Intramolecular [4 + 2]-Cycloadditions of Vinylnitrosonium Cations with Olefins

Scott E. Denmark,*[1a] Christopher J. Cramer,[1b] and Michael S. Dappen[1c]

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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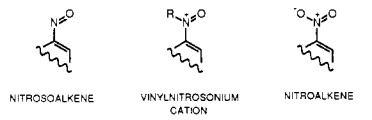
α,β-Epoxyketonitrones have been shown to be viable precursors of vinylnitrosonium cations upon treatment with trimethylsilyl trifluoromethanesulfonate. Variable-temperature NMR experiments indicate that this transformation occurs slowly at room temperature. The generated N=O heterodiene undergoes an intramolecular [4 + 2]-cycloaddition with a pendant, unactivated olefin. A strong dependence of the outcome of the reaction on the starting nitrone geometry was observed. A number of α,β-epoxyaldonitrones have been prepared, and variable-temperature NMR experiments indicate that under identical conditions these substrates generate vinylnitrosonium cations at −30 °C and undergo analogous cycloaddition. Trapping of the intermediate *N*-alkyl-5,6-dihydro-4*H*-1,2-oxazinium cations has been accomplished with aqueous potassium cyanide. The stereochemistry of the cycloadducts has been assigned on the basis of ^{1}H NMR analysis and the geometry of the transition states deduced therefrom. A marked preference for reaction via transition states which contain an allylic (trimethylsilyl)oxy group in the plane of the heterodiene has been observed with aldonitrone precursors. The folding of the side chain containing the dienophile has been observed to be exclusively exo to the heterodiene with ketonitrone precursors and predominantly exo for aldonitrone precursors.

Introduction

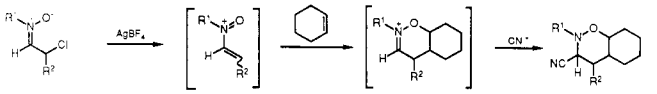
As part of an ongoing program aimed at the development of general methods for the construction of polycyclic ring systems incorporating heteroatom functionality, we have been investigating the [4 + 2]-cycloadditions of a variety of N=O heterodienes[2] (Chart I). We have recently reported successful intramolecular cycloadditions with nitrosoalkenes[3] and both intra- and intermolecular cycloadditions with nitroalkenes.[4] Subsequent elaboration of the respectively formed 5,6-dihydro-4*H*-1,2-oxazines and their *N*-oxides gives entry to a variety of 1,4-functionalized aliphatic and alicyclic systems with a high degree of stereocontrol.[3d,4b,c] We wish to report herein that vinylnitrosonium cations (VNC's) also serve as reactive 4π components in stereoselective cycloadditions with unactivated olefins.[3c]

Our initial studies on intramolecular cycloadditions of nitrosoalkenes, while successful,[3a,d] revealed a number of limitations which we sought to address by employing the related VNC's. The most important limitation we established was that simple unactivated nitrosoalkenes underwent cycloaddition only with nucleophilic dienophiles (e.g., enol ethers and thioenol ethers). This was further complicated by a strong dependence on the dienophile geometry, presumably due to secondary orbital overlap. Furthermore, for certain target molecules it was desirable to incorporate oxygen functionality into the allylic position of the heterodiene, and our initial attempts with suitable nitrosoalkene precursors proved unsuccessful.[5]

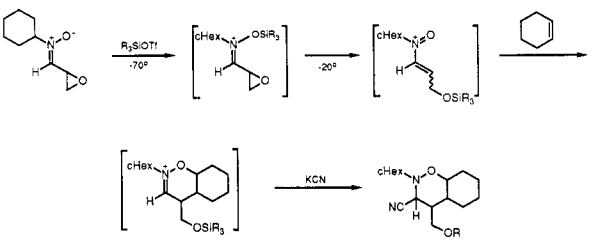
Chart I



Scheme I



Scheme II



Vinylnitrosonium cations appeared to provide an ideal solution to both problems. The extreme electrophilicity of these positively charged species was clearly demonstrated by Eschenmoser, who first investigated the use of VNC's in connection with the selective hydrolysis of amides in the final stages of the total synthesis of vitamin B_{12}.[6] Subsequently, extensive studies by the Eschenmoser[7] group on the generation of VNC's by the silver tetrafluoroborate induced dehalogenation of α-chloroaldo-

(1) (a) Fellow of the Alfred P. Sloan Foundation (1985–1987), NSF Presidential Young Investigator (1985–1990). (b) NSF Graduate Fellow, 1984–1987. (c) Taken in part from: Dappen, M. S. Ph.D. Thesis, University of Illinois, Urbana, 1985.

(2) For reviews of heterodiene cycloadditions see: (a) Hamer, J. H.; Ahmad, M. In *1,4 Cycloaddition Reactions*; Hamer, J. H., Ed.; Academic Press: New York, 1967. (b) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651. (c) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 212. For comprehensive reviews of intramolecular [4 + 2]-cycloadditions see: (d) Ciganek, E. *Org. React.* **1984**, *32*, 1. (e) Taber, D. F. *Intramolecular Diels–Alder and Alder–Ene Reactions*; Springer-Verlag: New York, 1984. (f) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183.

(3) (a) Denmark, S. E.; Dappen, M. S.; Sternberg, J. A. *J. Org. Chem.* **1984**, *49*, 4741. (b) Denmark, S. E.; Dappen, M. S.; Sternberg, J. A. *Abstracts of Papers*, 187th American Chemical Society Meeting, St. Louis, MO, April 1984; American Chemical Society: Washington, DC, 1984; ORGN 45. (c) Denmark, S. E.; Cramer, C. J. "Abstracts of Papers", 189th American Chemical Society Meeting, Miami, FL, April 1985; American Chemical Society: Washington, DC, 1985; ORGN 151. (d) Denmark, S. E.; Jacobs, R. T.; Sternberg, J. A., manuscript in preparation.

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(5) Denmark, S. E.; Dappen, M. S. *J. Org. Chem.* **1984**, *49*, 798.

(6) Schilling, W. Ph.D. Thesis, Eidgenossische Technische Hochschule, Zurich, 1974, Dissertation No. 5253.

(7) (a) Kempe, U. M.; Das Gupta, T. K.; Blatt, K.; Gygax, P.; Felix, D.; Eschenmoser, A. *Helv. Chem. Acta* **1972**, *55*, 2187. (b) Das Gupta, T. K.; Felix, D.; Kempe, U. M.; Eschenmoser, A. *Ibid.* **1972**, *55*, 2198. (c) Gygax, P.; Das Gupta, T. K.; Eschenmoser, A. *Ibid.* **1972**, *55*, 2205. (d) Petrizilka, M.; Felix, D.; Eschenmoser, A. *Ibid.* **1973**, *56*, 2950. (e) Schatzmiller, S.; Gygax, P.; Hall, D.; Eschenmoser, A. *Ibid.* **1973**, *56*, 2961. (f) Schatzmiller, S.; Eschenmoser, A. *Ibid.* **1973**, *56*, 2975. (g) Shalom, E.; Zenou, J.-L.; Shatzmiller, S. *J. Org. Chem.* **1977**, *42*, 4213. (h) Gygax, P., Ph.D. Thesis, Eidgenossische Technische Hochschule, Zurich, 1977, Dissertation No. 5901.

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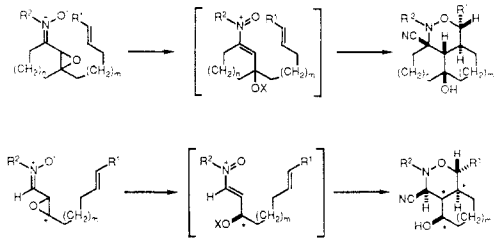
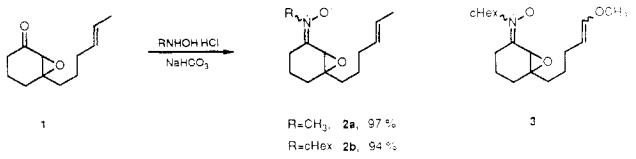
Scheme III



Scheme IV



nitrones showed that these heterodienes undergo facile cycloaddition with unactivated olefins (Scheme I). Indeed the major drawback of these species is their extreme reactivity, preferring electrophilic substitution with tri- and tetrasubstituted alkenes as well as arenes. When cycloaddition occurs, the resulting *N*-alkyl-5,6-dihydro-4*H*-1,2-oxazinium cations can be trapped nucleophilically with aqueous potassium cyanide to deliver a functionalized tetrahydrooxazine. Alternatively they can be deprotonated with potassium carbonate in which case the resulting 5,6-dihydro-2*H*-1,2-oxazine undergoes a spontaneous [4 + 2]-cycloreversion to generate an aldehyde and an unsaturated imine. Finally, it was established that the cycloadditions are stereospecific, preserving the stereochemical relationship of the olefinic protons in (*E*)- and (*Z*)-2-butene in the product.[7d]

Graf and Riediker[8] have extended this chemistry by employing α,β-epoxyaldonitrones as VNC precursors. Treatment of these nitrones with trialkylsilyl triflates at low temperature forms the *O*-silyl nitronium ethers. Upon warming to −25 °C a rapid silicon migration to the oxirane oxygen occurs with concomitant epoxide opening to generate the VNC bearing an allylic (trialkylsilyl)oxy substituent (Scheme II). This species is extremely unstable and cannot be detected. In the presence of dienophiles a cycloaddition occurs rapidly and the products are obtained by KCN addition as before. The major difficulty in this technology is the instability of the VNC. In the absence of a dienophile, decomposition pathways are many and varied leading to dihydrooxazolium cations, oxazetium cations, and unsaturated nitrones.[8a] Thus, to obtain useful yields of the cycloadduct, the VNC precursor is usually used in a two-to-fivefold excess over dienophile. The purpose of the investigation below was the study of the intramolecular version of this reaction. We anticipated that the ultimate attachment of the dienophile to the heterodiene would solve the major problems in the cycloaddition by enhancing the effective concentration of olefin and controlling the regio- and stereochemical issues. We chose to evaluate the viability of this reaction for both keto- and aldonitrones with regard to (1) ease of preparation, (2) conditions for heterodiene generation, (3) length and reactivity of dienophile tether, (4) stereoselectivity, and (5) manipulation of the products (Scheme III).

(8) (a) Riediker, M.; Graf, W. *Helv. Chim. Acta* **1979**, *62*, 205. (b) Riediker, M.; Graf, W. *Ibid.* **1979**, *62*, 1586. (c) Riediker, M.; Graf, W. *Ibid.* **1979**, *62*, 2053. (d) Riediker, M.; Graf, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 481. (e) Riediker, M.; Graf, W. *Ibid.* **1981**, *20*, 481. (f) Riediker, M., Ph.D. Thesis, Eidgenossische Technische Hochschule, Zurich, 1981, Dissertation No. 6757.

Table I. VT-NMR Experiments with Ketonitrones

		chemical shift, δ^a			
nitrone	Me_3SiOTf	C(2)–H	C(6)–H_{eq}	C(6)–H_{ax}	C(1′)–H
2aZ	None	4.42	2.56		3.70
	1.2 equiv		2.78		3.93
2aE	None	3.55	3.00	<2.20	3.91
	1.2 equiv	3.76	3.06	2.60	4.13
2bZ	None	4.42	2.66		4.04
	2.0 equiv	3.74	2.82		4.37
2bE	None	3.58	3.04	<2.20	4.39
	2.0 equiv	3.74	3.13	2.78	4.62
3Z	None	4.41	2.59		3.99
	2.0 equiv	3.70	2.65		4.40
3E	None	3.59		<2.10	4.39
	2.0 equiv	3.91	2.89	2.60	4.77

[a] Chemical shifts of nitrones at 20 °C, silylated nitrones at −50 °C.

