **11** clearly showed the H-8 proton signal at δ 8.27 (along with that of H-2 at δ 7.91). The 7′-methyl protons were detected at δ 0.95. In the mass spectrum, the molecular ion peak of **11** (*m/z* 319) and fragment ion peaks (*m/z* 304, 136, 135) were detected. The peak at *m/z* 317 may be due to the dehydrogenation of **11** and not to the molecular ion peak of **12**.

In conclusion, the photocyclization of the phenylthio-sugar nucleosides was effective for the formation of *C*-cycloadenosines having 5-,[1] 6-[1,2,6] and 7-membered rings, but not for 8-

membered ring formation.

Experimental

Melting points were determined with a Yanaco MP-3 melting point apparatus and are uncorrected. UV spectra were recorded on a Shimadzu UV-300 recording spectrophotometer. NMR spectra were recorded on a JEOL 100FT NMR spectrometer using tetramethylsilane as an internal standard. Chemical shifts are expressed as δ (ppm). The abbreviations used to describe the splittings are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Infrared spectra (IR) were recorded on a Hitachi 215 spectrophotometer. CD spectra were recorded on a JASCO J-40 spectropolarimeter with a data processor (8 accumulations) at room temperature. The photoreaction was carried out in a apparatus with an Eikosha PIL-60 60W low-pressure Hg lamp (quartz filter) in an argon atmosphere. The starting nucleoside adenosine was purchased from Yamasa Shoyu Co., Ltd. TLC was carried out with Merck TLC plates (60 F_{254}, precoated). Silica gel for column chromatography and PTLC was Wako gel C-200.

9-(5,6-Anhydro-2,3-*O*-isopropylidene-β-D-allo- and α-L-talofuranosyl)-N^6-benzoyladenine (2)——a) Dimethyloxosulfonium methylide was prepared by the reported method[16] from 50% NaH (800 mg) and trimethyloxosulfonium chloride (1.9 g) in dimethylsulfoxide (DMSO, 20 ml). This mixture was diluted with tetrahydrofuran (THF, 30 ml) at −10 °C. Compound **1**[12] (4.09 g) in THF (40 ml) was added dropwise. After stirring of the mixture for 1.5 h at room temperature, acetone–EtOH was added, and the solvent was removed *in vacuo* under 35 °C. The residue was partitioned between AcOEt and H_2O, the organic layer was dried over Na_2SO_4, and then the solvent was removed. The residue was applied to a column of silica gel (4 × 20 cm). The eluates with 2% EtOH–$CHCl_3$ were concentrated to leave **2** (1.37 g, 32.4%) as a foam. UV λ_{max}^{EtOH}: 280 nm. MS *m/z*: 423 (M^+). NMR ($CDCl_3$): 9.50 (1H, br s, HN-6), 8.85, 8.33 (1H, s each 1 : 1, H-8), 8.35, 8.28 (1H, s each, H-2), 8.10, 7.55 (5H, m, Ph), 6.33, 6.31 (1H, d, H-1′, J=2.0 Hz), 5.52 (1H, m, H-2′), 5.30 (1H, m, H-3′), 4.35 (1H, m, H-4′), 3.27 (2H, m, H-5′), 2.76 (2H, m, H-6′), 1.64, 1.41 (3H, each s, Me_2C).

b) Dimethyloxosulfonium methylide prepared in THF (30 ml) with 50% NaH (245 mg) and trimethyloxosulfonium chloride (655 mg) by the reported method[16] was treated with **1** (1.23 g in 20 ml of THF) at −10 °C. After work-up as in a), **2** (509 mg, 40%) was obtained.

N^6-Benzoyl-9-(6-deoxy-2,3-*O*-isopropylidene-6-methylsulfinyl-β-D-allo- and α-L-talofuranosyl)adenine (3)——From the eluate of the above chromatography in method a) with 8% EtOH–$CHCl_3$, 912 mg of **3** was obtained after removal of the solvent. UV λ_{max}^{EtOH}: 280 nm. MS *m/z*: 472 $(M-15)^+$. NMR ($CDCl_3$): 8.79 (1H, s, H-8), 8.36 (1H, s, H-2), 8.10, 7.57 (5H, m, Ph), 6.11 (1H, br s, H-1′), 5.17 (2H, m, H-2′, 3′), 4.46 (2H, m, H-4′, 5′), 2.93 (2H, m, H-6′), 2.67 (3H, m, MeSO), 1.53, 1.38 (3H each, s, Me_2C).

