Nucleosides and Nucleotides. 163. Synthesis of 3′-β-Branched Uridine Derivatives via Intramolecular Reformatsky-Type Reaction Promoted by Samarium Diiodide[1]

Satoshi Ichikawa, Satoshi Shuto, Noriaki Minakawa, and Akira Matsuda*

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan

Received August 29, 1996[⊗]

A novel efficient method for the synthesis of 3′-β-branched uridines starting from uridine was developed, in which a SmI_2-promoted intramolecular Reformatsky-type reaction was effectively used. 5′-*O*-(Bromoacetyl)-3′-ketouridine derivatives **12**, **26**, and **27** were synthesized from uridine and were subjected to an intramolecular Reformatsky-type reaction. When **12**, **26**, and **27** were treated with 2.0 equiv of SmI_2 in THF at −78 °C, intramolecular carbon−carbon bond formation at the 3′-β-position proceeded smoothly to give the corresponding 3′,5′-lactones **14**, **28**, and **29** in high yields, respectively. Treatment of **28** with NH_3/MeOH gave the 3′-β-branched uridine derivative **32** quantitatively, which was then deprotected to give 3′-*C*-(carbamoylmethyl)uridine (**33**).

Introduction

Considerable attention has been focused on branched-chain sugar nucleosides because of their biological importance. We recently developed stereoselective synthetic methods for 2′-branched-chain sugar nucleosides and have prepared a variety of 2′-modified nucleoside analogs.[2] We found that 1-(2-deoxy-2-methylene-β-D-*erythro*-pentofuranosyl)cytosine (DMDC, **1**)[2r−u] and 1-(2-*C*-cyano-2-deoxy-β-D-*arabino*-pentofuranosyl)cytosine (CNDAC, **2**)[2v−z] were potent antitumor nucleosides which significantly inhibited the growth of various human tumor cells both *in vitro* and *in vivo*.

Although there have also been several studies on 3′-branched-chain sugar nucleosides,[3] only a few 3′-branched ribonucleoside analogs (Figure 1, **I**), with both a hydroxyl group at the 3′-α-position and a carbon-substituent at the 3′-β-position, have been reported,[3a,m,n] and their biological activities have not been investigated in detail. This may be because efficient synthetic methods for preparing these 3′-β-branched ribonucleoside analogs have not been developed. However, it is important to investigate the biological effects of 3′-branched ribonucleosides, which may have efficient antitumor and/or antiviral activity, like 2′-branched-chain sugar nucleosides. On the basis of these results and considerations, we recently began a synthetic study of 3′-β-branched ribonucleoside analogs and found that 1-(3-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)-uracil (EUrd, **3**) has a remarkable antitumor activity both *in vitro* and *in vivo*.[4]

It has been recognized that addition reactions of carbon nucleophiles to 3′-keto nucleosides proceed with high stereoselectivity from the α-face to give the corresponding 3′-α-branched xylonucleoside analogs.[3c,e] Accordingly, we synthesized EUrd via glycosylation after constructing the corresponding 3-ethynyl sugar from D-xylose,[4] which

* Author to whom correspondence should be addressed.

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1997.

(1) For part 162 in the series, see: Ueno, Y.; Ogawa, A.; Nakagawa, A.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2811−2816.

(2) (a) Ueda, T.; Shuto, S.; Inoue, H. *Nucleosides Nucleotides* **1984**, *3*, 173−182. (b) Ueda, T.; Shuto, S.; Satoh, M.; Inoue, H. *Nucleosides Nucleotides* **1985**, *4*, 401−409. (c) Matsuda, A.; Itoh, H.; Takenuki, K.; Sasaki, T.; Ueda, T. *Chem. Pharm. Bull.* **1988**, *36*, 945−953. (d) Matsuda, A.; Satoh, M.; Nakashima, H.; Yamamoto, N.; Ueda. T. *Heterocycles* **1988**, *27*, 2545−2548. (e) Ueda, T.; Matsuda, A.; Yoshimura, Y.; Takenuki, K. *Nucleosides Nucleotides* **1989**, *8*, 743−752. (f) Takenuki, K.; Itoh, H.; Matsuda, A.; Ueda. T. *Chem. Pharm. Bull.* **1990**, *38*, 2947−2952. (g) Matsuda, A.; Takenuki, K.; Sasaki, T.;Ueda. T. *J. Med. Chem.* **1991**, *34*, 234−239. (h) Yoshimura, Y.; Iino, T.; Matsuda. A. *Tetrahedron Lett.* **1991**, *32*, 6003−6006. (i) Matsuda, A.; Azuma, A.; Nakajima, A.; Takenuki, K.; Dan, A.; Iino, T.; Yoshimura, Y.; Minakawa, N.; Tanaka, M.; Sasaki. T. In *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993; pp 1−22. (i) Kakefuda, A.; Yoshimura, Y.; Sasaki, T.; Matsuda. A. *Tetrahedron* **1993**, *49*, 8513−8528. (j) Awano, H.; Shuto, S.; Baba, M.; Kira, T.; Shigeta, S.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 367−370. (k) Hassan A. E. A.; Shuto, S.; Matsuda. A. *Tetrahedron* **1994**, *50*, 689−700. (l) Hassan, A. E. A.; Shuto, S.; Matsuda, A. *Nucleosides Nucleotides* **1994**, *13*, 197−211. (m) Iino, T.; Yoshimura, Y.; Matsuda. A. *Tetrahedron* **1994**, *50*, 10397−10406. (n) Kakefuda, A.; Shuto, S.; Nagahata, T.; Seki, J.; Sasaki, T.; Matsuda. A. *Tetrahedron* **1994**, *50*, 10167−10182. (o) Iino, T.; Shuto, S.; Matsuda, A. *Nucleosides Nucleotides* **1996**, *15*, 169−181. (p) Awano, H.; Shuto, S.; Miyashita, T.; Ashida, M.; Machida, M.; Kira, T.; Shigeta, S.; Matsuda, A. *Arch. Pharm. Pharm. Med. Chem.* **1996**, *329*, 66−72. (q) Hassan, A. E. A.; Nishizono, N.; Minakawa, N.; Shuto, S.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 6261−6267. (r) Takenuki, K.; Matsuda, A.; Ueda, T.; Sasaki, T.; Fujii, A.; Yamagami, K. *J. Med. Chem.* **1988**, *31*, 1063−1064. (s) Matsuda, A.; Takenuki, K.; Tanaka, M.; Sasaki, T.; Ueda, T. *J. Med. Chem.* **1991**, *34*, 812−819. (t) Yamagami, K.; Fujii, A.; Arita, M.; Okumoto, T.; Sakata, S.; Matsuda, A.; Ueda, T. *Cancer Res.* **1991**, *51*, 2319−2323. (u) Ono, T.; Fujii, A.; Yamagami, K.; Hosoya, M.; Okumoto, T.; Sakata, S.; Matsuda, A.; Sasaki, T. *Biochem. Pharmacol.* **1996**, *52*, 1279−1285. (v) Matsuda, A.; Nakajima, Y.; Azuma, A.; Tanaka, M.; Sasaki, T. *J. Med. Chem.* **1991**, *34*, 2917−2919. (w) Azuma, A.; Nakajima, Y.; Nishizono, N.; Minakawa, N.; Suzuki, M.; Hanaoka, K.; Kobayashi, T.; Tanaka, M.; Sasaki, T.; Matsuda, A. *J. Med. Chem.* **1993**, *36*, 4183−4189. (x) Tanaka, M.; Matsuda, A.; Terao, T.; Sasaki., T. *Cancer Lett.* **1992**, *64*, 67−74. (y) Azuma, A.; Hanaoka, K.; Kurihara, A.; Kobayashi, T.; Miyauchi, S.; Kamo, N.; Tanaka, M.; Sasaki, T.; Matsuda, A. *J. Med. Chem.* **1995**, *38*, 3391−3397. (z) Matsuda, A.; Azuma, A. *Nucleosides Nucleotides* **1995**, *14*, 461−471.

(3) For examples: (a) Nutt, R. F.; Dickinson, M. J.; Holly, F. W.; Walton, E. *J. Org. Chem.* **1968**, 33, 1789−1795. (b) Shuto, S.; Iwano, Y.; Inoue, H.; Ueda, T. *Nucleosides Nucleotides* **1982**, *1*, 263−270. (c) Hayakawa, H.; Tanaka, J.; Itoh, N.; Nakajima, M.; Miyasaka, T.; Yamaguchi, K.; Iitaka, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2605−2608. (d) Huss, S.; De las Heras, F. G.; Camarasa, M. J. *Tetrahedron* **1991**, *47*, 1727−1736. (e) Bender, S. L.; Moffett, K. K. *J. Org. Chem.* **1992**, *57*, 1646−1647. (f) Valazquez, S.; San-Felix, A.; Perez-Perez, M. J.; Balzarini, J.; De Clercq, E.; Camarasa, M. J. *J. Med. Chem.* **1993**, *36*, 3230−3239. (g) Lee, K.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 7808−7812. (h) Jorgensen, P. N.; Stein, P. C.; Wengel, J. *J. Am. Chem. Soc.* **1994**, *116*, 2231−2232. (i) Schmit, C.; Bevierre, M.-O.; De Mesmaeker, A.; Altamann, K.-H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1969−1974. (j) Hossain, N.; Plavec, J.; Chattopadhyaya, J. *Tetrahedron* **1994**, *50*, 4167−4178. (k) Johnson, C. R.; Rhumralkar, D. R.; De Clercq, E. *Nucleosides Nucleotides* **1995**, *14*, 185−194. (l) Becouarn, S.; Szernecki, S.; Valery, J.-M. *Tetrahedron Lett.* **1995**, *36*, 873−876. (m) Jung, P. M. J.; Burger, A.; Biellmann, J.-F. *Tetrahedron Lett.* **1995**, *36*, 1031−1034. (n) Auguste, S. P.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1995**, 395−404.

