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Fluorous Substituent-Based Enantiomer and Diastereomer Separation: Orthogonal Use of HPLC Columns for the Synthesis of Nonproteinogenic Polyfluoro Amino Acids and Peptides

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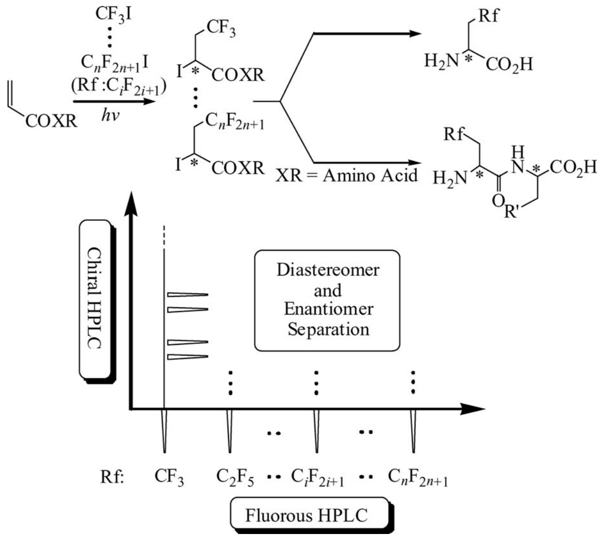
A variety of fluorine-containing amino acid and dipeptide precursors bearing different lengths of perfluoroalkyl chains were separated into their enantiomers and diastereomers, respectively, by the orthogonal use of fluorous and chiral HPLC columns. These results show the applicability of fluorous racemic mixture synthesis for various "fluorinated" chiral products without introducing conventional cleavable fluorous tags.

Introduction

An efficient synthesis and purification process to afford enantiopure compounds from racemic or achiral substrates bearing fluorous tags[1] has quite recently been reported, that is, the fluorous "racemic" mixture synthesis (FRMS).[2] FRMS can simultaneously solve the enantioseparation, demix, and identification problems associated with conventional solution-phase mixture synthesis.[3] In the combinatorial synthesis of a library of analogues,[4] the enantioseparation and identification of target analogues in one simultaneous demixing step are so effective as to diversify the library in enantiopure form. In FRMS, however, cleavable fluorous tags are introduced into the starting substrates in either the racemic or achiral form.

Fluorine-containing amino acids and peptides have received considerable attention because of their important applications as biologically active agents.[5] The photoinduced diastereoselective addition of perfluoroalkyl iodides to acrylcamphorsultam derivatives to give perfluoroalkylated α-iodo acid derivatives was reported, and the α-iodo acid derivatives can then be converted in a stereospecific (S_N2-type) manner[6] into fluorinated α-azido and α-amino acids. In principle, fluorine-containing dipeptides can be synthesized from acrylamide derivatives bearing α-amino acids (Scheme 1). In this synthesis, different lengths of perfluoroalkyl units can be introduced as substituents, but not as fluorous tags that are eventually cleaved. A variety of perfluoroalkyl iodides can be combined in the same pot with the acrylamide to give perfluoroalkylated iododipeptide derivatives; perfluoroalkylated iododipeptides can be separated first with fluorous[7] HPLC columns depending on the fluorine content of the resultant perfluoroalkyl iododipeptides and second with chiral HPLC[8] columns depending on the enantiomeric forms of the newly generated α-iodo stereogenic centers. We report here fluorous substituent-based enantiomer and diastereomer separation, namely, the



Scheme 1. Orthogonal use of HPLC columns for enantiomer and diastereomer separation of fluorinated compounds without fluorous tags.

