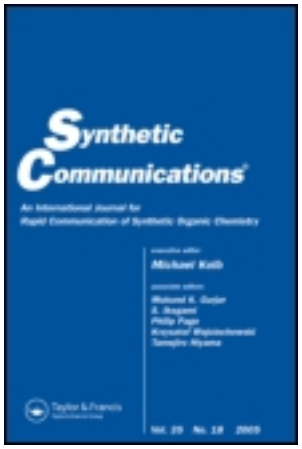

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TOTAL SYNTHESIS OF α-ELVUCITABINE

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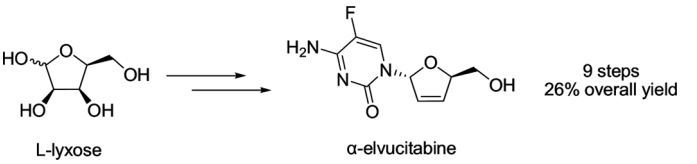
GRAPHICAL ABSTRACT



Abstract *Total synthesis of α-elvucitabine was achieved in 26% overall yield by a concise nine-step procedure starting from L-lyxose, with trimethylsilyl trifluoromethaneoulfonate (TMSOTf)–mediated stereocontrolled α-N-glycosidation and olefination through Barton–McCombie deoxygenation being the key steps, and the stereochemistry of the product was determined by nuclear Overhauser effect spectroscopy.*

Keywords Deoxygenation; α-elvucitabine; NOESY; nucleoside analoge; olefination; total synthesis

INTRODUCTION

Nucleoside analogs represent the most important class of antiviral drugs, which find wide application in the treatment of hepatitis B virus (HBV) and human immunodeficiency virus (HIV). Elvucitabine,[1–3] also known as ACH123,446 or β-L-Fd4C, is now in phase II clinical trials in development as an antiviral drug indicated for the treatment of HBV and HIV (Fig. 1). Elvucitabine is a nucleoside analog with an unnatural L-configuration designed to reduce the long-term adverse effects observed with the commonly encountered D-nucleoside analogs that are thought to be due to mitochondrial toxicity.

During the development of elvucitabine as an antiviral drug for the treatment of HBV, its α-anomer, α-elvucitabine, was needed for the assignment of the

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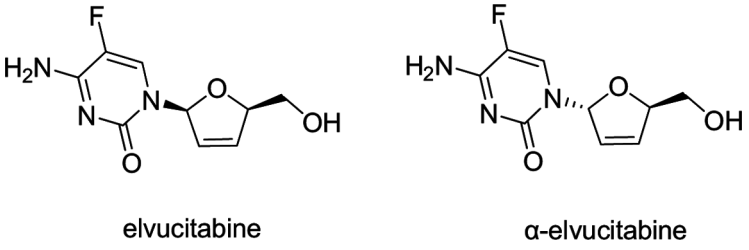
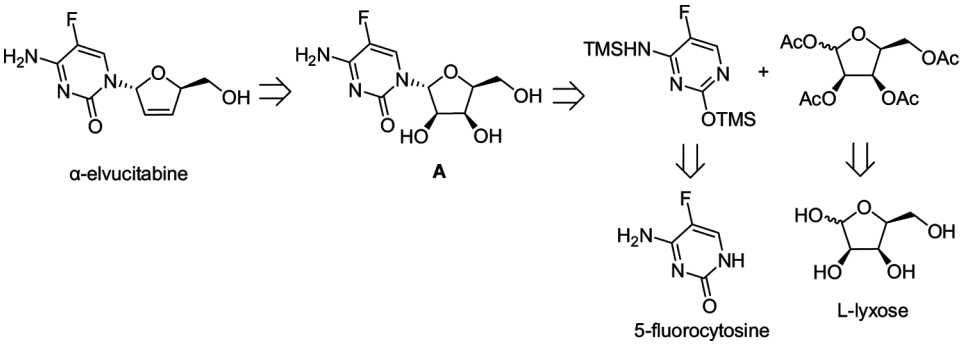


Figure 1. Structures of elvucitabine and α-elvucitabine.



