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# α-Amido sulfones from natural α-amino acids and their reaction with carbon nucleophiles

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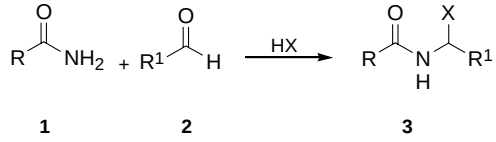
**Abstract**—Amides obtained from *N*-carbamoyl α-amino acids react with aldehydes in the presence of benzenesulfinic acid to give α-amido sulfones in good yield. These derivatives act as equivalents of *N*-acylimines in the reaction with nucleophiles leading to the corresponding addition products. The utilization of the lithium enolate of alkyl acetates as a nucleophile allows the preparation of α,β-dipeptides, while a two-step procedure involving nitromethylation and Nef conversion leads to the synthesis of α,α-dipeptides.


## 1. Introduction

α-Amino acids contain a well-known structural unit, which is present in a plethora of important biologically active compounds. Furthermore, natural α-amino acids represent a valuable and cheap source of enantiomerically pure compounds suitable for diastereoselective syntheses.[1] Recently proline and other peptide derivatives have been successfully employed as organocatalysts in a number of processes devoted to the synthesis of enantiomerically enriched compounds.[2] The carboxylic group in α-amino acids offers a number of synthetic opportunities of linkage with other organic frameworks such as amino derivatives giving *N*-substituted amides and peptides. A complementary approach consists of the conversion of the carboxylic group into an amido group that can be used as substrate in different coupling processes leading to a functional implementation of the original α-amino acid framework. Coupling reactions with diazoesters represent an effective procedure for the synthesis of peptides and oxazole derivatives.[3] Optically active α-amino amides are known to react with glyoxalate esters giving α-hydroxy *N*-acylamino derivatives that, after acetylation, are converted into biologically active compounds.[4] Condensation of *N*-unsubstituted amides **1** with aldehydes **2** in the presence of a nucleophile HX provides a general and straightforward entry to α-substituted *N*-acyl-amino derivatives **3** (Scheme 1).




**1** **2** **3**

**Scheme 1.**

Compounds **3** can be considered as stable precursors of reactive *N*-acylimines that are obtained by elimination of HX from **3** under basic conditions. *N*-Acylimines are strong electrophiles that quickly react with a large variety of nucleophilic reagents giving the corresponding addition products.[5] The utilization of α-amino acid amides in the synthesis of compounds **3** has been exploited several years ago by Katritzy et al. who prepared a number of those derivatives using benzotriazole as nucleophilic reagent.[6]

## 2. Results and discussion

In this paper, we report the synthesis of α-amidoalkylphenyl sulfones from optically active α-amino acid amides and their utilization as *N*-acylimino equivalents in the reaction with different nucleophiles.[7] Condensation of *N*-protected amino acid amides **4**[8] with aldehydes **5** in the presence of benzenesulfinic acid affords the corresponding sulfones **6** in good yield (Scheme 2, Table 1).

Contrary to what was observed in the synthesis of α-amido sulfones from chiral aldehydes that usually occurs with high *syn* diastereoselectivity, reaction of amides **4** gives rise to an almost equimolar mixture of diastereomers in sulfones **6**.[9] Grignard reagents are particularly effective in promoting

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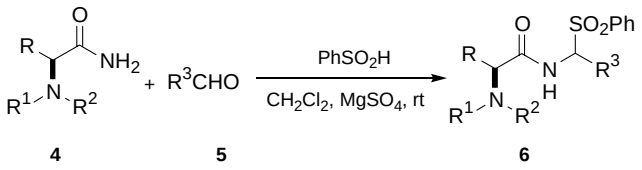



| 4 | R | $R^1$ | $R^2$ |
|---|---|---|---|
| **a** | $PhCH_2$ | H | Boc |
| **b** | $PhCH_2$ | H | Cbz |
| **c** | $PhCH_2$ | Phth | |
| **d** | $Me_2CH$ | H | Boc |
| **e** | Ph | H | Boc |
| **f** | $-(CH_2)_3-$ | | Boc |

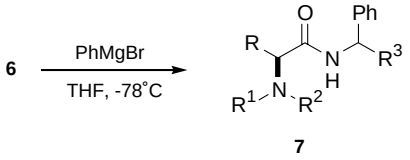
**Scheme 2.**

**Table 1**. Synthesis of α-amido sulfones **6** from α-amino acid amides **4**

| Entry | Amide **4** | Aldehyde **5**, $R^3$ | Sulfone **6** | Yield (%)[a] |
|---|---|---|---|---|
| 1 | **4a** | Et | **6a** | 85 |
| 2 | **4a** | $Ph(CH_2)_2$ | **6b** | 95 |
| 3 | **4a** | $Me_2CHCH_2$ | **6c** | 81 |
| 4 | **4a** | Me | **6d** | 93 |
| 5 | **4a** | Ph | **6e** | 81 |
| 6 | **4b** | Et | **6f** | 88 |
| 7 | **4b** | $Ph(CH_2)_2$ | **6g** | 89 |
| 8 | **4c** | Et | **6h** | 78 |
| 9 | **4d** | Et | **6i** | 91 |
| 10 | **4d** | $Ph(CH_2)_2$ | **6j** | 87 |
| 11 | **4d** | *c*-$C_6H_{11}$ | **6k** | 90 |
| 12 | **4d** | *n*-$C_9H_{19}$ | **6l** | 83 |
| 13 | **4e** | Et | **6m** | 92 |
| 14 | **4f** | Et | **6n** | 90 |

[a] Yields of pure, isolated products.

the tandem elimination–addition from α-amido sulfones and therefore, this class of nucleophilic reagents has been initially tested for the reaction with sulfones **6**.[10] Reaction of phenylmagnesium bromide with α-amido sulfones **6** leads to the corresponding adducts **7** in good yield but poor diastereoselectivity (dr=3:2) (Scheme 3, Table 2).



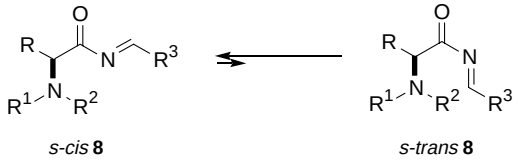

**Scheme 3.**

**Table 2**. Reaction of α-amido sulfones **6** with PhMgBr

| Entry | Sulfone **6** | Amide **7** | Yield (%)[a] |
|---|---|---|---|
| 1 | **6a** | **7a** | 85 |
| 2 | **6b** | **7b** | 90 |
| 3 | **6c** | **7c** | 77 |
| 4 | **6d** | **7d** | 84 |
| 5 | **6f** | **7e** | 88 |
| 6 | **6h** | **7f** | 71 |
| 7 | **6i** | **7g** | 91 |
| 8 | **6j** | **7h** | 82 |
| 9 | **6n** | **7i** | 87 |

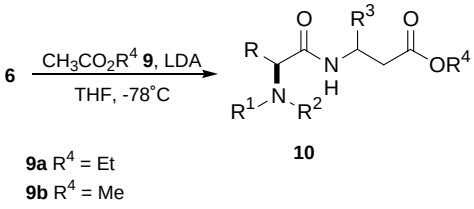
[a] Yields of pure, isolated products.

The disappointing stereochemical outcome of this reaction may be ascribed to the equilibrium in which rotamers **8** of the intermediate *N*-acylimine are involved (Scheme 4).




