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Novel synthesis of substituted pyrrolidines and piperidines via radical addition–ionic cyclization reaction of oxime ethers

Okiko Miyata, Shinya Takahashi, Akira Tamura, Masafumi Ueda, Takeaki Naito*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan

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Abstract

We have developed a novel synthetic route to nitrogen-containing heterocycles via radical addition–ionic cyclization reaction. Treatment of oxime ethers carrying the tosyloxy group with Et_3B and alkyl iodide in the presence of Lewis acid gave the substituted pyrrolidines and piperidines. The reaction of oxime ethers carrying the methoxycarbonyl group proceeded under the same conditions to give the amino esters, which were easily converted into the corresponding lactams by the treatment with concd HCl. On the other hand, the oxime ether bearing the phenoxycarbonyl group afforded directly alkylated lactams under the radical reaction conditions. The utility of this domino reaction was demonstrated by the synthesis of (±)-bgugaine and the formal synthesis of 5,8-disubstituted indolizidine alkaloids.

Keywords: Radical reaction; Pyrrolidine; Piperidine; Oxime ether; Indolizidine

1. Introduction

The nitrogen-containing heterocycles are common substructures found widely in biologically active materials and hence attract broad interest, particularly in the areas of synthetic methodology, bioorganic and medicinal chemistry, and natural product synthesis.[1]

Domino types of reactions[2a] are one-pot multi-step processes and hence very powerful for the rapid construction of complex organic molecules efficiently and elegantly in a convergent and eco-friendly manner with minimum waste generation. The biological importance of the nitrogen heterocycles and our continued interest in the synthesis of novel organic molecules employing tandem sequences prompted us to investigate the radical reactions of several oxime ethers bearing leaving group at the terminal position.

We have now developed a new methodology for the construction of substituted pyrrolidines and piperidines via the radical addition–nucleophilic substitution by using the oxime ether group as a nucleophile. Addition reactions[2b,c,3] of carbon fragments to C=N bonds of imines and related compounds are one of the typical techniques for the construction of divergently substituted heterocycles. Among the different types of imines, the oxime ethers are well-known[2b,c,3] to be excellent radical acceptors. We have also reported[3] that the intermolecular radical addition reactions to aldoximes proceeded smoothly. Additionally, we have recently found the tandem radical addition–aldol type reaction of α,β-unsaturated oxime ethers.[4]

We designed radical addition–cyclization reaction of the oxime ethers aiming at development of new strategy for the construction of heterocycles. We chose the oxime ethers **1** bearing leaving group at ω-position as the substrates. The Et_3B induced radical addition to oxime ethers **1** would proceed in the presence of various types of alkyl iodides to form the borylamines **B**, which are subjected to intramolecular nucleophilic substitution to give nitrogen-containing heterocycles. Since oxime ethers **1** have two electrophilic sites, the ionic reaction of substrate **1** with nucleophile could occur on not only imino group but also the tosyloxymethyl and the

* Corresponding author. Tel.: +81 78 441 7554; fax: +81 78 441 7556.
E-mail address: taknaito@kobepharma-u.ac.jp (T. Naito).

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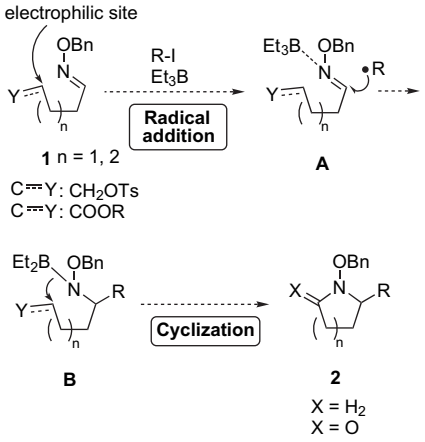
alkoxycarbonyl groups to form complex mixture, which is a drawback of normal ionic reactions (Scheme 1).



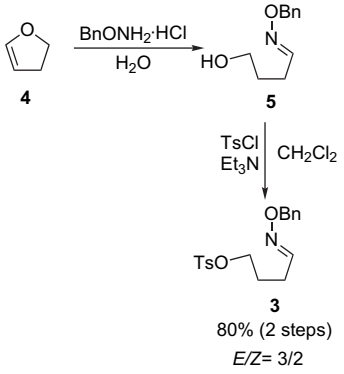
Scheme 1.

On the other hand, the alkyl radical would prefer addition reaction rather than substitution reaction. Therefore, the reaction of substrate with alkyl radical would chemoselectively proceed in the first step to form the borylamines **B**.

2. Results and discussion

*2.1. Preparation and radical addition–ionic cyclization reaction of oxime ethers **3**, **9**, and **14** carrying a tosyloxy group*

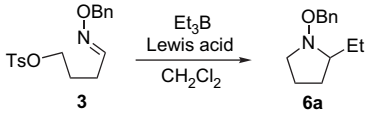
We first picked up oxime ether **3** carrying the tosyloxy group as a substrate, which was prepared from 2,3-dihydrofuran (**4**) by the treatment with benzyloxyamine[5] followed by tosylation (Scheme 2).



Scheme 2.

The domino reaction of oxime ether **3** was examined under various reaction conditions (Table 1). When the oxime ether **3** was treated with Et_3B at room temperature, only recovered starting material was obtained (entry 1). The pyrrolidine **6a** was obtained in 20% yield by heating at 40 °C (entry 2). The reaction was carried out in the presence of $BF_3\cdot Et_2O$[3] as a Lewis acid at room temperature to give the desired product **6a** in good yield (entry 3), while the yield of **6a** was decreased at the elevated temperature (entry 4). When the various types of Lewis acids were used in the place of $BF_3\cdot Et_2O$, **6a** was obtained only in moderate yields (entries 5–9).

Table 1
Radical addition–ionic cyclization of oxime ether **3**



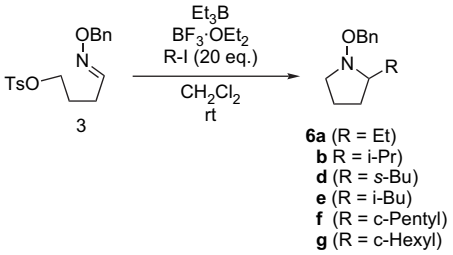
Entry	Lewis acid	Temperature (°C)	Time (h)	Yield (%)
1	None	rt	24	nr
2	None	40	7	20 (24)[a]
3	$BF_3\cdot OEt_2$ (2 equiv)	rt	3.5	75
4	$BF_3\cdot OEt_2$ (2 equiv)	40	2	45
5	$Cu(OTf)_2$ (2 equiv)	rt	4	27 (25)[a]
6	$Mg(ClO_4)_2$ (2 equiv)	rt	7	43
7	$Sc(OTf)_3$ (1 equiv)	rt	3.5	45 (20)[a]
8	TMSOTf (1 equiv)	rt	3.5	62
9	$Hf(OTf)_4$ (1 equiv)	rt	3.5	66

nr: no reaction.
[a] Yields in parentheses are for recovered starting material.

We next examined the reaction of oxime ether **3** in the presence of various types of alkyl iodides as radical precursors (Table 2). Et_3B and $BF_3\cdot OEt_2$ were further added when the radical reaction proceeded slowly (entries 1–8). The treatment of **3** with 10 equiv of *i*-PrI gave a mixture of **6b** and **6a** in 38 and 18% yields, respectively (entry 1). When 20 equiv of *i*-PrI was employed, the yield of **6b** was increased (entry 2).

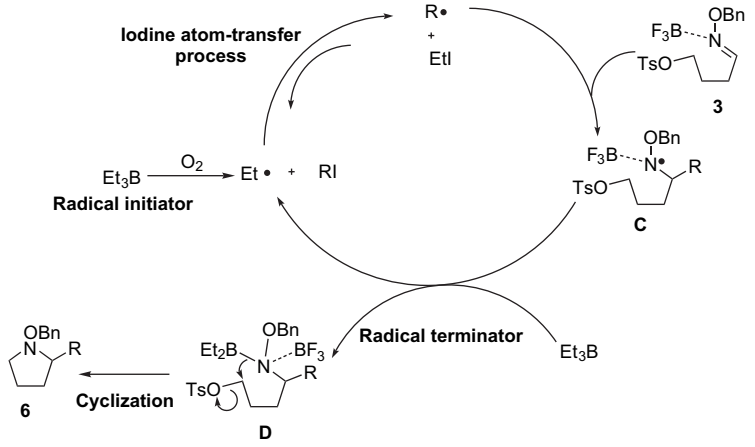
In the presence of other secondary alkyl iodides as radical precursors, the reactions also proceeded smoothly to give alkylated pyrrolidines **6d**, **6f**, and **6g** (entries 4, 6, and 7). In the cases using sterically hindered tertiary alkyl iodides, only

Table 2
Radical reaction of **3** with various types of alkyl iodides



Entry	R–I (equiv)	Et_3B (equiv)	$BF_3\cdot OEt_2$ (equiv)	Time (h)	Yield (%)	
					6b–h	**6a**
1	*i*-Pr–I (10)	6	4	23	38	18
2	*i*-Pr–I (20)	6	4	3	51	13
3	*t*-Bu–I (20)	9	6	23	nr	
4	*s*-Bu–I (20)	6	4	22	80	19
5	*i*-Bu–I (20)	6	4	23	13	44
6	*c*-Pentyl–I (20)	6	4	3	68	26
7	*c*-Hexyl–I (20)	6	4	4	64	32
8	Adamantyl–I (20)	6	4	23	nr	

nr: no reaction.



Scheme 3.

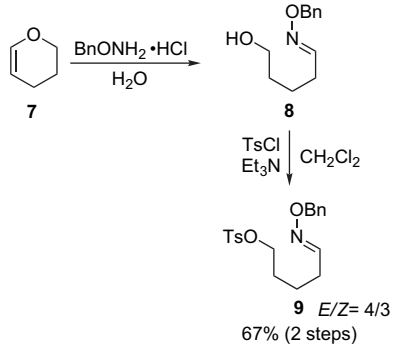
the starting oxime ether was recovered (entries 3 and 8). The reaction of **3** with primary alkyl iodide, that is, *i*-BuI gave **6a** as a major product along with **6e** (entry 5).

We propose possible reaction pathway for this reaction according to the reaction mechanism postulated in our previous reports[2c,3] (Scheme 3).

The ethyl radical is generated from Et_3B in the presence of O_2. In the presence of RI, the iodine atom-transfer reaction proceeds to form R radical, which adds intermolecularly to the $BF_3{\cdot}Et_2O$-activated oxime ether **3**. The aminyl radical **C** formed is then trapped by Et_3B to form the complex **D**. The desired product **6** is obtained as a result of the intramolecular cyclization of **D**.

In the case of primary alkyl iodide (*i*-BuI), the ethylated product **6a** was obtained as a major product. This result suggests that the iodine atom-transfer proceeds slowly because isobutyl radical formed is unstable. On the other hands, the iodine atom-transfer proceeds smoothly in the reaction using *tert*-butyl iodide and adamantyl iodide because the stable tertiary alkyl radicals are formed. However, the desired products **6** were not obtained because the radical addition reaction of stable alkyl radical to less reactive oxime ether **3** would proceed hardly.

The radical reaction was extended to the homologous system **9**, prepared from dihydropyran **7**[5] (Scheme 4).

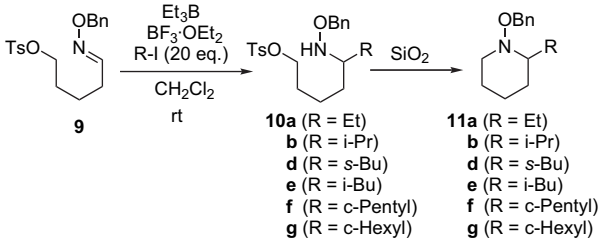


Scheme 4.

In this case, ^1H NMR spectrum of the crude reaction mixture did not show the existence of piperidines **11a**,**b**,**d**–**g**, but acyclic products **10a**,**b**,**d**–**g**, which easily cyclized during purification by silica gel chromatography to afford alkylated piperidines **11a**,**b**,**d**–**g** (Table 3). The radical reaction of **9** with various types of alkyl iodides showed a tendency similar to that of **3**. The tertiary alkyl radical did not work well (entries 3 and 8) and primary alkyl radical gave the corresponding product **11e** in low yield (entry 5). Et_3B and $BF_3{\cdot}OEt_2$ were further added when the radical reaction proceeded slowly (entries 3–8).