(4) (a) Matsuda, A.; Hattori, H.; Tanaka, M.; Sasaki, T. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1887−1892. (b) Tabata, S.; Tanaka, M.; Matsuda, A.; Fukushima, M.; Sasaki, T. *Oncol. Rep.* **1996**, *3*, 1029−1034. (c) Hattori, H.; Tanaka, M.; Fukushima, M.; Sasaki, T.; Matsuda, A. *J. Med. Chem.* **1996**, *39*, 5005−5011.

S0022-3263(96)01665-9 CCC: $14.00

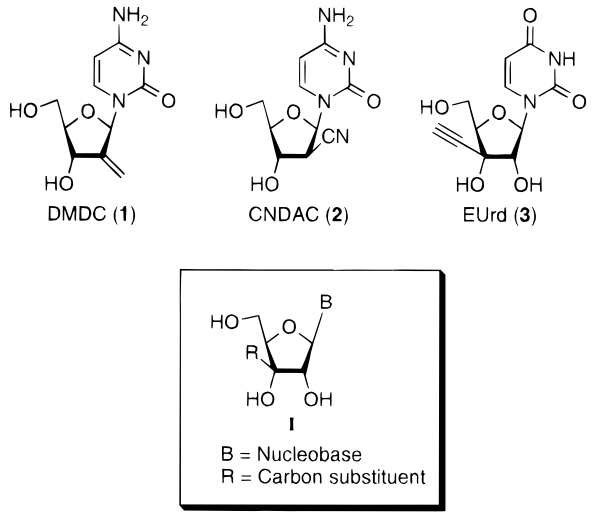


Figure 1. Structures of branched-chain sugar nucleosides synthesized by us.

needed rather long reaction steps. Therefore, to examine the biological effects of various 3′-branched ribonucleoside analogs, the development of more straightforward methods for their preparation is needed. In this paper, we describe a novel synthetic method for 3′-*β*-branched uridines starting from uridine, using the intramolecular SmI_2-promoted Reformatsky-type reaction as a key step.

Intramolecular Reformatsky-type reactions of haloacetates derived from α- or *β*-hydroxy ketones and aldehydes can be used for stereoselective intramolecular additions to carbonyls to give the corresponding hydroxy lactones. Intramolecular Barbier-type reactions of haloalkyl ketones or aldehydes are also among the simplest approaches to the formation of hydroxy carbocyclic ring structures. However, only limited success has been realized with both reactions due to low yields and/or inefficient stereoselectivity, when the reactions have been performed with zinc (for Reformatsky-type reaction),[5] and lithium or magnesium (for Barbier-type reaction)[6] as reductants. Over the past decade, it has been shown that samarium diiodide (SmI_2) can be used as an efficient electron-transfer reagent in a variety of transformations in organic chemistry due to its functional- and stereoselectivity.[7] This reagent can promote organic reactions that are difficult to accomplish by any other available methodologies.[7] It has recently been reported that SmI_2 also promotes intramolecular Reformatsky-type reactions to produce medium- and large-ring lactones,[8] as well as *β*-hydroxy six-membered-lactones as acyclic syn 1,3-diol equivalents via 1,3-asymmetric induction.[5] These reactions were unsuccessful when zinc was used as a promoter.[5,8] In addition to serving as a useful replacement for zinc in Reformatsky-type reactions, SmI_2 also provides advantages over lithium or magnesium as the reductant in Barbier-type reactions with which highly functionalized five- and six-membered carbocycles can be rapidly constructed in a stereocontrolled fashion.[6,9]

These results prompted us to explore a new method for producing 3′-*β*-branched ribonucleoside analogs via the SmI_2-promoted Reformatsky- or Barbier-type reactions of 3′-keto-nucleoside derivatives. 3′-Keto-nucleosides are known to be unstable, especially under basic conditions.[3e] We expected that SmI_2 could be effectively used in a carbon−carbon bond formation reaction with 3′-keto-nucleoside derivatives, since it promotes reactions under homogeneous neutral conditions. Our synthetic strategy is outlined in Scheme 1. If the Reformatsky-type reaction of 5′-*O*-(bromoacetyl)-3′-keto-nucleosides (**II**) or the Barbier-type reactions of 5′-*O*-(bromopropanoyl)- or 5′-*O*-[(bromomethyl)dimethylsilyl]-3′-keto-nucleosides (**III** or **IV**, respectively) with SmI_2 proceed as we expect, these would give the corresponding 3′,5′-ring-closure products, **V**, **VI**, or **VII**. Subsequent ring-cleavage would give the desired 3′-*β*-branched ribonucleoside analogs **I**.

Results and Discussion

First, we used 4-ethoxy-2(1*H*)-pyrimidone riboside (**5**) as a substrate for derivatization: the 4-ethoxy-2-pyrimidone moiety is inert under various reaction conditions compared to the uracil moiety of uridine itself, since it lacks both the acidic 3-NH and the reactive enone-system of uracil, and can be converted to either a uracil or cytosine residue after modification of the sugar moiety. Compound **5** was conveniently prepared from uridine (**4**) using the Mitsunobu reaction. One-pot treatment of uridine with Ac_2O/Et_3N/DMAP in MeCN and then with Ph_3P/diethyl azodicarboxylate (DEAD)/EtOH in THF, followed by removal of the acetyl groups of the sugar moiety with NaOEt in EtOH, gave **5** in 93% yield. This method provided **5** in high yield (Scheme 2) and was clearly superior to the previous method via a 4-chloropyrimidone riboside derivative.[2c] After the 5′-hydroxyl of **5** was selectively protected by a dimethoxytrityl (DMTr) group, it was treated with *tert*-butyldimethylsilyl chloride (TBSCl) in pyridine to give the 2′-*O*-TBS derivative **7** and the 3′-*O*-TBS derivative **8** in yields of 51% and 19%, respectively. PDC oxidation of **7** in CH_2Cl_2 gave the corresponding ketone **9**. The 5′-*O*-DMTr group was selectively removed by treating **9** with $ZnBr_2$ in CH_2Cl_2[10] to give 5′-hydroxy derivative **10**, which was too unstable to be isolated. Therefore, derivative **10** was used in the next reaction without purification. Crude **10** was treated with bromoacetyl bromide in the presence of 2,6-lutidine in CH_2Cl_2 at −78 °C to give 5′-*O*-bromoacetyl derivative **12**, the substrate of the intramolecular Reformatsky-type reaction, in 71% yield from **9**, after purification by silica gel column chromatography. 5′-*O*-Bromopropanoyl derivative **13**, the substrate of the intramolecular Barbier-type reaction, was prepared in a similar manner. Treat-

(5) Molander, G. A., Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556−6558, and references cited therein.

(6) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453−463, and references cited therein.

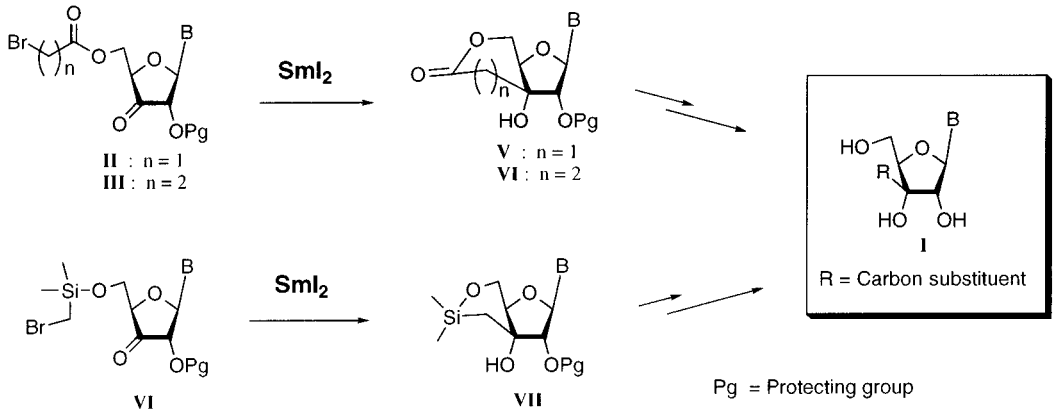
(7) (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698. (b) Molander, G. A. In *Comprehensive Organic Synthesis*; Shereiber, S. L., Ed.; Pergamon Press: New York,; Vol. 1, pp 251−282. (c) Soderquist, J. A. *Aldrichim. Acta* **1991**, *24*, 15−23. (e) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68. (f) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338.

