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Concise and diastereoselective approach to *syn*- and *anti*-*N*-tosyl-α-hydroxy β-amino acid derivatives

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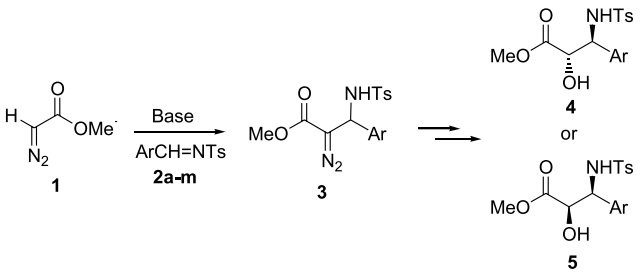
Abstract—The methyl diazoacetate and aryl (*N*-tosyl)imines can be transformed into *syn* or *anti* α-hydroxy β-amino esters with high diastereoselectivities in three steps: the base promoted nucleophilic condensation of the methyl diazoacetate and aryl (*N*-tosyl)imines to give β-(*N*-tosyl)amino α-diazoesters, followed by oxidation with Oxone® to generate α-oxo esters, which were reduced with $NaBH_4$ to yield the *anti*-*N*-tosyl-α-hydroxy β-amino ester, or hydrogenated with Pd/C (10%) as the catalyst to yield corresponding *syn* isomer, both in high diastereoselectivity.

1. Introduction

The stereoselective synthesis of β-amino acids and their derivatives have been an active research area in organic synthesis, due to the importance of the β-amino acid moiety in various fields.[1] In particular, the α-hydroxy β-amino acid moiety exist in some natural compounds with important biological activities, such as Taxol®.[2] The stereoselective synthesis of α-hydroxy β-amino acid is still a subject of considerable challenge, although progress has been made over the past decades.[3] So far, the most convenient approach to α-hydroxy β-amino acid derivatives is the amino-hydroxylation of α,β-unsaturated esters.[4] However, this approach is only easily applicable to the synthesis of *syn* α-hydroxy β-amino acid from *trans* α,β-unsaturated acids, because the *cis* precursor is less easily available. Moreover, this approach is in some cases associated with regio-selectivity problem. In this article, we introduce an alternative approach, which can give both *syn*- and *anti*-α-hydroxy β-amino esters with high diastereoselectivities (Scheme 1). This approach started from the easily available methyl diazoacetate, which was reacted with aryl (*N*-tosyl)-imines. Then the addition products were oxidized to give α-oxo esters. Finally, reduction of the α-oxo esters with $NaBH_4$ gave *anti*-*N*-tosyl-α-hydroxy β-amino esters, and hydrogenation with Pd/C (10%) as the catalyst gave the *syn* isomers.



Scheme 1.

2. Results and discussions

The first step of this novel approach was the nucleophilic condensation of methyl diazoacetate **1** with aryl (*N*-tosyl)-imines **2a**–**m**. The similar nucleophilic reaction of ethyl diazoacetate with aryl (*N*-tosyl)imines has been investigated previously in our laboratory.[5] The nucleophilic condensation was carried out with either NaH or catalytic DBU as the base. The reaction of methyl diazoacetate **1** gave the expected β-(*N*-tosyl)amino α-diazo esters **3a**–**m** in similar yields as compared with the corresponding reaction of ethyl diazoacetate (Table 1).

The diazo compounds **3a**–**m** were then oxidized to give α-oxo esters **6a**–**m**. The oxidation of diazo group is

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Table 1. Base-promoted reaction of **1** with aryl *N*-(tosyl) imine **2a–m**

Entry	Base	Imine **2** (Ar=)	Product	Yield (%)[a]
1	DBU	**2a**, C_6H_5	**3a**	54
2	NaH	**2b**, *p*-PhC_6H_4	**3b**	81
3	DBU	**2c**, *p*-FC_6H_4	**3c**	57
4	NaH	**2d**, *p*-ClC_6H_4	**3d**	90
5	NaH	**2e**, *o*-MeC_6H_4	**3e**	60
6	DBU	**2f**, *p*-$MeOC_6H_4$	**3f**	76
7	DBU	**2g**, *m*-$CF_3C_6H_4$	**3g**	51
8	DBU	**2h**, *m*-BrC_6H_4	**3h**	67
9	NaH	**2i**, *m*-CNC_6H_4	**3i**	83
10	NaH	**2j**, 2,4-$Cl_2C_6H_3$	**3j**	47
11	NaH	**2k**, 2,6-$Cl_2C_6H_3$	**3k**	57
12	DBU	**2l** 	**3l**	72
13	NaH	**2m** 	**3m**	82

[a] The yield after purification with silica gel column chromatography.

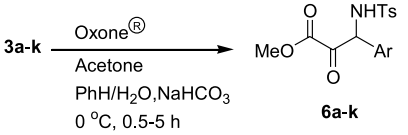
generally achieved with *m*-chloroperbenzoic acid (*m*-CPBA),[6] ozone[7] or dimethyldioxirane (DMD).[8] We found that for the diazo compounds **3a–k**, the oxidation occurred efficiently with commercially available Oxone® (potassium peroxomonosulfate) directly. Since, the preparation of dimethyldioxirane from Oxone® requires low temperature and the yield is usually low,[9] the direct oxidation with cheap Oxone® greatly simplifies the experimental operation and also makes use of the oxidant more efficiently. The oxidation of **3l** and **3m** under the same condition gave complex mixture (Scheme 2).