Results

A. Ketonitrones. 1. Preparation of Substrates. Our first experiments focused on the α,β-epoxyketonitrones formed from **1**[5] (Scheme IV). The nitrones were prepared in excellent yield by the method of Barton[9] to give a mixture of (*E*)- and (*Z*)-nitrone isomers. The facile formation of **2a**, **2b**, and **3** is in contrast to the usual sluggish production of ketonitrones and may ultimately rest in the activation by the oxirane. The complete separation of these geometrical isomers could not be achieved chromatographically, although fractions highly enriched in a single isomer could be obtained. However, reestablishment of equilibrium was quite rapid, with the (*E*)-nitrone being the thermodynamically favored isomer for each of **2a**, **2b**, and **3**. Assignment of nitrone geometry was made by NMR analysis, the anisotropy of the N–O bond imparting a deshielding influence on adjacent protons[9,10] (see Table I).

2. VT-NMR. Variable-temperature ^1H NMR experiments were done using **2** and **3**, and the results are presented in Table I. In all cases the nitrones (as a solution in CD_2Cl_2 or $CDCl_3$) were immediately O-silylated upon addition of trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) at −50 °C. Only the silylated nitrones were observable in the NMR spectra, and these species were stable until room temperature (20 °C) was reached. At 20 °C the (*Z*)-nitrone appeared to open rapidly, and cyclization followed to some extent. The appearance of a new methyl doublet signal at 1.5 ppm and the disappearance of the olefin and the allylic methyl signals were diagnostic. The (*E*)-nitrone opened very slowly, and only a small decrease in the olefin signal was noted. In both cases, no reaction was observed until 20 °C was reached, and then cyclization was only one of the many reaction pathways; however, cyclization took place to a much greater extent with the (*Z*)-nitrone. The expected VNC was never observed spectroscopically and rarely was the olefin more than 50% consumed. Furthermore, the disappearance of olefin was slow, on the order of 1 to 2 h.

In an attempt to accelerate the cycloaddition component of this reaction we examined the substrate **3** bearing an enol ether in the side chain. Variable-temperature ^1H NMR experiments (Table I) showed immediate O-silylation of the nitrone with Me_3SiOTf at −50 °C and persistence of the enol ether resonances up to 20 °C, at which time they rapidly disappeared. However, as shown in

(9) Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1764.

(10) We attempted to confirm these assignments by an LIS study with $Eu(fod)_3$, but the interpretation was complicated by competing complexation by the oxirane oxygen and isomerization of the nitrone.

Scheme V

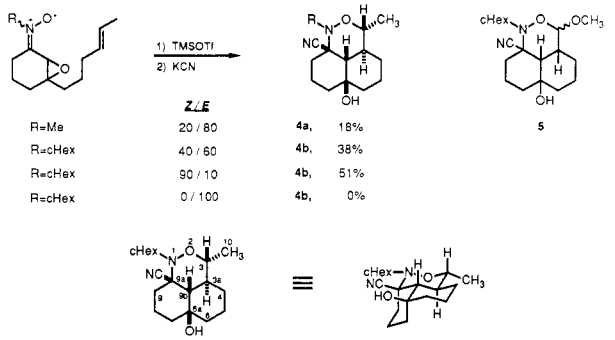


Figure 1. Stereochemistry of **4b**.

preparative experiments (vide infra), cyclization can account for only a small part of the consumption of the enol ether.

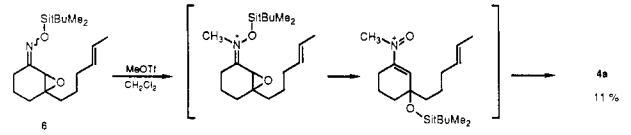
In summary, our NMR studies agree with those of Graf in the rapid and quantitative silylation of epoxyketonitrones at low temperature. However, these silylated species open much more slowly, requiring 20 °C in contrast to the −20 °C rearrangements of epoxyaldonitrone precursors. Finally, the (*Z*)-nitrone isomer opened more quickly than the (*E*)-isomer.

3. Cyclization and Characterization. The VT-NMR experiments suggested that the best conditions for preparative cyclizations would be to add Me_3SiOTf to a solution of the nitrone at low temperature, quickly warm the reaction to 20 °C and allow it to remain there for 1 hour prior to quenching with cyanide. This would consume only about 50% of the olefin, but it was felt that longer reaction times at 20 °C would lead to decomposition of the intermediate dihydrooxazinium cation. In all cases, TLC analysis of the reaction mixtures produced by following this protocol indicated many products, but only **4a** or **4b** were isolable (Scheme V).[11] A poor yield of cyclization product was obtained from **2a**, while a moderate yield, dependent upon the isomeric mixture of nitrones, could be obtained from **2b**.

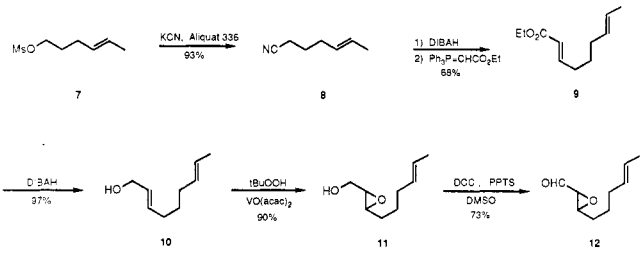
Products **4a** and **4b** were characterized by NMR, IR, and MS analysis. Only compound **4b** was obtained in quantities large enough to characterize further (combustion analysis, stereochemical studies). Extensive decoupling of the 200-MHz, ^1H NMR spectrum of **4b** at 60 °C,[12] including studies in which 1.3 mol % of the lanthanide shift reagent Eu(fod)$_3$[13] were added indicated couplings of 8.6 Hz for $^3J_{3\text{-}3a}$, 6.7 Hz for $^3J_{3\text{-}10}$, and 11.4 Hz for $^3J_{3a\text{-}9b}$ (see Figure 1). The large couplings for $^3J_{3\text{-}3a}$ and $^3J_{3a\text{-}9b}$ are indicative of the trans-diaxial arrangement of these protons. Furthermore, the large (0.4 ppm) shift downfield of the proton at C(9b) upon addition of Eu(fod)$_3$ indicates a syn arrangement of this proton with the hydroxyl group at C(6a). The only remaining stereocenter at C(9a) is assumed to arise from attack of cyanide on the less hindered face of the intermediate dihydrooxazinium cation.

Preparative scale cyclizations of the *E* and *Z* isomers of nitrone **3** were performed separately. As expected the *E* isomer gave no isolable cyclization products, while the *Z* isomer produced a 24% yield of four diastereomers **5** (Scheme V). The low yield and proliferation of diastereomers, presumably due to isomerization of the nitrone and hydrolysis of the enol ether, led us to abandon this reaction.

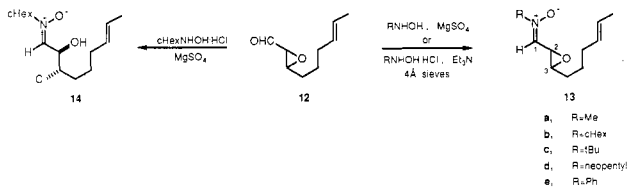
Scheme VI



Scheme VII



Scheme VIII



Since the success of these reactions appeared to depend on the nitrone geometry we briefly investigated the formation of various nitrones from isophorone oxide but found in all cases examined that isomerization to the thermodynamically more stable *E* isomer was rapid.

Finally, a new entry into VNC formation was investigated which could potentially avoid the problems of nitrone geometry. We envisioned the formation of the O-silylated nitrone intermediate by alkylation of a silyloxime.[14] Since we had demonstrated the ability to prepare geometrically homogeneous oximes,[5] the method could give rise to the requisite (*Z*)-nitrones. To evaluate the feasibility of this approach an *E*/*Z* mixture of silyloximes **6** in dichloromethane was treated with methyl triflate (MeOTf) at 20 °C and quenched with KCN after 8 h to produce an 11% yield of the cycloadduct **4a** (Scheme VI). Various other solvents were examined to accelerate the methylation, but most were incompatible with MeOTf.

B. Aldonitrones. 1. Preparation of Substrates. The preparation of penultimate cyclization substrate **12** is detailed in Scheme VII. Mesylate **7** (>96:4 *E*:*Z* by GC and NMR) was prepared as previously described.[5] Reaction of this substrate with potassium cyanide under phase-transfer conditions gave an excellent yield of nitrile **8**. Diisobutylaluminum hydride (DIBAH) reduction of **8** followed by hydrolysis gave an aldehyde which was directly treated with ethyl (triphenylphosphoranylidene)acetate. Attempted purification of the aldehyde gave significantly lower yields. Following this protocol, ester **9** could be obtained in 68% overall yield from nitrile **7**. Reduction with DIBAH proceeded cleanly to give the allylic alcohol **10** in 97% yield. Directed epoxidation with vanadyl acetoacetonate[15] afforded epoxyalcohol **11** in 90% yield, together with small amounts of oxidation to the unsaturated aldehyde. Finally, Pfitzner–Moffatt[16] oxidation of **11** gave

(11) ^1H NMR analysis of various chromatography fractions showed olefinic material remaining: only in fractions containing **4a** and **4b** was the olefin consumed.

(12) Spectra obtained at lower temperatures showed significant line broadening owing to hindered rotation of the *N*-cyclohexyl group.

(13) Eu(fod)$_3$ = tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium.

(14) After this work was completed a report appeared describing the methylation of silyloximes using Meerwein's reagent: Lebel, N. A.; Balasubramanian, N. *Tetrahedron Lett.* **1985**, *26*, 4331.

(15) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

Table II. Selected Spectroscopic Data for Aldonitrones

compd	method[a]	yield,[b] %	IR stretch, C=N[c]	^{1}H NMR data, δ (J)[d] C(1)–H	C(2)–H	C(3)–H
13a	A	70	1613 m	6.40 (7.1)	3.93 (7.0, 1.9)	2.96 (1.9, 6.0)
13b	A	75	1600 m	6.43 (7.0)	4.00 (7.0, 2.2)	2.95 (m)
13c	B	72	1580 m	6.55 (6.7)	4.00 (6.7, 2.2)	3.00 (m)
13d	A	43	1595 m	6.32 (7.0)	3.96 (7.0, 2.2)	2.98 (m)
13e	B	50	–	7.00 (7.0)	4.21 (7.0, 2.1)	3.13 (2.1, 4.3)

[a] See text or experimental for details of methods. [b] Yields are for isolated, purified material. [c] As a solution in chloroform. [d] As a solution in $CDCl_3$. Multiplicities for C(1)–H are doublet, for C(2)–H doublet of doublets, for C(3)–H, where reported, doublet of triplets; m refers to an unresolved multiplet.

Table III. VT-NMR Experiments with Aldonitrone 13b

conditions	chemical shift, δ[a] C(1)–H	C(2)–H	C(9)–H_3 (J)	–Si(CH_3)$_3$
before Me_3SiOTf	6.43	4.00	1.63 (4.8)	–
after Me_3SiOTf, temp <–30 °C	7.64	3.97	1.61 (4.8)	0.03
after Me_3SiOTf, temp >–30 °C	8.60	2.72	1.40 (6.3)	0.04

[a] Numbering of carbons is according to starting material **13b**; multiplicity for C(9)–H_3 is a doublet.

