A Convenient and Versatile Synthesis of 2' (and 3')-Amino (and azido)-2' (and 3')-deoxyadenosine as Diverse Synthetic Precursors of Cyclic Adenosine Diphosphate Ribose (cADPR)

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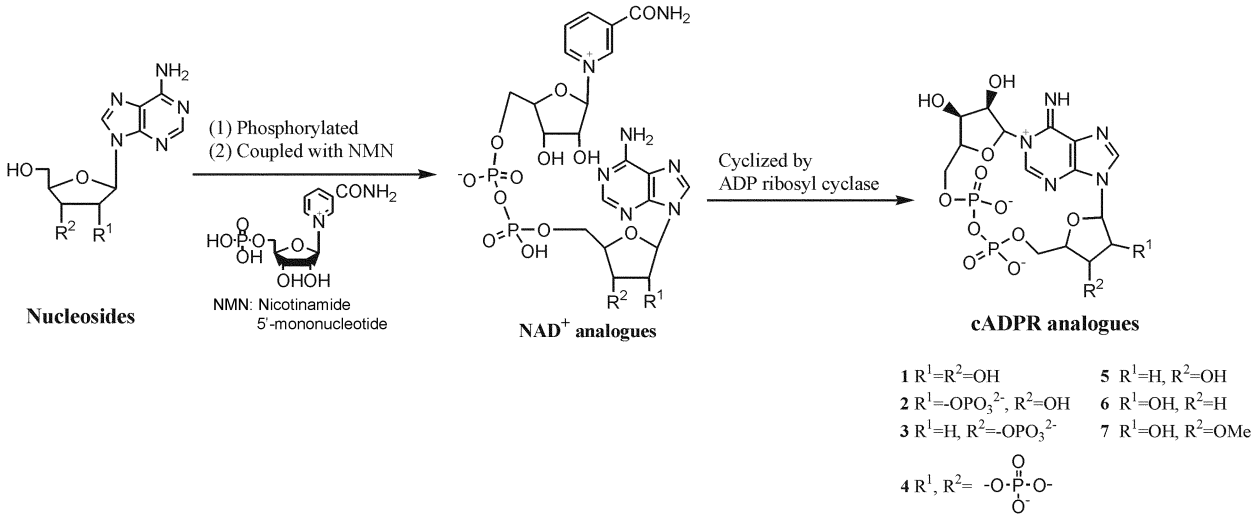
As diverse synthetic precursors of cyclic adenosine diphosphate ribose (cADPR), several adenosine derivatives in which azido or amino group is introduced at 2'- or 3'-position of the sugar moiety of adenosine were prepared from readily available adenosine via conventional protocols. These synthetic sequence employs very efficient reactions conditions that proceed at or below ambient temperature with actual yields of >80% for each individual step.

Key Words : Cyclic adenosine diphosphate ribose (cADPR), 2' (and 3')-Amino (and azido)- 2' (and 3')-deoxy-adenosine

Introduction

Cyclic adenosine diphosphate ribose (cADPR, **1**) is a naturally occurring cyclic nucleotide and a general mediator involved in Ca^{2+} signaling in a variety of mammalian and invertebrate tissues.[1] Also, recent studies reveal the involvement of cADPR in glucose-dependant insulin secretion in pancreatic cells, proliferation of human T-lymphocytes, and arrhythmogenic oscillations of intracelluar Ca^{2+} in heart cells etc.[2-4] Those findings suggest the therapeutic potential of cADPR itself or its derivatives against diabetes, immune and cardiovascular diseases. Therefore, considerable progress has been made in the synthesis of cADPR analogues and the evaluation of their biological effects. In general, the synthetic strategy to prepare cADPR analogues includes intracyclization of NAD^+ analogues (Figure 1), which can be prepared from the appropriately designed nucleosides/nucleotides.[5] However, the reported precedents have limitation for the facile preparation of various nucleosides/nucleotides from readily available starting materials.[1,5] To our knowledge, analogues of cADPR have been prepared from commercially available nucleosides/nucleotides as starting materials in most cases. So, there are still urgent needs for the development of new and diverse nucleosides with more convenient chemical routes.

