Intramolecular Ring Opening of Epoxides by Bis-Activated Carbanions. The Influence of Ring Size on Reactivity and Selectivity†

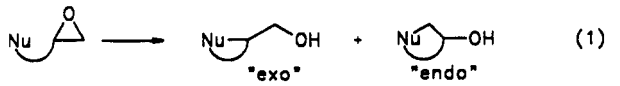
Fabio Benedetti,* Federico Berti, Silvio Fabrissin, and Teresa Gianferrara[1]

Dipartimento di Scienze Chimiche, Università di Trieste, Via L. Giorgieri 1, I-34127 Trieste, Italy

Received February 8, 1993®

A quantitative study on the effect of ring size in the intramolecular ring opening of epoxides by carbanions is described. Two series of substrates were examined: α,α-bis-sulfonyl ω-epoxides **1** and α-cyano-α-sulfonyl ω-epoxides **2**; in each series the carbanion is tethered to the epoxide by a chain of variable length from one to four methylene groups. The nucleophile can attack either electrophilic position of the oxirane ring, or both; exo ring opening of cyano sulfonyl epoxides **2** is followed by a second cyclization leading eventually to bicyclic, fused γ-lactones. Both series of epoxides show the same trend of reactivity as a function of ring size, in the formation of three- to seven-membered rings, with reactivity maxima corresponding to the formation of cyclopropane and cyclopentane derivatives. Unlike S_N2 ring closure of ω-halogeno carbanions, cyclization to a five-membered ring is the fastest process in this case. The ratio k_3/k_5 between formation of three- and five-membered rings drops from over 100, in the S_N2 cyclization of ω-iodo bis-sulfones, to less than 0.5, in the cyclization of ω-epoxy bis-sulfones **1**. The difference is discussed in terms of trajectory of approach of the carbanion to the nucleophilic center. Cyclization of cyano sulfonyl epoxide **2a**, in which the nucleophilic center and the epoxide are spaced by a single methylene group, is diastereoselective and leads to a bicyclic product with a *cis* fusion between the γ-lactone and the cyclopropane ring.

Cyclization of difunctional molecules is probably the most widely used synthetic route to ring compounds of all sizes, from micro- to macrocycles.[2] In difunctional molecules possessing a nucleophilic center and an epoxide cyclization *via* the intramolecular ring opening of the epoxide leads to the formation of a cyclic alcohol[3] (eq 1).



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This reaction is often used in synthesis for the high level of regio- and stereocontrol that can be obtained both in the formation and in the opening of the oxirane ring. Oxyanions, nitranions, carbanions, and double bonds are most frequently used as nucleophiles;[4] in the latter case, the reaction is usually initiated by coordination of the oxygen atom with a Lewis acid. Intramolecular nucleophilic ring opening of an epoxide has also recently been found to occur in some biosynthetic pathways.[5]

The effect of ring size on reactivity in the cyclization of difunctional molecules has been investigated in a wide range of reactions, such as, for example, the intramolecular S_N2 displacement of halides with carbon,[6] oxygen,[7] nitrogen,[8] and sulfur[9] nucleophiles, the base-catalyzed lactonization of bromo acids,[10] the ring closure of ω-alkenyl radicals.[11] However, reactivity as a function of ring size has seldom been investigated in the intramolecular nucleophilic ring opening of epoxides, and studies in this area are mainly concerned with the effect of ring size on regioselectivity. In a pioneering work,[12] Stork examined the cyclization of a series of epoxy nitriles concluding that attack at the carbon atom nearest to the nucleophile (exo mode)[13] was always preferred when both oxiranyl carbons are equally substituted. Later studies have shown that regioselectivity in the intramolecular ring opening of epoxides depends also on the stereochemistry of the

† This paper is dedicated to Professor Amerigo Risaliti on his 70th birthday.

® Abstract published in *Advance ACS Abstracts*, February 15, 1994.

(1) Present address: Dipartimento di Scienze Farmaceutiche, Università di Trieste.

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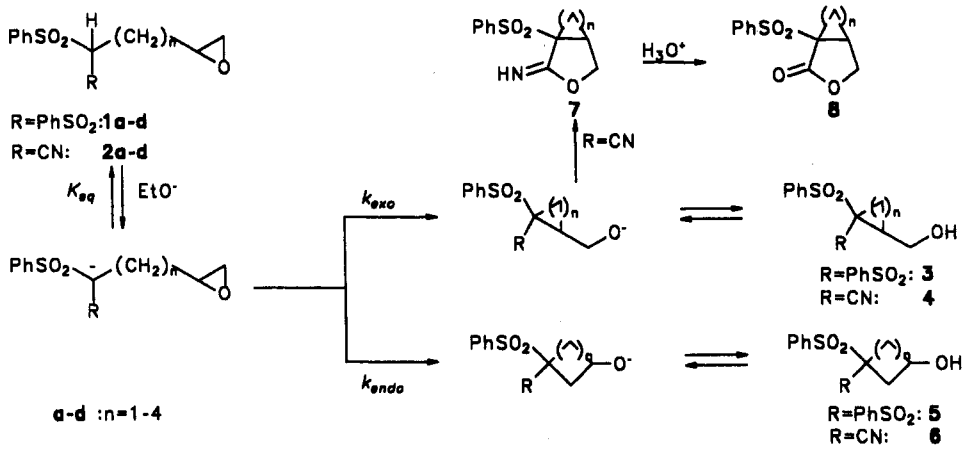
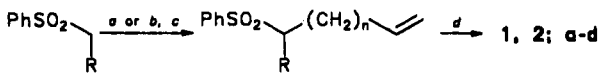
Scheme 1



Scheme 2[a]



R=PhSO2: 9a-d
R=CN: 10a-d

[a] Reagents: (a) NaH/DMF (for R = $PhSO_2$); (b) NaH or *n*-BuLi/THF (for R = CN); (c) $Br(CH_2)_nCH{=}CH_2$; (d) *m*-CPBA.

substituents present on the three-membered ring[14] and can be controlled by the choice of experimental conditions[15] and by structural modifications of the substrate.[16] While the effect of ring size on regioselectivity has been described in a number of reactions of synthetic utility, a quantitative analysis of reactivity as a function of ring size, in the way it has been carried out, for example, for intramolecular S_N2 displacements by carbanions,[6c,17] was still missing.

