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A versatile intermediate for the synthesis of 3′-substituted 2′,3′-didehydro-2′,3′-dideoxyadenosine (d4A): preparation of 3′-*C*-stannyl-d4A via radical-mediated desulfonylative stannylation

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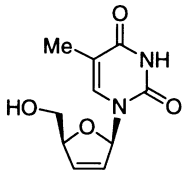
Abstract—A method is described for the introduction of a tributylstannyl group to the 3′-position of 2′,3′-didehydro-2′,3′-dideoxyadenosine (**2**: d4A). Transalkoxylation of Bu_3SnOMe with d4A and subsequent anionic O⟶C stannyl migration gave 3′-*C*-tributylstannyl-d4A (**5**), but only in a low yield. An alternative route involves several reactions starting from 9-[2,3-anhydro-5-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-N^6-pivaloyladenine (**14**): ring opening with NaSPh, oxidation of the 3′-*C*-phenylthio group, removal of the N^6-pivaloyl group, 2′-*O*-mesylation, elimination of methanesulfonic acid, and tin radical-mediated substitution of the 3′-*C*-benzenesulfonyl group. The overall yield of this approach was 55% from **14**. The synthetic utility of 5′-*O*-(*tert*-butyldimethylsilyl)-3′-*C*-tributylstannyl-d4A (**18**) thus obtained was briefly exemplified by the preparation of some 3′-substituted analogues (**19**–**23**: I, Br, Ph, vinyl, and phenylethynyl).

1. Introduction

2′,3′-Didehydro-2′,3′-dideoxynucleosides constitute an important class of compounds for anti-HIV drug candidates.[1] Although approval of stavudine (2′,3′-didehydro-3′-deoxythymidine: d4T, **1**)[2] as a drug for the treatment of AIDS has stimulated the synthesis[3] and evaluation[4–7] of this class of nucleosides, there seems to be no general synthetic method available to provide diversity at the 3′- (or 2′-) substituent.



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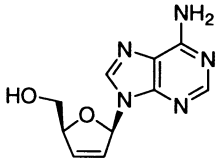

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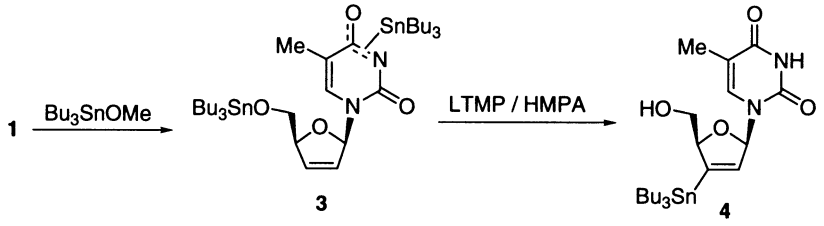
In this article, we describe a method for the introduction of a tributylstannyl group to the 3′-position of 2′,3′-didehydro-2′,3′-dideoxyadenosine (d4A, **2**) based on radical-mediated desulfonylative stannylation. Also described here is further manipulations of the introduced stannyl group, which allows the preparation of various types of 3′-substituted d4A analogues.

1.1. Attempted anionic stannyl migration of d4A

Since the transformation of a trialkylstannyl group attached to an sp^2-carbon atom to halogen and a range of carbon-substituents is well appreciated,[8] construction of a vinylstannane structure in d4A would be an ideal intermediate for the present purpose. As a part of our lithiation studies of



Scheme 1.

Keywords: nucleosides; tin and compounds; radicals and radical reactions.

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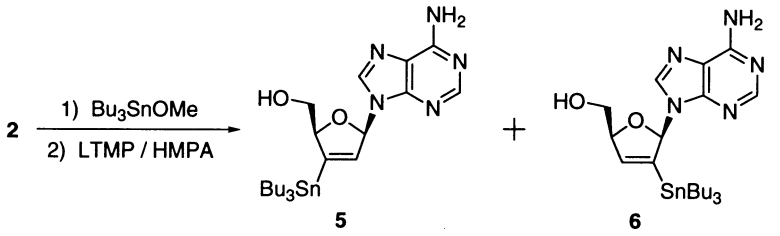


Scheme 2.

nucleosides,[9] we recently reported that reaction between Bu_3SnOMe and d4T (**1**) yielded the transalkoxylation product **3**, and that treatment of this compound with LTMP (lithium 2,2,6,6-tetramethylpiperidide)-HMPA in THF gave the 3′-*C*-tributylstannyl-d4T (**4**), as a result of lithiation-mediated stannyl migration from the 5′-oxygen to the 3′-carbon (Scheme 1).[10] We therefore initiated the present study which examines a purine version of this anionic migration.

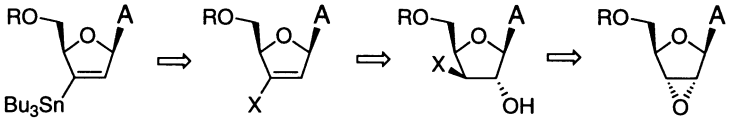
Transalkoxylation between d4A (**2**) and Bu_3SnOMe (3 equiv.) was carried out neat at 90°C for 2 h. The resulting product showed five ^{119}Sn-resonances (δ 27.2, 29,1, 86.3, 101.6, and 107.2) in its NMR spectrum measured in benzene-d_6. The two resonances, δ 86.3 and 101.6, were attributable to those of $(Bu_3Sn)_2O$[11] and Bu_3SnOMe, respectively. Among the remaining three ^{119}Sn-resonances, one at the lowest field (δ 107.2) was assigned to a tin atom attached to the 5′-oxygen by comparison with our previous data of **3**.[10] Unfortunately, this compound was not pure enough to confirm the presence of a 5′-*O*-Sn bond based on $^3J_{Sn,H}$-splitting of H-5′ by ^{1}H NMR spectroscopy.

