Pergamon

Tetrahedron 58 (2002) 4459–4479

TETRAHEDRON

Radical cyclization in heterocycle synthesis. Part 13: Sulfanyl radical addition–cyclization of oxime ethers and hydrazones connected with alkenes for synthesis of cyclic β-amino acids☆

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Received 8 March 2002; accepted 10 April 2002

Abstract—A combination of sulfanyl radical addition–cyclization of the oxime ethers and hydrazones connected with alkenes and subsequent conversion of a phenylsulfanylmethyl group to a carboxyl group provides a novel method for the construction of the cyclic β-amino acids. Upon treatment with thiophenol in the presence of AIBN, the oxime ethers and hydrazones smoothly underwent sulfanyl radical addition-cyclization to give the 2-(phenylsulfanylmethyl)cycloalkylamine. This method was successfully applied to the practical synthesis of 2-aminocyclopentanecarboxylic acid and 4-amino-3-pyrrolidinecarboxylic acid.

1. Introduction

The β-amino acids[2] have aroused considerable attention due to their important biological properties in the fields of drugs and natural products. Furthermore, they have been known as useful tools in the synthesis of modified peptides with increased activity and stability in vivo. Although much less abundant than their α-analogs, β-amino acids are also present in nature. β-Amino acid structures are found, for instance, in the anticancer agent taxol, macrocyclic peptides, and antibiotics (β-lactam, cispentacin, etc.). Recently, Seebach's[3,4] and Gellman's[3,5] groups found that peptide analogs (β-peptides) formed from β-amino acids fold into defined three-dimensional structures (helical structures) similar to those of natural peptides and they are much more resistant than the corresponding α-peptide to be cleavaged by pepsin and peptidase enzymes. β-Peptide **3** called as β-17[5] which was developed by Gellman's group,[3,5] is active against four species of bacteria, including vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus*. β-17 is composed of the β-amino acids, *trans*-2-aminocyclopentanecarboxylic acid **1** and *trans*-4-amino-3-pyrrolidinecarboxylic acid **2** (Fig. 1).

We have recently explored a new efficient carbon–carbon bond-forming reaction based on sulfanyl radical addition–cyclization,[6,7] which proceeds via the formation of a carbon centered radical species generated by the addition of a sulfanyl radical to a multiple bond and the following intramolecular addition of the resulting carbon-centered radical to a multiple bond. The synthetic potential has been demonstrated by the syntheses of anantine,[7b,h] oxo-parabenzlactone,[7e,k] α-kainic acid,[7f,g,j] cispentacin,[7i] and A-ring fragment of 1α,25-dihydroxyvitamin D_3.[7l] We have also found a new efficient carbon–carbon bond-forming reaction based on the radical addition–cyclization[8] of oxime ethers tethered to the carbonyl group. We disclose herein the full details of the sulfanyl radical addition–cyclization[7i] of oxime ethers and hydrazones connected with alkenes and the successful application of the reaction to synthesis of cyclic β-amino acids such as 2-aminocyclopentanecarboxylic acid **1** and 4-amino-3-pyrrolidinecarboxylic acid **2** both of which are crucial components of β-17.

The radical addition–cyclization using carbon–nitrogen multiple bonds as radical acceptor has been extensively studied for the preparation of cyclic amine derivatives by several organic chemists including our group.[6,8]

Our approach is shown in Scheme 1. Sulfanyl radical would attack the terminal alkenyl group in the substrates **4** to provide the alkyl radical species **A** which is expected to form the substituted cyclic amines **5** via the aminyl radical **B** as a result of 5-*exo-trig* cyclization of **A**. Subsequent conversion of the phenylsulfanylmethyl group into the carboxyl group would furnish the desired β-amino acids **6**. The

☆ For part 12 see Ref. 1.

Keywords: β-amino acid; thiophenol; radical cyclization; oxime ether; hydrazone.

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PII: S0040-4020(02)00412-X

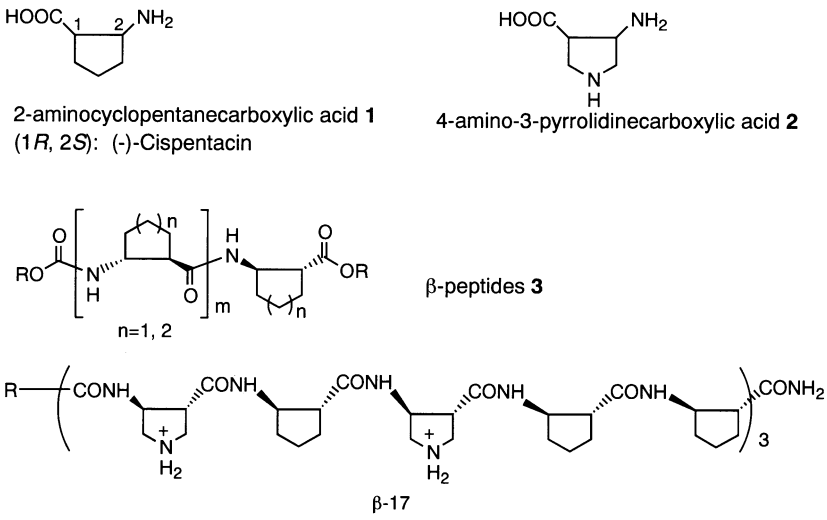
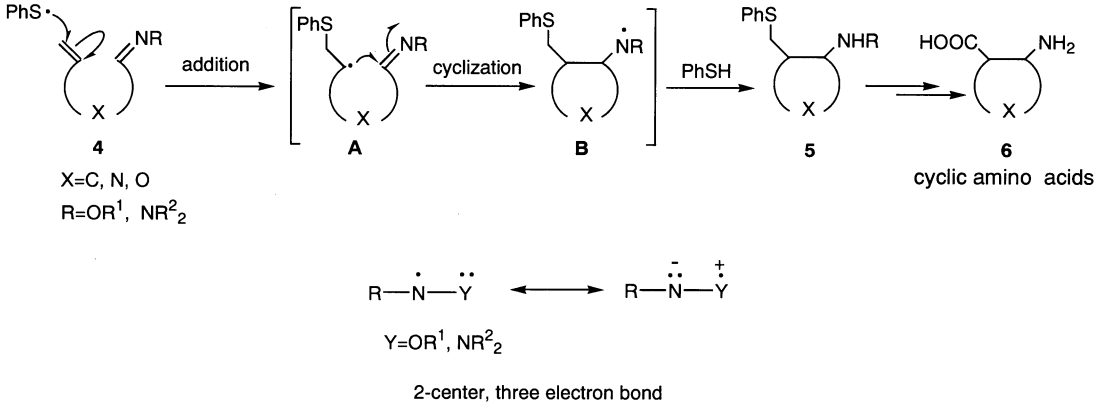


Figure 1. Cyclic β-amino acids and β-peptides.



Scheme 1.

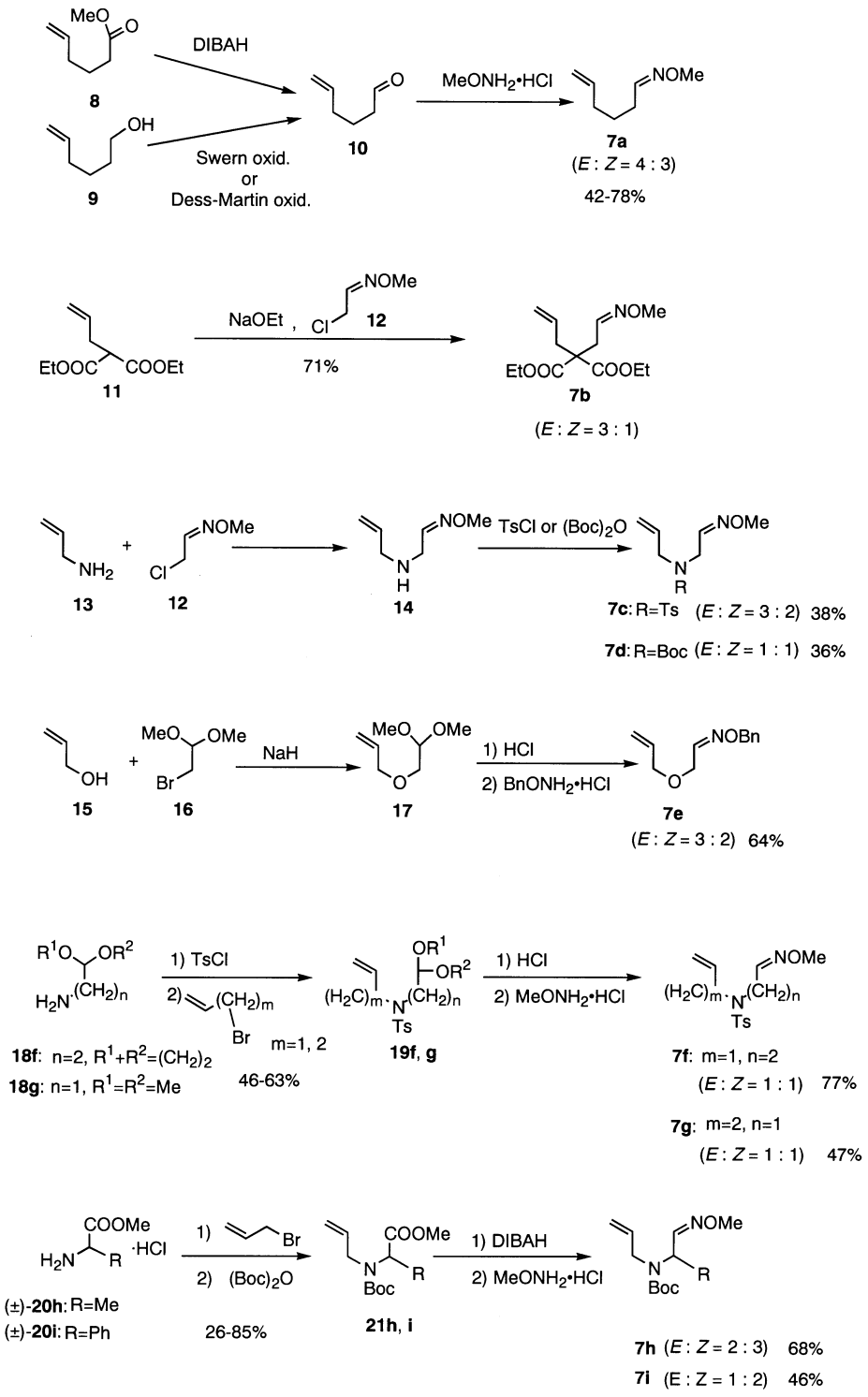
nitrogen radical stability is dependent upon the attached groups. The developing radical **B** would form a two-center, three-electron bond[8] with the lone pair of either second nitrogen present in the hydrazones or oxygen present in oxime ethers. This three-electron bond will be responsible for the stabilization of the developing nitrogen radical during the course of cyclization. Consequently, the cyclization of radical **A** proceeds smoothly to form the stable radical **B**.

2. Results and discussion

2.1. Preparation and radical addition–cyclization of the alkenyl-tethered-oxime ethers

The requisite substrates **7a–i** for the radical reaction were prepared as follows (Scheme 2). The aldehyde **10**, prepared either by reduction of the ester **8** with diisobutylaluminum hydride (DIBAH) or by Swern or Dess–Martin oxidation of the alcohol **9**, was treated with methoxyamine hydrochloride in the presence of sodium acetate to give the oxime ether **7a** in 42–78% yield. The oxime ether **7b** having a quaternary carbon was prepared from diethyl allylmalonate **11** by alkylation with an appropriate alkyl chloride **12**. The alkylation of allylamine followed by either tosylation or *t*-butoxycarbonylation gave **7c** and **7d** in 38 and 36% yields, respectively. The alkylation of allyl alcohol **15** with **16** followed by hydrolysis of the resulting acetal **17** and subsequent treatment with methoxyamine gave the oxime ether **7e**. The amino acetals **18f**, **g** were, respectively, converted into **7f**, **g** via tosylation, alkylation, deacetalization, and finally condensation with methoxyamine. The oxime ethers **7h** and **7i** having a chiral center were prepared from the corresponding (±)-amino esters **20h** and **20i** via alkylation, *t*-butoxycarbonylation, reduction of the ester to aldehyde, and finally, treatment with methoxyamine hydrochloride. The *E*/*Z* geometrical ratios of the aldoxime ether group in **7a–i** thus prepared were deduced by ^{1}H NMR spectroscopy. In general, the signal due to the imino hydrogen of the *E*-aldoxime ether is shifted downfield by the influence of the alkoxy group of the aldoxime ether moiety.[8i,j] In the case of **7a**, a signal due to the imino hydrogen of the *E*-isomer (δ 7.37) was shifted down field with respect to that of *Z*-isomer (δ 6.63).

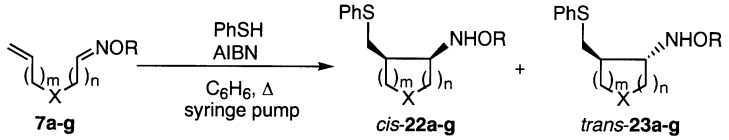
We then investigated the radical cyclization of oxime ethers **7a–g** (Table 1). As a typical example, a solution containing



Scheme 2.

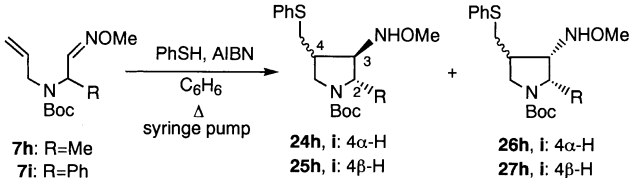
thiophenol (1 equiv.) and AIBN (0.5 equiv.) in benzene was added dropwise by a syringe pump over 2 h to a solution of the oxime ether **7b** in boiling benzene with stirring under nitrogen. The solution was then refluxed for further 2 h and concentrated to give a 4.0:1 mixture of the *cis*- and *trans*-cyclopentylamines **22b** and **23b** in good yield (entry 1). Under the same reaction conditions, sulfanyl radical addition–cyclization of the simple substrate **7a** gave a mixture of *cis*-**22a** and *trans*-**23a** in 49% combined yield (entry 2). Sulfanyl radical addition–cyclization of the oxime ethers **7c** and **7d** having the nitrogen atoms (X=NTs, NBoc) as a X group, proceeded smoothly to give the cyclized products **22c** and **23c**, and **22d** and **23d** in 88 and 62% yields, respectively (entries 3 and 4). Similarly, **7e** having oxygen atom as a X group gave almost the same result leading to the formation of a 3.0:1 mixture of *cis*-**22e** and *trans*-**23e** in good yield (entry 5). The newly found radical addition–cyclization was successfully extended to the formation of

Table 1. Sulfanyl radical addition–cyclization of oxime ethers



Entry	Substrate	X	R	*m*	*n*	PhSH (equiv.)	AIBN (equiv.)	Yield (%)	*cis*-**22**/*trans*-**23** ratio
1	**7b**	$C(COOEt)_2$	Me	1	1	1	0.5	76	4.0:1
2	**7a**	CH_2	Me	1	1	1	0.5	49	3.3:1
3	**7c**	NTs	Me	1	1	1	0.5	88	2.0:1
4	**7d**	NBoc	Me	1	1	1	0.5	62	3.0:1
5	**7e**	O	Bn	1	1	1	0.5	72	3.0:1
6	**7f**	NTs	Me	1	2	1	0.5	14	1.2:1
7	**7f**	NTs	Me	1	2	3	1.5	41	1.6:1
8	**7g**	NTs	Me	2	1	1	0.5	34	1:2.0
9	**7g**	NTs	Me	2	1	3	1.5	47	1:2.0

Table 2. Sulfanyl radical addition–cyclization of oxime ethers



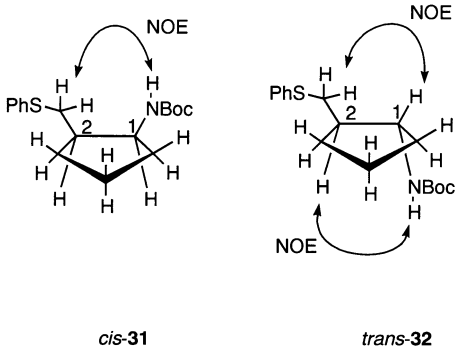
Entry	Substrate	R	PhSH (equiv.)	AIBN (equiv.)	Yield (%)	Ratio of **24**/**25**/**26**/**27**
1	**7h**	Me	1	0.5	75	3:1:1:1
2	**7i**	Ph	1	0.5	75	4:1 (an isomer)

6-membered ring product. Employment of PhSH (1 equiv.) and AIBN (0.5 equiv.) gave the products **22f** and **23f** in only 14% yield (entry 6) while an increased amount of PhSH (3 equiv.) and AIBN (1.5 equiv.) improved the yield to 41% (entry 7). Under the same conditions, radical addition–cyclization of **7g** gave 6-membered ring products **22g** and **23g** of which *trans*-isomer **23g** was the major product (entry 9).

