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A practical synthesis of 2′-aminoacylamino-2′-deoxyadenosines

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Abstract—A practical and efficient synthesis of 2′-aminoacylamino-2′-deoxyadenosine derivatives is reported. EDCI/HOBt-mediated coupling of a 3′,5′-diprotected 2′-amino-2′-deoxyadenosine derivative to various *N*-Cbz-L-amino acid derivatives followed by global deprotection affords analytically pure 2′-aminoacylamino-2′-deoxyadenosine derivatives without the necessity for preparative HPLC purification. These compounds are non-hydrolysable isosteres of 2′-aminoacyladenosines, which are of use in X-ray studies for the elucidation of the editing mechanism of various tRNA synthetases.

1. Introduction

2′-Aminoacyladenosines (**1**, Fig. 1) are produced in vivo as intermediates in protein biosynthesis, specifically in the aminoacylation reaction catalysed by the aminoacyl tRNA synthetases (aaRSs), a group of enzymes responsible for attaching a particular amino acid to its set of cognate tRNA isoacceptors.[1–3]

The fidelity of this process is critically dependant on the recognition of the amino acid and the tRNA isoacceptor by the enzyme. The ability of each aaRS to discriminate between the various amino acids is therefore of fundamental importance in the accuracy of protein synthesis. This presents a particular problem for pairs of structurally similar amino acids, for example, threonine/serine, threonine/valine and isoleucine/valine. For example, IleRS misincorporates one valine for every 200 isoleucine positions, which is a great deal higher than the maximum error tolerance of one in 10,000.[4] The misincorporation of a non-cognate amino acid is rectified by the so-called 'proof-reading' or editing mechanism. This hydrolytic editing identifies misactivated 5′-*O*-aminoacyl-adenylates (pre-transfer editing) and/or mischarged tRNAs (post-transfer editing). The elucidation of the mechanism of these editing steps generally depends on the solution of the X-ray crystal structure of complexes between the aaRS of interest and enzymatically non-hydrolysable substrate analogues. In the investigation of pre-transfer editing,[5] 5′-*O*-sulfamoyladenosine derivatives[6,7] have been employed. A 2′-aminoacylamino-2′-deoxyadenosine (**2**, R=*n*-propyl, Fig. 1) has previously been employed as a non-hydrolysable 2′-aminoacyladenosine analogue in the elucidation of the post-transfer editing mechanism of *Thermus thermophilus* LeuRS[5] and in a preliminary X-ray crystallographic study of the editing domain of *T. thermophilus* IleRS (**6a**, Fig. 1).[8,9] 2′-Aminoacylamino-2′-deoxyadenosine derivatives have also been employed in the study of ribosomal peptidyltransferases.[10]

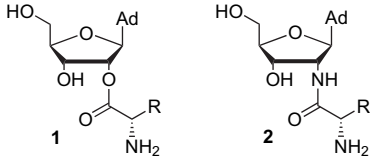

Figure 1. General structure of 2′-aminoacyladenosines (**1**, R=amino acid side chain) found as intermediates in the aminoacylation reaction catalysed by aaRSs and 2′-aminoacylamino-2′-deoxyadenosines (**2**).

As part of an investigation into the editing mechanism of the aaRSs, we required access to appreciable quantities of these compounds. Despite the increasing interest in these compounds for use in such studies, no practical, general method for their synthesis has been reported. Previous syntheses of the analogous 3′-aminoacylamino-3′-deoxyadenosines (mainly of interest as analogues of the nucleoside antibiotics puromycin[11] and the recently discovered cystocin[12]) generally employ *N*-Fmoc protected amino acids, and the removal conditions necessitate purification of the final compounds by preparative HPLC,[13–15] although one very recent synthesis of the unnatural L,L-puromycin employs *N*-Cbz-L-*O*-methyltyrosine.[16] The few published syntheses of 2′-amido-2′-deoxyadenosine derivatives are not amenable to the routine preparation of larger amounts of these compounds, in

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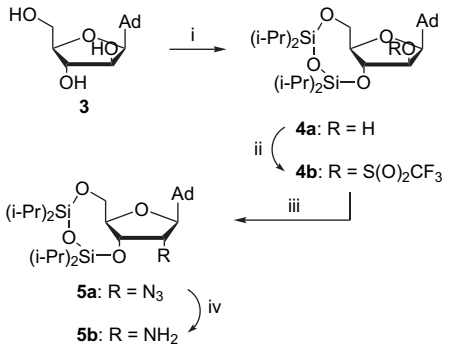
that they require the use of expensive solid-phase reagents (e.g., safety-catch resins[17–20]), the use of preparative HPLC[5] and TLC[10] or ion-exchange purification techniques.[21,22] The aminoacyl derivatives present an additional challenge in the necessity for protection/deprotection of the amino group of the amino acid, as well as the increased compound polarity due to the extra amino group.

Herein, we report a general method for the practical and efficient synthesis of this important class of compounds on a preparatively useful scale, which, most importantly, avoids the necessity for difficult or expensive purification methods (only silica gel column chromatography is used) and which allows rapid access to a wide array of 2′-aminoacylamino-2′-deoxyadenosine derivatives.

2. Results and discussion

Our synthetic pathway begins with 3′,5′-diprotected 2′-amino-2′-deoxyadenosine **3b**, which was prepared in good yield from vidarabine **1** according to literature procedures (Scheme 1).[5,13,17,23,24]



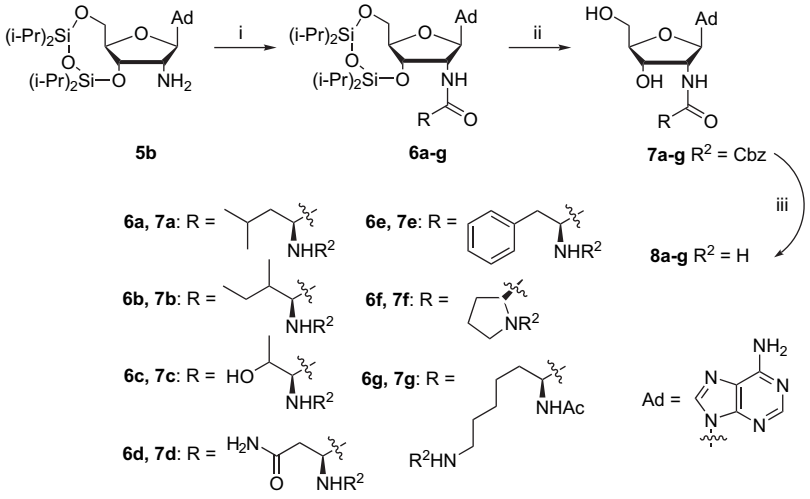
Scheme 1. Synthesis of 3′,5′-diprotected 2′-amino-2′-deoxyadenosine (**5b**). (i) $TIPDSCl_2$, pyridine, rt, 4 h, 86% yield; (ii) CF_3SO_2Cl, amino acids, DMAP, DCM, 0 °C, 1 h, 92% yield; (iii) NaN_3, DMF, rt, 5 h, 94% yield; (iv) 10% Pd/C, H_2, MeOH, rt, 15 h, 99% yield.

