Pergamon

Tetrahedron Vol. 50, No. 47, pp. 13335-13346, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00859-0

Enantiospecific Synthesis of [(2'*S*, 3'*S*)-Bis(hydroxymethyl)azetidin-1-yl] Pyrimidine Nucleosides as Potential Antiviral Agents[1]

Fumio Hosono, Shigeru Nishiyama, and Shosuke Yamamura

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223, Japan

Takao Izawa and Kuniki Kato *

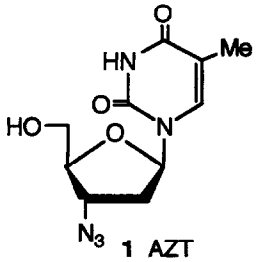
Research Laboratories, Pharmaceuticals Group, Nippon Kayaku Co. Ltd., 3-31-12 Shimo, Kita-ku, Tokyo 115, Japan

Yukimasa Terada

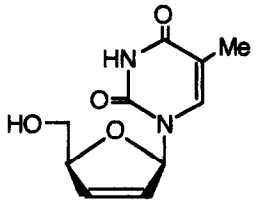
Faculty of Pharmacy, Meijo University, Tempaku-ku, Nagoya 468, Japan

Abstract: The enantiospecific synthesis of [(2'*S*, 3'*S*)-bis(hydroxymethyl)azetidin-1-yl]pyrimidine nucleosides **22**, **25**, and **27** was achieved *via* construction of the base on the 1-aminoazetidine **18** prepared from (+)-diethyl-L-tartrate, and they are the first members of a new class of nucleoside analogs in which the oxetane ring in oxetanocin-A **4** is replaced by an azetidine ring linked to a nucleic base through an N-N bond.

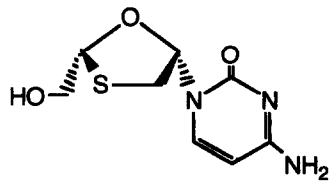
The unique nature of the replicative cycle of HIV-1 provides many potential targets for the discovery of chemotherapeutic intervention, i.e. inhibitors of reverse transcriptase, protease, and HIV-1 nuclear regulatory proteins tat and rev. The design and synthesis of potential these inhibitors therefore constitutes a rational strategy for the development of anti-AIDS agents which is presently being pursued by a large number of research groups. At present, besides AZT (3'-azido-3'-deoxythymidine) **1**, ddI (2',3'-dideoxyinosine) and ddC (2',3'-dideoxycytidine) being the only approved drugs for the clinical treatment of AIDS, some very recently prepared nucleosides such as d4T (2',3'-didehydro-3'-deoxythymidine) **2**[2] and (-)-3TC (β-L-(-)-2'-deoxy-3'-thiacytidine, Lamivudine™) **3**[3] show very promising anti-HIV activity and selectivity. However, it is critical to search for new and less toxic anti-HIV agents which are not cross-resistant with the existing drugs.



1 AZT



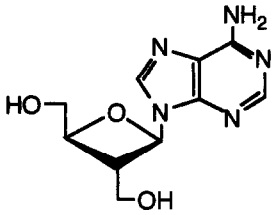
2 d4T



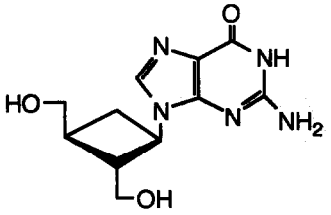
3 (-)-3TC

As a part of our continuing studies on the preparation and antiviral evaluation of analogs of the potent antiviral antibiotics oxetanocin-A **4**,[4] and carbocyclic oxetanocin-G **5**,[5] we became interested in developing a synthesis of (azetidin-1-yl)pyrimidine and purine nucleoside analogs possessing a flexible N-N glycosyl link.

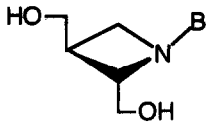
We describe herein the successful synthesis of [(2'*S*, 3'*S*)-bis(hydroxymethyl)azetidin-1-yl]pyrimidine nucleosides **6**.[6]



4 Oxetanocin-A

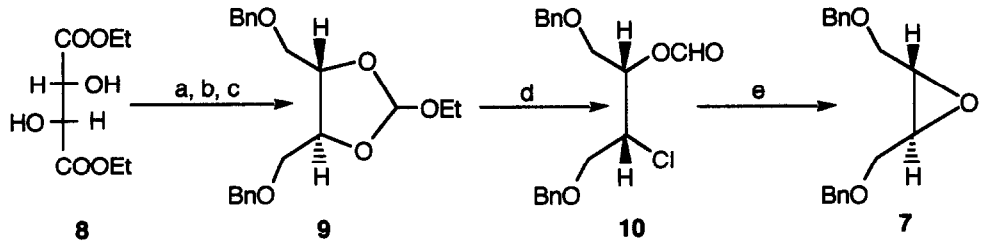


5 COXT-G



6 B = nucleic acid base

Synthesis of the N-aminoazetidine 18.- As shown in Scheme 2, the synthesis of the key intermediate azetidine **16** began with (*S*, *S*)-1,4-bis(benzyloxy)-2,3-epoxybutane **7** prepared from (+)-diethyl-L-tartrate **8** according to the protocol of Nicolaou *et al.*.[7] Reaction of **8** with triethyl orthoformate and pyridinium *p*-toluenesulfonate at 130-140 °C without solvent followed by lithium aluminum hydride reduction and protection of the resulting diol as a dibenzyl ether furnished the orthoformate **9** in 62 % overall yield. Treatment of **9** with phosphorus pentachloride led smoothly to the chloroformate **10** in 99 % yield which upon basic treatment gave the desired optically active epoxide **7** in 88 % yield (Scheme 1).