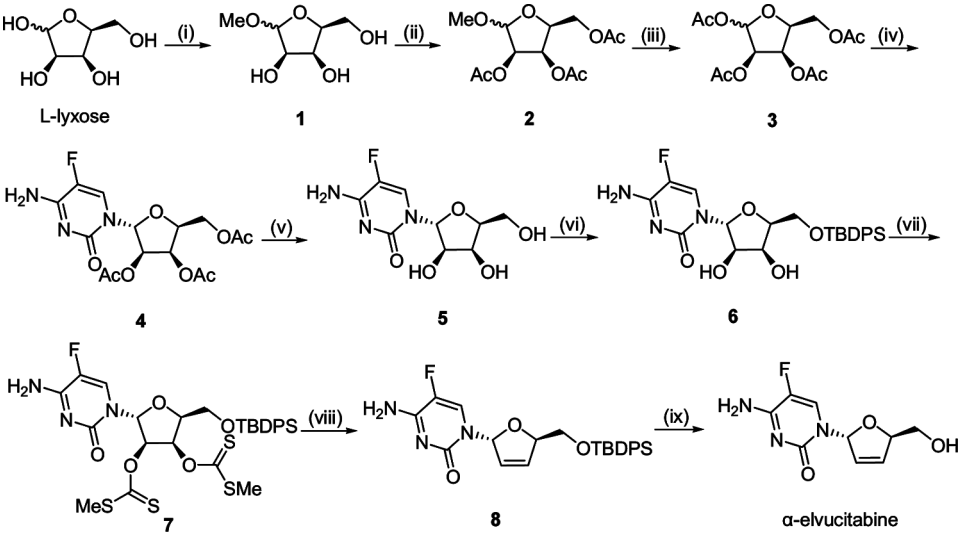
Scheme 1. Retrosynthetic analysis of α-elvucitabine.

impurities in the elvucitabine sample (Fig. 1). Herein we report a concise nine-step approach to the total synthesis of α-elvucitabine from L-lyxose (Schemes 1 and 2).

RESULTS AND DISCUSSION

Almost all the nucleoside analogs now in clinical use have a β-D-configuration (Fig. 2), and this configuration was designed to mimic that in the natural nucleosides. In these β-D-nucleoside analogs, the two groups at 1′- and 4′-positions adapt a *cis*-geometry with respect to the five-membered furanoside ring. Because of the prevalence of β-D-nucleoside analogs, a variety of stereocontrolled synthetic approaches both in laboratory and in industry are now available to construct the nucleoside analogs with β-D-configuration. However, stereocontrolled methods to build a nucleoside analog with α-L-configuration where the two groups at 1′- and 4′-positions adapt a *trans*-geometry are rarely found,[4] and most of the nucleoside analogs with a *trans*-geometry[1,5] were often isolated as by-products when a *cis*-geometry was intended. Consequently, total synthesis of α-elvucitabine with the rarely observed α-L-configuration corresponding to a *trans*-geometry by a stereocontrolled approach seems challenging.

Retrosynthetic analysis of α-elvucitabine is summarized in Scheme 1. The olefin functionality in the sugar moiety of α-elvucitabine can be built through Barton–McCombie bis-deoxygenation, and in view of the requirement for the α-induction of the 5-fluorocytosine moiety to the sugar moiety, both of the two hydroxyl groups to be removed in the sugar moiety should adapt β-configurations



Scheme 2. Synthetic approach to α-elvucitabine.

(see intermediate **A**), leading to the identification of the sugar needed as L-lyxose. The formation of nucleoside C-N bond through the coupling of the 5-fluorocytosine moiety and the L-lyxose moiety can be effected by the treatment of the mixture of bis-tetramethylsilane (TMS)-5-fluorocytosine and peracetylated L-lyxofuranose with trimethylsilyl trifluoromethane sulfonate(TMSOTf). Thus, herein we devise and report a stereocontrolled approach for the synthesis of α-elvucitabine starting from L-lyxose, and in L-lyxose the three substituents at 2′-, 3′-, and 4′-positions of the five-membered furanoside ring all adapt a β-orientation that can unambiguously lead to the desired α-anomeric center (Scheme 2).

