Supporting Information

Analogues of Key Precursors of Aspartyl Protease Inhibitors: Synthesis of Trifluoromethyl Amino Epoxides

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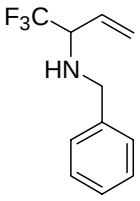
All reactions were performed in an oven-dried apparatus under an inert atmosphere of argon. ^{19}F NMR, ^{13}C NMR, ^{1}H NMR spectra were recorded on a 200 MHz or 400 MHz multinuclear spectrometer, ^{19}F NMR spectra are referenced to external $CFCl_3$, ^{1}H NMR and ^{13}C NMR spectra to TMS. In all NMR measurements $CDCl_3$ was used as a solvent. Elemental analyses were performed by the Service of Microanalyses at the "Faculty of Pharmacy", Châtenay-Malabry.

The diastereoselectivities were determined by ^{19}F NMR and GC.

1. Addition of vinyl Grignard reagent on imines 6a-c : General method.

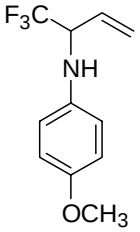
To imine **6a** or **6b** or **6c** (26.7 mmol) in anhydrous Et_2O (60 mL) was added the vinyl magnesium bromide (1M/THF) (29.4 mmol) at 0°C. After 2h of stirring, the reaction was hydrolyzed with a saturated aqueous solution of NH_4Cl (100 mL), then extracted with Et_2O (50 mL × 3). The combined organic layers were washed with a saturated solution of NaCl (30 mL), dried on $MgSO_4$, filtered, and solvents were evaporated. The residue was subjected to flash chromatography on silica gel (petroleum ether/ Et_2O, 8/2) affording the corresponding allyl amines **5a-c.**

***N*-benzyl-*N*-[1-(trifluoromethyl)prop-2-enyl]amine (5a).**



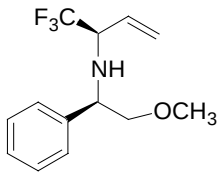
From imine **6a** (5 g, 26.7 mmol) and vinyl magnesium bromide (1M/THF) (29.4 mmol), **5a** was obtained (5.34 g, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.33 (m, 5H), 5.75 (ddd, J = 17.5, 10.6, 7.5 Hz, 1H), 5.45 (d, J = 10.6 Hz, 1H), 5.41 (d, J = 17.5 Hz, 1H), 3.98 (d, $J_{A\text{-}B}$ = 13.4 Hz, 1H), 3.85 (d, $J_{A\text{-}B}$ = 13.4 Hz, 1H), 3.62 (quint., J = 7.5 Hz, 1H), 1.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.2, 130.7, 128.5, 128.1, 127.6 (q, $^{1}J_{C\text{-}F}$ = 241.6 Hz), 127.3, 122.7, 61.7 (q, $^{2}J_{C\text{-}F}$ = 28.6 Hz), 50.7; ^{19}F NMR ($CDCl_3$, 188 MHz) δ -75.3 (d, J = 6.9 Hz). Anal. Calcd for $C_{11}H_{12}F_3N$: C, 61.39; H, 5.58; N, 6.50. Found: C, 61.41; H, 5.50; N, 6.53.

***N*-(4-methoxyphenyl)-*N*-[1-(trifluoromethyl)prop-2-enyl]amine (5b).**



From imine **6b** (7 g, 30.0 mmol) and vinyl magnesium bromide (1M/THF) (39 mL, 39 mmol), **5b** was obtained (5.34 g, 73%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.80 (m, 2H), 6.66 (m, 2H), 5.89 (ddd, *J* = 17.6, 10.3, 5.7 Hz, 1H), 5.50 (d, *J* = 17.6 Hz, 1H), 5.43 (d, *J* = 10.3 Hz, 1H), 4.35 (m, 1H), 3.76 (s, 3H), 3.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 153.2, 139.8, 130.1, 125.3 (q, $^{1}J_{C\text{-}F}$ = 282.9 Hz), 120.4, 115.6, 114.9, 59.5 (q, $^{2}J_{C\text{-}F}$ = 29.6 Hz), 55.4; ^{19}F NMR ($CDCl_3$, 188 MHz) δ -75.8 (d, *J* = 7.2 Hz); Anal. Calcd for $C_{11}H_{12}F_3NO$: C, 57.14; H, 5.23; N, 6.06. Found: C, 56.98; H, 5.16; N, 5.97.

