Supporting Information

A Novel Route to Dipeptides via Non-condensation of Amino Acids: 2-aminoperfluoropropane as a Synthon for Trifluoroalane Dipeptides

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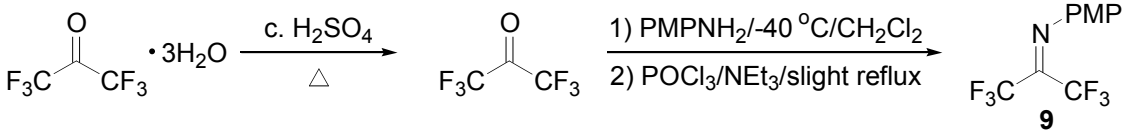
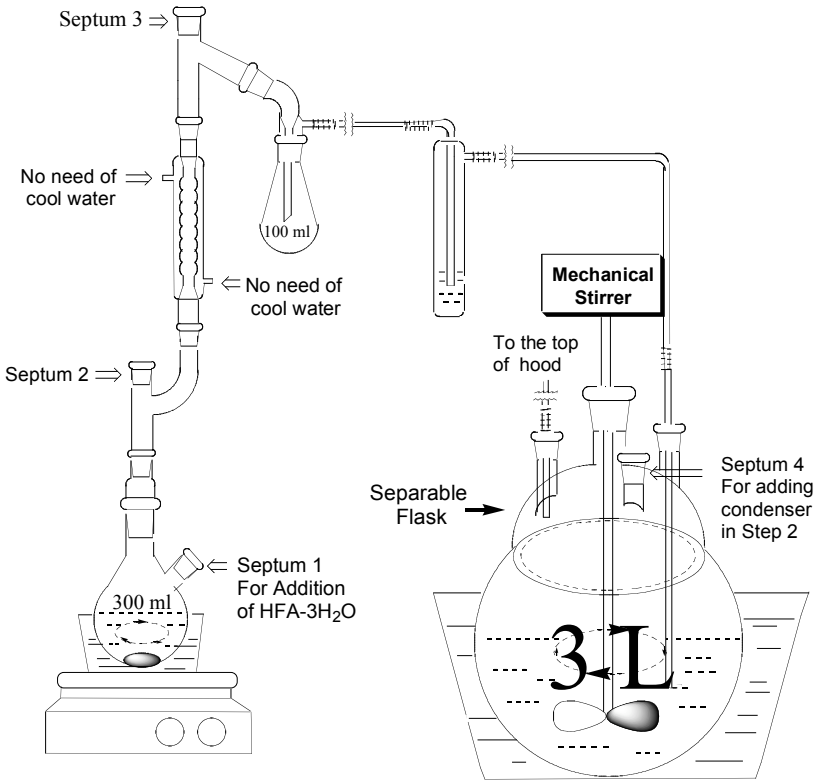
Experiment Section

^{1}H NMR spectra were recorded at 300, 500 or 600 MHz, ^{19}F NMR spectra were recorded at 282 MHz using $CDCl_3$. The chemical shifts are reported in δ (ppm) related to the $CHCl_3$ (7.26 ppm) and C_6F_6 (0 ppm). Coupling constants (J) are reported in hertz (Hz). All air and/or moisture sensitive reactions were carried out under argon atmosphere with dry, freshly distilled solvents. Dried THF was distilled from sodium and benzophenone. DMF was dried over calcium hydride. Diastereomeric excess values were measured on Chiralel OD-H column by HPLC or were determined by ^{19}F NMR if two diastereomers were of obviously different chemical shifts.

Synthesis of *N*-(*p*-methoxyphenyl) bis(trifluoromethyl)imine (9)



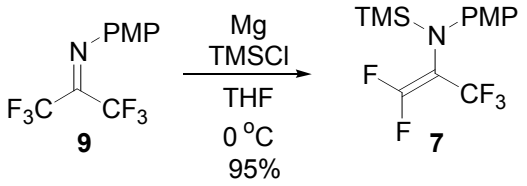


In a 3000 mL flask, a solution of *p*-anisidine (123 g, 1.0 mol) in 1500 mL dichloromethylene was cooled at about -40 ^{o}C, and then was bubbled into hexafluoroacetone gas which was generated by slowly dropping hexafluoroacetone trihydrate (265 g, 1.2 mol) to concentrated sulfuric acid (133 mL) at 90 ^{o}C over a period of 8 hours. A moisture-sensitive pale violet precipitate which was adduct of hexafluoroacetone with *p*-anisidine was gradually formed. Then, triethylamine (415 mL, 3.0 mmol) was added to the solution and the precipitate was dissolved. After that the flask was equipped with a condenser and phosphorous oxychloride (153 g, 1 mmol) was added dropwise at such a rate that gentle reflux was maintained. The solution turned to yellow and some precipitate formed. After removal of the solvent and the tertiary amine,

the residue was subjected to distillation under reduced pressure to give the crude product.

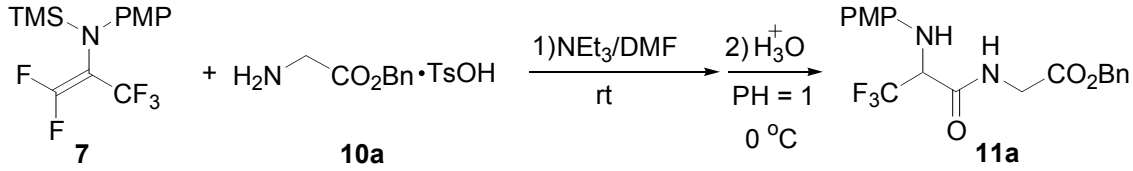
Distillation again afforded a yellow liquid **1** (158 g, 0.58 mmol, 58%)**.** Bp: 78-81 ^{o}C / 28 torr or 105-110 ^{o}C / 50 torr; IR (neat) 1600, 1506, 1250, 1164 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 6.94 (d, J = 9, 2H), 7.00 (d, J = 9, 2H); ^{19}F NMR ($CDCl_3$) δ 91.8 (s), 98.8 (s). Anal. Calcd for $C_{10}H_7F_6NO$: C, 44.29; H, 2.60; N, 5.17. Found: C, 44.08; H, 2.60; N, 5.45.

