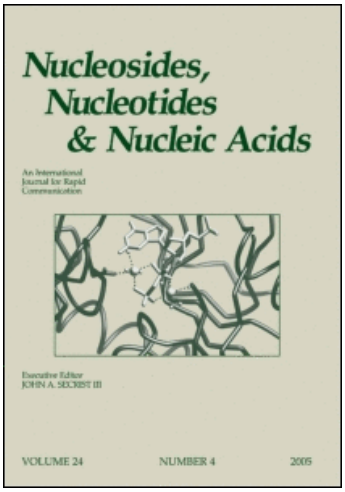

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Synthesis of 6,3'-Methanothymidine from a Ribofuranos-3-Ulose and 2,4-Dimethoxy-5,6-Dimethylpyrimidine

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SYNTHESIS OF 6,3'-METHANOTHYMIDINE FROM A RIBOFURANOS-3-ULOSE AND 2,4-DIMETHOXY-5,6-DIMETHYLPYRIMIDINE[1]

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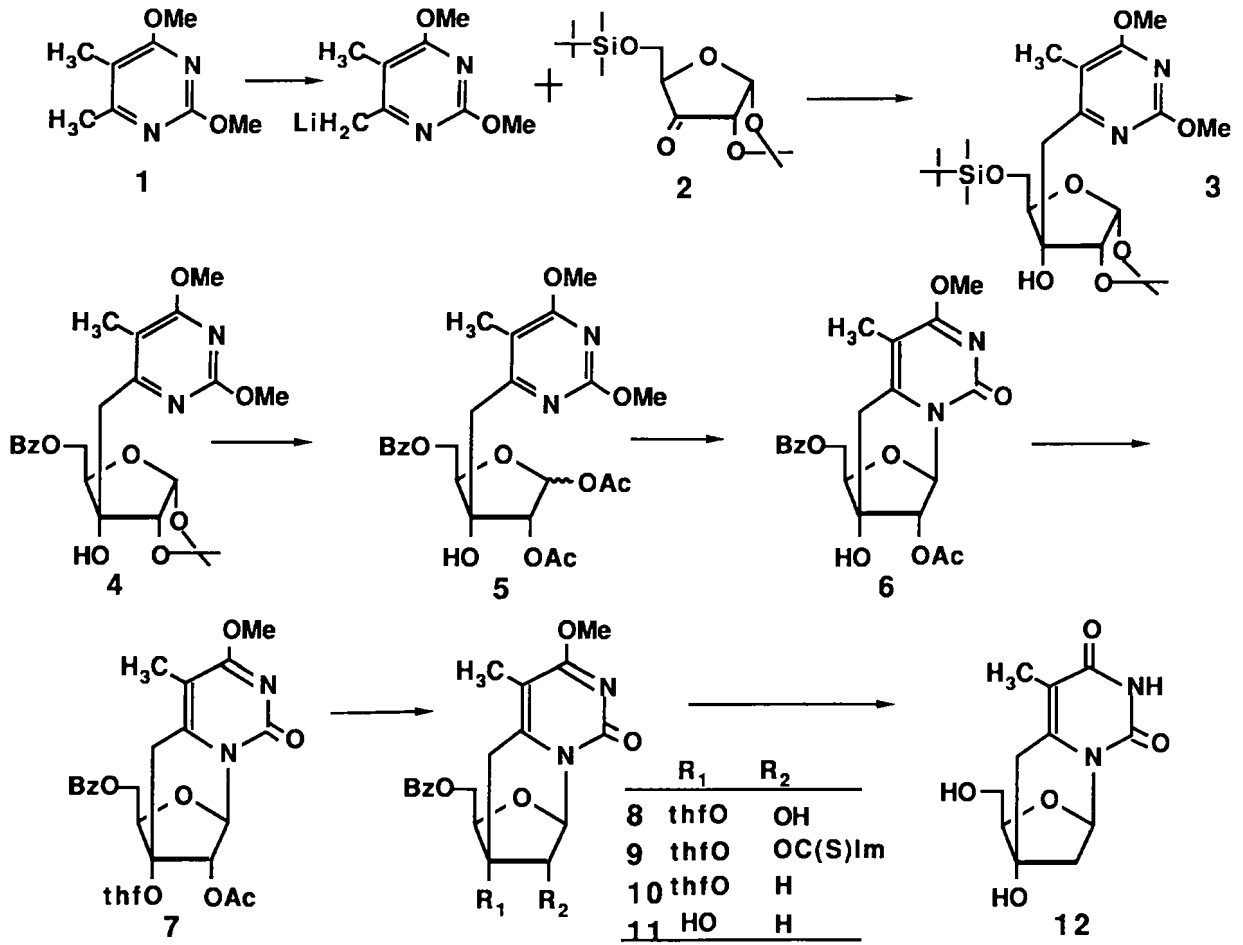
ABSTRACT: 6,3'-Methanothymidine, a thymidine analogue conformationally fixed by the 6,3'-methano-bridge, was synthesized by the sequence of condensation of a ribbofuranos-3-ulose and a pyrimidinylmethyllithium, intramolecular glycosylation, 2'-deoxygenation, and final deprotection.