(8) (a) Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889−3890. (b) Moriya, T.; Handa, Y.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1988**, *29*, 6947−6948. (c) Vedejs, E.; Ahmad, S. *Tetrahedron Lett.* **1988**, *29*, 2291−2294.

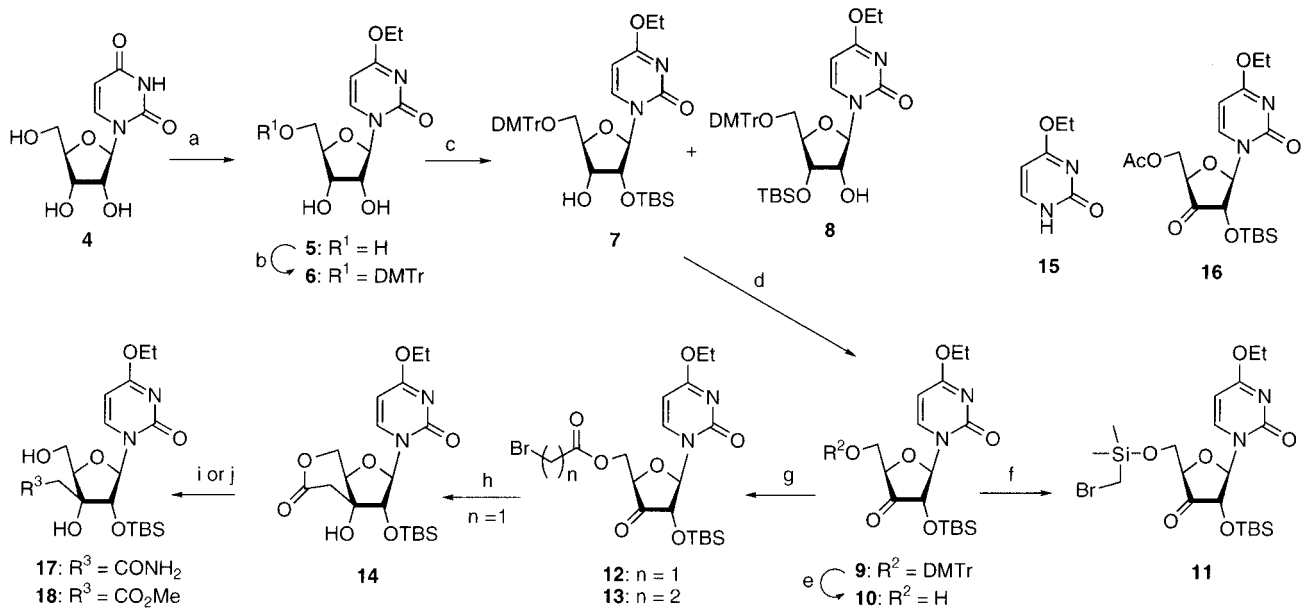
(9) (a) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, 51, 1778−1786. (b) Suginome, H.; Yamada, S. *Tetrahedron Lett.* **1987**, *28*, 3963−3966. (c) Otsubo, K.; Kwamura, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 1487−1490. (d) Sosnowske, J. J.; Danaher, E. B.; Murray, R. K. *J. Org. Chem.* **1985**, *50*, 2759−2763. (e) Lannoye, G.; Cook, J. M. *Tetrahedron Lett.* **1988**, *29*, 171−174.

(10) Kohli, V.; Blöcker, H.; Köster, H. *Tetrahedron Lett.* **1980**, *21*, 2683−3686.

Scheme 1



Scheme 2[a]



[a] Reagents: (a) (1) Ac_2O, Et_3N, DMAP, MeCN, (2) Ph_3P, DEAD, EtOH, THF, (3) NaOEt, EtOH; (b) DMTrCl, py; (c) TBSCl, py; (d) PDC,CH_2Cl_2; (e) $ZnBr_2$, CH_2Cl_2; (f) $BrCH_2(CH_3)_2SiCl$, Et_3N, imidazole, CH_2Cl_2; (g) $BrCH_2COCl$ or $BrCH_2CH_2COCl$, 2,6-lutidine, CH_2Cl_2; (h) SmI_2, THF; (i) NH_3/MeOH; (j) K_2CO_3, MeOH.

ment of crude **10** with (bromomethyl)chlorodimethylsilane in the presence of imidazole and Et_3N in CH_2Cl_2 gave **11**.[11]

Intramolecular reductive cyclization of **11**, **12**, and **13** with SmI_2 was investigated, and the results are summarized in Table 1. First, the Barbier-type reactions of **11** and **13** were examined. Treatment of 5′-*O*-bromopropionate **13** with 2.0 equiv of SmI_2 in THF at room temperature resulted in complete recovery of **13** (entry 1). It has been reported that HMPA enhances the electron-transfer ability of SmI_2 and often improves the yield of the desired products.[7a,12] However, when the reaction was performed in the presence of 5 equiv of HMPA, it did not give the desired cyclized product, but rather 4-ethoxy-2-pyrimidone (**15**) in 72% yield (entry 2). Similarly, reaction of 5′-*O*-(bromomethyl)dimethylsilyl derivative **11** was also unsuccessful. The intramolecular Reformatsky-type reaction of 5′-bromoacetate **12** was tried next. When **12** was treated with 2.0 equiv of SmI_2 in THF at room temperature, the Reformatsky-type reaction proceeded effectively to give the desired lactone **14** in 71% yield (entry 4). On the other hand, reaction of **12** with zinc as a reductant in toluene did not give **14**,

Table 1. Intramolecular Reformatsky- or Barbier-Type reactions of 3′-Ketouridine Derivatives Promoted by SmI_2[a]

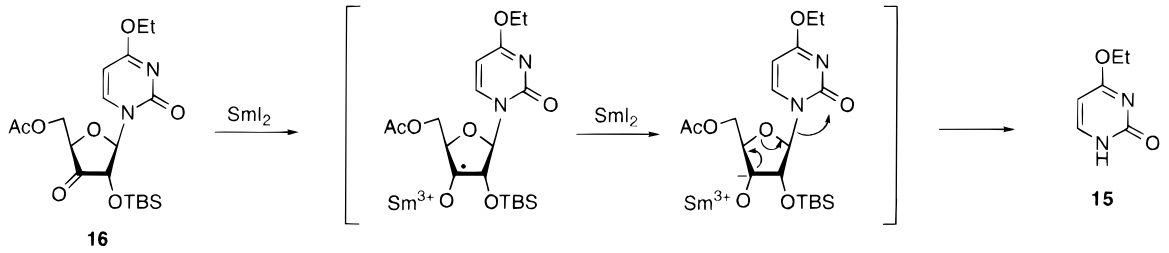
entry	substrate	temperature	additive (equiv)	product (% isolated yield)
1	**13**	room temp	none	no reaction
2	**13**	room temp	HMPA (5)	**15** (72)
3	**11**	room temp	HMPA (5)	**15** (69)
4	**12**	room temp	none	**14** (71)
5[b]	**12**	room temp	none	**16** (22)
6	**12**	0 °C	none	**14** (75)
7	**12**	−78 °C	none	**14** (90)
8	**12**	−78 °C	HMPA (5)	**14** (76), **15** (11)
9	**12**	−78 °C	*t*-BuOH (5)	**14** (61)
10	**27**	−78 °C	none	**29** (85)
11	**26**	−78 °C	none	**28** (65), **31** (18)
12[c]	**26**	−78 °C	none	**28** (85), **31** (trace)

[a] Reactions were done in the presence of 2.0 equiv of SmI_2 in THF except for entry 5 and 12. [b] Reaction was done with 1.0 equiv of zinc in toluene. [c] A soulution of **26** in THF was added slowly over 2 h to a 2.0 equiv of SmI_2 solution in THF.

(11) Compound **11** was used in the next reaction without purification because of its instability.

(12) (a) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485−1486. (b) Handa, Y.; Inanaga, J.; Yamaguchi, M. *J. Chem. Soc., Chem. Commun.* **1989**, 298−299. (c) Evans, W. J.; Gummersheimer, T. S.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 8999−9002.

Scheme 3



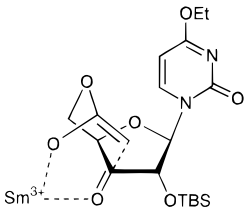


Figure 2. The conceivable chelation intermediate of the SmI_2-promoted Reformatsky-type reaction of **12**.

but only 5′-*O*-acetate **16** (entry 5). The yield of **14** increased when SmI_2-promoted reactions were performed at lower temperature; **14** was obtained in 75% yield at 0 °C (entry 6) and in 90% yield at −78 °C (entry 7), respectively. When HMPA was used as an additive, the yield of **14** was decreased and **15** was isolated in 11% yield (entry 8). Although *t*-BuOH has been shown to be an effective additive for SmI_2-promoted reactions,[13] it was ineffective in this reaction system (entry 9).

