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Asymmetric Conjugate Addition of Thiols to Chiral Methacryloyloxazolidinones

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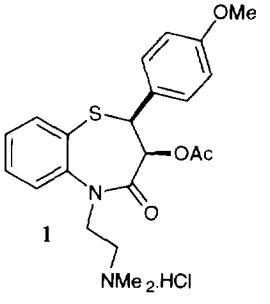
Key words: asymmetric conjugate addition, β-mercaptocarboxylic acid, chiral methacryloyloxazolidinone

Abstract: The conjugate addition of thioacetic acid (3 equivalents) to (4S)-4-phenyl-*N*-methacryloyloxazolidin-2-one (**3**) in the presence of $TiCl_4$ (1.5 equivalents) gave the addition adducts in 87% yield and only 14% de. When this reaction was carried out in the absence of $TiCl_4$, good diastereoselectivity (94% de) was observed. A similar result was obtained by employing thiobenzoic acid as a nucleophile. The reaction of **3** with other thiols, such as thiophenol, 4-methoxythiophenol, 2-methoxythiophenol, methyl 3-mercatopropionate, methyl thioglycolate and methyl thiosalicylate, required $TiCl_4$ (1.5 equivalents) to give the addition adducts in good chemical yields and the diastereoselectivities are ranging from 50 to 82% de. 2-Aminothiophenol was also employed in this study to give the addition adducts in 60% yield and 70% de when the reaction was carried out in the absence of $TiCl_4$. In the presence of $TiCl_4$, this reaction provided the addition adducts as racemic mixture in 28% yield along with 1,5-benzothiazepin-4-one **10** in 56% yield

β-Mercapto carboxylic acid derivatives have been found to exhibit interesting pharmaceutical activities. Many of these molecules contain stereogenic center at α, β, or both positions as exemplified by (+)-(2S, 3S)-cis-diltiazem **1**,[1] a potent vasodilating agent and captopril **2**,[2] the first orally active angiotensin converting enzyme inhibitor. A number of reports dealing with the preparation of enantiomerically pure compounds via the asymmetric conjugate addition reaction of thiols to α,β-unsaturated carboxylic acid derivatives have appeared.[3] Recently, we have described the Lewis acid catalyzed asymmetric conjugate addition of thiols to β-substituted-*N*-enoylsultams.[4] In many cases, the diastereomeric excess exceeded 60% and an unusual diastereomeric facial selectivity was observed. In order to exploit this concept to synthesize various mercaptans stereoselectively, we report herein the conjugate addition of thiols to a chiral *N*-methacryloyloxazolidinone.



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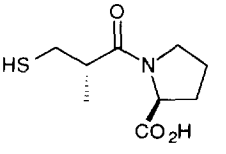

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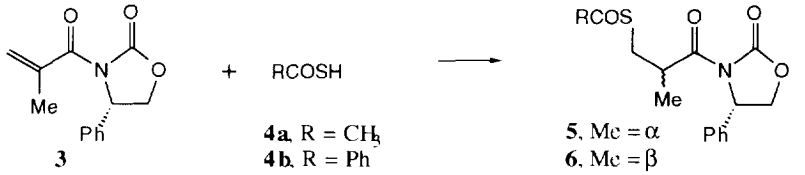
Our first attempt was carried out based on the optimal reaction conditions of the previous report.[4] Thus, reaction of (5S)-5-Phenyl-*N*-methacryloyl oxazolidinone (**3**)[5] with 3 equivalents of thioacetic acid in the presence of 1.5 equivalents of $TiCl_4$ at room temperature for 4 h gave the addition adducts **5a** and **6a** as a 57:43 mixture of diastereoisomers in 87% yield. Interestingly, when this reaction was carried out in the absence of $TiCl_4$, high asymmetric induction was observed. This reaction required a longer reaction time (24 h) to obtain 84% yield of a mixture of **5a** and **6a** in a diastereomeric ratio of 97:3. A similar result was obtained by employing thiobenzoic acid as a nucleophile, the results are summarized in Table 1. Compounds **5b** and **6b** were easily separated by flash column chromatography on silica gel (10% EtOAc in hexane as eluent). The structure of **5b** was unambiguously established by X-ray crystallography which indicated that the absolute configuration of C(α) is **S**.[6]

Table 1. Conjugate Addition of Thioacetic Acid and Thiobenzoic Acid to Compound **3**.

