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TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of enantiomerically pure 4,5-disubstituted pyrrolidinones from β-amino esters

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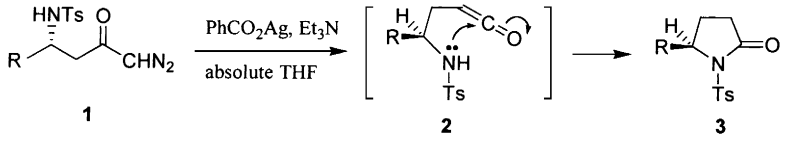
Abstract

α-Alkylation of *N*-tosyl-protected β-amino esters with LDA as the base led to high *anti* selectivity for the newly formed C–C bond. The α-alkylated β-amino esters were further transformed to enantiomerically pure 4,5-disubstituted pyrrolidinones through hydrolysis, diazotization, and Wolf rearrangement under AgO_2CPh/Et_3N/dry THF conditions.

1. Introduction

The syntheses of enantiomerically pure pyrrolidin-2-ones with different substituents have attracted considerable attention from synthetic organic chemists in recent years, and a number of synthetic methodologies have been developed.[1] We have recently reported an efficient route to enantiomerically pure *N*-tosyl-protected 5-substituted pyrrolidin-2-ones **3**, starting from β-amino acids.[2] The key step in this transformation is the intramolecular nucleophilic addition of the *N*-tosyl-protected amino group to the ketene, which is generated through the Wolff rearrangement[3,4] of the α-diazo carbonyl group (Scheme 1).



1 **2** **3**

Scheme 1.

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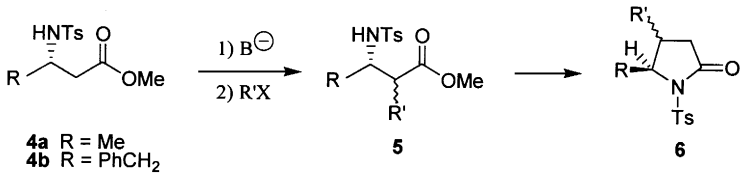
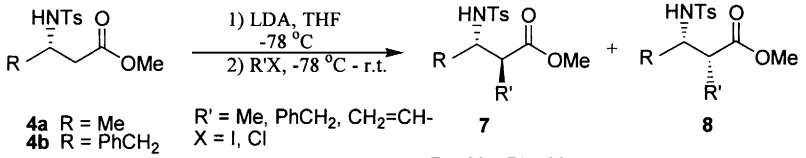
We envisaged that this approach might be extended to the synthesis of 4,5-disubstituted pyrrolidinones **6** through diastereoselective α-alkylation of the *N*-tosyl-protected β-amino esters **4** (Scheme 2). Here we wish to report the results of the investigation based on this consideration.



Scheme 2.

The key issue in this approach is the diastereoselective alkylation of *N*-tosyl-protected amino esters. The α-alkylation of β-amino esters has been studied by several groups, and their results suggest that high diastereoselectivity can be generally achieved.[5] Based on the results from these reports, we expected similarly high diastereoselectivity in the α-alkylation of *N*-tosyl-protected amino esters, for which the α-alkylation has not been previously studied. Thus, the *N*-tosyl-protected α-amino methyl esters **4a** and **4b**, which were prepared from L-alanine and L-phenylalanine,[2] were deprotonated with 2.2 equivalents of LDA in anhydrous THF followed by the addition of halide. ^{1}H and ^{13}C NMR analysis of the crude products provided the ratio of the diastereoisomers **7** and **8**, and the results are summarized in Scheme 3. As shown in Scheme 3, the diastereoselectivity of the α-alkylation is generally high. This is consistent with the results reported for the α-alkylation of *N*-benzyloxycarbonyl (Cbz)[5g] or benzoyl[5a] protected α-amino esters. The stereochemistry of the newly introduced stereogenic center was determined by chemical transformation to pyrrolidin-2-ones and ^{1}H NMR analysis (vide infra).