When the above stannylated d4A derivative was treated with LTMP (7.5 equiv.) in the presence of HMPA (15 equiv.) in THF at −78°C, an inseparable mixture of the 3′- and 2′-stannylated products (**5**/**6**=1/0.3) was obtained in only 20% yield with a large amount of d4A (**2**) being recovered (Scheme 2). Formation of adenine, which is assumed to have resulted from deprotonation of H-4′, was also detected. The depicted regiochemistry of **5** and **6** came from the ^{1}H NMR observation of $^3J_{Sn,H}$-splitting (28.0 Hz) in H-2′ of **5** (δ 5.91) and H-3′ of **6** (δ 6.40). The observed low yield formation of the desired **5**, which cannot be separated from **6**, led us to investigate an alternative method.

1.2. Radical-mediated desulfonylative stannylation

Literature survey as well as our own report suggested that tin radical-mediated substitution of vinyl selenides,[12] sulfides,[13] and sulfones[14] would be an appropriate approach to prepare the 3′-*C*-stannylated d4A, although the detailed mechanism of these reactions is not clear at the present time. Since 2′,3′-anhydroribonucleosides are known to undergo nucleophilic ring-opening regioselectively at the 3′-position,[15] one would readily propose a synthetic plan shown in Scheme 3.

We first attempted to construct a vinyl selenide structure (Scheme 4). Silylation of 9-(2,3-anhydro-β-D-ribofuranosyl)-adenine (**7**)[16] by a conventional method gave **8** in 88% yield. Nucleophilic opening of the oxirane ring of **8** with a selenide anion was carried out by using $(PhSe)_2/LiAlH_4$ which has been successfully employed for ring cleavage of various types of anhydro-uracilnucleosides.[17] The reaction proceeded with complete regioselectivity, forming the 3′-phenylselenenyl derivative **9** in 87% yield. When **9** was

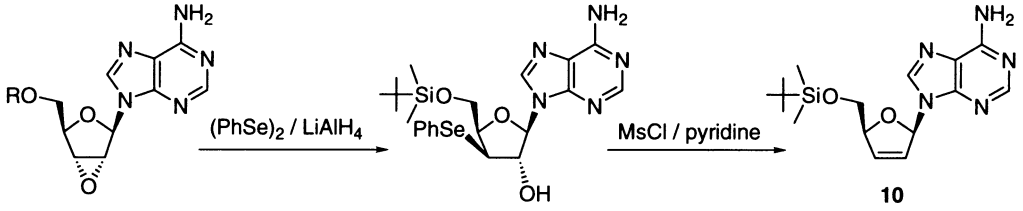


X = SePh, SPh, SO_2Ph

R = protecting group

A = adenin-9-yl or N^6-protected adenin-9-yl

Scheme 3.

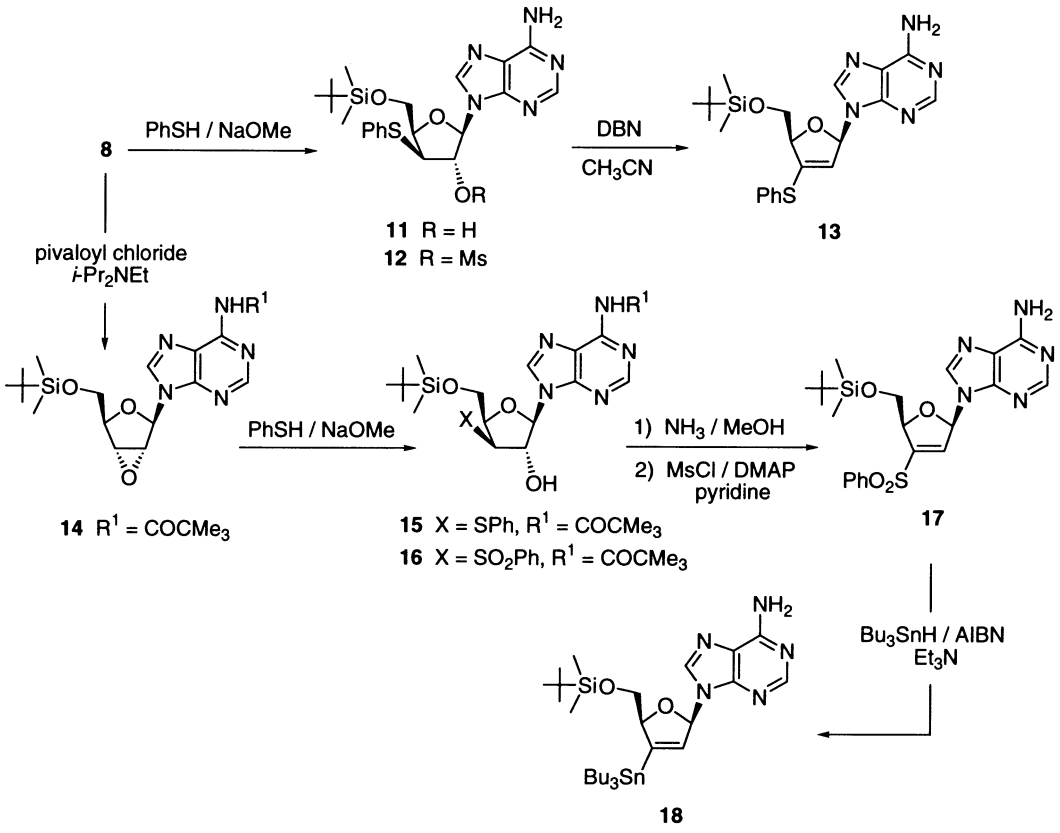


7 R = H

8 R = TBDMS

9

Scheme 4.



