Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 64 (2008) 2391–2396
Tetrahedron
www.elsevier.com/locate/tet

Synthesis of 4′-benzoyloxycordycepin from adenosine

Yutaka Kubota, Mayumi Kunikata, Nobuhide Ishizaki, Kazuhiro Haraguchi, Yuki Odanaka, Hiromichi Tanaka*

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

Received 14 December 2007; received in revised form 25 December 2007; accepted 2 January 2008
Available online 6 January 2008

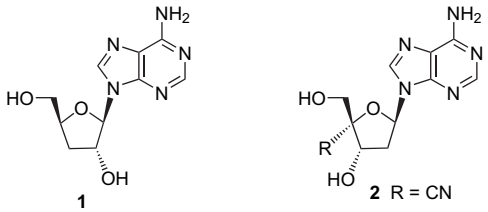
Abstract

With an aim to synthesize 4′-substituted cordycepins, the 4′-benzoyloxy precursor (**9**) was prepared from adenosine through an electrophilic addition (iodo-benzoyloxylation) to the 4′,5′-unsaturated derivative (**5**) and subsequent radical-mediated removal of the 3′-iodine atom of the resulting adducts (**6**). Usefulness of **9** was briefly verified by synthesizing the 4′-allyl (**12**) and 4′-cyano (**13**) analogues of cordycepin.

Keywords: Cordycepin; 4′-Substituted nucleoside; Stereochemistry; Organosilicon reagent

1. Introduction

Cordycepin was the first nucleoside antibiotic identified as a metabolite of the mold *Cordycep militaris* in 1951.[1] A wrong structure was initially assigned for it,[2] but later in 1964, 3′-deoxyadenosine (**1**) isolated from *Aspergillus nidulans* was shown to be identical to cordycepin.[3,4] The reported biological effects of cordycepin on RNA biosynthesis,[5] methyltransferase,[6] and purine biosynthesis[7] have stimulated the synthesis of its analogues with an aim to discover chemotherapeutically viable compounds,[8–10] but reported modification at its sugar moiety has been quite limited.[11]



As reviewed recently by Hayakawa et al.,[12] nucleosides analogues substituted at the 4′-position have attracted much attention as promising anti-HIV agents, which can be exemplified by the 2′-deoxyadenosine analogues having 4′-cyano (**2**, EC_{50} 0.051 μM) and 4′-ethynyl (**3**, EC_{50} 0.0098 μM) substituents.[13] In this context, we were interested in synthesizing 4′-carbon-substituted cordycepin derivatives. Although there have been several methods available to synthesize 4′-substituted nucleosides,[12] we intended to employ nucleophilic displacement at the 4′-position of cordycepin, as have been reported from our laboratory in the synthesis of 1′- and 4′-branched nucleosides.[14,15] To do so, introduction of a leaving group to the 4′-position of cordycepin was necessary.

In this paper, we describe the preparation of 4′-benzoyloxycordycepin from adenosine through halo-acyloxylation to the 3′,4′-unsaturated derivative and subsequent radical-mediated dehalogenation. Also, usefulness of 4′-benzoyloxycordycepin is very briefly demonstrated by the synthesis of the 4′-allyl and 4′-cyano analogues of cordycepin.

2. Results and discussion

2.1. Halo-acyloxylation of the 3′,4′-unsaturated derivative (5)

Adenosine was converted to the 3′,4′-unsaturated derivative **4** according to the method reported by Moffatt et al.[16] The 2′- and 5′-hydroxyl groups of **4** were protected with

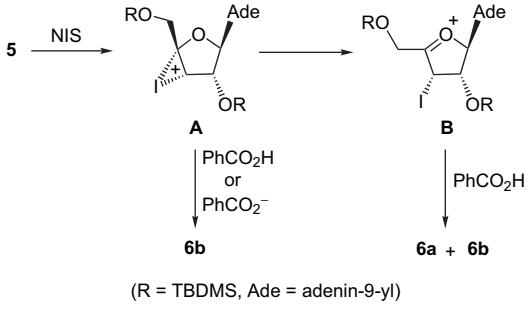
* Corresponding author.
E-mail address: hirotnk@pharm.showa-u.ac.jp (H. Tanaka).

0040-4020/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.01.018

Table 1
Iodo-benzoyloxylation of **5** by changing the solvent[a]

Entry	Solvent	Time (h)	Combined yield (%) of **6a**+**6b**	Ratio of **6a/6b**[b]
1	CH_2Cl_2	3	82	1:1.6
2	THF	2.5	45[c]	1:5.0
3	$CHCl_3$	3	51[c]	1:1.2
4	Pyridine	3	32	Only **6b**
5	CH_2Cl_2[d]	3.5	64	Only **6b**

[a] All reactions were carried out by using NIS (3.0 equiv) and $PhCO_2H$ (3.0 equiv) at rt in the solvent indicated (concentration of **5**, 42 mM).
[b] The ratio was determined by integrating the respective H-1′.
[c] Several unknown byproducts were also formed.
[d] DMAP (3.0 equiv) was added as an additive. Compound **5** was recovered in 23% yield.



Scheme 2.

