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Asymmetric Synthesis of β-Amino Acid Derivatives Incorporating a Broad Range of Substitution Patterns by Enolate Additions to *tert*-Butanesulfinyl Imines

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Addition of Ti(O*i*-Pr)$_3$ ester enolates to *tert*-butanesulfinyl aldimines and ketimines provided β-substituted, α,β- and β,β-disubstituted, α,β,β- and α,α,β-trisubstituted, and α,α,β,β-tetrasubstituted β-amino acid derivatives in high yields and with high diastereoselectivites. The *N*-sulfinyl-β-amino ester products were further employed as versatile intermediates for both standard solution-phase and solid-phase synthetic transformations, including the synthesis of β-peptide foldamers.

Introduction

β-Amino acids are an important class of building blocks for the synthesis of natural products and pharmaceutical agents.[1] In addition, they are the underlying monomers of β-peptides, which have received considerable attention due to their unique structural properties and interesting biological activities.[2,3]

The most prevalent methods for the asymmetric synthesis of β-amino acids rely on Arndt−Eistert homologations of α-amino acids (eq 1), conjugate additions of amine equivalents to acrylate derivatives (eq 2), hydrogenations of amino acrylates (eq 3), and enolate additions to imine derivatives (eq 4).[2,4−6] Both chiral directing groups and asymmetric catalysts have been used.[7] However, none of these reported methods provide general access to a broad range of highly substituted β-amino acids. Arndt−Eistert homologations have successfully been applied toward the synthesis of β-monosubstituted β-amino acid derivatives.[2] Recently, α-alkylation of the intermediate diazoketone was reported to yield α,β-disubstituted β-amino acids in moderate to high diastereoselectivities.[8] However, homologation of α,α-disubstituted α-amino acids is extremely problematic and results in low yields and diastereoselectivities.[2,6] Furthermore, the use of carbamate-protected α-amino acid inputs limits the diversity of side chains that may be introduced.

Michael additions of amine equivalents to acrylates represent one of the most direct methods for the synthesis of β-substituted β-amino acids. Asymmetric induction has been achieved with chiral amines, chiral acetates, and chiral catalysts.[2,9] In one account, α-substitution was reported via diastereoselective alkylation of the enolate resulting from conjugate addition.[10] To date, the enantioselective addition of an amine equivalent to an α,β-disubstituted acrylate or a β,β-disubstituted acrylate to afford α,β- or β,β-disubstituted β-amino acids, respectively, has not been reported.

Catalytic asymmetric hydrogenations of amino acrylates have been successfully applied toward the synthesis of β-substituted β-amino acids.[4,11] One promising example is the hydrogenation of *N*-acylamino acrylates with Rh-bisphosphine ligand systems described by Zhu et al.[11] Moderate to high enantioselectivities were observed for both *E*- and *Z*-β-alkyl β-amino acrylates; however, for β-aryl β-amino acrylates, little or no selectivity was observed. Furthermore, the hydrogenation of an α-sub-

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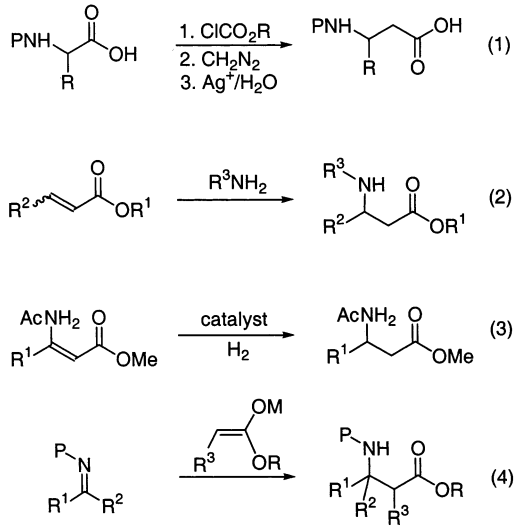


FIGURE 1. Alternative strategies for *β*-amino acid synthesis.

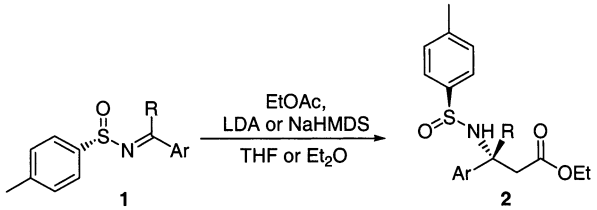
stituted amino acrylate has not been reported and higher substitution patterns (i.e., α,α- or *β*,*β*-disubstitution) are intrinsically not accessible.

Of the aforementioned strategies, asymmetric Mannich reactions provide a unique opportunity for directly and selectively introducing substituents at both the α- and *β*-positions through the choice of the aldimine/ketimine electrophile and the substituted enolate nucleophiles employed. Asymmetric induction has been achieved with chiral imine substituents (i.e., SAMP/RAMP, carbohydrates, *N*-sulfinyl imines), chiral carboxylate derivatives, and enolate formation with chiral bases such as sparteine.[4−6] Recently, catalytic, asymmetric Mannich reactions have been used to prepare a subset of α,α,*β*-trisubstituted *β*-amino acid derivatives with high enantioselectivities.[12,13]

Although imines are versatile intermediates for the synthesis of *β*-amino acid derivatives, high stereoselectivities have not been reported for most classes of highly substituted *β*-amino acids. In addition, the *N*-substituents necessary for achieving good diastereoselectivities are often inconvenient to remove, requiring multiple steps or harsh conditions.[12] One of the most promising methods, reported by Davis et al. in a limited study, is the addition of enolates of acetate esters to *N*-*p*-toluenesulfinyl imines **1**. Not only are the *N*-sulfinyl *β*-amino esters **2** obtained in high yields and with high diastereoselectivities, but the sulfinyl group can readily be removed by brief treatment with stoichiometric HCl in protic solvents (Scheme 1).[14−17]

In direct comparisons of nucleophilic additions to *p*-toluenesulfinyl imines and *tert*-butanesulfinyl imines,

SCHEME 1



		Yield, dr
Ar = Ph	R = H	82%, 98:2
Ar = Ph	R = Me	84%, 99:1
Ar = 3-pyridine	R = H	72%, 82:18

higher diastereoselectivities and fewer side reactions are observed for additions to *tert*-butanesulfinyl imines.[18,19] In addition, *tert*-butanesulfinyl imines **3** are readily prepared in high yields via the $CuSO_4$ or $Ti(OEt)_4$ mediated condensation of aldehydes or ketones with enantiopure *tert*-butanesulfinamide, which can be synthesized in 71−75% overall yield from inexpensive precursors.[20]

Prompted by the excellent results of Davis and the desirable properties of *tert*-butanesulfinyl imines we explored the addition of enolates to *tert*-butanesulfinyl imines and have published a preliminary communication on this work.[21] Since our initial report, Silverman and co-workers have reported the traceless solid-phase synthesis of aromatic *β*-amino acid containing peptides via enolate additions to *tert*-butanesulfinyl imines.[22]

In this paper, we offer a full account of our efforts utilizing *tert*-butanesulfinyl imines as precursors for the asymmetric synthesis of *β*-substituted, α,*β*- and *β*,*β*-disubstituted, α,*β*,*β*- and α,α,*β*-trisubstituted, and α,α,*β*,*β*-tetrasubstituted *β*-amino acid derivatives. Furthermore, we demonstrate that the *tert*-butanesulfinyl group can serve not only as an imine activating and chiral directing group, but also as a versatile amine protecting group for subsequent synthetic transformations. Last, we demonstrate that *tert*-butanesulfinyl protected *β*-amino acids are ideal building blocks for the efficient solid-phase synthesis of *β*-peptide foldamers.

Results and Discussion

Acetate Enolates. Initial studies explored the acetate ester enolate addition to sulfinyl aldimine **3d**, derived from benzaldehyde. Various metal enolates and solvents were examined for their effect on the diastereoselectivity of the addition. Low diastereoselectivity was observed with lithium enolates generated by treatment of methyl acetate with LDA in THF (entry 1, Table 1). Substituting a noncoordinating solvent (entry 2) or the more ionic sodium enolate (entry 3) did not increase the diastereo-

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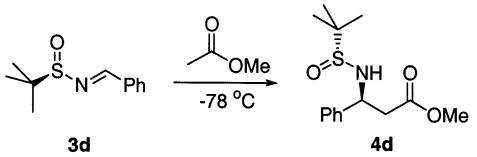
TABLE 1. Optimization of Enolate Additions to Sulfinyl Imine 3d

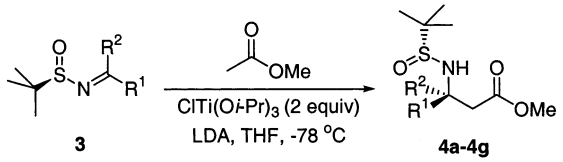


3d **4d**

entry	base	solvent	yield (%)	dr[a]
1	LDA	THF	76	83:17
2	LDA	Et_2O	91	67:33
3	NaHMDS	THF	89	75:25
4	NaHMDS	Et_2O	78	96:4
5	LDA/1 equiv of $ClTi(Oi\text{-}Pr)_3$	THF	90	87:13
6	LDA/2 equiv of $ClTi(Oi\text{-}Pr)_3$	THF	90	98:2
7	LDA/3 equiv of $ClTi(Oi\text{-}Pr)_3$	THF	90	99:1
8	LDA/4 equiv of $ClTi(Oi\text{-}Pr)_3$	THF	90	99:1

[a] Diastereomeric ratios determined through peak integration from HPLC analysis of MTPA amide derivatives prepared from crude reaction mixtures.

TABLE 2. Synthesis of β-Substituted Amino Esters 4 by Addition of Acetate Enolates to Imines 3



3 **4a-4g**

entry	imine	product	R^1	R^2	yield (%)	dr
1	**3a**	**4a**	Me	H	94	99:1[a]
2	**3b**	**4b**	*i*-Pr	H	85	98:2[a]
3	**3c**	**4c**	*i*-Bu	H	80	98:2[a]
4	**3d**	**4d**	Ph	H	90	98:2[a]
5	**3e**	**4e**	3-pyridine	H	70	95:5[b]
6	**3f**	**4f**	*i*-Pr	Me	85	99:1[a]
7	**3g**	**4g**	Ph	Me	89	98:2[a]

[a] Diastereomeric ratios determined through peak integration from HPLC analysis of MTPA amides prepared from crude reaction mixtures. [b] Diastereomeric ratios determined through ^1H NMR integration of crude reaction mixtures.

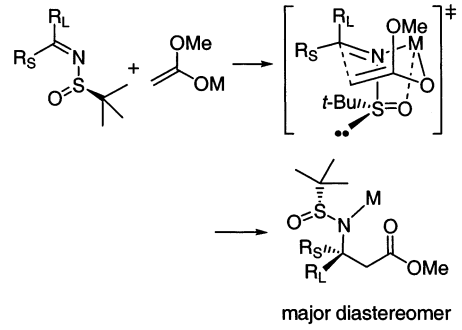
selectivity. Addition of the sodium enolate in Et_2O, however, provided a substantial increase in diastereoselectivity (entry 4), which is consistent with observations made by Davis and co-workers for the corresponding addition to the *p*-toluenesulfinyl imine **1** (R = H). However, additions of sodium enolates to other *N*-sulfinyl imines were not as selective.

Transmetalation of the lithium enolate to a more covalent titanium enolate provided higher diastereoselectivities (Table 1).[17,21] The equilibrium between the lithium enolate, the lithium−titanium−ate complex, and the titanium enolate can be modulated by varying the stoichiometry of $ClTi(Oi\text{-}Pr)_3$.[23] An appreciable improvement in diastereoselectivity was observed upon increasing the $ClTi(Oi\text{-}Pr)_3$ stoichiometry from 1 to 2 equiv. At higher stoichiometries of $ClTi(Oi\text{-}Pr)_3$, only slight improvements in diastereoselectivities were observed. Consequently, further acetate enolate additions were performed with 2 equiv of $ClTi(O\text{-}iPr)_3$. The enolate addition reactions were also typically performed with 2 equiv of enolate relative to the *N*-sulfinyl imine. Use of an excess of the inexpensive enolate is not required, but ensures that the reaction proceeds to completion.

Using these optimized conditions, titanium enolate additions to aryl-, branched alkyl-, and unbranched alkyl-*tert*-butanesulfinyl aldimines were explored. For all imine substrates the desired β-substituted *N*-sulfinyl-β-amino esters were obtained in high yields and with high diastereoselectivities (Table 2). Impressively, addition to 3-pyridyl imine **3e** proceeded with high selectivity (95:5 dr), while prior attempts by Davis and co-workers required the replacement of the *N*-*p*-toluenesulfinyl group with the sterically larger *N*-2-methoxynaphthylsulfinyl group to achieve an 89:11 dr.[16] Notably, enolate additions to *N*-*tert*-butanesulfinyl ketimines (entries 6 and 7) afforded β,β-disubstituted β-amino esters in very high yields and stereoselectivities.

The absolute configurations of the β-amino ester products **4a**[24] and **4e**[16] were determined by comparison of the optical rotation of the free amino esters with the literature values. The absolute configurations of **4d** and **4g**[14] were determined by comparison of the optical rotations of the *N*-benzoyl derivatives with the literature values. The configurations for other derivatives were assigned by analogy. Interestingly, the same sense of induction is observed in the addition of lithium, sodium, and titanium enolates to *tert*-butanesulfinyl imines. The observed diastereoselectivity can be explained through the six-membered transition state shown in Scheme 2 (vide infra), where the enolate addition occurs from the least hindered face of the imine.

SCHEME 2



Additions of α-Substituted Ester Enolates to Imines 3. We surmised that the high diastereoselectivities observed in the acetate ester enolate additions to sulfinyl imines **3** would translate into high diastereoselectivities for the corresponding addition of enolates prepared from α-substituted esters. Such additions would provide a unique entry into highly substituted β-amino acid derivatives with the selective formation of α,β-disubstituted or α,β,β-trisubstituted-β-amino esters.

Additions of titanium enolates of α-substituted esters to a variety of sulfinyl imines **3** afforded substituted *N*-sulfinyl-β-amino esters in high yields and diastereoselectivities (Table 3). Unbranched alkyl, branched alkyl, and aromatic substituents were successfully and stereoselectively incorporated at the β-position and alkyl and benzyl substitutents were successfully incorporated at the α-position, all with moderate to high diastereoselectivities (83:17:0:0 to 96:4:0:0). Impressively, similarly high diastereoselectivites were observed for the α,β,β-trisubstituted derivative **4q** (91:9:0:0).