12 in 73% yield as a colorless liquid which could be handled conveniently and showed excellent stability when stored at –20 °C. Following the above protocol, it was possible to produce multigram quantities of **12**.

We were able to prepare the requisite nitrones **13** by reaction of **12** with *N*-alkylhydroxylamines in the presence of magnesium sulfate as a drying agent[8a] (method B). Unfortunately, use of *N*-cyclohexylhydroxylamine hydrochloride under identical conditions led only to the isolation of chlorohydrin nitrone **14** (Scheme VIII). Given the relative instability of the free bases of many hydroxylamines as compared to their hydrochloride salts, we sought a set of reaction conditions which could use the more stable salts. Prior treatment of the salts in a dichloromethane solution with triethylamine for 5 min proved efficacious; subsequent addition of 4-Å sieves and epoxy aldehyde **12** gave epoxynitrones **13** uncontaminated by any chlorohydrin nitrones **14** (Method A). The yields and diagnostic spectral data for these compounds are summarized in Table II. The nitrone geometry in all cases was >95% *Z* as judged by ^{1}H NMR, in accordance with literature precedent.[7a,8a]

2. VT-NMR. Variable-temperature, ^{1}H NMR experiments were conducted using the *N*-cyclohexyl-α,β-epoxyaldonitrone **13b**. Treatment of a solution of this substrate in $CDCl_3$ with 1 equiv of Me_3SiOTf at –55 °C resulted in complete silylation of the nitrone oxygen. This species was stable up to –30 °C, at which time 80% of the olefinic protons were instantly consumed. These results are very similar to those of Graf,[8] and in contrast to our earlier experiments with ketonitrones (vide supra). The remaining olefinic protons failed to disappear with continued warming, and it must be assumed that these olefins were located in molecules whose VNC portion had undergone some reaction other than intramolecular cycloaddition. The data for this experiment are summarized in Table III. The chemical shifts observed for C(1)–H are especially diagnostic for the three unique species.

3. Cyclization and Characterization. With these results in hand, we assayed a number of preparative cycloadditions. In each case, 1 equiv of Me_3SiOTf was added to a dichloromethane solution of *N*-alkyl-α,β-epoxyaldonitrone at –78 °C, the solution warmed to –10 °C and recooled, and 10 equiv of potassium cyanide added as an aqueous solution. In each case, a number of cycloadducts were isolated (Scheme IX), which could either be isolated pure, or as isomerically enriched fractions following chromatography. The yields are summarized in Table IV.

Scheme IX

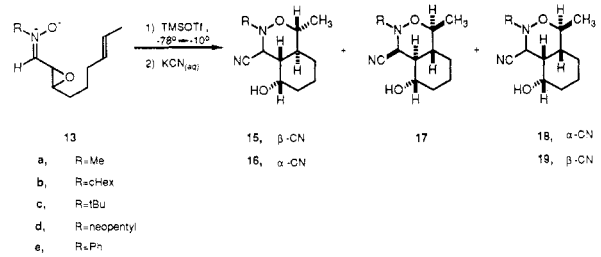


Table IV. Yields of Cycloadditions with Aldonitrones 13a–e

starting material	yield of products,[a] % 15	16	17	18	19
13a	29	31	5	3	4
13b	44	12	4	1	1
13c	46	2	7	2	4
13d	7	27	8	–	9
13e	35	9	5	–	2

[a] See experimental section for details on determination of yields.

Optimization of reaction concentration was performed for the cycloaddition of **13b**. These experiments indicate that above a concentration of 0.01 M yields start to fall off rapidly, while increasing dilution beyond this point seems to have little effect.

The potential for trapping the dihydrooxazinium cations with other nucleophiles was also investigated;[17] however in no case were cycloadducts, or indeed any characterizable products, isolated. NMR analyses of the crude reaction mixtures also gave no indication of cycloadducts. We are forced to conclude that either these reagents are not sufficiently nucleophilic to react with the dihydrooxazinium cation prior to its decomposition, or, in a few cases, that they are better bases than they are nucleophiles, and that they abstract a proton, resulting in cycloreversion.

The assignments of stereochemistry of the cycloadducts are based on exhaustive analysis of 200-MHz ^{1}H NMR spectra, including decoupling studies. These data are summarized in Table V. Although the amount of data is formidable, assignment of stereochemistry is actually quite straightforward (Figure 2). The centers requiring assignment are C(1), C(4), C(4a), and C(5) (the configuration at C(8a) is determined by that at C(1) because of

(16) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 566, 5670.

(17) Among the reagents assayed were triethylsilane, sodium borohydride, tetrabutylammonium cyanide, the trimethylsilyl enol ethers from both pinacolone and acetophenone, allyltributyltin, 2,2-dimethylketene methyl trimethylsilyl acetal, the pyrollidine enamine from pinacolone, and hydroperoxide anion.

Table V. Selected ^{1}H NMR Data for the Cycloadducts[a]

compd	δ C(1)–H	C(4)–H	C(4a)–H	C(5)–H	–OH
15a	3.57 (9.5, 6.3)	3.47 (10.7)		4.26 (br)	
15b	3.47 (9.5, 6.3)	3.96 (9.5)		4.25 (br)	
15c	3.49 (9.5, 6.3)	3.89 (9.6)		4.32 (br)	
15d	3.55 (9.5, 6.3)	3.65 (10.8)		4.27 (br)	
15e	3.80 (9.3, 6.3)	4.20 (9.8)	1.98 (10.8, 10.8, 2.0)	4.19 (br)	
16a	3.56 (8.8, 6.3)	3.72 (3.4)		4.07 (br)	
16b	3.48 (8.5, 6.3)	3.99 (3.2)	2.23 (m)	4.08 (br)	
16c	3.44 (9.5, 6.3)	3.88 (2.8)		4.06 (br)	
16d	3.50 (8.9, 6.3)	3.63 (3.5)		4.05 (br)	
16e	3.77 (9.3, 6.3)	4.41 (3.8)		4.15 (br)	
17a	3.54 (9.3, 6.4)	4.24 (3.9)		3.64 (10.2, 10.2, 4.4)	
17b	3.51 (9.3, 6.3)	4.50 (4.4)	1.68 (10.0, 10.0, 4.4)	3.65 (10.0, 10.0, 4.9)	
17c	3.52 (9.5, 6.3)	4.39 (4.1)	1.70 (m)	3.64 (10.1, 10.1, 4.4)	
17d	3.56 (9.2, 6.3)	3.92 (1.9)		3.62 (m)	
17e	3.82 (9.6, 6.3)	4.94 (4.3)	1.98 (10.3, 10.3, 4.5)	3.71 (10.3, 10.3, 4.6)	
18a	4.14 (11.0, 6.9)	4.35 (3.9)	1.86 (m)		
18b	3.95 (10.7, 6.3)	4.61 (2.0)	1.85 (5.0, 5.0, 2.0)	4.10 (br)	
18c	3.97 (m)	4.51 (1.9)	1.80 (m)	4.20 (br)	
19a	4.47 (10.7, 6.3)	3.97 (2.0)	2.02 (m)	4.20 (br)	5.09 (br)
19b	4.39 (10.5, 6.3)	4.26 (2.0)	2.00 (5.0, 5.0, 2.0)	4.18 (br)	5.29 (br)
19c	4.36 (10.0, 6.0)	4.20 (1.0)	1.96 (m)	4.10 (br)	5.70 (br)
19d	4.44 (10.6, 6.3)	4.13 (4.1)	2.03 (m)	4.22 (br)	5.30 (br)
19e	4.61 (10.4, 6.0)	4.57 (1.7)	2.14 (m)	4.37 (br)	

[a] As a solution in $CDCl_3$, δ (*J*) referenced to $CHCl_3$ at 7.26 ppm. Where *J* is reported, multiplicities are for C(1)–H doublet of quartets, for C(4)–H doublet, and for both C(4a)–H and C(5)–H doublet of doublets.

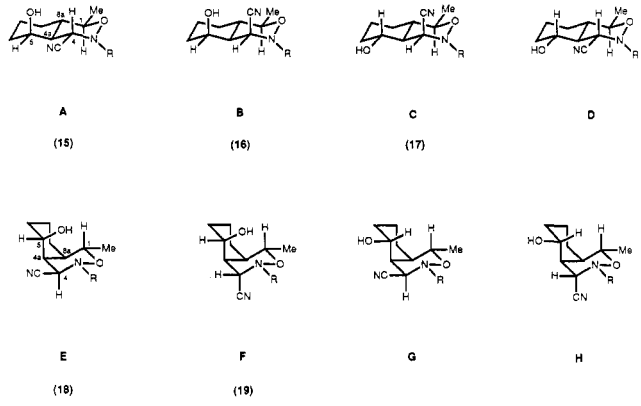


Figure 2. Conformational drawings of the eight possible diastereomers formed from cycloaddition of **13**.

the double-bond geometry—in this case all trans).

Compounds **17** are most easily identified: the trans diaxial coupling constants in the signals for the protons at C(4a) indicate a trans-fused ring system, and the observed coupling constants in the signals for the protons at C(1), C(4), and C(5) indicate them to be disposed axially, equatorially, and axially, respectively. The axial nature of C(5)–H is further established by its chemical shift, which is considerably upfield of all the other isomers (which will be shown to be equatorially disposed at this center). This identifies **17** as compound C (compounds **17** and C are enantiomerically portrayed in Scheme IX and Figure 2 to assist internal comparison).

Compounds **15** also yield easily to analysis. The observed trans-diaxial coupling constants in the signals for the protons at C(1) and C(4) necessitate axial orientations of the protons at C(4a) and C(8a), respectively, the only ones to which they couple. The only stereocenter remaining is C(5), and from the observed chemical shift and lack of a trans-diaxial coupling in the signals for its protons, these must be disposed equatorially. This identifies **15** as compound A.

For both compounds **18** and **19**, the proton at C(4a) is observed to have no trans-diaxial coupling—this rules out remaining structures B and D, which are trans fused, and G and H, which have one proton trans to that at C(4a) in all of their reasonable conformations.[18] This leaves only E and F. Further support for this assignment is the profound downfield shift observed for the protons at C(1) in both these compounds, a result of their enforced proximity to the hydroxyl group (a situation which occurs in none of the other isomers). By this process of elimination and by examination of E and F we have established all of the stereocenters in **18** and **19** but that at C(4) (and as expected the protons at C(1) show a trans-diaxial coupling, while those at C(4) and C(5) do not). Assignment of stereochemistry at C(4) is tentative and relies on the observation that the signals for the protons at C(4) in **18** are shifted upfield of those for **19**, consistent with them being axially disposed in the former (as in E) and equatorially in the latter (as in F). Interestingly, compounds **19** are noticeable for the unique chemical shifts of their hydroxyl protons, which furthermore are very slow to exchange in the presence of D_2O. This is clearly the result of the favorable disposition of the hydroxyl group with respect to hydrogen bonding to the nitrogen.

Only compounds **16** remain, and the lack of trans-diaxial couplings in the signals for the protons at C(4) and C(5) immediately rules out structures D, G, and H; thus, by process of elimination, **16** must be compound B. This assignment is further supported by the similarity in chemical shifts of C(1)–H in **15** (A) and **16**. There is also chemical support for this assignment, since attempted distillation of pure **15c** led to recovery of a 2:1 mixture of **15c** and **16c**. The only center for which an epimerization mechanism exists is the pseudoanomeric position C(4), and this supports the assignment of **15** and **16** as nitrile anomers A and B.