***N*-trimethylsilyl-*N*-*p*-methoxyphenyl-1-trifluoromethyl-2,2-difluoroethenamine (7)**



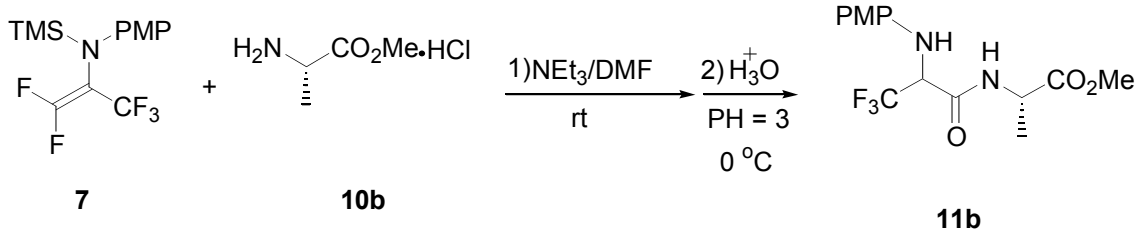
Under argon atmosphere, in a 1000 mL flask, were added Mg (4.86 g, 200 mmol), **9** (27.1 g, 100 mmol) and 400 mL anhydrous THF. The suspension was cooled at 0 ^{o}C and stirred. Chlorotrimethylsilane (50 mL, 400 mmol) was dropped into the suspension. The starting material **9** was completely consumed within 30 minutes determined by TLC monitoring. After decantation of Mg followed by evaporation of the solvent and chlorotrimethylsilane, subsequent addition of hexane to the residue to precipitate inorganic salt and filtration, the filtrate was evaporated and distillated under reduced pressure to afford product **7** (30.9 g, 95 mmol, 95%). Bp: 75 ^{o}C/1 torr; IR (neat) 2964, 1734, 1512, 1238 cm^{-1}; ^{1}H NMR δ 0.22 (s, 9H), 3.78 (s, 3H), 6.80 (d, J = 9, 2H), 6.98 (d, J = 9, 2H); ^{19}F NMR δ 76.3 (m, 1F), 78.3 (m, 1F), 97.4 (dd, J = 23.4, 11.6, 3F). Anal. Calcd for $C_{13}H_{16}F_5NOSi$: C, 47.99; H, 4.96; N, 4.31. Found: C, 47.60; H, 4.71; N, 4.56.

***N-p*-methoxyphenyl-3,3,3-trifluoroalanylglycine benzyl ester (11a)**



Under argon atmosphere in a 30 mL flask, were added **7** (325 mg, 1 mmol), DMF (1.4 mL), **10a** (505 mg, 1.5 mmol) and triethylamine (506 mg, 5 mmol) subsequently. The mixture was stirred at room temperature for 1.5 h. Then, into the mixture cooled at to 0 ^{o}C, was added 1.5 mL water and then hydrochloric acid was dropped into until the pH of the solution was 3. After stirring for 1 h, the mixture was poured into 10 mL water and extracted with ether (10 mL × 3). The combined organic phase was washed with saturated sodium hydrogen carbonate aqueous solution (10 mL) and saturated brine (5 mL × 3), and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (Hexane/EtOAc = 3/1) to afford a solid **11a** (362 mg, 0.91 mmol, 91%) which could be recrystallized from hexane and ethyl ether. Mp 97-99 ^{o}C;_IR (KBr) 3336, 1740, 1658, 1512, 1240 cm^{-1};_^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 4.10-4.18 (m, 2H), 4.28-4.32 (m, 1H), 4.36 (d, J = 6.0, 1H), 5.18 (s, 2H), 6.67-6.70 (m, 2H), 6.78-6.81 (m, 2H), 7.02 (br, 1H), 7.32-7.36 (m, 5H); ^{19}F NMR ($CDCl_3$) δ 89.0 (d, J = 7.1). Anal. Calcd for $C_{19}H_{19}F_3N_2O_4$: C, 57.57; H, 4.83; N, 7.07. Found: C, 57.32; H, 4.68; N, 6.95.

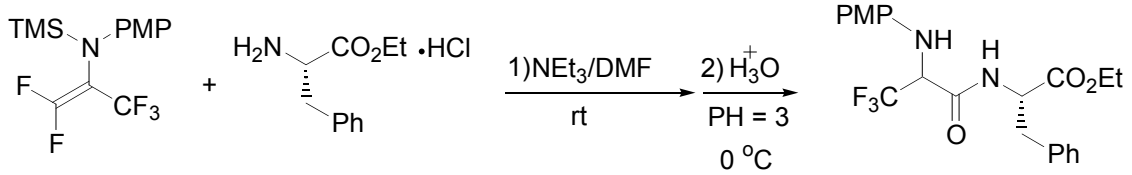
***N*-*p*-methoxyphenyl-3,3,3-trifluoroalanylalanine methyl ester (11b)**



7 **10b** **11b**

Under argon atmosphere in a 30 mL flask, were added **7** (325mg, 1mmol), DMF (1.4 mL), **10b** (208 mg, 1.5 mmol) and triethylamine (0.69 mL, 5 mmol) subsequently. The mixture was stirred at room temperature for 1.5 h. Then, into the mixture cooled at 0 ^{o}C, was added 1.4 mL water and then hydrochloric acid was dropped into until the pH of the solution was 3. After stirring for 1 h, the mixture was poured into 10 mL water and extracted with ethyl ether (10 mL × 3). The combined organic phase was washed with saturated sodium hydrogen carbonate aqueous solution (10 mL) and saturated brine (5 mL × 3), and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (Hexane/EtOAc = 3/1) to afford a solid **11b** (287 mg, 0.86 mmol, 86%). Mp 73-75 ^{o}C; IR (KBr) 3316, 1740, 1662, 1522, 1248 cm^{-1};_^{1}H NMR ($CDCl_3$) δ 1.43 (t, J = 6.9, 3H), 3.74 (s, 3H), 3.76 (m, 3H), 4.23-4.29 (m, 1H), 4.38 (br, 1H), 4.60-4.66 (m, 1H), 6.67-6.72 (m, 2H), 6.79-6.82 (m, 2H), 6.94 (d, J = 6.0, 0.44H), 7.04 (d, J = 6.0, 0.56H); ^{19}F NMR ($CDCl_3$) δ 89.0 (d, J = 6.8). Anal. Calcd for $C_{14}H_{17}F_3N_2O_4$: C, 50.30; H, 5.13; N, 8.38. Found: C, 50.30; H, 5.23; N, 8.14.