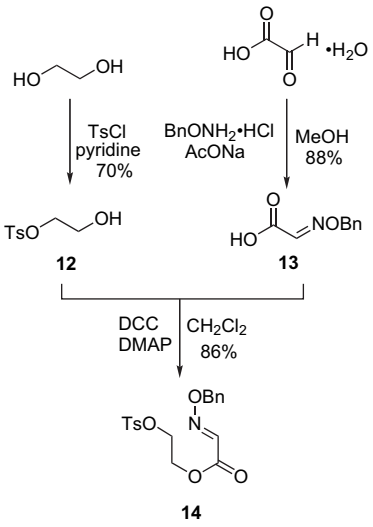
We then investigated the domino reaction using glyoxylic oxime ether **14** as a substrate expecting that more electrophilic oxime ethers may undergo the radical addition even in the absence of Lewis acid.[2c,3] The oxime ether **14** was prepared by the condensation of carboxylic acid **13**[6] with the alcohol **12**[7] (Scheme 5).

Table 3
Radical addition–ionic cyclization of oxime ether **9**



Entry	R–I	Et_3B (equiv)	$BF_3{\cdot}OEt_2$ (equiv)	Time (h)	yield (%)	
					11b–h	**11a**
1	—	3	2	4	—	51
2	*i*-Pr–I	3	2	6	38	9
3	*t*-Bu–I	9	6	23	0	16
4	*s*-Bu–I	6	4	16	30	16
5	*i*-Bu–I	6	4	23	16	16
6	*c*-Pentyl–I	6	4	5	57	15
7	*c*-Hexyl–I	6	4	4	54	16
8	Adamantyl–I	9	6	23	nr	

nr: no reaction.



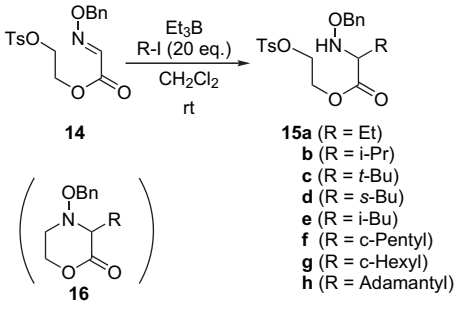
Scheme 5.

As expected, radical addition reaction of **14** proceeded very smoothly to give adducts **15a–h** (Table 4) but intramolecular cyclization did not occur even when **15a–h** were subjected to acidic conditions. Et_3B and $BF_3{\cdot}OEt_2$ were further added when the radical reaction proceeded slowly (entries 3 and 8). Interestingly, we obtained tertiary alkyl radical addition products **15c**,**h** in excellent yields (entries 3 and 8). The even stable tertiary alkyl radical adds easily to **14** because of high reactivity of oxime ether **14** as a radical acceptor.

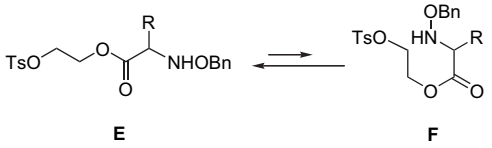
Wiberg[8] has reported that *Z*-rotamer of methyl formate is more stable than *E*-rotamer because of small dipole moment of *Z*-rotamer.

As described above, no cyclization of **15** was observed due to the stable zig-zag conformation **E** that makes it unsuitable for cyclization (Scheme 6).

Table 4
Radical addition–ionic cyclization of oxime ether **14**



Entry	R–I	Et_3B (equiv)	Time (h)	Yield (%)	
				15b–h	**15a**
1	—	3	2.5	—	79
2	*i*-Pr–I	3	2	81	10
3	*t*-Bu–I	6	2.3	86	0
4	*s*-Bu–I	3	5	71	26
5	*i*-Bu–I	3	3	22	61
6	*c*-Pentyl–I	3	4.5	75	10
7	*c*-Hexyl–I	3	4	70	24
8	Adamantyl–I	6	6	94	3



Scheme 6.

2.2. Preparation and radical addition–ionic cyclization reaction of oxime ethers *23*, *24*, *31*, and *32* carrying an ester group

In our second approach, we picked up oxime ethers **23** and **24**, which carry the ester group as a functional group (Table 5). The hydroxyl esters **19**[9] and **20**[9] that have different length carbon chains were prepared from lactones **17** and **18**, respectively. The hydroxyl esters **19** and **20** were converted into the requisite oxime ethers **23**[10] and **24** via oxidation and subsequent condensation with benzyloxyamine (Scheme 7).

In the presence of Lewis acid, two substrates **23** and **24** underwent alkyl radical addition in all cases to give adducts **25** and **26** (Table 5). Et_3B and $BF_3{\cdot}OEt_2$ were further added when the radical reaction proceeded slowly (entries 3, 5, 8, 11, 13, and 16). However, the products **25** and **26** did not cyclize under the radical conditions. On treatment with hydrochloric acid, these adducts **25** and **26** afforded the cyclized lactams **27** and **28** in good yields, except for the cyclization of **26h**.

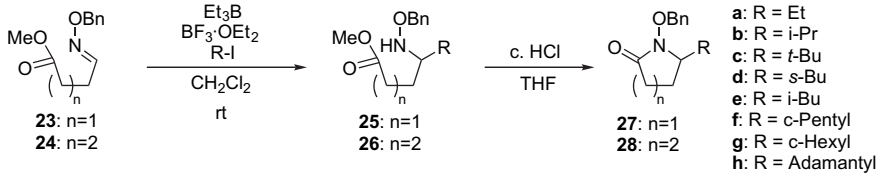
According to Landais's recent report,[11] we next employed the phenyl esters **31** and **32**, prepared from the corresponding methyl esters **23** and **24**, because the phenoxy group is a better leaving group than the methoxy group. Under the standard radical conditions, **31** and **32** gave the expectedly cyclized lactams **27** and **28** in good yields (Scheme 8, Table 6).

2.3. Synthesis of (±)-bgugaine and formal synthesis of 5,8-disubstituted indolizidine alkaloid

Based on these results, we then applied our method to the synthesis of a few alkaloids from common oxime ether **3** in order to evaluate the potentiality of our method. Most simple application is the synthesis of an alkaloid, bgugaine (**36**) (Scheme 9). (−)-Bgugaine is a 2-alkylpyrrolidine isolated from the tubers of *Arisarum vulgare*,[12,13] a toxic Araceae responsible for human and animal poisonings in Morocco. This alkaloid shows antibacterial activity against Gram positive bacteria and antimycotic activity against some *Candida and Cryptococcus* strains.[12–14]

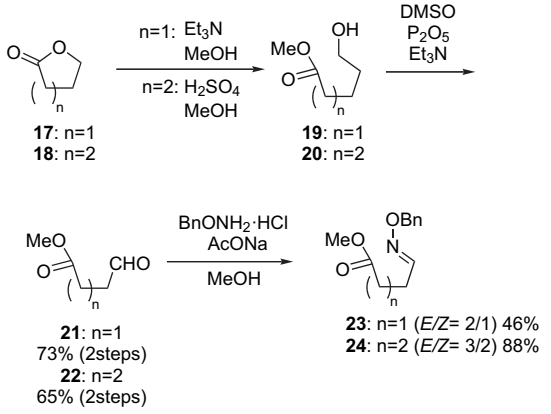
Radical reaction of oxime ether **3** with longer alkyl chain iodide **34** gave the alkylated and cyclized product **33** in moderate yield. The improvement of yield was difficult because of less effective iodine atom-transfer reaction of primary alkyl iodide **34**. Transformation of the functional groups involving reductive debenzyloxylation and reductive methylation afforded simple alkaloid, (±)-bgugaine (**36**). The physical and spectral properties of our prepared pyrrolidine **36** were identical with those of an authentic sample reported in the literature.[14]

Table 5
Intermolecular radical addition–ionic cyclization reaction of oxime ethers **23** and **24**



Entry	Substrate	R–I	Et_3B (equiv)	$BF_3\cdot OEt_2$ (equiv)	Time (h)	Yield (%)	
						25, **26**	**27**, **28**
1	**23**	—	3	2	2	**25a** (79)	**27a** (78)
2	**23**	*i*-Pr–I	3	2	2	**25b** (78)[a]	**27b** (79)
3	**23**	*t*-Bu–I	9	6	23	**25c** (39)	**27c** (65)
4	**23**	*s*-Bu–I	3	2	5	**25d** (83)[a]	**27d** (95)
5	**23**	*i*-Bu–I	9	6	24	**25e** (26)[a]	**27e** (85)
6	**23**	*c*-Pentyl–I	3	2	2	**25f** (63)[a]	**27f** (81)
7	**23**	*c*-Hexyl–I	3	2	2	**25g** (53)[a]	**27g** (85)
8	**23**	Adamantyl–I	3	6	24	**25h** (48)	**27h** (70)
9	**24**	—	3	2	2	**26a** (70)	**28a** (85)
10	**24**	*i*-Pr–I	3	2	2	**26b** (67)[b]	**28b** (78)
11	**24**	*t*-Bu–I	9	6	23	**26c** (24)	**28c** (70)
12	**24**	*s*-Bu–I	3	2	5	**26d** (55)[b]	**28d** (77)
13	**24**	*i*-Bu–I	9	6	24	**26e** (11)[b]	**28e** (83)
14	**24**	*c*-Penty–I	3	2	2	**26f** (62)[b]	**28f** (81)
15	**24**	*c*-Hexyl–I	3	2	2	**26g** (61)[b]	**28g** (70)
16	**24**	Adamantyl–I	3	6	24	**26h** (50)[b]	—

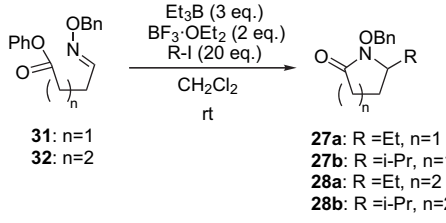
[a] The ethylated product **25a** was also obtained in 14–34% yield.
[b] The ethylated product **26a** was obtained in 13–44% yield.



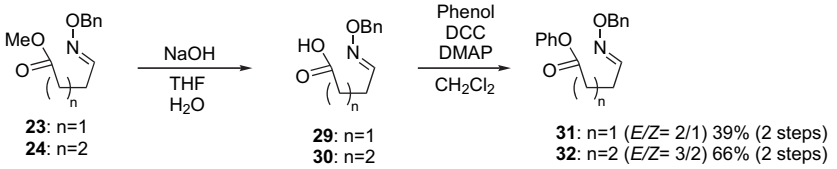
Scheme 7.

Another application is the formal synthesis of 5,8-disubstituted indolizidine alkaloids **37**,[15] which have been isolated from the skin of poison frogs of Dendrobatidae family (Scheme 10). Due to the extreme scarcity of these alkaloids from natural sources and their potent biological activities in neuroscience, considerable attention has been paid to the chemical synthesis of these alkaloids. The addition of secondary alkyl radical generated from **38**[16] to oxime ether **3** proceeded effectively to form the cyclized product **39**, which was a 1:1 mixture of two diastereomers **39a** and **39b**. After

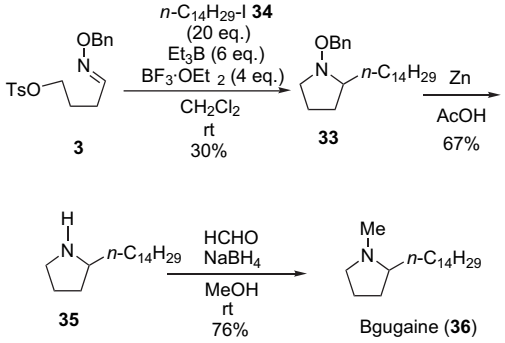
Table 6
Intermolecular radical addition–ionic cyclization reaction of oxime ethers **31** and **32**



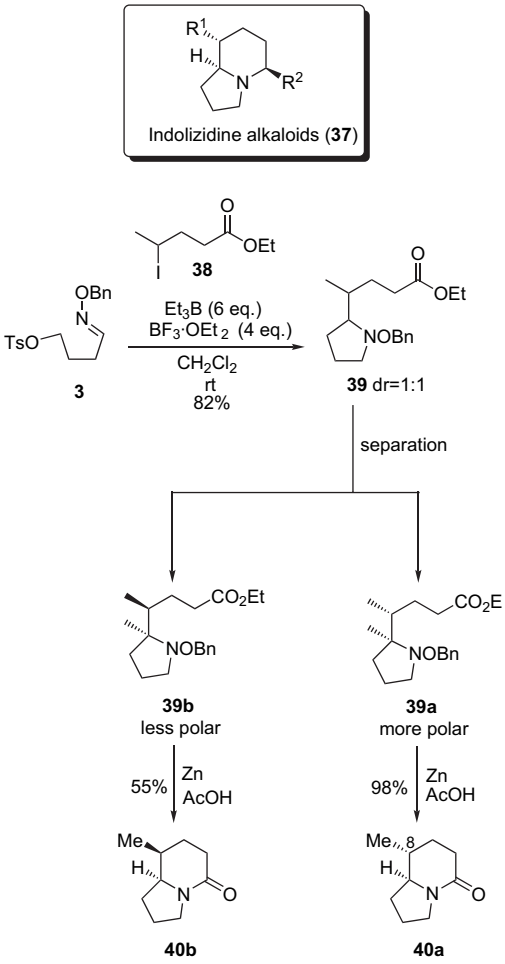
Entry	Substrate	R–I	Time (h)	Yield (%)	
				27b, **28b**	**27a**, **28a**
1	**31**	—	5	—	72
2	**31**	*i*-Pr–I	4	68	Trace
3	**32**	—	3	—	70
4	**32**	*i*-Pr–I	5	63	Trace



Scheme 8.



