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N-Tfa- and *N*-Fmoc-(α-aminoacyl)benzotriazoles as Chiral *C*-Acylating Reagents under Friedel−Crafts Reaction Conditions

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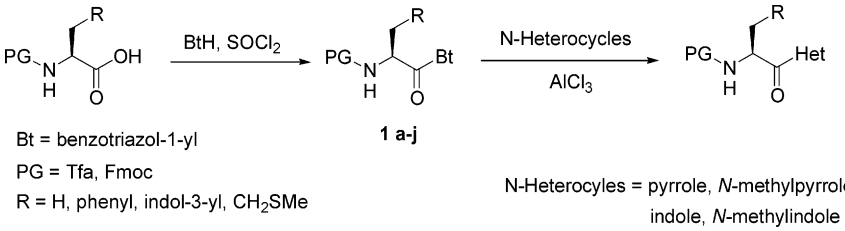

Chiral *N*-Tfa- and *N*-Fmoc-protected (α-aminoacyl)benzotriazoles **1a**−**j** undergo Friedel−Crafts-type reactions with indole, *N*-methylindole, pyrrole, *N*-methylpyrrole, and benzene in the presence of $AlCl_3$ in efficient two-step sequences leading to enantiomerically pure α-amino *N*-heterocyclic ketones **2**, **3**, **5**, **6**, and **7** or diketone **4**. In the absence of a reactive partner, Phe- and Trp-derivatives **1a**, **1d** undergo intramolecular cyclization to afford **12** and **13**, again with retention of chirality.

Introduction

Chiral N-protected α-amino ketones are useful precursors to many biologically active compounds including chiral α-amino alcohols,[1] pharmaceutically important chiral heterocycles,[2,3] and diamines.[1c,4] Preparations of α-amino aliphatic ketones and α-amino aryl ketones have been thoroughly investigated,[5] but much less attention has been directed toward the synthesis of α-aminoalkyl heterocyclic ketones and to our knowledge, no general method has been reported. Previous syntheses of chiral α-amino ketones utilized N-protected α-amino acids, esters, and amides (i) with organometallic reagents for nucleophilic substitution[6] or (ii) with $AlCl_3$ for Friedel−Crafts acylations.[7] The methods using organometallic reagents, though well-established, sometimes suffer from drawbacks such as tedious purification[6a] and competition between nucleophilic addition and nucleophilic substitution.[6b] Moreover, N-protected α-amino acid chlorides are often unstable and prone to racemization.[8]

N-Acylbenzotriazoles, which are easily prepared from carboxylic acids by (i) thionyl chloride and 1*H*-benzotriazole at 20 °C[9a] or (ii) $BtSO_2Me$ in the presence of Et_3N,[9b] are efficient *C*-acylating agents for heterocycles such as indoles, pyrroles,[10a] furan, and thiophene[10b] under Friedel-Craft conditions. Recently, we converted amino acids into enantiomerically pure N-protected (aminoacyl)-benotriazoles, which were then coupled with chiral amines,[11a] amino acids, and peptides.[11b−d] We now report the first syntheses of *C*-acylated indoles and pyrroles utilizing *N*-(Tfa- and Fmoc-α-aminoacyl)benzotriazoles under Friedel−Crafts conditions to obtain the corre-

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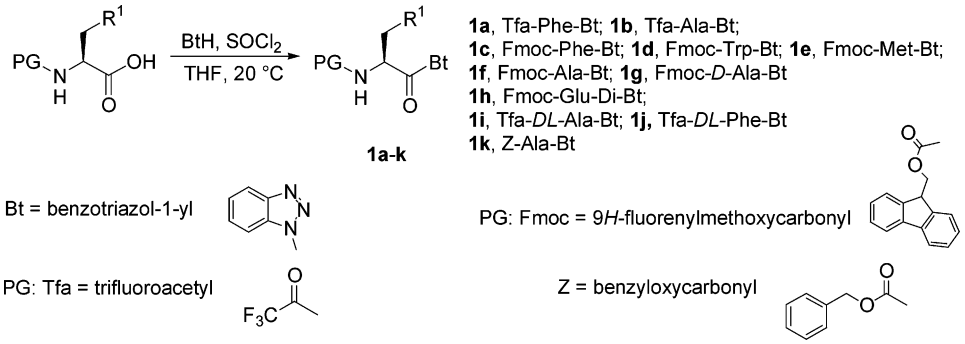
SCHEME 1. Preparation of N-Protected Aminoacylbenzotriazoles



sponding α-amino ketones with complete retention (>99%) of chirality.

Results and Discussion

Preparation of *N*-(Tfa- and Fmoc-α-aminoacyl)-benzotriazoles. The amino group of L-alanine and L-phenylalanine were protected with the *N*-trifluoroacetyl (Tfa) group using ethyl trifluoroacetate in the presence of Et_3N in methanol to generate the *N*-Tfa-α-amino acids.[12] The resultant *N*-Tfa-protected amino acids were treated with thionyl chloride and 4 equiv of benzotriazole to give *N*-(Tfa-α-aminoacyl)benzotriazoles **1a** and **1b** (Scheme 1). Racemic *N*-(Tfa-α-aminoacyl)benzotriazoles **1i** and **1j** were prepared similarly from DL-alanine and DL-phenylalanine, respectively. *N*-(Fmoc-α-aminoacyl)-benzotriazoles **1c**−**h** were prepared by the above method from commercially available *N*-Fmoc-L-phenylalanine, L-tryptophan, and L-methionine.[11d] The *Z*-protected aminoacylbenzotriazole **1k** was prepared by a previously reported method.[11b]

Friedel−Crafts Acylations of Pyrrole and *N*-Methylpyrrole. Reactions of **1a**−**e** in CH_2Cl_2 with 1.2 equiv of pyrrole in the presence of 3 equiv of anhydrous $AlCl_3$ under nitrogen at 20 °C for 3 h produced the corresponding amino ketones **2a**−**e**; reactions of **1a**−**e** with *N*-methylpyrrole under similar conditions also gave the corresponding amino ketones **3a**−**e** (Table 1). The *C*-acylations occurred specifically at C-2, and no 3-acylated products were observed.

When compounds with an Fmoc group and bulky aromatic side chains such as Fmoc-Phe-Bt (**1c**) and Fmoc-Trp-Bt (**1d**) were used, the corresponding ketones were obtained in lower yields than the ketones with aliphatic side chains. For the reaction of **1d** with *N*-methylpyrrole, the 45% yield was not improved even when the reaction time was extended to 24 h.

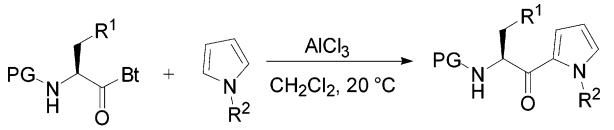
Furthermore, we extended this method to the preparation of the bis(acyl)-pyrrole **4** by using *N*-(Fmoc-aminodiacyl)benzotriazole **1h** (prepared from *N*-Fmoc-glutamic acid) in 35% yield (Scheme 2). The yield of the aminodiketone **4** was not as good as those from the monoacylation reactions, presumably due to the lack of solubility of **1h** in CH_2Cl_2. No mono-acylated compounds were observed during the purification of **4** by column chromatography.

However, attempted *C*-acylation of pyrrole with *Z*-Ala-Bt (**1k**) resulted in the loss of the Z group as indicated by their crude NMR spectra and no desired product was isolated.

Friedel−Crafts Acylations of Indole and *N*-Methylindole. Utilizing the procedure developed above for the acylation of pyrrole and *N*-methylpyrrole, *C*-acylations of indole to give **5a**−**e** and of *N*-methylindole to give **6a**−**g** were carried out in the presence of 3 equiv of $AlCl_3$. Most of the expected products were thus obtained in good to moderate yields (Table 2). Exceptionally, the reaction of Fmoc-Trp-Bt (**1d**) with indole failed to give expected product **5d**, and **1d** decomposed under the reaction conditions. However, *N*-TMS-indole readily reacted with **1d** in the presence of $TiCl_4$ or $AlCl_3$ in 15 min to give the product **5d** in 87% and 41% isolated yields, respectively. The TMS group was completely cleaved under these reaction conditions.

Friedel−Crafts Acylations of Benzene. Most literature syntheses of chiral aryl α-amino ketones via Friedel−Crafts type reactions involve N-protected α-amino acid chlorides.[7] However, the preservation of chirality of α-amino acid chlorides was not always successful due

TABLE 1. *C*-Acylations of Pyrrole and *N*-Methylpyrrole



reactant	amino ketone (yield. %)[a] from pyrrole	from *N*-methylpyrrole
Tfa-Phe-Bt (**1a**)	**2a** (82)	**3a** (78)
Tfa-Ala-Bt (**1b**)	**2b** (78)	**3b** (75)
Fmoc-Phe-Bt (**1c**)	**2c** (72)	**3c** (56)
Fmoc-Trp-Bt (**1d**)	**2d** (52)	**3d** (45)
Fmoc-Met-Bt (**1e**)	**2e** (66)	**3e** (60)

[a] Isolated yield.

