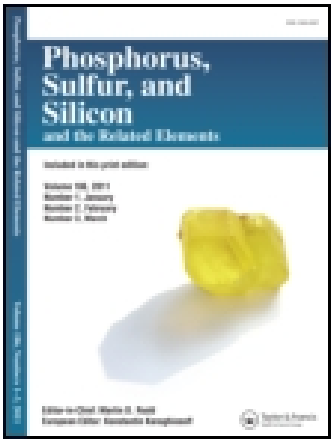

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Biological Activities of New Chiral Imidazolinone Derivatives

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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF NEW CHIRAL IMIDAZOLINONE DERIVATIVES

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New optically active 2-thio-4-imidazolinones 3 with a chiral carbon at position-3 were synthesized from isothiocyanates 2, which were obtained from aza-Wittig reactions of vinyliminophosphoranes 1 with CS_2, with easily accessible chiral* (S)- *or* (R)*-amino acid methyl ester hydrochlorides. 2-Methylthio-4*H*-imidazolin-4-ones 4 were obtained by the* S*-alkylation of compounds 3 in the presence of K_2CO_3 causing partial racemization of the enantiomeric pure products. These compounds were identified by MS, IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and elemental analysis. The structures of enantiomers 3c and 3d were also confirmed by X-ray diffraction analysis. The results of preliminary bioassay indicated that compounds 4 exhibited growth inhibition of barnyard grass and cole root and stalk, and fungicidal activities against* Fusarium oxysporium, Rhizoctonia solani, Gibberella zeae, Dothiorella gregaria*, and* Colletotrichum gossypii*.

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Keywords Aza-Wittig reaction; chiral agrochemicals; crystal structure; fungicidal activities; herbicidal activities; imidazolinone derivatives

INTRODUCTION

Imidazolinone derivatives have received increased attention over the past two decades due to their interesting biological activities. Some of them exhibit a broad spectrum of pharmacological activities, such as anticonvulsive,[1] antiviral,[2] antitumor,[3] antibacterial,[4] and anti-inflammatory.[5] Most importantly, some imidazolinone derivatives have been

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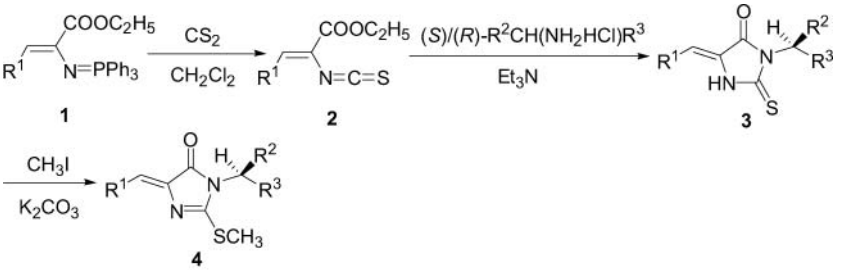
successfully used in crop protection. Imidazolinone herbicides, for example imazapyr, imazapic, imazethapyr, imazamox, imazamethabenz, and imazaquin are distinguished selective herbicides that act by inhibiting the enzyme acetohydroxyacid synthase (AHAS), also known as acetolactate synthase (ALS), which is a critical enzyme for the biosynthesis of branched-chain amino acids in plants.[6] Some imidazolinones also have been found to possess fungicidal activities, for example 5-methyl-2-methylthio-5-phenyl-3-phenylamine-3,5-dihydro-imidazolin-4-one (RPA407213) shows high fungicidal activities.[7] What deserves special mention is that the imidazolinone derivatives exhibited above as agrochemicals are chiral compounds. For instance, the imidazolinone ring of imidazolinone herbicide has a chiral carbon to which the methyl and isopropyl groups are attached. It has been reported that the *R*-enantiomer of imazethapyr and other pyridine imidazolinones are 10-fold more inhibitory to AHAS than the *S*-enantiomer.[8] Many compounds used in the pharmaceutical and agrochemical industries contain chiral centers, but they are often produced and used as racemic mixtures. Although chiral compounds have potential advantages in terms of regulatory, intellectual property, and marketing benefits, limited access to chiral raw materials and economic synthesis routes are key reasons why single isomers are less common than they might be.[9] Therefore, the development of more chiral routes is still an attractive topic of study on agrochemicals.

In recent years, the aza-Wittig reaction of iminophosphoranes has attracted considerable attention due to its high potential for the synthesis of nitrogen-containing heterocycles. This method provides one of the best procedures for the formation of carbon–nitrogen double bonds under mild and neutral reaction conditions.[10] Some imidazolinone derivatives, such as 2-alkylthio-*4H*-imidazolin-4-ones, have been synthesized by this method to evaluate their biological activities, and some of them exhibit herbicidal and fungicidal activities.[11] Based on the above idea, we now report the synthesis and biological activities of a series of new optically active imidazolinone derivatives with a chiral carbon at position-3.

RESULTS AND DISCUSSION

The synthetic pathway for 2-methylthio-*4H*-imidazolin-4-ones **4** is shown in Scheme 1. The intermediate vinyliminophosphorane **1** synthesized by the method in the literature[12] reacted with CS_2 to give isothiocyanates **2** via an aza-Wittig reaction.



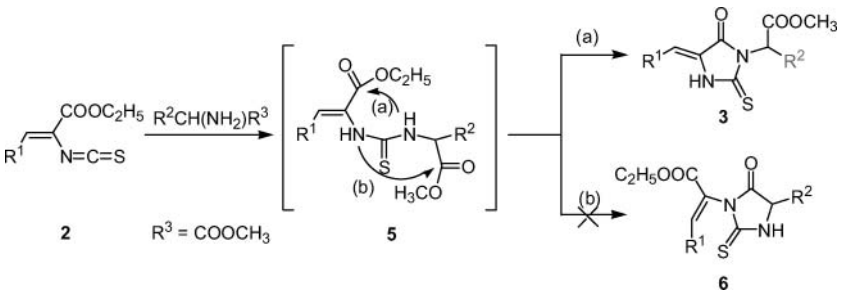
R^1 = Ph, 4-Cl-Ph, 4-CH_3-Ph, 4-CH_3OPh
R^2 = CH_3, $COOCH_3$, CH_2OH, 1*H*-Indol-3-yl, CH_2COOCH_3, $CH_2CH_2COOCH_3$
R^3 = CH_3, $COOCH_3$

