2,4(5)-Bis(2-mercaptoethyl)-1*H*-imidazole (34). To a solution of 0.99 g (2.68 mmol) of 2,4(5)-bis[2-[(phenylmethyl)thio]ethyl]-1*H*-imidazole in 50 mL of liquid ammonia was added small pieces of sodium until the blue color persisted for 45 min (±350 mg, 15 mmol). Next the solution was neutralized with 1 g (18 mmol) of NH_4Cl. The NH_3 was evaporated in a stream of N_2, and the residue was dissolved in 50 mL of $CHCl_3$ and washed with a dilute solution of $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (2 × 25 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica (eluent: $CHCl_3$/7% CH_3OH). The yield of **34** was 450 mg (2.39 mmol, 89%), obtained as a slightly yellow oil): R_f 0.25 ($CHCl_3$/7% CH_3OH); ^1H NMR ($CDCl_3/CD_3OD$) δ 2.6–3.0 (m, 8 H, 4 × CH_2), 4.5 (br, 3 H, SH + NH), and 6.74 (s, 1 H, 5(4)-H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 22.7 (t), 23.7 (t), 31.0 (t), 32.2 (t), 114.9 (d), 134.6 (s), and 145.7 (s); exact mass *m/e* calcd for $C_7H_{12}N_2S_2$ 188.044, found 188.043. On exposure to air, a precipitate formed within 15 min from a methanol solution as a result of oxidation.

4(5)-(Chloromethyl)-1*H*-imidazole (36). This compound was prepared by a method described in the literature,[57] from 6.9 g (51 mmol) of **35**. The yield of **36** was 7.65 g (50 mmol, 99%), obtained as a beige solid, mp 138–142 °C (lit.[57] mp 138–141 °C): ^1H NMR ($CDCl_3$) δ 4.88 (s, 2 H, CH_2), 5.1 (br, 2 H, NH), 7.73 (s, 1 H, 5(4)-H), and 9.90 (s, 1 H, 2-H).

1,6-Bis(imidazol-4(5)-yl)-2,5-dithiahexane (37a). To a solution of 1.17 g (12.5 mmol) of 1,2-ethanedithiol and 2.8 g (50 mmol) of KOH in 50 mL of absolute ethanol was slowly added 3.8 g (25 mmol) of **36** dissolved in 50 mL of absolute ethanol. The solution was refluxed for 3 h and left overnight at room temperature. After evaporation of the solvent, the residue was redissolved in 100 mL of a 1 N HCl solution, which was washed with $CHCl_3$ (3 × 50 mL). The aqueous solution was made alkaline (pH 9) with a NaOH solution and extracted with $CHCl_3$ (+ 10% C_2H_5OH) (6 × 50 mL). After evaporation of the solvent, the residue was chromatographed on silica (eluent: $CHCl_3$/10% CH_3OH). Recrystallization of the product from CH_3OH afforded 1.5 g (5.9 mmol, 47% yield) of **37a** as white crystals, mp 189–191 °C: R_f 0.19 ($CHCl_3$/10% CH_3OH); ^1H NMR (CD_3OD) δ 2.65 (s, 4 H, SCH_2CH_2S), 3.74 (s, 4 H, SCH_2Im), 6.93 (d, J = 1 Hz, 2 H, 5(4)-H), and 7.69 (d, J = 1 Hz, 2 H, 2-H); ^{13}C NMR (CD_3OD) δ 28.28 (t), 32.20 (t), 118.88 (d), 135.70 (s), and 136.55 (d); MS *m/e* (rel intensity) 254 (2) and 81 (100). Anal. Calcd for $C_{20}H_{14}N_4S_2$: C, 47.21; H, 5.55; N, 22.02; S, 25.22. Found: C, 46.96; H, 5.60; N, 21.75; S, 25.10.

1,7-Bis(imidazol-4(5)-yl)-2,6-dithiaheptane (37b). This compound was prepared as described for **37a**, from 1.35 g (12.5 mmol) of 1,3-propanedithiol. The yield of **37a** was 2.2 g (8.3 mmol, 66%), obtained as colorless crystals, mp 114–116 °C: R_f 0.08 ($CHCl_3$/10% CH_3OH); IR (KBr) 3500–2600 (br), 1460 and 840 cm^{-1}; ^1H NMR (CD_3OD) δ 1.81 (quintet, 2 H, $CH_2CH_2CH_2$), 2.60 (t, 4 H, SCH_2CH_2), 3.76 (s, 4 H, SCH_2Im), 6.92 (s, 2 H, 5(4)-H), and 7.75 (s, 2 H, 2-H); ^{13}C NMR (CD_3OD) δ 28.25 (t), 29.87 (t), 31.10 (t), 118.92 (d), 135.71 (s), and 136.47 (d); MS *m/e* (rel intensity) 268 (1) and 81 (100). An analysis within 0.3% could not be obtained for this compound.

Crystal Structure Determination of [24·Zn·$(H_2O)_2$]$(NO_3)_2$. Crystallographic details are available in the supplementary material.

Registry No. **7**, 111692-80-9; **7**·Zn·H_2O, 125329-57-9; **7**·Co·H_2O, 125329-58-0; **8**, 2150-44-9; **9**, 111682-05-4; **10**, 125329-36-4; **12a**, 111682-04-3; **12b**, 125329-39-7; **13**, 41383-84-0; **14**, 125329-43-3; **15a**, 29677-71-2; **15b**, 125329-44-4; (**16**·Zn)$_2$, 125329-67-1; **16**·Co, 125329-70-6; **17**, 125329-47-7; **17**·Zn, 125329-68-2; **19**, 1940-57-4; **20**, 125329-46-6; **21**, 7703-74-4; **22**, 125329-45-5; **23**, 108-48-5; **24**, 125357-28-0; **24**·Zn$(NO_3)_2$, 125329-66-0; [**24**·Zn·$(H_2O)_2$]$(NO_3)_2$, 125329-72-8; **24**·Co$(NO_3)_2$, 125329-64-8; **25**, 125329-48-8; **25**·Zn$(NO_3)_2$, 125329-62-6; **25**·Co$(NO_3)_2$, 125329-60-4; **26**, 125329-49-9; **27**, 125329-50-2; **28**, 125329-52-4; (**28**·Zn)$_2$, 125329-69-3; **29**, 110-65-6; **30**, 140-86-3; **31**, 125329-53-5; **32**, 5601-23-0; **33**, 125329-54-6; **34**, 125329-56-8; **35**, 32673-41-9; **36**, 38585-61-4; **37a**, 118090-72-5; **37b**, 119827-35-9; HLADH, 9031-72-5; $BrCH_2CH_2CH_2Br$, 109-64-8; H_2NCSNH_2, 62-56-6; CH_3SH, 74-93-1; $PhCH_2NH_2$, 100-46-9; CH_3COSH, 507-09-5; $PhCH_2SH$, 100-53-8; CH_3CN, 107-13-1; CH_3OH, 67-56-1; NH_3, 7664-41-7; $HSCH_2CH_2SH$, 540-63-6; $HSCH_2CH_2CH_2SH$, 109-80-8; methyl 3,5-bis(3-mercaptopropoxy)benzoate, 125329-37-5; histamine, 51-45-6; histamine-2HCl, 56-92-8; methyl 3,5-bis[3-(methylthio)propoxy]benzoate, 125329-38-6; 3,5-bis[3-(methylthio)propoxy]benzoic acid, 125329-40-0; 3,5-bis[3-(methylthio)propoxy]benzoyl chloride, 125357-27-9; 8,9-benzo-18-(methoxycarbonyl)-6,11-dithia-2,15-dioxabicyclo[14.3.1]eicosa-1(20),16,18-triene, 125329-41-1; 8,9-benzo-18-carboxy-6,11-dithia-2,15-dioxabicyclo[14.3.1]eicosa-1-(20),16,18-triene, 125329-42-2; 9-fluorenyl disulfide, 101796-83-2; 2,6-bis[2-methyl-2-(acetylthio)propyl]pyridine, 125329-51-3; 3-oxobuten-4-ol, 52642-66-7; 2,4(5)-bis[2-[(phenylmethyl)thio]-ethyl]-1*H*-imidazole, 125329-55-7; 9-mercaptofluorene, 19552-08-0.

Supplementary Material Available: Structural report, tables of bond distances, bond angles, root-mean-square amplitudes of thermal vibration, least-square planes, torsional angles, temperature factor expressions, positional parameters, and packing diagram from X-ray analysis of **24**·Zn·$(H_2O)_2(NO_3)_2$ and NMR (^{13}C and ^1H) spectra for **12a**, **14**, **25**, **27**, **32a,b**, and **37a** together with those for various intermediates (33 pages). Ordering information is given on any current masthead page.

(57) Turner, R. A.; Huebner, C. F.; Scholz, C. R. *J. Am. Chem. Soc.* **1949**, *71*, 2801.