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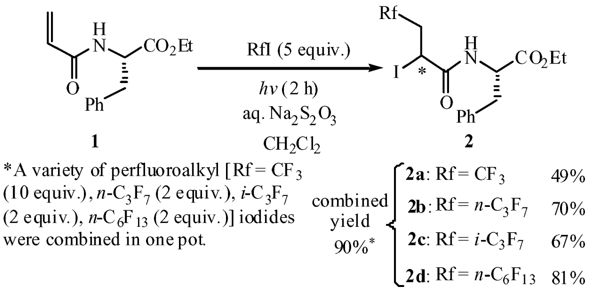
orthogonal use of fluorous and chiral HPLC columns for enantiomer and diastereomer separation, demix, and identification of fluorine-containing target molecules. Fluorous amino acids and peptides can be obtained selectively without the temporary introduction of fluorous tags (Scheme 1).

Results and Discussion

Fluorine-containing dipeptides bearing different lengths of a perfluoroalkyl chain (Rf = CF_3, n-C_3F_7, i-C_3F_7, n-C_6F_{13}) were synthesized from acrylamide derivatives **1** bearing α-amino acids, for example, L-phenylalanine (Scheme 2). Iododipeptides **2a**–**d** having perfluoroalkyl substituents were obtained in reasonable yields (49–81 %) in the presence of an aqueous solution of $Na_2S_2O_3$ to trap the iodine in situ via radical iodoperfluoroalkylation[9] under UV irradiation. Moreover, all four perfluoroalkyl iodides [RfI = CF_3I (10 equiv.), n-C_3F_7I (2 equiv.), i-C_3F_7I (2 equiv.), n-$C_6F_{13}I$ (2 equiv.)] were treated with acrylamide derivatives in the same pot to afford a mixture of perfluoroalkyl iododipeptides (90 % combined yield).



Scheme 2. Synthesis of iododipeptides having perfluoroalkyl substituents.

Fluorine-containing iododipeptides **2a**–**d** and their diastereomers could be demixed and diastereoseparated effectively by the orthogonal use of fluorous and chiral HPLC columns. Firstly, iododipeptides **2a**–**d** were separated into three fractions depending on the fluorine content thereof by a fluorous reverse-phase silica-gel column (FluoroFlash; Figure 1). It was confirmed that each compound could be separated in the order of increasing fluorine content of the perfluoroalkyl iododipeptides by using FluoroFlash.[7] Therefore, iododipeptides (**2b** and **2c**) bearing n-C_3F_7 and i-C_3F_7 chains, with the same fluorine content, could not be separated.

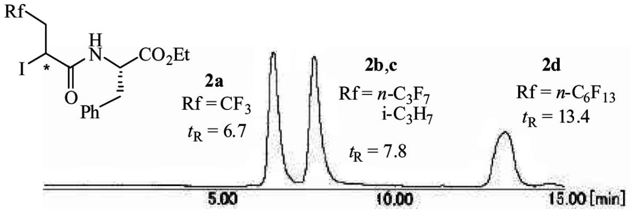


Figure 1. Separation of perfluoroalkyl iododipeptides by using fluorous HPLC (column: FluoroFlash; flow rate: 0.3 mL min^{-1}; column temperature: 20 °C; wavelength: 254 nm; mobile phase: $MeCN/H_2O$, 90:10).

Secondly, the separation of iododipeptides **2a**–**d** (CF_3, n-C_3F_7, i-C_3F_7, n-C_6F_{13}) into their eight diastereomers was investigated by using chiral HPLC column (CHIRALCEL OD-H) in the normal phase. As a result, each diastereomer was perfectly separated. Both iododipeptides (**2b** and **2c**) bearing n-C_3F_7 and i-C_3F_7 chains could be separated into two sets of diastereomers (Figure 2). Furthermore, the identification of these constitutional isomers can be easily executed by ^{19}F NMR spectroscopic analysis. In principle, HPLC–^{19}F NMR spectroscopy is so useful in this purpose.

