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Asymmetric Synthesis of Cyclic *cis*-β-Amino Acid Derivatives Using Sulfinimines and Prochiral Weinreb Amide Enolates

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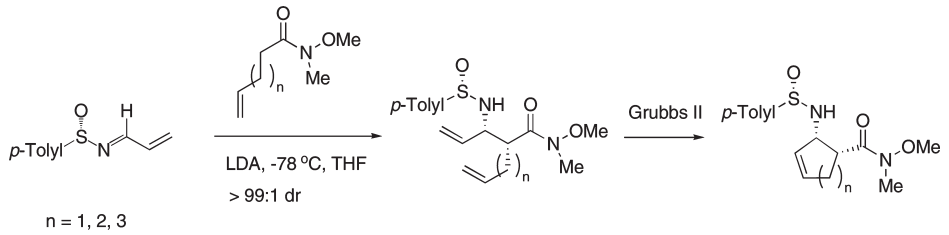

Cyclic *cis*-β-amino Weinreb amides, valuable building blocks for the asymmetric synthesis of cyclic β-amino acids derivatives, are readily prepared via ring-closing metathesis of sulfinimine-derived *N*-sulfinyl β-amino diene Weinreb amides. These unsaturated cyclic *cis*-β-amino Weinreb amides are valuable building blocks for the asymmetric synthesis of cyclic β-amino acid derivatives.

Introduction

The importance of Weinreb amides,[1] *N*-methoxy-*N*-methylamides, as acylating agents in organometallic reactions is well established.[2] For example, Weinreb amides react with organolithium and organomagesium reagents to give ketones, with reducing agents $LiAlH_4$ and DiBAL to give aldehydes, with enolates to give β-ketoesters, and with phosphonates anions to give β-ketophosphonates.[2] Most often Weinreb amides are prepared from an acid or acid derivative using *N*,*O*-dimethylhydroxlamine, which is commercially available.[2]

Enantiopure β-amino carbonyl moieties are found as structural units of natural products[3] and are important chiral building blocks for the synthesis of nitrogen-containing bioactive molecules. They have been employed in the synthesis of β-amino acids[4] and in the synthesis of 1,3-amino alcohols,[5−7] and they undergo Wittig-type condensations to give homoallylic amines.[4,5,8,9] The intramolecular Mannich cyclization of β-amino ketones with aldehydes is a particularly useful method for the asymmetric synthesis of stereodefined piperidones,[10] indolizidines,[11] tropinones,[12] homotropinones,[13] and other alklaloids.[14] Until recently there were few methods available for the synthesis of enantiopure β-amino ketones and aldehydes, and most of these were of limited scope.[15]

In 2005 we introduced *N*-sulfinyl β-amino Weinreb amides, which provided a general solution to the problem of enantiopure β-amino ketone and aldehyde synthesis (Figure 1).[16] Despite the fact that these Weinreb amides have an acidic NH proton, they react with lithium and Grignard

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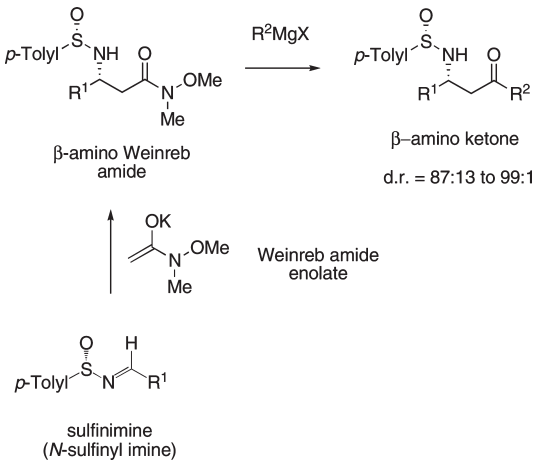

FIGURE 1. Synthesis of *N*-sulfinyl *β*-amino Weinreb amides and ketones.

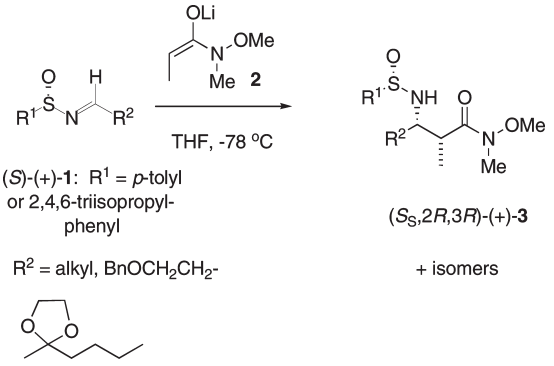

FIGURE 2. Synthesis of α-substituted *β*-amino Weinreb amides from Weinreb amide enolates.

reagents to give good yields of ketones and, on reduction with DIBAL, aldehydes. The addition of Weinreb amide enolates to sulfinimines (*N*-sulfinyl imines)[17,18] was used for the first time to prepare *N*-sulfinyl *β*-amino Weinreb amides.[19] The yields and diastereoselectivity were good to excellent and dependent on the substrate (R^1) and enolate counterion. Potassium enolates and alkyl aldehyde derived sulfinimines afforded the best selectivities (Figure 1).[7,12,16]

The current challenge is to prepare α-branched *β*-amino Weinreb amides for applications in the synthesis of bioactive nitrogen-containing compounds. For this reason we have been exploring the addition of prochiral Weinreb amide enolates to sulfinimines.[7b,11,13,20,21] We found, for example, that lithium Weinreb amide enolate **2**, derived from *N*-methoxy-*N*-methylpropylamide, adds to sulfinimine (*S*)-(+)-**1** to afford a mixture of diastereoisomers with the *syn*-α-methyl *β*-amino Weinreb amide **3** predominating (Figure 2).[12,15] For R^2 = alkyl, $BnO(CH_2)_2$, however, separable diastereoisomers were observed only for the *N*-2,4,6-triisopropylphenyl *N*-sulfinyl auxiliary (TIPP).[11c,15] The best selectivity for the addition of the lithium enolate of **2** to masked oxo sulfinimines was observed for the *p*-tolyl *N*-sulfinyl auxiliary (R^1 = *p*-tolyl).[13] In each case the *E*-geometry for the enolate and a chairlike transition state were evoked to explain the preference for the *syn*-product.[15,22] We describe here very high diastereoselectivities for the addition of unsaturated prochiral Weinreb amide enolates to an acrolein-derived sulfinimine. The resulting amino dienes were employed in the asymmetric synthesis of five-, six-, and seven-membered cyclic *cis*-*β*-amino acid derivatives.

