Radical Cyclization in Heterocycle Synthesis. 11.[1] A Novel Synthesis of α,β-Disubstituted γ-Lactones via Sulfanyl Radical Addition−Cyclization Using Hydroximates as a Tether

Okiko Miyata,[†] Atsuko Nishiguchi,[†] Ichiya Ninomiya,[†] Keiichi Aoe,[‡] Kimio Okamura,[‡] and Takeaki Naito*,[†]

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan, and Analytical Research Laboratory, Tanabe Seiyaku, Co. Ltd., Kashima, Yodogawa, Osaka 532-0031, Japan

taknaito@kobepharma-u.ac.jp

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A combination of sulfanyl radical addition−cyclization of dienes connected with hydroximates and subsequent conversion of the resulting cyclic hydroximate to the lactones provides a novel method for the construction of α,β-disubstituted γ-lactones. Upon treatment with thiophenol in the presence of AIBN, dienes connected with hydroximates smoothly underwent sulfanyl radical addition−cyclization to give cyclic *cis*- and *trans*-hydroximates. Hydrolysis of cyclic hydroximates gave the desired *cis*- and *trans*-lactones in high yield. This method was successfully applied to the practical synthesis of (±)-oxo-parabenzlactone.

Introduction

Free radical reactions are of paramount importance in organic synthesis.[2] In particular, free-radical-mediated cyclization has developed as a potential method for preparing various types of cyclic compounds via intramolecular carbon−carbon bond-forming processes. Most of the radical cyclizations are carried out using tributyltin hydride. However, because of the toxicity of tributyltin hydride, an area of continuing and important research is to develop new methods of radical generation that avoid the use of this reagent. We have recently explored a new efficient carbon−carbon bond-forming reaction based on sulfanyl radical addition−cyclization, which proceeds by the formation of a carbon-centered radical species generated by the addition of a sulfanyl radical to a multiple bond and then intramolecular addition of the resulting carbon-centered radical to a multiple bond.[3] The synthetic potentiality was demonstrated by the syntheses of anantine,[3a,g] oxo-parabenzlactone,[3d] α-kainic acid,[3e,f] and cispentacin.[3h]

We disclose herein the full details of the sulfanyl radical addition−cyclization[3c] of dienes connected with hydroximates, which are indispensable in cyclization and lactone synthesis, and application of this method to synthesis of a lignan of dibenzylbutyrolactone type, (±)-oxo-parabenzlactone.[3d] The lactone structures not only are found in many biologically active compounds[4] but also are known to be important intermediates for the synthesis of stereo-defined acyclic and other natural products. Among many known methods, construction of γ-lactones

* Tel: +81(78)-441-7554. Fax: +81(78)-441-7556.
[†] Kobe Pharmaceutical University.
[‡] Tanabe Seiyaku, Co. Ltd.

(1) Part 10: Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 6199−6207.

(2) For reviews, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1986. (b) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541−3676. (c) Curran, D. P. *Synthesis* **1988**, 417−439 and 489−513. (d) Jasperse, C. P.; Curran, D. P.; Fervig, T. *Chem. Rev.* **1991**, 1237−1286. (e) Crich, D. *Organosulfur Chemistry: Synthetic Aspects*; Page, P., Ed.; Academic Press: London, 1995; Vol. 1, pp 49−88. (f) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1996; Vol. 48, pp 301−856. (g) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177−194. (h) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594. (i) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562−2579. (j) Chatgilialoglu, C.; Bertrand, M. P.; Ferreri, C. *The Chemistry of Free Radicals: S-Centered Radicals*; Alfassi, Z. B., Ed.; John Wiley & Sons: Chichester, 1999; pp 311−348. (k) Naito, T. *Heterocycles* **1999**, *50*, 505−541. (l) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1−14.

(3) (a) Naito, T.; Honda, Y.; Miyata, O.; Ninomiya, I. *Chem. Pharm. Bull.* **1993**, *41*, 217−219. (b) Naito, T.; Honda, Y.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 19−26. (c) Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Naito, T.; Aoe, K.; Okamura, K. *Tetrahedron Lett.* **1996**, *37*, 229−232. (d) Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Naito, T. *Chem. Pharm. Bull.* **1996**, *44*, 1285−1287. (e) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Synlett* **1997**, 275−276. (f) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Aoe, K.; Hiramatsu, H.; Naito, T. *Heterocycles* **1997**, *46*, 321−333. (g) Naito, T.; Honda, Y.; Bhavakul, V.; Yamaguchi, S.; Fujiwara, A.; Miyata, O.; Ninomiya, I. *Chem. Pharm. Bull.* **1997**, *45*, 1932−1939. (h) Miyata, O.; Muroya, K.; Koide, J.; Naito, T. *Synlett* **1998**, 275−276. (i) Miyabe, H.; Tanaka, H.; Naito, T. *Tetrahedron Lett.* **1999**, *40*, 8387−8390.

(4) (a) MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207−1220. (b) Whiting, D. A. *Nat. Prod. Rep.* **1985**, 191−211. (c) Whiting, D. A. *Nat. Prod. Rep.* **1987**, 499−525. (d) Ward, R. S. *Nat. Prod. Rep.* **1993**, 1−28. (e) Van Oeveren, A.; Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.* **1994**, *59*, 5999−6007. (f) Driori, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Org. Chem.* **1998**, *63*, 2385−2388.

(5) (a) Walling, C.; Cooley, J. H.; Ponaras, A. A.; Racah, E. J. *J. Am. Chem. Soc.* **1966**, *88*, 5361−5363. (b) Surzur, J.-M.; Bertrand, M. P. *Pure Appl. Chem.* **1988**, *60*, 1659−1668. (c) Belletire, J. L.; Mahmoodi, N. O. *Tetrahedron Lett.* **1989**, *30*, 4363−4366. (d) Oumar-Mahamat, H.; Moustrou, C.; Surzur, J.-M. P. *J. Org. Chem.* **1989**, *54*, 5689−5688. (e) Lee, E.; Ko, S. B.; Jung, K. W. *Tetrahedron Lett.* **1989**, *30*, 827−828. (f) Clough, J. M.; Pattenden, G.; Wight, P. G. *Tetrahedron Lett.* **1989**, *30*, 7469−7472. (g) Barth, F.; Yang, C. *Tetrahedron Lett.* **1990**, *31*, 1121−1124. (h) Hanessian, S.; Di Fabo, R.; Marcoux, J.-F.; Prud'homme, M. *J. Org. Chem.* **1990**, *55*, 3436−3438. (i) Nakashima, H.; Seki, K.; Ozaki, N.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 985−990. (j) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746−2750. (k) Pirrung, F. O. H.; Steeman, W. J. M.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J.; Schoemaker, H. E.; Kamphuis, J. *Tetrahedron Lett.* **1992**, *33*, 5141−5144. (l) Lee, E.; Yoon, C. H.; Lee, T. H. *J. Am. Chem. Soc.* **1992**, *114*, 10981−10982. (m) Russell, G. A.; Li, C.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 9831−9840. (n) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604−8605. (o) Wang, C.; Russell, G. A. *J. Org. Chem.* **1999**, *64*, 2066−2069.

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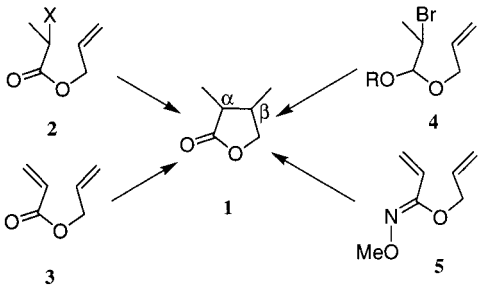
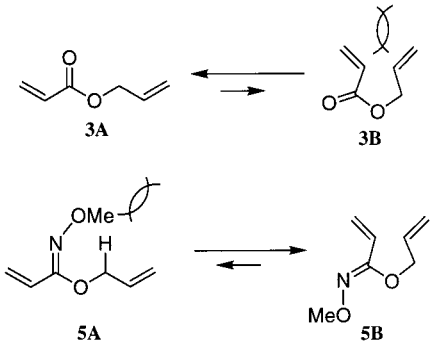
Scheme 1



Scheme 2



1 by formation of the Cα−Cβ bond has recently drawn the attention of synthetic chemists.

Radical cyclization methodology has been explored in this field.[5] The use of halogeno or dienyl esters **2** or **3** as precursors for the preparation of functionalized lactones seems to be a promising route (Scheme 1). However, the desired lactones **1** are obtained in low yield because the cyclization of the α-carbonyl radical takes place slowly. This is partially because ester **3** exists primarily in an *s-trans* conformer **3A**, while the cyclization process requires an *s-cis* conformer **3B** (Scheme 2).[5j] Therefore, Stork[6b] and Ueno[6a] have developed an indirect bromoacetal method for the preparation of lactones (**4** → **1**). Expecting that, contrary to the esters, the *Z-O*-alkylhydroximates **5** would exist in conformer **5B**, preferable for intramolecular cyclization over the less favored conformer **5A** as a result of the steric repulsion between the substituents on nitrogen and oxygen atoms in the conformer **5A**, we started systematic study of sulfanyl radical addition−cyclization of the hydroximates **5**.

Results and Discussion

Preparation and Sulfanyl Radical Addition−Cyclization of Hydroximates. To investigate the generality of the sulfanyl radical addition−cyclization, we chose the *Z*- and *E*-cinnamylhydroximate **8a** and **9a** as the substrate (Scheme 3). According to the known procedure,[7] **8a** and **9a** were prepared via two different routes (routes A and B). Acylation of methoxyamine with cinnamoyl chloride gave the hydroxamate **6a** in a quantitative yield.

