Formal total synthesis of α-elvucitabine

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A formal total synthesis of α-elvucitabine has been achieved. The key intermediate 2',3'-dideoxy-5-fluoro-5'-O-(t-butyldiphenylsilyl)-α-L-cytidine \( I \) has been prepared from inexpensive starting material t-arabinose in 29% overall yield.

Keywords: α-Elvucitabine, elvucitabine, \( \alpha \)-arabinose, deoxygenation

Nucleoside analogues constitute a major class of antiviral drugs. Elvucitabine\textsuperscript{1-3}, also known as ACH123, 446 or β-L-Fd4C, is now in phase II clinical trials under the development as an anti-HIV drug (Figure 1). Elvucitabine is among the L-nucleosides that are used as anti-viral agents.

During the development of elvucitabine as an anti-HBV drug by this group, its \( \alpha \)-anomer, \( \alpha \)-elvucitabine, was needed for the quality control during the production of elvucitabine (Figure 1). In an earlier work, the total synthesis of \( \alpha \)-elvucitabine has been accomplished starting from L-lyxose (pathway I in Scheme I)\textsuperscript{a}. However, the starting material, L-lyxose, is an uncommon sugar and therefore extremely expensive. Obviously, the quality control for the production of elvucitabine needs an appreciable amount of \( \alpha \)-elvucitabine as long as the development of elvucitabine is in progress and in particular when it is advanced to the market in the future. Consequently, it is very much necessary to find an economical synthetic route to \( \alpha \)-elvucitabine.

Results and Discussion

The retrosynthetic analysis of \( \alpha \)-elvucitabine is shown in Scheme I. The target molecule \( \alpha \)-elvucitabine can be prepared by cleavage of TBDPS (t-butyldiphenylsilyl) in the key intermediate \( I \). The C=C double bond in the sugar ring of \( I \) can be created by deoxygenation of the two hydroxyl groups at 2-and 3-positions in this ring starting from \( I-1 \) or \( I-2 \) via a sequence of reactions steps. Theoretically, there are four combinations for the orientations of the 2-and 3-substituents in the sugar ring in intermediate \( I \) as exemplified by \( I-1 \) and \( I-2 \), 2-\( \beta \)-3-\( \beta \), 2-\( \beta \)-3-\( \alpha \), 2-\( \alpha \)-3-\( \beta \) and 2-\( \alpha \)-3-\( \alpha \). However, in order to induce the incoming 5-fluorocytosine to adopt the desired \( \alpha \) orientation as in \( I-1 \) and \( I-2 \) during the coupling of \( N,O \)-bis(trimethylsilyl)-5-fluorocytosine \( II \) and 1,2,3,5-tetra-O-acetylpentofuranose such as \( III-1 \) and \( III-2 \), the orientation of the 2-substituent must be opposite to that of the desired \( \alpha \)-cytosine moiety, \textit{i.e.} \( \beta \)-orientation as shown in \( I-1 \) and \( I-2 \). In theory, the orientation of the remaining 3-substituent can be \( \beta \) as shown in \( I-1 \) or \( \alpha \) as shown in \( I-2 \). In order to maximize the steric inducing effect during the coupling of the cytosine moiety and the sugar donor to make sure of the \( \alpha \)-orientation for the incoming cytosine moiety, the sugar moiety with 3-\( \beta \)-substituent, \textit{i.e.} \( III-1 \), was selected in an earlier work\textsuperscript{4}. Since the orientations for the 2-, 3- and 4-substituents in \( III-1 \) are all \( \beta \), the incoming cytosine moiety was unambiguously induced to adopt the desired \( \alpha \)-orientation during the coupling, as shown in the synthetic route starting from L-lyxose in the earlier work (pathway I in Scheme I)\textsuperscript{3}. However, L-lyxose is extremely expensive as discussed above, even being 2-5 times more expensive than metallic gold depending on the suppliers, which prompted us to consider whether it was feasible to change the orientation of 3-substituent in the sugar donor to \( \alpha \) (pathway II in Scheme I). Obviously, it is more likely for the cytosine moiety to be induced to the
desired α-orientation during the coupling if a sugar donor with 2-β-3-β configuration such as III-1 is used than with a 2-β-3-α configuration such as III-2, because all the substituents in the former case are β-orientated while in the latter case the orientation of the 3-substituent is opposite to those of the 2- and 4-substituents, which may lead to decreased sterically inducing effect during the coupling. However, given the Baker’s 1,2-trans rule which states that the neighboring 2-substituent should be more powerful to exert the steric inducing effect on configuration of the incoming cytosine moiety during the coupling than any other positions that are farther than the anomeric position, it is still possible to use L-arabinose as starting material as shown in pathway II in Scheme I.