9-(6-Deoxy-2,3-*O*-isopropylidene-6-phenylthio-β-D-allo- and α-L-talofuranosyl)adenine (4)——Compound **2** (1.15 g) in DMF (10 ml) was treated with PhSH (0.6 ml) and 1 N NaOMe in MeOH (5 ml) under stirring at 60 °C for 24 h. Further 1 N NaOMe (1 ml) was added and the mixture was stirred overnight at room temperature. After neutralization of the mixture by addition of AcOH, the solvent was removed *in vacuo* and the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was dried over Na_2SO_4, and concentrated, and the residue was applied to a column of silica gel (4 × 16 cm). The eluate with 4% EtOH–$CHCl_3$ was concentrated to leave **4** as a foam (820 mg, 70%). A part of **4** was crystallized from EtOH to give an analytical sample, mp 197—198 °C. UV $\lambda_{max}^{H_2O}$: 254.5 nm (ε, 17500), $\lambda_{max}^{0.5\,N\,HCl}$: 254 nm (ε, 17800). MS *m/z*: 414 $(M-15)^+$. NMR ($CDCl_3$): 8.26, 8.33 (1H, s each, H-8), 7.93 (1H, s, H-2), 7.6—7.2 (5H, PhS), 6.47 (2H, br s, H_2N-6), 5.95 (1H, d, H-1′, J=4.0 Hz), 5.18 (2H, m, H-2′, 3′), 4.84, 4.64 (1H, m, H-4′), 4.00 (1H, m, H-5′), 3.20 (2H, m, H-6′), 1.67, 1.39 (3H each, s, Me_2C). *Anal.* Calcd for $C_{20}H_{23}N_5O_4S$: C, 55.91; H, 5.41; N, 16.31; S, 7.46. Found: C, 55.75; H, 5.41; N, 16.38; S, 7.42.

9-(6-Deoxy-2,3-*O*-isopropylidene-β-D-allo- and α-L-talofuranosyl)adenine (5)——A mixture of **4** (254 mg) and trimethyl phosphite (1 ml) in acetonitrile (300 ml) was irradiated for 3 h. This reaction was repeated on the same scale. The reaction solutions were combined, the solvent was removed *in vacuo*, and the residue was subjected to PTLC. After development with $CHCl_3$–MeOH (7 : 1) three times, the fastest-migrating band was excised and extracted with 50% EtOH–$CHCl_3$. The solvent was removed to leave **5** (174 mg, 45.7%) as a foam. UV $\lambda_{max}^{H_2O}$: 259 nm. MS *m/z*: 321 (M^+). NMR ($CDCl_3$): 8.32 (1H, s, H-8), 8.10 (1H, br s, H-2), 7.00 (2H, br s, H_2N-6), 5.97 (1H, br d, H-1′), 5.4—4.8 (3H, m, H-2′, 3′, HO-5′), 4.4—3.6 (2H, m, H-4′, 5′), 1.64 (3H, s, one of Me_2C), 1.5—1.15 (6H, m, one of Me_2C and H-6′).

8,6′-Cyclo-9-(6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranosyl)adenine (6a)——The middle band on the above PTLC was excised, and extracted with 50% EtOH–$CHCl_3$, then the solvent was evaporated off to leave **6a** as a powder (75 mg, 19.8%). UV $\lambda_{max}^{H_2O}$: 261.5 nm. MS *m/z*: 319 (M^+), 304 $(M-15)^+$, 301 $(M-18)^+$.

8,6′-Cyclo-9-(6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranosyl)adenine (7a)——From the slowest-migrating band on the above PTLC **7a** (66 mg, 17.4%), similar work-up gave **7a** as a powder. UV $\lambda_{max}^{H_2O}$: 260.5 nm. MS *m/z*: 319 (M^+), 304 $(M-15)^+$, 301 $(M-18)^+$.

