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A Stereocontrolled Total Synthesis of *C*-Nucleosides[1)]

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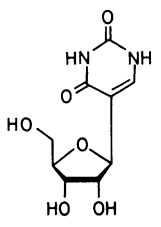
A stereocontrolled, general synthesis of chiral *C*-nucleosides has been achieved through a common lactonic *C*-β-glycoside intermediate which is readily obtainable from non-carbohydrate materials. Osmium tetraoxide-catalyzed *vic*-dihydroxylation of 8-oxabicyclo[3.2.1]oct-6-en-3-one gives, after acetonidation, (1*R**,5*S**,6*S**,7*R**)-6,7-isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3-one as a single stereoisomer. Baeyer-Villiger oxidation of the ketone affords the key intermediate, 2-(2,3-*O*-isopropylidene-β-ribofuranosyl)acetic acid lactone. The optically pure lactone having the natural D configuration is obtained through optical resolution of the seco acid by the Pirkle's method followed by relactonization. α-Aminomethylenation of the lactone with *t*-$C_4H_9OCH[N(CH_3)_2]_2$ yields 2-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-2-(dimethylaminomethylene)acetic acid lactone, which undergoes base-assisted condensation with urea followed by deprotection to furnish naturally occurring pseudouridine. Analogously, construction of heterocycles using thiourea and guanidine converts the aminomethylene lactone to unnatural pyrimidine *C*-nucleosides, 2-thiopseudouridine and pseudoisocytidine, respectively. Showdomycin in natural form can be prepared by two schemes. One approach consists of ozonolysis of the α-dimethylaminomethylene lactone, Wittig reaction using $(C_6H_5)_3PCHCONH_2$, and acid hydrolysis. The second entry makes use of 2-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)acetic acid lactone as the intermediate, which is converted to 2-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-2-furfurylideneacetic acid lactone by the aldol reaction with furfural and dehydration. Methanolysis of the furfurylidene lactone and *t*-butyldimethylsilylation are followed by ozonolysis, Wittig condensation with $(C_6H_5)_3PCHCONH_2$, and hydrolysis to give the maleimide *C*-nucleoside. In addition, 6-azapseudouridine and 6-aza-2-thiopseudouridine are obtainable *via* intramolecular ring closures of the semicarbazone and thiosemicarbazone of methyl 2-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)glyoxylate followed by deprotections, respectively. These overall transformations are accomplishable under complete stereochemical control.

C-Nucleosides are a class of compounds which possess a carbon–carbon linkage between the carbohydrate and heterocyclic moieties, and are distinguished from ordinary *N*-nucleosides in which an anomeric carbon (C-1′ position) of the sugar is linked to the aglycon by a carbon–nitrogen bond. Since the first isolation of pseudouridine (**1**) as a minor constituent in various transfer ribonucleic acids,[2)] a number of naturally occurring *C*-nucleosides have been isolated mainly from the culture filtrates of various *Streptomyces*.[3)] The *C*-nucleosides, based on their unique structural feature, have considerable stability to chemical hydrolysis and enzymatiac destruction and, as a consequence, most of them exhibit various biological properties of interest.[4–9)]



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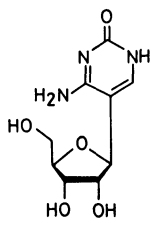

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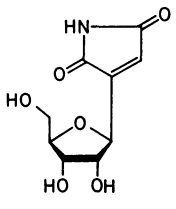

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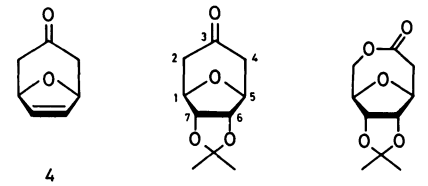
The biological importance has stimulated the exploration of synthetic routes leading to natural *C*-nucleosides as well as their artificial analogues. The synthetic processes fall into the following three main categories: (1) transformation of naturally occurring *C*-nucleosides, (2) elaboration of a nitrogen heterocycle onto a suitably modified carbohydrate, and (3) total synthesis starting from non-sugar precursors. Most of the existing approaches[10)] come under the first and second categories, which seem to lack effectiveness, however, because of difficulty in access of the starting materials and poor generality in the former case, and low stereoselectivity in the latter method. The third-category type of synthesis obviously allows maximum flexibility but development of any effective approaches of this type requires some new, efficient methodologies for creation of the four asymmetric centers in the ribose skeleton as well as a strategy for stereochemical control at the anomeric center so as to maintain the β-D-glycosyl structures.[11)] This paper discloses full accounts of our stereocontrolled, general entry to *C*-nucleosides starting from inexpensive non-carbohydrate substances. The highly chiral framework is created by simple operations *via* an intermediate having C_s symmetry; the ribose skeleton is made by the efficient [3+4] cyclocoupling between polybromo ketones and furans aided by low-valent transition metals[13)] and subsequent oxidative modification of the resulting oxa bicyclic structure.

Synthesis of Pyrimidine C-Nucleosides. This synthesis starts with the bicyclic enone **4**, which is readily obtainable by reductive cyclocoupling of α,α,α′,α′-tetrabromoacetone and furan promoted by $Fe_2(CO)_9$ in benzene[14)] or Zn/Ag couple in THF,[15)] followed by debromination with Zn/Cu couple in methanol. When **4** was treated with a slight excess of 70% solution of *t*-butyl hydroperoxide in *t*-butyl alcohol containing catalytic amounts of osmium tetraoxide and aqueous tetraethylammonium hydroxide at 0—25 °C[16)] and then with anhydrous $CuSO_4$ and *p*-toluenesulfonic acid in acetone, the oxygen functions were introduced to the double bond from the less hindered side[17)] with perfect stereoselectivity to give the acetonide **5** as a single, crys-

talline isomer in 68% yield. No stereoisomer was detected in the reaction mixture. The stereoselective conversion of **4** to **5** was also accomplished in 52% yield by the osmium tetraoxide-catalyzed reaction using 30% hydrogen peroxide as the oxidizing agent. The α stereochemistry of the acetonide was established on the basis of the ^{1}H NMR spectrum which exhibited a sharp singlet at δ 3.98 due to the equivalent H_6 and H_7 protons. A Dreiding model of this rigid tricyclic system indicated that the H–C(6)–C(5)–H (or H–C(7)–C(1)–H) dihedral angle is approximately 90°, consistent with the observed ~0 Hz spin-spin coupling constant; if the acetonide had alternative β orientation with the dihedral angle of 30—40°, a 5 to 6-Hz signal splitting would be anticipated.[18] Subsequent Baeyer-Villiger oxidation of **5**,[19] giving the key intermediate **6** of an adequate *C*-β-glycoside structure, was achieved in 81% yield (94% yield based on consumed **5**) in dichloromethane at room temperature by two equiv of trifluoroperacetic acid in the presence of buffer salts of Na_2HPO_4 and disodium dihydrogen ethylenediaminetetraacetate. The oxidation proceeded only slowly by use of *m*-chloroperbenzoic acid with a catalytic amount of 4,4′-thiobis(6-*t*-butyl-3-methylphenol), and the yield was reduced to 59%. The lactone formation was confirmed by the IR absorption at 1737 cm^{-1} (C=O). Thus the keystone intermediate having a highly chiral structure can be derived facilely starting from simple and symmetrical substances, acetone and furan. The optical resolution required for natural product synthesis was effected *via* the corresponding seco acid methyl ester **7**, obtained in 95% yield by methanolysis with sodium methoxide in methanol. We found that, in this case, the Pirkle's resolution procedure[20] was far superior to the traditional method involving salt formation.[1a] Heating of an equimolar mixture of racemic **7** and (*R*)-1-(1-naphthyl)ethyl isocyanate in toluene[20] followed by chromatographic separation produced the optically active, diastereomeric carbamates **8**, $[\alpha]_D^{15}$ −3.56° (*c* 0.337, $CHCl_3$), and **9**, $[\alpha]_D^{15}$ −1.25° (*c* 0.561, $CHCl_3$), in 43% and 46% yields, respectively. The desired seco acid methyl ester, D-**7**, was liberated from **8** in 80% yield by treatment with trichlorosilane and triethylamine in benzene.[20] The transformation of D-**7** to the optically pure lactone, D-**6**, mp 161—163 °C, $[\alpha]_D^{26}$ +84° (*c* 0.63, $CHCl_3$), was then achieved according to the known procedure.[21] This resolved lactone was identical in all respects with the authentic sample prepared from D-ribose.[22]

The synthetic sequence continues by introduction of formyl or its synthetic equivalent at position α to the lactone carbonyl. After many attempts without any respectable success, a Bredereck reagent was found to be among the most effective. Thus treatment of D-**6** with



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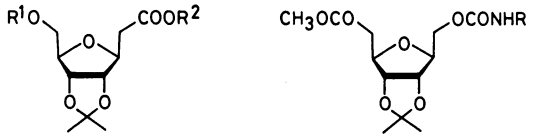
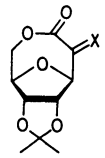


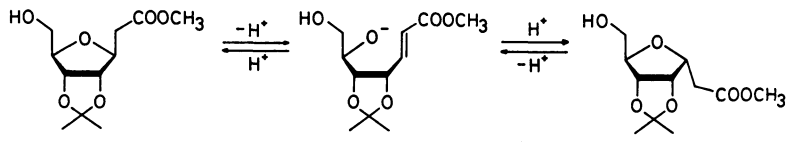
7, R^1 = H; R^2 = CH_3
8, R^1 = (*R*)-1-(1-naphthyl)-ethylaminocarbonyl; R^2 = CH_3
9, R = (*R*)-1-(1-naphthyl)ethyl



10, X = $CHN(CH_3)_2$
18, X = O
21, X = (*E*)-CHFur

t-$C_4H_9OCH[N(CH_3)_2]_2$[25] in DMF at 60 °C afforded the dimethylaminomethylene lactone, D-**10**, in 91% yield. The product showed the IR bands [1685 and 1680 cm^{-1} (C=O), and 1595 cm^{-1} (C=C)] and a UV absorption [296 nm (ε 13,500)] characteristic of α-dimethylaminomethylene lactone structure. The ^{1}H NMR spectrum displaying two sets of two singlets at δ 2.94 and 3.16 [$N(CH_3)_2$], and 6.69 and 7.34 (=CH) indicated that the product was a 1:2 mixture of the *E*- and *Z*-olefinic isomers. It should be noted that the hydroxy ester **7**, the seco form of **6**, is stereochemically quite labile under basic conditions and, hence, formylation or related operation by conventional standard procedures causes easy isomerization through the intramolecular retro-Michael reaction/recyclization sequence,[24,26] giving the more stable α epimer **11**. Use of the lactone **6** thus has the particular advantage in preservation of the "natural" stereochemical integrity at C-1′.[27]

The aminomethylene lactone, D-**10**, appeared to serve as a common intermediate for natural and unnatural pyrimidine *C*-nucleosides. For instance, when a mix-



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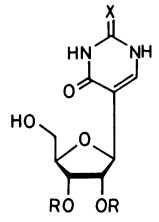
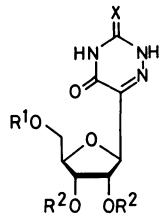
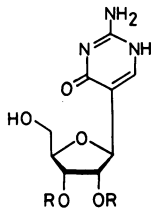
ture of D-**10** and urea was heated at reflux in 1 mol dm^{-1} ethanolic sodium ethoxide, there was obtained the uracil derivative, D-**12**,[29] mp 235—236 °C, $[\alpha]_D^{21}$ −18.1° (*c* 0.16, CH_3OH), in 60% yield. Removal of the isopropylidene group by exposure to 10% methanol solution of hydrogen chloride at 20 °C furnished pseudouridine (**1**), mp 243—244 °C, $[\alpha]_D^{21}$ −4.30° (*c* 0.47, H_2O), having spectral and physical properties identical with those of naturally occurring specimen. In addition, **1** is convertible to pseudocytidine (**2**),[29] a natural *C*-nucleoside, and 6-azapseudouridine (**13**),[30] an unnatural analogue, by the stereocontrolled, standard methods.