Table 2
Iodo-benzoyloxylation by varying concentration of **5** in CH_2Cl_2[a]

Entry	Concentration (mM) of **5**	Time (h)	Combined yield (%) of **6a**+**6b**	Ratio of **6a/6b**[b]
1	84	5.5	83	1:2.0
2	42	3.5	82	1:1.6
3	21	3.0	81	1:1.2
4	11	3.0	80	1.2:1
5	5.3	3.0	71	1.5:1
6	2.1	3.0	77	1.8:1
7	0.7	3.0	67	1.1:1
8	0.4	3.0	58	1:1.8

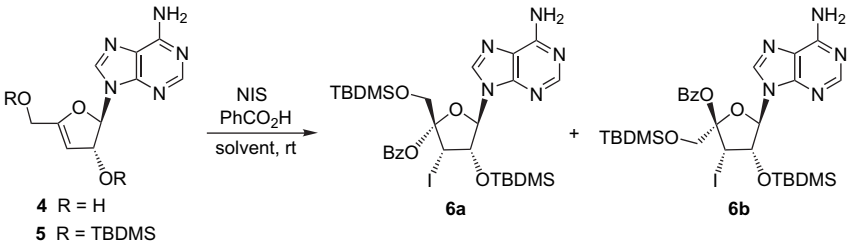
[a] All reactions were carried out by using NIS (3.0 equiv) and $PhCO_2H$ (3.0 equiv) in CH_2Cl_2 at rt.
[b] The ratio was determined by integrating the respective H-1′.

tert-butyldimethylsilyl (TBDMS) to give **5** as reported previously.[17] Halo-acyloxylation of **5** was first carried out by using NBS/$PhCO_2H$ in CH_2Cl_2, but this reaction gave an intractable mixture of products.[18] The use of NIS/$PhCO_2H$, on the other hand, allowed **5** to undergo the iodo-benzoyloxylation to give a mixture of the *syn*-(**6a**) and *anti*-(**6b**) adducts in 82% yield with a slight preponderance of the latter as shown in entry 1 of Table 1. The depicted stereochemistry of these adducts was assumed based on their NOE experiments (Scheme 1).[19] Concomitant formation of the *syn*-adduct (**6a**) suggested that the incipient 3′,4′-iodonium **A** was followed by the formation of a carboxonium intermediate **B** (Scheme 2). The observed stereochemistry of the iodonium formation was quite unexpected, since epoxidation of **5** with dimethyldioxirane took place exclusively at its β-face in our previous study.[17] At the moment, we have no explanation for the reversed stereochemistry of these electrophilic reactions.

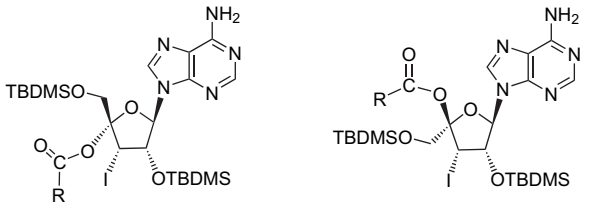
Use of THF or $CHCl_3$ as a solvent also gave a mixture of **6a** and **6b** with a lower combined yield (entries 2 and 3). In contrast to these cases, the reaction conducted in pyridine gave only the *anti*-adduct (**6b**), albeit in a low yield (entry 4). We assumed that the pyridine worked as a base to dissociate $PhCO_2H$. Under such circumstances, higher nucleophilicity of the resulting benzoate ion would allow its reaction with the initially formed 3′,4′-iodonium intermediate (**A**). In fact, when DMAP was used as an additive and the reaction was carried out in CH_2Cl_2, only **6b** was formed in 64% yield (entry 5).

We also examined the above iodo-benzoyloxylation by varying concentration of **5** in CH_2Cl_2 (Table 2). Although no dramatic change was observed in the ratio of **6a/6b**, there can be seen a trend, within entries 1–3, that formation of the *anti*-adduct (**6b**) was favored at higher concentration. At comparatively lower concentration shown in entries 4–6, reverse stereoselectivity was observed. One explanation for these results could possibly be made again based on Scheme 2: at higher concentration where nucleophilic attack of $PhCO_2H$ is statistically favored, **A** reacts as soon as it is formed, while at lower concentration, **A** has enough time before reacting with $PhCO_2H$ to form **B**, which undergoes preferential attack from its α-face due to the presence of adenine base. However, this explanation would be too simple and does not give the answer to entries 7 and 8 where formation of the *syn*-adduct (**6a**) became less favored again.

Carboxylic acids other than $PhCO_2H$ also work in this iodo-acyloxylation as exemplified by the formation of **7** (82%, **7a/7b**=1:1.9) and **8** (64%, **8a/8b**=1:4).[20] These adducts were prepared by reacting **5** with the respective acids under the conditions of entry 2 in Table 2.



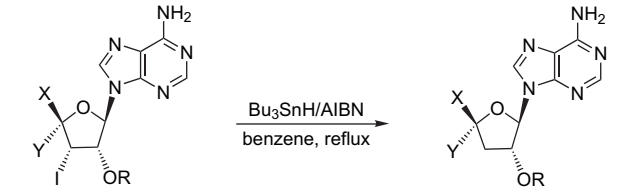
Scheme 1.



2.2. Radical-mediated deiodination of the adducts (6–8)

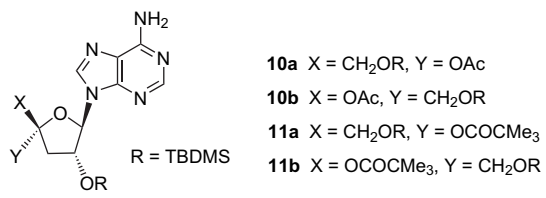
Removal of the iodine atom at the 3′-position of **6**–**8** was carried out. Upon hydrogenolysis of **6** in the presence of 5% Pd/C and an acid acceptor Et_3N in MeOH, the major reaction pathway was elimination to yield **5** (75%), the desired product **9** being isolated only in 22% yield. An apparent alternative, radical-mediated deiodination, was next examined, although one concern of this operation was well known 1,2-acyloxy migration.[21]

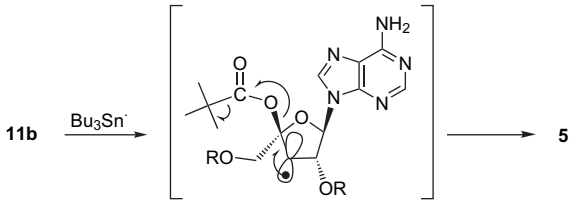
When the deiodination was carried out by reacting **6** (**6a**/**6b**=1:2) with Bu_3SnH/AIBN in refluxing benzene for 3 h (Scheme 3), **9** was obtained in 94% yield (**9a**/**9b**=1:2.2). Each diastereomer was isolated by HPLC separation ($CHCl_3$/MeOH=80:1).[22] Although a trace amount of the elimination product **5** was detected in this reaction, no product resulting from 1,2-acyloxy migration was formed.