**Scheme 4.**

As demonstrated for the reaction of structurally related *N*-arylacyliminium ion derivatives with nucleophiles, high diastereoselectivities are obtained when the conformation of the imino intermediate is locked as in rotamer *s-trans*-**8**.[11] However, the preferred conformation in *N*-acylimines is usually *s-cis*-**8** owing to the lower steric repulsion between the imino and the chain frameworks. In conformation *s-cis*-**8** the electrophilic carbon is located too far from the stereogenic center to ensure a consistent diastereoselection in the subsequent nucleophilic addition.[12] Direct coupling of amino acids usually represents the most exploited procedure to prepare dipeptides and related compounds. Functionalization at the α-position in *N*-substituted glycine derivatives also provides a complementary approach to the synthesis of dipeptide systems.[13] Sulfones **6** are amenable to be used as valuable substrates for the preparation of α,β-dipeptides using a synthetic approach based on the direct addition of an ester enolate to the corresponding *N*-acylimine. The interest in α,β-dipeptides is justified by their potential biological activity, furthermore these compounds are key intermediates in the synthesis of some interesting molecular targets.[14] Thus, reaction of sulfones **6** with the lithium enolate of alkyl acetates **9** at −78 °C affords the corresponding adducts **10** in good yield (Scheme 5, Table 3).



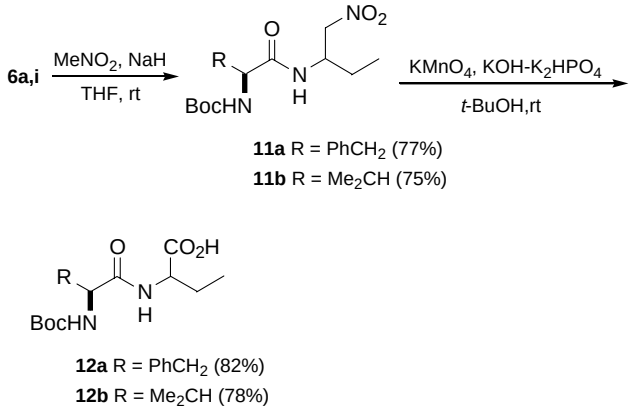

**Scheme 5.**

**Table 3**. Reaction of α-amido sulfones **6** with lithium enolate of alkyl acetates **9**

| Entry | Sulfone **6** | Acetate **2** | Dipeptide **10** | Yield (%)[a] |
|---|---|---|---|---|
| 1 | **6e** | **9a** | **10a** | 76 |
| 2 | **6f** | **9a** | **10b** | 72 |
| 3 | **6g** | **9b** | **10c** | 69 |
| 4 | **6h** | **9a** | **10d** | 72 |
| 5 | **6i** | **9a** | **10e** | 67 |
| 6 | **6k** | **9a** | **10f** | 75 |
| 7 | **6l** | **9b** | **10g** | 65 |
| 8 | **6m** | **9a** | **10h** | 78 |

[a] Yields of pure, isolated products.

Similarly to what was observed in the formation of derivatives **7**, the formation of α,β-dipeptides **10** occurs with poor diastereoselectivity. Attempt to use other metals such as zinc or titanium enolates did not provide any improvement in the efficiency of the process both in terms of chemical yield or in diastereoselectivity. Finally, we decided to apply our two-step procedure for the synthesis of α-amino acids to sulfones **6** with the aim to prepare α,α-dipeptides.[7h,15] Thus, representative sulfones **6a**,**i** have been made to react with nitromethane in the presence of sodium hydride to give the corresponding nitro derivatives **11** (Scheme 6). Nef conversion[16] of the nitromethyl group into a carboxylic group has been realized in oxidative conditions using $KMnO_4$ giving dipeptides **12**, once again as a diastereomeric mixture.




**Scheme 6.**

## 3. Conclusions

In conclusion, α-amido sulfones **6** can be prepared by reaction of *N*-carbamoyl amino acid amides with aldehydes in the presence of benzenesulfinic acid. These sulfones act as *N*-acylimino equivalents in the reaction with nucleophiles giving the corresponding adducts in good yield albeit with poor diastereoselectivity. Grignard reagents, lithium enolates of esters and sodium methanenitronate efficiently add to α-amido sulfones **6**. Among the products obtained with this procedure there are α,α- and α,β-dipeptide systems that are valuable synthetic intermediates and biologically active compounds.

## 4. Experimental

### 4.1. General

$^1$H NMR were recorded at 300 MHz on a Varian VXR300 in $CDCl_3$ as solvent. $^{13}$C NMR were recorded at 75 MHz in $CDCl_3$ as solvent. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments. IR spectra were recorded with a Perkin-Elmer Paragon 500 FT-IR. GLC analyses were performed on a Hewlett-Packard 5890 equipped with a capillary column of fused silica (0.32 mm×25 m), stationary phase SE54. THF was dried by heating over sodium wire then distilled. Dichloromethane was dried by heating over calcium hydride and then distilled. Ethyl acetate was dried by heating over $P_2O_5$ and then distilled All chemicals used are available commercially. *N*-Carbamoyl α-amino acid amides **4** were prepared as described.[8]

### 4.2. General procedure for the preparation of phenylsulfonyl derivatives 6

Amide **4** (6 mmol) was dissolved in dichloromethane (30 mL) and then benzenesulfinic acid (7.5 mmol), the appropriate aldehyde **5** (5 mmol) and anhydrous $MgSO_4$ (0.5 g) were sequentially added at room temperature. The mixture was stirred for 12 h at room temperature and then filtered over a short pad of Florisil. Removal of the solvent afforded the crude sulfone **6**, which was purified by column chromatography (7:3 hexanes/ethyl acetate).

**4.2.1. *tert*-Butyl *N*-(1-benzyl-2-oxo-2-[1-(phenylsulfonyl)propyl]aminoethyl)carbamate, 6a.** Yield 85%. White solid mp 85–87 °C. IR (cm$^{-1}$, KBr) 3400, 1690, 1370, 1145. $^1$H NMR diast. A. δ (ppm) 0.86 (t, 3H, $J$= 7.3 Hz); 1.49 (s, 9H); 1.60–1.83 (m, 2H); 2.79–2.95 (m, 2H); 4.15–4.26 (m, 1H); 4.73 (d, 1H, $J$=8.9 Hz); 5.02–5.19 (m, 1H); 6.55 (d, 1H, $J$=11.0 Hz); 7.06–7.18 (m, 2H); 7.20–7.37 (m, 3H); 7.48–7.67 (m, 3H); 7.87 (dt, 2H, $J$=1.8, 7.0 Hz). Diast. B δ: 0.95 (t, 3H, $J$=7.3 Hz); 1.49 (s, 9H); 1.60–1.83 (m, 2H); 2.79–2.95 (m, 2H); 4.15–4.26 (m, 1H); 4.66 (d, 1H, $J$=8.7 Hz); 5.02–5.19 (m, 1H); 6.75 (d, 1H, $J$=11.0 Hz); 7.06–7.18 (m, 2H); 7.20–7.37 (m, 3H); 7.48–7.67 (m, 3H); 7.87 (dt, 2H, $J$=1.8, 7.0 Hz). $^{13}$C NMR δ: 9.8, 10.0, 20.3, 20.4, 28.4, 28.5, 37.0, 38.1, 55.4, 56.3, 70.0, 70.3, 81.0, 81.4, 127.3, 129.0, 129.2, 129.4, 129.5, 134.3, 134.4, 136.2, 136.3, 155.4, 155.6, 171.3, 171.5. Anal. Calcd for $C_{23}H_{30}N_2O_5S$ (446.56): C, 61.86; H, 6.77; N, 6.27. Found: C, 61.93; H, 6.73; N, 6.31.