Thus, of the eight possible stereoisomers, five are observed. Isomers D, G, and H could not be identified in any of the reaction mixtures.

4. Attempted Elaboration of Cycloadducts. Considerable effort was directed toward the transformation of the cycloadducts into more usefully functionalized

(18) The disfavored conformers suffer from several 1,3-diaxial interactions.

molecules. Initially, the base-induced fragmentation to iminolactone was investigated.[7,8] However, testing a variety of bases, solvents, and temperatures failed to provide a preparatively useful procedure. While crude products could occasionally be obtained which appeared to be iminolactones, the results were never reproducible, nor were the yields ever greater than a few percent.[19]

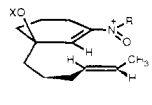
Oxidation of the alcohol to the ketone was also investigated with PCC, PDC, and under Swern conditions. In all of these cases, oxidation appeared to occur with substantial epimerization at both centers C(4) and C(4a). In any case, we did not wish to sacrifice one of our stereocenters as a general procedure for unmasking our cycloadducts, so these reactions were not further investigated.

Hydrogenolysis of the N,O bond in the tetrahydrooxazine was expected to be quite facile. However, hydrogenation (at pressures up to 100 psi) over palladium metal or platinum(II) hydroxide failed to effect any cleavage. Hydrogenation over Raney nickel in a variety of buffers either had no effect, or completely destroyed the starting material. The only tentatively identified product isolated from these reactions, occurring in about 2% yield, was the aldehyde corresponding to reductive hydrolysis of the nitrile. Reductive methods other than hydrogenation were also investigated, however aluminum amalgam, titanium trichloride, and zinc in acetic acid all failed to have any effect.

Finally, in an effort to increase the potential for reduction of the N,O-bond, we attempted to alkylate the nitrogen of the tetrahydrooxazine. However, heating the cycloadduct **15b** in a sealed vial at 60 °C in neat methyl iodide for 24 h resulted only in recovery of unreacted starting material.

Discussion

In the ketonitrone systems, observation of the direct relationship of yield to amount of starting (*Z*)-nitrone is in keeping with similar observations by Riediker[8c] and Eschenmoser.[7a] Apparently the *s-trans*-VNC derived from (*E*)-nitrone is transformed to other products before rotation about the C–N bond can occur.[20] While no such byproducts were identified, ring contraction or alkyl migrations to the electrophilic terminus of the VNC are feasible. the transition state for cyclization is easily deduced from the structure of **4b** and corresponds to the syn-exo conformation (structure i).[21]



i

The predominantly (*Z*)-aldonitrones are superior substrates in the reaction giving up to 72% yield of cyclization products. Analysis of the origin of stereocontrol in these more flexible VNC precursors is more difficult. To begin with, the stereochemistry of the cycloadducts is dependent on four factors. First, the relationship between C(1) and C(8a) is established by the double bond geometry. Second, the relationship of the centers at C(4a) and C(8a) derives from the folding of the sidechain exo or endo with respect to the heterodiene. Third, the relationship between C(5) and C(4a) is determined by the diastereofacial selectivity of attack of the olefin on the heterodiene. Finally, the center at C(4) is created by the topicity of attack of cyanide ion on the dihydrooxazinium cation.

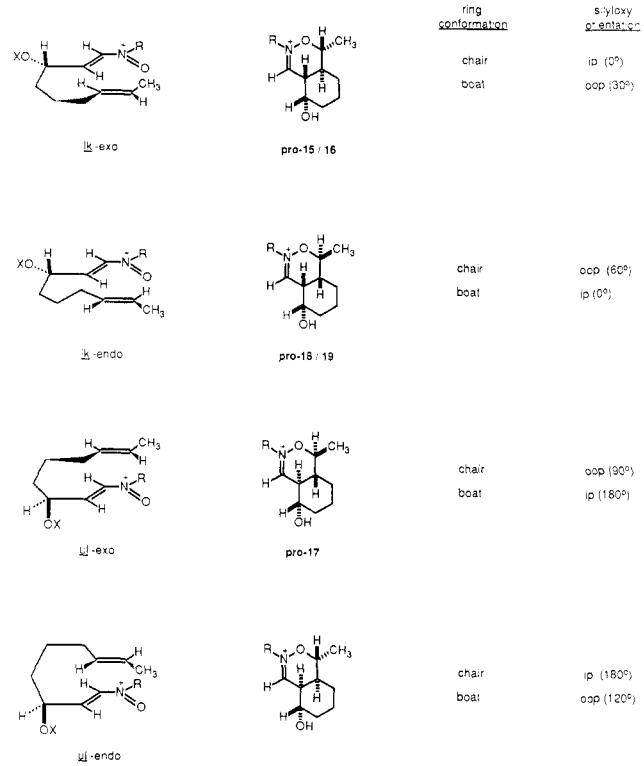


Figure 3. Conformational analysis of vinylnitrosonium cations.

In all of the cyclization products a trans relationship of H–C(1) and H–C(8a) was found as expected from a trans olefin.[7d] The relationship of the stereocenters at C(8a), C(4a), and C(5) can be understood by combination of the two variables mentioned above to generate four limiting reactive conformations[22] (Figure 3). Since two variables are considered, we require two descriptors to define the conformations. The first descriptor identifies the diastereoface selection by specifying the relationship between the resident stereocenter (*S* throughout) and the prochirality at the adjacent center (*Re* or *Si*). Extending the suggestions of Seebach and Prelog[23] we define *lk* and *ul* as the (*S*,*si*) and (*S*,*re*) pairs, respectively. As portrayed in Figure 3, attack of the dienophile form below is an *S*, *si*, or *lk* combination while attack from above is *ul*. The second descriptor identifies the folding of the sidechain, exo or endo with respect to the heterodiene. Thus, exo folding leads to trans-fused products while endo folding leads to cis. It can be seen that each reactive conformation leads to a unique cyclization product. These dihydrooxazinium cations are identified as the progenitors of the isolated products *pro*-**15**–**19**. Thus we can now relate the conformations with the products by focusing on the stereochemical relationships of the hydrogens in the following way: *lk*, exo → *pro*-**15**/**16**; *lk*, endo → *pro*-**18**/**19**; *ul*, exo → *pro*-**17**; the product from *ul*, endo was not observed. The yields of the cycloadducts with respect to the transition state from which they arose are summarized in Table VI.

(19) We speculated that the reaction might be complicated by the presence of the unprotected axial alcohol at C(5) and hence synthesized the trimethylsilyl protected product from **15** with Me_3SiOTf/Et_3N. However, we met with no more success in fragmenting this product than with **15**.

(20) The barrier to this rotation is not known, however, since it breaks the conjugation of a 4π system bearing a formal positive charge it is not expected to be insignificant.

(21) This is exactly analogous to very similar nitrosoalkene–olefin cycloadditions. See ref 3a.

(22) The $E_{C=C}$ geometry of the heterodiene is assumed throughout. While the $Z_{C=C}$ geometry is less likely, it cannot rigorously be ruled out.

(23) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.

Table VI. Yield of Products from Specific Conformations

starting material	yield, %					
	lk-exo **15 + 16**	*lk-endo* **18 + 19**	*ul-exo* **17**	*ul-endo*	*exo/endo*	*lk/ul*
13a	60	7	5	–	9.3:1	13:1
13b	56	2	4	–	30:1	15:1
13c	48	6	7	–	9.2:1	7.7:1
13d	34	9	8	–	4.7:1	5.4:1
13e	44	2	5	–	25:1	9.2:1

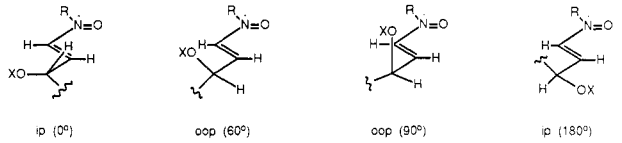


Figure 4. Allylic stereodynamics of the trimethylsilyloxy group.

To understand the origins of the preferences for the conformations leading to the major products, three additional components within each of the four conformations must be considered: (1) nonbonded interactions with the nitrone alkyl ligand; (2) two possible staggered conformations for each sidechain fold, one leading directly to a chair, the other to a boat conformation in the product and; (3) the allylic stereodynamics of the silyloxy substituent.

Inspection of Dreiding models suggests that nonbonded interaction with the nitrone ligand is only important for *E* olefins in the exo mode. However, the lack of dependence of exo/endo selectivity on the bulk of R (see Table VI) suggests that this interaction is weak. Only when R = neopentyl (**13d**) is the fraction of endo-mode cyclization significant (20%).

For each of the two diastereoface combinations (*lk* and *ul*) there are exo and endo foldings of the chain. First-order analysis suggests that exo folding should be preferred sterically due to interactions of the allylic methylene of the dienophile and the heterodiene in the transition state. This expectation is borne out in experiment: the exo/endo ratio (i.e., trans/cis ratio) is 5–30:1. No products from endo folding were observed in the *ul* family.

The reasons for the preponderance of products derived from the *lk* over the *ul* transition states (5–15:1) are more subtle. To evaluate the steric and stereoelectronic contributions of the silyloxy substituent it is necessary to make certain assumptions about its disposition for each of the exo and endo folds. As shown in Figure 3 two conformations of the sidechain are available for each fold leading to chair or boat conformations of the product. In addition these two conformations place the silyloxy substituent in a different position with respect to the heterodiene plane. We have identified two limiting orientations which are defined as in plane (ip) and out of plane (oop). Further specification focuses on the dihedral angle between the silyloxy group and the heterodiene, looking down the sp^3–sp^2 bond. These relationships are illustrated in Figure 4.

It is reasonable to assume throughout, from a conformational perspective, that the fold which leads directly to a chair will be the lower energy pathway. On the other hand, the preferred disposition of the allylic silyloxy group is less certain. Moreover, since the oxygen is a highly polarizing substituent, there are expected to be conformation-dependent activating effects on the double bond. The ground state conformations of allylic alcohols and ethers have been studied both experimentally[24] and computationally.[25] From microwave[26] and ^{1}H NMR[27] spectroscopy the two most populated conformations are the skewed (oop (60°)) and synplanar (ip (0°)) arrangements. Further the energy separation and barriers to interconversion of these states are dependent on the electronic nature of the double bond.[28] Most convincing evidence comes from Lessard[29] who demonstrated the change in axial preference of 7-substituted 2-methoxymethylenecyclohexanes as a function of methylene substituent (methoxy, >95%, axial; cyano, 13%, axial).[30]

We can now understand the selective formation of products from *lk* over *ul* transition states by assuming a preference for in-plane (0°) orientation of the silyloxy group due to the strong inductive and mesomeric electron withdrawing properties of the nitrosonium group. The major isomer (*pro*-**15**/**16**) arises from that conformation which simultaneously satisfies both criteria for ring conformation and silyloxy orientation. The minor isomers (*pro*-**18**/**19** and *pro*-**17**) arise from conformations which lead to chairs but are destabilized by nonideal alignment of the silyloxy group. Finally, the absence of products from the *ul*-endo transition state is a consequence of the highly disfavored[31] ip (180°) orientation of the silyloxy group in the chair conformation of the side chain.

Support for the assumption of a strong ip (0°) preference in this system can also be found in recent theoretical studies. Houk[32] has discussed the electronic consequences of these conformations in the ground state and in the transition states of reactions with nitrile oxides.[33,34] More recently Hehre and Kahn[35] have calculated the confor-

(24) For a review of rotational isomerism about the sp^2–sp^3 bond see: Karabatsos, G. J.; Fengolio, D. J. In *Topics in Stereochemistry*; Eliel, E.; Allinger, N. L., Eds.; Wiley: New York, 1970; Vol. 5, pp 167–203.