With the α-oxo β-(*N*-tosyl)amino esters **6a–k** in hand, we then proceeded to study their reduction. First, the α-oxo ester **6a** was taken as a model compound. The reduction with $NaBH_4$ at 0 °C in THF gave the *anti* α-hydroxy β-(*N*-tosyl)amino ester **4a** exclusively as judged by ^1H NMR (300 MHz) of the crude product.[10] The isolated yield of **4a** was 82%. On the other hand, when the α-oxo ester was hydrogenated with Pd/C (10%) as the catalyst in MeOH at room temperature, the *syn* isomer of α-hydroxy compound **5a** was formed, with high diastereoselectivity in 87% isolated yield. The assignment of the structure was made by the comparison of the spectra data of **5a** with that of the reported known compound (Scheme 3).[11]

The scope and limitations of the highly diastereoselective reduction with $NaBH_4$ and hydrogenation with Pd/C as the catalyst were summarized in Table 2. As shown by the data, the reduction with $NaBH_4$ gave *anti* products **4a–k** in generally high diastereoselectivities.[12] The hydrogenation, on the other hand, gave only *syn* isomer **5a–f** in most cases.[12] For α-oxo substrates **6g–k**, the hydrogenation failed to give the expected product, due to the side reaction of the substituents on the aromatic ring (entries 7–11).

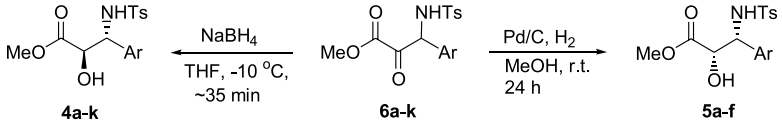
The stereochemistry of the *anti* product was confirmed by X-ray structure of **4c** (Fig. 1).[13]

The high diastereoselectivity observed in the reduction with $NaBH_4$ is rationalized as follows (Scheme 4). We speculate that hydrogen bonding between the N–H and carbonyl group may play an important role in the observed selectivity. The α-oxo ester substrate is considered to take



a. Ar = Ph, 85 %; **b**. Ar = *p*-PhC_6H_4, 96%;
c. Ar = *p*-FC_6H_4, 97 %; **d**. Ar = *p*-ClC_6H_4, 80 %;
e. Ar = *o*-MeC_6H_4, 97 %; **f**. Ar = *p*-$MeOC_6H_4$, 95 %;
g. Ar = *m*-$CF_3C_6H_4$, 81 %; **h**. Ar = *m*-BrC_6H_4, 98 %;
i. Ar = *m*-CNC_6H_4, 77 %; **j**. Ar = 2,4-$Cl_2C_6H_3$, 96 %;
k. Ar = 2,6-$Cl_2C_6H_3$, 98 %.

Scheme 2.



Scheme 3.

Table 2. Diastereoselective reduction of **6a–k** and hydrogenation of **6a–f**

Entry	α-Oxo ester **6**	Reduction with $NaBH_4$ dr; yield of **4** (%)[a]	Hydrogenation H_2, Pd/C (10%) dr; yield of **5** (%)[a]
1	**6a**, C_6H_5	>95:5; 82	>95:5; 87
2	**6b**, *p*-PhC_6H_4	>95:5; 72	>95:5; 92
3	**6c**, *p*-FC_6H_4	86:14; 70	83:17; 94
4	**6d**, *p*-ClC_6H_4	>95:5; 75	>95:5; 73
5	**6e**, *o*-MeC_6H_4	>95:5; 80	>95:5; 83
6	**6f**, *p*-$MeOC_6H_4$	>95:5; 95	>95:5; 75
7	**6h**, *m*-BrC_6H_4	>95:5; 74	—[b]
8	**6i**, *m*-CNC_6H_4	>95:5; 71	—[b]
9	**6j**, 2,4-$Cl_2C_6H_3$	97:3; 40	—[b]
10	**6k**, 2,6-$Cl_2C_6H_3$	94:6; 67	—[b]

[a] The diastereomeric ratio was determined by ^1H NMR (300 MHz). The yields refer to the pure compounds after purification with silica gel column chromatography.
[b] Expected products were not obtained due to side reactions.

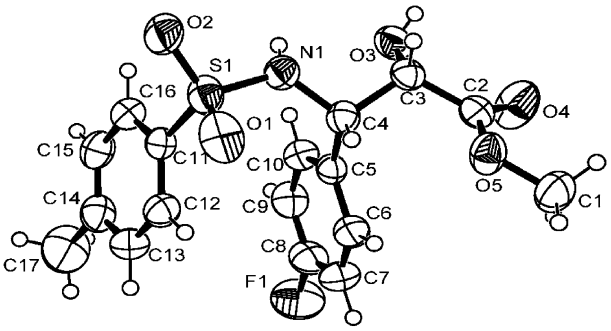
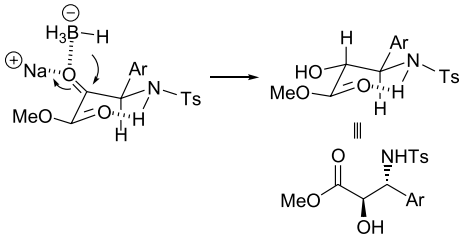


Figure 1. X-ray structure of **4c**.



Scheme 4.

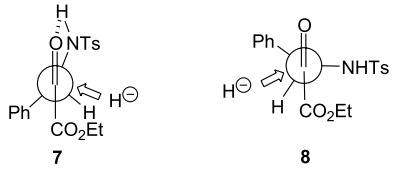


Figure 2. Hydrogen bonding model and Felkin's model.

a chair form conformation due to the hydrogen bonding. In the reduction with $NaBH_4$, the hydride is delivered from the axial direction to give the product with *anti* configuration, in which hydroxyl group occupies the equatorial position.[14]

Another way to interpret the stereochemical process is by the Newman projection **7** shown in Figure 2. The hydride reagent attacks the carbonyl group from the sterically less hindered direction to provide the *anti* product. This is similar to the metal chelation controlled reduction of α-ketols.[15] On the other hand, the Felkin's model **8**, in which it is assumed there is no intramolecular hydrogen bonding between the *N*-tosylamino group and the carbonyl group, predicts the *syn* product to be predominant.[16]

To confirm the role of the hydrogen bonding, we studied the corresponding reduction and hydrogenation with compound **9**, in which the hydrogen on the amino group was replaced with a methyl group. The reduction with $NaBH_4$ gave the α-hydroxyl products with essentially no diastereoselectivity (Scheme 5). Thus, the experimental result supported the proposed role of hydrogen bonding.