SCHEME 1

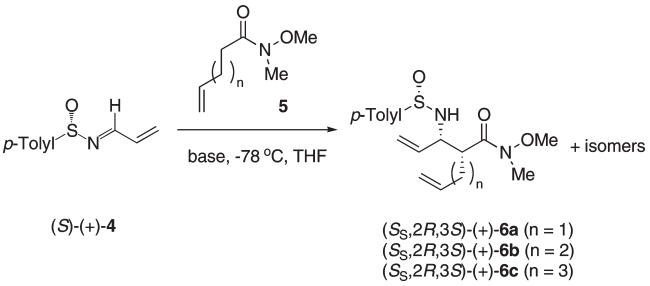

TABLE 1. Synthesis of α-Substituted Weinreb Amides at −78 °C in THF

entry	**5** (*n*)	base	**6**: yield (%)[a] (dr, *syn*:*anti*)[b]
1	**5a** (1)	KHMDS	**6a**: 92 (39:34:18:9)
2		NaHMDS	**6a**: 90 (68:10:10:6)
3		LiHMDS	**6a**: 90 (77:15:8:0)
4		LDA	**6a**: 89 (>99:1)
5	**5b** (2)	LDA	**6b**: 90 (>99:1)
6	**5c** (3)	LDA	**6c**: 90 (>99:1)

[a]Combined yields of inseparable isomers. [b]Determined by ^{1}H NMR on the crude reaction mixture.

Results and Discussion

The prochiral Weinreb amide enolate of *N*-methoxy-*N*-methyl-4-pentenamide (**5a**, n = 1) was generated at −78 °C by addition of 1.1 equiv of the appropriate base at −78 °C (Scheme 1). After 2 h, 0.5 equiv of (*S*)-(+)-*N*-(propylidene)-*p*-toluenesulfinamide (**4**)[23] was added to the preformed enolate, and TLC was used to monitor the reaction progress for completion (typically l h) (Scheme 1). Products were isolated by chromatography and are recorded in Table 1. Poor selectivities were found for the enolate of **5a** prepared using the bases KHMDS, NaHMDS, and LiHMDS (Table 1, entries 1−4). Significantly, only *syn*-α-(2-propenyl) *β*-amino Weinreb amide (**6**) was obtained, in excellent yield, when LDA was used to prepare the enolate (Table 1, entry 4). Similar single diastereoisomer formation was observed with this base and the Weinreb amide enolates prepared from *N*-methoxy-*N*-methyl-5-hexenamide (**5b**) and *N*-methoxy-*N*-methyl-6-heptenamide (**5c**) (Table 1, entries 5 and 6).

Cyclic *β*-Amino Acid Derivatives. Cyclic *β*-amino acids are important building blocks for the synthesis of natural products

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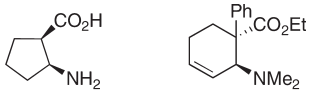
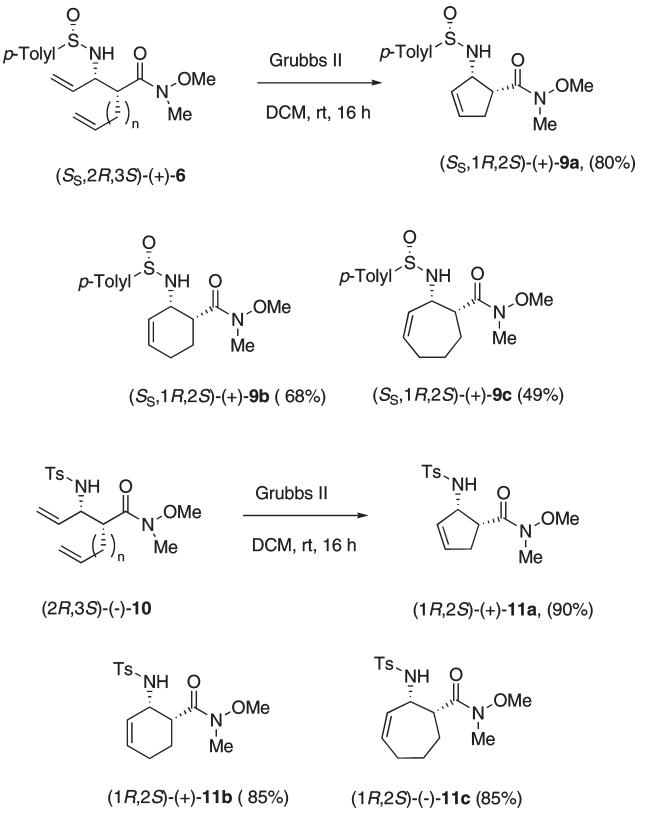


cispentacin **7** Tilidine **8**

FIGURE 3. Important cyclic β-amino acid derivatives.

