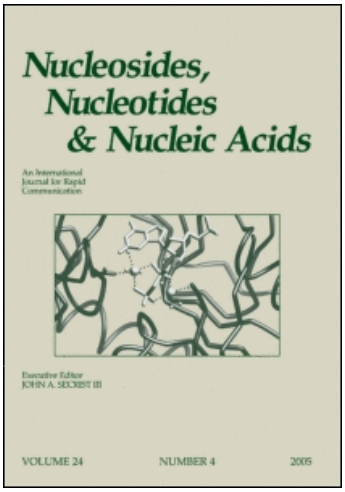

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A Ribonolactone-Based Approach to the Synthesis of 1'-Carbon-Substituted Thymine Ribonucleosides

Hiroyuki Hayakawa[a]; Michiko Miyazawa[a]; Hiromichi Tanaka[a]; Tadashi Miyasaka[a]
[a] School of Pharmaceutical Sciences, Showa University, Tokyo, Japan

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A RIBONOLACTONE-BASED APPROACH TO THE SYNTHESIS OF 1'-CARBON-SUBSTITUTED THYMINE RIBONUCLEOSIDES

Hiroyuki Hayakawa, Michiko Miyazawa, Hiromichi Tanaka,*
and Tadashi Miyasaka

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

Abstract Thymine ribonucleosides bearing a carbon substituent at the anomeric position were synthesized starting from D-ribonolactone by way of nucleophilic addition reaction of organolithium reagents and subsequent condensation with trimethylsilylated thymine.

Since the isolation of two ketohexofuranosyl nucleoside antibiotics psicofuranine (or angustmycin C: **1**) and decoyinine (or angustmycin A: **2**),[1] considerable efforts have been devoted to the synthesis of this class of 1'-carbon-substituted nucleosides and their analogues. In most of these studies, either D-psicose or D-fructose was used as the starting material to construct the sugar structure.[2-4]

The rare sugar D-psicose can be obtained through the reaction between diazomethane and D-ribonoyl chloride tetraacetate,[5] preparation of the latter being initiated by the use of D-ribonolactone. We reasoned, therefore, that nucleophilic addition of organolithium reagents[6] to D-ribonolactone and subsequent condensation with a nucleobase could provide a straightforward method for synthesizing a variety of 1'-carbon-substituted ribonucleosides.[7] A recent report describes the use of D-ribonolactone for the synthesis of 1-(1-

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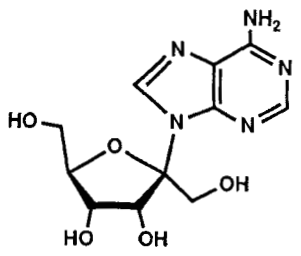
This paper is dedicated to the memory of Professor Roland K. Robins.



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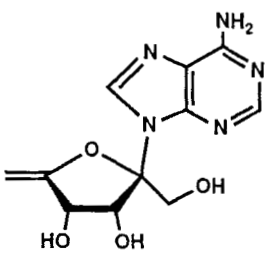

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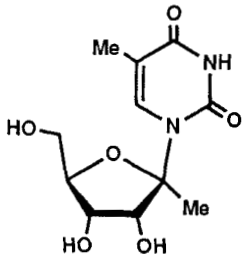
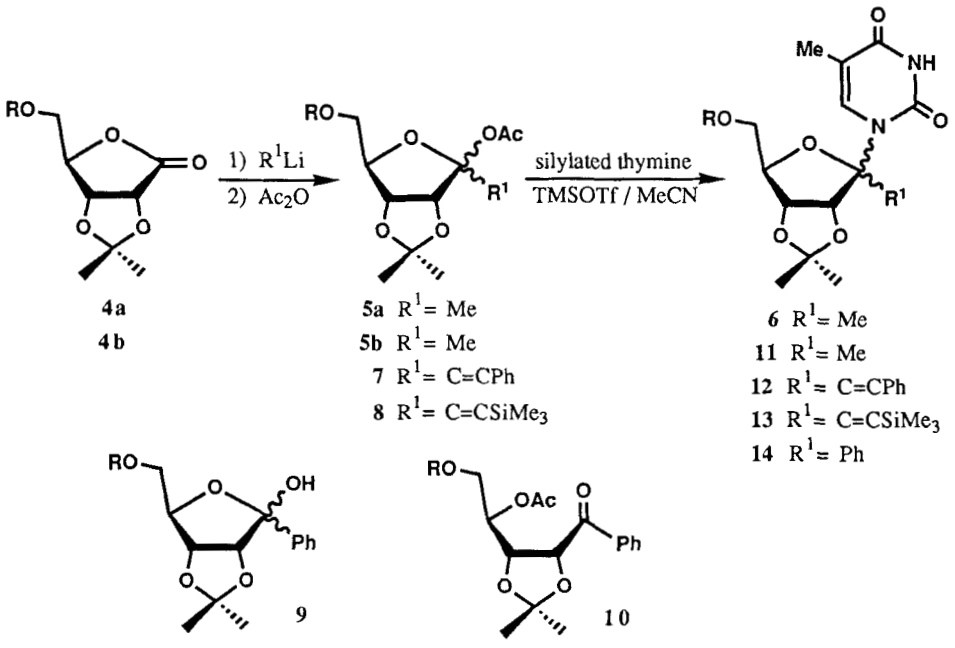


3

deoxy-β-D-psicofuranosyl)thymine (**3**).[8] This led us to present herein the results of our own study .

