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Asymmetric Synthesis of 2-Alkyl-Substituted 2,5-Dihydropyrroles from Optically Active Aza-Baylis−Hillman Adducts. Formal Synthesis of (−)-Trachelanthamidine.

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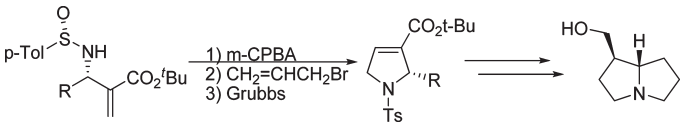

A series of optically active 2-alkyl-substituted 2,5-dihydropyrroles were prepared via the asymmetric aza-Baylis−Hillman equivalent reaction and subsequent ring-closure metathesis reaction. Optically active aza-Baylis−Hillman adducts underwent a smooth two-step conversion to *N*-allyl-*β*-amino-α-methylene esters in high yield, which gave chiral 2,5-dihydropyrroles, potential precursors for the aza-heterocyclic synthesis, almost quantitatively through RCM reaction catalyzed by Grubbs catalyst. The conversion was carried out without loss of the optical purity of the starting material. Synthetic application of the method to (−)-trachelanthamidine was examined. Hydrogenation of 2,5-dihydropyrrole took place smoothly to give the corresponding 2,3-disubstituted pyrrolidine in good yield. The stereoselectivity of the hydrogenation was sensitive to the presence or absence of the protective group in the C2-side chain. The TBS-protected 2,5-dihydropyrrole gave a 1:1 mixture of the *cis*/*trans* isomers, while free alcohol afforded the *trans*-2,3-disubstituted pyrrolidine in a selectivity of 6:1. The formal synthesis of (−)-trachelanthamidine was achieved in 11 steps from a chiral sulfinimine. This methodology provided a convenient procedure for the preparation of C2-alkyl-substituted 2,5-dihydropyroles with retention of high optical purity.

Introduction

The aza-Baylis−Hillman reaction has been recognized as a potentially useful reaction in organic synthesis because it provides a one-step preparation of α-methylene-*β*-amino esters from readily available α,*β*-unsaturated esters and imines.[1]

Recently, asymmetric syntheses of these compounds have been of interest. Many methods on the catalytic asymmetric modification of the reaction have been published.[2] For example, chiral amines derived from quinine derivatives[2b,d−f] or chiral phosphines[2c,g−i,m,q−w] have been examined as good catalysts for the asymmetric aza-Baylis−Hillman reaction. Most of the reports, however, are usually useful for aromatic imines; the use of aliphatic imines is very limited. This is probably due to the instability of aliphatic imines under the reaction conditions. To overcome this drawback, stable and readily accessible aliphatic imines are desired. Chiral sulfinimines are frequently used as stable imines in organic synthesis.[3] The sulfinyl group affords sufficient steric bias in the nucleophilic addition to the imino group and is readily removed by acidic treatment. Use of chiral sulfinimines in the aza-Baylis−Hillman reaction has been reported by Aggarwal, but only moderate levels of diastereomeric selectivity were observed.[4] Recently, we have reported an alternative method, in which we disclosed that a Michael/imino-aldol domino reaction of an acrylate and a chiral sulfinimine followed by a subsequent thermal elimination of sulfoxide gave aza-Baylis−Hillman products.[5] This methodology enabled us to prepare aza-Baylis−-Hillman adducts from aliphatic imines in high enantiomeric excesses, although the method requires a two-step sequence. To the best of our knowledge, there are only a few practical methods to prepare aza-Baylis−Hillman adducts from aliphatic imines.[6] To enhance the potential of this methodology in organic synthesis, we attempted to prepare chiral 2,5-dihydropyrroles, which are recognized as potential precursors for the preparation of aza-multicyclic organic compounds and often seen among natural products such as alkaloids.[7] With our method, the C2 aliphatic side chain is introduced with sufficient control of chirality. We also examined the preparation of (−)-trachelanthamidine in highly optically pure form.

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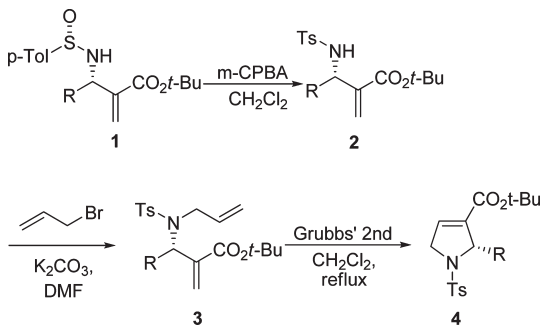
Results and Discussion

The optically active aza-Baylis−Hillman adducts **1** were prepared through the domino reaction of chiral sulfinimines[3] and *tert*-butyl acrylate.[5d] *N*-Allylation of **1** was carried out via oxidation to **2**[8] and subsequent basic treatment with allyl bromide to give **3** (Scheme 1). The ring-closure metathesis reaction of **3** proceeded smoothly to give 2,5-dihydropyrroles **4** in the presence of Grubbs' second-generation catalyst.[9] These results are summarized in Table 1.

For example, treatment of **1a** with *m*-CPBA at room temperature resulted in the oxidation of the sulfinimine unit to give the corresponding sulfonamine **2a** in 93% yield (entry 1). Subsequent *N*-allylation progressed under the weak basic

SCHEME 1



conditions by the presence of K_2CO_3 and furnished **3a** in 90% yield. It should be mentioned that no loss of enantiomeric excess in compound **3** was observed during the transformation. We have also examined homoallyl bromide for the alkylation, but the alkylation progressed sluggishly and a trace amount of alkylated products was obtained.

The ring-closure metathesis reaction of compound **3a** was examined. We employed the Grubbs' second-generation catalyst for the reaction. The transformation to 2,5-dihydropyrrole **4a** was achieved smoothly with an isolated yield of 97% (entry 1). The optical purity of **4a** was examined by HPLC analysis using a Chiral-Pak IC column, which revealed that the enantiomeric excess of **4a** was 90%, the same value as the starting material **2a**. Thus, no significant loss of enantiomeric excess was observed during the three-step transformation. Thus, we have successfully provided a new preparation of optically active 2-alkyl-substituted 2,5-dihydropyrroles from chiral aza-Baylis−Hillman adducts which are prepared in a few short steps from chiral sulfinimines.

Having established the methodology, we then examined the synthesis of a pyrrolizidine alkaloid. Pyrrolizidine alkaloids are important class of natural products, and due to their unique biological activity, there have been many efforts to synthesize these compounds.[10] Among these alkaloids, we chose (−)-trachelanthamidine as a synthetic target.[11]

Our synthesis started from the preparation of the optical active sulfinimine **6** (Scheme 2). This chiral sulfinimine was prepared from 1,4-butanediol **5** in three steps. Monoprotection of **5** was carried out using the literature method to give the diol mono-TBS ether in 83% yield,[12] which was then

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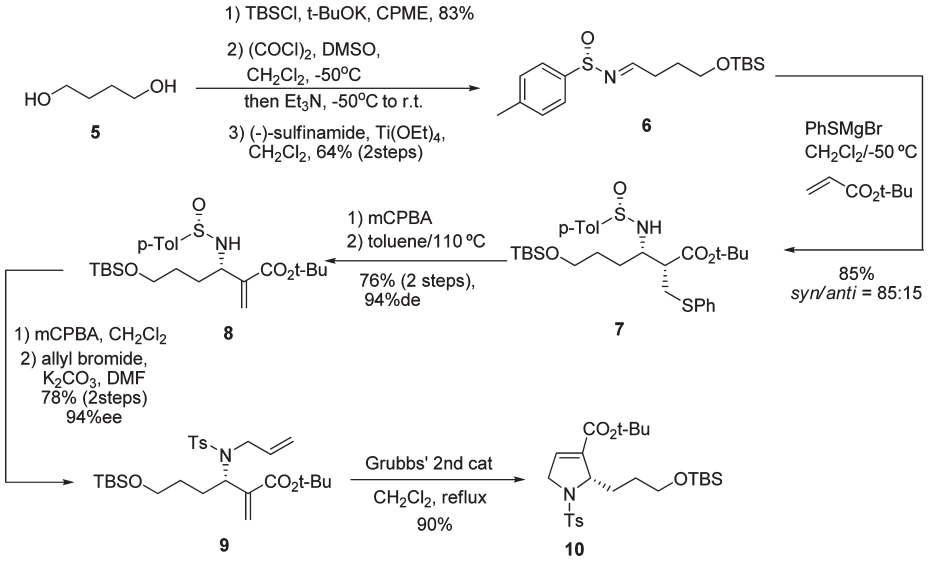
TABLE 1. Preparation of Optically Active 2,5-Dihydropyrroles 4

entry	R	**2**; yield[a] (%)	ee[b] (%)	**3**; yield[a] (%)	ee[b] (%)	**4**; yield[a] (%)	ee[b] (%)
1	Et	**2a**; 93	90	**3a**; 90	90	**4a**; 97	90
2	Pr	**2b**; 97	92	**3b**; 89	94	**4b**; 96	94
3	i-Pr	**2c**; 98	98	**3c**; 86	98	**4c**; 94	98
4	i-Bu	**2d**; 97	92	**3d**; 89	92	**4d**; 98	92
5	C_5H_{11}	**2e**; 97	92	**3e**; 73	92	**4e**; 95	92
6	c-C_6H_{11}	**2f**; 96	96	**3f**; 83	94	**4f**; 92	96
7	*p*-Tol	**2g**; 91	94	**3g**; 83	94	**4g**; 100	98

[a]Isolated yields. [b]Enantiomeric excesses determined by chiral HPLC analyses (ChiralPak-IC, AD).

