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SYNTHESES OF 1-(5-DEOXY-β-D-*arabino*-HEXOFURANOSYL)CYTOSINE

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ABSTRACT

1-(5-Deoxy-β-D-*arabino*-hexofuranosyl)cytosine (4′-homoara-C) (**11**), a higher homolog of the antileukemic agent ara-C (1-β-D-arabinofuranosylcytosine), was prepared by two independent routes. The first one involved the inversion of configuration at C-2′ of the D-*ribo* epimer (1-(5-deoxy-β-D-*ribo*-hexofuranosyl)cytosine, 4′-homocytidine) by the diphenylcarbonate technique; the 5-deoxy-D-*ribo*-hexofuranosyl moiety of 4′-homocytidine was obtained by way of an anti-Markovnikov addition of iodine trifluoroacetate to the double bond of 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-*ribo*-hex-5-enofuranose and reduction of the resulting iodide(s). In the second approach, 5-deoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-D-*xylo*-hexofuranose was acetolyzed and condensed with 4-acetyl-*N*-bis(trimethylsilyl)cytosine, and alkaline treatment gave **11** by way of a 2′,3′-anhydro intermediate. The structure of **11**, in particular the configuration at C-2′, was confirmed by its ^{1}H- and ^{13}C-n.m.r. spectra.

INTRODUCTION

1-β-D-Arabinofuranosylcytosine ("cytosine arabinoside", ara-C) is one of the most active antitumor agents in the treatment of acute leukemia[1]. After several years of controversy about its mode of action, it seems now generally accepted that ara-C, as its triphosphate (ara-CTP), inhibits the enzymic incorporation of 2′-deoxycytidine triphosphate (dCTP) into DNA by DNA polymerase[2,3]. An important feature of this analog of 2′-deoxycytidine is its high sensitivity to the pyrimidine nucleoside deaminase, which results into its rapid deamination to 1-β-D-arabinofuranosyluracil (ara-U) devoid of antitumor activity[4]. Furthermore, resistance to "cytosine arabinoside" rapidly develops by deletion of 2′-deoxycytidine kinase, the enzyme responsible for conversion of ara-C into its active phosphorylated form[5]. Numerous modifications of the molecule have been devised to overcome these two limitations. The most important analogs of ara-C are cyclocytidine[6]

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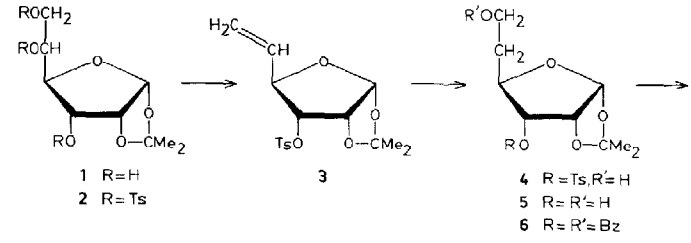
(2,2′-anhydro-1-β-D-arabinofuranosylcytosine) and 2,2′-anhydro-1-β-D-arabinofuranosyl-5-fluorocytosine[7], both of which exhibit an increased resistance to deamination[2,8], and have been studied in clinical trials[2]. Further modifications of ara-C include mostly formation of N or O derivatives, as carboxylic esters, amides[9–12], or phosphoric esters[13,14], but no alteration of the carbon chain at C-5′ has been reported. Owing to the noteworthy biological properties of 9-(5-deoxy-β-D-*ribo*-hexofuranosyl)adenine[15] and other "homonucleosides"[16–18], the preparation of 1-(5-deoxy-β-D-*arabino*-hexofuranosyl)cytosine (4′-homoara-C) (**11**) is of interest, and we describe herein two different approaches to this new analog of ara-C. The first one involves inversion of configuration at C-2′ of 4′-homocytidine[19], the 5-deoxy-D-*ribo*-hexose component of which has been prepared by a method developed in this laboratory[20]; in the second approach, a 1-(5-deoxy-D-*xylo*-hexofuranosyl)cytosine derivative was prepared and used as precursor of **11**.