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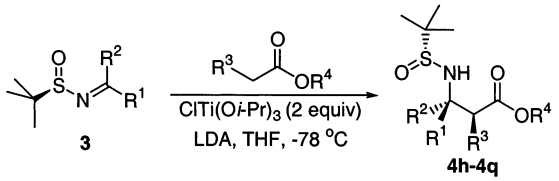
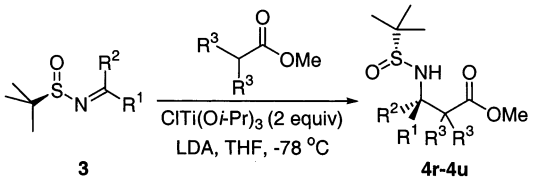
TABLE 3. Synthesis of α-Substituted *β*-Amino Esters



entry	imine	product	R_1	R_2	R_3	R_4	yield (%)	dr
1	**3a**	**4h**	Me	H	Me	Me	96	92:7:1:0[a]
2	**3c**	**4i**	*i*-Bu	H	Me	Me	81	95:3:2:0[a]
3	**3c**	**4j**	*i*-Bu	H	Me	CMe_3	87	59:19:17:5[a]
4	**3c**	**4k**	*i*-Bu	H	Me	4-MeOBn	85	88:12:0:0[b]
5	**3d**	**4l**	Ph	H	Me	Me	85	96:4:0:0[a]
6	**3i**	**4m**	Et	H	Bn	Me	67	90:10:0:0[a]
7	**3i**	**4n**	Et	H	Bn	4-MeOBn	70	93:7:0:0[b]
8	**3a**	**4o**	Me	H	4-MeOBn	Me	65	83:17:0:0[a]
9	**3a**	**4p**	Me	H	4-MeOBn	4-MeOBn	70	89:11:0:0[b]
10	**3g**	**4q**	Ph	Me	Me	Me	81	91:9:0:0[b]

[a] Diastereomeric ratios determined through peak integration from HPLC analysis of filtered, crude reaction mixtures. [b] Diastereomeric ratios determined through ^{1}H NMR integration of crude reaction mixtures; the other two isomers were not observed.

TABLE 4. Synthesis of α,α,*β*-Trisubstituted and α,α,*β*,*β*-Tetrasubstituted *β*-Amino Esters



entry	imine	product	R^1	R^2	R^3	yield (%)	dr[a]
1	**3c**	**4r**	*i*-Bu	H	Me	83	99:1
2	**3d**	**4s**	Ph	H	Me	86	99:1
3	**3g**	**4t**	Ph	Me	Me	86	99:1
4	**3g**	**4u**	Ph	Me	$-(CH_2)_5-$	65	99:1

[a] Diastereomeric ratios determined through peak integration of LC-MS analysis of filtered, crude reaction mixtures.

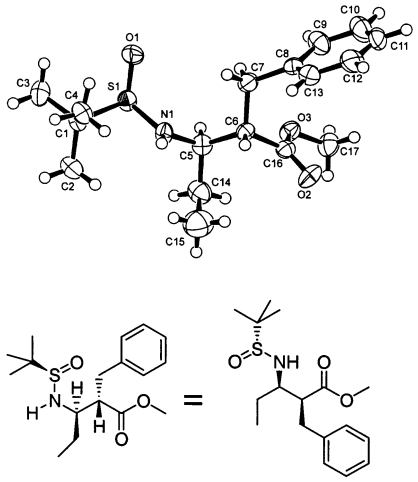


FIGURE 2. ORTEP diagram of **4m**.

Several alternatives to methyl esters were examined to facilitate deprotection of the α-substituted derivatives for further synthetic transformations (vide infra). Addition of the enolate of *tert*-butyl propionate to imine **3c** resulted in poor diastereoselectivity (entry 3). However, addition of enolates of the less sterically encumbered *p*-methoxybenzyl esters afforded the *N*-sulfinyl *β*-amino esters in comparable yields and diastereoselectivities to the corresponding methyl esters (entries 4, 7, and 9).

Significantly, when α,α-disubstituted enolates were employed (Table 4), α,α,*β*-trisubstituted and α,α,*β*,*β*-tetrasubstituted *β*-amino esters were obtained in moderate to high yields (65−86%) and with excellent diastereoselectivity (99:1 in all cases).

The absolute configuration of **4h** was determined by comparison of the optical rotation of the *N*-benzoyl methyl ester to the literature value.[25] The absolute configuration of **4i** was determined by comparison of the optical rotation of the *N*-Boc methyl ester to the literature value.[26] The absolute configuration of **4m** was determined by X-ray crystallography of the major diastereomer (Figure 2). The absolute configurations of other reaction products were assigned by analogy.

The observed diastereofacial selectivities (vide supra) for the additions are consistent with a Zimmerman−Traxler-type six-membered transition state **TS-1** with coordination of the imine nitrogen and the sulfinyl oxygen to titanium (Scheme 3). The *tert*-butyl substituent of the *N*-sulfinyl directing group shields the *Re* face resulting in selective attack of the enolate on the *Si* face. The relative stereochemistry of the α- and *β*-substituents in the product is further defined by the geometry of the sulfinyl imine substrate for which the *E*-isomer predominates.[19]

The *tert*-Butanesulfinyl Protecting Group. The *tert*-butanesulfinyl group possesses many desirable characteristics as a chiral directing group for the synthesis of a broad range of *β*-amino esters. In the following applications we further demonstrate that the *tert*-butanesulfinyl group also serves as a versatile protecting group that enables the direct incorporation of *N*-sulfinyl-

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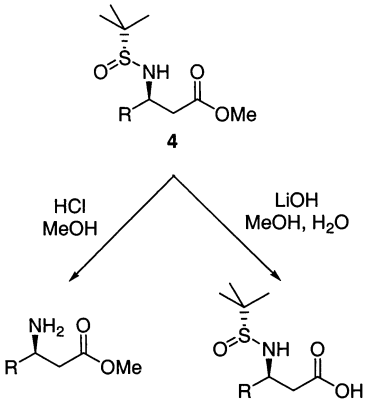
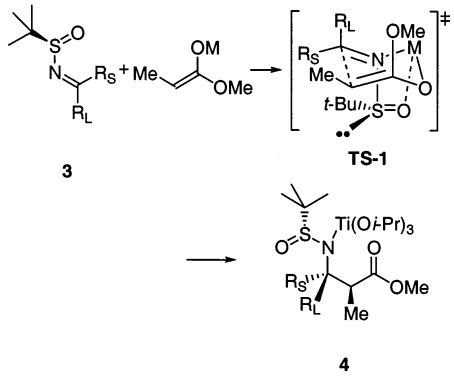


FIGURE 3. Orthogonal deprotection of **4**.

SCHEME 3

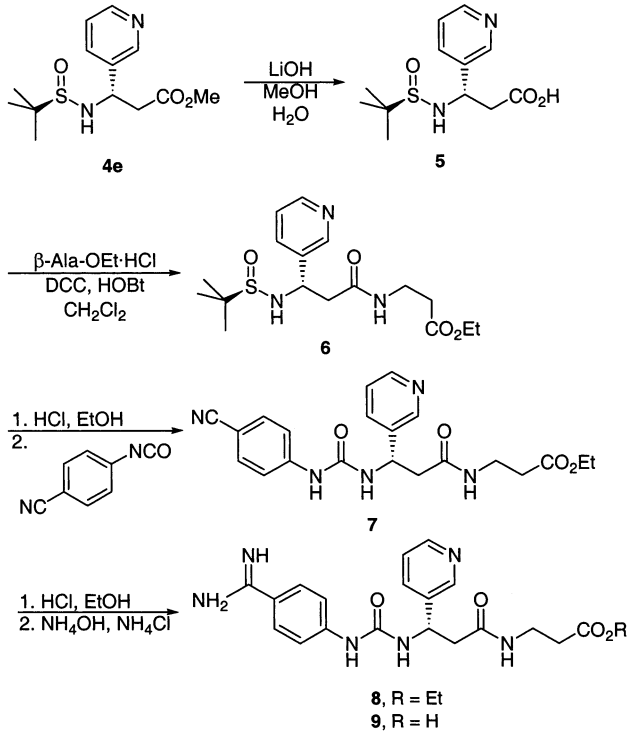


β-amino esters **4** into more complex structures. As shown in Figure 3, the *tert*-butanesulfinyl group parallels the reactivity of the Boc protecting group in that it is stable to base and is cleaved with acid. Furthermore, like the Boc group, the *tert*-butanesulfinyl group dramatically reduces the nucleophilicity of sulfinyl-substituted amines.

To demonstrate the utility of the *tert*-butanesulfinyl protecting group we carried out the formal synthesis of GPIIbIIIa antagonist **9** (Scheme 4) patented by Monsanto Co. (St. Louis) that contains a β-3-pyridyl-β-amino acid.[27] The enantiomerically pure starting material **4e** was prepared by addition of the enolate of methyl acetate to 3-pyridylmethylene-*N*-*tert*-butanesulfinyl imine **3e** (entry 5, Table 2). The methyl ester was saponified with LiOH, without cleavage of the sulfinyl group, to afford *N*-sulfinyl-β-amino acid **5** after workup. Acid **5** was then coupled under standard amide-bond forming conditions (DCC, HOBt) with β-alanine ethyl ester to provide **6** in 85% overall yield for the two steps, without acylation of the sulfinyl nitrogen. The *N*-sulfinyl group was then removed with 2 equiv of HCl in EtOH to afford the amine, which was reacted directly with 4-cyanophenylisocyanate to afford urea **7**. Subsequent conversion to amidine **8** constitutes a formal synthesis of the antagonist **9**.

With the considerable interest in β-peptides, we next examined the application of *N*-sulfinyl-protected β-amino acids in the solid-phase synthesis of a β-peptide **10** known to adopt a helical conformation and the corresponding

SCHEME 4



amide **11**.[28] Peptide **10** consists of three β-substituted β-amino acids **12**−**14** that are derived from *N*-sulfinyl-β-amino esters **4a**−**c** (Figure 4).

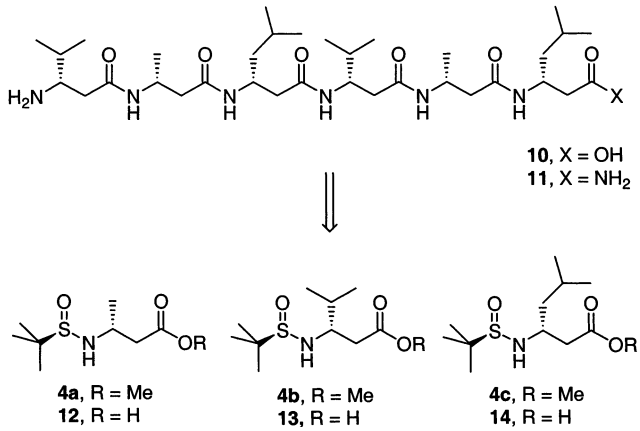


FIGURE 4. Retrosynthesis of hexapeptides **10** and **11**.

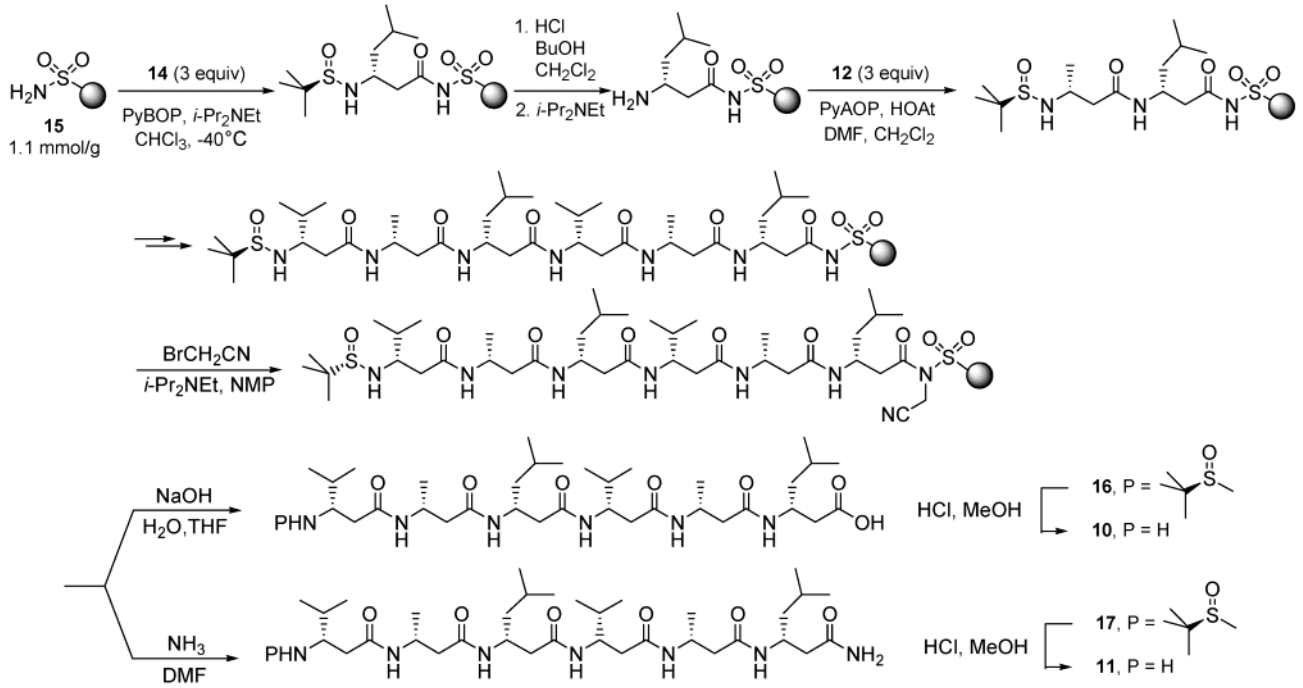
The solid-phase syntheses of **10** and **11** were performed on aminomethyl polystyrene derivatized with an alkanesulfonamide linker, 4-sulfamylbutyryl resin **15** (Scheme 5).[29] The initial *N*-sulfinyl β-amino acid **14** was introduced with a slight modification of the published conditions (3 equiv of **14**, 3 equiv of PyBOP, and 9 equiv of *i*-Pr_2NEt in $CHCl_3$ at −40 °C). The *N*-sulfinyl group was subsequently removed with HCl in $BuOH/CH_2Cl_2$. After rinsing with *i*-Pr_2NEt in CH_2Cl_2 to neutralize the amine, acylation of the primary amine was accomplished by treatment with 3 equiv of *N*-sulfinyl β-amino acid **12**, 3

(27) Tjoeng, F. S.; Toth, M. V.; McMackins, D. E.; Adams, S. P. U.S. Patent Number 5,314,902.

