HETEROCYCLES, Vol. 89, No. 1, 2014, pp. 143 - 169. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 9th November, 2013, Accepted, 4th December, 2014, Published online, 13th December, 2013
DOI: 10.3987/COM-13-12881

PREPARATION OF CYCLIC β-AMINO ACID DERIVATIVES WITH QUATERNARY CARBON CENTER VIA A RADICAL ADDITION-CYCLIZATION SEQUENCE

Norihiko Takeda,[a] Masafumi Ueda,[a] Seiko Kajisa,[a] Kenji Matsuno,[b] Takeaki Naito,[a] and Okiko Miyata*[a]

[a]Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan [b]Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University, Okayama 700-8530, Japan
*Corresponding author. E-mail: miyata@kobepharma-u.ac.jp (O. Miyata)

Abstract – A new method has been developed for the construction of α,α-disubstituted cyclic β-amino acid derivatives via the sulfanyl radical addition-cyclization reaction of oxime ether connected with acrylate. This reaction proceeded smoothly to give the cyclized products that contained a quaternary carbon center. Furthermore, the use of carbon centered radicals in the reaction allowed for the formation of cyclic amines containing various alkyl chains. The cyclized product with a quaternary carbon center could also be converted to sterically congested cyclic β-amino acid.

INTRODUCTION

Cyclic amino acids have recently attracted considerable attention because their incorporation into peptides can affect the conformational freedom of the resulting peptides, which can affect their bioactivity. Furthermore, cyclic amino acids can be used for the construction of peptidomimetics, which could be used as potential therapeutic agents. Among the different types of cyclic amino acids known in the literature, cyclic β-amino acid structures in particular can be found in number of biologically active compounds, including the potent antifungal agent cispentacin **1**,[1] the potent bacterial isoleucyl-tRNA synthetase inhibitor PLD-118 **2**,[2] and the potent influenza neuraminidase inhibitor A-192558 **3**[3] (Figure 1). In addition, cyclic β-amino acids such as *trans*-2-aminocyclopentanecarboxylic acid (ACPC) **4**,[4] *trans*-4-amino-3-pyrrolidinecarboxylic acid (APC) **5**,[4] and *trans*-2-aminocyclohexanecarboxylic acid

(ACHC) **6**[5] have been used as building blocks for the construction of biologically active and water-soluble β-peptides, which can fold into stable helical structures. β-Peptides, which are composed of ACPC **4** and APC **5**, tend to form 12-helical structures, whereas the oligomer of ACHC **6** is capable of forming a 14-helical structure in aqueous solution. For this reason, β-amino acid oligomers (β-peptides) have attracted increasing levels of interest from organic and medicinal chemists over the past decade. Some β-peptides consisting of the conformationally rigid alicyclic and heterocyclic β-amino acids, in particular, such as the antimicrobial 17 residue β-peptide **7**[4a] (called β-17) and the water-soluble short chain β-peptide **8**,[4b] display 12-helical secondary structures. In general, β-peptides show greater chemical stability than the corresponding α-peptides, as well as better stability towards enzymatic degradation, and are therefore cleared from the systemic circulation at a slower rate (i.e. longer half-lives *in vivo*). In contrast, however, they generally posses poorer solubility properties and may require intravenous administration.

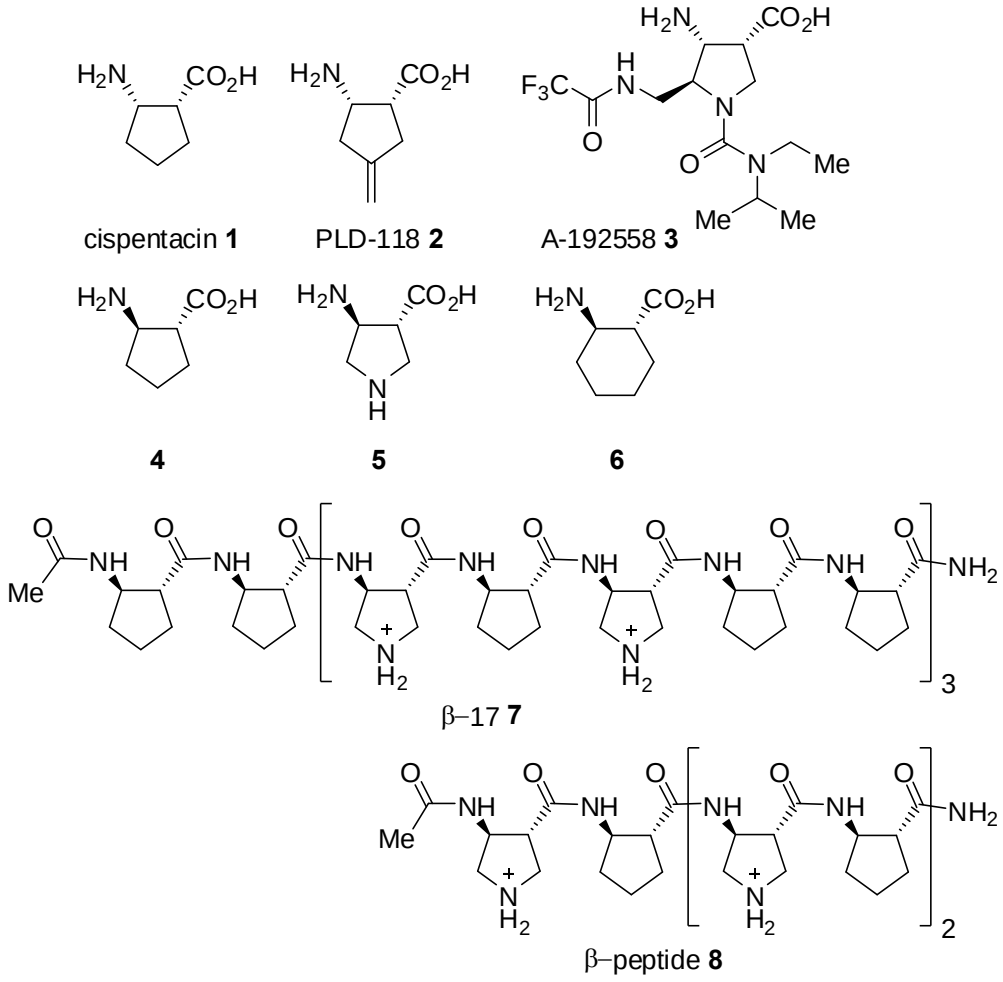
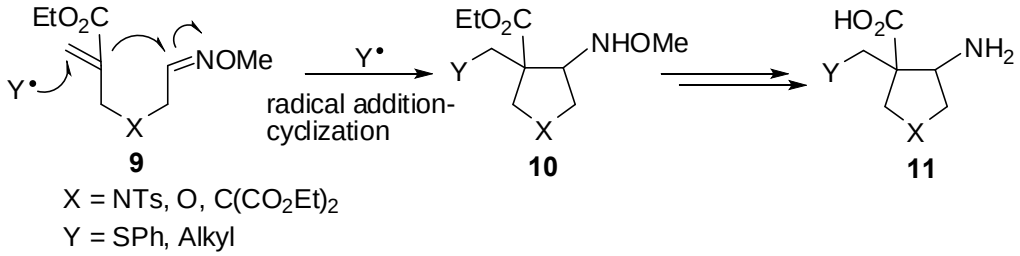


Figure 1. Cyclic β-amino acids and β-peptides

While it is well known that the incorporation of amino acids containing a quaternary carbon center into peptide chains generally leads to greater stability against metabolic degradation, changes of this type can also have a significant impact of the conformational rigidity, lipophilicity, and selectivity properties of the resulting peptides.[6] With this in mind, the synthesis of conformationally restricted cyclic β-amino acids containing a quaternary carbon center that could be embedded in β-peptides would be of considerable interest, and could give rise to a new class of polypeptide helices.

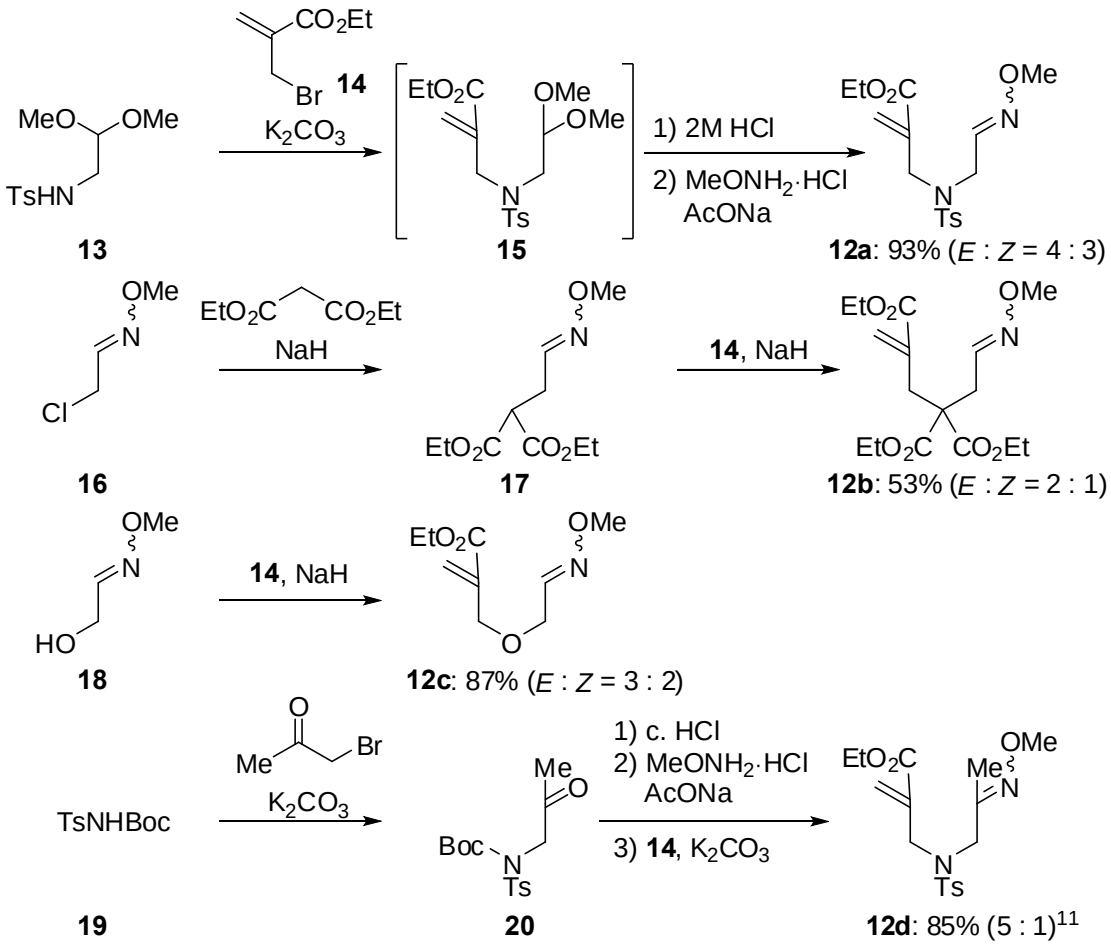
Although a variety of synthetic approaches have been described in the literature for the synthesis of α-monosubstituted cyclic β-amino acids,[7] the synthesis of α,α-disubstituted cyclic β-amino acids are relatively scarce,[8] and research towards the development of an effective synthetic method for the construction of sterically congested cyclic β-amino acids remains a major challenge. With this in mind, it was envisaged that the radical addition-cyclization reaction of the acrylate-tethered-oxime ether **9** would provide alicyclic amine **10** with a quaternary carbon center which could be readily converted to the α,α-disubstituted cyclic β-amino acid **11** using standard transformations (Scheme 1). Herein, we report the synthesis of cyclic β-amino acid derivatives containing a quaternary carbon center via the radical addition-cyclization reaction of oxime ether **9** involving sulfanyl as well as variety of alkyl radicals.[9,10]



Scheme 1. Radical addition-cyclization of oxime ether **9**

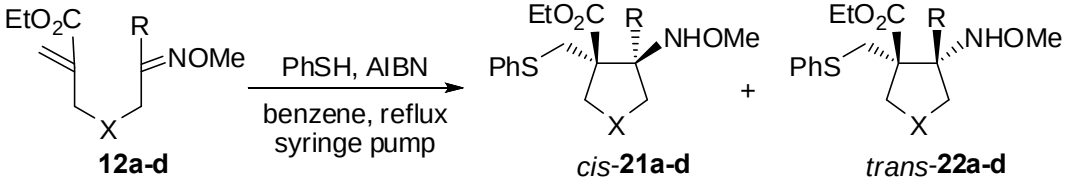
RESULTS AND DISCUSSION

The requisite substrates **12a-d** for the radical reaction were prepared as follows (Scheme 2). The alkylation of sulfonamide **13** with ethyl 2-(bromomethyl)acrylate **14** gave dimethyl acetal **15**, which was subsequently hydrolyzed with 2 M HCl before being treated with methoxyamine to give the oxime ether **12a**. The oxime ether **12b**, which contained a quaternary carbon center instead of an NTs group was prepared by the sequential alkylation of diethyl malonate with α-chloro oxime ether **16** and ethyl 2-(bromomethyl)acrylate **14** under basic conditions. The *O*-alkylation of the α-hydroxy oxime ether **18** with **14** afforded the oxime ether **12c**. The *N*-Boc tosylamine **19** was converted to ketoxime ether **12d**[11] via a four step linear sequence as follows. The alkylation of **19** with bromoacetone gave **20**, which was Boc-deprotected with 2 M HCl before being treated with methoxyamine to give the oxime ether. Subsequent alkylation of the oxime ether with **14** gave the **12d** in good yield.