Scheme 9.



Scheme 10.

separation of the isomers, each compound was converted into respective bicyclic lactams **40a** and **40b**, of which lactam **40a** is known as a synthetic key intermediate[17] of poison frog alkaloids.

3. Conclusion

We have succeeded in the development of radical addition–ionic cyclization method for the preparation of substituted pyrrolidines and piperidines. Additionally, this domino reaction was applied to the synthesis of (±)-bgugaine and the formal synthesis of 5,8-disubstituted indolizidine alkaloids.

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 50, 75, or 125 MHz for solution in deuteriochloroform (with tetramethylsilane as an internal reference), respectively. IR spectra were recorded using FTIR apparatus for solutions in chloroform except for KBr pellet. 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). Preparative TLC (PTLC) separations were carried out on precoated silica gel plates (E. Merck 60F_{254}).

4.2. (*E*/*Z*)-4-[[(4-Methylphenyl)sulfonyl]oxy]butanal *O*-(phenylmethyl)oxime (*3*)

To a solution of $BnONH_2 \cdot HCl$ (16 g, 100 mmol) in H_2O (80 mL) was added slowly 2,3-dihydrofuran (**4**) (7.6 mL, 100 mmol) under a nitrogen atmosphere at room temperature. After being stirred for 3.5 h, the reaction mixture was neutralized with $NaHCO_3$ and saturated with NaCl. The reaction mixture was diluted with H_2O and then extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. ^{1}H NMR spectrum of the residue proved the formation of desired oxime ether, which without further purification was subjected to the following reaction. To a solution of oxime ethers **5**[5] (2 g, 10 mmol) in CH_2Cl_2 (30 mL) were added Et_3N (1.9 mL, 13 mmol) and TsCl (2.4 g, 12 mmol) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to reach room temperature. After being stirred at room temperature overnight, the reaction mixture was diluted with H_2O and then extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. The crude product was purified by FCC (*n*-hexane/AcOEt=1:1) to afford **3** (2.9 g, 80%) as a colorless oil and a 3:2 mixture of *E*- and *Z*-isomers; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (2H, br d, J=8.5 Hz), 7.39–7.25 (7H+3/5H, m), 6.61 (2/5H, br t, J=6.0 Hz), 5.07 (4/5H, s), 5.00 (6/5H, s), 4.05 (6/5H, t, J=6.0 Hz), 4.02 (4/5H, t, J=6.0 Hz), 2.43 (3H, s), 2.41–2.17 (2H, m), 1.92–1.75 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 149.1, 144.7, 137.8, 137.5, 132.9, 132.9, 129.8, 128.3, 127.9, 127.8, 77.2, 75.8, 75.6, 69.5, 69.3, 25.6, 25.6, 22.1, 21.6; HRMS (EI, *m*/*z*) calcd for $C_{18}H_{21}NO_4S$ (M^+) 347.1190, found 347.1191.

4.2.1. 2-Ethyl-1-(phenylmethoxy)pyrrolidine (*6a*) (*Table 1, entry 3*)

To a solution of **3** (50 mg, 0.14 mmol) in CH_2Cl_2 (4.0 mL) were added $BF_3 \cdot OEt_2$ (0.04 mL, 0.28 mmol) and Et_3B (1 mol/L

in *n*-hexane) (0.42 mL, 0.42 mmol) under a nitrogen atmosphere at room temperature. After being stirred for 3.5 h, the reaction mixture was neutralized with K_2CO_3 and diluted with H_2O and then extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. The crude product was purified by MCC (*n*-hexane/AcOEt=3:1) to afford **6a** (22 mg, 75%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.25 (5H, m), 4.75 and 4.73 (2H, AB q, J=11.0 Hz), 3.23 (1H, ddd, J=12.0, 8.5, 4.5 Hz), 2.80 (2H, m), 1.95–1.88 (1H, m), 1.81–1.68 (3H, m), 1.41–1.33 (2H, m), 0.93 (3H, t, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 128.6, 128.3, 127.7, 75.7, 69.4, 55.7, 26.9, 26.3, 20.3, 11.1; HRMS (EI, *m/z*) calcd for $C_{13}H_{19}NO$ (M^+) 205.1466, found 205.1444.

*4.2.2. General procedure for alkyl radical addition–ionic cyclization reaction of oxime ether **3***

To a solution of **3** (50 mg, 0.14 mmol) in CH_2Cl_2 (4.0 mL) were added alkyl iodide (2.8 mmol), $BF_3\cdot OEt_2$ (0.03 mL, 0.28 mmol), and Et_3B (1 mol/L in *n*-hexane) (0.42 mL, 0.42 mmol) under a nitrogen atmosphere at room temperature. After being stirred for 1.5 h, additional $BF_3\cdot OEt_2$ (0.03 mL, 0.28 mmol) and Et_3B (1 mol/L in *n*-hexane) (0.42 mL, 0.42 mmol) were added to the solution. After being stirred for 1.5–21.5 h, the reaction mixture was neutralized with K_2CO_3, diluted with H_2O, and then extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. The crude product was purified by MCC (*n*-hexane/AcOEt=20:1) to afford pyrrolidines **6** as shown in Table 2.

*4.2.3. 2-(1-Methylethyl)-1-(phenylmethoxy)pyrrolidine (**6b**) (16 mg, 51%)*

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (5H, m), 4.74 and 4.71 (2H, AB q, J=11.0 Hz), 3.19 (1H, ddd, J=11.0, 8.0, 4.5 Hz), 2.80 (1H, m), 2.74 (1H, br q, J=7.0 Hz), 1.85 (1H, m), 1.81–1.72 (2H, m), 1.69–1.64 (1H, m), 1.44 (1H, m), 0.97 (3H, d, J=7.0 Hz), 0.90 (3H, d, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 128.3, 127.9, 127.3, 74.8, 73.4, 55.8, 29.4, 23.6, 20.7, 20.3, 17.6; HRMS (EI, *m/z*) calcd for $C_{14}H_{21}NO$ (M^+) 219.1622, found 219.1648.

*4.2.4. 2-(1-Methylpropyl)-1-(phenylmethoxy)pyrrolidine (**6d**) (27 mg, 80%)*

A colorless oil as a 1:1 mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (5H, m), 4.73 (1H, s), 4.71 (1H, s), 3.18 (1H, m), 2.86–2.72 (2H, m), 1.83–1.01 (7H, m), 0.97–0.87 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.2, 128.6, 128.2, 127.6, 75.3, 75.1, 73.0, 72.0, 56.1, 55.9, 36.6, 35.8, 29.7, 27.4, 24.9, 24.5, 23.0, 21.2, 20.7, 19.4, 16.8, 16.7, 14.1, 11.9, 11.7; HRMS (EI, *m/z*) calcd for $C_{15}H_{23}NO$ (M^+) 233.1778, found 233.1798.

*4.2.5. 2-(2-Methylpropyl)-1-(phenylmethoxy)pyrrolidine (**6e**) (4.2 mg, 13%)*

A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (5H, m), 4.75 and 4.71 (2H, AB q, J=11.0 Hz), 3.21 (1H, ddd, J=12.0, 7.0, 5.5 Hz), 2.98 (1H, m), 2.86–2.77 (1H, m), 1.99–1.26 (7H, m), 0.93 (3H, d, J=6.5 Hz), 0.89 (3H, d, J=6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 128.5, 128.3, 127.7, 75.6, 66.4, 55.6, 29.7, 27.9, 26.0, 23.5, 22.6, 20.8; HRMS (EI, *m/z*) calcd for $C_{15}H_{23}NO$ (M^+) 233.1778, found 233.1775.

*4.2.6. 2-Cyclopentyl-1-(phenylmethoxy)pyrrolidine (**6f**) (24 mg, 68%)*

A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.24 (5H, m), 4.73 (2H, s), 3.19 (1H, ddd, J=12.0, 7.0, 5.0 Hz), 2.91–2.80 (2H, m), 2.04–1.15 (13H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 128.5, 128.2, 127.6, 75.1, 72.7, 56.2, 43.2, 31.0, 29.7, 26.7, 25.6, 25.3, 21.3; HRMS(RI, *m/z*) calcd for $C_{16}H_{23}NO$ (M^+) 245.1779, found 245.1806.

*4.2.7. 2-Cyclohexyl-1-(phenylmethoxy)pyrrolidine (**6g**) (24 mg, 64%)*

A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (5H, m), 4.72 (2H, s), 3.18 (1H, m), 2.86–2.75 (2H, m), 1.89–0.86 (15H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.2, 128.6, 128.3, 127.6, 75.0, 73.2, 56.2, 40.1, 31.3, 29.0, 26.8, 26.5, 26.4, 24.9, 21.4; HRMS (EI, *m/z*) calcd for $C_{17}H_{25}NO$ (M^+) 259.1925, found 259.1935.

*4.3. (E/Z)-5-[[(4-Methylphenyl)sulfonyl]oxy]pentanal O-(phenylmethyl)oxime (**9**)*

According to the procedure given for the preparation of oxime ether **3**, the treatment of 3,4-dihydropyran **7** (4.3 mL, 48 mmol) with $BnONH_2\cdot HCl$ (4.0 g, 48 mmol) followed by tosylation of resulting alcohol **8**[5] (4.0 g, 19 mmol) with TsCl (4.5 g, 23 mmol) in the presence of Et_3N (3.5 mL, 25 mmol) gave **9** (4.7 g, 67%) as a colorless oil and a 4:3 mixture of *E*- and *Z*-isomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, br d, J=8.0 Hz), 7.39–7.26 (7H+4/7H, m), 6.61 (3/7H, br t, J=6.0 Hz), 5.08 (6/7H, s), 5.03 (8/7H, s), 4.02 (2H, t, J=6.0 Hz), 2.45 (3H, s), 2.32 (6/7H, br q, J=6.0 Hz), 2.15 (8/7H, br q, J=6.0 Hz), 1.71–1.50 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 150.2, 144.6, 137.8, 137.5, 132.9, 129.7, 128.2, 128.0, 127.8, 127.7, 127.6, 75.6, 75.4, 69.8, 69.8, 28.6, 28.2, 27.9, 25.5, 25.5, 24.8, 22.2, 21.9, 21.4; HRMS (EI, *m/z*) calcd for $C_{19}H_{23}NO_4S$ (M^+) 361.1346, found 361.1353.

*4.3.1. 2-Ethyl-1-(phenylmethoxy)piperidine (**11a**) (Table 3, entry 1)*

According to the procedure given for the preparation of pyrrolidine **6a**, the treatment of **9** (50 mg, 0.14 mmol) with Et_3B (1 mol/L in *n*-hexane) (0.42 mL, 0.42 mmol) in the presence of $BF_3\cdot OEt_2$ (0.04 mL, 0.28 mmol) followed by the purification by MCC (*n*-hexane/AcOEt=20:1) gave **11a** (16 mg, 51%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (5H, m), 4.73 and 4.69 (2H, AB q, J=10.0 Hz), 3.40 (1H, br d, J=10.5 Hz), 2.46 (1H, br t, J=10.5 Hz), 2.31 (1H, m), 2.00 (1H, m), 1.82 (1H, br d, J=10.5 Hz), 1.71 (1H, br d, J=10.5 Hz), 1.63 (1H, br d, J=10.5 Hz), 1.59–1.52 (1H, m), 1.43 (1H, m), 1.23 (2H, m), 0.91 (3H, t, J=7.5 Hz);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 128.7, 128.3, 127.8, 75.2, 68.3, 56.8, 30.2, 25.9, 25.6, 23.9, 9.8; HRMS (EI, *m/z*) calcd for $C_{14}H_{21}NO$ (M^+) 219.1622, found 219.1629.

