H), 4.04–3.98 (m, 6 H), 1.14 (td, J = 7.2, 1.2 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 132.9 (d), 128.52, 128.48, 128.3, 128.1, 128.0, 127.3, 126.6, 120.8 (d), 63.6 (d), 53.8 (d, $^1J_{PC}$ = 164.5 Hz), 16.1; ^{31}P NMR ($CDCl_3$) δ −37.1 (octet, $J \sim 8.1$ Hz); HRMS m/z 360.1487 ($(M - 31)^+$, calcd for $C_{20}H_{25}O_4P$ 360.1491), 345.1128 ($(M - 46)^+$, calcd for $C_{18}H_{20}O_4NP$ 345.1130); CIMS (solids probe, NH_3) 392 ($(M + 1)^+$, 100), 409 ($(M + 18)^+$, 0.2).

Diethyl [α-(Benzylideneamino)benzyl]phosphonate (22). Heating of **6c** (1 mmol) with 2 mL of $(EtO)_3P$ at 120–150 °C for 1–2 h produced a trace of 2-phenylindole (<10%), 34% of **22**, and 43% of **23**. Compound **22** isolated by chromatography with hexane (75%)–ethyl acetate (25%) had a purity of ~90% from ^{1}H NMR: ^{1}H NMR ($CDCl_3$) δ 8.41–7.28 (m, 11 H), 4.93 (d, $^2J_{PH}$ = 18.6 Hz, 1 H), 4.12–3.92 (m, 4 H), 1.23 (t, J = 7.2 Hz, 3 H), 1.20 (t, J = 7.2 Hz, 3 H); GC and HRMS m/z (relative intensity) 331.1332 (M^+, 45, calcd for $C_{18}H_{22}NO_3P$ 331.1338), 240 (56), 193 (33), 178 (28), 165 (18), 152 (8), 137 (23), 109 (37), 104 (100), 91 (20), 77 (15); CIMS (GC, NH_3) 332 ($(M + 1)^+$, 100), 349 ($(M + 18)^+$, 21), 663 ($(2M + 1)^+$, 3).

Diethyl (1-Anilino-2-phenylvinyl)phosphonate (23). The crude reaction product from the previous experiment showed only a single isomer of **23** by ^{1}H NMR but after column separation a second minor isomer was found. Major isomer: mp 103–104 °C; FTIR 3287 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.42–6.57 (m, 11 H), 7.00 (d, $^3J_{PH}$ = 16.8 Hz, 1 H), 5.59 (d, J = 7.2 Hz, D_2O exchangeable, 1 H), 4.22–4.01 (m, 4 H), 1.28 (t, J = 7.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 141.6, 134.0 ($^2J_{PC}$ = 19.6 Hz), 130.1, 129.8, 128.6, 128.3, 128.0, 126.5 (d, $^1J_{PC}$ = 198.3 Hz), 119.8, 115.6, 62.4 (d, J = 4.5 Hz), 16.2 (d, J = 6.4 Hz); GC and HRMS m/z (relative intensity) 331.1332 (M^+, 14, calcd for $C_{18}H_{22}NO_3P$ 331.1337), 228 (15), 193 (100), 165 (11), 116 (11), 91 (13), 77 (12); CIMS (GC, NH_3) 332 ($(M + 1)^+$, 100), 349 ($(M + 18)^+$, 20), 663 ($(2M + 1)^+$, 2). Anal. Calcd for $C_{18}H_{22}NO_3P$: C, 65.25; H, 6.69; N, 4.23; P, 9.35. Found: C, 64.97; H, 6.62; N, 4.13; P, 9.25.

The 2nd isomer isolated by chromatography had the following characteristics: FTIR 3167 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.58–7.21 (m, 10 H), 5.94 (s, 1 H), 5.15 (d, J = 6.3, 1 H), 4.05–3.87 (m, 4 H), 1.17 (td, J = 7.2, 0.9 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.7, 136.8 (d, $^1J_{PC}$ = 136.8 Hz), 129.2, 128.6, 128.3, 127.9, 127.8, 127.0, 116.1 (d), 62.9 (d), 15.9 (d); MS (solids probe) m/z (relative intensity) 331.1339 (M^+, 0.2, calcd for $C_{18}H_{22}NO_3P$ 331.1337), 303 (1), 274 (2), 243 (43), 127 (15), 105 (100), 91 (15), 77 (100).

Acknowledgment. Work was supported by grant CHE-8717871 from the National Science Foundation and by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Supplementary Material Available: ^{1}H NMR spectra for **1** (R = Me), **7** (R = Me), **12a,b**, **13** (R = Me), **20** and **21**, ^{13}C NMR spectra for **1** (R = Me), **3** (R = OPh), **13** (R = Me, Ph), and **21**, and ^{31}P NMR spectrum for **21** (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

A Facile Synthesis of Furo[3,4-*c*]isoxazoles: Precursors to 3,4-Disubstituted Isoxazoles

Hyung Jin Kim,[†,‡] Jae Hyun Lee,*[,†] Marilyn M. Olmstead,[‡] and Mark J. Kurth*[,‡]

Korea Research Institute of Chemical Technology, P.O. Box 9, Daedeog Danji, Daejoen, Korea 305-606, and Department of Chemistry, University of California, Davis, California 95616

Received July 6, 1992

Nitrile oxide–olefin cycloaddition reactions deliver heterocyclic products with a wide variety of functionality and provide a particularly powerful means of preparing substituted isoxazoles by the intermolecular 1,3-dipolar cycloaddition of a nitrile oxide with a monosubstituted alkyne to give a preponderance of the 3,5-disubstituted isoxazole. In this study, an extension of the intramolecular nitrile oxide–olefin cycloaddition reaction is reported for the facile synthesis of furo[3,4-*c*]isoxazoles (**5**) which are in turn shown to be useful precursors to 3,4-disubstituted or 3,4,5-trisubstituted isoxazole derivatives (**6**). The method consists of a high-yield preparation of a broad spectrum of furo[3,4-*c*]isoxazoles by intramolecular nitrile oxide–alkyne cycloaddition of acetylenic nitro ethers (**3**), in turn prepared by Michael addition of various propargylic alkoxides (**2**) to appropriate nitro olefins (**1**).

The INOC (intramolecular nitrile oxide–olefin cycloaddition) reaction continues to receive a great deal of synthetic attention as it both provides a particularly powerful means of relative stereochemical control[1] and delivers heterocyclic products with a wide variety of functionality.[2] With regard to the latter, INOC applications in the synthesis of new drugs and agrochemicals[3] containing substituted isoxazoles[4] are particularly important. Indeed, since Claisen's report in 1891,[5] many methods have been developed for the preparation of substituted isoxazoles which can generally be broken into two strategic categories. The first involves the condensation reaction of an hydroxylamine with a carbonyl compound (generally, α,β-dihalo ketones, β-alkoxy enones, β-chloro enones, or ynones)[3] and provides easy access to 3,5-disubstituted isoxazoles. Introduction of a substituent at C-4 by this method is, however, not convenient. The second category involves the 1,3-dipolar cycloaddition of a nitrile oxide with an alkyne. In this transformation, nitrile oxides react intermolecularly with monosubstituted

---

[†] Korea Research Institute of Chemical Technology.

[‡] University of California.

(1) (a) For a recent report from our laboratory concerning double diastereoselectivity in the INOC reaction, see: Kim, H. R.; Kim, H. J.; Duffy, J. L.; Olmstead, M. M.; Ruhlandt-Senge, K.; Kurth, M. J. *Tetrahedron Lett.* 1991, *32*, 4259. (b) Hassner, A.; Murthy, K. S. K.; Padwa, A.; Chiacchio, U.; Dean, D. C.; Schoffstall, A. M. *J. Org. Chem.* 1989, *54*, 5277. (c) Hassner, A.; Padwa, A. *Tetrahedron Lett.* 1988, *29*, 4169. (d) Hassner, A.; Murthy, K. S. K.; Padwa, A.; Bullock, W. H.; Stull, P. D *J. Org. Chem.* 1988, *53*, 5063.

(2) For recent reviews, see: (a) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH Publishers: New York, 1988. (b) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2. (c) Kozikowski, A. P. *Acc. Chem. Res.* 1984, *17*, 410.

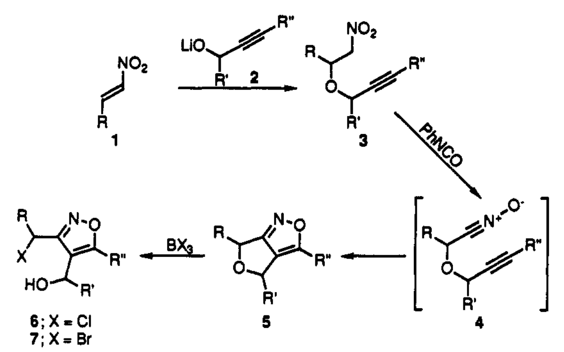
(3) For example, see: (a) Lang, A.; Lin, Y. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: Oxford, 1984; Vol. 6, pp 1–130. (b) Otsuji, Y.; Mizuno, K. Jpn Patent, JP 01070476 A2; *Chem. Abstr.* 1989, *111* (15), 134134r.

(4) (a) Boyd, G. V. *Prog. Heterocycl. Chem.* 1991, *3*, 166–85. (B) See ref 3c.

(5) Claisen, L. *Ber.* 1981, *24*, 3900.

0022-3263/92/1957-6513$03.00/0

Scheme I[a]



Compound 3/5/6/7	R	R'	R"	3 → 5 % Yield	5 → 6 % Yield	5 → 7 % Yield
a	4-MeC$_6$H$_4$	H	H	75	97	96
b	2-ClC$_6$H$_4$	H	H	79	98	98
c	2-ClC$_6$H$_4$	H	Me	86	95	85
d	4-ClC$_6$H$_4$	H	Me	85	88	85
e	4-ClC$_6$H$_4$	H	Et	88	90	83
[a] f & f'	2-ClC$_6$H$_4$	Me	H	64\80	87	89
[a] g & g'	*i*-Pr	4-ClC$_6$H$_4$	*n*-Pr	96	[b] → 8g/g'	[b] → 9g/g'

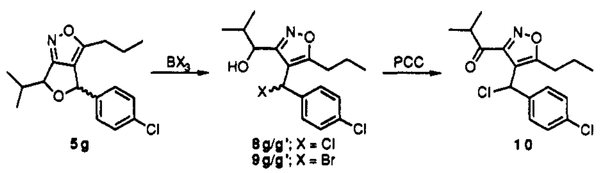
[a] In this series, **3**/**5**/**6**/**7** were obtained as a mixture of two diastereomers. [b] Here, benzylic ether cleavage results in the formation of chloroisoxazole **8g**/**8g′** and bromoisoxazole **9g**/**9g′** (see text).

alkynes to again give a preponderance of 3,5-disubstituted isoxazoles.[6] Floxane is a significant byproduct of this reaction. Herein we report extension of the INOC reaction to the facile synthesis of furo[3,4-*c*]isoxazoles which are in turn shown to be useful precursors to 3,4-disubstituted or 3,4,5-trisubstituted isoxazole derivatives.

