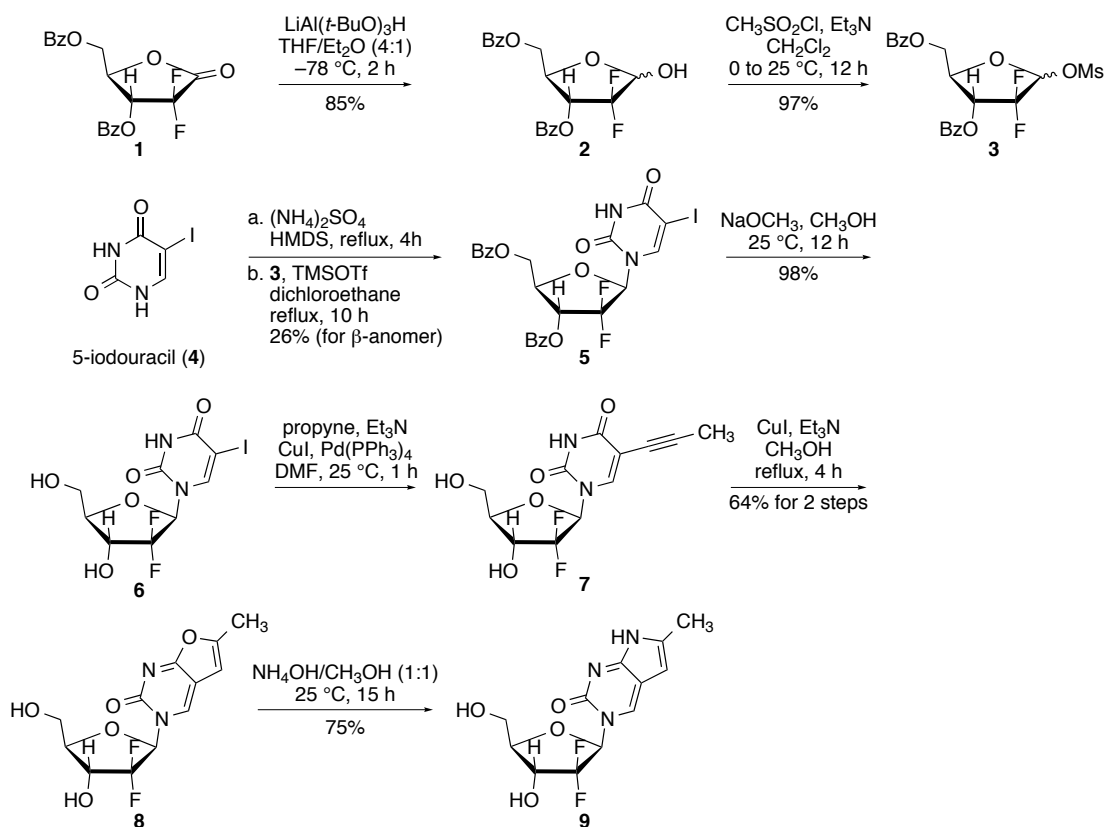
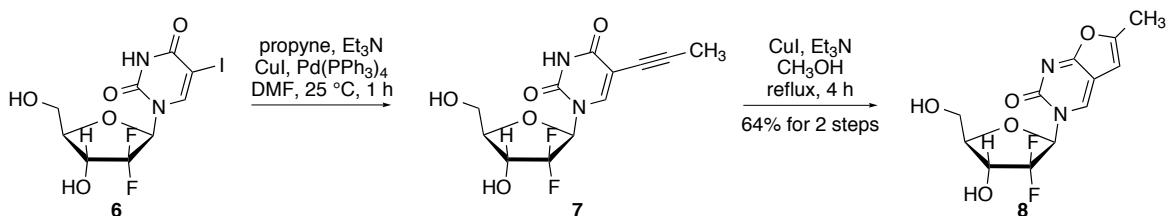