and β-peptides.[23] Peptides prepared with cyclic β-amino acids often exhibit enhanced biostability and activity.[24] Cispentacin (**7**) is a naturally occurring, powerful antifungal antibiotic[25] and is a constituent of amipurimycin, which is active against *Pyricularia oryzane*, the organism responsible for rice blast disease (Figure 3).[26] The pharmaceutical Tilidine (**8**) is an important opioid analgesic.[27] Hydroxy-functionalized cyclic β-amino esters have been explored as building blocks for the synthesis of natural products and drug candidates.[23,28,29] While a number of resolution and kinetic resolution procedures have been devised for the synthesis of cyclic optically active β-amino acids,[23,30,31] there are surprisingly few methods for their asymmetric synthesis, and most of these lack generality.[23b] Enantioselective routes to five- and six-membered cyclic *trans*-β-amino acids include intramolecular self-condensation routes,[32] the addition of chiral nucleophiles to unsaturated cyclic carboxylic acids,[33] ring-closing metathesis,[34] and cross-metathesis leading to both *cis*- and *trans*-fluorinated cyclic β-amino acids.[35] Enantioselective hydrogenation of cyclic β-(acylamino)acrylates affords five-, six-, and seven-membered cyclic *cis*-β-amino acids that can be isomerized to the trans isomers.[36]

SCHEME 2



It is well-known that ring-closing metathesis (RCM) is sensitive to both the electronic and steric properties of the alkene,[37−39] as well as the substituents on nitrogen.[34,37,40] However, our earlier studies on the synthesis of (+)-4-amino-cyclopentenone[41] and (−)-agelastatin A[42] demonstrated that the *N*-sulfinyl group is compatible with RCM. Reaction of *N*-sulfinyl β-amino diene Weinreb amides **6** with 2 mol % of Grubbs II in DCM at rt for 16 h gave the corresponding cyclic *cis*-β-amino Weinreb amides (S_S,1*R*,2S)-(+)-**9** in moderate to good yield (Scheme 2). For comparison the corresponding *N*-tosly β-amino diene Weinreb amides (−)-**10** were cyclized (Scheme 2). In each example there was a noticeable improvement in the yields, which may reflect poorer coordination of the catalyst to the *N*-tosyl group. Epimerization was not detected, and the *syn* relationship of the two substituents was established on the basis of NOE studies on the *N*-tosyl derivative of (+)-**11a**. These results confirm the *syn* orientation of the α-substituent in **6** and provide additional support for our transition state model.[15,22]

The availability of five-, six-, and seven-membered unsaturated cyclic *cis*-β-amino Weinreb amides **9** and **11** (Scheme 2) provide numerous opportunities for functionalization, affording new cyclic β-amino acid building blocks. These possibilities

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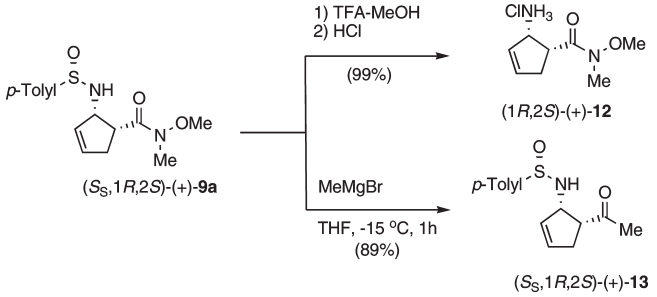
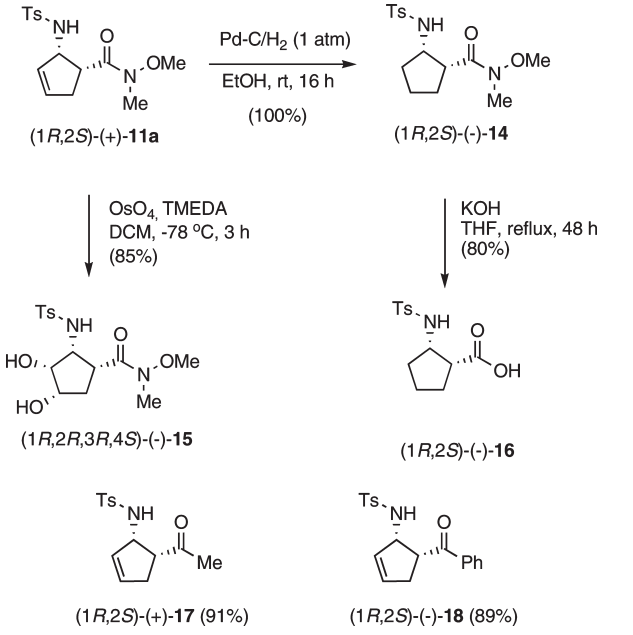
SCHEME 3



SCHEME 4



are illustrated for the five-membered β-amino Weinreb amide (+)-**9a**. Removal of the *N*-sulfinyl group was accomplished by treating (+)-**9a** with TFA/MeOH giving the amine (1*R*,2*S*)-(+)-**12** in quantitative yield and was isolated as the hydrochloride salt (Scheme 3). Treatment of (+)-**9a** with 7 equiv of MeMgBr afforded the methyl ketone (S_S,1*R*,2*S*)-(+)-**13** in 89% yield. However, attempts to obtain the acid by refluxing (+)-**9a** with KOH in THF for 48 h resulted in decomposition, and hydrogenation (H_2/Pd-C) failed to reduce the double bond, resulting in recovery of (+)-**9a** (>90%). To circumvent these problems, these transformations were carried out using the cyclic *N*-tosyl derivative (1*R*,2*S*)-(+)-**11a** (Scheme 4).