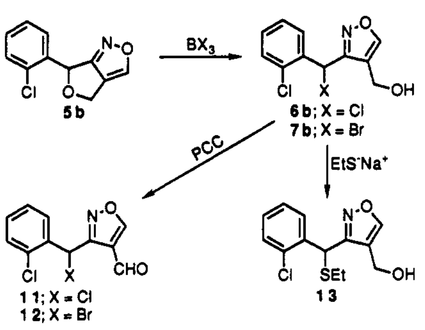
In a previous paper,[1a] we described the successful preparation of furo[3,4-*c*]isoxazolines from the corresponding nitro-substituted alkene/ether compounds which in turn are obtained by Michael addition of a lithioallyl oxide to a nitro olefin; a similar strategy has been developed by Hassner et al.[7] Expanding on this methodology, we now report the high-yield preparation of a broad spectrum of furo[3,4-*c*]isoxazoles by intramolecular nitrile oxide–alkyne cycloaddition of acetylenic nitro ethers (**3**), in turn prepared by Michael addition of various propargylic alkoxides (**2**) to appropriate nitro olefins (**1**) (Scheme I).

The nitro olefin starting material is readily formed by dehydrative condensation of nitromethane with the appropriate aldehyde (RCHO) and thus provides ready access to a wide variety of nitro olefins of general structure **1**.[8] Subsequent Michael addition of the alkoxide of a propargylic alcohol (**2**) in which both R′ and R″ are variable leads to acetylenic nitro ethers **3**. In those cases where a secondary propargylic alcohol is used in **1** → **3**, two diastereomeric Michael products are formed (i.e., **1** + **2** → **3f**/**3f′**[9] and **1** + **2** → **3g**/**3g′**;[9] while diastereomer **3f** and **3f′** were separable by silica gel column chromatography, diastereomer of **3g** and **3g′** proved to be inseparable). Acetylenic nitro ether **3** was transformed by phenyl isocyanate mediated dehydration in the presence of a catalytic amount of triethylamine[10] to nitrile oxide intermediate **4** which undergoes spontaneous cyclization to furo[3,4-*c*]isoxazole **5** in excellent yield (see Scheme I).

Scheme II



Scheme III



Employing a terminal propargylic alkoxide (i.e., **2** with R″ = H) in the Michael addition reaction of Scheme I results in a furo[3,4-*c*]isoxazole which, upon boron trihalide mediated ether cleavage, leads to a 3,4-disubstituted isoxazole. When a nonterminal propargylic alkoxide (i.e., **2** with R″ = alkyl or aryl) is employed, ether cleavage gives a 3,4,5-trisubstituted isoxazole. Not surprisingly, furo[3,4-*c*]isoazole **5** undergoes regiospecific benzylic ether bond cleavage; no nonbenzylic C–O bond cleavage is observed. For example, treating a methylene chloride solution of furo[3,4-*c*]isoxazole **5b** with an equimolar amount of boron trihalide (BX$_3$; X = Cl or Br) at −78 °C delivers either isoxazole **6b** (X = Cl) from reaction with boron trichloride or isoxazole **7b** (X = Br) from reaction with boron tribromide in nearly quantitative yield without damaging the isoxazole ring.

It is informative to note that boron trihalide mediated C–O bond cleavage of either pure diastereomer **5f** (i.e., the trans isomer) or pure diastereomer **5f′** (i.e., the cis isomer; the stereochemistry of **5f′** was determined by X-ray crystallographic analysis)[11] gives a mixture of diastereomeric chloroisoxazoles (*R**,*R**)-**6f** and (*R**,*S**)-**6f′** (the stereochemistry of **6f′** was determined by X-ray crystallographic analysis)[12]. Thus, reaction of pure *trans*-**5f** with boron trichloride produces an inseparable 2.2:1 mixture of **6f** and **6f′** while pure *cis*-**5f′** leads to a 1:1.6 mixture, respectively. Likewise, boron tribromide treatment of *trans*-**5f** and *cis*-**5f′** results in a 7.4:1 and 1:1.8 mixture of

---

(6) Caramella, P.; Grunanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley and Sons: New York, 1984; Vol. 1, pp 291–392.

(7) Hassner, A.; Dehaen, W. *Chem. Ber.* **1991**, *124*, 1181.

(8) (a) Campbell, N.; Anderson, W.; Gilmore, J. *J. Chem. Soc.* (*London*) **1940**, 446. (b) Sanno, Y.; Kurita, A.; Imai, K. J. *Pharm. Soc. Jpn.* **1955**, *75*, 1461.

(9) The relative stereochemistries of **3f**/**3f′**, **3g**/**3g′**, **5g**/**5g′**, **8g**/**8g′**, and **9g**/**9g′** are not assigned.

(10) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

(11) Compound **5f′** crystallizes from *n*-hexane/CH$_2$Cl$_2$ in the monoclinic space group $P2_1/c$. The crystal data at 130 K are as follows: a = 13.042 (4) Å, b = 10.193 (2) Å, c = 8.122 (3) Å, β = 103.28 (2)°; d_{calc} = 1.49 g cm^{-3}; Z = 4; Siemens R3m/V diffractometer; Mo Kα radiation; λ = 0.71073 Å; graphite monochromator; 2θ(max) = 58°; 2273 reflections with $F > 4\sigma(F)$ and 145 parameters used in refinement; R = 0.051; crystallographic programs SHELXTL PLUS, Version 4.2. A complete listing of the X-ray crystallographic data for **5f′** is available as supplementary material.

(12) Compound **6f′** crystallizes from *n*-hexane/acetone in the monoclinic space group $P2_1/c$. The crystal data at 130 K are as follows: a = 14.970 (8) Å, b = 6.079 (3) Å, c = 13.742 (6) Å, β = 97.22 (4)°; d_{calc} = 1.46 g cm^{-3}; Z = 4; Syntex P2$_1$ diffractometer; Mo Kα radiation; λ = 0.71073 Å; graphite monochromator; 2θ(max) = 58°; 1934 reflections with $F > 4\sigma(F)$ and 154 parameters used in refinement; R = 0.058; crystallographic programs SHELXTL PLUS, Version 4.2. A complete listing of the X-ray crystallographic data for **6f′** is available as supplementary material.

Table I.[a] **Isoxazole Fungicidal Activity**[b]

compd	RCB[c]	CGM[d]	TLB[e]	BPM[f]
5b	60	0	10	20
5c	100	81	55	27
5d	0	98	0	0
5e	0	0	0	99
5f	0	35	20	38
5g	24	0	43	20
6b	75	0	12	0
7b	95	0	30	10

[a] Control values are calculated by the formula

$$\text{control value (\%)} = \left[1 - \left(\frac{\text{percent of disease area in treatment}}{\text{percent of disease area in untreated control}}\right)\right] \times 100$$

[b] For experimental details, see the Experimental Section. [c] Rice blast (RCB; *Pyricularia oryzae*). [d] Cucumber gray mold (CGM; *Botrytis cinerea*). [e] Tomato late blight (TLB; *Phytophthora infestans*). [f] Barley powdery mildew (BPM; *Erysiphe graminis*).

bromoisoxazoles (R^*,S^*)-**7f** (the stereochemistry of **7f** was determined by X-ray crystallographic analysis)[13] and (R^*,R^*)-**7f′**, respectively.

Reaction of furo[3,4-*c*]isoxazole **5g′**[9] with boron trihalide also results in regiospecific benzylic C–O bond cleavage; this time leading to chloroisoxazoles **8g**/**8g′**[9] (1.2:1 mixture) from boron trichloride and bromoisoxazoles **9g**/**9g′**[9] (1.4:1 mixture) from boron tribromide. Subsequent oxidation of the chloroisoxazole **8g**/**8g′** mixture with pyridinium chlorochromate produced keto isoxazole **10** as the sole product in 90% yield (see Scheme II).

Indeed, the various functionalities of isoxazoles **6–9** provide numerous opportunites for further chemical elaboration. In parrallel to **8g**/**8g′** → **10**, oxidation of the primary hydroxy group of entries **a–e** delivers the corresponding aldehydoisoxazoles as illustrated by the pyridinium chlorochromate oxidation of isoxazole **6b** (X = Cl) to aldehyde **11** (93% yield) and **7b** to aldehyde **12** (93% yield). Furthermore, nucleophilic substitution of the benzylic chloride of **6b** (or bromide of **7b**) by ethanethiolate produces thio ether **13** (89% from **6b**; Scheme III). Collectively the transformations outlined in Scheme III establish that furo[3,4-*c*]isoxazole **5** is a versatile substrate for elaboration to isoxazoles **6**, **7**, **11**, **12**, and **13**.

Given the ready availability of variously substituted nitro olefins (**1**) and propargylic alkoxides (**2**), the three-step route outlined in Scheme I provides an efficient protocol for the preparation of substituted isoxazoles with terminal alkynes leading to 3,4-disubstituted isoxazoles (entries **a**, **b**, and **f**) and internal alkynes leading to 3,4,5-trisubstituted isoxazoles (entries **c**, **d**, **e**, and **g**). This versatility in alkyl and aryl substitution, coupled with the chemical transformations accessible from the hydroxyl and halo moieties, positions this chemistry to provide ready access to a broad spectrum of isoxazoles.

We next turned to a brief examination of the fungicidal activity of these isoxazoles.[14] Fungicidal activities were tested and control values were calculated against the four plant diseases rice blast (RCB; *Pyricularia oryzae*), cucumber gray mold (CGM; *Botrytis cinerea*), tomato late blight (TLB; *Phytophthora infestans*), and barley powdery mildew (BPM; *Erysiphe graminis*). The results of this study, which are summarized in Table I, indicate that isoxazoles **5c** and **7b** have excellent activity against RCB, isoxazole **5d** has excellent activity against CGM, and isoxazole **5e** has excellent activity against BPM. More potent analogs in this series will be reported elsewhere.

Experimental Section

Melting points are uncorrected. Infrared spectra were obtained on a Shimadzu IR-435 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained in CDCl$_3$ at 300 and 75.5 MHz, respectively. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane at 0.00. Column chromatography was performed using Merck Kieselgel 60 (230–400 mesh) as the stationary phase.

General Procedure for the Preparation of Nitro Ethers 3a–g. To a stirred solution of alkynol (10 mmol) dissolved in THF (10 mL) was slowly added *n*-BuLi (6.3 mL of 1.6 M *n*-hexane solution, 10 mmol) at −78 °C. The reaction solution was allowed to warm to 0 °C and then treated dropwise with nitroalkene **1** (5 mmol) in THF (1 mL) and stirred for 4 h at rt. Aqueous acetic acid (12 mL of a 1 N solution) was added to the reaction mixture with stirring, and the resulting two layers were separated. The aqueous layer was extracted with Et$_2$O (2 × 10 mL), and the combined organic solution was washed with saturated NaCl solution (10 mL), dried over MgSO$_4$, and concentrated, and the crude product was purified by flash column chromatography on silica gel.