SCHEME 2. Preparation of Aminodiketone 4

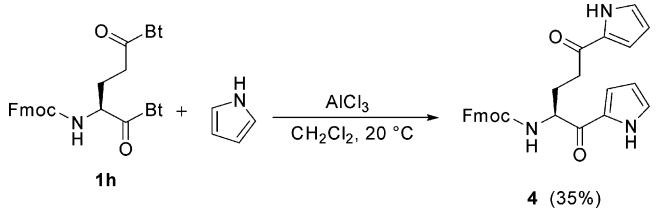


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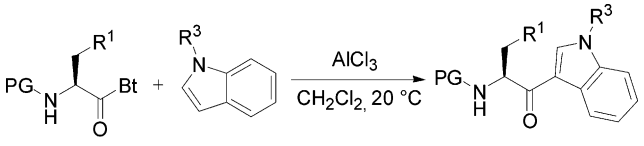
TABLE 2. *C*-Acylations of Indole and *N*-Methylindole

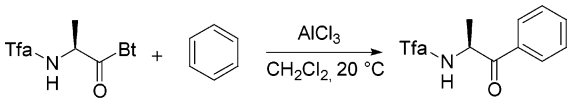


1a-e

reactant	amino ketone (yield, %)[a] from indole	amino ketone (yield, %)[a] from *N*-methylindole
Tfa-Phe-Bt (**1a**)	**5a** (85)	**6a** (62)
Tfa-Ala-Bt (**1b**)	**5b** (79)	**6b** (75)
Fmoc-Phe-Bt (**1c**)	**5c** (63)	**6c** (40)
Fmoc-Trp-Bt (**1d**)	**5d** (87)[b,c]	**6d** (45)
Fmoc-Met-Bt (**1e**)	**5e** (83)	**6e** (90)
Fmoc-L-Ala-Bt (**1f**)	*d*	**6f** (85)
Fmoc-D-Ala-Bt (**1g**)	*d*	**6g** (75)
Tfa-DL-Phe-Bt (**1j**)	*d*	**6j** (64)

[a] Isolated yield. [b] Reaction condition (*N*-TMS-indole 1.5 equiv, $TiCl_4$ 2 equiv, CH_2Cl_2, 10 min, 20 °C). [c] Reaction with 1*H*-indole gave no product. [d] Not attempted.

SCHEME 3. Acylation of Benzene



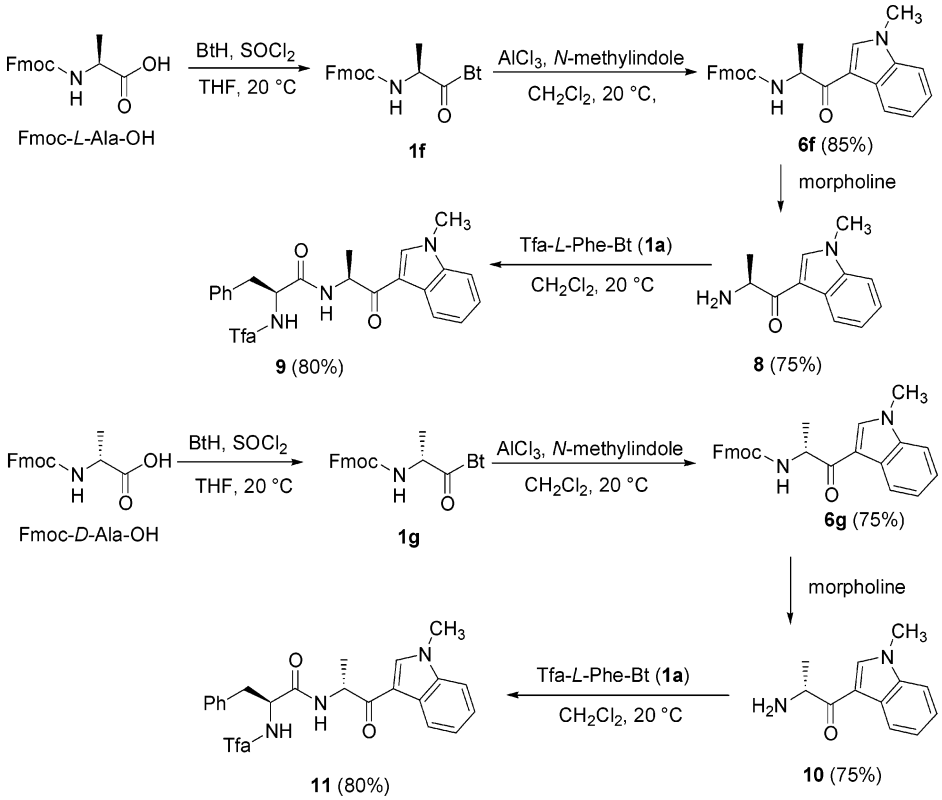
1b — **7** (63%)

to the instability of acid chlorides, which can react with an amino protecting group to form oxazolinones.[7a] To address this issue, we reacted Tfa-Ala-Bt (**1b**) with benzene to give α-aminoalaninyl phenyl ketone **7** in 63% yield. (Scheme 3) The ^1H NMR and melting point of **7** matches the literature report.[7c] While our yield was comparable to previous reports in the literature, the solid, chirally stable benzotriazole derivatives are clearly more convenient to handle than amino acid chlorides.

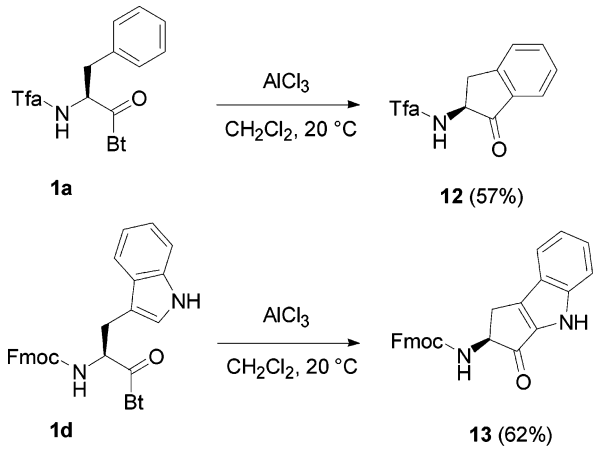
Configurational Analysis of Amino Ketones. Because one of the most important features of biologically active amino ketones is associated with the presence of the asymmetric α-carbon in their structures, total control of chirality represents a major goal during the synthesis of these amino ketones. To evaluate the chiral integrity of these reactions, we examined the syntheses of amino ketones **6a** (L) and **6j** (DL-mixture), prepared from *N*-methylindole and Tfa-L-Phe-Bt (**1a**) and Tfa-DL-Phe-Bt (**1j**), respectively as models. This study was accomplished by chiral HPLC comparison of the two acylated products of *N*-methylindole **6a** and **6j** starting from enantiomerically pure Tfa-L-phenylalanine and Tfa-DL-phenylalanine. Two peaks equal in ratio appeared for **6j** at 3.11 min corresponding to L-isomer and at 6.59 min corresponding to the D-isomer, whereas **6a** gave only one peak appearing at 3.11 min (solvent MeOH, flow rate 1.0 mL/min, UV detection at 254 nm). Since all of the acylations were carried out under the same conditions, the HPLC results supported the conclusion that *N*-(Tfa- and Fmoc-α-aminoacyl)benzotriazoles undergo Friedel−Crafts type reactions with nitrogen heterocycles and benzene in the presence of $AlCl_3$ with full preservation (>99%) of the configuration.

A NMR study utilizing diastereomers also supported the preservation of configuration during the *C*-acylation. Compound **9** was prepared by coupling of **1a** with **8** obtained by the cleavage of the Fmoc group of **6f**, which

SCHEME 4. Preparation of Diastereomers 9 and 11



SCHEME 5. Intramolecular Cyclization of 1a and 1d

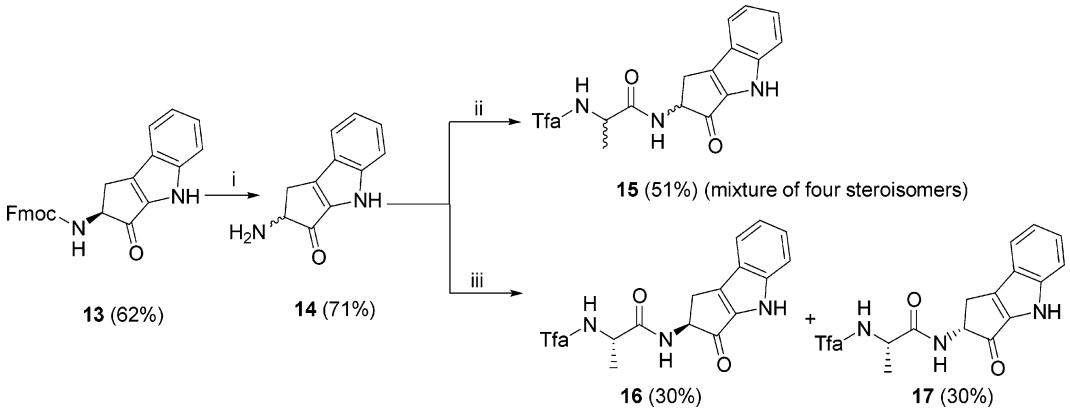


was generated from the acylation of Fmoc-L-Ala-Bt (**1f**) with *N*-methylindole. A similar process was used to prepare the other diastereomer **11**. (Scheme 4) The methyl group of the alanine moiety in a diastereomer **9** (L-Phe-L-Ala) displays a single doublet at 1.51 ppm, whereas **11** (L-Phe-D-Ala) exhibited a single doublet at 1.39 ppm. No trace was found of methyl peaks characteristic of **11** in the ^{1}H NMR spectrum of **9** and also nothing of **9** in the NMR of **11**.