The amino acids were employed, in general, as their *N*-Cbz protected derivatives (**6a–f**). The *N*-Cbz protecting group was chosen (in contrast to the previously used Fmoc group[5,13,24]) due to the volatility and/or ease of removal of the deprotection reagents and by-products. It was predicted that this would minimise or indeed eliminate the purification required for the final products (**8a–g**). The α-amino group of compound **8g** was protected as the corresponding *N*-acetate, with the side chain primary amino group protected with a Cbz group. Additionally, the order of removal of the protecting groups of fully protected 2′-aminoacylamino-2′-deoxyadenosines **6a–g**, i.e., removal of the tetraisopropyldisilyl (TIPDS) group first, was predicted to be critical to the success of this approach, as it was thought that *N*-Cbz compounds **7a–g** would possess sufficient lipophilicity to allow purification by normal phase silica gel chromatography, without having to resort to the use of reverse phase preparative HPLC.

The coupling of protected 2′-amino-2′-deoxyadenosine **5b** to various *N*-Cbz protected amino acid derivatives (**6a–g**, Scheme 2) was carried out using standard EDCI/HOBt-mediated amide bond formation[25] in dichloromethane overnight at room temperature.

The fully protected 2′-aminoacylamino-2′-deoxyadenosines were easily purified by aqueous workup followed by silica gel column chromatography, affording pure compounds **7a–g** in 62–76% yield. At room temperature, compound **7f** existed as a mixture of rotamers, due to hindered rotation about the nitrogen–carbon bond of the tertiary carbamate. For the preparation of *N*-acetyl lysine derivative **6g**, EDCI/HOBt-mediated coupling of *N*-acetyl-Lys(Cbz)-OH[26] to amine **5b** afforded the corresponding fully protected 2′-aminoacylamino-2′-deoxyadenosine **6g** in 79% isolated yield after silica gel column chromatography. No epimerization of the carboxy component was observed in any of these couplings, with all compounds being isolated as single diastereoisomers (by ^1H NMR spectroscopy).

The order of deprotection of fully protected compounds **6a–g** was important, as we wished to minimise the degree of

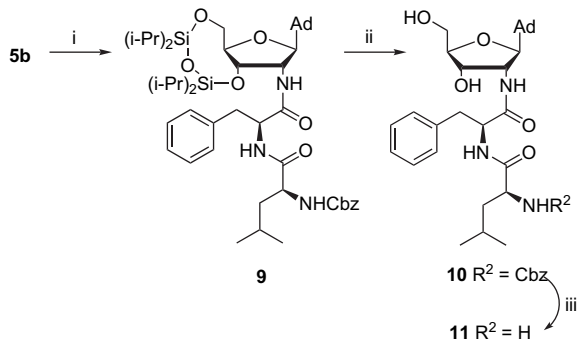


Scheme 2. Synthesis of 2′-aminoacylamino-2′-deoxyadenosines. (i) Protected amino acids, EDCI, HOBt, CH_2Cl_2, 0 °C to rt, 16 h, **6a** (62%), **6b** (67%), **6c** (66%), **6d** (71%), **6e** (75%), **6f** (76%), **6g** (79%); (ii) NH_4F, MeOH, reflux, 2 h, **7a** (88%), **7b** (67%), **7c** (89%), **7d** (78%), **7e** (87%), **7f** (89%), **7g** (88%); (iii) 10% Pd/C, H_2, MeOH, rt, 16 h, **8a** (96%), **8b** (99%), **8c** (97%), **8d** (96%), **8e** (81%), **8f** (99%), **8g** (86%).

purification required. It was intended that the *N*-Cbz group be removed last, as the deprotection conditions and by-products are more compatible with polar, water-soluble compounds. Accordingly, the 3′,5′-*O*-TIPDS group of compounds **6a–g** was removed using ammonium fluoride (10 equiv) in refluxing methanol.[27] The *N*-Cbz group of the corresponding diols **7a–g** conferred enough lipophilicity to permit purification by aqueous workup followed by conventional silica gel flash chromatography. Compounds **7a–g** were, as expected, quite polar (R_f~0.1 in all cases, eluting with 9:1 dichloromethane/methanol), but the use of a short silica gel column afforded analytically pure material in good yields (66–89%). *N*-Cbz proline derivative **7f** was again present as a rotameric mixture at room temperature (as determined by ^{1}H NMR spectroscopy).

The final deprotection step involved hydrogenolysis of the *N*-Cbz group from compounds **7a–g**. This was performed under standard conditions, i.e., 10% Pd on carbon and balloon pressure of hydrogen gas in methanol, with the reactions being allowed to stir overnight at room temperature. Simple filtration through a plug of Celite® followed by concentration of the filtrate afforded analytically pure compounds **8a–g** in excellent yields (81–99%) without the need for further purification. Proline derivative **8f** exhibited no signs of hindered rotation, confirming that the tertiary carbamate of the Cbz group was responsible for the rotameric mixtures encountered for compounds **6f** and **7f**.

In an extension of this methodology, we accomplished the synthesis of dipeptide–nucleoside conjugate **11** (Scheme 3). EDCI/HOBt-mediated coupling of *N*-protected dipeptide *N*-Cbz-IlePhe-OH (Scheme 3) to amine **5b** as before afforded protected dipeptide–nucleoside conjugate **9**. In common with the coupling of the protected amino acids to amine **5b**, no epimerization of the carboxyl component was observed, with compound **9** being isolated as a single diastereoisomer (by ^{1}H NMR spectroscopy) in 72% yield. Again, in order to facilitate purification by silica gel column chromatography, the 3′,5′-*O*-TIPDS protecting group of **9** was removed first using ammonium fluoride in refluxing methanol, affording diol **10** in 66% purified yield. The *N*-Cbz group of **8** was removed using the same conditions as previously described (vide supra), affording analytically pure, fully deprotected dipeptide adduct **11** in 94% yield, without recourse to additional purification beyond removal of the catalyst by filtration and concentration of the filtrate under reduced pressure.



Scheme 3. Synthesis of dipeptide conjugate **11**. (i) *N*-Cbz-Ile-Phe-OH, EDCI, HOBt, CH_2Cl_2, 0 °C to rt, 16 h, 72%; (ii) NH_4F, MeOH, reflux, 2 h, 66%; (iii) 10% Pd/C, H_2, MeOH, rt, 16 h, 94%.

3. Conclusions

In conclusion, we have developed a practical and efficient synthetic route to a range of 2′-aminoacylamino-2′-deoxyadenosines. The synthetic pathway is compatible with the introduction of a wide range of amino acids (both with and without heteroatom-bearing side chains) as well as dipeptides at the 2′-position of amine **5b**. Key benefits of this protocol are the avoidance of expensive reagents and the fact that only flash chromatography is required for purification. Crucially, this route is also amenable to the preparation of these useful compounds on a larger scale.

4. Experimental

4.1. General experimental methods

All reactions were performed under a nitrogen atmosphere. Solvents were dried using standard procedures. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra recorded at 100 MHz in the solvents specified. Spectra were referenced to residual non-deuterated solvent (^{1}H NMR: $CDCl_3$ 7.26 ppm, DMSO-d_6 2.55 ppm and ^{13}C NMR: $CDCl_3$ 77.2 ppm, DMSO-d_6 39.5 ppm). Coupling constant (*J*) values are quoted in hertz. The matrix used for FAB mass spectra was either 3-nitrobenzyl alcohol or glycerol. Acceleration voltage was 6 kV and scan time was 5 s. IR spectra were recorded as KBr disks. Flash chromatography was performed using Merck Geduran Si 60 (0.063–0.200 mm) silica gel. Thin layer chromatography (TLC) was performed using Merck Silica Gel 60 F_{254} aluminium-backed plates and visualised using UV light (254 and/or 366 nm). The solvents used to determine R_f values are the same as that used for chromatographic purification, unless otherwise stated. Nucleoside numbering is used throughout.