4.3.2. General procedure for alkyl radical addition–ionic cyclization reaction of oxime ether **9**

According to the procedure given for the preparation of pyrrolidine **6b**, the treatment of **9** (50 mg, 0.14 mmol) with Et_3B (1 mol/L in *n*-hexane) (0.42 or 0.84 mL, 0.42 or 0.84 mmol) in the presence of $BF_3\cdot OEt_2$ (0.04 or 0.08 mL, 0.28 or 0.56 mmol) and alkyl iodide (2.8 mmol) gave **11** as shown in Table 3.

4.3.3. 2-(1-Methylethyl)-1-(phenylmethoxy)piperidine (**11b**) (12 mg, 38%)

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (5H, m), 4.74 and 4.69 (2H, AB q, J=10.5 Hz), 3.43 (1H, m), 2.46 (2H, m), 2.28 (1H, br d, J=11.0 Hz), 1.67–1.51 (4H, m), 1.29–1.15 (2H, m), 0.95 (3H, d, J=7.0 Hz), 0.89 (3H, d, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 128.7, 128.3, 127.8, 74.7, 71.9, 57.2, 29.7, 26.8, 25.9, 24.0, 19.6, 16.1; HRMS (EI, *m/z*) calcd for $C_{15}H_{23}NO$ (M^+) 233.1778, found 233.1798.

4.3.4. 2-(1-Methylpropyl)-1-(phenylmethoxy)piperidine (**11d**) (10 mg, 30%)

A colorless oil as a 1:1 mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.28 (5H, m), 4.73 and 4.69 (1H, AB q, J=10.5 Hz), 4.71 and 4.63 (1H, AB, J=10.5 Hz), 3.42 (1H, br d, J=10.5 Hz), 2.46 (1H, br t, J=10.5 Hz), 2.34 (1H, m), 2.14–1.22 (9H, m), 0.96–0.87 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 128.8, 128.7, 128.3, 127.8, 127.7, 74.7, 72.5, 70.8, 57.2, 34.4, 34.0, 27.0, 25.9, 24.7, 24.3, 24.1, 24.0, 23.2, 16.2, 13.7, 12.8, 12.5; HRMS (EI, *m/z*) calcd for $C_{16}H_{25}NO$ (M^+) 247.1935, found 247.1922.

4.3.5. 2-(2-Methylpropyl)-1-(phenylmethoxy)piperidine (**11e**) (5.6 mg, 16%)

A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (5H, m), 4.71 (2H, s), 3.42 (1H, m), 2.50–2.30 (2H, m), 2.01–1.19 (9H, m), 0.93 (3H, d, J=7.5 Hz), 0.91 (3H, d, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 128.8, 128.3, 127.7, 75.2, 68.2, 56.8, 38.7, 30.4, 28.9, 25.9, 23.9, 23.7, 23.0; HRMS (EI, *m/z*) calcd for $C_{16}H_{25}NO$ (M^+) 247.1935, found 247.1943.

4.3.6. 2-Cyclopentyl-1-(phenylmethoxy)piperidine (**11f**) (21 mg, 57%)

A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.26 (5H, m), 4.70 (2H, s), 3.40 (1H, m), 2.49–1.26 (17H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 128.6, 128.3, 127.7, 74.6, 69.4, 56.7, 53.7, 42.6, 40.2, 29.5, 27.3, 26.0, 25.6, 23.8; HRMS (EI, *m/z*) calcd for $C_{17}H_{25}NO$ (M^+) 259.1935, found 259.1947.

4.3.7. 2-Cyclohexyl-1-(phenylmethoxy)piperidine (**11g**) (20 mg, 54%)

A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.26 (5H, m), 4.72 and 4.66 (2H, AB q, J=10.5 Hz), 3.43 (1H, br d, J=9.5 Hz), 2.46 (1H, br t, J=10.5 Hz), 2.27 (1H, dt, J=10.5, 3.0 Hz), 2.09–1.03 (17H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 128.9, 128.3, 127.8, 74.8, 72.0, 57.2, 38.2, 30.4, 27.1, 26.8, 25.9, 25.7, 24.1; HRMS (EI, *m/z*) calcd for $C_{18}H_{27}NO$ (M^+) 273.2091, found 273.2104.

4.4. 2-[[(4-Methylphenyl)sulfonyl]oxy]ethyl (*E*)-[(phenylmethoxy)imino]acetate (**14**)

To a solution of **12**[7] (830 mg, 3.84 mmol) and **13**[6] (229 mmol, 1.28 mmol) in CH_2Cl_2 (4 mL) were added DMAP (125 mg, 1.02 mmol) and DCC (291 mg, 1.41 mmol) under a nitrogen atmosphere at 0 °C. The mixture was allowed to reach room temperature. After being stirred for 5 h, the reaction mixture was filtered and the filtrate was diluted with 0.5 M HCl and then extracted with $CHCl_3$. The organic phase was diluted with satd aq $NaHCO_3$ and then extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. The crude product was purified by FCC (hexane/AcOEt=1:1) to afford **14** (414 mg, 86%) as a colorless oil; IR ($CHCl_3$) 1742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (2H, br d, J=8.5 Hz), 7.42 (1H, s), 7.38–7.30 (7H, m), 5.30 (2H, s), 4.42–4.27 (4H, m), 2.43 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 145.1, 140.2, 135.8, 132.7, 129.9, 128.6, 128.0, 78.3, 67.1, 62.5, 21.6; HRMS (EI, *m/z*) calcd for $C_{18}H_{19}NO_6S$ (M^+) 377.0932, found 377.0943.

4.4.1. 2-[[(4-Methylphenyl)sulfonyl]oxy]ethyl 2-[(Phenylmethoxy)amino]butanoate (**15a**) (Table 4, entry 1)

To a solution of **14** (50 mg, 0.13 mmol) in CH_2Cl_2 (3.7 mL) was added Et_3B (1 mol/L in *n*-hexane) (0.40 mL, 0.40 mmol) under a nitrogen atmosphere at room temperature. After being stirred for 2 h, the reaction mixture was neutralized with K_2CO_3, diluted with H_2O, and then extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. The crude product was purified by MCC (*n*-hexane/AcOEt=20:1) to afford **15a** (41 mg, 79%) as a colorless oil; IR ($CHCl_3$) 3275, 1742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, br d, J=8.0 Hz), 7.33–7.26 (7H, m), 5.87 (1H, br s), 4.66 (2H, s), 4.39–4.18 (4H, m), 3.48 (1H, t, J=7.0 Hz), 2.43 (3H, s), 1.60–1.40 (2H, m), 0.88 (3H, t, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 145.0, 137.7, 132.7, 129.9, 128.4, 128.3, 127.9, 127.8, 76.1, 67.4, 64.9, 61.8, 22.7, 21.6, 10.4; HRMS (EI, *m/z*) calcd for $C_{20}H_{25}NO_6S$ (M^+) 407.1401, found 407.1416.

4.4.2. General procedure for primary or secondary alkyl radical addition reaction of oxime ether **14**

To a solution of **14** (50 mg, 0.13 mmol) in CH_2Cl_2 (3.7 mL) were added alkyl iodide (2.7 mmol) and Et_3B (1 mol/L in *n*-hexane) (0.40 mL, 0.40 mmol) under a nitrogen atmosphere

at room temperature. After being stirred for 2–6 h, the reaction mixture was neutralized with K_2CO_3, diluted with H_2O and then extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. The crude product was purified by MCC (*n*-hexane/AcOEt=20:1) to afford **15** as shown in Table 4.

*4.4.3. N-(Phenylmethoxy)valine 2-[[(4-methylphenyl)-sulfonyl]oxy]ethyl ester (**15b**) (43 mg, 81%)*

A colorless oil; IR (neat) 3269, 1742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, br d, J=7.0 Hz), 7.33–7.25 (7H, m), 5.90 (1H, br s), 4.64 (2H, s), 4.40–4.21 (4H, m), 3.31 (1H, d, J=7.0 Hz), 2.43 (3H, s), 1.78–1.61 (1H, m), 0.87 (3H, d, J=7.0 Hz), 0.84 (3H, d, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 145.0, 137.7, 132.7, 129.9, 128.6, 128.2, 127.9, 127.8, 75.9, 69.4, 67.4, 61.7, 29.0, 21.6, 19.2, 19.2; HRMS (EI, *m/z*) calcd for $C_{21}H_{27}NO_6S$ (M^+) 421.1558, found 421.1555.

*4.4.4. N-(Phenylmethoxy)isoleucine 2-[[(4-methylphenyl)-sulfonyl]oxy]ethyl ester (**15d**) (41 mg, 71%)*

A colorless oil as a 1:1 mixture of diastereomers; IR (neat) 3269, 1739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, br d, J=8.5 Hz), 7.36–7.25 (7H, m), 5.91 (1H, br s), 4.64 (1H, s), 4.64 (1H, s), 4.40–4.21 (4H, m), 3.44 (1H, m), 2.44 (3H, s), 1.58–1.03 (3H, m), 0.85–0.78 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 145.0, 137.8, 132.8, 129.9, 128.6, 128.6, 128.3, 127.9, 127.8, 76.0, 68.0, 67.4, 61.8, 35.7, 35.3, 26.3, 25.9, 21.6, 15.5, 15.2, 11.3, 11.0; HRMS (EI, *m/z*) calcd for $C_{22}H_{29}NO_6S$ (M^+) 435.1714, found 435.1712.

*4.4.5. N-(Phenylmethoxy)leucine 2-[[(4-methylphenyl)-sulfonyl]oxy]ethyl ester (**15e**) (13 mg, 22%)*

A colorless oil; IR ($CHCl_3$) 3269, 1742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, br d, J=8.5 Hz), 7.37–7.29 (7H, m), 5.91 (1H, br s), 4.68 (1H, s), 4.35–4.21 (4H, m), 3.61 (1H, t, J=7.0 Hz), 2.44 (3H, s), 1.62 (1H, m), 1.29 (2H, m), 0.87 (3H, d, J=7.0 Hz, Me), 0.84 (3H, d, J=7.0 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 145.1, 137.8, 132.8, 130.0, 128.5, 128.3, 128.0, 127.8, 76.1, 67.4, 62.1, 61.9, 38.3, 25.0, 22.6, 22.1, 21.6; HRMS (EI, *m/z*) calcd for $C_{22}H_{29}NO_6S$ (M^+) 435.1714, found 435.1717.

*4.4.6. 2-[[(4-Methylphenyl)sulfonyl]oxy]ethyl 2-[(Phenylmethoxy)amino]cyclopentaneacetate (**15f**) (44 mg, 75%)*

A colorless oil; IR ($CHCl_3$) 3275, 1737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, br d, J=8.5 Hz), 7.33–7.25 (7H, m), 5.86 (1H, br s), 4.64 (2H, s), 4.39–4.21 (4H, m), 3.34 (1H, m), 2.43 (3H, s), 1.83–1.21 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 145.0, 137.7, 132.7, 129.9, 128.6, 128.2, 127.9, 127.8, 76.0, 68.2, 67.4, 61.7, 39.7, 30.0, 29.0, 24.9, 24.9, 21.6; HRMS (EI, *m/z*) calcd for $C_{23}H_{29}NO_6S$ (M^+) 447.1714, found 447.1715.

*4.4.7. 2-[[(4-Methylphenyl)sulfonyl]oxy]ethyl 2-[(Phenylmethoxy)amino]cyclohexaneacetate (**15g**) (43 mg, 70%)*

A colorless oil; IR ($CHCl_3$) 3269, 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (2H, br d, J=8.0 Hz), 7.36–7.25 (7H, m), 5.89 (1H, br s), 4.63 (2H, s), 4.43–4.23 (4H, m), 3.36 (1H, d, J=7.0 Hz), 2.44 (3H, s), 1.76–0.90 (11H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 145.0, 137.8, 132.8, 129.9, 128.6, 128.2, 127.9, 127.8, 75.9, 68.9, 67.4, 61.7, 38.4, 29.7, 29.5, 26.0, 25.9, 21.6; HRMS (EI, *m/z*) calcd for $C_{24}H_{31}NO_6S$ (M^+) 461.1870, found 461.1891.

