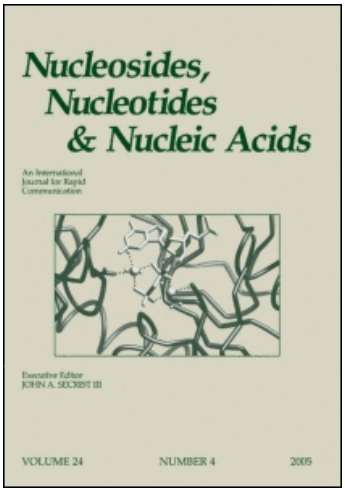

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Synthesis of 2'-Deoxy-6,2'-Ethano-Cyclouridine[1] (Nucleosides and Nucleotides. Part 57)

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SYNTHESIS OF 2'-DEOXY-6,2'-ETHANO-CYCLOURIDINE[1] (NUCLEOSIDES AND NUCLEOTIDES. PART 57).

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ABSTRACT

Synthesis of a carbon-bridged cyclouridine, 2'-deoxy-6,2'-ethano-cyclouridine, was accomplished starting from a 2'-ketouridine via the 2'-deoxy-2'-iodoethyl-5-chlorouridine derivative through a radical cyclization.

In our continuing studies on the synthesis of carbon-bridged cyclonucleosides we have reported the synthesis of 5'-deoxy-6,5'-cyclouridine[2], 5'-deoxy-6,5'-methano-cyclouridine[3], and 2',3'-dideoxy-6,3'-methano-cyclouridine[4] . For the systematic studies of carbon-bridged uridine derivatives, cyclonucleosides fixed between 6 and 2' position would be required. Our previous attempt at the preparation of 6,2'-methano-cyclouridine using the 2'-nitromethylene derivative of uridine resulted in a formation of a pyrrolopyrimidine compound[5]. We present here the synthesis of 2'-deoxy-6,2'-ethano-cyclouridine[6].

As has been described[5], the Moffatt oxidation of 3',5'-di-O-(tetraisopropyldisiloxane-1,3-diyl)uridine (1)[7] gave the 2'-ketouridine (2). Oxidation of 1 with DMSO and oxalyl chloride[8] in methylene chloride gave 2 in a better yield. Treatment of 2 with ethoxycarbonylmethylenetriphenylphosphorane afforded the Wittig product (3) as a foam in almost quantitative yield. Reduction of 3 with sodium borohydride in ethanol for relatively short period gave the 2'-deoxy-2'(S)-ethoxycarbonylmethyluridine (4). Although the

