Radical Cyclization in Heterocycle Synthesis. 6.[1] A New Entry to Cyclic Amino Alcohols via Stannyl Radical Cyclization of Oxime Ethers Connected with Aldehydes or Ketones

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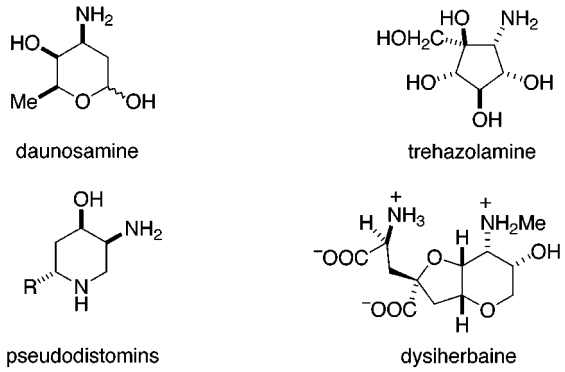
Oxime ethers connected by a tether to aldehydes or ketones efficiently cyclize via stannyl radical addition−cyclization to provide a new entry to cyclic amino alcohols. Upon treatment with tributyltin hydride in the presence of AIBN, oxime ethers connected with either an aldehyde or a ketone via a nitrogen atom smoothly underwent stannyl radical addition−cyclization to give five- to seven-membered cis- and trans-heterocyclic amino alcohols of which the trans-isomers were major products. The newly found radical cyclization provides a novel method for preparing not only bifunctionalized heterocyclic compounds but also adjacently functionalized amino alcohols carrying two quaternary carbons.

Introduction

Though free radical reactions have stimulated the research interest of organic chemists for nearly a century, it is only in the last two decades that this knowledge has been widely utilized in various areas of organic chemistry.[2] Strategies involving radical reactions have become potential tools in organic synthesis, in particular; free radical-mediated cyclization has developed as a preeminent method for preparing diverse cyclic compounds via carbon−carbon bond-forming processes. In the known[2] radical cyclizations, the majority employ methods utilizing conventional radical acceptors such as alkenes or typical radical precursors such as halides, selenides, and xanthates. One drawback in the traditional procedures using such radical acceptors and precursors is known to be loss of the inherent functional groups.

We have recently explored a new efficient carbon−carbon bond-forming reaction based on the radical addition−cyclization of oxime ethers tethered to either a carbonyl[1,3] or an alkene group[4] for the synthesis of highly functionalized cyclic compounds. In this paper, we describe full details of a new entry to cyclic amino alcohols via stannyl radical addition−cyclization. The newly found radical addition−cyclization provides a synthetically useful method for the construction of cyclic amino alcohols widely found in biologically active natural products such as amino sugars,[5] amino cyclitols,[6] pseudodistomins,[7] dysiherbaine,[8] and related compounds (Chart 1).

Chart 1



Results and Discussion

Preparation and Radical Addition−Cyclization of Oxime Ethers Connected with Carbonyl Groups. There have been a few examples of the radical cyclization of oxime ethers connected with a carbonyl group employing either zinc−TMSCl,[9] an electroreduction method,[10] or SmI_2.[11,12] During the course of this study, the Fallis and Fu groups have independently reported the related

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(2) For recent reviews, see: (a) Fossey, J.; Lefort, D.; Sorba, J. In *Free Radicals in Organic Chemistry*; Translated by Lomas, J.; John Wiley & Sons Inc.: New York, 1995; pp 151−158 and pp 243−255. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177−194. (c) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339−364. (d) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React. (N.Y.)* **1996**, *48*, 301−856.

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(4) Miyata, O.; Muroya, K.; Koide, J.; Naito, T. *Synlett* **1998**, 271−272.

(5) For recent syntheses of daunosamine, see: (a) Sibi, M. P.; Lu, J.; Edwards, J, *J. Org. Chem.* **1997**, *62*, 5864−5872. For a review of synthesis of 3-aminosugars, see: (b) Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35−67.

(6) For recent syntheses of trehazolamine, see: (a) Boiron, A.; Zillig, P.; Giese, B. *J. Org. Chem.* **1998**, *63*, 5864−5882. (b) De Gracia, I. S.; Dietrich, H.; Bobo, S.; Chiara, J. L. *J. Org. Chem.* **1998**, *63*, 5883−5889.

(7) For recent works on pseudodistomins, see: (a) Doi, Y.; Ishibashi, M.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 4573−4580. (b) Kobayashi, J.; Ishibashi, M. *Heterocycles* **1996**, *42*, 943−970. (c) Freyer, A. J.; Patil, A. D.; Killmer, L.; Troupe, N.; Mentzer, M.; Carte, B.; Faucette, L.; Johnson, R. K. *J. Nat. Prod.* **1997**, *60*, 986−990. (d) Ninomiya, I.; Kiguchi, T.; Naito, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1998; Vol. 50, pp 317−342. (e) Kiguchi, T.; Ikai, M.; Shirakawa, M.; Fujimoto, K.; Ninomiya, I.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 893−900.

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(9) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821−2824.

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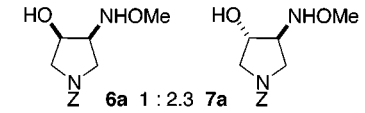
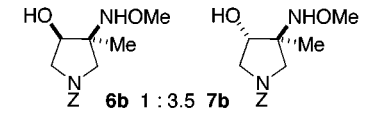
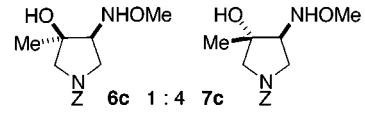
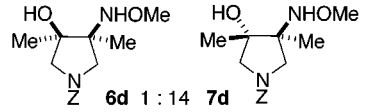
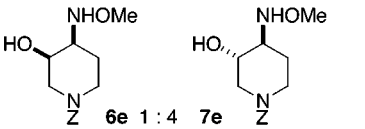
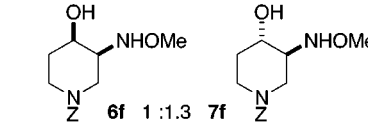
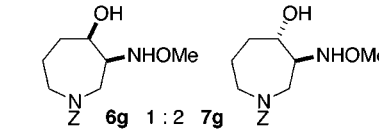
studies on the radical cyclizations using a hydrazone[13] or a carbonyl group[14] as a radical acceptor.

To disclose the scope and limitations of stannyl radical addition−cyclization of oxime ethers, we focused our attention on a systematic study employing readily available starting compounds in which two functional groups, oxime ether and carbonyl groups, are connected with a nitrogen atom with different carbon chains. The requisite substrates **5a**−**h** for the radical reaction were prepared via three different routes depending upon the stability of the substrates. The amino alcohols **1** were alkylated with an appropriate alkyl chloride having the oxime ether group, followed by protection by acylation with benzyloxycarbonyl chloride (Z-chloride) to give the alcohols **3a,c**−**d,f**−**h**. The alcohol **3e** was prepared via a slightly different route involving the alkylation of **1** with 3-chloropropionaldehyde diethyl acetal and exchange of the acetal group to the oxime ether. Oxidation of **3a,c**−**h** with CrO_3−pyridine gave the desired oxime ethers **5a,c**−**h**. The most unstable substrate **5b** was prepared via the reduction of the ester group of **4** by DIBALH reduction. The *E*/*Z* geometrical ratios of the aldoxime ether group in **3** and **5** thus prepared were deduced by ^{1}H NMR spectroscopy. In general, the signals due to the imino hydrogen of the *E*-aldoxime ether are shifted downfield by the influence of the alkoxy group of the aldoxime ether moiety.[15] In the case of **5a**, a signal due to the imino hydrogen of the *E*-isomer (δ 7.18) was shifted downfield with respect to that of *Z*-isomer (δ 6.82).

