

Wolff rearrangement of diazo ketones derived from *N*-*p*-tolylsulfonyl-protected α - and β -amino acids

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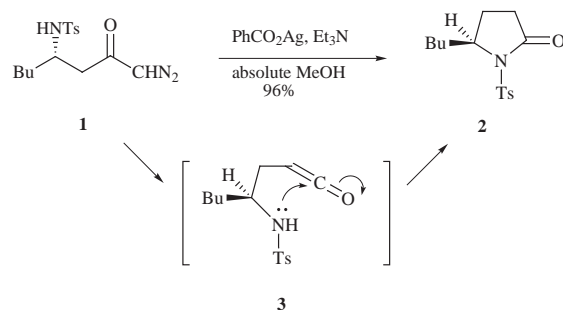
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Diazo ketones derived from *N*-*p*-tolylsulfonyl (tosyl)-protected α - and β -amino acids have been synthesized and their diazo decomposition under standard Wolff rearrangement conditions, $\text{PhCO}_2\text{Ag-Et}_3\text{N-MeOH}$, has been investigated. It is observed that, under these conditions, several different reaction pathways, including direct carbene N-H insertion, are possible. The reaction is markedly affected by the N-protecting group, the substrate structure and solvent. For those diazo ketones derived from *N*-tosyl-protected β -amino acids, the diazo decomposition with anhydrous THF as solvent and PhCO_2Ag dissolved in Et_3N as catalyst gives the corresponding γ -substituted pyrrolidinones in excellent yields.

Introduction

Application of the Wolff rearrangement to diazo ketones derived from α -amino acids has been well documented.¹ Because in most cases the rearrangement proceeds with retention of configuration at the chiral centre next to the carbonyl group, this approach has been applied in convenient syntheses of optically pure β -amino acids through an Arndt-Eistert homologation reaction sequence of the corresponding α -amino acids.² The Wolff rearrangement has also been successfully incorporated into several chiral syntheses of indolizidines, starting from L- or D- α -amino acids.³

It has been generally observed that if the rearrangement is performed in aqueous solution, the homologated acid is the expected product,³ while if the reaction is run in methanol or ammonia, the corresponding homologated ester or amide will be obtained.^{2,4} In an attempted synthesis of (+)-Pyrrolidine 197B,⁵ we unexpectedly observed that the Wolff rearrangement of diazo ketone **1** in anhydrous methanol gave exclusively γ -lactam **2** in excellent yield (Scheme 1). The formation of this

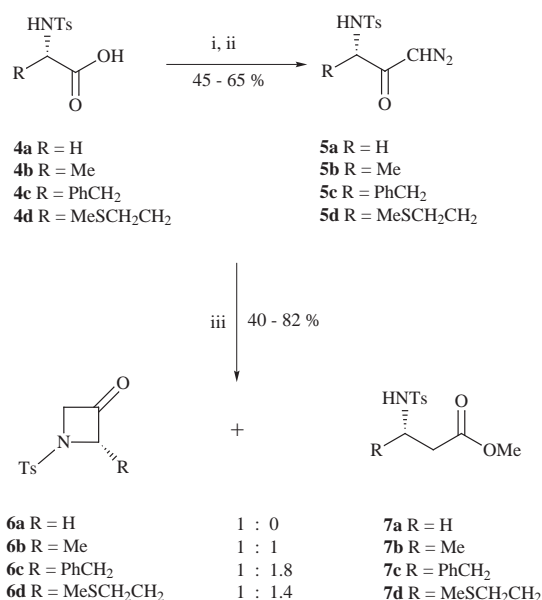


Scheme 1

intramolecular cyclization product is apparently due to nucleophilic attack of the intermediate ketene **3** by the tosyl-protected amino group. Although the solvent methanol can also serve as nucleophile, the exclusive formation of the γ -lactam indicates that intermolecular nucleophilic attack of the ketene intermediate **3** by methanol is not effective enough to compete with intramolecular nucleophilic attack by the tosyl-protected amino group. This observation aroused our interest in the generality of this reaction and its potential as a novel method for the direct synthesis of γ -lactams. We report here the results of our investigation of the Wolff rearrangement of several diazo ketones derived from *N*-tosyl-protected α -amino acids and β -amino acids.

Results and discussion

We first examined the Wolff rearrangements of diazo ketones derived from α -amino acids (Scheme 2). *N*-Tosyl-protected



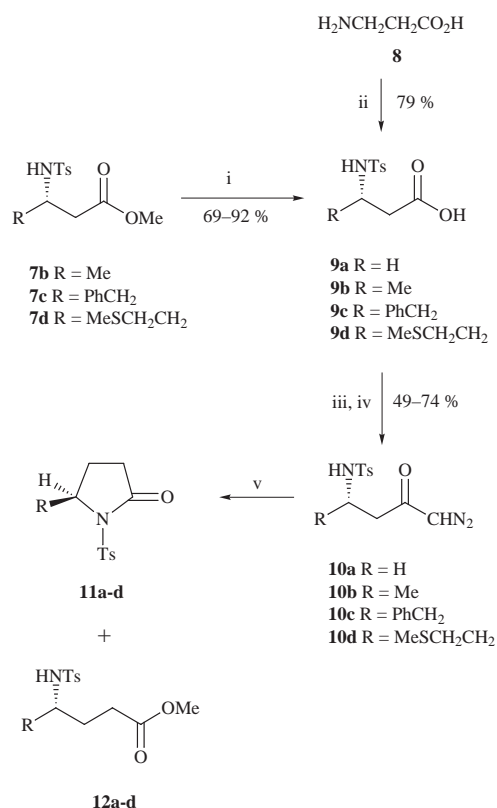
Scheme 2 Reagents and conditions: i, 1.2 mol equiv. $(\text{COCl})_2$, CH_2Cl_2 ; ii, CH_2N_2 , Et_2O ; iii, PhCO_2Ag (0.12 mol equiv.), Et_3N , anhydrous MeOH

