Supplementary Material: Synthesis of (3*S*)-Fluoro-L-Proline

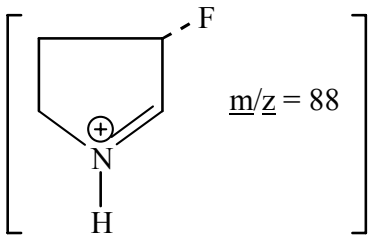
***N-tert*-Butyloxycarbonyl-*cis*-3-hydroxy-L-proline (1).** To a suspension of 1.31 g (10 mmol) of *cis*-3-hydroxy-L-proline in 50 mL of THF/H_2O (2:1 v/v) was added 4.4 mL of 10% NaOH, followed by 3.96 g (18 mmol) of Boc_2O at O^oC. The solution was stirred vigorously for 16 hr. at room temperature, and the solvent was evaporated. The residue was dissolved in ethyl acetate, and mixed with a saturated solution of $KHSO_4$ until the pH was 2. The organic layer was washed with water, then brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated. The oily product gradually afforded white crystals (2.26 g, 98%) of **1**, m.p. 124-125^o (dec.). ^{1}H NMR ($CDCl_3$): δ 1.38, 1.44 (1:1.2, s, 9H); 2.01, 2.02 (m,2H); 3.45, 3.61 (m,2H); 4.37, 4.41 (m,1H); 4.62 (m,1H); 6.45 (br s,2H). ESI-MS: m/z. 232 ($M+H^+$) (100%); 176 ($M+H^+$-56) (70%); 132 ($M+H^+$-56-44) (11%). The double peaks in the NMR spectrum correspond to *cis*, *trans* conformations on account of restricted rotation about the amide bond.

***N-tert*-Butyloxycarbonyl-*cis*-3-hydroxy-L-proline benzyl ester (2)**. A solution of 2.08g (9 mmol) of **1** in 8 mL anhydrous THF was cooled in an ice bath and mixed with 3 mL of diethylisopropylamine (17 mmol). To this mixture was added dropwise 1.7 mL (15 mmol) of benzyl bromide. After the mixture was stirred at room temperature for 18 hr, the solvent was evaporated, the residue was extracted with ethyl acetate, washed successively with 1N HCl, saturated solution of $NaHCO_3$, water, brine and dried (anhyd. Na_2SO_4). The residue left after evaporation of the solvent was subjected to flash column chromatography over silica gel. Elution with 1:2 EtOAc/hexanes afforded 2.54 g (88%) of **2** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 1.32, 1.41 (2:1, s,9H); 2.02, 2.16 (m,2H); 3.45, 3.62 (m,2H); 4.37 (d), 4.45 (d) (J = 5.2 Hz) (1H); 4.60 (d of d overlaps m, J = 6Hz, 3H); 5.16, 5.32 (two doublets, J = 6 Hz, 2H, minor conformn. benzyl protons); 5.21 (s,1H); 7.36 (m,5H). ESI-MS:m/z 322 ($M+H^+$, 100%), 266 ($M+H^+$-56, 65%), 222 ($M+H^+$-56, -44,. 15%).

***N-tert*-Butyloxycarbonyl-*trans*-3-fluoro-L-proline benzyl ester (3).** To a solution of 0.520 g (1.6 mmol) of **2** in 8 mL of anhydrous CH_2Cl_2, cooled to -78^{o}C, was added 0.97 mL (8 mmol) morph-DAST dropwise under an atmosphere of argon. The mixture was allowed to warm to room temperature while being stirred for 3 days. After evaporation of the solvent, the residue was dissolved in ethyl acetate, treated carefully with ice-cold, saturated solution of $NaHCO_3$, washed with water, then brine and dried. Evaporation of the solvent afforded a red-brown residue, which was subjected to flash chromatography over silica gel. Elution of the column with mixtures of EtOAc/hexanes (starting with 1:2.5) yielded 0.382 g (73%) of **3** as a light yellow liquid. ^{1}H NMR ($CDCl_3$) δ 1.30, 1.43 (2:1.2, s, 9H); 2.02, 2.18 (m,2H); 3.44, 3.63 (m,2H); 4.38 (d), 4.51 (d), J = 6 Hz, 1H; 4.60 (d of d overlaps m, J = 5.8Hz, 3H); 5.20 (d of d, J = 6Hz, 2H); 7.36 (m,5H). ESI-MS: m/z = 330 ($M+Li^+$), 274 ($M+Li^+$-56); 230 ($M+Li^+$-56–44); 310 ($M+Li^+$-HF).

***N-tert*-Butyloxycarbonyl-*trans*-3-fluoro-L-proline (4).** A solution of 0.323 g (1 mmol) of **3** in 19 mL 95% ethanol was mixed with 500 mg of 10% Pd/C and exposed to hydrogen at 55 psi for 48 hr in a Parr apparatus. Filtration of the catalyst, evaporation of the solvent, followed by flash chromatography on silica gel (EtOAc/hexanes 1.0:1.8) yielded 0.200 g (90%) of **4**. ESI-MS: m/z = 240 ($M+Li^+$). ^{1}H NMR ($CDCl_3$): δ 10.8 (CO_2H), absence of peak at δ 7.36.

(3*S*)-Fluoro-L-proline (5). A solution of 0.186 g (0.8 mmol) of **4** in 5 mL 1,4-dioxane was treated with 2.5 mL 4N HCl in dioxane at 0^{o} for 1 hr. The solution was concentrated by a stream of argon, extracted with CH_2Cl_2, followed removal of solvents *in vacuo* to afford 52mg (50%) of **5** as the hydrochloride salt. ESI-MS: m/z = 134 ($M+H^+$), 144 ($M+H^+$-HF), 88 ($M+H^+$-HCO_2H).



