Tandem 1,3-Dipolar Cycloaddition and Electrophilic Cyclization Reactions: Cyclic Ether Subunits of Polyether Antibiotics from Unsaturated Isoxazolines

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Received June 22, 1989

A new strategy for the construction of polyether antibiotic substructural units [spiroketals (I), tetrahydrofurans (II), and tetrahydropyrans (III)] consisting of bis-addition of an oxygen nucleophile across an α,ω-diene moiety (i.e., IV) is described. The method exploits a tandem 1,3-dipolar cycloaddition/electrophilic cyclization sequence that proceeds via the intermediacy of an isoxazoline. Experiments presented illustrate the versatility of this strategy, which provides a unique exploit of the control elements operative in dipolar cycloaddition and electrophilic cyclization chemistry.

Introduction

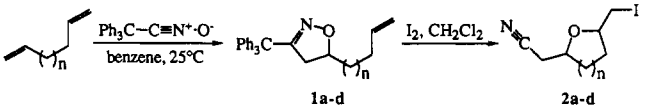
Development of methodology for the stereocontrolled synthesis of polyether antibiotics continues to receive significant attention,[2] and, in many regards, construction of these elaborate targets becomes an exercise in the preparation of cyclic ethers. As exemplified by lonomycin A, common substructural units encountered in this class of natural products include spiroketals, tetrahydrofurans, and tetrahydropyrans (I, II, and III, respectively; Figure 1).

A new isoxazoline-based method for the preparation of 2,5-disubstituted tetrahydrofurans[3] (i.e., derivatives of II) was recently reported from these laboratories, and it appeared to us that this protocol, which effects bis-addition of an oxygen nucleophile across an α,ω-diene (cf. IV) by a tandem 1,3-dipolar cycloaddition/electrophilic cyclization sequence, could be modified so as to deliver substructural units I and III in addition to II. The attractiveness of this strategy, particularly in light of its potential versatility in constructing various cyclic ethers with one protocol, is evident and provides a unique exploit of the control elements operative in dipolar cycloaddition and electrophilic cyclization chemistry. We report herein realization of this isoxazoline-based strategy as a general and versatile route to the cyclic ether substructural units common to polyether antibiotics.[4]

Results and Discussion

Tetrahydrofurans, Tetrahydropyrans, and Oxepanes. The cycloaddition of 1,5-hexadiene and triphenylacetonitrile oxide (prepared from triphenylmethyl chloride and silver fulminate)[5] furnishes isoxazoline **1a** in high yield as long as the diene is used in excess (8 equiv). With symmetrical dienes, increasing amounts of bis-cycloadducts are obtained as the diene/dipole ratio decreases, with the bis-adduct being obtained in nearly quantitative yield when the diene/dipole ratio is 0.5.

Table I. Cyclic Ether Preparation

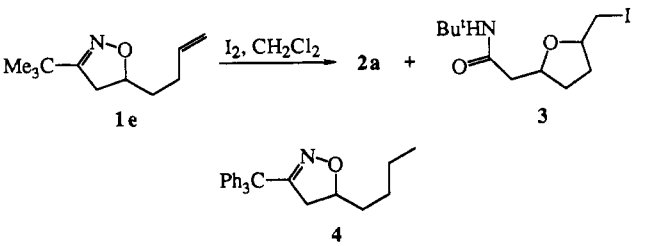


1a-d 2a-d

entry	yield of 1,[a] %	yield of 2,[b] %	cis:trans ratio of 2[c]
a, n = 1	100	85	1:4
b, n = 2	98	82	1:9
c, n = 3	96	80	1:3
d, n = 4	100		

[a] Based on triphenylacetonitrile oxide. [b] Overall yield from triphenylacetonitrile oxide. [c] Determined by capillary GC analysis of the crude reaction mixtures.

Scheme I



1e 3 4

As hoped, treating the heterocycle obtained from 1,5-hexadiene and triphenylacetonitrile oxide (**1a**) with iodine in refluxing dichloromethane resulted in an electrophilic cyclization giving tetrahydrofuran **2a** as a 1:4 cis:trans mixture in 60% overall yield from triphenylacetonitrile oxide. By simply increasing the diene chain length (n = Table I), sequential application of these two reactions readily accommodates the preparation of larger ring ethers: 1,6-heptadiene leading to tetrahydropyran **2b** (n = 2, entry b) and 1,7-octadiene leading to oxepane **2c** (n = 3, entry c). Attempts to prepare the corresponding eight-membered ring ether (n = 4, entry d) failed as isoxazoline **1d** gave only unidentifiable polymerized material upon treatment with iodine.

In each of the electrophilic cyclizations depicted in Table I, a trans arrangement of the CH_2I and $CH_2C{\equiv}N$ substituents on the cyclic ether is favored, with selectivity being highest for the tetrahydropyran derivative (**2b**; cis:trans 1:9). Presumably this trans selectivity is the consequence of kinetic olefin face selectivity in the electrophilic cyclization of **1** with stereoselectivity in **1** → **2** then reflecting dissimilar nonbonding interactions in the two competing isoxazolinium activated complexes: i.e., the

(1) Recipient of an Alfred P. Sloan Research Fellowship, 1987–1989.
(2) (a) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691–4. (b) Hoye, T. R., Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312–3. (c) Dauphin, G.; Cuer, A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 295–9. (d) Evans, D. A.; Bender, S. L. *Tetrahedron Lett.* **1986**, *27*, 799–802. (e) Bartlett, P. A.; Ting, P. C. *J. Org. Chem.* **1986**, *51*, 2230–40.
(3) Kurth, M. J.; Rodriguez, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 7577–7578.
(4) (a) Klein, E.; Rojahn, W. *Tetrahedron* **1965**, *21*, 2353–8. (b) Walba, D. M.; Wand, M. D.; Wilkes, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4396–7. (c) Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155–7. (d) Ting, P. C.; Bartlett, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 2668–71. (e) Bartlett, P. A.; Holm, K. H.; Morimoto, A. *J. Org. Chem.* **1985**, *50*, 5179–83. (f) Still, C. W.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105–6. (g) Morkawa, T.; Nishiwaki, T.; Iitaka, Y.; Kowayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 671–4. (h) Spino, C.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 731–4.
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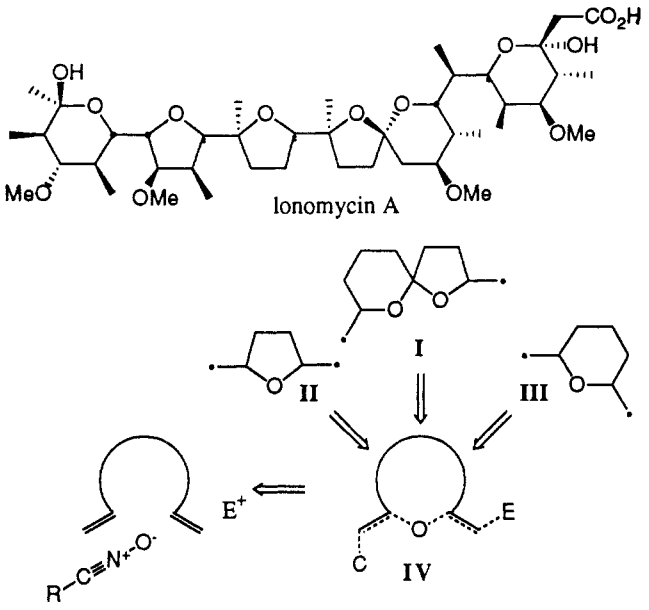


Figure 1.

