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Preparation of β-amino-α-mercapto acids and amides: stereocontrolled syntheses of 2′-sulfur analogues of the taxol C-13 side chain, both *syn* and *anti* *S*-acetyl-*N*-benzoyl-3-phenylisocysteine

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Abstract—Stereoselective syntheses of both *syn* and *anti* *S*-acetyl-*N*-benzoyl-3-phenylisocysteine as coupling-ready reagents via the ring-opening reactions of *trans*- and *cis*-oxazoline-5-carboxylates with thiolacetic acid were demonstrated. In addition, we report upon ring-opening reactions of oxazoline-5-carboxamides. Ab initio molecular calculations were used to explain the different reactivities of these oxazolines with respect to the ring-opening reaction.

1. Introduction

Paclitaxel (taxol), a complex natural product currently considered to be one of the most promising anticancer agent, bears the (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine unit (see Fig. 1) in its C-13 side chain. Although the specific roles of its functional group in microtubule binding are poorly understood, numerous efforts have been made to modify this side chain and to determine its structure–activity relationships. These studies have shown that 2′-hydroxyl functionality is crucial for microtubule binding,[1–3] perhaps acting as a hydrogen bond donor.[2a,c–e,g,3] In light of this hypothesis, the synthesis of analogues containing the 2′-thiol functionality, which is more acidic than the hydroxyl group, would be of considerable interest to those attempting to understand the features of paclitaxel binding site on microtubules and to the development of new compounds with more desirable properties than paclitaxel. As far as we are aware, no attempts have been previously made to synthesize this thiol derivative.

In addition, peptidomimetics[4] bearing a thiol moiety as zinc chelating group are of great interest in the development of potent inhibitors for numerous zinc-metalloproteases having exopeptidase[5,6] or endopeptidase activities,[7–11] which play a crucial role in the activation or inactivation of regulatory peptides.

Common used methods for the synthesis of β-amino-α-mercapto acids include the electrophilic sulfenylation of *N*-protected β-amino esters which can be available via the Arndt–Eistert homologation of the corresponding α-amino acids,[5] or of the aspartic acid derivatives[6b–d,12] in which the α-ester moiety is used for the introduction of the side chain using a regioselective tandem reduction-Wittig Horner reaction.[13]

As reported by the Roques[6b–d] and Baldwin groups,[12] the preferential attack of the sulfenylating agent on the least hindered face of the dianion is a key point in the sulfenylation step. Even though this approach must be an efficient way of preparing β-amino-α-mercapto acids, optically active β-amino acids are required as a starting material and furthermore, only *anti* isomers of β-amino-α-mercapto esters are accessible from these optically active β-amino acids.

The synthesis of DL-isocysteine from DL-thiomalic acid was also reported.[14] Although stereochemical integrity should in principle be maintained, since the literature methods do not involve any functional group transformation at the chiral center of isocysteine, literature methods are extremely limited in terms of the availability of optically active starting materials, and therefore this methodology cannot be easily extended to the substituted analogues.

Along with the aziridine-2-carboxylates,[15–17] oxazoline-5-

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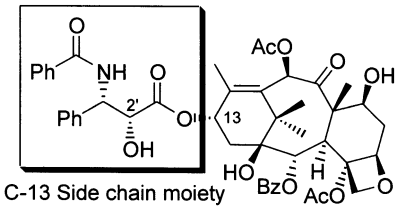


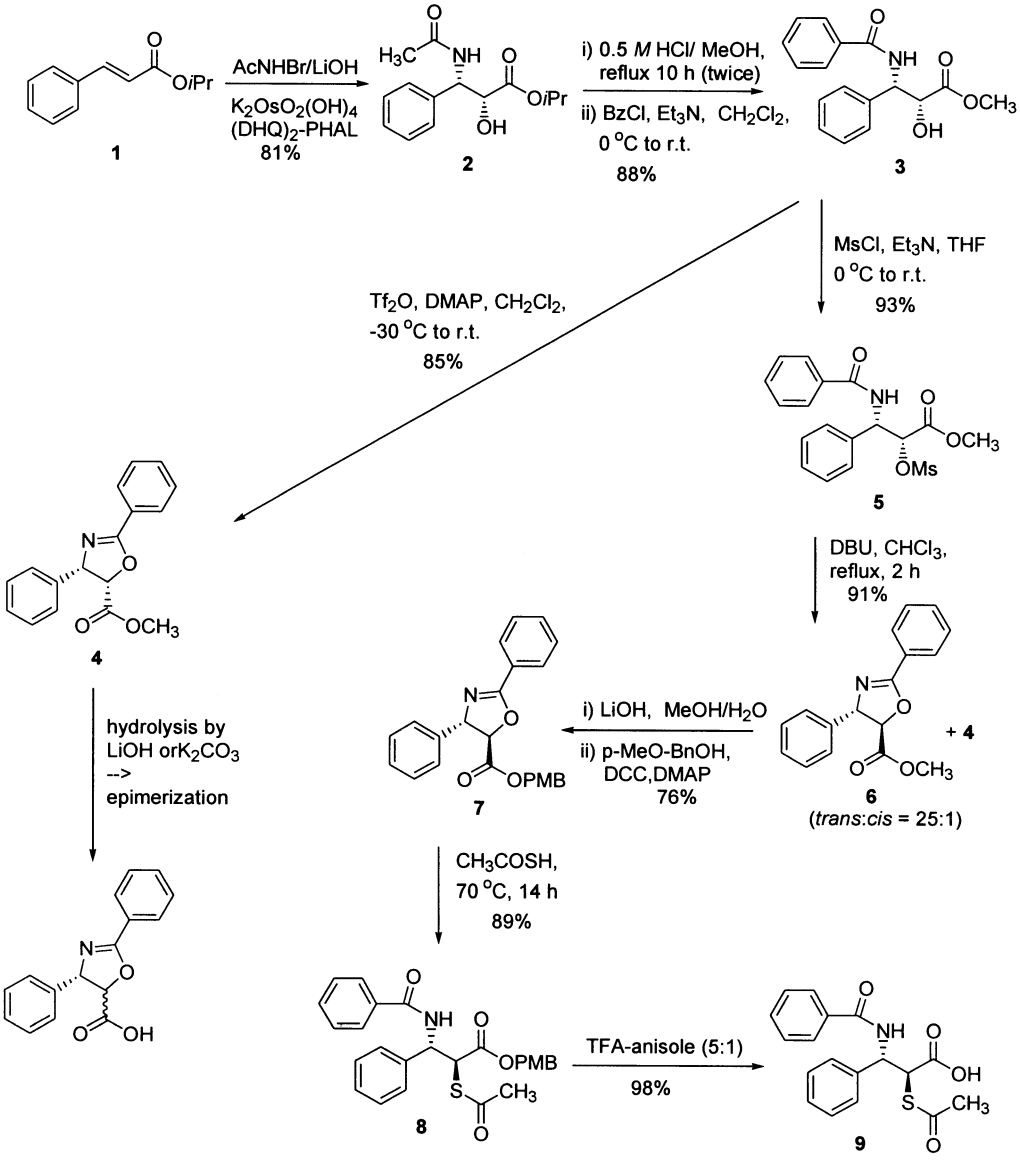
Paclitaxel (taxol)

Figure 1. Structure of Paclitaxel (taxol).

