Synthesis of 6,6′-Cyclo-5′,6′-dideoxy-1-(β-D-allofuranosyl)cytosine and Related Nucleosides (Nucleosides and Nucleotides. LXXXVIII)\(^1\)

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A new synthetic route to 6,6′-cyclo-5′,6′-dideoxy-1-(β-D-allofuranosyl)uracil, -cytosine, and -4-thiouracil is described. The method involves a base-catalyzed condensation of 2,4-dimethoxy-6-methylpyrimidine and 1-O-methyl-2,3-O-isopropylidene-β-D-ribopentofuranosylidene, followed by an intramolecular glycosylation, and derivatization of the base moiety. The relationship of the sign of the circular dichroism (CD) spectra of carbon-bridged cyclopentimidine nucleosides to the glycosyl torsion angle is discussed.

Keywords 6,6′-cyclo-5′,6′-dideoxy-1-(β-D-allofuranosyl)cytosine; carbon-bridged cyclonucleoside; nucleoside conformation; ceric chloride; Peterson olefination; CD spectra; NMR

Carbon-bridged cyclonucleosides (C-cyclonucleosides) have served as conformational probes for stereochemical investigation of nucleosides and nucleotides.\(^2\) We have been focusing on the synthesis of C-cyclonucleosides starting from naturally occurring nucleosides. However, other access to C-cyclonucleosides is needed, especially for largescale preparation. We have recently reported the synthesis of 6,3′-methano derivatives of uridine, cytidine, 2′-deoxyctydine,\(^3\) and thymidine\(^4\) by condensation of a 3-pentofuranose and a 6-methylpyrimidine followed by an intramolecular glycosylation as the key step.

We describe here a new route to the synthesis of 6,6′-cyclo-5′,6′-dideoxyhexofuranosyluracil\(^5\) and related nucleosides\(^6\) starting from a ribose-5-aldehyde and a 6-methylpyrimidine. We also summarize the discussion on the relationship of the circular dichroism (CD) spectral pattern and the glycosyl torsion angle (\(\chi\)) of C-cyclonucleoside nucleosides.\(^7\)

Treatment of the lithio derivative of 6-methyl-2,4-dimethoxy pyrimidine (1)\(^3\) with methyl 2,3-O-isopropylidene-β-D-ribopentodialdo-1,4-furanose\(^8\) (2) at -40 °C gave the adduct (3) in 65% yield as a diastereomeric mixture.

The 5-hydroxy group of 3 was removed by way of conversion to the 5-imidazolylthiocarbonate and successive reduction with tributyltin hydride to give 4 in 59% yield. The removal of the 5-hydroxy group of 3 was found to be necessary; with this hydroxy group (or protected hydroxy group) present, the dehydration took place in a later step involving the intramolecular glycosylation (data not shown). Since this was the case, another route to the preparation of 4 was to perform the Peterson reaction\(^9\) with 1 and 2 followed by hydrogenation of the olefinic bond.

Thus, 1 was converted to the 5-trimethylsilylmethylpyrimidine (5), which was condensed with 2 in the presence of lithium diisopropylamide (LDA) and ceric chloride.\(^{9c,d}\) The product was a mixture of 6 and the silanol (6A) as judged by nuclear magnetic resonance (NMR) measurement. The mixture was then treated with potassium hydride in tetrahydrofuran (THF) to ensure dehydration. However, the product, isolated as crystalline form, turned out to be a condensed pyrimidopyridine derivative (7). The structure of 7 was confirmed by NMR and mass spectrum (MS) measurement as well as by elemental analysis (see

![Chart 1](chart1.png)

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Experimental). The dissociation of the H-4 of 6 by the strong base must have initiated the nucleophilic attack of N-1 on C-3.

Therefore, the elimination of the silanol (6A) was promoted by acetylation of the hydroxy group of 6A in the mixture with 6 by treatment with acetyl chloride and disopropylethylamine, followed by treatment with tetrabutylammonium fluoride to furnish the olefin (6) as an E,Z mixture (74% yield, 2.2:1). Compound 6 could be separated by chromatography to give 6-E and 6-Z, the structure of each being confirmed by NMR and mass (MS) spectral analyses. Compound 6 was hydrogenated over Pd-carbon to give 4 (86% yield) as a foam. The physical properties of the product (4) were identical with those of the product obtained by the aforementioned route. This approach is superior to the other in that it eliminates a somewhat laborious separation of tributyltin compounds formed in the deoxygenation step of the former procedure.

