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A divergent approach to the preparation of cysteine and serine analogs

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Abstract: Malonate diesters containing a prochiral quaternary carbon have been successfully transformed into analogs of cysteine and serine. The chiral half-esters are obtained in good yield, and enantioselectivity by selective hydrolysis using Pig-Liver Esterase (PLE) as the catalyst. The resulting half-ester intermediates are transformed into $\alpha^{2,2}$-, $\beta^{2,2}$-, and $\beta^{3,3}$-analogs of cysteine and serine. The methodology described here allows for the preparation of both enantiomers of the amino-acid analogs by selective manipulation of the ester and acid functionalities. This divergent strategy allows a common synthetic strategy to be used to prepare a variety of unnatural amino-acid classes from a common intermediate which should prove useful in the design of novel peptide libraries. Copyright © 2008 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: amino acids; Curtius rearrangement; Wolff rearrangement; enzymatic desymmetrization

INTRODUCTION

Unnatural amino acids (UAAs) have found considerable utility in recent years in a number of fields. They have been used as peptidomimetics [1], foldamers [2], ligands [3,4], enzyme inhibitors, and as starting materials for advanced intermediates [5]. UAAs have shown an ability to impart proteolytic resistance to peptides and they have shown a propensity to stabilize secondary structural motifs in solution.

Much work has been done to improve the resistance of peptides toward proteolysis by incorporating UAAs into peptides of interest. Seebach has demonstrated that peptides composed entirely of β- and γ-amino acids exhibit remarkable stability toward proteolytic enzymes *in vitro* [6,7]. These β- and γ-peptides were subjected to various peptidase enzymes, under conditions that completely degraded the α-peptide controls within 1 h, and were shown to remain unchanged for at least 48 h. Recently, Seebach has shown that *in vivo* stability of peptidomimetics composed entirely of β-amino acids by administering a β-peptide to live mice. Interestingly, the β-peptide was detectable 24 h post injection in the kidney tissue of the mouse by MALDI-TOF imaging [8].

Gellman has shown that foldamers composed of α- and β-amino acid residues were capable of binding to the BH3-recognition cleft of the antiapoptotic Bcl-x_L protein [9]. The foldamer contained an α-peptide portion in the *C*-terminal region and a mixed α/β-peptide portion in the *N*-terminal region. The foldamer exhibited a K_i 17 times greater than the α-peptide Bak^{BH3}. However, the α-peptide portion proved susceptible to proteolytic degradation and studies were conducted to replace certain residues in the α-peptide portion with unnatural variants in order to improve the proteolytic stabilty.

The use of α,α-dialkyl amino acids has also been shown to impart remarkable resistance toward proteolysis when incorporated into peptides at select locations. The incorporation of 2-aminoisobutyric acid (Aib) can greatly improve the proteolytic stability of the antibiotic peptide BKBA-20 [10]. Interestingly, peptides containing the Aib residue BKBA-20 and BKAA-20 have shown similar antimicrobial activity to one another, whereas the peptide composed of entirely natural amino acids (AKAA-20) was not active.

The introduction of UAAs into peptides has shown a remarkable ability to stabilize secondary structure in peptides [11,12]. It is known that 15–20 α-amino acid residues are required to form stable secondary structures in solution [13]. However, it has also been shown that peptides composed of γ- or β-amino acids can adopt stable secondary structures in solution with as few as four residues [7]. Small peptides of four to six γ-amino acid residues form stable helical secondary structures in solution and in the solid state [14]. Peptides composed of alternating β- and α-amino acid residues have been prepared that display antimicrobial activity and a propensity to form helical structures in solution. Small helical bundles have been prepared using β-peptides as scaffolds. Gellman has shown that nucleobases incorporated into such β-peptide scaffolds form stable 14-helix structures in solution. The nucleobases were capable of forming stable duplexes with another β-peptide containing complimentary nucleobases [13].

UAAs containing a chiral quaternary carbon in the α position have also found use as effective

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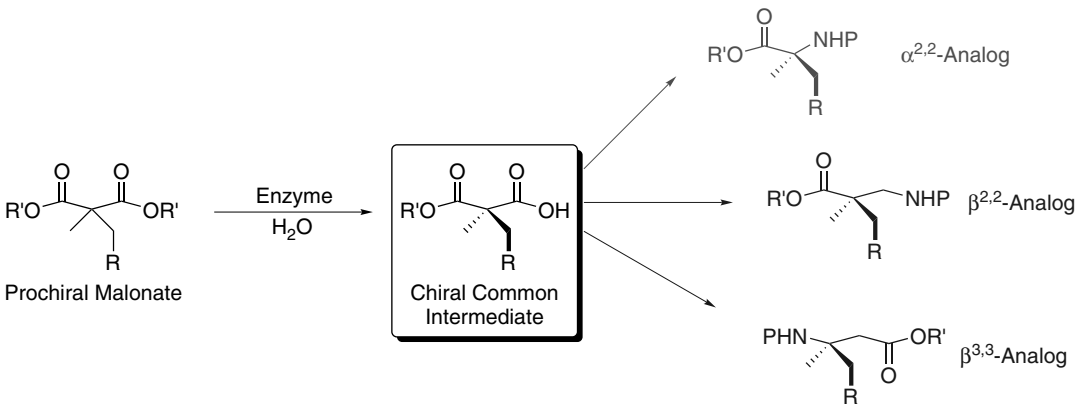
enzyme inhibitors. Berkowitz reported that racemic α-vinyl lysine and α-vinyl arginine analogs function as effective inhibitors of lysine decarboxylase and arginine decarboxylase respectively [15]. Berkowitz has demonstrated that an L-lysine analog containing an α-(2′-fluoro)vinyl moiety functions as an effective mechanism-based inhibitor for lysine decarboxylase [16]. The D-lysine analog was also prepared and showed no ability to inhibit lysine decarboxylase. The studies by Berkowitz clearly demonstrate the need to be able to make both enantiomers of an UAA for such studies because the L-lysine analog functions as a suicide substrate and the D-lysine analog functions only as a substrate.

The examples listed above illustrate the growing importance of UAAs in a variety of fields. The increased attention to the use of unnatural peptides as peptidomimetics has resulted in a significant research effort to develop novel and efficient methods for the synthetic preparation of UAAs [17–20]. Unnatural α-amino acids have been prepared using a wide variety of methodologies. α-Methyl amino acids have been prepared in good yields by nucleophilic ring opening of Bn_2N-α-methylserine-β-lactone with various *in situ* generated organocuprate reagents [21]. The organocuprate reagent attacks the methylene carbon of the β-lactone to give the α,α-dialkyl amino acids in good to excellent yields. A variety of α,α-disubstituted α-amino acids have been prepared from β-keto esters by the Schmidt rearrangment [22]. The key step in this protocol is the formation of an acetal chiral auxiliary from (*S*,*S*)-cyclohexane-1,2-diol that directs the alkylation of the resulting enolate in excellent diastereoselectivity (~95% de). Removal of the chiral auxiliary affords a β-keto ester which is then transformed into the amino acid by the Schmidt rearrangement [23,24]. Berkowitz has made use of chiral dianions of alanine to prepare α,α-disubstituted amino acids in good yields and excellent diastereoselectivity [25]. The dianions were derived from chiral esters prepared from alanine and (–)-8-phenylmenthol as the chiral auxiliary. Kedrowski has prepared both enantiomers of α-methyl cysteine using the Curtius rearrangement and clever manipulation of protecting groups on a chiral half-ester intermediate derived from enzymatic hydrolysis of a prochiral malonate [26]. Goodman and coworkers have also reported efficient syntheses of α-methyl cysteine using a variety of approaches [27,28].

Several syntheses have been reported for the preparation of β-amino acids [20]. Seebach has reported on the homologation of protected α,α-disubstituted α-amino acids by the use of the Wolff rearrangement on *N*-protected α,α-dialkyl amino acids to prepare β-amino acids [6,29]. Unfortunately, this methodology suffers from the competitive formation of an unreactive oxazolone intermediate that diminishes the overall yield of the desired β-amino acids. Enantioselective hydrogen atom transfer methods have been developed by Sibi that are capable of preparing β-amino acids in good yields and moderate to excellent enantioselectivities [30]. Chiral protonation strategies have also been developed by Sibi that can provide various β-amino acids in good yields and enantioselectivities [31].

We wish to report here on our efforts to develop a synthetic strategy capable of preparing a wide variety of UAAs from a common synthetic intermediate. We set out to develop a methodology that does not rely on expensive chiral auxiliaries and reagents. Our strategy described herein allows for the preparation of $\alpha^{2,2}$, $\beta^{2,2}$, and $\beta^{3,3}$ analogs of serine and cysteine from a chiral half-ester derived from a Pig-Liver Esterase (PLE) hydrolysis of a prochiral malonate containing the appropriate amino-acid side chain. Our strategy allows for a divergent approach to various amino-acid classes using a common synthetic strategy that is not readily attainable by many of the above-described syntheses. We also demonstrate that both enantiomers of the amino acids can be readily prepared from the same common intermediate. Scheme 1 illustrates our overall divergent strategy for the preparation of serine and cysteine analogs.



Scheme 1 General synthetic strategy.

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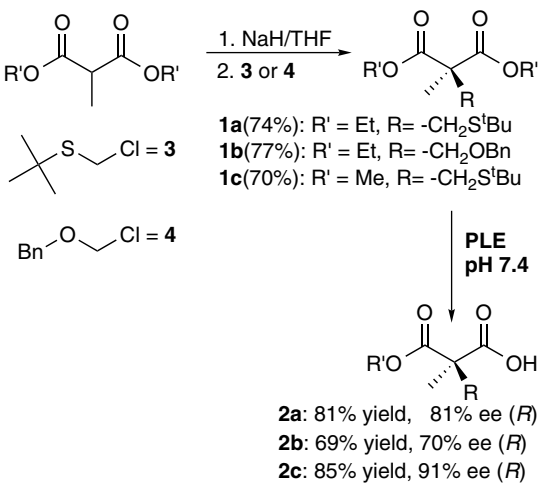
RESULTS AND DISCUSSION

Preparation of Half-ester Intermediates

The prochiral malonic esters were prepared by alkylation of either dimethyl methylmalonate or diethyl methylmalonate with the appropriate alkyl halides shown in Scheme 2. Alkyl halide **3** was best prepared in our hands by a slight modification of a literature procedure [26]. Diethyl methylmalonate (or dimethyl methylmalonate) was added to a suspension of sodium hydride in THF and then alkylated with **3** or **4** to provide diesters **1a–c**. The diesters **1a–c** were isolated in good yields by column chromatography. We found that vacuum distillation of the diesters resulted in decreased yield of pure materials and was not pursued further as a purification technique. We prepared diesters **1a** and **1c** in order to determine if the less expensive diethyl malonate **1a** could serve as an adequate PLE substrate with respect to yield and enantioselectivity.

