Stereoselective synthesis of *C*-4′-aminouridines (uracil *C*-4-amino-D-ribonucleosides)

Masataka Yokoyama,*[ab] Taku Ikenogami[b] and Hideo Togo[ab]

[a] *Department of Chemistry, Faculty of Science,* [b] *Graduate School of Science and Technology, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan*

Received (in Cambridge, UK) 14th March 2000, Accepted 4th May 2000
Published on the Web 9th June 2000

The first *C*-4′-aminouridines can be synthesized in an α,β-stereoselective manner starting from L-glutamic acid. For the synthesis of α-*C*-4′-aminouridine, a key compound **9** is cyclized with trifluoroacetic acid followed by reduction with $NaBH_3CN$, while **9** is reduced with $NaBH_4$ followed by mesylation to give β-*C*-4′-aminouridine. Further, an acetonide-protection method is preferred for the synthesis of α-*C*-4′-aminouridine.

Introduction

As part of our ongoing programme in the study of *C*-nucleosides as a new type of DNA and RNA subunit,[1] we have been interested in the so-called *C*-azanucleosides[2] in which the endocyclic ribosyl ring oxygen is replaced with a nitrogen atom.† Recently, *C*-amino-L-lyxonucleosides,[3] *C*-amino-2-deoxy-L-lyxonucleosides,[4] and *C*-amino-2,3-dideoxynucleosides[5] have been synthesized and shown to have no anti-HIV activity in our laboratory. Judging from these biological results, the enzymes which may function in the life cycle of HIV virus cannot recognize our *C*-aminonucleosides due to the abnormal type of sugar moiety. Therefore, we intended to synthesize *C*-aminouridines as a normal type of *C*-aminonucleoside. Herein, we present the first synthesis of *C*-aminouridines starting from commercially available L-glutamic acid.

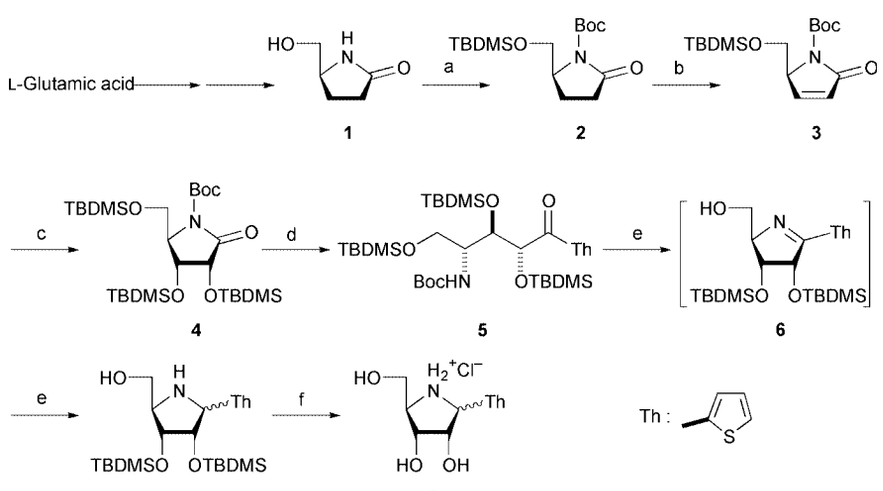
Results and discussion

For the synthesis of *C*-aminouridines we chose 5-(hydroxymethyl)pyrrolidin-2-one **1** as the starting material (Scheme 1). Compound **1** was prepared easily from L-glutamic acid by the usual procedure.[6] Next, **1** was protected with *tert*-butyldimethylsilyl (TBDMS) and *tert*-butoxycarbonyl (Boc) groups to afford **2** in 95% yield,[7] the phenylselenated product of which was then oxidized with H_2O_2, yielding **3** in 61% overall yield. When **3** was treated with OsO_4 in the usual way followed by protection with TBDMSCl, **4**[8] was obtained in 72% overall yield.

As a model experiment, to a stirred THF solution of **4** was added at 0 °C the thienylmagnesium bromide which was prepared from the reaction of 2-bromothiophene with magnesium by the usual way. The reaction mixture was subjected to usual purification to give **5** in 78% yield. A CH_2Cl_2 solution containing **5** and trifluoroacetic acid (TFA) was stirred at room temperature for 3 h. In this step a cyclic imine intermediate **6** could be observed by ^1H NMR spectroscopy. Without isolation of **6**, the reaction mixture was reduced with $NaBH_3CN$ at room temperature to give **7** in 71% yield (α : β = 7 : 1). **7** could be easily separated by usual column chromatograpy and each anomer **7a** and **7b** was then refluxed with HCl–MeOH to give the thiophene *C*-aminoribonucleosides **8α** and **8β** as their white, powdery HCl salts in 87 and 90% yield, respectively.

Next, the synthesis of a desired *C*-aminouridine was carried out in a similar way to that mentioned above by using the lithium reagent of 2,4-dimethoxypyrimidine which was prepared

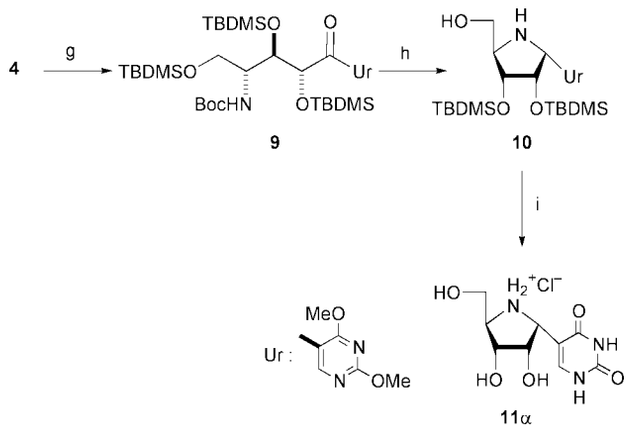
† In accordance with IUPAC–IUB systematic nomenclature, these compounds should instead be called iminonucleosides, and this terminology will be followed in this paper.