To obtain insight into the mechanism of cleavage of the glycosidic linkage during the course of the reaction, the lactone **14** and 5′-*O*-acetyl-3′-ketouridine derivative **16** were treated with the SmI_2−HMPA system in THF at room temperature. Although **14** was quantitatively recovered in the former case, SmI_2 cleaved the glycosidic linkage of **16** to give **15** in 62% yield. This suggests that the glycosidic linkage is cleaved via electron transfer from SmI_2 to the 3′-carbonyl of 3′-ketouridine derivatives and subsequent reductive cleavage of the carbon−oxygen bond[14] at the 4′-position, as shown in Scheme 3. A similar ring-opening reaction of tetrahydrofuran rings promoted by SmI_2 has been previously reported.[15]

In the intramolecular Reformatsky-type reaction with SmI_2, the transfer of two electrons from SmI_2 molecules would occur rapidly at the bromoacetyl moiety to generate the corresponding enolate. The efficiency of SmI_2 as the promoter of this reaction is due to the chelation of Sm^{3+}, generated in the reaction process, to the 5′-enolate of ester and the 3′-carbonyl, as shown in Figure 2, which can effectively promote the enolate addition reaction to the carbonyl.[5] In the reaction with zinc as a reductant, while the 5′-enolate would be generated, the subsequent addition reaction on the 3′-carbonyl did not proceed, probably due to the inability of Zn^{2+} to undergo such chelation. On the other hand, upon treatment of **11** or **13** with the SmI_2−HMPA system, electron transfer would rapidly occur at the 3′-carbonyl to generate an unstable 3′-ketyl radical, which would result in cleavage of the glycosidic linkage to give 4-ethoxy-2-pyrimidone (**15**).

Treatment of **14** with NH_3/MeOH at room temperature gave the desired amide **17** in 45% yield along with **15** in 52% yield.[16] When the reaction was performed at −70 °C, **17** was obtained quantitatively. Similar treatment of **14** with K_2CO_3 in MeOH gave methyl ester **18** in high yield. Although removal of the 4-*O*-ethyl group was investigated under various acidic and Lewis acidic conditions, cleavage of its glycosidic linkage occurred in preference to the desired deethylation.

Therefore, we next tried the Reformatsky-type reaction with 3-benzyloxymethyl (BOM) uridine derivative **27** as a substrate, since the BOM group can be removed by catalytic hydrogenation. The 3-position was selectively protected by treating uridine with BOMCl and DBU in DMF at 0 °C to give **19** quantitatively. Treatment of **19** with TBSCl in the presence of $AgNO_3$ and pyridine in THF[17] gave the 2′,5′-di-*O*-silylated product **21** in high yield, which was oxidized as reported elsewhere[18] to give the 3′-keto derivative **23**. 5′-Bromoacetate **27**, the substrate for the Reformatsky-type reaction, was obtained by the same procedure as described above for preparing **12**. When **27** was treated with 2.0 equiv of SmI_2 at −78 °C in THF, the intramolecular Reformatsky-type reaction proceeded rapidly, as in the case of **12**, to give the desired lactone **29** in 85% yield (Table 1, entry 10). Removal of the BOM group was achieved at this stage by catalytic hydrogenation. Although 3-hydroxymethyl derivative **30** was obtained as the major product using Pd-charcoal as a catalyst, deprotected lactone **28** was obtained quantitatively when the hydrogenation was performed with $Pd(OH)_2$ in MeOH.

We also examined the intramolecular Reformatsky-type reaction of base moiety-unprotected uridine derivative **26**, which was obtained from the known 2′-*O*-TBS-3′-ketouridine **24**.[18] Treatment of **26** with 2.0 equiv of SmI_2 at −78 °C in THF gave lactone **28** in 65% yield and 5′-*O*-acetyl derivative **31** in 18% yield (Table 1, entry 11). Lactone **28** was obtained in 85% yield as a sole product when a solution of **26** in THF was added slowly over 2 h, using a syringe-pump, to a SmI_2 solution in THF at −78 °C (entry 12). These results suggest that the 3-NH of the uracil moiety acts as a proton source to promote the reduction of the 5′-ester moiety. Treatment of **28** with NH_3/MeOH at −70 °C gave 2′-*O*-TBS-3′-*C*-(carbamoylmethyl)uridine (**32**) in high yield. Finally, the TBS group of **32** was removed by heating it with NH_4F in MeOH under reflux to give the target 3′-*C*-(carbamoylmethyl)-uridine (**33**).

(13) Yoneda, R.; Harusawa, S.; Kurihara, T. *Tetrahedron Lett.* **1989**, *30*, 3681−3684.

(14) Deoxygenation of α-oxygenated ketones or esters with SmI_2 has been reported: (a) Molander, G. A.; Harn, G. *J. Org. Chem.* **1986**, *51*, 1135−1138. (b) Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2945−2948.

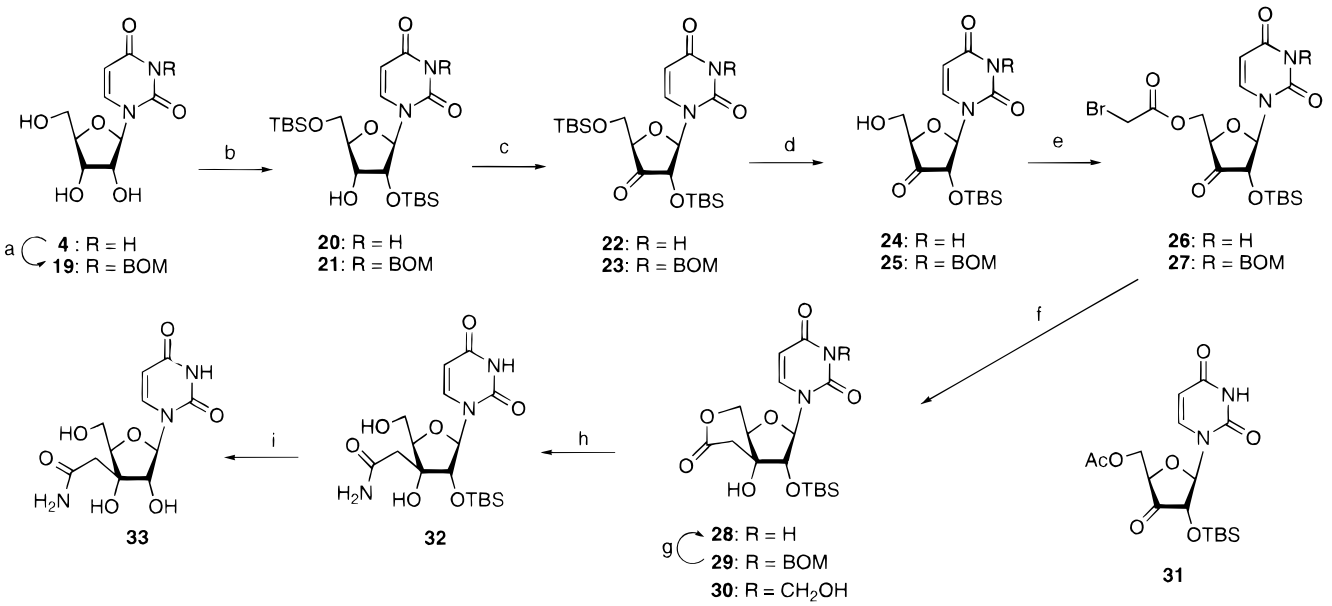
(15) Enholm, E. J.; Schreier, J. A. *J. Org. Chem.* **1995**, *60*, 1110−1111

(16) The cleavage of the glycosidic linkage thought to proceed via a 3′-keto derivative which could be generated by a retroaldol reaction of **14**, because **17** was stable in NH_3/MeOH at room temperature.

(17) Hakimelahi, G. H.; Proba, Z. A.; Ogilvie, K. K. *Tetrahedron Lett.* **1981**, *22*, 4775−4778.

(18) Robins, M. J.; Samano, V.; Johnson, M. D. *J. Org. Chem.* **1990**, *55*, 410−412.

Scheme 4[a]



[a] Reagents: (a) BOMCl, DBU, DMF; (b) TBSCl, $AgNO_3$, THF; (c) CrO_3, py, molecular seives 4A, Ac_2O, CH_2Cl_2; (d) aqueous TFA (90%); (e) $BrCH_2COCl$, 2,6-lutidine, CH_2Cl_2; (f) SmI_2, THF; (g) H_2, $Pd(OH)_2$, MeOH; (h) NH_3/MeOH; (i) NH_4F, MeOH.

We have demonstrated that SmI_2 effectively promoted the intramolecular Reformatsky-type reaction of 5′-*O*-(bromoacetyl)-3′-ketouridines to give the corresponding 3′,5′-lactones, and subsequent treatment of the lactones with nucleophiles gave the corresponding 3′-*β*-branched uridines. To our knowledge, this is the first example of the efficient use of a SmI_2-mediated carbon−carbon bond formation reaction in nucleoside chemistry. This method may be applicable to other pyrimidine and purine nucleosides for synthesizing the corresponding 3′-branched ribonucleoside analogs.