(25) (a) Kao, J.; Katz, T. *J. Mol. Struct.* **1984**, *108*, 229. (b) Aspiala, A.; Lotter, T.; Murto, J.; Räsänen, M. *J. Chem. Phys.* **1983**, *79*, 4183.

(26) (a) Murty, A. N.; Curl, R. F., Jr. *J. Chem. Phys.* **1967**, *46*, 4176. (b) Lum, D. K.; Bauman, L. E.; Mallory, T. B., Jr.; Cook, R. L. *J. Mol. Struct.* **1978**, *50*, 1. (c) Horn, A.; Markstokk, K.-M.; Mollendal, H.; Priebe, H. *Acta Chem. Scand.* **1983**, *A37*, 679. (d) Smith, Z.; Carballo, N.; Wilson, E. B.; Markstokk, K.-M.; Mollendal, H. *J. Am. Chem. Soc.* **1985**, *107*, 1951.

(27) (a) Bothner-By, A. A.; Ebersole, S. J.; Castellano, S.; Günther, J. *J. Am. Chem. Soc.* **1966**, *88*, 2466. (b) Martin, M. L.; Martin, G. J.; Caubere, P. *Bull. Soc. Chim. Fr.* **1964**, 3066. (c) Gonnella, N. C.; Nakanishi, K.; Martin, V. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 3775. (d) Stothers, J. B.; Brouwer, H. *Can. J. Chem.* **1972**, *50*, 1361.

(28) Tronchet, J. M. J.; Xuan, T. N. *Carbohydrate Res.* **1978**, *67*, 469. (b) Beaudet, R. A.; Wilson, E. B. *J. Chem. Phys.* **1962**, *37*, 1133. (c) Siegel, S. *Ibid.* **1957**, *27*, 289. (d) Beaudet, R. A. *Ibid.* **1963**, *38*, 2548. (e) Laurie, V. W. *Ibid.* **1960**, *32*, 1588.

(29) Lessard, J.; Saunders, J. K.; PhanViet, M. T. *Tetrahedron Lett.* **1982**, *23*, 2059.

(30) For another example of this phenomenon in α-halo oximes (vinylogous anomeric effect) see ref 5.

(31) Antiperiplanar conformations of allylic halides, ethers, or alcohols are only observed in systems with a large cis substituent, see ref 28b–e.

(32) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. R.; Jäger, V.; Schohe, R.; Franczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

(33) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1984**, *49*, 2762 and references cited therein.

(34) Many other reactions of allylic ethers and alcohols show diastereoface selectivity and various explanations have been advanced. (a) Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094 and references cited therein. (b) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. (c) Giese, B.; Bartman, D. *Tetrahedron Lett.* **1985**, *26*, 1197. (d) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. (e) Trost, B. M.; Lynch, J.; Renaut, P. *Tetrahedron Lett.* **1985**, *26*, 6313. (f) Franck, R. W.; John, T. V.; Olejniczak, K. *J. Am. Chem. Soc.* **1982**, *104*, 1106.

(35) Kahn, S. D.; Hehre, W. J. *Tetrahedron Lett.* **1985**, *26*, 3650.

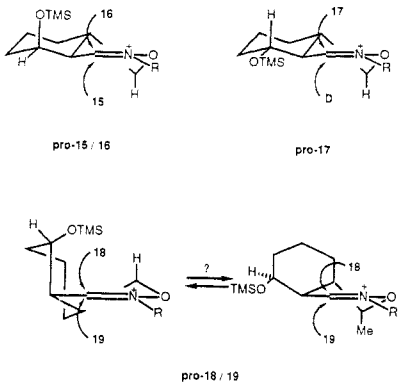


Figure 5. The three dihydrooxazinium cations.

mational energy surface for 3-buten-2-ol and have advanced a predictive model for the conformational dependence of reactivity of the olefin. These authors discuss the synplanar preference in terms of a "homoallyl anion" resonance ($n_O \rightarrow \pi^*_{CC}$) between the p-type oxygen lone pair and the π^*_{CC} orbital. An alternative picture invokes a hyperconjugative delocalization of σ-electron density (from higher lying σ_{CC} and σ_{CH} bonds) in a staggered fashion with τ-bonds.[36]

It should not be misconstrued that this is a violation of the Curtin–Hammett principle.[37] In these situations one must always be cognizant of the balance between energy cost (ground-state raising) of a higher lying conformation and the energy gain (transition-state lowering) of enhanced reactivity afforded by reaction via this conformation. Clearly an oop conformation will have a more electrophilic double bond and should react faster towards nucleophiles (olefins) than the more stable ip (0°) conformation. However, because of the extreme electrophilicity of the heterodiene in this case the oop conformations are further destabilized and the heterodiene is already sufficiently reactive that the incremental gain of σ^*_{CO} hyperconjugation is negligible.[38]

It is noteworthy that similar behavior has been documented in intramolecular Diels–Alder reactions only under Lewis acid catalysis. In contrast to the low diastereoselectivity observed on thermal cyclization of 7-(silyloxy)-undeca-2,8,10-trienoates[39] is the extreme *lk*-exo selectivity in the $EtAlCl_2$-catalyzed cyclization of the corresponding aldehydes.[40] Also of note is the dependence on the nature of the 7-substituent, silyloxy being much more selective than methoxymethoxy.[40] This argues against the importance of "homoallyl anion" resonance[35] as the origin for the in-plane stabilization.

The final question of stereochemistry which remains to be addressed is that of the stereocenter at C(4). The topicity of attack of cyanide anion upon the dihydrooxazinium cation will be dictated by two factors: the first a simple consideration of whether approach to a given face is sterically accessible, and the second an electronic consideration, namely the kinetic anomeric effect.[7d,8] This effect is manifested by a preference for cyanide to attack from an axial position.

The dihydrooxazinium cations, *pro*-**15**/**16**, *pro*-**17**, and *pro*-**18**/**19**, are drawn in conformational perspective in Figure 5. Compound **17** arise from the expected axial attack of cyanide while *unobserved isomer D* would result from contraanomeric attack. Since *pro*-**18**/**19** is conformationally mobile, attack upon either face of the cation can occur with anomeric stabilization, and the anomeric ratio observed in the products may reflect the conformational equilibrium. Analysis of the anomeric ratios for **15** and **16** is somewhat more complex. In analogy to *pro*-**17**, attack of cyanide might be expected to give only **16**. However, approach of cyanide to the preferred face of the cation is hindered by the bulk of the (trimethylsilyl)oxy group, hence a mixture of anomers is obtained.[41]

Conclusions

α,β-Epoxyketonitrones may be used to generate VNC's which cyclize entirely through a single predictable transition state. However, the difficulty of controlling nitrone geometry in the face of a thermodynamic preference of (*E*)-nitrone, and the requirement of (*Z*)-nitrone for successful cycloaddition limits the use of this method. α,β-Epoxyaldonitrones generate VNC's much more efficiently and give higher yields of cycloaddition products (51–72%). In all cases the dienophile geometry is preserved in the product stereochemistry (trans). For cyclohexylnitrones, the reaction is highly selective for formation of trans-fused products (30:1) and axially disposed hydroxyl groups (15:1). This selectivity can be understood in terms of the preferred in plane conformation of the silyloxy group next to the heterodiene. The use of this methodology is however complicated by its high dilution conditions and the difficulty of elaborating the cycloadducts. Although the use of analogous nitroalkenes solves some of these problems,[4] VNC technology is still useful if oxygen functionality is desired in the cycloadduct in the proper position.

Experimental Section

Bulb-to-bulb distillations were done on a Büchi GKR-50 kugelrohr; boiling points (bp) refer to air bath temperatures and are uncorrected. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Analytical TLC was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV light, phosphomolybdic acid, iodine, sulfuric acid/methanol, vanillin, and/or 2,4-DNP solution. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: cyclohexane (cHex), hexane, pentane, dichloromethane ($CaCl_2$), ether ($CaSO_4/FeSO_4$), and ethyl acetate (K_2CO_3). Dry solvents were distilled freshly before use. Benzene, hexane, dichloromethane, and dimethyl sulfoxide were distilled from powdered calcium hydride. All other reagents were recrystallized or distilled as necessary. Column (flash) chromatography was performed by the method of Still[42] (32–63-μm silica gel, Woelm). Analytical gas chromatography was performed on a Varian 3700 chromatograph fitted with a flame ionization detector (N_2 carrier gas, 30 mL/min) using a packed column of 11% QF-1 on 60-80 Chromosorb G (6 ft by $^1/_8$ in.). Retention times (T_R) and integrals were obtained from a Hewlett Packard 3390 recorder. Diisobutylaluminum hydride (DIBAH) was titrated iodometrically. Brine refers to a saturated aqueous solution of sodium chloride. All reactions were performed in oven (140 °C) or flame-dried glassware under an inert atmosphere of dry N_2 or Ar. Infrared spectra (IR) were obtained on either a Nicolet 7199C

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(38) This is also related to the exothermicity of the reaction which, by the Hammond Postulate, suggests an early transition state with much educt character.

(39) (a) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200. (b) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, *26*, 4327. (c) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611. (d) Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251.

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(41) Anomerization of the products under the slightly basic conditions is also a possibility.

(42) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

FT-IR, Perkin-Elmer 1320 IR, or IBM FTIR-32 spectrophotometer. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67–100%), m (medium, 34–66%), w (weak, 0–33%). ^1H NMR spectra were recorded on either Varian EM-390 (90 MHz ^1H), Varian XL-200 (200 MHz ^1H), Varian HA-220 (220 MHz ^1H), or Nicolet NT-360 (360 MHz ^1H) spectrometers in deuterochloroform with chloroform as an internal standard (δ 7.26) unless otherwise stated. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broadened), and exch (D_2O exchangeable). Coupling constants, J, are reported in hertz. Mass spectra were obtained on a Varian MAT CH-5 spectrometer with ionization voltages of 10 and 70 eV. Data are reported in the form m/z (intensity relative to base 100). High-resolution mass and fast atom bombardment spectra were obtained on either a Varian MAT-731 or MAT-311A spectrometer. Elemental combustion analyses were performed by the University of Illinois Microanalytical Service Laboratory.

***rel*-(2*R*,3*S*)-2,3-Epoxy-*N*-methyl-3-((*E*)-4-hexenyl)cyclohexan-1-one Nitrone[43] (2a).** To a magnetically stirred solution of **1**[5] (323 mg, 1.66 mmol) in absolute ethanol (5 mL) were added $NaHCO_3$ (716 mg, 8.52 mmol) and *N*-methylhydroxylamine hydrochloride (149 mg, 1.78 mmol). After 18 h the heterogeneous mixture was filtered to remove the $NaHCO_3$ and concentrated and the residue chromatographed on silica gel (EtOAc/MeOH 2/1) to afford 359 mg (97%) of **2a** as a mixture of geometrical isomers: ^1H NMR (90 MHz, $CDCl_3$) 5.32 (m, 2 H, –HC=CH–), 4.32 (s, 0.2 H, $HC(2)_Z$), 3.84 (s, 2.4 H, $-NCH_{3E}$), 3.68 (s, 0.6 H, $-NCH_{3Z}$), 3.49 (s, 0.8 H, $HC(2)_E$), 3.10–1.40 (m, 15 H); IR ($CHCl_3$) 2910 s, 1590 m, 1450 m, 1360 m, 1225 s, 1115 m, 1058 w, 969 s, 912 s; MS (70 eV) 151 (42), 150 (12), 148 (11), 138 (13), 137 (16), 136 (23), 126 (16), 125 (14), 124 (12), 123 (21), 122 (18), 121 (24), 120 (17), 110 (26), 109 (13), 107 (11), 97 (28), 95 (29), 93 (17), 91 (19), 82 (14), 81 (29), 80 (13), 79 (25), 77 (19), 69 (29), 68 (92), 67 (41), 65 (14), 55 (64), 54 (15), 53 (31), 43 (31), 42 (30), 41 (100), 39 (44); high-resolution MS (FAB) calcd for $C_{13}H_{22}NO_2$ + H 224.1651, found 224.1632.