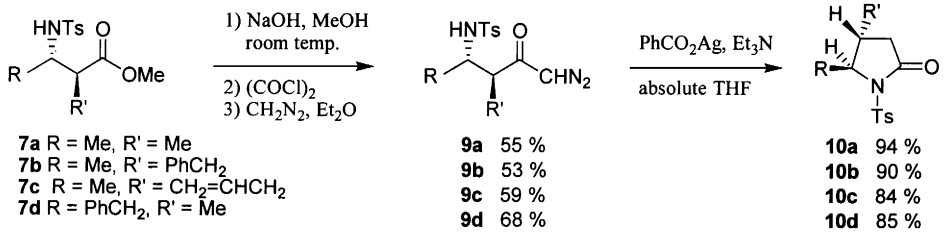


a R = Me, R' = Me	95 : 5
b R = Me, R' = $PhCH_2$	95 : 5
c R = Me, R' = CH_2=$CHCH_2$	> 95 : 5
d R = $PhCH_2$, R' = Me	91 : 9
e R = $PhCH_2$, R' = $PhCH_2$	75 : 25

Scheme 3.

The major alkylation products together with their corresponding minor diastereoisomers, which are not separable by column chromatography from the major isomers, were purified by column chromatography. The alkylated esters were subjected to hydrolysis at room temperature to give acids. The acids were then converted into their corresponding α-diazo carbonyls **9a**–**d** by the conventional procedure.[2,6] Finally, the Wolff rearrangement of the α-diazo carbonyl compounds **9a**–**d** under the conditions that we reported previously (AgO_2CPh/Et_3N/dry THF)[2] led to the corresponding 4,5-disubstituted pyrrolidin-2-ones **10a**–**d** (Scheme 4). Column chromatography separation isolated a major product in each case. ^{1}H and ^{13}C NMR spectra of the products indicated that the disubstituted pyrrolidinones were single diastereoisomers in each case. It is known that the Wolff rearrangement proceeds with the retention of the configuration at the carbon where the migration occurs.[2,3c] The fact that single diastereoisomers of 4,5-disubstituted pyrrolidin-2-ones are obtained in high yields through the transformation from the alkylated β-amino ester by hydrolysis, diazotization and the Wolff rearrangement suggests that the stereochemistry of the α-alkyl group is retained during these transformations.

The stereochemistry of the newly introduced substituent at the 4-position was established by NOESY spectra of the pyrrolidin-2-ones. In the NOESY spectrum of pyrrolidinones **10a**, an NOE effect was



Scheme 4.

observed between the 5-Me group and 4-H, and the 4-Me group and 5-H, respectively. This suggests that the two methyl groups have *anti* configuration. The NOE spectrum of **10d** showed similar results (Fig. 1).

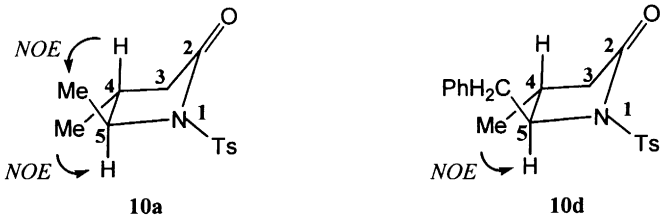


Fig. 1. NOE correlations in the NOESY spectra of **10a** and **10d**

From the stereochemistry of the 4,5-disubstituted pyrrolidinones, we can deduce that the major isomer of the α-alkylation products was **7a**–**e**. This shows that alkylation with LDA as the base results in high *anti* selectivity. The *anti* selectivity has been generally observed in the α-alkylation of β-amino esters.[5] This selectivity can be reasonably interpreted by considering the chelation of a lithium ion between enolate oxygen and the deprotonated amino group. The chelated enolate prefers to take the half-chair conformation with the R group occupying a pseudo-axial position (Fig. 2). The alkylation takes place by the attack of electrophile from the opposite side of the neighboring R group, leading to the alkylation product with *anti* selectivity. To test if the stereochemistry is controlled by the presence of a chelation complex, we used *N*-sodium bis(trimethylsilyl)amide (NaHMDS) as the base in the alkylation reaction. It was expected that diastereoselectivity would decrease, since the sodium ion does not form a strong chelation complex with enolates. However, the alkylation with this base led only to an *N*-alkylated product; no trace α-carbon alkylation product was obtained. The alkylation with LDA as the base in the presence of HMPA as co-solvent also led to the *N*-alkylation.

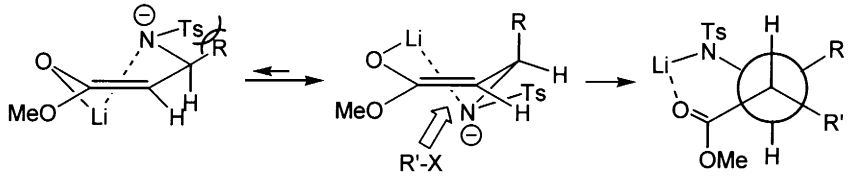


Fig. 2.

