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Novel Syntheses of Chiral β- and γ-Amino Acid Derivatives Utilizing N-Protected (Aminoacyl)benzotriazoles from Aspartic and Glutamic Acids

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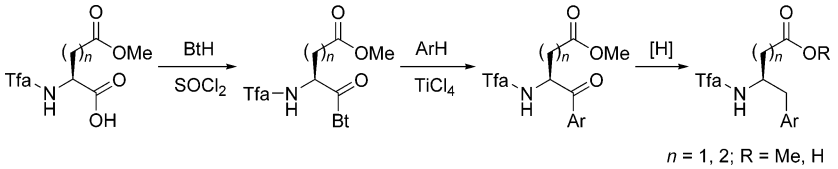

Friedel−Crafts reactions of N-protected (α-aminoacyl)benzotriazoles with hetero- and benzenoid- aromatics give α-amino ketones that can be reduced by either triethyl silane or sodium borohydride to form the corresponding β- and γ-amino acid derivatives. The preservation of chirality throughout this process is confirmed by chiral HPLC results.

Introduction

Non-natural β- and γ-amino acids have attracted considerable attention due to their important roles in the design and synthesis of bioactive molecules and in the study of biomimetic polymers that contain both secondary and tertiary structure analogous to those of natural proteins. Thus, β-amino acid derivatives are key components of a variety of biologically active molecules including the antitumor agent taxol,[1] antifungal jasplakinolide,[2] antibiotics,[3] and the enzyme inhibitor bestatin.[4] β-Amino acids are also of high interest as precursors for peptidomimetics[5,6] and β-lactams.[7,8] Likewise, γ-amino acids represent important roles in the structure of natural products with antitumor activity such as *Hapalosin*,[9−11] *Dolastatin*, and[12,13] *Caliculins*[14,15] and of various enzyme inhibitor γ-aminobutyric acid analogues.[16−19] In addition, they are attractive starting materials for the formation of peptides with helical secondary structures.[20,21]

Given this significance, the development of efficient methods for the synthesis of enantiomerically pure β- and γ-amino acids is important. Among previously reported methodologies for β-amino acids,[22] many use α-amino acids as starting materials because of their ready availability, low cost, and high enantiomeric purity. The extensively studied direct homologation of α-amino acids to β-amino acids following the Arndt−Eistert procedure[23−27] is not suitable for large-scale synthesis because

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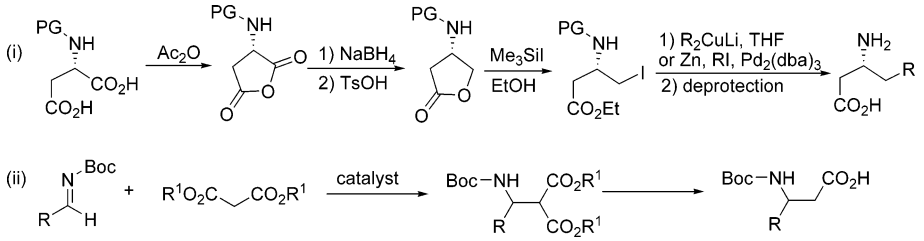
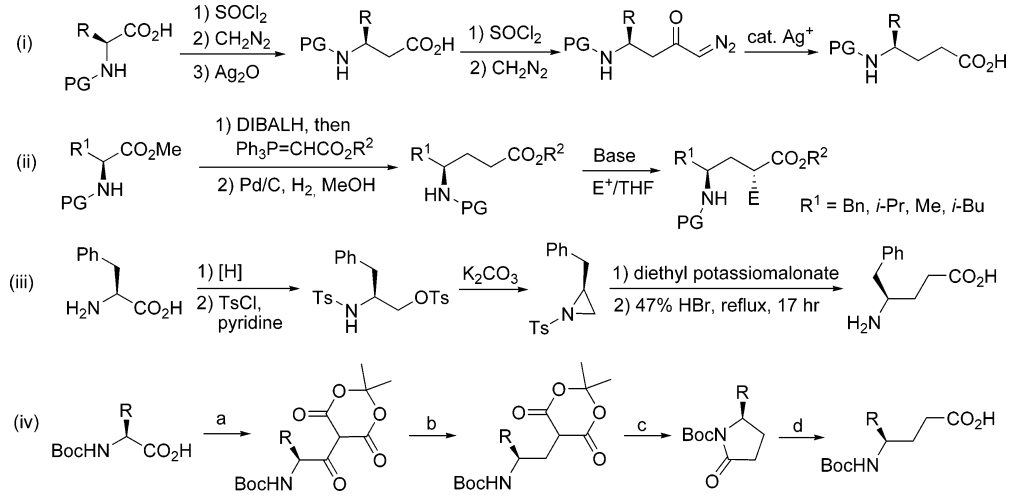
SCHEME 1. Literature Methods of Synthesis of *β*-Amino Acids



SCHEME 2. Literature Methods of Synthesis of *γ*-Amino Acids from α-Amino Acids[a]



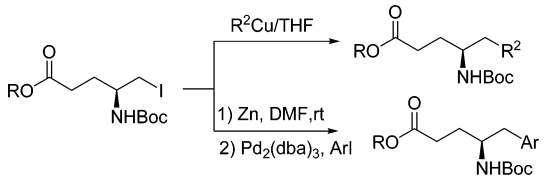
[a] Reagents and conditions: (a) Meldrum's acid, DCC, DMAP; (b) $NaBH_4$, AcOH; (c) toluene, reflux; (d) NaOH, acetone/water.

of the high cost of the silver catalyst and difficulties associated with handling of the hazardous reagent CH_2N_2.[22] Although Longobarbo's modification avoids the use of silver catalyst and CH_2N_2, the procedure requires four steps.[28]

Naturally occurring aspartic acid, possessing a *β*-amino carboxylic acid fragment, is an attractive precursor for the preparation of *β*-amino acids. In the literature, enantioselective synthesis of *β*-amino acids was demonstrated by (i) the stereoselective ring opening of either lactones or oxazolidinones prepared in four steps from L-aspartic acid[29−31] and the nucleophilic substitution of organocuprates[32] or organozinc reagents,[33] and (ii) the Mannich reaction of malonates with *N*-Boc-imines in the presence of catalytic *Cinchona* alkaloid derivatives[34] (Scheme 1).

Four methods (Scheme 2) for the synthesis of *γ*-amino acids from natural α-amino acids comprise (i) double Arndt−Eistert homologation,[35,36] which has disadvantages as discussed above; (ii) Wittig reaction of $Ph_3P{=}CHCO_2Et$ with aldehydes available from natural α-amino acids followed by reduction, which is limited to *γ*-alkyl-*γ*-amino acid derivatives;[37] (iii) reaction of diethyl potassiomalonate with *N*-tosylaziridines generated in situ from *N*,*O*-ditosyl-protected α-amino alcohols derived from α-amino acids,[38] but removal of the N-tosyl group in the presence of sensitive functionalities may require harsh reaction conditions (reflux in 47% aqueous HBr);[38] and (iv) synthesis of *γ*-substituted *γ*-amino acid via *N*-Boc-5-substituted pyrrolidinones, where the decarboxylative ring closure needs high temperature (77−110 °C).[39]

SCHEME 3. *γ*-Amino Acids from Glutamic Acids



Other reported syntheses of optically pure *γ*-amino acids utilizing glutamic acids (Scheme 3) are (i) the nucleophilic substitution of iodo derivatives of glutamic acid with organocuprates[32] and (ii) coupling of an organozinc reagent of glutamic acid with aryl iodides in the presence of Pd.[33] However, the