Scheme 1 *Reagents, conditions and yields*: (a) i. TBDMSCl, imidazole, DMF, 100%; ii. Boc_2O, DMAP, CH_3CN, rt, 95%. (b) i. LiHMDS, PhSeCl, THF, −78 °C, 83%; ii. H_2O_2, pyridine, CH_2Cl_2, 0 °C, 74%. (c) i. OsO_4, NMO, acetone–H_2O, 73%; ii. TBDMSCl, imidazole, DMAP, DMF, 98%. (d) ThMgBr, THF, 0 °C (3 h), 78%. (e) i. TFA, CH_2Cl_2, rt, 3 h; ii. $NaBH_3CN$, EtOH, rt, 2.5 h, 71% (α : β = 7 : 1). (f) conc. HCl, MeOH, reflux, 3 h, 87% (α); 90% (β).

DOI: 10.1039/b002063j

via halogen–metal exchange between 5-bromo-2,4-dimethoxypyrimidine and *n*-BuLi below −78 °C. The yield of **9** was 28% from **4**, and **10** was obtained in 40% yield from **9** in an α-selective manner (Scheme 2). This low conversion yield and α-selectivity

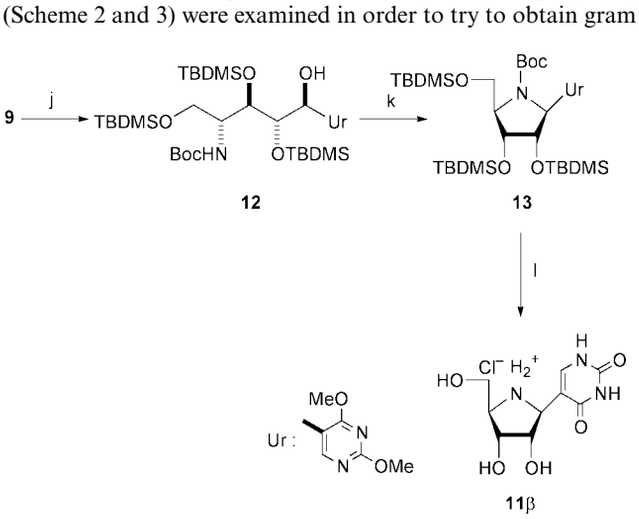


Scheme 2 *Reagents, conditions and yields*: (g) UrLi, THF, −78 °C (2 h), 28%. (h) i. TFA, CH_2Cl_2, rt, 3 h; ii. $NaBH_3CN$, EtOH, rt, 2.5 h, 40%. (i) conc. HCl, MeOH, reflux, 3 h, 85%.

may be caused by the fact that the hydride ion attacks only from the β-side of a cyclic imino intermediate (the compound corresponding to **6** shown in Scheme 1) due to its bulky OTBDMS group.

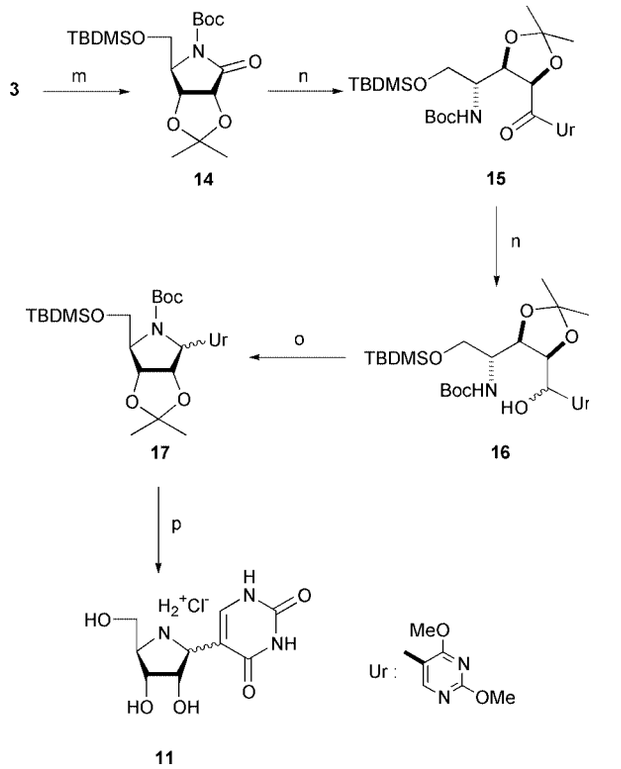
In order to obtain the β-*C*-aminouridine, reduction of ketone derivative **9** was examined. However, this was difficult because of the bulky groups around its carbonyl group. Among several reductive reagents such as $LiAlH_4$ (LAH), $LiBEt_3H$ (Superhydride), $Al(Bu^i)_2H$ (DIBAL-H), and $NaBH_4$, the following conditions gave the best result. An EtOH solution of **9** and $NaBH_4$ was stirred for 10 h at room temperature. The reaction mixture was quenched with aq. NH_4Cl (Scheme 3). Usual work-up gave an alcohol derivative **12** in 36% yield. The conversion yield is calculated as 59% based on consumed **9**. Next, **12** was stirred with MsCl and Et_3N to give a cyclic compound **13** in β-selective manner in 87% yield. Deprotection and purification of **13** was performed in the usual way to afford the desired β-aminouridine **11β** as white, powdery HCl salt in 95% yield.

Furthermore, attempts to increase the yields in steps g and j (Scheme 2 and 3) were examined in order to try to obtain gram



Scheme 3 *Reagents, conditions and yields*: (j) $NaBH_4$, EtOH, rt, 10 h, 36% (conversion yield: 59%). (k) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 87%. (l) conc. HCl, MeOH, reflux, 3 h, 95%.

quantities of compound **11**. Perhaps the bulky groups such as 3-OTBDMS of **4** and 2-OTBDMS of **9** hinder the nucleophilic attack of uracil-lithium and the hydride reduction, respectively. Therefore, the 3- and 4-OTBDMS groups of **4** were changed to a 3,4-isopropylidene dioxy group to give **14**[9] in 90% yield from the intermediate vicinal diol. The reaction of **14** with uracil-lithium gave **15**, which was then reduced with $NaBH_4$ to give **16** in an *R*-selective manner in a moderate yield, as expected (65%). The cyclization of **16** was performed by using MsCl and Et_3N to give **17α** and **17β** in 80, and 11% yield, respectively (Scheme 4).



