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A PRACTICAL SYNTHESIS OF 2-DEOXY-2-FLUORO-D-ARABINOFURANOSE DERIVATIVES*

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ABSTRACT

A seven-step synthesis of 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranose, a versatile intermediate in the synthesis of chemotherapeutically important nucleosides, was achieved from 1,2:5,6-di-*O*-isopropylidene-3-*O*-tosyl-α-D-allofuranose. The crucial steps were the fluorination by use of potassium fluoride in acetamide and the conversion of 6-*O*-benzoyl-3-deoxy-3-fluoro-D-glucofuranose into 5-*O*-benzoyl-2-deoxy-2-fluoro-3-*O*-formyl-D-arabinofuranose by periodate oxidation. Also described is the synthesis of 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine. This procedure affords good overall yields of products without formation of undesirable, isomeric intermediates and is suitable for large-scale preparations.

DISCUSSION

Previous studies from this laboratory[1] showed that 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine (**1**, 2′-F-Ara-C) has a growth inhibitory effect in an L1210-mouse, leukemia suspension-culture comparable with that of Ara-C (**2**) and Ara-FC (**3**) (1-β-D-arabinofuranosyl-5-fluorocytosine). As part of our program of synthesis of nucleosides of biochemical and chemotherapeutical potential, a practical synthesis of **1** and related nucleosides was undertaken. On the basis of many reports from our laboratory[2], it is clear that the direct introduction of a fluoro group in the 2′-"up" (*arabino*) position from a preformed nucleoside would be difficult, if not impossible, because of neighboring-group participation of the carbonyl group at C-2 of the pyrimidine moiety[2]. The success of this project rests on the development of a stereochemically controlled synthesis of a suitably protected 2-deoxy-2-fluoro-D-arabinofuranosyl derivative (*e.g.* **11**) amenable for condensation with **1**. The previous procedure[3] for the preparation of **1** gave isomeric mixtures that required laborious

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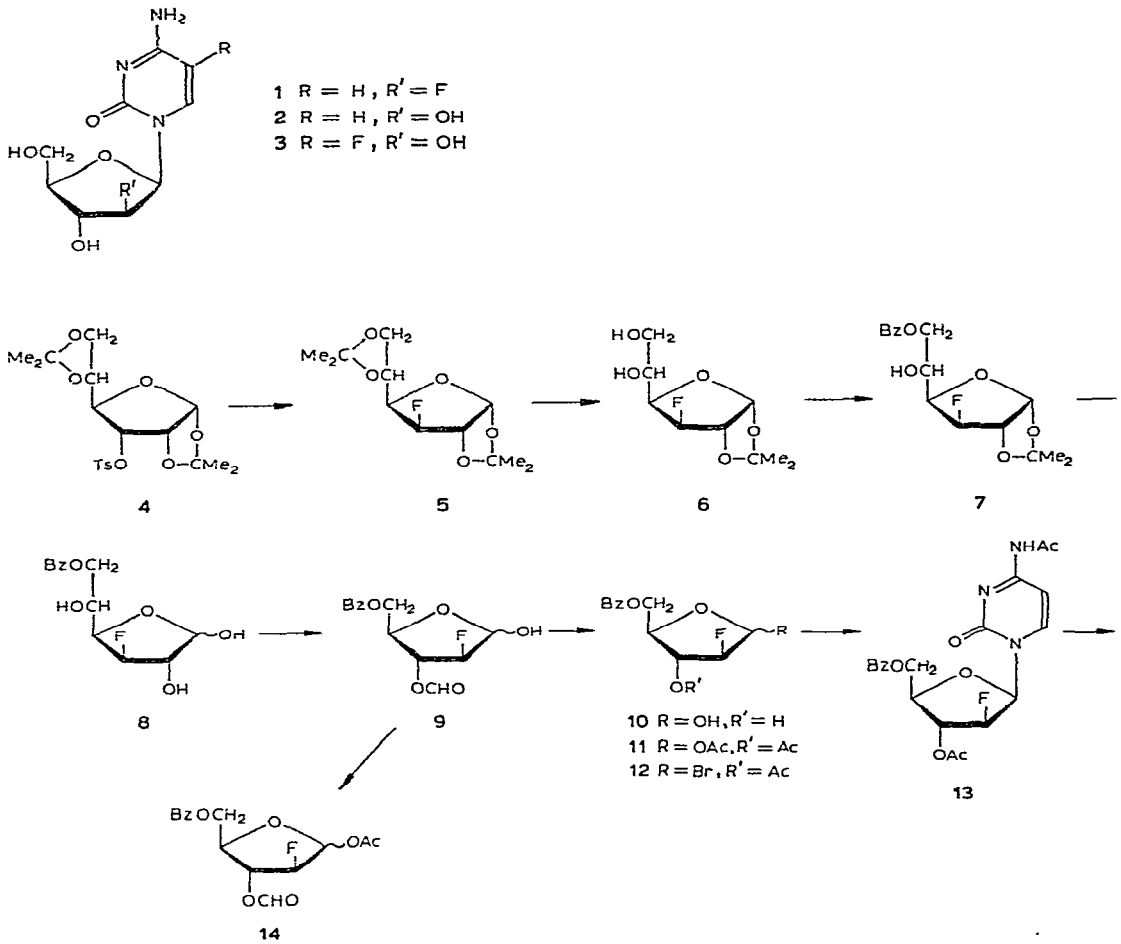
separation, and the overall yield of desired sugar was very low. Consequently, this approach to 2-deoxy-2-fluoro-D-arabinofuranosyl derivatives is not practical for large-scale preparations. We report herein a seven-step synthesis of **1** from the readily available[4] starting material **4**.