Scheme 5.

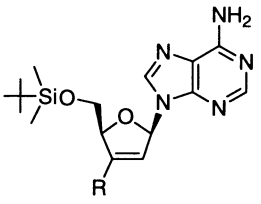
reacted with MsCl in pyridine (0°C, overnight), however, reductive elimination took place to give **10** in 72% yield.[18] Although the expected mesylate was formed upon conducting the reaction at 0°C in CH_3CN containing iPr_2NEt and DMAP, it was further converted to **10** during column chromatography. Simple extractive workup followed by treatment with KOBu-*t*/DMF also resulted in the sole formation of **10**. Although these results are in contrast to a transformation of 1-(2,3-anhydro-β-D-lyxofuranosyl)uracil to a vinyl selenide,[19] we turned our attention to prepare the vinyl sulfide and vinyl sulfone derivatives of d4A (Scheme 5).

Introduction of a phenylthio group into the 3′-position of **8** was carried out simply by reacting with NaSPh to give **11** in quantitative yield. Mesylation of **11** gave **12** (98%). The vinyl sulfide **13** was prepared in 78% yield by reacting **12** with DBN in refluxing CH_3CN. Compound **13** was, however, recovered unchanged (88%) upon treatment with Bu_3SnH/AIBN in refluxing benzene for 8 h. Similar reaction in refluxing toluene also met with recovery of **13**. This failure combined with successful precedents[13] led us to assume that, for reaction of tin-radical, conjugation of the 2′,3′-double bond with a carbonyl or sulfonyl group would be necessary, although this may not be the case for the reported similar reaction of vinyl selenides.[12]

Since attempted chemoselective oxidation of **13** resulted in concurrent N-oxidation of the adenine moiety, construction of a vinyl sulfone structure was started with N^6-pivaloylation of **8** (yield of **14**: 97%). Ring opening of **14** (yield of **15**: 90%) was followed by *m*-CPBA oxidation to give the β-hydroxysulfone **16** (100%). Removal of the N^6-pivaloyl group in **16** and subsequent mesylation by a conventional method (MsCl/DMAP/pyridine) directly furnished the vinyl sulfone **17** (81% for two steps).[20]

Radical-mediated desulfonylative stannylation of **17** proceeded efficiently by reacting with Bu_3SnH (3 equiv.)/AIBN in refluxing benzene for 5.5 h. Quite unexpectedly, however, elution of the reaction mixture from silica gel column gave only a trace amount of the desired product (**18**). After several attempts to overcome this problem, we found that the presence of Et_3N (4 equiv.) in the reaction medium enabled column chromatographic isolation of **18** in 76% yield, together with recovered **17** (17%). No appreciable amount of the reduced product (**10**) was formed in this reaction. *ipso*-Substitution with the tin radical was confirmed by HMBC (heteronuclear multiple bond connectivity) experiment of **18** in $CDCl_3$: the 3′-quaternary carbon (δ 149.6) showed correlation to H-1′ as well as to H-5′.

Finally, transformation of the 3′-*C*-stannyl derivative (**18**) was briefly examined. Iodination of **18** with iodine in THF gave **19** only in 42%, presumably due to depurination. Simple replacement of iodine with NIS increased the yield of **19** to 70%. Bromination was carried out in a similar manner by using NBS to give **20** in quantitative yield. The 3′-*C*-phenyl derivative **21** (66%) was prepared by the Stille reaction[21] between **18** and iodobenzene in DMF. As an example of reversed version of the Stille reaction, **19** was reacted with tributylvinyltin to give the 3′-*C*-vinyl derivative (**22**) in 51% yield. Cross-coupling reaction of **19** with a terminal alkyne[22] gave **23** in 89% yield.



19 R = I
20 R = Br
21 R = Ph
22 R = vinyl
23 R = (phenyl)ethynyl

2. Conclusions

Synthesis of 5′-*O*-(*tert*-butyldimethylsilyl)-3′-*C*-(tributylstannyl)-2′,3′-didehydro-2′,3′-dideoxyadenosine (**18**) was accomplished in 55% overall yield by a sequence of reactions starting from 9-[2,3-anhydro-5-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]adenine (**14**). The final and key step, radical-mediated displacement with tributylstannyl group did not work with vinyl sulfide, and it seems crucial to activate the 2′,3′-double bond by conjugation with the 3′-*C*-benzenesulfonyl group. Compound **18** can be readily converted to the 3′-iodo derivative **19**. The synthetic utility of these compounds (**18** and **19**) was briefly exemplified by the preparation of the 3′-carbon-substituted d4T analogues **21**–**23**.