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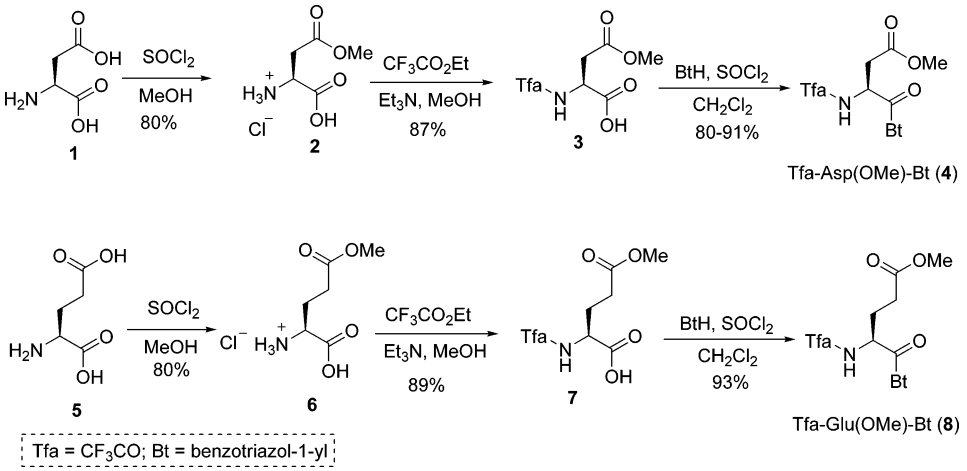
SCHEME 4. Preparation of *N*-(Tfa-α-aminoacyl)benzotriazoles

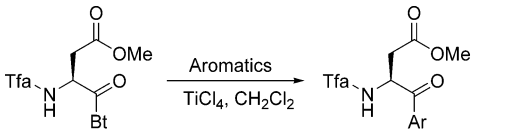


use of organometallic reagents can be limited by incompatibility with other functionality.[32,33,39]

Our group has developed *N*-acylbenzotriazoles as efficient acylating agents for N-,[40−45] C-,[46−51] O-,[49,52,53] and S-acylation reactions.[54] In particular, *N*-acylbenzotriazoles, which are advantageously stable toward moisture and storable for a relatively long period of time, are efficient for the C-acylation of reactive heterocycles such as indoles, pyrroles,[50] furan, and thiophene[51] in the presence of Lewis acid, such as $AlCl_3$. Recently, we have extended our work to the preparation of *N*-Tfa- and Fmoc-α-amino ketones by C-acylation of pyrroles and indoles with chiral N-protected (α-aminoacyl)benzotriazoles[42,44,55] in the presence of $AlCl_3$ with preservation of chirality as demonstrated by configurational analysis.[56]

We now report a novel and practical method for the synthesis of ω-aryl substituted β- (**10**−**12**) and γ-amino acid derivatives (**14**,**15**) by the Friedel−Crafts acylation of aromatics with chiral N-protected 1-(α-aminoacyl)benzotriazoles **4** and **8** (generated from L-aspartic or L-glutamic acid) followed by reduction of the intermediate ketones, with preservation (>99%) of the chirality.

SCHEME 5. Syntheses of γ-Keto-β-amino Esters 9a−f



Results and Discussion

Preparation of 1-(*N*-Tfa-α-aminoacyl)benzotriazoles 4 and 8. L-Aspartic acid (**1**) was reacted with methanol and thionyl chloride to form the γ-mono methyl ester **2** selectively in 80% yield.[57] Ester **2** was protected with a *N*-trifluoroacetyl (Tfa) group using ethyl trifluoroacetate in the presence of Et_3N (2 equiv) in methanol to generate *N*-Tfa-aspartic monoester **3**.[58] On treatment with thionyl chloride (1 equiv) and benzotriazole (3 equiv), ester **3** gave Tfa-Asp(OMe)-Bt (**4**) in 80−91% yield. Similarly, Tfa-Glu(OMe)-Bt (**8**) was simply synthesized in 66% overall yield from L-glutamic acid **5** via intermediates **6** and **7** (Scheme 4).

Syntheses of γ-Keto-β-amino Esters 9. Previously, we reported the synthesis of α-amino ketones via Friedel-Craft acylation of *N*-heterocycles utilizing chiral N-protected (α-aminoacyl)benzotriazoles in the presence of $AlCl_3$.[56] Unfortunately, attempted extension of this method to the preparation of γ-keto-β-amino esters **9** by acylation of aromatics with Tfa-Asp(OMe)-Bt (**4**) failed, resulting in decomposition of the latter. Screening Lewis Acids led us to $TiCl_4$ (starting materials were recovered when BF_3 or $ZnBr_2$ was used). The reaction of Tfa-Asp(OMe)-Bt (**4**) with aromatics (1.1 equiv) in the presence of $TiCl_4$ (1.5 equiv) at 20 °C for 1−3 h gave the expected amino γ-keto-β-amino esters **9a**−**f** in 35−89% yield (Scheme 5, Table 1).

γ-Aryl-β-amino Esters 10b,e,f, and 12 and γ-Aryl-β-amino Acid 11 from the Reduction of γ-Keto-β-amino Esters 9. Reaction of alkanophenone derivatives **9e,f** with triethyl silane (2.5 equiv) in the presence of trifluoroacetic acid (12.0 equiv) gave the corresponding γ-aryl-β-amino esters **10e,f** in 79% and 78% yield, respectively (Scheme 6).[59]

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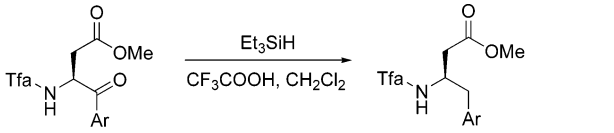
TABLE 1. Syntheses of γ-Keto-β-amino Esters 9a−f

entry	aromatics	γ-keto-β-amino esters **9** (%)
a	indole	67−82
b	*N*-methylindole	74−89
c	*N*-methylpyrrole	65
d	pyrrole	54
e	1,3-$(MeO)_2C_6H_4$	35
f	1,3,5-$(MeO)_3C_6H_3$	50

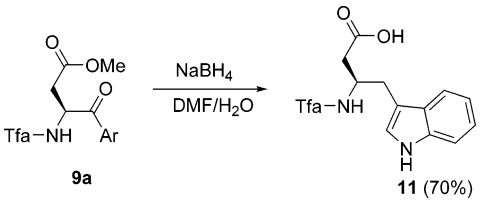
SCHEME 6. γ-Aryl-β-amino Esters 10e,f from the Reduction of γ-Keto-β-amino Esters 9e,f



9e Ar = 2,4-$(MeO)_2C_6H_3$
9f Ar = 2,4,6-$(MeO)_3C_6H_2$

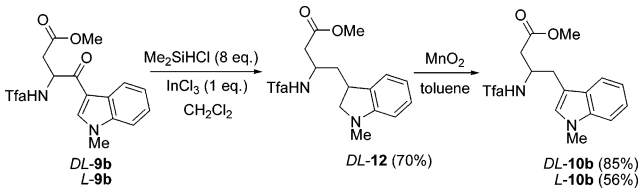
10e Ar = 2,4-$(MeO)_2C_6H_3$ (79%)
10f Ar = 2,4,6-$(MeO)_3C_6H_2$ (78%)

SCHEME 7



9a **11** (70%)

SCHEME 8



DL-**9b** *L*-**9b** *DL*-**12** (70%) *DL*-**10b** (85%) *L*-**10b** (56%)

However, attempted reduction of γ-keto-β-amino esters **9a−d** with triethyl silane in the presence of trifluoroacetic acid resulted in no reaction and recovery of the starting ketones. When γ-keto-β-amino ester **9a** was treated with 4 molar equiv of sodium borohydride in 75% aqueous DMF solution, the corresponding γ-(indol-3-yl)-β-amino acid **11** was isolated in 70% yield (Scheme 7).[60] Unlike **9a**, attempted reduction of *N*-methylindol-3-yl derivative **9b** resulted in complex set of products.