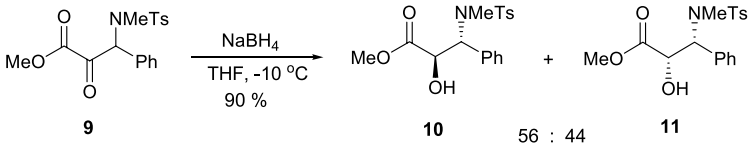
For the hydrogenation catalyzed with Pd/C, it was conceivable that the chair conformation exposed the less sterically hindered bottom face to hydrogen delivery and thus, providing the *syn* product (Scheme 6).[17] When compound **9** was subjected to the hydrogenation condition, it was found that the reaction became complicated. ^{1}H NMR spectrum of the crude product indicated the formation of *syn* product **11** in low yield. However, there was no *anti* product **10** identified from the ^{1}H NMR spectrum.

In summary, a novel approach to both *anti*- and *syn*-α-hydroxy β-amino acid derivatives with high diastereoselectivities has been developed. This approach requires only three steps from the easily available aryl (*N*-tosyl)-imine and methyl diazoester.[18] If the enantioselectivity can be controlled in the first step of the nucleophilic condensation, this approach can be further developed into a method to prepare non-racemic *syn*- and *anti*-α-hydroxy β-amino acid derivatives.[19] The investigation along this direction is currently under the way in our laboratory.

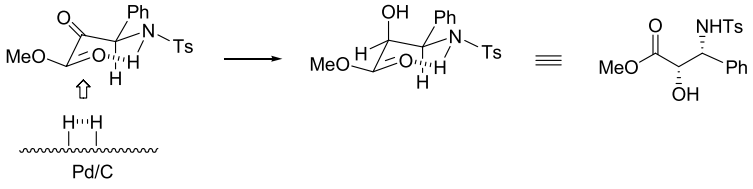
3. Experimental

3.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at 300 MHz (or 200 MHz) and 75 MHz (or 50 MHz) with Varian Mercury 300 (or 200) spectrometer, or at 400 and 100.6 MHz with Brucker ARX400 spectrometer. The chemical shifts were reported in ppm using TMS as the internal standard. All reactions were performed under a nitrogen atmosphere in a flame-dried reaction flask, and the components were added



Scheme 5.



Scheme 6.

via syringe. All solvents were distilled prior to use according to standard procedures. THF was distilled over sodium. For chromatography, 100–200 mesh silica gel (Qindao, China) was employed. IR spectra were recorded with a Nicolet 5MX-S infrared spectrometer. HPLC analysis was performed at HP 1100 apparatus with Chiracel column. Mass spectra were obtained on a VG ZAB-HS mass spectrometer.

3.2. General procedure for the reaction of methyl diazoacetate with aryl (*N*-tosyl)imines

(a) *With DBU as the base*. To a solution of methyl diazoacetate (1.0 mmol) in anhydrous MeCN (8 mL) was added DBU (0.25 mmol) at room temperature under N_2. Then the imine (0.85 mmol) was added. The reaction mixture was stirred at room temperature for about 1 h. The solvent was removed and the crude product was purified by column chromatography with petroleum ether/EtOAc.

(b) *With NaH as the base*. To a solution of methyl diazoacetate (1.0 mmol) in anhydrous THF (8 mL) was added 60% NaH (43 mg, 1.25 equiv), then the imine (0.85 mmol) was added, the reaction mixture was stirred for 1 h and quenched with saturated aqueous $NaHCO_3$ at 0 °C. The resulting slurry was extracted with CH_2Cl_2 (3× 15 mL). Usual work up gave a crude product, which was purified by column chromatography.

3.2.1. Methyl 2-diazo-3-phenyl-3-[(*N*-tosyl)amino] propanoate (3a). IR (film) 3262, 2097, 1691 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H), 3.62 (s, 3H), 5.33 (d, J= 7.6 Hz, 1H), 5.60 (w, 1H), 7.28–7.30 (m, 7H), 7.35 (d, J= 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.2, 51.7, 53.2, 126.0, 126.8, 128.0, 128.5, 129.2, 136.7, 137.3, 143.3, 165.4; EI-MS (*m/z*, relative intensity) 331 [$(M-28)^+$, 16], 260 (17), 164 (20), 139 (40), 91 (100). Anal. Calcd for $C_{17}H_{17}O_4N_3S$: C, 56.81; H, 4.77; N, 11.69. Found: C, 56.84; H, 4.79; N, 11.68.

3.2.2. Methyl 2-diazo-3-(*p*-phenyl)phenyl-3-[(*N*-tosyl)-amino]propanoate (3b). IR (film) 3265, 2098, 1697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.40(s, 3H), 3.61(s, 3H), 5.40 (d, J=7.5 Hz, 1H), 5.89 (d, J=7.5 Hz, 1H), 7.26–7.55 (m, 11H), 7.75 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 51.9, 53.5, 126.7, 126.9, 127.1, 127.4, 128.7, 129.5, 136.4, 136.8, 140.1, 141.1, 143.6, 165.6; EI-MS (*m/z*, relative intensity) 407 [$(M-28)^+$, 54], 375 (6), 220 (33), 193 (42), 164 (76), 91 (100); HRMS calcd for $C_{23}H_{21}NSO_4$ $(M-28)^+$ 407.1191, found 407.1200.