RESULTS AND DISCUSSION

The addition of pseudohalogens to unsaturated carbohydrates has been shown in this laboratory to provide a convenient route to deoxy sugars[21]; in particular, 5-deoxy-D-*xylo*- and -L-*arabino*-hexoses have been prepared by the anti-Markovnikov addition of iodine trifluoroacetate (F_3CCO_2I) to 5,6-unsaturated, 1,4-furanoid precursors and reduction of the resulting iodides, and have been converted into the corresponding adenine nucleosides[20]. In the present work, the same procedure was used to prepare the desired 5-deoxy-D-*ribo*-hexose derivatives from the tritosyl derivative **2** of 1,2-*O*-isopropylidene-α-D-allofuranose[22] (**1**): reductive elimination at C-5–C-6 of **2** with sodium iodide in butanone at reflux to give **3**, followed by addition of *in situ*-generated iodine trifluoroacetate to the double bond of **3**, and immediate hydrogenolysis of the resulting iodide(s) in the presence of a Raney nickel catalyst to afford 5-deoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-*ribo*-hexofuranose (**4**) in 36.5% overall yield from **1**. The structure of **4** was confirmed by the presence, in its ^{1}H-n.m.r. spectrum, of a 2-proton multiplet centered at δ 1.85 characteristic of the C-5 methylene group. Photochemically induced desulfonylation[20,23] of **4** proved to be very efficient and gave almost quantitatively 5-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**5**). The dibenzoate **6**, a compound that had been prepared by an independent route by David and de Sennyey[19] was obtained by benzoylation of **5**. Conversion of **6** into 1-(5-deoxy-β-D-*ribo*-hexopyranosyl)cytosine (4′-homocytidine, **9**) was achieved, in 43% overall yield, by acetolysis of **6**, condensation of the resulting diacetate **7** with 4-*N*-acetylbis(trimethylsilyl)cytosine in the presence of tin(IV) chloride, and deacylation of the nucleoside **8** under conditions very similar to those described earlier[19].

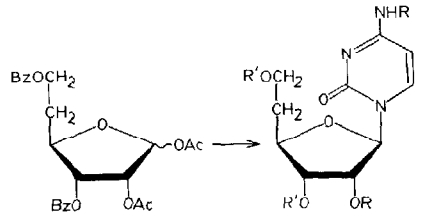
Several methods were available for the inversion of configuration at C-2′ of cytidine by way of a 2,2′-anhydro intermediate (cyclocytidine), the active form of cytidine being generated with such reagents as thionyl chloride[24], a Vilsmeier–Haack salt[25], acetic anhydride–boron trifluoride etherate[26], or diphenylcarbo-



1 R=H
2 R=Ts

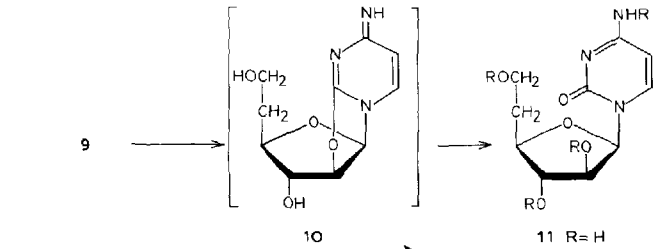
3

4 R=Ts,R'=H
5 R=R'=H
6 R=R'=Bz



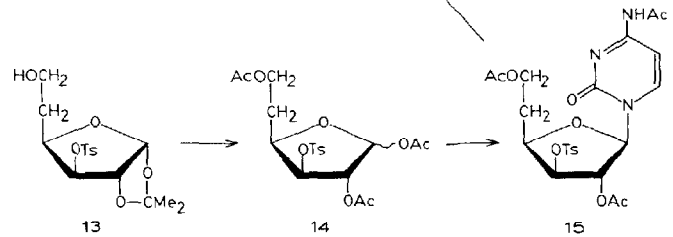
7

8 R=Ac, R'=Bz
9 R=R'=H



10

11 R=H
12 R=Ac



13 14 15

nate[27–29]. The diphenylcarbonate procedure is very convenient as three reactions (formation of the 2′,3′-*O*-carbonyl derivative, cyclization to the 2,2′-anhydro intermediate with loss of carbon dioxide, and hydrolysis to the β-D-*arabino* nucleoside) take place in one operation. Thus, treatment of **9** with diphenylcarbonate in *N,N*-dimethylformamide in the presence of sodium hydrogencarbonate afforded, after 25 min at 144° and chromatographic separation, a new compound (49% yield) that exhibited spectroscopic properties in agreement with the expected structure **11** (see later). No 2,2′-anhydro intermediate (**10**) was observed at the end of the reaction; as expected, this intermediate had been entirely hydrolyzed to **11** by traces of water present in the reaction mixture (see ref. 28).