12, R–R = $C(CH_3)_2$; X = O
14, R–R = $C(CH_3)_2$; X = S
15, R = H; X = S



13, $R^1 = R^2$ = H; X = O
27, $R^1 = Si(CH_3)_2$-*t*-C_4H_9; R^2–R^2 = $C(CH_3)_2$; X = O
29, $R^1 = Si(CH_3)_2$-*t*-C_4H_9; R^2–R^2 = $C(CH_3)_2$; X = S
30, $R^1 = R^2$ = H; X = S



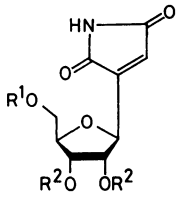
16, R–R = $C(CH_3)_2$
17, R = H

The lactone, D-**10**, underwent the sodium ethoxide-promoted condensation with thiourea in refluxing ethanol to produce the acetonide, D-**14**, $[\alpha]_D^{22}$ −8.0° (*c* 0.92, CH_3OH), in 81% yield. Subsequent deprotection with 10% solution of hydrogen chloride in methanol liberated 2-thiopseudouridine (**15**)[28] as a very hygroscopic solid in 90% yield.

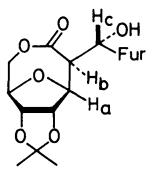
Chemotherapeutically significant pseudoisocytidine (**17**)[28,31] could be also synthesized from D-**10** in a similar manner. Thus, construction of the heterocyclic nucleus using guanidine hydrochloride and sodium ethoxide in hot ethanol gave rise to D-**16**, mp 170—174 °C, $[\alpha]_D^{22}$ −50.8° (*c* 0.73, CH_3OH), in 81% yield, methanolysis of which catalyzed by hydrogen chloride afforded hyrochloride of D-**17**,[28,31] mp 212—215 °C, $[\alpha]_D^{22}$ +14.3° (*c* 0.49 H_2O), in 93% yield.

Noteworthy is that during these all heterocycle formation-deprotection sequences no epimerization occurred at the glycosidic position.

Synthesis of Showdomycin. We conceived that the lactone D-**6** or D-**10** may be useful for the synthesis of nucleosides other than pyrimidine ribo-*C*-nucleosides. The possibility of synthesis of showdomycin (**3**), a natural maleimide *C*-nucleoside,[32] was examined in two different ways. One approach used again D-**10** as the intermediate. When this lactone was exposed to ozone in ethyl acetate at −78 °C and then dimethyl sulfide at −78 °C to room temperature,[33] the labile keto lactone D-**18** was afforded, displaying a strong IR band due to the lactonic and keto carbonyls at 1732 cm^{-1} and no absorption for a conjugated olefin. This was subjected immediately to the Wittig reaction with $(C_6H_5)_3PCHCONH_2$[32a,34] in DMF to give D-**19**, mp 142—143 °C, $[\alpha]_D^{24}$ −2.31° (*c* 1.07, $CHCl_3$), in 30% yield. Removal of the isopropylidene block with aqueous trifluoroacetic acid completed the synthesis of showdomycin (**3**), mp 151—152 °C, $[\alpha]_D^{24}$ +48.7° (*c* 1.4 H_2O), which was identified by comparison with the natural product.



19, R^1 = H; R^2–R^2 = $C(CH_3)_2$
25, $R^1 = Si(CH_3)_2$-*t*-C_4H_9; R^2–R^2 = $C(CH_3)_2$



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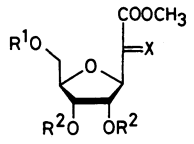

22, R^1 = H; R^2–R^2 = $C(CH_3)_2$; X = (*E*)-CHFur
23, $R^1 = Si(CH_3)_2$-*t*-C_4H_9; R^2–R^2 = $C(CH_3)_2$; X = (*E*)-CHFur
24, $R^1 = Si(CH_3)_2$-*t*-C_4H_9; R^2–R^2 = $C(CH_3)_2$; X = O
26, $R^1 = Si(CH_3)_2$-*t*-C_4H_9; R^2–R^2 = $C(CH_3)_2$; X = $NNHCONH_2$
28, $R^1 = Si(CH_3)_2$-*t*-C_4H_9; R^2–R^2 = $C(CH_3)_2$; X = $NNHCSNH_2$

Another entry to **3** utilizes aldol reaction of D-**6** and furfural assisted by lithium cyclohexylisopropylamide in THF at −78 °C, affording in 90% yield the adduct D-**20** (Fur=2-furyl), mp 139—141 °C, $[\alpha]_D^{21}$ +26° (*c* 2.63, $CHCl_3$). This was a single isomer and, on the basis of ^1H NMR, was revealed to have the *S* configuration at position α to the lactone carbonyl ($J_{Ha,Hb}$=5.0 Hz)[35] and the threo relationship[36] regarding the aldol moiety ($J_{Hb,Hc}$=9.0 Hz).[37] Dehydration of D-**20** was then effected by treatment with pivaloyl chloride in pyridine at 25 °C followed by heating in the same solvent at 90 °C, yielding D-**21**, mp 160—162 °C, $[\alpha]_D^{21}$ −143° (*c* 0.64, $CHCl_3$), quantitatively. The furfurylidene structure was proved by IR bands observed at 1715 (C=O) and 1627 cm^{-1} (C=C), and the ^1H NMR signal appearing as

a singlet at δ 7.24 (=CH). Ring-opening of the lactone with 0.05 mol dm^{-3} methanolic sodium methoxide at 0 °C, giving oily D-**22**, $[\alpha]_D^{21}$ +104° (*c* 2.90, $CHCl_3$), in 86% yield, followed by the silylation of the primary hydroxyl group with *t*-$C_4H_9(CH_3)_2SiCl$ and imidazole in DMF[38] gave quantitatively the methyl ester D-**23**, $[\alpha]_D^{21}$ −0.98° (*c* 0.44, $CHCl_3$), whose ^{1}H NMR data served to support its β-*C*-glycoside structure. The two isopropylidene-methyl singlets occurring at δ 1.25 and 1,56 with 0.31-ppm chemical shift difference is reminiscent of the spectral behavior of related isopropylidene ribonucleosides; the β anomers exhibit the chemical shift difference of >0.18 ppm, whereas the α anomers show the <0.10-ppm difference.[39] Ozonolysis of D-**23** in ethyl acetate at −78 °C followed by reductive workup with dimethyl sulfide yielded the unstable keto ester D-**24**, which without purification was subjected to the Wittig condensation with $(C_6H_5)_3PCHCONH_2$[32a,34] in chloroform to lead to D-**25**, $[\alpha]_D^{24}$ +2.1° (*c* 1.40, $CHCl_3$), in 29% yield (based on D-**23**). Subsequent trifluoroacetic acid-catalyzed hydrolysis produced showdomycin (**3**). Ozonolysis of the furfurylidene lactone, D-**21**, followed by the Wittig reaction also gave showdomycin acetonide, D-**19**, but only in 15% yield.

Such overall transformation have been achieved again without any epimerization at the anomeric center.

Synthesis of 1,2,4-Triazine C-Nucleosides. The keto ester D-**24** can be converted to certain 1,2,4-triazine *C*-nucleosides[40] in a stereospecific manner. For example, refluxing of a mixture of D-**24** and semicarbazide hydrochloride in aqueous methanol containing sodium acetate gave the semicarbazone D-**26**, $[\alpha]_D^{22}$ −1.6° (*c* 1.0, $CHCl_3$), in 30% yield (based on D-**23**) as a mixture of the syn and anti isomers. The isomeric ratio was assigned to be approximately 1:1 by the N–H ^{1}H NMR signals observed at δ 11.29 and 10.21,[41] respectively. Then the cyclization with 0.1 mol dm^{-3} ethanolic sodium ethoxide under reflux[42] furnished the 6-azauracil derivative, D-**27**, $[\alpha]_D^{25}$ −35.8° (*c* 8.90, $CHCl_3$), in 40% yield, hydrolysis of which gave 6-azapseudouridine (**13**),[30] mp 136—138 °C, $[\alpha]_D^{24}$ −23.4° (*c* 0.5, H_2O). In a similar fashion, treatment of D-**24** with thiosemicarbazide in refluxing methanol produced the thiosemicarbazone, D-**28**, $[\alpha]_D^{21}$ −0.71° (*c* 1.1, $CHCl_3$), in 25% yield (overall from D-**23**), which upon exposure to 0.1 mol dm^{-3} ethanolic sodium ethoxide at reflux temperature afforded D-**29**, $[\alpha]_D^{25}$ −1.4° (*c* 2.30, $CHCl_3$), in 56% yield. Deblocking of the protective groups with aqueous trifluoroacetic acid liberated 6-aza-2-thiopseudouridine (**30**),[30] mp 193—195 °C, $[\alpha]_D^{25}$ −3.5 °C(*c* 0.5, H_2O).

Conclusion. Our synthetic aim has thus in fact been realized. The salient feature of this total synthesis is use of the rigid bicyclic intermediates **4** and **6**. This allows strict stereochemical control throughout the overall transformation that consists of assembling the ribose moiety and elaboration of heterocyclic nuclei having the β configuration; the undesired stereomutation is precluded. In addition, the present route has practicability because of its directness and the ready availability of the starting materials. Of more importance is that this entry is capable of preparing various kinds of artificial *C*-nucleosides, particularly those with modified carbohydrate structures. Apparently this wide generality arises from the synthetic flexibility of the transition metal-mediated reductive cyclocoupling of appropriately substituted polybromo ketones and furan derivatives.[13,14] Analogues so far prepared by this method include various pyrimidine *C*-nucleosides containing 5′-alkylated,[43] 1′- or 4′-modified,[43a,44] 2′- or 3′-substituted,[43a,45] and 2′,3′-dialkylated ribose.[43a,46] Homo-*C*-nucleosides (homoshowdomycin,[47] homopyrazomycin,[47] and pyrimidine derivatives,[47a,48]) have been also synthesized.

