Diastereoselective Synthesis and Conformational Analysis of 4,5-Difluoropipeolic Acids

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SUPPORTING INFORMATION

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1. Reagents and instrumentation

All purchased reagents were used without further purification unless otherwise noted. All solvents were dried over 4Å molecular sieves before used unless stated otherwise. Reactions were stirred using Teflon-coated magnetic stirrers. Analytical TLC was performed with 0.20 mm silica gel 60F plates with a 254 nm fluorescent indicator. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent \( [(NH_4)_6MoO_4, Ce(SO_4)_2, H_2SO_4, H_2O] \) or a solution of 0.5% ninhydrin in \( n \)-butanol. Chromatographic purification of products was carried out by flash column chromatography on silica gel (230-400 mesh). Melting points were determined using a WRX-4 visual melting point apparatus. Both melting points and boiling points are uncorrected. NMR spectra were measured in CDCl\(_3\) (with TMS as internal standard) or DMSO-\( d_6 \) or CD\(_3\)OD or D\(_2\)O on a Bruker AV400 (1H at 400 MHz, \(^{13}\)C at 100 MHz) magnetic resonance spectrometer. Chemical shifts (\( \delta \)) are reported in ppm, and coupling constants (\( J \)) are in Hz. The following abbreviations are used to explain the multiplicities: \( s = \) singlet, \( d = \) doublet, \( t = \) triplet, \( q = \) quartet, \( m = \) multiplet. High-resolution mass spectra (HRMS) were recorded on a SYNAPT G2Si High Definition MS System operating in ESI mode.
2. Synthetic procedures and characterization data

General procedure for the synthesis of fluorinated pipecolic acid analogs (11)

Ruthenium (III) chloride trihydrate (0.024 mmol, 0.06 equiv) was added to a mixture of 15 (0.40 mmol, 1 equiv), sodium metaperiodate (7.2 mmol, 18 equiv), carbon tetrachloride (4 mL), acetonitrile (4 mL) and deionized water (5 mL), and the mixture was stirred at 25 °C until total consumption of the starting material. Isopropyl alcohol (5 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl, then dried with anhydrous sodium sulfate and concentrated in vacuo. The crude product was subjected to flash chromatography eluting with 200:1:1 dichloromethane/methanol/acetic acid to give the corresponding Boc-protected carboxylic acid.

The Boc-protected carboxylic acid synthesized above was dissolved in THF (3.0 mL), and to this solution was added dropwise 3N hydrogen chloride solution. The mixture was stirred at room temperature overnight. After TLC indicated the disappearance of the starting material, the solvent was removed to give the title compound.

\((2R,4R,5S)-4,5\text{-Difluoropiperidine-2-carboxylic acid hydrochloride (11a)}\)

The title compound was synthesized following the General Procedure above. Data for 11a: colorless solid (67%); \(^1\text{H NMR}\) (400 MHz, D\(_2\)O) \(\delta\) 5.12 (dddddd, \(J = 48.0, 9.0, 4.0, 2.0, 1.0\) Hz, H, H\(_3\)), 4.89 (dddddd, 44.0, 27.0, 11.0, 4.0, 2.0 Hz, H, H\(_4\)), 4.01 (dd, \(J = 12.5, 1.0\) Hz, 1H, H\(_2\)), 3.69 (dddddd, \(J = 14.6, 10.0, 5.0, 4.0\) Hz, 1H, H\(_{6a}\)), 3.26 (dd, \(J = 37.3, 14.6, 1.0\) Hz, 1H, H\(_{6b}\)), 2.54 (dddddd, \(J = 15.0, 5.0, 4.0, 1.0, 1.0\) Hz, 1H, H\(_{3a}\)), 2.16 (dddddd, \(J = 15.0, 12.5, 11.0, 8.0, 2.0\) Hz, 1H, H\(_{3b}\)); \(^{13}\text{C}^{[\text{H}]}\) NMR (100 MHz, D\(_2\)O) \(\delta\) 172.2 (COOH), 88.6 (dd, \(J = 183.0, 17.7\) Hz, C\(_3\)), 86.7 (dd, \(J = 178.5, 18.6\) Hz,
(2R,4S,5S)-4,5-Difluoropiperidine-2-carboxylic acid hydrochloride (11b)

