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A Highly Stereoselective Samarium Diiodide-Promoted Aldol Reaction with 1′-Phenylseleno-2′-keto Nucleosides. Synthesis of 1′α-Branched Uridine Derivatives

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Since 1′-branched nucleosides are biologically important targets in medicinal chemistry, more efficient methods for preparing them are required. The 1′α-branched uridine derivatives were successfully synthesized via a samarium diiodide (SmI_2)-promoted aldol reaction. Treatment of the 1′α-phenylseleno-2′-ketouridine derivative **6**, readily prepared from uridine, with SmI_2 at −78 °C in THF reductively cleaved the anomeric Se−C bond to generate the corresponding samarium enolate, which was highly stereoselectively condensed with aldehydes, such as PhCHO, MeCHO, *i*-PrCHO, or $(CH_2O)_n$, to give the corresponding 1′α-1″S-branched products **12a**−**d**. This is the first time an enolate has been generated by reductively cleaving a C−Se bond. The highly selective stereochemical results suggest that the aldol reaction proceeds via a chelation-controlled transition state. When an excess of aldehyde was used and the reaction mixture was gradually warmed, the tandem aldol-Tishchenko reaction proceeded to give the "arabino-type" nucleosides **14a**−**c**, having a 2′-"up" hydroxyl and 1′α-1″S-branched chain. 1′α-Hydroxymethyluridine (**21**), which is the uracil version of the antitumor antibiotic angustmycin C, was synthesized from the aldol reaction product **10**.

Introduction

Branched-chain sugar nucleosides are biologically important targets in medicinal chemistry, and a number of procedures for preparing them have been developed.[2]

The antibiotic angustmycin C (**1**), the structure of which was identified as the adenosine analogue bearing a hydroxymethyl group at the 1′α-position, is known to show antitumor activity.[3] 2′-Deoxy-1′-pivaloyluridine (**2**) proved useful in producing a radical at the 1′-position of the 2′-deoxyuridine residue in oligonucleotides, which was effective in studying the mechanism of oxidative damage of DNA.[4] Most recently, the North-form (3′-endo)-locked 1′-branched nucleoside derivative **3** was effectively used for investigating the relationship between the DNA/RNA duplex conformation and the RNase H cleavage reaction.[5] However, despite their biological importance, syntheses of nucleoside analogues branched at the anomeric 1′-position are not as common[6−8] as syntheses of nucleoside derivatives branched at the 2′- and 3′-positions.[2] Most 1′-branched nucleosides are prepared from the corresponding ribose derivatives branched at the 1-position via glycosidation or nucleobase construction.[6] These methods are not very practical and have drawbacks: (1) the preparation of the 1′-branched sugars requires many reaction steps and the overall yields are low and (2) the stereoselective introduction or construction of the nucleobase is tedious.

1′-Branched nucleosides are considered to be a kind of *C*-glycoside having both a nucleobase and a carbon substituent at the anomeric position of ribose or 2-deoxyribose. *C*-Glycosides are gaining increasing interest since they appear as fragments in the structures of a number of natural products.[9] Moreover, because of their resistance to hydrolysis, *C*-glycosides are expected to be stable

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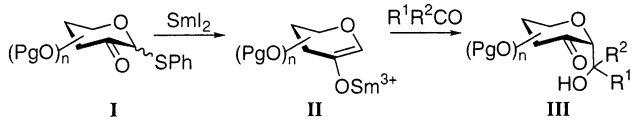
mimics for natural *O*-glycosides exhibiting biological activity.[10,11] Although the methods for the synthesis of *C*-glycosides have been extensively studied, stereoselective construction of the desired *C*-glycosidic linkage is often difficult.[12] These results on *C*-glycoside synthesis suggest that the difficulty in synthesizing 1′-branched nucleosides arises because both the α-*C*- and the *β*-*N*-glycosidic bonds have to be constructed stereoselectively.

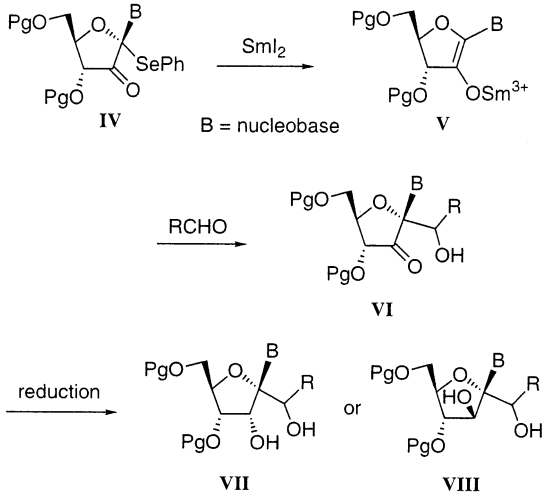
Several years ago, Tanaka and co-workers reported an efficient method for preparing 1′-branched nucleosides from common ribonucleosides, such as uridine, via an electrophilic addition reaction on a 1′,2′-unsaturated uridine derivative.[7] Using this method, they prepared the antitumor 1′-cyano cytosine nucleoside **4**.[7b] Most recently, we stereoselectively synthesized 1′-vinyl pyrimidine ribonucleosides starting from uridine, via a novel intramolecular radical cyclization reaction with a silyl tether[13] as the key step.[8] These are the only two practical examples reported so far that provide 1′-branched nucleosides in rather good overall yield because they use natural nucleosides as the synthon thereby shortening the reaction steps. However, the 1′-carbon substituents to be introduced by these two methods are limited, and the biological activities of 1′-branched nucleosides have not been systematically investigated. Consequently, alternative efficient methods, which would allow the preparation of a variety of 1′-branched nucleosides, are required.

We have already developed a very useful SmI_2-promoted[14] aldol-type *C*-glycosidation reaction (Scheme 1),[15] which offers several distinct advantages: (1) the phenylthio-2-ulose derivatives **I**, the precursors for generating the enolates, are stable and easy to prepare; (2) the regioselective enolization at the anomeric position of the ulose derivatives can be achieved by SmI_2-promoted reductive cleavage of a C−S bond at the anomeric

SCHEME 1



SCHEME 2



position to generate the enolate **II**; (3) the substrates, normally unstable under basic and/or acidic conditions, can now be used since the reaction proceeds under neutral conditions at −78 °C; and (4) the reaction is stereoselective to give the corresponding α-*C*-glycosides **III** as the major product in high yield. We carried out the first synthesis of the tricyclic-sugar nucleoside antibiotic herbicidin B using the SmI_2-promoted aldol-type *C*-glycosidation reaction as the key step.[15b] We also developed an efficient method of preparing 3′-branched nucleosides using the SmI_2-promoted intramolecular Reformatsky reaction as the key step,[16] showing that SmI_2 is particularly effective in nucleoside chemistry. With these encouraging results in mind, we decided to investigate the synthesis of 1′-branched nucleosides using the SmI_2-promoted aldol reaction as the key step.

Results and Discussion

Synthetic Plan. Our synthetic plan, using the 1′-phenylseleno-2′-ketouridine derivative **IV** as the precursor for the 1′-enolate, is summarized in Scheme 2. We previously reported that a phenylseleno group could be introduced stereoselectively at the 1′α-position of 2′-ketouridine derivatives,[8] which readily provides the substrate **IV** for the SmI_2-promoted aldol reaction. We speculated that if the phenylseleno group at the 1′-position of **VI** was reductively cleaved by SmI_2 like the anomeric phenylthio group of the ulose **I**, the samarium enolate **V** would be formed. The condensation reaction between the resulting enolate **V** and an aldehyde would give the corresponding 1′-branched nucleosides **VI** as the aldol reaction products. In this reaction, the stereochemistry of the product **VI** could be controlled via a chelation transition state due to the high affinity of samarium for

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(16) Ichikawa, S.; Shuto, S.; Minakawa, N.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 1368−1375.

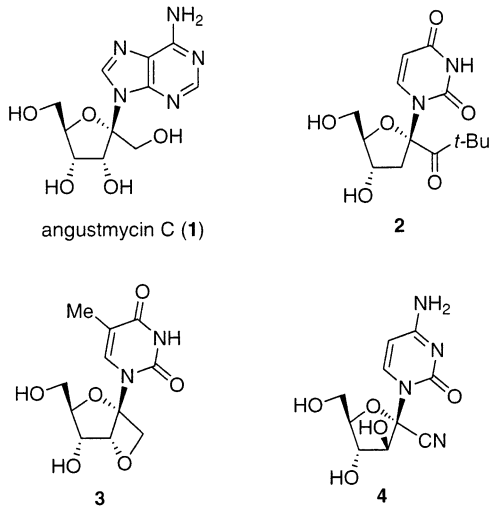


FIGURE 1. Examples of biologically important 1′-branched nucleosides.

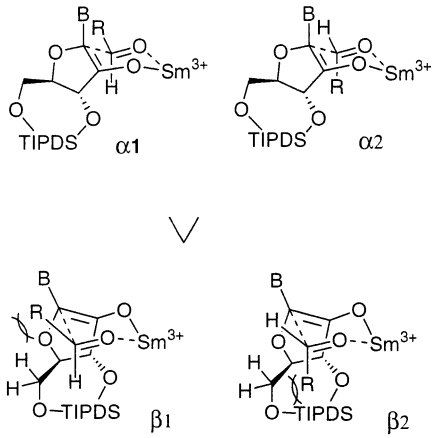
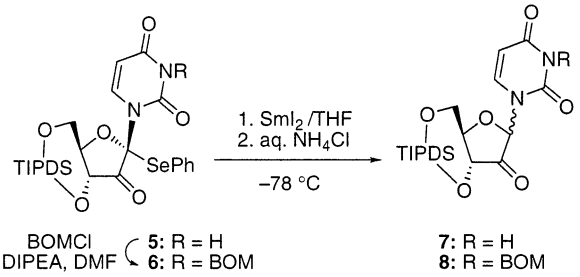


FIGURE 2. A possible chelation-controlled reaction pathway of the SmI_2-promoted aldol reaction to stereoselectively produce the 1′α-branched products.