Compounds **1a–c** were subjected to enzymatic hydrolysis by PLE at pH 7.4 resulting in good isolated yields of half-esters **2a–c** as shown in Scheme 2. The hydrolysis of **1c** to **2c** had been reported previously by Kedrowski and our experiments gave identical results to those reported [26]. Diester **1a** was in fact a suitable PLE substrate. However, it is known that PLE is sensitive to the nature of the ester (ethyl *vs* methyl) and this proved to be the case as we obtained **2a** in 81% ee as opposed to the 91% ee observed for **2c**. Interestingly, both **2a** and **2c** were of the (*R*) absolute stereochemistry as determined by the comparison of the optical rotations of **2a** and **2**c [32].

The enantioselectivity of the PLE hydrolysis of compound **1** to product **2c** could be readily determined by ^{1}H–NMR analysis of the salt formed when **2c** was treated with (*S*)-(−)-α-methylbenzylamine. Under these conditions, the methyl ester gave distinct diastereomeric signals that were readily integrated. However, the diastereomeric salt technique could not be used for half-esters **2a** and **2b** as the ester quartets were not sufficiently resolved to provide accurate integrations. Half-ester **2b** was readily resolved using chiral HPLC techniques and the enantioselectivity was determined by integration of the chromatographic peaks. The chiral HPLC chromatogram of **2b** was compared to a chromatogram of racemic **2b,** which was prepared by nonenzymatic hydrolysis, thereby confirming the identity of the enantiomeric pair. The optical purity of **2a** was determined by chiral HPLC analysis of a β-amino acid derivative prepared in this study (*vide infra*). The need to analyze the β-amino acid derivative was due to the inability to adequately resolve the enantiomers of **2a** using the chiral columns at our disposal. However, the chemistries utilized in preparing the derivative (the Wolff rearrangement [33] and the Curtius rearrangement [34]) are known to preserve the enantiomeric integrity of the starting materials.



Scheme 2 Preparation of chiral half-esters.

We attempted to improve the ee of the resulting half-esters **2b** and **2c** by recrystallization under various conditions. Fortunately, we were able to recrystallize acid ester **2c** from a 4 : 6, pentane : diethyl ether solvent mixture in thin transparent plates in >95% ee. This single recrystallization conveniently provides nearly optically pure material with good mass recovery (69% recovery). We also attempted several recrystallizations of **2b** in hopes of improving the ee of the serine precursor. However, all attempts to afford a simple recrystallization failed to give crystals. We were able to isolate crystals of **2b** as its salt with (*S*)-(−)-α-methylbenzylamine following a literature procedure [35]. Unfortunately, the free acid obtained from this recrystallization was of nearly the same enantiomeric purity as the starting **2b**.

Preparation of $\alpha^{2,2}$-Serine Analogs

Scheme 3 illustrates the conversion of **2b** into both enantiomers of the $\alpha^{2.2}$-serine analogs **5b** and **8b** in good isolated yields.

The (*S*)-$\alpha^{2.2}$-serine analog **5b** was prepared by treating **2b** with DPPA [36] to generate an acyl azide intermediate which was then heated to reflux solvent in order to promote a Curtius rearrangement to an isocyanate. The isocyanate was treated with a slight excess of *p*-methoxybenzyl alcohol (PMB-OH) to give **5b** in 70% isolated yield. In order to prepare the (*R*)-$\alpha^{2.2}$-serine analog **8b** the half-ester **2b** was first *tert*-butylated to prepare the mixed diester **6b**. Preparation of **6b** was carried out using an excess of isobutylene (IBE) with a catalytic amount of sulfuric acid giving **6b** in 93% isolated yield. **6b** was subjected to basic hydrolysis to provide half-ester **7b** in 75% isolated yield which was subjected to the Curtius rearrangement conditions as described above to give **8b** in 78% yield with the (*R*)-absolute stereochemistry (**8b**, major isomer).

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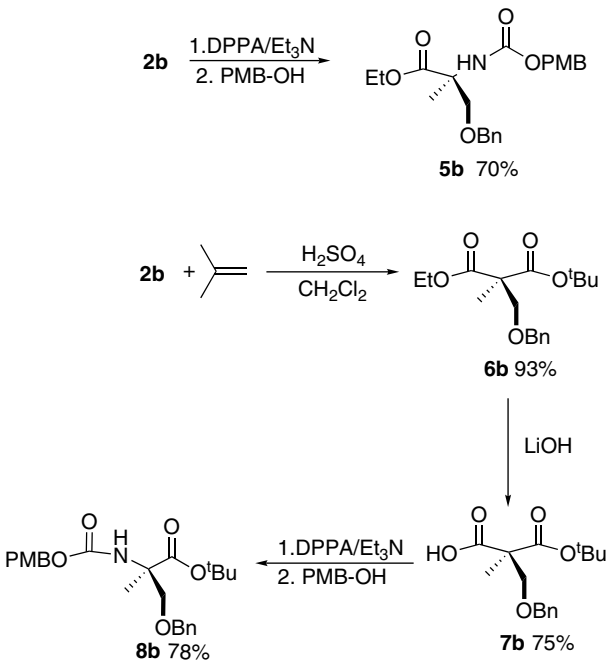


Scheme 3 Preparation of $\alpha^{2,2}$-serine analogs.

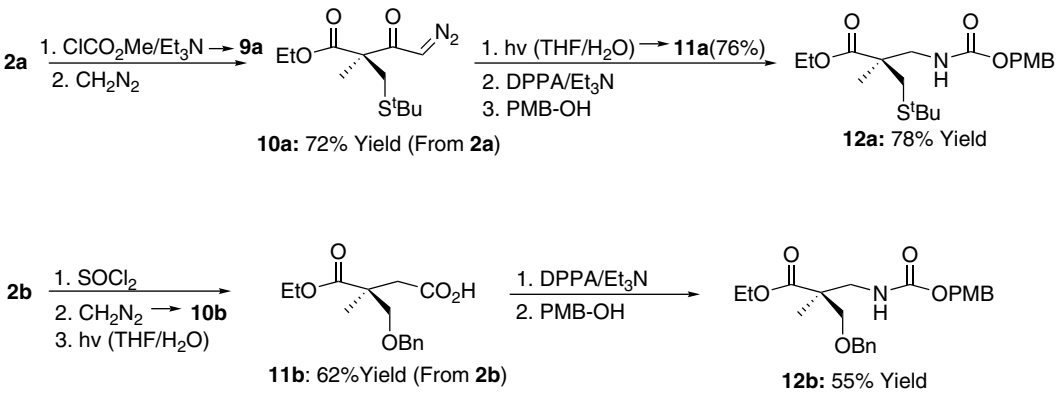
Preparation of $\beta^{2,2}$-Cysteine and $\beta^{2,2}$-Serine Analogs

Half-esters **2a** and **2b** were converted into $\beta^{2,2}$ analogs utilizing a tandem Wolff/Curtius rearrangement sequence. Scheme 4 highlights our efforts at preparing these novel $\beta^{2,2}$-cysteine and serine analogs.

We first had to activate the carboxylic acid present in half-esters **2a** and **2b**. We found that converting **2a** into the mixed anhydride **9a** proved more convenient and gave better yields than using the acid chloride. Mixed anhydride **9a** was used immediately in the next reaction without further purification [37]. It was treated with an anhydrous diazomethane solution in diethyl ether (Caution: diazomethane is highly toxic and potentially explosive) to give diazoketone **10a**. Our initial attempts to conduct the Wolff rearrangement on **10a** and **10b** involved the use of a Ag(I) catalyst. However, the use of Ag(I) failed to provide the homologous acids in acceptable yields (typically 15% crude yield) [33], presumably due to the steric congestion of the quaternary carbon center adjacent to the diazoketone, and so we switched our strategy to the photo-Wolff rearrangement. Attempts to photolyze the crude diazoketone **10a** resulted in a dramatically reduced yield of the homologous acid **11a** (~10% yield). We found that purified **10a** readily underwent photolysis to give **11a** in good yield. The homologous acid **11a** was conveniently transformed into the $\beta^{2,2}$-(*R*)-cysteine analog **12a** by a Curtius rearrangement. Compound **2b** did not suffer the same issues as **2a** and we were able to activate the carboxylic acid as an acid chloride. The acid chloride of **2b** was treated with anhydrous diazomethane to generate diazoketone **10b** that was used immediately in the next step without further purification. To our delight, we were able to isolate **11b** in 62% yield (from **2b**) by double extraction, avoiding the need for time-consuming chromatography. The isolated yield of **11b** is comparable to the optimized yield of **11a** (58% overall yield of **11a** from **2a**). The homologous acid **11b** was transformed into the $\beta^{2,2}$-(*S*)-serine analog **12b** by a Curtius rearrangement.

The $\beta^{2,2}$-analogs of stereochemistry opposite to those in Scheme 4 were also prepared using **2b** and **2c** as starting materials. Scheme 5 shows our route to prepare $\beta^{2,2}$-(*R*)-serine and $\beta^{2,2}$-(*S*)-cysteine analogs.