Scheme 4 *Reagents, conditions and yields*: (m) i. OsO_4, NMO, acetone–H_2O, 73%; ii. DMP (2,2-dimethoxypropane), *p*-TsOH, CH_2Cl_2, 90%. (n) i. UrLi, THF, −78 °C (2 h); ii. $NaBH_4$, EtOH, 65% (*R*:*S* = 7:1). (o) MsCl, Et_3N, CH_2Cl_2, 80% (α); 11% (β). (p) conc. HCl, MeOH, reflux, 3 h, 87% (α); 90% (β).

In the reduction of **9** and **15**, *S*- and *R*-selectivities can be explained by reasoning that their transition states exist respectively as TS-1 and TS-2: TS-1 has the pyrimidine moiety against the two bulky OTBDMS groups in the 2- and 3-positions, while TS-2 has the pyrimidine moiety avoiding the bulky groups (NHBoc and $CH_2OTBDMS$) in the 4-position due to the compact acetonide group (Fig. 1).

The superiority of acetonide protection over TBDMS protection is shown by comparison of the overall yields based on **3**: the former gives **11α** (29.8%) and **11β** (4.2%), while the latter gives **11α** (6.9%) and **11β** (8.3%). Therefore, the former method is better for **11α**.

The structures of **11α** and **11β** were determined mainly by NMR measurements. Their NOESY data are shown in Fig. 2; **11β** shows an NOE between 1-H and 4-H, which is characteristic of the β-form.

The bioassay of **11** will be reported in a separate paper in the near future.

Experimental

All reactions requiring anhydrous conditions were conducted in oven-dried (120 °C) apparatus under dry argon. Ether (Et_2O) and THF were distilled from sodium in the presence of benzophenone ketyl. ^1H NMR spectra were recorded on a JNM-LA-500 (500 MHz) spectrometer. ^{13}C NMR spectra were recorded on the JEOL JNM-LA-500 (125 MHz) spectrometer; p = primary, s = secondary, t = tertiary, q = quaternary in ^{13}C NMR data. *J*-Values are given in Hz. IR spectra were measured with a JASCO FT/IR-200. Mass spectra were recorded on a

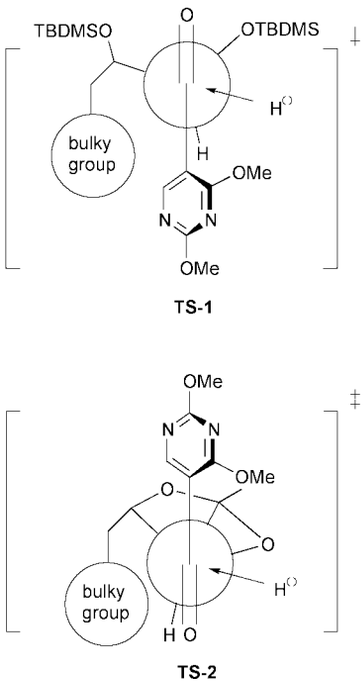


Fig. 1 Transition states of reduction of **9** and **15**.

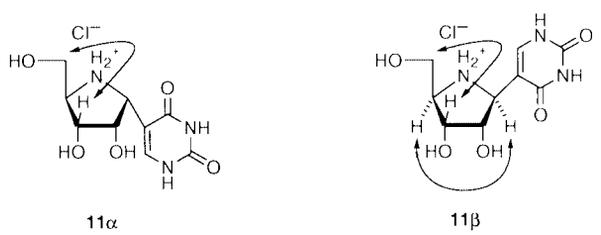


Fig. 2 NOE of **11α** and **11β**.

JEOL JMS-HX 110 mass spectrometer. For fast-atom bombardment (FAB) mass spectra, NBA refers to *m*-nitrobenzyl alcohol matrix. Optical rotations were measured with a JASCO DIP-370 polarimeter. Wakogel C-200, C-300 and Silicagel 60 (Kanto Chemical Co., Inc.) were used for column chromatography, Kieselgel 60 F_{254} (Merck) for TLC, and Wakogel B-5F for preparative TLC (PLC).

(2*R*,3*R*,4*R*)-4-(*tert*-Butoxycarbonylamino)-2,3,5-tris(*tert*-butyldimethylsilyloxy)-1-(2′-thienyl)pentan-1-one 5

To a solution of **4**[8] (1 mmol) in THF (3 ml) was added 2-thienylmagnesium bromide (2.5 mol equiv.) dropwise at 0 °C. After stirring for 3 h at the same temperature, the reaction mixture was quenched with 1 M HCl and then extracted with AcOEt. Purification was performed by the usual PLC method [developer: hexane–AcOEt (15 : 1)] to give ketone **5** in 78% yield. When the reaction mixture was quenched with aq. NH_4Cl, compound **5** and its cyclized compound were obtained in the same yield in the ratio 1 : 3.

Ketone **5**. Oil; ν_{max}/cm^{-1} (neat) 1260, 1470, 1500, 1680, 1720, 2860, 2930, 2960, 3450; MS (FAB) Calc. for $C_{32}H_{64}NO_6SSi_3$: *m*/*z* (M + H), 674.3761. Found: *m*/*z*, 674.3784; $\delta_H(CDCl_3)$ −0.02 (3H, s, SiMe), 0.02 (3H, s, SiMe), 0.02 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.11 (3H, s, SiMe), 0.11 (3H, s, SiMe), 0.81 (9H, s, SiBu′), 0.85 (9H, s, SiBu′), 0.93 (9H, s, SiBu′), 1.39 (9H, s, Boc), 3.69 (2H, m, 5-H_2), 3.99 (1H, m, 4-H), 4.38 (1H, m, 3-H), 4.74 (1H, m, 2-H), 7.12 (1H, dd, *J* 4.7 and 3.6, 4′-H), 7.64 (1H, d, *J* 4.7, 3′-H), 7.98 (1H, d, *J* 3.6, 5′-H); $\delta_C(CDCl_3)$ −5.35 (p), −5.25 (p), −4.93 (p), −4.58 (p), −4.36 (p), 1.12 (p), 18.14 (q), 18.36 (q), 25.85 (q), 25.96 (p), 26.00 (p), 26.15 (p), 28.51 (p), 55.12 (t), 61.69 (s), 74.44 (t), 78.86 (q), 80.82 (t), 127.93 (t), 133.86 (t), 133.95 (t), 142.20 (q), 155.50 (q), 193.08 (q).