8,6′-Cyclo-9-(5-*O*-acetyl-6-deoxy-2,3-*O*-isopropylidene-L-talofuranosyl)adenine (6b)——Compound **6a** (55 mg)

Ac_2O (0.2 ml) were dissolved in pyridine (2 ml) and the mixture was kept at room temperature overnight. The solvent was removed *in vacuo* and the residue was subjected to PTLC ($CHCl_3$–MeOH: 8:1). The appropriate band was excised, and extracted with 50% EtOH–$CHCl_3$, and the extract was concentrated. The residue was crystallized from EtOH to give **6b** (27 mg, 43%), mp 239—241 °C. UV $\lambda_{max}^{H_2O}$: 261.5 nm (ε, 16600). MS *m/z*: 361 (M^+), 346 $(M-15)^+$, 301 $(M-60)^+$. CD nm in H_2O (θ): 261 (+15200), 232 (0), 218 (−16200). NMR (DMSO-d_6): 8.16 (1H, s, H-2), 7.34 (2H, br s, H_2N-6), 6.16 (1H, s, H-1′), 5.28 (1H, d, H-2′ or 3′, $J_{2',3'}=7.5$ Hz), 5.17 (1H, d, H-3′ or 2′), 4.97 (1H, m, H-5′), 4.63 (1H, d, H-4′, $J_{4',5'}=5.0$ Hz), 3.38 (2H, m, H-6′), 2.27 (3H, s, Ac), 1.56, 1.41 (3H each, s, Me_2C). *Anal.* Calcd for $C_{16}H_{19}N_5O_5 \cdot 1/3H_2O$: C, 52.29; H, 5.40; N, 19.06. Found: C, 52.04; H, 5.33; N, 18.87.

8,6′-Cyclo-9-(5-*O*-acetyl-6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranosyl)adenine (7b)——Compound **7a** (64 mg) was acetylated in the same manner as above to give **7b** (30 mg, 41%) in a crystalline form from acetone–diisopropyl ether, mp 182—185 °C. UV $\lambda_{max}^{H_2O}$: 260.5 nm (ε, 14800). MS *m/z*: 361 (M^+), 346 $(M-15)^+$, 301 $(M-60)^+$. CD nm in H_2O (θ): 261 (+16300), 231 (0), 217 (−25000). NMR (DMSO-d_6): 8.10 (1H, s, H-2), 7.24 (2H, br s, H_2N-6), 6.17 (1H, s, H-1′), 5.15 (3H, m, H-2′, 3′, 5′), 4.69 (1H, d, H-4′, $J_{4',5'}=4.5$ Hz), 3.36 (2H, m, H-6′), 1.95 (3H, s, Ac), 1.50, 1.35 (3H each, s, Me_2C). *Anal.* Calcd for $C_{16}H_{19}N_5O_5$: C, 53.18; H, 5.30; N, 19.38. Found: C, 53.13; H, 5.30; N, 19.12.

N^6-Benzoyl-9-(5,6-dideoxy-2,3-*O*-isopropylidene-β-D-ribo-hept-5-enofuranosiduronyl)adenine Ethyl Ester (8a)——A mixture of **1** (1.0 g) and ethoxycarbonylmethylenetriphenylphosphorane (1.5 g) in $CHCl_3$ (30 ml) was stirred overnight at room temperature. The solution was directly applied to a column of silica gel (3.3 × 17 cm). The eluate with 1% EtOH–$CHCl_3$ was concentrated to leave **8a** (1.11 g) as a foam. MS *m/z*: 479 (M^+). NMR ($CDCl_3$): 8.81 (1H, s, H-8), 8.17 (1H, s, H-2), 8.05, 7.66 (5H, m, Ph), 7.01 (1H, dd, H-5′, $J_{5',6'}=16.5$ Hz, $J_{4',5'}=5.5$ Hz), 6.24 (1H, d, H-1′, $J_{1',2'}=1.5$ Hz), 5.86 (1H, dd, H-6′, $J_{4',6'}=1.5$ Hz), 5.60 (1H, dd, H-2′, $J_{2',3'}=6.0$ Hz), 5.18 (1H, dd, H-3′, $J_{3',4'}=3.0$ Hz), 4.86 (1H, m, H-4′), 4.14 (2H, q, $CH_3C\underline{H}_2$, $J=7.0$ Hz), 1.63, 1.41 (3H each, s, Me_2C), 1.22 (3H, t, $C\underline{H}_3CH_2$).