The attempted reduction of DL-**9b** with dimethylchlorosilane in the presence of catalytic indium chloride (0.2 equiv) in dichloromethane under reflux gave a low level of initial conversion of DL-**9b** to the target DL-**10b** (progress of the reaction was monitored by TLC using ethyl acetate/hexanes, 1:3) followed by disappearance of DL-**10b** and formation of a new spot (non-rising) on TLC after reflux for a prolonged time (Scheme 8). Addition of indium chloride (0.8 equiv) followed by reflux for 36 h allowed complete reduction of DL-**9b** to give the 1-methylindoline derivative DL-**12** (70%, as a mixture diastereoisomers). This suggests deactivation of indium chloride due to formation of a complex (non-rising spot on TLC) with the indoline nitrogen of DL-**12**. Compound DL-**12** was reoxidized to γ-(*N*-methylindol-3-yl)-β-amino ester DL-**10b** in 85% yield with active manganese dioxide (5 equiv) in toluene at 20 °C.

Similar reduction/oxidation of L-**9b**, without isolation of intermediate **12**, gave L-**10b** in 56% yield (Scheme 8).

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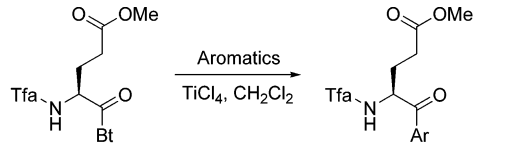
SCHEME 9. Syntheses of δ-Keto-γ-amino Esters 13

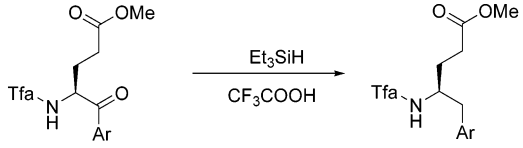


Tfa-Glu(OMe)-Bt (**8**) **13a-f** (46-70%)

TABLE 2. Syntheses of δ-Keto-γ-amino Esters 13

entry	aromatics	δ-keto-γ-amino esters **13** (%)
a	Indole	70
b	*N*-methylindole	59
c	*N*-methylpyrrole	56
d	pyrrole	61
e	1,3-$(MeO)_2C_6H_4$	46
f	1,3,5-$(MeO)_3C_6H_3$	46

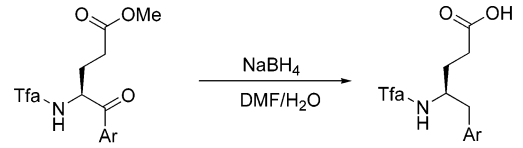
SCHEME 10. δ-Aryl-γ-amino Esters 14 from the Reduction of δ-Keto-γ-amino Esters 13



13e Ar = 2,4-$(MeO)_2C_6H_3$
13f Ar = 2,4,6-$(MeO)_3C_6H_2$

14e Ar = 2,4-$(MeO)_2C_6H_3$ (84%)
14f Ar = 2,4,6-$(MeO)_3C_6H_2$ (88%)

SCHEME 11. δ-Aryl-γ-amino Acids 15 from the Reduction of δ-Keto-γ-amino Esters 13



13a Ar = Indol-3-yl
13b Ar = 1-Me-indol-3-yl

15a Ar = Indol-3-yl (87%)
15b Ar = 1-Me-indol-3-yl (73%)

Syntheses of δ-Keto-γ-amino Esters 13. Following the method developed for the preparation of γ-keto-β-amino esters **9**, the reaction of Tfa-Glu(OMe)-Bt (**8**) with aromatics (1.1 equiv) in the presence of $TiCl_4$ (1.5 equiv) at 20 °C for 1 h produced the corresponding δ-keto-γ-amino esters **13** in 46−70% yield (Scheme 9, Table 2).

δ-Aryl-γ-amino Esters 14 and δ-Aryl-γ-amino Acids 15 from the Reduction of δ-Keto-γ-amino Esters 13. The reduction of δ-keto-γ-amino esters **13e,f** by triethylsilane in the presence of trifluoroacetic acid gave the corresponding δ-aryl-γ-amino esters **14e,f** in 84% and 88% yield, respectively (Scheme 10).[59] The reduction of δ-keto-γ-amino esters **13a,b** by sodium borohydride in 75% aqueous DMF solution provided the corresponding δ-aryl-γ-amino acids **15a,b** in 87% and 73% yield, respectively (Scheme 11).[60]

Configurational Study of γ-Aryl-β-amino Acid 11 and δ-Aryl-γ-amino Acid 15. Since the key feature of biologically active amino acid derivatives is associated with the absolute configuration of the carbon α to the amino group, total control of chirality represents a major goal in the synthesis of amino acid derivatives. To evaluate the chiral integrity of these reactions, we synthesized DL-4-(1-methyl-1*H*-indole-3-yl)-3-(2,2,2-trifluoroacetamido)butanoic acid DL-**11** and DL-5-(1-methyl-1*H*-indole-3-yl)-4-(2,2,2-trifluoroacetamido)pentanoic acid DL-**15b** starting from DL-aspartic or DL-glutamic acid, respec-

tively. The chirality control in the synthesis of γ-aryl-β-amino acid **11** was confirmed by comparison of chiral HPLC chromatograms of L-**11** with DL-**11** (CHIROBIOTIC T column; eluted with 0.1% TEAA solution in 30% aqueous methanol; flow rate 0.5 mL/min at room temperature; UV detection at 210 nm), which showed two signals of equal intensity for DL-**11** at 14.2 and 16.9 min and the single peak at 16.9 min for L-**11**. Similarly, comparison of the chiral HPLC of DL-**15b** (two distinct peaks of equal intensity at 13.2 and 13.7 min) with L-**15b** (one peak at 13.7 min) obtained under the same conditions (CHIROBIOTIC T column; eluted with 0.1% TEAA solution in 60% aqueous methanol (v/v); flow rate 0.4 mL/min at room temperature; UV detection at 210 nm) demonstrated full chiral preservation (>99%) in the synthesis of δ-aryl-γ-amino acids **15**.

Conclusion

Novel β- and γ-amino acid derivatives can be readily synthesized from aspartic and glutamic acid through their corresponding benzotriazole intermediates. Full preservation of chirality in these sequences was supported by chiral HPLC results.

Experimental Section

Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were obtained in $CDCl_3$ (unless otherwise stated) with TMS as the internal standard for ^1H (300 MHz) or the solvent as the internal standard for ^{13}C (75 MHz). Amino acids were used as supplied without additional purification. THF was used freshly distilled from sodium/benzophenone. All of the reactions were carried out under nitrogen. Column chromatography was performed on silica gel 200−425 mesh.

General Procedure for the Preparation of *N*-Tfa-(Aminoacyl)benzotriazoles 4 and 8. To a solution of benzotriazole (0.95 g, 6 mmol) in dichloromethane was added $SOCl_2$ (0.24 g, 2 mmol), and the reaction mixture was heated under reflux for 30 min. The reaction mixture was cooled to 0 °C, and the appropriate acid **3** or **7** (2 mmol) in dichloromethane (10 mL) was added dropwise. The reaction mixture was stirred at 20−25 °C for 2 h and filtered. The filtrate was washed with saturated aqueous Na_2CO_3 (until benzotriazole was completely removed) and dried over magnesium sulfate. The solvent was removed under vacuum to give the product **4** or **8**, suitable for further Friedel−Crafts acylation.

Methyl (3*S*)-4-(Benzotriazol-1-yl)-4-oxo-3-(2,2,2-trifluoroacetamido)butanoate (4). Colorless needles from diethyl ether (80−91%); mp 68−70 °C; ^1H NMR δ 8.27 (d, J = 8.2 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 7.88 (br s, 1H), 7.73 (apparent t, 1H), 7.58 (apparent t, 1H), 6.08−6.14 (m, 1H), 3.69 (s, 3H), 3.53 (dd, J = 17.3, 5.1 Hz, 1H), 3.30 (dd, J = 17.3, 4.9 Hz, 1H); ^{13}C NMR δ 170.3, 167.4, 157.0 (q, J = 38 Hz), 146.0, 131.3, 131.1, 127.0, 120.6, 115.5 (q, J = 288 Hz), 114.3, 52.5, 50.4, 36.3. Anal. Calcd for $C_{13}H_{11}F_3N_4O_4$: C, 45.36; H, 3.22; N, 16.28. Found: C, 45.48; H, 3.23; N, 15.91.