Scheme 1

Table I Synthesis of compounds **3a–m**

Compound	R^1	R^2	R^3	Yield (%)
3a	Ph	CH_3	$COOCH_3$	58
3b	Ph	$COOCH_3$	CH_3	57
3c	4-Cl−Ph	CH_3	$COOCH_3$	56
3d	4-Cl−Ph	$COOCH_3$	CH_3	55
3e	4-CH_3-Ph	CH_3	$COOCH_3$	50
3f	4-CH_3−Ph	$COOCH_3$	CH_3	61
3g	4-CH_3O−Ph	CH_3	$COOCH_3$	84
3h	4-CH_3O−Ph	$COOCH_3$	CH_3	81
3i	Ph	CH_2OH	$COOCH_3$	64
3j	4-CH_3O−Ph	CH_2OH	$COOCH_3$	67
3k	4-CH_3O−Ph	1*H*-indol-3-yl	CH_3	76
3l	4-CH_3O−Ph	CH_2COOCH_3	$COOCH_3$	78
3m	4-CH_3O−Ph	$CH_2CH_2COOCH_3$	$COOCH_3$	71

Compounds **2** reacted with easily accessible (*S*)- or (*R*)-amino acid methyl ester hydrochlorides in the presence of Et_3N to give new single chiral 2-thio-4-imidazolinones **3** by an intramolecular cyclocondensation at room temperature in 50–84% yields (Table I). As can be seen in Scheme 2, the reaction between isothiocyanates **2** and amino acid methyl esters should afford intermediates **5**. According to the previous reports,[11,13] from these intermediates **5**, the formation of two regioisomeric 2-thio-4-imidazolinones **3** and/or **6** could, in principle, take place. Pure compounds **3** were obtained separately from



Scheme 2

the reaction mixture on a silica gel column, but isomers **6** could not be isolated. Perhaps the main cause is that compounds **3** are more stable in structure in comparison with compounds **6**. Single crystal structures of the enantiomers **3c** and **3d** grown from CH_2Cl_2 and ether (1:1, v/v) were confirmed by X-ray diffraction analysis as shown in Figures 1 and 2. Diffraction measurements were carried out on a Bruker APEX area-detector diffractometer (graphite-monochromatized Mo-Kα radiation, $\lambda = 0.71073$ Å). The hydrogen atoms were added according to the theoretical models. The structures were refined by full-matrix least-squares method on F^2 with anisotropic thermal parameters for all non-hydrogen atoms. The programs for structure solution and refinement were SHELXS-97[14] and SHELXL-97,[15] respectively. Crystal data are summarized in Table II. The crystallographic data was deposited at CCDC.[16] The X-ray crystal structures of **3c** and **3d** indicated the compounds exist as *S*-configuration and *R*-configuration, respectively,

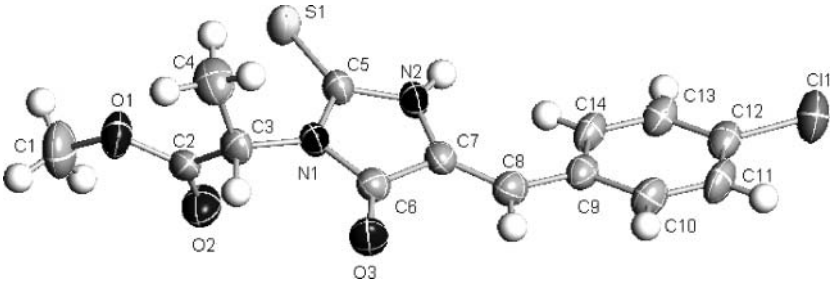


Figure 1 The molecular structure of **3c**, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

and they are enantiomers. The racemate of **3c** and **3d** was synthesized by the reaction of racemic alanine methyl esters hydrochloride and isothiocyanate and applied to determine the enantiomeric excess (ee) values of **3c** and **3d** by comparing their HPLC data. The ee values of both these compounds were 100% determined by HPLC on Chiralcel OD-H column.[17] The results demonstrated that **3c** and **3d** were pure optical compounds. The target compounds 2-methylthio-*4H*-imidazolin-4-ones **4** were obtained from compounds **3** by using K_2CO_3 as base in 67–92% yields (Table III). In view of using K_2CO_3 as the base in the course of the *S*-alkylation reaction, the racemate of **4c** and **4d** was synthesized in order to determine the optical purity of these compounds. The results showed that the ee values of **4c** and **4d** were 82% and 79%, respectively,[18] and indicated that the reaction proceeds caused about 10% racemization of pure optical compounds in the presence of K_2CO_3.

The biological activities in vitro of all compounds **4a**–**4m** were investigated according to a method reported in the literature.[11b] The results are summarized in Tables IV and V (available online in the Supplemental Materials for this article). As far as different configuration of compounds **4** was concerned, on the whole, the inhibitory activities on cole and barnyard grass (*Echinochloa crusgalli*) of *S*-enantiomers of the target compounds were better than those of *R*-enantiomers. But in view of biological activities of enantiomers, they did not show distinguished difference, which might be caused by the partial racemization of the target compounds under base conditions.

