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Tandem Carbon−Carbon Bond-Forming Radical Addition-Cyclization Reaction of Oxime Ether and Hydrazone

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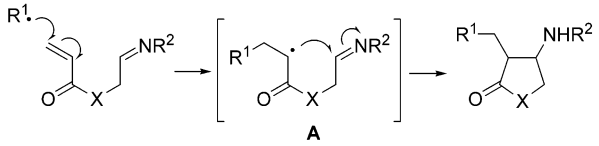
Received January 27, 2003

The novel tandem radical addition-cyclization of oxime ethers and hydrazones intramolecularly connected with the α,β-unsaturated carbonyl group is described. The radical reaction of oxime ethers **1**, **2**, and **4** connected with acryloyl and methacryloyl moieties proceeded smoothly to give the heterocycles via a tandem C−C bond-forming process. The tandem reaction of hydrazone **5** took place in the presence of $Zn(OTf)_2$ as a Lewis acid to give the *trans*-cyclic product **17** without the formation of the *cis*-isomer. The diastereoselective radical addition-cyclization reaction of chiral oxime ether **19** was also studied. The tandem reaction of **19** proceeded smoothly even in aqueous media, providing the novel method for asymmetric synthesis of γ-butyrolactones and β-amino acid derivatives.

Introduction

Strategies involving radical reactions have become preeminent tools in organic synthesis.[1] Free-radical-mediated cyclization has developed as a powerful method for preparing various types of cyclic compounds via carbon−carbon bond-forming processes. Although a number of extensive investigations into radical reactions were reported in recent years, the majority of them employ methods utilizing conventional radical acceptors such as alkenes or typical radical precursors such as halides, selenides, and xanthates. One drawback in traditional procedures using such radical acceptors and precursors is loss of the inherent functional groups. Our laboratory is interested in developing effective and convenient methods for the synthesis of highly functionalized cyclic compounds. For this purpose, we have focused our efforts on radical reactions using the oxime ether group as a radical acceptor.[2−4] In this paper, we describe full details of the radical addition-cyclization reaction of substrates having two different radical acceptors such as acrylate and aldimine moieties (Scheme 1).[5] A remarkable feature

SCHEME 1



of this reaction is the construction of two carbon−carbon bonds via a tandem process.[6]

Results and Discussion

Tandem Radical Addition-Cyclization of Oxime Ethers. Free-radical-mediated cyclization of imine derivatives has been an important method for the construction of various types of cyclic amino compounds. Although there has been extensive investigations into radical cyclization of oxime ethers and hydrazones,[7] the difficulty in achieving tandem construction of multiple carbon−carbon bonds has remained unresolved. Thus, the construction of two carbon−carbon bonds based on tandem radical reaction and its stereocontrol are subjects of

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(2) For reviews on the radical cyclization of imines, see: (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (b) Naito, T. *Heterocycles* **1999**, *50*, 505.

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10.1021/jo0341057 CCC: $25.00
Published on Web 06/18/2003

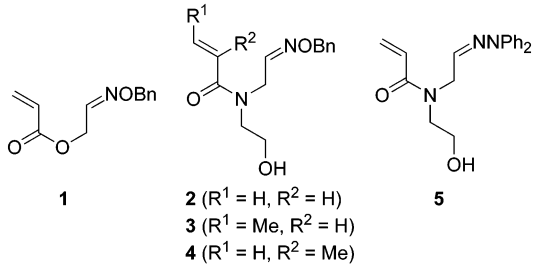
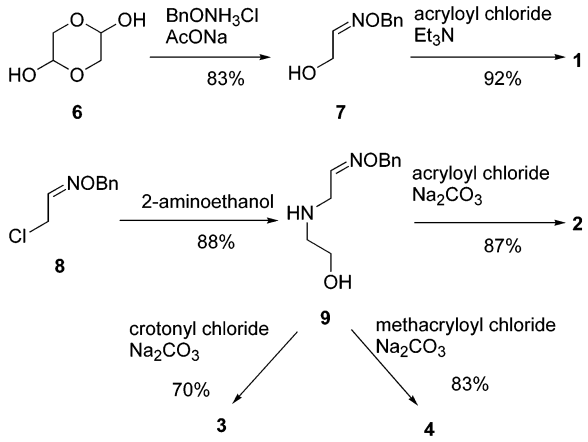


FIGURE 1. Oxime ethers **1**−**4** and hydrazone **5**.

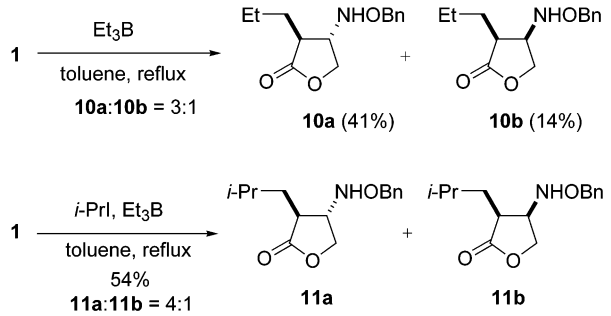
SCHEME 2



considerable interest. This investigation is the first example of the reaction between oxime ethers and carbonyl-stabilized radicals.

We investigated the reaction of several imine derivatives **1**−**5** (Figure 1). Oxime ethers **1**, **2**, **3**, and **4** were prepared as shown in Scheme 2. Oxime ether **7** was readily prepared from glycolaldehyde dimer **6** and *O*-benzylhydroxyamine hydrochloride. The reaction of **7** with acryloyl chloride gave the oxime ether **1** in 92% yield as an *E*/*Z* mixture in a 3:2 ratio. The *E*/*Z* ratios were determined by ^{1}H NMR spectroscopy. In general, the signals due to the imino hydrogen of the *E*-oxime ethers are shifted downfield by the influence of the alkoxy group

SCHEME 3



of the oxime ether moiety.[8] α-Chloroacetaldoxime ether **8** was prepared from chloroacetaldehyde and *O*-benzylhydroxyamine hydrochloride.[9] The reaction of **8** with commercially available 2-aminoethanol gave the secondary amine **9** in 88% yield. Oxime ethers **2**−**4** were readily prepared by the reaction of **9** with the corresponding acid chlorides in 87%, 70%, and 83% yields, respectively, as an *E*/*Z* mixture. In our recent studies on the radical reaction of oxime ethers, we have observed no remarkable effect of the geometry of the starting oxime ether group on either the chemical yield or stereoselectivity by employing geometrically pure *E*- and *Z*-isomers.[3c] Thus, oxime ethers **1**−**4** were subjected to the following radical reactions without the separation of *E*/*Z*-isomers.

At first, we examined the alkyl radical addition-cyclization reaction of oxime ether **1** (Scheme 3). Treatment of an *E*/*Z* mixture of **1** with 1 M Et_3B in hexane in boiling toluene gave a 3:1 mixture of two cyclized products **10a** and **10b** in favor of *trans*-product **10a**. We were able to separate and purify each isomer by either PTLC or medium-pressure column chromatography to give 41% yield of **10a** and 14% yield of **10b**. The relative stereochemistry of **10a** and **10b** was determined by NOESY experiments. Treatment of oxime ether **1** with isopropyl iodide and 1 M Et_3B in hexane in boiling toluene gave a 4:1 mixture of two isopropylated products *trans*-**11a** and *cis*-**11b** in 54% combined yield. A favorable experimental feature of this reaction is that the reaction proceeds smoothly even in the absence of toxic tin hydride or heavy metals via a route involving an iodine atom transfer process. However, it is also important to note the limitation that a primary radical and unstablized alkyl radical other than ethyl radical will not work under the iodine atom transfer reaction conditions.

The rationale of the reaction pathway of tandem reaction is that the alkyl radical initially reacted with acrylate moiety to form carbonyl-stabilized radical **B**, which attacked intramolecularly the oxime ether group as in 5-*exo*-*trig* radical cyclization (Figure 2). The intermediate benzyloxyaminyl radical **C** would be trapped by Et_3B to give the product **D** and ethyl radical; therefore, more than a stoichiometric amount of Et_3B was required. The following crucial points would make these reactions a success of this tandem reaction: (i) the overall difference in the intermolecular reactivity of a nucleophilic carbon radical between two electrophilic radical acceptors

(4) For intermolecular radical reactions of imines by using triethylborane, see: (a) Miyabe, H.; Ueda, M.; Naito, T. *Chem. Commun.* **2000**, 2059. (b) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176. (c) Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, *65*, 5043. (d) Miyabe, H.; Konishi C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443. (e) Miyabe, H.; Fujii, K.; Naito, T. *Org. Lett.* **1999**, *1*, 569. (f) Miyabe, H.; Ueda, M.; Yoshioka, N.; Naito, T. *Synlett* **1999**, 465.