Derivatization of **33** into various 3′-*β*-branched-chain sugar nucleosides and biological evaluations are under investigation.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded at 270 or 500 MHz (^{1}H) and at 125 MHz (^{13}C) and are reported in ppm downfield from TMS. Mass spectra were obtained by electron ionization (EI) or fast atom bombardment (FAB) method. Thin-layer chromatography was done on Merck coated plate $60F_{254}$. Silica gel chromatography was done with Merck silica gel 5715. SmI_2/THF was prepared according to a reported method.[19]

4-Ethoxy-1-*β*-D-ribofuranosyl-2(1*H*)-pyrimidone (5). A mixture of uridine (24.4 g, 100 mmol), Et_3N (31.2 mL, 330 mmol), Ac_2O (29.6 mL, 330 mmol), and DMAP (100 mg) in MeCN (400 mL) was stirred at room temperature for 30 min. After MeOH (20 mL) was added, the solution was evaporated under reduced pressure, and the residue was partitioned between EtOAc (1 L) and H_2O (200 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (200 mL × 2) and brine (200 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue and Ph_3P (26.7 g, 105 mmol) was dissolved in THF (300 mL), to which a solution of diethyl azodicarboxylate (19.5 mL, 105 mmol) in THF (50 mL) was added dropwise followed by an addition of EtOH (6.6 mL, 105 mmol) at 0 °C. The mixture was stirred at room temperature for 20 min and evaporated under reduced pressure. A mixture of the residue and 1 N NaOEt (2 mL, 2 mmol) in EtOH (500 mL) was stirred at room temperature for 4 h. After neutralization with AcOH, the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, 24% EtOH−$CHCl_3$) to give **5** (25.3 g, 93%) as a white solid, for which spectral data was in accord with that reported previously.[2c]

4-Ethoxy-1-[5-*O*-(dimethoxytrityl)-*β*-D-ribofuranosyl]-2(1*H*)-pyrimidone (6). A mixture of **5** (13.6 g, 50 mmol) and dimethoxytrityl chloride (DMTrCl, 20.4 g, 60 mmol) in pyridine (200 mL) was stirred at room temperature for 2 h. After MeOH (10 mL) was added, the solution was evaporated under reduced pressure, and the residue was partitioned between $CHCl_3$ (500 mL) and H_2O (200 mL). The organic layer was washed with brine (200 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 6% EtOH−$CHCl_3$) to give **6** (27.9 g, 98%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 (d, J = 8.1 Hz, 1H), 7.36−7.20 (m, 9H), 6.82 (d, 4H), 5.82 (d, J = 3.4 Hz, 1H), 5.50 (d, J = 8.1 Hz, 1H), 4.44 (br s, 1H), 4.36 (dd, J = 3.4, 4.7 Hz, 1H), 4.32 (dd, J = 2.5, 4.7 Hz, 1H), 4.24 (ddd, J = 2.3, 2.5, 3.0 Hz, 1H), 3.89 (q, J = 6.8 Hz, 2H), 3.78 (s, 6H), 3.49 (dd, J = 2.3, 10.9 Hz, 1H), 3.41 (dd, J = 3.0, 10.9 Hz, 1H), 3.19 (br s, 1H), 1.22 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.6, 158.9, 144.5, 137.8, 135.5, 135.4, 130.3, 128.0, 128.2, 127.4, 113.5, 102.0, 92.0, 87.3, 84.9, 76.5, 71.2, 62.7, 55.5, 36.5, 13.0; MS (FAB) m/z 575 (MH^+). Anal. Calcd for $C_{32}H_{34}N_2O_8$: C, 66.89; H, 5.96; N, 4.87. Found: C, 67.03; H, 6.04; N, 4.62.

4-Ethoxy-1-[2-*O*-(*tert*-butyldimethylsilyl)-5-*O*-(dimethoxytrityl)-*β*-D-ribofuranosyl]-2(1*H*)-pyrimidone (7). A mixture of **6** (6.90 g, 12 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl, 19.9 g, 33.0 mmol) in pyridine (100 mL) was stirred at room temperature for 48 h. After MeOH (5 mL) was added, the solution was evaporated under reduced pressure, and the residue was partitioned between EtOAc (500 mL) and H_2O (200 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 25−30% EtOAc−hexane) to give **7** (5.58 g, 51%) and **8** (2.13 g, 19%) as white forms. **7**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (d, J = 8.2 Hz, 1H), 7.27−7.12 (m, 9H), 6.72 (d, 4H), 5.90 (d, J = 3.0 Hz, 1H), 5.26 (d, J = 8.2 Hz, 1H), 4.22 (m, 2H), 4.00 (br s, 1H), 3.87 (q, J = 7.0 Hz, 2H), 3.77 (s, 6H), 3.40 (dd, J = 2.0, 10.9 Hz, 1H), 3.35 (dd, J = 2.4, 10.9 Hz, 1H), 2.54 (s, 1H), 1.09 (t, J = 7.0 Hz, 3H), 0.81 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.7, 159.0, 151.0, 144.6, 138.1, 135.5, 135.3, 130.4, 130.3, 128.4, 128.3, 127.4, 113.6, 113.4, 102.3, 89.3, 87.4, 83.8, 70.9, 62.8, 55.5, 36.4, 25.9, 18.2, 13.0,

(19) Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, 501−502.

−4.4, −4.9; MS (FAB) *m/z* 689 (MH^+). Anal. Calcd for $C_{38}H_{48}N_2O_8Si$: C, 66.25; H, 7.02; N, 4.07. Found: C, 66.09; H, 7.11; N, 4.20. **8**: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, J = 8.1 Hz, 1H), 7.30−7.25 (m, 9H), 6.84 (d, 4H), 6.00 (d, J = 4.0 Hz, 1H), 5.45 (d, J = 8.1 Hz, 1H), 4.38 (t, J = 5.2 Hz, 1.0 H), 4.13 (ddd, J = 4.0, 5.2, 5.8 Hz, 1H), 4.03 (ddd, J = 2.2, 2.5, 5.2 Hz, 1H), 4.00 (q, J = 7.0 Hz, 2H), 3.80 (s, 6H), 3.60 (dd, J = 2.2, 10.9 Hz, 1H), 3.30 (dd, J = 2.5, 10.9 Hz, 1H), 2.83 (d, J = 5.8 Hz, 1H), 1.22 (t, J = 7.0 Hz, 3H), 0.85 (s, 9H), 0.06 (s, 3H), −0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.7, 159.0, 151.2, 144.3, 138.1, 135.4, 135.3, 130.4, 130.4, 128.4, 128.2, 127.5, 113.5, 113.4, 102.3, 90.3, 87.3, 83.9, 71.4, 62.3, 55.5, 36.5, 25.9, 18.2, 13.0, −4.6, −4.7.

4-Ethoxy-1-[2-*O*-(*tert*-butyldimethylsilyl)-5-*O*-(dimethoxytrityl)-*β*-D-*erythro*-pentofran-3-ulosyl]-2(1*H*)-pyrimidone (9). A mixture of **7** (3.86 g, 5.61 mmol) and PDC (4.22 g, 11.2 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 12 h. The resulting mixture was diluted with EtOAc and filtered through a Celite pad. The filtrate was evaporated under reduced pressure, and the residue was partitioned between EtOAc (200 mL) and H_2O (50 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 20% EtOAc−hexane) to give **9** (2.90 g, 76%) as a white foam: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.61 (d, J = 8.2 Hz, 1H), 7.32−7.16 (m, 9H), 6.83 (d, 4H), 6.29 (d, J = 7.9 Hz, 1H), 5.49 (d, J = 8.2 Hz, 1H), 4.53 (d, J = 7.9 Hz, 1H), 4.27 (br s, 1H), 3.98 (q, J = 7.0 Hz, 2H), 3.77 (s, 6H), 3.62 (dd, J = 2.3, 10.5 Hz, 1H), 3.40 (dd, J = 2.0, 10.5 Hz, 1H), 1.19 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.17 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.8, 162.3, 159.1, 151.0, 144.4, 137.4, 135.2, 134.9, 130.3, 130.2, 129.4, 128.3, 128.2, 128.0, 127.5, 113.7, 113.6, 103.4, 87.6, 86.2, 80.8, 63.4, 55.5, 36.7, 25.9, 18.5, 12.9, −4.4, −5.2; MS (FAB) *m/z* 687 (MH^+). Anal. Calcd for $C_{38}H_{46}N_2O_8Si$: C, 66.45; H, 6.75; N, 4.08. Found: C, 66.22; H, 6.98; N, 3.85.

4-Ethoxy-1-[2-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofran-3-ulosyl]-2(1*H*)-pyrimidone (10). A mixture of **9** (686 mg, 1.00 mmol) and $ZnBr_2$ (4.50 g, 10.0 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 5 min, and then H_2O (20 mL) was added. The organic layer separated was washed with 1 N HCl (20 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give crude **10** (691 mg, quant). The residue was used immediately for the next reaction without further purification because of its instability.