Bartlett[16] has reported that the geometry of the oxime ether group does not influence the trans/cis selectivity of radical cyclization. Therefore, we investigated the radical addition−cyclization of a geometrical mixture of oxime ethers **5** without their isolation[17] (Table 1). A solution containing tributyltin hydride (2 equiv) and AIBN (0.2 equiv) in benzene was added dropwise (10 mL/h) to a solution of the oxime ether **5a** in boiling benzene while stirring under nitrogen. The solution was then refluxed for a further 3 h to give a 1:2.3 mixture of the cyclized cis- and trans-products **6a** and **7a**. Other examples of the cyclization are shown in Table 1. Under the same condition, the ketoxime ether **5b** carrying a formyl group gave almost the same result, leading to the formation of a 1:3.5 mixture of cis- and trans-products **6b** and **7b**. In the case of **5c** carrying a ketone carbonyl group, the reaction took place slowly compared with the substrates **5ab** having a formyl group, even in the presence of 1 equiv of AIBN, to afford a mixture of two cyclized compounds **6c** and **7c**. It is important to note that ketoxime ether **5d** connected with the ketone carbonyl group underwent the highly stereoselective radical cyclization to afford the cyclic amino alcohols **6d** and **7d** containing two adjacent quaternary carbons as a cis/trans mixture in a 1:14 ratio. Employment of 0.2 equiv of AIBN (conditions A) gave the products **6d** and **7d** in only 16% yield while an increased amount (1 equiv) of AIBN (conditions B) improved the yield to 38% yield. Furthermore, the addition of AIBN (1 equiv) in five portions of 20% each over 1 h (conditions C) improved the yield to 61% as a result of high concentration of AIBN.

The Fu group[18] has recently reported that attempted stannyl radical addition−cyclization of ketoxime ether connected with the ketone carbonyl group via only a carbon chain was unsuccessful. This remarkably different result would be explained as follows. **5d** would be more cyclizable than Fu's substrate due to the presence of the *N*-Z group which would put the ketone carbonyl and ketoxime ether groups in close proximity, thereby accelerating the cyclization.

Table 1. Radical Cyclization of 5

Entry	Substrate	Products	Yield[a] Conditions[b]
1	**5a**	 **6a** 1 : 2.3 **7a**	54%, A
2	**5b**	 **6b** 1 : 3.5 **7b**	48%,[c] A
3	**5c**	 **6c** 1 : 4 **7c**	52%, A 65%, B
4	**5d**	 **6d** 1 : 14 **7d**	16%, A 38%, B 61%, C
5	**5e**	 **6e** 1 : 4 **7e**	71%, A
6	**5f**	 **6f** 1 :1.3 **7f**	62%, A
7	**5g**	 **6g** 1 : 2 **7g**	44%, A 71%, B

[a] Isolated yield. [b] Procedure A, B, C: see Experimental Section. [c] Yield from **4**.

(11) (a) Chiara, J. L.; Marco-Contelles, J.; Khiar, N.; Gallego, P.; Destabel, C.; Bernabé, M. *J. Org. Chem.* **1995**, *60*, 6010−6011. (b) Grove, J. J. C.; Holzapfel, C. W. *Tetrahedron Lett.* **1997**, *38*, 7429−7432. (c) 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*, 7397−7412.

(12) For our recent work in the radical cyclization of oxime ethers connected by a tether to aldehydes by use of SmI_2, see: Miyabe, H.; Kanehira, S.; Kume, K.; Kandori, H., Naito, T. *Tetrahedron* **1998**, *54*, 5883−5892. See also ref 1.

(13) Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447−7448.

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(15) (a) McCarty, C. G. In *The Chemistry of Functional Groups; The chemistry of the carbon−nitrogen double bond*, Patai, S., Ed.; John Wiley & Sons Inc.: New York, 1970; pp 383−392. (b) Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martines-Grau, A. *J. Org. Chem.* **1992**, *57*, 2625−2631.

(16) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633−1634.

(17) We have also reported that the geometry of the oxime ether group does not influence the stereoselectivity in its radical cyclization, see ref 1.

(18) Tormo, J.; Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 201−202.

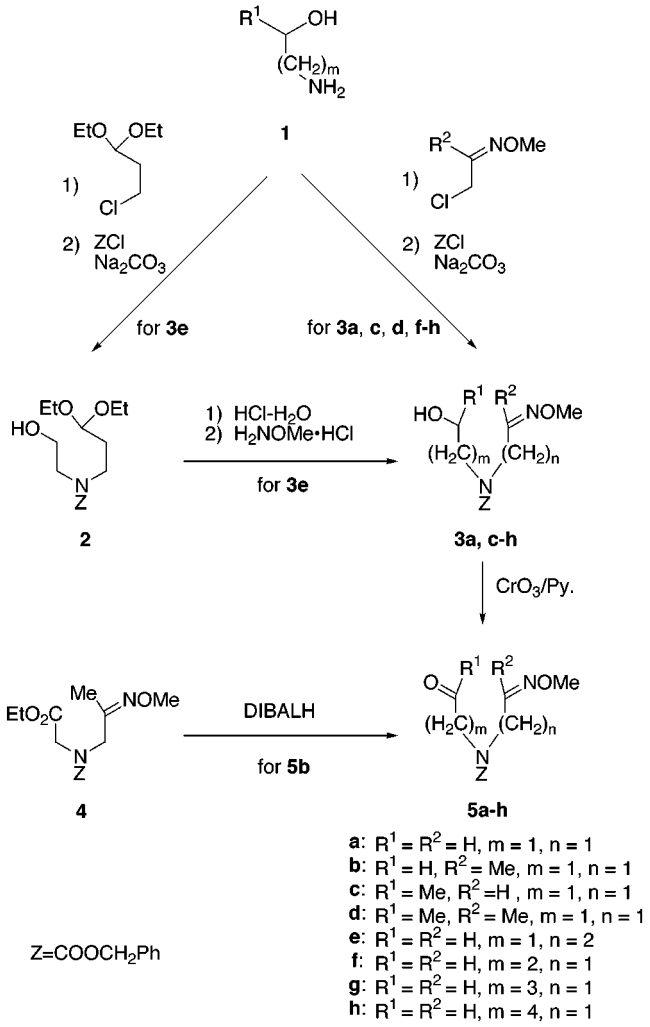
The newly found radical addition−cyclization was successfully extended to the oxime ethers **5e**−**g** connected with the formyl group via four or five atoms and gave six- and seven-membered cyclic products **6e**−**g** and **7e**−**g** of which trans-isomers **7e**−**g** were major products in every case. The yield of seven-membered products **6g** and **7g** improved from 44 to 71% yield when an increased equivalent (1 equiv) of AIBN was used. Irrespective of the length of the carbon chain between nitrogen and either the carbonyl or oxime ether group, the radical addition−cyclization proceeded smoothly to give the cyclic compounds **6** and **7** which were adjacently functionalized with the alkoxyamino and hydroxyl groups. However, attempted formation of an eight-membered product was unsuccessful, and the starting compound **5h** was mostly recovered. In every case, the two stereoisomeric products were readily separated by repeated chromatography.