4.2. Coupling of protected amino acids 6a–g with 2′-amino-2′-deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine 5b (general procedure A)

EDCI (1.1 equiv) and HOBt (1.1 equiv) were added at 0 °C to a solution of the appropriate protected amino acid (1 equiv) in dry CH_2Cl_2. The mixture was stirred at room temperature for 30 min. The mixture was cooled again to 0 °C and a solution of 2′-amino-2′-deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine **5b** (1 equiv) in dry CH_2Cl_2 was added. The mixture was stirred at room temperature under a nitrogen atmosphere until TLC analysis (9:1 CH_2Cl_2/MeOH) indicated that there was no **5b** left. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with water. The combined aqueous extracts were back-extracted with CH_2Cl_2 and the combined organic layers washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure affording the product as a solid, which was purified by silica gel column chromatography (eluting with 19:1 CH_2Cl_2/MeOH).

4.2.1. 2′-(*N*-α-Benzyloxycarbonyl-L-valinyl)-amino-2′-deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (6a). Using general procedure A, 144 mg of **5b** afforded 129 mg (62%) of **6a** as a white solid, $[\alpha]_D^{20}$ −27.5 (*c* 0.01, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3331, 1641, 1598; δ_H

(400 MHz, CD_3OD) 8.21 (1H, s), 8.12 (1H, s), 7.38–7.27 (5H, m), 5.90 (1H, d, J=4.0 Hz), 5.22–5.17 (1H, m), 5.07–5.04 (1H, m), 5.10 (1H, d, J=12.5 Hz), 5.02 (1H, d, J=12.8 Hz), 4.10–4.02 (4H, m), 2.10–2.00 (1H, m), 1.17–1.00 (28H, m), 0.89 (3H, d, J=7.0 Hz), 0.82 (3H, d, J=7.0 Hz); δ_C (100 MHz, CD_3OD) 156.0, 152.5, 140.5, 128.2, 127.8, 127.6, 88.3, 83.8, 70.2, 62.4, 66.5, 60.6, 55.1, 30.5, 18.5, 16.8, 16.6, 16.5, 16.4, 16.24, 16.19, 16.1, 13.5, 13.1, 12.8, 12.5; HRMS-FAB m/z [M+H$^+$] calcd for $C_{35}H_{55}N_7O_7Si_2$: 742.378; found: 742.370. Anal. Calcd for $C_{35}H_{55}N_7O_7Si_2$: C, 56.65; H, 7.47; N, 13.21. Found: C, 56.68; H, 7.43; N, 13.18.

4.2.2. 2′-(*N*-α-Benzyloxycarbonyl-L-isoleucinyl)-amino-2′-deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (6b). Using general procedure A, 150 mg of **5b** afforded 149 mg (67%) of **6b** as a white solid, $[\alpha]_D^{20}$ −29.5 (c 0.005, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3417, 2946, 2868, 2365, 1712, 1667, 1640, 1597, 1502, 1466, 1248, 1124, 1085, 1038, 885, 698; δ_H (400 MHz, CD_3OD) 8.12 (1H, s), 8.03 (1H, s), 7.28–7.14 (5H, m), 5.81 (1H, d, J=4.0 Hz), 5.20–5.03 (3H, m), 5.10 (1H, d, J=12.5 Hz), 5.01 (1H, d, J=12.4 Hz), 4.12–4.00 (5H, m), 1.73–1.62 (1H, m), 1.24–1.13 (1H, m), 1.06–0.84 (29H, m), 0.75 (3H, d, J=7.0 Hz), 0.67 (3H, t, J=7.4 Hz); δ_C (100 MHz, CD_3OD) 173.1, 157.3, 156.0, 152.5, 149.0, 140.5, 136.7, 128.2, 127.8, 127.6, 119.2, 88.0, 84.0, 70.3, 66.5, 62.5, 59.9, 55.1, 36.9, 24.3, 16.7, 16.5, 16.4, 16.3, 16.2, 16.1, 14.7, 13.2, 13.1, 12.9, 12.4, 10.3; HRMS-FAB m/z [M+H$^+$] calcd for $C_{36}H_{57}N_7O_7Si_2$: 756.394; found: 756.395; Anal. Calcd for $C_{36}H_{57}N_7O_7Si_2$: C, 57.2; H, 7.6; N, 13.0. Found: C, 57.2; H, 7.6; N, 12.8.

4.2.3. 2′-(*N*-α-Benzyloxycarbonyl-L-threoninyl)-amino-2′-deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (6c). Using general procedure A, 150 mg of **5b** afforded 145 mg (67%) of **6c** as a white solid, $[\alpha]_D^{20}$ −15.0 (c 0.01, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3334, 2947, 2862, 1648, 1499, 1248, 1040, 917, 882, 698, 605, 456; δ_H (400 MHz, CD_3OD) 8.19 (1H, s), 8.12 (1H, s), 7.40–7.24 (5H, m), 5.95 (1H, d, J=3.7 Hz), 5.25 (1H, t, J=7.0 Hz), 4.93–4.91 (1H, m), 4.18–4.00 (1H, m), 4.0–4.18 (6H, m); δ_C (100 MHz, CD_3OD) 172.3, 157.3, 156.0, 152.4, 148.9, 140.7, 136.6, 128.2, 127.8, 127.6, 119.3, 88.5, 83.7, 70.4, 66.9, 66.7, 62.5, 60.6, 55.6, 18.44, 16.6, 16.52, 16.49, 16.4, 16.24, 16.22, 16.1, 13.13, 13.07, 12.8, 12.5; HRMS-FAB m/z [M+H$^+$] calcd for $C_{34}H_{53}N_7O_8Si_2$: 744.349; found: 744.357; Anal. Calcd for $C_{34}H_{53}N_7O_8Si_2$: C, 54.9; H, 7.2; N, 13.2. Found: C, 54.8; H, 7.5; N, 13.5.