Methyl (4*S*)-5-(Benzotriazol-1-yl)-5-oxo-4-(2,2,2-trifluoroacetamido)pentanoate (8). Colorless needles from chloroform/hexanes (93%); mp 50−52 °C; $[\alpha]^{23}_D$ = −49.04° (*c* 6.67, chloroform); ^1H NMR δ 8.17 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 3.2 Hz, 1H), 7.99 (t, J = 8.0 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.29 (s, 1H), 5.98−6.04 (m, 1H), 3.71 (s, 3H), 2.44−2.55 (m, 2H), 2.0−2.37 (m, 2H); ^{13}C NMR δ 174.0, 168.8, 157.4 (q, J = 39.0 Hz), 146.0, 131.2, 130.9, 126.9, 120.5, 115.6 (q, J = 287.4 Hz), 114.2, 53.4, 52.4, 30.1, 26.4. Anal. Calcd for $C_{14}H_{13}F_3N_4O_4$: C, 46.93; H, 3.66; N, 15.64. Found: C, 46.95; H, 3.64; N, 14.91.

General Procedure for the Preparation of β-Keto-β-amino Esters 9a−f. To a solution of Tfa-Asp(OMe)-Bt (**4**) (0.34 g, 1 mmol) and aromatics (1.1 mmol) in anhydrous dichloromethane (10 mL) was added anhydrous 1 M $TiCl_4$ in dichloromethane (1.5 mL) at 0 °C. The mixture was stirred at room temperature for 1−3 h, and saturated aqueous sodium bicarbonate and charcoal were added. The mixture was stirred for 10−15 min and filtered. The product was extracted with dichloromethane, and the extract was washed successively with aqueous sodium bicarbonate and water, dried over magnesium sulfate, and after concentration under reduced pressure, purified by column chromatography on silica gel to give **9a−f**.

(*S*)-Methyl 4-(Indol-3-yl)-4-oxo-3-(2,2,2-trifluoroacetamido)-butanoate (9a). Gradient column chromatography using dichloromethane−dichloromethane/methanol (50:1); beige microcrystals from chloroform (67−82%, three experiments), mp 148−150 °C; $[\alpha]^{23}_D$ = −83.6° (*c* 2.44, chloroform); ^1H NMR δ 9.47 (br s, 1H), 8.32−8.28 (m, 1H), 8.11 (d, J = 3.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.43−7.39 (m, 1H), 7.31−7.27 (m, 2H), 5.68−5.62 (m, 1H), 3.70 (s, 3H), 2.99 (dd, J = 16.0, 5.2 Hz, 1H), 2.86 (dd, J = 16.0, 6.0 Hz, 1H); ^{13}C NMR δ 188.9, 171.3, 157.0 (q, J = 38.4 Hz), 136.5, 133.4, 125.6, 124.4, 123.4, 122.0, 115.7 (q, J = 288.0 Hz), 114.0, 111.9, 52.4, 51.5, 37.2. Anal. Calcd for $C_{15}H_{13}F_3N_2O_4$: C, 52.64; H, 3.83; N, 8.18. Found: C, 52.98; H, 3.86; N, 8.01.

Methyl 4-(1*H*-indol-3-yl)-4-oxo-3-(2,2,2-trifluoroacetamido)-butanoate (DL-9a). Beige microcrystals from diethyl ether (78%), mp 142−144 °C; ^1H NMR (acetone-d_6) δ 10.74 (br s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.34−8.29 (m, 1H), 8.22 (d, J = 3.3 Hz, 1H), 7.50−7.44 (m, 1H), 7.31−7.25 (m, 2H), 5.74−5.67 (m, 1H), 3.68 (s, 3H), 3.07 (dd, J = 16.1, 6.0 Hz, 1H), 2.86 (dd, J = 16.1, 6.3 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 188.8, 170.7, 156.4 (q, J = 37.8 Hz), 136.7, 133.5, 125.7, 123.7, 122.6, 121.8, 115.6 (q, J = 287.4 Hz), 113.8, 111.9, 51.8, 51.1, 36.4. Anal. Calcd for $C_{15}H_{13}F_3N_2O_4$: C, 52.64; H, 3.83; N, 8.18. Found: C, 52.99; H, 3.79; N, 8.22.

Methyl 4-(1-Methyl-1*H*-indol-3-yl)-4-oxo-3-(2,2,2-trifluoroacetamido)butanoate (9b). Column chromatography using dichloromethane/ethyl acetate 20:1; white needles from diethyl ether (74−89%, three experiments), mp 153−154 °C; $[\alpha]^{23}_D$ = −79.4° (*c* 2.4, chloroform); ^1H NMR δ 8.33−8.29 (m, 1H), 8.05 (s, 1H), 8.02 (d, J = 8.9 Hz, 1H), 7.37−7.30 (m, 3H), 5.63 (dt, J = 8.3, 5.8 Hz, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 2.99 (dd, J = 16.0, 5.6 Hz, 1H), 2.83 (dd, J = 16.0, 5.9 Hz, 1H); ^{13}C NMR δ 188.4, 171.0, 156.7 (q, J = 37.8 Hz), 137.7, 137.1, 126.4, 124.0, 123.4, 122.3, 115.7 (q, J = 288.0 Hz), 112.7, 110.0, 52.2, 51.3, 37.1, 33.8. Anal. Calcd for $C_{16}H_{15}F_3N_2O_4$: C, 53.94; H, 4.24; N, 7.86. Found: C, 53.88; H, 4.13; N, 7.79.

Methyl 4-(1-Methylindol-3-yl)-4-oxo-3-(2,2,2-trifluoroacetamido)butanoate (DL-9b). Needles from diethyl ether (70%), mp 133−134 °C; ^1H NMR δ 8.33−8.29 (m, 1H), 8.04 (s, 1H), 8.01 (br s, 1H), 7.37−7.30 (m, 3H), 5.63 (dt, J = 8.2, 5.8 Hz, 1H), 3.85 (s, 3H), 3.69 (s, 3H), 2.98 (dd, J = 16.0, 5.6 Hz, 1H), 2.83 (dd, J = 16.0, 6.0 Hz, 1H); ^{13}C NMR δ 188.4, 171.0, 156.7 (q, J = 37.8 Hz), 137.7, 137.1, 126.4, 124.0, 123.3, 122.3, 115.7 (q, J = 287.4 Hz), 112.7, 110.0, 52.2, 51.3, 37.1, 33.8. Anal. Calcd for $C_{16}H_{15}F_3N_2O_4$: C, 53.94; H, 4.24; N, 7.86. Found: C, 53.61; H, 4.26; N, 7.52.

Methyl (3*S*)-4-(1-Methyl-pyrrol-3-yl)-4-oxo-3-(2,2,2-trifluoroacetamido)butanoate (9c). Column chromatography using ethyl acetate/hexanes 1:3, colorless needles from chloroform/hexanes (65%), mp 70−71 °C; $[\alpha]^{23}_D$ = −68.7° (*c* 2.53, chloroform); ^1H NMR δ 7.73 (d, J = 6.3 Hz, 1H), 7.15 (dd, J = 4.2, 1.5 Hz, 1H), 6.95 (s, 1H), 6.21 (dd, J = 4.2, 2.4 Hz, 1H), 5.57−5.51 (m, 1H), 3.94 (s, 3H), 3.70 (s, 3H), 2.98 (dd, J = 15.9, 5.1 Hz, 1H), 2.82 (dd, J = 15.9, 6.0 Hz, 1H); ^{13}C NMR δ 183.8, 170.4, 156.5 (q, J = 38.1 Hz), 133.3, 127.2, 121.0, 115.7 (q, J = 286.3 Hz), 109.3, 52.2 (d, J = 2.9 Hz), 51.2, 37.7 (d, J = 8.6 Hz). Anal. Calcd for $C_{12}H_{13}F_3N_2O_4$: C, 47.07; H, 4.28; N, 9.15. Found: C, 46.91; H, 4.21; N, 9.24.