We have recently developed a facile procedure for the synthesis of 6,3'-carbon-bridged cyclopyrimidine nucleosides, i.e., 6,3'-methanocytidine and 6,3'-methanouridine, by the coupling of a ribofuranos-3-ulose derivative and 2,4-dimethoxypyrimidin-6-ylmethyllithium followed by an intramolecular glycosylation and appropriate derivatization.[2] Furthermore, the 2'-deoxygenation of the intermediate afforded 2'-deoxy-6,3'-methanocytidine and 2'-deoxy-6,3'-methanouridine.[2b] In our continuing studies on the synthesis of carbon-bridged cyclonucleosides,[3] we describe here an extension of this procedure for the synthesis of 6,3'-methanothymidine, a conformationally fixed thymidine by the 6,3'-methylene bridge.

For the synthesis of the title compound, 2,4-dimethoxy-5,6-dimethylpyrimidine (**1**), readily prepared from 5,6-dimethyluracil, was used as the pyrimidine part, since the lithiation of **1** would be expected to occur at the 6-methyl group rather than the 5-methyl group. Treatment of **1** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -55 C afforded the lithio derivative. This compound was reacted with 5-O-t-butyldimethylsilyl-1,2-O-isopropylidene-α-D-erythro-pentofuranos-3-ulose (**2**)[2] at -55°C to give the crystalline adduct (**3**) in a yield of 85%. The structure of **3** was readily confirmed by the ^{1}H-NMR measurement. The addition reaction at the C-3 of **2** was stereospecific and the product **3** had a 3(R)-configuration (vide infra). The use of n-butyllithium[2] in place of LDA in this carbanion formation resulted in a somewhat decreased yield of the condensation product. The 5'-O-silyl group of **3** was removed by treatment with tetra-n-butylammonium fluoride, then the 5'-hydroxyl group was benzoylated to give the crystalline 5'-O-benzoate (**4**).



SYNTHETIC STRATEGY

Prior to the intramolecular glycosylation, the 1,2-O-isopropylidene function of **4** was converted to the acetyl function by treatment with 90% trifluoroacetic acid followed by acetic anhydride to give the 1,2-di-O-acetate (**5**) as an anomeric mixture. Treatment of **5** with stannic chloride in acetonitrile at room temperature gave the 6,3'-methano-cyclonucleoside (**6**) in 64% isolated yield. The difference of the reactivity between anomeric acetates (**5**) in the intramolecular glycosylation was apparently not observed. The β-configuration of this cyclonucleoside (and hence the stereospecific addition in the formation of **3**) was confirmed by the ^{1}H-NMR spectra. Thus, the signals of H-1' and H-2' of **6** appeared as singlets, which is only possible when they are in the trans arrangement, i.e., the β-configuration at the anomeric position.

Although the deprotection of **6** would give 6,3'-methano-5-methyluridine, the 2'-deoxy derivative seemed to be more interesting as a thymidine analogue. Treatment of **6** with 2,3-dihydrofuran in the presence of p-toluenesulfonic acid gave the 3'-O-tetrahydrofuranyl (thf) derivative (**7**) as a diastereomeric mixture. Selective de-acetylation of **7** was achieved by treatment with methanolic triethylamine to afford **8**. Compound **8** was converted to the 2'-imidazolylthiocarbonate (**9**) by treatment with thiocarbonyldiimidazole. Compound **9** was subjected to the radical hydrogenation by treatment with tributyltin hydride and azobisisobutyronitrile (AIBN) to furnish the 2'-deoxynucleoside (**10**), which was deprotected by acid treatment to give crystalline product **11**. Alkaline treatment of **11** furnished 6,3'-methanothymidine (**12**) in a crystalline form. The ^{1}H-NMR, mass and UV spectral data as well as the elemental analysis were consistent with the structure **12**.

