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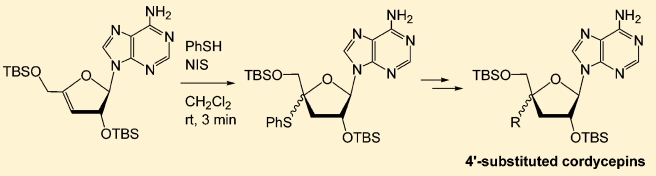
Phenylsulfanylation of 3′,4′-Unsaturated Adenosine Employing Thiophenol-*N*-Iodosuccinimide Leads to 4′-Phenylsulfanylcordycepin: Synthesis of 4′-Substituted Cordycepins on the Basis of Substitution of the Phenylsulfanyl Leaving Group

Yutaka Kubota,* Mariko Ehara, Kazuhiro Haraguchi,* and Hiromichi Tanaka

School of Pharmacy, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan

Supporting Information

ABSTRACT: Upon reaction of the 3′,4′-unsaturated adenosine derivative **2** with *N*-iodosuccinimide (NIS) and thiophenol, an unexpected electrophilic hydrophenylsulfanylation proceeded to provide 4′-phenylsulfanylcordycepin **7** in 79% yield with the ratio **7a**/**7b** = 6.6/1. A study of the reaction mechanism revealed that hydrogen iodide (HI) generated from NIS and PhSH acted as an active species. On the basis of a deuterium experiment using PhSD, initial protonation occurred at the β face of the double bond to furnish the β-π complex **III**, which underwent anti addition of PhSH as a major pathway. Nucleophilic substitution of N^6-pivaloylated **9** with various alcohols in the presence of *N*-bromosuccinimide (NBS) gave the respective 4′-α-alkoxycordycepins **15a**−**21a** as the major stereoisomers. Use of DAST in place of an alcohol gave the 4′-α-fluoro analogue **23a** stereoselectively. Radical-mediated carbon−carbon bond construction was also applicable to **7**, giving 4′-α-allylcordycepin (**24a**) and 4′-α-cyanoethylcordycepin (**25**) derivatives.



INTRODUCTION

The nucleoside antibiotic cordycepin (**1**; Figure 1) has been reported to possess biological effects on RNA biosynthesis,[1]

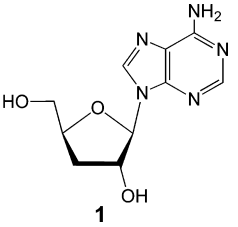


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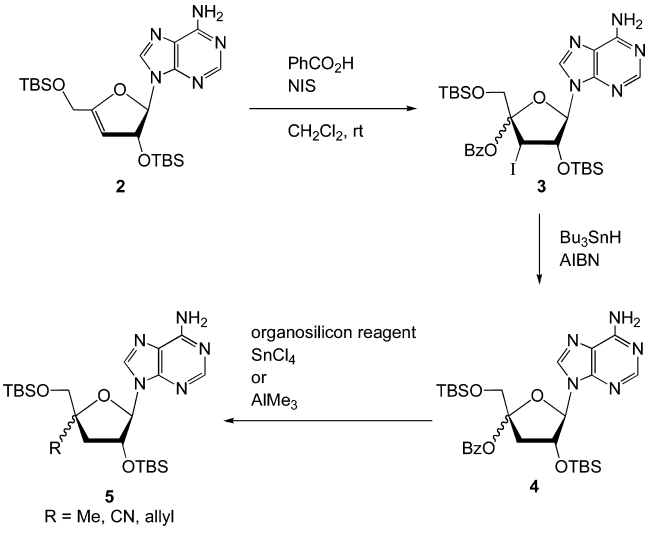
Figure 1. Structure of cordycepin (**1**).

methyl transferase,[2] and purine biosynthesis.[3] These facts have stimulated the synthesis of numerous analogues with the aim of discovering chemotherapeutically viable compounds;[4] however, reported modifications at its sugar moiety have been quite limited.[5] In the course of our ongoing research on the synthetic chemistry of unsaturated sugar nucleosides,[6] we have recently reported the iodobenzoyloxylation of the 3′,4′-unsaturated adenosine derivative **2** utilizing *N*-iodosuccinimide (NIS) and benzoic acid (Scheme 1).[7] Radical-mediated deiodination of the resulting adduct **3** furnished 4′-benzoyloxycordycepin (**4**), which served as a useful precursor for the synthesis of the novel 4′-carbon-substituted analogues **5** by nucleophilic substitution of the benzoyloxy leaving group with organosilicon or organoaluminum reagents.[8]

Phenylthioglycosides have been utilized as stable and useful glycosyl donors for the synthesis of *O*-glycoside,[9] glycosyl

Scheme 1. Synthesis of 4′-Carbon-Substituted Cordycepin from 2



fluoride,[10] and *C*-glycoside[11] through activation of the phenylsulfanyl group under neutral conditions. We envisioned that the versatility of the phenylsulfanyl substituent as a leaving group would enable the synthesis of novel 4′-substituted derivatives of cordycepin by substitution reactions of the phenylsulfanyl group. In accord with the synthetic route visualized in Scheme

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1, we have attempted to prepare **6** by reaction of **2** with NIS-thiophenol (PhSH) (Figure 2). Unexpectedly, instead of the

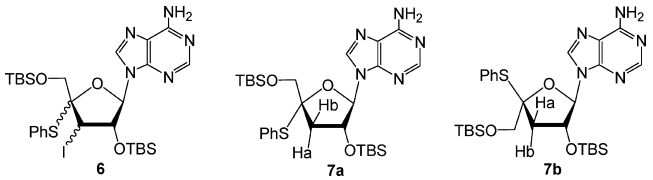

Figure 2. Structures of compounds **6** and **7a,b**.

desired **6**, the reaction gave the 4′-phenylsulfanylcordycepin derivatives **7a,b** lacking an iodo substituent at the 3′-position. Since this novel hydrosulfanylation reaction of **2** would constitute a more efficient route to 4′-substituted cordycepin, we intended to optimize the reaction conditions and clarify the reaction mechanism. In this paper, we will describe these results and demonstrate the scope of **7** for the synthesis of novel 4′-substituted analogues of cordycepin.

RESULTS AND DISCUSSION

When **2**[12] was reacted with NIS (3 equiv) and PhSH (3 equiv) in CH_2Cl_2 at room temperature for 3 min, a mixture of the β-D isomer **7a** and its 4′-epimer **7b** was obtained in 62% combined yield (**7a**/**7b** = 2.3/1). Compounds **7a,b** could be separated by HPLC (hexane/ethyl acetate 1/2). The depicted structures of **7a,b** were determined on the basis of their ^{1}H NMR spectrum, in which signals of H-3′a and H-3′b were observed as doublets of doublets at 2.15 and 2.85 ppm for **7a** and 2.34 and 2.69 ppm for **7b**.[13] Assignment of H-3′a/H-3′b and determination of the stereochemistry at the 4′-position were performed on the basis of NOE experiments: H-5′/H-8 (0.4%), H-2′/H-5′ (0.5%), H-5′/H-3′b (1.6%), H-1′/H-3′a (1.7%), and H-1′/H-Ph (2.2%) for **7a**; H-1′/H-5′b (1.7%), H-1′/H-3′b (3.7%), H-3′b/H-5′b (1.5%), H-3′a/H-8 (1.7%), and H-3′a/H-Ph (2.2%) for **7b**.

To optimize the reaction conditions, we have varied the amount of these reagents, and the results are summarized in Table 1, which includes the result in the case of 3 equiv of each

Table 1. Reaction of 2 with NIS-PhSH[a]

entry	amt of NIS (equiv)	amt of PhSH (equiv)	combined yield of **7** (%)	ratio **7a**/**7b**[b]
1	3	3	62	2.3/1
2	3	1.5	trace	
3	3	6	71	6.6/1
4	2	6	79	6.6/1
5	1	6	0	

[a]This reaction was carried out by reacting **2** with NIS and PhSH in CH_2Cl_2 at room temperature for 3 min. [b]These ratios were determined by ^{1}H NMR spectroscopy.

reagent in entry 1. Initially, the amount of PhSH decreased to 1.5 equiv, which resulted in retarding the reaction (entry 2), whereas 6 equiv of PhSH improved the isolated yield (71%) and gave the ratio of **7a**/**7b** (6.6/1) shown in entry 3. Next, the effect of varying the amount of NIS was examined. As shown in entry 4, NIS could be decreased to 2 equiv to give **7a,b** in 79% yield with the same diastereoselectivity, whereas no reaction was observed in the case of 1 equiv of NIS. As can be seen from the above results, the required molar ratio of PhSH/NIS is 2/1 (entry 3), which supports the proposed reaction mechanism shown in Scheme 2.