(*S*)-Methyl 3-(2,2,2-Trifluoroacetamido)-4-oxo-4-(1*H*-pyrrol-3-yl)butanoate (9d). Column chromatography using ethyl acetate/

hexanes 1:3, colorless needles (54%), mp 135−136 °C, $[\alpha]^{23}_D$ = −31.9° (*c* 0.8, chloroform); ^{1}H NMR δ 9.74 (br s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.16−7.13 (m, 2H), 6.38−6.35 (m., 1H), 5.58−5.51 (m, 1H), 3.69 (s, 3H), 2.99 (dd, *J* = 16.2, 5.4 Hz, 1H), 2.88 (dd, *J* = 16.2, 5.4 Hz, 1H); ^{13}C NMR δ 183.6, 170.6, 156.7 (q, *J* = 37.5 Hz), 128.4, 127.0, 118.5, 115.6 (q, *J* = 285.8 Hz), 111.9, 52.3 (q, *J* = 2.85 Hz), 50.7, 37.0. Anal. Calcd for $C_{11}H_{11}F_3N_2O_4$: C, 45.21; H, 3.79; N, 9.59. Found: C, 45.44; H, 3.76; N, 9.24.

Methyl (3*S*)-4-(2,4-Dimethoxyphenyl)-4-oxo-3-(2,2,2-trifluoroacetamido)butanoate (9e). Column chromatography using dichloromethane, colorless needles from chloroform/hexanes (35%), mp 109−110 °C, $[\alpha]^{23}_D$ = −2.6° (*c* 0.8, chloroform); ^{1}H NMR δ 7.84 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 6.60 (d, *J* = 2.1 Hz, 1H), 6.57 (d, *J* = 2.1 Hz, 1H), 6.47 (d, *J* = 2.1 Hz, 1H), 5.72−5.66 (m, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.64 (s, 3H), 3.05 (dd, *J* = 16.2, 4.5 Hz, 1H), 2.80 (dd, *J* = 16.2, 5.7 Hz, 1H); ^{13}C NMR δ 193,8, 170.5, 165.7, 160.4, 156.6 (q, *J* = 37.0 Hz), 134.0, 116.8, 115.7 (q, *J* = 286.3 Hz), 106.3, 98.0, 55.6 (2C), 52.0 (2C), 35.9. Anal. Calcd for $C_{15}H_{16}F_3NO_6$: C, 49.59; H, 4.44; N, 3.86. Found: C, 49.20; H, 4.39; N, 3.77.

(S)-Methyl 4-Oxo-3-(2,2,2-trifluoroacetamido)-4-(2,4,6-trimethoxyphenyl)butanoate (9f). Microcrystals from diethyl ether (45−50%), mp 90−92 °C, $[\alpha]^{23}_D$ = −13.4° (*c* 2.56, chloroform); ^{1}H NMR δ 7.75 (d, *J* = 8.0 Hz, 1H), 6.11 (s, 2H), 5.44−5.37 (m, 1H), 3.83 (s, 3H), 3.79 (s, 6H), 3.63 (s, 3H), 2.95−2.81 (m, 2H); ^{13}C NMR δ 196.7, 170.5, 163.6, 159.2, 156.4 (q, *J* = 37.8 Hz), 115.6 (q, *J* = 288.0 Hz), 107.9, 90.4, 55.7, 55.3, 51.8, 34.7. Anal. Calcd for $C_{16}H_{18}F_3NO_7$: C, 48.86; H, 4.61; N, 3.56. Found: C, 48.61; H, 4.74; N, 3.49.

Procedure for the Preparation of γ-Aryl-β-amino Esters 10e,f. To a solution γ-keto-β-amino esters **9e,f** (1 mmol) in dichloromethane (10 mL) at 20 °C was added trifluoroacetic acid (0.45 mL, 6 mmol) followed by triethylsilane (0.8 mL, 5 mmol). After 4 h of stirring at room temperature, water was added, and the product was extracted with ethyl acetate. The extract was dried over magnesium sulfate and concentrated under vacuum. The residue was purified by column chromatography on silica gel using gradient ethyl acetate/hexanes (1:6 → 1:3) to give **10e,f**.

(*R*)-Methyl 3-(2,2,2-trifluoroacetamido)-4-(2,4-dimethoxyphenyl)butanoate (10e). Colorless needles from chloroform/hexanes (79%), mp 87−88 °C, $[\alpha]^{23}_D$ = 5.7° (*c* 0.88, chloroform); ^{1}H NMR δ 7.61 (d, *J* = 6.9 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.47−6.43 (m, 2H), 4.44−4.35 (m, 1H), 3.82 (s. 3H), 3.80 (s, 3H), 3.71 (s, 3H), 2.98−2.85 (m, 2H), 2.65 (dd, *J* = 16.2, 4.5 Hz, 1H), 2.52 (dd, *J* = 16.5, 6.6 Hz, 1H); ^{13}C NMR δ 171.7, 160.2, 158.0, 156.9 (q, *J* = 36.5 Hz), 131.8, 117.0, 115.8 (q, *J* = 286.3 Hz), 104.6, 98.6, 55.3, 55.2, 51.8, 48.4, 36.5, 32.9. Anal. Calcd for $C_{15}H_{18}F_3NO_5$: C, 51.58; H, 5.19; N, 4.01. Found: C, 51.38; H, 5.18; N, 3.92.

(*R*)-Methyl 3-(2,2,2-Trifluoroacetamido)-4-(2,4,6-trimethoxyphenyl)butanoate (10f). Beige microcrystals from diethyl ether (78%), mp 116−118 °C, $[\alpha]^{23}_D$ = 7.2° (*c* 2.5, chloroform); ^{1}H NMR δ 7.60 (d, *J* = 6.6 Hz, 1H), 6.14 (s, 2H), 4.40−4.31 (m, 1H), 3.81 (s, 3H), 3.80 (s, 6H), 3.71 (s, 3H), 2.98 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.90 (dd, *J* = 13.8, 4.9 Hz, 1H), 2.64 (dd, *J* = 16.2, 4.8 Hz, 1H), 2.54 (dd, *J* = 16.2, 6.7 Hz, 1H); ^{13}C NMR δ 171.5, 160.4, 158.8, 156.6 (q, *J* = 36.0 Hz), 115.8 (q, *J* = 288.6 Hz), 105.1, 90.4, 55.4, 55.3, 51.6, 48.1, 36.8, 25.7. Anal. Calcd for $C_{16}H_{20}F_3NO_6$: C, 50.66; H, 5.31; N, 3.69. Found: C, 50.77; H, 5.33; N, 3.64.

Reduction of γ-Indol-3-yl-β-amino Ester 9a with Sodium Borohydride. To a stirred solution of **9a** (330 mg, 1 mmol) in 75% aqueous DMF (13 mL) was added sodium borohydride (150 mg, 4 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 20 °C, cooled to 0 °C, diluted with water, and acidified with 1 N hydrochloric acid to pH 5. The product was extracted with ethyl acetate, and the extract was washed with water, dried over magnesium sulfate, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexanes (1:1) to give (*R*)-4-(1*H*-indol-3-yl)-3-(2,2,2-trifluoroacetamido)butanoic acid L-**11** (220 mg, 70%), beige microcrystals from dichloromethane, mp 189−191 °C, $[\alpha]^{23}_D$ = 8.8° (*c* 2.2, acetone); ^{1}H NMR (acetone-d_6) δ 10.09 (br s, 1H), 8.49 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.22 (s, 1H), 7.13−7.02 (m, 2H), 4.71−4.59 (m, 1H), 3.20−3.06 (m, 2H), 2.72 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 172.9, 157.2 (q, *J* = 36.6 Hz), 137.7, 128.7, 124.5, 122.3, 119.7, 119.4, 117.1 (q, *J* = 288.0 Hz), 112.3, 111.5, 49.3, 38.0, 30.3. Anal. Calcd for $C_{14}H_{13}F_3N_2O_3$: C, 53.51; H, 4.17; N, 8.91. Found: C, 53.36; H, 4.25; N, 8.87.