(5) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071.

(6) Radical cascade reaction of oxime ethers was reported. See: Ryu, I.; Kuriyama, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. *J. Am. Chem. Soc.* **1999**, *121*, 12190.

(7) For some selected examples of the radical reaction of oxime ethers, see: (a) Friestad, G. K. *Org. Lett.* **1999**, *1*, 1499. (b) Zhang, J.; Clive, D. L. J. *J. Org. Chem.* **1999**, *64*, 770. (c) Keck, G. E.; Wager, T. T.; McHardy, S. F. *J. Org. Chem.* **1998**, *63*, 9164. (d) Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397. (e) Iserloh, U.; Curran, D. P. *J. Org. Chem.* **1998**, *63*, 4711. (f) Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem.* **1998**, *63*, 5877. (g) Marco-Contelles, J.; Balme, G.; Bouyssi, D.; Destabel, C.; Henriet-Bernard, C. D.; Grimaldi, J.; Hatem, J. M. *J. Org. Chem.* **1997**, *62*, 1202. (h) Marco-Contelles, J.; Gallego, P.; Rodríguez-Fernández, M.; Khiar, N.; Destabel, C.; Bernabé, M.; Martínez-Grau, A.; Chiara, J. L. *J. Org. Chem.* **1997**, *62*, 7397. (i) Noya, B.; Alonso, R. *Tetrahedron Lett.* **1997**, *38*, 2745. (j) Booth, S. E.; Jenkins, P. R.; Swain, C. J. *J. Chem. Soc., Chem. Commun.* **1991**, 1248. (k) Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1991**, *32*, 3555.

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(9) Stach, L. J. U.S. Patent 3,920,772, 1975; *Chem. Abstr.* **1976**, *84*, 89603d.

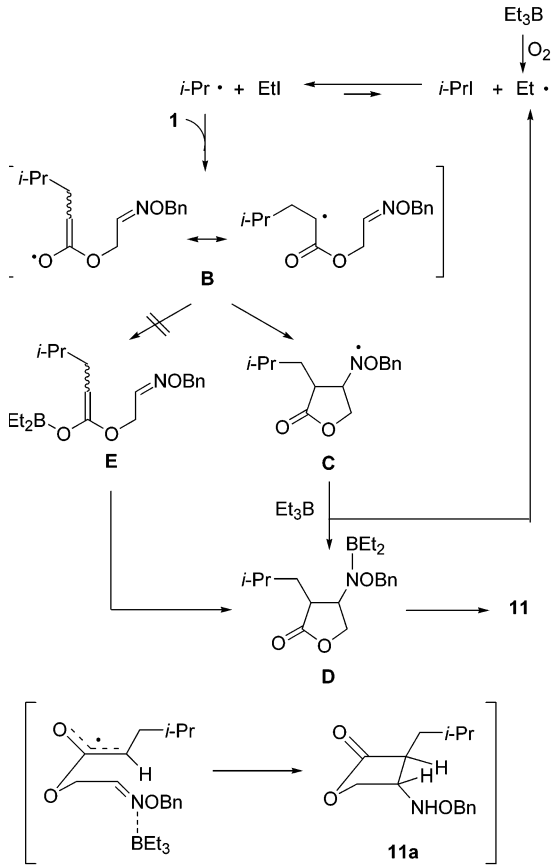
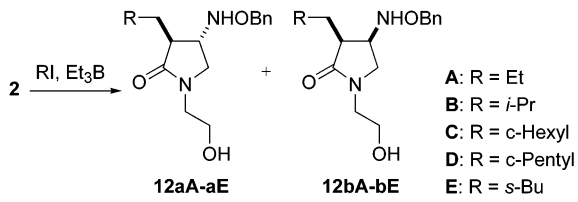


FIGURE 2. Reaction pathway and stereochemical feature.

SCHEME 4



in the first step, and (ii) the high reactivity of triethylborane as a trapping reagent toward a key intermediate aminyl radical **C**. The preferential formation of the *trans*-isomers could be explained by steric repulsions between the radical moiety and the oxime ether group as shown in Figure 2.

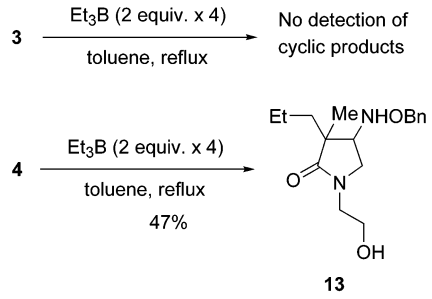
Oxime ether **2** having a 2-hydroxyethylated amide moiety, which would exist in the preferable conformer for intramolecular cyclization, has shown good reactivity (Scheme 4). Treatment of **2** with 1 M Et_3B in hexane in boiling toluene gave a 4:1 mixture of two cyclized products **12aA** and **12bA** in 69% combined yield in favor of *trans*-product **12aA** (Table 1, entry 1). Good chemical yields were also observed in the radical reaction using different radical precursors such as isopropyl, cyclohexyl, and cyclopentyl iodides under the iodine atom transfer reaction conditions (entries 2−5). From the viewpoint of elucidating the reaction mechanism, it is important to note that the tandem reaction of **2** proceeded even in aqueous media (entry 6). The observation suggests that the major reaction pathway is not a route involving the conversion of water-unstable boryl enolate **E** into cyclic product **D** but a tandem radical route involving the conversion of water-resistant radical intermediate **B** into cyclic product **D** (Figure 2).[10] In our recent studies on the radical addition to highly reactive acceptors such as glyoxylic oxime ethers and BF_3-activated aldoxime ethers, the competitive addition of an ethyl radical, generated from triethylborane, was observed as a significant side reaction.[4] In the present reactions, it is noteworthy that no competitive addition of ethyl radical was observed because of the slightly low reactivity of the acrylate moiety on **2** as a radical acceptor.

TABLE 1. Tandem Radical Addition-Cyclization of Oxime Ether 2

entry	RI	solvent	*T* (°C)	product[a]	yield (%)[b]
1	none	toluene	reflux	**12aA**:**12bA** = 4:1	69
2	*i*-PrI	toluene	80	**12aB**:**12bB** = 3:1	67
3	*c*-hexyl I	toluene	80	**12aC**:**12bC** = 3:1	58
4	*c*-pentyl I	toluene	80	**12aD**:**12bD** = 3:1	55
5	*s*-BuI	toluene	80	**12aE**:**12bE** = 4:1	71
6	*i*-PrI	H_2O	80	**12aB**:**12bB** = 3:1	63

[a] Selectivities were determined by ^1H NMR analysis. [b] Isolated yield.

SCHEME 5



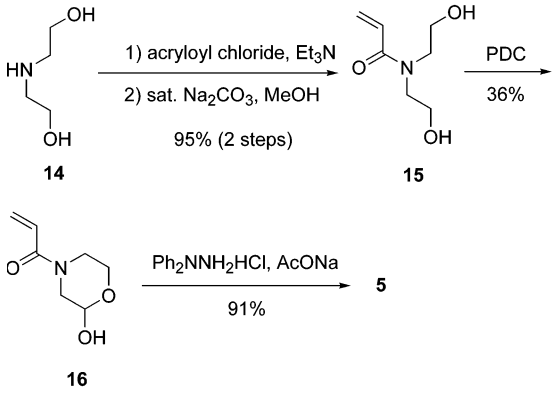
We next examined ethyl radical addition-cyclization reaction of oxime ethers **3** and **4** (Scheme 5). Oxime ether **3** having a crotonyl group did not work under similar reaction conditions. In the case of oxime ether **4** having a methacryloyl group, the tandem radical reaction proceeded slowly, compared with oxime ether **2** having a acryloyl group, to give cyclic product **13** having a quaternary carbon.