## Supplementary file 1

### Synthetic Approach to Furano- and Pyrrolo-Gemcitabines



### Preparation of Furano-Gemcitabine 8

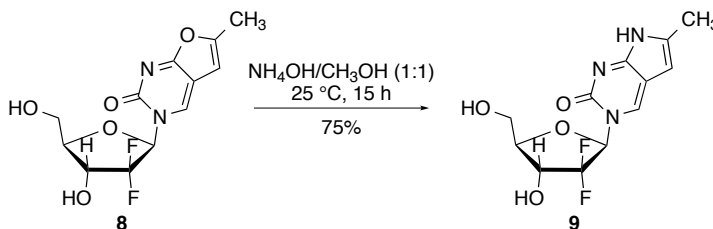


**[Sonogashira Coupling]** To a solution of known 2'-deoxy-2',2'-difluoro-5-iodo-uridine **6** (100 mg, 0.256 mmol) in  $\text{DMF}$  (3 mL, 0.085 M) were added  $\text{CuI}$  (12 mg, 0.062 mmol),  $\text{Et}_3\text{N}$  (71  $\mu\text{L}$ , 0.512 mmol), and  $\text{Pd}(\text{PPh}_3)_4$  (36.2 mg, 0.031 mmol)<sup>30</sup>. The resulting mixture was treated with propyne (150 mg, 3.753 mmol) and stirred for 1 h at  $25^\circ\text{C}$ . The reaction mixture was filtered through a pad of silica

gel ( $\text{CHCl}_3/\text{MeOH} = 9/1$ ) and concentrated *in vacuo*. The crude alkyne **7** was employed in the next step without further purification.

**[Cyclization]** To a stirred solution of **7** (55 mg, 0.182 mmol) in  $\text{Et}_3\text{N}/\text{MeOH}$  (3:7, 3 mL) was added  $\text{CuI}$  (5 mg, 0.026 mmol). After stirring for 4 h at reflux, the resulting mixture was concentrated *in vacuo*. The residue was purified by column chromatography ( $\text{SiO}_2$ ,  $\text{CHCl}_3/\text{MeOH} = 8/1$ ) to afford furano-gemcitabine **8** (50 mg, 64% for 2 steps) as a brown solid:  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.57 (s, 1H), 6.45 (t,  $J = 1.2$  Hz, 1H), 6.34 (d,  $J = 6.8$  Hz, 1H), 6.28 (t,  $J = 7.2$  Hz, 1H), 5.37 (t,  $J = 5.2$  Hz, 1H), 4.15–4.28 (m, 1H), 3.90–3.96 (m, 1H), 3.80–3.88 (m, 1H), 3.64–3.72 (m, 1H), 2.34 (s, 3H); HRMS (ESI)  $m/z$  303.0785  $[(\text{M}+\text{H})^+]$ ,  $\text{C}_{12}\text{H}_{13}\text{F}_2\text{N}_2\text{O}_5$  requires 303.0787].

### Preparation of Pyrrolo-Gemcitabine **9**



A solution of **8** (50 mg, 0.165 mmol) in  $\text{MeOH}$  (1.5 mL) was treated with  $\text{NH}_4\text{OH}$  (1.5 mL) at  $25^\circ\text{C}$ . After stirring for 15 h at the same temperature, the resulting mixture was concentrated *in vacuo*. The residue was purified by column chromatography ( $\text{SiO}_2$ ,  $\text{CHCl}_3/\text{MeOH} = 8/1$ ) to afford pyrrolo-gemcitabine **9** (37 mg, 75%) as a brown oil:  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.24 (s, 1H), 8.37 (s, 1H), 6.33 (t,  $J = 7.2$  Hz, 1H), 6.28 (d,  $J = 6.4$  Hz, 1H), 5.92 (s, 1H), 5.34 (t,  $J = 5.2$  Hz, 1H), 4.14–4.28 (m, 1H), 3.88 (dt,  $J = 8.8, 2.4$  Hz, 1H), 3.80–3.86 (m, 1H), 3.64–3.71 (m, 1H), 2.21 (s, 3H); HRMS (ESI)  $m/z$  302.0946  $[(\text{M}+\text{H})^+]$ ,  $\text{C}_{12}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_4$  requires 302.0947].