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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 1215–1220

Asymmetric induction in the conjugate addition of thioacetic acid to methacrylamides with chiral auxiliaries

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Received 29 December 2004; accepted 24 January 2005

Abstract—The conjugate addition of thioacetic acid to methacrylamides with chiral C_2-symmetric *trans*-2,5-disubstituted pyrrolidines afforded the addition products in excellent stereoselectivities (>99% de) and good yields (80–90%). The high selectivity was attributed mainly to the steric effect of the chiral auxiliaries. The cyclic nature of the chiral auxiliaries seemed also important for both the stereoselectivity and the reaction rate. Acidic hydrolysis of the adduct containing (2*R*,5*R*)-bis(methoxymethyl)pyrrolidine gave (*S*)-3-mercapto-2-methylpropanoic acid, a key intermediate for captopril, in 98% ee and 96% yield. The chiral auxiliary was recovered in the demethylated form of *N*-Boc-(2*R*,3*R*)-bis(hydroxymethyl)pyrrolidine in 90% yield.
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1. Introduction

Chiral β-mercaptocarboxylic acid derivatives are the key intermediates in the synthesis of some pharmaceutically important compounds, such as antihypertensives captopril[1] and diltiazem[2] (Fig. 1). These can be prepared in principle by the asymmetric conjugate addition of a thiol group to substituted acrylic acids or their derivatives.[3] The conjugate addition reactions have been widely used as an important method for the synthesis of complex organic molecules.[4] The recent progress in asymmetric catalysis[5] as well as stereocontrol by chiral auxiliaries[3,6] has shown that they could be effective methods for the asymmetric control of conjugate addition reactions. However, there have not been many reports on the stereoselective conjugate addition of the thiol group[3,5b,g,7,8] and the search for a highly stereoselective conjugate addition reaction of the sulfur functionality still remains a worthwhile challenge.

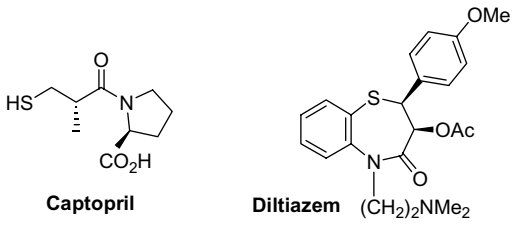

Figure 1.

As part of a program for developing an efficient way to prepare captopril and its derivatives, we have investigated the synthesis of chiral 3-mercapto-2-methylpropanoic acid via asymmetric conjugate addition of the thiol to methacrylamides with a chiral auxiliary. Excellent stereoselectivities over 99% de were observed in the conjugate addition to acrylic acid derivatives with C_2-symmetric pyrrolidines under mild reaction conditions and we herein report the results as follows.

2. Results and discussion

We began our investigation by examining the addition reactions of thioacetic acid to methacrylamides **1** that contain L-proline or its derivatives as a chiral auxiliary (Table 1). The required amides **1a–e** were easily prepared from the coupling reactions between methacryloyl chloride and L-proline or its derivatives. However, no useful selectivities were observed although some improvement in the selectivity was shown with the proline ester or amine derivatives (entries 2–5 vs 1). The sense of the asymmetric induction is also opposite to the desired one. The comparable asymmetric induction results were reported for similar compounds in the literature.[8] We thought that the low selectivity was due to the flexible conformation of the amide linkage of the

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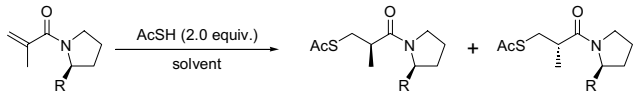
doi:10.1016/j.tetasy.2005.01.037

Table 1. Conjugate addition of thioacetic acid to methacrylamides of L-proline or its derivatives



1a-e **2a-e** **3a-e**

Entry	R	Solvent	Temp (°C)/ time (h)	Yield (%)	Ratio (**2**:**3**)[a]
1	**1a**: CO_2H	CH_2Cl_2	rt/20	73	50:50
2	**1b**: CO_2Me	$PhCH_3$	rt/40	86	69:31
3	**1c**: CO_2Ph	$PhCH_3$	rt/40	90	55:45
4	**1d**: CH_2NEt_2	$PhCH_3$	rt/14	50	67:33
5	**1e**: CH_2NHBn	$PhCH_3$	rt/12	62	75:25

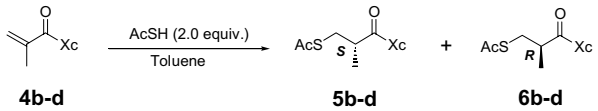
[a] Determined by gas chromatography.

L-proline derivatives in the addition reactions. Therefore, introduction of the chiral auxiliaries with C_2-symmetry around the nitrogen atom would produce the same chiral environment toward either face of the double bond of the methacrylamide, resulting in the higher selectivity.

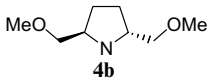
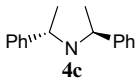
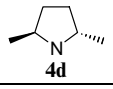
It has been well established that auxiliaries with a C_2-symmetry show good performance as a stereochemical director to provide a high level of asymmetric control in several reactions such as reductions,[9a–c] Diels–Alder reactions,[9d,e] halolactonizations,[9f,g] and alkylation reactions of enolates.[9h,i] While the conjugate addition reactions of alkyl radicals were known with moderate to good selectivity,[10] few studies using a C_2-symmetric chiral auxiliaries have been reported in the conjugate addition of a thiol group.