The title compound was synthesized following the General Procedure above. Data for 11b: colorless solid (72%); $^1$H NMR (400 MHz, D$_2$O) $\delta$ 5.04 (ddddd, $J = 43.0$, 3.8, 1.5, 1.5, 1.3 Hz, 1H, H$_5$), 4.98 (ddddd, $J = 43.5$, 4.0, 3.3, 2.0, 1.5 Hz, 1H, H$_4$), 4.15 (dd, $J = 13.3$, 3.3 Hz, 1H, H$_2$), 3.66 (dddd, $J = 14.8$, 12.0, 2.3, 1.5 Hz, 1H, H$_6$), 3.45 (dddd, $J = 41.0$, 14.8, 2.8, 1.3 Hz, 1H, H$_{6a}$), 2.57 (ddddd, $J = 15.0$, 12.5, 3.3, 3.26, 1.0 Hz, 1H, H$_{3a}$), 2.18 (ddddd, $J = 43.0$, 15.0, 13.3, 4.0, 2.0 Hz, 1H, H$_{3a}$); $^{13}$C($^1$H) NMR (100 MHz, D$_2$O) $\delta$ 170.4 (COOH), 82.6 (d, $J = 172.4$, 32.0 Hz, C$_5$), 81.8 (d, $J = 173.8$, 33.8 Hz, C$_4$), 51.3 (C$_2$), 42.6 (d, $J = 19.9$ Hz, C$_6$), 26.0 (d, $J = 20.0$ Hz, C$_3$); $^{19}$F NMR (376 MHz, D$_2$O) $\delta$ 196.5 (m, F$_5$), 197.4 (m, F$_4$); $^{19}$F($^1$H) NMR (376 MHz, D$_2$O) $\delta$ 196.5 (d, $J = 14.5$ Hz, F$_5$), 197.4 (d, $J = 14.5$ Hz, F$_4$).

(2R,4S,5R)-4,5-Difluoropiperidine-2-carboxylic acid hydrochloride (11d)

The title compound was synthesized following the General Procedure above. Data for 11d: colorless solid (68%); $^1$H NMR (400 MHz, D$_2$O) $\delta$ 4.99 (ddddd, $J = 46.0$, 18.0, 7.0, 3.0, 1.5 Hz, 1H, H$_5$), 4.93 (ddddd, $J = 43.0$, 23.0, 6.0, 3.0, 3.0 Hz, 1H, H$_4$), 4.21 (dd, $J = 8.9$, 4.5 Hz, 1H, H$_2$), 3.50 (dddd, $J = 14.0$, 7.5, 7.0, 2.5 Hz, 1H, H$_{6a}$), 3.42 (dddd, $J = 15.0$, 14.0, 4.0, 1.5 Hz, 1H, H$_{6a}$), 2.51 (ddddd, $J = 15.0$, 12.0, 6.0, 4.5, 3.0 Hz, 1H, H$_{3a}$), 2.20 (dddd, $J = 27.0$, 15.0, 8.9, 3.0, 1.0 Hz, 1H, H$_{3a}$); $^{13}$C($^1$H) NMR (100 MHz, D$_2$O) $\delta$ 172.6 (COOH), 87.1 (dd, $J = 179.7$, 17.4 Hz, C$_5$), 86.5 (dd, $J = 15.3$, 12.0 Hz, C$_4$), 57.3 (d, $J = 11.6$ Hz, C$_2$), 46.8 (dd, $J = 20.2$, 7.2 Hz, C$_6$), 28.4 (dd, $J = 24.3$, 3.8 Hz, C$_3$); $^{19}$F NMR (376 MHz, D$_2$O) $\delta$ 190.1 (d, $J = 43.8$ Hz, F$_3$), 207.4 (dd, $J = 14.3$ Hz, F$_4$); $^{19}$F($^1$H) NMR (376 MHz, D$_2$O) $\delta$ 190.1 (d, $J = 14.3$ Hz, F$_3$), 207.4 (d, $J = 14.3$ Hz, F$_4$).
180.1, 18.0 Hz, C₄), 54.8 (dd, J = 28.5, 5.7 Hz, C₆), 29.4 (dd, J = 21.7, 5.9 Hz, C₅); ^{19}F NMR (376 MHz, D₂O) δ –200.5 (m, F₅), –203.5 (m, F₄); ^{19}F{^1}H NMR (376 MHz, D₂O) δ –200.5 (F₅), –203.5 (F₄).