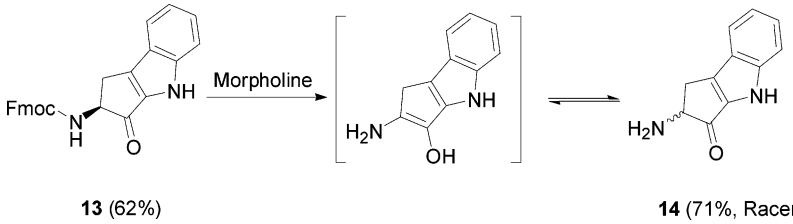
Intramolecular Cyclization of 1a and 1d. The lower yields of α-amino ketones **2d** (52%), **3c** (41%), and **6d** (45%) obtained from aromatic side chains containing aminoacylbenzotriazoles **1c** and **1d** (as compared to those from aminoacylbenzotriazoles **1a**,**b**,**e** containing alphatic side chains) suggested a competing intramolecular acylation reaction of the aromatic side chains in **1a** and **1d**. We reacted the two compounds **1a** and **1d** under the conditions used for the preparation of **5** and **6** but in the absence of indole and generated the cyclized products **12** and **13** in 57% and 62% yield, respectively (Scheme 5). The ^{1}H NMR spectra of **12** and **13** showed the disappearance of Bt signals in aromatic region, indicating the loss of the benzotriazolyl group during the reaction. The ^{13}C NMR spectrum of **12** showed a signal at 201.2 ppm corresponding to the carbonyl group of the cyclized ketone and the disappearance of the signal at 168.8 ppm belonging to the carbonyl group at the α position of the benzotriazolyl group in the starting material. Likewise, the ^{13}C NMR spectrum of **13** showed a signal for the cyclized ketone at 191.3 ppm and the disappearance of the signal of the α carbonyl group of the benzotriazolyl group at 172.2 ppm. The cyclization also was confirmed in ^{1}H NMR spectrum by the observation of four protons in the aromatic region of **12** due to the loss of one aromatic proton from the starting material. Furthermore, the splitting patterns of the two protons at the α position to the phenyl ring of **1a** and cyclized ketone **12** were different. Regarding **1a**, one of the two protons appeared at 3.37 ppm (dd, J = 13.8, 7.2 Hz) and the other one at 3.59 ppm (dd, J = 13.8, 5.1 Hz). In the ^{1}H NMR spectrum of **12**, one proton was observed at 3.05 ppm (dd, J = 16.8, 5.7 Hz) and the other at 3.89 ppm (dd, J = 16.8, 5.1 Hz). The difference of chemical shifts of the two protons (0.84 ppm) in **12** was much larger than that of the two protons (0.22 ppm) in **1a**, which can be rationalized by the formation of a five-membered ring system.

Configurational Analysis of Intramolecular Cyclization. A NMR study utilizing diastereomers was carried out to examine the preservation of configuration in products **12** and **13** from the intramolecular cyclizations of **1a** and **1d**. Tricyclic amine **14** was obtained by the cleavage of **13** using morpholine. The coupling of amine **14** with Tfa-DL-Ala-Bt (**1i**) gave as expected a mixture of the four stereoisomers **15** (two pairs of diastereomers). The coupling of amine **14** with Tfa-L-Ala-Bt (**1b**) did not give diastereomers **16** exclusively, but

SCHEME 6. Preparation of Diastereomers 15, 16, and 17



SCHEME 7. Mechanism of Racemization



another enantiomer **17** was obtained as a result of racemization (Scheme 6). There were two doublets observed in the NMR spectrum of **15** corresponding to the methyl group of the alanine moiety from Tfa-DL-Ala-Bt (**1i**), which was the same with the methyl group of the alanine moiety in the mixture of **16** and **17** at 1.49 and 1.51 ppm. This result suggested that racemization occurred during the preparation of the diastereomers. Since compound **13** has OPR value ($[\alpha]^{23}_D = -4.3$) and no racemization was observed for the coupling of amine **8** and Tfa-L-Phe-Bt (**1a**), it is reasonable to conclude that the racemization probably took place in the stage of the cleavage of Fmoc group (from **13** to **14**) as a result of the acidic proton at the α position to the carbonyl group of the cyclopentenone, which can be easily deprotonated to form an enol. (Scheme 7)

Conclusion

The syntheses of *N*-Tfa- and *N*-Fmoc-α-amino ketones containing *N*-heterocycles and benzene using *N*-(Tfa- and Fmoc-α-aminoacyl)benzotriazoles under the Friedel–Crafts conditions have been achieved in moderate to high yield. Full preservation (>99%) of chirality has been suggested by HPLC. This new method for the preparation of novel enantiomerically pure α-amino ketones containing heterocyclic moieties offers a facile access to potentially valuable biological and pharmacological compounds.

Experimental Section

General Procedure for the Preparation of N-Protected (Aminoacyl)benzotriazoles (1a–l). Thionyl chloride (10 mmol, 0.73 mL) was added to the 1*H*-benzotriazole (40 mmol, 4.76 g) dissolved in anhydrous THF (30 mL), and the solution was heated at 40 °C for 30 min. After cooling to 0 °C, a solution of N-protected amino acid (10 mmol) in anhydrous THF was added, and the mixture was stirred at 20 °C for 2 h. The white precipitate was filtered off, and the filtrate was concentrated and diluted with dichloromethane followed by washing with saturated sodium carbonate (50 mL×3) and water (50 mL) and drying with anhydrous $MgSO_4$. Evaporation of the solvent gave products **1a**–**l** in 63–83% yields, which were recrystallized from $CHCl_3$/hexanes for CHN analysis. Compounds **1d**, **1e**, and **1k** have been previously reported and fully characterized.[11b,d]

***N*-[(1*S*)-2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-benzyl-2-oxoethyl]-2,2,2-trifluoroacetamide (Tfa-L-Phe-Bt, 1a):** colorless needles; yield, 83%; mp 136–137 °C; $[\alpha]^{23}_D = +49.7$ (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.37 (dd, J = 14.4, 7.2 Hz, 1H), 3.59 (dd, J = 14.1, 5.1 Hz, 1H), 6.31 (dd, J = 12.9, 7.5 Hz, 1H), 7.04–7.09 (m, 3H), 7.26–7.29 (m, 3H), 7.60 (t, J = 8.1 Hz, 1H), 7.73 (t, J = 8.1 Hz, 1H), 8.19 (d, J = 7.3 Hz, 1H), 8.22 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 38.5, 54.2, 114.7, 115.5 (q, J = 288.0 Hz), 120.6, 127.0, 127.9, 128.9, 129.1, 130.8, 131.2, 133.8, 146.1, 156.7 (q, J = 38.4 Hz), 168.8. Anal. Calcd for $C_{17}H_{13}F_3N_4O_2$: C, 56.36; H, 3.62; N, 15.46. Found C, 56.55; H, 3.53; N, 15.34.

