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Fluoroolefin Containing Dipeptide Isosteres as Inhibitors of Dipeptidyl Peptidase IV(CD26)

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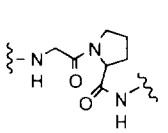
Abstract: (*Z*)-(*S*)Ala-Ψ[CF=C]-(*RS*)-Pro containing *N,O*-diacylhydroxamic acid type protease inhibitors have been prepared for the study of the influence of prolylamide bond geometry on the inhibition of dipeptidyl peptidase IV(CD26). The synthesis is based upon the use of *tert*-butyl α-fluoro-α-trimethylsilylacetate in a variation of the Peterson olefination procedure to construct the necessary functionalized fluoroolefin.

Prolyamides play a fundamental role in establishing the structure and function of peptides and proteins. The structural features unique to prolyamides are often critical to enzymatic recognition of proteins containing those residues.[1] In particular, the conformation around the P_1 and P_2-position[2] can be very important for the

$$H_3^+N - P_2 \overset{\downarrow}{-} Pro - P_{1'} - P_{2'} -$$

catalytic activity of proline specific peptidases.[3] It has previously been postulated that proline specific endopeptidase (EC 3.4.21.26) and dipeptidyl peptidase IV (EC 3.4.14.5, DPP IV, CD26)[4] possess a high conformational specificity for a *trans* P_2-Pro bond.



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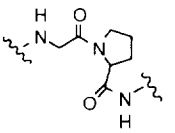


cis

DPP IV, discovered in 1966,[5] is a transmembrane serine peptidase found in a variety of human tissues and organs.[6] In particular DPP IV, when expressed on the surface of $CD4^+$ T-cells is identical with the CD26 antigen and is considered to be a lymphocyte activation marker.[7] Although the involvement of DPP IV in the immune response and regulation of lymphocyte activation has been implicated, the mechanism of the involvement is not clear. DPP IV has also been reported to be involved with the infection of T-cells with the human immunodeficiency virus[9] but this report has been questioned.[10]

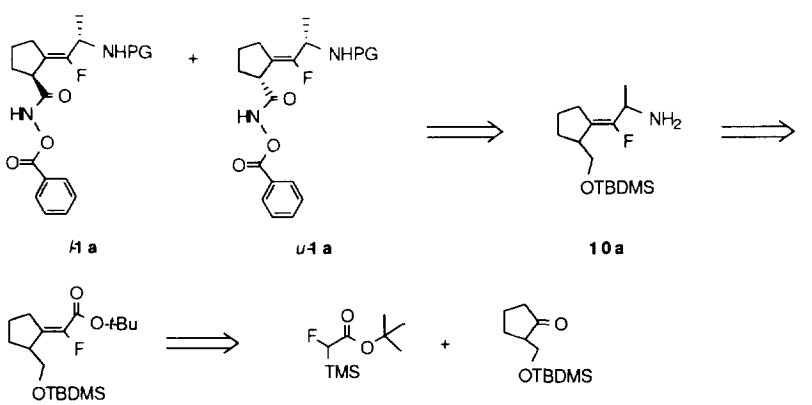
As a cell surface activation marker of lymphocytes,[11] failure to observe CD26 implies a reduced immune response.[12] The presence of DPP IV is associated with the capacity of cells to produce interleukin-2 (IL-2) and to proliferate strongly in response to mitogen stimulation.[13] Importantly binding of monoclonal antibodies to CD26 suppresses IL-2 production.[13b] CD26 modulation also can lead to enhanced cell proliferation proceeded by an increase in Ca^{2+} moblization.[14] CD26 is physically associated with CD45 (which

regulates T-cell activation pathways through protein tyrosine phosphatase action) apparently modulating the activity of CD45 by affecting the accessibility of critical substrates with the result that the CD2 / CD3 path amplifies the immune response.[15] Obviously inhibition of CD26 may critically effect T-cell activation and function and may potentially have therapeutic utility in the modulation of the rejection of transplanted tissue by the host organism.

Relatively few effective inhibitors of DPP IV have been reported.[16] Given the requirement for a DPP IV substrate to have a free *N*-terminal amino group, it is not surprising that the inhibitors which have been reported generally suffer from instability. The cyclization reaction of the free *N*-terminal amino group with the reactive site of the inhibitor does however require the molecule to assume the *cis* conformation, the conformation that was previously proposed to be unreactive with the DPP IV.[3] In order to obviate this mode of inactivation and to rigorously examine the *cis-trans* selectivity of DPP IV we prepared a series of conformationally constrained fluoroolefin dipeptide isosteres. The fluoroolefin dipeptide isostere was proposed as early as 1984[17] as a superior isoelectronic and isosteric replacement for the amide bond. Various synthetic approaches have been employed in the preparation of fluoroolefin containing dipeptide surrogates.[18] While theoretical studies have strongly supported the original hypothesis behind introduction of the fluoroolefin amide surrogate,[19] it was only recently that an experimental assessment of binding of these mimics was possible.[20]

RESULTS AND DISCUSSION

Synthetic Plan. We chose to prepare an acyl hydroxamic acid type inhibitor[21] to expedite our initial investigation of the importance of the P_2-Pro amide bond geometry. A brief retrosynthetic analysis for the target compound **1a** is outlined in Scheme 1. This strategy relies on the efficient construction of the fluoroolefin moiety by the Peterson olefination reaction followed by the further elaboration of the terminal functional groups to approach the target substances.

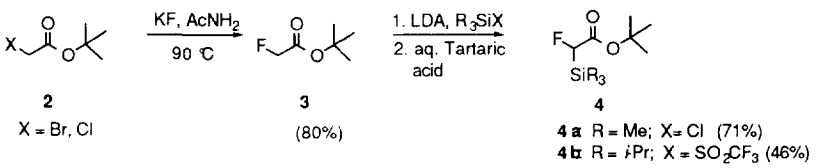


Scheme 1

Peterson Fluoroolefination Reaction. A key precursor for the entire synthetic sequence is a fluoroolefin such as **6a** bearing the appropriate latent functionalities . Although many methods have been used to construct fluoroolefins in the preparation of a variety of biologically active materials,[22] relatively few examples of these synthetic approaches have general applicability. The Peterson olefination reaction was first employed by our laboratory to prepare the fluoroolefin moieties of various fluorine-containing compounds.[23] Our previous

