Substituent Effects On Intramolecular Epoxide Cyclizations That Can Competitively Occur at Aromatic or Double Bond Positions[1]

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The effects of substituents on epoxides that can competitively cyclize at either a double bond or aromatic position were determined. Adding a group that would stabilize the transition state of the double bond cyclization of an epoxide that underwent predominantly aromatic cyclization increased the relative amount of the former pathway, but not dramatically. Adding a strong activating substituent to the aromatic group of an epoxide that underwent predominantly double bond cyclization increased the relative amount of aromatic cyclization, but a complex product mixture was obtained. An explanation of the behavior observed is presented.

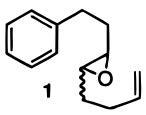
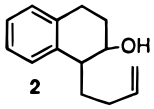
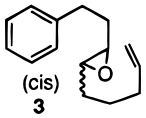
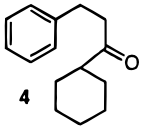
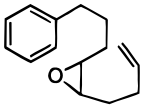
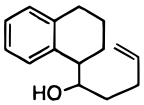
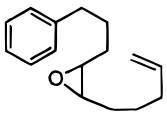
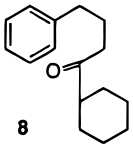
Introduction

Biomimetic cyclizations of epoxides, especially epoxy-ene cyclizations, have been investigated for some time.[2] Although epoxide cyclizations to aromatic positions (epoxy-arene cyclizations) is a newer area of study,[2−4] these reactions have already been used to make important natural and medicinal products in high yields.[2,5,6]

In previous studies comparing these two related areas of chemistry,[3] we determined the relative facility of epoxide cyclizations to intramolecular aromatic and double bond positions (Table 1). When an *exo* versus *endo* cyclization[7] can competitively occur, be it aromatic versus double bond or vice versa,[3] the *exo* process predominates. When both aromatic and double bond cyclization pathways are *endo*, the aromatic cyclization process occurrs (**1** → **2**). On the other hand, when both ring-forming pathways could be *exo*, the double bond cyclization process is favored (**7** → **8**).

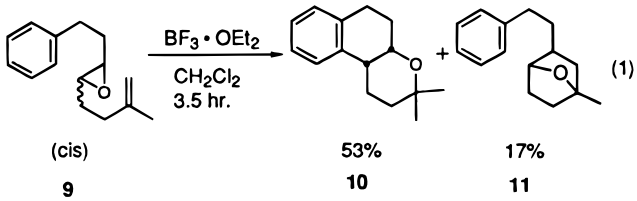
In this paper, we report studies on compounds which have activating substituents added to the previous compounds to see if the ring formation preferences could be reversed. For example, if a methoxy group was added to the aromatic ring of **3**, would this lead to epoxy-arene cyclization rather than the previously observed epoxy-ene cyclization? Alternatively, would a methyl group attached to the internal carbon of the double bond of **1** promote double bond cyclization since the resulting reactive species would resemble a tertiary cation?

Table 1. Cyclization Substrates and Major Products

Epoxide	designation of cyclization: double bond	aromatic	Major product
 **1**	*endo*	*endo*	 **2**
 (cis) **3**	*exo*	*endo*	 **4**
 **5**	*endo*	*exo*	 **6**
 **7**	*exo*	*exo*	 **8**

Results

Compounds **1** and **3** (Table 1) underwent exclusively epoxy-arene cyclizations. Compounds **9** (eq 1) and **13** (eq 2) differ from those compounds by having a methyl group on the olefin. These changes should favor epoxy-ene cyclization since the resulting double bond cyclization intermediate should resemble a tertiary cation. However, when **9** was treated with $BF_3{\cdot}OEt_2$ in dichlo-



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(1) A preliminary account of some of this work has been published: Taylor, S. K.; May, S. A.; Hopkins, J. A. *Tetrahedron Lett.* **1993**, *34*, 1283.

(2) For a recent review see (a) Taylor, S. K. *Org. Prep. Proc. Int.* **1992**, *24*, 245. For earlier reviews see (b) van Tamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111. (c) Sutherland, J. K. *Chem. Soc. Rev.* **1980**, *9*, 265. (d) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (e) Goldsmith, D. *Fortschr. Chem. Org. Naturst.* **1971**, *29*, 363.

(3) Taylor, S. K.; Bischoff, D. S.; Blankespoor, C. L.; Deck, P. A.; Harvey, S. M.; Johnson, P. L.; Marolweski, A. E.; Mork, S. W.; Motry, D. G.; Van Eenenaam, R. *J. Org. Chem.* **1990**, *55*, 4202. See correction: *Ibid.* **1991**, *56*, 5736.

(4) (a) Taylor, S. K.; Hockerman, G. H.; Karrick, G. L.; Lyle, S. B.; Schramm, S. B. *J. Org. Chem.* **1983**, *48*, 2449. (b) Taylor, S. K.; Davisson, M. E.; Hissom, B. R., Jr.; Brown, S. L.; Pristach, H. A.; Schramm, S. B.; Harvey, S. M. *Ibid.* **1987**, *52*, 425. (c) Taylor, S. K.; Bankespoor, C. L.; Harvey, S. M.; Richardson, L. J. *J. Org. Chem.* **1988**, *53*, 3309.

(5) (a) Broka, C. A.; Chan, S.; Peterson, B. *Ibid.* **1988**, *53*, 1586. (b) Burnell, R. H.; Dufour, J. M. *Can. J. Chem.* **1987**, *65*, 21.

(6) (a) Tanis, S. P.; Herrington, P. M. *J. Org. Chem.* **1983**, *48*, 4572. (b) Tanis, S. P.; Raggon, J. W. *Ibid.* **1987**, *52*, 819.

(7) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. For epoxide cyclizations, the *exo* cyclization results in ring formation with the resulting OH group outside the ring formed. *Endo* cyclizations result in the OH in the ring formed.