4.2.4. 2′-(*N*-α-Benzyloxycarbonyl-L-asparaginyl)-amino-2′-deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (6d). Using general procedure A, 190 mg of **5b** afforded 201 mg (71%) of **6d** as a white solid, $[\alpha]_D^{20}$ −0.002 (c 0.01, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3410, 2945, 2867, 2362, 2341, 1653, 1600, 1507, 1468, 1421, 1331, 1297, 1250, 1212, 1145, 1039, 918, 885, 863, 825, 696, 603, 456, 421; δ_H (400 MHz, $CDCl_3$) 8.24 (1H, s), 7.95 (1H, s), 7.67 (1H, d, J=4.4 Hz), 7.42–7.30 (5H, m), 6.45 (1H, d, J=8.4 Hz), 5.89 (1H, d, J=4.0 Hz), 5.84 (2H, br s), 5.23–5.16 (2H, m), 5.06 (1H, d, J=12.4 Hz), 4.85–4.77 (1H, m), 4.61–4.53 (1H, m), 4.10–3.99 (3H, m), 3.02–2.94 (1H, m), 2.52 (1H, dd, J=15.8, 5.5 Hz), 1.19–0.98 (28H, m); δ_C (100 MHz, $CDCl_3$) 175.3, 173.2, 156.3, 156.2, 153.1, 148.7, 139.9, 136.0, 128.8, 128.5, 128.4, 119.5, 89.0, 84.1, 71.0, 67.6, 63.2, 56.9, 51.9, 37.0, 17.7, 17.6, 17.5, 17.4, 17.3, 17.22, 17.16, 13.3, 13.2, 12.89, 12.86; HRMS-FAB m/z [M+H$^+$] calcd for $C_{34}H_{52}N_8O_8Si_2$: 757.345; found: 757.352. Anal. Calcd for $C_{34}H_{52}N_8O_8Si_2$: C, 53.95; H, 6.92; N, 14.80. Found: C, 53.91; H, 7.02; N, 14.71.

4.2.5. 2′-(*N*-α-Benzyloxycarbonyl-L-phenylalaninyl)-amino-2′-deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (6e). Using general procedure A, 215 mg of **5b** afforded 250 mg (75%) of **6e** as a white solid, $[\alpha]_D^{20}$ −18.0 (c 0.02, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3400, 2944, 2866, 2359, 1715, 1645, 1600, 1498, 1464, 1455, 1331, 1296, 1248, 1214, 1142, 1037, 918, 885, 862, 745, 697, 648, 604, 458, 418; δ_H (400 MHz, $CDCl_3$) 8.17 (1H, s), 7.95 (1H, s), 7.34–7.09 (10H, m), 5.89 (1H, d, J=3.6 Hz), 5.28 (1H, m), 5.16 (1H, d, J=12.5 Hz), 5.02 (1H, d, J=12.5 Hz), 4.53 (1H, m), 4.02–3.97 (3H, m), 3.11 (1H, m, J=7.3, 13.6 Hz, CHC*H*HPh), 2.98 (1H, dd, J=7.3, 13.6 Hz, CHCH*H*Ph), 1.16–1.03 (28H, m); δ_C (100 MHz, $CDCl_3$) 172.4, 156.4, 155.7, 152.6, 149.3, 140.2, 136.3, 129.2, 128.7, 128.6, 128.1, 127.0, 125.3, 119.8, 87.8, 83.8, 70.5, 67.0, 62.8, 56.5, 56.0, 38.0, 17.5, 17.4, 17.3, 17.2, 17.1, 17.0, 13.2, 13.1, 12.8, 12.6; HRMS-FAB m/z [M+H$^+$] calcd for $C_{39}H_{55}N_7O_7Si_2$: 790.370; found: 790.376; Anal. Calcd for $C_{39}H_{55}N_7O_7Si_2$: C, 59.4; H, 6.9; N, 12.4. Found: C, 59.5; H, 6.9; N, 12.4.

4.2.6. 2′-(*N*-α-Benzyloxycarbonyl-L-prolinyl)-amino-2′-deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (6f). Using general procedure A, 222 mg of **5b** afforded 245 mg (76%) **6f** as a white solid, $[\alpha]_D^{20}$ −47.0 (c 0.01, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3394, 2944, 2867, 2726, 1694, 1599, 1499, 1465, 1416, 1332, 1299, 1248, 1206, 1119, 1090, 919, 885, 863, 824, 772, 696, 647, 607, 451, 418; δ_H (400 MHz, $CDCl_3$) 8.28 (1H, s), 8.11 (1H, s), 8.06 (1H, s), 8.05 (1H, s), 7.35–7.21 (5H, m), 5.88 (1H, s), 5.77 (1H, d, J=9.0 Hz), 4.96–5.09 (7H, m), 4.78 (1H, d, J=13.2 Hz), 4.30–4.36 (2H, m), 3.92–4.00 (6H, m), 3.34–3.42 (4H, m), 2.07–2.18 (1H, m), 1.79–1.91 (6H, m) 0.91–1.15 (56H, m); δ_C (100 MHz, $CDCl_3$) 173.0, 156.0, 155.8, 152.7, 149.3, 140.3, 136.4, 128.5, 128.2, 127.8, 120.1, 88.3, 83.6, 70.5, 67.3, 62.8, 60.6, 56.5, 47.0, 28.7, 24.6, 17.5, 17.4, 17.2, 17.1, 13.2, 12.8, 12.6; HRMS-FAB m/z [M+H$^+$] calcd for $C_{35}H_{53}N_7O_7Si_2$: 740.355; found: 740.362.

4.2.7. 2′-(*N*-α-Acetyl-*N*-ω-benzyloxycarbonyl-L-lysinyl)-amino-2′-deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (6g). Using general procedure A, 150 mg of **5b** afforded 187 mg (79%) **6g** as a white solid, $[\alpha]_D^{20}$ −43.6 (c 0.01, CH_3OH); ν_{max} (KBr)/cm^{-1} 1690, 1638, 1541, 1466, 1255, 1142, 1039, 884, 697, 604; δ_H (400 MHz, DMSO-d_6) 8.33 (1H, d, J=7.7 Hz), 8.32 (1H, s), 8.07 (1H, s), 8.01 (1H, d, J=8.0 Hz), 7.38–7.30 (7H, m), 7.24 (1H, t, J=5.5 Hz), 5.86 (1H, d, J=2.6 Hz), 5.10–5.04 (2H, m), 5.00 (2H, s), 4.35 (1H, td, J=8.8, 4.4 Hz), 4.02–3.89 (3H, m), 2.94 (2H, br q, J=6.3 Hz), 1.80 (3H, s), 1.69–1.59 (1H, m), 1.51–1.21 (5H, m), 1.06–0.97 (28H, m); δ_C (100 MHz, DMSO-d_6) 172.8, 169.7, 159.7, 156.6, 153.1, 149.3, 140.7, 137.9, 128.9, 128.3, 119.8, 88.0, 82.8, 70.0, 65.6, 62.2, 54.6, 53.0, 42.3, 40.3, 40.1, 39.9, 33.1, 29.8, 23.4, 23.0, 17.9, 17.8, 17.42, 17.39, 17.36, 13.3, 13.1, 12.7, 12.6; HRMS-TSI-TOF m/z [M+H$^+$] calcd for

$C_{38}H_{60}N_8O_8Si_2$: 813.415; found: 813.415. Anal. Calcd for $C_{38}H_{60}N_8O_8Si_2$: C, 56.1; H, 7.4; N, 13.8. Found: C, 55.7; H, 7.4; N, 13.4.