In conclusion, the synthetic strategy presented here should be useful for further development in the synthesis of various types of carbon-bridged cyclonucleosides. The biological properties of this cyclonucleoside as well as related compounds will be a separate subject.

EXPERIMENTAL

Melting points were determined on a Yanagimoto MP-3 micro-melting points apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL FX-100FT or FX-270FT spectrometer in an appropriate solvent with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (δ), and signals are

described as s (singlet), d (doublet), t (triplet), m (multiplet) or br (broad). Exchangeable protons were confirmed by addition of D_2O. Ultraviolet absorption spectra (UV) were recorded on a Shimadzu UV-260 spectrophotometer. Mass spectra (MS) were measured on a JEOL D-300 spectrometer. Circular dichroism spectra (CD) were recorded on a JASCO J-500A spectropolarimeter at room temperature. Silica gel used for column chromatography was Merck Kieselgel 60 (70-200 mesh). Thin-layer chromatography (TLC) was carried out on Merck pre-coated $60F_{254}$ plates.

2,4-Dimethoxy-5,6-dimethylpyrimidine (1) ---- A suspension of 5,6-dimethyluracil[4] (10 g, 71.4 mmol) in $POCl_3$ (60 ml) was heated under reflux for 5 hr. The solution was concentrated in vacuo, the residue was poured into ice-water and the mixture was extracted with ether. The organic layer was washed with H_2O, then dried over $MgSO_4$. The solvent was removed, the residue was dissolved in MeOH containing NaOMe (0.7 M, 200 ml) and heated for 10 min under reflux. The solvent was removed in vacuo and the residue was taken up in ether. The solution was washed twice each with 30% NaOH and H_2O and the organic layer was dried over Na_2SO_4. The solvent was evaporated and the residue was crystallized from hexane to give 1 (7.97 g 66%), mp 36.5-37°C. MS m/z: 168 (M^+). ^{1}H-NMR ($CDCl_3$): 3.96, 3.94 (3H each, s, MeO), 2.35 (3H, s, Me-6), 2.03 (3H, s, Me-5). Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 56.93; H, 7.18; N, 16.77.

1,2-O-Isopropylidene-5-O-t-butyldimethylsilyl-3(R)-(2,4-dimethoxy-5-methylpyrimidin-6-ylmethyl)ribose (3) ---- LDA (1.1 eq in THF) was added dropwise to a solution of 1 in THF (3.36 g, 20 mmol in 30 ml) at -70°C. The temperature was raised to -55°C and the solution was stirred for 30 min. Compound 2[2b] (6.04 g, 20 mmol) in THF (30 ml) was added dropwise to the solution and the stirring was continued for 2.5 hr. The solution was neutralized by addition of AcOH, then the temperature was raised to 20°C, and the solvent was removed. The residue was partitioned between AcOEt and H_2O, the organic layer was separated, dried over Na_2SO_4, then the solvent was removed. The residue was chromatographed on silica gel (6.7x21 cm, 10-20% AcOEt in hexane). The eluate was concentrated and the residue was crystallized from i-PrOH to give 3 (8.02 g, 85%), mp 114°C. MS m/z: 470 (M^+), 455 (M^+-Me), 413 (M^+-t-Bu). ^{1}H-NMR: 5.71 (1H, d, H-1', J= 3.9 Hz), 5.74 (1H, s, HO-3'), 4.21 (1H, s, H-2'), 4.13-3.87 (3H, m, H-4',5'), 3.99, 3.94 (3H each, s, MeO), 2.87 (2H, dd, H-6'), 2.05 (3H, s, Me-5), 1.59, 1.29 (3H each, s, i-Pr), 0.90 (9H, s, t-Bu), 0.09 (6H, s, Me). Anal. Calcd for $C_{22}H_{38}N_2O_7Si$: C, 56.14; H, 8.14; N, 5.95. Found: C, 55.90; H, 8.09; N, 6.00.