1-(4-Methylphenyl)-2-nitro-1-(propargyloxy)ethane (3a). Propargyl alcohol (1.68 g, 30.0 mmol), 4-methyl-β-nitrostyrene (1.63 g, 10.0 mmol), and purification by flash column chromatography (*n*-hexane/EtOAc, 13:1) afforded **3a** as a colorless oil (1.81 g, 83%): IR (neat) 1545 (NO$_2$) cm^{-1}; ^{1}H NMR 2.35 (s, 3 H, CH$_3$), 2.43 (t, J = 2.4 Hz, 1 H, CCH), 3.89 (dd, J = 15.8, 2.4 Hz, 1 H, OC*H*H), 4.12 (dd, J = 15.8, 2.4 Hz, 1 H, OCH*H*), 4.40 (dd, J = 12.8, 3.6 Hz, 1 H, C*H*HNO$_2$), 4.65 (dd, J = 12.8, 9.9 Hz, 1 H, CH*H*NO$_2$), 5.30 (dd, J = 9.9, 3.6 Hz, 1 H, CHAr), 7.21 (d, J = 8.1 Hz, 2 H, Ar), 7.28 (d, J = 8.1 Hz, 2 H, Ar); ^{13}C NMR 21.0, 55.7, 75.1, 76.4, 79.8, 126.9, 129.7, 131.8, 139.2. Anal. Calcd for C$_{12}$H$_{13}$NO$_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.91; H, 5.85; N, 6.27.

1-(2-Chlorophenyl)-2-nitro-1-(propargyloxy)ethane (3b). Propargyl alcohol (2.58 g, 46.02 mmol), 2-chloro-β-nitrostyrene (2.81 g, 15.34 mmol), and purification by flash column chromatography (*n*-hexane/EtOAc, 10:1) afforded **3b** as a colorless oil (3.29 g, 90%): IR (neat) 1550 (NO$_2$) cm^{-1}; ^{1}H NMR 2.46 (t, J = 2.3 Hz, 1 H, CCH), 4.05 (dd, J = 15.7, 2.3 Hz, 1 H, OC*H*H), 4.25 (dd, J = 15.7, 2.3 Hz, 1 H, OCH*H*), 4.52 (dd, J = 13.2, 9.1 Hz, 1 H, C*H*HNO$_2$), 4.57 (dd, J = 13.2, 3.6 Hz, 1 H, CH*H*NO$_2$), 5.79 (dd, J = 9.1, 3.6 Hz, 1 H, OCH), 7.33–7.57 (m, 4 H, Ar); ^{13}C NMR 56.8, 73.8, 75.6, 77.9, 78.1, 127.6, 127.7, 130.2, 132.70, 132.8. Anal. Calcd for C$_{11}$H$_{10}$ClNO$_3$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.07; H, 4.15; N, 5.80.

1-(2-Butynyloxy)-1-(2-chlorophenyl)-2-nitroethane (3c). 2-Butyn-1-ol (2.10 g, 30 mmol), 2-chloro-β-nitrostyrene (1.84 g, 10 mmol), and purification by flash column chromatography (*n*-hexane/EtOAc, 10:1) afforded **3c** as a colorless oil (2.22 g, 88%): IR (neat) 1550 (NO$_2$) cm^{-1}; ^{1}H NMR 1.82 (t, J = 2.3 Hz, 3 H, CCCH$_3$), 4.01 (dq, J = 15.1, 2.3 Hz, 1 H, OC*H*HCC), 4.16 (dq, J = 15.1, 2.3 Hz, 1 H, OCH*H*CC), 4.49 (dd, J = 13.0, 9.1 Hz, 1 H, C*H*HNO$_2$), 4.56 (dd, J = 13.0, 3.5 Hz, 1 H, CH*H*NO$_2$), 5.76 (dd, J = 9.1, 3.5 Hz, 1 H, CHO), 7.29–7.57 (m, 4 H, Ar); ^{13}C NMR 3.4, 57.5, 73.5, 73.6, 78.2, 83.9, 127.5, 127.8, 129.8, 130.0, 132.6, 133.3. Anal. Calcd for C$_{12}$H$_{12}$ClNO$_3$: C, 56.81; H, 4.77; N, 5.52. Found: C, 56.72; H, 4.68; N, 5.60.

1-(2-Butynyloxy)-1-(4-chlorophenyl)-2-nitroethane (3d). 2-Butyn-1-ol (2.10 g, 30 mmol), 4-chloro-β-nitrostyrene (1.84 g, 10 mmol), and purification by flash column chromatography (*n*-hexane/EtOAc, 10:1) afforded **3d** as a colorless oil (1.52 g, 60%): IR (neat) 1540 (NO$_2$) cm^{-1}; ^{1}H NMR 1.84 (t, J = 2.3 Hz, 3 H, CH$_3$), 3.91 (dq, J = 15.3, 2.3 Hz, 1 H, C*H*HO), 4.12 (dq, J = 15.3, 2.3 Hz, 1 H, CH*H*O), 4.41 (dd, J = 12.8, 3.9 Hz, 1 H, C*H*HNO$_2$), 4.66 (dd, J = 12.8, 9.6 Hz, 1 H, CH*H*NO$_2$), 5.30 (dd, J = 9.6, 3.9 Hz, 1 H, CHO), 7.32–7.42 (m, 4 H, Ar); ^{13}C NMR 3.4, 56.8, 75.8, 76.6, 79.7, 83.7, 128.3, 129.2, 134.1, 135.0. Anal. Calcd for C$_{12}$H$_{12}$ClNO$_3$;

---

(13) Compound **7f** crystallizes from *n*-hexane/acetone in the monoclinic space group $P2_1/c$. The crystal data at 130 K are as follows: a = 15.009 (4) Å, b = 6.183 (2) Å, c = 13.655 (4) Å, β = 96.32 (2)°; d_{calc} = 1.67 g cm^{-3}; Z = 4; Siemens R3m/V diffractometer; Mo Kα radiation; λ = 0.71073 Å; graphite monochromator; 2θ(max) = 58°; 2330 reflections with $F > 4\sigma(F)$ and 157 parameters used in refinement; R = 0.051; crystallographic programs SHELXTL PLUS, Version 4.2. A complete listing of the X-ray crystallographic data for **7f** is available as supplementary material.

(14) Shepard, M. C. *Annu. Rev. Phytopathol.* **1987**, *25*, 189.

C, 56.81; H, 4.77; N, 5.52. Found: C, 56.65; H, 4.70; N, 5.51.

1-(4-Chlorophenyl)-1-(2-pentynyloxy)-2-nitroethane (3e). 2-Pentyn-1-ol (2.39 g, 28.4 mmol), 4-chloro-β-nitrostyrene (1.74 g, 9.46 mmol), and purification by flash column chromatography (*n*-hexane/EtOAc, 13:1) afforded **3e** as a colorless oil (1.423 g, 56%): IR (neat) 1540 ($\mathrm{NO_2}$) $\mathrm{cm^{-1}}$; ^{1}H NMR 1.11 (t, *J* = 7.5 Hz, 3 H, $\mathrm{CH_2C}H_3$), 2.18 (tq, *J* = 7.5, 2.2 Hz, 2 H, $\mathrm{C}H_2\mathrm{CH_3}$), 3.92 (dt, *J* = 15.4, 2.2 Hz, 1 H, $\mathrm{OC}H\mathrm{H}$), 4.13 (dt, *J* = 15.4, 2.2 Hz, 1 H, $\mathrm{OCH}H$), 4.44 (dd, *J* = 12.9, 3.6 Hz, 1 H, $\mathrm{C}H\mathrm{HNO_2}$), 4.66 (dd, *J* = 12.9, 9.7 Hz, 1 H, $\mathrm{CH}H\mathrm{NO_2}$), 7.34–7.40 (m, 4 H, Ar); ^{13}C NMR 12.1, 13.4, 56.7, 73.6, 75.6, 79.5, 89.4, 128.3, 129.0, 134.1, 134.7. Anal. Calcd for $\mathrm{C_{13}H_{14}ClNO_3}$: C, 58.32; H, 5.27; N, 5.23. Found: C, 57.70; H, 5.17; N, 5.14.

1-(2-Chlorophenyl)-1-[(1-methyl-2-propynyl)oxy]-2-nitroethane (3f and 3f′).[9] DL-3-Butyn-2-ol (2.10 g, 30 mmol), 2-chloro-β-nitrostyrene (1.84 g, 10 mmol), and purification of the resulting diastereomeric mixture by flash column chromatography (*n*-hexane/EtOAc, 12:1) afforded **3f** as a colorless oil [(1.132 g, 45%); IR (neat) 1545 ($\mathrm{NO_2}$) $\mathrm{cm^{-1}}$; ^{1}H NMR 1.45 (d, *J* = 6.4 Hz, 3 H, $\mathrm{CH_3}$), 2.25 (d, *J* = 2.2 Hz, 1 H, CCH), 4.33 (dq, *J* = 2.1, 6.6 Hz, 1 H, $\mathrm{C}H\mathrm{CH_3}$), 4.45 (dd, *J* = 13.4, 9.8 Hz, 1 H, $\mathrm{C}H\mathrm{HNO_2}$), 4.57 (dd, *J* = 13.4, 2.9 Hz, 1 H, $\mathrm{CH}H\mathrm{NO_2}$), 5.70 (dd, *J* = 9.8, 2.9 Hz, 1 H, $\mathrm{OC}H\mathrm{CH_2}$), 7.20–7.70 (m, 4 H, Ar); ^{13}C NMR 21.5, 66.0, 73.7, 74.0, 78.1, 82.5, 127.1, 128.4, 129.3, 129.7, 131.6, 134.6. Anal. Calcd for $\mathrm{C_{12}H_{12}ClNO_3}$; C, 56.81; H, 4.77; N, 5.52. Found: C, 56.73; H, 4.68; N, 5.45] and **3f′** as a white solid (mp 52–53.2 °C) [(0.772 g, 30%); IR ($\mathrm{CCl_4}$) 1555 ($\mathrm{NO_2}$) $\mathrm{cm^{-1}}$; ^{1}H NMR 1.45 (d, *J* = 6.6 Hz, 3 H, $\mathrm{CH_3}$), 2.50 (d, *J* = 2.0 Hz, 1 H, CCH), 4.07 (dq, *J* = 6.6, 2.0 Hz, 1 H, $\mathrm{OC}H\mathrm{CH_3}$), 4.50 (dd, *J* = 12.7, 8.9 Hz, 1 H, $\mathrm{C}H\mathrm{HNO_2}$), 4.56 (dd, *J* = 12.7, 3.8 Hz, 1 H, $\mathrm{CH}H\mathrm{NO_2}$), 5.96 (dd, *J* = 8.9, 3.8 Hz, 1 H, $\mathrm{OC}H\mathrm{CH_2NO_2}$), 7.21–7.51 (m, 4 H, Ar); ^{13}C NMR 21.8, 63.4, 72.7, 74.2, 78.4, 81.6, 127.5, 127.6, 130.1, 130.1, 133.0, 133.4. Anal. Calcd for $\mathrm{C_{12}H_{12}ClNO_3}$: C, 56.81; H, 4.77; N, 5.52. Found: C, 57.10; H, 4.68; N, 5.47].