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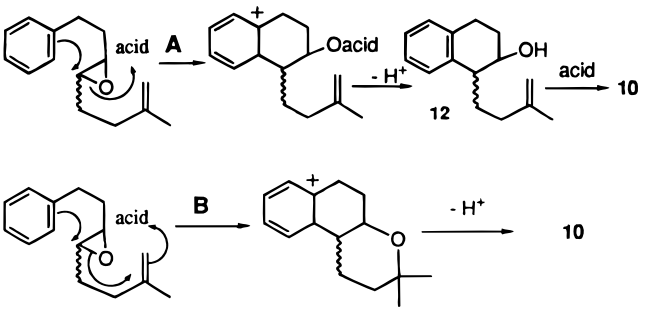
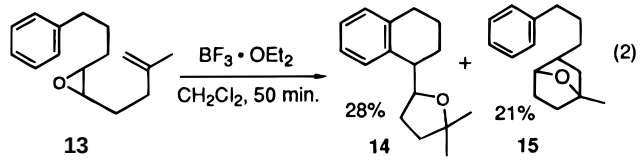
Scheme 1



romethane, an epoxy-arene product still predominated: **10** and **11** were isolated in 53% and 17% yields, respectively.[8] In this and the other cyclizations, the reactions were conducted under very dilute conditions to minimize intermolecular reactions.

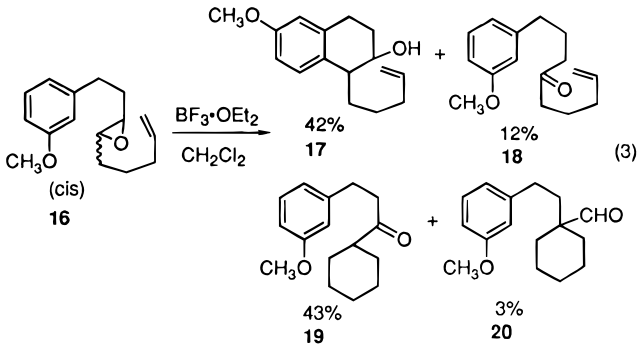
Although a single step could be envisioned for the two rings formed to give **10** (Scheme 1, pathway B), we showed they were formed in a stepwise fashion from an alcohol precursor (**12**) that we prepared independently (Scheme 1, pathway A). This compound was subjected to the reaction conditions, and it quickly formed **10** in >90% yield. Also, when the reaction was followed by NMR, the aromatic region changed rapidly, well before any changes occurred in the vinyl region. When the reaction was done using shorter reaction times or the weaker Lewis acid $SnCl_4$, we detected **12** in significant quantities by GCMS. These observations support the stepwise pathway A.

Compounds **14** and **15** resulted in 28% and 21% isolated yields (eq 2) when **13** was treated with BF_3•OEt similarly.[9] Compound **14** can be formed in a pathway similar to that shown in Scheme 1 pathway A. Here, the double bond cyclization product **15** is formed in significant but not predominant quantity.

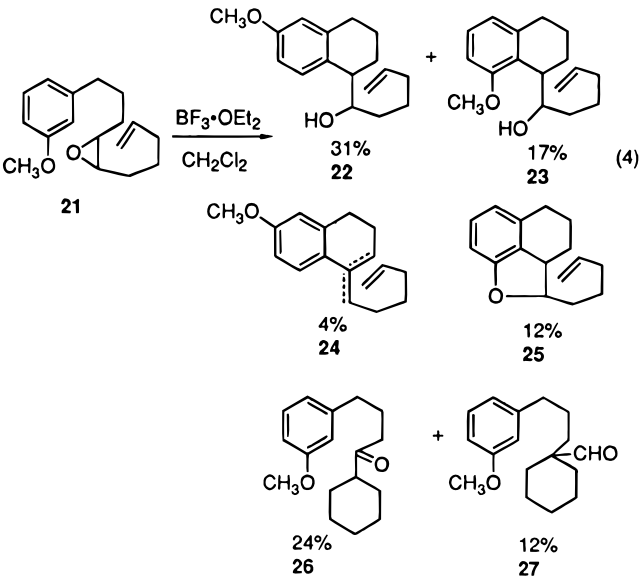


Compound **3** (Table 1) underwent exclusively double bond cyclization.[3] Compound **16** is similar to **3**, but it has a CH_3O activating group added to it. This compound cyclizes to a complex mixture of products, with the major four shown in their relative quantities (eq 3). The reaction was followed over time, and the products shown are those which result immediately after the epoxide is consumed.

The activating substituent makes a difference, but not as much as one might expect: the double bond and aromatic cyclization pathways compete almost equally well.



Epoxide **21** (eq 4) cyclizes to a complex mixture of products which were exceptionally difficult to separate and identify. HPLC and independent synthesis of some compounds were necessary to identify the products. Equation 4 shows the major products in their relative abundances. These compounds account for 80% of the volatile product composition with only one of the other unidentified compounds consisting of >2% of the mixture.

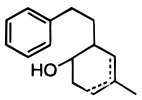


The epoxides used in this study were synthesized by the Wittig and epoxidation procedures developed earlier,[3] as shown in eqs 5 and 6. The aryl dienes used to make epoxides **16** and **21** gave >90% internal epoxidation products. The small amounts of side products were removed by HPLC as described below. The aryl diene precursors to epoxides **9** and **13** gave nearly equal amounts of terminal and internal epoxidation products. The two epoxides resulting from each epoxidation procedure were separated by HPLC. The resulting terminal epoxides were briefly tested for cyclization reactions, but no interesting results were observed.