The mixed ester **6b** allows for convenient preparation of **7b** by saponification. The saponification of ethyl ester allows for the interchange of chirality by switching the ester and acid functionalities. Half-ester **7b** was activated using the mixed anhydride method to avoid the possibility of *tert*-butyl ester deprotection. The activated ester was used immediately without purification to generate diazoketone **15b** by treatment with anhydrous diazomethane. **15b** was photolyzed in a mixture of THF/H_2O to generate the homologous acid **16b** in good isolated yield. **16b** was converted to the protected amino acid **17b** by the Curtius rearrangement as outlined previously. A complete deprotection of **17b** is all that would be required to obtain the enantiomer of **12b** (deprotected form)



Scheme 4 $\beta^{2,2}$- (*R*)-Cysteine and (*S*)-serine analogs.

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illustrated in Scheme 4. Half-ester **2c** was converted to **13c** as outlined previously with IBE. Compound **13c** was treated in the same manner as **6b** to ultimately provide **17c** in good isolated yield.

Preparation of $\beta^{3,3}$-Cysteine and $\beta^{3,3}$-Serine Analogs

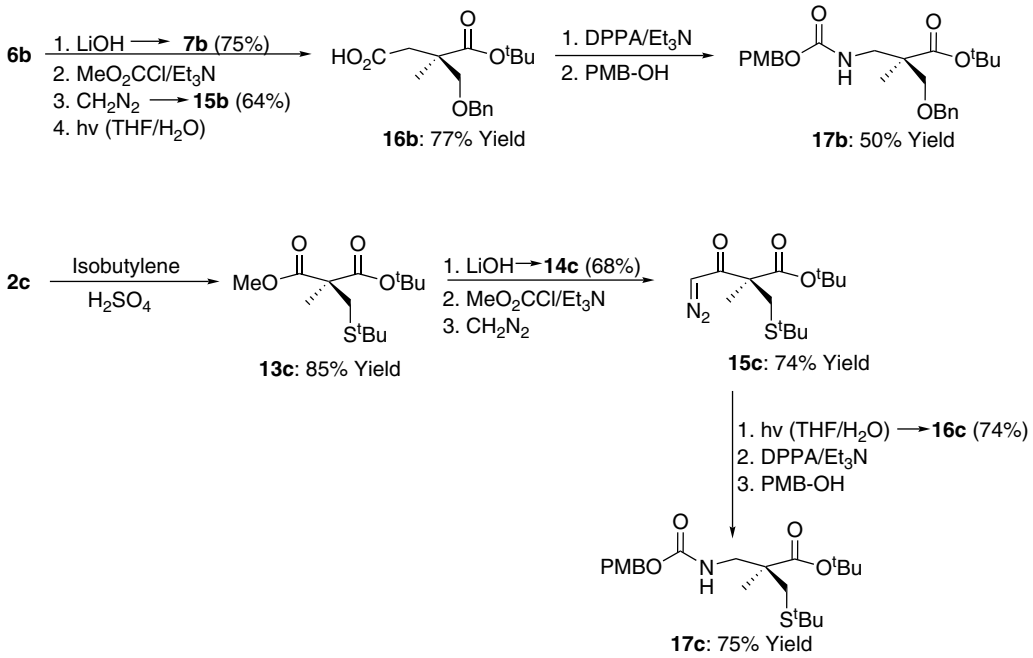
The $\beta^{3,3}$-analogs of cysteine and serine were prepared using **15b** and **15c** as the starting materials. Scheme 6 shows the steps used to convert **15b** and **15c** into the $\beta^{3,3}$-analogs **20b** and **20c**, respectively.

The photolysis of **15b** and **15c** in the presence of methanol cleanly afforded the mixed esters **18b** and **18c** respectively in moderate to good isolated yields. The *tert*-butyl esters were selectively hydrolyzed using KSF clay in refluxing acetonitrile to afford **19b** and **19c** [38]. The KSF clay hydrolysis is sufficiently mild, so we observed no hydrolysis of the methyl esters or deprotection of the thioether in **18c** by NMR analysis. The KSF clay deprotection allows us to interchange the acid and ester functionalities efficiently, allowing the flexibility to ultimately place the amino and acid functional groups in various locations at will. The resulting half-esters were subjected to the Curtius rearrangement conditions as previously described to give the $\beta^{3,3}$ analogs **20b** and **20c** in good isolated yield, both of which have the (*R*) absolute stereochemistry.

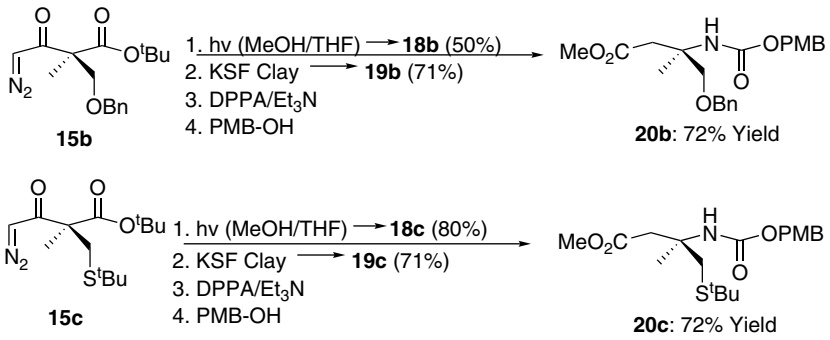
The $\beta^{3,3}$-analogs of the (*S*) absolute stereochemistry are also possible using our strategy, starting with the acid-esters **11b** and **11c**. We were able to prepare the (*S*)-enantiomers of the $\beta^{3,3}$ series using similar strategies outlined for all other amino-acid analogs presented herein (Scheme 7).

CONCLUSION

We have demonstrated that it is possible to use straightforward synthetic techniques to prepare a series of cysteine and serine analogs from a common



Scheme 5 $\beta^{2,2}$- (*S*)-Cysteine and (*R*)-serine analogs.



Scheme 6 $\beta^{3,3}$-(*R*)-Serine and (*R*)-cysteine analogs.

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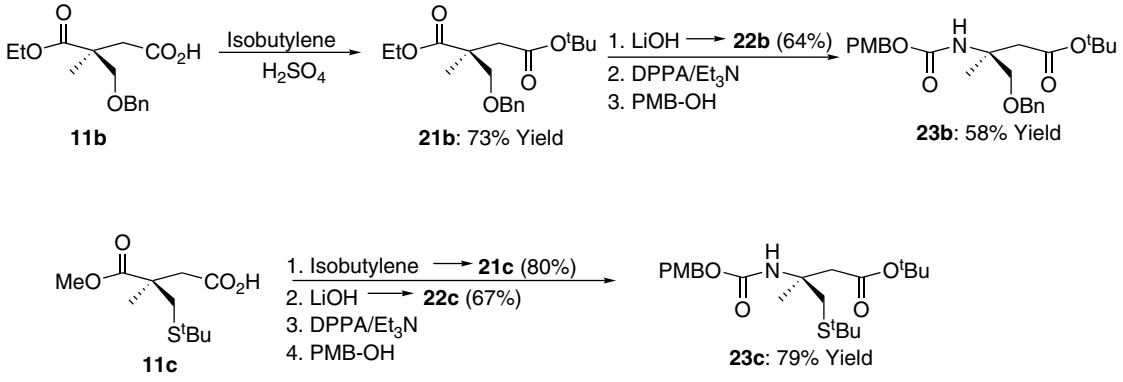

Scheme 7 $\beta^{3,3}$-(*S*)-Serine and (S)-cysteine analogs.

synthetic intermediate without the use of expensive chiral auxiliaries and reagents. To the best of our knowledge, this is the first time such amino acids have been prepared using a divergent strategy. The methodology allows for the preparation of $\alpha^{2,2}$-, $\beta^{2,2}$-, and $\beta^{3,3}$-analogs and allows for preparation of both the D- and L-isomers of each class by careful manipulation of the acid and ester moieties. The strategy makes extensive use of the Wolff and Curtius rearrangements in all cases. Judicious choice of when to use the Curtius and Wolff determines which amino-acid class will be prepared. This methodology should prove useful in the preparation of peptide libraries containing these novel, unnatural amino-acid residues. We are currently trying to optimize the enantioselectivity of the hydrolysis of **1b** by screening several enzyme/reaction condition combinations and we will report on these efforts in due course. We are currently applying the described methodology in the preparation of additional amino-acid analogs and using these amino-acid analogs to generate peptidomimetics. We will report on these efforts in due course.

MATERIALS AND METHODS

General Experimental

THF was distilled from sodium under a nitrogen atmosphere prior to use. Methylene chloride and 1,2-dichloroethane were distilled from CaH_2 under a nitrogen atmosphere prior to use. TEA was distilled from NaOH pellets under a nitrogen atmosphere prior to use. All NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer and referenced to either residual solvent protons or to TMS. IR spectra were recorded on a Thermo-Nicolet Nexus 470-FT-IR with a diamond anvil ATR accessory. UV/Vis spectra were recorded on an HP 8452 spectrophotometer. Optical rotation measurements were acquired on a Rudolph Research Autopol III autopolarimeter using a 1-dm cell at ambient temperature. TLC analysis was performed on EMD science silica-coated aluminum plates and visualized using UV or phosphomolybic acid stain. Flash chromatography was performed using Silicycle silica gel (Silia-P). Radial chromatography was performed on a Harrison Research Chromatotron using Analtech precoated plates. Flash columns were prepared using a specified volume of silica gel, using a beaker, and slurry packed with the specified solvent. Chiral HPLC was performed using a LabAlliance Series III isocratic pump coupled to a LabAlliance Model 500 UV/Vis detector. Chiral HPLC was performed using a Chiralcel OJ-H analytical column or a Chiralcel AD-H column from Chiral Technologies, Inc. at a flow rate of 1 ml/min. Diazomethane was prepared from Diazald using a mini-diazald apparatus from Aldrich Chemical. Ethereal solutions of diazomethane were dried at 0 °C over KOH pellets. Diazomethane solutions were assayed using UV/Vis spectrophotometry according to a literature procedure [39]. DPPA was prepared using a literature procedure [40]. *tert*-Butylchloromethyl sulfide was prepared using a literature procedure [26]. All other chemicals and enzymes were obtained from Aldrich Chemical and used as received, unless otherwise noted. HRMS analysis was performed at Old Dominion University on an Apex FT-MS using a 1:1, THF:MeOH solvent system with added NaCl to observe sodium adducts of the compounds of interest. Melting points were determined in an open capillary tube using a Hoover melting point apparatus and are uncorrected. Dimethyl methylmalonate was prepared according to a literature procedure [41]. Dimethyl 2-(*tert*-Butylthiomethyl)-2-methylmalonate (**1c**) was prepared according to a literature procedure [26].