We should add finally that successful examples were announced recently in preliminary disclosures for showdomycin synthesis *via* non-carbohydrate precursors, which laid on the Diels-Alder reaction between furan and an acrylic acid ester or an acetylenedicarboxylic acid derivative.[32e-g,49]

Experimental

General. Melting points uncorrected were obtained on a hot-stage apparatus. Elemental analyses were performed at the Faculty of Engineering of Nagoya University and the Fujisawa Pharmaceutical Co. Infrared (IR) spectra were recorded in a chloroform solution unless otherwise noted on a JASCO DS-402G or IRA-I spectrophotometer. Ultraviolet (UV)-visible light spectra in a stated solution were taken on a Hitachi 323 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) and proton decoupled ^{13}C NMR spectra were determined in a noted phase on Varian HA-100 and Varian CFT-20 instruments, respectively. Chemical shifts are given as parts per million (ppm) downfield from tetramethylsilane in δ units. In the ^{1}H NMR spectra, coupling constants are reported in hertz. Multiplicities are as follows: s; singlet, d; doublet, t; triplet, q; quartet, m; multiplet. Low-resolution mass spectra were measured on a Hitachi RMU-6C or JEOL D-100 instrument at an ionization potential of 70 eV and only a parent peak or prominent fragment peaks are described. Exact mass spectra were obtained at the Ono Pharmaceutical Co. or Institute for Molecular Science. Optical rotations were measured with a JASCO DIP-SL automatic polarimeter or a JASCO DIP-140 or 181 digital polarimeter. Analytical thin-layer chromatography (TLC) was done on a 5×2 cm of glass slide coated with 0.25-mm thickness of E. Merck Kieselgel 60 PF_{254}. For the preparative work, a 20×20 cm of glass plate coated with 1.0-mm thick layer of E. Merck Kieselgel 60 PF_{254} was employed. Use of E. Merck Kieselgel 60 (70—230 mesh) was made for column chromatography, unless otherwise state. High-performance liquid chromatography (HPLC) was achieved on a Waters 6000A instrument. All reactions in organic solutions were performed under an argon atmosphere. Concentration of solutions was carried out on a rotary evaporator under water aspirator pressures followed by a rotary oil vacuum pump. Organic solvents employed for the reactions were purified by standard procedures. *m*-Chloroperbenzoic acid was used after purification of commercially obtained material by the literature method.[53] Furfural was employed promptly after filtration through a short alumina column followed by distillation. A butyllithium–hexane solution required determination of the concentration by titration by the usual method.[54] *t*-Butoxybis(dimethylamino)methane was prepared according to the procedure of Bredereck.[25] Carbamoylmethylenetriphenylphosphorane made by the method of Trippett[34] was dried over P_2O_5 under 0.01 mmHg (1 mm Hg≈133.322 Pa) overnight before use.

(1R,5S*,6S*,7R*)-6,7-Isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3-one (5).* *A. By Oxidation with t-Butyl Hydroperoxide*: To a mixture of *t*-butyl alcohol solution (60 ml (1 ml=0.001 dm^3)) of 20% aq tetraethylammonium hydroxide (2.4 ml, 3.26 mmol) and 8-oxabicyclo[3.2.1]oct-6-en-3-one (**4**)[14,15] (3.72 g, 30 mmol) was added with vigorous stirring a 70% solution of *t*-butyl hydroperoxide in *t*-butyl alcohol (6.0 ml, 46.7 mmol) followed by a 0.02 mol dm^{-3} *t*-butyl alcohol solution of osmium tetraoxide (30 ml, 0.6 mmol) at 0 °C. The resulting yellow mixture was stirred at 0 °C for 30 min and at 20 °C for 5 h. The solution of *t*-butyl hydroperoxide (2.0 ml, 15.6 mmol), osmium tetraoxide (10 ml, 0.2 mmol), and aqueous tetraethylammonium hydroxide (1.0 ml, 1.4 mmol) were added renewedly and the reaction mixture was stirred again at 25 °C for 24 h. After quenching with 20% aq $Na_2S_2O_3$ solution (40 ml) at 0 °C, the mixture was stirred at 0 °C for 1 h. Viscous material obtained by evaporation was treated with acetone (100 ml) and the precipitates were removed by filtration through a Celite 545 pad. The filtrate was concentrated, giving an oil, which was dissolved in ethanol (50 ml) and then evaporated again. This dissolution-evaporation sequence was repeated twice more. A mixture of the resulting oil, anhydrous $CuSO_4$ (10 g, 62.7 mmol), and *p*-toluenesulfonic acid (100 mg) in acetone (100 ml) was stirred at 25 °C for 2 h. Removal of the insoluble material by filtration through a Celite 545 pad followed by concentration left an oily product, column chromatography of which with 1:1 ethyl acetate-hexane gave the acetonide **5** (4.05 g, 68%) as colorless crystals. Recrystallization from chloroform-hexane afforded an analytical sample, mp 119—121 °C: IR 1715 (C=O), 1378 and 1370 cm^{-1} (isopropylidene); ^1H NMR (benzene-d_6) δ=1.06 (s, isopropylidene CH_3), 1.47 (s, isopropylidene CH_3), 1.76 (d, J=16 Hz, $H_{2\beta}$ and $H_{4\beta}$), 2.08 (dd, J=6, 16 Hz, $H_{2\alpha}$ and $H_{4\alpha}$), 3.98 (s, H_6 and H_7), 4.23 (d, J=6 Hz, H_1 and H_5); mass spectrum m/z 198 (M^+). Anal. ($C_{10}H_{14}O_4$) C, H.

B. By Oxidation with Hydrogen Peroxide: Aqueous 30% hydrogen peroxide (100 ml, 863 mmol) was added at 0 °C over 2 h to a solution of **4** (11.6 g, 102 mmol), osmium tetraoxide (200 mg, 0.79 mmol), *t*-butyl alcohol (50 ml), and ether (50 ml) in acetone (500 ml). The reaction mixture was stirred at 20 °C for 13 h and then, after cooling to 0 °C, was quenched with $NaHSO_3$ (30 g). The resulting mixture was stirred at 20 °C for 3 h and evaporated until the volume was reduced to 50—100 ml. Extraction with ethyl acetate (200 ml×2, 100 ml) followed by concentration left an oil, which was mixed with anhydrous $CuSO_4$ (20 g, 125 mmol) and *p*-toluenesulfonic acid (50 mg) in acetone (200 ml), and stirred at 20 °C for 4 d. Removal of the insoluble solid by filtration followed by evaporation gave a viscous oil, whose column chromatography with a 1:3 to 2:1 ethyl acetate-hexane mixture as eluent afforded the colorless crystalline acetonide **5** (10.5 g, 52% yield), mp 119—121 °C.

(±)-2-(2,3-O-Isopropylidene-β-ribofuranosyl)acetic Acid Lactone (6). *A. With Trifluoroperacetic Acid*: A dichloromethane solution of trifluoroperacetic acid was prepared by mixing 90% hydrogen peroxide (9.62 ml, 255 mmol) and trifluoroacetic anhydride (43.3 ml, 305 mmol) in dichloromethane (200 ml) at 0 °C. This was added slowly with efficient stirring at 0 °C to a mixture of **5** (25.5 g, 127 mmol), Na_2HPO_4 (130 g, 915 mmol), and disodium dihydrogen ethylenediaminetetraacetate (2 g) in dichloromethane (200 ml), and the mixture was stirred at 25 °C for 12 h. After dilution with dichloromethane (200 ml) and addition of $Na_2S_2O_3 \cdot 5H_2O$ (40.5 g, 163 mmol) at 0 °C, the resulting mixture was further stirred at 25 °C for 5 h. Removal of insoluble material by filtration through a Celite 545 pad followed by evaporation produced a crude solid, which was subjected to column chromatography with a 1:1 to 3:1 ethyl acetate-hexane mixture, affording the unreacted ketone **5** (3.52 g, 14%) in the early fractions and the crystalline lactone **6** (22.1 g, 81% yield) in the late fractions. The yield of **6** based on consumed **5** was 94%. An analytical specimen of **6**, mp 146—147 °C (lit,[21] mp 140—141 °C), was collected by recrystallization from chloroform-hexane: IR 1737 cm^{-1} (C=O); ^1H NMR (benzene-d_6) δ=1.04 (s, 3 H, isopropylidne CH_3), 1.42 (s, isopropylidene CH_3), 2.16 (dd, J=3, 14 Hz, H_{2b}), 2.38 (dd, J=5.4, 14 Hz, H_{2a}), 3.10 (dd, J=3, 14 Hz, $H_{5'a}$), 3.51 (d, J=14 Hz, $H_{5'b}$), 3.96 (m, $H_{1'}$ and $H_{4'}$), 4.39 (d, J=6 Hz, $H_{2'}$), 4.58 (d, J=6 Hz, H_3); mass spectrum m/z 199 (M^+−15). Anal. ($C_{10}H_{14}O_5$) C, H.

B. With m-Chloroperbenzoic Acid: A 50-ml thick-glass tube charged with a magnetic stirring bar, **5** (2.0 g, 10 mmol), *m*-chloroperbenzoic acid (2.9 g, 16.8 mmol), sodium hydrogencarbonate (1.74 g, 20.7 mmol), and 4,4′-thiobis(6-*t*-butyl-3-methylphenol) (100 mg, 0.14 mmol) in chloroform (40 ml) was sealed and covered with an aluminum foil for shutting out the light. The ampule was immersed in a heating oil bath at 40—45 °C with stirring for 4 d. The resulting insoluble material was removed by filtration and washed with dichloromethane (20 ml). Concentration giving a yellow crystalline product followed by column chromatography with a 1:1 to 4:1 ether-hexane mixture afforded **6** (1.27 g, 59% yield) as colorless crystals, mp 146—147 °C after recrystallization. Unreacted **5** (810 mg, 41%) was recovered, hence the conversion yield was 99%.

(±)-Methyl 2-[(1S,2S*,3R*,4R*)-2,3-O-Isopropylidene-β-ribofuranosyl]acetate (7).* To a solution of the lactone **6** (200 mg, 1.00 mmol) in methanol (3 ml) was added dropwise 1 mol dm^{-3} methanolic sodium methoxide (1.20 ml) at room temperature over 5 min. Immediately after the addition was completed, the reaction mixture was quenched with 1 mol dm^{-3} solution of ammonium chloride in methanol (1.2 ml) and concentrated. The resulting residue was treated with water (5 ml) and extracted with dichloromethane (10 ml×3). The combined organic extracts were washed with brine and evaporated to give an oil, which was chromatographed on a silica-gel column (1:1 ethyl acetate-hexane) to afford **7** (233 mg, 95%) having the identical spectral data with those of the authentic sample alternatively prepared by the literature method.[24]

Methyl 5-O-(R)-1-(1-Naphthyl)ethylcarbamoyl-2-(2,3-O-isopropylidene-β-D-ribofuranosyl)acetate (8) and Methyl 5-O-(R)-1-(1-Naphthyl)ethylcarbamoyl-2-(2,3-O-bisopropylidene-β-L-ribofuranosyl)acetate (9). A mixture of **7** and (*R*)-1-(1-naphthyl)ethyl isocyanate in toluene (3 ml) was refluxed for 24 h under argon. Concentration of the resulting mixture gave a yellow oil, which was roughly purified by silica-gel column chromatography (35:65 ethyl acetate-hexane), yielding an oily mixture of the diastereomeric carbamates, **8** and **9**, (260 mg). This oil was subjected to preparative HPLC (10× 600 mm Hypersil-ODS, 40:60 H_2O-CH_3CN) to afford **8** [V_R 17.3 ml, 115 mg, 43% (86% theoretical yield)] and **9** [V_R 16.4 ml, 125 mg, 46% (92% theoretical yield)] as glassy syrups. **8**: $[\alpha]_D^{15}$ −3.56° (*c* 0.337, $CHCl_3$); IR 3440 (NH), 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.23 (s, isopropylidene CH_3), 1.45 (s, isopropylidene CH_3), 1.56 (d, J=6.5 Hz, $CHCH_3$), 2.5 (m, CH_2COOCH_3), 3.56 (s, $COOCH_3$), 4.0 (m, $H_{1'}$, $H_{4'}$, and 2 $H_{5'}$), 4.4 (m, $H_{2'}$ and $H_{3'}$), 5.10 (d, J=6.5 Hz, NH), 5.50 (seven-line m, J=6.5 Hz, CHNH), 7.1—8.1 (m, aromatic H). Found: m/z, 443.1936. Calcd for $C_{24}H_{29}NO_7$: 443.1942. **9**: $[\alpha]_D^{15}$ −1.25° (*c* 0.561, $CHCl_3$); IR 3440 (NH), 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.22 (s, isopropylidene CH_3), 1.43 (s, isopropylidene CH_3), 1.53 (d, J=6.5 Hz, $CHCH_3$), 2.47 (m, CH_2COOCH_3), 3.50 (s, $COOCH_3$), 4.0 (m, $H_{1'}$, $H_{4'}$, and 2 $H_{5'}$), 4.4 (m, $H_{2'}$ and $H_{3'}$), 5.07 (br d, J=7 Hz, NH), 5.49 (m, CHNH), 7.2—8.1 (m, aromatic H). Found: m/z, 443.1931. Calcd for $C_{24}H_{29}NO_7$: 443.1942.