***N*-[(1*S*)-2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-methyl-2-oxoethyl]-2,2,2-trifluoroacetamide (Tfa-L-Ala-Bt, 1b):** colorless needles; yield, 76%; mp 115–116 °C; $[\alpha]^{23}_D = -106.4$ (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.82 (d, J = 7.2 Hz, 3H), 6.04 (quintet, J = 7.5 Hz, 1H), 7.29 (d, J = 5.4 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.25 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.1, 49.8, 114.4, 115.8 (q, J = 285.7 Hz), 120.8, 127.2, 131.2, 131.4, 146.3, 156.9 (q, J = 38.2 Hz), 170.5. Anal. Calcd for $C_{11}H_9F_3N_4O_2$: C, 46.16; H, 3.17; N, 19.57. Found: C, 46.33; H, 3.05; N, 19.27.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-1-benzyl-2-benzotriazol-1-yl-2-oxoethyl] carbamate (Fmoc-L-Phe-Bt, 1c): colorless flakes; yield, 83%; mp 136–137 °C; $[\alpha]^{23}_D = +35.6$ (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 3.20 (dd, J = 13.8, 8.1 Hz, 1H), 3.47 (dd, J = 13.8, 4.5 Hz, 1H), 4.15 (t, J = 7.2 Hz, 1H), 4.29–4.42 (m, 2H), 5.86 (d, J = 7.4 Hz, 1H), 6.06–6.11 (m, 1H), 7.12–7.27 (m, 8H), 7.34 (t, J = 7.5 Hz, 2H), 7.44–7.54 (m, 3H), 7.60 (t, J = 7.5 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H), 8.19 (d, J = 7.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 25.7, 38.9, 55.8, 68.0, 114.4, 120.0, 120.4, 125.1, 126.6, 127.1, 127.4, 127.8, 128.8, 129.4, 130.9, 131.1, 135.3, 141.3, 143.7, 146.1, 155.8, 171.0. Anal. Calcd for $C_{30}H_{24}N_4O_3$: C, 73.75; H, 4.95; N, 11.47. Found: C, 73.53; H, 5.07; N, 11.24.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-2-(1*H*-1,2,3-benzotriazol-1-yl)-1-methyl-2-oxoethyl]carbamate (Fmoc-L-Ala-Bt, 1f): colorless microcrystals; yield, 85%; mp 160–161 °C; $[\alpha]^{23}_D = -96.8$ (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 1.59 (d, J = 7.2 Hz, 3H), 4.27 (t, J = 6.6 Hz, 1H), 4.38 (d, J = 6.9 Hz, 2H), 5.45 (quintet, J = 6.9 Hz, 1H), 7.34–7.47 (m, 4H), 7.65 (t, J = 7.8 Hz, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.77 (d, J = 2.7 Hz, 1H), 7.82 (t, J = 7.5 Hz, 1H), 7.92 (d, J = 7.2 Hz, 2H), 8.25–8.37 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 16.8, 46.6, 50.1, 65.9, 114.0, 120.1, 120.2, 125.2, 126.7, 127.1, 127.7, 130.6, 131.1, 140.8, 143.7, 145.3, 156.1, 172.5. Anal. Calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.48; H, 4.94; N, 13.41.

9*H*-Fluoren-9-ylmethyl *N*-[(1*R*)-2-(1*H*-1,2,3-benzotriazol-1-yl)-1-methyl-2-oxoethyl]carbamate (Fmoc-D-Ala-Bt, 1g): colorless microcrystals; yield, 85%; mp 161 °C; $[\alpha]^{23}_D = +95.6$ (*c* 1.6, DMF). ^{1}H NMR and ^{13}C NMR are the same with Fmoc-L-Ala-Bt (**1f**).

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-4-benzotriazol-1-yl-1-(benzotriazol-1-yl-carbonyl)-4-oxobutyl] carbamate-(Fmoc-Glu-Di-Bt, 1h): colorless flakes; yield, 63%; mp 166–167 °C; $[\alpha]^{23}_D = -19.7$ (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 2.40–2.64 (m, 2H), 3.71 (t, J = 6.6 Hz, 2H), 4.23 (t, J = 6.9 Hz, 1H), 4.34 (d, J = 6.9 Hz, 2H), 5.67–5.73 (m, 1H), 7.32 (t, J = 7.2 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.58–7.90 (m, 8H), 8.16 (d, J = 8.1 Hz, 1H), 8.24–8.28 (m, 3H), 8.46 (d, J = 6.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 24.9, 31.4, 46.6, 53.5, 65.9, 113.9, 114.0, 120.0, 120.1, 120.2, 125.2, 126.4, 126.8, 127.1, 127.6, 130.5, 130.7 (2C), 131.1, 140.7, 143.7, 145.3, 145.4, 156.2, 171.3, 171.5. Anal. Calcd for $C_{30}H_{24}N_4O_3$: C, 67.24; H, 4.41; N, 17.15. Found: C, 67.09; H, 4.23; N, 17.12.

***N*-[(1*R*,*S*)-2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-methyl-2-oxoethyl]-2,2,2-trifluoroacetamide (Tfa-DL-Ala-Bt, 1i):** colorless needles; yield, 80%; mp 110–112 °C. ^{1}H NMR and ^{13}C NMR are the same as for Fmoc-L-Phe-Bt (**1b**).

***N*-[(1*R*,S)-2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-benzyl-2-oxoethyl]-2,2,2-trifluoroacetamide (Tfa-DL-Phe-Bt, 1j):** colorless needles; yield, 89%; mp 132–133 °C. ^{1}H NMR and ^{13}C NMR are the same as for Fmoc-L-Phe-Bt (**1a**).

General Procedure for the Acylations of Nitrogen Heterocycles. $AlCl_3$ (0.4 g, 3 mmol) was added to the mixture of nitrogen heterocycle (2.4 mmol) and **1** (2 mmol) dissolved in anhydrous CH_2Cl_2 (20 mL) at 0 °C. After removing the ice-bath, the reaction mixture was stirred at room temperature for 3 h and then quenched by MeOH (1 mL). Removal of CH_2Cl_2 under reduced pressure gave the crude product, which was purified by column chromatography (EtOAc/hexanes = 4:1) to give the desired products **2**, **3**, **5**, **6**, and **7** in 40–90% yields, which were further recrystallized from $CHCl_3$/hexane for CHN analysis.

***N*-[(1*S*)-1-Benzyl-2-oxo-2-(1*H*-pyrrol-3-yl)ethyl]-2,2,2-trifluoroacetamide (2a):** white needles; yield, 82%; mp 171–172 °C; $[\alpha]^{23}_D = +44.3$ (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.18 (dd, J = 13.5, 5.1 Hz, 1H), 3.35 (dd, J = 13.5, 5.1 Hz, 1H), 5.47 (q, J = 7.5 Hz, 1H), 6.33–6.36 (m, 1H), 6.97–7.01 (m, 3H), 7.13 (s, 1H), 7.23–7.25 (m, 4H), 9.40 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 39.8, 55.2, 111.8, 115.7 (q, J = 287.8 Hz), 118.4, 126.7, 127.4, 128.5, 128.9, 129.4, 134.7, 156.4 (q, J = 37.8 Hz), 184.8. Anal. Calcd for $C_{15}H_{13}F_3N_2O_2$: C, 58.07; H, 4.22; N, 9.03. Found: C, 57.85; H, 4.16; N, 8.84.

2,2,2-Trifluoro-*N*-[(1*S*)-1-methyl-2-oxo-2-(1*H*-pyrrol-2-yl)ethyl]acetamide (2b): colorless needles; yield, 78%;. mp 142–143 °C; $[\alpha]^{23}_D = -2.0$ (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ

1.57 (d, J = 6.9 Hz, 3H), 5.28 (quintet, J = 6.9 Hz, 1H), 6.38 (quintet, J = 1.8 Hz, 1H), 7.07 (s, 1H), 7.16 (s, 1H), 7.58 (br s, 1H), 9.80 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.6, 50.8, 112.0, 115.9 (q, J = 285.2 Hz), 118.5, 127.0, 128.4, 156.7 (q, J = 37.6 Hz), 186.5. Anal. Calcd for $C_9H_9F_3N_2O_2$: C, 46.16; H, 3.87; N, 11.96. Found: C, 46.39; H, 3.77; N, 11.80.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-1-benzyl-2-oxo-2-(1*H*-pyrrol-2-yl)ethyl]carbamate (2c): colorless needles; yield, 72%; mp 186−187 °C; $[\alpha]^{23}_D$ = +16.7 (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 3.09 (dd, J = 13.8, 6.0 Hz, 1H), 3.26 (dd, J = 13.5, 6.0 Hz, 1H), 4.19 (t, J = 6.9 Hz, 1H), 4.29 (t, J = 6.9 Hz, 1H), 4.44 (dd, J = 10.2, 7.2 Hz, 1H), 5.29 (dd, J = 14.1, 6.6 Hz, 1H), 5.69 (d, J = 8.4 Hz, 1H), 6.29 (d, J = 3.3 Hz, 1H), 6.99 (s, 1H), 7.05 (d, J = 2.4 Hz, 2H), 7.20 (d, J = 6.3 Hz, 3H), 7.29 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.56 (t, J = 4.5 Hz, 2H), 7.76 (d, J = 7.5 Hz, 2H), 9.60 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 40.4., 47.4, 56.6, 67.1, 111.6, 118.0, 120.2, 125.4, 126.1, 127.1, 127.2, 127.9, 128.6, 129.7, 136.2, 141.5, 144.0, 144.1, 155.8, 187.2. Anal. Calcd for $C_{28}H_{24}N_2O_3$: C, 77.04; H, 5.54; N, 6.42. Found: C, 76.79; H, 5.70; N, 6.29.