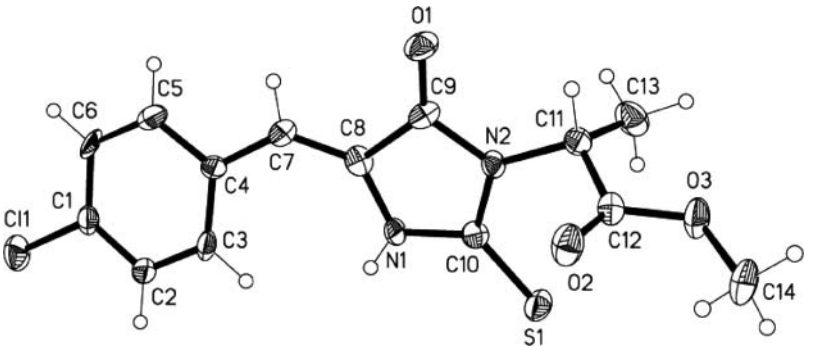


Figure 2 The molecular structure of **3d**, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

Table II Crystal data and summary of data collection and structure refinement of enantiomers **3c** and **3d**

Entry	**3c**	**3d**
Formal	$C_{14}H_{13}ClN_2O_3S$	$C_{14}H_{13}ClN_2O_3S$
Temperature	298(2) K	298(2) K
Wavelength	0.71073	0.71073
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a	7.0847(4) Å	6.6117(6) Å
b	6.6079(5) Å	7.0904(7) Å
c	30.902(2) Å	30.948(3) Å
α	90 °	90 °
β	90 °	90 °
γ	90 °	90 °
Volume	1446.69(17) $Å^3$	1450.8(2) $Å^3$
Z	4	4
Calculated density	1.491 Mg mm^{-3}	1.487 Mg mm^{-3}
Absorption coefficient	0.419 mm^{-1}	0.418 mm^{-1}
F(000)	672	672
Crystal size	0.48 × 0.19 × 0.17 mm	0.26 × 0.17 × 0.09 mm
θ Range for data collection	1.32–25.26 °	2.63–25.01 °
Limiting indices	$-8 \le h \le 5$, $-7 \le k \le 7$, $-37 \le l \le 35$	$-7 \le h \le 7$, $-8 \le k \le 8$, $-25 \le l \le 36$
Reflections collection/ unique	7723/2609 [R (int) = 0.0201]	7690/2566 [R (int) = 0.0531]
Completeness to $\theta = 25.19°$	99.9%	99.9%
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Goodness-of fit on F^2	1.156	1.035
Final R indices [$I > 2\sigma$ (I)]	$R_1 = 0.0440$, $wR_2 = 0.1151$	$R_1 = 0.0857$, $wR_2 = 0.2369$
Largest diff. Peak and hole	0.310 and −0.242 eA^{-3}	0.542 and −0.352 eA^{-3}

Table III Synthesis of compounds **4a–m**

Compound	R^1	R^2	R^3	Yield (%)
4a	Ph	CH_3	$COOCH_3$	79
4b	Ph	$COOCH_3$	CH_3	92
4c	4-Cl−Ph	CH_3	$COOCH_3$	70
4d	4-Cl−Ph	$COOCH_3$	CH_3	83
4e	4-CH_3−Ph	CH_3	$COOCH_3$	87
4f	4-CH_3−Ph	$COOCH_3$	CH_3	67
4g	4-CH_3O−Ph	CH_3	$COOCH_3$	72
4h	4-CH_3O−Ph	$COOCH_3$	CH_3	72
4i	Ph	CH_2OH	$COOCH_3$	67
4j	4-CH_3O−Ph	CH_2OH	$COOCH_3$	68
4k	4-CH_3O−Ph	1*H*-indol-3-yl	CH_3	80
4l	4-CH_3O−Ph	CH_2COOCH_3	$COOCH_3$	90
4m	4-CH_3O−Ph	$CH_2CH_2COOCH_3$	$COOCH_3$	83

CONCLUSIONS

In conclusion, we have developed an efficient synthesis of novel chiral 2-thio-4-imidazolinones **3** via a tandem aza-Wittig reaction that utilizes easily accessible starting material and allows mild reaction conditions with satisfactory yields. The structures of enantiomers **3c** and **3d** were confirmed by X-ray diffraction analysis. Due to the use of the base in the *S*-alkylation reaction of compounds **3**, racemization of a small proportion of the target 2-methylthio-*4H*-imidazolin-4-ones **4** was detected by HPLC. The results of the bioassay indicated some compounds **4** exhibited not only inhibition of barnyard and cole grass, but also fungicidal activities against *Fusarium oxysporium*, *Rhizoctonia solani*, *Gibberella zeae*, *Dothiorella gregaria*, and *Colletotrichum gossypii*.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained using an Avance-300 spectrometer 300 MHz for NMR and 75 MHz for ^{13}C NMR and reported as parts per million (ppm) from the internal standard TMS. IR spectra were taken on Equinox-55 Infrared spectrometer. The ee value determination was carried out using chiral P-E Series200 HPLC with a Chiralpak OD-H column on a Waters chromatograph with a P-E Series 200 UV/vis detector. Mass spectra were recorded on an Agilent 1100LC/MSD Trap SL spectrometer. Elementary analyses were taken on an Elementar Vario Micro analyzer. Optical rotations were measured with a Rudolph Autopol IV automatic polarimeter. Melting points were determined on X_4 microscopic melting apparatus (uncorrected).

General Preparation of 2-Thio-4-imidazolinones 3

To a solution of vinyliminophosphoranes **1** (5 mmol) in dry dichloromethane, excess CS_2 (50 mmol) was added, and the mixture was refluxed for 29 h under nitrogen. The solvent was removed under pressure and ether, and petroleum ether (20 mL, 1:2, v/v) was added to precipitate triphenylphosphine sulfide, which was removed by filtration. The filtrate was evaporated to give isothiocyanates **2**, which was used without purification. To a solution of the crude **2** in dry CH_3CN (20 mL), (*S*)- or (*R*)-amino acid methyl esters hydrochloride (5 mmol) and Et_3N (5 mmol) were added. The mixture was allowed to reflux for 3 h and then to cool to room temperature. After evaporation, the residue was separated by column chromatography (petroleum ether/ethyl acetate, 10:1, v/v) to afford 2-thio-4-imidazolinones **3**.

(S)-2-(4-Benzylidene-5-oxo-2-thio-imidazolidin-1-yl)propanoic acid methyl ester (3a). Appearance: yellow solid; mp 148–150°C; $[\alpha]_{20}^{D} = -6.9$ (c = 1; $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 (d, 3H, J = 7.3 Hz, CH_3), 3.76 (s, 3H, OCH_3), 5.40 (q, 1H, J = 7.3 Hz, CH), 6.75 (s, 1H, =C—H), 7.49-7.41 (m, 5H, Ar—H), 8.90 (s, 1H, N—H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.42, 50.89, 52.81, 114.09, 126.03, 129.19, 129.50, 129.88, 132.64, 162.82, 169.53, 177.29; IR (KBr) ν/cm^{-1}: 1269, 1440, 1642, 1726, 3414; MS: m/z = 291 (M^++1); calcd. for $C_{14}H_{14}N_2O_3S$ (%): C, 57.92; H, 4.86; N, 9.65; found (%): C, 57.89; H, 4.82; N, 9.69.