First, commercially available (2*S*,5*S*)-bis(methoxymethyl)pyrrolidine was used as a chiral auxiliary and its condensation reaction with methacryloyl chloride gave **4a** in 82–92% yield. The conjugate addition reaction of **4a** with thioacetic acid afforded the addition product **6a** as a major product in excellent stereoselectivity (>99% de) and high yield (90%) (Scheme 1). The addition product **5b**, which has the same configuration at the α-carbon to the carbonyl group as that of captopril, was also obtained as a major product in a similar selectivity and yield when the enantiomeric (2*R*,5*R*)-bis(methoxymethyl)pyrrolidine was employed (Table 2, entry 1). The ratio of the diastereomeric product mixture was determined by a GC analysis. Authentic amide **5b** and the 1:1 diastereomeric mixture of **5b** and **6b** were also prepared from the coupling reactions of (*S*)-3-acetylthio-2-methylpropanoic acid **9** and racemic 3-acetylthio-2-methylpropanoic acid with **4b**, respectively (Scheme 3). Compound **9** was obtained separately from

Table 2. Conjugate addition of thioacetic acid to methacrylamides with C_2-symmetric chiral auxiliaries

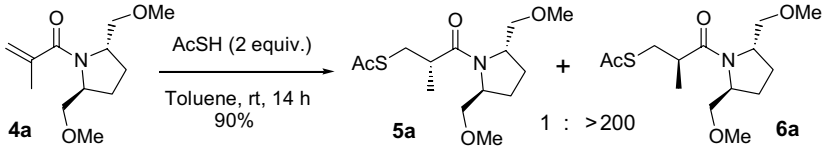


4b-d **5b-d** **6b-d**

Entry	Xc	Temp (°C)/ time	Yield (%)	De (%)	*R*/*S* (major)
1	 **4b**	rt/14 h	88	>99	*S*
2	 **4c**	rt/7 d	40	60	*R*
3	 **4d**	rt/20 h	82	>99	*S*

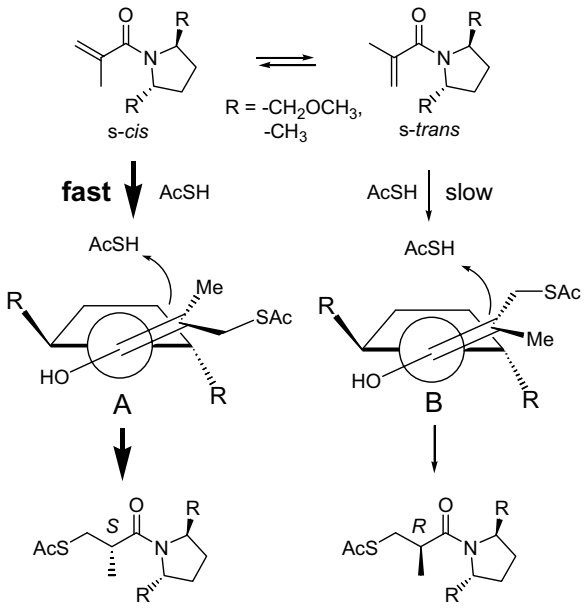
the acidic hydrolysis of commercially available captopril.

Other C_2-symmetric auxiliaries were examined further to account for the observed selectivity in the addition reactions (Table 2). Use of the commercially available acyclic (*S*,*S*)-*N*,*N*-bis(phenylethyl)amine resulted in the lower selectivity while the addition reaction was quite slow (entry 2). However, the conjugate addition of thioacetic acid to methacrylamide **4d** containing (2*S*,5*S*)-dimethylpyrrolidine afforded **5d** as a major product in excellent selectivity (>99% de) and good yield (82%) (entry 3). The required chiral amine, (2*S*,5*S*)-dimethylpyrrolidine, was synthesized according to the literature.[11] It was necessary to test whether the selectivity was induced by the chelating effect from the methoxymethyl group.[8] There is no adjacent heteroatom in the chiral auxiliary used for **4d** that can play a role of the chelation. Hence, the origin of the asymmetric induction herein is not necessarily the chelating effect but mainly the steric effect from the C_2-symmetric structure of the chiral auxiliary (Scheme 2). The enol form **A** after the addition of thioacetic acid to the *s-cis* conformer would be formed faster than **B** that is obtained by addition to the *s-trans* conformer because the larger CH_2SAc group prefers to be away from the sterically demanding pyrrolidine ring. The similar distorted conformation was proposed to be favored by Giese et al. for the radical conjugate addition reactions.[10a] The planar enamine-like structure would also experience the severe steric hindrance from the substituents at C-2 and C-5 positions of the pyrrolidine.[12] Then, the protonation would take place from the top face to give the (*S*)-configuration with the pyrrolidine chiral auxiliary having the (2*R*,5*R*)-configuration. It



4a **5a** **6a**

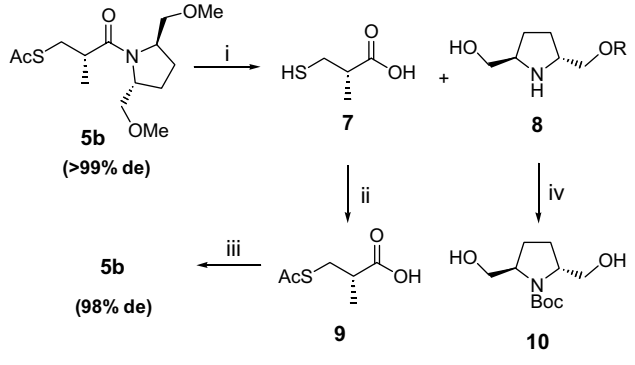
Scheme 1. Asymmetric conjugate addition of AcSH to **4a**.