3. Experimental

Melting points are uncorrected. NMR was measured at 400 MHz. Chemical shifts are reported relative to Me_4Si, except the cases of ^{119}Sn NMR where Me_4Sn was used as an internal standard. Mass spectra (MS) were taken in FAB mode with *m*-nitrobenzyl alcohol as a matrix. Column chromatography was carried out on silica gel (Silica Gel 60, Merck). Thin layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254}, Merck).

3.1. Anionic stannyl migration of d4A

A mixture of **2** (300 mg, 1.28 mmol) and Bu_3SnOMe (1.1 mL, 3.85 mmol) was heated at 90°C for 2 h with stirring. The mixture was dried under reduced pressure and then dissolved in THF (8 mL). The resulting solution was added to a mixture of LTMP (9.65 mmol) and HMPA (3.35 mL, 19.3 mmol) in THF (15 mL) at −78°C, under positive pressure of dry Ar. After 20 min, the reaction mixture was treated with saturated aqueous NH_4Cl, and extracted with EtOAc. The extract was purified twice by column chromatography (hexane/EtOAc=1/5) to give a mixture of **5** and **6** (132 mg, 20%, **5**/**6**=1/0.3 calculated by integrating H-2′ of **5** and H-3′ of **6**).

3.1.1. 9-[2,3-Anhydro-5-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]adenine (8). A mixture of **7** (5.0 g, 20.06 mmol), *tert*-butyldimethylsilyl chloride (6.0 g, 40.12 mmol), and imidazole (4.1 g, 60.18 mmol) in DMF (40 mL) was stirred at 0°C for 25 min. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. Column chromatography ($CHCl_3$/MeOH=30/1) of the organic layer gave **8** (6.4 g, 88%) as a solid: mp 166–174°C; UV (MeOH) λ_{max} 259 nm (ε 14,300), λ_{min} 226 nm (ε 300); ^1H NMR ($CDCl_3$) δ 0.02 and 0.04 (6H, each as s, SiMe), 0.85 (9H, s, SiBu-*t*), 3.76 (1H, dd, *J*=4.8 and 10.8 Hz, H-5′), 3.83 (1H, dd, *J*=6.0 and 10.8 Hz, H-5′), 4.09 (1H, d, *J*=2.8 Hz, H-2′), 4.37 (1H, dd, *J*=4.8 and 6.0 Hz, H-4′), 4.40 (1H, d, *J*=2.8 Hz, H-3′), 5.69 (2H, br, NH_2), 6.22 (1H, s, H-1′), 8.08 and 8.35 (2H, each as s, H-2 and H-8); FAB-MS *m*/*z* 364 (M^++H). Anal. calcd for $C_{16}H_{25}N_5O_3Si$: C, 52.87; H, 6.93; N, 19.27. Found: C, 52.62; H, 6.64; N, 19.44.

3.1.2. 9-[5-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3-*C*-phenylselenenyl-β-D-xylofuranosyl]adenine (9). To a solution of $(PhSe)_2$ (1.20 g, 3.84 mmol) in dioxane (10 mL) was added $LiAlH_4$ (109 mg, 2.88 mmol) under positive pressure of dry Ar, and the mixture was stirred for 0.5 h. To this was added a dioxane (10 mL) solution of **8** (583 mg, 1.60 mmol). The reaction mixture was stirred for 20 min at room temperature and then was refluxed for 4 h. After being quenched with AcOH, the reaction mixture was evaporated. Column chromatography ($CHCl_3$/MeOH=20/1) of the residue gave **9** (721 mg, 87%) as a foam: UV (MeOH) λ_{max} 261 nm (ε 17,700), λ_{min} 230 nm (ε 5900); ^1H NMR ($CDCl_3$) δ −0.11 and −0.10 (6H, each as s, SiMe), 0.69 (9H, s, SiBu-*t*), 3.90–3.96 (2H, m, H-5′ and H-3′), 4.06 (1H, dd, *J*=2.0 and 11.6 Hz, H-5′), 4.67–4.70 (1H, m, H-4′), 4.82 (1H, dd, *J*=5.6 and 10.0 Hz, H-2′), 5.76 (1H, d, *J*=5.6 Hz, H-1′), 6.13 (2H, br, NH_2), 7.28–7.30 (3H, m, Ph), 7.67–7.71 (2H, m, Ph), 8.07 and 8.77 (2H, each as s, H-2 and H-8); FAB-MS *m*/*z*: 520 for ^{78}Se and 522 for ^{80}Se (M^++H). Anal. calcd for $C_{22}H_{31}N_5O_3SeSi$: C, 50.76; H, 6.00; N, 13.45. Found: C, 50.80; H, 6.07; N, 13.33.

3.1.3. 5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxyadenosine (10). This compound was obtained as a foam: UV (MeOH) λ_{max} 260 nm (ε 14,300), λ_{min} 226 nm (ε 900); ^1H NMR ($CDCl_3$) δ 0.05 (6H, s, SiMe), 0.89 (9H, s, SiBu-*t*), 3.79–3.87 (2H, m, H-5′), 4.97–5.00 (1H, m, H-4′), 5.07 (2H, br, NH_2), 6.04–6.06 (1H, m, H-2′), 6.39–6.41 (1H, m, H-3′), 7.10–7.11 (1H, m, H-1′), 8.10 and 8.37 (2H, each as s, H-2 and H-8); FAB-MS *m*/*z*: 348 (M^++H). Anal. calcd for $C_{16}H_{25}N_5O_2Si$: C, 55.30; H, 7.25; N, 20.25. Found: C, 55.16; H, 7.26; N, 20.00.