Stereoselective Intramolecular Nitrone Cycloadditions Promoted by an Allylic Stereocenter

Rita Annunziata, Mauro Cinquini,* Franco Cozzi,* and Laura Raimondi

Centro CNR and Dipartimento di Chimica Organica e Industriale dell'Università, I-20133 Milano, Italy

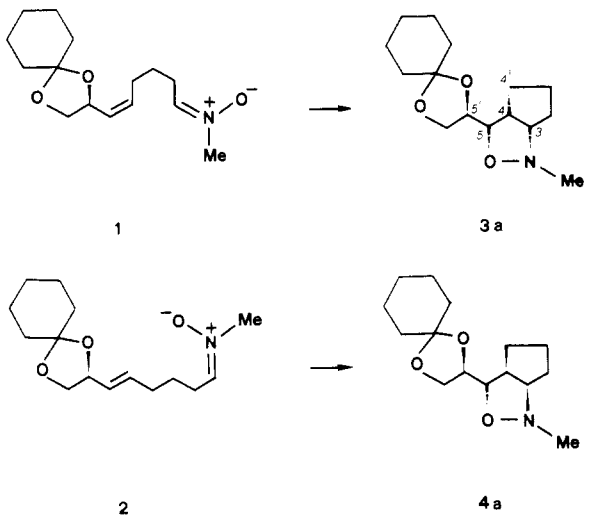
Received April 17, 1989

A series of intramolecular nitrone cycloadditions to chiral allyl ethers was studied in order to evaluate the influence on the stereochemical outcome exerted by several factors, including the nature of the substituents at the stereocenter and the steric and electronic features of the double bond. A comparison between the stereoselectivity of these reactions and that of related nitrile oxides cycloadditions suggests that they could proceed via similar transition states.

Nitrone cycloaddition to alkenes is an efficient method of constructing a variety of complex carbon frameworks.[1] In this process the stereochemical information present in the dipolarophile is completely retained in the cycloadduct,

0022-3263/90/1955-1901$02.50/0

Scheme I



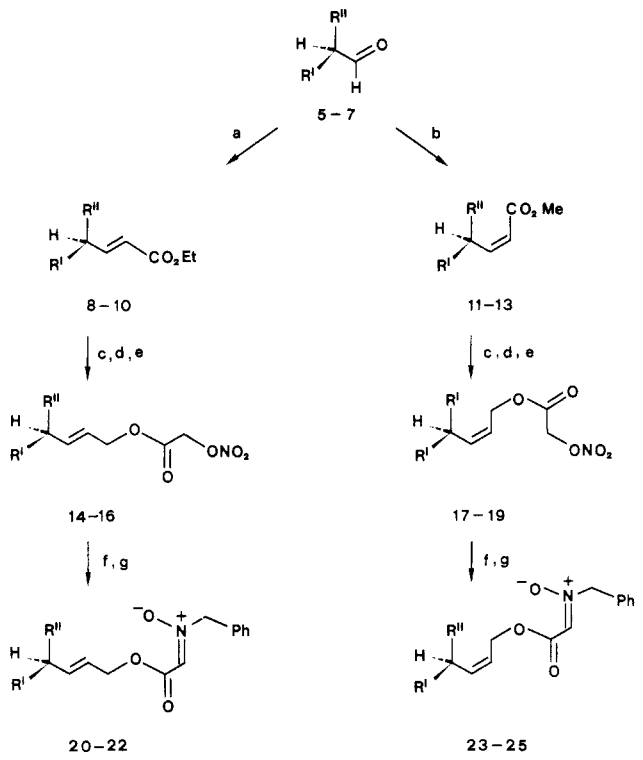
and the relative stereochemistry at C-4 and C-5 in the formed isoxazolidine is predetermined by alkene geometry.[1]

Stereoselection at C-3 and control of absolute stereochemistry have also been the subjects of recent research.[1,2] Intramolecular cycloadditions with a stereocenter inserted either on the nitrone nitrogen[1,3] or in the tether connecting dipole and dipolarophile[1,2,4] gave the best results.

The influence of an allylic stereocenter located outside the tether has been recently investigated by us in the reaction of nitrones **1** and **2** to give the corresponding cycloadducts **3** and **4** (Scheme I).[5,6] In the case of (*Z*)-alkenyl nitrone **1** a 96:4 mixture of 3,4-syn-4,5-syn-5,5′-anti, **3a**, and its syn-syn-syn isomer, **3b**, was obtained, while from (*E*)-alkenyl nitrone **2** the syn-anti-anti isoxazolidine **4a** was produced in a 92:8 excess over the syn-anti-syn isomer. [The numbering indicated in Scheme I is used throughout the discussion and in the tables. The Chemical Abstract numbering of the cycloadducts is used in the Experimental Section.] Thus in these reactions the allylic stereocenter can effectively control the formation of three new contiguous stereocenters, and one of eight possible stereoisomers is produced in a highly selective fashion.[7]

In this study we report a series of reactions related to that of Scheme I, in which we examined the influence of the substituents at the stereocenter, the alkene geometry, and the electronic nature of the double bond on the cycloaddition stereochemistry. These cycloadditions lead to highly functionalized carbon frameworks that can be considered useful precursors of various cyclic and acyclic molecules.

Scheme II[a]



5, 8, 11, 14, 17, 20, 23: R′ = OCH_2Ph; R″ = Me
6, 9, 12, 15, 18, 21, 24: R″,R′ = $OC(CH_2)_5OCH_2$
7, 10, 13, 16, 19, 22, 25: R′,R″ = $CH_2CH_2CH_2O$

[a] Reagents: (a) $(EtO)_2P(O)CH_2COOEt$, NaH, THF; (b) $(CF_3CH_2O)_2P(O)CH_2COOMe$, KH, THF; (c) DIBAH, CH_2Cl_2; (d) $BrCH_2COBr$, py, CH_2Cl_2; (e) $AgNO_3$, CH_3CN; (f) AcONa, DMSO; (g) $PhCH_2NHOH$, Et_2O.

Results and Discussion

The synthetic routes to the desired cycloadducts are reported in Scheme II–IV.

Starting from (*S*)-*O*-benzyllactaldehyde **5**,[8] (*R*)-*O*,*O*-cyclohexylideneglyceraldehyde **6**,[9] and (*R*,*S*)-2-tetrahydrofurfural **7**,[10] *E* esters **8–10** and *Z* esters **11–13** were obtained by standard methods.[11] DIBAH reduction to the alcohols,[11] and reaction with bromoacetyl bromide gave the corresponding α-bromo esters,[12a] which were converted by reaction with silver nitrate into the nitrate esters **14–19**. Treatment of the latter with sodium acetate in dimethyl sulfoxide[12a,b] gave the aldehydes, from which (*E*)- and (*Z*)-alkenyl nitrones **20–22** and **23–25**, respectively, were obtained by reaction with *N*-benzylhydroxylamine in diethyl ether/THF as solvent (Scheme II).

N-Benzyl-α-alkoxy carbonyl nitrones are known to exist in both *E* and *Z* configurations at C=N, the former being predominant in apolar solvents and the latter in polar solvents.[13] The NMR spectra of **20–25** showed only the presence of the *Z* nitrone[13] (together with limited amount

(1) Reviews: (a) Tufariello, J. J. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A. Ed.; Wiley-Interscience: New York 1984; Vol. 2, pp 83–168. (b) Padwa, A. *Ibid.* Vol. 2, pp 277–406. (c) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (d) Balasubramanian, N. *Org. Prep. Proced. Int.* **1985**, *17*, 23. (e) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1.

(2) For a review on stereocontrol of nitrone cycloaddition to alkenes, see: Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Gazz. Chim. Ital.* **1989**, *119*, 253.

(3) Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron* **1985**, *41*, 3455.

(4) (a) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990, 2400, 2411. (b) Baggiolini, E. G.; Lee, H. L.; Pizzolato, G.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 6460. (c) Ihara, M.; Takahashi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1988**, 9. (d) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1988**, 2881.

(5) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1987**, *43*, 4051.

(6) For a related study on nitrile oxide cycloaddition, see: Annunziata, R.; Cinquini, M.; Cozzi, F.; Gennari, C.; Raimondi, L. *J. Org. Chem.* **1987**, *52*, 4674.

(7) When a cyclohexane ring fused to the isoxazolidine heterocycle was formed, the stereocontrol at C-3/C-4 was less efficient, but still the C-5/C-5′ anti isomers largely predominate over the C-5/C-5′ syn ones.[5]

(8) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1983**, *48*, 3489.

(9) Grauert, M.; Schöllkopf, U. *Justus Liebigs Ann. Chem.* **1985**, 1817.

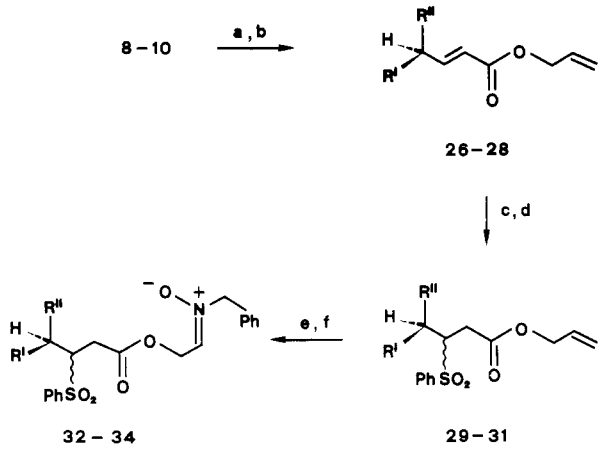
(10) Amouroux, R.; Chastrette, F.; Chastrette, M. *J. Heterocycl. Chem.* **1981**, *18*, 565.

(11) Annunziata, R.; Cinquini, M.; Cozzi, F.; Dondio, G.; Raimondi, L. *Tetrahedron* **1987**, *43*, 2369.

(12) (a) Melnick, M. J.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 850. (b) Kornblum, N.; Frazier, M. W. *J. Am. Chem. Soc.* **1966**, *88*, 865.