Diethyl 2-(tert-butylthiomethyl)-2-methylmalonate (1a). A 1-l three-neck round-bottomed flask was charged with 500 ml of dry THF, a stir bar, and 4.2 g of NaH (105.2 mmol, 60% dispersion in mineral oil). The flask was fitted with a rubber septum, a glass stopper, and a reflux condenser to which a nitrogen inlet was attached. The flask was placed in an ice bath and allowed to stir for 15 min. A solution of diethyl methylmalonate (16.6 g, 95.7 mmol in 200 ml dry THF) was added dropwise to the suspension at 0 °C. The reaction mixture was allowed to stir for 30 min until no further gas evolution was observed. The mixture was allowed to warm to ambient temperature and stirred at this temperature for 60 min. Then *tert*-butylchloromethyl sulfide (14.5 g, 105.2 mmol, 1.1 equiv.) was added dropwise over 5 min with stirring. The resulting solution was then heated to reflux solvent for 20 h. The solution was allowed to cool to ambient temperature and then diluted with 300 ml of ether and washed twice with 10% HCl, twice with brine, dried over $MgSO_4$, filtered, and the solution was concentrated *in vacuo*. The resulting liquid

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was purified by chromatography (4 : 1 Hexane/Et_2O), giving a clear colorless liquid (19.2 g, 74%, 70.8 mmol): TLC $R_f = 0.37$ (4 : 1 Hexane/Et_2O); ^{1}H–NMR (300 MHz, $CDCl_3$): 1.26 (6H, t, $J = 7.1$ Hz), 1.31 (9H, s), 1.49 (3H, s), 3.03 (2H, s), 4.19 (4H, q, $J = 3.5$, 10.7 Hz). ^{13}C–NMR (75 MHz, $CDCl_3$): 14.1, 19.8, 30.7, 33.4, 42.3, 53.9, 61.6, 171.2. IR (cm^{-1}) 2972, 1726, 1458, 1365, 1150, 1113, 1013, 850. HRMS $(C_{13}H_{24}O_4SNa)^+$ calcd = 299.1293, obsd = 299.1288.

Diethyl 2-(benzyloxymethyl)-2-methylmalonate (1b). Prepared in a manner similar to **1a** but using benzylchloromethyl ether as the alkylating agent. The crude material was purified by column chromatography (3 : 7 EtOAc/Hexanes) to give 8.63 g (29.3 mmol, 77% yield) of **1b** as a clear and colorless viscous liquid. The ^{1}H–NMR was identical to that reported in literature [35].

(R)-2-(tert-butylthiomethyl)-3-ethoxy-2-methyl-3-oxopropanoic acid (2a). Diester **1a** (5.55 g, 21.2 mmol) was suspended in 0.1 N phosphate buffer (400 ml, pH 7.40). PLE was added (90 units/mmol), and the heterogeneous mixture was stirred rapidly. The pH was maintained at 7.4 by addition of 1.21-N NaOH, using a 798 MPT Titrino in the pH stat mode. The reaction was complete after addition of 17 ml of titrant. The reaction was worked up by addition of 2 N NaOH to reach pH of 9, and the mixture was washed once with ether. The pH was then adjusted to 2 by addition of 1.2-N HCl, and the mixture was extracted with ether three times. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to give the product as a clear, colorless oil (4.2 g, 17.2 mmol, 81% yield). ^{1}H–NMR (300 MHz, $CDCl_3$): 1.27, (3H, t, $J = 5.2$ Hz), 1.32 (9H, s), 1.54 (3H, s), 3.08 (2H, q, $J = 3.3$, 11.2 Hz), 4.25 (2H, q, $J = 3.8$, 10.6 Hz). ^{13}C–NMR (75 MHz, $CDCl_3$): 14.1, 19.9, 30.8, 33.4, 42.5, 54.3, 62.1, 171, 177.1 $[\alpha]_D^{22} = -1.2$ ($c = 1.00$, $CHCl_3$). IR (cm^{-1}) 2960, 1708, 1458, 1365, 1278, 1201, 1159. The absolute stereochemistry was determined from the optical rotation of the amino ester (described below). The ee was determined to be 81% by HPLC of the β-amino ester (**12a**) described below. **2a** was converted to ethyl 3-(*tert*-butylthio)-2-amino-2-methylpropanoate(by Curtius Rearrangement of **2a** which gave 4-methoxybenzyl 2-(ethoxycarbonyl)-1-(*tert*-butylthio)propan-2-ylcarbamate followed by deprotection of the PMB protecting group with TFA) which has the optical rotation of $[\alpha]_D^{22} = +18.23$ ($c = 0.85$, EtOH). (*R*)-Methyl 3-(*tert*-butylthio)-2-amino-2-methylpropanoate was reported by Kedrowski and we compared the optical rotations to determine the absolute stereochemistry of **2a** [26].

(R)-2-(4-(benzyloxymethyl)-3-ethoxy-2-methyl-3-oxopropanoic acid (2b). Prepared in a manner similar to **2a**. 4.42 g (16.6 mmol, 69% yield, 70% ee) of a viscous clear liquid. The absolute stereochemistry was determined by optical rotation and comparison with literature values [35]. $[\alpha]_D^{22} = +7.69$ ($c = 0.21$, MeOH). The ee was determined by analytical chiral HPLC (Chiralcel OJ-H, 257 nm, 4% Ipr-OH/Hexane) $Rt_{(R)} =$ 16.90 min, $Rt_{(S)}$ 19.20 min.

(S)-ethyl-3-(benzyloxy)-2-((4-methoxybenzyloxy)carbonylamino)-2-methylpropanoate (5b). An amount of 0.67 g (2.51 mmol) of **2b** was dissolved in 10 ml of dichloroethane in a 50-ml round-bottomed flask with a magnetic stirbar. A volume of 596 µl (1.02 equiv., 2.77 mmol) of DPPA and 739 µl (2.1 equiv., 5.30 mmol) of Et_3N was added and the solution was brought to reflux solvent for 1.5 h, at which time 432 µl (1.39 equiv., 3.48 mmol) of PMB-OH was added and the solution was brought to reflux solvent for 12 h. The solution was concentrated *in vacuo* and the protected amino ester was purified by silica flash chromatography using 5 : 95 MeOH/$CHCl_3$ ($R_f = 0.6$). This gave 0.70 g (1.74 mmol, 70% yield, 70% ee) of a transparent, viscous oil. $\lambda_{max} = 286$ nm. $[\alpha]_D^{23} = -1.8$ ($c = 0.16$, CH_2Cl_2). IR (cm^{-1}) 3420 (br), 1717. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.22 (3H, t, $J = 7$ Hz), 1.54 (3H, s), 3.70 (1H, d, $J = 9$ Hz), 3.78 (4H, m), 4.18 (2H, m), 4.48 (2H, q, $J = 12$ Hz), 5.01 (2H, s), 5.77 (1H, bs), 6.87 (2H, d, $J = 9$ Hz), 7.30 (7H, m). ^{13}C–NMR (75 MHz, $CDCl_3$): 14.2, 20.3, 55.3, 60.4, 61.9, 66.3, 72.7, 73.3, 113.9, 127.6, 127.8, 128.4, 128.7, 130.0, 137.8, 155.2, 159.6, 172.7. HRMS: $(C_{22}H_{27}NO_6Na^+)$ calcd = 424.1736, obsd = 424.1739. The ee was determined by analytical chiral HPLC (Chiralcel OJ-H, 286 nm, 4% Ipr-OH/Hexane) $Rt_{(S)} = 46.42$ min $Rt_{(R)} = 61.45$ min.

(S)-1-tert-butyl 3-ethyl 2-(benzyloxymethyl)-2-methylmalonate (6b). An amount of 1.26 g (4.73 mmol) of **2b** was dissolved in 5 ml of dry CH_2Cl_2 and placed in a 20-ml sealable pressure tube at $-10\,^\circ$C. A quantity of 300 µl of conc. H_2SO_4 and 3 ml of condensed IBE was added, the tube was capped, and the reaction was allowed to stir overnight a room temperature. The tube was then placed in an ice bath for 15 min; then it was opened and allowed to stir at room temperature for 2 h to allow evaporation of any remaining IBE. The solution was diluted with 25 ml of CH_2Cl_2 and washed three times with 1.0-N NaOH, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a clear, viscous oil; 1.42 g (4.40 mmol, 93% yield). TLC (1 : 9 Ipr-OH/Hexane) $R_f = 0.54$. $[\alpha]_D^{21} = +0.6$ ($c = 0.10$, CH_2Cl_2). IR (cm^{-1}) 1725. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.24 (3H, t, $J = 7$ Hz), 1.42 (9H, s), 1.49 (3H, s), 3.77 (2H, m), 4.17 (2H, q, $J = 7$ Hz), 7.30 (5H, m). ^{13}C–NMR (75 MHz, $CDCl_3$): 14.3, 18.6, 28.0, 55.6, 61.3, 73.0, 73.6, 81.8, 127.7, 127.8, 128.5, 138.3 169.9, 171.2. HRMS $(C_{18}H_{26}O_5Na^+)$ calcd = 345.1672, obsd = 345.1683.

