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Asymmetric and diastereoselective Mannich reactions using hydantoin as a chiral auxiliary

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ABSTRACT

The Mannich reaction of titanium enolates of a chiral hydantoin with various aldimines smoothly occurred in good yields and with high *anti*-diastereoselectivity. The Mannich adducts can be readily cleaved by alcoholysis to afford several β-amino ester derivatives in good yields and in almost enantiomerically pure form.

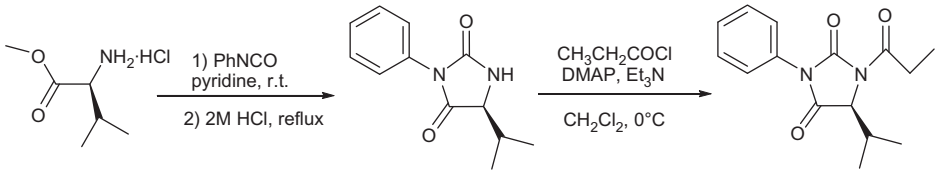
1. Introduction

β-Amino ester derivatives are key synthons in the synthesis of β-lactam antibiotics, which are important components of many natural products and therapeutic agents.[1] Therefore, the asymmetric synthesis of β-amino ester derivatives has become a field of increasing interest in organic synthetic chemistry over the past few years.[2] In fact, the asymmetric Mannich reaction is one of the most general methods widely used in these syntheses.[3]

Previously[4] we reported asymmetric aldol reactions which utilized hydantion as a chiral auxiliary to give aldols in reasonable yields and with high diastereoselectivity. When the aldol adducts were subjected to hydrolysis, the chiral auxiliary could be recovered quantitatively, and β-hydroxy acid derivatives were obtained as almost pure enantiomers. It has been proven that hydantoin is an excellent chiral auxiliary in asymmetric synthesis. With these results in mind, we herein report asymmetric Mannich reactions that utilize hydantoin as a chiral auxiliary, with a series of aldimines using a $TiCl_4$/DIPEA reagent system.

2. Results and discussion

Previously,[4] *N*-propionylhydantoin **3** was derived from L-valine methyl ester hydrochloride **1** (Scheme 1). The Mannich reaction of *N*-propionylhydantoin **3** with *N*-(4-methoxyphenyl)benzaldimine was examined first (Scheme 2). At first, $TiCl_4$ and the base [1 equiv of $TiCl_4$ and 2.5 equiv of the base] were added.[5] The use of diisopropylethylamine afforded higher chemical yields than the use of (−)-sparteine, since many by-products were obtained when we used (−)-sparteine. We attempted to use *n*-Bu_2BOTf or $Sn(OTf)_2$ as the Lewis acid, but neither of them gave the Mannich adduct **4a**. When the reaction temperature was changed from −78 °C to 0 °C, the diastereomeric ratio exhibited only small variations, but we obtained lower chemical yields when the reaction temperature was kept at



Scheme 1.

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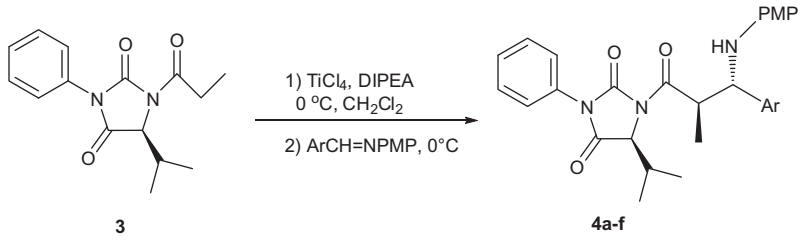


Scheme 2.

−78 °C. The Mannich reactions with other aldimines were next examined; these reactions resulted in similar diastereomeric ratios (91:9–96:4) (Table 1).

Table 1
Mannich reactions of N-propionylhydantion **3** with several aldimines

Entry	Product	Ar	Diastereomeric ratio[a]	Yield[b] (%)
1	**4a**	C_6H_5	91:9	71
2	**4b**	4-ClC_6H_4	96:4	82
3	**4c**	3-$O_2NC_6H_4$	92:8	74
4	**4d**	2,3-$(CH_3O)_2C_6H_3$	93:7	78
5	**4e**	2-Furyl	94:6	61
6	**4f**	2-Thienyl	94:6	58

[a] Determined by HPLC (C18 reversed-phase column, 254 nm, methanol/H_2O 80:20, 1.00 mL/min).
[b] Yield of product after silica gel chromatography.