**4.2.2. *tert*-Butyl *N*-(1-benzyl-2-oxo-2-[3-phenyl-1-(phenylsulfonyl)propyl]aminoethyl)carbamate, 6b.** Yield 95%. White solid mp 115–117 °C. IR (cm$^{-1}$, KBr) 3405, 1693, 1376, 1148. $^1$H NMR δ (ppm) 1.39 (s, 9H); 1.60–1.83 (m, 2H); 1.88–2.15 (m, 1H); 2.15–2.95 (m, 5H); 4.15–4.40 (m, 1H); 4.84–4.98 (m, 1H); 5.05–5.26 (m, 1H); 5.77–5.86 (m, 1H); 7.06–7.38 (m, 10H); 7.40–7.72 (m, 3H); 7.78–7.95 (m, 2H). Anal. Calcd for $C_{29}H_{34}N_2O_5S$ (522.66): C, 66.64; H, 6.56; N, 5.36. Found: C, 66.70; H, 6.61; N, 5.33.

**4.2.3. *tert*-Butyl *N*-(1-benzyl-2-[3-methyl-1-(phenylsulfonyl)butyl]amino-2-oxoethyl)carbamate, 6c.** Yield 81%. Colorless oil. IR (cm$^{-1}$, neat) 3390, 1698, 1372, 1145. $^1$H NMR δ (ppm) 0.70–1.03 (m, 6H); 1.45 (s, 9H); 1.55–1.78 (m, 1H); 1.89–2.12 (m, 2H); 2.65–3.04 (m, 2H); 4.08–4.25 (m, 1H); 4.55–4.78 (m, 1H); 5.15–5.36 (m, 2H); 6.30–6.50 (m, 1H); 7.06–7.18 (m, 2H); 7.20–7.40 (m, 3H); 7.44–7.78 (m, 3H); 7.82–7.95 (m, 2H). Anal. Calcd for $C_{25}H_{34}N_2O_5S$ (474.61): C, 63.27; H, 7.22; N, 5.90. Found: C, 63.22; H, 7.26; N, 5.95.

**4.2.4. *tert*-Butyl *N*-(1-benzyl-2-oxo-2-[1-(phenylsulfonyl)ethyl]aminoethyl)carbamate, 6d.** Yield 93%. White solid mp 103–105 °C. IR (cm$^{-1}$, KBr) 3380, 1695, 1375, 1145. $^1$H NMR diast. A. δ (ppm) 1.40 (s, 9H); 1.45 (d, 3H, $J$= 6.6 Hz); 2.62–2.91 (m, 2H); 4.11–4.30 (m, 1H); 4.78 (d, 1H, $J$=8.1 Hz); 5.19–5.37 (m, 1H); 6.64 (d, 1H, $J$=10.3 Hz);

7.06–7.12 (m, 2H); 7.18–7.33 (m, 3H); 7.48–7.67 (m, 3H); 7.85–7.93 (m, 2H). Diast. B. $\delta$: 1.41 (s, 9H); 1.60 (d, 3H, $J$=7.0 Hz); 2.75–2.98 (m, 2H); 4.15–4.28 (m, 1H); 4.71 (d, 1H, $J$=8.1 Hz); 5.25–5.30 (m, 1H); 6.84 (d, 1H, $J$=10.2 Hz); 7.06–7.12 (m, 2H); 7.18–7.33 (m, 3H); 7.48–7.67 (m, 3H); 7.85–7.93 (m, 2H). $^{13}$C NMR $\delta$: 13.0, 13.3, 28.4, 37.4, 38.4, 55.4, 56.0, 64.8, 65.0, 80.7, 81.0, 127.2, 127.3, 128.9, 129.2, 129.3, 129.4, 129.5, 134.1, 134.3, 136.2, 136.4, 155.4, 155.6, 170.7, 170.9. Anal. Calcd for $C_{22}H_{28}N_2O_5S$ (432.53): C, 61.09; H, 6.52; N, 6.48. Found: C, 61.14; H, 6.56; N, 6.53.

**4.2.5. Benzyl *N*-(1-benzyl-2-oxo-2-[phenyl(phenylsulfonyl)methyl]aminoethyl)carbamate, 6e.** Yield 81%. White solid mp 126–128 °C. IR (cm$^{-1}$, KBr) 3405, 1690, 1378, 1150. $^1$H NMR $\delta$ (ppm) 1.40 (s, 9H); 2.80–3.03 (m, 2H); 4.25–4.40 (m, 1H); 4.70–5.05 (m, 2H); 6.23 (d, 1H, $J$=11.3 Hz); 7.10–7.70 (m, 12H); 7.80–7.97 (m, 2H); 8.10–8.18 (m, 1H). Anal. Calcd for $C_{30}H_{28}N_2O_5S$ (528.62): C, 68.16; H, 5.34; N, 5.30. Found: C, 68.21; H, 5.37; N, 5.26.

**4.2.6. Benzyl *N*-(1-benzyl-2-oxo-2-[1-(phenylsulfonyl)propyl]aminoethyl)carbamate, 6f.** Yield 88%. White solid mp 138–140 °C. IR (cm$^{-1}$, KBr) 3400, 1690, 1370, 1145. $^1$H NMR $\delta$ (ppm) 0.72 (t, 3H, $J$=7.3 Hz, diast. A); 0.93 (t, 3H, $J$=7.3 Hz, diast. B); 1.53–1.86 (m, 1H); 2.08–2.40 (m, 1H); 2.65–2.97 (m, 2H); 4.40–4.58 (m, 1H); 5.00–5.30 (m, 3H); 5.46 (d, 1H, $J$=8.7 Hz, diast. B); 5.52 (d, 1H, $J$=8.9 Hz, diast. A); 7.06–7.70 (m, 13H); 7.80–7.98 (m, 2H). Anal. Calcd for $C_{26}H_{28}N_2O_5S$ (480.58): C, 64.98; H, 5.87; N, 5.83. Found: C, 65.03; H, 5.83; N, 5.88.

**4.2.7. Benzyl *N*-(1-benzyl-2-oxo-2-[3-phenyl-1-(phenylsulfonyl)propyl]aminoethyl)carbamate, 6g.** Yield 89%. White solid mp 121–123 °C. IR (cm$^{-1}$, KBr) 3390, 1696, 1370, 1145. $^1$H NMR $\delta$ (ppm) 2.37–2.50 (m, 2H); 2.61–2.69 (m, 2H); 2.80–3.00 (m, 2H); 4.22–4.50 (m, 1H); 4.97 (d, 1H, $J$=8.9 Hz); 5.06–5.35 (m, 3H); 6.83–7.70 (m, 19H); 7.79–7.90 (m, 2H). $^{13}$C NMR $\delta$: 28.4, 28.5, 31.2, 31.5, 35.4, 37.3, 38.5, 55.9, 56.4, 67.5, 68.4, 68.8, 126.6, 127.4, 128.3, 128.6, 128.7, 128.8, 129.0, 129.2, 129.3, 129.4, 129.5, 134.3, 134.4, 135.9, 136.0, 136.4, 136.6, 139.9, 140.0, 156.0, 156.3, 170.9. Anal. Calcd for $C_{32}H_{32}N_2O_5S$ (556.67): C, 69.04; H, 5.79; N, 5.03. Found: C, 69.00; H, 5.82; N, 4.99.

