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Asymmetric Synthesis of *anti*-α-Substituted β-Amino Ketones from Sulfinimines

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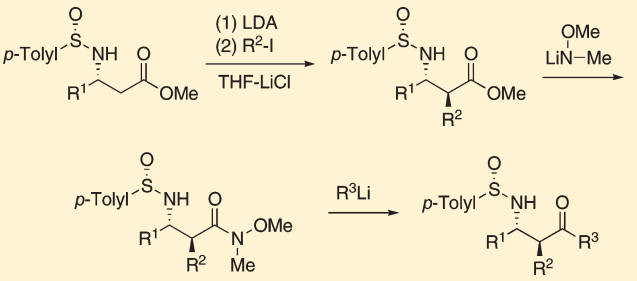
Supporting Information

ABSTRACT: Previously unknown, enantiopure, β-amino ketones were prepared in modest yield by addition of lithium reagents to *N*-sulfinyl *anti*-α-substituted β-amino Weinreb amides. Grignard reagents failed to add to these Weinreb amides in contrast to the *syn*-α-substituted isomers which did. The *anti*-α-substituted β-amino Weinreb amides were prepared by addition of LiN(OMe)Me to the corresponding *N*-sulfinyl *anti*-α-substituted β-amino esters because α-alkylation of *N*-sulfinyl β-amino Weinreb amide enolates resulted in poor diastereoselectivities.



INTRODUCTION

Enantiopure β-amino ketones have emerged as versatile chiral building blocks for the asymmetric synthesis of natural products and nitrogen-containing bioactive compounds.[1] Arguably the best and most reliable method for their synthesis is the addition of Grignard reagents to enantiopure *N*-sulfinyl β-amino Weinreb amides (Figure 1).[2,3] β-Amino Weinreb amides are readily prepared by addition of Weinreb enolates to sulfinimines (*N*-sulfinyl imines).[3,4] *syn*-α-Substituted β-amino Weinreb amides are available by addition of prochiral Weinreb amide enolates to the sulfinimines.[1,5] These enolate additions are highly diastereoselective, and the absolute stereochemistry of the new carbon−nitrogen stereocenter is predictable.[3,5] With Grignard reagents the β-amino Weinreb amides afford the corresponding ketones in excellent yield without epimerization.

The utility of α-substituted β-amino ketones in the asymmetric synthesis of stereodefined nitrogen heterocycles[1] makes the development of methods for the synthesis of *anti*-α-substituted β-amino ketones of considerable importance. To the best of our knowledge there are no reports of their syntheses in enantiopure form. Conceptually, the addition of lithium and Grignard reagents to the unknown *anti*-α-substituted β-amino Weinreb amides would represent a general route to such ketones. We describe here a new method for the asymmetric synthesis of *anti*-α-substituted β-amino Weinreb amides and their application in the first enantioselective syntheses of *anti*-α-substituted β-amino ketones.

RESULTS AND DISCUSSION

The α-alkylation of β-amino ester enolates is reported to occur with good to excellent levels of diastereoselectivity affording the *anti*-α-alkylation product.[6,7] The alkylation of β-amino Weinreb amide enolates has not been described, and to explore this method Weinreb amide (S_S,3*R*)-(+)-**1a** (Z = *p*-tolyl(S(O)−) was treated at −78 °C with 2.4 equiv of LDA followed by addition of MeI. Both the corresponding *anti*-(S_S,2*S*,2*R*)-(+)-**2a** and *syn*-(S_S,2*R*,3*R*)-(+)-**3a** β-amino Weinreb amides were formed in a 1:1 ratio (Table 1, entry 1) (Scheme 1). Addition of LiCl to the preformed enolate improved the *anti*:*syn* ratio to 2:1 (Table 1, entry 2). Importantly, alkylation of the *N*-tosyl enolate, derived from (*R*)-(+)-**1b**, under the reaction conditions, resulted in a 3:1 *anti*:*syn* ratio (Table 1, entry 3). Use of LiCl improved the *anti*:*syn* to 12:1 affording (2*S*,3*R*)-(+)-**2b** in 37% isolated yield (Table 1, entry 4).

Before trying to optimize the yield of (+)-**2b** it was necessary to determine whether it would react with Grignard and lithium reagents without epimerization at the α-center (Scheme 2). Surprisingly, reaction of (+)-**2b** with 3 to 5 equiv of methylmagnesium bromide under varying conditions resulted in no reaction. However, with 5 equiv of *n*-butyllithium (*n*-BuLi) a 61% yield of ketone (+)-**4** was obtained and epimerization was not detected. Removal of the *N*-tosyl group in (+)-**4** was next explored. While a number of methods are available for removal of *N*-tosyl amine groups (sodium naphthalide, Li/NH_3, HBr in HOAc) the harshness of these conditions would be incompatible with enolizable ketones such as (+)-**4**.[8] However, cleavage of arenesulfonamides by reduction with Mg-MeOH under ultrasonic conditions is reported to be tolerant of carbonyl groups.[8e] Sonication of (+)-**4** under varying conditions of time and temperature gave, under optimal conditions, the β-amino ketone **5** as an inseparable 3:1 mixture of isomers in poor yield (Scheme 2). For this reason the use of *N*-tosyl *anti*-β-amino-α-substituted β-amino Weinreb amides such as (+)-**2b** was abandoned as a practical method for the synthesis of the corresponding ketones.

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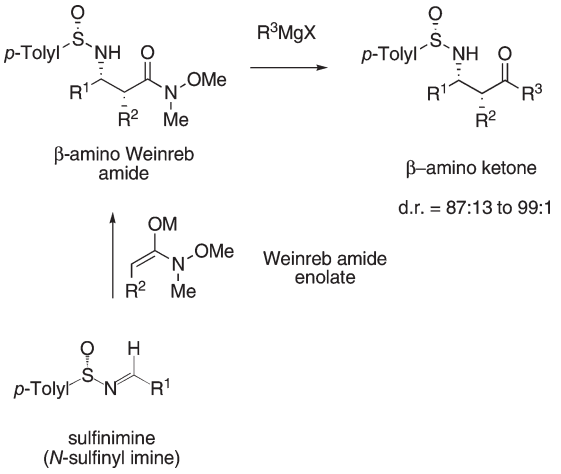


Figure 1. Synthesis of *N*-sulfinyl *β*-amino Weinreb amides and ketones.

Table 1. Alkylation of *β*-Amino Weinreb Amide Enolates at −78 °C

entry	**1** (Z =)	conditions	products *anti*:*syn* **2**:**3**[a] (% yield)
1	**1a** (*p*-tolylS(O)−)		1:1 (19)
2		10 equiv of LiCl	2:1 (46)[a,b]
3	**1b** (Ts)		3:1 (16)
4		10 equiv of LiCl	12:1 (37)[c]

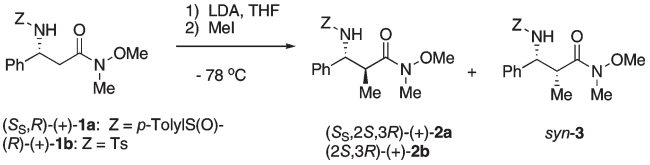
[a] Determined by ^{1}H NMR on the crude reaction mixture. [b] Combined yield of inseparable *anti*:*syn* isomers. [c] Isolated yield of pure diastereoisomer.

Our earlier studies had shown that *N*-sulfinyl *syn*-α-substituted *β*-amino Weinreb amides react with Grignard and lithium reagents to give good yields of the corresponding ketones, and the *N*-sulfinyl group was easily removed under mild acid conditions.[5] Epimerization at the α-center was not observed. Unfortunately, the selectivity for α-alkylation of *N*-sulfinyl *β*-amino Weinreb amide enolates was poor (Table 1, entries 1 and 2). Better selectivity was anticipated for the α-alkylation of *N*-sulfinyl *β*-amino ester enolates,[6,7,9] which can be readily transformed to the Weinreb amides by reaction with lithium *N*,*O*-dimethylhydroxy amine.[3]

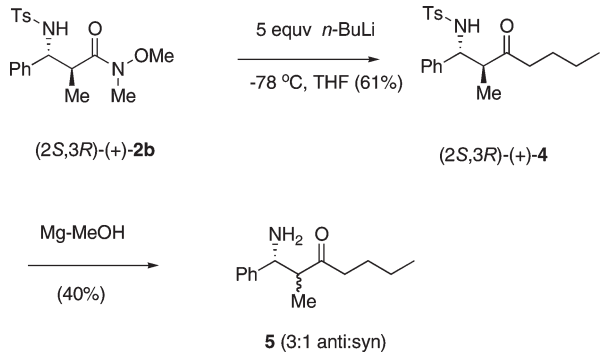
Treatment of (+)-**6a** with 2.4 equiv of LDA at −78 °C followed by addition of 1.6 equiv of MeI resulted in a 2:1 mixture of the *anti*- and *syn*-isomers **7a** and **8** (Scheme 3) (Table 2, entry 1). The selectivity improved to 7:1 on addition of 10 equiv of LiCl (Table 2, entry 2). Alkylation of the enolate of (+)-**6a** with allyl iodide and benzyl iodide afforded the corresponding α-substituted derivatives (+)-**7b** and (+)-**7c** in good yields and excellent selectivities (Table 2, entries 3 and 4). In each of these examples 5−10% (*E*)-methyl cinnamate (**9**) was observed resulting from elimination of *p*-toluenesulfinamide (*p*-TolylS(O)NH$_2$) (Table 2, entries 2−4). Enolate alkylations of *N*-sulfinyl *β*-amino esters (+)-**6b** (R = vinyl), (+)-**6c** (R = *n*-Pr), and (+)-**6d** (R = BnO(CH$_2$)$_2$) gave similar high *anti*:*syn* selectivities (Table 2, entries 5−9). However, in none of these examples was it possible to separate the isomers. Fortunately, the corresponding Weinreb amides were readily separable (see below).