(R)-2-(4-Benzylidene-5-oxo-2-thio-imidazolidin-1-yl)propanoic acid methyl ester (3b). Appearance: yellow solid; mp 147–149°C; $[\alpha]_{20}^{D} = +7.2$ (c = 1; $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70 (d, 3H, J = 7.3 Hz, CH_3), 3.75 (s, 3H, OCH_3), 5.40 (q, 1H, J = 7.3 Hz, CH), 6.74 (s, 1H, =C—H), 7.49-7.38 (m, 5H, Ar—H),

9.15 (s, 1H, N—H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.44, 50.91, 52.80, 114.12, 126.06, 129.23, 129.55, 129.80, 132.60, 162.78, 169.49, 177.27; IR (KBr) ν/cm^{-1}: 1267, 1443, 1640, 1725, 3410; MS: m/z = 291 (M^++1); calcd. for $C_{14}H_{14}N_2O_3S$ (%): C, 57.92; H, 4.86; N, 9.65; found (%): C, 57.88; H, 4.85; N, 9.60.

(S)-2-[4-(4-Chlorobenzylidene)-5-oxo-2-thio-imidazolidin-1-yl]propanoic acid methyl ester (3c). Appearance: yellow solid; mp 170–172°C; $[\alpha]_{20}{}^{D}$ = –4.0 (c = 1; $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 (d, 3H, J = 7.2 Hz, CH_3), 3.77 (s, 3H, OCH_3), 5.40 (q, 1H, J = 7.2 Hz, CH), 6.68 (s, 1H, = C—H), 7.37 (d, 2H, J = 8.6 Hz, Ar—H), 7.45 (d, 2H, J = 8.6 Hz, Ar—H), 8.63 (s, 1H, N—H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.41, 51.00, 52.85, 112.40, 126.29, 129.81, 130.37, 131.13, 135.89, 162.71, 169.44, 177.39; IR (KBr) ν/cm^{-1}: 1274, 1447, 1644, 1726, 3348; MS: m/z = 324 (M^+); calcd. for $C_{14}H_{13}ClN_2O_3S$ (%): C, 51.77; H, 4.03; N, 8.63; found (%): C, 51.66; H, 4.05; N, 8.69.

(R)-2-[4-(4-Chlorobenzylidene)-5-oxo-2-thio-imidazolidin-1-yl]propanoic acid methyl ester (3d). Appearance: yellow solid; mp 168–170°C; $[\alpha]_{20}{}^{D}$ = +3.9 (c = 1; $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 (d, 3H, J = 7.2 Hz, CH_3), 3.77 (s, 3H, OCH_3), 5.40 (q, 1H, J = 7.2 Hz, CH), 6.67 (s, 1H, = C—H), 7.38 (d, 2H, J = 8.6 Hz, Ar—H), 7.45 (d, 2H, J = 8.6 Hz, Ar—H), 8.95 (s, 1H, N—H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.36, 50.90, 52.83, 112.57, 126.16, 129.71, 130.41, 130.99, 135.80, 162.70, 169.44, 177.30; IR (KBr) ν/cm^{-1}: 1273, 1440, 1645, 1725, 3340; MS: m/z = 324 (M^+); calcd. for $C_{14}H_{13}ClN_2O_3S$ (%): C, 51.77; H, 4.03; N, 8.63; found (%): C, 51.70; H, 3.99; N, 8.65.

(S)-2-[4-(4-Methylbenzylidene)-5-oxo-2-thio-imidazolidin-1-yl]propanoic acid methyl ester (3e). Appearance: yellow solid; mp 161–162°C; $[\alpha]_{20}{}^{D}$ = –12.0 (c = 1; $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (d, 3H, J = 7.2 Hz, CH_3), 2.40 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 5.40 (q, 1H, J = 7.2 Hz, CH), 6.73 (s, 1H, = C—H), 7.28 (d, 2H, J = 8.5 Hz, Ar—H), 7.45 (d, 2H, J = 8.5 Hz, Ar—H), 8.98 (s, 1H, N—H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.42, 21.51, 50.92, 52.70, 114.14, 125.74, 129.14, 130.29, 131.03, 139.72, 162.70, 169.73, 176.92; IR (KBr) ν/cm^{-1}: 1271, 1449, 1645, 1729, 3438; MS: m/z = 305 (M^++1); calcd. for $C_{15}H_{16}N_2O_3S$ (%): C, 59.19; H, 5.30; N, 9.20; found (%): C, 59.23; H, 5.28; N, 9.15.

(R)-2-[4-(4-Methylbenzylidene)-5-oxo-2-thio-imidazolidin-1-yl]propanoic acid methyl ester (3f). Appearance: yellow solid; mp 160–161°C; $[\alpha]_{20}{}^{D}$ = +11.9 (c = 1; $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (d, 3H, J = 7.2 Hz, CH_3), 2.38 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 5.40 (q, 1H, J = 7.3 Hz, CH), 6.71 (s, 1H, = C—H), 7.25 (d, 2H, J = 8.5 Hz, Ar—H), 7.34 (d, 2H, J = 8.5 Hz, Ar—H), 9.11 (s, N—H, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.37, 21.48, 50.80, 52.74, 114.41, 125.26, 129.22, 129.74, 130.20, 140.52, 162.81, 169.51, 177.00; IR (KBr) ν/cm^{-1}: 1269, 1447, 1640, 1726, 3430; MS: m/z = 305 (M^++1); calcd. for $C_{15}H_{16}N_2O_3S$ (%): C, 59.19; H, 5.30; N, 9.20; found (%): C, 59.16; H, 5.24; N, 9.12.

