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A Protocol for an Asymmetric Synthesis of γ-Amino Acids

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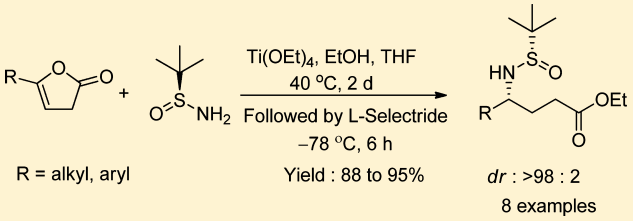
Supporting Information

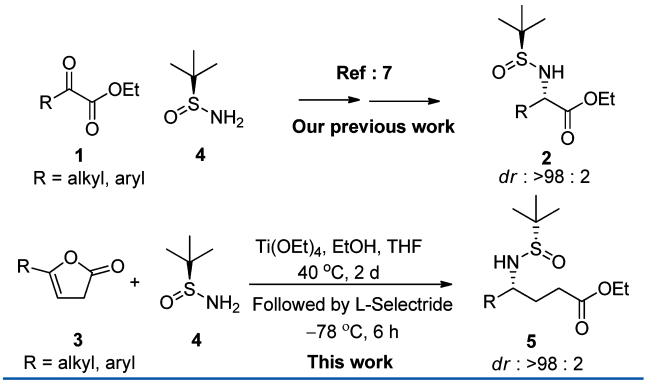
ABSTRACT: A new and practical method for the asymmetric synthesis of γ-amino acids from β,γ-butenolides by an in situ esterification, condensation, and reduction in a one-pot procedure is described. This method is quite general for the preparation of both enantiomers of aryl or aliphatic γ-amino acids in high yields. These γ-amino-acid derivatives were also shown to be versatile synthetic intermediates for further transformations by their conversion to γ-lactams, δ-amino alcohols, and hydrolysis products in high yields with no racemization.



INTRODUCTION

Enantiomerically enriched γ-amino acids (Scheme 1) are valuable synthons for the synthesis of γ-lactams, δ-amino alcohols, and α-substituted pyrrolidines. These building blocks are routinely utilized for the synthesis of a wide variety of bioactive natural products, peptido mimetics,[1,2] and other pharmaceutical compounds.[3] The asymmetric synthesis of γ-amino acids continues to be a fundamental challenge, and significant efforts have been made in this area.[4]

Scheme 1. Approach to γ-Amino Acids



The commercially available chiral *N-tert*-butanesulfinamides have been widely used as highly efficient auxiliaries in the synthesis of a variety of optically active amines by virtue of their excellent diastereocontrol and mild conditions for their cleavage.[5,6] Recently, we reported[7] an elegant method for the asymmetric synthesis of α-amino acids by a highly regio- and diastereoselective reduction of *N-tert*-butanesulfinyl ketimine esters. Further, we focused on the asymmetric synthesis of γ-amino acids and reasoned that a direct method to access enantioenriched γ-amino acids would be in situ esterification, condensation, and asymmetric reduction of β,γ-butenolides (**3**), which has not been described to the best of our knowledge (Scheme 2).[5,6] Herein, we report the results obtained in this research.

Scheme 2. Synthesis of *N-tert*-Butanesulfinyl Ketimine Ester 6a

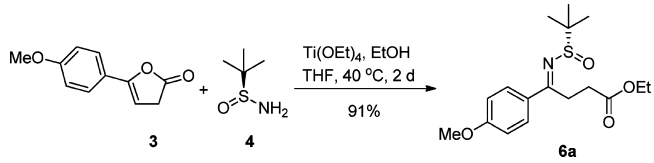
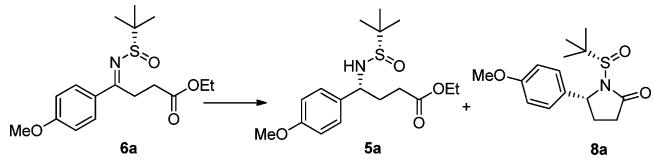


Table 1. Optimization of Reaction Conditions for the Reduction[a]



entry	conditions	5a (dr)	8a (dr)[b]
1	$LiBHEt_3$, −78 °C THF, 6 h	60 (98:2)	40 (98:2)
2	L-Selectride, −78 °C THF, 6 h	65 (98:2)	35 (98:2)
3	L-Selectride, $Ti(OEt)_4$, −78 °C, THF, 6 h	100 (98:2)	0

[a]Reaction was conducted on a 1.0 mmol scale of **6a**, unless otherwise specified. [b]Conversion and diastereoselectivity were determined by crude ^1H NMR analysis.