As an extension of the method developed by Reist *et al.*[30], and by Shimizu and Shimizu[31] for the synthesis of ara-U and of ara-C, respectively, our second approach to **11** involved the preparation of a suitable nucleoside precursor having a 5-deoxy-3-*O*-*p*-tolylsulfonyl-β-D-*xylo*-hexofuranosyl residue. Compound **13**, previously reported by this laboratory[20], constitutes the ideal starting material for this purpose. Acetolysis of **13** under standard conditions and condensation of the resulting triacetates **14** with 4-*N*-acetyl-bis(trimethylsilyl)cytosine in the presence of tin(IV) chloride afforded the desired cytosine derivative **15** in 36% overall yield. In the key step, compound **15** was treated with sodium hydroxide in methanol to give **11** in excellent yield (97%), most probably by way of 4-*N*-acetyl-1-(2,3-anhydro-5-deoxy-β-D-*ribo*-hexofuranosyl)cytosine and the 2,2′-anhydro intermediate **10** (or its 4-*N*-acetyl derivative).

The physico-chemical properties of the samples of **11** obtained by the two methods are identical and confirm its structure. Thus, the chemical shift of H-1′ (δ 6.15) in its ^{1}H-n.m.r. spectrum, and the corresponding $J_{1',2'}$ value (5 Hz) indicate clearly that **11** belongs to the β-D-*arabino* series (corresponding values[32] for ara-C: δ (H-1′) 6.18, $J_{1',2'}$ 4.8 Hz; for cytidine: δ (H-1′) 5.90, $J_{1',2'}$ 3.6 Hz; same values for 4′-homocytidine[19]). The ^{13}C-n.m.r. spectra of **9**, **11**, and the parent nucleosides cytidine and ara-C have been recorded for solutions in deuterium oxide and the data are listed in Table I (for ^{13}C-n.m.r. spectra of cytidine and ara-C under different conditions, see ref. 33). The signals of the carbon nuclei of the heterocyclic base are readily identified by comparison with the data of the reference nucleosides and analogs[34]. The signal appearing at δ ~35 in the spectra of **9** and **11** corresponds to the C-5′ methylene atom and constitutes a further proof of the "homo" (5-deoxy-D-hexofuranosyl) constitution of **9** and **11**. Inversion of configuration at C-2′ in both types of nucleosides is accompanied by characteristic changes of the chemical shifts of C-1′ and C-2′: the signal of C-1′ is shifted upfield (~ −5 p.p.m.), whereas the signal of C-2′ undergoes a slight downfield shift (~ +2 p.p.m.) upon the *ribo* to *arabino* configurational change. These effects are very similar to those observed[35] for the corresponding methyl β-D-(or -L)-pentofuranosides. Finally, "homologation" is found to alter substantially the chemical shift of C-3′ (~ +4 p.p.m.), an effect that is difficult to rationalize on the basis of the available data, whereas the slight upfield shift of C-4′ is entirely consistent with the suppression of the electronegative substituent at C-5′.

TABLE I

^{13}C-N M R CHEMICAL-SHIFT DATA[a]

Compound	*C-1'*	*C-2'*	*C-3'*	*C-4'*	*C-5'*	*C-6'*	*C-5*	*C-6*
Cytidine	90.52	74.15	69.42	83.92	60.88		96.22	141.71
Ara-C	86.19	75.64	75.64	83.40	60.95		95.38	142.81
9	91.17	73.89[b]	73.24[b]	80.62	35.19	58.55	96.41	141.78
11	86.25	75.70	79.52	80.49	35.06	58.62	95.25	142.94

[a]Solutions in deuterium oxide containing methanol as internal standard; chemical shifts (δ) converted to the tetramethylsilane scale (δ CH_3OH 49.039). [b]Assignments may be reversed.