The synthetic route of α-elvucitabine is summarized in Scheme 2. L-Lyxofuranose tetraacetate **3** was prepared as a mixture of anomers from L-lyxose according to a similar procedure reported earlier.[6] TMSOTf-mediated coupling of **3** and bis(TMS)-5-fluorocytosine[1] produced α-N-glycoside **4** with the desired α-configuration at the anomeric position. This α-configuration was determined by nuclear Overhauser effect spectroscopy (NOESY) of the finally isolated α-elvucitabine (Fig. 3) and confirmed by comparison of the ^{1}H NMR data of the finally isolated α-elvucitabine with those of the authentic elvucitabine sample,[2,3] and the stereoselectivity observed was also consistent with theoretical prediction and similar reported results.[4] Triacetate **4** was ammonolyzed with saturated NH_3/MeOH at room temperature to give rise to triol **5**, whose primary hydroxyl group was protected with a *t*-butyldiphenylsilyl (TBDPS) group following standard procedure to yield the vicinal diol **6**. Olefination to obtain **8** was accomplished by conversion of vicinal diol **6** to its corresponding bisxanthate **7** followed by Barton–McCombie

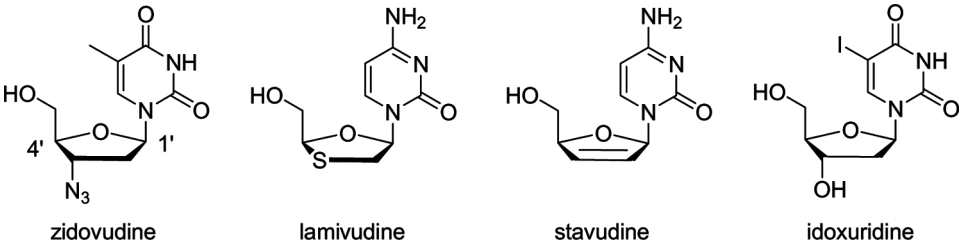


Figure 2. Selected nucleoside analogues with β-D-configuration.

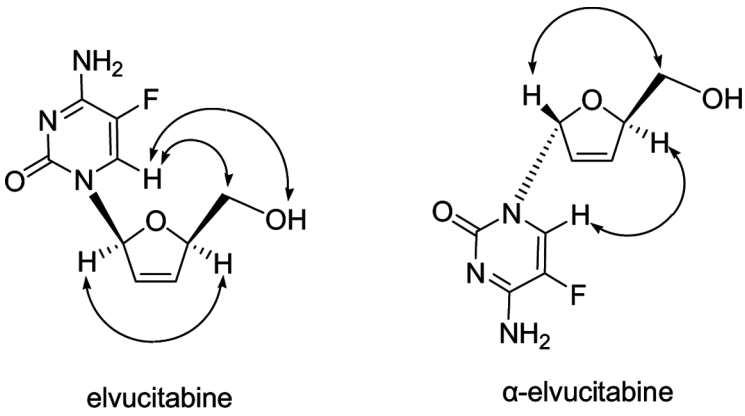


Figure 3. Useful NOEs observed in elvucitabine and α-elvucitabine.

deoxygenation with azobisisobutyronitrile (AIBN)-initiated *n*-Bu_3SnH reduction at reflux. Silyl ether **8** was treated with *n*-Bu_4NF in tetrahydrofuran (THF) at room temperature for the cleavage of the silyl ether functionality to smoothly furnish the desired α-elvucitabine.

The NOESY data of both the isolated α-elvucitabine and the authentic sample of elvucitabine were collected and examined, and as depicted in Fig. 3, some useful correlations were observed, which unambiguously confirmed the isolated product to be α-elvucitabine.

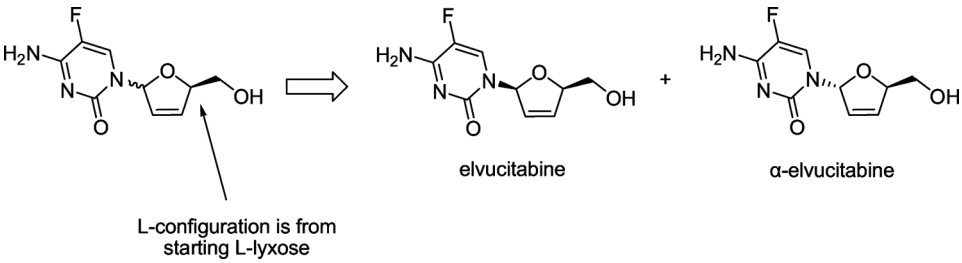


Figure 4. Two potential anomers of elvucitabine.

As depicted in Fig. 4, two stereogenic centers exist in the molecule of elvucitabine, and the one corresponding to the 4′-position was established by the starting L-lyxose. Therefore, variation at the other stereogenic center, the anomeric center, would lead to two potential anomers, α-elvucitabine and elvucitabine, and because the ^{1}H NMR data of the finally isolated product and the authentic sample were significantly different, the isolated product from this synthetic approach can be further confirmed to be α-elvucitabine.