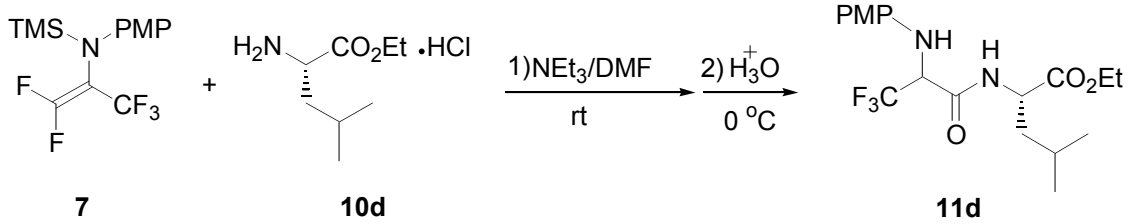
***N-p*-methoxyphenyl-3,3,3-trifluoroalanylphenylalanine ethyl ester (11c)**



7 **10c** **11c**

Under argon atmosphere in a 100 mL flask, were added **7** (1.63 g, 5 mmol), DMF (7.1 mL), **10c** (1.72 g, 7.5 mmol) and triethylamine (3.5 mL, 25 mmol) subsequently. The mixture was stirred at room temperature for 1.5 h. Then, into the mixture cooled at 0 ^{o}C, was added 7.1 mL water and then hydrochloric acid was dropped into until the pH of the solution was 3. After stirring for 3 h, the mixture was poured into 100 mL water and extracted with ethyl ether (50 mL × 3). The combined organic phase was washed with saturated sodium hydrogen carbonate aqueous solution (30 mL) and saturated brine (10 mL × 3), and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (Hexane/EtOAc = 3/1) to afford a solid **11c** (1.96 g, 4.63 mmol, 93%). Mp 104-106 ^{o}C;_IR (neat) (KBr) 3348, 1734, 1664, 1520, 1248 cm^{-1};_^{1}H NMR ($CDCl_3$) δ 1.20-1.27 (m, 3H), 3.10-3.19 (m, 2H), 3.76 (s, 3H), 4.14-4.22 (m, 3H), 4.25-4.37 (m, 1H), 4.84-4.93 (m, 1H), 6.61-6.68 (m, 2H), 6.77-6.81 (m, 2H), 6.85-6.89 (m, 1H), 6.98-7.00 (m, 2H) 7.18-7.23 (m, 3H); ^{19}F NMR ($CDCl_3$) δ 89.5 (d, J = 7.1, 0.62 × 3F), 89.6 (d, J = 7.1, 0.38 × 3F). Anal. Calcd for $C_{21}H_{23}F_3N_2O_4$: C, 59.43; H, 5.46; N, 6.60. Found: C, 59.42; H, 5.55; N, 6.56.

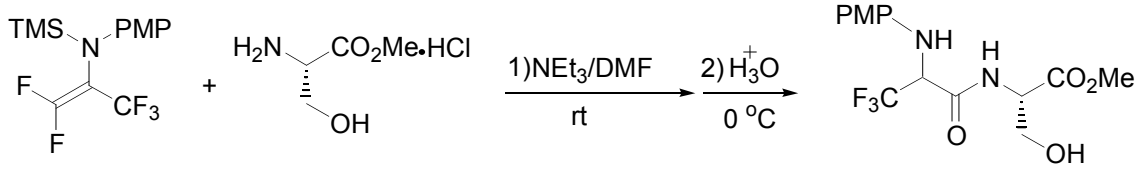
***N*-*p*-methoxyphenyl-3,3,3-trifluoroalanylleucine ethyl ester (11d)**



7 **10d** **11d**

Under argon atmosphere in a 30 mL flask, were added **7** (325mg, 1mmol), DMF (1.4 mL), **10b** (294 mg, 1.5 mmol) and triethylamine (0.69 mL, 5 mmol) subsequently. The mixture was stirred at room temperature for 1.5 h. Then, into the mixture cooled at 0 ^{o}C, was added 1.4 mL water and then hydrochloric acid was dropped into until the pH of the solution was 1. After stirring for 1 h, the mixture was poured into 10 mL water and extracted with ethyl ether (10 mL × 3). The combined organic phase was washed with saturated sodium hydrogen carbonate aqueous solution (10 mL) and saturated brine (5 mL × 3), and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (Hexane/EtOAc = 3/1) to afford a liquid **11d** (331 mg, 0.85 mmol, 85%). IR 3348, 1740, 1668, 1516, 1238 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87-0.89 (m, 6H), 1.21-1.27 (m, 3H), 1.53-1.68 (m, 3H), 3.75 (s, 3H), 4.13-4.20 (m, 2H), 4.24-4.33 (m, 1H), 4.35-4.47(m, 1H), 4.62-4.68 (m, 1H), 6.66-6.71 (m, 2H), 6.78-6.81 (m, 2H), 6.95 (d, J = 8.4, 1H); ^{19}F NMR ($CDCl_3$) _ 89.0 (d, J = 6.8 Hz, 0.72 × 3F), 89.1 (d, J = 7.1, 0.28 × 3F) (slightly overlapped). Anal. Calcd for Calcd for $C_{18}H_{25}F_3N_2O_4$: C, 55.38; H, 6.45; N, 7.18. Found: C. 55.32; H, 6.42; N, 7.21.

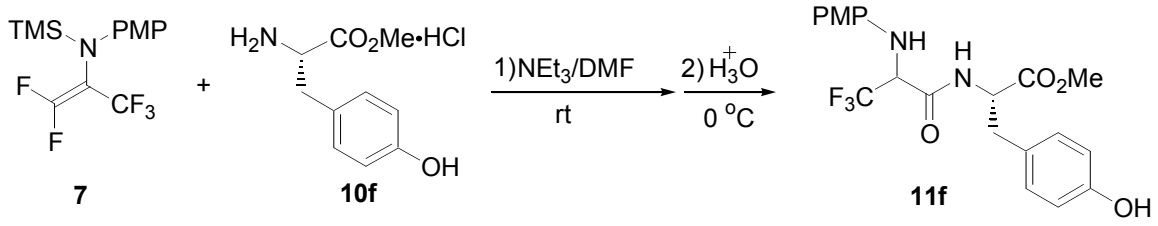
***N*-*p*-methoxyphenyl-3,3,3-trifluoroalanylserine methyl ester (11e)**