We next examined the radical addition–cyclization of α-substituted oxime ethers **7h** and **7i** (Table 2).

The radical addition–cyclization of oxime ether having the methyl group at α-position of the oxime ether group proceeded smoothly to give four cyclized products **24h**, **25h**, **26h**, and **27h** in 75% combined yield, of which 2,3-*trans*-3,4-*cis*-**24h** was the major product. Similarly, the substrate **7i** having the phenyl group gave 2,3-*trans*-3,4-*cis*-**24i** as the major product with better stereoselectivity than that of **7h**, in addition to one minor stereoisomer which could not be isolated.

The stereostructures of the cyclized products **22a**-**e**, **23a**-**e**, **24h**, **i**, **25h**, **26h**, and **27h** were firmly established by NOESY of the ^{1}H NMR spectra of either alkoxyamines **22b**-**e**, **23 b**, **d**, **e**, **24h**, **i**, **25h**, **26h**, and **27h**, or the corresponding carbamates **31**, **32**, and **45c** (see Fig. 2, Scheme 3, and Table 5). Taking *cis*-**31** and *trans*-**32**, prepared from **22a** and **23a**, as a typical example, the assignment of those configurations is based on the observed NOE correlations as shown in Fig. 2. In the case of *cis*-**31**, the NOE was observed between N*H*Boc and PhSCH_2. On the other hand, the NOE in *trans*-**32** was observed between PhSCH_2 and 1-*H*, and 2-*H* and N*H*Boc. The stereostructures of *cis*- and *trans*-piperidines **22f**, **g** and **23f**, **g** were established by coupling constants between 2-*H* and 3-*H*, and 3-*H* and 4-*H* in the ^{1}H NMR spectra.

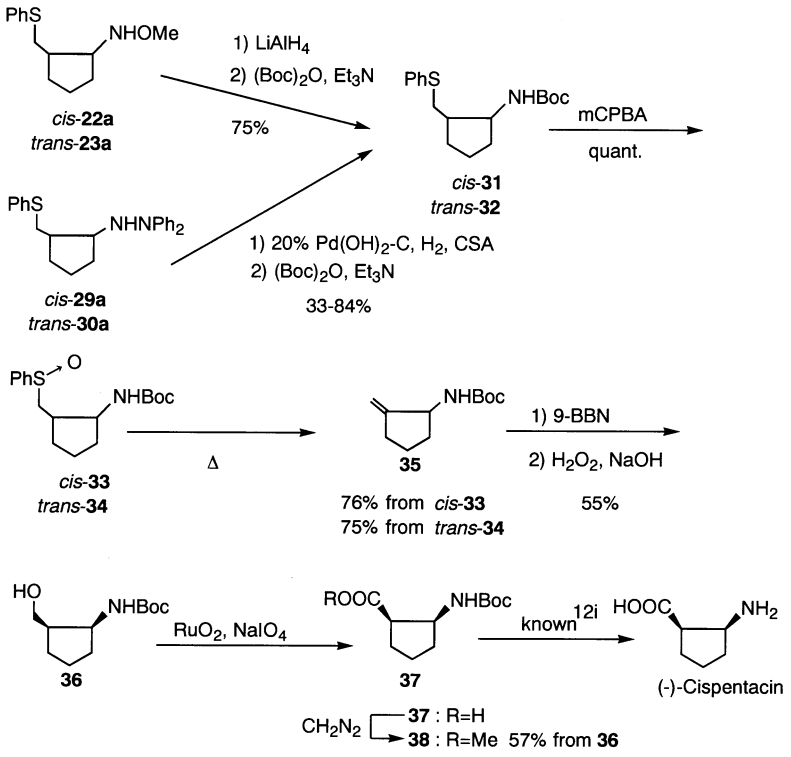


cis-**31** *trans*-**32**

Figure 2. NOE correlations of compounds *cis*-**31** and *trans*-**32**.

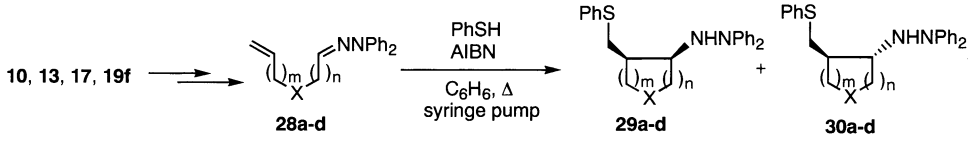
2.2. Preparation and radical addition–cyclization of the alkenyl-tethered-hydrazones

After successful cyclization of the oxime ethers **7a**–**i**, we then investigated the sulfanyl radical addition–cyclization of the hydrazones **28a**–**d** (Table 3). According to the procedure of the corresponding oxime ethers, the (*E*)-hydrazones **28a**–**d** were exclusively prepared. It is known[8f] that the condensation of carbonyl compounds with *N*,*N*-diphenylhydrazine provides only (*E*)-hydrazone as a sole



Scheme 3.

Table 3. Sulfanyl radical addition–cyclization of hydrazones



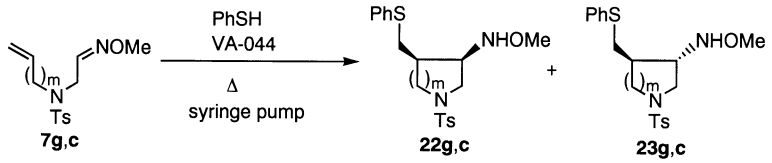
Entry	Substrate	X	*m*	*n*	PhSH (equiv.)	AIBN (equiv.)	Yield (%)	*cis*-**29**/*trans*-**30** ratio
1	**28a**	CH_2	1	1	1	0.5	73	2.0:1
2	**28b**	NTs	1	1	1	0.5	75	1.5:1
3	**28c**	O	1	1	1	0.5	84	1.3:1
4	**28d**	NTs	1	2	3	1.5	30	1:1.6

product. Radical addition–cyclization of the hydrazone **28a** proceeded smoothly to give a 2.0:1 mixture of *cis*-**29a** and *trans*-**30a** in 73% combined yield (entry 1). This result represents a much more efficient cyclization of the hydrazones than that of the oxime ether **7a**. Similar tendencies were observed for heterocycle synthesis, although stereoselectivities in the radical cyclization were lower (entries 2 and 3). In the case of the hydrazone **28d**, the 6-membered ring products *cis*-**29d** and *trans*-**30d** were obtained in lower yield and with reversed *cis*/*trans* ratio (entry 4). The stereostructures of the cyclized products **29a–d** and **30a–d** were firmly established by coupling constants and NOESY of the ^{1}H NMR spectra.

The sulfanyl radical addition–cyclization of the alkenyl-tethered-oxime ethers and hydrazones can be summarized as follows (Scheme 1). (a) Addition of sulfanyl radical to the terminal alkene and subsequent cyclization to the imine moieties proceeded regioselectively to give the desired products. Therefore, the reaction takes place exclusively in *exo–trig* manner, and no *endo–trig* products were formed. (b) In the case of the 5-membered ring products, the *cis*-isomers were preferentially formed. Beckwith[9] has explained that the preferential formation of the *cis*-product from the 1-substituted hexenyl radical is ascribed to the effects of orbital symmetry. In the case of 6-membered products, the stable *trans*-isomers were formed except for radical cyclization of **7f**. (c) In spite of existence in a stable zig-zag conformer which is unfavorable to intramolecular cyclization, the radical cyclization of **7a** and **28a** proceeded smoothly to give the desired products. (d) The cyclization yield of 5-membered product was higher than that of 6-membered product. In general, it is known[6f] that cyclization of 6-heptenyl radical proceeds about 40 times slower than that of the corresponding hexenyl radical.

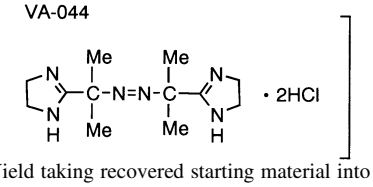
Thus, we have now succeeded in sulfanyl radical addition–cyclization of the alkenyl-tethered-oxime ethers and hydrazones for preparation of the multi-substituted cyclic amines.

Table 4. Sulfanyl radical addition–cyclization of oxime ethers in aqueous media



Entry	Substrate	*m*	PhSH (equiv.)	VA-044 (equiv.)[a]	Solvent	Yield (%)	Ratio of **22/23**
1	**7g**	2	1	0.5	H_2O	20 (45)[b]	1:1.5
2	**7g**	2	1	0.5	MeOH–H_2O (3:2)	39 (63)[b]	1:1.8
3	**7g**	2	3	1.5	MeOH–H_2O (3:2)	65 (83)[b]	1:1.8
4	**7c**	1	3	1.5	MeOH–H_2O (3:2)	76 (89)[b]	2.0:1

[a] VA-044



[b] Yield taking recovered starting material into account.

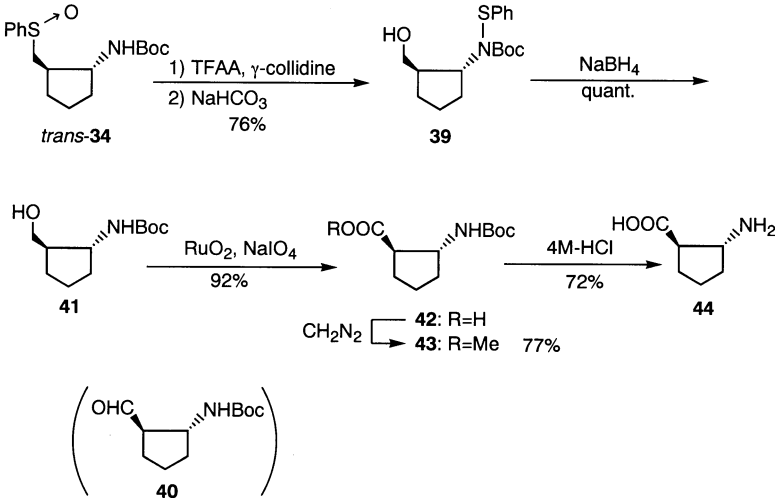
2.3. Radical addition–cyclization of the alkenyl-tethered-oxime ethers 7g and 7c in aqueous media

Due to the natural abundance of water as well as the inherent advantages of using water as a solvent, much interest has been recently growing in developing organic synthetic reaction in water.[10,11] We next investigated radical addition–cyclization of oxime ethers **7g** and **7c** in water using 2,2′-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-044) as water-soluble radical initiator (Table 4). Radical cyclization of **7g** in water (without methanol) using thiophenol (1 equiv.) and VA-044 (0.5 equiv.) gave the cyclized products **22g** and **23g** in only 20% yield because of a low water-solubility of the substrate (entry 1). Radical cyclization of the oxime ether **7g** in MeOH–H_2O (3:2) improved the cyclization yield (entry 2). The yield of 6-membered products **22g** and **23g** improved from 39 to 65% yield when an increased equivalent of thiophenol (3 equiv.) and VA-044 (1.5 equiv.) were used (entry 3). Under the same conditions, **7c** underwent smooth radical addition–cyclization in methanolic water to give a 2.0:1 mixture of 5-membered *cis*-**22c** and *trans*-**23c** (entry 4).

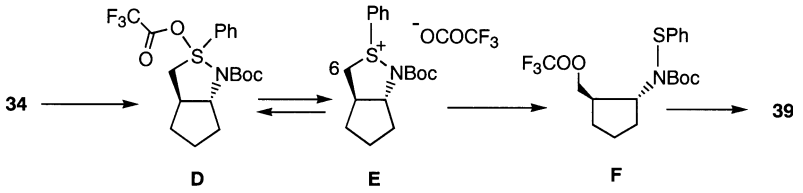
Thus, we have established that radical cyclization in methanolic water is an effective method for the formation of 5- and 6-membered products and also amount of organic solvents might be decreased as small as possible.

2.4. Synthesis of 2-aminocyclopentanecarboxylic acids

Conversion of the radically cyclized cyclopentylamines **22a**, **23a**, **29a**, and **30a** to the *cis*-2-aminocyclopentanecarboxylic acids (cispentacin) and its *trans*-isomer was readily achieved via the conventional reaction sequence as shown in Schemes 3 and 4. Cispentacin[12] is an antifungal antibiotic isolated from the culture broth of a *Bacillus cereus* strain. At first, the *cis*-methoxyamine **22a** and *cis*-hydrazine **29a** were converted step by step into the *exo*-methylene **35** as follows. Reductive cleavage of the *N*-methoxy group in *cis*-**22a** followed by *t*-butoxycarbonylation of



Scheme 4.



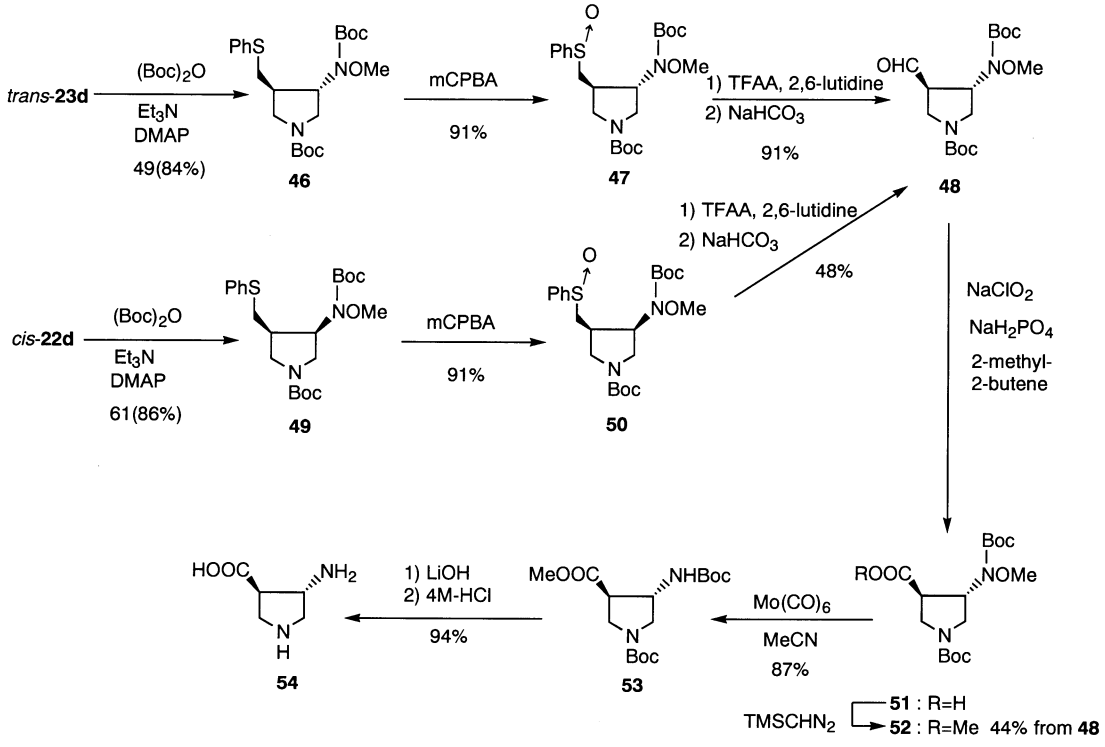
Scheme 5.

the resulting *cis*-amine gave *cis*-**31** in 75% yield, which was also obtained from *cis*-hydrazine **29a** via hydrogenolysis[8f] of the N–N bond and subsequent *t*-butoxycarbonylation. Oxidation of *cis*-**31** with *m*CPBA gave the *cis*-sulfoxide **33** as a 1:1 diastereomeric mixture, which was then subjected to pyrolysis to afford the *exo*-methylene **35**. Similarly, *trans*-**23a** and **30a** were converted into **35**. Hydroboration–oxidation of **35** with 9-BBN-H_2O_2 gave the desired *cis*-alcohol **36** with high regio- and diastereoselectivities as a result of attack of 9-BBN from the opposite face of the substituent. Finally, the oxidation of **36** with RuO_4 afforded the desired *cis*-*N*-Boc-amino acid **37**. The spectral data of **37** were identical with those reported in the literature.[12c] Since (±)-**37** had previously been transformed into (−)-cispentacin (**9b**) via the optical resolution and removal of *t*-butoxycarbonyl group, the present method provides a new synthesis of (−)-cispentacin.[12i]

