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Optically Active Fluorinated β-Lactam Building Blocks: A Novel Fluorinated Retroamide Isostere.

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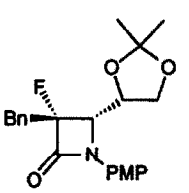
Abstract: A new and versatile synthesis of optically active α-fluoro-malonamides derivatives from enantiomerically pure 3-fluoro-2-azetidinones is described. A fluorinated retroamide isostere based on these α-fluoro-malonamide was introduced into a small peptidomimetic for use as an HIV-1 protease inhibitor.

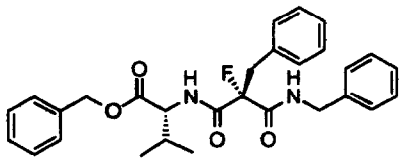
Employment of "retro-inverso" peptide isosteres in biologically relevant peptidomimetics has been growing.[1] The reversal of peptide bonds accompanied by the introduction of the appropriate enantiomerically configured amino acids can result in the construction of a peptide analog which is resistant to enzymatic degradation but exhibits enhanced potency or improved selectivity. Unfortunately the preparation of optically pure peptide analogs containing an alkylmalonamide residue, *m*Xaa,[2] has been encumbered by the configurational lability of malonyl unit under both neutral and basic conditions. The preparation of optically pure fluorinated malonamides, *mF*Xaa, which are configurationally fixed may overcome this problem.

Recently we have reported methods for the preparation of optically pure fluorinated β-lactams.[3] These substances are versatile materials for asymmetic synthesis in no small part as a result of the selectivity of the lactam enolates in alkylation and aldol reactions.[4] Optically pure (3*R*)-3-alkyl-3-fluoro-2-azetidinones such as **1** are readily available in multigram quantities.



1

In this article we will describe the conversion of **1** into *mF*Phe for incorporation into **2** an analog of 2-(benzyloxycarbonylvalylamino)-2,2-difluoro-3-oxo-5-phenylpentanoic acid benzylamide, **3**, a remarkably potent HIV - 1 protease inhibitor.[5]



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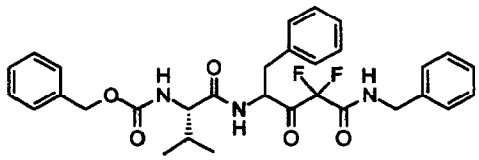

3

Benzylated azetidinone **1** was prepared according to published methods.[3] In a single pot transformation, deprotection and oxidative cleavage was effected with periodic acid[6] to form **4** in 90 % yield. Oxidation to acid **5** was followed by oxidative decarboxylation to **6** with lead tetracetate[7] in 65% yield for the two steps. Saponification of acetate **6** revealed the aminal **7** which was readily reduced to alcohol **8**. Protection of the alcohol with *tert*-butyldimethylchlorosilane formed **9** in nearly quantitative yield for the three steps combined. At this point the termini of the the building block must be differentiated to facilitate the reductive removal of the *p*-methoxyphenyl blocking group. Since the target molecule **2** contains an *N*-benzyl amide, it was determined that conversion of the *p*-methoxyphenyl amide to a tertiary amide was necessary to activate that carbonyl toward reduction in the presence of the secondary benzyl amide. Conversion of **9** to **10** was effected with methyl iodide upon deprotonation of *p*-methoxyphenyl amide with sodium hydride in dimethylsulfoxide.[8] Following deprotection of the alcohol function in the usual manner with *tetra-n*-butylammonium fluoride in THF, Jones oxidation of **11** yielded acid **12**. Benzylamine was coupled to the acid in the presence of dicyclohexylcarbodiimide and 1-hydroxybenzotriazole to form **13** in 79% yield. Chemoselective reduction of the tertiary *N*-methyl-*p*-methoxyphenylanilide was possible using a complex reducing agent prepared *in situ* from *n*-butyllithium and diisobutylaluminum hydride.[9] Complete reduction to the alcohol **14** was possible by the addition of sodium borohydride to the reaction mixture. Alcohol **14** was formed in 88% yield. Jones oxidation (77%) and coupling with the unnatural amino acid *O*-benzyl D-valine[10] under the previously described conditions[11] yielded the target compound **2** in 77% yield.

It was necessary to employ the unnatural D-configuration of the amino acid in order for the substrate to retain the topological features of **3** since the normal N-C progression of the peptide was inverted by the *mF*Phe isostere. Introduction of this Phe analog allows us to retain the P_1 [12] benzyl side chain matching the known selectivity of HIV-1 protease[13] and the P_2 valine identified as dramatically improving activity of the previously described analogs.[5] This compound as well as the corresponding L-valine analog are currently undergoing biological tests.