This reaction did not occur when PhSNa was used instead of PhSH or when DMAP was added to the reaction medium. These facts led us to postulate the reaction mechanism depicted in Scheme 2. Thus, hydrogen iodide would be generated from 2 PhSH plus NIS. In support of this PhSSPh generated accompanied by HI could be confirmed on the basis of ^{13}C NMR of the reaction mixture of PhSH and NIS. Next, HI protonates the N1 nitrogen group to form incipient intermediate **I** (entries 3 and 5 in Table 1). If 1 equiv more of HI is present, **I** is then transformed to the oxonium ion **II** through protonation of the 3′,4′-double bond. Finally, **II** undergoes nucleophilic attack by PhSH to furnish **7**. If the reaction mechanism is correct, an N^6-acylated substrate would give the desired product by using only 1 equiv of NIS because the amide nitrogen does not have sufficient basic character. As anticipated, when N^6-pivaloylated **8** was subjected to reaction with 6 equiv of PhSH in the presence of NIS (1 equiv), the desired product **9** was obtained as a diastereomeric mixture in 33% yield (Figure 3). It deserves additional comment that reactions utilizing NBS and NCS instead of NIS gave a complex mixture of products.

To see if the addition reaction proceeds in an anti or syn fashion, PhSD was used as the nucleophile instead of PhSH (Scheme 3). PhSD (deuteration degree 93%) was prepared from the reaction of PhSH and D_2O by the literature procedure.[14] To avoid deuterium exchange between PhSD and 6-NH_2, the *N*,*N*-dimethylamino 3′,4′-unsaturated adenosine derivative **10** was used as the substrate. Compound **10** was prepared from *N*,*N*-dimethyladenosine[15] according to the published procedure.[12] The four stereoisomers **11** (β-anti-adduct), **12** (β-syn-adduct), **13** (α-anti-adduct), and **14** (α-syn-adduct) were obtained in 77% combined isolated yield from the reaction under the conditions shown in entry 4 in Table 1. By comparison of the integration of H-1′ and H-3′ of **11**−**14** in the ^{1}H NMR spectrum of the mixture, the isomeric ratio was found to be as follows: **11**/**12**/**13**/**14** = 26/3.3/1.0/4.0. On the basis of the ratio **11** + **12**/**13** + **14**, β-π complex **III** was found to be formed predominantly over α-π complex **V** (**III**/**V** = 29.3/5.0). This stereochemical outcome was quite unexpected, since the iodobenzoyloxylation shown in Scheme 1 (**2** → **3**) proceeded through an α-iodonium ion as an intermediate. At the moment, we have no reasonable explanation for the reversed stereochemistry of the incoming electrophile. Concomitant formation of the β-syn adduct **12** and α-syn-adduct **14** indicates that **III** and **V** exist as an equilibrium mixture with the carboxonium ions **IV** and **VI**, respectively. These ions underwent preferential attack from their α-face due to the presence of the adenine base (**11** vs **12** and **13** vs **14**).

With the 4′-phenylsulfanyl cordycepin derivative **7** in hand, we next examined the synthesis of 4′-alkoxy analogues. Initially, **7** was reacted with MeOH in the presence of NBS. In this case, 8-brominated products having methoxy groups at the 4′-position were formed as byproducts. To avoid this side reaction, N^6-pivaloylated **9** was used for this alkoxylation.[16] Thus, when **9** was treated with NBS (1.5 equiv) in MeOH, a mixture of diastereomers of 4′-methoxy derivatives was obtained (Scheme 4 and entry 1 in Table 2). Due to partial depivaloylation during the reaction, the crude reaction mixture was treated with NH_3/MeOH to give a mixture of **15a** and **15b** in 93% combined yield (**15a**/**15b** = 1.6/1). The analytically pure sample could be obtained by HPLC separation ($CHCl_3$/

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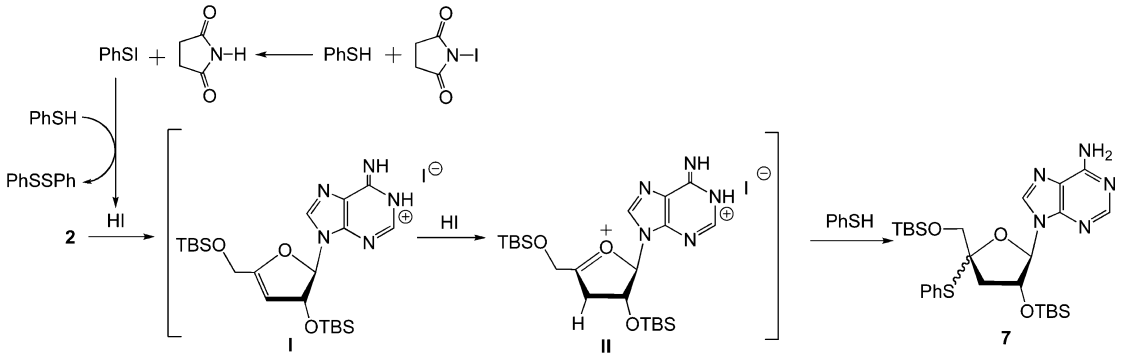
Scheme 2. Plausible Reaction Pathway for the Formation of 7



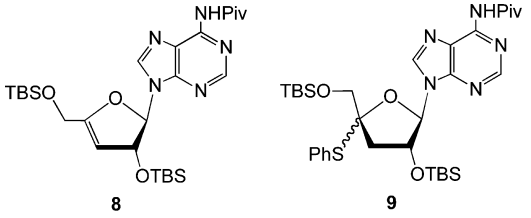


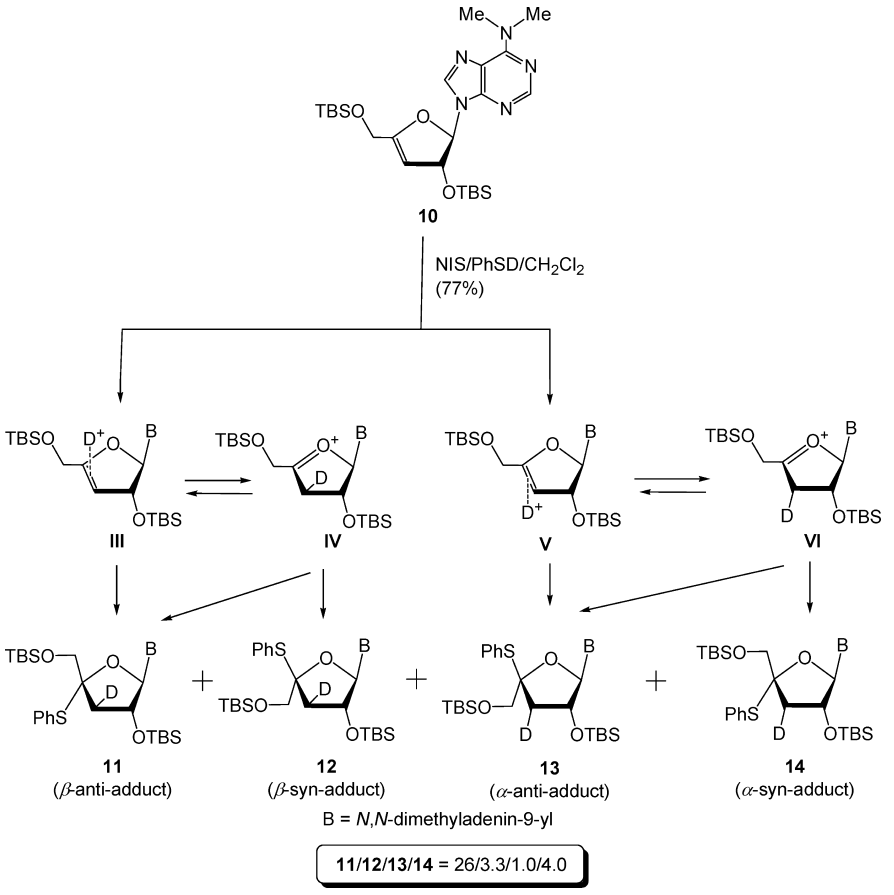
Figure 3. Structures of compounds **8** and **9**.

MeOH = 60/1). The depicted structures of **15a,b** were confirmed on the basis of NOE experiment: H-8/H-5′b (0.3%) and H-1′/OCH_3-4′ (0.7%) for **15a**; H-8/OCH_3 (2.8%) and H-1′/H-5′b (0.9%) for **15b**. In addition to higher primary alcohols, this reaction can also be applied to secondary and tertiary alcohols without loss of efficiency, as shown in entries 2–7 in Table 2.

As can be seen by the ratio of isomers, the major diastereomers were the β-D nucleosides **15a–21a**. We assumed that steric shielding by the N^6-pivaloyladenine moiety would be a determinant for the observed β-D-selectivity. In fact, we observed the trend that formation of the β-D isomer became more favorable upon increasing the bulkiness of the alcohol employed.

By reacting **9** with DAST/NBS in CH_2Cl_2, the 4′-fluoro analogues **23a,b** could be synthesized in 54% yield as a mixture of diastereomers (**23a**/**23b** = 2.4/1) after deprotection of the N^6-pivaloyl group of **22** by treatment of the crude mixture with NH_3/MeOH (Scheme 5).

