Nucleosides and Nucleotides. 108. Synthesis and Optical Properties of *Syn*-Fixed Carbon-Bridged Pyrimidine Cyclonucleosides[1,2]

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6,1′-Propanouridine (10), a carbon-bridged cyclouridine fixed in the *syn*-conformation, was synthesized from D-fructose. Two additional carbon-units were introduced at the 1′-position of 1′-hydroxymethyl-O^2,2′-anhydrouridine 13 and inversion of the 2′ hydroxyl group was achieved by sequential oxidation-reduction reactions. Finally, the spiro-carbon bridge was constructed by radical cyclization of the 1′-iodopropyl derivative of 5-chlorouridine. Dehydrochlorination followed by deprotection gave the desired 10. The circular dichroism (CD) spectrum of 10 showed a negative Cotton effect ($[\theta] = -6100$) at the main absorption region, whereas 5′-*O*-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-6,1′-propanouridine (30) showed almost no Cotton band at the same absorption region. These results suggest that the critical region in which the CD Cotton effect changes from negative to positive is present in the *syn* region where 10 is located. Correlation of the magnitude and the direction of the sign of the CD Cotton effect and the torsion angle (χ) is also discussed.

Keywords carbon-bridged cyclonucleoside; 6,1′-propanouridine; radical cyclization; nucleoside; CD spectrum; conformation; glycosyl torsion angle; *syn–anti* conformation

Several types of viral infection cause severe disease. Recently, human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), has spread all over the world to become a serious life-threatening disease. Therefore, the development of drugs to test such diseases is an important research target. Since the discovery of 3′-azido-3′-deoxythymidine (AZT) as a chemotherapeutic agent for AIDS,[3] a number of nucleoside analogues have been synthesized, and some of these compounds (*e.g.* 2′,3′-dideoxynucleosides[4] and their 2′,3′-didehydro analogues[5]) show potent activity against HIV. Most of these nucleosides are believed to be activated by host cell kinases and the resulting 5′ triphosphates inhibit the reverse transcriptase coded by HIV. However, only a few effective compounds have been obtained. This may be due to the specificity of host cell kinases. From this point of view, investigations of enzyme-substrate interactions would be important for the development of chemotherapeutic agents. Among these interactions, stereochemical factors such as *syn–anti* glycosyl conformation are important for biological activity. During the study of such stereochemical interactions, the use of nucleosides that can rotate around the glycosyl linkage can sometimes lead to erroneous interpretation of the results. For example, while 8-bromoadenosine adopts the *syn*-conformation in the solid state as well as in solution,[6] 8-bromoadenosine 5′-diphosphoribose is forced to change from the *syn* to the *anti*-conformation[7] when it binds to horse liver alcohol dehydrogenase. Therefore, for stereochemical studies of such interactions, nucleosides whose torsion angles are fixed at various values should be useful, and such fixation is possible in cyclonucleosides.

Although we[8-12] and others[13] have reported a variety of cyclonucleosides where a carbon-bridge between the base and the sugar portions (*C*-cyclonucleosides) fixes the conformation in the *anti* range, synthesis of *syn*-fixed *C*-cyclonucleosides has been limited to a few oxygen-bridged cyclonucleosides reported by Zavgorodny.[14]

In this paper, we describe the synthesis of the newly designed 6,1′-propanouridine (**10**), fixed in the *syn*-conformation by a six-membered spiro-carbon ring, from D-fructose. During the synthesis of **10**, we found a convenient method for converting a fructofuranose system to a psicofuranose. We also report the stereoselective synthesis of 1-β-D-psicofuranosyluracil (**25**) using this method. Finally, the circular dichroism (CD) spectra of *syn*-fixed *C*-cyclouridines and other *anti*-fixed *C*-cyclouridines are also discussed.

Results and Discussion

As described above, we have synthesized various *anti*-fixed *C*-cyclonucleosides.[8-12] During these syntheses we found that the intramolecular glycosylation reaction was useful for construction of the carbon-bridge.[9b,10,11b] Initially, we attempted to synthesize 6,2′-ethanouridine (**1**), fixed in a *syn*-conformation by the 5-membered spiro-ring, using an intramolecular glycosylation reaction (Chart 1).

6-Iodopyrimidine **2**[15] was cross-coupled with (trimethylsilyl)(TMS) acetylene using a palladium catalyst[16] to give 6-(TMS-ethynyl)pyrimidine **3**. The TMS group of **3** was so acid-labile that a small amount of deprotected product **4** was produced during column chromatographic purification. Therefore, after partial purification of **3**, the TMS group was removed using SiO_2–MeOH to afford **4** in 90% yield from **2**. Compound **4** was lithiated at the ethynyl group by lithium diisopropylamide (LDA) and treated with protected D-ribonolactone **6**,[17] by the method developed by Ogura and Takahashi,[18] to furnish the adduct **7** in 57% yield. Although **7** was a single diastereomer judging from the ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum, we could not determine which isomer was predominant. Compound **7** was hydrogenated and then acetylated at the tertiary hydroxyl group to afford **8**, which was then subjected to intramolecular glycosylation[9b,10,11b] using $SnCl_4$ in CH_3CN. However, none of the glycosylated product **9** was obtained under various conditions using Lewis acids. These results suggest that the steric interaction between the 5′-substituent on the sugar moiety and the 2-methoxy group of the pyrimidine ring may prevent intramolecular glycosylation. This prompted us to synthesize the 6-membered spiro-*C*-

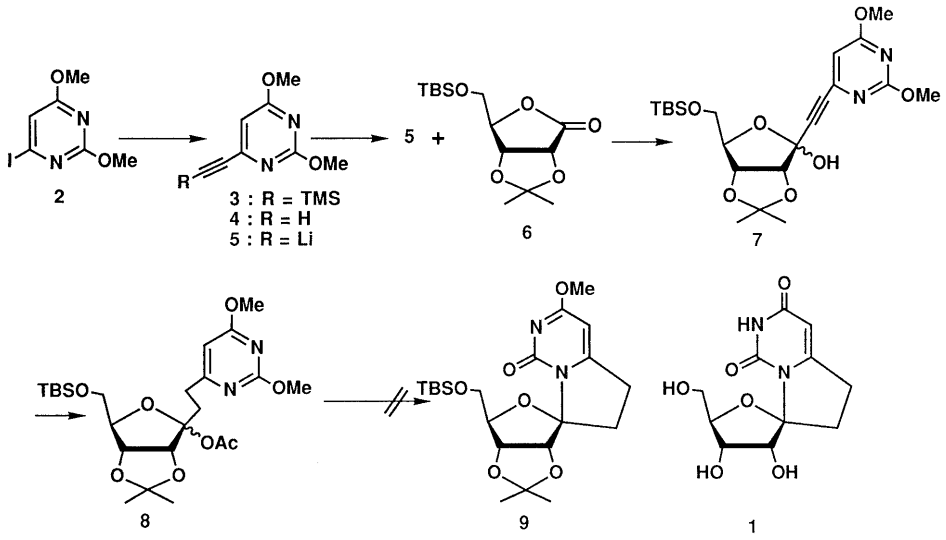


Chart 1

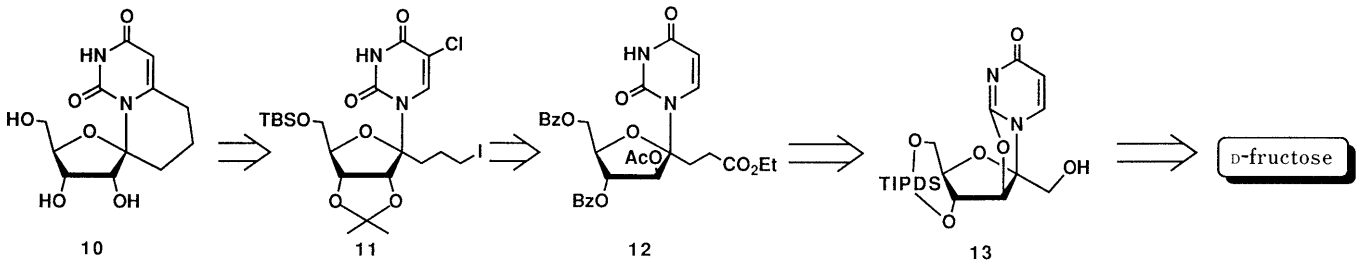


Chart 2

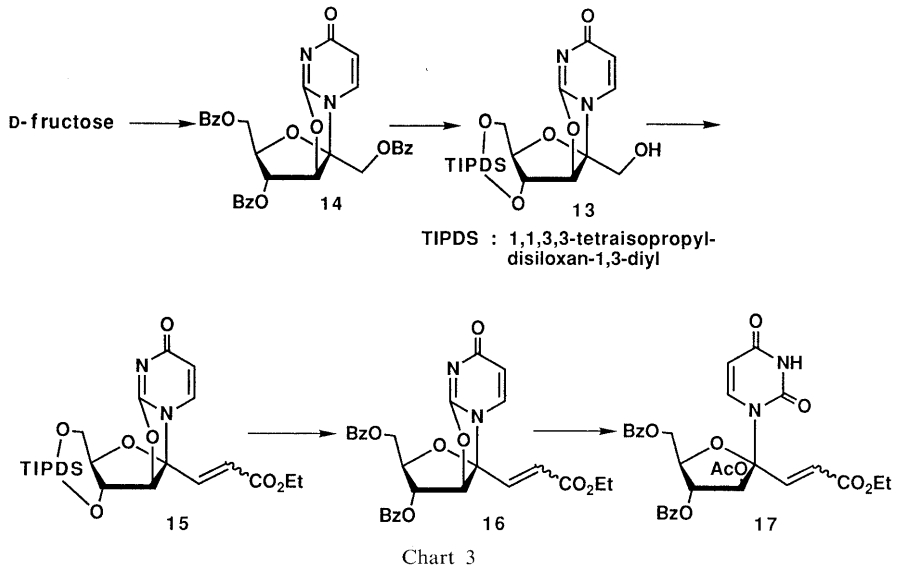


Chart 3

cyclouridine **10** using a radical cyclization reaction. Our synthetic plan is shown in Chart 2 in a retro-synthetic manner.