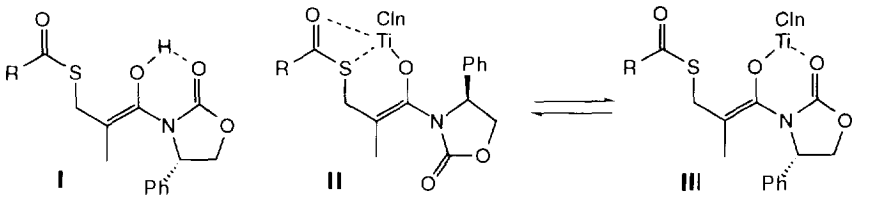


3 **4a**, R = CH_3 **5**, Me = α
4b, R = Ph **6**, Me = β

thiols	Lewis acid	products	diastereomeric ratio[a]	yield[b], %
4a	$TiCl_4$	**5a/6a**	57:43	87
4a	none	**5a/6a**	97: 3	84
4b	$TiCl_4$	**5b/6b**	60:40	83
4b	none	**5b/6b**	91: 9	65

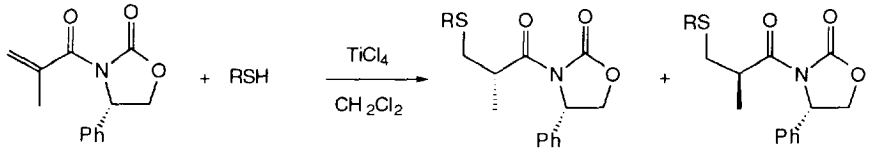
[a]Determined by using 200 MHz ^1H NMR spectroscopy of the crude products. [b]Isolated yield.

The high asymmetric inductions in the reactions of thioacetic acid and thiobenzoic acid with compound **3** in the absence of Lewis acid can be explained as follows: These two acids are acidic enough to protonate compound **3**. The protonation, followed by conjugate addition of the conjugate base to the protonated intermediate will form enol **I**. Protonation of enol **I** from the less hindered *re*-face will give the adducts **5a** and **5b** as the major products. Treatment of compound **3** with 10 equivalents of trifluoroacetic acid and 5 equivalents of thioacetic acid for 24 h at room temperature, did not produce any addition adduct but the starting material was recovered. These results suggest that the addition of the conjugate base is essential to obtain the conjugate addition adduct. When these reactions are catalyzed by $TiCl_4$, the initially formed titanium enolate **II** could, however, equilibrate to enolate **III**. Protonation of both enolates **II** and **III** would lead to a mixture of diastereomers (Scheme 1).



It should be noted that in the absence of $TiCl_4$ the reaction of compound **3** with other mercapto-containing nucleophiles, such as thiophenol, 4-methoxythiophenol, 2-methoxythiophenol, methyl 3-mercaptopropionate, methyl thioglycolate, and methyl thiosalicylate, under the described conditions did not give any of the addition adduct. However, in the presence of 1.5 equivalents of $TiCl_4$, these mercapto-containing nucleophiles reacted with compound **3** very rapidly even at -60 ~ -78 °C to give the addition adducts in good chemical yields and wide range of diastereoselectivities. These results are summerized in Table 2. Thus, good stereoselectivities were observed by employing thiophenol, 4-methoxythiophenol, methyl thiosalicylate, methyl thioglycolate, and methyl 3-mercaptopropionate as nucleophiles, while poor stereoselectivity was obtained by employing 2-methoxythiophenol as a nucleophile. The reason of the poor stereoselectivity is not clear. The structure of **8d** was unambiguously established by X-ray crystallography which indicated that the absolute configuration at C(α) is S.[6]

Table 2. Conjugate Addition of Thiols to Compound **3**.