2-[[1-(4-Chlorophenyl)-2-hexynyl]oxy]-3-methyl-1-nitrobutane (3g and 3g′).[9] 1-(4-Chlorophenyl)-2-hexyn-1-ol (4.30 g, 20.60 mmol), 3-methyl-1-nitrobutene (790 mg, 6.87 mmol), and purification of the resulting diastereomeric mixture by flash column chromatography (*n*-hexane/EtOAc, 7:1) afforded **3g**/**3g′** as an inseparable mixture of colorless oils (1.912 g, 86%): IR (neat) 1540 ($\mathrm{NO_2}$) $\mathrm{cm^{-1}}$; ^{1}H NMR 0.95 and 0.96 (t, *J* = 7.1 Hz, 3 H, $\mathrm{CH_2C}H_3$), 0.97 and 0.98 (d, *J* = 6.8 Hz, 3 H, $\mathrm{CHC}H_3$), 0.99 and 1.00 (d, *J* = 6.8 Hz, 3 H, $\mathrm{CHC}H_3$), 1.55 and 1.56 (hex, *J* = 7.1 Hz, 2 H, $\mathrm{CH_2C}H_2\mathrm{CH_3}$), 2.08 and 2.09 (dqq, *J* = 4.9, 6.8, 6.8 Hz, 1 H, $\mathrm{C}H\mathrm{(CH_3)_2}$), 2.23 and 2.25 (dt, *J* = 7.1, 2.2 Hz, 2 H, $\mathrm{CCC}H_2\mathrm{CH_2}$), 4.31 and 4.42 (dt, *J* = 7.1, 4.9 Hz, 1 H, $\mathrm{OC}H\mathrm{CH_2NO_2}$), 4.46 and 4.48 (dd, *J* = 10.5, 7.1 Hz, 1 H, $\mathrm{C}H\mathrm{HNO_2}$), 4.51 and 4.53 (dd, *J* = 10.5, 3.7 Hz, 1 H, $\mathrm{CH}H\mathrm{NO_2}$), 5.21 (br s, 1 H, OCHAr), 7.25–7.41 (m, 4 H, Ar); ^{13}C NMR 13.6, 17.3, 17.7, 17.8, 18.2, 20.8, 21.9, 22.0, 29.7, 30.8, 70.5, 71.2, 76.6, 76.9, 78.8, 79.3, 89.3, 89.5, 128.5, 128.7, 128.8, 134.1, 137.6, 137.8. Anal. Calcd for $\mathrm{C_{17}H_{22}ClNO_3}$; C, 63.05; H, 6.85; N, 4.32. Found: C, 63.10; H, 6.82; N, 4.24.

General Procedure for the Preparation of 4*H*,6*H*-Furo[3,4-*c*]isoxazoles 5a–g. To a mixture of **3** (5 mmol) and phenyl isocyanate (12.5 mmol) dissolved in dry benzene (30 mL) was added $\mathrm{Et_3N}$ (0.5 mmol), and the resulting mixture was stirred overnight at rt. Water (1 mL) was added, and the mixture was stirred for 2 h at which time the solids were removed by vacuum filtration. The filtrate was dried ($\mathrm{MgSO_4}$) and concentrated under reduced pressure, and the crude product was purified by flash column chromatography on silica gel using an *n*-hexane/EtOAc eluent.

6-(4-Methylphenyl)-4*H*,6*H*-furo[3,4-*c*]isoxazole (5a). Nitro ether **3a** (1.75 g, 7.983 mmol), phenyl isocyanate (2.377 g, 19.957 mmol), and $\mathrm{Et_3N}$ (81 mg, 0.798 mmol) followed by flash column chromatography (*n*-hexane/EtOAc, 8:1) afforded **5a** as a light yellow oil (1.20 g, 75%): IR (neat) 1625, 1500, 1395 (isoxazole) $\mathrm{cm^{-1}}$; ^{1}H NMR 2.33 (s, 3 H, $\mathrm{CH_3}$), 4.92 (dd, *J* = 11.8, 1.2 Hz, 1 H, $\mathrm{OC}H\mathrm{H}$), 4.99 (dt, *J* = 11.8, 1.2 Hz, 1 H, $\mathrm{OCH}H$), 6.06 (s, 1 H, CHAr), 7.18 (d, *J* = 7.9 Hz, 2 H, Ar), 7.32 (d, *J* = 7.9 Hz, 2 H, Ar), 8.02 (t, *J* = 1.2 Hz, 1 H, isoxazole); ^{13}C NMR 21.1, 63.8, 76.2, 122.9, 126.2, 129.3, 134.8, 138.3, 148.1, 172.4. Anal. Calcd for $\mathrm{C_{12}H_{11}NO_2}$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.60; H, 5.53; N, 6.81.

6-(2-Chlorophenyl)-4*H*,6*H*-furo[3,4-*c*]isoxazole (5b). Nitro ether **3b** (3.148 g, 13.13 mmol), phenyl isocyanate (4.693 g, 39.39 mmol), and $\mathrm{Et_3N}$ (133 mg, 1.313 mmol) followed by flash column chromatography (*n*-hexane/EtOAc, 10:1) afforded **5b** as a white solid (mp 71.5–72 °C from *n*-hexane/$\mathrm{CH_2Cl_2}$) (2.311 g, 79%): IR (neat) 1625, 1490, 1435 (isoxazole) $\mathrm{cm^{-1}}$; ^{1}H NMR 6.52 (ddd, *J* = 11.8, 1.3, 0.6 Hz, 1 H, $\mathrm{OC}H\mathrm{H}$), 5.09 (dt, *J* = 11.8, 1.3 Hz, 1 H, $\mathrm{OCH}H$), 6.46 (s, 1 H, OCH), 7.22–7.45 (m, 4 H, Ar), 8.07 (t, *J* = 1.3 Hz, 1 H, isoxazole); ^{13}C NMR 64.2, 74.1, 122.9, 127.0, 127.7, 129.7, 129.8, 132.7, 135.6, 148.3, 171.7. Anal. Calcd for $\mathrm{C_{11}H_8ClNO_2}$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.69; H, 3.63; N, 6.28.

6-(2-Chlorophenyl)-3-methyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (5c). Nitro ether **3c** (2.15 g, 8.478 mmol), phenyl isocyanate (2.52 g, 21.2 mmol), and $\mathrm{Et_3N}$ (86 mg, 0.848 mmol) followed by flash column chromatography (*n*-hexane/EtOAc, 10:1) afforded **5c** as a white solid (mp 88.7–89.2 °C from *n*-hexane/$\mathrm{CH_2Cl_2}$) (1.72 g, 86%): IR ($\mathrm{CCl_4}$) 1660, 1435, 1410 (isoxazole) $\mathrm{cm^{-1}}$; ^{1}H NMR 2.41 (t, *J* = 1.0 Hz, 3 H, $\mathrm{CH_3}$), 4.93 (dt, *J* = 11.3, 0.9 Hz, 1 H, $\mathrm{C}H\mathrm{HO}$), 5.01 (dt, *J* = 11.3, 1.1 Hz, 1 H, $\mathrm{CH}H\mathrm{O}$), 6.41 (s, 1 H, CHO), 7.22–7.45 (m, 4 H, Ar); ^{13}C NMR 11.0, 63.7, 73.6, 118.5, 126.5, 127.4, 129.2, 132.2, 135.7, 158.9, 172.1. Anal. Calcd for $\mathrm{C_{12}H_{10}ClNO_2}$: C, 61.16; H, 4.28; N, 5.94. Found: C, 61.21; H, 4.23; N, 5.93.

6-(4-Chlorophenyl)-3-methyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (5d). Nitro ether **3d** (1.52 g, 5.993 mmol), phenyl isocyanate (1.78 g, 14.9 mmol), and $\mathrm{Et_3N}$ (61 mg, 0.60 mmol) followed by flash column chromatography (*n*-hexane/EtOAc, 8:1) afforded **5d** as a white solid (mp 62–63 °C from *n*-hexane/$\mathrm{CH_2Cl_2}$) (1.206 g, 85%): IR ($\mathrm{CCl_4}$) 1660, 1485 (isoxazole) $\mathrm{cm^{-1}}$; ^{1}H NMR 2.40 (t, *J* = 1.0 Hz, 3 H, $\mathrm{CH_3}$), 4.87 (dt, *J* = 11.3, 0.6 Hz, 1 H, $\mathrm{C}H\mathrm{HO}$), 4.93 (dt, *J* = 11.3, 1.0 Hz, 1 H, $\mathrm{CH}H\mathrm{O}$), 3.61 (s, 1 H, CHO), 7.29–7.42 (m, 4 H, Ar); ^{13}C NMR 11.3, 63.7, 75.4, 118.6, 127.4, 128.4, 133.8, 136.6, 159.1, 172.8. Anal. Calcd for $\mathrm{C_{12}H_{10}ClNO_2}$: C, 61.16; H, 4.28; N, 5.94. Found: C, 61.20; H, 4.25; N, 5.88.

6-(4-Chlorophenyl)-3-ethyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (5e). Nitro ether **3e** (1.41 g, 5.269 mmol), phenyl isocyanate (1.569 g, 13.172 mmol), and $\mathrm{Et_3N}$ (53 mg, 0.527 mmol) followed by flash column chromatography (*n*-hexane/EtOAc, 8:1) afforded **5e** as a colorless oil (1.16 g, 88%): IR (neat) 1655, 1485 (isoxazole) $\mathrm{cm^{-1}}$; ^{1}H NMR 1.25 (t, *J* = 7.7 Hz, 3 H, $\mathrm{CH_2C}H_3$), 2.73 (tq, *J* = 7.7, 1.2 Hz, 2 H, $\mathrm{C}H_2\mathrm{CH_3}$), 4.89 (dt, *J* = 11.0, 1.2 Hz, 1 H, $\mathrm{C}H\mathrm{HO}$), 4.96 (dq, *J* = 10.2, 1.2 Hz, 1 H, $\mathrm{CH}H\mathrm{O}$), 5.98 (s, 1 H, OCHAr), 7.30–7.42 (m, 4 H, Ar); ^{13}C NMR 10.9, 19.5, 63.9, 75.4, 118.0, 127.5, 128.6, 134.0, 136.6, 164.5, 172.6. Anal. Calcd for $\mathrm{C_{13}H_{12}ClNO_2}$: C, 62.53; H, 4.85; N, 5.61. Found: C, 62.60; H, 4.86; N, 5.57.