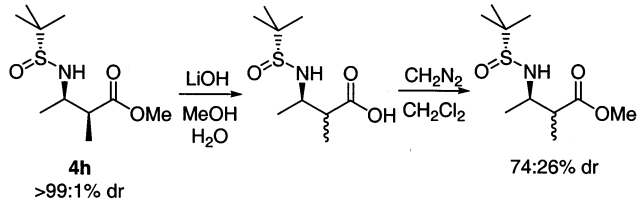
(28) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, (21), 2015−2022.

(29) Backes, B. J.; Ellman, J. A. *J. Org. Chem.* **1999**, *64* (7), 2322−2330.

SCHEME 5



SCHEME 6



equiv or PyAOP, 3 equiv of HOAt, and 9 equiv of *i*-Pr_2-NEt in CH_2Cl_2/DMF (9:1). Introduction of the remaining residues was accomplished through iterative cycles of deprotection and acylation with the appropriate *N*-sulfinyl *β*-amino acid to afford the support-bound *N*-sulfinyl hexapeptide. The *N*-sulfinyl peptides **16** and **17** were then released from support by activation of the acylsulfonamide with $BrCH_2CN$ followed by nucleophilic cleavage with NaOH and NH_3. Notably, by employing this activation and cleavage protocol, a wide range of alcohol and amine nucleophiles can clearly be introduced into the foldamer product.[30] Removal of the *N*-terminal sulfinyl protecting group was then accomplished with use of standard conditions to afford the desired peptides **10** and **11** in 35% and 40% overall yields, respectively.

Preparation of α-Substituted *β*-Amino Acids. A known complication in the preparation of α-substituted *β*-amino acids is the epimerization of the α-stereocenter under alkaline conditions.[26] Saponification of the methyl ester as described previously (LiOH in MeOH/H_2O) for α,*β*-disubstituted *N*-sulfinyl *β*-amino ester **4h** resulted in the partial epimerization of the α-stereocenter (Scheme 6). Seebach circumvented epimerization by the two-step process of Ti-mediated transesterification of the methyl esters of α-substituted *β*-amino acids to the corresponding benzyl esters followed by hydrogenation.[31]

We investigated nonalkaline methods for deprotection of the ester to develop a more efficient, single-step procedure for preparing diastereomerically pure *N*-sulfinyl *β*-amino acids with α-substitution. We first explored bis(tributyltin) oxide (BBTO) mediated hydrolysis of the methyl ester based upon a report of the BBTO-mediated hydrolysis of Boc- and Cbz-protected α,*β*-disubstituted *β*-phenylalanine esters without epimerization.[32] A modification of the original procedure by Salomon and coworkers[33] was used to deprotect ester **4o** and isolate *N*-sulfinyl *β*-amino acid **18** (Scheme 7). Treatment of **4o** with BBTO in toluene at 80 °C followed by filtration (see experimental details) through silica gel afforded acid **18** with minor tin impurities. The resulting residue was dissolved in MeOH and treated with tetraalkylammonium hydroxide resin to sequester the carboxylate via ionic interactions. The resin was then washed to remove the tin impurities followed by release of the pure carboxylic acid **18** (78% from **4o**) by treatment with acetic acid in MeOH. Although this one-step method is efficient and high yielding, one disadvantage is the disposal cost for large-scale reactions that results from the use of stoichiometric quantities of a toxic tin reagent.

We therefore explored orthogonal acid-labile ester protecting groups. To effect sulfinyl cleavage under acidic conditions an external nucleophile, e.g., Cl^- or methanol, is required. For this reason treatment of *N*-sulfinyl *β*-amino acid methyl ester **4h** with neat TFA does not result in cleavage of the *N*-sulfinyl group. In contrast, acid labile esters can be cleaved under these conditions and, therefore, should serve as convenient orthogonal protecting groups.

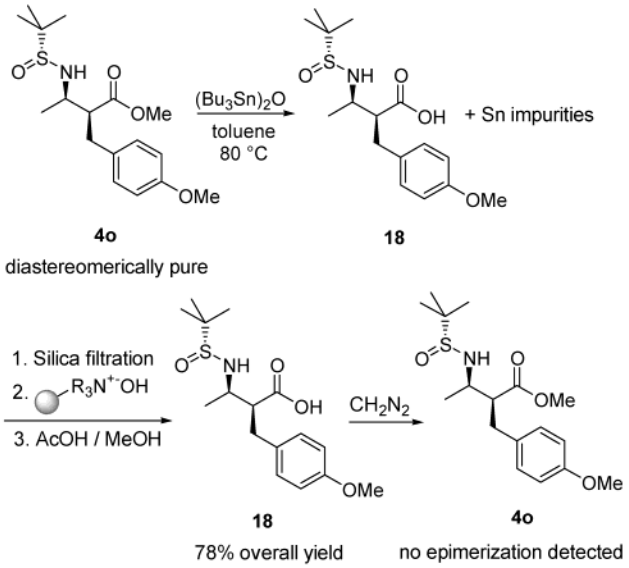
(30) Backes, B. J.; Virgilio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1996**, *118* (12), 3055−3056.

(31) Seebach, D.; Hungerbuehler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zueger, M. *Synth. Stuttgart* **1982**, (2), 138−141.

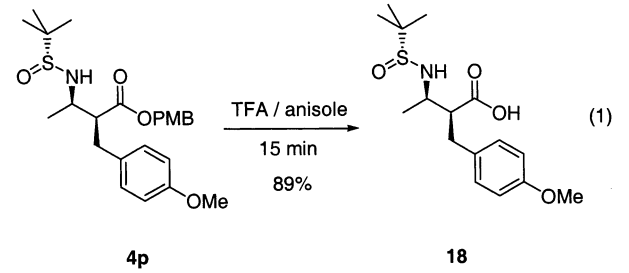
(32) Martin, L.; Cornille, F.; Turcaud, S.; Meudal, H.; Roques, B. P.; Fournie-Zaluski, M. C. *J. Med. Chem.* **1999**, *42* (3), 515−525.

(33) Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1991**, *32* (34), 4239−4242.

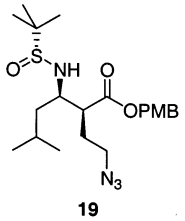
SCHEME 7



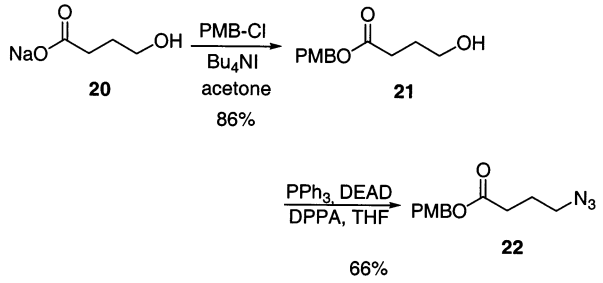
The addition of *tert*-butyl propionate to imine **3c** did not proceed with high diastereoselectivity, potentially due to the relatively large steric environment about the enolate (see entry 3, Table 3). The addition of PMB propionate to imine **3c**, however, proceeded with high diastereoselectivity (entry 4, Table 3), comparable to that observed for the corresponding methyl ester (entry 2, Table 3). Similarly high selectivities were also observed for PMB ester additions to form α,β-disubstituted derivatives **4n** and **4p** (Table 3). Treatment of PMB-protected *N*-sulfinyl β-amino ester **4p** with TFA/anisole afforded carboxylic acid **18** in 89% yield with <5% sulfinyl cleavage (eq 1).



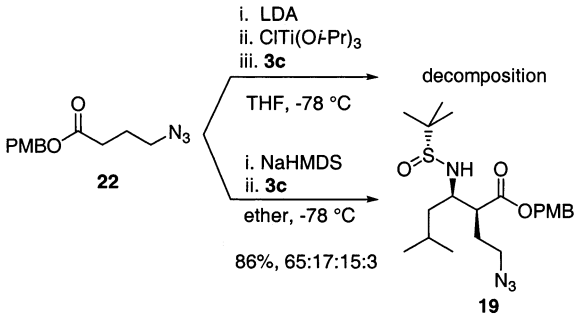
Amine-Containing Side Chains. In a collaborative effort with the Gellman research group to synthesize β-peptides that contain water-solubilizing functional groups, we developed a synthesis of the *N*-sulfinyl β-amino ester **19**, which incorporates an azide in the α-side chain. The azide is stable to the synthetic steps necessary for the preparation of β-peptides, but should readily be unmasked under mild reductive conditions to provide the desired primary amine.



SCHEME 8



SCHEME 9



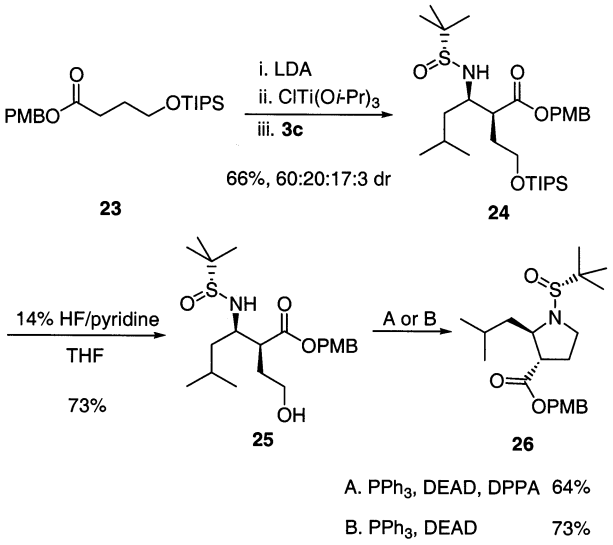
Synthesis of the azido-substituted ester **19** was initiated by the alkylation of sodium 4-hydroxybutyrate **20** with 4-methoxybenzyl chloride to afford alcohol **21** in 86% yield (Scheme 8). Alcohol **21** was then converted to the γ-azido ester **22** in 66% yield with use of standard Mistunobu reaction conditions.[34]

Formation of the lithium enolate of **22** followed by transmetalation with $ClTi(Oi\text{-}Pr)_3$ resulted in rapid decomposition even at −78 °C due to the incompatibility of the azide functionality with the Lewis acid. However, formation of the sodium enolate of **22** followed by treatment with sulfinyl imine **3c** afforded the desired azido-substituted *N*-sulfinyl β-amino ester **19** in 86% yield as a 65:17:15:3 mixture of diastereomers (Scheme 9). Although the reaction proceeds with only modest stereoselectivity, diastereomerically pure material can be isolated via preparative HPLC. The stereochemistry of diastereomerically pure **19** was confirmed by obtaining an X-ray crystal structure of the corresponding 4-nitrobenzyl amide (see Experimental Section). To our knowledge, α,β-disubstituted β-amino acids incorporating amine side chains have not previously been reported.

We also explored the addition of the enolate of the PMB ester of γ-triisopropylsilyloxybutanoic acid (**23**) to sulfinyl imine **3c** in an attempt to devise a more stereoselective approach to *N*-sulfinyl β-amino ester **19** (Scheme 10). The reaction proceeded in an acceptable 66% yield, but poor diastereoselectivity was observed, presumably due to the large size of the silyloxy group. Conversion of the silyl ether to the desired azide further proved to be problematic. The Mitsunobu reaction of intermediate alcohol **25** (DPPA, PPh_3, DEAD) resulted in competitive intramolecular alkylation of the sulfinyl nitrogen to provide the cyclic β-amino acid **26** as the exclusive product in 64% yield. By eliminating DPPA from the Mitsunobu conditions, the reaction yield of the cyclic β-amino ester

(34) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *18* (23), 1977−1980.

SCHEME 10



improved to 73%. While not the initial goal, the sequence shown in Scheme 10 provides rapid entry to constrained β-amino acids with substituents at the β-position.

Conclusion

A general method is described for the high-yielding and stereoselective synthesis of *N*-sulfinyl β-amino esters **4** with β-substitution, α,β- and β,β-disubstitution, α,β,β- and α,α,β-trisubstitution, and $\alpha,\alpha,\beta,\beta$-tetrasubstitution. The *N*-sulfinyl group was further developed as a versatile nitrogen-protecting group enabling the efficient application of the *N*-sulfinyl protected β-amino esters **4** in the synthesis of the IIbIIIa antagonist **9** and in the solid-phase synthesis of β-peptides **10** and **11**. Additionally, two alternative approaches were developed for the single step conversion of *N*-sulfinyl α-substituted β-amino esters to the corresponding acids without epimerization. The reported methods should have wide utility in the synthesis of pharmaceuticals, natural products, and foldamers due to the broad generality of the β-amino ester synthesis methods and the versatility of the *N*-sulfinyl-β-amino ester products.

Experimental Section

General Procedure. Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. 4-Sulfamylbutyryl resin **15** was purchased from Novabiochem. ClTi(O*i*-Pr)$_3$ was fractionally distilled and stored under N_2 as a neat liquid which solidified upon standing. All solvents were distilled under N_2 from the following drying agents immediately before use: tetrahydrofuran (THF) and diethyl ether Et_2O were distilled from Na/benzophenone ketyl; dichloromethane (CH_2Cl_2), diisopropylamine (*i*-Pr$_2$NH), diisopropylethylamine (*i*-Pr$_2$NEt), and pyridine were distilled from CaH_2. Unless otherwise noted, all reactions were carried out in flame-dried glassware under an inert N_2 atmosphere. Chromatography was carried out with Merck 60-Å 230−400 mesh silica gel. Reaction progress was monitored with thin-layer chromatography on Merck 60-Å F_{254} 0.25 μm silica plates. Unless otherwise noted, all organic layers were dried over anhydrous $MgSO_4$, and all solvents were removed with a rotary evaporator. IR spectra of liquids were recorded as thin films on NaCl plates and IR spectra of solids were recorded as KBr pellets and only partial data are listed. Unless otherwise noted, NMR spectra were obtained in $CDCl_3$ at room temperature. Chemical shifts in NMR spectra are expressed in ppm, and all coupling constants are expressed in Hz. Unless otherwise noted, analytical HPLC analysis was performed with a 25 cm × 5 μm ID Microsorb Si normal phase column with UV detection or HP Zorbax C8 reverse phase column with UV and electrospray ionization.