(13) Inouye, Y.; Hara, J.; Kakisawa, H. *Chem. Lett.* **1980**, 1407. We thank one of the referee for pointing our attention to this article.

Scheme III[a]



8, 26, 29, 32: R′ = OCH_2Ph; R″ = Me
9, 27, 30, 33: R″,R′ = $OC(CH_2)_5OCH_2$
10, 28, 31, 34: R′,R″ = $CH_2CH_2CH_2O$

[a] Reagents: (a) 2 N NaOH, H_2O, EtOH; (b) Cs_2CO_3, CH_2=CH-CH_2Br, H_2O, EtOH; (c) PhSH, Et_3N; (d) $KHSO_5$, MeOH, H_2O, or $Bu_4N^+SO_5^-$ CH_2Cl_2; (e) O_3, CH_2Cl_2, MeOH; (f) $PhCH_2NHOH$, Et_2O, THF.

Table I. Synthesis of Isoxazolidines 35–43, 46, and 47

entry	products	yield, %	diastereomer ratios[a]
1	**35a,b**	67	50:50
2	**36a,b**	91	86:14
3	**37a,b**	52	73:27
4	**38a,b**	90	91:9
5	**39a,b**	95	≥97:3[b]
6	**40a,b**	77	≥97:3[b]
7	**41a,b**	63	50:50
8	**42a,b**	55	≥97:3[b]
9	**43a,b**	63	77:23
10	**46a,b**	68[c]	93:7
11	**47a,b**	56[c]	≥97:3[b]

[a] As determined by ^1H and ^{13}C NMR spectroscopy. [b] A single isomer detected. [c] Overall yield from the aldehyde (see Scheme V).

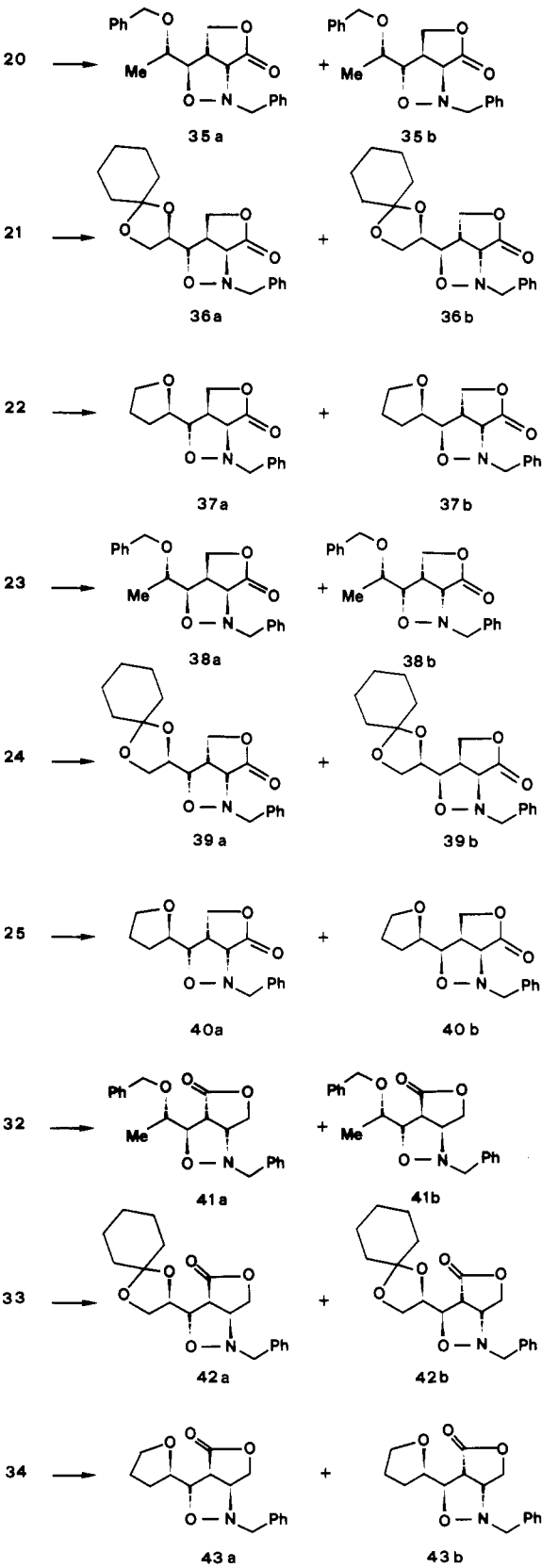
of the cycloaddition products); however, since these nitrones are known to equilibrate even at room temperature,[13] we could not establish which is the reacting isomer.

The precursors of electron-poor alkenyl nitrones corresponding to **20–22** were prepared according to the reaction sequence of Scheme III. E Esters **8–10** were converted into allyl derivatives **26–28** by hydrolysis and reaction with allyl bromide in the presence of cesium carbonate.[14] Thiophenol addition and oxidation gave the β-sulfonyl esters **29–31**, which, upon treatment with ozone to give the aldehyde and reaction with *N*-benzylhydroxylamine, were converted in nitrones **32–34**. These were obtained in the *Z* configuration as observed in a very similar case[4d] and as generally reported.[1,13]

Intramolecular cycloadditions occurred in refluxing benzene for nitrones **20–25**, and in refluxing CCl_4 in the presence of DBU[4d] for nitrones **32–34**, to give isoxazolidines **35–43** (Scheme IV).

Finally, cycloadducts **46** and **47** were prepared according to Scheme V. Esters (*E*)-**9** and (*Z*)-**12** were reduced to the alcohols and converted into **44** and **45**, respectively, by reaction with ethyl bromoacetate. Reduction to the aldehyde and reaction with *N*-benzylhydroxylamine gave the corresponding nitrones [also in this case the *Z* configuration at C=N could be attributed to the nitrones by analogy to a closely related system[5]], which, upon heating in benzene, afforded the cycloadducts. Chemical yields and diastereoisomeric ratios of the cycloaddition reactions are collected in Table I. In most cases the products were

Scheme IV[a]



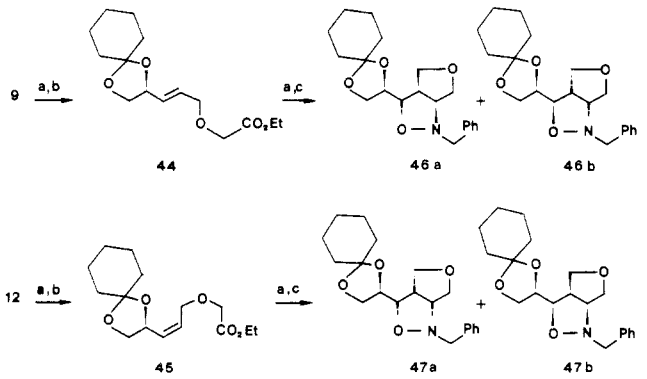
[a] In the case of compounds **37**, **40**, and **43**, only one enantiomer is shown for simplicity.

(14) Kunz, M.; Waldmann, M.; Klinkhammer, U. *Helv. Chim. Acta* **1988**, *71*, 121.

Table II. Relevant ^{13}C and ^{1}H NMR Data for Isoxazolidines 35–43, 46, and 47

	^{13}C NMR, δ				^{1}H NMR, δ				J, Hz		
compd	C-3	C-4	C-5	C-5′	H-3	H-4	H-5	H-5′	3/4	4/5	5/5′
35a	66.8	46.5	88.2	74.7	3.77	3.44	3.84	3.65	9.0	5.5	6.0
35b	66.7	45.4	86.8	73.2	3.75	3.35	4.04	3.69	8.0	5.6	6.0
36a	66.2	47.0	85.8	75.7	3.91	3.50	3.84	4.11	8.6	4.4	8.2
36b	66.5	45.5	83.4	73.8	3.77	3.46	4.12	4.28	8.0	5.2	5.2
37a	66.5	47.1	86.6	79.2	3.86	3.44	3.77	3.92	8.5	5.0	7.0
37b	66.6	45.9	86.0	77.6	3.78	3.43	3.99	4.02	8.0	7.0	2.0
38a	67.1	44.2	81.7	60.1	4.01	3.57	4.19	3.68	7.8	7.8	9.0
38b	66.5	45.3	83.7	60.8	3.96	3.52	4.37	3.74	8.5	5.5	8.0
39a	66.9	44.5	80.0	72.8	4.06	3.59	4.21	4.07	7.7	7.7	7.0
40	67.1	44.2	81.2	76.2	4.07	3.55	4.12	4.20	7.9	7.8	7.8
41a	67.5	49.5	84.2	72.9	3.56	3.69	4.20	3.82	7.8	4.5	2.1
41b	67.4	51.0	82.8	73.2	3.59	3.44	4.29	3.73	7.8	4.8	4.2
42a	67.7	50.1	81.1	73.9	3.66	3.61	4.20	4.32	8.0	4.0	4.0
43a	67.4	51.8	82.5	78.9	3.63	3.50	4.18	4.05	8.0	5.0	5.4
43b	67.9	49.6	82.3	77.1	3.66	3.52	4.25	4.07	8.0	5.0	2.5
46a	73.1	53.5	84.1	76.1	3.56	3.12	3.70	4.08	8.5	6.0	6.0
46b	–	–	–	–	3.66	3.26	3.82	4.50	–	–	8.0
47a	71.7	50.2	79.7	72.9	3.82	3.35	4.15	4.27	7.0	7.0	7.9

Scheme V[a]



[a] Reagents: (a) DIBAH, CH_2Cl_2; (b) $BrCH_2COOEt$, NaH, $Bu_4N^+I^-$, THF; (c) $PhCH_2NHOH$, benzene, room temperature → 80 °C.