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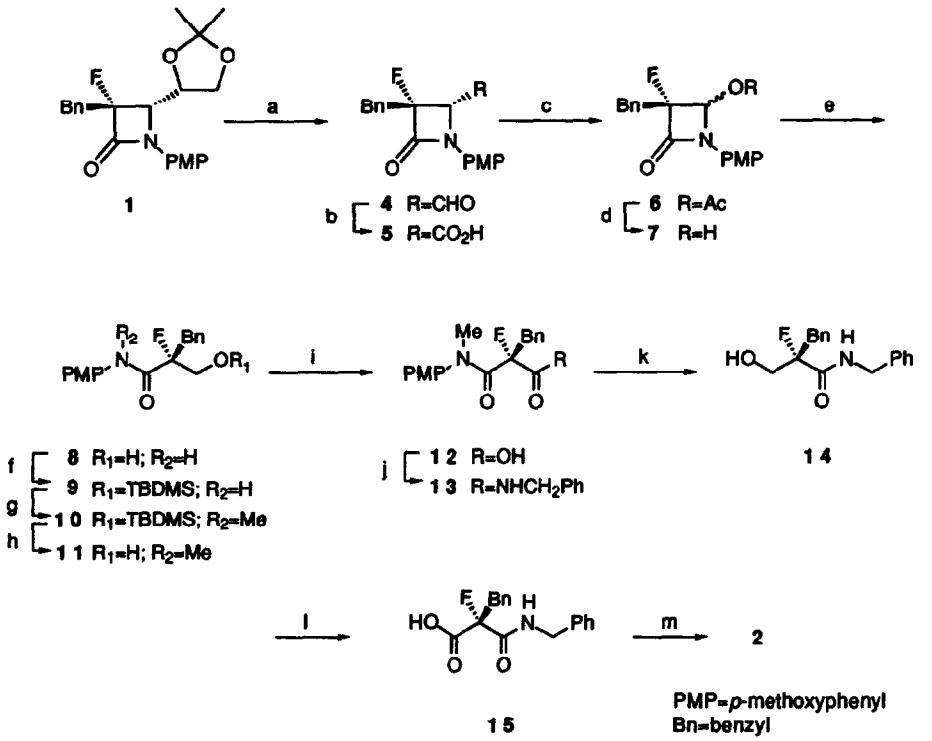
Experimental

General. NMR spectra were recorded on either a Varian XL-300 or a Gemini-300 (^{19}F, ^{1}H and ^{13}C) spectrometer, with $CDCl_3$ as a solvent and either tetramethylsilane (^{1}H and ^{13}C) or $CFCl_3$ (^{19}F) as internal



Scheme 1. Reagents and Conditions: a) H_5IO_6, Et_2O, 90% ; b) $KMNO_4$, K_2CO_3, THF/H_2O, 90% ; c) Lead tetraacetate, DMF/AcOH, 72% ; d) aq. NaOH, MeOH, 96% ; e) $NaBH_4$, EtOH, 95% ; f) TBDMS-Cl, imidazole, DMF, 100% ; g) NaH, DMSO, MeI, 93% ; h) TBAF, THF, 91% ; i) Jones' reagent, 80% ; j) Benzylamine, DCC, HOBt, 79% ; k) DIBAL-H, *n*-BuLi, THF, 0 °C, 88%, then $NaBH_4$; l) Jones' reagent, 77% ; m) (D)-Val-*O*-benzyl, DCC, HOBt, 77%.

standards. Multiplicities described in the ^{13}C NMR data reflect J_{C-F} coupling. Infrared (IR) spectra were taken on a Perkin-Elmer 1600 Series FTIR as pellets (KBr) or as neat thin films (NaCl plates). Analytical thin-layer chromatography (TLC) was used to monitor reactions. Column chromatography was performed using gravity chromatography with Davisil silica gel 62 (60-200 mesh). Melting point (mp) ranges are uncorrected. Optical rotations were measured on a Perkin-Elmer 241B polarimeter.

(3*R*,4*S*)-3-Benzyl-3-fluoro-4-formyl-N-(*p*-methoxyphenyl)-2-azetidinone, 4. To a solution of periodic acid (2.7 g, 11.8 mmol) in dry ether (25 mL) was added acetonide **1** (1.28 g, 3.3 mmol) and the resulting heterogeneous solution was stirred at room temperature for 6 h. The organic layer was decanted and washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed (hexane-ethylacetate) to afford 0.94 g of aldehyde (90 % yield) as a pale yellow liquid. $[\alpha]_D$ +239 (c= 1.3, CH_2Cl_2) ; IR (neat) 2960, 2938, 2838, 1764 (C=O), 1740 (C=O), 1514, 1251 cm^{-1} ; ^1H-NMR ($CDCl_3$) 3.28-3.48 (complex absorption, 2H, CH_2Ph), 3.75 (s, 3H, OCH_3), 4.45 (dd, $^3J_{H-F}$= 4.4 Hz, J= 2.9 Hz, 1H, CHCHO), 6.82 (d, J= 9.1 Hz, 2H, Ar), 7.15 (d, J= 9.1 Hz, 2H, Ar), 7.32 (s, 5H, Ph), 9.58

(dd, J= 2.9 Hz, $^4J_{H-F}$= 1.0 Hz, 1H, CHO) ; ^{19}F-NMR ($CDCl_3$) -165.14 (broad t, $^3J_{F-H}$= 20.0 Hz) ; ^{13}C-NMR ($CDCl_3$) 38.04 (d, $^2J_{C-F}$= 23.6 Hz, CH_2Ph), 55.41 (OCH_3), 66.41 (d, $^2J_{C-F}$= 23.3 Hz, CHCHO), 102.90 (d, $^1J_{C-F}$= 224.0 Hz, CF), 114.54 (Ar), 118.49 (Ar), 127.86 (Ph), 128.85 (Ph), 129.61 (Ph), 129.64 (Ph), 129.81 (Ph), 130.06 (Ar), 132.26 (Ph), 157.27 (Ar), 160.4 (d, $^2J_{C-F}$= 24.5 Hz, CON), 195.77 (d, $^3J_{C-F}$= 3.7 Hz, CHO) ; Anal. Calcd. for $C_{18}H_{16}FO_3N$: C, 69.00 ; H, 5.15. Found : C, 69.14 ; H, 5.36.