Tandem Radical Addition-Cyclization of Hydrazone. We next investigated the reaction of hydrazone **5**, which was prepared as shown in Scheme 6. The acylation of amino alcohol **14** with acryloyl chloride followed by treatment with saturated Na_2CO_3 in methanol gave the alcohol **15** in 95% yield. Selective oxidation of an alcohol in **15** with PDC gave the hemiacetal **16** in 36% yield. Hydrazone **5** was prepared as an *E*-isomer by the reaction of **16** and *N*,*N*-diphenylhydrazine hydrochloride in 91% yield.

The tandem addition-cyclization reaction of hydrazone **5** with an ethyl radical gave the desired cyclic product **17** and the *N*-ethylated cyclic product **18**, the latter of which was formed as a result of the additional *N*-

(10) The reaction between Et_3B and α-carbon radical of an ester is less effective than the corresponding reaction of the α-carbon radical derived from ketones and aldehydes. For the discussions, see: (a) Ollivier, C.; Renaud, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 925. (b) Brown, H. C.; Negishi, E. *J. Am. Chem. Soc.* **1971**, *93*, 3777. (c) Beraud, V.; Gnanou, Y.; Walton, J. C.; Maillard, B. *Tetrahedron Lett.* **2000**, *41*, 1195.

SCHEME 6



SCHEME 7

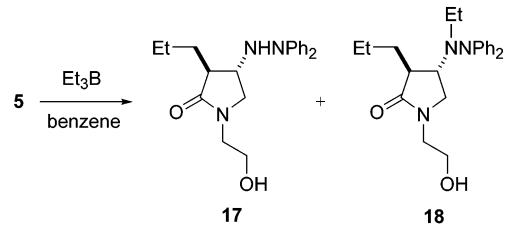


TABLE 2. Tandem Radical Addition-Cyclization of Hydrazone 5

				yield (%)[a]	
entry	Lewis acid	*T* (°C)	time (h)	**17**	**18**
1	none	20	24	0	19
2	none	reflux	3	18	58
3	$MgBr_2 \cdot OEt_2$	reflux	3	28	21
4	MAD	reflux	3	22	0
5	$Zn(OTf)_2$	reflux	3	50	0

[a] Isolated yield.

ethylation (Scheme 7). A remarkable feature of the reaction of hydrazone is the selective formation of *trans*-products **17** and **18** with no detection of *cis*-isomers. The results of the reaction of hydrazone **5** are summarized in Table 2. In the absence of Lewis acid, the reaction proceeded slowly at 20 °C to give the *N*-ethylated cyclic product **18** in 19% yield after 24 h (entry 1). The reaction in refluxing benzene proceeded smoothly to give the desired cyclic product **17** and the *N*-ethylated cyclic product **18** in 18% and 58% yields, respectively. To suppress the formation of the *N*-ethylated cyclic product **18**, several Lewis acids were employed (entries 3−5). In the presence of either MAD or $Zn(OTf)_2$, the formation of **18** was not observed giving 50% yield of the desired product **17** in the latter case (entries 4 and 5).

Diastereoselective Tandem Radical Addition-Cyclization of Oxime Ether. For the asymmetric synthesis of various types of γ-butyrolactones,[11] we next investigated the reaction of chiral oxime ether **19** having a bulky substituent (Figure 3). The six-membered ring formation employing chiral oxime ether **20** was also

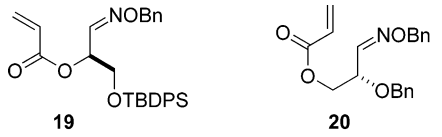


FIGURE 3. Chiral oxime ethers **19** and **20**.

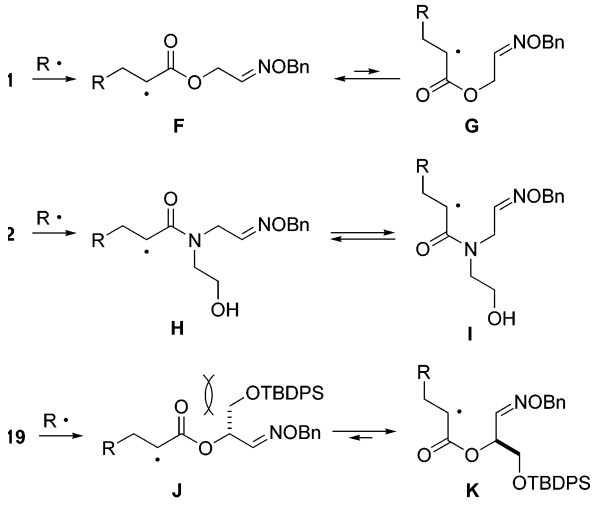


FIGURE 4. Conformation of intermediate radicals.

studied. As described above, the cyclization of conformationally flexible oxime ether **1** took place slowly because α-carbonyl radical exists in an *s-trans* conformer **F**, while the cyclization requires an *s-cis* conformer **G** (Figure 4). The oxime ether **2** having *N*-alkyl amide moiety would exist in preferable conformer **I** for cyclization; thus the reaction of **2** proceeded smoothly. Therefore, we expected that the presence of bulky substituent of chiral oxime ether **19** would be important not only for stereoselectivity but also for efficiency in cyclization. Studies concerning the conformer of ester moiety have been reported in the radical cyclization.[12] We have also reported the effective radical-mediated construction of γ-lactones using hydroximates as a tether.[13]

As shown in Scheme 8, the chiral substrates **19** and **20** having acrylate and aldoxime ether moieties were prepared from D-mannitol. Oxime ether **22** was prepared from chiral aldehyde **21** and *O*-benzylhydroxyamine hydrochloride.[14] The reaction of **22** with pyridinium *p*-toluenesulfonate in methanol gave the alcohol **23** in 89% yield. The alcohol **23** was protected as the TBDPS derivative **24** in good yield by treatment with *tert*-butyldiphenylsilyl chloride in the presence of imidazole. The reaction of **24** with acryloyl chloride gave the oxime ether **19** in 64% yield, as an *E*/*Z* mixture in a 3:1 ratio. For the preparation of oxime ether **20**, the benzyl derivative **25** was prepared from the alcohol **24** in 75%

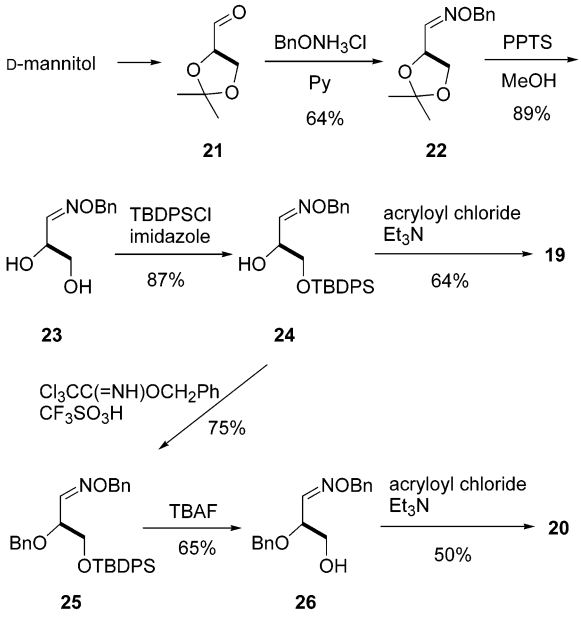
(11) For reviews on asymmetric synthesis of γ-butyrolactones and β-amino acids, see: (a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (c) Ogliaruso, M. A.; Wolfe, J. F. In *Synthesis of Lactones and Lactams*; John Wiley & Sons: New York, 1993.

(12) (a) Wang, C.; Russell, G. A. *J. Org. Chem.* **1999**, *64*, 2066. (b) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746. (c) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224. (d) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (e) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564.

(13) Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Aoe, K.; Okamura, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 6922.

(14) Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056.