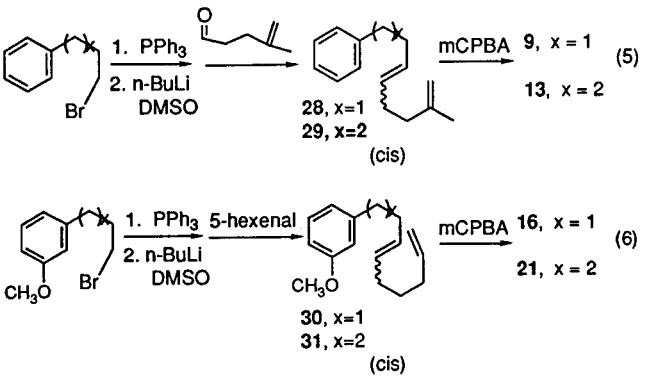
Discussion

In the previous study,[3] epoxides **1** and **3** (Table 1) gave exclusively aromatic cyclization and yielded one product each. Although **3** and **7** gave almost exclusively epoxy-ene cyclization, the product mixture was complex. This contrast between cyclization pathways was attributed to the reactive species involved in the two different reactions. The epoxy-arene pathway would go through an arenium ion whose primary subsequent step would be the loss of a proton to rearomatize the ring (see Scheme

(8) Products **10** and **11** account for 81% of the volatile product distribution of eq 2. Products analogous to those represented by the structure below account for another 9% as shown by GCMS and an NMR of the mixture of isomers. We were unable to separate these isomers, but they would be expected to accompany **10** and **12**.



(9) The yields of these products were undoubtedly higher, but these are the yields of pure, isolated compounds. Impure chromatographic fractions containing these compounds were not counted in the yields.



1, pathway A). The double bond cyclization would involve a carbocation-like species which could undergo proton migrations and eliminations almost isoenergetically. The result would be a complex product mixture, the behavior observed. In this work, our results were consistent with this conclusion. The cleanest reaction mixture was the one shown in eq 1, which gave the highest percentage of epoxy-arene ring formation (where we could account for 90% of the product mixture[8]).

Although the products obtained in this work are interesting and pertinent to biomimetic epoxide cyclizations,[2,3] it is unfortunate that the product compositions are not simpler. The methoxy group is known to activate the aromatic ring by three orders of magnitude[10] in certain cases, so it might be thought that the use of this group would have completely switched the epoxy-ene cyclizations to epoxy-arene ones. This probably did not occur because the rate-determining step involved in these reactions is not highly arenium-ion like.

It is noteworthy that in the cyclizations of **9** and **13**, the epoxide acts as the source of initiation and termination steps. This is somewhat rare[2a−e] and it may also be a reason for fewer products in these reactions: the oxygen termination step probably prevents further rearrangements.

Experimental Section

The equipment used has been described elsewhere.[3] The solvents used were dried immediately before use by distilling them from a drying agent under N_2. THF and ether were distilled from sodium/benzophenone, and CH_2Cl_2 was distilled from CaH_2. Boiling points and melting points are uncorrected. Semipreparative HPLC was done using a 25 cm × 10 mm silica gel column. ^{13}C NMR spectra were supplied for referee review to prove product purities (≥96% purity unless specified otherwise), and are referenced to the center peak of $CDCl_3$ set at 77.6 ppm. Elemental analyses were determined by Galbraith Labs, Inc. or Dornis and Kolbe. $BF_3{\cdot}OEt_2$ was used from a bottle sealed under N_2.

2-Methyl-8-phenyl-*cis*-1,5-octadiene (28). Under dry N_2, 7.3 mL of 2.4 M n-BuLi in hexane (17 mmol) was added dropwise to 14 mL of dry DMSO. After stirring 0.5 h, 7.9 g of the triphenylphosphonium bromide salt of 1-bromo-3-phenylpropane (17 mmol, made exactly as before[3]) in 45 mL of dry DMSO was added over 1.5 h. The resulting red-orange solution was stirred 0.5 h, and then 2.10 g (21 mmol) of 4-methyl-4-pentenal[11] in 5 mL of dry DMSO was added dropwise. After stirring 4 h, the reaction mixture was added to 85 mL of ice−water, and the resulting mixture was extracted with 85 mL of 9:1 hexane:ether. The organic layer was dried ($MgSO_4$), concentrated to 50 mL, and run through a 3 × 6 cm column of alumina with 200 mL of 9:1 hexane:ether. The concentrated organic layer was carefully distilled giving 1.33 g (41%, >97% GC purity)) of **28** (a later fraction had 10% *trans* isomer present), bp 74−76 °C (0.1 mm); ^1H NMR ($CDCl_3$) δ 1.7 (s, 3 H), 1.9−2.1 (m, 4 H), 2.3 (m, 2 H), 2.6 (t, 3 H), 4.7 (s, 1 H), 4.74 (s, 1 H), 5.4 (m, 2 H), 7.2−7.4 (m, 5 H): ^{13}C NMR ($CDCl_3$) δ 23.0, 26.1, 29.9, 36.6, 38.2, 110.6, 126.3, 126.4, 128.9, 129.1, 130.6, 142.7, 146.1; IR (NaCl disks) 1649 (m), 698 (s) cm^{-1}; mass spectrum *m/e* (relative intensity) 200 (5), 104 (19), 91 (100), 67 (24), 65 (21). Anal. Calcd for $C_{15}H_{20}$: C 89.91; H, 10.29. Found: C, 89.83; H, 10.11.

2-Methyl-9-phenyl-*cis*-1,5-nonadiene (29) was made as above by combining the triphenylphosphonium salt[3] of 1-bromo-4-phenylbutane (2.13 g, 4.5 mmol) with 2.2 mL of 2.2 M n-BuLi and 0.55 g of 4-methyl-4-pentenal[11] (5.6 mmol) to give **29** (*cis:trans* 9:1) in 45% yield, bp 78−79 °C (0.05 mm): ^1H NMR ($CDCl_3$) δ 1.8 (s, 3 H), 1.7−2.0 (m, 2 H), 2.1−2.5 (m, 6 H), 2.7 (t, 2 H), 4.7 (s, 1 H), 4.8 (s, 1 H), 5.5 (m, 2 H), 7.2−7.5 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 23.2, 26.3, 27.6, 32.2, 36.2, 38.5, 110.8, 126.4, 129.0, 129.2, 130.4, 131.0, 143.2, 146.2; IR (NaCl disks) 1650 (m), 760 and 700 (s) cm^{-1}. Anal. Calcd for $C_{16}H_{22}$: C, 89.66; H, 10.34. Found: C, 89.30; H, 10.41.