RESULTS AND DISCUSSION

The choice of using β,γ-butenolides (**3**) as starting materials to produce the corresponding ketimine esters is a novel option we investigated in the present study. As expected, the treatment of readily available β,γ-butenolide **3a** with (*S*)-*N-tert*-butanesulfinamide (**4**) (1.1 equiv) in the presence of $Ti(OEt)_4$ (2.0 equiv)[8] and EtOH (1.05 equiv) in THF at 40 °C produced *N-tert*-butanesulfinyl ketimine ester (**6a**)[9] in 91% yield. Encouraged by

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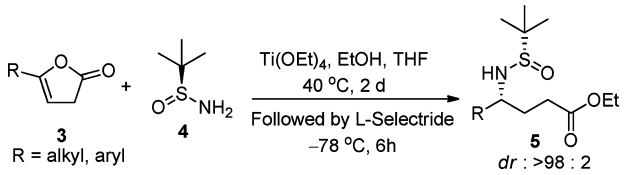
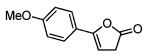
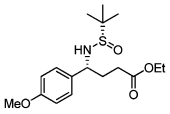
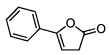
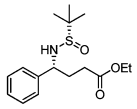
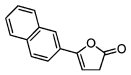
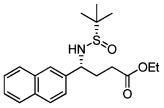
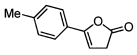
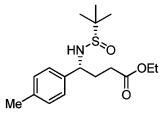
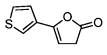
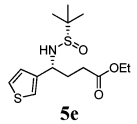
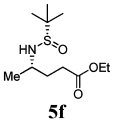
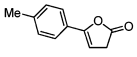
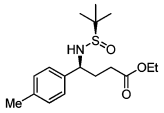
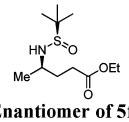
Table 2. Asymmetric Synthesis of γ-Amino Acids[a]



entry	substrate	product	yield	*dr*[b]
1	 **3a**	 **5a**	89	98 :2
2	 **3b**	 **5b**	91	98 :2
3	 **3c**	 **5c**	90	98 :2
4	 **3d**	 **5d**	95	98 :2
5	 **3e**	 **5e**	88	98 :2
6	 **3f**	 **5f**	94	98 :2
7[c]	 **3d**	 **Enantiomer of 5d**	88	98 :2
8[c]	 **3f**	 **Enantiomer of 5f**	95	98 :2

[a]Reaction conditions **3** (2.0 mmol), **4** (2.2 mmol), EtOH (2.1 mmol), $Ti(OEt)_4$ (4.0 mmol) in THF at 40 °C for 2 days, followed by L-Selectride (2.4 mmol) at −78 °C for 6 h, unless otherwise specified. [b]The diastereoselectivity was determined by ^1H NMR analysis. The "≥98:2" dr denotes that signals for only one diastereomer were observed. [c](R_S)-(**4**) is used.

this result, and with **6a** in hand, we explored the asymmetric reduction.

The reaction of *N*-*tert*-butanesulfinyl ketimine esters (*S*)-**6a** (1 equiv) with $LiBHEt_3$ (1.1 equiv, slow addition by syringe pump for 1 h) at −78 °C in THF for 6 h produced a mixture of γ-amino-acid derivative **5a** and γ-lactam derivative **8a** in a 60:40 ratio (Table 1, entry 1) in high yield (90%). Interestingly, we found that both products are formed in a high diastereomeric ratio (dr ≥ 98:2). Encouraged by this result, we investigated different reaction conditions to get a single product. Reduction with L-Selectride provided a similar result as did $LiBHEt_3$ (65:35 ratio of **5a** and **8a**, Table 1, entry 2). We were pleased to find that the use of $Ti(OEt)_4$ (1.1 equiv) and L-Selectide (1.2 equiv) at −78 °C in THF for 6 h selectively gave only the γ-amino-acid derivative **5a** in 94% yield with high a diastereomeric ratio (dr ≥ 98:2) (Table 1, entry 3).

These interesting results allowed us to develop the novel methodology for γ-amino acids from β,γ-butenolides in a one-pot procedure. Thus, β,γ-butenolide **3a** with **4** in the presence of $Ti(OEt)_4$ (2.0 equiv) and EtOH (1.05 equiv) in THF at 40 °C for 2 days, followed by addition of L-Selectride (1.2 equiv) at −78 °C, stirred for 6 h, produced the γ-amino-acid derivative **5a** (Table 2, entry 1) in excellent yield (89%) and a high diastereomeric ratio (dr ≥ 98:2). The diastereoselectivity of the reaction was determined to be ≥98: 2 by ^1H NMR analysis of the crude product. Encouraged by these results, we turned our attention to