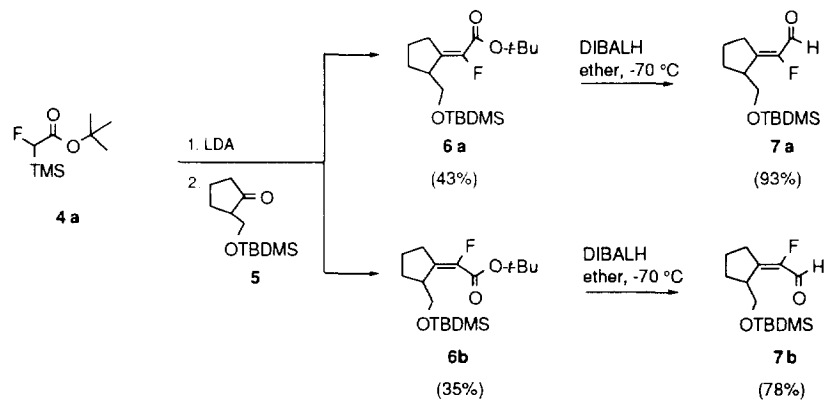
studies described the Peterson olefination of aryl aldehydes with 2,4,6-trimethylphenyl α-fluoro-α-trimethylsilylacetate led to the highly stereoselective formation of (*Z*)-fluoroalkenoates. In contrast, the reaction with aryl or alkyl ketones exhibited very low selectivity with (*E*)-fluoroalkenoates being formed in slight excess in most cases. The stereoselective potential of this reaction prompted us to extend the scope of this useful method for the preparation of fluoroolefins. Recently, an alternative route using a new α-fluoro-α-trialkylsilyl acetate, simple and convenient to prepare, was developed.[24] (Scheme 2)

As shown in Scheme 2 , treatment of commercially available *tert*-butyl α-chloroacetate or *tert*-butyl α-bromoacetate **2** with potassium fluoride easily yielded *tert*-butyl α-fluoroacetate **3** in 80% yield. The outcome of the direct *C*-silylation of **3** is highly depended on the molar ratio of the reagents employed, as well as the reaction temperature and time. It was found that *C,O*-bissilylation and Claisen condensation always accompanied the desired *C*-silylation reaction. After careful optimization, **4a** was formed in 71% yield by treatment of **3** with 4 equivalents of LDA and 6 equivalents of chlorotrimethylsilane at -78 °C. The purification of **4a** was achieved by fractional distillation where higher boiling point by-products were easily separated.



Scheme 2

Total Synthesis of Target Molecule **1a.** The choice of the amine protecting group for the target compound **1a** was a vexing problem. The desired protecting group had to be sufficiently labile so that it could be removed without affecting the hydroxamate functionality, also, ideally it should be compatible with standard *N*-terminal peptide synthesis protocols. Fortunately, Demuth[25] found that the *tert*-butoxycarbonyl (Boc) protecting group was removable by hydrochloric acid / acetic acid, conditions under which the hydroxamate functional group was uneffected.



Scheme 3

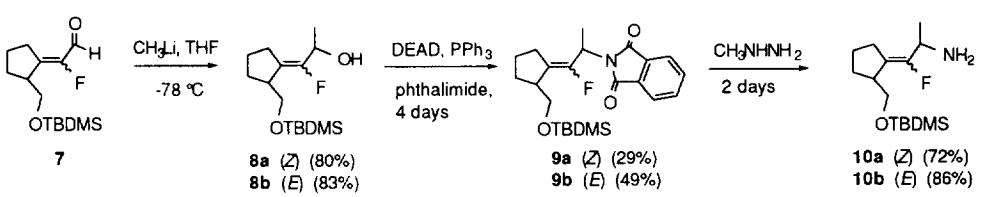
As shown in Scheme 3, the synthesis of the fluoroolefin began with Peterson olefination of the TBDMS-protected 2-(hydroxymethyl)cyclopentanone[26] **5** under our modified conditions employing *tert*-butyl α-fluoro-α-trimethylsilylacetate **4a**. The fluoroolefin product **6** was obtained as a 1.2 : 1 ratio of (*Z*): (*E*) isomers in 78% yield. The double bond isomers could be separated by column chromatography. Confirmation of the structural identity of the isomers was possible by comparison of the NMR spectra of the corresponding reduction product, aldehyde **7**, with the spectra reported in our earlier work.[23c] Earlier attempts to directly reduce the fluorinated α,β-unsaturated esters to the corresponding aldehydes with DIBALH in THF had been unsuccessful,[23c] the products being the corresponding primary alcohols. These results were consistent with an earlier report[27] on the reduction of nonfluorinated α,β-unsaturated esters. However, following the procedure of Wuts,[28] when **6a** or **6b** was treated with a slight excess of DIBALH (1.2 to 1.5 molar equivalents) in diethyl ether at -78 °C for 1 h, the corresponding aldehyde **7** was formed as nearly a single product in excellent yield. (Table 1)

Table 1. Reaction Conditions for Conversion of **6** to aldehyde **7**.

Esters	DIBALH Equivalents	Solvent	Ester **6** Reduction Products[a] Aldehyde **7** (%)	Alcohol (%)
6a	4.0	THF	10	87
6b	4.0	THF	9	84
6b	1.5	ether	78	12
6a	1.3	ether	89	4
6a	1.2	ether	93	0.2

a. Isolated yields after column chromatography.

Aldehyde **7** could then be converted to the desired α-amino-α-methyl moiety *via* several different synthetic approaches. Scheme 4 shows the practical synthetic route previously developed by our laboratory.[23c]

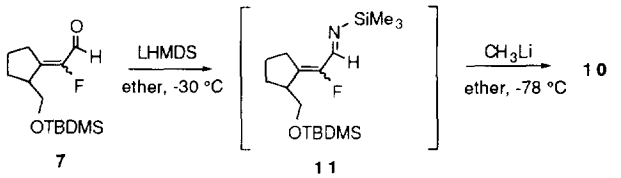


Scheme 4

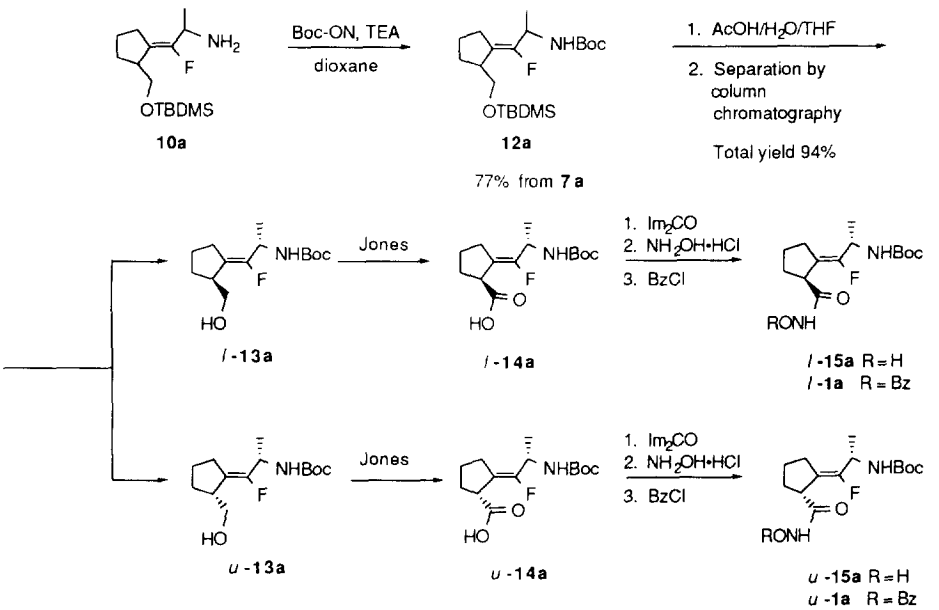
The selective 1,2-addition of methyllithium to aldehyde **7** was easily accomplished.[29] After purification by chromatography according to Still,[30] the combined yield of the separated diastereomers of the secondary alcohol **8** was 80%. Transformation of **8** to the protected amide **9** was carried out under standard Mitsunobu conditions over four days.[31] As could be anticipated, low yields resulted in both the (*E*) and (*Z*) cases (29% and 49%) probably as a result of the steric effect of secondary alcohol on the displacement reaction. Unfortunately, the phthalimide protecting group was not suitable in these cases because of the forcing conditions required for its removal; the phthalimide group could only be liberated by treatment of **9** with excess methylhydrazine at room