In solution enolates, including *β*-amino ester enolates,[10] exist as mixed aggregates and their dynamic structures can be influenced by additives such as LiCl. We speculate that the improved yields on addition of LiCl may reflect easier access of the alkylating species to the enolate. Enhanced intramolecular chelation caused by added LiCl, as illustrated in structure **13**, where the R group occupies a pseudoaxial position, could also explain the improved *anti*:*syn* stereoselectivities for **2** (Scheme 3).[6]

Scheme 1



Scheme 2



Assignment of Stereochemistry. Earlier studies suggested that the major isomer formed in the alkylation of *N*-sulfinyl *β*-amino ester enolates is the *anti*-isomer (Scheme 3).[6] To confirm these stereochemical assignments two methods were employed to establish the stereochemistry. Not only did these methods confirm the *anti*-stereochemistry, but they illustrate the utility of *anti*-α-substituted *β*-amino esters as valuable new chiral building blocks.

Removal and replacement of the *N*-sulfinyl group in (+)-**10b** with a Boc group gave amino diene (−)-**14** in 63% isolated yield for the two steps (Scheme 4). With 5 mol % of Grubbs II at rt for 8 h in DCM (−)-**14** gave *anti*-cyclopentene *β*-amino acid (+)-**15** in 58% yield as a single isomer, and hydrogenation (Pd−C/H$_2$) gave the cyclic *trans*-*β*-amino ester (+)-**16** in 90% yield. Cyclic *β*-amino ester (+)-**16** was previously prepared in 9 steps, 12% overall yield from (*S*)-methionine.[11] Cyclic *β*-amino acid derivatives are important building blocks for the synthesis of natural products and *β*-peptides.[1,12] Our synthesis of (+)-**16** is particularly efficient: five steps, 25% overall yield from *β*-amino ester (+)-**6b**. Furthermore the double bond (+)-**15** is readily functionalized making this route to cyclic *anti*-*β*-amino acids derivatives particularly useful.[1]

Treatment of the 7:1 *anti*:*syn* mixture of *β*-amino ester (+)-**7a** with 6 equiv of LiN(OMe)Me at −78 °C gave a 75% yield of *anti*-*β*-amino Weinreb amide (+)-**2a** (Scheme 5). Importantly, (+)-**2a** was obtained as a single isomer with spectral properties identical to those of an authentic sample.[5a] Similar results were found for the conversion of *β*-amine esters (+)-**10b**, (+)-**11**, and (+)-**12** to their corresponding Weinreb amides where single

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Scheme 3

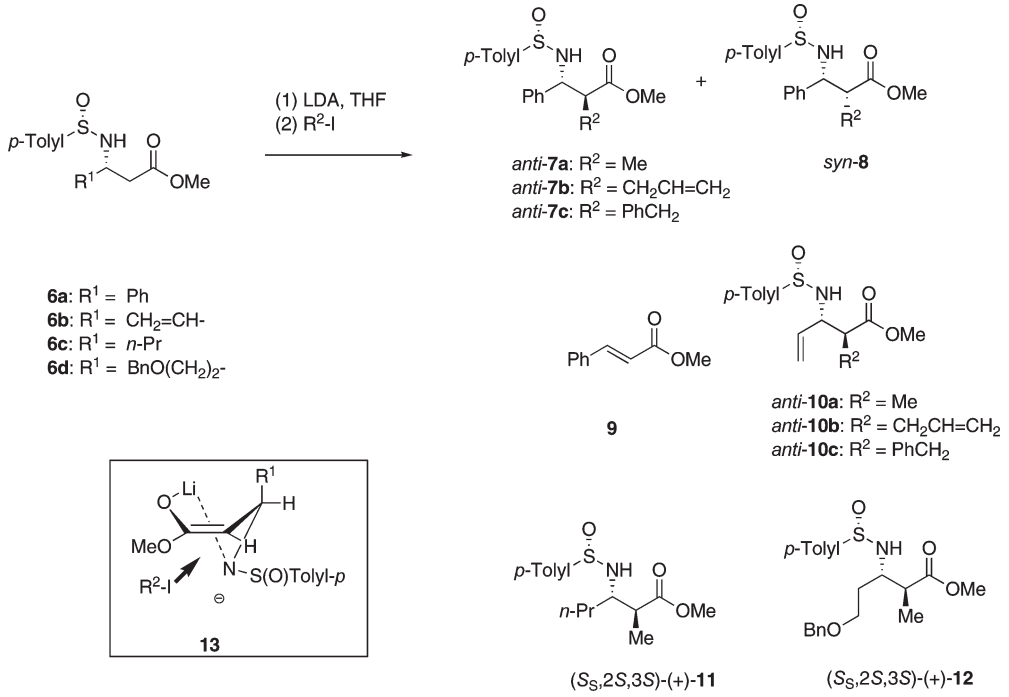

Table 2. Alkylation of *N*-Sulfinyl *β*-Amino Esters 6 with LDA in THF

entry	sster **6**: R^1 =	R^2I	added LiCl[a]	temp, °C	alkylation product: *anti*:*syn*[b] (% yield)[c]
1	**6a**: Ph	Me		−78	**7a**: 2:1 (NA)
2		Me	10	−78 to −50	**7a**: 7:1 (80)[d]
3		allyl	10	−50	**7b**: 92:8 (64)[d]
4		$BnCH_2$	10	−50	**7c**: 96:4 (72)[d]
5	**6b**: vinyl	Me	10	−50	**10a**: 89:11 (88)
6		allyl	10	−50	**10b**: 91:9 (76)
7		$BnCH_2$	10	−50	**10c**: 95:5 (82)
8	**6c**: *n*-Pr	Me	10	−50	**11**: >99:1(82)
9	**6d**: $BnO(CH_2)_2$	Me	10	−78	**12**: >99:1 (62)

[a] Equivalents of added LiCl. [b] Isomer ratio determined by ^{1}H NMR on the crude reaction mixture. [c] Combined yield of *anti*:*syn* isomers. [d] (*E*)-methyl cinnamate (**9**), 5−10% was isolated.

isomers were obtained in good yield (Scheme 5). In general the *anti*-α-protons in these Weinreb amides appear upfield compared to the syn isomers.[5a] For example, in *anti*-(+)-**2a** this proton comes at *δ* 4.49 ppm whereas in the syn isomer this proton is at *δ* 4.74 ppm.[5a]

Synthesis of *β*-Amino Ketones. Results for the addition of Grignard and lithium reagents to *anti*-α-methyl-*β*-amino Weinreb amides are given in Scheme 6 and summarized in Table 3. Addition of 5 or 10 equiv of methylmagnesium bromide to Weinreb amide (+)-**2a** at −78 °C resulted in no reaction (Table 3, entry 1). However, on addition at 0 °C a better than 95% yield of methyl ketone (+)-**20a** was obtained (Table 3, entry 2). Unexpectedly, reaction of (+)-**2a** with either *n*-butylmagnesium chloride or *n*-butylmagnesium bromide failed (Table 3, entries 3 and 4). Warming the reaction to 25 °C and addition of LiCl, $CeCl_3$, and HMPA had no effect, and starting material was recovered in all cases. However, with 5 equiv of *n*-butyllithium at −78 °C for 2 h the desired *n*-butyl ketone (+)-**20b** was formed in modest yield along with reduced amide (+)-**23a** and the starting material (+)-**2a** (Table 3, entry 6). Reduced amides such as (+)-**23a** are often observed in reactions of Weinreb amides with highly basic reagents, and they are thought to be formed via an E2 pathway with formation of formaldehyde.[2d,13,14] Increasing the amount of *n*-BuLi to 10 equiv, although decreasing the amount of recovered starting material, resulted in an increase in the reduced amide (+)-**23a** (Table 3, entry 7). Optimum conditions, 5 equiv of *n*-BuLi at −50 °C, afforded ketone (+)-**20b** (R^1 = *n*-Bu) and the reduced amide (+)-**23a** in 38% and 33% yield, respectively (Table 3, entry 8). Attempts to improve the yield of (+)-**20b** by varying the temperature, time, and amount of *n*-BuLi, or by addition of additives such as LiCl and $CeCl_3$ failed. However, under these conditions with 5 equiv of MeLi and PhLi better yields of the corresponding methyl and phenyl ketones (+)-**20a** (R^1 = Me), 73% and (+)-**20c** (R^1 = Ph), 61%, respectively, were observed (Table 3, entries 9 and 10). Interestingly little, if any, of the