We first examined the addition of MeLi (1.2 eq.) to 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribonolactone (**4a**) in THF at −78 °C. The resulting adduct was acetylated in a one-pot manner by the treatment with 5 eq. of Ac_2O to give **5a** in 65% yield.[9] When **5a** was reacted with 2,4-bis-*O*-(trimethylsilyl)thymine (5 eq.) in MeCN in the presence of trimethylsilyl triflate (TMSOTf, 5 eq.) at −30 °C for 1 h, **6** was obtained in 45% yield as a mixture of two anomers (α/β = 1/2, estimated by ^1H NMR spectroscopy after desilylation).



Scheme 1. R= $SiPh_2Bu$-*t* except **4a**, **5a**, and **6** in which R refers to $SiMe_2Bu$-*t*.

Table 1. Reaction of **4b** with R^1Li followed by Ac_2O.[a]

Entry	R^1Li (eq.)	Temp. (°C)[b]	Product	α : β [c]	Yield (%)
1	MeLi (1.2)	-78	**5b**	0 : 1	100
2	PhC=CLi (2.0)	-78 to -30	**7**	0 : 1	92
3	Me_3SiC=CLi (2.0)	-78 to -30	**8**	not determined	100
4	PhLi (1.2)	-78 to r.t.	**9**	not determined	97

[a] The addition reactions of R^1Li were carried out for 1 h in THF.

[b] The temperature refers to that of both the addition reaction and acetylation.

[c] With regard to the acetoxyl group.

Since the observed yields in both the addition and the condensation reactions were not quite satisfactory, **4b**[10] was next used in place of **4a**. The results obtained from the reactions between **4b** and several types of organolithium reagents are summarized in Table 1. Upon the reaction with MeLi followed by Ac_2O, the addition product **5b** was obtained as a single product in quantitative yield (entry 1). Lithium phenylacetylide also followed the same reaction course to give **7** (entry 2). The NOESY (two dimensional nuclear Overhauser enhancement) spectra of **5b** and **7** showed no significant enhancement correlation between protons of the introduced substituent and the rest of the molecule. However, by considering the availability of several precedents[6] that 2,3-*O*-isopropylidene-D-ribonolactones undergo nucleophilic attack with lithiated organic molecules preferentially from the α-face, if not exclusively, we assume **5b** and **7** have the β-configuration with regard to the acetoxyl group. The use of lithium (trimethylsilyl)acetylide and phenyllithium (entries 3 and 4) gave **8** and **9**, respectively, as an anomeric mixture. The hemiacetal structure of **9** was confirmed based on its IR spectrum: no carbonyl absorption was observed around 1700 cm^{-1}.

It should be noted that none of the corresponding acetate was obtained in the preparation of **9**. When the isolated **9** was acetylated with Ac_2O (5 eq.) in CH_2Cl_2 in the presence of DMAP and Et_3N, the acyclic acetate **10** was obtained (40% yield) as confirmed by IR spectroscopy that showed the presence of two carbonyl absorptions (1700 and 1750 cm^{-1}). In this acetylation, a 40% yield of **9** was also recovered.

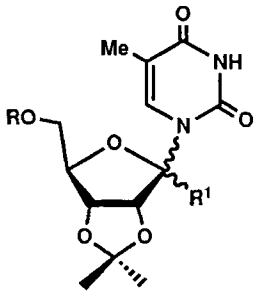
Table 2. Condensation of **5b**, **7**, **8**, and **9** with trimethylsilylated thymine.[a)]

Entry	Sugar	R^1	Eq. of thymine	Time (h)	Product	α : β	Yield (%)
1	**5b**	Me	1.2	1	**11**	1.2 : 1	65
2	**7**	C=CPh	2.2	4.5	**12**	1 : 2.4	94
3	**8**	$C{=}CSiMe_3$	2.2	4.5	**13**	not determined	97
4	**9**	Ph	1.2	3.5	**14**	1 : 0	27
5	**9**	Ph	2.2	17	**14**	1 : 0	25

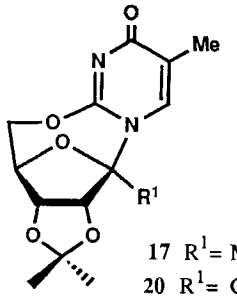
[a)] All reactions were carried out at 0 °C in the presence of TMSOTf (1.0 eq.) in CH_3CN, except entry 5 where the reaction mixture was allowed to warm gradually to room temperature.

Condensation of the above-prepared sugar components (**5b**, **7**, **8**, and **9**) with trimethylsilylated thymine was next examined, the results of which are summarized in Table 2. The use of **5b** gave **11** (inseparable mixture of α- and β-anomers) in an improved yield of 65% when compared with that of **6**, as given in entry 1. The condensations of ethynyl derivatives **7** and **8** were somewhat sluggish, but the desired thymine nucleosides **12** and **13** were obtained in almost quantitative yields (entries 2 and 3), again as inseparable mixtures. As can be anticipated from the poor leaving ability of hydroxyl group, the result obtained by employing the hemiacetal **9** was discouraging (entry 4): **14** was isolated only in 27% yield (a single anomer) together with several nonpolar unidentified by-products.[11] The yield of **14** could not be improved by increasing the amount of the silylated base and prolonging the reaction time (entry 5). The use of $EtAlCl_2$ or $SnCl_4$ as a catalyst resulted in a complex mixture of products.