General Procedure for the Ti Enolate Addition to *N*-*tert*-Butanesulfinyl Imines. A solution of *i*-Pr$_2$NH (2.20 equiv) in THF (0.20 M) was cooled to 0 °C. *n*-Butyllithium (*n*-BuLi) (2.00 M, 2.10 equiv) was added via syringe and the solution was stirred for 30 min. The solution was then cooled to −78 °C and a solution of the ester in 1 mL of THF (2.00 equiv) was added via syringe and the reaction solution was stirred for 30 min. To this solution was added ClTi(O*i*-Pr)$_3$ (4.20 equiv) in THF (1.00 M) and the orange-colored enolate was stirred for 30 min. A solution of the *N*-sulfinyl imine (1.00 equiv) in THF (5.00 M) was slowly added via syringe and the solution was stirred for 3 h at −78 °C. Upon reaction completion as determined by TLC, a saturated aqueous solution of NH_4Cl (10 equiv) was added and the suspension was warmed to room temperature. The mixture was diluted with H_2O and vigorously stirred to dissolve the Ti precipitate. The mixture was then decanted into a separatory funnel, and the remaining solid was diluted with equal parts of H_2O and EtOAc and vigorously stirred for 15 min. The mixture was then added to the separatory funnel and the organic layer was collected. The aqueous layer was then extracted with EtOAc (3×). The combined organic layers were washed with brine, dried, and concentrated to give the *N*-sulfinyl-β-amino ester product.

General Procedure for Conversion of *N*-Sulfinyl β-Amino Esters 4 to MTPA Amide Derivatives. Reactions were performed in flame-dried 13 × 100 mm^2 test tubes equipped with magnetic stir bars. To a solution of approximately 5 mg of the crude reaction product in 0.1 mL of MeOH was added 0.1 mL of 4 N HCl/dioxane. After stirring for 30 min, the solvent and HCl were removed under a stream of N_2. To the residue was added MeOH (0.5 mL). The solution was then stirred for 5 min and evaporated to remove residual HCl. Pyridine (0.1 mL) and CH_2Cl_2 (0.1 mL) were added to dissolve the amine. Two drops of neat (*R*)-(−)- or (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride were added to the solution and the solution was stirred for 1 h. To the solution was added 3-(*N*,*N*-dimethylamino)-1-propylamine (0.1 mL) and the solution was stirred for 10 min. The reaction mixture was then diluted with ether, washed (1 M HCl, sat. K_2CO_3, and sat. NaCl), then dried. The filtered Et_2O solution was concentrated to give the MTPA amide derivative.

(*R*$_S$,*R*)-(−)-Methyl *N*-(*tert*-Butanesulfinyl)-3-aminobutanoate (4a).[21] The general procedure was followed using 1.50 g (10.2 mmol) of imine **3a**, 2.94 mL (22.4 mmol) of *i*-Pr$_2$NH, 10.7 mL (21.4 mmol) of *n*-BuLi, 1.62 mL (20.4 mmol) of MeOAc, and 10.2 mL (42.8 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined by HPLC analysis of both the (+)- and (−)-MTPA amides, prepared from crude **4a** with the general procedure (99:1 dr, Si column, 20% MTBE/hexanes, 1 mL/min, 256 nm, (*R*,*S*)/(*S*,*R*) diastereomer, t_R = 22.4 min; (*R*,*R*)/(*S*,*S*) diastereomer, t_R = 18.2 min). Pure **4a** was obtained in 94% yield after silica gel chromatography with 50% EtOAc/hexanes as eluent: mp 69 °C; $[\alpha]^{23}_D$ −101.3 (*c* 1.0, $CHCl_3$); IR 1051, 1737, 3200 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.21 (s, 9H), 1.28 (d, 3H, *J* = 4.5 Hz), 2.55 (dd, 1H, *J* = 16, 6.5 Hz), 2.66 (dd, 1H, *J* = 15.8, 5.5 Hz), 3.69 (s, 3H), 4.01−4.03 (m, 1H), 4.11 (s, 1H); ^{13}C NMR (125 MHz) δ 22.5, 25.3, 41.8, 48.4, 51.7, 55.4, 172.1. Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 48.84; H, 8.65; N, 6.33. Found: C, 49.02; H, 8.42; N, 6.24.

(*R*$_S$,*S*)-(−)-Methyl *N*-(*tert*-Butanesulfinyl)-3-amino-4-methylpentanoate (4b).[21] The general procedure was followed using 1.50 g (8.56 mmol) of imine **3b**, 2.47 mL (18.8 mmol) of *i*-Pr$_2$NH, 9.00 mL (18.0 mmol) of *n*-BuLi, 1.36 mL (17.1 mmol) of MeOAc, and 8.59 mL (35.9 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined by HPLC analysis

of both the (+)- and (−)-MTPA amides, prepared from crude **4b** with the general procedure (98:2 dr, Si column, 90:10 hexanes/EtOAc, 1 mL/min, 260 nm, (*R*,*S*)/(*S*,*R*) diastereomer, t_R = 16.1 min; (*R*,*R*)/(*S*,*S*) diastereomer, t_R = 12.7 min). Pure **4b** was obtained in 89% yield after silica gel chromatography with 50% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −67.0 (*c* 1.0, $CHCl_3$); IR 1055, 1733, 3290 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (d, 3H, *J* = 6.8 Hz), 0.91 (d, 3H, *J* = 6.8 Hz), 1.21 (s, 9H), 1.85 (m, 1H), 2.61 (dd, 1H, *J* = 16, 6.2 Hz), 2.72 (dd, 1H, *J* = 16, 5.0 Hz), 3.30−3.34 (m, 1H), 3.68 (s, 3H), 4.06 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (125 MHz) δ 18.6, 18.9, 22.7, 32.2, 37.6, 51.7, 56.0, 59.3, 172.6. Anal. Calcd for $C_{11}H_{23}NO_3S$: C, 52.98; H, 9.30; N, 5.62. Found: C, 52.72; H, 9.23; N, 5.42.

(*R*$_S$,*S*)-(−)-Methyl *N*-(*tert*-Butanesulfinyl)-3-amino-5-methylhexanoate (4c).[21] The general procedure was followed using 1.50 g (7.92 mmol) of imine **3c**, 2.29 mL (17.4 mmol) of *i*-Pr_2NH, 8.32 mL (16.6 mmol) of *n*-BuLi, 1.26 mL (15.9 mmol) of MeOAc, and 7.95 mL (33.3 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined by HPLC analysis of both the (+)- and (−)-MTPA amides, prepared from crude **4c** with the general procedure (98:2 dr, Si column, 90:10 hexanes EtOAc, 1 mL/min, 260 nm, (*R*,*S*)/(*S*,*R*) diastereomer, t_R = 12.9 min; (*R*,*R*)/(*S*,*S*) diastereomer, t_R = 10.7 min). Pure **4c** was obtained in 90% yield after silica gel chromatography with 50% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −43.8 (*c* 0.33, $CHCl_3$); IR 1737, 3206 cm^{-1}; ^1H NMR (500 MHz) δ 0.87−0.90 (m, 6H), 1.19 (s, 9H), 1.50−1.60 (m, 1H), 1.70−1.80 (m, 2H), 2.59 (dd, 1H, *J* = 16, 5.5 Hz), 2.80 (dd, 1H, *J* = 16, 5.5 Hz), 3.59−3.61 (m, 1H), 3.68 (s, 3H), 4.08 (d, 1H, *J* = 9.5 Hz); ^{13}C NMR (125 MHz) δ 21.5, 22.3, 22.6, 23.0, 24.6, 40.6, 51.6, 52.2, 172.5. Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.34; H, 7.47; N, 4.94. Found: C, 59.39; H, 7.30; N, 4.80.

(*R*$_S$,*S*)-(−)-Methyl *N*-(*tert*-butanesulfinyl)-3-amino-3-phenylpropanoate (4d).[21] The general procedure was followed using 1.50 g (7.17 mmol) of imine **3d**, 2.07 mL (15.8 mmol) of *i*-Pr_2NH, 7.52 mL (15.1 mmol) of *n*-BuLi, 1.14 mL (14.3 mmol) of MeOAc, and 7.19 mL (30.1 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined by HPLC analysis of both the (+)- and (−)-MTPA amides, prepared from crude **4d** with the general procedure (98:2 dr, Si column, 90:10 hexanes/EtOAc, 1 mL/min, 260 nm, (*R*,*S*)/(*S*,*R*) diastereomer, t_R = 20.5 min; (*R*,*R*)/(*S*,*S*) diastereomer, t_R = 17.2 min). Pure **4d** was obtained in 90% yield after silica gel chromatography with 50% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −113.3 (*c* 1.0, $CHCl_3$); IR 1055, 1737, 3206 cm^{-1}; ^1H NMR (500 MHz) δ 1.23 (s, 9H), 2.87−2.89 (m, 2H), 3.67 (s, 3H), 4.68 (d, 1H, *J* = 4.1 Hz), 4.77−4.80 (m, 1H), 7.27−7.39 (m, 5H); ^{13}C NMR (125 MHz) δ 22.6, 42.0, 51.9, 55.5, 55.7, 127.2, 128.0, 128.6, 140.5, 171.8. Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.34; H, 7.47; N, 4.94. Found: C, 59.39; H, 7.30; N, 4.80.

(*R*$_S$,*S*)-(−)-Methyl *N*-(*tert*-Butanesulfinyl)-3-amino-3-(3-pyridine)propanoate (4e).[21] The general procedure was followed using 1.00 g (4.76 mmol) of imine **3e**, 1.37 mL (10.5 mmol) of *i*-Pr_2NH, 4.99 mL (9.99 mmol) of *n*-BuLi, 0.758 mL (9.51 mmol) of MeOAc, and 4.77 mL (20.0 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined by NMR integration of crude product (>95:5 dr). The identity of the minor diastereomer was confirmed by ^1H NMR analysis of a chromatographically enriched sample of the minor diastereomer. Pure **4e** was obtained through silica gel chromatography by first elution of unreacted imine **3e** with 50:50:1 CH_2Cl_2/CH_3CN/NH_4OH, then elution with 70:30:1 CH_2Cl_2/CH_3CN/NH_4OH to afford pure **4e** in 70% yield: $[\alpha]^{23}_D$ −100.3 (*c* 1.0, $CHCl_3$); IR 1049, 1655, 1731, 3426 cm^{-1}; ^1H NMR (500 MHz) δ 1.25 (s, 9H), 2.92 (m, 2H), 3.67 (s, 3H), 4.76 (d, 1H, *J* = 4.6 Hz), 4.82 (m, 1H), 7.29 (m, 1H), 7.65 (m, 1H), 8.54 (m, 1H), 8.60 (d, 1H, *J* = 2.0 Hz); ^{13}C NMR (125 MHz) δ 22.5, 41.5, 52.0, 53.5, 55.9, 122.5, 134.8, 135.5, 148.9, 149.3, 171.8. Anal. Calcd for $C_{13}H_{20}N_2O_3S$: C, 54.91; H, 7.09; N, 9.85. Found: C, 54.99; H, 6.76; N, 9.66.

(*R*$_S$,*S*)-(−)-Methyl *N*-(*tert*-Butanesulfinyl)-3-amino-3,4-dimethylpentanoate (4f).[21] The general procedure was followed using 0.500 g (2.64 mmol) of imine **3f**, 0.762 mL (5.81 mmol) of *i*-Pr_2NH, 2.77 mL (5.55 mmol) of *n*-BuLi, 0.421 mL (5.28 mmol) of MeOAc, and 2.65 mL (11.1 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined by HPLC analysis of both the (+)- and (−)-MTPA amides, prepared from crude **4f** with the general procedure (99:1 dr, Si column, 2.5% MTBE/hexanes to 20% MTBE/hexanes over 20 min, 1 mL/min, 260 nm, (*R*,*S*)/(*S*,*R*) diastereomer, t_R = 18.2 min; (*R*,*R*)/(*S*,*S*) diastereomer, t_R = 17.6 min). Pure **4f** was obtained in 85% yield after silica gel chromatography with 50% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −78.0 (*c* 1.0, $CHCl_3$); IR 1068, 1209, 1724, 3280 cm^{-1}; ^1H NMR (300 MHz) δ 0.73 (d, 3H, *J* = 10 Hz), 0.78 (d, 3H, *J* = 10 Hz), 1.08 (s, 9H), 1.14 (s, 3H), 1.87−1.92 (m, 1H), 2.45 (d, 1H, *J* = 20 Hz), 2.63 (d, 1H, *J* = 20 Hz), 3.54 (s, 3H), 4.04, (s, 1H); ^{13}C NMR (75 MHz) δ 16.9, 17.0, 22.1, 22.8, 35.3, 42.9, 51.5, 55.7, 58.9, 172.8. Anal. Calcd for $C_{12}H_{25}NO_3S$: C, 54.72; H, 9.57; N, 5.32. Found: C, 54.68; H, 9.60; N, 5.21.

(*R*$_S$,*S*)-(−)-Methyl *N*-(*tert*-Butanesulfinyl)-3-amino-3-phenylbutanoate (4 g).[21] The general procedure was followed using 0.500 g (2.24 mmol) of imine **3g**, 0.646 mL (4.93 mmol) of *i*-Pr_2NH, 2.35 mL (4.70 mmol) of *n*-BuLi, 0.357 mL (4.48 mmol) of MeOAc, and 2.25 mL (9.40 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined by HPLC analysis of both the (+)- and (−)-MTPA amides, prepared from crude **4g** with the general procedure (98:2 dr, Si column, 90:10 hexanes EtOAc, 1 mL/min, 260 nm, (*R*,*S*)/(*S*,*R*) diastereomer, t_R = 12.7; (*R*,*R*)/(*S*,*S*) diastereomer, t_R = 11.5 min). Pure **4g** was obtained in 89% yield after silica gel chromatography with 50% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −41.9 (*c* 1.0, $CHCl_3$); IR 1062, 1206, 1726, 3272 cm^{-1}; ^1H NMR (300 MHz) δ 1.30 (s, 9H), 1.73 (s, 3H), 3.10 (s, 2H), 3.60 (s, 3H), 5.51 (s, 1H), 7.25−7.49 (m, 5H); ^{13}C NMR (75 MHz) δ 23.3, 29.0, 46.7, 52.0, 56.9, 59.2, 125.6, 127.5, 128.8, 146.7, 172.7. Anal. Calcd for $C_{15}H_{23}NO_3S$: C, 60.58; H, 7.79; N, 4.71. Found: C, 60.33; H, 7.87; N, 4.59.