9*H*-Fluoren-9-ylmethyl-*N*-[(1*S*)-1-(1*H*-indol-3-ylmethyl)-2-oxo-2-(1*H*-pyrrol-2-yl)ethyl] carbamate (2d): white plates; yield, 52%; mp 196−197 °C; $[\alpha]^{23}_D$ = +32.5 (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 3.04 (dd, J = 14.7, 9.3 Hz, 1H), 3.22 (dd, J = 14.7, 5.1 Hz, 1H), 4.18−4.21 (m, 3H), 4.97−5.04 (m, 1H), 6.21−6.23 (m, 1H), 6.99 (t, J = 7.2 Hz, 1H), 7.04−7.09 (m, 2H), 7.13 (s, 1H), 7.19 (d, J = 2.1 Hz, 1H), 7.25−7.43 (m, 5H), 7.57 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 6.6 Hz, 2H), 7.87 (d, J = 7.5 Hz, 2H), 7.92 (s, 1H), 10.85 (s, 1H), 11.90 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.7, 46.6, 56.4, 65.7, 110.0, 110.2, 111.4, 116.8, 118.1, 118.4, 120.1, 120.9, 123.8, 125.3, 126.1, 127.0, 127.2, 127.6, 129.9, 136.1, 140.7, 143.8, 155.7, 188.2. Anal. Calcd for $C_{30}H_{25}N_3O_3$: C, 75.77; H, 5.30; N, 8.84. Found: C, 75.55; H, 5.18; N, 8.76.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-3-(methylsulfanyl)-1-(1*H*-pyrrol-2-ylcarbonyl) propyl]carbamate (2e): colorless plates; yield, 66%; mp 163−164 °C; $[\alpha]^{23}_D$ = −5.9 (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 1.92−2.01 (m, 1H), 2.06 (s, 3H), 2.14−2.26 (m, 1H), 2.51−2.60 (m, 2H), 4.21 (t, J = 6.9 Hz, 1H), 4.35−4.56 (m, 2H), 5.21 (dd, J = 9.3, 8.1 Hz, 1H), 5.83 (d, J = 8.4 Hz, 1H), 6.32 (d, J = 3.3 Hz, 1H), 7.08 (s, 1H), 7.12 (s, 1H), 7.28 (t, J = 7.2 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.59 (d, J = 7.2 Hz, 2H), 7.75 (d, J = 7.8 Hz, 2H), 9.80 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 15.6, 30.2, 34.2, 47.2, 54.6, 67.0, 111.5, 118.2, 120.0, 125.1, 126.3, 127.1, 127.7, 129.4, 141.3, 143.9, 156.1, 187.7. Anal. Calcd for $C_{24}H_{24}N_2O_3S$: C, 68.55; H, 5.75; N, 6.66. Found: C, 68.26; H, 5.85; N, 6.74.

***N*-[(1*S*)-1-Benzyl-2-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoethyl]-2,2,2-trifluoroacetamide (3a):** colorless needles; yield, 78%; mp 109−110 °C; $[\alpha]^{23}_D$ = +43.6 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.17 (dd, J = 13.8, 4.8 Hz, 1H), 3.31 (dd, J = 13.8, 6.6 Hz, 1H), 3.68 (s, 3H), 5.32 (dd, J = 12.6, 6.0 Hz, 1H), 6.62 (d, J = 1.5 Hz, 2H), 7.00−7.03 (m, 2H), 7.19−7.26 (m, 4H), 7.36 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 36.8, 39.3, 56.4, 109.9, 115.9 (q, J = 287.3 Hz), 122.3, 124.3, 127.3, 128.3, 128.5, 129.7, 135.4, 156.5 (q, J = 37.2 Hz), 190.1. Anal. Calcd for $C_{16}H_{15}F_3N_2O_2$: C, 59.26; H, 4.66; N, 8.64. Found: C, 59.17; H, 4.62; N, 8.47.

2,2,2-Trifluoro-*N*-[(1*S*)-1-methyl-2-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoethyl]-acetamide (3b): colorless needles; yield, 75%; mp 120−121 °C; $[\alpha]^{23}_D$ = −7.4 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.53 (d, J = 7.2 Hz, 3H), 3.73 (s, 3H), 5.13 (quintet, J = 6.3 Hz, 1H), 6.61−6.60 (m, 2H), 7.40 (t, J = 1.8 Hz, 1H), 7.73 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.9, 36.7, 51.4, 109.7, 115.7 (q, J = 286.4 Hz), 121.2, 124.1, 127.8, 156.2 (q, J = 37.0 Hz), 191.3. Anal. Calcd for $C_{10}H_{11}F_3N_2O_2$: C, 48.39; H, 4.47; N, 11.29. Found: C, 48.70; H, 4.38; N, 11.15.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-1-benzyl-2-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoethyl]carbamate (3c): colorless needles; yield, 56%; mp 172−173 °C; $[\alpha]^{23}_D$ = +9.9 (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 3.05 (dd, J = 13.8, 6.3 Hz, 1H), 3.25 (dd, J = 13.8, 5.7 Hz, 1H), 3.89 (s, 3H), 4.20 (t, J = 7.2 Hz, 1H), 4.29 (dd, J = 10.5, 7.5 Hz, 1H), 4.43 (dd, J = 10.2, 7.2 Hz, 1H), 5.31(q, J = 6.3 Hz, 1H), 5.68 (d, J = 8.4 Hz, 1H), 6.15 (q, J = 2.7 Hz, 1H), 6.87 (s, 1H), 7.03−7.05 (m, 3H), 7.21−7.23 (m, 3H), 7.30 (t, J = 7.5 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.57 (t, J = 6.6 Hz, 2H), 7.76 (d, J = 7.2 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 37.7, 40.5, 47.2, 56.7, 66.9, 108.8, 120.0, 120.5, 125.2, 125.3, 126.9, 127.1, 127.7, 128.3, 129.5, 132.3, 136.3, 141.3, 144.0, 155.6, 187.5. Anal. Calcd for $C_{29}H_{26}N_2O_3$: C, 77.31; H, 5.82; N, 6.22. Found: C, 76.93; H, 5.76; N, 6.21.

9*H*-Fluoren-9-ylmethyl-*N*-[(1*S*)-1-(1*H*-indol-3-ylmethyl)-2-oxo-2-(1-methyl-1*H*-pyrrol-2-yl)ethyl]carbamate (3d): gray microcrystals; yield, 45%; mp 154−155 °C; $[\alpha]^{23}_D$ = +35.6 (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 3.28 (dd, J = 14.1, 5.1 Hz, 1H), 3.41 (dd, J = 14.7, 6.6 Hz, 1H), 3.56 (s, 3H), 4.20 (t, J = 7.2 Hz, 1H), 4.29−4.42 (m, 2H), 5.25 (q, J = 6.3 Hz, 1H), 5.84 (d, J = 8.1 Hz, 1H), 6.54 (d, J = 2.1 Hz, 1H), 6.60 (s, 1H), 6.86 (d, J = 1.8 Hz, 1H), 7.05−7.10 (m, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.8 Hz, 3H), 7.39 (t, J = 7.5 Hz, 2H), 7.56 (t, J = 7.5 Hz, 3H), 7.75 (d, J = 7.5 Hz, 2H), 8.00 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 30.1, 36.8, 47.4, 57.0, 67.1, 109.9, 111.2, 119.1, 119.8, 120.1 (2C), 122.2, 123.1, 123.9, 125.4, 125.5, 127.3, 127.8 (2C), 128.0, 136.2, 141.5, 144.2, 156.1, 193.0; HRMS calcd for $C_{31}H_{27}N_3O_3$ $(M + H)^+$ 490.2125, found 490.2151.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-1-[(1-methyl-1*H*-pyrrol-2-yl)carbonyl]-3-(methylsulfanyl)propyl]carbamate (3e): light yellow needles; yield, 60%; mp 109−110 °C; $[\alpha]^{23}_D$ = −17.3 (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 1.86−2.00 (m, 1H), 2.06 (s, 3H), 2.14−2.25 (m, 1H), 2.44−2.63 (m, 2H), 3.66 (s, 3H), 4.21 (t, J = 6.3 Hz, 1H), 4.37 (d, J = 6.9 Hz, 2H), 5.07−5.13 (m, 1H), 5.84 (d, J = 8.4 Hz, 1H), 6.59 (t, J = 2.4 Hz, 1H), 6.65 (s, 1H), 7.26−7.32 (m, 2H), 7.38 (t, J = 6.0 Hz, 3H), 7.60 (d, J = 7.2 Hz, 2H), 7.75 (d, J = 7.5 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 15.7, 30.3, 34.2, 36.9, 47.3, 55.6, 67.0, 110.0, 120.1, 122.8, 124.1, 125.3, 127.2, 127.8, 128.0, 141.4, 143.9, 156.2, 192.7. Anal. Calcd for $C_{25}H_{26}N_2O_3S$: C, 69.10; H, 6.03; N, 6.45. Found: C, 69.11; H, 5.98; N, 6.46.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-4-oxo-4-(1*H*-pyrrol-2-yl)-1-(1*H*-pyrrol-2-ylcarbonyl)butyl]carbamate (4): light violet microcrystals; yield, 35%; mp 140−141 °C; $[\alpha]^{23}_D$ = +12.2 (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 1.80−1.92 (m, 1H), 2.09−2.20 (m, 1H), 2.80−3.03 (m, 2H), 4.22−4.27 (m, 3H), 4.83 (quintet, J = 7.5 Hz, 1H), 6.20 (d, J = 17.1 Hz, 2H), 6.94 (s, 1H), 7.10 (d, J = 16.8 Hz, 2H), 7.29 (s, 1H), 7.34 (t, J = 7.5 Hz, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.73 (t, J = 6.9 Hz, 2H), 7.82 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 7.5 Hz, 2H), 11.86 (d, J = 9.6 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 27.2, 33.8, 46.6, 55.4, 65.6, 109.7, 109.9, 116.3, 116.9, 120.1, 125.3, 125.9, 127.1, 127.6, 129.6, 131.5, 140.7, 143.7, 143.9, 156.1, 188.4, 188.8. Anal. Calcd for $C_{28}H_{25}N_3O_4$: C, 71.93; H, 5.39; N, 8.99. Found: C, 72.11; H, 5.41; N, 8.91.