**4.2.8. *N*1-[1-(Phenylsulfonyl)propyl]-2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)-3-phenylpropanamide, 6h.** Yield 78%. Colorless oil. IR (cm$^{-1}$, neat) 3300, 1690, 1370, 1145. $^1$H NMR $\delta$ (ppm) 0.98 (t, 3H, $J$=7.3 Hz, diast. B); 1.06 (t, 3H, $J$=7.3 Hz, diast. A); 1.65–1.90 (m, 1H); 2.20–2.44 (m, 1H); 3.29–3.35 (m, 2H); 4.79 (t, 1H, $J$=8.1 Hz, diast. A); 4.92 (dd, 1H, $J$=7.0, 9.5 Hz, diast. B); 5.18–5.25 (m, 1H); 7.00–7.20 (m, 5H); 7.40–7.90 (m, 9H). $^{13}$C NMR $\delta$: 10.0, 10.1, 20.1, 20.3, 34.7, 34.7, 55.8, 55.9, 70.3, 70.5, 123.7, 123.8, 127.2, 127.3, 128.7, 128.9, 129.1, 129.3, 134.2, 134.4, 134.5, 134.6, 136.1, 136.2, 136.4, 136.8, 167.9, 168.2, 168.5. Anal. Calcd for $C_{26}H_{24}N_2O_5S$ (476.55): C, 65.53; H, 5.08; N, 5.88. Found: C, 65.59; H, 5.12; N, 5.91.

**4.2.9. *tert*-Butyl *N*-[2-methyl-1-([1-(phenylsulfonyl)propyl]aminocarbonyl)propyl]carbamate, 6i.** Yield 91%. White solid mp 152–154 °C. IR (cm$^{-1}$, KBr) 3405, 1694, 1373, 1145. $^1$H NMR $\delta$ (ppm) diast. A. 0.64–0.88 (m, 6H); 1.04 (t, 3H, $J$=7.3 Hz); 1.49 (s, 9H); 1.75–1.95 (m, 1H); 1.98–2.10 (m, 2H); 3.80–3.98 (m, 1H); 4.67 (d, 1H, $J$=8.5 Hz); 5.08–5.27 (m, 1H); 6.58 (d, 1H, $J$=9.9 Hz); 7.46–7.70 (m, 3H); 7.85–7.96 (m, 2H). Diast. B. $\delta$: 0.64–0.88 (m, 6H); 1.02 (t, 3H, $J$=7.3 Hz); 1.47 (s, 9H); 1.75–1.95 (m, 1H); 2.20–2.43 (m, 2H); 3.63–3.79 (m, 1H); 4.82 (d, 1H, $J$=8.6 Hz); 5.08–5.27 (m, 1H); 6.58 (d, 1H, $J$=9.9 Hz); 7.46–7.70 (m, 3H); 7.85–7.96 (m, 2H). $^{13}$C NMR $\delta$: 10.0, 17.5, 19.4, 20.5, 20.7, 28.4, 28.5, 29.6, 30.3, 60.2, 70.0, 81.4, 129.3, 129.4, 134.2, 136.9, 155.3, 155.5, 171.5, 171.6. Anal. Calcd for $C_{19}H_{30}N_2O_5S$ (398.53): C, 57.26; H, 7.59; N, 7.03. Found: C, 57.31; H, 7.63; N, 6.98.

**4.2.10. *tert*-Butyl *N*-[2-methyl-1-([3-phenyl-1-(phenylsulfonyl)propyl]aminocarbonyl)propyl] carbamate, 6j.** Yield 87%. White solid mp 112–114 °C. IR (cm$^{-1}$, KBr) 3450, 1695, 1375, 1145. $^1$H NMR $\delta$ (ppm) diast. A. 0.70 (d, 3H, $J$=7.0 Hz); 0.84 (d, 3H, $J$=7.0 Hz); 1.48 (s, 9H); 1.80–2.25 (m, 3H); 2.42–2.90 (m, 2H); 3.83–3.90 (m, 1H); 4.85 (d, 1H, $J$=8.9 Hz); 5.10–5.37 (m, 1H); 7.08–7.30 (m, 6H); 7.46–7.66 (m, 3H); 7.85–7.96 (m, 2H). Diast. B. 0.73 (d, 3H, $J$=6.6 Hz); 0.76 (d, 3H, $J$=6.6 Hz); 1.43 (s, 9H); 1.80–2.25 (m, 3H); 2.42–2.90 (m, 2H); 3.70–3.79 (m, 1H); 5.02 (d, 1H, $J$=8.9 Hz); 5.10–5.37 (m, 1H); 7.08–7.30 (m, 6H); 7.46–7.66 (m, 3H); 7.85–7.96 (m, 2H). $^{13}$C NMR $\delta$: 14.3, 17.6, 19.4, 21.2, 28.4, 28.5, 28.6, 28.8, 30.6, 31.5, 59.8, 60.6, 68.3, 68.4, 80.5, 80.6, 126.6, 126.7, 128.4, 128.8, 129.1, 129.3, 134.2, 134.3, 136.6, 139.8, 140.0, 156.0, 156.2, 171.5, 171.9. Anal. Calcd for $C_{25}H_{34}N_2O_5S$ (474.61): C, 63.27; H, 7.22; N, 5.90. Found: C, 63.33; H, 7.19; N, 5.94.

**4.2.11. *tert*-Butyl *N*-[1-([cyclohexyl(phenylsulfonyl)methyl]aminocarbonyl)-2-methylpropyl] carbamate, 6k.** Yield 90%. Waxy solid. IR (cm$^{-1}$, neat) 3400, 1690, 1375, 1145. $^1$H NMR $\delta$ (ppm) diast. A. 0.66 (d, 3H, $J$=7.0 Hz); 0.81 (d, 3H, $J$=7.0 Hz); 0.98–1.45 (m, 5H); 1.50 (s, 9H); 1.60–1.88 (m, 4H); 1.89–2.07 (m, 1H); 2.10–2.22 (m, 1H); 2.40–2.58 (m, 1H); 3.70 (dd, 1H, $J$=6.6, 8.8 Hz); 4.68 (d, 1H, $J$=8.1 Hz); 5.13 (dd, 1H, $J$=3.7, 10.6 Hz); 6.79 (d, 1H, $J$=11.0 Hz); 7.47–7.65 (m, 3H); 7.88–7.95 (m, 2H). Diast. B. $^1$H NMR $\delta$: 0.69 (d, 3H, $J$=6.6 Hz); 0.78 (d, 3H, $J$=6.6 Hz); 0.98–1.45 (m, 5H); 1.48 (s, 9H); 1.60–1.88 (m, 4H); 1.89–2.07 (m, 1H); 2.10–2.22 (m, 1H); 2.40–2.58 (m, 1H); 3.87 (dd, 1H, $J$=5.8, 8.1 Hz); 4.85 (d, 1H, $J$=8.7 Hz); 5.13 (dd, 1H, $J$=3.7, 10.6 Hz); 6.79 (d, 1H, $J$=11.0 Hz); 7.47–7.65 (m, 3H); 7.88–7.95 (m, 2H). $^{13}$C NMR $\delta$: 17.6, 19.4, 19.5, 25.5, 25.8, 27.5, 28.5, 30.9, 36.8, 37.0, 60.2, 72.2, 80.7, 128.7, 128.9, 129.2, 134.1, 137.9, 156.0, 156.2, 171.4, 171.5. Anal. Calcd for $C_{25}H_{36}N_2O_5S$ (476.63): C, 63.00; H, 7.61; N, 5.88. Found: C, 63.06; H, 7.65; N, 5.82.