In this paper we now report a kinetic study on the cyclization of two series of terminal epoxy carbanions (Scheme 1), deriving from ω-epoxy bis-sulfones 1[18] and from ω-epoxy α-cyano sulfones 2. The effect of ring size will be examined on (i) regioselectivity (exo/endo selectivity); (ii) cyclization rates; (iii) diastereoselectivity in the cyclization of cyano sulfonyl epoxides 2.

Results and Discussion

Epoxides. All the epoxides were prepared by peracid oxidation of the corresponding terminal alkenes. These, in turn, were obtained by alkylation of bis(phenylsulfonyl)-methane[19] or (phenylsulfonyl)acetonitrile with the appropriate ω-bromo alkene as shown in Scheme 2.

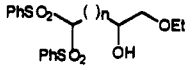
Epoxidation of cyanosulfonyl alkenes 10 (R = CN) with *m*-chloroperoxybenzoic acid in chloroform gave the epoxides 2 as approximately equimolar mixtures of diastereoisomers.

Table 1. Cyclization of ω-Epoxy Bis-Sulfones 1 and Cyano Sulfones 2

			products (%)[a]			
epoxide	R	*n*	*exo*	*endo*	k_{exo},[b] s^{-1}	k_{endo},[b] s^{-1}
1a	$C_6H_5SO_2$	1	**3a** (92)	–	0.0144	–
1b	$C_6H_5SO_2$	2	–	**5b** (68)[c]	–	0.000113
1c	$C_6H_5SO_2$	3	**3c** (77)	**5c** (14)	0.0404	0.00713
1d	$C_6H_5SO_2$	4	–	**5d** (45)[c]	–	0.000027
2a	CN	1	**8a** (95)	–	0.032	–
2b	CN	2	–	**6b**[d] (90)	–	0.0023
2c	CN	3	**4c**[e] (19); **8c**[f] (28)	**6c**[d] (41)	1.24	1.20
2d	CN	4	**8d**[g] (53)	**12**[h] (44)	0.0016	0.0013

[a] After hydrolysis with dilute acetic acid. [b] In sodium ethoxide/ethanol at $T = 25.0 \pm 0.1$ °C. [c] Remainder is ethoxy alcohol 11. [d] 1:1 Mixture of diastereoisomers. [e] [1*R**,2*R**] Isomer. [f] [1*R**,5*S**] Isomer from [1*S**,2*R**]-4c. [g] [1*R**,5*S**] Isomer. [h] From cyclization of alcohol 6d.

Products. Treatment of epoxy bis-sulfones 1 with sodium ethoxide in ethanol, at room temperature, gave the bis-sulfonyl cycloalkanes 3 and 5 by exo or endo cyclization of the corresponding carbanions (Scheme 1); yields are in Table 1. In two cases (1b, 1d) the slow intramolecular reaction was accompanied, at $[EtO^-] = 0.1$ M, by a competing intermolecular ring opening of the epoxide by ethoxide ion giving the hydroxy ethers 11 (Table 1). This reaction, being first order in base, can be suppressed at lower base concentrations.



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The reaction was more complex with the cyano sulfones 2 (Scheme 1): alcohols 4, obtained by exo opening of the epoxide ring, could not, but in one case, be isolated; in the reaction medium a base-catalyzed intramolecular addition of the alcohol to the nitrile group takes place giving imines 7. These compounds are not stable and can only be isolated in low yields, but they can be quantitatively hydrolyzed to the corresponding stable lactones 8; crude reaction mixtures from 2 were thus immediately hydrolyzed with dilute acetic acid: yields of alcohols (when isolated) and lactones are in Table 1.

Three products were isolated in the cyclization of epoxide 2c (Table 1). In this case only one of the diastereoisomers 4c, from exo ring opening of the epoxide,

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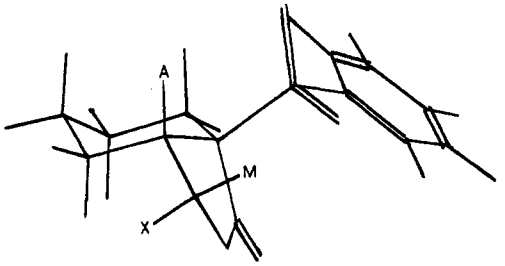
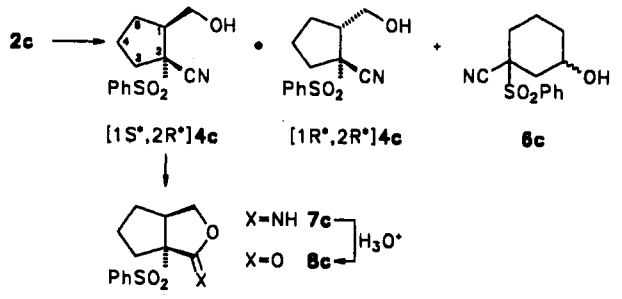
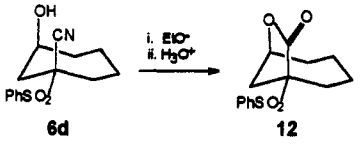


Figure 1. MM+ minimized structure of lactone **8d**.

undergoes a rapid cyclization to the corresponding lactone **8c**; the other diastereoisomer does not cyclize to imine even when left in 0.1 M sodium ethoxide for several hours. Inspection of molecular models indicates that, when the cyano and hydroxymethyl groups in **4c** are *cis*, there is no restriction to intramolecular addition; when they are *trans*, on the contrary, they are too far for the addition to take place. On this basis the isomer which does not cyclize is attributed the [1*R**,2*R**] configuration; the [1*S**,2*R**] configuration remains thus assigned to the other isomer.