Methyl 2-(2,3-O-Isopropylidene-β-D-ribofuranosyl)acetate (D-7). To a solution of **8** (83 mg, 0.19 mmol) and triethyl-

amine (46 mg, 0.45 mmol) in benzene (1.7 ml) was added trichlorosilane (31 mg, 0.23 mmol). The mixture was heated at reflux for 1 h under argon and quenched with water (3 ml). The organic layer was separated and the aqueous solution was extracted with dichloromethane (5 ml×3). The combined organic extracts were washed with brine (3 ml). Concentration gave an oil, which was subjected to column chromatography on silica gel (1:1 ethyl acetate–hexane) to give D-**7** (37 mg, 80%), $[\alpha]_D^{15}$ −6.28° (*c* 2.33, $CHCl_3$), identical in all respects with the authentic sample prepared according to the known procedure.[24]

2-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-2-(dimethylaminomethylene)acetic Acid Lactone (D-10). A mixture of the lactone D-**6** (2.14 g, 10.0 mmol), *t*-butoxybis(dimethylamino)methane[25] (10 ml), and DMF (5 ml) was heated at 60 °C for 1 h. Evaporation of the resulting mixture *in vacuo* left an oily residue, which was chromatographed on a column packed with ammonia-treated silica gel. Elution with 1:1 ethyl acetate–hexane afforded a yellow syrup, D-**10** (2.45 g, 91% yield): IR 1685, 1680, 1595, 1420 cm^{-1}; UV λ_{max} (CH_3OH) 296 nm (ε 13500); mass spectrum *m/z* 269 (M^+). The ^1H NMR spectrum ($CDCl_3$) showed that the product consisted of *ca.* 2:1 mixture of *Z*- and *E*-olefinic isomers: δ=1.32 (s, isopropylidene CH_3), 1.51 (s, isopropylidene CH_3), 2.94 and 3.16 (two s's (1:2), $N(CH_3)_2$), 4.1—5.1 (m, $H_{1'}$, $H_{2'}$, $H_{3'}$, $H_{4'}$, and 2 $H_{5'}$), 6.69 and 7.34 (two s's (1:2), =CH). An analytical sample, mp 78—80 °C, was obtained by recrystallization from ether–hexane. Anal. ($C_{13}H_{19}NO_5$) C, H, N.

5-(2,3-O-Isopropylidene-β-D-ribofuranosyl)uracil (D-12). A mixture of D-**10** (4.12 g, 15.3 mmol), urea (4.59 g, 76.6 mmol), and 1 mol dm^{-3} solution of sodium ethoxide in ethanol (77 ml) was heated at reflux for 5 h under argon atmosphere. Evaporation of the reaction mixture left a residual syrup, which was dissolved in water (10 ml), and carefully neutralized by 6 mol dm^{-3} hydrochloric acid under monitoring with a pH test paper. An oil produced by concentration was diluted with ethanol (80 ml) and the insoluble material was removed by filtration. Evaporation followed by column chromatography using a 1:5 to 1:3 methanol–chloroform mixture as eluent gave the compound D-**12** (2.61 g, 60% yield), R_f 0.29 (1:5 methanol–chloroform) as slightly yellow crystals. Recrystallization from methanol–acetone–hexane produced the analytical sample, mp 235—236 °C (lit,[29] 233—234 °C), $[\alpha]_D^{21}$ −18.1° (*c* 0.16, CH_3OH): UV λ_{max} (CH_3OH) 263 nm (ε 5960), λ_{max} (0.1 mol dm^{-3} NaOH) 284 nm (ε 7110); ^1H NMR (dimethyl-d_6 sulfoxide) δ=1.27 (s, isopropylidene CH_3), 1.49 (s, isopropylidene CH_3), 3.53 (br s, 2 $H_{5'}$), 3.91 (br q, *J*=4.0 Hz, $H_{4'}$), 4.6—5.0 (m, $H_{1'}$, $H_{2'}$, $H_{3'}$, and OH), 7.55 (s, H_6), 10.93 (br s, NH), 11.14 (br s, NH); ^{13}C NMR (dimethyl-d_6 sulfoxide) δ= 25.45, 27.42, 61.74, 80.30, 81.55, 83.91, 84.33, 110.40, 112.81, 140.03, 151.05, 163.27. These physical and spectral data were superimposable on those of the authentic sample prepared by the method of literature.[29]

5-(β-D-Ribofuranosyl)uracil (Pseudouridine) (1). A mixture of solution of D-**12** (321 mg, 1.14 mmol) in methanol (5 ml) and 10% methanolic hydrogen chloride (5 ml) was stirred at 20 °C for 5 h. During this period there occurred pseudouridine (**1**) as colorless crystalline material, which was collected by filtration. A viscous residue left by concentration was dissolved in ethanol (5 ml) and evaporated. Repetition of this evaporation procedure followed by washing of the residue with ether (5 ml×3) gave additional **1**. Totally 259 mg (93%) of **1** was obtained. Recrystallization from methanol afforded an analytical sample, mp 243—244 °C (lit,[28] 221—222 °C), $[\alpha]_D^{21}$ −4.30° (*c*, 0.47, H_2O): UV λ_{max} (CH_3OH) 264 nm (ε 4750), λ_{max} (0.1 mol dm^{-3} HCl) 263 nm (ε 7560), λ_{max} (0.1 mol dm^{-3} NaOH) 285 nm (ε 7360); ^1H NMR (dimethyl-d_6 sulfoxide) δ=3.3—4.0 (m, $H_{2'}$, $H_{3'}$, $H_{4'}$, and 2 $H_{5'}$), 4.51 (d, *J*=4.0 Hz, $H_{1'}$), 4.54 (br s, 3 OH), 7.52 (d, *J*=6.0 Hz, H_6), 10.85 (d, *J*=6.0 Hz, H_1), 11.07 (br s, H_3); ^{13}C NMR (dimethyl-d_6 sulfoxide) δ=61.36, 70.62, 73.93, 78.88, 83.47, 111.05, 139.62, 150.98, 163.57. This compound showed the spectral and physical behavior identical with that of the naturally occurring specimen.

5-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-2-thiouracil (D-14). A mixture of D-**10** (2.14 g, 7.96 mmol), thiourea (3.02 g, 39.8 mmol). and 1 mol dm^{-3} ethanolic sodium ethoxide (40 ml) was refluxed for 3 h under argon. Residue obtained by evaporation was dissolved in water (10 ml) and carefully neutralized with 6 mol dm^{-3} hydrochloric acid. Extraction with ethyl acetate (50 ml×5) and concentration of the combined organic layers afforded a yellow solid, which on column chromatography with a 1:30 to 1:5 methanol–chloroform mixture gave rise to D-**14** (1.93 g, 81% yield), R_f 0.65 (1:5 methanol–chloroform), as a slightly yellow foam, $[\alpha]_D^{22}$ −8.0° (*c*, 0.92, CH_3OH): UV λ_{max} (CH_3OH) 276 (ε 13930), 292 nm (12860), λ_{max} (0.1 mol dm^{-3} NaOH) 264 (ε 12920), 290 nm (10560); ^1H NMR (dimethyl-d_6 sulfoxide) δ=1.27 (s, isopropylidene CH_3), 1.49 (s, isopropylidene CH_3), 3.20 (br s, 2 $H_{5'}$), 3.91 (m, $H_{4'}$), 4.5—4.7 (m, $H_{1'}$, $H_{2'}$, and $H_{3'}$), 7.50 (s, H_6), 12.42 (br s, 2 NH); ^{13}C NMR (dimethyl-d_6 sulfoxide) δ=25.43, 27.36, 61.62, 79.94, 81.41, 84.02, 85.07, 112.84, 115.92, 139.11, 160.16, 175.39. Found: *m/z*, 300.07739. Calcd for $C_{12}H_{16}N_2O_5S$: 300.07798.

5-(β-D-Ribofuranosyl)-2-thiouracil (2-Thiopseudouridine) (D-15). A mixture of solution of D-**14** (763 mg, 2.56 mmol) in methanol (5 ml) and 10% solution of hydrogen chloride in methanol (7 ml) was stirred at 20 °C for 1 h and subsequently concentrated. The resulting residue was diluted with ethanol (7 ml) and evaporated. Dilution and evaporation sequence was repeated twice more to leave a colorless solid, which was washed with ether (7 ml×2). The solid was dried *in vacuo* producing 2-thiopseudouridine (D-**15**) (599 mg, 90% yield) as very hygroscopic, colorless crystals:[56] UV λ_{max} (CH_3OH) 275, 293 nm,[56] λ_{max} (0.1 mol dm^{-3} HCl) 274, 291 nm,[56] λ_{max} (0.1 mol dm^{-3} NaOH) 264, 284 nm;[56] ^1H NMR (dimethyl-d_6 sulfoxide) δ=3.5—4.1 (m, $H_{2'}$, $H_{3'}$, $H_{4'}$, and 2 $H_{5'}$), 4.59 (d, *J*=3.8 Hz, $H_{1'}$), 6.11 (br s, 3 OH), 7.60 (d, J=5.2 Hz, H_6), 12.28 (d, *J*=5.2 Hz, H_1), 12.37 (br s, H_3); ^{13}C NMR (dimethyl-d_6 sulfoxide) δ=62.26, 71.52, 74.76, 79.77, 84.37, 111.70, 140.58, 151.77, 164.44. The product was identical in all respects with an authentic sample of D-**15** synthesized according to the reported procedure.[28]

5-(2,3-O-Isopropylidene-β-D-ribofuranosyl)isocytosine (D-16). Guanidine hydrochloride (4.53 g, 45.5 mmol) was dissolved in 1 mol dm^{-3} solution of sodium ethoxide in ethanol (50 ml). This solution was added to D-**10** (2.45 g, 9.11 mmol) and heated at reflux for 3 h under argon. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in water (10 ml). After careful neutralization with 6 mol dm^{-3} hydrochloric acid by monitoring with a pH test paper, the aqueous solution was evaporated giving a viscous liquid, which was treated with ethanol (150 ml). Removal of the occurring precipitates by filtration followed by concentration gave rise to a colorless oil, which was chromatographed with a 1:30 to 1:5 methanol–chloroform mixture as eluent to produce D-**16** (2.09 g, 81% yield) as a colorless solid. Recrystallization from methanol gave an analytical specimen, mp 170—174 °C, $[\alpha]_D^{22}$ −50.8° (*c*. 0.73, CH_3OH); UV λ_{max} (CH_3OH) 226 (ε 5530), 290 nm (5390), λ_{max} (0.1 mol dm^{-3} NaOH) 233 (ε 12660), 277 nm (9860); ^1H NMR (dimethyl-d_6 sulfoxide) δ=1.27 (s, isopropylidene CH_3), 1.48 (s, isopylidene CH_3), 3.51 (br d, *J*=4.5 Hz, 2 $H_{5'}$), 3.93 (br q, *J*=3.8 Hz, $H_{4'}$), 4.5—4.9 (m, $H_{1'}$, $H_{2'}$, and $H_{3'}$), 6.97 (br s, NH_2), 7.63 (s, H_6); ^{13}C NMR (dimethyl-d_6 sulfoxide) δ=25.49, 27.52, 62.12, 81.77, 82.02, 83.57, 84.56, 112.27, 112.77, 152.81, 156.22, 163.25. Anal. ($C_{12}H_{17}N_3O_5$) C, H, N.