***N*-[(1*R*)-2-methoxy-1-phenylethyl]-*N*-[(1*R*)-1-(trifluoromethyl)prop-2-enyl]amine (5c).**

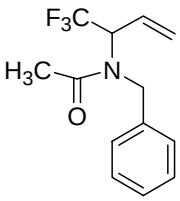


From imine **6c** (1 g, 4.33 mmol) and vinyl magnesium bromide (1M/THF) (5.63 mL, 5.63 mmol), **5c** was obtained (0.90 g, 86%) as a yellow oil; $[\alpha]_D^{20}$ –51 (c = 1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (m, 5H), 5.72 (ddd, *J* = 17.1, 10.2, 8.0 Hz, 1H), 5.46 (d, *J* = 10.2 Hz, 1H), 5.27 (d, *J* = 17.1 Hz, 1H), 4.03 (dd, *J* = 8.6, 4.8 Hz, 1H), 3.45 (s, 3H), 3.44 (m, 2H), 3.35 (quint., *J* = 8 Hz, 1H), 2.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.1, 130.5, 128.6, 127.9 (2C), 125.0 (q, $^{1}J_{C\text{-}F}$ = 280.0 Hz), 121.0, 77.5, 59.7 (q, $^{2}J_{C\text{-}F}$ = 29.2 Hz), 58.9, 58.7; ^{19}F NMR ($CDCl_3$, 188 MHz): δ -75.8 (d, *J* = 7.6 Hz); Anal. Calcd for $C_{13}H_{16}F_3NO$: C, 60.22 ; H, 6.22 ; N, 5.40. Found : C, 60.14 ; H, 6.18 ; N, 5.31.

2. Acylation of allyl amines 5 a-c : General method.

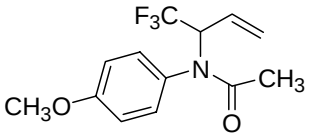
The allyl amine (9.73 mmol) was dissolved in acetic anhydride (10 mL). The solution was stirred at reflux. When the reaction was complete as indicated in GC, the mixture was then concentrated. The resulting oil was purified on silica gel (petroleum ether/ Et_2O, 8/2) to give **7a-c**.

N-benzyl-*N*-[1-(trifluoromethyl)prop-2-enyl]acetamide (7a).



From **5a** (2.10 g, 9.73 mmol) and acetic anhydride (10 mL) (2h), **7a** was obtained (2.13 g, 85%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.11 (m, 5H), 5.85 (quint., *J* = 8.1 Hz, 1H), 5.65 (ddd, *J* = 16.5, 10.2, 8.1 Hz, 1H), 5.39 (d, *J* = 16.5 Hz, 1H), 5.29 (d, *J* = 10.2 Hz, 1H), 4.50 (s, 2H), 1.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.4, 137.0, 128.6, 127.2, 126.8, 125.6, 124.6 (q, $^1J_{C\text{-}F}$ = 282.0 Hz), 124.1, 56.2 (q, $^2J_{C\text{-}F}$ = 30.5 Hz), 48.7, 21.7; ^{19}F NMR ($CDCl_3$, 188 MHz) δ -72.0 (d, *J* = 8.2 Hz). Anal. Calcd for $C_{13}H_{14}F_3NO$: C, 60.70; H, 5.49; N, 5.44. Found: C, 60.57; H, 5.50; N, 5.32.