4.2.8. 2′-(*N*-α-Benzyloxycarbonyl-L-IlePhe)-amino-2′-deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-adenosine (9). Using general procedure A, 220 mg of **5b** afforded 281 mg (72%) of **9** as a white solid, $[\alpha]_D^{20}$ −35.8 (*c* 0.01, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3324, 1706, 1652; δ_H (400 MHz, $CDCl_3$) 8.21 (1H, s), 7.95 (1H, s), 7.43–7.03 (10H, m), 5.90 (1H, d, *J*=3.4 Hz), 5.26 (1H, m), 5.10 (1H, d, *J*=12.1 Hz), 5.02 (1H, d, *J*=12.5 Hz), 4.78–4.73 (2H, m), 4.02–4.00 (4H, m), 3.12 (1H, dd, *J*=12.1 Hz, CHC*H*HPh), 2.91 (1H, dd, *J*=12.5 Hz, CHCH*H*Ph), 1.68–1.78 (1H, m), 1.32–1.24 (1H, m), 1.13–0.98 (29H, m), 0.81–0.77 (6H, m); δ_C (100 MHz, $CDCl_3$) 172.0, 156.5, 155.9, 152.9, 149.3, 140.4, 136.3, 136.2, 129.1, 128.5, 128.2, 128.0, 126.9, 120.0, 88.1, 83.5, 70.1, 67.0, 62.4, 59.8, 56.1, 54.4, 37.4, 37.0, 24.6, 17.5, 17.4, 17.3, 17.2, 17.08, 17.05, 17.0, 15.4, 13.1, 12.8, 12.6, 11.2; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{45}H_{66}N_8O_8Si_2$: 903.462; found: 903.462. Anal. Calcd for $C_{45}H_{66}N_8O_8Si_2$: C, 59.84; H, 7.37; N, 12.41. Found: C, 59.71; H, 7.46; N, 12.34.

4.3. Removal of the 1,1,3,3-tetraisopropyl-1,3-disiloxane-1,3-diyl protecting group of compounds 6a–g (general procedure B)

3′,5′-*O*-(Tetraisopropyldisiloxane-1,3-diyl)-protected compounds **6a–g** (1 equiv) were suspended in methanol (10 mL), ammonium fluoride (10 equiv) was added and the mixture was stirred at room temperature until TLC analysis (9:1 CH_2Cl_2/MeOH) indicated that there was no starting material left, usually taking at least 16 h. The solvent was removed under reduced pressure and the residue purified by column chromatography, eluting with 9:1 CH_2Cl_2/MeOH.

4.3.1. 2′-(*N*-α-Benzyloxycarbonyl-L-valinyl)-amino-2′-deoxyadenosine (7a). Using general procedure B, 208 mg of **6a** afforded 123 mg (88%) of **7a** as a white solid, $[\alpha]_D^{20}$ −59.0 (*c* 0.01, MeOH); ν_{max} (KBr)/cm^{-1} 3329, 1647, 1601; δ_H (400 MHz, CD_3OD) 8.20 (1H, s), 8.16 (1H, s), 7.37–7.23 (5H, m), 5.98 (1H, d, *J*=8.4 Hz), 5.99 (1H, dd, *J*=8.4, 3.2 Hz), 5.08 (1H, d, *J*=12.5 Hz), 5.03 (1H, d, *J*=12.5 Hz), 4.36 (1H, d, *J*=5.5 Hz), 4.24–4.16 (1H, m), 3.92–3.84 (2H, m), 3.77 (1H, dd, *J*=12.4, 2.2 Hz), 1.98–1.87 (1H, m), 0.82 (3H, d, *J*=7.0 Hz), 0.75 (3H, d, *J*=7.0 Hz); δ_C (100 MHz, CD_3OD) 173.1, 157.3, 156.2, 152.2, 149.0, 140.4, 136.8, 128.2, 127.8, 127.6, 119.6, 88.7, 88.3, 71.2, 66.5, 62.4, 60.8, 55.6, 30.1, 18.3, 16.9; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{23}H_{29}N_7O_6$: 500.218; found: 500.211. Anal. Calcd for $C_{23}H_{29}N_7O_6$: C, 55.3; H, 5.9; N, 19.6. Found: C, 55.3; H, 6.0; N, 19.9.

4.3.2. 2′-(*N*-α-Benzyloxycarbonyl-L-isoleucinyl)-amino-2′-deoxyadenosine (7b). Using general procedure B, 63 mg of **6b** afforded 29 mg (67%) of **7b** as a white solid, $[\alpha]_D^{20}$ −89.0 (*c* 0.01, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3336, 2963, 2367, 2344, 1772, 1734, 1700, 1684, 1647, 1601, 1576, 1560, 1540, 1508, 1457, 1420, 1374, 1333, 1252, 1095, 867, 798, 753, 648, 697; δ_H (400 MHz, CD_3OD) 8.21 (1H, s), 8.17 (1H, s), 7.39–7.23 (5H, m), 6.00 (1H, d, *J*=8.4 Hz), 5.19 (1H, dd, *J*=5.5, 8.4 Hz), 5.08 (1H, d, *J*=12.5 Hz), 5.04 (1H, d, *J*=12.5 Hz), 4.36 (1H, d, *J*=5.5 Hz), 4.24–4.16 (1H, m, *H*4′), 3.94 (1H, d, *J*=7.0 Hz), 3.88 (1H, dd, *J*=12.3, 2.4 Hz), 3.77 (1H, dd, *J*=12.3, 2.2 Hz), 1.73–1.60 (1H, m), 1.24–1.14 (1H, m), 0.69–0.81 (6H, m); δ_C (100 MHz, CD_3OD) 173.0, 157.3, 156.2, 152.2, 149.0, 140.4, 136.8, 128.2, 127.7, 127.6, 119.5, 88.7, 88.1, 71.2, 66.5, 62.4, 60.0, 55.6, 36.4, 24.3, 14.5, 10.1; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{24}H_{31}N_7O_6$: 514.234; found: 514.254. Anal. Calcd for $C_{24}H_{31}N_7O_6$: C, 56.1; H, 6.1; N, 19.1. Found: C, 56.4; H, 6.1; N, 18.9.

4.3.3. 2′-(*N*-α-Benzyloxycarbonyl-L-threoninyl)-amino-2′-deoxyadenosine (7c). Using general procedure B, 133 mg of **6c** afforded 80 mg (89%) of **7c** as a white solid, $[\alpha]_D^{20}$ −11.5 (*c* 0.01, MeOH); ν_{max} (KBr)/cm^{-1} 3333, 2930, 1652, 1603, 1509, 1424, 1376, 1334, 1301, 1253, 1092, 904, 867, 797, 737, 698, 644; δ_H (400 MHz, CD_3OD) 8.21 (1H, s), 8.16 (1H, s), 7.37–7.74 (5H, m), 6.00 (1H, d, *J*=8.0 Hz), 5.15–5.04 (3H, m), 4.40 (1H, d, *J*=5.5 Hz), 4.19–4.23 (1H, m), 3.95–4.05 (2H, m), 3.88 (1H, dd, *J*=12.4, 2.6 Hz), 3.77 (1H, dd, *J*=12.4, 2.6 Hz), 1.08 (3H, d, *J*=6.2 Hz); δ_C (100 MHz, CD_3OD) 172.0, 157.3, 156.2, 152.1, 148.9, 140.5, 136.7, 128.2, 127.8, 127.6, 119.6, 88.6, 88.5, 71.1, 66.9, 66.6, 62.4, 60.6, 56.0, 18.5; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{23}H_{29}N_7O_7$: 502.205; found: 502.206.