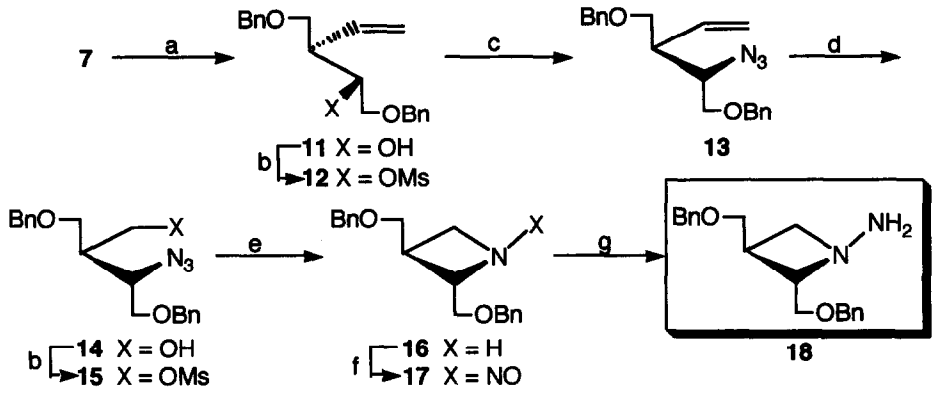


8 **9** **10** **7**

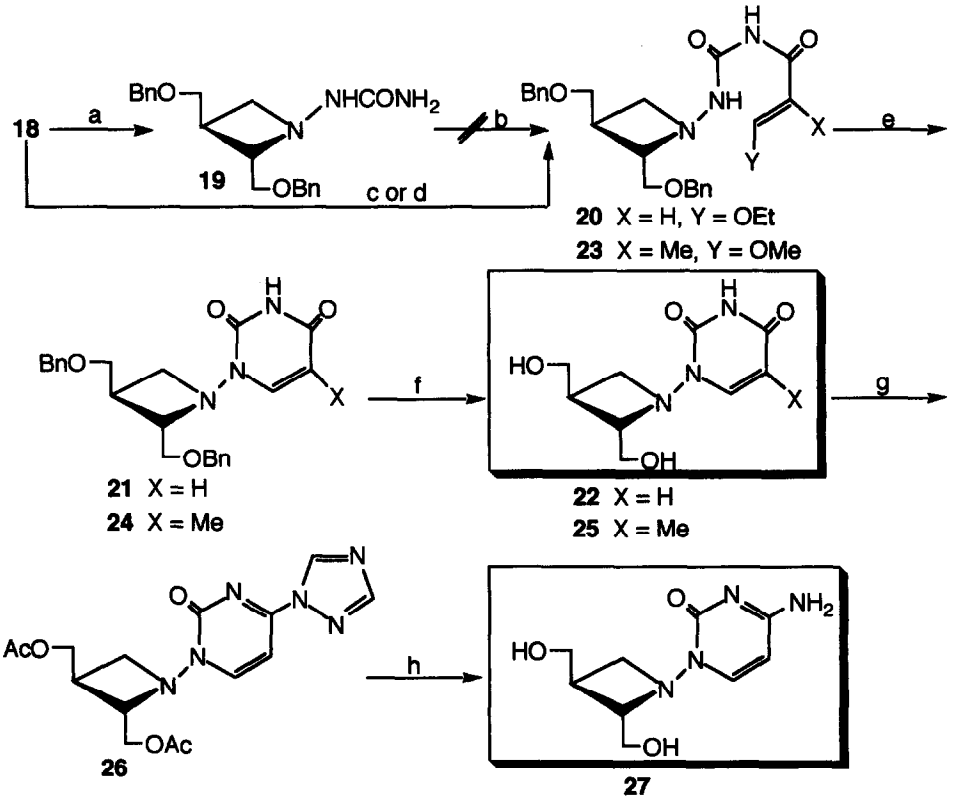
Scheme 1. *Reagents and conditions* : (a) $CH(OEt)_3$, PPTS, 130-140 °C, 2 h. (b) $LiAlH_4$, THF, 0 °C, 1 h. (c) BnBr, NaH, THF, 70 °C, 16 h. (d) PCl_5, CH_2Cl_2, rt, 3 h. (e) K_2CO_3, MeOH, rt, 18 h.

Starting from **7** thus obtained, reaction of **7** with vinylmagnesium bromide in the presence of CuI gave the vinyl-alcohol **11** in 94 % yield. Mesylation of **11** with methanesulfonyl chloride followed by an S_N2 substitution with sodium azide in DMF afforded the vinyl-azide **13** in 89 % yield (2 steps). Then **13** was subjected to the following two-step one pot procedure because of the rapid epimerization of the aldehyde obtained during aqueous work-up and/or silica gel chromatography. Ozonolysis of **13** in MeOH and subsequent *in situ* reduction of the ozonide with sodium borohydride yielded the azido-alcohol **14** in 77 % yield. Although several attempts to get the azetidine **16** by a reductive cyclization of **14** with triphenylphosphine[8] failed, compound **16** could be obtained as follows: mesylation of **14** with methanesulfonyl chloride gave the azido-mesylate **15**, which smoothly cyclized *in situ* during hydrogenation with Raney-Ni (W-2) to yield **16** in 86 % yield (2 steps). Compound **16** was nitrosated with excess isoamyl nitrite to give the nitroso-azetidine **17** in quantitative yield. Lithium aluminum hydride reduction of **17** gave the unstable 1-aminoazetidine **18** in 83 % yield.

Synthesis of Pyrimidine Nucleosides.- The synthetic route to the uracil analogs from **18** was based on a variant of the general methodology for the synthesis of uracils and thymines developed initially by Shaw and Warrener.[9] Initially, in order to obtain the uracil nucleoside **22** compound **18** was treated with trimethylsilyl isocyanate in CH_2Cl_2 to afford the urea **19** as a stable solid in 55 % yield. Attempted condensations of compound **19** with 3-ethoxyacryloyl chloride to give the intermediate acrylamide **20** were unsuccessful.



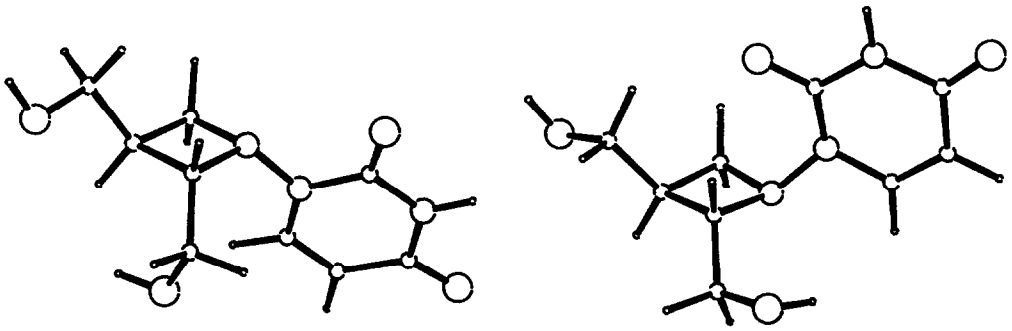
Scheme 2. *Reagents and conditions* : (a) CH_2=CHMgBr, CuI, Et_2O, -10 °C, 4.5 h. (b) MsCl, Et_3N, 0 °C, 4 h. (c) NaN_3, DMF, 100 °C, 1 h. (d) O_3, MeOH, -20 °C, then $NaBH_4$, rt, 10 h. (e) Raney-Ni W-2, EtOH, rt, 15 h. (f) isoamyl nitrite, 0 °C → rt, 20 h. (g) $LiAlH_4$, THF, -10 °C, 3.5 h.



Scheme 3. *Reagents and conditions* : (a) TMSNCO, CH_2Cl_2, rt, 15 h. (b) 3-ethoxyacryloyl chloride, pyridine. (c) 3-ethoxyacryloyl isocyanate, benzene-DMF, rt, 12 h. (d) 3-methoxy-2-methylacryloyl isocyanate, benzene-DMF, rt, 12 h. (e) 7% NH_4OH, EtOH, 80 °C, 8 h. (f) 20% $Pd(OH)_2$/C, cyclohexene, EtOH, refluxing temp., 3 h. (g) i: Ac_2O, pyridine, rt, 10 h, ii: *o*-$ClC_6H_4OPOCl_2$, 1,2,4-triazole, pyridine, -30 °C→ rt, 12 h. (h) 35% NH_4OH, MeOH, rt, 15 h.

Alternatively, treatment of **18** with 3-ethoxyacryloyl isocyanate generated *in situ* from 3-ethoxyacryloyl chloride and silver cyanate readily afforded **20** in 64 % yield, which cyclized smoothly upon treatment with 7 % NH_4OH in EtOH at 80 °C to provide the uracil **21** in 92 % yield. Deprotection of **21** by transfer hydrogenolysis with 20 % $Pd(OH)_2$ on carbon and cyclohexene afforded the target compound **22** in 64 % yield. The thymine nucleoside **25** was produced by treatment of **18** with 3-methoxy-2-methylacryloyl isocyanate in benzene to afford the intermediate acrylamide **23** in 51 % yield. Subsequent ring closure with 7 % NH_4OH in EtOH at 80 °C gave the thymine **24** in 41 % yield, which was then deblocked under the same reaction conditions tried for compound **21** to afford the target compound **25** in 40 % yield. The cytosine nucleoside **27** was prepared according to the procedure of Sung.[10] Treatment of the diacetate of **22** with *o*-chlorophenyl phosphorodichloridate and 1,2,4-triazole in pyridine provided the 4-triazolylpyrimidinone **26** in 26 % yield. Subsequent treatment of **26** with 35 % ammonium hydroxide in MeOH at room temperature produced the target compound **27** in 56 % yield (Scheme 3).

Although two isomers of α and β forms due to inversion at the azetidine nitrogen presumably exist, the NMR spectra of compounds **22**, **25**, and **27** bearing a bulky azetidine ring indicated the existence of one isomer, probably β one, respectively.[11] In fact, evaluation of relative stabilities of the two forms of (azetidin-1-yl)nucleoside was carried out by using MOPAC PM3 calculations, indicating that the β isomer is more stable than the α isomer by ca. 3.7 Kcal/mol, as shown in Fig. 1, and therefore more than 99 % of the total populations may be in the β form under thermal equilibrium conditions (> 80 °C).