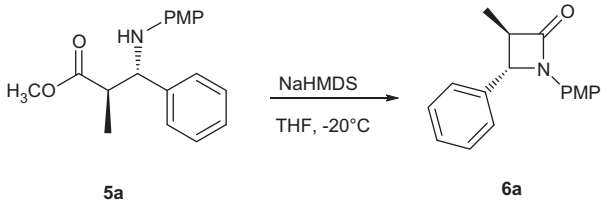
The Mannich adducts **4a–f** were subjected to alcoholysis,[6] which resulted in the quantitative recovery of chiral auxiliary **2** (Scheme 3), and afforded the corresponding methyl esters **5a–f** in good yields and in almost enantiomerically pure forms (Table 2).

Table 2
Alcoholysis of Mannich adducts **4a–f**

Entry	Product	Ar	Ee[a] (%)	Yield[b] (%)
1	**5a**	C_6H_5	>99	78
2	**5b**	4-ClC_6H_4	>99	85
3	**5c**	3-$O_2NC_6H_4$	>99	75
4	**5d**	2,3-$(CH_3O)_2C_6H_3$	>99	77
5	**5e**	2-Furyl	>99	70
6	**5f**	2-Thienyl	>99	80

[a] Determined by HPLC (Chiralcel® OD-H column, 254 nm, *n*-hexane/2-propanol 90:10, 1.00 mL/min).
[b] Yield of product after silica gel chromatography.

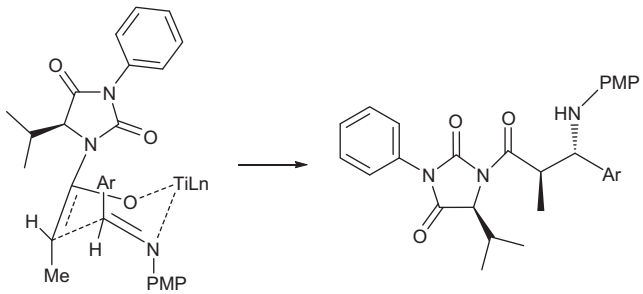
In order to determine the absolute configuration of the Mannich adducts, β-amino ester **5a** was treated with NaHMDS at −20 °C in anhydrous THF to afford the known β-lactam **6a** (Scheme 4).



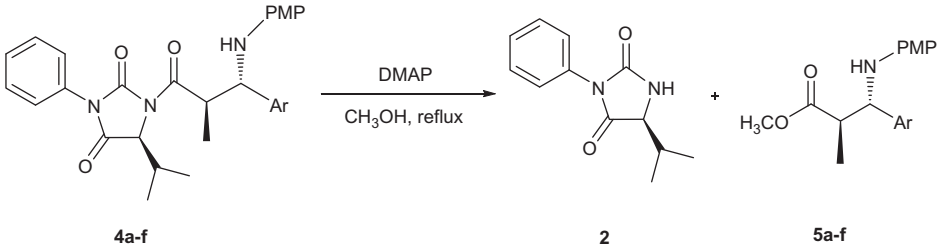
Scheme 4.

Comparison of the observed $J_{3,4}$ coupling constants ($J_{3,4}$ = 1.8 Hz) in the ^{1}H NMR spectrum with those reported in the literature[7] ($J_{3,4}$ = 5.8 Hz for the *syn*-isomer and $J_{3,4}$ = 2.2 Hz for the *anti*-isomer) revealed that the newly prepared β-lactam **6a** was an *anti*-isomer. Furthermore, comparing the specific rotation of the newly prepared β-lactam **6a** {$[\alpha]_D^{20} = -46.1$ (*c* 0.89, $CHCl_3$) versus literature[7] $[\alpha]_D^{25} = +45.2$ (*c* 1.01, $CHCl_3$) (3*S*, 4*R*)} allowed us to establish the absolute configuration of **6a** to be (3*R*,4*S*), which could be extended to the β-amino esters **5a–f** and the Mannich adducts **4a–f**.