3.2.3. Methyl 2-diazo-3-(*p*-fluoro)phenyl-3-[(*N*-tosyl)-amino]propanoate (3c). IR (KBr) 3442, 2113, 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 3.61(s, 3H), 5.32 (d, J=4.5 Hz, 1H), 5.72 (s, 1H), 6.95–7.01 (m, 2H), 7.23–7.31 (m, 4H), 7.72 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 51.9, 53.4, 115.6, 115.9, 127.1, 128.1, 128.2, 129.6, 133.4, 136.8, 143.9, 165.5; EI-MS (*m/z*, relative intensity) 349 [$(M-28)^+$, 27], 164 (29), 155 (32), 91 (100); HRMS calcd for $C_{17}H_{16}NSO_4F$ $(M-28)^+$ 349.0784, found 349.0794.

3.2.4. Methyl 2-diazo-3-(*p*-chloro)phenyl-3-[(*N*-tosyl)-amino]propanoate (3d). IR (KBr) 3548, 2111, 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 3.59 (s, 3H), 5.31(d, J=7.4 Hz, 1H), 5.73(d, J=7.4 Hz, 1H), 7.19–7.36 (m, 6H), 7.71 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.5, 52.0, 53.6, 127.1, 127.8, 129.0, 129.7, 134.4, 136.1, 136.8, 143.9, 165.5; EI-MS (*m/z*, relative intensity) 365 [$(M-28)^+$, 100], 333 (14), 304 (6), 178 (12), 91 (5); HRMS calcd for $C_{17}H_{16}NSO_4^{35}Cl$ $(M-28)^+$ 365.0489, found 365.0497.

3.2.5. Methyl 2-diazo-3-(*o*-methyl)phenyl-3-[(*N*-tosyl)-amino]propanoate (3e). IR (film) 3266, 2097, 1697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.23 (s, 3H), 2.43 (s, 3H), 3.62 (s, 3H), 5.27 (d, J=5.0 Hz, 1H), 5.50 (d, J=5.0 Hz, 1H), 7.15–7.30 (m, 6H), 7.75 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz) δ 18.9, 21.4, 50.1, 125.9, 126.3, 127.2, 128.2, 129.4, 130.8, 135.1, 136.6, 143.5, 165.6; EI-MS (*m/z*, relative intensity) 345 [$(M-28)^+$, 10], 274 (9), 258 (8), 158 (28), 130 (58), 91 (100); HRMS calcd for $C_{18}H_{19}NO_4S$ 345.1035, found 345.1037.

3.2.6. Methyl 2-diazo-3-(*p*-methoxy)phenyl-3-[(*N*-tosyl)-amino]propanoate (3f). IR (KBr) 3446, 2103, 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H), 3.62 (s, 3H), 3.77 (s, 3H), 5.28 (d, J=7.2 Hz, 1H), 5.52 (d, J=7.2 Hz, 1H), 6.79–6.85 (m, 2H), 7.15–7.21 (m, 2H), 7.29 (d, J= 8.6 Hz, 2H), 7.73(d, J=8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.5, 51.9, 53.5, 55.3, 114.2, 127.2, 127.6, 129.6, 129.6, 136.8, 143.7, 159.6, 165.7; EI-MS (*m/z*, relative intensity) 361 [$(M-28)^+$, 26], 329 (6), 290 (19), 164 (44), 147 (48), 132 (52), 91 (100). Anal. Calcd for $C_{18}H_{19}O_5N_3S$: C, 55.52; H, 4.92; N, 10.79. Found: C, 55.62; H, 4.99; N, 10.75.

3.2.7. Methyl 2-diazo-3-(*m*-trifluoromethyl)phenyl-3-[(*N*-tosyl)amino]propanoate (3g). IR (KBr) 3452, 2104, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H), 3.57 (s, 3H), 5.37 (d, J=7.8 Hz, 1H), 5.99 (d, J=7.8 Hz, 1H), 7.20–7.66 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 52.0, 53.7, 123.2, 125.1, 127.0, 127.3, 129.4, 129.7, 129.8, 130.9, 136.7, 138.7, 144.0, 165.4; EI-MS (*m/z*, relative intensity) 399 [$(M-28)^+$, 6], 164 (22), 155 (24), 139 (32), 91 (100); HRMS calcd for $C_{18}H_{16}NO_4SF_3$ 399.0752, found 321.0761.

3.2.8. Methyl 2-diazo-3-(*m*-bromo)phenyl-3-[(*N*-tosyl)-amino]propanoate (3h). IR (KBr) 3213, 2106, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 3.61 (s, 3H), 5.33 (d, J=8.0 Hz, 1H), 5.94 (d, J=8.0 Hz, 1H), 7.13–7.69 (m, 6H), 7.71 (d, J=1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 52.0, 53.4, 122.8, 124.9, 127.0, 129.4, 130.3, 131.4, 136.7, 139.8, 143.9, 165.4; EI-MS (*m/z*, relative intensity) 409 [$(M-28)^+$, 5], 279 (18), 167 (28), 149 (100); HRMS calcd for $C_{17}H_{16}NSO_4^{79}Br$: 408.9983, found 408.9983.

3.2.9. Methyl 2-diazo-3-(*m*-cyano)phenyl-3-[(*N*-tosyl)-amino]propanoate (3i). IR (KBr) 3427, 2103, 1749 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3H), 3.62 (s, 3H), 5.23 (d, J=8.8 Hz, 1H), 6.07 (d, J=8.8 Hz, 1H), 7.27–7.82 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 52.1, 53.4, 112.7, 118.2, 126.2, 126.9, 129.6, 129.7, 131.0, 131.8, 136.6, 139.2, 144.1, 165.3; EI-MS (*m/z*, relative intensity) 356 [$(M-28)^+$, 18], 292 (4), 164 (16), 155 (25), 91 (100), 65 (20); HRMS calcd for $C_{18}H_{16}N_2SO_4$ 356.0831, found 356.0827.