(5*R*)-3,4-*O*-Bis(*tert*-butyldimethylsilyloxy)-5-hydroxymethyl-2-(2′-thienyl)-Δ[1]-dihydropyrrole 6 and 2,3-*O*-bis(*tert*-butyldimethylsilyl)-1,4-dideoxy-1,4-imino-1-(2′-thienyl)-D-ribitol 7α and 7β

A mixture of **5** (0.17 mmol), TFA (15 mmol), and CH_2Cl_2 (3 ml) was stirred for 3 h at room temperature. After evaporation the residue was dissolved in EtOH (5 ml) and then treated with $NaBH_3CN$ (5.0 mol equiv.). The resulting mixture was stirred for 2.5 h at room temperature. After the reaction mixture was neutralized with aq. $NaHCO_3$, usual purification with PLC [developer: hexane–AcOEt (3 : 1)] gave **7α** and **7β** in 62 and 9% yield, respectively. When the first reaction mixture was quenched with aq. $NaHCO_3$, the pyrroline **6** was isolated.

Compound **6**. Oil; ν_{max}/cm^{-1} (neat) 1470, 1600, 2880, 2930, 2960, 3270; MS (FAB) Calc. for $C_{21}H_{39}NO_3SSi_2$: *m*/*z* (M + H), 442. Found: *m*/*z*, 442; $\delta_H(CDCl_3)$ −0.02 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.14 (3H, s, SiMe), 0.15 (3H, s, SiMe), 0.83 (9H, s, SiBu′), 0.94 (9H, s, SiBu′), 3.74 (1H, dd, *J* 11.6 and 3.9, 5-H^a), 4.07–4.19 (3H, m, 3- and 4-H and 5-H^b), 4.78 (1H, d, *J* 4.6, 2-H), 6.98–7.11 (2H, m, 3′- and 4′-H), 7.45 (1H, d, *J* 4.8, 5′-H).

Compound **7α**. Oil; ν_{max}/cm^{-1} (neat) 1040, 1120, 1160, 1250, 1470, 2860, 2930, 2960, 3300; MS (FAB) Calc. for $C_{21}H_{42}NO_3SSi_2$: *m*/*z*, (M + H), 444.2424. Found: *m*/*z*, 444.2411; $\delta_H(CDCl_3)$ −0.45 (3H, s, SiMe), 0.02 (3H, s, SiMe), 0.10 (3H, s, SiMe), 0.13 (3H, s, SiMe), 0.81 (9H, s, SiBu′), 0.92 (9H, s, SiBu′), 3.47 (1H, m, 4-H), 3.54 (1H, dd, *J* 11.0 and 3.5, 5-H^a), 3.69 (1H, dd, *J* 11.0 and 4.2, 5-H^b), 4.01 (1H, dd, *J* 3.4 and 3.3, 2-H), 4.14 (1H, dd, *J* 7.5 and 3.3, 3-H), 4.27 (1H, d, *J* 3.3, 1-H), 6.97 (2H, m, 3′- and 4′-H), 7.20 (1H, m, 5′-H); $\delta_C(CDCl_3)$ −5.20 (p), −4.69 (p), −4.04 (p), −3.66 (p), 18.26 (q), 18.32 (q), 26.17 (p), 26.22 (p), 60.52 (t), 61.68 (s), 62.62 (t), 75.39 (t), 76.90 (t), 124.27 (t), 125.19 (t), 126.66 (t), 142.90 (q).

Compound **7β**. Oil; ν_{max}/cm^{-1} (neat) 1090, 1160, 1260, 1470, 2860, 2930, 2960, 3350; MS (FAB) Found: *m*/*z* 444.2440; $\delta_H(CDCl_3)$ −0.45 (3H, s, SiMe), −0.04 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.08 (3H, s, SiMe), 0.86 (9H, s, SiBu′), 0.92 (9H, s, SiBu′), 3.38 (1H, m, 4-H), 3.50 (1H, dd, *J* 11.0 and 4.0, 5-H^a), 3.62 (1H, dd, *J* 11.0 and 4.4, 5-H^b), 3.79 (1H, dd, *J* 5.7 and 4.0, 2-H), 3.95 (1H, dd, *J* 4.0 and 3.9, 3-H), 4.54 (1H, d, *J* 5.7, 1-H), 6.97 (2H, m, 3′- and 4′-H), 7.18 (1H, dd, *J* 4.7 and 1.5, 5′-H); $\delta_C(CDCl_3)$ −5.30 (p), −4.66 (p), −4.55 (p), −4.38 (p), 18.01 (q), 18.06 (q), 25.89 (p), 25.89 (p), 61.80 (t), 62.58 (s), 63.46 (t), 74.10 (t), 80.62 (t), 123.69 (t), 123.77 (t), 126.90 (t), 148.65 (q).

1,4-Dideoxy-1,4-imino-1-(2′-thienyl)-D-ribitol 8α and 8β

A mixture of **7α** (0.37 mmol), MeOH (3 ml), and conc. HCl (3 ml) was refluxed for 3 h. After evaporation the residue was dissolved in a small amount of MeOH. Et_2O was added to the resulting solution to give the hydrochloride salt as a white precipitate. This reprecipitation was repeated to give pure **8α**·HCl in 87% yield. In the same way, **8β**·HCl was isolated starting from **7β** in 90% yield.