Most of structural modifications occurred on the adenosine moiety of cADPR, namely, purine and sugar. In particular, a few previous researches show that the structural modification in sugar, especially at 2' and/or 3'-position gives rise to remarkable changes in their activities, namely, considerable



1 $R^1=R^2=OH$
2 $R^1=-OPO_3^{2-}$, $R^2=OH$
3 $R^1=H$, $R^2=-OPO_3^{2-}$
4 R^1, $R^2=$ -O-P(=O)(O⁻)-O-
5 $R^1=H$, $R^2=OH$
6 $R^1=OH$, $R^2=H$
7 $R^1=OH$, $R^2=OMe$

Figure 1

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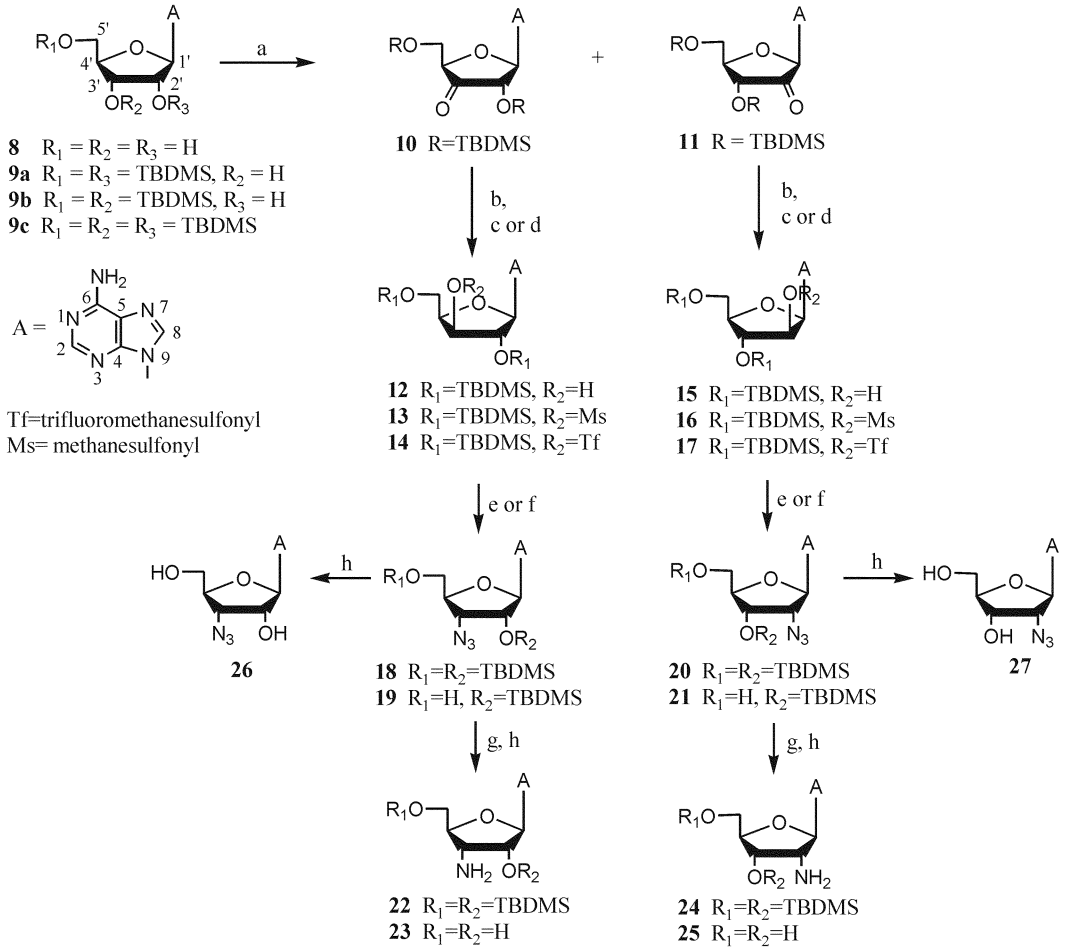

Scheme 1. (a) CrO_3/Py/Acetic anhydride, CH_2Cl_2, RT; (b) $NaBH_4$/Acetic acid, THF, 0 °C; (c) Methanesulfonyl chloride, DMAP, CH_2Cl_2, 0 °C; (d) Trifluorosulfonyl chloride, DMAP, CH_2Cl_2, 0 °C; (e) NaN_3, Li_2CO_3, DMF, 120 °C; (f) NaN_3, DMF, RT; (g) Pd/C, H_2, MeOH, RT; (h) NH_4F, MeOH, 60 °C.

change in agonistic activity (**2**, **5**, **6**), showing no activities (**3**, **4**), and even reversed activity (**7**). (Figure 1)[1a] As mentioned above, however, as the lack of sufficient analogues obtained to date, the relationship between the functionality at 2' /and or 3'-position in sugar moiety and their Ca^{2+} modulating capacities has not been fully understood.

