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Synthesis and Antibacterial Activities of 4-Pyrrolidinylthio Carbapenems: Containing Heteroaromatics as a Side Chain

The synthesis of a new series of 2-alkyl-4-pyrrolidinylthio-b-methylcarbapenems containing the substituted heteroaromatic moieties is described. Their *in vitro* antibacterial activities against both gram-positive and gram-negative bacteria were tested. The effect of substituents on the nitrogen atoms at heteroaromatic rings was investigated. Particular compounds (**14b**, **14c**) containing 3-methyl- and 3,5-dimethylpyrazolethio substituted moiety showed the most potent antibacterial activity.

Keywords: Carbapenems; Antibacterials; DHP-I stability

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Introduction

The discovery and development of new antibiotics has drawn significant attention in recent years due to the rising prevalence of multidrug-resistant bacteria. Imipenem [1], the first marketed carbapenem antibiotic, is highly valued in the clinic for its efficacy against serious bacterial infections. However, due to its instabilily to renal dehydropeptidase-I (DHP-I), Imipenem is used in combination with cilastatin, a DHP-I inhibitor. In 1984, Merck researchers [2] reported that the installment of a methyl group at the β-position of the carbapenem nucleus greatly improved both, the chemical and metabolic stabilities.

The carbapenem compounds with a pyrrolidine-3-ylthio group at the C-2 position in the carbapenem skeleton are noted for their broad and potent antibacterial activity [3–5]. Consequently a large number of derivatives has been synthesized and investigated [6–9]. Previously, we reported the synthesis and biological properties of carbapenems having the thiazolidinopyrrolidine and diazabicylcle moieties [10, 11].

In this report, we examined the relationship between the spacer length and activities in a related series to FR21818 [12, 13] that contains a carbon-nitrogen bond as the point of attachment of the heterocycles.

As a part of our program developing a new parental 1-β-methylcarbapenem with improved properties, activity, and stability to DHP-I, 1-β-methyl-2-(5-substituted pyrrolidin-3-yl-thio)carbapenems, bearing 2-substituted heteroaromatic compounds, were prepared.

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Chemistry

Our general synthetic route leading to new carbapenems involved the preparation of appropriately protected thiols containing heteroatoms as a side chain and their coupling reaction with the carbapenem diphenylphosphates, followed by deprotection of the resulting protected carbapenems in a usual manner.

In summary, the acetylthio derivatives (**10a–j**) were prepared by the sequence shown in Scheme 1. 4-Hydroxyproline (**1**) was treated with acetylchloride in MeOH under reflux to give the methyl ester (**2**), which was protected by allyl chloroformate to give **3** in high yield. Next, the hydroxy group of the N-protected compound (**3**) was protected with *tert*-butyldimethylchlorosilyl chloride (TBDMSCl) in the presence of imidazole in DMF at 0 oC leading to **4**. This compound was reduced with $NaBH_4$ in EtOH to give **5**, which was converted to the corresponding mesylate (**6**) with mesylchloride in CH_2Cl_2. The compounds (**7a–j**) were prepared by displacement of mesylate group with the heteroaromatics (**a–j**) as nucleophiles under basic conditions (NaH, *t*-BuOK) in DMF. Deprotection of the silyl ethers with 1 M tetrabutylammonium fluoride (TBAF) gave hydroxyl compounds (**8a–j**), which were subsequently converted to the mesylates (**9a–j**) with mesyl chloride. Treatment of **9a–j** with potassium thioacetate in DMF and followed by hydrolysis of the resulting acetylthio groups (**10a–j**) led to the thiol com-

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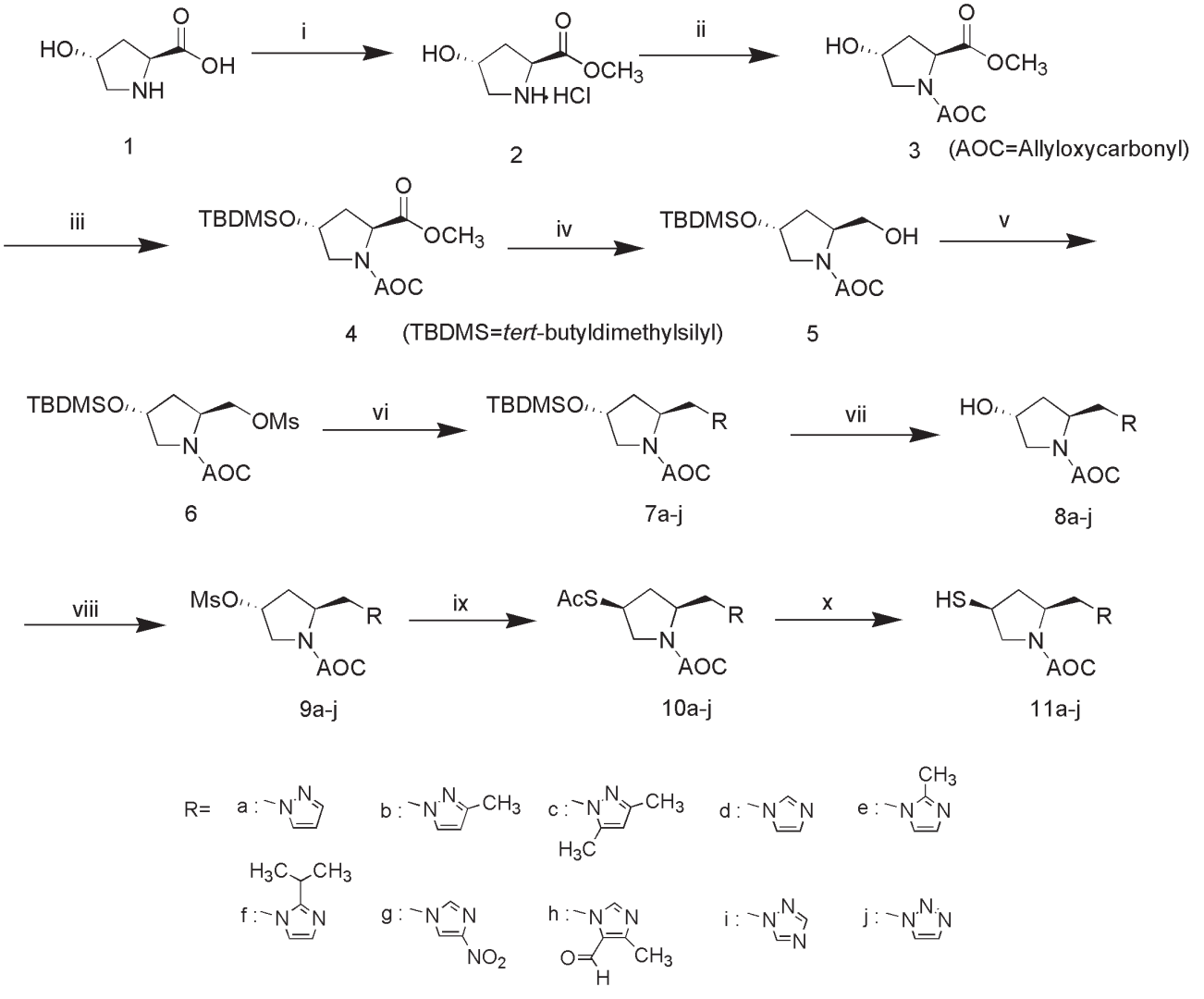
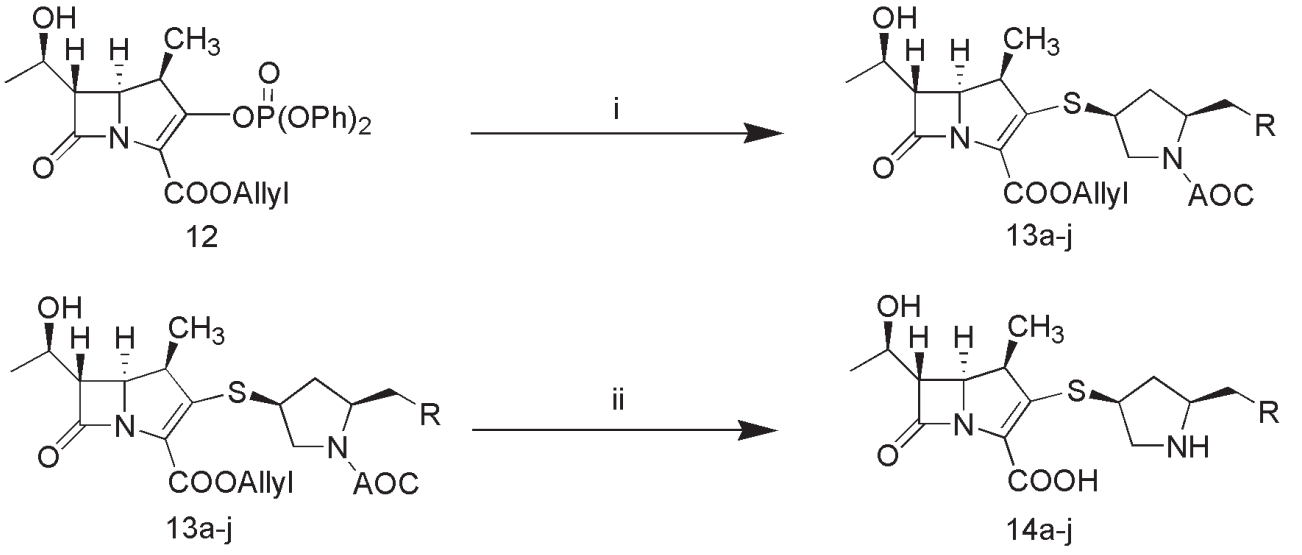