(3*R*,4*S*)-3-Benzyl-4-carboxy-3-fluoro-*N*-(*p*-methoxyphenyl)-2-azetidinone, 5. A mixture of aldehyde **4** (1.0 g, 3.2 mmol), potassium permanganate (2.5 g, 15.8 mmol) and potassium carbonate (2.6 g, 18.8 mmol) in tetrahydrofuran/water (30 mL, 2:1) was stirred at room temperature for 4 h under nitrogen. The reaction mixture was cooled at 0 °C and stirred for an additional 20 min. The precipitate was filtered off and the filtrate was acidified with 1 N hydrochloric acid to pH 4. The aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give 1.0 g of acid **5** (90% yield) as a white solid ; mp 134-136 °C. $[\alpha]_D$ +170 (c= 1, CH_2Cl_2) ; IR (KBr) 3250-2850 (COO-H), 1755 (C=O), 1726 (C=O), 1516, 1250 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) 3.38 (dd, $^3J_{H-F}$= 18.0 Hz, J_{gem}= 14.8 Hz, 2H, CH_2Ph), 3.70 (s, 3H, OCH_3), 4.51 (d, $^3J_{H-F}$= 4.14 Hz, 1H, CHCOOH), 6.75 (d, J= 8.71 Hz, 2H, Ar), 7.11 (d, J= 8.71 Hz, 2H, Ar), 7.32 (s, 5H, Ph), 9.1 (broad s, 1H, COOH) ; ^{19}F-NMR ($CDCl_3$) -162.75 (broad t, $^3J_{F-H}$= 18.1 Hz) ; ^{13}C-NMR ($CDCl_3$) 37.93 (d, $^2J_{C-F}$= 24.2 Hz, CH_2Ph), 55.44 (OCH_3), 61.46 (d, $^2J_{C-F}$= 24.7 Hz, CHCOOH), 101.90 (d, $^1J_{C-F}$= 229.1 Hz, CF), 114.42 (Ar), 118.60 (Ar), 127.81 (Ph), 128.76 (Ph), 129.96 (Ph), 132.1 (Ph), 132.15 (Ph), 157.21 (Ar), 160.88 (d, $^2J_{C-F}$= 24.6 Hz, CON), 171.1 (s, COOH) ; Anal. Calcd. for $C_{18}H_{16}FO_4N$: C, 65.65 ; H, 4.89 ; Found : C, 65.54 ; H, 4.78.

(3*R*,4*S*) and (3*R*,4*R*)-4-Acetoxy-3-benzyl-3-fluoro-1-(*p*-methoxyphenyl)-2-azetidinone, 6. Lead tetraacetate (4.1 g, 9.2 mmol) was added to a solution of acid **5** (1.0 g, 3.0 mmol) in DMF/AcOH (20 mL, 1:1). The mixture was heated at 95 °C for 2 h under nitrogen. Acetic acid was completely removed under reduced pressure, the resulting residue was poured into water (40 mL) and the aqueous layer was extracted with CH_2Cl_2 (3x20 mL), the combined organic layers were washed with saturated aqueous sodium bicarbonate and brine and dried over $MgSO_4$. The solvent was removed and the residue was chromatographed (hexane-ethylacetate) to produce 0.830 g of compound **6** (72% yield) as a yellow oil. $[\alpha]_D$ +123.3 (c= 1.2, CH_2Cl_2) ; IR (neat) 1774 (C=O), 1522 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.95 and 2.1 (s, 3H, $OCOCH_3$), 3.13-3.28 and 3.34-3.5 (complex absorption, 2H, CH_2Ph), 3.68 and 3.71 (s, 3H, OCH_3), 6.61 (d, $^3J_{H-F}$= 6.5 Hz, 1H, CHOAc) , 6.74 (d, J= 9.11 Hz, 2H, Ar), 6.81 (d, $^3J_{H-F}$= 9.11 Hz, 1H, CHOAc), 7.14 (d, J= 9 Hz, 2H, Ar), 7.2-7.3 (m, 5H, Ph) ; ^{19}F-NMR ($CDCl_3$) -161.40 (broad t, $^3J_{F-H}$= 25.7 Hz) and -166.22 (broad d, $^3J_{F-H}$= 30 Hz) ; ^{13}C-NMR ($CDCl_3$) 20.42 and 20.48 ($OCOCH_3$), 37.02 (d $^2J_{C-F}$ = 24.4 Hz, CH_2Ph) and 37.06 (d $^2J_{C-F}$ = 26 Hz, CH_2Ph), 55.3 (OCH_3), 81.28 (d, $^2J_{C-F}$= 20.2 Hz, CHOAc) and 81.3 (d, $^2J_{C-F}$= 22 Hz, CHOAc), 100.7 (d, $^1J_{C-F}$= 230.9 Hz, CF) and 103.34 (d, $^1J_{C-F}$= 219.4 Hz, CF), 114.35 and 114.52 (Ar), 119.30 and 119.34 (Ar), 127.14 (Ph), 127.55 (Ph), 128.30 (Ph), 128.62 (Ph), 129.74 (Ph), 129.02 (Ph), 132.10 (Ar), 132.2 (Ph), 157.41 (Ar), 160.2 (d, $^2J_{C-F}$= 24.0 Hz, CON) and 161.46 (d, $^2J_{C-F}$= 25.41 Hz, CON), 169.18 (s, $OCOCH_3$) and 169.94 (s, $OCOCH_3$) ; Anal. Calcd. for $C_{19}H_{18}FO_4N$: C, 66.46 ; H, 5.28 ; N, 4.08. Found : C, 66.53 ; H, 5.49 ; N, 4.09.