tert-Butyl (2S,4R,5S)-4-fluoro-5-hydroxy-2-(4-methoxyphenyl)piperidine-1-carboxylate (12d)

![Diagram of the reaction](image)

Dess-Martin periodinane (580 mg, 1.37 mmol) was added to a solution of alcohol 12a (142 mg, 0.44 mmol) in CH₂Cl₂ (10 mL). After the disappearance of starting material, saturated aqueous NaHCO₃ and excess Na₂S₂O₃ were added to the reaction mixture. After the solids were dissolved, the mixture was extracted with CH₂Cl₂. The combined organic layers were washed with saturated aqueous NaHCO₃, dried with MgSO₄, and filtered. After removal of the solvent under vacuo at 30 °C, the residue was purified by flash chromatography on silica gel using petroleum ether/EtOAc = 1:10 as the eluent, to afford an intermediate ketone which was used directly due to its instability.

The crude ketone obtained above was dissolved in MeOH (5 mL), to which was added NaBH₄ (50 mg, 1.32 mmol) at 0 °C. After reaction at this temperature for 1 h, the reaction was quenched with sat. aqueous NH₄Cl. Then, the mixture was extracted with EtOAc. The combined organic layers were washed with water, dried with anhydrous Na₂SO₄, and filtered. After removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel using petroleum ether/EtOAc = 1:10 as the eluent, to afford 12d (45 mg, 32%), with the recovery of the starting alcohol (49 mg, 35%).

Data for 12d: colorless oil; ^{1}H NMR (400 MHz, CDCl₃) δ 7.17 (d, J = 8.5 Hz, 2H, Ar), 6.86 (d, J = 8.8 Hz, 2H, Ar), 5.38 (d, J = 6.9 Hz, 1H, H₂), 4.91 (dt, J = 50.8, 2.9 Hz, 1H, H₄), 4.14 (dd, J = 13.1, 5.4 Hz, 1H, H₆), 3.78 (s, 3H, Ar-O-C(CH₃)₃), 3.66 (ddd, J = 26.9, 11.3, 5.5, 2.5 Hz, 1H, H₅), 2.94–2.79 (m, 2H, H₃, H₆), 2.25 (bs, 1H, OH), 2.09 (ddd, J = 47.0, 15.5, 7.1, 2.3 Hz, 1H, H₃), 1.47 (s, 9H, C(CH₃)₃); ^{13}C{^1}H NMR (100 MHz, CDCl₃) δ 158.4 (COO), 155.2 (Ar), 132.0 (Ar), 127.2 (d, J = 2.4 Hz, Ar), 113.8 (Ar), 89.9 (d, J = 174.2 Hz, C₄), 80.6 (O-C(CH₃)), 67.5 (d, J = 18.9 Hz, C₃), 55.3 (Ar-O-C(CH₃)), 49.7 (C₂), 40.8 (d, J = 3.7 Hz, C₅), 31.6 (d, J = 18.6 Hz, C₃), 28.5 (C(CH₃)₃); ^{19}F NMR (376 MHz, CDCl₃) δ –202.7 (tdd, J = 49.0, 26.8, 9.5 Hz); ^{19}F{^1}H NMR (376 MHz, CDCl₃) δ –202.7.
**tert-Butyl (2S,3S,5S)-3-fluoro-2-(fluoromethyl)-5-(4-methoxyphenyl)pyrrolidine-1-carboxylate (14a); and tert-butyl (2S,4R,5R)-4,5-difluoro-2-(4-methoxyphenyl)piperidine-1-carboxylate (15a)**

![Chemical Structure](image)

A mixture of fluoroxydrin 12a (65 mg, 0.2 mmol) and neat DAST (322 mg, 2.0 mmol, 0.33 mL) was stirred at 60 °C in a plastic reaction vessel overnight. The mixture was cooled to 0 °C, diluted with dichloromethane, and quenched slowly with NaHCO₃ at 0 °C. The crude product was subjected to flash chromatography eluting with 1:50 → 1:20 petroleum ether/ethyl acetate to give a product that was tentatively identified as 14a (22 mg, 36%) and product 15a (18 mg, 28%).