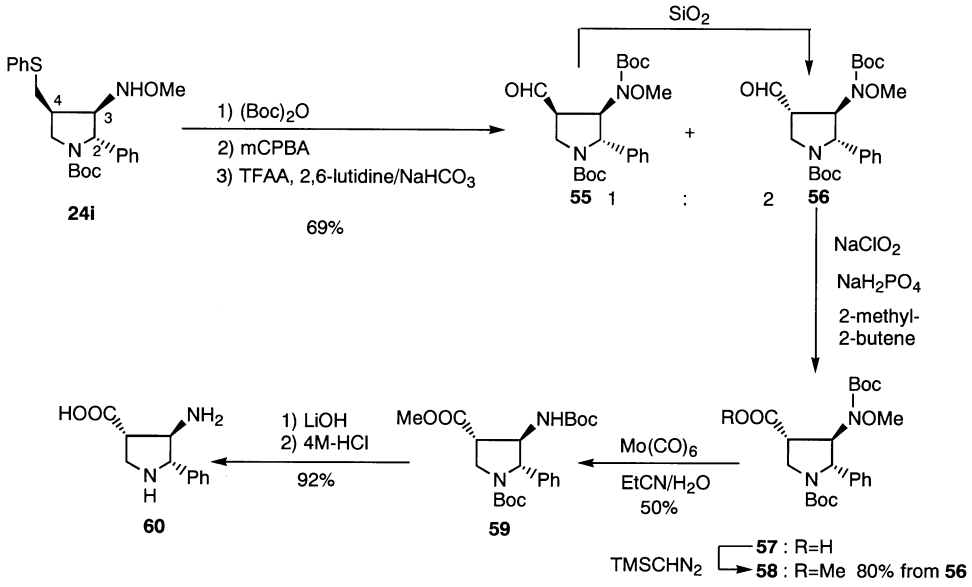
We next investigated conversion of *trans*-sulfoxide **34** into *trans*-2-aminocyclocpentanecarboxylic acid **44**, a component amino acid of β-peptide, β-17. The *trans*-sulfoxide **34** was subjected to the Pummerer rearrangement and subsequent hydrolysis to give unexpectedly the alcohol **39** in 76% yield with no isolation of the corresponding aldehyde **40**. The alcohol **39** would be formed via either the ligand coupling of the sulfurane **D**[13] or the attack of trifluoroacetate anion on C-6 position of the isothiazolidinium salt **E** leading to the CH_2–S bond cleavage followed by hydrolysis of the resulting trifluoroacetate **F** (Scheme 5). The alcohol **39** was converted into *trans*-2-aminocyclopentanecarboxylic acid **44** via reductive cleavage of N–S bond, oxidation of the alcohol, and hydrolysis. The spectral data of the corresponding methyl ester **43** of the acid **42** were identical with those reported in the literature.[14] Furthermore, the melting point of (±)-*trans*-amino acid 44 (mp 236–238°C (dec.)) was identical with that (lit.[15] mp 240°C (dec.)) reported in the literature.

2.5. Synthesis of 4-amino-3-pyrrolidinecarboxylic acids

We next investigated synthesis of *trans*-4-amino-3-pyrrolidinecarboxylic acid **54** and the related compound **60** (Schemes 6 and 7). According to the procedure established in the reaction of the cyclopentanes **22a** and **23a**, we first attempted reductive cleavage of N–O bond (Table 5). Treatment of *N*-tosyl-*trans*-pyrrolidine **23c** with $LiAlH_4$ followed by *t*-butoxycarbonylation of the resulting amine gave *N*-Boc-**45c** in low yield (entry 1). When $Mo(CO)_6$[16] was used as reagent for N–O bond fission, the desired **45c** was obtained in good yield (entry 2). However, the

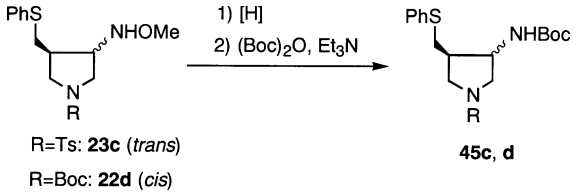


Scheme 6.



Scheme 7.

Table 5. Conversion of *N*-methoxyamine **23** into *N*-Boc-**45**



Entry	Substrate	Reagent	Yield **45** (%)
1	**23c**	$LiAlH_4$	18
2	**23c**	$Mo(CO)_6$	74
3	**22d**	$Mo(CO)_6$	38

conversion of *N*-Boc-*cis*-methoxyamine **22d** into *N*-Boc-amine **45d** via removal of the methoxy group with $Mo(CO)_6$ was not effective as shown in low yield of **45d** (entry 3). Consequently, we next examined the alternative conversion of cyclized products **23d** and **22d** into the amino acids by the sequence shown in Scheme 6. The *t*-butoxycarbonylation of **23d** in the presence of Et_3N and DMAP gave the dicarbamate **46**. The oxidation of the *trans*-sulfide **46** with *m*CPBA followed by Pummerer rearrangement of the resulting sulfoxide **47** in the presence of TFAA and subsequent hydrolysis gave the *trans*-aldehyde **48**. Similarly, the *cis*-sulfide **22d** was converted into the *cis*-sulfoxide **50** via *t*-butoxycarbonylation and oxidation. Pummerer rearrangement of *cis*-**50** followed by hydrolysis gave *trans*-aldehyde **48** in place of *cis*-aldehyde. This result suggests that transiently formed *cis*-aldehyde isomerizes to stable *trans*-isomer **48** under the hydrolytic basic conditions. The oxidation of aldehyde **48** with $NaClO_2$ in the presence of 2-methyl-2-butene gave the carboxylic acid **51**, which was treated with $TMSCHN_2$ to give the ester **52**. The cleavage of N–O bond in **52** with $Mo(CO)_6$ proceeded smoothly under refluxing MeCN (81°C) to give the ester **53** in good yield while attempted N–O bond fission of **52** by treatment with Na–Hg was unsuccessful. The hydrolysis of ester **53** with LiOH gave the carboxylic acid which was finally deprotected by treatment with 4 M-HCl to give the amino acid **54**.[5c,17]

In order to prepare the related cyclic β-amino acids, we finally investigated conversion of cyclized product **24i** into amino acid **60** by the similar sequence (Scheme 7). The *t*-butoxycarbonylation of **24i** followed by oxidation of the sulfides with *m*CPBA gave the sulfoxide as a mixture of the diastereomers which was subjected to Pummerer reaction to provide a 1:2 mixture of 2,3-*trans*-3,4-*cis*- and 2,3-*trans*-3,4-*trans*-aldehydes **55** and **56** as a result of plausible isomerization of the unstable 3,4-*cis*-aldehyde **55**. Actually, the fact that the aldehyde **55** was readily isomerized into the isomeric aldehyde **56** just by treatment with silica gel at room temperature clearly established that the aldehyde **55** is 3,4-*cis*-isomer while the aldehyde **56** is 3,4-*trans*-isomer. The oxidation of *trans*-aldehyde **56** with $NaClO_2$ followed by the methylation of the resulting carboxylic acid with diazomethane afforded the ester **58**. According to the procedure in the synthesis of **54** from **52**, **58** was treated with $Mo(CO)_6$ in refluxing MeCN. However, **58** was completely recovered with no formation of **59**. When the higher reaction temperature (refluxing in EtCN (97°C)) was used, the desired dicarbamate **59** was obtained in 50% yield. Finally, **59** was converted into the amino acid **60** via the hydrolysis by treatment with LiOH and deprotection with 4 M-HCl.

3. Conclusion

We have succeeded in the synthesis of cyclic β-amino acids based on the phenylsulfanyl radical addition–cyclization of oxime ethers and hydrazones connected with alkenes. The new methodology provides a synthetic approach to a wide range of both natural and unnatural cyclic β-amino acids.

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200, 300, or 500 MHz and at 75 or 125 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI method. Flash column chromatography (FCC) was performed using E. Merck Kieselgel 60 (230–400 mesh). Medium-pressure column chromatography (MPCC) was performed using Lobar größe B (E. Merck 310-25, Lichroprep Si60). Short column chromatography (SCC) was performed on a short glass filter using Silica gel 60F-254 (Merck) under reduced pressure. Preparative TLC (PTLC) was performed on precoated Silica gel 60F-254 plates (0.5 mm thick, Merck).

4.1.1. (*E*/*Z*)-5-Hexenal *O*-methyloxime (7a). (1) *Preparation from methyl 5-hexenoate (**8**).* To a stirred solution of methyl 5-hexenoate (**8**) (0.42 mL, 3 mmol) in Et_2O (6.2 mL) was added dropwise DIBAH (0.95 M in hexane) (5.05 mL, 4.8 mmol) at −78°C under a nitrogen atmosphere. After the solution was stirred at the same temperature for 4 h, MeOH (1.2 mL) was added to the reaction mixture. After being stirred at 0°C for 10 min, 36% aqueous potassium sodium tartrate (22 mL) was added and then the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude aldehyde **10** as a pale yellow oil. After being characterized by ^{1}H NMR spectrum, **10** was immediately subjected to the following reaction. To a stirred solution of the crude aldehyde **10** in CH_2Cl_2 (50 mL) was added AcONa (492 mg, 6 mmol) and $MeONH_2$·HCl (251 mg, 3 mmol) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 2.5 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was distilled to afford the oxime ether **7a** (297 mg, 78%) as a colorless oil and a 4:3 mixture of *E*- and *Z*-isomers; bp 140°C; IR ($CHCl_3$) 1640 (C=N) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52–1.65 (2H, m), 2.05–2.15 (2H, m), 2.20 (8/7H, br td, J=7, 6 Hz), 2.33 (6/7H, td, J=7.5, 5 Hz), 3.81 (12/7H, s), 3.86 (9/7H, s), 5.07–4.95 (2H, m), 5.80 (1H, m), 6.63 (3/7H, t, J=5 Hz), 7.37 (4/7H, t, J=6 Hz).; HRMS (EI, *m*/*z*) calcd for $C_7H_{13}NO$ (M^+) 127.1003, found 127.0997.

(2) *Preparation from 5-hexen-1-ol (**9**)*

(2)-1 Swern oxidation: to a stirred solution of oxalyl chloride (8 mL, 92 mmol) in CH_2Cl_2 (60 mL) was added dropwise a solution of DMSO (13 mL, 183 mmol) in CH_2Cl_2 (20 mL) at −78°C under a nitrogen atmosphere. After the solution was stirred at the same temperature for 0.5 h, a solution of 5-hexen-1-ol (**9**) (10 mL, 83.2 mmol) in CH_2Cl_2 (83 mL) was added to the reaction mixture. After being stirred at the same temperature for 20 min, Et_3N (58 mL, 416 mmol) was added and then the reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude aldehyde **10** as a pale yellow oil which was converted into the identical oxime ether **7a** (4.4 g, 42% from **9**) as a colorless oil by condensation with $MeONH_2$. This compound was identical with **7a** prepared from methyl 5-hexenoate (**8**).

(2)-2 Dess–Martin oxidation: to a stirred solution of 5-hexene-1-ol (**9**) (2.9 mL, 24 mmol) in CH_2Cl_2 (294 mL) was added Dess–Martin periodinane[18] (20 g, 48 mmol) at room temperature under a nitrogen atmosphere. After the solution was stirred at the same temperature for 4 h, saturated aqueous $NaHCO_3$ (208 mL) and $Na_2S_2O_3$ (52 g, 329 mmol) were added to the reaction mixture. The reaction mixture was extracted with Et_2O and the organic phase was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude aldehyde **10** as a pale yellow oil which was converted into the identical oxime ether **7a** (1.9 g, 63% from **9**) as a colorless oil by condensation with $MeONH_2$. This compound was identical with **7a** prepared from methyl 5-hexenoate (**8**).

4.1.2. Diethyl (*E*/*Z*)-[2-(methoxyimino)ethyl-2-propenyl]propanedioate (7b). To a stirred solution of NaOEt in EtOH prepared from Na (0.7 g, 30 mmol) and EtOH (5 mL) was added dropwise diethyl allylmalonate (**11**) (6 g, 30 mmol) at room temperature under a nitrogen atmosphere. After being stirred at the same temperature for 0.5 h, 2-chloroacetaldehyde *O*-methyloxime (**12**) (3.2 g, 30 mmol) was added dropwise at room temperature. After being refluxed for 2 h, the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 9:1) to afford **7b** (5.7 g, 71%) as a pale yellow oil and a 3:1 mixture of *E*- and *Z*-isomers; IR ($CHCl_3$) 1729 (COO), 1653 (C=N) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (6H, t, J=7 Hz), 2.62–2.70 (2H, m), 2.73 (6/4H, d, J=7 Hz), 2.83 (2/4H, d, J=5 Hz), 3.80 (9/4H, s), 3.86 (3/4H, s), 4.23 (2/4H, q, J=7 Hz), 5.18–5.08 (2H, m), 5.67 (1H, m), 6.89 (1/4H, t, J=5 Hz), 7.33 (3/4H, t, J=7 Hz); HRMS (EI, *m*/*z*) calcd for $C_{13}H_{21}NO_5$ (M^+) 271.1419, found 271.1417.

4.1.3. (*E*/*Z*)-*N*-[2-(Methoxyimino)ethyl]-4-methyl-*N*-(2-propenyl)benzenesulfonamide (7c). To a stirred solution of allylamine (**13**) (3.99 g, 70 mmol) in benzene (46.8 mL) was added a solution of chloroacetaldehyde *O*-methyloxime (**12**) (2.5 g, 23 mmol) in benzene (11.7 mL) at room temperature under a nitrogen atmosphere. After being stirred at 80°C for 5 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by SCC (AcOEt) to afford (*E*/*Z*)-(2-propenylamino)acetaldehyde *O*-methyloxime (**14**) (1.2 g, 41%) as a pale yellow oil. To a solution of **14** (1.28 g, 10 mmol) in CH_2Cl_2 (11.4 mL) were added Et_3N (1.89 mL, 13.6 mmol) and TsCl (2.29 g, 12 mmol) at 0°C under a nitrogen atmosphere. After being stirred at room temperature for 3 h, Et_3N (0.95 mL, 6.8 mmol) and TsCl (1.15 g, 6 mmol) at 0°C were added monitoring the reaction by TLC. After being stirred at room temperature for 1 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water, dried with Na_2SO_4, and

concentrated under reduced pressure. The residue was purified by FCC (hexane/AcOEt 1:1) to afford **7c** (2.6 g, 92%) as a pale yellow oil and a 3:2 mixture of *E*- and *Z*-isomers; IR ($CHCl_3$) 1645 (C═N), 1344, 1159 (NSO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (3H, s), 3.76–3.82 (2H, m), 3.79 (9/5H, s), 3.84 (6/5H, s), 3.88 (6/5H, d, J=6 Hz), 3.99 (4/5H, d, J=4 Hz), 5.13–5.22 (2H, m), 5.66 (1H, m), 6.62 (2/5H, t, J=4 Hz), 7.18 (3/5H, t, J=6 Hz), 7.31 (2H, br dd, J=8, 2 Hz), 7.70 (2H, br dd, J=8, 2 Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{18}N_2O_3S$ (M^+) 282.1038, found 282.1008.

4.1.4. 1,1-Dimethylethyl (*E/Z*)-*N*-[2-(methoxyimino)ethyl]-*N*-(2-propenyl)carbamate (7d). To a solution of **14** (1.43 g, 11 mmol) in CH_2Cl_2 (11.4 mL) were added Et_3N (1.89 mL, 13.6 mmol) and $(Boc)_2O$ (2.43 g, 11.2 mmol) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 7 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by FCC (hexane/AcOEt 5:1) to afford **7d** (2.24 g, 88%) as a pale yellow oil and a 1:1 mixture of *E*- and *Z*-isomers; IR ($CHCl_3$) 1690 (NCOO) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.46 (9H, s), 3.85 (2H, d, J=6 Hz), 3.87 (3H, s), 4.05 (2H, m), 5.11 (2H, m), 5. 76 (1H, m), 6.62 (1/2H, br t, J=5 Hz), 7.30 (1/2H, t, J=6 Hz); HRMS (EI, *m/z*) calcd for $C_{11}H_{20}N_2O_3$ (M^+) 228.1473, found 228.1466.

