brine and a 3% aqueous solution of $NaHCO_3$ and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced presure gave an oily residue, which was purified on silica gel chromatography to afford (S_C,R_C)-1-(phenylsulfinyl)-2-propanol ((S_S,R_C)-4) in a yield of 48 mg (95%) as a colorless powder: mp 134–135 °C. ^1H NMR and IR spectra were identical with that obtained by yeast reduction. The diastereomeric ratio was determined to be 95:5 (threo:erythro) by HPLC analysis.

Preparation of (S_S,S_C)-1-(Phenylsulfinyl)-2-propanol ((S_S,S_C)-4).[2d,f] To a solution of (*S*)-**3** (54.6 mg, 0.3 mmol) and zinc chloride (61 mg, 0.45 mmol) in THF (5 mL) was added a solution of diisobutylaluminum hydride in hexane (0.29 mL, 0.3 mmol) dropwise at −78 °C under an atmosphere of argon. After 15 min, phosphate buffer (pH 7) was added to quench the reaction. The same treatment as for (S_S,R_C)-4 afforded (S_S,S_C)-1-(phenylsulfinyl)-2-propanol ((S_S,S_C-4) as a colorless powder in a yield of 90%: mp 40 °C; ^1H NMR ($CDCl_3$) δ 1.32 (d, J = 6 Hz, 3 H), 2.83 (m, 2 H), 3.73 (br s, 1 H), 4.48 (m, 1 H), 7.56 (m, 5 H); IR (film) 3350, 2945, 1470, 1315, 1125, 1092, 1055, 1005, 760, 680 cm^{-1}. The diastereomeric ratio was 95:5 (erythro:threo) as determined by HPLC analysis.

1-(Phenylsulfenyl)-2-propanone (1). To a stirred solution of sodium benzenethiolate (80 mmol) in methanol (80 mL) was added chloroacetone (7.4 g, 80 mmol) dropwise over a period of 5 min. The mixture was stirred overnight at room temperature. After the usual workup, the crude oily product was distilled under reduced pressure to give 11.9 g (90%) of **1** as a colorless oil: bp 117 °C (5 mmHg); ^1H NMR (CCl_4) δ 2.20 (s, 3 H), 3.50 (s, 2 H), 7.00–7.40 (m, 5 H); IR (film) 3070, 3000, 2910, 1710, 1580, 1480, 1360, 1230, 1150, 740, 690 cm^{-1}; MS, m/e (rel intensity) 77 (15), 109 (26), 123 (100), 166 (78, M^+).

1-(Phenylsulfenyl)-2-propanol (2). To a stirred solution of thiophenol (5.5 g, 50 mmol) and triethylamine (5.56 g, 55 mmol) in diethyl ether (140 mL) was added 1,2-epoxypropane (2.90 g, 50 mmol) at room temperature over a period of 5 min. The resulting mixture was stirred overnight. After the usual workup, the crude oily mixture was distilled in vacuo to give 7.30 g (87%) of **2** as a colorless oil: bp 95–98 °C (0.45 mmHg); ^1H NMR (CCl_4) δ 1.23 (d, J = 7.2 Hz, 3 H), 2.30 (br s, 1 H), 3.27 (m, 2 H), 3.80 (m, 1 H), 7.15–7.50 (m, 5 H); IR (film 3400, 2985, 1585, 1480, 1440, 1375, 1130, 1070, 935, 740, 690 cm^{-1}; MS, m/e (rel intensity) 45 (100), 77 (50), 109 (87), 123 (33), 168 (38, M^+).

1-(Phenylsulfinyl)-2-propanone (3). A solution of perbenzoic acid in chloroform (0.33 M, 30.3 mL, 10 mmol) was reacted with 1-(phenylsulfenyl)-2-propanone (1.66 g, 10 mmol) at 0 °C for 1 h. The mixture was poured into 50 mL of an aqueous solution of $NaHCO_3$ and extracted with dichloromethane (150 mL × 3). The organic layer was washed sequentially with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by recrystallization from hexane–dichloromethane afforded **3** as colorless crystals in a yield of 1.76 g (97%): mp 69–70 °C; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H), 3.80 (s, 2 H), 7.20–7.70 (m, 5 H); IR (KBr disk) 2950, 1705, 1440, 1360, 1340, 1040, 995, 750, 730, 690 cm^{-1}; MS, m/e (rel intensity) 27 (20), 43 (42), 51 (55), 77 (59), 97 (49), 125 (100), 182 (26, M^+).

1-(Phenylsulfinyl)-2-propanol (4). To a solution of 1-(phenylsulfenyl)-2-propanol (**2**; 3.36 g, 20 mmol) in acetic acid (20 mL) was added 35% hydrogen peroxide (1.97 g, 20 mmol) dropwise with stirring in an ice–water bath. The resulting mixture was stirred for 3 h at the same temperature and poured into an aqueous solution of K_2CO_3. The mixture was extracted with dichloromethane (100 mL × 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The crude crystalline mixture was purified by column chromatography to afford 3.68 g (100%) of a diastereomeric mixture of **4** as colorless powders: mp 42–140 °C; ^1H NMR ($CDCl_3$) δ 1.18, 1.35 (d, J = 6.3 Hz, 3 H), 2.89 (m, 2 H), 4.37 (m, 1 H), 4.68 (s, 1 H), 7.32–7.96 (m, 5 H); IR (KBr disk) 3355, 2947, 1450, 1315, 1120, 1090, 1050, 1020, 755, 690 cm^{-1}; MS, m/e (rel intensity) 28 (60), 51 (45), 59 (36), 78 (92), 91 (27), 126 (100), 187 (12, $(M + H)^+$).