4.3.4. 2′-(*N*-α-Benzyloxycarbonyl-L-asparaginyl)-amino-2′-deoxyadenosine (7d). Using general procedure B, 89 mg of **6d** afforded 47 mg (78%) of **7d** as a white solid, $[\alpha]_D^{20}$ −58.6 (*c* 0.01, MeOH); δ_H (400 MHz, CD_3OD) 8.15 (1H, s), 8.09 (1H, s), 7.36–7.24 (5H, m), 5.93 (1H, d, *J*=8.4 Hz), 5.11 (1H, dd, *J*=8.2, 5.3 Hz), 5.06 (2H, s), 4.36–4.24 (2H, m), 4.21 (1H, br s), 3.87 (1H, dd, *J*=12.5, 2.2 Hz), 3.75 (1H, dd, *J*=12.5, 2.4 Hz), 2.59 (1H, dd, *J*=15.6, 6.1 Hz), 2.49 (1H, dd, *J*=15.6, 7.1 Hz); δ_C (100 MHz, CD_3OD) 175.0, 173.8, 158.3, 157.7, 153.5, 150.3, 142.1, 138.2 129.6, 129.2, 129.1, 121.2, 90.2, 89.9, 72.7, 68.0, 63.7, 57.3, 53.3, 37.9, 18.52; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{22}H_{26}N_8O_7$: 515.192; found: 515.200. Anal. Calcd for $C_{22}H_{26}N_8O_7$: C, 51.36; H, 5.09; N, 21.78. Found: C, 51.40; H, 5.16; N, 21.71.

4.3.5. 2′-(*N*-α-Benzyloxycarbonyl-L-phenylalaninyl)-amino-2′-deoxyadenosine (7e). Using general procedure B, 213 mg of **6e** afforded 128 mg (87%) of **7e** as a white solid, $[\alpha]_D^{20}$ −81.0 (*c* 0.01, MeOH); ν_{max} (KBr)/cm^{-1} 3310, 3170, 2918, 1731, 1652, 1603, 1516, 1496, 1454, 1375, 1336, 1301, 1223, 1093, 1044, 985, 905, 867, 797, 744, 697, 638, 492; δ_H (400 MHz, CD_3OD) 8.27 (1H, s), 8.15 (1H, s), 7.36–7.16 (10H, m), 5.99 (1H, d, *J*=8.1 Hz), 5.84 (1H, d, *J*=4.4 Hz), 5.60 (1H, dd, *J*=4.4, 7.0 Hz), 5.12–5.07 (1H, m), 4.93 (1H, d, *J*=12.5 Hz), 4.87 (1H, d, *J*=12.8 Hz), 4.27–4.24 (2H, m), 4.08 (1H, s), 2.91 (1H, dd, *J*=4.0, 13.5 Hz), 2.67 (1H, dd, *J*=10.6, 13.9 Hz); δ_C (100 MHz, CD_3OD) 172.3, 156.7, 156.3, 152.9, 149.9, 140.3, 138.5, 137.5, 129.7, 128.9, 128.6, 128.2, 128.0, 126.8, 119.9, 88.0, 86.9, 71.0, 65.9, 62.5, 56.7, 55.3, 38.0; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{27}H_{29}N_7O_6$: 548.218; found: 548.226.

4.3.6. 2′-(*N*-α-Benzyloxycarbonyl-L-prolinyl)-amino-2′-deoxyadenosine (7f). Using general procedure B, 227 mg

of **6f** afforded 136 mg (89%) of **7f** as a white solid, $[\alpha]_D^{20}$ −115.8 (*c* 0.01, MeOH); ν_{max} (KBr)/cm^{-1} 3306, 2915, 2359, 1711, 1678, 1644, 1604, 1524, 1407, 1357, 1339, 1301, 1098, 984, 798, 743, 695, 647; δ_H (400 MHz, CD_3OD) 8.20 (1H, s), 8.11 (1H, s), 7.35–7.21 (5H, m), 5.95 (1H, d, *J*=8.0 Hz), 5.75 (1H, s), 5.55–5.52 (1H, m), 5.07–4.93 (3H, m), 4.54 (1H, d, *J*=13.2 Hz), 4.27–4.22 (2H, m), 4.04 (1H, d, *J*=1.5 Hz), 3.70–3.67 (1H, m), 3.61–3.55 (1H, m), 3.36–3.21 (2H, m), 2.09–1.96 (1H, m), 1.79–1.73 (3H, m); δ_C (100 MHz, CD_3OD) 174.2, 156.2, 154.9, 152.3, 149.0, 140.2, 136.6, 126.8–128.2, 119.8, 88.8, 88.6, 71.2, 67.0, 62.6, 60.4, 55.9, 46.7, 29.8, 24.1; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{23}H_{27}N_7O_6$: 498.202; found: 498.210.

4.3.7. 2′-(*N*-α-Acetyl-*N*-ω-benzyloxycarbonyl-L-lysinyl)-amino-2′-deoxyadenosine (5g). Using general procedure B, 176 mg of **6g** afforded 111 mg (88%) of **7g** as a white solid, $[\alpha]_D^{20}$ −71.0 (*c* 0.1, MeOH); ν_{max} (KBr)/cm^{-1} 3420, 1701, 1684, 1650, 1542, 1260, 1094, 733, 698, 646; δ_H (400 MHz, CD_3OD) 8.20 (1H, s), 8.17 (1H, s), 7.33–7.26 (5H, m), 5.98 (1H, d, *J*=8.3 Hz), 5.14 (1H, dd, *J*=8.3, 5.5 Hz), 5.05 (2H, s), 4.38 (1H, d, *J*=5.5 Hz), 4.23–4.19 (2H, m), 3.88 (1H, dd, *J*=12.6, 2.6 Hz), 3.76 (1H, dd, *J*=12.6, 2.4 Hz), 3.07 (2H, t, *J*=7.0 Hz), 1.91 (3H, s), 1.67–1.40 (4H, 3×m), 1.32–1.19 (2H, m); δ_C (100 MHz, CD_3OD) 173.3, 172.1, 157.6, 156.2, 152.1, 148.9, 140.4, 137.1, 128.1, 127.6, 127.4, 119.6, 88.6, 88.5, 71.1, 66.0, 62.4, 55.7, 53.5, 40.1, 30.9, 29.2, 22.6, 21.0; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{26}H_{34}N_8O_7$: 570.263; found: 570.262.

4.3.8. 2′-(*N*-α-Benzyloxycarbonyl-L-IlePhe)-amino-2′-deoxyadenosine (10). Using general procedure B, 242 mg of **9** afforded 117 mg of **10** as a white solid, $[\alpha]_D^{20}$ −115.8 (*c* 0.01, MeOH); ν_{max} (KBr)/cm^{-1} 3320, 1648, 1599; δ_H (400 MHz, CD_3OD) 8.25 (1H, s), 8.13 (1H, s), 7.34–7.11 (10H, m), 5.96 (1H, d, *J*=8.1 Hz), 5.71 (1H, d, *J*=4.4 Hz), 5.54 (1H, dd, *J*=4.4, 7.0 Hz), 5.11–5.06 (1H, m), 5.06–4.97 (2H, m), 4.57–4.52 (1H, m), 4.24 (1H, t, *J*=2.8 Hz), 4.05 (1H, s), 3.79 (1H, t, *J*=8.4 Hz), 3.70–3.66 (1H, m), 3.60–3.54 (1H, m), 2.92 (1H, dd, *J*=4.8, 13.9 Hz), 2.73 (1H, dd, *J*=9.5, 13.9 Hz), 1.57–1.51 (1H, m), 1.27–1.20 (1H, m), 0.98–0.91 (1H, m), 0.70 (3H, t, *J*=7.3 Hz), 0.55 (3H, t, *J*=7.0 Hz); δ_C (100 MHz, CD_3OD) 171.7, 171.5, 156.7, 156.4, 152.9, 149.9, 140.2, 138.1, 137.6, 129.7, 128.9, 128.5, 128.3, 128.2, 126.7, 199.9, 87.9, 86.7, 71.1, 65.9, 62.4, 59.7, 55.2, 54.1, 49.2, 37.9, 36.9, 24.8, 15.6, 11.3; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{33}H_{40}N_8O_7$: 661.310; found: 661.311.