(S)-2-[4-(4-Methoxybenzylidene)-5-oxo-2-thio-imidazolidin-1-yl]propanoic acid methyl ester (3g). Appearance: yellow solid; mp 175–177°C; $[\alpha]_{20}{}^{D}$ = –23.2 (c = 1; $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 (d, 3H, J = 7.3 Hz, CH_3), 3.76 (s, 3H, OCH_3), 3.87 (s, 3H, Ar—OCH_3), 5.40 (q, 1H, J = 7.3 Hz, CH), 6.72 (s, 1H, = C—H), 6.99 (d, 2H, J = 8.8 Hz, Ar—H), 7.40 (d, 2H, J = 8.8 Hz, Ar—H), 8.73 (s, N—H, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.41, 50.87, 52.74, 55.48, 114.34, 115.12, 124.37, 125.21, 131.02, 161.03, 162.87, 169.55, 176.88; IR (KBr) ν/cm^{-1}: 1263, 1463, 1646, 1723, 3437; MS: m/z = 321 (M^++1); calcd. for $C_{15}H_{16}N_2O_4S$ (%): C, 56.24; H, 5.03; N, 8.74; found (%): C, 56.14; H, 5.05; N, 8.79.

(R)-2-[4-(4-Methoxybenzylidene)-5-oxo-2-thio-imidazolidin-1-yl]propanoic acid methyl ester (3h). Appearance: yellow solid; mp 174–176°C; $[\alpha]_{20}^{D} = +22.9$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.70 (d, 3H, J = 7.3 Hz, CH_3), 3.75 (s, 3H, OCH_3), 3.86 (s, 3H, Ar—OCH_3), 5.40 (q, 1H, J = 7.3 Hz, CH), 6.71 (s, 1H, CH), 6.99 (d, 2H, J = 8.8 Hz, Ar—H), 7.41 (d, 2H, J = 8.8 Hz, Ar—H), 8.96 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.37, 50.79, 52.74, 55.43, 114.45, 115.03, 124.25, 125.10, 131.05, 160.96, 162.85, 169.54, 176.79; IR (KBr) ν/cm^{-1}: 1262, 1461, 1645, 1720, 3430; MS: m/z = 321 (M^++1); calcd. for $C_{15}H_{16}N_2O_4S$ (%): C, 56.24; H, 5.03; N, 8.74; found (%): C, 56.20; H, 5.01; N, 8.76.

(S)-2-(4-Benzylidene-5-oxo-2-thio-imidazolidin-1-yl)-3-hydroxy-propanoic acid methyl ester (3i). Appearance: yellow solid; mp 189–190°C; $[\alpha]_{20}^{D} = +24.0$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 4.27-4.24 (m, 2H, CH_2), 5.51 (t, 1H, J = 5.2 Hz, CH), 6.80 (s, 1H, = C—H), 7.51-7.40 (m, 5H, Ar—H), 8.96 (s, N—H, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.91, 57.96, 60.56, 114.76, 125.86, 129.18, 129.57, 130.08, 132.56, 163.80, 167.87, 177.58; IR (KBr) ν/cm^{-1}: 1238, 1473, 1645, 1732, 3437; MS: m/z = 307 (M^++1); calcd. for $C_{14}H_{14}N_2O_4S$ (%): C, 54.89; H, 4.61; N, 9.14; found (%): C, 54.95; H, 4.66; N, 9.09.

(S)-3-Hydroxy-2-[4-(4-methoxybenzylidene)-5-oxo-2-thio-imidazolidin-1-yl]propanoic acid methyl ester (3j). Appearance: yellow solid; mp 220–222°C; $[\alpha]_{20}^{D} = +11.9$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 3.89 (s, 3H, Ar—OCH_3), 4.33-4.26 (m, 2H, CH_2), 5.53 (t, 1H, J = 5.0 Hz, CH), 6.78 (s, 1H, = C—H), 7.03 (d, 2H, J = 8.8 Hz, Ar—H), 7.42 (d, 2H, J = 8.8 Hz, Ar—H), 8.90 (s, 1H, N—H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.74, 55.51, 58.12, 60.70, 115.22, 125.66, 129.67, 133.45, 135.79, 161.42, 163.27, 167.46, 177.07; IR (KBr) ν/cm^{-1}: 1236, 1470, 1640, 1735, 3437; MS: m/z = 337 (M^++1); calcd. for $C_{15}H_{16}N_2O_5S$ (%): C, 53.56; H, 4.79; N, 8.33; found (%): C, 53.66; H, 4.73; N, 9.29.

(S)-3-(1H-Indol-3-yl)-2-[4-(4-methoxybenzylidene)-5-oxo-2-thio-imidazolidin-1-yl]propanoic acid methyl ester (3k). Appearance: yellow solid, mp 88–89°C; $[\alpha]_{20}^{D} = -215.9$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.93-3.72 (m, 8H, CH_2 & $COOCH_3$ & Ar—OCH_3), 5.71-5.66 (m, 1H, CH), 6.60 (s, 1H, = C—H), 7.99-6.91 (m, 10H, Ar—H & N—H), 8.56 (s, 1H, N—H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.18, 52.79, 55.45, 55.76, 111.07, 115.01, 118.66, 119.51, 122.05, 122.99, 124.19, 125.19, 130.96, 136.08, 160.91, 163.21, 169.09, 177.18; IR (KBr) ν/cm^{-1}: 1258, 1463, 1604, 1730, 3414; MS: m/z = 436 (M^++1); calcd. for $C_{23}H_{21}N_3O_4S$ (%): C, 63.43; H, 4.86; N, 9.65; found (%): C, 63.30; H, 4.90; N, 9.61.

(S)-2-[4-(4-Methoxybenzylidene)-5-oxo-2-thio-imidazolidin-1-yl]succinic acid dimethyl ester (3l). Appearance: yellow solid; mp 48–50°C; $[\alpha]_{20}^{D} = -79.6$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 3.47-3.12 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, Ar—OCH_3), 5.83-5.78 (m, 1H, CH), 6.72 (s, 1H, = C—H), 6.91 (d, 2H, J = 8.1 Hz, Ar—H), 7.41 (d, 2H, J = 8.1 Hz, Ar—H), 9.06 (s, 1H, N—H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.49, 51.14, 52.15, 53.10, 55.48, 114.03, 115.06, 124.03, 125.07, 131.27, 161.12, 163.17, 168.25, 170.44, 176.61; IR (KBr) ν/cm^{-1}: 1256, 1468, 1602, 1645, 1740, 3417; MS: m/z = 379 (M^++1); calcd. for $C_{17}H_{18}N_2O_6S$ (%): C, 53.96; H, 4.79; N, 7.40; found (%): C, 53.85; H, 4.75; N, 7.45.