1-(Phenylsulfonyl)-2-propanone (5). To a stirred solution of 1-(phenylsulfenyl)-2-propanone (**1**); (1.54 g, 10 mmol), catalytic amounts of Na_2WO_4, and cetyltrimethylammonium chloride in dichloromethane (50 mL) was added dropwise 35% hydrogen peroxide (2.42 g, 25 mmol) with vigorous stirring at room temperature. The resulting mixture was stirred at room temperature for 24 h. After the usual workup, recrystallization from hexane–dichloromethane afforded 1.97 g (99%) of **5** as colorless powders: mp 46–47 °C, ^1H NMR ($CDCl_3$) δ 2.43 (s, 3 H), 4.17 (s, 2 H), 7.40–8.00 (m, 5 H); IR (KBr disk) 2735, 1730, 1585, 1295, 1150, 840, 745, 725, 690, 625 cm^{-1}; MS, m/e (rel intensity) 43 (49), 51 (23), 77 (100), 91 (26), 134 (87), 141 (58), 156 (36), 199 (25, $(M + H)^+$).

1-(Phenylsulfonyl)-2-propanone (6). To a stirred solution of 1-(phenylsulfenyl)-2-propanol (**2**; 3.36 g, 20 mmol) in acetic acid (20 mL) was added 35% hydrogen peroxide (4.8 g, 50 mmol) at room temperature. The resulting mixture was stirred overnight and treated in a similar manner as in the case of **4** to afford **6** as colorless powders: mp 39–41 °C; ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 6.6 Hz, 3 H), 2.05 (br s, 1 H), 3.96 (m, 2 H), 4.38 (m, 1 H), 7.50–8.11 (m, 5 H); IR (KBr disk) 3530, 2985, 1585, 1495, 1450, 1300, 1140, 1080, 940, 750, 690 cm^{-1}; MS, m/e (rel intensity) 58 (54), 77 (100), 91 (53), 125 (32), 141 (85), 156 (77); 183 (33), 201 (44, $(M + H)^+$).

Addition of Organometallic Reagents to Cyclooctenyl Phenyl Sulfones[1]

Steven A. Hardinger and P. L. Fuchs*

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

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A series of cyclooctenyl and cyclooctadienyl phenyl sulfones were prepared and exposed to various organometallic reagents. The regio- and stereochemical results of these reactions are outlined below. The cuprate-induced reduction of epoxy vinyl sulfones **17** and **29** was explored; a mechanism involving two one-electron transfers was implicated.

Molecules containing an eight-membered carbocyclic ring remain a synthetic challenge. The theoretical and medicinal interest in compounds such as dactylol (**1**), albolic acid (**2**), stegnanacin (**3**), pleuromutilin (**4**), and acetoxycrenulide (**5**) has resulted in a plethora of synthetic approaches to these[2-6] and other similar targets (Scheme

(1) Synthesis via Vinyl Sulfones. 23. For the previous paper in this series, see: Hutchinson, D. K.; Fuchs, P. I., submitted for publication in *J. Am. Chem. Soc.*

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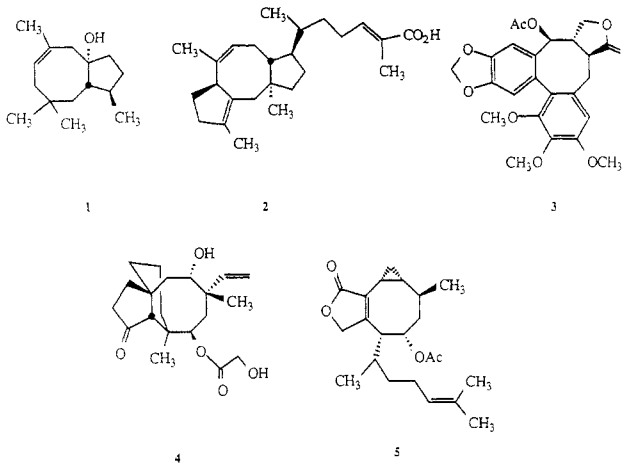
0022-3263/87/1952-2739$01.50/0