Scheme 2. Probable conformations for the protonation.

seems also important for the chiral auxiliary to have a rigid structure in order to generate a similar chiral environment around the nitrogen atom. The addition reaction proved much faster with the cyclic auxiliaries, as well.

Finally, several reaction conditions for effective hydrolysis of the adduct **5b** were screened to yield 3-mercapto-2-methylpropanoic acid without much racemization and to recover the chiral auxiliary efficiently (Scheme 3). Heating **5b** in aqueous 3 M HCl under reflux produced mercapto acid **7** and the monodemethylated auxiliary **8b** (R = Me) in 96% and 90% yield, respectively. The enantiomeric purity of **7** was determined after converting it back to the starting amide **5b** whose diastereomeric purity could be analyzed with GC. About 3% of racemization was observed. Milder reaction conditions such as lower temperature at 70 °C or the use of aqueous 1 M HCl did not reduce the degree of the racemization much. The least racemization was realized with BBr_3. When **5b** was treated with BBr_3 at room temperature



Scheme 3. Reagents and conditions: (i) BBr_3 in CH_2Cl_2, 0.5 h and then aq 1.0 M HCl, 70 °C, 4 h; **7**, 96% and **8a** (R = H), 90%; (ii) Ac_2O, aq 1.0 M NaOH, 92%; (iii) $(COCl)_2$, then (2*R*,5*R*)-bis(methoxymethyl)pyrrolidine, TEA, CH_2Cl_2, 86%; (iv) Boc_2O, TEA, *t*-BuOH/H_2O, 90%.

followed by heating in aqueous 1 M HCl at 70 °C, **7** was obtained with an enantiomeric purity of 98%. This result was also confirmed by the reaction of **7** with TFAA followed by the GC analysis using a chiral column, β-dex-110, SUPELCO. However, adduct **5d** was quite resistant to several hydrolytic conditions and no hydrolysis product was obtained in the present study. The chiral auxiliary in **5b** was recovered as the didemethylated form **8a** (R = H) that could be recycled to the starting (2*R*,5*R*)-bis(methoxymethyl)pyrrolidine after a simple dimethylation reaction without any loss of enantiomeric purity. The enantiomeric purity of **8a** was also assessed by conversion to its *N*-Boc derivative, whose specific rotation was compared with that reported in the literature.[13]

3. Conclusions

The use of chiral *trans*-2,5-disubstituted pyrrolidine auxiliaries with C_2-symmetry resulted in excellent stereoselectivities (>99% de) and good yields (80–90%) in the conjugate addition of thioacetic acid to the chiral methacrylamides. The desired chiral mercapto acid **7** and its enantiomer were prepared in high enantiomeric purity (98% ee) after hydrolysis, where a small degree of racemization was observed. The chiral auxiliary was recovered in the demethylated form with the same enantiomeric purity as the starting chiral auxiliary. The excellent asymmetric induction in the conjugate addition was attributed mainly to the steric effect of the chiral auxiliaries that favors the addition to the *s-cis* conformer. The cyclic nature of the chiral auxiliaries seemed also important for both the stereoselectivity and the reaction rate. The present result is another example of the C_2-symmetric chiral auxiliary being very effective in the conjugate addition reactions and provides an alternative way to prepare the pharmaceutically important chiral β-mercaptocarboxylic acid derivatives.

4. Experimental

Materials were obtained from commercial suppliers and used without further purification. Anhydrous toluene was obtained by distillation over sodium/benzophenone ketyl. Anhydrous CH_2Cl_2 was distilled from calcium hydride. All glassware, syringes, needles, and magnetic bars used in the moisture-sensitive reactions were oven-dried at 120 °C for at least 4 h and stored in desiccators until use. Reactions were monitored by TLC. Commercially available TLC plates (Silica gel 60 F_{254}, Merck) were visualized under UV light (254 or 365 nm) followed by molybdophosphoric acid staining. Dry-column flash chromatography was done on silica gel 60G (particle size 5–40 μm, Merck). IR spectra were recorded with a JASCO model FT-IR 200. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 and 75 MHz (JEOL JNM-LA 300), respectively, unless stated otherwise. Multiplicity was denoted by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet), and br (broad). Coupling constants (*J*) are given in hertz (Hz). Low resolution mass spectra were obtained from a

Hewlett-Packard 6890 mass selective detector. Optical rotations were measured with a JASCO P-1030 digital polarimeter with 10 mm cells. High resolution mass spectra were obtained from a JEOL JMS-AX505WA gas chromatography–mass spectrometer.