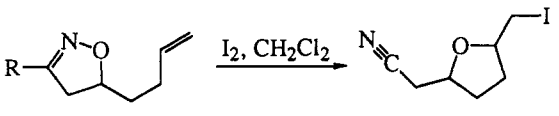
exo-isoxazolinium is kinetically favored over the endo-isoxazolinium activated complex. Irreversible loss of Ph_3C^+ with concomitant formation of the C≡N moiety and loss of the N–O bond then delivers **2**. It is interesting to note that changing solvent from dichloromethane [ϵ = 8.93 (25 °C)] to benzene [ϵ = 2.27 (25 °C)][6] in this electrophilic cyclization results in a complete loss of stereoselectivity for **1a** → **2a** (68%; cis:trans ratio 1:1). It was also found that switching from a triphenylmethyl (Ph_3C) group at C_3 of the isoxazoline (**1a**) to a *tert*-butyl (Me_3C) group also results in complete loss of stereoselectivity with **1e** giving **2a** as 1:1 cis:trans mixture in 59% yield, even in dichloromethane (Scheme I). Clearly, collapse of the isoxazolinium activated complex to **2** is also sensitive to the carbocation stability of the R^+ leaving group. These results suggest that the isoxazolinium derived from **1e** has a longer lifetime and undergoes significant equilibration, whereas the isoxazolinium derived from **1a** undergoes minimal equilibration, reflecting the kinetic selectivity of **1** → **2**. In support of this notion of variable equilibration between exo- and endo-isoxazoliniums, we note that the S_N1 reactivity of a triphenylmethyl group is $\approx 10^6$ times greater than the S_N1 reactivity of a *tert*-butyl group.[7] Formation of amide **3** (22%) in the electrophilic cyclization of **1e**, while not anticipated in advance of the experiment, is clearly the consequence of a C → N migration of Me_3C^+ moiety via a Beckmann-like rearrangement pathway which successfully competes with isoxazolinium fragmentation with loss of Me_3C^+.

There are two control experiments pertinent to electrophilic cyclization **1** → **2**. First, a 6.6:1 cis:trans mixture of **2a** does not undergo equilibration either under conditions identical with those employed for **1a** → **2a** or in the presence of iodotriphenylmethane. Second, isoxazoline **4**, which lacks the pendant C=C of **1a**, is stable to the iodocyclization conditions employed in **1** → **2** (I_2/CH_2Cl_2, 25 or 40 °C, 8 h), indicating that iodonium ion formation precedes isoxazoline fragmentation in these iodocyclizations.

(6) Przybytek, J. T. *Solvent Guide*; Burdick & Jackson Laboratories, Inc.: Muskegon, MI, 1980.

(7) (a) Freedman, H. H.; Olah, G. A. *Carbonium Ions*; Wiley-Interscience: New York, 1973; Vol. IV, Chapter 28. (b) Streitwieser Jr., A. *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962; p 181.

Table II. Electrophilic Cyclization of Isoxazolines 1f–h

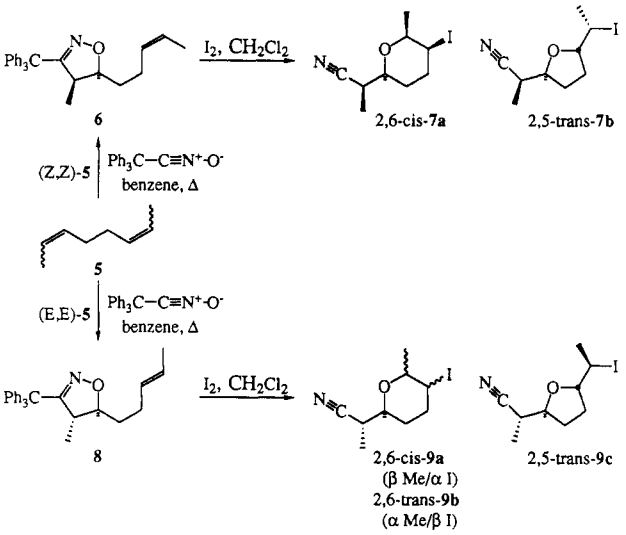


1f-h **2a**

entry	R	cis:trans[a]	yield of **2a**,[b] %
1f	Me_3Si	6.6:1	40
1g	$MeCH(OSiMe_3)$	1:1.4	59
1h	i-$PrCH(OSiMe_3)$	1:1.6	55

[a] Ratios determined by capillary GLC analysis of the crude reaction mixture. [b] Isolated, purified yields.

Scheme II



In addition to R = $C(Ph)_3$ and $C(Me)_3$ substituted isoxazolines, one trimethylsilyl (**1f**)[8] and two [(trimethylsilyl)oxy]methyl (**1g** and **1h**)[9] analogues of isoxazoline **1** were prepared, and their electrophilic cyclizations studied. The most striking feature in these results, which are summarized in Table II, is a complete reversal in stereoselectivity with the trimethylsilyl analogue. That is, trimethylsilyl-substituted **1f** gives a preponderance of *cis*-**2a** (R = $C(Ph)_3$; 6.6:1 cis:trans ratio) while triphenylmethyl-substituted **1a** gives a preponderance of *trans*-**2a** (1:4 cis:trans ratio). [(Trimethylsilyl)oxy]methyl analogues **1g** and **1h** gave only marginal selectivity.

Cycloaddition of triphenylacetonitrile oxide and the symmetrical diene (*Z,Z*)-2,6-octadiene[10] [(*Z,Z*)-**5**; prepared by Lindlar-catalyzed hydrogenation of 2,6-octadiyne] affords isoxazoline **6** in 71% yield together with its 1,3-dipolar cycloaddition regioisomer in 28% yield, which are easily separable by silica gel chromatography (Scheme II). Electrophilic cyclization of isoxazoline **6** leads to a separable 1:1 mixture of the tetrahydropyran **7a** and tetrahydrofuran **7b** in 60% isolated yield. While only the trans tetrahydrofuran isomer (**7b**) was detected in the crude reaction mixture, the tetrahydropyran product proved to be a 95:5 2,6-cis:2,6-trans mixture (by 300-MHz NMR). In

(8) (a) Prepared from 1,5-hexadiene and (trimethylsilyl)carbonitrile oxide, which in turn was generated in situ from trimethylsilyl bromide and mercury fulminate. (b) Brandi, A.; DeSarlo, F.; Guarna, A.; Speroni, G. *Synthesis* **1982**, 719–21.

(9) (a) Prepared from 1,5-hexadiene and $RCH(OSiMe_3)C{\equiv}NO$, which in turn was generated in situ from $RCH(OSiMe_3)CH_2NO_2$ by dehydration with phenyl isocyanate. (b) Curran, D. P.; Scanga, S. A.; Fenk, C. J. *J. Org. Chem.* **1984**, *49*, 3474–8.