(*R*$_S$,2*S*,3*R*)-(−)-Methyl 3-(*N*-*tert*-Butanesulfinyl)amino-2-methylbutanoate (4h). The general procedure was followed using 0.500 g (3.40 mmol) of imine **3a**, 0.979 mL (7.47 mmol) of *i*-Pr_2NH, 3.57 mL (7.13 mmol) of *n*-BuLi, 0.598 mL (6.79 mmol) of methyl propionate, and 3.41 mL (14.3 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined via HPLC analysis of filtered, crude reaction mixture (92:7:1:0 dr, Si column, 90:10 hexanes/*i*-PrOH; 1 mL/min; 215 nm, major diastereomer; t_R = 27.5, minor diastereomers t_R = 23.7, 25.6, 29.3). The HPLC peaks corresponding to each of the minor diastereomers were confirmed by ^1H NMR. Pure **4h** was obtained in 96% yield after silica gel chromatography with 50% EtOAc/hexanes as eluent: IR 1046, 1728, 3260 cm^{-1}; ^1H NMR (500 MHz) δ 1.18−1.22 (m, 15H), 2.80−2.85 (m, 1H), 3.54−3.60 (m, 1H), 3.70 (s, 3H), 4.17 (d, 1H, *J* = 6.2 Hz); ^{13}C NMR (125 MHz) δ 12.8, 17.8, 22.6, 45.1, 51.7, 53.1, 55.3, 174.8. Anal. Calcd for $C_{10}H_{20}NO_3S$: C, 51.03; H, 8.99; N, 5.95. Found: C, 51.19; H, 8.88; N, 5.81.

Benzoyl derivative for chemical correlation: $[\alpha]^{23}_D$ +40.0° (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz) δ 1.21−1.30 (m, 6H), 2.80−2.85 (m, 1H), 3.73 (s, 3H), 4.37−4.43 (m, 1H), 6.91 (d, 1H, *J* = 8.0 Hz), 7.41−7.50 (m, 3H), 7.77 (m, 2H); ^{13}C NMR (125 MHz) δ 13.8, 16.3, 43.8, 47.4, 51.8, 126.9, 128.5, 131.4, 134.6, 166.5, 174.9.

(*R*$_S$,2*S*,3*R*)-(−)-2,5-Dimethyl-3-(2-methylpropane-2-sulfinylamino)hexanoic Acid Methyl Ester (4i). The general procedure was followed using 0.500 g (2.64 mmol) of imine **3c**, 0.762 mL (5.81 mmol) of *i*-Pr_2NH, 2.77 mL (5.55 mmol) of *n*-BuLi, 0.509 mL (5.28 mmol) of methyl propionate, and 2.65 mL (11.09 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined via HPLC analysis of filtered, crude reaction mixture (95:3:2:0 dr, Si column, 97:3 hexanes/*i*-PrOH; 1 mL/min; 215 nm; major diastereomer, t_R = 27.8 min; minor diastereomers, t_R = 20.6, 22.3, 24.7). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. The HPLC peaks corresponding to each of the minor diastereomers were confirmed

by ^{1}H NMR. Pure **4i** was obtained in 81% yield after column chromatography with 30% EtOAc/hexanes to 75% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −7.3 (*c* 1.0, $CHCl_3$); IR 1048, 1736, 2955 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.78 (d, 3H, J = 6.7), 0.81 (d, 3H, J = 6.7), 1.07 (d, 3H, J = 7.2), 1.13 (s, 9H), 1.15−1.24 (m, 2H), 1.62−1.69 (m, 1H), 2.91−3.01 (m, 1H), 3.24−3.39 (m, 1H), 3.61 (s, 3H), 4.22 (d, 1H, J = 9.3); ^{13}C NMR (100 MHz) δ 13.1, 21.0, 22.6, 23.3, 24.3, 40.4, 44.3, 51.5, 55.8, 57.5, 174.8. Anal. Calcd for $C_{13}H_{27}NO_3S$: C, 56.28; H, 9.81; N, 5.05. Found: C, 56.05; H, 9.82; N, 4.94.

(*R*$_S$,2*S*,3*R*)-(−)-2,5-Dimethyl-3-(2-methylpropane-2-sulfinylamino)hexanoic Acid *tert*-Butyl Ester (4j). The general procedure was followed using 0.500 g (2.64 mmol) of imine **3c**, 0.762 mL (5.81 mmol) of *i*-Pr_2NH, 2.77 mL (5.55 mmol) of *n*-BuLi, 0.795 mL (5.28 mmol) of *tert*-butyl propionate, and 2.65 mL (11.09 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined via HPLC analysis of the filtered, crude reaction mixture (59:19:17:5 dr, Si column, 97:3 hexanes/*i*-PrOH; 1 mL/min; 215 nm; major diastereomer, t_R = 26.8 min; minor diastereomers, t_R = 19.7, 22.0, 24.9). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. The HPLC peaks corresponding to each of the minor diastereomers were confirmed by ^{1}H NMR. Pure **4j** was obtained in 87% yield after column chromatography with 30% EtOAc/hexanes to 75% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −6.4 (*c* 1.0, $CHCl_3$); IR 1049, 1733 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.79 (d, 3H, J = 6.7), 0.83 (d, 3H, J = 6.7), 1.10 (d, 3H, J = 7.2), 1.14 (s, 9H), 1.19−1.25 (m, 2H), 1.30 (s, 9H), 1.63−1.69 (m, 1H), 2.97−3.04 (m, 1H), 3.26−3.35 (m, 1H), 4.23 (d, 1H, J = 9.3); ^{13}C NMR (100 MHz) δ 13.3, 21.0, 22.6, 23.4, 24.3, 29.9, 40.3, 44.3, 55.9, 57.6, 68.3, 174.7. Anal. Calcd for $C_{16}H_{33}NO_3S$: C, 60.15; H, 10.41; N, 4.38. Found: C, 60.19; H, 10.37; N, 4.24.

(*R*$_S$,2*S*,3*R*)-(−)-2,5-Dimethyl-3-(2-methylpropane-2-sulfinylamino)hexanoic Acid 4-Methoxybenzyl Ester (4k). The general procedure was followed using 0.500 g (2.64 mmol) of imine **3c**, 0.762 mL (5.81 mmol) of *i*-Pr_2NH, 2.77 mL (5.55 mmol) of *n*-BuLi, 1.026 g (5.28 mmol) of 4-methoxybenzyl propionate, and 2.65 mL (11.09 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined by NMR integration of the crude reaction mixture (88:12 dr, undetectable amounts of the other two diastereomers). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. Pure **4k** was obtained in 85% yield after column chromatography with 30% EtOAc/hexanes to 75% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −7.4 (*c* 1.0, $CHCl_3$); IR 1031, 1614, 1710, 2956 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.82 (d, 3H, J = 6.6), 0.85 (d, 3H, J = 6.7), 1.14 (s, 9H), 1.16 (d, 3H, J = 7.2), 1.20−1.35 (m, 2H), 1.64−1.71 (m, 1H), 3.05−3.09 (m, 1H), 3.29−3.36 (m, 1H), 3.80 (s, 3H), 4.26 (d, 1H, J = 9.4), 5.01 (d, 1H, J = 12), 5.14 (d, 1H, J = 12), 6.88 (d, 2H, J = 8.7), 7.29 (d, 2H, J = 8.7); ^{13}C NMR (100 MHz) δ 13.4, 21.0, 22.6, 23.4, 24.3, 40.3, 44.7, 55.2, 55.9, 57.9, 66.2, 113.9, 127.7, 130.2, 159.6, 174.2. Anal. Calcd for $C_{20}H_{33}NO_4S$: C, 62.63; H, 8.67; N, 3.65. Found: C, 62.28; H, 8.88; N, 3.75.

(*R*$_S$,2*S*,3*S*)-(−)-2-Methyl-3-(2-methylpropane-2-sulfinylamino)-3-phenylpropionic Acid Methyl Ester (4l). The general procedure was followed using 0.500 g (2.39 mmol) of imine **3d**, 0.689 mL (5.26 mmol) of *i*-Pr_2NH, 2.51 mL (5.02 mmol) of *n*-BuLi, 0.460 mL (4.78 mmol) of methyl propionate, and 2.40 mL (11.9 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined by NMR integration of the crude reaction mixture (96:4 dr, undetectable amounts of other two diastereomers). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. Pure **4l** was obtained in 85% yield after column chromatography with 40% EtOAc/hexanes to 75% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −53.1 (*c* 1.0, $CHCl_3$); IR 1049, 1715, 2980 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.16 (d, 3H, J = 7.2), 1.24 (s, 9H), 2.92 (m, 1H), 3.65 (s, 3H), 4.47 (d, 1H, J = 3.5), 4.69 (m, 1H), 7.26−7.35 (m, 5H); ^{13}C NMR (100 MHz) δ 12.3, 22.7, 46.1, 52.0, 55.8, 59.8, 127.9, 127.9, 128.3, 139.1, 174.9. Anal. Calcd for $C_{15}H_{23}NO_3S$: C, 60.58; H, 7.79; N, 4.71. Found: C, 60.46; H, 7.52; N, 4.71.

(*R*$_S$,2*S*,3*R*)-(−)-2-Benzyl-3-(2-methylpropane-2-sulfinylamino)pentanoic Acid Methyl Ester (4m). The general procedure was followed using 0.500 g (3.10 mmol) of imine **3i**, 0.894 mL (6.82 mmol) of *i*-Pr_2NH, 3.26 mL (6.51 mmol) of *n*-BuLi, 1.02 g (6.20 mmol) of hydrocinnamic acid methyl ester, and 3.11 mL (13.0 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined via HPLC analysis of the filtered, crude reaction mixture (90:10:0:0 dr, Si column, 97:3 hexanes/*i*-PrOH; 1 mL/min; 215 nm; major diastereomer, t_R = 20.3 min; minor diastereomers, t_R = 14.2, 15.9, 17.5). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. The HPLC peaks corresponding to each of the minor diastereomers were confirmed by ^{1}H NMR. Pure **4m** was obtained in 67% yield after column chromatography with 40% EtOAc/hexanes to 75% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −52.4 (*c* 1.0, $CHCl_3$); IR 1049, 1733, 2977 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.92 (m, 3H), 1.21 (s, 9H), 1.37−1.40 (m, 1H), 1.62−1.68 (m, 1H), 2.79 (dd, 1H, J = 14, 7.3), 3.09 (dd, 1H, J = 14, 8.4), 3.19−3.23 (m, 1H), 3.30−3.35 (m, 1H), 3.63 (s, 3H), 4.20 (d, 1H, J = 8.4), 7.17−7.28 (m, 5H); ^{13}C NMR (125 MHz) δ 10.8, 22.7, 24.7, 34.4, 51.5, 51.8, 56.0, 59.2, 126.4, 128.5, 128.7, 138.6, 174.0. Anal. Calcd for $C_{17}H_{27}NO_3S$: C, 62.74; H, 8.36; N, 4.30. Found: C, 63.13; H, 8.71; N, 4.38. X-ray quality crystals were obtained from slow evaporation of solvent (Et_2O).

(*R*$_S$,2*S*,3*R*)-(−)-2-Benzyl-3-(2-methylpropane-2-sulfinylamino)pentanoic Acid 4-Methoxybenzyl Ester (4n). The general procedure was followed using 0.500 g (3.10 mmol) of imine **3i**, 0.894 mL (6.82 mmol) of *i*-Pr_2NH, 3.26 mL (6.51 mmol) of *n*-BuLi, 1.68 g (6.20 mmol) of hydrocinnamic acid 4-methoxybenzyl ester, and 3.11 mL (13.0 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined by ^{1}H NMR integration (93:7 dr, undetectable amounts of other two diastereomers). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. Pure **4n** was obtained in 70% yield after column chromatography with 40% EtOAc/hexanes to 75% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −31.4 (*c* 1.0, $CHCl_3$); IR 1036, 1162, 1602, 1732 cm^{-1} ; ^{1}H NMR (400 MHz) δ 0.89 (t, 3H, J = 7.3), 1.13 (s, 9H), 1.30−1.36 (m, 1H), 1.60−1.67 (m, 1H), 2.80 (dd, 1H, J = 14, 7.1), 3.11 (dd, 1H, J = 14, 8.6), 3.19−3.23 (m, 1H), 3.32−3.37 (m, 1H), 3.80 (s, 3H), 4.19 (d, 1H, J = 7.4), 4.94 (d, 1H, J = 12), 5.09 (d, 1H, J = 12), 6.86 (d, 2H, J = 8.7), 7.20 (m, 5H), 7.26 (d, 2H, J = 8.2); ^{13}C NMR (100 MHz) δ 10.8, 22.6, 24.7, 34.3, 51.6, 55.2, 55.9, 59.3, 66.4, 113.9, 126.3, 127.4, 128.5, 128.8, 130.2, 138.5, 159.7, 173.3. Anal. Calcd for $C_{24}H_{33}NO_4S$: C, 66.79; H, 7.71; N, 3.25. Found: C, 66.73; H, 7.68; N, 3.35.

(*R*$_S$,2*S*,3*R*)-(−)-2-(4-Methoxybenzyl)-3-(2-methylpropane-2-sulfinylamino)butyric Acid Methyl Ester (4o). The general procedure was followed using 0.500 g (3.40 mmol) of imine **3a**, 0.979 mL (7.47 mmol) of *i*-Pr_2NH, 3.57 mL (7.13 mmol) of *n*-BuLi, 1.32 g (6.79 mmol) of 3-(4-methoxyphenyl)-propionic acid methyl ester, and 3.41 mL (14.3 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined via HPLC analysis of the filtered, crude reaction mixture (83:17:0:0 dr, Si column, 90:10 hexanes/*i*-PrOH; 1 mL/min; 215 nm; major diastereomer, t_R = 26.8 min; minor diastereomers, t_R = 19.7, 22.0, 24.9). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. The HPLC peaks corresponding to each of the minor diastereomers were confirmed by mass spectrometry. Pure **4o** was obtained in 65% yield after column chromatography with 40% EtOAc/hexanes to 75% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −73.6 (*c* 1.0, $CHCl_3$); IR 1037, 1513, 1615, 1732 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.20 (s, 9H), 1.24 (d, 3H, J = 6.7), 2.76 (m, 1H), 2.97−3.05 (m, 2H), 3.56−3.60 (m, 1H), 3.62 (s, 3H), 3.78 (s, 3H), 4.09 (d, 1H, J = 5.9), 6.80−6.83 (m, 2H), 7.07−7.10 (m, 2H); ^{13}C NMR (100 MHz) δ 17.8, 22.5, 33.4, 51.6, 51.7, 53.0, 55.1, 55.5, 113.9, 129.6, 130.4, 158.1, 173.8. Anal.