4.1.5. (*E/Z*)-(2-Propenyloxy)acetaldehyde *O*-(phenylmethyl)oxime (7e). To a stirred solution of the acetal **17**[19] (3.18 g, 21.8 mmol), prepared from allyl alcohol (**15**) and the acetal **16**, in acetone (137 mL) was added 2 M-HCl (12.7 mL) at 10°C under a nitrogen atmosphere. After the solution was stirred at room temperature for 3.5 h, the reaction mixture was diluted with water, extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated under reduce pressure to give the crude aldehyde as yellow oil. After being characterized by NMR spectrum, the crude aldehyde was immediately subjected to the following reaction. To a stirred solution of the crude aldehyde in MeOH (102 mL) was added AcONa (3.57 g, 43.6 mmol) and $BnONH_2$·HCl (5.23 g, 32.7 mmol) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 19 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (hexane/AcOEt 5:1) to afford **7e** (2.8 g, 64%) as a pale yellow oil and a 3:2 mixture of *E*- and *Z*-isomers; IR ($CHCl_3$) 1644 (C═N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95–4.01 (2H, m), 4.08 (6/5H, d, J=6 Hz), 4.32 (4/5H, d, J=3.5 Hz), 5.10 (2H, s), 5.30–5.68 (2H, m), 5.89 (1H, m), 6.89 (2/5H, t, J=3.5 Hz)), 7.26–7.40 (10H, m), 7.52 (3/5H, t, J=6 Hz); HRMS (EI, *m/z*) calcd for $C_{12}H_{15}NO_2$ (M^+) 205.1103, found 205.1098.

4.1.6. (*E/Z*)-*N*-[3-(Methoxyimino)propyl]-4-methyl-*N*-(2-propenyl)benzenesulfonamide (7f). To a solution of 1,3-dioxolane-2-ethanamine (**18f**) (3.48 g, 0.03 mol) in CH_2Cl_2 (50 mL) were added Et_3N (4.05 g, 0.04 mol) and then a solution of TsCl (7.63 g, 0.04 mol) in CH_2Cl_2 (50 mL) under a nitrogen atmosphere at 0°C. After being stirred for 2 h at room temperature, the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude tosylate. To a solution of the crude tosylate and K_2CO_3 (5.6 g, 0.04 mol) in acetone (55 mL) was added allyl bromide (3.63 g, 0.03 mol) under a nitrogen atmosphere. After being refluxed for 5 h, the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by MPCC (hexane/AcOEt 5:1) afforded *N*-(2-propenyl)-*N*-[2-(1,3-dioxolan-2-yl)ethyl]-4-methylbenzenesulfonamide (**19f**) (1.69 g, 63%) as yellow oil. To a solution of the acetal **19f** (5.12 g, 4.2 mmol) in acetone (36 mL) was added 2 M-HCl (25 mL) under a nitrogen atmosphere at room temperature. After being stirred for a further 3 h, the reaction mixture was extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude aldehyde as a yellow oil. According to the procedure given for the conversion of **10** into **7a**, the crude aldehyde was treated with AcONa (673 mg, 8.2 mmol) and $MeONH_2$·HCl (342 mg, 4.1 mmol) to afford the oxime ether **7f** (939 mg, 77%) as a pale yellow oil and a mixture 1:1 of *E*- and *Z*-isomers; IR ($CHCl_3$) 1599 (C═N, C═C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (3H, s), 2.41–2.55 (2H, m), 3.30 (2H, m), 3.80 (3/2H, s), 3.82 (2H, m), 3.85 (3/2H, s), 5.13–5.24 (2H, m), 5.65 (1H, m), 7.26 (1/2H, t, J=5 Hz), 7.31 (1/2H, t, J=6 Hz), 7.32 (2H, br d, J=8 Hz), 7.70 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{14}H_{20}N_2O_3S$ (M^+) 296.1194, found 296.1190.

4.1.7. (*E/Z*)-*N*-(3-Butenyl)-*N*-[2-(methoxyimino)ethyl]-4-methylbenzenesulfonamide (7g). To a solution of 2-aminoacetoaldehyde dimethylacetal (**18g**) (3.15 g, 0.03 mol) in CH_2Cl_2 (50 mL) were added Et_3N (4.05 g, 0.04 mol) and then TsCl (7.63 g, 0.04 mol) in CH_2Cl_2 under a nitrogen atmosphere at 0°C. After being stirred for 2 h at room temperature, the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude tosylate. To a solution of the crude tosylate and K_2CO_3 (5.6 g, 0.04 mol) in acetone (55 mL) was added 4-bromo-1-butene (4.05 g, 0.03 mol) under a nitrogen atmosphere. After being refluxed for 5 h, the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was dried over Mg_2SO_4 and concentrate under reduced pressure. Purification of the residue by MPCC (hexane/AcOEt 5:1) afforded *N*-(3-butenyl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide (**19g**) (4.32 g, 46%) as a pale yellow oil. To a solution of the acetal **19g** (1.61 g, 5.14 mmol) in acetone (50 mL) was added 2 M-HCl (31 mL) under a nitrogen atmosphere at room temperature. After being stirred for 1 h, 2 M-HCl (31 mL) was again added to the reaction mixture. After being stirred a further 1 h, the reaction mixture was extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude aldehyde as a yellow oil. According to the procedure given for the conversion of **10** into **7a**, the crude aldehyde was treated with AcONa (845 mg, 10.3 mmol) and $MeONH_2$·HCl (429 mg, 5.14 mmol) to afford the oxime ether **7g** (718 mg, 47%) as a pale yellow oil and a mixture 1:1 of *E*- and *Z*-isomers; IR

($CHCl_3$) 1599 (C=N, C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (2H, q, J=7 Hz), 2.43 (3H, s), 3.21 (2H, t, J=7 Hz), 3.80 (3/2H, s), 3.86 (3/2H, s), 3.89 (1H, d, J=6 Hz), 4.02 (1H, d, J=6 Hz), 5.01–5.12 (2H, m), 5.71 (1H, m), 6.62 (1/2H, t, J=5 Hz), 7.18 (1/2H, t, J=6 Hz), 7.31 (2H, br d, J=8 Hz), 7.69 (2H, br d, J=8 Hz); HRMS (EI, m/z) calcd for $C_{14}H_{20}N_2O_3S$ (M^+) 296.1194, found 296.1168.

4.1.8. Methyl *N*-[(1,1-dimethylethoxy)carbonyl]-*N*-(2-propenyl)alaninate (21h). To a stirred solution of (±)-alanine methyl ester hydrochloride (**20 h**) (5.6 g, 40 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (5.6 mL, 40 mmol) and allyl bromide (3.5 mL, 40 mmol) at 0°C under a nitrogen atmosphere. After being stirred at room temperature for 24 h, the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was washed with water, dried with Na_2SO_4, and concentrated under reduced pressure to give the crude allylamine.

To a solution of the crude allylamine (215 mg, 1.5 mmol) in CH_2Cl_2 (30 mL) were added Et_3N (0.2 mL, 1.5 mmol) and $(Boc)_2O$ (327 mg, 1.5 mmol) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 24 h, the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 1:1) to afford **21h** (309 mg, 85%) as a pale yellow oil; IR ($CHCl_3$) 1687 (NCOO), 1742 (COOMe) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (3H, d, J=7 Hz), 1.44 (9H, s), 3.70 (3H, s), 3.63–4.60 (3H, m), 5.12–5.23 (2H, m), 5.78–5.90 (1H, m); HRMS (EI, m/z) calcd for $C_{12}H_{21}NO_4$ (M^+) 243.1469, found 243.1482.

4.1.9. 1,1-Dimethylethyl (*E*/*Z*)-*N*-[2-(methoxyimino)-1-methylethyl]-*N*-(2-propenyl)carbamate (7h). According to the procedure given for the conversion of **8** into **7a**, the reduction of the ester **21h** (140 mg, 0.58 mmol) with DIBAL (0.95 M in hexane) (1.53 mL, 1.45 mmol) followed by the treatment of the resulting aldehyde with AcONa (95 mg, 1.16 mmol) and $MeONH_2$·HCl (48 mg, 0.58 mmol) to afford the oxime ether **7h** (94 mg, 68%) as a pale yellow oil and a mixture 2:3 of *E*- and *Z*-isomers; IR ($CHCl_3$) 1684 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (6/5H, d, J=7 Hz) 1.34 (9/5H, d, J=7 Hz), 1.46 (9H, s), 3.74–3.94 (3H, m), 3.83 (3H, s), 3.86 (9/5H, s), 5.09–5.15 (2H, m), 5.72–5.85 (1H, m), 6.81 (3/5H, d, J=6 Hz), 7.39 (2/5H, dm, J=5 Hz); HRMS (EI, m/z) calcd for $C_{12}H_{22}N_2O_3$ (M^+) 242.1629, found 242.1631.

4.1.10. Methyl *N*-[(1,1-dimethylethoxy)carbonyl]-2-phenyl-*N*-(2-propenyl)glycininate (21i). To a stirred solution of (±)-phenylglycine methyl ester hydrochloride (**20i**) (10 g, 50 mmol) in CH_2Cl_2 (100 mL) were added Et_3N (6.8 mL, 50 mmol) and allyl bromide (4 mL, 50 mmol) at 0°C under a nitrogen atmosphere. After being stirred at room temperature for 24 h, the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude allylamine.

To a solution of the crude allylamine (3 g, 15 mmol) in CH_2Cl_2 (300 mL) were added Et_3N (4.2 mL, 30 mmol) and $(Boc)_2O$ (6.6 g, 30 mmol) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 48 h, the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was washed with water, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by FCC (hexane/AcOEt 10:1) to afford **21i** (1.2 g, 26%) as a pale yellow oil; IR ($CHCl_3$) 1686 (NCOO), 1746 (COOMe) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.48 (9H, s), 3.60 (1H, br dd, J=16, 6 Hz), 3.76 (3H, s), 3.87 (1H, dm, J=16 Hz), 4.88 (2H, m), 5.40–5.90 (2H, m), 7.26–7.34 (5H, m); HRMS (EI, m/z) calcd for $C_{17}H_{23}NO_4$ (M^+) 305.1625, found 305.1634.

4.1.11. 1,1-Dimethylethyl (*E*/*Z*)-*N*-[2-(methoxyimino)-1-phenylethyl]-*N*-(2-propenyl)carbamate (7i). According to the procedure given for the conversion of **8** into **7a**, the reduction of the ester **21i** (300 mg, 1 mmol) with DIBAH (0.95 M in hexane) (1.37 mL, 1.3 mmol) followed by the treatment of the resulting aldehyde with AcONa (328 mg, 4 mmol) and $MeONH_2$·HCl (166 mg, 2 mmol) to afford the oxime ether **7i** (139 mg, 46%) as pale yellow oil and a mixture 1:2 of *E*- and *Z*-isomers; IR ($CHCl_3$) 1687 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (9H, s), 3.75 (1H, m), 3.88 (2H, s), 3.86 (1H, s), 3.98 (1H, m), 5.09–5.15 (2H, m), 5.51–5.85 (2H, m), 6.81 (2/3H, d, J=6 Hz), 7.22–7.35 (5H, m), 7.39 (1/3H, dm, J=5 Hz); HRMS (EI, m/z) calcd for $C_{17}H_{24}N_2O_3$ (M^+) 304.1786, found 304.1792.

4.2. General procedure for radical cyclization of oxime ethers

To a boiling solution of the oxime ether **7a**–**i** (1 mmol) in benzene (10 mL) under a nitrogen atmosphere was added a solution of thiophenol (1 or 3 mmol) and AIBN (0.5 or 1.5 mmol) in benzene (20 mL) by a syringe pump (5 mL/h) over 2 h. After the reaction mixture was heated at reflux for a further 2 h, the solvent was evaporated under reduced pressure. Purification of the residue by MPCC afforded the cyclized products **22a**–**g**, **23a**–**g**, and **24**–**27h**, **i** as shown in Tables 1 and 2. In the case of **22d**, **23d**, **24h**, **i**, **25h**, **26h**, and **27h**, the presence of rotamers precluded a comprehensive assignment of all proton resonances.

4.2.1. *cis*-*N*-Methoxy-2-[(phenylsulfanyl)methyl]cyclopentanamine (22a). Pale yellow oil; IR ($CHCl_3$) 3450 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.64–2.16 (6H, m), 2.38 (1H, m), 3.11 (1H, dd, J=12.5, 8.5 Hz), 3.41 (1H, dd, J=12.5, 7 Hz), 3.73 (1H, m), 3.74 (3H, s), 5.75 (1H, br s), 7.30–7.60 (5H, m); HRMS (EI, m/z) calcd for $C_{13}H_{19}NOS$ (M^+) 237.1187, found 237.1180.

4.2.2. *trans*-*N*-Methoxy-2-[(phenylsulfanyl)methyl]cyclopentanamine (23a). Pale yellow oil; IR ($CHCl_3$) 3455 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21–2.00 (7H, m), 2.81 (1H, dd, J=12.5, 7.5 Hz), 3.01 (1H, dd, J=12.5, 6.5 Hz), 3.19 (1H, m), 3.43 (3H, s), 5.45 (1H, br s), 7.05–7.30 (5H, m); HRMS (EI, m/z) calcd for $C_{13}H_{19}NOS$ (M^+) 237.1187, found 237.1196.

4.2.3. Diethyl *cis*-3-(methoxyamino)-4-(phenylsulfanyl)-methyl-1,1-cyclopentanedicarboxylate (22b). Pale yellow

oil; IR ($CHCl_3$) 3566 (NH), 1725 (COO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (3H, t, J=7 Hz), 1.25 (3H, t, J=7 Hz), 2.26 (1H, dd, J=12.5, 11 Hz), 2.32 (1H, m), 2.41–2.49 (3H, m), 2.95 (1H, dd, J=13, 8 Hz), 3.11 (1H, dd, J=13, 7.5 Hz), 3.48 (3H, s), 3.58 (1H, br td, J=6, 4 Hz), 4.18 (2H, q, J=7 Hz), 4.55 (2H, q, J=7 Hz), 5.63 (1H, br s), 7.16–7.36 (5H, m). NOE was observed between NH (δ 5.63) and CH_2SPh (δ 3.11) in NOESY spectroscopy. HRMS (EI, m/z) calcd for $C_{19}H_{27}NO_5S$ (M^+) 381.1610, found 381.1600.

4.2.4. Diethyl *trans*-3-(methoxyamino)-4-(phenylsulfanyl)-methyl-1,1-cyclopentanedicarboxylate (23b). Pale yellow oil; IR ($CHCl_3$) 3525 (NH), 1726 (COO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (3H, t, J=7 Hz), 1.24 (3H, t, J=7 Hz), 1.97 (1H, dd, J=13, 9 Hz), 2.17 (1H, br sext, J=7 Hz), 2.28 (1H, dd, J=14, 6 Hz), 2.51, (1H, dd, J=14, 8 Hz), 2.67, (1H, dd, J=13, 8 Hz), 2.92 (1H, dd, J=13, 8 Hz), 3.16 (1H, dd, J=13, 6.5 Hz), 3.37 (1H, br q, J=7 Hz), 3.47 (3H, s), 4.17 (2H, q, J=7 Hz), 4.18 (2H, q, J=7 Hz), 5.63 (1H, br s), 7.16–7.36 (5H, m). NOE was observed between NH (δ 5.63) and 4-H (δ 2.17), and CH_2SPh (δ 2.92, 3.16) and 3-H (δ 3.36) in NOESY spectroscopy. HRMS (EI, m/z) calcd for $C_{19}H_{27}NO_5S$ (M^+) 381.1610, found 381.1603.

4.2.5. *cis*-*N*-Methoxy-1-(4-methylphenyl)sulfonyl-4-(phenylsulfanyl)methyl-3-pyrrolidinamine (22c). Pale yellow oil; IR ($CHCl_3$) 3540 (NH), 1345, 1161 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.33 (1H, br sext, J=7 Hz), 2.42 (3H, s), 2.75 (1H, dd, J=13, 8.5 Hz), 3.00 (1H, dd, J=13, 7 Hz), 3.11 (1H, br t, J=9 Hz), 3.27 (3H, s), 3.37 (1H, dd, J=11.5, 3.5 Hz), 3.40 (1H, dd, J=11.5, 6.5 Hz), 3.53 (1H, dd, J=10, 7.5 Hz), 3.57 (1H, m), 5.41 (1H, br s), 7.19–7.32 (7H, m), 7.71 (2H, br d, J=8 Hz). NOE was observed between NH (δ 5.41) and CH_2SPh (δ 3.00) in NOESY spectroscopy. HRMS (EI, m/z) calcd for $C_{19}H_{24}N_2O_3S_2$ (M^+) 392.1228, found 392.1242.