Free base **8α**. Powder; ν_{max}/cm^{-1} (KBr) 1410, 1560, 2360, 2930, 3310; MS (FAB) Calc. for $C_9H_{14}NO_3S$: *m*/*z* (M + H), 216.0694. Found: *m*/*z*, 216.0679; $\delta_H(CD_3OD)$ 3.23 (1H, m, 4-H), 3.62 (1H, dd, *J* 11.1 and 3.9, 5-H^a), 3.72 (1H, dd, *J* 11.1 and 5.8, 5-H^b), 4.00 (1H, dd, *J* 4.0 and 3.2, 2-H), 4.10 (1H, dd, *J* 7.7 and 4.0, 3-H), 4.48 (1H, d, *J* 3.2, 1-H), 6.97 (1H, dd, *J* 5.1 and 3.5, 4′-H), 7.07 (1H, d, *J* 3.5, 3′-H), 7.30 (1H, dd, *J* 5.1 and 1.0, 5′-H); $\delta_C(CD_3OD)$ 61.28 (t), 63.96 (s), 64.65 (t), 75.88 (t), 75.88 (t), 125.93 (t), 126.67 (t), 127.23 (t), 143.16 (q).

Free base **8β**. Powder; ν_{max}/cm^{-1} (KBr) 1410, 1560, 1660, 2360, 2930, 3340; MS (FAB) Calc for. $C_9H_{14}NO_3S$: *m*/*z* (M + H), 216.0694. Found: *m*/*z*, 216.0701; $\delta_H(CD_3OD)$ 3.06 (1H, m, 4-H), 3.57 (2H, m, 5-H^a and 5-H_2), 3.76 (1H, dd, *J* 7.0 and 5.9, 2-H), 3.85 (1H, dd, *J* 5.9 and 4.6, 3-H), 4.18 (1H, d, *J* 7.0, 1-H), 6.88 (1H, dd, *J* 5.1 and 3.5, 4′-H), 6.98 (1H, m, 3′-H), 7.19 (1H,

m, 5′-H); δ_C(CD_3OD) 62.83 (t), 63.12 (s), 66.09 (t), 73.27 (t), 79.25 (t), 125.57 (t), 125.75 (t), 128.02 (t), 145.45 (q).

(2*R*,3*R*,4*R*)-4-(*tert*-Butoxycarbonylamino)-2,3,5-tris(*tert*-butyldimethylsilyloxy)-1-(2′,4′-dimethoxypyrimidin-5′-yl)-pentan-1-one 9

To a solution of 5-bromo-2,4-dimethoxypyrimidine (3 mmol) in THF (15 ml) was added *n*-butyllithium (3 mmol) dropwise at −78 °C. After stirring of this mixture for 10 min, a solution of **4** (3 mmol) in THF (3 ml) was added to the solution at the same temperature. After additional stirring for 2 h at the same temperature, the reaction mixture was quenched with 1 M HCl and then extracted with AcOEt. Purification was performed by the usual PLC method [developer: hexane–AcOEt (4:1)] to give ketone **9** in 28% yield.

Ketone **9**. Oil; ν_{max}/cm^{-1} (neat) 1470, 1500, 1680, 1720, 2860, 2930, 2960, 3450; MS (FAB) Calc. for $C_{34}H_{68}N_3O_8Si_3$: *m*/*z* (M + H), 730. Found: *m*/*z*, 730; δ_H($CDCl_3$) −0.48 (3H, s, SiMe), −0.13 (3H, s, SiMe), 0.09 (3H, s, SiMe), 0.10 (3H, s, SiMe), 0.13 (3H, s, SiMe), 0.17 (3H, s, SiMe), 0.80 (9H, s, SiBu^t), 0.92 (9H, s, SiBu^t), 0.92 (9H, s, SiBu^t), 1.11 (9H, s, Boc), 3.38 (1H, m, 4-H), 3.88–4.06 (8H, m, 2 × OMe and 5-H_2), 4.29 (2H, m, 2- and 3-H), 4.89 (1H, br s, NH), 8.52 (1H, s, 6′-H); δ_C($CDCl_3$) −5.43 (p), −5.43 (p), −5.07 (p), −4.80 (p), −4.48 (p), −4.39 (p), 18.00 (q), 18.05 (q), 18.50 (q), 25.84 (p), 25.92 (p), 26.08 (p), 28.14 (p), 53.30 (p), 55.00 (p), 61.61 (s), 65.78 (t), 72.14 (t), 73.77 (t), 79.98 (q), 87.64 (q), 115.95 (q), 154.35 (q), 159.39 (t), 164.78 (q), 166.54 (q).

(1*R*)-2,3-*O*-Bis(*tert*-butyldimethylsilyl)-1,4-dideoxy-1-(2′,4′-dimethoxypyrimidin-5′-yl)-1,4-imino-D-ribitol 10

A mixture of **9** (0.22 mmol), TFA (13.2 mmol), and CH_2Cl_2 (5 ml) was stirred for 3 h at room temperature. After evaporation the residue was dissolved in EtOH (5 ml) and then $NaBH_3CN$ (5.0 mol equiv.) was added to this solution. The resulting mixture was stirred for 2.5 h at room temperature. Usual purification with PLC using AcOEt as developer gave **10** as the α-form in 40% yield.

Compound **10**. Oil; ν_{max}/cm^{-1} (neat) 1380, 1400, 1470, 1580, 1600, 2860, 2930, 2960, 3430; MS (FAB) Calc. for $C_{23}H_{46}N_3O_5Si_2$: *m*/*z* (M + H), 500.2976. Found: *m*/*z*, 500.2965; δ_H($CDCl_3$) −0.55 (3H, s, SiMe), −0.02 (3H, s, SiMe), 0.10 (3H, s, SiMe), 0.13 (3H, s, SiMe), 0.74 (9H, s, SiBu^t), 0.91 (9H, s, SiBu^t), 3.36 (1H, m, 4-H), 3.74 (1H, dd, *J* 11.2 and 4.8, 5-H^a), 3.77 (1H, dd, *J* 11.2 and 3.4, 5-H^b), 3.97 (3H, s, OMe), 3.98 (3H, s, OMe), 4.12 (2H, m, 2- and 3-H), 4.33 (1H, d, *J* 2.4, 1-H), 8.27 (1H, s, 6′-H); δ_C($CDCl_3$) −5.22 (p), −4.82 (p), −4.34 (p), −3.73 (p), 17.97 (q), 18.15 (q), 25.78 (p), 26.07 (p), 53.92 (p), 54.75 (p), 56.34 (t), 61.45 (s), 62.32 (t), 75.02 (t), 75.53 (t), 112.59 (q), 157.53 (t), 164.46 (q), 168.44 (q).