Scheme I



Scheme II

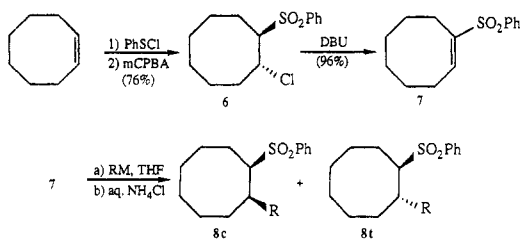


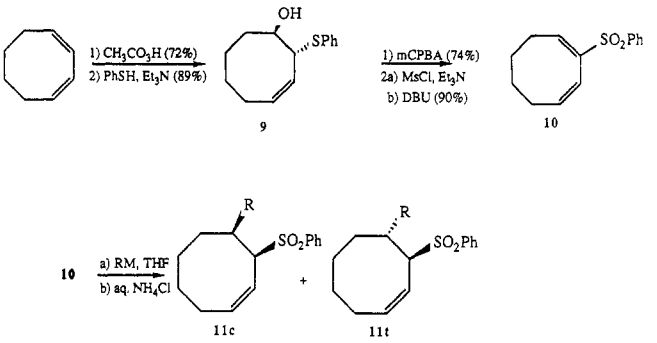
Table I. Reactions of 7 with Organometallics

entry	orgmetllic	conditions[a] temp, °C	time, h	yield, %	8c:8t[b]
1	MeLi	0	1	66	89:11
2	MeLi	0	1	44	72:28[c]
3	MeLi	0	1[d]	56	64:36
4	PhLi	0	1	93	92:8
5	*n*-BuLi	0	1	87	80:20
6	*t*-BuLi	0	1	75	100:0
7	MeMgBr	25	24	NR	
8	Me_2CuLi[e]	0	1	67	83:17
9	Ph_2CuLi[e]	65	24[f]	54[g]	90:10[c]
10	$MeCeCl_2$[h]	25	24	NR	
11	$MeTi(O\text{-}i\text{-}Pr)_3$[i]	25	24	NR	
12	$MeTi(O\text{-}i\text{-}Pr)_3$[j]	25	24	NR	

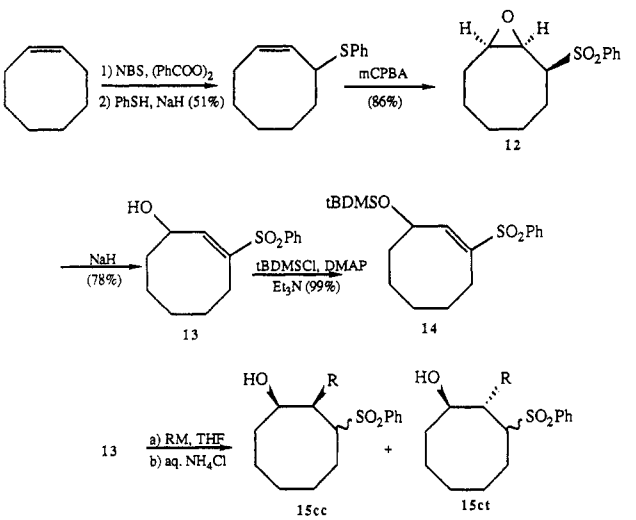
[a] THF solution unless otherwise indicated. [b] Ratio determined by NMR integration; stereochemical assignment by difference decoupling. [c] Quench at 0 °C. [d] Ether. [e] 5 equiv. [f] 1:1 Me_2S/THF. [g] 23% deconjugated starting material also detected. [h] See ref 12. [i] See ref 13. [j] 5% $ZnCl_2$ added; see ref 15. [k] NR = no reaction.

I). Virtually all of these synthetic efforts have employed acyclic precursors,[4,5b,7] ring expansions,[2a,4d,8] or fragmentation[5a,9] to construct the cyclooctane moiety. Syntheses from an intact cyclooctane ring are rare.

Scheme III



Scheme IV



We envisioned a general approach to these targets, starting with cyclooctene or 1,3-cyclooctadiene which

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Table II. Reactions of 10 with Organometallics

		conditions[a]			
entry	orgmetllic	temp, °C	time, h	yield, %	11c:11t[b]
1	MeLi	−78	4	81	52:48
2	PhLi	−78	4	99	70:30
3	MeMgBr	25	24	NR	
4	Me_2CuLi[c]	0	4	37	67:33
5	Ph_2CuLi[c]	65	24[d]	30	70:30

[a] THF solution unless otherwise indicated. [b] Ratio determined by NMR integration. [c] 5 equiv. [d] 1:1 Me_2S/THF.

Table III. Reactions of 13 with Organometallics

		conditions[b]			
entry	orgmetllic[a]	temp, °C	time, h	yield, %	15cc:15ct[c]
1	MeLi	0	8	63	100:0
2	PhLi	0	8	42	50:50
3	*t*-BuLi	25	24	*f*	
4	MeMgBr	25	24	NR	
5	Me_2CuLi[d]	0	8	NR	
6	Ph_2CuLi[d]	65	24[e]	NR	

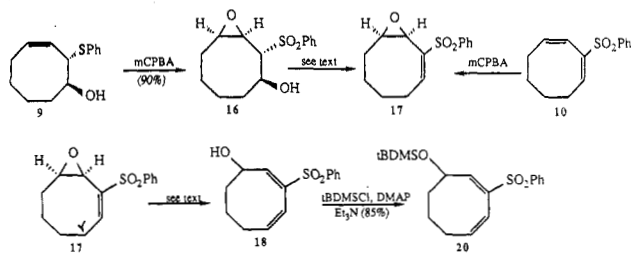
[a] 2 equiv unless otherwise indicated. [b] THF solution unless otherwise indicated. [c] Ratio determined by NMR integration. [d] 5 equiv. [e] 1:1 Me_2S/THF. [f] See text.

utilizes vinyl sulfones as the progenitors for key stereochemical and annulative transformations. Vinyl sulfones have proven to be especially fruitful substrates in multiply convergent syntheses involving five- and six-membered rings.[9] Investigation of the scope and limitations of similar strategies involving cyclooctenyl sulfones constitutes the subject of this study.