5-O-Benzoyl-1,2-O-isopropylidene-3(R)-(2,4-dimethoxy-5-methylpyrimidin-6-ylmethyl)ribose (4) ---- Bu_4NF (1 M in THF, 16 ml) was added to a solution of 3 (7.52 g, 16 mmol) in THF (50 ml) at room temperature. After stirring for 10 min, the solvent was removed in vacuo and the residue was dissolved in pyridine (60 ml). BzCl (4.65 ml, 40 mmol) was added and the solution was stirred overnight at room temperature. Water was added to the solution and the solvent was removed in vacuo. The residual pyridine was removed by co-distillation with toluene, and the residue was dissolved in $CHCl_3$. The solution was washed successively with saturated $NaHCO_3$-H_2O, H_2O, and saturated NaCl-H_2O, and the organic layer was dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel (7.5x16.5 cm, 20-40% AcOEt in hexane). The eluate was concentrated to give **4** (6.98 g, 95%). Crystallization from EtOH gave an analytical sample, mp 153-154°C. MS m/z: 460 (M^+), 445 (M^+-Me). ^{1}H-NMR ($CDCl_3$): 8.13-8.08 (2H, m, Bz), 7.67-7.33 (3H, m, Bz), 6.04 (1H, s, HO-3'), 5.83 (1H, d, H-1', J= 3.66 Hz), 4.69-4.36 (3H, m, H-4',5'), 4.25 (1H, d, H-2'), 4.00, 3.94 (3H each, s, MeO), 2.89 (2H, brs, H-6'), 2.06 (3H, s, Me-5), 1.61, 1.32 (3H each, s, i-Pr). Anal. Calcd for $C_{23}H_{28}N_2O_8$: C, 59.99; H, 6.13; N, 6.08. Found: C, 59.90; H, 6.16; N, 6.09.

1,2-Di-O-acetyl-5-O-benzoyl-3(R)-(2,4-dimethoxy-5-methylpyrimidin-6-ylmethyl)ribose (5) ---- Compound **4** (6.87 g, 14.9 mmol) was dissolved in 90% trifluoroacetic acid (50 ml) and kept at room temperature for 90 min. The solution was concentrated in vacuo and the residual acid was removed by co-distillation with i-PrOH. The residue was treated with Ac_2O (5.75 ml) in CH_2Cl_2-Et_3N (5:1, 60 ml) at room temperature for 3.5 hr. The solution was diluted with $CHCl_3$, washed with saturated $NaHCO_3$, then with H_2O. The organic layer was dried over Na_2SO_4 and the solvent was removed. The residue was chromatographed on silica gel (7.7x17 cm, 40% AcOEt in hexane). The eluate was concentrated to give **5** (7.09 g, 95%) as a foam. MS m/z: 504 (M^+), 461 (M^+-Ac), 445 (M^+-AcO). ^{1}H-NMR ($CDCl_3$): 8.13-7.99 (2H, m, Bz), 7.59-7.35 (3H, m, Bz), 6.45, 6.23 (1H total, d each, H-1', J= 5.13 and 1.83 Hz), 5.22, 5.04 (1H total, d each, H-2'), 4.75-4.36 (3H, m, H-4',5'), 3.98, 3.95, 3.93, 3.92 (6H total, s each, MeO), 3.34, 3.00 (1H total, d each, H-6'a, $J_{a,b}$= 15.87 Hz), 2.90 (1H, d, H-6'b), 2.14, 2.11, 2.07, 2.05, 2.03, 1.96 (9H total, s each, AcO, Me-5).

2'-O-Acetyl-5'-O-benzoyl-O^4,5-dimethyl-6,3'-methanouridine (6) ---- $SnCl_4$ (1.3 ml, 11 mmol) was added to a solution of **5** (2.79 g, 5.5 mmol) in acetonitrile (60 ml) under cooling in an