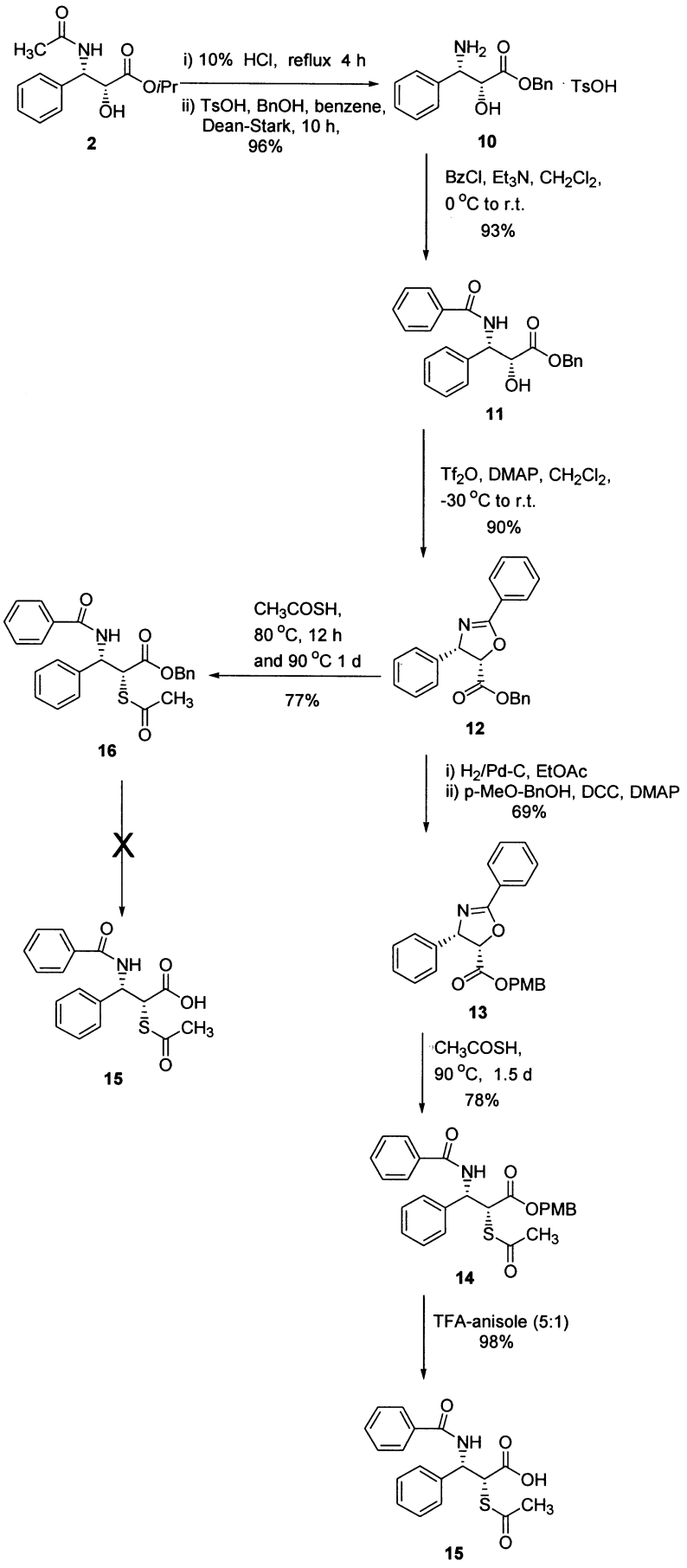
carboxylates can be useful intermediates as synthetic equivalents of an α-cation for the preparation of α-substituted β-amino esters. In our earlier report,[18] we demonstrated the potential utility of these intermediates for the synthesis of α-substituted β-amino esters. In a continuation of this work, we report here upon ring-opening reactions of oxazoline-5-carboxamides. Ab initio molecular calculations were used to explain the different reactivities of these oxazolines. In addition, we describe stereoselective syntheses of both *syn* and *anti* 2-acetylthio-3-benzoylamino-3-phenylpropanoic acids as coupling-ready reagents for the synthesis of 2′-sulfur analogues of taxol via the ring-opening reactions of *trans*- and *cis*-oxazoline-5-carboxylates with thiolacetic acid.

2. Results and discussion

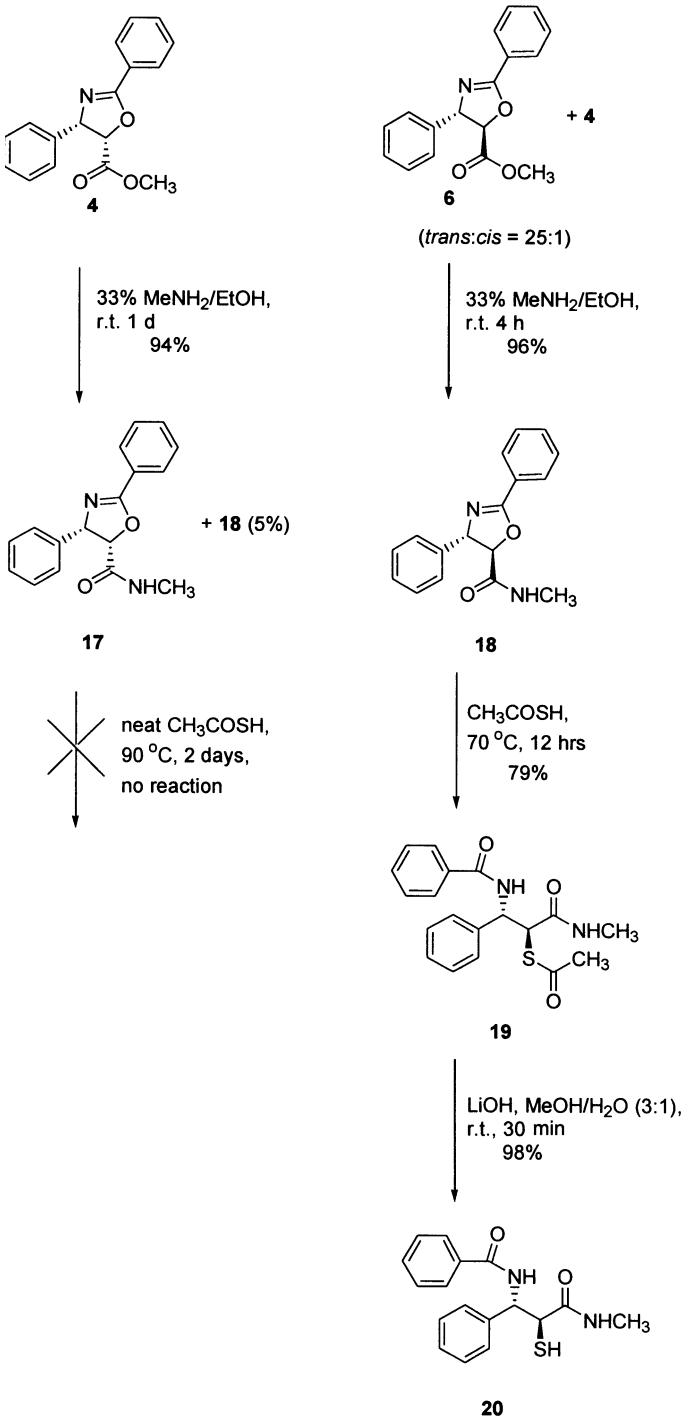
Our first objective was the synthesis of *anti* and *syn* β-amino-α-mercapto acids that can be directly used for coupling. In our earlier report,[18] we demonstrated the potential utility of oxazoline-5-carboxylates as the synthetic equivalent of an α-cation for the preparation of α-substituted β-amino esters. For the synthesis of both *syn* and *anti* β-amino-α-mercapto esters, a combination of protecting groups, namely, the *S*-acetyl group[19] and the methyl ester group were used. However, the methyl ester group cannot be



Scheme 1. Preparation of *anti* β-amino-α-mercapto acid.



Scheme 2. Preparation of *syn* β-amino-α-mercapto acid.



Scheme 3. Ring-opening reaction of oxazoline-5-carboxamide.

selectively removed by saponification without affecting the *S*-acetyl group because of the greater susceptibility of the latter. Moreover, in its ester form, the β-amino-α-mercapto acid is susceptible to epimerization at the α-center in basic condition.[6c,d,12] To avoid this, we chose another type of carboxylic acid protecting group, which can be removed under neutral or acidic conditions.