3.2.10. Methyl 2-diazo-3-(2,4-dichloro)phenyl-3-[(*N*-tosyl)amino]propanoate (3j). IR (KBr) 3189, 2110, 1659 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 3.59 (s, 3H), 5.58 (d, $J=8.2$ Hz, 1H), 6.21 (d, $J=8.2$ Hz, 1H), 7.13–7.40 (m, 5H), 7.71 (d, $J=8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 51.2, 51.9, 127.0, 127.2, 129.4, 129.5, 129.6, 132.8, 133.8, 134.5, 136.6, 143.9, 165.4; EI-MS (*m/z*, relative intensity) 399 [$(M-28)^+$, 8], 364 (10), 332 (9), 164 (16), 155 (30), 91 (10); HRMS calcd for $C_{17}H_{15}NO_4SCl_2$ 399.0099, found 399.0104.

3.2.11. Methyl 2-diazo-3-(2,6-dichloro)phenyl-3-[(*N*-tosyl)amino]propanoate (3k). IR (film) 3276, 2103, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 3.67 (s, 3H), 5.84 (d, $J=9.0$ Hz, 1H), 6.29 (d, $J=9.0$ Hz, 1H), 7.07–7.21 (m, 5H), 7.69 (d, $J=1.5$, 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 21.4, 48.2, 52.0, 127.1, 129.2, 129.5, 129.8, 132.2, 134.8, 136.5, 143.8, 165.3; EI-MS (*m/z*, relative intensity) 399 [$(M-28)^+$, 12], 364 (12), 155 (16), 91 (100). Anal. Calcd for $C_{17}H_{15}O_4N_3SCl_2$: C, 47.68; H, 3.53; N, 9.81. Found: C, 47.66; H, 3.72; N, 9.55.

3.2.12. Methyl 2-diazo-3-(2-furyl)-3-[(*N*-tosyl)amino]-propanoate (3l). IR (KBr) 3445, 2109, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 3H), 3.60 (s, 3H), 5.20 (d, $J=7.2$ Hz, 1H), 5.85 (d, $J=7.2$ Hz, 1H), 6.22–6.27 (m, 2H), 7.24–7.30 (m, 3H), 7.74 (dd, $J=1.8$, 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 48.4, 51.9, 107.9, 110.5, 127.1, 129.5, 136.8, 142.8, 143.7, 149.5, 165.3; EI-MS (*m/z*, relative intensity) 321[$(M-28)^+$, 8], 250 (12), 155 (26), 139 (24), 91 (100); HRMS calcd for $C_{15}H_{15}NSO_5$ 321.0671, found 321.0669.

3.2.13. Methyl 2-diazo-3-[2-(5-bromo)thienyl]-3-[(*N*-tosyl)amino]propanoate (3m). IR (film) 3204, 2104, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3H), 3.64 (s, 3H), 5.47 (d, $J=8.7$ Hz, 1H), 5.69 (s, 1H), 6.70 (d, $J=3.3$ Hz, 1H), 6.87 (d, $J=3.9$ Hz, 1H), 7.32 (d, $J=8.1$ Hz, 2H), 7.73 (d, $J=8.1$ Hz, 2H); ^{13}C NMR (DMSO-d_6, 50 MHz), δ 20.5, 48.5, 50.9, 111.0, 124.6, 125.8, 128.4, 128.9, 136.8, 142.2, 142.7; EI-MS (*m/z*, relative intensity) 417 [$(M-28)^+$, 18], 262 (26), 181 (38), 164 (26), 91 (100). Anal. Calcd for $C_{15}H_{14}O_4N_3S_2Br$: C, 40.55; H, 3.18; N, 9.46. Found: C, 40.55; H, 3.26; N, 9.49.

3.2.14. General procedure for the oxidation of α-diazo compounds 3a–k with Oxone®. At 0 °C, to a solution of diazo compounds **3a–k** (0.58 mmol) in benzene (4.26 mL), was added acetone (3.0 mL), H_2O (4.26 mL), and $NaHCO_3$ (1.88 g) in sequence, then was added Oxone® (3.53 g) in three times. The reaction mixture was stirred until the starting materials disappeared. The slurry was extracted by CH_2Cl_2 (3×15 mL), and then usual work up gave a crude product **6a–k**. The α-oxo β-(*N*-tosyl)amino esters **6a–k** were found unstable in silica gel column chromatography. The crude products were used in the next step without further purification. Representative data: methyl 2-diazo-3-(*o*-methyl)phenyl-3-[(*N*-tosyl)amino]propanoate (**6e**); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.23 (s, 3H), 2.39 (s, 3H), 3.66 (s, 3H), 5.94 (d, $J=7.4$ Hz, 1H), 6.08 (d, $J=7.4$ Hz, 1H), 6.78–7.34 (m, 6H), 7.55 (d, $J=8.4$ Hz, 2H); ^{13}C NMR (75 MHz) $\delta=18.9$, 21.4, 53.1, 59.0, 126.5, 126.7, 128.2, 129.1, 129.3, 130.1, 131.4, 136.8, 137.8, 143.3, 159.8, 187.9.