Synthesis of N-Acetyl-(3*S*)-3-Fluoro-L-Proline Methyl Ester

***N-tert*-Butyloxycarbonyl-*cis*-3-hydroxy-L-proline methyl ester (6).** To a suspension of 0.693g (3 mmol) of **1** in 15 mL of acetone was added 0.207 g (1.5 mmol) anhydrous K_2CO_3 and heated at reflux, followed by 1.42 g CH_3I (10 mmol). The mixture was heated for 2 days, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (eluent was EtOAc/hexanes 1:1.8) to afford 0.714 g (97%) of **6** as a slightly colored liquid. ^{1}H NMR ($CDCl_3$): δ 1.42, 1.47 (2:1) (s,9H); 2.02, 2.10 (m,2H); 3.47, 3.65 (m,2H); 3.68, 3.69 (s,3H); 4.35 (d), 4.44 (d) (2:1, m,1H); 4.58 (m,1H). ESI-MS: m/z = 252 ($M+Li^+$) (100%); 196 ($M+Li^+$-56) (10%); 152 ($M+Li^+$-56-44) (12%).

***N-tert*-Butyloxycarbonyl-*trans*-3-fluoro-L-proline methyl ester (7).** To a solution of 0.615 g (2.5 mmol) of **6** in 12 mL anhydrous CH_2Cl_2, cooled to -78°C, was added 0.97 mL (8 mmol) morph-DAST dropwise under an atmosphere of argon. The mixture was stirred at room temperature for 3 days, and the solvent was evaporated. The residue was dissolved in ethyl acetate, treated slowly with ice-cold, saturated solution of $NaHCO_3$, washed with water, brine and dried. Removal of the solvent was followed by flash chromatography over silica gel. Elution of the column with EtOAc/hexanes yielded 0.529 g (86%) of **7** as a light colored liquid. ^{1}H NMR ($CDCl_3$): δ 1.41, 1.50 (2.7:1, s,9H); 2.12, 2.24 (m,2H); 3.52, 3.70 (m,2H); 3.73, 3.74 (s,3H); 4.43 (d), 4.60 (d) (1H); 5.10 (m), 5.24 (m) (1H). ESI-MS m/z = 254 ($M+Li^+$), 234 ($M+Li^+$-HF).

***Trans*-3-Fluoro-L-proline methyl ester (8).** A mixture of 0.494 g (2 mmol) of **7** and 1.5 mL of 1:1 CH_2Cl_2/CF_3CO_2H was stirred at 0° for 4 hr and the solvent was evaporated to afford **8** as the trifluoroacetate salt. It was used in the next step without further purification.

***N*-Acetyl-(3*S*)-3-Fluoro-L-proline methyl ester (9).** The product from the previous step was treated dropwise with NEt_3 at 0° until no more fumes were seen. It was then dissolved in 2.5 mL $CHCl_3$, mixed with 1.5 mL Ac_2O, a drop of HOAc, and the mixture was stirred at room temperature for 16 hr. Evaporation of the solvent, followed by chromatography on silica gel, afforded 0.31 g (82%) of **9**. ESI-MS: m/z = 196 ($M+Li^+$), 176 (M+Li-HF), 133 ($M+Li^+$-63), $\left(M + Li^+\text{-}20\text{-}CH_3-C\overset{O}{\underset{H}{<}}\right)$, 100 ($M+Li^+$-20-44-$CH_3OH$).

Kinetic and activation parameters of of cis-trans isomerization from ^{19}F-NMR experiments.

In accord with previous analyses of cis-trans isomerization kinetics using spin-inversion transfer, the pulse sequence (Eberhardt, E.S., et al., *J. Am. Chem. Soc*. 1996, 118, 12261):

delay (d1) – (90°x – 1/2Δδ – 90°x) – τ – 90°x-acquire

was used where Δδ corresponds to the difference in chemical shift between the cis and trans resonance (for 3*R* the difference is ~2 ppm, for 3*S* the difference was ~0.99 ppm). The carrier frequency is placed on either the cis or the trans resonance, and the sequence provides a selective 180 pulse (90°x – 1/2Δδ – 90°x) that is then monitored as a function of time (τ) in an arrayed experiment. In a typical experiment, values of τ ranged from 0.01 to 40 ms. The rate of recovery back to magnetic equilibrium is governed by the longitudinal relaxation rate constants T_{1cis} and T_{1trans} of the cis and trans isomers, respectively, as well as the rate constants associated with cis-trans isomerization: k_{EZ} and k_{ZE}. Values of k_{EZ} and k_{ZE} were obtained by a joint analysis of two complimentary sets of data acquired at the same temperature, setting the carrier frequency on the cis resonance for one set and on the trans resonance for another set. Both sets of data were then analyzed using the Bayes Analysis package provided by Varian (Varian associates, Palo Alto, CA) to obtain the rate constants k_{EZ} and k_{ZE}.
The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ listed in Table I were obtained from non-linear least squares analysis to the Eyring equation:

$$\ln (k/T(K)) = -\Delta H^{\ddagger}/R^{*} (1/T) + \Delta S^{\ddagger}/R + \ln (k_B /h)$$

Where k is the rate constant obtained at temperature T (Kelvin), k_B is the Boltzman constant, *h* is Planck's constant, and R is the universal gas consant.
Values for the equilibrium constants reported are derived from the ratio of k_{ZE} to k_{EZ} at any temperature.

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Supplementary Figure 1. ^{19}F NMR spectra of Ac-(3*R*)-fluoroproline-OMe (**A**) and Ac-(3*S*)-fluoroproline-OMe (**B**). Spectra were acquired at 35°C. Spectra represent 8 transients, with a recycle delay of 15 seconds, and were processed with 40 Hz of line broadening.