9-(5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-ribo-hept-5-enofuranosiduronyl)adenine Ethyl Ester (8b)——2′,3′-*O*-Isopropylideneadenosine (1.7 g) was converted to the 5′-aldehyde by the reported procedure.[11] This was dissolved in DMSO (20 ml), ethoxycarbonylmethylenetriphenylphosphorane (2.12 g) was added and the mixture was kept overnight at room temperature. The solvent was removed *in vacuo* and the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was dried over Na_2SO_4 and concentrated. The residue was taken up in $CHCl_3$ and applied to a column of silica gel (3.4 × 12.5 cm). The eluate with 4% EtOH–$CHCl_3$ was concentrated and the residue was crystallized from EtOH to give **8b** (1.2 g, 57.7%), mp 104—106 °C. MS *m/z*: 375 (M^+). IR (Nujol): 1710 cm^{-1} ($\nu_{C=O}$). NMR of dried unsolvated sample ($CDCl_3$): 8.38 (1H, s, H-8), 7.96 (1H, s, H-2), 7.04 (1H, dd, H-5′, $J_{5',6'}=16.5$ Hz, $J_{4',5'}=5.5$ Hz), 6.37 (2H, br s, H_2N-6), 6.21 (1H, d, H-1′, $J_{1',2'}=1.5$ Hz), 5.84 (1H, dd, H-6′, $J_{4',6'}=1.5$ Hz), 5.63 (1H, dd, H-2′, $J_{2',3'}=6.0$ Hz), 5.19 (1H, dd, H-3′, $J_{3',4'}=3.5$ Hz), 4.86 (1H, m, H-4′), 4.16 (2H, q, $CH_3C\underline{H}_2$, $J=7.0$ Hz), 1.64, 1.41 (3H each, s, Me_2C), 1.23 (3H, t, $C\underline{H}_3CH_2$). *Anal.* Calcd for $C_{17}H_{21}N_5O_5 \cdot 1/2H_2O$: C, 54.24; H, 6.09; N, 17.58. Found: C, 54.32; H, 6.01; N, 17.75.

9-(5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-ribo-heptofuranosiduronyl)adenine Ethyl Ester (8c)——A mixture of **8a** (1.97 g), LiCl (1.7 g), and $NaBH_4$ (570 mg) in EtOH (100 ml) was stirred at room temperature for 34 h. The solvent was removed *in vacuo*, the residue was taken up in $CHCl_3$, the insoluble materal was filtered off, and the filtrate was applied to a column of silica gel (2.6 × 23 cm). The eluate with 4% EtOH–$CHCl_3$ was concentrated to leave **8c** (876 mg, 56%) as a foam. High-resolution MS *m/z*: 377.16882 (Calcd for $C_{17}H_{23}N_5O_5$: 377.16982). IR (neat): 1710 cm^{-1} ($\nu_{C=O}$). NMR ($CDCl_3$): 8.42 (1H, s, H-8), 7.97 (1H, s, H-2), 6.51 (2H, br s, H_2N-6), 6.11, (1H, d, H-1′, $J_{1',2'}=2.5$ Hz), 5.55 (1H, dd, H-2′, $J_{2',3'}=6.5$ Hz), 4.93 (1H, dd, H-3′, $J_{3',4'}=4.5$ Hz), 4.25 (1H, m, H-4′), 4.12 (2H, q, $CH_3C\underline{H}_2$, $J=7.0$ Hz), 2.6—1.8 (4H, m, H-5′, 6′), 1.61, 1.40 (3H each, s, Me_2C), 1.20 (3H, t, $C\underline{H}_3CH_2$). The eluate with 15% EtOH–$CHCl_3$ from the above column provided **9a** (143 mg, 13.5%) as a foam.

9-(5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-ribo-heptofuranosyl)adenine (9a)——a) A mixture of **8b** (2.72 g), LiCl (4.54 g) and $NaBH_4$ (4.10 g) in EtOH (20 ml) was stirred at room temperature for 4 d. The solvent was removed, the residue was taken up in $CHCl_3$, the insoluble material was filtered off, and the filtrate was applied to a column of silica gel. The eluate with 4% EtOH–$CHCl_3$ provided **9a** (2.40 g) after removal of the solvent. MS *m/z*: 335 (M^+). NMR ($CDCl_3$): 8.37 (1H, s, H-8), 7.96 (1H, s, H-2), 6.41 (2H, br s, H_2N-6), 6.09 (1H, d, H-1′, $J_{1',2'}=2.0$ Hz), 5.53 (1H, dd, H-2′, $J_{2',3'}=6.0$ Hz), 4.88 (1H, dd, H-3′, $J_{3',4'}=4.0$ Hz), 4.26 (1H, m, H-4′), 3.62 (2H, m, H-5′), 3.18 (2H, br s, H-7′), 1.72 (2H, m, H-6′), 1.61, 1.38 (3H each, s, Me_2C).

b) A mixture of **8c** (759 mg), LiCl (424 mg) and $NaBH_4$ (378 mg) in EtOH (40 ml) was stirred at room temperature for 6 d. **9a** (445 mg, 66%) was obtained by work-up as above.

c) A mixture of **8a** (300 mg) and $NaBH_4$ (300 mg) was stirred in EtOH (20 ml) for 4 d, and **9a** (120 mg, 57%) was obtained work-up as described above.