Scheme 2. Preparation of various oxime ethers **12a-d**

Table 1. Sulfanyl radical addition-cyclization reactions of the oxime ethers **12a-d**[a]



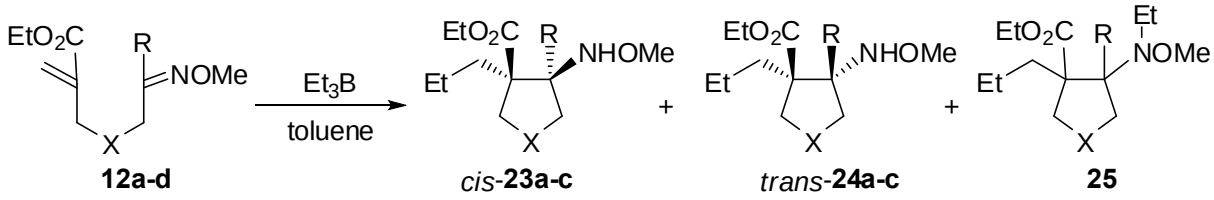
Entry	Substrate	X	R	Yield (%)[b]	*cis*-**21** / *trans*-**22** ratio
1	**12a**	NTs	H	94	60 : 40
2	**12b**	$C(CO_2Et)_2$	H	78	57 : 43
3	**12c**	O	H	86	50 : 50
4	**12d**	NTs	Me	25 (65)[c]	52 : 48[d]

[a] A solution of PhSH (1.3 eq.) and AIBN (0.5 eq.) in benzene was added dropwise by a syringe pump to the oxime ethers **12a-d** in refluxing benzene. [b]Isolated yields. [c]Yield in parentheses represents the recovered oxime ether. [d] The stereostructures of the *cis*- and *trans*-isomer have not been established.

We initially studied the sulfanyl radical addition-cyclization reactions of the oxime ethers **12a-d** (Table 1). The sulfanyl radical addition-cyclization reaction of **12a** with PhSH and AIBN proceeded smoothly to

give a 60 : 40 separable mixture of the *cis*- and *trans*-pyrrolidines **21a** and **22a** in 94% combined yield (Table 1, entry 1). The reactions of **12b** (X = $C(CO_2Et)_2$) and **12c** (X = O) proceeded in a similar manner to that of **12a** to give *cis*-**21b** and *trans*-**22b**, and *cis*-**21c** and *trans*-**22c** in 78 and 86% yields, respectively (entries 2 and 3). When the ketoxime ether **12d** was subjected to the same conditions, the sterically congested cyclic amines **21d** and **22d** were obtained in low yield together with recovered **12d** (entry 4). This method therefore provided access to the substituted pyrrolidines **21a** and **22a**, tetrahydrofurans **21c** and **22c**, and carbocyclic amines **21b** and **22b**, which all contained a quaternary carbon center, in good yields via the sulfanyl radical addition-cyclization reaction of the corresponding oxime ethers **12a-c**, although the stereoselectivities of these reactions were unsatisfied.

Table 2. Ethyl radical addition-cyclization reactions of oxime ethers using Et_3B[a]



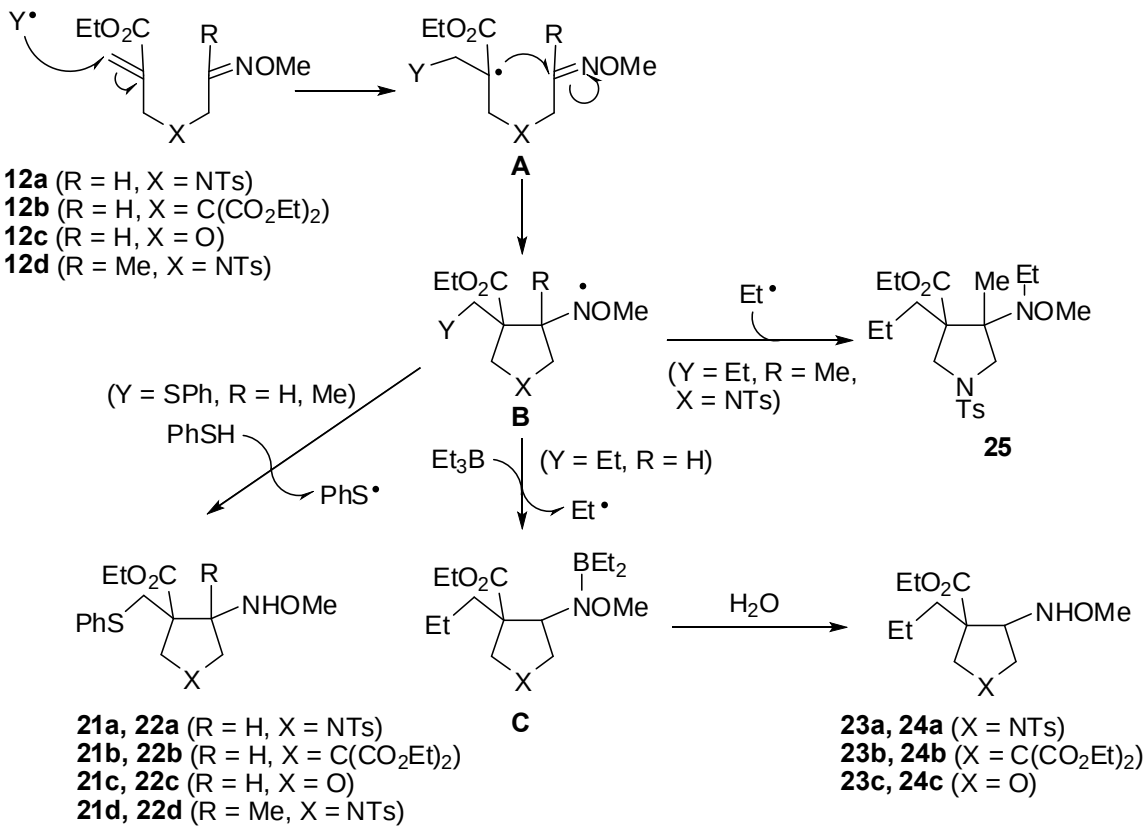
Entry	Substrate	X	R	Et_3B (eq.)	*T* (°C)	Yield (%)[b]	*cis*-**23**/*trans*-**24** ratio
1	**12a**	NTs	H	5.0	0	84	76 : 24
2	**12a**	NTs	H	10.0	-78	82	94 : 6
3	**12b**	$C(CO_2Et)_2$	H	10.0	-78	72	36 : 64
4	**12c**	O	H	10.0	-78	65	69 : 31
5	**12d**	NTs	Me	7.5	-40	98	-[c]

[a]The reactions of the oxime ethers **12a-d** were carried out with Et_3B in toluene. [b]Isolated yields. [c]Stereoselectivity was 52 : 48. The stereostructures of the *cis*- and *trans*-isomer **25** have not been established.

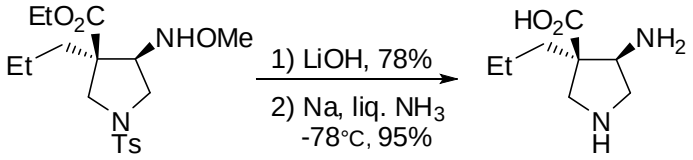
We then proceeded to examine the ethyl radical addition-cyclization reactions of the oxime ethers **12a-d** using triethylborane as an ethyl radical source (Table 2). The reaction of **12a** with Et_3B in toluene at 0 °C for 1 h afforded the cyclized products *cis*-**23a** and *trans*-**24a** in 84% combined yield with 76 : 24 stereoselectivity (Table 2, entry 1). Changing the reaction temperature from 0 to –78 °C showed significant effect in the stereoselectivity to predominately give *cis*-**23a** with high stereoselectivity (entry 2). In contrast, the application of the same reaction conditions to oxime ether **12b** resulted in the formation of the carbocyclic amines *cis*-**23b** and *trans*-**24b** in good yields with a reversal in the *cis*/*trans* ratio (entry 3). The oxime ether **12c** also reacted smoothly under these conditions to give the tetrahydrofurans *cis*-**23c** and *trans*-**24c** in a slightly lower yield compared with **12a** and **12b** (entry 4). In general, the reactivity of the ketoxime ether for the radical addition reaction was very low and therefore less developed than that of the aldoxime ether.[12] Surprisingly, the ethyl radical addition-cyclization

reaction of ketoxime ether **12d** proceeded smoothly even at –40 °C to give the *C*,*N*-diethylated product **25** containing a vicinal quaternary carbon center in 98% yields with none of the corresponding *cis*-**23d** or *trans*-**24d** being isolated (entry 5). The diethylated product **25** was presumably formed as a result of the *in situ* trapping of an *N*-centered radical by an ethyl radical.

Based on our current results, as well as previous results from the literature, we have proposed a possible reaction pathway for this transformation (Scheme 3).[13] The addition of both sulfanyl and ethyl radicals to the β-position of the alkene moiety followed by a 5-*exo*-*trig* cyclization onto the oxime ether via the generation of the α-carbonyl radical **A** would proceed regioselectively to give the aminyl radical **B** (**12**→**A**→**B**). In the sulfanyl radical addition-cyclization, the aminyl radical **B** would then be reduced by thiophenol to give the sulfanylated products **21a-d** and **22a-d**. The Et_3B induced radical reaction is well known to work not only as a radical initiator but also as a chain transfer agent. Therefore, when Et_3B is used as an ethyl radical source, aminyl radical **B** is then trapped by Et_3B to form the borylamine **C**. The desired products **23a-c** and **24a-c** would then be obtained following a work up procedure. In the case of ketoxime ether **12d** (R = Me), the corresponding **B** species was trapped by an ethyl radical to give the *C*,*N*-diethylated products **25**. The formation of this product was attributed to the sterically congested aminyl radical **B**, which presumably prevented the trapping of **B** with Et_3B.



Scheme 3. Reaction pathway for the radical addition-cyclization reactions of the acrylate-tethered-oxime ethers



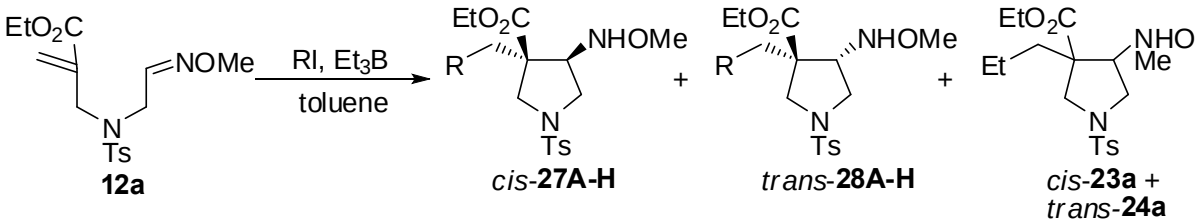
cis-**23a** (})-*cis*-**26**

Scheme 4. Conversion of *cis*-**23a** to α,α-disubstituted *cis*-β-amino acid **26**

The conversion of *cis*-**23a** to the α,α-disubstituted cyclic β-amino acid **26** was readily achieved via the conventional reaction sequence (Scheme 4). The hydrolysis of the ethoxycarbonyl group followed by the reductive cleavage of the methyloxy group with concomitant deprotection of the tosyl group under Birch reduction conditions gave the desired cyclic β-amino acid **26** containing a quaternary carbon center in 74% yield (2 steps). This conformationally restricted β-amino acid **26** represents an attractive building block that could give rise to a new class of polypeptide helices.