Scheme 1. (i) AcCl, MeOH; (ii) Allyl chloroformate,TEA, CH_2Cl_2; (iii) TBDMSCl, Imidazole, DMF; (iv) $NaBH_4$,EtOH; (v) MsCl, TEA, CH_2Cl_2; (vi) R=heteroaromatics, NaH or *t*-BuOK, DMF; (vii) 1*M* tetrabutylammonium fluoride, THF; (viii) MsCl,TEA, CH_2Cl_2; (ix) AcSK, DMF:Toluene=1:1; (x) 4*N* NaOH, MeOH

pounds (**11a–j**), which were reacted with **12**, *in situ*, using in the presence of diisopropylethylamine to provide the corresponding 2-substituted carbapenems (**13a–j**) (Scheme 2). Catalytic hydrogenation of the allyl esters resulted in the crude products, which were purified by HP-20 column chromatography yielding the pure carbapenems (**14a–j**).

Results and discussion

The *in vitro* antibacterial activities of the new carbapenems (**14a–j**) against gram-positive and gram-negative bacteria are listed in Table 1. For comparison, the MIC (minimum inhibitory concentration) values of Imipenem (IPM) and Meropenem (MPM) are also listed. Compound (**14c**) exhibited superior or similar antibacterial activity to Meropenem and Imipenem against gram-positive and gram-negative bacteria, except *P. aeruginosa*. Heteroaromatics with electron donating methyl or isopropyl groups were generally observed to have better activities than heteroaromatics with nitro or aldehyde groups which are electron withdrawing (**14g**, **14h**) against gram-positive and gram-negative bacteria. Among the three classes of compounds (pyrazole, imidazole, triazole), imidazole moieties showed the best ac-



Scheme 2. (i) **11a-j**, *i*-Pr_2EtN, CH_3CN; (ii) $Pd(OH)_2/H_2$, THF/H_2O=1/1

Table 1. *In vitro* antibacterial activity (MIC, μg/mL) and DHP-1 stability of the carbapenem derivatives.

STRAINS	**14a**	**14b**	**14c**	**14d**	**14e**	**14f**	**14g**	**14h**	**14i**	**14j**	**IMP**[a]	**MPM**[b]
Streptococcus pyogenes 77A	0.01	<0.01	<0.01	0.05	0.01	<0.01	0.01	0.02	<0.01	<0.01	<0.01	<0.01
Staphylococcus aureus SG511	0.10	0.05	0.05	0.78	0.20	0.10	0.10	0.39	0.39	0.39	0.01	0.10
Staphylococcus aureus 503	0.10	0.05	0.05	0.39	0.10	0.10	0.10	0.39	0.20	0.20	0.01	0.05
Escherichia coli DC2	0.10	0.10	0.05	0.39	0.20	0.10	0.10	0.20	0.20	0.20	0.39	0.01
Escherichia coli TEM	0.05	0.10	0.05	0.39	0.10	0.10	0.10	0.20	0.20	0.20	0.20	0.01
Pseudomonas aeruginosa 1771M	0.78	0.78	0.78	3.13	0.78	1.56	0.78	3.13	3.13	3.13	0.20	0.10
Salmonella typhimurium	0.20	0.10	0.10	0.78	0.20	0.10	0.20	0.39	0.39	0.39	0.78	0.05
Klebsiella aerogenes 1522E	0.20	0.10	0.10	0.78	0.20	0.10	0.20	0.39	0.39	0.39	0.20	0.05
Enterobactor cloacae 1321E	0.05	0.05	0.05	0.39	0.10	0.05	0.10	0.20	0.20	0.39	0.20	0.01
DHP-1[c]	1.59	1.32	1.10	3.89	2.74	2.51	1.69	2.86	1.80	1.70	0.21	1.00
Streptococcus pyogenes 308A	<0.01	<0.01	<0.01	0.05	0.01	<0.01	0.03	0.03	<0.01	<0.01	<0.01	0.01

[a] Imipenem; [b] Meropenem; [c] Human DHP-1 stability is given relative to Meropenem.

tivities against DHP-I. All these compounds have shown better activities than MPM and IPM.

Experimental

Melting point (mp): Thomas Hoover apparatus (Thomas Co., Philadelphia, PA, USA), uncorrected. UV spectra: Hewlett Packard 8451A UV-VIS spectrophotometer (Perkin Elmer, Ueberlingen, Germany). IR spectra: Perkin Elmer 16F-PC FT-IR Perkin Elmer, Norwalk, CO, USA). NMR spectra:Varian Gemini 300 spectrometer (Varian Associates Inc., Palo Alto, CA, USA), tetramethylsilane (TMS), as an internal standard. The mass spectrometry system was based on a HP5989A MS Engine (Hewlett Packard, Palo Alto, CA, USA). Diaion HP-column, Ion exchange resin (Mitsubishi Chemical Co., Tokyo, Japan).

Measurement of in vitro antibacterial activity

The MICs were determined by the agar dilution method using test agar. An overnight culture of bacteria in tryptosoy broth was diluted to about 10^6 cells mL^{-1} with the same broth and inoculated onto agar containing serial twofold dilutions of the test

compounds. Organisms were incubated at 37 °C for 18–20 h. The MICs of a compound was defined as the lowest concentration that visibly inhibited growth.

Determination of susceptibility to renal dehydropeptidase-1 (DHP-1)

The relative hydrolysis rate of carbapenems by porcine renal DHP-1 was determined, taking the initial hydrolysis rate of imipenem as 1.0. Partially purified porcine DHP-1 (final concentration, 0.3 U mL^{-1}) was incubated with 50 μM carbapenem at 35 °C in 50 mM MOPS buffer, pH 7.0. The initial hydrolysis rate was monitored spectrophotometrically. One unit of activity was defined as the amount of enzyme hydrolyzing 1 μM of glycyldehydrophenylalanine per min when the substrate, 50 μM, was incubated at 35 °C in 50 μM MOPS buffer, pH 7.0.

Methyl (2S,4R)-4-Hydroxypyrrolidine-2-carboxylate hydrochloride (**2**)

To a solution of **1** (77.0 g, 0.59 mol) in MeOH (200 mL) acetylchloride (63.0 mL, 0.88 mol) was added slowly at room temperature and the reaction mixture was refluxed for 8 h. The reaction mixture was concentrated under reduced pressure. The residue was triturated with ethyl ether and the resulting precipitate was collected by filtration, washed with ethyl ether and dried under reduced pressure to give **2** as a white solid. Yield: 92 %; mp: 157 °C; ^{1}H-NMR (DMSO-d_6): δ = 2.03–2.20 (m, 2 H), 3.06 (d, 1 H, *J* = 6.0 Hz), 3.36 (dd, 1 H, *J* = 2.0 Hz, *J* = 2.1 Hz), 3.74 (s, 3 H), 4.41 (m, 2 H); ^{13}C-NMR (DMSO-d_6): δ = 40.98, 57.01, 57.14, 61.52, 72.42, 173.00; IR (KBr): 3378 (NH), 1742 (C=O) cm^{-1}.

Methyl (2S,4R)-1-Allyloxycarbonyl-4-hydroxypyrrolidine-2-carboxylate (**3**)

A mixture of **2** (110 g, 0.76 mol) and triethylamine (221 mL, 1.67 mol) in CH_2Cl_2 (400 mL) was added dropwise to a solution of allylchloroformate (100 g, 0.83 mol) in CH2Cl2 (200 mL) at –5 °C. After stirring for 3 h at room temperature, the mixture was extracted with CH_2Cl_2: H_2O (1:1), dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel (n-Hexane : EtOAc (1:1) elution) to give **3** as a pale yellow oil. Yield: 88 %; ^{1}H-NMR ($CDCl_3$): δ = 2.02–2.11 (m, 1 H), 2.26–2.38 (m, 1 H), 3.52–3.67 (m, 2 H), 3.72 (d, 3 H, *J* = 5.3 Hz), 4.46–4.52 (m, 2 H), 4.58 (d, 2 H, *J* = 3.0 Hz), 5.16–5.33 (m, 2 H), 5.80–5.97 (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 39.33, 52.54, 55.39, 66.37, 69.38, 117.50, 132.64, 154.88, 173.45; IR (KBr): 3442 (NH), 1746 (C=O) cm^{-1}.