α-isomer
−116.364 Kcal/mol

β-isomer
−120.065 Kcal/mol

Fig. 1. Heat of formation of the two isomers based on MOPAC PM3 calculations.

Biological Activity: Evaluation of compounds **22**, **25**, and **27** against HSV-1 and HSV-2 in Vero cells by a plaque reduction assay at concentrations up to 10 μg/ml, and HIV-1 in MT-4 cells by an indirect immunofluorescence assay at concentrations up to 100 μg/ml revealed these compounds to be devoid of antiviral activity and cytotoxicity.

In summary we have developed the first synthesis of [(2'*S*, 3'*S*)-bis(hydroxymethyl)azetidin-1-yl]pyrimidine nucleosides as novel analogs of oxetanocin-A. The synthetic strategy outlined in this report seems to be efficient and applicable to the chiral synthesis of a number of potential antiviral pyrimidine derivatives of this new class.[12]

Experimental

^{1}H NMR spectra were recorded at 270 MHz with a JEOL JNM-EX 270, and ^{13}C NMR spectra were recorded at 67.8 MHz with a JEOL JNM-EX 270. Chemical shifts (δ) are expressed in ppm from Me_4Si as an internal standard. Mass spectra were recorded in the EI mode with a HITACHI M-80 Mass Spectrometer. Infrared spectra were recorded on a JASCO A-202 Infrared Spectrophotometer. Ultraviolet spectra were recorded on a JASCO UVIDEC-610. Optical rotations were recorded at the sodium D line and ambient temperatures with a JASCO DIP-360. Melting points were measured on a Yanaco MP-S3 and uncorrected. Only the strongest and/or structurally most important peaks are reported for the IR spectra. Silica gel column chromatography was carried out using Katayama K.K. Silica (60-200 mesh). Thin-layer chromatography (TLC) was carried out on 0.25 mm precoated silica gel plates of Silica Gel 60 F_{254} (E. Merck, Darmstadt). Reaction progress was monitored by either UV (254 nm) or stained with 5% phosphomolybdic acid in ethanol as developing agent, followed in the latter case by heating on an electric plate. Preparative-layer chromatography (PLC) was performed on 0.25, 0.5, 1, and 2 mm x 20 cm x 20 cm E. Merck precoated silica gel-60 plates (60F-254). Dichloromethane (CH_2Cl_2), N,N-dimethylformamide (DMF), and benzene were distilled over calcium hydride. Methanol (MeOH) and ethanol (EtOH) were distilled over magnesium. THF and diethyl ether (Et_2O) were distilled over sodium benzophenone ketyl prior to use. Reactions were carried out under an argon atmosphere unless otherwise stated. Reaction temperatures were measured externally. Yields refer to chromatographycally and spectroscopically pure compounds.

Diethyl L-Tartrate Cyclic Ethyl Orthoformate (8a): A mixture of (+)-diethyl-L-tartrate (12.08 g, 58.3 mmol), triethyl orthoformate (10.38 g, 70.0 mmol) and pyridinium *p*-toluenesulfonate (200 mg) was heated at 130-140 °C for 2 hr while the ethanol and the excess triethyl orthoformate were removed. Reaction progress was followed by TLC. At completion the reaction mixture was allowed to cool to room temperature and was purified by column chromatography on silica gel (750 g) with n-hexane / ethyl acetate (6 : 5) as an eluent to give the orthoformate **8a** as a colorless oil (14.71 g, yield : 96 %). $[\alpha]^{20}_D$ -25.7° (*c* 7.55, $CHCl_3$); IR υ_{max} (neat) 1755 and 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, t, J = 7.1 Hz, CH_3), 1.27 (3H, t, J = 7.2 Hz, CH_3), 1.28 (3H, t, J = 7.2 Hz, CH_3), 3.63 (1H, dq, J = 12.3 and 7.1 Hz, CHHO), 3.64 (1H, dq, J = 12.3 and 7.1 Hz, CHHO), 4.23 (2H, q, J = 7.2 Hz, CH_2O), 4.24 (2H, q, J = 7.2 Hz, CH_2O), 4.67 (1H, d, J = 4.1 Hz, CHO), 5.00 (1H, d, J = 4.1 Hz, CHO), and 6.02 (1H, s, CHOEt); Anal. Calcd for $C_{11}H_{18}O_7$: C, 50.37; H, 6.92. Found: C, 50.53; H, 7.03.

L-Threitol 2,3-Cyclic Ethyl Orthoformate (8b): To a suspension of lithium aluminum hydride (336 mg, 8.9 mmol) in dry THF (10 ml) was added a solution of the orthoformate **8a** (1.88 g,7.2 mmol) in dry THF (12 ml) under ice-water cooling. The reaction mixture was stirred for 1 hr at the same temperature, followed by addition of wet THF (THF 20 ml, water 4ml) and anhydrous $MgSO_4$ (10 g). After 30 min with stirring, the mixture was filtered through a Celite pad, and the filtercake was washed with THF (20 ml x 2) and EtOH (20 ml). The combined filtrate and the washings were concentrated under reduced pressure to give the diol **8b** as a colorless oil (0.98 g), which was used without purification in the next step. IR υ_{max} (neat) 3400 (broad) cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.22 (3H, t, J = 7.1 Hz, CH_3), 3.64 (2H, q, J = 7.1 Hz, CH_2), 3.74 (4H, complex, CH_2 x 2), 4.01 (1H, m, 2 or 3 CH), 4.10 (1H, m, 2 or 3 CH), and 5.87 (1H, s, CHOEt).

1,4-Di-O-benzyl-L-threitol 2,3-Cyclic Ethyl Orthoformate (9): To a suspension of sodium hydride (556 mg, 13.9 mmol, 60 % dispersion in mineral oil) in dry THF (4 ml) was added the unpurified diol **8b** (0.98 g) in dry THF (5 ml). The mixture was stirred at room temperature for 30 min, and then cooled to 0 °C and

treated with benzyl bromide (1.65 ml, 13.9 mmol). The reaction mixture was stirred at room temperature for 1 h and then 70 °C for 16 h. The cooled reaction mixture was treated with sat.aq.NH_4Cl (5 ml) and the aqueous phase was extracted with diethyl ether (40 ml x 2). The combined ethereal solution was washed with sat.aq.NaCl (30 ml) and was dried over anhydrous $MgSO_4$. Evaporation and purification by column chromatography on silica gel (110 g) with n-hexane / ethyl acetate (4 : 1) as an eluent afforded the dibenzyl orthoformate **9** as a colorless oil (1.56 g, yield : 65 % in 2 steps from **8a**). $[\alpha]^{22}_D$ -14.3° (*c* 1.00, $CHCl_3$); IR υ_{max} (neat) 1500, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 8.2 Hz, CH_3), 3.57-3.74 (4H, complex, 1-CH_2, 4-CH_2), 3.62 (2H, q, J = 8.2 Hz, CH_2), 4.11-4.26 (2H, complex, 2-CH, 3-CH), 4.57 (2H, s, Ph-C<u>H</u>$_2$), 4.58 (2H, s, Ph-C<u>H</u>$_2$), 5.88 (1H, s, C<u>H</u>OEt), and 7.25-7.38 (10H, complex, Ph x 2); Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.64; H, 7.20.