4.1. General procedure for the preparation of methacrylamide

To methacryloyl chloride (1.04 g, 10 mmol) in CH_2Cl_2 was added secondary amine (12 mmol) and TEA (1.3 g, 13 mmol) at 0 °C and then the reaction mixture warmed to room temperature. After stirring for 4–5 h, the resulting mixture was washed with aqueous 1 M HCl. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was chromatographed with SiO_2 to give methacrylamide.

4.1.1. 1-Methacryloyl-L-proline 1a. Colorless viscous oil (1.67 g, 91%). $R_f = 0.1$ (hexane–EtOAc–AcOH 15:5:1); IR (film) 2981 (br), 1739, 1652, 1583, 1457, 1184 cm^{-1}; ^1H NMR δ 1.85–2.27 (m, 4H), 1.90 (s, 3H), 3.58 (m, 2H), 4.49 (dd, 1H, $J = 5.0, 8.3$), 5.20 (s, 1H), 5.27 (s, 1H), 11.1 (br s, 1H); ^{13}C NMR (the major conformer) δ 19.2, 24.5, 28.7, 49.0, 58.5, 117.3, 139.9, 171.3, 174.4; MS (EI) *m/z* 183 (M^+, 3), 138 (78), 69 (100), 41 (36); $[\alpha]_D^{23} = -137.8$ (*c* 1.02, $CHCl_3$); HRMS (EI) calcd for $C_9H_{13}NO_3$ 183.0895, found 183.0892.

4.1.2. 1-Methacryloyl-L-proline methyl ester 1b. Colorless oil (1.34 g, 68%). $R_f = 0.25$ (hexane–EtOAc–AcOH 15:5:1); IR (film) 1747, 1652, 1622, 1435, 1197 cm^{-1}; ^1H NMR δ 1.85–2.05 (m, 3H), 1.97 (s, 3H), 2.23 (m, 1H), 3.62 (m, 2H), 3.72 (s, 3H), 4.48 (dd, 1H, $J = 4.4, 8.2$), 5.23 (s, 1H), 5.29 (s, 1H); ^{13}C NMR (the major conformer) δ 19.5 (=C*C*H_3), 25.0 (*C*H_2CH_2), 29.1 (*C*H_2CH_2), 49.0 (N*C*H_2), 52.1 (N*C*H), 58.4 (O*C*H_3), 117.0 (=*C*H_2), 140.6 (=*C*), 170.6 (*C*O), 172.0 (*C*O); MS (EI) *m/z* 197 (M^+, 15), 138 (100), 69 (87), 41 (22); $[\alpha]_D^{23} = -79.2$ (*c* 1.05, $CHCl_3$); HRMS (EI) calcd for $C_{10}H_{15}NO_3$ 197.1052, found 197.1061.

4.1.3. 1-Methacryloyl-L-proline phenyl ester 1c. Pale yellowish viscous oil (2.00 g, 77%). $R_f = 0.25$ (hexane–EtOAc–AcOH 15:5:1); IR (film) 1767, 1651, 1622, 1429, 1144 cm^{-1}; ^1H NMR δ 1.99 (s, 3H), 1.99–2.21 (m, 3H), 2.42 (m, 1H), 3.70 (m, 2H), 4.71 (dd, 1H, $J = 5.4, 8.2$), 5.28 (s, 1H), 5.32 (s, 1H), 7.12–7.39 (m, 5H); ^{13}C NMR (the major conformer) δ 19.5, 24.9, 28.8, 49.4, 59.0, 115.4, 117.8, 119.8, 129.3, 140.0, 156.3, 171.9, 174.9; MS (EI) *m/z* 166 (M^+−OPh, 84), 138 (100), 69 (70), 41 (18); $[\alpha]_D^{22} = -71.1$ (*c* 1.04, $CHCl_3$); HRMS (CI) calcd for $C_{15}H_{18}NO_3$ 260.1287, found 260.1295.

4.1.4. (*S*)-1-Methacryloyl-2-(diethylaminomethyl)pyrrolidine 1d. Colorless oil (360 mg, 53%). $R_f = 0.70$ ($CHCl_3$–MeOH–aq NH_3 80:18:2); IR (film) 1648, 1616, 1428 cm^{-1}; ^1H NMR δ 0.96–1.24 (br m, 6H), 1.79–2.10 (br m, 4H), 1.94 (s, 3H), 2.12–2.95 (br m, 6H), 3.48 (br m, 2H), 4.00 (br m, 0.3H), 4.22 (br m, 0.7H), 5.11 (s, 1H), 5.22 (s, 1H); ^{13}C NMR (the major conformer) δ 11.7, 19.5, 24.1, 28.5, 47.7, 48.7, 54.5, 55.6, 115.6, 141.5, 170.4; MS (EI) *m/z* 224 (M^+, 11), 86 (100), 69 (15); $[\alpha]_D^{17} = -112.7$ (*c* 1.00, $CHCl_3$); HRMS (EI) calcd for $C_{13}H_{24}N_2O$ 224.1889, found 224.1891.