In this point of view, as a part of our synthetic effort to synthesize nucleosides having diverse functionality at 2' or 3'-position of sugar moiety, we designed aminosugar (and azidosugar) nucleosides (**23**, **25**, **26** and **27**, Scheme 1) in which 2'- or 3'-hydroxy group in ribose moiety is replaced with primary amine group and azido group. Since amino group is similar to hydroxy group in size and in hydrogen-bonding character, and azido group shows interesting biological features when it is introduced to sugar moiety as shown in the example of AZT,[6] it is considered to be interesting to us to investigate the activity variation of cADPR with amine and azido functionality at sugar moiety. Although there are precedences for the preparation of 2' (and 3')-aminoadenosine analogues,[7-9] their synthetic routes are fairly laborious and furthermore each compound should be prepared in separate ways. So, our synthetic strategy was designed in a way that these target compounds (2' and 3'-substituted products) can be prepared very efficiently using the same reaction steps starting from the disilylated adenosine analogs (**9a** and **9b**) obtained simultaneously in first step (Scheme 1). We now describe the synthesis of 2' (and 3')-deoxy-2' (and 3')-azido-adenosine (**27**, **26**) and 2' (and 3')-deoxy-2' (and 3')-amino-adenosine (**25**, **23**) starting from adenosine in very efficient manner by employing conventional protocols with actual yields of >80% for each individual reaction steps (Scheme 1).

Results and Discussion

Treatment of adenosine with *tert*-butyldimethylsilyl (TBDMS) chloride gave silyl-protected compounds, 2',5'-bis-*O*-(*tert*-butyldimethylsilyl)adenosine (**9a**) and 3'5'-bis-*O*-(*tert*-butyldimethylsilyl)adenosine (**9b**) in 47% and 30% isolated yield, respectively, together with small amount of 2',3,5'-tris-*O*-(*tert*-butyldimethylsilyl)adenosine (**9c**).[10] Oxidation (chromium trioxide/pyridine/acetic anhydride) of these 2',5'- and 3',5'-*O*-TBDMS-protected adenosine gave the corresponding 3'-keto- and 2'-ketoadenosines (**10** and **11**) in about 90% yield.[11] These individual ketonucleotides are known to be useful intermediates for the synthesis of a

variety of sugar-modified nucleosides and have been employed to change configuration at C2' and C3' *via* oxidation-reduction sequence.[12] Although the oxidation of the protected alcohols **9a** and **9b** to their ketoadenosine **10** and **11**, occurred successfully eventually, the chemical properties of compound **11** deserve some mention. Thus, treatment of **9a** with the oxidizing agents gave ketoadenosine **10** very nicely with no incidence, which is easily identified by its clear TLC pattern.[11a] In the case of 2'-ketoadenosine (**11**), however, there were some problems in separation due to the broad TLC pattern (tailing), which caused difficulty in purification. The ^{1}H-NMR analysis of the crude compound **11** exhibited the line broadening and doubling of purine peaks, which is consistent with the results reported by F. Hansske *et al*.[11b] This is likely caused by the formation of Cr complex and its existence as equilibrium mixture of ketone and ketone hydrate.[10] In fact, isolated 2'-ketoadenosine **11** showed very low solubility in ethyl acetate and methylene chloride and the yield was not realized as reported. However, this low yield problem was overcome by using more polar elution solvent (EtOAc-MeOH = 9 : 1, v/v) during chromatography work, and the identity of 2'-ketoadenosine undefined on TLC was confirmed through consecutive reduction which gave arabinofuranosyl derivative (**15**). In other words, 2'-ketoadenosine **11** can be utilized directly for the next step without purification, although it seems to be impure by TLC after the oxidation.

2' (and 3')-Ketonucleosides **11** and **10** were converted to the corresponding arabino (**15**) and xylofuranosyl nucleoside (**12**) with high stereoselectivity according to the modified method of M. J. Robins.[11a] In original method, excess sodium triacetoxyborohydride was used rather than $NaBH_4$ as a reducing agent. However, it's not convenient to prepare sodium triacetoxyborohydride and a long reaction time (48 hours) and strict temperature (13 ^{o}C) control was required for their case. In contrast, in our modified method, THF was used as a reaction solvent in the preparation of sodium triacetoxyborohydride (generated in situ by adding excess AcOH to the suspension of $NaBH_4$ in THF at 0 ^{o}C) and reaction was performed at 0 ^{o}C. To our surprise, the reaction time became much more shorter (less than 4 hours) with the consistent high yields (> 90%).

Next we moved on to introduce azide group at 2' position of arabinofuranosyl nucleoside **15** and 3' position of xylofuranosyl nucleoside **12**. The first step to mesylate compounds **15** and **12** occurred with no incidence to produce compound **16** and **13** in 93% and 92% yield, respectively. Treatment of **16** and **13** with NaN_3 or LiN_3 according to known procedure,[6,13] however, produced the desired azido compound **20** and **18** in very poor yields (10-40%) along with 5'-deprotectd azido compounds **21** and **19** (6-15% yield). These problems, however, was easily overcome by utilizing triflate **17** and **14**. Thus, the azido group was quantitatively introduced into the 2' (and 3')-position of corresponding triflates (**17** and **14**) using NaN_3 at room temperature[14] to produce **20** and **18**.