1,4-Di-O-benzyl-2-chloro-2-deoxy-3-O-formyl-L-erythritol (10): The dibenzyl orthoformate **9** (4.16 g, 11.6 mmol) in dry CH_2Cl_2 (22 ml) was added to a solution of phosphorus pentachloride (3.57 g, 17.2 mmol) in dry CH_2Cl_2 (30 ml) under ice-water cooling. The reaction mixture was allowed to warm up to room temperature and stirred for 3 hr. The cooled reaction mixture was quenched with sat.aq.$NaHCO_3$ (25 ml), and extracted with $CHCl_3$ (20 x 4 ml). The combined organic solution was successively washed with sat.aq.$NaHCO_3$ (15 x 3 ml), water (10 ml), sat.aq.NaCl (10 ml), and dried over anhydrous $MgSO_4$. The organic solution was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel (150 g) with n-hexane / ethyl acetate (9 : 1) as an eluent to give the chloroformate **10** (4.01 g, yield : 99 %). $[\alpha]^{22}_D$ +13.6° (*c* 1.16, $CHCl_3$), IR υ_{max} (neat) 1725, 1500, 740, and 705cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71 (2H, dd, J = 4.8 and 10.2 Hz, 4-CH_2), 3.77 (2H, dd, J = 5.2 and 10.2 Hz, 1-CH_2), 4.35 (1H, dt, J = 5.1 and 4.8 Hz, 3-CH), 4.50 (1H, d, J = 14.2 Hz, Ph-CH<u>H</u>), 4.52 (1H, d, J = 14.2 Hz, Ph-CH<u>H</u>), 4.54 (1H, d, J = 14.2 Hz, Ph-CH<u>H</u>), 4.56 (1H, d, J = 14.2 Hz, Ph-CH<u>H</u>), 5.42 (1H, dt, J = 5.1 and 5.2 Hz, 2-CH), 7.14-7.41 (10H, complex, Ph x 2), and 8.02 (1H, s, CHO); Anal. Calcd for $C_{19}H_{21}O_4Cl$: C, 65.42; H, 6.07. Found: C, 65.15; H, 6.12.

(2*S*,3*S*)-1,4-Bis(benzyloxy)-2,3-epoxybutane (7): The chloroformate **10** (495 mg, 1.42 mmol) in dry MeOH (3 ml) was added to a suspension of potassium carbonate (526 mg, 3.8 mmol) in dry MeOH (1.5 ml) at room temperature. The reaction mixture was stirred for 18 h, and then diluted with ethyl acetate (20 ml). The organic solution was washed with sat.aq.NH_4Cl (5 x 2 ml), sat.aq.NaCl (10 ml), and dried over anhydrous $MgSO_4$. Evaporation and purification by column chromatography on silica gel (30 g) with n-hexane / ethyl acetate (4 : 1) as an eluent gave the epoxide **7** as an oil (354 mg, yield : 88%). $[\alpha]^{18}_D$ -8.9° (*c* 2.28, $CHCl_3$); IR υ_{max} (neat) 1500 and 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.12 (2H, ddd, J = 2.6, 4.3, and 5.3 Hz, 2-CH, 3-CH), 3.49 (2H, dd, J = 5.3 and 11.6 Hz, 1-CH<u>H</u>, 4-CH<u>H</u>), 3.75 (2H, dd, J = 2.6 and 11.6 Hz, 1-CH<u>H</u>, 4-CH<u>H</u>), 4.54 (2H, d, J = 12.0 Hz, Ph-CH<u>H</u> x 2), 4.60 (2H, d, J = 12.0 Hz, Ph-CH<u>H</u> x 2), and 7.29-7.33 (10H, complex, Ph x 2); Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.89; H, 7.16.

(2*R*,3*R*)-1,4-Bis(benzyloxy)-3-vinyl-2-butanol (11): To a suspension of powdered copper(I) iodide (2.61 g,13.7 mmol) in dry Et_2O (60 ml) at -10 °C was added vinylmagnesium bromide (1M THF solution, 26.6 ml, 26.6 mmol). The solution was allowed to warm up to 0 °C and stirred for 30 min. After that period a solution of the epoxide **7** (1.91 g, 6.73 mmol) in dry Et_2O (20 ml) was added with stirring and cooling at -10 °C. The reaction mixture was stirred for 4.5 hr at the same temperature, and then quenched with sat.aq.NH_4Cl (50 ml) and NH_4OH (5 ml). The ethereal layer was separated and the aqueous phase was extracted with Et_2O (50 ml x 4). The combined organic solution was washed with sat.aq.NH_4Cl (50 ml), sat.aq.NaCl (50 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography on silica gel (60 g)

with n-hexane / ethyl acetate (4 : 1) afforded the vinyl-alcohol **11** as a colorless oil (1.97 g, yield: 94 %). $[\alpha]^{23}_D$ -27.4° (*c* 1.04, $CHCl_3$); IR υ_{max} (neat) 3480, 1640, 1500, 920, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.57 (1H, m, 3-CH), 3.04 (1H, br, D_2O exchangeable, OH), 3.46 (1H, dd, J = 7.0 and 10.0 Hz, 4-CHH), 3.55 (1H, dd, J = 3.5 and 10.0 Hz, 4-CHH), 3.63 (1H, dd, J = 6.2 and 9.5 Hz, 1-CHH), 3.67 (1H, dd, J = 5.4 and 9.5 Hz, 1-CHH), 3.90 (1H, ddd, J = 3.5, 7.0, and 7.5 Hz, 3-CH), 4.47-4.60 (4H, complex, Ph-CH_2 x 2), 5.11 (1H, dd, J = 1.6 and 10.3 Hz, CH=CHH), 5.14 (1H, dd, J = 1.6 and 17.1 Hz, CH=CHH), 5.75 (1H, ddd, J = 8.6, 10.3, and 17.1 Hz, CH=CH_2), and 7.22-7.42 (10H, complex, Ph x 2); Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.13; H, 7.82.

(2*R*,3*R*)-1,4-Bis(benzyloxy)-3-vinyl-2-butanol Mesylate (12): Methanesulfonyl chloride (4.0 ml, 51.7 mmol) was added to a stirred solution of the vinyl-alcohol **11** (11.95 g, 38.3 mmol) and triethylamine (10 ml, 71.7 mmol) in dry CH_2Cl_2 (100 ml) under ice-water cooling. The reaction mixture was stirred at the same temperature for 4 h, and acidified with cold 2N aq.HCl (60 ml), and extracted with $CHCl_3$ (50 ml x 3). The organic solution was washed with sat.aq.$NaHCO_3$ (50 ml), sat.aq.NaCl (50 ml), and dried over anhydrous Na_2SO_4 (30 g). Concentration *in vacuo* and purification by column chromatography on silica gel (620 g) with n-hexane / ethyl acetate (4 : 1) as an eluent provided the mesylate **12** as a pale yellow oil (13.82 g, yield: 93 %). $[\alpha]^{19}_D$ -25.4° (*c* 1.84, $CHCl_3$); IR υ_{max} (neat) 1640, 1500, 1360, 1175, 920, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.81 (1H, m, 2-CH), 3.00 (3H, s, SO_2CH_3), 3.54-3.76 (4H, complex, 1-CH_2, 4-CH_2), 4.46 (1H, d, J = 11.9 Hz, Ph-CHH), 4.48 (1H, d, J = 11.9 Hz, Ph-CHH), 4.54 (1H, d, J = 12.2 Hz, Ph-CHH), 4.56 (1H, d, J = 12.2 Hz, Ph-CHH), 5.00 (1H, dt, J = 4.6 and 7.0 Hz, 3-CH), 5.19 (1H, dd, J = 1.1 and 10.7 Hz, CH=CHH), 5.21 (1H, dd, J = 1.1 and 16.9 Hz, CH=CHH), 5.79 (1H, ddd, J = 8.8, 10.7, and 16.9 Hz, CH=CH_2), and 7.20-7.42 (10H, complex, Ph x 2); Anal. Calcd for $C_{21}H_{26}O_5S$: C, 64.60; H, 6.71. Found: C, 64.39; H, 6.73.