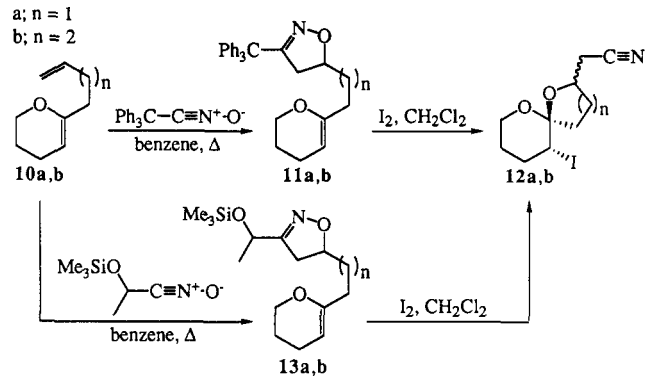
(10) Walba, D. M.; Wand, M. D.; Wilkes, M. C. *J. Org. Chem.* **1980**, *45*, 2259–2261.

similar fashion, (triphenylmethyl)carbonitrile oxide adds to (*E,E*)-2,6-octadiene [(*E,E*)-**5**; prepared by Na/NH_3 reduction of 2,6-octadiyne] to give a silica gel separable mixture of isoxazoline **8** (62% purified yield) and its 1,3-dipolar cycloaddition regioisomer (30% purified yield). Upon treatment with iodine, isoxazoline **8** underwent electrophilic cyclization, giving a separable 3.9:1 mixture of tetrahydropyran and tetrahydrofuran products in 64% isolated yield. As with **6**, **8** cyclizes to a mixture of two tetrahydropyran products (2,6-*cis*-**9a** and 2,6-*trans*-**9b** in a 3:1 ratio) and one tetrahydrofuran isomer (*trans*-**9c**). The relative stereochemistry of **9a**, the major tetrahydropyran isomer, was established by X-ray crystal structure analysis.[11] These iodocyclization results with isoxazolines **6** and **8**, taken in concert with those presented in Tables I and II, clearly indicate that stereoselectivity in the iodocyclization step is subject to subtle stereocontrol elements.

Spiroketals from Unsymmetrical Dienes. A tandem 1,3-dipolar cycloaddition/electrophilic cyclization sequence starting with an unsymmetrical diene in the cycloaddition step presents this protocol with the potential of providing access to considerably more elaborate cyclic ethers. However, an important new issue is introduced with this modification: namely, the question of chemoselectivity in the cycloaddition step. In simple olefins, both electronic and steric control elements are operative, with the net effect that the rate of nitrile oxide 1,3-dipolar cycloaddition generally increases as olefin substitution decreases.[12] Therefore, we reasoned that by exploiting substitution-based differences in dipolarophilicity, the less substituted olefin of an unsymmetrical diene could be selectively engaged in the cycloaddition step.

With the notion olefin selective cycloaddition in mind and with polyether antibiotic substructures as targets, our next objective was the preparation of spiroketals of general structure I. Thus, the olefin selectivity issue became one of C=C—C versus C=C—O olefin selectivity. While cyclic vinyl ethers like dihydrofuran and dihydropyran are known to readily react with nitrile oxides yielding bicyclic isoxazolines,[13] it was hoped that in appropriately designed substrates steric considerations would allow for the selective engagement of the C=C—C moiety in the cycloaddition step leaving the C=C—O moiety for a subsequent electrophilic cyclization reaction.

Scheme III



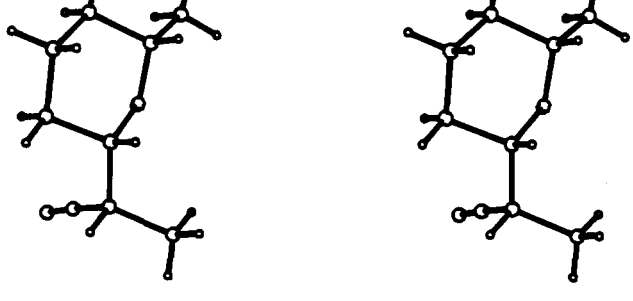
With a modified procedure developed by Boeckman,[14] unsaturated vinyl ethers **10** are readily available by alkylation of the corresponding lithiated dihydropyran. As hoped, (triphenylmethyl)carbonitrile oxide reacts stereospecifically with the terminal C=C moiety, leaving the vinyl ether moiety untouched. In contrast to symmetrical dienes, which must be used in large excess in the 1,3-dipolar cycloaddition step to avoid bis-cycloaddition, only 1 equiv of **10** is required since the C=C—C and C=C—O moieties display vastly dissimilar dipolarophilicity. Indeed, using 1 equiv of **10** delivers isoxazoline **11** in essentially quantitative yield (Scheme III).

Unfortunately, treatment of **11a** with iodine under gentle reflux in methylene chloride gave the desired 5,6-spiroketal **12a** in only 6% yield. With **11b**, none of 6,6-spiroketal **12b** was detected, and all attempts to improve the yield of **11** → **12** by altering reaction temperature, solvent, and time failed. Fortunately it was found that isoxazoline **13**, derived from **10** and $CH_3CH(OSiMe_3)C{\equiv}N^+{-}O^-$, gave dramatically improved results. Cycloaddition **10** → **13** proceeds at room temperature and in 70–80% yield with only a slight excess of diene **10**, and like the reaction of triphenylmethylcarbonitrile oxide, the reaction of $CH_3CH(OSiMe_3)C{\equiv}N{-}O$ with unsymmetrical diene **10** is completely regiospecific. Treating isoxazoline **13a** with iodine in dichloromethane at room temperature gave 5,6-spiroketal **12a** in 57% isolated yield. As anticipated, internal asymmetric induction for this reaction was excellent, but there was no relative asymmetric induction,[15] and **12a** was obtained as a 1:1 mixture of diastereomers epimeric at C_2. Interestingly, isoxazoline **13b** undergoes iodocyclization with complete internal as well as relative asymmetric induction giving **12b** in 25% isolated yield. That **12b** is one pure isomer is evident by ^{13}C NMR analysis and is apparently the consequence of both anomeric and steric effects.[16]

Experimental Section

General Experimental Procedures. Infrared spectra were determined on a IBM FTIR-32 with an IBM 9000 data system. NMR Spectra were determined on a Varian EM390 spectrometer (^1H at 90 MHz) or a General Electric QE-300 spectrometer (^1H at 300 MHz and ^{13}C at 75 MHz). Mass spectra were determined on a Du Pont 21-492B mass spectrometer. Melting points were determined on a Thomas Hoover Uni-Melt melting-point appa-

(11) Compound **9a** (formula) crystallizes from hexane in the triclinic space group $P\bar{1}$. The crystal data at 130 K are as follows: a = 5.500 (1) Å, b = 9.686 (2) Å, c = 10.410 (2) Å; α = 93.64 (2)°; β = 99.97 (2)°; γ = 95.01 (2)°; ρ(calcd) = 1.71 g cm^{-3} for Z = 2; 2θ(max) = 50; 1755 reflections with $F > 4\sigma(F)$ used, Mo Kα (graphite) (λ = 0.71069 Å), and ω scan, 20° min^{-1}; R = 0.033. SHELXTL programs on a DGC Eclipse S/230 computer. Complete X-ray crystallographic details are available as supplementary material (see the paragraph at the end of the paper).



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(13) (a) Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1963**, 140–42. (b) Minami, S.; Matsumoto, J. *J. Chem. Pharm. Bull.* **1967**, *15*, 366–9.

(14) Boeckman, R. K.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997–4006.

(15) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 1–72.