4.2.6. *trans*-*N*-Methoxy-1-(4-methylphenyl)sulfonyl-4-(phenylsulfanyl)methyl-3-pyrrolidinamine (23c). Pale yellow oil; IR ($CHCl_3$) 3556 (NH), 1346, 1162 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.17, (1H, m), 2.43, (3H, s), 2.70 (1H, dd, J=13.5, 8.5 Hz), 2.94 (1H, dd, J=13.5, 6.5 Hz), 3.08 (1H, dd, J=10, 5.5 Hz), 3.17 (1H, dd, J=10, 4 Hz), 3.37 (3H, s), 3.38 (1H, dd, J=10, 6 Hz), 3.41 (1H, m), 3.46 (1H, dd, J=10, 7 Hz), 5.37 (1H, br s), 7.19–7.32 (7H, m), 7.70 (2H, br d, J=8 Hz); HRMS (EI, m/z) calcd for $C_{19}H_{24}N_2O_3S_2$ (M^+) 392.1228, found 392.1227.

4.2.7. 1,1-Dimethylethyl *cis*-3-methoxyamino-4-[(phenylsulfanyl)methyl]pyrrolidine-1-carboxylate (22d). Pale yellow oil; IR ($CHCl_3$) 3556 (NH), 1686 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (9H, s), 2.46 (1H, m), 2.94 (1H, m), 3.12 (1H, m), 3.20 (1H, m), 3.40 (1H, m), 3.48–3.66 (4H, m), 3.52 (3H, s), 5.59 (1H, br s), 7.18–7.8 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.38, 31.68, 31.80, 40.36, 41.21, 49.16, 49.35, 49.57, 49.85, 59.91, 60.43, 62.03, 79.23, 126.32, 128.94, 129.52, 135.57, 154.41; HRMS (EI, m/z) calcd for $C_{17}H_{26}N_2O_3S$ (M^+) 338.1663, found 338.1676. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

4.2.8. 1,1-Dimethylethyl *trans*-3-methoxyamino-4-[(phenylsulfanyl)methyl]pyrrolidine-1-carboxylate (23d). Pale yellow oil; IR ($CHCl_3$) 3550 (NH), 1687 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (9H, s), 2.33 (1H, m), 2.88 (1H, m), 3.06 (1H, m), 3.22 (1H, m), 3.27 (1H, m), 3.48–3.70 (3H, m), 3.49 (3H, s), 5.58 (1H, br s), 7.18–7.8 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.09, 28.34, 35.67, 38.95, 39.77, 45.84, 49.21, 49.69, 61.67, 62.19, 34.16, 79.41, 82.13, 126.47, 128.90, 129.84, 130.13, 135.56, 154.18, 156.52; HRMS (EI, m/z) calcd for $C_{17}H_{26}N_2O_3S$ (M^+) 338.1663, found 338.1664. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

4.2.9. *cis*-Tetrahydro-*N*-phenylmethoxy-4-(phenylsulfanyl)methyl-3-furanamine (22e). Pale yellow oil; IR ($CHCl_3$) 3452 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.51, (1H, m), 2.92 (1H, dd, J=13, 9 Hz), 3.19 (1H, dd, J=13, 7.5 Hz), 3.65 (1H, t, J=8.5 Hz), 3.73 (1H, m), 3.87 (1H, dd, J=9.5, 3.5 Hz), 3.90 (1H, dd, J=9.5, 5 Hz), 3.96 (1H, t, J=8.5 Hz), 4.72 and 4.70 (2H, ABq, J=11 Hz), 5.69 (1H, br s), 7.18–7.36 (10H, m). NOE was observed between NH (δ 5.69) and CH_2SPh (δ 2.92, 3.19) in NOESY spectroscopy. HRMS (EI, m/z) calcd for $C_{18}H_{21}NO_2S$ (M^+) 315.1293, found 392.1315.

4.2.10. *trans*-Tetrahydro-*N*-phenylmethoxy-4-(phenylsulfanyl)methyl-3-furanamine (23e). Pale yellow oil; IR ($CHCl_3$) 3484 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.29, (1H, m), 2.91 (1H, dd, J=13, 8 Hz), 3.05 (1H, dd, J=13, 7 Hz), 3.56 (1H, dd, J=9, 5.5 Hz), 3.58 (1H, m), 3.71 (1H, dd, J=10, 3.5 Hz), 3.87 (1H, dd, J=10, 6 Hz), 4.00 (1H, dd, J=9, 7 Hz), 4.67 and 4.69 (2H, ABq, J=11.5 Hz), 5.50 (1H, br s), 7.18–7.35 (10H, m). NOE was observed between NH (δ 5.50) and 4-H (δ 2.29), and 3-H (δ 3.58) and CH_2SPh (δ 3.05) in NOESY spectroscopy. HRMS (EI, m/z) calcd for $C_{18}H_{21}NO_2S$ (M^+) 315.1293, found 315.1300.

4.2.11. *cis*-*N*-Methoxy-1-[(4-methylphenyl)sulfonyl]-3-[(phenylsulfanyl)methyl]-4-piperidinamine (22f). Pale yellow oil; IR ($CHCl_3$) 3485 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.63 (1H, m) 1.71 (1H, dtd, J=14, 9, 4 Hz), 2.12 (1H, m), 2.43 (3H, s), 2.71 (1H, m), 2.68–2.75 (2H, m), 2.91 (1H, dd, J=13, 10 Hz), 3.08 (1H, dt, J=9, 4 Hz), 3.16 (1H, dd, J=13, 4.5 Hz), 3.42 (3H, s), 3.47 (1H, br dt, J=10, 5 Hz), 3.57 (1H, br dd, J=11, 5 Hz), 5.33 (1H, br s), 7.17–7.40 (7H, m), 7.64 (2H, br d, J=8 Hz). NOE was observed between NH (δ 5.33) and CH_2SPh (δ 3.16), CH_2SPh (δ 2.91) and 5-Hax (δ 1.71), and 4-H (δ 3.08) and 6 and 2-H (δ 2.68–2.75) in NOESY spectroscopy. HRMS (EI, m/z) calcd for $C_{20}H_{26}N_2O_3S_2$ (M^+) 406.1383, found 406.1367.

4.2.12. *trans*-*N*-Methoxy-1-[(4-methylphenyl)sulfonyl]-3-[(phenylsulfanyl)methyl]-4-piperidinamine (23f). Pale yellow oil. IR ($CHCl_3$) 3485 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.63 (1H, dtd, J=14, 10, 5 Hz 1.93 (1H, m), 2.00 (1H, m), 2.42 (1H, dd, J=12, 9 Hz), 2.43 (3H, s), 2.55 (1H, ddd, J=12, 10, 3 Hz), 2.75 (1H, td, J=9, 4 Hz), 2.85 (1H, dd, J=14, 8.5 Hz), 3.31 (1H, dd, J=14, 4 Hz), 3.42 (3H, s), 3.52 (1H, br dt, J=12, 5 Hz), 3.72 (1H, ddd, J=12, 4, 2 Hz), 5.33 (1H, br s), 7.20–7.38 (7H, m), 7.58

(2H, br d, J=8 Hz). NOE was observed between NH (δ 5.33) and CH_2SPh (δ 2.85), and 4-H (δ 2.75) and 6-Hax (δ 2.85) in NOESY spectroscopy. HRMS (EI, m/z) calcd for $C_{20}H_{26}N_2O_3S_2$ (M^+) 406.1383, found 406.1362.

4.2.13. *cis*-*N*-Methoxy-1-[(4-methylphenyl)sulfonyl]-4-[(phenylsulfanyl)methyl]-3-piperidinamine (22g). Pale yellow oil; IR ($CHCl_3$) 3490 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.42 (1H, qd, J=12, 5 Hz), 1.56 (1H, m), 1.72 (1H, qd, J=12, 3 Hz), 2.12 (1H, dd, J=12, 2 Hz), 2.19 (1H, td, J=12, 3 Hz), 2.42 (3H, s), 2.86 (1H, dd, J=13.5, 8 Hz), 3.13 (1H, dd, J=13.5, 8 Hz), 3.34 (1H, br s), 3.76 (1H, dquint. J=12, 2 Hz), 4.06 (1H, br dt, J=12, 3 Hz), 5.85 (1H, br s), 7.13–7.32 (7H, m), 7.63 (1H, br d, J=8 Hz). NOE was observed between 4-H (δ 1.56) and 2-Hax (δ 2.12), and 4-H (δ 1.56) and 6-Hax (δ 2.19) in NOESY spectroscopy. HRMS (EI, m/z) calcd for $C_{20}H_{26}N_2O_3S_2$ (M^+) 406.1383, found 406.1376.

4.2.14. *trans*-*N*-Methoxy-1-[(4-methylphenyl)sulfonyl]-4-[(phenylsulfanyl)methyl]-3-piperidinamine (23g). Pale yellow oil. IR ($CHCl_3$) 3490 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44–1.54 (2H, m), 2.09 (1H, m), 2.18 (1H, dd, J=11, 9.5 Hz), 2.24 (1H, br td, J=11, 3 Hz), 2.43 (3H, s), 2.69 (1H, dd, J=13, 8 Hz), 2.94 (1H, br td, J=9.5, 4 Hz), 3.41 (1H, dd, J=13, 3 Hz), 3.44 (3H, s), 3.68 (1H, dtd, J=12, 4, 2 Hz), 3.95 (1H, ddd, J=11, 4, 2 Hz), 5.43 (1H, br s), 7.14–7.33 (7H, m), 7.63 (2H, br d, J=8 Hz); HRMS (EI, m/z) calcd for $C_{20}H_{26}N_2O_3S_2$ (M^+) 406.1383, found 406.1380.

4.2.15. 1,1-Dimethylethyl (2α,3β,4β)-3-(methoxyamino)-2-methyl-4-[(phenylsulfanyl)methyl]pyrrolidine-1-carboxylate (24h). Pale yellow oil; IR ($CHCl_3$) 3556 (NH), 1684 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (3H, br dm, J=6 Hz), 1.45 (9H, s), 2.59 (1H, m), 2.94 (1H, m), 3.07 (1H, m), 3.21 (1H, m), 3.27 (1H, m), 3.49 (3H, s), 3.51 (3H, s), 3.58 (1H, m), 3.96 (1H, m), 5.58 (1H, br s), 7.20–7.38 (5H, m). NOE was observed between 4-H (δ 2.59) and 2-Me (δ 1.15), 3-H (δ 2.27) and 2-Me (δ 1.15), and NH (δ 5.58) and CH_2SPh (δ 3.07) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.11, 19.48, 28.52, 32.12, 32.82, 38.10, 39.07, 49.61, 50.06, 55.35, 57.12, 61.35, 62.15, 66.73, 66.96, 79.27, 126.19, 126.48, 128.99, 129.05, 129.35, 129.73, 129.76, 135.78, 154.50; HRMS (EI, m/z) calcd for $C_{18}H_{28}N_2O_3S$ (M^+) 352.1819, found 352.1837. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

4.2.16. 1,1-Dimethylethyl (2α,3β,4β)-3-(methoxyamino)-2-methyl-4-[(phenylsulfanyl)methyl]pyrrolidine-1-carboxylate (25h). Pale yellow oil; IR ($CHCl_3$) 3556 (NH), 1684 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (3H, br d, J=6 Hz), 1.45 (9H, s), 2.27 (1H, m), 2.92 (1H, dd, J=13.5, 8.5 Hz), 3.05 (1H, m), 3.07 (1H, br dd, J=13.5, 9 Hz), 3.21 (1H, dd, J=13.5, 5.5 Hz), 3.49 (3H, s), 3.71 (1H, m), 3.89 (1H, m), 5.64 (1H, br s), 7.19–7.38 (5H, m). NOE was observed between 4-H (δ 2.27) and 2-H (δ 3.71) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.99, 28.50, 29.70, 36.46, 40.01, 49.51, 56.65, 62.42, 72.87, 79.40, 126.43, 129.03, 129.70, 135.76, 154.29; HRMS (EI, m/z) calcd for $C_{18}H_{28}N_2O_3S$ (M^+) 352.1819, found 352.1835. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

4.2.17. 1,1-Dimethylethyl (2α,3α,4β)-3-(methoxyamino)-2-methyl-4-[(phenylsulfanyl)methyl]pyrrolidine-1-carboxylate (26h). Pale yellow oil; IR ($CHCl_3$) 3556 (NH), 1685 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (3H, br dm, J=6 Hz), 1.45 (9H, s), 2.17 (1H, m), 2.88 (1H, m), 3.15 (1H, m), 3.29 (1H, s), 3.46 (1H, m), 3.50 (3H, s), 3.62 (1H, m), 5.67 (1H, br s), 7.19–7.37 (5H, m). NOE was observed between 4-H (δ 2.17) and NH (δ 5.67) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.12, 28.51, 36.44, 37.66, 38.83, 49.11, 49.57, 54.40, 54.80, 61.63, 65.23, 65.87, 79.36, 126.41, 129.03, 129.66, 135.87, 154.23; HRMS (EI, m/z) calcd for $C_{18}H_{28}N_2O_3S$ (M^+) 352.1819, found 352.1801. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

4.2.18. 1,1-Dimethylethyl (2α,3α,4α)-3-(methoxyamino)-2-methyl-4-[(phenylsulfanyl)methyl]pyrrolidine-1-carboxylate (27h). Pale yellow oil; IR ($CHCl_3$) 3556 (NH), 1684 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (3H, br dm, J=6 Hz), 1.45 (9H, s), 2.42 (1H, m), 2.87 (1H, dd, J=13, 9.5 Hz), 3.30 (2H, m), 3.52 (3H, s), 3.59 (2H, m), 3.93 (1H, m), 5.66 (1H, br s), 7.18–7.37 (5H, m). NOE was observed between 4-H (δ 2.42) and 2-H (δ 3.93), and NH (δ 5.66) and CH_2SPh (δ 2.87) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.11, 15.75, 28.52, 28.67, 32.82, 39.89, 40.65, 50.38, 55.35, 61.36, 61.68, 63.22, 63.61, 79.72, 126.19, 128.99, 129.36, 136.00, 154.82; HRMS (EI, m/z) calcd for $C_{18}H_{28}N_2O_3S$ (M^+) 352.1819, found 352.1833. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

4.2.19. 1,1-Dimethylethyl (2α,3β,4β)-3-(methoxyamino)-2-phenyl-4-[(phenylsulfanyl)methyl]pyrrolidine-1-carboxylate (24i). Pale yellow oil; IR ($CHCl_3$) 3556 (NH), 1686 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.56 (9H, s), 2.58 (1H, m), 2.95 (1H, dd, J=12.5, 8 Hz), 3.09 (1H, m), 3.39–3.51 (2H, m), 3.58 (3H, s), 3.86 (1H, br t, J=10 Hz), 3.89 (1H, m), 4.94 (1H, br s), 5.64 (1H, d, J=5 Hz), 7.13–7.32 (10H, m). NOE was observed between 2-H (δ 5.64) and NH (δ 4.94), and 2-H (δ 5.64) and CH_2SPh (δ 3.09) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.13, 28.47, 32.21, 37.60, 38.38, 50.27, 50.90, 62.07, 65.05, 68.82, 69.28, 79.60, 125.48, 126.47, 126.88, 128.29, 128.49, 128.98, 129.82, 135.77, 154.62; HRMS (EI, m/z) calcd for $C_{23}H_{30}N_2O_3S$ (M^+) 414.1975, found 414.1975. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

4.2.20. (*E*)-5-Hexenal diphenylhydrazone (28a). To a stirred solution of the aldehyde **10** (735 mg, 7.5 mmol) in CH_2Cl_2 (125 mL) was added Ph_2NNH_2·HCl (1.66 g, 7.5 mmol) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 2.5 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by FCC (hexane/AcOEt 20:1) to afford the hydrazone **28a** (1.51 g, 76%) as a

yellow oil; IR ($CHCl_3$) 1639 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.59 (2H, quint., J=7.5 Hz), 2.08 (2H, br q, J=7 Hz), 2.29 (2H, td, J=7.5, 5.5 Hz), 4.91–5.06 (2H, m), 5.80 (1H, ddt, J=17, 10, 6.5 Hz), 6.53 (1H, t, J=5.5 Hz), 7.03–7.18 (6H, m), 7.28–7.44 (4H, m); HRMS (EI, *m/z*) calcd for $C_{18}H_{20}N_2$ (M^+) 264.1626, found 264.1631.