EXPERIMENTAL

Melting points were determined with an XT-4 microscopic melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AV400 spectrometer, with dimethylsulfoxide (DMSO-d_6) as solvent and TMS as internal standard. The high-resolution mass spectrography (HR-MS) data were obtained on an Agilent Q-TOF 6510 mass spectrometer using the electrospray ionization (ESI) technique. The specific rotation was measured with a Perkin-Elmer automatic polarimeter with sodium (589 nm). The silica gel used in column chromatography was H60 (200–300 mesh) from Haiyang Chemical Ltd.

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

Synthetic Procedure of 1,2,3,5-Tetra-*O*-acetyl-α/β-L-lyxofuranoside (3)

A 250-mL, round-bottomed flask was charged with 5.00 g (33.3 mmol) of commercially available L-lyxose and 100 mL of methanol, and the resulting white slurry was stirred on an ice bath followed by dropwise addition of 1 mL of concentrated sulfuric acid. The reaction mixture was stirred at room temperature until all the starting L-lyxose was consumed completely as indicated by thin-layer chromatographic (TLC) analysis (typicaly 5 h).

The reaction mixture was cooled with an icewater bath once again, and 5 mL of pyridine was added dropwise. After addition, the reaction mixture was evaporated on a rotary evaporator to afford crude product **1** as a colorless oil, which was further chased with 30 mL × 3 of pyridine, and the residue was dissolved in 50 mL of pyridine. The mixture thus obtained was cooled with an ice-water bath, and 17.00 g (167 mmol) of acetic anhydride was added dropwise. The resulting mixture was stirred at room temperature overnight.

The reaction mixture was poured into 300 mL of icewater, and the mixture thus obtained was extracted with three 50-mL portions of dichloromethane. The combined extracts were washed successively with 200 mL of 2% hydrochloric acid and saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated on a rotary evaporator to afford the crude product **2** as a pale yellow oil.

The crude **2** was dissolved in 50 mL of glacial acetic acid and 15 mL of acetic anhydride, and the resulting mixture was stirred on an ice bath followed by addition of 2 mL of concentrated sulfuric acid. The reaction mixture was stirred at room

temperature until all the starting **2** was consumed completely as indicated by TLC analysis (typicaly 5 h).

The reaction mixture was poured into 300 mL of icewater, and the mixture was stirred at room temperature for 3 h and extracted with three 50-mL portions of dichloromethane. The combined extracts were washed sequentially with 200 mL of saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated on a rotary evaporator to afford the crude **3** as a pale yellow oil, which was purified by column chromatography (EtOAc/petroleum ether = 1/2 by v/v) to yield pure **3** as a colorless oil, 7.63 g (overall 72% from L-lyxose). The pure sample **4** was found to be an anomeric mixture by ^{1}H NMR.

Synthetic Procedure of 1-(2,3,5-Tri-*O*-acetyl-α-L-lyxofuranosyl)-5-fluorocytosine (4)

A dried 250-mL, round-bottomed flask was charged with 7.93 g (29 mmol) of bis(TMS)-5-fluorocytosine prepared according to a known procedure,[1] 7.58 g (23.8 mmol) of **3**, and 150 mL of dried dichloromethane. The resulting mixture was stirred on an ice bath, and 7.78 g (35 mmol) of TMSOTf in 20 mL of dried dichloromethane was added dropwise through a pressure-equalizing funnel. The mixture thus obtained was refluxed overnight under nitrogen until TLC analysis found that almost all the starting **3** was consumed.

On cooling, the reaction mixture was diluted with 100 mL of dichloromethane and slowly poured into 300 mL of icewater, and the resulting mixture was brought to pH 7–8 with saturated aqueous sodium bicarbonate and stirred for 5 min before the organic phase was separated. The aqueous phase was back-extracted with 50 mL of dichloromethane, and the combined extracts were washed in turn with 100 mL of saturated sodium bicarbonate and saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated on a rotary evaporator to afford the crude product **4** as a colorless oil, which was purified by column chromatography (EtOAc/MeOH/Et_3N = 100/2/1 by v/v) to afford the pure product **4** as a white foam.