Scheme 3.

The deiodination was also examined by using the 4′-acetoxy (**7**) and the 4′-pivaloyloxy (**8**) derivatives. While **7** (**7a**/**7b**=1:2.7) gave the expected product **10** in 87% yield (**10a**/**10b**=1:2.7) without forming the elimination product (**5**), the reaction of **8** (**8a**/**8b**=1:4) gave a considerable amount of **5** (11%) together with **11** (77%, **11a**/**11b**=1:3.6). By carrying out the reaction of **8a** and **8b** separately, it became apparent that the formation of **5** took place solely from **8b**: **5** (19%) and **11b** (74%). Although the stereoelectronic preference for an *anti*-coplanar arrangement is known to be much less dominant in radical-mediated β-elimination,[23] the result of **8b** suggests that the favorable generation of *tert*-butyl radical from the 4′-pivaloyloxy group as well as its *anti*-disposition caused the elimination pathway as shown in Scheme 4.

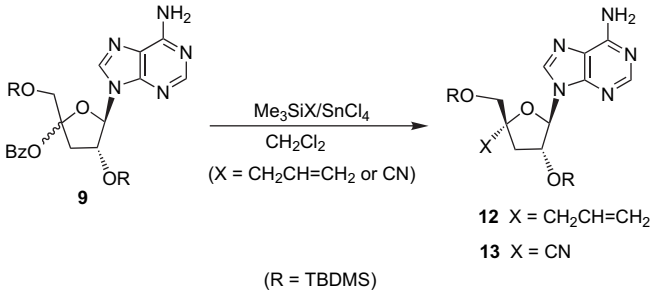




Scheme 4.

2.3. Reaction of 4′-benzoyloxycordycepin (9) with organosilicon reagents: synthesis of the 4′-allyl and 4′-cyano analogues

Finally, we intended to briefly demonstrate that the cordycepin derivative having a 4′-acyloxy group is a useful substrate for the synthesis of 4′-branched analogues. By using the 4′-benzoyloxy derivative (**9**), the reaction with organosilicon reagents in the presence of $SnCl_4$ was examined (Scheme 5).



Scheme 5.

Compound **9** (**9a**/**9b**=1:2) was reacted with $Me_3SiCH_2CH{=}CH_2$ (5 equiv) in the presence of $SnCl_4$ (5 equiv) in CH_2Cl_2 for 2 h. Two products isolated from the reaction mixture were the β-D-isomer of 4′-allylcordycepin (**12**, 44%)[24] and the elimination product (**5**, 9%). Neither the starting material nor the α-L-isomer was isolated. To see if the 4′-stereochemistry of **9** has any influence on the reactivity, **9a** and **9b** were reacted separately with $Me_3SiCH_2CH{=}CH_2/SnCl_4$, but no significant difference was observed: **12** (47%) and **5** (8%) from **9a**; **12** (43%) and **5** (9%) from **9b**. When Me_3SiCN was reacted with **9** (**9a**/**9b**=1:2) under similar reaction conditions to the above, the β-D-isomer of 4′-cyanocordycepin (**13**, 58%)[25] was again the sole 4′-substituted product with the elimination product (**5**) being isolated in 19% yield. At the present time, it is not known why the above reactions gave exclusively the β-D-isomer.

3. Experimental section

3.1. General

NMR spectra were recorded either at 400 MHz (JNM-GX 400) or at 500 MHz (JNM-LA 500). Chemical sifts are

reported relative to Me_4Si. Mass spectra (MS) were taken in FAB mode with *m*-nitrobenzyl alcohol as a matrix on a JNS-SX 102A. UV spectra were measured on a JASCO Ubest-55 spectrophotometer. Column chromatography was carried out on silica gel (Micro Bead Silica Gel PSQ 100B, Fuji Silysia Chemical Ltd.). Thin layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254}, Merck). High performance liquid chromatography (HPLC) was carried out on a Shimadzu LC-6AD with a Shim-pack PREP-SIL (H) KIT column (2×25 cm). THF was distilled from benzophenone ketyl.

*3.1.1. 4′-Benzoyloxy-2′,5′-bis-O-(tert-butyldimethylsilyl)-3′-deoxy-3′-iodoadenosine (**6a**) and 9-[4-benzoyloxy-2,4-bis-O-(tert-butyldimethylsilyl)-3-deoxy-3-iodo-α-L-lyxofuranosyl]adenine (**6b**)*

A mixture of **5** (1.0 g, 2.09 mmol), benzoic acid (0.77 g, 6.28 mmol), and NIS (1.4 g, 6.28 mmol) in CH_2Cl_2 (25 mL) was stirred at rt for 5.5 h under positive pressure of dry Ar. The reaction mixture was partitioned between EtOAc and saturated aqueous $Na_2S_2O_3$. The organic layer was further washed with saturated aqueous $NaHCO_3$. Column chromatography (hexane/EtOAc=1:1) of the organic layer gave a mixture of **6a** and **6b** as a pale yellow foam (1.26 g, 83%: **6a/6b**=ca. 1:2). HPLC separation ($CHCl_3$/MeOH=80:1) gave analytically pure **6a** (t_R=13.5 min, foam) and **6b** (t_R=15.5 min, foam).