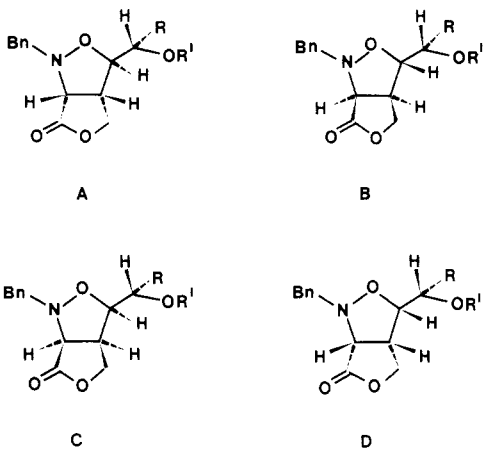


Figure 1. Suggested preferred conformations for **35–40** on the basis of NOE data; only the *S* configurated C-5′ stereocenter indicated for simplicity. A and B correspond to major and minor isomer from (*E*)-alkenes. C and D correspond to major and minor isomer from (*Z*)-alkenes.

separated by flash chromatography, thus affording isomerically pure compounds (see Experimental Section).

High-field ^{13}C and ^{1}H NMR spectroscopy allowed the determination of the structure of the cycloadducts and of the isomeric ratios. The relevant NMR data for compounds **35–43**, **46**, and **47** are collected in Table II.

Fused rather than bridged products were exclusively obtained as expected on the basis of steric arguments,[1,15] and in line with many similar intramolecular processes involving *C*-alkenyl nitrones and leading to isoxazolidines condensed to a five-membered ring.[1]

The assignment of configuration at the stereocenters in the cycloadducts is based on NMR spectroscopy and comparison with literature results.

For compounds **35–40** the attribution of the syn relative stereochemistry at C-3/C-4 is in agreement with a number of previous observations[1,4,5,15] and is supported by NOE experiments (see the supplementary material) that show 7–11% enhancements for H(C-3) upon saturation of H(C-4). The relative stereochemistry at C-4/C-5 can be inferred from alkene configuration[1] and is assigned as anti for (*E*)-alkene-derived compounds **35–37** and syn for (*Z*)-alkene-derived compounds **38–40**. NOE experiments confirmed this attribution: indeed, 6–8% enhancements were observed for H(C-4) upon saturation of H(C-5) for **38–40**, while no enhancements were observed for **35–37**.

Configurational assignment at C-5/C-5′ was based on the trend of the chemical shift value for H(C-5) and H(C-5′), which always increases on passing from anti (major) to syn (minor) isomers. This trend has been observed in all of the similar cases reported in the literature.[5,6,11,16] It must be noted that the H(C-5)/H(C-5′) coupling constant values proved to be unreliable in this as in the reported cases.[5,6,11,16] NOE experiments showed no H(C-5′) enhancements upon saturation of H(C-5) for major isomers and 5–10% enhancements for minor ones. Inspection of molecular models suggests that in the more stable conformation (Figure 1) of the cycloadducts the bulkier substituent at C-5′, i.e. alkyl group, should point away from the sterically congested bicyclic array of the molecule. In this hypothesis the NOE data are in full agreement with the assignment of C-5/C-5′ anti configuration to the major isomers and of C-5/C-5′ syn configuration to the minor ones.

In the case of compounds **41–43** the syn relative stereochemistry at C-3/C-4 is assigned by analogy with literature reports for similar system.[1,4c,d] Peak overlap prevented NOE evaluation for H(C-3)/H(C-4) in compound **41** and **42**; however a strong enhancement was observed for H(C-3)

(15) (a) Le Bel, N. A.; Whang, J. J. *J. Am. Chem. Soc.* **1959**, *81*, 6334. (b) Le Bel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc.* **1964**, *86*, 3759.

(16) (a) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1984**, *49*, 2762. (b) Jäger, V.; Schohe, R. *Tetrahedron* **1984**, *40*, 2199. (c) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Restelli, A. *Helv. Chim. Acta* **1985**, *68*, 1217.

upon saturation of H(C-4) in compound **43**. Configuration at C-4/C-5 was assigned as anti since base-promoted sulfinic acid elimination from a β-sulfonyl ester is known to deliver an (*E*)-alkene[4d,17] that is trapped by intramolecular cycloaddition.[4d] The attribution of C-5/C-5′ anti configuration to major isomers of **41–43** resided on the above-mentioned chemical shift value trend of the corresponding protons, the only exception being H(C-5′) for compound **41**. NOE experiments were useless in these cases, since similar enhancements for H(C-5′) upon saturation of H(C-5) were observed for both major and minor isomers.[18]

In the case of compounds **46** and **47** the syn relative stereochemistry at C-3/C-4 is assigned by analogy with compounds **3** and **4**.[5] In agreement with this attribution a 9% enhancement was observed for H(C-3) upon saturation of H(C-4) in **46a**. NOE data were not available for **47a** because of peak overlap. Configuration at C-4/C-5 followed once again from alkene geometry: the syn stereochemistry at these stereocenters in **47a** was supported by an 8% enhancement for H(C-5) upon saturation of H(C-4). The attribution of anti configuration at C-5/C-5′ of compound **46a** was based on the usual trend of the chemical shift values of the corresponding protons. The almost identical stereoselectivity of the cycloadditions leading to **46–47** and to **3–4**, two closely related system, supported the tentative attribution of the C-5/C-5′ anti configuration to isomers **46a** and **47a**.

A few trends clearly emerge from the results collected in Table I. Within homogeneous sets of reactions the best diastereoselections were achieved with glyceraldehyde-derived substrates (entries 2, 5, 8), as was also found in related nitrile oxide cycloadditions,[6,11,16a,b] and in other reactions of allyl ethers with electrophiles.[19] A stronger donor ability of the CH_2OR group compared to an alkyl group, due to lone pair participation of the homoallylic oxygen,[20] or a direct through-space interaction of the homoallylic oxygen lone pair with the alkene π bond, could rationalize this observation.[6,21]

(*Z*)-Alkenyl nitrones undergo more stereoselective cycloaddition than their *E* counterparts[22] (entries 1 vs 4, 2 vs 5, 3 vs 6, 10 vs 11), the (*Z*)-alkene giving at least 10:1 isomer ratio. In the case of *Z* olefins the stereoselectivity of the cycloaddition should be mainly ruled by steric effects; it seems reasonable that of the possible conformations of the stereocenter only those featuring the allylic hydrogen in the crowded "inside"[23] position must be considered for steric reasons, as in related intramolecular nitrile oxide cycloadditions,[6,11] and in electrophilic addition reactions to chiral alkenes.[23,24] Of the two transition states

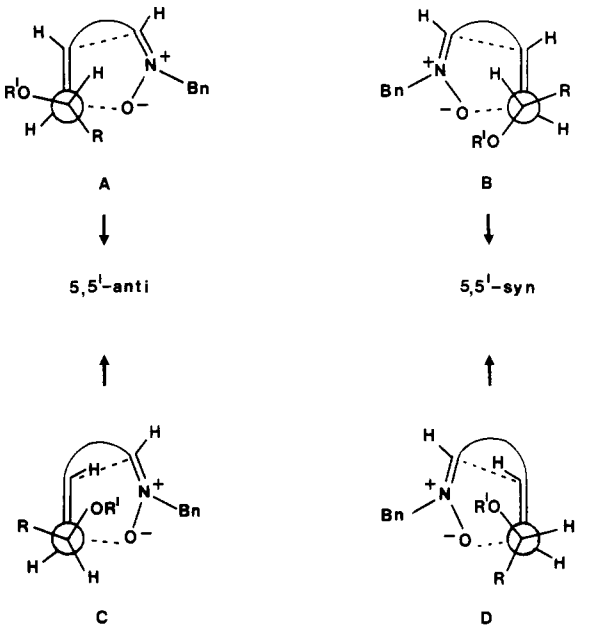


Figure 2. Proposed transition states for intramolecular cycloaddition. For simplicity only the *Z* nitrone and the *S* stereocenter are indicated. A and B refer to (*Z*)-alkenes; C and D to (*E*)-alkenes; Bn = $PhCH_2$.

depicted in Figure 2, B appears less favored than A because of repulsive interaction between the nitrone oxygen and the alkoxy group.

With (*E*)-alkenes steric factors are less stringent, and stereoelectronic effects must be considered. "Inside alkoxy" conformations[23] should be preferred in this case, once again in agreement with related nitrile oxide cycloadditions.[6,11,23] Of the two possible transition states C appears favored over D because the nitrone oxygen attacks away from the alkyl group located in the anti position and close to the allylic hydrogen located in the outside position. Both of these favorable factors are absent in transition state D (Figure 2).

On passing to electron-poor alkenes, that were obtained only in the *E* configuration, the diastereoselection remained virtually unchanged for isoxazolidines **41** and **43** and increased for **42**. In these cases transition states C and D, where the inside alkoxy group minimizes electron withdrawal from an electron-poor double bond,[25] should also be at work. The donor effect of the homoallylic oxygen in the glyceraldehyde-derived substrate (see above), seems to favor transition state C over D, leading to the increase of stereoselection observed for **42**.