In conclusion, we have demonstrated that high diastereoselectivity could be achieved in the α-alkylation of the *N*-tosyl-protected β-amino esters. The α-alkylated β-amino esters can be easily transformed to 4,5-substituted pyrrolidin-2-ones in four steps. Since enantiomerically pure *N*-tosyl-protected β-amino esters are easily available[7] and the stereochemistry of the amino group will stay unchanged in the reactions, this transformation should find application to the synthesis of enantiomerically pure polysubstituted pyrrolidin-2-ones in general.

2. Experimental

2.1. General

Melting points were determined in capillaries and are uncorrected. All reactions with air- and moisture-sensitive components were performed under a nitrogen atmosphere in a flame-dried reaction flask, and the components were added via syringe. All solvents were distilled prior to use. The boiling point of petroleum ether is between 30 and 60°C. THF was distilled from sodium prior to use. For chromatography, 100–200 mesh silica gel (Qingdao, China) was employed. For preparative TLC, 10–40 μm silica gel GF254 (Qingdao, China) was used. Recrystallization was from petroleum ether–ethyl acetate. Diazomethane solution in dry ether was prepared from *N*-methyl-*N*-nitrosourea. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz with a Varian Mercury 200 spectrometer, or at 400 and 100.6 MHz with a Bruker ARX400 spectrometer. Chemical shifts are reported in ppm using tetramethylsilane as internal standard. 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 in the Analysis Center of Peking University.

2.2. Typical procedure for the alkylation of β-amino esters **4a** and **4b**

Butyllithium (4 mL, 1.5 M in hexane, 6 mmol) was added dropwise to diisopropylamine (1.1 mL, 7.5 mmol) in absolute THF (20 mL) at 0°C under a nitrogen atmosphere. After the solution was stirred for about 15 min at the same temperature, it was cooled to −78°C. β-Amino ester **4a** or **4b** (3 mmol) in absolute THF (10 mL) was added dropwise. The solution was stirred for 30 min, during which time the temperature rose to −40°C. The solution was cooled to −78°C again and R′X (6 mmol) in absolute THF (3 mL) was added dropwise to the solution. The solution was stirred until the temperature rose to about 25°C. Saturated aqueous NH_4Cl was added and the THF was removed by evaporation. The residue was extracted with EtOAc (3×20 mL). The combined organic solution was washed with H_2O (20 mL) and saturated aqueous NaCl, and then dried over anhydrous $MgSO_4$. Removal of the drying agent and the solvent gave an oily residue which was purified by column chromatography with petroleum ether:EtOAc=5:1 as eluent.

2.3. Typical procedure for the hydrolysis of alkylated β-amino esters **7a–e**

The β-amino methyl ester **7a–e** (2 mmol) was dissolved in aqueous NaOH (3 mL, 1.0 M, 3 mmol). The homogenous solution was stirred at room temperature until the starting material disappeared. The solution was acidified to pH=2–3 with 10% aqueous HCl. The mixture was concentrated with evaporation to about one fourth of the original volume and it was then extracted with EtOAc (10 mL). The organic solution was extracted with 1 M NaOH (3×10 mL), and the combined basic solution was acidified to pH=2–3 with 10% aqueous HCl. The mixture was then extracted with EtOAc (4×10 mL). The combined organic solution was washed with brine and dried over $MgSO_4$. Removal of the solvent gave a crude solid, which was used for the next step without further purification.

2.3.1. N-*Tosyl-2(*S*)-methyl-*L*-β-homoalanine methyl ester **7a***

88%; Oil; IR 3560, 3240, 2960, 1720 (C=O), 1420, 1320, 1140, 1080 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.02 (d, J=6.7 Hz, 3H), 1.10 (d, J=7.2 Hz, 3H), 2.42 (s, 3H), 2.52–2.57 (m, 1H), 3.48–3.55 (m, 1H), 3.63 (s, 3H), 5.19 (d, J=9.2 Hz, 1H), 7.29 (d, J=8.5 Hz, 2H), 7.76 (d, J=8.5 Hz, 2H); ^{13}C NMR (50 MHz)

δ 13.88, 19.54, 21.41, 44.42, 51.55, 51.69, 126.90, 129.54, 138.37, 143.11, 174.92; MS (*m/z*, relative intensity) 286 (MH^+, 16), 285 (M^+, 0.5), 270 [$(M-Me)^+$, 15), 198 (96), 155 (89), 91 (100). HRMS: calcd for M^+ $C_{13}H_{19}O_4NS$, 285.1035; found, 285.1027; calcd for MH^+ $C_{13}H_{20}O_4NS$, 286.1113; found, 286.1109.