Orthogonal use of fluorous and chiral HPLC column separation should be so effective in the separation of

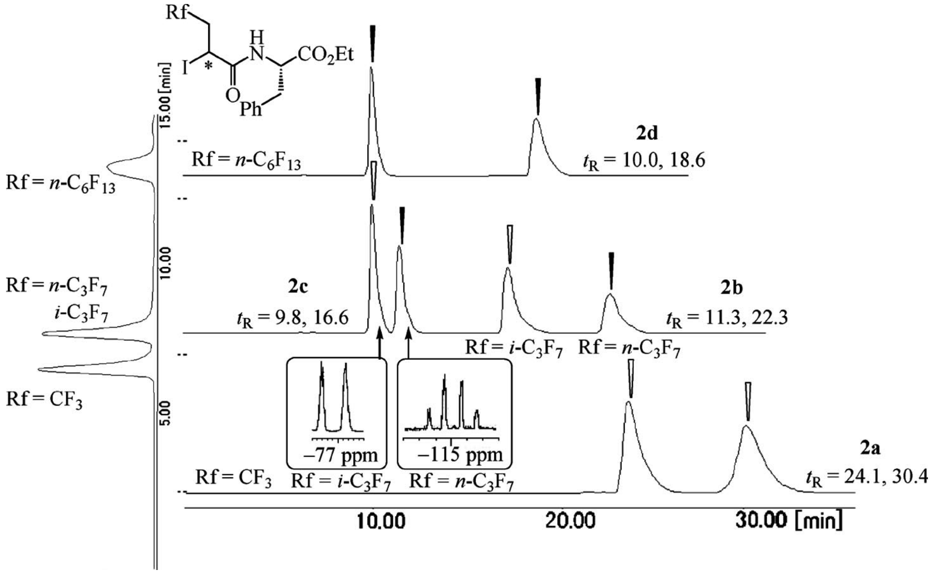
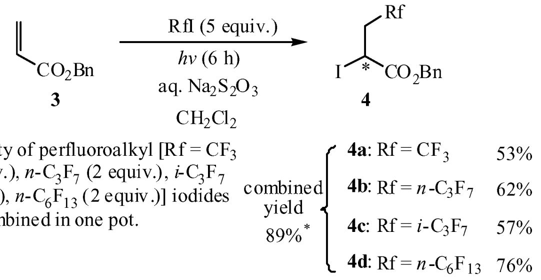


Figure 2. Separation of perfluoroalkyl iododipeptides by using chiral HPLC (column: CHIRALCEL OD-H; flow rate: 0.7 mL min^{-1}; column temperature: 20 °C; wavelength: 254 nm; mobile phase: hexane/2-propanol, 98:2).

enantiomers for fluorine-containing chiral compounds on the basis of their fluorine content and stereoisomeric nature. Fluorine-containing α-iodo acid derivatives bearing different lengths of perfluoroalkyl chains (R_f = CF_3, n-C_3F_7, i-C_3F_7, n-C_6F_{13}) were thus separated through the efficiency in orthogonal use of HPLC columns for enantiomeric separation.

Fluorinated chiral α-iodo acid derivatives **4a**–**d** as precursors for fluorinated α-azido or α-amino acids were synthesized by photoinduced radical addition of perfluoroalkyl iodides to acrylic acid derivatives **3** in the presence of an aqueous solution of $Na_2S_2O_3$ in reasonable yields (53–76%) (Scheme 3). The photoinduced addition reaction of a mixture of four perfluoroalkyl iodides [RfI = CF_3I (10 equiv.), n-C_3F_7I (2 equiv.), i-C_3F_7I (2 equiv.), n-$C_6F_{13}I$ (2 equiv.)] to benzyl acrylate **3** proceeded smoothly in one pot to give a mixture of perfluoroalkyl α-iodo acid esters in high yield (89% combined yield).



Scheme 3. Synthesis of α-iodo acid esters bearing different perfluoroalkyl chains.

α-Iodo acid derivatives **4a**–**d** were separated into their individual fractions by reverse-phase FluoroFlash (Figure 3). Each compound could be separated in the order of increasing fluorine content of the α-iodo acid esters.[7] α-Iodo acid esters (**4b** and **4c**) bearing n-C_3F_7 and i-C_3F_7 chains could not be separated due to the same fluorine content.