(2*S*,3*R*)-3-Azido-1,4-bis(benzyloxy)-2-vinylbutane (13): A mixture of the mesylate **12** (13.33 g, 34.1 mmol) and sodium azide (6.76 g, 104 mmol) in dry DMF (100 ml) was heated at 98-105 °C for 1 h with stirring. The reaction mixture was allowed to cool to room temperature, poured into water (100 ml), and extracted with ethyl acetate (200 x 2 ml). The combined organic solution was washed successively with sat.aq.NH_4Cl (100 ml), and sat.aq.NaCl (100 ml), and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* and purification by column chromatography on silica gel (620 g) with n-hexane / ethyl acetate (10 : 1) as an eluent afforded the vinyl-azide **13** as a pale yellow oil (10.34 g, yield : 90 %). $[\alpha]^{23}_D$ -23.9° (*c* 0.98, $CHCl_3$); IR υ_{max} (neat) 2100, 1640, 1495, 925, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.57 (1H, m, 2-CH), 3.41 (1H, dd, J = 5.4 and 9.4 Hz, 4-CHH), 3.53 (1H, dd, J = 8.1 and 9.4 Hz, 4-CHH), 3.54 (2H, d, J = 5.3 Hz, 1-CH_2), 4.00 (1H, m, 3-CHO), 4.49 (2H, s, Ph-CH_2), 4.49 (1H, d, J = 11.9 Hz, Ph-CHH), 4.55 (1H, d, J = 11.9 Hz, Ph-CHH), 5.10 (1H, dd, J = 2.1 and 10.6 Hz, CH=CHH), 5.11 (1H, dd, J = 2.1 and 16.8 Hz, CH=CHH), 5.66 (1H, ddd, J = 9.2, 10.6, and 16.8 Hz, CH=CH_2), and 7.24-7.38 (10H, complex, Ph x 2); Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 71.38; H, 6.79; N, 12.71.

(2*R*,3*R*)-3-Azido-1,4-bis(benzyloxy)-2-hydroxymethylbutane (14): Ozone gas (stream velocity of oxygen : 15 ml / min) was bubbled into a stirred solution of the vinyl-azide **13** (10.34 g, 30.6 mmol) in MeOH (100 ml) at –20 °C. After completion (3h), the flask was flushed with argon. Then $NaBH_4$ (8.17 g, 216 mmol) was carefully added to the reaction solution in 5 portions, and the mixture was allowed to warm up to room temperature and stirred for 10 h. The volume of the flask was concentrated to about 10 ml *in vacuo*, and then the residue was diluted with ethyl acetate (100 ml) and water (100 ml). The aqueous layer was extracted with ethyl acetate (50 x 2 ml), and the combined organic solution was washed with sat.aq.NaCl (50 ml), and dried over

anhydrous Na_2SO_4. Concentration *in vacuo* and purification by column chromatography on silica gel (530 g) with n-hexane / ethyl acetate (2 : 1) as an eluent gave the azido-alcohol **14** as a pale yellow oil (8.05 g, yield : 77% in 2 steps). $[\alpha]^{22}_D$ -37.1° (*c* 0.88, $CHCl_3$); IR υ_{max} (neat) 3450, 2100, 1500, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (1H, tt, J = 2.3, 3.5 Hz, 2-CH), 3.49 (1H, dd, J = 2.3 and 9.3 Hz, 1-CHH), 3.56 (1H, dd, J = 2.3 and 9.3 Hz, 1-CHH), 3.60 (1H, dd, J = 6.6 and 10.1 Hz, 4-CHH), 3.67 (1H, dd, J = 3.3 and 10.1 Hz, 4-CHH), 3.70 (2H, d, J = 3.5 Hz, CH_2OH), 3.88 (1H, dt, J = 3.3 and 6.6 Hz, 3-CH), 4.41 (1H, d, J = 12.0 Hz, Ph-CHH), 4.47 (1H, d, J = 12.0 Hz, Ph-CHH), 4.49 (1H, d, J = 12.7 Hz, Ph-CHH), 4.54 (1H, d, J = 12.7 Hz, Ph-CHH), and 7.21-7.39 (10H, complex, Ph x 2); Anal. Calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.65; H, 6.83; N, 12.56.

(2*S*,3*R*)-3-Azido-1,4-bis(benzyloxy)-2-hydroxymethylbutane Mesylate (15): Methanesulfonyl chloride (3.0 ml, 38.8 mmol) was added to a stirred solution of the azido-alcohol **14** (8.39 g, 24.6 mmol) and triethylamine (6.5 ml, 47 mmol) in dry CH_2Cl_2 (80 ml) under ice-water cooling. The reaction mixture was stirred for 4 h at the same temperature, and then acidified with cold 2N HCl (30 ml), and extracted with $CHCl_3$ (50 ml x 3). The organic solution was washed with sat.aq.$NaHCO_3$ (50 ml), sat.aq.NaCl (50 ml), and then dried over anhydrous Na_2SO_4. Concentration in vacuo and purification by column chromatography on silica gel (400 g) with n-hexane / ethyl acetate (1 : 1) as an eluent gave the azido-mesylate **15** as a pale yellow oil (10.12 g, yield: 98 %). $[\alpha]^{21}_D$ -28.4° (*c* 1.15, $CHCl_3$); IR υ_{max} (neat) 2105, 1500, 1360, 1180, 750, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (1H, m, 2-CH), 2.93 (3H, s, SO_2CH_3), 3.47 (1H, dd, J = 5.6 and 9.5 Hz, 1-CHH), 3.52 (1H, dd, J = 5.4 and 9.5 Hz, 1-CHH), 3.61 (1H, dd, J = 6.6 and 10.2 Hz, 4-CHH), 3.70 (1H, dd, J = 3.3 and 10.2 Hz, 4-CHH), 3.79 (1H, dt, J = 6.6 and 3.3 Hz, 3-CH), 4.29 (1H, dd, J = 6.6 and 9.9 Hz, CHHOSO$_2$), 4.38 (1H, dd, J = 5.0 and 9.9 Hz, CHHOSO$_2$), 4.45 (1H, d, J = 12.0 Hz, Ph-CHH), 4.49 (1H, d, J = 12.0 Hz, Ph-CHH), 4.52 (1H, d, J = 11.9 Hz, Ph-CHH), 4.57 (1H, d, J = 11.9 Hz, Ph-CHH), and 7.22-7.45 (10H, complex, Ph x 2); Anal. Calcd for $C_{20}H_{25}N_3O_5S$: C, 57.27; H, 6.01; N, 10.02. Found: C, 57.55; H, 5.93; N, 9.87.

(2*S*,3*S*)-2,3-Bis(benzyloxymethyl)azetidine (16): A mixture of the azido-mesylate **15** (4.49 g, 10.7 mmol) and freshly prepared Raney-nickel (W-2) (4.5 g) in EtOH (150 ml) was vigorously stirred under a hydrogen gas atmosphere for 15 h. After completion the reaction mixture was filtered and the catalyst was washed with EtOH (150 ml). The combined filtrate and the washings were concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (18 g) with $CHCl_3$ / MeOH (10 : 1) as an eluent to give the azetidine **16** as a colorless oil (2.29 g, yield : 92 %). $[\alpha]^{22}_D$ +25.0° (*c* 0.63, $CHCl_3$); IR υ_{max} (neat) 3340, 1500, 750, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.76 (1H, tq, J = 7.6, 5.9 Hz, 3-CH), 3.43 (1H, t, J = 7.6 Hz, 4-CHH), 3.53 (1H, t, J = 7.6 Hz, 4-CHH), 3.57 (4H, d, J = 5.9 Hz, CH_2 x 2), 3.91 (1H, q, J = 5.9 Hz, 2-CH), 4.51 (2H, s, Ph-CH_2), 4.56 (2H, s, Ph-CH_2), and 7.30-7.35 (10H, complex, Ph x 2); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 37.3 (d), 47.0 (t), 60.8 (d), 71.7 (t), 73.2 (t), 73.4 (t), 74.0 (t), 127.7 (d), 127.8 (d), 128.5 (d), and 138.4 (s); Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.54; H, 7.78; N, 4.85.

(2*S*,3*S*)-N^1-Nitroso-2,3-bis(benzyloxymethyl)azetidine (17): A mixture of the azetidine **16** (0.8 g, 3 mmol) and isoamyl nitrite (4 ml, 4 mmol) in dry THF (10 ml) was stirred at room temperature for 20 h. After the solvent and the excess reagent were removed *in vacuo*, the residue was purified by column chromatography on silica gel (20 g) with n-hexane / ethyl acetate (3 : 1) as an eluent to give the nitroso-azetidine **17** as a pale yellow oil (0.89 g, yield : ~100 %). $[\alpha]^{19}_D$ -29.6° (*c* 1.10, $CHCl_3$); IR υ_{max} (neat) 1490, 750, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.04 (1H, m, 3-CH), 3.59 (2H, complex, CH_2), 3.84 (1H, dd, J = 3.3 and 10.9 Hz, CHH),

3.97 (1H, dd, J = 5.6 and 13.5 Hz, 4-CHH), 4.05 (1H, dd, J = 3.3 and 10.9 Hz, CHH), 4.20 (1H, dd, J = 8.9 and, 13.5 Hz, 4-CHH), 4.54 (2H, s, Ph-CH_2), 4.58 (2H, s, Ph-CH_2), 5.06 (1H, m, 2-CH), and 7.24-7.38 (10H, complex, Ph x 2); Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.19; H, 6.93; N, 8.35.