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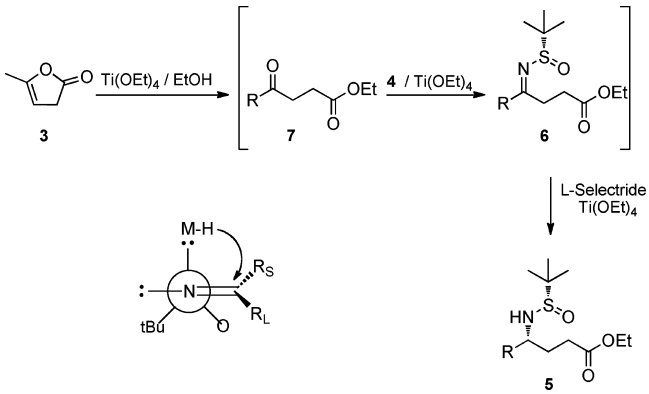
other substituted aromatic β,γ-butenolides such as **3b**−**3d**. They reacted smoothly under optimal conditions to afford the corresponding γ-amino-acid derivatives **5b**−**5d** (Table 2, entries 2−4, respectively) in high yields (90−95%) with high diastereomeric ratios (dr ≥ 98:2). Similarly, the hetero aromatic **3e** was reacted with **4** to produce the γ-amino-acid derivative **5e** (Table 2, entry 4) in good yield (88%) and with excellent diastereoselectivity (dr ≥ 98:2). In the same way, the reaction of aliphatic α-angelic lactone (**3f**) gave the γ-amino-acid derivative **5f** (Table 2, entry 5) in high yield (94%) with a high diastereomeric ratio (dr ≥ 98:2). Noticeably, the reaction of **3d** and **3h** with (*R*)-**4** under optimal conditions produced the corresponding γ-amino-acid derivatives *ent*-**5d** and *ent*-**5 h** (Table 2, entries 7 and 8) in 88% and 95% yield, respectively, with high diastereomeric ratios (dr ≥ 98:2). The structure and absolute stereochemistry of (R_S,*S*)-**5d** were confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information).

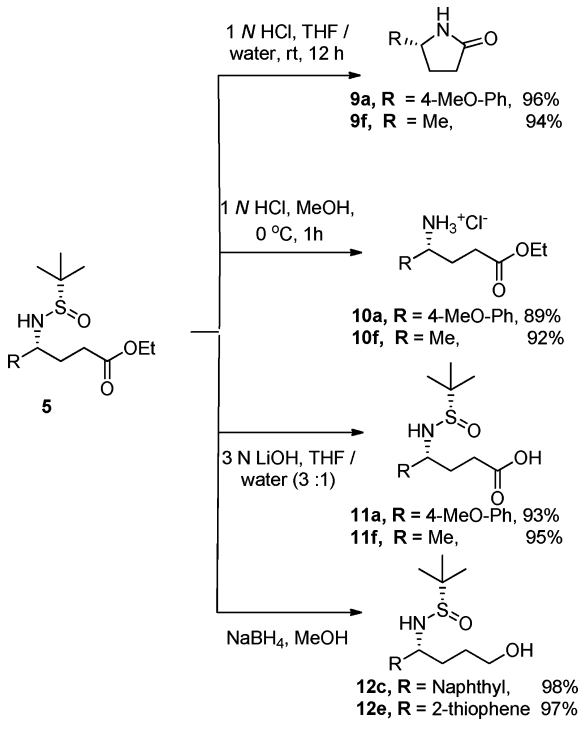
A possible mechanism for this reaction is depicted in Scheme 3. In the first step, β,γ-butenolide **3** reacts with EtOH in the presence of $Ti(OEt)_4$ to form the γ-keto ester **7**, which in turn reacts with **4** to form imine **6**. The diastereoselective reduction of imine **6** with L-Selectride produces the γ-amino-acid derivative **5**. The stereochemical model, TS1, explains the observed stereoselectivity of the product [(S_S,*R*)-**5**]. The poorly coordinating and rapidly reacting L-Selectride was posed to attack the electrophilic carbon atom in a sterically controlled fashion via an open transition state. Hence, delivery of the hydride would occur from the same face as the sulfur lone pair to give the (S_S,*R*) diastereomer (TS1).

A key feature of this methodology is the versatility of the γ-amino-acid derivatives **5** in subsequent transformations. Selective cleavage of the sulfinyl group can be accomplished under different reaction conditions to obtain different products in high yields with no loss of stereochemical purity (Scheme 4). The selective cleavage of the ester group of **5** can be achieved with 3 N LiOH in THF/water at 0 °C for 1 h in quantitative yield, without racemization. In addition, straightforward conversion of γ-amino-acid derivatives **5** to δ-amino alcohols **12** can be achieved with $NaBH_4$.