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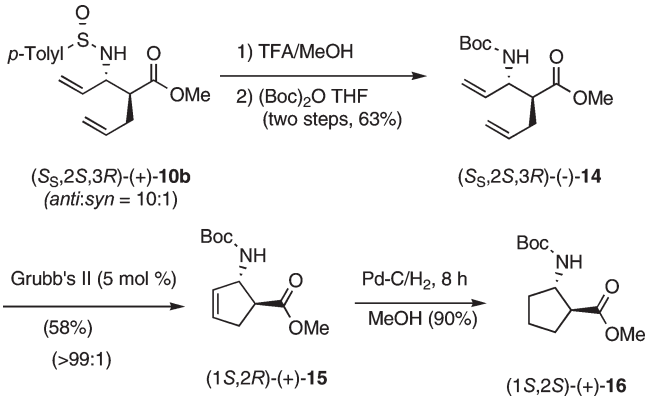
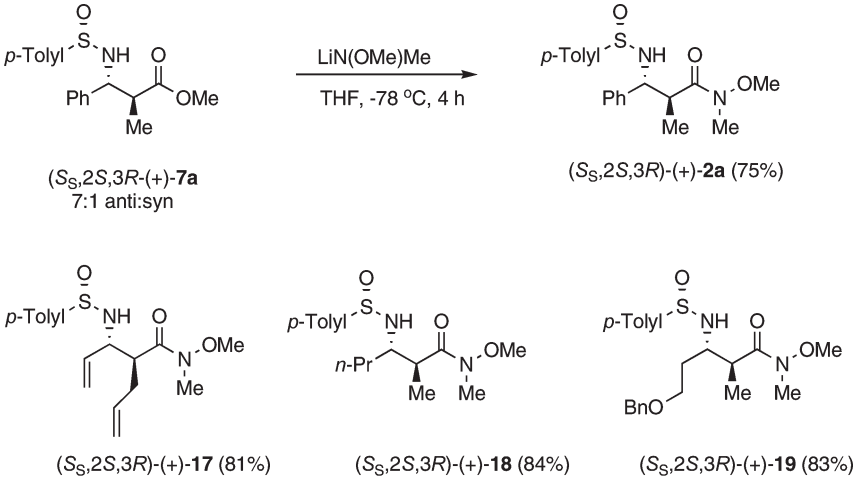
reduced amide (+)-**23a** was detected. Employing these optimized conditions *anti*-α-methyl *β*-amino Weinreb amides (+)-**18** (R = *n*-Pr) and (+)-**19** (R = $BnO(CH_2)_2$−) were treated with MeLi and *n*-BuLi at −50 °C to afford low to modest yields, 33−45%, of the corresponding ketones (+)-**21**, (+)-**22a**, and (+)-**22b** (Table 3, entries 11, 14, and 17). Methylmagnesiun bromide failed to react with either of these amides (Table 3, entries 12 and 15). In all cases epimerization at the α-center was not detected and is attributable to the protecting group ability of the *N*-sulfinyl group, which stabilizes anions at nitrogen.[4a]

Our results for the addition of Grignard and lithium reagents to *anti*-α-methyl *β*-amino Weinreb amides are puzzling. While MeMgBr reacts with *N*-sulfinyl *anti*-α-methyl *β*-amino Weinreb amide (+)-**2a** to give an excellent yield of the methyl ketone (+)-**20a** (Talbe 3, entry 2) it failed to add to the corresponding *N*-tosyl derivative (+)-**2b** or with Weinreb amides derived from *N*-alkyl sulfinimines, i.e. (+)-**18** and (+)-**19** (Scheme 2 and Table 3). On the other hand, lithium reagents react with these Weinreb amides to give the corresponding ketones, albeit in low to moderate yields, because addition competes with reduction of the Weinreb amide. By contrast the corresponding *N*-sulfinyl *syn*-α-methyl *β*-amino Weinreb amides give excellent yield of the corresponding ketones with lithium and Grignard reagents and reduction is not observed.[1,5]

Scheme 4



Scheme 5



Scheme 6

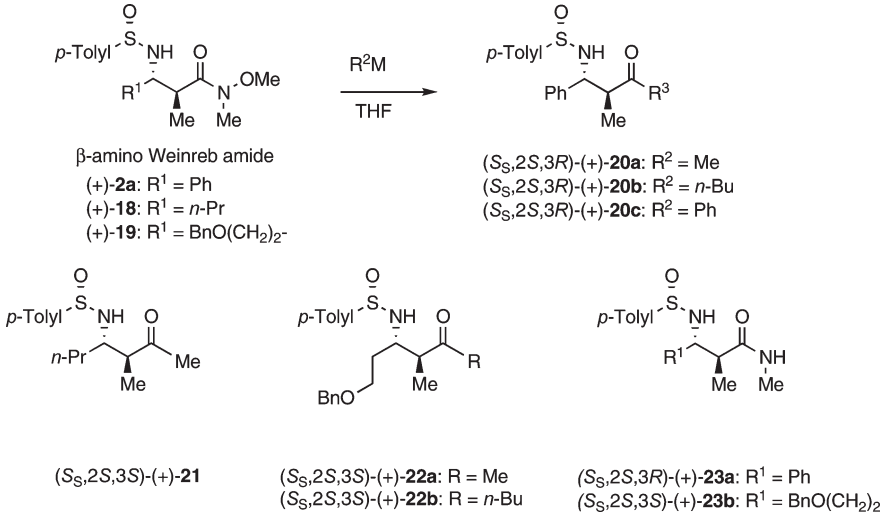


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Table 3. Synthesis of β-Amino Ketones from β-Amino Weinreb Amides in THF for 2 h

entry	Weinreb amide (R^1 =)	RM (equiv)	temp, °C	ketone (% yield)[a]
1	(+)-**2a** (Ph)	MeMgBr (10)	−78	no reaction
2		MeMgBr (10)	0	**20a** (95)
3		*n*-BuMgCl (10)	0	no reaction
4		*n*-BuMgBr (10)	0	no reaction
5		*n*-BuMgBr (10)	0 to 24	no reaction
6		*n*-BuLi (5)	−78	**20b**:**23a**:**2a** (34:16:50)[b]
7		*n*-BuLi (10)	−78	**20b**:**23a**:**2a** (38:41:21)[b]
8		*n*-BuLi (5)	−50	**21b** (38), **23a** (33)
9		MeLi (5)	−50	**20a** (73)[c]
10		PhLi (5)	−50	**20d** (61)[c]
11	(+)-**18** (*n*-Pr)	MeLi (5)	−50	**21** (33), **23c** (13)
12		MeMgBr (10)	0	no reaction
13	(+)-**19**- ($BnO(CH_2)_2$)	*n*-BuMgCl (10)	24	no reaction
14		MeLi	−50	**22a** (45), **23b** (20)
15		MeMgBr (10)	0	no reaction
16		*n*-BuLi (5)	−78	**22b** (25), **23b** (26)
17		*n*-BuLi (5)	−50	**22b** (40), **23b** (27)

[a] Isolated yield of pure diastereoisomer. [b] Ratio of products determined by ^{1}H NMR. [c] Reduced amide **23a** was detected.

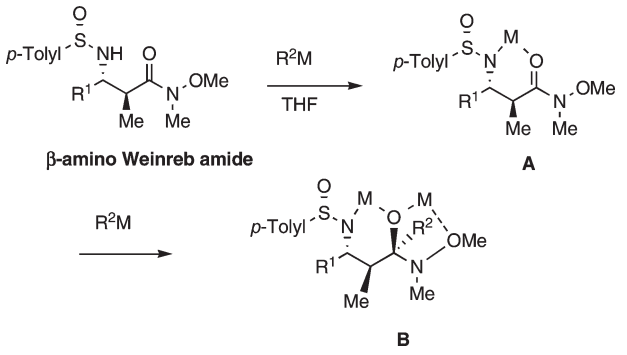

Figure 2. Reaction of β-amino Weinreb amides with organometallic reagents.