Data for 14a' (after deprotection of Boc group): colorless oil; ¹H NMR (400 MHz, D₂O) δ 7.52 (d, J = 8.7 Hz, 2H, Ar), 7.10 (d, J = 8.8 Hz, 2H, Ar), 5.61 (ddt, J = 52.0, 5.9, 2.9 Hz, 1H), 5.03 (t, J = 8.7 Hz, 1H), 4.97 (t, J = 4.0 Hz, 1H), 4.85 (t, J = 3.7 Hz, 1H), 4.52 – 4.30 (m, 1H), 3.87 (s, 3H), 3.11 – 2.91 (m, 1H), 2.69 (dddd, J = 27.5, 15.1, 8.5, 3.4 Hz, 1H); ¹³C NMR (100 MHz, D₂O) δ 162.5 (Ar), 132.2 (Ar), 128.4 (Ar), 117.3 (Ar), 95.6 (dd, J = 179.3, 5.7 Hz, FCH₂), 82.5 (dd, J = 169.9, 8.2 Hz, CHF-CH₂), 66.5 (dd, J = 26.2, 18.0 Hz, N-CH-CH₂F), 64.0 (Ar-O-CH₃), 58.0 (Ar-CH-N), 39.0 (d, J = 21.7 Hz, CHF-CH₂); ¹⁹F NMR (376 MHz, D₂O) δ −175.3 (dt, J = 52.9, 26.9, 19.5 Hz), −229.8 (td, J = 46.2, 27.5 Hz); ¹⁹F¹H NMR (376 MHz, D₂O) δ −175.3, −229.8; HRMS (ESI) calcd. for C₁₂H₁₆F₂NO⁺ [M+H]⁺ 228.1194, found 228.1197.

Data for 15a: colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.18 (d, J = 8.6 Hz, 2H, Ar), 6.87 (d, J = 8.8 Hz, 2H, Ar), 5.38 (d, J = 7.1 Hz, 1H, H₂), 5.06 (dd, J = 51.5, 6.3 Hz, 1H, H₃), 4.73–4.39 (m, 1I, H₆), 4.36–4.21 (m, 1H, H₆), 3.80 (s, 3H, Ar-O-CH₃), 3.24 (dd, J = 13.4, 11.2, 2.7 Hz, 1H, H₃), 2.84 (ddt, J = 14.7, 9.3, 4.7 Hz, 1H, H₄), 2.11 (dddd, J = 44.1, 15.7, 7.3, 2.1 Hz, 1H, H₅), 1.47 (s, 9H, C(CH₃)₃); ¹⁳C¹H NMR (100 MHz, CDCl₃) δ 158.5 (COO), 155.1 (Ar), 131.8 (Ar), 127.2 (d, J = 2.4 Hz, Ar), 113.9 (Ar), 87.0 (dd, J = 180.8, 16.6 Hz, C₃), 86.4 (dd, J = 187.0, 17.5 Hz, C₄), 81.0 (O-C(CH₃)), 56.9 (Ar-O-CH₃), 50.1 (C₂), 38.2 (dd, J = 30.8, 4.4 Hz, C₆), 36.1 (dd, J = 18.6, 4.7 Hz, C₇), 28.5 (C(CH₃)₃); ¹⁹F NMR (376 MHz, CDCl₃) δ −194.9 (d, J = 45.7 Hz), −202.0 (dddd, J = 53.3, 35.9, 21.0, 10.6 Hz); ¹⁹F¹H NMR (376 MHz, CDCl₃) δ −194.9 (d, J = 11.6 Hz), −202.0 (d, J = 11.6 Hz); HRMS (ESI) calcd. for C₁₇H₂₂F₂NaO₃⁺ [M+Na]⁺ 350.1538, found 350.1542.
**tert-Butyl (2R,3R,5S)-3-fluoro-2-(fluoromethyl)-5-(4-methoxyphenyl)pyrrolidine-1-carboxylate (14b); and tert-butyl (2S,4S,5S)-4,5-difluoro-2-(4-methoxyphenyl)piperidine-1-carboxylate (15b)**

A mixture of fluoro hydrin 12b\(^1\) (81 mg, 0.25 mmol) and neat DAST (405 mg, 2.5 mmol, 0.33 mL) was stirred at 60 °C in a plastic reaction vessel overnight. The mixture was cooled to 0 °C, diluted with dichloromethane, and quenched slowly with NaHCO\(_3\) at 0 °C. The crude product was subjected to flash chromatography eluting with 1:50→1:20 petroleum ether/ethyl acetate to give two isolated products: a compound tentatively identified as 14b (24 mg, 27%); and 15b (26 mg, 32%).