(3*R*,4*S*) and (3*R*,4*R*)-3-Benzyl-3-fluoro-4-hydroxy-1-(*p*-methoxyphenyl)-2-azetidinone, 7. To a solution of compound **6** (0.97 g, 2.8 mmol) in methanol (15 mL) was added sodium hydroxide (0.14 g,

3.5 mmol) in water (2 mL). After stirring for 30 min at room temperature, dichloromethane (15 mL) was added to the reaction mixture and stirred for an additional 10 min. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, 0.850 g of aminal **7** 96% yield) was obtained as a white solid ; mp 150-152 °C. $[\alpha]_D$ -123 (c= 1, CH_2Cl_2) ; IR (KBr) 3314 (O-H), 1669 (C=O), 1548, 1517 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) 3.2-3.4 (complex absorption, 2H, CH_2Ph), 3.8 (s, 3H, OCH_3), 4.6 (broad s, CHO), 6.76 (d, J = 9.2 Hz, 2H, Ar), 6.84 (d, J= 9.2 Hz, 2H, Ar), 7.0-7.2 (m, 5H, Ph), 7.6 (broad s, OH) ; ^{19}F-NMR ($CDCl_3$) -171.15 (broad t, $^3J_{F-H}$= 24.6 Hz) and -184.40 (broad d, $^3J_{F-H}$= 38.0 Hz) ; ^{13}C-NMR ($CDCl_3$) 40.17 (d, $^2J_{C-F}$= 20.1 Hz, CH_2Ph), 55.43 (OCH_3), 96.80 (d, $^1J_{C-F}$= 200.0 Hz, CF), 99.0 (d, $^2J_{C-F}$= 26.2 Hz, CHOH), 114.13 (Ar), 122.7 (Ar), 127.32 (Ph), 128.40 (Ph), 128.63 (Ph), 132.1 (Ph), 130.33 (Ph), 132.2 (Ar), 156.2 (Ar), 168.74 (d, $^2J_{C-F}$= 20.0 Hz, CON) ; Anal. Calcd. for $C_{17}H_{16}FO_3N$: C, 67.76 ; H, 5.35. Found : C, 67.69 ; H, 5.31.

(2*R*)-2-Fluoro-2[*N*-(*p*-methoxyphenyl) carbonyl]-3-phenylpropanal, 8. To a solution of aminal **7** (0.875 g, 2.9 mmol) in absolute ethanol (20 mL) was added sodium borohydride (0.120 g, 3.2 mmol). After 30 min of stirring at room temperature, monitoring by TLC showed the complete disappearance of the starting material. The solution was made neutral by addition of 10% aqueous HCl and then concentrated. The residue was filtered through a short column of silica gel with 1:4 hexane-ethylacetate, affording 0.836 g of alcohol **8** (95% yield) as a white solid ; mp 190-192 °C. $[\alpha]_D$ -111 (c= 1, DMF) ; IR (KBr) 3334 (O-H), 1664 (C=O), 1536, 1516 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) 2.73 (dd, $^3J_{H-F}$= 16.0 Hz, J_{gem}= 14.4 Hz, 1H, CH_2Ph), 3.3 (dd, $^3J_{H-F}$= 31.0 Hz, J_{gem} = 14.4 Hz, 1H, CH_2Ph), 3.7 (s, 3H, OCH_3), 3.90 (dd, $^3J_{H-F}$= 11.0 Hz, J_{gem}= 8.5 Hz, 1H, CH_2O), 4.14 (dd, $^3J_{H-F}$= 11.5 Hz, J_{gem}= 8.5 Hz, 1H, CH_2O), 6.0-6.14 (broad s, 1H, OH), 6.80-6.84 (m, 2H, Ar), 7.10-7.14 (m, 2H, Ar), 7.22-7.26 (m, 5H, Ph), 7.50 (broad s, 1H, NH) ; ^{19}F-NMR ($CDCl_3$) -170.80 (complex absorption) ; ^{13}C-NMR ($CDCl_3$) 40.44 (d, $^2J_{C-F}$= 20.1 Hz, CH_2Ph), 55.20 (OCH_3), 67.20 (d, $^2J_{C-F}$= 26.0 Hz, CH_2OH), 100.0 (d, $^1J_{C-F}$= 210.0 Hz, CF), 114.0 (Ar), 122.10 (Ar), 127.10 (Ph), 128.40 (Ph), 129.10 (Ph), 130.33 (Ph), 134.20 (Ar), 156.60 (Ar), 168.0 (d, $^2J_{C-F}$= 21.0 Hz, CON) ; Anal. Calcd. for $C_{17}H_{18}FO_3N$: C, 67.31 ; H, 5.98. Found : C, 67.37 ; H, 6.07.

