Synthesis of 3′-β-carbamoylmethylcytidine (CAMC) and its derivatives as potential antitumor agents†

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3′-β-Carbamoylmethylcytidine (CAMC) and its derivatives were synthesized using an intramolecular Reformatsky-type reaction promoted by SmI_2 as the key step. *In vitro* tumor cell growth inhibitory activity was evaluated and CAMC was found to exhibit potent cytotoxicity against various human tumor cell lines. From a structure–activity relationship study it was postulated that the cytotoxic mechanism of action of CAMC did not require phosphorylation at the 5′-hydroxyl group. This study provides a novel strategy for the development of a new type of antitumor nucleoside.

Introduction

Considerable attention has been focused on branched-chain sugar nucleosides because of their biological importance.[2–16] We have developed stereoselective synthetic methods for a variety of branched-chain sugar nucleosides. During the course of this project,[17–25] it was found that 2′-branched-chain sugar nucleosides such as 1-(2-deoxy-2-methylene-β-D-*erythro*-pentofuranosyl)cytosine (DMDC,[26–30] **1**) and 1-(2-*C*-cyano-2-deoxy-β-D-*arabino*-pentofuranosyl)cytosine (CNDAC,[31–36] **2**) were potent antitumor agents, and they are now under phase I clinical studies (Fig. 1).[37] Consequently, we thought it might be interesting to investigate the biological activity of 3′-branched-chain ribonucleosides, which may have efficient antitumor and/or antiviral activity similar to that of 2′-branched-chain sugar nucleosides. Thus, we synthesized 3′-β-branched-chain sugar ribonucleoside analogs and found that 1-(3-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)cytosine (ECyd,[38–50] **3**) had remarkably potent antitumor activity. It is also under phase I study.[37] However, despite the promising biological activity of these compounds, few synthetic studies have been reported[51] because of the lack of efficient synthetic methods for the preparation of 3′-β-branched-chain sugar ribonucleoside analogs. ECyd was synthesized *via* the construction of the corresponding 3-ethynyl ribose derivative from D-xylose followed by the introduction of a nucleobase *via* glycosylation.[38,39,41,47] Although this glycosylation is suitable for preparing sugar-modified nucleosides with a variety of nucleobases, rather lengthy synthetic routes are required. Therefore, we have developed an efficient and general synthetic method for 3′-β-branched-chain sugar pyrimidine nucleosides starting from uridine as shown in Scheme 1.[21] Introduction of a carbon substituent at the 3′-β-position of the nucleoside was achieved by the intramolecular SmI_2[52–57]-promoted Reformatsky-type[52] reaction of 5′-*O*-bromoacetyl-3′-ketouridine derivative **A** (Scheme 1), in which the precursor of the carbon substituent was installed at the β-face of the sugar moiety. Ring opening of the resulting lactone **B** with a nucleophile should provide the target 3′-β-branched-chain sugar uridines. This method allowed us to prepare a range of 3′-β-branched-chain pyrimidine ribonucleoside analogs quite efficiently. During this study, we found that 3′-β-carbamoylmethylcytidine (CAMC) showed cell growth inhibitory activity against mouse leukemic L1210 cells. This finding is rather unexpected because, from our previous structure–activity

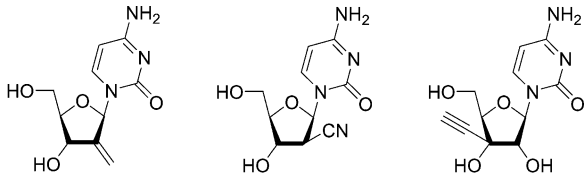
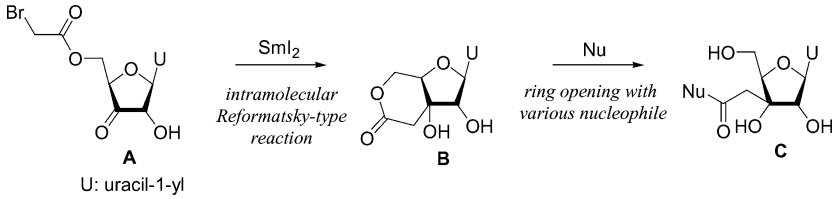


Fig. 1 Structures of branched-chain nucleosides exhibiting antitumor activity.



Scheme 1 Synthetic strategy for 3′-β-branched-chain pyrimidine nucleosides.

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relationship studies of Ecyd,[47] a less bulky carbon-substituent at the 3′-β-position is very important for potent antitumor activity. Namely, increasing the size of the 3′-β-substituent by introducing the alkyl group at the terminal acetylene or changing the ethynyl group to an ethenyl or an ethyl group resulted in decreased cytotoxicity. Generally nucleoside antimetabolites have to be metabolically activated by phosphorylation at the 5′-hydroxyl group. This substituent–structure relationship would be strongly related to the substrate specificity of the uridine–cytidine kinase 2 (UCK2).[44,58–60] Therefore, the cytotoxic mechanism of action of CAMC would be dissimilar to that of ECyd. With these considerations in mind, we decided to elucidate the structure–activity relationship of CAMC.

Chemistry

The structure–activity relationship study for ECyd explored only alkyl, alkenyl, and alkynyl groups at the 3′-position and not polar functional groups containing oxygen or nitrogen, which would have the ability to form additional interactions with target enzyme(s) by hydrogen bonding. Given the structure–activity relationship associated with ECyd, it is important to introduce a less-bulky carbon substituent at the 3′-β-position. It should be noted that 1-(3-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)uracil (EUrd), a uracil counterpart of ECyd, also exhibited potent cytotoxicity. Consequently, we decided to introduce carbamoylmethyl and cyanomethyl groups, which could be easily prepared from the key lactone **B** at the 3′-β-position of uridine and cytidine. The synthesis of the 3′-β-branched-chain sugar pyrimidine nucleosides **4**–**7** (Fig. 2) is shown in Scheme 2. 2′-*O*-TBS-3′-ketouridine **8**, which was easily obtained from uridine in three steps,[51] was acylated with

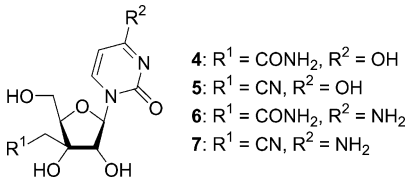
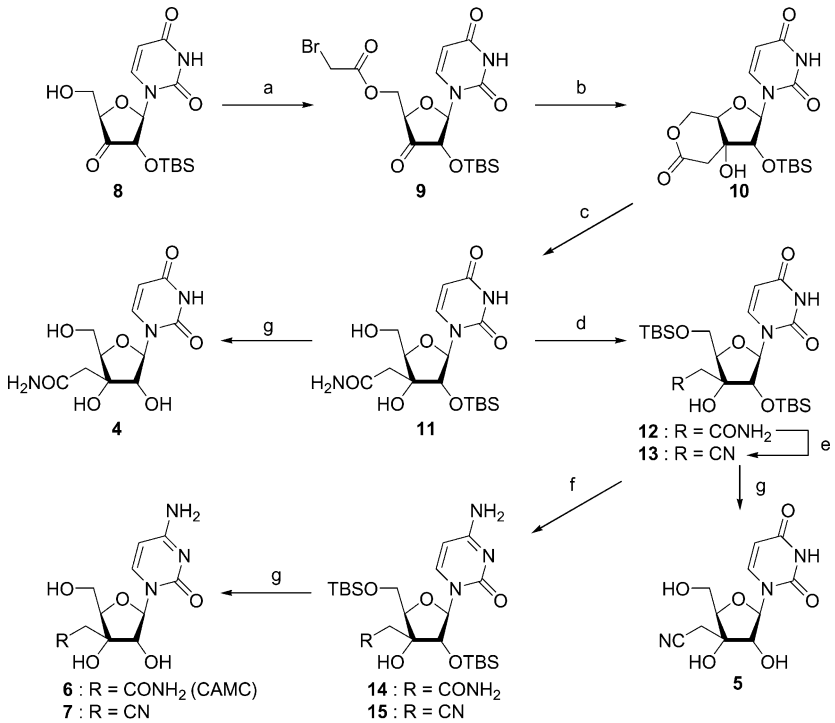


Fig. 2 Structures of target compounds.

a bromoacetyl group to give the 5′-*O*-bromoacetyl derivative **9**,[21] the precursor to the intramolecular Reformatsky-type reaction. Treatment of **9** with 2 equiv of SmI_2 in THF at −78 °C afforded the desired lactone **10** in good yield while the Reformatsky reaction with Zn failed to give **10** under standard conditions. This might be due to the strong ability of the samarium enolate to chelate the 3′-carbonyl oxygen forming a six-membered transition state. Since a THF solution of **9** was added dropwise to a solution of SmI_2 in THF, protection of the acidic NH group in a uracil moiety of **9** was unnecessary. Ammonolysis of the lactone **10** at −70 °C gave the 3′-carbamoylmethyluridine derivative **11**. When the reaction was carried out at room temperature, a large amount of uracil was obtained along with the desired **11**. A retro-aldol reaction of the hydroxylactone **10** followed by base-promoted β-elimination at the 1′, 2′-position of the resulting 5′-*O*-acetyl-3′-ketouridine would possibly explain the formation of uracil. The 5′-primary hydroxyl group of **11** was protected with a TBS group to give **12**, followed by dehydration of the amide using *p*-TsCl in pyridine to provide the 3′-cyanomethyl derivative **13**. Compounds **12** and **13** both were converted to the corresponding cytidine derivatives **14** and **15** by way of their 4-(4-dimethylamino)pyridinium derivatives followed by ammonolysis. Finally, treatment of **11**, **13**, **14** and **15** with NH_4F



Scheme 2 Synthesis of compounds **4**–**7**. Reagents and conditions: (a) $BrCH_2COBr$, CH_2Cl_2, −78 °C (70%); (b) SmI_2, THF, −78 °C (85%); (c) NH_3–MeOH, −70 °C (98%); (d) TBSCl, imidazole, DMF, room temperature (99%); (e) TsCl, pyridine, reflux (81%); (f) TPSCl, DMAP, Et_3N, MeCN, room temperature, then NH_4OH (76% for **14**, 99% for **15**); (g) NH_4F, MeOH (99% for **4**, 99% for **5**, 79% for **6**, 99% for **7**).

in refluxing MeOH gave 3′-β-carbamoylmethyluridine (**4**), 3′-β-cyanomethyluridine (**5**), 3′-β-carbamoylmethylcytidine (CAMC, **6**) and 3′-β-cyanomethylcytidine (**7**), respectively.