3.3. General procedure for the reduction of α-oxo compounds 6a–k with $NaBH_4$

The crude α-oxo compound **6a–k** (0.1 mmol) was dissolved in anhydrous THF (5 mL) and was cooled to −10 °C under N_2. To the solution was then added $NaBH_4$ (0.1 mmol). The reaction mixture was stirred for about 35 min at −10 °C until the starting compound was no longer present as monitored by TLC. Saturated aqueous solution of $NaHCO_3$ was then added at −10 °C. The mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography with petroleum ether, $CHCl_3$, and CH_3OH as the eluent to give pure product of **4a–k**. The melting points of white solid **4a–k** were not obtained due to the isomerization of *syn* and *anti* at high temperature.

3.3.1. *trans*-Methyl 2-hydroxy-3-phenyl-3′-(*N*-tosyl-amino)propanoate (4a). IR (KBr) 3483, 2359, 1740 cm^{-1}; ^1HNMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3H), 2.86 (d, $J=6.5$ Hz, 1H), 3.64 (s, 3H), 4.51(dd, $J=3.3$, 6.5 Hz, 1H), 4.83 (dd, $J=3.3$, 9.0 Hz, 1H), 5.61 (d, $J=9.0$ Hz, 1H), 6.97–7.26 (m, 7H), 7.52 (d, $J=8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 52.6, 59.2, 73.7, 126.8, 127.3, 127.9, 128.1, 129.2, 134.8, 137.4, 142.9, 171.5; EI-MS (*m/z*, relative intensity) 260 [$(M-89)^+$, 193], 155 (51), 91 (100). Anal. Calcd for $C_{17}H_{19}O_5NS$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.28; H, 5.44; N, 4.16.

3.3.2. *trans*-Methyl 2-hydroxy-3-(*p*-phenyl)phenyl-3′-(*N*-tosylamino)propanoate (4b). IR (KBr) 3480, 2362, 1751 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.27 (s, 3H), 3.09 (d, $J=6.6$ Hz, 1H), 3.68 (s, 3H), 4.58 (dd, $J=3.6$, 6.6 Hz, 1H), 4.89 (dd, $J=3.6$, 9.0 Hz, 1H), 7.03 (d, $J=9.0$ Hz, 1H), 7.02–7.53 (m, 13H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 52.7, 58.9, 73.6, 126.9, 126.9, 126.9, 127.5, 127.9, 128.7, 129.3, 133.7, 137.5, 140.3, 140.9, 143.1, 171.6; EI-MS (*m/z*, relative intensity) 336 [$(M-89)^+$, 71], 180 (29), 155 (36), 91 (100). Anal. Calcd for $C_{23}H_{23}O_5NS$: C, 64.92; H, 5.45; N, 3.29. Found: C, 64.81; H, 5.70; N, 2.98.

3.3.3. *trans*-Methyl 2-hydroxy-3-(*p*-fluoro)phenyl-3′-(*N*-tosylamino)propanoate (4c). IR (KBr) 3054, 2361, 1748 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.34 (s, 3H), 3.66 (s, 3H), 2.91(d, $J=5.8$ Hz, 1H), 4.52 (dd, $J=3.5$, 5.8 Hz, 1H), 4.83 (dd, $J=3.5$, 9.5 Hz, 1H), 5.62 (d, $J=9.5$ Hz, 1H), 6.76–7.26 (m, 6H), 7.50 (d, $J=8.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.4, 30.9, 52.8, 58.4, 73.4, 114.9, 115.4, 116.0, 126.9, 129.1, 129.4, 130.9, 137.5, 143.3, 171.4; EI-MS (*m/z*, relative intensity) 278 [$(M-89)^+$, 65], 155 (64), 91 (100); HRMS calcd for $C_{14}H_{13}NSO_2F$: 278.0651, found 278.0651.

3.3.4. *trans*-Methyl 2-hydroxy-3-(*p*-chloro)phenyl-3′-(*N*-tosylamino)propanoate (4d). IR (KBr) 3444, 2360, 1748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 2.92 (d, $J=5.8$ Hz, 1H), 3.66 (s, 3H), 4.51 (dd, $J=3.6$, 5.8 Hz, 1H), 4.81 (dd, $J=3.6$, 9.6 Hz, 1H), 5.63 (d,

J=9.6 Hz, 1H), 6.92 (d, J=8.4 Hz, 2H), 7.05–7.26 (m, 4H), 7.47 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 52.9, 58.5, 73.3, 126.9, 128.4, 128.9, 129.4, 133.4, 134.2, 137.4, 143.4, 171.3; EI-MS (*m/z*, relative intensity) 294 [$(M-89)^+$, 63], 155 (83), 91 (100); HRMS calcd for $C_{14}H_{13}NSO_2Cl$: 294.0356, found 294.0362.

3.3.5. *trans*-Methyl 2-hydroxy-3-(*o*-methyl)phenyl-3′-(*N*-tosylamino)propanoate (4e). IR (KBr) 3445, 2361, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.20 (s, 3H), 2.32 (s, 3H), 3.17 (br, 1H), 4.54 (dd, J=4.2, 6.6 Hz, 1H), 5.94 (dd, J=4.2, 9.3 Hz, 1H), 5.74 (br, 1H), 6.91–7.16 (m, 6H), 7.50 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 21.4, 52.5, 54.2, 72.9, 126.1, 126.8, 127.1, 127.9, 129.2, 130.4, 133.7, 135.3, 137.4, 143.1, 171.8; EI-MS (*m/z*, relative intensity) 274 [$(M-89)^+$, 100], 155 (54), 91 (100); MS (MALDI-TOF): 402 $(M+K)^+$, 386 $(M+Na)^+$; HRMS calcd for $C_{15}H_{16}NSO_2$ 274.0902, found 274.0902.