temperature for two days. The long reaction times and low yields of the Mitsunobu reaction when combined with the difficult deprotection resulted in depressingly low overall yields of amine **10**.

Literature precedent [32] for the direct alkylative amination of aldehydes encouraged us to develop a more efficient synthetic approach (Scheme 5). The sequential treatment of a nonenolizable aldehyde with lithium bis(trimethylsilyl)amide (LHMDS) followed by condensation with the desired organolithium or Grignard reagents in THF was reported to give the corresponding α-substituted alkyl amines,[32a] presumably *via* the intermediacy of a *N*-trimethylsilyl imine. The putative intermediate *N*-trimethylsilyl imines were not normally purified or characterized. Repeated attempts to form the desired amine **10** from aldehydes **7a** or **7b** under these conditions[19b,32] failed. Many unidentifiable products were generated as observed by ^{19}F NMR. After further investigation, it was found that the formation of the crucial intermediate **11** was highly dependent upon the reaction temperature employed and the choice of the solvent. Competitive vinylogous deprotonation of the imine by the organolithium or Grignard reagent to form the corresponding vinylogous azaenolate, appeared to be the major source of byproducts in this reaction.



Gratifyingly, the optimum conditions were found after extensive study. Treatment of aldehyde **7a** with LHMD (1.2 equiv.) in diethyl ether at -30 °C for 1 h, then subsequent addition of methyllithium (2.0 equiv.) in



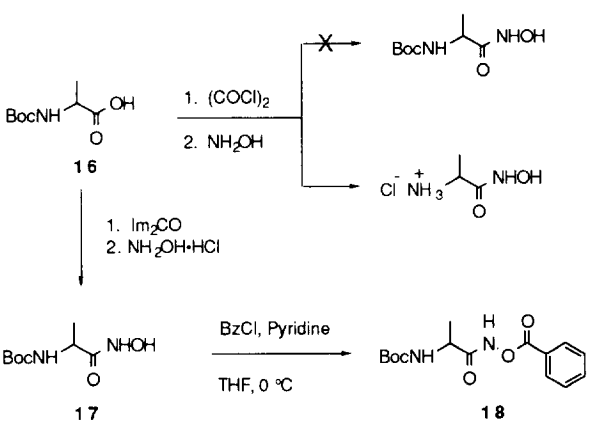
Scheme 5

ether at -78 °C followed by stirring for an additional hour afforded the desired amine **10a** in 93% yield as a 1.3:1 ratio of diastereomers. The observed ^{19}F resonances were consistent with those of amine products derived from the previously described synthetic route (Scheme 4). Interestingly, if the reaction was conducted under the same conditions in THF instead of diethyl ether, the desired product was formed in only very low yield.

Even though it was possible to separate the diastereomers of **10a** by chromatography, it was anticipated that it might be more convenient to delay the diastereomeric separation until preparation of the deprotected alcohol **13a**. Therefore, **10a**, as a mixture of diastereomers was protected using 2-(Boc-oxyimino)-2-phenylacetonitrile (Boc-ON) according to the standard procedure[33] in good yield (77%, overall from aldehyde **7a**).

Selective cleavage of the silyl ether **12a**, in the presence of the Boc-group, was accomplished by treatment with acetic acid-water-THF liberating the primary alcohol **13a** in 94% yield as a 1.2 : 1 ratio of diastereomers.[34] Following separation of the diastereomers by column chromatography, Jones oxidation of the alcohols *l*-**13a** and *u*-**13a**, respectively, yielded the corresponding crystalline carboxylic acids, *l*-**14a** and *u*-**14a**, without loss of the acid-sensitive Boc-group.

The final transformations necessary to form **1a** required the conversion of carboxylic acid **14a** to hydroxamic acid **15a**, and subsequent acylation of **15a** with benzoyl chloride. In a model study, we attempted to convert a model compound, *N*-Boc-alanine (**16**) to the acid chloride by using oxalyl chloride,[35] followed by hydroxylaminolysis of the crude acid chloride with hydroxylamine. The procedure failed when the hydrochloric acid generated during the reaction hydrolyzed the Boc-group (Scheme 6).



Scheme 6

However, hydroxamic acid **17** was readily formed in 78% yield from carboxylic acid **16** *via* addition of 1,1'-carbonyldiimidazole to form the reactive acylimidazole, which was subsequently condensed with hydroxylamine hydrochloride.[36] Boc-protected hydroxamic acid **17** was converted to the *N,O*-diacylhydroxylamine **18** in 94% yield by addition of equimolar amount of benzoyl chloride and pyridine.[35] One of the diastereomers **14a** was hydroxylaminated in the same manner to form the hydroxamic acid **15a** in 50% yield. Acylation of the **15a** with benzoyl chloride under the conditions described above formed the **1a** in 51% yield. We are currently optimizing the reaction conditions for each of these last two steps.

This synthesis can be easily adopted for the preparation of (*E*)-Ψ[CF=C] containing compounds as well. This flexible and efficient synthetic route can readily accommodate the introduction of other reactive functionality such as boronic acids common to effective serine protease inhibitors. Inhibition studies of these materials with DPP IV are in progress and will be reported elsewhere.