5-(β-D-Ribofuranosyl)isocytosine Hydrochloride (Pseudoisocytidine Hydrochloride) (Hydrochloride of D-17). To a suspension of D-**16** (1.24 g, 4.38 mmol) in methanol (10 ml) was added with efficient stirring 10% methanol solution (20 ml) of hydrogen chloride and the mixture was stirred at 20 °C for 1 h. The occurring colorless precipitates were collected by filtration. These crystals (1.14 g, 93% yield) were identified as pseudoisocytidine (D-**17**) hydrochloride by comparison of the spectral data and physical properties with the authentic sample, mp 212—215 °C (lit,[28] 215—216 °C), $[\alpha]_D^{22}$ +14.3° (*c* 0.49, H_2O): UV λ_{max} (CH_3OH) 225 (ε 9850), 290 nm (7000), λ_{max} (0.1 mol dm^{-3} NaOH) 233 (ε 9570), 277 nm (7270); ^1H NMR (dimethyl-d_6 sulfoxide) δ=3.4—4.0 (m, $H_{2'}$, $H_{3'}$, $H_{4'}$, and $H_{5'}$), 4.59 (d, *J*=2.7 Hz, $H_{1'}$), 7.83 (s, H_6), 8.53 (br s, NH_2).

2-(2,3-O-Isopropylidene-β-D-ribofuranosyl)maleimide (D-19) from D-10. To a solution of D-**10** (250 mg, 0.93 mmol) in ethyl acetate (20 ml) cooled at −78 °C was passed ozone for 10 min followed by nitrogen for 5 min. The resulting mixture was quenched by addition of dimethyl sulfide (1.0 ml, 846 mg, 13.6 mmol) and stirred at −78 °C for 1 h, at 0 °C for 3 h, and then at 20 °C for an additional 1 h. On removal of the solvent, there was left a yellow, oily material D-**18**; IR 1732 cm^{-1} (C=O), no olefinic absorption. This unstable compound was used for the subsequent reaction without further purification. To a solution of the crude product in DMF (3 ml) was added a solution of $(C_6H_5)_3PCHCONH_2$ (297 mg, 0.93 mmol) in DMF (3 ml) and the mixture was stirred at 20 °C for 1 h and at 50 °C for 2 h under argon. Evaporation under high vacuum afforded a residual oil, preparative TLC of which with ethyl acetate produced D-**19** (75.3 mg, 30% overall yield from D-**10**), mp 142—143 °C (ethyl acetate–hexane) (lit,[57] 140.5—141 °C), $[\alpha]_D^{24}$ −2.31° (*c* 1.07, $CHCl_3$). The product had identical spectral data and physical properties with those of the authentic sample prepared from natural showdomycin according to the known procedure.[57]

Preparation of Showdomycin Acetonide (D-19) from D-21. Ozone was passed through a solution of D-**21** (150 mg, 0.514 mmol) in ethyl acetate (20 ml) at −78 °C for *ca.* 10 min until the color of the solution became blue-violet. The excess ozone was removed by blowing nitrogen gas to the solution for 5 min. After quenching by addition of dimethyl sulfide (0.5 ml, 423 mg, 6.81 mmol), the mixture was stirred at −78 °C for 1 h, at 0 °C for 1 h, and at 25 °C for 1 h, and then concentrated. The resulting oil was dissolved in ethyl acetate (20 ml) and washed with brine (4 ml). The organic layer was dried over sodium sulfate and evaporated to yield a slightly yellow liquid. A mixture of this oil and $(C_6H_5)_3PCHCONH_2$ (180 mg, 0.565 mmol) in DMF (4 ml) was stirred at 25 °C for 1 h and then at 50 °C for 1 h under argon. Removal of the solvent *in vacuo* left a crude oil, whose preparative TLC with ethyl acetate produced the crystalline acetonide D-**19** (21 mg, 15% yield). Recrystallization from acetone–benzene afforded an analytical sample, mp 141—142 °C.

2-(β-D-Ribofuranosyl)maleimide (Showdomycin) (3). A mixture of D-**19** (100 mg, 0.37 mmol) and 80% aqueous trifluoroacetic acid (3 ml) was stirred at 20 °C for 10 min Evaporation *in vacuo* afforded a viscous residue, whose preparative TLC using 7:3 ethyl acetate–acetone gave rise to showdomycin (**3**) (77.9 mg, 92% yield). An analytical specimen displaying ^1H NMR and UV spectra and the optical rotation, $[\alpha]_D^{24}$ +48.7° (*c* 1.4, H_2O) (lit, +49.1°,[32f] +49.9°[57]), identical with the authentic natural product was obtained by recrystallization from acetone–benzene, mp 151—152 °C (lit, 152—153 °C,[32b] 153—154 °C,[6b] 154.5—156 °C,[32a] 160—161 °C[57]).

(2S)-2-(2,3-O-Isopropylidene-β-D-ribofuranosyl-2-[(S*)-(2-furyl)hydroxylmethyl]acetic Acid Lactone (D-20).* To a 0.3 mol dm^{-3} solution (10 ml) of lithium cyclohexylisopropylamide in THF–hexane was added at −78 °C a solution of D-**6** (500 mg, 2.3 mmol) in THF (10 ml) over 5 min with stirring. After 1.5 h, to this was added a solution of furfural (3.0 ml, 3.46 g, 36 mmol) in THF (5 ml) at −78 °C and stirring was continued for an additional 1 h. The reaction mixture was quenched with saturated aqueous oxalic acid solution (5 ml) and extracted with chloroform (100 ml, 50 ml, 30 ml). The combined organic extracts were washed with brine (10 ml), dried over sodium sulfate, and evaporated to yield a yellow crystalline product, which was subjected to column chromatography using successively a 1:1, 2:1, and 4:1 ether–hexane mixture, and finally with ether. The hydroxy lactone D-**20** (640 mg, 90% yield) was obtained as colorless crystals, mp 139—141 °C (from ethyl acetate–chloroform–hexane), $[\alpha]_D^{21}$ +26.0° (*c* 2.63, $CHCl_3$): IR 3200—3600 (OH), 1728 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.30 (s, isopropylidene CH_3), 1.46 (s, isopropylidene CH_3), 2.95 (d, *J*=7 Hz, OH), 3.48 (dd, *J*=5, 9 Hz, COCH), 3.97 (d, *J*=5 Hz, $H_{1'}$), 4.15 (dd, *J*=4.5, 14 Hz, $H_{5'a}$), 4.45 (dd, *J*=2.5, 4.5 Hz, $H_{4'}$), 4.55 (d, *J*=6 Hz, $H_{2'}$), 4.56 (dd, *J*=2.5, 14 Hz, $H_{5'b}$), 4.82 (d, *J*=6 Hz, $H_{3'}$), 5.25 (dd, *J*=7, 9 Hz, CHOH), 6.40 (m, furyl H_3 and H_4), 7.43 (m, furyl H_5); mass spectrum *m/z* 310 (M^+). Anal. ($C_{15}H_{18}O_7$) C, H.

2-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-2-furfurylideneacetic Acid Lactone (D-21). To a cooled (0 °C) solution of D-**20** (300 mg, 0.76 mmol) in pyridine (5 ml) was added a solution of pivaloyl chloride (0.47 ml, 458 mg, 3.8 mmol) in pyridine (5 ml) over 2 min with efficient stirring under argon. After stirring at 0 °C for an additional 1 h and then at room temperature for 24 h, the reaction mixture was diluted with benzene (50 ml), washed with water (10 ml), and dried over sodium sulfate. Concentration under high vacuum (<0.01 mmHg) at room temperature for 30 min left a pale violet oil which was passed through a short silica-gel column using ether as eluent. Removal of the solvent of the filtrate gave a yellow oil, a solution of which in pyridine (15 ml) was heated at 80—90 °C for 13 h under argon. Dilution of the reaction mixture with benzene (50 ml), followed by concentration to dryness afforded a dark brown oil. The preparative TLC with 5:1 ether–hexane produced D-**21** (222 mg, 100% overall yield) as a gummy material, yielding an analytical sample by recrystallization from chloroform–hexane, mp 160—162 °C, $[\alpha]_D^{21}$ −143° (*c* 0.64, $CHCl_3$): IR 1715 (C=O), 1627 cm^{-1} (C=C), ^1H NMR ($CDCl_3$) δ=1.35 (s, isopropylidene CH_3), 1.58 (s, isopropylidene CH_3), 4.25 (m, 2 $H_{5'}$), 4.50 (m, $H_{4'}$), 4.70 (d, *J*=6 Hz, $H_{2'}$), 4.99 (d, *J*=6 Hz, $H_{3'}$), 5.74 (s, $H_{1'}$), 6.52 (dd, *J*=2, 4 Hz, furyl H_4), 6.78 (d, *J*=4 Hz, furyl H_3), 7.24 (s, COC=CH), 7.62 (d, *J*=2 Hz, furyl H_5); mass specturm *m/z* 292 (M^+). Anal. ($C_{15}H_{16}O_6$) C, H.

Methyl 2-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-2-furfurylideneacetate (D-22). A solution of D-**21** (220 mg, 0.69 mmol) in methanol (7 ml) was mixed with a 90 mmol dm^{-3} methanolic sodium methoxide (10 ml) at 0 °C and stirred for 30 min. The resulting mixture was quenched by addition of an aqueous solution saturated with oxalic acid (5 ml) and extracted with chloroform (50 ml, 30 ml). The collected organic layers were washed with brine (10 ml) and dried over sodium sulfate. Evaporation *in vacuo* left an orange oil (210 mg), which was subjected to preparative TLC with 2:1 ethyl acetate–hexane, giving rise to D-**22** (190 mg, 86% yield) as a colorless liquid, $[\alpha]_D^{21}$ +104° (*c* 2.90, $CHCl_3$); IR 3620—3300 (OH), 1700 (C=O), 1635 cm^{-1} (C=C); ^1H NMR (benzene-d_6) δ=1.23 (s, isopropylidene CH_3), 1.58 (s, isopropylidene CH_3), 3.27 (s, OCH_3), 3.69 (dd, *J*=3, 12 Hz, $H_{5'a}$), 3.70 (br s, OH), 3.95 (dd, *J*=2, 12 Hz, $H_{5'b}$), 4.33 (m, $H_{4'}$), 5.13 (d, *J*=6 Hz, $H_{2'}$), 5.26 (d, *J*=6 Hz, $H_{3'}$), 5.95 (m, $H_{1'}$, and furyl H_4), 6.47 (d, *J*=3 Hz, furyl H_3), 6.93 (d, *J*=2 Hz, furyl H_5), 7.46 (s, COC=CH); mass spectrum *m/z* 324 (M^+). Anal. ($C_{16}H_{20}O_7$) C, H.