Next, we studied the structure–activity relationship of CAMC. As will be described in the biological activity section, CAMC (**6**) exhibited a tumor cell growth inhibitory activity against L1210 and KB cell lines. 3′-α-Carbamoylmethylcytidine **16**, 3′-β-carbamoylcytidine **17** and 3′-β-carbamoylethylcytidine **18**, which correspond to the 3′-epimer, one-carbon-truncated and one-carbon-extended analogs of CAMC, respectively, were designed to explore the suitable position of the carbamoyl group (Fig. 3). Compound **16** was synthesized as shown in Scheme 3. The aldol reaction between **21** and $LiCH_2CO_2Et$ at −78 °C gave the *xylo*-adduct **22** highly stereoselectively, and the corresponding *ribo*-adduct was not obtained at all. The complete α-selectivity exhibited in this reaction is typical of addition reactions of nucleophiles to 3′-ketonucleoside derivatives when the 5′-hydroxyl group is protected. This is one of the drawbacks in preparing 3′-β-branched-chain sugar nucleosides.[61] Thus, our method for the preparation of 3′-β-branched pyrimidine nucleosides using the intramolecular Reformatsky-type reaction was found to be effective. In a manner similar to the preparation of the cytidine derivatives **14** and **15**, **22** was converted to **23**. Ammonolysis of **23** followed by deprotection of the TBS groups afforded the desired **16**.

The synthesis of **17** and **18** is summarized in Scheme 4. The methyl ester **24** was prepared by a two-step sequence including methanolysis of the lactone **10** followed by TBS protection of the liberated 5′-hydroxyl group. Reduction of the methyl ester **24** with DIBAL-H followed by mesylation of the resulting hydroxyl group and displacement of the mesylate **26** with phenylselenide ion gave **27**. Oxidation of **27** with *m*CPBA furnished a diastereomeric mixture of selenoxides, which was heated to promote *syn*-elimination to provide the 3′-ethenyluridine **28**. Dihydroxylation of the alkene followed by oxidative cleavage of the resulting diol gave the aldehyde intermediate **29**, which was further oxidized to give the methyl ester **30** using I_2 and KOH in MeOH. Conversion of **30** to the cytosine derivative **31**, followed by ammonolysis of the methyl ester and deprotection of the TBS groups at the 2′ and 5′-hydroxyl groups afforded the 3′-β-carbamoylcytidine **17**. Wittig reaction of the aldehyde **29** with $Ph_3P{=}CHCO_2Et$ gave **32**. Conversion to the cytosine base and catalytic hydrogenation of the branched-chain double bond gave **34**. Finally, TBS deprotection followed by ammonolysis provided the 3′-β-carbamoylethylcytidine **18**.

A further series of CAMC analogs **19** and **20** shown in Fig. 3 was also synthesized to elucidate the structure–activity relationship. The *N*-alkyl amide analogs **19a**–**d** were prepared in a manner similar to the synthesis of CAMC, which is summarized in Scheme 5. Ring opening of the key lactone **10** with *N*-methylamine, *N*-ethylamine, *N*-benzylamine or *N*,*N*′-dimethylamine gave the corresponding *N*-alkyl amide analogs **35a**–**d**, in good yields with less retro-aldol reaction observed in the treatment of **10** with methanolic ammonia, possibly because of the inherent increased nucleophilicity of alkylamines compared to that of ammonia. Protection of the liberated 5′-hydroxyl group with a TBS group provided compounds **36a**–**d**, which were converted to the cytosine derivatives **37a**–**d** by the same procedure as for the synthesis of **14**. Finally, deprotection of the TBS groups afforded the desired compounds **19a**–**d**. The N^4-methylcytosine analog **20a** and the N^4,$N^{4\prime}$-dimethylcytosine analog **20b** were also prepared as shown in Scheme 6. Conversion of **12** to the 4-(4-dimethylamino)pyridinium derivative followed by substitution with *N*-methylamine or *N*,*N*′-dimethylamine gave **38a**,**b**. Subsequently, the TBS groups at the 2′ and 5′ positions were removed to provide the desired compounds **20a**,**b**.

Biological activity

The *in vitro* tumor cell growth inhibitory activities of the newly synthesized 3′-β-branched-chain sugar nucleoside analogs against L1210 and KB cells were evaluated using the MTT assay, and the

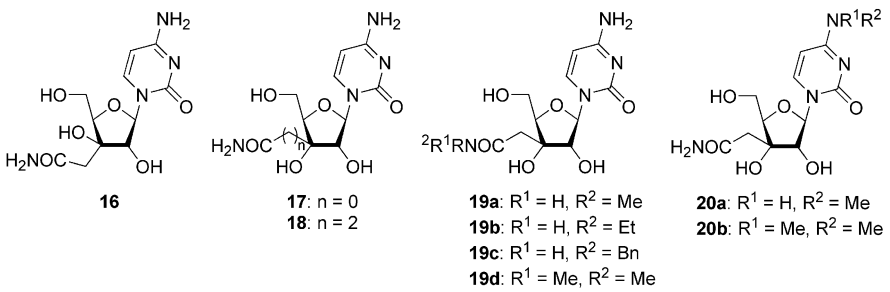
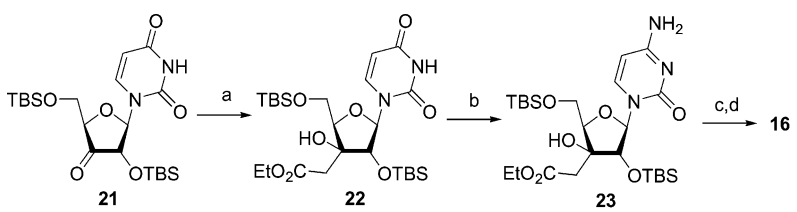
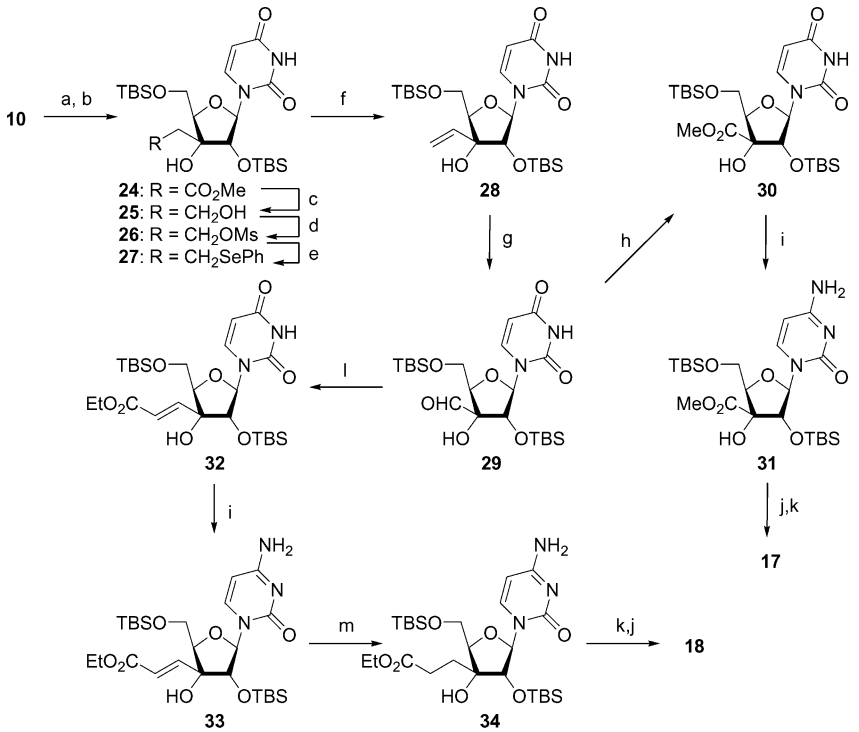


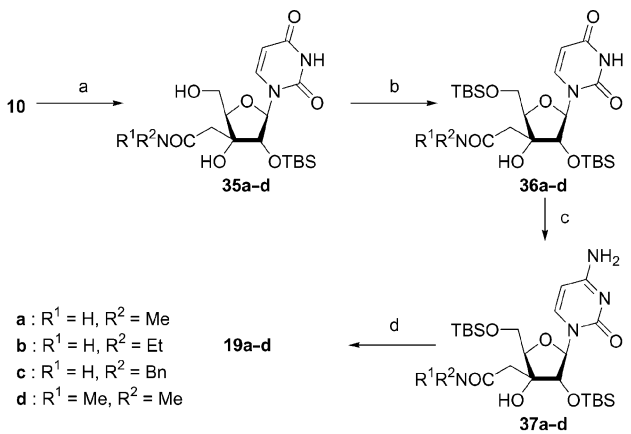
Fig. 3 Structures of CAMC analogs.



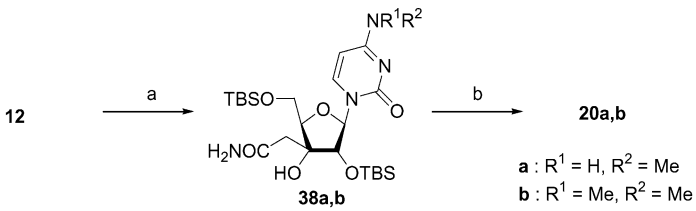
Scheme 3 Synthesis of α-CAMC. Reagents and conditions: (a) $LiCH_2CO_2Et$, THF, −78 °C (95%); (b) TPSCl, DMAP, Et_3N, MeCN, room temperature, then NH_4OH (71%); (c) NH_3–MeOH, reflux; (d) NH_4F, MeOH, reflux (2 steps 90%).



Scheme 4 Synthesis of **17** and **18**. Reagents and conditions: (a) K_2CO_3, MeOH, −20 °C; (b) TBSCl, imidazole, DMF, room temperature (2 times, 2 steps 87%); (c) DIBAL-H, THF, 0 °C (39%); (d) MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C (92%); (e) PhSeSePh, $NaBH_4$, EtOH, room temperature (98%); (f) *m*CPBA, CH_2Cl_2, 0 °C, then DMF, 80 °C (2 steps 49%); (g) OsO_4, NMO, aq. acetone, room temperature, then $NaIO_4$ (h) I_2, KOH, MeOH, room temperature (80% from **28**); (i) TPSCl, DMAP, Et_3N, MeCN, room temperature, then NH_4OH (97% for **30**, 98% for **32**); (j) NH_3–MeOH, reflux; (k) NH_4F, MeOH, reflux (2 steps 87% for **17**, 87% for **18**); (l) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, room temperature (83%); (m) H_2, Pd/C, MeOH, room temperature (quant.).



Scheme 5 Synthesis of amide-substituted CAMCs. Reagents and conditions: (a) R^1R^2NH–DMF, room temperature (99% for **35a**, 99% for **35b**, 99% for **35c**, 85% for **35d**); (b) TBSCl, imidazole, DMF, room temperature (99% for **36a**, 92% for **36b**, 93% for **36c**, 93% for **36d**); (c) TPSCl, DMAP, Et_3N, MeCN, room temperature, then NH_4OH (73% for **37a**, 99% for **37b**, 93% for **37c**, 69% for **37d**); (g) NH_4F, MeOH (86% for **19a**, 70% for **19b**, 71% for **19c**, 92% for **19d**).



Scheme 6 Synthesis of N^4-substituted CAMCs. Reagents and conditions: (a) TPSCl, DMAP, Et_3N, MeCN, room temperature, then R^1R^2NH (94% for **38a**, 86% for **38b**); (b) NH_4F, MeOH, reflux (98%); (b) NH_4F, MeOH, reflux (80% for **20a**, 76% for **20b**).

results are summarized in Table 1. Among **4**–**7**, only CAMC (**6**) was a potent inhibitor of tumor cell growth against L1210 and KB cell lines, with IC_{50} values of 0.33 and 5.61 μM, respectively. We next evaluated the inhibitory spectrum of CAMC on the growth of various human tumor cell lines *in vitro* (Table 2). CAMC showed a broad spectrum of cytotoxicity in a range of human tumor cell lines although the activities were moderate.