**4.2.12. *tert*-Butyl *N*-[2-methyl-1-([1-(phenylsulfonyl)decyl]aminocarbonyl)propyl]carbamate, 6l.** Yield 83%. White solid mp 95–98 °C. IR (cm$^{-1}$, KBr) 3400, 1690, 1370, 1145. $^1$H NMR $\delta$ (ppm) diast. A. 0.72 (d, 3H, $J$=6.6 Hz); 0.84 (t, 3H, $J$=7.0 Hz); 0.88–0.95 (m, 3H); 1.20–1.38 (m, 14H); 1.49 (s, 9H); 1.60–1.70 (m, 2H); 1.90–2.10 (m, 1H); 3.82–3.90 (m, 1H); 4.71 (d, 1H, $J$=8.6 Hz); 5.17–5.35 (m, 1H); 6.64–6.80 (m, 1H); 7.50–7.73 (m, 3H); 7.86–7.95 (m, 2H). Diast. B. 0.71 (d, 3H, $J$=6.6 Hz); 0.84

(t, 3H, $J=7.0$ Hz); 0.88–0.95 (m, 3H); 1.20–1.38 (m, 14H); 1.46 (s, 9H); 1.60–1.70 (m, 2H); 2.13–2.35 (m, 1H); 3.69–3.76 (m, 1H); 4.86 (d, 1H, $J=8.8$ Hz); 5.17–5.35 (m, 1H); 6.64–6.80 (m, 1H); 7.50–7.73 (m, 3H); 7.86–7.95 (m, 2H). $^{13}$C NMR $\delta$: 14.3, 17.5, 19.4, 19.5, 22.8, 24.9, 25.3, 27.0, 28.4, 30.4, 59.9, 60.0, 76.9, 81.4, 81.5, 129.1, 129.3, 129.4, 131.7, 134.2, 136.8, 155.9, 156.0, 171.4, 171.5. Anal. Calcd for $C_{26}H_{44}N_2O_5S$ (496.70): C, 62.87; H, 8.93; N, 5.64. Found: C, 62.93; H, 8.89; N, 5.61.

**4.2.13. *tert*-Butyl *N*-(2-oxo-1-phenyl-2-[1-(phenylsulfonyl)propyl]aminoethyl)carbamate, 6m.** Yield 92%. White solid mp 143–146 °C. IR (cm$^{-1}$, KBr) 3390, 1695, 1370, 1145. $^1$H NMR $\delta$ diast. A. 0.81 (t, 3H, $J=7.3$ Hz); 1.41 (s, 9H); 1.63–1.90 (m, 1H); 2.16–2.47 (m, 1H); 5.08–5.25 (m, 2H); 5.42 (d, 1H, $J=8.0$ Hz); 6.60–6.78 (m, 1H); 7.15–7.37 (m, 5H); 7.44–7.67 (m, 3H); 7.87–7.98 (m, 2H). Diast. B. 1.06 (t, 3H, $J=7.3$ Hz); 1.41 (s, 9H); 1.63–1.90 (m, 1H); 2.16–2.47 (m, 1H); 5.08–5.25 (m, 2H); 5.59 (d, 1H, $J=8.3$ Hz); 6.60–6.78 (m, 1H); 7.15–7.37 (m, 5H); 7.44–7.67 (m, 3H); 7.87–7.98 (m, 2H). $^{13}$C NMR $\delta$: 9.6, 10.0, 20.3, 20.6, 28.4, 58.6, 58.9, 70.2, 70.3, 77.4 80.5, 80.6, 127.3, 127.4, 128.5, 128.9, 129.3, 133.9, 134.2, 136.4, 136.6, 137.1, 137.2, 155.1, 155.2, 170.4, 171.4. Anal. Calcd for $C_{22}H_{28}N_2O_5S$ (432.53): C, 61.09; H, 6.52; N, 6.48. Found: C, 61.13; H, 6.58; N, 6.52.

**4.2.14. *tert*-Butyl 2-([1-(phenylsulfonyl)propyl]amino carbonyl)-1-pyrrolidinecarboxylate, 6n.** Yield 90%. Yellow oil. IR (cm$^{-1}$, neat) 3400, 1690, 1370, 1148. $^1$H NMR $\delta$ diast. A. 1.00 (t, 3H, $J=7.3$ Hz); 1.48 (s, 9H); 1.63–1.93 (m, 4H); 2.19–2.40 (m, 2H); 3.16–3.45 (m, 2H); 4.08–4.30 (m, 2H); 5.02–5.29 (m, 1H); 7.44–7.70 (m, 3H); 7.80–7.96 (m, 2H). Diast. B. 1.07 (t, 3H, $J=7.3$ Hz); 1.53 (s, 9H); 1.63–1.93 (m, 4H); 2.19–2.40 (m, 2H); 3.16–3.45 (m, 2H); 4.08–4.30 (m, 2H); 5.02–5.29 (m, 1H); 7.44–7.70 (m, 3H); 7.80–7.96 (m, 2H). Anal. Calcd for $C_{19}H_{28}N_2O_5S$ (396.50): C, 57.56; H, 7.12; N, 7.07. Found: C, 57.61; H, 7.16; N, 7.03.

### 4.3. General procedure for the reaction of phenylsulfonyl derivatives 6 with PhMgBr

Sulfone **6** (1 mmol) was dissolved in dry THF (15 mL) and the solution was cooled to −78 °C. Phenylmagnesium bromide (2 mmol, 1 M in THF) was then added dropwise over 5 min and after 1 h at −78 °C the mixture was quenched with saturated aqueous $NH_4Cl$ (8 mL). After extraction of the aqueous phase with $CH_2Cl_2$ (3×15 mL) the organic extracts were dried over $MgSO_4$. Evaporation of the solvent at reduced pressure gave the crude phenyl derivative, which was purified by column chromatography (hexanes/ethyl acetate 8:2).

**4.3.1. *tert*-Butyl *N*-1-benzyl-2-oxo-2-[(1-phenylpropyl)amino]ethylcarbamate, 7a.** Yield 85%. Colorless oil. IR (cm$^{-1}$, neat) 3405, 1695. $^1$H NMR $\delta$ (ppm) 0.74 (t, 3H, $J=$ 7.3 Hz, diast. A); 0.83 (t, 3H, $J=7.3$ Hz, diast. B); 1.41 (s, 9H); 1.57–1.85 (m, 2H); 2.95–3.18 (m, 2H); 4.23–4.40 (m, 1H); 4.70–4.90 (m, 1H); 5.03–5.21 (m, 1H); 6.10–6.22 (m, 1H); 7.05–7.38 (m, 10H). $^{13}$C NMR $\delta$: 10.6, 10.7, 27.0, 28.4, 29.2, 38.5, 55.0, 55.1, 56.2, 80.8, 126.7, 127.0, 127.1, 127.3, 127.4, 128.6, 128.8, 128.9, 129.4, 129.5, 136.8, 136.9, 141.7, 141.8, 155.6, 170.4, 170.5. Anal. Calcd for $C_{23}H_{30}N_2O_3$ (382.50): C, 72.22; H, 7.91; N, 7.32. Found: C, 72.27; H, 7.96; N, 7.33.

**4.3.2. *tert*-Butyl *N*-1-benzyl-2-[(1,3-diphenylpropyl)amino]-2-oxoethylcarbamate, 7b.** Yield 90%. Waxy solid. IR (cm$^{-1}$, neat) 3400, 1695. $^1$H NMR $\delta$ (ppm) 1.40 (s, 9H); 1.85–2.10 (m, 2H); 2.38–2.65 (m, 2H); 4.2–4.43 (m, 1H); 4.80–5.10 (m, 2H); 6.00–6.18 (m, 1H); 7.05–7.38 (m, 15H). $^{13}$C NMR $\delta$: 28.45, 32.4, 32.6, 37.9, 38.4, 53.3, 53.4, 56.3, 80.2, 126.1, 126.7, 127.1, 127.6, 127.8, 128.5, 128.6, 128.8, 128.9, 129.4, 129.5, 133.4, 136.8, 136.9, 141.3, 141.6, 157.1, 170.4, 170.5. Anal. Calcd for $C_{29}H_{34}N_2O_3$ (458.60): C, 75.95; H, 7.47; N, 6.11. Found: C, 76.01; H, 7.43; N, 6.13.