Scheme 3

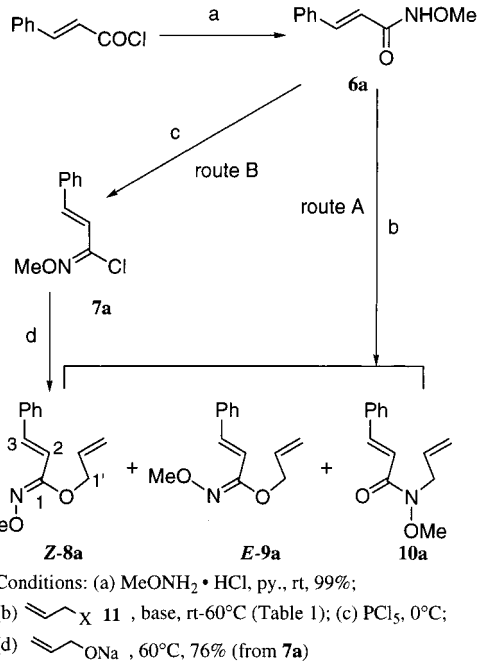


Table 1. Allylation of Hydroxamate 6a

entry	reagent **11**	additive	solvent	temp (°C)	time (h)	yield (%)	ratio *Z*-**8a**:*E*-**9a**:**10a**
1	X = Br	K_2CO_3	Me_2CO	rt	24	86	1:---:2.7
2	X = OTs	K_2CO_3	Me_2CO	rt	24	59	1:---:0.8
3	X = Br	K_2CO_3	DMF	60	2	98	1:---:1.2
4	X = OTs	K_2CO_3	DMF	60	2	87	1:---:0.4
5	X = Br	$AgNO_3$	Et_2O	rt	24	28	1:7.6:2

Then, we investigated the allylation of **6a** as shown in Table 1. Alkylation of **6a** with allyl bromide in the presence of potassium carbonate gave a 1:2.7 mixture of the *Z*-hydroximate **8a** and the amide **10a** in 86% combined yield (entry 1). On alkylation using allyl tosylate, a mixture of **8a** and **10a** was obtained in lower yield and with a ratio of 1:0.8 (entry 2). When DMF and allyl tosylate were used as the solvent and reagent, respectively, the desired *Z*-hydroximate **8a** was obtained as the major product (entry 4). Interestingly, reaction of **6a** with allyl bromide in the presence of silver nitrate afforded the *E*-hydroximate **9a** as the major product but in low yield (entry 5).[7] According to route B, chlorination of hydroxamate **6a** with phosphorus pentachloride followed by treatment of the resulting imidoyl chloride **7a** with sodium allylate gave the *Z*-hydroximate **8a** as the sole product in 76% yield. The *E*/*Z*-geometries of hydroximates **9a** and **8a** were determined by ^{1}H NMR spectroscopy (Figure 1).[7] The ^{1}H NMR spectra of the *Z*- and *E*-isomers are known to differ mainly in the chemical shifts of the methylene hydrogens (Ha and Hb) attached to the nitrogen and oxygen atoms of these molecules. It is known[7] that the hydroximates **12** exhibiting signals for the hydrogen Ha and Hb at lower field have *Z*-

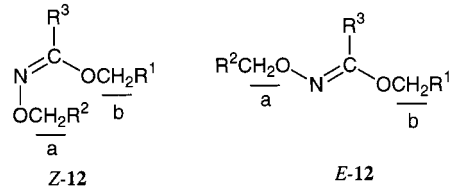


Figure 1. *Z*/*E*-Hydroximates.

(6) (a) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564−5566. (b) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741−3742. (c) Fukuzawa, S.; Tsuchimoto, T. *Synlett* **1993**, 803−804.

(7) (a) Johnson, J. E.; Springfield, J. R.; Hwang, J. S.; Hayes, L. J.; Cunningham, W. C.; McClaugherty, D. L. *J. Org. Chem.* **1971**, *36*, 284−294. (b) Johnson, J. E.; Ghafouripour, A.; Haug, Y. K.; Cordes, A. W.; Pennington, W. T. *J. Org. Chem.* **1985**, *50*, 993−997. (c) Johnson, J. E.; Nalley, E. A.; Kunz, Y. K.; Springfield, J. R. *J. Org. Chem.* **1976**, *41*, 252−259.

Table 2. ^{1}H NMR Data of 8a and 9a

δ (ppm)	**8a**	**9a**
OMe	3.89 (s)	3.83 (s)
1′-H_2	4.76 (dt, 6, 1)	4.62 (dt, 5.5, 1.5)
2-H	6.50 (d, 16)	7.09 (d, 16.5)
3-H	7.13 (d, 16)	7.26 (d, 16.5)

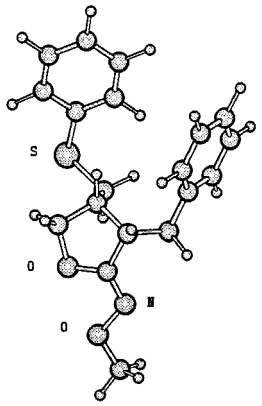


Figure 2. Crystal structure of **13a**.

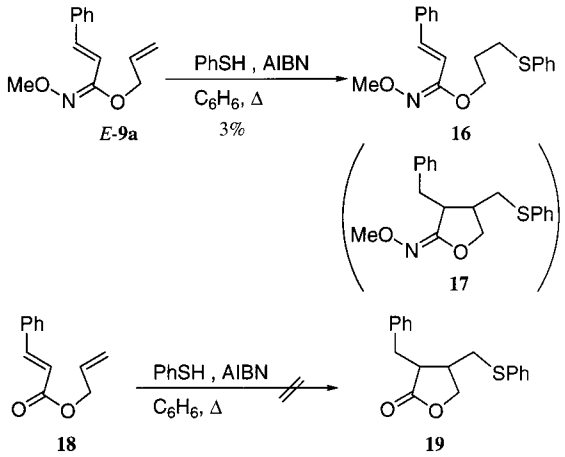
geometries, while the hydroximates **12** showing those at higher field have *E*-geometries (Figure 1). Signals due to methoxy and allylic hydrogens of *Z*-isomer **8a** (OMe: δ 3.89, 1′-H_2: δ 4.76) appeared downfield compared with those of *E*-isomer **9a** (OMe: δ 3.83, 1′-H_2: δ 4.62) (Table 2).

Next, we investigated the sulfanyl radical addition−cyclization of *Z*- and *E*-hydroximates **8a** and **9a** (Table 3). A solution containing thiophenol and AIBN in benzene was added dropwise (5 mL/h) to a solution of *Z*-**8a** in boiling benzene with stirring under nitrogen. The solution was then refluxed for further 2 h and concentrated to give a 1.8:1 mixture of cyclized *cis*- and *trans*-products **13a** and **14a** in 82% combined yield, both of which possess a phenylsulfanylmethyl group at the 4-position (entry 1). When triethylborane was used as a radical initiator, yield of cyclized product **13a** and **14a** decreased (entries 2 and 3).[3i]

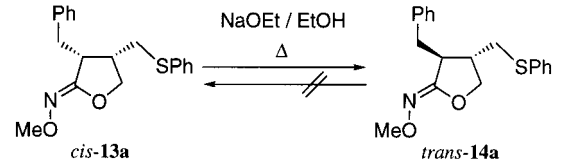
On the other hand, the sulfanyl radical addition−cyclization of *E*-hydroximate **9a** gave only adduct **16** in 3% yield, with no formation of the cyclized product **17**. To compare the reactivity of *Z*-hydroximate **8a** with that of the corresponding ester **18**, we investigated sulfanyl radical addition−cyclization of ester **18**. However, under the same reaction conditions, **18** did not give the cyclized product **19** and the substrate **18** was mostly recovered (Scheme 4).

The stereostructures of cyclized products *cis*-**13a** and *trans*-**14a** were firmly established by single-crystal X-ray analysis of *cis*-**13a** (Figure 2) and irreversible isomerization of *cis*-hydroximate **13a** to *trans*-isomer **14a** by treatment with sodium ethoxide (Scheme 5). Previously, Ikeda[8] and we[3b] have reported that, upon treatment with sodium ethoxide in ethanol, *cis*-3,4-dimethylpyrrolidin-2-ones were readily isomerized into the correponding stable *trans*-isomers. When the cyclic hydroximate **14a** was treated with sodium ethoxide in refluxing ethanol, it was recovered unchanged, while the cyclic hydroximate **13a** was converted into a 1:2 mixture of the two cyclic hydroximates **13a** and **14a**.

Scheme 4



Scheme 5



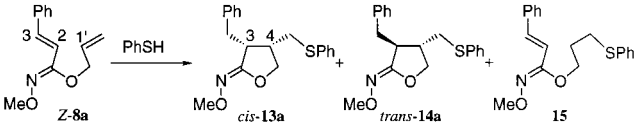
The sulfanyl radical addition−cyclization of cinnamylhydroximate can be summarized as follows. (a) The sulfanyl radical prefers to attack the allyl group. (b) The radical cyclization takes place exclusively in a 5-*exo*-*trig*-manner. (c) The *cis*-hydroximate **13a** is formed in preference to the *trans*-isomer **14a**. Beckwith[9a,b] has explained that the preferential formation of the *cis*-product from the 1-substituted hexenyl radical is ascribed to the effects of orbital symmetry. (d) The corresponding *E*-isomer **9a** and ester **18** did not give the cyclized products. We propose a plausible explanation for the non-cyclization of **9a** and **18** as follows. The *E*-isomer **9** would exist in a stable conformer **9C**, which is unfavorable for intramolecular cyclization. Another conformer **9B** is favorable for cyclization but has steric repulsion between the methoxy group and olefinic hydrogen. Furthermore, the zigzag conformation of **9A** has also steric repusion between the methoxy group and olefinic hydrogen. On the other hand, *Z*-isomer **8a** would exist in a conformer **8B**, which is preferable for the intramolecular cyclization to the less favored conformer **8A** as a result of steric repulsion between the substituents on the nitrogen and oxygen atoms in the conformer **8A** (Scheme 6). Examination of molecular models of the ground state provides some indication of the different reactivity between *Z*-**8a** and *E*-**9a**. The PM3-optimized ground state conformations **8C** and **9D** (R = H), which correspond to *Z*-**8a** and *E*-**9a**, are shown in Scheme 6.[9c] The PM3-optimized conformation **8C** (R = H) of *Z*-**8a** would be favorable for cyclization while the PM3-optimized conformation **9D** (R = H) of in *E*-**9a** would be unfavorable for intramolecular cyclization.