Scheme 3. Reaction of 10 with NIS-PhSD



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Scheme 4. Reaction of 9 with ROH in the Presence of NBS

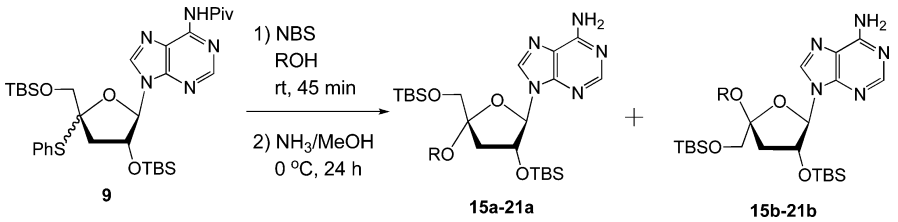
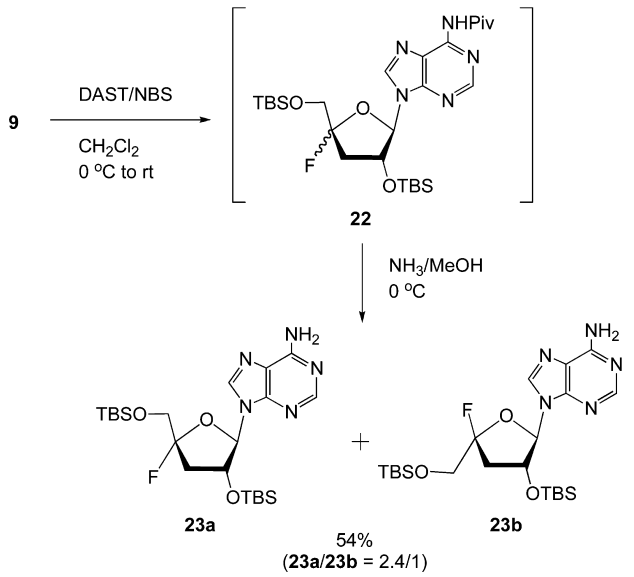


Table 2. Synthesis of 4′-Alkoxycordycepin[a]

entry	alcohol	products (R)	combined yield (%)	ratio of isomers[b]
1	MeOH	**15a** + **15b** (Me)	93	1.6/1
2	EtOH	**16a** + **16b** (Et)	86	1.5/1
3	*n*-PrOH	**17a** + **17b** (*n*-Pr)	99	1.9/1
4	*n*-BuOH	**18a** + **18b** (*n*-Bu)	98	2.0/1
5	*i*-PrOH	**19a** + **19b** (*i*-Pr)	91	1.8/1
6	*i*-BuOH	**20a** + **20b** (*i*-Bu)	100	2.3/1
7	*t*-BuOH	**21a** + **21b** (*t*-Bu)	88	2.6/1

[a]The reaction was carried out in the presence of *N*-bromosuccinimide (1.5 equiv) in ROH at room temperature for 45 min. [b]These ratios were determined by ^{1}H NMR spectroscopy.

Scheme 5. Reaction of 9 with DAST in the Presence of NBS



Finally, introduction of a carbon substituent was examined. We have already reported that reaction of the 1′-phenylsulfanyl-2′-deoxyuridine derivative with $Bu_3SnCH_2CH{=}CH_2$ in the presence of AIBN under reflux conditions gave the 1′-allyl-2′-deoxyuridine derivative.[17] Utilizing this procedure, **24a** (*β*-D isomer) was obtained in 7% yield. In contrast, **24a** could be obtained in 83% yield along with its epimer **24b** by carrying out the allylation under photochemical conditions initiated with $(Bu_3Sn)_2$ at room temperature (**24a**/**24b** = 3.8/1) (Figure 4). In addition to the above radical substitution reaction, a radical addition reaction could be also carried out by using acrylonitrile as a radical acceptor in the presence of Bu_3SnH and AIBN under reflux conditions to give the 4′-cyanoethyl derivative **25** in 49% yield.[18]

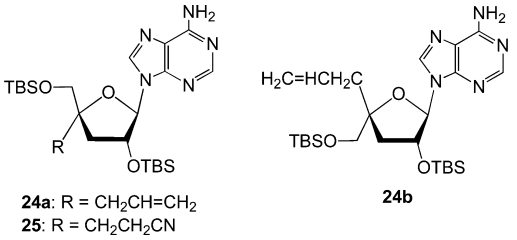


Figure 4. Structures of compounds **24a**,**b** and **25**.

CONCLUSION

In conclusion, we have developed a novel method for the synthesis of 4′-substituted cordycepin analogues by substitution of a phenylsulfanyl leaving group. Synthesis of 4′-phenylsulfanyl cordycepin **7** was carried out through a novel electrophilic hydrophenylsulfanylation reaction of the 3′,4′-unsaturated adenosine derivative **2** employing a NIS-PhSH system. A study of the reaction mechanism revealed that hydrogen iodide (HI) generated from NIS and PhSH acted as an active species. On the basis of a deuterium experiment using PhSD, initial protonation of the double bond occurred at the *β* face to furnish *β*-*π* complex **III**, which underwent anti addition of PhSH as a major pathway. Reaction of N^6-pivaloylated **9** with various alcohols in the presence of NBS gave the 4′-alkoxy analogues **15**−**21** with preferential formation of the *β*-D isomer. 4′-Fluorocordycepin **23** could also be prepared using DAST as a fluoride source. Furthermore, radical-mediated allylation and cyanoethylation of **7** gave 4′-allylcordycepin (**24**) and 4′-cyanoethylcordycepin (**25**) derivatives, respectively.

EXPERIMENTAL SECTION

NMR spectra were recorded either at 400 MHz or at 500 MHz. Chemical shifts are reported relative to Me_4Si. Mass spectra (MS) were taken in FAB mode with *m*-nitrobenzyl alcohol as a matrix. Column chromatography was carried out on silica gel. Thin-layer chromatography (TLC) was performed on silica gel F_{254} plates. When necessary, analytical samples were purified by high-performance liquid chromatography (HPLC) with a Shim-Pack PREP-SIL (H) KIT column (2 × 25 cm).

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-4′-phenylsulfanylcordycepin (7a) and 9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-4-phenylsulfanyl-*α*-L-lyxofuranosyl]adenine (7b). To a CH_2Cl_2 (5.0 mL) solution of **2** (300 mg, 0.63 mmol) and NIS (283 mg, 1.26 mmol) was added PhSH (0.39 mL, 3.77 mmol), and the mixture was stirred at room temperature for 3 min. After quenching with Et_3N (0.88 mL, 6.28 mmol), the reaction mixture was partitioned between AcOEt and saturated aqueous $Na_2S_2O_3$. The organic layer was washed with saturated aqueous $NaHCO_3$. Silica gel column chromatography (hexane/AcOEt = 1/2) of the organic layer gave a mixture of **7a** and **7b** as a pale yellow foam (293 mg, 79%: **7a**/**7b** = 6.6/1). HPLC separation (hexane/AcOEt = 1/2) gave analytically pure **7a** (t_R = 7.8 min, foam) and **7b** (t_R = 12.2 min, foam).

Physical Data for ***7a:*** UV (MeOH) λ_{max} 259 nm (*ε* 17 600), λ_{min} 234 nm (*ε* 4300); ^{1}H NMR ($CDCl_3$) *δ* −0.24, −0.13, 0.04, and 0.05

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(12H, each as s), 0.77 and 0.92 (18H, each as s), 2.15 (1H, dd, J = 7.3 and 13.2 Hz), 2.85 (1H, dd, J = 7.8 and 13.2 Hz), 3.68 (2H, s), 4.75 (1H, ddd, J = 6.3, 7.3, and 7.8 Hz), 5.70 (2H, br), 6.20 (1H, d, J = 6.3 Hz), 7.27−7.34 and 7.57−7.60 (5H, each as m), 8.07 (1H, s), 8.38 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.33, −5.26, −5.2, 17.8, 18.4, 25.5, 25.9, 41.8, 68.1, 75.7, 88.9, 93.8, 119.7, 128.7, 128.9, 130.9, 135.8, 139.1, 150.3, 153.2, 155.3; NOE ($CDCl_3$) H-5′/H-8 (0.4%), H-5′/H-3′b (δ 2.85) (1.6%), H-1′/H-3′a (δ 2.15 ppm) (1.7%), H-2′/H-3′b (10.1%), H-2′/H-5′ (0.5%), H-1′/H-Ph (2.2%); FAB-MS (m/z) 588 (M^+ + H). Anal. Calcd for $C_{28}H_{45}N_5O_3SSi_2$: C, 57.20; H, 7.71; N, 11.91. Found: C, 57.19; H, 7.82; N, 11.82.

Physical Data for ***7b:*** UV (MeOH) λ_{max} 259 nm (ε 17 800), λ_{min} 234 nm (ε 5300); ^{1}H NMR ($CDCl_3$) δ −0.11, −0.03, −0.02, and 0.01 (12H, each as s), 0.81 and 0.91 (18H, each as s), 2.34 (1H, dd, J = 6.6 and 13.8 Hz), 2.69 (1H, dd, J = 6.6 and 13.8 Hz), 3.66 and 3.79 (2H, each as d, J_{gem} = 10.6 Hz), 4.87 (1H, dt, J = 4.4 and 6.6 Hz), 5.76 (2H, br, 6-NH_2), 6.15 (1H, d, J = 4.4 Hz), 7.25−7.35 and 7.51−7.53 (5H, each as m), 8.33 (1H, s), 8.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.3, −5.11, −5.09, 17.8, 18.2, 25.6, 25.8, 40.8, 66.2, 76.4, 91.3, 97.1, 119.7, 128.8, 130.8, 135.2, 139.6, 150.2, 153.2, 155.3; NOE ($CDCl_3$) H-5′b (δ 3.79)/H-1′ (1.7%), H-1′/H-3′b (δ 2.69) (3.7%), H-3′b/H-5′b (1.5%), H-2′/H-3′a (δ 2.34) (4.2%), H-3′a/H-8 (1.7%), H-3′a/H-Ph (2.2%); FAB-MS (m/z) 588 (M^+ + H). Anal. Calcd for $C_{28}H_{45}N_5O_3SSi_2$: C, 57.20; H, 7.71; N, 11.91. Found: C, 57.21; H, 7.69; N, 12.06.