EXPERIMENTAL SECTION

General Methods. Infrared (IR) spectra were obtained on a Perkin-Elmer 1600 Series FTIR spectrometer. All ^{1}H NMR spectra were recorded at 300 MHz on a Gemini-300 NMR spectrometer with $CDCl_3$ as solvent and tetramethylsilane (TMS) or residual chloroform as the internal standard. All ^{13}C NMR spectra were recorded at 75.429 MHz on a Gemini XL-300 NMR spectrometer with $CDCl_3$ as solvent and tetramethylsilane (TMS) or residual chloroform as the internal standard. ^{19}F NMR spectra were recorded at 282.203 MHz on a Gemini XL-300 NMR spectrometer with $CDCl_3$ as solvent and chlorotrifluoromethane ($CFCl_3$) as the internal standard. Thin layer chromatography was performed with silica gel F_{254} (Merck) as the adsorbent on 0.2 mm thick, plastic-backed plates. The chromatograms were visualized under UV (254 nm), by staining with a 5% solution of phosphomolybdic acid in isopropanol followed by drying in an oven at 90 °C, or by spraying with a 95 : 5 mixture of 0.2% ninhydrin in *n*-butanol and 10% aqueous acetic acid followed by heating. Column chromatography was performed using silica gel 60 (70-230 mesh, Merck) and flash silica gel 60 (0.040-0.063 μm, 230-400 mesh, EM Science). Melting points were determined in open capillaries using a Büchi 510 melting point apparatus and are reported uncorrected. Boiling points are reported in degrees Centigrade at the indicated pressure in mm mercury (Hg) and are uncorrected.

***tert*-Butyl α-fluoroacetate (3).** To a mixture of acetamide (44.26 g, 750 mmol, recrystallized from MeOH/EtOH and dried) and potassium fluoride (43.58, 750 mmol, dried under vacuum using an Abderhalden apparatus at 110 °C for 24 h), was added *tert*-butyl α-chloroacetate **2** (46.58 g, 300 mmol). The mixture was heated to 90 °C and stirred well for at least 12 h to ensure complete conversion, which was then allowed to cool to room temperature. The reaction mixture was distilled under reduced pressure (71-72 °C / 145 mm Hg) to give pure **3** as colorless liquid (32.25 g, 80%). The further purification by the second distillation (131-133 °C / 760 mm Hg) might be needed to remove the trace amount of starting material **2**: Bp 131-133 °C (Lit.[37] 133-135 °C); IR (neat) 2982, 1762 (CO), 1444, 1396, 1370, 1314, 1162, 1082, 846 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -228.28 (t, J = 48.8 Hz); ^{1}H NMR ($CDCl_3$) δ 4.68 (d, J = 48.4 Hz, 2H), 1.48 (s, 9H).

***tert*-Butyl α-fluoro-α-trimethylsilylacetate (4a).** To a solution of diisopropylamine (33.4 mL, 240 mmol) in THF (120 mL), was added slowly *n*-butyllithium (95.4 mL, 240 mmol, 2.5 *M* solution in hexanes) at -30 °C. The solution was stirred for 15 min at -30 °C, then transferred via canula into the prepared solution of *tert*-butyl fluoroacetate **3** (8.00 g, 60 mmol) and chlorotrimethylsilane (45.7 mL, 360 mmol) in 320 mL of THF and 400 mL of pentane at -78 °C. The temperature was kept between -78 °C and -80 °C during the transfer, then warmed to 0 °C over a period of 3 hours. The mixture was immediately quenched with $NaHCO_3$ (120 mL) at 0 °C. The separated aqueous layer was extracted with ether (3 x 120 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated to a volume of 200 mL. Analysis of the ^{19}F NMR indicated a mixture of *C*- and *O*-bissilylated enol ether and monosilylated α-fluoro ester **4a**. Hydrolysis of this mixture with saturated tartaric acid aqueous solution (200 mL) at room temperature overnight yielded 7.33 g (71%) of *tert*-butyl α-fluoro-α-(trimethylsilyl)acetate **4a** after distillation: Bp 62-64 °C (30 mm Hg); IR (neat) 2956, 1749, 1253, 821 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -225.70 (d, J = 47.5Hz); ^{1}H NMR ($CDCl_3$) δ 4.53 (d, J = 47.9 Hz,

1H), 1.47 (s, 9H), 0.15 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 170.07 (d, J =19.2 Hz), 87.37 (d, J = 181.2 Hz), 81.74, 28.30, 2.92, 1.10, -3.71.

Peterson Olefination of 4a and TBDMS-protected 2-(hydroxymethyl)cyclopentanone (5). To a solution of diisopropylamine (2.4 mL, 17 mmol) in THF (105 mL), was added dropwise *n*-butyllithium (6.9 mL, 17 mmol, 2.5 *M* solution in hexane) at -25 °C. The solution was stirred for 15 min at -30 °C, then allowed to cool to -95 °C. *tert*-Butyl α-fluoro-α-trimethylsilyl acetate **4a** (3.10 g, 15.0 mmol) dissolved in THF (10 mL) was added to LDA solution and stirred for 40 min at -95 °C, followed by addition of 2-hydroxymethyl cyclopentanone derivative **5** (3.77 g, 16.5 mmol) in THF (10 mL). The reaction mixture was stirred for additional 10 min at -95 °C, and the cooling bath was removed. The reaction mixture was quenched with saturated NH_4Cl (25 mL) at 0 °C. The separated aqueous layer was extracted with hexanes (3 x 100 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (hexane/CH_2Cl_2; 6 : 4) to give 2.18 g of the (*Z*)-fluoroolefin, **6a**, and 1.80 g of the (*E*)-fluoroolefin, **6b** (overall yield: 78%): TLC (50% CH_2Cl_2 in hexanes: R_f 0.46, **6a**; R_f 0.52, **6b**). (*Z*)-isomer, **6a**: IR (neat) 2950, 2863, 1718, 1679, 1477, 1368, 1342, 1256, 1098, 836 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -125.43 (s); ^1H NMR ($CDCl_3$) δ 3.73 (dd, J = 9.6, 4.2 Hz, 1H), 3.46 (t, J = 8.7 Hz, 1H), 3.09 (m, 1H), 2.70-2.54 (m, 2H), 1.86-1.65 (m, 4H), 1.50 (s, 9H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.38 (d, J = 35.0 Hz), 142.87 (d, J = 246.3 Hz), 139.46 (d, J = 13.6 Hz), 81.91, 62.99 (d, J = 4.0 Hz), 45.93, 31.13, 28.55, 28.10, 25.83, 24.62, 18.22, –5.44, –5.54. (*E*)-isomer, **6b**: IR (neat) 2956, 2881, 1688, 1472, 1260, 1098, 1031, 836 cm^{-1}; ^{19}F NMR ($CDCl_3$)δ -120.88 (s); ^1H NMR ($CDCl_3$) δ 3.62 (dd, J = 9.3, 3.9 Hz, 1H), 3.45 (t, J = 8.7 Hz, 1H), 3.35 (m, 1H), 2.51-2.42 (m, 2H), 1.74-1.64 (m, 4H), 1.52 (s, 9H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.88 (d, J = 35.6 Hz), 142.99 (d, J = 245.9 Hz), 139.99 (d, J = 14.8 Hz), 82.06, 64.03 (d, J = 4.5 Hz), 44.63, 30.16, 29.53, 28.08, 25.88, 22.65, 18.26, –5.40, –5.54. Anal. Calcd for $C_{18}H_{33}FO_3Si$: C, 62.75; H, 9.65. Found: C, 63.11; H, 9.94.