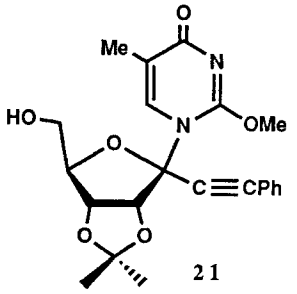
Finally, the stereochemical outcome of the present condensation reactions was investigated. Treatment of **11** with tetrabutylammonium fluoride (TBAF) in THF gave **15a** (33%) and **15b** (40%), each of which was isolated by silica gel column chromatography. In this particular case, their anomeric configurations can be readily addressed on the basis of Imbach's criterion.[12,13] The ^1H NMR spectrum of **15a** showed two methyl signals of the isopropylidene group at 1.38 and 1.60 ppm, giving a ΔδMe value (difference in



15a R= H, R^1= α-Me
15b R= H, R^1= β-Me
16 R= Ts, R^1= α-Me
18a R= H, R^1= α-C≡CPh
18b R= H, R^1= β-C≡CPh
19a R= Ts, R^1= α-C≡CPh
19b R= Ts, R^1= β-C≡CPh
23 R= H, R^1= β-Ph
24 R= Ts, R^1= β-Ph



17 R^1= Me
20 R^1= C≡CPh



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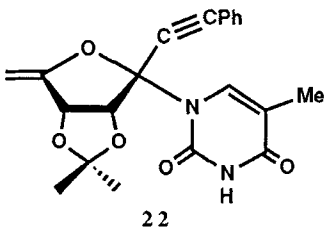

22

chemical shifts of the two methyl groups) of 0.22. Similarly, a ΔδMe value of 0.05 was obtained with **15b**. Thus, **15a** was deduced to be the β-nucleoside. The structure of **15a** was further confirmed by its conversion to the 5'-tosylate (**16**) followed by treatment with DBU (MeCN, 80 °C for 5 h), which gave the cyclonucleoside **17**.

The above cyclonucleoside chemistry was applied to determine anomeric configurations of other 1'-carbon-substituted derivatives. Desilylation of the (phenyl)ethynyl derivative (**12**) gave **18a** (51%) and **18b** (21%). The 5'-tosylate **19a** derived from the former appeared to cyclize under the conditions used for the formation of **17**, producing **20** and **21** after work-up using MeOH. When the other tosylate **19b** was subjected to the DBU treatment, an elimination product **22** was formed. These results provided confirmation of β- and α-nucleoside structures for **18a** and **18b**, respectively. The TBAF treatment of the (trimethylsilyl)ethynyl derivative (**13**), on the other hand, gave an unknown product in addition to a small amount of another product in which only the trimethylsilyl group had been removed. Therefore, the ratio of two anomers could not be determined in the case of **13**. The phenyl derivative (**14**) was converted to **23** (73%) and then to **24**, however no cyclized product was formed when **24** was reacted with DBU under the

conditions used for **16** and **19** (a 67% yield of **24** was recovered), suggesting that **14** has an α-nucleoside structure.

In conclusion, the present study shows that several types of organolithium reagents can be employed in the reaction with D-ribonolactone. This approach would be applicable to the synthesis of other pyrimidine and purine 1'-carbon-substituted nucleosides. We are currently investigating along this line.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured at 23 °C (internal standard, Me_4Si) with a JEOL JNM-GX 400 spectrometer. Mass spectra (MS) were taken on a JEOL SX-102A spectrometer in fast atom bombardment (FAB) mode (*m*-nitrobenzyl alcohol as a matrix). Ultraviolet spectra (UV) were recorded on a JASCO Ubest-55 spectrophotometer. Commercially available solutions of organolithiums were titrated before use with diphenylacetic acid in THF. THF was distilled from benzophenone ketyl. Column chromatography was carried out on silica gel (Wakogel® C-200). Thin layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254}, Merck).

5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-*O*-isopropylidene-D-ribonolactone (4b) This compound was prepared by treating a pyridine (5 mL) solution of D-ribonolactone (727 mg, 3.86 mmol) with *tert*-butyldiphenylsilyl chloride (1.20 mL, 4.63 mmol) at room temperature for 27 h. After usual work-up, the reaction mixture was purified by column chromatography (5-10% EtOAc in hexane). This gave **4b** (1.43 g, 87%), which was crystallized from EtOH (mp 96-97 °C, lit.[6c] mp 68 °C). *Anal.* Calcd for $C_{24}H_{30}O_5Si$: C, 67.59; H, 7.09. Found: C, 67.33; H, 7.23. ^{1}H NMR ($CDCl_3$) δ: 1.04 (9H, s, SiBu-*t*), 1.40 and 1.49 (6H, each as s, isop.-Me), 3.75 and 3.91(2H, dd, $J_{4,5}$= 1.5 and 2.6 Hz, J_{gem}= 11.7 Hz, H-5), 4.57-4.58 (1H, m, H-4), 4.73 (1H, d, $J_{2,3}$= 5.5 Hz, H-3), 4.89 (1H, d, H-2), 7.39-7.47 and 7.60-7.64 (10H, m, SiPh). MS *m/z*: 427 (M^++H).

General procedure for the preparation of 5b, 7, 8, and 9.
A typical procedure is given below for the preparation of 2-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-1-deoxy-3,4-*O*-isopropylidene-D-psicofuranose (**5b**). To a THF (30 mL) solution of **4b** (1.45 g, 3.4 mmol), an ether solution of MeLi (4.08 mmol) was added dropwise at below −70 °C and the mixture was stirred for 20 min. The mixture was treated with Ac_2O (1.6 mL, 17.0 mmol) and stirred further 30 min at below −70 °C. The resulting gelatinous mixture was partitioned beween CH_2Cl_2 and H_2O. Column chromatography (20% EtOAc in hexane) of the organic layer gave **5b** (1.64 g, 100%) as a syrup. *Anal.* Calcd for $C_{27}H_{36}O_6Si$: C, 66.93; H, 7.49. Found: C, 66.93; H, 7.65. ^{1}H NMR ($CDCl_3$) δ: 1.06 (9H, s, SiBu-*t*), 1.37 and 1.56 (6H, each as s, isop.-Me), 1.85 (3H, s, H-1), 2.09 (3H, s, OAc), 3.79 and 3.84 (2H, each as dd, $J_{5,6}$= 2.9 and 3.3 Hz, J_{gem}= 11.4 Hz, H-6), 4.25 (1H, m, H-5), 4.56 (1H, d, $J_{3,4}$= 6.6 Hz, H-3), 4.87 (1H, dd, $J_{4,5}$= 3.9 Hz, H-4), 7.37-7.44 and 7.65-7.69 (10H, m, SiPh). MS *m/z*: 425 (M^++H−AcOH). IR (nujol) cm^{-1}: 1750 (Ac).
Physical data of other compounds are as follows.