4.1.5. (*S*)-1-Methacryloyl-2-(benzylaminomethyl)pyrrolidine 1e. Colorless oil (1.34 g, 52%). $R_f = 0.75$ ($CHCl_3$–MeOH–aq NH_3 80:18:2); IR (film) 3250, 2950, 1651, 1616, 1455, 699 cm^{-1}; ^1H NMR δ 1.80–2.12 (m, 5H), 1.96 (s, 3H), 2.72 (dd, 1H, $J = 6.7, 11.7$), 2.92 (dd, 1H, $J = 4.3, 11.7$), 3.44 (m, 1H), 3.57 (m, 1H), 3.84 (s, 2H), 4.06 (br s, 0.2H), 4.29 (br m, 0.8H), 5.13 (s, 1H), 5.25 (s, 1H), 7.24–7.34 (m, 5H); ^{13}C NMR δ 19.7, 24.6, 29.1, 49.3, 52.0, 53.6, 56.8, 116.2, 126.7, 127.9, 128.2, 140.2, 141.7, 171.3; MS (EI) *m/z* 258 (M^+, 7), 173 (22), 139 (80), 69 (42); $[\alpha]_D^{13} = -67.6$ (*c* 0.99, $CHCl_3$); HRMS (EI) calcd for $C_{16}H_{22}N_2O$ 258.1732, found 258.1738.

4.1.6. (2*S*,5*S*)-1-Methacryloyl-2,5-bis(methoxymethyl)pyrrolidine 4a and its enantiomer 4b. Colorless oil (82–92%). $R_f = 0.4$ (hexane–EtOAc–AcOH 15:5:1); IR (film) 1617, 1421, 1116 cm^{-1}; ^1H NMR δ 1.87–2.22 (m, 4H), 1.99 (s, 3H), 3.20 (m, 2H), 3.30 (s, 3H), 3.35 (s, 3H), 3.41 (dd, 1H, $J = 7.3, 9.1$), 3.53 (dd, 1H, $J = 2.7, 9.3$), 4.20 (m, 1H), 4.32 (m, 1H), 5.17 (s, 1H), 5.25 (s, 1H); ^{13}C NMR δ 20.0, 25.1, 26.9, 56.3, 58.5, 58.8, 71.8, 73.8, 115.8, 141.8, 171.4; MS (EI) *m/z* 227 (M^+, 0.5), 182 (M^+−CH_2OCH_3, 100), 150 (12), 69 (63); **4a**: $[\alpha]_D^{24} = -76.5$ (*c* 1.00, $CHCl_3$), **4b**: $[\alpha]_D^{11} = +75.0$ (*c* 0.98, $CHCl_3$); HRMS (CI) calcd for $C_{12}H_{22}NO_3$ 228.1600, found 228.1605.

4.1.7. (*S*,*S*)-*N*-Methacryloyl-*N*,*N*-bis(phenylethyl)amine 4c. Colorless oil (2.49 g 85%). $R_f = 0.4$ (hexane–EtOAc–AcOH 15:5:1); IR (film) 1633, 1433, 1225, 697 cm^{-1}; ^1H NMR (C_6D_6): δ 1.52 (br d, 6H, $J = 6.9$), 1.78 (s, 3H), 4.72 (br q, 2H, $J = 6.9$), 4.79 (s, 1H), 4.92 (s, 1H), 7.10–7.27 (m, 10H); ^{13}C NMR δ 18.5, 20.6, 54.6, 113.7, 126.9, 127.7, 140.4, 142.3, 172.7; MS (EI) *m/z* 293 (M^+, 7), 188 (100), 174 (15), 105 (100), 69 (41); $[\alpha]_D^{23} = -95.7$ (*c* 1.00, $CHCl_3$); HRMS (EI) calcd for $C_{20}H_{23}NO$ 293.1780, found 293.1783.

4.1.8. (2*S*,5*S*)-1-Methacryloyl-2,5-dimethylpyrrolidine 4d. Colorless oil (1.42 g, 85%). $R_f = 0.35$ (hexane–EtOAc–AcOH 15:5:1); IR (film) 1616, 1423 cm^{-1}; ^1H NMR δ 1.09 (d, 3H, $J = 6.4$), 1.19 (d, 3H, $J = 6.4$), 1.50–1.70 (m, 2H), 1.98 (s, 3H), 2.00–2.30 (m, 2H), 4.19 (q, 1H, $J = 6.4$), 4.31 (q, 1H, $J = 6.4$), 5.13 (s, 1H), 5.19 (s, 1H); ^{13}C NMR δ 19.4, 20.4, 21.9, 29.1, 31.0, 52.8, 54.8, 115.3, 142.3, 171.1; MS (EI) *m/z* 167 (M^+, 50), 152 (89), 69 (100); $[\alpha]_D^{23} = +22.4$ (*c* 1.00, $CHCl_3$); HRMS (EI) calcd for $C_{10}H_{17}NO$ 167.1310, found 167.1314.

4.2. General procedure for the conjugate addition of thioacetic acid

To a stirred solution of methacrylamide (0.67 mmol) in solvent (5 mL) was added thioacetic acid (0.96 mL, 1.34 mmol) at room temperature. The stirring was continued until the methacrylamide content was smaller

than 2–5% by GC analysis. The reaction mixture was then concentrated and chromatographed with SiO_2 to give the addition product.