Fortunately, it was proved experimentally to be feasible using much cheaper L-arabinose as starting material. Herein is reported the alternative synthetic route to α-elvucitabine starting from a common sugar, L-arabinose, which is much cheaper, as indicated by the fact that L-arabinose is at least 50-fold cheaper than L-lyxose (Scheme II).

Sugar donor 4 was prepared from L-arabinose in 75% overall yield according to the procedure for the L-lyxose counterpart reported earlier. Coupling of sugar donor 4 with N,O-bistrimethylsilyl-5-fluorocytosine II (ref 1) mediated with TMSOTf proceeded smoothly to furnish the adduct 5 with the desired α-configuration at the anomeric position in 87% yield. The configuration was unambiguously verified by comparison of the 'H NMR spectra of 1 with that reported, as well as the 'H NMR spectra and specific rotation of the final α-elvucitabine obtained herein with those reported. Triacetate 5 was ammonolyzed with saturated NH₃/MeOH at RT to yield 6 in 93% yield. The primary hydroxyl group in 6

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**Figure 1** — Structures of elvucitabine and α-elvucitabine

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**Scheme I** — The retrosynthetic routes for α-elvucitabine
was selectively protected with TBDPS to produce 7 in 83% yield. Treatment of 7 with NaOH/CS₂/Mel in DMSO at 0°C to RT afforded the corresponding bisxanthate 8 in 80% yield, which was subjected to Barton-McCombie deoxygenation with AIBN-initiated n-Bu₃SnH reduction in refluxing toluene to yield the key intermediate 1 in 72% yield. The ¹H NMR spectrum for 1 is in good agreement with that reported, indicating the correct α-configurations at the anomeric positions in both 5 and 1. Conversion of 1 to α-elvucitabine followed the reported procedure, thus completing the formal total synthesis of α-elvucitabine. The specific rotation and ¹H NMR spectrum of the α-elvucitabine prepared herein are also in good agreement with those reported, further confirming the desired α-configuration in both 5 and 1.

In conclusion, the key intermediate 2',3'-dideoxy-5-fluoro-5′-O-(t-butyldiphenylsilyl)-α-L-cytidine 1 for the total synthesis of α-elvucitabine was successfully prepared from much cheaper starting material L-arabinose in 29% overall yield, leading to a practical new synthetic route to α-elvucitabine.

**Experimental Section**

Melting points were determined with an XT-4 microscopic melting point apparatus and are uncorrected. ¹H NMR spectra were recorded on a Bruker AV400 spectrometer, with DMSO-d₆ as solvent and TMS as internal standard.

Dried dichloromethane and DMF were distilled from calcium hydride at atmospheric pressure and under reduced pressure, respectively. Dried THF and toluene were distilled from sodium/benzophenone ketyl.

**Procedure for the synthesis of 1,2,3,5-tetra-O-acetyl-α/β-L-arabinofuranoside, 4**

To a cooled solution of L-arabinose (10.00 g, 66.6 mmol) in methanol (150 mL), was added dropwise concentrated sulfuric acid (2 mL). The reaction mixture was then stirred at RT until all the starting L-arabinose was consumed completely as indicated by TLC analysis.

The reaction mixture was cooled with an ice-water bath, and pyridine (10 mL) was added dropwise. After addition, the mixture was concentrated on a rotary evaporator to afford crude product 2 as a colorless oil, which was further chased with pyridine (3 x 30 mL), and the residue was dissolved in pyridine (100 mL). The mixture thus obtained was cooled with an ice-water bath, and acetic anhydride (34.00 g, 334 mmol) was added dropwise. The resulting mixture was stirred at RT overnight.
The reaction mixture was poured into ice-water (500 mL), and the mixture thus obtained was extracted with dichloromethane (3 × 100 mL). The combined extracts were washed successively with 200 mL 2% HCl and saturated aqueous NaCl, dried over anhyd. Na$_2$SO$_4$, and concentrated on a rotary evaporator to afford the crude product 3 as a pale yellow oil.

The crude 3 was dissolved in glacial acetic acid (100 mL) and acetic anhydride (30 mL), and the resulting mixture was stirred at RT overnight when TLC analysis demonstrated that almost all the starting 3 was consumed completely as indicated by TLC analysis (typically within 5 h).