**4.3.3. *tert*-Butyl *N*-1-benzyl-2-[(3-methyl-1-phenylbutyl)amino]-2-oxoethylcarbamate, 7c.** Yield 77%. White solid mp 148–151 °C. IR (cm$^{-1}$, KBr) 3400, 1690. $^1$H NMR $\delta$ (ppm) 0.86 (d, 3H, $J=6.6$ Hz); 0.89 (d, 3H, $J=6.6$ Hz); 1.44 (s, 9H); 1.5–1.83 (m, 3H); 2.91–3.15 (m, 2H); 4.20–4.36 (m, 1H); 4.80–5.20 (m, 2H); 5.90–6.10 (m, 1H); 7.05–7.38 (m, 10H). $^{13}$C NMR $\delta$: 22.4, 22.5, 24.9, 25.0, 28.4, 38.4, 45.7, 51.7, 51.9, 56.2, 80.4, 126.6, 1271, 127.3, 128.7, 128.9, 129.5, 129.6, 142.4, 142.6, 155.9, 170.3, 170.4. Anal. Calcd for $C_{25}H_{34}N_2O_3$ (410.55): C, 73.14; H, 8.35; N, 6.82. Found: C, 73.19; H, 8.31; N, 6.85.

**4.3.4. *tert*-Butyl *N*-1-benzyl-2-oxo-2-[(1-phenylpropyl)amino]methylcarbamate, 7d.** Yield 84% Spectroscopic data are in full agreement with those reported.[17]

**4.3.5. Benzyl *N*-1-benzyl-2-oxo-2-[(1-phenylpropyl)amino]ethyl carbamate, 7e.** Yield 88%. White solid mp 110–112 °C. IR (cm$^{-1}$, KBr) 3405, 1690. $^1$H NMR $\delta$ (ppm) 0.72 (t, 3H, $J=7.5$ Hz, diast. A); 0.80 (t, 3H, $J=7.3$ Hz, diast. B); 1.55–1.80 (m, 2H); 2.85–3.20 (m, 2H); 4.33–4.56 (m, 1H); 4.68–4.90 (m, 1H); 5.05 (s, 2H); 5.45–5.70 (m, 1H); 6.15–6.38 (m, 1H); 7.02–7.40 (m, 15H). $^{13}$C NMR $\delta$: 10.6, 10.7, 29.1, 38.8, 39.0, 55.1, 55.3, 56.6, 67.2, 126.6, 127.0, 127.4, 128.1, 128.3, 127.7, 128.9, 129.4, 129.5, 136.3, 136.7, 141.8, 156.1, 170.2, 170.3. Anal. Calcd for $C_{26}H_{28}N_2O_3$ (416.52): C, 74.98; H, 6.78; N, 6.73. Found: C, 74.92; H, 6.73; N, 6.75.

**4.3.6. *N*1-(1-Phenylpropyl)-2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)-3-phenylpropanamide, 7f.** Yield 71%. Waxy solid. IR (cm$^{-1}$, neat) 3400, 1695. $^1$H NMR $\delta$ (ppm) 0.70 (t, 3H, $J=7.3$ Hz, diast. A); 0.81 (t, 3H, $J=7.3$ Hz, diast. B); 1.50–1.80 (m, 2H); 3.33–3.84 (m, 2H); 4.20–4.36 (m, 1H); 4.55–4.77 (m, 1H); 5.47–5.55 (m, 1H, diast. A); 5.75–5.85 (m, 1H, diast. B); 6.80–7.30 (m, 11H); 7.38–7.60 (m, 2H); 7.78–7.90 (m, 1H). Anal. Calcd for $C_{26}H_{24}N_2O_3$ (412.48): C, 75.71; H, 5.86; N, 6.79. Found: C, 75.77; H, 6.85; N, 6.82.

**4.3.7. *tert*-Butyl *N*-(2-methyl-1-[(1-phenylpropyl)amino] carbonylpropyl)carbamate, 7g.** Yield 91%. Yellow oil. IR (cm$^{-1}$, neat) 3390, 1695. $^1$H NMR $\delta$ (ppm) 0.83–1.10 (m, 9H); 1.41 (s, 9H); 1.73–1.89 (m, 2H); 2.05–2.22 (m, 1H); 3.78–3.90 (m, 1H); 4.80–4.97 (m, 1H); 5.00–5.18 (m, 1H); 6.30 (d, 1H, $J=8.4$ Hz); 7.18–7.40 (m, 5H). $^{13}$C NMR $\delta$: 10.9, 11.0, 18.2, 19.5, 19.6, 27.1, 28.5,

29.3, 29.5, 30.6, 30.8, 55.0, 55.2, 60.6, 80.1, 126.7, 126.8, 127.4, 127.5, 128.8, 142.2, 156.2, 156.3, 171.1, 171.2. Anal. Calcd for $C_{19}H_{30}N_2O_3$ (334.45): C, 68.23; H, 9.04; N, 8.38. Found: C, 68.26; H, 9.00; N, 8.40.

**4.3.8. *tert*-Butyl *N*-(1-[(1,3-diphenylpropyl)amino] carbonyl-2-methylpropyl)carbamate, 7h.** Yield 82%. White solid 133–135 °C. IR ($cm^{-1}$, KBr) 3395, 1690. $^1H$ NMR $\delta$ (ppm) 0.88 (d, 3H, $J=7.0$ Hz); 0.98 (d, 3H, $J=7.0$ Hz); 1.41 (s, 9H); 1.62–1.81 (m, 1H); 2.07–2.30 (m, 2H); 2.50–2.76 (m, 2H); 3.78–3.90 (m, 1H); 4.92–5.15 (m, 2H); 6.26–6.42 (m, 1H); 7.15–7.40 (m, 10H). $^{13}C$ NMR $\delta$: 19.5, 19.7, 28.4, 30.5, 30.7, 32.6, 37.9, 38.1, 53.3, 53.4, 60.6, 80.2, 126.2, 126.7, 127.6, 128.5, 128.6, 128.9, 141.4, 141.5, 142.0, 156.1, 171.0. Anal. Calcd for $C_{25}H_{34}N_2O_3$ (410.55): C, 73.14; H, 8.35; N, 6.82. Found: C, 73.18; H, 8.36; N, 6.88.

**4.3.9. *tert*-Butyl 2-[(1-phenylpropyl)amino]carbonyl-1-pyrrolidinecarboxylate, 7i.** Yield 87%. Yellow oil. IR ($cm^{-1}$, neat) 3405, 1695. $^1H$ NMR $\delta$ (ppm) 0.86 (t, 3H, $J=$ 7.3 Hz, diast. A); 0.88 (t, 3H, $J=7.5$ Hz, diast. B); 1.44 (s, 9H); 1.65–1.98 (m, 4H); 2.10–2.45 (m, 2H); 3.20–3.50 (m, 3H); 4.18–4.45 (m, 1H); 4.80–4.95 (m, 1H); 7.18–7.37 (m, 5H). Anal. Calcd for $C_{19}H_{28}N_2O_3$ (332.44): C, 68.65; H, 8.49; N, 8.43. Found: C, 68.68; H, 8.53; N, 8.39.

### 4.4. General procedure for the preparation of α,β-dipeptides 10

To a solution of diisopropylamine (3 mmol) in dry THF (12 mL), BuLi (1.6 M in hexanes, 3.2 mmol, 2.0 mL) was added at 0 °C and stirring was continued for 0.5 h at 0 °C. Dry alkyl acetate **9** (3 mmol) was then added at −78 °C and after stirring at the same temperature for 0.5 h sulfone **6** (1 mmol) dissolved in dry THF (5 mL) was added. Stirring was continued for 1 h at −78 °C and then the mixture was quenched by addition of saturated aqueous $NH_4Cl$ (6 mL).The mixture was extracted with $CH_2Cl_2$ (4× 15 mL) and dried over $MgSO_4$. The crude product obtained after evaporation of the solvent was purified by column chromatography (hexanes/ethyl acetate 75:25).