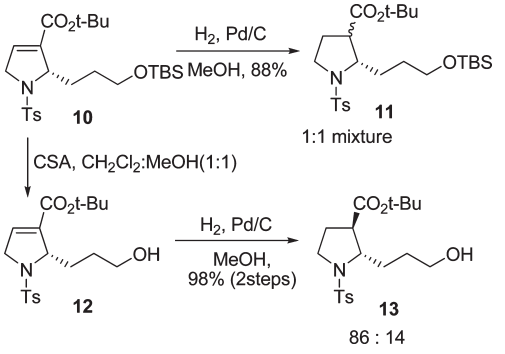
SCHEME 2



converted into the aldehyde by Swern oxidation. Treatment of the aldehyde with (−)-*p*-toluenesulfinamine gave the desired chiral sulfinimine **6** in 64% yield (Scheme 2). The Michael/imino-aldol domino reaction with **6** gave a diastereomeric mixture of chiral *β*-amino-α-phenylthiomethyl esters **7** in 85% yield. In the preparation of **7**, it was possible to scale up to 7 g in a one-pot manipulation. HPLC analysis revealed that the diastereomeric ratio of **7** was 85:15, indicating that the reaction progressed in a highly stereoselective manner. As we reported previously,[5d] the formation of the mixture of diastereomers was mainly caused by epimeric occurrence at the C2 position; thus, the asymmetric induction from the chiral of sulfinimine to the C3 position was almost 100%. Treatment of **7** with *m*-CPBA resulted in the formation of the corresponding sulfoxide which was treated under toluene refluxing conditions, giving **8** in 76% yield. HPLC analysis of **8** revealed that the diastereomeric ratio was 97:3. Oxidation and *N*-allylation of compound **8** was carried out in a manner similar to that shown in Scheme 1, and compound **9** was isolated in 78% yield in two steps. The ring-closure metathesis was achieved using the Grubbs' second-generation catalyst to afford chiral 2,5-dihydropyrrole **10** as a solid in 90% yield. HPLC examination of compound **10** indicated that the enantiomeric excess of **10** was 94%. Recrystallization of **10** enhanced the enantiomeric excess over 99%.

We next examined the reduction of compound **10** (Scheme 3).[13] Hydrogenation of **10** in the presence of a

SCHEME 3



10% Pd/C catalyst gave **11** in 88% yield. Unfortunately, **11** was isolated as a 1:1 mixture of diastereomers. Thus, the hydrogenation of **10** took place in a nonstereoselective manner. To improve the stereoselectivity of the reaction, we examined the hydrogenation of the deprotected compound **12**. The removal of the *O*-protecting group was accomplished quantitatively by acidic treatment to give alcohol **12**. No pyrrole formation was observed during the reaction. Free alcohol **12** was then reduced under standard hydrogenation conditions, giving **13** in 98% yield over two steps. Fortunately, the reduction of alcohol **12** progressed stereoselectively, and the diastereomeric ratio of compound **13** was estimated to be 86:14. The major isomer was separated by flash chromatography, and it was used for the next reaction.

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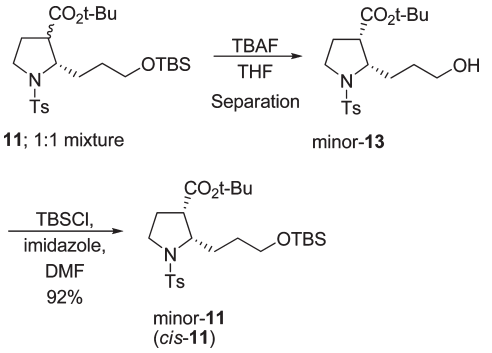
SCHEME 4

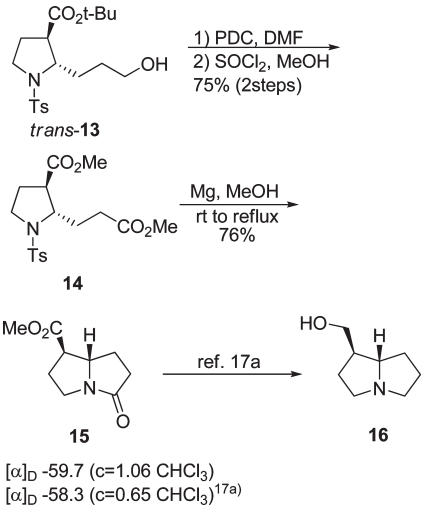


The configuration of compound **13** was determined in the following way (Scheme 4). The major isomer of compound **13** was an oil and did not yield good crystals for X-ray analysis. Then, we tried to isolate the minor isomer of **13** by using the 1:1 mixture of **11**. Compound **11** was desilylated by treatment with TBAF to give the mixture of isomers of compound **13** in 96% yield. Careful flash chromatography of the mixture of **13** enabled the separation of the two diastereomers of **13**. The hydroxyl group of minor-**13** was protected by a TBS group, and minor-**11** was prepared in 92% yield. Fortunately, minor-**11** gave a good crystal that was suitable for X-ray crystallographic analysis. The stereochemistry of minor-**11** was unambiguously determined to be the 2,3-*cis* configuration. Thus, the major-**11** and major **13** were determined to be 2,3-*trans*. As the absolute stereogenic center at C2 should be *S*,[5d] the absolute configuration of major-**13** was determined to be 2*S*,3*S*.

According to the reports by Lamaty, the hydrogenation of a 2,5-dihydropyrrole was expected to take place in a *trans*-selective manner, although a *N*-SES group was necessary to achieve high selectivity.[14] In our case, even starting with an *N*-tosylpyrrolidine, the high *trans*-selectivity in the hydrogenation are observed. The stereoselectivity for the hydrogenation step was very sensitive to the presence or absence of an *O*-protecting group in the C2 aliphatic side chain. Epimerization at the C3 position during hydrogenation was less likely.[14] Thus, we believe that the *trans*-selectivity is coming from the hydrogenation process itself. We are unsure of precise origin of the *trans*-selectivity, but the free hydroxyl group might be interacting with Pd/C surface which may cause good steric bias to achieve the *trans*-selectivity during the hydrogenation of dihydropyrrole.

To complete the total synthesis of (−)-trchelanthamidine, obtained alcohol **13** was exposed to PDC to give the corresponding carboxylic acid;[15] subsequent esterification gave diester **14** in 75% yield over two steps (Scheme 5). In the esterification stage, the *tert*-butyl ester was also hydrolyzed under the acidic conditions and converted to methyl ester in **14**. The *N*-tosyl protecting group was removed on treatment with magnesium metal in MeOH. Recently, this method has been widely used for the deprotection of the tosyl group because of the mild conditions.[16] In our case, intramolecular cyclization between the deprotected amine and the ester in the C2 side chain occurred simultaneously to give pyrolizidinone **15** in 76% yield in one step. The reduction step has already been reported in Nagao's total synthesis, and compound **15** was also known a compound.[17] The specific rotation of **15** was negative and had a value similar to the reported data.[17a] Thus, we have achieved the formal synthesis of (−)-trachelanthamidine **16**.