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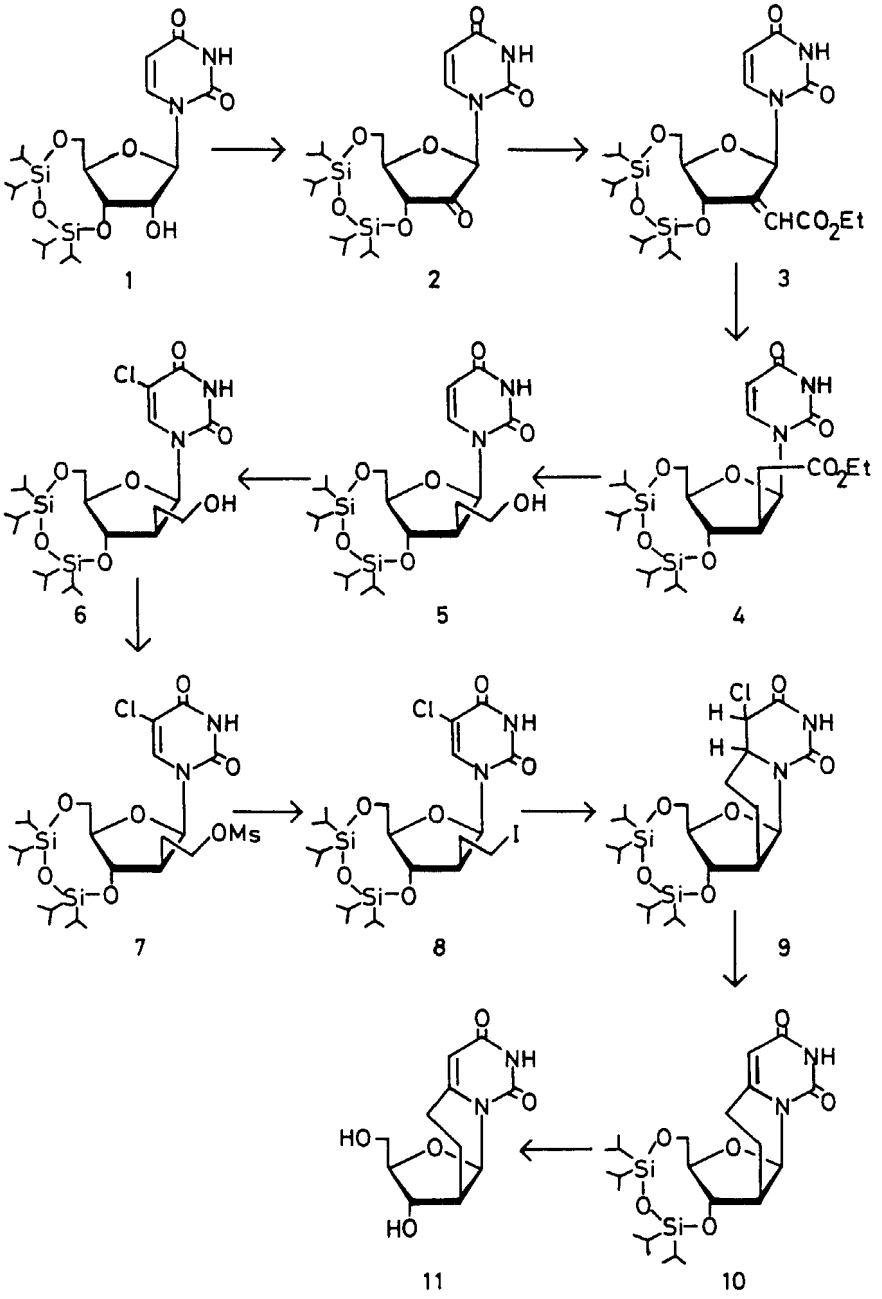

stereochemistry of the 2'-position of 4 was not fully established at this stage, it was confirmed by the later conversion. The formation of any amount of the (R)-epimer was not observed, probably due to the stereospecific hydride addition to 3 from the less hindered side. Further treatment of 4 with lithium borohydride in tetrahydrofuran gave the 2'(S)-hydroxyethyl derivative (5) in a crystalline form. Compound 5 was chlorinated by N-chlorosuccinimide to give the 5-chloro derivative (6), which was treated with methanesulfonyl chloride to furnish crystalline 2'-mesyloxyethyl derivative (7). Treatment of 7 with lithium iodide in 2-butanone gave the crystalline 2'-iodoethyl derivative (8), a precursor of the radical cyclization.

The dropwise addition of a mixture of tri-n-butyltin hydride and azobisisobutyronitrile (AIBN) to a refluxing solution of 8 in benzene under argon atmosphere gave the cyclo-dihydro intermediate (9), which was dehydrochlorinated by treatment with 1,5-diazabicyclo[5.4.0]undecene (DBU) in benzene. The physical data of the product obtained in a crystalline form satisfied for the structure 10. Deprotection of 10 with tetra-n-butylammonium fluoride furnished 2'-deoxy-6,2'-ethano-cyclouridine (11). This was crystallized from ethanol to furnish a suitable sample for the X-ray diffraction analysis. The molar ellipticity of 11 at its main absorption region resembled that of 2',3'-dideoxy-6,3'-methano-cyclouridine[4]. This would suggest that the conformation of the new six-membered ring should be C-7'-endo, the methylene group connected to the C-6 position being on the ribose ring, so that the glycosyl torsion angle of 11 becomes close to that of the 6,3'-methano-cyclo compound. In fact, the result of the X-ray diffraction analysis was consistent with this assumption, which will be reported separately[9].

EXPERIMENTAL

Melting points were determined on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. The ^{1}H-NMR

spectra were recorded on a JEOL FX-100FT or FX-200FT spectrometer in $CDCl_3$ or DMSO-d_6 as the solvents with tetramethylsilane as internal standard. Chemical shifts were reported in ppm (δ) and signals were described as s (singlet), d (doublet), t (triplet), m (multiplet), or b (broad). All exchangeable protons were confirmed by addition of D_2O. Ultraviolet absorption spectra (UV) were recorded with a Shimadzu UV-240 spectrophotometer. Mass spectra (MS) were measured on a JEOL D-300 spectrometer. Circular dichroism spectra (CD) were recorded on a JASCO J-40 spectropolarimeter at room temperature. Thin layer chromatography was carried out on Merck pre-coated plates $60F_{254}$. Silica gel for column chromatography was Wako gel C-200.

