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Organocatalytic Stereoselective Synthesis of Acyclic γ-Nitrothioesters with All-Carbon Quaternary Stereogenic Centers

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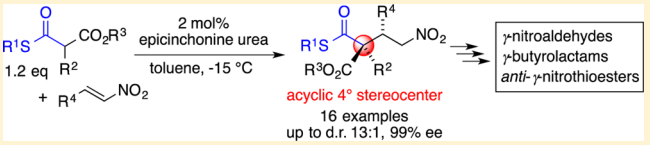
Supporting Information

ABSTRACT: A method for the stereoselective synthesis of acyclic thioesters bearing adjacent quaternary and tertiary stereogenic centers under mild organocatalytic conditions was developed. α-Substituted monothiomalonates (MTMs) were used as thioester enolate equivalents. They reacted cleanly with nitroolefins in the presence of 1−6 mol % of cinchona alkaloid urea derivatives, and provided access to γ-nitrothioesters with quaternary stereocenters in high yields and diastereo- and enantioselectivities. Mechanistic investigations provided insight into the parameters that determine the stereoselectivity and showed that the diastereoselectivity can be controlled by the nature of the MTM substrate. The different reactivities of the three functional groups (oxoester, thioester, nitro moieties) within the conjugate addition products allowed for straightforward access to other compounds with quaternary stereogenic centers, such as γ-nitroaldehydes and γ-butyrolactams.

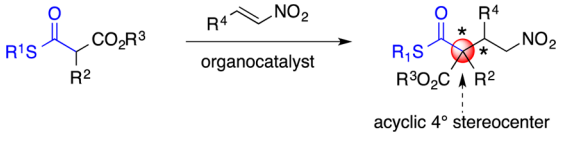


INTRODUCTION

Stereoselective C−C bond forming reactions between enolates and electrophiles that proceed under mild conditions and give rise to acyclic compounds with an all-carbon quaternary stereogenic center are among the most challenging reactions in organic synthesis.[1] Particularly useful are products of reactions of thioester enolates, since the thioester moiety is a versatile functional group. It is key in several biological pathways, e.g., the biosynthesis of polyketides,[2] and allows in organic synthesis for numerous further transformations, e.g., into aldehydes, ketones, or amides.[3] In comparison to analogous oxoester moieties, thioesters are ∼100 fold more reactive toward nucleophiles such as amines.[4] Whereas thioester enolates are convenient for introducing thioester moieties, their formation under mild organocatalytic conditions is not trivial because of the tendency of thioesters to react with nucleophiles and the comparatively high pK_a value of the proton at the α-carbon.[5,6] Barbas and Tan tackled this challenge by using electron-poor thioesters and dithiomalonates, respectively.[7−9] Inspired by nature, Ricci, our group, and others used malonic acid half thioesters (MAHTs) as thioester enolate equivalents that serve as building blocks for the biosynthesis of fatty acids and polyketides.[2,10−12] With all of these thioester enolate equivalents, stereoselective organocatalytic addition reactions to form chiral products bearing tertiary stereogenic centers have been achieved.[5−12] However, reactions that provide acyclic thioesters with an all-carbon quaternary stereogenic center adjacent to the thioester moiety are difficult. Even with extensively investigated α-ketoesters and α-cyanoacetates only a few examples for the stereoselective synthesis of *acyclic* addition products with an all-carbon quaternary stereocenter under metal-free conditions are known, which highlights how challenging such syntheses are.[1,13,14]

Previously we introduced monothiomalonates (MTMs) as protected variants of MAHTs that react with electrophiles in a significantly more controlled fashion than MAHTs.[15,16] In initial studies, unsubstituted MTMs were found to react cleanly and stereoselectively with β-nitroolefins.[15] More recently we found that reactions of α-substituted MTMs with imines enable the stereoselective formation of β-aminothioesters containing adjacent quaternary and tertiary stereocenters.[16] These results inspired us to investigate whether α-substituted MTMs also react with nitroolefins and allow access to acyclic γ-nitrothioesters with neighboring quaternary and tertiary stereocenters (Scheme 1).

Scheme 1. Conjugate Addition Reactions between Monothiomalonates (MTMs) and Nitroolefins



Herein we present reactions between α-substituted monothiomalonates (MTMs) and nitroolefins that provide in the presence of catalytic amounts of cinchona alkaloid derivatives γ-nitrothioesters with an all-carbon quaternary stereogenic center adjacent to a tertiary stereocenter in excellent yields and stereoselectivities. We also show that the three functional groups within the conjugate addition products are orthogonal and can be used to access *anti*-configured α,β-disubstituted-γ-nitrothioesters as well as other valuable compounds with an all-carbon quaternary stereogenic center (e.g., chiral γ-nitro-

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aldehydes and γ-butyrolactams) that are difficult to prepare by other routes.

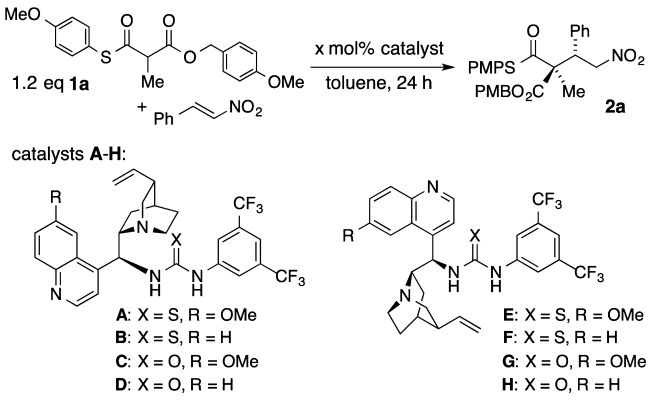
RESULTS AND DISCUSSION

We started our investigations by exploring the reactivity of α-methyl substituted MTM **1a** with β-nitrostyrene under similar conditions as those used before.[16] Thus, we explored cinchona alkaloid-(thio)urea derivatives (**A**–**H**) as catalysts[17,18] and used *p*-methoxyphenyl (PMP) thioester and *p*-methoxybenzyl (PMB) oxoester moieties on the α-substituted MTM that had in the previous studies been found to generate the products with the highest stereoselectivities.[16] The acid labile PMB group was also expected to allow for facile removal followed by decarboxylation of the resulting carboxylic acid moiety.

Remarkably, α-substituted MTM **1a** reacted readily with β-nitrostyrene in the presence of any of the tested cinchona alkaloid derived (thio)ureas **A**–**H**, and the desired conjugate addition product **2a** with a quaternary stereogenic center was generally obtained with good stereoselectivities (Table 1).

It is also notable that only a small excess of the MTM sufficed to achieve quantitative conversion of the nitroolefin. The best diastereo- and enantioselectivities were observed when the epicinchonine urea derivative **H** was used as catalyst (Table 1, entry 8). Other common chiral bifunctional catalysts such as unfunctionalized cinchona alkaloids or Takemoto's catalyst[19] were found to be less stereoselective.[20] Interestingly, for reactions with α-unsubstituted MTMs epiquinidine thiourea **E** and not **H** had been found to be the optimal catalyst.[15] This indicates that structural differences between substituted and unsubstituted MTMs are easily accommodated by cinchona alkaloid-urea catalysts.

Table 1. 1,4-Addition Reactions between MTM 1a and Nitrostyrene Catalyzed by Cinchona Alkaloid Derivatives A–H[a]



entry	catalyst	mol %	T (°C)	conv[b] (%)	dr[b]	ee[c] (%)
1	**A**	10	rt	quant.	2:1	79[d]
2	**B**	10	rt	quant.	2:1	81[d]
3	**C**	10	rt	quant.	3:1	82[d]
4	**D**	10	rt	quant.	3:1	91[d]
5	**E**	10	rt	quant.	4:1	97
6	**F**	10	rt	quant.	4:1	96
7	**G**	10	rt	quant.	6:1	94
8	**H**	10	rt	quant.	7:1	98
9	**H**	1	rt	55	7:1	97
10	**H**	1	0	75	9:1	98
11	**H**	1	−15	85	11:1	99
12	**H**	1	−35	55	13:1	nd[e]
13	**H**	2	−15	≥95	11:1	99
14[f]	**H**	2	−15	87[g]	11:1	99

[a]Reactions were performed using 0.12 mmol of **1a** and 0.10 mmol of nitrostyrene in 200 μL of toluene. [b]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c]Enantiomeric excess of the major stereoisomer determined by chiral stationary phase HPLC analysis. [d]The enantiomeric product was obtained. [e]Not determined. [f]Reaction was performed on a gram scale. [g]Isolated yield.