Scheme 3. A Possible Mechanism of the Reaction



Scheme 4. Useful Application for γ-Amino-Acid Derivatives



CONCLUSIONS

In conclusion, we have described a new and practical method for asymmetric synthesis of γ-amino acids from β,γ-butenolide by esterification, condensation, and reduction in a one-pot operation. This method is quite general for the preparation of enantiomers of either aryl or aliphatic γ-amino acids in good yields with high diastereoselectivity. These γ-amino-acid derivatives are versatile synthetic intermediates for further transformations.

EXPERIMENTAL SECTION

General Information. All the reactions were performed under dry nitrogen gas in glassware that was flame dried and equipped with a magnetic stirring bar. Thin layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm). Flash chromatography was performed using silica gel (40 μm particle size). All compounds were judged pure by TLC analysis (single spot, two-solvent systems) using a UV lamp or PMA for detection purposes. ^{1}H and ^{13}C NMR spectra were recorded on a FT-NMR spectrometer at 500 and 125 MHz, respectively. High-resolution mass spectroscopy (HRMS) was carried out in the electrospray mode on a premiere time of flight mass spectrometer. The reaction temperatures refer to internal reaction temperatures.

General Procedure (GP1) for the Synthesis of γ-Amino Acids 5. To a 100 mL, three-necked, round-bottomed flask were added β,γ-butenolide **3** (2.0 mmol), THF (20 mL), EtOH (2.0 mmol), *tert*-butanesulfinamide **4** (2.2 mmol), and $Ti(OEt)_4$ (4.0 mmol) in a nitrogen atmosphere. The reaction mixture was then heated at reflux at 40 °C for 2 days. After completion, the mixture was allowed to cool to −78 °C, and L-Selectride (2.4 mmol, 1.0 M solution in THF solution) was added (by syringe pump for 1 h). After being stirred for 6 h at −78 °C, the reaction mixture was quenched with a saturated $NaHCO_3$ solution (20 mL) and extracted with ethyl acetate (2 × 25 mL). The combined organic layer was washed with water and dried under vacuum to give the crude product. It was purified by column chromatography (silica gel, ethyl acetate/hexane) to produce the pure γ-amino acid **5**.

(*R*)-Ethyl 4-((*S*)-1,1-Dimethylethylsulfinamido)-4-(4-methoxyphenyl)butanoate 5a. Following the general procedure (GP1), the reaction of 5-(4-methoxyphenyl)furan-2(3*H*)-one **3a** (380 mg, 2.0 mmol) with (*S*)-*tert*-butanesulfinamide (268 mg, 2.2 mmol) gave 605 mg (89%) of pure (*R*)-ethyl 4-((*S*)-1,1-dimethylethylsulfinamido)-4-(4-methoxyphenyl)butanoate **5a** as a light yellow solid. Mp: 80−81 °C. ^{1}H NMR (501 MHz, $CDCl_3$): δ 7.19−7.23 (m, 2H), 6.84−6.89 (m, 2H), 4.34−4.41 (m, 1H), 4.05−4.12 (m, 2H), 3.80 (s, 3H), 3.71 (d, J = 2.52 Hz, 1H), 2.19−2.32 (m, 2H), 2.01−2.16 (m, 2H), 1.23 (t, J = 7.06 Hz, 3H), 1.18 (s, 9H). ^{13}C NMR (125 MHz,

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$CDCl_3$): δ 175.2, 159.2, 133.0, 128.7, 113.9, 60.5, 58.1, 55.2, 33.3, 30.8, 22.5, 14.1. HRMS (EI): calcd for $C_{17}H_{28}NO_4S$ [M + H], 342.1739; found, 342.1736.

(*R*)-Ethyl 4-((*S*)-1,1-Dimethylethylsulfinamido)-4-phenylbutanoate 5b. Following the general procedure (GP1), the reaction of 5-phenylfuran-2(3*H*)-one **3b** (320 mg, 2.0 mmol) with (*S*)-*tert*-butanesulfinamide (268 mg, 2.2 mmol) gave 568 mg (91%) of pure (*R*)-ethyl 4-((*S*)-1,1-dimethylethylsulfinamido)-4-phenylbutanoate **5b** as a viscous liquid. ^{1}H NMR (501 MHz, $CDCl_3$): δ 77.19−7.43 (m, 5H), 4.36−4.53 (m, 1H), 3.98−4.17 (m, 2H), 3.85 (d, *J* = 2.84 Hz, 1H), 2.22−2.39 (m, 2H), 2.05−2.20 (m, 2H), 1.22 (t, *J* = 7.09 Hz, 3H), 1.18 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 141.4, 126.5, 127.4, 60.5, 58.8, 55.5, 33.3, 30.8, 22.6, 14.1. HRMS (EI): calcd for $C_{16}H_{26}NO_3S$ [M + H], 312.1633; found, 312.1635.