Reaction of 8 with PhSH in the Presence of NIS: Formation of 9a,b. To a CH_2Cl_2 (6.3 mL) solution of **8** (460 mg, 0.82 mmol) and NIS (184 mg, 0.82 mmol) was added PhSH (0.51 mL, 4.92 mmol) and the mixture was stirred at room temperature for 3 min. The reaction mixture was partitioned between AcOEt and saturated aqueous $Na_2S_2O_3$. The organic layer was washed with saturated aqueous $NaHCO_3$. Silica gel column chromatography (hexane/AcOEt = 3/1) of the organic layer gave a mixture of **9a** and **9b** as a pale yellow foam (184 mg, 33%: **9a**/**9b** = 6.2/1).

9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-β-D-*glycero*-pent-3-enofuranosyl]-*N*^{6}-dimethyladenine (10). Compound **10** was prepared from *N*,*N*-dimethyladenosine[15] in 30% overall yield by four steps according to the published procedure.[12]

Physical Data for ***10:*** UV (MeOH) λ_{max} 274 nm (ε 18 400), λ_{min} 238 nm (ε 2600); ^{1}H NMR ($CDCl_3$) δ 0.04, 0.07, 0.09, and 0.10 (12H, each as s), 0.88 and 0.91 (18H, each as s), 3.52 (6H, br), 4.24 and 4.29 (2H, each as d, J = 14.8 Hz), 5.17 (1H, d, J = 0.9 Hz), 5.24 (1H, dd, J = 0.9 and 1.9 Hz), 6.44 (1H, d, J = 1.9 Hz), 7.73 (1H, s), 8.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.43, −5.41, −4.6, −4.5, 18.0, 18.3, 25.7, 25.8, 38.5, 58.6, 80.1, 91.6, 99.4, 119.9, 135.2, 150.2, 152.8, 154.9, 161.9; FAB-MS (m/z) 506 (M^+ + H). Anal. Calcd for $C_{24}H_{43}N_5O_3Si_2$: C, 56.99; H, 8.57; N, 13.85. Found: C, 56.83; H, 8.61; N, 13.61.

Deuterium Exchange Experiment. Undeuterated compounds (661 mg, β-D/α-L = 6.9/1) were obtained in 75% yield from **10** (725 mg, 1.43 mmol) as described for the synthesis of **7**.

Physical Data for 2′,5′-Bis-O-(tert-butyldimethylsilyl)-N^6*-dimethyl-4′-phenylsulfanylcordycepin (β-D Isomer):* UV (MeOH) λ_{max} 272 nm (ε 22 800), λ_{min} 237 nm (ε 6300); ^{1}H NMR ($CDCl_3$) δ −0.23, −0.12, 0.02, and 0.03 (12H, each as s), 0.77 and 0.91 (18H, each as s), 2.13 (1H, dd, J = 7.4 and 13.2 Hz), 2.86 (1H, dd, J = 7.8 and 13.2 Hz), 3.52 (6H, br), 3.64 (1H, d, J = 10.8 Hz), 3.67 (1H, d, J = 10.8 Hz), 4.76 (1H, ddd, J = 6.7, 7.4, and 7.8 Hz), 6.24 (1H, d, J = 6.7 Hz), 7.24−7.60 (5H, m), 7.92 (1H, s), 8.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.3, −5.24, −5.21, 17.8, 18.3, 25.5, 25.9, 38.5, 41.8, 67.9, 75.1, 88.2, 93.3, 120.2, 128.6, 128.8, 131.0, 135.8, 136.5, 150.9, 152.6, 154.9; NOE ($CDCl_3$): H-Ph/H-1′ (2.3%), H-1′/H-3′a (δ 2.13) (4.1%), H-3′b (δ 2.86)/H-8 (0.4%); FAB-MS (m/z) 616 (M^+ + H). Anal. Calcd for $C_{30}H_{49}N_5O_3SSi_2$: C, 58.50; H, 8.02; N, 11.37. Found: C, 58.49; H, 8.08; N, 11.10.

Physical Data for 9-[2,5-Bis-O-(tert-butyldimethylsilyl)-3-deoxy-4-phenylsulfanyl-α-L-lyxofuranosyl]-N^6*-dimethyladenine (α-L Isomer):* ^{1}H NMR ($CDCl_3$) δ −0.10, −0.05, −0.03, and 0.00 (12H, each as s), 0.81 and 0.90 (18H, each as s), 2.32 (1H, dd, J = 6.6 and 13.8 Hz), 2.67 (1H, dd, J = 6.3 and 13.8 Hz), 3.54 (6H, br), 3.63 (1H, d, J = 10.6 Hz), 3.76 (1H, d, J = 10.6 Hz), 4.82 (1H, ddd, J = 4.4, 6.3, and 6.6 Hz), 6.19 (1H, d, J = 4.4 Hz), 7.24−7.33 and 7.51−7.53 (5H, each as m), 8.33 (1H, s), 8.34 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.3, −5.13, −5.08, 17.9, 18.2, 25.6, 25.8, 38.5, 41.9, 66.0, 76.6, 91.2, 97.1, 120.1, 128.7, 128.7, 131.0, 135.1, 137.2, 150.7, 152.6, 154.9; NOE ($CDCl_3$): H-1′/H-5′b (δ 3.76) (1.8%), H-1′/H-3′b (δ 2.67) (4.1%), H-3′b/H-5′b (1.5%), H-8/H-3′a (δ 2.32) (0.2%); FAB-HRMS (m/z) calcd for $C_{30}H_{50}N_5O_3SSi_2$ 616.3173, found 616.3151 (M^+ + H).

Reaction of 10 with PhSD/NIS: Preparation of 11−14. Compounds **11**−**14** (191 mg, β-D/α-L = 6.2/1) were obtained in 77% yield from **10** (200 mg, 0.40 mmol) as described for the synthesis of **7**. The ratio **11**/**12**/**13**/**14** (=26/3.3/1.0/4.0) was calculated as shown in Table 3.

Table 3

chem shift (ppm)	integration	assigned proton
2.13	5.04	H-3′a (β-D isomer)
2.32	0.51	H-3′a (α-L isomer)
2.67	0.85	H-3′b (α-L isomer)
2.86	1.75	H-3′b (β-D isomer)
6.19	1.00	H-1′ (α-L isomer)
6.24	5.61	H-1′ (β-D isomer)

[a] **11**/**12**/**13**/**14** = (5.6 1− 1.75)/(1.00 − 0.51)/(1.00 − 0.85)/(5.61 − 5.04).

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-4′-phenylsulfanyl-*N*^{6}-pivaloylcordycepin (9a) and 9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-4-phenylsulfanyl-α-L-lyxofuranosyl]-*N*^{6}-pivaloyladenine (9b). A CH_2Cl_2 (20 mL) solution of a mixture of **7a** and **7b** (1.89 g, 3.21 mmol, β-D/α-L = 9/1), pivaloyl chloride (0.48 mL, 3.86 mmol), and *i*-Pr_2NEt (0.84 mL, 4.82 mmol) was stirred at room temperature for 3 h. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. Silica gel column chromatography (hexane/AcOEt = 3/1) of the organic layer gave **9** (1.92 g, 89%, β-D/α-L = 9/1) as a foam. HPLC separation (hexane/AcOEt = 2/1) gave analytically pure **9a** (t_R = 6.8 min, foam) and **9b** (t_R = 8.7 min, foam).

Physical Data for ***9a:*** UV (MeOH) λ_{max} 260 nm (ε 16 900), λ_{min} 235 nm (ε 5500); ^{1}H NMR ($CDCl_3$) δ −0.27, −0.13, 0.04, and 0.05 (12H, each as s), 0.76 and 0.91 (18H, each as s), 1.41 (9H, s), 2.16 (1H, dd, J = 7.5 and 13.2 Hz), 2.86 (1H, dd, J = 8.0 and 13.2 Hz), 3.65 and 3.69 (2H, each as d, J = 10.9 Hz), 4.76 (1H, ddd, J = 6.3, 7.5, and 8.0 Hz), 6.23 (1H, d, J = 6.3 Hz), 7.27−7.36 and 7.56−7.59 (5H, each as m), 8.21 (1H, s), 8.49 (1H, br), 8.78 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.34, −5.25, −5.1, 17.8 18.3, 25.4, 25.9, 27.4, 40.5, 41.8, 68.0, 75.5, 88.8, 93.8, 122.7, 128.7, 129.0, 130.6, 135.8, 141.1, 149.5, 151.9, 152.9, 175.6; FAB-MS (m/z) 673 (M^+ + H). Anal. Calcd for $C_{33}H_{53}N_5O_4SSi_2$: C, 58.98; H, 7.95; N, 10.42. Found: C, 58.82; H, 8.07; N, 10.42.