Further optimization of the reaction parameters showed that toluene is the best solvent in terms of both reactivity and stereoselectivity.[20] Variations in the temperature and the amount of catalyst revealed that at −15 °C a catalyst loading of 2 mol % sufficed to obtain a near quantitative conversion of nitrostyrene to the conjugate addition product.[20,21] Under these optimized conditions MTM **1a** reacted readily with nitrostyrene to γ-nitrothioester **2a**, which was obtained with a diastereoselectivity of 11:1 and an enantiomeric excess of 99% (Table 1, entry 13). These results were achieved both on a scale of 0.1 mmol as well as on a 30 fold larger scale (Table 1, entry 14).

Substrate Scope. With the optimized reaction conditions in hand we evaluated the scope of the conjugate addition reactions and reacted a range of different α-substituted MTMs and nitroolefins in the presence of 2–6 mol % of the epicinchonine urea **H** (Table 2). Various nitroolefins with both electron-rich and electron-poor aromatic as well as hetero-aromatic substituents reacted readily with the substituted MTM **1a**. The γ-nitrothioesters **2a**–**2m** with an all-carbon quaternary stereogenic center adjacent to a tertiary stereocenter were obtained in good yields, diastereoselectivities of 7:1–13:1, and excellent enantioselectivities of 97–99% ee (Table 2, entries 1–10).

MTMs **1b**–**1d** bearing ethyl, allyl, or propargyl groups at C(α) were also tolerated as substrates but required slightly higher catalyst loadings (5 or 6 mol %) to provide the desired addition products in good yields and enantioselectivities (Table 2, entries 11–13). Also the diastereoselectivities are in these cases lower compared to all other examples, which illustrates the challenge of forming a C–C bond in a sterically demanding environment with high stereoselectivities and underlines how remarkable the stereoselectivities that were obtained with conjugate addition products **2a**–**2j** are. Current limitations are MTMs bearing an aromatic substituent at the α-carbon and aliphatic nitroolefins, which did not react or only formed trace amounts of the desired γ-nitrothioester.

Mechanistic Considerations. The conjugate additions of the α-substituted MTMs proceed with a remarkably high stereodifferentiation between the seemingly similar oxo- and thioester moieties. A similarly high differentiation was previously observed for addition reactions of these MTMs to imines suggesting that it is general for this type of reactions.[16] To understand this observation, we performed experiments with MTMs bearing either two benzyl (-SBn, -OPMB) or two phenyl groups (-SPMP, -OPMP) at the thio- and the oxoester moieties. Conjugate additions with these MTMs provided the products without or only with low diastereoselectivity demonstrating that the combination of a rigid phenyl with a flexible benzyl ester within the MTM is important for high stereoselectivity (Figure 1a).[20] This finding showed that the directionality of the interaction between the MTM and the catalyst is controlled by the groups that are attached to the oxo- and thioester moieties. Taking this into account, it is plausible that the MTM coordinates to the urea moiety of the

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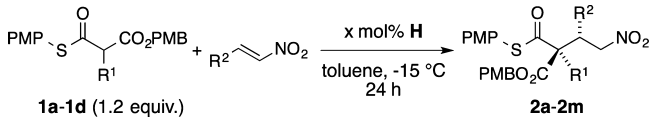
Table 2. Scope of 1,4-Addition Reactions between Substituted MTMs and Nitroolefins[a]



1a-1d (1.2 equiv.) **2a-2m**

entry	product	R^1	R^2	mol %	yield[b] (%)	dr[c]	ee[d] (%)
1	**2a**	Me	Ph	2	87	11:1	99
2	**2b**	Me	C_6H_4-4-F	2	77	9:1	98
3	**2c**	Me	C_6H_4-4-Cl	2	83	10:1	98
4	**2d**	Me	C_6H_4-4-Br	2	86	11:1	98
5	**2e**	Me	C_6H_4-4-OMe	3	86	9:1	98
6	**2f**	Me	C_6H_4-4-NO_2	2	85	7:1	97
7	**2g**	Me	C_6H_4-2-Br	2	81	11:1	99
8	**2h**	Me	C_6H_3-2,4-Cl_2	2	85	8:1	98
9	**2i**	Me	2-Naphthyl	2	87	13:1	98
10	**2j**	Me	2-Thienyl	2	80	10:1	98
11[e]	**2k**	Et	Ph	6	75	6:1	97
12	**2l**	$CH_2CH{=}CH_2$	Ph	5	70	3:1	95
13	**2m**	$CH_2C{\equiv}CH$	Ph	5	81	3:1	92

[a]Reactions were performed using 0.24 mmol of **1** and 0.20 mmol of the nitroolefin in 400 μL of toluene. [b]Isolated yields of the mixture of stereoisomers of γ-nitrothioesters. [c]Determined by ^{1}H NMR spectroscopy of the isolated product. [d]Determined by chiral stationary phase HPLC analysis. [e]1.2 equiv of the nitroolefin was used.

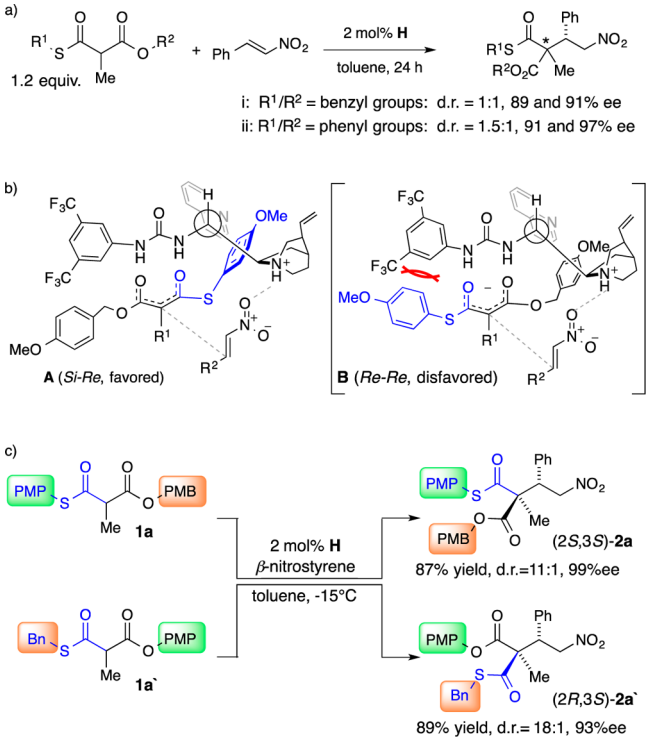


Figure 1. (a) Reactions with MTMs bearing two phenyl or two benzyl esters (i: R^1 = Bn, R^2 = PMB, ii: R^1 = R^2 = PMP), (b) proposed transition state model, and (c) substrate controlled formation of the quaternary stereogenic center. See Supporting Information for the determination of the absolute and relative stereochemistry.

catalyst[18,22] with the benzyl moiety on the same side as the 3,5-di(trifluoromethyl)phenyl group of the catalyst (Figure 1b, left) followed by addition of the MTM enolate from the *Si* face to the *Re* face of the nitroolefin. The depicted orientation of the nitroolefin will likely be favored by a H-bond between the quinuclidine moiety of the catalyst and the nitronate that is generated upon C−C bond formation.[23] This model is in agreement with the observed absolute and relative configuration of the major stereoisomer of the addition product that was determined by X-ray crystal structure and NOE spectroscopic analysis.[24] An alternative *Re*−*Re* face approach is less likely because of unfavorable steric interactions (Figure 1b, right).

To probe this transition state model we prepared MTM **1a′** within which the benzyl and phenyl groups have exchanged places compared to **1a** and are now on the thioester and oxoester moieties, respectively (Figure 1c). On the basis of our proposed transition state model, this MTM derivative was, upon reaction with nitroolefins in the presence of catalyst **H**, expected to provide the epimer of **2** in which the thio- and oxoester moieties have exchanged their places at the quaternary stereogenic center. This was found to be the case, and the conjugate addition product **2a′** was obtained as the major diastereoisomer (dr 18:1) with an enantiomeric excess of 93%. These results, which are similar to those previously obtained with imines as electrophiles,[16] not only support the proposed transition state model, but also show that diastereomeric products are easily accessible with the same catalyst by a simple variation of the functional groups within the substrate MTM.[25]

Derivatives of the γ-Nitrothioesters. Next, we explored the synthetic versatility of the conjugate addition products. The γ-nitrothioesters have a high density of orthogonal, functional groups at the quaternary stereogenic center that should allow access to other synthetically valuable chiral compounds by selective functionalization of the nitro (a), thioester (b), and oxoester (c) moieties.