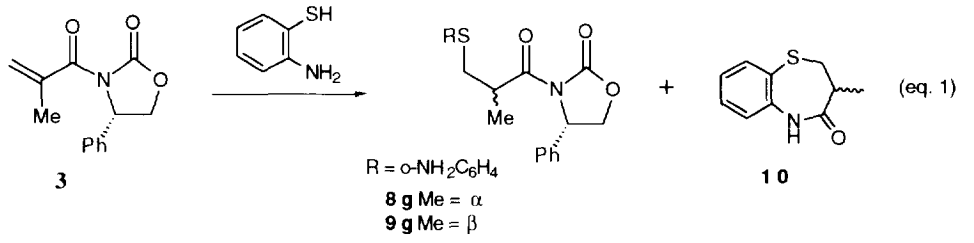


3 **7** **8** **9**

entry	nucleophiles	T(°C)/t(h)	products	ratio of **8** and **9**[a]	% yield of **8** and **9**[b]
1	**7a** (R = Ph)	-60/7	**8a/9a**	89:11	68
2	**7b** (R = p-$CH_3OC_6H_4$)	-78/7	**8b/9b**	91: 9	64
3	**7c** (R = o-$CH_3O_2CC_6H_4$)	-60/7	**8c/9c**	89:11	78
4	**7d** (R = $CH_3O_2CCH_2CH_2$)	-78/7	**8d/9d**	91: 9	79
5	**7e** (R = o-$CH_3OC_6H_4$)	-78/7	**8e/9e**	75:25	90
6	**7f** (R = $CH_3O_2CCH_2$)	-78/7	**8f/9f**	86:14	86

[a]Determined by using 200 MHz ^1H NMR spectroscopy of the crude products. [b]Isolated yield.

The reaction of 2-aminothiophenol with compound **3** in the absence of $TiCl_4$ at room temperature for 24 h gave **8g** and **9g** in 85:15 ratio in 60% yield.The configuration of the newly formed stereogenic centers of these two isomers were not determined. When the reaction was carried out in the presence of $TiCl_4$ at room temperature for 24 h, 56% yield of **10**[7] was obtained and 28% of **8g** and **9g** were isolated in 1:1 ratio. (eq 1)



In conclusion, the $TiCl_4$ promoted conjugate addition of thiols to chiral *N*-methacryloyloxazolidinone provided valuable informations to synthetic organic chemist. The mechanistic study on the poor stereoselectivities obtaining from the reactions of compound **3** with 2-aminothiophenol and 2-methoxythiophenol and optimization of these reaction conditions to obtain high diastereoselectivity are under investigation.

EXPERIMENTAL SECTION

Melting points were determined on a Yanaco MP apparatus and uncorrected. ^1H NMR and ^{13}C NMR were recorded on a Varian XL-200E spectrometer. All chemical shifts are reported in ppm using tetramethylsilane as internal standard. Elemental analysis were performed on a Hereus CHNO rapid analyser. Low resolution mass spectra were recorded on a JOEL SX-102A and high resolution spectra were recorded on a JOEL JMX-HX 110 spectrometer. Optical rotations were obtained on a Jasco-Dip-181 polarimeter.

General Procedure of Titanium Tetrachloride Promoted Conjugate Addition of Thiols to (4S)-4-Phenyl-N-methacryloyloxazolidin-2-one. (Method A) To a stirred solution of (4S)-4-phenyl-N-methacryloyloxazolidinone (0.231 g, 1 mmol) in dry CH_2Cl_2 (10 mL) was added $TiCl_4$ (1.5 mmol) at the temperature indicated in the text. Thiol (3 mmol) was then added into the reaction mixture. The resulting solution was stirred until all the starting material was consumed. The reaction mixture was poured into a saturated Na_2CO_3 solution and extracted with ether. The ethereal extracts were washed with 10% aqueous NaOH solution, brine and dried over anhydrous $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by flash column chromatography to give the products.

Method B: Same procedure as method A except that the reaction was carried out without adding $TiCl_4$.