Physical Data for ***9b:*** UV (MeOH) λ_{max} 260 nm (ε 16 900), λ_{min} 235 nm (ε 5500); ^{1}H NMR ($CDCl_3$) δ −0.12, −0.04, 0.02, and 0.01 (12H, each as s), 0.81 and 0.91 (18H, each as s), 1.42 (9H, s), 2.33 (1H, dd, J = 6.6 and 13.9 Hz), 2.71 (1H, dd, J = 6.3 and 13.9 Hz), 3.65 and 3.79 (2H, each as d, J = 10.6 Hz), 4.85 (1H, ddd, J = 4.4, 6.3, and 6.6 Hz), 6.22 (1H, d, J = 4.4 Hz), 7.25−7.35 and 7.50−7.53 (5H, each as m), 8.48 (1H, br), 8.59 (1H, s), 8.75 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.3, −5.1, −5.0, 17.8, 18.2, 25.6, 25.8, 27.4, 40.5, 40.7, 66.0, 76.5, 91.6, 97.3, 122.9, 128.8, 128.9, 130.7, 135.1, 141.9, 149.4, 151.8, 152.8, 175.7; FAB-MS (m/z) 672 (M^+ + H). Anal. Calcd for $C_{33}H_{53}N_5O_4SSi_2$: C, 58.98; H, 7.95; N, 10.42. Found: C, 58.97; H, 8.07; N, 10.48.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-4′-methoxycordycepin (15a) and 9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-4-methoxy-α-L-lyxofuranosyl]adenine (15b). Compound **9** (150 mg, 0.223 mmol, **9a**/**9b** = 9/1) and NBS (60 mg, 0.335 mmol) were dissolved in MeOH (3.0 mL), and the reaction mixture was stirred at room temperature for 45 min. Evaporation of the resulting solution was followed by washing with AcOEt and saturated aqueous $Na_2S_2O_3$.

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The organic layer was evaporated, and the residue was treated with NH_3/MeOH (ca. 30 mL) at 0 °C for 24 h. Evaporation of the solvent followed by column chromatography (hexane/AcOEt = 1/5) of the residue gave **15a,b** (105 mg, 93%, β-D/α-L = 1.6/1) as a foam. HPLC separation ($CHCl_3$/MeOH = 60/1) gave analytically pure β-D isomer (t_R = 6.6 min, foam) and α-L isomer (t_R = 8.2 min, foam).

Physical Data for ***15a:*** UV (MeOH) λ_{max} 260 nm (ε 14 200), λ_{min} 228 nm (ε 1100); ^{1}H NMR ($CDCl_3$) δ −0.23, −0.13, 0.14, and 0.16 (12H, each as s), 0.77 and 0.97 (18H, each as s), 2.20 (1H, dd, *J* = 7.8 and 13.7 Hz), 2.61 (1H, dd, *J* = 7.8 and 13.7 Hz), 3.43 (3H, s), 3.65 (1H, d, *J* = 10.2 Hz), 3.80 (1H, d, *J* = 10.2 Hz), 4.73 (1H, dt, *J* = 5.8 and 7.8 Hz), 6.13 (2H, br), 6.15 (1H, d, *J* = 5.8 Hz), 8.16 (1H, s), 8.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.44, −5.35, −5.30, −5.25, 17.8, 18.4, 25.5, 26.0, 39.2, 49.7, 66.2, 76.7, 89.5, 109.0, 119.6, 138.8, 150.1, 153.1, 155.6; NOE ($CDCl_3$): H-5′b (3.80 ppm)/H-8 (0.5%), H-1′/4′-OMe (0.9%); FAB-MS (*m*/*z*) 510 (M^+ + H). Anal. Calcd for $C_{23}H_{43}N_5O_4Si_2$: C, 54.19; H, 8.50; N, 13.74. Found: C, 53.89; H, 8.63; N, 13.51.

Physical Data for ***15b:*** UV (MeOH) λ_{max} 260 nm (ε 14 800), λ_{min} 228 nm (ε 1800); ^{1}H NMR ($CDCl_3$) δ −0.06, −0.01, 0.11 (12H, each as s), 0.83 and 0.94 (18H, each as s), 2.33 (1H, dd, *J* = 6.6 and 13.7 Hz), 2.38 (1H, dd, *J* = 5.9 and 13.7 Hz), 3.38 (3H, s), 3.72 (1H, d, *J* = 10.7 Hz), 3.88 (1H, d, *J* = 10.7 Hz), 4.94 (1H, ddd, *J* = 3.7, 5.9, and 6.6 Hz), 5.59 (2H, br), 6.09 (1H, d, *J* = 3.7 Hz), 8.07 (1H, s), 8.37 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.3, −5.1, −5.0, 17.8, 18.2, 25.6, 25.8, 41.5, 49.9, 63.3, 76.2, 91.0, 110.7, 119.8, 139.3, 150.1, 153.1, 155.4; NOE ($CDCl_3$): H-5′a (δ 3.72)/H-1′ (0.9%), H-8/4′-OMe (2.8%); FAB-MS (*m*/*z*) 510 (M^+ + H). Anal. Calcd for $C_{23}H_{43}N_5O_4Si_2$: C, 54.19; H, 8.50; N, 13.74. Found: C, 54.30; H, 8.71; N, 13.72.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-4′-ethoxycordycepin (16a) and 9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-4-ethoxy-α-L-lyxofuranosyl]adenine (16b). Compounds **16a** and **16b** were prepared as described above for **15** by starting from an EtOH (3.0 mL) solution of **9** (**9a**/**9b** = 9/1, 150 mg, 0.223 mmol) and NBS (60 mg, 0.335 mmol). HPLC separation ($CHCl_3$/MeOH = 60/1) of the reaction mixture (**16a**/**16b** = 1.5/1, 86% yield) gave analytically pure **16a** (t_R = 6.2 min, foam) and **16b** (t_R = 7.3 min, foam).

Physical Data for ***16a:*** UV (MeOH) λ_{max} 260 nm (ε 14 200), λ_{min} 228 nm (ε 1100); ^{1}H NMR ($CDCl_3$) δ −0.24, −0.14, 0.15, and 0.16 (12H, each as s), 0.77 and 0.97 (18H, each as s), 1.22 (3H, t, *J* = 6.9 Hz), 2.21 (1H, dd, *J* = 7.8 and 13.4 Hz), 2.60 (1H, dd, *J* = 8.0 and 13.4 Hz), 3.64−3.82 (4H, m), 4.67 (1H, ddd, *J* = 5.9, 7.8, and 8.0 Hz), 5.79 (2H, br), 6.15 (1H, d, *J* = 5.9 Hz), 8.18 (1H, s), 8.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.4, −5.33, −5.30, −5.25, 15.6, 17.8, 25.5, 26.0, 39.7, 57.7, 66.6, 76.9, 89.4, 108.9, 119.6, 138.8, 150.2, 153.1, 155.4; NOE ($CDCl_3$): H-1′/4′-OCH_2 (0.9%); FAB-MS (*m*/*z*) 524 (M^+ + H). Anal. Calcd for $C_{24}H_{45}N_5O_4Si_2$: C, 55.03; H, 8.66; N, 13.37. Found: C, 55.14; H, 8.82; N, 13.34.

Physical Data for ***16b:*** UV (MeOH) λ_{max} 260 nm (ε 14 400), λ_{min} 227 nm (ε 1800); ^{1}H NMR ($CDCl_3$) δ −0.03, 0.01, 0.10, and 0.11 (12H, each as s), 0.85 and 0.93 (18H, each as s), 1.23 (3H, t, *J* = 7.1 Hz), 2.31 (1H, dd, *J* = 6.5 and 13.9 Hz), 2.39 (1H, dd, *J* = 5.1 and 13.9 Hz), 3.60−3.75 (2H, m), 3.74 (1H, d, *J* = 10.7 Hz), 3.89 (1H, d, *J* = 10.7 Hz), 4.89 (1H, ddd, *J* = 3.4, 5.1, and 6.5 Hz), 5.85 (2H, br), 6.08 (1H, d, *J* = 3.4 Hz), 8.13 (1H, s), 8,36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.3, −5.1, −5.0, 15.4, 17.8, 18.2, 25.6, 41.4, 57.9, 64.0, 76.2, 91.1, 110.9, 119.8, 139.3, 149.9, 153.1, 155.4; NOE ($CDCl_3$): H-5′a (δ 3.74)/H-1′ (0.3%), H-8/4′-OCH_2 (0.9%); FAB-MS (*m*/*z*) 524 (M^+ + H). Anal. Calcd for $C_{24}H_{45}N_5O_4Si_2$: C, 55.03; H, 8.66; N, 13.37. Found: C, 54.83; H, 8.59; N, 13.39.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-4′-propyloxycordycepin (17a) and 9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-4-propyloxy-α-L-lyxofuranosyl]adenine (17b). Compounds **17a** and **17b** were prepared as described above for **15** by starting from a propanol (3.0 mL) solution of **9** (**9a**/**9b** = 9/1, 150 mg, 0.223 mmol) and NBS (60 mg, 0.335 mmol). HPLC separation ($CHCl_3$/MeOH = 70/1) of the reaction mixture (**17a**/**17b** = 9/1, 150 mg, 0.223 mmol) gave analytically pure **17a** (t_R = 6.6 min, foam) and **17b** (t_R = 7.8 min, foam).