(*R*)-Ethyl 4-((*S*)-1,1-Dimethylethylsulfinamido)-4-(naphthalen-2-yl)butanoate 5c. Following the general procedure (GP1), the reaction of 5-(naphthalen-2-yl)furan-2(3*H*)-one **3c** (420 mg, 2.0 mmol) with (*S*)-*tert*-butanesulfinamide (268 mg, 2.2 mmol) gave 650 mg (90%) of pure (*R*)-ethyl 4-((*S*)-1,1-dimethylethylsulfinamido)-4-(naphthalen-2-yl)butanoate **5c** as a white solid. Mp: 78−79 °C. ^{1}H NMR (401 MHz, $CDCl_3$): δ 7.67−7.89 (m, 4H), 7.36−7.53 (m, 3H), 4.55−4.64 (m, 1H), 3.94−4.14 (m, 3H), 2.10−2.44 (s and t, 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 138.5, 133.2, 133.1, 128.6, 127.9, 127.7, 127.1, 126.3, 126.1, 124.9, 60.6, 59.6, 55.6, 33.0, 30.9, 22.6, 14.1. HRMS (EI): calcd for $C_{20}H_{28}NO_3S$ [M + H], 362.1790; found, 362.1788.

(*R*)-Ethyl 4-((*S*)-1,1-Dimethylethylsulfinamido)-4-(4-methylphenyl)butanoate 5d. Following the general procedure (GP1), the reaction of 5-(4-methylphenyl)furan-2(3*H*)-one **3d** (348 mg, 2.0 mmol) with (*S*)-*tert*-butanesulfinamide (268 mg, 2.2 mmol) gave 618 mg (95%) of pure (*R*)-ethyl 4-((*S*)-1,1-dimethylethylsulfinamido)-4-(4-methylphenyl)butanoate **5d** as a viscous liquid. ^{1}H NMR (401 MHz, $CDCl_3$): δ 7.16 (q, *J* = 8.08 Hz, 4H), 4.29−4.47 (m, 1H), 4.09 (q, *J* = 7.07 Hz, 2H), 3.75 (d, *J* = 2.53 Hz, 1H), 2.34 (s, 3H), 2.17−2.32 (m, 2H), 1.96−2.17 (m, 2H), 1.23 (t, *J* = 7.06 Hz, 3H), 1.19 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 138.1, 137.4, 129.2, 127.4, 60.6, 58.4, 33.3, 30.7, 22.6, 21.1, 14.1. HRMS (EI): calcd for $C_{17}H_{28}NO_3S$ [M + H], 326.1790; found, 326.1794.

(*R*)-Ethyl 4-((*S*)-1,1-Dimethylethylsulfinamido)-4-(thiophen-2-yl)butanoate 5e. Following the general procedure (GP1), the reaction of 5-(thiophen-2-yl)furan-2(3*H*)-one **3e** (332 mg, 2.0 mmol) with (*S*)-*tert*-butanesulfinamide (268 mg, 2.2 mmol) gave 558 mg (88%) of pure (*R*)-ethyl 4-((*S*)-1,1-dimethylethylsulfinamido)-4-(thiophen-2-yl)butanoate **5e** as a viscous liquid. ^{1}H NMR (401 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 5.05, 3.03 Hz, 1H), 7.18 (d, *J* = 2.02 Hz, 1H), 7.02 (dd, *J* = 5.05, 1.26 Hz, 1H), 4.52−4.59 (m, 1H), 4.09 (q, *J* = 7.16 Hz, 2H), 3.95 (d, *J* = 3.54 Hz, 1H), 2.27−2.39 (m, 2H), 2.09−2.20 (m, 2H), 1.23 (t, *J* = 7.20 Hz, 3H), 1.20 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 142.5, 126.2, 126.1, 122.4, 60.5, 55.5, 54.7, 32.4, 30.6, 22.6, 14.1. HRMS (EI): calcd for $C_{14}H_{24}NO_3S_2$ [M + H], 318.1198; found, 318.1195.

(*S*)-Ethyl 4-((*S*)-1,1-Dimethylethylsulfinamido)pentanoate 5f. Following the general procedure (GP1), the reaction of 5-methylfuran-2(3*H*)-one **3f** (196 mg, 2.0 mmol) with (*S*)-*tert*-butanesulfinamide (268 mg, 2.2 mmol) gave 468 mg (94%) of (*S*)-ethyl 4-((*S*)-1,1-dimethylethylsulfinamido)pentanoate **5f** as a viscous liquid. ^{1}H NMR (401 MHz, $CDCl_3$): δ 4.06−4.19 (m, 2H), 3.30−3.44 (m, 1H), 2.95 (d, *J* = 7.57 Hz, 1H), 2.38 (t, *J* = 7.41 Hz, 2H), 1.72−1.89 (m, 2H), 1.31 (d, *J* = 6.31 Hz, 3H), 1.26 (t, *J* = 7.25 Hz, 3H), 1.21 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 60.3, 55.7, 52.4, 32.9, 30.7, 23.3, 22.5, 14.1. HRMS (EI): calcd for $C_{11}H_{24}NO_3S$ [M + H], 250.1477; found, 250.1475.