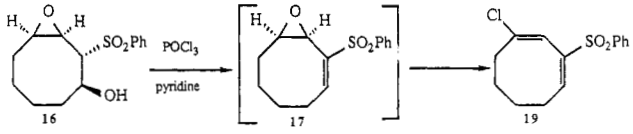
The parent cyclooctenyl sulfone **7** was prepared as outlined in Scheme II. Thus, chlorosulfenylation[11] of cyclooctene followed by mCPBA oxidation afforded crystalline chloro sulfone **6**, which was then eliminated with DBU in methylene chloride at reflux to produce vinyl sulfone **7** in 60% overall yield. This substrate reacted cleanly with organolithium and cuprate reagents, as outlined in Table I. Reactions of **7** were far more sluggish than the cyclopentenyl, cyclohexenyl, or cycloheptenyl counterparts,[14] which typically require only 10 min at −78 °C for completion. This is apparently a consequence of the steric shielding of the vinyl sulfone moiety by the remainder of the eight-membered ring.

Dienyl sulfones were prepared in the following manner: 1,3-cyclooctadiene was treated with peracetic acid, and the resulting monoepoxide[16] was reacted with thiophenol in the presence of triethylamine in DMF at 50 °C to afford only trans sulfide alcohol **9**, as judged from the NMR of the crude reaction product Scheme III. Sulfide oxidation is then effected with 2 equiv of mCPBA or peracetic acid and the product dehydrated, which affords dienyl sulfone

Scheme V



Scheme VI



10 in 43% overall yield from 1,3-cyclooctadiene.

Reactions of dienyl sulfone **10** with organometallics occurred at significantly faster rates than similar reactions of **7** (Table II). The additional unsaturation serves to flatten the cyclooctane ring, thereby decreasing the degree of steric shielding of the vinyl sulfone moiety. The faces of the intermediate allylic α-sulfonyl anion are also sterically less differentiated than the α-sulfonyl anion corresponding to **8**. This is manifested in diastereomeric product ratios obtained upon protonation, which are closer to unity for **11** than for **8**.

The syntheses of γ-oxygenated vinyl sulfones **13** and **14** are outlined in Scheme IV. Thus, allylic bromination[19] of cyclooctene, displacement with thiophenoxide, and subsequent oxidation afforded epoxy sulfone **12** as a single diastereomer (by ^1H and ^{13}C NMR). Base-induced epoxide opening afforded δ-hydroxy vinyl sulfone **13** in 33% overall yield from cyclooctene. Silylation of this material under standard conditions[20] proceeded to give a quantitative yield of γ-silyloxy vinyl sulfone **14**.

The reactions of **13** with organometallics showed significant rate deceleration over similar reactions of **7** (Table III). The diastereomeric products **15cc** and **15ct** (R = Ph) once again proved to be chromatographically inseperable; the product ratio was determined by 470-MHz ^1H NMR. That only two diastereomers were present was evident from routine proton–proton decoupling, but determination of their respective stereochemistries was hampered by undecipherable coupling patterns. Desulfonylation[21] afforded *cis*- and *trans*-2-phenylcyclooctanol.[22]

γ-Alkoxide anions are known to direct the incoming organometallics in the case of cyclopentenyl, cyclohexenyl, and cycloheptenyl sulfones, resulting in primarily cis adducts.[23] That this mechanism is in operation for the

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(21) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
(22) The cis compound had satisfactory spectral properties. The NMR of the trans compound agreed with that of: Taniguchi, H.; Brener, L.; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 7107.

Table IV. Reactions of 18 with Organometallics

entry	orgmetllic[a]	conditions[b] temp, °C	conditions[b] time, h	yield, %	21cc:21tc: 21tt[c]
1	MeLi	0	2	89	100:0:0
2	PhLi	0	2	71	0:15:85
3	MeMgBr	25	24	66	100:0:0
4	PhMgBr	0	8	76	0:0:100
5	Me_2CuLi[d]	0	24	NR	
6	Ph_2CuLi[d]	25	24[e]	*f*	

[a] 2 equiv unless otherwise indicated. [b] THF solution unless otherwise indicated. [c] Ratio determined by NMR integration. [d] 5 equiv. [e] 1:1 Me_2S/THF. [f] Complex mixture.

reactions of **13** with organolithium reagents is evidenced by the stereoselective addition of methyllithium (entry 1). However, this directed mode of addition was partially or fully suppressed when phenyllithium or *tert*-butyllithium were employed. Quench of the *t*-BuLi reaction with a large excess of D_2O resulted in a mixture of *t*-Bu adduct and sulfone-ring ortho-deuteriated material in approximately a 1:3 ratio.