These results may suggest the following three characteristic points. First, the radical addition−cyclization of aldo- or ketoxime ether connected via a nitrogen atom with a formyl or ketone carbonyl group proceeds smoothly to give a mixture of five- to seven-membered cis- and trans-cyclic amino alcohols of which the trans-isomers are major products. Second, the reaction takes place exclusively in *exo-trig* manner, and no *endo-trig* products were formed. Third, the reduction products of neither the carbonyl nor the oxime ether group are formed, and employment of a stoichiometric amount of AIBN and its portionwise addition improves the cyclization yield.

Stereostructures of Cyclized Products and Proposed Reaction Pathway. The stereostructures of five-membered cyclized products **6a**−**d** and **7a**−**d** were firmly established by the chemical reactions in addition to their spectral data (Scheme 2). Treatment of cis-amino alcohols **6a**−**d** with dimethoxypropane (DMP) and *p*-TsOH gave their corresponding acetonides **8a**−**d** while trans-congeners **7a**−**d** were recovered completely under the same reaction condition. Though the stereostructures of six-membered products **6ef** and **7ef** were deduced from their spectra, particularly ^{1}H NMR spectroscopies, those of seven-membered congeners **6g** and **7g** were firmly established by the chemical conversion of one isomer **7g** into the authentic sample[1] which was already characterized and employed as a crucial intermediate for the total synthesis of (−)-Balanol. The polar isomer **7g** was converted into *N*-Boc trans-amino alcohol **9** which was identical with the authentic sample[1] used for Balanol synthesis.

Next, we propose the possible reaction pathway of the stannyl radical addition−cyclization of oxime ethers in this study as follows (Scheme 3). The stannyl radical is known to be oxygenphilic[19] and, therefore, attacks the carbonyl group to form the ketyl radical **A** which would be trapped intramolecularly with the oxime ether. The oxime ether group is known[20,21] to be an excellent radical acceptor, and the resulting alkoxyaminyl radical **B** is stabilized by the adjacent oxygen atom. Therefore, the *exo-trig* cyclization would be favored over an *endo-trig* process. The trans-selectivity would be explained by the

Scheme 1



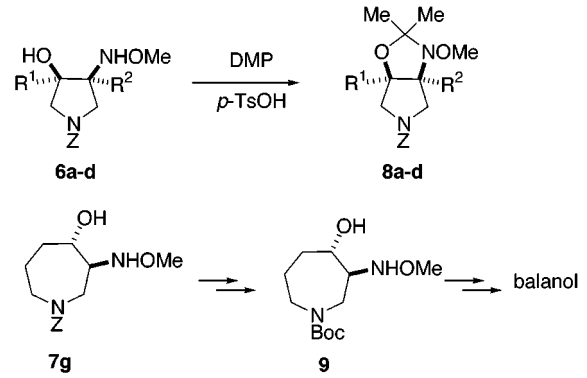
electronic repulsion[22] between the stannyloxy group and the nitrogen and/or oxygen atom in the oxime ether group in the transition state **C**. Possible steric repulsion

(19) For selected examples of the radical cyclization of *O*-stannyl ketyl radical to alkenes, see: (a) Enholm, E. J.; Prasad, G. *Tetrahedron Lett.* **1989**, *30*, 4939−4942. (b) Enholm, E. J.; Burroff, J. A. *Tetrahedron Lett.* **1992**, *33*, 1835−1838. (c) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4−5. (d) Enholm, E. J.; Burroff, J. A. *Tetrahedron* **1997**, *53*, 13583−13602. (e) Parson, A. F.; Pettifer, R. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 651−660.

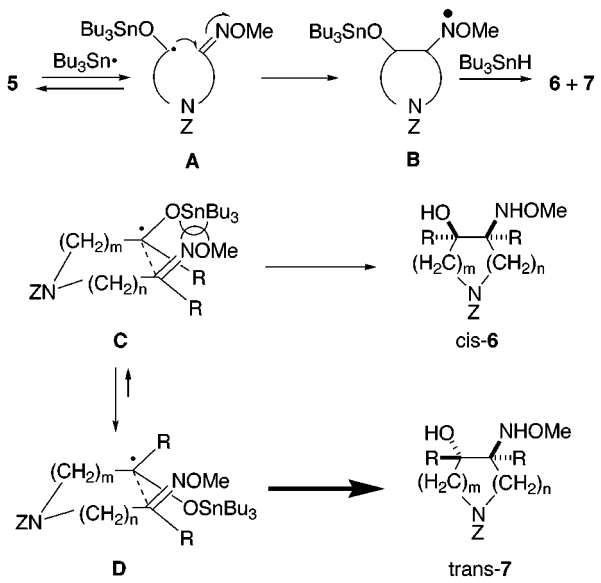
(20) For selected examples of intramolecular radical addition to oxime ethers published in recent five years, see: (a) Grissom, J. W.; Klingberg, D.; Meyenburg, S.; Stallman, B. L. *J. Org. Chem.* **1994**, *59*, 7876−7888. (b) Parker, K. A.; Fokas, D. *J. Org. Chem.* **1994**, *59*, 3927−3932. (c) Della, E. W.; Knill, A. M. *Aust. J. Chem.* **1994**, *47*, 1833−1841. (d) Booth, S. E.; Jenkins, P. R.; Swain, C. J.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3499−3508. (e) Chiara, J. L.; Marco-Contelles, J.; Khiar, N.; Gallego, P.; Destabel, C.; Bernabé, M. *J. Org. Chem.* **1995**, *60*, 6010−6011. (f) Keck, G. E.; McMardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289−7290. (g) Santagostino, M.; Kilburn, J. D. *Tetrahedron Lett.* **1995**, *36*, 1365−1368. (h) Hollingworth, G. J.; Pattenden, G.; Schulz, D. J. *Aust. J. Chem.* **1995**, *48*, 381−399. (i) Marco-Contelles, J.; Destael, C.; Chiara, J. L.; Bernabé, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1547−1550. (j) Bhat, B.; Swayze, E. E.; Wheeler, P.; Dimock, S.; Perbost, M.; Sanghvi, Y. S. *J. Org. Chem.* **1996**, *61*, 8186−8199. (k) Kim, S.; Lee, I. Y.; Yoon, J.-Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138−5139. (l) Keck, G. E.; Wager, T. T. *J. Org. Chem.* **1996**, *61*, 8366−8367. (m) Marco-Contelles, J.; Destabel, C.; Gallego, P.; Chiara, J. L.; Bernabé, M. *J. Org. Chem.* **1996**, *61*, 1354−1362. (n) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594. (o) Kim, S.; Kim, Y.; Yoon, K. S. *Tetrahedron Lett.* **1997**, *38*, 2487−2490. (p) Marco-Contelles, J.; Balme, G.; Bouyssi, D.; Destabel, C.; Henriet-Bernard, C. D.; Grimaldi, J.; Hatem, J. M. *J. Org. Chem.* **1997**, *62*, 1202−1209. (q) Clive, D. L. J.; Zhang, J. *Chem. Commun.* **1997**, 549−550.(r) Noya, B.; Alonso, R. *Tetrahedron Lett.* **1997**, *38*, 2745−2748. (s) Martínez-Grau, A.; Marco-Contelles, J. *Chem. Soc. Rev.* **1998**, *27*, 155−162. See also ref 1, 3, 15b, 16, and 18.