***trans*-6-(2-Chlorophenyl)-4-methyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (*trans*-5f).** Nitro ether **3f** (479 mg, 1.889 mmol), phenyl isocyanate (569 mg, 4.723 mmol), and $\mathrm{Et_3N}$ (19 mg, 0.189 mmol) followed by flash column chromatography (*n*-hexane/EtOAc, 10:1) afforded *trans*-**5f** as a white solid (mp 74–74.5 °C from *n*-hexane/$\mathrm{CH_2Cl_2}$) (284 mg, 64%): IR ($\mathrm{CCl_4}$) 1620, 1435, 1395 (isoxazole) $\mathrm{cm^{-1}}$; ^{1}H NMR 1.59 (d, *J* = 6.4 Hz, 3 H, $\mathrm{CH_3}$), 5.46 (tq, *J* = 6.4, 1.1 Hz, 1 H, $\mathrm{C}H\mathrm{CH_3}$), 6.54 (d, *J* = 1.1 Hz, 1 H, $\mathrm{C}H\mathrm{Ar}$), 7.22–7.45 (m, 4 H, Ar), 7.47 (d, *J* = 1.1 Hz, 1 H, isoxazole); ^{13}C NMR 21.9, 72.0, 73.4, 126.8, 127.1, 127.4, 132.3, 132.4, 148.3, 171.5. Anal. Calcd for $\mathrm{C_{12}H_{10}ClNO_2}$: C, 61.16; H, 4.28; N, 5.94. Found: C, 61.22; H, 4.27; N, 5.90.

***cis*-6-(2-Chlorophenyl)-4-methyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (*cis*-5f′).** Nitro ether **3f′** (740 mg, 2.918 mmol), phenyl isocyanate (869 mg, 7.295 mmol), and $\mathrm{Et_3N}$ (29 mg, 0.292 mmol) followed by flash column chromatography (*n*-hexane/EtOAc, 10:1) afforded *cis*-**5f′** as a white solid (mp 109–110 °C from *n*-hexane/$\mathrm{CH_2Cl_2}$) (550 mg, 80%): IR ($\mathrm{CCl_4}$) 1620, 1435, 1395 (isoxazole) $\mathrm{cm^{-1}}$; ^{1}H NMR 1.64 (d, *J* = 6.4 Hz, 3 H, $\mathrm{CH_3}$), 5.33 (tq, *J* = 6.3, 1.2 Hz, 1 H, $\mathrm{C}H\mathrm{CH_3}$), 6.46 (d, *J* = 1.2 Hz, 1 H, CHAr), 7.25–7.52 (m, 4 H, Ar), 8.07 (d, *J* = 1.2 Hz, 1 H, isoxazole); ^{13}C NMR 22.0, 72.0, 74.2, 127.0, 127.3, 128.1, 129.7, 133.0, 135.6, 148.4, 171.8. Anal. Calcd for $\mathrm{C_{12}H_{10}ClNO_2}$: C, 61.16; H, 4.28; N, 5.94. Found: C, 61.20; H, 4.25; N, 5.92. The stereochemistry of **5f′** was established by X-ray crystallographic analysis.[11]

4-(4-Chlorophenyl)-6-isopropyl-3-*n*-propyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (5g and 5g′).[9] Nitro ether **3g**/**3g′** (3.57 g, 11.028 mmol), phenyl isocyanate (3.28 g, 27.57 mmol), and $\mathrm{Et_3N}$ (111 mg, 1.102 mmol) followed by flash column chromatography (*n*-hexane/EtOAc, 20:1) afforded, as clear oils, **5g** [(1.648 g, 49%); IR (neat) 1640, 1415 (isoxazole) $\mathrm{cm^{-1}}$; ^{1}H NMR 0.81 (t, *J* = 7.4 Hz, 3 H, $\mathrm{CH_2C}H_3$), 1.04 (d, *J* = 6.8 Hz, 3 H, $\mathrm{CHC}H_3$), 1.08 (t, *J* = 6.8 Hz, 3 H, $\mathrm{CHC}H_3$), 1.46 (m, 2 H, $\mathrm{CH_2C}H_2\mathrm{CH_3}$), 2.11 (dqq, *J* = 6.0, 6.8, 6.8 Hz, 1 H, C*H*(CH$_3$)$_2$), 2.50 (m, 2 H, C*H*$_2$CH$_2$CH$_3$), 5.02 (dd, *J* = 6.0, 1.4 Hz, 1 H, OCHAr), 7.23–7.40 (m, 4 H, Ar); ^{13}C NMR 13.5, 17.3, 17.7, 20.4, 27.8, 32.7, 76.7, 80.7, 121.9, 128.2, 128.9, 134.4, 138.8, 164.2, 172.3. Anal. Calcd for $C_{17}H_{20}ClNO_2$: C, 66.77; H, 6.59; N, 4.58. Found: C, 66.71; H, 6.50; N, 4.49] and **5g′** [(1.599 g, 47%); IR (neat) 1645, 1485, 1420 (isoxazole) cm^{-1}; ^{1}H NMR 0.80 (t, *J* = 7.4 Hz, 3 H, CH$_2$C*H*$_3$), 1.08 (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$), 1.09 (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$), 1.44 (m, 2 H, CH$_2$C*H*$_2$CH$_3$), 2.09 (dqq, *J* = 6.6, 6.8, 6.8 Hz, 1 H, C*H*(CH$_3$)$_2$), 2.47 (m, 2 H, C*H*$_2$CH$_2$CH$_3$), 4.83 (dd, *J* = 6.6, 1.0 Hz, 1 H, OC*H*CH), 5.86 (br s, 1 H, OC*H*Ar), 7.28–7.37 (m, 4 H, Ar); ^{13}C NMR 13.4, 17.4, 18.08, 20.3, 27.5, 32.1, 76.1, 80.7, 121.5, 128.6, 134.3, 137.9, 163.9, 172.4. Anal. Calcd for $C_{17}H_{20}ClNO_2$: C, 66.77; H, 6.59; N, 4.58. Found: C, 66.75; H, 6.55; N, 4.56].

General Procedure for Reaction of 5 with BX$_3$. To a cooled solution of **5** (2 mmol) in dry CH$_2$Cl$_2$ (2 mL) at -78 °C was added a solution of BX$_3$ (2 mmol), and the mixture was stirred for 20 min. Et$_2$O (10 mL) was added, and the resulting solution was poured into cold water (5 mL) with good stirring, the organic layer was separated, and the aqueous layer was extracted with Et$_2$O (2 × 10 mL). The combined organic solution was dried (MgSO$_4$) and concentrated under reduced pressure, and the crude product was purified by flash column chromatography on silica gel using an *n*-hexane/EtOAc (2:1) eluent.

3-[Chloro(4-methylphenyl)methyl]-4-(hydroxymethyl)isoxazole (6a). Furo[3,4-*c*]isoxazole **5a** (201 mg, 1.0 mmol) and BCl$_3$ (1 mL of CH$_2$Cl$_2$ solution, 1.0 mmol) gave **6a** as a yellow syrup (231 mg, 97%): IR (CCl$_4$) 3385 (OH), 1600, 1405 (isoxazole) cm^{-1}; ^{1}H NMR 2.33 (s, 3 H, CH$_3$), 2.60 (br s, 1 H, OH), 4.31 (d, *J* = 13.5 Hz, 1 H, C*H*HOH), 4.48 (d, *J* = 13.5 Hz, 1 H, CH*H*OH), 6.24 (s, 1 H, CHCl), 7.17 (d, *J* = 8.0 Hz, 2 H, Ar), 7.34 (d, *J* = 8.0 Hz, 2 H, Ar), 8.32 (s, 1 H, isoxazole); ^{13}C NMR 21.0, 53.5, 54.0, 118.5, 127.3, 129.4, 133.7, 138.9, 157.5, 160.9. Anal. Calcd for $C_{12}H_{12}ClNO_2$: C, 60.64; H, 5.09; N, 5.89. Found: C, 60.55; H, 5.12; N, 5.78.

3-[Chloro(2-chlorophenyl)methyl]-4-(hydroxymethyl)isoxazole (6b). Furo[3,4-*c*]isoxazole **5b** (443 mg, 2.0 mmol) and BCl$_3$ (2 mL of CH$_2$Cl$_2$ solution, 2.0 mmol) gave **6b** as a white solid (mp 72–73 °C from *n*-hexane/acetone) (509 mg, 99%): IR (KBr) 3311 (OH), 1605, 1400 (isoxazole) cm^{-1}; ^{1}H NMR 2.66 (br s, 1 H, OH), 4.40 (dd, *J* = 13.4, 0.9 Hz, 1 H, HOC*H*H), 4.54 (dd, *J* = 13.4, 0.9 Hz, 1 H, HOCH*H*), 6.67 (s, 1 H, ClCH), 7.27–7.72 (m, 4 H, Ar), 8.35 (s, 1 H, isoxazole); ^{13}C NMR 50.3, 53.5, 116.5, 127.3, 129.6, 130.0, 130.2, 132.7, 134.4, 157.4, 160.1. Anal. Calcd for $C_{11}H_9Cl_2NO_2$: C, 51.19; H, 3.51; N, 5.43. Found: C, 51.20; H, 3.52; N, 5.39.

3-[Chloro(2-chlorophenyl)methyl]-4-(hydroxymethyl)-5-methylisoxazole (6c). Furo[3,4-*c*]isoxazole **5c** (570 mg, 2.419 mmol) and BCl$_3$ (2.5 mL of CH$_2$Cl$_2$ solution, 2.5 mmol) gave **6c** as a white solid (mp 91–91.5 °C from *n*-hexane/acetone) (630 mg, 96%): IR (KBr) 3395 (OH), 1630, 1440 (isoxazole) cm^{-1}; ^{1}H NMR 1.90 (br s, 1 H, OH), 2.40 (s, 3 H, CH$_3$), 4.41 (d, *J* = 12.9 Hz, 1 H, C*H*HOH), 4.51 (d, *J* = 12.9 Hz, 1 H, CH*H*OH), 6.69 (s, 1 H, CHAr), 7.27–7.76 (m, 4 H, Ar); ^{13}C NMR 11.1, 50.6, 53.5, 112.9, 127.4, 129.6, 130.2, 130.3, 132.7, 134.7, 161.4, 168.6. Anal. Calcd for $C_{12}H_{11}Cl_2NO_2$: C, 52.96; H, 4.08; N, 5.15. Found: C, 53.02; H, 4.08; N, 5.07.

3-[Chloro(4-chlorophenyl)methyl]-4-(hydroxymethyl)-5-methylisoxazole (6d). Furo[3,4-*c*]isoxazole **5d** (643 mg, 2.729 mmol) and BCl$_3$ (2.8 mL of CH$_2$Cl$_2$ solution, 2.8 mmol) gave **6d** as a colorless oil (658 mg, 88%): IR (neat) 3365 (OH), 1625, 1480 (isoxazole) cm^{-1}; ^{1}H NMR 2.03 (br s, 1 H, OH), 2.40 (s, 3 H, CH$_3$), 4.32 (d, *J* = 13.0 Hz, 1 H, C*H*HOH), 4.43 (d, *J* = 13.0 Hz, 1 H, CH*H*OH), 6.22 (s, 1 H, CHAr), 7.32–7.46 (m, 4 H, Ar); ^{13}C NMR 11.0, 53.3, 53.6, 112.7, 128.8, 129.1, 134.8, 135.5, 161.8, 168.9. Anal. Calcd for $C_{12}H_{11}Cl_2NO_2$: C, 52.96; H, 4.08; N, 5.15. Found: C, 52.99; H, 4.07; N, 4.98.