(2*S*,3*S*)-N^1-Amino-2,3-bis(benzyloxymethyl)azetidine (18): To a suspension of lithium aluminum hydride (67 mg, 1.8 mmol) in dry THF (3 ml) was added the nitroso-azetidine **17** (84 mg, 0.26 mmol) in dry THF (6 ml) at -10 °C . The reaction mixture was stirred for 3.5 h at the same temperature and quenched with 1 N aq.NaOH (15 ml). The mixture was extracted with $CHCl_3$ (20 ml x 3). The combined organic solution was washed with sat.aq.NaCl (15 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude amino-azetidine **18** as an oil (67 mg, crude yield : 83 %) which was unstable and was therefore used without purification in the next step. IR υ_{max} (neat) 3340, 1495, 735, and 700 cm^{-1}.

(2*S*,3*S*)-N^1-Ureido-2,3-bis(benzyloxymethyl)azetidine (19): A mixture of the crude amino-azetidine **18** (316 mg) and trimethylsilyl isocyanate (0.45 ml, 3.32 mmol) in dry CH_2Cl_2 (3 ml) was stirred at room temperature for 15 h. The reaction was quenched by the addition of MeOH (3 ml), and the solvent was removed under reduced pressure to leave an oily residue. The residue was purified by column chromatography on silica gel (18 g) with $CHCl_3$ / MeOH (20 : 1) as an eluent gave the urea **19** (199 mg, yield : 46% in 2 steps from compound **17**) as white crystals. mp 84.6-85.5 °C (recrystallized from Et_2O); $[\alpha]^{22}_D$ -3.7° (*c* 0.21, MeOH); IR υ_{max} (nujol) 3460, 1680, 1580, 1500, 743, and 703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.53 (1H, m, 3-CH), 3.16 (1H, t, J = 7.3 Hz, 4-CHH), 3.50 (2H, d, J = 7.3 Hz, CH_2), 3.53 (2H, d, J = 4.3 Hz, CH_2), 3.61 (1H, dt, J = 7.3 and 4.3 Hz, 2-CH), 3.74 (1H, t, J = 7.3 Hz, 4-CHH), 4.51 (2H, s, Ph-CH_2), 4.54 (2H, s, Ph-CH_2), 5.76 (1H, br, D_2O exchangeable, NH), and 7.29-7.37 (10H, complex, Ph x 2); ^{13}C NMR (C_6D_6), δ 31.3 (d), 59.0 (d), 59.1 (t), 70.7 (t), 71.7 (t), 73.0 (t), 73.3 (t),1 28.0 (d), 128.4 (d), 128.8 (d), 139.0 (s), and 160.7 (s); HRMS m/z 355.1894 calcd for $C_{20}H_{25}N_3O_3$ (M^+), found 355.1896; Anal. Calcd for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.79; H, 6.97; N, 11.69.

(2*S*,3*S*)-N^1-(3-Ethoxyacryloyl)ureido-2,3-bis(benzyloxymethyl)azetidine (20) To a stirred solution of the crude **18** (206 mg) in dry DMF (2.0 ml) at -20 °C was added 3-ethoxyacryloyl isocyanate in dry benzene (4.8 ml, 1.3 mmol, prepared from 3-ethoxyacryloyl chloride (257 mg, 1.91 mmol) and silver cyanate (1.19 g, 7.94 mmol) in dry benzene (7 ml)). The reaction mixture was allowed to warm up to room temperature, and stirred for 12 h. Concentration *in vacuo* and purification on PLC (0.5 mm x 3) with n-hexane / ethyl acetate (1 : 4) as developing solvent provided the ureido-azetidine **24** as a colorless oil (258 mg, yield : 64 % in 2 steps from compound **17**). IR υ_{max} (neat) 3225, 3100, 1705, 1670, 1530, 1495, 740, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, J = 7.1 Hz, OCH_2CH_3), 2.55 (1H, m, 3-CH), 3.46 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.56-3.85 (5H, complex, CH_2 x 2, 2-CH), 3.92 (1H, dd, J = 6.6 and 12.2 Hz, 4-CHH), 4.50 (4H, s, Ph-CH_2 x 2), 4.55 (1H, dd, J = 8.3, 12.2 Hz, 4-CHH), 5.35 (1H, d, J = 12.2 Hz, CH=CHOEt), 7.26-7.33 (10H, complex, Ph x 2), 7.60 (1H, d, J = 12.2 Hz, CH=CHOEt), 9.36 (1H, s, D_2O exchangeable, NH), and 9.75 (1H, s, D_2O exchangeable, NH); Anal. Calcd for $C_{25}H_{31}N_3O_5$: C, 66.20; H, 6.89; N, 9.27. Found: C, 66.41; H, 7.01; N, 9.12.

(2'*S*,3'*S*)-1-[2',3'-Bis(benzyloxymethyl)azetidinyl]uracil (21): A solution of the ureido-azetidine **20** (46 mg, 0.10 mmol) in EtOH (2.5 ml) and 7% NH_4OH (2.5 ml) was heated at 80 °C in a sealed tube for 8 h. The reaction mixture was allowed to cool to room temperature, and concentrated under reduced pressure. The residue was purified on PLC (2 mm) with n-hexane / ethyl acetate (2 : 3) as developing solvent gave the dibenzyluracil **21** (38 mg, yield : 92 %). $[\alpha]^{23}_D$ -45.1° (*c* 0.88, $CHCl_3$); IR υ_{max} (neat) 3180, 1710, 1690,

1680, 1495, 750, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (1H, m, 3'-CH), 3.56 (2H, d, J = 5.3 Hz, 5'-CH_2), 3.71 (2H, d, J = 7.0 Hz, 6'-CH_2), 3.76 (1H, t, J = 7.0 Hz, 4'-CHH), 4.39 (1H, t, J = 7.0 Hz, 4'-CHH), 4.50 (4H, s, Ph-CH_2 x 2), 4.76 (1H, dd, J = 7.0 and 5.3 Hz, 2'-CH), 5.47 (1H, d, J = 7.9 Hz, 5-CH), 7.29 (1H, d, J = 7.9 Hz, 6-CH), 7.26-7.33 (10H, complex, Ph x 2), and 9.34 (1H, br, D_2O exchangeable, NH); Anal. Calcd for $C_{23}H_{25}N_3O_4$: C, 67.79; H, 6.18; N, 10.31. Found: C, 67.96; H, 6.31; N, 10.13.