2.3.2. N-*Tosyl-2(*S*)-benzyl-*L*-β-homoalanine methyl ester* ***7b***

47%; M.p. 108–109°C; IR 3250 (NH), 2915, 1700 (C=O), 1410, 1315, 1200, 1140, 1065 cm^{-1}; ^1H NMR δ 1.02 (d, *J*=6.6 Hz, 3H), 2.41 (s, 3H), 2.62–2.90 (m, 3H), 3.55 (s, 3H), 3.51–3.65 (m, 1H), 5.42 (d, *J*=10.0 Hz, 1H), 7.05–7.27 (m, 5H), 7.29 (d, *J*=8.2 Hz, 2H), 7.77 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (50 MHz) δ 20.64, 21.50, 35.57, 50.16, 51.68, 52.60, 126.58, 126.98, 128.49, 128.84, 129.67, 138.43, 138.79, 143.23, 174.25; MS (*m/z*, relative intensity) 361 (M^+, 7), 318 (4), 256 (5), 198 (38), 155 (51), 116 (33), 91 (100); anal calcd for $C_{19}H_{23}O_4NS$: C, 63.16; H, 6.37; N, 3.87; found: C, 62.86; H, 6.37; N, 3.64.

2.3.3. N-*Tosyl-2(*S*)-vinyl-*L*-β-homoalanine methyl ester* ***7c***

71%; Oil; IR 3250 (NH), 2970, 1720 (C=O), 1420, 1320, 1145, 1080 cm^{-1}; ^1H NMR (400 MHz) δ 1.03 (d, *J*=6.8 Hz, 3H), 2.17–2.23 (m, 1H), 2.32–2.37 (m, 1H), 2.42 (s, 3H), 2.45–2.51 (m, 1H), 3.55–3.63 (m, 1H), 3.64 (s, 3H), 4.96 (d, br, *J*=4.0 Hz, 1H), 5.00 (s, 1H), 5.30 (d, *J*=9.6 Hz, 1H), 5.58–5.5.71 (m, 1H), 7.29 (d, *J*=8.1 Hz, 2H), 7.75 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (100 MHz) δ 20.40, 21.45, 33.58, 50.00, 50.32, 51.68, 117.41, 126.93, 129.57, 134.48, 138.62, 143.16, 174.18; MS (*m/z*, relative intensity) 311 (M^+, 6), 296 [$(M-Me)^+$, 22], 198 (100), 155 (96), 142 (46), 91 (194); HRMS calcd for M^+ $C_{15}H_{21}O_4NS$ 311.1191; found, 311.1201.

2.3.4. N-*Tosyl-2(*S*)-methyl-*L*-β-homophenylalanine methyl ester* ***7d***

82%; Oil; IR 3275 (NH), 2920, 1720 (C=O), 1595, 1440, 1320, 1150 cm^{-1}; ^1H NMR (400 MHz) δ 1.08 (d, *J*=7.2 Hz, 3H), 2.40 (s, 3H), 2.60–2.75 (m, 2H), 3.54–3.61 (m, 1H), 3.68 (s, 3H), 5.30 (s, 1H), 5.41 (d, *J*=8.9 Hz, 1H), 6.97–7.01 (m, 2H), 7.16–7.26 (m, 3H), 7.22 (d, *J*=8.5 Hz, 2H), 7.65 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (50 MHz) δ 14.48, 21.42, 40.10, 40.67, 51.83, 57.65, 126.68, 126.87, 128.59, 129.13, 129.55, 137.19, 138.11, 143.05; MS (*m/z*, relative intensity) 362 (MH^+, 6), 270 [$(M-C_6H_5CH_2)^+$, 100], 238 [$(M-C_6H_5CH_2-CH_3OH)^+$, 28], 155 (85), 91 (100); HRMS calcd $(MH)^+$ $C_{19}H_{24}O_4NS$ 362.1426; found, 362.1442.