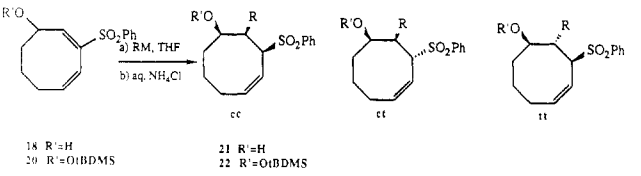
Silyl ether **14** proved inert to all organometallics to which it was exposed: MeLi, *n*-BuLi/KO-*t*-Bu, Me_2CuLi and Ph_2CuLi (reflux). The directed addition mode was unavailable to the silyl ether; apparently the eight-membered ring and silyl ether moieties provide complete steric shielding of the vinyl sulfone.

In order to study the alkoxide-directing effect on a dienyl sulfone, the synthesis of **18** was desired. The dienyl alcohol was envisioned to arise from γ-deprotonation and 1,4-epoxide opening of epoxide **17**, a substrate of interest in its own right in this study (vide infra). Thus, treatment of sulfide alcohol **9** with 3 equiv of mCPBA afforded epoxide **16** in 90% yield (Scheme V).

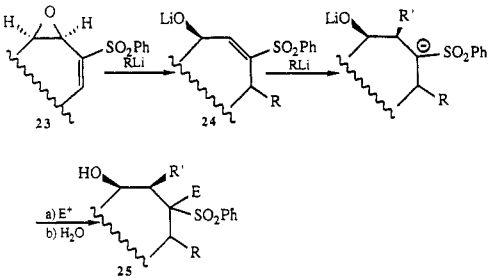
This material, however, proved to be recalcitrant to dehydration. It failed to form a mesylate (methanesulfonyl chloride, triethylamine)[24] and was destroyed by the Hendrickson conditions (triflic anhydride, triphenylphosphine oxide, and potassium carbonate).[25] Treatment with $POCl_3$ and pyridine produced vinyl chloride **19** in 49% yield (Scheme VI).[26] Reaction of **16** with trifluoroacetic anhydride followed by DBU resulted in the formation of the dienyl sulfone **18** directly in modest and unreproducible yields. The desired epoxide was indeed an intermediate in this reaction (as evidenced by TLC) but was never present in high concentration. Limited success was met with treatment of **16** with Burgess' reagent,[27] affording **17** in a disappointing yield of 37%.

A facile preparation of **17** was realized via a different approach. Epoxidation of dienyl sulfone **10** with mCPBA in $CHCl_3$ at reflux in the presence of 3,3′-thiobis(5-*tert*-butylcresol) as a radical inhibitor[28] afforded the desired epoxy vinyl sulfone **17** cleanly in 76% recrystallized yield. γ-Deprotonation with a catalytic quantity of DBU in THF at reflux produced the highly crystalline dienyl sulfone **18** in 87% yield. Silylation of this material with *tert*-butyldimethylchlorosilane in DMF and triethylamine with catalytic DMAP[20] produced in silyloxy diene **20** in 85% yield. The reactions of **18** with organometallic reagents are summarized in Table IV.

Scheme VII



Scheme VIII



Scheme IX

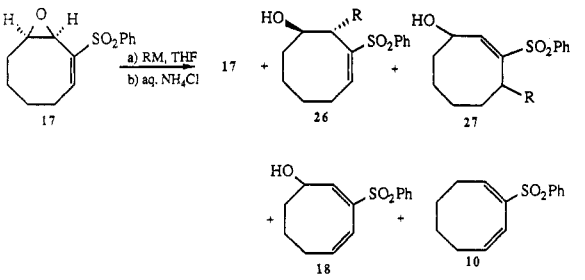


Table V. Reactions of 20 with Organometallics

entry	orgmetllic[a]	conditions temp, °C	conditions time, h	yield, %	22cc:22ct: 22tt[b]
1	MeLi	0	8	58	33:33:33[c]
2	PhLi	0	8	80	50:50:0
3	PhMgBr	25	24	NR	
4	Me_2CuLi[d]	0	8	NR	
5	Ph_2CuLi[d]	*f*	24[e]	77	30:70:0

[a] THF solution unless otherwise indicated. [b] Ratio determined by NMR integration. [c] Estimated. [d] 5 equiv. [e] 1:1 Me_2S/THF. [f] Reflux.

Addition of a second unsaturation within the cyclooctane ring forces dienyl sulfone **18** to be flatter than vinyl sulfone **13**. This effect presumably is the cause for the increased level of alkoxide-directed addition product for **18**. Steric factors may again override this directing effect; the larger nucleophile PhMgBr results in formation of product **21tt** (Scheme VII).

Analysis of the products formed upon treatment of silyloxy diene **20** with organometallic reagents showed a near complete loss of stereoselectivity, as well as reduced reaction rates (Table V).

The investigation next turned to epoxy vinyl sulfones. These substrates offer the prospect for formation of three new carbon–carbon bonds in one pot, with some potential for stereocontrol at the new centers (Scheme VIII). Thus, addition of RLi to generic epoxy vinyl sulfone **23** could result in a new γ-alkoxy vinyl sulfone **24**. Addition of a second organometallic (R′Li) would then proceed via the directed-addition mode; quenching of the resultant α-sulfonyl anion with an electrophile would afford highly functionalized sulfone alcohol **25**, ready for further manipulations.[9]

(23) Conrad, P. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1978**, *100*, 346. Saddler, J. C.; Conrad, P. C.; Fuchs, P. L. *Tetrahedron Lett.* **1978**, 5079.
(24) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
(25) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, 277.
(26) TLC indicated that epoxy sulfone **17** was an intermediate in this reaction; treatment of **17** with $POCl_3$ and pyridine also produced **19**.
(27) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
(28) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Sugiura, S.; Kakoi, H. *J. Chem. Soc., Chem. Commun.* **1972**, 64.