(21) For our recent works in intermolecular radical addition to oxime ethers, see: (a) Miyabe, H.; Ushiro, C.; Naito, T. *Chem. Commun.* **1997**, 1789−1790. (b) Miyabe, H.; Shibata, R.; Ushiro, C.; Naito, T. *Tetrahedron Lett.* **1998**, *39*, 631−634. (c) Miyabe, H.; Shibata, R.; Sangawa, M.; Ushiro, C.; Naito, T. *Tetrahedron* **1998**, *54*, 11431−11444.

Scheme 2



Scheme 3



between the R group (particularly Me) and the oxime ether group or the stannyloxy group would be not so large because the oxime ethers **5bc** gave preferably trans-products **7bc** as the main isomer via the transition state **D**. Steric repulsion between two methyl groups overlapped with electron repulsion as mentioned above to increase the instability of the transition state **C**, thus giving trans-isomer **7d** with high stereoselectivity.[23]

Conclusion

We have developed a general method for the intramolecular cyclization of oxime ethers tethered via a nitrogen atom to carbonyl groups, which is a promising synthetic method for preparing five- to seven-membered heterocycles functionalized adjacently with the amino and hydroxyl groups.

Experimental Section

General. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 60, 200, 300, or 500 MHz and at 75 or 125 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI method. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck 60F_{254}). Medium-pressure column chromatography was performed using Lobar grösse B (E. Merck 310−25, Lichroprep Si60). Flash column chromatography was performed using E. Merck Kieselgel 60 (230−400 mesh). Short column chromatography was undertaken on a short glass filter using E. Merck Kieselgel 60 (230−400 mesh) under reduced pressure.

General Procedure for Preparation of Alcohols 3. To a solution of amino alcohol **1** (150 mmol) in MeOH (150 mL) was added chloroacetaldehyde *O*-methyloxime[24] or chloroacetone *O*-methyloxime[25] (50 mmol) under a nitrogen atmosphere at 0 °C. The reaction mixture was heated at reflux for 3 h. After the solvent was evaporated at reduced pressure, the resulting residue was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. To a solution of the resulting residue in acetone (100 mL) was added a solution of Na_2CO_3 (50 mmol) in H_2O (25 mL) under a nitrogen atmosphere at room temperature. After a solution of benzyloxycarbonyl chloride (ZCl) (55 mmol) in acetone (10 mL) was added dropwise at 0 °C, the reaction mixture was stirred at room temperature for 3 h. The resulting solution was filtered through a pad of Celite, the filtrate was concentrated at reduced pressure, and the residue was diluted with H_2O and extracted with $CHCl_3$. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography or flash column chromatography (AcOEt/hexane 1:1−2:1) afforded **3** as colorless oils and mixtures of *E*/*Z*-oxime for **3a,c,f**−**h** and a mixture of rotamers for **3d**.

Phenylmethyl (2-Hydroxyethyl)[2-(methoxyimino)ethyl]carbamate (3a): yield 40%; IR ($CHCl_3$) 3447 (OH), 1697 (NCOO) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45−7.30 (28/5H, m), 6.75 (2/5H, m), 5.18 (2H, s), 4.25 (4/5H, m), 4.16 (6/5H, m), 3.90 (6/5H, s), 3.84 (9/5H, s), 3.82−3.41 (4H, m); HRMS (EI, *m*/*z*) calcd for $C_{13}H_{18}N_2O_4$ (M^+) 266.1265, found 266.1251.

Phenylmethyl (2-Hydroxypropyl)[2-(methoxyimino)ethyl]carbamate (3c): yield 60%; IR ($CHCl_3$) 3640−3220 (OH), 1696 (NCOO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.31 (28/5H, m), 6.73 (2/5H, m), 5.15 (2H, s), 4.21−3.92 (3H, m), 3.86 (6/5H, s), 3.81 (9/5H, s), 3.40−3.15 (2H, m), 1.17 (6/5H, d, J = 6 Hz), 1.16 (9/5H, d, J = 6 Hz); HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}N_2O_4$ (M^+) 280.1422, found 280.1438.

Phenylmethyl (2-Hydroxypropyl)[2-(methoxyimino)propyl]carbamate (3d): yield 39%; IR ($CHCl_3$) 3640−3350 (OH), 1697 (NCOO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.20 (5H, m), 5.17 (2H, s), 4.20−3.90 (3H, m), 3.80 (3H, s), 3.40−3.15 (2H, m), 1.85 (1H, br s), 1.73 (2H, br s), 1.17 (3H, m); HRMS (EI, *m*/*z*) calcd for $C_{15}H_{22}N_2O_4$ (M^+) 294.1578, found 294.1572.

Phenylmethyl (3-Hydroxypropyl)[2-(methoxyimino)ethyl]carbamate (3f): yield 34%; IR ($CHCl_3$) 3640−3350 (OH), 1686 (NCOO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.28 (28/5H, m), 6.63 (2/5H, br t, J = 4 Hz), 5.15 (2H, s), 4.15−3.38 (7H, m), 3.87 (6/5H, s), 3.83 (9/5H, s), 1.79−1.65 (2H, m); HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}N_2O_4$ (M^+) 280.1422, found 280.1412.

Phenylmethyl (4-Hydroxybutyl)[2-(methoxyimino)ethyl]carbamate (3g): yield 57%; IR ($CHCl_3$) 3650−3355 (OH), 1694 (NCOO) cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.53−7.26 (28/5H, m), 6.75 (2/5H, m), 5.25 (2H, s), 4.48−3.25 (6H, m), 3.99 (6/5H, s), 3.95 (9/5H, s), 2.23−1.46 (4H, m); HRMS (EI, *m*/*z*) calcd for $C_{15}H_{22}N_2O_4$ (M^+) 294.1579, found 294.1582.

Phenylmethyl (4-Hydroxypentyl)[2-(methoxyimino)ethyl]carbamate (3h): yield 30%; IR ($CHCl_3$) 3630−3340 (OH), 1694 (NCOO) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.22 (28/5H, m), 6.75 (2/5H, m), 5.12 (2H, s), 4.16−3.18 (6H, m), 3.87 (6/5H, s), 3.82 (9/5H, s), 1.68−1.21 (6H, m); HRMS (EI, *m*/*z*) calcd for $C_{16}H_{24}N_2O_4$ (M^+) 308.1735, found 308.1732.