Other factors should be considered in discussing the variation of selectivity, e.g. the electronic nature of the dipole or the conformational mobility of the chain in the transition state. [We thank one of the referees for pointing out this possibility.] While a separate evaluation of these two effects appears quite difficult, the latter factor seems to be of limited importance. Indeed, the presence of an ester function (as in the precursors of **35–43**) or of an ether function (as in the precursors of **46**, **47**) instead of a methylene group (as in the precursors of **3** and **4**)[5] in the chain connecting dipole and dipolarophile does not have a marked influence on the trend of stereoselectivity.

By comparing the results obtained in this study with other intramolecular nitrone cycloadditions,[1,4] it appears that an allylic stereocenter outside the tether between dipole and dipolarophile can control the steric course of

(17) Julià, M.; Badet, B. *Bull. Chim. Soc. Fr.* **1976**, 525.
(18) These results can be tentatively interpreted as follows: in order to avoid repulsive interactions between the alkoxy oxygen at C-5′ and the carbonyl oxygen the stereocenter could adopt two conformations that bring H(C-5) and H(C-5′) close to each other in both anti and syn isomers.
(19) See, for instance: Danishefsky, S. J.; Larson, E.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1274.
(20) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435.
(21) De Amici, M.; De Micheli, C.; Ortiz, A.; Gatti, G. Gandolfi, R.; Toma, L. *J. Org. Chem.* **1989**, *54*, 793.
(22) This effect was also observed in intramolecular nitrile oxide cycloadditions[6,11] although the difference in diastereoselectivity for (*E*)- and (*Z*)-alkenyl nitrile oxides was less marked.
(23) (a) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880. (b) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754.
(24) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247. (b) Vedeys, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094. (c) Fleming, I.; Sarkar, A. K.; Thomas, A. P. *J. Chem. Soc., Chem. Commun.* **1987**, 157.
(25) (a) Lassard, J.; Saunders, J. K.; Phan Viet, M. T. *Tetrahedron Lett.* **1982**, 2059. (b) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, 3951.

the cycloaddition more effectively than a chiral auxiliary located on the nitrone nitrogen atom,[3] likely too far away from the core of the transition state. On the other hand, the stereoselections observed when one or more stereocenters are inside the dipole–dipolarophile connecting chain are always very high and often complete.[1,2]

Another interesting comparison can be made between nitrone and nitrile oxide intramolecular cycloadditions,[6,12] the former being generally more stereoselective although carried out at higher temperatures. The factors determining the stereochemical outcome are common features of the two processes. This suggests that at least intramolecular nitrone cycloadditions could proceed through transition states similar to those proposed[2,6,23] for nitrile oxides. The bent structure of the nitrone dipole, more sterically demanding with respect to the linear nitrile oxide,[1] and the presence of a substituent at nitrogen that could make the reaction more sensitive to steric factors, can be tentatively invoked to explain the increase of diastereoselectivity observed for nitrone cycloadditions.

Experimental Section

^1H and ^{13}C NMR spectra were obtained on a Varian EM-390 or a Varian XL-300 spectrometer in $CDCl_3$ as solvent. Silica gel was used for analytical and flash chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure.

All reactions employing dry solvents were run under argon. THF and Et_2O were distilled from LAH; benzene from Na; DMSO, CH_2Cl_2, and Et_3N from CaH_2; CH_3CN from P_2O_5; MeOH from Mg turnings; pyridine from KOH; dry solvents were stored over molecular sieves under argon. The synthesis of esters **8**, **9**, **11**, and **12** was reported.[11] Esters **10** and **13** were obtained by the same procedure.

(*R,S*)-(*E*)-3-(2-Tetrahydrofuryl)propenoic acid ethyl ester (10): colorless oil; obtained in 76% yield (2.58 g, 15.2 mmol) with a 40:60 diethyl ether/hexanes mixture as eluant; IR (thin film) 2960, 1720, 1450, 1080, 1035 cm^{-1}; ^1H NMR δ 6.89 (dd, 1 H, C*H*=CHCOOEt, J = 15.6, 4.8 Hz), 5.94 (dd, 1 H, CH=C*H*COOEt, J = 15.6, 2.3 Hz), 4.35–4.65 (m, 1 H, CHO), 4.15 (q, 2 H, $MeCH_2O$, J = 6.8 Hz), 3.70–4.00 (m, 2 H, CH_2O), 1.40–2.15 (m, 4 H, CH_2CH_2), 1.15 (t, 3 H, CH_3, J = 6.8 Hz). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.38; H, 8.36.

(*R,S*)-(*Z*)-3-(2-Tetrahydrofuryl)propenoic acid methyl ester (13): colorless oil; obtained in 69% yield (2.15 g, 13.8 mmol) with a 35:65 diethyl ether/hexanes mixture as eluant; IR (thin film) 2960, 1730, 1450, 1065, 1030 cm^{-1}; ^1H NMR δ 6.25 (dd, 1 H, C*H*=CHCOOMe, J = 10.8, 6.3 Hz), 5.70 (dd, 1 H, CH=C*H*COOMe, J = 10.8, 2.4 Hz), 5.15–5.40 (m, 1 H, CHO), 3.75–4.10 (m, 2 H, CH_2O), 3.70 (s, 3 H, CH_3), 1.40–2.50 (m, 4 H, CH_2CH_2). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.60; H, 7.75.

General Procedure for the Synthesis of Cycloadducts 35–40. The products were prepared by a sequence of reactions from esters **8–13** involving (a) reduction to the alcohols, (b) synthesis of the bromoacetates, (c) synthesis of the nitrate esters, (d) conversion of the nitrate esters into the aldehydes, (e) synthesis of the nitrones, and (f) cycloadditions.

Reduction of Esters 8–13 to the Corresponding Alcohols.[11] To a stirred solution of esters (3 mmol) in CH_2Cl_2 (10 mL) cooled at −78 °C was added dropwise a 1 N solution of DIBAH in CH_2Cl_2 (9 mL, 9 mmol). The reaction was stirred at −78 °C and monitored by TLC until complete disappearance of the starting material. After quenching with a saturated aqueous solution of NH_4Cl, the organic phase was separated, dried, and evaporated to give the crude alcohols, which were used without further purification.

Synthesis of Bromoacetates.[12] To a stirred solution of alcohol (3 mmol) and pyridine (4.5 mmol, 0.36 mL) in CH_2Cl_2 (10 mL) cooled at 0 °C was added dropwise bromoacetyl bromide (3.3 mmol, 0.29 mL). The mixture was stirred for 30 min, poured onto ice, and extracted three times with CH_2Cl_2. The organic phase was washed with 5% HCl solution and with water, dried, and evaporated. The products were pure enough (by TLC and ^1H NMR) to be used without further purification.

Synthesis of Nitrate Esters 14–19.[12] To a stirred solution of bromo ester (3 mmol) in CH_3CN (5 mL) was added silver nitrate (6 mmol, 1.02 g) in one portion, and stirring was continued for 24 h. The solvent was then evaporated, and the residue was taken up in diethyl ether and filtered through a Celite cake, which was washed with a total of 50 mL of diethyl ether. The combined filtrate was washed with water and dried. Evaporation of the solvent gave the crude nitrate esters, which were purified by flash chromatography. These products were pale yellow oils, which decomposed upon distillation.

(*S*)-(Nitrooxy)acetic acid 4-(phenylmethoxy)-(*E*)-pent-2-enyl ester (14) was obtained from **8** in 65% overall yield (0.575 g) with a 30:70 diethyl ether/hexanes mixture as eluant: IR (thin film) 3040, 2940, 1760, 1650, 1265, 1100, 840 cm^{-1}; ^1H NMR δ 7.15–7.25 (m, 5 H, aromatic protons), 5.55–5.70 (m, 2 H, CH=CH), 4.70 (s, 2 H, CH_2ONO_2), 4.50–4.70 (m, 2 H, $=CCH_2O$), 4.20–4.50 (m, 2 H, CH_2Ph), 3.70–4.00 (m, 1 H, CHO), 1.10 (d, 3 H, J = 7.0 Hz, CH_3). Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 57.08; H, 5.90; N, 4.65.

(*S*)-(Nitrooxy)acetic acid 4-(1,4-dioxaspiro[4.5]dec-2-yl)-(*E*)-but-2-enyl ester (15) was obtained from **9** in 62% overall yield (0.56 g) with a 30:70 diethyl ether/hexanes mixture as eluant: IR (thin film) 2940, 1760, 1645, 1260, 1100, 840 cm^{-1}; ^1H NMR δ 5.65–5.90 (m, 2 H, CH=CH), 4.85 (s, 2 H, CH_2ONO_2), 4.65–4.80 (m, 2 H, $=CCH_2O$), 4.40–4.65 (m, 1 H, CHO), 4.05 (dd, 1 H, J = 6.5, 7.0 Hz, 1 H of OCH_2CHO), 3.55 (t, 1 H, J = 7.0 Hz, 1 H of OCH_2CHO), 1.30–1.70 (m, 10 H, C_6H_{10}). Anal. Calcd for $C_{13}H_{19}NO_7$: C, 51.82; H, 6.36; N, 4.65. Found: C, 51.69; H, 6.43; N, 4.71.