4.2.1. (*S*)-Acetylcaptopril 2a and 1-((2′*R*)-3′-acetylthio-2′-methylpropanoyl)-L-proline 3a. Viscous oil (2.1 g, 86%). $R_f = 0.05$ (hexane–EtOAc–AcOH 15:5:1) or 0.7 (CH_2Cl_2–MeOH–AcOH 8:1:1); IR (film) 2978 (br), 1744, 1691, 1622, 1610, 1446, 1190 cm^{-1}; ^1H NMR δ 1.02 (d, 3H, $J = 6.8$), 1.08 (d, 3H, $J = 6.8$), 1.13 (m, 2H), 1.27–1.64 (m, 4H), 1.79–1.91 (m, 2H), 1.82 (s, 3H), 1.86 (s, 3H), 2.55–2.69 (m, 3H), 2.87–2.99 (m, 4H), 3.11–3.33 (m, 3H), 4.33 (dd, 1H, $J = 3.1$, 8.4), 4.43 (dd, 1H, $J = 3.7$, 8.4), 8.77 (br s, 2H); ^{13}C NMR (C_6D_6, 60 °C, the major conformer): δ 16.2, 16.6, 24.7, 24.8, 28.5, 28.6, 30.1, 32.6, 32.9, 38.6, 38.7, 47.2, 47.3, 59.5, 59.7, 173.5, 173.8, 174.8, 174.9, 196.1, 196.2; MS (EI) *m/z* 259 (M^+, 2), 216 (39), 172 (52), 114 (33), 70 (100); HRMS (CI) calcd for $C_{11}H_{18}NO_4S$ 260.0957, found 260.0957.

4.2.2. (*S*)-Acetylcaptopril methyl ester 2b and 1-((2′*R*)-3′-acetylthio-2′-methylpropanoyl)-L-proline methyl ester 3b. Colorless oil (151 mg, 95%). $R_f = 0.3$ (hexane–EtOAc–AcOH 15:5:1); IR (film) 1747, 1690, 1651, 1430, 1198 cm^{-1}; ^1H NMR (C_6D_6): δ 1.11 (d, 3H, $J = 6.8$), 1.16 (d, 3H, $J = 6.8$), 1.17 (m, 2H), 1.51 (m, 6H), 1.83 (s, 3H), 1.85 (s, 3H), 2.67–2.82 (m, 3H), 3.06 (m, 3H), 3.25–3.48 (m, 4H), 3.31 (s, 3H), 3.36 (s, 3H), 4.47 (dd, 1H, $J = 4.4$, 8.0), 4.53 (t, 1H, $J = 6.0$); ^{13}C NMR ($CDCl_3$, 60 °C, the major conformer): 16.2, 16.5, 24.6, 24.7, 28.8, 28.9, 30.3, 32.2, 32.5, 38.0, 38.2, 46.7, 46.8, 51.7, 58.5, 58.7, 172.3, 172.4, 173.1, 195.5; MS (EI) *m/z* 273 (M^+, 9), 230 (63), 214 (34), 128 (38), 70 (100); HRMS (EI) calcd for $C_{12}H_{19}NO_4S$ 273.1035, found 273.1020.

4.2.3. *S*-Acetylcaptopril phenyl ester 2c and 1-((2′*R*)-3′-acetylthio-2′-methylpropanoyl)-L-proline phenyl ester 3c. Colorless oil (202 mg, 90%). $R_f = 0.3$ (hexane–EtOAc–AcOH 15:5:1); IR (film) 1767, 1695, 1652, 1429, 1195, 690, 627 cm^{-1}; ^1H NMR δ 1.23 (d, 3H, $J = 6.4$), 1.24 (d, 3H, $J = 6.4$), 2.00–2.50 (m, 8H), 2.25 (s, 3H), 2.32 (s, 3H), 2.76–3.03 (m, 4H), 3.18 (m, 2H), 3.54–3.69 (m, 3H), 3.86 (m, 1H), 4.67 (dd, 1H, $J = 4.0$, 8.3), 4.72 (dd, 1H, $J = 4.1$, 8.4), 7.05–7.38 (m, 10H); ^{13}C NMR (60 °C, the major conformer): δ 16.3, 16.5, 24.8, 28.9, 29.0, 30.2, 30.3, 32.2, 32.5, 38.0, 38.2, 46.7, 46.8, 58.8, 59.1, 121.2, 121.3, 125.5, 129.0, 129.1, 150.8, 170.4, 170.5, 173.3, 195.4; MS (EI) *m/z* 292 (M^+-CH_3CO, 5), 242 (M^+-OPh, 100), 214 (44), 145 (39), 70 (90); HRMS (CI) calcd for $C_{17}H_{22}NO_4S$ 336.1270, found 336.1276.

4.2.4. (2*S*)-1-((2′*S*)-3′-Acetylthio-2′-methylpropanoyl)-2-(diethylaminomethyl)pyrrolidine 2d and (2*S*)-1-((2′*R*)-3′-acetylthio-2′-methylpropanoyl)-2-(diethylaminomethyl)-pyrrolidine 3d. Colorless oil (105 mg, 52%). $R_f = 0.70$ ($CHCl_3$–MeOH–aq NH_3 80:18:2); IR (film) 1694, 1652, 1429, 795, 627 cm^{-1}; ^1H NMR (500 MHz): δ 0.87–1.04 (m, 12H), 1.06–1.23 (m, 6H), 1.85–1.99 (m, 8H), 2.10–2.33 (m, 3H), 2.27 (s, 3H), 2.29 (s, 3H), 2.34–2.55 (m, 6H), 2.56–2.80 (m, 5H), 2.83–3.16 (m, 4H), 3.30–3.59 (m, 4H), 4.00–4.18 (m, 2H); ^{13}C NMR (125 MHz, major conformer): δ 12.2, 12.5, 16.9, 17.7, 23.9, 24.0, 28.2, 28.4, 30.9, 31.0, 32.6, 33.4, 38.8, 38.9, 47.2, 48.5, 48.6, 54.6, 54.7, 56.8, 56.9, 173.3, 173.7, 196.4, 196.5; MS (EI) *m/z* 300 (M^+, 2), 152 (3), 86 (100); HRMS (EI) calcd for $C_{15}H_{28}N_2O_2S$ 300.1872, found 300.1859.

