SYNTHESIS OF 3'-AMINO-3'-DEOXYADENOSINE FROM LEVOGLUCOSENONE

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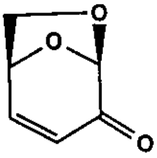
Abstract-----A synthesis of 3'-amino-3'-deoxyadenosine (**2**) was developed by utilizing levoglucosenone (**1**) as a starting material through regio- and stereoselective *cis*-oxyamination of the carbon-carbon double bond.

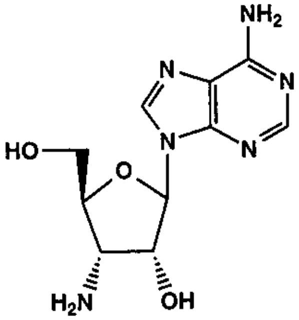
Levoglucosenone [1,6-anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose (**1**)][1] is widely known as a pyrolytic product of cellulose. It is a useful chiral source for synthesizing natural products[2] because of its highly functionalized structure which contains useful one chiral center. For several years, we have focused our attention mainly on its utilization for the synthesis of a variety of useful compounds as a chiral auxiliary.[3] Attention is now being directed to new applications for synthesizing this nucleoside derivative.

3'-Amino-3'-deoxyadenosine (**2**) was isolated from the microbial culture filtrates,[4-7] which inhibited the activity of protein biosynthesis[8] and showed remarkable antibiotic activity.[7,8] On the other hand, it was also reported that the 5'-triphosphate of 3'-amino-3'-deoxyadenosine (**2**) effectively inhibited the DNA-dependent RNA polymerase by being incorporated into the 3' end of the growing RNA chain.[9-11] Because of the interesting bioactivity of 3'-amino-3'-deoxyadenosine (**2**), there have been several reports about the synthesis of **2** to date.[12-19] Described here is a new approach to synthesize 3'-amino-3'-deoxyadenosine (**2**) with emphasis on the versatility of levoglucosenone (**1**) (Figure 1).

A practical synthesis is shown in Scheme 1. Compound (**3**) was easily prepared from levoglucosenone (**1**) in 2 steps by the reported procedure.[2,3] The oxyamination of the carbon-carbon double bond of **3** with OsO_4 and t-butyl *N*-chloro-*N*-sodiocarbamate under the Sharpless condition[20] afforded compound (**4**) as a single