EXPERIMENTAL

General methods. — Melting points were determined with a Fisher–Johns melting-point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer model 141 automatic polarimeter. I.r. spectra were recorded with a Perkin–Elmer 180 or a Beckman Acculab 6 spectrophotometer. U.v. spectra were obtained on a Unicam SP 800 spectrophotometer. The ^{1}H-n.m.r. spectra were recorded at 60 MHz with a Varian EM-360 or a Bruker HX-60 spectrometer for solutions in (^{2}H)chloroform with tetramethylsilane as the internal standard, or in deuterium oxide with sodium 4,4-dimethyl-4-silapentane-1-sulfonate as the internal standard. The ^{13}C-n.m.r. spectra were obtained at 15.09 MHz on a Bruker HX-60 spectrometer equipped with an FT60M Fourier-transform accessory; chemical shifts are given in δ downfield from the signals of the standards. T.l.c. was performed with Silica gel G as the adsorbent in the following solvent systems (v/v): (*A*) 1:2, (*B*) 1:1, (*C*) 4:1, and (*D*) 9:1 benzene–ethyl acetate; (*E*) ethyl acetate; (*F*) 3:1 hexane–ethyl acetate; (*G*) 20:1 ethyl acetate–ethanol; (*H*) ethanol; and (*I*) 2:1 ethanol–chloroform. The developed plates were air dried and compounds located by irradiation with a short-wavelength, u.v. lamp or by spraying with a solution of 1% cerium sulfate and 1.5% molybdic acid in 10% aqueous sulfuric acid and heating the plates at ~150° or by both methods. Preparative t.l.c. was performed on 20 × 20 cm plates coated with a 1-mm layer of Silica gel G. Column chromatography was performed on Silica gel 60 (70–230 mesh, Merck). U.v. irradiations were obtained with a 450-W Hanovia high-pressure, mercury-arc lamp (cat. No. 679A-36) contained in a water-cooled, quartz immersion-well; a Vycor 7010 filter-sleeve was employed.

*1,2-O-Isopropylidene-3,5,6-tri-*O*-p-tolylsulfonyl-α-*D*-allofuranose* (**2**). — A solution of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[22] (9 g) in 70% aqueous acetic acid (90 mL) was kept for 16 h at room temperature. The solvent was then removed under reduced pressure and the remaining crystalline mass was recrystallized (ethanol–hexane) to afford an almost quantitative yield of 1,2-*O*-isopropylidene-α-D-allofuranose (**1**), m.p. 128–130° (lit.[36] m.p. 129–130°).

To a solution of **1** (6.54 g, 30 mmol) in pyridine (30 mL) was added, at 0°, *p*-

toluenesulfonyl chloride (23 g, 120 mmol). The mixture was kept at room temperature for 4 days and then poured into ice–water. The precipitated solid mass was removed by filtration and recrystallized from dichloromethane–methanol to give pure **2** (17.4 g, 85.8%) as white needles, m.p. 158–159.5°, $[\alpha]_D^{23}$ +51.7° (*c* 1.3, chloroform); R_F 0.13 (solvent *F*); ν_{max}^{KBr} 1600, 1500, 1380, and 1180 cm^{-1}; ^{1}H-n.m.r.: δ 1.23 and 1.40 (2 s, 2 × 3 H, CMe_2), 2.45 (s, 9 H, 3 Ar*Me*), 3.63–5.0 (m's, 6 H, H-2, -3, -4, -5, -6a, and -6b), 5.40 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 7.30 and 7.73 (d and m, 12 H, 3 Ar).

Anal. Calc. for $C_{30}H_{34}O_{12}S_3$: C, 52.77; H, 5.02; S, 14.09. Found: C, 52.55; H, 5.02; S, 14.07.

*5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-*D*-ribo-hex-5-enofuranose* (**3**). — Sodium iodide (37 g, 250 mmol) was added to a solution of **2** (20.4 g, 30 mmol) in butanone (380 mL). The mixture was boiled at reflux for 4 h and then filtered. Fresh sodium iodide (29 g, 190 mmol) was added to the filtrate, and the mixture was boiled at reflux for 14 h. After this time, the salts were removed by filtration, and the filtrate was evaporated. The residue was dissolved in chloroform (350 mL), and the solution washed with aqueous sodium thiosulfate and then dried ($MgSO_4$). Pure **3** (8.2 g, 83%) was obtained after evaporation of the solvent and recrystallization of the remaining solid from methanol; m.p. 138–139° (dec.), $[\alpha]_D^{21}$ +58.6° (*c* 1.8, chloroform); R_F 0.40 (solvent *F*); ν_{max}^{KBr} 1640, 1600, 1490, 1375, and 1180 cm^{-1}; ^{1}H-n.m.r.: δ 1.30 and 1.57 (2 s, 2 × 3 H, CMe_2), 2.47 (s, 3 H, Ar*Me*), 4.07–4.63 (m's, 3 H, H-2, -3, and -4), 4.97–5.63 (m's, 3 H, H-5, -6a, and -6b), 5.73 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 7.33 and 7.83 (2 d, 2 × 2 H, Ar).