The synthesis of *anti S*-acetyl-*N*-benzoyl-3-phenylisocysteine (**9**) was relatively straightforward (Scheme 1). In our synthetic scheme, isopropyl cinnamate **1** was first functionalized to the *syn* acetylamino alcohol **2**, using $(DHQ)_2PHAL$ and *N*-bromoacetamide following a published procedure.[20] The *N*-protecting acetyl group was changed with a benzoyl group for the possible utility of these oxazoline-5-caboxylate as an intermediate for the synthesis of a modified taxol side chain. In this step, concomitant transesterification of the isopropyl ester to the methyl ester also occurred. Benzoylamino alcohol **3** was converted to its methanesulfonate **5** in 93% yield, treatment of methanesufonate **5** with DBU afforded both *trans*-**6** and *cis*-oxazoline **4** in the ratio 25:1, which was confirmed by

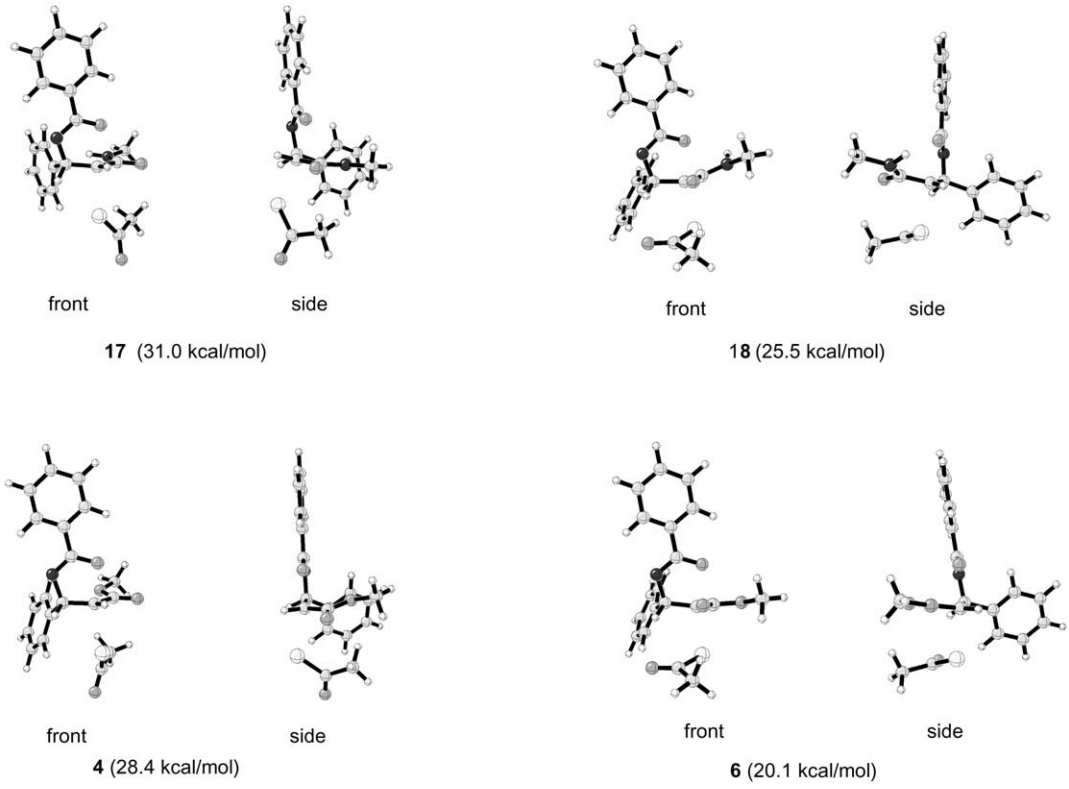


Figure 2. Transition states and their activation energies for ring-opening reactions of oxazoline esters (**4**, **6**) and amides (**17**, **18**).

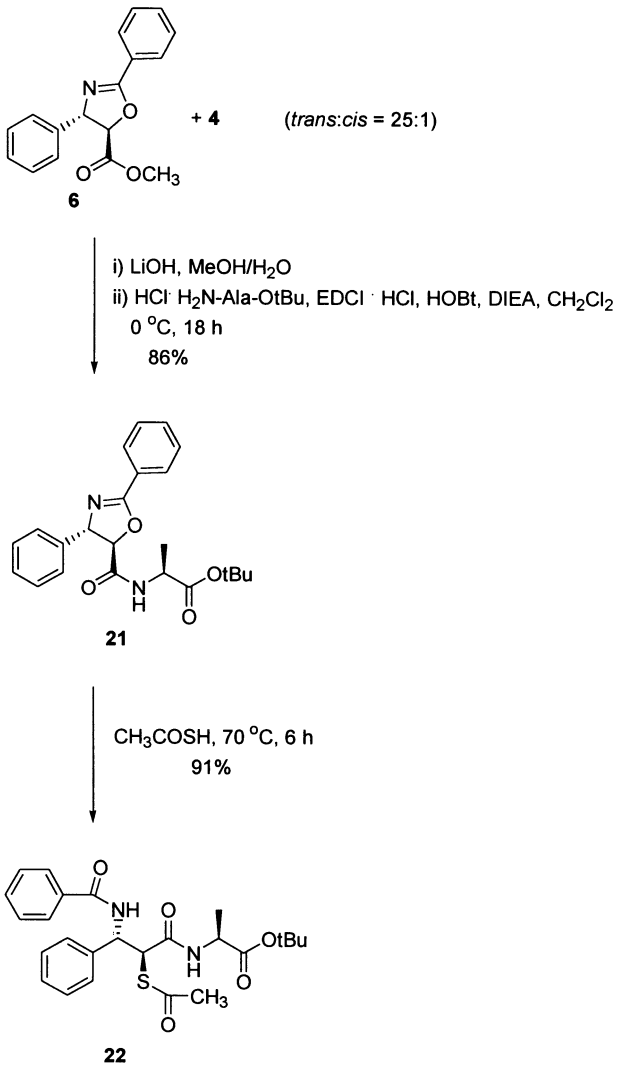
^{1}H NMR. As explained in our earlier report,[18] the DBU-induced cyclization proceeds via initial epimerization, prior to cyclization. However, we failed to isolate *trans*-oxazoline methyl ester **6** by column chromatography, but after transprotecting the carboxylic acid with the *p*-methoxybenzyl (PMB) group,[19] the *trans*-oxazoline PMB ester **7** was isolated with a yield of 76%. Ring-opening reaction with thiolacetic acid gave *anti* acetylthio ester **8** in 89% yield, which was then reacted with trifluoroacetic acid (TFA) and anisole to give (2*S*,3*S*)-2-acetylthio-3-benzoylamino-3-phenylpropanoic acid (**9**). This *anti* 3-phenylisocysteine derivative **9** has a coupling ready, free carboxylic acid group and an acetyl group, which can be easily cleaved, on its thiol moiety, and this was synthesized from isopropyl cinnamate (**1**) with an overall yield of 40%.

On the other hand, the preparation of *syn* *S*-acetyl-*N*-benzoyl-3-phenylisocysteine (**15**) was rather complex and the choice of protecting group was essential throughout the synthesis. For the synthesis of the *syn* isomer, we first started from the amino alcohol methyl ester **3**. As shown in Scheme 1, treatment of **3** with trifluoromethanesulfonic anhydride (Tf_2O) afforded the *cis*-oxazoline methyl ester **4** with a yield of 85%. However, hydrolysis of the methyl ester using either lithium hydroxide or potassium carbonate to make free acid led epimerization at the α-center.

Our next choice was the benzyl ester (Scheme 2), which can be removed under typical hydrogenation conditions. The *N*-acetyl group and the isopropyl ester of **2** were removed by acid hydrolysis,[20] and the free acid generated was converted to the benzyl ester.[21] A benzoyl group was introduced as a *N*-protecting group to give the amino alcohol benzyl ester **11**. Again, treatment of **11** with Tf_2O afforded the *cis*-oxazoline **12** in 90% yield. When this *cis*-oxazoline **12** was reacted with neat thiolacetic acid, *syn* acetylthio ester **16** (2*R*,3*S*) was obtained in 77% yield after heating for 12 h at 80°C and additional heating for 1 day at 90°C. Because of the lower reactivity of *cis*-oxazoline, compared to the *trans* isomer, the ring-opening reaction needed a higher reaction temperature and longer reaction time. However, we failed to deprotect the benzyl group to give its free acid under various hydrogenation conditions, which included both catalytic hydrogenation, and catalytic transfer hydrogenation that are known to be effective for some compounds that contains divalent sulfur, a poison for the hydrogenolysis catalyst.[19]

Finally, *cis*-oxazoline benzyl ester **12** was transformed to its PMB ester **13**. The ring-opening reaction of **13** with thiolacetic acid led to *syn* acetylthio PMB ester **14** (78% yield), which was then reacted with TFA–anisole to give (2*R*,3*S*)-2-acetylthio-3-benzoylamino-3-phenylpropanoic acid (**15**), i.e. a coupling-ready *syn* 3-phenylisocysteine derivative, in an overall yield of 34% from isopropyl cinnamate (**1**).