The sulfanyl and ethyl radical addition-cyclization reactions of acrylate tethered oxime ethers can be summarized as follows: (a) this reaction sequence proceeded in a regioselective manner to afford the desired cyclization products containing a quaternary carbon center via a 5-*exo*-*trig* cyclization reaction exclusively, with none of the 6-*endo*-*trig* products being obtained; (b) the sulfanyl radical addition-cyclization reactions of **12a-c** proceeded smoothly to give cyclized products in high yields; (c) the addition reactions of the ethyl radical to **12a-c** were more efficient than those of the sulfanyl radical, especially in terms of the high degree of stereocontrol observed in the ethyl radical addition-cyclization reaction of **12a** at –78 °C, where *cis*-**23a** was obtained as the major product; and (d) the ethyl radical reaction of ketoxime **12d** proceeded smoothly even at –40 °C to afford the cyclic amine **25** with a vicinal quaternary carbon centers. Thus, we have established that the sulfanyl and ethyl radical cyclization reactions represent effective methods for the formation of 5-membered products containing a quaternary carbon center. Moreover, the synthesis of the sterically congested cyclic β-amino acid **26** from *cis*-**23a** was easily achieved.

Table 3. Addition-cyclization reactions of oxime ether **12a** with various alkyl radicals



12a *cis*-**27A-H** *trans*-**28A-H** *cis*-**23a** + *trans*-**24a**

A: R = *i*-Pr, **B**: R = *s*-Bu, **C**: R = *c*-Hex, **D**: R = *t*-Bu, **E**: R = $Me(CH_2)_9$, **F**: R = $Me(CH_2)_{12}$,

G: R = $MeO_2C(CH_2)_{10}$, **H**: R = $Me(CH_2)_7CH(Me)$

Entry	RI (eq.)	Et_3B (eq.)	*T* (°C)	Yield (%)[b]		*cis* / *trans* ratio	
				27+**28**	**23a**+**24a**	**27** : **28**	**23a** : **24a**
1	*i*-PrI (10)	2.5	0	80	3	77 : 23	100 : 0[c]
2	*i*-PrI (10)	2.5	-78	40 (42)[d]	14	91 : 9	87 : 13
3	*s*-BuI (20)	5.0	-78	65 (4)[d]	19	87 :13	91 : 9
4	*c*-HexI (20)	5.0	-78	56	29	82 : 18	90 : 10
5	*t*-BuI (10)	2.5	-78	98	0	74 : 26	----
6	$Me(CH_2)_9I$ (60)	3.0	0	48	41	70 : 30	70 : 30
7	$Me(CH_2)_{12}I$ (60)	3.0	0	51	42	78 : 22	68 :32
8	$MeO_2C(CH_2)_{10}I$ (60)	3.0	0	46	53	70 : 30	58 : 42
9	$Me(CH_2)_7CH(Me)I$ (20)	3.0	0	72 (10)[d]	11	80 : 20	71 : 29

[a] All of the reactions were carried out with Et_3B in the presence of an alkyl iodide at low temperature.
[b] Isolated yields. [c] *trans*-**24a** could not be isolated. [d] Yields in parentheses represent the recovered **12a**.

To examine the scope of the transformation for various alkyl radials, we investigated the radical addition-cyclization of oxime ether **12a** using a wide variety of alkyl iodides as radical precursors (Table 3). Pleasingly, various alkyl radicals resulting from the iodine atom-transfer reaction reacted successfully with **12a** to give the desired cyclization products, even at low temperatures. For example, the isopropyl radical addition-cyclization reaction proceeded smoothly at 0 °C using isopropyl iodide (10 eq.) and Et_3B (2.5 eq.) to give a 77 : 23 mixture of the isopropylated products *cis*-**27A** and *trans*-**28A** in 80% combined yield, accompanying with a 3% yield of the ethylated product *cis*-**23a** resulting from the addition of the ethyl radical (Table 3, entry 1). To improve the stereoselectivity, the reaction was carried out at –78 °C. At this temperature, the reaction proceeded with a higher level of stereoselectivity to give *cis*-**27A**, although the yield for the transformation was decreased with the starting material **12a** being recovered (entry 2). When the reaction was conducted with other secondary alkyl radical, such as *sec*-butyl and cyclohexyl radicals, the corresponding alkylated products **27B** and **28B**, and **27C** and **28C** were formed, respectively, along with a significant amounts of the ethylated products **23a** and **24a** (entries 3 and 4). In contrast, the use of a *tert*-butyl radical species gave a much higher yield of the *tert*-butylated products **27D** and **28D**, with none of the ethylated product being formed because stable tertiary alkyl radical is formed by efficient iodine atom-transfer process (entry 5). We also examined the introduction of several longer alkyl chains according to this process and found that the use of large excesses of the alkyl iodides (60 eq.) allowed for the formation of the desired alkylated and cyclized products **27E-G** and **28E-G** in moderate yields (entries 6-8). The use of this strategy, however, also led to formation of the ethylated products **23** and **24** because the iodine atom-transfer reactions of primary decanyl, tridecanyl, and undecanyl iodides were less efficient than those of secondary and tertiary alkyl iodides. As expected, the addition-cyclization reaction of the secondary alkyl radical generated from 2-iododecane gave the four

cyclized products **27H**, **27H'**, **28H**, and **28H'** in 72% combined yield, with 3,4-*cis*-**27H** and **27H'** being formed as the major diastereomers and the formation of the ethylated products being suppressed (entry 9). We had succeeded in developing a method for the synthesis of cyclic β-amino acid analogues bearing not only secondary and tertiary alkyl groups but also longer alkyl groups via our radical addition-cyclization reaction.

CONCLUSION

In conclusion, we have successfully developed a radical addition-cyclization method for the preparation of various heterocyclic compounds containing a quaternary carbon center. In particular, the radical addition-cyclization reaction of oxime ether containing a nitrogen atom afforded α,α-disubstituted cyclic β-amino acid derivatives bearing a wide variety of alkyl groups, including longer alkyl chains. This new methodology could be used to provide access to various cyclic β-amino acids containing a quaternary carbon center.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 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 preformed using E. Merck Kieselgel 60 (230-400 mesh). Medium-pressure column chromatography (MCC) was performed using Lober Größe B (E. Merck 310-25, Lichroprep Si60).

Ethyl (*E*/*Z*)-2-[[[2-(Methoxyimino)ethyl][(4-methylphenyl)sulfonyl]amino]methyl]propenoate (12a)

To a solution of *N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide **13**[14] (2.00 g, 7.7 mmol) in acetone (11 mL) were added K_2CO_3 (3.21 g, 15.5 mmol) and ethyl 2-(bromomethyl)acrylate **14** (1.50 g, 7.7 mmol) in acetone (20 mL) at room temperature. After being stirred at reflux for 5 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the residue. ^{1}H NMR spectrum of the residue proved the formation of desired acrylate **15**, which was subjected to the following reaction without further purification. Ethyl 2-[(2,2-dimethoxyethyl)[(4-methylphenyl)sulfonyl]amino]methyl]propenoate (**15**) ^{1}H NMR (300 MHz, $CDCl_3$): δ: 7.71 (2H, br d, J = 8 Hz), 7.30 (2H, br d, J = 8 Hz), 6.32 (1H, br d, J = 1 Hz), 5.79 (1H, br d, J = 1 Hz), 4.43 (1H, t, J = 5 Hz), 4.17 (2H, q, J = 7 Hz), 4.16 (2H, s), 3.32 (6H, s), 3.27 (2H, d, J = 5 Hz), 2.43 (3H, s), 1.28 (3H, t, J = 7 Hz). To a solution of **15** prepared above (2.86 g, 7.7 mmol) in acetone (70 mL) was added 2M HCl (90 mL) at room temperature. After being stirred at the

same temperature for 24 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give desired aldehyde. This structure was confirmed by ^{1}H NMR in which the aldehyde proton signal was observed at 9.53 ppm (1H, s). The aldehyde was used to next reaction without further purification. To a solution of aldehyde prepared above (2.50 g, 7.7 mmol) in CH_2Cl_2 (120 mL) were added AcONa (1.47 g, 17.9 mmol) and $MeONH_2$·HCl (756.2 mg, 8.94 mmol) at room temperature. After being stirred at the same temperature for 20 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FCC (*n*-hexane:AcOEt = 3 : 1) to afford **12a** (2.72 g, 93%) as a colorless oil and a 4:3 mixture of *E*- and *Z*-isomers. IR ($CHCl_3$) 1709 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71 (2H, br d, *J* = 8 Hz), 7.33 (2H, br d, *J* = 8 Hz), 7.13 (4/7H, t, *J* = 6 Hz), 6.55 (3/7H, t, *J* = 6 Hz), 6.38 (1H, br dd, *J* = 3.5, 1 Hz), 5.88 (1H, br dd, *J* = 6, 1 Hz), 4.20 (2H, br q, *J* = 7 Hz), 4.04 (6/7H, d, *J* = 6 Hz), 4.04 (2H, br s), 3.91 (8/7H, d, *J* = 6 Hz), 3.83 (9/7H, s), 3.77 (12/7H, s), 2.44 (3H, s), 1.29 (3H, br t, *J* = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.4, 147.3, 144.8, 143.8, 143.6, 136.4, 136.0, 135.5, 135.4, 129.8, 129.7, 127.5, 127.3, 127.15, 127.12, 61.9, 61.5, 60.9, 60.8, 49.2, 47.8, 46.8, 43.9, 21.3, 14.0; HRMS (EI, *m/z*) calcd for $C_{16}H_{22}N_2O_5S$ (M^+) 354.1248, found 354.1257.

Diethyl (*E*/*Z*)-2-[2-(Methoxyimino)ethyl]propanedioate (17)

To a mixture of NaH (60% w/w in mineral oil) (164.5 mg, 4.11 mmol) in dry THF (7.8 mL) was added diethyl malonate (598 mg, 3.74 mmol) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 20 min, 2-chloroacetaldehyde *O*-methyloxime **16** (400 mg, 3.74 mmol) was added and the reaction mixture was stirred at reflux for 27 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FCC (*n*-hexane:AcOEt = 9:1) to give **17** (511 mg, 59%) as a colorless oil and a 2:1 mixture of *E*- and *Z*-isomers. IR ($CHCl_3$) 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (2/3H, t, *J* = 5 Hz), 6.73 (1/3H, t, *J* = 5 Hz), 4.22 (4H, br q, *J* = 7 Hz), 3.89 (3/3H, s), 3.80 (6/3H, s), 3.65 (2/3H, t, *J* = 8 Hz), 3.61 (1/3H, t, *J* = 7 Hz), 2.86 (2/3H, dd, *J* = 7, 5 Hz), 2.78 (4/3H, dd, *J* = 8, 5 Hz), 1.28 (6H, br t, *J* = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.35, 168.32, 146.9, 146.5, 61.61, 61.55, 61.46, 61.3, 49.0, 48.6, 28.5, 24.8, 13.9; HRMS (EI, *m/z*) calcd for $C_{10}H_{17}NO_5$ (M^+) 231.1106, found 231.1123.