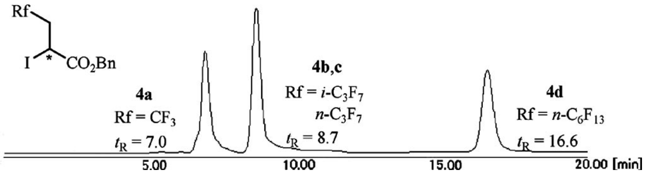


Figure 3. Separation of α-iodo acid esters bearing perfluoroalkyl chains by using fluorous HPLC (column: FluoroFlash; flow rate: 0.3 mL min^{-1}; column temperature: 20 °C; wavelength: 254 nm; mobile phase: $MeCN/H_2O$, 90:10).

The enantioseparation of α-iodo acid esters **4a**–**d** (CF_3, n-C_3F_7, i-C_3F_7, n-C_6F_{13}) was then investigated successively by using chiral normal-phase HPLC (CHIRALPAK AD-H) (Figure 4). Each enantiomer of the four α-iodo acid esters, which corresponded to each fraction after separation by FluoroFlash, was enantioseparated. Even α-iodo acid esters (**4b** and **4c**) bearing n-C_3F_7 and i-C_3F_7 chains, which could not be separated by FluoroFlash as a result of their same fluorine content, could also be enantioseparated into two sets of enantiomers. These constitutional isomers can also be easily determined by ^{19}F NMR spectroscopic analysis on the basis of their structural differences, as is the case with those of iododipeptides **2a**–**d**.

Conclusions

We demonstrated an efficient synthesis and purification method for fluorinated chiral compounds bearing perfluoroalkyl chains, such as fluorine-containing amino acids and dipeptides by the orthogonal use of fluorous and chiral

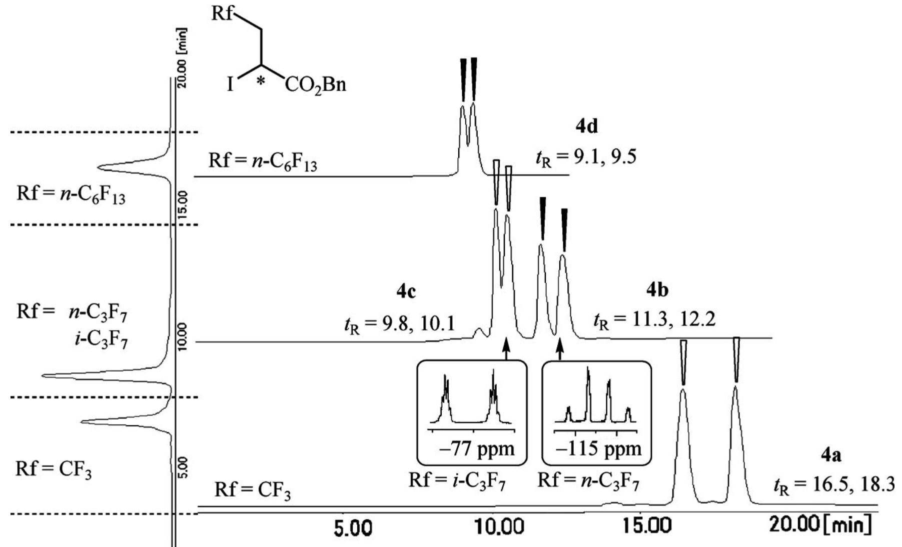


Figure 4. Separation of α-iodo acid esters bearing perfluoroalkyl chains by using chiral HPLC (column: CHIRALPAK AD-H; flow rate: 0.4 mL min^{-1}; column temperature: 20 °C; wavelength: 254 nm; mobile phase: hexane/2-propanol, 99:1).

HPLC columns. α-Iodo acids and iododipeptides as precursors for fluorinated α-azides or α-amino acid derivatives could thus be separated into their enantiomers and diastereomers, respectively. These results show the applicability of FRMS for various "fluorinated" chiral products without introducing cleavable fluorous tags.