Physical data for **6a**: UV (MeOH) λ_{max} 235 nm (ε 16,500) and 259 nm (ε 17,200), λ_{min} 223 nm (ε 11,700) and 246 nm (ε 13,800); ^{1}H NMR ($CDCl_3$) δ 0.07, 0.08, 0.12, and 0.22 (12H, each as s), 0.87 and 0.90 (18H, each as s), 4.07 (1H, d, J=11.0 Hz), 4.78 (1H, dd, J=1.2 and 5.7 Hz), 4.85 (1H, d, J=11.0 Hz), 5.33 (1H, d, J=5.7 Hz), 5.81 (2H, br), 6.22 (1H, d, J=1.2 Hz), 7.42–7.46, 7.56–7.61, and 8.16–8.19 (5H, each as m), 8.12 (1H, s), 8.31 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.52, −5.28, −4.59, −4.50, 18.18, 18.33, 25.82, 27.55, 61.72, 76.35, 91.84, 111.28, 120.01, 128.29, 130.02, 133.42, 139.24, 149.34, 153.15, 155.47, 164.32; FABMS (*m*/*z*) 726 (M^++H). Anal. Calcd for $C_{29}H_{44}IN_5O_5Si_2$: C, 47.99; H, 6.11; N, 9.65. Found: C, 48.03; H, 6.04; N, 9.52.

Physical data for **6b**: UV (MeOH): λ_{max} 234 nm (ε 16,500) and 259 nm (ε 15,300), λ_{min} 222 nm (ε 12,000) and 247 nm (ε 12,700); ^{1}H NMR ($CDCl_3$) δ −0.35, −0.05, −0.03, and 0.02 (12H, each as s), 0.78 and 0.79 (18H, each as s), 4.41 (1H, d, J=11.0 Hz), 4.76 (1H, d, J=11.0 Hz), 5.05 (1H, d, J=5.4 Hz), 5.12 (1H, dd, J=5.4 and 6.9 Hz), 5.67 (2H, br), 6.07 (1H, d, J=6.9 Hz), 7.46–7.50, 7.59–7.61, and 8.03–8.06 (5H, each as m), 7.62 (1H, s), 7.88 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.54, −5.52, −5.22, −5.02, 17.86, 18.08, 25.47, 25.63, 38.63, 66.05, 71.88, 90.42, 110.99, 120.24, 128.34, 129.76, 130.65, 133.06, 140.40, 149.84, 152.86, 155.47, 164.37; FABMS (*m*/*z*) 726 (M^++H). Anal. Calcd for $C_{29}H_{44}IN_5O_5Si_2$: C, 47.99; H, 6.11; N, 9.65. Found: C, 48.10; H, 6.09; N, 9.65.

*3.1.2. 4′-Acetoxy-2′,5′-bis-O-(tert-butyldimethylsilyl)-3′-deoxy-3′-iodoadenosine (**7a**) and 9-[4-acetoxy-2,5-bis-O-(tert-butyldimethylsilyl)-3-deoxy-3-iodo-α-L-lyxofuranosyl]adenine (**7b**)*

Column chromatography (hexane/EtOAc=1:2) of the reaction mixture gave **7** (82%, **7a/7b**=1:1.9). HPLC separation ($CHCl_3$/MeOH=50:1) gave analytically pure **7a** (t_R=4.1 min, foam) and **7b** (t_R=5.7 min, foam).

Physical data for **7a**: UV (MeOH) λ_{max} 259 nm (ε 13,600), λ_{min} 228 nm (ε 1700); ^{1}H NMR ($CDCl_3$) δ 0.12, 0.13, and 0.18 (12H, each as s), 0.92 and 0.96 (18H, each as s), 2.10 (3H, s), 3.99 (1H, d, J=10.8 Hz), 4.57 (1H, dd, J=1.7 and 5.4 Hz), 4.64 (1H, d, J=10.8 Hz), 5.07 (1H, d, J=5.4 Hz), 5.92 (2H, br), 6.24 (1H, d, J=1.7 Hz), 8.17 (1H, s), 8.32 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.49, −5.28, −4.79, −4.39, 18.07, 18.36, 22.01, 25.81, 25.88, 27.79, 61.82, 76.35, 91.15, 110.68, 119.91, 138.84, 149.32, 153.07, 155.44, 168.94; FABMS (*m*/*z*) 664 (M^++H). Anal. Calcd for $C_{24}H_{42}IN_5O_5Si_2$: C, 43.43; H, 6.38; N, 10.55. Found: C, 43.24; H, 6.30; N, 10.36.

Physical data for **7b**: UV (MeOH) λ_{max} 259 nm (ε 14,100), λ_{min} 226 nm (ε 2000); ^{1}H NMR ($CDCl_3$) δ −0.34, −0.02, 0.06, and 0.10 (12H, each as s), 0.79 and 0.91 (18H, each as s), 2.19 (3H, s), 4.29 (1H, d, J=11.0 Hz), 4.65 (1H, d, J=11.0 Hz), 4.82 (1H, d, J=5.1 Hz), 5.08 (1H, dd, J=5.1 and 6.8 Hz), 5.99 (1H, d, J=6.8 Hz), 6.08 (2H, br), 7.86 (1H, s), 8.33 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.51, −5.43, −5.22, −4.97, 17.83, 18.16, 22.11, 25.46, 25.71, 39.01, 65.69, 71.52, 90.62, 110.29, 120.53, 140.71, 149.82, 152.90, 155.72, 168.91; FABMS (*m*/*z*) 664 (M^++H). Anal. Calcd for $C_{24}H_{42}IN_5O_5Si_2$: C, 43.43; H, 6.38; N, 10.55. Found: C, 43.55; H, 6.23; N, 10.45.