It is reasonable to assume that addition of an organometallic reagent R^2M to the β-amino Weinreb amides results first in deprotonation of the acidic *N*-sulfinyl NH proton to give species **A** (Figure 2). Deprotonation of *N*-sulfinyl amines derived from addition of organometallic reagents to sulfinimine has often been used to explain the exceptional protecting group ability of the *N*-sulfinyl group in sulfinimine chemistry.[4] Species **A** is probably formed as a complex mixture of aggregates resulting from both intra- and intermolecular chelation. We speculated that formation of the tetrahedral intermediate **B** results from addition of the organometallic reagent R^2M to the amide carbonyl from the least hindered direction. For steric reasons this should be more favorable in the *syn*-α-substituted β-amino Weinreb amide than in the *anti*-derivative. Dimeric lithium acetylide is reported to react with Weinreb amides via a monosolvated monomer-based transition state to form the tetrahedral intermediate.[15] In a study of displacements at the nitrogen atom of lithioalkoxyamides by organometallic reagents, lithium reagents were more reactive than Grignard reagents, and this is consistent with our findings.[16] While this simple steric argument can be used to interpret our findings, the situation is undoubtedly much more complex because these organometallic species exist as mixtures of aggregates.

In summary, the first asymmetric synthesis of *anti*-α-substituted β-amino Weinreb amides and their corresponding ketones is reported. This was accomplished by reaction of lithium dimethylhydroxylamine with *N*-sulfinyl *anti*-α-substituted β-amino esters. Alkylation of *N*-sulfinyl β-amino Weinreb amide enolates resulted in poor diastereoselectivities. Grignard reagents do not react with *N*-sulfinyl *anti*-α-substituted β-amino Weinreb amides, perhaps for steric reasons. However, lithium reagents react with these Weinreb amides affording the corresponding ketones in low to moderate yields because addition competes with reduction of the Weinreb amide.

EXPERIMENTAL SECTION

Weinreb amide (S_S,3*R*)-(+)-*N*-(*p*-toluenesulfinyl)-3-amino-*N*-methoxy-*N*-methyl-3-phenylpropionamide (**1a**),[3] *N*-sulfinyl β-amino esters, (S_S,*R*)-(+)-methyl 3-(4-methylphenylsulfinamido)-3-phenylpropanoate (**6a**), and (S_S,*R*)-(+)-methyl 3-(4-methylphenylsulfinamido)-3-pent-4-enoate (**6b**) were prepared as previously described.[17]

(*S*)-(+)-*N*-(3-(Benzyloxy)propylidene)-*p*-toluenesulfinamide. In a flame-dried, 50-mL round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet were placed (*S*)-(+)-*p*-toluenesulfinamide (0.500 g, 3.23 mmol), 3-(benzyloxyl)-1-propanal (0.636 g, 3.88 mmol), and DCM (10 mL). To the solution was added $Ti(OEt)_4$ (3.56 mL, 16.15 mmol), then the reaction mixture was stirred for 8 h at rt at which time the solution was poured into a 50-mL ice/water mixture and stirred vigorously. The reaction mixture was filtered through Celite, and the Celite was washed with DCM (2 × 5 mL) and the organic phase was washed with satd aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. Chromatography (EtOAc/hexanes 1:1) gave 0.597 g (61%) of a clear oil: $[\alpha]^{25}_D$ +268 (*c* 1.7, $CHCl_3$); IR (thin film) 2865, 2365, 2335, 1624, 1094 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 2.80 (m, 2H), 3.78 (m, 2H), 4.50 (s, 2H), 7.32 (m, 7H), 7.55 (m, 2H), 8.30 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7, 36.7, 66.4, 73.5, 125.0, 125.7, 128.0, 128.2, 128.8, 128.82, 130.0, 130.2, 165.5. HRMS calcd for $C_{17}H_{20}NO_2S$ (M + H) 302.1215, found 302.1215.

(*R*)-(+)-*N*-Methoxy-*N*-methyl-3-phenyl-3-(tosylamino)-propanamide (1b). Into a 25-mL round-bottomed flask was placed

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m-CPBA (77% of 0.183 g, 0.820 mmol), then a solution of (+)-**1a** (0.142 g, 0.410 mmol) in dry $CHCl_3$ (6 mL) was added and the reaction mixture was stirred at rt for 8 h. At this time satd aqueous $Na_2S_2O_3$ (2 mL) was added, then the organic phase was washed with satd aqueous $NaHCO_3$ (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (EtOAc/hexane 50:50) gave 0.128 g (86%) of a white solid: mp 105−6 °C; $[\alpha]^{25}_D$ +58.3 (*c* 2.46, $CHCl_3$); IR (KBr) 1641, 1462, 1327 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H), 2.77 (dd, *J* = 5.6, 16.0 Hz, 1H), 2.97 (dd, *J* = 5.6, 16.0 Hz, 1H), 3.02 (s, 3H), 3.43 (s, 3H), 4.71 (q, *J* = 6.0, 13.2 Hz, 1H), 6.40 (d, *J* = 6.8 Hz, 1H), 7.17 (m, 7H), 7.59 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.8, 32.1, 38.4, 55.0, 61.6, 127.0, 127.5, 127.8, 128.7, 129.7, 138.0, 140.5, 143.3, 171.5. HRMS calcd for $C_{18}H_{23}N_2O_4S$ (M + H) 363.1379, found 363.1376.

(*S*S,3*S*)-(+)-Methyl 3-(4-Methylphenylsulfinamido)hexanoate (6c):

Typical Procedure In a Schlenk tube equipped with a magnetic stirring bar, rubber septum, and argon inlet were added NaHMDS solution (0.54 mmol, 0.54 mL of 1 M NaHMDS in THF) by syringe and ether (5 mL) at rt. The solution was cooled to −78 °C, a solution of methyl acetate (0.04 mL, 0.503 mmol) in ether (2 mL) was added dropwise, and the reaction mixture was stirred for 1 h. At this time (*S*)-(+)-*N*-butylidiene-*p*-toluenesulfinamide[16] (0.070 g, 0.335 mmol) in ether (2 mL) was added dropwise, then the reaction mixture was stirred at −78 °C for 40 min and quenched with satd aqueous NH_4Cl solution (2 mL). Water (2 mL) was added, the aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined organic phases were washed with satd aqueous NH_4Cl solution (2 mL) and brine (2 mL), dried ($MgSO_4$), and concentrated. Chromatography (hexanes/EtOAc, 67:33) gave 0.071 g (75%) of a clear oil: $[\alpha]^{25}_D$ +118 (*c* 1.0, $CHCl_3$); IR (thin film) 1738, 1178, 1092, 1061, 811 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.51 (m, 4 overlapping H), 2.36 (s, 3H), 2.55 (dq, *J* = 5.6, 12, 16 Hz, 2H), 3.61 (s, 3H), 3.62 (m, 1H), 4.56 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.53 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.6, 21.7, 38.3, 40.8, 52.0, 52.7, 125.9, 129.8, 141.6, 142.7, 172.4. HRMS calcd for $C_{14}H_{22}NO_3S$ (M + H) 284.1320, found 284.1319.

(*S*S,3*S*)-(+)-Methyl-3-(4-methylphenylsulfinamido)-5-benzyloxypentanoate (6d). The title compound was prepared from (*S*)-(+)-*N*-(3-(benzyloxy)propylidene)-*p*-toluenesulfinamide in 67% yield. Chromatography (hexanes/EtOAc, 67:33) gave 0.125 g (67%) of a clear oil: $[\alpha]^{25}_D$ +64 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 2360, 2340, 1734, 1459, 1094 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.94 (m, 2H), 2.40 (s, 3H), 2.62 (dq, *J* = 5.6, 16, 42 Hz, 2H), 3.62 (s, 3H), 3.63 (m, 2H), 3.90 (m, 1H), 4.51 (q, *J* = 11.6, 18.4 Hz, 2H), 4.86 (d, *J* = 9.2 Hz, 1H), 7.26 (m, 3H), 7.32 (m, 4H), 7.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.1, 35.1, 39.9, 49.6, 51.3, 66.5, 72.8, 125.3, 125.6, 127.1, 127.3, 127.4, 127.5, 127.9, 128.1, 129.2, 137.9, 140.9, 141.9, 171.7. HRMS calcd for $C_{20}H_{26}NO_4S$ (M + H) 376.1583, found 376.1580.