Based on the previous literature[2a,5] reports of asymmetric Mannich reactions directed by chiral auxiliaries, we proposed that N-propionylhydantoin **3** and the aldimines were subjected to $TiCl_4$ to form the *Z*-enolate, while the *anti*-products could be rationalized by a chelated transition state involving attack of the preformed *Z*-enolate on the less hindered Si face of the aldimines with the C=N azomethine bond in an *E*-configuration, which can place the imine Ar substituent in an axial position in the cyclic transition state and therefore afford the diastereoisomer with the relative *anti*-configuration (Scheme 5).



Scheme 5.



Scheme 3.

3. Conclusion

In conclusion, a very easy and efficient synthetic protocol for asymmetric Mannich reactions has been developed using hydantoin as a chiral auxiliary. Moreover, the Mannich adducts, after the alcoholysis reaction allowed recovery of the chiral auxiliary hydantoin, and afforded a series of β-amino ester derivatives in almost enantiomerically pure forms.

4. Experimental

4.1. General

The aldimines were prepared by condensation of the corresponding aldehyde and *p*-methoxyphenylamine under standard conditions in the literature.[8] All other reagents were used as purchased. All solvents were dried or purified by standard procedures before use. Separations by flash chromatography were performed on 300–400 mesh silica gel. Melting points were measured on a WRS-1A digital melting point apparatus. Optical rotations were measured using a sodium D line on WZZ-2B Automatic Polarimeter. HPLC analyses were carried out on a Dionex chromatograph equipped with a diode-array UV detector. IR spectra were obtained on KBr pellets or CH_2Cl_2 solvent. NMR spectra were recorded on a Varian Unity Inova 600 spectrometer in $CDCl_3$ (^1H at 600 MHz and ^{13}C at 150 MHz) using TMS as the internal standard. High-resolution mass spectra (HRMS) were recorded on a Varian 7.0T FTMS mass spectrometer using ESI (electrospray ionization).

4.2. Preparation of (*S*)-5-isopropyl-3-phenyl-1-propionylhydantoin 3

The general procedure for N-propionylhydantoin **3** was described in our previous Letter,[4] and compound **3** obtained in 64% from L-valine methyl ester hydrochloride **1**. $[\alpha]_D^{20} = +10.4$ (*c* 6.33, CH_2Cl_2); IR: 1792, 1732, 1713 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.95 (d, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 6.6 Hz, 3H), 2.64 (m, 1H), 3.02 (q, *J* = 7.2 Hz, 2H), 4.63 (d, *J* = 2.4 Hz, 1H), 7.32–7.49 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 8.37, 15.49, 18.01, 29.47, 30.84, 62.97, 126.41, 128.87, 129.23, 130.56, 153.02, 169.28, 173.03.

4.3. General procedure for Mannich reactions

The N-propionylhydantoin **3** (0.548 g, 2.0 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and placed in a dry flask under N_2. The solution was cooled to 0 °C, and $TiCl_4$ (0.22 mL, 2.0 mmol) was added dropwise. The solution was stirred at 0 °C for 15 min, then diisopropyl-ethylamine (0.87 mL, 5.0 mmoL) was added slowly. The solution was stirred at 0 °C for another 30 min, and then a solution of the corresponding aldimine (2.6 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 4–8 h, and then quenched with saturated aqueous NH_4Cl. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 8:1, v/v) gave the Mannich adducts **4a**–**f**.