(22) In the electroreductive cyclization of oxime ethers connected by a tether to aldehydes, the trans-selectivity was explained by the electronic repulsion between negative charge located on the oxygen and nitrogen atom in the oxime ethers, see ref 10.

(23) Recently Fu group has reported that cis-selectivity is observed in stannyl radical addition−cyclization of dicarbonyl compounds and is explained via 1,3,2-dioxastannolane as a cyclic intermediate, see ref 14.

(24) Stach, L. J. U.S. Patent 3920772, 1975 (*Chem. Abstr.* **1976**, *84*, 89603d).

(25) See the Supporting Information.

Phenylmethyl (3,3-Diethoxypropyl)(2-hydroxyethyl)-carbamate (2). To 2-amino-1-ethanol (3 g, 50 mmol) was added 3-chloropropionaldehyde diethylacetal (4.4 g, 25 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at room temperature for 48 h, the reaction mixture was diluted with 10% NaOH solution and extracted with AcOEt. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure to afford the crude amine. Following the same procedure as for **3**, the crude amine was protected with the Z group to give **2** (3 g, 37%) as a colorless oil after purification by medium-pressure column chromatography (AcOEt/hexane 3:1): IR ($CHCl_3$) 3436 (OH), 1691 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.29 (5H, m), 5.13 (2H, s), 4.52 (1H, m), 3.75 (2H, m), 3.68−3.32 (8H, m), 1.92 (2H, m), 1.56 (6H, t, J = 7 Hz); HRMS (EI, m/z) calcd for $C_{17}H_{27}NO_5$ (M^+) 325.1887, found 325.1915.

Phenylmethyl (2-Hydroxyethyl)[3-(methoxyimino)-propyl]carbamate (3e). To a solution of **2** (1.3 g, 4.0 mmol) in acetone (11 mL) was added 5 M HCl (12.5 mL) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 4 h, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure to afford the crude aldehyde. To a solution of the resulting crude aldehyde in MeOH (23 mL) were successively added NaOAc (754 mg, 9.2 mmol) and $NH_2OMe{\cdot}HCl$ (764 mg, 9.2 mmol) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated at reduced pressure. The resulting residue was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 2:1) afforded **3e** (1.12 g, 99%) as a colorless oil and a mixture of *E*/*Z*-oxime: IR ($CHCl_3$) 3436 (OH), 1693 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.23 (28/5H, m), 6.68 (2/5H, m), 5.13 (2H, s), 3.84 (6/5H, s), 3.81−3.65 (19/5H, m), 3.57−3.35 (3H, m), 2.68−2.38 (3H, m); HRMS (EI, m/z) calcd for $C_{14}H_{20}N_2O_4$ (M^+) 280.1422, found 280.1411.

General Procedure for Oxidation of Alcohols 3. To a solution of pyridine (24 mmol) in CH_2Cl_2 (30 mL) was portionwise added CrO_3 (12 mmol) under a nitrogen atmosphere at room temperature. After the solution was stirred at room temperature for 15 min, a solution of **3** (2 mmol) in CH_2Cl_2 (8 mL) was added to the reaction mixture. The reaction mixture was stirred at the same temperature for 2 h and then the solvent was evaporated at reduced pressure. The resulting residue was diluted with Et_2O and filtered through a pad of Celite, and the filtrate was concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography or flash column chromatography (AcOEt/hexane 1:1−3:2) afforded **5** as colorless oils and mixtures of *E*/*Z*-oxime for **5a,c,e**−**h** and a mixture of rotamers for **5d**. After being characterized by ^1H NMR spectra, unstable aldehydes **5a,e**−**h** were immediately subjected to the following radical cyclization.

Phenylmethyl [2-(Methoxyimino)ethyl](2-oxoethyl)-carbamate (5a): yield 34%; ^1H NMR (200 MHz, $CDCl_3$) δ 9.61 (1H, m), 7.48−7.29 (5H, m), 7.18 (2/5H, br t, J = 8 Hz), 6.82 (3/5H, br t, J = 8 Hz), 5.18 (2H, s), 4.50−3.69 (4H, m), 3.88 (9/5H, s), 3.84 (6/5H, s).

Phenylmethyl [2-(Methoxyimino)ethyl](2-oxopropyl)-carbamate (5c): yield 70%; IR ($CHCl_3$) 1720 (CO), 1705 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.23 (28/5H, m), 6.82 (2/5H, dd, J = 9, 5 Hz), 5.15 (6/5H, s), 5.10 (4/5H, s), 4.18−3.99 (4H, m), 3.84 (6/5H, s), 3.80 (9/5H, s), 2.13 (9/5H, s), 2.05 (6/5H, s); HRMS (EI, m/z) calcd for $C_{14}H_{18}N_2O_4$ (M^+) 278.1265, found 278.1255.

Phenylmethyl [2-(Methoxyimino)propyl](2-oxopropyl)carbamate (5d): yield 73%; IR ($CHCl_3$) 1737 (COO), 1702 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (5H, m), 5.18 (1H, s), 5.12 (1H, s), 4.20−3.95 (4H, m), 3.82 (3/2H, s), 3.81 (3/2H, s), 2.14, 2.05, 1.85, 1.77 (each 3/2H, s); HRMS (EI, m/z) calcd for $C_{15}H_{20}N_2O_4$ (M^+) 292.1422, found 292.1433.

Phenylmethyl [3-(Methoxyimino)propyl](2-oxoethyl)-carbamate (5e): yield 48%; ^1H NMR (60 MHz, $CDCl_3$) δ 9.47 (1H, m), 7.40−7.12 (28/5H, m), 6.55 (2/5H, m), 5.12 (2H, s), 4.08−3.85 (2H, m), 3.82 (6/5H, s), 3.73 (9/5H, s), 3.62 (2H, br t, J = 6 Hz), 2.48 (2H, m).

Phenylmethyl [2-(Methoxyimino)ethyl](3-oxopropyl)-carbamate (5f): yield 59%; ^1H NMR (60 MHz, $CDCl_3$) δ 9.72 (1H, m), 7.45−7.11 (28/5H, m), 6.59 (2/5H, br t, J = 4.5 Hz), 5.12 (2H, s), 4.24−3.37 (4H, m), 3.82 (6/5H, s), 3.79 (9/5H, s), 2.89−2.39 (2H, m).

Phenylmethyl [2-(Methoxyimino)ethyl](4-oxobutyl)-carbamate (5g): yield 58%; ^1H NMR (60 MHz, $CDCl_3$) δ 9.58 (1H, m), 7.38−7.10 (28/5H, m), 6.59 (2/5H, m), 5.12 (2H, s), 4.22−3.12 (4H, m), 3.84 (6/5H, s), 3.79 (9/5H, s), 2.61−1.50 (4H, m).

Phenylmethyl [2-(Methoxyimino)ethyl](5-oxopentyl)-carbamate (5h): yield 81%; ^1H NMR (60 MHz, $CDCl_3$) δ 9.58 (1H, m), 7.38−7.10 (28/5H, m), 6.59 (2/5H, m), 5.14 (2H, s), 4.18−3.92 (2H, m), 3.87 (6/5H, s), 3.82 (9/5H, s), 3.42−3.22 (2H, m), 2.52−2.32 (2H, m), 1.68−1.48 (4H, m).