1



2

Figure 1

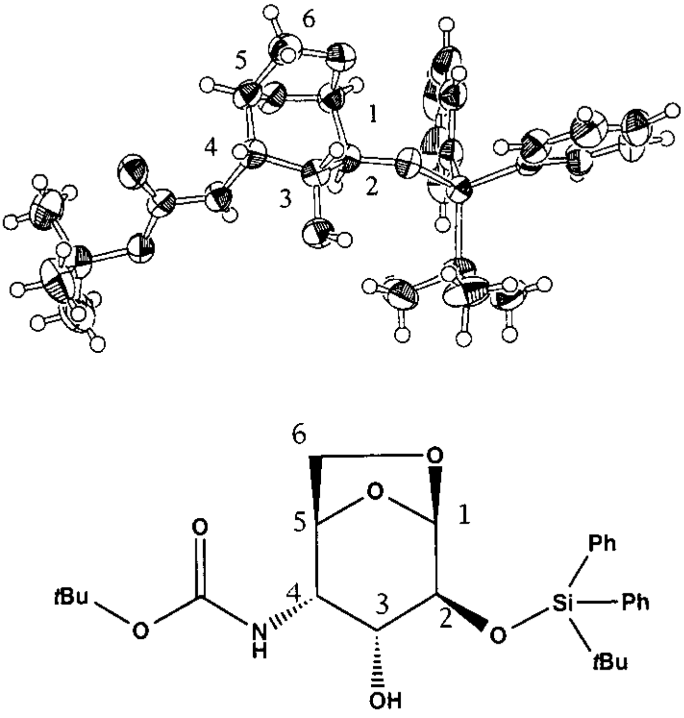
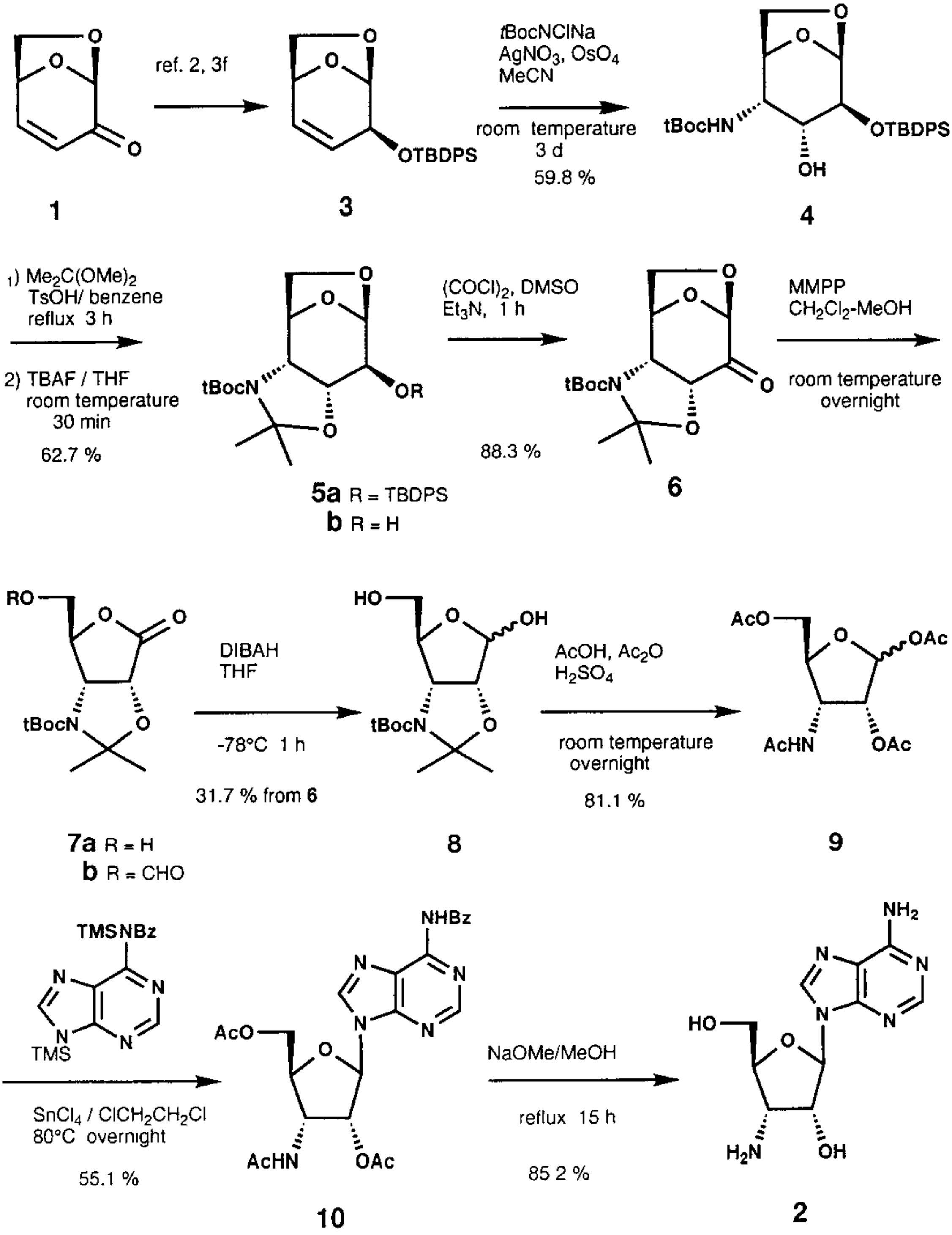


Figure 2 An ORTEP drawing of **4**.


1
ref. 2, 3f
3
OTBDPS
tBocNClNa
AgNO3, OsO4
MeCN
room temperature
3 d
59.8 %
4
tBocHN
OH
1) Me2C(OMe)2
TsOH/ benzene
reflux 3 h
2) TBAF / THF
room temperature
30 min
62.7 %
tBocN
OR
5a R = TBDPS
b R = H
(COCl)2, DMSO
Et3N, 1 h
88.3 %
6
MMPP
CH2Cl2-MeOH
room temperature
overnight
RO
7a R = H
b R = CHO
DIBAH
THF
-78°C 1 h
31.7 % from 6
HO
8
AcOH, Ac2O
H2SO4
room temperature
overnight
81.1 %
AcO
OAc
AcHN
9
TMSNBz
TMS
SnCl4 / ClCH2CH2Cl
80°C overnight
55.1 %
NHBz
10
NaOMe/MeOH
reflux 15 h
85 2 %
NH2
H2N
2