Methyl (2S,4R)-1-Allyloxycarbonyl-4-tert-butyldimethylsilyloxypyrrolidine-2-carboxylate (**4**)

To a solution of **3** (62.0 g, 0.27 mol) in DMF (120 mL), imidazole (44.0 g, 0.65 mol) and *tert*-butyldimethylchlorosilane (TBDMS-Cl) (49.0 g, 0.33 mol) were added and the solution stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc, washed thoroughly with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give **4** as a colorless oil. Yield: 83 %; ^{1}H-NMR ($CDCl_3$): δ = 0.01 (s, 6 H), 0.79 (s, 9 H), 1.91–2.02 (m, 1 H), 2.08–2.16 (m, 1 H), 3.32–3.42 (m, 1 H), 3.57 (dd, 1 H, *J* = 2.4 Hz, *J* = 2.4 Hz), 3.65 (d, 3 H, *J* = 5.0 Hz), 4.38 (m, 2 H), 4.51 (m, 2 H), 5.16 (m, 2 H), 5.82 (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ = –4.74, 18.07, 25.82, 39.05, 52.31, 54.84, 57.91, 66.01, 69.86, 117.11, 132.85, 154.40, 173.26; IR (KBr): 1746 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-tert-butyldimethylsilyloxy-2-hydroxymethylpyrrolidine (**5**)

To a solution of **4** (118.0 g, 0.34 mol) in EtOH (400 mL) $NaBH_4$ (65.0 g, 0.17 mol) was added at room temperature and the mixture was stirred for 4 h. The solution was quenched with water and 1 N HCl and concentrated under reduced pressure and the residue was diluted with EtOAc, washed thoroughly with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a crude residue. The residue was purified by column chromatography (n-Hexane : EtOAc (2:1) elution) to give **5** as a pale yellow oil. Yield: 78 %; ^{1}H-NMR ($CDCl_3$): δ = –0.11 (s, 6 H), 0.69 (s, 9 H), 1.64–1.68 (m, 1 H), 1.74–1.82 (m, 1 H), 3.28 (d, 2 H, *J* = 1.5 Hz), 3.36–3.43 (m, 1 H), 3.52–3.58 (m, 1 H), 3.89–3.91 (m, 1 H), 4.20 (s, 1 H), 4.38–4.43 (m, 2 H), 4.49–4.53 (m, 1 H), 4.99–5.14 (m, 2 H), 5.70–5.79 (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ = –4.83, 17.97, 25.77, 37.69, 55.71, 59.20, 65.17, 65.76, 70.04, 117.27, 132.96, 156.63; IR (KBr): 1746 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-tert-butyldimethylsilyloxy-2-methanesulfonyloxymethyl-pyrrolidine (**6**)

To a solution of **5** (68.0 g, 0.22 mol) and triethylamine (34.0 mL, 0.26 mol) in CH_2Cl_2 (200 mL) at 0 °C a solution of methanesulfonylchloride (MsCl) (20.0 mL, 0.26 mol) in CH_2Cl_2 (100 mL) was added dropwise. After stirring at 0 °C for 1 h, the mixture was quenched with water and separated. The residue was diluted with EtOAc, washed thoroughly with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a crude residue. The residue was purified by column chromatography (n-Hexane : EtOAc (2:1) elution) to give **6** as a pale yellow oil. Yield: 82 %; ^{1}H-NMR ($CDCl_3$): δ = 0.07 (s, 6 H), 0.86 (s, 9 H), 1.93–2.13 (m, 2 H), 2.99 (s, 3 H), 3.45 (d, 2 H, *J* = 1.5 Hz), 4.21–4.31 (m, 2 H), 4.40–4.43 (m, 1 H), 4.55–4.65 (m, 3 H), 5.20–5.33 (m, 2 H), 5.88–5.97 (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ = –4.59, 18.17, 25.92, 37.35, 38.35, 55.06, 55.50, 66.08, 70.12, 100.22, 118.11, 133.06, 155.69; IR (KBr): 1694 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-tert-butyldimethylsilyloxy-2-(pyrazol-1-ylmethyl)pyrrolidine (**7 a**)

To a solution of pyrazole (6.1 g, 15.5 μMol) in DMF (40 mL) at 0 °C NaH (60 % in oil, 0.87 g) was added and the mixture was stirred for 30 min at the same temperature. The mixture was added to a solution of **6** in DMF and stirred at 60–70 °C for 2 h. The mixture was quenched with ice water, then diluted with EtOAc, washed thoroughly with H_2O, dried over anhydrous $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (n-Hexane : EtOAc (5:1) elution) to give **7 a** as a pale yellow oil. Yield: 79 %; ^{1}H-NMR ($CDCl_3$): δ = 0.00 (s, 6 H), 0.82 (s, 9 H), 1.88–1.94 (m, 1 H), 2.04–2.17 (m, 1 H), 3.12–3.26 (m, 2 H), 3.62–3.70 (m, 1 H), 4.24–4.39 (m, 3 H), 5.22–5.35 (m, 2 H), 5.92–5.99 (m, 1 H), 6.26 (s, 1 H), 7.30 (s, 1 H), 7.49 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = –4.77, 18.10, 25.93, 37.59, 53.33, 54.82, 57.33, 66.01, 69.64, 106.18, 117.61, 130.36, 139.55; IR (KBr): 1704 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-hydroxy-2-(pyrazol-1-ylmethyl)pyrrolidine (**8 a**)

To a solution of **7 a** (3.4 g, 9.30 mmol) in THF (40 mL) added a solution of 1*M* tetrabutylammonium fluoride (TBAF) (14 ml, 13.95 mmol) in THF was slowly and then stirred for 2 h at room temperature. The mixture was diluted with EtOAc, washed thoroughly with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a crude residue. The residue was purified by column chromatography (EtOAc only for elution) to give **8 a** as a pale yellow oil. Yield: 92 %; ^{1}H-NMR ($CDCl_3$): δ = 1.68–1.79 (m, 1 H), 1.94–2.10 (m, 1 H), 3.11 (d, 1 H, *J* = 2.3 Hz), 3.15 (d, 1 H, *J* = 2.3 Hz), 3.41–3.45 (m, 1 H), 3.97–4.12 (m, 1 H), 4.30–4.40 (m, 3 H), 4.58–4.64 (m, 2 H), 5.23–5.36 (m, 2 H), 5.94–5.97 (m, 1 H), 6.25 (s, 1 H), 7.31 (s,

1 H), 1.47 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 20.00, 25.82, 52.91, 54.82, 57.09, 66.13, 69.48, 106.19, 117.71, 130.44, 139.53; IR (KBr): 3246 (OH), 1692 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-(pyrazol-1-ylmethyl)pyrrolidine (**9 a**)

A solution of **8 a** (3.1 g, 12.34 mmol) and triethylamine (1.8 mL, 13.57 mmol) in dry CH_2Cl_2 (30 mL) was cooled to –5 °C under nitrogen and treated with methanesulfonylchloride (1.05 mL, 13.57 mmol). The mixture was stirred at 0 °C for 1 h, diluted with EtOAc, and washed with cold water and brine. The organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* gave a crude residue, which was purified by silica gel column chromatography (n-Hexane : EtOAc (1:3) elution) to give **9 a** as a pale yellow oil. Yield: 87 %; ^{1}H-NMR ($CDCl_3$): δ = 2.47–2.52 (m, 3 H), 3.01 (s, 3 H), 3.15–3.19 (m, 1 H), 3.64–3.67 (m, 1 H), 4.36–4.41 (m, 3 H), 4.67–4.71 (m, 3 H), 5.26–5.37 (m, 2 H), 5.90–6.03 (m, 1 H), 6.29 (s, 1 H), 7.33 (s, 1 H), 7.52 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 29.93, 35.14, 38.74, 52.48, 52.80, 56.66, 66.42, 106.40, 118.10, 130.70, 139.97; IR (KBr): 1698 (C=O) cm^{-1}.

(2S,4S)-4-Acetylthio-1-allyloxycarbonyl-2-(pyrazol-1-ylmethyl)pyrrolidine (**10 a**)

A mixture of **9 a** (2.1 g, 6.38 mmol) and potassium thioacetate (2.2 g, 19.13 mmol) in DMF (20 mL) and toluene (20 mL) was stirred at 70 °C for 3 h under N_2 gas. After cooling, the reaction mixture was diluted with EtOAc, water and the aqueous layer was extracted with EtOAc. The combined solvent was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave a crude residue, which was purified by silica gel column chromatography (n-Hexane : EtOAc (1:1) elution) to give **10 a** as a pale yellow oil. Yield: 77 %; ^{1}H-NMR ($CDCl_3$): δ = 1.83–2.04 (m, 1 H), 2.29 (s, 3 H), 2.34–2.36 (m, 1 H), 2.81–2.92 (m, 1 H), 3.65–3.85 (m, 1 H), 3.90–4.08 (m, 1 H), 4.16–4.23 (m, 1 H), 4.47 (s, 2 H), 4.60 (d, 2 H, *J* = 2.6 Hz), 5.21–5.34 (m, 2 H), 5.87–5.98 (m, 1 H), 6.24 (s, 1 H), 7.32 (s, 1 H), 7.47 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 30.72, 33.79, 38.86, 52.52, 52.99, 57.99, 66.29, 106.16, 118.02, 130.18, 132.87, 139.63, 154.73; IR (KBr): 1696 (C=O) cm^{-1}.