(16) Deslongchamps, P.; Rovan, D.; Podner, N.; Suave', T.; Sanders, J. *Can. J. Chem.* **1981**, *59*, 1105–21.

ratus and are uncorrected. MPLC refers to column chromatography done at 10–50 psi through EM Lobar columns packed with LiChroprep Si60 (40–63 μm) or prepared columns packed with Florisil (60–100 mesh) with hexane/EtOAc eluent and monitored by refractive index detection. Chromatron refers to preparative, centrifugally accelerated, radial, thin-layer chromatography with silica gel 60 as stationary phase. Analytical thin-layer chromatography (TLC) was performed with Kodak 100-μm-thick silica gel plates. Capillary gas chromatography (GC) was performed on a Hewlett-Packard 5890A gas chromatograph using a DB-1701 column (30 m × 0.259 mm; film thickness = 0.25 mm): initial temperature = 90 °C; initial time = 1 min; rate = 2 °C/min; gas pressures (psi) He 60, N_2 32, air 34, H_2 20.

Procedure A: 5-(3-Butenyl)-3-(triphenylmethyl)-2-isoxazoline (1a). (Triphenylmethyl)acetonitrile oxide (567 mg, 1.98 mmol) and 1,5-hexadiene (1.30 g, 15.8 mmol) in anhydrous benzene (20 mL) was heated at reflux in a sealed tube for 48 h. The crude reaction mixture was cooled to room temperature and concentrated under reduced pressure giving a white solid. Purification by MPLC (25:75 EtOAc:hexanes, 2.5 mL/min) gave **1a** (727 mg, 1.98 mmol, 100%) as a white solid: mp = 86–88 °C (benzene); R_f = 0.69 (25/75 EtOAc/hexane); FT IR (KBr) 3201, 2925, 2255, 1957, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (m, 1 H), 1.75 (m, 1 H), 2.20 (m, 2 H, $CH_2CH{=}CH_2$), 2.23–2.50 (dd, J = 8.5, 12.7, 1 H, N=CC*H*H), 2.70–3.12 (dd, J = 8.5, 12.7, 1 H, N=CCH*H*), 4.60 (m, 1 H, *H*CO), 5.10 (m, 2 H, CH=CH_2), 5.99 (m, 1 H, C*H*=CH_2), 7.7 (m, 15 H, Ar H); ^{13}C ($CDCl_3$) δ 31, 35, 43, 62 ($C(Ar)_3$), 82 (HCO), 118 (=CH_2), 127, 129, 131, 139, 145, 163 (C=N); HRMS calcd for $C_{26}H_{25}NO$ 367.1936, found, 367.1936.

5-(4-Pentenyl)-3-(triphenylmethyl)-2-isoxazoline (1b). Following procedure A, 1,6-heptadiene gave **1b** (1.27 g, 3.33 mmol, 98%) as a white solid: mp 93–95 °C (benzene); R_f = 0.74 (20/80 EtOAc/hexane); FT IR (neat) 3202, 2922, 2255, 1957, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20–1.75 (m, 4 H), 2.20 (m, 2 H), 2.38 (dd, J = 9, 15 Hz, 1 H, N=CC*H*H), 2.90 (dd, J = 9, 15 Hz, 1 H, N=CCH*H*), 4.60 (m, 1 H, *H*CO), 5.10 (m, 2 H, CH=CH_2), 5.99 (m, 1 H, C*H*=CH_2), 7.6 (m, 15 H, Ar H); HRMS calcd for $C_{27}H_{27}NO$ 381.2093, found, 381.2092.

5-(5-Hexenyl)-3-(triphenylmethyl)-2-isoxazoline (1c). Following procedure A, 1,7-octadiene gave **1c** (660 mg, 1.67 mmol, 96%) as a white solid: mp 93–94 °C (benzene); R_f = 0.62 (20/80 EtOAc/hexane); FT IR (KBr) 3202, 2925, 2254, 1957, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22–1.70 (m, 6 H), 2.20 (m, 2 H), 2.31–2.50 (dd, J = 9, 15 Hz, 1 H, N=CC*H*H), 2.70–3.01 (dd, J = 9, 15 Hz, 1 H, N=CCH*H*), 4.60 (m, 1 H, *H*CO), 5.10 (m, 2 H, CH=CH_2), 5.99 (m, 1 H, C*H*=CH_2), 7.70 (m, 15 H); HRMS calcd for $C_{28}H_{29}NO$ 395.2249, found, 395.2249.

5-(6-Heptenyl)-3-(triphenylmethyl)-2-isoxazoline (1d). Following procedure A, 1,8-nonadiene gave **1d** (270 mg, 0.66 mmol, 100%) as a white solid: mp 71–73 °C (benzene); R_f = 0.62 (20/80 EtOAc/hexane); FT IR (neat) 3202, 2925, 2256, 1957, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20–1.70 (m, 8 H), 2.22 (m, 2 H), 2.31–2.55 (dd, J = 8.5, 12.5, 1 H, N=CC*H*H), 2.70–3.01 (dd, J = 8.5, 12.5, 1 H, N=CCH*H*) 4.60 (m, 1 H, *H*CO), 5.10 (m, 2 H, CH=CH_2), 5.99 (m, 1 H, C*H*=CH_2), 7.7 (m, 15 H, Ar *H*); HRMS calcd for $C_{29}H_{31}NO$ 409.2406, found, 409.2406.

5-(3-Butenyl)-3-(2,2-dimethylethyl)-2-isoxazoline (1e). Triethylamine (195 mg, 193 mmol) in anhydrous Et_2O (5 mL) was added with a syringe pump over 30 min to a solution of *tert*-butylhydroximic acid chloride (250 mg, 1.84 mmol) and 1,5-hexadiene (303 mg, 3.69 mmol) in anhydrous Et_2O (10 mL). The solution was allowed to stir at room temperature for an additional 24 h, at which time the crude reaction mixture was filtered and concentrated under reduced pressure. Purification by MPLC (25:75 EtOAc:hexanes, 2.5 mL/min) gave **1e** (330 mg, 1.82 mmol, 70%) as a viscous, colorless oil: R_f = 0.67 (EtOAc:hexanes); FT IR (neat) 3078, 2934, 1641, 1479, 1124 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 9 H, 3 CH_3's), 1.65 (m, 2 H), 2.05–2.50 (m, 2 H), 2.50–2.70 (dd, J = 7.8, 11.7, 1 H, N=CC*H*H), 2.90–3.20 (dd, J = 7.8, 11.7, 1 H, N=CCH*H*), 4.5 (m, 1 H, *H*CO), 5.0 (m, 2 H, CH=CH_2), 5.79 (m, 1 H, C*H*=CH_2); ^{13}C ($CDCl_3$) δ 29.0 (3 CH_3's), 30.7, 33.0 ($C(CH_3)_3$), 35.3, 40.3, 80.6 (HCO), 116.1 (=CH_2), 138 (CH=), 168.7 (C=N); HRMS calcd for $C_{11}H_{19}NO$ 181.1467, found, 181.1467.