(2*S*,3*R*)-(+)-*N*-Methoxy-*N*,2-dimethyl-3-phenyl-3-(tosylamino)propanamide (2b). In a Schlenk tube equipped with a magnetic stirring bar and rubber septum was placed LiCl (0.029 g, 0.691 mmol), then the tube was flame-dried under vacuum and filled with argon. This procedure was repeated three times, then the Schlenk tube was cooled to rt and diisopropylamine (0.036 mL, 0.259 mmol) and THF (1 mL) were added and the solution was cooled to 0 °C. At this time *n*-BuLi (0.207 mmol, 0.12 mL of 1.73 M in hexane) was added dropwise, then the solution was stirred for 15 min and cooled to −78 °C. In a separated 25 mL round-bottomed flask equipped with a magnetic stir bar and argon inlet was placed Weinreb amide (+)-**1b** (0.025 g, 0.0691 mmol) in THF (1 mL) and the solution was cooled to −78 °C. At this time the preformed LDA solution was added dropwise and the reaction mixture was stirred at −78 °C for 1 h, then MeI (0.180 mmol, 0.09 mL of a 2 M solution in *tert*-butyl methyl ether) was added dropwise at this time. The reaction mixture was stirred at this temperature for 1 h, warmed to −50 °C (dry ice/MeCN), stirred for 1 h, and quenched at this temperature by addition of satd aqueous NH_4Cl (2 mL). The solution was diluted with H_2O (2 mL), THF was evaporated, and the residue was extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (hexanes/EtOAc, 1:1) gave 0.0096 g (37%) of a clear oil: $[\alpha]^{25}_D$ +71.0 (*c* 0.3, $CHCl_3$); IR (thin film) 1639, 1452, 1329 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, *J* = 6.8 Hz, 3H), 2.31 (s, 3H), 2.99 (s, 3H), 3.10 (s, 3H), 3.28 (m, 1H), 4.56 (dd, *J* = 4.4, 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 7.05 (m, 4H), 7.10 (m, 3H), 7.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.5, 21.7, 32.0, 40.7, 61.1, 61.5, 126.8, 127.1, 127.2, 127.5, 128.5, 129.4, 138.8, 140.6, 142.8, 175.7. HRMS calcd for $C_{19}H_{25}N_2O_4S$ (M + H) 377.1535, found 377.1530.

(*S*S,2*S*,3*R*)-(+)-Methyl 2-Methyl-3-(4-methylphenylsulfinamido)-3-phenylpropanoate (7a):

Typical Procedure for the α-Alkylation of *N*-Sulfinyl *β*-Amino Esters In a Schlenk tube equipped with a magnetic stirring bar and rubber septum was placed LiCl (0.033 g, 0.789 mmol), then the tube was flame-dried under vacuum and filled with Argon. This procedure was repeated three times at which time the Schlenk tube was cooled to ambient temperature. To the Schlenk tube was added diisopropylamine (0.042 mL, 0.296 mmol) and THF (1 mL) and the solution was cooled to 0 °C. At this time *n*-BuLi (0.237 mmol, 0.14 mL of 1.73 M in hexane) was added dropwise, and the solution was stirred for 15 min and then cooled to −78 °C. To the preformed LDA solution was added dropwise *β*-amino ester (+)-**6a** (0.025 g, 0.0789 mmol) in THF (1 mL) and the reaction mixture was stirred at −78 °C for 1 h. At this time MeI (0.205 mmol, 0.1 mL of a 2 M solution in *tert*-butyl methyl ether) was then added dropwise and the solution was stirred at this temperature for 1 h and warmed to −50 °C (dry ice MeCN) and stirred for 1 h. The reaction mixture was quenched at −78 °C by addition of satd aqueous NH_4Cl (2 mL), warmed to rt, and diluted with H_2O (2 mL). The THF was evaporated, the residue was extracted with EtOAc (2 × 5 mL), and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (hexanes/EtOAc, 2:1) gave 0.020 g (80%) of a clear oil as a mixture of inseparable *anti/syn* (88:12) isomers: $[\alpha]^{25}_D$ +64.7 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 1423, 1263, 1218 cm^{-1}; major isomer ^1H NMR ($CDCl_3$): δ 1.06 (d, *J* = 7.2 Hz, 3H), 2.41 (s, 3H), 2.85 (m, 1H), 3.63 (s, 3H), 4.54 (dd, *J* = 5.2, 7.6 Hz, 1H), 5.09 (d, *J* = 5.6 Hz, 1H), 7.34 (m, 7H), 7.54 (d, *J* = 8.0 Hz, 2H); major isomer: ^{13}C NMR ($CDCl_3$) δ 15.5, 21.7, 46.7, 52.4, 61.2, 125.7, 125.8, 126.1, 127.6, 128.1, 128.4, 129.0, 129.9, 130.0, 140.2, 141.7, 142.7, 175.3. HRMS calcd for $C_{18}H_{22}NO_3S$ (M + H) 332.1320, found 332.1317.

(*S*S,2*S*,3*R*)-(+)-Methyl 2-(2-Propenyl)-3-(4-methylphenylsulfinamido)-3-phenylpropanoate (7b). Chromatography (hexanes/EtOAc, 2:1) gave 64% of a clear oil. Mixture of inseparable *anti/syn* (92:8) isomers: $[\alpha]^{25}_D$ +102 (*c* 1.7, $CHCl_3$); IR (thin film) 2365, 2340, 1734, 1059 cm^{-1}; major isomer: ^1H NMR ($CDCl_3$) δ 2.19 (m, 1H), 2.32 (m, 1H), 2.41 (s, 3H), 2.85 (m, 1H), 3.58 (s, 3H), 4.60 (t, *J* = 6.8 Hz, 1H), 5.03 (m, 2H), 5.17 (d, *J* = 6.4 Hz, 1H), 5.64 (m, 1H), 7.30 (m, 5H), 7.37 (m, 2H), 7.53 (m, 2H); major isomer: ^{13}C NMR ($CDCl_3$) δ 21.7, 34.5, 52.2, 52.5, 59.9, 118.1, 125.7, 125.9, 127.7, 128.1, 128.4, 128.9, 129.1, 129.9, 130.0, 134.5, 140.7, 141.7, 142.5, 174.2. HRMS calcd for $C_{20}H_{24}NO_3S$ (M + H) 358.1477, found 358.1474.

(*S*S,2*S*,3*R*)-(+)-Methyl 2-Benzyl-3-(4-methylphenylsulfinamido)-3-phenyl-propanoate (7c). Chromatography (hexanes/EtOAc, 2:1) gave 72% of a clear oil. Mixture of inseparable *anti/syn* (96:4) isomers: $[\alpha]^{25}_D$ +50.1 (*c* 1.2, $CHCl_3$); IR (thin film) 2365, 2340, 1734, 1459, 1059 cm^{-1}; major isomer: ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H), 2.77 (dd, *J* = 6, 13.6 Hz, 1H), 2.92 (m, 1H), 3.06 (m, 1H), 3.45 (s, 3H), 4.63 (t, *J* = 6.8 Hz, 1H), 5.33 (d, *J* = 6.8 Hz, 1H), 7.12 (m, 2H), 7.18 (m, 1H), 7.25 (m, 2H), 7.31 (m, 5H), 7.38 (m, 2H), 7.55 (m, 2H); major isomer: ^{13}C NMR ($CDCl_3$) δ 21.7, 36.5, 52.1, 54.9, 60.1,125.7, 125.9,

126.8, 126.9, 127.5, 128.1, 128.3, 128.5, 128.8, 129.10, 129.15, 129.9, 130.2, 138.7, 141.1, 141.7, 142.5, 174.2. HRMS calcd for $C_{24}H_{26}NO_3S$ (M + H) 408.1633, found 408.1624.

(*S*S,2*S*,3*R*)-(+)-Methyl 2-Methyl-3-(4-methylphenylsulfinamido)-3-pent-4-enonate (10a). Chromatography (hexanes/EtOAc, 2:1) gave 88% of a clear oil. Mixture of in separable *anti*/*syn* isomers: (89:11): $[\alpha]^{25}_D$ +92.3 (*c* 1.15, $CHCl_3$); IR (thin film) 2365, 2340, 1734, 1459, 1059 cm^{-1}; major isomer: ^1H NMR ($CDCl_3$) δ 1.11 (d, *J* = 7.2 Hz, 3H), 2.40 (s, 3H), 2.63 (m, 1H), 3.65 (s, 3H), 3.97 (dd, *J* = 1.2, 6.8 Hz, 1H), 4.76 (d, *J* = 7.2 Hz, 1H), 5.28 (m, 2H), 5.84 (m, 1H), 7.29 (m, 2H), 7.58 (m, 2H); major isomer: ^{13}C NMR ($CDCl_3$) δ 14.4, 21.7, 44.6, 52.2, 59.1, 118.4, 125.96, 126.02, 129.8, 136.0, 137.4, 141.7, 142.2, 175.0. HRMS calcd for $C_{14}H_{20}NO_3S$ (M + H) 282.1164, found 282.1163.