Anal. Calc. for $C_{16}H_{20}O_6S$: C, 56.46; H, 5.92; S, 9.42. Found: C, 56.63; H, 5.85; S, 9.48.

*5-Deoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-*D*-ribo-hexofuranose* (**4**). — To a solution of iodine (6.4 g, 25 mmol) in dry 1,2-dimethoxyethane (120 mL) was added a mixture of **3** (6 g, 17.6 mmol) and silver trifluoroacetate (5.5 g, 25 mmol) in dry 1,2-dimethoxyethane (150 mL). After having been vigorously stirred for 15 min in the dark at room temperature, the mixture was filtered through Celite and the filtrate concentrated to dryness. The residue was dissolved in chloroform, the solution washed with aqueous sodium thiosulfate and dried, and the solvent evaporated. The residue was hydrogenated in the presence of W-4 Raney nickel (0.3–0.35 MPa of hydrogen) in methanol (350 mL) containing triethylamine (3 mL) for 3 h. The catalyst was removed by filtration and the solvent evaporated. The residue was dissolved in chloroform (200 mL), the solution washed with 3% aqueous hydrochloric acid, and then with water, and dried. The solution was evaporated and the major component of the remaining syrup was separated by column chromatography (solvent *C*) which afforded 3.2 g (51%) of crystalline **4**, m.p. 110–112° (from ethanol–hexane), $[\alpha]_D^{24}$ +88.7° (*c* 1.2, chloroform); R_F 0.17 (solvent *C*); ν_{max}^{KBr} 3480, 1600, 1360, and 1190 cm^{-1}; ^{1}H-n.m.r. (after D_2O exchange): δ 1.28 and 1.53 (2 s, 2 × 3 H, CMe_2), 1.60–2.10 (m, 2 H, H-5a, -5b), 2.47 (s, 3 H, Ar*Me*), 3.68 (t, 2 H, H_2-6), 4.13–4.63 (m's, 3 H, H-2, -3, and -4), 5.75 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 7.38 and 7.89 (2 d, 2 × 2 H, Ar).

Anal. Calc. for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.19; S, 8.95. Found: C, 53.58; H, 6.13; S, 8.91.

5-Deoxy-1,2-O-isopropylidene-α-D-ribo-hexofuranose (**5**).— Compound **4** (3.23 g, 9 mmol) in anhydrous methanol (250 mL) containing sodium methoxide (from 230 mg of sodium) was submitted to u.v. irradiation for 10 h at 5–20°. The solution was decolorized with charcoal, the mixture filtered, and the filtrate concentrated. The residue was extracted with hot ethyl acetate (2 × 100 mL), the combined extracts evaporated, and the residual syrup purified by column chromatography (solvent *B*) to give 1.68 g (91%) of pure **5**, m.p. 76.5–77.5° (from ether–petroleum ether), $[\alpha]_D^{24}$ +50.3° (*c* 1.5, chloroform); R_F 0.20 (solvent *A*); ν_{max}^{KBr} 3440 and 3290 cm^{-1}.

Anal. Calc. for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.89; H, 7.90.

1-(5-Deoxy-β-D-ribo-hexofuranosyl)cytosine (homocytidine, **9***) from* **5**. — Compound **5** was treated with benzoyl chloride in pyridine to afford the dibenzoate **6** in 89% yield after usual processing and column chromatography (19:1, v/v, benzene–ethyl acetate); m.p. 89° (from ethanol–hexane) (lit.[19] m.p. 87°). Compound **6** was converted into **9** in three steps under conditions similar to those described by David and de Sennyey[19]: acetolysis of **6** to afford **7** (83%), condensation of **7** with 4-*N*-acetylbis(trimethylsilyl)cytosine in the presence of tin(IV) chloride to give **8** [62%; m.p. 188.5–189.5° (from ethanol) (lit.[19] m.p. 183°)], and deacylation of **8** to give **9** (84% yield) m.p. 114–116°(from ethanol–water) (lit.[19] m.p. 116–117°).