Displacement of the tosyloxy group at C-3 of **4** by a fluorine atom by use of tetrabutylammonium fluoride is known[4]. This procedure, however, suffers from the disadvantages inherent to the large-scale preparation of the fluorinating agent (a large excess of this agent is needed), the strictly anhydrous conditions required for the reaction, and the long reaction-time required. Similar problems were encountered with the commercially available tetraethylammonium fluoride. We found that the conversion of **4** to **5** proceeded quite readily (within 15 min) when **4** was treated with potassium fluoride in acetamide at ~210° (internal temperature). Pure 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**5**) was readily isolated in

~62% yield. This combination of reagents had been employed by Bergmann and co-workers[5] in their successful synthesis of benzyl 3-deoxy-3-fluoro-D-xylo-pyranosides from the corresponding 3-*O*-tosyl-α-D-xyloside and 2-*O*-tosyl-β-D-arabinoside derivatives (obviously *via* an epoxide intermediate). To our best knowledge, however, the conversion of **4** into **5** is the first example of the direct displacement of a secondary sulfonyloxy group by a fluorine atom by the use of potassium fluoride in acetamide (without anchimeric assistance or the intermediacy of an epoxide)*. The 5,6-*O*-isopropylidene group was removed selectively by a slight modification of a known procedure[4], and the product (**6**) was selectively benzoylated according to the method of Mitsunobu *et al.*[7] to afford the new crystalline monobenzoate **7**. We found, subsequently, that benzoyl chloride in pyridine is also effective for the selective benzoylation of **6**, and this is the method of choice for large-scale reactions.