Data for 14b: colorless oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.20 (d, \(J = 8.7\) Hz, 2H, Ar), 6.85 (d, \(J = 8.7\) Hz, 2H, Ar), 5.19 (dd, \(J = 51.7, 3.6\) Hz, 1H, N-CH\(\text{CH}_2\)), 4.87–4.75 (m, 2H, FCH\(\text{CH}_2\)), 4.65 (d, \(J = 8.8\) Hz, 1H, CH-CH\(\text{CH}_2\)-CHF), 4.30 (t, \(J = 27.0\) Hz, 1H, Ar-CH-N), 3.79 (s, 3H, Ar-O-CH\(_3\)), 2.54 (ddd, \(J = 19.6, 14.8, 6.6\) Hz, 1H, CH-CH\(\text{CH}_2\)-CHF), 2.08 (dt, \(J = 45.5, 12.8\) Hz, 1H, CHF), 1.15 (s, 9H, C(CH\(_3\))\(_3\)); \(^{13}\)C\(^{\{\text{H}\}\}\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 158.8 (COO), 155.1 (Ar), 135.8 (Ar), 127.2 (Ar), 113.8 (Ar), 93.9 (d, \(J = 177.8\) Hz, FCH\(_2\)), 82.6 (dd, \(J = 172.4, 11.9\) Hz, CHF-CH\(_2\)), 80.5 (O-CH(FCH\(_3\))\(_3\)), 67.3 – 63.9 (m, N-CH-CH\(_2\)-F), 60.7 (CHF-CH\(_2\)), 55.4 (d, \(J = 3.8\) Hz, Ar-O-CH\(_3\)), 42.6 (Ar-CH-N), 28.2 (C(CH\(_3\))\(_3\)); HRMS (ESI) calcd. for C\(_{17}\)H\(_{24}\)F\(_2\)N\(_3\)O\(_5\) \([\text{M+H}]^+\) 328.1719, found 328.1720.

Data for 15b: colorless oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.15 (d, \(J = 7.8\) Hz, 2H, Ar), 6.90 (d, \(J = 8.8\) Hz, 2H, Ar), 5.53 (bs, 1H, H\(_2\)), 4.84–4.71 (m, 0.5 H, H\(_6\)), 4.64 (ddt, \(J = 13.8, 6.5, 4.8\) Hz, 1H, H\(_3\)), 4.57–4.46 (m, 0.5 H, H\(_6\)), 4.45–4.32 (m, 1H, H\(_6\)), 3.80 (s, 3H, Ar-O-CH\(_3\)), 2.86–2.75 (m, 1H, H\(_3\)), 2.70 (ddd, \(J = 13.3, 10.8, 5.0\) Hz, 1H, H\(_4\)), 2.14–1.93 (m, 1H, H\(_3\)), 1.49 (s, 9H, C(CH\(_3\))\(_3\)); \(^{13}\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) 158.7 (COO), 155.8 (Ar), 130.2 (Ar), 127.3 (Ar), 114.4 (Ar), 89.7 (C\(_5\)), 87.9 (C\(_4\)), 80.7 (O-CH(CH\(_3\))\(_3\)), 66.0 (dd, \(J = 20.5, 3.2\) Hz, C\(_6\)), 55.4 (d, \(J = 4.1\) Hz, C\(_2\)), 52.4 (Ar-O-CH\(_3\)), 43.1 (d, \(J = 20.8\) Hz, C\(_5\)), 28.5 (C(CH\(_3\))\(_3\)); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) −187.4 (bs), −191.6 (dt, \(J = 50.9, 14.2\) Hz); \(^{19}\)F\(^{\{\text{H}\}\}\) NMR (376 MHz, CDCl\(_3\)) \(\delta\) −187.4, −191.6 (d, \(J = 13.6\) Hz); HRMS (ESI) calcd. for C\(_{17}\)H\(_{23}\)F\(_2\)N\(_3\)O\(_5\) \([\text{M+Na}]^+\) 350.1538, found 350.1542.
**tert-Butyl (2S,4S,5R)-4,5-difluoro-2-(4-methoxyphenyl)piperidine-1-carboxylate (15d); and tert-butyl (3S,6S)-3-fluoro-6-(4-methoxyphenyl)-3,6-dihydropyridine-1(2H)-carboxylate (17)**