3.3.6. *trans*-Methyl 2-hydroxy-3-(*p*-methoxyl)phenyl-3′-(*N*-tosylamino)propanoate (4f). IR (film) 3286, 1741, 1252 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 2.94 (d, J=6.8 Hz, 1H), 3.66 (s, 3H), 3.73 (s, 3H), 4.50 (dd, J=3.4, 6.8 Hz, 1H), 4.78 (dd, J=3.4, 9.5 Hz, 1H), 5.65 (d, J=9.5 Hz, 1H), 6.63 (d, J=7.9 Hz, 2H), 6.91 (d, J=7.9 Hz, 2H), 7.08 (d, J=8.1 Hz, 2H), 7.52 (d, J=8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 52.7, 55.2, 58.6, 73.6, 113.6, 126.9, 127.0, 128.5, 129.3, 137.6, 143.0, 159.4, 171.6; EI-MS (*m/z*, relative intensity) 290 [$(M-89)^+$, 100], 134 (23), 91 (84); HRMS calcd for $C_{15}H_{16}O_3NS$: 290.0851, found 290.0845.

3.3.7. *trans*-Methyl 2-hydroxy-3-(*m*-bromo)phenyl-3′-(*N*-tosylamino)propanoate (4h). IR (film) 3283, 1741, 1333, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3H), 3.35 (d, J=5.9 Hz, 1H), 3.67 (s, 3H), 4.57 (dd, J=3.3, 5.9 Hz, 1H), 4.81 (dd, J=3.3, 9.6 Hz, 1H), 6.15 (d, J=9.6 Hz, 1H), 6.98–7.52 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.4, 52.8, 58.7, 73.4, 122.2, 126.2, 126.7, 126.8, 129.3, 129.7, 130.7, 130.9, 136.9, 137.0, 143.3, 171.3; EI-MS (*m/z*, relative intensity) 340 [$(M-89)^+$, 63], 338 (60), 155 (100), 91 (99), 77 (20), 51 (11); HRMS calcd for $C_{14}H_{13}O_2NSBr$: 337.9850, found 337.9848.

3.3.8. *trans*-Methyl 2-hydroxy-3-(*m*-cyano)phenyl-3′-(*N*-tosylamino)propanoate (4i). IR (film) 3271, 1742, 1333, 1159 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 2.98 (d, J=5.2 Hz, 1H), 3.69 (s, 3H), 4.55 (dd, J=3.4, 5.2 Hz, 1H), 4.87 (dd, J=3.4, 9.3 Hz, 1H), 5.68 (d, J=9.3 Hz, 1H), 7.10–7.50 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 53.0, 58.4, 73.1, 112.3, 118.0, 126.8, 129.0, 129.5, 131.3, 131.6, 132.1, 136.4, 137.1, 143.7, 171.1; EI-MS (*m/z*, relative intensity) 286 [$(M-89)^+$, 14], 285 (78), 156 (10), 155 (93), 91 (100), 65 (22); HRMS calcd for $C_{15}H_{13}O_2N_2S$: 285.0698, found 285.0693.

3.3.9. *trans*-Methyl 2-hydroxy-3-(2,4-dichloro)phenyl-3′-(*N*-tosylamino)propanoate (4j). IR (KBr) 3447, 2361, 1631 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3H), 3.08 (d, J=6.6 Hz, 1H), 3.68 (s, 3H), 4.59 (dd, J=3.9, 6.6 Hz, 1H), 5.33 (d, J=3.9, 9.7 Hz, 1H), 5.80 (d, J=9.7 Hz, 1H), 6.97–7.57 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 29.7, 52.8, 54.6, 72.5, 126.9, 127.1, 129.4, 130.4, 131.5, 133.6, 134.6, 136.8, 143.6, 171.5; EI-MS (*m/z*, relative intensity) 328 [$(M-89)^+$, 52], 155 (74), 91 (100); MS (MALDI-TOF): 456 $(M+K)^+$, 440 $(M+Na)^+$, 418 $(M+H)^+$; HRMS for $C_{14}H_{12}NSO_2^{35}Cl_2$ 327.9966, found 327.9968.

3.3.10. *trans*-Methyl 2-hydroxy-3-(2,6-dichloro)phenyl-3′-(*N*-tosylamino)propanoate (4k). IR (KBr) 3450, 2362, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 3H), 2.86 (d, J=9.3 Hz, 1H), 3.86 (s, 3H), 4.62 (t, J=9.3 Hz, 1H), 5.44 (dd, J=9.3, 11.1 Hz, 1H), 6.03 (d, J=11.1 Hz, 1H), 6.99–7.28 (m, 6H), 7.56–7.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 29.7, 52.9, 56.8, 71.5, 126.7, 128.6, 129.2, 129.5, 129.7, 131.5, 133.3, 136.8, 143.3, 172.5; EI-MS (*m/z*, relative intensity) 328 [$(M-89)^+$, 46], 155 (58), 91 (100); MS (MALDI-TOF): 456 $(M+K)^+$, 440 $(M+Na)^+$; HRMS for $C_{14}H_{12}NSO_2^{35}Cl_2$ calcd 327.9966, found 327.9973.

3.4. General procedure for the hydrogenation of α-oxo compounds 6a–f catalyzed with Pd/C

To a solution of α-oxo compound **6a–f** (0.1 mmol) in anhydrous MeOH (15 mL) was added 10% Pd/C catalyst (10 mg). The reaction mixture was stirred for 24 h under 1 atm hydrogen atmosphere. Then Pd/C catalyst was removed by fast column chromatography with MeOH as the eluent. The solvent was evaporated to give a crude residue, which was purified by column chromatography with petroleum ether, $CHCl_3$, and MeOH to give the pure product of **5a–f**. The melting points of white solid **5a–f** were not obtained due to the isomerization of *syn* and *anti* at high temperature.