1-*O*-Acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-1-(phenyl)ethynyl-D-ribofuranose (7) This compound was obtained as a syrup. *Anal.* Calcd for $C_{34}H_{38}O_6Si \cdot H_2O$: C, 69.37; H, 6.85. Found: C, 69.48; H, 6.72. ^1H NMR ($CDCl_3$) δ: 1.06 (9H, s, SiBu-*t*), 1.39 and 1.60 (6H, each as s, isop.-Me), 2.16 (3H, s, OAc), 3.84 and 3.89 (2H, each as dd, $J_{4,5}$= 3.3 and 4.8 Hz, J_{gem}= 11.0 Hz, H-5), 4.38-4.39 (1H, m, H-4), 4.90 (1H, dd, $J_{2,3}$= 6.2 Hz, $J_{3,4}$= 2.2 Hz, H-3), 5.05 (1H, d, H-2), 7.23-7.42 and 7.66-7.70 (15H, m, SiPh and CCPh). MS *m/z*: 571 (M^++H).

1-*O*-Acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-1-(trimethylsilyl)ethynyl-D-ribofuranose (8) This compound (an anomeric mixture) was obtained as a syrup. *Anal.* Calcd for $C_{31}H_{42}O_6Si_2$: C, 65.71; H, 7.47. Found: C, 65.46; H, 7.75. ^1H NMR ($CDCl_3$) δ: 0.09 (9H, s, $SiMe_3$), 1.02 and 1.05 (9H, each as s, SiBu-*t*), 1.35, 1.38, 1.47, and 1.57 (6H, each as s, isop.-Me), 2.10 (3H, s, OAc), 3.72-3.91 (2H, m, H-5), 4.29 and 4.56 (1H, each as m, H-4), 4.71 and 4.84 (1H, d and dd, respectively, $J_{2,3}$= 5.5 and 6.6 Hz, $J_{3,4}$= 2.2 Hz, H-3), 4.88 and 4.92 (1H, each as d, H-2), 7.35-7.43 and 7.60-7.68 (10H, each as m, SiPh). MS *m/z*: 507 (M^++H−AcOH).

5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-1-phenyl-D-ribofuranose (9) This compound (an anomeric mixture) was obtained as a syrup. *Anal.* Calcd for $C_{30}H_{36}O_5Si$: C, 71.41; H, 7.19. Found: C, 71.46; H, 7.44. ^1H NMR ($CDCl_3$) δ: 1.07 and 1.12 (9H, each as s, SiBu-*t*), 1.24, 1.37, 1.39, and 1.54 (6H, each as s, isop.-Me), 3.77, 3.90, 3.95, and 3.99 (2H, each as dd, $J_{4,5}$= 3.3 and 3.7 Hz, J_{gem}= 11.4 Hz, H-5), 4.32-4.34 and 4.43-4.45 (1H, each as m, H-4), 4.47 and 4.48 (1H, each as s, OH), 4.63 and 4.67 (1H, each as d, $J_{2,3}$= 5.5 and 7.3 Hz, H-2), 4.92 and 4.94 (1H, each as d, $J_{3,4}$= 1.8 and 4.2 Hz, H-3), 7.30-7.47, 7.60-7.63, and 7.66-7.73 (15H, each as m, SiPh and Ph). MS *m/z*: 503 (M^+−H).

Preparation of 10 To a mixture of **9** (785 mg, 1.56 mmol) and DMAP (381 mg, 3.12 mmol) in CH_2Cl_2 (10 mL), Et_3N (1.09 mL, 7.80 mmol) and then Ac_2O (0.74 mL, 7.80 mmol) were added. The mixture was stirred at room temperature for 16 h. The resulting dark red solution was quenched with ice and partitioned between $CHCl_3$ and H_2O. Column chromatography (10% EtOAc in hexane) of the organic layer gave **10** (345 mg, 40%) as a syrup and **9** (314 mg, 40%). Physical data of **10** are as follows. *Anal.* Cald for $C_{32}H_{38}O_6Si$: C, 70.31; H, 7.01. Found: C, 70.03; H, 7.27. ^1H NMR ($CDCl_3$) δ: 1.03 (9H, s, SiBu-*t*), 1.27 (3H, s, OAc), 1.47 and 1.56 (6H, each as s, isop.-Me), 3.88 and 3.93 (2H, each as dd, $J_{4,5}$= 2.2 and 2.9 Hz, J_{gem}= 11.4 Hz, H-5), 4.74 (1H, ddd, $J_{3,4}$= 9.2 Hz, H-4), 5.06 (1H, dd, $J_{2,3}$= 6.6 Hz, H-3), 5.62 (1H, d, H-2), 7.31-7.43, 7.48-7.52, 7.58-7.65, and 7.97-7.99 (15H, each as m, SiPh and Ph). MS *m/z*: 547 (M^++H). IR (nujor) cm^{-1}: 1700 (COPh) and 1750 (OAc).