1-(1-Fluoro-2-oxoethylidene)-2-(*t*-butyldimethylsilyloxymethyl)cyclopentanes (7a and 7b). *tert*-Butyl ester **6a** (2.00 g, 5.80 mmol) was dissolved in dried diethyl ether (21 mL). The resulting solution was cooled to -78 °C, and diisobutylaluminum hydride (1.3 mL, 7.3 mmol) was added dropwise as 1 *M* solution in pentane (7.3 mL). The mixture was stirred at -78 °C for 1h and then quenched with H_2O (2 mL). The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The white solids were filtered and washed thoroughly with ether. The filtrate was dried over $MgSO_4$, concentrated *in vacuo*. The light yellow residue was submitted to a flash column chromatography using hexane/EtOAc (9 : 1) as eluent to provide the aldehyde **7a** (1.47 g, 93%): IR (neat) 2926, 2847, 2748, 1694, 1640, 1470, 1258, 1100, 836 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -133.69 (d, J = 16.2 Hz); ^1H NMR ($CDCl_3$) δ 9.57 (d, J = 16.4 Hz, 1H), 3.74 (dd, J = 9.7, 4.0 Hz, 1H), 3.64 (dd, J = 9.7, 6.8 Hz, 1H), 3.20-3.10 (m, 1H), 2.84-2.60 (m, 2H), 2.30-1.65 (m, 4H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 182.26 (d, J = 29.1 Hz), 149.86 (d, J = 248.8 Hz), 147.58 (d, J = 11.2 Hz), 63.16 (d, J = 3.9 Hz), 45.82, 29.05, 28.29, 25.81, 25.16, 18.21, –5.49, –5.56. Anal. Calcd for $C_{14}H_{25}FO_2Si$: C, 61.72; H, 9.25. Found: C, 61.67; H, 9.15.

Except that using 1.5 equivalents of diisobutylaluminum hydride, the aldehyde **7b** was prepared in the same manner in 78% yield: IR (neat) 2954, 2856, 2740, 1742, 1688, 1640, 1472, 1258, 1098, 938 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -129.40 (d, J = 19.0 Hz); ^1H NMR ($CDCl_3$) δ 9.53 (d, J = 19.0 Hz, 1H), 3.59 (dd, J = 9.7, 6.0 Hz, 1H), 3.38 (t, J = 9.3 Hz, 1H), 3.28 (br q, J = 7.4 Hz, 1H), 2.64-2.58 (m, 2H), 1.90-1.60 (m, 4H),

0.83 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 182.76 (d, J = 24.7 Hz),151.21 (d, J = 250.2 Hz), 146.88 (d, J = 13.2 Hz), 64.80 (d, J = 3.5 Hz), 42.77 (d, J = 5.4 Hz), 29.54, 29.10, 25.78, 25.72, 18.23, −5.47, −5.56. Anal. Calcd for $C_{14}H_{25}FO_2Si$: C, 61.72; H, 9.25. Found: C, 61.64; H, 9.09.

1-[1-Fluoro-(2-hydroxy-2-methyl)ethylidene)-2-(*t*-butyldimethylsilyloxymethyl]cyclopentanes (8a and 8b). Methyllithium (3.1 mL, 4.6 mmol, 1.5 *M* solution in diethyl ether) was added dropwise to a solution of (*E*)-aldehyde, **7b** (0.70 g, 2.6 mmol) in THF (66 mL) at -78 °C under N_2. The reaction mixture was stirred at -78 °C for 90 min. After the cooling bath was removed, the mixture was stirred at room temperature for another hour, then recooled to 0 °C and quenched with 30 mL of H_2O. To this quenched mixture was added 150 mL of CH_2Cl_2. The separated aqueous layer was extracted with CH_2Cl_2 (2 x 60 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. ^{19}F NMR analysis of the crude product show a 3.2 : 1 ratio of diastereomers which were separated by a column chromatography with hexane/EtOAc (9 : 1) to give 0.47 g of the major diastereomer, **8b'**, and 0.15 g of the minor isomer, **8b"** (total yield: 83%). **8b'**: IR (neat) 3416, 2956, 2858, 1712, 1472, 1388, 1362, 1256, 1172, 1094 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -123.40 (d, J = 24.4 Hz); ^{1}H NMR ($CDCl_3$) δ 4.44 (dq, J = 24.2 Hz, 1H), 3.51 (ddd, J = 10.0, 5.8, 1.8 Hz, 1H), 3.39 (t, J = 9.7 Hz, 1H), 2.83 (br q, J = 7.2 Hz, 1H), 2.47-2.27 (m, 2H), 1.81-1.45 (m, 4H), 1.31 (d, J = 6.0 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.36 (d, J = 253.0 Hz), 121.18 (d, J = 17.0 Hz), 66.24 (d, J = 3.0 Hz), 64.62 (d, J = 30.4 Hz), 42.61 (d, J = 5.3 Hz), 29.83, 26.76 (d, J = 3.6 Hz), 26.08, 23.31, 18.68, 18.58 (d, J = 4.2 Hz), −5.53, −5.56. **8b"**: IR (neat) 3392, 2956, 2858, 1712, 1472, 1362, 1256, 1096, 1004, 836 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -119.90 (d, J = 14.7 Hz); ^{1}H NMR ($CDCl_3$) δ 4.48 (br sext., J = 6.8 Hz, 1H), 3.71 (dd, J = 9.9, 5.4 Hz, 1H), 3.55 (t, J = 9.9 Hz, 1H), 3.11 (br q, J = 7.4 Hz, 1H), 2.82 (br s, 1H), 2.50-2.20 (m, 2H), 2.16-1.50 (m, 4H), 1.34 (d, J = 6.5 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.97 (d, J = 247.2 Hz), 119.41 (d, J = 16.8 Hz), 65.70 (d, J = 3.7 Hz), 65.45 (d, J = 35.0 Hz), 41.53 (d, J = 5.2 Hz), 29.61, 27.01 (d, J = 3.6 Hz), 25.93, 22.42, 20.70, 18.40, −5.51, −5.57. In the same method, **8a** was prepared in 80% yield as colorless oil. The major isomer, **8a'**: IR (neat) 3380, 2954, 2857, 1712, 1472, 1362, 1256, 1096, 836 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -132.05 (d, J = 25.8 Hz); ^{1}H NMR ($CDCl_3$) δ 4.47 (dq, J = 26.0, 6.6 Hz, 1H), 3.74 (dd, J = 9.8, 4.4 Hz, 1H), 3.37 (t, J = 9.6 Hz, 1H), 3.00-2.85 (m, 1H), 2.40-2.10 (m, 2H), 1.90-1.50 (m, 4H), 1.34 (d, J = 6.6 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.30 (d, J = 249.2 Hz), 120.70 (d, J = 15.4 Hz), 65.33 (d, J = 29.5 Hz), 63.85 (d, J = 3.1 Hz), 43.50, 29.18, 28.20 (d, J = 4.9 Hz), 25.95, 24.55, 19.87 (d, J = 2.2 Hz), −5.45, −5.51.