***rel*-(2*R*,3*S*)-*N*-Cyclohexyl-2,3-epoxy-3-((*E*)-4-hexenyl)cyclohexan-1-one Nitrone (2b).** To a magnetically stirred solution of **1**[5] (246 mg, 1.17 mmol) in absolute ethanol (6 mL) were added $NaHCO_3$ (495 mg, 5.89 mmol) and *N*-cyclohexylamine hydrochloride (356 mg, 2.34 mmol). After 25 h the heterogeneous mixture was filtered to remove the $NaHCO_3$, concentrated, poured into 20 mL of commercial pH 4.0 buffer, and extracted with ether (3 × 20 mL). The ether extracts were washed with pH 4.0 buffer (2 × 20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated, and the residue was chromatographed on silica gel (EtOAc) to afford 329 mg (91%) of **2b** as a 60:40 *E*:*Z* mixture of geometrical isomers: ^1H NMR (220 MHz, $CDCl_3$) 5.40 (m, 2 H, –HC=CH–), 4.42 (s, 0.4 H, $HC(2)_Z$), 4.40–4.10 (m, 1 H, HC(1″)) 3.58 (s, 0.6 H, $HC(2)_E$), 3.0–1.0 (m, 25 H); IR ($CHCl_3$) 2940 s, 2855 s, 1721 w, 1450 m, 1370 m, 1141 m, 1083 m, 972 m, 895 m; MS (70 eV) 259 (21), 258 (17), 230 (11), 216 (17), 204 (36), 192 (17), 191 (20), 190 (16), 189 (11), 178 (19), 176 (37), 148 (10), 122 (24), 96 (18), 93 (14), 91 (18), 83 (27), 81 (26), 80 (11), 79 (23), 77 (17), 69 (18), 68 (22), 67 (27), 56 (13), 55 (100), 54 (17), 53 (20), 41 (95), 39 (20); high-resolution MS (FAB) calcd for $C_{18}H_{30}NO_2$ + H 292.2277, found 292.2253.

***rel*-(3*R*,3a*S*,6a*S*,9a*S*,9b*S*)-9a-Cyano-6a-hydroxyl-1,3-dimethylperhydronaphtho[8,8a-*c*:8a,1-*d*][1,2]oxazine (4a).** To a cold (0 °C), magnetically stirred solution of **2a** (355 mg, 1.59 mmol) in dry dichloromethane (37 mL) was added trimethylsilyl trifluoromethanesulfonate (707 mg, 3.18 mmol) and the solution then warmed to room temperature. After 5 h the yellow-brown mixture was cooled to 0 °C and treated with a solution of potassium cyanide (1.24 g, 19.1 mmol) in water (5 mL). After 10 min the mixture was poured into water (100 mL) and extracted with ether (3 × 100 mL). The ether extracts were washed in series with saturated aqueous $NaHCO_3$ (100 mL), water (2 × 100 mL), and brine (100 mL), dried (Na_2SO_4), and concentrated, and the residue was chromatographed on silica gel (cHex/EtOAc 1/1) to afford 52 mg (11%) of **4a** as the only isolable product: ^1H NMR (220 MHz, $CDCl_3$) 3.61 (m, 1 H, HC(3)), 2.74 (s, 3 H, $-NCH_3$), 2.07–1.31 (m, 15 H); IR ($CHCl_3$) 3595 m, 3480 w, 3015 w, 2940 s, 2870 s, 2220 w, 1461 m, 1452 s, 1380 m, 1370 m, 1337 w, 1318 w, 1223 s, 1212 s, 1171 m, 1119 m, 1098 m, 1078 m, 1003 m, 975 m, 957 m, 928 s, 904 m,; MS (70 eV) 250 (M^+, 48), 188 (11), 187 (11), 186 (15), 161 (13), 160 (13), 134 (12), 133 (13), 95 (21), 91 (15), 79 (12), 77 (11), 74 (100), 68 (20), 67 (13), 55 (14), 43 (16), 42 (13), 41 (24).

***rel*-(3*R*,3a*S*,6a*S*,9a*S*,9b*S*)-9a-Cyano-1-cyclohexyl-6a-hydroxyl-3-methylperhydronaphtho[8,8a-*c*:8a,1-*d*][1,2]oxazine (4b).** To a magnetically stirred solution of **2b** (290 mg, 0.995 mmol) in dry dichloromethane (20 mL) was added trimethylsilyl trifluoromethanesulfonate (442 mg, 1.99 mmol). After 50 min the reaction was cooled to 0 °C and treated with a solution of potassium cyanide (650 mg, 9.95 mmol) in water (3 mL). After stirring for 15 min the mixture was poured into water (60 mL) and extracted with ether (3 × 100 mL). The ether extracts were washed with saturated aqueous $NaHCO_3$ (60 mL), water (60 mL), and brine (60 mL), dried (Na_2SO_4), and concentrated, and the residue was chromatographed on silica gel (cHex/EtOAc 2/1) to afford 120 mg (38%) of **4b** as the only isolable product. Analytical data are reported for a sample recrystallized from ether/hexane: mp 146.5–148 °C; ^1H NMR (200 MHz, CCl_4/C_6D_6, 60 °C) 3.39 (dq, J = 8.6, 6.4, 1 H, HC(3)), 3.00 (br, 1 H, HC(1′)), 1.84 (d, J = 11.4, 1 H, HC(9b)), 1.08 (d, J = 6.4, 3 H, $C(3)CH_3$), 2.20–0.80 (m, 25 H); ^1H NMR (200 MHz, CCl_4/C_6D_6 + Eu(fod)$_3$, 60 °C) 2.20 (d, J = 11.4, HC(6b)); IR ($CHCl_3$) 3592 w, 3480 w, 3010 w, 2937 s, 2855 m, 2220 w, 1450 m, 1379 w, 1368 w, 1211 w; MS (10 eV), 319 (M + 1, 28), 318 (M^+, 100), 276 (14), 275 (14), 273 (23), 257 (12), 256 (13), 255 (25), 248 (13), 241 (43), 236 (12), 231 (36), 230 (35), 229 (64), 228 (25), 227 (13), 218 (38), 217 (12), 210 (30), 209 (12), 206 (32), 195 (18), 192 (29), 179 (16), 178 (38), 177 (18), 176 (16), 175 (11), 174 (10), 160 (14), 147 (23), 146 (17), 119 (11), 98 (11), 97 (25), 60 (25), 56 (23). Anal. Calcd for $C_{19}H_{30}N_2O_2$: C, 71.66; H, 9.50; N, 8.80. Found: C, 72.00; H, 9.41; N, 8.80.

***rel*-(2*R*,3*S*)-2,3-Epoxy-3-((*E*)-4-hexenyl)cyclohexan-1-one (*tert*-Butyldimethylsilyl)oxime (6).** This compound was prepared by the general method C for silyloximation:[5] yield 97%, 56:44 *E*/*Z*, bp 120 °C/0.06 torr; ^1H NMR (90 MHz) 5.39 (m, 2 H, HC(4′), HC(5′)), 4.04 (s, 0.44 H, $HC(2)_Z$), 3.40 (s, 0.56 H, $HC(2)_E$), 2.85–1.30 (15 H), 1.04 (s, 9 H, $(CH_3)_3CSi$), 0.30 (s, 6 H, $(CH_3)_2Si$); IR 2860 w, 1355 w, 1242 m, 970 w, 950 s.

(*E*)-5-Heptenenitrile (8). To a vigorously stirred mixture of mesylate **7** (1.0 g, 5.6 mmol) in water (3 mL) were added potassium cyanide (1.1 g, 16.7 mmol) and 3 drops of Aliquat 336. After 5 h the mixture was refluxed for 3 h, stirred at room temperature for 4 h, poured into water (10 mL), and extracted with ether (3 × 12 mL). The ether extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated, and the residue was distilled to afford 0.56 g (93%) of **8**: bp 90 °C/25 torr; ^1H NMR (90 MHz, $CDCl_3$) 5.45 (m, 2 H, –HC=CH–), 2.20 (m, 4 H), 1.81 (m, 5 H). These data agree with those reported in the literature.[44]

Ethyl (*E*,*E*)-Nona-2,7-dienoate (9). To a cold (–50 °C), magnetically stirred solution of nitrile **8** (5.0 g, 45.8 mmol) in dry hexane (400 mL) was added DIBAH (1.01 M in CH_2Cl_2, 65.0 mL). The solution was stirred for 10 min at –50 °C, then saturated aqueous ammonium chloride (50 mL) was added, and after 10 min 5% aqueous sulfuric acid (100 mL) was added. The reaction mixture was extracted with ether (2 × 350 mL), and the ether extracts were washed with saturated aqueous $NaHCO_3$ (350 mL) and brine (350 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in 1,2-dichloroethane (100 mL) and ethyl triphenylphosporanylideneacetate (16.0 g, 5.8 mmol) was added. The solution was refluxed 5 h and then concentrated on the rotary evaporator. The residue was dissolved in a minimal volume of dichloromethane, chromatographed on silica gel (hexane/EtOAc 5/1), and distilled to afford 5.69 g (68% overall) of **9**: bp 84 °C/1.3 torr; ^1H NMR (200 MHz, $CDCl_3$) 6.90 (dt, J = 15.7, 7.0, 1 H, HC(3)), 5.80 (dt, J = 15.7, 1.6, 1 H HC(2)), 5.40 (m, 2 H, HC(7) and HC(8)), 4.10 (q, J = 7.0, 2 H, $H_2C(1')$), 2.20 (m, 2 H), 1.90 (m, 2 H), 1.60 (dd, J = 3.5, 1.1, 3 H, $H_3C(9)$), 1.50 (m, 2 H), 1.20 (t, J = 7.0, 3 H, $H_3C(2')$); IR ($CHCl_3$) 2940s, 2860 s, 1700 s, 1650 s, 1450 s, 1370 s, 1270 s, 1160 s, 1120 s, 1095 s, 1040 s, 970 s, 870

(43) The name nitrone in this paper is being used in the derivative sense rather than in the substitutive, implying the replacement of an oxo functionality by the C=NHO component of nitrone (H_2C=NHO).

(44) Lallemand, J. Y.; Oranga, M. *Tetrahedron Lett.* **1975**, *16*, 585.

m; MS (10 eV) 182 (M^+, 9), 137 (14), 127 14), 114 (100), 109 (26), 108 (22), 99 (26), 95 (15), 94 (27), 93 (13), 86 (53), 82 (13), 81 (21), 79 (14), 69 (29), 68 (51), 67 (41), 55 (25), 43 (12), 41 (33), 29 (13); TLC R_f 0.49 (hexane/EtOAc: 3/1); GC T_R 6.45 min, program, 90 °C (2 min), 25 °C/min, 230 °C. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.51; H, 10.02.