Methyl 2-[2,3-O-Isopropylidene-5-O-(t-butyldimethylsilyl)-β-D-ribofuranosyl]-2-furfurylideneacetate (D-23). A mixture

of D-**22** (190 mg, 0.59 mmol), *t*-butylchlorodimethylsilane (130 mg, 0.84 mmol), imidazole (120 mg, 1.8 mmol) in DMF (15 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with ether (50 ml) and washed with brine (10 ml). The organic layer was dried over sodium sulfate and concentrated to leave a yellow viscous oil. Preparative TLC with 1:1 ethyl acetate–hexane gave D-**23** (260 mg, 100% yield), $[\alpha]_D^{21}$ −0.98° (*c* 0.44, $CHCl_3$); IR 1710 (C=O), 1635 (C=C), 830 cm^{-1} (Si–O); ^1H NMR (benzene-d_6) δ=0.06 (s, $Si(CH_3)_2$), 0.98 (s, SiC_4H_9-*t*), 1.25 (s, isopropylidene CH_3), 1.56 (s, isopropylidene CH_3), 3.38 (s, OCH_3), 3.97 (d, *J*=6 Hz, $H_{5'a}$), 3.98 (d, *J*=5.5 Hz, $H_{5'b}$), 4.38 (q, *J*=6 Hz, $H_{4'}$), 5.02 (t, *J*=6 Hz, $H_{3'}$), 5.22 (dd, *J*=4, 6 Hz, $H_{2'}$), 5.90 (dd, *J*=2, 4 Hz, furyl H_4), 6.00 (d, *J*=4 Hz, $H_{1'}$), 6.41 (d, *J*=4 Hz, furyl H_3), 6.86 (d, *J*=2 Hz, furyl H_5), 7.44 (s, COC=CH); mass spectrum *m/z* 423 (M^+ −15). Anal. ($C_{22}H_{34}O_7Si$) C, H.

3-[2,3-O-Isopropylidene-5-O-(t-butyldimethylsilyl-β-D-ribofuranosyl]maleimide (D-25). Ozone was introduced into a solution of D-**23** (260 mg, 0.59 mmol) in dry ethyl acetate (30 ml) at −78 °C until the color of solution became blue-violet and then nitrogen gas was blown through this solution for 10 min at that temprature to remove an excess of ozone. After addition of dimethyl sulfide (1.0 ml, 846 mg, 13.6 mmol) at −78 °C, the reaction mixture was stirred at the same temperature for 1 h and for an additional 2 h under warming up to room temperature. Concentration gave a yellow crude product (430 mg), to which was added chloroform (30 ml) with vigorous shaking. Removal of the occurring precipitate by filtration through a Celite 545 pad, followed by evaporation of the filtrate left crude methyl 2-[2,3-*O*-isopropylidene-5-*O*-(*t*-butyldimethylsilyl)-β-D-ribofuranosyl]glyoxylate (D-**24**) as a yellow, viscous liquid; IR 1760 (shoulder, C=O), 1740 cm^{-1} (C=O); mass spectrum *m/z* 374 (M^+). This compound was so labile and attempted chromatography resulted in complete decomposition. Therefore this was employed in the next procedure without any purification.

A mixture of the crude D-**24** (obtained from 150 mg (0.40 mmol) of D-**32**) and $(C_6H_5)_3PCHCONH_2$ (270 mg, 0.80 mmol) in chloroform (20 ml) was stirred at room temperature. After 2 h, a solution of the phosphorane (130 mg, 0.39 mmol) in chloroform (5 ml) was added renewedly and stirring was continued for further 30 min. Concentration of the resulting mixture yielded an oily residue, which was subjected to preparative TLC with 2:1 ether–hexane, producing D-**25** (43 mg, 29% yield based on D-**23**), $[\alpha]_D^{24}$ +2.1° (*c* 1.40, $CHCl_3$); IR 3420 (NH), 1775 (C=O), 1726 (C=O), 1620 cm^{-1} (C=C); UV λ_{max} (CH_3OH) 221 nm (ε 13800); ^1H NMR ($CDCl_3$) δ=0.05 (s, $Si(CH_3)_2$), 0.85 (s, SiC_4H_9-*t*), 1.34 (s, isopropylidene CH_3) 1.59 (s, isopropylidene CH_3), 3.70 (br d, *J*=4.0 Hz, 2 $H_{5'}$), 4.20 (m, $H_{4'}$), 4.66 (m, $H_{2'}$ and $H_{3'}$), 4.82 (m, $H_{1'}$), 6.49 (t, *J*=2 Hz, H_3), 7.42 (br s, NH); mass spectrum *m/z* 368 (M^+ −15). Anal. ($C_{18}H_{29}NO_6Si$) C, H, N.

3-(β-D-Ribofuranosyl)maleimide (Showdomycin) (3). A mixture of D-**25** (130 mg, 0.339 mmol) and 80% aq trifluoroacetic acid (3 ml) was stirred at 25 °C for 10 min. Evaporation to dryness at room temperature under high vacuum (0.01 mmHg) left a white crystalline product. Column chromatography with 1:4 acetone–ethyl acetate gave showdomycin (**3**) 66 mg, 85% yield), mp 151—15 °C (acetone-benzene), which was consistent in all respects with the natural product.

Semicarbazone of Methyl 2-[2,3-O-Isopropylidene-5-O-(t-butyldimethylsilyl)-β-D-ribofuranosyl]glyoxylate (D-26). Into a cooled solution of D-**23** (720 mg, 1.70 mmol) in ethyl acetate (220 ml) at −78 °C was introduced ozone until the solution assumed blue-violet color. The solution was flushed with nitrogen gas in order to remove an excess of ozone for 10 min. The mixture was quenched with dimethyl sulfide (3.0 ml, 2.54 g, 4.08 mmol) at −78 °C and stirred at the same temperature for 1 h, at 0 °C for 1 h, and at room temperature for 1 h. Evaporation afforded a brown oil, which was dissolved in 66% aq methanol (45 ml) and to this were added semicarbazide hydrochloride (900 mg, 8.10 mmol) and sodium acetate (660 mg, 8.10 mmol). The mixture was stirred at 20 °C for 12 h and at 80 °C for 2 h, and then semicarbazide hydrochloride (600 mg, 5.40 mmol) and sodium acetate (440 mg, 5.40 mmol) were added renewedly. After stirring at 60 °C for 2 h, semicarbazide hydrochloride (300 mg, 2.70 mmol) and sodium acetate (220 mg, 2.70 mmol) in methanol (10 ml)–water (15 ml) were added again and the resulting mixture was maintained at 60 °C for an additional 2 h. An only residue obtained by concentration was treated with water (20 ml) and extracted with chloroform (150 ml, 100 ml, 50 ml). The combined organic extracts were washed with brine (20 ml) and dried over sodium sulfate. Removal of the solvent produced a viscous oil, preparative TLC of which using ethyl acetate gave D-**26** (220 mg, 30% yield from D-**23**) as an oil, $[\alpha]_D^{22}$ −1.6° (*c* 1.0, $CHCl_3$); IR 3520, 3400, 3300 (NH), 1703 (C=O), 1560 cm^{-1} (C=N); UV λ_{max} (CH_3OH) 265 nm (ε 8790); ^1H NMR ($CDCl_3$) δ=0.10 (s, $Si(CH_3)_2$), 0.89 (s, SiC_4H_9-*t*), 1.26 (s, isopropylidene CH_3), 1.29 and 1.37 (two s's, 1.5 H each, isopropylidene CH_3 of *E* or/and *Z* isomers), 3.70 (d, *J*=5 Hz, $H_{5'a}$), 3.87 (s, OCH_3), 3.6—4.0 (m, $H_{5'b}$), 4.1—5.2 (m, $H_{1'}$, $H_{2'}$, $H_{3'}$, and $H_{4'}$), 5.5—6.0 (br s, NH_2), 10.21 and 11.29 (two br s's, 0.5 H each NH of *E* or/and *Z* isomers). Anal. ($C_{18}H_{33}N_3O_7Si$) C, H, N.

6-[2,3-O-Isopropylidene-5-O-(t-butyldimethylsilyl-β-D-ribofuranosyl]-1,2,4-triazine-3,5(2H,4H)-dione (D-27). A mixture of the semicarbazone D-**26** (250 mg, 0.625 mmol) and a 0.1 mol dm^{-3} solution of sodium ethoxide in ethanol (12.5 ml, 1.25 mmol of sodium ethoxide) was refluxed for 3 h. A residual oil afforded by evaporation was dissolved in water (20 ml). The aqueous layer was acidified to pH 4 by careful addition of 0.5 mol dm^{-3} hydrochloric acid and extracted with ethyl acetate (50 ml×3). The collected organic extracts were washed with brine and dried over sodium sulfate. Removal of the solvent and the subsequent preparative TLC with 5:1 ether–chloroform produced D-**27** (100 mg, 40% yield) as an oil, $[\alpha]_D^{25}$ −35.8° (*c* 8.90, $CHCl_3$); IR 3500—3100 (NH), 1721 and 1698 cm^{-1} (C=O); UV λ_{max} (0.1 mol dm^{-3} HCl) 262 nm (ε 7420), λ_{max} (CH_3OH) 264 nm (ε 6920), λ_{max} (0.1 mol dm^{-3} NaOH) 258 (ε 5020), 293 nm (3230); ^1H NMR ($CDCl_3$) δ=0.04 (s, $Si(CH_3)_2$), 0.88 (s, SiC_4H_9-*t*), 1.37 (s, isopropylidene CH_3), 1.58 (s, isopropylidene CH_3), 3.77 (d, *J*=5 Hz, 2 $H_{5'}$), 4.20 (m, $H_{4'}$), 4.76 (dd, *J*=3, 6 Hz, $H_{2'}$), 5.0 (m, $H_{1'}$ and $H_{3'}$), 9.17 (br s, NH), 9.73 (br s, NH). Anal. ($C_{17}H_{29}N_3O_6Si$) C, H, N.