General procedure for the condesation reactions leading to 11-14 A typical procedure is given below for the preparation of 1-[6-*O*-(*tert*-butyldiphenylsilyl)-1-deoxy-3,4-*O*-isopropylidene-D-psicofuranosyl]thymine (**11**). To a solution of **5b** (1.54 g, 3.18 mmol) and thymine (527 mg, 4.18 mmol) in MeCN (10 mL), BSA (3.1 mL, 12.6 mmol) was added and the mixture was stirred at room temperature for 1.5 h under positive pressure of dry Ar. The mixture was cooled to 0 °C. To this, TMSOTf (674 μL, 3.49 mmol) was added and the reaction mixture was stirred for 1 h. Partition of the organic layer between $CHCl_3$ and saturated aqueous $NaHCO_3$ followed by column chromatography ($CHCl_3$) gave **11** (an anomeric mixture, 1.154 g, 66%) as a

syrup. UV absorption in MeOH: λ_{max} 267 and 270 nm. ^{1}H NMR ($CDCl_3$) δ: 1.02 and 1.09 (9H, each as s, SiBu-*t*), 1.32, 1.33, and 1.57 (6H, each as s, isop.-Me), 1.61 and 1.83 (3H, each as s, H-1'), 1.80 and 1.94 (3H, each as d, $J_{6,Me}$= 1.1 Hz, 5-Me), 3.66, 3.75, and 3.88 (2H, each as dd, $J_{5',6'}$= 3.3 and 4.8 Hz, J_{gem}= 11.5 Hz, H-6'), 4.17-4.20 and 4.38-4.40 (1H, each as m, H-5'), 4.55 and 4.82 (1H, each as dd, $J_{3',4'}$= 5.9 and 6.2 Hz, $J_{4',5'}$= 1.5 and 4.6 Hz, H-4'), 4.91 and 5.12 (1H, each as d, H-3'), 7.36-7.48, 7.56-7.58, and 7.67-7.69 (10H, each as m, SiPh), 7.72 (1H, d, H-6), 7.96 (1H, br, NH). MS *m/z*: 573 (M^++Na). High resolution MS *m/z*: 549.2409 (M^+−H) calcd. for $C_{30}H_{37}O_6N_2Si$ 549.2421. Physical data of other compounds are as follows.

1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-1-(phenyl)ethynyl-D-ribofuranosyl]thymine (12) This compound (an anomeric mixture) was obtained as a foam after column chromatography (0-5% EtOH in $CHCl_3$). UV absorption in MeOH: λ_{max} 243 nm (ε 23000) and 253 nm (ε 21200), $\lambda_{shoulder}$ 265 and 272 nm. *Anal.* Calcd for $C_{37}H_{40}N_2O_6Si \cdot 3/2H_2O$: C, 66.96; H, 6.53; N, 4.22. Found: C, 66.67; H, 6.27; N, 4.07. ^{1}H NMR ($CDCl_3$) δ: 1.03 and 1.07 (9H, each as s, SiBu-*t*), 1.33, 1.37, and 1.68 (6H, each as s, isop.-Me), 1.86 and 1.95 (3H, each as d, $J_{6,Me}$= 1.1 Hz, 5-Me), 3.77 and 3.94 (1H, each as dd, $J_{4',5'}$= 4.4 and 5.1 Hz, J_{gem}= 10.6 and 11.7 Hz), 3.88 and 4.02 (1H, each as dd, $J_{4',5'}$= 3.3 and 8.1 Hz, J_{gem}= 10.6 and 11.7 Hz), 4.52 and 4.57 (1H, each as m, H-4'), 4.68 and 4.89 (1H, each as dd, $J_{2',3'}$= 5.9 and 6.2 Hz, $J_{3',4'}$= 1.8 and 1.5 Hz, H-3'), 5.18 and 5.27 (1H, each as d, H-2'), 7.16-7.48 (10H, m, SiPh), 7.58-7.60 and 7.64-7.66 (5H, each as m, CCPh), 7.78 (1H, d, H-6), 8.18 (1H, br, NH). MS *m/z*: 637 (M^++H), 659 (M^++Na).

1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-1-(trimethylsilyl)ethynyl-D-ribofuranosyl]thymine (13) This compound (an anomeric mixture) was obtained as a solid after column chromatography (0-5% EtOH in $CHCl_3$). UV absorption in MeOH: λ_{max} 266 nm, $\lambda_{shoulder}$ 261 and 269 nm. ^{1}H NMR ($CDCl_3$) δ: 0.01 and 0.19 (9H, each as s, $SiMe_3$), 1.01 and 1.09 (9H, each as s, SiBu-*t*), 1.29, 1.30, 1.34, and 1.65 (6H, each as s, isop.-Me), 1.85 and 1.92 (3H, each as d, $J_{6,Me}$= 1.1 Hz, 5-Me), 3.73, 3.83, 3.88, and 3.98 (2H, each as dd, $J_{4',5'}$= 3.7, 4.4, 4.8, and 8.8 Hz, J_{gem}= 10.5 and 10.8 Hz, H-5'), 4.42-4.45 and 4.49-4.52 (1H, each as m, H-4'), 4.64 and 4.86 (1H, each as dd, $J_{3',4'}$= 1.5 and 2.2 Hz, $J_{2',3'}$= 5.9 and 6.2 Hz, H-3'), 5.09 and 5.15 (1H, each as d, H-2'), 7.36-7.48 and 7.56-7.69 (10H, each as m, SiPh), 7.50 and 7.71 (1H, each as d, H-6), 8.18 (1H, br, NH). MS *m/z*: 633 (M^++H), 655 (M^++Na). High resolution MS *m/z*: 633.2816 (M^++H) calcd. for $C_{34}H_{45}N_2O_6Si_2$ 633.2804.