4.4. Removal of the *N*-Cbz protecting group (general procedure C)

The *N*-Cbz protected compounds **7a–g** (1 equiv) was suspended in methanol (6 mL), 10% palladium on carbon was added and the mixture was stirred at room temperature under balloon pressure of hydrogen gas until TLC analysis (9:1 CH_2Cl_2/MeOH) indicated that there was no starting material left. The catalyst was filtered off through a pad of Celite® and washed well with methanol. The solvent was removed under reduced pressure affording the product as a white powder.

4.4.1. 2′-(L-Valinyl)-amino-2′-deoxyadenosine (8a). Using general procedure C, 109 mg of **7a** and 23 mg 10% Pd on C afforded 77 mg (96%) **8a** as a white powder, $[\alpha]_D^{20}$ −15.0 (*c* 0.01, MeOH); ν_{max} (KBr)/cm^{-1} 3333, 1649, 1603; δ_H (400 MHz, CD_3OD) 8.30 (1H, s), 8.18 (1H, s), 6.06 (1H, d, *J*=8.1 Hz), 5.26 (1H, dd, *J*=8.2, 5.3 Hz), 4.39 (1H, dd, *J*=5.1, 1.1 Hz), 4.23–4.18 (1H, m), 3.87 (1H, dd, *J*=12.5, 2.6 Hz), 3.77 (1H, dd, *J*=12.5, 2.6 Hz), 3.55 (1H, d, *J*=3.6 Hz), 2.15–2.05 (1H, m), 1.00 (3H, d, *J*=7.0 Hz), 0.94 (3H, d, *J*=7.0 Hz); δ_C (100 MHz, CD_3OD) 170.5, 156.2, 152.3, 149.0, 140.3, 119.5, 88.5, 87.7, 71.0, 62.3, 58.6, 55.8, 30.5, 17.7, 16.2; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{15}H_{23}N_7O_4$: 366.181; found: 366.186.

4.4.2. 2′-(L-Isoleucinyl)-amino-2′-deoxyadenosine (8b). Using general procedure C, 42 mg of **7b** and 9 mg 10% Pd on C afforded 31 mg (99%) of **8b** as a white powder, $[\alpha]_D^{20}$ −102.7 (*c* 0.01, MeOH); ν_{max} (KBr)/cm^{-1} 3333, 1648, 1603, 1516, 1479, 1423, 1375, 1303, 1248, 1093, 886, 648; δ_H (400 MHz, CD_3OD) 8.29 (1H, s), 8.18 (1H, s), 6.03 (1H, d, *J*=8.4 Hz), 5.21 (1H, dd, *J*=8.4, 5.5 Hz), 4.37 (1H, d, *J*=5.1 Hz), 4.23–4.19 (1H, m), 3.87 (1H, dd, *J*=2.9, 12.5 Hz), 3.77 (1H, dd, *J*=2.6, 12.4 Hz), 3.39 (1H, m), 1.69–1.61 (1H, m), 1.23–1.13 (2H, m), 0.85 (3H, d, *J*=7.0 Hz), 0.77 (3H, t, *J*=7.3 Hz); δ_C (100 MHz, CD_3OD) 175.5, 156.2, 152.3, 149.1, 140.4, 119.5, 88.6, 87.9, 71.3, 62.4, 59.4, 55.5, 38.3, 23.6, 14.7, 10.7; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{16}H_{25}N_7O_4$: 380.205; found: 380.209. Anal. Calcd for $C_{16}H_{25}N_7O_4$: C, 50.65; H, 6.64; N, 25.84. Found: C, 50.61; H, 6.73; N, 25.73.

4.4.3. 2′-(L-Threoninyl)-amino-2′-deoxyadenosine (8c). Using general procedure C, 45 mg of **7c** and 19 mg 10% Pd on C afforded 32 mg (97%) of **8c** as a white powder, $[\alpha]_D^{20}$ −56.4 (*c* 0.01, MeOH); ν_{max} (KBr)/cm^{-1} 3339, 1653, 1603, 1479, 1425, 1376, 1334, 1303, 1251, 1093, 900, 797, 645; δ_H (400 MHz, CD_3OD) 8.26 (1H, s), 8.17 (1H, s), 6.01 (1H, d, *J*=8.4 Hz), 5.16 (1H, dd, *J*=8.0, 5.5 Hz), 4.41 (1H, dd, *J*=5.5, 1.1 Hz), 4.24–4.19 (1H, m), 3.89 (1H, dd, *J*(AB)=12.5, 2.9 Hz, *H5′*), 3.85–3.81 (1H, m, $HOCH_2C\mathit{H}CH_3$), 3.77 (1H, dd, *J*(AB)=12.5, 2.6 Hz, *H5′*), 3.17–3.11 (2H, m, $HOC\mathit{H}_2CHCH_3$), 1.10 (3H, d, *J*=6.24 Hz, $C\mathit{H}_3$); ^{13}C NMR 174.0, 156.2, 152.2, 148.9, 140.5, 119.6, 88.5, 71.3, 67.9, 62.4, 60.1, 55.7, 18.5; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{15}H_{23}N_7O_5$: 380.205; found: 380.209.

4.4.4. 2′-(L-Asparaginyl)-amino-2′-deoxyadenosine (8d). Using general procedure C, 38 mg of **7d** and 20 mg 10% Pd on C afforded 27 mg (96%) of **8d** as a white powder, $[\alpha]_D^{20}$ −90.3 (*c* 0.01, MeOH); ν_{max} (KBr)/cm^{-1} 3341, 2931, 2362, 2342, 1653, 1603, 1578, 1560, 1541, 1522, 1508, 1580, 1422, 1377, 1335, 1302, 1253, 1092, 1064, 896, 867, 797, 728, 668, 645; δ_H (400 MHz, DMSO-d_6) 8.28 (1H, s), 8.17 (1H, s), 7.37 (1H, br s), 6.88 (1H, br s), 5.98 (1H, d, *J*=8.1 Hz), 5.86 (1H, d, *J*=4.4 Hz), 5.74 (1H, dd, *J*=7.7, 4.0 Hz), 5.04 (1H, m), 4.29 (1H, t, *J*=4.8 Hz), 4.09–4.11 (1H, m), 3.68–3.73 (1H, m), 3.60–3.66 (1H, m), 2.34 (1H, dd, *J*=14.7, 3.7 Hz), 2.04 (1H, dd, *J*=15.0, 9.5 Hz); δ_C (100 MHz, CD_3OD) 175.3, 174.4, 156.2, 152.2, 148.9, 140.7, 119.7, 88.5, 88.4, 71.4, 62.5, 55.9, 51.8, 39.5; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{14}H_{20}N_8O_5$: 381.163; found: 381.164. Anal. Calcd for

$C_{14}H_{20}N_8O_5$: C, 44.21; H, 5.30; N, 29.46. Found: C, 44.08; H, 5.38; N, 29.41.