4.2.21. 4-Methyl-*N*-[(diphenylhydrazono)ethyl]-*N*-(2-propenyl)benzenesulfonamide (28b). To a stirred solution of allylamine (**13**) (1.56 mL, 21 mmol) in benzene (12.6 mL) was added a solution of 1-bromo-2,2-dimethoxyethane (**16**) (0.83 mL, 7 mmol) in benzene (3.5 mL) at room temperature under a nitrogen atmosphere. After being stirred at 80°C for 4.5 h, the reaction mixture was washed with water and the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (AcOEt) to afford (*E*)-(2-propenylamino)acetaldehyde dimethylacetal (437 mg, 43%) as a yellow oil. To a solution of the acetal (437 mg, 3.01 mmol) in CH_2Cl_2 (9.0 mL) were added Et_3N (0.5 mL, 3.61 mmol) and TsCl (746 mg, 3.91 mmol) at 0°C under a nitrogen atmosphere. After being stirred at room temperature for 3 h, Et_3N (0.25 mL, 1.81 mmol) and TsCl (373 mg, 1.96 mmol) at 0°C were again added monitoring the reaction by TLC. After being stirred at room temperature for 1 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 3:1) to afford *N*-(2,2-dimethoxyethyl)-4-methyl-*N*-(2-propenyl)benzenesulfonamide (814 mg, 92%) as a yellow oil; ^1H NMR (200 MHz, $CDCl_3$) δ 2.43 (3H, s), 3.22 (2H, d, J=6 Hz), 3.38 (6H, s), 3.95 (2H, br d, J=6 Hz), 4.52 (1H, t, J=6 Hz), 5.05–5.20 (2H, m), 5.56 (1H, m), 7.30 (2H, br d, J=8 Hz), 7.70 (2H, br d, J=8 Hz).

To a stirred solution of the sulfonamide (300 mg, 1.02 mmol) in acetone (6.38 mL) was added 2 M-HCl (1.5 mL) at 10°C under a nitrogen atmosphere. After the solution was stirred at room temperature for 24 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduce pressure to give the crude aldehyde as a yellow oil. To a stirred solution of the crude aldehyde in MeOH (4.76 mL) was added Ph_2NNH_2·HCl (150 mg, 0.61 mmol) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 1 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/Et_2O 5:1) to afford **28b** (183 mg, 43%) as colorless amorphous; IR ($CHCl_3$) 1643 (C=N), 1345, 1160 (NSO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (3H, s), 3.79 (2H, d, J=6 Hz), 4.00 (2H, d, J=6.5 Hz), 5.13–5.22 (2H, m), 5.65 (1H, ddt, J=16.5, 10, 6.5 Hz), 6.22 (1H, t, J=6 Hz), 6.95–7.02 (4H, m), 7.11–7.28 (8H, m), 7.64 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{24}H_{25}N_3O_2S$ (M^+) 419.1667, found 419.1683.

4.2.22. (2-Propenyloxy)acetaldehyde diphenylhydrazone (28c). To a stirred solution of the crude aldehyde (400 mg, 4 mmol), prepared by hydrolysis of dimethyl acetal **17**, in MeOH (9.6 mL) was added Ph_2NNH_2·HCl (136 mg, 0.62 mmol) at 10°C under a nitrogen atmosphere. After being stirred at room temperature for 10 min, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 9:1) to afford **28c** (132 mg, 24%) as a pale yellow oil; IR ($CHCl_3$) 1646 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.00 (2H, br d, J=6 Hz), 4.18 (2H, d, J=5.5 Hz), 5.14–5.34 (2H, m), 5.91 (1H, m), 6.54 (1H, t, J=5.5 Hz), 7.06–7.44 (10H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{18}N_2O$ (M^+) 266.1419, found 266.1431.

4.2.23. 4-Methyl-*N*-[(diphenylhydrazono)propyl]-*N*-(2-propenyl)benzenesulfonamide (28d). To a solution of acetal **19f** (207 mg, 0.664 mmol) in acetone (10 mL) was added 2 M-HCl (5 mL) under a nitrogen atmosphere at room temperature. After being stirred for 2 h, the reaction mixture was extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude aldehyde as a yellow oil. To a solution of the crude aldehyde in CH_2Cl_2 was added Ph_2NNH_2·HCl (122.3 mg, 0.664 mmol) under a nitrogen atmosphere at room temperature. After being stirred for 1.5 h, the reaction mixture was extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by MPCC (hexane/AcOEt 5:1) affored **28d** (101 mg, 35%) as a pale yellow oil; IR ($CHCl_3$) 1594 (C=C, C=N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.41 (3H, s), 2.52 (2H, br dt, J=7, 5 Hz), 3.36 (2H, t, J=7 Hz), 3.81 (2H, d, J=7 Hz), 5.10–5.22 (2H, m), 5.63 (1H, m), 6.45 (1H, t, J=5 Hz), 7.02–7.40 (12H, m), 7.70 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{24}H_{27}N_3O_2S_2$ (M^+) 433.1823, found 433.1832.

4.3. General procedure for radical cyclization of hydrazones

According to the procedure given for radical cyclization of oxime ethers, to a boiling solution of the hydrazone **28a–d** (1 mmol) in benzene (10 mL) under a nitrogen atmosphere was added a solution of thiophenol (1 or 3 mmol) and AIBN (0.5 or 1.5 mmol) in benzene (20 mL) by a syringe pump (5 mL/h) over 2 h. After the reaction mixture was heated at reflux for a further 2 h, the solvent was evaporated under reduced pressure. Purification of the residue by MPCC afforded the cyclized products **29a–d** and **30a–d** as shown in Table 3.

4.3.1. *cis*-1,1-Diphenyl-2-[2-[(phenylsulfanyl)methyl]-cyclopentyl]hydrazine (29a). Colorless crystals; mp 85–86°C (MeOH); IR ($CHCl_3$) 3378 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.51–1.95 (6H, m), 2.13 (1H, m), 3.04 (1H, dd, J=12.5, 7.5 Hz), 3.14 (1H, dd, J=12.5, 8.5 Hz), 3.43 (1H, br td, J=5, 4 Hz), 4.14 (1H, br s), 6.99 (2H, br tt, J=8, 2 Hz), 7.17–7.30 (13H, m). NOE was observed between NH (δ 4.14) and CH_2SPh (δ 3.14) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{24}H_{26}N_2S$ (M^+) 374.1817, found 374.1832. Anal. calcd for $C_{24}H_{26}N_2S$:C, 76.96; H, 7.00; N, 7.48; S, 8.56. Found: C, 76.84; H, 6.99; N, 7.51; S, 8.48.

4.3.2. *trans*-1,1-Diphenyl-2-[2-(phenylsulfanyl)methylcyclopentyl]hydrazine (30a). Pale yellow oil; IR ($CHCl_3$) 3378 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (1H, m), 1.61–1.70 (3H, m), 1.80 (1H, m), 2.04–2.14 (2H, m), 2.84 (1H, dd, J=13, 7 Hz), 2.88 (1H, dd, J=13, 7.5 Hz), 3.27 (1H, m), 4.13 (1H, br s), 6.96–7.30 (15H, m). NOE was observed between NH (δ 4.13) and 2-H (δ 2.01–2.14), 1-H (δ 3.27) and CH_2SPh (δ 2.84, 2.88) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{24}H_{26}N_2S$ (M^+) 374.1817, found 374.1831.

4.3.3. *cis*-1-[(4-Methylphenyl)sulfonyl]-3-(2,2-diphenylhydrazino)-4-[(phenylsulfanyl)methyl]pyrrolidine (29b). Colorless crystals; mp 157–160°C (Et_2O); IR ($CHCl_3$) 3500 (NH), 1350, 1150 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.29 (1H, m), 2.42 (3H, s), 2.82 (1H, dd, J=13, 7.5 Hz), 3.01 (1H, dd, J=13, 8 Hz), 3.32 (1H, dd, J=11, 5.5 Hz), 3.34 (1H, t, J=9.5 Hz), 3.42 (1H, dd, J=11, 3 Hz), 3.55 (1H, m), 3.60 (1H, dd, J=9.5, 7.5 Hz), 3.99 (1H, br d, J=2 Hz), 6.98–7.04 (6H, m), 7.18–7.28 (11H, m), 7.69 (2H, br dd, J=8 Hz). NOE was observed between NH (δ 3.99) and CH_2SPh (δ 3.01) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{30}H_{31}N_3O_2S_2$ (M^+) 529.1857, found 529.1866. Anal. calcd for $C_{30}H_{31}N_3O_2S_2$: C, 68.02; H, 5.90; N, 7.93; S, 12.10. Found: C, 67.93; H, 5.90; N, 7.88; S, 12.20.

4.3.4. *trans*-1-[(4-Methylphenyl)sulfonyl]-3-(2,2-diphenylhydrazino)-4-[(phenylsulfanyl)methyl]pyrrolidine (30b). White amorphous; IR ($CHCl_3$) 3524 (NH), 1346, 1136 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.30 (1H, m), 2.43 (3H, s), 2.66 (1H, dd, J=13, 7.5 Hz), 2.69 (1H, dd, J=13, 8 Hz), 3.17 (1H, dd, J=11, 3 Hz,), 3.29 (1H, dd, J=10, 3.5 Hz), 3.39 (1H, dd, J=11, 6 Hz), 3.46 (1H, m), 3.53 (1H, dd, J=10, 7 Hz), 3.74 (1H, br d, J=2 Hz), 6.90–6.93 (4H, m), 6.99–7.25 (2H, m), 7.16–7.32 (11H, m), 7.71 (2H, br d, J=8 Hz). NOE was observed between NH (δ 3.74) and 4-H (δ 2.30), 3-H (δ 3.46) and CH_2SPh (δ 2.66, 2.69) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{30}H_{31}N_3O_2S_2$ (M^+) 529.1857, found 529.1868.

4.3.5. *cis*-2-[Tetrahydro-4-(phenylsulfanyl)methyl-3-furanyl]-1,1-diphenylhydrazine (29c). Pale yellow oil; IR ($CHCl_3$) 3446 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.53 (1H, m), 3.09 (1H, dd, J=13, 7.5 Hz), 3.13 (1H, dd, J=13, 9 Hz), 3.65 (1H, m), 3.74 (1H, dd, J=9.5, 5 Hz), 3.88 (1H, dd, J=9, 8 Hz), 3.98 (1H, dd, J=9.5, 2 Hz), 4.04 (1H, t, J=8 Hz), 4.38 (1H, br s), 7.00–7.32 (15H, m). NOE was observed between NH (δ 4.38) and CH_2SPh (δ 3.09, 3.13) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{23}H_{24}N_2OS$ (M^+) 376.1609, found 376.1635.

4.3.6. *trans*-2-[Tetrahydro-4-(phenylsulfanyl)methyl-3-furanyl]-1,1-diphenylhydrazine (30c). Pale yellow oil; IR ($CHCl_3$) 3448 (NH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.37 (1H, m), 2.85 (1H, dd, J=13, 8 Hz), 2.91 (1H, dd, J=13, 7.5 Hz), 3.57 (1H, m), 3.66 (1H, dd, J=9, 4.5 Hz), 3.77 (1H, dd, J=9.5, 3 Hz), 3.83 (1H, dd, J=9.5, 6 Hz), 4.02 (1H, br s), 4.18 (1H, dd, J=9, 7 Hz), 7.00–7.30 (15H, m). NOE was observed between NH (δ 4.02) and 4-H (δ 2.37), 3-H (δ 3.57) and CH_2SPh (δ 2.85, 2.91) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{23}H_{24}N_2OS$ (M^+) 376.1609, found 376.1615.

4.3.7. *cis*-1-[(4-Methylphenyl)sulfonyl]-4-(2,2-diphenylhydrazino)-3-[(phenylsulfanyl)methyl]piperidine (29d). Pale yellow oil; IR ($CHCl_3$) 3490 (NH), 1589 (C=C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.59 (1H, m), 1.88 (1H, dtd, J=13, 9, 4 Hz), 2.05–2.12 (1H, m), 2.45 (3H, s), 2.64 (2H, m), 2.95 (1H, m), 3.00 (1H, dd, J=13.5, 10.5 Hz), 3.26 (1H, br dd, J=13, 4.5 Hz), 3.42 (1H, m), 3.64 (1H, m), 3.71 (1H, br s), 6.97–7.28 (15H, m), 7.31 (2H, br d, J=8 Hz), 7.63 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{31}H_{33}N_3O_2S_2$ (M^+) 543.2012, found 543.2000.

4.3.8. *trans*-1-[(4-Methylphenyl)sulfonyl]-4-(2,2-diphenylhydrazino)-3-[(phenylsulfanyl)methyl]piperidine (30d). Pale yellow oil; IR ($CHCl_3$) 3490 (NH), 1589 (C=C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.61 (1H, m), 1.92 (1H, m), 2.03 (1H, m), 3.04 (1H, dd, J=11, 7 Hz), 2.48 (3H, s), 2.94–3.14 (5H, m), 3.27 (1H, br dd, J=11, 4 Hz), 3.76 (1H, br s), 6.92–7.28 (15H, m), 7.33 (2H, br d, J=8 Hz), 7.61 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{31}H_{33}N_3O_2S_2$ (M^+) 543.2012, found 543.2007.

4.4. General procedure for radical cyclization of oxime ethers 7g and 7c in aqueous media

To a boiling solution of oxime ether (0.34 mmol) in MeOH–H_2O (3:2) (5.2 mL) was added a solution of thiophenol (1.02 mmol) and VA-044 (0.51 mmol) in MeOH–H_2O (3:2) (9.2 mL) under nitrogen atmosphere by a syringe pump (4 mL/h) over 2.5 h. After being heated at reflux for a further 2.5 h, the reaction mixture was neutralized with 5% KOH and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by MPCC (hexane/AcOEt 5:1) afforded the cyclized compounds as shown in Table 4.

The products were identical with pyrrolidines **22g**, **c** and **23g**, **c** prepared by the radical reaction in benzene (Table 1).

4.4.1. 1,1-Dimethylethyl *cis*-[2-[(phenylsulfanyl)methyl]-cyclopentyl]carbamate (31). (1) *Preparation from cis-methoxyamine* **22a**. To a stirred solution of *cis*-methoxyamine **22a** (237 mg, 1 mmol) in THF (48.5 mL) was added $LiAlH_4$ (380 mg, 10 mmol) at room temperature under a nitrogen atmosphere. After the solution was refluxed for 8 h, usual work-up gave the crude amine as a yellow oil. After being characterized by NMR spectrum, the crude amine was subjected to the following reaction. To a stirred solution of the crude amine in CH_2Cl_2 (56 mL) were added Et_3N (0.21 mL, 1.5 mmol) and a solution of $(Boc)_2O$ (0.34 mL, 1.5 mmol) in CH_2Cl_2 (21 mL) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 5 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 5:1) to afford **31** (239 mg, 75%) as colorless crystals (mp 89–90°C (hexane)); IR ($CHCl_3$) 3444 (NH), 1705 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.40–1.65 (3H, m), 1.45 (9H, s), 1.69 (1H, m), 1.90–2.00 (2H, m), 2.22 (1H, m), 2.69 (1H, br dd, J=12, 10 Hz), 3.18 (1H, br dd, J=12, 5 Hz), 4.10 (1H, m), 4.48 (1H, br s),

7.34–7.12 (5H, m). NOE was observed between NH (δ 4.48) and CH_2SPh (δ 2.69) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{17}H_{25}NO_2S$ (M^+) 307.1606, found 307.1597; Anal. calcd for $C_{17}H_{25}NO_2S$:C, 66.41; H, 8.20; N, 4.56; S, 10.43. Found: C, 66.37; H, 8.39; N, 4.31; S, 10.62.

(2) *Preparation from cis-hydrazine* **29a**. To a stirred solution of *cis*-hydrazine **29a** (79 mg, 0.21 mmol) in MeOH (16.5 mL) was hydrogenated in the presence of 20% $Pd(OH)_2$–C (165 mg) and (±)-10-camphorsulfonic acid[8f] (106 mg, 0.42 mmol) at room temperature under a hydrogen atmosphere for 19.5 h. Usual work-up gave the crude amine as a yellow oil. To a stirred solution of the crude amine in CH_2Cl_2 (12 mL) were added Et_3N (0.06 mL, 0.43 mmol) and a solution of $(Boc)_2O$ (0.1 mL, 0.42 mmol) in CH_2Cl_2 (6 mL) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 4 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 5:1) to afford **31** (65 mg, 84%) as colorless crystals which was identical with **31** prepared from **22a**.