**4.4.1. Ethyl 3-(2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoylamino)-3-phenylpropanoate, 10a.** Yield 76%. Colorless oil. IR ($cm^{-1}$, neat) 3405, 1735, 1690. $^1H$ NMR $\delta$ (ppm) 1.12 (t, 3H, $J=7.3$ Hz, diast A); 1.13 (t, 3H, $J=$ 7.3 Hz, diast. B); 1.41 (s, 9H); 2.65–2.85 (m, 2H); 2.93–3.20 (m, 2H); 3.96–4.10 (m, 2H); 4.27–4.44 (m, 1H); 5.05–5.22 (m, 1H); 5.28–5.43 (m, 1H); 6.80–7.00 (m, 1H); 7.05–7.40 (m, 10H). $^{13}C$ NMR $\delta$: 14.0, 14.1, 28.2, 39.7, 39.9, 40.4, 49.3, 49.4, 55.9, 60.6, 60.7, 80.0, 80.1, 126.2, 126.3, 128.5, 128.6, 129.0, 1239.2, 129.3, 129.6, 129.7, 139.0, 140.0, 155.3, 170.3, 170.4, 170.5, 170.7. Anal. Calcd for $C_{25}H_{32}N_2O_5$ (440.53): C, 68.16; H, 7.32; N, 6.36. Found: C, 68.14; H, 7.35; N, 6.40.

**4.4.2. Ethyl 3-[(2-[(benzyloxy)carbonyl]amino-3-phenyl propanoyl)amino]pentanoate, 10b.** Yield 72%. Colorless oil. IR ($cm^{-1}$, neat) 3400, 1735, 1690. $^1H$ NMR $\delta$ (ppm) 0.65–0.82 (m, 3H); 1.17 (t, 3H, $J=7.0$ Hz, diast A); 1.19 (t, 3H, $J=7.0$ Hz, diast B); 1.28–1.40 (m, 2H); 2.30–2.48 (m, 2H); 2.90–4.10 (q, 2H, $J=7.0$ Hz + m, 1H); 4.23–4.42 (m, 1H); 5.02 (s, 2H); 5.63–5.75 (m, 1H); 6.47–6.78 (m, 1H); 7.10–7.38 (m, 10H). $^{13}C$ NMR $\delta$: 10.4, 10.5, 14.2, 26.9, 38.0, 38.3, 38.8, 47.5, 47.7, 56.5, 60.5, 66.8, 126.9, 128.0, 128.1, 128.5, 128.6, 129.3, 136.3, 136.7, 136.8, 155.9, 170.4, 171.4, 171.5. Anal. Calcd for $C_{24}H_{30}N_2O_5$ (426.51): C, 67.59; H, 7.09; N, 6.57. Found: C, 67.55; H, 7.05; N, 6.60.

**4.4.3. Methyl 3-[(2-[(benzyloxy)carbonyl]amino-3-phenylpropanoyl)amino]-5-phenylpentanoate, 10c.** Yield 69%. White solid mp 89–93 °C. IR ($cm^{-1}$, KBr) 3405, 1738, 1695. $^1H$ NMR $\delta$ (ppm) 1.62–1.81 (m, 2H); 2.35–2.57 (m, 4H); 3.00–3.35 (m, 2H); 3.61 (s, 3H); 4.10–4.25 (m, 1H); 4.28–4.47 (m, 1H); 5.10 (s, 2H); 5.30–5.43 (m, 1H); 6.28–6.40 (m, 1H); 7.10–7.40 (m, 15H). $^{13}C$ NMR $\delta$: 32.4, 32.6, 35.7, 35.9, 38.2, 38.4, 45.9, 46.1, 51.8, 56.8, 60.0, 60.3, 67.2, 67.5, 126.2, 126.3, 127.0, 127.1127.5, 128.2, 128.3, 128.5, 128.7, 128.8, 128.9, 129.4, 129.5, 136.3, 136.6, 141.3, 141.4, 156.8, 170.3, 170.5, 171.8, 172.0. Anal. Calcd for $C_{29}H_{32}N_2O_5$ (488.58): C, 71.29; H, 6.60; N, 5.73. Found: C, 71.28; H, 6.63; N, 5.70.

**4.4.4. Ethyl 3-[2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)-3-phenylpropanoyl]aminopentanoate, 10d.** Yield 72%. Waxy solid. IR ($cm^{-1}$, neat) 3395, 1740, 1690. $^1H$ NMR $\delta$ (ppm) 0.88 (t, 3H, $J=7.4$ Hz, diast. A); 0.89 (t, 3H, $J=7.4$ Hz, diast. B); 1.18 (8t, 3H, $J=7.0$ Hz); 1.45–1.78 (m 2H); 2.43–2.55 (m, 2H); 3.50–3.63 (m, 2H); 3.95–4.10 (m, 1H); 4.13–4.21 (m, 1H); 5.05–5.15 (m, 1H); 6.68–6.78 (m, 1H); 7.07–7.22 (m, 5H); 7.65–7.70 (m, 2H); 7.75–7.80 (m, 2H). $^{13}C$ NMR $\delta$: 10.7, 10.8, 14.2, 27.0, 27.2, 34.7, 34.9, 37.9, 34.1, 48.1, 48.2, 55.7, 56.0, 60.8, 123.6, 127.0, 128.7, 128.8, 129.0, 129.7, 131.6, 134.3, 136.9, 137.0, 168.0, 168.1, 170.7, 170.8, 171.8, 172.0. Anal. Calcd for $C_{24}H_{26}N_2O_5$ (422.48): C, 68.23; H, 6.20; N, 6.63. Found: C, 68.28; H, 6.17; N, 6.66.

**4.4.5. Ethyl 3-(2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoylamino)pentanoate, 10e.** Yield 67%. White solid mp 83–86 °C. IR ($cm^{-1}$, KBr) 3400, 1734, 1695. $^1H$ NMR $\delta$ (ppm) 0.88–0.98 (m, 9H); 1.25 (t, 3H, $J=7.0$ Hz, diast. B); 1.26 (t, 3H, $J=7.3$ Hz, diast. A); 1.44 (s, 9H); 1.50–1.65 (m, 2H); 2.08–2.25 (m, 1H); 2.52 (d, 1H, $J=5.1$ Hz, diast. B); 2.53 (d, 2H, $J=5.5$ Hz, diast. A); 3.80–3.95 (m, 1H); 4.10–4.25 (m, 3H); 5.03–5.15 (m, 1H); 6.37–6.57 (m, 1H). $^{13}C$ NMR $\delta$: 10.7, 10.8, 14.3, 19.4, 27.2, 28.4, 30.8, 31.1, 38.3, 38.5, 60.2, 60.3, 79.9, 155.9, 171.1, 171.2, 171.7. Anal. Calcd for $C_{17}H_{32}N_2O_5$ (344.45): C, 59.28; H, 9.36; N, 8.13. Found: C, 59.26; H, 9.33; N, 8.15.