(S)-2-(benzyloxymethyl)-3-tert-butoxy-2-methyl-3-oxopropanoic acid (7b). An amount of 2.03 g (6.30 mmol) of **6b** was dissolved in 50 ml of EtOH. An amount of 0.50 g (3.30 mmol) of LiOH was dissolved in 3 ml water and added to the reaction flask. The reaction mixture was allowed to stir at room temperature for 48 h after which time TLC (silica, 1 : 9 Ipr-OH/Hexane) showed that the reaction was no longer progressing. A quantity of 150 ml of 1.0 N NaOH was added to the reaction mixture. The basic aqueous layer was then washed three times with 150 ml portions of Et_2O. The aqueous layer was acidified to pH 1.0 using cold 10% HCl and extracted with three 200 ml portions of Et_2O. The organic layer was then combined and concentrated *in vacuo* to give 1.38 g (4.70 mmol, 75% yield) of a clear viscous liquid that crystallized upon standing. Mp = 70–76 °C. $[\alpha]_D^{24} = -3.8$ ($c = 0.03$, $CHCl_3$). IR (cm^{-1}) 3250, 1708. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.45 (9H, s), 1.48 (3H, s), 3.49 (2H, s), 3.77 (1H, d, $J = 11$ Hz), 3.80 (1H, d, $J = 11$ Hz), 4.56 (2H, s), 7.30 (5H, m). ^{13}C–NMR (75 MHz, $CDCl_3$): 18.7, 27.9, 55.4, 73.1, 73.7, 82.8, 127.7, 127.8, 128.5, 137.8, 170.3, 176.2. HRMS $(C_{16}H_{22}O_5Na^+)$ calcd = 317.1365, obsd = 317.1355.

(R)-tert-butyl-3-(benzyloxy)-2-((4-methoxybenzyloxy) carbonylamino)-2-methylpropanoate (8b). An amount of

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0.15 g (0.51 mmol) of **7b** was dissolved in 10 ml of dichloroethane in a 50-ml round-bottomed flask with a magnetic stirbar. A volume of 155 µl (0.56 mmol, 1.1 equiv.) of DPPA and 300 µl (2.13 mmol, 4.3 equiv.) of Et_3N was added and the solution was heated to reflux solvent for 3 h at which time 95 µl (0.77 mmol, 1.5 equiv.) of PMB-OH was added and the solution was allowed to reflux overnight. The mixture was then cooled and diluted with 50 ml of $CHCl_3$ and washed three times with 1.0-N NaOH. The organic layer was passed through a small plug of silica gel, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give an orange, transparent, viscous oil. This was purified by radial chromatography (Silica, 1 : 1 Et_2O/Hexane) to give 0.17 g (0.40 mmol, 78% yield, 70% ee) of a clear viscous oil. TLC (1 : 1 Et_2O/Hexane) $R_f = 0.36$. $[\alpha]_D^{24} = +0.8$ ($c = 0.06$, CH_2Cl_2). IR(cm^{-1}) 3419, 1717. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.43 (9H, s), 1.50 (3H, s), 3.67 (1H, d, $J = 9$ Hz), 3.79 (1H, d, $J = 9$ Hz), 3.79 (3H, s), 3.85 (1H, broad d, $J = 9$ Hz), 4.44 (1H, d, $J = 12$ Hz), 4.54 (1H, d, $J = 12$ Hz), 5.01 (2H, s), 5.80 (1H, bs), 6.86 (2H, d, $J = 9$ Hz), 7.30 (7H, m). ^{13}C–NMR (75 MHz, $CDCl_3$): 20.3, 28.0, 55.4, 60.7, 66.2, 72.9, 73.5, 82.2, 140.0, 127.7, 127.8, 128.5, 128.9, 130.0, 138.0, 155.2, 159.6, 171.9. HRMS ($C_{24}H_{31}NO_6Na^+$) calcd = 452.2049, obsd = 452.2033. The ee was determined by analytical chiral HPLC (Chiralcel AD-H, 257 nm, 4% Ipr-OH/Hexane) $Rt_{(S)} = 11.72$, $Rt_{(R)} = 13.73$.

(R)-ethyl 2-(tert-butylthiomethyl)-4-diazo-2-methyl-3-oxobutanoate (10a). Acid **2a** (1.00 g, 4.27 mmol) was dissolved in 5 ml of THF and cooled to −25 °C. A measure of 1.01 equiv. of Et_3N (617 ul, 4.48 mmol) and 1.05 equiv. of $ClCO_2Me$ (4.48 mmol, 404 ul) was added dropwise. The mixture was stirred for 2 h at −25 °C to give **9a** that was used immediately in the next step. The resulting white suspension of **9a** was allowed to warm to 0 °C and a solution of dry diazomethane (2 equiv., 8.5 mmol) in Et_2O was added. Stirring was continued for 12 h in the dark at 0 °C. Excess diazomethane was removed by passing N_2 through the solution for 30 min. The mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$, saturated aqueous NH_4Cl, and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude diazoketone (**10a**) was purified by column chromatography (8 : 2 Hexane/Et_2O), which gave a clear yellow oil (0.8 g, 3.11 mmol, 72% yield). ^{1}H–NMR (300 MHz, $CDCl_3$): 1.26 (3H, t, $J = 7.13$ Hz), 1.31 (9 H, s), 1.46 (3H, s), 2.90 (1H, d, $J = 10.6$ Hz), 3.08 (1H, d, $J = 10.6$ Hz), 4.21 (2H, q, $J = 3.5$, 10.1 Hz), 5.47 (1H, s).

(R)-ethyl-2-(benzyloxymethyl)-4-diazo-2-methyl-3-oxobutanoate (10b). Prepared in a manner to **10a**, except that $SOCl_2$ was used to activate the acid as an acid chloride. An amount of 2.59 g (8.9 mmol, >100%) of crude diazoketone **10b** was obtained as an orange, transparent, viscous oil. This material was used in the next step without further purification. IR (cm^{-1}) 2106, 1727. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.24 (3H, t, $J = 7$ Hz), 1.47 (3H, s), 3.78 (2H, q, $J = 9$ Hz), 4.18 (2H, q, $J = 7$ Hz), 4.54 (2H, s), 5.51 (1H, s), 7.29 (5H, m). ^{13}C–NMR (75 MHz, $CDCl_3$): 14.3, 18.5, 54.6, 58.8, 61.8, 73.1, 73.7, 127.8, 127.9, 128.6, 138.1, 171.6, 192.0.

(R)-3-(tert-butylthiomethyl)-4-ethoxy-3-methyl-4-oxobutanoic acid (11a). Diazoketone **10a** (0.80 g, 2.9 mmol) was dissolved in 10 ml of 3 : 7 H_2O/THF in a 25 ml round-bottomed flask. The flask was purged with nitrogen and the resulting solution was photolyzed with a Hanovia lamp (500 W) at a distance of approximately 10 cm. The photolysis was allowed to proceed for 72 h. The clear solution was concentrated *in vacuo* to remove THF, and the pH of the solution was increased to 9 and washed with ether. The basic aqueous solution was acidified to pH 2 and extracted three times with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and the ether was removed *in vacuo* to give the product as a clear yellowish oil (0.58 g, 2.2 mmol, 76%). TLC $R_f = 0.22$ (16 : 4 : 1 Hexane/Et_2O/AcOH). ^{1}H–NMR (300 MHz, $CDCl_3$): 1.26 (3H, t, $J = 7$ Hz), 1.35 (3H, s), 4.18 (2H, q, $J = 3.5$, 9.6 Hz), 2.66 (1H, d, $J = 9$ Hz), 2.84 (1H d, $J = 10$ Hz), 2.92 (1H, d, $J = 10$ Hz), 2.93 (1H, d, $J = 9$ Hz). ^{13}C–NMR (75 MHz, $CDCl_3$): 14.2, 22.8, 30.9, 36.0, 40.8, 42.3, 44.4, 61.3, 175.4, 176.8. $[\alpha]_D^{20} = +1.65$ ($c = 1.00$, $CHCl_3$). IR (cm^{-1}) 2959, 1729, 1576, 1456. HRMS ($C_{12}H_{22}O_4SNa^+$) calcd = 285.1131 obsd = 285.1142.

(S)-3-(4-(benzyloxy)methyl)-4-ethoxy-3-methyl-4-oxobutanoic acid (11b). Prepared in a method similar to that of **11a**. 1.31 g (4.70 mmol, 62% yield, 66% ee) of a clear viscous oil. TLC (1 : 3 Ipr-OH/Hexane) $R_f = 0.41$. $[\alpha]_D^{22} = -3.2$ ($c = 0.06$, CH_2Cl_2). IR (cm^{-1}) 3350, 1707. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.22 (3H, t, $J = 7$ Hz), 1.32 (3H, s), 2.62 (1H, d, $J = 16$ Hz), 2.90 (1H, d, $J = 16$ Hz), 3.52 (1H, d, $J = 9$ Hz), 3.65 (1H, d, $J = 9$ Hz), 4.16 (2H, q, $J = 7$ Hz), 4.51 (2H, s), 7.30 (m, 5H). ^{13}C–NMR (75 MHz, $CDCl_3$): 14.2, 20.9, 45.4, 61.2, 73.4, 74.4, 127.6, 127.8, 128.5, 138.2, 175.0, 177.4. HRMS ($C_{15}H_{20}O_5Na^+$) calcd = 303.1203, obsd = 303.1209. The ee was determined by analytical chiral HPLC (Chiralcel OJ-H, 257 nm, 4% Ipr-OH/Hexane) $Rt_{(S)} = 15.35$, $Rt_{(R)} = 16.82$.

(R)-ethyl-3-(tert-butylthio)-2-(((4-methoxybenzyloxy)carbonylamino)methyl)-2-methylpropanoate (12a). It was prepared by a Curtius rearrangement conducted similar to the method used to prepare **5b**. This gave the product as a clear colorless oil (0.35 g, 0.89 mmol, 78%). TLC $R_f = 0.15$ (4 : 1 Hexane/Et_2O). ^{1}H–NMR (300 MHz, $CDCl_3$): 1.24 (3H, s), 1.26 (3H, t, $J = 7$ Hz), 1.28 (9H, s), 2.69 (1H, d, $J = 11.7$ Hz), 2.76 (1H, d, $J = 11.5$ Hz), 3.38 (1H, dd, $J = 3.2$, 10.6 Hz), 3.48 (1H, dd, $J = 4.0$, 9.8 Hz), 3.81 (3H, s), 4.15 (2H, q, $J = 3.6$, 9.5 Hz), 5.03 (2H, s), 5.15 (1H, t, $J = 6$ Hz), 6.89 (2H, d, $J = 4.4$ Hz), 7.3 (2H, d, $J = 4.0$ Hz). ^{13}C–NMR (75 MHz, $CDCl_3$): 14.4, 21.2, 30.8, 34.9, 42.4, 47.0, 47.6, 55.5, 61.3, 66.8, 114.1, 128.9, 130.2, 156.9, 159.8, 175.2. $[\alpha]_D^{20} + 5.7$ ($c = 1.00$, $CHCl_3$). HRMS ($C_{20}H_{31}NO_3SNa^+$) calcd = 420.1811, obsd = 420.1815. IR (cm^{-1}) 3351, 2981, 1715, 1612, 1513. The ee was determined by analytical chiral HPLC (Chiralcel OJ-H, 286 nm, 2% Ipr-OH/Hexane) The ee was 81%. $Rt_{1(S)} = 37.38$, $Rt_{2(R)} = 42.23$.