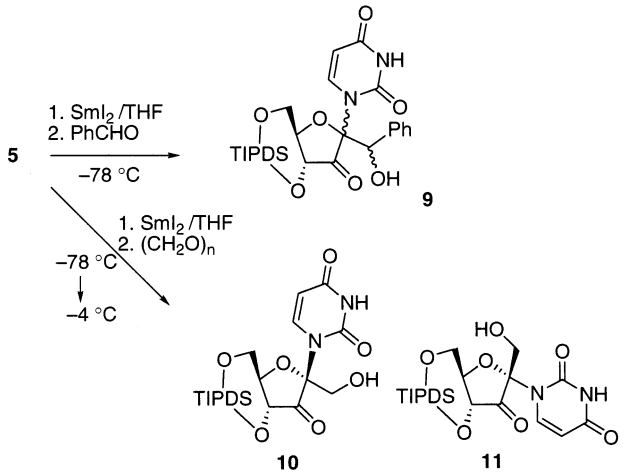
oxygen.[14] We anticipated that the chelation-controlled reaction would selectively occur from the α-direction at the 1′-position via the transition states α**1** or α**2** to give the corresponding α-product **VI** because of steric repulsion by the tetrahedral 5′-methylene moiety when the aldehyde approaches from the *β*-face via transition states *β***1** or *β***2** (Figure 2). Stereoselective reduction of the 2′-carbonyl of **VI** would give the "ribo-type" (**VII**) and the "arabino-type" (**VIII**) 1′-branched nucleosides.

SmI_2-Promoted Aldol Reaction of 2′-Keto Uracil Nucleosides. First, the SmI_2-promoted generation of the 1′-enolate **V** (Scheme 2) was examined. When 3′,5′-*O*-[tetraisopropyldisiloxane-1,3-diyl (TIPDS)]-1′-phenylseleno-2′-ketouridine (**5**) was treated with 2.5 equiv of SmI_2 at −78 °C in THF, the starting material immediately disappeared on TLC. After the reaction was quenched with aqueous NH_4Cl, the de-phenylselenated product **7** was obtained in about 90% yield as a mixture of anomers. The same treatment of the corresponding *N*-3-benzyloxymethyl (BOM) derivative **6** also gave the de-selenated product **8** in high yield. These results showed that SmI_2-promoted reductive removal of the

SCHEME 3



SCHEME 4



phenylseleno group occurred to generate the desired 1′-enolates.

The aldol reaction was subsequently investigated; the samarium enolate solution in THF prepared with 2.1 equiv of SmI_2 at −78 °C was treated with an aldehyde as the electrophile. The *N*-3-unprotected 2′-keto nucleoside **5** was first used as the substrate (Scheme 4), and thus **5** was successively treated with SmI_2 and PhCHO (3 equiv) at −78 °C in THF. Although the aldol reaction proceeded efficiently to produce the corresponding reaction product **9** in 89% yield, it was nonstereoselective and ^{1}H NMR analysis indicated that the product was a mixture of the four diastereomers at the 1′- and 1″-positions.[17,18] When a similar aldol reaction of **5** was examined with an excess of paraformaldehyde [$(CH_2O)_n$] as the electrophile, the 1′α-hydroxymethyl product **10** was stereoselectively obtained in 52% yield along with its 1′*β*-anomer **11** in 13% yield.

The aldol reactions of the *N*-3-BOM substrate **6** were next investigated, and the results are summarized in Table 1 and Scheme 5. When the samarium enolate prepared from **6** with SmI_2 (2.1 equiv) was subjected to the aldol reaction with PhCHO (3 equiv) as the electrophile at −78 °C in THF, the expected 1α′-branched nucleoside **12a** was obtained in 76% yield along with its anomer **13a** in 10% yield (entry 1). Surprisingly, the reaction was almost completely stereocontrolled at the 1″-position to produce the 1″*S*-product, the stereochemistry of which was confirmed as described below. A

(17) The numbering used in this paper considers the side-chain carbon adjacent to the 1′-position as 1″.

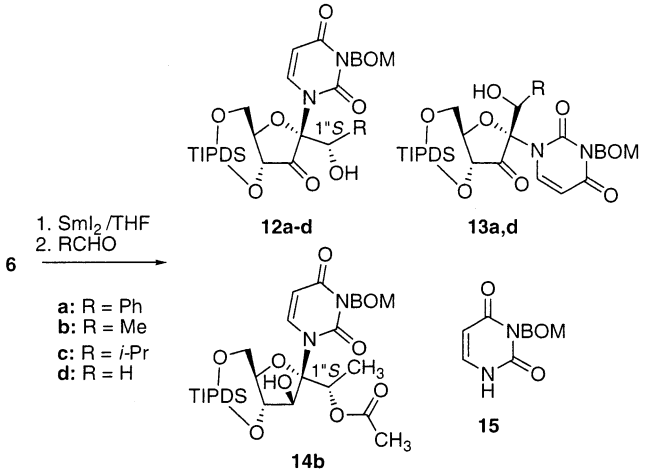
(18) A *β*-branched product seemed to be in equilibrium between the 2′-keto form and its 2′-hydrate.

TABLE 1. SmI_2-Promoted Aldol Reaction between 6 and Aldehydes.

entry	electrophile (equiv)	temp, °C	1′-branched products (yield, %)[a]		α/β
1	PhCHO (3)	−78	**12a** (76)	**13a** (10%)	7.6:1
2	PhCHO (1.2)	−78	**12a** (60)[b]		α
3	MeCHO (3)	−78	**12b** (29)	**14b** (52%)	α
4	*i*-PrCHO (3)	−78	**12c** (48)[b]		α
5	*i*-PrCHO (5)	−78	**12c** (59)[c]		α
6	*t*-BuCHO (3)	−78→rt	−[d]		
7	$(CH_2O)_n$ (3)	−78→0	**12d** (57%)	**13d** (12%)[d]	4.8:1

[a] Isolated yield. [b] The reduction product **8** was obtained (30% in entry 2, 33% in entry 4). [c] Reaction was quenched with TMSCl (10 equiv). [d] *N*-3-BOM-uracil (**15**) was obtained (81% in entry 6, 27% in entry 7).

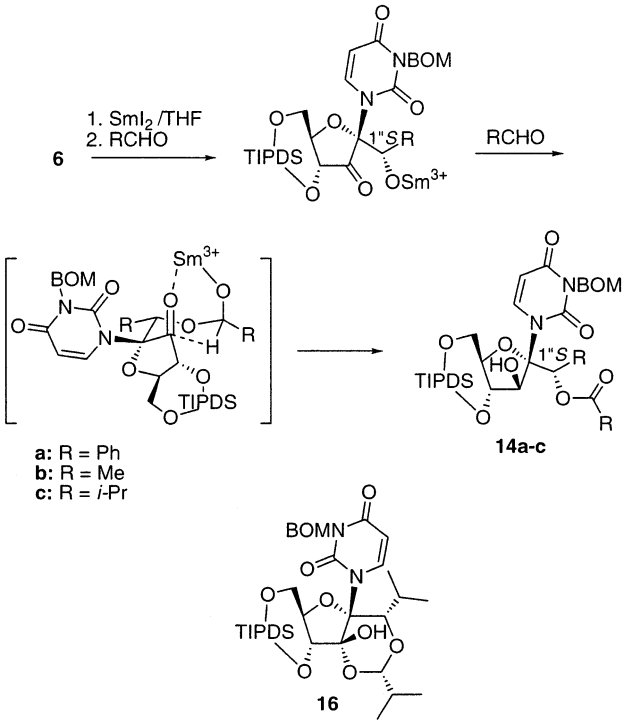
SCHEME 5



similar reaction with 1.2 equiv of PhCHO lowered the yield of the 1′α-branched nucleoside **12a** (60%) and the 1′-reduced product **8** was also formed in 30% yield (entry 2). Other aldehydes were examined as possible electrophiles. The reaction with 3 equiv of MeCHO instead of PhCHO under the same conditions as those for entry 1 gave a low yield of the aldol reaction product **12b** (29%) with the 1′α-branched-1″*S*-stereochemistry. In this reaction, the Tishchenko reaction of the aldol product **12b** occurred to afford the "arabino-type" 1′-α-branched nucleoside **14b** as the major product in 52% yield (entry 4). The reaction with 3 equiv of *i*-PrCHO at −78 °C was rather slow but gave the aldol product **12c** with the same 1′α-branched-1″*S*-stereochemistry in 48% yield accompanied by the reduction product **8** (33%). When the reaction was performed with 5 equiv of *i*-PrCHO in the presence of TMSCl, the yield of **12c** increased somewhat (59%, entry 5). The aldol reaction seemed to be sensitive to the steric hindrance of the electrophile. When the highly sterically hindered *t*-BuCHO was used as the electrophile, the aldol reaction did not proceed at −78 °C, and gradual warming of the reaction mixture to room temperature resulted in glycosidic bond cleavage to produce the 3-BOM-uracil (**15**) (entry 6). Although paraformaldehyde was also inactive as the electrophile at −78 °C, the aldol reaction proceeded slowly to give the α-product **12d** as the major product when the reaction mixture was warmed (entry 7).

This is the first example that generates an enolate by reductively cleaving a C−Se bond, although SmI_2 has

SCHEME 6



been known to reduce other carbon−heteroatom bonds, such as C−O or C−S bonds, when a carbonyl group is present at the adjacent position.[15,16,19]

SmI_2-Promoted Tandem Aldol-Tishchenko Reaction of the 2′-Keto Nucleoside 6. It is known that in SmI_2-promoted aldol reactions, the resulting aldols are often further reduced via the Tishchenko reaction.[20] Such reductions stereoselectively afford the corresponding *anti*-1,3-diol monoesters through a chelation-controlled pathway.[20] As described above, in this study the Tishchenko-type reduction of the aldol **12b** actually proceeded to afford the corresponding *anti*-1,3-diol product, the "arabino-type" 1′-branched nucleoside **14b**, when MeCHO was used as the electrophile (Table 1, entry 3). The biological activity of "arabino-type" 1′-branched nucleosides, i.e., nucleosides having 2′-"up" substituent, is interesting to us since various "arabino-type" nucleoside analogues are known to show potent antitumor and/or antiviral effect, as typified by the clinically useful antileukemic drug 1-β-D-arabinofuranosylcytosine (ara-C) and the antitumor "arabino-type" 1′-cyanocytosine nucleoside **4**.[7b] We therefore decided to investigate the tandem aldol-Tishchenko reaction of the 2′-keto nucleoside **6** (Scheme 6 and Table 2).