7 **10e** **11e**

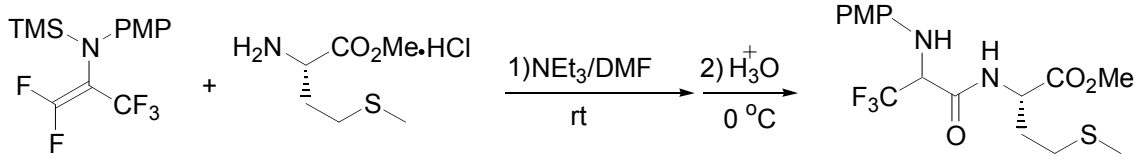
Under argon atmosphere in a 30 mL flask, were added **7** (325mg, 1mmol), DMF (1.4 mL), **10e** (234 mg, 1.5 mmol) and triethylamine (0.69 mL, 5 mmol) subsequently. The mixture was stirred at room temperature for 1.5 h. Then, into the mixture cooled at 0 ^{o}C, was added 1.4 mL water and then hydrochloric acid was dropped into until the pH of the solution was 3. After stirring for 1 h, the mixture was poured into 10 mL water and extracted with ethyl ether (10 mL × 3). The combined organic phase was washed with saturated sodium hydrogen carbonate aqueous solution (10 mL) and saturated brine (5 mL × 3), and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (Hexane/EtOAc = 2/1) to afford a solid **11e** (280 mg, 0.80 mmol, 80%). Mp 89-95 ^{o}C; IR (KBr) 3548, 3300, 1736, 1664, 1518, 1238 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.75-3.79 (m, 6H), 3.89-3.94 (m, 1H), 4.00-4.08 (m, 1H), 4.30-4.43 (m, 2H), 4.68-4.72 (m, 1H), 6.70-6.73 (m, 2H), 6.80-6.83 (m, 2H), 7.28-7.34 (m, 1H); ^{19}F NMR ($CDCl_3$) _ 89.0 (two groups of overlapped doublet, J = 7.1). Anal. Calcd for $C_{14}H_{17}F_3N_2O_5$: C, 48.00; H, 4.89; N, 8.00. Found: C. 48.20; H, 4.86; N, 7.96.

***N-p*-methoxyphenyl-3,3,3-trifluoroalanyltyrosine methyl ester (11f)**



Under argon atmosphere in a 30 mL flask, were added **7** (325mg, 1mmol), DMF (1.4 mL), **10f** (346mg, 1.5 mmol) and triethylamine (0.69 mL, 5 mmol) subsequently. The mixture was stirred at room temperature for 1.5 h. Then, into the mixture cooled at 0 ^{o}C, was added 1.4 mL water and then hydrochloric acid was dropped into until the pH of the solution was 3. After stirring for 1 h, the mixture was poured into 10 mL water and extracted with ethyl ether (10 mL × 3). The combined organic phase was washed with saturated sodium hydrogen carbonate aqueous solution (10 mL) and saturated brine (5 mL × 3), and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (Hexane/EtOAc = 2/1) to afford a solid **11f** (290 mg, 0.68 mmol, 68%). Mp 166-168 ^{o}C; IR (KBr) 3324, 1736, 1676, 1520, 1238 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.01-3.11 (m, 2H), 3.70-3.72 (3H), 3.75 (s, 3H), 4.18-4.38 (m, 2H), 4.81-4.92 (m, 1H), 6.60-6.68 (m, 4H), 6.78-6.83 (m, 4H), 6.89 (br, 1H); ^{19}F NMR ($CDCl_3$) _ 89.0 (d, J = 7.1, 0.59 × 3F), 89.1 (d, J = 7.1, 0.41 × 3F). Anal. Calcd for $C_{20}H_{21}F_3N_2O_5$: C, 56.34; H, 4.96; N, 6.57. Found: C. 55.93; H, 4.82; N, 6.50.

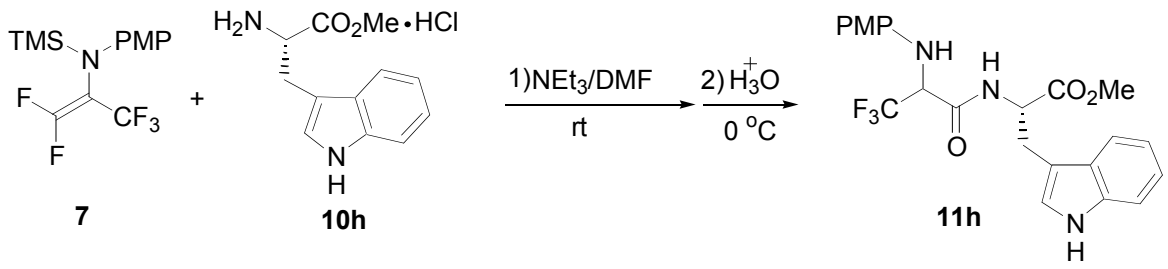
***N-p*-methoxyphenyl-3,3,3-trifluoroalanylmethionine methyl ester (11g)**



7 **10g** **11g**

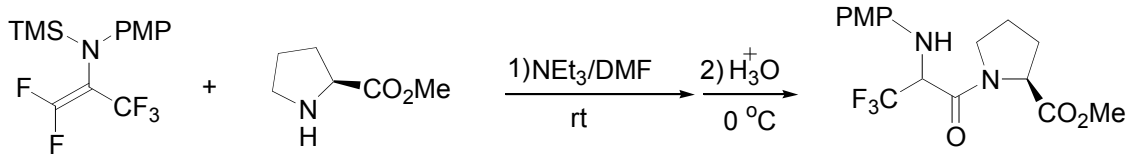
Under argon atmosphere in a 30 mL flask, were added **7** (325mg, 1mmol), DMF (1.4 mL), **10g** (330 mg, 1.5 mmol) and triethylamine (0.69 mL, 5 mmol) subsequently. The mixture was stirred at room temperature for 1.5 h. Then, into the mixture cooled at 0 ^{o}C, was added 1.4 mL water and then hydrochloric acid was dropped into until the pH of the solution was 1. After stirring for 1 h, the mixture was poured into 10 mL water and extracted with ethyl ether (10 mL × 3). The combined organic phase was washed with saturated sodium hydrogen carbonate aqueous solution (10 mL) and saturated brine (5 mL × 3), and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (Hexane/EtOAc = 3/1) to afford a solid **11g** (311 mg, 0.79 mmol, 79%). Mp 74-79 ^{o}C; IR (KBr) 3336, 1738, 1654, 1520, 1244 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.98-2.48 (m, 7H), 3.73-3.76 (m, 6H), 4.25-4.33 (m, 2H,), 4.73-4.79 (m, 1H), 6.68-6.72 (m, 2H), 6.79-6.82 (m, 2H), 7.10-7.25 (m, 1H); ^{19}F NMR ($CDCl_3$) _ 89.0 (two groups of overlapped doublet, J=7.1). Anal. Calcd for $C_{16}H_{21}F_3N_2O_4S$: C, 48.72; H, 5.37; N, 7.10. Found: C. 48.38; H, 5.43; N, 6.90