With these silyl protected azide compounds **20** and **18** in hand, several chemical transformations to produce our key intermediates were carried out. First, simple treatment of **20** and **18** with NH_4F/MeOH at 60 ^{o}C gave silyl group-deprotected azido compounds **27** and **26** quantitatively.[15] Second, the azido group of compounds **20** and **18** was reduced with H_2 in MeOH in the presence of Pd/C without loss of the TBDMS protecting groups to produce silyl group-protected amino compounds **24** and **22** in 90% and 92% yield, respectively. Third, the silyl group of amino compounds **24** and **22** can be deprotected under the same condition to give silyl group-deprotected amino compounds **25** and **23** in 87% and 85% purified yield, respectively. The desilylation step is apparently occurred in two-steps on the analysis of TLC, and so the selective desilylation of our particular compounds is possible upon needed.

In summary, these convenient and efficient sequence for the preparation of adenosine analogues (**23**, **25**, **26**, **27**), which are crucial intermediate for the structural modification of cADPR, were described. In particular, the improvement in the reduction procedure using THF as a co-solvent for the preparation of xylo- and arbinofuranosyl nucleoside (**12** and **15**) is noticeable in terms of efficiency and convenience. More importantly, compared to other precedent procedures, our synthetic strategy is convenient and versatile as well, from the points of view that several target compounds can be prepared using same starting material via continuous and consecutive processes. With these compounds in hand, the synthetic work for the preparation of cADPR analogs and further modification at adenine moiety is now in progress.

Experimental Section

Melting points were recorded on electrothermal melting point apparatus and are uncorrected. Mass spectra were recorded on a JEOL JMS-DX 303 mass spectrometer (3 KV). ^{1}H-NMR and ^{13}C-NMR data were obtained from Jeol 400 MHz spectrometer and chemical shifts (δ) were reported in ppm in relation to tetramethylsilane (δ 0.00) and $CDCl_3$ (δ 77.0) for ^{1}H and ^{13}C NMR, respectively; J values are in hertz (Hz). Thin layer chromatography was performed on pre-coated silica gel 60 F-254 (layer thickness 0.2 mm, Merck). The Flash Column Chromatography was performed on Merck silica gel type 60 (230-400 mesh). Unless specified otherwise the solvent system for all chromatography was EtOAc/Hexane (7 : 3, v/v). The organic solvents and chemicals were obtained from Aldrich. Co. and purified by the appropriate methods before use.

Silylation of Adenosine. TBDMSCl (8.46 g, 56.13 mmol) was added to a suspension of **8** (5.0 g, 18.7 mmol) in pyridine (35 mL) and stirred at ambient temperature for 48 h under Ar atmosphere. The solvent was evaporated and the residue partitioned (ice-cold 5% HCl/H_2O//CH_2Cl_2). The organic phase was washed (saturated $NaHCO_3$/H_2O and brine), dried ($MgSO_4$), and evaporated. The white solid was suspended in EtOAc and applied to a column and separated by Yamazen MPLC system (flow rate: 20 mL/min, detected at 254 nm) to give 2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-

adenosine (**9a**, 47%), 3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-adenosine (**9b**, 30%), 2',3',5'-tris-*O*-(*tert*-butyldimethylsilyl)adenosine (**9c**, 4%) as white powders with expected spectral properties.[10]

9-[2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-1-β-D-erythropentofuran-3'-ulosyl]adenine (10). Procedure A. pyridine (2.5 mL, 30.7 mmol) and Ac_2O (1.45 mL, 15.4 mmol) were added consecutively to an ice-cold suspension of CrO_3 (1.54 g, 15.4 mmol) in CH_2Cl_2 (50 mL) and stirred until homogeneous (10-15 min) at ambient temperature under Ar atmosphere. A solution of **9a** (3.81 g, 7.67 mmol) in CH_2Cl_2 (10 mL) was added, stirring was continued for 2 h. The reaction mixture was poured into cold EtOAc (1 L) and filtered (glass microfiber filter, GF/A). The filtrate was concentrated and purification (short column chromatography, EtOAc) gave **10** (3.37 g, 89%) as a colorless powder with reported properties.[11]

9-[3',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-1-β-D-erythropentofuran-3'-ulosyl]adenine (11). Oxidation of **9b** (1.50 g, 3.02 mmol) by procedure **A** [CrO_3 (0.61 g, 6.04 mmol)/pyridine (0.98 mL, 12.1 mmol)/Ac_2O (0.57 mL, 6.04 mmol)/CH_2Cl_2 (25 mL)] gave **11** (1.32 g, 89%) as a pale yellow powder with reported properties.[11] The purification was performed on the short column chromatography eluted with EtOAc-MeOH (9 : 1).