Scheme 1

isolable isomer in 59.8 % yield. The structure of **4** was confirmed by X-ray diffraction analysis. Good crystals of **4** were obtained after purification and they were submitted for X-ray analysis. The ORTEP view of **4** is shown in Figure 2. It clearly indicates that the amino and hydroxy groups are introduced with high regio- and stereoselectivities in the oxyamination of **3**. The 3,4-*O*,*N*-isopropylidene derivative (**5a**) was obtained by the reaction of **4** and 2,2-dimethoxypropane with *p*-toluenesulfonic acid. Treatment of **5a** with tetrabutylammonium fluoride gave the alcohol (**5b**) in 62.7 % yield. The oxidation of **5b** with oxalyl chloride and dimethyl sulfoxide under the Swern condition[21] afforded **6** in 88.3 % yield. Based on the studies of our group, it had been found that the Baeyer-Villiger oxidation was effective for the transformation of the levoglucosenone skeleton to the γ-lactone.[3] In this case, **7a** and **7b** were effectively obtained by the Baeyer-Villiger oxidation of **6** with monoperoxyphthalic acid magnesium salt. Furthermore, both **7a** and **7b** were converted to **8** by the reduction with diisobutylaluminium hydride. The acylation of **8** with acetic acid, acetic anhydride, and sulfuric acid as a catalyst, afforded **9** directly in 81.1 % yield. Tetraacetylaminoribofranose (**9**) was a mixture of the α- and β- forms, however, it was not necessary to separate their anomers for subsequent conversion into nucleosides by reaction with the adenine derivative. The coupling reaction of **9** and *N*^{6}-benzoyl-bis(trimethylsilyl)adenine was performed in the presence of $SnCl_4$/1,2-dichloroethane at 80°C[19] to afford **10** as a single isomer in 55.1 % yield. After deprotection with methanolic sodium methoxide it afforded 3'-amino-3'-deoxyadenosine (**2**) in 85.2 % yield. The physical data of our synthetic **2** were identical with those reported.[15,16]

In conclusion, a synthesis of 3'-amino-3'-deoxyadenosine (**2**) was achieved starting from levoglucosenone (**1**) in 11 steps and the overall yield was 3.3 %.

EXPERIMENTAL

The ir spectra were measured on a Jasco FT/IR-5000 photospectrometer. ^{1}H-Nmr spectra were recorded at 300 MHz on a Brucker AC-300P spectrometer. Optical rotations were measured on a Jasco DIP-370 polarimeter. Elemental analysis was performed on a Yanagimoto CHN recorder MT-3. Melting points were measured with a Yanagimoto melting point apparatus.

1,6-Anhydro-2-*t*-butyldiphenylsilyl-4-deoxy-4-*t*-butylcarbamide-β-D-altropyranose (4).

To a solution of *t*-butyl carbamate (3.51 g, 30.0 mmol) in methanol (20.0 ml), *t*-butyl hypochlorite (3.39 ml, 30.0 mmol) was carefully added dropwise at 0°C, after 15 min, a methanolic solution (40.0 ml) of sodium hydroxide (1.26 g, 31.5 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed to give the crude *t*-butyl *N*-chloro-*N*-sodiocarbamate as a white solid. Addition of acetonitrile (80.0 ml) and $AgNO_3$ (5.21 g, 30.0 mmol) resulted in the gradual appearance of a brown suspension. The reaction mixture was stirred at room temperature for 30 min, and then 1,6-anhydro-2-*t*-butyldiphenylsilyl-3,4-dideoxy-β-D-threo-hexo-3-enopyranose (3)[3f] (7.21 g, 20.0 mmol), 1M OsO_4/*t*-butyl alcohol (2.0 ml, 2.0 mmol), and water (1.7 ml) were added. The reaction suspension was stirred at room temperature for 3 d. Filtration of the reaction mixture through Celite gave a yellow-brown solution. The filtrate was refluxed for 3 h with 5% aqueous sodium sulfite (50.0 ml). The resulting mixture was concentrated and extracted with dichloromethane three times. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane:ethyl acetate=3:1). Furthermore, crystallization from the mixture of *n*-hexane and ethyl acetate afforded **4** (5.87 g, 59.8 % yield); mp 170-171.5°C; $[\alpha]^{25}_D$ -54.3° (c 0.56, $CHCl_3$); ^1H-nmr ($CDCl_3$) δ: 7.75-7.70 (4H, m, Ar-H), 7.48-7.36 (6H, m, Ar-H), 5.01 (1H, d, *J*=1.6 Hz, H-1), 4.78 (1H, br d, N-H), 4.52 (1H, m, H-5), 4.05 (1H, m, H-3), 3.98(1H, m, H-4), 3.84-3.73 (2H, m, H-6), 3.49 (1H, dd, *J*=8.2, 1.6 Hz, H-2), 2.07 (1H, br d, O-H), 1.42 (9H, s, *t*-Bu), 1.09 (9H, s, *t*-Bu); ir (KBr) 1700 (s), 1508 (s), 1429 (m), 1367 (m), 1168 (m), 1114 (s), 996 (m), 859 (m), 822 (m), 704 (m); Anal. Calcd for $C_{27}H_{37}NO_6Si$: C, 64.91; H, 7.44; N, 2.80. Found: C, 64.80; H, 7.43; N, 2.86.