9-(*m*-Methoxyphenyl)-*cis*-1,6-nonadiene (30) was made by adding 4.4 mL of 2.5 M (11 mmol) n-BuLi dropwise to 8.2 mL of DMSO. After 0.5 h, a mixture of 17 mL of DMSO and 5.0 g (10 mmol) of the triphenylphosphonium bromide salt (mp 127.5−128.5 °C) of 3-(*m*-methoxyphenyl)-1-bromopropane[12] was added over 35 min. The resulting mixture was stirred 4 h and worked up by adding the mixture to 100 mL of cold water and extracting the mixture three times with 50 mL portions of 4:1 hexane:ether. The combined organic layers were washed with water and run through alumina with 4:1 hexane:ether. The concentrated organic product was distilled, 1.41 g (60%), bp 90−92 °C (0.025 mm); NMR ($CDCl_3$) δ 1.5 (p, J = 7.3 Hz, 2 H), 2.1 (m, 4 H), 2.5 (m, 2 H), 2.7 (t, J = 7.3 Hz, 2 H); 3.9 (s, 3 H), 5.1 (m, 2 H), 5.5 (m, 2 H), 5.9 (m, 1 H), 6.9 (m, 3 H), 7.3 (t, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.4, 29.6, 29.9, 34.1, 36.8, 55.7, 111.8, 115.1, 115.2, 121.7, 129.8, 129.9, 131.0, 139.5, 144.4, 160.4; IR (NaCl disks) 1250 (s), 720 and 770 (s, *meta*) cm^{-1}; mass spectrum, *m/e* (relative intensity) 230 (10), 122 (69), 121 (100), 91 (38). Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 82.52; H, 9.38. The ^{13}C and ^1H NMR showed the compound was very pure.

10-(*m*-Methoxyphenyl)-*cis*-1,6-decadiene (31) was made from the triphenylphosphonium salt (mp 130−132 °C)[3] of 4-(*m*-methoxyphenyl)-1-bromobutane[12] and 5-hexenal by the Wittig procedure above in 56% distilled yield (*cis*:*trans* 9:1), bp 95−100 °C (0.01 mm); NMR ($CDCl_3$) δ 1.46 (p, J = 7 Hz, 2 H), 1.7 (m, 2 H), 2.1 (m, 6 H), 2.6, (m, 2 H), 3.8 (s, CH_3O), 5.0 (m, 2 H), 5.4 (m, 2 H), 5.8 (m, 1 H), 6.8 (m, 3 H), 7.2 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.4, 27.5, 29.6, 32.0, 34.0, 36.2, 55.8, 111.6, 114.9, 115.1, 121.6, 129.9, 130.3, 130.7, 139.5, 144.9; IR (NaCl disks) 1260 (s, CH_3O−Ar), 910 (s), 780 and 695 (s); mass spectrum *m/e* (relative intensity) 244 (4) 161 (23), 122 (8), 121 (21), 44 (22), 32 (100). Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.10; H, 9.82.

Epoxidation Procedure. The epoxides were prepared by the following procedure.

***cis*-3,4-Epoxy-7-methyl-1-phenyl-7-octene (9).** A solution of 1.72 g of 85% pure mCPBA (8.5 mol) in 40 mL of CH_2Cl_2 was added over 1 h to 1.33 (8.6 mmol) of **28** in 21 mL of CH_2Cl_2. The mixture was refluxed for 1.5 h and stirred for 6 h. The mixture was cooled and 25 mL of petroleum ether was added. After approximately 1 h, a white precipitate formed, and the mixture was suction filtered. The filtrate was washed twice with 20% $NaHSO_3$ and twice with 5% $NaHCO_3$. After drying ($MgSO_4$) and rotary evaporation of the solvent the product was short-path distilled, 83−86 °C (0.015 mm). Spinning band distillation was used in an unsuccessful attempt to separate the internal and terminal (~1:1) epoxides. HPLC (10 mm × 20 cm 10 μm silica gel column) with 90:10 trace hexane:CH_2Cl_2:EtOH gave >99% pure **9** (71 mg): ^1H NMR ($CDCl_3$) δ 1.6 (m, 4 H), 1.7 (s, 3 H), 1.9 (m, 2 H), 2.2 (m,

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(12) Trost, B. M.; Crimmin, M. J.; Butler, D. *J. Org. Chem.* **1978**, *43*, 4449.

2 H), 2.7−3.4 (2 overlapping multiplets, 4 H), 4.70 (s, 1 H), 4.74 (s, 1 H), 7.2−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 23.2, 26.7, 30.6, 33.6, 35.2, 57.4, 57.8, 111.2, 126.8, 129.2, 142.1, 145.5; IR (NaCl disks) 1650 (m), 890 (m), 750 (m), 699 (m); mass spectrum, *m/e* (relative intensity): 216 (0.4), 118 (14), 117 (35), 112 (17), 104 (19), 92 (23), 91 (100), 67 (36); exact mass *m/e* calcd for $C_{15}H_{20}0$ 216.1514, found 216.1528. ^{1}H and ^{13}C NMR and GC showed the compound was 98% pure.

***cis*-4,5-Epoxy-8-methyl-1-phenyl-8-nonene (13)** was prepared as described above using 391 mg of **29** (1.7 mmol) in 10 mL of CH_2Cl_2 and 510 mg of 65% mCPBA (1.9 mmol) in 5 mL of CH_2Cl_2. Reflux was conducted for 3 h, and the solution was stirred at room temperature for 6 h. Workup was as above. The crude product (0.4 g) was run through a plug of silica gel with 60:40 hexane:CH_2Cl_2 (0.266 g of product) and then purified by semipreparative HPLC (89:11 trace hexane:CH_2Cl_2:EtOH) to give 99% pure **13**. ^{1}H NMR ($CDCl_3$) δ 1.5−2.0 (m, 6 H), 1.7 (s, 3 H), 2.0−2.1 (m, 2 H), 2.6−2.8 (m, 2 H), 2.8−3.0 (m, 2 H), 4.71 (s, 1 H), 4.74 (s, 1 H), 7.2−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 23.0, 26.8, 28.0, 29.0, 35.2, 36.3, 57.3, 57.6, 111.1, 126.5, 129.0, 142.7, 145.4; IR (NaCl disks) 1649 (m), 891 (s), 749 (s), 699 (s); mass spectrum, *m/e* (relative intensity) 230 (6), 131 (50), 104 (100), 91 (100); exact mass *m/e* calcd for $C_{16}H_{22}O$ 230.1670, found 230.1700.