2.3.5. N-*Tosyl-2(*S*)-benzyl-*L*-β-homophenylalanine methyl ester* ***7e***

51%; Oil; IR 3285 (NH), 2965, 1720 (C=O), 1595, 1440, 1320, 1200, 1150, 1080, 1045 cm^{-1}; ^1H NMR (400 MHz) δ 2.40 (s, 3H), 2.62–2.92 (m, 5H), 3.56 (s, 3H), 3.68 (m, 1H), 5.70 (d, *J*=9.1 Hz, 1H), 6.90–7.00 (m, 4H), 7.17–7.21 (m, 6H), 7.25 (d, *J*=8.0 Hz, 2H), 7.72 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (50 MHz) δ 21.40, 35.21, 40.47, 48.17, 51.69, 55.90, 126.32, 126.60, 126.83, 128.23, 128.59, 129.03, 129.14, 129.50, 129.56, 136.77, 138.01, 143.12, 174.17; MS (*m/z*, relative intensity) 346 [$(M-C_6H_5CH_2)^+$, 82], 298 (72), 274 (24), 242 (15), 175 (91), 91 (100); HRMS calcd for $(M-C_6H_5CH_2)^+$ $C_{18}H_{20}O_4NS$ 346.1113; found, 346.1112.

2.3.6. N-*Tosyl-2(*S*)-methyl-*L*-β-homoalanine*

93%; M.p. 83–84°C; IR 3220 (OH), 2960, 1710 (C=O), 1430, 1310, 1120 cm^{-1}; ^1H NMR (200 MHz) δ 1.06 (d, *J*=7.0 Hz, 3H), 1.16 (d, *J*=7.0 Hz, 3H), 2.42 (s, 3H), 2.52–2.66 (m, 1H), 3.46–3.60 (m, 1H), 5.37 (d, *J*=9.2 Hz, 1H), 7.28 (d, *J*=8.2 Hz, 2H), 7.76 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (50 MHz) δ 13.82, 19.35, 21.48, 44.43, 51.41, 126.94, 129.64, 138.04, 143.33, 179.58; MS (*m/z*, relative intensity) 256

[$(M-Me)^+$, 9], 198 (69), 155 (70), 91 (100); anal. calcd for $C_{12}H_{17}NO_4S$: C, 53.14; H, 6.27; N, 5.17; found: C, 53.12; H, 6.31; N, 4.95.

2.3.7. N-*Tosyl-2(*S*)-benzyl-*L*-β-homoalanine*

93%; Oil; IR 3235 (OH), 2930, 1680 (C=O), 1420, 1300, 1220, 1135, 1065 cm^{-1}; ^1H NMR (200 MHz) δ 1.04 (d, *J*=6.8 Hz, 3H), 2.41 (s, 3H), 2.70–3.10 (m, 3H), 3.60 (m, 1H), 5.60 (d, *J*=9.6 Hz, 1H), 7.05–7.20 (m, 2H), 7.22–7.30 (m, 3H), 7.29 (d, *J*=8.5 Hz, 2H), 7.77 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (50 MHz) δ 20.32, 21.50, 34.99, 49.80, 52.47, 126.63, 127.03, 128.53, 128.90, 129.70, 138.27, 138.32, 143.42, 178.67; MS (*m/z*, relative intensity) 347 (M^+, 23), 301 (21), 256 [$(M-C_6H_5CH_2)^+$, 7], 198 (44), 155 (46), 91 (100); HRMS calcd for $C_{18}H_{21}O_4NS$ 347.1191; found: 347.1183.

2.3.8. N-*Tosyl-2(*S*)-vinyl-*L*-β-homoalanine*

96%; M.p. 110–112°C; IR 3230 (OH), 2950, 1690 (C=O), 1415, 1305, 1230, 1135, 1075 cm^{-1}; ^1H NMR (200 MHz) δ 1.07 (d, *J*=6.8 Hz), 2.22–2.76 (m, 3H), 2.42 (s, 3H), 2.53–3.70 (m, 1H), 4.96–5.04 (m, 1H), 5.07 (d, br, *J*=1.0 Hz, 1H), 5.45 (d, *J*=9.6 Hz, 1H), 5.62–5.79 (m, 1H), 7.30 (d, *J*=8.0 Hz, 2H), 7.76 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (50 MHz) δ 20.26, 21.48, 33.35, 49.74, 50.22, 117.78, 127.00, 129.67, 134.33, 138.30, 143.37, 178.45; MS (*m/z*, relative intensity) 297 (M^+, 3), 282 [$(M-Me)^+$, 19], 198 (71), 155 (80), 128 (35), 91 (100); anal. calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.39; N, 4.71; found: C, 56.37; H, 6.39; N, 4.52.