6-(β-D-Ribofuranosyl)-1,2,4-triazine-3,5(2H,4H)-dione (6-Azapseudouridine) (D-13). A mixture of D-**27** (158 mg, 0.406 mmol) and 80% aq trifluoroacetic acid (5 ml) was stirred at 25 °C for 10 min. The whole mixture was concentrated under reduced pressure to give a crystalline material. Recrystallization produced an analytical sample of D-**13** (65 mg, 63% yield) as colorless needles, mp 136—138 °C (lit,[30] 138—139 °C), $[\alpha]_D^{24}$ −23.4° (*c* 0.5, H_2O) [lit,[30] $[\alpha]_D^{25}$ −24.9° (*c* 0.5, H_2O)]; IR (KBr) 3400—3100 (NH and OH), 1720 and 1690 cm^{-1} (C=O); UV λ_{max} (CH_3OH) 264 nm (ε 6740); ^1H NMR (acetone-d_6) δ=3.0 (br s, OH), 3.54 (dd, *J*=3.3, 13.8 Hz, $H_{5'a}$), 3.74 (dd, *J*=2.7, 13.8 Hz, $H_{5'b}$), 3.97 (ddd, *J*=2.7, 3.3, 4.5 Hz, $H_{4'}$), 4.20 (dd, *J*=4.5, 5.3 Hz, $H_{2'}$), 4.45 (dd, *J*=5.3, 5.6 Hz, $H_{3'}$), 4.73 (d, *J*=5.6 Hz, $H_{1'}$), 11.70 (br s, 2 NH). These spectral and physical characters were identical with the reported ones.[30]

Thiosemicarbazone of Methyl 2-[2,3-O-Isopropylidene-5-O-(t-butyldimethylsilyl)-β-D-ribofuranosyl]glyoxylate (D-28). Through a solution of D-**23** (500 mg, 1.18 mmol) in ethyl acetate (150 ml) was blown ozone at −78 °C. When the solution took on blue color, introduction of ozone was stopped and nitrogen gas was blown into the solution at the same temperature for 5 min. The resulting colorless solution was

treated with dimethyl sulfide (2.0 ml, 1.69 g, 27.2 mmol) and then stirred at −78 °C for 1 h, at 0 °C for 1 h, and at room temperature for 1 h. Concentration gave a yellow oil, which was mixed with thiosemicarbazide (460 mg, 5.0 mmol) in methanol (25 ml) and refluxed for 12 h. After cooling, evaporation yielded a viscous oil, which was dissolved in chloroform (100 ml) and washed with water (15 ml). Concentration of the organic solution giving an orange oil, followed by preparative TLC with ether, afforded D-**28** (130 mg, 26% yield) as a colorless oil, $[\alpha]_D^{21}$ −0.71° (*c* 1.1, $CHCl_3$); IR 3520, 3380, 1731, 1715, 1582, 1465 cm^{-1}; UV λ_{max} (CH_3OH) 268 (ε 6760), 314 nm (5250); ^1H NMR ($CDCl_3$) δ=0.06 (s, $Si(CH_3)_2$), 0.87 (s, SiC_4H_9-*t*), 1.34 (br s, isopropylidene CH_3), 1.52 (br s, isopropylidene CH_3), 3.67 (s, OCH_3), 3.77 (m, 2 $H_{5'}$), 4.2—4.8 (m, $H_{1'}$, $H_{2'}$, $H_{3'}$, and $H_{4'}$), 6.0—6.4 (br s, NH_2), 7.12 and 9.17 (two br s's, 0.5 H each, NH of *E* and/or *Z* isomers); mass spectrum *m/z* 447 (M^+). Anal. ($C_{18}H_{33}N_3O_6SSi$) C, H, N, S.

6-[2,3-O-Isopropylidene-5-O-(t-butyldimethylsilyl)-β-D-ribofuranosyl]-3-thioxo-2,3-dihydro-1,2,4-triazin-5(4H)-one (D-29). A mixture of D-**28** (200 mg, 0.45 mmol) and a 0.1 mol dm^{-3} solution of sodium ethoxide in ethanol (10 ml, 1.0 mmol of sodium ethoxide) was heated at reflux for 3 h and then evaporated to dryness. To a solution of the resulting dark brown liquid in water (10 ml) was added carefully 0.5 mol dm^{-3} hydrochloric acid until the pH of solution reached 4 and the aqueous layer was promptly extracted with ethyl acetate (40 ml×3). The combined organic extracts were dried over sodium sulfate and concentrated, affording a brown liquid. Preparative TLC with 1:1 ether–chloroform gave rise to D-**29** (104 mg, 56% yield) as an oil, $[\alpha]_D^{25}$ −1.4° (*c* 2.30, $CHCl_3$); IR 3500—3200 (NH), 1707 cm^{-1} (C=O); UV λ_{max} (0.1 mol dm^{-3} HCl) 213 (ε 7420), 269 nm (14100), λ_{max} (CH_3OH) 213 (ε 3720), 272 nm (12100), λ_{max} (0.1 mol dm^{-3} NaOH) 226 (ε 16200), 258 (11500), 313 nm (3230); ^1H NMR ($CDCl_3$) δ= 0.06 (s, $Si(CH_3)_2$), 0.88 (s, SiC_4H_9-*t*), 1.38 (s, isopropylidene CH_3), 1.59 (s, isopropylidene CH_3), 3.75 (d, *J*=5 Hz, 2 $H_{5'}$), 4.17 (m, $H_{4'}$), 4.77 (dd, *J*=3, 6 Hz, $H_{3'}$), 5.0 (m, $H_{1'}$ and $H_{2'}$). Anal. ($C_{17}H_{29}N_3O_5SSi$) C, H, N, S.

6-(β-D-Ribofuranosyl)-3-thioxo-2,3-dihydro-1,2,4-triazin-5-(4H)-one (6-Azapseudouridine) (D-30). A mixture of D-**29** (100 mg, 0.247 mmol) and 80% aq trifluoroacetic acid (4 ml) was stirred at 25 °C for 20 min and then evaporated *in vacuo*. The resulting crude product was recrystallized from ethanol, affording an analytical specimen of D-**30** (47 mg, 70% yield) as colorless needles, mp 193—195 °C (lit,[30] 197—198 °C), $[\alpha]_D^{25}$ −3.5° (*c* 0.5, H_2O) [lit,[30] −3.7° (*c* 0.5, H_2O)]; IR (KBr) 3500—3100 (NH and OH), 1702 cm^{-1} (C=O); UV λ_{max} (0.1 mol dm^{-3} HCl) 215 (ε 10700), 269 nm (18600), λ_{max} (0.1 mol dm^{-3} NaOH) 259 (ε 13500), 313 nm (7580); ^1H NMR (acetone-d_6) δ=3.06 (br s, OH), 3.57 (dd, *J*=3.6, 12.7 Hz, $H_{5'a}$), 3.83 (dd, *J*=2.5, 12.7 Hz, $H_{5'b}$), 4.00 (ddd, *J*=2.5, 3.6, 4.2 Hz, $H_{4'}$), 4.24 (dd, *J*=4.2, 5.7 Hz, $H_{2'}$), 4.48 (dd, *J*=5.0, 5.7 Hz, $H_{3'}$), 4.80 (d, *J*=5.0 Hz, $H_{1'}$), 11.15 (br s, 2 NH).

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References

1) *C*-Nucleoside Synthesis. 17. For part 16 see: T. Sato, H. Kobayashi, and R. Noyori, *Heterocycles*, **15**, 321 (1981). See also preliminary works of this paper: a) R. Noyori, T. Sato, and Y. Hayakawa, *J. Am. Chem. Soc.*, **100**, 2561 (1978); b) T. Sato, R. Ito, Y. Hayakawa, and R. Noyori, *Tetrahedron Lett.*, **1978**, 1829.

2) W. E. Cohn, *Biochim. Biophys. Acta*, **32**, 569 (1959); *J. Biol. Chem.*, **235**, 1488 (1960).

3) For reviews: R. W. Chambers, *Prog. Nucleic Acid Res. Mol. Biol.*, **5**, 349 (1966); E. Goldwasser and R. L. Heinrikson, *ibid.*, **5**, 399 (1966).

4) Oxazinomycin (minimycin) inhibits the growth of bacteria[5] and is active against transplantable tumors.[5] Showdomycin (**3**) shows antibacterial and antitumor behavior as well as inhibiting nucleic acid synthesis.[6] Pyrazomycin and pyrazomycin B inhibit virus multiplication.[7] Formycin has significant antiviral and antitumor activities, and supresses DNA, RNA, and protein synthesis.[8] Formycin B inhibits the pathogenic bacterium for rice plant decrease caused by *X. oryzae*[5a] and shows antiviral properties against influenza virus.[9] For the detail of biological activities of *C*-nucleosides, see the following reviews: R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, Chapters 9—11 (1970). P. Roy-Burman, "Analogues of Nucleic Acid Components," Springer-Verlag, New York (1970). S. Nakamura and H. Kondo, *Heterocycles*, **8**, 583 (1977).

5) a) S. Aizawa, T. Hidaka, N. Otake, H. Yonehara, K. Isono, N. Igarashi, and S. Suzuki, *Agr. Biol. Chem.*, **29**, 375 (1956); b) G. Koyama and H. Umezawa, *J. Antibiot.*, **18**, 175 (1965); c) T. Haneishi, T. Okazaki, T. Hata, C. Tamura, M. Nomura, A. Naito, I. Seki, and M. Arai, *ibid.*, **24**, 797 (1971); d) Y. Kusakabe, J. Nagatsu, M. Shibuya, O. Kawaguchi, C. Hirose, and S. Shirato, *ibid.*, **25**, 44 (1972).

6) a) S. Matsuura, O. Shiratori, and K. Katagiri, *J. Antibiot.*, **17A**, 234 (1964); b) H. Nishimura, M. Mayama, Y. Komatsu, H. Kato, N. Shimaoka, and Y. Tanaka, *ibid.*, **17A**, 148 (1964).

7) a) K. Gerzon, D. C. DeLong, and J. C. Cline, *Pure Appl. Chem.*, **28**, 489 (1971); b) F. Streightoff, J. A. Nelson, J. C. Cline, K. Gorzon, R. H. Williams, and D. C. DeLong, 9th Conference on Antimicrobial Agents and Chemotherapy, Washington D.C., 1969, American Chemical Society, Washington D.C., Abstr. No. 18; c) G. E. Gutowski, M. O. Chaney, N. D. Jones, R. L. Hamill, F. A. Davis, and R. D. Miller, *Biochem. Biophys. Res. Commun.*, **51**, 312 (1973).

8) M. Hori, E. Ito, T. Takida, G. Koyama, T. Takeuchi, and H. Umezawa. *J. Antibiot.*, **17A**, 96 (1964); M. Ishizuka, T. Sawa, S. Hori, H. Takayama, T. Takeuchi, and H. Umezawa, *ibid.*, **21A**, 1 (1968); H. Umezawa, T. Sawa, Y. Fukagawa, G. Koyama, M. Murase, M. Hamada, and T. Takeuchi, *ibid.*, **18A**, 178 (1965); R. H. Williams, K. Gerzon, M. Hoehen, and D. C. DeLong, 158th National Meeting of the American Chemical Society, New York, N.Y., 1969, American Chemical Society, Washington D.C., Abstract Micr. 38.

9) T. Kunimoto, T. Wakashiro, I. Okamura, T. Asajima, and M. Hori, *J. Antibiot.*, **21A**, 468 (1968); T. Takeuchi, J. Iwanaga, T. Aoyagi, M. Murase, T. Sawa, and H. Umezawa, *ibid.*, **20A**, 297 (1967).