1-[5-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-1-phenyl-D-ribofuranosyl]thymine (14) This compound (a single anomer) was obtained as a syrup after column chromatography ($CHCl_3$). UV absorption in MeOH: λ_{max} 267 nm. ^{1}H NMR ($CDCl_3$) δ: 0.98 (9H, s, SiBu-*t*), 1.39 and 1.42 (6H each as s, isop.-Me), 1.99 (3H, d, $J_{6,Me}$= 1.1 Hz, 5-Me), 3.38 and 3.48 (2H, each as dd, $J_{4',5'}$= 5.5 Hz, J_{gem}= 11.4 Hz, H-5'), 4.32 (1H, m, H-4'), 4.88 (1H, dd, $J_{2',3'}$= 5.9 Hz, $J_{3',4'}$= 4.0 Hz, H-3'), 5.67 (1H, d, H-2'), 7.25-7.50 (15H, m, SiPh and Ph), 7.80 (1H, br, NH), 7.83 (1H, d, H-6). MS *m/z*: 611 (M^+−H). High resolution MS *m/z*: 611.2496 (M^+−H) calcd. for $C_{35}H_{39}N_2O_6Si$ 611.2537.

General procedure for removal of *tert*-butyldiphenylsilyl group A typical procedure is given for the preparation of **15a** and **15b**. To a THF (1.0 mL) solution of **11** (84 mg, 0.15 mmol), TBAF (1M solution in THF, 0.18 mmol) was added and the mixture was stirred at room temperature for 3 h. After quenching with AcOH, the reaction mixture was evaporated and purified by preparative TLC (5% EtOH in $CHCl_3$). This gave **15a** (16 mg, 33%) and **15b** (19 mg, 40%). Physical data of **15a**, **15b**, **18a**, **18b**, and **23** are as follows.

1-[1-deoxy-3,4-*O*-isopropylidene-β-D-psicofuranosyl]thymine (15a) This compound was obtained as a solid, which was crystallized from EtOH (mp 206-207 °C). UV absorption in MeOH: λ_{max} 268 nm (ε 9200). *Anal.* Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 53.88; H, 6.51; N, 8.88. ^{1}H NMR ($CDCl_3$) δ: 1.38 and 1.60 (6H, each as s, isop.-Me), 1.65 (3H, s, H-1'), 1.92 (3H, d, $J_{6,Me}$= 1.1 Hz, 5-Me), 2.99 (1H, br, 6'-OH), 3.66-3.71 and 3.78-3.83 (2H, each as m, H-6'), 4.41-4.43 (1H, m, H-5'), 4.72 (1H, dd, $J_{3',4'}$= 6.6 Hz, $J_{4',5'}$= 2.2 Hz, H-4'), 5.18 (1H, d, H-3'), 7.68 (1H, d, H-6), 7.97 (1H, br, NH). MS *m/z*: 313 (M^++H).

1-[1-deoxy-3,4-*O*-isopropylidene-α-D-psicofuranosyl]thymine (15b) This compound was obtained as a syrup. UV absorption in MeOH: λ_{max} 269 nm. ^{1}H NMR ($CDCl_3$) δ: 1.33 and 1.38 (6H, each as s, isop.-Me), 1.83 (3H, s, H-1'), 1.95 (3H, d, $J_{6,Me}$= 1.1 Hz, 5-Me), 2.96 (1H, br, 6'-OH), 3.74-3.77 and 3.88-3.92 (2H, each as m, H-6'), 4.20-4.24 (1H, m, H-5'), 4.79 (1H, t, $J_{3',4'}$= $J_{4',5'}$= 5.5 Hz, H-4'), 4.93 (1H, d, H-3'), 7.58 (1H, d, H-6), 7.99 (1H, br, NH). MS *m/z*: 313 (M^++H). High resolution MS *m/z*: 311.1218 (M^+–H) calcd. for $C_{14}H_{19}N_2O_6$ 311.1243.

1-[2,3-*O*-isopropylidene-1-(phenyl)ethylnyl-β-D-ribofuranosyl]thymine (18a) This compound was obtained as a solid, which was crystallized from MeOH-ether (mp 280-281 °C). UV absorption in MeOH: λ_{max} 261 nm (ε 36500), $\lambda_{shoulder}$ 284 and 293 nm. *Anal.* Calcd for $C_{21}H_{22}N_2O_6 \cdot 1/3H_2O$: C, 62.37; H, 5.65; N, 6.93. Found: C, 62.51; H, 5.66; N, 7.02. ^{1}H NMR ($CDCl_3$) δ: 1.40 and 1.65 (6H each as s, isop.-Me), 1.94 (3H, d, $J_{6,Me}$= 1.1 Hz, 5-Me), 3.18 (1H, br, 5'-OH), 3.83 (1H, m, H-5'), 3.95 (1H, dd, $J_{4',5'}$= 2.2 Hz, J_{gem}= 12.1 Hz, H-5'), 4.46 (1H, m, H-4'), 5.10 (1H, dd, $J_{2',3'}$= 7.0 Hz, $J_{3',4'}$= 3.3 Hz, H-3'), 5.43 (1H, d, H-2'), 7.35-7.44 and 7.53-7.55 (5H, each as m, CCPh), 7.99 (1H, d, H-6). MS *m/z*: 399 (M^++H).