Preparations of **7 b**–**j** were carried out by a method similar to that described for **7 a** from the appropriate starting materials.

(2S,4R)-1-Allyloxycarbonyl-4-tert-butyldimethylsilyloxy-2-(3-methylpyrazol-1-ylmethyl)pyrrolidine (**7 b**)

Yield: 81 %; ^{1}H-NMR ($CDCl_3$): δ = –0.08 (s, 6 H), 0.82 (s, 9 H), 1.80–1.87 (m, 1 H), 2.02–2.14 (m, 1 H), 2.20 (s, 3 H), 3.13–3.27 (m, 2 H), 3.53–3.60 (m, 1 H), 4.11–4.26 (m, 3 H), 4.58 (d, 2 H, *J* = 2.1 Hz), 5.15–5.29 (m, 2 H), 5.83–5.90 (m, 1 H), 5.95 (s, 1 H), 7.10 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = –4.80, 13.62, 17.96, 25.79, 38.19, 54.29, 54.43, 57.21, 65.71, 69.41, 105.59, 117.27, 130.86, 132.62, 148.26, 155.11; IR (KBr): 1710 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-tert-butyldimethylsilyloxy-2-(3,5-dimethylpyrazol-1-ylmethyl)pyrrolidine (**7 c**)

Yield: 80 %; ^{1}H-NMR ($CDCl_3$): δ = 0.00 (s, 6 H), 0.84 (s, 9 H), 1.84–1.92(m, 2 H), 2.21 (s, 6 H), 2.31–2.35 (m, 1 H), 3.23–3.33 (m, 2 H), 3.80–3.86 (m, 1 H), 4.15–4.23 (m, 3 H), 4.63 (d, 2 H, *J* = 2.4 Hz), 5.21–5.35 (m, 2 H), 5.80 (s, 1 H), 5.92–5.96 (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ = –4.5, 11.1, 13.9, 18.3, 26.1, 37.8, 50.8, 54.6, 57.5, 66.2, 70.0, 105.8, 117.8, 133.4, 140.0, 147.9, 155.7; IR (KBr): 1716 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-tert-butyldimethylsilyloxy-2-(imidazol-1-ylmethyl)pyrrolidine (**7 d**)

Yield: 80 %; ^{1}H-NMR ($CDCl_3$): δ = –0.13 (s, 6 H), 0.69 (s, 9 H), 1.55–1.61 (m, 1 H), 1.75–1.81 (m, 1 H), 3.03–3.08 (m, 1 H), 3.17–3.21 (m, 1 H), 3.65–3.67 (m, 1 H), 3.92–3.96 (m, 1 H), 4.07–4.11 (m, 1 H), 4.33–4.39 (m, 1 H), 4.52 (s, 2 H), 5.09–5.22 (m, 2 H), 5.78–5.85 (m, 1 H), 6.73 (s, 1 H), 6.91 (s, 1 H), 7.27 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = –5.09, 17.73, 25.39, 37.37, 48.15, 54.78, 56.40, 65.71, 69.16, 117.36, 129.45, 132.63, 137.52, 155.33; IR (KBr): 1698 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-tert-butyldimethylsilyloxy-2-(2-methylimidazol-1-ylmethyl)pyrrolidine (**7 e**)

Yield: 82 %; ^{1}H-NMR ($CDCl_3$): δ = –0.05 (s, 6 H), 0.77 (s, 9 H), 1.62–1.68 (m, 1 H), 1.81–1.89 (m, 1 H), 2.32 (s, 3 H), 3.18–3.41 (m, 2 H), 3.91–4.16 (m, 4 H), 4.53–4.57 (m, 2 H), 5.15–5.28 (m, 2 H), 5.84–5.93 (m, 1 H), 6.69 (s, 1 H), 6.83 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = –4.67, 13.22, 18.07, 25.84, 37.76, 47.69, 55.05, 57.12, 66.08, 69.69, 117.74, 120.09, 127.63, 132.98, 145.22, 155.71; IR (KBr): 1706 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-tert-butyldimethylsilyloxy-2-(2-isopropylimidazol-1-ylmethyl)pyrrolidine (**7 f**)

Yield: 79 %; ^{1}H-NMR ($CDCl_3$): δ = 0.03 (s, 6 H), 0.79 (s, 9 H), 1.24–1.30 (m, 6 H), 1.65–1.69 (m, 1 H), 1.83–1.89 (m, 1 H), 2.95–3.03 (m, 1 H), 3.23–3.28 (m, 2 H), 3.99–4.26 (m, 4 H), 4.59–4.62 (m, 2 H), 5.18–5.32 (m, 2 H), 5.87–5.96 (m, 1 H), 6.69 (s, 1 H), 6.92 (s, 1 H); ^{13}C- NMR ($CDCl_3$): δ = –4.66, 18.09, 22.21, 22.45, 35.52, 37.85, 47.15, 55.21, 57.18, 66.13, 69.75, 117.77, 119.47, 127.69, 133.00, 155.86, 155.83; IR (KBr): 1702 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-tert-butyldimethylsilyloxy-2-(4-nitroimidazol-1-ylmethyl)pyrrolidine (**7 g**)

Yield: 76 %; ^{1}H-NMR ($CDCl_3$): δ = 0.02 (s, 6 H), 0.84 (s, 9 H), 1.58–1.65 (m, 1 H), 1.93–1.96 (m, 1 H), 2.57 (s, 3 H), 3.23–3.28 (m, 1 H), 3.42–3.46 (m, 1 H), 4.04–4.07 (m, 1 H), 4.12–4.20 (m, 1 H), 4.25–4.30 (m, 2 H), 4.65 (d, 2 H, *J* = 2.6 Hz), 5.24–5.36 (m, 2 H), 5.91–5.97 (m, 1 H), 7.40 (s, 1 H), 9.95 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = –4.93, 13.32, 17.93, 25.69, 37.80, 46.91, 54.82, 56.58, 66.05, 69.57, 117.74, 126.72, 132.88, 138.27, 143.15, 153.39, 178.92; IR (KBr): 1696 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-tert-butyldimethylsilyloxy-2-(4-methyl-5-formylimidazol-1-yl-methyl)pyrrolidine (**7 h**)

Yield: 62 %; ^{1}H-NMR ($CDCl_3$): δ = –0.03 (s, 6 H), 0.78 (s, 9 H), 1.58–1.66 (m, 1 H), 1.98–2.00 (m, 1 H), 3.10–3.15 (m, 1 H), 3.40–3.58 (m, 1 H), 4.04–4.27 (m, 4 H), 4.58–4.63 (m, 3 H), 5.18–5.29 (m, 2 H), 5.83–5.94 (m, 1 H), 7.35 (s, 1 H), 7.73 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = –4.70, 18.05, 25.79, 37.89, 49.68, 55.74, 56.65, 66.32, 69.57, 118.05, 120.49, 132.75, 137.09, 148.31, 156.05; IR (KBr): 1696 (C=O), 1546(C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-tert-butyldimethylsilyloxy-2-(1,2,4-triazol-1-ylmethyl)pyrrolidine (**7 i**)

Yield: 77 %; ^{1}H-NMR ($CDCl_3$): δ = 0.01 (s, 6 H), 0.81 (s, 9 H), 1.94–2.00 (m, 2 H), 3.08–3.12 (m, 1 H), 3.31–3.36 (m, 1 H), 3.83–3.85 (m, 1 H), 4.35–4.36 (m, 1 H), 4.63–4.66 (m, 3 H), 4.83–4.88 (m, 1 H), 5.19–5.33 (m, 2 H), 5.89–5.98 (m, 1 H), 7.58 (s, 1 H), 7.68 (s, 1 H); ^{13}C-NMR ($CDCl_3$) : δ = –5.01, 17.86, 25.67, 37.50, 50.97, 55.02, 56.49, 65.84, 69.43, 117.40, 124.79, 132.87, 133.72, 155.43; IR (KBr): 1704 (C=O) cm^{-1}.

*(2S,4R)-1-Allyloxycarbonyl-4-tert-butyldimethylsilyloxy-2-(1,2,3-tirazol-1-ylmethyl)pyrrolidine (***7 j**)

RLD.5Yield: 69 %; ^{1}H-NMR ($CDCl_3$): δ = 0.00 (s, 6 H), 0.83 (s, 9 H), 1.94–1.99 (m, 2 H), 3.04–3.09 (m, 1 H), 3.33–3.36 (m, 1 H), 3.86–3.88 (m, 1 H), 4.32–4.34 (m, 1 H), 4.63–4.68 (m, 3 H), 4.86–4.91 (m, 1 H), 5.22–5.34 (m, 2 H), 5.91–5.98 (m, 1 H), 7.51 (s, 1 H), 7.70 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = –4.80, 18.12, 25.88, 37.76, 51.17, 55.35, 56.73, 66.16, 69.62, 117.79, 124.83, 133.00, 134.08, 155.75; IR (KBr): 1704 (C=O) cm^{-1}.

Preparations of **8 b**–**j** were carried out by a method similar to that described for **8 a** from the appropriate starting materials.