SCHEME 8



SCHEME 9

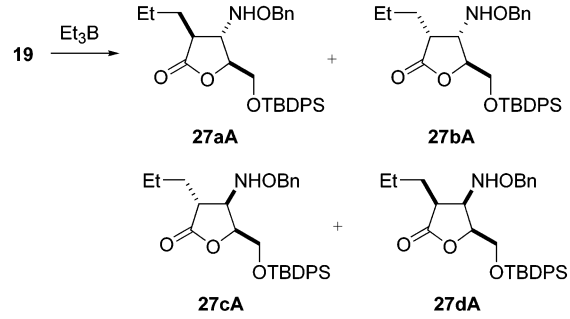


TABLE 3. Tandem Ethyl Radical Addition-Cyclization of Oxime Ether 19

entry	solvent	*T* (°C)	yield (%)[a]	selectivity[b] **27aA**:**27bA**
1	toluene	reflux	70	8:1
2	benzene	reflux	64	12:1
3	toluene	20	53	18:1
4	CH_2Cl_2	20	53	10:1
5	H_2O/MeOH (1:4, v/v)	reflux	55	9:1

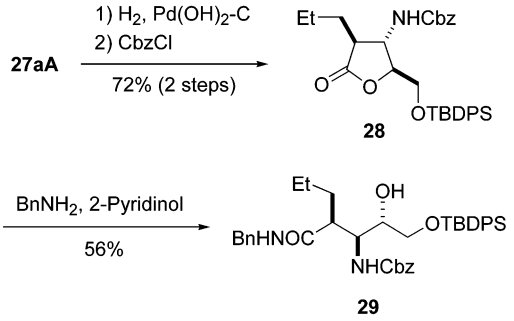
[a] Isolated yield of major diastereomer. [b] Selectivities were determined by ^1H NMR analysis which indicates the ratio of a major diastereomer and a second diastereomer.

yield under the mild reaction conditions.[15] After the deprotection of the TBDPS group, acylation with acryloyl chloride gave the oxime ether **20** in 50% yield, as an *E*/*Z* mixture in a 3:1 ratio. Oxime ethers **19** and **20** were subjected to the following radical reactions, without the separation of *E*/*Z*-isomers.

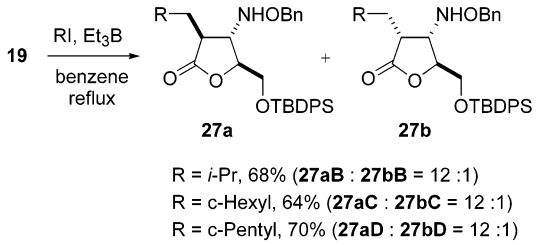
We initially studied the reaction of oxime ether **19** with an ethyl radical by using triethylborane (Scheme 9). The reaction in refluxing toluene proceeded smoothly to give a major diastereomer **27aA** in 70% yield along with a small amount of another diastereomer **27bA** (Table 3, entry 1). Extensive studies of this reaction showed that

(15) (a) Iversen, T.; Bundle, D. R. *Chem. Commun.* **1981**, 1240. (b) White, J. D.; Kawasaki, M. *J. Org. Chem.* **1992**, *57*, 5292.

SCHEME 10



SCHEME 11



trace amount of other diastereomers **27cA** and **27dA** were also formed. The relative stereochemistry of **27aA**-**27dA** was determined by NOESY experiments. The reaction in refluxing benzene also gave **27aA** in 64% with moderate diastereoselectivity (entry 2). The degree of stereoselectivity was shown to be dependent on the reaction temperature; thus, changing the temperature to 20 °C in toluene led to an increase in diastereoselectivity to 18:1 (entry 3). The reaction in CH_2Cl_2 at 20 °C gave **27aA** in 53% isolated yields with moderate diastereoselectivity (entry 4). Interestingly, the tandem reaction of **19** proceeded even in aqueous media to afford **27aA** in 55% yield (entry 5).

As shown in Scheme 10, the γ-butyrolactone **27aA** was converted to a β-amino acid derivative **29**. Hydrogenolysis of the benzyloxyamino group of **27aA** in the presence of $Pd(OH)_2$−C gave the amine, which was protected as the *N*-Cbz derivative **28** by treatment with CbzCl. The treatment of **28** with benzylamine in the presence of 2-pyridinol[16] gave β-amino acid derivative **29** in 56% yield.

For the asymmetric synthesis of various types of chiral γ-butyrolactones, we next investigated the reaction using different radical precursors under the iodine atom transfer reaction conditions (Scheme 11). The tandem reaction of **19** with an isopropyl radical was carried out in boiling benzene for 15 min by using isopropyl iodide (6 equiv) and triethylborane (3 equiv). As expected, the reaction proceeded smoothly to give the isopropylated product **27aB** in 68% yield along with a small amount of another diastereomer **27bB**. Other secondary alkyl radicals worked well under similar reaction conditions, allowing facile incorporation of structural variety. Under the iodine atom transfer reaction conditions, the tandem reaction of **19** also proceeded in aqueous media to afford **27aB**−**27aD** (Scheme 12).

(16) (a) Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9073. (b) Openshaw, H. T.; Whittaker, N. *J. Chem. Soc. C* **1969**, 89.

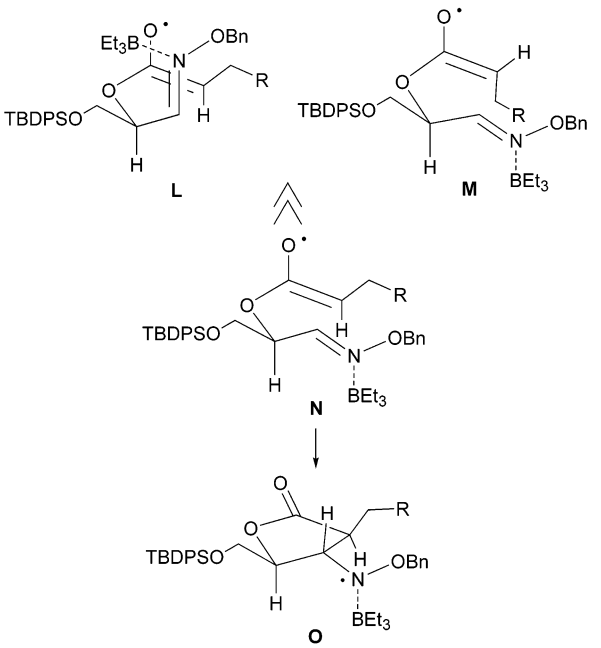
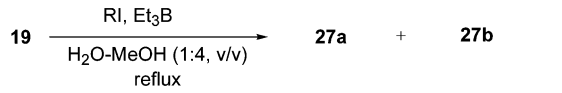


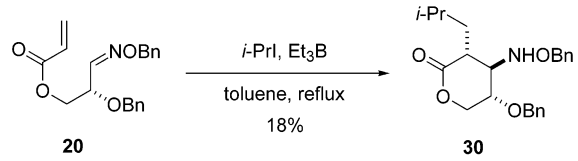
FIGURE 5. Stereochemical feature.

SCHEME 12



R = *i*-Pr, 80% (**27aB** : **27bB** = 7 :1)
R = c-Hexyl, 56% (**27aC** : **27bC** = 8 :1)
R = c-Pentyl, 47% (**27aD** : **27bD** = 11 :1)

SCHEME 13



The preferential formation of the *trans*-isomers **27aA**−**27aD** could be explained by invoking a favorable conformer minimizing $A^{1,3}$-strain effects between the Et_3B bonding-oxime ether group and substituents at the chiral carbon (Figure 5). There are less steric repulsions in the radical **N** leading to the *trans*-isomer **27aA**−**27aD** than those in the radicals **L** and **M** leading to the *cis*-isomers **27dA**−**27dD** and **27bA**−**27bD**.

We finally studied the reaction of oxime ether **20** with an isopropyl radical under the iodine atom transfer reaction conditions (Scheme 13). Although the tandem radical reaction of **20** proceeded slowly, the desired six-membered product **30** was obtained in 18% yield as a major diastereomer.

Conclusions

We have shown new free-radical-mediated tandem reactions of oxime ethers for the synthesis of heterocycles via two C−C bond-forming processes. In addition to radical cyclization of oxime ethers, the tandem radical reactions disclosed a broader aspect of the utility of oxime ethers as a radical acceptor for the synthesis of various types of amino compounds. Additionally, the reactions of oxime ethers with carbonyl-stabilized radicals is a new alternative to the intramolecular Mannich reaction.[17]

Experimental Section

Tandem Radical Reaction of 1 with Et_3B. To a boiling solution of **1** (200 mg, 0.91 mmol) in toluene (40 mL) was added Et_3B (1.0 M in hexane, 4.6 mL, 4.6 mmol) at reflux. After being stirred at reflux for 15 min, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue (a *trans*/*cis* mixture in 3:1) by preparative TLC (hexane/AcOEt 4:1, 2-fold development) afforded *trans*-**10a** (94 mg, 41%) and *cis*-**10b** (31 mg, 14%).