The reactions were carried out as follows: To the THF solution of the samarium enolate of **6**, prepared with 2.1 equiv of SmI_2, was added 5 equiv of an aldehyde at −78 °C, and the mixture was warmed gradually. The reaction with PhCHO produced the expected *anti*-1,3-diol product, the "arabino-type" 1′-branched nucleosides **14a**, in 74% yield (entry 1). A similar treatment with MeCHO suc-

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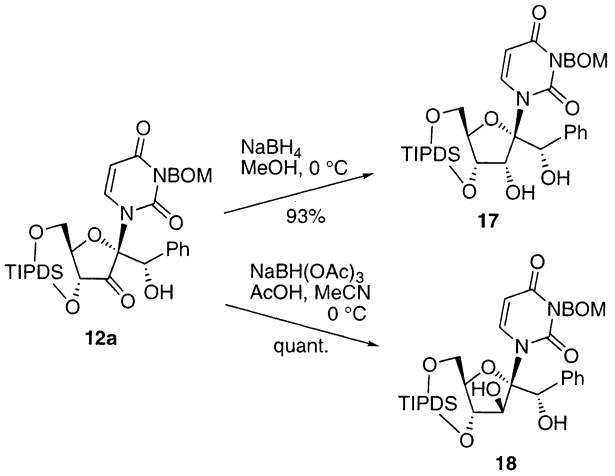
TABLE 2. SmI_2-Promoted Tendem Aldol-Tishchenco Reaction of 6

entry	electrophile (equiv)	temp (°C)	1′-branched products (yield, %)[a]	
1	PhCHO (5)	−78 to rt	**14a** (74)	
2	MeCHO (5)	−78 to −10	**14b** (83)	
3	*i*-PrCHO (5)	−78 to −10	**14c** (55)	**16** (41)

[a] Isolated yield.

SCHEME 7



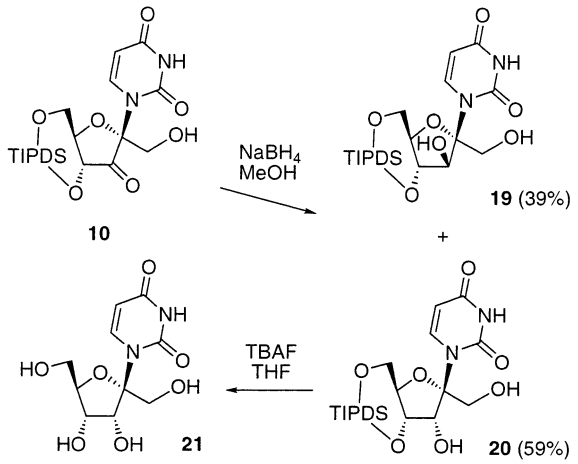
cessfully gave the desired product **14b** in 83% yield (entry 2). When *i*-PrCHO was used as an electrophile, the reaction also stereoselectively proceeded to give the corresponding *anti*-1,3-diol product (entry 3), which was obtained as the cyclic hemiketal **16** (41%), along with the usual *O*-acylated product **14c** (55%). These results showed that the tandem aldol-Tishchenko reaction effectively proceeded via the six-membered chelation-controlled pathway as shown in Scheme 6.

Reduction of the 2′-Carbonyl of the Aldol Reaction Products by Hydride Reagents. The aldol reaction product **12a** was subjected to reduction at the 2′-keto moiety with hydride reagents. We found that complete stereochemical reversal of the 2′-carbonyl reduction of **12a** was possible, depending upon the reducing reagent, as shown in Scheme 7. Thus, the "ribo-type" **17** was stereoselectively obtained in high yield when **12a** was reduced with $NaBH_4$ in MeOH, where the "arabino-type" **18** was quantitatively produced by reduction with $NaBH(OAc)_3$ in MeCN.

On the other hand, although reductions of the 1′-hydroxymethyl-2′-keto derivatives **10** and **12d** with various reagents, such as $NaBH_4$, K-selectride, DIBAL-H, or $LiAlH(Ot\text{-}Bu)_3$, were examined, none of these was highly stereoselective. For example, **10** was reduced with $NaBH_4$ in MeOH to give a mixture of the "arabino-type" **19** and the "ribo-type" **20** in about 2:3 ratio, which could be readily separated by the usual silica gel column chromatography. Deprotection of **20** with TBAF in THF furnished the 1′α-hydroxymethyl uridine (**21**), which is the uracil version of angustmycin C (Scheme 8).

Stereochemistry of the SmI_2-Promoted Aldol Reaction. The structures of the products including stereochemistry were confirmed by NOE experiments, NOESY and HMBC spectra, and modified Mosher's method, as shown in Figure 3.

SCHEME 8



Compound **17**, obtained via the aldol reaction with PhCHO, was derivatized into the corresponding 2′,3′-*O*-isopropylidene derivative **22**, which clearly showed its 2′,3′-*cis*-diol structure. The 1α′-branched-1″*S* stereochemistry of **17** was successfully determined by the NOESY spectrum, after its conversion into the corresponding 1″,2′-*O*-isopropylidene derivative **23** (Figure 3A). The 1′α-1″*S*-stereochemical result of the aldol reaction with *i*-PrCHO was determined based on the structure analysis of the hemiketal product **16** by its HMBC and NOESY spectra, as shown in Figure 3B. The 1″-configuration of the aldol reaction with MeCHO was also confirmed as *S* by the modified Mosher's method,[21] after conversion of the aldol-Tishchenko reaction product **14b** into the corresponding *R*- and *S*-MTPA esters **24R** and **24S**. Its 2′*S*-configuration was confirmed by NOE experiments (Figure 3C). Compound **21** was identified as the uracil version of angustmycin C from NOE experiments of the diacetate **25** (Figure 3D).

Therefore, the aldol reactions of **6** were highly stereoselective with the major products having the same 1′α-branched-1″*S*-stereochemisty. The reactions with MeCHO and *i*-PrCHO as the electrophile, in particular, produced only the 1′α-branched-1″*S*-products (Table 1, entries 2−5). The highly selective formation of the 1′α-branched products may be explained by the steric repulsion due to the tetrahedral 5′-methylene moiety when the aldehyde approaches from the *β*-face via the transition states *β***1** or *β***2**. The highly selective 1″*S*-stereochemical results suggest that the aldol reaction proceeds via the chelation-controlled pathway of the transition state α**2** rather than transition state α**1** (Figures 2 and 4).[22] Dubois and co-workers reported that the stereochemical results of the chelation-controlled aldol reaction of 2-substituted cyclopentanones could be dependent upon the bulkiness of the 2-substituent (R), as shown in Figure 5.[23] On the other hand, Tanaka and co-worker reported that in 2′-substituted 1′,2′-unsaturated uracil nucleosides, the 1′,2′-unsaturated bond is not conjugated with the uracil base,[24] which suggests that in the samarium enolate **V** (Scheme 2), the enol moiety is not conjugated with the base moiety,

(21) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(22) It might be that the oxygen of the 2-keto and/or BOM moiety also interacts with the Sm^{3+} in the chelation-controlled pathway.

(23) Fellmann, P.; Dubois, J.-E. *Tetrahedron* **1978**, *34*, 1349−1357.

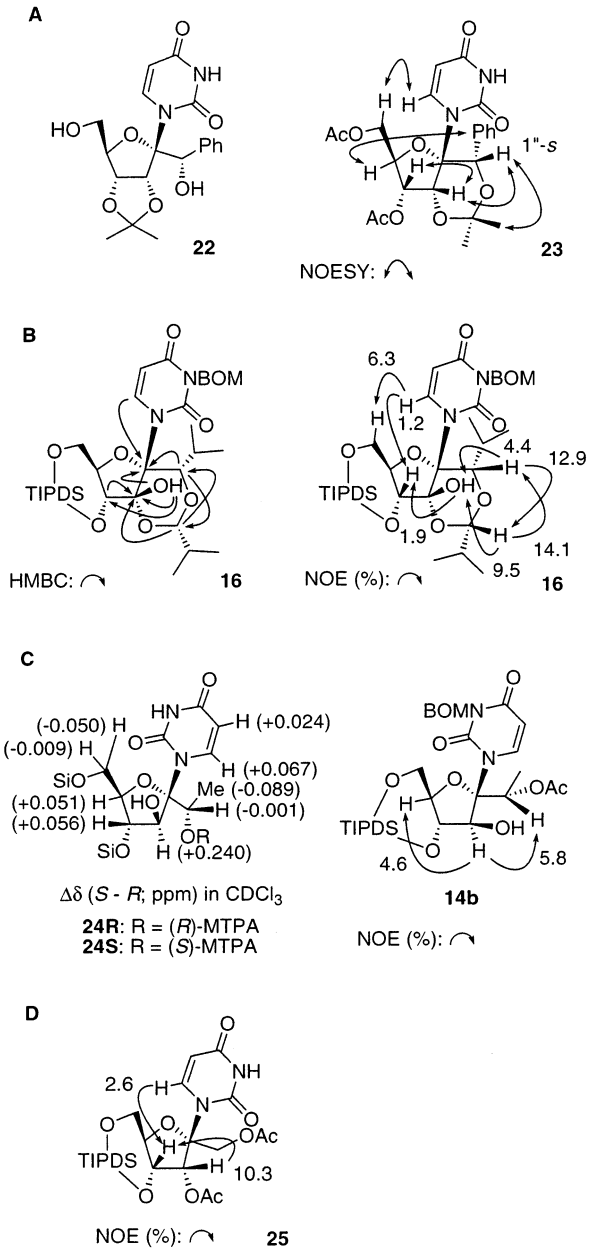


FIGURE 3. Structural determination of the compounds.