*4.4.8. General procedure for tertiary alkyl radical addition reaction of oxime ether **14** (Table 4, entries 3 and 8)*

To a solution of **14** (50 mg, 0.13 mmol) in CH_2Cl_2 (3.7 mL) were added alkyl iodide (2.65 mmol) and Et_3B (1 mol/L in *n*-hexane) (0.40 mL, 0.40 mmol) under a nitrogen atmosphere at room temperature. After being stirred for 1.5 h, an additional Et_3B (1 mol/L in *n*-hexane) (0.40 mL, 0.40 mmol) was added to the solution. After being stirred for 1–4.5 h, the reaction mixture was neutralized with K_2CO_3, diluted with H_2O, and then extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. The crude product was purified by MCC to afford **15c**,**h** as shown in Table 4.

*4.4.9. 3-Methyl-N-(phenylmethoxy)valine 2-[[(4-methylphenyl)sulfonyl]oxy]ethyl ester (**15c**) (50 mg, 86%)*

A colorless oil; IR ($CHCl_3$) 3285, 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (2H, br d, J=8.0 Hz), 7.33–7.25 (7H, m), 5.99 (1H, br s), 4.62 (2H, s), 4.32–4.20 (4H, m), 3.26 (1H, s), 2.43 (3H, s), 0.86 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.5, 145.0, 137.8, 132.7, 129.9, 128.7, 128.2, 127.9, 127.7, 75.7, 71.9, 67.4, 61.6, 33.0, 26.9, 21.6; HRMS (EI, *m/z*) calcd for $C_{22}H_{29}NO_6S$ (M^+) 435.1713, found 435.1727.

*4.4.10. 2-[[(4-Methylphenyl)sulfonyl]oxy]ethyl 2-[(phenylmethoxy)amino]tricycle[3.3.1.$1^{3,7}$]-decane-1-acetate (**15h**) (63 mg, 94%)*

Colorless crystals; mp 123–125 °C (hexane/AcOEt); IR ($CHCl_3$) 3280, 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, br d, J=8.5 Hz), 7.36–7.29 (7H, m), 6.04 (1H, br s), 4.61 (2H, s), 4.39–4.23 (4H, m), 3.20 (1H, s), 2.44 (3H, s), 1.91–1.26 (15H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 145.0, 137.8, 132.8, 129.9, 128.6, 128.2, 127.9, 127.7, 75.7, 72.9, 67.4, 61.6, 40.4, 39.1, 36.7, 35.1, 28.2, 21.6; HRMS (EI, *m/z*) calcd for $C_{28}H_{35}NO_6S$ (M^+) 513.2183, found 513.2174.

*4.5. Methyl 4-oxobutanoate (**21**)*

To a solution of **19**[9] (2.7 g, 23 mmol) in CH_2Cl_2 (116 mL) were added DMSO (3.3 mL, 46 mmol) and P_2O_5 (6.6 g, 46 mmol) under a nitrogen atmosphere at room temperature. After being stirred for 2 h, the mixture was cooled to 0 °C and then Et_3N (11 mL, 81 mmol) was added. After being stirred for 1.5 h, the reaction mixture was diluted with 10% HCl and

then extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. The crude product was purified by FCC (hexane/AcOEt=1:1) to afford **21** (2.0 g, 73%) as a colorless oil.

The spectral data were identical with those reported in literature.[9]

4.5.1. Methyl 5-oxopentanoate (22)

According to the procedure given for the preparation of **21**, the treatment of hydroxyl ester **20**[9] (2.6 g, 20 mmol) with DMSO (2.8 mL, 40 mmol) in the presence of P_2O_5 (5.7 g, 40 mmol) gave **22** (1.7 g, 65%) as a colorless oil.

The spectral data were identical with those reported in literature.[9]

4.5.2. Methyl (E/Z)-4-[(phenylmethoxy)imino]butanoate (23)

To a solution of **21** (0.75 g, 6.5 mmol) in MeOH (30 mL) were added $BnONH_2 \cdot HCl$ (1.6 g, 9.7 mmol) and AcONa (1.1 g, 13 mmol) under a nitrogen atmosphere at room temperature. After the reaction mixture was stirred overnight, the reaction mixture was concentrated at reduced pressure and neutralized with $NaHCO_3$. Then the reaction mixture was diluted with H_2O and then extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. The crude product was purified by FCC (hexane/AcOEt=5:1) to afford **23**[10] (0.66 g, 46%) as a colorless oil and a 2:1 mixture of *E*- and *Z*-isomers; IR (neat) 1737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (2/3H, br t, J=5.0 Hz), 7.37–7.28 (5H, m), 6.74 (1/3H, br t, J=5.0 Hz), 5.11 (2/3H, s), 5.04 (4/3H, s), 3.68 (3/3H, s), 3.66 (6/3H, s), 2.67–2.47 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 149.8, 148.9, 137.7, 137.5, 128.2, 128.1, 127.8, 127.7, 75.7, 75.5, 51.5, 30.4, 30.3, 24.8, 21.2; HRMS (EI, *m/z*) calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1051, found 221.1066.

4.5.3. Methyl (E/Z)-5-[(phenylmethoxy)imino]pentanoate (24)

According to the procedure given for the preparation of oxime ether **23**, the treatment of aldehyde **22** (1.7 g, 13 mmol) with $BnONH_2 \cdot HCl$ (3.1 g, 19 mmol) in the presence of AcONa (2.1 g, 26 mmol) gave **24** (2.7 g, 88%) as a colorless oil and a 3:2 mixture of *E*- and *Z*-isomers; IR ($CHCl_3$) 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (3/5H, br t, J=6.0 Hz), 7.37–7.26 (5H, m), 6.68 (2/5H, br t, J=6.0 Hz), 5.09 (4/5H, s), 5.05 (6/5H, s), 3.67 (3H, s), 2.47–2.19 (4H, m), 1.90–1.76 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 173.2, 150.9, 150.0, 137.8, 137.5, 128.2, 128.1, 127.8, 127.7, 127.6, 77.2, 76.6, 75.6, 75.5, 51.4, 33.3, 32.9, 28.7, 25.1, 21.6, 21.4; HRMS (EI, *m/z*) calcd for $C_{13}H_{17}NO_3$ (M^+) 235.1207, found 235.1202.

4.5.4. Methyl 4-[(phenylmethoxy)amino]hexanoate (25a) (Table 5, entry 1)

According to the procedure given for the preparation of pyrrolidine **6a**, the treatment of **23** (50 mg, 0.23 mmol) with Et_3B (1 mol/L in *n*-hexane) (0.68 mL, 0.68 mmol) in the presence of $BF_3 \cdot OEt_2$ (0.06 mL, 0.45 mmol) gave **25a** (45 mg, 79%) as a colorless oil; IR ($CHCl_3$) 3264, 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (5H, m), 4.67 (2H, s), 3.65 (3H, s), 2.77 (1H, br quint, J=6.0 Hz), 2.39 (2H, t, J=7.5 Hz), 1.86–1.68 (4H, m, 0.91 (3H, t, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 138.0, 128.4, 128.3, 127.7, 76.4, 61.2, 51.5, 30.6, 26.7, 24.5, 10.1; HRMS (EI, *m/z*) calcd for $C_{14}H_{21}NO_3$ (M^+) 251.1520, found 251.1546.

4.5.5. General procedure for alkyl radical addition reaction of oxime ether 23

According to the procedure given for the preparation of pyrrolidine **6b**, the treatment of **23** (50 mg, 0.23 mmol) with Et_3B (1 mol/L in *n*-hexane) (0.68 or 2.04 mL, 0.68 or 2.04 mmol) in the presence of $BF_3 \cdot OEt_2$ (0.06 or 0.18 mL, 0.45 or 1.35 mmol) and alkyl iodide (4.5 mmol) gave **25** as shown in Table 5.

4.5.6. Methyl 5-methyl-4-[(phenylmethoxy)amino]-hexanoate (25b) (47 mg, 78%)

A colorless oil; IR (neat) 3280, 1739 cm^{-1}; ^1H NMR (200 Hz, $CDCl_3$) δ 7.36–7.26 (5H, m), 5.54 (1H, br s), 4.66 (2H, s), 3.65 (3H, s), 2.60 (1H, ddd, J=9.0, 5.5, 4.0 Hz), 2.51–2.28 (2H, m), 2.01–1.73 (2H, m), 1.67–1.48 (1H, m), 0.92 (3H, d, J=7.0 Hz), 0.89 (3H, d, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 138.0, 128.4, 128.3, 127.7, 76.2, 65.3, 51.5, 31.5, 28.9, 23.7, 19.1, 18.0; HRMS (EI, *m/z*) calcd for $C_{15}H_{23}NO_3$ (M^+) 265.1677, found 251.1687.

4.5.7. Methyl 5,5-dimethyl-4-[(phenylmethoxy)amino]-hexanoate (25c) (25 mg, 39%)

A colorless oil; IR (neat) 3286, 1739 cm^{-1}; ^1H NMR (200 Hz, $CDCl_3$) δ 7.34–7.26 (5H, m), 5.58 (1H, br s), 4.64 (2H, s), 3.65 (3H, s), 2.67–2.35 (3H, m), 1.98–1.54 (2H, m), 0.95 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.6, 138.1, 128.3, 128.3, 127.6, 77.2, 75.9, 68.7, 51.4, 34.4, 32.6, 27.3, 24.2; HRMS (CI, *m/z*) calcd for $C_{16}H_{26}NO_3$ ($M+H^+$) 280.1911, found 280.1927.

4.5.8. Methyl 5-methyl-4-[(phenylmethoxy)amino]-heptanoate (25d) (52 mg, 83%)

A colorless oil as a 1:1 mixture of diastereomers; IR (neat) 3264, 1739 cm^{-1}; ^1H NMR (300 Hz) δ 7.34–7.26 (5H, m), 5.51 (1H, br s), 4.65 (2H, s), 3.65 (3H, s), 2.78–2.69 (1H, m), 2.51–2.30 (2H, m), 1.84–1.03 (5H, m), 0.92–0.82 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 138.1, 138.1, 128.4, 128.4, 128.3, 127.7, 76.2, 76.2, 64.0, 63.7, 51.4, 36.0, 35.4, 31.7, 31.6, 26.1, 25.1, 24.5, 23.0, 15.1, 13.9, 11.9, 11.9; HRMS (EI, *m/z*) calcd for $C_{16}H_{25}NO_3$ (M^+) 279.1833, found 279.1845.

4.5.9. Methyl 6-methyl-4-(phenylmethoxy)amino]-heptanoate (25e) (16 mg, 26%)

A colorless oil; IR (neat) 3264, 1737 cm^{-1}; ^1H NMR (300 Hz, $CDCl_3$) δ 7.35–7.26 (5H, m), 5.40 (1H, br s), 4.67 (2H, s), 3.66 (3H, s), 2.92 (1H, m), 2.39 (2H, t, J=7.5 Hz),

1.83–1.09 (5H, m), 0.88 (6H, d, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 138.0, 128.4, 128.3, 127.7, 76.5, 57.7, 51.5, 41.2, 30.4, 27.6, 24.9, 22.9, 22.7; HRMS (EI, *m/z*) calcd for $C_{16}H_{25}NO_3$ (M^+) 279.1833, found 279.1819.

*4.5.10. Methyl 4-[(phenylmethoxy)amino]cyclopentane-butanoate (**25f**) (41 mg, 63%)*

A colorless oil; IR (neat) 3280, 1731 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.35–7.26 (5H, m), 5.57 (1H, br s), 4.68 (2H, s), 3.66 (3H, s), 2.62 (1H, td, J=8.5, 3.5 Hz), 2.45 (2H, t, J=7.5 Hz), 2.01–1.87 (2H, m), 1.83–1.14 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 138.0, 128.4, 128.3, 127.7, 76.4, 64.8, 51.5, 41.6, 30.6, 30.0, 29.7, 26.0, 25.3, 25.3; HRMS (EI, *m/z*) calcd for $C_{17}H_{25}NO_3$ (M^+) 291.1833, found 291.1854.