Hydrogenation (Pd-C/H_2) of (+)-**11a** gave the saturated cyclic β-amino Weinreb amide (−)-**14** in quantitative yield (Scheme 4). Dihydroxylation of (+)-**11a** with OsO_4/TMEDA for 4 h gave the dihydroxy compound (−)-**15** in 85% as a single isomer. The stereochemistry was determined by NOE studies and is consistent with hydroxylation from the more hindered face of the cyclopentene ring directed by hydrogen bonding.[43] All attempts to hydrolyze the amide group in (+)-**11a** (refluxing KOH/THF) again failed and resulted in decomposition. However, hydrolysis of the saturated derivative (−)-**14** (refluxing KOH/THF) afforded the desired acid (−)-**16** in 80% yield without epimerization. Despite the enhanced acidity of the *N*-tosyl proton in (+)-**11a**, treatment with 3−5 equiv of a Grignard reagent (MeMgBr and PhMgBr) readily afforded the corresponding ketones (+)-**17** (R = Me, 91%) and (−)-**18** (R = Ph, 89%) in excellent yield (Scheme 4). By analogy similar functionalization of the 6- and 7-membered cyclic β-amino Weinreb amides (+)-**11b** and (+)-**11c** can be envisioned. Removal of the *N*-tosyl group can be easily accomplished without epimerization, via reduction with sodium naphthalide, Mg/MeOH, Na(Hg), and cleavage with HBr in HOAc.[44] In our studies we have found that Na/NH_3 (liq) is particularly effective for removal of the *N*-*p*-toluenesulfonyl protecting group.[44g] These reductive methods are tolerant of carbonyl and olefinic functionalities.

In summary, new, general methodology has been introduced for the asymmetric synthesis of functionalized cyclic five-, six-, and seven-membered *cis*-β-amino Weinreb amides (+)-**7**, valuable building blocks for the synthesis of cyclic β-amino acid derivatives. This protocol involves RCM of *N*-sulfinyl β-amino diene Weinreb amides (+)-**6** or the *N*-tosyl derivatives (+)-**10**, which are readily available via the highly diastereoselective addition of unsaturated prochiral Weinreb amide enolates to sulfinimines.

Experimental Section

(*S*)-(+)-*N*-(Propylidene)-*p*-toluenesulfinamide (**4**),[42a] *N*-methoxy-*N*-methyl-4-pentenamide (**5a**),[45] and *N*-methoxy-*N*-methyl-4-hexenamide (**5b**)[45] were prepared according to literature procedures.

***N*-Methoxy-*N*-methyl-6-heptenamide (5c).** This material was prepared using the procedure of Guillaume and co-workers using a modified procedure.[45] In an oven-dried 100 mL one-neck round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed 6-heptenoic acid (0.38 g, 2.95 mmol) in dichloromethane (30 mL). *N*-Methylpiperidine (2.93 g, 29.52 mmol) was added, the solution was stirred for 10 min at rt, and trimethylacetyl chloride (0.53 g, 4.43 mmol) was added dropwise via syringe. The yellow-colored solution was stirred at 0 °C for 2 h, *N*,*O*-dimethylhydroxylamine hydrochloride (0.52 g, 5.31 mmol) was added, and the reaction mixture was stirred at rt for 16 h. At this time the reaction mixture was diluted with 1.0 M aqueous hydrochloric acid (20 mL). The organic phase was washed with satd $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. Chromatography (50% EtOAc/hexanes) gave 0.50 g (99%) of a clear oil: ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 2H), 1.64 (m, 2H), 2.06 (m, 2H), 2.41 (t, J = 7.96 Hz, 2H), 3.16 (s, 3H), 3.67 (s, 3H), 4.95 (m, 2H), 5.79 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.1, 28.6, 31.7, 32.1, 33.5, 61.2, 114.5, 138.6, 174.6; IR (film) 3077, 1642 cm^{-1}. HRMS calcd for $C_9H_{18}NO_2$ (M + H) 172.1332, found 172.1335.

(S_S,3*S*,2*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-*N*-methoxy-*N*-methyl-2-(2-propenyl)-pent-4-ene-amide (6a). In an oven-dried 50 mL one-neck round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed **5a** (0.19 g, 1.34 mmol) in THF (3.0 mL), the solution was cooled

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to −78 °C, LDA (1.97 mL, 1.475 mmol, 0.75 M solution in THF) was added via syringe, and the reaction mixture was stirred for 2 h at this temperature. At this time a solution of (*S*)-(+)-**4** (0.13 g, 0.67 mmol) in THF (4.0 mL) was added via syringe, and the reaction was monitored for completion by TLC (typically less than 1 h). The reaction mixture was quenched by addition of satd NH_4Cl (5 mL) at −78 °C, warmed to rt, and extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with brine (2 × 30 mL), dried ($MgSO_4$), and concentrated. Chromatography (50% EtOAc/hexanes) gave 0.20 g (89%) of a colorless oil as a single isomer: $[\alpha]^{20}_D$ +149.60 (*c* 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.29 (m, 1H), 2.40 (s, 3H), 2.42 (m, 1H), 3.12 (s, 3H), 3.17 (m, 1H), 3.63 (s, 3H), 4.11 (m, 1H), 4.73 (d, J = 3.7 Hz, 1H), 5.03 (m, 2H), 5.35 (m, 2H), 5.67 (m, 1H), 5.99 (m, 1H), 7.27 (d, J = 8.05 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 32.0, 45.2, 58.4, 61.5, 117.2, 119.1, 125.4, 129.4, 135.3, 135.9, 141.2, 142.3, 173.7; IR (film) 3233, 1639 cm^{-1}. HRMS calcd for $C_{17}H_{25}N_2O_3S$ (M + H) 337.1580, found 337.1582.

(S_s,3*S*,2*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-*N*-methoxy-*N*-methyl-3-amino-2-(but-3-enyl)-pent-4-enamide(6b). $[\alpha]^{20}_D$ +114.84 (*c* 1.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.96 (m, 4H), 2.36 (s, 3H), 3.06 (s, 3H), 3.10 (m, 1H), 3.60 (s, 3H), 4.04 (m, 1H), 4.75 (d, J = 3.8 Hz, 1H), 4.96 (m, 2H), 5.30 (m, 2H), 5.69 (m, 1H), 5.96 (m, 1H), 7.24 (m, 2H), 7.53 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2, 26.6, 31.3, 32.0, 44.5, 58.3, 61.4, 115.2, 118.8, 125.4, 129.4, 136.1, 137.6, 141.1, 142.2, 174.1; IR (film) 3223, 3077, 1642 cm^{-1}. HRMS calcd for $C_{18}H_{27}N_2O_3S$ (M + H) 351.1737, found 351.1741.