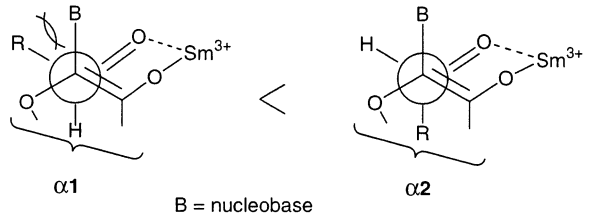


FIGURE 4. A possible chelation-controlled reaction pathway of the SmI_2-promoted aldol reaction to stereoselectively produce the 1′α-branched-1″*S*-products.

namely, the two moieties do not lie in the same plane. Accordingly, the steric repulsion by the base moiety would be rather significant in the aldol reaction to produce the 1″*S*-product highly stereoselectively via the α**2** transition state, which is similar to Dubois' cyclopentanone model. This would be in agreement with the fact that the stereoselectivity decreased in the reaction of the *N*-3-free substrate **5**, in which the base moiety is less bulky compared with that of **6**.

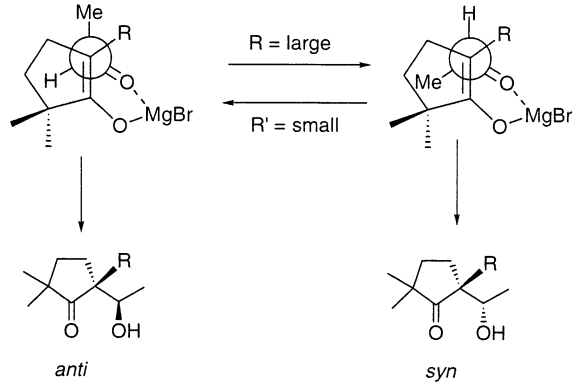


FIGURE 5. Dubois' chelation-controlled model.

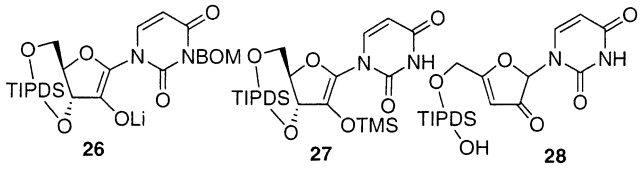


FIGURE 6.

We examined the aldol reaction between the lithium 1′-enolate **26**[25] (Figure 5) and PhCHO under various conditions. As a result, the reaction was nonstereoselective to give a mixture of the aldol reaction product in low yield. Although we also investigated the Lewis acid-promoted aldol reaction with 2-*O*-TMS-enol ether **27**[26] as the substrate, it produced the enone **28** as the major product. These experiments clearly demonstrate the usefulness of the SmI_2-promoted aldol reaction with the 1′α-phenylseleno-2′-ketouridine derivative **6** as the substrate.

Conclusion

The 1′-samarium enolate was successfully prepared from the 1′α-phenylseleno-2′-ketouridine derivative **6** by treating it with SmI_2, which was highly stereoselectively condensed with aldehydes to give the corresponding 1′α-1″*S*-branched uridine products **12a**−**d**. The excellent stereochemical results suggest that the aldol reaction proceeds via a chelation-controlled transition state. The SmI_2-promoted tandem aldol-Tishchenko reaction of **6** also effectively proceeded to produce the "arabino-type" 1′α-1″*S*-branched nucleoside products **14a**−**c**, when an excess of the aldehyde was used. This is the first example in nucleoside chemistry in which an aldol reaction was used effectively.

Experimental Section

NMR chemical shifts are reported in ppm downfield from TMS and *J* values are given in hertz. The ^{1}H NMR assign-

(24) Kumamoto, H.; Shindoh, S.; Tanaka, H.; Itoh, Y.; Haraguchi, K.; Gen, E.; Kittaka, A.; Miyasaka, T.; Kondo, M.; Nakamura, K. T. *Tetrahedron* **2000**, *56*, 5363−5371.

(25) Prepared from *N*-3-BOM-3′,5′-*O*-TIPDS-2′-ketouridine by treating it with lithium hexamethyldisilazide in THF.

(26) The 1′-lithium enolate of 3′,5′-*O*-TIPDS-2′-ketouridine (see ref 8) was treated with TMSCl at −78 °C in THF to afford **27**.

ments reported for key compounds are in agreement with 2D NMR spectra. Thin-layer chromatography was done on Merck coated plates $60F_{254}$. Silica gel chromatography was done on Merck silica gel 5715 or Kanto Chemical silica gel 60 N (neutral). Reactions were carried out under an argon atmosphere.

Reductive De-phenylselenation of 5 and 6. To a solution of SmI_2 (0.10 M solution in THF, 2.5 mL, 0.25 mmol) was added dropwise a solution of **5** (64 mg, 0.10 mmol) or **6** (76 mg, 0.10 mmol) in THF (1.5 mL) at −78 °C. After **5** or **6** disappeared on TLC, saturated aqueous NH_4Cl was added to the mixture, and the whole was warmed to room temperature. The mixture was partitioned between AcOEt and H_2O, the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, hexane:AcOEt = 3:1 then 2:1) to give **7** (43 mg, 0.089 mmol, 89%) or **8** (54 mg, 0.090 mmol, 90%).

3-*N*-Benzyloxymethyl-1-[1-phenylseleno-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*erythro*-2-pentosulofuranosyl]uracil (6). A mixture of **5** (2.74 g, 4.28 mmol), benzyloxymethyl chloride (712 μL, 5.14 mmol), and *N*,*N*-diisopropylethylamine (1.49 mL, 8.56 mmol) in DMF (30 mL) was stirred at room temperature for 20 min. After addition of EtOH (1.0 mL), the resulting mixture was stirred at the same temperature for 5 min and then partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (neutral SiO_2, 15% AcOEt in hexane) to give **84** (2.93 g, 90% as a pale yellow solid): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.47 (d, 1 H, J = 8.3), 7.56−7.21 (m, 10 H), 5.80 (d, 1 H, J = 8.3), 5.36, 5.32 (each d, each 1 H, J = 9.9), 5.00 (d, 1 H, J = 7.5), 4.60, 4.59 (each d, each 1 H, J = 12.3), 4.07−4.01 (m, 3 H), 1.17−1.01 (m, 28 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.19, 161.74, 150.20, 141.62, 137.27, 135.76, 129.61, 129.21, 127.94, 127.43, 127.33, 125.01, 101.95, 96.78, 80.78, 72.00, 71.11, 70.32, 62.75, 17.39, 17.26, 17.23, 16.95, 16.88, 16.81, 13.39, 13.06, 12.54, 12.48; FAB-HRMS calcd for $C_{35}H_{49}N_2O_8SeSi_2$ 761.2192, found 761.2173 (MH^+). Anal. Calcd for $C_{35}H_{48}N_2O_8SeSi_2$: C, 55.32; H, 6.32; N, 3.69. Found: C, 55.03; H, 6.23; N, 3.68.

Typical Procedure for the Aldol Reaction (Table 1). 3-*N*-Benzyloxymethyl-1-[(1*S*)-1-phenyl-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*erythro*-2,3-hexodiulofuranosyl]uracil (12a) and 3-*N*-Benzyloxymethyl-1-[1-phenyl-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-D-*erythro*-2,3-hexodiulofuranosyl]uracil (13a). A solution of **6** (76 mg, 0.10 mmol) in THF (1.0 mL) was added dropwise to a solution of SmI_2 (0.10 M solution in THF, 2.1 mL, 0.21 mmol) at −78 °C. After **6** disappeared on TLC, oxygen was bubbled into the mixture. To the mixture was added a solution of PhCHO (2.0 M solution in THF, 150 μL, 0.30 mmol) at −78 °C, and the resulting mixture was stirred at the same temperature for 1 h. Saturated aqueous NH_4Cl was added to the mixture, and the whole was warmed to room temperature. The mixture was partitioned between AcOEt and H_2O and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, hexane:AcOEt = 4:1, 3:1, then 2:1) to give **12a** (55 mg, 0.077 mmol, 76%) as a white foam and **13a** (7 mg, 0.010 mmol, 10%, as a colorless oil). **12a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, 1 H, H-6, J = 8.5), 7.36−7.27 (m, 10 H, Ph × 2), 5.73 (d, 1 H, H-5, J = 8.5), 5.39 (s, 2 H, NCH_2O), 5.36 (d, 1 H, H-1′, J = 7.6), 4.89 (d, 1 H, H-4′, J = 7.2), 4.62 (s, 2H, OCH_2Ph), 4.00 (dd, 1 H, H-6′a, J = 11.7, 7.5), 3.93 (dd, 1 H, H-6′b, J = 11.7, 3.4), 3.61 (d, 1 H, OH-1′, J = 7.6), 3.34 (ddd, 1 H, H-5′, J = 7.5, 7.2, 3.4), 1.09−0.81 (m, 28 H, isopropyl × 4); FAB-HRMS calcd for $C_{36}H_{51}N_2O_9Si_2$ 711.3133, found 711.3123 (MH^+). Anal. Calcd for $C_{36}H_{50}N_2O_9Si_2$: C, 60.61; H, 6.96; N, 3.72. Found: C, 60.23; H, 7.24; N, 4.03. **13a**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.58 (d, 1 H, J = 8.3), 7.38−7.24 (m, 10 H, Ph × 2), 5.81 (d, 1 H, J = 8.3), 5.47 (d, 1 H, J = 9.9), 5.40 (d, 1 H, J = 9.9), 5.20 (d, 1 H, J = 10.0), 4.70, 4.70 (each s, each 1 H), 4.32 (ddd, 1H, J = 8.3, 7.9, 3.6), 3.89 (dd, 1 H, J = 11.5, 3.6), 3.48 (d, 1 H, J = 10.0), 3.36 (dd, 1 H, J = 11.5, 7.9), 3.14 (dd, 1 H, J = 8.3), 1.04−0.85 (m, 28 H, isopropyl × 4); FAB-HRMS calcd for $C_{36}H_{51}N_2O_9Si_2$ 711.3133, found 711.3123 (MH^+).