(2*R*)-2-Benzyl-2-fluoro-3-(*tert*-butyldimethylsilyloxy)-propion-(*p*-methoxyphenyl) amide, 9. To a solution of alcohol **8** (0.550 g, 1.8 mmol) and imidazole (0.270 g, 4.0 mmol) in dry DMF (12 mL) was added *tert*-butyldimethylsilyl chloride (0.402 g, 2.7 mmol) at room temperature under inert atmosphere. The reaction mixture was stirred overnight, then poured into water (20 mL). After extraction with hexanes (4x15 mL), the combined organic layers were washed with brine and dried over magnesium sulfate. After evaporation of solvent, the residue was filtered through a short column of silica gel with hexanes affording 0.760 g of compound **9** (100% yield) as a white solid ; mp 86-88 °C. $[\alpha]_D$ -51 (c= 1, CH_2Cl_2) ; IR (CH_2Cl_2) 2956, 2931, 2857, 1644 (C=O), 1513, 1246 cm^{-1} ; ^{1}H-NMR ($CDCl_3$); 0.16 [s, 9H, $SiC(CH_3)_3$], 1.0 [s, 6H, $Si(CH_3)_2$], 3.18 (AB system, J_{H-F}= 14.3 Hz, 1H, CH_2Ph), 3.21 (AB system, J_{H-F}= 14.1 Hz, 1H, CH_2Ph), 3.80 (s, 3H, OCH_3), 3.89 (dd, $^3J_{H-F}$= 18.5 Hz, J_{gem}= 11.5 Hz, 1H, CH_2OSi), 4.14 (dd, $^3J_{H-F}$= 29.0 Hz, J_{gem} = 11.5 Hz, 1H, CH_2OSi), 6.80 (d, J= 7.0 Hz, 2H, Ar), 6.81 (d, J= 7.0 Hz, 2H, Ar), 7.20 (s, 5H, Ph), 7.62 (broad s, 1H, NH) ; ^{19}F-NMR ($CDCl_3$) -170.72 (complex absorption) ; ^{13}C-NMR ($CDCl_3$) 1.01 [$Si(CH_3)_2$], 19.94 [$SiC(CH_3)_3$], 25.71 [$SiC(CH_3)_3$], 38.92 (d, $^2J_{C-F}$= 21.0 Hz, CH_2Ph), 55.37 (OCH_3), 66.53 (d, $^2J_{C-F}$= 21.0 Hz, CH_2OSi), 100.61 (d, $^1J_{C-F}$= 196.0 Hz, CF), 114.03 (Ar), 122.20 (Ar), 127.03 (Ph), 128.22 (Ph), 129.01 (Ph), 130.23 (Ph), 134.20 (Ar), 156.74 (Ar), 167.63 (d, $^2J_{C-F}$= 20.4 Hz, CON) ; Anal. Calcd. for $C_{23}H_{32}FO_3NSi$: C, 66.16 ; H, 7.72. Found : C, 65.94 ; H, 7.81.

(2*R*)-2-Benzyl-2-fluoro-3-(*tert*-butyldimethylsilyloxy)-*N*-methyl-*N*-(*p*-methoxyphenyl) amide, 10. Sodium hydride (50% dispersion in oil, 0.170 g, 7.1 mmol) was washed several times with hexanes to remove mineral oil and DMSO (3 mL) was added at room temperature. After stirring for 5 min the secondary amide **9** (0.750 g, 1.8 mmol) was slowly added, followed immediately by iodomethane (0.510 g, 3.6 mmol). The reaction mixture was stirred for an additional 15 min then slowly poured into water (15 mL). The aqueous phase was extracted with AcOEt (3 x 10 mL). The organic extracts were combined, washed with water, dried ($MgSO_4$), filtered and concentrated. Chromatography (hexane-ethylacetate) gave 0.720 g of amide **10** (93% yield) as a pale yellow liquid. $[\alpha]_D$ +7.5 (c= 0.8, CH_2Cl_2) ; IR (CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) ; 0.08 [s, 6H, $Si(CH_3)_2$], 0.92 [s, 9H, $SiC(CH_3)_3$], 2.85 (broad t, J= 13.5 Hz, 1H, CH_2Ph), 3.06 (s, 3H, NCH_3), 3.25 (dd, $^3J_{H-F}$= 34.2 Hz, J_{gem}= 13.5 Hz, 1H, CH_2Ph), 3.70-3.80 (complex absorption, 4H, OCH_3 and CH_2OSi), 4.18 (dd, $^3J_{H-F}$= 27.4 Hz, J_{gem} = 10.8 Hz, 1H, CH_2OSi), 6.80-6.82 (m, 2H, Ar), 6.88-7.00 (m, 2H, Ar), 7.30 (s, 5H, Ph) ; ^{19}F-NMR ($CDCl_3$) -162.60 (septet, $^3J_{F-H}$= 15.0 Hz) ; ^{13}C-NMR ($CDCl_3$) -5.3 [$Si(CH_3)_2$], 18.51 [$SiC(CH_3)_3$], 25.93 [$SiC(CH_3)_3$], 40.36 (NCH_3), 40.62 (d, $^2J_{C-F}$= 21.0 Hz, CH_2Ph), 55.22 (OCH_3), 68.32 (d, $^2J_{C-F}$= 21.0 Hz, CH_2OSi), 100.8 (d, $^1J_{C-F}$= 198.0 Hz, CF), 113.22 (Ar), 126.75 (Ar), 127.31 (Ph), 127.90 (Ph), 128.74 (Ph), 130.70 (Ph), 135.0 (Ph), 136.80 (Ar), 157.90 (Ar), 168.43 (d, $^2J_{C-F}$= 19.2 Hz, CON) ; Anal. Calcd. for $C_{24}H_{34}FO_3NSi$: C, 66.79 ; H, 8.41. Found : C, 66.53 ; H, 8.15.