The reaction mixture was poured into ice-water (500 mL), and the mixture was stirred at RT for 3 h and extracted with dichloromethane (3 × 100 mL). The combined extracts were washed sequentially with saturated aqueous NaHCO$_3$, dried over anhyd. Na$_2$SO$_4$, and concentrated on a rotary evaporator to afford the crude product 4 as a pale yellow oil, which was purified by column chromatography over silica gel (EtOAc/petroleum ether = 1/2 by v/v) to yield pure 4 as a colorless oil, 16.18 g (overall 75% from L-arabinose). The pure sample 4 was found to be an anomic mixture by $^1$H NMR.

**Procedure for the synthesis of 1-(2,3,5-tri-O-acetyl-α-L-arabinofuranosyl)-5-fluorocytosine, 5**

A dried 250 mL round-bottomed flask was charged with bis(TMS)-5-fluorocytosine (39.05 g, 142.8 mmol) prepared according to a known procedure$^1$, 4 (15.16 g, 47.6 mmol) and dried dichloromethane (200 mL). The resulting mixture was stirred on an ice bath, followed by addition of concentrated H$_2$SO$_4$ (5 mL). The reaction mixture was poured into ice-water (500 mL), and the mixture thus obtained was refluxed overnight under nitrogen to give a colorless residue, which was triturated with methanol (20 mL) and concentrated on a rotary evaporator to afford the crude product 5 as a colorless oil, which was purified by column chromatography over silica gel (EtOAc/MeOH/Et$_3$N = 100/2/1 by v/v) to afford the pure product 5 as a white foam.

White foam; yield: 87%; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.99-8.01 (d, 1H, J = 7.2 Hz, Ar-H), 7.89 (bs, 1H, NH), 7.62 (bs, 1H, NH), 5.78-5.79 (d, 1H, J = 3.6 Hz, CH), 5.57-5.59 (t, 1H, J = 4.0 Hz, CH), 5.20-5.23 (m, 1H, CH), 4.75-4.79 (m, 1H, CH), 4.23-4.24, 4.26-4.27 (dd, 1H, J = 3.6 Hz and 12.0 Hz, CH$_3$), 4.10-4.11, 4.13-4.14 (dd, 1H, J = 6.0 Hz and 12.0 Hz, CH$_3$), 2.06 (s, 3H, CH$_3$), 2.05 (s, 3H, CH$_3$), 2.03 (s, 3H, CH$_3$).

**Procedures for the synthesis of 1-(α-L-arabinofuranosyl)-5-fluorocytosine, 6**

A dried 100 mL round-bottomed flask was charged with 5 (16.26 g, 42 mmol) and saturated NH$_3$/MeOH (ca 16% by w/w, 120 mL) prepared by bubbling dried ammonia into cooled methanol, and the resulting white slurry was stirred at RT to give a colorless solution. The stirring was continued until all the starting 5 was consumed completely as indicated by TLC analysis (typically 5 h).

The reaction mixture was concentrated on a rotary evaporator to afford the crude product 6 as a white residue, which was triturated with methanol (20 mL) and isopropanol (80 mL) to yield the pure product 6 as a white solid after suction filtration and drying in vacuo at RT.

White solid; m.p. 173-76°C; yield: 93%; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.81-7.83 (d, 1H, J = 7.2 Hz, Ar-H), 7.67 (bs, 1H, NH), 7.46 (bs, 1H, NH), 5.69 (s, 1H, CH), 5.61-5.62 (d, 1H, J = 4.8 Hz, CH), 5.35-5.36 (d, 1H, J = 3.6 Hz, CH), 4.91-4.93 (t, 1H, J = 5.2 Hz, CH), 4.15-4.19 (m, 1H, CH$_2$), 4.03-4.04 (m, 1H, CH$_2$), 3.90-3.91 (m, 1H, OH), 3.45-3.57 (m, 2H, OH).

**Procedure for the synthesis of 1-[5-O-(t-butyl-diphenyl)-α-L-arabinofuranosyl]-5-fluorocytosine, 7**

A dried 100 mL round-bottomed flask was charged with 6 (9.40 g, 36 mmol), imidazole (7.36 g, 108 mmol) and dried DMF (40 mL), and the resulting mixture was stirred on an ice bath, followed by addition of TBDPSCl (11.87 g, 43.2 mmol) in a dropwise manner. After addition, the reaction mixture was stirred at RT overnight when TLC analysis demonstrated that almost all the starting 6 was consumed completely.