Removal of the acetal group of **7** with Amberlite IR-120 (H^+) gave **8**, which was oxidized with potassium metaperiodate to give **9**. Acetylation of **9** afforded crystalline 1-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-3-*O*-formyl-α-D-arabinofuranose (**14**). The proof of the structure of **14** rests on the following data: The n.m.r. spectrum (chloroform-*d*) gave signals for one acetyl group (δ 1.25) and one benzoyl group. The H-3 signal appeared at lower field (δ 5.45), indicating that the hydroxyl group at C-3 was acylated. Elemental analyses were fully consistent with structure **10** bearing a formyl group. Crystalline **14**, which was obtained as the major product from **9**, was found to possess the α configuration, as shown by its n.m.r. spectrum (H-1, δ 6.45, $J_{1,2} \sim 0$ Hz)†. The β anomer was present in the mother liquor of crystallization. These data attest to the cyclization of **9** following oxidation of **8**, an important step in this series of reactions. It should be noted that **8** could possibly rearrange to the isomeric pyranose form, which would also give 2-deoxy-2-fluoro-D-arabinofuranose by periodate oxidation followed by *O*-deformylation and cyclization. However, the good overall-yield of crystalline **14** from **8** (>60%) and the presence of a formyl group in **14** prove that a major proportion, if not all, of **8** possesses the furanose structure as shown.

After a brief treatment of **9** with methanolic sodium methoxide, the 1,3-dihydroxy sugar derivative **10** was obtained as an anomeric mixture (ratio of α to β anomer 4:1) that could be partially separated into the pure anomers by column chromatography. The anomeric mixture (**10**) was acetylated to give a mixture of the anomeric diacetates **11** (ratio of α to β anomers, 4:1) that could also be separated by column chromatography. No advantage was gained from these separations since either pure anomers of **11** after treatment with hydrogen bromide–acetic acid in dichloromethane afforded the α-D-glycosyl **12** with only trace amounts of the β anomer. Condensation of **12** with trimethylsilylated N^4-acetylcytosine in dichloromethane afforded the protected nucleoside **13** as the major component, along with

*Sarel-Imber and Bergmann[6] reported unsuccessful attempts to replace secondary tosyloxy groups of two carbohydrate derivatives by this reagent.

†As shown by Lemieux and Lineback[8], a very small $J_{1,2}$ value establishes a 1,2-*trans* relationship for furanose derivatives.

partially deacylated products (slower-moving spots on t.l.c.). Trace amounts of the α-nucleoside (less than 1%) may have been formed in this reaction, as indicated from chromatographic and n.m.r. analyses. The formation of partially deacylated derivatives of **13** was not unexpected. It was found that an analytically-pure sample of **13** underwent partial deacylation after being kept in a 14:1 chloroform–methanol solution for a few days at room temperature. After deacylation of **13**, the unprotected nucleoside **1** was isolated in crystalline form as the hydrochloride salt. The identity of **1** with the previously reported 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine hydrochloride[3] was established by comparing their m.p., optical rotation, and n.m.r. and u.v. spectral properties. Nucleoside **1** was also obtained in good yield from the crude condensation products (**13** and partially deacylated components) without purification of **13**. The almost exclusive formation of β-nucleoside in this condensation reaction (**12** → **13**) is akin to the stereoselectivity observed in Hilbert–Johnson, silyl type reactions with tri-*O*-benzyl-α-D-arabinofuranosyl chloride[9]. Possible mechanisms accounting for such stereoselectivity have been discussed[10].

It should be noted that the synthesis of the 2-deoxy-2-fluoro-D-arabino sugar **11** described herein, though lengthy, affords good overall-yields (~20% from **4**). The formation of isomeric sugars, a problem which was encountered in the previously reported[3] synthesis of 2-deoxy-2-fluoro-D-arabinofuranosyl derivatives, does not occur and the separation of anomers is not required. Moreover, each step of the synthesis (**4** → **11**) is suitable for large-scale preparations.

EXPERIMENTAL

General. — Melting points were determined with a Hoover–Thomas capillary apparatus and are corrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. N.m.r. spectra were obtained on a Varian A-60 instrument, and tetramethylsilane was the internal standard; chemical shifts are reported in p.p.m. (δ) and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), or m (complex multiplet); coupling constants are first-order. Thin-layer chromatography (t.l.c.) was performed on microscope slides coated with Silica Gel GF_{254} (Merck), and column chromatography on Silica Gel 60 (70–230 mesh, ASTM, Merck) with a proportion of substance to silica gel of 1:50 (w/w)[11].