***trans*-Dihydro-4-[(phenylmethoxy)amino]-3-propyl-2(3*H*)-furanone (10a).** A colorless oil: IR ($CHCl_3$) 2965, 1773, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42−7.28 (5H, m), 5.62−5.38 (1H, br m), 4.70 (2H, s), 4.32 (1H, dd, J = 9.6, 6.3 Hz), 4.13 (1H, dd, J = 9.6, 4.5 Hz), 3.63 (1H, br m), 2.45 (1H, m), 1.75 (1H, m), 1.55 (1H, m), 1.45 (2H, m), 0.94 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 178.0, 137.0, 128.7, 128.5, 128.2, 77.1, 69.6, 61.9, 42.7, 31.2, 20.2, 13.8; HRMS calcd for $C_{14}H_{19}NO_3$ (M^+) 249.1364, found 249.1377.

***cis*-Dihydro-4-[(phenylmethoxy)amino]-3-propyl-2(3*H*)-furanone (10b).** A colorless oil: IR ($CHCl_3$) 2965, 1774, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4−7.3 (5H, m), 5.62−5.45 (1H, br m), 4.71, 4.68 (each 1H, d, J = 11.5 Hz), 4.37 (1H, d, J = 10.0 Hz), 4.20 (1H, dd, J = 10.0, 4.5 Hz), 3.78 (1H, br dd, J = 6.5, 4.5 Hz), 2.52 (1H, m), 1.80 (1H, m), 1.55−1.4 (3H, m), 0.96 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 177.7, 137.0, 128.6, 128.5, 128.2, 76.9, 70.1, 58.5, 42.2, 25.8, 21.1, 14.0; HRMS calcd for $C_{14}H_{19}NO_3$ (M^+) 249.1364, found 249.1391.

Tandem Radical Reaction of 1 with *i*-PrI and Et_3B. To a solution of **1** (200 mg, 0.91 mmol) and *i*-PrI (0.45 mL, 4.6 mmol) in toluene (40 mL) was added Et_3B (1.0 M in hexane, 4.6 mL, 4.6 mmol) at reflux. After being stirred at reflux for 15 min, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 4:1, 2-fold development) afforded **11a** and **11b** (a *trans*/*cis* mixture in 4:1, 129 mg, 54%). Purification of the mixture of *trans*/*cis* isomers by preparative TLC (hexane/AcOEt 4:1, 4-fold development) afforded *trans*-**11a** as a sole isolable isomer.

***trans*-Dihydro-3-[(2-methyl)propyl]-4-[(phenylmethoxy)amino]-2(3*H*)-furanone (11a).** A colorless oil: IR ($CHCl_3$) 2962, 1771, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41−7.29 (5H, m), 5.62−5.41 (1H, br m), 4.70 (2H, s), 4.32 (1H, dd, J = 9.6, 6.3 Hz), 4.15 (1H, dd, J = 9.9, 3.9 Hz), 3.59 (1H, br m), 2.51 (1H, m), 1.80 (1H, m), 1.62 (1H, m), 1.40 (1H, m), 0.95, 0.92 (each 3H, d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 178.3, 136.9, 128.5, 128.3, 128.0, 76.8, 69.3, 62.2, 41.0, 38.1, 25.6, 22.5, 21.7; HRMS calcd for $C_{15}H_{21}NO_3$ (M^+) 263.1520, found 263.1508.

Tandem Radical Reaction of 2 with Et_3B. To a solution of **2** (200 mg, 0.76 mmol) in toluene (6 mL) was added Et_3B (1.0 M in hexane, 2.3 mL, 2.3 mmol) at reflux. After the reaction mixture was stirred at the same temperature for 25 min, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue containing a 4:1 mixture of *trans*/*cis* isomers by preparative TLC (AcOEt) afforded **12aA** (154 mg, 69%).

(17) For a review on the Mannich reaction, see: (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (b) Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1007. (c) Tramontiti, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791.

***trans*-1-(2-Hydroxyethyl)-4-[(phenylmethoxy)amino]-3-propyl-2-pyrrolidinone (12aA).** A colorless oil: IR ($CHCl_3$) 3401, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38−7.30 (5H, m), 5.66−5.40 (1H, br m), 4.70 (2H, s), 3.72 (2H, t, J = 5.0 Hz), 3.57−3.50 (2H, m), 3.43 (1H, m), 3.36−3.30 (2H, m), 2.30 (1H, dt, J = 8.5, 4.5 Hz), 2.08−1.90 (1H, br m), 1.71 (1H, m), 1.51−1.36 (3H, m), 0.92 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 176.6, 137.3, 128.6, 128.5, 128.1, 76.7, 60.6, 59.2, 51.5, 46.1, 45.8, 32.0, 20.2, 14.0; HRMS calcd for $C_{16}H_{24}N_2O_3$ (M^+) 292.1785, found 292.1803.

***cis*-1-(2-Hydroxyethyl)-4-[(phenylmethoxy)amino]-3-propyl-2-pyrrolidinone (12bA).** A colorless oil: IR ($CHCl_3$) 3371, 1673, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37−7.30 (5H, m), 5.69−5.43 (1H, br m), 4.69 (1H, d, J = 11.5 Hz), 4.66 (1H, d, J = 11.5 Hz), 3.71 (2H, t, J = 5.0 Hz), 3.49−3.29 (4H, m), 2.51−2.47 (1H, m), 1.75−1.71 (1H, m), 1.47−1.33 (3H, m), 0.94 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 176.2, 137.2, 128.7, 128.5, 128.1, 76.5, 60.5, 56.1, 51.3, 46.1, 44.8, 26.1, 21.1, 14.1; HRMS calcd for $C_{16}H_{24}N_2O_3$ (M^+) 292.1785, found 292.1781.

General Procedure for Tandem Radical Reaction of 2 with RI and Et_3B. To a solution of **2** (100 mg, 0.38 mmol) and RI (11.5 mmol) in toluene (3 mL) was added Et_3B (1.0 M in hexane, 1.15 mL, 1.15 mmol) three times in every 5 min at reflux. After being stirred at reflux for 25 min, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by preparative TLC (AcOEt) afforded pyrrolidinones **12aB**−**12bE**.

***trans*-1-(2-Hydroxyethyl)-3-(2-methylpropyl)-4-[(phenylmethoxy)amino]-2-pyrrolidinone (12aB).** A colorless oil: IR ($CHCl_3$) 2959, 1670, 1488, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.25 (5H, m), 5.69−5.43 (1H, br m), 4.70 (2H, s), 3.78−3.63 (2H, m), 3.60−3.23 (6H, m), 2.34 (1H, m), 1.82−1.50 (2H, m), 1.40−1.21 (1H, m), 0.928 (3H, d, J = 6.2 Hz), 0.908 (3H, d, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 176.7, 137.3, 128.6, 128.4, 128.1, 76.7, 60.4, 59.6, 51.2, 45.9, 44.1, 39.1, 25.8, 23.1, 21.8; HRMS calcd for $C_{17}H_{26}N_2O_3$ (M^+) 306.1941, found 306.1955.

***cis*-1-(2-Hydroxyethyl)-3-(2-methylpropyl)-4-[(phenylmethoxy)amino]-2-pyrrolidinone (12bB).** A colorless oil: IR ($CHCl_3$) 2959, 1674, 1486, 1467 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.25 (5H, m), 5.62−5.39 (1H, br m), 4.69 (1H, d, J = 11.8 Hz), 4.66 (1H, d, J = 11.8 Hz), 3.79−3.62 (3H, m), 3.58−3.23 (4H, m), 3.18−2.97 (1H, br m), 2.57 (1H, m), 1.80−1.21 (3H, m), 0.926 (3/3H, d, J = 6.2 Hz), 0.911 (3/3H, d, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 176.3, 137.0, 128.6, 128.3, 128.0, 76.4, 60.5, 56.2, 51.2, 46.0, 42.8, 32.5, 26.0, 23.1, 21.7; HRMS calcd for $C_{17}H_{26}N_2O_3$ (M^+) 306.1941, found 306.1941.