4-Ethoxy-1-[5-*O*-[(bromomethyl)dimethylsilyl]-2-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofran-3-ulosyl]-2(1*H*)-pyrimidone (11). A mixture of crude **10** (prepared from 1.00 mmol of **9**), (bromomethyl)dimethylchlorosilane (163 μL, 1.20 mmol), Et_3N (104 μL, 1.20 mmol), and imidazole (82 mg, 1.20 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 10 min. After MeOH (1 mL) was added, the solution was diluted with CH_2Cl_2 (30 mL). The resulting solution was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give crude **11** (863 mg, quant). The residue was used immediately for the next reaction without further purification because of its instability.

4-Ethoxy-1-[5-*O*-(bromoacetyl)-2-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofran-3-ulosyl]-2(1*H*)-pyrimidone (12). A mixture of crude **10** (prepared from 1.00 mmol of **9**), 2,6-lutidine (163 μL, 1.20 mmol), and bromoacetyl bromide (104 μL, 1.20 mmol) in CH_2Cl_2 (10 mL) was stirred for 5 min at −78 °C. After MeOH (1 mL) was added, the solution was diluted with CH_2Cl_2 (30 mL). The resulting solution was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 30% EtOAc−hexane) to give **12** (395 mg, 78% from **9**) as a yellow foam: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40 (d, J = 8.1 Hz, 1H), 5.95 (d, J = 6.8 Hz, 1H), 5.86 (d, J = 8.1 Hz, 1H), 4.56 (dd, J = 5.0, 16.6 Hz, 1H), 4.49 (d, J = 6.8 Hz, 1H), 4.45 (br s, 1H), 4.44 (dd, J = 3.9, 16.6 Hz, 1H), 4.00 (q, J = 7.1 Hz, 2H), 3.90 (s, 2H), 1.21 (t, J = 7.1 Hz, 3H), 0.86 (s, 9H), 0.17 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.0, 166.1, 161.8, 150.8, 137.9, 103.7, 88.8, 78.5, 75.2, 64.4, 36.5, 25.37, 25.3, 18.1, 12.7, −4.7, −5.4; MS (FAB) *m/z* 505, 507 (MH^+).

4-Ethoxy-1-[5-*O*-(bromopropionyl)-2-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofran-3-ulosyl]-2(1*H*)-pyrimidone (13). A mixture of crude **10** (prepared from 1.00 mmol of **9**), 2,6-lutidine (163 μL, 1.20 mmol), 3-bromopropionyl chloride (100 μL, 1.20 mmol), and DMAP (10 mg) in CH_2Cl_2 (10 mL) was stirred at room temperature for 2 h. After MeOH (1 mL) was added, the solution was diluted with CH_2Cl_2 (30 mL). The resulting solution was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 30% EtOAc−hexane) to give **13** (343 mg, 69%) as a colorless glass: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30 (d, J = 8.0 Hz, 1H), 5.85 (d, J = 8.0 Hz, 1H), 5.82 (d, J = 6.2 Hz, 1H), 4.59 (dd, J = 4.4, 12.4 Hz, 1H), 4.48 (br s, 2H), 4.38 (dd, J = 5.2, 12.4 Hz, 1H), 3.99 (q, J = 6.9 Hz, 2H), 3.59 (q, J = 6.3 Hz, 2H), 2.97 (t, J = 6.3 Hz, 2H), 1.21 (t, J = 6.9 Hz, 3H), 0.86 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.0, 170.0, 162.1, 151.0, 138.6, 103.6, 90.4, 79.1, 75.0, 63.6, 37.8, 36.7, 25.6, 18.3, 12.9, −4.4, −5.1; MS (FAB) *m/z* 518, 520 (MH^+). Anal. Calcd for $C_{20}H_{31}BrN_2O_7Si$: C, 46.24; H, 6.02; N, 5.39. Found: C, 46.49; H, 6.30; N, 5.11.

4-Ethoxy-1-[2-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(carboxymethyl)-*β*-D-*ribo*-pentofuranosyl]-2(1*H*)-pyrimidone 3′,5′-Lactone (14). A solution of **12** (506 mg, 1.00 mmol) in THF (10 mL) was added to a SmI_2 solution in THF (0.1 M, 22.0 mL, 2.20 mmol) at −78 °C. After warming the mixture to room temperature, EtOAc (50 mL) and 1 N HCl (10 mL) were added, and the resulting mixture was partitioned. The organic layer was washed with H_2O (20 mL × 2) and brine (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 30% EtOAc−hexane) to give **14** (384 mg, 90%) as a colorless glass: mp 175−177 °C (MeOH−$CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.10 (d, J = 8.1 Hz, 1H, H-6), 6.07 (d, J = 7.6 Hz, 1H, H-1′), 5.87 (d, J = 8.2 Hz, 1H, H-5), 4.46 (d, J = 12.9 Hz, 1H, H-5′a), 4.40 (br s, 1H, H-4′), 4.37 (dd, J = 2.3, 12.9 Hz, 1H, H5′b), 4.00 (q, J = 7.0 Hz, 2H, 4-C*H*$_2$CH$_3$), 3.65 (d, J = 7.6 Hz, 1H, H-2′), 3.52 (s, 1H, 3′-OH), 2.78 (d, J = 15.2 Hz, 1H, H-3″a), 2.71 (d, J = 15.2 Hz, 1H, H-3″b), 1.21 (t, J = 7.0 Hz, 3H, 4-CH$_2$C*H*$_3$), 0.89 (s, 9H, *tert*-Bu), 0.10 (s, 3H, Me), −0.06 (s, 3H, Me); NOE, irradiate H-3″a, observed H-5′b (6.0%), H-3″b (4.3%), and no NOE enhancement was observed at H-4′; irradiate H-3″b, observed H-2′ (7.1%), H-3″a (7.4%), and no NOE enhancement was observed at H-4′; irradiate H-2′, observed H-6 (13.1%), H-1′ (2.8%), H-3′b (2.8%), and no NOE enhancement was observed at 3′-OH; irradiate 3′-OH, observed H-1′ (4.5%), H-4′ (1.9%), H-2′ (1.3%), H-3″b (1.9%) and no NOE enhancement was observed at H-6; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6, 161.9, 151.0, 136.4, 104.1, 85.6, 81.3, 74.1, 68.4, 40.7, 36.7, 25.7, 18.0, 12.9, −4.5, −4.8; MS (FAB) *m/z* 427 (MH^+). Anal. Calcd for $C_{19}H_{30}N_2O_7Si$: C, 53.50; H, 7.09; N, 6.57. Found: C, 53.61; H, 7.18; N, 6.21.

Reaction of 12 with Zinc. A mixture of **12** (47 mg, 0.1 mmol) and zinc (6.5 mg, 0.1 mmol) in toluene (10 mL) was heated under reflux for 2 h. The resulting mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 50% EtOAc−hexane) to give **16** (9 mg, 22%) as a white foam: ^1H NMR ($CDCl_3$, 500 MHz) δ 8.33 (br s, 1H), 7.34 (d, J = 8.1 Hz, 1H), 5.78 (d, J = 7.5 Hz, 1H), 5.84 (d, J = 8.1 Hz, 1H), 4.44 (m, 3H), 4.34 (dd, J = 5.1, 13.2 Hz, 1H), 2.10 (s, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); MS (EI) *m/z* 369 (M^+ − Me).

4-Ethoxy-1-[2-*O*-(*tert*-butyldimethylsilyl)-3-*C*-[(methoxycarbonyl)methyl]-*β*-D-*ribo*-pentofuranosyl]-2(1*H*)-pyrimidone (18). To a solution of **14** (214 mg, 0.500 mmol) in MeOH (5 mL) was added K_2CO_3 (62 mg, 0.50 mmol) at −70 °C. The mixture was stirred at the same temperature for 3 h. The insoluble K_2CO_3 was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 5% MeOH−$CHCl_3$) to give **18** (197 mg, 86%) as a colorless glass: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, J = 8.0 Hz, 1H), 5.80 (d, J = 8.0 Hz, 1H), 5.34

(d, J = 7.6 Hz, 1H), 4.80 (d, J = 7.6 Hz, 1H), 4.40 (br s, 1H), 4.00−3.98 (m, 4H), 3.73 (s, 3H), 3.15 (br s, 1H), 3.10 (d, J = 16.1 Hz, 1H), 2.66 (d, J = 16.1 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), −0.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.4, 163.6, 152.7, 143.5, 104.3, 96.1, 88.2, 63.8, 53.4, 40.54, 37.9, 27.1, 19.2, 14.2, −3.41; MS (EI) m/z 458 (M^+). Anal. Calcd for $C_{20}H_{34}N_2O_8Si$: C, 52.38; H, 7.47; N, 6.11. Found: C, 52.70; H, 7.74; N, 5.81.