(*S*S,2*S*,3*R*)-(+)-Methyl 2-(2-Propenyl)-3-(4-methylphenylsulfinamido)-3-pent-4-enonate (10b). Chromatography (hexanes/EtOAc, 2:1) gave 76% of a clear oil. Mixture of inseparable *anti*/*syn* (91:9) isomers: $[\alpha]^{25}_D$ +51.4 (*c* 0.8, $CHCl_3$); IR (thin film) 2365, 2340, 1734, 1459, 1169, 1059 cm^{-1}; major isomer: ^1H NMR ($CDCl_3$) δ 2.19 (m, 1H), 2.36 (m, 1H), 2.41 (s, 3H), 2.62 (dt, *J* = 5.6, 8.8 Hz, 1H), 3.63 (s, 3H), 3.98 (m, 1H), 4.90 (d, *J* = 7.6 Hz, 1H), 5.03 (m, 2H), 5.27 (m, 2H), 5.63 (m, 1H), 5.88 (dq, *J* = 7.2, 10.4, 17.2 Hz, 1H), 7.29 (m, 2H), 7.57 (m, 2H); major isomer: ^{13}C NMR ($CDCl_3$) δ 21.7, 33.9, 50.2, 52.1, 58.0, 117.7, 117.8, 118.0, 126.0, 129.9, 134.9, 137.7, 137.9, 141.7, 142.1, 174.1. HRMS calcd for $C_{16}H_{22}NO_3S$ (M + H) 308.1320, found 308.1316.

(*S*S,2*S*,3*R*)-(+)-Methyl 2-Benzyl-3-(4-methylphenylsulfinamido)-3-pent-4-enonate (10c). Chromatography (hexanes/EtOAc, 2:1) gave 78% of a clear oil. Mixture of inseparable *anti*/*syn* (95:5) isomers: $[\alpha]^{25}_D$ +40.7 (*c* 1.25, $CHCl_3$); IR (thin film) 2360, 2340, 1734, 1459, 1059 cm^{-1}; major isomer: ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H), 2.85 (m, 2H), 2.95 (m, 1H), 3.53 (s, 3H), 4.03 (m, 1H), 4.97 (d, *J* = 8.0 Hz, 1H), 5.29 (m, 2H), 5.91 (m, 2H), 7.14 (m, 2H), 7.20 (m, 1H), 7.28 (m, 4H), 7.60 (m, 2H); major isomer: ^{13}C NMR ($CDCl_3$) δ 21.7, 35.7, 52.0, 52.4, 58.2, 117.8, 117.9, 126.1, 126.9, 128.9, 129.0, 129.2, 129.4, 129.9, 135.6, 138.1, 138.9, 141.8, 142.1, 174.1; HRMS calcd for $C_{20}H_{24}NO_3S$ (M + H) 358.1477, found 358.1475.

(*S*S,2*S*,3*S*)-(+)-Methyl 2-Methyl-3-(4-methylphenylsulfinamido)hexanoate (11). Chromatography (hexanes/EtOAc, 50:50) gave 89% of a clear oil: $[\alpha]^{25}_D$ +108 (*c* 0.97, $CHCl_3$); IR (thin film) 3205, 2962, 1728, 1199, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 7.2 Hz, 3H), 1.45 (m, 3H), 1.58 (m, 1H), 2.40 (s, 3H), 2.67 (m, 1H), 3.43 (m, 1H), 3.66 (s, 3H), 4.63 (d, *J* = 9.6 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.59 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 19.8, 21.7, 37.4, 43.6, 52.1, 57.8, 126.0, 129.8, 141.6, 142.8, 175.7. HRMS calcd for $C_{15}H_{24}NO_3S$ (M + H) 298.1477, found 298.1474.

(*S*S,2*S*,3*S*)-(+)-Methyl 2-Methyl-3-(4-methylphenylsulfinamido)-5-benzyloxy-5-benzyloxpentanoate (12). Chromatography (hexanes/EtOAc 1:1) gave 70% of a clear oil: $[\alpha]^{25}_D$ +67 (*c* 0.8, $CHCl_3$); IR (thin film) 1734, 1454, 1204, 1089 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (d, *J* = 7.6 Hz, 3H), 1.86 (q, *J* = 5.6, 6.8 Hz, 2H), 2.64 (m, 1H), 3.58 (m, 1H), 3.62 (s, 3H), 3.65 (m, 1H), 4.50 (s, 2H), 4.87 (d, *J* = 9.2 Hz, 1H), 7.26 (m, 3H), 7.32 (m, 4H), 7.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.6, 21.7, 35.1, 43.6, 52.1, 55.1, 67.3, 73.4, 125.8, 126.0, 128.0, 128.1, 128.8, 129.8, 138.6, 141.5, 142.5, 175.7. HRMS calcd for $C_{21}H_{28}NO_4S$ (M + H) 390.1739, found 390.1735.

(2*S*,3*R*)-(−)-Methyl 2-(2-Propenyl)-3-(*tert*-butoxycarbonylamino)pent-4-enonate (14). In a single-necked, oven-dried, 25-mL round-bottomed flask equipped with a magnetic stirring bar and rubber septum was placed (+)-**10b** (0.064 g, 0.208 mmol) in MeOH (4 mL) and HCl Et_2O solution (1.04 mmol, 1.04 mL of 1 M hydrogen chloride in ether, 1.04 mmol) was added via syringe at rt. The reaction mixture was stirred for 2 h and concentrated, then the residue was dissolved with DCM (10 mL), and the solution was neutralized to pH 8 by dropwise addition of satd aqueous $NaHCO_3$. The aqueous phase was extracted with DCM (5 mL), and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. To the residue was added DCM (2 mL) and $(Boc)_2O$ solution (1 mmol, 1 mL of 1 M $(Boc)_2O$ in THF) and the reaction mixture was stirred for 8 at rt. At this time satd aqueous $NaHCO_3$ (4 mL) was added, the solution was diluted with H_2O (2 mL), and the mixture was extracted with EtOAc (2 × 5 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (hexanes/EtOAc, 80:20) gave 0.048 g (86%) of a clear oil: $[\alpha]^{25}_D$ −45.9 (*c* 1.7, $CHCl_3$); IR (thin film) 2980, 1721, 1506, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 2.33 (m, 1H), 2.40 (m, 1H), 2.68 (m, 1H), 3.64 (s, 3H), 4.36 (m, 1H), 5.11 (m, 4H), 5.43 (d, *J* = 8.8 Hz, 1H), 5.74 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.7, 28.7, 34.2, 49.2, 52.9, 53.3, 115.8, 118.0, 134.8, 137.1, 155.8, 174.7. HRMS calcd for $C_{14}H_{23}NNaO_4$ (M + Na) 292.1525, found 292.1522.

(1*S*,2*R*)-(+)-Methyl-2-(*tert*-butoxycarbonylamino)cyclopentene Carboxylate (15). In a Schlenk tube equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed Grubbs II catalyst (0.012 g, 0.0138 mmol). The brown solid were dried under vacuum for 5 min and then the tube was filled with argon. After the above procedure was repeated three times, a solution of (−)-**14** (0.074 g, 0.275 mmol) in DCM (3 mL) was added at rt and the reaction mixture was stirred overnight. The solution was concentrated and chromatography (hexanes/EtOAc, 80:20) gave 0.038 g (58%) of a clear oil: $[\alpha]^{25}_D$ +98.5 (*c* 0.65, $CHCl_3$); IR (thin film) 2978, 1699, 1508, 1169 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 2.60 (m, 1H), 2.74 (m, 1H), 2.83 (m, 1H), 3.72 (s, 3H), 4.63 (br s, 1H), 4.96 (br s, 1H), 5.62 (d, *J* = 2.8 Hz, 1H), 5.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.7, 30.0, 35.7, 51.0, 52.4, 61.1, 130.9, 132.4, 155.4, 175.3. HRMS calcd for $C_{12}H_{19}NNaO_4$ (M + Na) 264.1212, found 264.1208.

(1*S*,2*S*)-(+)-Methyl 2-(*tert*-Butoxycarbonylamino)cyclopentanecarboxylate (16). In a 25-mL round-bottomed flask equipped with a magnetic stirring bar and rubber septum were placed (+)-**15** (0.021 g, 0.0871 mmol) and 10% Pd/C (0.004 g, 20% w/w). The flask was connected to the vacuum, then filled with hydrogen. After this procedure was repeated three times, MeOH (2 mL) was added via syringe and the dark suspension was stirred at rt for 4 h. At this time the solution was filtered through a short pad of Celite, the Celite was washed with MeOH (2 × 2 mL), and the combined solutions were concentrated to give 0.019 g (90%) of a white solid: mp 66−67 °C; $[\alpha]^{25}_D$ +39.3 (*c* 0.9, $CHCl_3$); IR (thin film) 2971, 1717, 1522, 1172 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.47 (m, 1H), 1.65 (m, 1H), 1.72 (m, 2H), 1.87 (m, 1H), 1.98 (m, 1H), 2.11 (m, 1H), 2.57 (dd, *J* = 8.0, 16.0 Hz, 1H), 3.68 (s, 3H), 4.10 (m, 1H), 4.58 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.1, 28.5, 28.7, 30.0, 33.2, 51.2, 52.2, 56.4, 155.6, 175.6. HRMS calcd for $C_{12}H_{21}NNaO_4$ (M + Na) 266.1368, found 266.1367.