The effect of CAMC on the synthesis of DNA (incorporation of [^{3}H]thymidine), RNA (incorporation of [^{3}H]uridine), and protein (incorporation of [^{3}H]leucine) was also examined with L1210 cells (Fig. 4). At 10 μg mL^{-1} concentrations of CAMC, DNA synthesis was inhibited by 83%. In addition to DNA synthesis, RNA and protein syntheses were also inhibited by 48 and 61%, respectively. Although CAMC has a ribonucleoside structure, it inhibited not only RNA synthesis, but also DNA and protein synthesis. It might be suggested that the mode of action of CAMC in exhibiting tumor cell growth inhibitory activities might not be the same as the known nucleoside antimetabolites.

Most of the nucleoside antitumor agents have to be phosphorylated at the 5′-hydroxyl group by a nucleoside kinase to show

Table 1 Growth inhibitory effects of 3′-β-branched nucleosides against L1210 and KB cells[a]

	IC_{50}/μM	
	L1210	KB
4	>100	>100
5	>100	>100
6 (CAMC)	0.33	5.61
7	74	>100
14	43	>100
16	>100	>100
17	>100	>100
18	73	100
19a	>100	>100
19b	74	>100
19c	>100	>100
19d	>100	>100
20a	67	>100
20b	17	>100

[a] IC_{50} (μM) was given as a concentration of 50% inhibition of cell growth.

Table 2 Inhibitory effects of CAMC on several tumor cells *in vitro*

Cell lines	Origin	IC_{50}[a]/μM
MKN-28	Human stomach adenocarcinoma	11
MKN-45	Human stomach adenocarcinoma	12
KATO-III	Human stomach adenocarcinoma	37
NUGC-4	Human stomach adenocarcinoma	10
AGS	Human stomach adenocarcinoma	8.7
Colo320DM	Human colon adenocarcinoma	10
HT-1080	Human fibrosarcoma	13
K562	Human leukemia	11
KB	Human oral epidermal adenocarcinoma	5.7
L1210	Murine leukemia	0.33

[a] IC_{50} (μM) was given as a concentration of 50% inhibiton of cell growth.

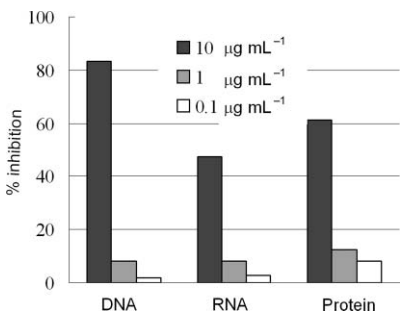


Fig. 4 The effect of CAMC (**6**) on the synthesis of DNA, RNA, and protein. After L1210 cells (2.5×10^5 cells/mL) were incubated for 24 h, **6** was added to the culture and incubated for 1 h. Before cell harvest, cells were pulse-labelled for 30 min with [^{3}H]thymidine, [^{3}H]uridine or [^{3}H]leucin. The radioactivity of the acid-insoluble fractions was measured by a liquid scintillation counter.

cytotoxic activity. In order to evaluate whether CAMC acts as an antimetabolite in DNA and/or RNA synthesis, the competitive inhibition assay against a range of natural nucleosides was conducted. However, the tumor cell growth inhibitory activity of CAMC was not reduced in the presence of the nucleosides, including cytidine (Fig. 5). Since the phosphorylation of these natural nucleosides by certain nucleoside and/or nucleotide

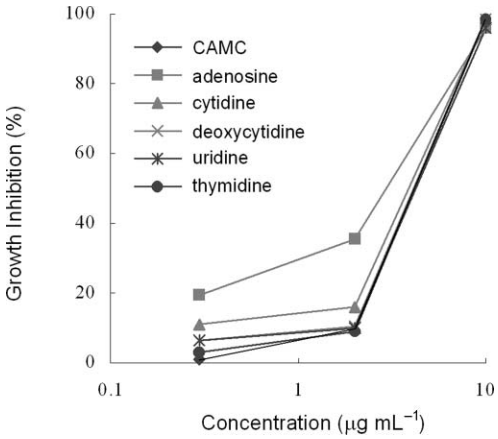


Fig. 5 Competitive effects of common nucleosides on the cytotoxicity of CAMC (**6**) against the growth of L1210 cells. L1210 cells (10^4 cells/mL) were seeded in a 96-well microplate, and treated with graded concentrations of **6** and each common nucleosides were simultaneously added in tripicate to each well. The plate was incubated for 3 d at 37 °C in a humidified atmosphere of 5% CO_2. The cytotoxicity of **6** was evaluated by MTT assay.

kinases would be competitive with that of CAMC, the cytotoxicity should be largely reduced if CAMC required phosphorylation to show cytotoxicity. This suggests that CAMC possesses a unique property to exhibit growth inhibitory activity without phosphorylation of the 5′-hydroxyl group. This was also indicated by the fact that the inhibitory activity against L1210 cells of the 2′,5′-di-*O*-TBS-protected CAMC **14** still remained ($IC_{50} = 43$ μM). The cyanomethyl analog **7** had no activity and it was suggested that the amide oxygen and/or amide hydrogen(s) are important in exhibiting activity. In addition, the N^4-amino functionality on the nucleobase moiety is also a significant factor for the activity as seen by comparison of **6** with the uridine analog **4**.

To determine the structure–activity relationship of the carbamoyl group, we synthesized several CAMC analogs and evaluated their activities (Table 1). The N^4-alkyl derivatives **20a** and **20b** showed weak cytotoxicity whereas the *N*-alkylamide derivatives **19a–d** exhibited no cytotoxicity. These results suggested that both hydrogen atoms on the carbamoyl group, which are hydrogen bond donors, are necessary to exhibit tumor cell growth inhibitory activity. The 3′-epimer of CAMC **18**, the carbamoyl analog **19** and the carbamoylethyl analog **20** showed no cytotoxicity, which would indicate that the orientation of the carbamoyl group is also an important factor.

Phosphorylation of 5′-hydroxyl groups, the first metabolic step, is one of the rate-limiting steps in the metabolic pathway of nucleoside derivatives and its efficiency sometimes plays an important role in exhibiting cytotoxic activity. Generally, chemically modified nucleosides result in decreased efficiency of phosphorylation, which was also seen in the structure–activity relationship study of ECyd. Development of antitumor nucleosides as antimetabolites should overcome this drawback. This study suggests that CAMC exhibited cytotoxic activity without phosphorylation, which is unusual for antimetabolic nucleoside derivatives. The nucleoside analog TSAO[62] is an anti-HIV agent with HIV reverse transcriptase (RT) inhibition as the mode of action. TSAO possesses TBS groups at the 2′ and 5′ positions and inhibited HIV RT without

phosphorylation of the 5′-hydroxyl group and is known as a non-nucleoside RT inhibitor (NNRTI). However, an antitumor nucleoside analog with the above-mentioned mechanism would be very rare. Structurally, ECyd shares a similar structure to CAMC as 3′-β-branched ribonucleoside analogs. However, it is phosphorylated at 5′-hydroxyl group and exhibits more than one order of magnitude more potent than CAMC. Different biological activity would be due to the different mode of action between these agents. Therefore, further study of the mechanism of action of CAMC is needed to elucidate new targets of CAMC.

Conclusion

A series of 3′-β-branched pyrimidine nucleosides was synthesized using an intramolecular Reformatsky-type reaction promoted by SmI_2 as the key step. Their tumor cell growth inhibitory activity was evaluated and 3′-β-carbamoylmethylcytidine (CAMC, **6**) was found to exhibit potent tumor cell growth inhibitory activity. A structure–activity relationship was conducted and it was found that CAMC showed activity without phosphorylation at the 5′-hydroxyl group. This study provided a novel strategy for the development of a new type of antitumor nucleoside.

Experimental

General methods

NMR spectra were obtained on a JEOL EX270, JEOL GX270, JEOL AL400 or Bruker ARX-500 and were reported in parts per million (δ) relative to tetramethylsilane (0.00 ppm) as an internal standard otherwise noted. Coupling constant (J) was reported in Hertz (Hz). Abbreviations of multiplicity were as follows; s: singlet, d; doublet, t: triplet, q: quatlet, m: multiplet, br: broad. Data were presented as follows; chemical shift (multiplicity, integration, coupling constant). FAB-MS were obtained on a JEOL JMS-HX101 or JEOL JMS-700TZ. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60F_{254} plates. Normal-phase column chromatography was performed on Merck silica gel 5715 or Kanto Chemical silica gel 60 N (neutral). Flash column chromatography was performed on Merck silica gel 60. Dichloromethane and acetonitorile were distilled from P_2O_5 and then CaH_2. Methanol was distilled from sodium metal or directly used HPLC grade solvent from Kanto Chemical Co., Inc. Toluene was distilled from sodium metal–benzophenone ketyl. *N*,*N*-Dimethylformamide and dimethylsulfoxide were distilled from CaH_2 under reduced pressure or purchased in dehydrated solvent from Kishida Chemical Co., Ltd. Tetrahydrofuran was purchased in dehydrated stabilizer free solvent from Kanto Chemical Co., Inc.

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(carbamoylmethyl)-β-D-*ribo*-pentofuranosyl]cytosine (14). A solution of **12**[21] (1.05 g, 2.00 mmol), DMAP (487 mg, 4.00 mmol), and Et_3N (0.28 mL, 4.00 mmol) in MeCN (50 mL) was treated with 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl, 1.21 g, 4.00 mmol), and the mixture was stirred at room temperature for 24 h. Then, 28% NH_4OH (20 mL) was added, and the mixture was stirred for additional 2 h. The mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 20% MeOH–$CHCl_3$) to give **14** (830 mg, 76%) as a white solid: mp 160 °C (crystallized from MeOH–$CHCl_3$): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (d, 1H, J = 8.2 Hz), 7.23 (br s, 1H), 6.31 (d, 1H, J = 7.2 Hz), 5.95 (br s, 1H), 5.49 (br s, 1H), 4.24 (br s, 1H), 4.06 (d, 1H, J = 7.3 Hz), 4.01 (d, 1H, J = 11.8 Hz), 3.89 (dd, 1H, J = 2.0, 12.2 Hz), 2.61 (d, 1H, J = 15.1 Hz), 2.57 (d, 1H, J = 15.1 Hz), 0.96 (s, 9H), 0.85 (s, 9H), 0.17 (s, 3H), 0.06 (s, 3H), 0.01 (s, 3H), −0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ173.0, 164.1, 156.2, 141.6, 92.9, 87.9, 85.3, 79.6, 26.3, 26.0, −4.4, −4.6, −5.1, −5.4; FAB-MS m/z 530 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(cyanomethyl)-β-D-*ribo*-pentofuranosyl]cytosine (15). Compound **15** was prepared from **13** (102 mg, 0.20 mmol) as described above for the synthesis of **14**. After purification by column chromatography (SiO_2, 5% MeOH–$CHCl_3$) to give **15** (110 mg, 99%) as a white glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (d, 1H, J = 7.4 Hz), 6.19 (d, 1H, J = 6.8 Hz), 5.83 (d, 1H, J = 7.4 Hz), 4.18 (br s, 1H), 4.08 (d, 1H, J = 6.7 Hz), 3.97 (dd, 1H, J = 2.7, 12.4 Hz), 3.93 (dd, 1H, J = 1.9, 12.4 Hz), 3.58 (s, 1H), 2.84 (d, 1H, J = 16.5 Hz), 2.67 (d, 1H, J = 16.5 Hz), 0.96 (s, 9H), 0.89 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H), 0.02 (s, 3H), −0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ164.7, 157.2, 147.9, 140.4, 122.3, 116.4, 97.2, 86.2, 84.3, 78.3, 62.5, 26.3, 26.0, −4.7, −4.8, −4.8, −4.9; FAB-MS m/z 511 (MH^+).