2'-Keto-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)uridine (2)---- To a solution of oxalyl chloride (4.5 mL) in 150 mL of CH_2Cl_2 cooled at -70°C was added dropwise a solution of DMSO (8.2 mL) in 70 mL of CH_2Cl_2 over a period of 20 min. After stirring for 30 min, 1 (19.5 g in 80 mL of CH_2Cl_2) was added dropwise to the solution, and the mixture was stirred for 30 min. The solution was neutralized by dropwise addition of 33.5 mL of triethylamine and, after standing at room temperature, H_2O (200 mL) was added. The organic layer was separated, washed with H_2O, passed through a Whatman 1PS filter paper, and concentrated. The residue was crystallized from AcOEt-hexane to give 14.8 g (77.5%) of 2, mp 178-178.5°C. MS (m/z): 484 (M^+), 441 (M-iPr). NMR (200 MHz, $CDCl_3$): 8.72 (bs, 1, HN^3), 7.12 (d, 1, H-6), 5.75 (dd, 1, H-5), 5.04 (d, 1, H-3'), 4.99 (s, 1, H-1'), 4.13 (d, 2, H-5'), 3.98-3.91 (m, 1, H-4'), 1.09 (m, 28, iPr). Anal Calcd for $C_{21}H_{36}N_2O_7Si_2$: C, 52.03; H, 7.53 ; N, 5.78. Found: C, 52.03; H, 7.53; N, 5.74. This compound was identical with that obtained by the previous procedure[5], except the mp.

2'-Deoxy-2'-ethoxycarbonylmethylidene-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)uridine (3)---- Compound 2 (14.5 g) was dissolved in 500 mL of CH_2Cl_2 and ethoxycarbonylmethylenetriphenylphosphorane (11.5 g, 1.1 eq.) was added to the solution. After 30 min stirring, the solvent

was removed in vacuo and the residue was applied to a silica gel column and eluted with 10%-AcOEt in $CHCl_3$. The eluate wascollected and the solvent was evaporated to leave 16.3 g (97.5%) of 3 as a foam. MS (m/z): 511 (M-iPr). NMR (200 MHz, $CDCl_3$): 8.16 (bs, 1, HN^3), 7.23 (d, 1, H-6), 6.45 (dd, 1, H-2''), 6.16 (dd, 1, H-1'), 5.65 (dd, 1, H-5), 5.36-5.30 (m, 1, H-3'), 4.16 (q, 2, ethyl), 4.07 (d, 2, H-5'), 3.69-3.60 (m, 1, H-4'), 1.27 (t, 3, ethyl). $J_{5,3}$= 2.2 Hz, $J_{5,6}$= 7.8 Hz, $J_{1',2''}$= 1.95 Hz, $J_{1',3'}$= 2.44 Hz, $J_{2'',3'}$= 1.95 Hz, $J_{3',4'}$= 8.3 Hz, $J_{4',5'}$= 6.0 Hz.

2'-Deoxy-2'(S)-ethoxycarbonylmethyl-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)uridine (4)---- To a solution of 3 (8.3 g) in 300 mL of abs.EtOH was added 3.75 g of $NaBH_4$. Addition of $NaBH_4$ (3.75 g) was repeated twice in every 90 min and, after 6 hr from the initial addition, the solution was neutralized with AcOH. The solvent was removed in vacuo and the residue was partitioned between AcOEt-H_2O. The organic layer was passed through a Whatman 1PS paper and concentrated. The residue dissolved in $CHCl_3$ was applied to a column of silica gel and eluted with 10% AcOEt-$CHCl_3$. The eluate was concentrated to leave 4 (4.8 g, 57.7%) as a foam. MS (m/z): 513 (M-iPr). NMR (200 MHz, $CDCl_3$): 8.34 (bs, 1, HN^3), 7.70 (d, 1, H-6), 6.20 (d, 1, H-1'), 5.68 (dd, 1, H-5), 4.35-4.0 (m, 4, H-5' and Et), 3.84 (m, 1, H-4'), 3.23-3.10 (m, 1, H-2'), 2.61 (dd, 1, H-2''a), 2.22 (dd, 1, H-2''b), 1.25 (t, 3, Et), 1.10 (m, iPr). $J_{5,6}$= 8.3 Hz, $J_{1',2'}$= 7.3 Hz, $J_{2',2''a}$= 4.4 Hz, $J_{2',2''b}$= 9.7 Hz, $J_{2''a,b}$= 15.6 Hz.

