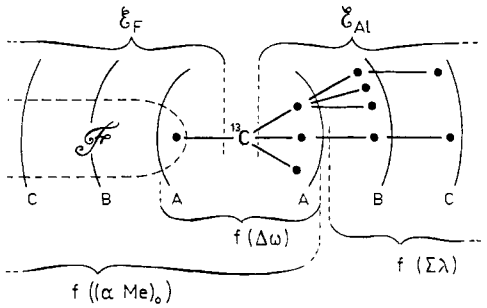

Figure 8. Active environment effects on the different terms of the DARC–PULFO model for a sp^3 ^{13}C site. In the examples investigated, the differential sensitivity $\Delta\omega^{c-1,c}$ depends on the sites directly bonded to the ^{13}C site (rank A atoms). The limiting effect $(\alpha\text{-Me})_0^{c-1,c}$ is affected by functional environment $\mathscr{E}_F$ and rank A atoms of alkyl environment $\mathscr{E}_{Al}$. The term $\sum\lambda_r$ is related to the presence of carbons atoms in ranks B and C of the alkyl environment $\mathscr{E}_{Al}$. $f((\alpha\text{-Me})_0)$ is the range of influence of $(\alpha\text{-Me})_0$ etc.

conformations.

Conclusion

The use of topological models in ^{13}C NMR is particularly attractive insofar as chemical shifts minutely reflect the influence exerted by the various parts of a ^{13}C environment. The complexity of α-Me effects that is observed when they are analyzed is partly due to the major role played by the *degree of substitution* of the resonant atom and partly due to the *overlapping of the various active environments* acting on the different components of the α-Me effects. These different contributions can be identified and analyzed with the PULFO model. Hence, sites directly bonded to a ^{13}C site (constituting environment A) simultaneously affect the $\Delta\omega$ differential sensitivities and the $(\alpha\text{-Me})_0$ limiting effects, whereas sites in rank B and C of the alkyl environment affect only the term $\sum\lambda_r$ (Figure 8). This term, in all likelihood, is largely composed of the influence on ^{13}C of steric polarization of the γ type between the incoming methyl substituent and the carbon atoms at the β-position of the alkyl environment.

The influence of conformational effects associated with specific functional families was also analyzed with the PULFO model. The variable environment for each functional family dealt with herein contains only alkyl radicals whose influence is represented by the λ_r parameters. A study on the introduction of heteroatoms into the various environments is under way. We are also in the process of determining the topological parameters of functionalized groups (λ_F) and investigating the potential of the PULFO model and its sensitivity to real geometric distortions and local strain release.

Experimental Section

^{13}C spectra of ketones and acids were recorded on a JEOL PFT 100 spectrometer operating at 25.15 MHz with Fourier transform, ^2H Lock, and complete ^1H noise decoupling. Spectra were run at room temperature on 10% w/v solutions in CD_2Cl_2 for acids or CCl_4 for ketones (the lock signal was then obtained from a D_2O capillary inserted in the sample tube). Chemical shifts were measured from the solvent peak as internal standard and converted to Me_4Si scale.

Acknowledgment. We are grateful to Dr. C. Lion for preparing crowded carboxylic acids and ketones and to M. Carabédian for helpful discussions.

Supplementary Material Available: Tables VI–VIII listing α-Me values observed and calculated with the PULFO model and all ^{13}C δ values for the acid and ketone series herein (17 pages). Ordering information is given on any current masthead page.

Application of Two-Dimensional FT NMR to the Relative Configurational Assignment of 8-Methyl-4-oxo-10-(trimethylsiloxy)tetracyclo[7.2.1.0^{2,8}.0^{3,7}]dodecane-10-carbonitrile

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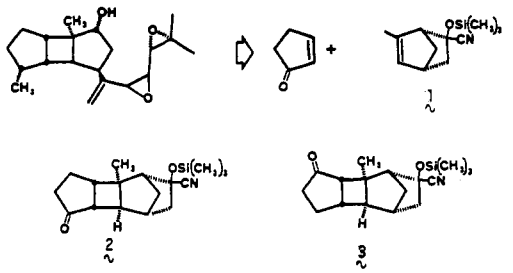
The relative configuration of 8-methyl-4-oxo-10-*endo*-(trimethylsiloxy)-*cis*-*anti*-*cis*-tetracyclo[7.2.1.0^{2,8}.0^{3,7}]-dodecane-10-*exo*-carbonitrile (**2x**) was assigned by joint application of ^{13}C–^1H two-dimensional J spectroscopy (2DJ spectroscopy) and ^{13}C–^1H two-dimensional shift correlation spectroscopy. The utility of vicinal ^{13}C–^1H coupling for configurational analysis is demonstrated. The structural assignment described can serve as a model for application of two-dimensional FT NMR techniques to the structural analysis of organic compounds.

Introduction

In connection with studies on the synthesis of spatol,[1] photocycloaddition of cyclopent-2-en-1-one with 6-methyl-2-(trimethylsiloxy)bicyclo[2.2.1]hept-5-ene-2-carbonitrile (**1**) was examined. Fortunately, a single major product which is the needed structural isomer **2** (vide infra)



is readily isolated from the photoreaction in 61% yield. Selective generation of an exo-anti adduct **2** or **3** was expected owing to the proclivity for exo addition to bicy-

(1) (a) Spatol is a minor metabolite produced by a tropical marine alga, *Spatoglossum schmitti*.[1b] It is potently cytotoxic against human skin and brain tumor cells, and it inhibits synchronous cell division of the fertilized sea urchin egg, suggesting inhibition of microtubule assembly as a target of its biological activity.[1c] (b) Gerwick, W. H.; Fenical, W.; Van Engen, C.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 7991. (c) Jacobs, R. S.; White, S.; Wilson, L. *Fed. Proc., Fed. Am. Exp. Biol.* **1981**, *40*, 26.