***N*-Phthalimide-1-[(1'-fluoro-2'-amino)propylidene-2-(*t*-butyldimethylsilyloxy)methyl] cyclopentanes (9a and 9b).** The major isomer, **8a'** (0.61 g, 2.1 mmol), triphenylphosphine (0.72 g, 2.7 mmol) and phthalimide (0.41 g, 2.7 mmol) in THF (20 mL) was treated dropwise with diethylazodicarboxylate (0.50 g, 2.73 mmol) as a 2 mL solution in THF at room temperature. After stirring at ambient temperature for 4 days, the solvent was evaporated *in vacuo*. The syrupy residue was dissolved in a minimum amount of CH_2Cl_2 and transferred to a column. Elution with hexane/EtOAc (9 : 1) yielded 0.427 g (49%) of **9b'** as yellow oil: IR (neat) 2954, 2856, 1778, 1716, 1470, 1380, 1254, 1094, 1004, 838 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -118.40 (d, J = 30.2 Hz); ^{1}H NMR ($CDCl_3$) δ 7.81 (dd, J = 5.4, 2.9 Hz, 2H), 7.68 (dd, J = 5.4, 3.1 Hz, 2H), 5.37 (dq, J = 29.9, 7.4 Hz, 1H), 3.49 (dd, J = 7.4, 2.4 Hz, 2H), 3.10-3.00 (m, 1H), 2.35-2.30 (m, 2H), 1.74 (d, J = 7.4 Hz, 3H), 1.70-1.52 (m, 4H), 0.91 (s, 9H), 0.091 (s, 3H), 0.089 (s, 3H). (*Z*)-isomer, **9a** was made in the

same manner in 29 %: ^{19}F NMR ($CDCl_3$) δ -119.14 (d, J = 24.4 Hz), -120.09 (d, J = 24.4 Hz); ^1H NMR ($CDCl_3$) δ 7.84-7.65 (m, 8H), 5.27-5.09 (m, 2H), 3.70 (dd, J = 9.9, 4.2 Hz, 1H), 3.66 (dd, J = 9.6, 3.9 Hz, 1H), 3.43 (t, J = 9.2 Hz, 1H), 3.34 (dd, J = 9.0 Hz, 1H), 3.00-2.85 (m, 2H), 2.38-2.27 (m, 4H), 1.67 (d, J = 6.3 Hz, 3H), 1.65 (d, J = 5.7 Hz, 3H), 1.79-1.53 (m, 8H), 0.86 (s, 9H), 0.76 (s, 9H), 0.015 (s, 6H).

1-[(1'-fluoro-2'-amino)propylidene-2-(*t*-butyldimethylsilyloxy)methyl]cyclopentanes (10a and 10b). Method A (Scheme 4): Methylhydrazine (92 mg, 2.0 mmol) was added dropwise to a solution of **9b'** (84.0 mg, 0.20 mmol) in 4 mL of freshly distilled CH_2Cl_2. The reaction mixture was stirred at room temperature and monitored by TLC. After 48 hours, TLC analysis indicated that the reaction was complete. The solvent was evaporated and the residue was treated with 5 mL of EtOAc. The white solids were filtered and washed with EtOAc. Concentration of the filtrate gave a crude amine product, which was purified by a column chromatography (4% MeOH in CH_2Cl_2), affording free amine **10b'** (49 mg, 86%): IR (neat) 3376, 3303, 2956, 2858, 1710, 1637, 1472, 1256, 1099, 1006, 836, 786 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -129.09 (d, J = 24.4 Hz); ^1H NMR ($CDCl_3$) δ 3.39-3.28 (m, 3H), 2.77-2.69 (m, 1H), 2.36-2.23 (m, 2H), 1.82-1.58 (m, 6H), 1.28 (d, J = 6.5 Hz, 3H), 0.86 (s, 9H), 0.012 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 156.29 (d, J = 248.5 Hz), 118.81 (d, J = 14.7 Hz), 65.29 (d, J = 4.1 Hz), 46.07 (d, J = 25.8 Hz), 43.10 (d, J = 5.3 Hz), 29.41, 27.13, 27.08, 25.96, 23.28, 18.41, −5.32, −5.38. (Z)-isomer **10a** was prepared by following the same procedure in 72% yield.

Method B (Scheme 5): A hexane solution of *n*-butyllithium (1.5 mL, 3.8 mmol, 2.5 *M* solution in hexane) was slowly added to a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.67 g, 4.2 mmol) in diethyl ether (32 mL) cooled in an ice-water bath. The cooling bath was removed and the solution was stirred at room temperature for 30 min. The mixture was cooled to -30 °C and to this lithium bis(trimethylsilyl)amide solution was added a solution of 0.87 g (3.2 mmol) of the aldehyde **7a** in 8 mL of ether. The mixture was stirred at -30 °C for 1 h, then cooled to -78 °C. The resulting solution containing *N*-trimethylsilyl imine was treated with methyllithium (4.3 mL, 6.40 mmol, 1.5 *M* solution in ether) at -78 °C. The mixture was stirred at -78 °C for 1 h and then at room temperature for an additional 2 h. The solution was cooled to 0 °C again, quenched with 32 mL of saturated aqueous NH_4Cl, and extracted with CH_2Cl_2 (4 x 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. To remove some nonpolar impurities, the residue was subjected to a purification on a very short silica column using hexane/CH_2Cl_2 (1 : 1) as the eluent to give a 1.3 : 1 ratio of diastereomers, **10a** (0.86 g, 93%). The mixture of diastereomers was carried over to the next step without isolation: IR (neat) 3377, 3282, 2956, 2861, 1710, 1654, 1472, 1257, 1098, 838, 776 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -132.08 (d, J = 25.8 Hz), -132.08 (d, J = 27.1 Hz); ^1H NMR ($CDCl_3$) δ 3.73-3.56 (m, 2H), 3.37 and 3.33 (dt, J = 9.4, 9.6 Hz, 1H), 2.95-2.82 (m, 1H), 2.78-2.10 (m, 2H), 1.80-1.47 (m, 6H), 1.21 and 1.20 (d, J = 6.7, 6.7 Hz, 3H), 0.86 and 0.85 (s, 9H), 0.010 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.51 (d, J = 249.5 Hz), 155.33 (d, J = 248.7 Hz), 117.85 (d, J = 15.9 Hz), 117.74 (d, J = 15.9 Hz), 64.00 (d, J = 3.4 Hz), 63.96 (d, J = 3.4 Hz), 46 58 (d, J = 28.5 Hz), 46.47 (d, J = 28.5 Hz), 43.27, 29.27, 28.26 (dd, J = 5.5, 4.4 Hz), 28.19, 28.13, 25.90, 24.82, 24.58, 20.56, 20.12, 18.31, 18.28, −5.31, −5.36, −5.53.