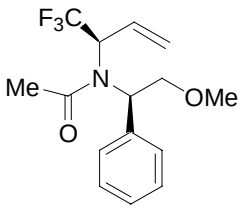
N-(4-Methoxy-phenyl)-*N*-(1-trifluoromethyl-allyl)-acetamide (7b).



From **5b** (7.6 g, 32.9 mmol) and acetic anhydride (38 mL) (2h), **7b** was obtained as a colorless oil (65 %); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (bm, 2H), 6.90 (bm, 2H), 5.97 (quint., *J* = 7.9 Hz, 1H), 5.56 (m, 2H), 5.45 (m, 1H), 3.84 (s, 3H), 1.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 159.8, 131.5, 131.2, 127.8, 124.4 (q, $^1J_{C\text{-}F}$ = 283.1 Hz), 124.1,

114.5, 57.6 (q, $^{2}J_{C\text{-}F}$ = 31.1 Hz), 55.4, 22.5; ^{19}F NMR ($CDCl_3$, 188 MHz) δ -71.5 (d, *J* = 8.3 Hz); Anal. Calcd for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13. Found: C, 57.12; H, 5.29; N, 5.01.

_N_-[(1_R_)-2-methoxy-1-phenylethyl]-_N_-[(1_R_)-1-(trifluoromethyl)prop-2-enyl]acetamide (7c).

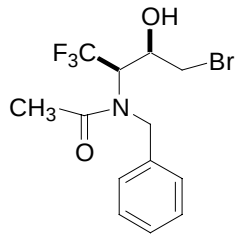


From **5c** (188 mg, 0.73 mmol) and acetic anhydride (2 mL) (4 days), **7c** was obtained (114 mg, 52%) as white crystals. Addition of a Lewis acid ($InCl_3$) strongly increased reaction rate (2h); mp. 66°C (Et_2O); $[\alpha]_D^{20}$ +34 (c = 1, MeOH); ^{1}H NMR ([D]DMSO, 400 MHz, 117°C) δ 7.3 (m, 5H), 6.04 (ddd, *J* = 17.0, 10.1, 8.0 Hz, 1H), 5.2 (d, *J* = 10.1 Hz, 1H), 5.05 (d, *J* = 17.0 Hz, 1H), 4.95 (t, *J* = 5.0 Hz, 1H), 4.88 (quint., *J* = 8.0 Hz, 1H), 4.08 (dd, *J* = 10.0, 6.4 Hz, 1H), 3.85 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.35 (s, 3H), 2.12 (s, 3H); ^{13}C NMR ([D]DMSO, 100 MHz, 117°C) δ 172.0, 139.0, 128.5, 128.0, 124.5 (q, $^{1}J_{C\text{-}F}$ = 283.0 Hz), 122.8, 74.3, 60.5, 60.0, 58.5, 23.5; ^{19}F NMR ([D]DMSO, 376 MHz, 117°C) δ -67.7 (d, *J* = 8.4 Hz); Anal. Calcd for $C_{15}H_{18}F_3NO_2$: C, 59.79 ; H, 6.02 ; N, 4.65. Found : C, 59.85 ; H, 6.06 ; N, 4.61.

3. Preparation of bromhydrins 8a-c : General method.

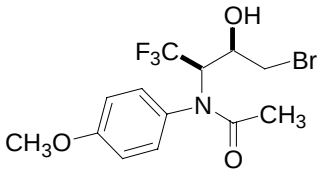
To a solution of **5a** or **5b** or **5c** (1.1 mmol) in CH_2Cl_2 (4 mL) was added bromine (1M/CH_2Cl_2) (2.1 mL, 2.1 mmol) at 0°C. After 2h of stirring, the solution was successively washed with aqueous solution of $NaHSO_3$ (20 mL), $NaHCO_3$ (20 mL), and NaCl (20 mL). The organic phase was dried over $MgSO_4$, and filtered. The solvent was removed and the residue was purified by flash chromatography on silica gel with petroleum ether/ether (9/1) as eluent to afford **8a-c**. In the case of the **5c** the oxazolinium intermediate **B** has been characterized by NMR before hydrolysis.