We envisaged that the spiro-ring in **10** could be constructed by radical cyclization of a side chain attached to the 1′-position. For the radical cyclization, it would be necessary to synthesize 1′-alkylated nucleosides. Holy has already reported the stereoselective synthesis of 1′-hydroxymethyl-*O*-cyclouridines from D-fructose[19] and this method was adopted for the synthesis of **13** by Tatsuoka *et al.*[20] We selected **13** as a starting material and anticipated that a two-carbon elongation of the side chain of **13** followed by inversion of the 2′-hydroxyl group would lead to the intermediate (**11**) required for the radical cyclization reation.

Moffatt oxidation[20,21] of the 1′-hydroxymethyl group of **13** gave the corresponding aldehyde,[20] which was further treated with (ethoxycarbonylmethylene)triphenylphosphorane to afford **15** in a ratio $E:Z=2:1$ (see Experimental section). It was necessary to replace the tetraisopropyldisiloxy group with acid-resistant benzoyl groups before acidic

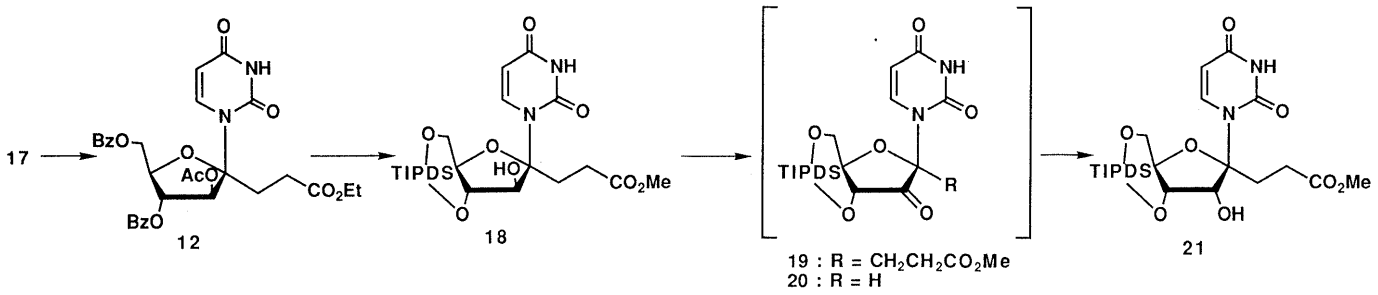


Chart 4

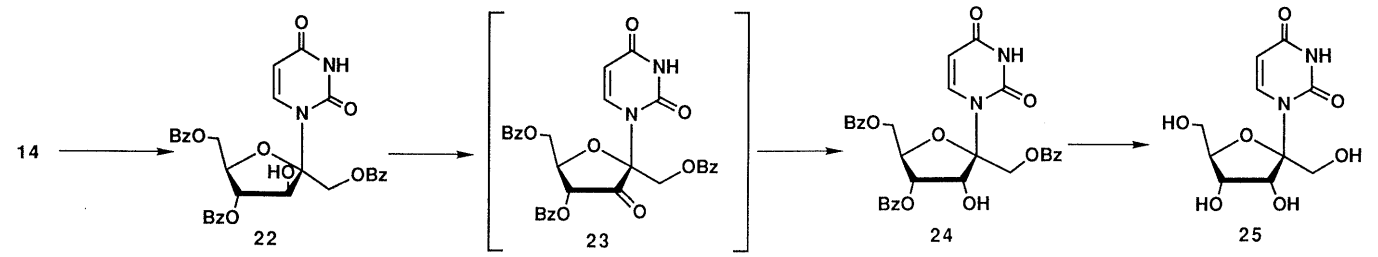


Chart 5

hydrolysis of the O^2,2′-anhydro linkage[22] of **15**. Compound **15** was converted to **16** in one step by treatment with benzoic anhydride in the presence of tetrabutylammonium fluoride (TBAF) in 96% yield. Acid hydrolysis of the O^2,2′-anhydro linkage of **16** with aqueous HCl in *N*,*N*-dimethylformamide (DMF) followed by acetylation of the 2′-hydroxyl group gave **17** (Chart 3).

Reduction of the olefinic side chain in **17** was next tried in two ways. First, we attempted hydrosilylation of **17** with triethylsilane in the presence of tris(triphenylphosphine)-rhodium chloride[23] at 100 °C in CH_3CN, which gave the desired **12** in 40% yield together with a large amount of uracil. When other transition metal catalysts such as tris(triphenylphosphine)palladium chloride were used instead of the rhodium catalyst, deglycosylation was the predominant reaction, possibly due to oxidative addition of Pd(0) catalyst generated under the reaction conditions. Hydrogen transfer reduction using polymethylhydrosiloxane (PMHS) as a hydrogen donor[24] was more successful. Thus, catalytic hydrogenation of **17** with PMHS over Pd–carbon afforded the reduced product **12** in 92% yield without cleavage of the glycosyl linkage. Quite interestingly, the choice of the hydrogen donor was important in this reduction. The reduction using hydrogen gas did not give any **12** and cyclohexene gave **12** in poor yield, due to deglycosylation (data not shown).

For the next step, inversion of the 2′-hydroxyl group in **18** was required. After deprotection of **12** with sodium methoxide, the 3′-and 5′-hydroxyls[25] were reprotected with a tetraisopropyldisiloxanediyl (TIPDS) group to give **18** in 78% yield. Inversion of the 2′-hydroxyl group in an S_N2 manner (*e.g.* trifluoromethanesulfonylation followed by treatment with sodium acetate, or Mitsunobu reaction with benzoic acid[26]) was not successful because this position is highly sterically hindered. Therefore, the 2′-hydroxyl group of **18** was oxidized by the modified Robins method[27] and the resulting 2′-ketonucleoside **19** was further treated with sodium borohydride to furnish a 5 : 1 mixture of diastereomers **21** and **18**, respectively, in 87% combined yield. Generally, 2′-ketonucleosides (R = H, **20**) when treated with sodium borohydride[27] or organolithium reagent[28] give *arabino* nucleosides as the major product because the β-face is sterically more crowded than the α-face due to the presence of a nucleobase. In contrast to those cases, the *ribo* nucleoside **21** was the major product from the 1′-alkylated 2′-ketonucleoside **19**. This result suggests that both the C-1′ and C-3′ substituents block the α-face more strongly than the base moiety at the C1′-position blocks the β-face. We have applied this method to the synthesis of psicofuranosyluracil (**25**), which was previously prepared in unsatisfactory yield by Hrebabecky and Farkas[29] using a glycosylation method. Moffatt *et al.*[30] also reported a synthesis of angustmycin A and its base analogues by a similar glycosylation method, but in rather low yield because of the accompanying α-anomer formation. The *O*-cyclonucleoside **14** was treated with hydrochloric acid to cleave the O^2,2′-anhydro linkage, giving **22**. The *arabino* nucleoside **22** was oxidized by the method described above, and the resulting 2′-keto derivative **23** was reduced with sodium borohydride to give a mixture of **24** and **22**, respectively. The ^{1}H-NMR spectrum of the crude mixture showed that the desired *ribo*-isomer was predominant, as we had expected, and that the ratio of the diastereomers was 5 : 1 for **24** and **22**, respectively. Careful separation of both diastereomers by chromatography, followed by crystallization gave diastereomerically pure **24**, which was deprotected with sodium methoxide to afford psicofuranosyluracil (**25**).[29]

Compound **21** was deprotected by TBAF, the 2′,3′-*cis*-diol moiety of the resulting free nucleoside was protected by isopropylidenation, and the remaining primary hydroxyl group was protected with a *tert*-butyldimethylsilyl (TBS) group[31] to give **26**. Treatment of **26** with lithium borohydride in refluxing tetrahydrofuran (THF), followed by mesylation of the primary alcohol gave **27**. Compound **27** was chlorinated at the C-5 position by *N*-chlorosuccinimide to furnish **28**, which was further converted to the substrate for the radical cyclization by treatment with