ice-bath. The solution was stirred at room temperature for 4 hr, the solvent was removed in vacuo and the residue was poured into $CHCl_3$ and H_2O. The precipitate was filtered off through a celite bed and the filtered organic layer was dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel (3.3x23 cm, 1%-MeOH in $CHCl_3$). The eluate was concentrated and the residue was crystallized from EtOH to give **6** (1.53 g, 64%), mp 201-202°C. UV λmax (MeOH) nm: 283. MS m/z: 430 (M^+), 370 (M^+-AcO). ^{1}H-NMR ($CDCl_3$): 7.94-7.85 (2H, m, Bz), 7.67-7.28 (3H, m, Bz), 6.55 (1H, s, H-1'), 5.06 (1H, s, H-2'), 4.64-4.35 (3H, m, H-4',5'), 3.92 (3H, s, MeO), 3.39 (1H, d, H-6'a), $J_{a,b}$= 18.1 Hz), 3.29 (1H, s, HO-3'), 3.05 (1H, d, H-6'b), 2.22 (3H, s, AcO), 1.76 (3H, s, Me-5). Anal. Calcd for $C_{21}H_{22}N_2O_8.1/4H_2O$: C, 58.00; H, 5.21; N, 6.44. Found: C, 58.04; H, 5.34; N, 6.25.

2'-O-Acetyl-5'-O-benzoyl-O^4,5-dimethyl-3'-O-tetrahydrofuranyl-6,3'-methanouridine (7) ---- A mixture of **6** (1.2 g, 2.79 mmol), 2,3-dihydrofuran (0.42 ml, 5.55 mmol), and p-toluenesulfonic acid (30 mg) in dioxane (20 ml) was stirred for 22 hr at room temperature. The solution was neutralized by addition of anhydrous K_2CO_3, the precipitate was filtered off, and the filtrate was concentrated . The residue was dissolved in AcOEt, the solution was washed with H_2O, and the organic layer was dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel (3.2x15 cm, $CHCl_3$). The eluate was concentrated to leave **7** (1.19 g, 85%) as a foam. MS m/z: 500 (M^+), 430 (M^+-tetrahydrofuranyl(thf)). ^{1}H-NMR ($CDCl_3$): 7.94-7.89 (2H,m, Bz), 7.58-7.35 (3H, m, Bz), 6.57, 6.48 (1H total, s each, H-1'), 5.55, 5.35 (1H total, brd, H-2 of thf), 5.37, 5.29 (1H total, s, H-2'), 4.62-4.33 (3H, m, H-4',5'), 3.94 (3H, s, MeO), 3.91-3.80 (2H, m, H-5 of thf), 3.35, 3.29 (2H dd, H-6'a,b, $J_{a,b}$= 18.7 Hz), 2.19 (3H, s, AcO), 1.97-1.78 (4H, m, H-3,4 of thf), 1.78 (3H, s, Me-5).

5'-O-Benzoyl-O^4,5-dimethyl-3'-O-tetrahydrofuranyl-6,3'-methanouridine (8) ---- Compound **7** (1.19 g, 2.38 mmol) was dissolved in MeOH-Et_3N (10:1, 22 ml) and kept at room temperature for 3 hr. The solvent was removed in vacuo and the residue was chromatographed on silica gel (3.2x10 cm, 0-1% MeOH in $CHCl_3$). The eluate was concentrated to leave **8** (930 mg, 85%) as a foam. MS m/z: 458 (M^+), 388 (M^+-thf) ^{1}H-NMR ($CDCl_3$): 7.95-7.88 (2H, m, Bz), 7.58-7.35 (3H, m, Bz), 6.59, 6.51 (1H total, s, H-1'), 5.64, 5.52 (1H, brd, H-2 of thf), 4.77-4.34 (4H, m, HO-2', H-4',5'), 4.20-4.13 (1H, brs, H-2'), 4.02-3.89 (2H, m, H-5 of thf), 3.93 (3H, s, MeO), 3.25-3.06 (2H, m, H-6'a,b), 2.06-1.86 (4H, m, H-3,4 of thf), 1.77, 1.73 (3H total, s, Me-5).

5'-O-Benzoyl-O^4-methyl-3'-O-tetrahydrofuranyl-2'-O-imidazolylthiocarbonyl-6,3'-methanouridine (9) ---- A mixture of **8** (230 mg, 0.5 mmol) and thiocarbonyldiimidazole (200 mg, 1.0 mmol) in DMF (2 ml) was stirred at room temperature for 1 day. The solvent was removed in vacuo and the residue was partitioned between AcOEt and H_2O. The organic layer was separated, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (1.7x13 cm, $CHCl_3$). The eluate was concentrated to leave **9** (230 mg, 81%) as a foam. MS m/z: 568 (M^+), 498 (M^+-thf). ^{1}H-NMR ($CDCl_3$): 8.41-8.39 (1H, brs, H-2 of imidazolyl), 7.94-7.90 (2H, m, Bz), 7.69, 7.68 (1H total, brs, H-5 of imidazolyl), 7.60-7.37 (3H, m, Bz), 7.11 (1H, brs, H-4 of imidazolyl), 6.81, 6.77 (1H total, s, H-1'), 6.00, 5.86 (1H total, s, H-2'), 5.56, 5.39 (1H total, brd, H-2 of thf), 4.67-4.47 (3H, m, H-4',5'), 3.94 (3H, s, MeO), 3.94-3.69 (2H, m, H-5 of thf), 3.54 (1H, brd, H-6'a), 3.33, 3.23 (1H total, d, H-6'b), 1.96-1.77 (4H, m, H-3,4 of thf), 1.80, 1.73 (3H total, s, Me-5).