4-(1*H*-Indol-3-yl)-3-(2,2,2-trifluoroacetamido)butanoic Acid (DL-11). White microcrystals from dichloromethane (86%), mp 176−178 °C; ^{1}H NMR (acetone-d_6) δ 10.09 (br s, 1H), 8.47 (d, *J* = 6.9 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.23 (s, 1H), 7.14−7.02 (m, 2H), 4.70−4.60 (m, 1H), 3.20−3.07 (m, 2H), 2.73 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 172.9, 157.2 (q, *J* = 36.6 Hz), 137.7, 128.7, 124.5, 122.4, 119.7, 119.4, 117.1 (q, *J* = 288.0 Hz), 112.3, 111.6, 49.3, 38.0, 30.3. Anal. Calcd for $C_{14}H_{13}F_3N_2O_3$: C, 53.51; H, 4.17; N, 8.91. Found: C, 53.57; H, 4.33; N, 8.81.

Reduction of DL-9b to DL-12 with Chlorodimethylsilane in the Presence of Indium Chloride. A mixture of methyl 4-(1-methyl-indol-3-yl)-4-oxo-3-(2,2,2-trifluoroacetamido)butanoate DL-**9b** (0.36 g, 1 mmol), indium chloride (220 mg, 1 mmol), and chlorodimethylsilane (added in three portions every 12 h; total 0.9 mL, 0.77 g, 8 mmol) in dichloromethane (40 mL) was gently heated under reflux under nitrogen for 36 h. After cooling, saturated aqueous sodium bicarbonate and charcoal was added; the mixture was stirred for 30 min and filtered. The organic layer was separated, dried over magnesium sulfate, and concentrated under vacuum to dryness. The residue was purified by column chromatography on silica gel using gradient ethyl acetate/hexanes eluent (1:4 → 1:3) to give two diastereoisomers of methyl 4-(1-methylindolin-3-yl)-3-(2,2,2-trifluoroacetamido)butanoate DL-**12** (total yield 65%). *First isomer*: oil (45%); ^{1}H NMR δ 7.44 (d, *J* = 8.9 Hz, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.48 (d, *J* = 7.7 Hz, 1H), 4.48−4.36 (m, 1H), 3.71 (s, 3H), 3.50 (t, *J* = 8.4 Hz, 1H), 3.23−3.13 (m, 1H), 3.02 (dd, *J* = 8.7, 7.1 Hz, 1H), 2.73 (s, 3H), 2.72−2.56 (m, 2H), 2.15 (ddd, *J* = 14.1, 10.7, 3.7 Hz, 1H), 1.75 (ddd, *J* = 14.1, 10.5, 3.7 Hz, 1H); ^{13}C NMR δ 171.8, 157.0 (q, *J* = 36.9 Hz), 152.9, 132.3, 128.0, 123.0, 117.8, 115.8 (q, *J* = 288.0 Hz), 107.4, 61.3, 52.0, 44.9, 38.1, 37.7, 37.5, 35.8. Anal. Calcd for $C_{16}H_{19}F_3N_2O_3$: C, 55.81; H, 5.56; N, 8.14. Found: C, 55.79; H, 6.14; N, 7.58. *Second isomer*: oil (20%); ^{1}H NMR δ 7.42 (d, *J* = 8.8 Hz, 1H), 7.18−7.10 (m, 2H), 6.71 (t, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 4.51−4.40 (m, 1H), 3.71 (s, 3H), 3.39 (t, *J* = 8.4 Hz, 1H), 3.20−3.11 (m, 1H), 3.04 (dd, *J* = 8.5, 5.4 Hz, 1H), 2.73 (s, 3H), 2.65 (dd, *J* = 16.6, 4.8 Hz, 1H), 2.56 (dd, *J* = 16.6, 4.8 Hz, 1H), 2.00−1.94 (m, 2H); ^{13}C NMR δ 171.9, 156.7 (q, *J* = 36.6 Hz), 152.6, 132.2, 128.1, 123.9, 118.1, 115.8 (q, *J* = 288.0 Hz), 107.7, 62.2, 52.0, 45.3, 38.0, 37.8, 37.5, 36.0. Anal. Calcd for $C_{16}H_{19}F_3N_2O_3$: C, 55.81; H, 5.56; N, 8.14. Found: C, 55.44; H, 5.92; N, 7.83.

Oxidation to DL-10b. A mixture of the diastereoisomers of methyl 4-(1-methylindolin-3-yl)-3-(2,2,2-trifluoroacetamido)butanoate DL-**12** (175 mg, 0.5 mmol) with active manganese dioxide (400 mg, 4 mmol) in toluene (20 mL) was stirred under nitrogen until the starting material was consumed (10−12 h; progress of the reaction was monitored by TLC). The mixture was filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel using gradient ethyl acetate/hexanes eluent (1:3 → 2:5) to give methyl 4-(1-methyl-1*H*-indol-3-yl)-3-(2,2,2-trifluoroacetamido)butanoate DL-**10b** (145 mg, 85%), beige microcrystals from diethyl ether, mp 106−107 °C; ^{1}H NMR δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.32−7.22 (m, 3H), 7.16−7.11 (m, 1H), 6.88 (s, 1H), 4.63−4.52 (m, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.16 (dd, *J* = 14.5, 5.6 Hz, 1H), 3.04 (dd, *J* = 14.5, 8.2 Hz, 1H), 2.66−2.53 (m, 2H); ^{13}C NMR δ 172.0, 156.6 (q, *J* = 37.0 Hz), 137.0, 127.7, 127.5, 121.9, 119.2, 118.6, 115.7 (q, *J* = 288.0 Hz), 109.3, 108.8,

51.9, 47.6, 35.9, 32.6, 28.9. Anal. Calcd for $C_{16}H_{17}F_3N_2O_3$: C, 56.14; H, 5.01; N, 8.18. Found: C, 56.43; H, 5.38; N, 8.14.

Reduction/Oxidation of L-9b to L-10b. The mixture of (*S*)-methyl 4-(1-methyl-1*H*-indol-3-yl)-4-oxo-3-(2,2,2-trifluoroacetamido)butanoate L-**9b** (0.36 g, 1 mmol), indium chloride (220 mg, 1 mmol), and chlorodimethylsilane (added in three portions every 12 h; total 0.9 mL, 0.77 g, 8 mmol) in dichloromethane (40 mL) was heated under reflux under nitrogen for 36 h. After cooling, saturated aqueous sodium bicarbonate and charcoal were added, and the mixture was stirred for 30 min, and filtered. The organic layer was separated, dried over magnesium sulfate, and concentrated under vacuum to dryness. The residue of (3*R*)-methyl 4-(1-methylindolin-3-yl)-3-(2,2,2-trifluoroacetamido)butanoate L-**12** (not purified) was dissolved in toluene (30 mL), and active manganese dioxide (870 mg, 10 mmol) was added at 20 °C. The mixture was stirred under nitrogen at 20 °C until the starting material was consumed (10−12 h, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using gradient dichloromethane → dichloromethane/ethyl acetate (20:1) to give (*R*)-methyl 4-(1-methyl-indol-3-yl)-3-(2,2,2-trifluoroacetamido)butanoate L-**10b** (190 mg, 56%), beige microcrystals from diethyl ether, mp 115−116 °C, $[\alpha]^{23}_D = 2.95°$ (*c* 2.1, chloroform); ^{1}H NMR δ 7.60 (d, J = 7.9 Hz, 1H), 7.33−7.20 (m, 3H), 7.15−7.10 (m, 1H), 6.87 (s, 1H), 4.561−4.51 (m, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.14 (dd, J = 14.6, 5.6 Hz, 1H), 3.02 (dd, J = 14.6, 8.1 Hz, 1H), 2.58 (d, J = 5.2 Hz, 2H); ^{13}C NMR δ 172.0, 156.6 (q, J = 37.2 Hz), 137.0, 127.7, 127.5, 121.9, 119.3, 118.6, 115.7 (q, J = 287.5 Hz), 109.3, 108.9, 51.9, 47.6, 35.9, 32.6, 28.9. Anal. Calcd for $C_{16}H_{17}F_3N_2O_3$: C, 56.14; H, 5.01; N, 8.18. Found: C, 55.91; H, 5.10; N, 7.96.