Scope and Limitations. To establish the generality of the sulfanyl radical addition−cyclization, we also investigated the reactions of the *Z*-hydroximates **8b−d**

(8) Sato, T.; Wada, Y.; Nishimoto, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 879−886.

(9) (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073−3100. (b) Curran, D. P.; Poter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines and Synthetic Application*; VCH: Weinheim, 1995. (c) Optimized ground state conformations were calculated with a semiempirical MOPAC method utilizing a PM3 Hamiltonian and CAChe system (SONY Tektronix).

Table 3. Sulfanyl Radical Addition−Cyclization of *Z*-8a



entry	solvent	radical initiator	temp (°C)	yield (%)	*cis*-**13a**:*trans*-**14a**:**15**
1	benzene	AIBN (method A)	80	82	1.8:1:---
2	toluene	Et_3B (method B)	rt	30	2.4:1:1
3	toluene	Et_3B (method B)	60	47	1.8:1:0.9

Scheme 6

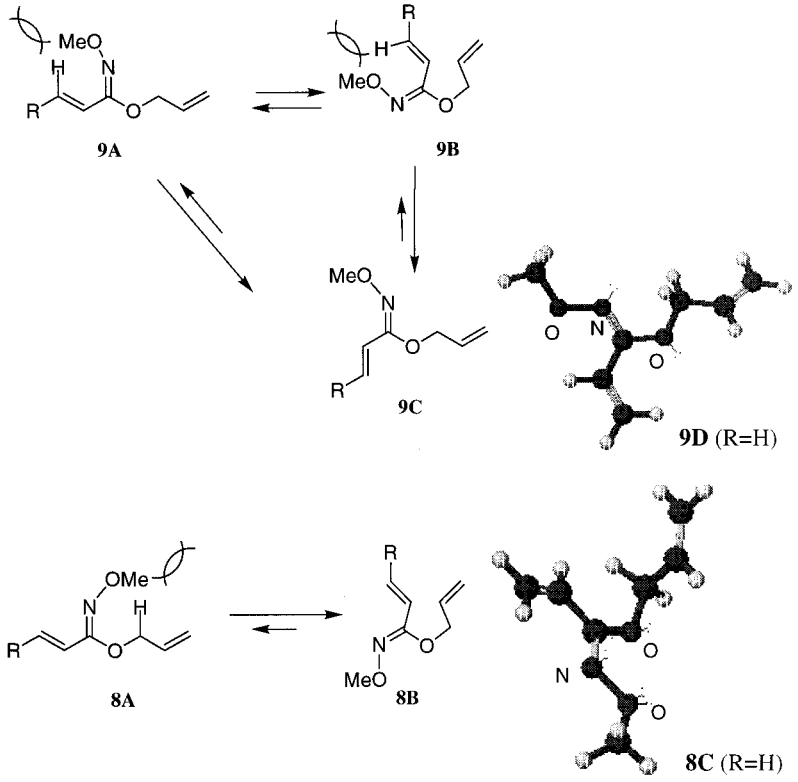
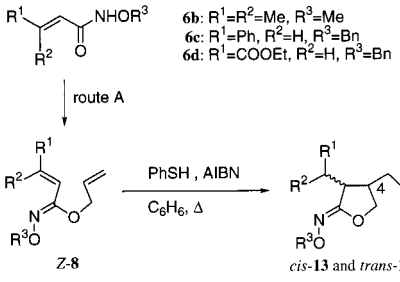


Table 4. Sulfanyl Radical Addition−Cyclization of 8b−d



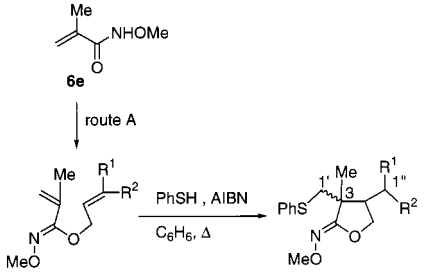
entry	substrate	R^1	R^2	R^3	yield (%)	ratio *cis*-**13**:*trans*-**14**
1	**8b**	Me	Me	Me	80	1.7:1.0
2	**8c**	Ph	H	Bn	94	1.8:1.0
3	**8d**	COOEt	H	Bn	78	0.8:1.0

and **20a−e,** which were prepared from the corresponding hydroxamates via route A. The results of the sulfanyl radical addition−cyclization of *Z*-hydroximates **8b−d** with substituents at the *β*-position of the unsaturated hydroximate group are summarized in Table 4. Sulfanyl radical addition−cyclization of hydroximate **8b** having a dimethyl group proceeded smoothly to give a 1.7:1.0 mixture of *cis*-**13b** and *trans*-**14b** in 80% combined yield (entry 1). The hydroximate **8c**, including a benzyloxy group on the nitrogen atom, gave cyclized products **13c** and **14c** in slightly better yield (entry 2). The cyclization of hydroximate **8d** having an ethoxycarbonyl group also afforded the cyclized products **13d** and **14d** (entry 3).

Absence of the substituents at the *β*-position in the unsaturated hydroximates **20a−e** influenced markedly the regioselectivity of the addition of the phenylsulfanyl radical, resulting in the exclusive formation of the 3-phenylsulfanylmethyl products *cis*-**21a−e** and *trans*-**22a−e** as shown in Table 5. The sulfanyl radical addition−cyclization of hydroximates **20a−d** having phenyl, dimethyl, and ethoxycarbonyl groups gave a mixture of *cis*-**21a−d** and *trans*-**22a−d**. In the case of hydroximate **20e** with no substituent at the terminal olefins, the sulfanyl radical attacked the olefin to give *cis*-**21e** and *trans*-**22e**. These results suggest that the dienes connected with *Z*-hydroximates undergo a smooth 5-*exo*-*trig* type of radical cyclization though its regiochemistry depends on the substituents attached to the dienes.

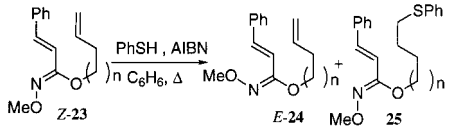
Next, we also investigated the reactions of the *ω*-alkenylhydroximates **23a−c** with a longer carbon chain (Table 6). However, **23a−c** underwent no cyclization, and instead, addition of thiophenol to the allyl group and partial isomerization of the oxime ether group took place to give adducts **25b**,**c** and *E*-hydroximates **24a−c** both in low yields, along with recovered *Z*-hydroximates (entries 1−3).

Table 5. Sulfanyl Radical Addition−Cyclization of 20a−e



entry	substrate	R^1	R^2	yield (%)	*cis*-**21**:*trans*-**22**
1	**20a**	Ph	H	78	1.7:1.0
2	**20b**	Me	H	56	1.4:1.0
3	**20c**	Me	Me	58	1.1:1.0
4	**20d**	COOEt	H	49	1.3:1.0
5	**20e**	H	H	31	1.5:1.0

Table 6. Reaction of 23a−c with Thiophenol

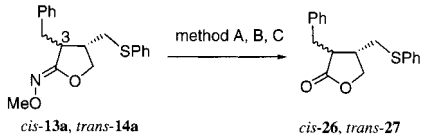


entry	substrate	*n*	yield (%) **24**	**25**
1	**23a**	1	24	---
2	**23b**	2	37	3
3	**23c**	3	15	5

Conversion of Cyclic Hydroximates to Lactones. We next investigated conversion of the cyclic hydroximates to the lactones. To our knowledge, there are few examples of the transformation of the hydroximates to the esters or lactones, though several groups reported both the conversion[10a] of the imidates into the esters or lactones and the regeneration[10b−f] of the carbonyl compounds from the oximes, oxime ethers, and hydrazones.[10] To convert cyclic hydroximates into the lactones, we investigated four different sets of conditions (methods A−D) as shown in Tables 7 and 8. The results employing hydrolysis are summarized in Table 7. The *cis*-hydroximate **13a** was treated with Amberlyst 15 in the presence of paraformaldehyde at 80 °C for 24 h to give the *cis*-lactone **26** in 50% yield (entry 1). Similarly, *trans*-**14a** was converted into *trans*-lactone **27** (entry 2). Reaction of *cis*-**13a** and *trans*-**14a** with hydrochloric acid proceeded smoothly even at room temperature and for a short time to afford **26** and **27** in excellent yield, respectively (entries 3 and 4). Hydrolysis of *trans*-**14a** under the basic conditions (10% NaOH/MeOH) gave the desired lactone **27** in 79% yield (entry 6), while *cis*-**13a** gave not the lactone **26** but a complex mixture under the same conditions (entry 5).