(*S*S,2*S*,3*R*)-(+)-*N*-Methoxy-*N*,2-dimethyl-3-(4-methylphenylsulfinamido)-3-phenylpropanamide (2a):

Typical Procedure In a Schlenk tube equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed *N*,*O*-dimethyl hydroxylamine hydrochloride (0.187 g, 1.88 mmol, Aldrich) in THF (3 mL). The formed suspension was cooled to −78 °C, *n*-BuLi (3.71 mmol, 1.48 mL of 2.5 M in hexane) was added dropwise, the reaction mixture was slowly warmed to rt, and the solution was stirred for 1 h. At this time the solution was cooled to −78 °C and a solution of (+)-**6a** (0.104 g, 0.314 mmol) in THF (2 mL) was added dropwise, then the reaction mixture was stirred for 4 h and quenched by addition of satd aqueous NH_4Cl (3 mL). The solution was warmed to rt and diluted with H_2O (3 mL), the aqueous phase was extracted with EtOAc (2 × 5 mL), and the combined organic phases were washed with satd aqueous NH_4Cl (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (EtOAc:*n*-hexane, 50:50) gave 0.085 g (75%) of a clear oil: $[\alpha]^{25}_D$ +133.6 (*c* 1.73, $CHCl_3$); IR ($CHCl_3$) 2404, 1640, 1518, 1428, 1217 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (d, *J* = 6.8 Hz, 3H), 2.4 (s,

3H), 3.03 (s, 3H), 3.27 (s, 3H), 4.49 (t, 1H), 5.97 (d, J = 6.8 Hz, 1H), 7.25 (m, 3H), 7.33 (m, 4H), 7.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.5, 21.7, 32.2, 41.6, 61.6, 62.0, 125.6, 126.1, 127.6, 127.9, 128.5, 128.8, 129.0, 129.8, 130.0, 141.4, 142.2, 142.7, 175.9. HRMS calcd for $C_{19}H_{25}N_2O_3S$ (M + H) 361.1586, found 361.1588.

(*S*$_S$,3*S*,3*R*)-(+)-*N*-Methoxy-*N*-methyl-2-(2-propenyl)-3-(4-methylphenylsulfinamido)pent-4-eneamide (17). Chromatography (EtOAc:*n*-hexane, 33:67) gave 81% of a clear oil: $[\alpha]^{25}_D$ +94.3 (*c* 1.15, $CHCl_3$); IR (thin film) 3260, 2935, 1644, 1389 cm^{-1}; ^{1}H NMR (CDCl3) δ 2.27 (m, 1H), 2.39 (s, 3H), 2.41 (m, 1H), 3.09 (s, 3H), 3.62 (s, 3H), 3.92 (m, 1H), 4.98 (m, 1H), 5.07 (dd, J = 1.6 , 17.2 Hz, 1H), 5.22 (m, 2H), 5.55 (d, J = 8 Hz, 1H), 5.64 (m, 1H), 5.90 (m, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.58 (m, 2H); ^{13}C NMR ($CDCl_3$) 21.7, 32.3, 34.3, 44.9, 58.5, 61.9, 116.9, 117.7, 125.8, 126.2, 129.8, 135.4, 139.1, 141.4, 142.2, 174.9. HRMS calcd for $C_{17}H_{24}N_2O_3S$ (M + H) 337.1586, found 337.1584.

(*S*$_S$,2*S*,3*S*)-(+)-*N*-Methoxy-*N*,2-dimethyl-3-(4-methylphenylsulfinamido)-3-hexanamide (18). Chromatography (hexanes/EtOAc, 50:50) gave 87% of a clear oil: $[\alpha]^{25}_D$ +103 (*c* 0.5, $CHCl_3$); IR (thin film) 1657, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 6.8 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 1.39 (m, 1H), 1.50 (m, 2H), 1.59 (m, 1H), 2.39 (s, 3H), 3.15 (m, 4 overlapping H), 3.35 (m, 1H), 3.68 (s, 3H), 5.41 (d, J = 9.2 Hz, 1H), 7.27 (d, J = 9.2 Hz, 2H), 7.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.3, 14.2, 20.0, 21.7, 32.3, 38.2, 38.4, 59.0, 62.0, 126.1, 129.7, 141.3, 143.2, 176.9. HRMS calcd for $C_{16}H_{27}N_2O_3S$ (M + H) 327.1742, found 327.1742.

(*S*$_S$2*S*,3*S*)-(+)-*N*-Methoxy-*N*,2-dimethyl-3-(4-methylphenylsulfinamido)-5-benzyloxypentanamide (19). Chromatography (hexanes/EtOAc 1:1) gave 83% of a clear oil: $[\alpha]^{25}_D$ +66 (*c* 0.5, $CHCl_3$); IR (thin film) 1654, 1459, 1089, 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.17 (d, J = 14 Hz, 1H), 1.89 (m, 2H), 2.40 (s, 1H), 3.13 (s, 3H), 3.61 (m, 1H), 3.62 (s, 3H), 3.69 (s, 1H), 4.53 (dd, J = 5.6, 12 Hz, 2H), 5.61 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.29 (m, 1H), 7.34 (m, 4H), 7.55 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 17.6, 23.6, 34.1, 38.0, 40.5, 57.9, 63.8, 69.2, 75.1, 75.3, 127.7, 127.9, 129.9, 130.0, 130.1, 130.4, 130.6, 131.6, 140.5, 143.1, 144.9, 178.7. HRMS calcd for $C_{22}H_{31}N_2O_4S$ (M + H) 419.2005, found 419.2004.

(*S*$_S$,2*S*,3*R*)-(+)-*N*-(4-*p*-Toluenesulfinyl)-4-amino-3-methyl-4-phenylbutan-2-one (20a):

Typical Procedure In a Schlenk tube equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed a solution of compound (+)-**2a** (0.014 g, 0.0389 mmol) in THF (2 mL) at rt. The solution was cooled to 0 °C, MeMgBr (0.389 mmol, 0.13 mL of 3.0 M in THF) was added dropwise, and the reaction mixture was stirred at 0 °C for 10 min and warmed to rt. After 1 h the solution was cooled to −78 °C and quenched by dropwise addition of satd aqueous NH_4Cl (1 mL). The mixture was warmed to rt then diluted with H_2O (1 mL), and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (EtOAc:*n*-hexane, 50:50) gave 0.011 g (90%) of a clear oil: $[\alpha]^{25}_D$ +125.9 (*c* 2.73, $CHCl_3$); IR (thin film) 2404, 1525, 1428, 1217 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 7.2 Hz, 3H), 1.98 (s, 3H), 2.34 (s, 3H), 2.90 (m, 1H), 4.46 (dd, J = 5.2, 7.6 Hz, 1H), 4.98 (d, J = 5.6 Hz), 7.26 (m, 3H), 7.35 (m, 4H), 7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.3, 21.7, 29.8, 53.4, 60.9, 125.8, 128.2, 128.4, 129.0, 129.1, 129.9, 130.0, 140.0, 141.7, 142.5, 212.2. HRMS calcd for $C_{18}H_{22}NO_2S$ (M + H) 316.1371, found 316.1365.

(*S*$_s$,2*S*,3*R*)-(+)-2-Methyl-3-(4-methylphenylsulfinamido)-1-butyl-3-phenyl-3-phenylpropan-1-one (20b). Chromatography (EtOAc:*n*-hexane, 50:50) gave (0.011 g) 38% of a clear oil: $[\alpha]^{25}_D$ +109 (*c* 0.5, $CHCl_3$); IR (thin film) 3190, 2958, 2931, 2872, 1709, 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.8 (t, J = 7.2 Hz, 3H), 1.06 (d, J = 7.2 Hz, 3H), 1.15 (m, 2H), 1.38 (m, 2H), 2.12 (dt, J_1 = 7.2 Hz, J_2 = 17.2 Hz, 1H), 2.27 (dt, J_1 = 7.2 Hz, J_2 = 17.2 Hz, 1H), 2.41 (s, 3H), 2.98 (m, 1H), 4.53 (t, J = 6.4 Hz, 1H), 5.19 (d, J = 5.6 Hz, 1H), 7.29 (m, 3H), 7.36 (m, 4H), 7.54 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 15.7, 21.7, 22.5, 25.6, 42.8, 52.4, 61.3, 125.8, 127.9, 128.2, 129.0, 129.9, 140.9, 141.6, 142.7, 214.7. HRMS calcd for $C_{21}H_{28}NO_2S$ (M + H) 358.1841, found 358.1840.