4.3.1. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-phenyl-propionyl]hydantoin 4a

Yield: 71%; white solid; Mp 66.2–66.9 °C; $[\alpha]_D^{20} = -21.3$ (*c* 1.04, CH_2Cl_2); IR: 3372, 1787, 1734, 1706 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.70 (d, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 6.0 Hz, 3H), 1.16 (d, *J* = 7.2 Hz, 3H), 2.52 (m, 1H), 3.65 (s, 3H), 4.46 (m, 1H), 4.49 (d, *J* = 9.6 Hz, 1H), 4.62 (d, *J* = 3.6 Hz, 1H), 6.51 (d, *J* = 9.0 Hz, 2H), 6.65 (d, *J* = 9.0 Hz, 2H), 7.18–7.52 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.09, 15.35, 17.91, 29.61, 45.00, 55.53, 63.53, 63.59, 114.55, 115.53, 126.54, 127.03, 127.50, 128.60, 129.13, 129.38, 130.43, 140.72, 141.05, 152.23, 153.79, 169.08, 175.29; HRMS calculated for $C_{29}H_{31}N_3O_4$ $[M+Na]^+$: 508.2213, found 508.2206.

4.3.2. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-(*p*-chloro-phenyl)-propionyl]hydantoin 4b

Yield: 82%; white solid; Mp 73.8–74.7 °C; $[\alpha]_D^{20} = -24.2$ (*c* 1.11, CH_2Cl_2); IR: 3383, 1788, 1732, 1703 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.72 (d, *J* = 6.6 Hz, 3H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.17 (d, *J* = 7.2 Hz, 3H), 2.51 (m, 1H), 3.67 (s, 3H), 4.44 (m, 1H), 4.47 (d, *J* = 9.6 Hz, 1H), 4.61 (d, *J* = 3.6 Hz, 1H), 6.49 (d, *J* = 7.2 Hz, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 7.24–7.53 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.96, 15.21, 17.83, 29.57, 44.74, 55.49, 63.41, 63.47, 114.51, 114.57, 126.45, 128.39, 128.71, 129.11, 129.32, 130.29, 133.14, 139.51, 140.14, 152.40, 153.73, 168.88, 174.85; HRMS calculated for $C_{29}H_{30}ClN_3O_4$ $[M+Na]^+$: 542.1823, found 542.1820.

4.3.3. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-(*m*-nitro-phenyl)-propionyl]hydantoin 4c

Yield: 74%; yellow solid; Mp 80.3–81.5 °C; $[\alpha]_D^{20} = -23.5$ (*c* 0.92, CH_2Cl_2); IR: 3377, 1789, 1732, 1704 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.73 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 6H), 2.55 (m, 1H), 3.67 (s, 3H), 4.51 (m, 1H), 4.63 (d, *J* = 3.6 Hz, 1H), 4.65 (d, *J* = 9.6 Hz, 1H), 6.53 (d, *J* = 7.2 Hz, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 7.35–8.19 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.03, 15.28, 17.83, 29.62, 44.60, 55.48, 63.54, 63.56, 114.70, 115.84, 121.97, 122.77, 126.44, 129.20, 129.38, 129.68, 130.24, 133.36, 139.62, 143.36, 148.42, 153.01, 153.74, 168.80, 174.30; HRMS calculated for $C_{29}H_{30}N_4O_6$ $[M+Na]^+$: 553.2063, found 553.2052.

4.3.4. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-(2″,3″-dimethoxyphenyl)-propionyl]hydantoin 4d

Yield: 78%; white solid; Mp 71.9–72.6 °C; $[\alpha]_D^{20} = -30.6$ (*c* 1.85, CH_2Cl_2); IR: 3373, 1788, 1732, 1704 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.78 (d, *J* = 6.0 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 7.2 Hz, 3H), 2.58 (m, 1H), 3.66 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 4.54 (m, 1H), 4.66 (d, *J* = 3.0 Hz, 1H), 4.89 (d, *J* = 9.6 Hz, 1H), 6.60–7.53 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.08, 15.13, 17.88, 29.51, 44.37, 55.47, 55.50, 55.53, 60.90, 63.48, 111.41, 114.38, 115.91, 119.66, 123.97, 126.53, 128.98, 129.28, 130.50, 140.91, 140.99, 147.25, 152.36, 152.39, 153.51, 169.22, 175.62; HRMS calculated for $C_{31}H_{35}N_3O_6$ $[M+Na]^+$: 568.2424, found 568.2417.