We next examined the oxidative method (method D) using commercially available hypervalent organoiodo reagents, [hydroxy(tosyloxy)iodo]benzene (HTIB) and

Table 7. Conversion of Hydroximates into Lactones under Acidic and Basic Conditions



entry	substrate	method	conditions	yield (%) *cis*-**26**	*trans*-**27**
1	*cis*-**13a**	A	$(CH_2O)_n$, Amberlyst 15	50	---
2	*trans*-**14a**		acetone/H_2O (10:1) 80 °C, 24 h	---	60
3	*cis*-**13a**	B	10% HCl/THF	93	--
4	*trans*-**14a**		rt, 0.5 h	--	95
5	*cis*-**13a**	C	10% KOH/MeOH	--	--
6	*trans*-**14a**		50 °C, 8 h	--	79

[bis(trifluoroacetoxy)iodo]benzene (BTIB) (Table 8). Treatment of *cis*-**13a** with 1 equiv of HTIB gave *cis*-sulfinyllactone **28** and *cis*-sulfinylhydroximate **30** in 47% and 52% yield, respectively (entry 1). Under the same conditions, **30** was converted into **28** in good yield. When 3 equiv of HTIB was used, *cis*-**28** was obtained in 79% yield as the sole product (entry 3). Similarly, *trans*-sulfinyllactone **29** was obtained from *trans*-**14a** in 77% yield (entry 4). Although oxidation of *cis*-**13a** with BTIB gave *cis*-**30**, lactone **28** could not be detected in the reaction mixture (entry 5). Thus, we succeed in a generation of the lactones from the corresponding cyclic hydroximates under both hydrolytic and oxidative conditions. The sulfoxides **28**−**31** were obtained as 1:1 diastereomeric mixture based on the phenylsulfinyl group.

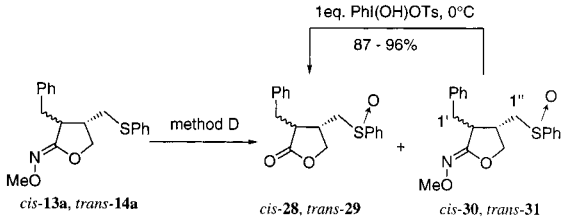
Synthesis of (±)-Oxo-parabenzlactone. We then applied this methodology to the synthesis of (±)-oxo-parabenzlactone **40** (Scheme 7). (+)-Oxo-parabenzlactone[11] was recently isolated from the wood of *Protium tenuifolium* (Burseraceae). Previously, the enantiomer of **40** was obtained as an oxidation product of a lignan, (−)-parabenzlactone, which had been isolated from *Parabenzoin trilobum* Nakai.[12] The lignans of the dibenzylbutyrolactone type exhibit various biological activities such as antitumor and platelet-activating factor (PAF) antagonistic activities in addition to inhibitory effects on microsomal monooxygenase in insects.[4] Sulfanyl radical addition−cyclization of the allyl hydroximate **33**, prepared from the hydroxamate **32**, in the presence of thiophenol (1 equiv) and AIBN (0.5 equiv) proceeded smoothly to give a ca. 1:2 mixture of the cyclic products **34** and **35** in 73% combined yield, which was readily separated. The unstable *cis*-**35** was readily isomerized into the *trans*-**34** upon treatment with sodium ethoxide in ethanol. Hydrolytic conversion of the cyclic hydroximate **34** into the lactone **36** was readily achieved in 96% yield by treatment with 10% HCl in methanol. Oxidation of the *trans*-sulfide **36** with *m*-chloroperbenzoic acid (mCPBA) at 0 °C gave the corresponding sulfoxide **37** in 81% yield. However, oxidative conversion of the cyclic hydroximate **34** into the desired sulfinyl lactone **37** proceeded ineffectively to give the lactone **37** in only 19% yield under the conditions using HTIB as an oxidant.

(10) (a) Perrin, C. L. *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons: Chichester, 1991; Vol. 2, pp 147−229. (b) Corey, E. J.; Pynes, G. *Tetrahedron Lett.* **1983**, *24*, 2821−2824. (c) Ballini, R.; Petrini, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2563−2565. (d) Sakamoto, T.; Kikugawa, Y. *Synthesis* **1993**, 563−564. (e) Moriarty, R. M.; Varid, R. K.; Koser, G. F. *Synlett* **1990**, 365−383. (f) Barton, D. H.; Jaszberenyi, J. Cs.; Shinada, T. *Tetrahedron Lett.* **1993**, *34*, 7191−7194.

(11) Siqueira, J. B. G.; Zoghbi, M. d. G. B.; Cabral, J. A.; Filho, W. W. *J. Nat. Prod.* **1995**, *58*, 730−732.

(12) (a) Wada, K.; Munakata, K. *Tetrahedron Lett.* **1970**, 2017−2019. (b) Niwa, M.; Iguchi, M.; Yamamura, S.; Nishibe, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3359−3360.

Table 8. Conversion of Hydroximates into Lactones under Oxidative Conditions



			yield (%)			
entry	substrate	conditions	*cis*-**28**	*trans*-**29**	*cis*-**30**	*trans*-**31**
1	*cis*-**13a**	1 equiv PhI(OH)OTs, 0 °C	47	---	52	---
2	*trans*-**14a**	1 equiv PhI(OH)OTs, 0 °C	---	48	---	38
3	*cis*-**13a**	3 equiv PhI(OH)OTs, 0 °C	79	---	---	---
4	*trans*-**14a**	3 equiv PhI(OH)OTs, 0 °C	---	77	---	---
5	*cis*-**13a**	3 equiv $PhI(OCOCF_3)_2$, 0 °C	---	---	80	---

Introduction of an aryl group into the 1″-position in **37** was readily achieved according to a conventional route involving Pummerer rearrangement and subsequent Grignard reaction. The *trans*-sulfoxide **37** was subjected to the Pummerer reaction and subsequent hydrolysis to obtain the desired *trans*-aldehyde **38** in 84% yield. Treatment of the aldehyde **38** with a Grignard reagent gave a diastereomeric mixture of the adducts **39**, which without separation was converted into the ketone **40** (mp. 138−139 °C (lit.[11] (+)-**40** 105−106 °C) by oxidation with pyridinium chlorochromate (PCC) in 45% yield. The ketone **40** obtained was identical with oxo-patabenzlactone[11] upon comparison of the spectral data with those of the authentic sample.

Conclusion

We have developed for the first time radical cyclization of the dienes connected with the hydroximates. The feasibility of sulfanyl radical addition−cyclization is dependent upon the structure of substrates. The radical cyclization of *Z*-hydroximates proceeded smoothly to give the cyclized product in good yield, while the corresponding *E*-isomer did not undergo the radical cyclization. The newly found radical cyclization of the hydroximates provides a novel method for the construction of the substituted lactones, which were effectively derived by either hydrolysis or oxidation. This method was successfully applied to the practical synthesis of (±)-oxopatabenzlactone.

Experimental Section

General. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 200, 300, or 500 MHz and at 50 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI method. Flash column chromatography was preformed using E. Merck Kieselgel 60 (230−400 mesh). Medium-pressure column chromatography was performed using Lober Grösse B (E. Merck 310−25, Lichroprep Si60).

Preparation of the Hydroxamates 6a−b. To a stirred solution of the corresponding acid chloride (0.15 mol) in CH_2Cl_2 (600 mL) was added *N*-methoxyamine hydrochloride (13.8 g, 0.165 mol) under a nitrogen atmosphere at room temperature. After the solution was stirred at the same temperature for 15 min, pyridine (28 mL, 0.351 mol) was added dropwise to the reaction mixture at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by recrystallization (hexane/$CHCl_3$) afforded the hydroxamate **6**. The compound **6a** had the following properties. The properties for compounds **6b−e** are provided in the Supporting Information.

(*E*)-*N*-Methoxy-3-phenyl-2-propenamide (6a): 23 g (yield 87%) from cinnamoyl chloride (25 g); colorless crystals; mp 93−95 °C; IR ($CHCl_3$) 3449 (NH), 1686 (CON) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.65 (1H, br s), 7.76 (1H, d, J = 16 Hz), 7.60−7.28 (5H, m), 6.49 (1H, d, J = 16 Hz), 3.85 (3H, s); HRMS (EI, m/z) calcd for $C_{10}H_{11}NO_2$ (M^+) 177.0791, found 177.0766. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.75; H, 6.26; N, 7.78.

Preparation of Hydroximate 8a−d, 20a−e, and 23a−c. Route A (Table 1, entries 1 and 2). To a solution of **6a** (1.77 g, 10 mmol) and K_2CO_3 (1.38 g, 10 mmol) in acetone (50 mL) was added dropwise a solution of either allyl bromide (1.21 g, 10 mmol) or allyl tosylate[13] (1.98 g, 10 mmol) in acetone (5 mL) under a nitrogen atmosphere at room temperature. After being stirred at room temperature for 24 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 3:1) afforded **8a** (521 mg, 23% in entry 1) (716 mg, 33% in entry 2) and **10a** (1.35 g, 63% in entry 1) (564 mg, 26% in entry 2).

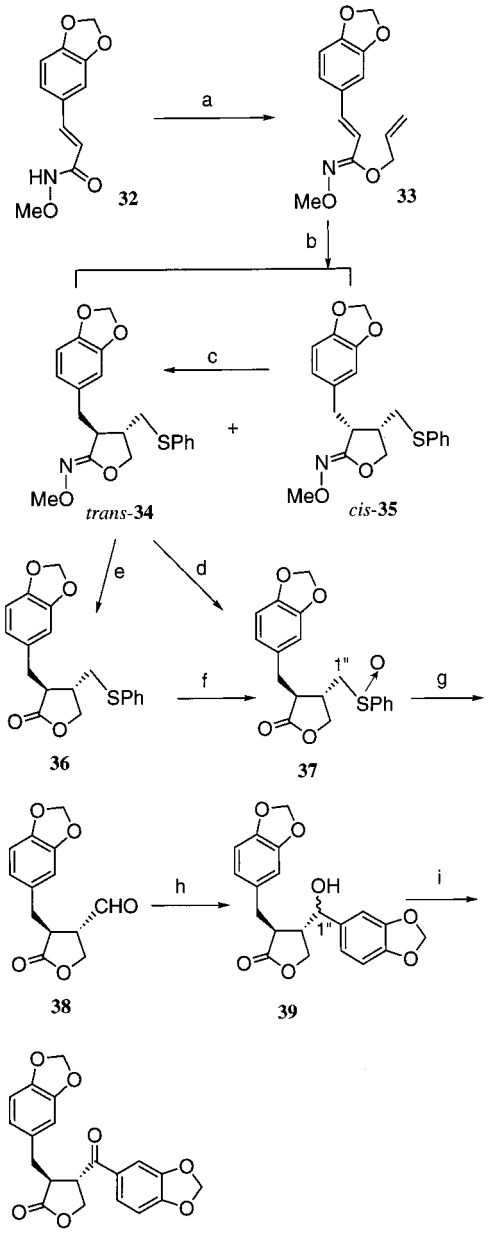
Route A (Table 1, entries 3 and 4). To a solution of **6a** (35 mg, 0.2 mmol) and K_2CO_3 (28 mg, 0.2 mmol) in DMF (2 mL) was added a solution of either allyl bromide (24 mg, 0.4 mmol) or allyl tosylate (79 mg, 0.4 mmol) in DMF (0.2 mL) under a nitrogen atmosphere at 60 °C. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 3:1) afforded **8a** (20 mg, 45% in entry 3) (27 mg, 62% in entry 4) and **10a** (23 mg, 53% in entry 3) (11 mg, 25% in entry 4). **8b−d** and **20a−e** were prepared by the same procedure.