(S)-2-[4-(4-Methoxybenzylidene)-5-oxo-2-thio-imidazolidin-1-yl]pentanedioic acid dimethyl ester (3m). Appearance: yellow solid; mp 70–72°C; $[\alpha]_{20}^{D} = -16.8$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.70-2.17 (m, 4H, $2CH_2$), 3.67 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.87 (s, 3H, Ar—OCH_3), 5.41-5.36 (m, 1H,

CH), 6.71 (s, 1H, = C−H), 6.98 (d, 2H, J = 8.4 Hz, Ar−H), 7.42 (d, 2H, J = 8.4 Hz, Ar−H), 8.98 (s, 1H, N−H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.85, 30.55, 51.84, 52.85, 54.33, 55.51, 114.91, 115.02, 124.06, 125.11, 131.35, 161.10, 163.34, 168.80, 172.84, 177.32; IR (KBr) ν/cm^{-1}: 1257, 1440, 1510, 1580, 1740, 3410; MS: m/z = 393 (M^++1); calcd. for $C_{18}H_{20}N_2O_6S$ (%): C, 55.09; H, 5.14; N, 7.14; found (%): C, 54.92; H, 5.10; N, 7.19.

General Preparation of 2-Methylthio-*4H*-imidazolin-4-ones 4

A mixture of 2-thio-4-imidazolinones **3** (0.77 mol) in dry acetonitrile (20 mL), CH_3I (1.54 mmol), and solid K_2CO_3 (1.3 mmol) was stirred for 3 h at room temperature and then filtered. The filtrate was concentrated under reduced pressure, and the residue was separated by column chromatography (petroleum ether/ethyl acetate, 15:1, v/v) to afford 2-methylthio-*4H*-imidazolin-4-ones **4**.

(S)-2-(4-Benzylidene-2-methylthio-5-oxo-4,5-dihydro-imidazol-1-yl)propanoic acid methyl ester (4a). Appearance: yellow solid; mp 70–71°C; $[\alpha]_{20}^{D} = -10.6$ (c = 1; $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (d, 3H, J = 7.4 Hz, CH_3), 2.77 (s, 3H, SCH_3), 3.76 (s, 3H, OCH_3), 4.82 (q, 1H, J = 7.4 Hz, CH), 6.97 (s, 1H, = C−H), 7.44-7.36 (m, 3H, Ar−H), 8.15 (d, 2H, J = 8.0 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.50, 15.51, 49.96, 52.80, 124.29, 128.63, 129.87, 131.97, 134.39, 137.88, 163.88, 169.27, 169.68; IR (KBr) ν/cm^{-1}: 1269, 1400, 1440, 1640, 1730; MS: m/z = 305 (M^++1); calcd. for $C_{15}H_{16}N_2O_3S$ (%): C, 59.19; H, 5.30; N, 9.20; found (%): C, 59.12; H, 5.27; N, 9.27.

(R)-2-(4-Benzylidene-2-methylthio-5-oxo-4,5-dihydro-imidazol-1-yl)propanoic acid methyl ester (4b). Appearance: yellow solid; mp 72–74°C; $[\alpha]_{20}^{D} = +11.8$ (c = 1; $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (d, 3H, J = 7.3 Hz, CH_3), 2.77 (s, 3H, SCH_3), 3.76 (s, 3H, OCH_3), 4.81 (q, 1H, J = 7.3 Hz, CH), 6.97 (s, 1H, = C−H), 7.45-7.36 (m, 3H, Ar−H), 8.15 (d, 2H, J = 8.0 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.56, 15.53, 49.51, 52.79, 124.31, 128.65, 129.89, 132.01, 134.40, 137.89, 163.91, 169.26, 169.66; IR (KBr) ν/cm^{-1}: 1265, 1404, 1438, 1645, 1729; MS: m/z = 305 (M^++1); calcd. for $C_{15}H_{16}N_2O_3S$ (%): C, 59.19; H, 5.30; N, 9.20; found (%): C, 59.14; H, 5.31; N, 9.24.

(S)-2-[4-(4-Chlorobenzylidene)-2-methylthio-5-oxo-4,5-dihydro-imidazol-1-yl]propanoic acid methyl ester (4c). Appearance: yellow solid; p 104–106°C; $[\alpha]_{20}^{D} = -32.0$ (c = 1; $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68 (d, 3H, J = 7.3Hz, CH_3), 2.78 (s, 3H, SCH_3), 3.80 (s, 3H, Ar−OCH_3), 4.81 (q, 1H, J = 7.3 Hz, CH), 6.89 (s, 1H, = C−H), 7.41 (d, 2H, J = 8.5 Hz, Ar−H), 8.09 (d, 2H, J = 8.5 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.52, 15.52, 51.02, 52.89, 122.43, 128.80, 133.02, 135.50, 138.14, 164.69, 169.45, 169.92; IR (KBr) ν/cm^{-1}: 1243, 1491, 1637, 1722; MS: m/z = 339 (M^++1); calcd. for $C_{15}H_{15}ClN_2O_3S$ (%): C, 53.17; H, 4.46; N, 8.27; found (%): C, 53.13; H, 4.41; N, 8.20.