2.3.9. N-*Tosyl-2(*S*)-methyl-*L*-β-homophenylalanine*

91%; Oil; IR 3240 (OH), 2955, 1690 (C=O), 1585, 1440, 1400, 1240, 1140, 1070 cm^{-1}; ^1H NMR (200 MHz) δ 1.18 (d, *J*=7.2 Hz, 3H), 2.39 (s, 3H), 2.53–2.85 (m, 3H), 3.55–3.68 (m, 1H), 5.70 (d, *J*=8.8 Hz, 1H), 6.98–7.04 (m, 2H), 7.11–7.19 (m, 3H), 7.20 (d, *J*=8.1 Hz, 2H), 7.64 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (50 MHz) δ 13.99, 21.44, 39.57, 40.77, 57.49, 126.65, 126.83, 128.58, 129.09, 129.59, 137.07, 137.61, 143.18, 180.03; MS (*m/z*, relative intensity) 256 [$(M-C_6H_5CH_2)^+$, 46], 238 [$(M-C_6H_5CH_2-H_2O)^+$, 7], 155 (36), 91 (100); HRMS calcd for $(M-C_6H_5CH_2)^+$ $C_{11}H_{14}O_4NS$ 256.0643; found, 256.0640.

2.4. Typical procedure for the preparation of α-diazo carbonyl compounds ***9a–d***

The acid (5 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and the solution was cooled in an ice bath under N_2. To the solution was added dropwise oxalyl chloride (6 mmol) and 1 drop DMF. The solution was stirred for 3 h, during which time the temperature rose to about 25°C. The solvent and excess reagent were removed under reduced pressure. The acyl chloride thus obtained was dissolved in absolute THF (20 mL), and this solution was added dropwise to an ethereal solution of CH_2N_2 (15–20 mmol, 40 mL) at 0°C. The solution was stirred at between 0 and 25°C for 4 h. Solvent and excess reagent were removed under reduced pressure and the crude residue was purified by column chromatography with petroleum ether:EtOAc=3:1 as eluent.

*2.4.1. Diazo-[*N-*tosyl-2(*S*)-methyl-*L*-β-homoalanyl]methane* ***9a***

59%; Oil; IR 3260 (NH), 2960, 2090 (C=N_2), 1615 (C=O), 1440, 1370, 1330, 1145, 1080 cm^{-1}; ^1H NMR (200 MHz) δ 1.05 (d, *J*=6.8 Hz, 3H), 1.07 (d, *J*=7.2 Hz, 3H), 2.41 (s, 3H), 2.32–2.50 (m, 1H), 3.41–3.55 (m, 1H), 5.24 (s, br, 1H), 5.50 (d, *J*=9.0 Hz, 1H), 7.28 (d, *J*=8.2 Hz, 2H), 7.74 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (50 MHz) δ 14.57, 19.84, 21.43, 48.77, 52.29, 55.34, 126.89, 129.52, 138.48, 143.05, 197.24; MS (*m/z*, relative intensity) 265 (15), 252 [$(M-N_2-Me)^+$, 2], 198 (38), 155 (68), 91 (100). HRMS calcd for $(M-N_2)^+$ $C_{13}H_{17}NO_3S$ 267.0929; found, 267.0932.

*2.4.2. Diazo-[*N*-tosyl-2(*S*)-phenyl-*L*-β-homoalanyl]methane* ***9b***

57%; Oil; IR 3245 (NH), 3080, 2055 (C=N_2), 1720, 1600, 1360, 1320, 1155, 1080 cm^{-1}; ^1H NMR (200 MHz) δ 1.05 (d, *J*=6.8 Hz, 3H), 2.40 (s, 3H), 2.49–2.96 (m, 3H), 3.60 (m, 1H), 4.95 (s, 1H), 5.88 (d, *J*=9.2 Hz, 1H), 7.02–7.10 (m, 2H), 7.13–7.31 (m, 3H), 7.28 (d, *J*=8.5 Hz, 2H), 7.77 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (50 MHz) δ 20.49, 21.47, 36.17, 51.37, 56.07, 56.30, 126.92, 128.55, 128.90, 129.60, 131.10, 135.90, 138.50, 143.11, 196.79; MS (*m/z*, relative intensity) 343 [$(M-N_2)^+$, 9], 279 (53), 252 [$(M-C_6H_5CH_2-N_2)^+$, 75], 188 (64), 155 (100), 117 (75), 91 (98); HRMS calcd for $(M-N_2)^+$ $C_{19}H_{21}O_3NS$ 343.1242; found, 343.1241.