Experimental Section

General Methods: All reactions were performed with a high-pressure Hg lamp (Toshiba, 460W). ^{1}H NMR spectra were recorded with a JEOL AL-400 (400 MHz) spectrometer with CDCl$_3$ as the solvent and tetramethylsilane as an internal standard unless otherwise noted. ^{13}C NMR spectra were recorded with the same instrument operating at 100.5 MHz with CDCl$_3$ as the solvent and internal standard (δ = 77.0 ppm). ^{19}F NMR spectra were recorded with a Bruker AV300M (300 MHz) spectrometer with CDCl$_3$ as the solvent and internal standard (δ = –63.24 ppm). IR spectra were recorded with a SHIMADZU FTIR-8700 spectrometer. Mass spectra (EI+) were obtained with a JEOL JMS-700 mass spectrometer. HPLC analysis was performed with a JASCO HPLC system (pump: PU-1580, gradient unit: LG-1580-04, degasser: DG-1580-54, column oven: CO-1560, UV and CD detector: CD-1595, auto sampler: AS-1555). Peak areas were calculated by JASCO-BORWIN as an automatic integrator. Fluorous column (FluoroFlash PF-C8, 15 cm × 4.6 mm i.d; Fluofix 120E, 25 cm × 4.6 mm i.d.) or polysaccharide-based chiral columns (DAICEL CHIRALCEL OD-H, 25 cm × 4.6 mm i.d.; CHIRALPAK AD-H, 25 cm × 4.6 mm i.d.) with a GL cart (0.5 cm × 4.6 mm i.d.) as a guard column and a JASCO HPLC system [pump: PU-1580, gradient unit: LG-1580–04, degasser: DG-1580–54, column oven: CO-1560, UV and CD detector: CD-995 (1595), auto sampler: AS-1555]. Peak areas were calculated by JASCO-BORWIN as an automatic integrator.

Typical Procedure for a Fluorous "Racemic" Mixture Synthesis. Photoinduced Addition of Perfluoroalkyliodides to Acrylamide Derivatives: To a Pyrex glass tube was added the acrylamide derivative of L-phenylalanine (0.5 mmol), four kinds of perfluoroalkyl iodides [CF$_3$I (10 equiv.), *n*-C$_3$F$_7$I (2 equiv.), *i*-C$_3$F$_7$I (2 equiv.), *n*-C$_6$F$_{13}$I (2 equiv.)] and CH$_2$Cl$_2$ (5 mL). Then, Na$_2$S$_2$O$_3$ (1.25 mmol) and water (1 mL) were added. After sealing the tube, the mixture was shaken and then irradiated with a Hg lamp at room temperature. After the reaction was complete, the products were extracted with CH$_2$Cl$_2$. The extract was washed with brine, dried with Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash silica-gel column chromatography to afford pure products in 90% combined yield. Yield was determined by ^{1}H NMR spectroscopy by using (CHCl$_2$)$_2$ as an internal standard. The mixture thus obtained was separated into four compounds and their eight diastereomers by fluorous (FluoroFlash) and chiral (CHIRALCEL OD-H, CHIRALPAK AD-H) HPLC columns.