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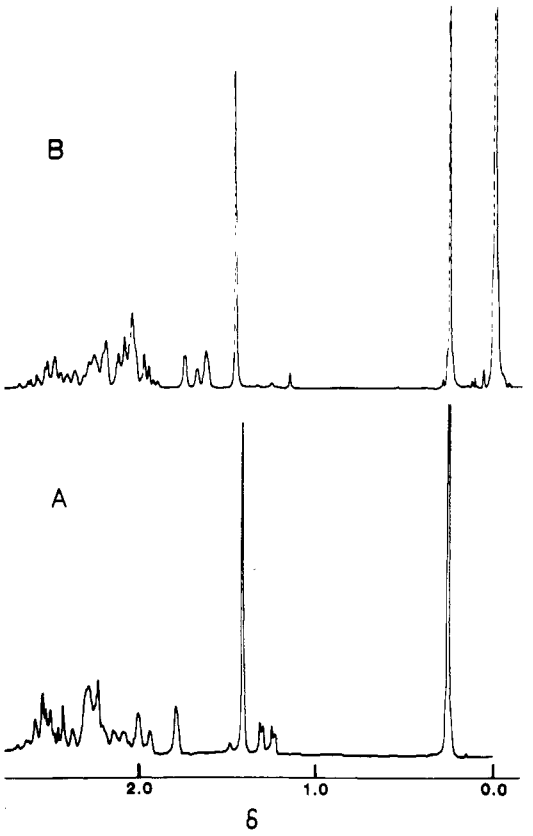


Figure 1. 200-MHz ^1H NMR spectrum of (A) **2x** (10% in $CDCl_3$) and (B) **2n**.

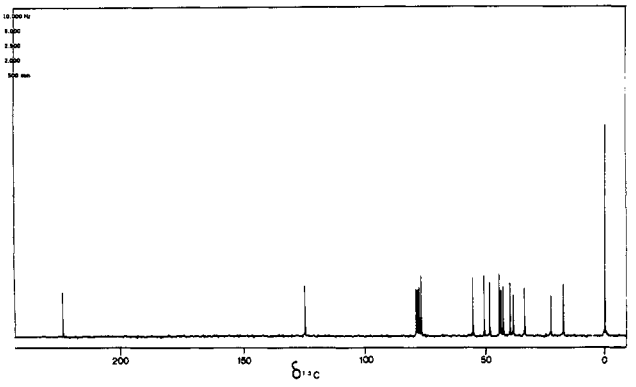


Figure 2. 50-MHz ^{13}C NMR spectrum of **2x** (10% on $CDCl_3$). Spectrum was acquired by using quadrature detection, 15-kHz sweep width, 12K data points, 40 transients, and 4-μs (30°) pulse. The free induction decay was zero filled to 16K data points and exponentially weighted to provide 1.0-Hz linebroadening.

clo[2.2.1]heptenes[2] and steric hinerance of exo-syn addition. However, neither precedent nor a 200-MHz ^1H NMR spectrum of the photoproduct allowed a definite choice between structural isomers of types **2** or **3**. Thus, the only resonances that were resolved are the singlets for the trimethylsiloxy and C-8 methyls and the doublet of doublets for H_{endo} on C-11. The remaining proton resonances occur as a complex pattern of overlapping multiplets between 1.5 and 2.5 ppm, even at 200 MHz (Figure 1A).

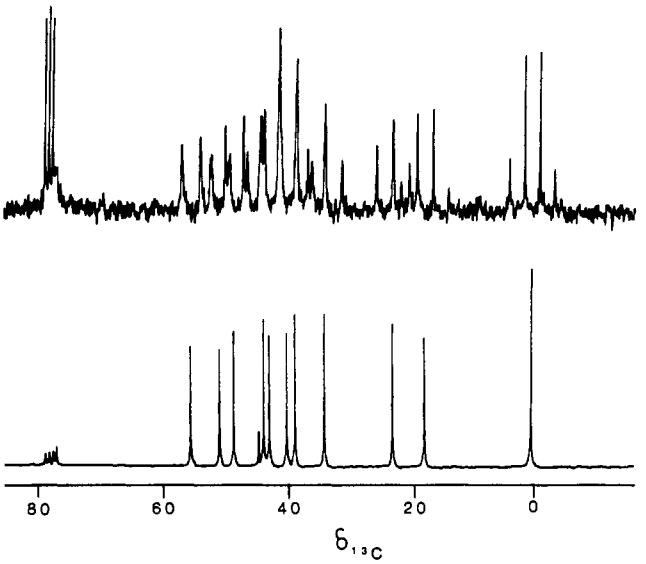
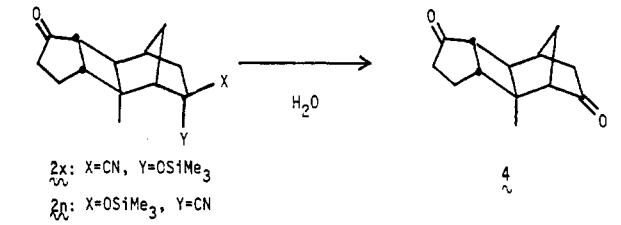


Figure 3. Upfield portion of the ^{13}C spectrum of **2x** (bottom) with broad band proton decoupling and (top) with single-frequency off-resonance decoupling.

Two-dimensional Fourier transform NMR (2D-FT NMR)[3] has become an invaluable technique for obtaining spectral simplification that would otherwise not be achieved even at resonance frequencies much higher than those obtainable with currently available technology. The application of ^{13}C–^1H two-dimensional J spectroscopy (2DJ spectroscopy) and ^{13}C–^1H chemical shift correlation spectroscopy to the structural analysis of the major photocycloadduct is described which establishes that this product is the exo carbonitrile epimer **2x**. The endo



carbonitrile **2n** is also isolated (3%) from the photoreaction. The epimeric relationship between **2x** and **2n** was demonstrated by hydrolysis which affords the same diketone **4** from both *O*-silyl cyanohydrins. The ^1H NMR spectral basis for assigning the carbonitrile stereochemistries in **2x** and **2n** is also described.

Results

^{13}C Multiplicities. As a first step toward configurational assignment, the ^{13}C resonances were assigned to methyl, methylene, methine, and quaternary carbons. As will be demonstrated, this will eliminate other possible peak assignments, simplify assignments, and provide added evidence to confirm the relative configurational assignments made. The proton-decoupled ^{13}C spectrum of **2x** in $CDCl_3$ is illustrated in Figure 2. The chemical shifts are given in Table I. Single-frequency off-resonance decoupling (SFORD) allows identification of peaks at 221.7, 122.8, 75.5, and 43.4 ppm (relative to Me_4Si) as singlets arising from quaternary carbons. These are readily assigned on the basis of chemical shift to C-4, CN, C-10, and

(2) Photocycloadditions of carbonyl-conjugated alkenes to bicyclo[2.2.1]hept-2-ene have been shown to occur with exclusive exo stereospecificity: Hara, M.; Odaira, Y.; Tsutsumi, S. *Tetrahedron* **1966**, *23*, 95. Nevertheless, some caution is warranted since endo photocycloadditions of other substrates to bicyclo[2.2.1]hept-2-ene are also known. E.g.: Scharf, D.; Korte, F. *Tetrahedron Lett.* **1964**, 821. Theoretical explanations for the exo selectivity generally observed for the bicyclo[2.2.1]-hept-2-ene double bond have been presented: Spanget-Larsen, J.; Gleiter, Rolf. *Tetrahedron Lett.* **1982**, 2435 and references cited therein.