*2.4.3. Diazo-[*N*-tosyl-2(*S*)-vinyl-*L*-β-homoalanyl]methane* ***9c***

61%; Oil; IR 3240 (NH), 3080, 2960, 2090 (C=N_2), 1615 (C=O), 1340, 1320, 1150, 1080 cm^{-1}; ^1H NMR (200 MHz) δ 1.04 (d, *J*=6.8 Hz, 3H), 2.15–2.47 (m, 3H), 2.41 (s, 3H), 3.54–3.67 (m, 1H), 4.96 (d, *J*=6.6 Hz, 1H), 5.03 (s, 1H), 5.26 (s, br, 1H), 5.68–5.70 (m, 1H), 5.71 (d, *J*=9.6 Hz, 1H), 7.28 (d, *J*=8.0 Hz, 2H), 7.75 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (50 MHz) δ 20.31, 21.43, 33.89, 50.84, 54.17, 56.90, 117.62, 126.87, 129.55, 134.56, 138.75, 143.06, 196.44; MS (*m/z*, relative intensity) 294 [$(MH-N_2)^+$, 20], 251 (22), 229 (14), 214 (11), 198 (22), 155 (51), 91 (100). HRMS calcd for $(M-N_2)^+$ $C_{15}H_{19}O_3NS$ 293.1085; found, 293.1084.

*2.4.4. Diazo-[*N*-tosyl-2(*S*)-methyl-*L*-β-homophenylalanyl]methane* ***9d***

75%; M.p. 110–102°C; IR 3325 (NH), 2955, 2920, 2095 (C=N_2), 1720 (C=O), 1615, 1440, 1355, 1160, 1080 cm^{-1}; ^1H NMR (200 MHz) δ 1.05 (d, *J*=7.2 Hz, 3H), 2.39 (s, 3H), 2.60–2.81 (m, 3H), 3.50–3.62 (m, 1H), 5.16 (s, 1H), 5.89 (d, *J*=8.4 Hz, 1H), 6.98–7.08 (m, 2H), 7.18–7.28 (m, 5H), 7.67 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (50 MHz) δ 15.43, 21.46, 40.28, 44.30, 55.61, 58.49, 126.65, 126.78, 128.64, 128.99, 129.53, 137.69, 138.48, 142.92, 185.12; MS (*m/z*, relative intensity) 343 [$(M-N_2)^+$, 10], 328 [$(M-Me)^+$, 13], 279 (94), 264 (38), 252 [$(M-C_6H_5CH_2)^+$, 14], 188 (74), 155 (41), 91 (100); HRMS calcd for $(M-N_2)^+$ $C_{19}H_{21}O_3NS$ 343.1242; found, 343.1244.

2.5. Typical procedure for the Wolff rearrangement of α-diazo ketones

The α-diazo ketone (1.0 mmol) was dissolved in absolute THF (10 mL). To the solution was added dropwise a solution of AgO_2CPh (0.13 mmol) in triethylamine (1.3 mL). The mixture was set to stir at room temperature for 2 h. The solvent was removed under reduced pressure and the crude residue was subjected to column chromatography with petroleum ether:EtOAc=4:1 as eluent.

*2.5.1. (*R*)-Methyl-5(*S*)-methyl-*N*-tosylpyrrolidin-2-one* ***10a***

94%; M.p. 124–125°C; $[\alpha]_D^{30}$=+39.7 (*c* 1.6, CH_2Cl_2); IR 2950, 1710 (C=O), 1340, 1195, 1150, 1070 cm^{-1}; ^1H NMR (200 MHz) δ 1.00 (d, *J*=6.8 Hz, 3H), 1.47 (d, *J*=6.2 Hz, 3H), 1.92 (m, 1H), 2.01 (m, 1H), 2.73 (q, *J*=8.4, 1H), 4.02 (qd, *J*=6.8, 1.0 Hz, 1H), 7.32 (d, *J*=8.6 Hz, 2H), 7.93 (d, *J*=8.6 Hz, 2H); ^{13}C NMR (50 MHz) δ 19.77, 21.05, 21.56, 33.98, 38.35, 63.65, 128.05, 129.41, 135.86, 144.84, 172.73; MS (*m/z*, relative intensity) 268 [$(MH)^+$, 22], 252 [$(M-Me)^+$, 15], 203 (53), 188 (94), 155 (34), 91 (100%); anal. calcd for $C_{13}H_{17}O_3NS$: C, 58.41; H, 6.41; N, 5.24; found: C, 58.14; H, 6.40; N, 4.84.