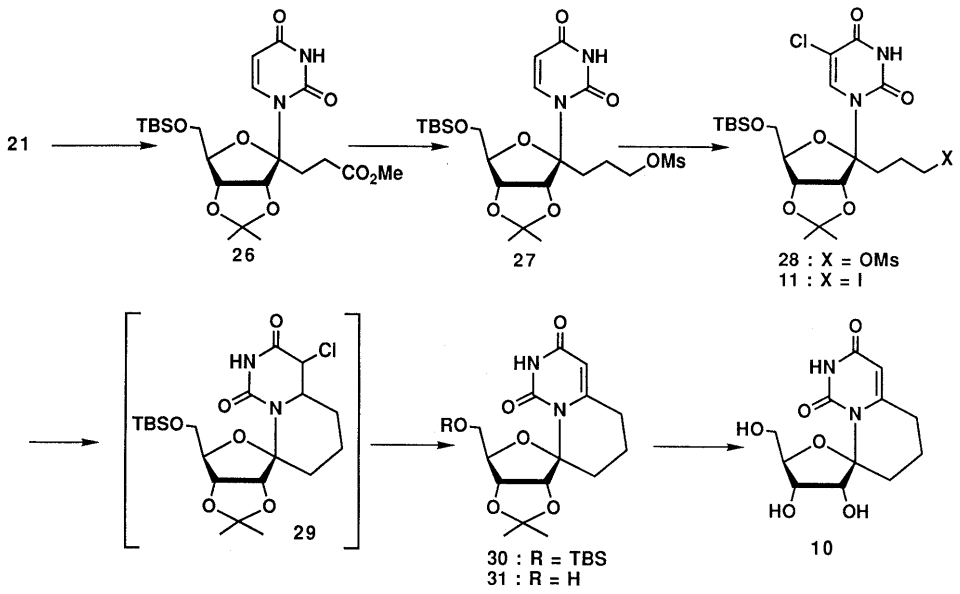


Chart 6

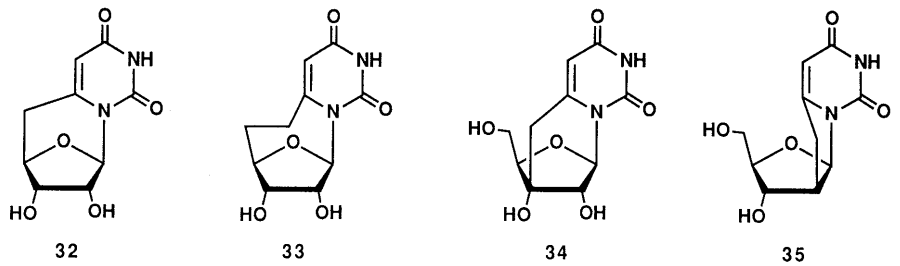


Fig. 1. Structures of *Anti*-Fixed *C*-Cyclouridines

lithium iodide in 2-butanone to afford **11**. The radical cyclization[8,9a,12] of **11** was achieved by treatment with tributyltin hydride in the presence of AIBN in refluxing benzene at high dilution (4 mM) to give **29**. Thin layer chromatography (TLC) of the reaction mixture showed that **29** was a mixture of at least three diastereoisomers; therefore, after partial purification, **29** was subjected to an elimination reaction with DBU in dioxane to afford the spiro-nucleoside **30** in 74% yield from **29**. Compound **30** has a maximal absorption at 264 nm in the ultraviolet (UV) spectrum, which is similar to those of *anti*-fixed *C*-cyclouridines. The ^{1}H-NMR spectrum revealed, in addition to all the expected signals, the C-5 proton at δ 5.45 ppm as a singlet, and the carbon-bridge protons at δ 2.80—2.73, 2.60, 2.20—2.15, 2.10, and 1.92—1.74 ppm as three sets of axial and equatorial protons, respectively. The electron impact-mass spectrum (EIMS) and high-resolution mass spectrum also supported the structure of **30** (see Experimental section). For comparison of CD spectra, the 5′-deprotected *C*-cyclouridine **31** was also prepared by treatment with TBAF, in 92% yield. Finally, compound **30** was deblocked by acid hydrolysis to furnish 6,1′-propanouridine (**10**) in 66% yield (Chart 6).

C-Cyclonucleosides show characteristic CD spectral patterns since the chromophore attached to the anomeric position is fixed by the carbon-bridge, and it is considered that the CD spectral pattern reflects the glycosyl torsion angle. In other words, the sign and magnitude of the Cotton effect of the CD spectra of *C*-cyclonucleosides are functions

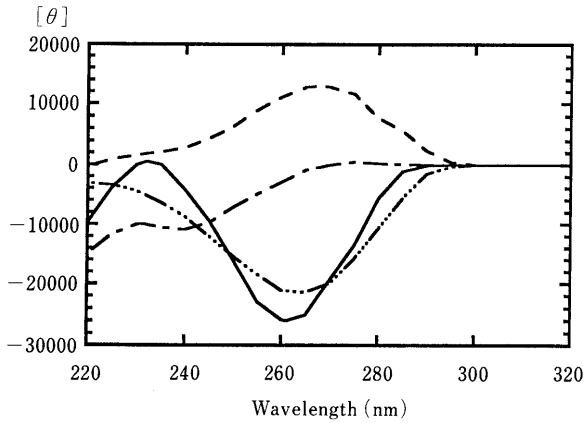


Fig. 2. CD Spectra of *Anti*-Fixed *C*-Cyclouridines in MeOH
– – –, **32**; — — —, **33**; ——— —, **34**; ———, **35**.

of their glycosyl torsion angles.

In Figs. 1 and 2, the structures and CD spectra of various *anti*-fixed *C*-cyclouridines[8-11] are summarized. These results establish that the sign of the Cotton effect changes from positive to negative when the glycosyl conformation changes from *anti* to high-*anti*, and that within the negative region, the magnitude of the Cotton effect increases as the value of the glycosyl torsion angle (χ) is increased (Fig. 3). It is noteworthy that 6,6′-cyclouridine (**33**),[9] whose χ value is $-117°$,[33] shows a very weak negative Cotton effect ($[\theta] = -900$) at the main absorption region, which establishes that a critical region for reversal of the sign of

Cotton effects should be present at around $\chi = -117°$, close to the χ value of 6,6′-cyclouridine.[1,9b]

On the other hand, 6,1′-propanouridine (**10**), which is fixed in the *syn*-conformation, exhibits a negative Cotton effect ($[\theta] = -6100$ in H_2O and -8800 in MeOH) at the main absorption region. The 2′,3′-*O*-isopropylidene derivative **31** shows a similar CD spectrum (Fig. 4, they were compared in MeOH). However, the CD pattern of **30**, in sharp contrast to those of **10** and **31**, actually has no CD band at the main absorption region. Since the TBS group at the 5′-position would not affect the ellipticity, it is possible that the 5′-substituent causes subtle sugar conformational changes. The $J_{2',3'}$ and $J_{3',4'}$ values of 6.8 and 4.9 Hz, respectively, observed for **30** compare with values of 7.3 and 4.9 Hz for **31**. Although these differences are rather small, slight conformational changes could alter the glycosyl torsion angles, and these subtle torsion angle changes could result in large CD spectral changes if these nucleosides sit at or near the transition point for sign reversal. Inspection of Dreiding models suggests that these spiro compounds are flexible, which would fit in with **31**, **30**, and **10** having slightly different conformational preferences, and hence different CD spectra. It was also observed that a critical region in which the CD Cotton effect is changed from positive to negative is present at around the glycosyl torsion angle of 6,6′-cyclouridine.[1,9b] We conclude that a similar critical region in which the CD Cotton effect changes from negative to positive is also present in the *syn* region, and that 6,1′-propanouridine is located near the transition region. In addition, the similarity of the CD pattern of **10** and **31** strongly indicates that no anomerization occurred during the acidic hydrolysis of **1**.

compd.	χ (°)	$[\theta]$
32	−150	13000
33	−117	−850
34	−95	−21500
35	−74	−26000

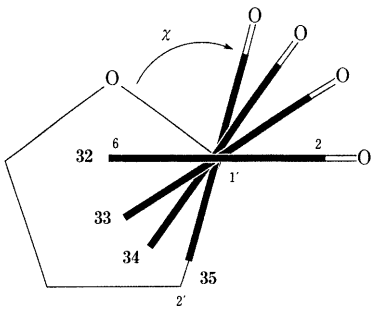


Fig. 3. Glycosidic Torsion Angles of *C*-Cyclouridines

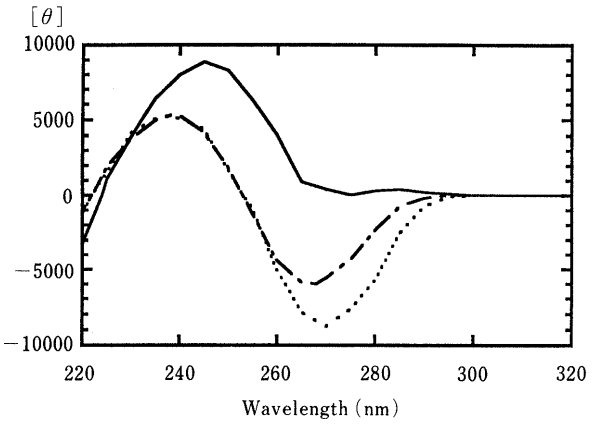


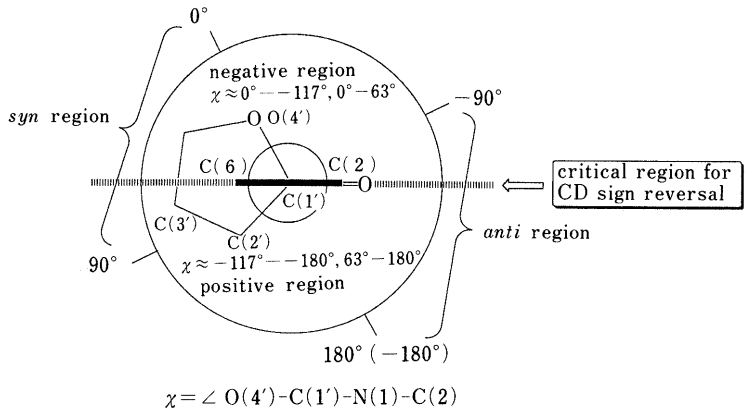
Fig. 4. CD Spectra of *Syn*-Fixed *C*-Cyclouridines in MeOH
---, **10**, ——, **30**, ———, **31**.