3-[Chloro(4-chlorophenyl)methyl]-5-ethyl-4-(hydroxymethyl)isoxazole (6e). Furo[3,4-*c*]isoxazole **5e** (495 mg, 1.983 mmol) and BCl$_3$ (2 mL of CH$_2$Cl$_2$ solution, 2 mmol) gave **6e** as a colorless oil (511 mg, 90%): IR (neat) 3360 (OH), 1615, 1485 (isoxazole) cm^{-1}; ^{1}H NMR 1.28 (t, *J* = 7.6 Hz, 3 H, CH$_2$C*H*$_3$), 2.03 (br s, 1 H, OH), 2.77 (q, *J* = 7.6 Hz, 2 H, C*H*$_2$CH$_3$), 4.34 (d, *J* = 13.0 Hz, 1 H, C*H*HOH), 4.43 (d, *J* = 13.0 Hz, 1 H, CH*H*OH), 6.23 (s, 1 H, CHAr), 7.32–7.47 (m, 4 H, Ar); ^{13}C NMR 12.0, 19.1, 53.1, 53.6, 111.8, 128.8, 129.1, 134.8, 135.5, 161.8, 173.6. Anal. Calcd for $C_{13}H_{13}Cl_2NO_2$: C, 54.56; H, 4.58; N, 4.89. Found: C, 54.50; H, 4.55; N, 4.80.

3-[Chloro(2-chlorophenyl)methyl]-4-(1-hydroxyethyl)isoxazole ((*R,*R**)-6f and (*R**,*S**)-6f′).** Furo[3,4-*c*]isoxazole *trans*-**5f** (345 mg, 1.464 mmol) and BCl$_3$ (1.5 mL of CH$_2$Cl$_2$ solution, 1.5 mmol) gave a 2.2:1 (*R**,*R**)-**6f**:(*R**,*S**)-**6f′** inseparable mixture (347 mg, 87.2%), while furo[3,4-*c*]isoxazole *cis*-**5f′** (160 mg, 0.679 mmol) and BCl$_3$ (0.7 mL of a CH$_2$Cl$_2$ solution, 0.7 mmol) gave a 1:1.6 (*R**,*R**)-**6f**:(*R**,*S**)-**6f′** inseparable mixture as a colorless oil which partially solidified on standing (347 mg, 87%): IR (CCl$_4$) 3400 (OH), 3380 (OH) cm^{-1}; ^{1}H NMR (*R**,*R**)-**6f** 1.51 (d, *J* = 6.5 Hz, 3 H, CH$_3$), 2.08 (br s, 1 H, OH), 4.93 (dq, *J* = 6.5, 0.7 Hz, 1 H, C*H*CH$_3$), 6.78 (s, 1 H, CHAr), 7.28–7.82 (m, 4 H, Ar), 8.33 (d, *J* = 0.7 Hz, 1 H, isoxazole); ^{1}H NMR (*R**,*S**)-**6f′** 1.48 (d, *J* = 6.5 Hz, 3 H, CH$_3$), 2.08 (br s, 1 H, OH), 4.72 (dq, *J* = 6.5, 0.7 Hz, 1 H, C*H*CH$_3$), 6.79 (s, 1 H, CHAr), 7.28–7.71 (m, 4 H, Ar), 8.35 (d, *J* = 0.7 Hz, 1 H, isoxazole); ^{13}C NMR (*R**,*R**)-**6f** 23.6, 50.2, 60.7, 123.1, 127.3, 129.5, 130.2, 130.5, 132.6, 134.7, 156.0, 160.1; ^{13}C NMR (*R**,*S**)-**6f′** 23.6, 50.1, 60.7, 123.1, 127.5, 129.6, 130.2, 130.3, 132.7, 134.9, 156.2, 159.9. Anal. Calcd for $C_{12}H_{11}Cl_2NO_2$: C, 52.96; H, 4.08; N, 5.15. Found: C, 52.99; H, 4.08; N, 5.05. Recrystallization of this partially solidifed **6f**/**6f′** mixture (*n*-hexane/acetone) gave an analytical sample of **6f′** (mp 90–91 °C) suitable for X-ray crystallographic analysis.[12] Partially purified diastereomer **6f** remained as a colorless oil.

3-[Bromo(4-methylphenyl)methyl]-4-(hydroxymethyl)isoxazole (7a). Furo[3,4-*c*]isoxazole **5a** (990 mg, 4.920 mmol) and BBr$_3$ (1.479 mg, 558 μL, 5.904 mmol) gave **7a** as a light yellow oil (1.325 g, 96%): IR (neat) 3375 (OH), 1600, 1400 (isoxazole) cm^{-1}; ^{1}H NMR 2.33 (s, 3 H, CH$_3$), 3.22 (br s, 1 H, OH), 4.38 (dd, *J* = 13.4, 0.8 Hz, 1 H, C*H*HOH), 4.53 (dd, *J* = 13.4, 0.8 Hz, 1 H, CH*H*OH), 6.28 (s, 1 H, CHBr), 7.16 (d, *J* = 8.0 Hz, 2 H, Ar), 7.40 (d, *J* = 8.0 Hz, 2 H, Ar), 8.36 (s, 1 H, isoxazole); ^{13}C NMR 21.1, 42.4, 53.6, 118.3, 128.2, 134.0, 139.0, 157.5, 161.0. Anal. Calcd for $C_{12}H_{12}BrNO_2$: C, 51.08; H, 4.29; N, 4.96. Found: C, 51.29; H, 4.38; N, 4.91.

3-[Bromo(2-chlorophenyl)methyl]-4-(hydroxymethyl)isoxazole (7b). Furo[3,4-*c*]isoxazole **5b** (1.769 g, 7.979 mmol) and BBr$_3$ (2.40 g, 905 μL, 9.575 mmol) gave **7b** as a white solid (mp 90–90.5 °C from *n*-hexane/acetone) (2.37 g, 98%): IR (KBr) 3325 (OH), 1610, 1395 (isoxazole) cm^{-1}; ^{1}H NMR 2.65 (br s, 1 H, OH), 4.43 (dd, *J* = 13.3, 0.8 Hz, 1 H, HOC*H*H), 4.53 (dd, *J* = 13.3, 0.8 Hz, 1 H, HOCH*H*), 6.70 (s, 1 H, BrCH), 7.24–7.39 (m, 4 H, Ar), 8.37 (s, 1 H, isoxazole); ^{13}C NMR 37.7, 53.5, 116.2, 127.4, 129.6, 130.2, 131.3, 132.4, 134.8, 157.4, 160.2. Anal. Calcd for $C_{11}H_9BrClNO_2$: C, 43.67; H, 3.00; N, 4.63. Found: C, 43.69; H, 2.98; N, 4.59.

3-[Bromo(2-chlorophenyl)methyl]-4-(hydroxymethyl)-5-methylisoxazole (7c). Furo[3,4-*c*]isoxazole **5c** (674 mg, 2.860 mmol) and BBr$_3$ (860 mg, 324 μL, 3.432 mmol) gave **7c** as a white solid (mp 91.2–92 °C from *n*-hexane/acetone) (770 mg, 85%): IR (KBr) 3405 (OH), 1630, 1430 (isoxazole) cm^{-1}; ^{1}H NMR 2.35 (s, 1 H, OH), 2.37 (s, 3 H, CH$_3$), 4.35 (d, *J* = 12.9 Hz, 1 H, C*H*HOH), 4.49 (d, *J* = 12.9 Hz, 1 H, CH*H*OH), 6.72 (s, 1 H, CHBr), 7.25–7.76 (m, 4 H, Ar); ^{13}C NMR 11.1, 38.1, 53.4, 112.7, 127.4, 129.5, 130.1, 131.4, 132.4, 135.1, 161.3, 168.4. Anal. Calcd for $C_{12}H_{11}BrClNO_2$: C, 45.52; H, 3.50; N, 4.42. Found: C, 45.51; H, 3.42; N, 4.39.

3-[Bromo(4-chlorophenyl)methyl]-4-(hydroxymethyl)-5-methylisoxazole (7d). Furo[3,4-*c*]isoxazole **5d** (533 mg, 2.262 mmol) and BBr$_3$ (680 mg, 256 μL, 2.712 mmol) gave **7d** as a white solid (mp 80–82 °C from *n*-hexane/acetone) (607 mg, 85%): IR (CCl$_4$) 3385 (OH), 1625, 1485 (isoxazole) cm^{-1}; ^{1}H NMR 2.36 (s, 3 H, CH$_3$), 2.69 (s, 1 H, OH), 4.32 (d, *J* = 12.9 Hz, 1 H, C*H*HOH), 4.47 (d, *J* = 12.9 Hz, 1 H, CH*H*OH), 6.24 (s, 1 H, CHBr), 7.27–7.50 (m, 4 H, Ar); ^{13}C NMR 11.0, 41.5, 53.2, 112.7, 128.7, 129.8, 134.6, 135.8, 161.8, 168.5. Anal. Calcd for $C_{12}H_{11}BrClNO_2$: C, 45.52; H, 3.50; N, 4.42. Found: C, 45.60; H, 3.49; N, 4.30.

3-[Bromo(4-chlorophenyl)methyl]-5-ethyl-4-(hydroxymethyl)isoxazole (7e). Furo[3,4-*c*]isoxazole **5e** (495 mg, 1.983 mmol) and BBr$_3$ (596 mg, 225 μL, 2.379 mmol) gave **7e** as a colorless oil (540 mg, (83%): IR (neat) 3370 (OH), 1615, 1480 (isoxazole) cm^{-1}; ^{1}H NMR 1.26 (t, *J* = 7.6 Hz, 3 H, CH$_2$C*H*$_3$), 2.45 (s, 1 H, OH), 2.75 (q, *J* = 7.6 Hz, 2 H, C*H*$_2$CH$_3$), 4.35 (d, *J* = 12.9 Hz, 1 H, C*H*HOH), 4.49 (d, *J* = 12.9 Hz, 1 H, CH*H*OH), 6.25 (s, 1 H, CHBr), 7.26–7.50 (m, 4 H, Ar); ^{13}C NMR 11.9, 19.1, 41.6, 53,1, 111.8, 128.7, 129.9, 134.7, 135.9, 161.8, 173.2. Anal. Calcd for

$C_{13}H_{13}BrClNO_2$: C, 47.23; H, 3.96; N, 4.23. Found: C, 47.44; H, 3.91; N, 4.10.