White foam, 8.20 g, yield 89%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.09–8.11 (d, 1H, J = 7.2 Hz), 7.92 (bs, 1H), 7.66 (bs, 1H), 5.88–5.89 (d, 1H, J = 6.4 Hz), 5.79–5.82 (m, 1H), 5.54–5.56 (m, 1H), 4.88–4.91 (m, 1H), 4.15–4.16, 4.18–4.19 (dd, 1H, J = 4.2 Hz and 11.8 Hz), 4.07–4.08, 4.10–4.11 (dd, 1H, J = 7.4 Hz and 11.8 Hz), 2.11 (s, 3H), 2.01 (s, 3H), 1.97 (s, 3H). HR-ESI-MS, calcd. for $C_{15}H_{19}FN_3O_8$ ($[M + H]^+$) 388.3245; found 388.3251.

Synthetic Procedure of 1-(α-L-Lyxofuranosyl)-5-fluorocytosine (5)

A dried 100-mL, round-bottomed flask was charged with 8.13 g (21 mmol) of **4** and 60 mL of saturated NH_3/MeOH (ca 16% by w/w) prepared by bubbling dried ammonia into cooled methanol, and the resulting white slurry was stirred at room temperature to give a colorless solution. The stirring was continued until all the starting **4** was consumed completely as indicated by TLC analysis (typicaly 5 h).

The reaction mixture was evaporated on a rotary evaporator to afford the crude product **5** as a white residue, which was triturated with 10 mL of methanol

and 40 mL of isopropanol to yield the pure product **5** as a white solid after suction filtration and drying in vacuo at room temperature.

White solid, mp 232–233 °C, 4.99 g, yield 91%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.95–7.97 (d, 1H, $J = 7.2$ Hz), 7.74 (bs, 1H), 7.50 (bs, 1H), 5.75–5.76, 5.77–5.78 (dd, 1H, $J = 1.6$ Hz and 7.2 Hz), 5.23–5.24 (d, 1H, $J = 6.4$ Hz), 4.93–4.94 (d, 1H, $J = 4.0$ Hz), 4.57–4.60 (t, 1H, $J = 5.6$ Hz), 4.28–4.33 (m, 2H), 3.99–4.02 (m, 1H), 3.56–3.61 (m, 1H), 3.44–3.50 (m, 1H). HR-ESI-MS, calcd. for $C_9H_{13}FN_3O_5$ ($[M + H]^+$) 262.2145; found 262.2143.

Synthetic Procedure of 1-[5-*O*-(*t*-Butyldiphenylsilyl)-α-L-lyxofuranosyl]-5-fluorocytosine (6)

A dried 100-mL, round-bottomed flask was charged with 4.70 g (18 mmol) of **5**, 3.68 g (54 mmol) of imidazole, and 20 mL of dried DMF, and the resulting mixture was stirred on an ice bath, followed by addition of 7.42 g (27 mmol) of TBDPSCl in a dropwise manner. After addition, the reaction mixture was stirred at room temperature overnight when TLC analysis demonstrated that almost all the starting **5** was consumed.

The reaction mixture was poured into 200 mL of saturated aqueous sodium chloride, and the mixture thus obtained was extracted with three 50-mL of portions of dichloromethane. The combined extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated on a rotary evaporator to afford the crude product as a colorless oil, which was purified by column chromatography (EtOAc/MeOH/Et_3N = 100/5/1.5 by v/v) to give rise to the pure product **6** as a white foam.

White foam, 7.73 g, yield 86%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.99–8.01 (d, 1H, $J = 6.8$ Hz), 7.77 (bs, 1H), 7.63–7.66 (m, 4H), 7.52 (bs, 1H), 7.39–7.47 (m, 6H), 5.78–5.79, 5.80–5.81 (dd, 1H, $J = 1.6$ Hz and 7.2 Hz), 5.25–5.27 (d, 1H, $J = 6.4$ Hz), 4.99–5.00 (d, 1H, $J = 4.0$ Hz), 4.52–4.56 (m, 1H), 4.31–4.35 (m, 1H), 4.03–4.06 (m, 1H), 3.86–3.90 (m, 1H), 3.69–3.73 (m, 1H), 0.98 (s, 9H). HR-ESI-MS, calcd. for $C_{25}H_{30}FN_3NaO_5Si$ ($[M + Na]^+$), 522.5959; found 522.5960.