1-[1-Phenyl-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*erythro*-2,3-hexodiulofuranosyl]uracil (9). Purification was accomplished by flash column chromatography (SiO_2, hexane:AcOEt = 4:1, 3:1. 2:1, then 1:1) to give the diastereomeric mixture **9** (53 mg, 0.089 mmol, 89%) as a white foam. From the mixture **9** (44 mg, ca. 0.074 mmol), the three diastereomers **9-1** (14 mg, 0.024 mmol), **9-2** (13 mg, 0.022 mmol), and **9-3** (14 mg, 0.024 mmol) were obtained in a pure form by preparative HPLC separation (YMC D-ODS-5-A, 250 mm × 20 mm; 85% aqueous MeCN, 20 mL/min; 260 nm). The remaining diastereomer (**9-4**) could not be isolated. **9-1**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.72 (br s, 1 H), 7.65 (d, 1 H, J = 8.3), 7.33−7.29 (m, 5 H), 5.70 (dd, 1 H, J = 8.5, 1.8), 5.40 (s, 1 H), 4.82 (d, 1 H, J = 7.4), 3.99 (dd, 1 H, J = 11.8, 7.2), 3.94 (dd, 1 H, J = 11.8, 3.3), 3.35 (ddd, 1 H, J = 7.4, 7.2, 3.3), 1.07−0.80 (m, 28 H). **9-2**, which was in equilibrium between the keto and the corresponding hydrate forms: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.55 (br s, 1 H), 8.24 (br s, 1 H), 7.66 (d, 1 H, J = 8.2), 7.38−7.18 (m, 10 H), 6.95 (d, 1 H, J = 8.4), 5.81 (dd, 1 H, J = 8.2, 1.9), 5.65 (s, 1 H), 5.51 (s, 1 H), 5.36 (dd, 1 H, J = 8.4, 1.7), 5.22 (s, 1 H), 4.74 (d, 1 H, J = 8.5), 4.32 (ddd, 1 H, J = 8.3, 8.0, 3.4), 4.24 (dd, 1 H, J = 12.5, 5.0), 4.15 (br s, 1 H), 4.10 (dd, 1 H, J = 12.5, 3.0), 3.99−3.88 (m, 2 H), 3.37 (dd, 1 H, J = 11.7, 8.0), 3.13 (d, 1 H, J = 8.3), 1.16−0.58 (m, 56 H). **9-3**, which was in equilibrium between the keto and the corresponding hydrate forms: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.72 (br s, 0.6 H), 8.59 (br s, 1 H), 8.19 (d, 1 H, J = 8.4), 7.75 (d, 0.6 H, J = 8.3), 7.63−7.31 (m, 8 H), 5.74 (d, 1 H, J = 8.4), 5.70 (d, 0.6 H, J = 8.3), 5.66 (s, 0.6 H), 5.57 (br s, 0.6 H), 5.21 (s, 1 H), 4.43 (ddd, 1 H, J = 7.4, 7.3, 3.3), 4.06 (dd, 1 H, J = 11.8, 3.3), 3.96 (dd, 0.6 H, J = 11.7, 2.8), 3.83−3.78 (m, 1 H), 3.80 (dd, 1 H, J = 11.8, 7.3), 3.45 (dd, 0.6 H, J = 11.7, 8.3), 3.21 (d, 0.6 H, J = 8.5), 3.14 (d, 1 H, J = 7.4), 1.09−0.70 (m, 45 H).

1-[4,6-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*erythro*-2,3-hexodiulofuranosyl]uracil (10) and 1-[4,6-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-α-D-*erythro*-2,3-hexodiulofuranosyl]uracil(11). Purification was accomplished by column chromatography (SiO_2, hexane:AcOEt = 2:1 then 1:1) to give **10** (27.7 mg, 0.054 mmol, 54%) as a white foam and **11** (9 mg, 0.016 mmol, 16%). **10**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.10 (br s, 1 H, NH-3), 7.66 (d, 1 H, H-6, J = 8.2), 5.77 (br d, 1 H, H-5, J = 8.2), 5.07 (d, 1 H, H-4′, J = 7.3), 4.07−3.97 (m, 5 H, H-1′, H-5′, H-6′), 2.83 (br s, 1 H, OH-1′), 1.12−1.02 (m, 28 H, isopropyl × 4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.46, 162.43, 150.13, 140.83, 102.47, 86.30, 80.86, 72.19, 63.96, 59.92, 17.41, 17.29, 17.26, 17.23, 16.81, 16.78, 16.75, 13.32, 13.06, 12.53, 12.28; FAB-HRMS calcd for $C_{22}H_{39}N_2O_8Si_2$ 515.2245, found 515.2216 (MH^+). **11**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.85 (br s, 1 H), 7.44 (d, 1 H, J = 8.2), 5.77 (dd, 1 H, J = 8.5, 2.0), 4.70 (d, 1 H, J = 9.7), 4.60 (d, 1 H, J = 9.4), 4.11(br d, 1 H, J = 13.9), 4.07−4.02 (m, 2 H), 3.81 (dd, 1 H, J = 8.4, 5.2), 1.14−1.05 (m, 28 H, isopropyl × 4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.69, 161.63, 151.32, 139.85, 103.01, 88.85, 82.66, 71.58, 62.90, 60.40, 17.24, 17.17, 17.16, 16.88, 16.74, 16.70, 13.60, 12.87, 12.61, 12.44; FAB-HRMS calcd for $C_{22}H_{39}N_2O_8Si_2$ 515.2245, found 515.2267 (MH^+).

3-*N*-Benzyloxymethyl-1-[(1*S*)-1-methyl-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*erythro*-2,3-hexodiulofuranosyl]uracil (12b) and 3-*N*-Benzyloxymethyl-1-[(1*S*)-1-*O*-acetyl-1-methyl-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*arabino*-2-hexulofuranosyl]uracil (14b). Purification was accomplished by column chromatography (SiO_2, hexane:AcOEt = 4:1, 3:1, then 2:1) to give **12b** (18.9 mg, 0.029 mmol, 29%) and **14b** (36 mg, 0.052 mmol, 52%) as a colorless oil. **12b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (d, 1 H, H-6, J = 8.4), 7.33−7.26 (m, 5 H, Ph), 5.76 (d, 1 H, H-5,

J = 8.4), 5.40 (d, 1 H, NCH_2O, J = 9.8), 5.37 (d, 1 H, NCH_2O, J = 9.8), 5.03 (d, 1 H, H-4′, J = 5.6), 4.63, 4.64 (each d, each 1 H, OCH_2Ph, J = 12.5), 4.26 (m, 1 H, H-1′), 4.10−4.03 (m, 3 H, H-5′, H-6′), 2.81 (d, 1 H, OH-1′, J = 9.2), 1.40 (d, 3 H, Me-1′, J = 6.6), 1.17−0.99 (m, 28 H, isopropyl × 4); FAB-HRMS calcd for $C_{31}H_{49}N_2O_9Si_2$ 649.2276, found 649.2296 (MH^+). **14b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (d, 1 H, H-6, J = 8.5), 7.35−7.24 (m, 5 H, Ph), 6.34 (q, 1 H, H-1′, J = 6.4), 5.76 (d, 1 H, H-5, J = 8.5), 5.48, 5.46 (each d, each 1 H, NCH_2O, J = 9.8), 4.66 (s, 2 H, OCH_2Ph), 4.55 (dd, 1 H, H-3′, J = 7.8, 2.2), 4.15 (dd, 1 H, H-6′a, J = 13.2, 2.0), 4.10 (dd, 1 H, H-4′, J = 9.2, 7.8), 4.00 (dd, 1 H, H-6′b, J = 13.2, 2.5), 3.89 (ddd, 1 H, H-5′, J = 9.2, 2.5, 2.0), 3.32 (d, 1 H, OH-3′, J = 2.2), 2.13 (s, 3 H, −CH(*OAc*)Me), 1.11−0.98 (m, 31 H, isopropyl × 4 and Me-1′); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.79 (*C*OCH$_3$), 162.61 (C-4), 152.52 (C-2), 139.20 (C-6), 137.78 (OCH$_2$*Ph*), 128.35 (OCH$_2$*Ph*), 127.74 (OCH$_2$*Ph*), 127.71 (OCH$_2$*Ph*), 101.54 (C-5), 96.64 (C-2′), 82.20 (C-5′), 78.35 (C-3′), 73.32 (C-4′), 72.23 (O*C*H$_2$Ph), 70.91 (C-1′), 70.55 (N*C*H$_2$O), 60.14 (C-6′), 21.19 (CO*C*H$_3$), 17.54, 17.39, 17.35, 17.26, 17.06, 16.97, 16.81, 16.76, 13.73, 13.53, 13.04, 12.99, 12.34; FAB-HRMS calcd for $C_{33}H_{52}N_2O_{10}Si_2Na$ 715.3057, found 715.3060 (MNa^+). Anal. Calcd for $C_{33}H_{52}N_2O_{10}Si_2$: C, 57.20; H, 7.56; N, 4.04. Found: C, 57.60; H, 7.73; N, 3.70.