9-[2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-1-β-D-xylofuranosyl]adenine (12). Procedure B. Ketone **10** (1.0 g, 2.03 mmol) was added to a mixture of $NaBH(OAc)_3$/THF/AcOH [generated in situ by addtion of AcOH (7 mL) to a suspension of $NaBH_4$ (0.92 g, 24.3 mmol) in THF (50 mL) and then stirred for 1.5 h at 0 °C under Ar atmosphere]. The reaction was stirred for 4 h at 0 °C, and volatiles were evaporated. The residue was partitioned (EtOAc/sat. aqueous $NaHCO_3$), and the aqueous layer was extracted with EtOAc. The combined organic phase was washed (H_2O, brine), dried over $MgSO_4$, filtered, and evaporated. The oily residue was applied to flash column chromatography to give **12** (0.90 g, 90%) as a colorless powder with reported properties.[11a]

9-[3',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-1-β-D-arabinofuranosyl]adenine (15). Treatment of ketone **11** (1.30 g, 2.63 mmol) by procedure **B** [$NaBH_4$ (1.20 g, 31.6 mmol) in THF (60 mL)/AcOH (9 mL)] gave **15** (1.02 g, 79%) as a colorless powder with reported properties.[11a]

9-[3'-*O*-(Trifluormethanesulfonyl)-2',5'-Bis-*O*-(*tert*-butyldimethylsilyl)-1-β-D-xylofuranosyl]adenine (14). Procedure C. To a solution of **12** (2.26 g, 4.56mmol) and DMAP (1.68 g, 13.68 mmol) in CH_2Cl_2 (15 mL) was added fresh trifluoromethanesulfonyl chloride (0.53 mL, 5.01 mmol) at 0 °C under Ar atmosphere. The reaction was stirred for 15 min at this temperature and then checked by TLC. A second portion of trifluoromethanesulfonyl chloride (0.1 mL, 0.94 mmol) was added and stirring was continued for 15 min at 0 °C. The reaction was partitioned (ice-cold 1% aqueous AcOH/CH_2Cl_2), and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was washed (ice-cold saturated aqueous $NaHCO_3$, ice-cold brine), dried over $MgSO_4$, filtered, and evaporated. Flash chromatography gave colorless powder of **13** (2.23 g, 78%): mp: 48-52 °C (softening); ^{1}H-NMR, $CDCl_3$ δ 8.20 (s, 1H, H8), 7.91 (s, 1H, H2), 6.43 (br, 2H, NH_2), 5.95 (d, 1H, J = 2.0 Hz, H1'), 5.01 (m, 1H, H2'), 4.82 (m, 1H, H3'), 4.42 (m, 1H, H4'), 3.99 (m, 2H, H5'a, H5'b), 0.79 (s, 9H, *t*-butyl), 0.75 (s, 9H, *t*-butyl) 0.00 (s, 6H, methyl × 2), -0.02 (s, 3H, methyl), -0.10 (s, 3H, methyl); ^{13}C-NMR δ 155.63, 152.93, 149.48, 137.79, 119.60, 89.74, 88.38, 80.46, 79.06, 60.07, 25.46, 25.33, 18.24, 17.65, -5.16, -5.34, -5.59, -5.60.

9-[2'-*O*-(Trifluormethanesulfonyl)-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-1-β-D-arabinofuranosyl]adenine (17). Treatment of **15** (1.39 g, 2.80 mmol) by procedure **C** [DMAP (1.03 g, 8.41 mmol) in CH_2Cl_2 (10 mL)/trifluoromethanesulfonyl chloride (0.33 mL, 3.08 mmol and 0.07 mL, 0.66 mmol)] gave **16** (1.45 g, 82%) as a colorless powder: mp: 116-118 °C; ^{1}H-NMR, $CDCl_3$ δ 8.25 (s, 1H, H8), 7.89 (s, 1H, H2), 6.48 (d, 1H, J = 4.0 Hz, H1'), 5.59 (br, 2H, NH_2), 5.10 (m, 1H, H2'), 4.67 (m, 1H, H3'), 3.93 (m, 1H, H4'), 3.80 (dd, 2H, J = 4.4, 10.8 Hz, H5'a), 3.72 (dd, 1H, J = 6.4, 10.8 Hz, H5'b), 0.83 (s, 9H, *t*-butyl), 0.82 (s, 9H, *t*-butyl) 0.07 (s, 6H, methyl × 2), 0.00 (s, 6H, methyl × 2).