(Z)-*N*-*t*-Butyloxycarbonyl-1-[(1'-fluoro-2'-amino)propylidene-2-(*t*-butyldimethylsilyloxy) methyl]cyclopentanes (12a). To a solution of amine **10a** (0.86 g, 3.0 mmol) in dioxane (60 mL) were added triethylamine (0.62 mL, 4.5 mmol) and 2-(*t*-butoxycarbonyloxyimino)-2-phenyl acetonitrile (Boc-ON) (0.88 g, 3.6 mmol). The mixture was stirred for 20 h at room temperature and the solvent was evaporated. Elution of

the crude by a slow column chromatography with hexane/EtOAc (20 : 1) yield 0.88 g of **12a** (77% from aldehyde **7a**): IR (neat) 3450, 3346, 2956, 2862, 1712, 1498, 1366, 1250, 1170, 1096, 1052, 838 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -130.09 (d, J = 24.4 Hz), -130.78 (d, J = 24.4 Hz); ^1H NMR ($CDCl_3$) δ 4.76 (br s, 1H), 4.47 (br d, J = 24.7 Hz, 1H), 3.68 and 3.63 (dd, J = 8.5, 4.5 Hz and 9.5, 4.5 Hz, 1H), 3.38 and 3.32 (t, J = 8.3, 9.6 Hz), 2.89 (m, 1H), 2.38 (m, 1H), 2.16 (m, 1H), 1.85-1.53 (m, 4H), 1.40 (s, 9H), 1.23 and 1.22 (d, J = 6.9, 6.9 Hz, 3H), 0.86 and 0.85 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.80, 154.77, 153.13 (d, J = 248.2 Hz), 119.68 (br s), 79.37, 63.90 (d, J = 3.6 Hz), 63.78 (d, J = 3.3 Hz), 43.39, 43.26, 29.31, 28.36, 25.91, 25.88, 24.79, 24.44, 18.75, 18.38, 18.29, 18.26, −5.37, −5.41, −5.45.

(*Z*)-*N*-*t*-Butyloxycarbonyl-1-[(1'-fluoro-2'-amino)propylidene)-2-(hydroxy)methyl] cyclopentanes (13a). A solution of **12a** (0.77 g, 2.0 mmol) in AcOH/H_2O/THF (100 mL, 13 : 7 : 3) was stirred for 16 h at room temperature. The solvent was then removed under vacuum. The yellow liquid residue was treated with solid $NaHCO_3$ until the mixture was slightly basic, and H_2O (8 mL) was added. The mixture was extracted with EtOAc (4 x 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexane/EtOAc, 4 : 1) to provide 0.28 g of one diastereomer **13a'** (51%) and 0.23 g of the other isomer, **13a"** (43%). **13a'**: IR (neat) 3440, 3340 (br, s), 2976, 2872, 1692, 1518, 1453, 1366, 1248, 1168, 1054 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -130.50 (d, J = 28.5 Hz); ^1H NMR ($CDCl_3$) δ 4.74 (br s, 1H), 4.38 (br d, J = 28.5 Hz, 1H), 3.57 (d, J = 4.5 Hz, 2H), 2.97-2.88 (m, 1H), 2.49-2.35 (m, 1H), 2.28-2.13 (m, 1H), 1.92-1.51 (m, 5H), 1.40 (s, 9H), 1.24 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 154.97, 151.99 (d, J = 249.3 Hz), 119.17 (d, J = 14.7 Hz), 79.64, 64.13 (d, J = 3.8 Hz), 46.05 (d, J = 26.8 Hz), 43.45, 29.64, 28.41, 28.31, 24.85, 17.90. Data for **13a"**: ^{19}F NMR ($CDCl_3$) δ -129.28 (d, J = 29.8 Hz); ^1H NMR ($CDCl_3$) δ 4.80 (br s, 1H), 4.45 (br d, J = 27.0 Hz, 1H), 3.62 (dd, J = 10.5, 5.1 Hz, 1H), 3.44 (t, J = 9.2 Hz, 1H), 2.93 (m, 1H), 2.43 (m, 1H), 2.19 (m, 1H), 1.87 (m, 1H), 1.77-1.52 (m, 4H), 1.39 (s, 9H), 1.23 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 154.82, 152.67 (d, J = 248.1 Hz), 119.32 (d, J = 14.1 Hz), 79.50, 64.18 (d, J = 3.7 Hz), 46.62 (d, J = 29.5 Hz), 43.46, 29.39, 28.32, 28.13 (d, J = 5.3 Hz), 24.77, 18.63. Anal. Calcd for $C_{14}H_{24}FNO_3$: C, 61.52; H, 8.85. Found: C, 61.41; H, 8.99.

(*Z*)-*N*-*t*-Butyloxycarbonyl-1-[(1'-fluoro-2'-amino)propylidene]-2-cyclopentane Carboxylic Acid (14a). Jones reagent (0.30 mL, 2.8 mmol) was dropwise added to a solution of alcohol **13a'** (0.15 g, 0.56 mmol) in dry acetone (9 mL) at 0 °C. The solution turned orange to greenish. The reaction mixture was stirred for 1 h at 0 °C, then quenched with H_2O (14 mL), extracted with EtOAc (3 x 30 mL). The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (hexane/EtOAc, 3 : 2) yielded the carboxylic acid **14a'** (0.12 g, 73%) as a white solid: Mp 122-126 °C: IR (CH_2Cl_2) 3490-2567 (br, s), 3300, 3264, 2978, 2862, 1710, 1653, 1406, 1252, 1166, 1056, 910, 734 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -123.26 (d, J = 25.8 Hz); ^1H NMR ($CDCl_3$) δ 4.83 (br s, 1H), 4.47 (br d, J = 28.9 Hz, 1H), 3.48 (br s, 1H), 2.62-2.40 (m, 1H), 2.32-2.17 (m, 1H), 2.01-1.84 (m, 4H), 1.41 (s, 9H), 1.25 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 179.34, 154.99, 153.16 (d, J = 254.5 Hz), 117.79 (d, J = 13.9 Hz), 79.69, 45.59 (d, J = 30.0 Hz), 45.45, 31.65, 28.28, 28.09 (d, J = 3.8 Hz), 25.74, 18.00. The other diastereomer **14a"** was made in the same manner in 74% yield: Mp 98-103 °C; ^{19}F NMR ($CDCl_3$) δ -124.90 (d, J = 25.8 Hz); ^1H NMR ($CDCl_3$) δ 4.76 (br s, 1H), 4.49 (br d, J = 27.1 Hz, 1H), 3.52 (m, 1H), 2.60-2.47 (m, 1H), 2.41-2.26 (m, 1H), 2.08-1.81 (m, 4H), 1.41 (s, 9H), 1.27 (d, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 179.68, 154.91, 153.20 (d, J = 251.4

Hz), 117.53 (d, J = 15.3 Hz), 79.64, 45.59 (d, J = 30.0 Hz), 45.22, 31.61, 28.35, 28.00 (d, J = 3.9 Hz), 25.76, 18.12. Anal. Calcd for $C_{14}H_{22}FNO_4$: C, 58.52; H, 7.72. Found: C, 58.19; H, 7.77.