1,2,6-Tri-O-acetyl-5-deoxy-3-O-p-tolylsulfonyl-D-xylo-hexofuranoses (**14**). — To a mixture of 5-deoxy-1,2-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexofuranose[20] (**13**), acetic anhydride (23 mL), and glacial acetic acid (23 mL) was added slowly, at 0°, conc. sulfuric acid (1.4 mL). The mixture was stirred for 3 days at room temperature and then cooled in an ice bath. Sodium acetate (4 g) was added in portions and the mixture stirred for 1 h. The solvent was removed *in vacuo* and the residue dissolved in water (100 mL) and dichloromethane (200 mL). The separated organic layer was washed successively with saturated aqueous sodium hydrogencarbonate and with water, and dried ($MgSO_4$). The solvent was evaporated, and the remaining, light-brown syrup purified by column chromatography (solvent *C*) to give 1.02 g (78%) of pure, syrupy **14**, $[\alpha]_D^{24}$ +37.5° (*c* 2.2, chloroform); R_F 0.30 (solvent *C*); ν_{max}^{film} 1750, 1600, 1370, 1230, 1180, and 1020 cm^{-1}.

Anal. Calc. for $C_{19}H_{24}O_{10}S$: C, 51.35; H, 5.44; S, 7.21. Found: C, 51.22; H, 5.63; S, 7.09.

4-N-Acetyl-1-(2,6-di-O-acetyl-5-deoxy-3-O-p-tolylsulfonyl-β-D-xylo-hexofuranosyl)cytosine (**15**). — To a solution of **14** (1.51 g, 3.4 mmol) in dry 1,2-dichloroethane (100 mL) was added, with stirring, a solution of tin(IV) chloride (1.2 mL, 3 equiv.) in 1,2-dichloroethane and, after 10 min, a solution of 4-*N*-acetyl-bis(trimethylsilyl)cytosine (1.3 g, 1.2 equiv.) in dichloroethane (20 mL). After 4.5 h at room temperature, additional equivalents of tin(IV) chloride (0.4 mL) and 4-*N*-acetyl-bis(trimethylsilyl)cytosine (0.87 g) in dichloroethane (5 mL) were added to

the mixture. After having been stirred overnight at room temperature, the mixture was diluted with dichloromethane (100 mL) and poured into a vigorously stirred, saturated aqueous sodium hydrogencarbonate solution. The precipitated solids were removed by filtration through Celite; the organic layer of the filtrate was separated, washed with water (100 mL), and dried ($MgSO_4$). The solvent was evaporated and the major component of the remaining syrup was separated by column chromatography (50:1, v/v, ethyl acetate–ethanol) to afford pure **15** as a foam (0.84 g, 46%), $[\alpha]_D^{24}$ +50.9° (*c* 1.1, chloroform); R_F 0.34; ν_{max}^{film} 3240, 1740, 1665, 1555, 1490, 1375, 1225, 1180, and 1105 cm^{-1}; λ_{max}^{EtOH} 216 (ε 11 300), 230 (ε 10 300), 249 (ε 9750), 298 nm (ε 4500); ^{1}H-n.m.r.: δ 2.08, 2.12, 2.28, 2.40 (4 s and overlapped m, 14 H, H_2-5′, 2 AcO, AcN, *Me*Ar), 4.0–4.67 (m, 3 H, H-3′, -6′a, and -6′b), 5.05 (s + d, 2 H, H-2′, -3′), 5.92 (s, 1 H, H-1′), 7.40 and 7.77 (AB, 2 H, *J* 8 Hz, H-5, -6), 7.27 and 7.70 (2 d, 4 H, C_6H_4Me).

Anal. Calc. for $C_{23}H_{27}N_3O_{10}S$: C, 51.39; H, 5.06; N, 7.82; S, 5.96. Found: C, 51.45; H, 5.26; N, 7.69; S, 5.80.