Table VI. Reactions of 17 with Organometallics

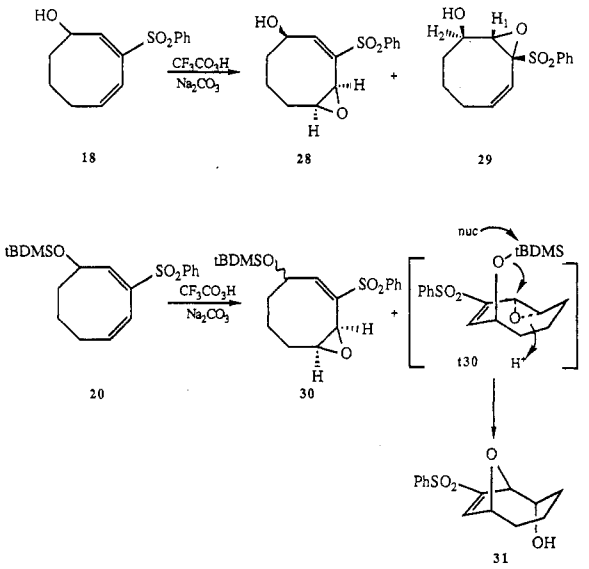
entry	orgmetllic	conditions[a] temp, °C	conditions[a] time	yield, % 17[b]	26	27[c]	18	10
1	MeLi	−78	8 h	0	0	90	10	0
2	MeLi	0	45 min	0	0	84	16	0
3	MeLi	−78	8 h[d]	56	0	25	19	0
4	MeLi	−78	8 h[e]	57	0	17	25	0
5	MeLi	−78	8 h[f]	34	0	54	13	0
6	MeLi	−78	8 h[g]	0	0	44	56	0
7	PhLi	−78	8 h	0	0	87	11	0
8	MeMgBr	25	24 h	*m*	*m*	*m*	*m*	*m*
9	MeMgBr[h]	25	24 h	0	50	50	0	0
10	Me_2CuLi	−78	40 min	0	0	5	0	31
11	Me_2CuLi[j]	−78	15 min	0	0	0	0	56
12	MeCu[i]	0	1 h	0	47	39	14	0
13	MeCu[h]	0	1 h	0	0	74	0	0
14	Ph_2CuLi[i]	−78	20 min[k]	0	0	79	0	0
15	Me_3ZnLi[l]	−78	20 min	0	36	55	0	9
16	$MeTi(O\text{-}i\text{-}Pr)_3$	25	24 h	100	0	0	0	0
17	$MeCeCl_2$	25	24 h	100	0	0	0	0

[a] THF solution unless otherwise indicated. [b] Ratio determined by NMR integration. [c] Cis/trans ratio could not be determined. [d] Toluene. [e] 9:1 THF/TMEDA. [f] CH_2Cl_2. [g] 1:1 ether/CH_2Cl_2; 1 equiv of $LiClO_4$ added. [h] 1.5 equiv of Me_3Al added; see ref 29. [i] 5 equiv. [j] 1 equiv of BF_3 added to cuprate prior to vinyl sulfone. [k] 1:1 Me_2S/THF. [l] See ref 30. [m] Complex mixture.

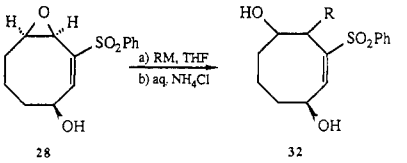
Accordingly, the reactions of epoxy vinyl sulfone **17** were studied; these results are summarized in Table VI. As expected, **17** was considerably more reactive than **7**. Treatment of **17** with methyllithium under a variety of conditions afforded mixtures of recovered starting material, conjugate adduct **27**, and γ-deprotonation product **18** in widely varying ratios (Scheme IX). Direct addition to the epoxide moiety of **17** (affording adduct **26**) occurred only when MeMgBr/Me_3Al,[29] MeCu, or Me_3ZnLi[30] were employed. This is perhaps a result of the propensity of these reagents to add to epoxides in the presence of other functional groups. Examination of molecular models indicated the vinyl sulfone and epoxide moieties of **17** to be orthogonal and thus not disposed to synergism. While Ph_2CuLi and MeCu added as expected, Me_2CuLi in THF reacted rapidly to form the previously prepared dienyl sulfone **10** as the major product in moderate yield, as well as a small quantity of the conjugate adduct **27**. While pretreatment of the cuprate with boron trifluoride etherate[31] resulted in a slight increase in yield, no significant change in the product distribution resulted. Further studies with other epoxy vinyl sulfones and other organocopper reagents aided in elucidating the nature of this deoxygenation reaction (vide infra). Although other functional groups have been reported to be reduced when exposed to cuprates,[32] this is the first example of the reduction of a vinyl epoxide in this manner (for a mechanistic rationale, see Scheme XIII).