1-(*m*-methoxyphenyl)-*cis*-3,4-epoxy-8-nonene (16) was prepared by dropwise addition of a solution of 1.09 g of 55% pure mCPBA (4.05 mmol) and 23 mL of CH_2Cl_2 to 0.9 g (3.9 mmol) of **30** in 13 mL of CH_2Cl_2. The mixture was refluxed 1.5 h and stirred 4.5 h at room temperature. To the ice-cooled mixture was added 13 mL of petroleum ether. The resulting mixture was filtered, and the solid was washed with hexane. The combined organic wash and filtrate was extracted with 40 mL of 20% $NaHSO_3$, 5% $NaHCO_3$ (three times), and brine and dried ($MgSO_4$). The product left after solvent removal was column chromatographed (80:20:trace hexane:EtOAc:EtOH), giving 0.60 g (62%) of product. This compound was purified by HPLC (85:15 trace hexanes:EtOAc:EtOH) for the analytically pure compound used in cyclization studies: ^{1}H NMR ($CDCl_3$) δ 1.4−1.7 (m, 4 H), 1.8 (q, J = 7 Hz, 2 H), 2.1 (m, 2 H), 2.7−3.0 (2 overlapping multiplets, 4 H), 3.8 (s, 3 H), 5.0 (m, 2 H), 5.7 (m, 1 H), 6.8 (m, 3 H), 7.2 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.4, 27.9, 30.4, 33.6, 34.2, 55.8, 57.2, 57.9, 111.9, 114.9, 115.6, 121.5, 130.1, 138.9, 143.7, 160.4; IR (NaCl disks) 1250 (s), 900 (s), 760 (s), 690 (s) cm^{-1}; mass spectrum *m/e* (relative intensity) 246 (15), 134 (88), 121 (97), 91 (85), 78 (49), 65 (41), 55 (69), 43 (14), 41 (100). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.93; H, 8.69.

1-(*m*-Methoxyphenyl)-*cis*-4,5-epoxy-9-decene (21) was prepared as above using 1.05 g of 85% pure mCPBA (4 mmol) in 22 mL of CH_2Cl_2 and 0.92 g (3.8 mmol) of **31** in 12 mL of CH_2Cl_2. Workup was conducted as described above. Flash chromatography (85:14:1 hexane:CH_2Cl_2:EtOH) gave fractions that were 92−95% pure (0.15 g, 66%). One of the fractions was chromatographed (HPLC) (70:20:1 hexane:CH_2Cl_2:EtOH) to afford 97% (by GC) pure compound: ^{1}H NMR ($CDCl_3$) δ 1.5−1.7 (m, 6 H), 1.7−2.0 (m, 2 H), 2.0−2.2 (m, 2H), 2.6−2.8 (m, 2 H), 2.9−3.0 (m, 2 H), 3.8 (s, 3 H), 5.0 (m, 2 H), 5.8 (m, 1 H), 6.7−6.8 (m, 3 H), 7.2 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.5, 28.0, 28.1, 29.0, 34.2, 36.4, 55.8, 57.6 (2 C), 111.8, 114.9, 115.6, 121.5, 130.0, 139.0, 144.3, 160.3; IR (NaCl disks) 1250 (s), 910 (s), 760 and 690 (s); mass spectrum *m/e* (relative intensity) 260 (14), 161 (60), 134 (100), 122 (38). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.38; H, 9.46.

Cyclizations of 9 and 13. In a typical reaction, 71 mg (0.33 mmol) of **9** in 2 mL of dry methylene chloride was added dropwise under N_2 to 9 μL (0.073 mmol) of BF_3·OEt_2 in 15 mL of dry methylene chloride. The solution was stirred at room temperature for 3.5 h, and then it was washed with 5% $NaHCO_3$ and saturated NaCl and dried ($MgSO_4$). The products were purified directly by semipreparative HPLC using a 92:8 mixture of hexane:ethyl acetate (trace of EtOH). The yield of the reaction was determined by GC using **12** (as a standard) that had been prepared independently. Compound **13** was treated similarly only the reaction time was 50 min, and yields were of isolated, pure compounds. Subsequent reactions were followed by GC, and the existence of **12** was verified by GCMS comparison with the authentic sample. The products were identified as described below.

Cyclizations of 16 and 21. A solution of 0.10 g of **16** in 0.5 mL of CH_2Cl_2 was added dropwise to a solution of 6 μL of BF_3·OEt_2 in 18 mL of CH_2Cl_2. The reaction progress was followed by GC by taking aliquots (10 μL) of the reaction solution at 5, 15, and 25 min. At 1 h, 1.6% epoxide was left whereas 30% of **16** was present at 5 min. The reaction was stopped after 1 h, and the mixture was washed three times with 25 mL of 5% $NaHCO_3$ and once with brine and dried ($MgSO_4$). Rotary evaporation left 96 mg of the product distribution shown in eq 3. Products were separated by HPLC (85:15 trace hexane:EtOAc:EtOH).

Epoxide **21** was treated similarly by adding 0.12 g (49 mmol) of **31** in 0.5 mL of CH_2Cl_2 to a solution of 7 μL of BF_3·OEt_3 in 21.5 mL of CH_2Cl_2. After 0.5 h, the reaction mixture was worked up as above giving 0.11 g of crude product (eq 4). HPLC using 60:40 trace hexane:CH_2Cl_2:EtOH gave the products indicated.