amino acids **4a-d**, which were prepared according to the literature,⁶ were converted into their corresponding diazo ketones **5a-d** by the standard procedure.⁷ Although not rigorously verified, this reaction sequence to α -diazo ketones has been shown to proceed without racemization.⁷ The diazo ketones **5a-d** were then subjected to the conditions of Wolff rearrangement with silver benzoate dissolved in triethylamine as catalyst in anhydrous methanol.^{4b} As shown in Scheme 2, under the above conditions diazo decomposition gave both normal Wolff rearrangement products **7a-d** and direct N-H insertion products **6a-d**. When R = H, the diazo decomposition gave exclusively the N-H insertion product azetidin-3-one **6a**. For substrates **5b-d**, a mixture of β -amino esters **7b-d** and 2-substituted azetidin-3-ones **6b-d** were produced, with **6**:**7** ratios of 1:1, 1:1.8 and 1:1.4, respectively. The formation of products from direct N-H insertion suggests the possibility of the involvement of free carbene as a discrete reaction intermediate in the diazo decomposition under the above con-

ditions.⁸ The different product ratios of direct N–H insertion vs. Wolff rearrangement observed in the diazo decomposition of substrates **5a–d** can be explained by the different degrees of steric hindrance of the side chain of the amino acid derivatives. The less sterically hindered side chain (R = H) makes direct carbene N–H insertion more favourable, while a bulkier side chain (R = PhCH₂) hampers direct insertion, thus leading to an increase in Wolff rearrangement product.

It has been reported that diazo decompositions of α -diazocarbonyl compounds derived from *N*-fluoren-9-ylmethoxycarbonyl (Fmoc)-, *N*-*tert*-butoxycarbonyl (Boc)- and *N*-benzyloxycarbonyl (Cbz)-protected α -amino acids give the corresponding Wolff rearrangement products in good yields.² The results from our study indicate that the nature of the protecting group can markedly influence the pathway of the reaction. When a tosyl group is employed as the N-protecting group in α -diazocarbonyl compounds, direct N–H insertion by the carbene intermediate becomes effectively competitive to the Wolff rearrangement. This might be due to the change of the electron density of the amino N–H bond. Consequently, a tosyl group is not suitable as the N-protecting group for the α -diazocarbonyl compounds derived from α -amino acids if the Wolff rearrangement approach is applied to the synthesis of β -amino esters. On the other hand, the β -lactams, which might be anticipated from Wolff rearrangement followed by direct nucleophilic attack of the ketene intermediate, were not observed and homologated β -amino esters **7b–d** were the only isolated Wolff rearrangement products. This is probably due to the unfavourable steric strain of the four-membered ring of β -lactams.

Next, we turned our attention to the Wolff rearrangement of α -diazocarbonyl compounds derived from *N*-tosyl-protected β -amino acids (Scheme 3 and Table 1). The *N*-tosyl-protected



Scheme 3 Reagents and conditions: i, aq. NaOH, MeOH, rt, 6 h; ii, TsCl, Et₃N, acetone; iii, 1.2 mol equiv. (COCl)₂, CH₂Cl₂; iv, CH₂N₂, Et₂O; v, PhCO₂Ag (0.12 mol equiv.), Et₃N, anhydrous MeOH or THF

β -amino acids **9b–d** were easily obtained by hydrolysis of β -amino esters **7b–d**. Acid **9a** was prepared by *N*-tosyl protection of commercially available β -alanine **8**. The β -amino acids were then converted into the corresponding α -diazocarbonyl

Table 1 The ratio and yield of the diazo decomposition products of diazo ketones **10a–d** by PhCO₂Ag in MeOH or THF

R	Solvent = MeOH		Solvent = THF	
	Yield (%) (11 + 12)	11 : 12	Yield (%) (11 + 12)	11 : 12
a H	81	0:100	93	100:0
b Me	89	100:0	85	100:0
c PhCH ₂	91	100:0	86	100:0
d MeSCH ₂ CH ₂	91	25:75	81	100:0

compounds **10a–d**. Similar diazo decomposition of compound **10a** with silver benzoate as catalyst in anhydrous methanol in the presence of triethylamine give γ -amino ester **12a** as the only product in 81% yield. For compound **10d**, the same reaction gave a mixture of γ -lactam **11d** and γ -amino ester **12d** in approximately 1:3 ratio. The same reaction for compounds **10b** and **10c** gave exclusively γ -lactams **11b** and **11c** in 89 and 91% yield, respectively. These results suggest that, under these reaction conditions, the formation of γ -lactam is not guaranteed to be the major reaction pathway. Depending on the structure of the α -diazocarbonyl substrates, the ketene intermediate could be attacked by methanol solvent to yield γ -amino esters. However, in contrast to the diazo decomposition of compounds **5a–d**, direct carbene insertion into the N–H bond was not observed for the diazo decomposition of α -diazocarbonyl compounds **10a–d**, and the Wolff rearrangement is the predominant pathway in all cases.

We then run the same diazo decomposition but with anhydrous THF as solvent instead of anhydrous MeOH (Scheme 3). Not surprisingly, since there was no external nucleophile in this case, for all α -diazocarbonyl substrates **10a–d** the corresponding γ -lactam was obtained as the only product, in good yield. Although only limited α -diazocarbonyl substrates have been investigated, the formation of γ -lactam under these conditions seems to be general. Since optically pure *N*-tosyl-protected β -amino acids can be easily prepared,⁹ the Wolff rearrangement under these conditions can be applied as a straightforward synthesis of optically active 5-substituted pyrrolidinones.¹⁰

In summary, this investigation has demonstrated that several different reaction pathways are possible for the diazo decomposition of diazo ketones derived from α - and β -amino acids. This reaction can be markedly affected by the N-protecting group, the substrate structure and solvent. Consequently, it is necessary to take these factors into consideration when applying the Wolff rearrangement in organic synthesis, especially in the homologation of amino acids.

Experimental

Mps were determined in capillary tubes and are uncorrected. All reactions with air- and moisture-sensitive components were performed under nitrogen in a flame-dried reaction flask, and the components were added *via* syringe. All solvents were distilled prior to use. The boiling range of petroleum spirit is 30–60 °C. MeOH and CH₂Cl₂ were freshly distilled from CaH₂ before use. THF was distilled from sodium. For chromatography, 100–200 mesh silica gel (Qingdao, China) was employed. For preparative TLC, 10–40 μm silica gel GF₂₅₄ (Qingdao, China) was used. TLC for detection was Merck Kieselgel 60 F₂₅₄ silica gel. Recrystallization was from petroleum spirit–ethyl acetate. Diazomethane solution in dry diethyl ether was prepared from *N*-methyl-*N*-nitrosoourea. ¹H and ¹³C NMR spectra were recorded at 200 MHz and 50 MHz with a Varian Mercury 200 spectrometer, and chemical shifts are reported in ppm using tetramethylsilane as internal standard. *J*-Values are given in Hz. IR spectra were recorded with a Nicolet 5-MX-S infrared spectrometer. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. Elemental

analyses were performed at the Institute of Chemistry, Chinese Academy of Sciences. Optical rotations were measured on a Perkin-Elmer 291 polarimeter; $[a]_D$ -values are given in units of 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$.