SCHEME 5



In conclusion, we have successfully developed the efficient synthesis of chiral 2-alkyl-substituted 2,5-dihydropyrroles from optically active aza-Baylis−Hillman adducts. The conversion requires three steps and was achieved in high yields with simple manipulation. No loss of enantiomeric excesses was observed. This conversion was also successfully employed in the preparation of an optically active pyrrolidine alkaloid. The formal synthesis of (−)-trachelanthamidine was achieved in 11 steps in 22% overall yield from a chiral sulfinimine. During the synthesis, the high *trans*-selectivity in the hydrogenation was observed. Since optically active 2,5-dihydropyrroles are regarded as potential precursors in many heterocyclic syntheses, our methodology will provide a convenient route in the synthesis of these natural products.

Experimental Section

General Methods. All of the reactions in this paper were performed under nitrogen atmosphere unless otherwise mentioned. CH_2Cl_2 was dried over CaH_2 and distilled under nitrogen before use. High-resolution mass spectra (HRMS) were performed by EI or FAB for ionization method.

Preparation of (*S*)-*tert*-Butyl 2-Methylene-3-(4-methylphenylsulfonamido)pentanoate (2a). Typical Procedure. To a solution of **1a** (741.2 mg, 2.29 mmol) in CH_2Cl_2 (20 mL) was added *m*-CPBA (77%, 567.7 mg, 2.52 mmol) at room temperature, and the resulting mixture was stirred for 2 h. The reaction mixture was washed with $Na_2S_2O_3$−$NaHCO_3$(aq) (10 mL x× 2) and brine (10 mL). The organic phase was separated and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure, and the residue was subjected flash chromatography (hexane−EtOAc, 10:1) to give **2a** in 93% yield (2.12 mmol) as a colorless oil: enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 16.8 min (minor), t_R 22.1 min (major)

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[Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 0.70 mL/min] as 90% ee; $[\alpha]_D$ +7.4 ($CHCl_3$, *c* 1.04); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (d, 2 H, J = 7.9 Hz), 7.23 (d, 2 H, *J* = 7.9 Hz), 5.83 (s, 1 H), 5.53 (d, 1 H, 9.8 Hz), 5.37 (s, 1 H), 3.88 (dd, 1 H, *J* = 7.6, 17.0 Hz), 2.40 (s, 3 H), 1.56−1.64 (m, 2 H), 1.41 (s, 9 H), 0.82 (t, 3 H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 164.8, 142.9, 139.6, 138.2, 129.4, 127.1, 126.5, 81.5, 58.9, 28.4, 27.9, 21.4, 10.8; HRMS (EI M) *m*/*z* 339.1504, calcd for $C_{17}H_{25}NO_4S$ 339.1504.

(***S***)-***tert*-Butyl 2-methylene-3-(4-methylphenylsulfonamido)hexanoate (2b):** colorless oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 10.2 min (minor), t_R 14.6 min (major) [Chiralpak IC (0.46 cm × 25 cm)) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 92% ee; $[\alpha]_D$ +10.0 ($CHCl_3$, *c* 0.99); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (d, *J* = 8.2 Hz, 2 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 5.80 (s, 1 H), 5.57 (d, *J* = 9.5 Hz, 1 H), 5.38 (s, 1 H), 3.99 (dd, *J* = 7.5, 17.2 Hz, 1 H), 2.39 (s, 3 H), 1.70−1.15 (m, 4 H), 1.41 (s, 9 H), 0.84 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 164.7, 142.9, 139.9, 138.1, 129.3, 127.1, 126.1, 81.4, 56.8, 37.3, 27.9, 21.4, 19.2, 13.4. Anal. Calcd for $C_{18}H_{27}NO_4S$: C, 61.16; H, 7.70; N, 3.96. Found: C, 60.93; H,7.32; N, 3.64.

(***S***)-***tert*-Butyl 4-methyl-2-methylene-3-(4-methylphenylsulfonamido)pentanoate (2c):** colorless oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 12.2 min (minor), t_R 16.0 min (major) [Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 98% ee; $[\alpha]_D$ +8.0 ($CHCl_3$, *c* 1.00); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (d, *J* = 8.1 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 5.79 (s, 1 H), 5.56 (d, *J* = 10.0 Hz, 1 H), 5.27 (s, 1 H), 3.59 (t, *J* = 9.4 Hz, 1 H), 2.39 (s, 3 H), 2.12−1.71 (m, 1 H), 1.41 (s, 9 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 0.74 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 165.1, 142.8, 138.8, 138.2, 129.3, 127.2, 127.0, 81.5, 63.6, 31.8, 27.9, 21.4, 19.9, 19.4; HRMS (EI M) *m*/*z* 353.1662, calcd for $C_{18}H_{27}NO_4S$ 353.1661.

(***S***)-***tert*-Butyl 5-methyl-2-methylene-3-(4-methylphenylsulfonamido)hexanoate (2d):** colorless oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 8.1 min (minor), t_R 12.9 min (major) [Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 92% ee; $[\alpha]_D$ +14.8 ($CHCl_3$, *c* 1.01); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, *J* = 8.3 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 5.78 (s, 1 H), 5.49 (d, *J* = 9.8 Hz, 1 H), 5.38 (s, 1 H), 4.13−3.99 (m, 1 H), 2.39 (s, 3 H), 1.73−1.47 (m, 2 H), 1.41 (s, 9 H), 1.38−1.28 (m, 1 H), 0.85 (d, *J* = 6.4 Hz, 3 H), 0.84 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 164.8, 142.9, 140.1, 138.2, 129.3, 127.1, 126.0, 81.5, 55.4, 44.4, 27.9, 24.5, 22.4, 21.8, 21.4; HRMS (EI M) *m*/*z* 367.1819, calcd for $C_{19}H_{29}NO_4S$ 367.1817.

(***S***)-***tert*-Butyl 2-methylene-3-(4-methylphenylsulfonamido)octanoate (2e):** colorless oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 8.6 min (minor), t_R 12.8 min (major) [Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 92% ee: $[\alpha]_D$ +8.4 ($CHCl_3$, *c* 1.01); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, *J* = 8.1 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 5.81 (s, 1 H), 5.55 (d, *J* = 9.4 Hz, 1 H), 5.38 (s, 1 H), 3.96 (dt, *J* = 7.5, 9.7 Hz, 1 H), 2.39 (s, 3 H), 1.72−1.45 (m, 2 H), 1.41 (s, 9 H), 1.34−1.08 (m, 6 H), 0.83 (t, *J* = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 164.8, 142.9, 140.0, 138.1, 129.3, 127.1, 126.1, 81.4, 57.1, 35.2, 31.1, 27.9, 25.7, 22.3, 21.4, 13.9. Anal. Calcd for $C_{20}H_{31}NO_4S$: C, 62.96; H, 8.19; N, 3.67. Found: C, 63.04; H,8.19; N, 3.63.

(***S***)-***tert*-Butyl 2-(cyclohexyl(4-methylphenylsulfonamido)methyl)acrylate (2f):** colorless oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 10.1 min (minor), t_R 12.6 min (major) [Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 96% ee; $[\alpha]_D$ +19.2 ($CHCl_3$, *c* 1.09); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 5.77 (d, *J* = 1.1 Hz, 1 H), 5.59 (d, *J* = 10.1 Hz, 1 H), 5.24 (s, 1 H), 3.65 (t, *J* = 9.6 Hz, 1 H), 2.39 (s, 3 H), 2.05 (d, *J* = 13.0 Hz, 1 H), 1.78−1.44 (s, 5 H), 1.41 (s, 9 H), 1.13 (m, 3 H), 0.94−0.72 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 142.8, 138.5, 138.3, 129.3, 127.2, 127.1, 81.5, 62.6, 40.8, 30.3, 29.8, 28.0, 26.2, 25.9, 25.8, 21.5; HRMS (EI M) *m*/*z* 393.1984, calcd for $C_{21}H_{31}NO_4S$ 393.1974.

(***S***)-***tert*-Butyl 2-((4-methylphenylsulfonamido)(*p*-tolyl)methyl)acrylate (2g):** yellow semisolid; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 11.3 min (minor), t_R 12.3 min (major) [Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 94% ee; $[\alpha]_D$ +23.4 ($CHCl_3$, *c* 1.13); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (d, *J* = 8.1 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 1 H), 7.01 (s, 4 H), 6.09 (s, 1 H), 5.67 (s, 1 H), 5.63 (d, *J* = 8.9 Hz, 1 H), 5.22 (d, *J* = 8.9 Hz, 1 H), 2.40 (s, 3 H), 2.27 (s, 3 H), 1.30 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 164.6, 143.2, 140.0, 137.8, 137.2, 136.0, 129.4, 129.1, 127.2, 126.6, 126.3, 81.7, 58.9, 27.8, 21.4, 20.9; HRMS (EI M) *m*/*z* 401.1655, calcd for $C_{22}H_{27}NO_4S$ 401.1661.