Calcd for $C_{17}H_{27}NO_4S$: C, 59.80; H, 7.97; N, 4.10. Found: C, 59.87; H, 7.85; N, 4.08.

(*R*$_S$,2*S*,3*R*)-(−)-2-(4-Methoxybenzyl)-3-(2-methylpropane-2-sulfinylamino)butyric Acid 4-Methoxybenzyl Ester (4p). The general procedure was followed using 0.500 g (3.40 mmol) of imine **3a**, 0.979 mL (7.47 mmol) of *i*-Pr$_2$NH, 3.57 mL (7.13 mmol) of *n*-BuLi, 2.04 g (6.79 mmol) of 3-(4-methoxyphenyl)propionic acid 4-methoxybenzyl ester, and 3.41 mL (14.3 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined by ^{1}H NMR integration of the crude reaction mixture (89:11 dr, undetectable amounts of other two diastereomers as determined by ^{1}H NMR integration). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. Pure **4p** was obtained in 70% yield after column chromatography with 40% EtOAc/hexanes to 75% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −44.8 (*c* 1.0, $CHCl_3$); IR 1035, 1513, 1613, 1727 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.19 (d, 3H, J = 6.6), 1.26 (s, 9H), 2.74−2.78 (m, 1H), 2.93−3.01 (m, 1H), 3.03−3.08 (m, 1H), 3.55−3.59 (m, 1H), 3.76 (s, 3H), 3.79 (s, 3H), 4.08 (d, 1H, J = 6.0), 4.95 (d, 1H, J = 12), 5.02 (d, 1H, J = 12), 6.78 (d, 2H, J = 8.7), 6.83 (d, 2H, J = 8.7), 7.06 (d, 2H, J = 8.7), 7.15 (d, 2H, J = 8.7); ^{13}C NMR (100 MHz) δ 17.9, 22.4, 33.5, 51.9, 53.2, 55.1, 55.2, 55.5, 66.3, 113.8, 113.9, 127.5, 129.7, 130.2, 130.3, 158.1, 159.6, 173.2. Anal. Calcd for $C_{24}H_{33}NO_5S$: C, 64.40; H, 7.43; N, 3.13. Found: C, 64.25; H, 7.53; N, 3.20.

(*R*$_S$,2*S*,3*S*)-(−)-2-Methyl-3-(2-methylpropane-2-sulfinylamino)-3-phenylbutyric Acid Methyl Ester (4q). The general procedure was followed using 0.500 g (2.24 mmol) of imine **3g**, 0.646 mL (4.93 mmol) of *i*-Pr$_2$NH, 2.35 mL (4.70 mmol) of *n*-BuLi, 0.431 mL (4.48 mmol) of methyl propionate, and 2.25 mL (9.40 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined by NMR integration of crude reaction mixture (dr 91:9, undetectable amounts of other two diastereomers). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. Pure **4q** was obtained in 81% yield after column chromatography with 40% EtOAc/hexanes to 75% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −71.6 (*c* 1.0, $CHCl_3$); IR 1068, 1715, 2979 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.04 (d, 3H, J = 7.1), 1.31 (s, 9H), 1.88 (s, 3H), 2.63 (q, 1H, J = 7.2), 3.66 (s, 3H), 5.15 (s, 1H), 7.23−7.42 (m, 5H); ^{13}C NMR δ 12.9, 22.9, 28.3, 51.8, 57.0, 61.4, 127.2, 127.3, 127.8, 142.2, 176.0, quat C not found. Anal. Calcd for $C_{16}H_{25}NO_3S$: C, 61.70; H, 8.09; N, 4.50. Found: C, 61.80; H, 7.90; N, 4.52.

(*R*$_S$,3*R*)-(−)-2,2,5-Trimethyl-3-(2-methyl-propane-2-sulfinylamino)-hexanoic acid methyl ester (4r). The general procedure was followed using 0.500 g (2.64 mmol) of imine **3c**, 0.762 mL (5.81 mmol) of *i*-Pr$_2$NH, 2.77 mL (5.55 mmol) of *n*-BuLi, 0.605 mL (5.28 mmol) of methyl isobutyrate, and 2.65 mL (11.1 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined via reverse-phase LC-MS analysis of the crude reaction mixture (dr 99:1, C8 column, 70−95% MeOH/H_2O over 10 min, 210 nm, t_R(major) = 4.94 min, t_R(minor) = 4.21 min). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. Molecular ions were observed for the major and minor diastereomers. Pure **4r** was obtained in 83% yield after column chromatography with 40% EtOAc/hexanes to 75% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −15.3 (*c* 1.0, $CHCl_3$); IR 1731, 2957 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.85 (d, 3H, J = 6.5), 0.87 (d, 3H, J = 6.7), 1.22 (s, 9H), 1.23 (s, 3H), 1.24 (s, 3H), 1.25−1.32 (m, 2H), 1.71−1.77 (m, 1H), 3.20−3.26 (m, 1H), 3.68 (s, 3H), 4.08 (d, 1H, J = 7.48); ^{13}C NMR (100 MHz) δ 20.81, 20.82, 22.9, 23.0, 23.7, 23.9, 24.4, 42.4, 46.5, 51.8, 61.9, 177.2. Anal. Calcd for $C_{14}H_{29}NO_3S$: C, 57.69; H, 10.03; N, 4.81. Found: C, 57.60; H, 10.07; N, 4.73.

(*R*$_S$,3*S*)-(−)-2,2-Dimethyl-3-(2-methylpropane-2-sulfinylamino)-3-phenylpropionic Acid Methyl Ester (4s). The general procedure was followed using 0.500 g (2.39 mmol) of imine **3d**, 0.689 mL (5.26 mmol) of *i*-Pr$_2$NH, 2.51 mL (5.02 mmol) of *n*-BuLi, 0.548 mL (4.78 mmol) of methyl isobutyrate, and 2.40 mL (10.0 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined via reverse-phase LC-MS analysis of the crude reaction mixture (dr 99:1, C8 column, 70−95% MeOH/H_2O over 10 min, 210 nm, t_R(major) = 3.72 min, t_R(minor) = 2.96 min). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. Molecular ions were observed for the major and minor diastereomers. Pure **4s** was obtained in 86% yield after column chromatography with 40% EtOAc/hexanes to 75% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −88.0 (*c* 1.0, $CHCl_3$); IR 1607, 1715 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.14 (s, 3H), 1.16 (s, 3H), 1.17 (s, 9H), 3.70 (s, 3H), 4.45 (d, 1H, J = 3.5), 4.54 (d, 1H, J = 3.1), 7.27−7.31 (m, 5H); ^{13}C NMR (100 MHz) δ 20.5, 22.5, 24.1, 46.9, 52.2, 55.6, 64.6, 127.75, 127.80, 129.0, 138.0, 178.0. Anal. Calcd for $C_{16}H_{25}NO_3S$: C, 61.70; H, 8.09; N, 4.50. Found: C, 61.67; H, 8.00; N, 4.45.

(*R*$_S$,3*S*)-(−)-2,2-Dimethyl-3-(2-methylpropane-2-sulfinylamino)-3-phenylbutyric Acid Methyl Ester (4t). The general procedure was followed using 0.500 g (2.24 mmol) of imine **3g**, 0.646 mL (4.93 mmol) of *i*-Pr$_2$NH, 2.35 mL (4.70 mmol) of *n*-BuLi, 0.457 mL (4.48 mmol) of methyl isobutyrate, and 2.25 mL (9.40 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined via reverse-phase LC-MS analysis of the crude reaction mixture (dr 99:1, C8 column, 70−95% MeOH/H_2O over 10 min, 210 nm, t_R(major) = 4.44 min, t_R(minor) = 3.49 min). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. Molecular ions were observed for the major and minor diastereomers. Pure **4t** was obtained in 86% yield after column chromatography with 40% EtOAc/hexanes to 75% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −91.8 (*c* 1.0, $CHCl_3$); IR 1599, 1716 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.88 (s, 3H), 1.23 (s, 3H), 1.31 (s, 9H), 1.82 (s, 3H), 3.73 (s, 3H), 5.54 (s, 1H), 7.27−7.31 (m, 3H), 7.39−7.41 (m, 2H); ^{13}C NMR (100 MHz) δ 21.4, 21.6, 23.0, 25.8, 50.6, 52.2, 56.9, 64.2, 127.2, 127.4, 129.1, 140.3, 171.8. Anal. Calcd for $C_{17}H_{27}NO_3S$: C, 62.74; H, 8.36; N, 4.30. Found: C, 62.52; H, 8.20; N, 4.26.

(*R*$_S$,1′*S*)-(−)-1-[1′-(2′-Methylpropane-2′-sulfinylamino)-1′-phenylethyl]cyclohexanecarboxylic Acid Methyl Ester (4u). The general procedure was followed using 0.500 g (2.24 mmol) of imine **3g**, 0.646 mL (4.93 mmol) of *i*-Pr$_2$NH, 2.35 mL (4.70 mmol) of *n*-BuLi, 0.637 mL (4.48 mmol) of cyclohexanecarboxylic acid methyl ester, and 2.25 mL (9.40 mmol) of ClTi(O*i*-Pr)$_3$. Diastereoselectivity was determined via reverse-phase LC-MS analysis of the crude reaction mixture (dr 99:1, C8 column, 70−95% MeOH/H_2O over 10 min, 210 nm, t_R(major) = 6.86 min, t_R(minor) = 6.21 min). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. Molecular ions were observed for the major and minor diastereomers. Pure **4u** was obtained in 65% yield after column chromatography with 40% EtOAc/hexanes to 75% EtOAc/hexanes as eluent: $[\alpha]^{23}_D$ −74.5 (*c* 1.0, $CHCl_3$); IR 1600, 1713 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.58 (m, 1H), 0.79−0.82 (m, 1H), 0.98−1.02 (m, 1H), 1.20−1.25 (m, 2H), 1.21 (s, 9H), 1.38−1.55 (m, 2H), 1.61−1.64 (m, 1H), 2.04−2.08 (m, 1H), 2.31−2.34 (m, 1H), 2.80 (s, 3H), 3.76 (s, 3H), 5.03 (s, 1H), 7.31−7.39 (m, 5H); ^{13}C NMR (100 MHz) δ 23.0, 23.4, 23.9, 25.0, 26.5, 29.3, 29.3, 51.7, 56.2, 57.0, 64.7, 127.0, 127.3, 129.4, 141.0, 175.9. Anal. Calcd for $C_{20}H_{31}NO_3S$: C, 65.72; H, 8.55; N, 3.83. Found: C, 65.65; H, 8.78; N, 3.78.

(*R*$_S$,*S*)-(−)-3-(*N*-*tert*-Butanesulfinyl)amino-(3-pyridine)-propanoic Acid (5).[21] To a solution of **4e** (0.50 g, 1.76 mmol) in 0.90 mL of MeOH and 0.30 mL of H_2O was added LiOH (126 mg, 5.28 mmol). The solution was stirred overnight then concentrated. The residue was dissolved in 15% MeOH/CH_2Cl_2 and filtered through a short silica column to remove inorganic salts. Crude **5** was determined to be of sufficient purity for the next reaction: ^{1}H NMR (300 MHz, CD_3OD) δ 1.21 (s, 9H), 2.83 (dd, 1H, J = 16, 7.1), 3.03 (dd, 1H, J = 16, 7.0), 4.83 (t, 1H, J = 7.0), 4.90 (s, 3H), 7.44 (m, 1H), 7.90 (m, 1H), 8.47 (d, 1H, J = 3.7), 8.58 (s, 1H); ^{13}C NMR (75 MHz,

CD_3OD) δ 25.8, 45.7, 58.5, 60.0, 128.2, 132.1, 132.8, 140.5, 152.3, 152.5.

Ethyl β-[[3-(*tert*-Butanesulfinyl)amino(3-pyridine)propanoyl]amino]propanoate (6).[21] To a solution of **5** (25.5 mg, 0.0944 mmol), HOBt (25.52 mg, 0.1889 mmol), and β-Ala-OEt·HCl (29.02 mg, 0.1889 mmol) in 0.500 mL of CH_2Cl_2 was added DCC (38.97 mg, 0.1889 mmol). The solution was stirred for 12 h. The reaction mixture was concentrated, 1 mL of EtOAc added, and the precipitate removed by filtration through Celite. EtOAc was removed in vacuo. The residue was purified by silica gel chromatography with 60:40:1 $CH_2Cl_2/CH_3CN/NH_4$-OH eluent and pure **6** was obtained in 85% yield for two steps from **4e**: $[\alpha]^{23}_D$ −71.5 (*c* 1.0, $CHCl_3$); IR 1043, 1555, 1649, 1731, 3271 cm^{-1}; ^1H NMR (500 MHz) δ 1.16 (m, 12H), 2.39 (m, 2H), 2.65 (m, 2H), 3.36 (m, 2H), 4.02 (q, 2H, J = 7.2 Hz), 4.70 (m, 1H), 5.70 (d, 1H, J = 4.3 Hz), 7.05 (t, 1H, J = 5.8 Hz), 7.20 (m, 1H), 7.62 (m, 1H), 8.44 (m, 1H), 8.50 (s, 1H); ^{13}C NMR (125 MHz) δ 14.1, 22.6, 33.8, 34.9, 42.9, 54.1, 55.8, 60.6, 123.4, 134.9, 136.9, 148.7, 148.9, 170.3, 172.2. Anal. Calcd for $C_{17}H_{27}N_3O_4S$: C, 55.26; H, 7.37; N, 11.37. Found: C, 55.14; H, 7.41; N, 11.39.