Two products are obtained from **2d** (Table 1): exo ring opening gives alcohol **4d**, as a single diastereoisomer, which cyclizes to lactone **8d** (Scheme 1); similarly, in the seven-membered alcohol **6d** obtained by endo cyclization of **2d**, the OH and CN groups are optimally aligned for intramolecular addition which yields the lactone **12**. Six- and five-membered alcohols **6b** and **6c**, obtained from **2** by the endo pathway (Scheme 1), do not show the same intramolecular reactivity.



While the relative configuration of the chiral centers of **12**, and hence that of the precursor **6d**, is fixed by the lactone bridge, the relative configuration of **8d** was determined from its 400-MHz NMR spectrum. The cis-fused structure shown in Figure 1, with the sulfone group occupying an equatorial position, was found to be most consistent with the spectrum; in particular, the coupling constants J_{AX} = 1.7 Hz and J_{AM} = 5.5 Hz, measured for the AMX system, are in good agreement with the 89.2° and 34.5° H_A–H_X and H_A–H_M dihedral angles, calculated for the molecular mechanics minimized structure of Figure 1.

Mechanism. In sodium ethoxide/ethanol bis-sulfonyl epoxides **1** and cyano sulfonyl epoxides **2** are rapidly converted into the corresponding carbanions (Scheme 1). α-Bis-sulfones and α-cyano sulfones have comparable acidities: for example the pK_a's of bis(phenylsulfonyl)-methane and (phenylsulfonyl)acetonitrile in DMSO are 12.25 and 12.0, respectively.[20] This ensures that, when the base is present in excess, the preequilibrium in Scheme 1 lies well to the carbanion side for both series of epoxides **1** and **2**. First-order rate constants k_{exo} and k_{endo} can be obtained spectrophotometrically by monitoring the disappearance of the strong absorption band of the carbanions at 300 nm;[21] rate constants, at 25 °C, were calculated from at least five runs at [EtO⁻] = 0.1 M; results are in Table 1. Consistently with the proposed mechanism all reactions were zero order in base.

The base-catalyzed cyclization of alcohols **4** to give imines **7** (Scheme 1) is, in general, faster than the ring opening of epoxides. This has been demonstrated by quenching the reaction after one half-life. Only lactones **8** and starting materials **2** were isolated, thus indicating that there is no accumulation of the intermediates **4**. The only exception was the [1*R**,2*R**] isomer of **4c**, which has already been discussed.

Relative Reactivity of Cyano Sulfonyl and Bis-Sulfonyl Carbanions. Cyano sulfonyl carbanions are more reactive than the corresponding bis-sulfonyl carbanions by a factor of 2 to 100, the reactivity difference being larger for the slow closure of longer chains (Table 1). Steric rather than electronic reasons are likely to be at the origin of the higher nucleophilicity of cyano sulfones: in bis-sulfonyl carbanions the nucleophilic carbon is hindered by two large sulfone groups, while replacement of a sulfone by a cyano group makes the carbanion more accessible to electrophiles, without significatively affecting its pK_a.[20] As a consequence of the higher reactivity of cyano sulfonyl carbanions, intermolecular ring opening of the epoxide by the competing external nucleophile EtO⁻ is never observed in the cyclization of substrates **2**.

The Effect of Ring Size on Regioselectivity and Rates. The partitioning of epoxy carbanions between exo and endo ring opening is strongly dependent upon the length of the chain connecting the carbanion with the oxirane ring (Table 1): both series of epoxides **1** and **2**, with the exception of compounds **1d** and **2d**, show the same selectivity.

The first members of the two series (**1a**, **2a**) cyclize exclusively by the exo pathway giving the cyclopropyl derivatives **3a** and **8a**, respectively (Scheme 1, Table 1). No trace of four-membered rings, formed by endo attack on the oxirane, was detected. Formation of four-membered rings by nucleophilic ring closure of 1,4-difunctional compounds is always slower than the corresponding reactions leading to three-membered rings[6c,7c,22] and the cyclization of epoxy carbanions is no exception.[12,21,23]

Complete regioselectivity is observed in the reaction of the higher homologs **1b** and **2b** (Table 1, Scheme 1): both compounds cyclize by the endo pathway, which requires attack at the less-substituted position of the oxirane ring, to give cyclopentanols **5b** and **6b**, respectively.[24] The preference for the 5-endo over the 4-exo pathway[13] is by

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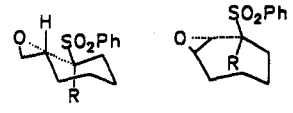
(24) Surprisingly, the corresponding monoactivated epoxy carbanions, in which the negative charge is adjacent either to a single nitrile or sulfonyl group, failed to give any cyclic product (refs 14, 15b).

no means general in the intramolecular ring opening of epoxides. When both carbon atoms on the epoxide are equally substituted, either four- or five-membered rings can be formed, depending upon the stereochemistry around the oxirane ring,[12,14] while the 5-endo pathway is completely inhibited when it requires attack at a tetrasubstituted carbon atom.[12] It appears that, in the cyclization of epoxy carbanions, the 4-exo and 5-endo approaches do not differ significantly in energy and thus the regioselectivity depends mainly on the substitution pattern at the three-membered ring.

Ring closure of the trimethylene compounds **1c** and **2c**, leads to mixtures of five- and six-membered rings with low selectivity, confirming earlier results in the cyclization of the corresponding mono-sulfonyl epoxide.[25] The more favorable exo geometry[13] is compensated by the fact that endo attack takes place at a less-substituted position.

Substrates **1d** and **2d** show different selectivities. Thus only the seven-membered alcohol **5d** is formed by endo cyclization of the bis-sulfonyl epoxide **1d**, while the cyano sulfone **2d** cyclizes by both the exo and the endo pathways giving eventually the bicyclic lactones **8d** and **12**. The different behavior can be explained considering the geometries of the corresponding transition states. In the cyclization of the bis-sulfone **1d**, formation of a six-membered ring requires one of the bulky sulfone groups to be in a pseudo-axial position, as in **13a**; this interaction is partially relieved in the more flexible seven-membered transition state **13b** where a strictly axial orientation of either sulfone group is not required.[26,27] In the cyclization of the corresponding cyano sulfone **2d** the sulfonyl group can occupy a pseudoequatorial position both in the six- and seven-membered transition states **14a** and **14b**, with the small cyano group axially oriented. Formation of the more stable six-membered ring by the exo pathway, as in **14a**, is thus balanced by the less-hindered attack at the terminal, unsubstituted, epoxide carbon of **14b**: both



R=PhSO$_2$: **13a** **13b**
R=CN: **14a** **14b**

cyclohexane **4d** and cycloheptane **6d**, leading, eventually, to lactones **8d** and **12** (Scheme 1, Table 1), are thus obtained in comparable yields.