3-Deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**5**). — A mixture of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[4] (80 g, prepared according to the procedure of Baker *et al.*[12]), potassium fluoride (140 g), and acetamide (700 g) was heated to 210° (internal). The reaction was monitored by t.l.c. until all the starting material disappeared (~15 min). After 45 min, the dark reaction-mixture was cooled to 90° and poured into a saturated solution of sodium hydrogencarbonate (1200 ml). The mixture was filtered from insoluble tar. Both the tar and filtrate were extracted with ether (2 × 200 ml and 4 × 400 ml, respectively). The combined ether extracts were washed with water (2 × 300 ml), dried with sodium sulfate, and evaporated to a yellow syrup which was purified by column chromatography with 9:1 (v/v) benzene–

ether as the eluent. Pure **5** (31 g, 62%) was obtained as a pale-yellow syrup, identical with an authentic sample, as shown by n.m.r. spectrum and optical rotation, $[\alpha]_D^{27}$ −21° (*c* 1, chloroform), prepared by use of tetrabutylammonium fluoride in acetonitrile as the fluorinating agent[4].

3-Deoxy-3-fluoro-1,2-O-isopropylidene-α-D-glucofuranose (**6**). — This compound was prepared according to Foster *et al.*[4] with a slight modification. A solution of **5** (31 g) in 1:1 methanol–0.7% aqueous sulfuric acid (320 ml) was stirred at room temperature. After the starting material disappeared (10 h, monitored by t.l.c. in 9:1, v/v, benzene–ethanol), the mixture was neutralized with barium carbonate, boiled for 10 min, and filtered. The filtrate was concentrated and the residual syrup was dried by several additions and evaporations of benzene. The residue (23 g, pale-yellow syrup) was used directly in the next step. A small portion was purified by column chromatography (9:1, v/v, benzene–ethanol). Pure **6** slowly crystallized upon being kept to give, after one recrystallization from toluene–petroleum ether, colorless crystals, m.p. 52–56°, $[\alpha]_D^{27}$ −18° (*c* 0.8, chloroform); lit.[4]: m.p. 50–52°, $[\alpha]_D$ −18° (*c* 0.8, chloroform).

6-O-Benzoyl-3-deoxy-3-fluoro-1,2-O-isopropylidene-α-D-glucofuranose (**7**). — *Method A.* To a cold (−15°) stirred solution of **6** (20 g) in dry pyridine (250 ml) was added dropwise a mixture of benzoyl chloride (13 g) in dichloromethane (90 ml). After the addition was completed, the reaction mixture was kept at −15° for an additional 4 h. The solvents were removed by evaporation. The residue was dissolved in chloroform (200 ml), and the solution was washed with a saturated sodium hydrogencarbonate solution (3 × 150 ml), water (2 × 150 ml), dried with sodium sulfate, and evaporated to a colorless solid. Crystallization from ethanol gave pure **7** (11 g), m.p. 132–133°, $[\alpha]_D^{27}$ −7.8° (*c* 0.6, chloroform); n.m.r. (chloroform-*d*): δ 1.35 (s, 3 H, isopropylidene CH_3), 1.50 (s, 3 H, isopropylidene CH_3), 2.80 (d, 2 H, H-6,6'), 4.59 (q, 1 H, $J_{4,F} \sim 19$ Hz, $J_{3,4} \sim 2$ Hz, H-4), 5.12 (q, 1 H, $J_{3,F} \sim 54$ Hz, $J_{3,4} \sim 2.0$ Hz, H-3), and 6.0 (d, 1 H, $J_{1,2} \sim 4$ Hz, H-1).