3-*N*-Benzyloxymethyl-1-[(1*S*)-1-isopropyl-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*erythro*-2,3-hexodiulofuranosyl]uracil (12c). Purification was accomplished by column chromatography (SiO_2, AcOEt in hexane = 15%, 20%, then 30%) to give **12c** (32 mg, 0.048 mmol, 48%) and **8** (20 mg, 0.033 mmol, 33%). **12c**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (d, 1 H, H-6, J = 8.6), 7.26−7.19 (m, 5 H, Ph), 5.71 (d, 1 H, H-5, J = 8.6), 5.32 (s, 2 H, NCH_2O), 4.96 (d, 1 H, H-4′, J = 5.9), 4.57 (s, 2 H, OCH_2Ph), 4.08−3.91 (m, 4 H, H-5′, H-6′, H-1′), 2.63 (br d, 1 H, OH-1′, J = 8.6), 1.94 (m, 1 H, C*H*Me$_2$-1′), 1.07−0.79 (m, 34 H, isopropyl × 4, CH*Me*$_2$-1′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.03, 161.48, 151.48, 139.08, 137.26, 127.99, 127.39, 127.31, 101.92, 88.59, 82.61, 75.60, 72.01, 71.51, 70.27, 63.64, 28.25, 22.30, 17.43, 17.26, 16.87, 16.81, 16.76, 16.70, 13.41, 13.04, 12.73, 12.33; FAB-HRMS calcd for $C_{33}H_{53}N_2O_9Si_2$ 677.3289, found 677.3250 (MH^+). Anal. Calcd for $C_{33}H_{52}N_2O_9Si_2$: C, 58.55; H, 7.74; N, 4.14. Found: C, 58.68; H, 7.85; N, 4.05.

3-*N*-Benzyloxymethyl-1-[4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*erythro*-2,3-hexodiulofuranosyl]uracil (12d) and 3-*N*-Benzyloxymethyl-1-[4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-D-*erythro*-2,3-hexodiulofuranosyl]uracil (13d). Purification was accomplished by column chromatography (SiO_2, hexane:AcOEt = 3:1, 2:1, 1:1, then 1:2) to give **12d** (36 mg, 0.057 mmol, 57%) as a white foam, **13d** (8 mg, 0.012 mmol, 12%) as a white glass, and **15** (6 mg, 0.027 mmol, 27%) as a white solid. **12d**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 (d, 1 H, H-6, J = 8.3), 7.32−7.26 (m, 5 H, Ph), 5.77 (d, 1 H, H-5, J = 8.3), 5.38 (s, 2 H, NCH_2Ph), 5.14 (d, 1 H, H-3′, J = 7.3), 4.63 (s, 2 H, OCH_2Ph), 4.13−3.96 (m, 5 H, H-5′, H-6′, and H-1′), 2.69 (br s, 1 H, OH-1′), 1.16−0.98 (m, 28 H, isopropyl × 4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.82 (C-3′), 161.89 (C-4), 151.94 (C-2), 139.59 (C-6), 137.72 (OCH$_2$*Ph*), 128.36 (OCH$_2$*Ph*), 127.75 (OCH$_2$*Ph*), 127.72 (OCH$_2$-*Ph*), 102.66 (C-5), 87.04 (C-2′), 81.42 (C-5′), 72.28 (O*C*H$_2$Ph), 72.26 (C-4′), 70.51 (N*C*H$_2$O), 64.15 (C-1′), 60.30 (C-6′), 17.47, 17.36, 17.29, 16.91, 16.87, 16.86, 13.48, 13.16, 12.68, 12.42; FAB-HRMS calcd for $C_{30}H_{47}N_2O_9Si_2$ 635.2821, found 635.2853 (MH^+). **13d**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.26 (m, 6 H, H-6, Ph), 5.78 (d, 1 H, H-5, J = 8.3), 5.45, 5.39 (each d, each 1 H, NCH$_2$O, J = 9.8), 4.70−4.63 (m, 4 H, H-4′, H-5′, OCH_2Ph), 4.07 (dd, 1 H, H-6′a, J = 13.5, 1.3), 4.03 (dd, 1 H, H-6′b, J = 13.5, 2.5), 3.90, 3.88 (each d, each 1 H, H-1′, J = 12.2), 2.65 (br s, 1 H, OH-1′), 1.14−1.02 (m, 28 H, isopropyl × 4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.63 (C-3′), 161.86 (C-4), 152.69 (C-2), 138.88 (C-6), 137.73 (OCH$_2$*Ph*), 128.33 (OCH$_2$*Ph*), 127.83 (OCH$_2$*Ph*), 127.73 (OCH$_2$*Ph*), 102.83 (C-5), 88.97 (C-2′), 82.95 (C-5′), 72.30 (O*C*H$_2$Ph), 71.66 (C-4′), 70.49 (N*C*H$_2$O), 63.45 (C-1′), 60.93 (C-6′), 17.38, 17.28, 17.24, 16.98, 16.83, 16.75, 13.61, 12.91, 12.63, and 12.57 (isopropyl carbons); FAB-HRMS calcd for $C_{30}H_{47}N_2O_9Si_2$ 635.2821, found 635.2823 (MH^+).

Typical Procedure for the Aldol-Tishchenko Reaction. 3-*N*-Benzyloxymethyl-1-[(1*S*)-1-*O*-benzoyl-1-phenyl-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*arabino*-2-hexulofuranosyl]uracil (14a). To a solution of the samarium enolate in THF, which was prepared from **6** (0.10 mmol) according to the above-mentioned procedure, was added dropwise a solution of PhCHO (2.0 M solution in THF) at the same temperature. The mixture was warmed to room temperature over 2 h and was stirred further for 1 h. Saturated aqueous NH_4Cl was added to the mixture, and the resulting mixture was stirred for 5 min at room temperature. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, hexane:AcOEt = 9:1, 8:1, then 7:1) to give **14a** (60 mg, 0.074 mmol, 74%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (d, 2 H, *o*-Bz, J = 7.5), 7.68 (d, 1 H, H-6, J = 8.5), 7.60−7.11 (m, 14 H, Ar−H and C*H*(Ph)OBz), 5.53 (d, 1 H, H-5, J = 8.5), 5.49, 5.46 (each d, each 1 H, NCH_2O, J = 9.8), 4.88 (dd, 1 H, H-3′, J = 7.4, 1.8), 4.65, 4.64 (each d, each 1 H, OCH_2Ph, J = 12.1), 4.28−4.19 (m, 3 H, H-4′, H-5′, H-6′a), 4.12 (dd, 1 H, H-6′b, J = 13.6, 3.2), 3.73 (d, 1 H, OH-3′, J = 1.8), 1.12−0.96 (m, 28 H, isopropyl × 4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.13 (*C*OPh), 162.47 (C-4), 152.87 (C-2), 139.04 (C-6), 137.78, 134.64, 133.42, 129.78, 128.98, 128.61, 128.39, 128.23, 128.19, 127.71, and 127.58 (Ph carbons), 101.23 (C-5), 97.32 (C-2′), 82.72 (C-5′), 79.34 (C-3′), 75.45 (C-1′), 73.99 (C-4′), 71.93 (O*C*H$_2$Ph), 70.42 (N*C*H$_2$O), 60.55 (C-6′), 17.52, 17.35, 17.23, 17.05, 16.97, 16.83, 16.79, 13.54, 13.24, 13.08, 12.94, and 12.38 (isopropyl carbons); FAB-HRMS calcd for $C_{43}H_{56}N_2O_{10}Si_2Na$ 839.3371, found 839.3326 (MNa^+). Anal. Calcd for $C_{43}H_{56}N_2O_{10}Si_2$: C, 63.21; H, 6.91; N, 3.43. Found: C, 63.08; H, 6.92; N, 3.50.

3-*N*-Benzyloxymethyl-1-[(1*S*)-1-*O*-acetyl-1-methyl-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*arabino*-2-hexulofuranosyl]uracil (14b). Purification was accomplished by column chromatography (SiO_2, hexane:AcOEt = 9:1, 7:1, then 4:1) to give **14b** (58 mg, 0.083 mmol, 83%) as a colorless oil, the physical data of which was ubi supra.

3-*N*-Benzyloxymethyl-1-[(1*S*)-1-isopropyl-1-*O*-isobutyryl-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*arabino*-2-hexulofuranosyl]uracil (14c) and Cyclic Hemiketal 16. Purification was accomplished by column chromatography (SiO_2, AcOEt in hexane = 5%, 10%, then 15%) to give **14c** (41.8 mg, 0.056 mmol, 55%) as a clorless glass and **16** (30.7 mg, 0.041 mmol, 41%). **14c**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (d, 1 H, H-6, J = 8.6), 7.34−7.24 (m, 5 H, Ph), 6.37 (d, 1 H, H-1′, J = 2.9), 5.78 (d, 1 H, H-5, J = 8.6), 5.51, 5.47 (each d, each 1 H, NCH_2O, J = 9.8), 4.66 (each d, each 1 H, OCH_2Ph, J = 12.6), 4.37 (d, 1 H, H-3′, J = 8.2), 4.16 (dd, 1 H, H-6′a, J = 13.5, 1.2), 4.02 (dd, 1 H, H-4′, J = 9.4, 8.2), 3.99 (dd, 1 H, H-6′b, J = 13.5, 2.5), 3.85 (ddd, 1 H, H-5′, J = 9.4, 2.5, 1.2), 3.24 (br s, 1 H, OH-3′), 2.67 (qq, 1 H, C*H*Me$_2$-1′, J = 7.0, 7.0), 1.80 (dqq, 1 H, −OCOC*H*Me$_2$, J = 6.8, 6.8, 2.9), 1.26, 1.25 (each d, each 3 H, OCOCH*Me*$_2$, J = 7.0), 1.10−0.92 (m, 28 H, isopropyl × 4), 0.88, 0.84 (each d, each 3 H, −CH(OCOCHMe$_2$)CH*Me*$_2$, J = 6.8); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.54, 162.71, 152.72, 139.08, 137.80, 128.33, 127.71, 127.68, 101.56, 97.56, 82.16, 79.37, 75.75, 72.37, 72.13, 70.52, 60.01, 34.43, 28.73, 20.88, 19.39, 19.13, 17.53, 17.39, 17.35, 17.24, 17.08, 17.05, 16.99, 16.77, 13.53, 13.02, 13.00, 12.39; FAB-HRMS calcd for $C_{37}H_{60}N_2O_{10}Si_2Na$ 711.3684, found 711.3688 (MNa^+). **16**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23 (d, 1 H, H-6, J = 8.5), 7.35−7.27 (m, 5 H, Ph), 6.36 (s, 1 H, OH-3′), 5.85 (d, 1 H, H-5, J = 8.5), 5.55, 5.47 (each d, each 1 H, NCH_2O, J = 9.9), 4.86 (d, 1 H, OC*H*(CHMe$_2$)O, J = 4.5), 4.78 (d, 1 H, H-1′, J = 7.4), 4.63 (s, 2 H, OCH_2Ph), 4.24 (d, 1 H, H-6′a, J = 13.8), 4.10 (dd, 1 H, H-5′, J = 9.6, 1.9), 4.05 (d, 1 H, H-4′, J = 9.6), 4.00 (dd, 1 H, H-6′b, J = 13.8, 1.9), 1.98−1.92 (m, 2 H, C*H*Me$_2$), 1.10−0.90 (m, 37 H,Si(C*HMe*$_2$) × 4 and CH*Me*$_2$ × 3),