5'-O-Benzoyl-O^4-methyl-6,3'-methanothymidine (11) ---- A mixture of **9** (250 mg, 0.44 mmol), Bu_3SnH (0.35 ml, 1.30 mmol) and AIBN (10 mg) in toluene (5 ml) was heated under reflux for 1 hr. The solvent was removed in vacuo and the residue was chromatographed on silica gel (1.7x18 cm, 0-1% MeOH in $CHCl_3$). The eluate was concentrated to leave the product **10** (127 mg, 65%). This was used in the next step without further purification. Compound **10** (117 mg, 0.265 mmol) in 90% trifluoroacetic acid (5 ml) was stirred for 15 min at room temperature. The solvent was removed in vacuo and the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was dried over Na_2SO_4. The solvent was removed and the residue was crystallized from EtOH to give **11** (70 mg, 71%), mp 253-254°C. MS m/z: 372 (M^+). ^{1}H-NMR ($CDCl_3$): 7.94-7.90 (2H, m, Bz), 7.60-7.38 (3H, m, Bz), 6.72 (1H, d, H-1', J= 4.77 Hz), 4.52 (1H, dd, H-5'a, $J_{a,b}$= 12.09 Hz, $J_{4',5'a}$= 5.49 Hz), 4.40 (1H, dd, H-5'b, $J_{4',5'b}$= 4.77 Hz), 4.25 (1H, m, H-4'), 3.93 (3H, s, MeO), 3.28 (1H, dd, H-6'a, $J_{a,b}$= 18.32 Hz, $J_{2'a,6'a}$= 2.02 Hz), 3.00 (1H, d, H-6'b), 2.67 (1H, ddd, H-2'a, $J_{a,b}$= 11.36 Hz), 2.09 (1H, d, H-2'b), 1.79 (3H, s, Me-5). Anal. Calcd for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.06; H, 5.50; N, 7.56.

6.3'-Methanothymidine (12) ---- A solution of **11** (200 mg, 0.538 mmol) in 2N NaOH-dioxane (1:1, 10 ml) was stirred at 100 C for 15 min and then at room temperature for 30 min. The solution was neutralized by addition of Dowex 50W-X8 (H^+ form). The resin was filtered off, the filtrate was concentrated, and the residue was chromatographed on silica gel (1.7x8.5 cm, 2-4-8% MeOH in

$CHCl_3$). The eluate was concentrated to give **12** (104 mg, 76%). Analytically pure sample of **12** was obtained by crystallization from EtOH. mp 253-254°C. UV λmax (H_2O) nm (ε): 272 (10400). CD [θ] in H_2O: -14900 at 270 nm. MS m/z: 254 (M^+), 236 (M^+-18). ^{1}H-NMR (D_2O, sodium trimethylsilylpropanesulfonate): 6.42 (1H, d, H-1', $J_{1',2'a}$= 4.77 Hz), 3.98 (1H, m, H-4', $J_{4',5'a}$= 3.26 Hz, $J_{4',5'b}$= 6.41 Hz), 3.84 (1H, dd, H-5'a, $J_{a,b}$= 12.27 Hz), 3.62 (1H, dd, H-5'b), 3.23 (1H, brdd, H-6'a, $J_{a,b}$= 18.51 Hz), 3.03 (1H, brd, H-6'b), 2.61 (1H, ddd, H-2'a, $J_{a,b}$= 11.72 Hz, $J_{2'a,6'a}$= 2.57 Hz), 2.15 (1H, d, H-2'b), 1.84 (3H, s, Me-5). Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.55; N, 11.02. Found: C, 51.82; H, 5.51; N, 11.03.

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