***N*-[(1*S*)-1-Benzyl-2-(1*H*-indol-3-yl)-2-oxoethyl]-2,2,2-trifluoroacetamide (5a):** gray needles; yield, 85%; mp 198−199 °C; $[\alpha]^{23}_D$ = +22.0 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.22 (dd, J = 13.5, 5.1 Hz, 1H), 3.31 (dd, J = 13.5, 6.3 Hz, 1H), 5.47 (dd, J = 12.9, 7.2 Hz, 1H), 7.05 (t, J = 3.6 Hz, 2H), 7.20−7.22 (m, 3H), 7.33−7.44 (m, 3H), 7.55 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 3.0 Hz, 1H), 8.33−8.35 (m, 1H), 8.83 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 39.8, 56.4, 111.7, 115.2, 115.7 (q, J = 285.8 Hz), 122.2, 123.5, 124.5, 125.3, 127.3, 128.5, 129.5, 132.5, 135.2, 136.2, 156.6 (q, J = 37.0 Hz), 190.1. Anal. Calcd for $C_{13}H_{11}F_3N_2O_2$: C, 63.33; H, 4.20; N, 7.77. Found: C, 62.98; H, 4.08; N, 7.75.

2,2,2-Trifluoro-*N*-[(1*S*)-2-(1*H*-indol-3-yl)-1-methyl-2-oxoethyl]acetamide (5b): colorless microcrystals; yield, 79%; mp 189−190 °C; $[\alpha]^{23}_D$ = −7.0 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.61 (d, J = 6.9 Hz, 3H), 5.31 (quintet, J = 6.9 Hz, 1H), 7.23 (br s, 1H), 7.33−7.45 (m, 2H), 7.44−7.48 (m, 1H), 7.97 (d, J = 3.3 Hz, 1H), 8.35 (t, J = 5.4 Hz, 1H), 8.89 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.4, 51.5, 111.7, 114.2, 115.7 (q, J = 286.4 Hz), 122.3, 123.5, 124.5, 125.5, 132.0, 136.4, 156.5 (q, J = 37.6 Hz), 191.5. Anal. Calcd for $C_{13}H_{11}F_3N_2O_2$: C, 54.93; H, 3.90; N, 9.86. Found: C, 54.98; H, 3.91; N, 9.85.

9*H*-Fluoren-9-ylmethyl-*N*-[(1*S*)-1-benzyl-2-oxo-2-(1*H*-indol-3-yl)ethyl]carbamate (5c): yellow flakes; yield, 63%; mp 101−102 °C; $[\alpha]^{23}_D = -18.3$ (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 3.08 (dd, J = 13.8, 6.0 Hz, 1H), 3.23 (dd, J = 13.8, 6.3 Hz, 1H), 4.11−4.17 (m, 1H), 4.24−4.30 (m, 1H), 4.38−4.44 (m, 1H), 5.25 (dd, J = 14.7, 6.3 Hz 1H), 6.00 (d, J = 7.1 Hz, 1H), 7.06−7.39 (m, 14 H), 7.52 (t, J = 7.2 Hz, 2H), 7.73 (d, J = 7.2 Hz, 1H), 8.34 (d, J = 8.4 Hz, 1H), 9.30 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 40.3, 47.3, 57.8, 67.3, 119.3, 115.6, 120.1, 122.3, 123.2, 124.2, 125.3, 125.7, 127.0, 127.3, 127.9, 128.6, 129.7, 132.8, 136.5, 136.6, 141.4, 143.9, 156.2, 192.8. Anal. Calcd for $C_{32}H_{26}N_2O_3$: C, 78.99; H, 5.39; N, 5.76. Found: C, 78.78; H, 5.65; N, 6.20.

9*H*-Fluoren-9-ylmethyl-*N*-[(1*S*)-2-(1*H*-indol-3-yl)-1-(1*H*-indol-3-ylmethyl)-2-oxoethyl]carbamate (5d): To a solution of Fmoc-Trp-Bt (**1d**) (1.06 g, 2 mmol) and *N*-TMS-indole[13] (0.58 g, 3 mmol) in CH_2Cl_2 (30 mL) was added $TiCl_4$ (1 M CH_2Cl_2 solution) (4 mL, 4 mmol) was added quickly at 0 °C. The reaction mixture was stirred for 15 min at the temperature and quenched with MeOH (2 mL). The solution was directly subjected to column chromatography (EtOAc/hexanes = 1:2) to give the desired product **5d** in 0.9 g (87%), which was further recrystallized in $CHCl_3$/hexanes to provide brown microcrystals: yield, 87%; mp 194−195 °C; $[\alpha]^{23}_D = +28.3$ (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 3.12 (dd, J = 14.6, 8.7 Hz, 1H), 3.29 (dd, J = 14.7, 5.5 Hz, 1H), 4.20 (s, 3H), 5.16 (dd, J = 14.0, 8.2 Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H), 7.07 (t, J = 7.0 Hz, 1H), 7.21−7.51 (m, 9H), 7.62−7.68 (m, 3H), 7.86 (d, J = 7.4 Hz, 2H), 7.96 (d, J = 8.3 Hz, 1H), 8.24−8.33 (m, 2H), 10.8 (s, 1H), 12.0 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.7, 46.6, 56.9, 65.7, 110.4, 111.3, 112.2, 114.4, 118.3, 120.0, 120.8, 121.4, 121.9, 123.0, 123.7, 125.3, 125.8, 127.0, 127.3, 127.6, 133.8, 136.1, 136.5, 140.6, 143.8, 155.8, 193.7. Anal. Calcd for $C_{34}H_{27}N_3O_3$: C, 77.70; H, 5.18; N, 7.99. Found: C, 77.47; H, 5.28; N, 7.90.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-1-(1*H*-indol-3-ylcarbonyl)-3-(methylsulfanyl)-propyl]carbamate (5e): colorless plates; yield, 83%; mp 128−129 °C; $[\alpha]^{23}_D = -51.2$ (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 1.90−2.01 (m, 2H), 2.05 (s, 3H), 2.54−2.62 (m, 2H), 4.20−4.30 (m, 3H), 4.96−5.03 (m, 1H), 7.22−7.28 (m, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.40 (td, J = 6.9, 2.1 Hz, 2H), 7.50−7.52 (m, 1H), 7.23 (t, J = 6.9 Hz, 2H), 7.85 (s, 1H), 7.89 (d, J = 7.5 Hz, 2H), 8.22 (d, J = 6.6 Hz, 1H), 8.42 (d, J = 3.0 Hz, 1H), 12.05 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.6, 30.1, 31.9, 46.7, 55.7, 65.6, 112.2, 113.9, 120.1, 121.3, 121.9, 123.0, 125.3, 125.7, 127.0, 127.6, 133.8, 136.5, 140.7, 143.8, 156.0, 193.6 Anal. Calcd for $C_{28}H_{26}N_2O_3S$: C, 71.46; H, 5.57; N, 5.95. Found: C, 71.16; H, 5.89; N, 5.55.