1,6-Anhydro-4-deoxy-3,4-isopropylidene-4-*t*-butylcarbamide-β-D-altropyranose (5b).

To a solution of **4** (2.4 g, 5.0 mmol) in benzene (30.0 ml), 2,2-dimethoxypropane (20.0 ml, 162.7 mmol) and *p*-toluenesulfonic acid (0.1 g) as a catalyst were added, and the mixture was refluxed for 3 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted with dichloromethane three times. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was solved in 30.0 ml of tetrahydrofuran (THF). Further, 1.0 M tetrabutylammonium fluoride/THF (6.0 ml, 6.0 mmol) was added and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted with dichloromethane three times. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane:ethyl acetate=2:1) to give **5b** (0.94 g, 62.7 % yield); mp 103-105°C; $[\alpha]^{25}_D$ -218.9° (c 0.52, $CHCl_3$); ^1H-nmr ($CDCl_3$) δ: 5.53 (1H, d, *J*=3.8 Hz, H-1), 4.92 (1H, m, H-5), 4.16 (1H, dd, *J*=7.3, 1.9

Hz, H-3), 3.97-3.71 (4H, m, H-2,4,6), 2.48 (1H, d, *J*=9.2 Hz, O-H), 1.72-1.41 (6H, m, Me), 1.49 (9H, s, *t*-Bu); ir (KBr) 3460 (br), 2978 (m), 1694 (s), 1394 (s), 1369 (s), 1249 (m), 1158 (s), 1077 (s), 977 (m), 890 (m), 774 (m); Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.81; H, 7.67; N, 4.64. Found: C, 55.64; H, 7.54; N, 4.75.

1,6-Anhydro-4-deoxy-3,4-isopropylidene-4-*t*-butylcarbamide-β-D-glycero-hexopyrano-2-ulose (6).

A solution of dimethyl sulfoxide (0.64 g, 8.2 mmol) in dry dichloromethane (4.0 ml) was slowly added dropwise to a solution of oxalyl chloride (0.46 g, 3.6 mmol) in dry dichloromethane (8.0 ml) at -60°C and the mixture was stirred at the same temperature for 15 min. Further, **5b** (0.45 g, 1.5 mmol) in dry dichloromethane (8.0 ml) was added dropwise to this mixture, stirring of the reaction mixture was continued for 40 min. After treatment of the mixture with triethylamine (2.3 g, 22.8 mmol), the reaction temperature was raised to 25°C. The reaction mixture was poured into water and dichloromethane, and extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (n-hexane:ethyl acetate=3:1) to give **6** (0.40 g, 88.3 % yield); mp 159-160.5°C; $[\alpha]^{25}_D$ -125.5° (c 0.51, $CHCl_3$); ^{1}H-nmr ($CDCl_3$) δ: 5.28 (1H, s, H-1), 5.50 (1H, br s, H-5), 4.58 (1H, d, *J*=7.8 Hz, H-3), 4.30 (1H, d, *J*=7.8 Hz, H-4), 3.93 (1H, s, H-6), 3.91 (1H, s, H-6), 1.72-1.40 (6H, m, Me), 1.53 (9H, s, *t*-Bu); ir (KBr) 2976 (m), 1746 (s), 1694 (s), 1396 (m), 1371 (s), 1238 (m), 1174 (m), 1147 (m), 1112 (m), 1093 (m), 969 (s), 872 (m), 808 (m), 756 (m); Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.21; H, 7.05; N, 4.68. Found: C, 55.97; H, 6.93; N, 4.70.