*3.1.3. 2′,5′-Bis-O-(tert-butyldimethylsilyl)-3′-deoxy-3′-iodo-4′-pivaloyloxyadenosine (**8a**) and 9-[2,5-bis-O-(tert-butyldimethylsilyl)-3-deoxy-3-iodo-4-pivaloyloxy-α-L-lyxofuranosyl]adenine (**8b**)*

Column chromatography (hexane/EtOAc=1:2) of the reaction mixture gave **8** (64%, **8a/8b**=1:4). HPLC separation ($CHCl_3$/MeOH=50:1) gave analytically pure **8a** (t_R=10.7 min, foam) and **8b** (t_R=11.3 min, foam).

Physical data for **8a**: UV (MeOH) λ_{max} 260 nm (ε 16,100), λ_{min} 227 nm (ε 3200); ^{1}H NMR ($CDCl_3$) δ 0.06, 0.10, and 0.17 (12H, each as s), 0.90 and 0.92 (18H, each as s), 1.27 (9H, s), 3.94 (1H, d, J=10.8 Hz), 4.64 (1H, d, J=10.8 Hz), 4.73 (1H, dd, J=2.0 and 6.1 Hz), 5.28 (1H, d, J=6.1 Hz), 5.64 (2H, br), 6.18 (1H, d, J=2.0 Hz), 8.05 (1H, s), 8.32 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.53, −5.33, −4.63, −4.38, 18.33, 18.35, 25.88, 25.92, 27.03, 28.42, 39.87, 61.85, 76.37, 91.61, 110.42, 119.99, 139.40, 149.41, 153.19, 155.35, 176.61; FABMS (*m*/*z*) 706 (M^++H). Anal. Calcd for $C_{27}H_{48}IN_5O_5Si_2$: C, 45.95; H, 6.86; N, 9.92. Found: C, 45.63; H, 6.81; N, 9.71.

Physical data for **8b**: UV (MeOH) λ_{max} 259 nm (ε 15,400), λ_{min} 227 nm (ε 3000); ^{1}H NMR ($CDCl_3$) δ −0.30, −0.03, 0.05, and 0.09 (12H, each as s), 0.78 and 0.90 (18H, each as s), 1.29 (9H, s), 4.33 (1H, d, J=11.0 Hz), 4.51 (1H, d, J=11.0 Hz), 4.76 (1H, dd, J=5.1 and 6.8 Hz), 4.85 (1H, d, J=5.1 Hz), 5.62 (2H, br), 6.11 (1H, d, J=6.8 Hz), 7.96 (1H, s), 8.35 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.45, −5.30, −5.24, −5.07, 17.90, 18.34, 25.46, 25.88, 27.17, 30.91, 37.19, 39.37,

66.40, 73.02, 89.54, 109.92, 120.18, 139.78, 150.13, 153.15, 155.54, 176.13; FABMS (*m/z*) 706 (M^++H). Anal. Calcd for $C_{27}H_{48}IN_5O_5Si_2$: C, 45.95; H, 6.86; N, 9.92. Found: C, 45.91; H, 6.88; N, 9.95.

*3.1.4. 4′-Benzoyloxy-2′,5′-bis-O-(tert-butyldimethylsilyl)cordycepin (**9a**) and 9-[4-benzoyloxy-2,5-bis-O-(tert-butyldimethylsilyl)-3-deoxy-α-L-arabinofuranosyl]adenine (**9b**)*

To a benzene (12 mL) solution of **6** (**6a/6b**=1:2, 1.0 g, 1.38 mmol) and AIBN (0.34 g, 2.07 mmol) was added Bu_3SnH (1.11 mL, 4.14 mmol). The resulting solution was refluxed for 3 h. Column chromatography (hexane/EtOAc=1:1) of the reaction mixture gave **9** (**9a/9b**=1:2.2, 0.77 g, 94%) as a foam. HPLC separation ($CHCl_3$/MeOH=80:1) gave analytically pure **9a** (t_R=13.0 min, foam) and **9b** (t_R=14.1 min, foam).

Physical data for **9a**: UV (MeOH) λ_{max} 233 nm (ε 16,900) and 259 nm (ε 16,000), λ_{min} 223 nm (ε 12,900) and 246 nm (ε 12,300); ^{1}H NMR ($CDCl_3$) δ −0.16, −0.12, 0.14, and 0.15 (12H, each as s), 0.70 and 0.96 (18H, each as s), 2.79 (1H, dd, *J*=5.4 and 14.1 Hz), 2.98 (1H, dd, *J*=7.1 and 14.1 Hz), 4.06 (1H, d, *J*=10.4 Hz), 4.22 (1H, d, *J*=10.4 Hz), 4.78 (1H, ddd, *J*=4.4, 5.4, and 7.1 Hz), 5.76 (2H, br), 6.43 (1H, d, *J*=4.4 Hz), 7.42−7.46, 7.55−7.59, and 8.04−8.06 (5H, each as m), 8.16 (1H, s), 8.36 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.43, −5.33, −5.29, −5.18, 17.77, 18.39, 25.40, 25.92, 39.36, 64.54, 76.42, 91.15, 112.10, 119.73, 128.31, 129.84, 130.22, 133.25, 138.73, 149.92, 153.19, 155.42, 165.20; FABMS (*m/z*) 600 (M^++H). Anal. Calcd for $C_{29}H_{45}N_5O_5Si_2$: C, 58.06; H, 7.56; N, 11.67. Found: C, 58.45; H, 7.72; N, 11.87.