(S)-ethyl-3-(benzyloxy)-2-(((4-methoxybenzyloxy)carbonylamino)methyl)-2-methylpropanoate (12b). Prepared in a manner similar to that of **12a.** The crude product was purified by flash chromatography (silica, 5 : 95 Ipr-OH/Hexane) to give 0.414 g (1.00 mmol, 55% yield, 68% ee) of a clear, viscous oil. TLC $R_f = 0.24$. $[\alpha]_D^{22} = -0.9$ ($c = 0.04$, CH_2Cl_2). IR(cm^{-1}) 1726. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.15 (3H, s), 1.41 (3H, t, $J = 7$ Hz), 3.41 (1H, d, $J = 9$ Hz), 3.49 (2H, dd, $J = 6$ Hz), 3.64 (1H, d, $J = 9$ Hz), 3.80 (3H, s), 4.13 (2H, q, $J = 2$ Hz), 4.48 (2H, s), 5.01 (2H, s), 5.25 (1H, bt, $J = 6$ Hz), 6.88 (2H, d, $J = 9$ Hz), 7.29 (m, 7H). ^{13}C–NMR (75 MHz, $CDCl_3$): 14.3, 18.6, 45.7, 48.2, 55.5,

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61.1, 66.7, 73.5, 74.5, 114.0, 127.6, 127.8, 128.6, 128.9, 130.1, 138.1, 157.0, 159.7, 175.1. HRMS ($C_{23}H_{29}NO_6Na^+$) calcd = 438.1887, obsd = 438.1879. The ee was determined by analytical chiral HPLC (Chiralcel OJ-H, 282 nm, 5% IPr-OH/Hexane) $Rt_{(S)} = 69.73$, $Rt_{(R)} = 93.73$.

(S)-1-tert-butyl-3-methyl-2-(tert-butylthiomethyl)-2-methyl-malonate (13c). This procedure was adapted from the procedure of Kedrowski [26]. The product was obtained as a colorless oil (2.04 g, 7.25 mmol, 85%). All spectral data match that of literature values.

(S)-3-tert-butoxy-2-(tert-butylthiomethyl)-2-methyl-3-oxopropanoic acid (14c). This procedure was adapted from the procedure of Kedrowski [26]. The solid product obtained (1.1 g, 68%, 3.9 mmol) had identical spectral data to those reported in literature.

(S)-tert-butyl-2-(benzyloxymethyl)-4-diazo-2-methyl-3-oxobutanoate (15b). An amount of 1.31 g (4.50 mmol) of **7b** and 1.42 ml of Et_3N (9.50 mmol, 2.1 equiv.) was dissolved in 25 ml of dry THF under a blanket of N_2 at −50 °C. A volume of 360 µl (4.70 mmol, 1.05 equiv.) of methyl chloroformate was added slowly to the solution via syringe. The solution was allowed to stir at −50 °C for 3 h. An ethereal solution of dry diazomethane (21.6 mmol) was added dropwise to the mixed anhydride solution via syringe and allowed to react, without stirring, overnight at 0 °C. The excess diazomethane was removed by bubbling dry N_2 into the solution for 15 min and then filtered. The crude **15b** was purified using 4 : 6 Et_2O/Hexane and a flash column with 200 ml of silica gel. The pure fractions were then concentrated *in vacuo* in a flask wrapped in foil to give 0.91 g (2.89 mmol, 64% yield) of transparent, orange, viscous oil. TLC (4 : 6 Et_2O/Hexane) $R_f = 0.38$. IR (cm^{-1}) 2106, 1725. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.44 (3H, s), 1.45 (9H, s), 3.73 (1H, d, $J = 9$ Hz), 3.80 (1H, d, $J = 9$ Hz), 4.55 (2H, s), 5.50 (1H, s), 7.33 (5H, m). ^{13}C–NMR (75 MHz, $CDCl_3$): 18.5, 28.0, 54.1, 59.4, 73.2, 73.7, 82.1, 127.7, 127.8, 128.5, 138.1, 170.6, 192.3.

(S)-tert-butyl-2-(tert-butylthiomethyl)-4-diazo-2-methyl-3-oxobutanoate (15c). The method of preparation was similar to that of **15b**. Purification of the diazoketone by flash chromatography (8 : 2 Hexane/Et_2O) rendered the product as a clear yellow liquid (74%, 0.80 g, 1.0 mmol). ^{1}H–NMR (300 MHz, $CDCl_3$): 1.31 (9H, s), 1.41 (3H, s), 1.47 (9H, s), 2.91 (1H, d, $J = 11.0$ Hz), 3.03 (1H, d, $J = 11.0$ Hz), 5.44 (1H, s). ^{13}C–NMR (75 MHz, $CDCl_3$): 20.0, 28.0, 30.9, 33.7, 42.4, 49.6, 58.5, 82.4, 171.0, 192.5. IR(cm^{-1}) 3131, 2104, 1720, 1615, 1352.

(R)-3-(benzyloxymethyl)-4-tert-butyl-3-methyl-4-oxobutanoic acid (16b). A measure of 0.200 g (0.63 mmol) of **15b** was dissolved in 10 ml of 30% H_2O/THF in a 25 ml round-bottomed flask. Dry N_2 was passed through the solution for 15 min to degas the solution. The solution was then irradiated with a 500-W Hanovia lamp at a distance of approximately 10 cm. The photo-induced Wolff rearrangement was monitored by the disappearance of the diazo stretch at 2106 cm^{-1} by IR spectroscopy. The reaction was complete after 48 h. The solution was diluted with 50 ml of Et_2O and extracted three times with 1.0 N NaOH. The basic aqueous layers were combined, acidified to pH ≈ 2.0 with 10% HCl, and extracted three times with CH_2Cl_2. These CH_2Cl_2 washes were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.150 g (0.486 mmol, 77% yield) of a clear, viscous oil. $[\alpha]_D^{22} = +3.6$ ($c = 0.05$, CH_2Cl_2). IR(cm^{-1}) 1705. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.29 (3H, s), 1.42 (9H, s,), 2.56 (1H, d, $J = 16$ Hz), 2.87 (1H, d, $J = 16$ Hz), 3.48 (1H, d, $J = 9$ Hz), 3.65 (1H, d, $J = 9$ Hz), 4.52 (2H, s), 7.31 (7H, m). ^{13}C–NMR (75 MHz, $CDCl_3$): 21.1, 28.0, 39.5, 45.9, 73.5, 74.7, 81.3, 127.6, 127.8, 128.5, 138.3, 174.2, 177.6. HRMS ($C_{17}H_{24}O_5Na^+$) calcd = 466.2200, obsd = 466.2193.

(S)-4-tert-butoxy-3-(tert-butylthiomethyl)-3-methyl-4-oxobutanoic acid (16c). Prepared in a manner similar to that of **16b**. The product was obtained as a clear, yellowish oil (0.55 g, 74%, 1.7 mmol). TLC $R_f = 0.2$ (16 : 4 : 1 Hexane/Et_2O/AcOH). ^{1}H–NMR (300 MHZ, $CDCl_3$): 1.30 (9H, s), 1.31(3H, s), 1.45 (9H, s), 2.58 (1H, d, $J = 12$ Hz), 2.81 (1H, d, $J = 12$ Hz), 2.86 (1H, d, $J = 9$ Hz), 2.89 (1H, d, $J = 9$ Hz). ^{13}C–NMR (75 MHz, $CDCl_3$): 23.1, 28.0, 30.9, 36.1, 40.9, 42.2, 44.8, 81.5,174.7,176.6. IR (cm^{-1}) 3363, 2976, 2877, 2112,1638. $[\alpha]_D^{20} = -1.8$ ($c = 0.90$, $CHCl_3$). HRMS ($C_{14}H_{26}O_4SNa^+$) calcd = 313.1444, obsd = 313.1439.

(R)-tert-butyl-3-(benzyloxy)-2-(((4-methoxybenzyloxy) carbonylamino)methyl)-2-methylpropanoate (17b). It was prepared using a Curtius rearrangement in a manner similar to the preparation of **5b**. The product, obtained as a transparent orange oil, was purified by flash chromatography (200 ml of silica gel, $R_f = 0.65$, 3 : 7 EtOAc/Hexane) to give 0.106 g (50% yield, 0.24 mmol, 69% *ee*) of a clear, viscous oil. $[\alpha]_D^{22} = +1.5$ ($c = 0.03$, CH_2Cl_2). IR(cm^{-1}) 3420, 1717. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.11 (3H, s), 1.41 (9H, s), 3.45 (3H, m), 3.60 (1H, d, $J = 9$ Hz), 3.78 (3H, s), 4.48 (2H, m), 5.00 (2H, s), 5.31 (1H, bt, $J = 6$ Hz), 6.87 (2H, d, $J = 9$ Hz), 7.28 (7H, m). ^{13}C–NMR (75 MHz, $CDCl_3$): 18.6, 28.1, 45.7, 48.5, 55.4, 66.5, 73.5, 74.8, 81.1, 114.0, 127.5, 127.7, 128.5, 128.9, 130.1, 138.2, 156.9, 159.6, 174.2. HRMS ($C_{25}H_{33}NO_6Na^+$) calcd = 466.2200, obsd = 466.2193. The ee was determined by analytical chiral HPLC (Chiralcel OJ-H, 282 nm, 6% Ipr-OH/Hexane) $Rt_{(S)} = 29.24$, $Rt_{(R)} = 41.78$.