Route A (Table 1, entry 5). According to the literature procedure,[7a] to a solution of **6a** (1.77 g, 10 mmol) in 95% EtOH (7.1 mL) and 29% NH_3 (0.65 mL) was added a solution of $AgNO_3$ (1.8 g, 10 mmol) in H_2O (2.5 mL) under a nitrogen atmosphere at room temperature. The precipitated silver salt was separated from the solution by filtration, washed with acetone, and dried. To a suspension of the silver salt in Et_2O (3 mL) was added a solution of allyl bromide (6.0 mmol) in Et_2O (0.3 mL) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was filtered to remove AgBr. The filtrate was concentrated at reduced pressure and the residue was purified by medium-pressure column chromatography (hexane/AcOEt 3:1) to afford **8a** (59 mg, 2.7%), **9a** (434 mg, 20%), and **10a** (118 mg, 5.3%).

Route B. To a solution of **6a** (87 mg, 0.5 mmol) in benzene (1 mL) was added phosphorus pentachloride (156 mg, 0.75

(13) Földi, Z. *Chem. Ber.* **1920**, *53*, 1836−1839.

Scheme 7



Oxo-parabenzlactone **40**

Conditions: (a) 1) CBr_4, Ph_3P, 80°C, quant.; 2) NaH, allyl alcohol, 61%; (b) PhSH, AIBN, 80°C, 73% (*trans*-**34** : *cis*-**35**= 1 : 2.1); (c) NaOEt, 80°C, 73%; (d) PhI(OH)OTs, 0°C, 19%; (e) 10%HCl, rt, 96%; (f) mCPBA, 0°C, 81%; (g) 1) TFAA-2,6-lutidine, 0°C, 2) $NaHCO_3$, 84%; (h) 3,4-methylenedioxyphenylmagnesium bromide, 40°C, 45%; (i) PCC, rt, 52%.

mmol) by small portions under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 2 h, H_2O was added to the reaction mixture. The resulting solution was extracted with CH_2Cl_2, and the organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure to afford the crude hydroximoyl chloride **7a**. After being characterized by NMR spectra, **7a** was immediately subjected to the following reaction. To a suspension of NaH (60% oil suspension) (100 mg, 2.5 mmol) in THF was added allyl alcohol (145 mg, 2.5 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at room temperature for 20 min, a solution of the crude hydroximoyl chloride in THF (5 mL) was added at reflux. The reaction mixture was heated at reflux for a further 2 h, then cooled at 0 °C, diluted with H_2O, and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/CH_2Cl_2 1:1) afforded **8a** (82 mg, 76%) as colorless oil. **23a**−**c** were prepared by the same procedure.

The compound **8a**, **9a**, and **10a** had the following properties. The properties for compounds **8b**−**d**, **20a**−**e**, and **23a**−**c** are provided in the Supporting Information.

2-Propenyl (*Z*,*E*)-*N*-methoxy-3-phenyl-2-propenimidate (8a): colorless oil; IR ($CHCl_3$) 1634 (C=N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52−7.24 (5H, m), 7.13 (1H, d, J = 16 Hz), 6.50 (1H, d, J = 16 Hz), 6.04 (1H, ddt, J = 17, 10, 6 Hz), 5.40 (1H, dq, J = 17, 1 Hz), 5.28 (1H, dq, J = 10, 1 Hz), 4.76 (2H, dt, J = 6, 1 Hz), 3.89 (3H, s); ^{13}H NMR ($CDCl_3$) δ 154.7, 135.6, 134.7, 133.1, 128.7, 128.5, 126.9, 118.8, 118.1, 72.2, 62.1; HRMS (EI, *m*/*z*) calcd for $C_{13}H_{15}NO_2$ (M^+) 217.1104, found 217.1100.

2-Propenyl (*E*,*E*)-*N*-methoxy-3-phenyl-2-propenimidate (9a): colorless oil; IR ($CHCl_3$) 1636 (C=N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54−7.29 (5H, m), 7.26 (1H, d, J = 16.5 Hz), 7.09 (1H, d, J = 16.5 Hz), 6.09 (1H, ddt, J = 17, 10.5, 5.5 Hz), 5.41 (1H, dq, J = 17, 1.5 Hz), 5.27 (1H, dq, J = 10.5, 1.5 Hz), 4.62 (2H, dt, J = 5.5, 1.5 Hz), 3.83 (3H, s). NOE was observed between the methoxyl group (δ 3.83) and 2-H (δ 7.09) in NOESY spectroscopy. ^{13}H NMR ($CDCl_3$) δ 158.5, 136.3, 135.7, 133.1, 129.0, 128.5, 127.5, 117.4, 111.6, 67.2, 61.8; HRMS (EI, *m*/*z*) calcd for $C_{13}H_{15}NO_2$ (M^+) 217.1104, found 217.1100.

(*E*)-*N*-Methoxy-3-phenyl-*N*-(2-propenyl)-2-propenamide (10a): colorless oil; IR ($CHCl_3$) 1651 (CON) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.77 (1H, d, J = 16 Hz), 7.62−7.26 (5H, m), 7.04 (1H, d, J = 16 Hz), 5.93 (1H, ddt, J = 16, 10, 6 Hz), 5.30 (1H, dq, J = 16, 1 Hz), 5.24 (1H, dq, J = 10, 1 Hz), 4.36 (2H, dt, J = 6, 1 Hz), 3.78 (3H, s); HRMS (EI, *m*/*z*) calcd for $C_{13}H_{15}NO_2$ (M^+) 217.1104, found 217.1105.

General Procedure for Radical Cyclization. Method A. To a boiling solution of the hydroximate **8a** (109 mg, 0.5 mmol) in benzene (5 mL) under nitrogen atmosphere was added (5 mL/h) by a syringe pump over 2 h a solution containing thiophenol (0.05 mL, 0.5 mmol) and AIBN (41 mg, 0.25 mmol) in benzene (10 mL). After the reaction mixture was heated at reflux for a further 2 h, the solvent was evaporated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 3:1) afforded the *cis*-**13a** (173 mg, 53%) and *trans*-**14a** (95 mg, 29%) as shown in Table 3. **8b**−**d**, **20a**−**e**, and **23a**−**c** underwent the radical reaction by the same procedure.

Method B. To a solution of the hydroximate **8a** (109 mg, 0.5 mmol) and thiophenol (0.06 mL, 0.6 mmol) in toluene (4 mL) was added Et_3B (1.0 M in hexane) (0.1 mL, 0.1 mmol) under nitrogen atmosphere at either room temperature or 60 °C. After being stirred at the same temperature for 2 h, the reaction mixture was neutralized with 5% KOH and extracted with AcOEt. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 3:1) afforded the *cis*-**13a** (26.8 mg, 16.4% in entry 2) (37.4 mg, 22.9% in entry 3), *trans*-**14a** (11 mg, 6.8% in entry 2) (20.8 mg, 12.7% in entry 3), and **15** (11 mg, 6.8% in entry 2) (18.5 mg, 11.4% in entry 3) as shown in Table 3.

The compounds **13a**, **14a**, and **15** had the following properties. The properties for compounds **13b**−**d**, **14b**−**d**, **21a**−**e**, **22a**−**e**, **24a**−**c**, and **25b**,**c** are provided in the Supporting Information.

[*Z*(*cis*)]-*N*-[Tetrahydro-3-phenylmethyl-4-(phenylsulfanyl)-methylfuran-2-ylidene]-*O*-methylhydroxyamine (13a): colorless crystals, mp 103−105 °C (hexanes/Et_2O); IR ($CHCl_3$) 1672 (C=N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−6.86 (10H, m), 4.51 (1H, dd, J = 9.5, 1.5 Hz), 4.16 (1H, ddd, J = 9.5, 5, 1.5 Hz), 3.83 (3H, s), 3.39 (1H, ddd, J = 12, 7.5, 5 Hz), 3.28 (1H, dd, J = 15, 5 Hz), 3.21 (1H, ddd, J = 13.5, 3.5, 1.5 Hz), 2.72 (1H, dd, J = 15, 12 Hz), 2.60 (1H, dd, J = 13.5, 12 Hz), 2.44 (1H, m); ^{13}H NMR ($CDCl_3$) δ 158.6, 138.0, 134.3, 128.7, 128.5, 128.2, 126.3, 125.7, 72.9, 62.0, 43.0, 38.3, 31.3, 29.8; HRMS (EI, *m*/*z*) calcd for $C_{19}H_{21}NO_2S$ (M^+) 327.1294, found 327.1303. Crystal data of **13a**: $C_{19}H_{21}NO_2S$, space group *Pbca* with a = 18.131(3), b = 26.611 (2), c = 14.575 (1) Å, V = 7032.4 (1.5) $Å^3$, final R value 0.060 for 5980 reflections.