(1*R*)-1,4-Dideoxy-1-(2′,4′-Dioxo-1′,2′,3′,4′-tetrahydropyrimidin-5′-yl)-1,4-imino-D-ribitol 11α

Deprotection of **10** was performed by the same method as described in the preparation of **8α** and **8β**. The pure salt **11α** was obtained in 85% yield.

Salt **11α**·HCL. Powder; ν_{max}(KBr)/cm^{-1} 1110, 1120, 1220, 1400, 1440, 1670, 1720, 2930, 3420; MS (FAB) Calc. for $C_9H_{14}N_3O_5$: *m*/*z* (M + H), 244.0933. Found: *m*/*z*, 244.0922; δ_H(D_2O) 3.61 (1H, m, 4-H), 3.75 (1H, dd, *J* 12.6 and 5.7, 5-H^a), 3.86 (1H, dd, *J* 12.6 and 3.4, 5-H^b), 4.23–4.28 (2H, m, 2- and 3-H), 4.54 (1H, d, *J* 2.7, 1-H), 7.83 (1H, s, 6′-H); δ_C(D_2O) 59.65 (t), 61.09 (s), 64.95 (t), 74.33 (t), 74.56 (t), 106.71 (q), 146.57 (t), 155.10 (q), 168.32 (q).

(1*S*,2*S*,3*R*,4*R*)-4-(*tert*-Butoxycarbonylamino)-2,3,5-tris(*tert*-butyldimethylsilyloxy)-1-(2′,4′-dimethoxypyrimidin-5′-yl)-pentan-1-ol 12

A mixture of **9** (0.21 mmol), EtOH (5 ml), and $NaBH_4$ (1.5 mol equiv.) was stirred for 10 h at room temperature. After being quenched with aq. NH_4Cl, the reaction mixture was extracted with AcOEt and the solvent was then removed by rotary evaporation to give the residue, which was then purified by using PLC on silica gel [developer: hexane–AcOEt (4:1)] to give 55 mg of compound **12** and 91 mg of recovered **9**. The yield of **12** is 36% and the conversion yield is 59%.

Alcohol **12**. Oil; ν_{max}/cm^{-1} (neat) 1570, 1600, 1720, 2860, 2900, 2930, 2960, 3310, 3430; MS (FAB) Calc. for $C_{34}H_{70}N_3O_8Si_3$: *m*/*z* (M + H), 732.4471. Found: *m*/*z*, 732.4481; δ_H($CDCl_3$) −0.43 (3H, s, SiMe), 0.01 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.12 (3H, s, SiMe), 0.85 (9H, s, SiBu^t), 0.88 (9H, s, SiBu^t), 0.91 (9H, s, SiBu^t), 1.43 (9H, s, Boc), 3.71–3.81 (3H, m, 4- and 5-H_2), 3.97 (3H, s, OMe), 3.98 (3H, s, OMe), 4.00–4.02 (2H, m, 2- and 3-H), 4.90 (1H, br s, NH), 5.04 (1H, br s, 1-H), 8.36 (1H, s, 6′-H); δ_C($CDCl_3$) −5.61 (p), −5.48 (p), −5.26 (p), −5.14 (p), −4.06 (p), −3.92 (p), 18.13 (q), 18.21 (q), 18.28 (q), 25.74 (p), 25.90 (p), 26.07 (p), 28.40 (p), 53.91 (p), 54.74 (p), 61.59 (s), 67.88 (t), 71.93 (t), 72.43 (t), 75.64 (t), 79.23 (q), 115.09 (q), 155.51 (q), 157.85 (t), 167.67 (q), 174.52 (q).

N-(*tert*-Butoxycarbonyl)-2,3,5-*O*-tris(*tert*-butyldimethylsilyl)-1,4-dideoxy-1-(2′,4′-dimethoxypyrimidin-5′-yl)-1,4-imino-D-ribitol 13

A mixture of **12** (0.06 mmol), CH_2Cl_2 (5 ml), Et_3N (0.12 mmol), and MsCl (0.12 mmol) was stirred for 1 h at 0 °C. The reaction mixture was extracted with $CHCl_3$. Usual purification by using PLC [developer: hexane–AcOEt (4:1)] gave compound **13** in 87% yield.

Compound **13**. Oil; ν_{max}/cm^{-1} (neat) 1570, 1600, 1700, 2860, 2930, 2960; MS (FAB) Calc. for $C_{34}H_{68}N_3O_7Si_3$: *m*/*z* (M + H), 714.4365. Found: *m*/*z*, 714.4347; δ_H(DMSO) −0.28 (3H, s, SiMe), −0.16 (3H, s, SiMe), −0.05 (3H, s, SiMe), −0.04 (3H, s, SiMe), −0.01 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.69 (9H, s, SiBu^t), 0.77 (9H, s, SiBu^t), 0.82 (9H, s, SiBu^t), 1.13 (9H, s, Boc), 3.57 (1H, m, 4-H), 3.66 (1H, dd, *J* 10.4 and 4.1, 5-H^a), 3.78 (3H, s, OMe), 3.81 (3H, s, OMe), 3.87 (1H, dd, *J* 10.4 and 7.3, 5-H^b), 4.05–4.08 (2H, m, 2- and 3-H), 4.50 (1H, d, *J* 5.5, 1-H), 8.19 (1H, s, 6′-H); δ_C($CDCl_3$) −5.48 (p), −5.31 (p), −5.10 (p), −4.96 (p), −4.65 (p), −4.15 (p), 18.02 (q), 18.09 (q), 18.52 (q), 25.68 (p), 26.10 (p), 26.21 (p), 28.36 (p), 53.43 (p), 53.92 (p), 54.67 (p), 61.15 (s), 66.78 (t), 71.28 (t), 71.71 (t), 74.80 (t), 79.99 (q), 114.83 (q), 155.32 (q), 164.42 (t), 168.20 (q), 178.12 (q).