**4.4.6. Ethyl 3-(2-[(*tert*-butoxycarbonyl)amino]-3-methyl butanoylamino)-3-cyclohexylpropanoate, 10f.** Yield 75%. Colorless oil. IR ($cm^{-1}$, neat) 3405, 1735, 1690. $^1H$ NMR $\delta$ (ppm) 0.85–1.00 (m, 8H); 1.10–1.22 (m, 3H); 1.25 (t, 3H, $J=7.3$ Hz); 1.42 (s, 9H); 1.60–1.80 (m, 6H); 2.08–1.30 (1H); 2.50–2.55 (m, 2H); 3.75–3.96 (m, 1H); 4.00–4.20 (m, 3H); 4.95–5.15 (m, 1H); 6.45 (d, 1H, $J=9.1$ Hz). Anal. Calcd for $C_{21}H_{38}N_2O_5$ (398.54): C, 63.29; H, 9.61; N, 7.03. Found: C, 63.33; H, 9.58; N, 7.00.

**4.4.7. Ethyl 3-(2-[(*tert*-butoxycarbonyl)amino]-3-methyl butanoylamino)dodecanoate, 10g.** Yield 65%. Spectroscopic data are in full agreement with those reported.[14c]

**4.4.8. Ethyl 3-(2-[(*tert*-butoxycarbonyl)amino]-2-phenyl acetylamino)pentanoate, 10h.** Yield 78%. Waxy solid. IR ($cm^{-1}$, neat) 3405, 1735, 1690. $^1H$ NMR $\delta$ (ppm) diast. A. 0.67 (t, 3H, $J=7.0$ Hz); 1.23 (dt, 3H, $J=1.1$, 7.0 Hz); 1.40 (s, 9H); 1.41–1.60 (m, 2H); 2.50 (d, 2H, $J=5.1$ Hz); 4.13 (dq, 2H, $J=1.1$, 7.0 Hz); 4.14–4.25 (m, 1H); 5.00–5.17 (m, 1H); 5.78–5.95 (m, 1H); 6.41 (d, 1H, $J=10.0$ Hz); 7.22–7.36 (m, 5H). Diast. B. 0.89 (t, 3H, $J=7.0$ Hz); 1.15 (dt, 3H, $J=1.1$, 7.0 Hz); 1.40 (s, 9H); 1.41–1.60 (m, 2H); 2.39 (d, 2H, $J=5.1$ Hz); 3.95 (dq, 2H, $J=1.1$, 7.0 Hz); 4.14–4.25 (m, 1H); 5.00–5.17 (m, 1H); 5.78–5.95 (m, 1H); 6.31 (d, 1H, $J=10.0$ Hz); 7.22–7.36 (m, 5H). $^{13}C$ NMR $\delta$: 10.4, 10.8, 14.2, 14.3, 27.1, 28.4, 37.9, 38.4, 47.9, 48.0, 58.9, 60.7, 60.7, 77.4, 80.1, 127.6, 128.3, 128.4, 129.0, 129.1, 138.7, 138.9, 155.2, 169.7, 169.8, 171.6, 171.8. Anal. Calcd for $C_{20}H_{30}N_2O_5$ (378.46): C, 63.47; H, 7.99; N, 7.40. Found: C, 63.43; H, 8.02; N, 7.44.

### 4.5. General procedure for preparation of nitro derivatives 11

To a stirred suspension of NaH (3 mmol) in dry THF (10 mL), nitromethane (3 mmol) was added dropwise at room temperature. After stirring for 30 min, the appropriate sulfone **6** (1 mmol) dissolved in dry THF (5 mL) was added and the white suspension was stirred at room temperature for 30 min. The reaction was quenched by addition of saturated aqueous $NH_4Cl$ (4 mL), was extracted with $CHCl_3$ ($4\times15$ mL) and then dried over $MgSO_4$. The crude nitro derivative **11** obtained after removal of the solvent was purified by column chromatography (hexanes/ethyl acetate 7:3).

**4.5.1. *tert*-Butyl *N*-(2-[1-(nitromethyl)propyl]amino-2-oxo-1-phenylethyl)carbamate, 11a.** Yield 77%. White solid mp 73–77 °C. IR ($cm^{-1}$, KBr) 3400, 1695, 1550. $^1H$ NMR $\delta$ (ppm) 0.87 (t, 3H, $J=7.3$ Hz, diast. A); 0.92 (t, 3H, $J=7.3$ Hz, diast. B); 1.42 (s, 9H, diast. A); 1.43 (s, 9H, diast. B); 1.50–1.70 (m, 2H); 2.98–3.17 (m, 2H); 4.20–4.42 (m, 3H); 4.45–4.55 (m, 1H); 4.90–5.08 (m, 1H); 6.23–6.42 (m, 1H); 7.16–7.40 (m, 5H). Anal. Calcd for $C_{17}H_{25}N_3O_5$ (351.40): C, 58.11; H, 7.17; N, 11.96. Found: C, 58.15; H, 7.20; N, 11.99.

**4.5.2. *tert*-Butyl *N*-[2-methyl-1-([1-(nitromethyl)propyl] aminocarbonyl)propyl]carbamate, 11b.** Yield 75%. White solid mp 105–107 °C. IR ($cm^{-1}$, KBr) 3400, 1690, 1555. $^1H$ NMR $\delta$: 0.90–1.03 (m, 9H); 1.44 (s, 9H, diast. A); 1.45 (s, 9H, diast. B); 1.50–1.78 (m, 2H); 2.10–2.25 (m, 1H); 3.82–3.96 (m, 2H); 4.28–4.42 (m, 1H); 4.55–4.63 (m, 1H); 5.03–5.18 (m, 1H); 6.59 (d, 1H, $J=$ 8.1 Hz). Anal. Calcd for $C_{14}H_{17}N_3O_5$ (317.38): C, 52.98; H, 8.57; N, 13.24. Found: C, 53.00; H, 8.55; N, 13.26.

### 4.6. General procedure for preparation of α,α-dipeptides 12

Nitroderivative **11** (0.5 mmol) dissolved in *t*BuOH (4 mL) was treated with aqueous buffered KOH (0.5 M in KOH and 1.25 M in $K_2HPO_4$, 3 mL) at room temperature. The mixture was stirred for 5 min and then aqueous $KMnO_4$ (0.5 M, 4 mL, 2 mmol) was added dropwise mantaining the temperature below 25 °C by occasional cooling. After stirring at room temperature for 1 h the mixture was cooled by ice bath and then saturated $Na_2SO_3$ (10 mL) was added. The mixture was then acidified with 2 M HCl until pH ~5 and then extracted with ethyl acetate ($4\times15$ mL). The organic solutuion was dried over $MgSO_4$ and after evaporation of the solvent the crude acid **12** was purified by column chromatography (dichloromethane/methanol 9:1).

**4.6.1. 2-(2-[(*tert*-Butoxycarbonyl)amino]-2-phenylacetyl amino)butanoic acid, 12a**

Yield 82%. Waxy solid. IR ($cm^{-1}$, neat) 3400, 1710, 1690. $^1H$ NMR $\delta$: 0.78 (t, 3H, $J=7.0$ Hz, diast. A); 0.96 (t, 3H, $J=7.0$ Hz, diast. B); 1.39 (s, 9H); 1.65–2.00 (m, 2H); 2.95–3.18 (m, 2H); 4.45–4.68 (m, 2H); 5.36 (m, 1H, diast. A); 5.58–5.70 (m, 1H, diast. B); 6.55 (br s, 1H); 6.95–7.15 (m, 1H); 7.20–7.35 (m, 5H). Anal. Calcd for $C_{17}H_{24}N_2O_5$ (336.38): C, 60.70; H, 7.19; N, 8.33. Found: C, 60.66; H, 7.20; N, 8.29.

**4.6.2. 2-(2-[(*tert*-Butoxycarbonyl)amino]-3-methyl butanoylamino)butanoic acid, 12b**

Yield 78%. Spectroscopic data are in full agreement with those reported.[18]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