To prepare dipeptide containing the β-amino-α-mercapto acid group, we examined the ring-opening reactions of oxazoline-5-carboxamides with thiolacetic acid. Both *cis*- and *trans*-oxazoline-5-carboxylates (**4**, **6**) were transformed to their carboxamides (**17**, **18**) (Scheme 3). Treatment of *trans*-oxazoline-5-carboxamide **18** with thiolacetic acid led to the *anti* acetylthio amide **19** in 79% yield. Removal of the acetyl group using lithium hydroxide gave the *anti* thiol amide **20**. On the other hand, *cis*-oxazoline-5-carboxamide



Scheme 4. Preparation of *anti* β-amino-α-mercapto acid containing dipeptide.

17 was not ring-opened to give the desired *syn* acetylthio amide even at higher temperature and longer reaction time.

In order to explain the poor reactivity of *cis*-oxazoline-5-carboxamide **17**, we carried out ab initio molecular orbital calculations (Fig. 2). All the calculations were carried out using Gaussian 94.[22] At the transition state of ring-opening upon thiolacetic acid attacks, *cis*-oxazoline-5-carboxylate **4** was found to be less reactive than the *trans* isomer **6** by 8.3 kcal/mol at the RHF/6-31G* level. *cis*-Oxazoline-5-carboxamide **17** was also found to be less reactive than *trans*-oxazoline-5-carboxamide **18** by 5.5 kcal/mol at the same theory level. This activation energy difference is equivalent to more than a 100-fold difference of the relative reaction rate at room temperature. At the transition state, the ester or amide group takes a perpendicular orientation to the forming and breaking bonds, to maximize the resonance between the *p*-orbitals of the carbonyl and the reaction center carbons. This makes the steric repulsion between the phenyl and the ester or amide groups in the *cis*-orientation at the transition state more severe compared to the reactant. These results clearly explain the reason why *cis*-oxazoline-5-carboxamide **17** is so unreactive toward the ring-opening reaction with thiolacetic acid compared from other substrates.

To demonstrate the possible utility of this method, *trans*-oxazoline-5-carboxylate **6** was coupled with L-alanine *t*-butyl ester after **6** was hydrolyzed to its free acid (Scheme 4). Again, ring-opening reaction with thiolacetic acid gave the model dipeptide **22** in 91% yield. This dipeptide contains the acetylthio and *t*-butyl ester groups which can be easily manipulated for further use. In principle, other amino acids or dipeptides can be used for the coupling reaction, and ring-opening reagents other than thiolacetic acid, such as trimethylsilyl azide or thiophenol, can be used.[18]

3. Conclusions

In conclusion, we have stereoselectively synthesized both *anti* and *syn* *S*-acetyl-*N*-benzoyl-3-phenylisocysteine (**9**, **15**) as coupling-ready reagents for dipepetide or 2′-sulfur analogues of the taxol C-13 side chain. In our synthesis, the stereoselective ring-opening reactions of *trans*- and *cis*-oxazoline-5-carboxylates with thiolacetic acid were utilized as a key step. These compounds contain a coupling-ready free carboxylic acid and labile acetyl group on their thiol moiety. In addition, we have developed steroselective ring-opening reactions of *trans*-oxazoline-5-carboxamides with thiolacetic acid. Basically, these methods can be further utilized with any amino acid and other ring-opening reagents such as trimethylsilyl azide or thiophenol to prepare di- or tri-peptide containing α-substituted β-amino acid. Ab initio molecular calculations were used to explain the different reactivities of these *cis*- and *trans*-oxazolines with respect to the ring-opening reaction.

4. Experimental

4.1. General methods

NMR spectra were recorded using a JEOL JNM-LA 300 spectrometer at 300 MHz (for ^{1}H NMR) and at 75 MHz (for ^{13}C NMR). Chemical shifts were obtained in ppm, using TMS as an internal standard. Mass spectra were obtained using a JEOL JMS AX505WA spectrometer. Infrared spectra were recorded with a JASCO FTIR-200 Spectrometer. Melting points were determined in open capillaries, and are uncorrected. Optical rotations were determined using a JASCO DIP 1000 polarimeter. Elemental analyses were performed using Elementar Vario EL at Korea Basic Science Institute. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh). Thin layer chromatography was carried out using Merck 60 F_{254} plates with a 0.25 mm thickness. The $CHCl_3$, CH_2Cl_2, and MeOH were distilled from CaH_2. THF and ether were distilled from sodium-benzophenone ketyl.

4.1.1. (2*R*,3*S*)-3-Acetylamino-2-hydroxy-3-phenylpropanoic acid isopropyl ester (2). This compound was prepared in 81% yield, according to the reported acetamide-based Sharpless aminohydroxylation protocol:[20] mp 111–112°C; $[\alpha]_D^{18}=+28.3°$ (c=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz)

δ 1.29 (d, *J*=6.2 Hz, 3H), 1.31 (d, *J*=6.2 Hz, 3H), 2.01 (s, 3H), 3.26 (d, *J*=3.8 Hz, 1H), 4.48 (dd, *J*=2.0, 3.8 Hz, 1H), 5.11 (sept, *J*=6.2 Hz, 1H), 5.56 (dd, *J*=2.0, 9.2 Hz, 1H), 6.30 (br d, *J*=9.2 Hz, 1H), 7.20–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.48, 21.65, 23.14, 54.31, 70.79, 73.25, 126.86, 127.74, 128.58, 138.88, 169.28, 172.40; HRMS (CI) *m*/*z*=266.1400 $(M+H)^+$, calcd for $C_{14}H_{20}N_1O_4$=266.1392.

4.1.2. (2*R*,3*S*)-3-Benzoylamino-2-hydroxy-3-phenylpropanoic acid methyl ester (3). Compound **2** (1000 mg, 3.77 mmol) was treated with 0.5 M HCl in MeOH (100 mL), and heated under reflux for 10 h. After removal of the solvent under reduced pressure, the residue was again treated with 0.5 M HCl in MeOH (100 mL) and heated under reflux for an additional 10 h. After removal of the solvent under reduced pressure, the residue was re-dissolved in fresh MeOH (2×60 mL) and re-evaporated. To this residue, dry CH_2Cl_2 (80 mL) was added and it was then cooled to 0°C. To this suspension, Et_3N (2.63 mL, 18.9 mmol) in CH_2Cl_2 (5 mL) was added, followed by BzCl (530 mg, 3.77 mmol) in CH_2Cl_2 (3 mL), and the reaction mixture was stirred for 1 h at 0°C and then for 1 h at room temperature. The reaction mixture was then passed through a short silica gel plug (~20 cm^3) and further eluted with EtOAc (200 mL). The combined filtrate was then concentrated under reduced pressure, and the residue was crystallized from EtOAc–hexane to afford **3** (990 mg, 3.31 mmol, 88%) as a off-white solid. An analytical sample was obtained by re-crystallization ($CHCl_3$–hexane): mp 178–181°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.30 (d, *J*=3.9 Hz, 1H), 3.85 (s, 3H), 4.64 (dd, *J*=2.0, 3.9 Hz, 1H), 5.75 (dd, *J*=2.0, 9.0 Hz, 1H), 6.99 (br d, *J*=9.0 Hz, 1H), 7.20–7.60 (m, 8H), 7.70–7.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 53.28, 54.80, 73.20, 126.88, 127.04, 127.94, 128.63, 128.73, 131.76, 134.03, 138.66, 166.85, 173.38; HRMS (FAB) *m*/*z*=300.1240 $(M+H)^+$, calcd for $C_{17}H_{18}N_1O_4$=300.1236.