Triethyl (*E*/*Z*)-1-[2-(Methoxyimino)ethyl]-3-butene-1,1,3-tricarboxylate (12b)

To a mixture of NaH (60% w/w in mineral oil) (136.4 mg, 3.41 mmol) in dry THF (16.4 mL) was added

17 (715.3 mg, 3.1 mmol) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 20 min, ethyl 2-(bromomethyl)acrylate **14** (598.3 mg, 3.1 mmol) was added and the reaction mixture was stirred at reflux for 16 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by MCC (*n*-hexane:AcOEt = 15:1) to give **12b** (942.8 mg, 89%) as a colorless oil and a 2:1 mixture of *E*- and *Z*-isomers. IR ($CHCl_3$) 1724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.37 (2/3H, t, *J* = 6 Hz), 6.71 (1/3H, t, *J* = 5 Hz), 6.30 (2/3H, d, *J* = 1.5 Hz), 6.30 (1/3H, d, *J* = 1.5 Hz), 5.70 (2/3H, br d, *J* = 1.5 Hz), 5.63 (1/3H, br d, *J* = 1.5 Hz), 4.27-4.10 (6H, m), 3.86 (3/3H, s), 3.80 (6/3H, s), 3.03 (2H, br s), 2.83 (2/3H, d, *J* = 5 Hz), 2.69 (4/3H, d, *J* = 6 Hz), 1.29 (3H, t, *J* = 7 Hz), 1.26 (6H, t, *J* = 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.2, 166.0, 145.9, 135.3, 128.7, 60.9, 60.6, 60.2, 56.0, 55.2, 33.9, 33.5, 32.2, 28.5, 13.4, 13.3. HRMS (EI, *m/z*) calcd for $C_{16}H_{25}NO_7$ (M^+) 343.1629, found 343.1627.

Ethyl (*E*/*Z*)-2-[[[2-(Methoxyimino)ethyl]oxy]methyl]propenoate (12c)

To a mixture of NaH (60% w/w in mineral oil) (42 mg, 1.04 mmol) in dry THF (1.6 mL) was added oxime ether **18** (92.6 mg, 1.04 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 1 h, ethyl 2-(bromomethyl)acrylate **14** (100 mg, 0.52 mmol) in dry THF (1.6 mL) was added and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by MCC (*n*-hexane:AcOEt = 9:1) to give **12c** (91.1 mg, 87%) as a colorless oil and a 3:2 mixture of *E*- and *Z*-isomers. IR ($CHCl_3$) 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.45 (3/5H, t, *J* = 6 Hz), 6.86 (2/5H, t, *J* = 4 Hz), 6.34-6.31 (1H, m), 5.88-5.86 (1H, m), 4.32 (4/5H, d, *J* = 4 Hz), 4.27-4.19 (4H, m), 4.13 (6/5H, d, *J* = 6 Hz), 3.874 (6/5H, s), 3.867 (9/5H, s), 1.31 (3H, br t, *J* = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.2, 149.4, 146.4, 136.9, 136.8, 136.5, 125.5, 69.1, 68.3, 67.1, 64.7, 61.7, 61.3, 60.4, 13.9; HRMS (EI, *m/z*) calcd for $C_9H_{15}NO_4$ (M^+) 201.1000, found 201.0998.

1,1-Dimethylethyl *N*-[4-Methylphenyl]sulfonyl]-*N*-(2-oxopropyl)carbamate (20)

To a solution of *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide **19** (626 mg, 2.3 mmol) in acetone (43 mL) were added K_2CO_3 (952 mg, 6.9 mmol) and bromoacetone (315 mg, 2.3 mmol) at room temperature. After being stirred at reflux for 4 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FCC (*n*-hexane:AcOEt = 3:1) to give ketone **20** (731.1 mg, 97%) as colorless crystals. mp

73.5-74.5 °C (*n*-hexane/AcOEt); IR ($CHCl_3$) 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.91 (2H, br d, *J* = 8 Hz), 7.31 (2H, br d, *J* = 8 Hz), 4.62 (2H, s), 2.43 (3H, s), 2.21 (3H, s), 1.29 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 201.1, 150.1, 144.1, 136.3, 128.8, 128.2, 84.3, 54.2, 27.3, 26.3, 21.2; HRMS (EI, *m/z*) calcd for $C_{15}H_{21}NO_5S$ (M^+) 327.1139, found 327.1135. Anal. Calcd for $C_{15}H_{21}NO_5S$: C, 55.03; H, 6.47; N, 4.28. Found : C, 55.13; H, 6.42; N, 4.28.

Ethyl (*E*/*Z*)-2-[[[2-(Methoxyimino)propyl][(4-methylphenyl)sulfonyl]amino]methyl]propenoate (12d)

To a solution of ketone **20** (2.47 g, 7.54 mmol) in 1,4-dioxane (56.7 mL) was added conc. HCl (37.8 mL) at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give sulfonamide. The formation of the sulfonamide was confirmed by the ^1H NMR spectrum in which the *t*-butyl signal of the Boc group (δ: 1.29 (9H, s) in ketone **20**) was not observed. The sulfonamide was used to next reaction without further purification. To a solution of sulfonamide prepared above (1.70 g, 7.50 mmol) in CH_2Cl_2 (115 mL) were added AcONa (2.48 g, 30.2 mmol) and $MeONH_2$·HCl (1.26 g, 15.1 mmol) at room temperature. After being stirred at the same temperature for 28 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FCC (*n*-hexane:AcOEt = 2:1) to give ketoxime ether (1.81 g, 93%) as colorless crystals and a 5:1 mixture of geometric isomers. (*E*/*Z*)-*N*-[2-(Methoxyimino)propyl]-4-methylphenylsulfonamide: ^1H NMR (300 MHz, $CDCl_3$) δ: 7.74 (2H, br d, *J* = 8 Hz), 7.32 (2H, br d, *J* = 8 Hz), 5.31 (1/6H, br t, *J* = 6 Hz), 5.17 (5/6H, br t, *J* = 5.5 Hz), 3.78 (3H, br s), 3.73 (2/6H, d, *J* = 6 Hz), 3.62 (10/6H, d, *J* = 5.5 Hz), 2.43 (3H, s), 1.82 (3/6H, s), 1.76 (15/6H, s). The stereostructures have not been established. To a solution of ketoxime ether prepared above (353.5 mg, 1.38 mmol) in acetone (28 mL) were added K_2CO_3 (571 mg, 4.14 mmol) and ethyl 2-(bromomethyl)acrylate **14** (266.7 mg, 1.38 mmol) at room temperature. After being stirred at reflux for 4 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by FCC (*n*-hexane:AcOEt = 3:1) to give **12d** (475.8 mg, 94%) as a colorless oil and a 5:1 mixture of geometric isomers. The stereostructures have not been established. IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.69 (2H, br d, *J* = 8 Hz), 7.31 (2H, br d, *J* = 8 Hz), 6.32 (5/6H, br s), 6.29 (1/6H, br s), 5.84 (5/6H, br s), 5.74 (1/6H, br s), 4.17 (2H, br q, *J* = 7 Hz), 4.04 (2/6H, br s), 3.99 (10/6H, br s), 3.83 (10/6H, br s), 3.79 (2/6H, br s), 3.75 (3H, br s), 2.43 (3H, s), 1.89 (3/6H, s), 1.79 (15/6H, s), 1.28 (3H, br t, *J* = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.7, 152.5, 143.6, 136.1, 135.5, 135.4, 129.73, 129.67, 128.5,

127.5, 127.32, 127.26, 61.6, 61.0, 60.9, 52.8, 49.9, 48.1, 21.5, 14.1, 12.5; HRMS (EI, *m/z*) calcd for $C_{17}H_{24}N_2O_5S$ (M^+) 368.1405, found 368.1389.

General procedure for radical addition-cyclization reactions of oxime ethers 12a-d with PhSH-AIBN combination

To a boiling solution of the oxime ethers **12a-d** (0.20 mmol) in benzene (3 mL) under a nitrogen atmosphere was added a solution of thiophenol (29 mg, 0.26 mmol) and AIBN (16mg, 0.10 mmol) in benzene (5 mL) by syringe pump (5 mL/h) over 1 h. After the reaction mixture was heated at reflux for a further 3 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by MCC (*n*-hexane:AcOEt = 5:1) to afford the cyclized products **21a-d** and **22a-d** as shown in Table 1.

Ethyl (3*R,4*R**)-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-(phenylsulfanyl)methyl-3-pyrrolidinecarboxylate (*cis*-21a)**

A yellow oil; IR ($CHCl_3$) 3670, 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.72 (2H, br d, *J* = 8 Hz), 7.34-7.19 (7H, m), 5.78 (1H, br d, *J* = 5 Hz), 3.96-3.85 (2H, m), 3.67 (1H, d, *J* = 10 Hz), 3.57 (1H, d, *J* = 10 Hz), 3.60-3.52 (2H, m), 3.31 (1H, d, *J* = 13 Hz), 3.27 (1H, dd, *J* = 10, 3 Hz), 3.17 (3H, s), 2.98 (1H, d, *J* = 13 Hz), 2.41 (3H, s), 1.13 (3H, t, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.3, 143.6, 135.4, 133.3, 130.6, 129.7, 129.0, 127.7, 126.9, 65.3, 61.9, 61.4, 56.4, 52.5, 50.0, 40.3, 21.5, 13.9; HRMS (EI, *m/z*) calcd for $C_{22}H_{28}N_2O_5S_2$ (M^+) 464.1438, found 464.1432.

Ethyl (3*R,4*S**)-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-(phenylsulfanyl)methyl-3-pyrrolidinecarboxylate (*trans*-22a)**

A yellow oil; IR ($CHCl_3$) 3350, 1730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.70 (2H, br d, *J* = 8 Hz, ArH), 7.34-7.19 (7H, m), 5.72 (1H, br d, *J* = 5 Hz), 3.91-3.81 (3H, m), 3.73 (1H, d, *J* = 10 Hz), 3.57 (1H, dd, *J* = 10.5, 7 Hz), 3.47 (1H, d, *J* = 10 Hz), 3.36 (1H, dd, *J* = 10.5, 5 Hz), 3.32 (1H, d, *J* = 13 Hz), 3.31 (3H, s), 3.09 (1H, d, *J* = 13 Hz), 2.41 (3H, s), 1.10 (3H, t, *J* = 7 Hz). NOE was observed between 4-N*H* (δ 5.72) and 3-CH_2 (δ 3.32, 3.09) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.7, 143.6, 135.4, 133.6, 130.6, 129.6, 129.0, 127.6, 127.0, 62.9, 62.2, 61.7, 56.5, 54.2, 50.6, 35.6, 21.5, 13.8; HRMS (EI, *m/z*) calcd for $C_{22}H_{28}N_2O_5S_2$ (M^+) 464.1438, found 464.1441.

Triethyl (3*R,4*S**)-4-(Methoxyamino)-3-(phenylsulfanyl)methyl-1,1,3-cyclopentanetricarboxylate (*cis*-21b)**

A yellow oil; IR ($CHCl_3$) 3691, 1726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.41-7.16 (5H, m), 5.89 (1H, br s), 4.20 (2H, q, *J* = 7 Hz), 4.14 (2H, br q, *J* = 7 Hz), 4.05 (2H, br q, *J* = 7 Hz), 3.63 (1H, dd, *J* = 9, 7 Hz), 3.58 (1H, d, *J* = 13 Hz), 3.42 (3H, s), 3.17 (1H, d, *J* = 13 Hz), 3.04 (1H, d, *J* = 15 Hz), 2.56 (1H, dd, *J* = 14, 7 Hz), 2.52 (1H, d, *J* = 15 Hz), 2.44 (1H, dd, *J* = 14, 9 Hz), 1.25 (3H, t, *J* = 7 Hz), 1.21 (3H, t, *J* = 7 Hz), 1.20 (3H, t, *J* = 7 Hz). NOE was observed between 4-*H* (δ 3.63) and 2-*H* (δ 2.52), 2-*H* (δ 2.52) and C*H*$_2$SPh (δ 3.58, 3.17) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.7, 172.5, 171.3, 136.7, 130.4, 128.8, 126.4, 67.6, 61.9, 61.8, 61.6, 61.2, 57.1, 57.0, 41.5, 39.8, 36.7, 13.98, 13.96, 13.93; HRMS (EI, *m/z*) calcd for $C_{22}H_{31}NO_7S$ (M^+) 453.1820, found 453.1821.