Physical Data for ***17a:*** UV (MeOH) λ_{max} 259 nm (ε 14 600), λ_{min} 228 nm (ε 2200); ^{1}H NMR ($CDCl_3$) δ −0.23, −0.14, 0.15, and 0.16 (12H, each as s), 0.77 (9H, s), 0.95 (3H, t, *J* = 7.3 Hz), 0.97 (9H, s), 1.59 (2H, hex, *J* = 7.3 Hz), 2.20 (1H, dd, *J* = 7.6 and 13.4 Hz), 2.60 (1H, dd, *J* = 7.8 and 13.4 Hz), 3.54−3.65 (2H, m), 3.65 (1H, d, *J* = 10.4 Hz), 3.81 (1H, d, *J* = 10.4 Hz), 4.66 (1H, ddd, *J* = 5.9, 7.6, and 7.8 Hz), 5.92 (2H, br), 6.16 (1H, d, *J* = 5.9 Hz), 8.12 (1H, s), 8.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.4, −5.34, −5.30, −5.27, 10.6, 17.8, 18.4, 23.3, 25.5, 26.0, 39.7, 63.8, 66.6, 77.0, 89.5, 108.9, 119.5, 138.8, 150.1, 153.1, 155.4; NOE ($CDCl_3$): H-5′b (δ 3.81)/H-8 (1.1%), H-1′/4′-OCH_2 (1.4%); FAB-MS (*m*/*z*) 538 (M^+ + H). Anal. Calcd for $C_{25}H_{47}N_5O_4Si_2$: C, 55.83; H, 8.81; N, 13.02. Found: C, 55.91; H, 9.01; N, 13.02.

Physical Data for ***17b:*** UV (MeOH) λ_{max} 259 nm (ε 15 400), λ_{min} 228 nm (ε 3100); ^{1}H NMR ($CDCl_3$) δ −0.03, 0.01, 0.10, and 0.11 (12H, each as s), 0.85 (9H, s), 0.93 (3H, t, *J* = 7.3 Hz), 0.94 (9H, s), 1.62 (2H, ddq, *J* = 6.8, 7.1, and 7.3 Hz), 2.31 (1H, dd, *J* = 6.3 and 13.9 Hz), 2.40 (1H, dd, *J* = 5.1 and 13.9 Hz), 3.54 (1H, dt, *J* = 6.8 and 8.8 Hz), 3.60 (1H, dt, *J* = 7.1 and 8.8 Hz), 3.75 (1H, d, *J* = 10.7 Hz), 3.89 (1H, d, *J* = 10.7 Hz), 4.88 (1H, ddd, *J* = 3.2, 5.1, and 6.3 Hz), 6.01 (2H, br), 6.08 (1H, d, *J* = 3.2 Hz), 8.12 (1H, s), 8.35 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, −5.1, −5.0, 10.7, 17.8, 18.2, 23.1, 25.6, 25.8, 41.2, 63.98, 64.03, 76.1, 91.1, 110.9, 119.8, 139.3, 149.9, 153.0, 155.5; NOE ($CDCl_3$) H-8/4′-OCH_2 (1.2%); FAB-MS (*m*/*z*) 538 (M^+ + H). Anal. Calcd for $C_{25}H_{47}N_5O_4Si_2$: C, 55.83; H, 8.81; N, 13.02. Found: C, 55.91; H, 8.99; N, 13.12.

4′-Butyloxy-2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cordycepin (18a) and 9-[4-Butyloxy-2,5-bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-α-L-lyxofuranosyl]adenine (18b). Compounds **18a** and **18b** were prepared as described above for **15** starting from an *n*-butanol (3.0 mL) solution of **9** (**9a**/**9b** = 9/1, 150 mg, 0.223 mmol) and NBS (60 mg, 0.335 mmol). HPLC separation ($CHCl_3$/MeOH = 80/1) of the reaction mixture (**18a**/**18b** = 2.0/1.0, 98%) gave analytically pure **18a** (t_R = 6.5 min, foam) and **18b** (t_R = 7.5 min, foam).

Physical Data for ***18a:*** UV (MeOH) λ_{max} 259 nm (ε 14 700), λ_{min} 228 nm (ε 2300); ^{1}H NMR ($CDCl_3$) δ −0.23, −0.14, 0.14, and 0.16 (12H, each as s), 0.77 (9H, s), 0.92 (3H, t, *J* = 7.3 Hz), 0.97 (9H, s), 1.35−1.44 (2H, m), 1.52−1.59 (2H, m), 2.20 (1H, dd, *J* = 7.6 and 13.4 Hz), 2.60 (1H, dd, *J* = 7.8 and 13.4 Hz), 3.57−3.71 (3H, m), 3.80 (1H, d, *J* = 10.5 Hz), 4.66 (1H, ddd, *J* = 5.9, 7.6, and 7.8 Hz), 5.92 (2H, br), 6.15 (1H, d, *J* = 5.9 Hz), 8.18 (1H, s), 8.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.4, −5.34, −5.30, −5.27, 13.9, 17.8, 18.4, 19.3, 25.5, 26.0, 32.1, 39.7, 66.6, 77.0, 89.5, 108.9, 119.6, 138.8, 150.1, 153.1, 155.4; NOE ($CDCl_3$) H-1′/4′-OCH_2 (1.6%), H-5′b (δ 3.80)/H-8 (0.5%); FAB-MS (*m*/*z*) 552 (M^+ + H). Anal. Calcd for $C_{26}H_{49}N_5O_4Si_2$: C, 56.59; H, 8.95; N, 12.69. Found: C, 56.73; H, 9.21; N, 12.77.

Physical Data for ***18b:*** UV (MeOH) λ_{max} 260 nm (ε 14 400), λ_{min} 228 nm (ε 2300); ^{1}H NMR ($CDCl_3$) δ −0.02, 0.02, 0.10, and 0.11 (12H, each as s), 0.85 (9H, s), 0.92 (3H, t, *J* = 7.6 Hz), 0.94 (9H, s), 1.33−1.43 (2H, m), 1.55−1.62 (2H, m), 2.30 (1H, dd, *J* = 6.5 and 13.9 Hz), 2.40 (1H, dd, *J* = 4.9 and 13.9 Hz), 3.58 (1H, dt, *J* = 6.8 and 8.8 Hz), 3.65 (1H, dt, *J* = 7.1 and 8.8 Hz), 3.75 (1H, d, *J* = 10.7 Hz), 3.89 (1H, d, *J* = 10.7 Hz), 4.87 (1H, ddd, *J* = 3.2, 4.9, and 6.5 Hz), 6.06 (2H, br), 6.08 (1H, d, *J* = 3.2 Hz), 8.12 (1H, s), 8.35 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, −5.1, −5.0, 13.9, 17.8, 18.2, 19.4, 25.6, 25.8, 31.9, 41.2, 62.2, 64.0, 76.1, 91.1, 110.9, 119.8, 139.3, 149.9, 153.0, 155.5; NOE ($CDCl_3$) H-8/4′-OCH_2 (1.0%), H-1′/H-5′a (δ 3.75) (0.7%); FAB-MS (*m*/*z*) 552 (M^+ + H). Anal. Calcd for $C_{26}H_{49}N_5O_4Si_2$: C, 56.59; H, 8.95; N, 12.69. Found: C, 56.64; H, 9.11; N, 12.72.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-4′-isopropyloxycordycepin (19a) and 9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-4-isopropyloxy-α-L-lyxofuranosyl]adenine (19b). Compounds **19a** and **19b** were prepared as described above for **15** by starting from an isopropyl alcohol (3.0 mL) solution of **9** (**9a**/**9b** = 9/1, 150 mg, 0.223 mmol) and NBS (60 mg, 0.335 mmol). HPLC separation ($CHCl_3$/MeOH = 80/1) of the reaction mixture (**19a**/**19b** = 1.8/1, 91%) gave

analytically pure **19a** (t_R = 7.0 min, foam) and **19b** (t_R = 8.7 min, foam).