(S)-tert-butyl-3-(tert-butylthio)-2-(((4-methoxybenzyloxy) carbonylamino)methyl)-2-methylpropanoate (17c). Prepared in a manner similar to that of **17b**. This rendered the product as a clear colorless oil (0.11 g, 0.26 mmol, 75%). TLC $R_f = 0.11$ (6 : 1 Hexane/EtOAc). ^{1}H–NMR (300 MHz, $CDCl_3$): 1.21 (3H, s), 1.28 (9H, s), 1.44 (9H, s), 2.64 (1H, d, $J = 10.4$ Hz), 2.72 (1H, d, $J = 10.4$ Hz), 3.33 (1H, dd, $J = 4.04$, 7.8 Hz), 3.44 (1H, dd, $J = 4.04$, 7.8 Hz), 3.79 (3H, s), 5.02 (2H, s), 5.19 (1H, t, $J = 6$ Hz), 6.87 (2H, d, $J = 4$ Hz), 7.3 (2H, d, $J = 4.2$ Hz). ^{13}C–NMR (75 MHz, $CDCl_3$): 21.1, 27.9, 30.6, 34.8, 42.0, 46.8, 47.6, 55.2, 66.5, 81.3, 113.8, 128.6, 130.0, 156.7, 159.5, 174.2. $[\alpha]_D^{20} = -3.3$ ($c = 0.10$, $CHCl_3$). IR (cm^{-1}) 2976, 1711, 1459, 1368. HPLC (Chiralcel OJ-H, 280 nm, 4% Ipr-OH/Hexane) $Rt_{1(S)} = 11.93$, $Rt_{2(R)} = 15.05$ 91% *ee*. HRMS ($C_{22}H_{35}NO_5SNa^+$) calcd = 448.2128, obsd = 448.2111.

(R)-1-tert-butyl-4-methyl-2-(benzyloxymethyl)-2-methyl-succinate (18b). An amount of 0.70 g (2.2 mmol) of **15b** was dissolved in 10 ml of dry MeOH in a 25 ml round-bottomed flask. Dry N_2 was passed through the solution for 15 min to remove dissolved oxygen. The solution was then irradiated with a 500-W Hanovia lamp. The photo-induced Wolff rearrangement was monitored by the disappearance of the diazo

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stretch (2106 cm^{-1}). The reaction was complete after 48 h and the crude reaction mixture was concentrated *in vacuo* to give a clear, viscous oil that was purified by flash chromatography (4 : 6 Et_2O/Hexane, $R_f = 0.38$) to give 0.352 g (1.10 mmol, 50% yield) of a clear, viscous oil. $[\alpha]_D^{21} = +5.4$ ($c = 0.08$, CH_2Cl_2). IR (cm^{-1}) 1724. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.27 (3H, s), 1.43 (9H, s), 2.53 (1H, d, $J = 16$ Hz), 2.79 (1H, d, $J = 16$ Hz), 3.50 (1H, d, $J = 9$ Hz), 3.61 (1H, d, $J = 9$ Hz), 3.63 (2H, s), 4.51 (2H, s), 7.31 (5H, m). ^{13}C–NMR (75 MHz, $CDCl_3$): 21.0, 28.0, 39.3, 46.0, 51.5, 73.4, 74.7, 80.8, 127.55, 127.64, 128.4, 128.5, 138.5, 172.1, 174.0. HRMS ($C_{18}H_{26}O_5Na^+$) calcd = 345.1672, obsd = 345.1669.

(S)-1-tert-butyl-4-methyl-2-(tert-butylthiomethyl)-2-methylsuccinate (18c). Prepared in a manner similar to that of **18b**. The product was purified by flash chromatography, which rendered the product as a clear, colorless oil (0.32 g, 1.04 mmol, 80%). $[\alpha]_D^{20} = +1.5$ ($c = 0.1$, $CHCl_3$). ^{1}H–NMR (300 MHz, $CDCl_3$): 1.24 (3H, s), 1.27 (9H, s), 1.42 (9H, s), 2.54 (1H, d, $J = 16.2$ Hz), 2.76 (1H, d, $J = 16.2$ Hz), 2.82 (2H, s), 3.62 (3H, s). ^{13}C–NMR (75 MHz, $CDCl_3$): 22.8, 28.0, 30.9, 35.9, 41.0, 42.0, 44.8, 51.5, 81.0, 171.7, 174.3. IR (cm^{-1}) 2972, 1726,1458, 1365,1150. HRMS ($C_{15}H_{28}NO_4SNa^+$) calcd = 327.1600, obsd = 327.1592.

(R)-2-((benzyloxy)methyl)-4-methoxy-2-methyl-4-oxobutanoic acid (19b). In a 50-ml round-bottomed flask 0.352 g (1.10 mmol) of **18b** was dissolved in 20 ml of dry CH_3CN, and 1 ml of water was added. A measure of 1.0 g of KSF clay was added and the solution was heated to reflux solvent. The reaction was monitored by TLC (4 : 6 Et_2O/Hexane) and was determined to be complete after 7 h. The KSF clay was removed by vacuum filtration, and the filtrate was washed with CH_3CN. The CH_3CN was removed *in vacuo* to give a clear, viscous oil that was purified by flash chromatography (1 : 9 MeOH/$CHCl_3$, $R_f = 0.50$) to give 0.207 g (0.77 mmol, 71% yield) of a clear, viscous oil. $[\alpha]_D^{21} = +4.8$ ($c = 0.04$, CH_2Cl_2). IR (cm^{-1}) 1736, 1703. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.34 (3H, s), 2.62 (1H, d, $J = 16$ Hz), 2.82 (1H, d, $J = 16$ Hz), 3.56 (1H, d, $J = 9$ Hz), 3.62 (3H, s), 3.65 (1H, d, $J = 9$ Hz), 4.52 (2H, s), 7.31 (5H, m), 10.00 (1H, bs). ^{13}C–NMR (75 MHz, $CDCl_3$): 20.8, 28.9, 38.9, 45.5, 51.8, 73.5, 74.0, 127.7, 127.8, 128.5, 138.1, 171.9, 181.2. HRMS: ($C_{14}H_{18}O_5Na^+$) calcd = 289.1046, obsd = 289.1039.

(S)-2-(tert-butylthiomethyl)-4-methoxy-2-methyl-4-oxobutanoic acid (19c). Prepared in a manner similar to that of **19b**. The product was purified by column chromatography (3 : 7 Et_2O/Hexane). The product was a colorless oil (0.18 g, 71%, 0.74 mmol). $[\alpha]_D^{20} = +1.9$ ($c = 0.06$, $CHCl_3$). ^{1}H–NMR (300 MHz, $CDCl_3$): 1.27 (9H, s), 1.32 (3H, s), 2.65 (1H, d, $J = 16.7$ Hz), 2.81 (1H, d, $J = 16.7$ Hz), 2.85 (1H, d, $J = 12.0$ Hz), 2.91 (1 H, d $J = 12.0$ Hz), 3.64 (3H, s). ^{13}C–NMR (75 MHz, $CDCl_3$): 22.7, 28.8, 30.9, 35.4, 40.5, 42.4, 44.4, 51.8, 171.7, 181.7. HRMS ($C_{11}H_{20}NO_4SNa^+$) calcd = 271.0974, obsd = 271.0967.

(R)-methyl-4-(benzyloxy)-3-(((4-methoxybenzyloxy) carbonylamino)methyl)-3-methylbutanoate (20b). Prepared using a Curtius rearrangement similar to the preparation of **5b**. The product was purified by flash chromatography (200 ml of silica gel, 3 : 7 EtOAc/Hexane) to give 0.195 g (0.49 mmol, 72% yield, 66% *ee*) of a clear, viscous oil. TLC $R_f = 0.39$. $[\alpha]_D^{14} = +1.7$ ($c = 0.04$, CH_2Cl_2). IR(cm^{-1}) 3369, 1717. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.43 (3H, s), 2.70 (1H, d, $J = 14$ Hz), 2.81 (1H, d, $J = 14$ Hz), 3.58 (5H, s), 3.79 (3H, s), 4.49 (2H, s), 4.99 (2H, s), 5.50 (1H, bs), 6.87 (2H, d, $J = 7$ Hz), 7.30 (7H, m). ^{13}C–NMR (75 MHz, $CDCl_3$): 22.4, 40.7, 51.7, 54.6, 55.4, 66.1, 73.4, 74.6, 114.0, 127.75, 127.8, 128.1, 128.5, 128.7, 128.9, 130.0, 138.2, 138.1, 155.3, 159.6, 171.8. HRMS ($C_{22}H_{27}NO_6Na^+$) calcd = 424.1701, obsd = 424.1720. The ee was determined by analytical chiral HPLC (Chiralcel OJ-H, 280 nm, 4% Ipr-OH/Hexane) $Rt_{(S)} = 99.703$, $Rt_{(R)} = 122.183$.

(R)-methyl-4-(tert-butylthio)-3-((4-methoxybenzyloxy) carbonylamino)-3-methylbutanoate (20c). Prepared using a Curtius rearrangement similar to the preparation of **5b**. The product was purified by flash chromatography ($R_f = 0.35$, 7 : 3 Hexane/EtOAc). This rendered the product as a clear, colorless oil (0.16 g, 72%, 0.522 mmol, 91% ee). $[\alpha]_D^{20} = +3.7$ ($c = 0.05$, $CHCl_3$). ^{1}H–NMR (300 MHz, $CDCl_3$): 1.3 (9H, s), 1.45 (3H, s), 2.71 (2H, d, $J = 14$ Hz), 2.94 (1H, d, $J = 12$ Hz), 3.06 (1H, d, $J = 12$ Hz), 3.65 (3H, s), 3.81 (3H, s), 5.00 (2H, s), 5.38 (1H, bs), 6.87 (2H, d, $J = 8$ Hz), 7.28 (2H, d, $J = 8$ Hz). ^{13}C–NMR (75 MHz, $CDCl_3$): 31.1, 42.4, 51.8, 54.1, 55.4, 114.0, 130.0, 159.6, 171.6. HRMS ($C_{19}H_{29}NO_5SNa^+$) calcd = 406.1658, obsd = 406.1648. IR (cm^{-1}) 2974, 2253, 1717, 1613, 1514, 1460. HPLC (Chiralcel OJ-H, 280 nm, 3% Ipr-OH/Hexane) $Rt_{1(S)} = 37.18$, $Rt_{2(R)} = 42.31$ 91% *ee*.