(a). Reduction of the Nitro Group. The distinctly different reactivities of oxo- and thioesters toward nucleophilic amines[4] were envisioned to allow for a controlled lactamization upon reduction of the nitro group with the thioester group. Such γ-lactams are widespread in natural products with biological activity.[26] Indeed, reaction of γ-nitrothioester **2a** with Zn/AcOH provided γ-lactam **3a** without a detectable trace of the lactam derived from cyclization at the oxoester (Scheme 2a, top). Noteworthy, related conjugate addition products derived

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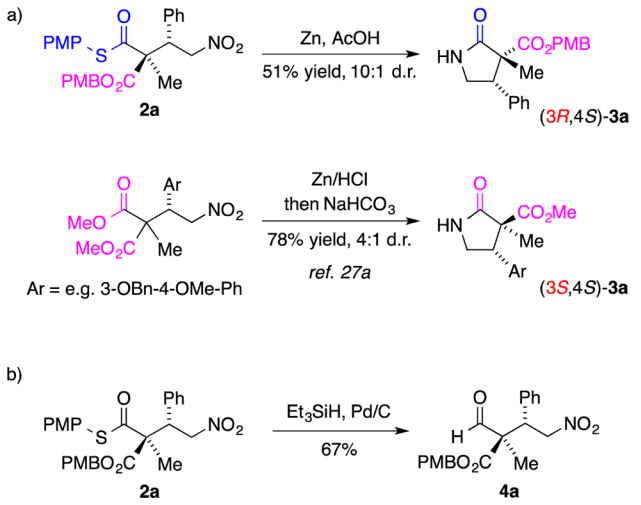
from symmetric malonates only allow access to the diastereoisomeric (3*S*,4*S*)-configured lactams (Scheme 2a, bottom).[27]

Scheme 2. Synthesis of Lactam 3a and γ-Nitroaldehyde 4a



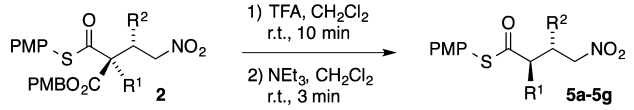
(b). Reduction of the Thioester Moiety. Reaction of **2a** under Fukuyama's conditions[28] yielded γ-nitroaldehyde **4a**, without affecting the integrity of the stereogenic centers (Scheme 2b, bottom). Related γ-nitroaldehydes are readily available by 1,4-addition reactions between aldehydes and nitroolefins utilizing chiral amines as catalysts.[29] However, despite the numerous chiral amines that have been developed for such Michael additions, reactions of α,α-disubstituted aldehydes bearing an alkyl and an ester moiety at the α-carbon have so far not been achieved. The presented 1,4-addition reaction of MTMs with nitroolefins therefore provides not only a convenient entry to these synthetically valuable γ-nitroaldehydes with an all-carbon quaternary stereogenic center but is also an attractive alternative to the synthesis of γ-nitroaldehydes via a route that relies on an enamine-based mechanism.

(c). Decarboxylation of the Oxoester Moiety. Finally we explored the reactivity of the oxoester moiety and reacted several of the γ-nitrothioesters **2** with trifluoroacetic acid to remove the acid-sensitive PMB protecting group.[30] Treatment with base induced then decarboxylation of the resulting carboxylic acid moiety and yielded γ-nitrothioesters **5a**–**g** (Table 3).

Remarkably, these two steps proceeded not only smoothly but provided all of the desired γ-nitrothioesters *anti*-selectively in an *anti*:*syn* ratio of ~5:1.[31] The diastereoisomers were easily separable by silica gel column chromatography so that diastereomerically pure *anti*-α-alkyl-β-aryl-γ-nitrothioesters **5a**–**5g** were isolated in good yields. The *anti* configuration of **5a**–**5g** was determined by crystal structure analysis (**5a** and **5c**), derivatization to the corresponding lactams followed by NOE spectroscopic analysis (**5f** and **5g**), or by analogy of the NMR spectra (see Supporting Information). A plausible rationale for the *anti*-selectivity involves coordination of the thioester enolate to the nitromethane moiety followed by protonation from the less hindered site (Scheme 3).

The enantioselective formation of such *anti*-configured stereoisomers under mild organocatalytic conditions has proven to be difficult[32] since *syn*-configured α,β-disubstituted carbonyl

Table 3. *anti*-Selective Decarboxylation of γ-Nitrothioesters 2



entry	product	R^1	R^2	dr[a] *anti*:*syn*	yield[b] (%) *anti*-**5**
1	**5a**	Me	Ph	5:1	80
2	**5b**	Me	C_6H_4-4-F	5:1	78
3[c]	**5c**	Me	C_6H_4-4-Cl	5:1	71
4	**5d**	Me	C_6H_4-4-Br	5:1	66
5	**5e**	Me	C_6H_4-4-OMe	5:1	80
6	**5f**	$CH_2CH{=}CH_2$	Ph	5:1	51
7	**5g**	$CH_2C{\equiv}CH$	Ph	5:1	70

[a]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b]Isolated yield of the *anti*-stereoisomers of the γ-nitrothioesters. [c]**5c** was formed with an enantioselectivity of 95% ee as determined by comparison with a racemic sample.[31]

compounds are typically the major stereoisomers formed in addition reactions of carbonyl compounds to nitroolefins that are catalyzed by chiral amines.[29] Thus, this *anti*-selective decarboxylation of the γ-nitrothioesters provides an attractive complementary approach to organocatalytic reactions relying on an enamine-based mechanism.

CONCLUSIONS

In conclusion we have introduced a route to access synthetically versatile acyclic γ-nitrothioesters with an all-carbon quaternary stereogenic center in high yields and stereoselectivities. The method relies on reactions between α-substituted monothiomalonates and nitroolefins that proceed under mild organocatalytic conditions and require only low catalyst loadings. The functional groups within the γ-nitrothioesters are orthogonal and can be selectively modified to provide access to many other valuable compounds with all-carbon quaternary stereogenic centers as well as *anti*-configured γ-nitroaldehydes. In addition, the stereochemistry of the quaternary stereocenter can be controlled by the choice of the substituents on the thio- and oxoester moieties of the MTMs. The results also show that substituted MTMs are valuable thioester enolate equivalents for asymmetric addition reactions in general and suggest that they will enable the synthesis of numerous other synthetically valuable chiral thioesters bearing quaternary stereogenic centers under mild conditions.

EXPERIMENTAL SECTION

General Aspects. Materials and reagents were of the highest commercially available grade and used without further purification. Reactions were monitored by thin layer chromatography using silica gel 60 F254 plates. Compounds were visualized by UV and $KMnO_4$. Flash chromatography was performed using silica gel, high-purity grade, pore size 60 Å, particle size 230–400 mesh. ^{1}H and ^{13}C NMR spectra were recorded on 300, 400, and 600 MHz NMR spectrometers. Chemical shifts are reported in ppm using TMS or the residual solvent peak as a reference. HPLC analyses were performed on an analytical HPLC with a diode array detector. IR spectra were recorded on a FT-IR spectrometer. High resolution mass spectra were recorded on a ESI-Q-TOF instrument.

4-Methoxybenzyl-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (**1a**), 4-methoxybenzyl-2-ethyl-3-((4-methoxyphenyl)thio)-3-oxopropanoate (**1b**), 4-methoxybenzyl-2-allyl-3-((4-methoxyphenyl)-

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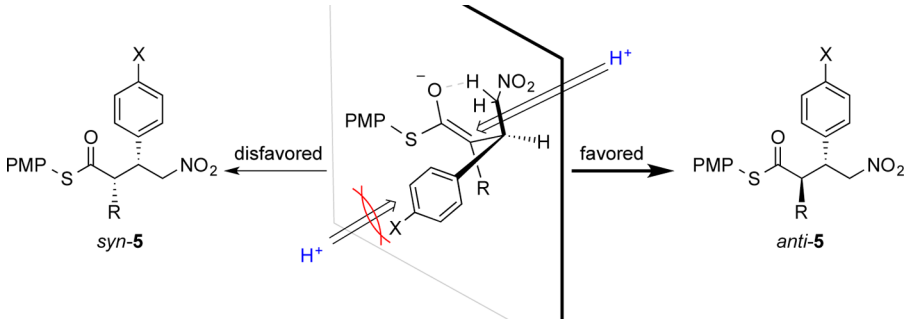
Scheme 3. Model for the *anti*-Selectivity of the Decarboxylation of Products 2



thio)-3-oxopropanoate (**1c**), 4-methoxybenzyl-3-((4-methoxyphenyl)-thio)-3-oxo-2-propargylpropanoate (**1d**), 4-methoxyphenyl-3-(benzylthio)-2-methyl-3-oxopropanoate (**1a′**), 4-methoxybenzyl-3-(benzylthio)-2-methyl-3-oxopropanoate (**1e**), 4-methoxyphenyl-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (**1f**) were synthesized according to the previously published procedure.[16]

General Procedure for Conjugate Addition Reactions of MTMs 1a−1f to Nitroolefins. The MTM **1a-1f** (1.2 equiv) and the nitroolefin (1 equiv) were dissolved in toluene (0.5 M), and the resulting mixture was cooled to −15 °C. The catalyst (2 mol %) was added to the mixture, which was then stirred for 24 h at −15 °C. The reaction mixture was then washed with saturated aqueous NH_4Cl (3 × 5 mL per mmol of nitroolefin) and extracted with EtOAc (3 × 5 mL per mmol of nitroolefin). The combined organic layers were dried over $MgSO_4$, concentrated at reduced pressure, and the crude product was purified by flash column chromatography on silica gel using a gradient of hexane:EtOAc from 15:1 to 5:1 to afford the γ-nitrothioesters **2a**−**2m**. Reactions were typically performed on a 0.2 mmol scale, in a screw top vial, unless otherwise stated.