The results are summarized in Fig. 5. A transition line in the *anti* region where the CD Cotton effect changes from positive to negative should be present at around $\chi = -117°$, corresponding to 6,6′-cyclouridine,[1,9b] and a transition line in the *syn* region where the CD band changes from negative to positive might be present at around the opposite site ($\chi = 63°$).[1] The conformation with χ = about 63° is also realistic judging from Dreiding models. Therefore, when the C-2 position of uridines is located in the northern half defined by the transition region, the CD spectrum should show a negative Cotton effect, and when in the southern half, CD bands should appear as positive bands in the main absorption region. Although a similar prediction has already been reported by Rogers and Ulbricht,[34] there are slight differences in the critical region. This may be due to the different chromophores of *O*-cyclonucleosides, which are more electronically disturbed than carbon-bridged cyclonucleosides, and are therefore not as good models.

In summary, we have achieved the synthesis of 6,1′-propanouridine (**10**), fixed in the *syn* conformation by a spiro carbon-bridge, whose CD spectrum shows a negative Cotton effect. Judging from a comparison with the CD spectra of other protected derivatives, the structure of **10** lies near the transition region in which the Cotton effect would change from negative to positive. Further investigation of the optical properties in the *syn* region is in progress and the results will be reported in the future.

Experimental

General Methods Physical data were measured as follows. Melting



$\chi = \angle$ O(4′)-C(1′)-N(1)-C(2)

Fig. 5. Critical Region for CD Sign Reversal in Carbon-Bridged Pyrimidine Cyclonucleosides

points were determined on a Yanagimoto Mp-3 micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on JEOL JNM FX-100, JEOL GX-270, and JEOL JNM EX-400 instruments in $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane as an internal standard. UV spectra were recorded with a Shimadzu UV-260 spectrophotometer. Low- and high-resolution mass spectra were taken on a JEOL JMS DX-303 or JEOL JMS HX-110 spectrometer. CD spectra were recorded on a JASCO J-500A spectrophotometer at room temperature. High performance liquid chromatography (HPLC) was performed on a JASCO Trirotar-V system using Inertsil ODS (GL Sciences, Inc., 20.0 × 250 mm) with 10% aqueous MeOH as an eluting solvent at a flow rate of 9 ml/min. Preparative, centrifugally accelerated, radial TLC was done by using a Chromatotron™ (model 8924, Harrison Res., Palo Alto) with a 4 mm thick silica gel plate.

THF was freshly distilled under argon from sodium/benzophenone before use whereas diisopropylamine was distilled from calcium hydride. CH_2Cl_2 was distilled from phosphorus pentoxide and stored over 4A molecular sieves. TLC and preparative TLC were carried out on Merck pre-coated plates Kieselgel 60F_{254}. Silica gel for column chromatography was YMC-GEL SIL 60—230/70.

6-Ethynyl-2,4-dimethoxypyrimidine (4) A mixture of 6-iodo-2,4-dimethoxypyrimidine[17] (**2**, 7.40 g, 27.8 mmol), bis(triphenylphosphine)palladium chloride (975 mg, 1.39 mmol), triethylamine (5.81 ml, 41.7 mmol), copper (I) iodide (795 mg, 4.17 mmol), and (trimethylsilyl)acetylene (5.9 ml, 41.7 mmol) in CH_3CN (150 ml) was stirred at room temperature for 1.5 h. Hydrogen sulfide was bubbled into the mixture and the resulting precipitate was removed by filtration through a Celite pad. The filtrate was concentrated *in vacuo* and the residue was purified on a silica gel column (7.7 × 6.5 cm) with 40% AcOEt in hexane. The appropriate fractions were collected and the solvent was removed under reduced pressure. The crude **3** was dissolved in MeOH (200 ml) and silica gel (30 g) was added. The mixture was stirred for 2 h at room temperature, and was concentrated to dryness *in vacuo*. The silica gel was applied to the top of a silica gel column (6.3 × 14 cm), and eluted with 40—60% AcOEt in hexane. The appropriate fractions were evaporated to leave **4** (4.10 g, 90%) as a foam. An analytically pure sample was obtained by crystallization from hexane–AcOEt: mp 189.5—190.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.05 (s, 1H, H-6), 3.68 (s, 1H, CH), 3.54, 3.34 (s, each 3H, OMe). UV λ_{max}^{MeOH} nm: 291. EIMS *m/z* (relative intensity): 164 (M^+, 100), 107 (51), 79 (32), 66 (96). *Anal.* Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.38; H, 4.86; N, 16.88.

5-*O*-*tert*-Butyldimethylsilyl-1-[2-(2,4-dimethoxypyrimidin-6-yl)ethynyl]-2,3-*O*-isopropylidene-D-ribofuranose (7) A solution of **4** (821 mg, 5.0 mmol) in THF (5 ml) was added dropwise to a stirred solution of LDA (5 mmol) in THF (10 ml), prepared from *n*-butyllithium and diisopropylamine at −80 °C under an argon atmosphere. The mixture was stirred at −70 °C for 0.5 h, then a solution of **6** (1.51 g, 5.0 mmol) in THF (5 ml) was added dropwise, and the whole was stirred at −50 °C for 2 h. The reaction was quenched with aqueous 1 N NH_4Cl solution (10 ml), and the mixture was extracted with AcOEt (50 ml × 3), and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified on a silica gel column (5 × 9.5 cm) with 40—60% AcOEt in hexane to give **7** (1.32 g, 57%) as a foam. An analytically pure sample was obtained by crystallization from hexane–AcOEt, mp 153.0—154.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.06 (s, 1H, H-6), 5.78 (br s, 1H, 1′-OH), 4.82 (d, 1H, J=5.7 Hz, H-2′), 4.62 (d, 1H, H-3′), 4.45 (br s, 1H, H-4′), 3.82—3.79 (m, 2H, H-5′), 3.57, 3.34 (s, each 3H, OMe), 1.53, 1.37 (s, each 3H, ipr), 0.94 (s, 9H, *tert*-Bu), 0.17, 0.16 (s, total 6H, Me_2Si). UV λ_{max}^{MeOH} nm: 294. EIMS *m/z* (relative intensity): 467 (M^++1, 0.57), 451 (4.8), 409 (43), 351 (32), 117 (68), 75 (100). *Anal.* Calcd for $C_{22}H_{34}N_2O_7Si$: C, 56.63; H, 7.34; N, 6.00. Found: C, 56.50; H, 7.40; N, 5.86.

2,2′-Anhydro-1′-(2-ethoxycarbonylvinyl)-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)uridine (15) Compound **13** (4.80 g, 9.62 mmol) was added to a stirred solution of dicyclohexylcarbodiimide (DCC) (6.55 g, 75.0 mmol), pyridine (0.78 ml, 9.62 mmol), trifluoroacetic acid (0.37 ml, 4.81 mmol), and dimethyl sulfoxide (DMSO) (12 ml) in benzene (35 ml) at 0 °C. After being stirred at room temperature for 17 h, the reaction mixture was quenched with aqueous saturated $NaHCO_3$ (200 ml). The mixture was diluted with AcOEt (200 ml) and the separated H_2O phase was extracted by AcOEt (100 ml × 3), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (100 ml). (Ethoxycarbonylmethylene)triphenylphosphorane (5.02 g, 14.4 mmol) was added to this solution and the mixture was stirred for 1 h at room temperature, then concentrated under reduced pressure. The residue was purified on a silica gel column (6.3 × 18 cm) with 0—1% EtOH in $CHCl_3$ to afford **15** (4.66 g, 85%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 7.20 (d, 0.35H, J=7.8 Hz, H-6*Z*), 7.12 (d, 0.65 H, J=7.8 Hz, H-6*E*), 6.84 (d, 0.65H, J=15.6 Hz, H-1″*E*), 6.42 (d, 0.65H, H-2″*E*), 6.30 (d, 0.35H, J=12.2 Hz, H-1″*E*), 6.25 (d, 0.35H, H-2″*E*), 6.09 (d, 0.65H, H-5*E*), 6.02 (d, 0.35H, H-5*Z*), 5.23 (d, 0.35H, J=3.4 Hz, H-2′*Z*), 5.11 (d, 0.65H, J=3.9 Hz, H-2′*E*), 4.59 (dd, 0.65H, J=7.3 Hz, H-3′*E*), 4.56 (dd, 0.35 H, J=7.8 Hz, H-3′*Z*), 4.28 (q, 1.3 H, J=7.1 Hz, $OC\underline{H}_2CH_3$-*E*), 4.23—4.14 (m, 0.7H, $OC\underline{H}_2CH_3$-*Z*), 4.13—3.87 (m, 3H, H-4′, 5′), 1.34 (t, 1.95H, $OCH_2C\underline{H}_3$-*E*), 1.26 (t, 1.05H, $OCH_2C\underline{H}_3$-*Z*), 1.09—0.96 (m, 28H, ipr). EIMS *m/z* (relative intensity); 566 (M^+, 5.4) [HRMS Calcd for $C_{26}H_{42}N_2O_8Si_2$: 566.2480. Found: 566.2478], 523 (100), 493 (15), 455 (16), 397 (27), 329 (1.5), 277 (1.5).