N-Tosyl-protected amino acids **4a–d** were prepared according to the literature.⁶

***N*-Tosylglycine 4a.** Mp 147–148 °C (lit.,^{6b} 119–121 °C); $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3360 (OH), 3000, 1710 (C=O), 1430, 1315, 1245 and 1145; $\delta_{\text{H}}(\text{CDCl}_3\text{--}[\text{H}_6]\text{DMSO})$ 2.42 (3 H, s, CH_3), 3.68 (2 H, d, J 4.6, CH_2), 5.82 (1 H, br s, NHTs), 7.30 (2 H, d, J 8.2, MeC_6H_4) and 7.75 (2 H, d, J 8.2, MeC_6H_4); $\delta_{\text{C}}(\text{CDCl}_3\text{--}[\text{H}_6]\text{DMSO})$ 21.36, 43.79, 127.03, 129.51, 133.50, 143.30 and 170.39.

***N*-Tosyl-L-alanine 4b.** Mp 133–134 °C (lit.,^{6a} 132–133 °C); $[a]_D^{18}$ -18.7 (c 1.0, CH_2Cl_2); $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3280 (OH), 3050, 1710 (C=O), 1435, 1345, 1240 and 1160; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.47 (3 H, d, J 7.2, CH_3), 2.42 (3 H, s, $\text{CH}_3\text{C}_6\text{H}_4$), 2.51 (2 H, d, J 5.2, CH_2CO_2), 4.00 (1 H, m, CHMe), 5.33 (1 H, d, J 8.2, NHTs), 7.35 (2 H, d, J 8.2, MeC_6H_4) and 7.74 (2 H, d, J 8.2, MeC_6H_4); $\delta_{\text{C}}(\text{CDCl}_3)$ 19.56, 21.51, 51.12, 127.15, 129.75, 136.72, 143.90 and 176.69.

***N*-Tosyl-L-phenylalanine 4c.** Mp 160–161 °C (lit.,^{6b} 160 °C); $[a]_D^{18}$ -4.7 (c 1.0, CH_2Cl_2); $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3280 (OH), 3070, 1720 (C=O), 1675, 1420, 1330, 1205, 1155 and 1075; $\delta_{\text{H}}(\text{CDCl}_3)$ 2.40 (3 H, s, CH_3), 3.05 (2 H, m, CH_2Ph), 4.20 (1 H, m, CH-NHTs), 5.13 (1 H, br s, NHTs), 7.08 (2 H, m, C_6H_5), 7.23 (5 H, m, C_6H_5 and MeC_6H_4) and 7.59 (2 H, d, J 8.2, MeC_6H_4); $\delta_{\text{C}}(\text{CDCl}_3)$ 21.50, 38.84, 56.35, 127.09, 127.28, 128.61, 129.45, 129.64, 134.80, 136.46, 143.71 and 174.64.

***N*-Tosyl-L-methionine 4d.** Mp 77–78 °C (lit.,^{6a} 77–78 °C); $[a]_D^{18}$ $+8.2$ (c 1.0, CH_2Cl_2); $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3400 (OH), 3280, 2920, 1740 (C=O), 1320, 1160, 1130 and 1085; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.82–2.21 (2 H, m, CH_2), 2.02 (3 H, s, CH_3S), 2.42 (3 H, s, $\text{CH}_3\text{C}_6\text{H}_4$), 2.40–2.65 (2 H, m, CH_2SMe), 4.05–4.20 (1 H, m, CHNHTs), 5.62 (2 H, d, J 8.6, NHTs), 7.29 (2 H, d, J 8.4, MeC_6H_4) and 7.74 (2 H, d, J 8.4, MeC_6H_4); $\delta_{\text{C}}(\text{CDCl}_3)$ 15.14, 21.52, 29.58, 32.07, 54.26, 127.21, 129.74, 136.42, 144.00 and 176.14.

***N*-Tosyl- β -alanine 9a.** Mp 119–121 °C (lit.,^{6c} 119–121 °C); $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3240 (OH), 2920, 1720 (C=O), 1440, 1320, 1160 and 1080; $\delta_{\text{H}}(\text{CDCl}_3)$ 2.43 (3 H, s, CH_3), 2.63 (2 H, t, J 5.6, $\text{CH}_2\text{CO}_2\text{H}$), 3.18 (2 H, t, J 5.8, CH_2NHTs), 5.91 (1 H, br s, NHTs), 7.32 (2 H, d, J 8.2, MeC_6H_4) and 7.75 (2 H, d, J 8.2, MeC_6H_4); $\delta_{\text{C}}(\text{CDCl}_3)$ 21.52, 33.81, 38.29, 127.00, 129.83, 136.85, 143.64 and 175.63.

General procedure for the hydrolysis of methyl esters **7b–d**

Methyl ester (2 mmol) was dissolved in methanol (7 cm^3). Aq. NaOH (1 M; 3 cm^3 , 3 mmol) was added and the solution was stirred at rt for 6 h before being acidified with 10% aq. HCl to pH \sim 2–3. The mixture was concentrated under reduced pressure to about one-quarter of its original volume. Ethyl acetate (5 cm^3) was added and the mixture was extracted with saturated aq. Na_2CO_3 (4 \times 5 cm^3). The combined aqueous extract was acidified with 10% aq. HCl to pH \sim 2–3. The mixture was then extracted with ethyl acetate (4 \times 10 cm^3). The combined organic solution was washed with saturated aq. NaCl and dried over anhydrous MgSO_4 . Removal of the drying agent and the solvent gave a crude acid, which was recrystallized from petroleum spirit–ethyl acetate.