Preparation of (*S*)-*tert*-Butyl 3-(*N*-Allyl-4-methylphenylsulfonamido)-2-methylenepentanoate (3a). Typical Procedure. A mixture of **2a** (678.2 mg, 2.00 mmol), allyl bromide (0.19 mL, 2.20 mmol), and K_2CO_3 (830.7 mg, 6.00 mmol) in DMF (2.0 mL) was stirred at room temperature for 1 h. Additional allyl bromide (0.08 mL) was added, and the reaction mixture was stirred for an additional 5 h. Water (10 mL) was added, and the resulting aqueous solution was extracted with ether (10 mL × 3). The organic phase was combined, washed with brine (10 mL), and dried over Na_2SO_4. After filtration, the ether solution was concentrated by rotary evaporator and the residue was subjected to flash chromatography (hexane−EtOAc 10:1) to give **3a** in 90% yield (681.4 mg): colorless oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 23.4 min (minor), t_R 24.7 min (major) [CHIRALPAK IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 0.70 mL/min] as 90% ee: $[\alpha]_D$ −48.4 ($CHCl_3$, *c* 1.06); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, *J* = 8.1 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 6.23 (s, 1 H), 5.87−5.68 (m, 1 H), 5.63 (s, 1 H), 5.10 (d, *J* = 17.2 Hz, 1 H), 5.04 (d, *J* = 10.1 Hz, 1 H), 4.77 (t, *J* = 7.5 Hz, 1 H), 3.86−3.69 (m, 2 H), 2.39 (s, 3 H), 1.94−1.70 (m, 2 H), 1.42 (s, 9 H), 0.87 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 165.7, 142.7, 139.8, 138.3, 135.8, 129.2, 127.7, 126.2, 117.2, 81.1, 58.9, 47.8, 27.9, 25.0, 21.4, 11.4; HRMS (EI M) *m*/*z* 379.1817, calcd for $C_{20}H_{29}NO_4S$ 379.1817.

(***S***)-***tert*-Butyl 3-(*N*-allyl-4-methylphenylsulfonamido)-2-methylenehexanoate (3b):** colorless oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 13.0 min (minor), t_R 13.8 min (major) [Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 0.70 mL/min] as 94% ee; $[\alpha]_D$ −41.4 ($CHCl_3$, *c* 1.02); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, *J* = 8.2 Hz, 2 H), 7.23 (d, *J* = 7.9 Hz, 2 H), 6.20 (s, 1 H), 5.98−5.68 (m, 1 H), 5.61 (s, 1 H), 5.10 (td, *J* = 1.3, 17.2 Hz, 1 H), 5.04 (td, *J* = 1.3, 10.1 Hz, 1 H), 4.88 (t, *J* = 7.5 Hz, 1 H), 3.79 (d, *J* = 6.5 Hz, 2 H), 2.39 (s, 3 H), 2.01−1.55 (m, 2 H), 1.43 (s, 9 H), 1.35−1.19 (m, 2 H), 0.88 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 165.6, 142.7, 140.1, 138.2, 135.7, 129.1, 127.6, 126.0, 117.1, 81.1, 57.0, 47.7, 33.9, 27.9, 21.4, 19.8, 13.7; HRMS (EI^+ M) *m*/*z* 393.1974, calcd for $C_{21}H_{31}NO_4S$ 393.1974.

(***S***)-***tert*-Butyl 3-(*N*-allyl-4-methylphenylsulfonamido)-4-methyl-2-methylenepentanoate (3c):** colorless oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 13.2 min (minor), t_R 16.1 min (major) [CHIRALPAK IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 98% ee; $[\alpha]_D$ −48.9 ($CHCl_3$, *c* 0.99); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 7.8 Hz, 2 H), 6.29 (s, 1 H), 6.20−6.17 (m, 1 H), 5.86−5.74 (m, 1 H), 5.73 (s, 1 H), 5.10 (d, *J* = 17.2 Hz, 1 H), 5.02 (d, *J* = 10.1 Hz, 1 H), 4.53 (d, *J* = 11.2 Hz, 1 H), 3.92−3.74 (m, 2 H), 2.38 (s, 3 H), 2.35−2.24 (m, 1 H), 1.41 (s, 9 H), 1.05 (d, *J* = 6.4 Hz, 3 H), 0.83 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 165.8, 142.6, 139.3, 138.3, 135.8, 129.1, 127.9, 127.6, 117.2, 81.0, 63.5, 47.8, 29.2, 27.9, 21.4, 20.6, 20.4; HRMS (FAB M + 1) *m*/*z* 394.2054, calcd for $C_{21}H_{32}NO_4S$ 394.2052.

(*S*)-*tert*-Butyl 3-(*N*-allyl-4-methylphenylsulfonamido)-5-methyl-2-methylenehexanoate (**3d**): colorless oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 8.0 min (minor), t_R 8.4 min (major) [Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 92% ee; $[\alpha]_D$ −40.8 ($CHCl_3$, *c* 1.00); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, J = 8.1 Hz, 2 H), 7.23 (d, J = 8.3 Hz, 2 H), 6.17 (s, 1 H), 6.00−5.65 (m, J = 6.1, 10.2, 16.4 Hz, 1 H), 5.55 (s, 1 H), 5.11 (d, J = 17.2 Hz, 1 H), 5.05 (d, J = 10.1 Hz, 1 H), 4.98 (t, J = 7.2 Hz, 1 H), 3.88−3.70 (m, 2 H), 2.39 (s, 3 H), 1.76−1.65 (m, 1 H), 1.57−1.46 (m, 2 H), 1.44 (s, 9 H), 0.90 (d, J = 6.1 Hz, 3 H), 0.87 (d, J = 6.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 165.6, 142.7, 140.2, 138.1, 135.9, 129.2, 127.6, 125.8, 117.0, 81.1, 55.4, 47.6, 40.7, 27.9, 24.7, 22.6, 22.0, 21.4. Anal. Calcd for $C_{22}H_{33}NO_4S$: C, 64.83; H, 8.16; N, 3.44. Found: C, 64.85; H, 8.22; N, 3.65.

(*S*)-*tert*-Butyl 3-(*N*-allyl-4-methylphenylsulfonamido)-2-methyleneoctanoate (**3e**): colorless oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 12.2 min (major), t_R 21.0 min (minor) [Chiralpak AD (0.46 cm × 25 cm) hexane/*i*-PrOH, 98/2, 1.00 mL/min] as 92% ee; $[\alpha]_D$ −46.6 ($CHCl_3$, *c* 0.99); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, J = 8.1 Hz, 2 H), 7.23 (d, J = 8.0 Hz, 2 H), 6.21 (s, 1 H), 5.86−5.68 (m, J = 6.3, 16.5 Hz, 1 H), 5.61 (s, 1 H), 5.10 (d, J = 17.2 Hz, 1 H), 5.04 (d, J = 10.1 Hz, 1 H), 4.83 (t, J = 7.4 Hz, 1 H), 3.79 (d, J = 6.0 Hz, 2 H), 2.39 (s, 3 H), 1.91−1.60 (m, 2 H), 1.43 (s, 9 H), 1.36−1.15 (m, 6 H), 1.04−0.80 (m, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.0, 142.6, 140.4, 138.5, 135.8, 129.2, 127.6, 126.0, 117.2, 81.1, 57.5, 47.7, 31.8, 31.4, 27.9, 26.2, 22.4, 21.4, 13.9; HRMS (FAB M + 1) m/z 422.2363, calcd for $C_{23}H_{36}NO_4S$ 422.2365.