9-(5,6-Dideoxy-β-D-ribo-heptofuranosyl)adenine (9b)——Compound **9a** (280 mg) was treated with 80% trifluoroacetic acid (5 ml) for 30 min at room temperature. The solvent was evaporated off, and co-evaporation with aqueous EtOH was repeated several times. The residue was crystallized from H_2O to give **9b** (200 mg), mp 179—180 °C (lit.,[10] 179—180 °C). The physical data of **9b** were consistent with those reported.[10]

9-(5,6,7-Trideoxy-2,3-*O*-isopropylidene-7-phenylthio-β-D-ribo-heptofuranosyl)adenine (10)——Tosyl chloride (820 mg) was added to a solution of **9a** (1.20 g) in anhydrous pyridine (20 ml) under stirring at 0 °C for 20 min. The

mixture was kept at −20 °C overnight, then H_2O (0.1 ml) was added and the solvent was removed *in vacuo* at below 35 °C. The residue was partitioned between AcOEt and H_2O. The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. A mixture of Na (100 mg) and PhSH (0.55 ml) in liq. NH_3 (50 ml) was added to the above residue at −35 °C, and the whole was kept at room temperature until the NH_3 had vaporized. EtOH was added to the residue, the insoluble material was filtered off, and the filtrate was evaporated. The residue was taken up in $CHCl_3$ and applied to a column of silica gel (3.5 × 10 cm). The eluate with 8% EtOH–$CHCl_3$ was concentrated to leave **10** (1.18 g, 77%) as a foam. UV $\lambda_{max}^{H_2O}$: 253 nm. High-resolution MS *m/z*: 427.16538 (Calcd for $C_{21}H_{25}N_5O_3S$: 427.16778). NMR ($CDCl_3$): 8.28 (1H, s, H-8), 7.84 (1H, s, H-2), 7.17 (5H, br s, PhS), 5.97 (1H, d, H-1′, $J_{1',2'}$ = 1.5 Hz), 5.58 (1H, dd, H-2′, $J_{2',3'}$ = 6.0 Hz), 4.86 (1H, m, H-3′), 4.09 (1H, m, H-4′), 2.80 (2H, m, H-7′), 1.70 (4H, m, H-5′, 6′), 1.53, 1.32 (3H each, s, Me_2C).

9-(5,6,7-Trideoxy-2,3-*O*-isopropylidene-β-D-ribo-heptofuranosyl)adenine (11)——A mixture of **10** (340 mg) and trimethyl phosphite (1.0 ml) in acetonitrile (300 ml) was irradiated for 2 h. The solvent was removed *in vacuo*, the residue was taken up in $CHCl_3$, and the solution was subjected to PTLC (developed with $CHCl_3$–MeOH, 7:1). The appropriate band was excised and eluted with 50% EtOH–$CHCl_3$. The solvent was removed *in vacuo* and the residue was crystallized from diisopropyl ether to give **11** (173 mg, 67%). UV $\lambda_{max}^{H_2O}$: 258 nm. High-resolution MS *m/z*: 319.16365 (Calcd for $C_{15}H_{21}N_5O_3$: 319.16435). MS *m/z*: 319 (M^+), 317, 304 $(M-15)^+$, 302, 177, 163, 149, 136 $(B+2H)^+$, 135 $(B+H)^+$, 108. NMR (CCl_4): 8.27 (1H, s, H-8), 7.91 (1H, s, H-2), 7.32 (2H, br s, H_2N-6), 6.02 (1H, br d, H-1′), 5.60 (1H, dd, H-2′), 4.88 (1H, m, H-3′), 4.11 (1H, m, H-4′), 5.40 (2H, br t, H-5′), 1.56 (5H, br s, H-6′ and one of Me_2C), 1.34 (3H, s, one of Me_2C), 0.95 (3H, br t, H-7′).

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