[*Z*(*trans*)]-*N*-[Tetrahydro-3-phenylmethyl-4-(phenylsulfanyl)methylfuran-2-ylidene]-*O*-methylhydroxyamine (14a): colorless oil; IR ($CHCl_3$) 1670 (C═N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.06 (10H, m), 4.32 (1H, dd, J = 9.5, 7 Hz), 4.07 (1H, dd, J = 9.5, 6 Hz), 3.84 (3H, s), 3.15 (1H, dd, J = 14, 5 Hz), 2.96 (1H, ddd, J = 10, 6, 4 Hz), 2.71 (2H, m), 2.59 (1H, dd, J = 14, 9.5 Hz), 2.36 (1H, m); ^{13}H NMR ($CDCl_3$) δ 159.6, 137.6, 134.2, 129.7, 128.7, 128.6, 128.2, 126.4, 126.2, 74.0, 61.8, 45.2, 40.6, 37.3, 36.0; HRMS (EI, *m*/*z*) calcd for $C_{19}H_{21}NO_2S$ (M^+) 327.1294, found 327.1295.

3-(Phenylsulfanyl)propyl (*Z*,*E*)-*N*-Methoxy-3-phenyl-2-propenimidate (15): colorless oil; IR ($CHCl_3$) 1637 (C═N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.50−7.15 (10H, m), 7.09 (1H, d, J = 16 Hz), 6.48 (1H, d, J = 16 Hz), 4.37 (2H, t, J = 6 Hz), 3.86 (3H, s), 3.13 (2H, t, J = 7 Hz), 2.08 (2H, tt, J = 7, 6 Hz); HRMS (EI, *m*/*z*) calcd for $C_{19}H_{21}NO_2S$ (M^+) 327.1294, found 327.1314.

3-(Phenylsulfanyl)propyl (*E*,*E*)-*N*-Methoxy-3-phenyl-2-propenimidate (16). 9a (109 mg, 0.5 mmol) was subjected to sulfanyl radical addition−cyclization using thiophenol (0.05 mL, 0.5 mmol) and AIBN (41 mg, 0.25 mmol) to afford the adduct **16** (10 mg, 3%) as colorless oil: IR ($CHCl_3$) 1637 (C═N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.55−7.15 (10H, m), 7.20 (1H, d, J = 16.5 Hz), 7.05 (1H, d, J = 16.5 Hz), 4.20 (2H, t, J = 6 Hz), 3.81 (3H, s), 3.10 (2H, t, J = 7 Hz), 2.10 (2H, tt, J = 7, 6 Hz); HRMS (EI, *m*/*z*) calcd for $C_{19}H_{21}NO_2S$ (M^+) 327.1294, found 327.1304.

Isomerization of Two Cyclic Hydroximates *cis*-13a and *trans*-14a. According to the literature procedure,[3b,8] sodium (19.1 mg, 0.675 mmol) was dissolved in anhydrous ethanol (30 mL), and an aliquot of the resulting solution (1 mL) was diluted to 2 mL by the addition of further ethanol (1 mL). To this solution was added *cis*-**13a** (10 mg, 0.03 mmol). The resulting solution was refluxed for 2.5 h, then diluted with aqueous ammonium chloride, and finally extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. The ^1H NMR spectrum of the residue showed that the product consisted of a 1:2 mixture of the *cis*-**13a** and *trans*-**14a**. Under the same conditions, the *trans*-**14a** was recovered quantitatively.

Conversion of the Cyclic Hydroximates into Lactones. Method A. (Table 7, entries 1 and 2). To a stirred solution of the cyclic hydroximate **13a** or **14a** (17 mg, 0.05 mmol) in acetone (4.5 mL) and H_2O (0.5 mL) was added paraformaldehyde (15 mg) and Amberlyst 15E (10 mg) under a nitrogen atmosphere at room temperature. After the solution was stirred at 80 °C for 24 h, the reaction mixture was filtered to remove Amberlyst 15E. The filtrate was diluted with CH_2Cl_2 and washed with water. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 3:1) afforded **26** (8 mg, 50%) or **27** (12 mg, 60%).

Method B. (Table 7, entries 3 and 4). A solution of **13a** or **14a** (33 mg, 0.1 mmol) in concentrated HCl (1.5 mL) and THF (3.5 mL) was stirred at room temperature for 30 min, and H_2O was added to the reaction mixture. The resulting solution was extracted with CH_2Cl_2, and the organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 3:1) afforded **26** (28 mg, 93%) or **27** (28.3 mg, 95%).

Method C. (Table 7, entries 5 and 6). A solution of **14a** (33 mg, 0.1 mmol) in a methanolic solution of KOH (10%, 5 mL) was stirred at 50 °C for 8 h. The reaction mixture was made acidic with 5% HCl and then extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 3:1) afforded **27** (24 mg, 79%).

Method D. (Table 8, entries 1 and 2). To a solution of **13a** or **14a** (33 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added HTIB (118 mg, 0.1 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 4 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt) afforded **28** (15 mg, 47%) and **30** (19 mg, 52%) or **29** (15 mg, 48%) and **31** (13 mg, 38%).

(Table 8, entries 3 and 4). To a solution of **13a** or **14a** (33 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added HTIB (118 mg, 0.3 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 4 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (AcOEt) afforded **28** (25 mg, 79%) or **29** (24 mg, 77%).

***cis*-Dihydro-3-phenylmethyl-4-(phenylsulfanyl)methyl-2(3*H*)-furanone (26):** colorless crystals, mp 116−117 °C (Et_2O); IR ($CHCl_3$) 1773 (lactone) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40−6.90 (10H, m), 4.47 (1H, dd, J = 9, 1 Hz), 4.19 (1H, dd, J = 9, 5 Hz), 3.36 (1H, dd, J = 15, 5 Hz), 3.27−3.10 (2H, m), 2.75 (1H, dd, J = 15, 12 Hz), 2.64−2.48 (2H, m); ^{13}H NMR ($CDCl_3$) δ 177.2, 137.8, 134.2, 128.9, 128.7, 128.6, 128.1, 126.6, 126.0, 69.5, 43.9, 37.3, 30.8, 30.7; HRMS (EI, *m*/*z*) calcd for $C_{18}H_{18}O_2S$ (M^+) 298.1027, found 298.1027. Anal. Calcd for $C_{18}H_{18}O_2S$: C, 72.45; H, 6.08; S, 10.74. Found: C, 72.19; H, 6.09; S, 10.87.

***trans*-Dihydro-3-phenylmethyl-4-(phenylsulfanyl)-methyl-2(3*H*)-furanone (27):** colorless oil; IR ($CHCl_3$) 1771 (lactone) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35−7.05 (10H, m), 4.29 (1H, dd, J = 9.5, 7.5 Hz), 3.91 (1H, dd, J = 9.5, 7.5 Hz), 3.18 (1H, dd, J = 13.5, 4.5 Hz), 2.90−2.40 (5H, m); ^{13}H NMR ($CDCl_3$) δ 177.6, 137.3, 134.2, 130.1, 128.9, 128.6, 126.8, 126.7, 70.4, 46.0, 39.3, 36.4, 35.1; HRMS (EI, *m*/*z*) calcd for $C_{18}H_{18}O_2S$ (M^+) 298.1027, found 298.1035.

***cis*-Dihydro-3-phenylmethyl-4-(phenylsulfinyl)methyl-2(3*H*)-furanone (28)**: the sulfoxide **28** was obtained as a 1:1 diastereomeric mixture based on the phenylsulfinyl group, which was separated by medium-pressure column chromatography (AcOEt).

Less polar isomer: colorless oil; IR ($CHCl_3$) 1776 (lactone) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.54−7.05 (10H, m), 4.61 (1H, dd, J = 10, 1.5 Hz), 4.23 (1H, dd, J = 10, 5.5 Hz), 3.18 (1H, dd, J = 15, 4.5 Hz), 3.13−2.96 (2H, m), 2.92−2.74 (2H, m), 2.60 (1H, dd, J = 15, 9.5 Hz); HRMS (EI, *m*/*z*) calcd for $C_{18}H_{18}O_3S$ (M^+) 314.0976, found 314.0980.

Polar isomer: colorless oil; IR ($CHCl_3$) 1777 (lactone) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.55−7.15 (10H, m), 4.32 (1H, dd, J = 9, 3 Hz), 4.23 (1H, dd, J = 9, 5.5 Hz), 3.28−2.98 (3H, m), 2.93−2.78 (2H, m), 2.73 (1H, dd, J = 14.5, 9 Hz); HRMS (EI, *m*/*z*) calcd for $C_{18}H_{18}O_3S$ (M^+) 314.0976, found 314.0982.

***trans*-Dihydro-3-phenylmethyl-4-(phenylsulfinyl)-methyl-2(3*H*)-furanone (29):** the sulfoxide **29** was obtained as a 1:1 diastereomeric mixture based on the phenylsulfinyl group, which was separated by medium-pressure column chromatography (AcOEt).

Less polar isomer: colorless oil; IR ($CHCl_3$) 1771 (lactone) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.54−7.15 (10H, m), 4.21 (1H, dd, J = 9.5, 7.5 Hz), 3.89 (1H, dd, J = 9.5, 8.5 Hz), 3.29 (1H, dd, J = 14, 4.5 Hz), 2.86 (1H, dd, J = 14, 9 Hz), 2.84 (1H, m), 2.67 (1H, m), 2.65 (1H, dd, J = 13, 9 Hz), 2.45 (1H, dd, J = 13, 4 Hz); HRMS (EI, *m*/*z*) calcd for $C_{18}H_{18}O_3S$ (M^+) 314.0976, found 314.0983.