***N-p*-methoxyphenyl-3,3,3-trifluoroalanyltryptophan methyl ester (11h)**



Under argon atmosphere in a 30 mL flask, were added **7** (325mg, 1mmol), DMF (1.4 mL), **10h** (382 mg, 1.5 mmol) and triethylamine (0.69 mL, 5 mmol) subsequently. The mixture was stirred at room temperature for 1.5 h. Then, into the mixture cooled at 0 ^{o}C, was added 1.4 mL water and then hydrochloric acid was dropped into until the pH of the solution was 3. After stirring for 1 h, the mixture was poured into 10 mL water and extracted with ethyl ether (10 mL × 3). The combined organic phase was washed with saturated sodium hydrogen carbonate aqueous solution (10 mL) and saturated brine (5 mL × 3), and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (Hexane/EtOAc = 3/1) to afford a liquid **11h** (354 mg, 0.79 mmol, 79%). Mp 177-180 ^{o}C; IR (KBr) 3448, 1740, 1658, 1516, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.30-3.43 (m, 2H), 3.68-3.76 (m, 6H), 4.15-4.24 (m, 2H), 4.93-4.99 (m, 1H), 6.55-6.64 (m, 2H), 6.74-6.81 (m, 2H), 6.84-6.91 (m, 1H), 6.95-7.00 (m, 1H), 7.14-7.20 (m, 1H), 7.33-7.42 (m, 1H), 8.00 (br, 1H). ^{19}F NMR ($CDCl_3$) of the recrystallized product δ 89.0 (d, J = 7.1, 0.65 × 3F), 89.2 (d, J = 7.1, 0.35 × 3F). Anal. Calcd for $C_{22}H_{22}F_3N_3O_4$: C, 58.79; H, 4.93; N, 9.35. Found: C. 58.09; H, 4.97; N, 9.15.

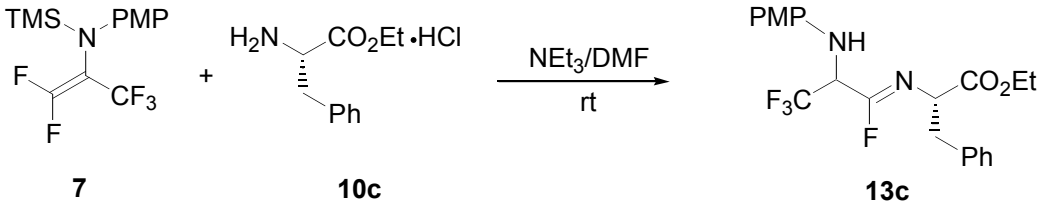
***N-p*-methoxyphenyl-3,3,3-trifluoroalanylproline methyl ester (11i)**



7 **10i** **11i**

Under argon atmosphere in a 30 mL flask, were added **7** (325mg, 1mmol), DMF (1.4 mL), **10i** (249 mg, 1.5 mmol) and triethylamine (0.69 mL, 5 mmol) subsequently. The mixture was stirred at room temperature for 1.5 h. Then, into the mixture cooled at 0 ^{o}C, was added 1.4 mL water and then hydrochloric acid was dropped into until the pH of the solution was 3. After stirring for 1 h, the mixture was poured into 10 mL water and extracted with ethyl ether (10 mL × 3). The combined organic phase was washed with saturated sodium hydrogen carbonate aqueous solution (10 mL) and saturated brine (5 mL × 3), and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (Hexane/EtOAc = 2/1) to afford a liquid **11i** (248 mg, 0.69 mmol, 69%). IR (Film) 3340, 2960, 1746, 1664, 1516, 1244 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.94-2.14 (m, 4H), 2.19-2.32 (m, 1H), 3.68-3.83 (m, 8H), 4.52-4.65 (m, 3H), 6.66-6.84 (m, 4H); ^{19}F NMR ($CDCl_3$) δ 88.7 (d, J = 4.5, 0.7 × 3), 88.8 (d, J = 4.8, 0.3× 3F), (partly overlapped). Anal. Calcd for $C_{21}H_{20}F_3N_3O_4$: Calcd for $C_{16}H_{19}F_3N_2O_4$: C, 53.33; H, 5.31; N, 7.77. Found: C. 53.22; H, 5.32; N, 7.65.

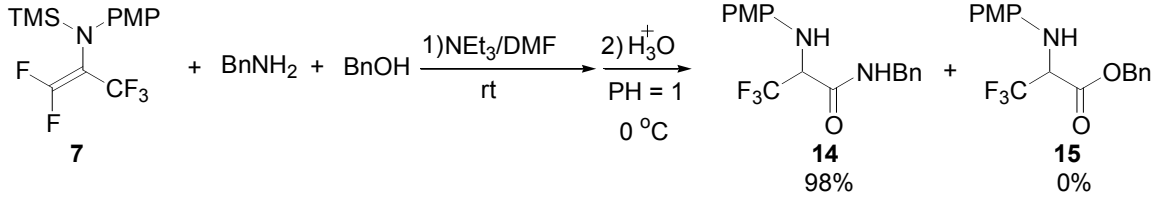
3-phenyl-2-[1,3,3,3-tetrafluoro-2-(4-methoxyphenylamino)propylideneamino]-propionic acid ethyl ester (13c)



7 **10c** **13c**

Under argon atmosphere in a 50 mL flask, were added **7** (1.74 g, 5.35 mmol), DMF (15 mL), **10c** (1.73 g, 7.5 mmol) and triethylamine (3.5 mL, 25 mmol) subsequently. The mixture was stirred at room temperature for 1.5 hours. Then, 150 mL water was added into the mixture and the mixture was extracted with ethyl ether (100 mL × 3). The combined organic phase was washed with saturated brine (30 mL × 3), and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (Hexane/EtOAc = 5/1) to afford a yellow liquid **13c** (1.78 g, 4.2 mmol, 79%).