Ethyl β-[[3-[[(4-Cyanophenyl)amino]carbonyl]amino-(3-pyridine)propanoyl]amino]propanoate (7).[21,36] To a solution of **6** (30 mg, 0.07 mmol) in MeOH (1 mL) was added 1 mL of 4 N HCl/dioxane (excess). The solution was stirred for 30 min then concentrated. To the residue was added 1 mL of DMF, 5 drops of *i*-Pr_2NEt, and 11 mg of 4-cyanophenylisocyanate (0.07 mmol). The solution was stirred overnight then concentrated. Pure **7** was obtained in 92% yield after silica gel chromatography, first with 70:30:1 $CH_2Cl_2/CH_3CN/NH_4$-OH to elute excess isocyanate, then with 10% MeOH/CH_2Cl_2 to elute **8**: $[\alpha]^{23}_D$ −37.1 (*c* 1.0, CH_2Cl_2); IR 716, 846, 1544, 1590, 1633, 1689, 1722, 2409, 3308, 3391 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.12 (m, 3H), 2.31 (m, 2H), 2.68 (m, 2H), 3.24 (m, 2H), 3.97 (m, 2H), 5.19 (m, 1H), 7.32 (m, 1H), 7.47 (m, 4H), 7.75 (m, 1H), 8.34 (m, 1H), 8.48 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 11.6, 31.9, 33.3, 39.7, 47.7, 58.8, 102.6, 116.6, 117.3, 122.3, 131.3, 133.5, 136.9, 142.8, 145.7, 146.0, 153.3, 169.3, 170.3; FAB-MS (MH^+) calcd for $C_{21}H_{23}N_5O_4$ 410, found 410.

Ethyl β-[[3-[[[[4-(Aminoiminomethyl)phenyl]amino]-carbonyl]amino](3-pyridine)propanoyl]amino]propanoate (8).[21,37] A solution of **7** (21.2 mg, 0.052 mmol) in EtOH (3 mL) was cooled to 0 °C and bubbled with HCl gas for 15 min. The solution was stirred for an additional 12 h at room temperature. The solution was concentrated and the remaining oil was redissolved in EtOH. The solution was treated with NH_4Cl (200 mg, 3.70 mmol) and NH_4OH (2 mL) for 4 h at room temperature. Solvent was removed on a rotary evaporator. Pure **8** was obtained from silica gel chromatography with 20% MeOH/CH_2Cl_2 as eluent: $[\alpha]^{23}_D$ −15.0 (*c* 1.0, CH_2Cl_2); IR 1642, 3437 cm^{-1}; ^1H NMR (500 MHz) δ 1.20 (m, 3H), 2.42 (m, 2H), 2.78 (m, 2H), 3.39 (m, 2H), 4.08 (m, 2H), 5.32 (m, 1H), 7.46 (m, 1H), 7.62 (m, 1H), 7.71 (m, 1H), 7.93 (m, 1H), 8.60 (s, 1H); ^{13}C NMR (125 MHz) δ 13.0, 33.3, 34.8, 41.5, 49.2, 60.3, 117.7, 120.2, 124.0, 128.7, 135.3, 138.5, 145.5, 146.9, 147.3, 154.9, 166.0, 170.8, 171.8; FAB-MS (MH^+) calcd for $C_{21}H_{26}N_6O_4$ 427, found 427.

(R_S,3*R*)-3-(2-Methylpropane-2-sulfinylamino)butyric Acid (12). To a solution of 197 mg of *N*-sulfinyl β-amino ester **4a** (0.950 mmol) in 3.56 mL of MeOH and 1.19 mL of H_2O (0.200 M of a 3:1 MeOH:H_2O solution) was added 45.5 mg of LiOH (1.90 mmol). The solution was then stirred for 24 h or until the reaction was determined to be complete by TLC. The solution was then concentrated and diluted with 3 mL of EtOAc and acidified with a solution of 1 N $NaHSO_4$. The aqueous layer was extracted (3×) with EtOAc and the organic layers were combined, dried, and concentrated. The residue was diluted with toluene and concentrated. Crude **12** was determined to be of sufficient purity for the next reaction: $[\alpha]^{23}_D$ −57.5 (*c* 1.0, $CHCl_3$); IR 1014, 1715, 2978, 3200 cm^{-1}; ^1H NMR (400 MHz) δ 1.25 (s, 9H), 1.26−1.29 (m, 3H), 2.44 (dd, 1H, J = 16, 7.0), 2.73 (dd, 1H, J = 16, 4.0), 3.75−3.80 (m, 1H), 4.76−4.80 (m, 1H); ^{13}C NMR (100 MHz) δ 21.2, 22.6, 41.6, 48.7, 55.9, 174.1; FAB-MS (MH^+) calcd for $C_8H_{18}NO_3S$ 208.1007, found 208.1007.

(R_S,3*R*)-4-Methyl-3-(2-methylpropane-2-sulfinylamino)-pentanoic Acid (13). To a solution of 224 mg of *N*-sulfinyl β-amino ester **4b** (0.950 mmol) in 3.56 mL of MeOH and 1.19 mL of H_2O (0.200 M of a 3:1 MeOH:H_2O solution) was added 45.5 mg of LiOH (1.90 mmol). The solution was then stirred for 24 h or until the reaction was determined to be complete by TLC. The solution was then concentrated and diluted with 3 mL of EtOAc and acidified with a solution of 1 N $NaHSO_4$. The aqueous layer was extracted (3×) with EtOAc and the organic layers were combined, dried, and concentrated. The residue was diluted with toluene and concentrated. Crude **13** was determined to be of sufficient purity for the next reaction: $[\alpha]^{23}_D$ −42.1 (*c* 1.0, $CHCl_3$); IR 1016, 1710, 3204 cm^{-1}; ^1H NMR (400 MHz) δ 0.89 (d, 3H, J = 6.8), 0.95 (d, 3H, J = 6.8), 1.27 (s, 9H), 1.97−2.06 (m, 1H), 2.54 (dd, 1H, J = 16, 6.5), 2.73 (dd, 1H, J = 16, 4.1), 3.34−3.37 (m, 1H), 4.68 (d, 1H); ^{13}C NMR (100 MHz) δ 18.3, 19.1, 22.8, 31.7, 36.7, 56.6, 59.5, 173.9; FAB-MS (MH^+) calcd for $C_{10}H_{21}NO_3S$ 236.1322, found 236.1322.

(R_S,3*R*)-5-Methyl-3-(2-methylpropane-2-sulfinylamino)-hexanoic Acid (14). To a solution of 237 mg of *N*-sulfinyl β-amino ester **4c** (0.950 mmol) in 3.56 mL of MeOH and 1.19 mL of H_2O (0.200 M of a 3:1 MeOH:H_2O solution) was added 45.5 mg of LiOH (1.90 mmol). The solution was then stirred for 24 h or until the reaction was determined to be complete by TLC. The solution was then concentrated and diluted with 3 mL of EtOAc and acidified with a solution of 1 N $NaHSO_4$. The aqueous layer was extracted (3×) with EtOAc and the organic layers were combined, dried, and concentrated. The residue was diluted with toluene and concentrated. Crude **14** was determined to be of sufficient purity for the next reaction: $[\alpha]^{23}_D$ −21.3 (*c* 1.0, $CHCl_3$); IR 1011, 1713, 3203 cm^{-1}; ^1H NMR (400 MHz) δ 0.87 (d, 3H, J = 6.4), 0.89 (d, 3H, J = 6.4), 1.25 (s, 9H), 1.63−1.75 (m, 3H, two overlapping sets of peaks), 2.48 (dd, 1H, J = 17, 4.5), 2.85 (dd, 1H, J = 17, 4.8), 3.56−3.59 (m, 1H), 4.70 (d, 1H), carboxylic acid proton not observed; ^{13}C NMR (125 MHz) δ 21.5, 22.7, 22.8, 24.5, 40.2, 44.3, 52.6, 56.5, 173.9; FAB-MS (MH^+) calcd for $C_{11}H_{24}NO_3S$ 250.1477, found 250.1475.

3-[3-(3-{3-[3-(3-Amino-4-methylpentanoylamino)butyryl-amino]-5-methylhexanoylamino}-4-methylpentanoylamino)butyrylamino]-5-methylhexanoic Acid (10). Sulfamylbutyryl resin **15** (335 mg, 0.375 mmol, 1.12 mmol/g) was purged with N_2 in an Argonaut Quest 210 synthesizer equipped with a Julabo cooler. The resin was then swelled with $CHCl_3$ for 30 min and drained. To the resin was added 280 mg of *N*-sulfinyl β-amino acid **14** (1.13 mmol) dissolved in 1.90 mL of $CHCl_3$ (0.200 M) and *i*Pr_2NEt (0.540 mL, 3.38 mmol) and the solution was cooled to −40 °C. To this mixture was added, as a solid, 683 mg of PyBOP (1.31 mmol) and the reaction mixture was allowed to agitate for 8 h. The reaction solution was drained and the resin was washed with $CHCl_3$ (3×), DMF (3×), and CH_2Cl_2 (3×). The support-bound monomer was then swelled with 2 mL of CH_2Cl_2:BuOH (3:1). To this mixture was added 0.5 mL of 4 N HCl/dioxane and the reaction mixture was allowed to agitate for 1 h. The reaction solution was drained and the resin was washed with CH_2Cl_2 (3×), CH_2Cl_2:*i*-Pr_2NEt (10:1) (3×), and CH_2Cl_2 (3×).[38] To the resin was added 82.0 mg of *N*-sulfinyl β-amino acid **12** (0.363 mmol) dissolved in 0.800 mL of CH_2Cl_2:DMF (9:1 mixture, 0.150 M), *i*Pr_2NEt

(35) Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79* (4), 913−941.

(36) Reaction conditions for the formation of a similar urea were obtained from: Tjoeng, F. S.; Toth, M. V.; McMackins, D. E.; Adams, S. P., U.S. Patent 5,314,902, 1993.

(37) Reaction conditions for the conversion of a similar cyanophenyl derivative to the corresponding amidine were obtained from: Tjoeng, F. S.; Toth, M. V.; McMackins, D. E.; Adams, S. P., U.S. Patent 5,-314,902, 1993.

(0.180 mL, 1.09 mmol), and 66 mg of HOAt (0.484 mmol). To this mixture was added 190 mg of PyAOP (0.363 mmol) and the mixture was agitated for 6 h. The mixture was then filtered and the resin was washed with DMF (3×) and CH_2Cl_2 (3×). The four subsequent residues were introduced via deprotection and acylation, according to the aforementioned procedure, to afford the desired resin-bound *N*-sulfinyl hexapeptide. To the resin was added 0.200 mL of $BrCH_2CN$, 0.200 mL of iPr_2NEt, and 1.60 mL of NMP and the mixture was agitated for 12 h. The resin was filtered and washed with NMP (3×) and THF (3×). At this stage, the resin was separated into two equal portions for cleavage to the acid and the primary amide. To the resin was added a solution containing 1 mL of 1 N NaOH and 1 mL of THF and the mixture was agitated for 24 h. The peptide-containing filtrate was collected into a flask equipped with a magnetic stir bar. To the solution was added 2 mL of 2 N HCl and the solution was stirred for 12 h. The solution was then evaporated, diluted with toluene, and evaporated again to give crude **10**. Pure **10** was isolated via preparative HPLC (C18, gradient elution 40−95% MeOH/H_2O) in 35% overall yield based on 0.38 mmol/g initial loading: ^{1}H NMR and ^{13}C NMR (500 MHz, CD_3OD) data were identical with those previously reported.[35] ES-MS (MH^+) calcd for $C_{34}H_{64}N_6O_7$ 669.5, found 669.5.

3-[3-(3-{3-[3-(3-Amino-4-methylpentanoylamino)butyrylamino]-5-methylhexanoylamino}-4-methylpentanoylamino)butyrylamino]-5-methylhexanoic Acid Amide (11). To the cyanomethylacylsulfonamide resin prepared in the previous procedure was added a saturated solution of NH_3 in DMF. IR 1655, 1645, 1562, 1450 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 0.88−0.95 (m, 18H), 1.09 (d, 6H, J = 6.9), 1.14 (d, 3H, J = 6.7), 1.19 (d, 3H, J = 6.6), 1.24−1.31 (m, 2H), 1.38−1.55 (m, 2H), 1.57−1.68 (m, 2H), 1.70−1.80 (m, 1H), 2.05−2.10 (m, 1H), 2.25−2.65 (m, 8H), 2.68−2.74 (m, 2H), 2.77−2.83 (m, 2H), 3.52−3.57 (m, 1H), 4.17−4.23 (m, 1H), 4.32−4.40 (m, 1H), 4.41−4.48 (m, 1H), 4.50−4.60 (m, 1H), 7.63 (d, 1H, J = 8.4), 7.69 (d, 1H, J = 9.3), 7.97 (d, 1H, J = 9.4), 8.26 (d, 1H, J = 9.0), expected amine and primary amide protons not observed; ^{13}C NMR (125 MHz) δ 16.7, 17.7, 17.8, 18.0, 19.4, 19.7, 21.5, 21.8, 22.2, 24.5, 30.6, 32.4, 34.7, 37.5, 40.2, 40.5, 41.6, 41.85, 41.94, 42.2, 44.2, 44.3, 44.7, 45.0, 51.3, 54.9, 169.8, 170.1, 170.6, 171.1, 171.7, 174.2, two carbons not observed; FAB-MS (MH^+) calcd for $C_{34}H_{66}N_7O_6$ 668.5, found 668.5.

2-(4-Methoxybenzyl)-3-(2-methylpropane-2-sulfinylamino)butyric Acid (18). Method A (BBTO mediated hydrolysis of methyl ester): To a solution of **4o** (200 mg, 0.584 mmol) in 3 mL of toluene was added 0.595 mL of bis(tributyltin)oxide (0.696 g, 1.17 mmol). The solution was heated under reflux for 24 h. The crude reaction mixture was filtered through silica gel and the filtrate evaporated to give impure **18**. Organotin impurities were then removed using solid-supported sequestering techniques. Tetraalkylammonium hydroxide functionalized polystyrene resin (BioRad AG1-X4, hydroxide form, 1.0 mequiv/g, 10 equiv) was washed with a 1 N solution of NaOH in H_2O, then treated with a solution of crude **18** in MeOH. The slurry was stirred for 2 h or until **18** is no longer visible by TLC, at which time the slurry was filtered and washed with MeOH (3×). Pure **18** was released by treatment of the resin with 25% AcOH/MeOH (3×). The solvent was evaporated and pure **18** was isolated in 78% overall yield.

Method B (TFA mediated hydrolysis of PMB ester): To a neat solution of **4p** and anisole (1.2 equiv) was added TFA. The resulting solution was stirred for 15 min, at which time the TFA was evaporated, diluted with toluene, and evaporated to remove residual TFA. The residue was purified by flash chromatography (5% MeOH/CH_2Cl_2) to afford pure **18**: IR 3212 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.22 (s, 9H), 1.27 (d, 3H, J = 5.5), 2.63−2.66 (m, 1H), 3.07−3.10 (m, 2H), 3.50−3.67 (m, 1H), 3.77 (s, 3H), 4.74 (m, 1H), 6.81 (d, 2H, J = 8.04), 7.12 (d, 2H, J = 8.1); ^{13}C NMR (125 MHz) δ 17.1, 22.6, 32.9, 52.5, 52.7, 55.2, 56.3, 113.9, 129.7, 130.7, 158.1, carboxylic acid carbon not observed; ES-MS (MH^+) calcd for $C_{16}H_{26}NO_4S$ 328.1582, found 328.1583.