(2'*S*,3'*S*)-1-[2',3'-Bis(hydroxymethyl)azetidinyl]uracil (22): A mixture of the dibenzyluracil **21** (9 mg, 0.02 mmol), cyclohexene (0.3 ml, 3 mmol) and 20 % $Pd(OH)_2$ on carbon (5 mg) in EtOH (0.6 ml) was refluxed for 3 h. After completion the reaction mixture was filtered. The filtrate and the washings with MeOH (5 ml) were combined, and concentrated *in vacuo* to dryness. The residue was purified on PLC (0.5 mm) with $CHCl_3$ / MeOH (4 : 1) as developing solvent to give the uracil **22** (3.2 mg, yield : 64%) as a colorless foam. $[\alpha]^{22}_D$ -35.7° (*c* 0.69, MeOH); UV λ_{max} 263 nm (ε 8943, MeOH); IR υ_{max} (neat) 3440, 1685, 1650, 1590, and 1575 cm^{-1}; ^1H NMR (CD_3OD) δ 2.45 (1H, m, 3'-CH), 3.59 (1H, dd, J = 5.6, 11.9 Hz, 5'-CHH), 3.67 (1H, dd, J = 3.6 and 11.9 Hz, 5'-CHH), 3.74 (1H, t, J = 7.1 Hz, 4'-CHH), 3.80 (2H, d, J = 7.1 Hz, 6'-CH_2), 4.29 (1H, t, J = 7.1 Hz, 4'-CHH), 4.59 (1H, ddd, J = 3.6, 5.6, and 7.1 Hz, 2'-CH), 5.55 (1H, d, J = 8.1 Hz, 5-CH), and 7.69 (1H, d, J = 8.1 Hz, 6-CH); ^{13}C NMR (CD_3OD): δ 34.1 (d), 56.2 (d), 64.4 (t), 64.8 (t), 72.3 (t), 101.2 (d), 149.6 (d), 152.0 (s), and 166.3 (s); HRMS m/z 227.0905 calcd for $C_9H_{13}N_3O_4$ (M^+), found 227.0886

(2*S*,3*S*)-N^1-(3-Methoxy-2-methylacryloyl)ureido-2,3-bis(benzyloxymethyl)azetidine (23): To a stirred solution of the crude **18** (240 mg, 0.77 mmol) in dry DMF (3.0 ml) at -20 °C was added 3-methoxy-2-methylacryloyl isocyanate in dry benzene (4.8 ml, 1.3 mmol, prepared from 3-methoxy-2-methylacryloyl chloride (261 mg) and silver cyanate (1.16 g) in dry benzene (6 ml)). The reaction mixture was allowed to warm up to room temperature, and stirred for 12 h. Concentration *in vacuo* and purification on PLC (2 mm x 3) with $CHCl_3$ / MeOH (30 :1) as developing solvent provided the ureido-azetidine **23** as a colorless oil (177 mg, yield: 51 % in 2 steps from compound **17**). IR υ_{max} (neat) 3240, 1700, 1660, 1530, 1500, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (3H, s, CH_3), 2.54 (1H, m, 3-H), 3.68 (3H, s, OCH_3), 3.56-3.85 (5H, complex, CH_2 x 2, 2-H), 3.92 (1H, dd, J = 6.6 and 12.2 Hz, 4-CHH), 4.51 (2H, s, Ph-CH_2), 4.54 (1H, d, J = 5.3 Hz, PhCHH), 4.55 (1H, dd, J = 8.3 and 12.2 Hz, 4-CHH), 4.58 (1H, d, J = 5.3 Hz, PhCHH), 7.26-7.33 (10H, complex, Ph x 2), 7.47 (1H, s, C=CHOMe), 9.50 (1H, s, D_2O exchangeable, NH), and 9.67 (1H, s, D_2O exchangeable, NH); Anal. Calcd for $C_{25}H_{31}N_3O_5$: C, 66.20; H, 6.89; N, 9.27. Found: C, 66.41; H, 6.95; N, 9.11.

(2'*S*,3'*S*)-1-[2',3'-Bis(benzyloxymethyl)azetidinyl]thymine (24): A mixture of the ureido-azetidine **23** (60 mg, 0.13 mmol) in EtOH (3 ml) and 7 % NH_4OH (3 ml) was heated at 80 °C in a sealed tube for 8 h. The reaction mixture was allowed to cool to room temperature, and concentrated under reduced pressure. The residue was purified on PLC (1 mm x 2) with n-hexane / ethyl acetate (1:1) as developing solvent to give the dibenzylthymine **24** (23 mg, yield: 41%). IR υ_{max} (neat) 3200, 1710, 1690, 1660, 1500, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78 (3H, s), 2.50 (1H, m, 3'-H), 3.56 (2H, d, J = 5.3 Hz, 5'-CH_2), 3.71 (2H, d, J = 7.0 Hz, 6'-CH_2), 3.76 (1H, t, J = 7.0 Hz, 4'-CHH), 4.39 (1H, t, J = 7.0 Hz, 4'-CHH), 4.50 (4H, s, Ph-CH_2 x 2), 4.75 (1H, dd, J = 7.0 and 5.3 Hz, 2'-H), 7.15 (1H, s, 6-H), 7.25-7.31 (10H, complex, Ph x 2), and 8.83 (1H,br, D_2O exchangeable, NH); Anal. Calcd for $C_{24}H_{27}N_3O_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, 68.23; H, 6.50; N, 9.82.

(2'*S*,3'*S*)-1-[2',3'-Bis(hydroxymethyl)azetidinyl]thymine (25): A mixture of the dibenzylthymine **24** (15 mg, 0.04 mmol), 20 % $Pd(OH)_2$ on carbon (10 mg), and cyclohexene (0.5 ml) in EtOH (1 ml) was

refluxed for 3 h. After completion the reaction mixture was filtered. The filtrate and the washings with MeOH (5 ml) were combined, and concentrated *in vacuo* to dryness. The residue was purified on PLC (0.5 mm) with $CHCl_3$ / MeOH (4 : 1) as an eluent to give the thymine **25** as a colorless foam (7.6 mg, yield: 78 %). $[\alpha]^{20}_D$ -115.3° (*c* 0.67, MeOH); UV λ_{max} 268 nm (ε 8895, MeOH); IR υ_{max}(neat) 3420, 1690, and 1660 cm^{-1}; ^1H NMR (CD_3OD) δ 1.86 (3H, s, 5-Me), 2.46 (1H, m, 3'-H), 3.59 (1H, dd, J = 5.4 and 11.8 Hz, OCH), 3.66 (1H, dd, J = 4.0 and 11.8 Hz, OCH), 3.73 (1H, t, J = 7.1 Hz, 4'-H), 3.80 (2H, d, J = 6.6 Hz, OCH_2), 4.26 (1H, t, J = 7.1 Hz, 4'-H), 4.57 (1H, m, 2'-H), and 7.55 (1H, s, 6-H); HRMS m/z 242.1140 calcd for $C_{10}H_{16}N_3O_4$ (M^++1), found 242.1150.

(2'*S*, 3'*S*)-1-[2, 3-Bis(acetoxymethyl)azetidinyl]-4-(1,2,4-triazole-1-yl)-2(1H)-pyrimidinone (26): A mixture of the diol **22** (36 mg, 0.16 mmol) in pyridine (1 ml) and acetic anhydride (1 ml) was stirred at room temperature for 10 h. After evaporation of the solvent *in vacuo*, the residue was purified on PLC (1 mm x 2) with n-hexane / ethyl acetate (1 : 1) as developing solvent to give (2'*S*, 3'*S*)-1-[2, 3-bis(acetoxymethyl)azetidinyl]uracil as a colorless oil (49 mg, 96 %). IR υ_{max}(neat) 3500, 3200, 1740, 1718, and 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.08 (3H, s, OAc), 2.12 (3H, s, OAc), 2.54 (1H, m, 3'-H), 3.73 (1H, dd, J = 6.9 and 7.6 Hz, 4'-H), 4.01 (1H, dd, J = 5.8 and 12.0 Hz, OCH), 4.31 (2H, d, J = 7.6 Hz, OCH_2), 4.33 (1H, dd, J = 3.6 and 12.0 Hz, OCH), 4.46 (1H, dd, J = 6.9 and 7.6 Hz, 4'-H), 4.88 (1H, m, 2'-H), 5.55 (1H, d, J = 8.2 Hz, 5-H), 7.28 (1H, d, J = 8.2 Hz, 6-H), and 10.01 (1H, br, D_2O exchangeable, NH); Anal. Calcd for $C_{13}H_{17}N_3O_6$: C, 50.16; H, 5.50; N, 13.50. Found: C, 50.39; H, 5.43; N, 13.69.