(2*R*)-2-Fluoro-2-[*N*-methyl-*N*-(*p*-methoxyphenyl) carbonyl]-3-phenylpropanol, 11. To a solution of compound **10** (0.700 g, 1.6 mmol) in THF (16 mL) was added tetrabutyl ammonium fluoride (0.461 g, 1.5 mmol) at room temperature. The reaction mixture was stirred for 30 min, then poured into water (15 mL). After extraction with AcOEt (3 x 15 mL), the combined organic layers were washed with brine and dried ($MgSO_4$). After evapoaration of solvent, the residue was chromatographed (hexane-ethylacetate) to give 0.470 g of alcohol **11** (91% yield). $[\alpha]_D$ + 5.8 (c= 1.9, CH_2Cl_2) ; IR (CH_2Cl_2) 3419 (O-H), 2925, 1669 (C=O), 1517, 1400 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) 2.84 (dd, $^3J_{H-F}$= 16.4 Hz, J_{gem}= 14.2 Hz, 1H, C<u>H</u>$_2$Ph), 3.02(s, 3H, NC<u>H</u>$_3$), 3.24 (dd, $^3J_{H-F}$= 32.2 Hz, J_{gem}= 14.2 Hz, 1H, C<u>H</u>$_2$Ph), 3.67 (s, 3H, OC<u>H</u>$_3$), 3.85 (dd, $^3J_{H-F}$= 11.5 Hz, J_{gem}= 8.5 Hz, 1H, C<u>H</u>$_2$O), 3.92 (dd, $^3J_{H-F}$= 11.6 Hz, J_{gem}= 8.5 Hz, 1H, C<u>H</u>$_2$O), 5.8-6.0 (broad s, 1H, OH), 6.82-6.86 (m, 2H, Ar), 7.12-7.18 (m, 2H, Ar), 7.20-7.24 (m, 5H, Ph) ; ^{19}F-NMR ($CDCl_3$) -162.48 (sextet, J= 14.3 Hz) ; ^{13}C-NMR ($CDCl_3$) 40.30 (N<u>C</u>H$_3$), 40.62 (d, $^2J_{C-F}$= 20.4 Hz, <u>C</u>H$_2$Ph), 55.20 (O<u>C</u>H$_3$), 67.0 (d, $^2J_{C-F}$= 25.4 Hz, <u>C</u>H$_2$OH), 101.0 (d, $^1J_{C-F}$= 200.0 Hz, <u>C</u>F), 113.55 (Ar), 126.95 (Ar), 127.42 (Ph), 128.10 (Ph), 130.64 (Ph), 135.10 (Ph), 136.64 (Ar), 157.82 (Ar) 168.64 (d, $^2J_{C-F}$= 20 Hz, <u>C</u>ON) ; Anal. Calcd. for $C_{18}H_{20}FO_3N$: C, 68.12 ; H, 6.35 ; N, 4.41. Found : C, 68.16 ; H, 6.44 ; N, 4.48.

(2*S*)-2-Fluoro-2-[*N*-methyl-*N*-(*p*-methoxyphenyl) carbonyl]-3-phenylpropanoic acid, 12. To a solution of alcohol **11** (0.470 g, 1.5 mmol) in acetone (6 mL, distilled from potassium permanganate) was slowly added Jones' reagent (7.4 mmol) at 0 °C for 15 min. After stirring at room temperature for 2h, the reaction mixture is poured into a mixture of isopropanol/water (10 mL, 1:1). The aqueous layer was extracted with AcOEt (4 x 10 mL). The organic extracts were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated to afford 0.390 g of acid **12** (80% yield) as a white solid ; mp 158-160 °C. $[\alpha]_D$ +54 (c= 0.5, CH_2Cl_2) ; IR (KBr) 2946 (COO-H), 1774 (C=O), 1627 (C=O), 1517 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) 3.13 (s, 3H, NCH_3), 3.27 (dd, $^3J_{H-F}$= 26 Hz, Jgem= 14.5 Hz, 1H, CH_2Ph), 3.50 (dd, $^3J_{H-F}$=

24.5 Hz, J_{gem}= 14.4Hz, 1H, CH_2Ph), 3.63 (s, 3H, OCH_3), 6.45 (d, J= 8.9 Hz, 2H, Ar), 7.01 (broad s, 2H, Ar), 7.30-7.60 (m, 5H, Ph), 8.40-8.60 (broad s, 1H, COOH) ; ^{19}F-NMR ($CDCl_3$) -157.02 (broad t, $^3J_{F-H}$= 24.4 Hz) ; ^{13}C-NMR ($CDCl_3$) 40.50 (NCH_3), 42.34 (d, $^2J_{C-F}$= 21.7 Hz, CH_2Ph), 55.32 (OCH_3), 95.69 (d, $^1J_{C-F}$= 209.8 Hz, CF), 114.12 (Ar), 127.48 (Ar), 128.30 (Ph), 128.55 (Ph), 130.64 (Ph), 133.27 (Ph), 134.03 (Ar), 159.17 (Ar), 165.62 (d, $^2J_{C-F}$= 20.0 Hz, CON), 189.36 (d, $^2J_{C-F}$= 14.0 Hz, COOH) ; Anal. Calcd. for $C_{18}H_{18}FO_4N$: C, 65.25 ; H, 5.47. Found : C, 65.41 ; H, 5.57.