9-[3'-*O*-(Methanesulfonyl)-2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-1-β-D-xylofuranosyl]adenine (13). Procedure D. To a solution of **12** (1.50 g, 3.02 mmol) and DMAP (1.11 g, 9.08 mmol) in CH_2Cl_2 (10 mL) was added fresh methanesulfonyl chloride (0.28 mL, 3.63 mmol) at 0 °C under Ar atmosphere. The reaction was stirred for 3 h at this temperature and then checked by TLC. A second portion of methanesulfonyl chloride (0.1mL, 1.29 mmol) was added and stirring was continued for 1 h at 0 °C. The reaction was partitioned between ice-cold 1% aqueous AcOH and CH_2Cl_2, and the aqueous layer was extracted once more with CH_2Cl_2. The combined organic phase was washed (ice-cold sat. aqueous $NaHCO_3$, ice-cold brine), dried over $MgSO_4$, filtered, and evaporated to give **13** (1.59 g, 92%) as a colorless solid: mp: 57-58 °C; ^{1}H-NMR, $CDCl_3$ δ 8.27 (s, 1H, H8), 8.05 (s, 1H, H2), 6.20 (br, 2H, NH_2), 6.04 (d, 1H, J = 2.0 Hz, H1'), 4.88 (m, 1H, H2'), 4.76 (m, 1H, H3'), 4.45 (dd, 1H, J = 4.4, 10.8 Hz, H4'), 3.96 (dd, 1H, J = 4.8, 10.8 Hz, H5'a), 3.91 (dd, 1H, J = 6.8, 10.8 Hz, H5'b), 2.92 (s, 3H, -SO_2CH_3), 0.86 (s, 9H, *t*-butyl), 0.82 (s, 9H, *t*-butyl), 0.07 (s, 3H, methyl), 0.06 (s, 3H, methyl), 0.00 (s, 6H, methyl × 2); ^{13}C-NMR δ 155.54, 153.12, 149.67, 138.33, 119.46, 89.71, 80.68, 79.62, 60.22, 38.08, 25.80, 25.46, 18.26, 17.72, -5.08, -5.10, -5.34, -5.42.

9-[2'-*O*-(Methanesulfonyl)-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-1-β-D-arabinofuranosyl]adenine (16) Treatment **15** (1.07 g, 2.16 mmol) by procedure **D** [DMAP (0.79 g, 6.48 mmol) in CH_2Cl_2 (20 mL)/methanesulfonyl chloride (0.2 mL, 2.59 mmol/0.1 mL, 1.29 mmol)] gave **16** (1.15 g, 93%) as a colorless solid: mp: 62-64 °C; ^{1}H-NMR, $CDCl_3$ δ 8.25 (s, 1H, H8), 7.98 (s, 1H, H2), 6.45 (d, 1H, J = 4.4 Hz, H1'), 6.14 (br, 2H, NH_2), 5.01 (t, 1H, J = 4.4 Hz, H2'), 4.64 (t, 1H, J = 4.0 Hz, H3'), 3.91 (m, 1H, H4'), 3.78 (m, 1H, H5'a, H5'b), 2.45 (s, 3H, -SO_2CH_3), 0.82 (s, 18H, *t*-butyl × 2), 0.08 (s, 3H, methyl), 0.06 (s, 3H, methyl), 0.01 (s, 3H, methyl), 0.00 (s, 3H, methyl); ^{13}C-NMR δ 155.60, 153.21, 149.41,

139.63, 119.10, 84.81, 82.63, 82.45, 74.94, 61.77, 37.85, 25.89, 25.60, 18.38, 17.81, -4.62, -4.97, -5.39, -5.42.

3'-Azido-3'-deoxy-2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-adenosine (18). Procedure E. NaN_3 (0.11 g, 1.71 mmol) was added to a solution of **14** (0.22 g, 0.34 mmol) in anhydrous DMF (4 mL) and the reaction was stirred at ambient temperature for 3 h under Ar atmosphere. The reaction was diluted with H_2O (20 mL) and then extracted with EtOAc (20 mL × 2). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give 18 (0.19 g, 99%) as a colorless powder: mp: 106-109 °C; IR (KBr) cm^{-1} 2107 (strong, $-N_3$); ^{1}H-NMR, $CDCl_3$ δ 8.17 (s, 1H, H8), 8.01 (s, 1H, H2), 5.96 (br, 2H, NH2), 5.88 (d, 1H, *J* = 4.0 Hz, H1'), 4.71 (t, 1H, *J* = 4.0 Hz, H2'), 4.07 (m, 1H, H3'), 3.92 (m, 1H, H4'), 3.91 (m, 1H, H5'a), 3.68 (dd, 1H, *J* = 2.0, 11.6 Hz, H5'b), 0.79 (s, 9H, *t*-butyl), 0.71 (s, 9H, *t*-butyl), 0.00 (s, 3H, methyl), -0.01 (s, 3H, methyl), -0.08 (s, 3H, methyl), -0.19 (s, 3H, methyl); ^{13}C-NMR δ 155.53, 153.01, 149.61, 138.84, 119.92, 88.88, 81.99, 76.96, 62.39, 60.88, 25.94, 25.55, 18.43, 17.90, -5.08, -5.14, -5.36, -5.51; MS (FAB) $[M+H]^+$ 521.