1-[3-*C*-(Carbamoylmethyl)-β-D-*ribo*-pentofuranosyl]cytosine (6). A mixture of **14** (105 mg, 0.20 mmol) and NH_4F (148 mg, 4.01 mmol) in MeOH (10 mL) was heated under reflux for 2 h. The mixture was evaporated under reduced pressure, and the residue was partitioned between $CHCl_3$ (20 mL) and H_2O (20 mL). The aqueous layer was washed $CHCl_3$ (20 mL × 2) and evaporated under reduced pressure. The residue was dissolved in H_2O, and the charcoal was added until the UV absorption of the solution disappeared. The suspension was mounted on the column, and the charcoal was washed with H_2O (50 mL) and eluted with 50% aqueous MeOH. The UV positive fractions were collected and concentrated to give **6** (47.5 mg, 79%) as a white powder: mp 253 °C dec (H_2O–MeOH): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.90 (d, 1H, J = 7.4 Hz), 7.47 (br s, 1H), 7.17 (br s, 2H), 7.05 (br s, 1H), 5.88 (d, 1H, J = 7.9 Hz), 5.75 (br s, 1H), 5.41 (d, 1H, J = 6.2 Hz), 5.22 (t, 1H, J = 4.5 Hz), 5.13 (s, 1H), 3.98 (dd, 1H, J = 7.1, 7.1 Hz), 3.93 (br s, 1H), 3.66 (ddd, 1H, J = 2.9, 4.5, 9.8 Hz), 3.57 (ddd, 1H, J = 2.4, 4.5, 9.8 Hz), 2.55 (d, 1H, J = 16.3 Hz), 2.49 (d, 1H, J = 16.3 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.1, 165.3, 156.0, 142.4, 94.5, 87.3, 86.7, 77.3, 77.2, 76.4, 61.0; FAB-MS m/z 253 (MH^+); Anal. Calcd for $C_{11}H_{16}N_4O_6$: C, 44.00; H, 5.37; N, 18.66. Found: C, 43.79; H, 5.35; N, 18.37.

1-[3-*C*-(Cyanomethyl)-β-D-*ribo*-pentofuranosyl]cytosine (7). Compound **7** was prepared from **15** (281 mg, 0.68 mmol) as described above for the synthesis of **4**. After purification by desalting (charcoal, 50% aqueous MeOH) to give **7** (205 mg, 99%) as a white powder: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.83 (d, 1H, J = 7.5 Hz), 7.27 (br s, 2H), 5.89 (d, 1H, J = 7.8 Hz), 5.77 (d, 1H, J = 7.5 Hz), 5.63 (d, 1H, J = 6.0 Hz), 5.51 (t, 1H, J = 4.4 Hz), 5.42 (s, 1H), 3.97 (dd, 1H, J = 6.0, 7.8 Hz), 3.89 (br s, 1H), 3.67 (ddd, 1H, J = 3.0, 4.4, 12.4 Hz), 3.62 (ddd, 1H, J = 2.4, 4.4, 12.4 Hz), 2.86 (d, 1H, J = 17.0 Hz), 2.78 (d, 1H, J = 17.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 165.5, 155.8,

146.7, 118.2, 94.7, 87.2, 85.3, 76.0, 75.7, 60.4; FAB-MS *m/z* 283 (MH^+); ESI-HRMS calcd for $C_{11}H_{14}N_4NaO_5$ 305.0862, found 305.0852 (MNa^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(ethoxycarbonylmethyl)-β-D-*xylo*-pentofuranosyl]uracil (22). *n*-Butyllithium (1.51 mL, 2.50 mmol, 1.66 M solution in hexane) was added dropwise to a solution of HMDS (528 mg, 2.50 mmol) in THF (5 mL) at −10 °C and the mixture was stirred for 20 min, and then cooled to −78 °C. Ethyl acetate (0.25 mL, 2.5 mmol) in THF (5 mL) was added, and the mixture was stirred for 20 min at the same temperature. A solution of **21**[63] (470 mg, 1.00 mmol) in THF (2 mL) was added and the mixture was stirred for 30 min before the addition of saturated aqueous NH_4Cl (2 mL). The mixture was partitioned between EtOAc (100 mL) and H_2O (100 mL), and the organic layer was washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 40% EtOAc–hexane) to give **22** (547 mg, 95%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.95 (br s, 1H), 7.88 (d, 1H, $J = 8.2$ Hz), 5.73 (s, 1H), 5.64 (dd, 1H, $J = 2.2$, 8.2 Hz), 4.47 (s, 1H), 4.26 (s, 1H), 4.19–4.12 (m, 3H), 4.02 (dd, 1H, $J = 3.8$, 11.1 Hz), 3.96 (dd, 1H, $J = 4.5$, 11.1 Hz), 2.82 (d, 1H, $J = 17.0$ Hz), 2.70 (d, 1H, $J = 17.0$ Hz), 1.27 (t, 3H, $J = 8.0$ Hz), 0.92 (s, 9H), 0.89 (s, 9H), 0.21 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.1, 163.6, 150.4, 141.2, 100.8, 91.5, 84.1, 82.2, 79.4, 61.0, 35.9, 25.9, 25.8, 18.0, −4.3, −4.4, −4.4; FAB-MS *m/z* 559 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(ethoxycarbonylmethyl)-β-D-*xylo*-pentofuranosyl]cytosine (23). Compound **23** was prepared from **22** (450 mg, 0.81 mmol) as described above for the synthesis of **14**. After purification by chromatography (SiO_2, 4% MeOH–$CHCl_3$) to give **23** (318 mg, 71%) as a yellow foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (d, 1H, $J = 8.6$ Hz), 5.64 (br s, 1H), 5.71 (s, 1H), 4.28 (s, 2H), 4.18–4.10 (m, 3H), 4.03–3.98 (m, 2H), 2.82 (d, 1H, $J = 17.1$ Hz), 2.69 (d, 1H, $J = 17.1$ Hz), 1.25 (t, 3H, $J = 7.1$ Hz), 0.92 (s, 9H), 0.89 (s, 9H), 0.28 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H); NOE, irradiate H-3″a (δ 2.69), observed at H-1′ (δ 5.64, 1.1%); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 166.3, 156.4, 142.9, 94.1, 93.3, 84.5, 82.6, 79.9, 61.5, 36.4, 26.5, 26.1, 18.6, −3.6, −3.6, 3.7, −4.9; FAB-MS *m/z* 558 (MH^+).

1-[3-*C*-(Carbamoylmethyl)-β-D-*xylo*-pentofuranosyl]cytosine (16). Compound **23** (106 mg, 0.20 mmol) was treated with methanolic ammonia (20 mL), and the mixture was stirred at room temperature for 2 h. The mixture was evaporated under reduced pressure. The residue was dissolved in MeOH (5 mL), and the solution was heated with NH_4F (148 mg, 4.00 mmol) under reflux for 2 h. The mixture was evaporated under reduced pressure. The residue was suspended in aqueous MeOH, and the resulting white solid was collected to give **16** (55 mg, 90%) as a white powder: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.75 (d, 1H, $J = 7.4$ Hz), 7.66 (br s, 1H), 7.27 (br s, 1H), 7.17 (br d, 2H), 5.99 (d, 1H, $J = 4.9$ Hz), 5.76 (s, 1H), 5.69 (d, 1H, $J = 7.4$ Hz), 5.61 (s, 1H), 4.80 (t, 1H, $J = 4.6$ Hz), 3.89 (d, 1H, $J = 4.9$ Hz), 3.80–3.70 (m, 2H), 3.57 (ddd, 1H, $J = 2.4$, 4.6, 13.0 Hz), 2.48 (d, 1H, $J = 15.3$ Hz), 2.41 (d, 1H, $J = 15.3$ Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 172.0, 165.9, 156.4, 143.0, 94.1, 92.8, 84.4, 82.6, 79.9, 63.0; FAB-MS *m/z* 301 (MH^+). FAB-HRMS calcd for $C_{11}H_{17}N_4O_6$ 301.1070, found 301.1162 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(methoxycarbonylmethyl)-β-D-*ribo*-pentofuranosyl]uracil (24). A solution of **10** (3.18 g, 8.00 mmol) in MeOH (50 mL) was treated with K_2CO_3 (1.10 g, 8.00 mmol) at −70 °C for 3 h. The remaining K_2CO_3 was filtered off, and the filtrate was evaporated under reduced pressure. The residue in DMF (50 mL) was treated with imidazole (3.26 g, 48.0 mmol) and TBSCl (3.62 g, 24.0 mmol) at room temperature for 30 min. The mixture was partitioned between EtOAc (150 mL) and H_2O (150 mL), and the organic layer was washed with H_2O (150 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 25% EtOAc–hexane) to give **24** (2.30 g, 84%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.47 (br s, 1H), 7.98 (d, 1H, $J = 8.1$ Hz), 6.18 (d, 1H, $J = 7.3$ Hz), 5.72 (dd, 1H, $J = 2.2$, 8.1 Hz), 4.37 (s, 1H), 4.08 (d, 1H, $J = 7.2$ Hz), 4.06 (dd, 1H, $J = 1.1$, 11.8 Hz), 4.04 (d, 1H, $J = 7.3$ Hz), 3.91 (dd, 1H, $J = 2.1$, 11.8 Hz), 3.73 (s, 3H), 3.08 (s, 1H), 2.81 (d, 1H, $J = 15.6$ Hz), 2.62 (d, 1H, $J = 15.6$ Hz), 0.95 (s, 9H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.03 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 163.2, 151.0, 140.5, 103.5, 86.1, 85.1, 78.8, 78.3, 63.3, 40.7, 26.2, 25.8, 18.5, 18.0, 11.7, −4.4, −4.5, −5.1, −5.5; FAB-MS *m/z* 517 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(2-hydroxyethyl)-β-D-*ribo*-pentofuranosyl]uracil (25). To a solution of **24** (2.90 g, 5.33 mmol) in THF (50 mL), DIBAL-H (21.7 mL, 0.93 M solution in hexane, 21.3 mmol) was added dropwise at −20 °C and the mixture was stirred for 2 h. After the addition of saturated aqueous NH_4Cl (20 mL), the mixture was extracted with EtOAc (100 mL × 2). The combined organic layers were washed with H_2O (100 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 60% EtOAc–hexane) to give **25** (2.57 g, 39%) as a white foam and **24** (recovered, 1.25 g): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (br s, 1H), 8.03 (d, 1H, $J = 8.4$ Hz), 6.14 (d, 1H, $J = 7.2$ Hz), 5.72 (dd, 1H, $J = 2.3$, 8.2 Hz), 4.20 (s, 1H), 4.08 (d, 1H, $J = 7.2$ Hz), 4.00–3.88 (m, 4H), 2.92 (s, 1H), 2.31 (br s, 1H), 2.03 (ddd, 1H, $J = 5.8$, 11.9, 14.7 Hz), 1.81 (ddd, 1H, $J = 5.8$, 11.3, 14.7 Hz), 0.95 (s, 9H), 0.90 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.04 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.0, 150.6, 103.0, 86.2, 85.5, 80.0, 78.6, 63.4, 58.6, 34.6, 18.3, 17.7, −4.5, −4.6, −4.7, −4.8; FAB-MS *m/z* 489 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(2-mesyloxyethyl)-β-D-*ribo*-pentofuranosyl]uracil (26). A solution of **25** (2.03 g, 4.45 mmol), Et_3N (935 μL) and DMAP (814 mg, 6.68 mmol) in CH_2Cl_2 (30 mL) was treated with methanesulfonic anhydride (1.16 g, 6.68 mmol), and the mixture was stirred at room temperature for 30 min. After the addition of H_2O (20 mL), the organic layer was washed with brine (50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 40% EtOAc–hexane) to give **26** (2.42 g, 92%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (br s, 1H), 8.00 (d, 1H, $J = 8.0$ Hz), 6.15 (d, 1H, $J = 7.2$ Hz), 5.73 (dd, 1H, $J = 2.2$, 8.0 Hz), 4.49–4.43 (m, 2H), 4.13–4.08 (m, 2H), 3.96 (dd, 1H, $J = 1.6$, 12.4 Hz), 3.90 (dd, 1H, $J = 2.0$, 12.4 Hz), 2.79 (s, 1H), 2.28 (ddd, 1H, $J = 7.8$, 14.4,