***N*-Benzyl-*N*-(3-bromo-2-hydroxy-1-trifluoromethyl-propyl)- acetamide (8a).**



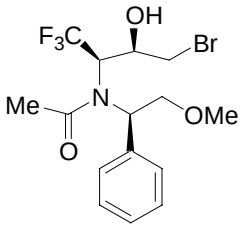
From **7a** (274 mg, 1.1 mmol) and bromine (2.1 mL, 2.1 mmol), **8a** was obtained (0.37 g, 98%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.24 (m, 5H), 5.35 (ddd, J = 8.6, 5.4, 3.9, Hz, 1H), 4.15 (d, $J_{A\text{-}B}$ = 12.9 Hz, 1H), 3.87 (d, $J_{A\text{-}B}$ = 12.9 Hz, 1H), 3.59 (m, 2H), 3.44 (m, 1H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.0, 139.0, 128.5, 127.5, 119.0 (q, $^{1}J_{C\text{-}F}$ = 296.4 Hz), 70.4, 57.6 (q, $^{2}J_{C\text{-}F}$ = 26.8 Hz), 52.0, 28.5, 20.5; ^{19}F NMR ($CDCl_3$, 188 MHz): δ -71.5 (d, J = 7.2 Hz). Anal. Calcd for $C_{13}H_{15}BrF_3NO_2$: C, 44.08; H, 4.26; N, 3.95. Found: C, 44.34; H, 4.03; N, 3.73.

***N*-(3-Bromo-2-hydroxy-1-trifluoromethyl-propyl)-*N*-(4-methoxy-phenyl)-acetamide (8b).**



From **7b** (450 mg, 1.6 mmol) and bromine (0.16 mL, 3.1 mmol), **8b** was obtained (0.58 g, 95%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.77 (m, 4H), 5.42 (ddd, J = 8.4, 5.4, 1.8 Hz, 1H), 4.41 (m, 1H), 3.69 (s, 3H), 3.49 (m, 2H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.9, 153.5, 139.5, 125,0 (q, $^{1}J_{C\text{-}F}$ = 286.2 Hz), 115.6, 114.9, 70.1, 56.2 (q, $^{2}J_{C\text{-}F}$ = 29.0 Hz), 55.5, 27.9, 20.5; ^{19}F NMR ($CDCl_3$, 188 MHz) δ -73.7 (d, J = 7.1 Hz); Anal. Calcd for $C_{13}H_{15}BrF_3NO_3$: C, 42.18; H, 4.08; N, 3.78. Found: C, 41.84; H, 4.03; N, 3.53.

***N*-[(1*R*,2*R*)-3-bromo-2-hydroxy-1-(trifluoromethyl)propyl]-*N*-[(1*R*)-2-methoxy-1-phenylethyl]acetamide (8c).**



From **7c** (156 mg, 0.5 mmol) and bromine (0.05 mL, 0.9 mmol), **8c** (0.16 g, 81%) was obtained as a yellow oil: $[\alpha]_D^{20}$ -57 (c = 1, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36 (m, 5H), 5.39 (ddd, *J* = 8.2, 5.8, 2.5 Hz, 1H), 4.25 (dd, *J* = 7.5, 5.0 Hz, 1H), 3.70 (m, 1H), 3.69 (m, 1H), 3.54 (m, 1H), 3.45 (m, 2H), 3.37 (s, 3H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ169.3, 139.5, 128.4, 128.0, 127.8, 125.4 (q, $^1J_{C\text{-}F}$ = 281.5 Hz), 77.5, 70.7, 61.2, 58.8, 56.5 (q, $^2J_{C\text{-}F}$ = 27.9 Hz), 29.2, 20.6; ^{19}F NMR ($CDCl_3$, 188 MHz): δ -73.2 (d, *J* = 7.6 Hz); Anal. Calcd for $C_{15}H_{19}BrF_3NO_3$: C, 45.24 ; H, 4.81 ; N, 3.52. Found : C, 45.37 ; H, 4.94 ; N, 3.50.