Rates of intramolecular reactions show a marked dependence from ring size and, in the formation of small rings, variations of reactivity with ring size can be very large.[7bc,22,28] Intramolecular S_N2 displacements, in particular, show a characteristic behavior, with reactivity maxima corresponding to the formation of three- and five-membered rings, while four-membered rings correspond invariably to a minimum.[6-8] Recently,[6c] in a study on the base-catalyzed ring closure of ω-halogeno bis-sulfones (eq 2, X = Cl, I), it was shown that, with chloride as leaving

$$(PhSO_2)_2\bar{C}\text{-}(CH_2)_n\text{-}CH_2\text{-}X \longrightarrow (PhSO_2)_2C\text{-}(CH_2)_n\text{-}\dot{C}H_2 + X^- \quad (2)$$

group, a cyclopropane was formed over 60 times faster than the corresponding cyclopentane. The ratio k_3/k_5 between rates of formation of a three- and a five-membered ring further increased to 100 when the leaving group was iodide.

Table 2. Relative Rates of Cyclization of Halides (eq 2) and Epoxides (1 and 2)

product ring size	halogeno bis-sulfones[a] (eq 2)		epoxy bis-sulfones (1)		epoxy cyano sulfones (2)	
	X = Cl	X = I	exo	endo	exo	endo
3	61	101	0.36	–	0.026	–
4	4.1×10^{-4}	0.0011	–	–	–	–
5[b]	1 (0.015)	1 (3.6)	1 (0.04)	1 (0.001)	1 (1.24)	1 (0.0023)
6	1.7×10^{-4}	1.6×10^{-4}	–	64	–	521
7		7.2×10^{-6}	–	0.24	0.0013	0.56

[a] From ref 6c. [b] Observed rate constants (s^{-1}) in brackets.

The fast formation of three-membered rings, which appears to be general for the S_N2 cyclization of carbanions,[6] has inspired many speculations, and several explanations have been proposed in order to account for the phenomenon: conjugative interactions between electron-accepting groups and the incipient cyclopropane;[29] nonbonded interactions;[30] σ-assistance and σ-resistance;[31] ability to form bent bonds.[32] Experimental evidences, however, indicate that, in the S_N2 cyclization of ω-halogeno carbanions of eq 2, the very fast formation of a cyclopropane is due to the favorable activation entropy, associated to the closure of the shortest chain, which prevails over the slightly unfavorable enthalpic term, partially reflecting the strain of the product.[6c,17]

In Table 2, reactivities, as a function of ring size, are compared in the intramolecular displacement of chloride by bis-sulfonyl carbanions (eq 2) and in the cyclization of epoxy carbanions **1** and **2** (Scheme 1). The exo and endo pathways are considered separately, as they involve attack at a trisubstituted and at a disubstituted carbon atom, respectively.

The three series show qualitatively a similar trend of reactivity. There is however a significant difference: in the epoxide cyclization, formation of a cyclopropane is slower than the reaction leading to the corresponding cyclopentane derivative: the k_3/k_5 ratio drops dramatically from 61, for the S_N2 displacement of chloride of eq 2 (k_3/k_5 = 101 for iodides), to only 0.026 for the cyclization of cyano sulfonyl epoxides **2** and 0.36 for the bis-sulfonyl epoxides **1**. Epoxide thus becomes a worse leaving group than chloride in the closure of a three-membered ring.

In the ring opening of an epoxide the ideal trajectory of approach by the nucleophile has been calculated to be in the plane of the ring, at an angle of approximately 165° with the C–O bond, as in **15**.[33] Thus, in the intramolecular reaction **16**, the distorsion required to close a three-membered ring is even larger than in the corresponding S_N2 displacement of halides **17**, while no such effect is observed for the formation of five-membered rings where the nucleophile and electrophile are optimally aligned. It

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(28) Stirling, C. J. M. *Tetrahedron* **1985**, *41*, 1613.
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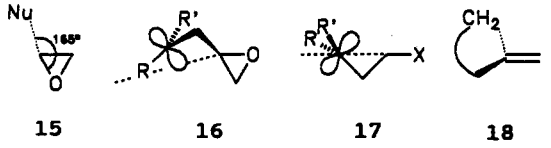
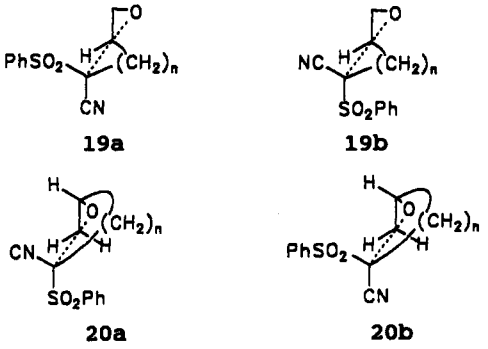


15 16 17 18

should be noted that the same trend of reactivity was observed in the intramolecular addition of radicals to double bonds, where the geometrical requirements are very similar (18).[11]

In the endo cyclization of epoxy carbanions (Table 2) the more favorable trajectory corresponds to the formation of a six-membered ring, while smaller rings require a higher distortion of the carbon chain. It should be noted that the reactivity difference between the formation of six- and seven-membered rings is almost identical in the three series: in this range, little or no strain is required to close the ring, and the difference reflects the higher entropy loss associated with the freezing of more internal rotations in the cyclization of the longer chain.

