Supplementary Material

Synthesis of (*L*)-4,4-Difluoroglutamic Acid via Electrophilic Difluorination of a Lactam.

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General Methods. Column chromatography was performed with silica gel 60 (230-400 mesh). ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker AVANCE DRX300 and DRX500 spectrometers using the XWinNMR software. Chemical shifts are reported in parts per million (ppm) upfield or downfield from tetramethylsilane (internal standard for ^{1}H and ^{13}C) or trifluoroacetic acid (external standard for ^{19}F). Mass spectra were obtained with a VG 70-250-S mass spectrometer made by Micromass (UK) and an Opus data system.

(*S*)-5-(hydroxymethyl)-2-pyrrolidinone **5** was synthesized by the method of Pickering *et. al.*[1] (5*S*)-2,2-dimethyl-8-oxo-1-aza-3-oxa-bicyclo<3.3.0>octane **4** was synthesized by a modification of the method of Allen *et. al.*[2] All other reagents and starting materials were obtained from Sigma-Aldrich or Fisher-Acros and used without further purification unless noted otherwise. Tetrahydrofuran (THF) was freshly distilled from sodium / benzophenone. Diisopropyl amine was distilled from sodium hydroxide. Air- and moisture-sensitive reactions were run in flame- or oven-dried (T > 100 °C overnight) glassware under an atmosphere of dry argon.

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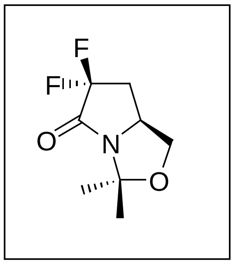
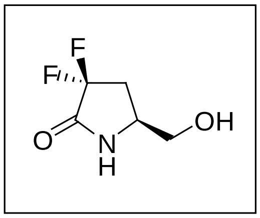
[1] Pickering, L.; Malhi, B.S.; Coe, P.L.; Walker, R.T. *Nucleosides Nucleotides* **1994**, *13*, 1493-1506.

[2] Allen, N.E.; Boyd, D.B.; Campbell, J.B.; Deeter, J.B.; Elzey, T.K.; Foster, B.J.; Hatfield, L.D.; Hobbs, J.N.; Hornback, W.J.; Hunden, D.C.; Jones, N.D.; Kinnick, M.D.; Morin, J.M.; Munroe, J.E.; Swartzendruber, J.K.; Vogt, D.G. *Tetrahedron*, **1989**, *45*, 1905-1928.

General procedure for electrophilic fluorinations. Diisopropyl amine (1.3 eq.) was added to THF with magnetic stirring and the solution was cooled to -78°C in a dry ice-iPrOH bath. N-butyllithium (1.1 eq., 1.6M in hexanes) was added slowly and the mixture was stirred for 60 minutes. A solution of the fluorination substrate (in THF) was then added dropwise and a yellow color appeared. The mixture stirred an additional 45 minutes at -78°C before the addition of a solution of NFSi (1.3 eq. in THF). Finally, after stirring for another 30 minutes, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The flask was allowed to warm slowly to room temperature and then the THF was removed *in vacuo*. The remaining residue was partitioned between EtOAc and water and, after separation of layers, the water layer was extracted further (2X) with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to leave the crude product which was purified by silica gel column chromatography.



(5*S*)-2,2-dimethyl-7,7-difluoro-8-oxo-1-aza-3-oxa-bicyclo<3.3.0>octane 6. The general fluorination procedure was carried out using **4** (3.2g, 20.6mmol) as a substrate. The intermediate monofluorinated lactam was purified by silica gel column chromatography (EtOAc / hexane, 3:2) and obtained as a pale yellow oil which was an inseparable 1.2:1.0 mixture of diastereomers (2.1g, 12.1mmol, 59% yield). A portion of this mixture (1.6g, 9.2mmol) was subjected to the same fluorination procedure a second time and the desired difluorinated lactam **6** was obtained as an off-white solid after purification by silica gel column chromatography ($CHCl_3$ / EtOAc, 4:1) (1.25g, 6.5mmol, 71% yield); $\mathbf{R_f}$ = 0.64 ($CHCl_3$ / EtOAc, 4:1) ; **mp** 41-43°C ; **^{1}H NMR** ($CDCl_3$, 300MHz) δ 1.54 (s, 3H), 1.69 (s, 3H), 2.14 (m, 1H), 2.77 (m, 1H), 3.46 (dd, 1H), 4.13 (m, 1H), 4.26 (dd, 1H) ; **^{13}C NMR** ($CDCl_3$, 75.5MHz) δ 23.58, 26.55, 35.41 (t[3], $^2J_{C-F}$ = 23.3 Hz, 23.5 Hz), 54.21, 69.98, 92.66, 121.34 (t[3], $^1J_{C-F}$ = 254.9 Hz, 257.7 Hz), 160.06 (t[3], $^2J_{C-F}$ = 30.5 Hz, 31.1 Hz) ; **^{19}F NMR** ($CDCl_3$, 282 MHz) δ -27.4 (ddd, $^2J_{F-F}$ = 264.4 Hz, $^3J_{H-F}$ = 13.7 Hz, 21.3 Hz), -26.0 (dd, $^2J_{F-F}$ = 264.4 Hz, $^3J_{H-F}$ = 13.7 Hz); **MS** (CI w/ NH_3) *m / e* (rel. intensity) 192.1 (MH^+, 6.77), 176.1 (MH^+-15, 100.00), 84.1 (50.43); **HRMS** (CI w/ NH_3) *m / e* calcd. for $C_8H_{12}NO_2F_2$ (MH^+) 192.0836, found 192.0831.