(*S*)-*tert*-Butyl 2-((*N*-allyl-4-methylphenylsulfonamido)(cyclohexyl)methyl)acrylate (**3f**): white solid; mp 108−109 °C; the enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 8.8 min (minor), t_R 9.4 min (major) [Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 94% ee; $[\alpha]_D$ −34.8 ($CHCl_3$, *c* 1.04); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 2 H), 6.27 (d, J = 0.9 Hz, 1 H), 5.76 (dddd, J = 5.6, 7.3, 10.1, 17.3 Hz, 1 H), 5.70 (s, 1 H), 5.10 (dd, J = 1.4, 17.2 Hz, 1 H), 5.02 (dd, J = 1.3, 10.1 Hz, 1 H), 4.63 (d, J = 11.2 Hz, 1 H), 3.86 (dd, J = 7.3, 16.3 Hz, 1 H), 3.77 (dd, J = 5.6, 16.3 Hz, 1 H), 2.38 (s, 3 H), 2.05−1.48 (m, 7 H), 1.41 (s, 9 H), 1.24−0.79 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 142.6, 139.0, 138.3, 135.8, 129.1, 127.9, 127.6, 117.1, 81.0, 62.4, 47.7, 38.4, 30.8, 30.6, 27.9, 26.3, 26.1, 25.9, 21.4; HRMS (FAB M + 1) m/z 434.2365, calcd for $C_{24}H_{36}NO_4S$ 434.2365.

(*S*)-*tert*-Butyl 2-((*N*-allyl-4-methylphenylsulfonamido)(*p*-tolyl)methyl)acrylate (**3g**): colorless oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 16.7 min (major), t_R 38.1 min (minor) [Chiralpak AD (0.46 cm × 25 cm) hexane/-*i*-PrOH, 98/2, 1.00 mL/min] as 94% ee; $[\alpha]_D$ +141.7 ($CHCl_3$, *c* 1.04); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, J = 8.1 Hz, 2 H), 7.26 (d, J = 8.5 Hz, 2 H), 7.01 (d, J = 7.7 Hz, 2 H), 6.86 (d, J = 7.9 Hz, 2 H), 6.31 (s, 1 H), 6.03 (s, 1H), 5.61 (s, 1 H), 5.41−5.08 (m, 1 H), 4.84 (d, J = 19.0 Hz, 1 H), 4.81 (d, J = 11.2 Hz, 1 H), 3.81 (dd, J = 7.3, 16.0 Hz, 1 H), 3.73 (dd, J = 5.2, 16.0 Hz, 1 H), 2.43 (s, 3 H), 2.29 (s, 3 H), 1.26 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 165.1, 143.1, 140.9, 137.9, 137.6, 134.5, 134.4, 129.3, 129.0, 128.5, 127.5, 126.0, 117.4, 81.2, 61.8, 48.3, 27.7, 21.5, 21.0; HRMS (EI M) m/z 441.1959, calcd for $C_{25}H_{31}NO_4S$ 441.1974.

Preparation of (*S*)-*tert*-Butyl 2-Ethyl-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4a). Grubbs' catalyst (70.6 mg, 0.084 mmol) was added to a solution of **3a** (633.6 mg, 1.67 mmol) in CH_2Cl_2 (167 mL), and the reaction mixture was stirred at refluxing temperature for 1 h. The resulting solution was concentrated in vacuo, and the residue was subjected to flash chromatohgraphy (hexane−EtOAc 10:1) to give **4a** in 97% yield. (566.0 mg): brown oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 27.5 min (major), t_R 32.5 min (minor) [Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 0.70 mL/min] as 90% ee: $[\alpha]_D$ +93.9 ($CHCl_3$, *c* 1.02); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 6.48 (s, 1 H), 4.76 (s, 1 H), 4.20 (s, 2 H), 2.42 (s, 3 H), 2.02 (dqd, J = 4.3, 7.4, 14.7 Hz, 1 H), 1.91 (dqd, J = 3.9, 7.3, 14.5 Hz, 1 H), 1.45 (s, 9 H), 0.83 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.6, 143.5, 135.9, 135.4, 134.8, 129.7, 127.3, 81.5, 66.8, 55.2, 28.0, 26.7, 21.5, 7.6; HRMS (EI M) m/z 351.1503, calcd for $C_{18}H_{25}NO_4S$ 351.1504.

(*S*)-*tert*-Butyl 2-propyl-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**4b**): brown oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 10.0 min (major), t_R 11.7 min (minor) [Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 92% ee: $[\alpha]_D$ +104.1 ($CHCl_3$, *c* 1.02); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 6.8 Hz, 2 H), 6.44 (s, 1 H), 4.75 (s, 1 H), 4.20 (s, 2 H), 2.41 (s, 3 H), 2.08−1.63 (m, 2 H), 1.44 (s, 9 H), 1.43−1.14 (m, 2 H), 0.90 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.5, 143.5, 136.5, 135.0, 134.6, 129.7, 127.2, 81.4, 66.0, 54.9, 36.0, 27.9, 21.4, 16.9, 14.0; HRMS (EI M) m/z 365.1661, calcd for $C_{19}H_{27}NO_4S$ 365.1661.

(*S*)-*tert*-Butyl 2-isopropyl-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**4c**): brown oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 9.9 min (major), t_R 11.0 min (minor) [Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 98% ee: $[\alpha]_D$ +105.6 ($CHCl_3$, *c* 0.63); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 8.1 Hz, 2 H), 7.27 (d, J = 8.1 Hz, 2 H), 6.39 (s, 1 H), 4.69 (s, 1 H), 4.20 (dd, J = 2.7, 18.2 Hz, 1 H), 4.07 (dd, J = 4.1, 18.2 Hz, 1 H), 2.40 (s, 3 H), 2.14 (dtd, J = 3.2, 6.9, 13.8 Hz, 1 H), 1.43 (s, 9 H), 1.07 (d, J = 6.9 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 161.8, 143.5, 136.9, 135.6, 134.4, 129.5, 127.4, 81.3, 71.3, 55.7, 33.0, 27.8, 21.4, 19.3, 17.0; HRMS (EI M) m/z 365.1662, calcd for $C_{19}H_{27}NO_4S$ 365.1661.

(*S*)-*tert*-Butyl 2-isobutyl-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**4d**): brown oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 8.9 min (major), t_R 11.3 min (minor) [Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 92% ee: $[\alpha]_D$ +128.4 ($CHCl_3$, *c* 0.99); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 8.3 Hz, 2 H), 7.28 (d, J = 8.5 Hz, 2 H), 6.37 (s, 1 H), 4.78−4.69 (m, 1 H), 4.21 (s, 2 H), 2.41 (s, 3 H), 1.90 (tq, J = 6.4, 12.8 Hz, 1 H), 1.74−1.54 (m, 2 H), 1.44 (s, 9 H), 1.01 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 161.6, 143.6, 138.0, 134.9, 134.5, 129.7, 127.4, 81.4, 68, 65.1, 54.6, 43.1, 28.0, 24.2, 23.9, 22.5, 21.5. Anal. Calcd. for $C_{20}H_{29}NO_4S$: C, 63.30; H, 7.70; N, 3.69. Found: C, 63.47; H, 7.58; N, 3.77.

(*S*)-*tert*-Butyl 2-pentyl-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**4e**): brown oil; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 8.7 min (major), t_R 10.4 min (minor) [CHIRALPAK IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 92% ee: $[\alpha]_D$ +118.4 ($CHCl_3$, *c* 1.01); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, J = 8.1 Hz, 2 H), 7.30 (d, J = 8.5 Hz, 2 H), 6.46 (s, 1 H), 4.80−4.57 (br, 1 H), 4.20 (s, 1 H), 2.41 (s, 3 H), 2.08−1.75 (m, 2 H), 1.45 (s, 9 H), 1.40−1.03 (m, 6 H), 0.86 (t, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 161.5, 143.5, 136.4, 135.1, 134.7, 129.7, 127.3, 81.4, 66.1, 55.0, 33.6, 31.6, 27.9, 23.0, 22.4, 21.4, 13.9; HRMS (EI M) m/z 393.1969, calcd for $C_{21}H_{31}NO_4S$ 393.1974.

(*S*)-*tert*-Butyl 2-cyclohexyl-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**4f**): brown solid; mp 88−89 °C; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 9.9 min (major), t_R 10.6 min (minor) [Chiralpak IC (0.46 cm ×25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 96%ee. $[\alpha]_D$ +119.4 ($CHCl_3$, c 0.68); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.67 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 7.9 Hz, 2 H), 6.36−6.33 (m, 1H), 4.65 (t, J = 2.8 Hz, 1 H), 4.18 (ddd, J = 0.8, 2.7, 18.2 Hz, 1H), 4.04 (ddd, J = 1.8, 4.1, 18.3 Hz, 1 H), 2.39 (s, 3 H), 1.57−1.85 (m, 6 H), 1.42 (s, 9 H), 1.57−0.99 (m, 5 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 161.9, 143.5, 136.9, 135.4, 129.9, 129.5, 127.1, 81.3, 71.0, 55.7,

43.1, 29.9, 27.9, 27.8, 27.6, 26.4, 26.2, 21.4; HRMS (EI M) m/z 405.1972. Calcd for $C_{22}H_{31}NO_4S$ 405.1974.