Anal. Calc. for $C_{16}H_{19}FO_6$: C, 58.9; H, 5.8; F, 5.8. Found: C, 59.0; H, 5.9; F, 5.7.

From the mother liquor of crystallization a further quantity of **7** (12.5 g) having the same m.p. was obtained for a total yield of 80%.

Method B. To a solution of **6** (2 g) and triphenylphosphine (2.36 g) in hexamethylphosphoric triamide (9 ml) was added dropwise a stirred solution of benzoic acid (1.1 g) and diethyl azodicarboxylate (1.57 g) in hexamethylphosphoric triamide (9 ml). After 2 days, precipitated triphenylphosphine oxide was filtered off and the filtrate was poured into water (200 ml). A syrup separated and slowly solidified. After one recrystallization from benzene–petroleum ether, pure **7** (1 g, 35%) was obtained as colorless needles, m.p. 132–133°.

6-O-Benzoyl-3-deoxy-3-fluoro-D-glucofuranose (**8**). — A mixture of **7** (22 g), water (400 ml), and *p*-dioxane (400 ml) was warmed to 80° and stirred until a clear solution was obtained. The solution was stirred with Amberlite IR-120 (H^+) ion-exchange resin (125 ml) for 20 h at 80°, and then the resin was removed by filtration.

The filtrate was concentrated to a syrup which was purified on a silical gel column with 7:1 (v/v), benzene–ethanol as the eluent. Pure **8** (15 g, 78%) was obtained as a colorless syrup, $[\alpha]_D^{27}$ +40° (*c* 0.9, ethanol).

Anal. Calc. for $C_{13}H_{15}FO_6$: C, 54.5; H, 5.2; F, 6.6. Found: C, 54.7; H, 5.4; F, 6.5.

5-O-Benzoyl-2-deoxy-2-fluoro-3-O-formyl-D-arabinofuranose (**9**). — To a solution of **8** (14 g) in water (700 ml) was added portionwise potassium metaperiodate (14 g). The mixture was stirred overnight at room temperature and then extracted with chloroform (4 × 400 ml). The combined extracts were dried with sodium sulfate, and evaporated to a syrup **9** (12.5 g) which was used directly in the next step.

1-O-Acetyl-5-O-benzoyl-2-deoxy-2-fluoro-3-O-formyl-α-D-arabinofuranose (**14**). — A mixture of **9** (200 mg), pyridine (6 ml), and acetic anhydride (1 ml) was stirred for 24 h at room temperature, and then poured into ice–water (50 ml). The semi-crystalline precipitate was extracted with benzene (2 × 50 ml). The extracts were dried (sodium sulfate) and evaporated, and the residue was crystallized from benzene–petroleum ether. Compound **14** (130 mg) was obtained as colorless needles, m.p. 122–124°, $[\alpha]_D^{27}$ +46.8 (*c* 0.7, chloroform); n.m.r. (chloroform-*d*): δ 2.12 (s, 3 H, OAc), 4.60 (s, 3 H, H-4,5,5'), 5.12 (d, 1 H, $J_{2,F} \sim 50$ Hz, H-2), 5.45 (m, 1 H, $J_{3,F} \sim 22$ Hz, H-3), 6.45 (d, 1 H, $J_{1,2} \sim 0$, $J_{1,F}$ 9.5 Hz, H-1), and ~7.2–8.2 (m, 6 H, aromatic and formyl).

Anal. Calc. for $C_{15}H_{15}FO_7$: C, 55.2; H, 4.6; F, 5.8. Found: C, 55.4; H, 4.8; F, 5.6.

5-O-Benzoyl-2-deoxy-2-fluoro-D-arabinofuranose (**10**). — A solution of **9** (12 g) in methanol (200 ml) was treated dropwise with M sodium methoxide in methanol. The reaction was monitored by t.l.c. (7:1, v/v, benzene–ethanol). When the reaction was completed, the mixture was neutralized with Dowex 50 (H^+) ion-exchange resin. After filtration, the filtrate was evaporated to a syrup which was purified by column chromatography with 7:1 (v/v) benzene–ethanol as the eluent. Compound **10** (10 g) was obtained as a colorless, syrupy anomeric mixture, $[\alpha]_D^{27}$ +32° (*c* 0.9, chloroform).