3.1.4. 9-[5-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3-*C*-phenylthio-β-D-xylofuranosyl]adenine (11). A mixture of PhSH (5.5 mL, 53.5 mmol) and NaOMe (2.0 g, 38.3 mmol) in MeOH (50 mL) was stirred for 20 min at room temperature. To this was added **8** (2.78 g, 7.65 mmol). The reaction mixture was refluxed for 6.5 h, and then evaporated. Column chromatography ($CHCl_3$/MeOH=10/1) of the residue gave **11** (3.6 g, 100%) as a foam: UV (MeOH) λ_{max} 258 nm (ε 21,400), λ_{min} 231 nm (ε 4900); ^1H NMR ($CDCl_3$) δ −0.85 and 0.00 (6H, each as s, SiMe), 0.70 (9H, s, SiBu-*t*), 3.90 (1H, dd, *J*=2.4 and 11.6 Hz, H-5′), 4.00–4.05 (2H, m, H-5′ and H-3′), 4.64–4.67 (1H, m, H-4′), 4.78 (1H, dd, *J*=5.6 and 9.6 Hz, H-2′), 5.84 (1H, d, *J*=5.6 Hz, H-1′), 5.94 (2H, br, NH_2), 7.22–7.33 (3H, m, Ph), 7.51–7.54 (2H, m, Ph), 8.10 and 8.28 (2H, each as s, H-2 and H-8); FAB-MS *m*/*z*: 474 (M^++H). Anal. calcd for $C_{22}H_{31}N_5O_3SSi$: C, 55.79; H, 6.60; N, 14.79. Found: C, 55.90; H, 6.75; N, 14.61.

3.1.5. 9-[5-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-2-*O*-methanesulfonyl-3-*C*-phenylthio-β-D-xylofuranosyl]-adenine (12). To a pyridine (13 mL) solution containing **11**

(500 mg, 1.05 mmol) and DMAP (193 mg, 1.58 mmol) was added MsCl (325 μL, 4.2 mmol) at 0°C. After stirring for 2 h at room temperature, the reaction mixture was partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$. Column chromatography ($CHCl_3$/MeOH=30/1) of the organic layer gave **12** (569 mg, 98%) as a foam: UV (MeOH) λ_{max} 257 nm (ε 20,900), λ_{min} 230 nm (ε 5300); ^{1}H NMR ($CDCl_3$) δ 0.22 (6H, s, SiMe), 0.99 (9H, s, SiBu-*t*), 3.05 (3H, s, OMs), 4.07 (1H, dd, *J*=3.2 and 11.6 Hz, H-5′), 4.12–4.17 (2H, m, H-5′and H-3′), 4.66–4.70 (1H, m, H-4′), 5.50 (1H, dd, *J*=4.4 and 6.4 Hz, H-2′), 6.27 (1H, d, *J*=4.4 Hz, H-1′), 7.28–7.36 (5H, m, Ph), 8.31 and 8.41 (2H, each as s, H-2 and H-8); FAB-MS *m/z*: 552 (M^++H). Anal. calcd for $C_{23}H_{33}N_5O_5S_2Si$: C, 50.07; H, 6.03; N, 12.69. Found: C, 50.31; H, 6.03; N, 12.46.

3.1.6. 5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-3′-*C*-phenylthioadenosine (13). A mixture of **12** (544 mg, 0.98 mmol) and DBN (363 μL, 2.94 mmol) in CH_3CN (9 mL) was refluxed for 12 h. Evaporation of the solvent followed by column chromatography ($CHCl_3$/MeOH=30/1) of the residue gave **13** (348 mg, 78%) as a foam: UV (MeOH) λ_{max} 262 nm (ε 20,000), λ_{min} 229 nm (ε 9200); ^{1}H NMR ($CDCl_3$) δ 0.13 (6H, s, SiMe), 0.95 (9H, s, SiBu-*t*), 3.89–3.96 (2H, m, H-5′), 4.93–4.94 (1H, m, H-4′), 5.29–5.30 (1H, m, H-2′), 5.62 (2H, br, NH_2), 7.01–7.02 (1H, m, H–1′), 7.39–7.43 (3H, m, Ph), 7.56–7.59 (2H, m, Ph), 8.19 and 8.33 (2H, each as s, H-2 and H-8); FAB-MS *m/z*: 456 (M^++H). Anal. calcd for $C_{22}H_{29}N_5O_2SSi$: C, 57.99; H, 6.42; N, 15.37. Found: C, 57.76; H, 6.49; N, 15.16.

3.1.7. 9-[2,3-Anhydro-5-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-N^6-pivaloyladenine (14). A mixture of **8** (5.9 g, 16.23 mmol), pivaloyl chloride (3.5 mL, 29.21 mmol), and *i*-Pr_2NEt (5.0 mL, 29.21 mmol) in CH_2Cl_2 (70 mL) was stirred at 0°C for 90 min. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. Column chromatography ($CHCl_3$/MeOH=40/1) of the organic layer gave **14** (7.0 g, 97%) as a foam: UV (MeOH) λ_{max} 271 nm (ε 14,600), λ_{min} 230 nm (ε 600); ^{1}H NMR ($CDCl_3$) δ 0.01 and 0.03 (6H, each as s, SiMe), 0.84 (9H, s, SiBu-*t*), 1.41 (9H, s, COBu-*t*), 3.74 (1H, dd, *J*=4.6 and 10.9 Hz, H-5′), 3.79 (1H, dd, *J*=6.5 and 10.9 Hz, H-5′), 4.11 (1H, d, *J*=2.7 Hz, H-2′), 4.38 (1H, dd, *J*=4.6 and 6.4 Hz, H-4′), 4.45 (1H, d, *J*=2.7 Hz, H-3′), 6.25 (1H, s, H-1′), 8.22 (1H, s, H-2 or H-8), 8.51 (1H, br, NH), 8.76 (1H, s, H-2 or H-8); FAB-MS *m/z* 448 (M^++H). Anal. calcd for $C_{21}H_{33}N_5O_4Si$: C, 56.35; H, 7.43; N, 15.65. Found: C, 56.36; H, 7.46; N, 15.43.