2,2′-Anhydro-3′,5′-di-*O*-benzoyl-1′-(2-ethoxycarbonylvinyl)uridine (16) Benzoic anhydride (5.46 g, 24.1 mmol) was added to a solution of **15** (4.56 g, 8.04 mmol) in THF (70 ml) at room temperature followed by TBAF (1 M THF solution, 16.1 ml, 16.1 mmol). The mixture was stirred overnight at room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in AcOEt (300 ml), and this solution was washed with H_2O (200 ml), aqueous saturated $NaHCO_3$ solution (200 ml × 2), and brine (200 ml). The separated organic phase was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified on a silica gel column (5.1 × 20.5 cm) with 0—2% EtOH in $CHCl_3$ to give **16** (4.09 g, 96%) as a white foam. ^{1}H-NMR ($CDCl_3$) δ: 8.16—7.97 (m, 4H, Bz), 7.66—7.44 (m, 6H, Bz), 7.17 (d, 0.35H, J=7.3 Hz, H-6*Z*), 7.16 (d, 0.65 H, J=7.3 Hz, H-6*E*), 6.95 (d, 0.65H, J=15.1 Hz, H-1″*E*), 6.58 (d, 0.65H, H-2″*E*), 6.49 (d, 0.35H, J=12.2 Hz, H-2″*Z*), 6.28 (d, 0.35 H, H-2″*Z*) 6.10 (d, 0.65H, H-5*E*), 6.04 (d, 0.35H, H-5*Z*), 5.83—5.81 (m, 1H, H-3′), 5.54 (br s, 0.35 H, H-2′*Z*), 5.33 (br s, 0.65H, H-2′*E*), 4.90—4.85 (m, 1H, H-4″), 4.54 (dd, 0.65H, J=6.3, 12.2 Hz, H-5′a-*E*), 4.48 (dd, 0.35 H, J=6.8, 12.2 Hz, H-5′a-*Z*), 4.47 (dd, 0.65H, J=5.4 Hz, H-5′b-*E*), 4.37 (dd, 0.35H, J=5.9 Hz, H-5′b-*Z*), 4.28 (q, 1.3H, J=7.1 Hz, $OC\underline{H}_2CH_3$-*E*), 4.18—4.09 (m, 0.7H, $OC\underline{H}_2CH_3$-*Z*), 1.33 (t, 1.95H, $OCH_2C\underline{H}_3$-*E*), 1.23 (t, 1.05 H, $OCH_2C\underline{H}_3$-*Z*). EIMS *m/z* (relative intensity): 532 (M^+, 3.2), [HRMS Calcd for $C_{28}H_{24}N_2O_9$: 532.1482. Found: 532.1480], 487 (1.1), 459 (12), 427 (3.5), 411 (1.7), 397 (2.5), 364 (1.5), 215 (4.6), 105 (100), 77 (27).

1-[2-*O*-Acetyl-3,5-di-*O*-benzoyl-1-(2-ethoxycarbonylvinyl)-β-D-*arabino*-furanosyl]uracil (17) Aqueous 2 N HCl (80 ml) was added to a solution of **16** (4.09 g, 7.68 mmol) in DMF (200 ml) and the mixture was stirred overnight at room temperature, then neutralized with aqueous 2 N NaOH (80 ml). The solvent was removed under reduced pressure and the residue was dissolved in AcOEt (350 ml); this solution was washed with H_2O (200 ml × 3), followed by brine (150 ml). The separated organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. Acetic anhydride (1.6 ml) and 4-dimethylaminopyridine (20 mg) were added to the above residue in pyridine (80 ml) and the mixture was stirred for 5 h at room temperature. After addition of ice, the solvent was removed *in vacuo* and coevaporated with toluene (× 2). The residue was dissolved in AcOEt (350 ml), and this solution was washed with H_2O, saturated $NaHCO_3$, and brine (each 200 ml). The separated organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified on a silica gel column (4.9 × 14.5 cm) with 50% AcOEt in hexane to give **17** (3.31 g, 72%) as a white foam. ^{1}H-NMR ($CDCl_3$) δ: 9.23 (br s, 1H, NH), 8.08—7.96 (m, 4H, *o*-Bz), 7.85 (d, 1H, J=8.3 Hz, H-6), 7.62—7.39 (m, 7H, Bz and H-1″), 6.34 (d, 1H, J=15.6 Hz, H-2″), 6.04 (s, 1H, H-2′), 5.74 (br d, 1H, H-5), 5.39 (d, 1H, J=2.2 Hz, H-3′), 4.85 (dd, 1H, J=4.2, 12.0 Hz, H-5′a), 4.69 (dd, 1H, J=5.6 Hz, H-5′b), 4.61—4.57 (m, 1H, H-4′), 4.25—4.17 (m, 2H, $OC\underline{H}_2CH_3$), 1.81 (s, 3H, OAc), 1.27 (t, 3H, $OCH_2C\underline{H}_3$). UV λ_{max}^{MeOH} nm: 263, 231. EIMS *m/z* (relative intensity): 592 (M^+, 0.14) [HRMS Calcd for $C_{30}H_{28}N_2O_{11}$: 592.1693. Found: 592.1692], 547 (1.5), 481 (10), 467 (1.3), 299 (3.5), 237 (4.7), 223 (10), 195 (33), 105 (100), 77 (25).

1-[2-*O*-Acetyl-3,5-di-*O*-benzoyl-1-(2-ethoxycarbonylethyl)-β-D-*arabino*-furanosyl]uracil (12) Method A: A mixture of **17** (516 mg, 0.871 mmol), triethylsilane (417 μl, 2.61 mmol), and tris(triphenylphosphine)rhodium chloride (81 mg, 0.0871 mmol) in CH_3CN (10 ml) was heated at 100 °C for 1 h under an argon atmosphere in a sealed glass tube. The precipitate was removed by filtration through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified on a silica gel column (2.4 × 9 cm) with 20—40% AcOEt in hexane to give **12** (206 mg, 40%).

Method B; A mixture of **17** (3.82 g, 6.45 mmol), 10% Pd carbon (800 mg), and polymethylhydrosiloxane (2.6 ml) in EtOH (80 ml) was heated at 60 °C for 2.5 h under an argon atmosphere. Insoluble material was removed by filtration through a Celite pad and the filtrate was concentrated to dryness. The residue was purified on a silica gel column (4.9 × 19.5 cm) with 30—50% AcOEt in hexane to afford **12** (3.54 g, 92%) as a white foam. ^{1}H-NMR ($CDCl_3$) δ: 9.15 (br s, 1H, NH), 8.10—8.01 (m, 4H, *o*-Bz), 7.81

(d, 1H, J=8.3 Hz, H-6), 7.65—7.42 (m, 6H, Bz), 5.83 (s, 1H, H-2′), 5.70 (dd, 1H, J=2.0 Hz, H-5), 5.35 (d, 1H, J=2.9 Hz, H-3′), 4.86 (dd, 1H, J=3.4, 12.2 Hz, H-5′a), 4.67 (dd, 1H, J=4.4 Hz, H-5′b), 4.51 (ddd, 1H, H-4′), 4.07 (q, 2H, J=7.1 Hz, $OC\underline{H}_2CH_3$), 2.99 (ddd, 1H, J=6.8, 8.3, 14.9 Hz, H-2″a), 2.56 (ddd, 1H, J=6.8, 7.8, 14.9 Hz, H-2″b), 2.40—2.26 (m, 2H, H-1″), 1.72 (s, 3H, OAc), 1.20 (t, 3H, $OCH_2C\underline{H}_3$). EIMS m/z (relative intensity): 549 (M^+-45, 0.35), 483 (15), 469 (1.4), 301 (3.1), 239 (67), 197 (21), 105 (100), 77 (23). *Anal.* Calcd for $C_{30}H_{30}N_2O_{11}$: C, 60.60; H, 5.09; N, 4.71. Found: C, 60.48, H, 4.97; N, 4.61.