***N*-Tosyl-L- β -homoalanine 9b.** 82%; Mp 87–88 °C; $[a]_D^{18}$ -26.8 (c 1.1, CHCl_3) [lit.,^{9b} for D-isomer, $[a]_D^{20}$ $+25.8$ (c 1.1, CHCl_3)]; $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3280 (NH), 3100 and 1710 (C=O); $\delta_{\text{H}}(\text{CDCl}_3)$ 1.15 (3 H, d, J 7.0, CH_3), 2.43 (3 H, s, $\text{CH}_3\text{C}_6\text{H}_4$), 2.51 (2 H, d, J 5.2, CH_2), 3.62 (3 H, s, CH_3O), 3.70 (1 H, m, CHNHTs), 5.53 (1 H, d, J 8.2, NHTs), 7.30 (2 H, d, MeC_6H_4) and 7.76 (2 H, d, J 8.2, MeC_6H_4); $\delta_{\text{C}}(\text{CDCl}_3)$ 21.04, 21.51, 40.54, 46.27, 126.99, 129.72, 137.66, 143.50 and 176.19.

***N*-Tosyl-L- β -homophenylalanine 9c.** 92%; Mp 85 °C (Found: C, 61.1; H, 5.7; N, 3.9. $\text{C}_{17}\text{H}_{19}\text{NO}_4\text{S}$ requires C, 61.24; H, 5.74; N, 4.20%); $[a]_D^{19}$ -22.4 (c 0.55, acetone); $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3320

(OH), 1710 (C=O), 1415, 1320, 1160 and 1090; $\delta_{\text{H}}(\text{CDCl}_3)$ 2.41 (3 H, s, CH_3), 2.55 (2 H, d, J 5.0, CH_2), 2.83 (2 H, m, PhCH_2), 3.70 (1 H, m, CHNHTs), 5.49 (1 H, d, J 9.0, NHTs), 6.99–7.04 (2 H, m, C_6H_5), 7.18–7.25 (5 H, m, C_6H_5 and MeC_6H_4) and 7.62 (2 H, d, J 8.2, MeC_6H_4); $\delta_{\text{C}}(\text{CDCl}_3)$ 21.52, 37.46, 40.47, 51.64, 126.89, 126.98, 128.72, 129.21, 129.69, 136.67, 137.21, 143.42 and 175.57.

***N*-Tosyl-L- β -homomethionine 9d.** 69%; Mp 84–85 °C (Found: C, 49.3; H, 5.7; N, 4.1. $\text{C}_{13}\text{H}_{19}\text{NO}_4\text{S}_2$ requires C, 49.19; H, 6.03; N, 4.41%); $[a]_D^{19}$ -10.8 (c 1.0, acetone); $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3280 (OH), 2920, 1700 (C=O), 1430, 1320, 1155 and 1080; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.72–1.87 (2 H, m, CH_2), 1.98 (3 H, s, CH_3S), 2.26–2.48 (2 H, m, CH_2), 2.43 (3 H, s, $\text{CH}_3\text{C}_6\text{H}_4$), 2.53 (2 H, d, J 4.2, CH_2), 3.60–3.70 (1 H, m, CHNHTs), 5.75 (1 H, d, J 9.0, NHTs), 7.32 (2 H, d, J 8.2, MeC_6H_4) and 7.80 (2 H, d, J 8.2, MeC_6H_4); $\delta_{\text{C}}(\text{CDCl}_3)$ 15.24, 21.54, 30.39, 33.32, 38.39, 49.38, 127.04, 129.79, 137.63, 143.65 and 176.27.

General procedure for the preparation of α -diazocarbonyl compounds **5a–d** and **10a–d**

The *N*-tosyl 2-amino acids **4a,b** (5 mmol) were mixed with dry dichloromethane (20 cm^3). The mixture was cooled and stirred under nitrogen atmosphere. Oxalyl dichloride (6 mmol) was then introduced, followed by the addition of 1 drop of DMF. The temperature of the reaction mixture was allowed to rise to ambient during 3 h. The solvent was then removed under reduced pressure and the acyl chloride thus obtained was used in the next step without further purification.

The acyl chloride was dissolved in anhydrous diethyl ether or THF (20 cm^3). The solution was added dropwise to a solution of diazomethane (13–20 mmol) in diethyl ether at 0 °C. The mixture was stirred for 4 h, during which the temperature slowly rose to ambient. Solvent was removed under reduced pressure and the residue was purified by column chromatography with petroleum spirit–ethyl acetate (3 : 1) as eluent.

Diazo-*(N*-tosylglycyl)methane 5a. 61%; Mp 118–120 °C (lit.,¹¹ 138–140 °C); $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3280 (NH), 3100, 2120 (CHN_2), 1645 (C=O), 1380, 1320, 1160 and 1060; $\delta_{\text{H}}(\text{CDCl}_3)$ 2.43 (3 H, s, CH_3), 3.72 (2 H, d, J 5.2, CH_2NHTs), 5.42 (1 H, s, COCHN_2), 5.45 (1 H, s, NHTs), 7.31 (2 H, d, J 8.2, MeC_6H_4) and 7.73 (2 H, d, J 8.2, MeC_6H_4); $\delta_{\text{C}}(\text{CDCl}_3)$ 21.51, 49.16, 54.24, 127.14, 129.82, 135.92, 143.93 and 188.60.

Diazo-*(N*-tosyl-L-alanyl)methane 5b. 45%; Mp 75–76 °C (lit.,¹¹ 75–76 °C); $[a]_D^{18}$ -133 (c 1.0, CHCl_3) {lit.,¹¹ $[a]_D^{20}$ -12.0 (CHCl_3)}; $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3280 (NH), 3225, 2115 (CHN_2), 1640 (C=O), 1605, 1355 and 1160; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.26 (3 H, d, J 7.4, CH_3), 2.43 (3 H, s, $\text{CH}_3\text{C}_6\text{H}_4$), 3.84 (1 H, m, CHNHTs), 5.48 (1 H, s, COCHN_2), 5.57 (1 H, d, J 7.4, NHTs), 7.30 (2 H, d, J 8.2, MeC_6H_4) and 7.72 (2 H, d, J 8.2, MeC_6H_4); $\delta_{\text{C}}(\text{CDCl}_3)$ 19.41, 21.51, 53.92, 55.33, 127.11, 129.75, 136.80, 143.80 and 192.77.