2'-Azido-2'-deoxy-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-adenosine (20). Treatment of **17** (0.80 g, 1.27 mmol) by procedure **E** [NaN_3 (0.42 g, 6.37 mmol)/DMF (15 mL)] gave 20 (0.66 g, 99%) as a colorless powder: mp: 132-135 °C; ^{1}H-NMR, $CDCl_3$ δ 8.27 (s, 1H, H8), 8.01 (s, 1H, H2), 6.06 (br, 2H, NH_2), 6.05 (d, 1H, *J* = 5.2 Hz, H1'), 4.63 (t, 1H, *J* = 5.2 Hz, H2'), 4.41 (t, 1H, *J* = 4.8 Hz, H3'), 4.04 (m, 1H, H4'), 3.88 (dd, 1H, *J* = 3.6, 11.2 Hz, H5'a), 3.68 (d, 1H, *J* = 11.2 Hz, H5'b), 0.88 (s, 9H, *t*-butyl), 0.81 (s, 9H, *t*-butyl) 0.10 (s, 3H, methyl), 0.08 (s, 3H, methyl), 0.00 (s, 3H, methyl), -0.01 (s, 3H, methyl); ^{13}C-NMR δ 155.70, 153.13, 149.58, 139.08, 120.00, 86.03, 85.50, 72.30, 65.12, 61.86, 25.89, 25.85, 18.35, 18.03, -4.72, -4.98, -5.36, -5.47; MS (FAB) $[M+H]^+$ 521.

Azidation of compound 13. Procedure F. To the mixture of NaN_3 (0.13 g, 1.93 mmol) and Li_2CO_3 (0.142 g, 1.93 mmol) in anhydrous DMF (4 mL) pre-heated at 120 °C for 3 hours was added **13** (0.22 g, 0.39 mmol) and stirred at 120 °C and was stirred for 3 days. The reaction was diluted with H_2O (50 mL) and then extracted with EtOAc (50 mL × 3). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was applied to flash column chromatography to give **18** (0.08 g, 43%) and **19** (0.01 g, 6%) as a white powder: **19**: mp: 190-192 °C; ^{1}H-NMR, $CDCl_3$ δ 8.43 (s, 1H, H8), 7.91 (s, 1H, H2), 7.36 (d, 1H, *J* = 12.0 Hz, -OH, exch), 6.07 (br, 2H, NH_2), 5.84 (d, 1H, *J* = 7.2 Hz, H1'), 5.46 (dd, 1H, *J* = 7.2, 8.0 Hz, H2'), 4.36 (d, 1H, *J* = 6.0 Hz, H3'), 4.24 (m, 1H, H4'), 4.04 (d, 1H, *J* = 12.4 Hz, H5'a), 3.79 (m, 1H, H5'b), 0.88 (s, 9H, *t*-butyl), 0.00 (s, 3H, methyl), -0.35 (s, 3H, methyl); ^{13}C-NMR δ 156.03, 152.56, 148.48, 140.81, 121.22, 90.74, 85.48, 74.61, 63.95, 63.46, 25.48 17.76, 18.03, -5.16, -5.98.

Azidation of Compound 16. Treatment of **16** by **procedure F** (0.37 g, 0.65 mmol) [NaN_3 (0.21 g, 3.24 mmol)/Li_2CO_3 (0.24 g, 3.24 mmol) for 4 days] gave **20** (0.05 g, 15%) and **21** (0.05 g, 15%) as a white powder: **21**: mp: 193-195 °C; ^{1}H-NMR, $CDCl_3$ δ 8.10 (s, 1H, H8), 8.02 (s, 1H, H2), 6.89 (br, 2H, NH_2), 6.13 (d, 1H, *J* = 4.4 Hz, -OH, exch), 5.89 (d, 1H, *J* = 3.2 Hz, H1'), 4.52 (m, 1H, H2'), 4.30 (dd, 1H, *J* = 4.8, 10.4 Hz, H3'), 4.15 (m, 1H, H4'), 3.80 (m, 2H, H5'a, H5'b), 0.80 (s, 9H, *t*-butyl), 0.00 (s, 6H, methyl × 2); ^{13}C-NMR δ 155.67, 155.61, 152.47, 149.13, 118.75, 88.19, 78.29, 66.28, 61.29, 25.45, 17.79, -5.78, -5.92.