(1*S*)-1,4-Dideoxy-1-(2′,4′-dioxo-1′,2′,3′,4′-tetrahydropyrimidin-5′-yl)-1,4-imino-D-ribitol 11β

A mixture of **13** (0.064 mmol), MeOH (5 ml), and conc. HCl (5 ml) was refluxed for 3 h. Work-up was performed by the same way as described in the preparation of **11α** to give pure salt **11β** in 95% yield.

Salt **11β**·HCl. Powder; ν_{max}(KBr)/cm^{-1} 1130, 1260, 1420, 1630, 1660, 1710, 3280, 3390, 3450, 3520; MS (FAB) Calc. for $C_9H_{14}N_3O_5$: *m*/*z* (M + H), 244.0933. Found: *m*/*z*, 244.0929; δ_H(D_2O) 3.65 (1H, m, 4-H), 3.75 (1H, dd, *J* 12.7 and 5.5, 5-H^a), 3.79 (1H, dd, *J* 12.7 and 4.3, 5-H^b), 4.21 (1H, dd, *J* 5.2 and 3.7, 3-H), 4.25 (1H, d, *J* 8.5, 1-H), 4.41 (1H, dd, *J* 8.5 and 5.2, 2-H), 7.64 (1H, s, 6′-H); δ_C(D_2O) 61.29 (s), 62.64 (t), 68.22 (t), 73.21 (t), 74.24 (t), 106.98 (q), 146.79 (t), 155.42 (q), 168.29 (q).

(2*R*,3*R*,4*R*)-4-(*tert*-Butoxycarbonylamino)-5-(*tert*-butyldimethylsilyloxy)-1-(2′,4′-dimethoxypyrimidin-5′-yl)-2,3-(isopropylidenedioxy)pentan-1-one 15 and (2*S*,3*R*,4*R*)-4-(*tert*-butoxycarbonylamino)-5-(*tert*-butyldimethylsilyloxy)-1-(2′,4′-dimethoxypyrimidin-5′-yl)-2,3-(isopropylidenedioxy)pentan-1-ol 16

The reaction of **14**[9] with 5-lithio-2,4-dimethoxypyrimidine was carried out by the same method as described in the preparation of **9**. Purification was performed by column chromato-

graphy [eluent: hexane–AcOEt (2:1)] to give ketone **15**, which was then reduced with $NaBH_4$ (1 mmol) in EtOH (10 ml). The mixture was stirred for 3 h at room temperature and then quenched with aq. NH_4Cl. Usual work-up using PLC [developer: hexane–AcOEt (2:1)] gave alcohol **16** in 65% yield.

Ketone **15**. Oil; ν_{max}/cm^{-1} (neat) 1590, 1700, 2860, 2930, 2960, 3450; MS (FAB) Calc. for $C_{25}H_{44}N_3O_8Si$: *m/z* (M + H), 542.2898. Found: *m/z*, 542.2898; $\delta_H(CDCl_3)$ 0.00 (3H, s, SiMe), 0.02 (3H, s, SiMe), 0.83 (9H, s, SiBu^t), 1.20 (3H, s, isopropylidene-Me), 1.42 (9H, s, Boc), 1.57 (3H, s, isopropylidene-Me), 3.56 (1H, m, 4-H), 3.68 (1H, dd, *J* 10.1 and 6.0, 5-H^a), 3.82 (1H, dd, *J* 10.1 and 3.0, 5-H^b), 3.96 (3H, s, OMe), 3.98 (3H, s, OMe), 4.23–4.65 (3H, m, 2- and 3-H and NH), 8.23 (1H, s, 6′-H); $\delta_C(CDCl_3)$ −5.66 (p), −5.43 (p), 17.96 (q), 24.89 (p), 25.69 (p), 27.93 (p), 28.15 (p), 62.40 (t), 63.12 (s), 63.60 (p), 64.20 (p), 80.03 (t), 80.60 (t), 84.77 (t), 87.50 (q), 109.85 (q), 112.39 (q), 153.87 (q), 157.36 (t), 164.09 (q), 166.28 (q).

Alcohol **16**. Oil; ν_{max}/cm^{-1} (neat) 1580, 1600, 1720, 2860, 2930, 2960, 2990, 3400; MS (FAB) Calc. for $C_{25}H_{46}N_3O_8Si$: *m/z* (M + H), 544.3054. Found: *m/z*, 544.3053; $\delta_H(CDCl_3)$ 0.04 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.88 (9H, s, SiBu^t), 1.22 (3H, s, isopropylidene-Me), 1.25 (3H, s, isopropylidene-Me), 1.42 (9H, s, Boc), 3.72 (1H, dd, *J* 10.1 and 3.0, 5-H^a), 3.91 (1H, dd, *J* 10.1 and 3.4, 5-H^b), 3.94 (3H, s, OMe), 3.95 (3H, s, OMe), 4.00 (1H, m, 4-H), 4.24 (1H, dd, *J* 9.3 and 4.9, 3-H), 4.43 (1H, dd, *J* 9.5 and 4.9, 2-H), 4.87 (1H, d, *J* 9.5, 1-H), 8.19 (1H, s, 6′-H); $\delta_C(CDCl_3)$ −5.49 (p), −5.44 (p), 18.37 (q), 25.52 (p), 25.91 (p), 27.63 (p), 28.35 (p), 53.85 (t), 54.66 (p), 54.73 (p), 63.08 (s), 65.48 (t), 76.17 (t), 78.79 (t), 80.35 (q), 107.97 (q), 115.57 (q), 156.30 (q), 157.67 (t), 164.64 (q), 169.04 (q).

N-(*tert*-Butoxycarbonyl)-5-*O*-(*tert*-butyldimethylsilyl)-1,4-dideoxy-1-(2′,4′-dimethoxypyrimidin-5′-yl)-1,4-imino-2,3-*O*-isopropylidene-D-ribitol 17α and 17β

A mixture of **16** (0.65 mmol), CH_2Cl_2 (5 ml), Et_3N (1.3 mmol), and MsCl (1.3 mmol) was treated by the same method as described in the preparation of **13**. Purification was carried out by usual PLC [developer: hexane–AcOEt (2:1)] to give compounds **17α** and **17β** in 80 and 11% yield, respectively. Compounds **17α** and **17β** were deprotected by the usual method using HCl–MeOH to give thiols **11α** and **11β** in 87 and 90% yield, respectively.