(4S)-N-[(2S)-2-Methyl-3-acetylthiopropanoyl]-4-phenyloxazolidin-2-one and (4S)-N-[(2R)-2-methyl-3-acetylthiopropanoyl]-4-phenyloxazolidin-2-one (5a and 6a). Prepared by the reaction of **3** with thioacetic acid according to method A at 25 °C for 4 h to give a 57:43 mixture of **5a** and **6a** in 87% yield. Pure **5a** was obtained as a white solid upon purification by flash column chromatography over silica gel (10% EtOAc in hexane as eluent). $[\alpha]_D^{25}$ -5.9 (c 0.16, CH_2Cl_2); mp 102-103 °C (recrystallized from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.26-7.41 (m, 5 H), 5.42 (dd, 1 H, J = 8.8, 4.0 Hz), 4.70 (t, 1 H, J = 8.8 Hz), 4.23 (dd, 1 H, J = 8.8, 4.0 Hz), 3.95 (sintet, 1 H, J = 6.8 Hz), 3.07 (d, 2 H, J = 6.8 Hz), 2.25 (s, 3 H), 1.23 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 194.9, 174.8, 153.2, 138.8, 129.1, 128.7, 126.0, 69.9, 57.9, 38.5, 31.6, 30.5, 16.8; Anal. Calcd for $C_{15}H_{17}NO_4S$: C, 58.61; H, 5.57; N, 4.55. Found: C, 58.65; H, 5.62; N, 4.60.

Pure **6a** was obtained as a white solid. $[\alpha]_D^{25}$ + 183.0 (c 0.20, CH_2Cl_2); mp 86-87 °C (recrystallized from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.25-7.39 (m, 5 H), 5.41 (dd, 1 H, J = 8.8, 3.8 Hz), 4.73 (t, 1 H, J = 8.8 Hz), 4.27 (dd, 1 H, J = 8.8, 3.8 Hz), 3.87-4.02 (m, 1 H), 3.17 (dd, 1 H, J = 13.8, 5.5 Hz), 3.02 (dd, 1 H, J = 13.8, 7.6 Hz), 2.32 (s, 3 H), 1.21 (d, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 195.3, 174.4, 153.2, 139.0, 129.2, 128.7, 125.7, 70.0, 57.7, 38.7, 31.2, 30.5, 16.9; Anal. Calcd for $C_{15}H_{17}NO_4S$: C, 58.62; H, 5.57; N, 4.56. Found: C, 58.44; H, 5.67; N, 4.66.

The reaction of compound **3** with thioacetic acid according to method B gave **5a** and **6a** as a 97:3 mixture of diastereoisomers and in 84% yield.

(4S)-N-[(2S)-2-Methyl-3-benzoylthiopropanoyl]-4-phenyloxazolidin-2-one and (4S)-N-[(2R)-2-methyl-3-benzoylthiopropanoyl]-4-phenyloxazolidin-2-one (5b and 6b). Prepared by the reaction of **3** with thiobenzoic acid according to method A at 25 °C for 4 h to give a 60:40 mixture of **5b** and **6b** in 83% yield. Pure **5b** was obtained by flash column chromatography over silica gel (10% EtOAc in hexane as eluent) as a white solid. $[\alpha]_D^{25}$ -78.8 (c 0.25, CH_2Cl_2); mp 131-132 °C (recrystallized from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.89 (d, 2 H, J = 7.2 Hz), 7.58 (t, 1 H, J = 7.2 Hz), 7.44 (t, 2 H, J = 7.2 Hz), 5.44 (dd, 1 H, J = 8.8, 4.0 Hz), 4.70 (t, 1 H, J = 8.8 Hz), 4.25 (dd, 1 H, J = 8.8, 4.0 Hz), 4.11 (sintet, 1 H, J = 6.6 Hz), 3.29 (d, 2 H, J = 5.6 Hz), 1.32 (d, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 192.7, 176.4, 154.5, 140.0, 138.0, 134.6, 130.2, 129.8, 129.7, 128.4, 127.1, 70.5, 58.4, 39.1, 31.8, 17.1; Anal. Calcd for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79. Found: C, 64.93; H, 5.18; N, 3.87.