4.2.5. (2*S*)-1-((2′*S*)-3′-Acetylthio-2′-methylpropanoyl)-2-(benzylaminomethyl)pyrrolidine 2e and (2*S*)-1-((2′*R*)-3′-acetylthio-2′-methylpropanoyl)-2-(benzylaminomethyl)-pyrrolidine 3e. Colorless oil (139 mg, 62%). $R_f = 0.70$ ($CHCl_3$–MeOH–aq NH_3 80:18:2); IR (film) 2969, 1694, 1645, 1428, 1135, 627 cm^{-1}; ^1H NMR (500 MHz): δ 1.07 (d, 3H, $J = 6.8$), 1.09 (d, 3H, $J = 6.8$), 1.69–2.30 (m, 16H), 2.65–3.03 (m, 6H), 3.20–3.64 (m, 6H), 4.24–4.69 (m, 6H), 7.02–7.35 (m, 10H); ^{13}C NMR (the major conformer) δ 16.3, 21.3, 21.5, 23.6, 27.7, 27.9, 30.2, 32.2, 32.7, 38.1, 46.3, 47.0, 51.8, 51.9, 54.5, 55.4, 126.2, 127.1, 128.6, 137.2, 171.4, 173.2, 195.2, 195.3; MS (EI) *m/z* 333 (M^+, 31), 214 (37), 145 (39), 91 (44), 70 (100); HRMS (EI) calcd for $C_{18}H_{25}N_2O_2S$ 333.1637, found 333.1639.

4.2.6. (2*R*,5*R*)-1-((2′*S*)-3′-Acetylthio-2′-methylpropanoyl)-2,5-bis(methoxymethyl)pyrrolidine 5b and its enantiomer 6a. Colorless oil (180 mg, 89%). $R_f = 0.65$ (CH_2Cl_2–MeOH 20:1); IR (film) 1692, 1639, 1422, 1114 cm^{-1}; ^1H NMR δ 1.21 (d, 3H, $J = 6.1$), 1.93 (m, 3H), 2.13 (m, 1H), 2.34 (s, 3H), 2.95 (m, 3H), 3.21 (d, 2H, $J = 6.6$), 3.28–3.38 (m, 1H), 3.32 (s, 3H), 3.35 (s, 3H), 3.60 (dd, 1H, $J = 3.1$, 9.2), 4.11 (q, 1H, $J = 7.1$), 4.24 (m, 1H); ^{13}C NMR δ 17.0, 25.1, 26.8, 30.4, 33.9, 38.0, 56.8, 57.2, 58.6, 58.9, 70.9, 74.3, 174.1, 195.7; MS (EI) *m/z* 258 ($M^+-MeOCH_2$, 67), 216 (4), 145 (13), 114 (100); **5b**: $[\alpha]_D^{19} = -46.6$ (*c* 1.01, $CHCl_3$), **6a**: $[\alpha]_D^{24} = +45.9$ (*c* 1.01, $CHCl_3$); HRMS (CI) calcd for $C_{14}H_{26}NO_4S$ 304.1583, found 304.1578.

4.2.7. (*S*,*S*)-*N*-((2′*S*)-3′-Acetylthio-2′-methylpropanoyl)-*N*,*N*-bis(phenylethyl)amine 5c and (*S*,*S*)-*N*-((2′*R*)-3′-acetylthio-2′-methylpropanoyl)-*N*,*N*-bis(phenylethyl)amine 6c. Colorless oil (99 mg, 40%). $R_f = 0.70$ (CH_2Cl_2–MeOH 20:1); IR (film) 1689, 1634, 1435, 1137, 701, 627 cm^{-1}; ^1H NMR δ 0.52 (br d, 3H, $J = 6.2$), 1.17 (br d, 3H, $J = 6.4$), 1.63 (d, 3H, $J = 7.1$), 1.64 (d, 3H, $J = 7.1$), 1.68 (d, 3H, $J = 7.1$), 1.71 (d, 3H, $J = 7.1$), 2.17 (s, 3H), 2.26 (s, 3H), 2.60 (m, 1H), 2.70–2.88 (m, 4H), 3.05 (dd, 1H, $J = 7.7$, 13.2), 4.80 (br q, 1H, $J = 7.1$), 4.92 (br q, 1H, $J = 7.1$), 5.20 (br s, 1H), 5.77 (br s, 1H), 6.77–7.23 (m, 20H); ^{13}C NMR (60 °C): δ 16.7, 19.5, 30.3, 32.9, 33.7, 38.0, 38.6, 52.7, 53.5, 127.2, 128.1, 128.4, 128.6, 140.9, 141.5, 175.1, 175.6, 195.3, 195.8; MS (EI) *m/z* 264 ($M^+-CH(Ph)CH_3$, 70), 145 (15), 120 (100), 105 (94); HRMS (CI) calcd for $C_{22}H_{28}NO_2S$ 370.1841, found 370.1836.