General Procedure for the Preparation of δ-Keto-γ-amino esters 13. To a solution of Tfa-Glu(OMe)-Bt (**8**) (0.34 g, 1 mmol) and aromatics (1.1 mmol) in anhydrous dichloromethane (10 mL) was added anhydrous 1 M $TiCl_4$ in dichloromethane (1.5 mL) at 0 °C. The mixture was stirred at room temperature for 1−2 h and purified by chromatography (dry loading method, ethyl acetate/hexanes 1:3) to give **13a**−**f**.

Methyl (4*S*)-5-(1*H*-Indol-3-yl)-5-oxo-4-(2,2,2-trifluoroacetamido)pentanoate (13a). Light yellow microcrystals from chloroform/hexanes (70%); mp 132−133 °C, $[\alpha]^{23}_D = 4.50°$ (*c* 2.0, chloroform); ^{1}H NMR δ 9.26 (br s, 1H), 8.35−8.32 (m, 2H), 7.76 (d, J = 7.5 Hz, 1H), 7.46−7.43 (m, 1H), 7.36−7.31 (m, 2H), 5.55−5.49 (m, 1H), 3.72 (s, 3H), 2.54−2.42 (m, 3H), 1.97−1.92 (m, 1H); ^{13}C NMR δ 190.5, 173.7, 157.6 (q, J = 37.6 Hz), 136.4, 133.5, 125.5, 124.4, 123.4, 122.1, 115.8 (q, J = 285.8 Hz), 114.2, 111.8, 54.1, 52.0, 30.2, 29.4. Anal. Calcd for $C_{16}H_{15}F_3N_2O_4$: C, 53.94; H, 4.24; N, 7.86. Found: C, 54.22; H, 4.27; N, 7.69.

Methyl (4*S*)-5-(1-Methyl-indol-3-yl)-5-oxo-4-(2,2,2-trifluoroacetamido)pentanoate (13b). Colorless needles from chloroform/hexanes (59%), mp 137−139 °C, $[\alpha]^{23}_D = 15.3°$ (*c* 2.0, chloroform); ^{1}H NMR δ 8.32−8.35 (m, 1H), 8.21 (s, 1H), 7.89 (d, J = 7.5 Hz, 1H), 7.33−7.36 (m, 3H), 5.45−5.51 (m, 1H), 3.88 (s, 3H), 3.71 (s, 3H), 2.40−2.55 (m, 3H), 1.93−2.01 (m, 1H); ^{13}C NMR δ 190.2, 173.6, 157.5 (q, J = 37.1 Hz), 137.8, 137.6, 126.6, 124.2, 123.5, 122.5, 116.0 (q, J = 286.3 Hz), 112.9, 110.2, 54.3, 52.1, 34.0, 30.3, 29.6. Anal. Calcd for $C_{17}H_{17}F_3N_2O_4$: C, 55.14; H, 4.63; N, 7.56. Found: C, 55.04; H, 4.61; N, 7.44.

Methyl 5-(1-Methyl-indol-3-yl)-5-oxo-4-(2,2,2-trifluoroacetamido)pentanoate (DL-13b). Beige microcrystals from dichloromethane (83%), mp 170−173 °C; ^{1}H NMR δ 8.35−8.33 (m, 1H), 8.22 (s, 1H), 7.71 (d, J = 7.4 Hz, 1H), 7.38−7.34 (m, 3H), 5.49−5.43 (m, 1H), 3.91 (s, 3H), 3.73 (s, 3H), 2.54−2.39 (m, 3H), 1.99−1.91 (m, 1H); ^{13}C NMR δ 190.0, 173.4, 157.3 (q, J = 37.8 Hz), 137.6, 137.4, 126.4, 124.0, 123.4, 122.3, 115.8 (q, J = 288.0 Hz), 112.6, 110.0, 54.0, 51.9, 33.9, 30.3, 29.4.

Methyl (4*S*)-5-(1-Methylpyrrol-3-yl)-5-oxo-4-(2,2,2-trifluoroacetamido)pentanoate (13c). Colorless needles from chloroform/hexanes (56%), mp 131−132 °C, $[\alpha]^{23}_D = 13.73°$ (*c* 0.83, chloroform); ^{1}H NMR δ 7.59 (d, J = 6.0 Hz, 1H), 7.29 (d, J = 3.9 Hz, 1H), 6.95 (s, 1H), 6.24−6.22 (m, 1H), 5.40 (dt, J = 8.1, 3.0 Hz, 1H), 3.95 (s, 3H), 3.70 (s, 3H), 2.49−2.36 (m, 3H), 2.04−1.89 (m, 1H); ^{13}C NMR δ 185.6, 173.2, 157.2 (d, J = 37.0 Hz), 135.5, 127.6, 121.7, 116.0 (d, J = 286.3 Hz), 109.6, 53.9, 52.0, 37.8, 29.9, 29.6.

Methyl (4*S*)-5-(1*H*-Pyrrol-2-yl)-5-oxo-4-(2,2,2-trifluoroacetamido)pentanoate (13d). Colorless microcrystals from chloroform/hexanes (61%), mp 81−82 °C; $[\alpha]^{23}_D = 38.70°$ (*c* 2.0, chloroform); ^{1}H NMR δ 9.74 (br s, 1H), 7.56 (br s, 1H), 7.27−7.24 (m, 1H), 7.17−7.15 (m, 1H), 6.40−6.37 (m, 1H), 5.43−5.37 (m, 1H), 3.72 (s, 3H), 2.53−2.39 (m, 3H), 2.01−1.94 (m, 1H); ^{13}C NMR δ 185.1, 173.3, 157.2 (q, J = 37.0 Hz), 128.6, 126.9, 118. 9, 115.7 (q, J = 285.7 Hz), 111.9, 53.5, 52.0, 29.6, 29.5. Anal. Calcd for $C_{12}H_{13}F_3N_2O_4$: C, 47.07; H, 4.28; N, 9.15. Found: C, 46.91; H, 4.19; N, 8.75.

Methyl (4*S*)-5-(2,4-Dimethoxyphenyl)-5-oxo-4-(2,2,2-trifluoroacetamido)pentanoate (13e). Colorless needles from chloroform/hexanes (46%), mp 137 °C, $[\alpha]^{23}_D = 7.29°$ (*c* 1.40, chloroform); ^{1}H NMR δ 7.94 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 6.60 (dd, J = 9.0, 2.1 Hz, 1H), 6.48 (d, J = 2.4 Hz, 1H), 5.71−5.66 (m, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.64 (s, 3H), 2.44−2.26 (m, 3H), 1.96−1.88 (m, 1H); ^{13}C NMR δ 194.5, 173.0, 166.1, 161.2, 156.9 (q, J = 37.0 Hz), 134.1, 116.4, 115.8 (q, J = 285.7 Hz), 106.3, 98.3, 57.5, 55.8, 55.7, 51.8, 29.8, 27.2. Anal. Calcd for $C_{16}H_{18}F_3NO_6$: C, 50.93; H, 4.81; N, 3.71. Found: C, 50.97; H, 4.78; N, 3.70.