Diastereoselectivity. The relative configuration of the asymmetric centers of alcohols **4** and **6**, and their cyclization products **8** and **12**, depends on the mode of attack of the α-cyano α-sulfonyl carbanion on to the epoxide ring. Cyclization of compounds **2a** and **2d** is diastereoselective, while mixtures of diastereoisomeric lactones and alcohols, in ratios close to 1:1, are obtained from **2b** and **2c** (Table 1); thus, for $n = 2$ and $n = 3$, transition states **19a** and **19b** must have similar energies and the same is true, of course, for endo transition states **20a** and **20b**, indicating that the



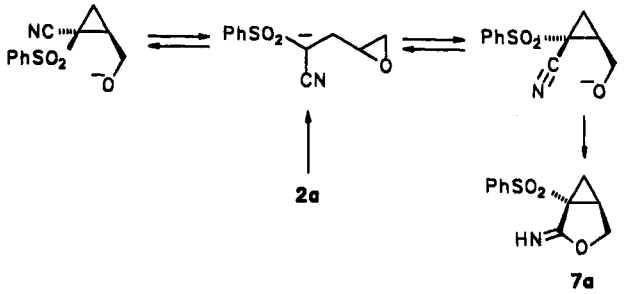
19a **19b**

20a **20b**

relative orientation of the cyano and sulfonyl groups is not important in the approach of the carbanion to the oxirane.

While the origin of diastereoselectivity in the cyclization of **2d** can be attributed to the preference for the equatorial transition states **14a** and **14b**, cyclization of the epoxide **2a** is surprising in this respect: the reaction leads to a single product, the lactone **8a**, with a *cis* fusion between the rings. The formation of a single diastereoisomer appears to be in contrast with the pattern found for other members of the series. However, we have shown that intramolecular ring opening of an epoxide by a bis-activated carbanion is reversible, when leading to a three-membered ring,[21] because the alcohol thus generated can back-attack the activated cyclopropane. Ring opening of electrophilic cyclopropanes by external nucleophiles is well documented in intermolecular[34] reactions and has also been

Scheme 3



reported intramolecularly.[35] A reversible reaction, in the cyclization of **2a**, would lead to the situation described in Scheme 3: the two cylopropanes generated by cyclization of the epoxy carbanion are in equilibrium, but, clearly, only the one with the cyano and the hydroxymethyl groups *cis* can cyclize to the imine. The equilibrium is thus drawn to the formation of compound **7a**, the precursor of lactone **8a**, through the only irreversible pathway, irrespective of the relative rates at which the two alcohols are formed or their ratio at equilibrium.[36]

The diastereoselective formation of *cis* lactone **8a** is interesting from the synthetic point of view as a possible entry to *cis*-disubstituted cyclopropanes. Further evaluation of the synthetic potential of this reaction is in progress and will be reported elsewhere.

Experimental Section

General information on equipment and methods have been previously reported.[21] 400-MHz ^{1}H NMR spectra were recorded on a JEOL JNM-EM400 spectrometer. High-resolution mass spectra (HRMS) were obtained on a VG 70/70 H spectrometer, at 10.000 resolution. The preparation of the bis-sulfonyl epoxide **1a** and ring opening to cyclopropane **3a** have been described previously.[21] Imines **7**, from cyanosulfonyl epoxides **2**, were not stable and their purification was not attempted; when isolated they were characterized only by their IR and/or NMR spectra. Compounds **2b**, **2d**, **5c**, **6c**, **10a**, **10b**, **10d**, **11d** (undistillable oils), and **4c** could not be characterized by their elemental analysis; their purity was assessed from ^{1}H or ^{13}C NMR spectra (available as supplementary material). Molecular mechanics calculations were carried out with the MM+ force field, as implemented in the Hyperchem package, distributed by Autodesk, Inc.

Kinetics. Commercial ACS grade ethanol (H_2O < 0.05%) was used for all the kinetic work. Reactions were followed on a Perkin-Elmer Lambda 2 double beam spectrophotometer thermostated at 25.0 ± 0.1 °C, the change in absorption at 310 nm being monitored. The very fast cyclizations of epoxides **11** and **16** were followed on a Hi-Tech SF 3L stopped-flow spectrophotometer operating at the same wavelength. Substrate concentrations were between 5×10^{-5} M and 2×10^{-4} M, the base (NaOEt) concentration being 0.1 M. Test reactions carried out at different concentrations of the base (1 to 0.001 M) showed that the reaction is zero order in base.

5,5-Bis(phenylsulfonyl)-1-pentene (9b). Bis(phenylsulfonyl)methane (2.96 g, 10 mmol) in 10 mL of dry DMF was added, under argon, at 50 °C, to a well-stirred suspension of sodium hydride (11 mmol) in 10 mL of the same solvent; the suspension was stirred for 15 min and 4-bromo-1-butene (1.5 g, 11 mmol) was added with a syringe. The reaction mixture was stirred for 2 h at 70 °C, cooled, poured into 100 mL of 10% aqueous NH_4Cl, and extracted with dichloromethane (3 × 30 mL); the extracts were washed with water and saturated brine, dried and evaporated

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(36) For other examples of formation of cis-fused [3.1.0] bicycles following intramolecular ring opening of an epoxide see: (a) Turcant, A.; Le Corre, M. *Tetrahedron Lett.* **1977**, 792. (b) Babler, J. H.; Tortorello, A. J. *J. Org. Chem.* **1976**, *41*, 885.

under reduced pressure to give the crude alkene (99%) mp 73–74 °C (from ethanol); IR (KBr) 1630 (C=C), 1320 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 2.45 (m, 4 H), 4.65 (m, 1 H), 4.9–6.0 (m, 3 H, $CH=CH_2$), 7.65–8.45 (m, 10 H, phenyl); MS, *m/e* 309 (0.5, M – C_3H_5), 209 (84, M – $C_6H_5SO_2$), 141 (33), 125 (36), 77 (100). Anal. Calcd for $C_{17}H_{18}O_4S_2$: C, 58.3; H, 5.18; S, 18.30. Found: C, 58.6; H, 5.13; S, 18.22.