4.2.8. (2*S*,5*S*)-1-((2′*S*)-3′-Acetylthio-2′-methylpropanoyl)-2,5-dimethylpyrrolidine 5d. Colorless oil (134 mg, 82%). $R_f = 0.40$ (hexane–EtOAc–AcOH 15:5:1); IR (film) 1692, 1637, 1463, 1136 cm^{-1}; ^1H NMR δ 1.12 (d, 3H, $J = 6.5$), 1.17 (d, 3H, $J = 6.5$), 1.21 (d, 3H, $J = 6.6$), 1.51–1.65 (m, 2H), 2.02–2.30 (m, 2H), 2.34 (s, 3H), 2.80 (m, 1H), 2.94 (dd, 1H, $J = 6.8$, 13.2), 3.07 (dd, 1H, $J = 7.9$, 13.2), 4.12 (qn, 1H, $J = 6.5$), 4.24

(qn, 1H, $J = 6.5$); ^{13}C NMR δ 17.2, 18.8, 22.2, 28.9, 30.5, 30.7, 34.0, 37.8, 53.1, 53.3, 172.9, 196.1; MS (EI) *m*/*z* 243 (M^+, 17), 200 (76), 168 (20), 126 (89), 44 (100); $[\alpha]_D^{24} = -96.0$ (*c* 1.01, $CHCl_3$); HRMS (CI) calcd for $C_{12}H_{22}NO_2S$ 244.1359, found 244.1363.

4.2.9. (*S*)-3-Acetylthio-2-methylpropanoic acid 9 and (2*R*,5*R*)-*N*-Boc-2,5-bis(hydroxymethyl)pyrrolidine 10. To a stirred solution of **5b** (50 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was added 1.0 M BBr_3 (1.65 mL, 1.65 mmol) in CH_2Cl_2 at room temperature. After stirring for 30 min, solvent and excess BBr_3 were evaporated under reduced pressure. Distilled H_2O (2 mL) was then added to the residue and the resulting solution neutralized with saturated $NaHCO_3$ solution. After removal of water under reduced pressure, the residue was extracted with $CHCl_3$ (3 mL) and the organic layer dried over $MgSO_4$, filtered, and concentrated. Aqueous 1 M HCl (3 mL) was added to the concentrate and the reaction temperature increased to 70 °C. After stirring for 4 h, the reaction mixture was extracted with EtOAc (3×5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford **7** as colorless oil (19 mg, 96%). To a solution of **7** (600 mg, 5 mmol) in H_2O (20 mL) were added Ac_2O (0.95 mL, 10 mmol) and NaOH (610 mg, 15 mmol) at 0 °C. The reaction mixture was stirred until **7** was not observed on TLC (0.5–1.0 h) at the same temperature and then acidified by addition of aqueous 2 M HCl. The resulting mixture was extracted with CH_2Cl_2 (2×20 mL), and the organic layers were dried over $MgSO_4$, concentrated, and chromatographed to give **9** (742 mg, 92%) as a colorless oil. $R_f = 0.4$ (hexane–EtOAc–AcOH 15:5:1); IR (film) 1697, 1134, 627 cm^{-1}; ^1H NMR δ 1.29 (d, 3H, $J = 7.1$), 2.35 (s, 3H), 2.73 (m, 1H), 3.05 (dd, 1H, $J = 6.0, 13.6$), 3.13 (dd, 1H, $J = .6, 13.6$); ^{13}C NMR δ 16.6, 30.5, 31.3, 39.9, 181.0, 195.4; MS (EI) *m*/*z* 162 (M^+, 3), 144 (2), 102 (28), 61 (20), 43 (100); HRMS (CI) calcd for $C_6H_{11}O_3S$ 163.0429, found 163.0427.

On the other hand, the aqueous layer was concentrated and 4 mL of a mixture of solvents (H_2O–*t*-BuOH 1:1) added to the residue. To the resulting solution were added with stirring Boc_2O (58 mg, 0.33 mmol) and TEA (0.070 mL, 0.50 mmol) at room temperature. After 12 h, the resulting mixture was extracted with EtOAc (2×5 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated. Chromatography of the crude product with SiO_2 gave (2*R*,5*R*)-*N*-Boc-2,5-bis(hydroxymethyl)pyrrolidine **10** (39 mg, 90%) as colorless oil. $R_f = 0.60$ (CH_2Cl_2–EtOH–AcOH 8:1:1); ^1H NMR δ 1.49 (s, 9H), 1.63–2.18 (m, 4H), 3.45–3.67 (m, 2H), 3.68–3.76 (m, 2H), 3.90 (br m, 1H), 4.05 (br m, 1H), 4.28 br (m, 1H). $[\alpha]_D^{24} = +77.5$ (*c* 0.5, MeOH).[13]

Acknowledgements

This work was supported in part by the BK 21 Project and in part by a grant no. KOSEF 97-0502-0901-5 from the Korea Science and Engineering Foundation.

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