Ethyl 2-(2-Iodo-3-trifluoromethylpropionylamino)-3-phenylpropionate (2a): IR (KBr): $\tilde{\nu}$ = 3325, 3023, 2993, 1729, 1650, 1533, 1356, 1258, 1101, 1012, 698 cm^{-1}. MS: *m*/*z* (%) = 443 (2) [M]$^+$, 370 (18), 176 (100), 120 (47), 91 (62), 58 (93). HRMS: calcd. for C$_{15}$H$_{17}$F$_3$INO$_3$ 443.0205; found 443.0211. Major diastereoisomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.20 (m, 5 H), 6.21 (br. s, 1 H), 4.84 (td, J = 5.6, 7.6 Hz, 1 H), 4.38 (dd, J = 5.6, 9.2 Hz, 1 H), 4.20 (q, J = 6.8 Hz, 2 H), 3.34 (m, 1 H), 3.19 (dd, J = 5.6, 14.0 Hz, 1 H), 3.12 (dd, J = 5.6, 14.0 Hz, 1 H), 2.73 (m, 1 H), 1.27 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.0, 168.1, 135.3, 129.2, 128.6, 127.2, 125.2 (q, J = 258.4 Hz), 61.9, 53.8, 40.7 (q, J = 28.8 Hz), 37.5, 14.1, 9.2 (d, J = 3.3 Hz) ppm. Minor diastereoisomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.24 (m, 5 H), 6.21 (br. s, 1 H), 4.87 (td, J = 5.2, 7.6 Hz, 1 H), 4.38 (dd, J = 5.2, 9.2 Hz, 1 H), 4.19 (q, J = 6.8 Hz, 2 H), 3.33 (m, 1 H), 3.18 (dd, J = 5.6, 14.0 Hz, 1 H), 3.13 (dd, J = 5.6, 14.0 Hz, 1 H), 2.66 (m, 1 H), 1.26 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.0, 168.0, 135.2, 129.4, 128.5, 127.1, 125.1 (q, J = 277.1 Hz), 61.1, 53.5, 40.9 (q, J = 29.7 Hz), 38.0, 14.2, 9.1 (d, J = 2.5 Hz) ppm.

Ethyl 2-(2-Iodo-3-perfluoropropylpropionylamino)-3-phenylpropionate (2b): IR (KBr): $\tilde{\nu}$ = 3343, 3317, 3004, 2995, 1726, 1651, 1530, 1352, 1219, 1037, 926, 728 cm^{-1}. MS: *m*/*z* (%) = 543 (1) [M]$^+$, 470 (10), 176 (100), 120 (38), 91 (43), 58 (81). HRMS: calcd. for C$_{17}$H$_{17}$F$_7$INO$_3$ 543.0141; found 543.0138. Major diastereoisomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.20 (m, 5 H), 6.20 (br. s, 1 H), 4.85 (td, J = 5.6, 8.0 Hz, 1 H), 4.47 (dd, J = 3.6, 9.6 Hz, 1 H), 4.21 (q, J = 7.6 Hz, 2 H), 3.43 (m, 1 H), 3.16 (dd, J = 5.6, 14.2 Hz, 1 H), 3.11 (dd, J = 5.6, 14.2 Hz, 1 H), 2.66 (m, 1 H), 1.27 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.0, 168.2, 135.3, 129.1, 128.4, 127.2, 61.8, 53.7, 38.0, 37.8 (t, J = 20.6 Hz), 14.1, 7.7 ppm. ^{19}F NMR (282 MHz, CDCl$_3$): δ = –80.4 (t, J = 8.7 Hz, 3 F), –115.0 (q, J = 295.8 Hz, 2 F), –127.8 (m, 2 F) ppm. Minor diastereoisomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.35 (m, 5 H), 6.20 (br. s, 1 H), 4.88 (td, J = 5.6, 8.0 Hz, 1 H), 4.50 (dd, J = 4.0, 9.2 Hz, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 3.41 (m, 1 H), 3.20 (dd, J = 5.6, 14.0 Hz, 1 H), 3.14 (dd, J = 5.6, 14.0 Hz, 1 H), 2.66 (m, 1 H), 1.26 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.0, 168.2, 135.2, 129.5, 128.5, 127.2, 61.9, 53.5, 37.7 (t, J = 20.6 Hz), 37.6, 14.1, 7.9 ppm. ^{19}F NMR (282 MHz, CDCl$_3$): δ = –80.4 (t, J = 8.7 Hz, 3 F), –115.0 (q, J = 295.8 Hz, 2 F), –127.8 (m, 2 F) ppm.