3-[Bromo(2-chlorophenyl)methyl]-4-(1-hydroxyethyl)isoxazole ((*R,*S**)-7f and (*R**,*R**)-7f′).** Furo[3,4-*c*]isoxazole *trans*-**5f** (297 mg, 1.260 mmol) and BBr_3 (379 mg, 143 μL, 1.512 mmol) gave a 7.4:1 (*R**,*S**)-**7f**:(*R**,*R**)-**7f′** inseparable mixture (355 mg, 89%, white solid, mp 108–112 °C), while furo[3,4-*c*]isoxazole *cis*-**5f′** (126 mg, 0.534 mmol) and BBr_3 (160 mg, 61 μL, 0.640 mmol) gave a 1:1.8 (*R**,*S**)-**7f**:(*R**,*R**)-**7f′** inseparable mixture (149 mg, 89%, colorless oil): IR (KBr) 3350 (OH), 1605, 1405, 1260 (isoxazole) cm^{-1}; ^1H NMR (*R**,*S**)-**7f** 1.44 (d, *J* = 6.5 Hz, 3 H, CH_3), 2.41 (br s, 1 H, OH), 4.65 (dq, *J* = 6.5, 0.7 Hz, 1 H, $CHCH_3$), 6.74 (s, 1 H, CHBr), 7.24–7.70 (m, 4 H, Ar), 8.37 (d, *J* = 0.7 Hz, 1 H, isoxazole); ^1H NMR (*R**,*R**)-**7f′** 1.48 (d, *J* = 6.5 Hz, 3 H, CH_3), 2.41 (br s, 1 H, OH), 4.88 (dq, *J* = 6.5, 0.7 Hz, 1 H, $CHCH_3$), 6.83 (s, 1 H, CHBr), 7.23–7.85 (m, 4 H, Ar), 8.32 (d, *J* = 0.7 Hz, 1 H, isoxazole); ^{13}C NMR (*R**,*S**)-**7f** 23.5, 37.5, 60.6, 122.8, 127.5, 129.6, 130.2, 131.2, 132.5, 135.3, 156.2, 159.8; ^{13}C NMR (*R**,*R**)-**7f′** 23.4, 37.3, 60.6, 122.8, 127.4, 129.5, 130.1, 131.8, 132.3, 135.1, 155.9, 160.1. Anal. Calcd for $C_{12}H_{11}BrClNO_2$: C, 45.52; H, 3.50; N, 4.42. Found: C, 45.70; H, 3.48; N, 4.40. Recrystallization of this partially solidified **7f**/**7f′** mixture (*n*-hexane/acetone) gave an analytical sample of **7f** (mp 111–112 °C) suitable for X-ray crystallographic analysis.[13] Partially purified diastereomer **7f′** remained as a colorless oil.

4-[Chloro(4-chlorophenyl)methyl]-3-(1-hydroxy-2-methylpropyl)-5-*n*-propylisoxazole (8g and 8g′).[9] Furo[3,4-*c*]isoxazole **5g′** (989 mg, 3.074 mmol) and BCl_3 (3.7 mL of CH_2Cl_2 solution, 3.7 mmol) gave a 1.2:1 **8g**:**8g′** inseparable mixture as a white solid (mp 78–84 °C) (1.00 g, 91%): IR (CCl_4) 3355 (OH), 1605, 1485 (isoxazole) cm^{-1}; ^1H NMR **8g** 0.89 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.01 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.63 (m, 2 H, $CH_2CH_2CH_3$), 1.93 (dqq, *J* = 7.8, 6.6, 6.6 Hz, 1 H, $CH(CH_3)_2$), 2.56 (m, 2 H, $CH_2CH_2CH_3$), 2.73 (br s, 1 H, OH), 4.49 (d, *J* = 7.8 Hz, 1 H, CHOH), 6.43 (s, 1 H, CHAr), 7.26–7.43 (m, 4 H, Ar); ^1H NMR **8g′** 0.80 (d, *J* = 6.8 Hz, 3 H, $CHCH_3$), 0.85 (t, *J* = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 0.86 (d, *J* = 6.8 Hz, 3 H, $CHCH_3$), 1.54 (m, 2 H, $CH_2CH_2CH_3$), 2.19 (dqq, *J* = 7.8, 6.6, 6.6 Hz, $CH(CH_3)_2$), 2.51 (m, 2 H, $CH_2CH_2CH_3$), 2.78 (br s, 1 H, OH), 4.45 (d, *J* = 7.8 Hz, 1 H, CHOH), 6.45 (s, 1 H, CHAr), 7.26–7.43 (m, 4 H, Ar); ^{13}C NMR **8g** 13.8, 18.0, 19.0, 20.4, 28.3, 33.3, 52.6, 72.6, 113.7, 128.5, 128.6, 134.1, 137.3, 162.8, 172.8; ^{13}C NMR **8g′** 13.7, 18.2, 19.0, 20.3, 28.5, 33.1, 52.6, 73.0, 114.2, 128.5, 128.6, 133.9, 137.4, 163.0, 172.8. Anal. Calcd for $C_{17}H_{21}Cl_2NO_2$: C, 59.65; H, 6.19; N, 4.09. Found: C, 59.68; H, 6.20; N, 4.05.

4-[Bromo(4-chlorophenyl)methyl]-3-(1-hydroxy-2-methylpropyl)-5-*n*-propylisoxazole (9g and 9g′).[9] Furo[3,4-*c*]isoxazole **5g′** (272 mg, 0.889 mmol) and BBr_3 (267 mg, 100 μL, 1.066 mmol) gave a 1.4:1 **9g**:**9g′** inseparable colorless oil (302 mg, 88%): IR (neat) 3360 (OH), 1605, 1485 (isoxazole) cm^{-1}; ^1H NMR **9g** 0.93 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.02 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.09 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.69 (m, 2 H, $CH_2CH_2CH_3$), 2.22 (dqq, *J* = 8.3, 6.6, 6.6 Hz, 1 H, $CH(CH_3)_2$), 2.63 (m, 2 H, $CH_2CH_2CH_3$), 2.78 (br s, 1 H, OH), 4.50 (d, *J* = 8.3 Hz, 1 H, CHOH), 6.54 (s, 1 H, CHBr), 7.27–7.41 (m, 4 H, Ar); ^1H NMR **9g′** 0.78 (d, *J* = 6.8 Hz, 3 H, $CHCH_3$), 0.88 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 0.89 (d, *J* = 6.8 Hz, 3 H, $CHCH_3$), 1.62 (m, 2 H, $CH_2CH_2CH_3$), 2.04 (dqq, *J* = 8.3, 6.6, 6.6 Hz, 1 H, $CH(CH_3)_2$), 2.56 (m, 2 H, $CH_2CH_2CH_3$), 2.78 (br s, 1 H, OH), 4.48 (d, *J* = 8.3 Hz, 1 H, CHOH), 6.59 (s, 1 H, CHBr), 7.27–7.44 (m, 4 H, Ar); ^{13}C NMR **9g** 13.8, 18.2, 19.1, 20.1, 28.6, 33.2, 42.4, 72.9, 114.4, 128.5, 129.4, 133.9, 137.3, 162.3, 173.0; ^{13}C NMR **9g′** 13.9, 18.2, 19.0, 20.0, 28.9, 33.1, 42.1, 72.7, 113.6, 128.6, 129.4, 134.1, 137.4, 162.7, 173.2. Anal. Calcd for $C_{17}H_{21}BrClNO_2$: C, 52.80; H, 5.47; N, 3.62. Found: C, 52.77; H, 5.46; N, 3.58.

4-[Chloro(4-chlorophenyl)methyl]-3-(2-oxo-3-methylpropyl)-5-*n*-propylisoxazole (10). To a stirred suspension of PCC (958 mg, 4.44 mmol) in CH_2Cl_2 (5 mL) was added a solution of **8g**/**8g′** (796 mg, 2.22 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred for 2.5 h at rt. Et_2O (5 mL) was added, the supernatant liquid was decanted, and the insoluble residue was washed with Et_2O (3 × 5 mL). The combined organic solution was passed through a short pad of Florisil, and the solvent was evaporated. Flash column chromatography using *n*-hexane/EtOAc eluent (8:1) gave **10** as a colorless oil (679 mg, 90%): IR (neat) 1690 (C=O) cm^{-1}; ^1H NMR 0.93 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.18 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$), 1.22 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$), 1.65 (m, 2 H, $CH_2CH_2CH_3$), 2.72 (m, 2 H, $CH_2CH_2CH_3$), 3.62 (heptet, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 6.83 (s, 1 H, CHAr), 7.29–7.39 (m, 4 H, Ar); ^{13}C NMR 13.7, 18.0, 18.4, 20.5, 28.6, 38.4, 51.5, 115.3, 128.4, 128.5, 133.9, 137.6, 156.1, 173.9, 200.2. Anal. Calcd for $C_{17}H_{19}Cl_2NO_2$: C, 60.01; H, 5.63; N, 4.12. Found: C, 60.19; H, 5.60; N, 4.10.

3-[Chloro(2-chlorophenyl)methyl]-4-formylisoxazole (11). To a stirred suspension of PCC (608 mg, 2.82 mmol) in CH_2Cl_2 (5 mL) was added a solution of **6b** (364 mg, 1.410 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred for 2.5 h at rt. Et_2O (5 mL) was added, the supernatant liquid was decanted, and the insoluble residue was washed with Et_2O (3 × 5 mL). The combined organic solution was passed through a short pad of Florisil. The solvent was evaporated, and the crude product was purified by flash column chromatography using *n*-hexane/EtOAc (4:1) as eluent to give **11** as a colorless oil (315 mg, 93%): IR (neat) 1690 (C=O) cm^{-1}; ^1H NMR 6.99 (s, 1 H, CHCl), 7.26–7.41 (m, 4 H, Ar), 9.06 (s, 1 H, isoxazole), 9.96 (s, 1 H, HC=O); ^{13}C NMR 49.5, 119.8, 127.2, 129.5, 129.6, 130.2, 132.9, 134.1, 159.6, 165.9, 181.8. Anal. Calcd for $C_{11}H_7Cl_2NO_2$: C, 51.59; H, 2.76; N, 5.47. Found: C, 51.63; H, 2.79; N, 5.46.

3-[Bromo(2-chlorophenyl)methyl]-4-formylisoxazole (12). To a stirred suspension of PCC (897 mg, 4.16 mmol) in CH_2Cl_2 (5 mL) was added a solution of **7b** (631 mg, 2.085 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 2.5 h at rt at which time Et_2O (7 mL) was added and the supernatant liquid was decanted. The insoluble residue was washed with Et_2O (3 × 5 mL), and the combined organic solution was passed through a short pad of Florisil. The solvent was evaporated, and the crude product was purified by flash column chromatography using an *n*-hexane/EtOAc (4:1) eluent to give **12** as a white solid (mp 79–80 °C from *n*-hexane) (583 mg, 93%): IR (KBr) 1695 (C=O) cm^{-1}; ^1H NMR 7.02 (s, 1 H, BrCH), 7.25–7.68 (m, 4 H, Ar), 9.07 (s, 1 H, isoxazole), 9.98 (s, 1 H, HC=O); ^{13}C NMR 36.9, 119.6, 127.3, 129.7, 130.2, 130.9, 132.9, 134.5, 160.0, 165.9, 181.8. Anal. Calcd for $C_{11}H_7BrClNO_2$: C, 43.96; H, 2.35; N, 4.66. Found: C, 44.05; H, 2.30; N, 4.59.