3.1.8. 9-[5-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-phenylthio-β-D-xylofuranosyl]-N^6-pivaloyladenine (15). A MeOH (60 mL) solution of thiophenol (5.13 mL, 50 mmol) and NaOMe (1.35 g, 25 mmol) was stirred for 20 min at room temperature. Compound **14** (5.6 g, 12.5 mmol) was added to this solution, and the mixture was stirred at refluxing temperature for 2.5 h. The whole reaction mixture was evaporated and purified by column chromatography ($CHCl_3$/MeOH=30/1) to give **15** (6.2 g, 90%) as a foam: UV (MeOH) λ_{max} 260 nm (ε 17,300), λ_{min} 233 nm (ε 4500); ^{1}H NMR ($CDCl_3$) δ 0.00 (6H, s, SiMe), 0.69 (9H, s, SiBu-*t*), 1.41 (9H, s, COBu-*t*), 3.91 (1H, dd, *J*=2.5 and 11.3 Hz, H-5′), 4.01–4.06 (2H, m, H-5′ and H–3′), 4.66–4.68 (1H, m, H-4′), 4.82 (1H, ddd, *J*=2.8, 5.2, and 9.5 Hz, H-2′), 5.32 (1H, d, *J*=2.8 Hz, D_2O-exchangeable, OH), 5.89 (1H, d, *J*=5.2 Hz, H-1′), 7.23–7.33 (3H, m, Ph), 7.50–7.52 (2H, m, Ph), 8.25 and 8.71 (2H, each as s, H-2 and H-8), 8.54 (1H, br, NH); FAB-MS *m/z* 558 (M^++H). Anal. calcd for $C_{27}H_{39}N_5O_4SSi$: C, 58.14; H, 7.05; N, 12.56. Found: C, 57.92; H, 7.15; N, 12.37.

3.1.9. 9-[3-*C*-Benzenesulfonyl-5-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-β-D-xylofuranosyl]-N^6-pivaloyladenine (16). A mixture of **15** (2.3 g, 4.12 mmol) and *m*-CPBA (>65%, 2.6 g, 9.06 mmol) in MeOH (30 mL) was stirred at 0°C for 2.5 h. After treatment with Et_3N (1.26 mL, 9.06 mmol), the reaction mixture was evaporated and partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. Column chromatography ($CHCl_3$/MeOH=30/1) of the organic layer gave **16** (2.43 g, 100%) as a foam: UV (MeOH) λ_{max} 272 nm (ε 16,100), λ_{min} 233 nm (ε 1400); ^{1}H NMR ($CDCl_3$) δ 0.04 and 0.06 (6H, each as s, SiMe), 0.83 (9H, s, SiBu-*t*), 1.42 (9H, s, COBu-*t*), 4.09–4.12 (1H, m, H-3′), 4.29–4.30 (2H, m, H-5′), 4.76–4.80 (1H, m, H-4′), 5.24 (1H, dd, *J*=5.8 and 7.9 Hz, H-2′), 5.60 (1H, br, D_2O-exchangeable, OH), 5.85 (1H, d, *J*=5.8 Hz, H-1′), 7.56–7.59 (2H, m, Ph), 7.65–7.68 (1H, m, Ph), 8.01–8.03 (2H, m, Ph), 8.24 and 8.44 (2H, each as s, H-2 and H-8), 8.52 (1H, br, NH); FAB-MS *m/z* 590 (M^++H). Anal. calcd for $C_{27}H_{39}N_5O_6SSi\cdot 1/4H_2O$: C, 54.57; H, 6.70; N, 11.78. Found: C, 54.30; H, 6.55; N, 11.40.

3.1.10. 3′-*C*-Benzenesulfonyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxyadenosine (17). Compound **16** (6.3 g, 10.75 mmol) in NH_3/MeOH (90 mL) was placed in a sealed tube and kept in a refrigerator overnight. After evaporation to dryness, the resulting foam was dissolved in pyridine (120 mL) containing DMAP (1.9 g, 16.1 mmol). To this was added MsCl (3.32 mL, 43 mmol) at 0°C, and the mixture was stirred at 0°C for 1 h and then at room temperature overnight. Partition of the reaction mixture ($CHCl_3$-saturated aqueous $NaHCO_3$) followed by column chromatography ($CHCl_3$/MeOH=30/1) of the organic layer gave **17** (4.26 g, 81%) as a foam: UV (MeOH) λ_{max} 260 nm (ε 17,400), λ_{min} 230 nm (ε 16,000); ^{1}H NMR ($CDCl_3$) δ 0.00 and 0.01 (6H, each as s, SiMe), 0.82 (9H, s, SiBu-*t*), 3.94 (1H, dd, *J*=2.0 and 12.0 Hz, H-5′), 4.06 (1H, dd, *J*=2.8 and 12.0 Hz, H-5′), 5.06–5.08 (1H, m, H-4′), 5.94 (2H, br, NH_2), 6.70–6.71 (1H, m, H-2′), 7.06–7.07 (1H, m, H-1′), 7.59–7.63 (2H, m, Ph), 7.69–7.73 (1H, m, Ph), 7.97–7.99 (2H, m, Ph), 8.13 and 8.30 (2H, each as s, H-2 and H-8); FAB-MS *m/z* 488 (M^++H). Anal. calcd for $C_{22}H_{29}N_5O_4SSi\cdot 1/10H_2O$: C, 53.99; H, 6.01; N, 14.31. Found: C, 53.73; H, 5.91; N, 14.19.