Polar isomer: colorless oil; IR ($CHCl_3$) 1772 (lactone) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.58−7.17 (10H, m), 4.56 (1H, dd, J = 10, 7 Hz), 4.09 (1H, br dd, J = 10, 8.5 Hz), 3.18 (1H, m), 2.81 (1H, dd, J = 13.5, 10 Hz), 2.73−2.52 (3H, m), 2.40 (1H, dd, J = 13.5, 3 Hz); HRMS (EI, *m*/*z*) calcd for $C_{18}H_{18}O_3S$ (M^+) 314.0976, found 314.0981.

[*Z*(*cis*)]-*N*-[Tetrahydro-3-phenylmethyl-4-(phenylsulfinyl)methyl-furan-2-ylidene]-*O*-methylhydroxyamine (30): the sulfoxide **30** was obtained as a 1:1 diastereomeric mixture based on the phenylsulfinyl group, which was separated by medium-pressure column chromatography (AcOEt).

Less polar isomer: colorless oil; IR ($CHCl_3$) 1673 (C═N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60−7.18 (10H, m), 4.60 (1H, br d, J = 9.5 Hz), 4.33 (1H, dd, J = 9.5, 4 Hz), 3.79 (3H, s), 3.30 (1H, m), 3.11 (1H, dd, J = 15, 5.5 Hz), 2.90−2.76 (3H,

m), 2.57 (1H, dd, J = 15, 10 Hz); HRMS (EI, m/z) calcd for $C_{19}H_{21}NO_3S$ (M^+) 343.1241, found 343.1226.

Polar isomer: colorless oil; IR ($CHCl_3$) 1674 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.54−7.14 (10H, m), 4.30 (1H, dm, J = 9 Hz), 4.21 (1H, dm, J = 9 Hz), 3.78 (3H, s), 3.33 (1H, m), 3.14 (1H, br dd, J = 15, 5 Hz), 2.96−2.79 (3H, m), 2.69 (1H, dd, J = 15, 10 Hz); HRMS (EI, m/z) calcd for $C_{19}H_{21}NO_3S$ (M^+) 343.1241, found 343.1228.

[*Z*(*trans*)]-*N*-[Tetrahydro-3-phenylmethyl-4-(phenylsulfinyl)methyl-furan-2-ylidene]-*O*-methylhydroxyamine (31): the sulfoxide **31** was obtained as a 1:1 diastereomeric mixture based on the phenylsulfinyl group, which was separated by medium-pressure column chromatography (AcOEt).

Less polar isomer: colorless oil; IR ($CHCl_3$) 1671 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.55−7.15 (10H, m), 4.42 (1H, dd, J = 9.5, 7.5 Hz), 3.93 (1H, dd, J = 9.5, 7 Hz), 3.84 (3H, s), 3.27 (1H, dd, J = 13.5, 4 Hz), 2.98−2.49 (4H, m), 2.30 (1H, dd, J = 13.5, 4.5 Hz); HRMS (EI, m/z) calcd for $C_{19}H_{21}NO_3S$ (M^+) 343.1241, found 343.1221.

Polar isomer: colorless oil; IR ($CHCl_3$) 1672 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.55−6.99 (10H, m), 4.56 (1H, dd, J = 9.5, 7 Hz), 4.13 (1H, dd, J = 9.5, 7 Hz), 3.82 (3H, s), 3.17 (1H, dd, J = 13.5, 4.5 Hz), 2.94−2.31 (5H, m); HRMS (EI, m/z) calcd for $C_{19}H_{21}NO_3S$ (M^+) 343.1241, found 343.1223.

(*E*)-3-(1,3-Benzodioxol-5-yl)-*N*-methoxy-2-propenamide (32). According to the procedure described in the preparation of **6a**, acylation of methoxyamine hydrochloride (9.2 g, 0.11 mol) with 3,4-methylenedioxycinnamoyl chloride (21 g, 0.1 mol) gave the hydroxamate **32** (9.2 g, 96%) as colorless crystals: mp 145−147 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 3392 (NH), 1676 (CON) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.55 (1H, br s), 7.66 (1H, d, J = 15.5 Hz), 7.03 (1H, br s), 7.01 (1H, br d, J = 8.5 Hz), 6.79 (1H, br d, J = 8 Hz), 6.30 (1H, very br), 6.00 (2H, s), 3.83 (3H, s); HRMS (EI, m/z) calcd for $C_{11}H_{11}NO_4$ (M^+) 221.0688, found 221.0700. Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.44; H, 4.98; N, 6.27.

2-Propenyl (*Z*,*E*)-3-(1,3-Benzodioxol-5-yl)-*N*-methoxy-2-propenimidate (33). To a solution of **32** (221 mg, 1 mmol) and triphenylphosphine (524 mg, 2 mmol) in acetonitrile (15 mL) was added carbon tetrabromide (664 mg, 2 mmol) under a nitrogen atmosphere at room temperature. The reaction mixture was heated at reflux for 5 h. After the solvent was evaporated at reduced pressure, purification of the residue by medium-pressure column chromatography (hexane/AcOEt 7:1) afforded the corresponding hydroximoyl bromide (283 mg, quant) as colorless crystals. After being characterized by NMR spectra, the hydroximoyl bromide was immediately subject to the following reaction. To a suspension of NaH (60% oil suspension) (22 mg, 0.54 mmol) in THF was added the allyl alcohol (0.05 mL, 0.72 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at room temperature for 20 min, a solution of the hydroximoyl bromide (40 mg, 0.18 mmol) in THF (5 mL) was added to the reaction mixture. After being refluxed at 60 °C for 8 h, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 5:1) afforded **33** (22 mg, 61%) as colorless crystals: mp 43−46 °C (Et_2O); IR ($CHCl_3$) 1636 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40 (1H, d, J = 16 Hz), 6.96 (1H, d, J = 1.5 Hz), 6.90 (1H, dd, J = 8, 1.5 Hz), 6.77 (1H, d, J = 8 Hz), 6.32 (1H, d, J = 16 Hz), 6.03 (1H, ddt, J = 17, 10, 6 Hz), 5.97 (2H, s), 5.38 (1H, dq, J = 17, 1.5 Hz), 5.27 (1H, dq, J = 10, 1.5 Hz), 4.74 (2H, dt, J = 6, 1.5 Hz), 3.87 (3H, s); ^{13}H NMR ($CDCl_3$) δ 158.6, 148.5, 148.1, 136.0, 133.1, 130.2, 123.3, 117.4, 109.8, 108.3, 106.2, 101.2, 67.2, 61.8; HRMS (EI, m/z) calcd for $C_{14}H_{15}NO_4$ (M^+) 261.1000, found 261.1006. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.33; H, 5.73; N, 5.22.

Sulfanyl Radical Addition−Cyclization of the Hydroximate 33. According to the procedure described in the preparation of **13a** (method A), sulfanyl radical addition−cyclization of the hydroximate **33** (131 mg, 0.5 mmol) using thiophenol (0.05 mL, 0.5 mmol) and AIBN (41 mg, 0.25 mmol) followed by purification of the crude product by medium-pressure column chromatography (hexane/AcOEt 10:1) afforded *cis*-**35** (92 mg, 49%) as colorless crystals and *trans*-**34** (44 mg, 24%) as colorless oil.

[*Z*(*cis*)]-*N*-[3-[(1,3-Benzodioxol-5-yl)methyl]tetrahydro-4-(phenylsulfanyl)methylfuran-2-ylidene]-*O*-methylhydroxyamine (35): mp 112−114 °C (Et_2O); IR ($CHCl_3$) 1671 (C=N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18−6.97 (5H, m), 6.77 (1H, d, J = 8 Hz), 6.73 (1H, d, J = 1.5 Hz), 6.69 (1H, dd, J = 8, 1.5 Hz), 5.97 (2H, m), 4.50 (1H, dd, J = 9.5, 2 Hz), 4.17 (1H, ddd, J = 9.5, 5, 1.5 Hz), 3.82 (3H, s), 3.29 (1H, ddd, J = 11, 6.5, 5.5 Hz), 3.20 (1H, ddd, J = 13.5, 3.5, 1.5 Hz), 3.17 (1H, dd, J = 15, 5.5 Hz), 2.64 (1H, dd, J = 15, 11 Hz), 2.61 (1H, dd, J = 13.5, 12 Hz), 2.46 (1H, m); ^{13}H NMR ($CDCl_3$) δ 158.6, 147.7, 146.1, 134.4, 131.8, 128.7, 128.6, 121.3, 108.6, 108.2, 100.8, 73.0, 62.1, 43.2, 38.5, 31.1, 30.1; HRMS (EI, m/z) calcd for $C_{20}H_{21}NO_4S$ (M^+) 371.1191, found 371.1190. Anal. Calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77; S, 8.63. Found: C, 64.63; H, 5.55; N, 3.74; S, 8.80.

[*Z*(*trans*)]-*N*-[3-[(1,3-Benzodioxol-5-yl)methyl]tetrahydro-4-(phenylsulfanyl)methylfuran-2-ylidene]-*O*-methylhydroxyamine (34): IR ($CHCl_3$) 1670 (C=N) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27−7.12 (5H, m), 6.69 (1H, d, J = 8 Hz), 6.66 (1H, d, J = 1.5 Hz), 6.56 (1H, dd, J = 8, 1.5 Hz), 5.95 (2H, m), 4.34 (1H, dd, J = 9.5, 7 Hz), 4.07 (1H, dd, J = 9.5, 6 Hz), 3.83 (3H, s), 3.05 (1H, dd, J = 14, 4.5 Hz), 2.90 (1H, ddd, J = 9.5, 6, 4.5 Hz), 2.78 (1H, dd, J = 13.5, 5.5 Hz), 2.65 (1H, dd, J = 14, 9.5 Hz), 2.62 (1H, dd, J = 13.5, 9.5 Hz), 2.36 (1H, m); ^{13}H NMR ($CDCl_3$) δ 159.8, 147.6, 146.2, 134.3, 131.4, 130.0, 128.8, 126.5, 121.9, 109.2, 108.1, 100.7, 74.3, 62.1, 45.5, 40.7, 37.3, 36.3; HRMS (EI, m/z) calcd for $C_{20}H_{21}NO_4S$ (M^+) 371.1191, found 371.1176.