(*S*)-Ethyl 4-((*R*)-1,1-Dimethylethylsulfinamido)-4-(4-methylphenyl)butanoate *ent*-5d. Following the general procedure (GP1), the reaction of 5-(4-methylphenyl)furan-2(3*H*)-one **3d** (349 mg, 2.0 mmol) with (*R*)-*tert*-butanesulfinamide (268 mg, 2.2 mmol) gave 601 mg (88%) of pure (*S*)-ethyl 4-((*R*)-1,1-dimethylethylsulfinamido)-4-(4-methylphenyl)butanoate *ent*-**5d** as a white solid. Mp: 85−86 °C. ^{1}H NMR (401 MHz, $CDCl_3$): δ 7.16 (q, *J* = 8.17 Hz, 4H), 4.36−4.43 (m, 1H), 4.09 (q, *J* = 7.24 Hz, 2H), 3.77 (d, *J* = 2.78 Hz, 1H), 2.34 (s, 3H), 2.04−2.31 (m, 4H), 1.23 (t, *J* = 7.20 Hz, 3H), 1.19 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 138.1, 137.5, 129.2, 127.5, 60.6, 58.4, 55.5, 33.3, 30.7, 22.6, 21.1, 14.2. HRMS (EI): calcd for $C_{17}H_{28}NO_3S$ [M + H], 326.1790; found, 326.1788.

(*R*)-Ethyl 4-((*R*)-1,1-Dimethylethylsulfinamido)pentanoate *ent*-5f. Following the general procedure (GP1), the reaction of 5-methylfuran-2(3*H*)-one **3f** (198 mg, 2.0 mmol) with (*S*)-*tert*-butanesulfinamide (268 mg, 2.2 mmol) gave 470 mg (95%) of (*R*)-ethyl 4-((*R*)-1,1-dimethylethylsulfinamido)pentanoate *ent*-**5f** as a viscous liquid. ^{1}H NMR (401 MHz, $CDCl_3$): δ 4.07−4.18 (m, 2H), 3.31−3.43 (m, 1H), 3.08 (d, *J* = 7.83 Hz, 1H), 2.39 (t, *J* = 7.58 Hz, 2H), 1.72−1.86 (m, 2H), 1.31 (d, *J* = 6.57 Hz, 3H), 1.26 (t, *J* = 7.07 Hz, 3H), 1.21 (s, 98 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 60.3, 55.7, 52.4, 32.8, 30.7, 23.3, 22.5, 14.1. HRMS (EI): calcd for $C_{11}H_{24}NO_3S$ [M + H], 250.1477; found, 250.1479.

General Procedure (GP2) for the Hydrolysis of Ester 5. To a round-bottomed flask containing LiOH (120 mg, 10 mmol, 10 equiv) was added distilled H_2O (7.5.0 mL), and the resulting solution was cooled to 0 °C. A solution of **5** (1.0 mmol, 1.0 equiv) in THF (2.5 mL) was added to the reaction flask. The resulting solution was stirred at 0 °C for 1 h. The reaction mixture was then concentrated to remove the THF, and the remaining material was diluted with distilled H_2O (5 mL) and EtOAc (10 mL). The reaction mixture was neutralized with a saturated $NaHSO_4$ solution to pH ∼2. The organic layers were separated, washed with water (2 × 5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product **11** was isolated, with no further purification, as a white solid.

(*R*)-4-((*S*)-1,1-Dimethylethylsulfinamido)-4-(4-methoxyphenyl)-butanoic Acid 11a. Following the general procedure (GP2), hydrolysis of (*R*)-ethyl 4-((*S*)-1,1-dimethylethylsulfinamido)-4-(4-methoxyphenyl)butanoate **5a** (341 mg, 1.0 mmol) with LiOH (120 mg, 5 mmol) produced compound (*R*)-4-((*S*)-1,1-dimethylethylsulfinamido)-4-(4-methoxyphenyl)butanoic acid **11a** (292 mg, 93%) as a white solid. Mp: 125−128 °C. ^{1}H NMR (501 MHz, $CDCl_3$): δ 10.45 (br s, 1H), 7.24 (d, *J* = 8.51 Hz, 2H), 6.87 (d, *J* = 8.83 Hz, 2H), 4.81 (s, 1H), 4.39 (t, *J* = 6.46 Hz, 1H), 3.80 (s, 3H), 2.14−2.34 (m, 3H), 1.91−2.05 (m, 1H), 1.20 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.9, 159.2, 132.9, 128.9, 114.0, 58.4, 55.9, 55.2, 33.4, 30.7, 22.7. HRMS (EI): calcd for $C_{15}H_{22}NO_4S$ [M − H], 312.1270; found, 312.1274.