4.3.5. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-(2″-furyl)-propionyl]hydantoin 4e

Yield: 61%; white solid; Mp 64.5–66.0 °C; $[\alpha]_D^{20} = -28.4$ (*c* 0.83, CH_2Cl_2); IR: 3364, 1787, 1734, 1706 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.81 (d, *J* = 6.6 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 2.54 (m, 1H), 3.68 (s, 3H), 4.56 (m, 1H), 4.59 (d, *J* = 9.6 Hz, 1H), 4.64 (d, *J* = 3.0 Hz, 1H), 6.15–7.50 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.58, 15.19, 17.86, 29.40, 43.42, 55.48, 57.74, 63.36, 107.81, 110.01, 114.44, 116.14, 126.48, 129.00, 129.27, 130.43, 140.59, 141.95, 152.75, 153.29, 153.41, 169.10, 174.87; HRMS calculated for $C_{27}H_{29}N_3O_5$ $[M+Na]^+$: 498.2005, found 498.2000.

4.3.6. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-(2″-thienyl)-propionyl]hydantoin 4f

Yield: 58%; white solid; Mp 62.5–63.1 °C; $[\alpha]_D^{20} = -25.9$ (*c* 1.45, CH_2Cl_2); IR: 3367, 1789, 1732, 1698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.74 (d, *J* = 6.6 Hz, 3H), 1.16 (d, *J* = 7.2 Hz, 3H), 1.23 (d, *J* = 7.2 Hz, 3H), 2.51 (m, 1H), 3.68 (s, 3H), 4.53 (m, 1H), 4.63 (d, *J* = 3.0 Hz, 1H), 4.79 (d, *J* = 8.4 Hz, 1H), 6.58–7.52 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.08, 15.21, 17.83, 29.47, 45.72, 55.41, 59.52, 63.36, 114.47, 115.78, 124.31, 126.45, 126.72, 129.02, 129.27, 130.33, 132.50, 140.39, 140.43, 152.61, 153.43, 168.96, 174.82; HRMS calculated for $C_{27}H_{29}N_3O_4$ $[M+Na]^+$: 514.1777, found 514.1772.

4.4. General procedure for the alcoholysis of Mannich adducts 4a–f

To a solution of Mannich adducts **4a**–**f** (1.0 mmol) in methanol (50 mL) was added DMAP (0.244 g, 2.0 mmol), after which the reaction mixture was refluxed for 8 h. Next, the mixture was concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 6:1, v/v) recovered the chiral hydantoin **2** and gave β-amino esters **5a**–**f**.

4.4.1. (2*R*,3*S*)-Methyl 2-methyl-3-(*p*-methoxyphenylamino)-3-phenylpropanoate 5a

Yield: 78%; $[\alpha]_D^{20} = -50.8$ (*c* 1.02, CH_2Cl_2); IR: 3377, 1731 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.13 (d, *J* = 7.2 Hz, 3H), 2.84 (m, 1H), 3.63 (s, 3H), 3.66 (s, 3H), 4.43 (d, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 2H), 6.65 (d, *J* = 9.0 Hz, 2H), 7.20–7.30 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.20, 46.63, 51.80, 55.55, 61.68, 114.54, 114.99, 126.82, 127.36, 128.48, 140.68, 141.02, 152.02, 175.47.

4.4.2. (2*R*,3*S*)-Methyl 2-methyl-3-(*p*-methoxyphenylamino)-3-(*p*-chloro-phenyl) propanoate 5b

Yield: 85%; $[\alpha]_D^{20} = -43.1$ (*c* 0.57, CH_2Cl_2); IR: 3393, 1731 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.15 (d, *J* = 7.2 Hz, 3H), 2.81 (m, 1H), 3.64 (s, 3H), 3.67 (s, 3H), 4.41 (d, *J* = 6.6 Hz, 1H), 6.47 (d, *J* = 7.8 Hz, 2H), 6.67 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.21, 46.46, 51.87, 55.59, 61.01, 114.62, 114.93, 128.21, 128.70, 133.00, 139.76, 140.44, 152.17, 175.20.