1-[1-(2-Methoxycarbonylethyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranosyl]uracil (18) An MeOH solution of 1 N NaOMe (25 ml) was added to a solution of **12** (3.54 g, 5.95 mmol) in MeOH (80 ml) and the mixture was stirred overnight at room temperature. After neutralization of the mixture by Dowex 50 W × 8 (H^+ form), the resin was removed by filtration and the filtrate was concentrated under reduced pressure. The residual solvent was removed by co-distillation with EtOH, benzene (× 2), and pyridine. The residue was dissolved in DMF–pyridine (1 : 1, 80 ml) and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (2.81 ml, 8.93 mmol) was added. The mixture was stirred overnight at room temperature, and the solvent was removed under reduced pressure. The residue was dissolved in AcOEt (350 ml), and the solution was washed with H_2O (150 ml × 3) and brine (150 ml). The separated organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified on a silica gel column (5.1 × 16 cm) with 50% AcOEt in hexane to give **18** (2.65 g, 78%) as a white foam. ^{1}H-NMR ($CDCl_3$) δ: 9.37 (br s, 1H, NH), 7.92 (d, 1H, J=8.3 Hz, H-6), 5.71 (dd, 1H, J=2.0 Hz, H-5), 4.45 (dd, 1H, J=4.4, 5.9 Hz, H-2′), 4.14 (dd, 1H, J=7.3 Hz, H-3′), 4.04—3.96 (m, 3H, H-5′, 2′-OH), 3.78 (ddd, 1H, J=3.4, 3.9, 7.3 Hz, H-4′), 3.64 (s, 3H, OMe), 3.16—3.09 (m, 1H, H-2″a), 2.38—2.19 (m, 3H, H-1″, H-2″b), 1.10—0.98 (m, 28H, ipr). EIMS m/z (relative intensity): 529 (M^+-43, 35), 417 (60), 329 (19), 261 (25), 235 (46), 183 (100), 115 (46). *Anal.* Calcd for $C_{25}H_{44}N_2O_9Si_2$: C, 52.42; H, 7.74; N, 4.89. Found: C, 52.71; H, 7.86; N, 4.71.

1-[1-(2-Methoxycarbonylethyl)-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]uracil (21) Pyridine (2.8 ml, 34.6 mmol) was added to a solution of chromium oxide (1.73 g, 17.3 mmol) and powdered 4 A molecular sieves (2.5 g) in CH_2Cl_2 (50 ml) at 0 °C under an argon atmosphere, and the mixture was stirred for 30 min at 0 °C. Acetic anhydride (1.63 ml, 17.3 mmol) was added to the mixture, which was further stirred for 30 min. Compound **18** (2.48 g, 4.33 mmol) in a small amount of CH_2Cl_2 was then added at room temperature under an argon atmosphere. The mixture was stirred for 30 min at room temperature and poured into AcOEt (600 ml). The resulting precipitate was removed by filtration through a silica gel bed. The filtrate was concentrated under reduced pressure and the residual pyridine was removed by co-distillation with toluene. The residue was dissolved in AcOEt (300 ml), and this solution was washed with aqueous saturated $NaHCO_3$ (150 ml × 3). The separated organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give **19**. Sodium borohydride (820 mg, 21.7 mmol) was added in small portions to an MeOH solution (50 ml) of **19** at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was neutralized with AcOH and the solvent was removed under reduced pressure. The residue was dissolved in AcOEt (300 ml), and this solution was washed with H_2O, aqueous saturated $NaHCO_3$, and brine (each 150 ml). The separated organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified on a silica gel column (5.2 × 10 cm) with 30—50% AcOEt in hexane to leave a diastereomeric mixture of **21** and **18** (*ca.* 5 : 1, 2.15 g, 87%) as a white foam: ^{1}H-NMR ($CDCl_3$) δ: 9.49 (br s, 0.18 H, NH-b), 9.24 (br s, 0.82H, NH-a), 7.97 (d, 0.82H, J=8.3 Hz, H-6a), 7.91 (d, 0.18H, J=8.3 Hz, H-6b), 5.71 (br dd, H-5b), 5.68 (br dd, total 1H, J=2.0 Hz, H-5a), 4.66 (dd, 0.82H, J=1.7, 4.4 Hz, H-2′a), 4.46 (dd, 0.18 H, J=3.9, 5.9 Hz, H-2′b), 4.20—4.11 (m, 2.64H, H-3′a, H-4′a, H-5′aa, H-3′b), 4.01—3.99 (m, 0.36H, H-5′b), 3.95 (dd, 0.82H, J=2.4, 13.2 Hz, H-5′ba), 3.89 (br d, 0.18 H, 2′-OHb), 3.80—3.77 (m, 0.18H, H-4′b), 3.64 (s, 0.54H, OMe-b), 3.63 (s, 2.46H, OMe-a), 3.32 (br d, 0.82H, 2′-OHa), 3.13—3.11 (m, 0.18H, H-2″ab), 2.89 (ddd, 0.82H, J=6.8, 8.3, 15.9 Hz, H-2″aa), 2.54 (ddd, 0.82H, J=6.4, 8.8, 14.9 Hz, H-2″ba), 2.35 (ddd, J=6.4, 8.3, 15.9 Hz, H-1″aa), 2.36—2.22 (m, H-2″bb, H-1″b), 2.20 (ddd, total 3H, J=6.8, 8.8, 15.6 Hz, H-1″ba), 1.09—0.98 (m, 28H, ipr). EIMS m/z (relative intensity): 529 (M^+-43, 15), 497 (13), 461 (21), 443 (19), 417 (23), 329 (23), 261 (33), 235 (25), 183 (100), 115 (60). *Anal.* Calcd for $C_{25}H_{44}N_2O_9Si_2$: C, 52.42; H, 7.74; N, 4.89. Found: C, 52.17; H, 7.89; N, 4.88.

2-(1,4,6-Tri-*O*-benzoyl-β-D-fructofuranosyl)uracil (22) Aqueous 2 N HCl (120 ml) was added to a solution of **14** (8.24 g, 14.5 mmol) in DMF (400 ml) and the mixture was stirred for 2 d at room temperature. After being neutralized with aqueous 4 N NaOH (60 ml), the mixture was poured into H_2O (2 l) and the resulting precipitate **22** was collected by filtration. The crude product was dissolved in $CHCl_3$ (500 ml), and this solution was washed with brine (300 ml). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified on a silica gel column (7.7 × 9 cm) with 50—65—75% AcOEt in hexane to give **22** (6.40 g, 75%, crystallized from hexane–AcOEt): mp 205.2—205.7 °C. ^{1}H-NMR ($CDCl_3$) δ: 9.63 (br s, 1H, NH), 8.12—7.93 (m, 6H, *o*-Bz), 7.82 (d, 1H, J=8.3 Hz, H-6), 7.63—7.38 (m, 9H, Bz), 5.68 (br dd, 1H, J=1.5, 8.3 Hz, H-5), 5.55 (d, 1H, J=2.0 Hz, H-4′), 5.10 (d, 1H, J=11.7 Hz, H-1′a), 5.01 (d, 1H, J=6.4 Hz, H-3′), 4.89 (d, 1H, H-1′b), 4.79—4.76 (m, 1H, H-5′), 4.70—4.68 (m, 2H, H-6′), 4.39—4.36 (m, 1H, 3′-OH). UV λ_{max}^{MeOH} nm: 263, 232. EIMS m/z (relative intensity): 586 (M^+, 1.5), 481 (2.4), 475 (4.2), 451 (6.1), 231 (2.3), 214 (2.2), 122 (6.5), 105 (100), 77 (35). *Anal.* Calcd for $C_{31}H_{26}N_2O_{10}$: C, 63.48; H, 4.47; N, 4.78. Found: C, 63.50; H, 4.44; N, 4.80.

2-(1,4,6-Tri-*O*-benzoyl-β-D-psicofuranosyl)uracil (24) Compound **22** (6.40 g, 10.9 mmol) was subjected to the procedure described for the synthesis of **21**. After aqueous work-up, the solvent was removed *in vacuo* and the residue was purified on a silica gel column (4.9 × 20.5 cm) with 30—50% AcOEt in hexane to afford a mixture of **24** and **22** (5.04 g, 79%, as a 5 : 1 mixture) as a white foam. Diastereomerically pure **24** was obtained as follows: *ca.* 1 g of the mixture was taken up in a small amount of $CHCl_3$ and applied to a Chromatotron™ (4 mm thick plate), which was eluted with 30% AcOEt in hexane. The appropriate fractions (containing trace amounts of **22**) were collected and evaporated to dryness. The residue was crystallized from hexane–AcOEt to give epimerically pure **24**, mp 175.5—176.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.49 (br s, 1H, NH), 8.19—7.88 (m, 6H, *o*-Bz), 7.67 (d, 1H, J=8.3 Hz, H-6), 7.64—7.40 (m, 9H, *m*, *p*-Bz), 5.92 (d, 1H, J=5.9 Hz, H-4′), 5.57 (dd, 1H, J=2.4, 8.3 Hz, H-5), 5.05 (dd, 1H, J=3.4, 5.9 Hz, H-3′), 5.03 (d, 1H, J=12.2 Hz, H-1′a), 4.88 (dd, 1H, J=3.4, 12.2 Hz, H-6′a), 4.83 (dd, 1H, J=2.5, 3.4 Hz, H-5′), 4.81 (d, 1H, H-1′b), 4.60 (d, 1H, J=3.4 Hz, 3′-OH), 4.40 (dd, 1H, J=2.5, 12.2 Hz, H-6′b). EIMS m/z (relative intensity): 569 (M^+-17, 0.56), 475 (8.3), 451 (1.9), 231 (6.1), 153 (2.5), 122 (4.9), 105 (100), 77 (22). *Anal.* Calcd for $C_{31}H_{26}N_2O_{10}$: C, 63.48; H, 4.47; N, 4.78. Found: C, 63.52; H, 4.34; N, 4.81.