4.1.3. (4*S*,5*S*)-2,4-Diphenyl-2-oxazoline-5-carboxylic acid methyl ester (4): procedure A. Tf_2O (423 mg, 1.50 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of **3** (299 mg, 1.00 mmol) and DMAP (367 mg, 3.00 mmol) in CH_2Cl_2 (30 mL) at −30°C under N_2. After being stirred for 1 h at −30°C, the reaction mixture was warmed to room temperature. The reaction mixture was then passed through a short silica gel plug (~10 cm^3) and further eluted with EtOAc–hexane (60 mL, 1:1). The combined filtrate was then concentrated under reduced pressure, and purification of the residue by flash chromatography (hexane–EtOAc, 6:1) afforded **4** as a white solid. This was further purified by re-crystallization (hexane) yielding **4** (240 mg, 0.853 mmol, 85%) as white needles: mp 92.5–93.5°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.21 (s, 3H), 5.39 (d, *J*=10.8 Hz, 1H), 5.75 (d, *J*=10.8 Hz, 1H), 7.20–7.60 (m, 8H), 8.05–8.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.57, 73.51, 81.10, 126.75, 127.76, 128.11, 128.16, 128.46, 128.72, 131.96, 136.90, 164.78, 168.49; HRMS (FAB) *m*/*z*=282.1126 $(M+H)^+$, calcd for $C_{17}H_{16}N_1O_3$=282.1130.

4.1.4. (2*R*,3*S*)-3-Benzoylamino-2-methanesulfonyloxy-3-phenylpropanoic acid methyl ester (5). MsCl (342 mg, 3.00 mmol) in THF (2 mL) was added dropwise to a stirred solution of **3** (599 mg, 2.00 mmol) and Et_3N (558 μL, 4.00 mmol) in THF (25 mL) at 0°C under N_2. After being stirred for 30 min at 0°C, the reaction mixture was stirred for an additional 1 h at room temperature. After removal of the solvent under reduced pressure, the residue was suspended in EtOAc (20 mL) and then passed through a short silica gel plug (~10 cm^3) and further eluted with EtOAc (100 mL). The combined filtrate was concentrated under reduced pressure, and the crude product was crystallized from EtOAc–hexane to afford **5** (700 mg, 1.85 mmol, 93%) as a white solid: mp 127.5–128.5°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.81 (s, 3H), 3.83 (s, 3H), 5.35 (d, *J*=2.7 Hz, 1H), 5.99 (dd, *J*=2.7, 9.2 Hz, 1H), 6.90 (br d, *J*=9.2 Hz, 1H), 7.25–7.60 (m, 8H), 7.75–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.67, 53.30, 54.02, 80.22, 126.57, 127.13, 128.58, 128.75, 129.03, 132.07, 133.57, 136.62, 166.92, 167.38; HRMS (FAB) *m*/*z*=378.1022 $(M+H)^+$, calcd for $C_{18}H_{20}N_1O_6S_1$=378.1011.

4.1.5. (4*S*,5*R*)-2,4-Diphenyl-2-oxazoline-5-carboxylic acid methyl ester (6). DBU (357 mg, 2.34 mmol) was added to a stirred solution of compound **5** (590 mg, 1.56 mmol) in dry $CHCl_3$ (30 mL) at room temperature, and the resulting solution was heated under reflux for 2 h. After being cooled to room temperature, the reaction mixture was then passed through a short silica gel plug (~10 cm^3) and further eluted with EtOAc (100 mL). The combined filtrate was then concentrated under reduced pressure, and purification of the residue by flash chromatography (hexane–EtOAc, 6:1) afforded **6** (400 mg, 1.42 mmol, 91%) as a colorless oil (*trans*-oxazoline **6**/*cis*-oxazoline **4**=25:1 by ^{1}H NMR analysis): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.87 (s, 3H), 4.92 (d, *J*=6.4 Hz, 1H), 5.45 (d, *J*=6.4 Hz, 1H), 7.20–7.60 (m, 8H), 8.05–8.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.74, 74.62, 83.13, 126.46, 126.76, 128.04, 128.45, 128.71, 128.85, 131.93, 141.09, 163.99, 170.63; HRMS (FAB) *m*/*z*=282.1125 $(M+H)^+$, calcd for $C_{17}H_{16}N_1O_3$=282.1130.

4.1.6. (4*S*,5*R*)-2,4-Diphenyl-2-oxazoline-5-carboxylic acid *p*-methoxybenzyl ester (7). 1 M LiOH solution (990 μL, 0.990 mmol) was added dropwise to a stirred solution of **6** (252 mg, 0.896 mmol) in a MeOH–water mixture (8 mL, 3:1) at 0°C. After being stirred for 30 min at 0°C, the reaction mixture was stirred for an additional 2 h at 45°C. The resulting solution was then poured to a mixture of EtOAc (30 mL)—5% aqueous citric acid (30 mL), and the organic phase was separated. The aqueous phase was extracted with EtOAc (5×30 mL), and the combined organic extract was dried over $MgSO_4$ and evaporated. To this residue, DMAP (11 mg, 0.09 mmol) and *p*-methoxybenzylalcohol (149 mg, 1.08 mmol) was added, followed by a THF–CH_2Cl_2 mixture (30 mL, 1:1), and the resulting solution was then cooled to 0°C. To this solution, DCC (203 mg, 0.986 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The reaction mixture was stirred for 3 h at 0°C and for an additional 3 h at room temperature. The reaction mixture was then filtered to remove the solid precipitated during the reaction period. The filtrate was concentrated under reduced pressure, and purification of the residue by flash chromatography (hexane–EtOAc, 6:1) afforded **7** (264 mg, 0.681 mmol, 76%) as a sticky oil, which slowly solidified on standing: mp 73.5–75.5°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.81 (s, 3H), 4.90 (d, *J*=6.6 Hz, 1H), 5.18 (d, *J*=11.9 Hz, 1H), 5.29 (d, *J*=11.9 Hz, 1H), 5.37 (d, *J*=6.6 Hz, 1H),

6.80–7.00 (m, 2H), 7.20–7.65 (m, 10H), 8.00–8.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.30, 67.25, 74.62, 83.20, 114.07, 126.52, 126.82, 127.28, 128.02, 128.46, 128.76, 128.84, 130.31, 131.94, 141.10, 159.92, 164.11, 169.99; HRMS (FAB) m/z=388.1544 $(M+H)^+$, calcd for $C_{24}H_{22}N_1O_4$=388.1549.

4.1.7. (2*S*,3*S*)-2-Acetylthio-3-benzoylamino-3-phenylpropanoic acid *p*-methoxybenzyl ester (8): procedure B. Thiolacetic acid (1 mL) was added to compound **7** (244 mg, 0.630 mmol) in a 6 mL vial at room temperature. The vial was then closed tightly with a teflon disk lid, and the reaction mixture was heated to 70°C for 14 h with occasional swirling. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (hexane–EtOAc, 3:1) to afford **8** as a white solid. This was further purified by re-crystallization (EtOAc–hexane) yielding **8** (260 mg, 0.561 mmol, 89%) as white needles: mp 117–118°C; $[\alpha]_D^{19}$=−87.2° (c=1, $CHCl_3$); IR (KBr) 3374, 1736, 1700, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 3.80 (s, 3H), 4.82 (d, J=4.2 Hz, 1H), 4.96 (d, J=11.9 Hz, 1H), 5.01 (d, J=11.9 Hz, 1H), 5.64 (dd, J=4.2, 9.2 Hz, 1H), 6.75–6.90 (m, 2H), 7.00–7.15 (m, 2H), 7.20–7.60 (m, 8H), 7.75–7.90 (m, 2H), 8.00 (br d, J=9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.21, 49.58, 54.79, 55.24, 67.51, 113.92, 126.28, 126.67, 127.07, 127.95, 128.61, 128.70, 129.99, 131.72, 133.88, 138.38, 159.77, 166.65, 170.74, 192.44; HRMS (FAB) m/z=464.1515 $(M+H)^+$, calcd for $C_{26}H_{26}N_1O_5S_1$=464.1532; Anal. calcd for $C_{26}H_{26}N_1O_5S_1$: C, 67.22; H, 5.64; N, 3.02; S, 6.90. Found: C, 67.22; H, 5.80; N, 2.95; S, 6.70.