(*E*,*E*)-Nona-2,7-dien-1-ol (10). To a cold (6 °C), magnetically stirred solution of ester **9** (0.1 g, 0.55 mmol) in dry benzene (4 mL) was added DIBAH (1.01 M in CH_2Cl_2, 2.17 mL). The reaction mixture was warmed to room temperature, quenched with saturated aqueous ammonium chloride (2.0 mL) and 5% aqueous sulfuric acid (8.0 mL), and then extracted with ether (2 × 25 mL). The ether extracts were washed with 5% aqueous sulfuric acid (25 mL), saturated aqueous $NaHCO_3$ (25 mL), water (25 mL), and brine (25 mL). The dried (K_2CO_3) extracts were concentrated, and the residue was distilled to afford 75 mg (97%) of **10**: bp 100 °C/0.2 Torr; ^1H NMR (200 MHz, $CDCl_3$) 5.60 (m, 2 H), 5.40 (m, 2 H), 4.10 (m, 2 H, $H_2C(1)$), 2.00 (m, 4 H), 1.60 (dd, J = 4.7, 1.3, 3 H, $H_3C(9)$), 1.40 (m, 2 H), 1.30 (t exch, J = 5.7, 1 H, –OH); IR ($CHCl_3$) 3620 m, 3460 m, 3010 s, 2940 s, 2870 s, 1670 w, 1455 m, 1440 m, 1380 m, 1225 m, 1090 m, 975 s; MS (10 eV), 109 (11), 107 (12), 96 (12), 94 (14), 93 (25), 84 (18), 83 (17), 81 (23), 80 (22), 79 (18), 70 (12), 69 (25), 68 (100), 67 (54), 57 (17), 56 (17), 55 (61), 54 (13), 41 (50), 29 (11); TLC R_f 0.52 (hexane/EtOAc 1/1); GC T_R 4.97 min, program, 90 °C (2 min), 25 °C/min, 230 °C. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.71, H, 11.57.

(*E*)-*trans*-2,3-Epoxynon-7-en-1-ol (11). To a magnetically stirred solution of **10** (3.86 g, 27.5 mmol) in dry benzene (20 mL) were added vanadyl acetylacetonate (0.15 g, 0.55 mmol) and 90% *tert*-butyl hydroperoxide (4.6 mL, 41.3 mmol). The deep red mixture was stirred for 6 h at 20 °C. The reaction mixture was concentrated and the residue chromatographed on silica gel (hexane/EtOAc 3/2) to afford small amounts of starting material, (*E*,*E*)-2,7-nonadienal, and the desired product which was distilled to afford 3.88 g (90%) of **11** as a white wax: mp 30–31 °C; bp 110 °C/0.02 torr; ^1H NMR (200 MHz, $CDCl_3$) 5.40 (m, 2 H, –HC=CH–), 3.90 (m, 1 H, HC(2)), 3.60 (m, 1 H, HC(3)), 2.90 (m, 2 H, $H_2C(1)$), 2.00 (m, 2 H), 1.80 (br exch, 1 H, –OH), 1.60 (d, J = 4.1, 3 H, $H_3C(9)$), 1.50 (m, 4 H); IR ($CHCl_3$) 3600 m, 3460 m, 3000 s, 2940 s, 2860 s, 1615 w, 1505 s, 1380 m, 1220 m, 1080 m, 1030 m, 975 s, 910 s; MS (10 eV), 81 (11), 68 (100), 67 (32), 55 (19); TLC R_f 0.37 (hexane/EtOAc 1/1). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.97; H, 10.24.

(*E*)-*trans*-2,3-Epoxynon-7-enal (12). To a magnetically stirred solution of alcohol **11** (4.27 g, 27.3 mmol) in dry DMSO (200 mL) were added sequentially dicyclohexylcarbodiimide (22.6 g, 109 mmol) and pyridinium *p*-toluenesulfonate (3.43 g, 13.7 mmol). After 16 h oxalic acid dihydrate (10.3 g, 81.9 mmol) was added *carefully*. The resulting mixture was vigorously stirred until no further gas evolution was observed. The mixture was filtered through a Celite pad with large volumes of ether. The filtrate was poured into water (300 mL) and extracted with ether (5 × 300 mL). The ether extracts were washed with water (300 mL) and brine (200 mL). The dried (K_2CO_3) extract was concentrated, and the residue was distilled to afford 3.07 g (73%) of **12** as a colorless, mobile liquid: bp 80 °C/0.5 torr; ^1H NMR (200 MHz, $CDCl_3$) 9.00 (d, J = 6.3, 1 H, HC(1)), 5.40 (m, 2 H, –HC=CH–), 3.20 (dt, J = 1.7, 5.4, 1 H, HC(3)), 3.10 (dd, J = 6.3, 1.7, 1 H, HC(2)), 2.00 (m, 2 H), 1.60 (m, 7 H); IR (CCl_4) 3025 m, 2940 s, 2859 s, 2818 m, 2732 w, 1732 s, 1696 w, 1653 w, 1437 s, 1379 m, 1293 w, 1213 w, 1183 w, 1146 m, 1075 w, 968 s, 855 s; MS (10 eV) 69 (11), 68 (100), 67 25), 55 (31), 41 (18); TLC R_f 0.46 (hexane/EtOAc 2/1); GC T_R 6.78 min, program, 70 °C (2 min), 30 °C/min, 230 °C; high resolution MS calcd for $C_9H_{14}O_2$ 154.0994, found 154.0991.

(*E*)-*anti*-2-Chloro-*N*-cyclohexyl-3-hydroxynon-7-enal (*Z*)-Nitrone (14). To a slurry of *N*-cyclohexylhydroxylamine hydrochloride (30 mg, 0.2 mmol) and magnesium sulfate (95 mg, 0.78 mmol) in dry dichloromethane (1 mL) was added aldehyde **12** (30 mg, 0.2 mmol). The reaction mixture was stirred for 5 h, filtered, and concentrated, and the residue crystallized from ether to afford 40 mg (71%) of **14** as light yellow crystals: mp 97–99 °C; ^1H NMR (200 MHz, $CDCl_3$) 6.98 (d, J = 7.3, 1 H, HC(1)), 5.35 (m, 2 H, –HC=CH–), 5.17 (dd, J = 7.0, 3.1, 1 H, HC(2)), 3.85 (m, 1 H, HC(3)), 3.70 (tt, J = 11.4, 3.8, 1 H, HC(1′)), 2.71 (br exch, 1 H, –OH), 2.00–1.00 (m, 19 H); IR ($CHCl_3$) 3580 m, 3360 m, 3000 s, 2940 s, 2860 s, 1580 m, 1455 s, 1380 m, 1345 m, 1300 m, 1220 m, 1160 m, 1145 m, 1080 m, 972 s, 900 m; MS (10 eV), 289 (M + 2, 0.8), 287 (M^+, 2.4), 177 (32), 176 (11), 175 (98), 104 (27), 95 (34), 93 (100), 83 (96), 82 (13), 70 (14), 68 (15), 67 (14), 56 (16), 55 (67), 41 (13), 36 (12); TLC R_f 0.43 hexane/EtOAc 1/1. Anal. Calcd for $C_{15}H_{26}ClNO_2$: C, 62.59; H, 9.11; N, 4.87. Found: C, 62.20, H; 9.35; N, 4.80.

General Procedures for Synthesis of (*E*)-*trans*-*N*-Alkyl-2,3-epoxynon-7-enal (*Z*)-Nitrones (13). Method A. To a magnetically stirred solution of triethylamine (4.0 equiv) in dry dichloromethane (0.87 M) were added sequentially the *N*-alkylhydroxylamine hydrochloride (1.0 equiv), after 5 min a spatula of 4-Å sieves, and again after 5 min aldehyde **12** (1.0 equiv) either neat or as a solution in a minimal volume of dry dichloromethane. When TLC monitoring indicated completion (1–4 h), the mixture was filtered. The filtrate was poured into commercial pH 4.0 buffer and extracted with 2 volumes of dichloromethane. The dichloromethane layers were washed with one volume each of water and brine. The dried (K_2CO_3) organic extract was concentrated and the residue crystallized from pentane (R = cHex), pentane/ether (R = Me), or chromatographed on silica gel (EtOAc) (R = neopentyl).

Method B. To a magnetically stirred solution of aldehyde **12** (1.0 equiv) in dry dichloromethane (0.25 M) were added sequentially *N*-alkylhydroxylamine (1.0–1.2 equiv) and magnesium sulfate (4.0 equiv). Monitoring and workup proceeded as in Method A, with purification by chromatography on silica gel (hexane/EtOAc 1/1).

(*E*)-*trans*-2,3-Epoxy-*N*-methylnon-7-enal (*Z*)-nitrone (13a): yield 70%, method A: mp 45–45.5 °C; ^1H NMR (360 MHz, $CDCl_3$) 6.40 (d, J =7.1, 1 H, HC(1)), 5.40 (m, 2 H, –HC=CH–), 3.93 (dd, J = 7.1, 1.9, 1 H, HC(2)), 3.68 (s, 3 H, $H_3C(1')$), 2.96 (dt, J = 1.9, 6.0, 1 H, HC(3)), 2.00 (m, 2 H, $H_2C(6)$), 1.60 (d, J =4.9, 3 H, $H_3C(9)$), 1.70–1.40 (m, 4 H); IR ($CHCl_3$) 3047 w, 3034 m, 3030 m, 2940 s, 2920 s, 2858 m, 1613 m, 1453 m, 1428 s, 1404 s, 1394 s, 1305 m, 1286 w, 1232 s, 1226 s, 1179 m, 1136 s, 968 s, 940 m, 875 s; MS (10 eV) 96 (12), 95 (16), 88 (11), 84 (35), 81 (32), 68 (36), 67 (69), 55 (46), 45 (10), 44 (13), 43 (10), 42 (100), 41 (21); TLC R_f 0.47 (EtOAc/methanol 2/1). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.70; H, 9.21; N, 7.78.

(*E*)-*trans*-*N*-Cyclohexyl-2,3-epoxynon-7-enal (*Z*)-nitrone (13b): yield, 75%, method A: mp 81–83 °C; ^1H NMR (200 MHz, $CDCl_3$) 6.43 (d, J = 7.0, 1 H, HC(1)), 5.40 (m, 2 H, –HC=CH–), 4.00 (dd, J = 7.0, 2.2, 1 H, HC(2)), 3.63 (tt, J = 11.4, 3.6, 1 H, HC(1′)), 2.95 (m, 1 H, HC(3)), 1.63 (d, J = 4.5, 3 H, $H_3C(9)$), 2.10–1.0 (m, 16 H); IR ($CHCl_3$) 2950 s, 2870 s, 1600 m, 1455 s, 1350 m, 1300 m, 1150 m, 1120 m, 1030 m, 980 m, 940 m, 880 m; MS (10 eV), 251 (M^+, 0.4), 152 (13), 112 (10), 110 (12), 95 (18), 83 (100), 81 (30), 74 (17), 70 (14), 68 (20), 67 (45), 55 (65), 41 (12); TLC R_f 0.37 (hexane/EtOAc 1/1). Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.55, H; 10.22; N, 5.45.