Pure **6b** was obtained as a white solid. $[\alpha]_D^{25}$ +180.0 (c 0.54, CH_2Cl_2); mp 106-108 °C (recrystallized from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.98 (dd, 2 H, J = 7.0, 1.4 Hz), 7.26-7.62 (m, 8 H), 5.42 (dd, 1 H, J = 8.8, 3.8 Hz), 4.72 (t, 1 H, J = 8.8 Hz), 4.26 (dd, 1 H, J = 8.8, 3.8 Hz), 4.06 (m, 1 H), 3.38 (dd, 1 H, J = 13.6, 5.4 Hz), 3.23 (dd, 1 H, J = 13.6, 7.8 Hz), 1.28 (d, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 193.0, 176.0, 154.6, 140.3, 138.0, 130.4, 129.9, 129.7, 128.4, 126.8, 70.6, 58.2, 39.3, 31.2, 17.3; Anal. Calcd for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79. Found: C, 64.93; H, 5.20; N, 3.85.

The reaction of compound **3** with thiobenzoic acid according to method B gave **5b** and **6b** as a 91:9 mixture of diastereoisomers and in 65% yield.

(4S)-N-[(2S)-2-Methyl-3-phenylthiopropanoyl]-4-phenyloxazolidin-2-one and (4S)-N-[(2R)-2-methyl-3-phenylthiopropanoyl]-4-phenyloxazolidin-2-one (8a and 9a). Prepared by the reaction of **3** with thiophenol according to method A at -60 °C for 7 h to give a 89:11 mixture of **8a** and **9a** in 68% yield. Pure **8a** was obtained by flash column chromatography over silica gel (10% EtOAc in hexane as eluent) as an oil. $[\alpha]_D^{25}$ -47.3 (c 0.26, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.17-7.41 (m, 10 H), 5.43 (dd, 1 H, J = 8.8, 4.2 Hz), 4.66 (t, 1 H, J = 8.8 Hz), 4.22 (dd, 1 H, J = 8.8, 4.2 Hz), 4.10 (sintet, 1 H, J = 6.8 Hz), 3.22 (dd, 1 H, J = 13.0, 7.9 Hz), 2.92 (dd, 1 H, J = 13.0, 6.4 Hz), 1.27 (d, 1 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 175.0, 153.2, 138.7, 136.0, 129.8, 129.1, 128.9, 128.6, 126.3, 125.9, 69.8, 57.9, 38.2, 37.5, 17.0. EI(MS) 341 (M^+, 100), 232 (74), 150 (63), 123 (53); HRMS calcd for $C_{19}H_{19}NO_3S$ 341.1086, found 341.1084.

Pure **9a** was obtained as a white solid. $[\alpha]_D^{25}$ +146.0 (c 0.55, CH_2Cl_2); mp 54-55 °C (recrystallized from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.20-7.41 (m, 10 H), 5.35 (dd, 1 H, J = 8.8, 3.7 Hz), 4.61 (t, 1 H, J = 8.8 Hz), 4.22 (dd, 1 H, J = 8.8, 3.7 Hz), 4.02-4.12 (m, 1 H), 3.28 (dd, 1 H, J = 13.4, 8.4 Hz), 2.94 (dd, 1 H, J = 13.4, 5.6 Hz), 1.22 (d, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 174.6, 153.1, 139.0, 135.9, 130.1,

129.2, 128.9, 128.7, 126.5, 125.6, 69.9, 57.6, 38.5, 36.8, 17.4; Anal. Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.76; H, 5.78; N, 4.25.