(2*R*)-2-Fluoro-2-[*N*-methyl-*N*-(*p*-methoxyphenyl) carbonyl]-3-phenylpropanoic acid benzylamide, 13. A solution of acid **12** (0.200 g, 0.6 mmol), benzylamine (0.063 g, 0.6 mmol) and 1-hydroxybenzotriazole (0.08 g, 0.6 mmol) in dry tetrahydrofuran (5 mL) was stirred and cooled in an ice-water bath while dicyclohexylcarbodiimide (0.130 g, 0.6mmol) was added. Stirring was continued for 1 h at 0 °C and an additional 15 h at room temperature. The *N, N'*-dicyclohexylurea formed during the reaction was removed by filtration and the filtrate was poured into a mixture of AcOEt (10 mL) and aqueous saturated solution of $NaHCO_3$ (5 mL). The organic phase was extracted with 10% solution of citric acid in water (5 mL), then washed with saturated $NaHCO_3$ and water. The solution was dried over $MgSO_4$, filtered and concentrated. The resulting residue was chromatographed (hexanes-ethylacetate) to afford 0.20 g of compound **13** (79% yield) as a white solid ; mp 158-160 °C. $[\alpha]_D$ -11 (c= 1, CH_2Cl_2) ; IR (KBr) 3356, 2946, 1670 (C=O), 1654(C=O), 1522, 1508 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) 3.26 (s, 3H, NCH_3), 3.46-3.66 (complex absorption, 2H, CH_2Ph), 3.73 (s, 3H, OCH_3), 4.08 (dd, Jgem= 14.3 Hz, J= 6.4 Hz, 2H, CH_2N), 5.14 (broad s,1H, NH), 6.64 (d, J= 8.8 Hz, 2H, Ar), 6.75 (d, J= 8.8 Hz, 2H, Ar), 7.06-7.30 (m, 10H, Ph) ; ^{19}F-NMR ($CDCl_3$) -155.90 (dd, $^3J_{F-H}$ = 36.0 Hz, J_{F-H} = 18.0 Hz)) ; ^{13}C-NMR ($CDCl_3$) 40.14 (NCH_3), 41.58 (d, $^2J_{C-F}$= 21.0Hz, CH_2Ph), 43.72 ($NHCH_2Ph$), 55.34 (OCH_3), 97.29(d, $^1J_{C-F}$= 204.8 Hz, CF), 113.77, 126.85, 127.38, 127.81, 127.99, 128.31, 130.17, 130.50, 134.07, 134.24, 136.17, 158.83, 164.61 (d, $^2J_{C-F}$= 20.3 Hz, CONMe), 166.53 (d, $^2J_{C-F}$= 20.5 Hz, CONH) ; Anal. Calcd. for $C_{25}H_{25}FO_3N_2$: C, 71.41 ; H, 5.99 ; N, 6.66. Found : C, 71.64 ; H, 5.81 ; N, 6.56.

(2*S*)-2-Fluoro-2-benzylamide-3-phenylpropanol, 14. To a solution of compound **13** (0.100 g, 0.24 mmol) in dry tetrahydrofuran (2.5 mL) was slowly added, at 0 °C, the ate complex (0.5 M solution, 0.48 mmol) generated from DIBAL-H and *n*-butyllithium in tetrahydrofuran-hexane. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 1 h after which sodium borohydride (0.02 g, 0.53 mmol) in absolute ethanol (1 mL) was added. The reaction mixture was stirred for an additional 30 min, then poured into 10% aqueous solution of hydrochloric acid. The aqueous layer was extracted with AcOEt. The combined organic layers were washed with saturated $NaHCO_3$, brine and dried over magnesium sulfate and concentrated. The residue was chromatographed (hexane-ethylacetate) to afford 0.060 g of alcohol **14** (88% yield). $[\alpha]_D$ +14 (c= 0.5, CH_2Cl_2) ; IR (CH_2Cl_2) 3335 (O-H), 1653 (C=O), 1544 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) 2.70 (broad s, 1H, OH), 3.07 (dd, $^3J_{H-F}$= 17.0 Hz, J_{gem}= 14.2 Hz, 1H, CH_2Ph), 3.21 (dd, $^3J_{H-F}$= 35.2 Hz, J_{gem}= 14.2 Hz, 1H, CH_2Ph), 3.94 (dd, $^3J_{H-F}$= 23.7 Hz, J_{gem}= 8.14 Hz, 1H, CH_2O, 3.98 (dd, $^3J_{H-F}$= 23.8 Hz, J_{gem}= 8.14 Hz, 1H, CH_2OH), 4.15 (dd, J_{gem}= 15.0 Hz, J= 5.1 Hz, 1H, CH_2N), 4.35 (dd, J_{gem}= 15.0 Hz, J= 6.4 Hz, 1H, NCH_2Ph), 6.35 (broad s, 1H, NH), 6.83-7.21 (m, 10H, Ph) ; ^{19}F-NMR ($CDCl_3$) -172.33 (complex absorption) ; ^{13}C-NMR ($CDCl_3$) 39.32 (d, $^2J_{C-F}$= 20.4 Hz, CH_2Ph), 42.97 ($NHCH_2Ph$), 65.92 (d, $^2J_{C-F}$= 24.2 Hz, CH_2OH), 99.72 (d, $^1J_{C-F}$= 191.9 Hz, CF), 127.12, 127.47, 128.35, 128.59, 130.20, 130.37, 133.96, 137.06, 170.0 (d, $^2J_{C-F}$= 21.2 Hz, CON) ; Anal. Calcd. for $C_{17}H_{18}FO_2N$: C, 71.06 ; H, 6.31. Found : C, 70.89 ; H, 6.27.