2'-Deoxy-2'(S)-(2-hydroxyethyl)-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)uridine (5)---- Compound 4 (5.5 g) in 150 mL of tetrahydrofuran was treated with 1.1 g (10 eq.) of $LiBH_4$ at 60°C overnight. After neutralization of the solution with 1 N HCl, the solvent was removed in vacuo and the residue was partitioned between AcOEt-H_2O. The organic layer was separated, passed through a Whatman 1 PS filter paper, and evaporated. The residue was crystallized from n-hexane-AcOEt to give 3.0 g (58.3 %) of 5, mp 162.5-

163.0°C. MS (m/z): 471 (M-iPr). NMR (200 MHz, $CDCl_3$): 8.30 (bs, 1, HN^3), 7.84 (d, 1, H-6), 6.31 (d, 1, H-1'), 5.66 (dd, 1, H-5), 4.14-4.06 (m, 3, H-3',5'), 3.78-3.73 (m, 3, H-4',7'), 2.74-2.71 (m, 1, H-2'), 1.80-1.40 (m, 2, H-6'), 1.05 (m, iPr). H-7' denotes for the methylene protons of the 2'-hydroxyethyl group attached by a hydroxyl group, and H-6' denotes for those of methylene connected to C-2'. $J_{5,6}$= 7.8 Hz, $J_{1',2'}$= 7.0 Hz. Anal. Calcd for $C_{23}H_{42}N_2O_7Si_2$: C, 53.67; H, 8.22; N, 5.44. Found: C, 53.58; H, 7.97; N, 5.30.

2'-Deoxy-2'(S)-(2-hydroxyethyl)-3',5'-O-(tetraisopropyl-disiloxane-1,3-diyl)-5-chlorouridine (6)---- Compound 5 (1.2 g) and N-chlorosuccinimide (0.95 g, 3 eq.) were dissolved in a mixture of dimethylformamide and AcOH (15 mL each), and were heated at 50 C under stirring for 8 hr. After evaporation of the solvent the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was separated and applied to a column of silica gel. The eluate with 1.5% MeOH in $CHCl_3$ was concentrated to leave 6 (0.75 g, 55.6 %) as a foam. MS (m/z): 507, 505 (M-iPr). UV max (MeOH): 275 nm. NMR (200 MHz, $CDCl_3$): 9.23 (bs, 1, HN^3), 7.93 (s, 1, H-6), 6.26 (d, 1, H-1'), 4.20-4.06 (m, 3, H-3',5'), 3.78-3.70 (m, 3, H-4',7'), 2.36 (m, 1, H-2'), 1.66 (m, 2, H-6'), 1.10 (m, iPr).

2'-Deoxy-2'(S)-(2-methanesulfonyloxyethyl)-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-5-chlorouridine (7)---- Compound 6 (1.68 g) and MsCl (0.3 mL, 1.25 eq.) were dissolved in 40 mL of pyridine and the solution was stirred for 1 hr at room temperature. The solvent was removed in vacuo and the residue was partitioned between AcOEt-H_2O. The organic layer was separated and the residue was dissolved in $CHCl_3$, which was applied to a column of silica gel. The eluate with 1% MeOH in $CHCl_3$ was concentrated and the residue was crystallized from n-hexane-AcOEt to give 1.68 g (86%) of 7, mp 165.5-166°C. MS (m/z): 584 (M-iPr). Anal. Calcd for $C_{24}H_{43}ClN_2O_9SSi_2$: C, 45.95; H, 6.90; Cl, 5.65; N, 4.46; S, 5.11. Found: C, 46.28; H, 6.86; Cl, 5.86; N, 4.44; S, 5.13.

2'-Deoxy-2'(S)-(2-iodoethyl)-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-5-chlorouridine (8)----Compound 7 (1.64 g) and LiI (0.7 g, 2 eq.) were dissolved in 45 mL of 2-butanone and the mixture was heated for 20 min under reflux. The precipitate was filtered off and the filtrate was concentrated. The residue was partitioned between AcOEt-H_2O and the organic layer was washed with sodium thiosulfate solution, and with H_2O, and passed through a Whatman 1 PS filter paper. The solvent was evaoporated and the residue was crystallized from EtOH-n-hexane to give 1.1 g (65%) of 8, mp 189-189.5°C. MS (m/z): 617, 615 (M-iPr). Anal. Calcd for $C_{23}H_{40}ClIN_2O_6Si_2$: C, 41.91; H, 6.12; Cl, 5.38; I, 19.26; N, 4.25. Found: C, 41.91; H, 6.16; Cl, 5.48; I, 19.57; N, 4.08.