(4S)-N-[(2S)-2-Methyl-3-(4-methoxyphenylthio)propanoyl]-4-phenyloxazolidin-2-one and (4S)-N-[(2R)-2-methyl-3-(4-methoxyphenylthio)propanoyl]-4-phenyloxazolidin-2-one (8b and 9b). Prepared by the reaction of **3** with 4-methoxythiophenol according to method A at -60 °C for 7 h to give a 90:10 mixture of **8b** and **9b** in 64% yield. Pure **8b** was obtained by flash column chromatography over silica gel (10% EtOAc in hexane as eluent) as a white solid. $[\alpha]_D^{25}$ -62.2 (c 0.25, CH_2Cl_2); mp 114-116 °C (recrystallized from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.30-7.39 (m, 5 H), 7.27 (d, 2 H, J = 8.9 Hz), 6.81 (d, 2 H, J = 8.8 Hz), 5.43 (dd, 1 H, J = 8.8, 4.2 Hz), 4.66 (t, 1 H, J = 8.8 Hz), 4.23 (dd, 1 H, J = 8.8, 4.2 Hz), 3.97-4.13 (m, 1 H), 3.78 (s, 3 H), 3.13 (dd, 1 H, J = 13.0, 8.0 Hz), 2.79 (dd, 1 H, J = 13.0, 6.3 Hz), 1.23 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 175.2, 159.1, 153.3, 138.8, 133.7, 129.1, 128.7, 126.2, 125.9, 114.6, 69.8, 57.9, 55.3, 39.7, 38.4, 17.0; Anal. Calcd for $C_{20}H_{21}NO_4S$: C, 64.66; H, 5.69; N, 3.77. Found: C, 64.25; H, 5.65; N, 3.87.

(4S)-N-[(2S)-2-Methyl-3-(2-methoxycarbonylphenylthio)propanoyl]-4-phenyloxazolidin-2-one (8c). Prepared by the reaction of **3** with methyl thiosalicylate according to method A at -60 °C for 7 h to give a 89:11 mixture of **8c** and **9c** in 78% yield. Pure **8c** was obtained by flash column chromatography over silica gel (10 % EtOAc in hexane as eluent) as an oil. $[\alpha]_D^{25}$ -48.0 (c 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.92 (dd, 1 H, J = 7.8, 1.6 Hz), 7.27-7.45 (m, 7 H), 7.15 (td, 1 H, J = 7.8, 1.3 Hz), 5.44 (dd, 1 H, J = 8.8, 4.4 Hz), 4.68 (t, 1 H, J = 8.8 Hz), 4.17-4.25 (m, 2 H), 3.90 (s, 3 H), 3.26 (dd, 1 H, J = 12.4, 7.2 Hz), 2.92 (dd, 1 H, J = 12.4, 6.9 Hz), 1.34 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 175.0, 166.8, 153.3, 140.7, 138.6, 132.3, 131.2, 129.2, 128.6, 128.3, 126.2, 125.8, 124.2, 69.9, 58.1, 52.0, 37.4, 35.6, 17.3; EI(MS) 399 (M^+, 100), 232 (84), 208 (45), 167 (42); HRMS calcd for $C_{21}H_{21}NO_5S$ 399.1140, found 399.1136; Anal calcd for $C_{21}H_{21}NO_5S$: C, 63.14; H, 5.30; N, 3.51. Found: C, 62.12; H, 5.30; N, 3.44.

(4S)-N-[(2S)-2-Methyl-3-(2-methoxycarbonylethylthio)propanoyl]-4-phenyloxazolidin-2-one (8d). Prepared by the reaction of **3** with methyl 3-mercaptopropionate according to method A at -78 °C for 7 h to give a 91:9 mixture of **8d** and **9d** in 79% yield. Pure **8d** was obtained by flash column chromatography over silica gel (10% EtOAc in hexane as eluent) as a white solid. $[\alpha]_D^{25}$ +13.1 (c 0.16, CH_2Cl_2); mp 64-66 °C (recrystallized from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.29-7.37 (m, 5 H), 5.43 (dd, 1 H, J = 8.8, 4.0 Hz), 4.68 (t, 1 H, J = 8.8 Hz), 4.23 (dd, 1 H, J = 8.8, 4.0 Hz), 4.05 (sintet, 1 H, J = 7.4 Hz), 3.66 (s, 3 H), 2.42-2.90 (m, 6 H), 1.23 (d, 1 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 174.9, 172.0, 153.2, 138.6, 128.8, 128.4, 125.7, 69.7, 57.7, 51.5, 38.2, 35.3, 34.3, 27.1, 16.4; Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.98. Found: C, 58.17; H, 6.06; N, 4.12.