(3) Bax, A. D. "Two Dimensional NMR Spectroscopy in Liquids", Reidel: Boston, 1982.

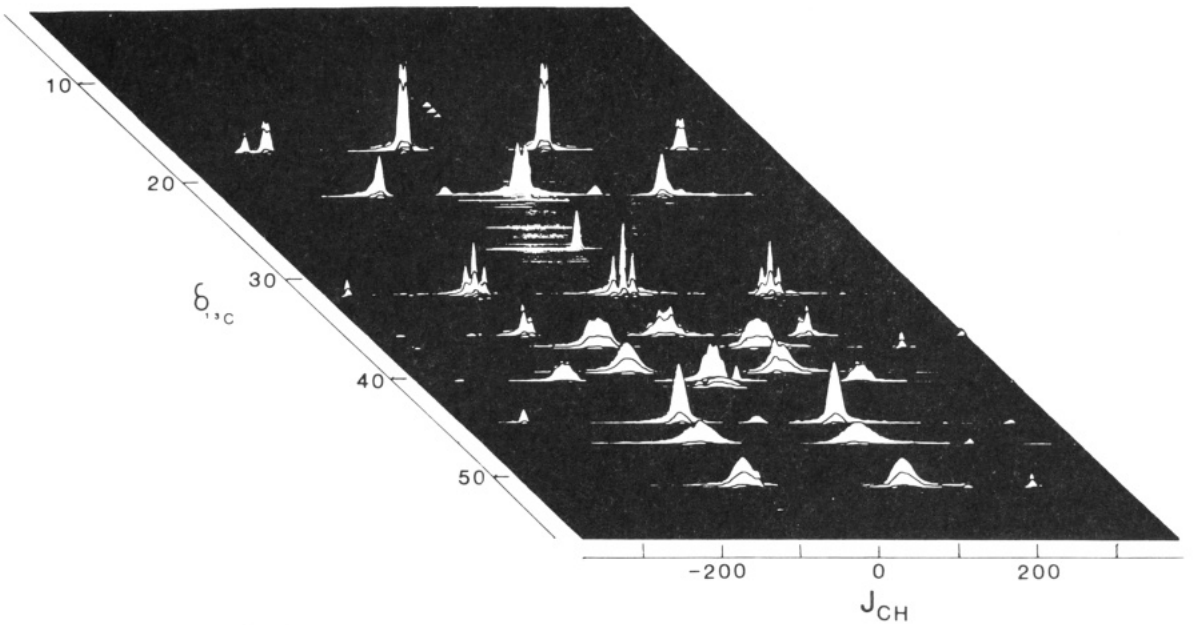


Figure 4. Stacked plot of the ^{13}C–^{1}H heteronuclear 2DJ spectrum of **2x** (30% in $CDCl_3$). ^{13}C chemical shifts of the upfield region (5–55 ppm) are plotted along the vertical direction, and J_{CH} is plotted in the horizontal dimension. Spectral acquisition and processing parameters are given in the Experimental Section.

C-8, respectively.[4] The upfield portion of the decoupled and single-frequency off-resonance decoupled (SFORD) ^{13}C spectra are shown in Figure 3. The peaks at 0.6 and 17.0 ppm are easily identified as quartets in the SFORD spectrum while the peak at 22.6 ppm is a doublet of doublets. The methyl resonances are assigned to the trimethylsiloxy group (0.6 ppm) and the C-8 methyl group (17.0 ppm).

The remaining peak assignments are difficult to sort as they are dispersed over only a 20 ppm range. These assignments might be made by using any one of a number of techniques. Heteronuclear 2DJ spectroscopy[5] was chosen for its additional information content. With this experiment, it is possible to resolve long-range ^{13}C–^{1}H coupling which is also useful for structural analysis. This valuable information is either lost or not resolved in spectra from other experiments such as the INEPT,[6] APT,[7] or DEPT[8] that are also useful for ^{13}C multiplicity assignments.

In the ^{13}C–^{1}H 2DJ experiment the chemical shift of the observed nucleus (^{13}C) defines the axis of the first dimension, and heteronuclear scalar coupling (J_{CH}) defines the axis in the second dimension. A stacked plot of the upfield region (10–60 ppm) of the 2DJ spectrum of **2x** is illustrated in Figure 4. The multiplicity of each carbon resonance is easily resolved in the horizontal dimension at frequencies (in the vertical dimension) corresponding to the chemical shifts of the carbon resonances. The data from this experiment is summarized in the first four columns of Table I in entries 1–12. As an example, the C-8 methyl at δ_{13C} 17.0 can now be resolved as a quartet in the horizontal dimension, without overlap from the doublet of doublets at 22.6 ppm. It is possible to interpret multiplicities directly, and long-range coupling is easily resolved (e.g., the triplet ($^{1}J_{CH}$ = 135 Hz) at 33.4 ppm is further split to a triplet of triplets due to long-range coupling ($^{3}J_{CH}$ = 9 Hz)).

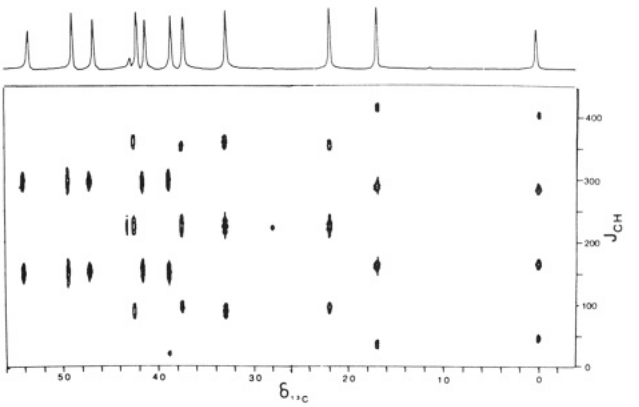


Figure 5. Same spectrum as Figure 4 plotted in the form of vertical contours with the normal ^{13}C spectrum across the top.