0.69 (d, 3 H, CH*Me*$_2$, J = 6.8); NOE (400 MHz, $CDCl_3$) irradiated H-6, observed H-4′ (1.2%), H-6′(6.3%); irradiated H-1′, observed OH-3′ (4.4%), OC*H*($CHMe_2$)O (12.9%); irradiated OC*H*($CHMe_2$)O, observed H-1′ (14.1%), OH-3′ (9.5%); irradiated OH-3′, observed H-4′ (1.9%); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.23, 154.31, 139.87, 137.49, 128.37, 127.81, 102.33, 101.30, 98.61, 93.80, 82.78, 78.80, 72.10, 71.30, 70.57, 59.47, 32.47, 28.11, 19.71, 19.31, 17.62, 17.47, 17.40, 17.22, 17.09, 16.99, 16.80, 16.69, 16.04, 13.52, 13.27, 12.93, 12.65, 12.34; FAB-HRMS calcd for $C_{37}H_{61}N_2O_{10}Si_2$ 749.3865, found 749.3888 (MH^+).

3-*N*-Benzyloxymethyl-1-[(1*S*)-1-phenyl-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*ribo*-2-hexulofuranosyl]uracil (17). A solution of **12a** (7.1 mg, 10 μmol) and $NaBH_4$ (1.0 mg, 0.03 mmol) in MeOH (0.2 mL) was stirred at 0 °C for 30 min. After AcOEt (1 mL) and saturated aqueous NH_4Cl (1 mL) were added to the solution, the mixture was warmed to room temperature and was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 10%, 15%, then 20% AcOEt in hexane) to give **17** (6.6 mg, 9.3 μmol, 93%, as a colorless glass) along with a trace of **18**; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.12 (m, 11 H, H-6, Ph × 2), 5.95 (d, 1 H, H-1′, J = 2.4), 5.49 and 5.44 (each d, each 1 H, NC*H*$_2$O, J = 9.8), 5.31 (d, 1 H, H-5, J = 8.4), 4.97 (d, 1 H, H-3′, J = 5.2), 4.67 and 4.66 (each d, each 1 H, OC*H*$_2$Ph, J = 12.0), 4.40 (ddd, 1 H, H-5′, J = 8.9, 2.2, 2.1), 4.27−4.25 (m, 2 H, H-4′, H-6′a), 4.04−4.01 (m, 2 H, H-6′b, OH-1′), 3.44 (br s, 1 H, 2′-OH), 1.10−0.93 (m, 28 H, isopropyl × 4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.78, 162.55, 151.29, 138.36, 137.79, 136.94, 128.52, 128.36, 12.09, 127.71, 127.57, 112.78, 100.39, 97.87, 84.18, 73.24, 71.93, 70.11, 69.10, 60.03, 17.38, 17.22, 17.19, 17.09, 17.01, 16.98, 16.88, 16.84, 13.46, 12.98, 12.78, 12.57; FAB-LRMS m/z 735 (MNa^+). Anal. Calcd for $C_{36}H_{52}N_2O_9$: C, 60.65; H, 7.35; N, 3.93. Found: C, 60.76; H, 7.12; N, 4.10.

3-*N*-Benzyloxymethyl-1-[(1*S*)-1-phenyl-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*arabino*-2-hexulofuranosyl]uracil (18). $NaBH(OAc)_3$ (11 mg, 50 μmol) was added to a solution of **12a** (7 mg, 10 μmol) in 5% AcOH/MeCN (0.5 mL) at 0 °C. After the resulting mixture was stirred at the same temperature for 3 h, AcOEt (2 mL) and saturated aqueous NH_4Cl (1 mL) were added to the mixture. The whole was warmed to room temperature and partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 10%→15%→20% AcOEt in hexane) to give **18** (7 mg, 10 μmol, 100%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, 1 H, H-6, J = 8.5), 7.35−7.12 (m, 10 H, Ph × 2), 5.92 (br s, 1 H, H-1′), 5.49 (d, 1 H, H-5, J = 8.5), 5.42 and 5.38 (each d, each 1 H, NC*H*$_2$O, J = 10.0), 5.10 (br d, 1 H, H-3′, J = 7.6), 4.54 (s, 2 H, OC*H*$_2$Ph), 4,20−4.14 (m, 2 H, H-4′, H-6′a), 4.09 (ddd, 1 H, H-5′, J = 9.4, 2.4, 2.1), 4.02 (dd, 1 H, H-6′b, J = 13.5, 2.4), 3.62 (br s, 1 H, OH-1′), 2.75 (br s, 1 H, OH-3′), 1.10−0.96 (m, 28 H, isopropyl × 4); FAB-LRMS m/z 735 (MNa^+). Anal. Calcd for $C_{36}H_{52}N_2O_9$: C, 60.65; H, 7.35; N, 3.93. Found: C, 60.76; H, 7.12; N, 4.10.

1-[4,6-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*arabino*-2-hexulofuranosyl]uracil (19) and 1-[4,6-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-*β*-D-*ribo*-2-hexulofuranosyl]uracil (20). A solution of **10** (18 mg, 0.035 mmol) and $NaBH_4$ (4 mg, 0.1 mmol) in MeOH (1 mL) was stirred at 0 °C for 30 min. After addition of saturated aqueous NH_4Cl (5 mL), the mixture was warmed to room temperature and extracted with AcOEt (10 mL × 3). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 50%, 60%, then 70% AcOEt in hexane) to give **19** (7 mg, 14 μmol, 39%) as a white powder and **20** (11 mg, 21 μmol, 59%) as a colorless glass. **19**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.27 (br s, 1 H, NH-3, D_2O exchangeable), 8.04 (d, 1 H, J = 7.6), 5.72 (dd, 1 H, J = 7.6, 3.8), 4.24−4.09 (m, 4 H), 4.01 (dd, 1 H, J = 13.5, 2.6), 3.80 (ddd, 1 H, J = 8.8, 2.3, 2.3), 3.73 (br d, 1 H, J = 3.5), 3.11 (br s, 1 H), 1.11−0.96 (m, 28 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.30, 151.62, 141.27, 101.56, 96.81, 80.78, 77.50, 72.49, 65.20, 59.91, 17.47, 17.34, 17.30, 17.19, 17.00, 16.90, 16.76, 16.73, 13.43, 12.96, 12.92, 12.24; FAB-HRMS calcd for $C_{22}H_{41}N_2O_8Si_2$ 517.2402, found 517.2369 (MH^+). **20**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.84 (br s, 1 H), 7.97 (d, 1 H, J = 8.2), 5.69 (dd, 1 H, J = 8.2, 2.3), 4.78 (br s, 1 H), 4.27−4.22 (m, 5 H), 3.99 (br d, 1 H, J = 13.5), 3.36 (br s, 1 H), 2.90 (br s, 1 H), 1.28−0.86 (m, 28 H, isopropyl × 4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.28, 150.08, 140.83, 101.04, 97.76, 81.92, 75.09, 68.58, 63.33, 59.41, 17.39, 17.29, 17.20, 17.07, 16.95, 16.92, 16.86, 16.76, 13.39, 12.88, 12.76, 12.39; FAB-HRMS calcd for $C_{22}H_{41}N_2O_8Si_2$ 517.2402, found 517.2369 (MH^+).

1-(*β*-D-*ribo*-2-Hexulofuranosyl)uracil (21). A solution of TBAF (1.0 M in THF, 50 μL, 50 μmol) was added to a solution of **20** (12 mg, 24 μmol) in THF at room temperature, and the mixture was stirred at the same temperature for 20 min. The solvent was evaporated, and the residue was purified by column chromatography (SiO_2, 10%, 15%, 20%, then 25% MeOH in $CHCl_3$) to give **21** (6 mg, 22 μmol, 91%), the spectrum data of which were in accord with those reported previously.[6g]

1-[(1*S*)-1-Phenyl-3,4-*O*-isopropylidene-*β*-D-*ribo*-2-hexulofuranosyl]uracil (22). A mixture of **17** (108.0 mg, 0.15 mmol) and Pd (10% on carbon, 300 mg) in MeOH (3 mL) was vigorously stirred under atmospheric pressure of hydrogen at room temperature for 40 h. After the insoluble material was filterd off on Celite, the filtrate was evaporated. The residue was purified by column chromatography (SiO_2, hexane:AcOEt = 2:1) to give the corresponding *N*-3-free product as a colorless glass (91 mg, 0.15 mmol, 100%). A mixture of the product (59 mg, 100 μmol) and TBAF (1.0 M in THF, 200 μL, 0.2 μmol) in THF (1.0 mL) was stirred at 0 °C for 20 min. The solvent was evaporated, and the residue was purified by column chromatography (SiO_2, 5% then 10% MeOH in AcOEt) to give the corresponding TIPDS-deprotected product as a white glass (26 mg, 74 μmol, 74%). A mixture of the product (7 mg, 20 μmol), PPTS (1 mg, 4 μmol), 2,2-dimethoxypropane (88 μL, 1.0 mmol), and $CuSO_4$ (100 mg) in acetone (1 mL) was stirred at room temperature for 72 h. After K_2CO_3 (10 mg) was added to the solution, the insoluble material was filterd off on Celite, the filtrate was evaporated. The residue was purified by column chromatography (SiO_2, 5%, 7%, then 10% MeOH in $CHCl_3$) to give **22** a colorless glass (1 mg, 2.7 μmol, 13%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29−7.24 (m, 5 H, Ph), 7.02 (d, 1 H, H-6, J = 8.3), 5.64 (d, 1 H, H-1′, J = 3.3), 5.46 (d, 1 H, H-3′, J = 6.8), 5.14 (d, 1 H, H-5, J = 8.3), 4.86 (ddd, 1 H, H-4′, J = 6.8, 3.7, 3.1), 4.73 (dd, 1 H, H-5′, J = 6.5, 3.1), 3.89 (dd, 1 H, H-6′a, J = 11.7, 3.1), 3.77 (dd, 1 H, H-6′b, J = 11.7, 3.7), 3.64 (s, 1 H, OH-6′), 3.45 (d, 1 H, OH-1′, J = 3.3), 1.91, 1.46 (each s, each 3 H, Me × 2); FAB-HRMS calcd for $C_{19}H_{23}N_2O_7$ 391.1505, found 391.1506 (MH^+).