3-Deoxy-2,3-isopropylidene-3-*t*-butylcarbamide-D-ribofuranose (8).

A solution of monoperoxyphthalic acid magnesium salt hexahydrate (0.59 g, 1.2 mmol) in methanol (4.0 ml) was added to **6** (0.49 g, 1.6 mmol) in dichloromethane (2.0 ml) at 0°C. The reaction temperature was raised to 25°C and the mixture was stirred overnight. After removing the precipitate by filtration, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane:ethyl acetate=1:1) to give a mixture of **7a** and **7b** (0.25 g). Under an argon atmosphere, 1.5 M diisobutylaluminium hydride/THF solution (3.5 ml, 5.3 mmol) was slowly added dropwise to this mixture (0.25 g) in dry THF (35.0 ml) at -78°C and the reaction solution was stirred at the same temperature for 1 h. A small amount of water was added and the temperature was raised to 25°C. Further, a large amount of THF was added and after drying the mixture over anhydrous magnesium sulfate, the precipitate was extracted with

THF and chloroform several times. The filtrate and extract were combined and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane:ethyl acetate=1:1) to give **8** (0.15 g, 31.7 % yield) as a colorless oil; $[\alpha]^{25}_{D}$ -52.7° (c 0.27, $CHCl_3$); ^{1}H-nmr ($CDCl_3$) δ: 5.44, 5.40 (0.5H, s, H-1a, b), 4.58-4.45 (2H, m, H-2,4), 4.33 (1H, m, H-3), 3.96-3.71 (2H, m, H-5), 1.69 (1.5H, s, Me), 1.63 (1.5H, s, Me), 1.59 (1.5H, s, Me), 1.48 (9H, s, *t*-Bu), 1.45 (1.5H, s, Me); ir (film) 3396 (br), 2980 (m), 2940 (m), 1707 (s), 1688 (s), 1396 (s), 1369 (s), 1257 (m), 1160 (m), 1077 (s); Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.98; H, 7.99; N, 4.84. Found: C, 53.92; H, 7.73; N, 4.86.

3-Amino-3-deoxy-1,2,3,5-tetraacetyl-D-ribofuranose (9).

Sulfuric acid (25 µl) was added to a solution of **8** (100 mg, 0.35 mmol) in acetic acid (3.0 ml) and acetic anhydride (1.3 ml, 13.8 mmol) at 0°C. After raising the temperature from 0 to 25°C, the reaction was continued overnight. The mixture was poured into saturated aqueous sodium bicarbonate (in the case of pH <7, addition of sodium bicarbonate is necessary) and extracted with chloroform three times. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate) to give **9** (89 mg, 81.1 % yield) as a colorless oil; $[\alpha]^{25}_{D}$ 46.1° (c 0.59 $CHCl_3$); ^{1}H-nmr ($CDCl_3$) δ: 6.44 (0.22H, d, *J*=4.3 Hz, H-1a), 6.12 (0.78H, s, H-b), 5.96 (0.22H, d, *J*=7.7 Hz, N-Ha), 5.65 (0.78H, d, *J*=8.9 Hz, N-Hb), 5.26 (0.22H, dd, *J*=7.7, 4.3 Hz, H-2a), 5.08 (0.78H, d, *J*=4.9 Hz, H-2b), 4.89 (0.78H, ddd, *J*=8.9, 8.9, 4.6 Hz, H-3b), 4.63 (0.22H, ddd, *J*=7.9, 7.9, 3.9 Hz, H-3a), 4.11-4.05 (3H, m, H-4,5), 2.24-1.98 (12H, m, $COCH_3$); ir (film) 1746 (s), 1663 (m), 1543 (m), 1375 (m), 1224 (s), 1027 (m); hrms Calcd for $C_{13}H_{20}NO_8$ (M^++1): 318.11889. Found: 318.122103.

9-(3'-Amino-3'-deoxy-2',3',5'-triacetyl-D-ribofuranosyl)-*N*^{6}-benzoyladenine (10).