4-Ethoxy-1-[2-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(carbamoylmethyl)-β-D-*ribo*-pentofuranosyl]-2(1*H*)-pyrimidone (17). To a solution of **14** (214 mg, 0.500 mmol) in MeOH (1 mL) was added saturated methanolic ammonia (5 mL) at −70 °C. The mixture was stirred at the same temperature for 3 h and then evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 10% MeOH−$CHCl_3$) to give **17** (217 mg, 98%) as a colorless glass: mp 170−172 °C (MeOH−$CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51 (d, J = 8.0 Hz, 1H), 6.68 (br s, 1H), 5.81 (d, J = 8.0 Hz, 1H), 5.66 (d, J = 7.6 Hz, 1H), 5.50 (br s, 1H), 4.58 (d, J = 7.4 Hz, 1H), 4.28 (br s, 1H), 4.00 (q, J = 7.1 Hz, 2H), 3.90 (dd, J = 2.2 Hz, 12.7 Hz, 1H), 3.79 (d, J = 12.7 Hz, 1H), 3.64 (br s, 1H), 2.86 (d, J = 15.9 Hz, 1H), 2.61 (d, J = 15.9 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), −0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 161.7, 151.1, 140.1, 138.8, 102.1, 86.8, 86.1, 78.0, 77.7, 60.9, 38.3, 35.6, 25.7, 17.8, 12.8, −4.2, −5.0; MS (FAB) m/z 443 (M^+). Anal. Calcd for $C_{19}H_{33}N_3O_7Si$: C, 51.45; H, 7.50; N, 9.47. Found: C, 51.45; H, 7.77; N, 9.79.

3-[(Benzyloxy)methyl]-1-(β-D-ribofuranosyl)uracil (19). A mixture of uridine (24.4 g, 100 mmol), DBU (30 mL, 200 mmol), and benzyl chloromethyl ether (20.8 mL, 150 mmol) in DMF (300 mL) was stirred at 0 °C for 30 min. After MeOH (10 mL) was added, the solution was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 10% EtOH−$CHCl_3$) to give **19** (33.9 g, 93%) as a white crystal: mp 265−268 °C (MeOH−$CHCl_3$); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.98 (d, J = 8.2 Hz, 1H), 7.35−7.26 (m, 5H), 5.81 (d, J = 4.8 Hz, 1H), 5.78 (d, J = 8.2 Hz, 1H), 5.41 (d, J = 5.6 Hz, 1H), 5.33 (d, J = 12.5 Hz, 1H), 5.30 (d, J = 12.5 Hz, 1H), 5.12 (t, J = 5.0 Hz, 1H), 5.09 (d, J = 5.4 Hz, 1H), 4.59 (s, 2H), 4.03 (ddd, J = 5.6, 4.8 Hz, 1H), 3.97 (ddd, J = 5.4, 5.0 Hz, 1H), 3.87 (m, 1H), 3.75 (ddd, J = 3.2, 5.0, 12.2 Hz, 1H), 3.65 (ddd, J = 3.2, 5.0, 12.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 172.4, 163.6, 152.7, 143.5, 104.3, 96.1, 88.2, 63.8, 53.4, 40.5, 37.9, 27.1, 19.2, 14.2, −3.41; MS (EI) m/z 364 (M^+). Anal. Calcd for $C_{17}H_{20}N_2O_7$: C, 56.04; H, 5.53; N, 7.69. Found: C, 56.01; H, 5.55; N, 7.50.

3-[(Benzyloxy)methyl]-1-[2,5-*O*-bis(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]uracil (21). A mixture of **19** (3.64 g, 10.0 mmol), $AgNO_3$ (3.74 g, 22.0 mmol), pyridine (4.04 mL, 50.0 mmol), and *tert*-butyldimethylsilyl chloride (3.32 g, 22.0 mmol) in THF (100 mL) was stirred at room temperature for 24 h. After MeOH (5 mL) was added, the precipitate was filtered off. The filtrate was evaporated under reduced pressure, and the residue was partitioned between EtOAc (1 L) and H_2O (300 mL). The organic layer was washed with water (200 mL × 3) and brine (200 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 30% EtOAc−hexane) to give **21** (5.28 g, 89%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 (d, J = 8.2 Hz, 1H), 7.27−7.16 (m, 5H), 5.86 (d, J = 3.7 Hz, 1H), 5.61 (d, J = 8.2 Hz, 1H), 5.39 (s, 2H), 4.60 (s, 2H), 4.06 (t, J = 4.0 Hz, 1H), 4.03−4.3.98 (m, 2H), 3.91 (dd, J = 1.3, 11.7 Hz, 1H), 3.73 (dd, J = 1.2, 11.7 Hz, 1H), 2.48 (br s, 1H), 0.85 (s, 9H), 0.81 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.9, 151.2, 138.9, 138.2, 128.6, 128.5, 128.3, 127.8, 102.0, 89.8, 89.5, 84.9, 72.3, 70.4, 70.3, 62.6, 26.1, 25.9, 18.6, 18.2, 11.7, −4.4, −5.0, −5.3, −5.4; MS (FAB) m/z 593 (MH^+). Anal. Calcd for $C_{29}H_{48}N_2O_7Si_2$: C, 58.75; H, 8.16; N, 4.72. Found: C, 58.56; H, 8.30; N, 4.52.

3-[(Benzyloxy)methyl]-1-[2,5-*O*-bis(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofran-3-ulosyl]uracil (23). To a mixture of molecular sieves 4A (8.00 g) and CrO_3 (3.20 g, 32.0 mmol) in CH_2Cl_2 (100 mL) was added pyridine (5.16 mL, 64.0 mmol) at 0 °C. The mixture was stirred for 30 min, Ac_2O (3.04 mL, 32.0 mmol) was added at the same temperature, and the whole was stirred for additional 15 min. Compound **21** (4.72 g, 8.00 mmol) in CH_2Cl_2 (50 mL) was added to the resulting mixture, which was stirred at room temperature for 30 min. The solution was diluted with Et_2O (1.5 L) and filtered through a Celite pad, and the filtrate was evaporated under reduced pressure. The residue was partitioned between EtOAc (500 mL) and H_2O (300 mL). The organic layer was washed with water (200 mL × 2) and brine (100 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 25% EtOAc−hexane) to give **23** (3.77 g, 80%) as a colorless glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (d, J = 8.2 Hz, 1H), 7.31−7.18 (m, 5H), 6.24 (d, J = 8.0 Hz, 1H), 5.79 (d, J = 8.2 Hz, 1H), 5.44 (d, J = 13.4 Hz, 1H), 5.41 (d, J = 13.4 Hz, 1H), 4.62 (s, 2H), 4.17 (s, 1H), 4.10 (d, J = 8.0 Hz, 1H), 3.87 (dd, J = 1.9, 11.3 Hz, 1H), 3.83 (dd, J = 1.6, 11.3 Hz, 1H), 0.83 (s, 9H), 0.77 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.6, 162.5, 151.4, 138.0, 128.5, 127.9, 103.5, 85.9, 82.2, 72.3, 70.6, 63.1, 26.0, 25.6, 18.5, 18.4, 11.7, −4.6, −5.2, −5.4, −5.5; MS (FAB) m/z 591 (MH^+). Anal. Calcd for $C_{29}H_{46}N_2O_7Si_2$: C, 58.95; H, 7.85; N, 4.74. Found: C, 58.68; H, 7.71; N, 4.39.

3-[(Benzyloxy)methyl]-1-[2-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofran-3-ulosyl]uracil (25). A solution of **23** (590 mg, 1.00 mmol) in 90% aqueous TFA (10 mL) was stirred at 0 °C for 30 min. The mixture was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, $CHCl_3$) to give **25** (323 mg, 68%) as a yellow glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 (d, J = 8.1 Hz, 1H), 7.27−7.16 (m, 5H), 5.77 (d, J = 8.1 Hz, 1H), 5.70 (d, J = 7.6 Hz, 1H), 5.40 (d, J = 13.5 Hz, 1H), 5.37 (d, J = 13.5 Hz, 1H), 4.58 (s, 2H), 4.57 (d, J = 7.6 Hz, 1H), 4.16 (br s, 1H), 3.85 (dd, J = 2.3, 12.1 Hz, 1H), 3.80 (dd, J = 2.2, 12.1 Hz, 1H), 0.75 (s, 9H), 0.01 (s, 3H), −0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.6, 162.4, 151.5, 140.6, 137.8, 128.6, 128.1, 127.9, 103.5, 91.0, 82.5, 75.1, 72.5, 70.6, 62.0, 25.9, 25.7, 18.3, −4.41, −5.3; MS (EI) m/z 476 (M^+).

3-[(Benzyloxy)methyl]-1-[5-*O*-(bromoacetyl)-2-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofran-3-ulosyl]-uracil (27). Compound **27** was prepared from **25** (323 mg, 0.68 mmol) as described above for the synthesis of **12**. After purification by column chromatography (SiO_2, 30% EtOAc−hexane), **27** was obtained as a yellow foam (348 mg, 86%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 (d, J = 8.1 Hz, 1H), 7.36−7.20 (m, 5H), 5.96 (d, J = 6.8 Hz, 1H), 5.88 (d, J = 8.1 Hz, 1H), 5.48 (d, J = 11.7 Hz, 1H), 5.47 (d, J = 11.7 Hz, 1H), 4.68 (s, 2H), 4.56 (dd, J = 1.0, 11.3 Hz, 1H), 4.49 (d, J = 6.8 Hz, 1H), 4.46 (br s, 1H), 4.45 (dd, J = 3.8, 11.3 Hz, 1H), 3.90 (s, 2H), 0.85 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.1, 166.3, 162.2, 151.4, 139.0, 137.9, 128.6, 128.0, 127.9, 103.6, 89.1, 75.3, 72.4, 70.65, 64.6, 26.0, 25.6, 25.5, 18.3, −4.4, −5.0; MS (FAB) m/z 597, 599 (MH^+).