Phenylmethyl (Ethoxycarbonylmethyl)[2-(methoxyimino)propyl]carbamate (4). To a solution of glycine ethyl ester HCl (17.2 g, 123 mmol) and Et_3N (9.6 g, 95 mmol) in EtOH (125 mL) was added chloroacetone *O*-methyloxime (5 g, 41 mmol) under a nitrogen atmosphere at 0 °C. The reaction mixture was heated at reflux for 3 h. After the solvent was evaporated at reduced pressure, the resulting residue was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. To a solution of the resulting residue in acetone (70 mL) was added a solution of Na_2CO_3 (4.3 g, 41 mmol) in H_2O (20 mL) under a nitrogen atmosphere at room temperature to give the crude amine. Following the same procedure as for **3**, the crude amine was protected with the Z group to give **4** (6.3 g, 48%) as a colorless oil and a mixture of rotamers after purification by flash column chromatography (AcOEt/hexane 1:4): IR ($CHCl_3$) 1748 (COO), 1702 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.30 (5H, m), 5.19 (1H, s), 5.16 (1H, s), 4.26−3.90 (6H, m), 3.83 (3/2H, s), 3.82 (3/2H, s), 1.86 (3/2H, s), 1.78 (3/2H, s), 1.26 (3/2H, t, J = 7 Hz), 1.18 (3/2H, t, J = 7 Hz); HRMS (EI, m/z) calcd for $C_{16}H_{22}N_2O_5$ (M^+) 322.1527, found 322.1540.

Phenylmethyl [2-(Methoxyimino)propyl](2-oxoethyl)-carbamate (5b). To a solution of **4** (1 g, 3.1 mmol) in dry Et_2O (55 mL) was added dropwise DIBALH (0.95 mol in hexane) (4.9 mL, 4.65 mmol) under a nitrogen atmosphere at −78 °C. After the mixture was stirred at the same temperature for 1.5 h, H_2O (0.55 mL) was added to the reaction mixture, and the reaction mixture was allowed to warm to room temperature. After the solution was stirred at room temperature for 0.5 h, AcOEt and Celite were added to the reaction mixture, and the whole was stirred at the same temperature for a further 0.5 h. The resulting solution was filtered through a pad of Celite, and the filtrate was washed with H_2O and brine. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure to afford the crude aldehyde **5b** as a pale yellow oil and a mixture of rotamers. After being characterized by NMR spectra, unstable **5b** was immediately subjected to the following radical cyclization: ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 (1/2H, s), 9.53 (1/2H, s), 7.50−7.20 (5H, m), 5.18 (2H, br s), 4.30−3.90 (4H, m), 3.82 (3H, br s), 1.85 (3/2H, s), 1.76 (3/2H, s).

General Procedure for Radical Cyclization. Conditions A. To a boiling solution of **5** (1.5 mmol) in benzene (12 mL) was added dropwise (10 mL/h) a solution of Bu_3SnH (3 mmol) and AIBN (0.3 mmol) in benzene (7 mL) under a nitrogen atmosphere. The reaction mixture was heated at reflux for a further several hours as shown (**5a**, 3 h; **5b**, 2 h; **5c**, 7 h; **5d**; 2 h; **5e**, 6 h; **5f**, 4 h; **5g**, 7 h), and then the solvent was evaporated at reduced pressure. The resulting residue was diluted with acetonitrile, and the acetonitrile phase was washed with hexane and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt/hexane 1:1−4:1) afforded **6** and **7**. The presence of rotamers precluded a comprehensive assignment of all proton and carbon resonances.

Conditions B. To a boiling solution of **5** (1.5 mmol) in benzene (12 mL) was added dropwise (10 mL/h) a solution of Bu_3SnH (3 mmol) and AIBN (1.5 mmol) in benzene (7 mL) under a nitrogen atmosphere. The reaction mixture was heated at reflux for 9 h followed by workup as in conditions A.

Conditions C. To a boiling solution of **5** (1.5 mmol) in benzene (12 mL) was added dropwise (10 mL/h) a solution of Bu_3SnH (3 mmol) and AIBN (0.3 mmol) in benzene (7 mL) under a nitrogen atmosphere. The reaction mixture was heated at reflux, and additional solution of AIBN (0.3 mmol) in benzene (3 mL) was added four times at 1 h intervals. After 6 h (total), the reaction mixture was treated by workup as in conditions A.

Phenylmethyl *cis*-3-Hydroxy-4-(methoxyamino)-1-pyrrolidinecarboxylate (6a): yield 16% (conditions A); a colorless oil; IR ($CHCl_3$) 3600−3300 (OH, NH), 1697 (NCOO) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45−7.24 (5H, m), 5.95 (1H, br s), 5.11 (2H, s), 4.31 (1H, m, 3-H), 3.75−3.28 (5H, m), 3.55 (3H, s), 3.17 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 136.7, 128.5, 128.0, 127.9, 69.1, 68.3, 67.0, 62.4, 62.3, 62.2, 61.6, 53.2, 52.9, 45.8, 45.7; HRMS (EI, *m*/*z*) calcd for $C_{13}H_{18}N_2O_4$ (M^+) 266.1265, found 266.1244.

Phenylmethyl *trans*-3-Hydroxy-4-(methoxyamino)-1-pyrrolidinecarboxylate (7a): yield 38% (conditions A); a colorless oil; IR ($CHCl_3$) 3600−3300 (OH, NH), 1692 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.27 (5H, m), 5.65 (1H, br s), 5.10 (2H, s), 4.30 (1H, m), 4.24−4.22 (3H, m), 3.74−3.22 (5H, m), 3.52 (3H, s), 2.62 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 138.7, 130.6, 130.1, 130.0, 74.6, 73.7, 69.1, 68.5, 67.9, 64.9, 64.8, 54.4, 54.0, 49.6, 49.4; HRMS (EI, *m*/*z*) calcd for $C_{13}H_{18}N_2O_4$ (M^+) 266.1265, found 266.1280.

Phenylmethyl *cis*-3-Hydroxy-4-(methoxyamino)-4-methyl-1-pyrrolidinecarboxylate (6b): yield 11% (conditions A); a colorless oil; IR ($CHCl_3$) 3600−3300 (OH, NH), 1698 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.30 (5H, m), 5.95 (1H, br s), 5.12 (2H, s), 3.98 (1H, m), 3.67 (1/2H, dd J = 12, 4.5 Hz), 3.63 (1/2H, dd, J = 12, 5 Hz), 3.56 (3/2H, s), 3.55 (3/2H, s), 3.52 (1H, m), 3.36−3.25 (2H, m), 2.93 (1/2H, br s), 2.83 (1/2H, br s), 1.26 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 136.7, 128.5, 128.0, 127,9, 74.6, 73.8, 66.9, 66.1, 65.3, 63.1, 63.0, 53.1, 52.8, 52.6, 52.4, 20.7; HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}N_2O_4$ (M^+) 280.1422, found 280.1402.