To a solution of the diacetate (39 mg, 0.13 mmol) and 1,2,4-triazole (25 mg, 0.36 mmol) in pyridine (0.5 ml) was added *o*-chlorophenyl phosphorodichrolidate (0.028 ml, 0.17 mmol) at -30 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 12 h. After completion the solvent was evaporated under reduced pressure. The residue was dissolved with ethyl acetate (30 ml), and the solution was washed with water, sat.aq.NaCl, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified on PLC (1 mm x 2) with n-hexane / ethyl acetate (1 : 3) as developing solvent to give the triazole **26** (12 mg, 26 %) as a colorless foam. IR υ_{max}(neat) 1740, 1690, 1680, 1624, and 1546 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (3H, s, OAc), 2.14 (3H, s, OAc), 2.64 (1H, m, 3'-H), 3.70 (1H, dd, J = 6.7 and 7.9 Hz, 4'-H), 3.99 (1H, dd, J = 5.5 and 12.2 Hz, OCH), 4.37 (2H, d J = 5.5 Hz, OCH_2), 4.39 (1H, dd, J = 3.1 and 12.2 Hz, OCH), 4.69 (1H, dd, J = 6.7 and 7.9 Hz, 4'-H), 5.12 (1H, m, 2'-H), 6.91 (1H, d, J = 7.3 Hz, 5-H), 7.92 (1H, d, J = 7.3 Hz, 6-H), 8.12 (1H, s, triazolyl 3-H), and 9.24 (1H, s, triazolyl 5-H); HRMS m/z 363.1416 calcd for $C_{15}H_{19}N_6O_5$ (M^++1), found 363.1451.

(2'*S*, 3'*S*)-1-[2', 3'-bis(hydroxymethyl)azetidinyl]cytosine (27): A solution of the triazole **26** (12 mg, 0.03 mmol) in 35 % aqueous ammonia (0.5 ml) and EtOH (0.5 ml) was stirred at room temperature for 15 h. After evaporation of the solvent *in vacuo* the residue was purified on PLC (1 mm) with $CHCl_3$ / MeOH (3 : 1) as developing solvent to afford the cytosine **27** (4 mg, 56 %) as a colorless foam. $[\alpha]^{20}_D$ -128.8° (*c* 0.73, MeOH); UV λ_{max} 273 nm (ε 7218, MeOH); IR υ_{max}(neat) 3360, 3200, 1665, and 1610 cm^{-1}; ^1H NMR (CD_3OD) δ 2.43 (1H, m, 3'-H), 3.53 (1H, dd, J = 5.5 and 11.7 Hz, OCH), 3.60 (1H, dd, J = 3.9 and 11.7 Hz, OCH), 3.66 (1H, t, J = 7.3 Hz, 4'-H), 3.78 (2H, d, J = 7.3 Hz, OCH_2), 4.30 (1H, t, J = 7.3 Hz, 4'-H), 4.59 (1H, m, 2'-H), 5.73 (1H, d, J = 7.6 Hz, 5-H), and 7.64 (1H, d, J = 7.6 Hz, 6-H); HRMS m/z 227.1143 calcd for $C_9H_{14}N_4O_3$ (M^++1), found 227.1135.

Acknowledgments:

We wish to recognize the efforts of Ryuji Ikeda and Jun-ichi Seki (Department of Biology, Nippon Kayaku Research Laboratories) for assistance in obtaining antiviral evaluation data.

References and Notes:

1. Preliminary report of a part of this work: Hosono, F.; Nishiyama, S.; Yamamura, S.; Izawa, T.; Kato, K. *Bioorganic & Medicinal Chemistry Lett.* **1994**, *4*, 2083-2086.
2. Mullah, K. B.; Rao, T. S.; Balzarini, J.; De Clercq, E.; Bentrude, W. G. *J. Med. Chem.* **1992**, *35*, 2728-2735.
3. Coates, J. A. V.; Cammack, N.; Jenkinson, H. J.; Mutton, I. M.; Pearson, B. A.; Storer, R.; Cameron, J. M.; Penn, C. R. *Antimicrob. Agent Chemother.* **1992**, *36*, 733-739.
4. *Isolation*: Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. *J. Antibiot.* **1986**,*39*, 1623-1625. *Antiviral activities*: Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. *J. Antibiot.* **1987**, *40*, 1077-1078. Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Fujioka, H.; Shimada, N.; Takahashi, K. *J. Antibiot.* **1989**, *42*, 1308-1311. *Synthesis*: Niitsuma, S.; Ichikawa, Y.; Kato. K.; Takita. T. *Tetrahedron Lett.* **1987**, *28*, 3967-3968 and 4713-4714. Nishiyama, S.; Yamamura, S.; Kato, K.; Takita, T. *Tetrahedron Lett.* **1988**, *29*, 4739-4742 and 4743-4746. Norbeck, D. W.; Kramer, J. B. *J. Am. Chem. Soc.* **1988**, *110*, 7217-7218. Wilson F. X.; Fleet, G. W. J.; Vogt, K.; Wang, Y.; Witty, D. R.; Choi, S.; Storer, R.; Meyers, P. L.; Wallis, C. J. *Tetrahedron Lett.* **1990**, *31*, 6931-6934. Humbalek, R.; Just, G. *Tetrahedron Lett.* **1990**, *31*, 5445-5448. Nagai, M.; Kato, K.; Takita, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron*, **1990**, *46*, 7703-7710.
5. *Synthesis*: Honjo, M.; Maruyama, T.; Sato, Y.; Horii, T. *Chem Pharm. Bull.* **1989**, *37*, 1413-1415. Ichikawa, Y.; Narita, A.; Shiozawa, A.; Hayashi, Y.; Narasaka, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1919-1921. Slusarchyk, W. A.; Young, M. G.; Bisacchi, G. S.; Hockstein, D. R.; Zahler, R. *Tetrahedron Lett.* **1989**, *30*, 6453-6456. Katagiri, N.; Sato, H.; Kaneko, C. *Chem. Pharm. Bull.* **1990**, *38*, 288-290. Ito, H.; Taguchi, T.; Hanzawa, Y. Tetrahedron Lett. **1993**, *34*, 7639-7640. *Antiviral activities*: Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Daikoku, T.; Ichikawa, Y.; Takahashi, K. *J. Antibiot.* **1989**, *42*, 1854-1859. Maruyama, T.; Sato, Y.; Horii, T.; Shiota, H.; Nitta, K.; Shirasaka, T.; Mitsuya, H.; Honjo, M. *Chem. Pham. Bull.* **1990**, *38*, 2719-2725. Bissachi, G. S.; Braitman, A.; Cianci, C. W.; Clark, J. M.; Field, A. K.; Terry, B. J.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1991**, *34*, 1415-1421.
6. Very recently nucleoside analogs containing a pyrrolidine ring linked to the base *via* the heteroatom have been developed. Harnden, M. R.; Jarvest, R. L. *Tetrahedron Lett.* **1991**, *32*, 3863-3866. Lee, Y. H.; Kim, H. K.; Youn, I. K.; Chae,Y. B. *Bioorgnic & Medicinal Chemistry Lett.* **1991**, *1*, 287-290. Mansour, T. K.; Jin, H. *Bioorganic & Medicinal Chemistry Lett.* **1991**, *1*, 757-760. Harnden, M. R.; Jarvest, R. L.; Parratt, M. J. *J. Chem. Soc., Perkin Trans.* 1 **1992**, 2259-2263.
7. Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440-1456.
8. Szmuskovics, J.; Kane, M. P.; Laurian, L. G.; Chidester, C. G.; Scahill, T. A. *J. Org. Chem.* **1981**, *46*, 3562-3564. Thijs, L.; Porskamp, Jos J. M.; van Loon, Adriaan A. W. M.; Derks, M. P. W.; Feenstra, Rolf W.; Legters Johan; Zwanenburg, Binne.*Tetrahedron* **1990**, *46*, 2611-2622.
9. Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1958**, 153-156.
10. Sung, W. L. *J. Org. Chem.* **1982**, *47*, 3623-3628.
11. Irradiation of the 6-H signal did not produce the significant NOE enhancement for the 2'-H signal and both of the 4'-H signals.
12. Further studies on the synthesis of purine nucleoside analogs of this class and the results of biological testing will be reported in future publications.

(*Received in Japan* 5 *September* 1994; *accepted* 30 *September* 1994)