***N*-[(1*S*)-1-Benzyl-2-(1-methyl-1*H*-indol-3-yl)-2-oxoethyl]-2,2,2-trifluoroacetamide (6a):** colorless needles; yield, 62%; mp 176−177 °C; $[\alpha]^{23}_D = +32.9$ (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.24 (d, J = 2.1 Hz, 1H), 3.26 (d, J = 3.3 Hz, 1H), 3.75 (s, 3H), 5.43 (q, J = 6.3 Hz, 1H), 7.07−7.10 (m, 2H), 7.19−7.22 (m, 3H), 7.34−7.38 (m, 3H), 7.51 (s, 1H), 7.62 (d, J = 7.5 Hz, 1H), 8.32−8.35 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 33.5, 39.8, 56.4, 109.9, 115.4 (q, J = 285.7 Hz), 113.4, 122.3, 123.3, 124.0, 126.2, 127.1, 128.4, 129.6, 135.6., 136.9, 137.5, 156.5 (q, J = 37.0 Hz), 189.5. Anal. Calcd for $C_{20}H_{17}F_3N_2O_2$: C, 64.17; H, 4.58; N, 7.48. Found: C, 64.36; H, 4.41; N, 7.46.

2,2,2-Trifluoro-*N*-[(1*S*)-1-methyl-2-(1-methyl-1*H*-indol-3-yl)-2-oxoethyl] acetamide (6b): colorless needles; yield, 75%; mp 161−162 °C; $[\alpha]^{23}_D = -84.2$ (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.60 (d, J = 6.9 Hz, 3H), 3.90 (s, 3H), 5.29 (quintet, J = 6.9 Hz, 1H), 7.35−7.40 (m, 3H), 7.77 (d, J = 5.4 Hz, 1H), 7.88 (s, 1H), 8.30−8.34 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.7, 34.1, 51.6, 110.3, 112.7, 116.0 (q, J = 287.8 Hz), 122.6, 123.6, 124.3, 126.5, 136.5, 137.9, 156.7 (q, J = 37.8 Hz), 191.1. Anal. Calcd for $C_{14}H_{13}F_3N_2O_2$: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.44; H, 4.33; N, 9.31.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-1-benzyl-2-(1-methyl-1*H*-indol-3-yl)-2-oxoethyl] carbamate (6c): colorless needles; yield, 40%; mp 153−154 °C; $[\alpha]^{23}_D = +13.1$ (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 3.16 (dd, J = 13.5, 5.7 Hz, 1H), 3.23 (dd, J = 13.8, 7.2 Hz, 1H), 3.74 (s, 3H), 4.20 (t, J = 7.2 Hz, 1H), 4.30 (dd, J = 10.2, 7.2 Hz, 1H), 4.42 (dd, J = 10.2, 7.2 Hz, 1H), 5.25 (dd, J = 14.4, 6.9 Hz, 1H), 5.97 (d, J = 8.4 Hz, 1H), 7.11−7.44 (m, 12 H), 7.53 (s, 1H), 7.57 (t, J = 5.1 Hz, 2H), 7.75 (d, J = 7.2 Hz, 1H), 8.37−8.39 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 33.6, 40.5, 47.2, 57.7, 67.0, 109.8, 114.2, 120.0, 120.9, 122.6, 123.1, 123.8, 125.2, 125.3, 126.7, 127.1, 127.7, 128.3, 129.7, 136.8, 137.5, 141.3, 143.9, 155.8, 191.9. Anal. Calcd for $C_{33}H_{28}N_2O_3$: C, 79.18; H, 5.64; N, 5.60. Found: C, 78.98; H, 5.81; N, 5.79.

9*H*-Fluoren-9-ylmethyl-*N*-[(1*S*)-1-(1*H*-indol-3-ylmethyl)-2-oxo-2-(1-methyl-1*H*-indol-2-yl)ethyl]carbamate (6d): colorless microcrystals; yield, 45%; mp 191−192 °C; $[\alpha]^{23}_D = +32.9$ (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 3.11 (dd, J = 14.7, 9.0 Hz, 1H), 3.27 (dd, J = 14.4, 5.4 Hz, 1H), 3.83 (s, 3H), 4.18−4.23 (m, 3H), 5.13 (dd, J = 14.1, 8.4 Hz, 1H), 6.99 (t, J = 7.2 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 7.21−7.42 (m, 8H), 7.54 (d, J = 7.2 Hz, 1H), 7.66 (t, J = 6.6 Hz, 3H), 7.86−7.92 (m, 3H), 8.26 (d, J = 7.2 Hz, 1H), 8.32 (s, 1H), 10.84 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.8, 33.2, 46.6, 57.0, 65.7, 110.4, 110.6, 111.3, 113.2, 118.3, 120.0, 120.8, 121.5, 122.2, 123.0, 123.6. 125.3 (2C), 126.2, 127.0, 127.3, 127.6, 136.0, 137.2, 137.4, 140.6, 143.8, 155.8, 193.3. Anal. Calcd for $C_{35}H_{29}N_3O_3$: C, 77.90; H, 5.42; N, 7.79. Found: C, 77.70; H, 5.48; N, 7.61.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-1-[(1-methyl-1*H*-indol-3-yl)carbonyl]-3-(methylsulfanyl)propyl] carbamate (6e): colorless microcrystals; yield, 90%; mp 140−141 °C; $[\alpha]^{23}_D = -41.5$ (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 1.95−2.05 (m, 1H), 2.08 (s, 3H), 2.19−2.29 (m, 1H), 2.49−2.69 (m, 2H), 3.85 (s, 3H), 4.22 (t, J = 7.2 Hz, 1H), 4.34−4.44 (m, 2H), 5.27 (dd, J = 10.2, 8.1 Hz, 1H), 5.94 (d, J = 6.9 Hz, 1H), 7.30 (t, J = 7.8 Hz, 2H), 7.34−7.41 (m, 5H), 7.59 (t, J = 7.2 Hz, 2H), 7.75 (d, J = 7.2 Hz, 2H), 8.00 (s, 1H), 8.39 (d, J = 6.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 15.8, 30.5, 34.0, 34.3, 47.4, 55.3, 61.2, 110.1, 114.0, 120.2, 122.7, 123.3, 124.1, 125.3, 126.7, 127.2, 127.9, 136.9, 137.8, 141.5, 144.0, 156.4, 192.6. Anal. Calcd for $C_{29}H_{28}N_2O_3S$: C, 71.87; H, 5.82; N, 5.78. Found: C, 71.48; H, 5.76; N, 6.31.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-1-methyl-2-(1-methyl-1*H*-indol-3-yl)-2-oxo-ethyl]carbamate (6f): colorless needles; mp 144−145 °C; yield, 85%; $[\alpha]^{23}_D = -60.1$ (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 1.52 (d, J = 6.9 Hz, 3H), 3.85 (s, 3H), 4.23 (t, J = 7.2 Hz, 1H), 4.38 (d, J = 7.2 Hz, 2H), 5.10 (quintet, J = 7.2 Hz, 1H), 6.00 (d, J = 4.8 Hz, 1H), 7.27−7.42 (m, 7H), 7.61 (d, J = 7.2 Hz, 2H), 7.60 (d, J = 7.5 Hz, 2H), 7.86 (s, 1H), 8.34−8.39 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 21.1, 33.9, 47.4, 52.4, 67.1, 110.0, 113.5, 120.2, 122.7, 123.3, 124.0, 125.4, 126.7, 127.3, 127.9, 136.3, 137.8, 141.5, 144.1, 155.9, 193.5. Anal. Calcd for $C_{27}H_{24}N_2O_3$: C, 76.40; H, 5.70; N, 6.60. Found: C, 76.52; H, 5.71; N, 6.61.

***N*-[(1*R*,*S*)-1-Benzyl-2-(1-methyl-1*H*-indol-3-yl)-2-oxoethyl]-2,2,2-trifluoroacetamide (6j):** colorless needles; yield, 64%; mp 170−172 °C; ^{1}H NMR and ^{13}C NMR are the same as for *N*-[(1*S*)-1-benzyl-2-(1-methyl-1*H*-indol-3-yl)-2-oxoethyl]-2,2,2-trifluoroacetamide (**6a**).

Procedure for *C*-Acylations of Benzene. $AlCl_3$ (0.4 g, 3 mmol) was added to **1d** (2 mmol) dissolved in benzene (20 mL) at 0 °C. After removing the ice-bath, the reaction mixture was stirred at room temperature for 3 h and then quenched by MeOH (1 mL). Removal of solvent under reduced pressure gave the crude product, which was directly purified by column chromatography (EtOAc/hexane = 1:10) to give product **7** in 63% yield.

***N*-[(1*S*)-1-Benzyl-2-oxo-2-phenylethyl]-2,2,2-trifluoroacetamide (7):** colorless needles; mp 64−65 °C (lit.[7c] mp 62−63 °C); yield, 63%; ^{1}H NMR ($CDCl_3$) δ 1.57 (d, J = 7.2 Hz, 3H), 5.13 (quintet, J = 7.2 Hz, 1H), 6.70 (br s, 1H), 7.29−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.2, 50.0, 116.0 (q, J = 287.3 Hz), 126.4, 128.3, 129.2, 141.1, 156.6 (q, J = 37.0 Hz), 195.1.