Competitive reaction of enamine 7 with benzyl amine and benzyl alcohol

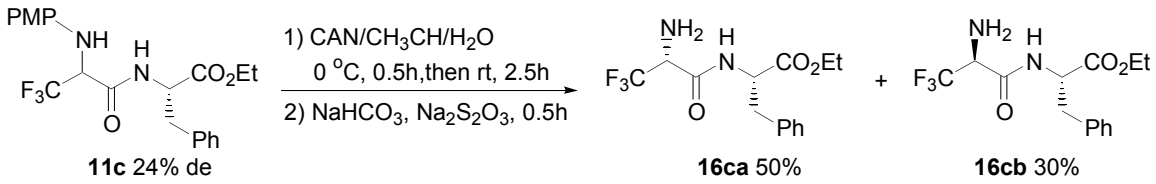


7 **14** 98% **15** 0%

Under argon atmosphere in a 30 ml flask, were added **7** (100 mg, 0.31 mmol), DMF (1 mL), benzyl amine (50 mg, 0.47 mmol) and benzyl alcohol (50 mg, 0.47 mmol) and triethylamine (0.21 mL, 1.6 mmol) subsequently. The mixture was stirred at room temperature for 2 h. Then, into the mixture cooled at 0 ^{o}C, was added 1 mL water and then perchloric acid was dropped into until the pH of the solution was 1. After stirring for 5 h, the mixture was poured into 10 ml water and extracted with ethyl ether (10 mL ×

3). The combined organic phase was washed with saturated sodium hydrogen carbonate aqueous solution (10 mL) and saturated brine (5 mL x 3), and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (Hexane/EtOAc = 4/1) to afford a white solid **14** (102 mg, 0.30 mmol, 98%) without **15**. **14**: Mp 110-112 ^{o}C;_IR (neat) cm^{-1} 3320, 1660, 1522; ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3H), 4.26 (q, J = 7.5 Hz, 1H), 4.39 (br, 1H), 4.50-4.58 (m, 2H), 6.66-6.78 (m, 3H), 6.78-6.82 (m, 2H), 7.18-7.21 (m, 2H), 7.26-7.35 (m, 3H);_^{19}F NMR ($CDCl_3$) δ 89.0 (d, J = 7.1 Hz). Anal. Calcd for $C_{17}H_{17}F_3N_2O_2$: C, 60.35; H, 5.06; N, 8.28. Found: C, 60.65; H, 5.45; N, 8.58.

3,3.3-trifluoroalanylphenylalanine ethyl ester (16ca and 16cb)

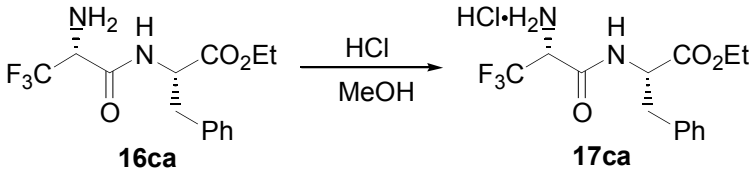


11c 24% de **16ca** 50% **16cb** 30%

To a solution of **11c** (1.58 g, 3.73 mmol) in 37 mL acetonitrile at 0 ^{o}C, was dropped an aqueous solution of CAN (6.13 g, 11.2 mmol) in 13 mL water. The reaction took place at 0 ^{o}C for 0.5 h and at room temperature for another 2.5 h. Then, the reaction solution was neutralized with $NaHCO_3$ aqueous solution, reduced by $Na_2S_2O_3$ (630 mg, 4 mmol) and stirred for 30 minutes. After filtration, the filtrate was extracted by ethyl acetate, washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was subjected column chromatography over silica gel (hexane/AcOEt = 2.5/1 to 2/1) to separate the either diastereomer of the product **16ca** (601 mg, 1.88 mmol, 50%) and **16cb** (354 mg, 1.11 mmol, 30%). **16ca**: Mp 89-91 ^{o}C;_IR (KBr) cm^{-1} 3344,

1736, 1666;_^{1}H NMR ($CDCl_3$) δ: 1.24-1.29 (t, J = 7.1Hz, 3H), 3.10-3.24 (m, 2H), 3.86 (q, J = 7.8 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 4.86 (dt, J = 7.8, 5.9 Hz, 1H), 7.08-7.11(m, 2H), 7.21-7.34 (m, 5H);_ ^{19}F NMR ($CDCl_3$) δ 87.1 (d, J = 9.3 Hz). Anal. Calcd for $C_{14}H_{17}F_3N_2O_3$: C, 52.83; H, 5.38; N, 8.80. Found: C, 52.90; H, 5.51; N, 8.89. **16cb**: Mp 86-88 ^{o}C;_IR (KBr) 3332, 1734, 1660 cm^{-1};_^{1}H NMR ($CDCl_3$) δ 1.24-1.28 (m, 3H), 3.11-3.19 (m, 2H), 3.82 (q, J = 7.6 Hz, 1H), 4.17-4.21 (m, 2H), 4.85-4.89 (m, 1H), 7.10-7.12 (m, 3H), 7.23-7.30 (m, 3H);_^{19}F NMR ($CDCl_3$) δ 87.0 (d, J = 7.1 Hz). Anal. Calcd for $C_{14}H_{17}F_3N_2O_3$: C, 52.83; H, 5.38; N, 8.80. Found: C, 52.91; H, 5.32; N, 9.05.

3,3.3-trifluoroalanylphenylalanine ethyl ester hydrochloric acid salt (17ca)