3-[(Benzyloxy)methyl]-1-[2-*O*-(*tert*-butyldimethylsilyl)-3-*C*-(carboxymethyl)-β-D-*ribo*-pentofuranosyl]uracil 3′,5′-Lactone (29). Compound **29** was prepared from **27** (338 mg, 0.57 mmol) as described above for the synthesis of **14**. After purification by column chromatography (SiO_2, 30% EtOAc−hexane), **29** was obtained as a yellow glass (236 mg, 80%): mp 114−117 °C (MeOH−$CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.25 (m, 5H), 7.13 (d, J = 8.1 Hz, 1H), 6.06 (d, J = 7.5 Hz, 1H), 5.99 (d, J = 8.1 Hz, 1H), 5.48 (d, J = 11.7 Hz, 1H), 5.47 (d, J = 11.7 Hz, 1H), 4.67 (s, 2H), 4.46 (d, J = 13.1, 1H), 4.42 (br s, 1H), 4.38 (dd, J = 1.4, 13.1 Hz, 1H), 3.64 (d, J = 7.5 Hz, 1H), 3.52 (s, 1H), 2.78 (d, J = 15.3 Hz, 1H), 2.71 (d, J = 15.3 Hz, 1H), 0.87 (s, 9H), 0.09 (s, 3H), −0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.4, 137.3, 128.6, 128.0, 127.9, 104.3, 85.5, 81.3, 74.1, 72.3, 70.6, 68.4, 40.6, 25.7, 17.9, −4.55, −4.68; MS (FAB) m/z 519 (MH^+). Anal. Calcd for $C_{25}H_{34}N_2O_8Si$: C, 57.90; H, 6.61; N, 5.40. Found: C, 57.64; H, 6.64; N, 5.76.

1-[5-*O*-(Bromoacetyl)-2-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofran-3-ulosyl]uracil (26). Compound **26** was prepared from **24**[18] (4.48 g, 12.6 mmol) as described above for the synthesis of **12**. After purification by column chromatography (SiO_2, 30% EtOAc−hexane), **26** (4.21 g, 70%) was obtained as a yellow foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.69 (br s, 1H), 7.49 (d, J = 8.2 Hz, 1H), 5.97 (d, J = 7.1 Hz, 1H),

5.84 (d, J = 8.1 Hz, 1H), 4.56 (d, J = 11.9 Hz, 1H), 4.47 (d, J = 7.1 Hz, 1H), 4.44 (dd, J = 2.0, 3.5 Hz, 1H), 4.41 (dd, J = 3.6, 11.9 Hz, 1H), 3.91 (s, 2H), 0.83 (s, 9H), 0.09 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.2, 166.4, 163.2, 150.6, 140.3, 104.1, 87.9, 78.8, 75.4, 64.5, 25.8, 25.6, 25.5, 18.3, −4.4, −5.0; MS (FAB) m/z 477, 479 (MH^+).

1-(2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-(carboxymethyl)-*β*-D-*ribo*-pentofuranosyl]uracil 3′,5′-Lactone (28). A solution of **26** (477 mg, 1.00 mmol) in THF (10 mL) was added dropwise over 2 h by a syringe pump to a SmI_2 solution in THF (0.1 M, 22.0 mL, 2.20 mmol) at −78 °C. After warming the mixture to room temperature, EtOAc (50 mL) and 1 N HCl (10 mL) were added, and the resulting mixture was partitioned. The organic layer was washed with H_2O (20 mL × 2) and brine (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 50% EtOAc−hexane) to give **28** (337 mg, 85%) as a white solid: mp 243−244 °C (MeOH−$CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (br s, 1H, NH), 7.16 (d, J = 8.1 Hz, 1H, H-6), 5.98 (d, J = 7.5 Hz, 1H, H-1′), 5.84 (d, J = 8.1 Hz, 1H, H-5), 4.46 (d, J = 13.1, 1H, H-5′a), 4.41 (br s, 1H, H-4′), 4.37 (dd, J = 2.4, 13.1 Hz, 1H, H-5′b), 3.66 (d, J = 7.5 Hz, 1H, H-2′), 3.49 (s, 1H, 3′-OH), 2.78 (d, J = 15.3 Hz, 1H, H-3″a), 2.71 (d, J = 15.3 Hz, 1H, H-3″b), 0.91 (s, 9H, *tert*-Bu), 0.11 (s, 3H, Me), −0.02 (s, 3H, Me); NOE, irradiate H-3″a, observed H-5′b (9.5%), H-3″b (6.1%), and no NOE enhancement was observed at H-4′; irradiate H-3″b, observed H-2′ (8.7%), H-3″a (5.3%), and no NOE enhancement was observed at H-4′; irradiate H-2′, observed H-6 (12.6%), H-1′ (2.7%), H-3″b (2.1%), and no NOE enhancement was observed at 3′-OH; irradiate 3′-OH, observed H-1′ (4.3%), H-4′ (1.5%), H-2′ (1.2%), H-3″b (1.5%), and no NOE enhancement was observed at H-6; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6, 162.4, 150.3, 131.6, 104.4, 85.0, 81.4, 74.1, 68.4, 40.6, 25.7, 18.0, 11.7, −4.5, −4.6; MS (FAB) m/z 399 (MH^+). Anal. Calcd for $C_{17}H_{26}N_2O_7Si$: C, 51.24; H, 6.58; N, 7.03. Found: C, 51.00; H, 6.67; N, 7.06.

Synthesis of 28 by Debenzyloxymethylation of 29. A mixture of **29** (59 mg, 0.10 mmol) and $Pd(OH)_2$ (5 mg) in MeOH (3 mL) was stirred under atmospheric hydrogen for 30 min. The resulting mixture was filtered through a Celite pad, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, $CHCl_3$) to give **28** (42 mg, 98%) as a white powder.

1-[2-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-(carbamoylmethyl)-*β*-D-*ribo*-pentofuranosyl]uracil (32). To a solution of **28** (808 mg, 2.03 mmol) in MeOH (5 mL) was added saturated methanolic ammonia (20 mL) at −70 °C. The mixture was stirred at the same temperature for 3 h and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 10% MeOH−$CHCl_3$) to give **32** (825 mg, 98%) as a colorless glass: mp 242−243 °C (MeOH−$CHCl_3$); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.3 (br s, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.45 (br s, 1H), 7.02 (br s, 1H), 5.93 (d, J = 7.6 Hz, 1H), 5.01 (d, J = 8.2 Hz, 1H), 4.09 (d, J = 7.6 Hz, 1H), 4.00 (br s, 1H), 3.71 (d, J = 10.5 Hz, 1H), 3.57 (d, J = 10.5 Hz, 1H), 3.64 (br s, 1H), 2.47 (d, J = 12.5 Hz, 1H), 2.46 (d, J = 12.5 Hz, 1H), 0.79 (s, 9H), 0.00 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 172.4, 162.9, 151.1, 140.8, 102.6, 86.5, 85.0, 77.5, 60.7, 38.1, 25.6, 17.6; MS (FAB) m/z 415 (M^+). Anal. Calcd for $C_{17}H_{29}N_3O_7Si$: C, 49.14; H, 7.03; N, 10.11. Found: C, 49.10; H, 7.02; N, 10.13.

1-[3-*C*-(Carbamoylmethyl)-*β*-D-*ribo*-pentofuranosyl]uracil (33). A mixture of **32** (281 mg, 0.678 mmol) and NH_4F (502 mg, 13.6 mmol) in MeOH (20 mL) was heated under reflux for 2 h and evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ (50 mL) and H_2O (50 mL). The aqueous layer was washed with $CHCl_3$ (30 mL × 2) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 10% MeOH−$CHCl_3$) to give **33** (205 mg, 99%) as a white powder: mp 242 °C dec (H_2O−MeOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.45 (br s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.47 (br s, 1H), 7.06 (br s, 1H), 5.91 (d, J = 7.9 Hz, 1H), 5.67 (d, J = 8.1 Hz, 1H), 5.56 (d, J = 6.1 Hz, 1H), 5.23 (t, J = 3.9 Hz, 1H), 5.19 (s, 1H), 3.96 (br s, 1H), 3.94 (dd, J = 6.3, 7.8 Hz, 1H), 3.71 (ddd, J = 1.5, 3.4, 12.0 Hz, 1H), 3.59 (ddd, J = 3.0, 3.4, 12.7 Hz, 1H), 2.57 (d, J = 15.3 Hz, 1H), 2.50 (d, J = 15.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 173.0, 163.1, 151.1, 141.0, 102.1, 86.9, 85.6, 77.1, 76.3, 60.7; MS (FAB) m/z 302 (MH^+). Anal. Calcd for $C_{11}H_{15}N_3O_7$: C, 43.86; H, 5.02; N, 13.95. Found: C, 43.97; H, 4.84; N, 13.65.

JO961665F