Diazo-*(N*-tosyl-L-phenylalanyl)methane 5c. 65%; Mp 99–100 °C (Found: C, 59.4; H, 4.9; N, 12.0. $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3\text{S}$ requires C, 59.46; H, 4.99; N, 12.24%); $[a]_D^{20}$ -78.1 (c 1.0, CH_2Cl_2); $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3280 (NHTs), 3080, 2100 (CHN_2), 1630 (C=O), 1370, 1330 and 1160; $\delta_{\text{H}}(\text{CDCl}_3)$ 2.42 (3 H, s, $\text{CH}_3\text{C}_6\text{H}_4$), 2.87 (2 H, d, J 6.8, CH_2Ph), 3.93 (1 H, m, CHNHTs), 5.05 (1 H, d, J 7.8, NHTs), 5.41 (1 H, s, COCHN_2), 6.97 (2 H, m, C_6H_5), 7.24 (5 H, m, C_6H_5 and MeC_6H_4) and 7.55 (2 H, d, J 8.2, MeC_6H_4); $\delta_{\text{C}}(\text{CDCl}_3)$ 21.54, 38.87, 54.76, 60.71, 127.10, 127.27, 128.82, 129.27, 129.72, 135.04, 136.35, 143.76 and 192.29; m/z (EI) 315 $[(\text{M} - \text{N}_2)^+$, 5%], 258 (17), 155 (30), 144 (48) and 91 (100).

Diazo-*(N*-tosyl-L-methionyl)methane 5d. 53%; Mp 101–102 °C (Found: C, 47.8; H, 5.0; N, 12.9. $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_3\text{S}_2$ requires C, 47.69; H, 5.23; N, 12.83%); $[a]_D^{20}$ -37.1 (c 1.0, CH_2Cl_2); $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3410 (NH), 3270, 3095, 2140 (CHN_2), 1615 (C=O), 1380, 1340 and 1160; $\delta_{\text{H}}(\text{CDCl}_3)$ 1.69–1.96 (2 H, m, CH_2), 1.98 (3 H, s, CH_3S), 2.43 (3 H, s, $\text{CH}_3\text{C}_6\text{H}_4$), 2.49 (2 H, t, J 6.8, MeSCH_2), 3.95 (1 H, m, CHNHTs), 5.42 (1 H, s, COCHN_2), 5.67 (1 H, d, J 8.2, NHTs), 7.30 (2 H, d, J 8.2,

MeC₆H₄) and 7.72 (2 H, d, *J* 8.2, MeC₆H₄); δ_C(CDCl₃) 15.32, 21.55, 29.75, 32.29, 54.53, 58.48, 127.23, 129.74, 136.68, 143.87 and 191.87; *m/z* (EI) 299 [(M - N₂)⁺, 8%], 258 (17), 155 (30), 144 (48) and 91 (100).

Diazo-(*N*-tosyl-β-alanyl)methane 10a. 74%; Mp 116–118 °C (lit.,¹¹ 113–115 °C); ν_{max}(KBr)/cm⁻¹ 3240 (NH), 3090, 2110 (CHN₂), 1620 (C=O), 1400, 1355, 1160 and 1065; δ_H(CDCl₃) 2.43 (3 H, s, CH₃), 2.56 (2 H, t, *J* 5.3, CH₂), 3.20 (2 H, dd, *J* 11.6 and 6.2, CH₂NHTs), 5.19 (1 H, d, *J* 7.5, NHTs), 5.24 (1 H, s, COCHN₂), 7.31 (2 H, d, *J* 8.2, MeC₆H₄) and 7.74 (2 H, d, *J* 8.2, MeC₆H₄); δ_C(CDCl₃) 21.46, 38.73, 39.53, 55.32, 126.98, 129.71, 136.84, 143.42 and 193.00.

Diazo-(*N*-tosyl-L-β-homoalanyl)methane 10b. 49%; Mp 80–82 °C (Found: C, 51.5; H, 5.2; N, 14.7. C₁₂H₁₅N₃O₃S requires C, 51.23; H, 5.37; N, 14.94%); [α]_D¹⁸ -80.8 (*c* 1.0, CH₂Cl₂); ν_{max}(KBr)/cm⁻¹ 3300 (NH), 2120 (CHN₂), 1600 (C=O), 1385, 1320, 1155 and 1085; δ_H(CDCl₃) 1.14 (3 H, d, *J* 7.0, CH₃), 2.40 (2 H, d, *J* 6.9, CH₂), 2.41 (3 H, s, CH₃C₆H₄), 2.65 (1 H, m, CHNHTs), 5.19 (1 H, s, COCHN₂), 5.34 (1 H, d, *J* 7.8, NHTs), 7.29 (2 H, d, *J* 8.6, MeC₆H₄) and 7.74 (2 H, d, *J* 8.6, MeC₆H₄); δ_C(CDCl₃) 21.26, 21.51, 46.03, 47.26, 55.80, 127.06, 129.66, 137.82, 143.33 and 192.51; *m/z* (EI) 253 [(M - N₂)⁺, 3%], 184 (12), 155 (58) and 91 (100).

Diazo-(*N*-tosyl-L-β-homophenylalanyl)methane 10c. 63%; Mp 109–110 °C (Found: C, 60.45; H, 5.3; N, 11.7. C₁₈H₁₉N₃O₃S requires C, 60.49; H, 5.36; N, 11.76%); [α]_D¹⁸ -43.2 (*c* 1.0, CH₂Cl₂); ν_{max}(KBr)/cm⁻¹ 3240 (NH), 3100, 2110 (CHN₂), 1620 (C=O), 1450, 1390, 1325, 1155 and 1060; δ_H(CDCl₃) 2.38 (m, 1 H, CHNHTs), 2.41 (3 H, s, CH₃C₆H₄), 2.42 (2 H, d, *J* 4.8, CH₂Ph), 2.82 (2 H, d, *J* 7.4, CH₂), 5.15 (1 H, s, COCHN₂), 5.36 (1 H, d, *J* 7.6, NHTs), 6.99–7.03 (2 H, m, C₆H₅), 7.18–7.26 (5 H, m, C₆H₅ and MeC₆H₄) and 7.61 (2 H, d, *J* 8.6, MeC₆H₄); δ_C(CDCl₃) 22.12, 41.41, 43.70, 53.15, 56.48, 127.40, 127.62, 129.27, 129.81, 131.20, 137.63, 137.90, 143.84 and 193.32; *m/z* (EI) [(M - N₂)⁺, 13%], 238 [(M - N₂ - C₇H₇)⁺, 55], 155 (78), 117 (97) and 91 (100).