Triethyl (3*R,4*R**)-4-(Methoxyamino)-3-(phenylsulfanyl)methyl-1,1,3-cyclopentanetricarboxylate (*trans*-22b)**

A yellow oil; IR ($CHCl_3$) 3545, 1727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.23-7.16 (5H, m), 5.95 (1H, br s), 4.17 (2H, q, *J* = 7 Hz), 4.15 (2H, q, *J* = 7 Hz), 3.97 (2H, br q, *J* = 7 Hz), 3.85 (1H, t, *J* = 7 Hz), 3.48 (3H, s), 3.44 (1H, d, *J* = 13 Hz), 3.22 (1H, d, *J* = 13 Hz), 2.96 (1H, d, *J* = 15 Hz), 2.67 (1H, dd, *J* = 15, 7 Hz), 2.66 (1H, d, *J* = 15 Hz), 2.44 (1H, dd, *J* = 15, 7 Hz), 1.24 (3H, t, *J* = 7 Hz), 1.23 (3H, t, *J* = 7 Hz), 1.16 (3H, t, *J* = 7 Hz). NOE was observed between 4-*H* (δ 3.85) and 2β-*H* (δ 2.96), 2α-*H* (δ 2.66) and C*H*$_2$SPh (δ 3.44, 3.22) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.6, 171.9, 171.6, 136.4, 130.4, 128.8, 126.5, 65.4, 62.0, 61.8, 61.7, 61.3, 57.4, 57.2, 40.7, 37.9, 36.9, 14.0, 13.9; HRMS (EI, *m/z*) calcd for $C_{22}H_{31}NO_7S$ (M^+) 453.1820, found 453.1833.

Ethyl (3*R,4*R**)-Tetrahydro-4-(methoxyamino)-3-(phenylsulfanyl)methyl-3-furancarboxylate (*cis*-21c)**

A colorless oil; IR ($CHCl_3$) 3691, 1726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.39-7.17 (5H, m), 4.13 (1H, dd, *J* = 9, 1 Hz), 4.11 (1H, dd, *J* = 10, 7 Hz), 4.10-4.01 (2H, m), 3.99 (1H, d, *J* = 9 Hz), 3.75 (1H, dd, *J* = 10, 5 Hz), 3.62 (1H, dd, *J* = 7, 5 Hz), 3.46 (1H, dd, *J* = 13, 1 Hz), 3.45 (3H, s), 3.15 (1H, d, *J* = 13 Hz), 1.22 (3H, t, *J* = 7 Hz). NOE was observed between 4-*H* (δ 3.62) and 2β-*H* (δ 3.99), 4-*H* (δ 3.62) and C*H*$_2$SPh (δ 3.46, 3.15), 2β-*H* (δ 3.99) and C*H*$_2$SPh (δ 3.46, 3.15) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.1, 136.2, 130.2, 128.9, 126.6, 72.7, 70.7, 67.8, 61.9, 61.2, 57.5, 40.5, 14.0; HRMS (EI, *m/z*) calcd for $C_{15}H_{21}NO_4S$ (M^+) 311.1190, found 311.1180.

Ethyl (3R*,4S*)-Tetrahydro-4-(methoxyamino)-3-(phenylsulfanyl)methyl-3-furancarboxylate (*trans*-22c)

A colorless oil; IR ($CHCl_3$) 3700, 1726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.41-7.19 (5H, m), 4.20 (1H,

d, *J*=9 Hz), 4.10 (1H, dd, *J*=12, 7 Hz), 4.09 (1H, dd, *J*=8, 7 Hz), 4.09-3.99 (2H, m), 3.86 (1H, d, *J*=9 Hz), 3.82 (1H, dd, *J* = 12, 8 Hz), 3.52 (3H, s), 3.48 (1H, d, *J* = 12.5 Hz), 3.30 (1H, d, *J* = 12.5 Hz), 1.19 (3H, t, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.7, 136.1, 130.4, 129.0, 126.7, 74.6, 71.3, 64.8, 62.2, 61.5, 57.9, 35.2, 14.0; HRMS (EI, *m/z*) calcd for $C_{15}H_{21}NO_4S$ (M^+) 311.1190, found 311.1205.

Ethyl 4-(Methoxyamino)-4-methyl-1-[(4-methylphenyl)sulfonyl]-3-(phenylsulfanyl)methyl-3-pyrrolidinecarboxylate (21d and 22d)

According to the procedure given for the preparation of pyrrolidines **21a** and **22a**, the reaction was carried out for 6 h to afford cyclized products **21d** and **22d**. The stereostructures of the *cis*- and *trans*-isomer (52:48) have not been established. *The major less polar product*; A yellow oil; IR ($CHCl_3$) 3694, 1731 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.74 (2H, br d, *J* = 8 Hz), 7.30-7.18 (7H, m), 5.68 (1H, br s), 3.92 (1H, dq, *J* = 11, 7 Hz), 3.83 (1H, d, *J* = 11 Hz), 3.80 (1H, dq, *J* = 11, 7 Hz), 3.73 (1H, dd, *J* = 11, 2 Hz), 3.54 (1H, d, *J* = 10 Hz), 3.52 (1H, dd, *J* = 13, 2 Hz), 3.46 (3H, s), 3.34 (1H, d, *J* = 10 Hz), 2.74 (1H, d, *J* = 13 Hz), 2.39 (3H, s), 1.11 (3H, t, *J* = 7 Hz), 0.96 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.5, 143.6, 135.5, 133.7, 130.6, 129.7, 128.9, 127.4, 126.8, 66.5, 62.9, 61.4, 59.5, 56.0, 51.7, 36.8, 21.5, 20.1, 14.0; HRMS (CI, isobutane, *m/z*) calcd for $C_{23}H_{31}N_2O_5S_2$ (QM^+) 479.1673, found 479.1667. *The minor more polar product*; A yellow oil; IR ($CHCl_3$) 3650, 1729 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.74 (2H, br d, *J* = 8 Hz), 7.32-7.20 (7H, m), 5.14 (1H, br s), 3.97 (1H, dq, *J* = 11, 7 Hz), 3.87 (1H, dd, *J* = 11, 2 Hz), 3.82 (1H, dd, *J* = 11, 2 Hz), 3.80 (1H, dq, *J* = 11, 7 Hz), 3.59 (1H, d, *J* = 11 Hz), 3.38 (1H, dd, *J* = 13, 2 Hz), 3.16 (3H, s), 3.06 (1H, d, *J* = 11 Hz), 2.70 (1H, d, *J* = 13 Hz), 2.39 (3H, s), 1.28 (3H, s), 1.13 (3H, t, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.8, 143.5, 135.3, 133.5, 130.8, 129.7, 129.0, 127.7, 127.0, 69.3, 62.4, 61.2, 58.0, 54.5, 52.0, 38.6, 21.5, 16.7, 14.0; HRMS (CI, isobutane, *m/z*) calcd for $C_{23}H_{31}N_2O_5S_2$ (QM^+) 479.1673, found 479.1673.

General procedure for radical addition-cyclization reactions of oxime ethers 12a-c with Et_3B

Oxime ethers **12a-c** (0.15 mmol) was dissolved in toluene (10 mL) under air atmosphere. To a solution of oxime ethers **12a-c** in toluene was added Et_3B (1.01M in *n*-hexane) (0.37 mL, 0.375 mmol) under a nitrogen atmosphere at –78 °C. After being stirred at the same temperature for 15 min, Three further portions of Et_3B (1.01M in *n*-hexane) (each 0.37 mL, 0.375 mmol) were added at 15 min intervals. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by MCC (*n*-hexane:AcOEt = 5:1-3:1) afforded cyclized products **23a-c** and **24a-c** as shown in Table 2.

Ethyl (3*R,4*R**)-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-propyl-3-pyrrolidinecarboxylate (*cis*-23a)**

Colorless crystals; mp 79.0-79.5 °C (*n*-hexane/AcOEt); IR ($CHCl_3$) 3560, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.75 (2H, br d, *J* = 8 Hz), 7.34 (2H, br d, *J* = 8 Hz), 5.75 (1H, br s), 4.11 (2H, br q, *J* = 7 Hz), 3.55 (1H, dd, *J* = 11, 6 Hz), 3.52 (1H, d, *J* = 10 Hz), 3.42 (1H, d, *J* = 10 Hz), 3.41-3.37 (1H, m), 3.32 (1H, dd, *J* = 11, 3 Hz), 3.16 (3H, s), 2.43 (3H, s) 1.61-1.54 (1H, m), 1.33 (1H, br td, *J* = 12, 5 Hz), 1.22 (3H, t, *J* = 7 Hz), 1.27-1.08 (2H, m), 0.81 (3H, t, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.1, 143.7, 133.9, 129.8, 127.9, 66.3, 62.2, 61.2, 55.8, 52.2, 50.2, 38.3, 21.7, 18.1, 14.33, 14.31; HRMS (EI, *m/z*) calcd for $C_{18}H_{28}N_2O_5S$ (M^+) 384.1717, found 384.1716; Anal. Calcd for $C_{18}H_{28}N_2O_5S$: C, 56.23; H, 7.34; N, 7.29. Found : C, 56.17; H, 7.55; N, 7.32.

Ethyl (3*R,4*S**)-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-propyl-3-pyrrolidinecarboxylate (*trans*-24a)**

Colorless crystals; mp 90.5-91.0 °C (*n*-hexane/AcOEt); IR ($CHCl_3$) 3540, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.72 (2H, br d, *J* = 8 Hz), 7.33 (2H, br d, *J* = 8 Hz), 5.60 (1H, br s), 4.11-4.00 (2H, m), 3.77-3.73 (1H, m), 3.73 (1H, d, *J* = 10 Hz), 3.47 (1H, dd, *J*=10, 6 Hz), 3.39 (1H, dd, *J* = 10, 4 Hz), 3.35 (3H, s), 3.25 (1H, d, *J* = 10 Hz), 2.43 (3H, s), 1.64-1.56 (1H, m), 1.44-1.36 (1H, m), 1.20 (3H, t, *J* = 7 Hz), 1.20-1.08 (2H, m), 0.84 (3H, t, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.2, 143.4, 133.9, 129.6, 127.6, 62.8, 62.0, 61.3, 55.7, 53.6, 50.7, 32.1, 21.5, 18.5, 14.3, 14.0; HRMS (EI, *m/z*) calcd for $C_{18}H_{28}N_2O_5S$ (M^+) 384.1717, found 384.1725; Anal. Calcd for $C_{18}H_{28}N_2O_5S$: C, 56.23; H, 7.34; N, 7.29. Found : C, 56.06; H, 7.51; N, 7.20.

Triethyl (3*R,4*S**)-4-(Methoxyamino)-3-propyl-1,1,3-cyclopentanetricarboxylate (*cis*-23b)**

A yellow oil; IR ($CHCl_3$) 3540, 1727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 5.91 (1H, br s), 4.24-4.10 (6H, m), 3.45 (3H, s), 3.41 (1H, dd, *J* = 7, 6.5 Hz), 2.91 (1H, d, *J* = 14.5 Hz), 2.54 (1H, dd, *J* = 14, 6.5 Hz), 2.48 (1H, dd, *J* = 14, 7 Hz), 2.35 (1H, d, *J* = 14.5 Hz), 1.87 (1H, br td, *J* = 13.5, 4.5 Hz), 1.40 (1H, br td, *J* = 13.5, 4.5 Hz), 1.35-1.18 (2H, m), 1.26 (6H, t, *J* = 7 Hz), 1.25 (3H, t, *J* = 7 Hz), 0.89 (3H, t, *J* = 7 Hz). NOE was observed between 4-*H* (δ 3.41) and 2β-*H* (δ 2.35), 4-*H* (δ 3.41) and C*H*$_2$Et (δ 1.87, 1.40), 2β-*H* (δ 2.35) and C*H*$_2$Et (δ 1.87, 1.40) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.0, 172.8, 171.8, 68.5, 61.83, 61.77, 61.6, 60.7, 57.3, 56.3, 39.38, 39.35, 36.8, 18.4, 14.4, 14.1, 13.99, 13.97; HRMS (EI, *m/z*) calcd for $C_{18}H_{31}NO_7$ (M^+) 373.2098, found 373.2103.

Triethyl (3*R,4*R**)-4-(Methoxyamino)-3-propyl-1,1,3-cyclopentanetricarboxylate (*trans*-24b)**

A yellow oil; IR ($CHCl_3$) 3541, 1728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 5.83 (1H, br s), 4.25-4.10 (6H, m), 3.74 (1H, dd, *J* = 6.5, 6 Hz), 3.49 (3H, s), 2.82 (1H, d, *J* = 14.5 Hz), 2.64 (1H, dd, *J* = 14.5, 6 Hz), 2.50 (1H, d, *J* = 14.5 Hz), 2.34 (1H, dd, *J* = 14.5, 6.5 Hz), 1.72 (1H, ddd, *J* = 13.5, 12, 5 Hz), 1.45 (1H, ddd, *J* = 13.5, 12, 4.5, Hz), 1.30-1.11 (2H, m), 1.25 (6H, t, *J* = 7 Hz), 1.24 (3H, t, *J* = 7 Hz), 0.90 (3H, t, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.2, 172.3, 171.9, 65.3, 61.9, 61.7, 61.6, 60.9, 57.3, 56.6, 40.0, 36.9, 34.1, 18.6, 14.5, 14.1, 14.0; HRMS (EI, *m/z*) calcd for $C_{18}H_{31}NO_7$ (M^+) 373.2098, found 373.2104.