(2*R*)-2-Fluoro-2-benzylamide-3-phenylpropanoic acid, 15. To a solution of alcohol **14** (0.05 g, 0.17 mmol) in acetone (2 mL, distilled from potassium permanganate) was slowly added Jones' reagent (0.9 mmol) at 0 °C for 5 min. The reaction mixture was stirred at room temperature for 3 h. After the usual workup, 0.040 g of acid **15** was obtained (77% yield) as a white solid ; mp 140-142 °C. $[\alpha]_D$ -24 (c= 0.5, CH_2Cl_2) ; IR (KBr) 2960 (COO-H), 1770 (C=O), 1630 (C=O), 1520 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) 3.43-3.60 (complex absorption, 2H, CH_2Ph), 4.22 (dd, J_{gem}= 14.6 Hz, J= 5.0 Hz, 1H, NCH_2Ph), 4.41 (dd, J_{gem}= 14.6 Hz, J= 6.4 Hz, 1H, NCH_2Ph), 6.90 (broad s, 1H, NH), 7.0-7.30 (m, 10H, Ph), 8.82-9.0 (broad s, 1H, COOH) ; ^{19}F-NMR ($CDCl_3$) -167.96 (dd, $^3J_{F-H}$= 31.0 Hz, $^3J_{F-H}$= 18.0 Hz) ; ^{13}C-NMR ($CDCl_3$) 42.05 (d, $^2J_{C-F}$= 21.3 Hz, $CFCH_2Ph$), 43.84 ($NHCH_2Ph$), 94.87 (d, $^1J_{C-F}$= 205.6 Hz, CF), 127.57, 127.76, 127.84, 128.52, 128.66, 130.21, 132.03, 135.60, 167.65 (d, $^2J_{C-F}$= 21.0 Hz, CON), 189.3 (d, $^2J_{C-F}$= 14.3 Hz, COOH) ; Anal. Calcd. for $C_{17}H_{16}FO_3N$: C, 67.76 ; H, 5.35. Found : C, 67.62 ; H, 5.25.

(2*R*)-2-Fluoro-2-(benzyloxy-*D*-valylcarbonyl)-3-phenylpropanoic acid benzylamide, 2. A solution of acid **15** (0.04 g, 0.13 mmol), *D*-valine benzylester *p*-toluenesulfonate (0.051 g, 0.13 mmol) 1-hydroxybenzotriazole (0.018 g, 0.13 mmol) and *N*-methylmorpholine (0.013 g, 0.13 mmol) in dry tetrahydrofuran (2 mL) was stirred and cooled in an ice-water bath while dicyclohexylcarbodiimide (0.029 g, 0.13 mmol) was added. Stirring was continued for 2 h at 0 °C and an additional 20 h at room temperature. The *N*, *N'*-dicyclohexylurea formed during the reaction was removed by filtration and the filtrate was poured into a mixture of AcOEt (10 mL) and an aqueous saturated solution of $NaHCO_3$ (5 mL). The organic phase was extracted with 10% solution of citric acid in water (5 mL), then washed with saturated $NaHCO_3$ and water. The solution was dried over $MgSO_4$, filtered and concentrated. The resulting residue was chromatographed (hexanes-ethylacetate) to afford 0.050 g of compound **2** (77% yield) as a white solid ; mp 116-118 °C. $[\alpha]_D$ +7.3 (c= 1.5, CH_2Cl_2) ; IR (KBr) 3345, 3040, 2977, 1740 and 1734 (C=O), 1688 (C=O), 1541 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) 0.80 [d, J= 6.9 Hz, 3H, $CH(CH_3)_2$], 0.84 [d, J= 6.9 Hz, 3H, $CH(CH_3)_2$], 2.0-2.15 [complex absorption, 1H, $CH(CH_3)_2$], 3.32 (AB system, J= 4.8 Hz, 1H, CH_2Ph), 3.41 (AB system, J= 14.1 Hz, 1H, CH_2Ph), 4.18 (dd, J_{gem}= 14.7 Hz, J= 5.3 Hz, 1H, NCH_2Ph), 4.37 (dd, J_{gem}= 14.7 Hz, J= 6.5 Hz, 1H, NCH_2Ph), 4.5 (dd, J= 8.5 Hz, J= 5.2 Hz, 1H, $CHCO_2CH_2Ph$), 5.06 (d, J= 2.6 Hz, 2H, CO_2CH_2Ph), 7.0 (broad s, 1H, NH), 7.10-7.5 (m, 15H, Ph) ; ^{19}F-NMR ($CDCl_3$) -169.62 (dd, $^3J_{F-H}$= 21.4 Hz) ; ^{13}C-NMR ($CDCl_3$) 17.64 [$CH(CH_3)_2$], 19.1 [$CH(CH_3)_2$], 31.34 [$CH(CH_3)_2$], 43.02 (d, $^2J_{C-F}$= 21.0 Hz, CH_2Ph), 43.42 ($NHCH_2Ph$), 57.32 (OCH_2Ph), 67.04 (CHCO), 96.23 (d, $^1J_{C-F}$= 200.0 Hz, CF), 127.38, 127.40, 127.46, 128.20, 128.26, 128.33, 128.45, 128.51, 130.22, 132.7, 135.10, 136.70, 166.57 (d, $^2J_{C-F}$= 23.5Hz, CON), 166.64 (d, $^2J_{C-F}$= 22.0 Hz, CON), 170.40 (s, CO_2CH_2Ph) ; Anal. Calcd. for $C_{29}H_{31}FO_4N_2$: C, 71.0 ; H, 6.37 ; N, 5.71. Found : C, 70.98 ; H, 6.27 ; N, 5.70.

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