6,6-Bis(phenylsulfonyl)-1-hexene (9c): 78% from bis(phenylsulfonyl)methane and 5-bromo-1-pentene, in DMF, as described for **9b**; mp 117 °C (from ethanol). Anal. Calcd for $C_{18}H_{20}O_4S_2$: C, 59.3; H, 5.53; S, 17.60. Found: C, 59.4; H, 5.79; S, 17.07.

7,7-Bis(phenylsulfonyl)-1-heptene (9d). Bis(phenylsulfonyl)methane (2.31 g, 7.8 mmol), 6-bromo-1-hexene (3.91 g, 24 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 3.65 g, 24 mmol) in 150 mL of dichloromethane were heated at reflux for 4 days. The reaction mixture was washed with water (2 × 50 mL), 0.1 M HCl (50 mL), and brine (50 mL), dried, and evaporated under reduced pressure; the crude product was purified by flash chromatography to give **9d** (1.06 g, 36%): mp 63–64 °C (from ethanol). Anal. Calcd for $C_{19}H_{22}O_4S_2$: C,60.3; H, 5.86. Found: C, 60.3; H, 5.96.

4-(Phenylsulfonyl)-4-cyano-1-butene (10a). A 2 M solution of *n*-butyllithium in hexane (13.8 mL, 28 mmol) was added dropwise, at –78 °C under argon, to a solution of (phenylsulfonyl)-acetonitrile (5.0 g, 28 mmol) in 25 mL of dry THF. The mixture was stirred for 15 min and allyl bromide (3.3 g, 28 mmol) was then added in one portion. The reaction mixture was stirred overnight at –78 °C and then allowed to warm up to room temperature and poured into 100 mL of aqueous 10% ammonium chloride. The aqueous phase was extracted with chloroform (3 × 20 mL). The combined extracts were washed with saturated brine (20 mL), dried, and rotary evaporated to give an oily residue. Flash chromatography purification of this material gave **10a** as a colorless oil (55%): IR (film) 2250 (CN), 1640 (C=C), 1330 and 1160 cm^{-1} (SO_2); ^1H NMR (80 MHz; $CDCl_3$) δ 2.75 (m, 2 H), 4.20 (dd, 1 H), [5.25 (m, 2 H) and 5.75 (m, 1 H), $CH=CH_2$], 7.5–8.4 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 35.3, 57.1, 113.0, 118.2, 128.7, 134.5, 136.1, 137.1; HRMS calcd for $C_{11}H_{11}NO_2S$ *m/e* 221.0510, found *m/e* 221.0515.

5-(Phenylsulfonyl)-5-cyano-1-pentene (10b). (Phenylsulfonyl)acetonitrile (5.0 g, 28 mmol) in 15 mL of dry THF was added dropwise, at 50 °C and under argon, to a stirred suspension of 80% sodium hydride (670 mg, 35 mmol) in dry THF (10 mL). The mixture was heated for 15 min, and 4-bromo-1-butene (3.7 g, 28 mmol) was then added in one portion. The reaction mixture was heated under reflux for 6 h, cooled to room temperature, and poured into 100 mL of aqueous 10% ammonium chloride. Workup as before and flash chromatography of the crude product gave **10b** as a colorless oil (4.9 g, 75%): HRMS calcd for $C_{12}H_{13}NO_2S$ *m/e* 235.0667, found *m/e* 235.0664.

With the same method were obtained:

6-(Phenylsulfonyl)-6-cyano-1-hexene (10c): 70% from (phenylsulfonyl)acetonitrile and 5-bromo-1-pentene; mp 60.1 °C (from ethanol). Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.6; H, 6.1; N, 5.6; S, 12.9. Found: C, 62.8; H, 5.9; N; 5.8; S, 12.8.

7-(Phenylsulfonyl)-7-cyano-1-heptene (10d): 80% from (phenylsulfonyl)acetonitrile and 6-bromo-1-hexene; colorless oil; HRMS calcd for $C_{14}H_{17}NO_2S$ *m/e* 263.0980, found *m/e* 263.0971.

[3,3-Bis(phenylsulfonyl)propyl]oxirane (1b). General Procedure for the Epoxidation of the Alkenes. 85% *m*-CPBA (2.58 g, 13 mmol) was added in small portions, at 5 °C, to a solution of the alkene **9b** (3.50 g, 13 mmol) in 50 mL of chloroform. The reaction mixture was stirred overnight at room temperature and *m*-chlorobenzoic acid was filtered off; the clear solution was washed with 10% aqueous sodium metabisulfite (4 × 10 mL), 10% aqueous $NaHCO_3$, and brine (10 mL each), dried, and evaporated. Flash chromatography purification of the crude product gave the oxirane **1b** (3.11 g, 85%): mp 86 °C (from ethanol); IR (KBr) 1330 and 1160 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 1.2–2.25 (m, 4 H), [2.45 (m, 1 H), 2.8 (m, 2H), oxirane], 4.95 (t, 1 H), 7.5–8.3 (m, 10 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 22.4, 31.0, 69.1, 69.7, 83.0, 122.4, 130.0, 135.0, 138.1; MS, *m/e* 309 (2, M – C_3H_5O), 143 (12), 141 (15), 125 (35), 77 (100). Anal. Calcd for $C_{17}H_{18}O_5S_2$: C, 55.7; H, 4.95; S, 17.50. Found: C, 55.5; H, 4.71; S, 16.93.

With the same method were obtained:

[4,4-Bis(phenylsulfonyl)butyl]oxirane (1c): 85% from **9c**; mp 128 °C (from ethanol). Anal. Calcd for $C_{18}H_{20}O_5S_2$: C, 56.8; H, 5.30; S, 16.85. Found: C, 56.9; H, 5.34; S, 16.86.

[5,5-Bis(phenylsulfonyl)pentyl]oxirane (1d): 65% from **9d**; mp 54 °C (from ethanol). Anal. Calcd for $C_{19}H_{22}O_5S_2$: C, 57.8; H, 5.62; S, 16.25. Found: C, 57.4; H, 5.34; S, 16.06.