(*S*)-4-((*S*)-1,1-Dimethylethylsulfinamido)pentanoic Acid 11f. Following the general procedure (GP2), hydrolysis of (*S*)-ethyl 4-((*S*)-1,1-dimethylethylsulfinamido)pentanoate **5a** (250 mg, 1.0 mmol) with LiOH (120 mg, 5 mmol) produced compound (*S*)-4-((*S*)-1,1-dimethylethylsulfinamido)pentanoic acid **11f** (208 mg, 95%) as a viscous liquid. ^{1}H NMR (501 MHz, $CDCl_3$): δ 10.52 (br s, 1H), 3.67 (d, *J* = 7.57 Hz, 1H), 3.29−3.50 (m, 1H), 2.29−2.44 (m, 2H), 1.66−1.88 (m, 2H), 1.30 (d, *J* = 6.62 Hz, 3H), 1.22 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2, 56.2, 52.7, 32.7, 30.6, 22.9, 22.7. HRMS (EI): calcd for $C_9H_{18}NO_3S$ [M − H], 220.1007; found 220.1010.

General Procedure (GP3) for Synthesis of γ-Lactam 9. To a solution of **5** (1 mmol) in THF (5 mL) was added a 1 N HCl solution (4 mL). After the mixture was stirred at room temperature for 12 h, it was diluted with ethyl acetate (20 mL) and water (10 mL) and neutralized with saturated K_2CO_3 solutions to pH ∼12. The organic phase was separated and washed with water (2 × 10 mL). The organic layer contracted to dryness to yield pure γ-lactam **9**.

(*R*)-5-(4-Methoxyphenyl)pyrrolidin-2-one 9a. Following the general procedure (GP3), the reaction of **5a** (340 mg, 1.0 mmol) with a 1 N HCl solution (4 mL) gives the (*R*)-5-(4-methoxyphenyl)pyrrolidin-2-one **9a** (185 mg, 96%) as a white solid. Mp: 100−102 °C. ^{1}H NMR (501 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.83 Hz, 2H), 6.88 (d, *J* = 8.83 Hz, 2H), 6.67 (br s, 1H), 4.69 (t, *J* = 7.09 Hz, 1H), 3.79 (s, 3H), 2.29−2.63 (m, 3H), 1.78−2.02 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.5, 159.2, 134.5, 126.3, 114.2, 57.6, 55.3, 31.4, 30.4. HRMS (EI): calcd for $C_{11}H_{14}NO_2$ [M + H], 192.1025; found, 192.1023.

(*S*)-5-Methylpyrrolidin-2-one 9f. Following the general procedure (GP3), the reaction of **5a** (250 mg, 1.0 mmol) with a 1 N HCl solution (4 mL) gives the (*S*)-5-methylpyrrolidin-2-one **9f** (93 mg, 94%) as a viscous liquid. ^{1}H NMR (501 MHz, $CDCl_3$): δ 7.62 (br s, 1H), 3.75−3.98 (m, 1H), 2.33−2.54 (m, 2H), 2.19−2.34 (m, 1H), 1.55−1.75 (m, 1H), 1.26 (d, *J* = 6.31 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ

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178.8, 50.9, 30.6, 28.9, 21.9. HRMS (EI): calcd for $C_5H_{10}NO$ [M + H], 100.0762; found, 100.0758.

General Procedure (GP4) for Synthesis of Amine 10. To a solution of **5** (1 mmol) in MeOH (5 mL) was added 1 N HCl solution (in dioxane, 3 mL). After the mixture was stirred at room temperature for 1 h, it was concentrated to dryness and diethyl ether (20 mL) was added. The solid was collected by filtration, washed with diethyl ether (20 mL), and dried at room temperature for 2 h under vacuum to yield a pure hydrochloride salt of **10**.

