Fourier maps. Full-matrix least-squares refinement (anisotropic temperature factors for all atoms except hydrogen which were treated isotropically) yielded $R(F_o)$ = 0.057 (all data). Form factors for Fe, C, and O (and anomalous dispersion corrections for Fe) were taken from the International Tables, Vol. III, Kynoch Press, Birmingham, England, 1962, pp 202–203, and from Vol. IV, pp 149–50, respectively. The H atom form factors were from R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965). Two data sets were collected at −100 °C on two *different* crystals. The first data set contained 3225 unique data only and was used to solve the structure while a much more extensive data set was collected on a smaller crystal with less absorption. Although the derived positional parameters for all atoms are the same for both data sets within the estimated standard deviations, only those for the second data set are given because of the expectedly higher precision.

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(9) The iron atom labeling scheme used in the figure is identical with that used by Manassero et al.[11] for [HFe$_4(\eta^2$-CO)(CO)$_{12}^-$].
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Applications of Bridgehead Alkenes to Organic Synthesis. Regio- and Stereochemical Control in the Diels–Alder Route to Polyfunctional Cyclohexenes and Cyclohexanes
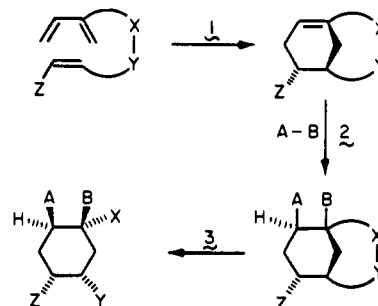
Sir:

Suitably functionalized bicyclic molecules occupy an important role in synthetic organic chemistry. The well-defined stereochemical relationship of the carbon framework permits simultaneous control over the relative configuration of a number of asymmetric centers. The stereochemical information contained in these bicyclic molecules can be retrieved in a subsequent fragmentation or cleavage reaction.
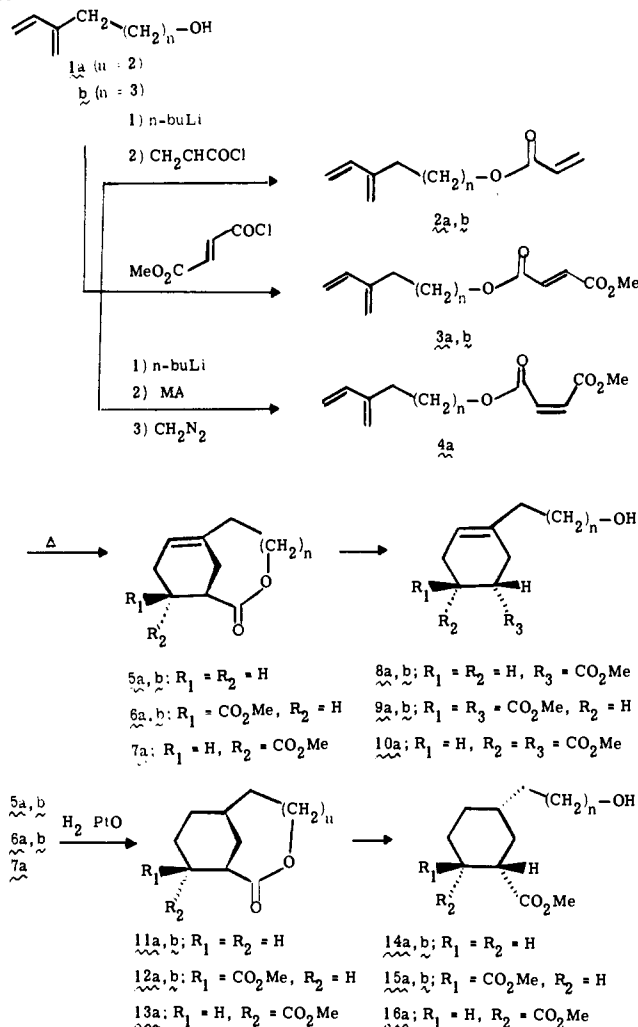
We report herein an application of this methodology to control stereo- and regiochemistry in the synthesis of polysubstituted cyclohexenes and cyclohexanes. Our approach is outlined in Scheme I. A key step in the synthesis is an intramolecular Diels–Alder reaction that results in formation of a medium-ring bicyclic lactone containing a *bridgehead double bond*.[1] We illustrate, for the first time, the utility of bridgehead alkanes in organic synthesis by the ad-