Compound 4 was next subjected to acid hydrolysis to remove the sugar-protecting group by treatment with trifluoroacetic acid, then the hydrolyzate was acetylated to give the tri-O-acetate (8). Intramolecular glycosylation of 8 by treatment with stannic chloride\(^{10}\) in acetonitrile at room temperature gave the product (9) as a foam. The ultraviolet (UV), MS and NMR data were consistent with the structure 9. The "endo"-puckering of the carbon bridge (i.e., gauche-gauche conformation at C-5') of 9 was confirmed by an nuclear Overhauser effect (NOE) experiment showing NOE between H-3' and H-6' (3.6%), and H-3' and H-5' (2.7%), respectively. Compound 9 was converted to the uridine, cytidine and 4-thiouridine counterparts by the following procedures.

Deprotection of 9 by treatment with aqueous sodium hydroxide in dioxane afforded the cyclouridine (10) as a foam; the physical data were identical with those of an authentic sample.\(^{5}\) Treatment of 9 with methanolic ammonia in a stainless steel tube at 100 °C overnight afforded the cycloctydine (11) which was crystallized as the hydrochloride salt. Treatment of 9 with liquid hydrogen sulfide in pyridine\(^{11}\) for 3 d at 60 °C was effective to convert the 4-methoxy group to the 4-thio group, to give the di-O-acetate of the cyclo-4-thiouridine (12) in crystalline form. Deacetylation of 12 with methanolic triethylamine at room temperature furnished the cyclo-4-thiouridine (13).

The procedure described here seems to be a versatile alternative method for the synthesis of pyrimidine nucleosides fixed in an anti form by one methylene bridge between the 5'- and 6-positions.

We shall next consider the features of the CD spectra of 6,6'-cyctopyrimidine nucleosides in relation to those of other cyclouridines. As we have discussed in previous papers,\(^{3,12}\) the sign and magnitude of the CD spectra of cyclouridines are a function of their glycosyl torsion angle, \(\chi\), for O1'-C1'-N1'-C6'. Whereas the cyclouridines fixed by a 6,5'-bridge\(^{2,13}\) exhibited strong positive CD bands (\(\theta = +10000 - +19000\)) around their main absorption regions, the cyclouridines bridged by 6,3'-methano,\(^{3,4,14}\) 6,2'-methano,\(^{15}\) and 6,2'-ethano\(^{12}\) linkages showed strong negative bands (\(\theta = -18000 - -20000\)). The CD spectra of 6,6'-cyclouridine\(^{3}\) (10) showed an intermediate pattern having a negative band (\(\theta = 240 \text{ nm}, -10300\)) at a shorter wavelength region than the main absorption region (UV \(\lambda_{\text{max}}\) 266 nm). Moreover, in the case of the 2,3'-O-isopropylidene derivative of 9, a weak positive band at 275 nm (\(\theta = +2900\)) was observed along with the negative band at 245 nm (\(\theta = -13000\)).\(^{3}\)

It is evident that the glycosyl torsion angle of 10 is intermediate between that of 6,5'-cyclo and 6,3'-methano derivatives, since the stable conformation of 10 at the 5'-position is expected to be gauche-gauche, as depicted in Fig. 1, on the basis of the NOE experiment of 9 as well as the X-ray analysis of 10. As the conformation at the 4'-5'-6'-6' linkage of 10 (that reflects the \(\chi\)-value) is expected to be more flexible than in the rest of the cyclonucleosides, the difference between the \(\theta\) values of 10 and its isopropylidene derivative may be due to a slight change of the glycosyl torsion angle.

It is therefore of interest to measure the CD spectra of...
other 6,6'-cyclopyrimidine nucleosides in addition to 10. The cyclocytidine (11) in neutral solution showed no extreme of the CD band around the main absorption region (275 nm) and showed negative ellipticity at the shorter wavelength region around 218 nm (θ = −29000). By contrast, the protonated form of 11 showed a weak positive band at 275 nm (θ = +43000). The cyclo-4-ribouridine (13) exhibited a weak negative peak at the main absorption region (θ = −1600 across 330 nm). Thus, all the 6,6'-cyclopyrimidine nucleosides showed very weak CD bands at their main absorption regions with either positive or negative sign, probably because their χ-values are very close to the transition angle for the reversal of the sign of the CD bands.