(S_s,3*S*,2*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-*N*-methoxy-*N*-methyl-3-amino-2-(pent-4-enyl)-pent-4-enamide (6c). $[\alpha]^{20}_D$ +131.62 (*c* 0.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.71 (m, 3H), 2.05 (m, 3H), 2.40 (s, 3H), 2.42 (m, 1H), 3.09 (m, 1H), 3.13 (s, 3H), 3.65 (s, 3H), 4.72 (d, J = 3.6 Hz, 1H), 4.94 (m, 2H), 5.35 (m, 2H), 5.76 (m, 1H), 6.01 (m, 1H), 7.28 (m, 2H), 7.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 26.8, 27.2, 32.1, 33.6, 45.2, 58.5, 61.5, 114.7, 118.9, 125.4, 129.4, 136.2, 138.2, 141.2, 142.3, 174.4; IR (film) 3223, 3077, 1642 cm^{-1}. HRMS calcd for $C_{19}H_{29}N_2O_3S$ (M + H) 365.1899, found 365.1899.

(3*S*,2*R*)-(−)-*N*-(*p*-Toluenesulfonyl)-3-amino-*N*-methoxy-*N*-methyl-2-(2-propenyl)-pent-4-ene-amide (10a) (typical procedure). In an oven-dried 25 mL one-neck round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**6a** (0.067 g, 0.2 mmol) in DCM (5 mL), *m*-chloroperoxybenzoic acid (0.052 g, 0.3 mmol) in DCM (3 mL) was slowly added via syringe, and the solution was stirred for 1 h at rt. At this time the reaction mixture was quenched by addition of satd sodium bisulfite (3 mL) and stirred for 10 min. The phases were separated, the aqueous phase was extracted with DCM (2 × 5 mL), and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (50% EtOAc/hexanes) afforded 0.065 g (92%) of a white solid, mp 84−85 °C: $[\alpha]^{20}_D$ −13.23 (*c* 1.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.27 (m, 1H), 2.35 (m, 1H), 2.40 (s, 3H), 3.08 (s, 3H), 3.17 (m, 1H), 3.65 (s, 3H), 3.88 (q, J = 7.2 Hz, 1H), 4.98 (m, 4H), 5.11 (d, J = 7.6 Hz, 1H), 5.68 (m, 1H), 5.78 (m, 1H), 7.27 (bd, J = 7.8 Hz, 2H), 7.70 (td, J = 2.0 Hz, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 31.9, 32.7, 45.6, 57.8, 61.6, 117.3, 117.7, 127.3, 129.4, 134.8, 134.9, 137.4, 143.2, 173.4; IR (film) 3233, 1639 cm^{-1}. HRMS calcd for $C_{17}H_{25}N_2O_4S$ (M + H) 353.1530, found 353.1531.

(3*S*,2*R*)-(−)-*N*-(*p*-Toluenesulfonyl)-*N*-methoxy-*N*-methyl-3-amino-2-(but-3-enyl)-pent-4-enamide (10b). Chromatography (50% EtOAc acetate/hexanes) gave 0.078 g (89%) of a white solid, mp 84−85: $[\alpha]^{20}_D$ −12.89 (*c* 1.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.57 (m, 1H), 1.73 (m, 1H), 1.98 (m, 2H), 2.40 (s, 3H), 3.07 (s, 3H), 3.11 (m, 1H), 3.65 (s, 3H), 3.86 (m, 1H), 4.95 (m, 4H), 5.09 (d, J = 7.6 Hz, 1H), 5.75 (m, 2H), 7.25 (m, 2H), 7.70 (td, J = 2.0 Hz, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 27.2, 31.2, 32.0, 44.9, 57.9, 61.5, 115.3, 117.5, 127.3, 129.4, 135.3, 137.4, 137.5, 143.2, 173.8; IR (film) 3265, 1643, 1598 cm^{-1}. HRMS calcd for $C_{18}H_{27}N_2O_4S$ (M + H) 367.1686, found 367.1687.

(3*S*,2*R*)-(−)-*N*-(*p*-Toluenesulfonyl)-*N*-methoxy-*N*-methyl-3-amino-2-(pent-4-enyl)-pent-4-enamide (10c). Chromatography (50% EtOAc/hexanes) gave 0.075 g (91%) of a white solid, mp 111−112 °C: $[\alpha]^{20}_D$ −10.08 (*c* 1.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.31 (m, 1H), 1.47 (m, 1H), 1.60 (m, 1H), 1.98 (q, J = 7.2 Hz, 2H), 2.42 (s, 3H), 3.06 (m, 1H), 3.08 (s, 3H), 3.65 (s, 3H), 3.84 (q, J = 7.2 Hz, 1H), 4.95 (m, 4H), 5.10 (d, J = 7.2 Hz, 1H), 5.76 (m, 2H), 7.25 (bd, J = 8.4 Hz, 2H), 7.70 (td, J = 2.0 Hz, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 26.6, 27.8, 31.9, 33.6, 45.6, 58.0, 61.5, 114.8, 117.4, 127.3, 129.4, 135.3, 137.4, 138.2, 143.2, 174.1; IR (film) 3265, 1643, 1598 cm^{-1}. HRMS calcd for $C_{19}H_{29}N_2O_4S$ (M + H) 381.1843, found 381.1848.