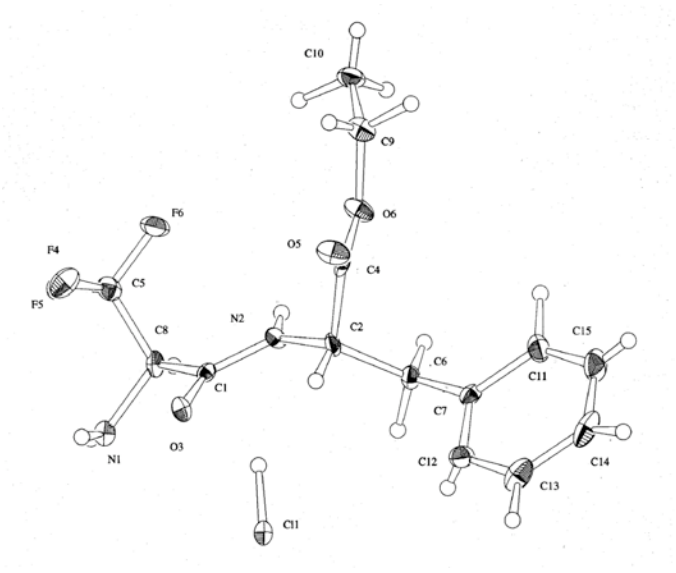
16ca **17ca**

To a solution of **16ca** (200 mg, 0.63mmol) in ethyl acetate was added a solution of hydrochloric acid in methanol (1M, 1mL). After evaporation of all solvent and recrystallization in methanol and ethyl acetate, a white crystalline compound (200 mg, 0.56 mmol, 90%) was obtained. Mp 150-157 ^{o}C;_IR (KBr) cm^{-1} 3268, 2996, 1706, 1578, 1504;_^{1}H NMR (d-DMSO) δ 1.09 (t, J = 7.1, 3H), 3.04 (d, J = 7, 2H), 4.04 (q, J = 7.2, 2H), 4.57 (q, J = 7.1, 1H), 4.90 (q, J = 7.5, 1H), 7.17-7.40 (m, 5H), 9.42 (d, J = 6.8, 1H);_^{19}F NMR (d-DMSO, trifluoroacetic acid (86.0 ppm) as internal standard) δ 91.8 (d, J = 9.3). Calcd for $C_{14}H_{18}ClF_3N_2O_3$: C, 47.40; H, 5.11; N, 7.90. Found: C, 47.31; H, 5.29; N, 8.16.

HPLC analysis of the ratio of diastereomers of trifluoroalanine dipeptides 11:

The HPLC analysis of the ratio ofdiastereomers of trifluoroalanine dipeptides **11** was performed by Shimazu LC-10AT with a chiral column of OD-H (Daicel Chem. Co Ltd.). The elution solvent was a miture of hexane:i-PrOH=9:1 which was passed on the flow rate of 0.5 ml/min.