(*R*)-4-Ethoxy-1-(4-methoxyphenyl)-4-oxobutan-1-aminium Chloride 10a. Following the general procedure (GP4), the reaction of **5a** (340 mg, 1.0 mmol) with a 1 N HCl solution (in dioxane, 3 mL) gives the (*R*)-4-ethoxy-1-(4-methoxyphenyl)-4-oxobutan-1-aminium chloride **10a** (242 mg, 89%) as a white solid. Mp: >200 °C dec. ^{1}H NMR (501 MHz, $CDCl_3$): δ 7.16−7.25 (m, 2H), 6.76−6.90 (m, 2H), 4.10 (q, J = 7.25 Hz, 2H), 3.88 (t, J = 6.94 Hz, 1H), 3.79 (s, 3H), 2.19−2.34 (m, 2H), 1.88−2.07 (m, 2H), 1.23 (t, J = 7.25 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 158.7, 137.7, 127.3, 113.3, 60.2, 55.2, 54.9, 34.4, 31.3, 14.2. HRMS (EI): calcd for $C_{13}H_{20}NO_3$ [M + H], 238.1443; found, 238.1445.

(*S*)-5-Ethoxy-5-oxopentan-2-aminium Chloride 10f. Following the general procedure (GP4), the reaction of **5a** (250 mg, 1.0 mmol) with a 1 N HCl solution (in dioxane, 3 mL) gives the (*S*)-5-ethoxy-5-oxopentan-2-aminium chloride **10f** (175 mg, 92%) as a white solid. Mp: >200 °C dec. ^{1}H NMR (501 MHz, $CDCl_3$): δ 8.34 (br s, 3H), 4.13 (q, J = 6.94 Hz, 2H), 3.42−3.59 (m, 1H), 2.41−2.63 (m, 2H), 2.18 (dd, J = 13.87, 6.94 Hz, 1H), 1.87−2.08 (m, 1H), 1.45 (d, J = 6.31 Hz, 3H), 1.25 (t, J = 7.25 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 60.7, 51.8, 47.8, 30.3, 29.6, 18.4, 14.1. HRMS (EI): calcd for $C_7H_{16}NO_2$ [M + H], 146.1181; found, 146.1184.

General Procedure (GP5) for the Amino Alcohol 12. To a solution of **5** (1 mmol) in MeOH (5 mL) was added $NaBH_4$ (10.0 mmol, 10 equiv). After the mixture was stirred at room temperature for 1 h, it was quenched with water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (20 mL) and concentrated to dryness to obtain pure amino alcohol **12**.

(*S*)-*N*-(*R*)-4-(Hydroxy-1-(naphthalen-2-yl)butyl)-2-methylpropane-2-sulfinamide 12c. Following the general procedure (GP5), the reaction of **5c** (340 mg, 1.0 mmol) with $NaBH_4$ (380 mg, 10.0 mmol) gives the (*S*)-*N*-(*R*)-4-(hydroxy-1-(naphthalen-2-yl)butyl)-2-methylpropane-2-sulfinamide (311 mg, 98%) as a white solid. Mp: 110−111 °C. ^{1}H NMR (401 MHz, $CDCl_3$): δ 7.70−7.86 (m, 4H), 7.37−7.51 (m, 3H), 4.48−4.62 (m, 1H), 4.10 (br s, 1H), 3.46−3.72 (m, 2H), 3.35 (br s, 1H), 1.87−2.09 (m, 2H), 1.40−1.66 (m, 2H), 1.15 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.5, 133.2, 132.9, 128.4, 127.6, 126.8, 126.2, 125.0, 62.0, 59.5, 55.6, 35.2, 29.2, 22.6. HRMS (EI): calcd for $C_{18}H_{26}NO_2S$ [M + H], 320.1684; found, 320.1682.

(*S*)-*N*-(*R*)-4-(Hydroxy-1-(thiophen-2-yl)butyl)-2-methylpropane-2-sulfinamide 12e. Following the general procedure (GP5), the reaction of **5e** (318 mg, 1.0 mmol) with $NaBH_4$ (380 mg, 10.0 mmol) gives the (*S*)-*N*-(*R*)-4-(hydroxy-1-(thiophen-2-yl)butyl)-2-methylpropane-2-sulfinamide **12e** (268 mg, 97%) as a white solid. Mp: 89−91 °C. ^{1}H NMR (401 MHz, $CDCl_3$): δ 7.27 (dd, J = 4.55, 2.27 Hz, 1H), 7.15 (s, 1H), 7.01 (d, J = 4.80 Hz, 1H), 4.51 (d, J = 2.27 Hz, 1H), 4.02 (br s, 1H), 3.51−3.78 (m, 3H), 1.93 (q, J = 7.07 Hz, 2H), 1.49−1.63 (m, 2H), 1.18 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.4, 126.2, 126.0, 122.1, 61.8, 55.6, 55.3, 34.6, 28.9, 22.6. HRMS (EI): calcd for $C_{12}H_{22}NO_2S_2$ [M + H], 276.1092; found, 276.1090.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra for all the compounds and X-ray crystallographic data for compound *ent*-**5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Dr. J. S. Yadav (Director, IICT, India) on the occasion of his 62nd birthday.

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