*(2S,3S)-4-Methoxybenzyl-2-(((4-methoxyphenyl)thio)carbonyl)-2-methyl-4-nitro-3-phenylbutanoate (**2a**).* Colorless viscous oil (89 mg, 87%, dr = 11:1, 99% ee): ^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.18−7.07 (m, 4H), 7.05−6.94 (m, 5H), 6.74−6.69 (m, 2H), 6.67−6.62 (m, 2H), 5.07−4.91 (m, 4H), 4.52 (dd, *J* = 10.0, 4.2 Hz, 1H), 3.24 (s, 3H), 3.17 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6, 25 °C) 197.2, 170.0, 161.5, 160.5, 136.9, 135.5, 131.0, 129.8, 128.9, 128.6, 128.4, 127.4, 115.3, 114.3, 77.8, 68.0, 64.3, 54.9, 54.8, 49.5, 20.6; IR (neat) ν_{max}/cm^{-1} 3021, 2961, 1734, 1685, 1592, 1551, 1249; HRMS (ESI) *m*/*z* calculated for $C_{27}H_{27}NO_7S$ [M + NH_4]$^+$ 527.1846, found 527.1850. The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 90:10, 25 °C) at 1.0 mL/min, UV detection at 254 nm, t_R = 28.0 min (minor enantiomer), 33.4 min (major enantiomer).

Gram-Scale Synthesis of Conjugate Addition Product 2a (Table 1, entry 14). MTM **1a** (1.00 g, 2.8 mmol) and *trans*-β-nitrostyrene (0.50 g, 3.4 mmol) were dissolved in toluene (5.6 mL), and the resulting mixture was cooled to −15 °C. The catalyst (31 mg, 56 μmol, 2 mol %) was added to the mixture, which was then stirred for 22 h at −15 °C. The reaction mixture was then washed with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated at reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using a gradient of *n*-hexane:EtOAc from 15:1 to 5:1 to afford the γ-nitrothioester (2*S*,3*S*)-**2a** as a colorless viscous oil (1.30 g, 87%, dr = 11:1, 99% ee). The characterization data was identical to the one described above for **2a**.

*(2S,3S)-4-Methoxybenzyl-3-(4-fluorophenyl)-2-(((4-methoxyphenyl)thio)carbonyl)-2-methyl-4-nitrobutanoate (**2b**).* Colorless viscous oil (81 mg, 77%, dr = 9:1, 98% ee): ^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.18−7.09 (m, 4H), 6.80−6.76 (m, 2H), 6.73−6.67 (m, 2H), 6.67−6.56 (m, 4H), 5.06−4.92 (m, 2H), 4.91−4.77 (m, 2H), 4.43 (dd, *J* = 8.1, 6.3 Hz, 1H), 3.23 (s, 3H), 3.15 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6, 25 °C) 197.1, 169.9, 162.9 (d, *J* = 270 Hz), 161.5, 160.6, 136.8, 131.5 (d, *J* = 8 Hz), 131.2 (d, *J* = 3 Hz), 131.0, 127.2, 116.9, 115.8 (d, *J* = 21 Hz), 115.4, 114.4, 77.6, 68.0, 64.2, 54.9, 54.8, 48.7, 20.4; IR (neat) ν_{max}/cm^{-1} 3012, 2942, 2837, 1734, 1681, 1551, 1494, 1245; HRMS (ESI) *m*/*z* calculated for $C_{27}H_{26}FNO_7S$ [M + Na]$^+$ 550.1306, found 550.1307. The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 90:10, 25 °C) at 1.0 mL/min, UV detection at 254 nm, t_R = 25.0 min (minor enantiomer), 33.0 min (major enantiomer).

*(2S,3S)-4-Methoxybenzyl-3-(4-chlorophenyl)-2-(((4-methoxyphenyl)thio)carbonyl)-2-methyl-4-nitrobutanoate (**2c**).* Colorless viscous oil (90 mg, 83%, dr = 10:1, 98% ee): ^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.16−7.09 (m, 4H), 6.95−6.88 (m, 2H), 6.74−6.68 (m, 4H), 6.67−6.61 (m, 2H), 4.98 (d, *J* = 11.9 Hz, 1H), 4.92 (d, *J* = 11.9 Hz, 1H), 4.86−4.82 (m, 2H), 4.39 (dd, *J* = 8.5, 5.7 Hz, 1H), 3.24 (s, 3H), 3.15 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6, 25 °C) 197.0, 169.8, 161.5, 160.6, 136.8, 134.5, 134.0, 131.2, 131.1, 129.1, 127.2, 116.9, 115.4, 114.4, 77.4, 68.0, 64.1, 54.9, 54.8, 48.8, 20.5; IR (neat) ν_{max}/cm^{-1} 3011, 2971, 1730, 1686, 1549, 1514, 1243; HRMS (ESI) *m*/*z* calculated for $C_{27}H_{26}ClNO_7S$ [M + NH_4]$^+$ 561.1457, found 561.1458. The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 90:10, 25 °C) at 1.0 mL/min, UV detection at 254 nm, t_R = 25.0 min (minor enantiomer), 31.3 min (major enantiomer).

*(2S,3S)-4-Methoxybenzyl-3-(4-bromophenyl)-2-(((4-methoxyphenyl)thio)carbonyl)-2-methyl-4-nitrobutanoate (**2d**).* Colorless viscous oil (101 mg, 86%, dr = 11:1, 98% ee): ^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.15−7.04 (m, 6H), 6.74−6.67 (m, 2H), 6.67−6.60 (m, 4H), 4.96 (d, *J* = 11.9 Hz, 1H), 4.94 (d, *J* = 11.9 Hz, 1H), 4.85−4.82 (m, 2H), 4.36 (dd, *J* = 8.6, 5.6 Hz, 1H), 3.24 (s, 3H), 3.15 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6, 25 °C) 197.0, 169.8, 161.5, 160.6, 136.8, 134.5, 132.1, 131.5, 131.1, 127.2, 122.8, 116.9, 115.4, 114.4, 77.3, 68.0, 64.0, 54.85, 54.84, 48.8, 20.5; IR (neat) ν_{max}/cm^{-1} 3005, 2980, 1731, 1692, 1589, 1528; HRMS (ESI) *m*/*z* calculated for $C_{27}H_{26}BrNO_7S$ [M + NH_4]$^+$ 605.0952, found 605.0951. The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 95:5, 40 °C) at 1.0 mL/min, UV detection at 210 nm, t_R = 42.4 min (minor enantiomer), 47.6 min (major enantiomer).

*(2S,3S)-4-Methoxybenzyl-3-(4-methoxyphenyl)-2-(((4-methoxyphenyl)thio)carbonyl)-2-methyl-4-nitrobutanoate (**2e**).* Light yellow viscous oil (93 mg, 86%, dr = 9:1, 98% ee): ^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.20−7.10 (m, 4H), 6.99−6.90 (m, 2H), 6.73−6.68 (m, 2H), 6.67−6.61 (m, 2H), 6.61−6.55 (m, 2H), 5.08−4.90 (m, 4H), 4.51 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.23 (s, 3H), 3.22 (s, 3H), 3.15 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6, 25 °C) 197.3, 170.1, 161.5, 160.5, 159.9, 136.9, 131.0, 130.9, 127.4, 127.1, 117.2, 115.3, 114.4, 114.3, 78.0, 67.9, 64.5, 54.83, 54.80, 54.6, 49.0, 20.7; IR (neat) ν_{max}/cm^{-1} 3018, 2969, 1739, 1690, 1568, 1516, 1247; HRMS (ESI) *m*/*z* calculated for $C_{28}H_{29}NO_8S$ [M + NH_4]$^+$ 557.1952, found 557.1948. The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 90:10, 25 °C) at 1.0 mL/min, UV detection at 254 nm, t_R = 34.4 min (minor enantiomer), 49.5 min (major enantiomer).