To study the alkoxide-directed addition to epoxy vinyl sulfones, **28** was prepared according to Scheme X. Thus, epoxidation of dienyl sulfone **18** with trifluoroperacetic acid buffered with sodium carbonate (**18** was inert to mCPBA

Scheme X



Scheme XI



in chloroform at reflux) afforded the desired epoxide **28** (24% yield) in addition to the undesired epoxide **29** (44% yield). The stereochemistry of epoxide **29** was ambiguous from NMR analysis (J_{12} = 8 Hz) but was assumed to be anti based on studies of a similar system.[33] Oxidation of the corresponding silyl ether **20** under similar conditions (**20** was also inert to mCPBA) afforded a mixture of the desired material **30** and bicyclo vinyl sulfone **31**[34] in a 3.4:1 ratio (92% combined yield). This latter compound apparently arises from in situ transannular desilylative cyclization of *trans*-**30**. All attempts to prepare **31** via inversion of the alcohol center of **28** failed. Control exper-

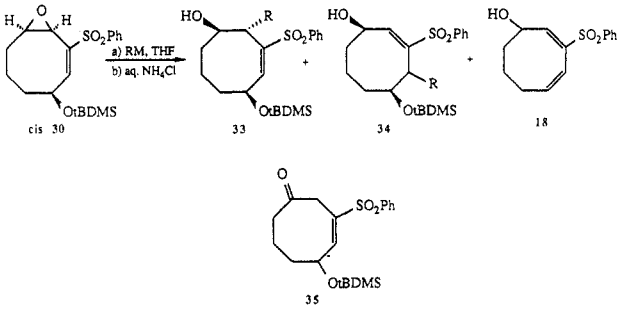
(29) Saddler, J. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2112.
(30) Watson, R. A.; Kjonaas, R. A. *Tetrahedron Lett.* **1986**, *27*, 1437. We thank Prof. Kjonaas for helpful discussion and a generous sample of $ZnCl_2$–TMEDA complex.
(31) Yamamoto, Y.; Yamamoto, S.; Yatagi, H.; Isihara, Y.; Maryuma, K. *J. Org. Chem.* **1982**, *47*, 119. Smith, A. B., III; Jerris, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 194.
(32) For other examples of cuprates acting as reducing agents, see: Ibuka, T.; Chu, G.-N.; Yoneda, F. *Tetrahedron Lett.* **1984**, *25*, 3247. Clark, G. R.; Lin, J.; Nikaido, M. *Tetrahedron Lett.* **1984**, *25*, 2645. Claesson, A.; Sahlberg, C. *Tetrahedron Lett.* **1978**, 5049. Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1983**, *48*, 4763. Danishefsky, S.; Kahn, M. *Tetrahedron Lett.* **1981**, *22*, 485. Ruden, R. A.; Litterer, W. E. *Tetrahedron Lett.* **1975**, 2034. Nilsson, A.; Ronlan, A.; Parker, V. D. *Tetrahedron Lett.* **1975**, 1107. Logusch, E. W. *Tetrahedron Lett.* **1979**, 3365. Ishihara, T.; Maekawa, T.; Yamasaki, Y.; Ando, T. *J. Org. Chem.* **1987**, *51*, 300.
(33) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *Tetrahedron Lett.* **1976**, 3157.
(34) Brief experimentation indicated that **31** reacted with organometallics in a manner similar to **28**.

Table VII. Reactions of 28 with Organometallics

entry	orgmetllic[a]	conditions[b] temp, °C	time	yield, %
1	MeLi	−78	8 h	71
2	PhLi	0	4 h	39
3	MeMgBr	0	8 h	70
4	Me_2CuLi[c]	0	30 min	59
5	MeCu[c]	25	24 h	NR
6	Ph_2CuLi[c]	0	4 h[d]	84

[a] 2 equiv unless otherwise stated. [b] THF solution unless otherwise stated. [c] 5 equiv. [d] 1:1 Me_2S/THF.

Scheme XII



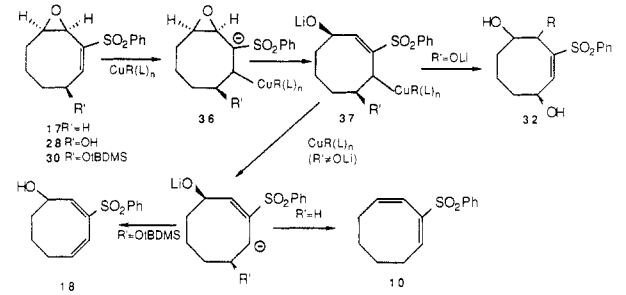
iments indicated that **28** was inert to trifluoroacetic acid (**31** was not formed).