Physical data for **9b**: UV (MeOH): λ_{max} 234 nm (ε 16,900) and 259 nm (ε 15,200), λ_{min} 223 nm (ε 12,900) and 247 nm (ε 12,200); ^{1}H NMR ($CDCl_3$) δ −0.15, −0.03, 0.09, and 0.13 (12H, each as s), 0.82 and 0.93 (18H, each as s), 2.69 (1H, dd, *J*=7.1 and 14.1 Hz), 2.87 (1H, dd, *J*=7.6 and 14.1 Hz), 4.06 (1H, d, *J*=10.5 Hz), 4.13 (1H, d, *J*=10.5 Hz), 5.34 (1H, ddd, *J*=5.1, 7.1, and 7.6 Hz), 5.82 (2H, br), 6.14 (1H, d, *J*=5.1 Hz), 7.43−7.47, 7.56−7.61, and 8.00−8.03 (5H, each as m), 8.18 (1H, s), 8.19 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.43, −5.32, −5.15, −5.12, 17.79, 18.24, 25.52, 25.82, 40.64, 65.55, 74.92, 91.57, 111.19, 119.74, 128.42, 129.73, 130.27, 133.33, 139.47, 150.21, 153.11, 155.33, 164.73; FABMS (*m/z*) 600 (M^++H). Anal. Calcd for $C_{29}H_{45}N_5O_5Si_2$: C, 58.06; H, 7.56; N, 11.67. Found: C, 58.12; H, 7.63; N, 11.57.

*3.1.5. 4′-Acetoxy-2′,5′-bis-O-(tert-butyldimethylsilyl)-cordycepin (**10a**) and 9-[4-acetoxy-2,5-bis-O-(tert-butyldimethylsilyl)-3-deoxy-α-L-lyxofuranosyl]-adenine (**10b**)*

These compounds (**10a/10b**=1:2.7) were obtained in 87% yield from **7** (**7a/7b**=1:2.7, 227.4 mg, 0.343 mmol) by the procedure described for the preparation of **9**: Bu_3SnH (0.28 mL, 1.028 mmol), AIBN (84.5 mg, 0.515 mmol). The reaction was continued for 1 h. HPLC separation ($CHCl_3$/MeOH=60:1) gave analytically pure **10a** (t_R=6.4 min, foam) and **10b** (t_R=8.1 min, foam).

Physical data for **10a**: UV (MeOH): λ_{max} 259 nm (ε 14,600), λ_{min} 227 nm (ε 2200); ^{1}H NMR ($CDCl_3$) δ −0.13, −0.07, 0.12, and 0.13 (12H, each as s), 0.80 and 0.95 (18H, each as s), 2.08 (3H, s), 2.64 (1H, dd, *J*=5.6 and 13.9 Hz), 2.85 (1H, dd, *J*=7.2 and 13.9 Hz), 3.92 (1H, d, *J*=10.3 Hz), 4.01 (1H, d, *J*=10.3 Hz), 4.76 (1H, ddd, *J*=4.6, 5.6, and 7.2 Hz), 5.74 (2H, br), 6.34 (1H, d, *J*=4.6 Hz), 8.11 (1H, s), 8.35 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.43, −5.34, −5.20, −5.15, 17.83, 18.40, 21.99, 25.51, 25.92, 33.40, 39.29, 64.60, 76.09, 90.92, 111.22, 119.79, 138.89, 149.98, 153.19, 155.28, 169.58; FABMS (*m/z*) 538 (M^++H). Anal. Calcd for $C_{24}H_{43}N_5O_5Si_2$: C, 53.60; H, 8.06; N, 13.02. Found: C, 53.74; H, 8.22; N, 13.02.

Physical data for **10b**: UV (MeOH): λ_{max} 259 nm (ε 14,300), λ_{min} 227 nm (ε 2000); ^{1}H NMR ($CDCl_3$) δ −0.17, −0.05, 0.10, and 0.12 (12H, each as s), 0.80 and 0.95 (18H, each as s), 2.09 (3H, s), 2.56 (1H, dd, *J*=6.8 and 14.0 Hz), 2.68 (1H, dd, *J*=7.2 and 14.0 Hz), 3.89 (1H, d, *J*=10.5 Hz), 3.96 (1H, d, *J*=10.5 Hz), 5.23 (1H, ddd, *J*=5.0, 6.8, and 7.2 Hz), 5.73 (2H, br), 6.07 (1H, d, *J*=5.0 Hz), 8.14 (1H, s), 8.34 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.45, −5.34, −5.19, −5.15, 17.77, 18.26, 21.98, 25.50, 25.83, 40.61, 65.67, 74.83, 91.37, 110.35, 119.74, 139.40, 150.25, 153.15, 155.33, 169.38; FABMS (*m/z*) 538 (M^++H). Anal. Calcd for $C_{24}H_{43}N_5O_5Si_2$: C, 53.60; H, 8.06; N, 13.02. Found: C, 53.77; H, 8.22; N, 12.98.

*3.1.6. 2′,5′-Bis-O-(tert-butyldimethylsilyl)-4-pivaloyloxycordycepin (**11a**) and 9-[2,5-bis-O-(tert-butyldimethylsilyl)-3-deoxy-4-pivaloyloxy-α-L-lyxofuranosyl]adenine (**11b**)*

These compounds (**11a/11b**=1:3.6) were obtained in 77% yield from **8** (**8a/8b**=1:4.0, 147.5 mg, 0.209 mmol) by the procedure described for the preparation of **9**: Bu_3SnH (0.17 mL, 0.627 mmol), AIBN (52 mg, 0.314 mmol). The reaction was continued for 3 h. HPLC separation ($CHCl_3$/MeOH=70:1) gave analytically pure **11a** (t_R=7.6 min, foam) and **11b** (t_R=8.1 min, foam).