Phenylmethyl *trans*-3-Hydroxy-4-(methoxyamino)-4-methyl-1-pyrrolidinecarboxylate (7b): yield 37% (conditions A); a colorless oil; IR ($CHCl_3$) 3600−3300 (OH, NH), 1697 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.30 (5H, m), 5.37 (1H, br s), 5.12 (1H, s), 5.11 (1H, s), 4.22 (1H, m), 3.84 (1H, m), 3.51 (3/2H, s), 3.50 (3/2H, s), 3.42−3.30 (3H, m), 2.23 (1H, m), 1.26 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 136.7, 128.5, 128.0, 127.9, 73.3, 72.5, 67.3, 67.0, 66.9, 66.4, 66.9, 63.3, 52.8, 52.5, 52.3, 51.9, 16.3; HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}N_2O_4$ (M^+) 280.1422, found 280.1408.

Phenylmethyl *cis*-3-Hydroxy-4-(methoxyamino)-3-methyl-1-pyrrolidinecarboxylate (6c): yield 11% (conditions A), 14% (conditions B); a colorless oil; IR ($CHCl_3$) 3600−3350 (OH, NH), 1692 (NCOO) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45−7.25 (5H, m), 5.87 (1H, br s), 5.11 (2H, s), 3.80−3.20 (5H, m), 3.55 (9/5H, s), 3.54 (6/5H, s), 2.98 (3/5H, s), 2.78 (2/5H, s), 1.40 (6/5H, s), 1.37 (9/5H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 136.7, 128.5, 128.0, 127.9, 75.8, 75.1, 66.9, 65.7, 65.0, 62.3, 62.2, 58.3, 58.0, 47.5, 24.6, 24.5; HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}N_2O_4$ (M^+) 280.1422, found 280.1414.

Phenylmethyl *trans*-3-Hydroxy-4-(methoxyamino)-3-methyl-1-pyrrolidinecarboxylate (7c): yield 41% (conditions A), 51% (conditions B); a colorless oil; IR ($CHCl_3$) 3600−3300 (OH, NH), 1694 (NCOO) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40−7.20 (5H, m), 5.52 (1H, br s), 5.09 (2H, s), 3.86−3.28 (5H, m), 3.48 (3H, s), 2.62 (1H, br s), 1.31 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 136.7, 128.4, 128.0, 127.8, 77.9, 77.1, 67.6, 67.0, 66.9, 62.2, 57.7, 57.4, 48.6, 48.5, 20.8; HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}N_2O_4$ (M^+) 280.1422, found 280.1433.

Phenylmethyl *cis*-3-Hydroxy-4-(methoxyamino)-3,4-dimethyl-1-pyrrolidinecarboxylate (6d): yield 1% (conditions A), 3% (conditions B), 4% (conditions C); a colorless oil; IR ($CHCl_3$) 3600−3300 (OH, NH), 1697 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.28 (5H, m), 5.85 (1H, br s), 5.11 (2H, s), 3.56 (1H, m), 3.55 (3/2H, s), 3.53 (3/2H, s), 3.46 (1/2H, br d, J = 10.5 Hz), 3.45 (1/2H, br d, J = 10.5 Hz), 3.42 (1/2H, d, J = 12 Hz), 3.38 (1/2H, d, J = 11.5 Hz), 3.37 (1/2H, d, J = 10.5 Hz), 3.33 (1/2H, d, J = 10.5 Hz), 3.22 (1/2H, br s), 2.97 (1/2H, br s), 1.32 (3/2H, s), 1.29 (3/2H, s), 1.27 (3/2H, s), 1.26 (3/2H, s); HRMS (EI, *m*/*z*) calcd for $C_{15}H_{22}N_2O_4$ (M^+) 294.1578, found 294.1579.

Phenylmethyl *trans*-3-Hydroxy-4-(methoxyamino)-3,4-dimethyl-1-pyrrolidinecarboxylate (7d): yield 15% (conditions A), 35% (conditions B), 57% (conditions C); a colorless oil; IR ($CHCl_3$) 3600−3300 (OH, NH), 1696 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.28 (5H, m), 5.26 (1 H, br s), 5.14 and 5.11 (1H, ABq, J = 13 Hz), 5.12 (1H, s), 3.68 (1/2H, d, J = 11.5 Hz), 3.67 (1/2H, d, J = 11 Hz), 3.57 (1/2H, br d, J = 11.5 Hz), 3.56 (1/2H, br d, J = 11.5 Hz), 3.48 (3/2H, s), 3.47 (1/2H, d, J = 11 Hz), 3.46 (3/2H, s), 3.44 (1/2H, d, J = 11 Hz), 3.37 (1/2H, d, J = 11 Hz), 3.35 (1/2H, d, J = 11.5 Hz), 1.97 (1/2H, br s), 1.93 (1/2H, br s), 1.25 (3/2H, s), 1.24 (3/2H, s), 1.23 (3/2H, s),1.22 (3/2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 136.8, 128.4, 127.9, 127.8, 78.7, 77.9, 68.8, 68.0, 66.8, 63.0, 58.6, 58.2, 53.1, 52.8, 19.1, 19.0, 15.1, 14.9; HRMS (EI, *m*/*z*) calcd for $C_{15}H_{23}N_2O_4$ [$(M+H)^+$] 295.1656, found 295.1666.

Phenylmethyl *cis*-3-Hydroxy-4-(methoxyamino)-1-piperidinecarboxylate (6e): yield 14% (conditions A); a colorless oil; IR ($CHCl_3$) 3600−3150 (OH, NH), 1692 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (5H, m), 5.13 (2H, s), 4.28 (1H, br d, J = 13 Hz), 4.17 (1H, m), 4.02 (1H, m), 3.55 (3H, s), 3.07 (1H, ddd, J = 12, 6, 4 Hz), 2.96 (1H, br d, J = 13 Hz), 2.88 (1H, m), 1.60 (1H, br qd, J = 12, 4 Hz), 1.45 (1H, br dq, J = 12, 4 Hz); HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}N_2O_4$ (M^+) 280.1422, found 280.1432.

Phenylmethyl *trans*-3-Hydroxy-4-(methoxyamino)-1-piperidinecarboxylate (7e): yield 57% (conditions A); a colorless oil; IR ($CHCl_3$) 3650−3100 (OH, NH), 1692 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (5H, m), 5.10 (2H, s), 4.29 (1H, br d, J = 11 Hz), 4.15 (1H, m), 3.54 (3H, s), 3.53 (1H, m), 2.81 (1H, ddd, J = 12, 9, 4 Hz), 2.78 (1H, m), 2.64 (1H, br t, J = 12 Hz), 1.85 (1H, br dq, J = 12, 4 Hz), 1.45 (1H, br qd, J = 12, 5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 136.5, 128.5, 128.0, 127.9, 69.3, 68.2, 67.4, 64.1, 63.5, 62.9, 48.6, 42.8, 27.8, 27.4 HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}N_2O_4$ (M^+) 280.1422, found 280.1414.