The reaction mixture was poured into saturated aqueous NaCl (300 mL), and the mixture thus obtained was extracted with dichloromethane...
(3 x 100 mL). The combined extracts were washed with saturated aqueous NaCl, dried over anhyd. Na₂SO₄ and concentrated on a rotary evaporator to afford the crude product as a colorless oil, which was purified by column chromatography over silica gel (EtOAc/MeOH/Et₂N = 100/5/1.5 by v/v) to give rise to the pure product 7 as a white solid.

White solid; m.p. 161-62°C; yield 83%; ¹H NMR (400 MHz, DMSO-d₆): δ 7.87-7.89 (d, 1H, J = 7.2 Hz, Ar-H), 7.70 (bs, 1H, NH), 7.64-7.67 (m, 4H, Ar-H, NH), 7.41-7.49 (m, 7H, Ar-H), 5.74-5.75 (m, 1H, CH), 4.31-4.32 (m, 1H, CH), 4.05-4.08 (m, 2H, CH, 3.74-3.78 (m, 2H, OH), 1.01 (s, 9H, CH₃).

Procedure for the synthesis of 1-[5-O-t-butyl-diphenyl-2,3-di-O-[methylthio(thiocarbonyl)]-α-L-arabinofuranosyl]-5-fluoro-α-cytosine, 8

A dried 250 mL round-bottomed flask was charged with 7 (14.98 g, 30 mmol), carbon disulfide (6.84 g, 74 mmol), and Na₂SO₄ (7.34 g, 76 mmol), and the mixture was stirred on an ice bath, followed by addition of NaOH (90 mmol) and DMSO (80 mL), and the mixture was stirred at RT for 2 h. The reaction mixture was poured into saturated aqueous NaCl, dried over anhyd. Na₂SO₄ and concentrated on a rotary evaporator to afford the crude product 8 as a yellow oil, which was purified by column chromatography over silica gel (EtOAc/petroleum ether = 4/1 by v/v) to furnish the pure product 8 as a white oil, which was obtained was extracted with dichloromethane (3 x 100 mL). The combined extracts were washed with saturated aqueous NaCl, dried over anhyd. Na₂SO₄ and concentrated on a rotary evaporator to afford the crude product 8 as a yellow oil, which was purified by column chromatography over silica gel (EtOAc/MeOH = 5/1) to yield the pure product 8 as a white solid.

White solid; m.p. 129-31°C; yield: 89%; ¹H NMR (400 MHz, DMSO-d₆): δ 7.76 (bs, 1H, NH), 7.51 (bs, 1H, NH), 7.46-7.47 (d, 1H, J = 6.8 Hz, Ar-H), 6.85-6.86 (m, 1H, CH), 6.34-6.36 (m, 1H, CH), 5.89-5.90 (m, 1H, CH), 5.24 (s, 1H, CH), 3.75-3.76, 3.78-3.79 (dd, 1H, J = 4.0 Hz and 10.8 Hz, CH₂), 3.67-3.68, 3.69-3.70 (dd, 1H, J = 4.0 and 10.8 Hz, CH₂), 0.99 (s, 9H, CH₃).

Procedure for the synthesis of α-α-elvucitabine

A dried 100-mL round-bottomed flask was charged with 7.44 g (16 mmol) of 1 and 40 mL of dried THF, and the mixture thus obtained was stirred at room temperature followed by addition of 18 mL (18 mmol) of 1.0 M n-Bu₄NF in THF. The stirring was continued for one hour when all the starting 1 was consumed completely as shown by TLC analysis.

The reaction mixture was evaporated on a rotary evaporator to afford the crude product as a yellow oil, which was purified by column chromatography (EtOAc/MeOH = 5/1) to yield the pure α-elvucitabine as a white solid.

White foam; yield 72%; ¹H NMR (400 MHz, DMSO-d₆): δ 7.81 (bs, 1H, Ar-H), 7.63-7.65 (m, 4H, Ar-H, NH), 7.51-7.53 (bs+d, 2H, for doublet J = 6.8 Hz, Ar-H, NH), 7.42-7.49 (m, 6H, Ar-H), 6.93-6.94 (m, 1H, CH), 6.38-6.39 (m, 1H, CH), 5.97-5.99 (m, 1H, CH), 5.24 (s, 1H, CH), 3.75-3.76, 3.78-3.79 (dd, 1H, J = 4.0 Hz and 10.8 Hz, CH₂), 3.67-3.68, 3.69-3.70 (dd, 1H, J = 4.0 and 10.8 Hz, CH₂), 0.99 (s, 9H, CH₃).

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References