*(2S,3S)-4-Methoxybenzyl-2-(((4-methoxyphenyl)thio)carbonyl)-2-methyl-4-nitro-3-(4-nitrophenyl)butanoate (**2f**).* Colorless viscous

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oil (94 mg, 85%, dr = 7:1, 97% ee): ^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.64−7.54 (m, 2H), 7.17−7.03 (m, 4H), 6.74−6.62 (m, 6H), 4.97 (d, J = 11.8 Hz, 1H), 4.93 (d, J = 11.8 Hz, 1H), 4.91−4.75 (m, 2H), 4.36 (dd, J = 9.7, 4.5 Hz, 1H), 3.28 (s, 3H), 3.15 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6, 25 °C) 196.8, 169.5, 161.7, 160.8, 147.9, 142.1, 136.8, 131.2, 130.4, 127.0, 123.7, 116.5, 115.5, 114.4, 77.0, 68.2, 63.8, 54.90, 54.89, 48.8, 20.6; IR (neat) ν_{max}/cm^{-1} 3008, 2973, 1742, 1678, 1592; HRMS (ESI) m/z calculated for $C_{27}H_{26}N_2O_9S$ [M + Na]$^+$ 577.1251, found 577.1254. The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (n-hexane/i-PrOH 90:10, 25 °C) at 1.0 mL/min, UV detection at 254 nm, t_R = 62.8 min (minor enantiomer), 87.5 min (major enantiomer).

(2S,3R)-4-Methoxybenzyl-3-(2-bromophenyl)-2-(((4-methoxyphenyl)thio)carbonyl)-2-methyl-4-nitrobutanoate (**2g**). Brownish viscous oil (95 mg, 81%, dr = 11:1, 99% ee): ^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.28−7.20 (m, 3H), 7.14−7.07 (m, 2H), 7.01 (dd, J = 7.9, 1.6 Hz, 1H), 6.78−6.63 (m, 5H), 6.59−6.48 (m, 1H), 5.46 (dd, J = 9.8, 4.0 Hz, 1H), 5.18−5.08 (m, 2H), 5.03−4.90 (m, 2H), 3.23 (s, 3H), 3.16 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6, 25 °C) 197.8, 169.9, 161.6, 160.5, 137.0, 136.2, 133.9, 131.1, 129.7, 128.7, 127.3, 116.9, 115.4, 114.3, 78.4, 67.9, 65.2, 54.9, 54.8, 46.8, 21.2; [2 × arom. C underneath C_6D_6 peaks] IR (neat) ν_{max}/cm^{-1} 3013, 2943, 1735, 1689, 1549, 1514, 1244; HRMS (ESI) m/z calculated for $C_{27}H_{26}BrNO_7S$ [M + NH_4]$^+$ 605.0952, found 605.0955. The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (n-hexane/i-PrOH 90:10, 25 °C) at 1.0 mL/min, UV detection at 254 nm, t_R = 23.9 min (minor enantiomer), 44.0 min (major enantiomer).

(2S,3R)-4-Methoxybenzyl-3-(2,4-dichlorophenyl)-2-(((4-methoxyphenyl)thio)carbonyl)-2-methyl-4-nitrobutanoate (**2h**). Colorless viscous oil (98 mg, 85%, dr = 8:1, 98% ee): ^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.24−7.19 (m, 2H), 7.14−7.05 (m, 3H), 7.03 (d, J = 2.2 Hz, 1H), 6.80−6.63 (m, 5H), 5.30 (dd, J = 10.6, 3.4 1H), 5.11−4.73 (m, 4H), 3.24 (s, 3H), 3.16 (s, 3H), 1.46 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6, 25 °C) 197.6, 169.7, 161.6, 160.6, 136.9, 136.6, 134.7, 133.0, 131.6, 131.2, 130.3, 129.5, 127.1, 116.7, 115.4, 114.4, 77.8, 68.0, 64.9, 54.87, 54.85, 43.7, 21.0; IR (neat) ν_{max}/cm^{-1} 3022, 2958, 1734, 1689, 1554, 1514, 1244; HRMS (ESI) m/z calculated for $C_{27}H_{25}Cl_2NO_7S$ [M + NH_4]$^+$ 595.1067, found 595.1066. The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (n-hexane/i-PrOH 80:20, 40 °C) at 0.7 mL/min, UV detection at 210 nm, t_R = 12.1 min (minor enantiomer), 16.7 min (major enantiomer).

(2S,3S)-4-Methoxylbenzyl-2-(((4-methoxyphenyl)thio)carbonyl)-2-methyl-3-(naphthalene-2-yl)-4-nitrobutanoate (**2i**). Light brown solid (97 mg, 87%, dr = 13:1, 98% ee): ^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.60−7.42 (m, 4H), 7.24−7.18 (m, 2H), 7.14−7.10 (m, 5H), 6.73−6.66 (m, 2H), 6.65−6.59 (m, 2H), 5.20−4.98 (m, 4H), 4.71 (dd, J = 10.8, 3.3 Hz, 1H), 3.24 (s, 3H), 3.14 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6, 25 °C) 197.3, 170.1, 161.5, 160.5, 136.9, 133.7, 133.5, 133.1, 131.0, 129.7, 128.9, 128.5, 127.4, 126.8, 126.6, 126.5, 117.1, 115.3, 114.4, 77.8, 68.0, 64.5, 54.83, 54.81, 49.7, 20.8 [1 × C arom. underneath C_6D_6 peaks]; IR (neat) ν_{max}/cm^{-1} 3001, 2879, 1720, 1673, 1545, 1254; HRMS (ESI) m/z calculated for $C_{31}H_{29}NO_7S$ [M + NH_4]$^+$ 577.2003, found 577.2001. The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (n-hexane/i-PrOH 90:10, 25 °C) at 1.0 mL/min, UV detection at 254 nm, t_R = 47.0 min (minor enantiomer), 56.3 min (major enantiomer).

(2S,3S)-4-Methoxybenzyl-2-(((4-methoxyphenyl)thio)carbonyl)-2-methyl-4-nitro-3-(thiophen-2-yl)butanoate (**2j**). Light yellow viscous oil (83 mg, 80%, dr = 10:1, 98% ee): ^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.20−7.10 (m, 4H), 6.74−6.60 (m, 6H), 6.54 (dd, J = 5.2, 3.5 Hz, 1H), 5.05 (d, J = 11.8 Hz, 1H), 5.02 (d, J = 11.8 Hz, 1H), 4.99−4.75 (m, 3H), 3.23 (s, 3H), 3.14 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6, 25 °C) 196.8, 169.8, 161.5, 160.5, 137.6, 136.8, 130.9, 129.1, 127.3, 126.9, 126.3, 116.9, 115.3, 114.3, 79.0, 68.1, 64.6, 54.82, 54.80, 45.6, 20.2; IR (neat) ν_{max}/cm^{-1} 3031, 2962, 1728, 1689, 1595, 1555, 1514, 1244; HRMS (ESI) m/z calculated for $C_{25}H_{25}NO_7S_2$ [M + NH_4]$^+$ 533.1411, found 533.1408. The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (n-hexane/i-PrOH 90:10, 25 °C) at 1.0 mL/min, UV detection at 254 nm, t_R = 29.4 min (minor enantiomer), 38.2 min (major enantiomer).

(2S,3S)-4-Methoxybenzyl-2-ethyl-2-(((4-methoxyphenyl)thio)carbonyl)-4-nitro-3-phenylbutanoate (**2k**). Colorless viscous oil (79 mg, 75%, dr = 6:1, 97% ee): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) 7.41−7.35 (m, 2H), 7.33−7.15 (m, 5H), 7.01−6.87 (m, 6H), 5.30 (d, J = 11.8 Hz, 1H), 5.24 (d, J = 11.8 Hz, 1H), 5.01 (dd, J = 13.8, 3.0 Hz, 1H), 4.89 (dd, J = 13.8, 10.9 Hz, 1H), 4.22 (dd, J = 10.9, 3.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.02 (dq, J = 14.7, 7.3 Hz, 1H), 1.65 (dq, J = 14.7, 7.3 Hz, 1H), 0.93 (apt. t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 197.4, 169.8, 161.3, 160.3, 136.7, 136.4, 135.3, 131.2, 129.0, 128.9, 128.5, 126.7, 115.3, 114.3, 78.7, 68.2, 67.7, 55.6, 55.5, 46.4, 28.1, 8.5; IR (neat) ν_{max}/cm^{-1} 3011, 2973, 1735, 1681, 1551, 1514, 1249; HRMS (ESI) m/z calculated for $C_{28}H_{29}NO_7S$ [M + NH_4]$^+$ 541.2003, found 541.1997. The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (n-hexane/i-PrOH 90:10, 25 °C) at 1.0 mL/min, UV detection at 254 nm, t_R = 19.9 min (minor enantiomer), 22.4 min (major enantiomer).