(S)-*tert*-Butyl 2-*p*-tolyl-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (4g): brown solid; mp 121−122 °C; enantiomeric purity was determined by HPLC analysis (230 nm, 40 °C) t_R 19.4 min (major), t_R 32.9 min (minor) [Chiralpak IC (0.46 cm × 25 cm) hexane/*i*-PrOH, 80/20, 1.00 mL/min] as 98% ee: $[\alpha]_D$ −46.6 ($CHCl_3$, c 0.99); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (d, J = 7.9 Hz, 2 H), 7.11 (d, J = 7.9 Hz, 2 H), 7.07 (d, J = 7.7 Hz, 2 H), 7.01 (d, J = 7.7 Hz, 2 H), 6.69 (s, 1 H), 5.62 (s, 1 H), 4.45 (d, J = 16.8 Hz, 1 H), 4.31 (dd, J = 5.6, 16.7 Hz, 1 H),2.35 (s, 2 H), 2.30 (s, 3 H), 1.25 (s, 9 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.0, 142.9, 137.4, 137.3, 136.5, 135.7, 134.4, 129.2, 128.6, 127.6, 127.0, 81.4, 68.7, 54.6, 27.7, 21.3, 21.0; HRMS (EI M) m/z 413.1642, calcd for $C_{23}H_{27}NO_4S$ 413.1661.

Preparation of (*S*)-*N*-(4-(*tert*-Butyldimethylsilyloxy)butylidene)-4-methylbenzenesulfinamide (6). Under nitrogen atmosphere, a solution of 1,4-butanediol **5** (9.013 g, 100.0 mmol) in cyclopentyl methyl ether (CPME, 25 mL) was added to a solution of *t*-BuOK (11.225 g, 100.0 mmol) in CPME (150 mL) at 0 °C. After being stirred for 30 min, a solution of TBSCl (15.088 g, 100.0 mmol) in CPME (25 mL) was added. The reaction mixture was stirred for 6 h at room temperature. Water (50 mL) was added to the solution, and the organic phase was separated. The water phase was extracted with CPME (50 mL × 3). The organic phase was combined and dried over Na_2SO_4. After filtration and concentration in vacuo, the residue was subjected to flash chromatography (hexane−EtOAc 20:1 then 5:1) to give 4-(*tert*-butyldimethylsilyl)oxy-1-butanol in 83% yield (16.885 g): colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.57−3.69 (m, 4 H), 2.78−2.82 (br, 1 H, J = 6.8 Hz), 1.57−1.66 (m, 4 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 63.4, 62.7, 30.2, 29.9, 25.9, 25.7, 18.3, −5.4.

Under nitrogen atmosphere, DMSO (4.58 mL, 64.48 mmol) was added slowly over 10 min to a solution of oxalyl chloride (3.32 mL, 38.69 mmol) in CH_2Cl_2 (119 mL) at −50 °C. 4-(*tert*-Butyldimethylsilyl)oxy-1-butanol (6.5886 g, 32.24 mmol) in CH_2Cl_2 (10 mL) was added to the solution, and the resulting solution was stirred at −50 °C for 10 min. Et_3N (9.82 mL, 70.93 mmol) was added to the solution, and the reaction mixture was stirred at −50 °C for 10 min and gradually warmed to room temperature over 1.5 h. Water (60 mL) was added to the reaction mixture, and the organic phase was separated. The water phase was extracted with CH_2Cl_2 (60 mL × 2). The organic phase was combined, washed with brine (30 mL), and dried over Na_2SO_4. After filtration, concentration of the filtrate in vacuo gave crude 4-(*tert*-butyldimethylsilyl)oxybutraldehyde, which was used for the next stage without further purification: 96% yield (6.236 g); pale yellow oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.72 (t, 1 H, J = 1.7 Hz), 3.65 (t, 2 H, J = 6.0 Hz), 2.50 (dt, 2 H, J = 1.7, 7.0 Hz), 1.80−1.91 (m, 2 H), 0.88 (s, 9 H), 0.04 (s, 6 H).

A mixture of the aldehyde (6.236 g, 30.81 mmol), $Ti(OEt)_4$ (28.96 mL), and (*S*)-(+)-*p*-toluenesulfinamide (4.777 g, 30.81 mmol) in CH_2Cl_2 (350 mL) was heated at refluxing temperature overnight. The mixture was cooled and water (90 mL) was added. The resulting precipitate was filtered over a glass filter and washed with CH_2Cl_2 (100 mL × 2). The organic phase of the filtrate was separated, washed with water (60 mL × 2) and brine (60 mL), and dried over Na_2SO_4. After filtration, concentration of the filtrate gave crude product which was purified by flash chromatography (hexane−EtOAc 20:1, 15:1, 10:1 then 5:1) to give **6** in 64% yield for two steps (6.6874 g): yellow oil; $[\alpha]_D$ +174.5 ($CHCl_3$, c 1.08); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.25 (t, J = 4.6 Hz, 1 H), 7.55 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 7.9 Hz, 2 H), 3.62 (t, J = 6.1 Hz, 2 H), 2.55 (td, J = 4.6, 7.4 Hz, 2 H), 2.39 (s, 3 H), 1.89−1.74 (m, 2 H), 0.86 (s, 9 H), 0.00 (s, 3 H), −0.01 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 167.6, 142.0, 141.5, 129.6, 124.4, 61.7, 32.1, 28.0, 25.6, 21.0, 18.0; HRMS (FAB M + 1) m/z 340.1776, calcd for $C_{17}H_{30}NO_2SSi$ 340.1767.

Preparation of (2*R*,3*S*)-*tert*-Butyl 6-(*tert*-Butyldimethylsilyloxy)-3-((*S*)-4-methylphenylsulfinamido)-2-(phenylthiomethyl)hexanoate (7). Under nitrogen atmosphere, methylmagnesium bromide (13.59 mL, 19.02 mmol, 1.4 M in toluene/tetrahydrofuran (75:25)) was added to a solution of thiophenol (1.62 mL, 15.85 mmol) in CH_2Cl_2 (40 mL) at −50 °C, and the mixture was stirred for 10 min. *tert*-Butyl acrylate (2.32 mL, 15.85 mmol) and a solution of sulfinimine (5.3831 g, 15.85 mmol) in CH_2Cl_2 (13 mL) were added to the mixture at −50 °C, and the mixture was stirred at −50 °C for 37 h. Saturated NH_4Cl(aq) (50 mL) was added to the mixture and the mixture allowed to warm to 0 °C for 10 min. The organic phase was separated, and the water phase was extracted with EtOAc (100 mL × 3). The organic phase was combined, washed with brine (50 mL), and dried over anhydrous Na_2SO_4. After filtration, the resulting solution was concentrated under reduced pressure, and crude residue was purified by flash chromatography (hexane−EtOAc 50:1, 20:1, 10:1, then 5:1) to give **7** in 85% yield as a mixture of the two diastereoisomers (7.7611 g): pale yellow oil; HPLC analysis revealed the *syn*/*anti* ratio was 85:15. *syn*-**7**, major isomer, was separated by further careful chromatography: $[\alpha]_D$ +42.8 ($CHCl_3$, c 1.02); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.2 Hz, 2 H), 7.37−7.17 (m, 7 H), 4.73 (d, J = 8.8 Hz, 1 H), 3.67−3.58 (m, 3 H), 3.05 (d, J = 5.3 Hz, 1 H), 3.02 (d, J = 5.3 Hz, 1 H), 2.77 (td, J = 6.0, 7.4 Hz, 1 H), 2.40 (s, 3 H), 1.80−1.48 (m, 4 H), 1.42 (s, 9 H), 0.88 (s, 9 H), 0.04 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 142.5, 141.4, 135.8, 129.6, 129.0, 126.6, 125.7, 125.4, 81.9, 62.7, 55.8, 51.2, 33.6, 29.4, 25.8, 25.7, 21.3, 21.2, 18.2, −5.2. Anal. Calcd. for $C_{30}H_{47}NO_4S_2Si$: C, 62.35; H, 8.20; N, 2.42. Found: C, 62.47; H, 8.26; N, 2.46.