2'-Deoxy-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-6,2'-ethano-cyclo-5-chloro-5,6-dihydrouridine (9)---- Compound 8 (720 mg) was dissolved in 60 mL of benzene in Ar atmosphere. To the refluxing solution a mixture of tri-n-butyltin hydride (0.36 mL, 1.25 eq.) and AIBN (80 mg) in 15 mL of benzene was added dropwise over a period of 45 min. After addition of the reagent the solution was refluxed for an additional 35 min. After evaporation of the solvent, the residue was partitioned between CH_3CN and n-hexane. The CH_3CN layer was separated and the solvent was evaporated to leave 0.54 g (94%) of 9 as a foam. This was used for the next step without further purification.

2'-Deoxy-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-6,2'-ethano-cyclouridine (10)---- Compound 9 (0.53 g) and DBU (0.45 mL) in benzene (15 mL) were heated for 2.5 hr under reflux. After addition of AcOH to neutralize the solution, the solvent was evaporated and the residue was taken up in $CHCl_3$. This was applied to a column of silica gel. The eluate with 20 % AcOEt in $CHCl_3$ was evaporated and the residue was crystallized from n-hexane to give 0.36 g (73%) of 10, mp 201-202°C. MS (m/z): 454 (M-iPr), UV λmax (MeOH): 260 nm. NMR (200MHz, $CDCl_3$): 8.05 (bs, 1, HN^3), 6.26 (d, 1, H-1'), 5.52 (s, 1, H-5), 4.24 (dd, 1, H-3'), 4.07

(dd, 1, H-5'a), 3.90 (dd, 1, H-5'b), 3.73 (m, 1, H-4'), 2.68-2.65 (m, 3, H-2', 7'), 1.88 (m, 2, H-6'), 1.07 (m, 28, iPr). $J_{1',2'}$= 7.8 Hz, $J_{2',3'}$= 6.34 Hz, $J_{3',4'}$= 6.34 Hz, $J_{4',5'a}$= 3.4 Hz, $J_{4',5'b}$= 5.4 Hz, $J_{5'a,b}$= 7.9 Hz. Anal. Calcd for $C_{23}H_{40}N_2O_6Si_2$: C, 55.61; H, 8.12; N, 5.64. Found: C, 55.43; H, 8.20; N, 5.56.

2'-Deoxy-6,2'-ethano-cyclouridine (11)---- Compound 10 (40 mg) was dissolved in 0.1 mL of tetrahydrofuran and tetra-n-butylammonium fluoride (in tetrahydrofuran, 2 eq.) was added. After stirring for 10 min, the solvent was removed in vacuo and the residue was partitioned between $CHCl_3$ and H_2O. The aqueous layer was extracted three times with $CHCl_3$ and was concentrated. The residue was dissolved in a small volume of MeOH and applied to a preparative TLC plate, and developed with MeOH-$CHCl_3$ (1:5). The appropriate band was extracted with EtOH-$CHCl_3$ (1:1) and the solvent was removed. The residue was crystallized from EtOH to give 19 mg of 11 (93%), mp 219-221°C. MS (m/z): 254 (M^+). UV λmax (H_2O): 262 nm; ε, 12300. CD in H_2O: 261 nm (θ= -19400). NMR (200 MHz, pyridine-d_5-D_2O): 6.66 (d, 1, H-1'), 5.61 (s, 1, H-5), 4.59 (dd, 1, H-3'), 4.20 (m, 3, H-4',5'), 2.87 (m, 1, H-2'), 2.76 (dd, 1, H-7'a), 2.38 (m, 1, H-7'b), 2.00 (m, 1, H-6'a), 1.65 (m, 1, H-6'b). $J_{1',2'}$= 7.3 Hz, $J_{2',3'}$= 5.4 Hz, $J_{3',4'}$= 6 Hz, $J_{7'a,b}$= 15.6 Hz, $J_{6'a,b}$= 18.6 Hz. Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.97; H,5.55; N, 11.02. Found: C, 51.97; H, 5.51; N, 10.93.

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