It is often more convenient to plot and interpret 2D-FT NMR data if they are presented in a different format. A commonly used method is that of a contour plot (Figure 5). The appearance of this type of display is as if viewing the spectrum in Figure 4 from directly above. Unlike the stacked plot, peaks are not hidden behind much larger ones. Most of the spectrum is noise, and the signals in many two-dimensional spectra lie along a limited number of "slices", corresponding to the ^{13}C shifts in this instance. A convenient alternative, therefore, is to plot only the individual "slices". This involves much less data processing, and line listings of individual spectra provide the most accurate method of determining peak positions. Plots of individual slices from the 0–60 ppm region of the 2DJ spectrum of **2x** are illustrated in Figure 6. These slices unambiguously identify the multipliciites (due to ^{13}C–^{1}H scalar coupling) of each carbon resonance and provide supplementary information due to the additional fine structure.

(4) Levy, G. C.; Lichter, R. L.; Nelson, G. A. "Carbon-13 Nuclear Magnetic Resonance Spectroscopy for Organic Chemists", 2nd ed.; Wiley: New York, 1980.

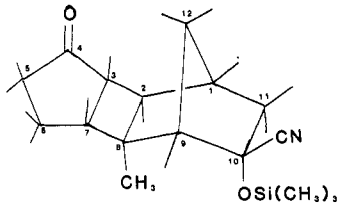
(5) Bodenhausen, G. A.; Freeman, R. J.; Turner, D. L. *J. Chem. Phys.* **1976**, *65*, 839.

(6) (a) Freeman, R.; Morris, G. A. *J. Chem. Soc., Chem. Commun.* **1978**, 684. (b) Morris, G. A.; Freeman, R. J. *J. Am. Chem. Soc.* **1979**, *101*, 760.

(7) (a) LeCocq, C.; Lallemand, J. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 150. (b) Brown, D. W.; Nakashima, T. T.; Rabenstein, D. L. *J. Magn. Reson.* **1981**, *45*, 302.

(8) Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.*, **1982**, *48*, 323.

Table I. ^{13}C and ^{1}H NMR Spectral Parameters for 2x[a]

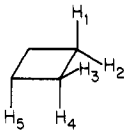


2x

entry	^{13}C[b]	multiplicity (^{13}C)[c]	J_{CH}, Hz[c]	^{1}H[d]	multiplicity (^{1}H)[d]	J_{HH}, Hz[d]	resonance assignments
1	0.6	q	119	0.25[f]	s		OTMS
2	17.0	q	126	1.37[f]	s		CH_3
		d	6				
3	22.6	dd	125.5, 132.3	1.75-2.55	m		C_5
4	33.4	t	135	1.98	AB	12	C_{12}
		t	9	2.15			
5	37.7	dd	124.5, 127.5	2.05-2.85	m		C_6
		d	7				
6	39.0	d	148	2.26	d	7.5	C_1
		t	7				
7	41.8	d	143	2.55	t	9	C_7
8	42.7	t	135	1.29[f]	dd	13, 3.5	$C_{11}H_{endo}$
		m	6	2.45	dd	13, 7.5	$C_{11}H_{exo}$
9	43.4	s					C_8
10	47.3	d	144	2.28	d	9	C_3
11	49.6	d	141	1.77	s		C_2
12	54.2	d	144	2.22	s		C_9
13	75.5	s					C_{10}
14	122.8	s					CN
15	221.7	s					C_4

[a] Except for the large (100-150 Hz) splittings the terms triplet and doublet are used loosely as line positions and are only accurate to ca. ±0.5 Hz. Values are given in ppm relative to Me_4Si. [b] Relative to $CDCl_3$ at 77.0 ppm. [c] Obtained from ^{13}C-^{1}H heteronuclear two-dimensional J spectroscopy. [d] Obtained from ^{13}C-^{1}H cross-correlated heteronuclear two-dimensional NMR spectrum. [e] Assignments in boldface are independent of the stereochemistry chosen. [f] Obtained from one-dimensional ^{1}H NMR spectrum.

Table II. Representative Values for *J* Coupling in Cyclobutanes



coupling	*J*, Hz	ref
1,2 gem	10-15	9, 10
1,3 vic cis	7-10	9, 10
1,4 vic trans	3-9 (0-3)[a]	9, 10
1,5 4-bond W	0-2	10

[a] For rigid systems analogous to **2x** see text.

^{1}H Chemical Shifts and Scalar Couplings. Relative configurational assignments are routinely made on the basis of vicinal ^{1}H-^{1}H scalar couplings. In the case of cyclobutanes, model values are presented in Table II.[9,10] Although there is significant overlap of the expected ranges for vicinal J_{cis} and J_{trans} couplings in cyclobutanes, the rigid nature of **2x** allows definition of the dihedral angles between vicinal protons. For cis protons on the cyclobutane ring of 2, dihedral angles close to 0° are expected and result in coupling constants close to 10 Hz. For trans protons, dihedral angles close to 60° are expected and result in coupling constants in the range of 0–3 Hz.

Similarly, the exo or endo nature of the cyclobutane ring system might be determined from the endo or exo nature of H-2. Representative values for coupling in the norbornane ring system are presented in Table III.[11,12]

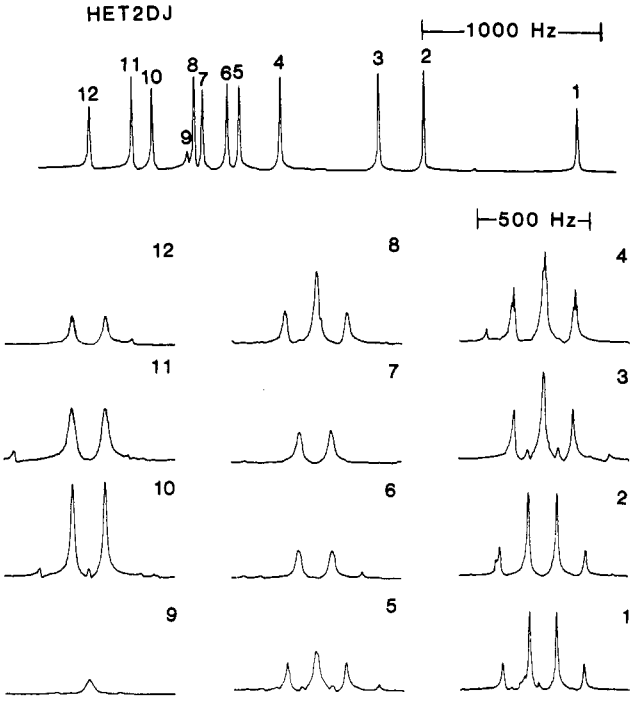
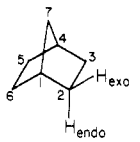


Figure 6. Slices from the ^{13}C-^{1}H heteronuclear 2DJ spectrum in Figure 5. The slices are numbered to correlate them with the peaks in the upfield (0–60 ppm) portion of the normal ^{13}C spectrum (top).