(2S,4R)-1-Allyloxycarbonyl-4-hydroxy-2-(3-methylpyrazol-1-ylmethyl)pyrrolidine (**8 b**)

Yield: 92 %; ^{1}H-NMR ($CDCl_3$): δ = 1.95–2.00 (m, 2 H), 2.23 (s, 3 H), 3.17 (dd, 1 H, *J* = 2.3 Hz, *J* = 2.3 Hz), 3.33–3.56 (m, 2 H), 4.04–4.27 (m, 3 H), 4.63 (s, 2 H), 5.22–5.35 (m, 2 H), 5.91–5.97 (m, 1 H), 6.00 (s, 1 H), 7.19 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 13.64, 37.27, 53.46, 54.74, 57.21, 66.08, 69.01, 105.87, 117.66, 131.20, 138.69, 148.51, 155.41; IR (KBr): 3418 (OH), 1704 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-hydroxy-2-(3,5-dimethylpyrazol-1-ylmethyl)pyrrolidine (**8 c**)

Yield: 93 %; ^{1}H-NMR ($CDCl_3$): δ = 1.80–1.85 (m, 1 H), 2.06 (s, 3 H), 2.09 (s, 1 H), 2.15 (s, 2 H), 2.14–2.22 (m, 1 H), 3.21–3.29 (m, 2 H), 3.93–3.99 (m, 2 H), 4.00–4.28 (m, 3 H), 4.50 (d, 2 H, *J* = 2.4 Hz), 5.10–5.25 (m, 2 H), 5.69 (s, 1 H), 5.80–5.85 (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 14.92, 17.44, 41.37, 54.45, 58.41, 61.06, 70.03, 72.84, 109.69, 121.60, 137.03, 144.08, 151.59, 159.57; IR (KBr): 3398 (OH), 1694 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-hydroxy-2-(imidazol-1-ylmethyl)pyrrolidine (**8 d**)

Yield: 93 %; mp: 85 °C; ^{1}H-NMR ($CDCl_3$): δ = 1.53–1.59 (m, 1 H), 1.82–1.86 (m, 1 H), 3.02–3.07 (m, 1 H), 3.30–3.38 (m, 1 H), 3.82–3.86 (m, 1 H), 3.97–4.01 (m, 1 H), 4.08–4.12 (m, 1 H), 4.23–4.29 (m, 1 H), 4.46 (s, 2 H), 5.05–5.19 (m, 2 H), 5.74–5.83 (m, 1 H), 6.72 (s, 1 H), 6.80 (s, 1 H), 7.23 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 37.19, 48.46, 55.05, 56.84, 66.00, 68.13, 117.63, 120.36, 128.76, 132.70, 137.65, 155.51; IR (KBr): 3376(OH), 1692 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-hydroxy-2-(2-methylimidazol-1-ylmethyl)pyrrolidine (**8 e**)

Yield: 92 %; ^{1}H-NMR ($CDCl_3$): δ = 1.69–1.77 (m, 1 H), 2.00–2.04 (m, 1 H), 2.33 (s, 3 H), 3.31–3.36 (m, 1 H), 3.47–3.58 (m, 1 H), 3.94–4.25 (m, 5 H), 4.60–4.63 (m, 2 H), 5.22–5.36 (m, 2 H), 5.88–6.01 (m, 1 H), 6.74 (s, 1 H), 6.82 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 12.96, 37.66, 48.02, 55.05, 57.14, 66.23, 68.53, 117.88, 120.28, 126.90, 132.96, 145.19, 155.76; IR (KBr): 3142 (OH), 1694 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-hydroxy-2-(2-isopropylimidazol-1-ylmethyl)pyrrolidine (**8 f**)

Yield: 91 %; ^{1}H-NMR ($CDCl_3$): δ = 1.02–1.08 (m, 1 H), 1.54–1.61 (m, 1 H), 1.70–1.82 (m, 1 H), 2.81–2.90 (m, 1 H), 3.14–3.16 (m, 1 H), 3.32–3.43 (m, 1 H), 3.70–3.78 (m, 1 H), 4.01–4.16 (m, 3 H), 4.40–4.43 (m, 2 H), 4.99–5.15 (m, 2 H), 5.67–5.78 (m, 1 H), 6.54 (s, 1 H), 6.63 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 22.28, 25.54, 37.50, 47.28, 55.05, 57.07, 65.95, 68.07, 117.56, 119.52, 126.69, 132.83, 153.67, 155.64; IR (KBr): 3346 (OH), 1666 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-hydroxy-2-(4-nitroimidazol-1-ylmethyl)pyrrolidine (**8 g**)

Yield: 90 %; ^{1}H-NMR ($CDCl_3$): δ = 1.58–1.61 (m, 1 H), 1.87–1.89 (m, 1 H), 2.31 (s, 3 H), 3.10–3.21(m, 1 H), 3.33–3.46 (m, 1 H), 4.06–4.15 (m, 3 H), 4.39–4.44 (m, 3 H), 5.05–5.18 (m, 2 H), 5.71–5.78 (m, 1 H), 7.37 (s, 1 H), 9.68 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 13.23, 37.48, 46.52, 54.98, 55.92, 66.18, 68.44, 117.82, 126.78, 132.70, 138.62, 142.99, 153.10, 179.18; IR (KBr): 3390 (OH), 1680 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-hydroxy-2-(4-methyl-5-formylimidazol-1-ylmethyl)pyrrolidine (**8 h**)

Yield: 88 %; ^{1}H-NMR (DMSO-d_6): δ = 1.70–1.89 (m, 2 H), 3.17–3.22 (m, 1 H), 3.31–3.39 (m, 1 H), 4.02–4.09 (m, 1 H), 4.14–4.28 (m, 3 H), 4.33–4.53 (m, 2 H), 5.00 (s, 1 H), 5.10–5.30 (m, 2 H), 5.30–5.94 (m, 1 H), 7.74 (s, 1 H), 8.29 (s, 1 H); ^{13}C-NMR (DMSO-d_6): δ = 37.17, 49.95, 55.26, 56.79, 65.72, 68.38, 117.52, 122.84, 134.08, 138.46, 147.68, 155.41; IR (KBr): 3360 (OH), 1670 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-hydroxy-2-(1,2,4-triazol-1-ylmethyl)pyrrolidine (**8 i**)

Yield: 91 %; ^{1}H-NMR ($CDCl_3$): δ = 1.83–1.86 (m, 2 H), 2.91–2.95 (m, 1 H), 3.27–3.41 (m, 1 H), 3.85–3.91 (m, 1 H), 4.11–4.25 (m, 2 H), 4.39–4.50 (m, 3 H), 5.01–5.13 (m, 2 H), 5.67–5.78 (m, 1 H), 7.71 (s, 1 H), 7.90 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 33.54, 41.34, 59.10, 60.29, 70.07, 72.55, 121.71, 136.72, 148.06, 155.56, 159.50; IR (KBr): 3410 (OH), 1694 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-hydroxy-2-(1,2,3-tirazol-1-ylmethyl)pyrrolidine (**8 j**)

Yield: 90 %; ^{1}H-NMR ($CDCl_3$): δ = 1.84–1.92 (m, 2 H), 2.96–3.01 (m, 1 H), 3.34–3.37 (m, 1 H), 3.92–3.96 (m, 1 H), 4.20–4.22 (m, 1 H), 4.47–4.55 (m, 3 H), 4.66–4.68 (m, 1 H), 5.07–5.19 (m, 2 H), 5.77–5.81 (m, 1 H), 7.44 (s, 1 H), 7.53 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 37.02, 50.90, 54.79, 56.30, 65.89, 68.37, 117.50, 124.68, 132.40, 133.59, 155.36; IR (KBr): 3394 (OH), 1692 (C=O) cm^{-1}.

Preparations of **9 b**–**j** were carried out by a method similar to that described for **9 a** from the appropriate starting materials.

(2S,4R)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-(3-methylpyrazol-1-ylmethyl)pyrrolidine (**9 b**)

Yield: 90 %; ^{1}H-NMR ($CDCl_3$): δ = 2.20 (s, 3 H), 2.21–2.53 (m, 2 H), 2.94 (s, 3 H), 3.14–3.17 (m, 1 H), 3.34–3.87 (m, 1 H), 4.20–4.39 (m, 3 H), 4.51–4.84 (m, 3 H), 5.18–5.34 (m, 2 H), 5.86–5.95 (m, 1 H), 5.99 (s, 1 H), 7.14 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 13.70, 35.02, 38.60, 52.54, 52.65, 56.64, 66.37, 78.44, 105.95, 117.95, 131.14, 139.08, 149.04, 154.78; IR (KBr): 3418 (OH), 1698 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-(3,5-dimethylpyrazol-1-ylmethyl)pyrrolidine (**9 c**)

Yield: 91 %; ^{1}H-NMR ($CDCl_3$): δ = 2.08 (s, 6 H), 2.02–2.04 (m, 1 H), 2.39–2.48 (m, 1 H), 2.84 (s, 3 H), 3.20–3.26 (m, 1 H), 3.56–3.68 (m, 1 H), 3.87–4.11 (m, 4 H), 4.44–4.48 (m, 2 H), 4.63–4.70 (m, 1 H), 5.05–5.22 (m, 2 H), 5.64 (s, 1 H), 5.73–5.82 (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 10.57, 13.21, 34.98, 38.14, 49.56, 52.07, 56.45, 65.87, 78.22, 105.55, 117.57, 132.61, 139.68, 147.57, 154.55; IR (KBr): 3412 (OH), 1694 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-(imidazol-1-ylmethyl)pyrrolidine (**9 d**)