[3-(Phenylsulfonyl)-3-cyanopropyl]oxirane (2b): 70% from **10b**; pair of diastereoisomers in 1:1 ratio (by ^{13}C NMR); oil; HRMS calcd for $C_{12}H_{13}NO_3S$ *m/e* 251.0616, found *m/e* 251.0611.

[4-(Phenylsulfonyl)-4-cyanobutyl]oxirane (2c): 73% from **10c**; 1:1 mixture of diastereoisomers; mp 107.1 °C (from ethanol). Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.9; H, 5.7. Found: C, 59.1; H, 5.8.

[5-(Phenylsulfonyl)-5-cyanopentyl]oxirane (2d): 3:7 mixture of diastereoisomers; 80% from **10d**; oil; HRMS calcd for $C_{14}H_{17}NO_3S$ *m/e* 279.0929, found *m/e* 279.0935.

[2-(Phenylsulfonyl)-2-cyanoethyl]oxirane (2a). Epoxidation of alkene **10a** with *m*-chloroperoxybenzoic acid (4 equiv) in refluxing chloroform buffered[37] with solid $NaHCO_3$ (4 equiv) for 8 days gave **2a** (10%): mp 70 °C (from ethanol); IR (KBr) 2250 (CN), 1330 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 2.3 (m, 2 H), 2.9 (m, 3 H, oxirane), 4.1 (m, 1 H), 7.5–8.3 (m, 5 H, phenyl). Anal. Calcd for $C_{11}H_{11}NO_3S$: C, 55.7; H, 4.6; S, 13.5. Found: C, 55.8; H, 4.5; S, 13.4.

Ring Opening of the Epoxides. General Procedure. The epoxide (2.5 mmol) was dissolved in 100 mL of a 0.5 M solution of sodium ethoxide in ethanol and kept at 25 °C for a time corresponding to at least 20 half-lives. The reaction mixture was then poured into 350 mL of water and extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with 50 mL of brine, dried, and rotary evaporated to give the crude products.

3,3-Bis(phenylsulfonyl)cyclopentanol (5b). Ring opening of the epoxide **1b** gave two products that were separated by column chromatography. The main product was the alcohol **5b** (68%): mp 160 °C (from ethanol); IR (KBr) 3550 (OH), 1340 and 1160 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 1.9 (m, 2 H), 2.7 (m, 4 H), 3.1 (m, 1 H, OH), 4.3 (m, 1 H), 7.4–8.3 (m, 10 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 30.2, 35.8, 40.7, 72.9, 93.3, 129.0, 131.6 and 131.8, 135.0, 136.2; MS *m/e* 366 (0.5, M^+), 225 (21, M – $C_6H_5SO_2$), 143 (22), 125 (100), 77 (49). Anal. Calcd for $C_{17}H_{18}O_5S_2$: C, 55.7; H, 5.0; S, 17.5. Found: C, 56.1; H, 5.3; S, 17.6. The second product was **1-ethoxy-2-hydroxy-5,5-bis(phenylsulfonyl)pentane (11b)** (23%): oil; IR ($CHCl_3$) 3570 (OH), 1330 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 1.2 (t, 3 H, CH_3), 1.8 (m, 2 H), 2.4 (m, 2 H), 3.3 (m, 3 H), 3.5 (q, 2 H), 4.9 (t, 1 H), 7.4–8.2 (m, 10 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 15.2, 22.7, 30.8, 67.0, 70.3, 74.4, 83.2, 129.4, 130.0, 134.8, 135.2; MS *m/e* 412 (1, M^+), 353 (50, M – $C_2H_5OCH_2$), 143 (26), 125 (100).

2,2-Bis(phenylsulfonyl)cyclopentanemethanol (3c) and 3,3-Bis(phenylsulfonyl)cyclohexanol (5c). Ring opening of 1c gave two products that were separated by flash chromatography. The main product was **3c** (80%): mp 170–171 °C (from ethanol); IR (KBr) 3250 (OH), 1320 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 2.0 (m, 4 H), 2.4 (m, 1 H, OH), 2.6 (m, 2 H), 3.0 (m, 1 H), 3.9 (t, 2 H), 7.6–8.5 (m, 10 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 24.8, 31.3, 34.8, 52.9, 61.4, 95.9, 128.8 and 129.2, 132.1, 135.0 and 135.1, 138.5; MS *m/e* 239 (4, M – $C_6H_5SO_2$), 209 (51), 143 (36), 125 (100), 77 (97). Anal. Calcd for $C_{18}H_{20}O_5S_2$: C, 56.8; H, 5.30; S, 16.85. Found: C, 57.3; H, 5.33; S, 16.73. The second product was the six-membered alcohol **5c** (10%); oil; HRMS calcd for $C_{18}H_{20}O_5S_2$ *m/e* 380.0752, found *m/e* 380.0752.

3,3-Bis(phenylsulfonyl)cycloheptanol (3d). Ring opening of the epoxide **1d** gave two products that were separated by column chromatography. The alcohol **3d** eluted first (42%): mp 152.5 °C (from toluene/hexane). Anal. Calcd for $C_{19}H_{22}O_5S_2$: C, 57.8; H, 5.62; S, 16.25. Found: C, 57.4; H, 5.68; S, 16.15. The second product was **1-ethoxy-2-hydroxy-7,7-bis(phenylsulfonyl)heptane (11d),** (52%) oil.