3.4.1. *cis*-Methyl 2-hydroxy-3-phenyl-3′-(*N*-tosylamino)-propanoate (5a). IR (film) 3281, 1738, 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3H), 3.31 (d, J=4.5 Hz, 1H), 3.76 (s, 3H), 4.35 (dd, J=4.5, 2.4 Hz, 1H), 4.85 (dd, J=9.2, 2.4 Hz, 1H), 5.75 (d, J=9.2 Hz, 2H), 7.07–7.26 (m, 7H), 7.53 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 53.2, 58.9, 74.2, 126.9, 127.0, 127.8, 128.4, 129.3, 137.4, 137.5, 143.2, 172.5. EI-MS (*m/z*, relative intensity) 260 [$(M-89)^+$, 100], 155 (41), 91 (54). MS (MALDI-TOF) 388 $(M+K)^+$, 372 $(M+Na)^+$. Anal. Calcd for $C_{17}H_{19}O_5NS$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.39; H, 5.63; N, 3.76.

3.4.2. *cis*-Methyl 2-hydroxy-3-(*p*-phenyl)phenyl-3′-(*N*-tosylamino)propanoate (5b). IR (KBr) 3303, 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.28 (s, 3H), 3.34 (d, J=4.2 Hz, 1H), 3.78 (s, 3H), 4.39 (br, 1H), 4.91(d, J=9.8 Hz, 1H), 5.75 (d, J=9.8 Hz, 1H), 7.06–7.55 (m, 13H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 53.3, 58.8, 74.2, 126.9, 127.1, 127.4, 128.8, 129.3, 136.3, 136.4, 137.5, 137.6, 140.5, 140.8, 143.2, 172.5; EI-MS (*m/z*, relative intensity) 336 [$(M-89)^+$, 100], 180 (18), 155 (36), 91 (83). MS (MALDI-TOF): 448 $(M+K)^+$, 464 $(M+Na)^+$. Anal. Calcd for $C_{23}H_{23}O_5NS$: C, 64.92; H, 5.45; N, 3.29. Found: C, 65.08; H, 5.30; N, 3.14.

3.4.3. *cis*-Methyl 2-hydroxy-3-(*p*-fluoro)phenyl-3′-(*N*-tosylamino)propanoate (5c). IR(KBr) 3445, 2361, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H),

3.45 (br, 1H), 3.77 (s, 3H), 4.32 (s, 1H), 4.83 (dd, J=2.1, 9.9 Hz, 1H), 5.93 (d, J=9.9 Hz, 1H), 6.79–7.14 (m, 6H), 7.52 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.3, 53.2, 58.4, 74.2, 115.0, 115.3, 126.9, 128.7, 128.8, 129.3, 133.2, 137.4, 143.3, 160.6, 163.9, 172.4; EI-MS (*m/z*, relative intensity) 278 [$(M-89)^+$, 68], 155 (66), 91 (100); HRMS calcd for $C_{14}H_{13}NSO_2F$: 278.0651, found 278.0648.

3.4.4. *cis*-Methyl 2-hydroxy-3-(*p*-chloro)phenyl-3′-(*N*-tosylamino)propanoate (5d). IR (KBr) 3448, 2361, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 3.16 (d, J=4.0 Hz, 1H), 3.76 (s, 3H), 4.35 (dd, J=4.0, 2.3 Hz, 1H), 4.85 (dd, J=2.3, 9.8 Hz, 1H), 5.47 (d, J=9.8 Hz, 1H), 7.09–7.20 (m, 6H), 7.52 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 53.3, 58.9, 74.1, 126.8, 127.0, 127.9, 128.4, 129.3, 137.4, 137.5, 143.2, 172.4. EI-MS (*m/z*, relative intensity) 327 [$(M-56)^+$, 5], 294 [$(M-89)^+$, 14], 260 (100), 155 (76), 91 (100); HRMS calcd for $C_{14}H_{13}NSO_2Cl$: 294.0356, found 294.0357.

3.4.5. *cis*-Methyl 2-hydroxy-3-(*o*-methyl)phenyl-3′-(*N*-tosylamino)propanoate (5e). IR (KBr) 3269, 2361, 1749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 3H), 3.44 (br, 1H), 3.79 (s, 3H), 4.24 (br, 1H), 5.15 (dd, J=2.1, 9.7 Hz, 1H), 6.02 (d, J=9.7 Hz, 1H), 6.95–7.10 (m, 6H), 7.48 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1, 21.3, 53.2, 54.9, 73.1, 126.0, 126.8, 127.4, 129.1, 130.2, 134.3, 135.3, 137.3, 142.9, 172.7; EI-MS (*m/z*, relative intensity) 274 [$(M-89)^+$, 74], 155 (58), 91 (100); HRMS calcd for $C_{15}H_{16}NSO_2$: 274.0902 [$(M-89)^+$], found 274.0904.

3.4.6. *cis*-Methyl 2-hydroxy-3-(*p*-methoxyl)phenyl-3′-(*N*-tosylamino)propanoate (5f). IR (film) 3282, 1739, 1250, 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.33 (s, 3H), 3.32 (d, J=4.6 Hz, 1H), 3.74 (s, 6H), 4.31 (dd, J=2.4, 4.6 Hz, 1H), 4.78 (dd, J=2.4, 9.6 Hz, 1H), 5.71 (d, J=9.6 Hz, 1H), 6.66–6.71 (m, 2H), 7.03–7.26 (m, 4H), 7.53 (d, J=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.4, 53.1, 55.2, 58.6, 74.3, 113.7, 127.0, 128.0, 129.2, 129.4, 137.5, 143.0, 159.1, 172.6; EI-MS (*m/z*, relative intensity) 290 [$(M-89)^+$, 100], 155 (38), 134 (21), 92 (10); HRMS calcd for $C_{15}H_{16}O_3NS$: 290.0851, found 290.0844.

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