(*E*)-*trans*-2,3-Epoxy-*N*-(1,1-dimethylethyl)non-7-enal (*Z*)-nitrone (13c): yield 72%, method B: ^1H NMR (200 MHz, $CDCl_3$) 6.55 (d, J = 6.7, 1 H, HC(1)), 5.40 (m, 2 H, –HC=CH–), 4.00 (dd, J = 6.7, 2.2, 1 H, HC(2)), 3.00 (m, 1 H, HC(3)), 2.05 (m, 2 H, $H_2C(6)$), 1.80–1.50 (m, 7 H), 1.49 (s, 9 H, *t*-Bu); IR ($CHCl_3$) 3000 s, 1580 m, 1480 m, 1430 m, 1395 m, 1360 s, 1090 s, 1040 m, 970 s, 910 s, 880 s; MS (10 eV) 86 (15), 84 (22), 81 (12), 68 (17), 67 (21), 57 (100), 55 (12), 41 (14); TLC R_f 0.28 (hexane/EtOAc 1/1); high-resolution MS calcd for $C_{13}H_{23}NO_2$ 225.1729, found 225.1733.

(*E*)-*trans*-2,3-Epoxy-*N*-(2,2-dimethylpropyl)non-7-enal (*Z*)-nitrone (13d): yield 43%, method A: ^1H NMR (200 MHz, $CDCl_3$) 6.32 (d, J = 7.0, 1 H, HC(1)), 5.45 (m, 2 H, –HC=CH–), 3.96 (dd, J = 7.0, 2.2, 1 H, HC(2)), 3.57 (s, 2 H, $H_2C(1')$), 2.98 (m, 1 H, HC(3)), 2.02 (m, 2 H, $H_2C(6)$), 1.90–1.50 (m, 7 H), 1.07 (s, 9 H, *t*-Bu); IR ($CHCl_3$) 3000 s, 1595 m, 1475 s, 1430 s, 1405 m, 1395 m, 1370 s, 1280 s, 1120 s, 1035 m, 970 s, 910 s, 875 s; MS (10 eV), 239 (M^+, 0.4), 182 (15), 140 (14), 138 (12), 137 (11), 114 (22), 109 (10), 98 (11), 96 (14), 95 (28), 88 (14), 81 (48), 72 (11), 71 (100), 70 (20), 68 (28), 67 (69), 57 (20) 55 (34), 43 (79), 42 (14), 41 (13); TLC R_f 0.45 (EtOAc); high-resolution MS, calcd for $C_{14}H_{25}NO_2$ 239.1885; found 239.1884.

(*E*)-*trans*-2,3-Epoxy-*N*-phenylnon-7-enal (*Z*)-nitrone (13e): yield 50%, method B: ^1H NMR (360 MHz, $CDCl_3$) 7.70 (m, 2 H, ArH), 7.47 (m, 3 H, ArH), 7.00 (d, J = 7.0, 1 H, HC(1)),

5.44 (m, 2 H, –HC=CH–), 4.21 (dd, J = 7.0, 2.1, 1 H, HC(2)), 3.13 (dt, J = 2.1, 4.3, 1 H, HC(3)), 2.05 (m, 2 H, $H_2C(6)$), 1.66 (d, J = 4.9, 3 H, $H_3C(9)$), 1.80–1.40 (m, 4 H); TLC R_f 0.32 (hexane/EtOAc 3/2).

General Procedure for Vinylnitrosonium Cation Cycloadditions. To a cold (–78 °C), magnetically stirred solution of epoxynitrone **13** (1.0 equiv) in dry dichloromethane (0.01 M) was added trimethylsilyl trifluoromethanesulfonate (1.0 equiv). The solution was then warmed to –10 °C, cooled again to –60 °C, and a solution of potassium cyanide (10.0 equiv) in water (4.0 M) added all in one portion. The reaction mixture was warmed to 0 °C, poured into water, and extracted with 2 volumes of dichloromethane. The dichloromethane extracts were washed with one volume each of saturated aqueous $NaHCO_3$ and brine. The dried (K_2CO_3) organic extract was concentrated, and the residue chromatographed on silica gel (hexane/EtOAc 3/1 to EtOAc gradient). In several instances inseparable mixtures of isomers were obtained, in which case the major isomer was fractionally crystallized from pentane/ether, and the minor isomers characterized by their contribution to the ^1H NMR spectrum of the mixture. The yields for the minor isomers are based on integration ratios of diagnostic peaks in those spectra compared to the isolated yields of the major isomers, or the total mass in those cases where no isomers crystallized. The ^1H NMR spectral data for the minor isomers may be found in Table V of the text. The yields for all isomers may be found in Table IV of the text.

***rel*-(1*R*,3*S*,4*S*,4a*S*,5*S*,8a*S*)-4-Cyano-5-hydroxy-1,3-dimethylperhydrobenz[*d*][1,2]oxazine (15a)**: mp 61–62 °C; ^1H NMR (200 MHz, $CDCl_3$) 4.26 (br, 1 H, HC(5)), 3.57 (dq, J = 9.5, 6.3, 1 H, HC(1)), 3.47 (d, J =10.7, 1 H, HC(4)), 2.78 (s, 3 H, $H_3C(1')$), 1.95–1.35 (m, 9 H), 1.12 (d, J = 6.3, 3 H, $H_3C(9)$), 0.93 (m, 1 H); IR (CCl_4) 3629 w, 3518 m, 2975 s, 2944 s, 2787 w, 2249 w, 1449 m, 1408 w, 1370 m, 1317 m, 1223 m, 1172 m, 1111 s, 1063 s, 1007 m, 909 s; MS (10 eV), 211 (M + 1, 14), 210 (M^+, 100), 195 (12), 192 (37), 175 (29), 148 (10), 147 (28), 146 (12), 139 (29), 133 (15), 120 (16), 119 (16), 109 (11), 108 (62), 107 (33), 97 (11), 95 (13), 93 (26), 85 (11), 81 (12), 80 (12), 79 (37), 69 (16), 42 (11); TLC R_f 0.45 (hexane/EtOAc 2/1); GC T_R 7.58 min, program, 70 °C (2 min) 30 °C/min, 230 °C. Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.90; H, 8.93; N, 13.31.

***rel*-(1*R*,3*S*,4*S*,4a*S*,5*S*,8a*S*)-4-Cyano-3-cyclohexyl-5-hydroxy-1-methylperhydrobenz[*d*][1,2]oxazine (15b)**: mp 120–121 °C; ^1H NMR (200 MHz, $CDCl_3$) 4.25 (br, 1 H, HC(5)), 3.96 (d, J = 9.5, 1 H, HC(4)), 3.47 (dq, J = 9.5, 6.3, 1 H, HC(1)), 2.92 (m, 1 H, HC(1')), 1.10 (d, J = 6.3, 3 H, $H_3C(9)$), 2.00–0.80 (m, 19 H); IR ($CHCl_3$) 3610 w, 2930 s, 2860 s, 2240 w, 1450 s, 1370 m, 1345 m, 1315 m, 1160 m, 1110 m, 1090 m, 1060 m, 1000 m, 975 m, 910 s; MS (10 eV), 279 (M + 1, 25), 278 (M^+, 85), 236 (29), 235 (100), 178 (44), 138 (19), 137 (12), 134 (10), 125 (14), 109 (14), 108 (27), 107 (23), 98 (11), 83 (15); TLC R_f 0.65 (hexane/EtOAc 1/1); GC T_R 7.60 min, program, 70 °C (2 min), 30 °C/min, 230 °C. Anal. Calcd for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.95; H, 9.47; N, 10.04.

***rel*-(1*R*,3*S*,4*S*,4a*S*,5*S*,8a*S*)-4-Cyano-3-(1,1-dimethylethyl)-5-hydroxy-1-methylperhydrobenz[*d*][1,2]oxazine (15c)**: mp 77–78 °C; ^1H NMR (200 MHz, $CDCl_3$) 4.32 (br, 1 H, HC(5)), 3.89 (d, J =9.6, 1 H, HC(4)), 3.49 (dq, J = 9.4, 6.3, 1 H, HC(1)), 2.00–1.30 (m, 8 H), 1.25 (s, 9 H, t-Bu), 1.12 (d, J =6.3, 3 H, $H_3C(9)$), 0.92 (m, 1 H); IR ($CHCl_3$) 3625 m, 3500 w, 2980 s, 2940 s, 2880 m, 2245 w, 1480 w, 1450 m, 1395 m, 1370 s, 1350 w, 1320 m, 1300 w, 1220 m, 1155 m, 1095 m, 1065 m, 1045 m, 1005 m, 975 m, 940 w, 915 s, 890 m, 860 w, 840 w; MS (10 eV), 253 (M + 1, 10), 252 (M^+, 73), 237 (27), 197 (14), 196 (100), 178 (14), 163 (10), 125 (12), 74 (14); TLC R_f 0.30 (hexane/EtOAc 3/1). Anal. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.68; H, 9.64; N, 11.11.

***rel*-(1*R*,3*S*,4*R*,4a*S*,5*S*,8a*S*)-4-Cyano-5-hydroxy-1,3-dimethylperhydrobenz[*d*][1,2]oxazine (16a)**: mp 154–154.5 °C; ^1H NMR (200 MHz, $CDCl_3$) 4.07 (br, 1 H, HC(5)), 3.72 (d, J = 3.4, 1 H, HC(4)), 3.56 (dq, J = 8.8, 6.3, 1 H, HC(1)), 2.70 (s, 3 H, $H_3C(1')$), 2.00–1.40 (m, 9 H), 1.18 (d, J = 6.3, 3 H, $H_3C(9)$), 0.92 (m, 1 H); IR (CCl_4) 3484 m, 2900 s, 2240 w, 1703 m, 1447 m, 1366 m, 1275 w, 1246 m, 1169 m, 1097 m, 1078 m, 916 w; MS (10 eV), 211 (M + 1, 10), 210 (M^+, 79), 175 (27), 147 (22), 146 (17), 120 (10), 119 (17), 118 (10), 109 (13), 108 (100), 107 (47), 97 (17), 93 (27), 86 (12), 85 (18), 81 (10), 79 (37), 69 (12), 42 (10); TLC R_f = 0.16 (hexane–EtOAc 2/1). Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.76; H, 8.63; N, 13.26.

***rel*-(1*R*,3*S*,4*R*,4a*S*,5*S*,8a*S*)-4-Cyano-3-cyclohexyl-5-hydroxy-1-methylperhydrobenz[*d*][1,2]oxazine (16b)**: mp 133–133.5°C; ^1H NMR (200 MHz, $CDCl_3$) 4.08 (br, 1 H, HC(5)), 3.99 (d, J = 3.2, 1 H, HC(4)), 3.48 (dq, J = 2.5, 6.3, 1 H, HC(1)), 2.74 (m, 1 H, HC(1')), 2.23 (m, 1 H, HC(4a)), 1.17 (d, J = 6.3, 3 H, $H_3C(9)$), 2.20–0.80 (m, 18 H); IR ($CHCl_3$) 3620 m, 2940 s, 2870 s, 2240 w, 1450 s, 1375 m, 1355 m, 1320 m, 1110 m, 1080 m, 1060 m, 1000 m, 980 m, 915 m, 890 w, 860 w; MS (10 eV), 279 (M + 1, 17), 278 (M^+, 100), 236 (11), 235 (66), 196 (13), 178 (14), 148 (10), 109 (12), 108 (56), 107 (17), 83 (16); TLC R_f 0.42 (hexane/EtOAc 1/1). Anal. Calcd for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.14, H; 9.57; N, 10.04.

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Supplementary Material Available: Improved, large-scale preparations of *N*-cyclohexyl- and *N*-methylhydroxylamine hydrochloride are reported (1 page). Ordering information is given on any current masthead page.