(R)-2-[4-(4-Chlorobenzylidene)-2-methylthio-5-oxo-4,5-dihydro-imidazol-1-yl]propanoic acid methyl ester (4d). Appearance: yellow solid; mp 105–107°C; $[\alpha]_{20}^{D} = +31.1$ (c = 1; $(CH_3)_2CO$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67 (d, 3H, J = 7.4 Hz, CH_3), 2.78 (s, 3H, SCH_3), 3.77 (s, 3H, Ar−OCH_3), 4.80 (q, 1H, J = 7.3 Hz, CH), 6.90 (s, 1H, = C−H), 7.39 (d, 2H, J = 8.5 Hz, Ar−H), 8.10 (d, 2H, J = 8.4 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.57, 15.52, 49.97, 52.88, 122.75, 128.91, 133.02, 135.75, 138.13, 164.35, 169.15, 169.67; IR (KBr) ν/cm^{-1}: 1241, 1500, 1639, 1725; MS:

m/z = 339 (M^++1); calcd. for $C_{15}H_{15}ClN_2O_3S$ (%): C, 53.17; H, 4.46; N, 8.27; found (%): C, 53.21; H, 4.43; N, 8.32.

(S)-2-[4-(4-Methylbenzylidene)-2-methylthio-5-oxo-4,5-dihydro-imidazol-1-yl]propanoic acid methyl ester (4e). Appearance: yellow oil; $[\alpha]_{20}{}^{D} = -39.9$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.68 (d, 3H, J = 7.2 Hz, CH_3), 2.40 (s, 3H, CH_3), 2.76 (s, 3H, SCH_3), 3.76 (s, 3H, OCH_3), 4.82 (q, 1H, J = 7.2 Hz, CH), 6.96 (s, 1H, = C−H), 7.25 (d, 2H, J = 7.8 Hz, Ar−H), 8.06 (d, 2H, J = 7.8 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.46, 15.35, 21.58, 49.67, 52.78, 124.76, 129.54, 130.66, 131.76, 132.05, 140.57, 161.22, 169.19, 169.89; IR (LF) ν/cm^{-1}: 1254, 1497, 1595, 1710; MS: m/z = 319 (M^++1); calcd. for $C_{16}H_{18}N_2O_3S$ (%): C, 60.36; H, 5.70; N, 8.80; found (%): C, 60.48; H, 5.74; N, 8.76.

(R)-2-[4-(4-Methylbenzylidene)-2-methylthio-5-oxo-4,5-dihydro-imidazol-1-yl]propanoic acid methyl ester (4f). Appearance: yellow oil; $[\alpha]_{20}{}^{D} = +41.1$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.65 (d, 3H, J = 7.2 Hz, CH_3), 2.40 (s, 3H, CH_3), 2.71 (s, 3H, SCH_3), 3.73 (s, 3H, OCH_3), 4.84 (q, 1H, J = 7.3 Hz, CH), 6.84 (s, 1H, = C−H), 7.27 (d, 2H, J = 7.8 Hz, Ar−H), 8.06 (d, 2H, J = 7.8 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.51, 15.45, 21.73, 49.89, 52.82, 124.96, 129.61, 130.82, 131.81, 132.14, 140.59, 161.02, 169.29, 169.98; IR (LF) ν/cm^{-1}: 1253, 1490, 1589, 1715; MS: m/z = 319 (M^++1); calcd. for $C_{16}H_{18}N_2O_3S$ (%): C, 60.36; H, 5.70; N, 8.80; found (%): C, 60.45; H, 5.76; N, 8.75.

(S)-2-[4-(4-Methoxybenzylidene)-2-methylthio-5-oxo-4,5-dihydro-imidazol-1-yl]propanoic acid methyl ester (4g). Appearance: yellow solid; mp 95–97°C; $[\alpha]_{20}{}^{D} = -27.9$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.64 (d, 3H, J = 7.4 Hz, CH_3), 2.70 (s, 3H, SCH_3), 3.71 (s, 3H, OCH3), 3.80 (s, 3H, Ar−OCH_3), 4.77 (q, 1H, J = 7.4 Hz, CH), 6.92-6.89 (m, 3H, Ar−H & = C−H), 8.10 (d, 2H, J = 8.8 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.46, 15.52, 49.80, 52.78, 55.29, 114.23,, 124.62, 127.27, 133.83, 136.13, 161.13, 162.10, 169.32, 169.87; IR (KBr) ν/cm^{-1}: 1253, 1500, 1597, 1711; MS: m/z = 335 (M^++1); calcd. for $C_{16}H_{18}N_2O_4S$ (%): C, 57.47; H, 5.43; N, 8.38; found (%): C, 57.37; H, 5.48; N, 8.35.

(R)-2-[4-(4-Methoxybenzylidene)-2-methylthio-5-oxo-4,5-dihydro-imidazol-1-yl]propanoic acid methyl ester (4h). Appearance: yellow solid; mp 97–99°C; $[\alpha]_{20}{}^{D} = +28.8$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.64 (d, 3H, J = 7.3 Hz, CH_3), 2.72 (s, 3H, SCH_3), 3.75 (s, 3H, OCH_3), 3.82 (s, 3H, Ar−OCH_3), 4.78 (q, 1H, J = 7.3 Hz, CH), 6.93-6.90 (m, 3H, Ar−H & = C−H), 8.11 (d, 2H, J = 8.8 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.45, 15.50, 49.73, 52.77, 55.27, 113.86, 114.19, 124.62, 127.21, 133.79, 136.07, 161.06, 162.10, 169.31, 169.83; IR (KBr) ν/cm^{-1}: 1252, 1501, 1598, 1710; MS: m/z = 335 (M^++1); calcd. for $C_{16}H_{18}N_2O_4S$ (%): C, 57.47; H, 5.43; N, 8.38; found (%): C, 57.40; H, 5.40; N, 8.42.

(S)-2-(4-Benzylidene-2-methylthio-5-oxo-4,5-dihydro-imidazol-1-yl)-3-hydroxypropanoic acid methyl ester (4i). Appearance: yellow oil; $[\alpha]_{20}{}^{D} = -8.0$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.72 (s, 3H, SCH_3), 3.81 (s, 3H, OCH_3), 4.24-4.22 (m, 2H, CH_2), 4.64 (t, 1H, J = 5.0 Hz, CH), 6.98 (s, 1H, = C−H), 7.44-7.35 (m, 3H, Ar−H), 8.15 (d, 2H, J = 8.0 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$): 13.59, 52.98, 58.11, 60.71, 125.49, 128.67, 130.18, 132.16, 134.17, 137.70, 164.03, 167.93, 170.47; IR (LF) ν/cm^{-1}: 1258, 1497, 1633, 1738; MS: m/z = 321 (M^++1); calcd. for $C_{15}H_{16}N_2O_4S$ (%): C, 56.24; H, 5.03; N, 8.74; found (%): C, 56.30; H, 5.05; N, 8.70.