4.1.8. (2*S*,3*S*)-2-Acetylthio-3-benzoylamino-3-phenylpropanoic acid (9): procedure C. Compound **8** (150 mg, 0.324 mmol) in a 6 mL vial was treated with a mixture of TFA–anisole (3 mL, 5:1). The vial was then closed tightly with a teflon disk lid, and the reaction mixture was stirred for 20 min at room temperature. After removal of the solvent under reduced pressure, the residue was re-dissolved in fresh CH_2Cl_2 (3×30 mL) and re-evaporated, and finally dried in high vacuum to give viscous oil. This residue was treated with a mixture of CH_2Cl_2–hexane (5 mL, 1:4) to give white precipitates, and this was washed several times with hot hexane to afford **9** (109 mg, 0.317 mmol, 98%) as white solid: mp 161–163°C; $[\alpha]_D^{19}$=−34.4° (c=1, MeOH); IR (KBr) 3374, 3058–2464(b), 1710, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 4.81 (d, J=4.2 Hz, 1H), 5.64 (dd, J=4.2, 9.3 Hz, 1H), 6.91 (br s, 1H), 7.20–7.65 (m, 8H), 7.75–7.90 (m, 2H), 8.08 (br d, J=9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.19, 48.91, 54.92, 126.45, 127.21, 128.11, 128.76, 128.79, 132.09, 133.44, 138.12, 167.84, 173.44, 192.85; HRMS (FAB) m/z=344.0963 $(M+H)^+$, calcd for $C_{18}H_{18}N_1O_4S_1$=344.0957; Anal. calcd for $C_{18}H_{18}N_1O_4S_1$: C, 62.77; H, 5.27; N, 4.07; S, 9.31. Found: C, 62.67; H, 5.11; N, 3.81; S, 9.17.

4.1.9. (2*R*,3*S*)-3-Amino-2-hydroxy-3-phenylpropanoic acid *p*-toluenesulfonate (10). Compound **2** (1000 mg, 3.77 mmol) was treated with 10% aqueous HCl (20 mL), and heated under reflux for 4 h. After being cooled to room temperature, the solvent was then evaporated to dryness to afford white crystalline residue. To this residue, TsOH·H_2O (753 mg, 3.96 mmol) and benzyl alcohol (8 mL) was added, and the resulting suspension was then evaporated using rotary evaporator under water aspirator vacuum for 1 h at 75°C to give clear solution. To this solution, benzene (20 mL) was added, and the resulting solution was refluxed using dean-stark apparatus for 10 h. After removal of the solvent under reduced pressure, dry ether (30 mL) was added to the resulting residue. The crude precipitate was collected and re-crystallized from MeOH–ether to afford **10** (1600 mg, 3.61 mmol, 96%) as white crystalline solid: mp 188–190°C; $[\alpha]_D^{19}$=−13.7° (c=1, MeOH); IR (KBr) 3221–2631(b), 1758, 1511 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) δ 2.36 (s, 3H), 4.47 (d, J=7.7 Hz, 1H), 4.51 (d, J=7.7 Hz, 1H), 4.99 (d, J=12.1 Hz, 1H), 5.05 (d, J=12.1 Hz, 1H), 7.05–7.50 (m, 12H), 7.65–7.75 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 21.31, 58.81, 68.19, 73.71, 126.96, 129.08, 129.38, 129.49, 129.81, 130.29, 130.81, 134.71, 136.49, 141.69, 143.47, 171.87; HRMS (FAB) m/z=272.1277 $(M+H)^+$, calcd for $C_{16}H_{18}N_1O_3$=272.1287; Anal. calcd for $C_{16}H_{18}N_1O_3$: C, 62.14; H, 5.90; N, 3.15; S, 7.21. Found: C, 62.00; H, 6.03; N, 3.14; S, 7.42.

4.1.10. (2*R*,3*S*)-3-Benzoylamino-2-hydroxy-3-phenylpropanoic acid benzyl ester (11). Benzoyl chloride (430 mg, 3.06 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of compound **10** (1331 mg, 3.00 mmol) and Et_3N (1.254 mL, 9.00 mmol) in CH_2Cl_2 (60 mL) at 0°C. The reaction mixture was then stirred for 1 h at 0°C, and for a further hour at room temperature. After removal of the solvent under reduced pressure, the residue was treated with EtOAc (5×50 mL) and passed through a short silica gel plug (~15 cm^3). The combined filtrate was concentrated under reduced pressure, and the residue was re-crystallized from EtOAc–hexane to afford **11** (1050 mg, 2.80 mmol, 93%) as white needles: mp 145–146.5°C; $[\alpha]_D^{20}$=+2.54° (c=1, $CHCl_3$); IR (KBr) 3458, 3363, 3031, 2952, 1732, 1642 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.31 (d, J=4.0 Hz, 1H), 4.66 (dd, J=2.4, 4.0 Hz, 1H), 5.20 (d, J=11.9 Hz, 1H), 5.27 (d, J=11.9 Hz, 1H), 5.77 (dd, J=2.2, 9.0 Hz, 1H), 6.99 (br d, J=9.0 Hz, 1H), 7.20–7.60 (m, 13H), 7.65–7.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 54.89, 68.32, 73.27, 126.88, 127.02, 127.86, 128.52, 128.64, 128.66, 131.65, 133.95, 134.61, 138.38, 166.77, 172.69; HRMS (FAB) m/z=376.1543 $(M+H)^+$, calcd for $C_{23}H_{22}N_1O_4$=376.1549; Anal. calcd for $C_{23}H_{22}N_1O_4$: C, 73.39; H, 5.89; N, 3.72. Found: C, 73.02; H, 5.93; N, 3.66.

4.1.11. (4*S*,5*S*)-2,4-Diphenyl-2-oxazoline-5-carboxylic acid benzyl ester (12). Application of procedure A to 1000 mg of **11** (2.66 mmol), 1127 mg of Tf_2O (3.99 mmol) and 976 mg of DMAP (7.99 mmol) gave 860 mg of **12** (2.41 mmol, 90%) as white needles after flash chromatography (hexane–EtOAc, 8:1) followed by re-crystallization (hexane): mp 104–105°C; $[\alpha]_D^{21}$=−68.2° (c=1, $CHCl_3$); IR (KBr) 3063, 3031, 2937, 1747, 1674 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.29 (d, J=12.3 Hz, 1H), 4.73 (d, J=12.3 Hz, 1H), 5.66 (d, J=10.8 Hz, 1H), 5.84 (d, J=10.8 Hz, 1H), 6.95–7.40 (m, 10H), 7.50–7.70 (m, 3H), 7.95–8.10 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 66.57, 72.96, 80.96, 127.00, 128.18, 128.38, 128.46, 128.58, 128.74, 129.26, 132.56, 135.20, 137.77, 163.82, 168.34; HRMS (FAB) m/z=358.1449 $(M+H)^+$, calcd for $C_{23}H_{20}N_1O_3$=358.1443;

Anal. calcd for $C_{23}H_{20}N_1O_3$: C, 77.08; H, 5.62; N, 3.91. Found: C, 77.01; H, 5.75; N, 3.85.