Yield: 90 %; ^{1}H-NMR ($CDCl_3$): δ = 1.80–1.88 (m, 1 H), 2.26–2.31 (m, 1 H), 2.94 (s, 3 H), 3.17–3.24 (m, 1 H), 3.76–3.80 (m,

1 H), 4.06–4.10 (m, 1 H), 4.23–4.27 (m, 1 H), 4.47–4.53 (m, 1 H), 4.61 (s, 2 H), 4.78–4.83 (m, 1 H), 5.19–5.31 (m, 2 H), 5.83–5.93 (m, 1 H), 6.80 (s, 1 H), 7.00 (s, 1 H), 7.37 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 35.15, 38.71, 47.77, 52.99, 56.47, 66.52, 77.89, 118.31, 120.23, 129.79, 132.59, 138.07, 155.03; IR (KBr): 1698 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-(2-methylimidazol-1-ylmethyl)pyrrolidine (**9 e**)

Yield: 89 %; ^{1}H-NMR ($CDCl_3$): δ = 1.77–1.83 (m, 1 H), 2.20–2.27 (m, 4 H), 2.88 (s, 3 H), 3.25–3.31 (m, 1 H), 3.73–4.15 (m, 3 H), 4.51–4.53 (m, 2 H), 4.82–4.88 (m, 1 H), 5.11–5.24 (m, 2 H), 5.76–5.87 (m, 1 H), 6.65 (s, 1 H), 6.76 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 13.20, 35.38, 38.63, 47.12, 52.88, 56.65, 66.40, 78.03, 118.15, 120.01, 127.82, 132.59, 145.26, 155.04; IR (KBr): 1698 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-(2-isopropylimidazol-1-ylmethyl)pyrrolidine (**9 f**)

Yield: 88 %; ^{1}H-NMR ($CDCl_3$): δ = 1.03–1.13 (m, 6 H), 1.71–1.79 (m, 1 H), 2.12–2.16 (m, 1 H), 2.79 (s, 3 H), 3.20–3.24 (m, 1 H), 3.64–3.80 (m, 1 H), 3.94–4.15 (m, 3 H), 4.40–4.45 (m, 2 H), 4.76–4.83 (m, 1 H), 5.01–5.14 (m, 2 H), 5.68–5.77 (m, 1 H), 6.53 (s, 1 H), 6.70 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 22.44, 25.64, 35.46, 38.55, 46.56, 52.88, 56.70, 66.31, 78.16, 118.02, 119.34, 127.67, 132.59, 153.80, 155.00; IR (KBr): 1694 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-(4-nitroimidazol-1-ylmethyl)pyrrolidine (**9 g**)

Yield: 89 %; ^{1}H-NMR ($CDCl_3$): δ = 1.74–1.95 (m, 1 H), 2.39–2.47 (m, 1 H), 2.51 (s, 3 H), 3.02 (s, 3 H), 3.37–3.44 (m, 1 H), 3.86–3.94 (m, 1 H), 4.32 (bs, 2 H), 4.51–4.79 (m, 3 H), 5.25–5.37 (m, 2 H), 5.91–5.94 (m, 1 H), 7.40 (s, 1 H), 9.83 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 13.38, 25.71, 38.61, 46.77, 52.98, 56.16, 66.29, 78.27, 118.15, 126.75, 132.48, 138.46, 143.28, 155.20, 179.21; IR (KBr): 1694 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-(4-methyl-5-formylimidazol-1-ylmethyl)pyrrolidine (**9 h**)

Yield: 86 %; ^{1}H-NMR ($CDCl_3$): δ = 1.93–2.01 (m, 1 H), 2.45–2.49 (m, 1 H), 3.02 (s, 3 H), 3.36 (dd, 1 H, *J* = 3.6Hz, *J* = 3.3 Hz), 3.89–4.07 (m, 1 H), 4.27–4.34 (m, 2 H), 4.60–4.65 (m, 3 H), 5.08 (s, 1 H), 5.24–5.33 (m, 2 H), 5.87–5.97 (m, 1 H), 7.41 (s, 1 H), 7.80 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 35.51, 38.87, 49.10, 53.37, 56.31, 66.79, 77.92, 118.60, 120.67, 132.40, 137.17, 148.39, 155.35; IR (KBr): 1698 (C=O), 1545(C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-(1,2,4-triazol-1-ylmethyl)pyrrolidine (**9 i**)

Yield: 88 %; ^{1}H-NMR ($CDCl_3$): δ = 2.26–2.28 (m, 2 H), 2.89 (s, 3 H), 3.04–3.10 (m, 1 H), 3.66–3.92 (m, 1 H), 4.18–4.32 (m, 3 H), 4.47–4.49 (m, 2 H), 4.86 (s, 1 H), 5.08–5.19 (m, 2 H), 5.86–5.94 (m, 1 H), 7.77 (s, 1 H), 7.93 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 35.43, 38.65, 49.74, 53.04, 55.94, 66.32, 78.36, 118.00, 132.61, 144.61, 152.05, 154.85; IR (KBr): 1698 (C=O) cm^{-1}.

(2S,4R)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-(1,2,3-tirazol-1-ylmethyl)pyrrolidine (**9 j**)

Yield: 86 %; mp: 97 °C; ^{1}H-NMR ($CDCl_3$): δ = 2.09–2.18 (m, 1 H), 2.24–2.31 (m, 1 H), 2.91 (s, 3 H), 3.03–3.08 (m, 1 H), 3.69–3.79 (m, 1 H), 4.24–4.28 (m, 1 H), 4.52–4.59 (m, 3 H), 4.76–4.80 (m, 2 H), 5.10–5.21 (m, 2 H), 5.77–5.86 (m, 1 H), 7.45 (s, 1 H), 7.57 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 35.23, 38.58, 50.42, 53.07, 56.02, 66.35, 78.44, 118.03, 125.23, 132.64, 134.03, 154.91; IR (KBr): 1698 (C=O) cm^{-1}.

Preparations of **10 b**–**j** were carried out by a method similar to that described for **10 a** from the appropriate starting materials.

(2S,4S)-4-Acetylthio-1-allyloxycarbonyl-2-(3-methylpyrazol-1-ylmethyl)pyrrolidine (**10 b**)

Yield: 87 %; ^{1}H-NMR ($CDCl_3$): δ = 1.86–2.06 (m, 1 H), 2.17–2.28 (m, 7 H), 3.74–2.83 (m, 1 H), 3.96–3.99 (m, 3 H), 4.07 (s, 2 H), 4.55 (d, 2 H, *J* = 1.8 Hz), 5.17–5.30 (m, 2 H), 5.80–5.92 (m, 1 H), 5.95 (s, 1 H), 7.16 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 13.69, 30.53, 33.76, 38.79, 52.72, 57.85, 66.21, 105.61, 117.90, 130.91, 138.80, 148.57, 154.61, 195.24; IR (KBr): 1743 (C=O) cm^{-1}.

(2S,4S)-4-Acetylthio-1-allyloxycarbonyl-2-(3,5-dimethylpyrazol-1-ylmethyl)pyrrolidine (**10 c**)

Yield: 83 %; ^{1}H-NMR ($CDCl_3$): δ = 1.90–2.75 (m, 11 H), 2.97–3.00 (m, 1 H), 3.74–2.79 (m, 1 H), 3.97–4.00 (m, 3 H), 4.40–4.44 (m, 1 H), 4.51 (d, 2 H, *J* = 2.7 Hz), 5.12–5.26 (m, 2 H), 5.69 (s, 1 H), 5.80–5.86 (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 10.80, 13.35, 30.46, 33.89, 39.04, 50.34, 52.55, 65.95, 105.06, 117.69, 132.51, 139.41, 147.44, 154.62, 195.06; IR (KBr): 1694 (C=O) cm^{-1}.

(2S,4S)-4-Acetylthio-1-allyloxycarbonyl-2-(imidazol-1-ylmethyl)-pyrrolidine (**10d**)

Yield: 83 %; ^{1}H-NMR ($CDCl_3$): δ = 1.51–1.55 (m, 1 H), 2.22 (s, 3 H), 2.27–2.31 (m, 1 H), 2.83–2.89 (m, 1 H), 3.71–3.76 (m, 1 H), 3.89–3.94 (m, 1 H), 4.05–4.07 (m, 1 H), 4.18–4.21 (m, 2 H), 4.52 (d, 2 H, *J* = 2.4 Hz), 5.13–5.25 (m, 2 H), 5.80–5.89 (m, 1 H), 6.79 (s, 1 H), 6.95 (s, 1 H), 7.34 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 30.70, 33.99, 38.74, 48.22, 52.54, 57.78, 66.39, 118.21, 119.99, 129.92, 132.67, 137.86, 154.82, 194.82; IR (KBr): 1695 (C=O) cm^{-1}.