Preparation of (3*S*)-*tert*-Butyl 6-(*tert*-butyldimethylsilyloxy)-2-methylene-3-(4-methylphenylsulfinamido)hexanoate (8). *m*-CPBA (75 wt %, 1.1568 g, 5.03 mmol) was added to a solution of **7** (2.6325 g, 4.56 mmol) in CH_2Cl_2 (45 mL) at 0 °C, and the resulting mixture was stirred at the same temperature for 1 h. The reaction mixture was washed with $NaHCO_3$(aq) (10 mL × 2) and brine (10 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in toluene (40 mL) and heated at 110 °C for 1 h. The reaction mixture was subjected to flash chromatography (hexane−EtOAc 10:1 then 5:1) to give **8** in 76% yield (1.6246 g). HPLC analysis revealed 94% de: white solid; mp 92−93 °C; $[\alpha]_D$ +74.7 ($CHCl_3$, c 1.06); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 2 H), 7.25 (d, J = 7.9 Hz, 2 H), 5.98 (s, 1 H), 5.40 (s, 1 H), 4.92 (d, J = 8.8 Hz, 1 H), 4.05 (q, J = 7.4 Hz, 1 H), 3.61 (t, J = 6.1 Hz, 2 H), 2.39 (s, 3 H), 1.89−1.71 (m, 2 H), 1.63−1.49 (m, 2 H), 1.47 (s, 9 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 142.5, 142.0, 141.0, 129.3, 125.8, 125.2, 81.2, 62.7, 56.3, 32.76, 29.5, 28.0, 26.0, 21.3, 18.3, −5.1, −5.3. Anal. Calcd for $C_{24}H_{41}NO_4SSi$: C, 61.63; H, 8.84; N, 2.99. Found: C, 61.55; H, 8.65; N, 2.90.

Preparation of (*S*)-*tert*-Butyl 3-(*N*-allyl-4-Methylphenylsulfonamido)-6-(*tert*-butyldimethylsilyloxy)-2-methylenehexanoate (9). *m*-CPBA (77 wt %, 1.4292 g, 6.38 mmol) was added to a solution of **9** (2.9745 g, 6.37 mmol) in CH_2Cl_2 (64 mL) at room temperature, and the resulting solution was stirred for 2 h. An additional portion of *m*-CPBA (0.1420 g, 0.63 mmol) was added to the mixture, and the mixture was stirred for 30 min at room temperature. The reaction mixture was washed with $NaHCO_3$-(aq) (20 mL × 2) and brine (20 mL) successively and dried over Na_2SO_4. After filtration, concentration of the filtrate in vacuo gave crude sulfonamide which was used for the next step without further purification.

The crude sulfonamide was dissolved in DMF (10 mL), and K_2CO_3 (2.6777 g, 19.37 mmol) and allyl bromide (0.60 mL, 7.10 mmol) were added at room temperature. The resulting mixture was stirred at room temperature for 21 h. The reaction mixture was poured into water (50 mL), and the resulting mixture was extracted Et_2O (50 mL × 3). The organic phase was combined,

washed with brine (20 mL), and dried over Na_2SO_4. After filtration, concentration of the filtrate under reduced pressure gave crude **9** which was purified by flash chromatography (hexane−EtOAc 20:1) to give **9** in 78% yield as colorless oil: 96% ee; $[\alpha]_D$ −23.2 ($CHCl_3$, *c* 1.04); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1 Hz, 2 H), 7.22 (d, J = 8.0 Hz, 2 H), 6.22 (s, 1 H), 5.76 (td, J = 6.3, 16.6 Hz, 1 H), 5.65 (s, 1 H), 5.10 (d, J = 17.2 Hz, 1 H), 5.03 (d, J = 10.1 Hz, 1 H), 4.87 (t, J = 7.5 Hz, 1 H), 3.78 (d, J = 6.1 Hz, 2H), 3.64−3.50 (m, 2 H), 2.39 (s, 3 H), 1.97−1.67 (m, 2 H), 1.45−155 (m, 2 H), 1.42 (s, 9 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 142.7, 140.0, 138.3, 135.8, 129.2, 127.7, 126.3, 117.3, 81.2, 62.6, 57.2, 47.7, 30.0, 28.5, 27.9, 25.9, 21.4, 18.3, −5.4. Anal. Calcd for $C_{27}H_{45}NO_5SSi$: C, 61.91; H, 8.66; N, 2.67. Found: C, 61.76; H, 8.53; N, 2.71.

Preparation of (*S*)-*tert*-Butyl 2-(3-(*tert*-Butyldimethylsilyloxy)-propyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (10). Under nitrogen atmosphere, Grubbs' second-generation catalyst (0.3658 g, 0.43 mmol) was added to a solution of **9** (4.6330 g, 8.69 mmol) in CH_2Cl_2 (869 mL) at room temperature, and the reaction mixture was heated at refluxing temperature for 3 h. After the mixture was heated to room temperature, DMSO (0.30 mL) was added, and the mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (hexane−EtOAc 20:1 then 5:1) to give **10** in 90% yield as a white solid (3.8589 g). The enantiomeric excess of the product was enhanced to >99% ee by recrystallization from MeOH: mp 101−102 °C; $[\alpha]_D$ +99.7 ($CHCl_3$, *c* 1.01); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 6.46 (s, 1 H), 4.79 (s, 1 H), 4.19 (s, 1 H), 3.62 (dd, J = 8.1, 14.5 Hz, 1 H), 3.55 (dd, J = 6.8, 16.0 Hz, 1 H), 2.42 (s, 1 H), 1.99−1.90 (m, 1 H), 1.64−1.69 (m, 1 H), 1.51−1.63 (m, 2 H), 1.44 (s, 9 H), 0.89 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5, 143.6, 136.3, 135.3, 134.3, 129.7, 127.4, 81.5, 65.9, 63.2, 55.0, 30.3, 28.0, 27.0, 26.0, 21.5, 18.3, −5.3, −5.4. Anal. Calcd for $C_{25}H_{41}NO_5SSi$: C, 60.57; H, 8.34; N, 2.83. Found: C, 60.42; H, 8.13; N, 2.83.

Preparation of (2*S*,3S)- and (2*S*,3*R*)-*tert*-Butyl 2-(3-Hydroxy-propyl)-1-tosylpyrrolidine-3-carboxylate (13). 10% Pd−C (145 mg) was added to a solution of **10** (1.4485 g, 2.92 mmol) in MeOH (30 mL), and the resulting suspension was stirred vigorously under hydrogen atmosphere at room temperature for 24 h. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane−EtOAc 3:1 then EtOAc) to give a 1:1 diastereomeric mixture of **11** in 88% yield (1.3600 g), which was used for the next step without further purification.

A THF solution of TBAF (1.0 M, 1.85 mL) was added to a solution of 1:1 mixture of **11** (833 mg, 1.68 mmol) in THF (10 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. NH_4Cl(aq) (10 mL) was added, and organic solvent was removed by rotary evaporator. The aqueous residue was extracted with EtOAc (30 mL × 3), and the organic phase was washed with brine (10 mL). After being dried over Na_2SO_4, the organic solution was concentrated and the residue was subjected to flash chromatography (hexane−EtOAc 5:1. 3:1, then 1:1) to give a diastereomeric mixture of **13** in 96% yield (617.8 mg). This mixture was separated by careful chromatography. *cis*-**13**: colorless oil; $[\alpha]_D$ +65.9 ($CHCl_3$, *c* 0.99); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 7.7 Hz, 2 H), 7.33 (d, J = 7.8 Hz, 2 H), 4.10 (dd, J = 6.6, 12.9 Hz, 1 H), 3.77−3.63 (m, 2 H), 3.49 (t, J = 9.6 Hz, 1 H), 3.21 (dd, J = 8.7, 19.2 Hz, 1 H), 2.44 (s, 3 H), 2.41−2.35 (m, 1 H), 2.21−2.10 (m, 1 H), 1.86−1.73 (m, 3 H), 1.58 (m, 1 H), 1.52−1.45 (m, 1 H), 1.43 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 143.8, 134.9, 129.9, 127.6, 81.6, 62.9, 61.1, 48.2, 46.7, 29.0, 28.1, 28.0, 26.0, 21.6; HRMS (FAB M + 1) m/z 384.1853, calcd for $C_{19}H_{30}NO_5S$ 384.1845. *trans*-**13**: colorless oil; $[\alpha]_D$ +63.3 ($CHCl_3$, *c* 0.99); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 7.9 Hz, 2 H), 3.89−3.82 (m, 1 H), 3.75−3.67 (m, 2 H), 3.42 (dd, J = 6.5, 16.7 Hz, 1 H), 3.30 (dd, J = 7.1, 17.0 Hz, 1 H), 2.64 (dd, J = 5.9, 10.8 Hz, 1 H), 2.41 (s, 3 H), 2.03−1.87 (m, 2 H), 1.60−1.79 (d, 4 H), 1.27 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 143.6, 134.4, 129.7, 127.8, 81.2, 62.7, 62.6, 50.0, 48.6, 33.2, 28.7, 27.8, 27.6, 21.6; HRMS (FAB M + 1) m/z 384.1833, calcd for $C_{19}H_{30}NO_5S$ 384.1845.