Anal. Calc. for $C_{12}H_{13}FO_5$: C, 56.2; H, 5.1; F, 7.4. Found: C, 55.9; H, 5.1; F, 7.0.

Rechromatography of this mixture of anomers with 10:1 (v/v) benzene–ethanol enabled isolation of the pure anomers, the α anomer being eluted from the column first. The anomers showed the following characteristics:

α Anomer: N.m.r. (chloroform-*d*): δ 4.98 (d, 1 H, $J_{1,2} = J_{2,3} \sim 0$, $J_{2,F} \sim 68$ Hz, H-2) and 5.3 (d, 1 H, $J_{1,2} \sim 0$, $J_{1,F}$ 9.5 Hz, H-1), $[\alpha]_D^{27}$ +58.4° (*c* 0.6, chloroform).

Anal. Calc. for $C_{12}H_{13}FO_5$: C, 56.2; H, 5.1; F, 7.4. Found: C, 56.0; H, 5.2; F, 7.1.

β Anomer: N.m.r. (chloroform-*d*): δ 4.88 (m, $J_{2,F} \sim 68$ Hz, H-2) and 5.28 (q, 1 H, $J_{1,2} \sim 3.5$, $J_{1,F} \sim 12$ Hz, H-1); $[\alpha]_D^{27}$ −61° (*c* 0.9, chloroform).

Anal. Calc. for $C_{12}H_{13}FO_5$: C, 56.2; H, 5.1; F, 7.4. Found: C, 55.9; H, 5.0; F, 7.2.

1,3-Di-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-D-arabinofuranose (**11**). — The

anomeric mixture of **10** (8 g) was acetylated in pyridine (150 ml) with acetic anhydride (8 g) at room temperature overnight. The reaction mixture was poured into ice–water (200 ml) and extracted with chloroform (3 × 250 ml). The chloroform extracts were dried (sodium sulfate) and evaporated to a syrup; several additions of ethanol, followed by evaporation removed traces of pyridine. Compound **11** (8.5 g, 80%) was obtained as a colorless, syrupy anomeric mixture, $[\alpha]_D^{27}$ −17° (*c* 0.9, chloroform).

Anal. Calc. for $C_{16}H_{17}FO_7$: C, 56.5; H, 5.0; F, 5.6. Found: C, 56.2; H, 5.1, F, 5.6.

Chromatography of this mixture of anomers with 60:1 (v/v) benzene–ethanol enabled isolation of the pure anomers, the β anomer being eluted first. The anomers showed the following characteristics:

α *Anomer*: N. m.r.(chloroform-*d*): δ 2.09 (s, 6 H, OAc), 4.51 (s, 2 H, H-5,5′), 5.00 (d, 1 H, $J_{1,2} = J_{2,3} \sim 0$ Hz, $J_{2,F} \sim 48.0$ Hz, H-2), 5.24 (m, 1 H, $J_{3,F} \sim 22.0$ Hz, H-3), and 6.33 (d, 1 H, $J_{1,2} \sim 0$, $J_{1,F} \sim 10$ Hz, H-1); $[\alpha]_D^{27}$ +17.9° (*c* 1.0, chloroform).

Anal. Calc. for $C_{16}H_{17}FO_7$: C, 56.5; H, 5.0; F, 5.6. Found: C, 56.4; H, 5.0; F, 5.5.

β *Anomer*: N.m.r. (chloroform-*d*): δ 2.0 (s, 3 H, OAc), 2.16 (s, 3 H, OAc), and 6.1 (q, 1 H, $J_{1,2} \sim 4$, $J_{1,F} \sim 40$ Hz, H-1); $[\alpha]_D^{27}$ −154° (*c* 0.9, chloroform).