3,3-Dimethyl-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]-chromene (10) had a 22 mL retention volume on HPLC (98% GC purity): ^{1}H NMR ($CDCl_3$) δ 1.1 (s, 3 H), 1.3 (s, 3 H), 1.3 (2 H under singlet), 1.8 (m, 1 H), 2.0−2.2 (m, 2 H), 2.3 (m, 1 H), 2.6 (m, 1 H), 2.8 (d, J = 2.5 Hz, 1 H), 3.1 (q of d, J = 16.1, 12.7 and 5.4 Hz), 4.1 (t, J = 5 Hz, 1 H), 7.1−7.3 (m, 4 H). The spectrum is very complex, and we can provide a complex analysis of all the spin systems and 2D NMR upon request. ^{13}C NMR ($CDCl_3$) δ 23.3, 24.9, 25.6, 29.4, 31.8, 32.3, 36.8, 67.4, 71.7, 126.0, 126.4, 127.3, (2 C), 129.4, 129.5; IR (NaCl disks) no C=O or OH bands, 1229 (m), 737 (ortho) cm^{-1}; mass spectrum *m/e* (relative intensity) 216 (39), 129 (100), 115 (56), 43 (55) exact mass *m/e* calcd for $C_{15}H_{20}O$ 216.1509, found 216.1514.

1-Methyl-3-(2-phenylethyl)-7-oxabicyclo[2.2.1]-heptane (11) had a 35 mL retention volume on the above HPLC: ^{1}H NMR ($CDCl_3$) δ 1.1−1.9 (m, 9 H), 1.5 (s, 3 H), 2.6 (t, J = 7 Hz, 2 H), 4.2 (d, J= 5 Hz, 1 H), 7.2−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.6, 32.2, 34.5, 36.3, 38.0, 44.9, 45.3, 81.3, 84.4, 126.3 (2 C) 128.0, 129.1 (2 C), 143.1; IR (NaCl disks) 1207 (m), 748 and 699 (monosubst benzene) mass spectrum *m/e* (relative intensity) 216 (2), 198 (43), 104 (211), 91 (100), 43 (94), exact mass *m/e* calcd for $C_{15}H_{20}O$ 216.1509, found 216.1481.

α-(3-Methyl-3-buten-1-yl)-1,2,3,4-tetrahydro-2-naphthol (12). A solution of 1.61 g (11 mmol) of β-tetralone in 3 mL of THF was added dropwise to a suspension of 0.48 g (12 mmol) of 60% NaH (12 mmol, in mineral oil) at −5 to −10 °C. The suspension was stirred 15 min, and 1.34 g (9 mmol) of 4-bromo-3-methyl-1-butene in 3 mL of THF was added dropwise to the mixture at −10 °C. After 45 min at −8 °C, the mixture was stirred 1 h at room temperature and refluxed 4.5 h. The mixture was diluted with 25 mL of ether, and 20 mL of saturated NH_4Cl was added. The organic layer was washed with brine, dried ($MgSO_4$), and rotary evaporated, leaving 1.8 g of crude product.

One gram of the product was distilled, bp 92−95 °C (0.01 mm), giving 0.17 g of 78% pure product. This compound was purified further by rotary thin-layer chromatography (80:20 trace hexane:CH_2Cl_2:EtOH) giving 63 mg of 96% pure compound 1-(3-methyl-3-buten-1-yl)-3,4-dihydro-1*H*-naphthalen-2-one (**32**): ^{1}H NMR ($CDCl_3$) δ 1.7 (s, 3 H), 1.9−2.1 (m 4 H), 2.4−2.7 (m, 2 H), 2.9−3.1 (m, 1 H), 3.1−3.2 (m, 1 H), 3.35−3.45 (m, 1 H), 4.68 (s, 1 H), 4.73 (s, 1 H), 7.1−7.3 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 23.1, 28.6, 30.4, 35.5, 38.2, 53.9, 111.1, 127.4, 127.5, 128.6, 128.7, 137.2, 138.0, 145.6, 212.9; mass spectrum *m/e* (relative intensity) 214 (30), 158 (23), 146 (100); exact mass calcd for $C_{15}H_{18}O$ 214.1353, found 214.1353. This compound was reduced with $LiAlH_4$ to give **12**: **32** (90 mg, 4.2 mmol) in 5 mL of ether was added to a slurry of 2.10 mg of $LiAlH_4$ (excess) and 15 mL of ether. Workup includes adding 0.4 mL of 15% NaOH and then 1 mL of H_2O to form a solid. The solid was vacuum filtered, and the filtrate was column chromatographed (hexanes:8−20% EtOAc:trace EtOH) gave a fraction that was predominantly one stereoisomer **(12)**: ^{1}H NMR ($CDCl_3$) δ 1.5 (broad s, 1 H), 1.8 (s, 3 H), 2.0 (m, 4 H), 2.2 (m, 2 H), 2.8 (m, 2 H), 3.0 (m, 1 H), 4.2 (m, 1 H),

4.748 (s, 1 H), 4.757 (s, 1 H), 7.1−7.2 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 23.1, 27.1, 28.5, 36.5, 44.2, 69.4, 110.8, 126.3, 126.8, 129.3 (2 C), 129.4, 136.2, 146.6; IR (NaCl disks) 3600−3200, 1047 (s), 886 (s), 752 (s, ortho); mass spectrum *m/e* (relative intensity) 216 (14), 160 (56), 142 (100), 129 (70), 117 (60), 115 (67); exact mass calcd for $C_{15}H_{20}O$, 216.1509, found 216.1514. Alcohol (13.1 mg) **12** was added slowly to a solution of 3 μL of BF_3·OEt_2 in 3 mL of dry CH_2Cl_2, and the solution was stirred 35 min. The solution was washed three times with 5% $NaHCO_3$ and once with brine and dried ($MgSO_4$). A GC yield of product **10** was 83%.