15.0 Hz), 1.92 (ddd, 1H, J = 5.3, 11.1, 14.4 Hz), 0.96 (s, 9H), 0.89 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H), 0.04 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.5, 150.4, 140.4, 103.1, 103.0, 86.0, 85.1, 78.3, 66.0, 63.4, 37.3, 32.3, 18.2, 17.8, −4.5, −4.6, −4.7, −4.7; FAB-MS m/z 595 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(2-phenylselenylethyl)-β-D-*ribo*-pentofuranosyl]uracil (27). A solution of diphenyldiselenide (1.47 g, 4.93 mmol) in EtOH (30 mL) was treated with $NaBH_4$ (610 mg, 16.1 mmol), and the mixture was stirred at room temperature for 15 min. A solution of **26** (2.25 g, 3.97 mmol) in EtOH (30 mL) was added, and the whole was stirred at 60 °C for 1 h, and evaporated under reduced pressure. The residue was dissolve in EtOAc (200 mL), and the solution was washed with H_2O (100 mL × 3) and brine (50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 30% EtOAc–hexane) to give **27** (2.44 g, 98%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (d, 1H, J = 8.1 Hz), 7.96 (br s, 1H), 7.50 (m, 2H), 7.25 (m, 3H), 6.11 (d, 1H, J = 7.2 Hz), 5.69 (dd, 1H, J = 2.2, 8.1 Hz), 4.11 (br s, 1H), 4.00 (d, 1H, J = 7.2 Hz), 3.91 (dd, 1H, J = 2.3, 12.0 Hz), 3.76 (d, 1H, J = 12.0 Hz), 3.21 (dt, 1H, J = 5.0, 12.0 Hz), 2.74 (dt, 1H, J = 5.0, 12.0 Hz), 2.62 (s, 1H), 2.12 (dt, 1H, J = 5.0, 14.1 Hz), 1.90 (dt, 1H, J = 5.0, 14.1 Hz), 0.94 (s, 9H), 0.81 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), −0.10 (s, 3H), −0.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.9, 150.6, 140.6, 133.3, 133.2, 129.8, 129.7, 127.5, 102.9, 86.3, 84.8, 79.7, 78.4, 63.4, 32.1, 26.0, 25.6, 11.5, −4.6, −4.7, −5.5, −5.6; FAB-MS m/z 657 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-ethenyl-β-D-*ribo*-pentofuranosyl]uracil (28). A solution of **27** (2.38 g, 3.63 mmol) in CH_2Cl_2 (25 mL) was treated with *m*CPBA (751 mg, 4.36 mmol) at 0 °C, and the mixture was stirred for 10 min before the addition of saturated aqueous $Na_2S_2O_3$ (2 mL). The mixture was partitioned between EtOAc (200 mL) and H_2O (100 mL), and the organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was dissolved in DMF (50 mL), and the solution was heated at 60 °C for 1 h. The mixture was partitioned between EtOAc (200 mL) and H_2O (200 mL), and the organic layers were washed with H_2O (200 mL) brine (50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 25% EtOAc–hexane) to give **28** (851 mg, 49%) as a white foam and **27** (recovered, 990 mg, 47%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.11 (br s, 1H), 8.03 (d, 1H, J = 8.0 Hz), 6.22 (d, 1H, J = 7.4 Hz), 6.02 (dd, 1H, J = 10.5, 17.1 Hz), 5.73 (dd, 1H, J = 2.1, 8.0 Hz), 5.65 (dd, 1H, J = 1.6, 17.1 Hz), 5.39 (dd, 1H, J = 1.6, 10.5 Hz), 4.14 (d, 1H, J = 7.4 Hz), 4.03 (br s, 1H), 3.86 (dd, 1H, J = 2.2, 11.5 Hz), 3.65 (d, 1H, J = 11.5 Hz), 2.82 (s, 1H), 0.94 (s, 9H), 0.83 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), −0.05 (s, 3H), −0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.1, 150.6, 140.5, 136.2, 118.6, 102.9, 86.7, 86.3, 80.5, 79.4, 63.4, 18.3, 17.7, −4.4, −4.4, −4.9, −4.9; FAB-MS m/z 657 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(methoxycarbonyl)-β-D-*ribo*-pentofuranosyl]uracil (30). A solution of **28** (200 mg, 0.40 mmol) and 4-methylmorphrine *N*-oxide (48 mg, 0.80 mmol) in acetone–H_2O (9 : 1, 10 mL) was treated with OsO_4 (5 mg/1 mL *t*-BuOH solution, 0.50 mL, 0.20 mL), and the mixture was stirred at room temperature for 3 d. $NaIO_4$ (87 mg, 0.40 mmol) was added, and the mixture was stirred for additional 10 min. The mixture was partitioned between EtOAc (200 mL) and H_2O (100 mL), and the organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give the crude aldehyde **29**, which was used in the next step without further purification. A solution of the aldehyde **29** in CH_2Cl_2 (10 mL) was treated with a solution of I_2 (132 mg, 0.52 mmol) and KOH (58 mg, 1.04 mmol) in MeOH, and the mixture was stirred at 0 °C for 1 h. The mixture was neutralized with 1 M aqueous HCl and partitioned between EtOAc (100 mL) and H_2O (100 mL), and the organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 25% EtOAc–hexane) to give **30** (161 mg, 80%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 (br s, 1H), 7.74 (d, 1H, J = 8.2 Hz), 6.06 (d, 1H, J = 7.3 Hz), 5.77 (dd, 1H, J = 3.7, 11.3 Hz), 3.80 (s, 3H), 3.78 (dd, 1H, J = 3.7, 11.3 Hz), 3.57 (s, 1H), 0.91 (s, 9H), 0.85 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.5, 163.0, 150.6, 140.4, 103.4, 86.7, 86.0, 79.9, 62.7, 52.9, 26.1, 25.7, 18.6, 18.1, −4.7, −4.7, −5.2, −5.6; FAB-MS m/z 531 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(methoxycarbonyl)-β-D-*ribo*-pentofuranosyl]cytosine (31). Compound **31** was prepared from **28** (79.5 mg, 0.15 mmol) as described above for the synthesis of **14**. After purification by column chromatography (SiO_2, 1% MeOH–$CHCl_3$) to give **31** (78 mg, 97%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (d, 1H, J = 7.4 Hz), 6.17 (d, 1H, J = 6.9 Hz), 5.80 (d, 1H, J = 7.4 Hz), 4.62 (d, 1H, J = 6.9 Hz), 4.12 (t, 1H, J = 3.7 Hz), 3.86 (dd, 1H, J = 3.9, 16.2 Hz), 3.79 (dd, 1H, J = 3.9, 16.2 Hz), 3.78 (s, 3H), 3.77 (s, 1H), 0.90 (s, 9H), 0.84 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.00 (s, 3H), −0.02 (s, 3H); FAB-MS m/z 511 (MH^+).

1-[3-*C*-(Carbamoyl)-β-D-*ribo*-pentofuranosyl]cytosine (17). A solution of **30** (20.5 mg, 0.04 mmol) was dissolved in methanolic ammonia (10 mL, saturated at 0 °C) and heated at 80 °C in a sealed tube for 24 h. The mixture was allowed to cool to room temperature and evaporated under reduced pressure. The residue in MeOH (10 mL) containing NH_4F (20 mg, 0.80 mmol) was heated under reflux for 2 h. The mixture was evaporated under reduced pressure, and the residue was partitioned between $CHCl_3$ (50 mL) and H_2O (50 mL). The aqueous layer was washed $CHCl_3$ (50 mL × 2) and evaporated under reduced pressure. The residue was dissolved in H_2O, and the charcoal was added until the UV absorption of the solution disappeared. The suspension was mounted on the column, and the charcoal was washed with H_2O (50 mL) and eluted with 50% aqueous MeOH. The UV positive fractions were collected and concentrated to give **17** (10.8 mg, 2 steps 87%) as a white powder: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.87 (d, 1H, J = 7.3 Hz), 7.50 (br s, 1H), 7.39 (br s, 1H), 7.21 (br s, 1H), 7.14 (br s, 1H), 5.92 (d, 1H, J = 7.0 Hz), 5.77 (d, 1H, J = 7.4 Hz), 5.75 (d, 1H, J = 6.1 Hz), 5.60 (s, 1H), 4.80 (t, 1H, J = 5.3 Hz), 4.26 (dd, 1H, J = 6.1, 7.0 Hz), 3.76 (br s, 1H), 3.45 (m, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 174.5, 171.9, 165.4, 155.5, 141.7, 94.7, 86.9, 86.4, 79.2, 76.2, 61.2; EI-MS m/z 286 (M^+); ESI-HRMS calcd for $C_{10}H_{14}N_4NaO_6$ 309.0811, found 309.0822 (MNa^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(*trans*-ethoxycarbonylethenyl)-βD-*ribo*-pentofuranosyl]uracil (32). A solution of **28**