Anal. Calc. for $C_{16}H_{17}FO_7$: C, 56.5; H, 5.0; F, 5.6. Found: C, 56.4; H, 5.1; F, 5.5.

*3-O-Acetyl-5-O-benzoyl-2-deoxy-2-fluoro-*D*-arabinofuranosyl bromide* (**12**). — To a solution of **11** (anomeric mixture, 8 g) in dichloromethane (100 ml) was added 30% hydrogen bromide in acetic acid (10 ml). After 1 h at room temperature, the solvent was removed by evaporation (<35°) and traces of acetic acid were removed by several additions of toluene followed by evaporation. Compound **12** was obtained as a yellow syrup (8.2 g); n.m.r. (chloroform-*d*): δ 2.11 (s, 3 H, OAc), ~4.6 (3 H, H-4,5,5′), 5.18 (m, 1 H, $J_{3,F} \sim 23$ Hz, H-3), 5.34 (d, 1 H, $J_{2,F} \sim 50$ Hz, H-2), and 6.45 (d, 1 H, $J_{1,2} \sim 0$, $J_{1,F} \sim 12$ Hz, H-1); $[\alpha]_D^{27}$ +30° (*c* 1.0, chloroform). Compound **12** was not further purified but used directly in the next step.

*1-(3-O-Acetyl-5-O-benzoyl-2-deoxy-2-fluoro-β-*D*-arabinofuranosyl)-*N^4*-acetylcytosine* (**13**). — To a stirred solution of **12** (8.2 g) in dichloromethane (100 ml) was added crude N^4-acetyl-bis(trimethylsilyl)cytosine[12] (prepared from 8 g of N^4-acetylcytosine) in dichloromethane (75 ml), and the mixture was stirred for 5 days at room temperature. Methanol (5 ml) was added and the suspension was filtered through a Celite pad which was thoroughly washed with dichloromethane. T.l.c. (10:1, v/v, chloroform–methanol) showed that the filtrate contained one major component contaminated with some partially deacylated products. The major component was purified by column chromatography with 30:1 (v/v) chloroform–methanol as the eluent. After one recrystallization from ethanol, **13** (4.2 g) showed m.p. 198–201°; $[\alpha]_D^{27}$ +40° (*c* 0.8, chloroform); n.m.r. (chloroform-*d*): δ 2.13 (s, 3 H, OAc), 2.25 (s, 3 H, OAc), 4.37 (m, 1 H, H-4), 4.60 (d, 2 H, H-5,5′), 5.24 (q, 1 H, $J_{1,2} \sim 2.5$, $J_{2,3} \sim 0$, $J_{2,F}$ 47 Hz, H-2), 5.31 (q, 1 H, $J_{3,4} \sim 2.0$, $J_{3,F} \sim 16$ Hz, H-3), and 6.18 (q, 1 H, $J_{1,2} \sim 2.5$, $J_{1,F} \sim 20$ Hz, H-1).

Anal. Calc. for $C_{20}H_{20}FN_3O_7$: C, 55.4; H, 4.6; F, 4.4; N, 9.7. Found: C, 55.1; H, 4.6; F, 4.5; N, 9.7.

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine (**1**). — Compound **13** (4.2 g) was dissolved in saturated methanolic ammonia (250 ml). After 10 h, the solvent was removed by distillation and the syrupy residue was triturated with saturated methanolic hydrogen chloride (50 ml). Crystals (2.7 g, 42% yield based on **11**) were collected and recrystallized from ethanol. Compound **1** obtained as the hydrochloride salt was identical with the authentic sample prepared by Wright *et al.*[3], as shown by m.p. (240–242°, dec), optical rotation, u.v. and n.m.r. spectral characteristics. Crude condensation products also gave **1** in similar yields by the same treatment.

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