(4S)-N-[(2S)-2-Methyl-3-(2-methoxyphenylthio)propanoyl]-4-phenyloxazolidin-2-one and (4S)-N-[(2R)-2-methyl-3-(2-methoxyphenylthio)propanoyl]-4-phenyloxazolidin-2-one (8e and 9e). Prepared by the reaction of **3** with 2-methoxythiophenol according to method A at -78 °C for 7 h to give a 75:25 mixture of **8e** and **9e** in 90% yield. The stereoisomers were separated by flash column chromatography over silica gel (10% EtOAc in hexane as eluent). The major isomer was obtained as an oil.

$[\alpha]_D^{25}$ -37.9 (c 0.19, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.20-7.45 (m, 7 H), 6.79-6.97 (m, 2 H), 5.47 (dd, 1 H, J = 8.8, 4.0 Hz), 4.72 (t, 1 H, J = 8.8 Hz), 4.32 (dd, 1 H, J = 8.8, 4.0 Hz), 3.92-4.10 (m, 1 H), 2.99 (dd, 1 H, J = 12.5, 8.9 Hz), 2.72 (dd, 1 H, J = 12.5, 5.5 Hz), 1.24 (d, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 174.9, 156.9, 153.2, 138.6, 135.9, 131.3, 129.2, 128.8, 126.0, 125.9, 120.7, 118.7, 115.1, 69.9, 58.0, 39.7, 38.4, 17.2; MS(EI) 371 (M^+, 100), 232 (45), 140 (34); HRMS calcd for $C_{20}H_{21}NO_4S$ 371.1191, found 371.1191.

The minor isomer was obtained as a white solid. $[\alpha]_D^{25}$ +196.0 (c 0.05, CH_2Cl_2); mp 118-119 °C (recrystallized from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.18-7.39 (m, 7 H), 6.83-6.93 (m, 2 H), 5.44 (dd, 1 H, J = 8.8, 4.2 Hz), 4.68 (t, 1 H, J = 8.8 Hz), 4.24 (dd, 1 H, J = 8.8, 4.2 Hz), 4.04 (sintet, 1 H, J = 7.3 Hz), 3.87 (s, 3 H), 3.19 (dd, 1 H, J = 12.9, 7.5 Hz), 2.86 (dd, 1 H, J = 12.9, 6.8 Hz), 1.27 (d, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 175.8, 158.6, 153.7, 139.2, 132.0, 129.6, 129.1, 128.6, 126.4, 124.1, 121.5, 11.2, 70.3, 58.4, 56.2, 38.7, 36.7, 17.5; Anal Calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.37. Found: C, 64.68; H, 5.84; N, 3.94.

(4S)-N-[(2S)-2-Methyl-3-methoxycarbonylmethylthiopropanoyl]-4-phenyloxazolidin-2-one (8f). Prepared by the reaction of **3** with methyl thioglycolate according to method A at -78 °C for 7 h to give a 86:14 mixture of **8f** and **9f** in 86% yield. Pure **8f** was obtained by flash column chromatography over silica gel (10 % EtOAc in hexane as eluent) as a white solid. $[\alpha]_D^{25}$ +35.5 (c 0.22, CH_2Cl_2); mp 60-61 °C (recrystallized from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.28-7.39 (m, 5 H), 5.45 (dd, 1 H, J = 8.8, 4.1 Hz), 4.71 (t, 1 H, J = 6.8 Hz), 4.27 (dd, 1 H, J = 8.8, 4.1 Hz), 4.10 (sintet, 1 H, J = 6.8 Hz), 3.72 (s, 3 H), 3.17 (d, 2 H, J = 1.1 Hz), 2.95 (dd, 1 H, J = 13.6, 8.0 Hz), 2.61 (dd, 1 H, J = 13.6, 6.4 Hz), 1.25 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 175.3, 171.1, 153.6, 138.8, 129.2, 128.8, 126.0, 69.8, 57.9, 52.2, 38.0, 35.8, 33.4, 16.5; Anal. Calcd for $C_{16}H_{19}NO_5S$: C, 56.96; H, 5.68; N, 4.15. Found: C, 56.89; H, 5.75; N, 4.33.