Procedure B: 5-(3-Butenyl)-3-[1-((trimethylsilyl)oxy)-ethyl]-2-isoxazoline (1g). 2-[(Trimethylsilyl)oxy]-1-nitropropane (1.0 g, 5.64 mmol), 1,5-hexadiene (2.31 g, 28.2 mmol), phenyl isocyanate (1.34 g, 11.2 mmol), and benzene (25 mL) were placed in a 50-mL round-bottom flask and flushed with nitrogen. A solution of triethylamine (78 μL, 0.56 mmol) in benzene (1 mL) was added through the condenser over 10 min via a syringe pump. The mixture was refluxed for a total of 50 h and, upon cooling, filtered through Celite. Water (25 drops) was added, and the crude reaction mixture stirred vigorously for 2 h, then filtered, dried ($MgSO_4$), and concentrated under reduced pressure to give a brown oil. Purification by MPLC (10/90 EtOAc/cyclohexane, 2.5 mL/min) gave **1g** (710 mg, 2.94 mmol, 52%) as a yellow oil which proved to be a nearly 1:1 mixture of inseparable diastereomers; R_f = 0.73 (20/80 EtOAc/hexane); FT IR (neat) 3079, 2979, 1642, 1556, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.2 (s, 9 H, 3 CH_3's), 1.0–1.5 (m, 3 H), 1.5–2.0 (m, 2 H), 2.1 (m, 2 H), 2.5–3.3 (m, 2 H, N=CCH_2), 4.6 (m, 1 H, HCO), 4.7 (m, 1 H, *H*C(CH_3)), 5.0 (m, 2 H, CH=CH_2), 5.8 (m, 2 H, C*H*=CH_2); HRMS calcd for $C_{12}H_{23}SiNO_2$ 241.1498, found, 241.1498.

5-(3-Butenyl)-3-[1-((trimethylsilyl)oxy)-2-methylpropyl]-2-isoxazoline (1h). Following procedure B, 2-[(trimethylsilyl)oxy]-3-methyl-1-nitrobutane gave **1h** (746 mg, 2.8 mmol, 57%) as a pale yellow oil which proved to be a nearly 1:1 mixture of inseparable diastereomers; R_f = 0.70 (20/80 EtOAc/hexane); FT IR (neat) 3079, 2979, 1642, 1556, 1388, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.2 (s, 9 H, 3 CH_3's), 0.6–1.0 (m, 6 H, 2 CH_3), 1.4–1.8 (m, 2 H), 2.2 (m, 1 H), 2.4–3.3 (m, 2 H, N=CCH_2), 4.2 (d, J = 6.3 Hz, 1 H, *H*COTMS), 4.7 (m, 1 H, HCO), 5.0 (m, 2 H, CH=CH_2), 5.8 (m, 1 H, C*H*=CH_2); HRMS calcd for $C_{14}H_{27}NO_2Si$ 269.1811, found, 269.1811.

Procedure C: (2*R,5*R**)- and (2*R**,5*S**)-2-(Cyanomethyl)-5-(iodomethyl)tetrahydrofuran (2a).** Iodine (1.4 g, 5.4 mmol) was added in one portion to a solution of the isoxazoline **1a** (1.0 g, 2.7 mmol) in methylene chloride (30 mL), and the resulting mixture refluxed under nitrogen for 48 h, at which point TLC indicated complete disappearance of starting isoxazoline **1a**. The cooled reaction mixture was added to a mixture of ether (30 mL) and saturated aqueous sodium bisulfite solution (20 mL), the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by MPLC (25/75 EtOAc/hexanes, 2.5 mL/min) gave **2a** (580 mg, 2.3 mmol, 85%) as a pale yellow oil with a cis:trans ratio of 1:4 as judged by capillary GC (cis 33 min/trans 33.2 min). The cis/trans isomers were separated by HPLC (5/95 EtOAc/hexanes, 3.0 mL/min) giving *cis*-**2a** at 14 min [R_f = 0.38 (25/75 EtOAc/hexane); FT IR (neat) 2878, 2251 (CN), 1061, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.8 (m, 2 H), 2.1 (m, 2 H), 2.63 (dd, J = 4, 15 Hz, 1 H, C*H*HCN), 2.69 (dd, J = 5.6, 15 Hz, 1 H, CH*H*CN), 3.25 (dd, J = 5.6, 11.2 Hz, 1 H, C*H*HI), 3.28 (dd, J = 5.6, 11.2 Hz, 1 H, CH*H*I), 4.0 (m, 1 H, CHO), 4.2 (m, 1 H, CHO); ^{13}C ($CDCl_3$) δ 9.4, 24.4, 30.5, 31.3, 75.2 (CHO), 79.5 (CHO), 117.1 (CN); HRMS calcd for $C_7H_{10}INO$ 250.9807, found, 250.9807] and *trans*-**2a** at 15.4 min [R_f = 0.38 (25/75 EtOAc/hexane); FT IR (neat) 2878, 2251 (CN), 1061, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.85 (m, 2 H), 2.3 (m, 2 H), 2.63 (dd, J = 5.6, 15 Hz, 1 H, C*H*HCN), 2.66 (dd, J = 3.7, 15 Hz, 1 H, CH*H*CN), 3.27 (dd, J = 6.7, 11.2 Hz, 1 H, C*H*HI), 3.29 (dd, J = 4, 11.2 Hz, 1 H, CH*H*I), 4.19 (m, 1 H, CHO), 4.35 (m, 1 H, CHO); ^{13}C ($CDCl_3$) δ 10.0, 24.1, 31.5, 32.3, 74.8 (CHO), 78.9 (CHO), 117.1 (CN). Anal. Calcd for $C_7H_{10}INO$: C, 33.49; H, 4.01; N, 5.58. Found: C, 33.37; H, 4.06; N, 5.59].

(2*R,6*R**)- and (2*R**,6*S**)-2-(Cyanomethyl)-6-(iodomethyl)tetrahydropyran (2b).** Following procedure C, isoxazoline **1b** gave a yellow oil of **2b** (770 mg, 2.9 mmol, 82%) as an inseparable 1:9 cis:trans mixture (as judged by 300-MHz ^1H NMR): R_f = 0.38 (20/80 EtOAc/hexane); FT IR (neat) 2878, 2251 (CN), 1034, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20–2.01 (m, 6 H), 2.62 (m, 2 H, CH_2CN), 3.23 (d, J = 6.3 Hz, 2 H, CH_2I), 3.32–4.23 (m, 2 H, HCO); ^{13}C ($CDCl_3$, cis/trans) δ 7.7/9.5, 17.3/22.3, 22.8/24.5, 27.7/28.6, 29.8/30.3, 66.6/71.7 (HCO), 72.6/76.9 (HCO), 117 (CN). Anal. Calcd for $C_8H_{12}INO$: C, 36.25; H, 4.56; N, 5.28. Found: C, 35.92; H, 4.58; N, 5.29.

(2*R,7*R**)- and (2*R**,7*S**)-2-(Cyanomethyl)-7-(iodomethyl)oxepane (2c).** Following procedure C, isoxazoline **1c** gave a yellow oil of **2c** (168 mg, 0.60 mmol, 80%) as an inseparable 1:3 cis:trans mixture (as judged by 300-MHz ^1H NMR): R_f = 0.38

(20/80 ethyl acetate/hexane); FT IR (neat) 2878, 2249 (CN), 1084, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20–2.01 (m, 8 H), 2.59 (m, 2 H, CH_2CN), 3.20 (d, J = 8.5 Hz, 2 H, CH_2I), 3.61–4.20 (m, 2 H, HCO); ^{13}C ($CDCl_3$, *trans*-**2c**) δ 11.3, 11.2, 25.1, 25.2, 26.1, 36.3, 72.7 (HCO), 81.4 (HCO), 119 (CN). Anal. Calcd for $C_9H_{14}INO$: C, 38.73; H, 5.06; N, 5.02. Found: C, 38.47; H, 5.09; N, 4.97.