Preparation of *cis*-(2*S*,3*S*)-*tert*-Butyl 2-(3-*tert*-Butyldimethyl-silyloxypropyl)-1-tosylpyrrolidine-3-carboxylate (*cis*-11) by TBS Protection of *cis*-13. A solution of TBSCl (55.1 mg, 0.35 mmol), imidazole (66.1 mg, 0.96 mmol), and *cis*-**13** (124.1 mg, 0.32 mmol) in DMF (2 mL) was stirred at room temperature for 24 h. TBSCl (55.1 mg) was added, and the reaction mixture was stirred for an additional 24 h. Water (10 mL) was added, and the resulting mixture was extracted with ether (10 mL × 4). The combined organic phase was washed with brine (10 mL) and dried over Na_2SO_4. After filtration, the filtrate was concentrated, and the residue was purified by flash chromatography (hexane−EtOAc 10:1) to give *cis*-**11** in 93% yield (145.7 mg): white solid; mp 67−68 °C; $[\alpha]_D$ +53.7 ($CHCl_3$, *c* 1.03); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 2 H), 7.31 (d, J = 7.9 Hz, 2 H), 4.04 (ddd, J = 4.3, 7.7, 8.9 Hz, 1 H), 3.71−3.53 (m, 2 H), 3.50−3.39 (m, 1 H), 3.22 (dt, J = 8.3, 11.0 Hz, 1 H), 2.42 (s, 3 H), 2.30−2.41 (m, 1 H), 2.22−2.04 (m, 1 H), 1.85−1.44 (m, 5 H), 1.40 (s, 9 H), 0.87 (s, 9 H), 0.02 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.1, 143.7, 135.1, 130.0, 127.6, 81.4, 62.9, 61.4, 48.0, 46.5, 29.2, 28.0, 27.7, 25.9, 25.8, 21.5, 18.3, −5.4, −5.4; Anal. Calcd for $C_{25}H_{43}NO_5SSi$: C, 60.32; H, 8.71; N, 2.81. Found: C, 60.21; H, 8.50; N, 2.82.

Preparation of (2*S*,3*R*)-*tert*-Butyl 2-(3-Hydroxypropyl)-1-to-sylpyrrolidine-3-carboxylate (*trans*-13) by Hydrogenation Reaction of Free Alcohol 12. CSA (0.3206 g, 1.28 mmol) was added to a solution of **10** (3.1719 g, 6.40 mmol) in MeOH/CH_2Cl_2 (1:1) (64 mL) at room temperature, and the mixture was stirred for 1 h. The reaction mixture was poured into $NaHCO_3$(aq) (20 mL) and extracted with CH_2Cl_2 (30 mL × 4). The organic phase was washed with brine (20 mL) and dried over Na_2SO_4. After filtration, concentration of the solution in vacuo to give crude **12** which was used for the next step without further purification: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.70 (d, J = 8.3 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 6.46 (d, J = 1.7 Hz, 1 H), 4.77 (t, J = 4.8 Hz, 1 H), 4.24−4.17 (m, 2 H), 3.65 (t, J = 7.2 Hz, 2 H), 2.42 (s, 3 H), 2.10−1.85 (m, 2 H), 1.57 (s, 3 H), 1.44 (s, 9H).

Crude **12** was dissolved in MeOH (60 mL), and 10% Pd−C was added to the solution. The reaction mixture was stirred vigorously under hydrogen atmosphere for 48 h. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane−EtOAc 3:1, then EtOAc) to give a diastereomeric mixture of **13** in 98% yield (2.3995 g). The diastereomeric ratio was determined by HPLC analysis, which revealed the ratio was *cis*/*trans* = 14/86. Anal. Calcd for $C_{19}H_{29}NO_5S$: C, 59.51; H, 7.62; N, 3.65. Found: C, 59.26; H, 7.31; N, 3.90.

Preparation of (2*S*,3*R*)-Methyl 2-(3-Methoxy-3-oxopropyl)-1-tosylpyrrolidine-3-carboxylate (14). PDC (1.8333 g, 4.88 mmol) was added to a solution of *trans*-**13** (0.4690 g, 1.22 mmol) in DMF (3.77 mL) at room temperature, and the mixture was stirred for overnight. The reaction mixture was poured into water (20 mL) and extracted with ether (20 mL × 4). The organic phase was dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give crude carboxylic acid which was used for the next step without further purification. The carboxylic acid was dissolved in MeOH (20 mL), and $SOCl_2$ (0.39 mL, 3.28 mmol) was added to the solution at 0 °C under nitrogen atmosphere. The reaction mixture was

heated at refluxing temperature for 12 h. After cooling, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane−EtOAc 3:1) to give **14** in 75% yield as a yellow oil (0.3375 g): $[\alpha]_D$ +68.9 ($CHCl_3$, c 0.35); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 2 H), 7.32 (d, J = 7.9 Hz, 2 H), 4.01 (td, J = 3.9, 6.5 Hz, 1 H), 3.71 (s, 3 H), 3.42 (s, 3 H), 3.47−3.32 (m, 2 H), 2.73−2.66 (m, 1 H), 2.54 (dd, J = 1.5, 7.9 Hz, 1 H), 2.52 (d, J = 8.2 Hz, 1 H), 2.43 (s, 3 H), 2.14−1.90 (m, 3 H), 1.79 (td, J = 5.7, 12.8 Hz, 1 H); ^{13}C NMR (101 MHz, CDCl3) δ 173.5, 172.5, 143.5, 134.2, 129.5, 127.8, 62.2, 52.0, 51.7, 48.7, 48.3, 31.7, 30.4, 27.3, 21.5. Anal. Calcd for $C_{17}H_{23}NO_6S$: C, 55.27; H, 6.28; N, 3.79. Found: C, 55.18; H, 6.09; N, 3.92.

Preparation of (1*R*,7a*S*)-Methyl 5-Oxohexahydro-1*H*-pyrrolizine-1-carboxylate (15). To a solution of **14** (0.4048 g, 1.10 mmol) in MeOH (20 mL) was added Mg (0.5364 g, 22.06 mmol), and the mixture was stirred for 2 h. The reaction mixture was then heated at refluxing temperature for 4 h. After the mixture was cooled to room temperature, dilute HCl was added to the mixture until all precipitates dissolved. The reaction mixture was extracted with EtOAc (50 mL × 4). The organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane−EtOAc 1:3, then EtOAc) to give **15** in 76% yield as a yellow oil (0.1528 g): $[\alpha]_D$ −59.7 ($CHCl_3$, *c* 1.06) [lit.[14] $[\alpha]_D$ −58.3 ($CHCl_3$, *c* 0.65)]; ^1H NMR (400 MHz, $CDCl_3$) δ 4.10 (td, J = 7.2, 16.2 Hz, 1 H), 3.74 (s, 3 H), 3.65 (td, J = 8.3, 11.7 Hz, 1 H), 3.22 (ddd, J = 3.9, 8.0, 11.7 Hz, 1 H), 2.76 (td, J = 9.6, 16.9 Hz, 1 H), 2.62−2.47 (m, 2 H), 2.47−2.28 (m, 3 H), 1.89 (dtd, J = 7.3, 10.1, 13.0 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 172.4, 64.4, 52.2, 49.3, 40.7, 34.4, 30.7, 25.9; HRMS (EI M) m/z 183.0892, calcd for $C_9H_{13}NO_3$ 183.0895.

Supporting Information Available: Spectroscopic charts for compounds **2**−**4**, **6**−**10**, *cis*-**11**, *cis*-**13**, *trans*-**13**, **14**, and **15**, chiral HPLC charts for **2**−**4**, preparation and spectral data for **1f**,**g**, and X-ray crystallographic data for *cis*-**11**. This material is available free of charge via the Internet at http://pubs.acs.org.