(S_S,1*R*,2*S*)-(+)-*N*-Methoxy-*N*-methyl-2-(*N*-p-toluenesulfinyl-amino)-cyclopent-3-enyl Amide (9a) (typical procedure). In an oven-dried 100 mL one-neck round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**6a** (0.15 g, 0.43 mmol) in DCM (40 mL), and a solution of Grubb's second generation catalyst (0.02 g, 0.02 mmol) in DCM (5 mL) was added via cannula. The reaction mixture was stirred for 20 h at rt and concentrated. Chromatography (60% EtOAc/hexanes) gave 0.11 g (80%) of a colorless oil: $[\alpha]^{20}_D$ +209.03 (*c* 1.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.44 (m, 1H), 2.82 (m, 1H), 3.18 (s, 3H), 3.56 (s, 3H), 3.62 (m, 1H), 4.50 (m, 1H), 4.83 (d, J = 10.4 Hz, 1H), 5.85 (m, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2, 32.2, 34.8, 42.5, 60.8, 61.3, 126.0, 129.4, 132.2, 132.3, 140.9, 141.6, 173.6; IR (film) 3223, 1642, 1610 cm^{-1}. HRMS calcd for $C_{15}H_{21}N_2O_3S$ (M + H) 309.1273, found 309.1275.

(S_S,1*R*,2*S*)-(+)-*N*-Methoxy-*N*-methyl-2-(*N*-*p*-toluenesulfinyl-amino)-cyclohex-3-enyl Amide (9b). Chromatography (60% EtOAc/hexanes) gave 0.053 g (68%) of a colorless oil: $[\alpha]^{20}_D$ +236.75 (*c* 1.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 2H), 1.97 (m, 3H), 2.33 (s, 3H), 3.06 (s, 3H), 3.12 (m, 1H), 3.55 (s, 3H), 4.03 (m, 1H), 4.93 (d, J = 8.8 Hz, 1H), 5.84 (m, 2H), 7.20 (m, 2H), 7.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 22.0, 23.1, 27.6, 31.9, 41.6, 50.6, 61.4, 126.0, 129.1, 129.2, 129.4, 140.9, 142.1, 173.5; IR (film) 3223, 1642, 1610 cm^{-1}. HRMS calcd for $C_{16}H_{23}N_2O_3S$ (M + H) 323.1424, found 323.1422.

(S_S,1*R*,2*S*)-(+)-*N*-Methoxy-*N*-methyl-2-(*N*-*p*-toluenesulfinyl-amino)-cyclohept-3-enyl Amide (9c). Chromatography (60% EtOAc/hexanes) gave 0.050 g (49%) of a colorless oil: $[\alpha]^{20}_D$ +111.28 (*c* 2.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.52 (m, 1H), 1.73 (m, 2H), 2.13 (m, 2H), 2.45 (m, 1H), 2.32 (s, 3H), 3.03 (s, 3H), 3.19 (m, 1H), 3.61 (s, 3H), 4.16 (m, 1H), 5.14 (d, J = 5.6 Hz, 1H), 5.91 (m, 2H), 7.20 (m, 2H), 7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.2, 24.8, 27.9, 28.5, 31.8, 44.5, 53.8, 61.5, 125.4, 129.4, 130.7, 134.4, 140.9, 142.7, 175.3; IR (film) 3223, 1642, 1590 cm^{-1}. HRMS calcd for $C_{17}H_{25}N_2O_3S$ (M + H) 337.1580, found 337.1583.

(1*R*,2*S*)-(+)-*N*-Methoxy-*N*-methyl-2-(*N*-*p*-toluenesulfonyl-amino)-cyclopent-3-enyl Amide (11a). In an oven-dried, 25 mL round-bottomed one-neck flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (−)-**10a** (0.03 g, 0.085 mmol) in DCM (10 mL). A solution of Grubbs second generation catalyst (0.004 g, 0.004 mmol) in DCM (1 mL) was added via syringe, and the solution was stirred for 16 h at rt, and concentrated. Chromatography (60% EtOAc/hexanes) gave 0.025 g (90%) of a white solid, mp 129−130 °C: $[\alpha]^{20}_D$ +75.41 (*c* 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 2.46 (m, 1H), 2.68 (m, 1H), 3.10 (s, 3H), 3.61 (s, 3H), 3.72 (m, 1H), 4.67 (m, 1H), 5.30 (m, 1H), 5.45 (d, J = 10.15 Hz, 1H), 5.80 (m, 1H), 7.27 (bd, J = 8.0 Hz, 2H), 7.72 (td, J = 1.9 Hz, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 32.0, 35.3, 40.8, 60.2, 61.5, 127.0, 129.5, 130.0, 132.8, 138.4, 143.1, 173.3; IR (film) 3265, 1643, 1598 cm^{-1}. HRMS calcd for

$C_{15}H_{21}N_2O_4S$ (M + H) 325.1222, found 325.1217. NOE: Upon irradiation of *N*-OCH_3 at δ 3.61, a positive NOE was observed on the Ar-CH_3 at δ 2.41; upon irradiation of the C-5 proton at δ 2.68, a positive NOE was observed on the Ar-CH_3 at δ 2.41, confirming a *cis* relationship between the C-1 proton and C-2 proton.

(1*R*,2*S*)-(+)-*N*-Methoxy-*N*-methyl-2-(*N*-*p*-toluenesulfonylamino)-cyclohex-3-enyl Amide (11b). Chromatography (60% EtOAc/hexanes) gave 0.036 g (85%) of a white solid, mp 149−150 °C: $[\alpha]^{20}_D$ +54.12 (*c* 1.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.77 (m, 1H), 1.96 (m, 3H), 2.40 (s, 3H), 3.06 (s, 3H), 3.14 (m, 1H), 3.59 (s, 3H), 4.07 (m, 1H), 5.40 (m, 2H), 5.72 (m, 1H), 7.27 (bd, *J* = 8.0 Hz, 2H), 7.73 (td, *J* = 2.0 Hz, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 22.0, 22.8, 31.8, 40.5, 49.2, 61.4, 127.0, 129.2, 138.3, 143.0, 173.0; IR (film) 3265, 3028, 2922, 1643, 1598 cm^{-1}. HRMS calcd for $C_{16}H_{23}N_2O_4S$ (M + H) 339.1373, found 339.1377.