4.4.3. (2*R*,3*S*)-Methyl 2-methyl-3-(*p*-methoxyphenylamino)-3-(*m*-nitro-phenyl) propanoate 5c

Yield: 75%; $[\alpha]_D^{20} = -48.2$ (*c* 1.16, CH_2Cl_2); IR: 3398, 1733 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.21 (d, *J* = 7.2 Hz, 3H), 2.92 (m, 1H), 3.65 (s, 3H), 3.68 (s, 3H), 4.58 (d, *J* = 7.8 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 7.48–8.21 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.21, 46.13, 52.10, 55.62, 61.10, 114.69, 115.00, 121.88, 122.65, 129.51, 133.14, 139.75, 143.29, 148.42, 152.53, 174.67.

4.4.4. (2*R*,3*S*)-Methyl 2-methyl-3-(*p*-methoxyphenylamino)-3-(2′,3′-dimethoxyphenyl) propanoate 5d

Yield: 77%; $[\alpha]_D^{20} = -53.7$ (*c* 2.20, CH_2Cl_2); IR: 3390, 1733 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.13 (d, *J* = 7.2 Hz, 3H), 2.97 (m, 1H), 3.63 (s, 3H), 3.67 (s, 3H), 3.83 (s, 3H), 3.90 (s, 3H), 4.77 (d, *J* = 7.8 Hz, 1H), 6.58–6.97 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.87, 45.90, 51.99, 55.78, 55.79, 55.84, 60.93, 111.59, 114.82, 114.84, 119.91, 123.80, 124.10, 147.19, 152.37, 152.68, 152.81, 176.28.

4.4.5. (2*R*,3*S*)-Methyl 2-methyl-3-(*p*-methoxyphenylamino)-3-(2′-furyl)-propanoate 5e

Yield: 70%; $[\alpha]_D^{20} = -47.6$ (*c* 1.05, CH_2Cl_2); IR: 3372, 1732 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.12 (d, *J* = 7.2 Hz, 3H), 3.03 (m, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 4.61 (d, *J* = 7.8 Hz, 1H), 6.15 (d, *J* = 3.0 Hz, 1H), 6.24 (dd, *J* = 1.8, 3.0 Hz, 1H), 6.61 (d, *J* = 9.0 Hz, 2H), 6.72 (d, *J* = 9.0 Hz, 2H), 7.31 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.38, 44.33, 51.98, 55.66, 56.10, 107.54, 110.15, 114.68, 115.84, 140.69, 141.96, 152.74, 153.59, 175.27.

4.4.6. (2*R*,3*S*)-Methyl 2-methyl-3-(*p*-methoxyphenylamino)-3-(2′-thienyl)-propanoate 5f

Yield: 80%; $[\alpha]_D^{20} = -45.8$ (*c* 1.10, CH_2Cl_2); IR: 3384, 1732 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.19 (d, *J* = 7.2 Hz, 3H), 2.93 (m, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 4.76 (d, *J* = 7.2 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 2H), 6.70 (d, *J* = 9.0 Hz, 2H), 6.89–6.92 (m, 2H), 7.15 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.95, 46.98, 52.15, 55.75, 57.89, 114.76, 115.53, 124.46, 125.06, 126.88, 140.63, 145.91, 152.64, 175.26.

4.5. Preparation of (3*R*,4*S*)-1-(4-methoxyphenyl)-3-methyl-4-phenylazetidin-2-one 6a

The β-amino ester **5a** (0.224 g, 0.75 mmol) was dissolved in anhydrous THF (15 mL) and placed in a dry flask under N_2. The solution was cooled to −20 °C, then a solution of NaHMDS (0.75 mmol) in THF (0.38 mL, 2 M) was added dropwise. The reaction mixture was then stirred at −20 °C for 30 min, and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 8:1, v/v) gave a white needle solid **6a** (0.178 g, 89%). Mp 122–124 °C; $[\alpha]_D^{20} = -46.1$ (*c* 0.89, $CHCl_3$); IR: 1745 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.47 (d, *J* = 7.2 Hz, 3H), 3.11 (dq, *J* = 2.4, 7.2 Hz, 1H), 3.73 (s, 3H), 4.54 (d, *J* = 1.8 Hz, 1H), 6.77 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 9.6 Hz, 2H), 7.31–7.38 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.23, 55.50, 55.57, 63.03, 114.50, 118.41, 126.02, 128.53, 129.23, 131.69, 138.27, 156.13, 167.85.

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