*4.5.11. Methyl 4-[(phenylmethoxy)amino]cyclohexane-butanoate (**25g**) (37 mg, 53%)*

A colorless oil; IR (neat) 3274, 1734 cm^{-1}; ^{1}H NMR (200 Hz, $CDCl_3$) δ 7.40–7.26 (5H, m), 5.57 (1H, br s), 4.65 (2H, s), 3.65 (3H, s), 2.59 (1H, ddd, J=9.0, 5.5, 3.5 Hz), 2.46–2.36 (2H, m), 1.92–0.91 (13H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 138.1, 128.4, 128.3, 127.7, 76.2, 64.8, 51.5, 39.0, 31.5, 29.5, 28.7, 26.6, 26.4, 24.2; HRMS (EI, *m/z*) calcd for $C_{18}H_{27}NO_3$ (M^+) 305.1990, found 305.2013.

*4.5.12. Methyl 4-[(phenylmethoxy)amino]tricyclo-[3.3.1.1^{3,7}]decane-1-butanoate (**25h**) (39 mg, 48%)*

A colorless oil; IR (neat) 3264, 1734 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.36–7.27 (5H, m), 5.70 (1H, br s), 4.64 (2H, s), 3.65 (3H, s), 2.58 (1H, ddd, J=16.0, 9.0, 6.5 Hz), 2.41 (1H, ddd, J=16.0, 9.0, 6.5 Hz), 2.26 (1H, dd, J=10.5, 3.0 Hz), 1.97–1.55 (17H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 138.2, 128.3, 128.2, 127.6, 77.2, 75.9, 69.4, 51.4, 39.3, 37.1, 36.4, 32.6, 29.2, 28.5, 22.7; HRMS (EI, *m/z*) calcd for $C_{22}H_{31}NO_3$ (M^+) 357.2302, found 357.2309.

*4.5.13. General procedure for cyclization reaction of amino ester **25***

To a solution of **25** (8.2–53 mg, 0.03–0.20 mmol) in THF (1.4–11 mL) was added concd HCl (2 drops by a syringe) under a nitrogen atmosphere at reflux. After being stirred for 1.5–5 h, the mixture was concentrated at reduced pressure. The resulting residue was purified by PTLC (*n*-hexane/AcOEt=1:1) to afford **27a–h** as shown in Table 5.

*4.5.14. 5-Ethyl-1-(phenylmethoxy)-2-pyrrolidinone (**27a**)*

A colorless oil; IR ($CHCl_3$) 1698 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.47–7.34 (5H, m), 5.06 and 4.94 (2H, AB q, J=10.0 Hz), 3.38 (1H, m), 2.35 (1H, ddd, J=17.0, 9.5, 6.0 Hz), 2.27 (1H, ddd, J=17.0, 9.5, 7.0 Hz), 2.05 (1H, dddd, J=13.0, 9.5, 7.0, 5.5 Hz), 1.82 (1H, br dqd, J=14.0, 7.0, 4.0 Hz), 1.61 (1H, m), 1.39 (1H, br dquint, J=14.0, 7.0, Hz), 0.87 (3H, t, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 135.2, 129.3, 128.6, 128.4, 76.9, 59.1, 27.0, 25.5, 21.1, 8.7; HRMS (EI, *m/z*) calcd for $C_{13}H_{17}NO_2$ (M^+) 219.1258, found 219.1265.

*4.5.15. 5-(1-Methylethyl)-1-(phenylmethoxy)-2-pyrrolidinone (**27b**)*

A colorless oil; IR (neat) 1698 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.46–7.34 (5H, m), 5.04 and 4.96 (2H, AB q, J=10.5 Hz), 3.37 (1H, ddd, J=8.5, 5.5, 3.5 Hz), 2.31 (1H, ddd, J=17.0, 9.5, 6.5 Hz), 2.25 (1H, m), 2.15 (1H, m), 1.92–1.64 (2H, m), 0.87 (3H, d, J=7.0 Hz), 0.84 (3H, d, J=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.0, 135.3, 129.4, 128.7, 128.5, 77.2, 62.3, 28.6, 27.2, 18.1, 16.4, 15.5; HRMS (EI, *m/z*) calcd for $C_{14}H_{20}NO_2$ (M^+) 234.1493, found 234.1500.

*4.5.16. 5-(1,1-Dimethylethyl)-1-(phenylmethoxy)-2-pyrrolidinone (**27c**)*

A colorless oil; IR (neat) 1706 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.46–7.33 (5H, m), 5.04 and 4.95 (2H, AB q, J=10.5 Hz), 3.25 (1H, dd, J=8.0, 5.0 Hz), 2.33 (1H, ddd, J=17.0, 9.5, 6.0 Hz), 2.22 (1H, ddd, J=17.0, 9.5, 6.0 Hz), 1.97–1.72 (2H, m), 0.96 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 134.9, 129.7, 128.8, 128.5, 77.2, 75.1, 65.8, 34.8, 27.1, 26.3, 18.7; HRMS (EI, *m/z*) calcd for $C_{15}H_{22}NO_2$ ($M+H^+$) 248.1649, found 248.1657.

*4.5.17. 5-(1-Methylpropyl)-1-(phenylmethoxy)-2-pyrrolidinone (**27d**)*

A colorless oil as a 1:1 mixture of diastereomers; IR (neat) 1709 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.45–7.33 (5H, m), 5.05 and 4.97 (1H, AB q, J=10.5 Hz), 5.05 and 4.93 (1H, AB q, J=10.5 Hz), 3.43 (1H, m), 2.31–2.25 (2H, m), 1.96–0.96 (5H, m), 0.93–0.79 (6H, m), ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 171.0, 135.4, 135.3, 129.4, 128.8, 128.5, 76.5, 76.4, 62.2, 61.1, 36.1, 34.8, 27.2, 25.5, 22.8, 17.3, 16.0, 14.6, 12.5, 12.0, 11.9; HRMS (EI, *m/z*) calcd for $C_{15}H_{21}NO_2$ (M^+) 247.1571, found 247.1566.

*4.5.18. 5-(2-Methylpropyl)-1-(phenylmethoxy)-2-pyrrolidinone (**27e**)*

A colorless oil; IR ($CHCl_3$) 1698 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.46–7.36 (5H, m), 5.06 and 4.94 (2H, AB q, J=10.5 Hz), 3.49–3.38 (1H, m), 2.41–2.20 (2H, m), 2.11–1.12 (5H, m), 0.90 (3H, d, J=6.5 Hz), 0.81 (3H, d, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 135.4, 129.5, 128.8, 128.5, 77.2, 56.8, 41.9, 27.1, 24.6, 23.6, 22.5, 21.8; HRMS (EI, *m/z*) calcd for $C_{15}H_{21}NO_2$ (M^+) 247.1571, found 247.1556.

*4.5.19. 5-Cyclopentyl-1-(phenylmethoxy)-2-pyrrolidinone (**27f**)*

A colorless oil; IR ($CHCl_3$) 1691 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.50–7.29 (5H, m), 5.06 and 4.93 (2H, AB q, J=10.5 Hz), 3.44 (1H, br q, J=6.5 Hz), 2.40–2.25 (2H, m), 2.23–1.15 (11H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 135.1, 129.4, 128.7, 128.4, 76.5, 61.2, 42.8, 29.5, 27.8, 27.2, 25.7, 25.0, 19.9; HRMS (CI, *m/z*) calcd for $C_{16}H_{22}NO_2$ ($M+H^+$) 260.1649, found 260.1641.

*4.5.20. 5-Cyclohexyl-1-(phenylmethoxy)-2-pyrrolidinone (**27g**)*

A colorless oil; IR (neat) 1703 cm^{-1}; ^1H NMR (300 Hz, $CDCl_3$) δ 7.46–7.33 (5H, m), 5.05 and 4.96 (2H, AB q, J=10.5 Hz), 3.32 (1H, m), 2.36–2.18 (2H, m), 1.93–0.92 (13H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 135.4, 129.4, 128.7, 128.5, 76.4, 62.2, 39.1, 28.8, 27.3, 26.4, 26.3, 26.3, 25.9, 17.6; HRMS (EI, *m/z*) calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1727, found 273.1711.

*4.5.21. 5-Tricyclo[3.3.1.1^{3,7}]dec-1-yl-1-(phenylmethoxy)-2-pyrrolidinone (**27h**)*

Colorless crystals; mp 81–83 °C (hexane/AcOEt); IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR (300 Hz, $CDCl_3$) δ 7.46–7.36 (5H, m), 5.03 and 4.94 (2H, AB q, J=10.5 Hz), 3.05 (1H, dd, J=8.5, 4.0 Hz), 2.37–2.13 (2H, m), 1.98–1.50 (17H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 135.0, 129.7, 128.8, 128.5, 75.2, 66.3, 38.4, 36.9, 36.9, 28.1, 27.4, 17.4; HRMS (CI, *m/z*) calcd for $C_{21}H_{28}NO_2$ ($M+H^+$) 326.2095, found 326.2107.

*4.5.22. Methyl 5-[(phenylmethoxy)amino]heptanoate (**26a**)*

According to the procedure given for the preparation of pyrrolidine **6a**, the treatment of **24** (50 mg, 0.21 mmol) with Et_3B (l mol/L in *n*-hexane) (0.64 mL, 0.64 mmol) in the presence of $BF_3{\cdot}OEt_2$ (0.05 mL, 0.43 mmol) gave **26a** (39 mg, 70%) as a colorless oil; IR ($CHCl_3$) 3258, 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (5H, m), 5.49 (1H, br s), 4.69 (2H, s), 3.66 (3H, s), 2.78 (1H, br quint, J=6.0 Hz), 2.30 (2H, t, J=7.5 Hz), 1.75–1.35 (6H, m), 0.90 (3H, t, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 138.1, 128.4, 128.3, 127.7, 76.5, 61.5, 51.5, 34.2, 30.9, 24.4, 21.3, 10.0; HRMS (EI, *m/z*) calcd for $C_{15}H_{23}NO_3$ (M^+) 265.1677, found 265.1685.

*4.5.23. General procedure for alkyl radical addition reaction of oxime ether **24***

According to the procedure given for the preparation of pyrrolidine **6b**, the treatment of **24** (50 mg, 0.21 mmol) with Et_3B (l mol/L in *n*-hexane) (0.64 or 1.9 mL, 0.64 or 1.9 mmol) in the presence of $BF_3{\cdot}OEt_2$ (0.05 or 0.15 mL, 0.43 or 1.3 mmol) and alkyl iodide (2.8 mmol) gave **26** as shown in Table 5.

*4.5.24. Methyl 6-methyl-5-[(phenylmethoxy)amino]-heptanoate (**26b**) (40 mg, 67%)*

A colorless oil; IR ($CHCl_3$) 3269, 1734 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.37–7.26 (5H, m), 5.59 (1H, br s), 4.69 (2H, s), 3.66 (3H, s), 2.64 (1H, dt, J=6.0, 4.5 Hz), 2.30 (2H, t, J=7.5 Hz), 2.02–1.26 (5H, m), 0.90 (3H, d, J=7.0 Hz), 0.89 (3H, d, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 138.1, 128.4, 128.3, 127.7, 76.3, 65.5, 51.5, 34.2, 28.7, 27.7, 22.2, 18.9, 18.0; HRMS (EI, *m/z*) calcd for $C_{16}H_{25}NO_3$ (M^+) 279.1833, found 279.1833.

*4.5.25. Methyl 6,6-dimethyl-5-[(phenylmethoxy)amino]-heptanoate (**26c**) (15 mg, 24%)*

A colorless oil; IR (neat) 3274, 1737 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.41–7.25 (5H, m), 5.57 (1H, br s), 4.66 (2H, s), 3.66 (3H, s), 2.44 (1H, dd, J=9.0, 3.0 Hz), 2.32 (2H, m), 1.97–1.30 (4H, m), 0.92 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 138.2, 128.3, 128.3, 127.6, 75.8, 69.2, 51.4, 34.3, 34.2, 28.3, 27.3, 26.8, 23.6; HRMS (CI, *m/z*) calcd for $C_{17}H_{28}NO_3$ ($M+H^+$) 294.2067, found 294.2043.

*4.5.26. Methyl 6-methyl-5-[(phenylmethoxy)amino]-octanoate (**26d**) (34 mg, 55%)*

A colorless oil as a 1:1 mixture of diastereomers; IR ($CHCl_3$) 3264, 1734 cm^{-1}; ^1H NMR (300 Hz, $CDCl_3$) δ 7.35–7.26 (5H, m), 5.51 (1H, br s), 4.68 (1H, s), 4.66 (1H, s), 3.66 (3H, s), 2.76 (1H, m), 2.30 (2H, m), 1.78–1.02 (7H, m), 0.92–0.82 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 138.1, 138.1, 128.4, 128.4, 128.3, 127.7, 76.3, 64.2, 64.1, 51.4, 35.8, 35.4, 34.2, 28.4, 27.0, 26.0, 25.2, 22.4, 22.3, 14.9, 14.1, 12.0, 12.0; HRMS (EI, *m/z*) calcd for $C_{17}H_{27}NO_3$ (M^+) 293.1989, found 293.2003.