1-[2,3-*O*-isopropylidene-1-(phenyl)ethylnyl-α-D-ribofuranosyl]thymine (18b) This compound was obtained as a foam. UV absorption in MeOH: λ_{max} 261 nm, $\lambda_{shoulder}$ 284 and 292 nm. ^{1}H NMR ($CDCl_3$) δ: 1.41 and 1.60 (6H, each as s, isop.-Me), 2.05 (3H, d, $J_{6,Me}$= 1.1 Hz, 5-Me), 3.92 and 4.02 (2H, each as dd, $J_{4',5'}$= 1.1 and 2.6 Hz, J_{gem}= 12.2 Hz, H-5'), 4.58-4.60 (1H, m, H-4'), 5.00 (1H, d, $J_{2',3'}$= 6.9 Hz, H-2'), 5.21 (1H, dd, $J_{3',4'}$= 3.3 Hz, H-3'), 7.29-7.38 and 7.63-7.65 (5H, each as m, CCPh), 7.43 (1H, d, H-6). MS *m/z*: 399 (M^++H), 421 (M^++Na). High resolution MS *m/z*: 399.1541 calcd. for $C_{21}H_{23}N_2O_6$ 399.1555.

1-(2,3-*O*-isopropylidene-1-phenyl-α-D-ribofuranosyl)thymine (23) This compound was obtained as a solid. UV absorption in MeOH: λ_{max} 268 nm. ^{1}H NMR ($CDCl_3$) δ: 1.40 and 1.44 (6H, each as s, isop.-Me), 2.00 (3H, d, $J_{6,Me}$= 1.1 Hz, 5-Me), 3.37 and 3.53 (2H, each as dd, $J_{4',5'}$= 4.0 and 5.5 Hz, J_{gem}= 12.5 Hz, H-5'), 4.37-4.40 (1H, m, H-4'), 4.90 (1H, dd, $J_{2',3'}$= 5.9 Hz, $J_{3',4'}$= 3.3 Hz, H-3'), 5.78 (1H, d, H-2'), 7.32-7.40 and 7.43-7.46 (5H, aech as m, Ph), 7.89 (1H, d, H-6), 8.46 (1H, br, NH). MS *m/z*: 397 (M^++Na). High resolution MS *m/z*: 373.1391 calcd. for $C_{19}H_{21}N_2O_6$ 373.1399.

General procedure for tosylation of 15a, 18a, 18b, and 23

A typical procedure is given below for the preparation of 1-[3,4-*O*-isopropylidene-1-deoxy-6-*O*-(*p*-toluenesulfonyl)-β-D-psicofuranosyl]thymine (**16**). A mixture of **15a** (24 mg, 0.077 mmol) and DMAP (9 mg, 0.077 mmol) in MeCN was cooled to 0 °C. To this, Et_3N (16 μL, 0.116 mmol) and then TsCl (22 mg, 0.116 mmol) dissolved in MeCN (0.5 mL) were added dropwise. After quenching with ice, the reaction mixture was extracted with EtOAc and then purified by preparative TLC (5% EtOH in $CHCl_3$). This gave **16** (30 mg, 83%) as a solid. UV absorption in MeOH: λ_{max} 267 nm. ^{1}H NMR ($CDCl_3$) δ: 1.35 and 1.57 (6H, each as s, isop.-Me), 1.61 (3H, s, H-1'), 1.89 (3H, d, $J_{6,Me}$= 0.7 Hz, 5-Me), 2.46 (3H, s, Me of

Ts), 4.13 and 4.19 (2H, each as dd, $J_{5',6'}$= 2.9 and 4.4 Hz, J_{gem}= 11.0 Hz, H-6'), 4.51-4.53 (1H, m, H-5'), 4.61 (1H, dd, $J_{3',4'}$= 6.6 Hz, $J_{4',5'}$= 1.8 Hz, H-4'), 5.15 (1H, d, H-3'), 7.35 and 7.70 (4H, each as d J= 8.1 Hz, Ts), 7.53 (1H, d, H-6), 8.83 (1H, br, NH). MS *m/z*: 467 (M^++H), 489 (M^++Na). Physical data of other tosylates are as follows.

1-[2,3-*O*-isopropylidene-1-(phenyl)ethynyl-5-*O*-(*p*-toluenesulfonyl)-β-D-ribofuranosyl]thymine (19a) This compound was obtained as a solid in 74% yield from **18a**. UV absorption in MeOH: λ_{max} 230, 242, and 253 nm, $\lambda_{shoulder}$ 263 and 270 nm. ^{1}H NMR ($CDCl_3$) δ: 1.38 and 1.64 (6H, each as s, isop.-Me), 1.92 (3H, d, $J_{6,Me}$= 1.1 Hz, 5-Me), 2.45 (3H, s, Me of Ts), 4.23 and 4.30 (2H, each as dd, $J_{4',5'}$= 3.3 and 4.8 Hz, J_{gem}= 11.0 Hz, H-5'), 4.59-4.62 (1H, m, H-4'), 4.76 (1H, dd, $J_{2',3'}$= 6.6 Hz, $J_{3',4'}$= 3.3 Hz, H-3'), 5.20 (1H, d, H-2'), 7.31-7.38, 7.47-7.49, and 7.73-7.75 (10H, each as m, CCPh, Ts, and H-6), 7.90 (1H, br, NH). MS *m/z*: 553 (M^++H), 575 (M^++Na).

1-[2,3-*O*-isopropylidene-1-(phenyl)ethynyl-5-*O*-(*p*-toluenesulfonyl)-α-D-ribofuranosyl]thymine (19b) This compound was obtained as a solid in 75% yield from **18b**. UV absorption in MeOH: λ_{max} 262 nm, $\lambda_{shoulder}$ 270, 284, and 293 nm. ^{1}H NMR ($CDCl_3$) δ: 1.40 and 1.60 (6H, each as s, isop.-Me), 2.02 (3H, d, $J_{6,Me}$= 1.1 Hz, 5-Me), 2.41 (3H, s, Me of Ts), 4.21 and 4.33 (2H, each as dd, $J_{4',5'}$= 2.2 and 2.6 Hz, J_{gem}= 11.2 Hz, H-5'), 4.65 (1H, m, H-4'), 5.03 (1H, d, $J_{2',3'}$= 6.6 Hz, H-2'), 5.11 (1H, dd, $J_{3',4'}$= 3.3 Hz, H-3'), 7.31-7.41, 7.52-7.54, and 7.69-7.77 (8H, m, CCPh, Ts, and H-6), 7.78 (2H, d, J= 8.4 Hz, Ts). MS *m/z*: 553 (M^++H).