Compound **17α**. Oil; $[\alpha]_D^{25}$ -75.1×10^{-1} deg cm^2 g^{-1} (*c* 0.20 in $CHCl_3$); ν_{max}/cm^{-1} (neat) 1470, 1580, 1600, 1700, 2360, 2860, 2930, 2960; MS (FAB) Calc. for $C_{25}H_{44}N_3O_7Si$: *m/z* (M + H), 526.2949. Found: *m/z*, 526.2940; δ_H(DMSO) 0.00 (3H, s, SiMe), 0.02 (3H, s, SiMe), 0.85 (9H, s, SiBu^t), 1.02 (3H, s, isopropylidene-Me), 1.14 (12H, s, Boc and isopropylidene-Me), 3.70 (1H, m, 5-H^a), 3.83 (3H, s, OMe), 3.84 (3H, s, OMe), 3.97 (2H, m, 4-H and 5-H^b), 4.66 (2H, m, 2- and 3-H), 4.99 (1H, d, *J* 5.8, 1-H), 7.81 (1H, s, 6′-H); δ_C(DMSO) −6.27 (p), −6.18 (p), 17.17 (q), 23.93 (p), 24.65 (p), 25.11 (p), 27.27 (p), 52.96 (p), 53.62 (p), 58.21 (q), 61.73 (s), 63.26 (t), 78.50 (t), 78.66 (t), 81.30 (t), 110.21 (q), 112.27 (q), 152.87 (q), 156.26 (t), 163.32 (q), 167.00 (q).

Compound **17β**. Oil; ν_{max}/cm^{-1} (neat) 1470, 1570, 1600, 1700, 2360, 2860, 2930, 2960; MS (FAB) Found: *m/z* 526.2927; δ_H(DMSO) 0.00 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.80 (9H, s, SiBu^t), 1.23 (3H, s, isopropylidene-Me), 1.28 (9H, s, Boc), 1.39 (3H, s, isopropylidene-Me), 3.67 (1H, dd, *J* 10.3 and 4.5, 5-H^a), 3.75 (1H, dd, *J* 10.3 and 4.0, 5-H^b), 3.84 (3H, s, OMe), 3.91 (3H, s, OMe), 4.00 (1H, ddd, *J* 4.5, 4.0 and 1.4, 4-H), 4.53 (1H, dd, *J* 5.7 and 2.2, 2-H), 4.58 (1H, dd, *J* 5.7 and 1.4, 3-H), 4.81 (1H, d, *J* 2.2, 1-H), 8.03 (1H, s, 6′-H); δ_C(DMSO) −5.65 (p), −5.65 (p), 17.83 (q), 25.25 (p), 25.62 (p), 27.29 (p), 27.85 (p), 53.93 (p), 54.34 (p), 62.63 (s, q), 65.50 (t), 79.63 (t), 81.08 (t), 84.59 (t), 110.96 (q), 112.92 (q), 153.47 (q), 155.83 (t), 164.16 (q), 167.71 (q).

References

1 (*a*) H. Togo, M. Aoki and M. Yokoyama, *Tetrahedron Lett.*, 1991, **32**, 6559; (*b*) H. Togo, S. Ishigami and M. Yokoyama, *Chem. Lett.*, 1992, 1673; (*c*) H. Togo, M. Aoki, T. Kuramochi and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2417; (*d*) M. Yokoyama, T. Tanabe, A. Toyoshima, T. Akiba and H. Togo, *Synthesis*, 1993, 517; (*e*) M. Yokoyama, A. Toyoshima, A. Akiba and H. Togo, *Chem Lett.*, 1994, 265; (*f*) S. Ishigami, H. Togo and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2407; (*g*) H. Togo, S. Ishigami, M. Fujii, T. Ikuma and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2931; (*h*) M. Yokoyama, T. Akiba and H. Togo, *Synthesis*, 1995, 638; (*i*) M. Yokoyama, M. Nomura, T. Tanabe and H. Togo, *Heteroatom. Chem.*, 1995, **6**, 189; (*j*) M. Yokoyama, M. Nomura, H. Togo and H. Seki, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2145; (*k*) M. Yokoyama, H. Toyoshima, M. Shimizu and H. Togo, *J. Chem. Soc., Perkin Trans. 1*, 1997, 29; (*l*) W. Hei, H. Togo, H. Ogawa and M. Yokoyama, *Heteroatom. Chem.*, 1997, **8**, 411.

2 Reviews: (*a*) A. Momotake, H. Togo and M. Yokoyama, *Yuki Gosei Kagaku Kyokaishi*, 1998, **56**, 1036 (*in Japanese*) (*Chem. Abstr.*, 1999, **130**, 66671d); (*b*) M. Yokoyama and A. Momotake, *Synthesis*, 1999, 1541.

3 (*a*) M. Yokoyama, T. Akiba, Y. Ochiai, A. Momotake and H. Togo, *J. Org. Chem.*, 1996, **61**, 6079; (*b*) A. Momotake, J. Mito, K. Yamaguchi, H. Togo and M. Yokoyama, *J. Org. Chem.*, 1998, **63**, 7207.

4 M. Yokoyama, T. Ikeue, Y. Ochiai, A. Momotake, K. Yamaguchi and H. Togo, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2185.

5 A. Momotake, H. Togo and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1193.

6 H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, 1948, **70**, 3121.

7 K.-C. Woo and K. Jones, *Tetrahedron Lett.*, 1991, **32**, 6949.

8 G. Rassu, L. Pinna, P. Spanu, F. Ulgheri and G. Casiraghi, *Tetrahedron Lett.*, 1994, **35**, 4019.

9 H. Yoda, T. Oguchi and K. Takabe, *Tetrahedron: Asymmetry*, 1996, **7**, 2113.