Procedure for Preparation of Amines 8, 10, and 14 by Cleavage of Fmoc Protecting Group. Carbamate **6f** or **6g** (0.42 g, 1 mmol) was dissolved in morpholine (10 mL, 10

mmol). After 30 min of stirring, 300 mL of water was added. After the mixture was extracted with hexane until the TLC showed the disappearance of the first spot, indicating the elimination of 9-methylene-9*H*-fluorene, the water phase was further extracted with EtOAc. Then the EtOAc organic phase was dried with $MgSO_4$, and the evaporation of solvent gave crude product (2*S*)-2-amino-1-(1-methyl-1*H*-indol-3-yl)-1-propanone (**8**) [or (2*R*)-2-amino-1-(1-methyl-1*H*-indol-3-yl)-1-propanone (**10**) from **6g**] in 75% yield (75% from **10** as well), which can be used for the next step without further purification. The cleavage of 9*H*-fluoren-9-ylmethyl *N*-[(2*S*)-3-oxo-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl]carbamate (**13**) following the same procedure gave racemic 2-amino-1,2-dihydrocyclopenta-[*b*]indol-3(4*H*)-one (**14**) in 71% yield. We used these three compounds as crude staring materials for the next coupling reaction without purification. Therefore, we do not provide their characterization.

Procedure for the Preparation of Diastereomers 9 and 11. Amine **8** (or **10**) 0.21 g (1 mmol) was stirred with Tfa-L-Phe-Bt (**1a**) (0.36 g, 1 mmol) in CH_2Cl_2 (20 mL) at 20 °C for 1 h. Evaporation of solvent gave crude product, which can be purified by column chromatography (EtOAc/hexane = 1:6).

(2*S*)-*N*-[(1*S*)-1-Methyl-2-(1-methyl-1*H*-indol-3-yl)-2-oxoethyl]-3-phenyl-2-[(2,2,2-trifluoroacetyl) amino]propanamide (9): colorless needles; mp 212−214 °C; yield, 80%; $[\alpha]^{23}_D$ = −12.1 (*c* 1.6, DMF); ^{1}H NMR ($CDCl_3$) δ 1.50 (d, *J* = 6.9 Hz, 3H), 3.14 (d, *J* = 6.9 Hz, 2H), 3.87 (s, 3H), 5.01 (q, *J* = 7.2 Hz, 1H), 5.37 (quintet, *J* = 7.2 Hz, 1H), 7.15 (s, 5H), 7.33−7.40 (m, 3H), 7.49 (d, *J* = 6.9 Hz, 1H), 8.04 (s, 1H), 8.34−8.37 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 33.6, 38.8, 51.0, 54.7, 109.9, 112.9, 115.8 (q, *J* = 285.7 Hz), 122.5, 123.2, 123.9, 126.5, 127.3, 128.6, 129.2, 135.3, 136.9, 137.7, 156.7 (q, *J* = 37.6 Hz), 168.8, 192.4. Anal. Calcd for $C_{23}H_{22}F_3N_3O_3$: C, 62.02; H, 4.98; N, 9.43. Found: C, 61.95; H, 4.91; N, 9.34.

(2*S*)-*N*-[(1*R*)-1-Methyl-2-(1-methyl-1*H*-indol-3-yl)-2-oxoethyl]-3-phenyl-2-[(2,2,2-trifluoroacetyl) amino]propanamide (11): colorless needles; mp 212−214 °C; yield, 80%; $[\alpha]^{23}_D$ = −14.0; ^{1}H NMR ($CDCl_3$) δ 1.39 (d, *J* = 6.6 Hz, 3H), 3.24 (d, *J* = 7.2 Hz, 2H), 3.75 (s, 3H), 5.24 (q, *J* = 7.2 Hz, 1H), 5.38 (quintet, *J* = 7.2 Hz, 1H), 7.01 (t, *J* = 7.2 Hz, 1H), 7.22−7.34 (m, 8H), 7.86 (d, *J* = 6.9 Hz, 1H), 7.95 (s, 1H), 8.32−8.34 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.7, 33.6, 39.6, 51.5, 54.7, 110.1, 112.9, 115.8 (q, *J* = 285.7 Hz), 122.5, 123.2, 123.9, 126.7, 127.2, 128.8, 129.3, 136.0, 137.8, 156.7 (q, *J* = 37.6, Hz), 169.4, 192.9. Anal. Calcd for $C_{23}H_{22}F_3N_3O_3$: C, 62.02; H, 4.98; N, 9.43. Found: C, 61.95; H, 4.91; N, 9.34.

Procedure for the Intramolecular Acylations of 1a and 1d. $AlCl_3$ (0.4 g, 3 mmol) was added to **1a** (or **1d**) (2 mmol) dissolved in anhydrous CH_2Cl_2 (20 mL) at 0 °C. After removing the ice-bath, the reaction mixture was stirred at room temperature for 3 h and then quenched by MeOH (1 mL). Removal of solvent under reduced pressure gave the crude product, which was purified by column chromatography (EtOAc/hexanes = 6:1) to give the intramolecular acylated products **12** (**13** from **1d**). They were further recrystallized from $CHCl_3$/hexanes for CHN analysis.

2,2,2-Trifluoro-*N*-[(2*S*)-1-oxo-2,3-dihydro-1*H*-inden-2-yl]acetamide (12): white flakes; yield, 57%; mp 207−208 °C; $[\alpha]^{23}_D$ = −3.2 (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 3.05 (dd, *J* = 16.8, 5.4 Hz, 1H), 3.55 (dd, *J* = 16.8, 8.4 Hz, 1H), 4.61−4.68 (m, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.69−7.76 (m, 2H), 9.96 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) 32.1, 54.6, 115.8 (q, *J* = 286.9 Hz), 123.5, 126.8, 127.8, 134.6, 135.6, 151.4, 156.3 (q, *J* = 36.5 Hz), 201.2. Anal. Calcd for $C_{11}H_8F_3NO_2$: C, 54.33; H, 3.32; N, 5.76. Found: C, 54.31; H, 3.24; N, 5.70.

9*H*-Fluoren-9-ylmethyl *N*-[(2*S*)-3-oxo-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-yl]carbamate (13): white flakes; yield, 62%; 235 °C (dec.); $[\alpha]^{23}_D$ = −39.0 (*c* 1.6, DMF); ^{1}H NMR (DMSO-d_6) δ 2.88 (dd, *J* = 16.2, 3.0 Hz, 1H), 3.51 (dd, *J* = 16.2, 6.9 Hz, 1H), 4.24−4.38 (m, 3H), 4.53 (quintet, *J* = 6.9 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.33−7.48 (m, 6H), 7.72 (d, *J* = 7.5 Hz, 4H), 7.90−8.01 (m, 2H), 11.76 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 28.1, 46.7, 59.6, 65.6, 113.6, 120.1, 121.4, 122.8, 127.8, 125.9, 126.9, 127.1, 127.6, 136.6, 140.7, 140.9, 143.4, 143.8, 155.9, 191.3. Anal. Calcd for $C_{26}H_{20}N_2O_3$: C, 76.45; H, 4.94; N, 6.86. Found: C, 76.24; H, 4.88; N, 6.72.

Procedure for the Preparation of Diastereomers 15 (16 and 17). Amine **14** (0.17 g, 1 mmol) was stirred with Tfa-DL-Ala-Bt (**1i**) or Tfa-L-Ala-Bt (**1b**) (0.28 g, 1 mmol) in CH_2Cl_2 (20 mL) at 20 °C for 1 h. Evaporation of solvent gave the corresponding crude product which can be purified by column chromatography (EtOAc/hexanes = 1:3).

***N*-(1-Oxo-1,2,3,8-tetrahydrocyclopenta[a]inden-2-yl)-2-[(2,2,2-trifluoroacetyl)amino] propanamide (15):** white plates; yield, 52%; mp 257−258 °C; ^{1}H NMR (DMSO-d_6) (diastereomeric mixture) δ 1.49 (d, *J* = 7.0 Hz, 3H), 1.50 (d, *J* = 7.0 Hz, 3H), 2.93−3.03 (m, 2H), 3.12 (br s, 2H), 3.57−3.66 (m, 2H), 4.58−4.79 (m, 2H), 4.76−4.92 (m, 2H), 7.16 (t, *J* = 6.9 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 8.01−8.08 (m, 2H), 8.58 (br s, 2H), 10.8 (s, 2H); ^{13}C NMR (DMSO-d_6) (diastereomeric mixture) δ17.4, 17.5, 28.4, 28.5, 49.3 (2C), 59.0, 59.3, 113.6, 116.2 (q, *J* = 285.2 Hz), 120.5, 120.6, 121.5, 123.5, 127.2 (2C), 136.8, 136.9, 143.9(2C), 156.4 (q, *J* = 40.0 Hz), 170.9, 190.0, 190.1; HRMS calcd for $C_{17}H_{15}F_3N_2O_3$ $(M + 2H)^+$ 354.1191, found 354.1185.

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