(5*S*)-3,3-difluoro-5-hydroxymethyl-2-pyrrolidinone 7. Compound **6** (1.25g, 6.5mmol) was stirred in a mixture of acetic acid, acetonitrile, and water (14:3:3) (15ml). The solution was heated and the temperature was maintained between 90°C and 95°C for 24 hours. The flask was allowed to cool to room temperature and the solvents were removed *in vacuo*. The resulting crude solid residue was purified by silica gel column chromatography (CH_2Cl_2 / MeOH 5:1) to obtain the product as a white solid (735mg, 4.87 mmol, 75% yield). **R_f**=0.57 (CH_2Cl_2 / MeOH, 5:1); **mp** 126-129°C; **^{1}H NMR** (DMSO, 300MHz) δ 2.32 (m, 1H), 2.51 (m, 1H), 3.35 (m, 2H), 3.64 (m, 1H), 5.04 (t, 1H, OH), 8.92 (br, 1H, NH); **^{13}C NMR** (MeOH, 75.5MHz) δ 33.66 (t, $^2J_{C-F}$ = 22.7 Hz), 51.92, 64.50, 119.93 (t[3], $^1J_{C-F}$ = 248.8 Hz, 248.5 Hz), 168.09 (t[3], $^2J_{C-F}$ = 30.8 Hz, 31.0 Hz). **^{19}F NMR** ($CDCl_3$, 282 MHz) δ -29.9 (ddd, $^2J_{F-F}$ = 270.1 Hz, $^3J_{H-F}$ = 16.1 Hz, 17.8 Hz), -28.6 (dddd, $^2J_{F-F}$ = 270.1, $^3J_{H-F}$ =17.4 Hz, 12.8 Hz, $^4J_{H-F}$ = 3.8 Hz); **MS** (CI w/ NH_3) *m / e* (rel. intensity) 169.2 ($M+NH_4^+$, 100.00), 152.1 (10.11); **HRMS** (CI w/ NH_3) *m / e* calcd. for $C_5H_{11}F_2N_2O_2$ ($M+NH_4^+$) 169.0788 found 169.0785.

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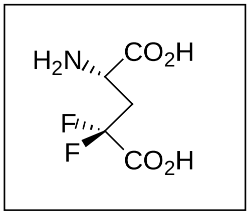
3) Peak appears as an unsymmetrical triplet. Values given are the distances between the center line and each of the two outer lines of the triplet.



(*L*)-4,4-difluoroglutamic acid 8. Difluoropyroglutaminol **7** (664mg, 4.39 mmol) was dissolved in wet acetone (15ml) and the Jones reagent was added periodically in portions while monitoring the disappearance of starting material and the reaction progress by TLC. When the reaction was complete, iPrOH was added and stirring continued for 30 minutes to quench any remaining Jones reagent. The reaction mixture was then diluted with an equal volume of water and the acetone was removed by distillation under reduced pressure. The remaining dark blue aqueous layer was adjusted to pH = 3.0 with saturated aqueous $NaHCO_3$ and then extracted continuously with EtOAc for 36 hours. Evaporation of the extract left crude difluoropyroglutamate as an off-white solid which was not purified further. This solid was dissolved in 6N aqueous HCl and warmed to 80°C for 2 hours. Removal of the solvent left the crude (*L*)-4,4-difluoroglutamic acid hydrochloride.

The hydrochloride was dissolved in dd H_2O and applied to a column of *Bio-Rad* AG3-X4 resin which had been equilibrated with dd H_2O. The column was eluted with dd H_2O and then an increasing gradient of TFA up to 0.25N. The fractions which contained product were pooled and lyophilized to yield the crude (*L*)-4,4-difluoroglutamic acid as yellow-orange solid. A portion of this material (130mg) was crystallized from iPrOH / H_2O to give the product as small white needles (100mg, 0.54mmol, 45% yield from **7**). **mp** 173-176°C (dec.) (lit [racemic][4] 175-177°C); **$[\alpha]^{25}_D$** = +12.11 (c 0.9, ddH_2O); **^{1}H NMR** (D_2O, 500.0 MHz) δ 2.68 (m, 1H), 2.85 (m, 1H), 4.35 (dd, 1H); **^{13}C NMR** (D_2O, 125.8 MHz) δ 34.02 (t, $^2J_{C-F}$ = 24.6 Hz), 47.82, 115.71 (t, $^1J_{C-F}$ = 251 Hz), 168.29 (t, $^2J_{C-F}$ = 28 Hz), 170.55; **^{19}F NMR** (D_2O, 470.5 MHz) δ -26.36 (ddd, $^2J_{F-F}$ = 252 Hz, $^3J_{H-F}$ = 11 Hz, 22 Hz), -27.16 (ddd, $^2J_{F-F}$ = 252 Hz, $^3J_{H-F}$ = 14 Hz, 21 Hz); **MS** (DCI w/ NH_3) *m* / *e* (rel. intensity) 183.1 (M+NH_4-H_2O, 100.00), 166.1 (25.61), 120.0 (12.65); **HRMS** (DCI w/ NH_3) *m* / *e* calcd. for $C_5H_9F_2N_2O_3$ (M+NH_4-H_2O) 183.0581 found

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[4] Tsukamoto, T.; Kitazume, T.; McGuire, J.J.; Coward, J.K. *J. Med. Chem.* **1996**. *39*. 66-72.

183.0586.