Therefore, it can be stated, in general, that the usual pyrimidine nucleosides of anti configuration show positive CD bands like 6,5'-cyclocytidine (θ = +38.1°), and have the average glycosyl torsion angle smaller than 63° which is the measured value of 10 by the X-ray analysis [166]. Pyrimidine nucleosides of anti configuration having the glycosyl torsion angle greater than that will show negative CD bands like 6,3'-methanouridine (θ = −88.1°) and 2'-deoxy-6,2'-ethanouridine (θ = −88.1°). Therefore, the transition glycosyl torsion angle will be around 60°. If the pyrimidine nucleosides adopt syn-conformation, there will be another set of torsion angle region showing positive and negative CD bands.

Experimental

Melting points were determined on a Yanagimoto M-3 micro melting point apparatus and are uncorrected. The 1H NMR spectra were recorded on a JEOL FX-100FT or FX-200FT spectrometer in CDC13, D2O, or DMSO-d6 as the 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). All exchangeable protons were confirmed by addition of D2O. UV spectra were recorded with a Shimadzu UV-240 spectrophotometer. MS were measured on a JEOL D-300 spectrometer. CD spectra were recorded on a JASCO J-500A spectropolarimeter at room temperature. Thin layer chromatography (TLC) was carried out on Merck pre-coated plates 60F254. Silica gel for column chromatography was SIL-60A 230/70 mesh.

Methyl 5-Deoxy-5-(2,4-dimethoxyphosphinyl-6-yl)methyl-2,3-O-isopropylidene-β-D-ribofuranoside (3) 2,4-Dimethoxy-6-methylpyrimidine (1, 2.48 g, 16.1 mmol) was dissolved in THF (100 ml) and the solution was cooled to −48°C. BuLi (11.5 ml of 1.34 M solution in hexane, 1.5 eq) was then added dropwise, and the solution was kept for 30 min with stirring in an Ar atmosphere. Compound 2 (3.26 g, 16.1 mmol) in THF (20 ml) was slowly added to the above solution through a syringe and the whole was stirred for 2 h at −43°C. After neutralization by addition of AcOH, the solution was brought to room temperature and the solvent was removed in vacuo.

The residue was partitioned between AcOEt and H2O. The organic layer was separated, dried over Na2SO4 and filtered, and the filtrate was concentrated. This was applied to a column of silica gel (6.6 x 12 cm) and the column was eluted with 10—20% AcOEt in hexane. The eluate containing the product was concentrated to leave 3 as a syrup (3.7 g, 65%). UV λmax nm: 260. MS m/z: 356 (M+), 341, 325, 183, 154. 1H-NMR (CDCl3): 6.29 (1H, s, H-5), 4.79 (2H, m, H-1 and H-2), 4.59 (1H, d, H-3, J3,1 = 6.6 Hz), 4.11 (1H, d, H-4), J4,6 = 6.6 Hz), 4.05—3.97 (1H, m, H-5'), 3.97, 3.96 (each s, Me-O and 2), 3.29 (3H, s, Me-O), 3.29 (3H, s, Me-O), 2.94 (1H, dd, H-6′, J6′,8 = 14.7 Hz, J8,3 = 3.7 Hz), 2.77 (1H, dd, H-6b, J6b,8 = 7.7 Hz), 1.48, 1.33 (3H each, s, Me-C).
for 2.5 h. The mixture was taken from the cool bath, and mixed with saturated NaHCO₃ solution. The precipitate was filtered off through a celite bed, and washed with ether three or four times in a small vol. The combined ether solution was dried (Na₂SO₄), and the solvent was removed in vacuo. The residue was taken up in CH₂Cl₂ (80 ml), diisopropylamine (2 ml, 11 mmol) and acetyl chloride (0.71 ml, 10 mmol) were added, and the whole was stirred overnight at room temperature. Saturated NaCl (aq) solution was added and the mixture was extracted with CHCl₃. The organic layer was dried (Na₂SO₄) and the solvent was removed in vacuo. The residue was dissolved in THF (50 ml), Bu₄NF (7 ml of 1 M in THF) was added and the whole was stirred for 20 min at room temperature. The solvent was removed in vacuo and the residue was dissolved in ether. The other solution was washed twice with H₂O and saturated NaCl, dried (Na₂SO₄), and concentrated. The residue was chromatographed on silica gel (49.5 × 13.5 cm, eluted with 10–20% AcOEt in hexane). The eluate was concentrated to leave 6 (2.5 g, 74%), E: Z = 2:2:1, contaminated with a trace of 1. A portion of 6 was recrystallized on silica gel with 5% AcOEt in hexane to separate 6 as a less polar component and E as a more polar component.