(9) Gaudemer, A. In "Stereochemistry: Fundamentals and Methods"; Kagan, H. B., Ed.; Thieme: Stuttgart, 1977; Vol. I, p 85.
(10) Bovey, F. A. "Nuclear Magnetic Resonance Spectroscpy"; Academic Press: New York, 1969; p 362.

Table III. Representative Values for *J* Coupling in Norbornanes



coupling	*J*, Hz	ref
1,2 (exo)	3-4	11
1,2 (endo)	0-2	11, 12
2 (endo),3 (endo)	6-8	11, 12
2 (exo),3 (exo)	9-10	11, 12
2 (endo),3 (exo)	2.5-5.0	11
1,7	0-3.5	11

Coupling between the bridgehead proton and vicinal exo and endo protons are usually in the range of 3–4 and 0–2 Hz, respectively.

Because the spectral are complex, only a limited number of resonances in the ^1H NMR spectrum of **2x** (Figure 1A) are assignable. The C-8 methyl and trimethylsiloxy singlets are clearly resolved at 1.37 and 0.25 ppm, respectively. In addition, a doublet of doublets is clearly distinguished at 1.29 ppm. This resonance arises from H_{endo} on C-11 of **2x**. Little additional information is obtainable from the proton spectrum.

Any one of a number of two-dimensional NMR experiments could be performed at this point in order to resolve ^1H coupling. In order to relate the ^1H resonance with ^{13}C assignments, ^{13}C–^1H chemical shift correlated spectroscopy (HETCOR)[13] was performed. The spectra obtained from this experiment contain ^{13}C chemical shift plotted in the first dimension and ^1H chemical shift in the second dimension. However, the ^1H spectrum of a single slice, corresponding to the chemical shift of an individual carbon atom, consists of the ^1H spectrum of only the protons attached to that carbon atom. Therefore, a great deal of dispersion can be achieved for the ^1H resonances without the use of extremely high magnetic fields. The slices from this spectrum are displayed in Figure 7, and the proton chemical shifts and coupling constants are summarized in columns 5, 6, and 7 of Table I. The numbering of the slices in Figure 7 correlates these spectra with the carbon resonances as labeled in Figure 6.

Before interpretation is considered, the limitations of the data should be emphasized. Since spectra are obtained by observation of ^{13}C in a 10-mm sample tube as opposed to the 5-mm sample tubes used for ^1H NMR, magnetic field homogeneity is poor and the line widths are relatively broad (0.5–1.0 Hz). Data memory and storage requirements are very high, and so data point resolution is limited (1.5 Hz/point) in the ^1H chemical shift dimension. Consequently, small couplings (<3–4 Hz) are not resolved, and larger couplings are only accurate to within ca. ±1 Hz. Due to second-order effects and some characteristics of the experiments spectral artifacts are present. These are usually easily distinguished. For example, an artifact is frequently observed in the center of the second dimension spectra in a manner similar to that found in one-dimensional spectra when quadrature detection is used. Additionally, since resonances are broad at the base, components of a multiplet from one slice of the 2D spectrum may be seen in other slices.

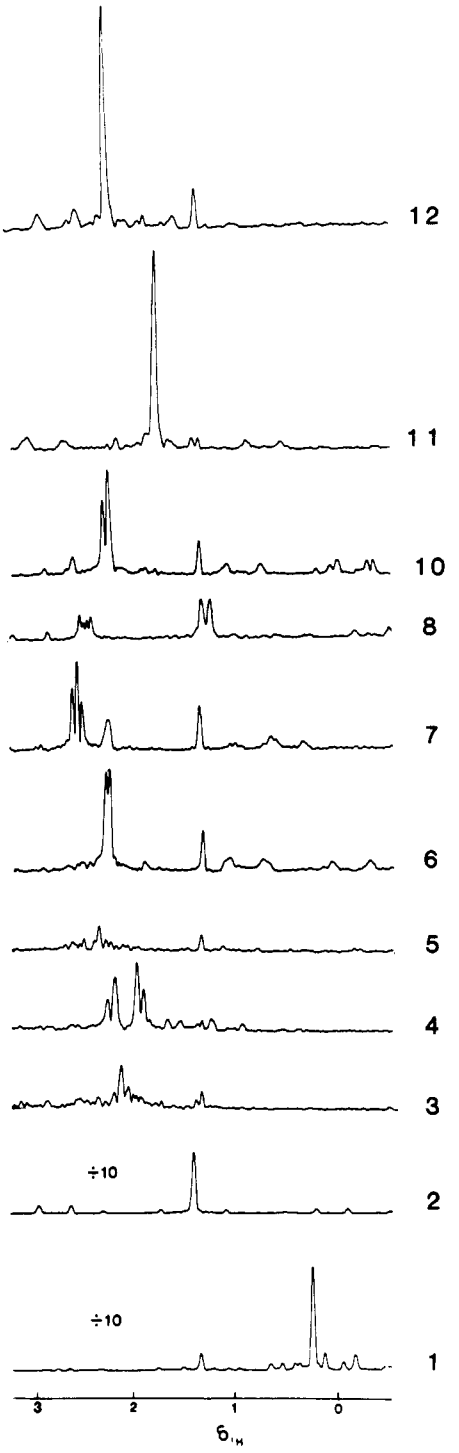


Figure 7. Slices from the ^{13}C–^1H chemical shift correlated spectrum of **2x**. The slices are numbered to correlate them with the carbons having resonances as numbered in the ^{13}C spectrum in Figure 6. These slices illustrate the proton resonances of only the protons directly bound to these carbons. Spectral acquisition and processing parameters are described in the Experimental Section.