Diazo-(*N*-tosyl-L-β-homomethionyl)methane 10d. 61%; Mp 78–79 °C (Found: C, 49.3; H, 5.4; N, 12.15. C₁₄H₁₉N₃O₃S₂ requires C, 49.25; H, 5.61; N, 12.31%); [α]_D¹⁸ -58.1 (*c* 1.0, CH₂Cl₂); ν_{max}(KBr)/cm⁻¹ 3220 (NH), 3085, 2010 (CHN₂), 1600 (C=O), 1380, 1320, 1160, 1120 and 1080; δ_H(CDCl₃) 1.25–1.91 (4 H, m, 2 × CH₂), 1.94 (3 H, s, CH₃S), 2.43 (3 H, s, CH₃C₆H₄), 2.01–2.48 (2 H, m, CH₂), 5.20 (1 H, s, COCHN₂), 5.67 (2 H, d, *J* 9.0, NHTs), 7.31 (2 H, d, *J* 8.1, MeC₆H₄) and 7.77 (2 H, d, *J* 8.1, MeC₆H₄); δ_C(CDCl₃) 15.29, 21.51, 30.48, 33.67, 43.69, 50.56, 55.93, 127.07, 129.66, 137.81, 143.42 and 192.60; *m/z* (EI) 313 [(M - N₂)⁺, 31%], 238 (17), 210 (20), 158 (56), 155 (33) and 91 (100).

General procedure of the PhCO₂Ag-catalysed diazo compound decomposition in anhydrous MeOH or THF

The diazo ketone was dissolved in anhydrous MeOH or THF (0.1 M). To the solution was then added dropwise a solution of silver benzoate (0.13 mol equiv. of the diazo ketone) in triethylamine (the volume of triethylamine was about one-eighth that of anhydrous MeOH or THF) at rt. The mixture was stirred at the same temperature for 2 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography with petroleum spirit–ethyl acetate (1:4) as eluent.

Diazo decomposition of diazo-(*N*-tosylglycyl)methane 5a. Diazo decomposition of substrate **5a** in anhydrous MeOH gave *N*-tosylazetidin-3-one **6a** as the only product in 40% yield, mp 143–144 °C (lit.,¹² 142–143 °C); ν_{max}(KBr)/cm⁻¹ 1830 (C=O), 1600 and 1150; δ_H(CDCl₃) 2.47 (3 H, s, CH₃), 4.63 (4 H, s, 2 × CH₂), 7.40 (2 H, d, *J* 8.4, MeC₆H₄) and 7.80 (2 H, d, *J* 8.4, MeC₆H₄); δ_C(CDCl₃) 21.53, 72.40, 128.32, 130.06, 131.37, 145.05 and 192.54.

Diazo decomposition of diazo-(*N*-tosyl-L-alanyl)methane 5b. Diazo decomposition of substrate **5b** in anhydrous MeOH

gave 2(*S*)-methyl-*N*-tosylazetidin-3-one **6b** and *N*-tosyl-L-β-homoalanine methyl ester **7b** as a 1:1 mixture. Compound **6b**: 34%; mp 76–77 °C (lit.,¹² 75–76 °C; lit.,¹³ 78–79 °C); [α]_D²⁰ +55 (*c* 1.0, CHCl₃) [lit.,¹³ [α]_D²⁰ +80 (*c* 1.0, CHCl₃)]; ν_{max}(KBr)/cm⁻¹ 2935, 1830 (C=O), 1160 and 955; δ_H(CDCl₃) 1.46 (3 H, d, *J* 6.8, CH₃), 2.47 (3 H, s, CH₃C₆H₄), 4.50 (2 H, s, CH₂), 4.77 (1 H, q, *J* 6.8, CHMe), 7.40 (2 H, d, *J* 8.0, MeC₆H₄) and 7.80 (2 H, d, *J* 8.0, MeC₆H₄); δ_C(CDCl₃) 15.69, 21.59, 69.55, 80.96, 128.39, 130.02, 131.75, 144.93 and 196.66. Compound **7b**:¹⁴ 35%; mp 78–79 °C; [α]_D¹⁹ -27.4 (*c* 0.71, CH₂Cl₂); ν_{max}(KBr)/cm⁻¹ 3250 (NH), 3000, 1740 (C=O), 1600, 1440, 1335, 1160 and 1080; δ_H(CDCl₃) 1.14 (3 H, d, *J* 6.6, CH₃), 2.43 (3 H, s, CH₃C₆H₄), 2.43 (2 H, s, CH₂), 3.62 (3 H, s, CH₃O), 3.68 (1 H, m, CHNHTs), 5.23 (1 H, d, *J* 8.6, NHTs), 7.30 (2 H, d, *J* 7.8, MeC₆H₄) and 7.76 (2 H, d, *J* 7.8, MeC₆H₄); δ_C(CDCl₃) 20.71, 21.17, 40.27, 46.22, 51.35, 126.69, 129.33, 137.64, 142.98 and 171.17.

Diazo decomposition of diazo-(*N*-tosyl-L-phenylalanyl)-methane 5c. Diazo decomposition of substrate **5c** in anhydrous MeOH gave 2(*S*)-benzyl-*N*-tosylazetidin-3-one **6c** and *N*-tosyl-L-β-homophenylalanine methyl ester **7c** in 1:1.8 ratio. Compound **6c**: 29%; mp 97–98 °C (Found: C, 64.8; H, 5.2; N, 4.3. C₁₇H₁₇NO₃S requires C, 64.74; H, 5.43; N, 4.44%); [α]_D²⁰ +4.7 (*c* 1.0, CHCl₃); ν_{max}(KBr)/cm⁻¹ 2940, 1820 (C=O), 1595, 1340, 1160 and 1110; δ_H(CDCl₃) 2.47 (3 H, s, CH₃C₆H₄), 3.17 (2 H, br s, CH₂), 4.18 (1 H, d, *J* 16.4, CH₂), 4.45 (1 H, d, *J* 16.4, CH₂), 4.98 (1 H, br s, CHBzl), 7.10–7.35 (m, 5 H, C₆H₅), 7.38 (2 H, d, *J* 7.6, MeC₆H₄) and 7.76 (2 H, d, *J* 7.6, MeC₆H₄); δ_C(CDCl₃) 21.60, 36.58, 69.85, 85.24, 127.02, 128.34, 128.43, 129.93, 130.04, 134.88, 140.50, 144.92 and 195.92; *m/z* (EI) 315 (M⁺, 2%), 287 [(M - CO)⁺, 3], 155 (20), 132 (100) and 91 (66). Compound **7c**: 53%; mp 96–98 °C (Found: C, 62.1; H, 5.9; N, 3.85. C₁₈H₂₁NO₄S requires C, 62.22; H, 6.09; N, 4.03%); [α]_D¹⁹ -18.1 (*c* 0.62, CH₂Cl₂); ν_{max}(KBr)/cm⁻¹ 3310 (NH), 2940, 1740 (C=O), 1600, 1440, 1335, 1160 and 1090; δ_H(CDCl₃) 2.42 (3 H, s, CH₃), 2.48 (2 H, d, *J* 5.2, PhCH₂), 2.80 (2 H, d, *J* 6.4, CH₂CO₂Me), 3.64 (3 H, s, CH₃O), 3.77 (1 H, m, CHNHTs), 5.19 (1 H, d, *J* 8.2, NHTs), 7.02 (2 H, m, C₆H₅), 7.21 (5 H, m, C₆H₅ and MeC₆H₄) and 7.63 (2 H, d, *J* 7.4, MeC₆H₄); δ_C(CDCl₃) 21.47, 37.80, 40.73, 51.71, 51.81, 126.78, 126.96, 128.62, 129.22, 129.57, 136.67, 137.44, 143.18 and 171.62; *m/z* (EI) 274 [(M - CH₂CO₂Me)⁺, 7%], 256 [(M - C₇H₇)⁺, 92], 155 (62) and 91 (100).