Cyclization of Isoxazoline 1e: (2*R,5*R**)- (2a) and (2*R**,5*S**)-*N*-*tert*-Butyl[5-(iodomethyl)tetrahydrofuranyl]acetamide (3).** Following procedure C, isoxazoline **1e** gave a yellow oil which, upon purification by MPLC (1/2/2 EtOAc/chloroform/cyclohexane, 2.5 mL/min) gave **2a** [650 mg, 2.59 mmol, 59% (1:1::cis:trans ratio as judged by capillary GC)] and **3** [311 mg, 0.96 mmol, 22% (1:2::cis:trans ratio as judged by capillary GC)]: FT IR (neat) 3324 (NH), 1648 (C=O), 1545, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.4 (s, 9 H, 3 CH_3's), 1.7 (m, 2 H), 2.2 (m, 2 H), 2.4 (d, J = 6.3 Hz, 2 H, CH_2C=O), 3.3 (d, J = 6.0 Hz, 2 H, CH_2I), 4.4–3.9 (m, 2 H), 6.3 (m, 1 H); ^{13}C ($CDCl_3$, cis/trans) δ 10.3/10.5, 28.8 (CH_3), 31.2, 32.2/32.4, 43.4/44.1, 50.9, 78.6/78.8 (CHO), 170 (C=O); HRMS calcd for $C_{11}H_{20}INO_2$ 325.0539, found 325.0539.

One-Pot Preparation and Cyclization of 5-(3-Butenyl)-3-(trimethylsilyl)-2-isoxazoline (1f → 2a). Trimethylsilyl bromide (740 mg, 4.86 mmol) was added in one portion to a suspension of $Hg(CNO)_2$ (590 mg, 2.43 mmol) in anhydrous benzene (15 mL). After stirring for 1.5 h at room temperature, the salts were removed by transferring the solution under positive nitrogen pressure via cannula into a dry, 50-mL round-bottom flask equipped with a vacuum valve and septum. An excess of 1,5-hexadiene (2.0 g, 25 mmol) was added and the solution was stirred at room temperature. After 42 h, the solvent was removed under high vacuum and replaced with methylene chloride (15 mL). A methylene chloride (20 mL) solution of iodine (1.23 g, 4.86 mmol) was then added in one portion, and the mixture stirred an additional 12 h. Ether (20 mL) and saturated aqueous sodium bisulfite (20 mL) were added, and the organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting brown oil was purified by MPLC (25/75 EtOAc/cyclohexanes, 2.0 mL/min) giving **2a** (480 mg, 1.91 mmol, 40%) as yellow oil with a cis:trans ratio of 6.6:1 (as judged by capillary GC; cis 33 min/trans 33.2 min).

Cyclization of Isoxazoline 1g (1g → 2a). Iodine (228 mg, 0.828 mmol) was added in one portion to a solution of the isoxazoline **1g** (106 mg, 0.414 mmol) in methylene chloride (4 mL), and the reaction mixture was allowed to stir at room temperature under nitrogen for 5 h, at which time TLC indicated complete disappearance of starting isoxazoline **1g**. The reaction mixture was added to a mixture of ether (20 mL) and saturated aqueous sodium bisulfite solution (20 mL), the layers were separated, and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (1 × 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by MPLC (25/75 EtOAc/cyclohexanes, 2.5 mL/min) gave **2a** (67 mg, 0.27 mmol, 59%) as a pale yellow oil with a cis:trans ratio of 1:1.4 (as judged by capillary GC; cis 33 min/trans 33.2 min).

Cyclization of Isoxazoline 1h: (1h → 2a). As with **1g**, **1h** gave **2a** (53 mg, 0.21 mmol, 55%) as a pale yellow oil with a cis:trans ratio of 1:1.6 (as judged by capillary GC; cis 33 min/trans 33.2 min).

5-Butyl-3-(triphenylmethyl)-2-isoxazoline (4). Triphenylacetonitrile oxide (110 mg, 0.38 mmol), 1-hexene (649 mg, 7.71 mmol), and anhydrous benzene (20 mL) were sealed in a tube and heated at 85 °C for 48 h. After cooling to room temperature, the tube was opened, and the solution concentrated under reduced pressure. Purification by MPLC (10/90 EtOAc/hexanes, 2.5 mL/min) gave **4** (727 mg, 0.38 mmol, 100%) as a white solid: mp 123–125 °C (benzene); R_f = 0.63 (20/80 ethyl acetate/hexane); FT IR (neat) 3201, 2925, 1958, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J = 4.3 Hz, 3 H, CH_3), 1.21–1.80 (m, 6 H, CH_2), 2.29–2.50 (dd, J = 6.7, 14 Hz, 1 H, N=CC*H*H), 2.70–2.98 (dd, J = 6.7, 14 Hz, 1 H, N=CCH*H*), 4.60 (m, 1 H, HCO), 7.36 (m, 15 H, Ar H); HRMS calcd for $C_{26}H_{27}NO$ 369.2093, found, 369.2094.

Procedure D: (±)-*cis*-(*Z*)-4-Methyl-5-(3-pentenyl)-3-(triphenylmethyl)-2-isoxazoline (6). Triphenylacetonitrile oxide (100 mg, 0.35 mmol), (*Z*,*Z*)-2,6-octadiene [(*Z*,*Z*)-**5**; 0.27 g, 2.45 mmol], and anhydrous benzene (25 mL) were sealed in a tube and heated at 70 °C for 48 h. After cooling to room temperature, the tube was opened, and the solution concentrated under reduced pressure. Purification by Chromatatron (4/96 EtOAc/hexanes) gave, in order of elution, **6** (99 mg, 0.25 mmol, 71%) as a viscous, colorless oil [**6**: R_f = 0.73 (20/80 ethyl acetate/hexane); FT IR (neat) 3201, 2925, 2255, 1957, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.45 (d, J = 7.0 Hz, 3 H, CH_3), 1.65 (d, J = 6.0 Hz, 3 H, CH_3), 1.82–2.02 (m, 2 H), 2.15–2.41 (m, 2 H), 3.16 (dq, J = 6.7, 6.7 Hz, 1 H, N=CC*H*H), 4.52 (m, 1 H, HCO), 5.45–5.63 (m, 2 H, CH=CH), 7.7 (m, 15 H, Ar H); HRMS calcd for $C_{28}H_{29}NO$ 395.2249, found 395.2249] and its regioisomer [39 mg, 0.10 mmol, 27%; R_f = 0.65 (20/80 EtOAc/hexane); FT IR (neat) 3211, 2925, 2258, 1958 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.5 (d, J = 7.0 Hz, 3 H, CH_3), 2.2 (d, J = 7.0 Hz, 3 H, CH3), 1.7–2.0 (m, 4 H), 2.7 (m, 1 H, N=CC*H*H), 4.2 (dq, J = 6.7, Hz, 1 H, HCO), 4.8 (m, 1 H, C*H*=CH), 5.2 (m, 1 H, CH=C*H*), 7.7 (m, 15 H, Ar H); HRMS calcd for $C_{28}H_{29}NO$ 395.2249, found 395.2249].