*4.5.27. Methyl 7-methyl-5-[(phenylmethoxy)amino]-octanoate (**26e**) (7 mg, 11%)*

A colorless oil; IR (neat) 3285, 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (5H, m), 5.44 (1H, br s), 4.68 (2H, s), 3.67 (3H, s), 2.90 (1H, br quint, J=6.0 Hz), 2.31 (2H, t, J=7.5 Hz), 1.72–1.11 (7H, m), 0.88 (3H, d, J=6.5 Hz), 0.87 (3H, t, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 137.6, 128.4, 128.2, 127.8, 75.6, 58.2, 41.2, 34.2, 32.1, 24.9, 23.1, 22.6, 21.8, 21.1; HRMS (EI, *m/z*) calcd for $C_{17}H_{27}NO_3$ (M^+) 293.1991, found 293.1993.

*4.5.28. Methyl 5-[(phenylmethoxy)amino]-cyclopentanepentanoate (**26f**) (40 mg, 62%)*

A colorless oil; IR ($CHCl_3$) 3280, 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (5H, m), 4.69 (2H, s), 3.66 (3H, s), 2.67–2.58 (1H, m), 2.30 (2H, t, J=7.5 Hz), 2.01–1.10 (14H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 138.1, 128.3, 128.3, 127.7, 76.3, 65.1, 51.4, 41.6, 34.3, 30.1, 30.0, 29.7, 25.3, 25.3, 21.2; HRMS (EI, *m/z*) calcd for $C_{18}H_{27}NO_3$ (M^+) 305.1990, found 305.1993.

*4.5.29. Methyl 5-[(phenylmethoxy)amino]-cyclohexanepentanoate (**26g**) (41 mg, 61%)*

A colorless oil; IR ($CHCl_3$) 3280, 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (5H, m), 4.69 (2H, s), 3.66 (3H, s), 2.67–2.58 (1H, m), 2.30 (2H, t, J=7.5 Hz, 2-H_2), 2.01–1.10 (14H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 138.1, 128.4, 128.3, 127.7, 76.2, 65.0, 51.4, 39.0, 34.2, 29.4, 28.8, 28.2, 26.7, 26.5, 26.5, 22.1; HRMS (EI, *m/z*) calcd for $C_{19}H_{29}NO_3$ (M^+) 319.2145, found 319.2145.

*4.5.30. Methyl 5-[(phenylmethoxy)amino]tricyclo-[3.3.1.1^{3,7}]decane-1-pentanoate (**26h**) (40 mg, 50%)*

A colorless oil; IR (neat) 3275, 1737 cm^{-1}; ^1H NMR (300 Hz) δ 7.41–7.25 (5H, m), 5.66 (1H, br s), 4.66 (2H, s),

3.66 (3H, s), 2.32 (1H, m), 2.25 (2H, dd, J=9.5, 3.0 Hz), 2.09–1.23 (19H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 138.2, 128.3, 128.2, 127.6, 75.8, 51.4, 39.3, 37.2, 36.2, 34.2, 28.5, 26.7, 23.6; HRMS (EI, *m/z*) calcd for $C_{23}H_{33}NO_3$ (M^+) 371.2458, found 371.2460.

4.5.31. General procedure for cyclization reaction of amino ester **26**

To a solution of **26** (8.2–53 mg, 0.03–0.20 mmol) in THF (1.4–11 mL) were added concd HCl (2 drops by a syringe) under a nitrogen atmosphere at reflux. After being stirred for 1.5–5 h, the mixture was concentrated at reduced pressure. The resulting residue was purified by PTLC (*n*-hexane/AcOEt=1:1) to afford **28** as shown in Table 5.

4.5.32. 6-Ethyl-1-(phenylmethoxy)-2-piperidinone (**28a**)

A colorless oil; IR (neat) 1663 cm^{-1}; ^{1}H NMR (200 Hz, $CDCl_3$) δ 7.46–7.26 (5H, m), 5.02 and 4.91 (2H, AB q, J=10.0 Hz), 3.37 (1H, m), 2.44 (2H, m), 2.03–1.41 (6H, m), 0.88 (3H, t, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 135.5, 129.4, 128.5, 128.4, 75.9, 61.9, 33.4, 27.5, 25.0, 18.3, 9.7; HRMS (EI, *m/z*) calcd for $C_{14}H_{19}NO_2$ (M^+) 233.1415, found 233.1416.

4.5.33. 6-(1-Methylethyl)-1-(phenylmethoxy)-2-piperidinone (**28b**)

A colorless oil; IR (neat) 1663 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.47–7.33 (5H, m), 5.01 and 4.91 (2H, AB q, J=10.0 Hz), 3.37 (1H, m), 2.54–2.31 (3H, m), 1.89–1.46 (4H, m), 0.88 (3H, d, J=7.0 Hz), 0.87 (3H, d, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 135.4, 129.5, 128.6, 128.4, 75.3, 65.1, 33.6, 28.3, 23.4, 19.2, 18.6, 15.8; HRMS (EI, *m/z*) calcd for $C_{15}H_{22}NO_2$ ($M+H^+$) 248.1649, found 248.1635.

4.5.34. 6-(1,1-Dimethylethyl)-1-(phenylmethoxy)-2-piperidinone (**28c**)

A colorless oil; IR ($CHCl_3$) 1646 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.44–7.31 (5H, m), 4.92 and 4.88 (2H, AB q, J=10.5 Hz), 3.30 (1H, m), 2.53–2.27 (3H, m), 1.85–1.19 (4H, m), 0.99 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 135.2, 130.0, 128.6, 128.4, 74.2, 67.3, 36.3, 33.5, 28.4, 26.7, 19.2; HRMS (EI, *m/z*) calcd for $C_{16}H_{23}NO_2$ (M^+) 261.1728, found 261.1713.

4.5.35. 6-(1-Methylpropyl)-1-(phenylmethoxy)-2-piperidinone (**28d**)

A colorless oil as a 1:1 mixture of diastereomers; IR (neat) 1664 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.47–7.31 (5H, m), 5.03 and 4.91 (1H, AB q, J=10.0 Hz), 5.01 and 4.86 (1H, AB q, J=10.0 Hz), 3.47 (1H, m), 2.52–2.30 (2H, m), 2.23–0.99 (7H, m), 0.93 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 168.3, 135.5, 135.4, 129.6, 129.5, 128.6, 128.4, 75.4, 75.3, 65.4, 63.8, 35.7, 34.9, 33.6, 33.6, 25.9, 24.4, 23.3, 19.4, 19.3, 15.3, 13.1, 12.2, 12.2; HRMS (EI, *m/z*) calcd for $C_{16}H_{23}NO_2$ (M^+) 261.1728, found 261.1720.

4.5.36. 6-(2-Methylpropyl)-1-(phenylmethoxy)-2-piperidinone (**28e**)

A colorless oil; IR (neat) 1663 cm^{-1}; ^{1}H NMR (300 H, $CDCl_3$) δ 7.43–7.29 (5H, m), 4.99 and 4.92 (2H, AB q, J=10.5 Hz), 3.42 (1H, br quint, J=5.0 Hz), 2.46–2.32 (2H, m), 1.84–1.33 (7H, m), 0.90 (3H, d, J=6.5 Hz), 0.82 (3H, d, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 135.6, 129.5, 128.6, 128.4, 75.9, 58.9, 41.3, 33.2, 28.1, 24.9, 23.7, 21.4, 17.8; HRMS (EI, *m/z*) calcd for $C_{16}H_{23}NO_2$ (M^+) 261.1728, found 261.1721.

4.5.37. 6-Cyclopentyl-1-(phenylmethoxy)-2-piperidinone (**28f**)

A colorless oil; IR (neat) 1662 cm^{-1}; ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.46–7.34 (5H, m), 5.00 and 4.92 (2H, AB q, J=10.0 Hz), 3.36 (1H, br q, J=6.0 Hz), 2.45 (2H, m), 2.27–1.13 (13H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 135.5, 129.5, 128.5, 128.4, 75.3, 63.8, 43.1, 33.2, 30.5, 28.5, 26.8, 25.6, 24.7, 18.2; HRMS (EI, *m/z*) calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1727, found 273.1726.

4.5.38. 6-Cyclohexyl-1-(phenylmethoxy)-2-piperidinone (**28g**)

A colorless oil; IR (neat) 1667 cm^{-1}; ^{1}H NMR (200 Hz, $CDCl_3$) δ 7.48–7.34 (5H, m), 5.03 and 4.88 (2H, AB q, J=10.5 Hz), 3.32 (1H, m), 2.60–2.30 (2H, m), 2.10–0.94 (15H, m); ^{13}C NMR (75 MHz) δ 168.2, 135.5, 129.5, 128.6, 128.4, 75.4, 64.9, 39.3, 33.5, 29.5, 26.9, 26.7, 26.6, 26.2, 24.9, 19.3; HRMS (CI, *m/z*) calcd for $C_{18}H_{26}NO_2$ ($M+H^+$) 288.1962, found 288.1968.

4.6. Phenyl (*E*/*Z*)-4-[(phenylmethoxy)imino]butanoate (**31**)

To a solution of NaOH (99 mg, 2.5 mmol) in THF–H_2O (12–6 mL) was added **23** (500 mg, 2.3 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 3.5 h, the reaction mixture was acidified with 10% HCl and then extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. ^{1}H NMR spectrum of the residue proved the formation of desired carboxylic acid **29**, which without further purification was subjected to the following reaction. To a solution of crude carboxylic acid **29** and phenol (101 mg, 1.1 mmol) in CH_2Cl_2 (1.1 mL) were added DMAP (105 mg, 0.9 mmol) and DCC (243 mg, 1.2 mmol) under a nitrogen atmosphere at 0 °C. After being stirred for 7 h at the same temperature, the reaction mixture was filtered and the filtrate was acidified with 0.5 M HCl and then extracted with $CHCl_3$. The organic phase was washed with satd aq $NaHCO_3$ and then extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. The crude product was purified by MCC (hexane/AcOEt=3:1) to afford **31** (254 mg, 39%) as a colorless oil and a 2:1 mixture of *E*- and *Z*-isomers; IR (neat) 1761 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (2/3H, br t, J=5.0 Hz), 7.35–6.81 (10H+1/3H, m), 5.14 (2/3H, s), 5.07

(4/3H, s), 2.82–2.77 (2H, m), 2.63 (2H, br q, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 150.6, 149.6, 148.7, 137.6, 129.4, 129.4, 128.4, 128.3, 128.0, 127.9, 125.8, 121.5, 76.0, 75.8, 30.8, 25.0, 21.4; HRMS (CI, *m/z*) calcd for $C_{17}H_{18}NO_3$ ($M+H^+$) 284.1286, found 284.1281.

4.6.1. Phenyl (E/Z)-5-[(phenylmethoxy)imino]pentanoate (**32**)

According to the procedure given for the preparation of oxime ether **31**, the treatment of **24** (500 mg, 2.1 mmol) with NaOH (94 mg, 2.3 mmol) followed by esterification of resulting carboxylic acid **30** with phenol (200 mg, 2.1 mmol) in the presence of DCC (482 mg, 2.3 mmol) and DMAP (207 mg, 1.7 mmol) gave **32** (418 mg, 66%) as a colorless oil and a 3:2 mixture of *E*- and *Z*-isomers; IR (neat) 1758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (3/5H, t, J=6.0 Hz), 7.38–6.71 (10H+2/5H, m), 5.12 (4/5H, s), 5.07 (6/5H, s), 2.58 (2H, t, J=7.5 Hz), 2.50 (4/5H, br q, J=7.5 Hz), 2.32 (6/5H, br q, J=7.5 Hz), 1.94 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 150.8, 150.5, 150.0, 137.8, 137.5, 129.4, 129.3, 128.3, 128.2, 127.9, 127.8, 127.7, 125.7, 121.4, 115.2, 77.2, 75.7, 75.5, 33.6, 33.2, 28.7, 25.0, 21.5, 21.4; HRMS (EI, *m/z*) calcd for $C_{18}H_{19}NO_3$ (M^+) 297.1364, found 297.1381.