Scheme I

Scheme II

5a,b: R_1 = R_2 = H
6a,b: R_1 = CO$_2$Me, R_2 = H
7a: R_1 = H, R_2 = CO$_2$Me

8a,b; R_1 = R_2 = H, R_3 = CO$_2$Me
9a,b; R_1 = R_3 = CO$_2$Me, R_2 = H
10a; R_1 = H, R_2 = R_3 = CO$_2$Me

11a,b; R_1 = R_2 = H
12a,b; R_1 = CO$_2$Me, R_2 = H
13a; R_1 = H, R_2 = CO$_2$Me

14a,b; R_1 = R_2 = H
15a,b; R_1 = CO$_2$Me, R_2 = H
16a; R_1 = H, R_2 = CO$_2$Me

dition–cleavage sequence shown in steps 2 and 3 in Scheme I. The addition step establishes the relative configuration of three asymmetric centers; cleavage of the original linkage between diene and dienophile results in formation of a di-, tri-, or tetrasubstituted cyclohexane with control over all asymmetric centers.

The specific compounds used to illustrate this sequence are the triene esters **2–4**, chosen because of the ease of cleavage of the lactone bridge and the activating influence of the carbonyl group in the intramolecular Diels–Alder step.[2,3]

Esterification of dienols **1a**[4] and **1b**[5] by the methods outlined in Scheme II results in 40–60% yields of triene esters **2–4**.[6] Intramolecular cycloaddition was accomplished by heating 0.1 M solutions in xylene. Cycloadditions were complete in 5–6 h. Typical reaction conditions: 185 °C for **2a**, **2b**, and **4a**, and 130 °C for **3a** and **3b**. The bridgehead alkenes (**5–7**), formed in 40–60% yield, are sufficiently stable to allow isolation by

Scheme III

14a (58%) 20 (42%)

H₂/PtO

22 (60%) + 23 (40%)
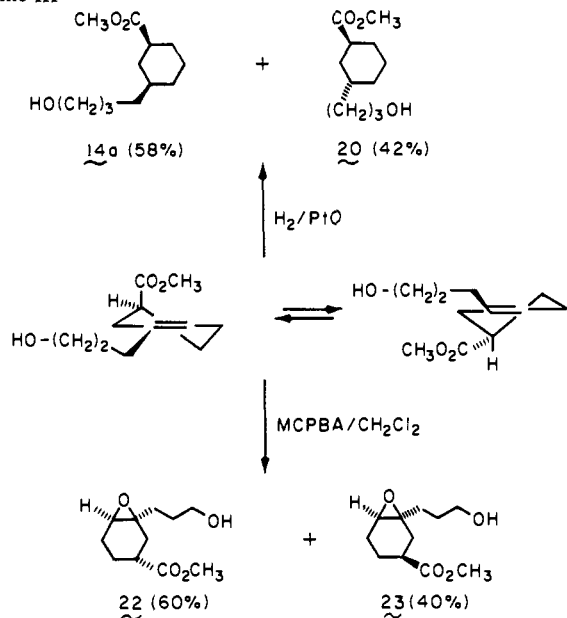
concentration under reduced pressure followed by chromatographic workup. Structure confirmation was obtained by a combination of spectroscopy[6] and chemical correlation with the cycloadducts obtained from the bimolecular Diels–Alder reaction. For example, the product from cycloaddition of **2a**, bridgehead lactone **5a**, when treated with methoxide (NaOMe, HOMe, 0 °C, 1 min) produces a single cyclohexene derivative **8a**; this isomer corresponds to the minor component from the bimolecular Diels–Alder reaction between dienol **1a** and methyl acrylate (eq 1).[7] (Compounds **8a** and **17** are only partially separated by capillary VPC.)

8a 17
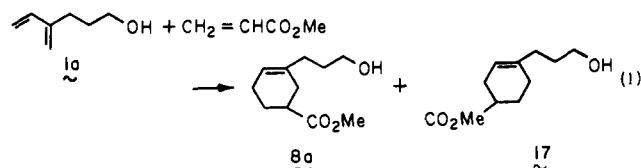
Similarly, triene esters **3a** and **4a** afford a single adduct. This is consistent with our previous finding demonstrating regiospecificity when there are as many as five atoms in the bridge joining dienophile and diene.[3,8] Indeed, regiospecificity is still high (>92%) with six atoms in the bridge. For example, cycloaddition of triene ester **2b** gave a mixture of cycloadducts, **5b** and **18**, in a ratio of 92:8. The minor component was separated chromatographically and characterized both spectroscopically[6] and by correlation with the *major* component of the bimolecular Diels–Alder reaction (**19**), eq 2.