Phenylmethyl *cis*-4-Hydroxy-3-(methoxyamino)-1-piperidinecarboxylate (6f): yield 27% (conditions A); a colorless oil; IR ($CHCl_3$) 3600−3100 (OH, NH), 1692 (NCOO) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.46−7.25 (5H, m), 5.15 (2H, s), 4.04 (1H, dt, J = 6, 4 Hz), 3.80−3.18 (4H, m), 3.52 (3H, s), 3.10 (1H, m), 1.90−1.52 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 136.7, 128.5, 128.1, 127.9, 67.3, 65.4, 62.6, 59.0, 41.7, 39.4, 30.4; HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}N_2O_4$ (M^+) 280.1421, found 280.1421.

Phenylmethyl *trans*-4-Hydroxy-3-(methoxyamino)-1-piperidinecarboxylate (7f): yield 35% (conditions A); a colorless oil; IR ($CHCl_3$) 3600−3100 (OH, NH), 1692 (NCOO) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.46−7.26 (5H, m), 5.14 (2H, s), 4.32 (1H, m), 4.14 (1H, m), 3.64 (1H, ddd, J = 11, 10, 4 Hz), 3.53 (3H, s), 2.96−2.70 (3H, m), 1.98 (1H, m), 1.50 (1H, br qd, J = 12, 4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 136.6, 128.5, 128.1, 127.9, 69.6, 67.3, 62.9, 62.8, 45.3, 42.3, 32.6; HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}N_2O_4$ (M^+) 280.1421, found 280.1417.

Phenylmethyl *cis*-Hexahydro-4-hydroxy-3-(methoxyamino)-1*H*-azepine-1-carboxylate (6g): yield 14% (conditions A), 22% (conditions B); a colorless oil; IR ($CHCl_3$) 3630−3250 (OH, NH), 1694 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.29 (5H, m), 5.73 (1/2H, br s), 5.67 (1/2H, br s), 5.19−5.12 (2H, m), 4.08 (1H, m), 3.74−3.20 (4H, m), 3.55 (3/2H, s), 3.49 (3/2H, s), 3.14 (1/2H, dt, J = 9, 4 Hz), 3.10 (1/2H, dt, J = 9, 4 Hz), 2.09−1.58 (4H, m), 2.79 (1/2H, br s), 2.55 (1/2H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 156.2, 136.9, 128.5, 128.0, 127.8, 67.9, 67.2, 63.9, 63.6, 62.5, 62.3, 47.1, 47.0, 43.0, 42.4, 30.0, 29.8, 20.3, 19.7; HRMS (EI, *m*/*z*) calcd for $C_{15}H_{22}N_2O_4$ (M^+) 294.1574, found 294.1590.

Phenylmethyl *trans*-Hexahydro-4-hydroxy-3-(methoxyamino)-1*H*-azepine-1-carboxylate (7g): yield 30% (conditions A), 49% (conditions B); mp 108−110 °C (a colorless needless from Et_2O); IR ($CHCl_3$) 3600−3300 (OH, NH), 1690 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.28 (5H, m), 6.15 (1/2H, br s), 5.95 (1/2H, br s), 5.19−5.11 (2H, m), 3.87 (1/2H, dd, J = 14, 4 Hz), 3.74 (1/2H, dd, J = 14, 4 Hz), 3.65−3.07 (5H, m), 2.84 (1H, m), 3.53 (3/2H, s), 3.45 (3/2H, s), 2.03−1.48 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 156.0, 136.7, 128.5, 128.0, 127.8, 127.3, 72.8, 72.7, 67.2, 66.8, 66.5, 62.4, 47.2, 46.7, 45.9, 44.6, 31.7, 31.6, 23.5, 22.5; HRMS (EI, *m*/*z*) calcd for $C_{15}H_{22}N_2O_4$ (M^+) 294.1579, found 294.1565; Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.50; H, 7.39, N, 9.53.

General Procedure for Acetonide Formation of 6a−d. To a solution of cis-product **6** (0.1 mmol) and *p*-TsOH (0.015 mmol) in C_6H_6 (1 mL) was added DMP (0.2 mmol) under a nitrogen atmosphere at room temperature. After being heated at reflux for 1−5 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic phase was washed with brine and dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography or preparative TLC (AcOEt/hexane 2:1−2:3) afforded **8** as colorless oils. The presence of rotamers precluded a comprehensive assignment of all proton resonances.

Phenylmethyl *cis*-Hexahydro-3-methoxy-2,2-dimethyl-5*H*-pyrrolo[3,4-*d*]oxazole-5-carboxylate (8a): yield 98%; IR ($CHCl_3$) 1694 (NCOO) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45−7.25 (5H, m), 5.15 (2H, s), 4.61 (1H, td, J = 7, 2 Hz), 4.02−3.40 (5H, m), 3.60 (3H, s), 1.41 and 1.28 (each 3H, s); HRMS (ELI, *m*/*z*) calcd for $C_{16}H_{22}N_2O_4$ (M^+) 306.1578, found 306.1575.

Phenylmethyl *cis*-Hexahydro-3-methoxy-2,2,4a-trimethyl-5*H*-pyrrolo[3,4-*d*]oxazole-5-carboxylate (8b): yield 56%; IR ($CHCl_3$) 1697 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.28 (5H, m), 5.13 (2H, s), 4.08 (1H, m), 3.86 (1H, m), 3.75 (1H, m), 3.57 (3/2H, s), 3.55 (3/2H, s), 3.48 (1H, m), 3.21 (1H, m), 1.40 (3H, s), 1.34 (6H, s); HRMS (EI, *m*/*z*) calcd for $C_{17}H_{24}N_2O_4$ (M^+) 320.1735. found 320.1744.

Phenylmethyl *cis*-Hexahydro-3-methoxy-2,2,6a-trimethyl-5*H*-pyrrolo[3,4-*d*]oxazole-5-carboxylate (8c): yield 42%; IR ($CHCl_3$) 1692 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.28 (5H, m), 5.14 (2H, s), 3.93−3.31 (5H, m), 3.60 (3H, s), 1.43, 1.42 and 1.30 (each 3H, s); HRMS (EI, *m*/*z*) calcd for $C_{17}H_{24}N_2O_4$ (M^+) 320.1735, found 320.1717.

Phenylmethyl *cis*-Hexahydro-3-methoxy-2,2,3a,6a-tetramethyl-5*H*-pyrrolo[3,4-*d*]oxazole-5-carboxylate (8d): yield 65%; IR ($CHCl_3$) 1694 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.28 (5H, m), 5.12 (2H, s), 4.14 (1H, m), 3.84 (1/2H, d, J = 12 Hz), 3.80 (1/2H, d, J = 12 Hz), 3.61 (3/2H, s), 3.58 (3/2H, s), 3.19 (1/2H, d, J = 12 Hz), 3.18 (1/2H, d, J = 12 Hz), 1.39 (3H, s), 1.34, 1.32, 1.29, 1.28, 1.27, 1.26 (each 3/2H, s); HRMS (EI, *m*/*z*) calcd for $C_{18}H_{26}N_2O_4$ (M^+) 334.1891, found 334.1886.

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Supporting Information Available: Experimental procedures for the conversion of **7g** to **9** and for the preparation of chloroacetone *O*-methyloxime. Copies of ^1H NMR spectra for compounds **6a−g** and **7a−g** and ^{13}C NMR spectra for compounds **6a,b,e−g** and **7a−g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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