Under an argon atmosphere, 1,1,1,3,3,3-hexamethyldisilazane (8.5 ml, 40.3 mmol)and dry pyridine (1.9 ml, 23.5 mmol) were added to *N*^{6}-benzoyladenine (263 mg, 1.10 mmol) and the mixture was refluxed for 5 h. The mixture was cooled and concentrated *in vacuo* for 3 h. A solution of **9** (225 mg. 0.71 mmol) in dry 1,2-dichloroethane (25.0 ml) was added to the residue at 25°C. Further. 1M $SnCl_4$/dichloromethane (1.8 ml, 1.80 mmol) was slowly added dropwise, and the mixture was stirred at 80°C overnight. The mixture was poured into saturated aqueous sodium bicarbonate and extracted with chloroform-methanol (10:1) three times. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform:methanol=15:1) and

NH-silica gel (chloroform:methanol=20:1) to give **10** (194 mg, 55.1 % yield) as a white solid; $[\alpha]^{25}_{D}$ -4.7° (c 0.21 MeOH); ^{1}H-nmr ($CDCl_3$) δ: 8.98 (1H, s, N-H), 8.85 (1H, s, H-8), 8.16 (1H, s, H-2), 8.03 (2H, d, *J*=7.0 Hz, Ar-H), 7.63-7.50 (3H, m, Ar-H), 6.11 (1H, d, *J*=1.7 Hz, H-1'), 5.76 (1H, dd, *J*=6.1, 1.8 Hz, H-2'), 5.60 (1H, d, *J*=8.8 Hz, N-H), 5.42 (1H, m, H-3'), 4.55 (1H, d, *J*=10.1 Hz, H-5'), 4.37-4.23 (2H, m, H-4',5'), 2.23 (3H, s, $COCH_3$), 2.08 (6H, s, $COCH_3$), hrms Calcd for $C_{23}H_{25}N_6O_7$ (M^{+}+1): 497.17847. Found: 497.18155.

3'-Amino-3'-deoxyadenosine (2).

A methanolic solution (1.6 ml) of **10** (20.2 mg, 0.04 mmol) containing 4.1 N methanolic NaOMe solution (0.3 ml) was refluxed for 15 h. The mixture was purified by column chromatography on iatrobeads (chloroform:methanol:25 % aq. NH_3=30:10:1) to give **2** (9.2 mg, 85.2 % yield); mp 265-268°C (decomp.); $[\alpha]^{25}_{D}$ -32.9° (c 0.24, 0.1N HCl) [lit.,[15] mp 264-266°C (decomp.), $[\alpha]^{20}_{D}$ -37°(0.1N HCl), lit.,[16] mp 270-272°C (decomp.), $[\alpha]^{25}_{D}$ -35° (0.1N HCl)]; ^{1}H-nmr (D_2O) δ: 8.21 (1H, s, H-8), 8.10 (1H, s, H-2), 5.98 (1H, d, *J*=3.2 Hz, H-1'), 4.51 (1H, dd, *J*=5.6, 3.2 Hz, H-2'), 3.97 (1H, m, H-4'), 3.84 (1H, dd, *J*=12.9, 2.3 Hz, H-5'), 3.69 (1H, dd, *J*=13.0, 2.3 Hz, H-5'), 3.52 (1H, dd, *J*=7.2, 5.6 Hz, H-3'), hrms Calcd for $C_{12}H_{15}N_6O_3$ (M^{+}+1): 267.12056. Found: 267.12359.

Table 1. Summary of Crystal Data and Data Collection Parameters

crystal system	orthorhombic
space group	$P2_12_12_1$
crystal dimension, mm^3	0.20 x 0.20 x 0.15
lattice parameter	a=11.2398 Å
	b=25.5606 Å
	c=9.5142 Å
	V=2733.3921 Å^3
Z value	4
d(calcd.)	1.214 g cm^{-3}
diffractometer	MXC18
monochrometer	graphite
radiation	Cu Ka
scan type	w / 2q
2q max	128.7 °
No. of reflection measured	total: 2746
	unique: 2646
final R	0.037
final R_w	0.043

X-Ray Diffraction of 4.

The crystal was mounted on a glass fiber. The cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using a setting angle of 2 carefully centered reflections. Intensities was collected on an MXC1 diffractometer at room temperature. The data was corrected for lorentz and polarization effects. The crystal data and data collection parameters are summarized in Table 1.

The structure was solved by the direct method using MITHRIL84 and expanded by Fourier Techniques using DIRDIF92. Full-matrix least-squares refinement included anisotropic thermal parameters for non-H atoms as well as isotropic thermal parameters for H atoms. Convergence was reached at R=0.037 and R_W=0.043.

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