X-ray crystalografic analysis of 17ca



ORTEP drawing of X-ray structure of **17ca**

Cl F data of **17ca**

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O(5)	C(4)	1.208(10)	.	.	yes

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 O(6)    C(4)    1.314(9)  . . yes
 O(6)    C(9)    1.45(1)   . . yes
 N(1)    C(8)    1.47(1)   . . yes
 N(2)    C(1)    1.326(9)  . . yes
 N(2)    C(2)    1.454(9)  . . yes
 C(1)    C(8)    1.513(9)  . . yes
 C(2)    C(4)    1.51(1)   . . yes
 C(2)    C(6)    1.54(1)   . . yes
 C(5)    C(8)    1.50(1)   . . yes
 C(6)    C(7)    1.498(9)  . . yes
 C(7)    C(11)   1.41(1)   . . yes
 C(7)    C(12)   1.37(1)   . . yes
 C(9)    C(10)   1.49(1)   . . yes
 C(11)   C(15)   1.40(1)   . . yes
 C(12)   C(13)   1.39(1)   . . yes
 C(13)   C(14)   1.39(2)   . . yes
 C(14)   C(15)   1.37(2)   . . yes
#------------------------------------------------------------------------------
loop_
_geom_angle_atom_site_label_1
_geom_angle_atom_site_label_2
_geom_angle_atom_site_label_3
_geom_angle
_geom_angle_site_symmetry_1
_geom_angle_site_symmetry_2
_geom_angle_site_symmetry_3
_geom_angle_publ_flag
  C(4)    O(6)    C(9)    120.1(6)  . . . yes
  C(1)    N(2)    C(2)    122.4(6)  . . . yes
  O(3)    C(1)    N(2)    124.7(6)  . . . yes
  O(3)    C(1)    C(8)    119.4(6)  . . . yes
                                        S26
  N(2)    C(1)    C(8)    115.9(6)  . . . yes
  N(2)    C(2)    C(4)    109.4(6)  . . . yes
  N(2)    C(2)    C(6)    109.9(6)  . . . yes
  C(4)    C(2)    C(6)    113.1(6)  . . . yes
  O(5)    C(4)    O(6)    122.2(8)  . . . yes
  O(5)    C(4)    C(2)    125.4(7)  . . . yes
  O(6)    C(4)    C(2)    112.3(6)  . . . yes
  F(4)    C(5)    F(5)    106.7(6)  . . . yes
  F(4)    C(5)    F(6)    107.1(7)  . . . yes
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  F(4)    C(5)    C(8)    111.5(7)  . . . yes
  F(5)    C(5)    F(6)    108.3(7)  . . . yes
  F(5)    C(5)    C(8)    110.7(6)  . . . yes
  F(6)    C(5)    C(8)    112.4(7)  . . . yes
  C(2)    C(6)    C(7)    114.1(6)  . . . yes
  C(6)    C(7)    C(11)   118.9(7)  . . . yes
  C(6)    C(7)    C(12)   121.2(7)  . . . yes
  C(11)   C(7)    C(12)   119.9(7)  . . . yes
  N(1)    C(8)    C(1)    109.5(6)  . . . yes
  N(1)    C(8)    C(5)    112.2(6)  . . . yes
  C(1)    C(8)    C(5)    112.4(6)  . . . yes
  O(6)    C(9)    C(10)   108.7(7)  . . . yes
  C(7)    C(11)   C(15)   119.1(9)  . . . yes
  C(7)    C(12)   C(13)   121.3(8)  . . . yes
  C(12)   C(13)   C(14)   118.9(9)  . . . yes
  C(13)   C(14)   C(15)   120.6(8)  . . . yes
  C(11)   C(15)   C(14)   120.2(10) . . . yes
#------------------------------------------------------------------------------
loop_
_geom_torsion_atom_site_label_1
_geom_torsion_atom_site_label_2
_geom_torsion_atom_site_label_3
_geom_torsion_atom_site_label_4
_geom_torsion
_geom_torsion_site_symmetry_1
_geom_torsion_site_symmetry_2
                                        S27
_geom_torsion_site_symmetry_3
_geom_torsion_site_symmetry_4
_geom_torsion_publ_flag
 F(4)    C(5)    C(8)    N(1)    67.0(8)   . . . . yes
 F(4)    C(5)    C(8)    C(1)    -56.8(9)  . . . . yes
 F(5)    C(5)    C(8)    N(1)    -51.6(9)  . . . . yes
 F(5)    C(5)    C(8)    C(1)    -175.4(6) . . . . yes
 F(6)    C(5)    C(8)    N(1)    -172.7(7) . . . . yes
 F(6)    C(5)    C(8)    C(1)    63.4(9)   . . . . yes
 O(3)    C(1)    N(2)    C(2)    4(1)      . . . . yes
 O(3)    C(1)    C(8)    N(1)    -30.9(9)  . . . . yes
 O(3)    C(1)    C(8)    C(5)    94.4(8)   . . . . yes
 O(5)    C(4)    O(6)    C(9)    -4(1)     . . . . yes
 O(5)    C(4)    C(2)    N(2)    123.6(8)  . . . . yes
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 O(5)    C(4)    C(2)    C(6)    -113.6(9)  . . . . yes
 O(6)    C(4)    C(2)    N(2)    -53.7(8)   . . . . yes
 O(6)    C(4)    C(2)    C(6)    69.1(8)    . . . . yes
 N(1)    C(8)    C(1)    N(2)    149.8(7)   . . . . yes
 N(2)    C(1)    C(8)    C(5)    -84.9(8)   . . . . yes
 N(2)    C(2)    C(6)    C(7)    -173.4(6)  . . . . yes
 C(1)    N(2)    C(2)    C(4)    -111.6(7)  . . . . yes
 C(1)    N(2)    C(2)    C(6)    123.7(7)   . . . . yes
 C(2)    N(2)    C(1)    C(8)    -176.8(7)  . . . . yes
 C(2)    C(4)    O(6)    C(9)    173.1(7)   . . . . yes
 C(2)    C(6)    C(7)    C(11)   -111.3(8)  . . . . yes
 C(2)    C(6)    C(7)    C(12)   71.2(9)    . . . . yes
 C(4)    O(6)    C(9)    C(10)   -158.9(7)  . . . . yes
 C(4)    C(2)    C(6)    C(7)    64.0(8)    . . . . yes
 C(6)    C(7)    C(11)   C(15)   -178.9(8)  . . . . yes
 C(6)    C(7)    C(12)   C(13)   177.7(8)   . . . . yes
 C(7)    C(11)   C(15)   C(14)   3(1)       . . . . yes
 C(7)    C(12)   C(13)   C(14)   0(1)       . . . . yes
 C(11)   C(7)    C(12)   C(13)   0(1)       . . . . yes
 C(11)   C(15)   C(14)   C(13)   -3(1)      . . . . yes
 C(12)   C(7)    C(11)   C(15)   -1(1)      . . . . yes
                                      S28
 C(12)   C(13)   C(14)   C(15)   2(1)       . . . . yes
 C(12)   C(13)   C(14)   C(15)   2(1)       . . . . yes
#------------------------------------------------------------------------------
loop_
_geom_contact_atom_site_label_1
_geom_contact_atom_site_label_2
_geom_contact_distance
_geom_contact_site_symmetry_1
_geom_contact_site_symmetry_2
_geom_contact_publ_flag
 Cl(1)   N(1)    3.136(7)  . 3_446 ?
 Cl(1)   N(1)    3.191(7)  . . ?
 Cl(1)   C(1)    3.227(7)  . . ?
 Cl(1)   O(3)    3.238(5)  . 3_446 ?
 Cl(1)   N(1)    3.240(6)  . 3_546 ?
 Cl(1)   C(8)    3.420(9)  . . ?
 Cl(1)   O(3)    3.480(5)  . . ?
 Cl(1)   N(2)    3.594(7)  . . ?
 F(4)    F(5)    3.011(7)  . 1_655 ?
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 F(5)    C(9)    3.25(1)   . 4_646 ?
 F(5)    O(6)    3.323(8)  . 4_646 ?
 F(5)    O(3)    3.513(7)  . 1_455 ?
 F(5)    C(10)   3.53(1)   . 4_646 ?
 F(5)    C(11)   3.55(1)   . 4_646 ?
 F(6)    O(5)    3.252(9)  . 1_455 ?
 F(6)    C(15)   3.37(1)   . 4_746 ?
 O(3)    N(1)    2.865(9)  . 3_546 ?
 O(3)    C(8)    3.103(9)  . 1_655 ?
 O(3)    N(1)    3.154(9)  . 1_655 ?
 O(5)    N(2)    2.855(9)  . 1_655 ?
 O(5)    O(6)    3.252(8)  . 1_655 ?
 C(6)    C(13)   3.39(1)   . 1_455 ?
#------------------------------------------------------------------------------
loop_
_geom_hbond_atom_site_label_D
                                                S29
_geom_hbond_atom_site_label_H
_geom_hbond_atom_site_label_A
_geom_hbond_site_symmetry_D
_geom_hbond_site_symmetry_H
_geom_hbond_site_symmetry_A
_geom_hbond_site_distance_DH
_geom_hbond_site_distance_HA
_geom_hbond_site_distance_DA
_geom_hbond_angle_DHA
_geom_hbond_publ_flag
N(1)    H(17)   F(4)    . . . 0.66(5) 2.73(4) 2.928(8) 100(4) no
N(1)    H(17)   O(3)    . . . 0.66(5) 2.52(4) 2.706(7) 98(4) no
N(2)    H(15)   F(6)    . . . 0.71(5) 2.69(5) 3.055(7) 114(4) no
N(2)    H(15)   O(6)    . . . 0.71(5) 2.64(5) 2.759(8) 92(4) no
F(4)    O(3)    3.130(7) . . . -0.2830 0.6586 0.7268 92(4) no
F(4)    N(1)    2.928(8) . . . -0.3075 0.6490 0.5774 92(4) no
F(5)    N(1)    2.773(8) . . . -0.3094 0.6446 0.3054 92(4) no
F(6)    N(2)    3.055(7) . . . -0.1870 0.7117 0.5147 92(4) no
O(3)    F(4)    3.130(7) . . . -0.2393 0.6187 0.8028 92(4) no
O(3)    N(1)    2.706(7) . . . -0.2300 0.5756 0.7034 92(4) no
N(1)    F(5)    2.773(8) . . . -0.2966 0.6087 0.3550 92(4) no
N(1)    H(17)   Cl(1)   . . 3_566 0.66(5) 2.48(5) 3.136(6) 169(4) no
N(1)    H(18)   O(3)    . . 1_455 0.8(1) 2.6(1) 3.154(7) 123(>>) no
N(2)    H(15)   O(5)    . . 1_455 0.71(5) 2.17(5) 2.855(8) 162(5) no
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