3'-Amino-3'-deoxy-2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-adenosine (22). Procedure G. A solution of **18** (0.10 g, 0.19 mmol) in MeOH (10 mL) was hydrogenated at ambient pressure and temperature in the presence of 10% Pd/C (20 mg) for 16 hours. The mixture was filtered with the aid of celite, and the filtrate was evaporated. The residue was applied to flash column chromatography to give **22** (0.09 g, 92%) as a colorless powder: mp: 167-169 °C; ^{1}H-NMR, $CDCl_3$ δ 8.22 (s, 1H, H8), 8.20 (s, 1H, H2), 5.91 (s, 1H, H1'), 5.79 (br, 2H, NH_2), 4.25 (t, 1H, *J* = 3.6 Hz, H2'), 3.98 (d, 1H, *J* = 9.6 Hz, H5'a), 3.80 (m, 1H, H4'), 3.79 (m, 1H, H5'b), 3.49 (dd, *J* = 4.4, 8.0 Hz, H4'), 0.83 (s, 9H, *t*-butyl), 0.82 (s, 9H, *t*-butyl) 0.09 (s, 3H, methyl), 0.03 (s, 3H, methyl), 0.02 (s, 3H, methyl), 0.00 (s, 3H, methyl); ^{13}C-NMR δ 155.30, 152.76, 149.35, 139.07, 119.95, 89.74, 84.93, 77.82, 61.91, 52.19, 26.02, 25.77, 18.56, 18.03, -4.50, -5.04, -5.30, -5.44; MS (FAB) $[M+H]^+$ 495.

2'-Amino-2'-deoxy-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-adenosine (24). Hydrogenation of **20** (0.5 g, 0.96 mmol) by procedure **G** gave **24** (0.43 g, 90%) as a colorless powder: mp: 145-147 °C; ^{1}H-NMR, DMSO-d6 δ 8.15 (s, 1H, H8), 7.97 (s, 1H, H2), 7.13 (br, 2H, NH_2), 5.53 (d, 1H, *J* = 7.6 Hz, H1'), 4.08 (d, 1H, *J* = 4.8 Hz, H3'), 4.01 (dd, 1H, *J* = 4.8, 7.6, H2'), 3.79 (m, 1H, H4'), 3.73 (dd, 1H, *J* = 4.4, 11.2, H5'a), 3.52 (dd, *J* = 4.0, 11.2 Hz, H5'b), 1.59 (br, 1.5H, H2'-NH_2, exch), 0.78 (s, 9H, *t*-butyl), 0.73 (s, 9H, *t*-butyl), 0.00 (s, 6H, methyl × 2), -0.09 (s, 6H, methyl × 2); ^{13}C-NMR δ 156.05, 152.48, 149.72, 139.80, 119.22, 87.94, 85.64, 73.80, 62.86, 56.20, 25.78, 25.76, 18.00, 17.89, -4.72, -4.78, -5.49, -5.51; MS (FAB) $[M+H]^+$ 495.

3'-Amino-3'-deoxyadenosine (23). Procedure H. A solution of **22** (0.1 g, 0.20 mmol) and NH_4F (0.09 g, 1.76 mmol) in MeOH (10 mL) was stirred in oil bath at 60 °C for 12 hours. The solvent was evaporated and the resulting solid was partitioned between H_2O/EtOAc. The aqueous phase was concentrated to 3 mL and applied to ion-exchange resin column chromatography (Dowex 1 × 20-200, OH- form, 2 × 18 cm). The column was washed with H_2O and eluted with 20-50% MeOH. The chromatographically identical fractions (BuOH-AcOH-H_2O = 60 : 15 : 25) were collected, and the solvent evaporated to give **23** (0.05 g, 85%) with reported properties.[7]

2'-Amino-2'-deoxyadenosine (25). Treatment of **24** (0.39 g, 0.78 mmol) by procedure **H** [NH_4F (0.29 g, 7.88 mmol) in MeOH (15 mL)] gave **25** (0.18 g, 87%) as a colorless powder with reported properties.[8]

3'-Azido-3'-deoxyadenosine (26). Treatment of **18** (0.50 g, 0.90 mmol) by procedure H [NH_4F (0. 50 g, 12.63 mmol) in MeOH (15 mL)] gave **26** (0.28 g, 99%) as a colorless

powder with reported properties.[9]

2'-Azido-2'-deoxyadenosine (27). Treatment of **20** (0.60 g, 1.15 mmol) by procedure H [NH_4F (0.60 g, 16.13 mmol) in MeOH (15 mL)] gave **27** (0.34 g, 99%) as a colorless powder with reported properties.[9]

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