***trans*-3-(Cyclohexylmethyl)-1-(2-hydroxyethyl)-4-[(phenylmethoxy)amino]-2-pyrrolidinone (12aC).** A colorless oil: IR ($CHCl_3$) 2926, 1671, 1488, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.25 (5H, m), 4.70 (2H, s), 3.70 (2H, t, J = 5.2 Hz), 3.61−3.26 (6H, m), 2.37 (1H, m), 1.77−0.83 (14H, m); ^{13}C NMR ($CDCl_3$) δ 177.1, 137.3, 128.6, 128.5, 128.1, 76.7, 60.4, 59.7, 51.2, 45.9, 43.4, 37.6, 35.2, 33.9, 32.5, 26.5, 26.2, 26.1; HRMS calcd for $C_{20}H_{30}N_2O_3$ (M^+) 346.2254, found 346.2249.

***cis*-3-(Cyclohexylmethyl)-1-(2-hydroxyethyl)-4-[(phenylmethoxy)amino]-2-pyrrolidinone (12bC).** A colorless oil: IR ($CHCl_3$) 2926, 1674, 1486, 1449 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.25 (5H, m), 5.61−5.33 (1H, br m), 4.71 (1H, d, J = 11.6 Hz), 4.65 (1H, d, J = 11.6 Hz), 3.72 (2H, t, J = 5.0 Hz), 3.66 (1H, m), 3.52−3.24 (4H, m), 3.15−2.92 (1H, br m), 2.59 (1H, m), 1.80−0.45 (13H, m); ^{13}C NMR ($CDCl_3$) δ 176.5, 137.2, 128.8, 128.5, 128.2, 76.5, 60.7, 56.5, 51.3, 46.2, 42.3, 35.6, 33.9, 32.7, 31.2, 26.5, 26.3, 26.2; HRMS calcd for $C_{20}H_{30}N_2O_3$ (M^+) 346.2254, found 346.2239.

***trans*-3-(Cyclopentylmethyl)-1-(2-hydroxyethyl)-4-[(phenylmethoxy)amino]-2-pyrrolidinone (12aD).** A colorless oil: IR ($CHCl_3$) 2952, 2468, 1670, 1489, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.25 (5H, m), 4.70 (2H, s), 3.71 (2H, t, J = 5.6 Hz), 3.62−3.26 (6H, m), 2.30 (1H, m), 2.02−0.90 (11H, m); ^{13}C NMR ($CDCl_3$) δ 176.7, 137.2, 128.5, 128.3, 127.9, 76.5, 60.3, 59.2, 51.2, 45.9, 45.2, 37.6, 36.0, 32.9, 32.1, 25.1, 24.8; HRMS calcd for $C_{19}H_{28}N_2O_3$ (M^+) 332.2098, found 332.2112.

***cis*-3-(Cyclopentylmethyl)-1-(2-hydroxyethyl)-4-[(phenylmethoxy)amino]-2-pyrrolidinone (12bD).** A colorless oil: IR ($CHCl_3$) 3401, 2951, 2464, 1678, 1485 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.25 (5H, m), 5.72−5.28 (1H, br m), 4.71 (1H, d, J = 11.6 Hz), 4.65 (1H, d, J = 11.6 Hz), 3.76−3.67 (3H, m), 3.52−3.24 (4H, m), 3.18−2.81 (1H, br m), 2.51 (1H, m), 2.00−1.00 (11H, m); ^{13}C NMR ($CDCl_3$) δ 176.2, 137.1, 128.6, 128.3, 128.0, 76.4, 60.5, 56.3, 51.2, 46.1, 44.1, 38.0, 33.0, 32.0, 29.7, 25.0, 24.9; HRMS calcd for $C_{19}H_{28}N_2O_3$ (M^+) 332.2099, found 332.2127.

***trans*-1-(2-Hydroxyethyl)-3-(2-methylbutyl)-4-[(phenylmethoxy)amino]-2-pyrrolidinone (12aE)** (1:1 mixture of diastereomers concerning *sec*-butyl group). A colorless oil: IR ($CHCl_3$) 3396, 2963, 1664, 1488, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.25 (5H, m), 4.70 (2H, s), 3.71 (2H, t, J = 5.4 Hz), 3.61−3.24 (5H, m), 2.42−2.30 (1H, m), 1.78−0.80 (11H, m); ^{13}C NMR ($CDCl_3$) δ 176.4, 137.2, 128.5, 128.4, 128.3, 127.9, 76.5, 60.3, 59.7, 59.4, 51.2, 51.0, 45.8, 43.8, 43.7, 37.1, 36.7, 31.94, 31.85, 29.9, 28.4, 19.2, 18.3, 11.1, 10.9; HRMS calcd for $C_{18}H_{28}N_2O_3$ (M^+) 320.2098, found 320.2088.

***cis*-1-(2-Hydroxyethyl)-3-(2-methylbutyl)-4-[(phenylmethoxy)amino]-2-pyrrolidinone (12bE)** (1:1 mixture of diastereomers concerning *sec*-butyl group). A colorless oil: IR ($CHCl_3$) 3401, 2962, 1674, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.25 (5H, m), 4.71 (1H, d, J = 11.6 Hz), 4.65 (1H, d, J = 11.6 Hz), 3.75−3.65 (3H, m), 3.52−3.24 (4H, m), 2.64−2.50 (1H, m), 1.80−0.80 (11H, m); ^{13}C NMR ($CDCl_3$) δ 176.3, 137.0, 128.6, 128.4, 128.0, 76.4, 60.5, 56.6, 56.0, 51.22, 51.18, 46.1, 42.7, 42.6, 32.3, 32.2, 30.6, 30.14, 30.08, 28.5, 19.4, 18.5, 11.3, 11.0; HRMS calcd for $C_{18}H_{28}N_2O_3$ (M^+) 320.2098, found 320.2088.

1-(2-Hydroxyethyl)-3-methyl-4-[(phenylmethoxy)amino]-3-propyl-2-pyrrolidinone (13). To a solution of oxime ether **4** (100 mg, 0.36 mmol) in boiling toluene was added Et_3B (1.0 M in hexane, 0.72 mL, 0.72 mmol) four times in every 15 min. After being heated at reflux for 1 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 1:3) afforded **13** (52 mg, 47%) as a colorless oil. The presence of *trans*/*cis* isomers precluded a comprehensive assignment of all protons and carbons: IR ($CHCl_3$) 3401, 3022, 2963, 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (5H, m), 5.70−5.38 (1H, br m), 4.68 (2H, s), 3.70 (2H, t, J = 5.1 Hz), 3.56−3.23 (5H, m), 1.51−1.05 (7H, m), 0.88 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 178.8, 137.1, 128.5 (2C), 128.3, 128.2, 127.9, 76.2, 63.1, 60.2, 59.9, 50.2, 49.9, 46.8, 46.4, 45.7, 39.4, 34.0, 21.8, 17.5, 17.3, 16.2, 14.5, 14.3; HRMS calcd for $C_{17}H_{26}N_2O_3$ (M^+) 306.1942, found 306.1935.

Tandem Radical Reaction of 5 with Et_3B. To a solution of **5** (52 mg, 0.16 mmol) in benzene (5 mL) was added Et_3B (1.0 M in hexane, 0.39 mL, 0.39 mmol) three times in every 1 h at reflux. After being stirred at reflux for 8 h, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by preparative TLC ($CHCl_3$/MeOH 30:1) afforded monoethylated product **17** (10 mg, 18%) and diethylated product **18** (34 mg, 58%).

***trans*-1-(2-Hydroxyethyl)-4-(2,2-diphenylhydrazino)-3-propyl-2-pyrrolidinone (17).** A colorless oil: IR ($CHCl_3$) 3386, 1671 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33−7.02 (10H, m), 4.18−3.82 (1H, br m), 3.80−3.72 (2H, m), 3.53−3.35 (5H, m), 3.10−2.83 (1H, br m), 2.31 (1H, m), 1.65 (1H, m), 1.41 (1H, m), 1.34−1.26 (2H, m), 0.88 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 177.1, 147.7, 129.3, 122.9, 120.3, 61.1, 56.1, 51.8, 47.7, 46.4, 31.7, 20.5, 14.0; HRMS calcd for $C_{21}H_{27}N_3O_2$ (M^+) 353.2102, found 353.2109.