Ethyl 2-(2-Iodo-3-perfluoroisopropylpropionylamino)-3-phenylpropionate (2c): IR (KBr): $\tilde{\nu}$ = 3372, 3270, 3096, 1750, 1657, 1557, 1229, 1053, 988, 699 cm^{-1}. MS: *m*/*z* (%) = 543 (2) [M]$^+$, 470 (21), 176 (100), 120 (63), 102 (45), 91 (72). HRMS: calcd. for C$_{17}$H$_{17}$F$_7$INO$_3$ 543.0141; found 543.0137. Major diastereoisomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.20 (m, 5 H), 6.29 (d, J = 7.6 Hz, 1 H), 4.86 (td, J = 5.6, 7.6 Hz, 1 H), 4.52 (dd, J = 2.8, 9.6 Hz, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 3.57 (m, 1 H), 3.14 (dd, J = 5.6, 14.4 Hz, 1 H), 3.08 (dd, J = 5.6, 14.0 Hz, 1 H), 2.64 (m, 1 H), 1.26 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 170.9, 168.2, 135.3, 129.1, 128.5, 127.2, 61.8, 53.7, 38.0, 35.3 (d, J = 19.0 Hz), 14.2, 9.2 ppm. ^{19}F NMR (282 MHz, CDCl$_3$): δ = –76.4 (m, 3 F), –77.2 (m, 3 F), –187.5 (m, 1 F) ppm. Minor diastereoisomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.24 (m, 5 H), 6.30 (d, J = 7.2 Hz, 1 H), 4.90 (td, J = 5.6, 7.2 Hz, 1 H), 4.54 (dd, J = 2.8, 9.8 Hz, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 3.55 (m, 1 H), 3.17 (dd, J = 5.6, 14.0 Hz, 1 H), 3.09 (dd, J = 5.6, 14.0 Hz, 1 H), 2.63 (m, 1 H), 1.26 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.0, 168.2, 135.2, 129.5, 128.5, 127.1, 61.9, 53.4, 37.6, 35.3 (d, J = 18.9 Hz), 14.1, 9.3 ppm. ^{19}F NMR (282 MHz, CDCl$_3$): δ = –76.7 (m, 3 F), –77.1 (m, 3 F), –187.5 (m, 1 F) ppm.

Ethyl 2-(2-Iodo-3-perfluorohexylpropionylamino)-3-phenylpropionate (2d): IR (KBr): $\tilde{\nu}$ = 3337, 3319, 1730, 1661, 1229, 1201, 1166, 1153, 701 cm^{-1}. MS: *m*/*z* (%) = 693 (1) [M]$^+$, 620 (15), 176 (100), 120 (46), 102 (31), 91 (48). HRMS: calcd. for C$_{20}$H$_{17}$F$_{13}$INO$_3$ 693.0046; found 693.0060. Major diastereoisomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.18 (m, 5 H), 6.35 (d, J = 7.8 Hz, 1 H), 4.86 (td, J = 5.9, 7.8 Hz, 1 H), 4.51 (dd, J = 3.4, 9.8 Hz, 1 H), 4.20 (q, J = 7.3 Hz, 2 H), 3.44 (m, 1 H), 3.14 (dd, J = 5.9, 14.0 Hz, 1 H), 3.10 (dd, J = 5.9, 14.0 Hz, 1 H) 2.67 (m, 1 H), 1.27 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 170.9, 168.1, 135.3, 129.2, 128.5, 127.1, 61.8, 53.8, 38.2 (t, J = 18.8 Hz), 37.9, 14.2, 7.9 ppm. Minor diastereoisomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.25 (m, 5 H), 6.49 (d, J = 7.8 Hz, 1 H), 4.89 (td, J = 5.9, 7.8 Hz, 1 H), 4.58 (dd, J = 3.9, 9.3 Hz, 1 H), 4.19 (q, J = 7.3 Hz, 2 H), 3.42 (m, 1 H), 3.16 (dd, J = 5.9, 14.2 Hz, 1 H), 3.09 (dd, J = 5.9, 14.2 Hz, 1 H), 2.68 (m, 1 H), 1.26 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 171.0, 168.3, 135.2, 129.5, 128.5, 127.2, 61.9, 53.5, 38.0 (t, J = 19.8 Hz), 37.6, 14.1, 8.0 ppm.