(2S,3S)-4-Methoxybenzyl-2-allyl-2-(((4-methoxyphenyl)thio)carbonyl)-4-nitro-3-phenylbutanoate (**2l**). Colorless viscous oil (75 mg, 70%, dr = 3:1, 95% ee): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) 7.40−7.35 (m, 2H), 7.34−7.16 (m, 5H), 7.01−6.88 (m, 6H), 5.78−5.67 (m, 1H), 5.31 (d, J = 11.7 Hz, 1H), 5.25 (d, J = 11.7 Hz, 1H), 5.22−5.05 (m, 4H), 5.03−4.86 (m, 2H), 4.21 (dd, J = 10.9, 3.1 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.75 (ddt, J = 14.9, 6.4, 1.5, 1H), 2.42−2.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 196.8, 169.5, 161.3, 160.3, 136.6, 135.0, 131.2, 130.4, 129.1, 129.0, 128.6, 126.6, 120.6, 116.5, 115.3, 114.3, 78.5, 68.4, 67.1, 55.6, 55.5, 47.0, 39.3; IR (neat) ν_{max}/cm^{-1} 3003, 2981, 1731, 1687, 1548, 1510; HRMS (ESI) m/z calculated for $C_{29}H_{29}NO_7S$ [M + NH_4]$^+$ 553.2003, found 553.1998. The enantiomeric excess was determined by HPLC using two Chiracel columns connected to each other (1st column; OD-H, second column; AS-H), (n-hexane/EtOH 97.5:2.5, 40 °C) at 0.8 mL/min, UV detection at 254 nm, t_R 58.8 min (minor enantiomer), 69.3 min (major enantiomer).

(2S,3S)-4-Methoxybenzyl-2-(((4-methoxyphenyl)thio)carbonyl)-4-nitro-3-phenyl-2-propargylbutanoate (**2m**). Colorless viscous oil (86 mg, 81%, dr = 3:1, 92% ee): peaks of major diastereoisomer, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) 7.41−7.36 (m, 2H), 7.34−7.14 (m, 5H), 7.09−7.04 (m, 2H), 6.98−6.88 (m, 4H), 5.31 (d, J = 11.8, 1H), 5.26 (d, J = 11.8, 1H), 5.15 (d, J = 13.8, 2.9 Hz, 1H), 4.92 (dd, J = 13.8, 11.2 Hz, 1H), 4.52 (dd, J = 11.2, 2.9 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.98 (dd, J = 17.6, 2.7 Hz, 1H), 2.46 (dd, J = 17.6, 2.7 Hz, 1H), 2.24 (apt. t., J = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 195.0, 168.3, 161.3, 160.4, 136.6, 134.8, 131.3, 130.5, 129.0, 128.7, 126.4, 116.2, 115.3, 114.3, 77.8, 74.0, 68.7, 68.3, 66.2, 55.6, 55.5, 45.7, 25.5; IR (neat) ν_{max}/cm^{-1} 3290, 3020, 2956, 1729, 1683, 1554, 1517; HRMS (ESI) m/z calculated for $C_{29}H_{27}NO_7S$ [M + NH_4]$^+$ 551.1846, found 551.1842. The enantiomeric excess was determined by HPLC using a Chiracel AS-H column (n-hexane/i-PrOH 90:10, 40 °C) at 0.8 mL/min, UV detection at 210 nm, t_R = 28.6 min (minor enantiomer), 43.1 min (major enantiomer).

(2R,3S)-4-Methoxyphenyl-2-((benzylthio)carbonyl)-2-methyl-4-nitro-3-phenylbutanoate (**2a′**). Colorless viscous oil (85 mg, 89%, dr = 18:1, 93% ee): ν_{max} (neat)/cm^{-1} 3010, 2951, 1740, 1681, 1552, 1503, 1248, 1175; ^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.15−7.10 (m, 2H), 7.08−6.92 (m, 8H), 6.74−6.69 (m, 2H), 6.62−6.55 (m, 2H), 4.82 (dd, J = 11.4, 2.0, 1H), 4.78−4.64 (m, 2H), 3.94 (d, J = 13.8 Hz, 1H), 3.85 (d, J = 13.8 Hz, 1H), 3.18 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6, 25 °C) 197.4, 168.5, 157.7, 144.0, 136.9, 134.7, 129.6, 128.9, 128.5, 128.5, 128.2, 127.4, 121.8, 114.3, 76.8, 63.0, 54.7, 48.3, 33.5, 18.2; HRMS (ESI) m/z calculated for $C_{26}H_{25}NO_6S$ [M + Na]$^+$ 502.1295, found 502.1294; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (n-hexane/i-PrOH 90:10, 25 °C) at 0.8 mL/min, UV detection at 254 nm, t_R = (minor enantiomer) = 25.5 min, (major enantiomer) = 38.0 min.

(2S,3S)-4-Methoxybenzyl-2-(((4-chlorophenyl)thio)carbonyl)-2-methyl-4-nitro-3-phenylbutanoate (**2a-Cl**). Colorless viscous oil that slowly crystallized (28 mg, 55%, dr = 7:1, 98% ee): ν_{max} (neat)/cm^{-1}

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3008, 2971, 1745, 1677, 1548, 1250; ^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.14−7.08 (m, 2H), 6.99−6.90 (m, 7H), 6.87−6.81 (m, 2H), 6.73−6.66 (m, 2H), 5.00 (d, J = 11.8, 1H), 4.94 (d, J = 11.8, 1H), 4.91−4.76 (m, 2H), 4.48 (dd, J = 10.2, 4.0 Hz, 1H), 3.23 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6, 25 °C) 195.8, 169.7, 160.6, 136.4, 136.3, 135.3, 131.0, 129.8, 129.7, 128.9, 128.5, 127.2, 125.1, 114.3, 77.6, 76.9, 68.1, 64.3, 54.8, 49.3, 20.2; HRMS (ESI) m/z calculated for $C_{26}H_{24}ClNO_6S$ [M + K]$^+$ 552.0644, found 552.0643; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (n-hexane/i-PrOH 90:10, 25 °C) at 1.0 mL/min, UV detection at 254 nm, t_R = (minor enantiomer) = 23.9 min, (major enantiomer) = 30.8 min. The absolute configuration was determined by X-ray crystallographic analysis.

General Procedure for the Synthesis of Lactams 3a−3d. To a solution of the thioester **2** (1 equiv) and acetic acid (12 equiv) in EtOAc (0.05 M) was added freshly activated (washed with 2 M HCl, H_2O, EtOH and Et_2O and then dried in vacuo) zinc powder (10 equiv). The resulting mixture was stirred at room temperature for 4 h and filtered through Celite, which was carefully rinsed with EtOAc. The combined filtrates were concentrated under reduced pressure, and the resulting crude material was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH.

*(3R,4S)-4-Methoxybenzyl-3-methyl-2-oxo-4-phenylpyrrolidine-3-carboxylate (**3a**).* Colorless oil (41 mg, 51%, dr = 10:1): ν_{max} (neat)/cm^{-1} 3300, 3020, 2972, 2865, 1702, 1514; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) 8.26 (s, 1H), 7.33−7.27 (m, 3H), 7.20−7.15 (m, 2H), 7.09−7.04 (m, 2H), 6.91−6.85 (m, 2H), 4.78 (s, 2H), 3.75 (s, 3H), 3.67 (dd, J = 10.2, 9.0 Hz, 1H), 3.56 (dd, J = 10.2, 7.6 Hz, 1H), 3.45 (dd, J = 9.0, 7.6 Hz, 1H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) 174.2, 169.9, 159.1, 136.5, 129.7, 128.4, 127.9, 127.4, 127.3, 113.8, 65.9, 56.0, 55.1, 51.5, 43.4, 19.1; HRMS (ESI) m/z calculated for $C_{20}H_{21}NO_4$ [M + Na]$^+$ 362.1363, found 362.1369.