4.4.5. 2′-(L-Phenylalaninyl)-amino-2′-deoxyadenosine (8e). Using general procedure C, 90 mg of **7e** and 25 mg 10% Pd on C afforded 55 mg (81%) of **8e** as a white powder, $[\alpha]_D^{20}$ −94.1 (*c* 0.01, MeOH); ν_{max} (KBr)/cm^{-1} 3308, 3166, 2916, 2359, 1676, 1644, 1603, 1519, 1477, 1301, 1096, 987, 867, 797, 700, 648, 534, 488; δ_H (400 MHz, CD_3OD) 8.31 (1H, s), 8.15 (1H, s), 7.36 (2H, s), 7.12 (2H, d, *J*=1.8 Hz), 6.99 (1H, t, *J*=3.2 Hz), 5.93 (1H, d, *J*=8.4 Hz), 5.88 (1H, s), 5.63 (1H, s), 5.06 (1H, d, *J*=4.4 Hz), 4.22 (1H, d, *J*=3.3 Hz), 4.06 (1H, s), 3.71–3.69 (1H, m), 3.61–3.58 (1H, m), 3.38 (1H, t, *J*=4.8 Hz), 2.73 (1H, dd, *J*=4.4, 13.2 Hz), 2.54 (1H, dd, *J*=8.1, 13.6 Hz, CHCH*H*Ph); δ_C (100 MHz, CD_3OD) 174.9, 156.7, 152.9, 149.9, 140.4, 138.7, 129.7, 128.6, 119.9, 88.1, 87.1, 71.4, 62.5, 56.4, 54.8, 40.8; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{19}H_{23}N_7O_4$: 414.189; found: 414.189. Anal. Calcd for $C_{19}H_{23}N_7O_4$: C, 55.20; H, 5.61; N, 23.72. Found: C, 55.08; H, 5.69; N, 23.65.

4.4.6. 2′-(L-Prolinyl)-amino-2′-deoxyadenosine (8f). Using general procedure C, 110 mg of **7f** and 32 mg 10% Pd on C afforded 80 mg (99%) of **8f** as a white powder, $[\alpha]_D^{20}$ −112.4 (*c* 0.01, MeOH); ν_{max} (KBr)/cm^{-1} 3303, 3164, 2912, 2341, 1679, 1631, 1606, 1526, 1478, 1421, 1302, 1242, 1100, 983, 871, 798, 692, 668; δ_H (400 MHz, CD_3OD) 8.29 (1H, s), 8.10 (1H, s), 5.91 (1H, d, *J*=8.4 Hz), 4.93–4.87 (1H, m), 4.20 (1H, d, *J*=4.8 Hz), 4.09 (1H, s), 3.71 (1H, d, *J*=10.8 Hz), 3.61 (1H, d, *J*=10.8 Hz), 3.44 (1H, dd, *J*=5.2, 9.2 Hz), 2.86–2.80 (1H, m), 2.72–2.66 (1H, m), 1.78–1.70 (1H, m), 1.49–1.34 (2H, m), 1.31–1.24 (1H, m); δ_C (100 MHz, CD_3OD) 175.0, 156.6, 152.8, 149.7, 140.1, 119.8, 88.4, 87.6, 71.5, 62.5, 60.6, 55.2, 47.1, 30.9, 26.1; HRMS-FAB: *m/z* [M+H$^+$] calcd for $C_{15}H_{21}N_7O_4$: 364.173; found: 364.173. Anal. Calcd for $C_{15}H_{21}N_7O_4$: C, 49.58; H, 5.83; N, 26.98. Found: C, 49.46; H, 5.83; N, 26.86.

4.4.7. 2′-(*N*-α-Acetyl-L-lysinyl)-amino-2′-deoxyadenosine (8g). Using general procedure C, 86 mg of **7g** and 16 mg 10% Pd on C afforded 56 mg (86%) of **8g** as an off-white solid, $[\alpha]_D^{20}$ −93.3 (*c* 0.75, MeOH); ν_{max} (KBr)/cm^{-1} 3406, 2930, 2863, 1653, 1603, 1575, 1558, 1544, 1429, 1377, 1335, 1303, 1253, 1095, 648; δ_H (400 MHz, CD_3OD) 8.22 (1H, s), 8.17 (1H, s), 5.99 (1H, d, *J*=8.2 Hz), 5.14 (1H, dd, *J*=8.2, 5.3 Hz), 4.37 (1H, d, *J*=5.3 Hz), 4.24–4.21 (2H, m), 3.88 (1H, dd, *J*=12.5, 2.6 Hz), 3.77 (1H, dd, *J*=12.5, 2.6 Hz), 2.60 (2H, t, *J*=7.3 Hz), 1.93 (3H, s), 1.67–1.49 (2H, 2×m), 1.43 (2H, quintet, *J*=7.3 Hz), 1.21–1.34 (2H, m); δ_C (100 MHz, CD_3OD) 173.2, 172.1, 156.2, 152.1, 149.0, 140.4, 119.6, 88.6, 88.4, 71.1, 62.4, 55.7, 53.5, 40.6, 31.2, 31.1, 22.7, 21.0; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{18}H_{28}N_8O_5$: 437.226; found: 437.226.

4.4.8. 2′-(L-IlePhe)-amino-2′-deoxyadenosine (11). Using general procedure C, 40 mg of **10** and 13 mg 10% Pd on C afforded 30 mg (94%) of **11** as a white powder, $[\alpha]_D^{20}$ −74.3 (*c* 0.004, MeOH); ν_{max} (KBr)/cm^{-1} 3326, 1652, 1601; δ_H (400 MHz, CD_3OD) 8.21 (1H, s), 8.17 (1H, s), 7.22–7.13 (5H, m), 5.99 (1H, d, *J*=8.4 Hz), 5.15 (1H, dd, *J*=5.5, 8.4 Hz), 4.60 (1H, dd, *J*=6.2, 8.0 Hz), 4.27 (1H, d, *J*=5.5 Hz), 3.86 (1H, dd, *J*=2.3, 12.4 Hz), 3.75 (1H, dd, *J*=2.1, 10.3 Hz), 3.02–2.95 (1H, m), 2.86–2.81 (1H, m), 1.55–1.47 (1H, m), 1.19–1.11 (1H, m), 0.96–0.88 (1H, m), 0.74 (3H, t, *J*=7.3 Hz), 0.67 (3H, d, *J*=7.0 Hz); δ_C (100 MHz, CD_3OD) 175.7, 172.4, 156.2, 152.1, 149.0, 140.5, 136.9, 128.9, 128.2, 126.5, 119.7, 88.6, 88.2, 71.2, 64.1, 62.4, 55.6, 54.5, 37.8, 37.4, 23.8, 14.6, 10.5; HRMS-FAB *m/z* [M+H$^+$] calcd for $C_{25}H_{34}N_8O_5$: 527.273; found: 527.273.

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Supplementary data

^{1}H NMR spectra of compounds **7f**, **8g**, **10** and **11**, and ^{13}C NMR spectra for compounds **7c**, **7e**, **8a**, **8c**, **8f** and **10**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.04.038.

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