Physical Properties of 6-2. UV (MeCN) nm: 285, 338 (M1)*, 323, 210, 195. Exact MS: Caled for 338.14786. Found: 338.14827. [1H-NMR (CDCl₃)] (δ, s, H-5): 6.22 (1H, d, H-6', J₁₂ = 11.7 Hz, J₁₁ = 11.1 Hz), 6.13 (1H, d, H-4'), 6.04 (1H, d, H-5', J₁₂ = 8.1 Hz), 5.04 (1H, d, H-2'), 4.28 (1H, d, H-3'), 5.22 (1H, s, J₁₁ = 5.9 Hz), 4.06, 3.96 (3H each, s, Me-O-2 and 4), 3.41 (3H, s, Me-O1). 13C (1H, s, Me-C).

1.5. 6-5-Oxy-2,4-(dimethoxytrimethylsilanyloxy)-1,2,3-tri-0-acetyl-β-d-fructofuranose (Compound 4) (1.28 g, 3.76 mmol) dissolved in trifluoroacetic acid (70%, 10 ml) and the mixture was stirred for 4 h. The solvent was removed in vacuo and the acid residue was removed by co-distillation with toluene three times. The residue was taken up in acetonitrile and to this solution, Ac₂O (3 ml) and Et₃N (12 ml) were added. The mixture was stirred overnight at room temperature. The solvent was removed and the residue was partitioned between AcOEt and H₂O. The organic layer was dried (Na₂SO₄) and concentrated, and the residue was chromatographed on silica gel (2.8 × 16 cm, eluted with 20–30% AcOEt in hexane). The eluate was concentrated to leave 8 (111 g, 72%) as a foam. MS m/z: 412 (M⁺), 293, 251, 154. [1H-NMR (CDCl₃)] (δ, s, H-5): 6.14 (1H, d, H-1', J₁₂ = 10.1 Hz), 5.34 (1H, dd, H-2', J₁₂ = 4.6 Hz, J₁₁ = 5.2 Hz, 1H, dd, H-3', J₁₂ = 11.2 Hz), 4.29–4.01 (1H, m, H-4'), 3.97, 3.95 (3H each, s, Me-O-2 and 4), 2.82–2.63 (2H, m, H-5'), 2.29–1.86 (2H, m, H-6'), 1.22–1.05 (3H each, s, Me-C).

3.2. 6-5-Oxy-2,4-(dimethoxytrimethylsilanyloxy)-1,2,3,4-tetrahydro-β-d-fructofuranose (Compound 4) (1.11 g, 2.69 mmol) in acetonitrile (10 ml) was added to a solution of SnCl₄ (0.38 ml, 3.32 mmol) in acetonitrile (30 ml) in an ice-water bath. The mixture was stirred at room temperature for 2.5 h. After the removal of the solvent in vacuo, the residue was taken up in CHCl₃, then saturated NaHCO₃ solution (50 ml) was added, and the mixture was stirred vigorously. The precipitate was filtered off through a celite bed and the organic layer was separated. The aqueous layer was neutralized by addition of 2N HCl, then extracted with CHCl₃ several times. The combined organic layer was dried (Na₂SO₄) and the solvent was removed in vacuo. The residue was chromatographed on silica gel (2.4 × 15 cm, eluted with 1% EtOH in CHCl₃) to give 9 (600 mm, 66%) as a foam. UV (MeCN) nm: 280, 338 (M*) (279), 166, 140. Exact MS: Caled for 338.1144. Found: 338.1127. [1H-NMR (CDCl₃)] (δ, t, J = 8.0 Hz): 7.04 (1H, d, H-2', J₁₂ = 8.1 Hz, 1H, s, H-5), 5.49 (1H, dd, H-2', J₁₁ = 6.2 Hz, J₁₂ = 5.3 Hz), 5.48 (1H, d, H-3'), 4.56 (1H, t, H-4'), 3.77 (3H, s, Me-O-4), 2.89 (3H, s, H-5'), 4.66 (4H, d, H-6, J₁₂ = 6.1 Hz), 4.16–4.08 (4H, m), 2.89 (4H, d, H-6, J₁₂ = 11.7 Hz), 2.17–2.01 (2H, m, H-5'), 2.14, 2.13 (3H each, s, Me-C₃).


16) Personal communication from Dr. Y. Yamagata, Osaka University.