1-β-D-Psicofuranosyluracil (25) An MeOH solution of 1 N NaOMe (0.25 ml) was added to a solution of **24** (100 mg, 0.170 mmol) in MeOH (5 ml) and the mixture was stirred for 2 h at room temperature. After neutralization with Dowex 50W × 8 (H^+ form), the resin was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was purified on a silica gel column (1.7 × 9 cm) with 15—30% EtOH in $CHCl_3$ to give a solid, which was further purified by HPLC (Inertsil ODS, 20.0 × 250 mm, flow 9 ml/min), eluted with 10% MeOH in H_2O. The fractions corresponding to a retention time of 7 min were collected and the solvent was removed *in vacuo* to leave **25** (36 mg, 77%) as a white amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 11.10 (br s, 1H, NH), 7.93 (d, 1H, J=8.3 Hz, H-6), 5.44 (br dd, 1H, J=1.3, 8.3 Hz, H-5), 5.31 (d, 1H, J=4.6 Hz, 3′-OH), 4.93 (t, 1H, J=5.3 Hz, 6′-OH), 4.89 (d, 1H, J=6.8 Hz, 4′-OH), 4.74 (t, 1H, J=6.2 Hz, 1′-OH), 4.61 (t, 1H, J=4.5 Hz, H-3′), 4.13 (dd, 1H, J=11.7 Hz, H-1′a), 3.94—3.91 (m, 1H, H-5′), 3.86—3.91 (m, 1H, H-4′), 3.71—3.66 (m, 1H, H-6′a), 3.64 (dd, 1H, H-1′b), 3.49—3.43 (m, 1H, H-6′b). UV $\lambda_{max}^{H_2O}$ nm: 264. EIMS m/z (relative intensity): 256 (M^+-18, 0.21), 243 (5.8), 171 (6.3), 133 (9.4), 112 (100), 97 (18), 69 (75), 57 (47). *Anal.* Calcd for $C_{10}H_{14}N_2O_7$: C, 43.80; H, 5.15; N, 10.22. Found: C, 43.69; H, 5.26; N, 10.02.

1-[5-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-1-(2-methoxycarbonylethyl)-β-D-ribofuranosyl]uracil (26) TBAF (1 M THF solution, 7.8 ml, 7.8 mmol) was added to a solution of **21** (2.03 g, 3.54 mmol) in THF (30 ml) at room temperature. The mixture was stirred for 10 min at room temperature, then the solvent was removed under reduced pressure. 2,2-Dimethoxypropane (1.5 ml) and 70% perchloric acid (0.9 ml) were added to a solution of the above residue in acetone (60 ml) at room temperature. The mixture was stirred for 2 h and neutralized with anhydrous K_2CO_3. Insoluble materials were removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was partially purified on a silica gel column (5.1 × 11 cm) with 4—8% EtOH in $CHCl_3$ and the appropriate fractions were collected and concentrated to dryness. *tert*-Butyldimethylchlorosilane (800 mg, 5.31 mmol) and diisopropylethylamine (925 μl, 5.31 mmol) were added to a solution of the residue in DMF (25 ml) at room temperature. The mixture was stirred overnight at room temperature, then the solvent was removed under reduced pressure. The residue was partitioned between AcOEt (200 ml) and H_2O (150 ml × 3), and brine (150 ml). The separated organic phase

was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified on a silica gel column (5.1 × 7 cm) with 30—50% AcOEt in hexane to give **26** (1.01 g, 59%) as an amorphous white solid. ^{1}H-NMR ($CDCl_3$) δ: 8.00 (br s, 1H, NH), 7.75 (d, 1H, J=8.3 Hz, H-6), 5.61 (dd, 1H, J=2.5 Hz, H-5), 5.06 (d, 1H, J=6.1 Hz, H-2′), 4.67 (dd, 1H, J=1.5 Hz, H-3′), 4.44 (br m, 1H, H-4′), 3.77 (dd, 1H, J=2.4, 11.7 Hz, H-5′a), 3.67 (dd, 1H, J=3.9 Hz, H-5′b), 3.62 (s, 3H, OMe), 2.78—2.69 (m, 1H, H-2″a), 2.42—2.34 (m, 1H, H-2″b), 2.25—2.13 (m, 2H, H-1″), 1.61, 1.37 (s, each 3H, ipr), 0.84 (s, 9H, *tert*-Bu), 0.03, 0.01 (s, each 3H, SiMe). EIMS m/z (relative intensity): 469 (M^+-15, 2.4), 395 (2.2), 373 (25), 315 (44), 183 (27), 151 (25), 115 (100), 73 (81), 43 (65). *Anal.* Calcd for $C_{22}H_{36}N_2O_8Si$: C, 54.53; H, 7.49; N, 5.78. Found: C, 54.28; H, 7.51; N, 5.86.

1-[5-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-1-(3-methanesulfonyloxypropyl)-β-D-ribofuranosyl]uracil (27) Lithium borohydride (79 mg, 3.53 mmol) was added to a solution of **26** (342 mg, 0.71 mmol) in THF (10 ml) under an argon atmosphere, and the mixture was heated under reflux overnight. After being cooled to room temperature, the mixture was neutralized with aqueous 1 N HCl. This solution was diluted with brine (50 ml) and extracted with AcOEt (15 ml × 4). The combined organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was taken up in pyridine (10 ml), and methanesulfonyl chloride (82 μl, 1.06 mmol) was added to the solution at 0 °C. The mixture was stirred for 2 h at room temperature, then the solvent was removed *in vacuo*, and residual solvent was removed by co-distillation with toluene. The residue was dissolved in AcOEt (50 ml), and this solution was washed with H_2O (30 ml) and saturated NaCl solution (30 ml). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified on a silica gel column (2.3 × 6.5 cm) with 50% AcOEt in hexane to leave **27** (253 mg, 67%). Analytically pure **27** was obtained by crystallization from hexane–AcOEt, mp 128.5—129.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.99 (br s, 1H, NH), 7.78 (d, 1H, J=8.3 Hz, H-6), 5.63 (dd, 1H, J=2.4 Hz, H-5), 5.05 (d, 1H, J=6.2 Hz, H-2′), 4.67 (dd, 1H, J=1.5 Hz, H-3′), 4.47 (br m, 1H, H-4′), 4.23—4.16 (m, 2H, H-3″), 3.79 (dd, 1H, J=2.4, 11.7 Hz, H-5′a), 3.68 (dd, 1H, J=3.9 Hz, H-5′b), 2.99 (s, 3H, $MeSO_3$), 2.57—2.49 (m, 1H, H-2″a), 1.92—1.80 (m, 2H, H-2″b, 1″a), 1.59, 1.37 (s, each 3H, ipr), 1.54—1.41 (m, 1H, H-1″b), 0.84 (s, 9H, *tert*-Bu), 0.03, 0.02 (s, each 3H, SiMe). EIMS m/z (relative intensity): 519 (M^+-15, 2.4), 463 (1.5), 423 (19), 365 (44), 153 (44), 69 (100). *Anal.* Calcd for $C_{22}H_{38}N_2O_9SSi$: C, 49.42; H, 7.16; N, 5.24. Found: C, 49.62; H, 7.17; N, 5.40.

1-[5-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-1-(3-methanesulfonyloxypropyl)-β-D-ribofuranosyl]-5-chlorouracil (28) *N*-Chlorosuccinimide (165 mg, 1.23 mmol) was added to a solution of **27** (220 mg, 0.411 mmol) in AcOH (10 ml) under an argon atmosphere, and the mixture was heated at 50 °C for 6 h. The solvent was removed under reduced pressure, the residual solvent was removed by co-distillation with toluene. The residue was partitioned between AcOEt (50 ml) and saturated $NaHCO_3$ (50 ml) and the separated organic phase was washed with brine (50 ml), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified on a silica gel column (1.7 × 11 cm) with 30—50% AcOEt in hexane to afford **28** (194 mg, 83%) as a white foam. ^{1}H-NMR ($CDCl_3$) δ: 8.43 (br s, 1H, NH), 7.95 (s, 1H, H-6), 5.02 (d, 1H, J=6.1 Hz, H-2′), 4.69 (dd, 1H, J=1.5 Hz, H-3′), 4.52 (br s, 1H, H-4′), 4.24—4.18 (m, 2H, H-3″), 3.85 (dd, 1H, J=2.0, 11.7 Hz, H-5′a), 3.72 (dd, 1H, J=3.4 Hz, H-5′b), 3.00 (s, 3H, $MeSO_3$), 2.55—2.47 (m, 1H, H-1″a), 1.92—1.82 (m, 2H, H-1″b, 2″a), 1.59, 1.37 (s, each 3H, ipr), 1.49—1.42 (m, 1H, H-2″b), 0.84 (s, 9H, *tert*-Bu), 0.05, 0.02 (s, each 3H, SiMe). UV λ_{max}^{MeOH} nm: 279. FABMS m/z (relative intensity): 1137 ($2M^+ + 1$, 4.9), 569 ($M^+ + 1$, 9.7) [HRFABMS Calcd for $C_{22}H_{38}ClN_2O_9SSi$: 569.1756. Found: 569.1779], 553 (13), 424 (100), 365 (100), 154 (75), 137 (88), 87 (100).