1-[(1*S*)-4,6-Di-*O*-acetyl-1,3-*O*-isopropylidene-1-phenyl-*β*-D-*ribo*-2-hexulofuranosyl]uracil (23). Compoud **17** (108 mg, 0.15 mmol), hydrogenated as described above, gave the corresponding *N*-3-free product (90.5 mg, 0.15 mmol, 100%). To a stirring solution of the product (30 mg, 50 μmol), 2,2-dimethoxypropane (88 μL, 1.0 mmol), and PPTS (2.5 mg, 10 μmol) in DMF (1.0 mL) was added 2-methoxypropene (20 μL, 0.20 mmol) at room temperature 5 times (total 100 μL, 2.0 mmol). The resulting mixture was stirred further at the same temperature for 12 h, then was poured into aqueous saturated $NaHCO_3$. The mixture was extracted with Et_2O (×5), and the organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, 5%, 10%, then 20% AcOEt in hexane) to give the corresponding acetonide (27 mg, 43 μmol, 86%). A solution of the acetonide and TBAF (1.0 M in THF, 100 μL, 0.1 mmol) was stirred at room temperature for 30 min. The mixture was evaporated and then purified by column chromatography (SiO_2, hexane:AcOEt:MeOH = 1:1:0, 20:80:1, 10:40:1, then 10:40:2) to give the desilylated product (7 mg). A mixture of the product, Ac_2O (3.8 μL, 0.04 mmol),

Et_3N (5.6 μL, 0.04 mmol), and DMAP (0.5 mg, 0.004 mmol) in MeCN (0.5 mL) was stirred at room temperature. After 30 min, MeOH was added to the solution, and the resulting mixture was partitioned between Et_2O and aqueous saturated $NaHCO_3$, H_2O, and then brine. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, hexane:AcOEt = 4:1, 3:1, then 2:1) to give **23** (6 mg, 82%) as a white glass: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.09 (br s, 1 H, NH-3), 7.31−7.21 (m, 5 H, Ph), 7.07 (d, 1 H, H-6, J = 8.3), 5.79 (d, 1 H, H-3′, J = 3.5), 5.60 (s, 1 H, H-1′), 5.42 (dd, 1 H, H-5, J = 8.3, 2.0), 4.97 (dd, 1 H, H-4′, J = 9.5, 3.5), 4.74 (ddd, 1 H, H-5′, J = 9.5, 3.0, 2.2), 4.28 (dd, 1 H, H-6′a, J = 13.1, 3.0), 4.25 (dd, 1 H, H-6′b, J = 13.1, 2.2), 2.13, 1.95 (each s, each 3 H, Ac × 2), 1.87, 1.57 (each s, each 3 H, Me × 2).^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.19, 169.97. 163.29, 150.27, 141.55, 133.40, 128.94, 128.87, 128.02, 100.59, 99.78, 92.01, 79.18, 71.43, 70.86, 70.09, 61.13, 29.02, 20.74, 20.70, 20.62; FAB-HRMS calcd for $C_{23}H_{27}N_2O_9$ 475.1717, found 475.1730 (MH^+).

MTPA Esters 24R and 24S. A mixture of **14b** (171.6 mg, 0.30 mmol) and Pd (10% on carbon, 300 mg) in AcOEt−EtOH−AcOH (95:95:10, 2 mL) was vigorously stirred at room temperature under atmospheric pressure of hydrogen for 4 days. After the insoluble material was filtered off on Celite, the filtrate was evaporated. The residue was purified by column chromatography (SiO_2, hexane:AcOEt = 2:1) to give the corresponding *N*-3-free product. A mixture of the product and K_2CO_3 (41 mg, 0.30 mmol) in MeOH−THF (3:1, 4 mL) was vigorously stirred at 4 °C for 5 h. The reaction was quenched with saturated aqueous NH_4Cl, and the resulting mixture was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, hexane:AcOEt = 2:1 then 1:1) to give the diol derivative (90 mg, 0.17 mmol) as a white solid. A solution of (*S*)- or (*R*)-MTPA acid (3.5 mg, 15 μmol) and EDC (2.9 mg, 15 μmol) in CH_2Cl_2 (100 μL) was stirred at room temperature for 10 min. To the resulting mixture was added a solution of the diol (5.3 mg, 10 μmol) in THF (100 μL), and the mixture was stirred at room temperature. After 2 h, DMAP (1 mg) was added to the mixture. The resulting mixture was stirred further at the same temperature for 10 h, then partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, hexane:AcOEt = 2:1 then 1:1) to give **24S** (2.8 mg, 3.7 μmol, 37%) or **24R** (3.3 mg, 4.4 μmol, 44%). **24R**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.70 (br s, 1 H, NH-3), 7.960 (d, 1 H, H-6, J = 8.5), 7.53−7.46 (m, 5 H, Ph), 6.441(5) (q, 3 H, H-1′, J = 6.2), 5.679(5) (d, 1 H, H-5, J = 8.5), 4.451(5) (dd, 1 H, H-3′, J = 8.1, 3.3), 4.005 (d, 1 H, H-4′, J = 8.1), 3.984(5) (br d, 1 H, H-6′a), 3.809 (dd, 1 H, H-6′b, J = 13.5, 2.5), 3.668 (br s, 1 H, OH-3′), 3.534 (m, 1 H, H-5′), 3.503 (s, 3 H, O*Me*), 1.179 (d, 3 H, 1′-*Me*, J = 6.2), 1.09−0.95 (m, 28 H, isopropyl × 4). **24R**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.52 (br s, 1 H, NH-3), 7.892(5) (d, 1 H, H-6, J = 8.5), 7.56−7.39 (m, 5 H, Ph), 6.442 (q, 3 H, H-1′, J = 6.3), 5.655(5) (dd, 1 H, H-5, J = 8.5, 2.0), 4.203(5) (dd, 1 H, H-3′, J = 8.0, 3.3), 4.034 (d, 1 H, H-6′a, J = 13.5, 1.4), 3.949 (dd, 1 H, H-4′, J = 9.2, 8.0), 3.818 (dd, 1 H, H-6′b, J = 13.5, 2.5), 3.559 (s, 3 H, O*Me*), 3.483 (ddd, 1 H, H-5′, J = 9.2, 2.5, 1.4), 3.446 (br s, 1 H, OH-3′), 1.268 (d, 3 H, 1′-*Me*, J = 6.3), 1.09−0.93 (m, 28 H, isopropyl × 4).

1-[1,3-Di-*O*-acetyl-4,6-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-*ribo*-2-hexulofuranosyl]uracil (25). A mixture of **20** (9 mg, 0.018 mmol), Ac_2O (8 μL, 0.090 mmol), Et_3N (13 μL, 0.090 mmol), and DMAP (1 mg, 0.08 mmol) in MeCN (1.0 mL) was stirred at room temperature for 10 min. After addition of AcOEt (5 mL) and EtOH (0.1 mL), the resulting mixture was further stirred for 10 min at room temperature and then partitioned between AcOEt and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, hexane:AcOEt = 4:1) to give **25** (11 mg, 0.027 mmol, 91%) as a colorless glass: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (d, 1 H, H-6, J = 8.5), 7.93 (d, 1 H, H-6, J = 8.2), 6.08 (d, 1 H, H-2′, J = 5.0), 5.71 (dd, 1 H, H-5, J = 8.5, 2.3), 4.76, 4.65 (each d, each 1 H, CH_2OAc, J = 12.0), 4.26 (dd, 1 H, H-3′, J = 9.7, 5.0), 4.21 (d, 1 H, H-5′a, J = 13.5), 4.06 (m 1 H, H-4′), 3.95 (dd, 1 H, H-5′, J = 13.5, 2.5), 2.17, 2.01 (each s, each 3 H, Ac), 1.07−0.88 (m, 28 H, isoproryl × 4); NOE (400 MHz, $CDCl_3$) irradiated H-6, observed H-3′ (2.6%); irradiated H-2′, observed H-3′ (10.3%); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.64, 167.89, 162.67, 149.18, 140.10, 100.95, 94.96, 74.77, 67.33, 62.52, 58.76, 20.60, 20.51, 17.36, 17.20, 17.15, 17.04 16.89, 16.81, 16.72, 16.69, 13.43, 12.87, 12.70, 12.58; FAB-HRMS calcd for $C_{26}H_{45}N_2O_{10}Si_2$ 601.2613, found 601.2627 (MH^+).

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Supporting Information Available: ^{1}H NMR spectral charts of **9-1**, **9-2**, **9-3**, **10**, **11**, **12a**, **12b**, **12c**, **12d**, **13d**, **14a**, **14b**, **14c**, **16**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, **24R**, **24S**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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