Synthetic Procedure of 1-{5-*O*-*t*-Butyldiphenylsilyl-2,3-di-*O*-[methylthio(thiocarbonyl)]-α-L-lyxofuranosyl}-5-fluorocytosine (7)

A dried 100-mL, round-bottomed flask was charged with 7.49 g (15 mmol) of **6**, 3.42 g (45 mmol) of carbon disulfide, and 40 mL of DMSO, and the mixture was stirred on an ice bath, followed by addition of 1.52 g (38 mmol) of sodium hydroxide dissolved in 5 mL of water. After addition, the stirring was continued for half an hour on an ice-water bath, and 5.39 g (38 mmol) of methyl iodide was added in one portion. The resultant mixture was stirred at room temperature for 2 h.

The reaction mixture was poured into 200 mL of saturated aqueous sodium chloride, and the mixture thus obtained was extracted with three 50-mL portions of dichloromethane. The combined extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated on a rotary evaporator to give rise the crude product as a yellow oil, which was purified by column

chromatography (EtOAc/petroleum ether = 4/1 by v/v) to furnish the pure product **7** as a white foam.

White foam, 7.96 g, yield 78%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.11–8.12 (d, 1H, J = 6.8 Hz), 7.96 (bs, 1H), 7.69 (bs, 1H), 7.58–7.61 (m, 4H), 7.39–7.48 (m, 6H), 6.78–6.80 (t, 1H, J = 5.4 Hz), 6.63–6.65 (t, 1H, J = 4.6 Hz), 5.98–5.99 (d, 1H, J = 6.0 Hz), 5.08–5.09 (m, 1H), 3.78–3.80, 3.81–3.83 (dd, 1H, J = 3.2 Hz and 10.4 Hz), 3.69-3.70, 3.71–3.73 (dd, 1H, J = 5.8 Hz and 10.2 Hz), 2.54 (s, 3H), 2.49 (s, 3H), 0.95 (s, 9H). HR-ESI-MS, calcd. for $C_{29}H_{35}FN_3O_5S_4Si$ ($[M+H]^+$) 680.9487; found 680.9490.

Synthetic Procedure of 2′,3′-Dideoxy-5-fluoro-5′-*O*-(*t*-butyldiphenylsilyl)-α-l-cytidine (8)

A dried 100-mL, round-bottomed flask was charged with 7.48 g (11 mmol) of **7**, 14.55 g (50 mmol) of *n*-Bu_3SnH, 0.82 g (5 mmol) of AIBN, and 60 mL of dried toluene, and the resulting mixture was refluxed under nitrogen for 1 h when TLC analysis indicated that all the starting **7** was consumed completely.

On cooling, the reaction mixture was evaporated on a rotary evaporator to afford the crude product **8** as a yellow oil, which was purified by column chromatography (EtOAc/MeOH = 20/1) to produce the pure product **8** as a white foam.

White foam, 3.89 g, yield 76%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.80 (bs, 1H), 7.62–7.64 (m, 4H), 7.50–7.51 (bs + d, 2H, for the doublet J = 6.8 Hz), 7.40–7.48 (m, 6H), 6.92–6.93 (m, 1H), 6.37–6.39 (m, 1H), 5.96–5.98 (m, 1H), 5.22–5.24 (m, 1H), 3.74–3.75, 3.77–3.78 (dd, 1H, J = 3.8 Hz and 10.6 Hz), 3.66–3.67, 3.69–3.70 (dd, 1H, J = 4.0 Hz and 10.8 Hz), 0.98 (s, 9H). HR-ESI-MS, calcd. for $C_{25}H_{29}FN_3O_3Si$ ($[M+H]^+$), 466.5994; found 466.5999.

Synthetic Procedure of α-Elvucitabine

A dried 100-mL, round-bottomed flask was charged with 3.72 g (8 mmol) of **8** and 20 mL of dried THF, and the mixture thus obtained was stirred at room temperature followed by addition of 9 mL (9 mmol) of 1.0 M *n*-Bu_4NF in THF. The stirring was continued for 1 h when all the starting **8** 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 solid, mp 128–130 °C, 1.60 g, yield 88%. $[\alpha]_D^{20} = +262.3°$ (c = 1, MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.76 (bs, 1H), 7.52 (bs, 1H), 7.45–7.47 (d, 1H, J = 6.8 Hz), 6.84–6.85 (m, 1H), 6.34–6.36 (m, 1H), 5.88–5.90 (m, 1H), 5.06–5.08 (m, 1H), 4.82 (s, 1H), 3.41–3.47 (m, 2H). HR-ESI-MS, calcd. for $C_9H_{11}FN_3O_3$ ($[M+H]^+$), 228.1998; found 228.2002. NOESY data were collected, and the useful correlations are summarized in Fig. 3.

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