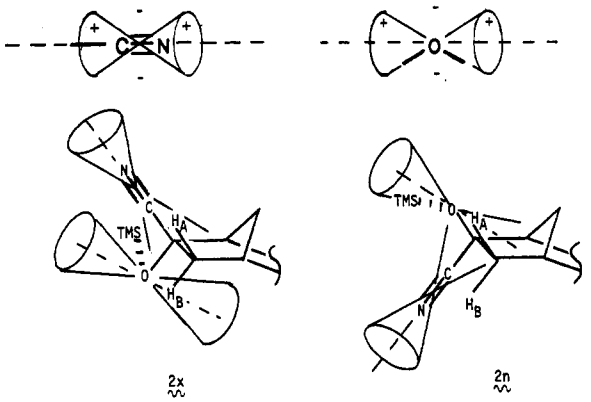
Discussion

Spectral analysis is greatly simplified if those resonances that can be assigned independent of stereochemistry are first considered. The remaining resonances can then be compared with spectra predicted from the different permutations of stereochemistry possible.

Resonances That Are Assigned Independent of Stereochemistry. Some of the resonance assignments can be made directly from the appearances of the proton multiplets in the slices of the HETCOR spectrum (Figure

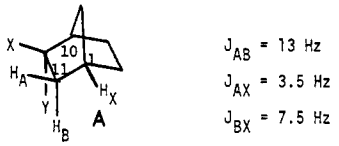
(11) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Elmsford, N. Y., 1969; p 289.
(12) Reference 10, p 367.
(13) Bax, A.; Morris, G. A. *J. Magn. Reson.* **1981**, *42*, 501.

Chart I



7). Since the quaternary carbon (line 9) has no corresponding ^1H resonance, no spectrum is observed at δ_{13C} 43.4 in the HETCOR experiment. Slices 1 and 2 in Figure 7 correspond to the two methyls, which appear as singlets as expected. Carbon resonances 3, 4, 5, and 8 correspond to methylenes (carbons 5, 6, 11 and 12), as determined from their multiplicities in Figure 6. The proton spectra (Figure 7) of the protons attached to these atoms in conjunction with the ^{13}C chemical shift allows unambiguous assignment of these resonances.

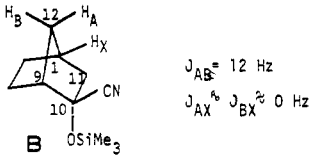
Spectrum 8 in Figure 7 is readily assigned to the protons attached to C-11. The doublet of doublets at 1.29 ppm (H_{endo}) in the normal ^1H spectrum appears as a doublet due to the poorer resolution obtained in the two-dimensional NMR spectrum (coupling less than 3–4 Hz is not resolved in any of the spectra presented). This spectrum allows unambiguous assignment of the stereochemistry of the cyanohydrin at C-10. In the two-dimensional spectrum it is now possible to resolve the entire AB portion of an ABX pattern for the C-11 methylene protons, as indicated schematically in structure A. The exo proton (H_A,



structure **A**, δ 2.45) exhibits a larger coupling to the bridgehead proton (H_X) than does the endo proton (H_B, δ 1.29), as expected for bicyclo[2.2.1]heptanes (see Table III), because the dihedral angle between C-11–H_A and C-1–H_X is approximately 0° compared to the 60° dihedral angle relationship between C-11–H_B and C1-H_X. The large magnitudes found for these couplings compared to the model values in Table III result from the electronegative substituents on C-10.

As stated above, major (**2x**) and minor (**2n**) isomers, which are epimeric at C-10, were obtained from the synthesis. The stereochemistry at C-10 can be assigned by considering the shielding anisotropies of the nitrile and ether functionalities (Chart I).[14,15] In epimer **2x**, H_{endo} is in the shielding region of the ether group, while in epimer **2n**, H_{endo} is in the deshielding region of the nitrile. The one-dimensional ^1H NMR spectra of the major (**2x**) and minor (**2n**) isomers are shown in Figure 1, parts A and B, respectively. The doublet of doublets for H_{endo} is shifted significantly downfield (by 0.44 ppm) in the minor isomer. Therefore, this isomer is assigned structure **2n**, since a syn-periplanar orientation of H_{endo} with respect to the nitrile substituent on C-10 is expected to result in deshielding.

Only geminal coupling should be resolved for the methylenes on C-12 (structure B) since vicinal coupling to the

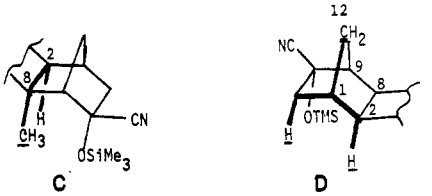


bridgehead protons is generally small (0–3.5 Hz, Table III). The C-12 proton syn to the nitrile group in **2x** should be deshielded by that substituent resulting in an AB pattern as seen for spectrum 4 in Figure 7. The remaining methylene protons on carbons 5 and 6 will appear as complex multiplets, as seen for spectra 3 and 5 in Figure 7. These can be assigned on the basis of their ^{13}C chemical shifts. The carbon α to the carbonyl (C-5) is assigned to resonance 5 (δ_{13C} 42.7) in Figure 6, and C-6 is assigned to resonance 3 (δ_{13C} 22.6). These assignments follow from the fact that a carbon α to a carbonyl substituent is deshielded significantly.[4]

Only one of the methine resonances can be assigned without considering stereochemistry. By matching of the unique 7.5-Hz coupling measured in spectrum 6 of Figure 7 with the vicinal coupling of 7.5 Hz measured for H_{exo} on C-11 (spectrum 8, δ 2.45), spectrum 6 is assigned to the bridgehead proton on C-1.

Stereochemistry of Cyclobutane Ring Formation—Exo vs. Endo Stereochemistry. Since the resonance for the C-1 bridgehead proton (spectrum 6 in Figure 7) shows only one 7.5-Hz coupling, it is flanked by only a single vicinal exo proton. Since this exo proton is found on C-11, the proton on C-2 must be endo, and the cyclobutane ring must be exo fused. Additional evidence to support this conclusion is provided by ^{13}C–^1H vicinial coupling.