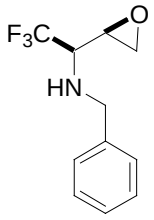
Intermediate B :

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (m, 3H), 7.47 (m, 2H), 5.80 (td, *J* = 4.6, 2.9 Hz, 1H), 5.74 (dd, *J* = 8.6, 4.1 Hz, 1H), 4.92 (qd, *J* = 5.8, 4.6 Hz, 1H), 4.32 (dd, *J* = 10.7, 8.6 Hz, 1H), 4.26 (dd, *J* = 10.7, 4.1 Hz, 1H), 4.02 (dd, *J* = 12.7, 4.7 Hz, 1H), 3.85 (dd, *J* = 12.6, 2.8 Hz, 1H), 3.57 (s, 3H), 2.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.0, 131.1, 130.2, 128.6, 128.5, 120.0 (q, $^1J_{C\text{-}F}$ = 270.0 Hz), 83.5, 70.0, 65.5 (q, $^2J_{C\text{-}F}$ = 34.0 Hz), 64.5, 60.0, 31.0, 17.0; ^{19}F NMR ($CDCl_3$, 188 MHz): δ -71.8 (d, *J* = 5.8 Hz).

3. Synthesis of epoxides 3a-c: General method.

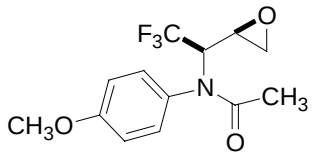
To a solution of **8a** or **8b** or **8c** (1.64 mmol) in dry THF (10 mL) was added *t*-BuOK (369 mg, 3.30 mmol) at 0°C. After 1h stirring at room temperature, the solution was hydrolyzed with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The solvents were removed and the residue was purified by flash chromatography on silica gel with petroleum ether/Et_2O (8/2) as eluent to afford epoxides **3a-c**.

***N*-Benzyl-*N*-(2,2,2-trifluoro-1-oxiranyl-ethyl)-amine (3a).**



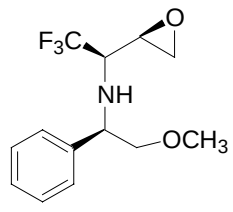
From **8a** (583 mg, 1.64 mmol) and *t*-BuOK (369 mg, 3.30 mmol), **3a** was obtained (0.3 g, 80%) as a yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.59 (m, 5H), 4.32 (d, $J_{A\text{-}B}$ = 13.4 Hz, 1H), 4.22 (d, $J_{A\text{-}B}$ = 13.4 Hz, 1H), 3.44 (m, 1H), 3.32 (m, 1H), 3.06 (m, 2H), 2.02 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.1, 128.4, 128.1, 127.3, 125.8 (q, $^{1}J_{C\text{-}F}$ = 287.8 Hz), 59.4 (q, $^{2}J_{C\text{-}F}$ = 27.4 Hz), 51.5, 49.5, 43.4; ^{19}F NMR ($CDCl_3$, 188 MHz) δ -73.6 (d, J = 6.9 Hz); Anal. Calcd for $C_{11}H_{12}F_3NO$: C, 57.14; H, 5.23; N, 6.06. Found: C, 56.57; H, 5.41; N, 5.81.