4.1.12. (4*S*,5*S*)-2,4-Diphenyl-2-oxazoline-5-carboxylic acid *p*-methoxybenzyl ester (13). A 10% Pd/C catalyst (164 mg) was added to a stirred solution of **12** (822 mg, 2.30 mmol) in EtOAc (35 mL). The mixture was then hydrogenated under atmospheric H_2 (balloon) at room temperature for 30 h, and filtered through a short Celite® pad (~5 cm^3), and further eluted with EtOAc (150 mL). The combined filtrate was concentrated under reduced pressure, and dried in high vacuum. The resulting slightly yellow solid was dissolved in a THF–CH_2Cl_2 mixture (30 mL, 1:2), and *p*-methoxybenzyl alcohol (381 mg, 2.76 mmol) and DMAP (28 mg, 0.23 mmol) was added. To this solution, DCC (498 mg, 2.41 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0°C. The reaction mixture was stirred for 12 h at room temperature, and then filtered to remove the solid precipitated during the reaction period. The filtrate was concentrated under reduced pressure, and purification of the residue by flash chromatography (hexane–EtOAc, 6:1) afforded **13** as a white solid. This was further purified by re-crystallization (hexane) yielding **13** (612 mg, 1.58 mmol, 69%) as white needles: mp 101.5–102.5°C; $[\alpha]_D^{21}=-64.9°$ (c=1, $CHCl_3$); IR (KBr) 3058, 3031, 2926, 1742, 1668 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.74 (s, 3H), 4.19 (d, J=11.9 Hz, 1H), 4.66 (d, J=11.9 Hz, 1H), 5.62 (d, J=10.8 Hz, 1H), 5.81 (d, J=10.8 Hz, 1H), 6.80–7.05 (m, 4H), 7.10–7.40 (m, 5H), 7.50–7.70 (m, 3H), 7.95–8.05 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 55.03, 65.94, 72.43, 80.39, 113.65, 126.50, 126.57, 127.66, 127.83, 127.92, 128.06, 128.73, 130.03, 132.02, 137.25, 159.20, 163.30, 167.83; HRMS (FAB) m/z=388.1563 $(M+H)^+$, calcd for $C_{24}H_{22}N_1O_4$=388.1549; Anal. calcd for $C_{24}H_{22}N_1O_4$: C, 74.21; H, 5.71; N, 3.60. Found: C, 74.23; H, 5.75; N, 3.59.

4.1.13. (2*R*,3*S*)-2-Acetylthio-3-benzoylamino-3-phenylpropanoic acid *p*-methoxybenzyl ester (14). Application of procedure B to 378 mg of **13** (1.00 mmol) and 1.2 mL of thiolacetic acid at 90°C for 36 h gave 360 mg of **14** (0.777 mmol, 78%) after flash chromatography (hexane–EtOAc, 3:1); IR (neat) 3293, 3060, 2924, 1737, 1703, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H), 3.79 (s, 3H), 4.75 (d, J=9.2 Hz, 1H), 4.94 (s, 2H), 5.67 (dd, J=9.0, 9.2 Hz, 1H), 6.75–6.90 (m, 2H), 7.00–7.15 (m, 3H), 7.20–7.55 (m, 8H), 7.60–7.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.29, 51.36, 55.21, 55.46, 67.58, 113.86, 126.77, 126.91, 127.11, 128.24, 128.51, 128.69, 130.22, 131.62, 133.65, 138.46, 159.73, 166.23, 168.33, 195.41; HRMS (FAB) m/z=464.1532 $(M+H)^+$, calcd for $C_{26}H_{26}N_1O_5S_1$=464.1532.

4.1.14. (2*R*,3*S*)-2-Acetylthio-3-benzoylamino-3-phenylpropanoic acid (15). Application of procedure C to 90 mg of **14** (0.194 mmol) and TFA–anisole (2 mL, 5:1) gave 65 mg of **15** (0.189 mmol, 98%). Treatment with a mixture of CH_2Cl_2–hexane (5 mL, 1:4) appeared in procedure C was unnecessary since a white solid was obtained upon drying in high vacuum: mp 166–168°C; $[\alpha]_D^{19}$=+86.7° (c=1, MeOH); IR (KBr) 3368–2500(b), 1710, 1653 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.34 (s, 3H), 4.61 (d, J=11.2 Hz, 1H), 5.45 (dd, J=9.3, 11.2 Hz, 1H), 7.20–7.90 (m, 10H), 8.95 (br d, J=9.3 Hz, 1H), 12.84 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 30.21, 50.95, 52.90, 127.39, 127.75, 127.82, 128.25, 128.31, 131.40, 134.13, 139.53, 165.98, 170.45, 193.49; HRMS (FAB) m/z=344.0955 $(M+H)^+$, calcd for $C_{18}H_{18}N_1O_4S_1$=344.0957.

4.1.15. (2*R*,3*S*)-2-Acetylthio-3-benzoylamino-3-phenylpropanoic acid benzyl ester (16). Application of procedure B to 140 mg of **12** (0.392 mmol) and 0.8 mL of thiolacetic acid at 80°C for 12 h and 90°C for 1 d gave 131 mg of **16** (0.302 mmol, 77%) as white needles after flash chromatography (hexane–EtOAc, 7:2) followed by re-crystallization (EtOAc–hexane): mp 128–129°C; $[\alpha]_D^{21}=+90.2°$ (c=0.70, $CHCl_3$); IR (KBr), 3374, 3047, 2937, 1731, 1708, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 4.78 (d, J=9.3 Hz, 1H), 5.02 (s, 2H), 5.69 (dd, J=9.0, 9.2 Hz, 1H), 7.01 (br d, J=8.4 Hz, 1H), 7.10–7.55 (m, 13H), 7.65–7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.37, 51.32, 55.52, 67.74, 126.97, 127.17, 128.33, 128.37, 128.46, 128.56, 128.60, 128.80, 131.71, 133.68, 134.68, 138.50, 166.31, 168.38, 195.52; HRMS (FAB) m/z=434.1423 $(M+H)^+$, calcd for $C_{25}H_{24}N_1O_4S_1$=434.1426; Anal. calcd for $C_{25}H_{24}N_1O_4S_1$: C, 69.10; H, 5.57; N, 3.22; S, 7.38. Found: C, 69.14; H, 5.51; N, 3.19; S, 7.62.

4.1.16. (4*S*,5*S*)-2,4-Diphenyl-2-oxazoline-5-carboxylic acid methylamide (17). Compound **4** (150 mg, 0.533 mmol) in a 6 mL vial was treated with 33% $MeNH_2$/EtOH solution (1.5 mL). The vial was then closed tightly with a teflon disk lid, and the reaction mixture was stirred for 1 d at room temperature. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (hexane–EtOAc, 4:5) to afford **18** (8 mg, 0.029 mmol, 5%) and **17** (140 mg, 0.499 mmol, 94%) as a white solid: mp 137–139°C; $[\alpha]_D^{21}=-227°$ (c=1, $CHCl_3$); IR (KBr) 3410, 3279, 3105, 3031, 1668, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45 (d, J=5.0 Hz, 3H), 5.30 (d, J=10.4 Hz, 1H), 5.73 (d, J=10.4 Hz, 1H), 6.07 (br d, J=5.0 Hz, 1H), 7.10–7.65 (m, 8H), 8.05–8.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.32, 72.84, 82.87, 126.62, 127.63, 128.00, 128.10, 128.59, 128.65, 132.22, 136.62, 163.59, 167.69; HRMS (FAB) m/z=281.1294 $(M+H)^+$, calcd for $C_{17}H_{17}N_2O_2$=281.1290; Anal. calcd for $C_{17}H_{17}N_2O_2$: C, 72.58; H, 6.09; N, 9.96. Found: C, 72.13; H, 6.08; N, 9.77.

4.1.17. (4*S*,5*R*)-2,4-Diphenyl-2-oxazoline-5-carboxylic acid methylamide (18). Compound **6** (205 mg, 0.729 mmol) in a 6 mL vial was treated with 33% $MeNH_2$/EtOH solution (2 mL). The vial was then closed tightly with a teflon disk lid, and the reaction mixture was stirred for 4 h at room temperature. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (hexane–EtOAc, 3:2) to afford **18** (197 mg, 0.703 mmol, 96%) as a sticky oil; IR (neat) 3303, 3059, 2923, 1657, 1544 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.91 (d, J=5.0 Hz, 3H), 4.85 (d, J=6.6 Hz, 1H), 5.52 (d, J=6.6 Hz, 1H), 6.41 (br d, J=5.0 Hz, 1H), 7.20–7.75 (m, 8H), 8.05–8.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.92, 74.62, 84.42, 126.56, 126.79, 127.79, 128.48, 128.67, 128.79, 132.13, 141.66, 162.49, 170.69; HRMS

(FAB) m/z=281.1296 $(M+H)^+$, calcd for $C_{17}H_{17}N_2O_2$= 281.1290.