1-[5-*O*-*tert*-Butyldimethylsilyl-1-(3-iodopropyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl]-5-chlorouracil (11) A mixture of lithium iodide (238 mg, 1.79 mmol) and **28** (405 mg, 0.712 mmol) in 2-butanone (15 ml) was heated under reflux for 2 h. The solvent was removed *in vacuo* and the residue was partitioned between AcOEt (70 ml) and brine (50 ml). The separated organic phase was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified on a silica gel column (2.1 × 24 cm) with 20—30% AcOEt in hexane to leave **11** (337 mg, 79%) as a syrup. ^{1}H-NMR ($CDCl_3$) δ: 8.08 (br s, 1H, NH), 7.93 (s, 1H, H-6), 5.01 (d, 1H, J=5.9 Hz, H-2′), 4.69 (dd, 1H, J=1.5 Hz, H-3′), 4.52 (br s, 1H, H-4′), 3.84 (dd, 1H, J=2.0, 11.7 Hz, H-5′a), 3.71 (dd, 1H, J=3.2 Hz, H-5′b), 3.22—3.09 (m, 2H, H-3″), 2.50—2.44 (m, 1H, H-1″a), 2.04—1.88 (m, 2H, H-1″b, 2″a), 1.62, 1.38 (s, each 3H, ipr), 1.66—1.50 (m, 1H, H-2″b), 0.84 (s, 9H, *tert*-Bu), 0.05, 0.02 (s, each 3H, SiMe). EIMS m/z (relative intensity): 585 (M^+-15, 1.5), 487 (M^+-113, 1.1) [HRMS Calcd for $C_{15}H_{21}ClIN_2O_6$: 487.0135. Found: 487.0162], 485 (2.9), 455 (38), 397 (38), 197 (63), 97 (100), 69 (88), 43 (69).

5′-*O*-*tert*-Butyldimethylsilyl-2′,3′-*O*-isopropylidene-6,1′-propanouridine (30) A mixture of tributyltin hydride (150 μl, 0.56 mmol) and AIBN (20 mg) in benzene (15 ml) was added dropwise to a solution of **11** (320 mg, 0.53 mmol) in benzene (120 ml) at reflux temperature under an argon atmosphere. After the addition was completed, heating was continued under reflux for 75 min. The solvent was removed *in vacuo* and the residue was partially purified on a silica gel column (1.7 × 16.5 cm) with 10—20—30% AcOEt in hexane. The appropriate fractions were collected and concentrated to give a diastereomixture of **29**. DBU (398 μl, 2.66 mmol) was added to a solution of **29** in 1,4-dioxane (15 ml) under an argon atmosphere and the mixture was heated at 60 °C for 8 h. After being cooled to room temperature, the mixture was neutralized with aqueous 1 N NH_4Cl (10 ml) and AcOH. The mixture was extracted with AcOEt (25 ml × 4) and the combined organic phase was dried (Na_2SO_4). The solvent was removed and the residue was purified on a silica gel column (1.7 × 12 cm) with 20—33—50% AcOEt in hexane. The less polar fractions contained **29** (80 mg) and the more polar fractions contained **30** (147 mg), isolated as a foam. The recovered **29** was subjected to the procedure described above to give another 25 mg of **30** (total yield 74%). ^{1}H-NMR ($CDCl_3$) δ: 8.22 (br s, 1H, NH), 5.45 (br s, 1H, H-5), 5.30 (d, 1H, J=6.8 Hz, H-2′), 4.86 (dd, 1H, J=4.9, 6.8 Hz, H-3′), 3.98 (m, 1H, H-4′), 3.85 (dd, 1H, J=5.4, 10.5 Hz, H-5′a), 3.81 (dd, 1H, J=4.9 Hz, H-5′b), 2.80—2.73 (m, 1H, H-3″a), 2.60 (dq, 1H, J=1.5, 5.9, 11.7, 17.1 Hz, H-3″b), 2.20—2.15 (m, 1H, H-1″a), 2.10 (ddd, 1H, J=3.4, 11.7, 14.7 Hz, H-1″b), 1.92—1.74 (m, 2H, H-2″), 1.52, 1.33 (s, each 3H, ipr), 0.88 (s, 9H, *tert*-Bu), 0.05, 0.01 (s, each 3H, SiMe). CD in MeOH [θ] (nm): +400 (285), 0 (275), +8900 (245), 0 (224). In this case, the values were calculated on the basis that ε is 10000. UV λ_{max}^{MeOH} nm: 264. EIMS m/z (relative intensity): 439 ($M^+ + 1$, 0.42), 438 (M^+, 0.14) [HRMS Calcd for $C_{21}H_{34}N_2O_6Si$: 438.2186. Found: 438.2190], 423 (15), 381 (94), 323 (92), 305 (25), 197 (1.8), 177 (100), 75 (63).

2′,3′-*O*-Isopropylidene-6,1′-propanouridine (31) TBAF (1 M THF solution, 60 μl, 0.06 mmol) was added to a solution of **30** (25 mg, 0.057 mmol) in THF (3 ml) at room temperature. The mixture was stirred for 1 h, then further TBAF (1 M THF solution, 100 μl, 0.1 mmol) was added and the mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was purified by preparative TLC ($CHCl_3$: EtOH = 15 : 1), to afford **31** (17 mg, 92%). An analytically pure sample of **31** was obtained by crystallization from $CDCl_3$. mp > 200 °C. ^{1}H-NMR ($CDCl_3$) δ: 9.25 (br s, 1H, NH), 5.49 (br s, 1H, H-5), 5.36 (d, 1H, J=7.3 Hz, H-2′), 5.17 (dd, 1H, J=4.9, 7.3 Hz, H-3′), 4.06—4.03 (m, 1H, H-4′), 3.90 (br dd, 1H, J=2.7, 12.0 Hz, H-5′a), 3.83 (br dd, 1H, J=3.7 Hz, H-5′b), 3.08 (br s, 1H, 5′-OH), 2.81—2.74 (br m, 1H, H-3″a), 2.63 (dq, 1H, J=1.5, 5.4, 10.3, 17.1 Hz, H-3″b), 2.22 (ddd, 1H, J=3.7, 10.9, 14.7 Hz, H-1″a), 2.12—2.06 (m, 1H, H-1″b), 1.90—1.76 (m, 2H, H-2″), 1.54, 1.35 (s, each 3H, ipr). CD in MeOH [θ] (nm): −6000 (268), 0 (253), +5400 (239), 0 (222). In this case, the values were calculated on the basis that ε 10000. EIMS m/z (relative intensity): 325 ($M^+ + 1$, 2.1), 309 (18), 266 (9.6), 235 (17), 199 (94), 181 (72), 138 (30), 68 (50), 55 (100). *Anal.* Calcd for $C_{15}H_{20}N_2O_6$: C, 55.55; H, 6.22; N, 8.64. Found: C, 55.51; H, 6.23; N, 8.56.

6,1′-Propanouridine (10) Compound **30** (136 mg, 0.31 mmol) was dissolved in aqueous 1 N HCl–THF solution (1 : 3, 10 ml) and the mixture was stirred for 3 d at room temperature. After neutralization of the mixture with concentrated NH_4OH, the solvent was removed under reduced pressure. The residue was purified on a silica gel column (1.7 × 10.5 cm) with 4—8% MeOH in $CHCl_3$ to give **31** (26 mg, 26%) as a less polar product, and **10** (58 mg, 66%) as a more polar product. An analytically pure sample of **10** was obtained by crystallization from EtOH–H_2O, mp 175.5—177.0 °C. ^{1}H-NMR (DMSO-d_6 + D_2O) δ: 5.39 (s, 1H, H-5), 4.71 (t, 1H, J=7.1 Hz, H-2′), 4.17 (t, 1H, J=7.1 Hz, H-3′), 3.63—3.55 (m, 2H, H-4′, H-5′a), 3.51—3.45 (m, 1H, H-5′b), 2.75—2.71 (br m, 1H, H-3″a), 2.60 (ddd, 1H, J=6.6, 9.9, 17.5 Hz, H-3″b), 2.15 (ddd, 1H, J=3.7, 11.0, 14.6 Hz, H-1″a), 1.92—1.87 (m, 1H, H-1″b), 1.67—1.61 (m, 2H, H-2″). UV $\lambda_{max}^{H_2O}$ nm (ε: 267 11400). CD in H_2O [θ] (nm): −6100 (270), 0 (253), +5300 (238), 0 (222). CD in MeOH [θ] (nm): −8800 (270), 0 (253), +4500 (238), 0 (222). EIMS m/z (relative intensity): 284 (M^+, 0.42), 266 ($M^+ - 18$, 11), 248 (28), 181 (49), 151 (96), 139 (55), 126 (70), 108 (100), 55 (96). *Anal.* Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.43; H, 5.66; N, 10.00.

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