Ethyl (3*R,4*R**)-Tetrahydro-4-(methoxyamino)-3-propyl-3-furanecarboxylate (*cis*-23c)**

A colorless oil; IR ($CHCl_3$) 3526, 1723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 6.09 (1H, br s), 4.19 (2H, q, *J* = 7 Hz), 4.11 (1H, d, *J* = 9 Hz), 4.05 (1H, dd, *J* = 10, 6 Hz), 3.84 (1H, dd, *J* = 10, 4 Hz), 3.75 (1H, d, *J* = 9 Hz), 3.47 (3H, s), 3.45 (1H, dd, *J* = 6, 4 Hz), 1.75 (1H, br td, *J* = 13.5, 5 Hz), 1.56 (1H, br td, *J* = 13.5, 5 Hz), 1.35-1.18 (2H, m), 1.29 (3H, t, *J* = 7 Hz), 0.91 (3H, t, *J* = 7 Hz). NOE was observed between 4-*H* (δ 3.45) and 3-C*H*$_2$ (δ 1.75, 1.56) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.7, 72.5, 70.7, 68.0, 62.1, 60.8, 56.5, 38.8, 18.2, 14.3, 14.2; HRMS (EI, *m/z*) calcd for $C_{11}H_{21}NO_4$ (M^+) 231.1469, found 231.1489.

Ethyl (3*R,4*S**)-Tetrahydro-4-(methoxyamino)-3-propyl-3-furanecarboxylate (*trans*-24c)**

A colorless oil; IR ($CHCl_3$) 3515, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 5.70 (1H, br s), 4.25 (1H, d, *J* = 9 Hz), 4.19 (2H, br q, *J* = 7 Hz), 4.01 (1H, dd, *J* = 9, 6 Hz), 3.96 (1H, dd, *J* = 6, 4 Hz), 3.80 (1H, dd, *J* = 9, 4 Hz), 3.65 (1H, d, *J* = 9 Hz), 3.53 (3H, s), 1.72 (1H, ddd, *J* = 13, 12, 5 Hz), 1.64-1.54 (1H, m), 1.34-1.18 (2H, m), 1.27 (3H, t, *J* = 7 Hz), 0.93 (3H, t, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.4, 74.2, 71.6, 64.3, 62.0, 61.1, 57.1, 31.8, 19.1, 14.6, 14.2; HRMS (EI, *m/z*) calcd for $C_{11}H_{21}NO_4$ (M^+) 231.1469, found 231.1486.

Ethyl 4-[(Ethyl)(methoxy)amino]-4-methyl-1-[(4-methylphenyl)sulfonyl]-3-propyl-3-pyrrolidine-carboxylate (25)

According to the procedure for given for the preparation of pyrrolidines **23a** and **24a**, the reaction was carried out at –40 °C to afford cyclized products **25** and isomer. The stereostructures of the *cis*-**25** and *trans*-**25** (52:48) have not been established. *The major less polar product*; A colorless oil; IR ($CHCl_3$) 1721 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.50 (2H, br d, *J* = 8 Hz), 7.35 (2H, br d, *J* = 8 Hz), 4.08 (2H, br q, *J* = 7 Hz), 3.85 (1H, dd, *J* = 11, 1.5 Hz), 3.59 (3H, s), 3.48 (1H, d, *J*=10 Hz), 3.45 (1H, d, *J* = 11 Hz), 3.30 (1H, d, *J* = 10 Hz), 3.07-2.95 (1H, m), 2.58-2.49 (1H, m), 2.45 (3H, s), 1.85-1.78 (1H, m), 1.21 (3H, t, *J* = 7 Hz), 1.14 (3H, t, *J* = 7 Hz), 1.14-0.95 (3H, m), 0.89 (3H, s), 0.79 (3H, t, *J* = 7 Hz); ^{13}C NMR (125

MHz, $CDCl_3$) δ: 171.9, 143.6, 133.6, 129.7, 127.5, 72.3, 64.4, 61.0, 59.4, 57.9, 52.9, 48.0, 33.4, 21.5, 18.3, 14.9, 14.4, 14.0, 13.8; HRMS (EI, *m/z*) calcd for $C_{21}H_{34}N_2O_5S$ (M^+) 426.2186, found 426.2198. *The minor more polar product*; A colorless oil; IR ($CHCl_3$) 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.76 (2H, br d, *J* = 8 Hz), 7.34 (2H, br d, *J* = 8 Hz), 4.03 (1H, dq, *J* = 11, 7 Hz), 3.75 (1H, d, *J* = 10 Hz), 3.79-3.72 (1H, m), 3.57 (1H, br d, *J* = 9 Hz), 3.45 (1H, d, *J* = 9 Hz), 3.45 (3H, s), 3.31 (1H, d, *J* = 10 Hz), 2.75-2.68 (1H, m), 2.68-2.60 (1H, m), 2.44 (3H, s), 1.88-1.78 (1H, m), 1.28-1.20 (3H, m), 1.15 (3H, s), 1.06 (3H, t, *J* = 7 Hz), 1.05 (3H, t, *J* = 7 Hz), 0.86 (3H, t, *J* = 7 Hz), ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.5, 143.2, 134.7, 129.5, 127.5, 73.1, 64.1, 60.6, 58.5, 58.2, 54.9, 48.5, 35.6, 21.5, 19.1, 14.7, 14.0, 13.6, 13.4. HRMS (EI, *m/z*) calcd for $C_{21}H_{34}N_2O_5S$ (M^+) 426.2186, found 426.2181.

(3*R,4*R**)-4-Amino-3-propyl-3-pyrrolidinecarboxylic Acid (26)**

To a solution of *cis*-**23a** (166 mg, 0.43 mmol) in THF (12.2 mL) was added a solution of $LiOH·H_2O$ (902 mg, 21.5 mmol) in H_2O (18 mL) at room temperature under a nitrogen atmosphere. After being stirred at reflux for 24 h, the reaction mixture was acidified to pH 3 and extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by FCC (*n*-hexane:AcOEt (2:1)→AcOEt:MeOH (95:5) to give desired (±)-carboxylic acid (120 mg, 78%) as pale yellow crystals. mp 110-111 °C (Et_2O); IR ($CHCl_3$) 3500-2300, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.74 (2H, br d, *J* = 8 Hz), 7.34 (2H, br d, *J* = 8 Hz), 3.59 (1H, d, *J* = 10 Hz), 3.56 (1H, dd, *J* = 10, 4 Hz), 3.44-3.39 (1H, m), 3.39 (1H, d, *J* = 10 Hz), 3.31 (1H, dd, *J* = 10, 3 Hz), 3.21 (3H, s), 2.43 (3H, s), 1.66-1.56 (1H, m), 1.44-1.16 (3H, m), 0.83 (3H, t, *J* = 7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.9, 143.6, 133.2, 129.6, 127.5, 65.9, 61.8, 55.5, 51.9, 49.8, 37.8, 21.4, 17.8, 13.9; HRMS (EI, *m/z*) calcd for $C_{16}H_{24}N_2O_5S$ (M^+) 356.1405, found 356.1413. Sodium (20 mg, 0.87 mmol) was added slowly to liquid ammonia (15 mL) at –78 °C until the color of the mixture remaind dark blue. A solution of (±)-carboxylic acid (45.8 mg, 0.13 mmol) in THF (2 mL) was added slowly to the sodium/liquid ammonia mixture. The reaction was stirred for 30 min at the same temperature. The reaction mixture was quenched with isoprene (1 mL) and allowed to reach to room temperature in order to allow the ammonia to fully evaporate. The residue was acidified by aqueous 2 M HCl 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 elute under reduced pressure, cyclic β-amino acid **26** (21 mg, 95%) was obtained as white solid. IR (Nujol) 3700-2500, 1670, 1627, 1461 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ: 3.89 (1H, br d, *J* = 11 Hz), 3.66-3.52 (2H, m), 3.18-3.10 (1H, m), 3.04 (1H, br d, *J* = 11 Hz), 1.98-1.80 (1H, m), 1.52-1.20 (3H, m), 0.95 (3H, br t, *J* = 7 Hz); HRMS (CI, isobutane, *m/z*) calcd for $C_8H_{17}N_2O_2$ (QM^+) 173.1289, found 173.1282.

General procedure for alkyl radical addition-cyclization reactions of oxime ether 12a (Table 3, entries 2, 3, and 5)

Oxime ether **12a** (50 mg, 0.14 mmol) was dissolved in toluene (6 mL) under air atmosphere. To a solution of oxime ether **12a** in toluene were added corresponding alkyl iodide (1.4 or 2.8 mmol) and Et_3B (1.01M in *n*-hexane) (0.35 or 0.70 mmol) under a nitrogen atmosphere at –78 °C. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by MCC (*n*-hexane:AcOEt = 3:1) afforded cyclized products **27A**, **B**, **D** and **28A**, **B**, **D** as shown in Table 3.

Ethyl (3*R,4*R**)-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-(2-methylpropyl)-3-pyrrolidine-carboxylate (*cis*-27A)**

A colorless oil; IR ($CHCl_3$) 3552, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.75 (2H, br d, *J* = 8 Hz), 7.34 (2H, br d, *J* = 8 Hz), 5.73 (1H, br d, *J* = 4 Hz), 4.16-4.06 (2H, m), 3.56 (1H, dd, *J* = 11, 6 Hz), 3.55 (1H, d, *J* = 10 Hz), 3.45 (1H, d, *J* = 10 Hz), 3.38-3.33 (1H, m), 3.29 (1H, dd, *J* = 11, 3 Hz), 3.16 (3H, s), 2.43 (3H, s), 1.68-1.58 (2H, m), 1.40-1.36 (1H, m), 1.23 (3H, t, *J* = 7 Hz), 0.84 (3H, d, *J* = 6 Hz), 0.79 (3H, d, *J* = 6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.2, 143.4, 133.6, 129.5, 127.6, 66.5, 61.8, 61.0, 55.0, 52.0, 49.7, 44.1, 24.8, 24.0, 23.0, 21.4, 13.9; HRMS (EI, *m/z*) calcd for $C_{19}H_{30}N_2O_5S$ (M^+) 398.1873, found 398.1885.

Ethyl (3*R,4*S**)-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-(2-methylpropyl)-3-pyrrolidine-carboxylate (*trans*-28A)**

A colorless oil; IR ($CHCl_3$) 3690, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.73 (2H, br d, *J* = 8 Hz), 7.32 (2H, br d, *J* = 8 Hz), 5.55 (1H, br s), 4.10-3.98 (2H, m), 3.82 (1H, d, *J* = 10 Hz), 3.77-3.73 (1H, m), 3.44 (1H, dd, *J* = 10, 4 Hz), 3.39 (1H, dd, *J* = 10, 6 Hz), 3.33 (3H, s), 3.24 (1H, d, *J* = 10 Hz), 2.43 (3H, s), 1.62 (1H, dd, *J* = 13.5, 6 Hz), 1.56-1.47 (1H, m), 1.44 (1H, dd, *J* = 13.5, 6 Hz), 1.20 (3H, t, *J* = 7 Hz), 0.84 (3H, d, *J* = 6 Hz), 0.83 (3H, d, *J* = 6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.5, 143.3, 134.0, 129.6, 127.5, 63.6, 62.0, 61.3, 55.5, 53.9, 50.4, 38.5, 25.5, 23.5, 23.3, 21.5, 13.9. HRMS (EI, *m/z*) calcd for $C_{19}H_{30}N_2O_5S$ (M^+) 398.1873, found 398.1899.