4.1.18. (2*S*,3*S*)-2-Acetylthio-3-benzoylamino-3-phenylpropanoic acid methylamide (19). Application of procedure B to 176 mg of **18** (0.628 mmol) and 1 mL of thiolacetic acid at 70°C for 12 h gave 178 mg of **19** (0.499 mmol, 79%) as white needles after flash chromatography (hexane–EtOAc, 5:3) followed by re-crystallization (EtOAc–hexane): mp 187–190°C; $[\alpha]_D^{20}=-137°$ (c=1, $CHCl_3$); IR (KBr) 3337, 3279, 3110, 2937, 1695, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3H), 2.65 (d, J=4.8 Hz, 3H), 4.39 (d, J=3.3 Hz, 1H), 5.60 (dd, J=3.3, 8.8 Hz, 1H), 6.04 (br d, J=4.8 Hz, 1H), 7.10–7.70 (m, 8H), 7.85–8.10 (m, 2H), 9.21 (br d, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.36, 30.42, 49.50, 55.67, 126.41, 127.25, 127.93, 128.61, 128.72, 131.71, 133.86, 139.17, 166.52, 171.20, 195.82; HRMS (FAB) m/z= 357.1282 $(M+H)^+$, calcd for $C_{19}H_{21}N_2O_3S_1$=357.1273; Anal. calcd for $C_{19}H_{21}N_2O_3S_1$: C, 63.84; H, 5.92; N, 7.78; S, 8.97. Found: C, 63.84; H, 6.12; N, 7.80; S, 9.14.

4.1.19. (2*S*,3*S*)-3-Benzoylamino-2-mercapto-3-phenylpropanoic acid methylamide (20). 1 M LiOH solution (315 μL, 0.315 mmol) was added dropwise to a stirred solution of **19** (107 mg, 0.300 mmol) in a MeOH–water mixture (degassed, 4 mL, 3:1) at room temperature under N_2. After being stirred for 30 min at room temperature, the reaction mixture was concentrated (~2 mL) under reduced pressure, and then poured to a mixture of H_2O (20 mL)–$CHCl_3$ (20 mL). The pH of the aqueous phase was adjusted to 2–3 using 1N HCl, and the organic phase was separated. The aqueous phase was extracted with $CHCl_3$ (4×20 mL), and the combined organic extract was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography ($CHCl_3$–MeOH, 20:1) to afford **20** (92 mg, 0.293 mmol, 98%) as a white solid: mp 219–222°C; $[\alpha]_D^{19}=-48.0°$ (c=0.93, $CHCl_3$); IR (KBr) 3310, 3058, 2921, 2555(HS), 1658, 1642 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.49 (d, J=10.3 Hz, 1H), 2.68 (d, J=5.0 Hz, 3H), 3.60 (dd, J=3.7, 10.2 Hz, 1H), 5.53 (dd, J=3.7, 8.4 Hz, 1H), 5.89 (br d, J=5.0 Hz, 1H), 7.15–7.65 (m, 8H), 7.85–8.00 (m, 2H), 8.81 (br d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.38, 45.51, 58.26, 126.28, 127.12, 127.95, 128.67, 128.72, 131.79, 133.81, 139.62, 167.12, 172.48; HRMS (FAB) m/z=315.1168 $(M+H)^+$, calcd for $C_{17}H_{19}N_2O_2S_1$=315.1168.

4.1.20. *N*-[(4*S*,5*R*)-2,4-Diphenyl-2-oxazoline-5-carbonyl]-alanine *tert*-butyl ester (21). 1 M LiOH solution (1.564 mL, 1.564 mmol) was added dropwise to a stirred solution of **6** (400 mg, 1.422 mmol) in a MeOH–water mixture (12 mL, 3:1) at 0°C. After being stirred for 30 min at 0°C, the reaction mixture was stirred for an additional 2 h at 45°C. The reaction mixture was then poured to a mixture of EtOAc (50 mL)—5% aqueous citric acid (50 mL), and the organic phase was separated. The aqueous phase was extracted with EtOAc (5×50 mL), and the combined organic extract was dried over $MgSO_4$ and evaporated. To this residue, L-alanine *t*-butyl ester·HCl salt (310 mg, 1.706 mmol), HOBt·H_2O (261 mg, 1.706 mmol), and DIEA (310 μL, 1.780 mmol) was added, followed by THF (30 mL), and the resulting solution was then cooled to 0°C. To this stirred solution, a mixture of EDCI·HCl salt (327 mg, 1.706 mmol) and DIEA (310 μL, 1.780 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred for 30 min at 0°C and for an additional 18 h at room temperature. After removal of the solvent under reduced pressure, the residue was treated with CH_2Cl_2 (10 mL) and then passed through a short silica gel plug (~10 cm^3) and further eluted with EtOAc (50 mL). The combined filtrate was concentrated under reduced pressure, and purification of the residue by flash chromatography (hexane–EtOAc, 9:2) afforded **21** as a white solid. This was further purified by re-crystallization (hexane) to afford **21** (480 mg, 1.217 mmol, 86%) as a white crystalline solid: mp 108–110°C; $[\alpha]_D^{19}=+96.4°$ (c=1, $CHCl_3$); IR (KBr) 3421, 3063, 2989, 1737, 1689, 1663 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 1.46 (d, J=7.0 Hz, 3H), 4.51 (dq, J=7.0, 7.1 Hz, 1H), 4.84 (d, J=6.8 Hz, 1H), 5.54 (d, J=6.8 Hz, 1H), 7.06 (br d, J=7.1 Hz, 1H), 7.20–7.65 (m, 8H), 8.05–8.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.20, 28.56, 49.27, 75.03, 83.03, 85.02, 127.25, 127.48, 128.42, 129.18, 129.29, 129.43, 132.67, 142.35, 163.31, 170.12, 172.00; HRMS (FAB) m/z=395.1974 $(M+H)^+$, calcd for $C_{23}H_{27}N_2O_4$=395.1970; Anal. calcd for $C_{23}H_{27}N_2O_4$: C, 69.85; H, 6.88; N, 7.08. Found: C, 70.06; H, 6.91; N, 6.90.

4.1.21. *N*-[(2*S*,3*S*)-2-Acetylthio-3-benzoylamino-3-phenylpropionyl]-alanine *tert*-butyl ester (22). Application of procedure B to 395 mg of **21** (1.00 mmol) and 1.5 mL of thiolacetic acid at 70°C for 6 h gave 430 mg of **22** (0.914 mmol, 91%) a off-white solid after flash chromatography (benzene–EtOAc, 7:1): mp 168–170°C; $[\alpha]_D^{19}=-115°$ (c=1, $CHCl_3$); IR (KBr) 3321, 3247, 3058, 2979, 1753, 1732, 1700, 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (d, J=7.0 Hz, 3H), 1.39 (s, 9H), 2.41 (s, 3H), 4.22 (dq, J=7.0, 7.0 Hz, 1H), 4.49 (d, J=3.5 Hz, 1H), 5.65 (dd, J=3.5, 8.8 Hz, 1H), 6.45 (br d, J=7.0 Hz, 1H), 7.15–7.65 (m, 8H), 7.85–8.05 (m, 2H), 8.94 (br d, J= 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.76, 27.80, 30.35, 48.92, 49.82, 55.45, 82.20, 126.42, 127.22, 127.85, 128.55, 128.67, 131.63, 133.89, 138.94, 166.54, 169.70, 170.90, 195.21; HRMS (FAB) m/z=471.1954 $(M+H)^+$, calcd for $C_{25}H_{31}N_2O_5S_1$=471.1954.

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