Benzyl 2-Iodo-3-trifluoromethylbutanoate (4a): IR (neat): $\tilde{\nu}$ = 3037, 1734, 1457, 1260, 1151, 969, 753, 698 cm^{-1}. MS: m/z (%) = 231 (84) [M – I]$^+$, 107 (66), 91 (100). HRMS: calcd. for $C_{11}H_{10}F_3O_2$ 231.0632; found 231.0654. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.37 (m, 5 H), 5.20 (s, 2 H), 4.54 (dd, J = 4.4, 9.8 Hz, 1 H), 3.26 (m, 1 H), 2.77 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 169.7, 134.6, 128.6, 128.3, 125.2 (q, J = 275.5 Hz), 68.1, 41.1 (q, J = 29.7 Hz), 5.9 (q, J = 3.3 Hz) ppm.

Benzyl 2-Iodo-3-perfluoropropylbutanoate (4b): IR (neat): $\tilde{\nu}$ = 3038, 1739, 1354, 1225, 1186, 1127, 909, 737, 698 cm^{-1}. MS: m/z (%) = 331 (71) [M – I]$^+$, 107 (65), 91 (100). HRMS: calcd. for $C_{13}H_{10}F_7O_2$ 331.0569; found 331.0591. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.37 (m, 5 H), 5.22 (d, J = 12.4 Hz, 1 H), 5.19 (d, J = 12.4 Hz, 1 H), 4.65 (dd, J = 4.0, 10.8 Hz, 1 H), 3.32 (m, 1 H), 2.68 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 169.9, 134.6, 128.7, 128.6, 128.3, 68.2, 38.2 (t, J = 20.6 Hz), 4.9 (t, J = 3.3 Hz) ppm. ^{19}F NMR (282 MHz, CDCl$_3$): δ = –80.4 (t, J = 8.5 Hz, 3 F), –115.1 (q, J = 262.3 Hz, 2 F), –127.8 (m, 2 F) ppm.

Benzyl 2-Iodo-3-perfluoroisopropylbutanoate (4c): IR (neat): $\tilde{\nu}$ = 3038, 1743, 1648, 1225, 1154, 1120, 1054, 697 cm^{-1}. MS: m/z (%) = 331 (67) [M – I]$^+$, 107 (67), 91 (100). HRMS: calcd. for $C_{13}H_{10}F_7O_2$ 331.0569; found 331.0544. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.37 (m, 5 H), 5.20 (d, J = 12.8 Hz, 1 H), 5.18 (d, J = 12.8 Hz, 1 H), 4.66 (dd, J = 3.2, 11.2 Hz), 3.42 (m, 1 H), 2.69 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 169.9, 134.5, 128.6, 128.5, 128.4, 68.2, 35.8 (d, J = 18.9 Hz), 6.6 (d, J = 4.2 Hz) ppm. ^{19}F NMR (282 MHz, CDCl$_3$): δ = –76.6 (m, 3 F), –77.2 (m, 3 F), –186.7 (m, 1 F) ppm.

Benzyl 2-Iodo-3-perfluorohexylpropanoate (4d): IR (neat): $\tilde{\nu}$ = 3009, 1734, 1452, 1391, 1235, 1202, 1144, 698 cm^{-1}. MS: m/z (%) = 481 (65) [M – I]$^+$, 107 (68), 91 (100). HRMS: calcd. for $C_{16}H_{10}F_{13}O_2$ 481.0473; found 481.0451. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.37 (m, 5 H), 5.22 (d, J = 12.4 Hz, 1 H), 5.19 (d, J = 12.4 Hz, 1 H), 4.65 (dd, J = 3.5, 10.6 Hz, 1 H), 3.34 (m, 1 H), 2.72 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 170.2, 134.8, 128.9, 128.8, 128.6, 68.4, 38.7 (t, J = 20.4 Hz), 5.1 (t, J = 2.9 Hz) ppm.

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