3.1.11. 5′-*O*-(*tert*-Butyldimethylsilyl)-3′-*C*-(tributylstannyl)-2′,3′-didehydro-2′,3′-dideoxyadenosine (18). A mixture of **17** (286 mg, 0.586 mmol), Et_3N (326 μL, 2.34 mmol), Bu_3SnH (472 μL, 1.76 mmol), and AIBN (29 mg, 0.176 mmol) in benzene (8.3 mL) was heated at 80°C with stirring. After 2.5 h, the same amount of AIBN was added to the reaction mixture, and heating was continued for further 3 h. The reaction mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. Short column chromatography (hexane/EtOAc=1/2) of the

organic layer gave **18** (284 mg, 76%, solid). Elution with EtOAc gave the recovered **17** (48 mg, 17%).

Physical data of **18**: mp 82–83°C; UV (MeOH) λ_{max} 260 nm (ε 17,200), λ_{min} 231 nm (ε 5200); ^{1}H NMR ($CDCl_3$) δ 0.00 and 0.01 (6H, each as s, SiMe), 0.85 (9H, s, SiBu-*t*), 0.91 (9H, t, J=7.2 Hz, $Sn(CH_2)_3CH_3$), 1.04–1.08 (6H, m, $Sn(CH_2)_3$), 1.30–1.39 (6H, m, $Sn(CH_2)_3$), 1.50–1.58 (6H, m, $Sn(CH_2)_3$), 3.75–3.82 (2H, m, H-5′), 5.01–5.04 (1H, m, H-4′), 5.62 (2H, br, NH_2), 5.99 (1H, m, $J_{Sn,H\text{-}2'}$=28.0 Hz, H-2′), 7.01–7.02 (1H, m, H-1′), 7.95 and 8.38 (2H, each as s, H-2 and H-8); FAB-MS m/z 674 for ^{118}Sn and 676 for ^{120}Sn (M^++H). Anal. calcd for $C_{28}H_{51}N_5O_2SiSn$: C, 52.84; H, 8.08; N, 11.00. Found: C, 53.23; H, 8.23; N, 10.86.

3.1.12. 5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-3′-iodoadenosine (19). A mixture of **18** (246 mg, 0.386 mmol) and NIS (104 mg, 0.463 mmol) in THF (2.5 mL) was stirred at room temperature under positive pressure of dry Ar for 4.5 h in total. Additional NIS was added to the mixture after 3 h (69 mg, 0.308 mmol) and after 4 h (43 mg, 0.193 mmol). The reaction mixture was partitioned between EtOAc and aqueous $Na_2S_2O_3$. Column chromatography ($CHCl_3$/MeOH=30/1) of the organic layer gave **19** (127 mg, 70%) as a solid: mp 199–204°C; UV (MeOH) λ_{max} 260 nm (ε 15,500), λ_{min} 232 nm (ε 2200); ^{1}H NMR ($CDCl_3$) δ 0.11 (6H, s, SiMe), 0.92 (9H, s, SiBu-*t*), 3.91 (1H, dd, J=1.6 and 12.0 Hz, H-5′), 4.06 (1H, dd, J=2.4 and 12.0 Hz, H-5′), 4.85–4.86 (1H, m, H-4′), 5.62 (2H, br, NH_2), 6.38 (1H, m, H-2′), 7.02–7.03 (1H, m, H-1′), 8.22 and 8.38 (2H, each as s, H-2 and H-8); FAB-MS m/z 474 (M^++H). Anal. calcd for $C_{16}H_{24}IN_5O_2Si$: C, 40.60; H, 5.11; N, 14.79. Found: C, 40.82; H, 4.94; N, 14.62.

3.1.13. 3′-Bromo-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxyadenosine (20). A mixture of **18** (100 mg, 0.157 mmol) and NBS (55 mg, 0.314 mmol) in THF (4 mL) was stirred at room temperature for 5.5 h under positive pressure of dry Ar. The reaction mixture was partitioned between $CHCl_3$ and aqueous $NaHCO_3$. Column chromatography ($CHCl_3$/MeOH=30/1) of the organic layer gave **20** (66 mg, 100%) as a solid: mp 173–178°C; UV (MeOH) λ_{max} 259 nm (ε 19,100), λ_{min} 230 nm (ε 9000); ^{1}H NMR ($CDCl_3$) δ −0.01 and 0.00 (6H, each as s, SiMe), 0.81 (9H, s, SiBu-*t*), 3.82 (1H, dd, J=1.6 and 12.0 Hz, H-5′), 3.91 (1H, dd, J=2.4 and 12.0 Hz, H-5′), 4.76–4.78 (1H, m, H-4′), 5.70 (2H, br, NH_2), 6.09–6.10 (1H, m, H-2′), 6.93–6.94 (1H, m, H-1′), 8.17 and 8.26 (2H, each as s, H-2 and H-8); FAB-MS m/z 426 and 428 (M^++H). Anal. calcd for $C_{16}H_{24}BrN_5O_2Si$: C, 45.07; H, 5.67; N, 16.42. Found: C, 45.09; H, 5.65; N, 16.32.