(±)-*trans*-(*Z*)-4-Methyl-5-(3-pentenyl)-3-(triphenylmethyl)-2-isoxazoline (8). Following procedure D, (*E*,*E*)-2,6-octadiene [(*E*,*E*)-**5**] gave, in order of elution, **8** (1.24 g, 3.1 mmol, 62%) as a viscous, colorless oil [R_f = 0.72 (20/80 EtOAc/hexane); FT IR (neat) 3201, 2925, 2255, 1957, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.72 (d, J = 7.0 Hz, 3 H, CH_3), 0.98 (d, J = 5.6 Hz, 1 H), 1.03–1.84 (m, 4 H), 1.96–2.28 (m, 2 H), 2.80 (dq, J = 6.7, 6.7 Hz, 1 H, N=CC*H*H), 4.18 (dt, J = 6.7, 6.7 Hz, 1 H, N=CCH*H*), 5.50 (m, 2 H), 7.7 (m, 15 H, ArH); HRMS calcd for $C_{28}H_{29}NO$ 395.2249, found, 395.2249] and its regioisomer [0.6 g, 1.5 mmol, 30%; R_f = 0.68 (20/80 EtOAc/hexane); FT IR (neat) 3211, 2925, 2258, 1958 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.3 (d, J = 7.0 Hz, 3 H, CH_3), 1.6 (d, J = 7.0 Hz, 3 H, CH_3), 1.65 (br m, 1 H), 1.8 (bm, 1 H), 2.7 (m, 1 H, N=CC*H*H), 4.5 (m, 1 H, HCO), 4.9 (m, 1 H, C*H*=CH), 5.2 (m, 1 H, CH=C*H*), 7.7 (m, 15 H, Ar H); HRMS calcd for $C_{28}H_{29}NO$ 395.2249, found 395.2249].

[6*S[6α(*R**),2(*S**),3(*S**)]]-6-(1-Cyanoethyl)-2-methyl-3-iodotetrahydropyran (7a) and [2*S**[2α(*R**),5α(*S**)]]-2-(Cyanoethyl)-5-(iodoethyl)tetrahydrofuran (7b).** Following procedure C, isoxazoline **6** gave 2,6-*cis*-tetrahydropyran **7a** [24 mg, 0.086 mmol, 30%, 95:5 cis:trans mixture as judged by 300-MHz ^1H NMR; R_f = 0.57 (20/80 EtOAc/hexane); FT IR (neat) 2878, 2241 (CN), 1115, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 3 H, CH_3), 1.9 (d, 3 H, CH_3), 1.6–2.01 (m, 4 H), 2.86 (m, 1 H, CHCN), 3.85 (m, 1 H), 4.4 (m, 1 H, HCO), 4.2 (m, 1 H, HCO); HRMS calcd for ($C_9H_{14}NO$ – I) 152.1075, found 152.1075] and 2,5-*trans*-tetrahydrofuran **7b** [24 mg, 0.086 mmol, 30%; R_f = 0.57 (20/80 EtOAc/hexane); FT IR (neat) 2870, 2241 (CN), 1103, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 3 H, CH_3), 1.4 (d, 3 H, CH_3), 2.4 (br m, 4 H), 2.87 (m, 1 H, CHCN), 3.75 (m, 1 H), 3.85 (m, 1 H, HCO), 4.25 (m, 1 H, HCO); HRMS calcd for ($C_9H_{14}NO$ – I) 152.1075, found 152.1073.

[6*S[6α(*S**),2(*S**),3(*R**)]]-6-(1-Cyanoethyl)-2-methyl-3-iodotetrahydropyran (9a), [6*S**[6α(*S**),2(*S**),3(*R**)]]-6-(1-Cyanoethyl)-2-methyl-3-iodotetrahydropyran (9b), and [2*S**[2α(*S**),5α(*R**)]]-2-(Cyanoethyl)-5-(iodoethyl)tetrahydrofuran (9b).** Following procedure C, isoxazoline **8** gave 2,6-*cis*-tetrahydropyran **9a**[11] [140 mg, 0.51 mmol, 38%; mp 83–85 °C (hexane); FT IR (neat) 2870, 2239 (CN), 1105, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (d, J = 9.2 Hz, 3 H, CH_3), 1.79 (m, 2 H), 1.9 (d, J = 6.9 Hz, 3 H, CH_3), 2.21 (m, 2 H), 2.71 (m, 1 H, CHCN), 3.8 (m, 1 H, CHI), 4.1 (m, 1 H, HCO), 4.2 (q, J = 6.9 Hz, 1 H, HCO); ^{13}C ($CDCl_3$) δ 14.8 (CH_3), 24.6 (CH_3), 30.4 (CH), 31.6, 32.3 (CH), 33.1, 79.9 (HCO), 84.1 (HCO), 120.9 (CN); HRMS calcd for ($C_9H_{14}NO$ – I) 152.1075, found, 152.1075], 2,6-*trans*-tetrahydropyran **9b** [46 mg, 0.17 mmol, 13%; FT IR (neat) 2878, 2241 (CN), 1115, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.4 (d, J = 9.0 Hz, 3 H, CH_3), 1.95 (d, J = 6.9 Hz, 3 H, CH_3), 1.7–2.25 (m, 4 H), 2.75 (m, 1 H, CHCN), 3.82 (m, 1 H, CHI), 4.05 (m, 1 H, HCO), 4.19 (m, 1 H, HCO); ^{13}C ($CDCl_3$) δ 16.0 (CH_3), 22.1, 26.3 (CH_3), 30.6 (CH), 31.0, 32.2 (CH), 82.1 (HCO), 86.8 (HCO), 120.1 (CN); HRMS calcd for ($C_9H_{14}NO$ – I) 152.1075, found, 152.1075], and 2,5-*trans*-tetrahydrofuran **9c** [48 mg, 0.17 mmol, 13%; FT IR (neat) 2878, 2241 (CN), 1115, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.3 (d, J = 9.0 Hz, 3 H, CH_3), 1.45 (d, J = 6.9 Hz, 3 H, CH_3), 1.6 (m, 2 H), 2.2 (m, 1 H), 2.6 (m, 1 H, CHCN), 2.7 (m, 1 H), 3.5 (m, 1 H, HCO), 3.7 (m, 1 H, CHI), 3.8 (m, 1 H, HCO); ^{13}C ($CDCl_3$) δ 14.9 (CH_3), 24.9, 29.0 (CH_3), 31.3, 31.4 (CH), 31.7 (CH), 80.4 (HCO), 84.5 (HCO), 115 (CN); HRMS calcd for ($C_9H_{14}NO$

- I) 152.1075, found, 152.1075. Anal. Calcd for $C_9H_{14}INO$: C, 38.73; H, 5.06; N, 5.02. Found: C, 38.57; H, 5.22; N, 4.86].

Procedure E: 5-[2-(4,5-Dihydro-2*H*-pyranyl)ethyl]-3-[1-((trimethylsilyl)oxy)ethyl]-2-isoxazoline (13a). A benzene (1 mL) solution of triethylamine (26 mg, 0.25 mmol) was added dropwise to a solution of 2-[(trimethylsilyl)oxy]-1-nitropropane (302 mg, 1.71 mmol), dihydropyran **10a** (472 mg, 3.41 mmol), and *p*-chlorophenyl isocyanate (524 mg, 3.41 mmol) in benzene (30 mL). The resulting solution was heated at reflux for 50 h and then cooled, filtered through Celite, and treated with water (25 drops). After 2 h of vigorous stirring, the mixture was again filtered through Celite, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by MPLC (Florisil column, 2:98 EtOAc:hexanes, 2.5 mL/min) gave **13a** (380 mg, 1.28 mmol, 75%) as a yellow oil: R_f = 0.68 (25/75 ethyl acetate/hexane); FT IR (neat) 2953, 1252, 1089, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9 H, $Si(CH_3)_3$), 1.32 (d, J = 6.3 Hz, 3 H, CH_3), 1.54-2.03 (m, 9 H), 2.50 (dd, J = 9, 15 Hz, 1 H, N=C*H*HCO), 2.92 (dd, J = 9, 15 Hz, 1 H, N=CH*H*CO), 3.86 (t, J = 3.2 Hz, 2 H, CH_2O), 4.42 (t, J = 2.6 Hz, 1 H, CH=), 4.60 (m, 1 H, HCO); HRMS calcd for $C_{15}H_{27}NO_3Si$ FAB+ 298.1838, found, 298.1839.