Diazo decomposition of diazo-(*N*-tosyl-L-methionyl)methane 5d. Diazo decomposition of substrate **5d** in anhydrous MeOH gave 2(*S*)-[2-(methylthio)ethyl]-*N*-tosylazetidin-3-one **6d** and *N*-tosyl-L-β-homomethionine methyl ester **7d** in 1:1.4 ratio. Compound **6d**: 34%; mp 83–84 °C (Found: C, 52.25; H, 5.6; N, 4.55. C₁₃H₁₇NO₃S₂ requires C, 52.15; H, 5.72; N, 4.68%); [α]_D²⁰ +65.0 (*c* 1.00, CHCl₃); ν_{max}(KBr)/cm⁻¹ 2920, 1810 (C=O), 1345, 1160, 1085 and 1025; δ_H(CDCl₃) 2.04 (3 H, s, CH₃S), 2.14 (2 H, q, *J* 6.6, CH₂), 2.48 (3 H, s, CH₃C₆H₄), 2.71 (2 H, dt, *J* 5.8 and 1.6, CH₂), 4.45 (1 H, d, *J* 15.8, CH₂), 4.63 (1 H, dd, *J* 15.8 and 4.2, CH₂), 4.79–4.90 (1 H, m, CH), 7.41 (2 H, d, *J* 8.0, MeC₆H₄) and 7.80 (2 H, d, *J* 8.0, MeC₆H₄); δ_C(CDCl₃) 14.73, 21.64, 29.06, 29.27, 70.48, 83.15, 128.56, 130.09, 130.98, 145.05 and 196.31; *m/z* (EI) 299 (M⁺, 2%), 184 (2), 155 (6), 144 (38), 91 (21) and 43 (100). Compound **7d**: 48%; mp 72–74 °C (Found: C, 50.7; H, 6.2; N, 4.1. C₁₄H₂₁NO₄S₂ requires C, 50.73; H, 6.39; N, 4.23%); [α]_D¹⁹ -13.1 (*c* 0.54, CH₂Cl₂); ν_{max}(KBr)/cm⁻¹ 3240 (NH), 1720 (C=O), 1440, 1240, 1210, 1140 and 1095; δ_H(CDCl₃) 1.71–1.79 (4 H, m, 2 × CH₂), 2.00 (3 H, s, CH₃S), 2.35–2.43 (2 H, m, CH₂), 2.38 (3 H, s, CH₃C₆H₄), 3.63 (3 H, s, CH₃O), 3.62–3.78 (1 H, m, CHNHTs), 5.42 (1 H, d, *J* 8.0, NHTs), 7.31 (2 H, d, *J* 8.3, MeC₆H₄) and 7.77 (2 H, d, *J* 8.3, MeC₆H₄); δ_C(CDCl₃) 15.28, 21.52, 30.39, 33.60, 38.32, 49.69, 51.79, 127.05, 129.71, 137.96, 143.45 and 171.61; *m/z* (EI) 331 (M⁺, 10%), 258 [(M - CH₂CO₂Me)⁺, 11], 176 (82), 155 (40), 128 (71), 102 (53) and 91 (100).

Diazo decomposition of diazo-(*N*-tosyl-β-alanyl)methane 10a. Diazo decomposition of substrate **10a** with PhCO₂Ag–Et₃N in

anhydrous MeOH gave methyl 4-(tosylamino)butanoate **12a** as the only isolated product, in 81% yield. The same reaction with anhydrous THF as solvent gave *N*-tosylpyrrolidin-2-one **11a** as the only product, in 93% yield. Lactam **11a**: mp 143–144 °C (lit.,¹⁵ 142–143 °C); ν_{\max} (KBr)/cm⁻¹ 1720 (C=O), 1360, 1160 and 1120; δ_{H} (CDCl₃) 2.10 (2 H, m, CH₂), 2.43 (2 H, t, *J* 7.8, CH₂), 2.44 (3 H, s, CH₃C₆H₄), 3.90 (2 H, t, *J* 7.1, CH₂), 7.34 (2 H, d, *J* 8.1, MeC₆H₄) and 7.92 (2 H, d, *J* 8.1, MeC₆H₄); δ_{C} (CDCl₃) 18.15, 21.64, 32.19, 47.22, 128.03, 129.62, 135.10, 145.11 and 173.28. Ester **12a**: mp 92–93 °C (lit.,¹⁶ 92–93 °C); ν_{\max} (KBr)/cm⁻¹ 3280 (NH), 2970, 1720 (C=O), 1435, 1330, 1205 and 1160; δ_{H} (CDCl₃) 1.83 (2 H, m, CH₂), 2.36 (2 H, t, *J* 7.0, CH₂), 2.43 (3 H, s, CH₃C₆H₄), 2.98 (2 H, dd, *J* 12.0 and 6.4, CH₂), 5.10 (1 H, br s, NHTs), 7.30 (2 H, d, *J* 8.2, MeC₆H₄) and 7.74 (2 H, d, *J* 8.2, MeC₆H₄); δ_{C} (CDCl₃) 21.14, 24.34, 30.57, 42.15, 51.34, 126.70, 129.34, 136.61, 143.02 and 173.19.