*(3R,4S)-S-Benzyl 3-methyl-2-oxo-4-phenylpyrrolidine-3-carbothioate (**3b**).* Colorless oil (6 mg, ∼17%, dr = 4:1, after purification): ν_{max} (neat)/cm^{-1} 3042, 2957, 1693, 1514; ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C) major diastereoisomer; 8.37 (s, 1H), 7.35−7.17 (m, 8H), 7.04−7.00 (m, 2H), 3.90 (d, J = 12.0 Hz, 1H), 3.82 (d, J = 12.0 Hz, 1H), 3.76−3.72 (m, 1H), 3.61−3.57 (m, 1H), 3.47 (ddd, J = 9.3, 7.7, 1.5 Hz, 1H), 1.46 (s, 3H); minor diastereoisomer; 8.25 (s, 1H), 7.35−7.17 (m, 8H), 7.08−7.05 (m, 2H), 4.12 (d, J = 12.0 Hz, 1H), 4.10 (d, J = 12.0 Hz, 1H), 4.13−4.09 (m, 1H), 3.67−3.62 (m, 1H), 3.57−3.54 (m, 1H), 0.97 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6, 25 °C) maj. diastereoisomer 198.1, 173.9, 136.8, 135.9, 128.7, 128.3, 128.2, 128.2, 127.3, 127.0, 62.3, 52.1, 43.3, 32.1, 18.4; min diastereoisomer 200.0, 174.3, 137.5, 136.6, 128.8, 128.4, 128.3, 128.1, 127.1, 62.0, 48.9, 42.6, 32.5, 14.1 [1 × C arom. not visible (weak)], HRMS (ESI) m/z calculated for $C_{19}H_{19}NO_2SNa$ [M + Na]$^+$ 348.1029, found 348.1032.

*(3S,4S)-4-Methoxyphenyl 1-hydroxy-3-methyl-2-oxo-4-phenylpyrrolidine-3-carboxylate (**3b′**).* Colorless oil (6 mg, ∼17%, dr = 10:1, after purification): ν_{max} (neat)/cm^{-1} 3500, 3002, 2878, 1654; ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C), major diastereoisomer; 10.21 (s, 1H), 7.41−7.37 (m, 2H), 7.35−7.32 (m, 1H), 7.30−7.27 (m, 2H), 7.10−7.06 (m, 2H), 7.03−6.98 (m, 2H), 4.30−4.26 (m, 1H), 4.01−3.99 (m, 1H), 3.90−3.87 (m, 1H), 3.77 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6, 25 °C) 170.9, 167.3, 157.0, 143.6, 135.8, 128.5, 128.2, 127.5, 122.2, 114.5, 55.4, 53.9, 49.9, 43.0, 14.7; HRMS (ESI) m/z calculated for $C_{19}H_{19}NO_5Na$ [M + Na]$^+$ 364.1155, found 364.1151.

*(3R,4R)-3-Allyl-4-phenylpyrrolidin-2-one (**3c**).* From pure ***anti*-5f**. White, gummy solid (4 mg, ∼17%): ν_{max} (neat)/cm^{-1} 3440, 3034, 2962, 2865, 1682; ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C) 7.84 (br. s, 1H), 7.33−7.28 (m, 2H), 7.25−7.21 (m, 1H), 7.21−7.18 (m, 2H), 5.67 (dddd, J = 17.2, 10.3, 7.0, 6.2 Hz, 1H), 4.89−4.85 (m, 1H), 4.80 (dq, J = 17.2, 1.7 Hz, 1H), 3.68−3.59 (m, 2H), 3.30−3.27 (m, 1H), 2.67 (ddd, J = 9.4, 8.0, 5.2 Hz, 1H), 2.19−2.11 (m, 1H), 1.54 (dddt, J = 15.1, 9.6, 7.0, 1.4 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6, 25 °C) 177.1, 140.8, 136.5, 128.3, 127.8, 126.7, 115.5, 46.2, 44.9, 42.9, 30.0; HRMS (ESI) m/z calculated for $C_{13}H_{15}NONa$ [M + Na]$^+$ 224.1046, found 224.1051.

*(3R,4R)-4-Phenyl-3-(prop-2-yn-1-yl)pyrrolidin-2-one (**3d**).* From pure ***anti*-5g**. White, gummy solid (9 mg, 47%): ν_{max} (neat)/cm^{-1} 3280, 2987, 2972, 2865, 1681; ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C) 7.96 (s, 1H), 7.35−7.30 (m, 2H), 7.28−7.21 (m, 3H), 3.73−3.69 (m, 1H), 3.67−3.60 (m, 1H), 3.37 (dtd, J = 10.0, 2.0, 1.0 Hz, 1H), 2.84 (ddd, J = 10.0, 8.5, 4.0 Hz, 1H), 2.72 (t, J = 2.7 Hz, 1H), 2.28−2.21 (m, 1H), 1.57 (dddd, J = 17.0, 10.0, 2.7, 1.0 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6, 25 °C) 175.6, 140.0, 128.3, 127.8, 126.8, 82.4, 71.7, 46.1, 45.1, 42.6, 15.5; HRMS (ESI) m/z calculated for $C_{13}H_{13}NONa$ [M + Na]$^+$ 222.0889, found 222.0892.

*(2R,3S)-4-Methoxybenzyl-2-formyl-2-methyl-4-nitro-3-phenylbutanoate (**4a**).* To a mixture of the thioester **2a** (51 mg, 0.1 mmol) and Pd/C (10% Pd, 5 mg, 5 μmol, 5 mol %) in acetone (250 μL) was added triethylsilane (48 μL, 0.3 mmol). The resulting mixture was stirred at room temperature for 4 h and filtered through Celite, which was flushed with EtOAc. The combined filtrates were concentrated under reduced pressure. The resulting crude mixture was characterized by ^{1}H NMR spectroscopy, and if the starting material **2a** was not fully consumed, it was again subjected to the reduction under the above conditions. After full conversion of **2a** was obtained, the crude product was purified by flash column chromatography on silica gel by eluting with EtOAc/hexane (1:5) to give 25 mg of the product **4a** as colorless oil (67%): ν_{max} (neat)/cm^{-1} 2953, 1743, 1715, 1555, 1514, 1246; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) 9.67 (s, 1H), 7.29−7.23 (m, 5H), 7.09−7.04 (m, 2H), 6.93−6.88 (m, 2H), 5.16 (d, J = 11.8 Hz, 1H), 5.12 (d, J = 11.8 Hz, 1H), 4.87 (dd, J = 13.5, 11.0 Hz, 1H), 4.74 (dd, J = 13.5, 3.9 Hz, 1H), 4.16 (dd, J = 11.0, 3.9 Hz, 1H), 3.82 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 197.6, 170.2, 160.3, 134.5, 130.8, 129.1, 129.0, 128.7, 126.8, 114.3, 76.5, 68.0, 60.2, 55.5, 47.3, 16.9; HRMS (ESI) m/z calculated for $C_{20}H_{21}NO_6$ [M + Na]$^+$ 394.1261, found 394.1269.

General Procedure for *anti*-Selective Decarboxylation to γ-Nitrothioesters 5a−5g. The conjugate addition product **2** (0.1 mmol, 1 equiv) was placed in a 5 mL round-bottom flask, and 50% v/v trifluoroacetic acid in CH_2Cl_2 (1 mL) was added. The resulting mixture was stirred at room temperature for 10 min and then concentrated under reduced pressure. A small amount of CH_2Cl_2 (<1 mL) was added to the residue and evaporated again, which was repeated 3 times to fully remove any remaining TFA. After the resulting solid was dried in vacuo for ca. 15 min, a 1 M solution of triethylamine in CH_2Cl_2 (1 mL, 10 equiv) was added. The mixture was stirred at room temperature for 3 min and concentrated under reduced pressure. The resulting crude product was immediately purified by flash column chromatography on silica gel using a gradient of a mixture of hexane:EtOAc from 15:1 to 5:1, to afford product **5**. All given yields are based on a 0.1 mmol reaction scale.

*(2R,3R)-S-(4-Methoxyphenyl)-2-methyl-4-nitro-3-phenylbutanethioate (**5a**).* White solid (28 mg, 80%, *anti*-isomer): ν_{max} (neat)/cm^{-1} 3010, 2951, 1681, 1533, 1492, 1244; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) 7.39−7.27 (m, 3H), 7.25−7.19 (m, 2H), 7.11−7.04 (m, 2H), 6.93−6.85 (m, 2H), 4.85 (dd, J = 13.0, 5.4, 1H), 4.78 (dd, J = 13.0, 9.7, 1H) 3.87 (ddd, J = 9.7, 7.8, 5.4, Hz, 1H), 3.80 (s, 3H), 3.14 (dq, J = 7.8, 7.0 Hz, 1H), 1.34 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 200.5, 160.9, 137.1, 136.1, 129.0, 128.4, 128.2, 117.7, 115.0, 77.3, 55.5, 51.0, 46.7, 15.2; HRMS (ESI) m/z calculated for $C_{18}H_{19}NO_4S$ [M + Na]$^+$ 368.0927, found 368.0932; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (n-hexane/i-PrOH 90:10, 25 °C) at 0.8 mL/min, UV detection at 210 nm, t_R = (major) = 20.5 min.