*2.5.2. (*R*)-Benzyl-5(*S*)-methyl-*N*-tosylpyrrolidin-2-one* ***10b***

85%; Oil; $[\alpha]_D^{30}$=+67.6 (*c* 1.6, CH_2Cl_2); IR 2920, 1725 (C=O), 1595, 1440, 1350, 1160, 1080 cm^{-1}; ^1H NMR (400 MHz) δ 1.41 (d, *J*=6.5 Hz, 3H), 2.14 (dd, *J*=17.6, 1.8 Hz), 2.22–2.28 (m, 1H), 2.45 (s, 3H), 2.58 (dd, *J*=13.8, 7.7 Hz, 1H), 2.67 (dd, *J*=13.8, 8.3 Hz, 2H), 2.71 (dd, *J*=17.6, 7.9 Hz), 4.17 (qd,

J=6.4, 1.0 Hz, 1H), 7.05 (d, *J*=7.0 Hz, 2H), 7.04–7.32 (m, 3H), 7.35 (d, *J*=8.2 Hz, 2H), 7.95 (d, *J*=8.2 Hz, 2H); ^{13}C NMR δ 21.26, 21.61, 36.23, 39.72, 40.50, 60.76, 126.69, 128.13, 128.67, 128.78, 129.48, 135.87, 137.90, 144.97, 172.41; MS (*m/z*, relative intensity) 343 (10), 328 [(M−Me)$^+$, 13], 279 (94), 264 (38), 252 [(M−$C_6H_5CH_2$)$^+$, 14], 188 (74), 155 (41), 91 (100%); HRMS calcd M$^+$ $C_{19}H_{21}NO_3S$ 343.1242; found, 343.1223.

*2.5.3. (*R*)-Vinyl-5(*S*)-methyl*-N-*tosylpyrrolidin-2-one* ***10c***

84%; M.p. 53–54°C; $[\alpha]_D^{30}$=+50.2 (*c* 1.5, CH_2Cl_2); IR 2960, 2900, 1705 (C=O), 1345, 1155, 1065 cm^{-1}; ^{1}H NMR δ 1.47 (d, *J*=6.4 Hz, 3H), 2.01–2.13 (m, 4H), 2.44 (s, 3H), 2.64–2.79 (m, 1H), 4.16 (q, *J*=6.6 Hz, 1H), 5.03 (d, *J*=25.4 Hz, 1H), 5.04 (s, 1H), 5.55–5.72 (m, 1H), 7.33 (d, *J*=8.5 Hz, 2H), 7.93 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (50 MHz) δ 21.47, 21.63, 36.22, 38.18, 38.42, 60.98, 118.29, 128.24, 129.47, 134.10, 135.93, 144.96, 172.53; MS (*m/z*, relative intensity) 294 (MH$^+$, 5), 229 (41), 200 (15), 187 (32), 155 (35), 91 (100); anal. calcd for $C_{15}H_{19}NO_3S$: C, 61.40; H, 6.53; N, 4.77; found: C, 61.38; H, 6.37; N, 4.59.

*2.5.4. (*R*)-Methyl-5(*S*)-benzyl*-N-*tosylpyrrolidin-2-one* ***10d***

85%; M.p. 148–150°C; $[\alpha]_D^{30}$=+80.6 (*c* 0.5, CH_2Cl_2); IR 2920, 2890, 1710 (C=O), 1440, 1335, 1145, 1095, 1070 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.82 (d, *J*=6.8 Hz, 3H), 2.19–2.42 (m, 3H), 2.44 (s, 3H), 2.90 (dd, *J*=13.6, 9.0 Hz, 1H), 3.32 (dd, *J*=13.6, 3.4 Hz, 1H), 4.16 (dd, *J*=8.6, 3.4 Hz, 1H), 7.21–7.31 (m, 5H), 7.34 (2H, *J*=8.4 Hz, 2H), 7.97 (2H, *J*=8.4 Hz, 2H); ^{13}C NMR (50 MHz) δ 20.77, 21.65, 29.92, 38.29, 40.79, 68.34, 127.00, 128.26, 128.75, 129.43, 129.51, 135.68, 136.38, 145.06, 172.97; MS (*m/z*, relative intensity) 343 (M$^+$, 9), 252 [(M−$C_6H_5CH_2$)$^+$, 73], 155 (61), 91 (100); anal. calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08; found: C, 66.39; H, 6.12; N, 3.87.

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