Physical data for **11a**: ^{1}H NMR ($CDCl_3$) δ −0.20, −0.12, 0.13, and 0.14 (12H, each as s), 0.77 and 0.96 (18H, each as s), 1.23 (9H, s), 2.54 (1H, dd, *J*=6.8 and 13.8 Hz), 2.90 (1H, dd, *J*=7.4 and 13.8 Hz), 3.91 (1H, d, *J*=10.1 Hz), 3.97 (1H, d, *J*=10.1 Hz), 4.76 (1H, ddd, *J*=5.4, 6.8, and 7.4 Hz), 5.65 (2H, br), 6.32 (1H, d, *J*=5.4 Hz), 8.10 (1H, s), 8.35 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.43, −5.36, −5.20, 17.94, 18.37, 25.54, 25.92, 27.00, 39.32, 40.27, 64.91, 76.38, 90.51, 110.49, 119.71, 138.95, 150.05, 153.19, 155.30, 177.03; FABMS (*m/z*) 580 (M^++H). FAB-high resolution MS (*m/z*) calcd for $C_{27}H_{50}N_5O_5Si_2$: 580.3351, found: 580.3339 (M^++H).

Physical data for **11b**: UV (MeOH): λ_{max} 259 nm (ε 14,400), λ_{min} 228 nm (ε 2500); ^{1}H NMR ($CDCl_3$) δ −0.13, −0.03, 0.10, and 0.12 (12H, each as s), 0.81 and 0.95 (18H, each as s), 1.21 (9H, s), 2.55 (1H, dd, *J*=6.3 and 14.4 Hz), 2.61 (1H, dd, *J*=7.1 and 14.4 Hz), 3.89 (1H, d, *J*=10.5 Hz),

3.98 (1H, d, J=10.5 Hz), 5.15 (1H, ddd, J=4.6, 6.3, and 7.1 Hz), 5.62 (2H, br), 6.10 (1H, d, J=4.6 Hz), 8.19 (1H, s), 8.34 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.42, −5.39, −5.16, −5.14, 17.77, 18.25, 25.52, 25.83, 27.01, 39.31, 40.52, 65.70, 75.21, 91.27, 110.51, 119.65, 139.17, 150.19, 153.14, 155.32, 176.80; FABMS (m/z) 580 (M^++H). Anal. Calcd for $C_{27}H_{43}N_5O_5Si_2$: C, 55.92; H, 8.52; N, 12.08. Found: C, 55.95; H, 8.48; N, 12.38.

*3.1.7. 4′-Allyl-2′,5′-bis-O-(tert-butyldimethylsilyl)cordycepin (**12**)*

To a CH_2Cl_2 (5.0 mL) solution of **9** (**9a/9b**=1:2, 50 mg, 0.083 mmol) were added $Me_3SiCH_2CH{=}CH_2$ (0.07 mL, 0.417 mmol) and then $SnCl_4$ (1.0 M in CH_2Cl_2, 0.42 mL, 0.417 mmol) at 0 °C under positive pressure of dry Ar. The reaction mixture was stirred at rt for 2 h. After being quenched with saturated aqueous $NaHCO_3$, the reaction mixture was filtered through a Celite pad. The filtrate was extracted with CH_2Cl_2. Column chromatography (hexane/EtOAc=1:2) gave **12** (19 mg, 44%) as a syrup.

UV (MeOH): λ_{max} 260 nm (ε 14,800), λ_{min} 229 nm (ε 2200); ^{1}H NMR ($CDCl_3$) δ −0.18, −0.11, 0.12, and 0.14 (12H, each as s), 0.79 and 0.96 (18H, each as s), 2.00 (1H, dd, J=7.1 and 12.9 Hz), 2.39 (1H, dd, J=7.3 and 12.9 Hz), 2.46 (2H, d, J=7.1 Hz), 3.56 (1H, d, J=10.5 Hz), 3.76 (1H, d, J=10.5 Hz), 4.82 (1H, ddd, J=5.1, 7.1, and 7.3 Hz), 5.14–5.19 (2H, m), 5.84–5.91 (3H, m), 5.99 (1H, d, J=5.1 Hz), 8.22 (1H, s), 8.35 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.42, −5.37, −5.23, −5.20, 17.81, 18.44, 25.52, 26.01, 38.88, 42.27, 68.38, 77.27, 86.74, 90.05, 119.07, 119.68, 132.90, 139.15, 150.00, 152.89, 155.33; FABMS (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, 57.87; H, 8.91; N, 13.25.

*3.1.8. 2′,5′-Bis-O-(tert-butyldimethylsilyl)-4′-cyanocordycepin (**13**)*

This compound was obtained in 58% yield from **9** (**9a/9b**=1:2, 50 mg, 0.083 mmol) by the procedure described for the preparation of **12**: Me_3SiCN (0.053 mL, 0.42 mmol), $SnCl_4$ (1.0 M in CH_2Cl_2, 0.42 mL, 0.42 mmol). The reaction mixture was stirred at rt for 3 h.

UV (MeOH): λ_{max} 259 nm (ε 15,100), λ_{min} 228 nm (ε 2900); IR (neat) 2240 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$) δ 0.10 and 0.11 (12H, each as s), 0.91 and 0.93 (18H, each as s), 2.34 (1H, dd, J=2.2 and 13.7 Hz), 2.90 (1H, dd, J=5.4 and 13.7 Hz), 3.92 (1H, d, J=10.8 Hz), 4.11 (1H, d, J=10.8 Hz), 5.00 (1H, ddd, J=2.0, 2.2, and 5.4 Hz), 5.72 (2H, br), 6.11 (1H, d, J=2.0 Hz), 8.02 (1H, s), 8.33 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.50, −5.44, −5.09, −4.86, 17.83, 18.41, 25.51, 25.80, 39.89, 66.15, 75.86, 80.82, 93.53, 118.94, 120.17, 139.14, 149.34, 153.07, 155.40; FABMS (m/z) 505 (M^++H). Anal. Calcd for $C_{23}H_{40}N_6O_3Si_2$: C, 54.73; H, 7.99; N, 16.65. Found: C, 54.78; H, 8.09; N, 16.39.