(200 mg, 0.40 mmol) and NMO (48 mg, 0.80 mmol) in acetone–H_2O (9 : 1, 10 mL) was treated with OsO_4 (5 mg/1 mL *t*-BuOH solution, 0.50 mL, 0.20 mL), and the mixture was stirred at room temperature for 3 d. $NaIO_4$ (87 mg, 0.40 mmol) was added, and the mixture was stirred for additional 10 min. The mixture was partitioned between EtOAc (200 mL) and H_2O (100 mL), and the organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give crude aldehyde **29**, which was used in the next step without further purification. A solution of the aldehyde **29** in CH_2Cl_2 (10 mL) was treated with a solution of $Ph_3P{=}CHCO_2Et$ (167 mg, 0.48 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 25% EtOAc–hexane) to give **32** (194 mg, 85%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (d, 1H, J = 8.1 Hz), 8.01 (br s, 1H), 7.10 (d, 1H, J = 15.5 Hz), 6.35 (d, 1H, J = 15.5 Hz), 6.23 (d, 1H, J = 7.3 Hz), 5.75 (dd, 1H, J = 2.1, 8.1 Hz), 4.26 (d, 1H, J = 7.3 Hz), 4.26 (q, 2H, J = 7.2 Hz), 4.12 (br s, 1H), 3.89 (dd, 1H, J = 2.2, 11.8 Hz), 3.63 (d, 1H, J = 11.8 Hz), 3.03 (s, 1H), 1.30 (t, 3H, J = 7.2 Hz), 1.00 (s, 9H), 0.82 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), −0.08 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.7, 162.9, 150.6, 145.9, 140.3, 125.3, 103.4, 87.0, 86.8, 80.6, 79.6, 63.5, 60.8, 26.2, 25.6, 14.5, −4.4, −4.8, −5.2, −5.6; FAB-MS m/z 572 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(ethoxycarbonylethenyl)-β-D-*ribo*-pentofuranosyl]cytosine (33). Compound **33** was prepared from **32** (80 mg, 0.14 mmol) as described above for the synthesis of **14**. After purification by column chromatography (SiO_2, 4% MeOH–$CHCl_3$), **33** (78 mg, 98%) was obtained as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92 (d, 1H, J = 7.5 Hz), 7.10 (d, 1H, J = 15.3 Hz), 7.02 (br s, 2H), 6.33 (d, 1H, J = 15.3 Hz), 6.32 (d, 1H, J = 7.5 Hz), 5.96 (d, 1H, J = 7.2 Hz), 4.18 (m, 3H), 4.06 (br s, 1H), 3.82 (br d, 1H, J = 11.3 Hz), 3.59 (br d, 1H, J = 11.3 Hz), 3.42 (s, 1H), 1.29 (t, 3H, J = 7.2 Hz), 0.96 (s, 9H), 0.74 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H), −0.01 (s, 3H), −0.17 (s, 3H); FAB-MS m/z 569 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(ethoxycarbonylethyl)-β-D-*ribo*-pentofuranosyl]cytosine (34). A solution of **33** (57 mg, 0.10 mmol) and 10% Pd/C (10 mg) in MeOH (5 mL) was vigorously stirred under H_2 atmosphere at room temperature for 30 min. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 4% MeOH–$CHCl_3$) to give **34** (58 mg, quant.) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (d, 1H, J = 7.4 Hz), 6.18 (d, 1H, J = 7.6 Hz), 5.76 (d, 1H, J = 7.4 Hz), 4.18 (q, 2H, J = 7.4 Hz), 4.21 (br s, 1H), 3.94 (dd, 1H, J = 2.9, 12.1 Hz), 3.74 (dd, 1H, J = 2.0, 11.3 Hz), 3.67 (s, 1H), 2.63 (ddd, 1H, J = 1.2, 3.0, 12.8 Hz), 2.31 (ddd, 1H, J = 2.8, 6.9, 12.8 Hz), 1.28 (t, 3H, J = 7.4 Hz), 0.96 (s, 9H), 0.84 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), −0.02 (s, 3H), −0.18 (s, 3H); FAB-MS m/z 571 (MH^+).

1-[3-*C*-(Carbamoylethyl)-β-D-*ribo*-pentofuranosyl]cytosine (18). A solution of **33** (20.5 mg, 0.04 mmol) and NH_4F (20 mg, 0.80 mmol) in MeOH (10 mL) was heated under reflux for 2 h. The mixture was evaporated under reduced pressure, and the residue was dissolved in methanolic ammonia (10 mL, saturated at 0 °C). The mixture was heated at 80 °C in a sealed tube for 24 h and allowed cool to room temperature. The mixture was evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ (10 mL) and H_2O (50 mL). The aqueous layer was washed $CHCl_3$ (10 mL × 2) and evaporated under reduced pressure. The residue was dissolved in H_2O, and the charcoal was added until UV absorption of the solution was disappeared. The suspension was mounted on the column, and the charcoal was washed with H_2O (50 mL) and eluted with 50% aqueous MeOH. The UV positive fractions were collected and concentrated to give **18** (8.2 mg, 2 steps 87%) as a white powder: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.92 (d, 1H, J = 7.5 Hz), 7.21 (br s, 1H), 7.14 (br s, 1H), 7.29 (br s, 1H), 6.71 (br s, 1H), 5.84 (d, 1H, J = 7.8 Hz), 5.74 (d, 1H, J = 7.4 Hz), 5.24 (d, 1H, J = 6.6 Hz), 5.14 (t, 1H, J = 3.8 Hz), 4.70 (s, 1H), 3.93 (dd, 1H, J = 6.6, 7.8 Hz), 3.76 (br s, 1H), 3.51 (m, 2H), 2.31 (ddd, 1H, J = 5.6, 10.7, 15.7 Hz), 2.17 (ddd, 1H, J = 5.1, 10.8, 15.7 Hz), 1.87 (ddd, 1H, J = 5.1, 5.6, 13.6 Hz), 1.76 (ddd, 1H, J = 10.7, 13.6, 10.8 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 175.4, 165.4, 155.7, 142.9, 94.6, 88.0, 87.0, 77.9, 77.0, 61.1, 29.6, 29.2; EI-MS m/z 316 (M^+); ESI-HRMS calcd for $C_{12}H_{18}N_4NaO_6$ 337.1124, found 337.1124 (MNa^+).

1-[2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-(*N*-methylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]uracil (35a). A solution of **10** (398 mg, 1.00 mmol) containing methylamine hydrochloride (333 mg, 5.00 mmol) and Et_3N (0.7 mL, 5.00 mmol) in DMF (5 mL) was stirred at room temperature for 7 h. The mixture was partitioned between EtOAc (100 mL) and H_2O (100 mL). The organic layer was washed with H_2O (100 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 4% MeOH–$CHCl_3$) to give **35a** (456 mg, 99%) as a yellow glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (br s, 1H), 7.70 (d, 1H, J = 8.2 Hz), 6.60 (d, 1H, J = 4.7 Hz), 5.79 (dd, 1H, J = 2.2, 8.2 Hz), 6.17 (d, 1H, J = 7.3 Hz), 4.27 (br s, 1H), 3.88 (dd, 1H, J = 2.4, 12.6 Hz), 3.76 (dd, 1H, J = 1.2, 12.6 Hz), 3.54 (s, 1H), 2.83 (d, 3H, J = 4.7 Hz), 2.80 (d, 1H, J = 15.7 Hz), 2.56 (d, 1H, J = 15.7 Hz), 0.89 (s, 9H), 0.63 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 170.9, 162.6, 104.6, 85.2, 85.0, 77.1, 76.9, 59.7, 25.6, 24.8, −4.5, −4.6; FAB-MS m/z 430 (MH^+).

1-[2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-(*N*-ethylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]uracil (35b). Compound **35b** was prepared from **10** (398 mg, 1.00 mmol), ethylamine (408 mg, 5.00 mmol), and Et_3N (0.7 mL, 5.00 mmol) as described above for the synthesis of **35a**. After purification by column chromatography (SiO_2, 5% MeOH–$CHCl_3$) to give **35b** (462 mg, 99%) as a yellow glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.28 (br s, 1H), 7.78 (d, 1H, J = 8.1 Hz), 6.80 (d, 1H, J = 5.3 Hz), 5.79 (d, 1H, J = 7.3 Hz), 5.71 (dd, 1H, J = 2.2, 8.1 Hz), 4.40 (d, 1H, J = 7.3 Hz), 4.20 (br s, 1H), 4.17 (s, 1H), 4.01 (br s, 1H), 3.80 (dd, 1H, J = 1.0, 12.1 Hz), 3.73 (dd, 1H, J = 5.0, 12.1 Hz), 3.26 (dq, 2H, J = 5.3, 7.1 Hz), 2.73 (d, 1H, J = 15.7 Hz), 2.51 (d, 1H, J = 15.7 Hz), 1.12 (t, 3H, J = 7.1 Hz), 0.89 (s, 9H), 0.63 (s, 3H), −0.01 (s, 3H); FAB-MS m/z 444 (MH^+).

1-[2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-(*N*-benzylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]uracil (35c). Compound **35c** was prepared from **10** (398 mg, 1.00 mmol), benzylamine (546 μM, 5.00 μmol), and Et_3N (0.7 mL, 5.00 mmol) as described above for

the synthesis of **35a**. After purification by column chromatography (SiO_2, 5% MeOH–$CHCl_3$) to give **35c** (405 mg, 80%) as a colorless glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (br s, 1H), 8.05 (d, 1H, $J = 8.3$ Hz), 7.35–7.33 (m, 5H), 7.15 (t, 1H, $J = 5.6$ Hz), 6.15 (d, 1H, $J = 7.3$ Hz), 5.72 (dd, 1H, $J = 2.3$, 8.1 Hz), 4.56 (d, 2H, $J = 11.2$ Hz), 4.19 (br s, 1H), 4.07 (d, 1H, $J = 7.3$ Hz), 3.87 (dd, 1H, $J = 1.2$, 12.5 Hz), 3.82 (dd, 1H, $J = 2.1$, 12.5 Hz), 3.40 (br s, 1H), 2.68 (d, 1H, $J = 15.5$ Hz), 2.44 (d, 1H, $J = 15.5$ Hz), 0.89 (s, 9H), 0.18 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.9, 162.7, 150.9, 140.6, 140.5, 102.5, 86.8, 86.7, 84.8, 77.7, 77.6, 77.4, 60.7, 37.1, 35.7, 34.8, 25.5, −4.5, −4.6, −5.0, −5.0; EI-MS m/z 316 (M^+).