1-[2,3-*O*-isopropylidene-1-phenyl-5-*O*-(*p*-toluenesulfonyl)-α-D-ribofuranosyl]thymine (24) This compound was obtained as a solid in 21% yield from **23**. UV absorption in MeOH: λ_{max} 267 nm. ^{1}H NMR ($CDCl_3$) δ: 1.38 and 1.42 (6H, each as s, isop.-Me), 1.97 (3H, d, $J_{6,Me}$= 1.1 Hz, 5-Me), 2.44 (3H, s, Me of Ts), 3.64-3.71 (2H, m, H-5'), 4.42-4.46 (1H, m, H-4'), 4.73 (1H, dd, $J_{2',3'}$= 5.9 Hz, $J_{3',4'}$= 3.3 Hz, H-3'), 5.78 (1H, d, H-2'), 7.27 and 7.55 (4H, each as d, J= 8.1 Hz, Ts), 7.31-7.33 and 7.38-7.40 (5H, each as m, Ph), 7.78 (1H, d, H-6), 8.22 (1H, br, NH). MS *m/z*: 529 (M^++H).

Reaction of 16 with DBU A mixture of **16** (25 mg, 0.054 mmol) and DBU (12 μL, 0.081 mmol) in MeCN (2.0 mL) was heated at 80 °C for 5 h. After evaporation of the solvent, the reaction mixture was purified by preparative TLC (5% EtOH in $CHCl_3$). This gave **17** (12 mg, 76%) as a solid. UV absorption in MeOH: λ_{max} 248 nm. ^{1}H NMR ($CDCl_3$) δ: 1.37 and 1.57 (6H, each as s, isop.-Me), 1.84 (3H, s, 1'-Me), 2.01 (3H, d, $J_{6,Me}$= 1.1 Hz, 5-Me), 4.11 and 4.42 (2H, each as dd, $J_{4',5'}$= 1.1 and 1.5 Hz, J_{gem}= 12.7 Hz, H-5'), 4.65 (1H, m, H-4'), 4.80 (1H, d, $J_{2',3'}$= 5.5 Hz, H-3'), 5.01 (1H, d, H-2'), 7.42 (1H, d, H-6). MS *m/z*: 295 (M^++H).

Reaction of 19a with DBU The reaction was carried out under the same conditions used for the preparation of **17**, using **19a** (25 mg, 0.045 mmol) in MeCN (2.0 mL) and DBU (14 μL, 0.09 mmol). The reaction mixture was diluted with MeOH and evaporated to dryness. The residue was purified by preparative TLC (3% EtOH in $CHCl_3$). This gave **20** (a solid, 2 mg, 11%) and **21** (a solid, 9 mg, 49%). Physical data of **20** are as follows. UV absorption in MeOH: λ_{max} 243 and 253 nm. ^{1}H NMR ($CDCl_3$) δ: 1.42 and 1.62 (6H, each as s, isop.-Me), 2.04 (3H, d, $J_{6,Me}$= 1.1 Hz, 5-Me), 4.18 and 4.47 (2H, each as d, J_{gem}= 12.1 Hz, H-5'), 4.78 (1H, s, H-4'), 4.99 (1H, d, $J_{2',3'}$= 5.1 Hz, H-3'), 5.07 (1H, d, H-2'), 7.40-7.50 and 7.57-7.59 (5H, each as m, CCPh), 8.25 (1H, d, H-6). MS *m/z*: 381 (M^++H). Physical data of **21**

are as follows. UV absorption in MeOH: λ_{max} 242 and 253 nm. ^{1}H NMR ($CDCl_3$) δ: 1.41 and 1.68 (6H, each as s, isop.-Me), 1.93 (3H, d, $J_{6,Me}$= 1.1 Hz, 5-Me), 3.46 (1H, br, OH), 3.81-3.83 and 3.94-3.97 (2H, each as m, H-5'), 4.05 (3H, s, 2-OMe), 4.65 (1H, m, H-4'), 4.90 (1H, dd, $J_{2',3'}$= 5.9 Hz, $J_{3',4'}$= 1.8 Hz, H-3'), 5.08 (1H, d, H-2'), 7.29-7.38 and 7.42-7.44 (5H, each as m, CCPh), 7.82 (1H, d, H-6). MS *m/z*: 413 (M^++H), 425 (M^++Na).

Reaction of 19b with DBU The reaction was carried out under the same conditions used for the preparation of **17**, using **19b** (12 mg, 0.022 mmol) in MeCN (1.0 mL) and DBU (7 μL). Purification of the reaction mixture by preparative TLC (3% EtOH in $CHCl_3$) gave **22** (4 mg, 50%) as a solid. UV absorption in MeOH: λ_{max} 239 and 260 nm, $\lambda_{shoulder}$ 275, 295, and 340 nm. ^{1}H NMR ($CDCl_3$) δ: 1.42 and 1.64 (6H, each as s, isop.-Me), 1.97 (3H, d, $J_{6,Me}$= 1.1 Hz, 5-Me), 4.52 (1H, d, *J*= 5.5 Hz, H-5'), 4.74-4.76 (2H, m, H-3' and H-5'), 5.47 (1H, d, $J_{2',3'}$= 5.5 Hz, H-2'), 7.28-7.44 (6H, m, H-6 and CCPh). MS *m/z*: 381 (M^++H).

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