A mixture of fluorohydrin 13 (132 mg, 0.4 mmol) and neat DAST (644 mg, 4 mmol, 0.52 mL) was stirred at 60 °C in a plastic reaction vessel overnight. The mixture was cooled to 0 °C, diluted with dichloromethane, and quenched slowly with NaHCO₃ at 0 °C. The crude product was subjected to flash chromatography eluting with 1:50→1:20 petroleum ether/ethyl acetate to give the two isolated products 15d (45 mg, 35%) and 17 (35 mg, 29%).

Data for 15d: colorless oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.20–7.10 (m, 2H, Ar), 6.89 (d, \(J = 8.8\) Hz, 2H, Ar), 5.66 (bs, 1H, H₂), 4.74 (dt, \(J = 50.9, 3.9\) Hz, 1H, H₅), 4.63–4.39 (m, 2H, H₆), 3.79 (s, 3H, Ar-O-CH₃), 2.85 (ddt, \(J = 38.3, 15.3, 1.4\) Hz, 1H, H₄), 2.62–2.50 (m, 1H, H₃), 2.50–2.39 (m, 1H, H₃), 1.49 (s, 9H, C(CH₃)₃); \(^{13}\)C\(^{1}\)H NMR (100 MHz, CDCl\(_3\)) \(\delta\) 158.9 (COO), 155.7 (Ar), 129.7 (Ar), 127.1 (Ar), 114.5 (Ar), 86.8 (dd, \(J = 183.5, 18.7\) Hz, C₃), 85.9 (dd, \(J = 183.5, 16.7\) Hz, C₄), 80.9 (O-C(CH₃)), 55.4 (Ar-O-CH₃), 52.2 (d, \(J = 12.9\) Hz, C₂), 42.9 (dd, \(J = 20.4, 7.3\) Hz, C₀), 28.4 (C(CH₃)₃), 27.5 (dd, \(J = 19.2, 2.4\) Hz, C₃); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) –190.4 (d, \(J = 45.7\) Hz), –207.7 (dddt, \(J = 52.1, 38.4, 26.9, 13.4\) Hz); \(^{19}\)F\(^{1}\)H NMR (376 MHz, CDCl\(_3\)) \(\delta\) –190.4 (bs), –207.7 (d, \(J = 15.7\) Hz); HRMS (ESI) calcd. for C\(_{17}\)H\(_{25}\)F\(_2\)N\(_2\)O\(_5\) \[M+Na\]^+ 350.1538, found 350.1541.

Data for 17: colorless oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.32–7.20 (m, 2H, Ar), 6.92–6.78 (m, 2H, Ar), 6.27 (s, 1H, CHF-CH=CH), 6.16 (ddt, \(J = 10.1, 5.3, 1.6\) Hz, 1H, CHF-CH=CH), 5.90–5.55 (m, 1H, Ar-CH), 5.00–4.76 (m, 1H, N-CH₂), 4.57–4.27 (m, 1H, N-CH₂), 3.79 (s, 3H, Ar-O-CH₃), 3.06 (ddd, \(J = 38.1, 15.3, 2.4\) Hz, 1H, CHF-CH₂), 1.48 (s, 9H, C(CH₃)₃); \(^{13}\)C\(^{1}\)H NMR (100 MHz, CDCl\(_3\)) \(\delta\) 159.4 (COO), 154.8 (Ar), 135.7 (Ar), 130.6 (d, \(J = 4.8\) Hz, CHF-CH=CH), 129.0 (Ar), 122.6 (Ar), 114.0 (CHF-CH=CH), 82.0 (d, \(J = 171.0\) Hz, CFH), 80.4 (O-C(CH₃)), 55.4 (Ar-O-CH₃), 53.2 (N-CH₂), 42.5 (Ar-CH-N), 28.5 (C(CH₃)₃); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) –169.7 (m, 0.5F), –170.1 (m, 0.5F) [two rotamers]; \(^{19}\)F\(^{1}\)H NMR (376 MHz, CDCl\(_3\)) \(\delta\) –169.7 (s, 0.5F), –170.1 (s, 0.5F) [two rotamers].
3. Selected NMR spectra