2,2-Dimethyl-5-(1,2,3,4-tetrahydronaphthalen-1-yl)tetrahydrofuran (14) was isolated by HPLC (30 mL retention volumn) as described above: ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.29 (s, 3 H), 1.5−2.0 (m, 6 H), 2.7 (t, J = 6.4 Hz, 2 H), 3.0 (q, J = 6.4 Hz, 2 H), 4.4 (q, J = 6.8 Hz, 1 H), 7.0−7.5 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 22, 25, 27, 28, 30, 39, 42, 53, 81, 82, 126.2, 126.3, 129.0, 129.1, 129.2, 138; IR (NaCl disks) 1144 (s), 1052 (s), 740 (s, ortho); mass spectrum *m/e* (relative intensity) 230 (1), 131 (29), 99 (100), 81 (84), 43 (38); exact mass calcd for $C_{16}H_{22}O$ 230.1665, found 230.1662.

1-Methyl-3-(3-phenylpropyl)-7-oxabicyclo[2.2.1]-heptane (15) was isolated by HPLC (36 mL retention volume): ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 3 H), 1.2−1.8 (m, 11 H), 2.6 (t, J = 6 Hz, 2 H), 4.1 (d, J = 5 Hz, 1 H), 7.1−7.3 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.6, 30.2, 30.3, 32.2, 36.0, 36.1, 36.7, 44.8, 45.7, 81.3, 84.3, 126.3, 128.9, 129.0 (2 C), 143.3; IR (NaCl disks) 1090 (m), 747 and 699 (monosubst benzene); mass spectrum *m/e* (relative intensity) 230 (4), 212 (38), 111 (32), 108 (36), 104 (66), 91 (100), 43 (85); exact mass calcd for $C_{16}H_{22}O$ 230.1671, found 230.1664.

1-(4-Penten-1-yl)-6-methoxy-1,2,3,4-tetrahydro-2-naphthol (17), isolated by HPLC (85:15 trace hexane:EtOAc:EtOH), gave a fraction of **17** that was 93% pure by GC: ^{1}H NMR ($CDCl_3$) δ 1.5−2.2 (m, 2 H) 2.5−3.1 (m, 3 H), 3.7 (s, 3 H), 4.2 (m, 1 H), 5.0 (m, 2 H), 5.8 (m, 1 H), 6.6 (s, 1 H), 6.7 (m, 2 H), 7.1 (d, J = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.1, 28.2, 28.3, 31, 37, 45, 57, 61, 113, 114 (2 C), 115, 132, 140; IR (NaCl disks) 3600−3200 (s), 1260 (s), 1038 (s), 870 (m), 810 (m); mass spectrum *m/e* (relative intensity) 246 (33), 238 (48), 177 (66), 44 (100) (The aromatic region was exactly the same as that of (1-(*m*-methoxyphenyl)-1-methanol made earlier.[4b])

4-(4-Penten-1-yl)-5-methoxy-1,2-dihydronaphthalene (18) could not be purified by HPLC and was tentatively identified based on the similarity of its GCMS data to that of **26**: 230 (69), 134 (100).

1-Cyclohexyl-3-(*m*-methoxyphenyl)-1-propanone (19) was isolated by HPLC and also prepared independently. A Grignard reagent was prepared from 1-(*m*-methoxyphenyl)-2-bromoethane[4b] (4.6 g, 21 mmol) and 0.52 g of Mg turnings (21 mmol) in 10 mL of ether and 10 mL of THF. A solution of 2.4 g (21 mmol) of cyclohexanecarbaldehyde and 10 mL of ether was added dropwise, and the mixture was stirred overnight. The mixture was cooled with an ice bath, and 10% H_2SO_4 was added slowly to neutralize the mixture. After 5% $NaHCO_3$ and aqueous washes, the dried ($MgSO_4$) organic layer was rotary evaporated. The product was triturated and recrystallized using hexane, giving 3.68 g (64%) of 1-cyclohexyl-3-(*m*-methoxyphenyl)-1-propanol (**33**): mp 54−55.2 °C; ^{1}H NMR ($CDCl_3$) δ 1−2.0 δ (m, 14 H), 2.6 (m, 1 H), 2.8 (m, 1 H), 3.8 (m, 1 H), 3.8 (s, 3 H), 6.8 (m, 3 H), 7.2 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.1, 27.0, 27.2, 28.5, 29.8, 33.1, 36.5, 44.5, 55.8, 76.3, 111.7, 114.9, 121.5, 130.0, 144.8, 160.3; IR (melt) 3600−3200 (s), 1250 (s), 770 and 680 (s, meta). Anal. Calcd for $C_{17}H_{24}O_2$; C, 77.38; H, 9.74. Found: 77.72; H, 9.74.

33 (2.15 g, 8.6 mmol) was oxidized with pyridinium dichromate (5.6 g, 26 mmol) in 21 mL of dry CH_2Cl_2 using standard methods.[3,13] The product was distilled 112−116 °C (0.01 mm), giving 0.93 g of **19** (44% yield, 96% GC pure): ^{1}H NMR ($CDCl_3$) δ 1.1−1.5 (m, 5 H), 1.5−2.0 (m, 5 H), 2.3 (m, 1 H) 2.7−2.9 (m, 4 H), 3.7 (s, 3 H), 6.7 (m, 3 H), 7.2 (t, J = 7 Hz, 1 H); ^{13}C NMR δ 26.3 (2 C), 26.5, 29.1 (2 C), 30.4, 42.8, 51.5, 55.7, 112.0, 114.7, 121.3, 130.1, 143.7, 160.4, 213.5; IR (NaCl disks) 1700 (s), 1250 (s), 770 and 690 (s, meta) cm^{-1}; mass spectrum *m/e* (relative intensity) 246 (36), 135 (100), 121 (45), 83 (37), 55 (49). Anal. Calcd for $C_{16}H_{22}O_2$; C, 78.01; H, 9.00. Found: C, 77.98; H, 9.07.