1-[2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-(*N*,*N*′-dimethylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]uracil (35d). Compound **35d** was prepared from **10** (398 mg, 1.00 mmol), dimethylamine hydrochloride (408 mg, 5.00 mmol), and Et_3N (0.7 mL, 5.00 mmol) as described above for the synthesis of **35a**. After purification by column chromatography (SiO_2, 5% MeOH–$CHCl_3$) to give **35c** (441 mg, 99%) as a yellow glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (br s, 1H), 7.32 (d, 1H, $J = 8.0$ Hz), 5.77 (dd, 1H, $J = 2.2$, 8.0 Hz), 5.41 (d, 1H, $J = 7.7$ Hz), 4.75 (d, 1H, $J = 7.7$ Hz), 4.39 (br s, 1H), 3.83 (dd, 1H, $J = 2.3$, 13.1 Hz), 3.57 (dd, 1H, $J = 1.0$, 13.1 Hz), 3.03 (s, 3H), 2.97 (s, 3H), 2.99 (d, 1H, $J = 16.5$ Hz), 2.75 (d, 1H, $J = 16.5$ Hz), 0.89 (s, 9H), 0.16 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 169.9, 162.8, 151.1, 140.8, 102.5, 86.4, 85.0, 77.5, 60.7, 33.3, 25.5, 17.5, 14.5, −4.6, −4.6; FAB-MS m/z 444 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(*N*-methylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]uracil (36a). Compound **36a** was prepared from **35a** (300 mg, 0.70 mmol) as described above for the synthesis of **12**. After purification by column chromatography (SiO_2, 40% EtOAc–hexane) to give **36a** (398 mg, 99%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (br s, 1H), 8.03 (d, 1H, $J = 8.2$ Hz), 6.79 (d, 1H, $J = 4.7$ Hz), 6.16 (d, 1H, $J = 7.2$ Hz), 5.73 (dd, 1H, $J = 2.2$, 8.1 Hz), 4.22 (br s, 1H), 4.06 (d, 1H, $J = 7.2$ Hz), 3.88 (br s, 2H), 3.52 (s, 1H), 2.81 (d, 3H, $J = 4.7$ Hz), 2.63 (d, 1H, $J = 15.5$ Hz), 2.51 (d, 1H, $J = 15.5$ Hz), 0.96 (s, 9H), 0.89 (s, 9H), 0.18 (s, 3H), 0.10 (s, 3H), 0.03 (s, 3H), −0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 163.2, 151.0, 140.7, 103.4, 86.3, 85.2, 78.8, 78.5, 63.4, 40.7, 26.2, 25.8, −4.4, −4.5, −5.0, −5.5; FAB-MS m/z 544 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(*N*-ethylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]uracil (36b). Compound **36** was prepared from **35b** (222 mg, 0.50 mmol) as described above for the synthesis of **12**. After purification by column chromatography (SiO_2, 40% EtOAc–hexane) to give **36b** (257 mg, 92%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.01 (d, 1H, $J = 8.1$ Hz), 7.70 (br s, 1H), 6.81 (br s, 1H), 6.16 (d, 1H, $J = 7.1$ Hz), 5.73 (d, 1H, $J = 8.2$ Hz), 4.21 (br s, 1H), 4.05 (d, 1H, $J = 7.2$ Hz), 3.87 (br s, 2H), 3.28 (q, 2H, $J = 7.3$ Hz), 2.60 (d, 1H, $J = 15.4$ Hz), 2.50 (d, 1H, $J = 15.4$ Hz), 1.13 (t, 3H, $J = 7.3$ Hz), 0.94 (s, 9H), 0.88 (s, 9H), 0.16 (s, 6H), 0.08 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 162.5, 151.2, 102.5, 86.5, 85.0, 77.6, 77.4, 60.6, 33.3, 25.9, 25.0, 17.6, 14.7, −4.7, −4.8, −5.2, −5.6; FAB-MS m/z 544 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(*N*-benzylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]uracil (36c). Compound **36c** was prepared from **35c** (404 mg, 0.80 mmol) as described above for the synthesis of **12**. After purification by column chromatography (SiO_2, 40% EtOAc–hexane) to give **36c** (460 mg, 93%) as a colorless glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (br s, 1H), 8.01 (d, 1H, $J = 8.3$ Hz), 7.37–7.26 (m, 5H), 7.13 (t, 1H, $J = 5.7$ Hz), 6.15 (d, 1H, $J = 7.3$ Hz), 5.72 (dd, 1H, $J = 2.3$, 8.1 Hz), 4.46 (t, 2H, $J = 11.6$ Hz), 4.19 (br s, 1H), 4.07 (d, 1H, $J = 7.3$ Hz), 3.87 (dd, 1H, $J = 1.2$, 12.5 Hz), 3.82 (dd, 1H, $J = 2.1$, 12.5 Hz), 3.40 (br s, 1H), 2.68 (d, 1H, $J = 15.5$ Hz), 2.44 (d, 1H, $J = 15.5$ Hz), 0.96 (s, 9H), 0.89 (s, 9H), 0. 18 (s, 3H), 0.17 (s, 3H), 0.03 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4, 150.8, 140.6, 138.5, 128.5, 128.0, 127.8, 103.4, 86.2, 85.2, 78.8, 78.6, 63.3, 43.7, 41.0, 26.3, 25.8, −4.3, −4.4, −4.5, −5.3; FAB-MS m/z 620 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(*N*,*N*′-dimethylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]uracil (36d). Compound **36d** was prepared from **35d** (192 mg, 0.44 mmol) as described above for the synthesis of **12**. After purification by column chromatography (SiO_2, 40% EtOAc–hexane) to give **36d** (205 mg, 85%) as a yellow glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (br s, 1H), 7.88 (d, 1H, $J = 8.1$ Hz), 6.23 (d, 1H, $J = 7.5$ Hz), 5.71 (dd, 1H, $J = 2.3$, 8.1 Hz), 4.46 (br s, 1H), 4.04 (d, 1H, $J = 7.4$ Hz), 3.88 (dd, 1H, $J = 1.2$, 12.0 Hz), 3.86 (dd, 1H, $J = 2.4$, 12.0 Hz), 3.51 (s, 3H), 2.80 (d, 1H, $J = 16.3$ Hz), 2.71 (d, 1H, $J = 16.3$ Hz), 0.95 (s, 9H), 0.90 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.04 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 162.8, 150.4, 140.5, 102.8, 102.7, 86.5, 85.8, 78.6, 78.6, 63.5, 37.3, 35.4, 25.9, 25.6, −4.5, −4.5, −4.6, −4.7; FAB-MS m/z 558 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(*N*-methylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]cytosine (37a). Compound **37a** was prepared from **36a** (217 mg, 0.40 mmol) as described above for the synthesis of **14**. After purification by column chromatography (SiO_2, 10% MeOH–$CHCl_3$) to give **37a** (157 mg, 73%) as a white glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (d, 1H, $J = 8.2$ Hz), 7.05 (d, 1H, $J = 4.5$ Hz), 6.23 (d, 1H, $J = 6.7$ Hz), 6.15 (br s, 1H), 4.19 (br s, 1H), 4.05 (d, 1H, $J = 6.7$ Hz), 3.99 (d, 1H, $J = 11.5$ Hz), 3.87 (d, 1H, $J = 11.5$ Hz), 2.80 (d, 3H, $J = 4.5$ Hz), 2.60 (d, 1H, $J = 15.1$ Hz), 2.53 (d, 1H, $J = 15.1$ Hz), 0.95 (s, 9H), 0.84 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H), −0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.5, 162.5, 155.2, 141.3, 93.6, 86.2, 85.5, 78.8, 78.1, 63.5, 27.6, 25.9, 24.7, −4.6, −4.7, −5.2, −5.3; FAB-MS m/z 543 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(*N*-ethylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]cytosine (37b). Compound **37b** was prepared from **36b** (280 mg, 0.50 mmol) as described above for the synthesis of **14**. After purification by column chromatography (SiO_2, 40% EtOAc–hexane) to give **37b** (280 mg, 99%) as a colorless glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (d, 1H, $J = 7.5$ Hz), 7.10 (br s, 1H), 6.31 (d, 1H, $J = 7.5$ Hz), 6.31 (d, 1H, $J = 7.1$ Hz), 4.15 (br s, 1H), 4.05 (d, 1H, $J = 7.1$ Hz), 3.95 (d, 1H, $J = 11.8$ Hz), 3.85 (d, 1H, $J = 11.8$ Hz), 3.27 (dq, 2H, $J = 7.2$ Hz), 2.59 (d, 1H, $J = 16.8$ Hz), 2.52 (d, 1H, $J = 16.8$ Hz), 1.13 (t, 3H, $J = 7.2$ Hz), 0.95 (s, 9H), 0.86 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H), −0.04 (s, 3H), −0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.1, 163.4, 151.1, 140.6, 103.5, 86.5, 85.2, 78.7, 77.9, 62.9, 33.7, 25.5, 24.7, 17.5, 14.6, −4.6, −4.6, −5.0, −5.6; FAB-MS m/z 557 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(*N*-benzylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]cytosine (37c). Compound **37c**

was prepared from **36c** (404 mg, 0.80 mmol) as described above for the synthesis of **14**. After purification by column chromatography (SiO_2, 40% EtOAc–hexane) to give **37c** (460 mg, 93%) as a colorless glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (d, 1H, J = 7.4 Hz), 7.56 (br s, 1H), 7.34–7.24 (m, 5H), 6.31 (d, 1H, J = 7.3 Hz), 5.88 (br s, 1H), 4.44 (s, 2H), 4.15 (br s, 1H), 4.06 (d, 1H, J = 7.3 Hz), 3.97 (d, 1H, J = 11.8 Hz), 3.82 (dd, 1H, J = 1.9, 11.8 Hz), 2.65 (d, 1H, J = 15.1 Hz), 2.59 (d, 1H, J = 15.1 Hz), 0.95 (s, 9H), 0.82 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H), −0.04 (s, 3H), −0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 158.2, 141.8, 138.6, 128.6, 127.6, 127.3, 106.6, 88.8, 86.5, 84.8, 79.3, 78.5, 63.1, 43.3, 40.9, 26.1, 25.6, −4.7, −4.8, −5.3, −5.6; FAB-MS m/z 619 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(*N*,*N*′-dimethylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]cytosine (37d). Compound **37d** was prepared from **36d** (167 mg, 0.3 mmol) as described above for the synthesis of **14**. After purification by column chromatography (SiO_2, 40% EtOAc–hexane) to give **37d** (115 mg, 69%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (d, 1H, J = 6.5 Hz), 6.30 (br s, 1H), 6.23 (d, 1H, J = 7.3 Hz), 4.43 (br s, 1H), 4.03 (d, 1H, J = 7.3 Hz), 3.87 (br s, 2H), 2.98 (s, 3H), 2.96 (s, 3H), 2.76 (d, 1H, J = 16.8 Hz), 2.74 (d, 1H, J = 16.8 Hz), 0.93 (s, 9H), 0.88 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.02 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.0, 162.6, 154.6, 143.5, 91.6, 87.6, 84.2, 79.0, 78.6, 63.5, 37.5, 34.7, 25.8, 25.1, −4.2, −4.3, −5.3, −5.4; FAB-MS m/z 619 (MH^+).