(2*S*,3*R*)-(+)-2-Methyl-3-(4-methylphenylsulfonyl)-1-butyl-3-phenylpropan-1-one (4). To a 25-mL round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed a solution of compound (+)-**2b** (0.025 g, 0.0665 mmol) in THF (2 mL) at rt. The solution was cooled to −50 °C, *n*-BuLi (0.333 mmol, 0.13 mL of 2.48 M in hexane) was added dropwise, and the reaction mixture was stirred at −50 °C for 1 h. At this time the reaction was quenched by dropwise addition of satd aqueous NH_4Cl (1 mL), the solution was diluted with H_2O (1 mL), and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (EtOAc:*n*-hexane, 50:50) gave 0.015 g (61%) of a white solid: mp 78−79 °C; $[\alpha]^{25}_D$ +39.2, (*c* 0.5, $CHCl_3$); IR (thin film) 3275, 2960, 2360, 1709, 1459 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.76 (t, J = 7.6 Hz, 3H), 1.08 (m, 2H), 1.11 (d, J = 7.2 Hz, 3H), 1.29 (m, 2H), 1.98 (dt, J = 7.2, 17.6 Hz, 1H), 2.27 (dt, J = 7.2, 17.6 Hz, 1H), 2.30 (s, 3H), 2.96 (m, 1H), 4.50 (dd, J = 5.6, 9.2 Hz, 1H), 6.23 (d, J = 9.2 Hz, 1H), 6.97 (m, 2H), 7.04 (d, J = 7.6 Hz, 2H), 7.09 (m, 3H), 7.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 15.9, 21.7, 22.3, 25.4, 43.2, 51.5, 60.7, 126.8, 127.2, 127.6, 128.6, 129.5, 138.3, 139.8, 143.1, 215.4. HRMS calcd for $C_{20}H_{26}NO_3S$ (M + H) 374.1790, found 374.1785.

(*S*$_S$,2*S*,3*R*)-(+)-2-Methyl-3-(4-methylphenylsulfinamido)-1,3-diphenylpropan-1-one (20c). Chromatography (EtOAc:*n*-hexane, 50:50) gave 61% of a clear oil: $[\alpha]^{25}_D$ +35.7 (*c* 0.95, $CHCl_3$); IR (thin film) 3195, 3060, 2924, 1680, 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 3H), 2.39 (s, 3H), 3.92 (m, 1H), 4.78 (m, 1H), 5.17 (d, J = 5.2 Hz, 1H), 7.28 (m, 4H), 7.38 (m, 6H), 7.53 (m, 2H), 7.81 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.8, 21.7, 47.4, 61.5, 125.9, 128.3, 128.7, 129.0, 129.1, 129.8, 133.7, 136.6, 140.4, 141.6, 142.7, 203.4. HRMS calcd for $C_{23}H_{24}NO_2S$ (M + H) 378.1528, found 378.1524.

(*S*$_S$,3*S*,4*S*)-(+)-*N*-(4-*p*-Toluenesulfinyl)-4-amino-3-methyl-4-heptan-2-one (21). Chromatography (EtOAc:*n*-hexane, 50:50) gave 33% of a clear oil: $[\alpha]^{25}_D$ +126.5 (*c* 0.2, $CHCl_3$); IR (thin film) 3219, 2959, 2922, 1705, 1454 cm^{-1}; ^{1}H $[\alpha]^{25}_D$ +126.5 (*c* 0.2, $CHCl_3$); IR (thin film), 1705, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3H), 1.10 (d, J = 7.2 Hz, 3H), 1.42 (m, 4H), 2.09 (s, 3H), 2.41 (s, 3H), 2.75 (m, 1H), 3.47 (m, 1H), 4.61 (d, J = 9.2 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.59 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.3, 14.2, 19.9, 21.7, 29.9, 36.7, 50.9, 57.4, 125.9, 129.9, 141.6, 142.7, 212.0. HRMS calcd for $C_{15}H_{24}NO_2S$ (M + H) 282.1528. HRMS calcd for $C_{15}H_{24}NO_2S$ (M+) 282.1528, found 282.1529.

***N*-[(*S*$_S$,3*S*,4*S*)-(+)-1-(Benzyloxy)-4-methyl-5-oxohexan-3-yl]-4-methylbenzenesulfinamide (22a).** Chromatography (EtOAc:*n*-hexane, 50:50) gave 45% of a clear oil: $[\alpha]^{25}_D$ +64.8 (*c* 0.5, $CHCl_3$); IR (thin film) 3232, 2922, 2868, 1709, 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.01 (d, J = 7.2 Hz, 3H), 1.76 (m, 2H), 1.97 (s, 3H), 2.34 (s, 3H), 2.66 (m, 1H), 3.50 (m, 1H), 3.57 (m, 2H), 4.43 (m, 2H), 4.89 (d, J = 9.2 Hz, 1H), 7.19 (m, 3H), 7.25 (m, 4H), 7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.6, 21.7, 29.8, 34.7, 50.6, 54.8, 67.5, 73.4, 126.1, 128.1, 128.2, 128.8, 129.8, 138.6, 141.6, 142.4, 212.2. HRMS calcd for $C_{21}H_{28}NO_3S$ (M + H) 374.1790, found 374.1786.

***N*-[(*Ss*,3*S*,4*S*)-(+)-1-(Benzyloxy)-4-methyl-5-oxononan-3-yl]-4-methylbenzenesulfinamide (22b).** Chromatography (EtOAc:*n*-hexane, 50:50) gave 40% of a clear oil: $[\alpha]^{25}_D$ +68.5 (*c* 1.25, $CHCl_3$); IR (thin film) 3365, 2919, 2852, 1708, 1449, 1049 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.2 Hz, 3H), 1.07 (d, J = 7.2 Hz, 3H), 1.22 (m, 2H), 1.43 (m, 2H), 1.81 (m, 2H), 2.31 (m, 2H), 2.41 (s, 3H), 2.71 (m, 1H), 3.57 (m, 1H), 3.64 (m, 2H), 4.5 (s, 2H), 5.07 (d, J = 8.8 Hz, 1H), 7.26 (m, 3 overlapping H), 7.33 (m, 4H), 7.53 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$)

δ 14.0, 14.2, 21.7, 22.6, 25.9, 34.9, 42.4, 49.6, 54.9, 67.5, 73.4, 125.8, 126.1, 128.0, 128.1, 128.2, 128.6, 128.7, 129.8, 138.6, 141.5, 141.6, 142.5, 214.7. HRMS calcd for $C_{24}H_{34}NO_3S$ (M + H) 416.2259, found 416.2259.

(S_S,2*S*,3*R*)-(+)-3-Amino-*N*,2-dimethyl-3-(4-methylphenylsulfinamido)- 3-phenylpropanamide (23a). Chromatography (EtOAc:*n*-hexane, 50:50) gave 24% of a clear oil; $[\alpha]^{25}_D$ +153.4 (*c* 0.5, $CHCl_3$); IR 3293, 2920, 1651, 1556 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (d, *J* = 7.2 Hz, 3H), 2.40 (s, 3H), 2.51 (m, 1H), 2.63 (d, *J* = 5.2 Hz, 3H), 4.46 (t, *J* = 5.6 Hz, 1H), 5.29 (br s, 1H), 5.82 (d, *J* = 5.6 Hz, 1H), 7.32 (m, 7H), 7.56 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.7, 21.7, 26.5, 47.9, 61.8, 125.9, 127.5, 127.7, 128.1, 128.9, 129.8, 141.5, 141.8, 142.7, 174.9. HRMS calcd for $C_{18}H_{23}N_2O_2S$ (M + H) 353.1300, found 353.1302.

(S_S,2*S*,3*S*)-(+)-*N*,2-Dimethyl-3-(4-methylphenylsulfinamido)-5-benzyloxypentanamide (19). Chromatography (EtOAc:*n*-hexane, 50:50) gave 30% of a clear oil; $[\alpha]^{25}_D$ +47.7 (*c* 0.3, $CHCl_3$); IR 3296, 2918, 2850, 1666, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (d, *J* = 6.8 Hz, 3H), 1.95 (m, 1H), 2.09 (m, 1H), 2.40 (s, 3H), 2.49 (m, 1H), 3.23 (s, 3H), 3.40 (m, 1H), 3.62 (m, 2H), 4.51 (m, 2H), 5.29 (d, *J* = 8.8 Hz, 1H), 6.46 (br s, 1H), 7.31 (m, 7H), 7.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.9, 21.7, 30.1, 36.3, 44.0, 56.7, 68.2, 71.5, 73.7, 126.2, 128.3, 128.8, 128.9, 129.8, 138.2, 141.5, 142.2, 175.9. HRMS calcd for $C_{21}H_{28}N_2O_3S$ (M+) 388.1821, found 388.1821.

■ ASSOCIATED CONTENT

Supporting Information. Experimental general procedures and spectroscopic data, ^1H and ^{13}C NMR, for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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