***trans*-4-(1-Ethyl-2,2-diphenylhydrazino)-1-(2-hydroxyethyl)-3-propyl-2-pyrrolidinone (18).** A colorless oil: IR

($CHCl_3$) 3609, 1670, 1492 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36−6.90 (10H, m), 3.62−3.15 (6H, m), 2.88−2.52 (4H, m), 1.68−1.22 (4H, m), 1.11 (3H, t, J = 7.0 Hz), 0.93 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 176.9, 146.6, 129.1, 128.9, 122.8, 121.8, 120.2, 118.5, 117.8, 63.6, 61.2, 50.4, 48.9, 46.0, 43.9, 32.3, 20.1, 14.0, 12.9; HRMS calcd for $C_{23}H_{31}N_3O_2$ (M^+) 381.2415, found 381.2418.

General Procedure for Tandem Radical Reaction of 19. To a solution of **19** (100 mg, 0.205 mmol) and R^2I (2.46 or 1.23 mmol) in solvent (20 mL) was added Et_3B (1.0 M in hexane, 0.615 or 1.23 mmol) at reflux or 20 °C. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 6:1) or preparative TLC (hexane/AcOEt 6:1, 2-fold development) afforded **27aA**−**bD**.

[3*S*-(3α,4*β*,5α)]-Dihydro-5-[[(1,1-dimethylethyl)diphenylsilyloxy]methyl]-4-[(phenylmethoxy)amino]-3-propyl-2(3*H*)-furanone (27aA). A colorless oil: $[\alpha]^{25}_D$ −38.4 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 2932, 1770, 1428 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68−7.61 (4H, m), 7.46−7.26 (11H, m), 5.62−5.54 (1H, br m), 4.64 (2H, s), 4.34 (1H, m), 3.88, 3.76 (each 1H, dd, J = 11.5, 3.5 Hz), 3.67 (1H, br dd, J = 8.0, 6.0 Hz), 2.66 (1H, m), 1.81−1.73 (1H, m), 1.64−1.55 (1H, m), 1.51−1.39 (2H, m), 1.04 (9H, s), 0.92 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 177.3, 137.1, 135.7, 135.6, 132.9, 132.6, 129.92, 129.89, 128.6, 128.5, 128.2, 127.8, 80.6, 76.8, 63.5, 62.8, 42.7, 31.4, 26.8, 20.1, 19.2, 13.9; HRMS calcd for $C_{31}H_{39}NO_4Si$ (M^+) 517.2647, found 517.2661.

[3*R*-(3α,4α,5*β*)]-Dihydro-5-[[(1,1-dimethylethyl)diphenylsilyloxy]methyl]-4-[(phenylmethoxy)amino]-3-propyl-2(3*H*)-furanone (27bA). A colorless oil: $[\alpha]^{25}_D$ +8.92 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 2932, 1772, 1472, 1428 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66−7.60 (4H, m), 7.46−7.27 (11H, m), 5.58 (1H, br m), 4.67 (2H, s), 4.47 (1H, m), 3.89 (1H, dd, J = 11.5, 3.5 Hz), 3.75 (1H, dd, J = 11.5, 3.0 Hz), 3.78−3.74 (1H, m), 2.92 (1H, m), 1.84−1.75 (1H, m), 1.55−1.42 (3H, m), 1.03 (9H, s), 0.95 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 178.2, 137.0, 135.6, 135.5, 132.7, 132.2, 130.0, 128.52, 128.48, 128.1, 127.9, 81.8, 76.7, 64.7, 60.4, 42.2, 26.8, 26.1, 21.4, 19.2, 14.0; HRMS calcd for $C_{31}H_{39}NO_4Si$ (M^+) 517.2647, found 517.2636.

[3*R*-(3α,4*β*,5*β*)]-Dihydro-5-[[(1,1-dimethylethyl)diphenylsilyloxy]methyl]-4-[(phenylmethoxy)amino]-3-propyl-2(3*H*)-furanone (27cA). A colorless oil: $[\alpha]^{25}_D$ −41.4 (*c* 0.59, $CHCl_3$); IR ($CHCl_3$) 2932, 1772, 1590, 1428 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67−7.61 (4H, m), 7.48−7.27 (11H, m), 6.18 (1H, br m), 4.64 (2H, s), 4.50 (1H, m), 4.09 (1H, dd, J = 11.5, 2.5 Hz), 3.95 (1H, dd, J = 11.5, 3.5 Hz), 3.77 (1H, br dd, J = 17, 9.5 Hz), 2.59 (1H, m), 1.80−1.72 (1H, m), 1.60−1.52 (2H, m), 1.50−142 (1H, m), 1.01 (9H, s), 0.95 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 177.3, 137.5, 135.6, 135.5, 132.5, 131.8, 130.0, 128.5, 128.4, 128.0, 127.94, 127.92, 127.8, 79.0, 76.5, 63.6, 63.0, 43.5, 32.1, 26.8, 19.9, 19.0, 13.8; HRMS calcd for $C_{31}H_{39}NO_4Si$ (M^+) 517.2646, found 517.2640.

[3*S*-(3α,4α,5α)]-Dihydro-5-[[(1,1-dimethylethyl)diphenylsilyloxy]methyl]-4-[(phenylmethoxy)amino]-3-propyl-2(3*H*)-furanone (27dA). A colorless oil: $[\alpha]^{25}_D$ +26.8 (*c* 1.16, $CHCl_3$). IR ($CHCl_3$) 2961, 1773, 1464, 1428 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66−7.60 (4H, m), 7.46−7.16 (11H, m), 5.82 (1H, br m), 4.52, 4.43 (each 1H, d, J = 12 Hz), 4.47−4.20 (1H, m), 4.09 (2H, d, J = 6.5 Hz), 3.71 (1H, dd, J = 7, 5 Hz), 2.56 (1H, dt, J = 7, 2 Hz), 1.90−1.80, 1.66−1.58 (each 1H, m), 1.53−145 (2H, m), 1.03 (9H, s), 0.96 (3H, t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 177.4, 136.9, 135.8, 135.62, 135.55, 135.5, 133.0, 132.8, 129.9, 132.8, 129.9, 128.5, 128.4, 128.3, 128.2, 128.0, 127.92, 127.89, 127.85, 127.8, 80.5, 75.7, 62.2, 60.0, 43.4, 26.9, 26.8, 26.1, 21.2, 19.2, 14.1; HRMS calcd for $C_{31}H_{39}NO_4Si$ (M^+) 517.2646, found 517.2627.

[3*S*-(3α,4*β*,5α)]-Dihydro-5-[[(1,1-dimethylethyl)diphenylsilyloxy]methyl]-3-[(2-methyl)propyl]-4-[(phenylmethoxy)amino]-2(3*H*)-furanone (27aB). A colorless oil: $[\alpha]^{23}_D$ +115.0 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 2932, 1771, 1428 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67−7.61 (4H, m), 7.46−7.27 (11H, m), 4.67 (2H, s), 4.37 (1H, m), 3.88, 3.75 (each 1H, dd, J = 12.0, 3.0 Hz), 3.64 (1H, br dd, J = 7.5, 7.0 Hz), 2.73 (1H, m), 1.88−1.79 (1H, m), 1.74−1.68 (1H, m), 1.52−1.45 (1H, m), 1.034 (9H, s), 1.030, 0.92 (each 3H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 177.5, 137.1, 135.6, 135.5, 132.9, 132.5, 129.89, 129.86, 128.6, 128.5, 128.2, 127.9, 127.81, 127.80, 80.6, 76.8, 63.63, 63.56, 40.7, 39.2, 26.8, 25.5, 22.8, 21.9, 19.2; HRMS calcd for $C_{32}H_{41}NO_4Si$ (M^+) 531.2803, found 531.2784.