(S)-4-tert-butyl 1-ethyl 2-(benzyloxymethyl)-2-methylsuccinate (21b). An amount of 0.540 g (1.9 mmol) of **11b** was dissolved in 5 ml of dry CH_2Cl_2 and placed in a 20 ml pressure tube at −10 °C. A volume of 250 µl of H_2SO_4 and 15 ml of condensed IBE was added; the tube was sealed and the reaction was allowed to stir overnight at room temperature. The tube was then placed in an icebath at 0 °C for 15 min and then opened, and allowed to stir at room temperature for 2 h to allow evaporation of any remaining IBE. The solution was diluted with 25 ml of Et_2O and washed three times with 1.0-N NaOH, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a clear, viscous oil. 0.51 g (4.4 mmol, 73% yield). TLC (1 : 1 Et_2O/Hexane) $R_f = 0.34$. $[\alpha]_D^{23} = -3.8$ ($c = 0.02$, CH_2Cl_2). IR (cm^{-1}) 1726. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.24 (3H, t, $J = 7$ Hz), 1.30 (3H, s), 1.41 (9H, s), 2.46 (1H, d, $J = 16$ Hz), 2.74 (1H, d, $J = 16$ Hz), 3.54 (1H, d, $J = 9$ Hz), 3.59 (1H, d, $J = 9$ Hz), 4.15 (2H, q, $J = 7$ Hz), 4.51 (2H, s), 7.31 (5H, m). ^{13}C–NMR (75 MHz, $CDCl_3$): 14.3, 20.7, 28.2, 40.9, 45.6, 60.8, 73.4, 74.8, 80.8, 127.6, 127.7, 128.5, 138.5, 170.6, 175.1. HRMS ($C_{19}H_{28}O_5Na^+$) calcd = 359.1829, obsd = 359.1824.

(R)-4-tert-butyl 1-methyl 2-(tert-butylthiomethyl)-2-methylsuccinate (21c). Acid **11c** [made the way **11a** was prepared: 80% yield $[\alpha]_D^{20} = +1.8$ ($c = 0.25$, $CHCl_3$) ^{1}H–NMR (300 MHz, $CDCl_3$): 1.29 (9H, s), 1.35 (3H, s), 2.67 (H, d, $J = 10$ Hz), 2.85 (1H, d, $J = 8$ Hz), 2.89 (1H, d, $J = 8$ Hz), 2.92 (1H, d, $J = 10$ Hz), 3.72 (3H, s). ^{13}C–NMR (75 MHz, $CDCl_3$): 22.7, 30.9, 36.1, 40.9, 42.4, 44.5, 52.5, 175.9, 176.4. IR(cm^{-1}) 2960, 1707, 1459, 1359,1197, 1159. HRMS ($C_{11}H_{20}O_4SNa^+$) calcd = 271.0974, obsd = 271.0971.] (0.6 g, 2.06 mmol) was converted to **21c** in a similar manner as for **21b** to give the product as a clear oil (0.625 g, 80%, 1.64 mmol). $[\alpha]_D^{20}$ −2.7 ($c = 0.20$, $CHCl_3$). ^{1}H–NMR (300 MHz, $CDCl_3$): 1.29 (9H, s), 1.30 (3H, s), 1.42 (9H, s), 2.51 (1H, d, $J = 15$ Hz), 2.78 (1H, d, $J = 15$ Hz), 2.82 (1H, d, $J = 11$ Hz), 2.87 (1H, d, $J = 11$ Hz),

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3.71 (3H, s). ^{13}C–NMR (75 MHz, $CDCl_3$): 22.4, 28.2, 30.9, 36.3, 42.2, 43.0, 44.7, 52.2, 81.0, 170.4. 176.0. IR(cm^{-1}) 2972, 1727, 1458, 1434, 1365. HRMS ($C_{15}H_{28}NO_4SNa^+$) calcd = 327.1593, obsd = 327.1600.

(S)-2-(benzyloxymethyl)-4-tert-butoxy-2-methyl-4-oxobutanoic acid (22b). An amount of 0.658 g (2.00 mmol) of **21b** was dissolved in 7 ml of THF. As much as 0.140 g (5.9 mmol, 3 equiv.) of LiOH was dissolved in 3 ml of water and added to the reaction flask. The reaction mixture was allowed to stir at room temperature for 72 h. The THF was removed *in vacuo* and 30 ml of 1.0 N NaOH was added to the reaction mixture. The basic aqueous layer was then washed three times with 50 ml portions of Et_2O, acidified to pH 1.0 using cold 10% HCl, then extracted with three 50 ml portions of Et_2O. The Et_2O extracts were combined and concentrated *in vacuo* to give 0.395 g (1.30 mmol, 64% yield) of a clear, viscous liquid. TLC (2 : 8 Ipr-OH/Hexane) $R_f = 0.48$. $[\alpha]_D^{21} = -2.9$ ($c = 0.02$, $CHCl_3$). IR (cm^{-1}) 1726. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.36 (3H, s), 1.42 (9H, s), 2.51 (1H, d, $J = 16$ Hz), 2.75 (1H, d, $J = 16$ Hz), 3.59 (2H, s), 4.55 (2H, s), 4.99 (2H, s), 7.33 (5H, m). ^{13}C–NMR (75 MHz, $CDCl_3$): 20.6, 28.1, 40.9, 45.6, 73.6, 74.4, 81.3, 127.7, 127.8, 128.6, 138.2, 170.5, 181.3 HRMS ($C_{17}H_{24}O_5Na^+$) calcd = 331.1516, obsd = 331.1509.

(R)-4-tert-butoxy-2-(tert-butylthiomethyl)-2-methyl-4-oxobutanoic acid (22c). Preparation was similar to that of **22b.** The product was obtained as a solid product (0.400 g, 67%, 1.37 mmol). $[\alpha]_D^{20} = -1.9$ ($c = 0.22$, $CHCl_3$). ^{1}H–NMR (300 MHz, $CDCl_3$): 1.30 (9H, s), 1.32 (3H, s), 1.43 (9H, s), 2.55 (1H, d, $J = 16$ Hz), 2.76 (1H, d, $J = 16$ Hz), 2.88 (2H, s). ^{13}C–NMR (75 MHz, $CDCl_3$): 22.4, 28.2, 30.9, 35.7, 42.3, 42.5, 44.5, 81.3, 170.35, 181.8. IR (cm^{-1}) 2974, 1704, 1459, 1366, 1151. HRMS ($C_{14}H_{26}NO_4SNa^+$) calcd = 313.1444, obsd = 313.1434.

(S)-tert-butyl 4-(benzyloxy)-3-((4-methoxybenzyloxy) carbonylamino)-3-methylbutanoate (23b). Prepared using a Curtius rearrangement similar to that of **5b.** The product was purified by flash chromatography (200 ml of silica gel, 1 : 1 Et_2O/Hexane, $R_f = 0.18$) to give 0.366 g (0.76 mmol, 58% yield, 69% *ee*) of a clear, viscous oil. $[\alpha]_D^{22} = -3.2$ ($c = 0.09$, CH_2Cl_2). IR 3361, 1726. ^{1}H–NMR (300 MHz, $CDCl_3$): 1.41 (12H, s), 2.64 (1H, d, $J = 14$ Hz), 2.72 (1H, d, $J = 14$ Hz), 3.59 (2H, m), 3.79 (3H, s), 4.51 (2H, s), 4.99 (2H, s), 5.57 (1H, bs), 6.87 (2H, d, $J = 8.6$ Hz), 7.30 (7H, m). ^{13}C–NMR (75 MHz, $CDCl_3$): 22.2, 28.2, 42.2, 54.6, 55.4, 66.1, 73.4, 74.5, 81.0, 114.0, 127.7, 127.8, 128.5, 128.9, 130.0, 138.2, 155.2, 159.6, 170.7. HRMS ($C_{25}H_{33}NO_6Na^+$) calcd = 466.2200, obsd = 466.2190. The ee was determined by analytical chiral HPLC (Chiralcel OJ-H, 6% Ipr-OH/Hexane, 286 nm) $Rt_{(S)} = 29.24$, $Rt_{(R)} = 41.78$.

(S)-tert-Butyl 4-(tert-butylthio)-3-((4-methoxybenzyloxy) carbonylamino)-3-methylbutanoate (23c). Preparation was using a Curtius rearrangement similar to the preparation of **5b**. The product was purified by flash chromatography (4 : 1 Hexane/EtOAc). This rendered the product as a clear, colorless oil (0.46 g, 79%, 1.08 mmol): TLC $R_f = 0.31$ (4 : 1 Hexane/EtOAc). $[\alpha]_D^{20} = -3.5$ ($c = 0.02$, $CHCl_3$). ^{1}H–NMR (300 MHz, $CDCl_3$): 1.29 (9H, s), 1.42 (9H, s), 1.45 (3H, s), 2.48 (1H, d, $J = 11.47$ Hz), 2.72 (1H, d, $J = 11$ Hz), 3.01 (2H, dd, $J = 3.2$, 10.5 Hz), 3.79 (3H, s), 4.99 (2H, s), 5.46 (1H, bs), 6.87 (2H, d, $J = 8.8$ Hz), 7.28 (2H, d, $J = 8$ Hz). ^{13}C–NMR (75 MHz, $CDCl_3$): 24.3, 28.1, 31.0, 37.8, 42.3, 44.3, 54.2, 55.4, 71.6, 81.1, 113.9, 129.5, 130.0, 154.5,159.5, 170.5. HPLC (Chiralcel OJ-H, 280 nm, 4% Ipr-OH/Hexane) $Rt_{1(S)} = 10.05$, $Rt_{2(R)} = 14.51$. HRMS ($C_{22}H_{35}NO_5SNa^+$) calcd = 448.212, obsd = 448.2120. IR (cm^{-1}) 2916, 1719,1514, 1460.

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