Isomerization of *cis*-35 to *trans*-34. According to the procedure described in the isomerization of *cis*-**13a**, a solution of *cis*-**35** (37 mg, 0.1 mmol) and NaOEt (153 mg, 2.25 mmol) in EtOH (10 mL) was refluxed for 10 h. After usual workup, crude product was purified by medium-pressure column chromatography (hexane/AcOEt 10:1) to afford *trans*-**34** (27 mg, 73%) as colorless oil, which was identical with *trans*-**34** obtained by the radical cyclization of **33**.

***trans*-3-[(1,3-Benzodioxol-5-yl)methyl]dihydro-4-(phenylsulfanyl)-methyl-2(3*H*)-furanone (36).** A solution of **34** (501 mg, 1.35 mmol) in concentrated HCl (19 mL) and MeOH (49 mL) was stirred at room temperature for 1 h, and H_2O was added to the reaction mixture. The resulting solution was extracted with CH_2Cl_2, and the organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 3:1) afforded the lactone **36** (443 mg, 96%) as colorless oil: IR ($CHCl_3$) 1770 (lactone) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.16 (5H, m), 6.70 (1H, d, J = 8 Hz), 6.62 (1H, d, J = 1.5 Hz), 6.53 (1H, dd, J = 8, 1.5 Hz, ArH), 5.95 (2H, m), 4.31 (1H, dd, J = 9.5, 7.5 Hz), 3.92 (1H, dd, J = 9.5, 8 Hz), 3.13−2.38 (6H, m); ^{13}H NMR ($CDCl_3$) δ 177.6, 147.8, 146.4, 134.3, 130.9, 130.3, 129.0, 126.9, 122.1, 109.3, 108.3, 100.9, 70.6, 46.3, 39.3, 36.6, 34.9; HRMS (EI, m/z) calcd for $C_{19}H_{18}O_4S$ (M^+) 342.0919, found 342.0913.

***trans*-3-[(1,3-Benzodioxol-5-yl)methyl]dihydro-4-(phenylsulfinyl)-methyl-2(3*H*)-furanone (37). By Oxidation of 36.** To a solution of the lactone **36** (443 mg, 1.3 mmol) in CH_2Cl_2 (50 mL) was added dropwise a solution mCPBA (70% assay) (319 mg, 1.3 mmol) in CH_2Cl_2 (50 mL) under a nitrogen atmosphere at 0 °C. The reaction mixture was made alkaline with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 1:1) afforded the sulfoxide **37** (376 mg, 81%) as a 1:1 diastereomeric mixture based on a sulfinyl group, which was separated by medium-pressure column chromatography (AcOEt).

Less polar isomer: colorless oil; IR ($CHCl_3$) 1772 (lactone) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58−7.46 (5H, m), 6.76

(1H, d, J = 8 Hz), 6.69 (1H, d, J = 1.5 Hz), 6.64 (1H, dd, J = 8, 1.5 Hz), 5.99−5.92 (2H, m), 4.35 (1H, dd, J = 9.5, 7.5 Hz), 3.90 (1H, dd, J = 9.5, 8 Hz), 3.17 (1H, J = 13.5, 5 Hz), 2.92−2.58 (5H, m); HRMS (EI, m/z) calcd for $C_{19}H_{18}O_5S$ (M^+) 358.0854, found 358.0856.

Polar isomer: colorless oil; IR ($CHCl_3$) 1773 (lactone) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60−7.42 (5H, m), 6.65 (1H, d, J = 8 Hz), 6.47 (1H, d, J = 1.5 Hz), 6.36 (1H, dd, J = 8, 1.5 Hz), 5.99−5.92 (2H, m), 4.59 (1H, br dd, J = 10, 7 Hz), 4.10 (1H, br dd, J = 10, 8.5 Hz), 3.14−2.44 (6H, m); HRMS (EI, m/z) calcd for $C_{19}H_{18}O_5S$ (M^+) 358.0854, found 358.0854.

By Oxidation of 34. According to the procedure described in the preparation of **28**, oxidation of **34** (341 mg, 0.1 mmol) with HTIB (118 mg, 0.3 mmol) followed by purification of the crude product by medium-pressure column chromatography (hexane/AcOEt 1:1) afforded the sulfoxide **37** (7 mg, 19%). This compound was identical with **37** obtained by oxidation of **36**.

***trans*-3-[(1,3-Benzodioxol-5-yl)methyl]-4-formyldihydro-2(3*H*)-furanone (38).** To a solution of the sulfoxide **37** (119 mg, 0.33 mmol) and 2,6-lutidine (0.15 mL, 1.33 mmol) in dry MeCN (3.3 mL) was added a solution of TFAA (0.19 mL, 1.33 mmol) in dry MeCN (1.5 mL) under a nitrogen atmosphere at 0 °C. After being stirred at same temperature for 1 h, once again 2,6-lutidine (0.15 mL, 1.33 mmol) and TFAA (0.19 mL, 1.33 mmol) were added to the reaction mixture. After being stirred at same temperature for 1 h, a solution of $NaHCO_3$ (672 mg, 8 mmol) in H_2O (10 mL) was added to the reaction mixture. The resulting solution was stirred at same temperature for 2 h. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with 5% HCl, saturated aqueous $NaHCO_3$, and H_2O, dried over Na_2SO_4, and concentrated at reduce pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 1:1) afforded the aldehyde **38** (69 mg, 84%) as colorless oil. After being characterized by NMR spectra, unstable **38** was immediately subjected to the following reaction. IR ($CHCl_3$) 1772 (lactone) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.37 (1H, d, J = 1.5 Hz), 6.70 (3H, m), 5.95 (2H, d, J = 4.5 Hz), 4.37 (1H, dd, J = 9.5, 7.5 Hz), 4.25 (1H, dd, J = 9.5, 8.5 Hz), 3.40−2.75 (4H, m).

***trans*-4-[(1,3-Benzodioxol-5-yl)hydroxymethyl]-3-[(1,3-benzodioxol-5-yl)methyl]dihydro-2(3*H*)-furanone (39).** To a suspension of Mg (34 mg, 1.39 mmol) in dry Et_2O (2 mL) was added 4-bromo-1,2-methylenedioxybenzene (0.27 mL, 2.22 mmol) under a nitrogen atmosphere at room temperature. After being heated under reflux for 1 h, the reaction mixture was cooled to 0 °C in an ice bath. A solution of the aldehyde **38** (69 mg, 0.28 mmol) in dry THF (2 mL) was added dropwise to the reaction mixture. After being stirred at same temperature for 1.5 h, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by medium-pressure column chromatography (hexane/AcOEt 1:1) afforded the alcohol **39** (47 mg, 45%) as a 1:1 diastereomeric mixture based on 1″-position: colorless oil; IR ($CHCl_3$) 3589 (OH), 1765 (lactone) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.90−6.45 (6H, m), 6.00−5.85 (4H, m), 4.61 (1/3H, dd, J = 6.5, 2.5 Hz), 4.38 (2/3H, dd, J = 6, 2.5 Hz), 4.16−4.06 (5/3H, m), 3.93 (1/3H, d, J = 7.5 Hz), 2.99−2.46 (4H, m), 2.04 (1/3H, d, J = 2.5 Hz), 2.01 (2/3H, d, J = 2.5 Hz); HRMS (EI, m/z) calcd for $C_{20}H_{18}O_7$ (M^+) 370.1052, found 370.1059.

(±)-Oxo-parabenzlactone (40). To a solution of the alcohol **39** (23 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) was added PCC (32 mg, 0.15 mmol) under a nitrogen atmosphere at room temperature. After being stirred at same temperature for 4 h, the reaction mixture 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 (hexane/AcOEt 3:1) afforded the ketone **40** (12 mg, 52%) as colorless crystals. This compound was identical with authentic sample upon comparison of their spectral data: mp 138−139 °C (Et_2O/benzene) (lit.[11] (+)-**40** mp 105−106 °C); IR ($CHCl_3$) 1772 (lactone) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.27 (1H, dd, J = 8, 2 Hz), 7.21 (1H, d, J = 2 Hz), 6.81 (1H, dd, J = 8, 2 Hz), 6.62 (1H, d, J = 8 Hz), 6.61 (1H, d, J = 2 Hz), 6.53 (1H, dd, J = 8, 2 Hz), 6.07 (2H, s), 5.90 (1H, d, J = 1 Hz), 5.89 (1H, d, J = 1 Hz), 4.40 (1H, t, J = 8.5 Hz), 4.14 (1H, t, J = 8.5 Hz), 4.01 (1H, q, J = 8.5 Hz), 3.47 (1H, br td, J = 9, 6 Hz), 3.06 (1H, dd, J = 14, 5.5 Hz), 2.92 (1H, dd, J = 14, 7.5 Hz); HRMS (EI, m/z) calcd for $C_{20}H_{16}O_7$ (M^+) 368.0895, found 368.0898.

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Supporting Information Available: General experimental details and materials, as well as complete experimental procedures and characterization data for compounds **6b**−**e**, **8b**−**d**, **20a**−**e**, **23a**−**c**, **13b**−**d**, **14b**−**d**, **21a**−**e**, **22a**−**e**, **24 a**−**c**, and **25b**,**c** and X-ray crystallographic data for compound **13a**. These materials are available free of charge via the Internet at http://pubs.acs/org.

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