4.4.2. 1,1-Dimethylethyl *cis*-[2-[(phenylsulfinyl)methyl]-cyclopentyl]carbamate (33). To a stirred solution of *cis*-*N*-Boc **31** (316 mg, 1.03 mmol) in CH_2Cl_2 (26 mL) was added dropwise *m*CPBA (assay 70%) (177 mg, 1.03 mmol) in CH_2Cl_2 (37.5 mL) over 4 h under nitrogen atmosphere at 0°C. After being stirred at the same temperature for 30 min, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 5:1→AcOEt) to afford **33** (332 mg, 99%) as colorless powders and as a 1:1 diastereomeric mixture based on the sulfinyl group; IR ($CHCl_3$) 3444 (NH), 1705 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35–2.20 (6H, m), 1.38 (9/2H, s), 1.43 (9/2H, s), 2.36 (1/2H, m), 2.42 (1/2H, m), 2.54 (1/2H, br t, *J*=12 Hz), 2.77 (1/2H, dd, *J*=13, 7 Hz), 2.90 (1/2H, dd, *J*=13, 7.5 Hz), 3.11 (1/2H, br dd, *J*=12, 3 Hz), 4.05 (1/2H, m), 4.20 (1/2H, m), 4.51 (1/2H, br s), 4.62 (1/2H, br s), 7.47–7.54 (3H, m), 7.62–7.70 (2H, m); HRMS (CI, isobutane, *m/z*) calcd for $C_{17}H_{25}NO_3S+H$ (QM^+) 323.1555, found 323.1537.

4.4.3. 1,1-Dimethylethyl *trans*-[2-[(phenylsulfanyl)-methyl]cyclopentyl]carbamate (32). (1) *Preparation from trans-methoxyamine* **23a**. According to the procedure described in the preparation of *cis*-*N*-Boc **31** from **22a**, the demethoxylation and *t*-butoxycarbonylation of the *trans*-methoxyamine (355 mg, 1.5 mmol) afforded *trans*-*N*-Boc **32** (345 mg, 75%) as colorless crystals (mp 84–86°C (hexane)); IR ($CHCl_3$) 3442 (NH), 1705 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36–1.48 (2H, m), 1.45 (9H, s), 1.58–1.67 (2H, m), 1.85 (1H, m), 1.98 (1H, m), 2.07 (1H, m), 2.78 (1H, dd, *J*=12, 10 Hz), 3.28 (1H, br dd, *J*=12, 4 Hz), 3.70 (1H, m), 4.45 (1H, br s), 7.14–7.34 (5H, m). NOE was observed between NH (δ 4.45) and 2-H (δ 1.85), 1-H (δ 3.70) and CH_2SPh (δ 2.78) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{17}H_{25}NO_2S$ (M^+) 307.1606, found 307.1619; Anal. calcd for $C_{17}H_{25}NO_2S$:C, 66.41; H, 8.20; N, 4.56; S, 10.43. Found: C, 66.38; H, 8.40; N, 4.53; S, 10.68.

(2) *Preparation from trans-hydrazine* **30a**. According to the procedure described in the preparation of *cis*-*N*-Boc **31** from **29a**, the demethoxylation and *t*-butoxycarbonylation of the *trans*-hydrazine **30a** (68 mg, 0.18 mmol) afforded *trans*-*N*-Boc **32** (18 mg, 33%) as colorless crystals.

This compound was identical with **32** prepared from **23a**.

4.4.4. 1,1-Dimethylethyl *trans*-[2-[(phenylsulfinyl)-methyl]cyclopentyl]carbamate (34). According to the procedure described in the preparation of *cis*-sulfoxide **33**, the oxidation of *trans*-**32** (137 mg, 0.45 mmol) with *m*CPBA gave **34** (127 mg, 99%) as colorless powders and as a 1:1 diastereomeric mixture based on the sulfinyl group; IR ($CHCl_3$) 3440 (NH), 1703 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35–2.30 (7H, m), 1.40 (9/2H, s), 1.44 (9/2H, s), 2.62 (1/2H, br t, *J*=12 Hz), 2.84 (1/2H, dd, *J*=13.5, 7 Hz), 3.01 (1/2H, dd, *J*=13.5, 7.5 Hz), 3.11 (1/2H, dd, *J*=13, 3.5 Hz), 3.69 (1/2H, m), 3.75 (1/2H, m), 4.54 (1/2H, br s), 4.79 (1/2H, br s), 7.46–7.52 (3H, m), 7.61–7.67 (2H, m); HRMS (CI, isobutane, *m/z*) calcd for $C_{17}H_{25}NO_3S+H$ (QM^+) 323.1555, found 323.1577.

4.4.5. 1,1-Dimethylethyl [2-(methylene)cyclopentyl]carbamate (35). (1) *Preparation from cis-sulfoxide* **33**. A stirred solution of *cis*-sulfoxide **33** (182 mg, 0.56 mmol) and NaOAc (300 mg, 3.66 mmol) in *o*-dichlorobenzene (2.7 mL) was refluxed under nitrogen atmosphere for 3 h. The reaction mixture was filtered to remove NaOAc and the filtrate was concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 9:1) to afford **35** (85 mg, 76%) as a pale yellow oil; IR ($CHCl_3$) 3444 (NH), 1707 (NCOO), 1656 (C=C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.38–2.14 (4H, m), 1.46 (9H, s), 2.29–2.42 (2H, m), 4.34 (1H, m), 4.51 (1H, br s), 4.96 (1H, q-like, *J*=2 Hz), 4.99 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{11}H_{19}NO_2$ (M^+) 197.1416, found 197.1422.

(2) *Preparation from trans-sulfoxide* **34**. According to the procedure described for pyrolysis of *cis*-sulfoxide **33**, pyrolysis of *trans*-sulfoxide **34** (183 mg, 0.57 mmol) gave **35** (82 mg, 75%). This compound was identical with **35** prepared from *cis*-sulfoxide **33**.

4.4.6. 1,1-Dimethylethyl *cis*-[2-(hydroxymethyl)cyclopentyl]carbamate (36). To a stirred solution of the *exo*-olefin **35** (110 mg, 0.51 mmol) in THF (0.71 mL) was added 9-BBN (0.5 M in hexane) (3.05 mL, 1.52 mmol) at 0°C under a nitrogen atmosphere. After the solution was stirred at room temperature for 1 h, 9-BBN (0.5 M in hexane) (3.05 mL, 1.52 mmol) was again added at 0°C. After being stirred at room temperature for 7 h, 6 M-NaOH (1.38 mL) and 30% H_2O_2 (1.38 mL) were added at 0°C. After being stirred at room temperature for 16 h, the reaction mixture was diluted with water and extracted with Et_2O. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduce pressure. The residue was purified by FCC (hexane/AcOEt 3:1) to afford the alcohol **36** (66 mg, 55%) as colorless crystals

(mp 113–114°C (hexane)) [lit.[12c] mp 111–112°C]; IR ($CHCl_3$) 3445 (OH, NH), 1685 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (1H, m), 1.45 (9H, s), 1.75–1.40 (4H, m), 2.00 (1H, m), 2.14 (1H, m), 3.38 (1H, br t, J=10 Hz), 3.57 (1H, td, J=10, 4 Hz), 3.89 (1H, br dd, J=10, 3 Hz), 4.10 (1H, m), 4.49 (1H, br d, J=5 Hz); HRMS (EI, *m/z*) calcd for $C_{11}H_{21}NO_3$ (M^+) 215.1521, found 215.1519.

4.4.7. Methyl *cis*-2-[[(1,1-dimethylethoxy)carbonyl]amino]cyclopentanecarboxylate (37). To a stirred solution of the *cis*-alcohol **36** (57 mg, 0.26 mmol) in water–acetone (3:2) (1.3 mL) were added $NaIO_4$ (180 mg, 0.84 mmol) and $RuO_2{\cdot}H_2O$ (15 mg, 0.12 mmol) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 7 h, *i*-PrOH (1.3 mL) was added and the reaction mixture was acidified with 1 M-HCl and extracted with AcOEt. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude *N*-Boc-carboxylic acid **37** as colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20–2.25 (6H, m), 1.45 (9H, s), 3.06 (1H, br q, J=7 Hz), 4.30 (1H, m), 5.10 (1H, br s). The spectral data of **37** were identical with those reported in the literature.[12c]

To a stirred solution of the crude *N*-Boc-carboxylic acid in MeOH (10 mL) was added a solution of CH_2N_2 (0.52 mmol) in Et_2O at 0°C under a nitrogen atmosphere. After being stirred at room temperature for 1 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by PTLC (hexane/AcOEt 3:1) to afford the ester **38** (37 mg, 57%) as a pale yellow oil; IR ($CHCl_3$) 3440 (NH), 1725 (COO), 1710 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (9H, s), 1.52–2.01 (6H, m), 3.00 (1H, br q, J=8 Hz), 3.69 (3H, s), 4.22 (1H, br quint., J=8 Hz), 4.92 (1H, br d, J=7 Hz); HRMS (CI, isobutene, *m/z*) calcd for $C_{12}H_{21}NO_4$+H (QM^+) 243.1470, found 243.1456. The spectral data of **38** were identical with those reported in the literature.[12c]

4.4.8. 1,1-Dimethylethyl *trans*-*N*-[2-(hydroxymethyl)cyclopentyl]-*N*-(phenylsulfanyl)carbamate (39). To a solution of the sulfoxide **34** (66 mg, 0.21 mmol) and γ-collidine (0.08 mL, 0.61 mmol) in dry MeCN (3.3 mL) was added a solution of TFAA (0.06 mL, 0.41 mmol) in dry MeCN (1.5 mL) under a nitrogen atmosphere at 0°C. After being stirred at same temperature for 1 h, a solution of $NaHCO_3$ (310 mg, 3.69 mmol) in H_2O (5.2 mL) was added to the reaction mixture. The resulting solution was stirred at same temperature for 2 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with 5% HCl, saturated aqueous $NaHCO_3$, and water, and then dried over Na_2SO_4, and concentrated at reduce pressure. Purification of the residue by MPCC (hexane/AcOEt 3:1) afforded the alcohol **39** (50 mg, 76%) as colorless oil; IR ($CHCl_3$) 3463 (OH), 1676 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.45 (1H, m), 1.55 (1H, m), 1.69 (1H, m), 1.73–1.80 (2H, m), 1.86 (1H, m), 2.00 (1H, m), 3.52 (1H, dd, J=11.5, 5.5 Hz), 3.56 (1H, dd, J=11.5, 4.5 Hz), 4.52 (1H, br q, J=8 Hz), 7.12–7.31 (5H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{25}NO_3S$ (M^+) 323.1555, found 323.1537.

4.4.9. 1,1-Dimethylethyl *trans*-[2-(hydroxymethyl)cyclopentyl]carbamate (41). To a solution of the alcohol **39** (51 mg, 0.16 mmol) in MeOH (4.7 mL) was added $NaBH_4$ (59 mg, 1.56 mmol) at room temperature under a nitrogen atmosphere. After being stirred at the same temperature for 1.5 h, usual work-up gave the crude product, which was purified by SCC (hexane→AcOEt) to afford the alcohol **41** (34 mg, 99%) (mp 74–76°C (hexane)) as colorless crystals; IR ($CHCl_3$) 3440 (OH, NH), 1686 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.36 (1H, m), 1.39 (1H, m), 1.44 (9H, s), 1.56–1.70 (2H, m), 1.87–1.78 (2H, m), 2.04 (1H, dtd, J=13, 8, 6 Hz), 3.50 (1H, m), 3.63 (1H, m), 3.68 (1H, m), 3.74 (1H, m), 4.64 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{11}H_{21}NO_3$ (M^+) 215.1521, found 215.1532; Anal. calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.20; H, 10.11; N, 6.63.

4.4.10. *trans*-2-[(1,1-Dimethylethoxy)carbonyl]amino]cyclopentanecarboxylic acid (42). To a stirred solution of the *trans*-alcohol **41** (25 mg, 0.12 mmol) in water–acetone (3:2) (0.6 mL) were added $NaIO_4$ (81 mg, 0.38 mmol) and $RuO_2{\cdot}H_2O$ (7 mg, 0.05 mmol) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 14 h, *i*-PrOH (0.6 mL) was added and the reaction mixture was acidified with 1 M-HCl and extracted with AcOEt. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford the *N*-Boc-carboxylic acid **42** (26 mg, 92%) (mp 142–145°C (hexane–Et_2O)) as colorless crystals; IR ($CHCl_3$) 3444 (NH), 3440–2500, 1742 (COOH), 1709 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.46 (1H, m), 1.71 (2H, br quint., J=7 Hz), 1.89 (1H, m, 5-H), 2.10 (1H, m), 2.13 (1H, m), 2.75 (1H, m), 4.03 (1H, m), 4.92 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{11}H_{19}NO_4$ (M^+) 229.1314, found 229.1285; Anal. calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.35; H, 8.22; N, 6.10.

4.4.11. Methyl *trans*-2-[[(1,1-dimethylethoxy)carbonyl]amino]cyclopentanecarboxylate (43). To a stirred solution of the *trans*-*N*-Boc-carboxylic acid **42** (10 mg, 0.04 mmol) in MeOH (10 mL) was added a solution of CH_2N_2 (0.1 mmol) in Et_2O at 0°C under a nitrogen atmosphere. After being stirred at room temperature for 1 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by PTLC (hexane/AcOEt 3:1) to afford the ester **43** (8 mg, 77%) (mp 62–63°C (hexane)) [lit.[14] (−)-**43** mp 73–74°C, (+)-**43** mp 66–67°C] as colorless crystals; IR ($CHCl_3$) 3448 (NH), 1720 (COO), 1710 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.40–2.02 (6H, m), 2.59 (1H, br q, J=8 Hz), 3.69 (3H, s), 4.11 (1H, br quint., J=8 Hz), 4.58 (1H, br s); HRMS (CI, isobutene, *m/z*) calcd for $C_{12}H_{21}NO_4$+H (QM^+) 243.1470, found 243.1492.

The spectral data of **43** were identical with those reported in the literature.[14]

4.4.12. *trans*-2-Aminocyclopentanecarboxylic acid (44). A solution of the *N*-Boc-carboxylic acid **43** (34 mg, 0.15 mmol) in 4 M-HCl-dioxane (0.32 mL, 1.19 mmol) was stirred at room temperature under a nitrogen atmosphere for 2 h and then concentrated under reduced

pressure. The residue was dissolved in H_2O and loaded on resin (Amberlite IR-120B) in a column and washed with water, and then 0.5 M-NH_4OH. After concentration of the eluate under reduced pressure, the residue was recrystallized from EtOH to give the amino acid **44** (14 mg, 72%) as colorless crystals: mp 236–238°C (dec.) [lit.[20] mp 240°C (dec.)]; IR (nujol) 3320, 3138–2363, 1627, 1568 (N^+H_3, COO^-) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.55–2.25 (6H, m), 2.69 (1H, br q, J=8 Hz), 3.76 (1H, br q, J=8 Hz); HRMS (EI, m/z) calcd for $C_{10}H_{11}NO_2$ (M^+) 129.0790, found 129.0817.

4.4.13. 1,1-Dimethylethyl *trans*-[1-(4-methylphenyl)-sulfonyl-4-(phenylsulfanyl)methyl-3-pyrrolidinyl]carbamate (45c). To a stirred solution of *trans*-**23c** (500 mg, 1.28 mmol) in H_2O–MeCN (1:15) (25 mL) was added $Mo(CO)_6$ (236 mg, 0.89 mmol) at room temperature under a nitrogen atmosphere. After the solution was refluxed for 2 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude amine as a yellow oil. To a stirred solution of the crude amine in CH_2Cl_2 (109 mL) were added Et_3N (0.27 mL, 1.91 mmol) and a solution of $(Boc)_2O$ (0.44 mL, 1.91 mmol) in CH_2Cl_2 (41 mL) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 3 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 5:1) to afford **45c** (438 mg, 74%) as colorless crystals (mp 181–184°C (hexane)); IR ($CHCl_3$) 3437 (NH), 1710 (NCOO), 1161 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.41 (9H, s), 2.14 (1H, m), 2.43 (3H, s), 2.52 (1H, br dd, J=13, 10 Hz), 2.96 (1H, br t, J=8 Hz), 3.04 (1H, br dd, J=13, 5 Hz), 3.09 (1H, m), 3.46 (1H, br t, J=8 Hz), 3.59 (1H, br t, J=8 Hz), 3.87 (1H, m), 4.54 (1H, br d, J=7 Hz), 7.18–7.34 (7H, m), 7.68 (2H, br d, J=8 Hz); NOE was observed between NH (δ 4.54) and 4-H (δ 2.14), and CH_2SPh (δ 3.04) and 3-H (δ 3.87) in NOESY spectroscopy. HRMS (EI, m/z) calcd for $C_{23}H_{30}N_2O_4S_2$ (M^+) 462.1647, found 462.1661; Anal. calcd for $C_{23}H_{30}N_2O_4S_2$: C, 59.71; H, 6.54; N, 6.06; S, 13.86. Found: C, 59.46; H, 6.52; N, 6.04; S, 13.82.