(*Z*)-*N*-*t*-Butyloxycarbonyl-1-[(1'-fluoro-2'-amino)propylidene]-2-cyclopentane Hydroxamic Acid (15a). Carboxylic acid **14a'** (80.0 mg, 0.28 mmol) was stirred with 1,1'-carbonyldiimidazole (49.7 mg, 0.31 mmol) in THF (3 mL) at room temperature for 18 hours in a flask fitted with a gas outlet. The reaction was monitored by TLC until no starting material **14a'** was detected. To the solution containing the active carbonyldiimide was then added NH_2OH•HCl (39.1 mg, 0.56 mmol). The resulting cloudy solution was stirred at room temperature for 9 h. The positive 5% $FeCl_3$ test indicated the formation of hydroxamic acid (deep purple color). The complete reaction mixture was diluted with 5 mL of H_2O, then extracted with diethyl ether (4 x 10 mL). The combined organic extracts were washed with 10 mL of H_2O, dried ($MgSO_4$) and concentrated. Purification by chromatography on silica gel (30 to 50% EtOAc in hexanes) gave 16.6 mg of hydroxamic acid **15a'** (20%) as off-white solid: IR (CCl_4) 3314, 3240, 2972, 2935, 1708, 1682, 1634, 1530, 1454, 1368, 1244, 1170, 1060 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -125.03 (d, J = 23.0 Hz); ^1H NMR ($CDCl_3$) δ 9.82 (br s, 1H), 4.71 (br s, 1H), 4.22 (dq, J = 25.9, 6.7 Hz, 1H), 3.58 (d, J = 2.4 Hz, 1H), 2.65-2.51 (m, 1H), 2.34-1.59 (m, 5H), 1.43 (s, 9H), 1.26 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.11, 155.83, 152.65 (d, J = 254.5 Hz), 117.47 (d, J = 14.3 Hz), 80.67, 46.21 (d, J = 26.2 Hz), 44.93, 31.75, 28.27, 27.44 (d, J = 3.0 Hz), 24.48, 16.79. The other diastereomer **15a"** was prepared by the same procedure. Recrystallization from ethyl acetate gave pure **15a"** in 50% yield as white crystals: Mp 177-179 °C; ^{19}F NMR (CD_3OD) δ -122.74 (d, J = 25.8 Hz); ^1H NMR (CD_3OD) δ 4.86 (br s, 1H), 4.38 (dq, J = 27.1, 6.7 Hz, 1H), 3.60 (br s, 1H), 2.64-2.52 (m, 1H), 2.43-2.30 (m, 1H), 2.02-1.77 (m, 3H), 1.70-1.58 (m, 1H), 1.42 (s, 9H), 1.24 (d, J = 7.1 Hz, 3H); ^{13}C NMR (CD_3OD) δ 173.85, 157.36, 154.75 (d, J = 252.2 Hz), 119.31 (d, J = 15.3 Hz), 80.26, 46.92 (d, J = 25.2 Hz), 45.15, 32.84, 29.45 (d, J = 4.0 Hz), 28.76, 27.06, 17.71. Anal. Calcd for $C_{14}H_{23}FN_2O_4$: C, 55.62; H, 7.67. Found: C, 55.42; H, 7.74.

(*Z*)-*N*-*t*-Butyloxycarbonyl-1-[(1'-fluoro-2'-amino)propylidene]-2-cyclopentane Benzoyl Hydroxamate (1a). Hydroxamic acid **15a'** (15.0 mg, 0.050 mmol) was dissolved in dry THF (0.5 mL) and cooled to 0 °C. Pyridine (4.5 μL, 0.056 mmol) was added and the solution was allowed to stirr for 15 min, then a 0.5 mL solution of benzoyl chloride (6.2 μL, 0.053 mmol) in THF was added. A white precipitate formed immediately. The reaction mixture was further stirred for 40 min and was then transferred to a separatory funnel containing 3 mL of ethyl acetate/hexanes (1 : 1). The organic layer was washed with 0.1 *M* HCl (1 mL), H_2O (1 mL), brine (1 mL) and dried over $MgSO_4$. Filtration followed by removal of solvents *in vacuo* yielded the crude product which was purified by chromatography (20 to 30% EtOAc in hexanes) to obtain pure **1a'** (10.2 mg, 51%) as white solid: IR (CCl_4) 3460, 3219 (br,s), 2976, 2870, 1770, 1682, 1506, 1452, 1254, 1166, 1060, 788, 706 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -123.95 (d, J = 24.5 Hz); ^1H NMR ($CDCl_3$) δ 10.16 (br s, 1H), 8.05 (d, J = 7.0 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 9.0 Hz, 2H), 4.72 (br s, 1H), 4.29 (dq, J = 26.6, 6.6 Hz, 1H), 3.69 (br s, 1H), 2.73 (m, 1H), 2.32-2.21 (m, 2H), 2.02-1.77(m, 3H), 1.31 (s, 9H), 1.30 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.34, 164.46, 155.77, 152.89 (d, J = 254.6 Hz), 133.77, 129.97, 128.51, 127.20, 118.11 (d, J = 14.2 Hz), 80.30, 46.25 (d, J = 26.8 Hz), 45.77 (d, J = 2.7 Hz), 32.10, 28.18, 27.72 (d, J = 3.2 Hz), 24.76, 16.95. The other diastereomer **1a"** was made in the same manner in 32% yield: ^{19}F NMR ($CDCl_3$) δ -120.70 (d, J = 23.0 Hz); ^1H NMR ($CDCl_3$) δ 9.53 (br s, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 4.74 (br s, 1H), 4.49 (dq, J = 26.1, 6.7 Hz, 1H), 3.62 (br

s, 1H), 2.63-2.48 (m, 1H), 2.46-2.32 (m, 1H), 2.26-2.13 (m, 1H), 2.00-1.85 (m, 3H), 1.42 (s, 9H), 1.34 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.33, 164.82, 154.89, 154.00 (d, J = 250.7 Hz), 134.12, 129.97, 128.65, 126.73, 117.90 (d, J = 12.6 Hz), 79.85, 45.71 (d, J = 26.6 Hz), 44.16, 30.49, 28.37, 27.76 (d, J = 3.3 Hz), 25.65, 18.10.

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