2-(2-Azidoethyl)-5-methyl-3-(2-methylpropane-2-sulfinylamino)hexanoic Acid 4-Methoxybenzyl Ester (19). To a −78 °C solution of 9.56 mL of NaHMDS (9.56 mmol) in 40 mL of Et_2O (0.200 M) was added via syringe a solution of the ester **22** (2.00 g, 7.97 mmol) in Et_2O and the reaction solution was stirred for 1 h. A solution of the *N*-sulfinyl imine **3c** (1.51 g, 7.97 mmol) in Et_2O (1.60 mL, 5.00 M) was slowly added via syringe and the solution was stirred for 3 h at −78 °C. Upon reaction completion as determined by TLC, a saturated aqueous solution of NH_4Cl (10 equiv) was added and the suspension was warmed to room temperature. The aqueous layer was then extracted with EtOAc (3×). The combined organic layers were washed with brine, dried, and concentrated to give crude **19**, which was purified by flash chromatography with 30% to 66% EtOAc/hexanes as eluent to afford pure **19** (86% yield). Diastereoselectivity was determined via HPLC analysis of the filtered, crude reaction mixture (65:17:15:3 dr, Si column, 97:3 hexanes/*i*-PrOH; 1 mL/min; 215 nm). An authentic mixture of diastereomers was prepared by the nonstereoselective addition of the corresponding lithium enolate. The HPLC peaks corresponding to each of the minor diastereomers were confirmed by ^{1}H NMR: $[\alpha]^{23}_D$ −16.1 (*c* 1.0, $CHCl_3$); IR 1035, 1615, 1731, 2096, 2957; ^{1}H NMR (400 MHz) δ 0.83 (d, 3H, J = 5.6), 0.85 (d, 3H, J = 5.6 Hz), 1.13 (s, 9H), 1.22−1.28 (m, 1H), 1.66−1.69 (m, 2H), 3.00−3.03 (m, 1H), 3.24−3.31 (m, 1H), 3.39−3.45 (m, 2H), 3.82 (s, 3H), 4.12 (d, 1H, J = 7.1), 5.03 (d, 1H, J = 11.8), 5.20 (d, 1H, J = 11.7), 6.89 (d, 2H, J = 8.7), 7.31 (d, 2H, J = 8.7); ^{13}C NMR (100 MHz) δ 14.1, 21.0, 22.5, 26.3, 28.1, 41.0, 48.1, 49.7, 55.2, 56.0, 57.0, 66.6, 114.0, 127.4, 130.4, 159.3, 172.8. Anal. Calcd for $C_{21}H_{34}N_4O_4S$: C, 57.51; H, 7.81; N, 12.77. Found: C, 57.47; H, 7.68; N, 12.49.

Preparation of 4-nitrobenzylamide derivative: To diastereomerically pure **19** was added 2 equiv of anisole in trifluoroacetic acid (see procedure for **18**, Method B). To the crude carboxylic acid (1.00 equiv, 20.0 mg, 0.063 mmol) was added 4-nitrobenzylamine hydrochloride (1.20 equiv, 15.0 mg, 0.075 mmol), HOBt (1.20 equiv, 13.0 mg, 0.075 mmol), and DCC (1.20 equiv, 15.5 mg, 0.075 mmol). The reaction was stirred for 6 h then concentrated. The resulting residue was purified by column chromatography (50:50 EtOAc/hexanes as eluent) to afford 25.0 mg of pure 4-nitrobenzylamide (87.9%): ^{1}H NMR (300 MHz) δ 0.83 (d, 3H, J = 5.6), 0.87 (d, 3H, J = 5.6 Hz), 1.15 (s, 9H), 1.18−1.26 (m, 1H), 1.66−1.75 (m, 2H), 3.00−3.03 (m, 1H), 3.15−3.22 (m, 1H), 3.35−3.42 (m, 2H), 4.12 (d, 1H, J = 7.1), 4.48 (d, 1H, J = 10.6), 4.53 (d, 1H, J = 10.6), 7.45 (d, 2H, J = 8.8), 8.16 (d, 2H, J = 8.7). X-ray quality crystals were obtained from slow evaporation of solvent (Et_2O).

4-Hydroxybutyric Acid 4-Methoxybenzyl Ester (21). To a solution of sodium 4-hydroxybutyrate (3.00 g, 23.8 mmol) and tetrabutylammonium iodide (399 mg, 1.08 mmol) in acetone was added 4-methoxybenzyl chloride (2.93 mL, 21.6 mmol). The reaction mixture was heated at reflux for 24 h. The solvent was evaporated and the product was diluted with EtOAc and H_2O. The organic layer was collected and the water layer was extracted with EtOAc (3×). The organic extracts were combined, dried, and filtered to give **21**, which was determined to be of sufficient purity for the next reaction. IR 1710 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.78 (s, 1H), 1.86−1.91 (m, 2H), 2.45−2.49 (m, 2H), 3.37−3.68 (m, 2H), 3.81 (s, 3H), 5.06 (s, 2H), 6.88 (d, 2H, J = 8.5), 7.29 (d, 2H, J = 8.4); ^{13}C NMR (125 MHz) δ 27.6, 31.0, 55.2, 62.0, 66.2, 113.9, 128.0, 130.0, 159.6, 173.8. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.25; H; 7.16.

(38) At this point, acylation of a small aliquot of resin (20 mg) with Fmoc-Ala-OH using standard conditions and Fmoc quantitation revealed a resin loading level of 0.38 mmol/g (0.76 theoretical, 50% efficiency). A similarly low loading level was observed in a control experiment to determine the initial loading level of the sulfonamide resin by acylation with Fmoc-Ala-OH and Fmoc quantitation. Therefore, the low-loading level can potentially be attributed to an incorrectly printed loading level from the source of the resin.

4-Azidobutyric Acid 4-Methoxybenzyl Ester (22). To a solution of **21** (3.20 g, 14.3 mmol) in 70 mL of THF was added Ph_3P (4.50 g, 17.1 mmol), DEAD (2.70 mL, 17.1 mmol), and DPPA (4.31 mL, 20 mmol). The reaction mixture was stirred for 12 h or until the reaction was determined to be complete by TLC. The solvent was evaporated and the residue was purified via column chromatography 30% to 75% EtOAc/hexanes to afford pure **22** (2.35 g, 66%): IR 2098 cm^{-1}; ^1H NMR (500 MHz) δ 1.88−1.95 (m, 2H), 2.43 (t, 2H, J = 7.3), 3.33 (t, 2H, J = 6.7), 3.81 (s, 3H), 5.07 (s, 2H), 6.90 (d, 2H, J = 8.7), 7.27 (d, 2H, J = 8.5); ^{13}C NMR (125 MHz) δ 24.2, 31.2, 50.6, 55.2, 66.2, 113.9, 126.1, 130.1, 159.7, 172.5. Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.80; H, 5.98; N, 16.73.

4-(Triisopropylsilanyloxy)butyric Acid 4-Methoxybenzyl Ester (23). To a 0 °C solution of **21** (4.85 g, 21.6 mmol) in 100 mL of THF was added imidazole (3.00 g, 43.2 mmol) followed by triisopropylsilyl chloride (4.62 mL, 21.6 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 24 h. The solvent was evaporated and the residue was dissolved in hexanes and filtered. The solvent was evaporated and the residue was purified by column chromatography with 20% to 40% EtOAc/hexanes as eluent to afford pure **23** (5.84, 71%): IR 1715 cm^{-1}; ^1H NMR (500 MHz) δ 1.02−1.06 (m, 21H), 1.83−1.89 (m, 2H), 2.46 (t, 2H, J = 7.5), 3.71 (t, 2H, J = 6.1), 3.81 (s, 3H), 5.05 (s, 2H), 6.88 (d, 2H, J = 8.7), 7.29 (d, 2H, J = 8.8); ^{13}C NMR (125 MHz) δ 11.9, 17.9, 28.1, 30.7, 55.2, 65.9, 113.9, 128.2, 130.0, 159.5, 173.6. Anal. Calcd for $C_{21}H_{36}O_4Si$: C, 66.27; H, 9.53. Found C, 66.17; H, 9.50.

5-Methyl-3-(2-methylpropane-2-sulfinylamino)-2-(2-(triisopropylsilanyloxy)ethyl)hexanoic Acid 4-Methoxybenzyl Ester (24). The general procedure was followed using 0.500 g (5.28 mmol) of imine **3c**, 0.730 mL (11.1 mmol) of *i*-Pr_2-NH, 2.60 mL (10.6 mmol) of *n*-BuLi, 1.50 g (7.92 mmol) of ester **23**, and 2.70 mL (22.2 mmol) of $ClTi(Oi\text{-}Pr)_3$. Diastereoselectivity was determined via HPLC analysis of the crude reaction mixture (60:20:17:3 dr, 99:1 to 90:10 hexanes/^{i}PrOH, major diastereomer; 215 nm; major diastereomer, t_R = 18.6 min, minor diastereomers, t_R = 15.3, 16.5, 17.9 min). The identity of the peaks was confirmed by LC-MS of individual HPLC fractions. Pure **24** was obtained in 66% yield after column chromatography with 25:3:7 to 20:3:7 to 15:3:7 hexanes:CH_3CN:CH_2Cl_2 as eluent: $[\alpha]^{23}_D$ −23.9 (*c* 1.0, $CHCl_3$); IR 1609, 1705 cm^{-1}; ^1H NMR (500 MHz) δ_0.79−0.83 (m, 6H), 0.98−1.02 (m, 21H), 1.10 (s, 9H), 1.61−1.67 (m, 2H), 1.94−2.03 (m, 2H), 2.93−3.02 (m, 1H), 3.39−3.45 (m, 1H), 3.58−3.69 (m, 1H), 3.70−3.73 (m, 1H), 3.76 (s, 3H), 4.05 (d, 1H, J = 8.8), 4.97 (d, 1H, J = 12), 5.12 (d, 1H, J = 11.8), 6.83 (d, 2H, J = 8.6), 7.25 (d, 2H, J = 8.5); ^{13}C NMR (125 MHz) δ 11.7, 17.9, 21.2, 22.5, 23.1, 24.2, 31.4, 41.0, 46.7, 55.1, 55.8, 56.4, 61.5, 66.2, 113.8, 127.7, 130.3, 159.6, 173.7. Anal. Calcd for $C_{30}H_{55}NO_5SSi$: C, 63.22; H, 9.73; N, 2.46. Found: C, 63.12; H, 9.70; N, 2.40.

2-(2-Hydroxyethyl)-5-methyl-3-(2-methylpropane-2-sulfinylamino)hexanoic Acid 4-Methoxybenzyl Ester (25). In a Falcon polypropylene tube was added a solution of **24** (60 mg, 0.105 mmol) in 2 mL of THF, and the solution was cooled to 0 °C. To the second tube was added 2 mL of 14% HF/pyridine (prepared from 70% HF/pyridine) and the solution was stirred for 24 h. The solution was poured into a separatory funnel containing 100 mL of $NaHCO_3$ (sat.) and 25 mL of EtOAc. The aqueous layer was washed with EtOAc (3×) and the combined organic layers were washed with brine, dried, and concentrated. Pure **25** was obtained in 73% yield after column chromatography with 50% to 100% EtOAc/hexanes: $[\alpha]^{23}_D$ −11.5 (*c* 1.0, $CHCl_3$); IR 1608, 1705; ^1H NMR (400 MHz) δ 0.74−0.77 (m, 6H), 1.06 (s, 9H), 1.61−1.67 (m, 2H), 1.90−2.00 (m, 1H), 2.94−2.98 (m, 1H), 3.22−3.25 (m, 1H), 3.49−3.55 (m, 2H), 3.61−3.68 (m, 2H), 3.73 (s, 3H), 4.24 (d, 1H, J = 9.2), 4.93 (d, 1H, J = 12), 5.09 (d, 1H, J = 12), 6.81 (d, 2H, J = 8.7), 7.23 (d, 2H, J = 8.7); ^{13}C NMR (100 MHz) δ 20.9, 22.6, 23.4, 24.2, 31.5, 41.3, 47.8, 55.1, 56.0, 56.9, 60.2, 66.3, 113.8, 127.5, 130.3, 159.7, 173.7. Anal. Calcd for $C_{21}H_{35}NO_5S$: C, 60.99; H, 8.53; N, 3.39. Found: C, 60.89; H, 8.51; N, 3.30.

2-Isobutyl-1-(2-methylpropane-2-sulfinyl)pyrrolidine-3-carboxylic Acid 4-Methoxybenzyl Ester (26). To a solution of **25** (36.0 mg, 0.087 mmol) in 0.500 mL of THF was added PPh_3 (27.4 mg, 0.104 mmol) and DEAD (16.5 μL, 0.104 mmol). The solution was stirred for 24 h and then concentrated. Pure **25** (25.0 mg) was obtained in 73% yield after column chromatography with 40% to 100% EtOAc/hexanes: $[\alpha]^{23}_D$ −51.9 (*c* 1.0, $CHCl_3$); IR 1605, 1706; ^1H NMR (500 MHz) δ_0.80−0.89 (m, 6H), 1.16 (s, 9H), 1.40−1.46 (m, 2H), 1.53−1.60 (m, 2H), 2.04−2.10 (m, 2H), 2.58−2.63 (m, 1H), 2.74−2.79 (m, 1H), 3.80 (s, 3H), 3.83−3.99 (m, 1H), 5.04−5.10 (m, 2H), 6.81 (d, 2H, J = 8.7), 7.29 (d, 2H, J = 8.7); ^{13}C NMR (125 MHz) δ 14.1, 22.6, 23.9, 31.5, 41.1, 46.8, 50.2, 55.2, 58.7, 60.3, 66.1, 66.5, 113.9, 127.8, 130.2, 159.6, 172.9. Anal. Calcd for $C_{21}H_{33}NO_4S$: C, 63.76; H, 8.41; N, 3.54. Found: C, 63.70; H, 8.34; N, 3.51.

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Supporting Information Available: Tables of X-ray crystallographic data for structure determination of **4m** and the 4-nitrobenzylamide of **19**, as well as a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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