[3S-(3α,4*β*,5α)]-3-[(Cyclohexyl)methyl]dihydro-5-[[(1,1-dimethylethyl)diphenylsilyloxy]methyl]-4-[(phenylmethoxy)amino]-2(3*H*)-furanone (27aC). A colorless oil: $[\alpha]^{23}_D$ +89.7 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 2930, 1771, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67−7.61 (4H, m), 7.45−7.26 (11H, m), 4.68 (2H, s), 4.39 (1H, m), 3.89, 3.76 (each 1H, dd, J = 12.0, 3.0 Hz), 3.64 (1H, m), 2.78 (1H, m), 1.78−0.84 (13H, m), 1.03 (9H, s); ^{13}C NMR ($CDCl_3$) δ 177.5, 136.9, 135.5, 135.4, 132.8, 132.4, 129.7, 128.4, 128.3, 127.9, 127.6, 80.6, 76.3, 63.43, 63.39, 39.9, 37.5, 34.6, 33.3, 32.3, 26.6, 26.3, 26.0, 25.8, 19.0; HRMS calcd for $C_{35}H_{45}NO_4Si$ (M^+) 571.3115, found 571.3102.

[3S-(3α,4*β*,5α)]-3-[(Cyclopentyl)methyl]dihydro-5-[[(1,1-dimethylethyl)diphenylsilyloxy]methyl]-4-[(phenylmethoxy)amino]-2(3*H*)-furanone (27aD). A colorless oil: $[\alpha]^{23}_D$ +143.5 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 2933, 1770, 1428 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67−7.64 (4H, m), 7.45−7.27 (11H, m), 5.62−5.45 (1H, br m), 4.65 (2H, s), 4.35 (1H, m), 3.88, 3.75 (each 1H, dd, J = 12.0, 3.5 Hz), 3.67 (1H, br dd, J = 7.5, 6.0 Hz), 2.66 (1H, m), 2.04−1.96 (1H, m), 1.86−1.01 (10H, m), 1.03 (9H, s); ^{13}C NMR ($CDCl_3$) δ 177.5, 137.1, 135.7, 135.6, 132.9, 132.6, 129.88, 129.86, 128.6, 128.5, 128.1, 127.8, 80.9, 76.7, 63.6, 63.4, 42.1, 37.4, 36.1, 32.9, 32.3, 26.8, 25.1, 25.0, 19.2; HRMS calcd for $C_{34}H_{43}NO_4Si$ (M^+) 557.2959, found 557.2952.

[3*S*-(3α,4*β*,5α)]-Dihydro-5-[[(1,1-dimethylethyl)diphenylsilyloxy]methyl]-4-[[(phenylmethoxy)carbonyl]amino]-3-propyl-2(3*H*)-furanone (28). A suspension of 10% $Pd(OH)_2$−C (629 mg) in MeOH (5 mL) was stirred under a hydrogen atmosphere at room temperature for 30 min. To this suspension was added a solution of **27aA** (500 mg, 0.97 mmol) in MeOH (2 mL). After being stirred under a hydrogen atmosphere at room temperature for 10 h, the reaction mixture was filtered, and the filtrate was concentrated at reduced pressure to afford the crude amine. To a solution of the resulting crude amine in acetone (5 mL) was added a solution of Na_2CO_3 (200 mg, 1.9 mmol) in H_2O (3 mL) under a nitrogen atmosphere at room temperature. After a solution of CbzCl (330 mg, 1.9 mmol) in acetone (2 mL) was added dropwise at room temperature, the reaction mixture was stirred at room temperature for 14 h. After the reaction mixture was concentrated at reduced pressure, the resulting residue was diluted with water and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 4:1) afforded **28** (377 mg, 72%) as a colorless oil: $[\alpha]^{28}_D$ +158.1 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 2962, 1774, 1723, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72−7.63 (4H, m), 7.45−7.22 (11H, m), 5.32 (1H, br m), 4.62 (2H, s), 4.4−4.28 (1H, br m), 4.18−4.09 (1H, br m), 3.86, 3.77 (each 1H, br m), 2.64−2.53 (1H, br m), 1.8−1.3 (4H, m), 1.04 (9H, br s), 0.90 (3H, br t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 176.4, 155.6, 140.6, 135.4, 132.6, 132.4, 129.6, 128.3, 128.2, 127.8, 127.6, 127.2, 126.7, 82.3, 66.7, 64.6, 61.9, 45.6, 30.6, 26.4, 19.4, 18.9, 13.7; HRMS calcd for $C_{32}H_{39}N_{10}O_5Si$ (M^+) 545.2596, found 545.2588.

(2*S*,3*S*,4*S*)-4-Hydroxy-5-[(1,1-dimethylethyl)diphenylsilyloxy]-3-[[(phenylmethoxy)carbonyl]amino]-*N*-phenylmethyl-2-propylpentanamide (29). To a solution of **28** (100 mg, 0.18 mmol) in THF (8 mL) were added benzylamine (0.5 mL, 4.6 mmol) and 2-pyridinol (87 mg, 0.92 mmol) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 20 h, the reaction mixture was concentrated at reduced pressure and then diluted with

Et_2O. The organic phase was washed with 5% HCl, water, and brine, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 2:1) afforded **29** (67.4 mg, 56%) as colorless crystals: mp 145−148 °C (AcOEt/hexane); $[\alpha]^{28}_D$ −8.65 (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) 2962, 1721, 1666, 1428 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65−7.55 (4H, m), 7.45−7.10 (16H, m), 5.98 (1H, br m), 5.43 (1H, br m), 4.66 (2H, s), 4.36, 4.31 (each 1H, d, J = 5.0 Hz), 4.23 (1H, m), 3.97 (1H, m), 3.80−3.60 (2H, br m), 2.41 (1H, br m), 1.75−1.10 (4H, br m), 1.06 (9H, s), 0.86 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 173.4, 156.5, 140.8, 137.9, 135.5, 132.7, 132.4, 129.8, 128.5, 128.4, 128.3, 127.9, 127.73, 127.65, 127.4, 127.3, 126.8, 71.8, 66.7, 65.5, 65.1, 55.5, 43.4, 31.3, 26.8, 20.7, 19.0, 13.9; HRMS calcd for $C_{39}H_{48}N_2O_5Si$ (M^+) 652.3330, found 652.3354.

[3*R*-(3α,4*β*,5α)]-Tetrahydro-3-[(2-methyl)propyl]-5-phenylmethoxy-4-[(phenylmethoxy)amino]-2*H*-pyran-2-one (30). To a solution of **20** (130 mg, 0.38 mmol) and *i*-PrI (0.46 mL, 4.6 mmol) in toluene (20 mL) was added Et_3B (1.0 M in hexane, 1.15 mL, 1.15 mmol) at reflux. After the mixture was stirred at the same temperature for 10 min, *i*-PrI (0.46 mL, 4.6 mmol) and Et_3B (1.0 M in hexane, 1.15 mL, 1.15 mmol) were added to the reaction mixture. After being stirred at the same temperature for 10 min, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 6:1) afforded **30** (26.4 mg, 18%) a colorless oil: $[\alpha]^{22}_D$ +36.28 (*c* 0.69, $CHCl_3$); IR ($CHCl_3$) 3014, 1742, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38−7.22 (10H, m), 5.55 (1H, br s), 5.08 (1H, br m), 4.61 (2H, s), 4.58 (2H, d, J = 11.5 Hz), 4.38 (1H, dd, J = 12, 5.5 Hz), 4.12 (1H, dd, J = 12, 6.5 Hz), 3.92−3.88 (1H, m), 3.45 (1H, br m), 2.89 (1H, br dd, J = 13, 7 Hz), 1.85−1.79 (1H, m), 1.73−1.64 (1H, m), 1.36−1.29 (1H, m), 0.92, 0.91 (each 3H, d, J = 4 Hz); ^{13}C NMR ($CDCl_3$) δ 173.2, 137.6, 137.0, 128.7, 128.6, 128.5, 128.1, 128.0, 127.7, 76.6, 72.7, 71.6, 67.5, 61.1, 36.8, 34.4, 25.2, 22.9, 22.0; HRMS calcd for $C_{23}H_{29}NO_4$ (M^+) 383.2095, found 383.2094.

Acknowledgment. We thank a Grant-in-Aid for Scientific Research (B) from Japan Society for the Promotion of Science and the Science Research Promotion Fund of the Japan Private School Promotion Foundation for research grants.

Supporting Information Available: Preparation procedure and characterization data for compounds **1**−**5**, **7**, **9**, **15**, **16**, **19**, **20**, and **23**−**26**, NOESY data for **27aA**−**27dA**, and ^1H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0341057