While geminal coupling in hydrocarbons is small (0–3 Hz), the magnitude of vicinal coupling exhibits the same Karplus-type dependence on dihedral angle as found for ^1H–^1H vicinal coupling, with maximum values on the order of 5–9 Hz.[16] Thus resolvable coupling of this sort should be seen when the coupled nuclei are either syn-periplanar or anti-periplanar with respect to one another. For example, since the methyl group on C-8 bears such a relationship with respect to the proton on C-2 (structure C),

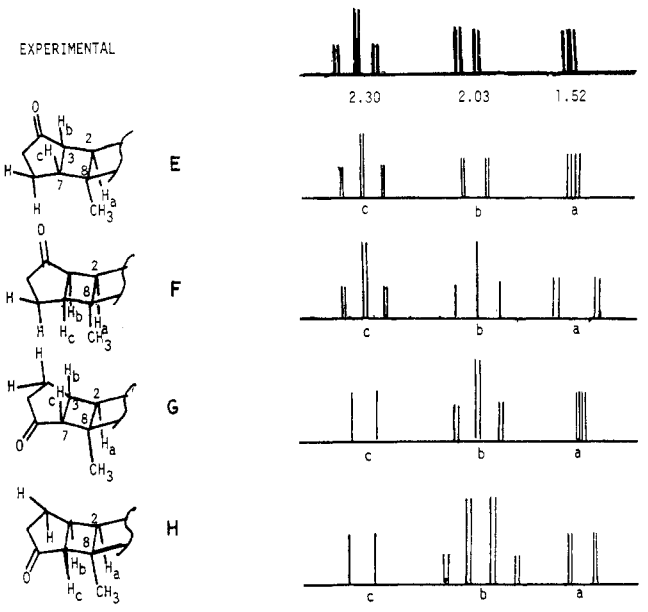


the ^{13}C quartet at 17.0 ppm in Figure 4 exhibits ^{13}C–^1H vicinal coupling (doublet, J = 6 Hz).

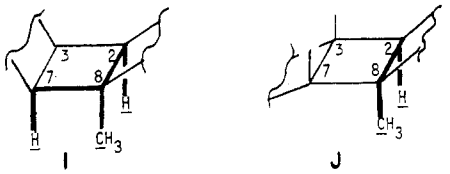
Such long-range vicinal ^{13}C–^1H coupling provides additional evidence supporting the conclusion that the cyclobutane ring is exo fused. The ^{13}C triplet which was assigned to C-12 (δ 33.4 in Figure 4) also exhibits ^{13}C–^1H long-range coupling (triplet, J = 9 Hz) with two vicinal protons that describe dihedral angles close to either 0° or 180° with respect to C-12. This is only possible if the proton on C-2 is endo as shown in structure D, and consequently the cyclobutane ring is exo.

(14) Reference 11, p 81.
(15) Reference 11, Chapter 2-2.
(16) Wehrli, F. W.; Wirthlin, T. "Interprelation of Carbon-13 NMR Spectra"; Heyden: Philadelphia, 1978; p 56.

Chart II



Syn vs. Anti Stereochemistry of Cyclobutane Fragment and Proximal vs. Distal Relationship of the Carbonyl Relative to the C-8 Methyl. Only four sets of resonances (entries 7, 10, 11, and 12 in Table I) remain to be assigned. These correspond to the bridgehead (C-9) and the cyclobutane hydrogens (positions 2, 3, and 7). These assignments cannot be made without considering the remaining possibilities for the stereochemistry of the cyclobutane ring system. These are outlined by partial structures E, F, G, and H in Chart II. An anti configuration about the cyclobutane is indicated by the absence of more than one resolvable vicinal ^{13}C–^{1}H coupling in the C-8 methyl quartet (δ_{13_C} 17.0 in Figure 4). Thus, a *syn*-cyclobutane (as in partial structure I) would result in a



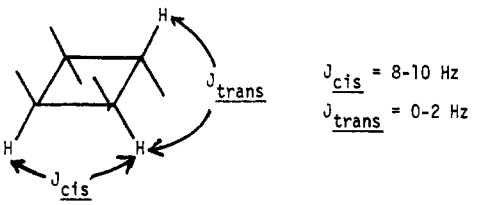
triplet fine structure superimposed on the large quartet because two cis-periplanar protons are coupled with the C-8 methyl. However, only a doublet fine structure is observed, as expected for a single cis-periplanar proton (as in partial structure J).

One of the apparent proton singlets (either entry 11 or 12, Table I) must be assigned to the bridgehead proton on C-9 (no resolved coupling to protons on C-12). We have tentatively assigned the proton resonance at δ 1.97 (entry 12) to the bridgehead proton on the basis of the expected shift range for this position. This is the same assignment that would be made by comparing the ^{13}C chemical shift (54.2 ppm) with the shift predicted (60 ppm) when substituent chemical shift additivities are used.[17] Fortunately, the stereochemical assignment does not rely on these relative resonance assignments, since substituent chemical shift additivity rules are unreliable when so many neighboring substituents are present.

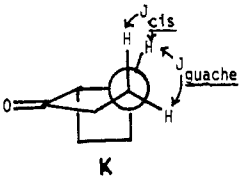
The cyclobutane proton resonances have apparent multiplicities of singlet (δ 1.52), doublet (δ 2.03), and triplet (δ 2.30) as indicated by the top entry in Chart II. Although

(17) Reference 4, p 61.

Chart III



there is considerable overlap of the cis and trans vicinal proton coupling ranges in cyclobutanes (Table II), the rigid polycyclic system being studied allows accurate definition of the dihedral angles and consequently the vicinal couplings. Vicinal cis and trans cyclobutane protons in this polycyclic system will define dihedral angles close to 0° and 120°, respectively. The cis and trans vicinal couplings will therefore be in the upper (8–10 Hz) and lower (0–2 Hz) ends of their respective ranges (Chart III). By use of these values of couplings and the presence of additional large cis (8 Hz) and small gauche (0–3 Hz) vicinal couplings to the methylene protons in the cyclopentanone ring system (as in partial structure K), spectral patterns can be predicted for each of the partial structures E, F, G, and H. These predicted patterns are outlined in Chart II. Only the large couplings are resolved in the experimental spectra. By comparison of these patterns with the experimental spectra, structures F and H can be eliminated immediately. The relative proton shifts of H_b and H_c are not reliably assigned. Therefore, the relative positions



of the doublet and triplet are not a dependable indication of whether structure E or structure G is the correct one. However, the ^{13}C shifts of C-3 (47.3) vs. C-7 (41.8) are a reliable indication that C-3 is α to the carbonyl group,[4] thus confirming **2x** as the correct structure.