*(2R,3R)-S-(4-Methoxyphenyl)-3-(4-fluorophenyl)-2-methyl-4-nitrobutanethioate (**5b**).* White solid (28 mg, 78%, *anti*-isomer): ν_{max} (neat)/cm^{-1} 3006, 2969, 1692, 1542; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) 7.24−7.17 (m, 2H), 7.11−7.00 (m, 4H), 6.94−6.85 (m, 2H), 4.82 (dd, J = 12.9, 5.2, 1H), 4.73 (dd, J = 12.9, 9.9, 1H), 3.87−3.79 (m, 1H), 3.81 (s, 3H), 3.11 (dq, J = 8.5, 7.0 Hz, 1H), 1.35 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 200.3, 162.5 (d, J = 274 Hz), 161.0, 136.1, 132.8 (d, J = 3 Hz), 130.1 (d, J = 8 Hz) 117.5, 115.9 (d, J = 22 Hz), 115.1, 77.6, 55.5, 51.0, 46.2, 15.5; HRMS (ESI) m/z calculated for $C_{18}H_{18}FNO_4S$ [M + Na]$^+$ 386.0833, found 386.0838; The enantiomeric excess was determined by HPLC using a Chiracel

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AD-H column (*n*-hexane/*i*-PrOH 90:10, 25 °C) at 0.8 mL/min, UV detection at 210 nm, t_R = (major) = 25.2 min.

*(2R,3R)-S-(4-Methoxyphenyl)-3-(4-chlorophenyl)-2-methyl-4-nitrobutanethioate (**5c**).* White solid (27 mg, 71%, *anti*-isomer, 95% ee): ν_{max} (neat)/cm^{-1} 3021, 2972, 1680, 1549, 1515, 1496, 1250; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) 7.36−7.30 (m, 2H), 7.19−7.15 (m, 2H), 7.11−7.06 (m, 2H), 6.93−6.88 (m, 2H), 4.82 (dd, *J* = 13.0, 5.1 Hz, 1H), 4.73 (dd, *J* = 13.0, 9.9 Hz, 1H), 3.86−3.79 (m, 1H), 3.81 (s, 3H), 3.11 (dq, *J* = 8.3, 7.0 Hz, 1H), 1.35 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 200.3, 161.0, 136.1, 135.6, 134.2, 129.8, 129.2, 117.4, 115.1, 77.3, 55.5, 50.8, 46.2, 15.5; HRMS (ESI) *m*/*z* calculated for $C_{18}H_{18}ClNO_4S$ $[M + Na]^+$ 402.0537, found 402.0543; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 90:10, 25 °C) at 0.8 mL/min, UV detection at 210 nm, t_R = (minor) = 27.1 min, (major) = 30.4 min.

*(2R,3R)-S-(4-Methoxyphenyl)-3-(4-bromophenyl)-2-methyl-4-nitrobutanethioate (**5d**).* White solid (28 mg, 66%, *anti*-isomer): ν_{max} (neat)/cm^{-1} 3009, 2972, 1678, 1595, 1537, 1489; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) 7.51−7.44 (m, 2H), 7.14−7.05 (m, 4H), 6.94−6.87 (m, 2H), 4.82 (dd, *J* = 13.0, 5.2 Hz, 1H), 4.73 (dd, *J* = 13.0, 9.9 Hz, 1H), 3.86−3.77 (m, 1H), 3.81 (s, 3H), 3.11 (dq, *J* = 8.2, 7.0 Hz, 1H), 1.34 (d, *J* = 7.0 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 200.3, 161.0, 136.13, 136.09, 132.1, 130.1, 122.3, 117.4, 115.1, 77.2, 55.5, 50.7, 46.3, 15.5; HRMS (ESI) *m*/*z* calculated for $C_{18}H_{18}BrNO_4S$ $[M + Na]^+$ 446.0032, found 446.0034; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 90:10, 25 °C) at 0.8 mL/min, UV detection at 210 nm, t_R = (minor) = 25.3 min, (major) = 29.1 min.

*(2R,3R)-S-(4-Methoxyphenyl)-3-(4-methoxyphenyl)-2-methyl-4-nitrobutanethioate (**5e**).* White solid (30 mg, 80%, pure *anti*-isomer): ν_{max} (neat)/cm^{-1} 3014, 2969, 1679, 1550, 1514, 1495, 1249; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) 7.17−7.07 (m, 4H), 6.92−6.84 (m, 4H), 4.82 (dd, *J* = 12.8, 5.3 Hz, 1H), 4.73 (dd, *J* = 12.8, 9.8 Hz, 1H), 3.84−3.77 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.15−3.06 (dq, *J* = 8.3, 7.0 Hz, 1H), 1.33 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 200.6, 160.9, 159.4, 136.1, 129.4, 129.0, 117.8, 115.0, 114.3, 77.7, 55.5, 55.4, 51.1, 46.1, 15.3; HRMS (ESI) *m*/*z* calculated for $C_{19}H_{21}NO_5S$ $[M + Na]^+$ 398.1033, found 398.1035; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 90:10, 25 °C) at 0.8 mL/min, UV detection at 210 nm, t_R = (minor) = 26.4 min, (major) = 31.5 min.

*(2R,3R)-S-(4-Methoxyphenyl)-2-allyl-4-nitro-3-phenylbutanethioate (**5f**).* White solid (19 mg, 51%, pure *anti*-isomer): ν_{max} (neat)/cm^{-1} 3035, 2956, 1690, 1558, 1244; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) 7.38−7.27 (m, 3H), 7.25−7.19 (m, 2H), 7.07−6.99 (m, 2H), 6.91−6.84 (m, 2H), 5.87−5.73 (m, 1H), 5.19−5.16 (m, 1H), 5.15−5.12 (m, 1H), 4.87 (dd, *J* = 13.0, 5.3, 1H), 4.79 (dd, *J* = 13.0, 9.8, 1H), 3.89 (ddd, *J* = 9.8, 8.0, 5.3 Hz, 1H), 3.80 (s, 3H), 3.13 (ddd, *J* = 8.5, 8.0, 5.0 Hz, 1H), 2.52 (ddd apt. t., *J* = 14.4, 8.5, 7.3, 1.2, 1H), 2.43 (ddd apt. t., *J* = 14.3, 6.5, 5.0, 1.4, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 199.3, 160.9, 136.7, 136.0, 133.7, 129.0, 128.5, 128.3, 118.7, 117.8, 115.0, 77.4, 56.0, 55.5, 45.6, 34.1; HRMS (ESI) *m*/*z* calculated for $C_{20}H_{21}NO_4S$ $[M + H]^+$ 372.1264, found 372.1270; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 90:10, 25 °C) at 0.8 mL/min, UV detection at 254 nm, t_R = (major) = 26.6 min, (minor) = 32.7 min.

*(2R,3R)-S-(4-Methoxyphenyl)-4-nitro-3-phenyl-2-propargylbutanethioate (**5g**).* White solid (26 mg, 70%, pure *anti*-isomer): ν_{max} (neat)/cm^{-1} 3290, 3041, 2973, 2866, 1685, 1548, 1249, 1055; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) 7.39−7.29 (m, 3H), 7.25−7.21 (m, 2H), 7.12−7.04 (m, 2H), 6.94−6.86 (m, 2H), 4.98 (dd, *J* = 13.2, 5.4 Hz, 1H), 4.89 (dd, *J* = 13.2, 9.6 Hz, 1H), 4.06 (ddd, *J* = 9.6, 7.8, 5.4 Hz, 1H), 3.80 (s, 3H), 3.25 (ddd, *J* = 7.8, 6.8, 6.5 Hz, 1H), 2.69 (ddd, *J* = 17.0, 6.5, 2.7 Hz, 1H), 2.55 (ddd, *J* = 17.0, 6.8, 2.7 Hz, 1H), 2.19 (t, *J* = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) 198.1, 161.1, 136.1, 135.9, 129.0, 128.6, 128.5, 117.3, 115.1, 79.8, 77.5, 72.2, 55.5, 54.4, 45.2, 19.8; HRMS (ESI) *m*/*z* calculated for $C_{20}H_{19}NO_4S$ $[M + H]^+$ 370.1108, found 370.1111; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 90:10, 25 °C) at 0.8 mL/min, UV detection at 254 nm, t_R = (major) = 41.1 min, (minor) = 49.4 min.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental details, NMR spectra including NOEs, HPLC traces, and crystal structures (CIF). 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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