Ethyl (3*R,4*R**)-4-(Methoxyamino)-3-(2-methylbutyl)-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidine-carboxylate (*cis*-27B)**

A colorless oil; IR ($CHCl_3$) 3546, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.75 (2H, br d, *J* = 8 Hz),

7.34 (2H, br d, *J* = 8 Hz), 4.16-4.06 (2H, m), 3.58 (1/2H, dd, *J* = 10.5, 6 Hz), 3.57 (1/2H, dd, *J* = 13, 7 Hz), 3.53 (1H, br d, *J* = 10 Hz), 3.44 (1/2H, d, *J* = 10 Hz), 3.43 (1/2H, d, *J* = 10 Hz), 3.38-3.35 (1H, m), 3.33 (1/2H, dd, *J* = 13, 5 Hz), 3.30 (1/2H, dd, *J* = 10.5, 3 Hz), 3.15 (3/2H, s), 3.14 (3/2H, s), 2.42 (3H, s), 1.68 (1/2H, dd, *J* = 14, 4 Hz), 1.56 (1/2H, dd, *J* = 14, 7.5 Hz), 1.49 (1/2H, dd, *J* = 14, 4 Hz), 1.41-1.33 (1H, m), 1.32 (1/2H, dd, *J* = 14, 7 Hz), 1.239 (3/2H, t, *J* = 7 Hz), 1.236 (3/2H, t, *J* = 7 Hz), 1.25-1.15 (1H, m), 1.13-1.02 (1H, m), 0.84 -0.75 (6H, m). NOE was observed between 4-*H* (δ 3.38-3.35) and 3-C*H*$_2$ (δ 1.68, 1.56, 1.49, 1.3) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.4, 172.3, 143.4, 133.72, 133.66, 129.59, 129.58, 127.66, 127.65, 66.5, 66.1, 61.91, 61.85, 61.0, 55.1, 55.0, 52.7, 51.8, 49.79, 49.78, 42.5, 42.4, 31.1, 30.9, 30.8, 30.3, 21.5, 20.6, 19.7, 14.00, 13.98, 11.14, 11.10; HRMS (EI, *m/z*) calcd for $C_{20}H_{32}N_2O_5S$ (M^+) 412.2030, found 412.2051.

Ethyl (3*R,4*S**)-4-(Methoxyamino)-3-(2-methylbutyl)-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidine-carboxylate (*trans*-28B)**

A colorless oil; IR ($CHCl_3$) 3660, 1724 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.73 (2H, br d, *J* = 8 Hz), 7.32 (2H, br d, *J* = 8 Hz), 4.10-3.97 (2H, m), 3.84 (5/11H, d, *J* = 10 Hz), 3.79 (6/11H, d, *J* = 10 Hz), 3.77 (5/11H, dd, *J* = 6, 3 Hz), 3.74 (6/11H, dd, *J* = 6, 4 Hz), 3.47-3.35 (2H, m), 3.35 (18/11H, s), 3.33 (15/11H, s), 3.25 (6/11H, d, *J* = 10 Hz), 3.24 (5/11H, d, *J* = 10 Hz), 2.43 (3H, s), 1.73 (6/11H, dd, *J* = 14, 4 Hz), 1.57 (5/11H, dd, *J* = 14, 5 Hz), 1.51 (5/11H, dd, *J* = 14, 7 Hz), 1.37 (6/11H, dd, *J* = 14, 7.5 Hz), 1.30-1.18 (3H, m), 1.21 (18/11H, t, *J* = 7 Hz), 1.20 (15/11H, t, *J* = 7 Hz), 0.83-0.78 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.5, 173.4, 143.4, 143.3, 134.1, 134.0, 129.58, 129.57, 127.6, 63.7, 63.5, 62.08, 62.05, 61.4, 55.7, 55.4, 54.2, 53.7, 50.5, 50.3, 37.1, 36.2, 31.7, 31.6, 30.5, 30.4, 21.5, 20.0, 19.6, 13.9, 11.24, 11.20; HRMS (EI, *m/z*) calcd for $C_{20}H_{32}N_2O_5S$ (M^+) 412.2030, found 412.2041.

Ethyl (3*R,4*R**)-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-(2,2-dimethylpropyl)-3-pyrrolidine-carboxylate (*cis*-27D)**

A colorless oil; IR ($CHCl_3$) 3548, 1724 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.75 (2H, br d, *J* = 8 Hz), 7.34 (2H, br d, *J* = 8 Hz), 4.15-4.03 (2H, m), 3.64 (1H, d, *J* = 10 Hz), 3.59 (1H, dd, *J* = 10.5, 6 Hz), 3.57 (1H, d, *J* = 10 Hz), 3.37 (1H, dd, *J* = 6, 4 Hz), 3.19 (1H, dd, *J* = 10.5, 4 Hz), 3.19 (3H, s), 2.43 (3H, s), 1.84 (1H, d, *J* = 14.5 Hz), 1.48 (1H, d, *J* = 14.5 Hz), 1.24 (3H, t, *J* = 7 Hz), 0.90 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.4, 143.4, 133.9, 129.6, 127.6, 67.6, 61.9, 61.1, 54.7, 52.8, 49.2, 48.2, 31.7, 30.6, 21.5, 13.8; HRMS (EI, *m/z*) calcd for $C_{20}H_{32}N_2O_5S$ (M^+) 412.2030, found 412.2027.

Ethyl (3*R,4*S**)-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-(2,2-dimethylpropyl)-3-pyrrolidine-**

carboxylate (*trans*-28D)

A colorless oil; IR ($CHCl_3$) 3547, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.73 (2H, br d, *J* = 8 Hz), 7.32 (2H, br d, *J* = 8 Hz), 4.07-3.93 (2H, m), 3.99 (1H, d, *J* = 10 Hz), 3.79 (1H, br dd, *J* = 5, 2 Hz), 3.49 (1H, dd, *J* = 10.5, 2 Hz), 3.33 (3H, s), 3.26 (1H, dd, *J* = 10.5, 5.5 Hz), 3.21 (1H, d, *J* = 10 Hz), 2.43 (3H, s), 1.79 (1H, d, *J* = 14 Hz), 1.56 (1H, d, *J* = 14 Hz), 1.19 (3H, t, *J* = 7 Hz,), 0.88 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.6, 143.2, 134.5, 129.5, 127.5, 64.9, 62.0, 61.4, 55.5, 54.3, 49.6, 43.0, 31.4, 30.3, 21.5, 13.7; HRMS (EI, *m/z*) calcd for $C_{20}H_{32}N_2O_5S$ (M^+) 412.2030, found 412.2026.

Ethyl (3*R,4*R**)-3-Cyclohexylmethyl-4-(methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidine-carboxylate (*cis*-27C) and ethyl (3*R**,4*S**)-3-cyclohexylmethyl-4-(methoxyamino)-1-[(4-methyl-phenyl)sulfonyl]-3-pyrrolidinecarboxylate (*trans*-28C) (Table 3, entry 4)**

Oxime ether **12a** (50 mg, 0.14 mmol) was dissolved in toluene (6 mL) under air atmosphere. To a solution of oxime ether **12a** in toluene were added cyclohexyl iodide (296.5 mg, 1.4 mmol) and Et_3B (1.01M in *n*-hexane) (0.37 mL, 0.35 mmol) under a nitrogen atmosphere at –78 °C. After being stirred at the same temperature for 30 min, an additional cyclohexyl iodide (296.5 mg, 1.4 mmol) and Et_3B (1.01M in *n*-hexane) (0.37 mL, 0.35 mmol) were added to the solution. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by MCC (*n*-hexane:AcOEt = 3:1) afforded cyclized products **27C** and **28C**.

cis-**27C**. Colorless crystals; mp 100-101 °C (*n*-hexane/$CHCl_3$); IR ($CHCl_3$) 3552, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.75 (2H, br d, *J* = 8 Hz), 7.32 (2H, br d, *J* = 8 Hz), 4.16-4.05 (2H, m), 3.56 (1H, dd, *J* = 11, 6 Hz), 3.55 (1H, d, *J* = 10 Hz), 3.43 (1H, d, *J* = 10 Hz), 3.36 (1H, dd, *J* = 6, 3 Hz), 3.31 (1H, dd, *J* = 11, 3 Hz), 3.17 (3H, s), 2.42 (3H, s), 1.66-1.55 (3H, m), 1.60 (1H, dd, *J* = 14, 7 Hz), 1.52-1.46 (2H, m), 1.33 (1H, dd, *J* = 14, 5 Hz), 1.30-1.02 (4H, m), 1.23 (3H, t, *J* = 7 Hz), 0.91-0.77 (2H, m). NOE was observed between 4-*H* (δ 3.36) and 3-CH_2 (δ 1.60, 1.33) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.3, 143.4, 133.7, 129.6, 127.6, 66.5, 61.9, 61.0, 54.8, 52.2, 49.8, 43.0, 34.5, 34.2, 33.7, 26.13, 26.12, 26.0, 21.5, 14.0; HRMS (EI, *m/z*) calcd for $C_{22}H_{34}N_2O_5S$ (M^+) 438.2186, found 438.2188; Anal. Calcd for $C_{22}H_{34}N_2O_5S$: C, 60.25; H, 7.81; N, 6.39. Found : C, 60.26; H, 7.81; N, 6.38.

trans-**28C**. A colorless oil; IR ($CHCl_3$) 3551, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.73 (2H, br d, *J* = 8 Hz), 7.33 (2H, br d, *J* = 8 Hz), 4.12-3.98 (2H, m), 3.82 (1H, d, *J* = 10 Hz), 3.74 (1H, dd, *J* = 6, 4 Hz), 3.42 (1H, dd, *J* = 10, 4 Hz), 3.40 (1H, dd, *J* = 10, 6 Hz), 3.33 (3H, s), 3.23 (1H, d, *J* = 10 Hz), 2.43 (3H, s), 1.66-1.49 (5H, m), 1.41 (1H, dd, *J* = 14, 6 Hz), 1.28-1.04 (5H, m), 1.20 (3H, t, *J* = 7 Hz), 0.91-0.80 (2H,

m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.5, 143.4, 134.1, 129.6, 127.6, 63.7, 62.1, 61.3, 55.3, 53.9, 50.4, 37.2, 34.8, 34.1, 33.8, 26.2, 26.1, 26.0, 21.5, 14.0; HRMS (EI, *m/z*) calcd for $C_{22}H_{34}N_2O_5S$ (M^+) 438.2186, found 438.2175.

General procedure for alkyl radical addition-cyclization reactions of oxime ether 12a (Table 3, entries 6-9)

Oxime ether **12a** (50 mg, 0.14 mmol) was dissolved in toluene (10 mL) under air atmosphere. To a solution of oxime ether **12a** in toluene were added corresponding alkyl iodide (0.70 or 2.10 mmol) and Et_3B (1.01M in *n*-hexane) (0.10 mL, 0.105 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 15 min, Three further portions of corresponding alkyl iodide (0.70 or 2.10 mmol) and Et_3B (1.01M in *n*-hexane) (each 0.10 mL, 0.105 mmol) were added at 15 min intervals. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by MCC (*n*-hexane:AcOEt = 7:1-5:1) afforded cyclized products **27E-H** and **28E-H** as shown in Table 3. 1-Iodotridecane, methyl 11-iodoundecanoate, and 2-iododecane were prepared according to the literature procedure.[15]

Ethyl (3*R,4*R**)-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-undecanyl-3-pyrrolidine-carboxylate (*cis*-27E)**

A colorless oil; IR ($CHCl_3$) 3550, 1725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.75 (2H, br d, *J* = 8 Hz), 7.33 (2H, br d, *J* = 8 Hz), 5.75 (1H, br s), 4.12 (2H, q, *J* = 7 Hz), 3.54 (1H, dd, *J* = 10.5, 6 Hz), 3.52 (1H, d, *J* = 10 Hz), 3.41 (1H, d, *J* = 10 Hz), 3.39 (1H, dd, *J* = 6, 3 Hz), 3.33 (1H, dd, *J* = 10.5, 3 Hz), 3.17 (3H, s), 2.42 (3H, s), 1.62-1.46 (1H, m), 1.38-1.00 (19H, m), 1.22 (3H, t, *J* = 7 Hz), 0.88 (3H, t, *J* = 7 Hz). NOE was observed between 4-*H* (δ 3.39) and 3-CH_2 (δ 1.62-1.46) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.9, 143.4, 133.7, 129.6, 127.6, 66.0, 63.1, 61.9, 61.0, 55.5, 52.0, 50.0, 35.9, 29.62, 29.59, 29.58, 29.57, 29.53, 29.50, 29.4, 29.3, 24.5, 21.5, 14.1. HRMS (EI, *m/z*) calcd for $C_{26}H_{44}N_2O_5S$ (M^+) 496.2968, found 496.2966.