(2S,4S)-4-Acetylthio-1-allyloxycarbonyl-2-(2-methylimidazol-1-ylmethyl)pyrrolidine (**10 e**)

Yield: 82 %; ^{1}H-NMR ($CDCl_3$): δ = 1.66–1.72 (m, 1 H), 2.42 (s, 3 H), 2.43–2.62 (m, 4 H), 3.13–3.19 (m, 1 H), 3.87–4.39 (m, 5 H), 4.61 (d, 2 H, *J* = 2.9 Hz), 5.23–5.35 (m, 2 H), 5.89–5.98 (m, 1 H), 6.77 (s, 1 H), 6.90 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 13.38, 30.87, 34.28, 39.44, 47.91, 52.91, 57.98, 66.55, 118.32, 119.93, 127.79, 132.70, 145.35, 155.12, 194.87; IR (KBr): 1696 (C=O) cm^{-1}.

(2S,4S)-4-Acetylthio-1-allyloxycarbonyl-2-(2-isopropylimidazol-1-ylmethyl)pyrrolidine (**10 f**)

Yield: 80 %; ^{1}H-NMR ($CDCl_3$): δ = 1.17–1.26 (m, 6 H), 1.60–1.66 (m, 1 H), 2.26 (s, 3 H), 2.27–2.38 (m, 4 H), 2.95–3.13 (m, 1 H), 3.79–4.07 (m, 4 H), 4.53 (d, 2 H, *J* = 2.6 Hz), 5.15–5.26 (m, 2 H), 5.80–5.92 (m, 1 H), 6.67 (s, 1 H), 6.86 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 22.23, 25.77, 30.78, 34.26, 39.33, 47.30, 52.80, 58.06, 66.39, 118.13, 119.25, 127.71, 132.66, 153.73, 155.01, 194.67; IR (KBr): 1696 (C=O) cm^{-1}.

(2S,4S)-4-Acetylthio-1-allyloxycarbonyl-2-(4-nitroimidazol-1-ylmethyl)pyrrolidine (**10 g**)

Yield: 82 %; ^{1}H-NMR ($CDCl_3$): δ = 1.63–1.77 (m, 2 H), 2.37 (s, 3 H), 2.52 (s, 3 H), 3.22–3.24 (m, 1 H), 3.77–3.96 (m, 1 H), 4.06–4.10 (m, 2 H), 4.26–4.28 (m, 1 H), 4.41–4.45 (m, 2 H), 5.23–5.37 (m, 2 H), 5.86–5.97 (m, 1 H), 7.44 (s, 1 H), 9.95 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 13.49, 30.75, 34.39, 38.87, 46.54, 52.44, 57.44, 66.53, 118.20, 126.87, 132.67, 138.09, 143.04, 153.62, 179.05, 194.95; IR (KBr): 1692 (C=O) cm^{-1}.

(2S,4S)-4-Acetylthio-1-allyloxycarbonyl-2-(4-methyl-5-formylimidazol-1-ylmeth-yl)pyrrolidine (**10 h**)

Yield: 80 %; ^{1}H-NMR ($CDCl_3$): δ = 1.61–1.76 (m, 1 H), 2.34 (s, 3 H), 2.51–2.56 (m, 1 H), 3.05–3.07 (m, 1 H), 3.86–3.93 (m, 1 H), 4.02–4.06 (m, 1 H), 4.18–4.22 (m, 1 H), 4.31–4.42 (m,

2 H), 4.60–4.63 (m, 2 H), 5.25–5.35 (m, 2 H), 5.88–5.93 (m, 1 H), 7.41 (s, 1 H), 7.75 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 30.62, 34.23, 38.61, 49.74, 52.38, 57.47, 66.32, 117.95, 120.77, 132.51, 137.06, 148.07, 154.85, 194.64; IR (KBr): 1694 (C=O) cm^{-1}.

(2S,4S)-4-Acetylthio-1-allyloxycarbonyl-2-(1,2,4-triazol-1-ylmethyl)pyrrolidine (**10i**)

Yield: 80 %; ^{1}H-NMR ($CDCl_3$): δ = 1.95–2.00 (m, 1 H), 2.26 (m, 1 H), 2.38–2.44 (m, 1 H), 2.82–2.84 (m, 1 H), 3.77–3.80 (m, 1 H), 3.95–3.99 (m, 1 H), 4.12–4.14 (m, 1 H), 4.43–4.58 (m, 2 H), 5.17–5.28 (m, 2 H), 5.82–5.91 (m, 1 H), 7.87 (s, 1 H), 7.99 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 30.74, 34.10, 38.73, 50.44, 52.52, 57.43, 66.47, 118.26, 132.62, 144.22, 152.10, 154.90, 195.04; IR (KBr): 1694 (C=O) cm^{-1}.

(2S,4S)-4-Acetylthio-1-allyloxycarbonyl-2-(1,2,3-triazol-1-ylmethyl)pyrrolidine (**10j**)

Yield: 79 %; ^{1}H-NMR ($CDCl_3$): δ = 1.72–1.76 (m, 1 H), 2.17 (s, 3 H), 2.29–2.32 (m, 1 H), 2.72–2.75 (m, 1 H), 3.66–3.71 (m, 1 H), 4.10–4.14 (m, 1 H), 4.47 (d, 2 H, *J* = 2.6 Hz), 4.59–4.63 (m, 2 H), 5.75–5.81 (m, 1 H), 7.45 (s, 1 H), 7.56 (s, 1 H); ^{13}C-NMR ($CDCl_3$): δ = 30.67, 33.79, 38.57, 50.94, 52.43, 57.36, 66.29, 118.05, 124.41, 132.66, 134.05, 154.75, 194.96; IR (KBr): 1696 (C=O) cm^{-1}.

Allyl (4R,5S,6S)-3-[(2S,4S)-1-allyloxycarbonyl-2-(imidazoliomethyl)pyrrolidine-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**13a**)

A solution of Allyl (4*R*,5*S*,6*S*)-3-(diphenylphosphoryloxy)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2carboxylate (**12**, 0.38 g, 0.68 mmol) in CH_3CN (10 mL) was cooled to 0 ¡É under N2. To this solution diisopropylethylamine (0.12 g, 0.68 mmol) and a solution of the mercapto compound **11a** (0.21 g, 0.68 mmol) in CH_3CN (5 mL) was added. After stirring for 2 hours, the mixture was diluted with EtOAc, washed with 10 % $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. Evaporation *in vacuo* yielded a foam, which was purified by silica gel chromatography to give **13a** as a yellow foam solid. Yield: 76 %; ^{1}H-NMR ($CDCl_3$): δ = 1.16 (d, 3 H, *J* = 3.6 Hz), 1.28 (d, 3 H, *J* = 3.2 Hz), 1.60–1.63 (m, 1 H), 2.34–2.39 (m, 1 H), 3.11–3.19 (m, 2 H), 3.54–3.59 (m, 1 H), 3.89–3.92 (m, 1 H) 4.02–4.39 (m, 5 H), 4.57–4.64 (m, 4 H), 4.72–4.78 (m, 1 H), 5.17–5.40 (m, 4 H), 5.41–5.94 (m, 2 H), 6.87 (s, 1 H), 7.00 (s, 1 H), 7.45 (s, 1 H); IR (KBr): 3306 (OH), 1694 (C=O) cm^{-1}.

(4R,5S,6S)-6-[(1R)-hydroxyethyl]-4-methyl-3-[(2S,4S)-2-imidazoliomethyl]pyrrolidine-4-yl]thio-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (**14a**)

Compound **13a** (0.31 g, 0.16 mmol) and 0.19 g of $Pd(OH)_2$/C (20 %) were dissolved in THF/phosphate buffer (pH = 7) (1 : 1, 10 mL each). The mixture was hydrogenated at 45 psi for 2 h. The solution was filtered through celite and washed with water. The combined filtrate was washed with ethyl ether and lyophilized to give a yellow powder which was purified on a Diaion HP-20 column, eluted with 2 % THF in water. Fractions having UV absorption at 298 nm were collected and lyophilized again to give the title compound **14a** as a white powder.

Yield: 47 %; UV λ_{max}: 298 nm; mp: 133–134 oC (dec.); ^{1}H-NMR (D_2): δ = 1.03 (d, 3 H, *J* = 4.1 Hz), 1.10 (d, 3 H, *J* = 8.0 Hz), 1.58–1.68 (m, 1 H), 2.59–2.69 (m, 1 H), 2.91–2.93 (m, 1 H), 3.15–3.33 (m, 2 H), 3.50–3.60 (m, 1 H), 3.85–4.02 (m, 1 H), 4.05–4.09 (m, 2 H), 4.30 (bs, 1 H), 4.39–4.48 (m, 2 H), 6.27 (s, 1 H), 7.52 (s, 1 H), 7.60 (s, 1 H); IR (KBr): 3350 (OH), 1675 (C=O) cm^{-1}.