*Physical Data for **19a**:* UV (MeOH) λ_{max} 259 nm (ε 14 600), λ_{min} 228 nm (ε 2100); ^{1}H NMR ($CDCl_3$) δ −0.23, −0.14, 0.15, and 0.17 (12H, each as s), 0.77 and 0.97 (18H, each as s), 1.18 and 1.22 (6H, each as d, J = 6.1 Hz), 2.15 (1H, dd, J = 7.8 and 13.4 Hz), 2.63 (1H, dd, J = 7.8 and 13.4 Hz), 3.62 (1H, d, J = 10.2 Hz), 3.79 (1H, d, J = 10.2 Hz), 4.18 (1H, sept, J = 7.1 Hz), 4.63 (1H, dt, J = 5.9 and 7.8 Hz), 5.92 (2H, br), 6.18 (1H, d, J = 5.9 Hz), 8.20 (1H, s), 8.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.4, −5.33, −5.29, −5.25, 17.8, 18.4, 24.6, 24.6, 25.5, 26.0, 41.0, 65.7, 66.8, 77.0, 89.4, 109.4, 119.6, 138.8, 150.2, 153.1, 155.4; NOE ($CDCl_3$) H-8/H-5′b (δ 3.79) (0.4%), H-1′/4′-OCH (4.6%); FAB-MS (m/z) 538 (M^+ + H). Anal. Calcd for $C_{25}H_{47}N_5O_4Si_2$: C, 55.83; H, 8.81; N, 13.02. Found: C, 55.87; H, 9.00; N, 13.11.

*Physical Data for **19b**:* UV (MeOH) λ_{max} 260 nm (ε 14 900), λ_{min} 228 nm (ε 2200); ^{1}H NMR ($CDCl_3$) δ −0.02, 0.02, 0.11, and 0.12 (12H, each as s), 0.85 and 0.94 (18H, each as s), 1.14 and 1.18 (6H, each as d, J = 7.1 Hz), 2.29 (1H, dd, J = 6.6 and 14.0 Hz), 2.42 (1H, dd, J = 4.6 and 14.0 Hz), 3.76 (1H, d, J = 10.7 Hz), 3.89 (1H, d, J = 10.7 Hz), 4.21 (1H, sept, J = 7.1 Hz), 4.82 (1H, ddd, J = 3.2, 4.6, and 6.6 Hz), 5.59 (2H, br), 6.07 (1H, d, J = 3.2 Hz), 8.19 (1H, s), 8.35 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, −5.01, −4.97, 17.9, 18.2, 24.2, 24.3, 25.7, 25.8, 41.6, 64.7, 66.1, 75.6, 91.1, 111.4, 119.8, 139.8, 149.9, 153.0, 155.3; NOE ($CDCl_3$) H-8/4′-OCH(CH_3)$_2$ (4.4%), H-1′/H-5′a (δ 3.76) (1.0%); FAB-MS (m/z) 538 (M^+ + H). Anal. Calcd for $C_{25}H_{47}N_5O_4Si_2$: C, 55.83; H, 8.81; N, 13.02. Found: C, 55.80; H, 9.08; N, 12.91.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-4′-isobutyloxycordycepin (20a) and 9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-4-isobutyloxy-α-L-lyxofuranosyl]adenine (20b). Compounds **20a** and **20b** were prepared as described above for **15**, by starting from an isobutyl alcohol (3.0 mL) solution of **9** (**9a**/**9b** = 9/1, 150 mg, 0.223 mmol) and NBS (60 mg, 0.335 mmol). HPLC separation ($CHCl_3$/MeOH = 80/1) of the reaction mixture (**20a**/**20b** = 2.3/1, 100%) gave analytically pure **20a** (t_R = 6.7 min, foam) and **20b** (t_R = 7.9 min, foam).

*Physical Data for **20a**:* UV (MeOH) λ_{max} 260 nm (ε 14 800), λ_{min} 228 nm (ε 2200); ^{1}H NMR ($CDCl_3$) δ −0.23, −0.15, 0.15, and 0.16 (12H, each as s), 0.77 (9H, s), 0.92 and 0.94 (6H, each as d, J = 6.6 Hz), 0.97 (9H, s), 1.82 (1H, tsept, J = 6.6 Hz), 2.20 (1H, dd, J = 7.6 and 13.4 Hz), 2.61 (1H, dd, J = 8.0 and 13.4 Hz), 3.37 (1H, dd, J = 6.6 and 8.7 Hz), 3.65 (1H, d, J = 10.2 Hz), 3.81 (1H, d, J = 10.2 Hz), 4.44 (1H, dd, J = 6.6 and 8.7 Hz), 4.64 (1H, ddd, J = 5.6, 7.6, and 8.0 Hz), 5.82 (2H, br), 6.15 (1H, d, J = 5.6 Hz), 8.19 (1H, s), 8.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.4, −5.32, −5.29, −5.26, 17.9, 18.4, 19.35, 19.41, 25.5, 26.0, 28.8, 39.7, 66.5, 68.7, 77.2, 89.6, 109.0, 119.6, 138.8, 150.1, 153.1, 155.4; NOE ($CDCl_3$) H-1′/4′-OCH_2 (4.6%); FAB-MS (m/z) 552 (M^+ + H). Anal. Calcd for $C_{26}H_{49}N_5O_4Si_2$: C, 56.59; H, 8.95; N, 12.69. Found: C, 56.68; H, 9.21; N, 12.89.

*Physical Data for **20b**:* UV (MeOH) λ_{max} 260 nm (ε 14 300), λ_{min} 227 nm (ε 900); ^{1}H NMR ($CDCl_3$) δ −0.02, 0.02, 0.10, and 0.11 (12H, each as s), 0.85 (9H, s), 0.92 (3H, d, J = 6.6 Hz), 0.93 (9H, s), 0.94 (3H, d, J = 6.6 Hz), 1.82 (1H, ddsept, J = 6.6 Hz), 2.20 (1H, dd, J = 6.3 and 13.9 Hz), 2.61 (1H, dd, J = 4.9 and 13.9 Hz), 3.37 and 3.44 (2H, each as dd, J = 6.6 and 8.3 Hz), 3.65 (1H, d, J = 10.6 Hz), 3.81 (1H, d, J = 10.6 Hz), 4.64 (1H, ddd, J = 3.4, 4.9, and 6.3 Hz), 5.83 (2H, br), 6.15 (1H, d, J = 3.2 Hz), 8.19 (1H, s), 8.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, −5.1, −5.0, 17.9, 18.2, 19.5, 25.6, 25.8, 28.7, 41.0, 64.0, 68.9, 76.1, 91.2, 110.9, 119.9, 139.4, 149.9, 153.0, 155.4; NOE ($CDCl_3$) H-8/4′-OCH_2CH (1.6%), H-1′/H-5′a (δ 3.65) (1.0%); FAB-MS (m/z) 552 (M^+ + H). Anal. Calcd for $C_{26}H_{49}N_5O_4Si_2$: C, 56.59; H, 8.95; N, 12.69. Found: C, 56.64; H, 9.19; N, 12.48.

4′-*tert*-Butoxy-2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-cordycepin (21a) and 9-[4-*tert*-Butoxy-2,5-bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-α-L-lyxofuranosyl]adenine (21b). Compounds **21a** and **21b** were prepared as described above for **15**, by starting from a *tert*-butyl alcohol (3.0 mL) solution of **9** (**9a**/**9b** = 9/1, 150 mg, 0.223 mmol) and NBS (60 mg, 0.335 mmol). HPLC separation ($CHCl_3$/MeOH = 80/1) of the reaction mixture (**21a**/**21b** = 2.6/1, 88%) gave analytically pure **21a** (t_R = 6.9 min, foam) and **21b** (t_R = 8.5 min, foam).

*Physical Data for **21a**:* UV (MeOH) λ_{max} 260 nm (ε 15 000), λ_{min} 228 nm (ε 2300); ^{1}H NMR ($CDCl_3$) δ −0.21, −0.13, 0.15, and 0.17 (12H, each as s), 0.78 and 0.98 (18H, each as s), 1.36 (9H, s), 2.19 (1H, dd, J = 7.6 and 13.0 Hz), 2.70 (1H, dd, J = 7.6 and 13.0 Hz), 3.57 (1H, d, J = 10.1 Hz), 3.94 (1H, d, J = 10.1 Hz), 4.56 (1H, dt, J = 5.5 and 7.6 Hz), 6.03 (2H, br), 6.23 (1H, d, J = 5.5 Hz), 8.24 (1H, s), 8.37 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.4, −5.31, −5.25, −5.2, 17.8, 18.5, 25.5, 26.0, 31.0, 44.3, 68.1, 76.1, 77.2, 89.4, 109.9, 119.5, 138.8, 150.1, 153.1, 155.5; NOE ($CDCl_3$) H-1′/4′-O-*t*Bu (4.6%), H-8/H-5′b (δ 3.94) (0.8%); FAB-MS (m/z) 552 (M^+ + H). Anal. Calcd for $C_{26}H_{49}N_5O_4Si_2$: C, 56.59; H, 8.95; N, 12.69. Found: C, 56.61; H, 9.17; N, 12.84.