(*R,S*)-(Nitrooxy)acetic acid 4-(2-tetrahydrofuryl)-(*E*)-but-2-enyl ester (16) was obtained from **10** in 65% overall yield (0.45 g) with a 40:60 diethyl ether/hexanes mixture as eluant: IR (thin film) 2940, 1755, 1650, 1260, 1105, 850 cm^{-1}; ^1H NMR δ 5.55–5.85 (m, 2 H, CH=CH), 4.85 (s, 2 H, CH_2ONO_2), 4.55–4.70 (m, 2 H, $=CHCH_2O$), 4.05–4.40 (m, 1 H, CHO), 3.60–3.90 (m, 2 H, CH_2CH_2O), 1.50–2.05 (m, 4 H, CH_2CH_2). Anal. Calcd for $C_9H_{13}NO_6$: C, 46.75; H, 5.67; N, 6.06. Found: C, 46.88; H, 5.55; N, 6.00.

(*S*)-(Nitrooxy)acetic acid 4-(phenylmethoxy)-(*Z*)-pent-2-enyl ester (17) was obtained from **11** in 57% overall yield (0.504 g) with a 25:75 diethyl ether/hexane mixture as eluant: IR (thin film) 3040, 2950, 1760, 1650, 1265, 1100, 840 cm^{-1}; ^1H NMR δ 7.20–7.30 (m, 5 H, aromatic protons), 5.50–5.65 (m, 2 H, CH=CH), 4.85 (s, 2 H, CH_2ONO_2), 5.60–5.75 (m, 2 H, $=CCH_2O$), 4.25–4.55 (m, 2 H, CH_2Ph), 4.15–4.45 (m, 1 H, CHO), 1.20 (d, 3 H, J = 7.0 Hz, CH_3). Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.84; H, 5.88; N, 4.66.

(*S*)-(Nitrooxy)acetic acid 4-(1,4-dioxaspiro[4.5]dec-2-yl)-(*Z*)-but-2-enyl ester (18) was obtained from **12** in 58% overall yield (0.528 g) with a 30:70 diethyl ether/hexanes mixture as eluant: IR (thin film) 2940, 1760, 1650, 1260, 1100, 840 cm^{-1}; ^1H NMR δ 5.60–5.80 (m, 2 H, CH=CH), 4.70–5.10 (m, 5 H, CH_2ONO_2, $=CCH_2O$, CHO), 4.15 (dd, 1 H, J = 6.5, 7.0 Hz, 1 H of OCH_2CHO), 3.60 (t, 1 H, J = 7.0 Hz, 1 H of OCH_2CHO), 1.30–1.70 (m, 10 H, C_6H_{10}). Anal. Calcd for $C_{13}H_{19}NO_7$: C, 51.82; H, 6.36; N, 4.65. Found: C, 51.93; H, 6.28; N, 4.60.

(*R,S*)-(Nitrooxy)acetic acid 4-(2-tetrahydrofuryl)-(*E*)-but-2-enyl ester (19) was obtained from **13** in 54% overall yield (0.374 g) with a 30:70 diethyl ether/hexanes mixture as eluant: IR (thin film) 2960, 1760, 1650, 1260, 1105, 845 cm^{-1}; ^1H NMR δ 5.45–5.70 (m, 2 H, CH=CH), 4.80 (s, 2 H, CH_2ONO_2), 4.05–4.70 (m, 3 H, $=CCH_2O$, CHO), 3.55–3.90 (m, 2 H, CH_2CH_2O), 1.50–2.10 (m, 4 H, CH_2CH_2). Anal. Calcd for $C_9H_{13}NO_6$: C, 46.75; H, 5.67; N, 6.06. Found: C, 46.69; H, 5.68; N, 6.12.

Synthesis of Aldehydes.[12] To a stirred solution of the nitrate ester (1.5 mmol) in DMSO (3 mL) was added anhydrous sodium acetate (2 mmol, 0.164 g). The mixture was stirred for 1 h at room temperature, poured into brine, and extracted with a total of 30 mL of ethyl acetate. The organic phase was washed with a saturated sodium bicarbonate solution and with water, and the combined aqueous phases were extracted with ethyl acetate. The combined organic extracts were dried and evaporated to give the crude aldehydes. Since these products proved to be unstable,[12] they were used without further purification.

Synthesis of Nitrones and Intramolecular Cycloadditions. *N*-Benzylhydroxylamine (1.5 mmol, 0.185 g) was added to a stirred

solution of crude aldehyde in a mixture of diethyl ether (5 mL) and THF (1 mL). After overnight stirring at room temperature, TLC analysis showed no traces of the aldehyde. The solvent was evaporated to give the crude nitrones, which showed the *N*-benzyl methylene signal in the range 3.80–4.10 ppm, thus indicating the *Z* configuration at C=N.[13] The ^{1}H NMR spectrum showed also limited amount of the corresponding cycloadduct. The crude nitrones were dissolved in benzene (10 mL) and refluxed for 12 h. Evaporation of the solvent gave the crude cycloadducts that were purified by flash chromatography, which allowed diastereoisomer separation. Yields and diastereoisomeric ratios are reported in Table I; relevant NMR data are collected in Table II. NOE data are collected in the supplementary material.

[3*R*,3a*R*,6a*R*(*S*)]- and [3*S*,3a*S*,6a*S*(*S*)]-tetrahydro-3-(1-(phenylmethoxy)ethyl)-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (35a,b) were obtained with a 1:1 diethyl ether/hexanes mixture as eluant: IR (KBr) 3040, 2980, 1780, 1455, 1380, 1120, 740, 700 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.51; H, 6.46; N, 4.00. **35a** had $[\alpha]^{23}_D$ −14.6° (*c* 1.13, $CHCl_3$); mp 62–63 °C. **35b** had $[\alpha]^{23}_D$ +42.6° (*c* 0.95, $CHCl_3$); mp 60–61 °C.

[3*S*,3a*S*,6a*S*(*R*)]- and [3*R*,3a*R*,6a*R*(*R*)]-3-(1,4-dioxaspiro[4.5]dec-2-yl)tetrahydro-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (36a,b) were obtained with a 80:20 diethyl ether/hexanes mixture as eluant: IR ($CHCl_3$) 3040, 2960, 1780, 1455, 1385, 1100, 740, 700 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.96; H, 6.96; N, 3.91. **36a** had $[\alpha]^{23}_D$ +13.2° (*c* 0.73, $CHCl_3$); mp 87–88 °C; **36b** had $[\alpha]^{23}_D$ +21.8° (*c* 0.31, $CHCl_3$); mp 120–122 °C.

3-(2-Tetrahydrofuryl)tetrahydro-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (*rac*-37a and *rac*-37b) were obtained with diethyl ether as eluant: IR ($CHCl_3$) 3040, 2960, 1780, 1455, 1380, 1100, 745, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.29; H, 6.70; N, 4.77. **37a** had mp 96–97 °C; **37b**, low-melting material.

[3*R*,3a*S*,6a*S*(*S*)]- and [3*S*,3a*R*,6a*R*(*S*)]-3-(1-(phenylmethoxy)ethyl)tetrahydro-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (38a,b) were obtained with a 1:1 diethyl ether/hexanes mixture as eluant: IR (thin film) 3040, 2976, 1780, 1455, 1380, 1120, 745, 700 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.46; H, 6.59; N, 3.92. **38a** had $[\alpha]^{23}_D$ +40.9° (*c* 0.2, $CHCl_3$); mp 92–94 °C; **38b** had $[\alpha]^{23}_D$ −11.2° (*c* 0.28, $CHCl_3$); low-melting material.

[3*S*,3a*R*,6a*R*(*R*)]-3-(1,4-Dioxaspiro[4.5]dec-2-yl)tetrahydro-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (39a) was obtained with a 80:20 diethyl ether/hexanes mixture as eluant: IR ($CHCl_3$) 3040, 2960, 1780, 1450, 1385, 1100, 740, 700 cm^{-1}. It had $[\alpha]^{23}_D$ −26.4° (*c* 2.0, $CHCl_3$); mp 60–61 °C. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.76; H, 7.08; N, 3.86.

***rac*-3-(2-Tetrahydrofuryl)tetrahydro-1-(phenylmethyl)-1*H*,6*H*-furo[3,4-*c*]isoxazol-6-one (40a)** was obtained with diethyl ether as eluant: IR (KBr) 3040, 2960, 1780, 1455, 1380, 1100, 740, 700 cm^{-1}; mp 114–116 °C. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.51; H, 6.51; N, 4.89.

General Procedure for the Synthesis of Cycloadducts 41–43. The products were prepared by a sequence of reaction from esters **8–10** involving (a) hydrolysis to the acid, (b) Cs_2CO_3-promoted allyl ester formation, (c) conjugate addition of thiophenol, (d) oxidation to sulfone, (e) ozonization to the aldehyde, (f) synthesis of the nitrones, and (g) base-promoted elimination of sulfinic acid and intramolecular cycloaddition.

Hydrolysis of Esters 8–10 to the Corresponding Acids. A mixture of ester (1 mmol) and 2 N aqueous NaOH (1 mL) was stirred at room temperature for 4 h; 1 N aqueous HCl (2 mL) was then added, and the reaction was extracted with CH_2Cl_2. The organic phase was dried, and the solvent was evaporated to give a residue, which was filtered through a short silica gel column to give the product that was used without further purification.