4.6.2. Ethyl radical addition–ionic cyclization reaction of oxime ether **31**

According to the procedure given for the preparation of pyrrolidine **6a**, the treatment of **31** (50 mg, 0.18 mmol) with Et_3B (l mol/L in *n*-hexane) (0.53 mL, 0.53 mmol) in the presence of $BF_3\cdot OEt_2$ (0.04 mL, 0.35 mmol) gave **27a** (28 mg, 72%) as a colorless oil.

4.6.3. Isopropyl radical addition–ionic cyclization reaction of oxime ether **31**

According to the procedure given for the preparation of pyrrolidine **6b**, the treatment of **31** (50 mg, 0.18 mmol) with Et_3B (l mol/L in *n*-hexane) (0.53 mL, 0.53 mmol) in the presence of $BF_3\cdot OEt_2$ (0.04 mL, 0.35 mmol) and *i*-PrI (0.35 mmol, 3.5 mmol) gave **27b** (28 mg, 68%) as a colorless oil.

4.6.4. Ethyl radical addition–ionic cyclization reaction of oxime ether **32**

According to the procedure given for the preparation of pyrrolidine **6a**, the treatment of **32** (50 mg, 0.17 mmol) with Et_3B (l mol/L in *n*-hexane) (0.50 mL, 0.50 mmol) in the presence of $BF_3\cdot OEt_2$ (0.04 mL, 0.34 mmol) gave **28a** (28 mg, 70%) as a colorless oil.

4.6.5. Isopropyl radical addition–ionic cyclization reaction of oxime ether **32**

According to the procedure given for the preparation of pyrrolidine **6b**, the treatment of **32** (50 mg, 0.17 mmol) with Et_3B (l mol/L in *n*-hexane) (0.50 mL, 0.50 mmol) in the presence of $BF_3\cdot OEt_2$ (0.04 mL, 0.34 mmol) and *i*-PrI (0.33 mmol, 3.4 mmol) gave **28b** (26 mg, 63%) as a colorless oil.

4.7. 1-Iodotetradecane (**34**)

To a solution of 1-bromotetradecane (2.0 mL, 6.85 mmol) in acetone (4.0 mL) was added NaI (2.6 g, 17 mmol) under a nitrogen atmosphere. After being refluxed for 27 h, the reaction mixture was filtered. The filtrate was concentrated at reduced pressure, diluted with satd aq $Na_2S_2O_3$, and then extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure to afford **34** (2.2 g, 99%) as a colorless oil. The spectral data were identical with those reported in literature.[18]

4.7.1. 2-Tetradecyl-1-(phenylmethoxy)pyrrolidine (**33**)

According to the procedure given for the preparation of pyrrolidine **6e**, the treatment of **3** (96 mg, 0.28 mmol) with Et_3B (l mol/L in *n*-hexane) (0.83 mL, 0.83 mmol) in the presence of $BF_3\cdot OEt_2$ (0.07, 0.55 mmol) and *n*-$C_{14}H_{29}I$ (1.8 g, 5.6 mmol) gave **33** (31 mg, 30%) as a colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.26 (5H, m), 4.74 (2H, s), 3.23 (1H, m), 2.87–2.73 (2H, m), 1.74–1.26 (30H, m), 0.88 (3H, t, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 128.6, 128.2, 127.7, 77.2, 75.6, 68.1, 55.6, 33.6, 31.9, 29.9, 29.7, 29.7, 29.4, 27.4, 26.9, 22.7, 20.5, 14.1; HRMS (EI, *m/z*) calcd for $C_{25}H_{43}NO$ (M^+) 373.3343, found 373.3341.

4.7.2. 2-Tetradecylpyrrolidine (**35**)

To a solution of **33** (25 mg, 0.09 mmol) in AcOH (1.2 mL) was added zinc dust (49 mg, 0.75 mmol) under a nitrogen atmosphere at 65 °C. After being stirred at the same temperature for 3 h, the reaction mixture was filtrated. The filtrate was concentrated at reduced pressure and was neutralized with K_2CO_3. The mixture was diluted with H_2O and then extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. The crude product was purified by FCC ($CHCl_3$–MeOH=20:1) to afford **35** (6.7 mg, 67%) as a colorless oil.

4.7.3. (±)-N-Methyl-2-tetradecylpyrrolidine ((±)-bgugaine) (**36**)

According to the reported procedure,[14c] the treatment of **35** (15 mg, 0.06 mmol) with 37% aq HCHO (0.12 mL) and $NaBH_4$ in MeOH (0.4 mL) gave **36** (12 mg, 76%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.49 (1H, m), 2.57 (3H, s), 2.11–2.01 (2H m), 1.82–1.60 (6H, m), 1.26 (24H, m), 0.88 (3H, t, J=7.0 Hz); HRMS (EI, *m/z*) calcd for $C_{19}H_{39}NO$ (M^+) 281.3081, found 281.3070.

The spectral data were identical with those reported in literature.[14]

4.7.4. Alkyl radical addition–cyclization reaction of oxime ether **3**

According to the procedure given for the preparation of pyrrolidine **6d**, the treatment of **3** (200 mg, 0.58 mmol) with Et_3B (l mol/L in *n*-hexane) (1.7 mL, 1.7 mmol) in the presence of $BF_3\cdot OEt_2$ (0.14 mL, 1.2 mmol) and γ-iodovalerate **38**[16] (1.5 g, 5.8 mmol) gave polar isomer **39a** (62 mg, 41%) as a colorless oil and less polar isomer **39b** (62 mg, 41%) as a colorless oil.

Ethyl (*R**,*S**)-4-[2-[1-(phenylmethoxy)]pyrrolidinyl]pentanoate (**39a**). IR (neat) 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (5H, m), 4.71 (2H, s), 4.12 (2H, q, J=7.5 Hz), 3.18 (1H, m), 2.80 (2H, m), 2.44–2.17 (2H, m), 1.85–1.38 (7H, m), 1.24 (3H, t, J=7.5 Hz), 0.89 (3H, d, J=7.5 Hz); ^{13}C NMR (75 MHz) δ 173.9, 138.0, 128.6, 128.2, 127.6, 75.2, 71.8, 60.2, 55.8, 34.0, 32.4, 29.8, 23.2, 20.8, 14.4, 14.2; HRMS(EI, *m/z*) calcd for $C_{18}H_{27}NO_3$ (M^+) 305.1990, found 305.1982.

Ethyl (*R**,*R**)-4-[2-[1-(Phenylmethoxy)]pyrrolidinyl]pentanoate (**39b**). IR (neat) 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (5H, m), 4.71 (2H, s), 4.13 (2H, q, J=7.0 Hz), 3.18 (1H, m), 2.80 (2H, m), 2.43–2.17 (2H, m), 2.00–1.31 (7H, m), 1.26 (3H, t, J=7.0 Hz), 0.94 (3H, d, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 138.0, 128.7, 128.2, 127.7, 75.1, 72.4, 60.2, 56.0, 34.3, 32.5, 27.3, 24.0, 21.0, 16.9, 14.3; HRMS (EI, *m/z*) calcd for $C_{18}H_{27}NO_3$ (M^+) 305.1990, found 305.1990.

*4.7.5. cis-Hexahydro-8-methyl-5(1H)-indolizinone (**40a**)*

To a solution of **39a** (25 mg, 0.08 mmol) in AcOH (1.1 mL) was added zinc dust (43 mg, 0.65 mmol) under a nitrogen atmosphere at room temperature. After being stirred at room temperature for 27 h, additional zinc dust (43 mg, 0.65 mmol) and AcOH (1.1 mL) were added to the solution. After being stirred at room temperature for 21 h, the reaction mixture was filtrated. The filtrate was concentrated at reduced pressure and was neutralized with K_2CO_3. The reaction mixture was diluted with H_2O and then extracted with $CHCl_3$. The organic phase was washed with brine, dried over $MgSO_4$, and then concentrated at reduced pressure. The crude product was purified by FCC ($CHCl_3$–MeOH=10:1) to afford **40a** (12.3 mg, 98%) as a colorless oil; IR (neat) 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.64–3.00 (3H, m), 2.52–2.29 (2H, m), 2.20–1.32 (7H, m), 1.03 (3H, d, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 65.1, 45.2, 35.3, 32.2, 31.4, 29.9, 22.1, 18.1; HRMS (EI, *m/z*) calcd for $C_9H_{15}NO$ (M^+) 153.1153, found 153.1147.

The spectroscopic data of **40a** were identical with those previously reported.[17]

*4.7.6. trans-Hexahydro-8-methyl-5(1H)-indolizinone (**40b**)*

According to the procedure given for the preparation of indolizidine **40a**, the treatment of **39b** (30 mg, 0.10 mmol) with zinc dust (51 mg, 0.79 mmol) and AcOH (1.3 mL) gave **40b** (8.2 mg, 55%) as a colorless oil; IR 1619 (neat) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.65–3.43 (3H, m), 2.34 (2H, m), 2.23–1.35 (7H, m), 0.89 (3H, d, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 61.9, 45.2, 29.2, 28.3, 28.1, 27.1, 22.2, 11.2; HRMS (EI, *m/z*) calcd for $C_9H_{15}NO$ (M^+) 153.1153, found 153.1151.

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References and notes

1. (a) Gribble, G. W. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, p 207; (b) Balasubramanian, M.; Keay, J. G. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5, p 245.
2. (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K. M., Eds.; Wiley-VCH: Weinheim, 2006; p 219; (b) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2; (c) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140.
3. (a) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071; (b) Miyabe, H.; Fujii, K.; Tanaka, H.; Naito, T. *Chem. Commun.* **2001**, 831; (c) Miyabe, H.; Ueda, M.; Fujii, K.; Nishimura, A.; Naito, T. *J. Org. Chem.* **2003**, *68*, 5618; (d) Miyabe, H.; Shibata, R.; Ushiro, C.; Naito, T. *Tetrahedron Lett.* **1998**, *39*, 631; (e) Miyabe, H.; Shibata, R.; Sangawa, M.; Ushiro, C.; Naito, T. *Tetrahedron* **1998**, *54*, 11431; (f) Miyabe, H.; Yamakawa, K.; Yoshioka, N.; Naito, T. *Tetrahedron* **1999**, *55*, 11209; (g) Miyabe, H.; Fujii, K.; Naito, T. *Org. Biomol. Chem.* **2003**, *1*, 381.
4. Ueda, M.; Miyabe, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6190.
5. Martin, D. *J. Prakt. Chem.* **1995**, *337*, 599.
6. Kolasa, T.; Sharma, S. K.; Miller, M. J. *Tetrahedron* **1988**, *44*, 5431.
7. Bradshaw, J. S.; Krakowiak, K. E.; Lindh, G. C.; Izatt, R. M. *Tetrahedron* **1987**, *43*, 4271.
8. Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935.
9. Gannett, P. M.; Nagel, D. L.; Reilly, P. J.; Lawson, T.; Sharpe, J.; Toth, B. *J. Org. Chem.* **1988**, *53*, 1064.
10. Kim, S.; Song, H.; Choi, T.; Yoon, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2524.
11. Godineau, E.; Schäfer, C.; Landais, Y. *Org. Lett.* **2006**, *8*, 4871.
12. Melhaoui, A.; Jossang, A.; Bodo, B. *J. Nat. Prod.* **1992**, *55*, 950.
13. Melhaoui, A.; Mallea, M.; Jossang, A.; Bodo, B. *Nat. Prod. Lett.* **1993**, *2*, 237.
14. The synthesis of bgugaine. (a) Enders, D.; Thiebes, C. *Pure Appl. Chem.* **2001**, *73*, 573; (b) Takahata, H.; Ihara, K.; Kubota, M.; Momose, T. *Heterocycles* **1997**, *46*, 349; (c) Jossang, A.; Melhaoui, A.; Bodo, B. *Heterocycles* **1996**, *43*, 755; (d) Enders, D.; Thiebes, C. *J. Indian Chem. Soc.* **1999**, *76*, 561.
15. (a) Flitsch, W. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 8, p 237; (b) Momose, T.; Toyooka, N. *J. Org. Chem.* **1994**, *59*, 943.
16. Kolb, M.; Barth, J. *Synth. Commun.* **1981**, *11*, 763.
17. (a) Song, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **2002**, *43*, 8635; (b) Aubé, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, *35*, 1141; (c) Satake, A.; Shimizu, I. *Tetrahedron: Asymmetry* **1993**, *4*, 1405.
18. Nakajima, R.; Morita, K.; Hara, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3599.