Conclusion

By using a combination of 2D-FT NMR techniques, it is possible to assign the relative configuration of the major photoadduct from cyclopent-2-en-1-one and 1 as 8-methyl-4-oxo-10-*endo*-(trimethylsiloxy)-*cis*-*anti*-*cis*-tetracyclo[7.2.1.0.^{2,8}0^{3,7}]dodecane-10-*exo*-carbonitrile (**2x**). Such assignment is not possible with any other technique short of an X-ray crystal structure. It would likewise be difficult to make the structural assignment of **2x** with any single NMR technique. However, joint application of two 2D-FT NMR techniques greatly simplified the spectral analysis and allowed the assignments to be made. For the solution of this structural problem, the abilities to observe and utilize vicinal ^{13}C–^{1}H coupling and to correlate individual proton resonances with ^{13}C shifts via 2D-FT NMR were extremely powerful methods. Similar joint application of these and other 2D-FT NMR techniques will be indispensible analytical methods for structural analysis of complex molecules and will supersede efforts to use higher magnetic fields for spectral simplification.

Experimental Section

The preparation of compound **2x** will be described elsewhere. NMR spectra were recorded by direct observation of ^{13}C on a 30% solution of **2x** in $CDCl_3$ contained in a 10-mm sample tube using a Varian XL-200 spectrometer. Normal one-dimensional ^{13}C

spectra were obtained with a 4.0-μs (30°) pulse, a 15-kHz spectral window, quadrature detection, and 16K data points to give 0.92-Hz data point resolution. Free induction decays were weighted to give 1-Hz line broadening. ^{13}C chemical shifts reported in Table I were obtained from the one-dimensional ^{13}C spectrum and are referenced relative to $CDCl_3$ having a chemical shift of 77.0 ppm. All other chemical shifts and coupling constants were obtained from the 2D-FT NMR spectrum unless otherwise noted.

2D-FT NMR spectra were obtained with HET2DJ and HETCOR pulse sequences supplied in the instrument manufacturer's software package. These sequences cycle the phases of the spectra in order to provide the equivalent of quadrature phase detection in both frequency dimensions. Spectra were obtained in the unlocked mode using a sweep width of 3200 Hz (^{13}C range to cover the upfield portion of the spectrum), 1024 points, 13-μs (90°) ^{13}C and 50-μs (90°) ^1H pulse widths, 0.16-s acquisition time, and 2-s repetition rate. A total of 256 spectra (consisting of 32 transients each) were obtained by varying the evolution time between pulses to provide the equivalent of a 750-Hz sweep width in the second frequency dimension. The free induction decays in the second dimension (obtained by Fourier transformation of each of the 256 spectra followed by transposition of the data matrix) were zero filled to 1024 points and Fourier transformed to provide 1.5 Hz/point resolution in the second dimension (J_{CH} or $^1H\delta$). Spectra were displayed in the absolute value mode to avoid phasing problems. Free induction decays in both dimensions were resolution enhanced and Gaussian weighted ($e^{t/0.04}$ and apodization function = 0.08, respectively) to minimize line broadening and spectral distortion effects caused by the use of the absolute value display mode.

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Utilization of Vinylsilanes in [4 + 2] Cycloaddition Reactions

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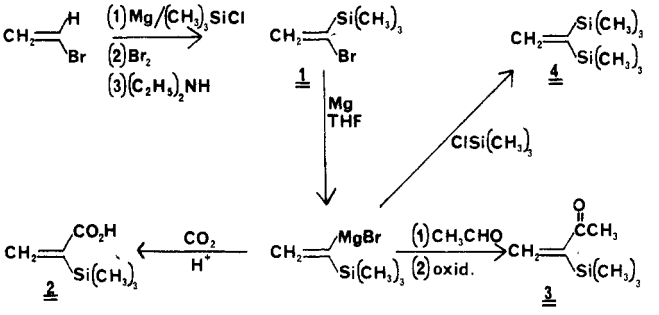
The reaction of several vinylsilanes with benzonitrile oxide, 2-diazopropane, *C*-carboethoxy-*N*-phenylnitrile imine, and substituted 1,3-butadienes has been examined. The 1,3-dipolar cycloadditions followed frontier orbital predictions and gave silylated isoxazoles, nonsilylated pyrazolines, and silylated pyrazolines, respectively. The orientation observed can be explained in terms of maximum orbital overlap of the dipole LUMO–vinylsilane HOMO. The [4 + 2] cycloaddition of several dienes with (2-nitrovinyl)trimethylsilane gave Diels–Alder adducts in good yield. Relative rates for some of the cycloadditions were determined.

In recent years, the utilization of silicon-based reagents has increased greatly in various synthetic transformations.[1-3] Allyltrialkylsilanes have been intensively studied because of their ability to undergo reactions with electrophiles to form carbon–carbon or other bonds with a concomitant double bond shift and cleavage of silicon.[1-3] Vinylsilanes have also been shown to be versatile synthetic intermediates undergoing electrophilic desilylation with retention of stereochemistry.[4-11] These compounds can serve as useful precursors for carbonyl compounds, vinyl halides, and olefins of predictable geometry. Despite their extensive use in organic synthesis, vinylsilanes have been infrequently employed in [4 + 2] cycloaddition reactions. Only occasional examples have been reported that make use of these substrates in Diels–Alder reactions.[12,13] Our interest in utilizing 1,3-dipolar cycloadditions in organic synthesis[14,15] focused our attention on the reaction of various 1,3-dipoles with vinylsilanes.[16] In this paper we wish to describe the results of a study of the profiles of reactivity of several easily accessible 1,3-dipoles toward cycloaddition with a selection of vinylsilanes bearing electron-withdrawing groups.

Results and Discussion

While 1,3-dipolar cycloadditions of nitrile oxides to electron-deficient alkenes have been of extensive value in organic synthesis, the low regioselectivity in the reactions with simple olefins has detracted from the synthetic method. We thought that one approach to circumvent this complication would be to utilize α-silyl-substituted dipolarophiles that undergo regiospecific cycloaddition. This

Scheme I



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