3-[(2-Chlorophenyl)(ethylthio)methyl]-4-(hydroxymethyl)isoxazole (13). To a suspension of NaH (60% mineral oil dispersion, 80 mg, 1.98 mmol) in THF (3 mL) was added ethanethiol (123 mg, 1.98 mmol). After the mixture was stirred for 20 min, a solution of **6b** (500 mg, 1.65 mmol) in THF (1 mL) was added, and stirring was continued for 1 h at rt. Water (3 mL) was added, and the mixture was extracted with Et_2O (2 × 10 mL). The extracts were dried ($MgSO_4$), concentrated, and purified by flash column chromatography on silica gel using *n*-hexane/EtOAc (4:1) as eluent to afford **13** as a white solid (mp 40–40.5 °C from *n*-hexane/CH_2Cl_2) (417 mg, 89%): IR (KBr) 3370 (OH) cm^{-1}; ^1H NMR 1.25 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 2.56 (dq, *J* = 7.4, 1.2 Hz, 2 H, CH_2CH_3), 2.79 (br s, OH), 4.43 (dd, *J* = 13.3, 0.8 Hz, 1 H, HOC*H*H), 4.48 (dd, *J* = 13.3, 0.8 Hz, 1 H, HOCH*H*), 5.80 (s, 1 H, SCH), 7.20–7.73 (m, 4 H, Ar), 8.32 (s, 1 H, isoxazole); ^{13}C NMR 14.1, 29.0, 40.2, 53.4, 118.5, 127.3, 129.1, 129.4, 130.4, 133.3, 135.3, 157.0, 160.5. Anal. Calcd for $C_{13}H_{14}ClNO_2S$: C, 55.02; H, 4.97; N, 4.94. Found: C, 55.10; H, 4.95; N, 4.88.

Biological Tests. Test furo[3,4-*c*]isoxazole (**5b–g**) and isoxazole (**6b** and **7b**) compounds (12.5 mg) were readily dispersed in a standard formulation of 5 mL of acetone and 45 mL of Tween 20 solution (250 ppm). The resulting solution was evenly sprayed onto plants while rotated on a turntable, and all tests were run in two-pot replicates.

Test 1. Evaluation of activity against rice blast was done by foliage spray onto rice plants (second leaf stage) grown in 5-cm pots. After the spray deposit had dried, the plants were inoculated with a suspension of condia in water (1 × 10^6 spores/mL) and placed in a dew chamber at 25 °C for 24 h. For inoculum preparation, rice blast fungus (*Pyricularia oryzae*) was incubated on rice polish agar medium at 26 °C for 2 weeks and then scratched airial mycelia with rubber and irradiated with near UV light for 2 d. The plants were then held in lighted growth chamber (26 ± 2 °C) for an additional 5 d and rated on the disease severity.

Test 2. Evaluation of activity against cucumber gray mold was done by foliage spray onto cucumber plants (first stage) grown in 5-cm pots. After the spray deposit had dried for 1 day, the treated cucumber foliage was inoculated with condia (1 × 10^6

spores/mL) of *Botrytis cinerea* (incubated on potato dextrose agar medium at 25 °C for 15 d) by leaf spray on all sides until just before runoff. The plants were then held in lighted dew chamber (20 ± 2 °C) for an additional 4–5 d and rated on the disease severity.

Test 3. Evaluation of activity against tomato late blight was done by foliage spray to run off onto 14-day-old tomato plants grown in 5-cm polyvinyl pots. After the spray deposit had dried for 1 day, the treated plants were inoculated by spraying with a suspension of zoosporangia (1×10^5 zoosporangia/mL; incubated on V-8 juice agar medium at 20 °C for 2 weeks). The plants were then held in lighted dew chamber (20 ± 2 °C) for an additional 4 d and rated on the disease severity.

Test 4. Evaluation of activity against barley powdery mildew was made by foliage spray of the first leaf of wheat (cultivar, Chukwang) grown in polyvinyl pots (diameter, 5 cm) for 7 d. After the spray deposit dried, plants were dusted with a uredospores colonied on the second leaf and placed in a moist chamber at 20 °C for 24 h. One day after inoculation, plants were moved to the plant growth chamber (20 °C, 70% relative humidity) to induce disease. The plants were then held in growth chamber (20 ± 2 °C) for an additional 10 d and rated on the disease severity.

Acknowledgment. We are grateful to the National Science Foundation (Grant CHE-9108231) for partial support of this research. M.J.K. is recipient of Alfred P. Sloan Research (1987–1991) and NIH RCDA (1989–1994; ES00182) fellowships.

Supplementary Material Available: X-ray crystallographic data for *cis*-6-(2-chlorophenyl)-4-methyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (**5f′**), (*R**,*S**)-3-[chloro(2-chlorophenyl)methyl]-4-(1-hydroxyethyl)isoxazole (**6f′**), and (*R**,*S**)-3-[bromo(2-chlorophenyl)methyl]-4-(1-hydroxymethyl)isoxazole (**7f**) (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Asymmetric Synthesis of 2,6-Diaminopimelic Acids

Robert M. Williams* and Chenguang Yuan

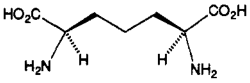
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received July 2, 1992

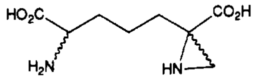
The preparations of (*R*,*R*)-2,6-diaminopimelic acid, (*S*,*S*)-2,6-diaminopimelic acid, (*S*,*R*)-2,6-diaminopimelic acid, and (*S*,*S*)-2,7-diaminosuberic acid are described. The synthesis of mono-N-protected (*S*,*R*)-2,6-diaminopimelic acid is also described.

Introduction

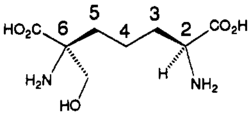
Diaminopimelic acid (1, DAP) is an important, naturally occurring amino acid biosynthesized in bacteria and higher plants.[1] L,L- and *meso*-DAP serve as the penultimate biosynthetic precursor of the essential amino acid L-lysine. *meso*-DAP functions as a cross-linking constituent of virtually all Gram-negative and some Gram-positive bacterial peptidoglycan and also serves to anchor various membrane-associated macromolecules, such as lipoprotein to the cell wall. Recognition of the pivotal roles DAP plays in microbial metabolism[2] and cell wall structure has resulted in an increased level of interest in possible means to selectively disrupt the DAP biosynthetic pathway. A flurry of recent papers[3] on the synthesis of DAP and, more significantly, structural analogs of DAP that can function as substrate-based inhibitors of key biosynthetic transformations attests to the potential importance of the DAP/lysine pathway as a viable target for antibiotic design. Recent studies in several laboratories demonstrate that a number of compounds, which inhibit the formation or metabolism of 2,6-diaminopimelic acid in bacteria possess antibiotic activity.[4] Since mammals lack the diaminopimelate pathway and require L-lysine in their diet,[5] specific inhibitors of the enzymes along this route are potential antimicrobial and herbicidal agents that should display low mammalian host toxicity. Thus, the potential importance of inhibiting the DAP pathway through the design and synthesis of functionalized DAP analogs renders this class of amino acids an attractive and worthy synthetic problem. A recent example is the (stereorandom) preparation of the aziridino DAP (2, "AZIDAP") that was shown[6] to be a potent inhibitor of L,L-DAP epimerase and exhibits antimicrobial activity.



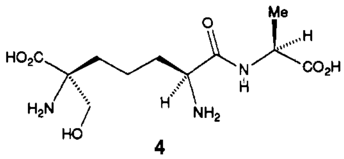
R,S-1



2



3



4

Despite the apparent simplicity of these amino acids, there were no stereochemically unambiguous syntheses of *meso*-DAP nor asymmetric syntheses of (*S*,*S*)-DAP prior to 1992. Two recent exceptions are the synthesis of β-

---

(1) Patte, J.-C. In *Amino Acids: Biosynthesis and Genetic Regulation*; Hermann, K. M., Somerville, R. L., Eds.; Addison-Wesley: Reading, MA, 1983; pp 213–218.

(2) Certain bacteria bypass the L,L form of DAP by means of *meso*-DAP D-dehydrogenase: (a) Bartlett, A. T. M.; White, P. J. *J. Gen. Microbiol.* **1985**, *131*, 2145. (b) Misono, H.; Ogasawara, M.; Nagasaki, S. *Agric. Biol. Chem.* **1986**, *50*, 2729.

(3) (a) Berges, D. A.; DeWolf, W. E., Jr.; Dunn, G. L.; Grappel, S. F.; Newman, D. J.; Taggart, J. J.; Gilvarg, C. *J. Med. Chem.* **1986**, *29*, 89. (b) Berges, D. A.; DeWolf, W. F., Jr.; Dunn, G. L.; Newman, D. J.; Schmidt, S. J.; Taggart, J. J.; Gilvarg, C. *J. Biol. Chem.* **1986**, *261*, 6160. (c) Kelland, J. G.; Arnold, L. D.; Palcic, M. M.; Pickard, M. A.; Vederas, J. C. *J. Biol. Chem.* **1986**, *261*, 13216. (d) Girodeau, J.-M.; Agouridas, C.; Masson, M.; Pineau, R.; LeGoffic, F. *J. Med. Chem.* **1986**, *29*, 1023. (e) Lam, L. K. P.; Arnold, L. D.; Kalantar, T. H.; Kelland, J. G.; Lane-Bell, P. M.; Palcic, M. M.; Pickard, M. A.; Vederas, J. C. *J. Biol. Chem.* **1988**, *263*, 11814. (f) Baumann, R. J.; Bohme, E. H.; Wiseman, J. S.; Vaal, M.; Nichols, J. S. *Antimicrob. Agents Chemother.* **1988**, *32*, 1119. (g) Bohme, E. H.; Gerhart, F.; Higgins, W. U.S. Patent 4,7300,006, 1988; *Chem. Abstr.* **1988**, *109*, 6981m. (h) O'Donnell, M. J.; Bruder, W. A.; Eckrich, T. M.; Shullenberger, D. F.; Staten, G. S. *Synthesis* **1984**, 127. (i) Wade, R.; Birnbaum, S. M.; Winitz, M.; Koegel, R. J.; Greenstein, J. P. *J. Am. Chem. Soc.* **1957**, *79*, 648. (j) Assche, I.; Soroka, M.; Haemers, A.; Hooper, M.; Blanot, D.; van Heijenoort, J. *Eur. J. Med. Chem.* **1991**, *26*, 505.

(4) See also references in: Lin, Y.; Myhrman, R.; Schrag, M. L.; Gelb, M. H. *J. Biol. Chem.* **1988**, *263*, 1622.

(5) Jouanneau, J.; Stragier, P.; Bouvier, J.; Patte, J.-C.; Yaniv, M. *Eur. J. Biochem.* **1985**, *146*, 173 and references cited therein.

(6) (a) Gerhart, F.; Higgins, W.; Tardif, C.; Ducep, J.-B. *J. Med. Chem.* **1990**, *33*, 2157. (b) Higgins, W.; Tardif, C.; Richaud, C.; Krivanek, M. A.; Cardin, A. *Eur. J. Biochem.* **1989**, *186*, 137.

0022-3263/92/1957-6519$03.00/0