(*S*)-Methyl 4-(2,2,2-Trifluoroacetamido)-5-(2,4,6-trimethoxyphenyl)-5-oxopentanoate (13f). Colorless needles from chloroform/hexanes (46%), mp 99−100 °C; ^{1}H NMR δ 7.55 (d, J = 7.5 Hz, 1H), 6.13 (s, 2H), 5.36−5.30 (m, 1H), 3.84 (s, 3H), 3.80 (s, 6H), 3.64 (s, 3H), 2.37−2.27 (m, 3H), 2.03−1.90 (m, 1H); ^{13}C NMR δ 198.4, 173.0, 163.7, 159.3, 156.7 (q, J = 37.0 Hz), 115.6 (q, J = 285.7 Hz), 108.1, 90.5, 58.5, 55.7 (2C), 55.3, 51.5, 29.2, 26.1. Anal. Calcd for $C_{17}H_{20}F_3NO_7$: C, 50.13; H, 4.95; N, 3.44. Found: C, 50.13; H, 4.93; N, 3.40.

General Procedure for the Preparation of δ-Aryl-γ-amino Esters 14e,f. To γ-keto-γ-amino ester **13e,f** (1 mmol) in dichloromethane were added trifluoroacetic acid (0.45 mL) and triethylsilane (0.4 mL, 2.5 mmol). After 4 h of stirring at room temperature, water was added, and the mixture was extracted with diethyl ether. The ether layer was dried with magnesium sulfate. The solvent was removed under vacuum, and the residue was purified by chromatography (ethyl acetate/hexanes 1:6).

Methyl (4*S*)-5-(2,4-Dimethoxyphenyl)-4-(2,2,2-trifluoroacetamido)pentanoate (14e). Beige microcrystals from dichloromethane (84%), mp 85−86 °C, $[\alpha]^{23}_D = -8.33°$ (*c* 1.92, chloroform); ^{1}H NMR δ 7.06−7.00 (m, 2H), 6.46−6.43 (m, 2H), 4.16−4.04 (m, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.67 (s, 3H), 2.83−2.80 (m, 2H), 2.51−2.31 (m, 2H), 2.01−1.77 (m, 2H); ^{13}C NMR δ 173.7, 160.1, 157.9, 157.0 (q, J = 36.4 Hz), 131.7, 117.3, 115.9 (q, J = 288.3 Hz), 104.6, 98.6, 55.4, 55.2, 51.8, 51.7, 33.8, 30.6, 29.1. Anal. Calcd for $C_{16}H_{20}F_3NO_5$: C, 52.89; H, 5.55; N, 3.85. Found: C, 53.18; H, 5.71; N, 3.72.

(*S*)-Methyl 4-(2,2,2-Trifluoroacetamido)-5-(2,4,6-trimethoxyphenyl)pentanoate (14f). Colorless microcrystals from chloroform/hexanes (88%), mp 88−89 °C; ^{1}H NMR δ 7.15 (d, J = 7.0 Hz, 1H), 6.13 (s, 2H), 4.04−3.98 (m, 1H), 3.81 (s, 3H), 3.80 (s, 6H), 3.68 (s, 3H), 2.87 (dd, J = 13.9, 3.9 Hz, 1H) 2.76 (dd, J = 13.9, 9. 5 Hz, 1H), 2.55−2.35 (m, 2H), 2.04−1.84 (m, 2H); ^{13}C NMR δ 173.9, 160.2, 158.6, 157.1 (q, J = 36.5 Hz), 115.9 (q, J = 286.9 Hz), 105.5, 90.4, 55.5 (2C), 55.3, 51.7, 51.6, 30.6, 29.5, 26.4. Anal. Calcd for $C_{17}H_{22}F_3NO_6$: C, 51.91; H, 5.64; N, 3.56. Found: C, 51.72; H, 5.61; N, 3.44.

General Procedure for the Preparation of δ-Aryl-γ-amino Acids 15a,b. $NaBH_4$ (0.05 g, 1.3 mmol) was added to a solution of γ-keto-γ-amino ester **13a,b** (0.33mmol) in 75% aqueous DMF (13 mL). The mixture was stirred at room temperature for 1.5 h and quenched with water (15 mL). Then the reaction mixture was acidified with 1 N aqueous hydrochloric acid to pH 5, followed by

extraction with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate. After removing solvent, the product was purified by recrystallization from chloroform/hexane.

(4*S*)-5-(1*H*-Indol-3-yl)-4-(2,2,2-trifluoroacetamido)pentanoic Acid (15a). Beige microcrystals from chloroform/hexanes (87%); mp 127−130 °C; $[\alpha]^{23}_D = 14.48°$ (*c* 0.67, chloroform); ^{1}H NMR (DMSO-d_6) δ 12.10 (br s, 1H), 10.85 (s, 1H), 9.27 (d, $J = 8.4$ Hz, 1H), 7.55 (d, $J = 7.7$ Hz, 1H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.12−6.96 (m, 3H), 4.14−3.98 (m, 1H), 2.91 (d, $J = 7.0$ Hz, 2H), 2.31−2.16 (m, 2H), 1.92−1.73 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 174.1, 156.1 (q, $J = 36.0$ Hz), 136.2, 127.4, 123.3, 121.0, 118.4, 118.3, 116.0 (q, $J = 288.6$ Hz), 111.4, 110.5, 50.5, 30.5, 29.8, 28.5. Anal. Calcd for $C_{15}H_{15}F_3N_2O_3$: C, 54.88; H, 4.61; N, 8.53. Found: C, 54.64; H, 4.71; N, 8.35.

(4*S*)-5-(1-Methyl-1*H*-indol-3-yl)-4-(2,2,2-trifluoroacetamido)-pentanoic Acid (15b). Beige microcrystals from chloroform/hexanes (73%); mp 185−186 °C; $[\alpha]^{23}_D = 12.24°$ (*c* 0.67, chloroform); ^{1}H NMR (DMSO-d_6) δ 12.09 (br s, 1H), 9.27 (d, $J = 8.5$ Hz, 1H), 7.56 (d, $J = 7.7$ Hz, 1H), 7.37 (d, $J = 8.1$ Hz, 1H), 7.16−7.09 (m, 2H), 7.02 (t, $J = 7.6$ Hz, 1H), 4.04−3.99 (m, 1H), 3.72 (s, 3H), 2.89 (d, $J = 6.9$ Hz, 2H), 2.25−2.18 (m, 2H), 1.85−1.75 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 174.0, 156.1 (q, $J = 36.1$ Hz), 136.6, 127.8, 127.7, 121.1, 118.5, 118.4, 116.0 (q, $J = 288.6$ Hz), 109.8, 109.6, 50.6, 32.3, 30.5, 29.7, 28.3. Anal. Calcd for $C_{16}H_{17}F_3N_2O_3$: C, 56.04; H, 5.01; N, 8.18. Found: C, 56.01; H, 5.22; N, 7.56.

5-(1-Methylindol-3-yl)-4-(2,2,2-trifluoroacetamido)pentanoic Acid (DL-15b). Beige microcrystals from chloroform/hexanes (56%), mp 148−150 °C; ^{1}H NMR (DMSO-d_6) δ 12.10 (br s, 1H), 9.28 (d, $J = 8.5$ Hz, 1H), 7.56 (d, $J = 7.8$ Hz, 1H), 7.37 (d, $J = 8.1$ Hz, 1H), 7.16−7.10 (m, 2H), 7.02 (t, $J = 7.4$ Hz, 1H), 4.10−3.94 (m, 1H), 3.73 (s, 3H), 2.90−2.88 (m, 2H), 2.30−2.12 (m, 2H), 1.90−1.67 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 174.0, 156.1 (q, $J = 36.1$ Hz), 136.6, 127.8, 127.7, 121.1, 118.5, 118.4, 116.0 (q, $J = 288.6$ Hz), 109.8, 109.6, 50.6, 32.3, 30.5, 29.7, 28.3. Anal. Calcd for $C_{16}H_{17}F_3N_2O_3$: C, 56.14; H, 5.01; N, 8.18. Found: C, 55.95; H, 5.03; N, 8.32.

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