14b: Yield: 55 %; UV λ_{max}: 298 nm; mp: 122–126 °C (dec.); ^{1}H-NMR (D_2): δ = 1.05 (d, 3 H, *J* = 3.6 Hz), 1.13 (d, 3 H, *J* = 3.5 Hz), 1.55–1.63 (m, 1 H), 2.10 (s, 3 H), 2.58–2.63 (m, 1 H), 3.17–3.32 (m, 3 H), 3.53–3.60 (m, 1 H), 3.88–3.91 (m, 1 H), 3.98–4.11 (m, 3 H), 4.34–4.38 (m, 2 H), 6.06 (s, 1 H), 7.47 (s, 1 H); IR (KBr): 3320 (OH), 1690 (C=O) cm^{-1}.

14c: Yield: 52 %; UV λ_{max}: 298, 310 nm; mp: 131–134 °C (dec.); ^{1}H-NMR (D_2): δ = 1.17 (d, 3 H, *J* = 3.2 Hz), 1.26 (d, 3 H, *J* = 3.2 Hz), 1.51–1.55 (m, 1 H), 2.15 (s, 3 H), 2.24 (s, 3 H), 2.55–2.59 (m, 1 H), 3.17–3.21 (m, 1 H), 3.30–3.34 (m, 1 H), 3.41–3.47 (m, 2 H), 3.80–3.88 (m, 2 H), 4.16–4.27 (m, 4 H), 5.96 (s, 1 H); IR (KBr): 3360 (OH), 1692 (C=O) cm^{-1}.

14d: Yield: 51 %; UV λ_{max}: 298 nm; mp: 140–143 °C (dec.); ^{1}H-NMR (D_2): δ = 0.99 (d, 3 H, *J* = 3.5 Hz), 1.08 (d, 3 H, *J* = 3.2 Hz), 1.46–1.55 (m, 3 H), 2.45–2.55 (m, 1 H), 3.06–3.25 (m, 2 H), 3.35–3.41 (m, 1 H), 3.77–3.85 (m, 2 H), 3.99–4.07 (m, 2 H), 4.24–4.31 (m, 2 H), 7.04 (s, 1 H), 7.18 (s, 1 H), 7.99 (s, 1 H); IR (KBr): 3326 (OH), 1690 (C=O) cm^{-1}.

14e: Yield: 47 %; UV λ_{max}: 298 nm; mp: 150–152 °C (dec.); ^{1}H-NMR (D_2): δ = 1.08 (d, 3 H, *J* = 3.3 Hz), 1.15 (d, 3 H, *J* = 3.3 Hz), 2.52 (s, 3 H), 2.59–2.66 (m, 1 H), 3.21–3.33 (m, 2 H), 3.46–3.61 (m, 4 H), 3.88–3.94 (m, 2 H), 4.07–4.12 (m, 2 H), 4.36–4.43 (m, 2 H), 7.22 (s, 1 H), 7.32 (s, 1 H); IR (KBr): 3426 (OH), 1694 (C=O) cm^{-1}.

14f: Yield: 46 %; UV λ_{max}: 298 nm; mp: 162–165 °C (dec.); ^{1}H-NMR (D_2): δ = 1.11–1.38 (m, 12 H), 1.83–1.89 (m, 1 H), 2.80–2.84 (m, 1 H), 3.01–3.04 (m, 1 H), 3.30–3.49 (m, 3 H), 3.63–3.74 (m, 1 H), 3.86–3.93 (m, 1 H), 3.99–4.22 (m, 3 H), 4.65 (d, 2 H, *J* = 3.0 Hz), 7.41 (s, 1 H), 7.46 (s, 1 H); IR (KBr): 3360 (OH), 1691 (C=O) cm^{-1}.

14g: Yield: 48 %; UV λ_{max}: 299 nm; mp: 170–174 °C (dec.); ^{1}H-NMR (D_2): δ = 1.06 (d, 3 H, *J* = 3.5 Hz), 1.09 (d, 3 H, *J* = 3.2 Hz), 1.52–1.73 (m, 1 H), 2.50 (s, 3 H), 2.59–2.70 (m, 1 H), 3.24–3.33 (m, 2 H), 3.72–3.77 (m, 1 H), 4.01–4.10 (m, 4 H), 4.45 (d, 2 H, *J* = 3.0 Hz), 8.51 (s, 1 H), 9.75 (s, 1 H); IR (KBr): 3346 (OH), 1690 (C=O), 1667 (C=O) cm^{-1}.

14h: Yield: 37 %; UV λ_{max}: 298 nm; mp : 142–145 °C (dec.); ^{1}H-NMR (D_2): δ = 1.06 (d, 3 H, *J* = 3.5 Hz), 1.14 (d, 3 H, *J* = 2.9 Hz), 1.34–1.59 (m, 1 H), 2.46–2.58 (m, 1 H), 3.14–3.29 (m, 3 H), 3.51–3.54 (m, 3 H), 3.64–3.74 (m, 1 H), 4.08–4.11 (m, 3 H), 7.28 (s, 1 H), 7.99 (s, 1 H); IR (KBr): 3365 (OH), 1690 (C=O) cm^{-1}.

14i: Yield: 38 %; UV λ_{max}: 298 nm; mp: 142–145 °C (dec.); ^{1}H-NMR (D_2): δ = 0.99 (d, 3 H, *J* = 3.6 Hz), 1.07 (d, 3 H, *J* = 4.1 Hz), 1.50–1.73 (m, 1 H), 2.45–2.66 (m, 1 H), 2.89–2.93 (m, 1 H), 3.16–3.25 (m, 2 H), 3.47–3.57 (m, 2 H), 3.86–3.95 (m, 2 H), 4.05–4.07 (m, 2 H), 4.32–4.36 (m, 1 H), 7.66 (s, 1 H), 7.91 (s, 1 H); IR (KBr): 3400 (OH), 1670 (C=O) cm^{-1}.

14j: Yield: 32 %; UV λ_{max}: 298 nm; mp: 136–138 °C (dec.); ^{1}H-NMR (D_2): δ = 0.94 (d, 3 H, *J* = 3.6 Hz), 1.06 (d, 3 H, *J* = 3.2 Hz), 1.31–1.35 (m, 1 H), 2.34–2.45 (m, 1 H), 2.77–2.89 (m, 1 H), 3.08–3.20 (m, 2 H), 3.32–3.50 (m, 2 H), 3.78–3.88 (m, 2 H), 3.98–4.12 (m, 3 H), 8.55 (s, 1 H), 9.44 (s, 1 H); IR (KBr): 3440 (OH), 1640 (C=O) cm^{-1}.

References

[1] W. J. Leanza, K. J. Wildonger, T. W. Miller, B. G. Christensen, *J. Med. Chem.* **1979**, *22*, 1435–1436.

[2] D. H. Shih, F. Baker, L. Cama, B. G. Christensen, *Heterocycles*, **1984**, *21*, 29–40.

[3] G. Albers-Schonberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogstein, B. G. Christensen, *J. Am. Chem. Soc.* **1978**, *100*, 6491–6499.

[4] K. M. J. Brands, R. B. Jobson, K. M. Conrad, J. M. Williams, B. Pipik, M. Cameron, A. J. Davies, P. G. Houghton, M. S. Ashwood, I. F. Cottrell, R. A. Reamer, D. J. Kennedy, U. H. Dolling, P. J. Reider, *J. Org. Chem.* **2002**, *67*, 4771–4776.

[5] Y. Iso, T. Irie, Y. Nishino, K. Motokawa, Y. Nishitani, *J. Antibiot.* **1996**, *49*, 199–209.

[6] H. Azami, D. Barrett, A. Tanaka, H. Sasaki, K. Matsuda, T. Chiba, Y. Matsumoto, S. Matsumoto, C. Morinaga, K. Ishiguro, S. Tawara, K. Sakane, H. Takasugi, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2199–2202.

[7] H. Azami, D. Barrett, A. Tanaka, H. Sasaki, K. Matsuda, M. Sakurai, T. Terasawa, F. Shirai, T. Chiba, Y. Matsumoto, S. Tawara, *Bioorg. Med. Chem. Lett.* **2001**, *9*, 961–982.

[8] R. Wise, *Antimicrobial Agents Chemother.* **1986**, *30*, 343–349.

[9] D. Livingstone, M. J. Gill, R. Wise, *J. Antimicrob. Chemother.* **1995**, *35*, 1–5.

[10] C.-H. Oh, H.-W. Cho, I.-K. Lee, J.-Y. Gong, J.-H. Choi, J.-H. Cho, *Arch. Pharm. Pharm. Med. Chem.* **2002**, *335*, 152–158.

[11] C.-H. Oh, H.-G. Dong, H.-W. Cho, S.-J. Park, J.-H. Hong, D.-J. Baek, J.-H. Cho, *Arch. Pharm. Pharm. Med. Chem.* **2002**, *335*, 200–206.

[12] H. Azami, D. Barrett, A. Tanaka, H. Sasaki, K. Matsuda, T. Chiba, Y. Matsumoto, S. Matsumoto, C. Morinaga, K. Ishiguro, S. Tawara, K. Sakane, H. Takasugi, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2199–2202.

[13] H. Azami, D. Barrett, A. Tanaka, H. Sasaki, K. Matsuda, M. Sakurai, Y. Matsumoto, S. Tawara, T. Chiba, K. Sakane, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1409–1414.