Synthesis of the Allyl Esters 26–28. These were prepared according to the method recently reported by Kunz et al.[14]

(*S*)-(*E*)-4-(Phenylmethoxy)pent-2-enoic acid prop-2-enyl ester (26) was obtained as an oil in 83% yield (0.204 g) with a 20:80 diethyl ether/hexanes mixture as eluant: IR (thin film) 3040, 2960, 2940, 1720, 1640, 1455, 1070, 740 cm^{-1}; ^{1}H NMR δ 7.15–7.25 (m, 5 H, aromatic protons), 6.85 (dd, 1 H, C*H*CHCOO, *J* = 16.0, 5.7 Hz), 5.95 (dd, 1 H, CH=C*H*COO, *J* = 16.0, 1.6 Hz), 5.70–6.00 (m, 1 H, CH_2CH=), 5.05–5.40 (m, 2 H, =CH_2), 4.55–4.70 (m, 2 H, CH_2OCO), 4.45 (d, 2 H, CH_2Ph, *J* = 5.0 Hz), 3.90–4.15 (m, 1 H, CHO), 1.25 (d, 3 H, CH_3, *J* = 7.0 Hz). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.10; H, 7.43.

(*S*)-(*E*)-4-(1,4-Dioxaspiro[4.5]dec-2-yl)but-2-enoic acid prop-2-enyl ester (27) was obtained as an oil in 77% yield (0.194 g) with a 20:80 diethyl ether/hexanes mixture as eluant: IR (thin film) 2980, 2940, 1720, 1645, 1455, 1070, 740 cm^{-1}; ^{1}H NMR δ 6.85 (dd, 1 H, C*H*=CHCOO, *J* = 15.5, 4.5 Hz), 6.05 (dd, 1 H, CH=C*H*COO, *J* = 15.5, 1.5 Hz), 5.70–6.00 (m, 1 H, CH_2CH=), 5.10–5.40 (m, 2 H, =CH_2), 4.40–4.85 (m, 3 H, CHO and CH_2OCO), 4.15 (dd, 1 H, 1 H of OCH_2CHO, *J* = 7.5, 7.0 Hz), 3.75 (dd, 1 H, 1 H of OCH_2CHO, *J* = 7.5, 7.0 Hz), 1.30–1.70 (m, 10 H, C_6H_{10}). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.76; H, 8.05.

(*R*,*S*)-(*E*)-4-(2-Tetrahydrofuryl)but-2-enoic acid prop-2-enyl ester (28) was obtained as an oil in 80% yield (0.146 g) with a 40:60 diethyl ether/hexanes mixture as eluant: IR (thin film) 2980, 2940, 1725, 1640, 1455, 1075, 740 cm^{-1}; ^{1}H NMR δ 6.90 (dd, 1 H, C*H*=CHCOO, *J* = 15.5, 4.5 Hz), 5.95 (dd, 1 H, CH=C*H*COO, *J* = 15.5, 1.6 Hz), 5.70–6.00 (m, 1 H, CH_2CH=), 5.10–5.40 (m, 2 H, =CH_2), 4.50–4.75 (m, 2 H, CH_2OCO), 4.35–4.65 (m, 1 H, CHO), 3.70–4.00 (m, 2 H, CH_2CH_2O), 1.65–2.15 (m, 4 H, CH_2CH_2). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.03; H, 7.80.

Synthesis of Sulfides. A mixture of allyl ester (1 mmol), thiophenol (1 mmol, 0.102 mL), and triethylamine (2 drops) was heated at 90 °C for 4 h under an Ar atmosphere. The cooled mixture was then filtered through a short column of silica gel to give the products in 90% yield as roughly 1:1 mixtures of diastereoisomers.

Synthesis of Sulfones 29–31. These products were synthesized following the described procedures,[26] as roughly 1:1 mixtures of diastereomers.

(3*R*,4*S*)- and (3*S*,4*S*)-3-(phenylsulfonyl)-4-(phenylmethoxy)pentanoic acid prop-2-enyl esters (29) were obtained[26a] as a thick oil in 93% yield (0.361 g) with a 1:1 diethyl ether/hexanes mixture as eluant: IR (thin film) 3060, 2960, 2940, 1740, 1455, 1310, 1140, 1070, 740 cm^{-1}; ^{1}H NMR δ 7.15–7.95 (m, 10 H, aromatic protons), 5.55–6.05 (m, 1 H, CH=), 5.10–5.40 (m, 2 H, =CH_2), 4.00–4.60 (m, 6 H, CH_2OCO, CH_2Ph, $CHSO_2$, CHO), 2.80–2.90 (m, 2 H, CH_2CO), 1.10–1.40 (m, 3 H, CH_3). Anal. Calcd for $C_{21}H_{24}O_5S$: C, 64.93; H, 6.23. Found: C, 65.06; H, 6.17.

(3*R*,4*R*)- and (3*S*,4*R*)-3-(phenylsulfonyl)-4-(1,4-dioxaspiro[4.5]dec-2-yl)butanoic acid prop-2-enyl esters (30) were obtained[26b] as a thick oil in 73% yield (0.288 g) with a 1:1 diethyl ether/hexanes mixture as eluant: IR (thin film) 3050, 2980, 2940, 1740, 1455, 1315, 1140, 1070, 740 cm^{-1}; ^{1}H NMR δ 7.40–8.00 (m, 5 H, aromatic protons), 5.55–6.05 (m, 1 H, CH=), 5.10–5.40 (m, 2 H, =CH_2), 4.30–4.60 (m, 3 H, =CHCH_2 and CHO), 3.70–4.20 (m, 3 H, $CHSO_2$ and OCH_2CHO), 2.70–2.90 (m, 2 H, CH_2CO), 1.20–1.70 (m, 10 H, C_6H_{10}). Anal. Calcd for $C_{20}H_{26}O_6S$: C, 60.89; H, 6.64. Found: C, 61.00; H, 6.66.

***rac*-3-(Phenylsulfonyl)-4-(2-tetrahydrofuryl)butanoic acid prop-2-enyl esters (31)** were obtained[26a] as a thick oil in 86% yield (0.279 g) with a 60:40 diethyl ether/hexanes mixture as eluant: IR (thin film) 3050, 2970, 2940, 1740, 1450, 1310, 1150, 1070, 740 cm^{-1}; ^{1}H NMR δ 7.40–8.00 (m, 5 H, aromatic protons), 5.65–6.05 (m, 1 H, =CH), 5.05–5.40 (m, 2 H, =CH_2), 4.50–4.60 (m, 2 H, CH_2OCO), 3.95–4.30 (m, 1 H, CHO), 3.40–3.95 (m, 3 H, CH_2CH_2O and $CHSO_2$), 2.60–2.95 (m, 2 H, CH_2CO), 1.70–2.20 (m, 4 H, CH_2CH_2). Anal. Calcd for $C_{16}H_{20}O_5S$: C, 59.24; H, 6.21. Found: C, 59.18; H, 6.24.

Synthesis of Aldehydes. A stream of ozone was passed through a solution of sulfone (1 mmol) in CH_2Cl_2 (10 mL) and MeOH (2 mL) cooled at −78 °C. The reaction was quenched by the addition of 1 mL of Me_2S and was allowed to warm up to room temperature. After 3 h of stirring the solvent was evaporated to give the crude aldehydes, which were used without further purification.

Synthesis of Nitrones 32–34. *N*-Benzylhydroxylamine (1 mmol, 0.123 g) was added to a solution of crude aldehyde (1 mmol)

(26) (a) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, 1287. (b) Trost, B. M.; Braslan, R. *J. Org. Chem.* **1988**, *53*, 532.

in Et_2O (5 mL) and THF (1 mL). After overnight stirring at room temperature, the solvent was evaporated to give the crude nitrones as mixtures of diastereoisomers, which were purified by flash chromatography, with a mixture of diethyl ether/methanol as eluant. Overall yields from **29–31** were 60–70%.

Intramolecular Cycloaddition.[4d] To a refluxing solution of nitrone (1 mmol) in CCl_4 (10 mL) was added DBU (1 mmol, 0.149 mL), and the mixture was refluxed overnight. Evaporation of the solvent afforded the crude cycloadducts, which were purified by flash chromatography, which allowed isomer separation. Yields and diastereoisomeric ratios are reported in Table I; relevant NMR data are collected in Table II.

[3*R*,3a*R*,6a*R*(*S*)]- and [3*S*,3a*S*,6a*S*(*S*)]-3-(1-(phenylmethoxy)ethyl)tetrahydro-1-(phenylmethyl)-1*H*,4*H*-furo[3,4-*c*]isoxazol-4-ones (41a,b) were obtained as low-melting solids with a 70:30 diethyl ether/hexanes mixture as eluant: IR (thin film) 3040, 2980, 1770, 1455, 1380, 1100, 750, 700 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.30; H, 6.66; N, 3.93. **41a** had $[\alpha]^{23}_D$ +37.9° (*c* 0.13, $CHCl_3$); **41b** had $[\alpha]^{23}_D$ −28.2° (*c* 0.16, $CHCl_3$).

[3*S*,3a*S*,6a*S*(*R*)]-3-(1,4-Dioxaspiro[4.5]dec-2-yl)tetrahydro-1-(phenylmethyl)-1*H*,4*H*-furo[3,4-*c*]isoxazol-4-one (42a) was obtained with a 80:20 diethyl ether/hexanes mixture as eluant: IR (KBr) 3040, 2960, 1770, 1450, 1380, 1100, 750, 700 cm^{-1}; $[\alpha]^{23}_D$ −42.4° (*c* 0.29, $CHCl_3$); mp 79–80 °C. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.76; H, 7.00; N, 3.84.