4.4.14. 1,1-Dimethylethyl *cis*-3-[(1,1-dimethylethoxycarbonyl)amino]-4-[(phenylsulfanyl)methyl]-1-pyrrolidinecarboxylate (45d). According to the procedure given for the conversion of **23c** into **45c**, demethoxylation of the *cis*-methoxyamine **22d** (39 mg, 0.12 mmol) with $Mo(CO)_6$ (42 mg, 0.12 mmol) followed by *t*-butoxycarbonylation of the resulting amine with $(Boc)_2O$ (25 mg, 0.12 mmol) afford *N*-Boc-**45d** (18 mg, 38%) as a pale yellow oil; IR ($CHCl_3$) 1689 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (18H, s) 2.38–2.60 (1H, br s), 2.66–2.84 (1H, m), 3.10 (1H, dd, J=11, 9 Hz), 3.05–3.40 (2H, m), 3.51 (1H, m), 3.42–3.76 (1H, m), 4.28 (1H, br s), 4.65 (1H, br s), 7.20–7.40 (5H, m); HRMS (EI, m/z) calcd for $C_{21}H_{32}N_2O_4S$ (M^+) 408.2081, found 408.2089.

The presence of rotamers precluded a comprehensive assignment of all proton resonances.

4.4.15. 1,1-Dimethylethyl *trans*-3-[(methoxy)(1,1-dimethylethoxycarbonyl)amino]-4-[(phenylsulfanyl)methyl]-1-pyrrolidinecarboxylate (46). To a solution of *trans*-methoxyamine **23d** (324 mg, 0.96 mmol) in CH_2Cl_2 (14 mL) were added Et_3N (0.13 mL, 0.96 mmol), DMAP (50 mg, 0.41 mmol), and $(Boc)_2O$ (1.0 g, 4.8 mmol) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 48 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by MCC (hexane/AcOEt 3:1) to afford **46** (199 mg, 49%) (mp 72–73°C (hexane)) as colorless crystals; IR ($CHCl_3$) 1688 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (9H, s), 1.52 (9H, s), 2.50–2.88 (2H, m), 3.02–3.16 (1H, m), 3.19 (1H, dd, J=12, 3.5 Hz), 3.28–3.48 (1H, m), 3.50–3.87 (2H, m), 3.62 (3H, s), 4.39 (1H, br q, J=8.5 Hz), 7.15–7.40 (5H, m); HRMS (EI, m/z) calcd for $C_{22}H_{34}N_2O_5S$ (M^+) 438.2186, found 438.2173.

The presence of rotamers precluded a comprehensive assignment of all proton resonances.

4.4.16. 1,1-Dimethylethyl *cis*-3-[(methoxy)(1,1-dimethylethoxycarbonyl)amino]-4-[(phenylsulfanyl)methyl]-1-pyrrolidinecarboxylate (49). According to the procedure given for the conversion of **23d** into **46**, *t*-butoxycarbonylation of *cis*-methoxyamine **22d** (324 mg, 0.96 mmol) with $(Boc)_2O$ (1.0 mg, 4.8 mmol) afford *N*-Boc-**49** (248 mg, 61%) as pale yellow oil; IR ($CHCl_3$) 1687 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (9H, s), 1.52 (9H, s), 2.46 (1H, m), 2.80–2.92 (1H, m), 3.15 (1H, dd, J=13, 5 Hz), 3.33 (1H, br q, J=10 Hz), 3.52–3.78 (3H, m), 3.70 (3H, s), 4.63 (1H, m), 7.16–7.36 (5H, m); HRMS (EI, m/z) calcd for $C_{22}H_{34}N_2O_5S$ (M^+) 438.2187, found 438.2175.

The presence of rotamers precluded a comprehensive assignment of all proton resonances.

4.4.17. 1,1-Dimethylethyl *trans*-3-formyl-4-[(methoxy)-(1,1-dimethylethoxycarbonyl)amino]-1-pyrrolidinecarboxylate (48). (1) *Preparation from trans*-**46**. To a solution of **46** (172 mg, 0.39 mmol) in CH_2Cl_2 (14 mL) was added dropwise a solution *m*CPBA (70% assay) (67 mg, 0.39 mmol) in CH_2Cl_2 (21 mL) under a nitrogen atmosphere at 0°C. The reaction mixture was made alkaline with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by MPCC (hexane/AcOEt 1:5) afforded the sulfoxide **47** (147 mg, 83%) as a pale yellow oil and as a 1:1 diastereomeric mixture based on a sulfinyl group; HRMS (CI, isobutene, m/z) calcd for $C_{22}H_{34}N_2O_6S+H$ (QM^+) 455.2214, found 455.2218. To a solution of the sulfoxide **47** (62 mg, 0.14 mmol) and 2,6-lutidine (0.06 mL, 0.55 mmol) in dry MeCN (1.5 mL) was added a solution of TFAA (0.08 mL, 0.55 mmol) in dry MeCN (0.4 mL) under a nitrogen atmosphere at 0°C. After being stirred at same temperature for 2 h, a solution of $NaHCO_3$ (140 mg, 1.66 mmol) in H_2O (3 mL) was added to the reaction mixture. The resulting solution was stirred at same temperature for 2 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic phase washed with 5% HCl, saturated aqueous $NaHCO_3$, and water, and then dried over Na_2SO_4 and concentrated under reduced

pressure. Purification of the residue by MPCC (hexane/AcOEt 2:1) afforded the aldehyde **48** (43 mg, 91%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (9H, s), 1.51 (9H, s), 3.20–3.36 (1H, m), 3.46–3.52 (1H, m), 3.60–3.74 (3H, s), 4.85 (1H, br s), 9.67 (1H, d, J=3 Hz). After being characterized by NMR spectrum, the aldehyde **48** was immediately subjected to the following reaction.

(2) *Preparation from cis*-**49**. According to the procedure given for the conversion of **46** into **48**, the oxidation of *cis*-methoxyamine **49** (324 mg, 0.96 mmol) with *m*CPBA (1.0 mg, 4.8 mmol) followed by Pummerer rearrangement afford aldehyde **48** (102 mg, 44% from **49**) as pale yellow oil. This compound was identical with **48** prepared from *trans*-**46**.

4.4.18. 1-(1,1-Dimethylethyl) 3-methyl *trans*-4-[(methoxy)(1,1-dimethylethoxycarbonyl)amino]-1,3-pyrrolidinedicarboxylate (52). To a solution of the aldehyde **48** (43 mg, 0.125 mmol) in a mixture of THF (0.53 mL), *t*-BuOH (0.53 mL), and H_2O (0.19 mL) were added 2-methyl-2-butene (2.0 M in THF, 0.51 mL), NaH_2PO_4 (1.0 M in H_2O, 0.38 mL), and then 80% $NaClO_2$ (43 mg, 0.38 mmol) under nitrogen atmosphere at room temperature. The reaction mixture was stirred at the same temperature for 24 h and then concentrated under reduced pressure. After dilution with aqueous $KHSO_4$ (0.5 M), the aqueous phase was extracted with AcOEt. The organic phase was washed with water, saturated aqueous Na_2SO_3, and brine, and then dried over $MgSO_4$ and concentrated under reduced pressure to give the crude carboxylic acid **51** as pale yellow amorphous. To a stirred solution of the carboxylic acid **51** (36 mg, 0.1 mmol) in MeOH/benzene (2:7) (0.86 mL) was added a solution of $TMSCHN_2$ (2 M in hexane, 0.07 mL, 0.14 mmol) at room temperature under a nitrogen atmosphere. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 2:1) to afford the ester **52** (19 mg, 42%) (mp 63–64°C (Et_2O/hexane)) as colorless crystals; IR ($CHCl_3$) 3448 (NH), 1720 (COO), 1710 (NCOO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (9H, s), 1.51 (9H, s), 3.26–3.47 (2H, m), 3.55 (1H, dd, J=11, 9 Hz), 3.72 (3H, s), 3.76 (3H, s), 4.82 (1H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{30}N_2O_7$ (M^+) 374.2051, found 374.1058.

The presence of rotamers precluded a comprehensive assignment of all proton resonances.

4.4.19. 1-(1,1-Dimethylethyl) 3-methyl *trans*-4-[1,1-dimethylethoxycarbonyl)amino]-3-pyrrolidinecarboxylate (53). According to the procedure given for the demethoxylation of **23c**, **52** (19 mg, 0.05 mmol) was treated with $Mo(CO)_6$ (18 mg, 0.07 mmol) to afford *N*-Boc-**53** (15 mg, 87%) as pale yellow oil; IR ($CHCl_3$) 3441 (NH), 1736 (COO), 1692 (NCOO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.46 (9H, s), 2.97 (1H, br q, J=7 Hz), 3.18 (1H, br dd, J=11, 6 Hz), 3.64 (2H, br d, J=8 Hz), 3.76 (1H, dd, J=11, 6 Hz), 3.73 (3H, s), 4.36 (1H, br quint. J=6.5 Hz), 4.71 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{16}H_{28}N_2O_6$ (M^+) 344.1945, found 344.1958.

The presence of rotamers precluded a comprehensive assignment of all proton resonances.

4.4.20. *trans*-4-Amino-3-pyrrolidinecarboxylic acid (54). To a solution of **53** (17 mg, 0.05 mmol) in MeOH/H_2O (3:1) (1.5 mL) was added a solution of LiOH (24 mg, 0.57 mmol) at 0°C under nitrogen atmosphere. After being stirred at the same temperature for 1 h, the reaction mixture was acidified to pH 3 and extracted with $CHCl_3$. The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude *N*-Boc-carboxylic acid. A solution of the carboxylic acid (17 mg, 0.05 mmol) in 4 M-HCl-dioxane (0.1 mL, 0.4 mmol) was stirred at room temperature under a nitrogen atmosphere for 1 h and concentrated under reduced pressure. The residue was dissolved in H_2O and loaded on resin (Amberlite IR-120B) in a column and washed with water and then 0.5 M-NH_4OH. After concentration of the eluate under reduced pressure, β-amino acid **54** (6 mg, 94%) was obtained as yellow amorphous; IR (nujol) 3390, 3165–2373, 1585, 1561 (N^+H_3, COO^-) cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 2.59 (1H, ddd, J=7.5, 6, 5 Hz), 2.79 (1H, dd, J=12, 5 Hz), 3.16 (1H, m), 3.26 (1H, dd, J=12, 6 Hz), 3.28–3.32 (2H, m), 3.67 (1H, dt, J=6, 5 Hz); HRMS (CI, isobutene, *m/z*) calcd for $C_5H_{11}N_2O_2$ (QM^+) 131.0820, found 131.0835.

The presence of rotamers precluded a comprehensive assignment of all proton resonances.

4.5. Conversion of sulfide 24i into aldehydes 55 and 56

According to the procedure given for the conversion of **23d** into **48**, *t*-butoxycarbonylation of **24i** with $(Boc)_2O$, oxidation with *m*CPBA, and then Pummerer rearrangement gave the *cis*-**55** (23%) and *trans*-**56** (46%).

4.5.1. 1,1-Dimethylethyl (2α,3β,4β)-4-formyl-3-[(methoxy)(1,1-dimethylethoxycarbonyl)amino]-2-phenyl-1-pyrrolidinecarboxylate (55). Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (9H, br s), 1.47 (9H, br s), 1.51 (9H, s), 3.22 (1H, br q, J=7 Hz), 3.72 (3H, s), 3.83 (1H, m), 4.10 (1H, br dd, J=10, 7 Hz), 5.16 (1H, m), 7.17–7.40 (5H, m), 9.71 (1H, br s). The presence of rotamers precluded a comprehensive assignment of all proton resonances. After being characterized by NMR spectrum, the aldehyde **55** was immediately subjected to the following reaction.

4.5.2. 1,1-Dimethylethyl (2α,3β,4α)-4-formyl-3-[(methoxy)(1,1-dimethylethoxycarbonyl)amino]-2-phenylpyrrolidine-1-carboxylate (56). Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (9H, br s), 1.27 (9H, br s), 3.33 (1H, br qd, J=8, 3 Hz), 3.84 (3H, s), 3.81–4.08 (2H, m), 4.72–4.93 (2H, m), 7.18–7.38 (5H, m), 9.66 (1H, br d, J=3 Hz). The presence of rotamers precluded a comprehensive assignment of all proton resonances. After being characterized by NMR spectrum, the aldehyde **56** was immediately subjected to the following reaction.

4.6. Isomerization of the *cis*-aldehyde 55 to the trans-aldehyde 56

A suspension of the *cis*-aldehyde **55** (9 mg, 0.02 mmol) and

SiO_2 (39 g) in CH_2Cl_2 (1 mL) was stirred at room temperature for 2 h. SiO_2 was filtered off and the filtrate was concentrated to give the *trans*-aldehyde **56** (6 mg, 67%) whose spectral data were identical with those of an authentic sample obtained from the sulfide **24i**.

4.6.1. 1-(1,1-Dimethylethyl) 3-methyl (3α,4β,5α)-4-[(methoxy)(1,1-dimethylethoxycarbonyl)amino]-5-phenyl-1,3-pyrrolidinedicarboxylate (58). According to the procedure given for the conversion of **48** into **52**, oxidation of **56** with $NaClO_2$ followed by methylation of the resulting carboxylic acid **57** with $TMSCHN_2$ afforded the ester **58** (80%) as a pale yellow oil; IR ($CHCl_3$) 3441 (NH), 1731 (COO), 1690 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (9H, s), 1.21 (9H, s), 3.39 (1H, td, J=10, 8 Hz), 3.72 and 3.84 (each 3H, s), 3.77 (1H, t, J=10 Hz), 4.11 (1H, dd, J=10, 8 Hz), 4.68–4.84 (2H, m), 7.18–7.36 (5H, m); HRMS (EI, *m/z*) calcd for $C_{23}H_{34}N_2O_7$ (M^+) 450.2363, found 450.2365.

The presence of rotamers precluded a comprehensive assignment of all proton resonances.

4.6.2. 1-(1,1-Dimethylethyl) 3-methyl (3α,4β,5α)-4-[1,1-dimethylethoxycarbonyl)amino]-5-phenyl-1,3-pyrrolidinedicarboxylate (59). According to the procedure given for the demethoxylation of **23c**, a solution of **58** (28 mg, 0.062 mmol) and $Mo(CO)_6$ (46 mg, 0.174 mmol) in $EtCN/H_2O$ (15:1) (1 mL) was refluxed for 4 h to give *N*-Boc-**59** (13 mg, 50%) (mp 172–174°C (Et_2O)) as colorless crystals; IR ($CHCl_3$) 3440 (NH), 1731 (COO), 1690 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (9H, s), 1.42 (9H, s), 3.16 (1H, m), 3.56 (3H, br s), 3.96 (2H, m), 4.28 (1H, m), 4.67 (1H, m), 4.79 (1H, m), 7.18–7.36 (5H, m); HRMS (EI, *m/z*) calcd for $C_{22}H_{32}N_2O_6$ (M^+) 420.2259, found 420.2254.

The presence of rotamers precluded a comprehensive assignment of all proton resonances.

4.6.3. (3α,4β,45α)-4-Amino-5-phenyl-3-pyrrolidinecarboxylic acid (60). According to the procedure given for the conversion of **53** into **54**, the deprotection of **59** afforded β-amino acid **60** (92%) (mp 234–236°C (EtOH)); IR (nujol) 3445, 3269–2357, 1627, 1545 (N^+H_3, COO^-) cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 2.80–4.20 (6H, m), 7.38 (5H, m); HRMS (CI, isobutene, *m/z*) calcd for $C_{11}H_{15}N_2O_2+H$ (QM^+) 207.1133, found 207.1124.

The presence of rotamers precluded a comprehensive assignment of all proton resonances.

Acknowledgements

This work was supported in part by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan and a research grant from the Science Research Promotion Fund of the Japan Private School Promotion Foundation.

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