Diazo decomposition of diazo-(*N*-tosyl-L-β-homoalanyl)-methane 10b. Diazo decomposition of substrate **10b** with PhCO₂Ag–Et₃N in anhydrous MeOH gave 5(*S*)-methyl-*N*-tosylpyrrolidin-2-one **11b** as the only isolated product, in 89% yield. The same reaction with anhydrous THF as solvent gave lactam **11b** as the only product, in 85% yield. **Compound 11b**: mp 136–138 °C (Found: C, 56.95; H, 5.8; N, 5.4. C₁₂H₁₅NO₃S requires C, 56.90; H, 5.97; N, 5.53%); $[\alpha]_{\text{D}}^{20} + 55.9$ (*c* 1.5, CH₂Cl₂); ν_{\max} (KBr)/cm⁻¹ 1720 (C=O), 1355, 1160, 1120 and 1080; δ_{H} (CDCl₃) 1.48 (3 H, d, *J* 6.8, CH₃), 1.77 (2 H, m, CH₂), 2.39 (2 H, m, CH₂), 2.45 (3 H, s, CH₃C₆H₄), 4.54 (1 H, t, *J* 5.9, CHMe), 7.33 (2 H, d, *J* 8.0, MeC₆H₄) and 7.96 (2 H, d, *J* 8.0, MeC₆H₄); δ_{C} (CDCl₃) 21.15, 21.30, 26.30, 30.19, 56.00, 127.96, 129.12, 135.82, 144.52 and 172.84; *m/z* (EI) 253 (M⁺, 2%), 238 [(M – Me)⁺, 3], 189 (96), 174 (100), 155 (85) and 91 (97).

Diazo decomposition of diazo-(*N*-tosyl-L-β-homophenylalanyl)methane 10c. Diazo decomposition of substrate **10c** with PhCO₂Ag–Et₃N in anhydrous MeOH gave 5(*S*)-benzyl-*N*-tosylpyrrolidin-2-one **11c** as the only isolated product, in 91% yield. The same reaction with anhydrous THF as solvent gave compound **11c** as the only product, in 86% yield. **Compound 11c**: mp 103–105 °C (Found: C, 65.6; H, 5.8; N, 4.1. C₁₈H₁₉NO₃S requires C, 65.63; H, 5.81; N, 4.25%); $[\alpha]_{\text{D}}^{18.5} + 81.9$ (*c* 1.31, CH₂Cl₂); ν_{\max} (KBr)/cm⁻¹ 2930, 1720 (C=O), 1355, 1160 and 1105; δ_{H} (CDCl₃) 1.81–2.20 (4 H, m, 2 × CH₂), 2.44 (3 H, s, CH₃), 2.87 (1 H, dd, *J* 8.8 and 13.4, PhCH₂), 3.33 (1 H, dd, *J* 3.2 and 13.4, PhCH₂), 4.64 (1 H, br s, CHBzl), 7.20–7.37 (7 H, m, C₆H₅ and MeC₆H₄) and 8.00 (2 H, d, *J* 8.2, MeC₆H₄); δ_{C} (CDCl₃) 21.67, 22.87, 30.40, 40.66, 60.93, 127.04, 128.37, 128.77, 129.55, 136.03, 136.33, 145.08 and 173.44; *m/z* (EI) 329 (M⁺, 3%), 238 [(M – C₇H₇)⁺, 73], 155 (72) and 91 (100).

Diazo decomposition of diazo-(*N*-tosyl-L-β-homomethionyl)-methane 10d. Diazo decomposition of substrate **10d** with PhCO₂Ag–Et₃N in anhydrous MeOH gave 5(*R*)-[2-(methylthio)ethyl]-*N*-tosylpyrrolidin-2-one **11d** and methyl 6-methylthio-4(*R*)-tosylaminohexanoate **12d** as a 1:3 mixture in 91% yield. Compounds **11d** and **12d** were found to be inseparable by column chromatography and TLC. The same reaction with anhydrous THF as solvent gave 5(*R*)-[2-(methylthio)ethyl]-*N*-tosylpyrrolidin-2-one **11d** as the only product, in 93% yield. **Compound 11d**: mp 64–65 °C (Found: C, 53.85; H, 6.15; N, 4.2. C₁₄H₁₉NO₃S₂ requires C, 53.65; H, 6.11; N, 4.47%); $[\alpha]_{\text{D}}^{20} + 65.8$ (*c* 1.84, CH₂Cl₂); ν_{\max} (KBr)/cm⁻¹ 2920, 1730 (C=O), 1360, 1200, 1165 and 1100; δ_{H} (CDCl₃) 1.80–2.04 (2 H, m, CH₂), 2.20 (3 H, s, CH₃S), 2.44 (3 H, s, CH₃C₆H₄), 2.24–2.60 (6 H, m, 3 × CH₂), 4.54 (1 H, m, CH), 7.34 (2 H, d, *J* 8.2, MeC₆H₄) and 7.95 (2 H, d, *J* 8.2, MeC₆H₄); δ_{C} (CDCl₃) 15.29, 21.63, 23.55, 29.65, 30.56,

33.54, 59.16, 128.26, 129.49, 153.79, 145.03 and 173.25; *m/z* (EI) 313 (M⁺, 6%), 238 [(M – CH₂CH₂SCH₃)⁺, 3], 158 (84), 155 (28), 91 (80) and 84 (100). Compound **12d**: the ¹H NMR and ¹³C NMR spectra of compound **12d** were obtained by comparison of the spectra of pure compound **11d** and the mixture of products **11d** and **12d**. δ_{H} (CDCl₃) 1.58–1.82 (4 H, m, 2 × CH₂), 2.05 (3 H, s, CH₃S), 2.25–2.57 (4 H, m, 2 × CH₂), 2.52 (3 H, s, CH₃C₆H₄), 3.42 (1 H, m, CHNHTs), 3.65 (3 H, s, CH₃O), 5.02 (1 H, d, *J* 8.0, NHTs), 7.30 (2 H, d, *J* 8.2, MeC₆H₄) and 7.75 (2 H, d, *J* 8.2, MeC₆H₄); δ_{C} (CDCl₃) 15.12, 21.37, 29.57, 29.89, 29.94, 34.32, 51.56, 52.71, 126.87, 129.54, 138.06, 143.18 and 173.71.

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