18 (8%) 19
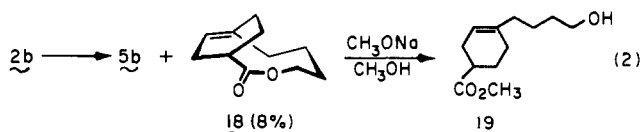
Thus, at least within the limited series studied, the intramolecular route offers a novel approach to the regiochemistry problem of 2-substituted dienes.[9]

These results also establish that the cycloadditions are stereospecific at the dienophile; trans- and cis-triene esters **3a** and **4a** result in formation of exo and endo bicyclolactones **6a** and **7a**, respectively. Our efforts to extend the series to bridgehead lactones containing four atoms in the lactone bridge have thus far been unsuccessful; despite the fact that the resulting bridgehead compounds would contain only a *trans*-cyclono-

nene ring, the triene esters are reluctant to undergo cycloadditon.

Addition reactions to the carbon–carbon double bond of bridgehead alkenes occurs with almost complete syn stereoselectivity; the bicyclic framework denies access of reagents to the back side of the molecule.[10] The additon reaction fixes the relative configuration of three asymmetric centers; cleavage of the X–Y bridge unmasks the substituted cyclohexane.

Catalytic reduction of bridgehead lactones **5–7** affords a quantitative yield of bicyclic lactones **11, 12,** and **13.** Hydrolysis and esterification (CH_2N_2) gives the epimerically pure di- and trisubstituted cyclohexanes **14, 15,** and **16.** As expected, catalytic reduction of conformationally flexible cyclohexenes **8** and **9** gives isomeric mixtures (Scheme III).[11] Thus, reduction of **8a** (obtained from cleavage of lactone **5a**) results in a 58:42 mixture of cis- and trans-1,3-disubstituted cyclohexanes **14a** and **20**; reduction of **5a** followed by hydrolysis and esterification yields pure *cis*-**14a**.

Utilization of the remaining asymmetric center is accomplished by the epoxidation-cleavage sequence illustrated in eq 3. Treatment of bridgehead alkene **5a** with 1 equiv of *m*-

5a 21 22 (3)
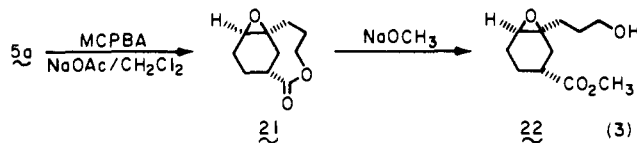
chloroperbenzoic acid yields bridgehead epoxylactone (**21**) (78%).[6] Treatment of **21** with 1 equiv of sodium methoxide gives a single cyclohexane epoxide, **22.** This isomer corresponds to one of the products obtained from epoxidation of cyclohexenol **8a** (Scheme II).

The reactivity of the bridgehead double bond coupled with its high stereospecificity holds considerable promise for the application of bridgehead alkenes in organic synthesis. Work along these lines is underway.

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(4) E. Bertele and P. S. Schudel, *Helv. Chim. Acta*, **50**, 2445 (1967).
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(6) The yields have not been optimized. Satisfactory spectral data (IR, ¹H and ¹³C NMR, MS) were obtained for all new compounds. Tables of spectroscopic data for all new compounds are available in as supplementary material. See paragraph at the end of the paper.
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Investigation of Crystalline Naphthazarin B by 13C NMR Spectroscopy Using "Magic Angle" Spinning Techniques and by X-ray Diffraction: Evidence for a Dynamic Disordered Structure

Sir:

Few organic molecules have been the subject of as many X-ray structural investigations as has naphthazarin.[1,2] Several investigations of each of the three crystalline forms (designated A, B, and C) have led to the conclusion that in the crystalline state the molecule is centrosymmetric and, hence, can best be represented not as **1a** but as a resonance hybrid of structures such as **2a** and **2b**, i.e., the symmetrical form **2**.[3]
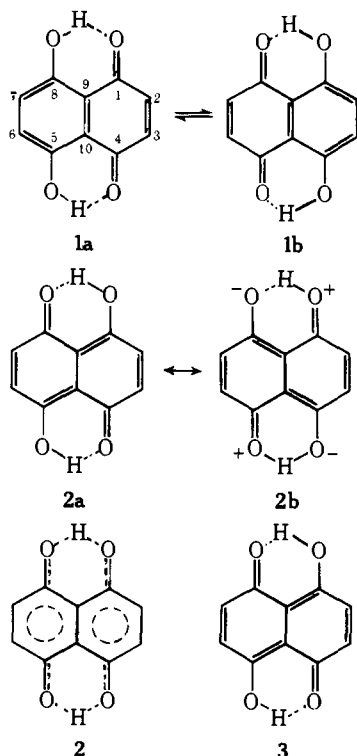
In contrast, solution studies such as dipole moment determination[5] and NMR[1,3,6] and IR[7] spectroscopy have been interpreted in terms of structures **1a** and **1b** which are in rapid equilibrium on the NMR time scale down to −75 °C; an indirect argument has been made[7] that an isolated molecule of the 1,5-quinone **3** should be very much less stable than **1a**. As a result, there appears to be acceptance of the belief that the molecular structure in the solid state (**2**) is different from that in solution (**1a** or **1b**) owing to the effect of crystal packing forces.[1,7] The structure of naphthazarin is of interest not only

in its own right, but because this assembly of functional groups occurs in clinically important antitumor antibiotics[8] as well as in other natural products.[1,2b]

It has recently been shown[9] that, by a combination of high power proton decoupling, cross polarization,[10] and "magic angle" spinning[11] techniques, it is possible to obtain relatively well-resolved high-resolution 13C NMR spectra of solid materials.[12] An important feature of these high-resolution 13C experiments in solids is that the chemical shift values obtained are the "isotropic" values for the solid state and may, therefore, be compared directly with those from solution NMR; these solid-state signals are averaged by chemical exchange processes in the same way as solution spectra[13] and may thus be used to distinguish motions in the solid state which involve chemical exchange from those which do not.

In this communication we report the application of high-resolution solid-state 13C NMR spectroscopy using these techniques and a further detailed X-ray structural study to this problem.

Interchange between the two tautomeric forms **1a** and **1b** involves primarily the movement of only two hydrogen atoms and might thus occur readily in the solid state; this process is accompanied by interchange between carbonyl and hydroxylic carbons which are both well resolved in the 13C NMR spectrum and easily assignable. Our new data strongly suggest that the structure of crystalline naphthazarin is dynamically disordered and involves a tautomeric equilibrium which is fast at room temperature (in the solid state).

The 13C NMR spectrum of a stationary sample of polycrystalline naphthazarin B[2,14] is shown in Figure 1A. Only broad, relatively featureless absorptions are observed, as would be expected since each of the carbons in the molecule should show a large shift anisotropy. The spectrum of the same sample recorded under identical conditions except that it is now also being spun rapidly (~3.5 kHz) at the "magic angle" is shown in Figure 1B. Well-resolved ($\Delta V_{1/2} \simeq 25$ Hz) peaks are now observed in the spectrum. The fact that broad absorptions are observed for the stationary sample under the same experimental conditions rules out the possibility that the sharp absorptions in the MAS spectrum are due to very mobile, noncrystalline material or to some experimental artifact. Under a whole variety of experimental conditions only three peaks are observed in the spectrum, and no peak is observed at low field where the carbonyl groups would be expected to absorb, facts that are indicative of a fast chemical exchange process. This is confirmed by comparison of the solid-state spectrum (Figure 1B) with the high-resolution 13C spectrum from solution whose signals have been artificially line broadened (Figure 1C). The two spectra are identical, indicating that the same chemical exchange process is occurring in both phases. The peak assignments given in the caption to the figure are taken from the high-resolution solution spectrum[15] and are confirmed by the different cross-polarization rates in the solid-state experiment where the four equivalent carbons which bear protons cross polarize much more efficiently than the other six.

When the temperature is lowered to −160 °C, there is a dramatic change in the spectrum (Figure 2). The highest field line assigned to carbons 9 and 10 is unchanged, and the other two absorptions each clearly split into two lines as would be expected for the freezing out of the dynamic exchange process.[16]

Dark-red prismatic crystals of the B form of naphthazarin from benzene or chloroform solution were examined by X-ray methods. Crystal data: $C_{10}H_{16}O$; mol wt, 190.2; monoclinic; $a = 5.419$ (1), $b = 6.382$ (2), $c = 11.838$ (3) Å; $\beta = 91.51$ (2)°; $V = 409.3$ Å³; $Z = 2$, space group $P2_1/c$. A total of 635 reflections was considered significantly above zero at the 2σ level out of a possible 699 within the Cu Kα sphere ($2\theta \leq 130°$). Full-matrix refinement of a model with hydroxyl hydrogen