Acknowledgements

Financial support from Showa University Research Grant for Young Researchers (Y.K.) is gratefully acknowledged.

References and notes

1. Cunningham, K. G.; Hutchinson, S. A.; Manson, W.; Spring, F. S. *J. Chem. Soc.* **1951**, 2299.
2. Bentley, H. R.; Cunningham, K. G.; Spring, F. S. *J. Chem. Soc.* **1951**, 2301.
3. Kaczka, E. A.; Dulaney, E. L.; Gitterman, C. O.; Woodruff, H. B.; Folkers, K. *Biochem. Biophys. Res. Commun.* **1964**, *14*, 452.
4. Kaczka, E. A.; Trenner, N. R.; Arison, B.; Walker, R. W.; Folkers, K. *Biochem. Biophys. Res. Commun.* **1964**, *14*, 456.
5. Shigeura, H. T.; Gordon, C. N. *J. Biol. Chem.* **1965**, *240*, 806.
6. Glazer, R. I.; Peale, A. L. *Biochem. Biophys. Res. Commun.* **1978**, *81*, 521.
7. Hunting, D.; Henderson, J. F. *Biochem. Pharmacol.* **1978**, *27*, 2163.
8. Walton, E.; Holly, F. W.; Boxer, G. E.; Nutt, R. F.; Jenkins, S. R. *J. Med. Chem.* **1965**, *8*, 659.
9. Hayakawa, H.; Tanaka, H.; Sasaki, K.; Haraguchi, K.; Saitoh, T.; Takai, F.; Miyasaka, T. *J. Heterocycl. Chem.* **1989**, *26*, 189.
10. Ikejiri, M.; Ohshima, T.; Kato, K.; Toyama, M.; Murata, T.; Shimotohno, K.; Maruyama, T. *Bioorg. Med. Chem.* **2007**, *15*, 6882.
11. (a) Koole, L. H.; Buck, H. M.; Bazin, H.; Chattopadhyaya, J. *Tetrahedron* **1987**, *43*, 2989; (b) Bazin, H.; Chattopadhyaya, J. *Chem. Scr.* **1986**, *26*, 13.
12. Hayakawa, H.; Kohgo, S.; Kitano, K.; Ashida, N.; Kodama, E.; Mitsuya, H.; Ohrui, H. *Antiviral Chem. Chemother.* **2004**, *15*, 169.
13. The EC_{50} values of these compounds were taken from Ref. 7.
14. Itoh, Y.; Haraguchi, K.; Tanaka, H.; Gen, E.; Miyasaka, T. *J. Org. Chem.* **1995**, *60*, 656.
15. Haraguchi, K.; Sumino, M.; Tanaka, H. *J. Org. Chem.* **2006**, *71*, 4433.
16. Jain, T. C.; Jenkins, I. D.; Russell, A. F.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 30.
17. Kubota, Y.; Haraguchi, K.; Kunikata, M.; Hayashi, M.; Ohkawa, M.; Tanaka, H. *J. Org. Chem.* **2006**, *71*, 1099.
18. Compound **5**, upon reacting with NBS/MeOH by using CH_2Cl_2 as a solvent, gave the corresponding addition product in high yield, which contrasts to this particular reaction with NBS/$PhCO_2H$.
19. NOE data for the *syn*-adduct (**6a**): H-5′b/H-8 (0.5%); H-5′b/H-3′ (1.1%). NOE data for the *anti*-adduct (**6b**): H-5′b/H-1′ (0.5%); H-8/H-3′ (0.2%). Of the two protons at the 5′-position, the one that appears at a higher field is designated as H-5′a, and the other as H-5′b. This applies to notes 20, 22, 24 and 25.
20. NOE data for **7a**: H-3′/H-8 (4.3%); H-8/H-5′b (0.4%); H-5′b/H-8 (0.5%); H-5′b/H-3′ (1.1%); H-5′a/H-3′ (2.3%); acetoxy/H-1′ (0.5%). NOE data for **7b**: H-5′a/H-1′ (0.7%); acetoxy/H-2 (1.0%); acetoxy/H-8 (0.2%); acetoxy/H-2′ (0.3%); acetoxy/H-3′ (0.1%). NOE data for **8a**: H-8/H-3′ (2.1%); H-5′a/H-3′ (1.7%). NOE data for **8b**: H-5′a/H-1′ (0.6%); pivaloyloxy/H-2 (3.7%); pivaloyloxy/H-8 (3.7%); pivaloyloxy/H-2′ (2.3%); pivaloyloxy/H-3′ (0.9%).
21. For radical-mediated 1,2-acyoxy migration: Itoh, Y.; Haraguchi, K.; Tanaka, H.; Matsumoto, K.; Nakamura, K. T.; Miyasaka, T. *Tetrahedron Lett.* **1995**, *36*, 3867 and references cited therein.
22. NOE data for **9a**: H-5′a/H-8 (0.7%); H-5′b/H-3′b (1.1%); H-8/H-3′b (0.7%). NOE data for **9b**: H-1′/H-3′a (1.0%); H-5′b/H-1′ (0.5%); H-5′b/H-3′a (1.4%); H-5′a/H-1′ (0.9%); H-5′a/H-3′a (2.0%).
23. Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic: London, UK, 1992.
24. NOE data for **12**: H-2′/H-5′b (0.3%); H-5′b/H-8 (0.8%); H-5′b/H-2′ (0.9%); H-3′a/H-8 (0.8%); H-3′a/H-2′ (11.1%); H-3′a/H-5′a (2.4%).
25. NOE data for **13**: H-5′a/H-8 (0.3%); H-5′a/H-3′b (1.7%); H-5′b/H-8 (0.4%); H-5′b/H-3′b (1.1%); H-8/H-3′b (0.8%); H-8/H-5′b (0.3%).