(1*R*,2*S*)-(−)-*N*-Methoxy-*N*-methyl-2-(*N*-*p*-toluenesulfonylamino)-cyclohept-3-enyl Amide (11c). Chromatography (60% EtOAc/hexanes) gave 0.028 g (85%) of a white solid, mp 91−92 °C: $[\alpha]^{20}_D$ −39.52 (*c* 1.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.58 (m, 2H), 1.88 (m, 1H), 2.10 (m, 3H), 2.42 (s, 3H), 3.12 (s, 3H), 3.27 (m, 1H), 3.66 (s, 3H), 4.14 (m, 1H), 5.40 (m, 1H), 5.57 (m, 2H), 7.28 (bd, *J* = 7.6 Hz, 2H), 7.74 (td, *J* = 2.0 Hz, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 23.2, 28.3, 28.7, 31.9, 46.0, 53.4, 61.5, 127.2, 129.5, 130.2, 131.2, 137.7, 143.1, 174.2; IR (film) 3265, 3028, 2922, 1643, 1598 cm^{-1}. HRMS calcd for $C_{17}H_{25}N_2O_4S$ (M + H) 353.1530, found 353.1535.

(1*R*,2*S*)-(+)-2-Amino-*N*-methoxy-*N*-methylcyclopent-3-enecarboxamide Hydrochloride (12). In an oven-dried 25 mL one-neck round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**9a** (0.110 g, 0.356 mmol) in MeOH (10.0 mL). Trifluoroacetic acid (0.275 mL, 3.566 mmol) was added at 0 °C via syringe, and the reaction was monitored for completion by TLC (typically 2 h). At this time the reaction mixture was concentrated, the residue was dissolved in 10% aqueous hydrochloric acid (10 mL), and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The aqueous phase was freeze-dried to give 0.073 g (99%) of a solid, mp 84−85 °C: $[\alpha]^{20}_D$ +54.61 (*c* 0.26, MeOH); ^{1}H NMR (D_2O) δ (italics denote values for the rotamer) 2.78 (m, 2H, same for both rotamers), 2.99 (s, 3H), *3.25* (s, 3H), 3.55 (q, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), *3.89* (s, 3H), *3.91* (q, *J* = 8.4 Hz, 1H), 4.48 (m, 1H, same for both rotamers), 5.84 (m, 1H, same for both rotamers), 6.30 (m, 1H, same for both rotamers); ^{13}C NMR (D_2O) δ 31.8 (*34.8*), 34.1 (*34.5*), 39.8 (*43.6*), 55.8 (56.8), 61.1 (*61.7*), 125.6 (*125.8*), 138.6 (*138.7*), 172.5 (*175.5*); IR (film) 3400, 1660 cm^{-1}. HRMS calcd for $C_8H_{15}N_2O_2$ (M) 171.1134, found 171.1130.

1-(S_S,1*R*,2*S*)-2-(*N*-*p*-Toluenesulfinylamino)cyclopent-3-enyl)-ethanone (13). In an oven-dried 25 mL one-neck round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**9a** (0.063 g, 0.204 mmol) in THF (5.0 mL), and the solution was cooled to −15 °C. Methylmagnesium bromide (0.5 mL, 1.5 mmol, 3.0 M solution in THF) was added slowly via syringe at −15 °C, and the reaction mixture was monitored by TLC for completion (typically 2 h). At this time the solution was quenched by addition of satd NH_4Cl solution (2.0 mL) at 0 °C and warmed to rt, and H_2O (15 mL) was added. The solution was extracted with EtOAc (3 × 15 mL), and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated. Chromatography (50% EtOAc/hexanes) gave 0.045 g (84%) of colorless oil: $[\alpha]^{20}_D$ +200.00 (*c* 1.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3H), 2.32 (m, 1H), 2.41 (s, 3H), 2.71 (m, 1H), 3.35 (m, 1H), 4.48 (m, 1H), 4.54 (bd, *J* = 10.8 Hz, 1H), 5.85 (m, 1H), 7.30 (bd, *J* = 7.6 Hz, 2H), 7.54 (bd, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 31.0, 33.4, 53.0, 60.0, 125.8, 129.5, 131.8, 132.8, 141.4, 208.5; IR (film) 3210, 3055, 1709 cm^{-1}. HRMS calcd for $C_{14}H_{18}NO_2S$ (M + H) 264.1058, found 264.1053.

(1*R*,2*S*)-(−)-*N*-Methoxy-*N*-methyl-2-(*N*-p-toluenesulfonylamino)-cyclopentyl Amide (14). In an oven-dried 25 mL one-neck round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**11a** (0.035 g, 0.108 mmol) in ethanol (10 mL). Palladium (0.02 g, 20% palladium on carbon) was added, and the reaction mixture was stirred for 16 h at rt under hydrogen atmosphere (balloon). The solution was filtered through Celite, and the filtrate was concentrated. Chromatography (60% EtOAc/hexanes) gave 0.035 g (100%) of a white solid, mp 94−95 °C: $[\alpha]^{20}_D$ −11.41 (*c* 0.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.44 (m, 1H), 1.75 (m, 5H), 2.40 (s, 3H), 3.08 (s, 3H), 3.23 (m, 1H), 3.54 (s, 3H), 3.76 (m, 1H), 5.89 (d, *J* = 8.4 Hz, 1H), 7.27 (m, 2H), 7.73 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 22.1, 28.5, 31.8, 33.3, 41.9, 56.5, 61.4, 127.1, 129.5, 138.1, 142.9, 174.8; IR (film) 3258, 1643 cm^{-1}. HRMS calcd for $C_{15}H_{23}N_2O_4S$ (M + H) 327.1373, found 327.1374.