*Physical Data for **21b**:* UV (MeOH) λ_{max} 260 nm (ε 14 600), λ_{min} 228 nm (ε 1100); ^{1}H NMR ($CDCl_3$) δ −0.04, 0.02, 0.10, and 0.12 (12H, each as s), 0.84 and 0.95 (18H, each as s), 1.29 (9H, s), 2.31 (1H, dd, J = 6.6 and 13.7 Hz), 2.47 (1H, dd, J = 5.1 and 13.7 Hz), 3.83 (1H, d, J = 10.7 Hz), 3.93 (1H, d, J = 10.7 Hz), 4.78 (1H, ddd, J = 3.4, 5.1, and 6.6 Hz), 5.95 (2H, br), 6.23 (1H, d, J = 3.4 Hz), 8.25 (1H, s), 8.37 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.31, −5.26, −5.0, −4.9, 17.9, 18.2, 25.7, 25.9, 31.1, 44.2, 66.0, 76.1, 76.4, 91.0, 112.4, 119.6, 139.6, 150.1, 153.1, 155.4; NOE ($CDCl_3$) H-1′/H-5′a (δ 3.83) (1.2%); FAB-MS (m/z) 552 (M^+ + H). Anal. Calcd for $C_{26}H_{49}N_5O_4Si_2$: C, 56.59; H, 8.95; N, 12.69. Found: C, 56.49; H, 9.16; N, 12.75.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-4′-fluorocordycepin (23a) and 9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-4-fluoro-α-L-lyxofuranosyl]adenine (23b). To a CH_2Cl_2 (6.0 mL) solution of a mixture of **9** (100 mg, 0.15 mmol, **9a**/**9b** = 8.2/1) and NBS (39.2 mg, 0.22 mmol) was added DAST (0.059 mL, 0.45 mmol) at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 30 min and quenched with saturated aqueous $NaHCO_3$. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. Silica gel column chromatography (hexane/AcOEt = 6/1) of the residue afforded **22a**,**b** (65.8 mg, 75%, **22a**/**22b** = 2.4/1) as a foam. Compound **22** was treated with NH_3/MeOH (ca. 50 mL) at 0 °C for 48 h. The reaction mixture was evaporated to dryness, and silica gel column chromatography (hexane/AcOEt = 3/1) of the residue gave **23** (85.4 mg, 95%) as a foam. HPLC separation ($CHCl_3$/MeOH = 80/1) gave analytically pure **23a** (t_R = 7.5 min, foam) and **23b** (t_R = 8.8 min, foam). Stereochemistry at the 4′-position of **23b** was determined by NOE measurments of its 2′,5′-diacetate.

*Physical Data for **23a**:* UV (MeOH) λ_{max} 259 nm (ε 14 500), λ_{min} 226 nm (ε 2200); ^{1}H NMR ($CDCl_3$) δ −0.01, 0.00, 0.10, and 0.11 (12H, each as s), 0.85 and 0.92 (18H, each as s), 2.23 (1H, ddd, J = 3.4, 14.4, and 17.8 Hz), 2.89 (1H, ddd, J = 6.8, 14.4, and 25.1 Hz), 3.79 (1H, dd, J = 3.7 and 10.7 Hz), 3.88 (1H, dd, J = 7.3 and 10.7 Hz), 4.80 (1H, ddd, J = 3.2, 3.4, and 6.8 Hz), 5.83 (1H, br s), 6.30 (1H, dd, J = 1.2 and 3.2 Hz), 8.06 (1H, s), 8.34 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, −5.1, −5.0, 17.8, 18.4, 25.5, 25.9, 39.8, 40.1, 63.9, 64.4, 75.7, 92.7, 119.4, 120.0, 121.6, 138.8, 149.6, 153.2, 155.4; NOE ($CDCl_3$) H-8/H-3′b (δ 2.89) (2.0%), H-1′/H-3′a (δ 2.23) (1.8%); FAB-MS (m/z) 498 (M^+ + H). Anal. Calcd for $C_{22}H_{40}FN_5O_3Si_2$: C, 53.09; H, 8.10; N, 14.07. Found: C, 53.02; H, 8.17; N, 13.89.

*Physical Data for **23b**:* UV (MeOH) λ_{max} 259 nm (ε 14 800), λ_{min} 227 nm (ε 2500); ^{1}H NMR ($CDCl_3$) δ −0.12, −0.05, 0.09, and 0.10 (12H, each as s), 0.80 and 0.91 (18H, each as s), 2.48 (1H, ddd, J = 7.1, 13.6, and 26.3 Hz), 2.51 (1H, ddd, J = 7.1, 13.6, and 26.6 Hz), 3.75−3.85 (2H, m), 5.01 (1H, dt J = 4.6 and 7.1 Hz), 5.95 (2H, br), 6.16 (1H, dd, J = 4.6 and 6.1 Hz), 8.06 (1H, s), 8.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.41, −5.35, −5.21, −5.16, 17.8, 18.3, 25.5, 25.8, 40.7, 49.9, 64.4, 64.8, 75.8, 91.4, 119.6, 120.1, 122.4, 138.6, 138.6, 150.1, 153.3, 155.5; NOE ($CDCl_3$) H-1′/H-3′a (δ 2.50) (1.0%), H-2′/H-3′b (δ 3.06) (5.9%), H-3′a/H-5′a (δ 4.34) (2.5%); FAB-MS (m/z) 498 (M^+ + H). Anal. Calcd for $C_{22}H_{40}FN_5O_3Si_2$: C, 53.09; H, 8.10; N, 14.07. Found: C, 53.41; H, 8.28; N, 14.04.

4′-Allyl-2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cordycepin (24a)[7] and 9-[4-Allyl-2,5-bis-*O*-(*tert*-butyldimethylsilyl)-3-

deoxy-α-L-lyxofuranosyl]adenine (24b). A benzene (5.0 mL) solution of a mixture of **7** (200 mg, 0.34 mmol, **7a**/**7b** = 6.1/1), allyltributylstannane (0.31 mL, 1.02 mmol), and bis(tributylstannane) (0.09 mL, 0.17 mmol) was irradiated with a high-pressure mercury lamp at room temperature for 30 min. Silica gel column chromatography (hexane/AcOEt = 4/1) of the reaction mixture afforded **24a,b** (146.4 mg, 83%, **24a** /**24b** = 3.8/1) as a foam.

*Physical Data for **24b**:* UV (MeOH) λ_{max} 259 nm (ε 15 000), λ_{min} 228 nm (ε 2400); ^{1}H NMR ($CDCl_3$) δ −0.13, −0.04, 0.09, and 0.10 (12H, each as s), 0.81 and 0.94 (18H, each as s), 2.48 (1H, dd, J = 5.5 and 13.3 Hz), 2.51 (1H, dd, J = 7.0 and 13.3 Hz), 3.48 (2H, d, J = 3.4 Hz), 3.75−3.85 (2H, m), 4.97−5.17 (3H, m), 5.79 (2H, br), 5.84−5.98 (2H, m), 7.93 (1H, s), 8.35 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.43, −5.37, −5.1, 17.8, 18.2, 25.6, 25.9, 38.8, 41.4, 67.6, 75.6, 87.0, 91.6, 118.8, 120.3, 133.5, 139.4, 149.8, 152.9; NOE ($CDCl_3$) H-3′a (δ 2.48)/H-5′ (3.7%), H-3′b (δ 2.51)/−CH_2CH=CH_2 (3.1%); FAB-MS (m/z) 520 (M^+ + H). Anal. Calcd for $C_{25}H_{45}N_5O_3Si_2$: C, 57.76; H, 8.73; N, 13.47. Found: C, 57.39; H, 8.82; N, 13.67.

2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-4′-cyanoethylcordycepin (25). To a toluene (5.0 mL) solution of a mixture of **7** (200 mg, 0.34 mmol) and acrylonitrile (0.11 mL, 1.70 mmol) was added dropwise Bu_3SnH (0.10 mL, 0.37 mmol) and AIBN (31 mg, 0.19 mmol) dissolved in toluene (5.0 mL) over 1 h under a positive pressure of dry Ar, and the solution was refluxed. The reaction mixture was stirred for 3 h. Silica gel column chromatography (hexane/AcOEt = 1/3) of the reaction mixture afforded **25** (88.3 mg, 49%) as a foam.

*Physical Data for **25**:* ^{1}H NMR ($CDCl_3$) δ −0.09, −0.04, 0.09, and 0.11 (12H, each as s), 0.83 and 0.92 (18H, each as s), 1.91 (1H, dd, J = 5.4 and 13.1 Hz), 2.10 (1H, ddd, J = 6.6, 9.3, and 14.1 Hz), 2.21 (1H, ddd, J = 6.1, 9.3, and 14.1 Hz), 2.45−2.56 (2H, m), 2.60 (1H, dd, J = 6.8 and 13.1 Hz), 3.55 (1H, d, J = 10.5 Hz), 3.81 (1H, d, J = 10.5 Hz), 5.08 (1H, ddd, J = 4.1, 5.4, and 6.8 Hz), 5.93 (1H, d, J = 4.1 Hz), 6.07 (2H, br), 8.04 (1H, s), 8.33 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.4, −5.1, −5.0, 12.0, 17.7, 18.2, 25.5, 25.8, 32.9, 40.3, 67.3, 76.0, 86.3, 91.7, 119.7, 120.0, 139.4, 149.5, 152.8, 155.5; NOE ($CDCl_3$) H-8/H-5′b (δ 3.81) (0.3%), H-2′/H-5′b (1.0%); FAB-HRMS (m/z) calcd for $C_{25}H_{45}N_6O_3Si_2$ 533.3092, found 533.3114 (M^+ + H).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +81 3 3784 8187. Fax: +81 3 3784 8252. E-mail: y-kubota@pharm.showa-u.ac.jp; harakazu@pharm.showa-u.ac.jp.

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