1-[3-*C*-(*N*-Methylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]-cytosine (19a). Compound **19a** was prepared from **37a** (108 mg, 0.20 mmol) as described above for the synthesis of **6**. After purification by desalting (charcoal, 50% aqueous MeOH) to give **19a** (54 mg, 86%) as a white powder: mp 262 °C dec (crystallized from aqueous MeOH): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.05 (d, 1H, J = 8.1 Hz), 7.90 (q, 1H, J = 4.5 Hz), 7.28 (d, 2H), 5.91 (d, 1H, J = 8.0 Hz), 5.68 (d, 1H, J = 8.1 Hz), 5.58 (d, 1H, J = 6.0 Hz), 5.25 (t, 1H, J = 3.9 Hz), 5.10 (s, 1H), 3.96–3.93 (m, 2H), 3.75 (ddd, 1H, J = 1.5, 3.9, 12.1 Hz), 3.59 (ddd, 1H, J = 1.5, 3.5, 12.7 Hz), 2.55 (d, 1H, J = 16.2 Hz), 2.54 (d, 1H, J = 16.2 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.6, 166.1, 156.5, 143.0, 95.0, 88.0, 87.3, 77.9, 76.9, 61.6, 26.1; FAB-MS m/z 315 (MH^+); FAB-HRMS calcd for $C_{12}H_{19}N_4O_6$ 314.1226, found 315.1318 (MH^+).

1-[3-*C*-(*N*-Ethylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]-cytosine (19b). Compound **19b** was prepared from **37b** (124 mg, 0.20 mmol) as described above for the synthesis of **6**. After purification by desalting (charcoal, 50% aqueous MeOH) to give **19b** (55 mg, 70%) as a white powder: mp 244 °C dec (crystallized from aqueous MeOH): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.32 (d, 1H, J = 7.8 Hz), 8.03 (t, 1H, J = 5.4 Hz), 6.95 (br s, 2H), 6.08 (d, 1H, J = 7.8 Hz), 5.93 (d, 1H, J = 7.8 Hz), 5.76 (d, 1H, J = 6.5 Hz), 5.33 (t, 1H, J = 3.2 Hz), 5.21 (s, 1H), 4.56 (dq, 2H, 5.4, 7.3 Hz), 4.02 (br s, 1H), 3.96 (dd, 1H, J = 6.5, 7.8 Hz), 3.77 (ddd, 1H, J = 1.3, 3.2, 12.5 Hz), 3.61 (ddd, 1H, J = 3.2, 3.2, 12.7 Hz), 2.55 (d, 1H, J = 15.3 Hz), 2.54 (d, 1H, J = 15.3 Hz).; ^{13}C NMR (DMSO-d_6, 125 MHz) δ 172.6, 165.2, 155.6, 143.2, 95.1, 88.5, 87.7, 78.0, 76.6, 63.5, 33.3, 17.4, 14.2; FAB-MS m/z 329 (MH^+); ESI-HRMS calcd for $C_{13}H_{20}N_4NaO_6$ 351.1281, found 351.1293 (MNa^+).

1-[3-*C*-(*N*-Benzylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]-cytosine (19c). Compound **19c** was prepared from **37c** (124 mg, 0.20 mmol) as described above for the synthesis of **6**. After purification by desalting (charcoal, 50% aqueous MeOH) to give **19c** (55 mg, 71%) as a white powder: mp 235 °C dec (crystallized from aqueous MeOH): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.45 (br t, 1H, J = 5.8 Hz), 7.91 (d, 1H, J = 7.4 Hz), 7.33–7.22 (m, 5H), 7.16 (br s, 2H), 5.99 (d, 1H, J = 7.9 Hz), 5.78 (br s, 1H), 5.42 (d, 1H, J = 6.1 Hz), 5.20 (t, 1H, J = 4.4 Hz), 5.02 (s, 1H), 4.30 (d, 2H, J = 11.6), 4.02 (dd, 1H, J = 6.1, 7.9 Hz), 3.96 (br s, 1H), 3.70 (ddd, 1H, J = 1.2, 4.4, 11.9 Hz), 3.58 (ddd, 1H, J = 1.2, 4.4, 11.9 Hz), 2.65 (d, 1H, J = 15.1 Hz), 2.61 (d, 1H, J = 15.1 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 170.5, 165.5, 155.9, 142.4, 139.2, 128.2, 127.3, 126.7, 94.4, 87.4, 86.7, 77.4, 76.4, 61.0, 42.1; FAB-MS m/z 391 (MH^+); FAB-HRMS calcd for $C_{18}H_{23}N_4O_6$ 390.1539, found 390.1612 (MH^+).

1-[3-*C*-(*N*,*N*′-Dimethylcarbamoylmethyl)-β-D-*ribo*-pentofuranosyl]cytosine (19d). Compound **19d** was prepared from **37d** (111 mg, 0.20 mmol) as described above for the synthesis of **6**. After purification by desalting (charcoal, 50% aqueous MeOH) to give **19d** (61 mg, 92%) as a white powder: mp 220 °C dec (crystallized from aqueous MeOH): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.96 (d, 1H, J = 7.3 Hz), 7.26 (br d, 1H, J = 5.8 Hz), 5.91 (d, 1H, J = 8.1 Hz), 5.75 (d, 1H, J = 7.3 Hz), 5.27 (t, 1H, J = 3.9 Hz), 5.26 (d, 1H, J = 5.4 Hz), 5.17 (s, 1H), 4.03 (br s, 1H), 3.97 (dd, 1H, J = 5.4, 7.3 Hz), 3.58 (br s, 2H), 2.99 (s, 3H), 2.85 (s, 3H), 2.80 (d, 1H, J = 15.3 Hz), 2.70 (d, 1H, J = 15.3 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.5, 166.3, 156.2, 143.6, 95.2, 87.6, 87.1, 78.1, 77.3, 60.5, 36.5, 34.6; FAB-MS m/z 329 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(carbamoylmethyl)-β-D-*ribo*-pentofuranosyl]-4-*N*-methylcytosine (38a). A solution of **12** (265 mg, 0.50 mmol), DMAP (182 mg, 1.50 mmol), and Et_3N (105 μL, 1.50 mmol) in MeCN (20 mL) was treated with 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl, 450 mg, 1.50 mmol), and the mixture was stirred at room temperature for 24 h. Then, 50% aqueous methylamine (5 mL) was added, and the mixture was stirred for additional 2 h. The mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 5% MeOH–$CHCl_3$) to give **38a** (256 mg, 94%) as a yellow glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (br s, 1H), 7.79 (d, 1H, J = 8.1 Hz), 7.05 (br s, 1H), 6.24 (d, 1H, J = 7.2 Hz), 5.71 (br s, 1H), 5.47 (br s, 1H), 4.21 (br s, 1H), 4.10 (d, 1H, J = 7.2 Hz), 3.86 (br s, 2H, J = 11.8 Hz), 2.81 (d, 3H), 2.60 (t, 2H, J = 15.8 Hz), 0.93 (s, 9H), 0.86 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H), −0.01 (s, 3H), −0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 162.5, 152.1, 92.6, 87.6, 84.2, 79.0, 78.4, 63.2, 34.3, 29.4, 25.1, 24.1, −4.5, −4.6, −4.8, −4.9; FAB-MS m/z 543 (MH^+).

1-[2,5-Di-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(carbamoylmethyl)-β-D-*ribo*-pentofuranosyl]-4-*N*,*N*′-dimethylcytosine (38b). Compound **38b** was prepared from **12** (167 mg, 0.30 mmol) as described above for the synthesis of **38a**. After purification by column chromatography (SiO_2, 5% MeOH–$CHCl_3$) to give **38b** (240 mg, 86%) as a yellow glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, 1H, J = 7.9 Hz), 7.10 (br s, 1H), 6.27 (d, 1H, J = 6.7 Hz), 5.82 (d, 1H, J = 7.6 Hz), 5.39 (br s, 1H), 4.18 (br s, 1H), 4.08 (d, 1H, J = 6.7 Hz), 3.38 (dd, 1H, J = 2.9, 12.2 Hz), 3.28 (s, 3H), 3.12 (s, 3H), 2.62 (d, 1H, J = 15.7 Hz), 2.54 (d, 1H, J = 15.7 Hz), 0.97 (s, 9H), 0.86 (s, 9H), −0.17 (s, 3H), −0.17 (s, 3H), −0.01 (s,

3H), −0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4, 163.3, 155.9, 141.4, 92.2, 87.0, 84.6, 79.4, 78.3, 63.2, 40.8, 26.3, 25.9, −4.4, −4.6, −5.1, −5.4; FAB-MS m/z 543 (MH^+).

1-[3-*C*-(Carbamoylmethyl)-β-D-*ribo*-pentofuranosyl]-4-*N*-methylcytosine (20a). Compound **20a** was prepared from **38a** (108 mg, 0.20 mmol) as described above for the synthesis of **6**. After purification by desalting (charcoal, 50% aqueous MeOH) to give **20a** (50 mg, 80%) as a white powder: mp 223 °C dec (crystallized from aqueous MeOH): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.96 (d, 1H, J = 7.4 Hz), 7.28 (br d, 1H), 7.24 (d, 2H), 5.93 (d, 1H, J = 7.9 Hz), 5.78 (d, 1H, J = 7.4 Hz), 5.50 (d, 1H, J = 6.0 Hz), 5.32 (t, 1H, J = 4.2 Hz), 5.10 (s, 1H), 4.03 (t, 2H, J = 4.2, 7.4 Hz), 3.97 (br s, 1H), 3.74 (ddd, 1H, J = 3.0, 4.2, 11.9 Hz), 3.62 (ddd, 1H, J = 3.2, 4.2, 11.9 Hz), 2.63 (d, 3H, J = 4.5 Hz), 2.57 (s, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.6, 163.0, 155.8, 141.3, 91.9, 87.6, 84.7, 78.8, 78.3, 63.7, 26.5; FAB-MS m/z 315 (MH^+); FAB-HRMS calcd for $C_{12}H_{19}N_4O_6$ 314.1226, found 315.1330 (MH^+).

1-[3-*C*-(Carbamoylmethyl)-β-D-*ribo*-pentofuranosyl]-4-*N*,*N*′-dimethylcytosine (20b). Compound **20b** was prepared from **38b** (112 mg, 0.20 mmol) as described above for the synthesis of **6**. After purification by desalting (charcoal, 50% aqueous MeOH) to give **20b** (48 mg, 76%) as a yellow glass: ^{1}H NMR (DMSO-d_6 + D_2O, 500 MHz) δ 7.47 (d, 1H, J = 7.7 Hz), 6.27 (d, 1H, J = 7.7 Hz), 5.87 (d, 1H, J = 8.4 Hz), 4.43 (dd, 1H, J = 3.6, 12.7 Hz), 4.23 (dd, 1H, J = 3.6, 12.7 Hz), 4.12 (br s, 1H), 3.62 (m, 1H), 3.11 (s, 6H), 2.76 (s, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 172.0, 163.2, 153.8, 141.4, 91.4, 87.8, 84.6, 79.0, 78.3, 63.4, 35.6, 29.5; FAB-MS m/z 329 (MH^+); ESI-HRMS calcd for $C_{13}H_{20}N_4NaO_6$ 351.1281, found 351.1280 (MNa^+).

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