$^1$H NMR (400 MHz, D$_2$O) of 11a

$^{13}$C($^1$H) NMR (100 MHz, D$_2$O) of 11a
$^{19}$F NMR (376 MHz, D$_2$O) of 11a

$^{19}$F{$^1$H} NMR (376 MHz, D$_2$O) of 11a
$^1$H-$^1$H COSY of compound 11a

$^1$H-$^1$H NOESY of compound 11a
$^1$H NMR (400 MHz, D$_2$O) of 11b

$^{13}$C$^1$H NMR (100 MHz, D$_2$O) of 11b
$^{19}$F NMR (376 MHz, D$_2$O) of 11b

$^1$H NMR (376 MHz, D$_2$O) of 11b
$^1$H-$^1$H COSY of compound 11b

$^1$H-$^1$H NOESY of compound 11b
$^1$H NMR (400 MHz, D$_2$O) of 11d

$^{13}$C$[^1]$H NMR (100 MHz, D$_2$O) of 11d
$^{19}\text{F NMR}$ (376 MHz, D$_2$O) of 11d

$^{19}\text{F}[^1\text{H}]$ NMR (376 MHz, D$_2$O) of 11d
$^1$H-$^1$H COSY of compound 11d

$^1$H-$^1$H NOESY of compound 11d
$^1$H NMR (400 MHz, CDCl$_3$) of 12d

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) of 12d
$^{19}\text{F NMR}$ (376 MHz, CDCl$_3$) of 12d

$^{19}\text{F}[^1\text{H}]$ NMR (376 MHz, CDCl$_3$) of 12d
$^1$H NMR (400 MHz, D$_2$O) of 14a$'$

$^{13}$C($^1$H) NMR (100 MHz, D$_2$O) of 14a$'$
$^{19}$F NMR (376 MHz, D$_2$O) of 14a'

$^{19}$F ($^1$H) NMR (376 MHz, D$_2$O) of 14a'
$^1$H NMR (400 MHz, CDCl$_3$) of 15a

$^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$) of 15a
$^{19}\text{F} \text{NMR} \ (376 \text{ MHz, CDCl}_3) \ of \ 15\text{a}$

$^{19}\text{F}^{1}\text{H} \text{NMR} \ (376 \text{ MHz, CDCl}_3) \ of \ 15\text{a}$
$^1$H NMR (400 MHz, CDCl$_3$) of 15b

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) of 15b
$^{19}$F NMR (376 MHz, CDCl$_3$) of 15b

$^{19}$F$^1$H NMR (376 MHz, CDCl$_3$) of 15b
$^1$H NMR (400 MHz, CDCl$_3$) of 15d

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) of 15d
$^{19}$F NMR (376 MHz, CDCl$_3$) of 15d

$^{19}$F-$^1$H NMR (376 MHz, CDCl$_3$) of 15d
$^1$H NMR (400 MHz, CDCl₃) of 17

$^{13}$C$^1$H NMR (100 MHz, CDCl₃) of 17
$^{19}$F NMR (376 MHz, CDCl$_3$) of 17

$^{19}$F-$^1$H NMR (376 MHz, CDCl$_3$) of 17
4. Conformational analysis details

Accurate $J$-values of compound 11a

**Simulated $^1$H NMR spectrum**

**Experimental $^1$H NMR spectrum**

$J$-values (Hz):

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Accurate $J$-values of compound 11b

**Simulated $^1H$ NMR spectrum**

**Experimental $^1H$ NMR spectrum**

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Accurate $J$-values of compound 11d

Simulated $^1H$ NMR spectrum

Experimental $^1H$ NMR spectrum

$J$-values (Hz):

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