1-(*m*-Methoxyphenethyl)cyclohexanecarbaldehyde (20) was identified based on NMR comparison with a para-substituted analog independently synthesized, and on GCMS data: ^{1}H NMR ($CDCl_3$) δ 1.1−1.9 (m, 10 H), 2.1 (d, J = 13 Hz, 2 H), 2.7 (m, 2 H), 3.8 (s, 3 H), 6.8 (m, 3 H), 7.2 (m, J = 8 Hz, 1 H) *m/e* (relative intensity); IR (NaCl disks) 1702 (s), 1260 (s); mass spectrum *m/e* 246 (13), 134 (26), 122 (100), 121 (44). See below for analysis of the analog.

1-(6-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)hex-5-en-1-ol (22): ^{1}H NMR ($CDCl_3$) δ 1.4−2.2 (m, 11 H), 2.3 (m, 3 H), 3.8 (s, 3 H), 3.8 (overlapping multiplet, 1 H), 5.0 (m, 2 H), 5.8 (m, 1 H), 6.7 (m, 2 H), 7.1 (d, J = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.7, 25.6, 26.1, 30.4, 33.9, 34.4, 43.8, 55.8, 75.3, 112.1, 114.8, 115.2, 129.8, 131.1, 139.5, 140.1, 158.5; IR (NaCl disks) 3600−3200, 1260 (s), 1044 (s) 817 and 875 (1,2,4-trisubstituted benzene); mass spectrum *m/e* (relative intensity) 260 (3) 162 (33), 161 (100), exact mass calcd for $C_{17}H_{24}O_2$ 260.1776, found 260.1782. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 77.48; H, 9.29.

1-(8-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)hex-5-en-1-ol (23): ^{1}H NMR ($CDCl_3$) 1.2−2.2 (m, 11 H), 2.8 (m, 2 H), 3.2 (1 H), 3.7 (t, J = 7 Hz, 1 H), 3.8 (s, 3 H), 5.0 (m, 2 H), 5.8 (m, 1 H), 6.70 and 6.76 (doublets, J = 8 Hz, 2 H), 7.1 (t, J = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.5, 24.8, 25.1, 28.8, 29.7, 33.8, 35.7, 37.5, 55.4, 74.8, 107.4, 114.3, 122.5, 126.6, 127.2, 138.9, 139.1, 157.2; IR (NaCl disks) 3600−3200, 1254 (s), 770 and 744 (1,2,3-trisubstituted benzene) cm^{-1}; mass spectrum *m/e* (relative intensity) 191 (3), 162 (100), 161 (64), 115 (31).

2-Pent-4-enyl-2a,3,4,5-tetrahydro-2*H*-naphtho[1,8-*bc*]-furan (25): ^{1}H NMR ($CDCl_3$) δ 1.2−2.2 (m, 8 H), 2.5−2.9 (m 5 H), 4.2−4.3 (ddd, J = 10.8, 7.3 and 5.4 would suggest a *cis* stereochemistry, 1 H), 5.0 (m, 2 H), 5.8 (m, 1 H), 6.7 (d, J = 7 Hz, 1 H), 6.9 (d, J = 7 Hz, 1 H), 7.0 (t, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.8, 25.8, 26.0, 27.1, 34.4, 34.5, 45, 77.2, 93.6, 106.4, 115.5, 120.0 (2 C), 128.6, 139.1; IR (NaCl disks) 1250 (s), 1230 (s), 760 and 730 (m; 1,2,3-trisubstituted) cm^{-1}; mass spectrum *m/e* (relative intensity) 228 (54), 171 (100), 147 (62), 145 (69), 131 (45), 115 (44); exact mass calculated for $C_{16}H_{20}O$ 228.1514, found 228.1519.

1-Cyclohexyl-4-(*m*-methoxyphenyl)-1-butanone (26): ^{1}H NMR ($CDCl_3$) δ 1.1−2.0 (m, 10 H), 2.3 (m, 1 H), 2.3 (t, J = 7 Hz, 2 H), 2.6 (t, J = 7 Hz), 3.8 (s, 3 H), 6.7 (m, 3 H), 7.2 (t, J = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.7, 26.3, 26.5, 29.1, 35.9, 40.4, 51.5, 55.7, 111.9, 114.8, 121.6, 130.0, 144.1, 214.6; IR (NaCl disks) 1710 (s), 1260 (s), 780 and 700 (m, meta substituted) cm^{-1}; mass spectrum *m/e* (relative intensity) 260 (23), 134 (100). Anal. Calcd for $C_{17}H_{24}O_2$; C, 78.20; H, 9.29. Found: C, 78.38; H, 9.37.

1-[3−(*m*-Methoxyphenyl)propyl]cyclohexane-carbaldehyde (27) could not be isolated pure as it was present in small amounts and also air-oxidized very rapidly. It was identified by comparison with the para isomer made by exactly the procedures described earlier[3] for the preparation of 1-(3-phenylpropyl)cyclohexanecarbaldehyde (**27** − CH_3O). This entails reacting the enolate of cyclohexanocarbonitrile with 3-(3-methoxyphenyl)-1-bromopropane[12] and then reducing the product with diisobutylaluminum hydride (43% yield); flash chromatography (80:20 trace hexane:CH_2Cl_2:EtOH) yielded analytically pure **27**: ^{1}H NMR ($CDCl_3$) 1.1−2.0 (m, 12 H), 2.5 (t, J = 7 Hz, 2 H), 3.8 (s, 3 H), 6.8 (d, J = 8 Hz, 2 H), 7.06 (d, J = 8 Hz, 2 H), 9.3 (s, 1 H); ^{13}C NMR δ 23.3, 26.1, 26.5, 26.6, 31.7, 36.1, 36.6, 50.3, 55.9, 114.4, 129.02, 129.9, 134.6, 158.4, 207.9; IR (NaCl disks) 1710 (s), 1250 (s), 740 and 690 (m, meta); mass spectrum *m/e* (relative intensity) 260 (22), 121 (100). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.21. Found: C, 78.52; H, 9.50.

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Supporting Information Available: Copies of ^{13}C NMR spectra of compounds **9**−**15**, **17**, **23**, and **25** and ^{1}H NMR of **20** and **25** reported in the Experimental Section (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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