(1*R*,2*R*,3*R*,4*S*)-(−)-3,4-Dihydroxy-*N*-methoxy-*N*-methyl-2-(tosylamino)cyclopentane-carboxamide (15). In an oven-dried 25 mL one-neck round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**11a** (0.013 g, 0.04 mmol) in DCM (4.0 mL), and TMEDA (0.037 mL, 0.246 mmol) was slowly added at −78 °C via syringe. After stirring for 5 min, OsO_4 (0.7 mL, 0.044 mmol, 0.065 M solution in DCM) was added via syringe, and the reaction mixture was stirred at −78 °C for 4 h and concentrated. The residue was dissolved in THF (4 mL), satd sodium sulfite solution (4 mL) was added, and the reaction mixture was refluxed for 2 h and filtered through Celite. Chromatography (EtOAc) gave 0.012 g (85%) of a clear oil: $[\alpha]^{20}_D$ −20.0 (*c* 0.41, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.85 (M, 1H), 2.01 (M, 1H), 2.41 (S, 3H), 3.05 (S, 3H), 3.49 (S, 3H), 3.58 (m, 1H), 3.84 (m, 1H), 3.92 (m, 1H), 4.05 (m, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.05 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 31.8, 33.8, 37.2, 58.9, 61.4, 69.9, 77.9, 127.2, 129.6, 137.4, 143.4, 174.5; IR (film) 3350, 2950, 1650 cm^{-1}. HRMS calcd for $C_{15}H_{23}N_2O_6S$ (M + H) 359.1277, found 359.1266. NOE: Upon irradiation of the C-2 proton at δ 3.84, a positive NOE was observed at the C-4 proton at δ 4.05, confirming the *cis* relationship at C-2 proton, the C-3 proton, and the C-4 proton.

(1*R*,2*S*)-(−)-2-(*N*-*p*-Toluenesulfonylamino)cyclopentanoic Acid (16). In an oven-dried, 25 mL one-neck round-bottomed flask equipped with a magnetic stirring bar, and rubber septum was placed the (−)-**14** (0.015 g, 0.046 mmol) in ethanol (2.0 mL). Potassium hydroxide solution (2.0 mL, 2.0 M aqueous solution) was added, and the solution was refluxed for 48 h. At this time conc HCl was added until pH 2 was reached, and the solution was extracted with EtOAc (4 × 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (EtOAc) afforded 0.010 g (80%) of a white solid, mp 104−105 °C: $[\alpha]^{20}_D$ −28.73 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 1H), 1.68 (m, 3H), 1.95 (m, 2H), 2.45 (s, 3H), 2.91 (m, 1H), 3.78 (m, 1H), 6.30 (d, *J* = 8.8 Hz, 1H), 7.30 (m, 2H), 7.75 (td, *J* = 1.6 Hz, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 21.7, 27.8, 31.6, 46.2, 56.2, 127.0, 129.7, 137.5, 143.5, 178.1; IR (film) 3258, 1707 cm^{-1}. HRMS calcd for $C_{13}H_{18}NO_4S$ (M + H) 284.0951, found 284.0944.

(1*R*,2*S*)-(−)-2-(*N*-*p*-Toluenesulfonylamino)-cyclopent-3-enyl Phenyl Ketone (18). In an oven-dried 25 mL one-neck round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**11a** (0.017 g, 0.054 mmol) in THF (5.0 mL). Phenylmagnesium chloride (0.08 mL, 0.161 mmol, 2.0 M solution in THF) was added to the solution via syringe at −15 °C, and the reaction progress was monitored by TLC (typically 2 h). At this time the reaction mixture was quenched by addition of satd NH_4Cl (2.0 mL) solution, diluted with water (5 mL), extracted with EtOAc (3 × 10 mL), dried

($MgSO_4$), and concentrated. Chromatography (50% EtOAc/hexanes) afforded 0.016 g (89%) of a white solid, mp 81−82 °C: $[\alpha]^{20}_D$ −6.15 (*c* 0.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H), 2.60 (m, 1H), 2.68 (m, 1H), 4.11 (m, 1H), 4.82 (m, 1H), 5.38 (d, J = 10.4 Hz, 1H), 5.58 (m, 1H), 5.83 (m, 1H), 6.99 (m, 2H), 7.39 (m, 2H), 7.54 (m, 3H), 7.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 35.8, 45.6, 60.9, 126.9, 128.3, 128.4, 128.5, 129.5, 131.3, 131.7, 133.2, 136.0, 137.4, 143.0, 199.7; IR (film) 3265, 1673, 1596 cm^{-1}. HRMS calcd for $C_{19}H_{20}NO_3S$ (M + H) 342.1158, found 342.1152.

(1*R*,2*S*)-(+)-2-(*N*-p-Toluenesulfonylamino)-cyclopent-3-enyl Methyl Ketone (17). Chromatography (solvent) gave (91%) of a solid, mp 131−132 °C: $[\alpha]^{20}_D$ +69.54 (*c* 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H), 2.36 (m, 1H), 2.43 (s, 3H), 2.69 (m, 1H), 3.41 (dt, J = 6.0 Hz, J = 8.8 Hz, 1H), 4.68 (m, 1H), 4.88 (d, J = 10.4 Hz, 1H), 5.16 (m, 1H), 5.78 (m, 1H), 7.31 (bd, J = 8.0 Hz, 2H), 7.73 (td, J = 8.0 Hz, J = 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 30.5, 33.0, 52.2, 60.1, 127.1, 129.3, 129.8, 133.3, 137.8, 143.6, 207.9; IR (film) 3220, 3055, 1709, 1601 cm^{-1}. HRMS calcd for $C_{14}H_{18}NO_3S$ (M + H) 280.1007, found 280.1001.

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Supporting Information Available: Spectroscopic data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.