10) For comprehensive reviews see: a) L. Goodman, "Basic Principles in Nucleic Acid Chemistry", ed by P. O. P. Tso, Academic Press, New York (1974), Vol. 1, p 93; b) G. D. Daves, Jr. and C. C. Cheng, *Prog. Med. Chem.*, **13**, 303 (1976); c) S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biochem.*, **33**, 111 (1976); d) S. D. Gero, J. Cleophax, D. Mercier, and A. Olesker, "Synthetic Methods for Carbohydrates", ed by H. S. El Khadem, American Chemical Society, Washington D.C. (1976), p 64; e) Y. Mizuno, O. Mitsunobu, and T. Hata, "Synthesis of Nucleosides and

Nucleotides (in Japanese)," Maruzen, Tokyo (1977), pp. 16—32; f) T. Sato and R. Noyori, *Kagaku* **33**, 74 (1978); g) K. Galankievicz, *Khim. Geterotsikl. Soedin.*, **1978**, 723; h) S. R. James, *J. Carbohydr. Nucl. Nucl.*, **6**, 417 (1979); i) H. Ogura and H. Takahashi, *Yuki Gosei Kagaku Kyokai Shi.*, **38**, 756 (1980); j) T. Sato and R. Noyori, *ibid.*, **38**, 862 (1980); k) T. Sato and R. Noyori, *ibid.*, **38**, 947 (1980); l) M. Ohno, "Anticancer Agents Based on Natural Product Models," ed by J. M. Cassady and J. D. Douros, Academic Press, New York (1980), pp 73—84; m) J. G. Buchanan, *Prog. Chem. Org. Natural Products*, **44**, 243 (1983).

11) Only two exceptions, pyrazomycin B[7c] and indochrome BIII,[12] have been known thus far.

12) H.-J. Knackmuss and J. Briaire, *Justus Liebigs Ann. Chem.*, **736**, 68 (1970); H.-J. Knackmuss, *Angew. Chem., Int. Ed. Engl.*, **12**, 139 (1973).

13) For reviews see: R. Noyori, *Acc. Chem. Res.*, **12**, 61 (1979); R. Noyori, *Ann. N. Y. Acad. Sci.*, **295**, 225 (1977); R. Noyori, *Kagaku Sosetsu*, **19**, 139 (1978); R. Noyori and Y. Hayakawa, *Org. React.*, **29**, 163 (1983).

14) H. Takaya, S. Makino, Y. Hayakawa, and R. Noyori, *J. Am. Chem. Soc.*, **100**, 1765 (1978).

15) T. Sato and R. Noyori, *Bull. Chem. Soc. Jpn.*, **51**, 2745 (1978).

16) K. B. Sharpless and K. Akashi, *J. Am. Chem. Soc.*, **98**, 1986 (1976). See also: V. VanRheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Lett.*, **1976**, 1973; V. VanRheenen, D. Y. Cha, and W. M. Hartley, *Org. Synth.*, **58**, 43 (1978).

17) For the stereoselctive reaction of bicyclo[3.2.1]octan-3-one and related systems, see: A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Wattz, *Tetrahedron*, **6**, 319 (1959); Y. Hayakawa and R. Noyori, *Bull. Chem. Soc. Jpn.*, **47**, 2617 (1974); G. Büchi, H. Fliri, and R. Shapiro, *J. Org. Chem.*, **42**, 2192 (1977); Y. Hayakawa, Y. Baba, S. Makino, and R. Noyori, *J. Am. Chem. Soc.*, **100**, 1786 (1978), and references cited therein.

18) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

19) T. Sato, H. Kobayashi, and R. Noyori, *Bull. Chem. Soc. Jpn.*, **56**, 2661 (1983); T. Sato, H. Kobayashi, and R. Noyori, *Tetrahedron Lett.*, **21**, 2569 (1980); R. Noyori, H. Kobayashi, and T. Sato, *ibid.*, **21**, 2573 (1980).

20) W. H. Pirkle and M. S. Hoekstra, *J. Org. Chem.*, **39**, 3904 (1974).

21) a) W. J. Gensler, S. Chan, and D. B. Ball, *J. Am. Chem. Soc.*, **97**, 436 (1975); b) W. J. Gensler, S. Chan, and D. B. Ball, *J. Org. Chem.*, **46**, 3407 (1981).

22) The conversion was done according to the following sequence of known reactions: (1) acetonidation,[23] (2) Wittig condensation with methoxycarbonylmethylenetriphenylphosphorane,[24] (3) hydrolysis with sodium hydroxide,[21] and (4) lactonization.[21] For the recent work, see also: K. A. Cruickshank and C. B. Reese, *Synthesis*, **1983**, 199.

23) N. A. Hughes and P. R. H. Speakman, *Carbohydr. Res.*, **1**, 171 (1965).

24) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, *J. Am. Chem. Soc.*, **97**, 4602 (1975).

25) H. Bredereck, G. Simchen, S. Rebsdat, W. Kantlehner, P. Horn, R. Wahl, H. Hoffmann, and P. Grieshaber, *Chem. Ber.*, **101**, 41 (1968).

26) H. Ohrui and S. Emoto, *J. Org. Chem.*, **42**, 1951 (1977).

27) Possibility of the *C*-nucleoside synthesis *via* the lactone **6** has been suggested previously.[21a] However, its direct formylation is quite difficult and, at least in our hand, no conditions were found which gave the formylated compound or the derivatives in satisfactory yield. The introduction of a C_1 unit, despite lack of stereochemical control, has been done with the ester **7** rather than the lectone **6**.[28]

28) C. K. Chu, K. A. Watanabe, and J. J. Fox, *J. Heterocycl. Chem.*, **12**, 817 (1975); C. K. Chu, I. Wempen, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **41**, 2793 (1976).

29) A. M. Michelson and W. E. Cohn, *Biochem.*, **1**, 490 (1962).

30) M. Bobek, J. Farkaš, and F. Šorm, *Collect. Czech. Chem. Commun.*, **34**, 1690 (1969); *Tetrahedron Lett.*, **1968**, 1543.

31) J. H. Burchenal, K. Ciovacco, K. Kalahar, T. O'Toole, R. Kiefner, M. D. Dowling, C. K. Chu, K. A. Watanabe, I. Wempen, and J. J. Fox, *Cancer Res.*, **36**, 1520 (1976).

32) Previous synthesis of showdomycin: a) G. Trummlitz and J. G. Moffatt, *J. Org. Chem.*, **38**, 1841 (1973); b) L. Kalvoda, J. Farkaš, and F. Šorm, *Tetrahedron Lett.*, **1970**, 2297; c) L. Kalvoda, *J. Carbohydr. Nucl. Nucl.*, **3**, 47 (1976); d) T. Inoue and I. Kuwajima, *J. Chem. Soc., Chem. Commun.*, **1980**, 251; e) A. P. Kozikowski and A. Ames, *J. Am. Chem. Soc.*, **103**, 3923 (1981); f) Y. Ito, T. Shibata, M. Arita, H. Sawai, and M. Ohno, *ibid.*, **103**, 6739 (1981); g) G. Just, T. J. Liak, M.-L. Lim, P. Potvin, and Y. S. Tsantrizos, *Can. J. Chem.*, **58**, 2024 (1980).

33) J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, **1966**, 4273.

34) S. Trippett and D. M. Walker, *J. Chem. Soc.*, **1959**, 3874.

35) In the alternative *R* stereoisomer, the coupling constant is expected to be close to 0 Hz. See: Y. Hayakawa, Y. Baba, S. Makino, and R. Noyori, *J. Am. Chem. Soc.*, **100**, 1786 (1978).

36) For the reasonable erythro/threo nomenclature see: footnote 8 in R. Noyori, I. Nishida, and J. Sakata, *J. Am. Chem. Soc.*, **103**, 2106 (1981), and footnote 32 in *idem, ibid.*, **105**, 1598 (1983).

37) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973). R. A. Auerbach, D. S. Crumrine, D. L. Ellison, and H. O. House, *Org. Synth.*, **54**, 49 (1974).

38) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).

39) J. L. Imbach, *Ann. N. Y. Acad. Sci.*, **255**, 177 (1975).

40) Such *C*-nucleosides have been prepared only by transformation of pseudouridine (**1**).[30]

41) G. Just and S. Kim, *Can. J. Chem.*, **55**, 427 (1977).

42) The cyclization was carried out according to the method cited in Ref 41.

43) a) T. Sato, M. Watanabe, H. Kobayashi, and R. Noyori, *Bull. Chem. Soc. Jpn.*, **56**, 2680 (1983); b) T. Sato, M. Watanabe, and R. Noyori, *Chem. Lett.*, **1978**, 1297; *Tetrahedron Lett.*, **1978**, 4403.

44) T. Sato, M. Watanabe, and R. Noyori, *Tetrahedron Lett.*, **1979**, 2897; *Heterocycles*, **14**, 761 (1980); T. Sato and R. Noyori, *Tetrahedron Lett.*, **21**, 2535 (1980).

45) T. Sato, H. Kobayashi, and R. Noyori, *Tetrahedron Lett.*, **21**, 1971 (1980); *Heterocycles*, **15**, 321 (1981).

46) T. Sato, M. Watanabe, and R. Noyori, *Chem. Lett.*, **1980**, 679.

47) a) T. Sato and R. Noyori, *Bull. Chem. Soc. Jpn.*, **56**, 2700 (1983); *ibid.*, **53**, 1195 (1980); b) T. Sato and R. Noyori, *Heterocycles*, **13**, 141 (1979).

48) T. Sato, K. Marunouchi, and R. Noyori, *Tetrahedron Lett.*, **1979**, 3669.

49) The Diels-Alder adducts also opened the preparation of a number of artificial *C*-nucleosides involving 2'-deoxyshowdomycin[50] and a bishomopyrazomycin analogue.[51] Use of cyclopentadiene in place of furan for the Diels-Alder reaction gave carboribosidic analogues.[52] Further, an approach to a 1,2,4-triazole homo-*C*-nucleoside was achieved through the key cycloaddition of furan and tetrachlorocyclopropene yielding 2,3,4,4-tetrachloro-8-oxabicyclo[3.2.1.]octa-2,6-diene.[21]

50) G. Just and M.-I. Lim, *Can. J. Chem.*, **55**, 2993 (1977).

51) G. Just, M. Ramjeesingh, and T. J. Liak, *Can. J. Chem.*, **54**, 2940 (1976). See also: G. Just and M. Ramjeesingh, *Tetrahedron Lett.*, **1975**, 985.

52) G. Just and B. Chalard-Faure, *Can. J. Chem.*, **54**, 861 (1976). G. Just and R. Ouellet, **54**, 2925 (1976); G. Just and S. Kim, *ibid.*, **54**, 2935 (1976); *ibid.*, **55**, 427 (1977).

53) N. N. Schwartz and J. H. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).

54) S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).

55) The 60-MHz ^{1}H NMR analysis of this lactone in benzene-d_6 was discussed independently by Gensler and his collaborators,[21b] who commented on our previously reported result[1a] and claimed that no splitting was detected due to the geminal spin-spin coupling between two protons α to the lactone carbonyl. In fact, however, the 100-MHz spectrum showed the clear AB splitting pattern with J=14 Hz for the geminal H_{1a} and H_{1b} hydrogens. In addition, there was observed the geminal coupling, J=14 Hz, between ribose-$H_{5'a}$ and -$H_{5'b}$ protons.

56) Optical rotation and molar extinction coefficient of UV absorptions have not been measured because of the extreme hygroscopicity.

57) Y. Nakagawa, H. Kano, Y. Tsukuda, and H. Koyama, *Tetrahedron Lett.*, **1967**, 4105.