***N*-(4-Methoxy-phenyl)-*N*-(2,2,2-trifluoro-1-oxiranyl-ethyl)-acetamide (3b).**



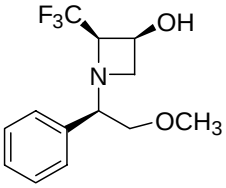
From **8b** (516 mg, 1.39 mmol) and *t*-BuOK (374 mg, 3.34 mmol), **3b** was obtained (0.26 g, 64%) as a deep yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.41 (m, 2H), 7.11 (m, 2H), 5.15 (quint., J = 8.1 Hz, 1H), 4.0 (s, 3H), 3.13 (m, 1H), 3.03 (m, 2H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.1, 159.9, 131.2, 130.7, 123.7 (q, ^{1}J = 283.8 Hz), 114.8, 58.6 (q, $^{2}J_{C\text{-}F}$ = 29.2 Hz), 55.4, 47.7, 46.9, 22.4; ^{19}F NMR ($CDCl_3$, 188 MHz) δ -70.1 (d, J = 7.6 Hz); Anal. Calcd for $C_{13}H_{14}F_3NO_3$: C, 53.98; H, 4.88; N, 4.84. Found: C, 54.36; H, 5.38; N, 4.47.

***N*-[(1*R*)-2-methoxy-1-phenylethyl]-*N*-{(1*R*)-2,2,2-trifluoro-1-[(2*R*)-oxiran-2-yl]ethyl}amine (3c).**



From **8c** (164 mg, 0.41 mmol) and *t*-BuOK (111 mg, 0.98 mmol), **3c** was obtained (0.07 g, 65%) as a yellow oil: $[\alpha]_D^{20}$ -75 (c = 1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (m, 5H), 4.24 (dd, *J* = 9.4, 3.7 Hz, 1H), 3.38 (dd, *J* = 19.0, 9.5 Hz, 1H), 3.34 (m, 1H), 3.18 (ddd, *J* = 6.4, 3.6, 2.7 Hz, 1H), 2.96 (quint., *J* = 7.2 Hz, 1H), 2.90 (t, *J* = 4 Hz, 1H), 2.71 (dd, *J* = 4.8, 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 129.0, 127.8, 126.5, 125.0 (q, $^1J_{C\text{-}F}$ = 292.0 Hz), 77.7, 60.0, 59.0, 57.0 (q, $^2J_{C\text{-}F}$ = 28.2 Hz), 49.0, 43.5; ^{19}F NMR ($CDCl_3$, 188 MHz) δ -74.3 (d, *J* = 8.3 Hz); Anal. Calcd for $C_{13}H_{16}F_3NO_2$: C, 56.72 ; H, 5.86 ; N, 5.09. Found : C, 56.55 ; H, 6.02 ; N, 5.07.

(2*R*,3*S*)-1-[(1*R*)-2-methoxy-1-phenylethyl]-2-(trifluoromethyl)azetidin-3-ol (9c).



Epoxide **3c** (100 mg, 0.36 mmol) was dissolved in *i*-PrOH (4.5 mL). The solution was stirred at reflux for 5 days. The solvent was evaporated. The crude product was purified by chromatography on silica gel (petroleum ether/ether, 8/2) to afford **9c** as white crystals (0.08 g, 84%): mp. 127°C (diisopropyle oxide); $[\alpha]_D^{20}$ +5 (c = 1, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (m, 5H), 4.55 (qd, *J* = 8.1, 3.0 Hz, 1H), 3.80 (quint., *J* = 7.2 Hz, 1H), 3.75 (m, 1H), 3.73 (m, 1H), 3.70 (m, 1H), 3.56 (dd, *J* = 8.6, 3.0 Hz, 1H), 3.53 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.33 (s, 3H), 2.26 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2, 128.4, 128.3, 127.9, 124.2 (q, $^1J_{C\text{-}F}$ = 280.6 Hz), 75.6, 67.9, 66.8 (q, $^2J_{C\text{-}F}$ = 29.3 Hz), 63.9 (q, $^3J_{C\text{-}F}$ = 2.2 Hz), 59.6, 58.9; ^{19}F NMR ($CDCl_3$, 188 MHz) δ -69.7 (d, *J* = 7.6 Hz); Anal. Calcd for $C_{13}H_{16}F_3NO_2$: C, 56.72 ; H, 5.86 ; N, 5.09. Found : C, 56.51 ; H, 6.03 ; N, 4.94.

Figure 1. ORTEP view of **9c**