5-[2-(4,5-Dihydro-2*H*-pyranyl)propyl]-3-[1-((trimethylsilyl)oxy)ethyl]-2-isoxazoline (13b). Following procedure E, dihydropyran **10b** gave **13b** (411, 1.4 mmol, 70%) as a pale yellow oil: R_f = 0.68 (25/75 EtOAc/hexane); FT IR (neat) 2953, 1252, 1089, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9 H, $Si(CH_3)_3$), 1.18-2.22 (m, 13 H), 2.53 (dd, J = 7, 15 Hz, 1 H, N=CC*H*HCO), 3.13 (dd, J = 7, 15 Hz, 1 H, N=CCH*H*CO), 3.95 (t, J = 2.2 Hz, 2 H, CH_2O), 4.54 (br m, 2 H, HCO), 4.75 (m, 1 H, CH=); HRMS calcd for $C_{16}H_{29}NO_3Si$ 311.1917, found, 311.1916.

Procedure F: (5*S,6*R**,8*R**)- and (5*S**,6*R**,8*S**)-8-(Cyanomethyl)-5-iodo-1,7-dioxaspiro[5.4]decane (12a).** A solution of iodine (121 mg, 0.48 mmol) in methylene chloride (10 mL) was added in one portion to a methylene chloride (20 mL) solution of isoxazoline **13a** (94.8 mg, 0.318 mmol). The reaction mixture was stirred at room temperature for 5 h and then diluted with Et_2O (10 mL) and saturated aqueous sodium bisulfite solution (5 mL), and the layers separated. The aqueous phase was extracted with Et_2O (3 × 25 mL), and the combined organic extracts were washed with brine (1 × 10 mL), dried (Mg_2SO_4), filtered, and concentrated under reduced pressure. Purification by Chromatron (90/10 EtOAc/hexanes) gave spiroketal **12a** (55.7 mg, 0.18 mmol, 57%) as a pale yellow oil and inseparable 1:1 mixture of CH_2CN epimers; R_f = 0.57 (20/80 ethyl acetate/hexane); FT IR (neat) 2947, 2874, 2249 (CN), 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40-2.35 (m, 9 H), 2.58 (m, 2 H, CH_2CN), 3.69 (m, 1 H, C*H*HO), 3.86 (m, 1 H, CH*H*O), 4.35 (m, 1 H, *H*CO); ^{13}C ($CDCl_3$) δ 21.0/25.3, 26.0/26.8, 29.9/30.7, 34.4/34.5, 38.2/39.4, 62.8 (CH_2O), 72.8 (CHI), 75.3 (HCO), 106.7 (OCO), 117.6/117.7 (CN); HRMS calcd for ($C_{10}H_{14}NO_2$ - I) 180.1024, found 180.1025.

(2*S,6*R**,11*S**)-2-(Cyanomethyl)-11-iodo-1,7-dioxaspiro[5.5]undecane (12b).** Following procedure F, dihydropyran **13b** gave spiroketal **12b** (22 mg, 0.07 mmol, 25%) as a pale yellow oil: R_f = 0.33 (20/80 EtOAc/hexane); FT IR (neat) 2943, 2872, 2251 (CN), 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.09-1.17 (m, 11 H), 2.45 (d, J = 6.3 Hz, 2 H, CH_2CN), 3.65 (m, 2 H, CH_2O), 3.92 (m, 1 H, HCO); ^{13}C NMR ($CDCl_3$) δ 18.27, 18.30, 24.66, 25.10 (HCI), 30.23, 34.70, 35.37, 60.66 (CH_2O), 65.18 (HCO), 96.12 (OCO), 117.66 (CN); HRMS calcd for $C_{11}H_{16}INO_2$ 321.0225, found 321.0222.

Acknowledgment. We are pleased to acknowledge support of this work by the National Science Foundation through Grant CHE-8704836.

Registry No. **1a**, 123622-54-8; **1b**, 123622-55-9; **1c**, 123622-56-0; **1d**, 123622-57-1; **1e**, 123622-58-2; **1g** (isomer 1), 123622-60-6; **1g** (isomer 2), 123622-61-7; **1h** (isomer 1), 123622-63-9; **1h** (isomer 2), 123622-64-0; *cis*-**2a**, 123622-65-1; *trans*-**2a**, 123622-66-2; *cis*-**2b**, 123622-68-4; *trans*-**2b**, 123622-69-5; *cis*-**2c**, 123622-70-8; *trans*-**2c**, 123622-71-9; *cis*-**3**, 123622-67-3; *trans*-**3**, 123622-87-7; **4**, 123622-72-0; (*E*,*E*)-**5**, 18152-31-3; (*Z*,*Z*)-**5**, 18680-11-0; **6**, 123622-73-1; **6** (4,5-regioisomer), 123622-88-8; 2,6-*cis*-**7a**, 123622-76-4; 2,6-*trans*-**7a**, 123622-77-5; **7b**, 123622-78-6; **8**, 123622-74-2; **8** (4,5-regioisomer), 123622-75-3; **9a**, 123622-79-7; **9b**, 123622-80-0; **9c**, 123673-08-5; **10a**, 123622-81-1; **10b**, 123622-83-3; **12a** (isomer 1), 123622-85-5; **12a** (isomer 2), 123673-09-6; **12b**, 123622-86-6; **13a**, 123622-82-2; **13b**, 123622-84-4; $Hg(CNO)_2$, 628-86-4; $Ph_3CC{\equiv}N^+O^-$, 13412-55-0; 1-hexene, 592-41-6; 1,5-hexadiene, 592-42-7; 1,6-heptadiene, 3070-53-9; 1,7-octadiene, 3710-30-3; (±)-2-[(trimethylsilyl)oxy]-3-methyl-1-nitrobutane, 123622-62-8; (±)-2-[(trimethylsilyl)oxy]-1-nitropropane, 123622-59-3; *tert*-butylhydroximic acid chloride, 3273-26-5.

Supplementary Material Available: Labeled drawings of **9a** and listings of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen atom coordinates (6 pages). Ordering information is given on any current masthead page.

Oxidative Degradation of 6-Hydroxy-1,2,3,4-tetrahydroisoquinolines and 7-Hydroxy-2-benzazepines. A Novel Route to Heterocyclic Quinones

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Received March 31, 1989

A novel route toward 4,5-indolequinones and 5,8-quinolinequinones, based on the Fremy's salt promoted oxidative degradation of 6-hydroxy-1,2,3,4-tetrahydroisoquinolines and 7-hydroxy-2-benzazepines, is described.

The significant pharmacological properties associated with many synthetic and naturally occurring quinones has spurred much interest in the search for a new methodology for the synthesis of the quinone functionality.[1]

Our recent work in this field has led us to develop the so-called oxidative degradation approach (ODA) for the synthesis of simple 1,4-benzoquinones.[2] In essence, the success of this approach lies in the fact that the amino group of the starting phenolic *N*,*N*-dimethylbenzylamines serves two main purposes in the plan. As illustrated in Scheme I, it was first needed as a directing group for metalation (and subsequent functionalization) of the unprotected phenol,[3] and secondly, its role in the oxidative degradation process was to promote side-chain cleavage

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