***rac*-3-(2-Tetrahydrofuryl)tetrahydro-1-(phenylmethyl)-1*H*,4*H*-furo[3,4-*c*]isoxazol-4-ones (43a and 43b)** were obtained as thick oils with diethyl ether as eluant: IR (thin film) 3040, 2960, 1770, 1455, 1380, 1100, 750, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.50; H, 6.55, N, 4.89.

General Procedure for the Synthesis of Cycloadducts 46, 47. The products were prepared by a sequence of reactions from esters **9** and **12** involving (a) reduction to the allylic alcohols as described above, (b) etherification with ethyl bromoacetate, (c) reduction to the aldehydes, (d) synthesis of the nitrones and intramolecular cycloadditions.

Synthesis of Esters 44 and 45. To a stirred suspension of oil-free NaH (1 mmol) in THF (5 mL) cooled at 0 °C was added dropwise the allylic alcohol (1 mmol). After 30 min of stirring at 0 °C, tetrabutylammonium iodide (0.1 mmol, 0.037 g) was added followed, after 10 min by ethyl bromoacetate (2.5 mmol, 0.280 mL). The mixture was allowed to warm up to room temperature and stirred overnight. The reaction was quenched by the addition of saturated NH_4Cl solution and worked up in the usual way. The products were purified by flash chromatography.

(*R*)-(*E*)-((3-(1,4-Dioxaspiro[4.5]dec-2-yl)prop-2-enyl)oxy)acetic acid ethyl ester (44) was obtained as an oil in 48% yield (0.136 g) with a 40:60 diethyl ether/hexanes mixture as eluant: IR (thin film) 2960, 2940, 1750, 1450, 1200, 1140, 1040, 840 cm^{-1}; ^1H NMR δ 5.60–5.90 (m, 2 H, CH=CH), 4.35–4.65 (m, 1 H, CHO), 3.90–4.30 (m, 7 H, OCH_2Me, $=CCH_2O$, OCH_2CO, and 1 H of OCH_2CHO), 3.60 (t, 1 H, 1 H of OCH_2CHO, J = 7.0 Hz), 1.20–1.65 (m, 10 H, C_6H_{10}), 1.20 (t, 3 H, CH_3, J = 7.0 Hz). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.24; H, 8.47.

(*S*)-(*Z*)-((3-(1,4-Dioxaspiro[4.5]dec-2-yl)prop-2-enyl)oxy)acetic acid ethyl ester (45) was obtained as an oil in 45% yield (0.128 g) with a 40:60 diethyl ether/hexanes mixture as eluant: IR (thin film) 2960, 2940, 1760, 1455, 1205, 1140, 1050, 850 cm^{-1}; ^1H NMR δ 5.40–5.85 (m, 2 H, CH=CH), 4.60–4.90 (m, 1 H, CHO), 3.90–4.30 (m, 7 H, OCH_2Me, $=CCH_2O$, OCH_2CO, and 1 H of OCH_2CHO), 3.50 (t, 1 H, 1 H of OCH_2CHO, J = 7.0 Hz), 1.20–1.70 (m, 10 H, C_6H_{10}), 1.25 (t, 3 H, CH_3, J = 7.0 Hz). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.26; H, 8.58.

Reduction to the Aldehydes. A solution of ester (1 mmol) in CH_2Cl_2 (10 mL) cooled at −78 °C was treated with a 1 N solution of DIBAH in CH_2Cl_2 (1 mmol, 1 mL). After 30 min of stirring at −78 °C the reaction was worked up as described above. The aldehydes were purified by flash chromatography with a 1:1 diethyl ether/hexanes mixture as eluant. The yields were 77% and 74% for the *E* and the *Z* isomer, respectively.

Synthesis of the Nitrones and Intramolecular Cycloadditions. A benzene (10 mL) solution of aldehyde (1 mmol) and *N*-benzylhydroxylamine (1 mmol, 0.123 g) was stirred at room temperature for 6 h and then refluxed overnight. Evaporation of the solvent gave the crude cycloadducts, which were purified by flash chromatography. Yields and diastereoisomeric ratios are collected in Table I; relevant NMR data in Table II.

[3*S*,3a*R*,6a*S*(*R*)]- and [3*R*,3a*S*,6a*R*(*R*)]-3-(1,4-dioxaspiro[4.5]dec-2-yl)tetrahydro-1-(phenylmethyl)-1*H*-furo[3,4-*c*]isoxazoles (46a and 46b) were obtained with diethyl ether as eluant: IR (thin film) 3040, 2960, 1450, 1360, 1100, 1040, 920, 740 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.69; H, 7.80; N, 4.01. Only **46a** was obtained diastereomerically pure: $[\alpha]^{23}_D$ −21.0° (*c* 1.08, $CHCl_3$); mp 56–58 °C.

[3*S*,3a*S*,6a*R*(*R*)]-3-(1,4-Dioxaspiro[4.5]dec-2-yl)tetrahydro-1-(phenylmethyl)-1*H*-furo[3,4-*c*]isoxazole (47a) was obtained as a thick oil with diethyl ether as eluant: IR (thin film) 3040, 2960, 1455, 1370, 1105, 1040, 920, 740 cm^{-1}; $[\alpha]^{23}_D$ +23.4° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.63; H, 7.79; N, 4.00.

Acknowledgment. Partial financial support by Ministero Pubblica Istruzione (Rome) is gratefully acknowledged.

Registry No. 8, 113034-36-9; 8 (acid), 124891-22-1; 8 (alcohol), 119242-59-0; 9, 112980-46-8; 9 (acid), 124891-23-2; 9 (alcohol), 124988-77-8; (±)-10, 124890-93-3; (±)-10 (acid), 124891-24-3; (±)-10 (alcohol), 124890-95-5; 11, 112489-56-2; 11 (alcohol), 119242-60-3; 12, 112980-54-8; 12 (alcohol), 124988-78-9; (±)-13, 124890-94-4; (±)-13 (alcohol), 124890-96-6; 14, 124891-02-7; 14 (bromoacetate), 124890-97-7; 15, 124891-03-8; 15 (bromoacetate), 124890-98-8; (±)-16, 124891-04-9; (±)-16 (bromoacetate), 124890-99-9; 17, 124891-05-0; 17 (bromoacetate), 124891-00-5; 18, 124891-06-1; 18 (bromoacetate), 124891-01-6; (±)-19, 124891-07-2; (±)-19 (bromoacetate), 124919-03-5; 20, 124891-14-1; 20 (aldehyde), 124891-08-3; 21, 124891-15-2; 21 (aldehyde), 124891-09-4; (±)-22, 124891-16-3; (±)-22 (aldehyde), 124891-10-7; 23, 124891-17-4; 23 (aldehyde), 124891-11-8; 24, 124891-18-5; 24 (aldehyde), 124891-12-9; (±)-25, 124919-04-6; (±)-25 (aldehyde), 124891-13-0; 26, 124891-25-4; 27, 124891-26-5; 28, 124891-27-6; 29 (isomer 1), 124891-33-4; 29 (isomer 2), 124891-34-5; 29 (sulfide, isomer 1), 124891-28-7; 29 (sulfide, isomer 2), 124891-29-8; 30 (isomer 1), 124891-35-6; 30 (isomer 2), 124891-36-7; 30 (sulfide, isomer 1), 124891-30-1; 30 (sulfide, isomer 2), 124891-31-2; (±)-31 (isomer 1), 124891-37-8; (±)-31 (isomer 2), 124891-38-9; (±)-31 (sulfide, isomer 1), 124891-32-3; (±)-31 (sulfide, isomer 2), 124919-05-7; 32 (isomer 1), 124891-45-8; 32 (isomer 2), 124891-46-9; 32 (aldehyde, isomer 1), 124891-39-0; 32 (aldehyde, isomer 2), 124891-40-3; 33 (isomer 1), 124891-47-0; 33 (isomer 2), 124891-48-1; 33 (aldehyde, isomer 1), 124891-41-4; 33 (aldehyde, isomer 2), 124891-42-5; (±)-34 (isomer 1), 124891-49-2; (±)-34 (isomer 2), 124891-50-5; (±)-34 (aldehyde, isomer 1), 124891-43-6; ±)-34 (aldehyde, isomer 2), 124891-44-7; 35a, 124891-19-6; 35b, 124988-79-0; 36a, 124891-20-9; 36b, 124988-80-3; (±)-37a, 124891-21-0; (±)-37b, 124988-81-4; 38a, 124988-82-5; 38b, 124988-83-6; 39a, 124988-84-7; (±)-40a, 124988-85-8; 41a, 124891-51-6; 41b, 124988-86-9; 42a, 124891-52-7; (±)-43a, 124891-53-8; (±)-43b, 124988-87-0; 44, 124891-54-9; 44 (aldehyde), 124891-56-1; 45, 124891-55-0; 45 (aldehyde), 124891-57-2; 46a, 124891-58-3; 46b, 124988-88-1; 47a, 124988-89-2; $BrCH_2COBr$, 598-21-0; $PhCH_2NHOH$, 622-30-0; $CH_2{=}CHCH_2Br$, 106-95-6; PhSH, 108-98-5; $BrCH_2COOEt$, 105-36-2.

Supplementary Material Available: ^1H nuclear Overhauser enhancement data for compounds **35–43, 46,** and **47** (2 pages). Ordering information is given on any current masthead page.