3.1.14. 5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-3′-*C*-phenyladenosine (21). A mixture of **18** (230 mg, 0.361 mmol), PhI (121 μL, 1.08 mmol), $Pd(PPh_3)_4$ (41 mg, 0.036 mmol), and CuI (13 mg, 0.072 mmol) in DMF (1.5 mL) was stirred at room temperature for 28 h. The reaction mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. Column chromatography ($CHCl_3$/MeOH=20/1) of the organic layer gave **21** (100 mg, 66%) as a foam: UV (MeOH) λ_{max} 257 nm (ε 29,000), λ_{min} 224 nm (ε 9600); ^{1}H NMR ($CDCl_3$) δ −0.21 and −0.17 (6H, each as s, SiMe), 0.72 (9H, s, SiBu-*t*), 3.95 (1H, dd, J=2.8 and 12.0 Hz, H-5′), 4.00 (1H, dd, J=2.0 and 12.0 Hz, H-5′), 5.45–5.48 (1H, m, H-4′), 5.91 (2H, br, NH_2), 6.18–6.19 (1H, m, H-2′), 7.21–7.22 (1H, m, H-1′), 7.36–7.45 (5H, m, Ph), 8.37 and 8.40 (2H, each as s, H-2 and H-8); FAB-MS m/z 424 (M^++H). Anal. calcd for $C_{22}H_{29}N_5O_2Si$: C, 62.38; H, 6.90; N, 16.53. Found: C, 62.36; H, 6.91; N, 16.43.

3.1.15. 5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-3′-*C*-vinyladenosine (22). A mixture of **19** (70 mg, 0.147 mmol), $Bu_3SnCH{=}CH_2$ (128 μL, 0.441 mmol), $(MeCN)_2PdCl_2$ (3.8 mg, 0.0147 mmol), and CuI (5.5 mg, 0.0294 mmol) in DMF (1 mL) was stirred at room temperature for 42 h. The reaction mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. Column chromatography ($CHCl_3$/MeOH=30/1) of the organic layer gave **22** (28 mg, 51%) as a solid: mp 154–157°C; UV (MeOH) λ_{max} 259 nm (ε 20,900), λ_{min} 245 nm (ε 17,600); ^{1}H NMR ($CDCl_3$) δ −0.01 (6H, s, SiMe), 0.86 (9H, s, SiBu-*t*), 3.97–4.01 (2H, m, H-5′), 5.12–5.13 (1H, m, H-4′), 5.40–5.50 (2H, m, $CH{=}CH_2$), 5.58 (2H, br, NH_2), 5.96 (1H, m, H-2′), 6.55 (1H, dd, J=11.2 and 17.6 Hz, $CH{=}CH_2$), 7.06 (1H, m, H–1′), 8.21 and 8.38 (2H, each as s, H-2 and H-8); FAB-MS m/z 374 (M^++H). Anal. calcd for $C_{18}H_{27}N_5O_2Si$: C, 57.88; H, 7.29; N, 18.75. Found: C, 58.16; H, 7.45; N, 18.48.

3.1.16. 5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-3′-*C*-(phenyl)ethynyladenosine (23). A mixture of **19** (50 mg, 0.105 mmol), phenylacetylene (20 μL, 0.157 mmol), $Pd(PPh_3)_2Cl_2$ (8.5 mg, 0.011 mmol), and CuI (4.6 mg, 0.021 mmol) in DMF (2 mL) containing Et_3N (25 μL, 0.157 mmol) was heated at 80°C for 2 h. After passing through a short column ($CHCl_3$/MeOH=10/1), the reaction mixture was bubbled with H_2S gas, and then partitioned between EtOAc and saturated aqueous $NaHCO_3$. Column chromatography ($CHCl_3$/MeOH=30/1) of the organic layer gave **23** (42 mg, 89%) as a solid: mp 136–139°C; UV (MeOH) λ_{max} 260 nm (ε 37,200), 273 nm (ε 45,500), and 288 nm (ε 31,600), λ_{min} 231 nm (ε 16,700), 263 nm (ε 36,900), and 283 nm (ε 25,600); ^{1}H NMR ($CDCl_3$) δ 0.10 (6H, s, SiMe), 0.91 (9H, s, SiBu-*t*), 4.01 (1H, dd, J=2.0 and 11.6 Hz, H-5′), 4.07 (1H, dd, J=2.8 and 11.6 Hz, H-5′), 4.99–5.01 (1H, m, H-4′), 5.69 (2H, br, NH_2), 6.24–6.25 (1H, m, H-2′), 7.20–7.21 (1H, m, H-1′), 7.34–7.50 (5H, m, Ph), 8.29 and 8.38 (2H, each as s, H-2 and H-8); FAB-MS m/z 448 (M^++H). Anal. calcd for $C_{24}H_{29}N_5O_2Si$: C, 64.40; H, 6.53; N, 15.65. Found: C, 64.49; H, 6.67; N, 15.31.

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