(4S)-N-[(2S)-2-Methyl-3-(2-aminophenylthio)propanoyl]-4-phenyloxazolidin-2-one and (4S)-N-[(2R)-2-methyl-3-(2-aminophenylthio)propanoyl]-4-phenyloxazolidin-2-one (8g and 9g). Prepared by the reaction of **3** with 2-aminothiophenol according to method A at 25 °C for 24 h to give a 55:45 mixture of **8g** and **9g** in 28% yield along with **10** in 56% yield. Compounds **8g** and **9g** were obtained in 60 % yield as a 86:14 mixture of diastereomers according to method B. The isomers were separated by flash column chromatography over silica gel (10 % EtOAc in hexane as eluent). The major diastereomer was obtained as a white solid. mp 83-84 °C (recrystallized from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.10-7.41 (m, 7 H), 6.68-6.80 (m, 2 H), 5.28 (dd, 1 H, J = 8.8, 3.6 Hz), 4.60 (t, 1 H, J = 8.8 Hz), 4.25 (bs, 2 H), 4.20 (dd, 1 H, J = 8.8, 3.6 Hz), 3.90-4.08 (m, 1 H), 3.17 (dd, 1 H, J = 13.0, 8.6 Hz), 2.76 (dd, 1 H, J = 13.0, 5.0 Hz), 1.18 (d, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 174.5, 153.0, 148.2, 139.0, 136.2, 129.9, 129.0, 128.5, 125.5, 118.5, 117.2, 115.0, 69.8, 57.4, 38.6, 36.8, 17.3; Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86. Found: C, 64.01; H, 5.72; N, 8.08.

The minor isomer was also obtained as a white soild. mp 91-92 °C (recrystallized from EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 7.04-7.39 (m, 7 H), 6.60-6.69 (m, 2 H), 5.42 (dd, 1 H, J = 8.8, 4.0 Hz), 4.65 (t, 1 H, J = 8.8 Hz), 4.24 (dd, 1 H, J = 8.8, 4.0 Hz), 4.12 (bs, 2 H), 3.90-4.10 (m, 1 H), 3.03 (dd, 1 H, J = 12.5, 8.5 Hz), 2.73 (dd, 1 H, J = 12.5, 5.9 Hz), 1.22 (d, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 175.0, 153.1, 147.8,

138.7, 135.9, 129.8, 129.0, 128.6, 126.0, 125.5, 118.4, 117.5, 115.0, 69.7, 57.8, 38.4, 38.0, 17.0; Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86. Found: 64.17; H, 5.74; N, 7.84.

2,3-Dihydro-3-methyl-1,5-benzothiazepin-4(5H)-one (10). as a white solid. mp 180-181 °C; ^1H NMR ($CDCl_3$) δ 7.90 (bs, 1 H), 7.59 (dd, 1 H, J = 7.5, 1.5 Hz), 7.36 (td, 1 H, J = 7.7, 1.4 Hz), 7.08-7.20 (m, 2 H), 3.49 (dd, 1 H, J = 11.1, 5.9 Hz), 3.00 (t, 1 H, J = 12.5 Hz), 2.77 (m, 1 H), 1.82 (d, 3 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 175.7, 141.1, 135.1, 129.7, 127.7, 126.5, 123.4, 41.5, 36.3, 15.4; Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.14; H, 5.73; N, 7.24. Found: C, 62.40; H, 5.76; N, 7.19.

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(6) X-ray crystallographic data of compounds **5b** and **8d** have been deposited with the Cambridge Crystallographic Data Centre. The Coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CBZ 1EZ, UK.

(7) The optical purity of compound **10** was determined to be 6 % ee by ^1H NMR spectra in the presence of tris[(3-heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium (III)

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