Ethyl (3*R,4*S**)-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-undecanyl-3-pyrrolidine-carboxylate (*trans*-28E)**

A colorless oil; IR ($CHCl_3$) 3550, 1724 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.72 (2H, br d, *J* = 8 Hz), 7.32 (2H, br d, *J* = 8 Hz), 5.59 (1H, br s), 4.14-4.00 (2H, m), 3.75 (1H, dd, *J* = 6, 4.5 Hz), 3.73 (1H, d, *J* = 10 Hz), 3.47 (1H, dd, *J*=10, 6 Hz), 3.39 (1H, dd, *J* = 10, 4.5 Hz), 3.35 (3H, s), 3.24 (1H, d, *J* = 10 Hz),

2.43 (3H, s), 1.60 (1H, ddd, *J* = 13, 12, 4.5 Hz), 1.40 (1H, ddd, *J* = 13, 11, 5 Hz), 1.34-1.04 (18H, m), 1.20 (3H, t, *J* = 7 Hz), 0.88 (3H, t, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.2, 143.4, 133.9, 129.6, 127.5, 62.7, 62.0, 61.3, 55.7, 53.6, 50.7, 31.9, 30.0, 29.8, 29.6, 29.55, 29.46, 29.29, 29.27, 25.1, 22.6, 21.5, 14.1, 14.0; HRMS (EI, *m/z*) calcd for $C_{26}H_{44}N_2O_5S$ (M^+) 496.2968, found 496.2972.

Ethyl (3*R,4*R**)-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-tetradecanyl-3-pyrrolidine-carboxylate (*cis*-27F)**

Colorless crystals; mp. 54-54.5 °C (*n*-hexane); IR ($CHCl_3$) 3510, 1724 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.75 (2H, br d, *J* = 8 Hz), 7.33 (2H, br d, *J* = 8 Hz), 4.12 (2H, q, *J* = 7 Hz), 3.54 (1H, dd, *J* = 10.5, 6 Hz), 3.52 (1H, d, *J* = 10 Hz), 3.40 (1H, d, *J* = 10 Hz), 3.39 (1H, dd, *J* = 6, 3 Hz), 3.33 (1H, dd, *J* = 10.5, 3 Hz), 3.17 (3H, s), 2.42 (3H, s), 1.62-1.46 (1H, m), 1.38-1.00 (25H, m), 1.22 (3H, t, *J* = 7 Hz), 0.88 (3H, t, *J* = 7 Hz). NOE was observed between 4-*H* (δ 3.39) and 3-C*H*$_2$ (δ 1.62-1.46) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.9, 143.5, 133.7, 129.6, 127.6, 66.0, 63.1, 62.0, 61.0, 55.5, 52.0, 50.0, 36.0, 32.8, 31.9, 29.67, 29.65, 29.59, 29.52, 29.4, 29.35, 29.32, 25.7, 24.5, 22.7, 21.5, 14.1; HRMS (EI, *m/z*) calcd for $C_{29}H_{50}N_2O_5S$ (M^+) 538.3438, found 538.3432; Anal. Calcd for $C_{29}H_{50}N_2O_5S$: C, 64.65; H, 9.35; N, 5.20. Found : C, 64.64; H, 9.30; N, 5.18.

Ethyl (3*R,4*S**)-4-(Methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-tetradecanyl-3-pyrrolidine-carboxylate (*trans*-28F)**

A colorless oil; IR ($CHCl_3$) 3570, 1725 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.72 (2H, br d, *J* = 8 Hz), 7.32 (2H, br d, *J* = 8 Hz), 4.10-4.00 (2H, m), 3.75 (1H, dd, *J* = 6, 4 Hz), 3.73 (1H, d, *J* = 10 Hz), 3.47 (1H, dd, *J* = 10.5, 6 Hz), 3.39 (1H, dd, *J* = 10.5, 4 Hz), 3.35 (3H, s), 3.24 (1H, d, *J* = 10 Hz), 2.43 (3H, s), 1.60-1.54 (1H, m), 1.44-1.36 (1H, m), 1.36-1.00 (24H, m), 1.20 (3H, t, *J* = 7 Hz), 0.88 (3H, t, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.3, 143.4, 134.0, 129.6, 127.6, 63.1, 62.8, 62.0, 61.3, 55.8, 53.6, 50.7, 32.8, 30.0, 29.8, 29.7, 29.64, 29.61, 29.59, 29.5, 29.4, 29.35, 29.31, 25.7, 25.1, 21.5, 14.0. HRMS (EI, *m/z*) calcd for $C_{29}H_{50}N_2O_5S$ (M^+) 538.3438, found 538.3422.

Methyl 3-(Ethoxycarbonyl)-4-(methoxyamino)-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidinedodecanoate (27G and 28G)

Cyclized products **27G** and **28G** (70:30) were inseparable. A colorless oil; IR ($CHCl_3$) 3527, 1729 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (2H, br d, *J* = 8 Hz), 7.34 (2H, br d, *J* = 8 Hz), 4.18-4.00 (2H, m), 3.67 (3H, s), 3.60-3.10 (5H, m), 3.35 (9/10H, s), 3.16 (21/10H, s), 2.43 (3H, s), 2.35 (6/10H, t, *J* = 7 Hz), 2.30 (14/10H, t, *J* = 7 Hz), 1.80-1.00 (20H, m), 1.24 (9/10H, t, *J* = 7 Hz), 1.23 (21/10H, t, *J* = 7 Hz); ^{13}C

NMR (75 MHz, $CDCl_3$) δ: 174.3, 172.2, 143.4, 135.5, 129.6, 127.6, 66.1, 61.9, 61.0, 55.5, 51.9, 51.4, 49.9, 49.7, 34.1, 33.7, 30.4, 29.4, 29.2, 29.1, 28.4, 26.7, 24.9, 21.5, 21.0, 14.1; HRMS (EI, *m/z*) calcd for $C_{28}H_{46}N_2O_7S$ (M^+) 554.3023, found 554.3029.

Ethyl (3*R,4*R**)-4-(Methoxyamino)-3-(2-methyldecanyl)-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidinecarboxylate (*cis*-27G and *cis*-27G')**

The stereostructures of the *cis*-**27G** and *cis*-**27G'** (59:41) have not been established. *The minor less polar product*; A colorless oil; IR ($CHCl_3$) 3556, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.75 (2H, br d, *J* = 8 Hz), 7.33 (2H, br d, *J* = 8 Hz), 4.10 (2H, br q, *J* = 7 Hz), 3.56 (1H, dd, *J* = 10.5, 6 Hz), 3.54 (1H, d, *J* = 9.5 Hz), 3.45 (1H, d, *J* = 9.5 Hz), 3.36 (1H, dd, *J* = 6, 3 Hz), 3.30 (1H, dd, *J* = 10.5, 3 Hz), 3.16 (3H, s), 2.42 (3H, s), 1.67 (1H, dd, *J* = 14, 4.5 Hz), 1.50-1.36 (1H, m), 1.31 (1H, dd, *J* = 14, 7 Hz), 1.34-0.98 (14H, m), 1.24 (3H, t, *J* = 7 Hz), 0.88 (3H, t, *J* = 7 Hz), 0.82 (3H, d, *J* = 7 Hz). NOE was observed between 4-*H* (δ 3.36) and 3-CH_2 (δ 1.67, 1.31) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.3, 143.4, 133.7, 129.6, 127.7, 66.2, 61.9, 61.0, 55.1, 52.7, 49.8, 42.9, 37.9, 31.9, 29.8, 29.6, 29.3, 26.8, 22.6, 21.5, 21.0, 14.1, 14.0. HRMS (EI, *m/z*) calcd for $C_{26}H_{44}N_2O_5S$ (M^+) 496.2969, found 496.2970. *The major more polar product*; A colorless oil; IR ($CHCl_3$) 3530, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.75 (2H, br d, *J* = 8 Hz), 7.33 (2H, br d, *J* = 8 Hz), 5.75 (1H, br s), 4.15-4.06 (2H, m), 3.57 (1H, dd, *J* = 11, 6 Hz), 3.53 (1H, d, *J* = 10 Hz), 3.42 (1H, d, *J* = 10 Hz), 3.36 (1H, dd, *J* = 6, 3 Hz), 3.30 (1H, dd, *J* = 11, 3 Hz), 3.14 (3H, s), 2.42 (3H, s), 1.56 (1H, dd, *J* = 14, 8 Hz), 1.49 (1H, dd, *J* = 14, 4 Hz), 1.50-1.40 (1H, m), 1.32-1.00 (14H, m), 1.24 (3H, t, *J* = 7 Hz), 0.89 (3H, t, *J* = 7 Hz), 0.76 (3H, d, *J* = 7 Hz). NOE was observed between 4-*H* (δ 3.36) and 3-CH_2 (δ 1.56, 1.49) in NOESY spectroscopy. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.4, 143.4, 133.7, 129.6, 127.7, 66.5, 61.9, 61.1, 55.1, 52.0, 49.8, 42.8, 38.4, 31.9, 29.9, 29.6, 29.5, 29.3, 26.8, 22.7, 21.5, 20.2, 14.1, 14.0; HRMS (EI, *m/z*) calcd for $C_{26}H_{44}N_2O_5S$ (M^+) 496.2969, found 496.2975.

Ethyl (3*R,4*S**)-4-(Methoxyamino)-3-(2-methyldecanyl)-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidinecarboxylate (*trans*-28G and *trans*-28G')**

The stereostructures of the *trans*-**28G** and *trans*-**28G'** (57:43) have not been established. *The minor less polar product*; A colorless oil; IR ($CHCl_3$) 3525, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.73 (2H, br d, *J* = 8 Hz), 7.32 (2H, br d, *J* = 8 Hz), 4.09-3.97 (2H, m), 3.84 (1H, d, *J* = 10 Hz), 3.76 (1H, dd, *J* = 6, 3.5 Hz), 3.44 (1H, dd, *J* = 11, 3.5 Hz), 3.37 (1H, dd, *J* = 11, 6 Hz), 3.33 (3H, s), 3.23 (1H, d, *J* = 10 Hz), 2.43 (3H, s), 1.72 (1H, dd, *J* = 13, 4 Hz), 1.35 (1H, dd, *J* = 13, 8 Hz), 1.36-1.14 (15H, m), 1.20 (3H, t, *J* = 7 Hz), 0.88 (3H, t, *J* = 7 Hz), 0.80 (3H, d, *J* = 6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.5, 143.3, 134.1,

129.6, 127.6, 63.8, 62.0, 61.4, 55.7, 54.2, 50.3, 38.0, 37.5, 31.9, 30.1, 29.8, 29.6, 29.3, 26.9, 22.6, 21.5, 20.4, 14.1, 13.9; HRMS (EI, *m/z*) calcd for $C_{26}H_{44}N_2O_5S$ (M^+) 496.2969, found 496.2966. *The major more polar product*; A colorless oi; IR ($CHCl_3$) 3551, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.73 (2H, br d, *J* = 8 Hz), 7.32 (2H, br d, *J* = 8 Hz), 5.77 (1H, br s), 4.10-3.97 (2H, m), 3.79 (1H, d, *J* = 10 Hz), 3.74 (1H, dd, *J* = 6, 4 Hz), 3.44 (1H, dd, *J* = 10.5, 4 Hz), 3.41 (1H, dd, *J* = 10.5, 6 Hz), 3.33 (3H, s), 3.23 (1H, d, *J* = 10 Hz), 2.43 (3H, s), 1.54 (1H, dd, *J* = 14, 5 Hz), 1.34-1.00 (16H, m), 1.21 (3H, t, *J* = 7 Hz), 0.89 (3H, t, *J* = 7 Hz), 0.80 (3H, d, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.6, 143.3, 134.1, 129.6, 127.6, 63.5, 62.1, 61.4, 55.4, 53.8, 50.6, 38.0, 36.6, 31.9, 30.1, 29.8, 29.6, 29.3, 26.9, 22.7, 21.5, 20.0, 14.1, 13.9; HRMS (EI, *m/z*) calcd for $C_{26}H_{44}N_2O_5S$ (M^+) 496.2969, found 496.2975.

ACKNOWLEDGEMENTS

This work was supported by Grants-in Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT), and the MEXT-Supported Program for the Strategic Research Foundation at Private Universities.

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