(S)-3-Hydroxy-2-[4-(4-methoxybenzylidene)-2-methylthio-5-oxo-4,5-dihydro-imidazol-1-yl]propanoic acid methyl ester (4j). Appearance: yellow oil; $[\alpha]_{20}{}^{D} = -4.0$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.66 (s, 3H, SCH_3), 3.74 (s, 3H, OCH_3), 3.81 (s, 3H, Ar—OCH_3), 4.22-4.15 (m, 2H, CH_2), 4.63 (t, 1H, J = 5.2 Hz, CH), 6.92-6.89 (m, 3H, Ar—H & = C—H), 8.08 (d, 2H, J = 8.7 Hz, Ar—H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.54, 52.89, 55.35, 58.11, 60.71, 114.28, 125.68, 127.12, 134.08, 135.99, 161.37, 162.36, 167.99, 170.48; IR (LF) ν/cm^{-1}: 1258, 1490, 1637, 1736; MS: m/z = 351 (M^++1); calcd. for $C_{16}H_{18}N_2O_5S$ (%): C, 54.85; H, 5.18; N, 7.99; found (%): C, 54.92; H, 5.15; N, 7.92.

(S)-3-(1H-Indol-3-yl)-2-[4-(4-methoxybenzylidene)-2-methylthio-5-oxo-4,5-dihydro-imidazol-1-yl]propanoic acid methyl ester (4k). Appearance: yellow oil; $[\alpha]_{20}{}^{D} = -263.8$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.58 (s, 3H, SCH_3), 3.85-3.68 (m, 8H, CH_2 & Ar—OCH_3 & $COOCH_3$), 4.98-4.93 (m, 1H, CH), 8.10-6.89 (m, 11H, Ar—H & = C—H & N—H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.58, 25.02, 52.84, 55.33, 55.42, 111.17, 114.25, 118.38, 119.58, 122.11, 123.03, 124.51, 127.34, 133.81, 136.22, 161.11, 162.09, 168.70, 169.33; IR (LF) ν/cm^{-1}: 1255, 1439, 1499, 1597, 1704, 1742; MS: m/z = 450 (M^++1); calcd. for $C_{24}H_{23}N_3O_4S$ (%): C, 64.13; H, 5.16; N, 9.35; found (%): C, 64.25; H, 5.14; N, 9.39.

(S)-2-[4-(4-Methoxybenzylidene)-2-methylthio-5-oxo-4,5-dihydro-imidazol-1-yl]succinic acid dimethyl ester (4l). Appearance: yellow solid; mp 137–138°C; $[\alpha]_{20}{}^{D} = -103.9$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.77 (s, 3H, SCH_3), 3.42-3.35 (m, CH_2, 2H), 3.71 (s, 3H, $COOCH_3$), 3.78 (s, 3H, OCH_3), 3.87 (s, 3H, Ar—OCH_3), 5.14-5.09 (m, 1H, CH), 6.96-6.93 (m, 3H, Ar—H & = C—H), 8.12 (d, 2H, J = 8.8 Hz, Ar—H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.64, 34.17, 51.40, 52.24, 53.26, 55.42, 114.36, 125.07, 127.28, 133.98, 135.85, 161.31, 162.25, 168.92, 169.54, 171.51; IR (KBr) ν/cm^{-1}: 1244, 1434, 1502, 1596, 1735; MS: m/z = 393 (M^++1); calcd. for $C_{18}H_{20}N_2O_6S$ (%): C, 55.09; H, 5.14; N, 7.14; found (%): C, 55.13; H, 5.10; N, 7.11.

(S)-2-[4-(4-Methoxybenzylidene)-2-methylthio-5-oxo-4,5-dihydro-imidazol-1-yl]pentanedioic acid dimethyl ester (4m). Appearance: yellow oil; $[\alpha]_{20}{}^{D} = -71.6$ (c = 1; $(CH_3)_2CO$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.42-2.38 (m, 4H, $2CH_2$) 2.75 (s, 3H, SCH_3), 3.67 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.86 (s, 3H, Ar—OCH_3), 4.80-4.75 (m, 1H, CH), 6.96-6.93 (m, 3H, Ar—H & = C—H), 8.13 (d, 2H, J = 8.7 Hz, Ar—H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.57, 24.41, 30.19, 51.76, 52.84, 53.67, 55.34, 114.29, 125.01, 127.25, 133.90, 135.93, 161.25, 162.31, 169.01, 169.63, 172.63; IR (LF) ν/cm^{-1}: 1257, 1440, 1501, 1599, 1739; MS: m/z = 407 (M^++1); calcd. for $C_{19}H_{22}N_2O_6S$ (%): C, 56.15; H, 5.46; N, 6.89; found (%): C, 56.10; H, 5.43; N, 6.84.

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16. Crystallographic data for the structure **3c** and **3d** in this article have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 704007 and 704008, respectively. Copies of the data can be obtained free of change on application to CCDC, 12 Union Road, Cambridge CB21EZ, U. K.; e-mail: deposit@ccdc.cam.ac.uk.
17. HPLC-separation conditions of **3c**: Chiralcel OD−H, 22°C, 254 nm, 80:20 hexane:*i*-PrOH, 0.8 mL/min; $t_R = 18.6$ min (*S*); HPLC-separation conditions of **3d**: Chiralcel OD−H, 22°C, 254 nm, 80:20 hexane:*i*-PrOH, 0.8 mL/min; $t_R = 13.3$ min (*R*).
18. HPLC-separation conditions of **4c**: Chiralcel OD−H, 22°C, 254 nm, 80:20 hexane:*i*-PrOH, 0.8 mL/min; $t_R = 9.7$ min (*R*), $t_R = 11.3$ min (*S*); HPLC-separation conditions of **4d**: Chiralcel OD−H, 22°C, 254 nm, 80:20 hexane:*i*-PrOH, 0.8 mL/min; $t_R = 9.6$ min (*R*), $t_R = 10.9$ min (*S*).