[1*R,5*S**]-1-(Phenylsulfonyl)-2-oxo-3-oxabicyclo[3.1.0]hexane (8a).** Ring opening of **2a** gave **[1*R**,5*S**]-1-(phenylsulfonyl)-2-imino-3-oxabicyclo[3.1.0]hexane (7a)** in 95%

(37) Swern, D. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1971; Vol. II, pp 355–533.

yield: mp 110 °C; IR (KBr) 3300 (NH), 1680 (C=N), 1310 and 1150 cm^{-1} (SO_2). The crude imine (1.0 g) was hydrolyzed overnight in 200 mL of aqueous 10% acetic acid at room temperature; the reaction mixture was then extracted with chloroform (3 × 20 mL), and the combined organic phases were washed with aqueous 0.1 M NaOH (3 × 10 mL), dried, and rotary evaporated to give the lactone **8a** in 95% yield from **2a**: mp 85 °C (from ethanol); IR (KBr) 1760 (C=O), 1310 and 1140 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$, 400 MHz) δ [1.48 (t), 2.18 (dd), 3.18 (m), 3 H, cyclopropane (J_{gem} = 5.4 Hz; J_{trans} = 5.4 Hz; J_{cis} = 8.6 Hz)], [4.17 (dd) and 4.36 (dd), 2 H, CH_2 (J_{gem} = 9.8 Hz; J_{trans} = 0.75 Hz; J_{cis} = 4.8 Hz)], 7.5–8.3 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 20.0, 27.2, 46.5, 67.4, 129.4, 134.8, 139.7, 168.2; MS *m/e* 238 (0.3, M^+), 97 (20, $M - C_6H_5SO_2$), 81 (66), 77 (100). Anal. Calcd for $C_{11}H_{10}O_4S$: C, 55.5; H, 4.20; S, 13.5. Found: C, 55.6; H, 4.30; S, 13.1.

3-(Phenylsulfonyl)-3-cyanocyclopentanol (6b): 90% from oxirane **2b**; 1:1 mixture of diastereoisomers; mp 70 °C (from ethanol); IR (KBr) 3500 (OH), 2250 (CN), 1305 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 2.2 (d, 2 H), 2.4–2.8 (m, 5 H, CH_2 and OH), 5.6 (m, 1 H), 7.5–8.3 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 32.6 and 32.7, 34.9 and 35.1, 43.2 and 43.4, 65.1 and 65.7, 72.1 and 73.0, 111.9, 129.5, 130.4, 134.9, 135.2; MS *m/e* 251 (1, M^+), 141 (45), 110 (47, $M - C_6H_5SO_2$), 77 (100). Anal. Calcd for $C_{12}H_{12}NO_3S$: C, 57.37; H, 5.18. Found: C, 57.55; H, 5.32.

[1*R,2*R**]-2-Cyano-2-(phenylsulfonyl)cyclopentanemethanol (4c), [1*R**,5*S**]-1-(Phenylsulfonyl)-2-oxo-3-oxabicyclo[3.3.0]octane (8c), and 3-(Phenylsulfonyl)-3-cyanocyclohexanol (6c).** Ring opening of the oxirane **2c** (700 mg), in 0.1 M sodium ethoxide for 15 min, gave three products which were separated by flash chromatography (1:4 ethyl acetate in petroleum ether, then methanol). **4c** eluted first (116 mg, 19%): mp 121.3 °C (from ethanol); IR (KBr) 3500 (OH), 2250 (CN), 1320 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) (400 MHz) δ 1.8–2.1 (m, 5H), 2.4 (m, 1H), 3.0 (m, 2H), [4.0–4.1 m, 4.2–4.4 m, 2H, CH_2O], 7.6–8.1 (m, 5H, phenyl); ^{13}C NMR [$(CD_3)_2CO$] δ 23.3, 29.6, 36.9, 55.1, 61.7, 67.9, 119.9, 129.5, 130.4, 135.3, 135.9; HRMS calcd for $C_{13}H_{15}NO_3S$ *m/e* 265.0773, found *m/e* 265.0777. The second product was the alcohol **6c** (287 mg, 41%): HRMS calcd for $C_{13}H_{15}NO_3S$ *m/e* 265.0773, found *m/e* 265.0775. The third product was the imine **[1*R**,5*S**]-1-(phenylsulfonyl)-2-imino-3-oxabicyclo[3.3.0]octane (7c)** (198 mg, 28%): IR (KBr) 3500 (NH), 1680 (C=N), 1320 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 1.5–2.5 (m, 7 H), 2.8 (m, 1 H, NH), 4.4 (m, 2 H), 7.5–8.3 (m, 5 H, phenyl). Hydrolysis of the crude imine, as described, gave the lactone **8c**, mp 130.5 °C (from ethanol). Anal. Calcd for $C_{13}H_{14}O_4S$: C, 58.6; H, 5.3; S, 12.0. Found: C, 58.4; H, 5.7; S, 11.5.

[1*R,5*S**]-1-(Phenylsulfonyl)-2-oxo-3-oxabicyclo[4.3.0]nonane (8d) and 1-(Phenylsulfonyl)-2-oxo-3-oxabicyclo[4.2.1]nonane (12).** Ring opening of **2d** and hydrolysis of the crude reaction mixture gave two products in a 1:1 ratio; **8d** eluted first (53%): mp 144.3 °C (from ethanol). Anal. Calcd for $C_{14}H_{16}O_4S$: C, 60.0; H, 5.8; S, 11.4. Found: C, 59.8; H, 5.7; S, 11.1. The second product was the lactone **12** (44%): mp 164.1 °C (from ethanol); IR (KBr) 1760 (C=O), 1300 and 1140 cm^{-1} (SO_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.5 (m, 1H), 1.7 (m, 4H), 2.0 (m, 2H), 2.25 (m, 1H), [2.36 d, 1H (J = 13.2 Hz), 3.20 dd, 1H (J_1 = 13.2 Hz, J_2 = 3.7 Hz), CH_2], 4.95 (m, 1H, CHO), 7.4–8.0 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 21.7, 23.9, 31.4, 32.4, 33.7, 70.7, 76.6, 128.8, 131.2, 134.4, 134.8, 172.8. Anal. Calcd for $C_{14}H_{16}O_4S$: C, 60.0; H, 5.8; S, 11.4. Found: C, 59.9; H, 5.8; S, 11.5.

Acknowledgment. Financial support from the Consiglio Nazionale delle Ricerche (Roma) is gratefully acknowledged.

Supplementary Material Available: Spectral data for compounds **1c,d, 2b–d, 3d, 5c, 6c, 8c,d, 9c,d, 10b–d, 11d**; copies of ^1H NMR spectra of **2d, 4c, 5c, 6c, 8d, 10a,b,d, 11d, 12**; ^{13}C NMR spectrum of **2b** (16 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.