*1-(5-Deoxy-β-*D*-arabino-hexofuranosyl)cytosine* (**11**). — *(a) From* **9**. A mixture of **9** (144 mg, 0.56 mmol), diphenylcarbonate (155.5 mg, 1.3 equiv.), and sodium hydrogencarbonate (7.1 mg, 0.15 equiv.) in dry *N*,*N*-dimethylformamide (0.3 mL) was heated for 25 min at 144–145°. After this time, t.l.c. (solvent *1*) indicated that all of the starting material (R_F 0.35) had been converted into a faster-moving compound (R_F 0.48). The mixture was applied to a preparative t.l.c. plate, which was developed successively with 7:3 and 1:5 (v/v) chloroform–ethanol. Collection of the band corresponding to the new product and elution of the product with ethanol afforded, after evaporation of the solvent, homogeneous **11** (71 mg, 49%) as a slightly colored solid, m.p. 185–192° (from ethanol–water).

(b) From **15**. To a solution of **15** (0.252 g, 0.47 mmol) in 20% aqueous methanol (10 mL) was added, with stirring, aqueous M sodium hydroxide (0.8 mL) over a period of 2 h, and the mixture was stirred for an additional 4 h. The methanol was removed *in vacuo* and the remaining solution loaded onto a column of strongly acidic, ion-exchange resin [CGC-240 (H^+), 20 mL]. The column was washed with water (100 mL) and the product then eluted with 1% aqueous ammonia (150 mL). Evaporation of the eluate to dryness afforded pure **15** (117 mg, 97%), m.p. 218–220° (from ethanol), $[\alpha]_D^{18}$ +164.6° (*c* 1.1, water); R_F 0.48 (solvent *1*); ν_{max}^{KBr} 3340, 3300, 3190, and 1640 cm^{-1}; $\lambda_{max}^{H_2O}$ 271 (ε 8500), 230 sh (ε 5900), $\lambda_{min}^{H_2O}$ 250 nm (ε 4400); ^{1}H-n.m.r. (D_2O): δ 2.07 (broad q, 2 H, *J* ~6.5 Hz, H_2-5′), 3.78 (t, 2 H, *J* ~6.5 Hz, H_2-6′), ~4.0 (m, 2 H, H-3′, -4′), 4.37 (m, 1 H, H-2′), 6.03 (d, 1 H, $J_{5,6}$ 8 Hz, H-5), 6.15 (d, 1 H, $J_{1',2'}$ 5 Hz, H-1′), and 7.70 (d, 1 H, H-6).

Anal. Calc. for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88; N, 16.33. Found: C, 46.58; H, 5.93; N, 16.32.

*4-*N*-Acetyl-1-(2,3,6-tri-*O*-acetyl-5-deoxy-β-*D*-arabino-hexofuranosyl)cytosine* (**12**). — Compound **15** was treated with acetic anhydride in pyridine under standard conditions to give **12** as white needles, after purification by preparative t.l.c. and recrystallization from ethanol; m.p. 187–188°, $[\alpha]_D^{22}$ +99.6° (*c* 0.97, chloro-

form); R_F 0.16 (solvent *E*); ν_{max}^{KBr} 3220, 1750, 1730, 1660, 1630, 1610, 1550, 1485, and 1235 cm^{-1}; λ_{max}^{EtOH} 249 (ε 17 400), 299 nm (ε 8160); λ_{min}^{EtOH} 227 (ε 4430), 275 nm (ε 4610); ^{1}H-n.m.r.: δ 1.98, 2.09, 2.17, 2.31 (4 s and overlapped m, 14 H, H_2-5′, 3 AcO, AcN), ~4.2 (m, 3 H, H-4′, H_2-6′), 5.0 (m, 1 H, $J_{2',3'}$ ~1, $J_{3',4'}$ ~3 Hz, H-3′), 5.48 (dd, 1 H, $J_{1',2'}$ 4.0 Hz, H-2′), 6.30 (d, 1 H, H-1′), 7.48 (d, 1 H, $J_{5,6}$ 7.5 Hz, H-5), and 7.90 (d, 1 H, H-6).

Anal. Calc. for $C_{18}H_{23}N_3O_9$: C, 50.82; H, 5.45; N, 9.88. Found: C, 50.76; H, 5.65; N, 9.69.

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