Treatment of silyl ether **30** with tetra-*n*-butylammonium fluoride in THF at 0 °C, HF in acetonitrile–water, or HF–pyridine resulted in a mixture of **28** and **31** in a ratio of 5–6:1 and in nearly quantitative yield.[35] Recovery of bicyclo vinyl sulfone **31** from this deprotection indicated that **30** was a cis/trans mixture, and *trans*-**30** was not completely converted to **31** under the epoxidation conditions. To verify this supposition, **20** was treated with CF_3CO_3H, to afford a mixture of **30**, **31**, and recovered **18** in 31%, 15%, and 42% yields, respectively. This sample of **30** was then deprotected (HF in CH_3CN), to afford 77% of epoxide **28** and 20% of **31**. Reprotection under the usual conditions, (71% yield), followed by deprotection with HF afforded **28**, free from bicyclo compound **31**. NMR (470 MHz) analysis of **30** showed it to be a major component (*cis*-**30**) and a minor component (*trans*-**30**) in a ratio of 85:15, consistent with the ratio of **28** to **31** observed upon deprotection of **30**. These results confirmed that **30** was an inseparable mixture of cis and trans isomers.

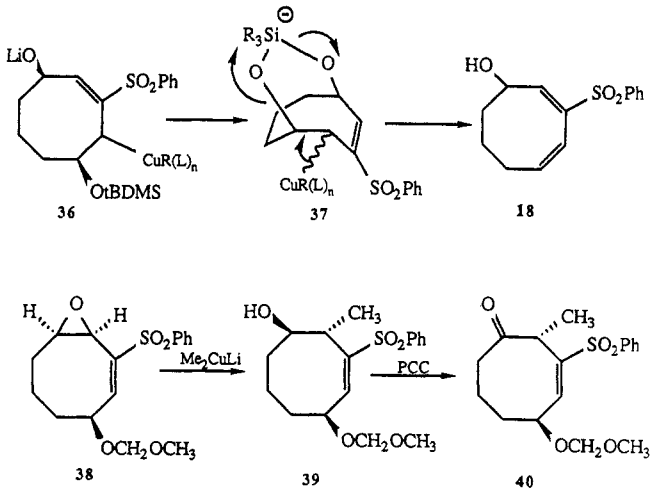
Reactions of epoxy vinyl sulfone alcohol **28** with organometallic reagents provided an arena in which to explore the combination of epoxy vinyl sulfone reactivity with γ-alkoxide directing effect (Scheme XI). The results of these experiments are recorded in Table VII.

The reactions of γ-hydroxy vinyl sulfone **28** are less revealing that other substrates examined, as the products resulting from 1,2-addition to the epoxide or conjugate addition to the vinyl sulfone are equivalent. However, while the conjugate addition product may be a mixture of two diastereomers at the new center, the 1,2-adduct would be expected to be entirely trans. Analysis of the diastereomeric ratio would therefore give some insight into the mode of addition. This seemingly simple problem was complicated by loss of resolution in the proton NMR of diols **32**, due to conformational mobility.

Scheme XIII



Scheme XIV



It should be noted that **28** was not reduced when exposed to organocopper reagents under conditions in which **17** was deoxygenated.

Reactions of **30** again showed a large rate decrease relative to the corresponding free alcohol (Table VIII). As was observed with epoxy vinyl sulfone **17**, reaction with lithium *diphenyl*cuprate resulted in addition to form **33** and **34**, while treatment with lithium *dimethyl* cuprate gave primarily reduction product 18 (Scheme XII). Interestingly, lithium trimethylferrate[38] gave 12% reduction product **18** in addition to 63% of rearrangement product **35**.

To further explore the nature of the epoxide reduction reactions noted above, **30** was exposed to a variety of copper(I) reagents (Table VIII). Only those reagents with a transferrable ligand (entries 6–11 and 13–17) afforded reduction product **18**; the only exception being lithium diphenylcuprate (entry 6). That the reduction required more than one electron is exemplified by the MeCu experiments (entries 16 and 17): 1 equiv was insufficient to allow the reduction to go to completion. These data are consistent with the mechanism of Scheme XIII.

The product distributions of the reactions of **30** with simple homocuprates does *not* correspond well with the reduction potentials for these organometallic reagents.[39] The reduction potentials for the more complex mixed homocuprates have not yet been reported.

Examination of molecular models indicated that an alternate mechanism involving pentavalent silicon intermediate **37** (Scheme XII) was a formal possibility.[40] As a test substrate, MOM ether **38** was prepared[41] and treated

(35) Treatment of **28** with HF in CH_3CN afforded only recovered **28**.
(36) Lipshutz, B. H.; Weilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928. For a review of higher order cuprates, see: Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005.
(37) Corey, E. J.; Kyler, K.; Raju, N. *Tetrahedron Lett.* **1984**, *25*, 5115.
(38) Corey, E. J.; Posner, G. H.; *Tetrahedron Lett.* **1970**, 315.
(39) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.
(40) Although oxygen-to-oxygen silicon migrations are well-known, migrations involving a pentavalent silicon atom in the bridge of a bicyclic intermediate are rare. For an example, see: Torisawa, Y.; Shibasaki, M.; Ikegami, S. *Tetrahedron Lett.* **1979**, 1865.

Table VIII. Reactions of 30 with Organometallics

entry	organometallic	conditions[a]		yield, %		
		temp, °C	time	30	33 + 34[b]	18
1	MeLi	25	24 h	*j*	*j*	*j*
2	MeMgBr	25	24 h	100	0	0
3	Me_3FeLi	−78	20 min	0	0	12[c]
4	$MeTi(O\text{-}i\text{-}Pr)_3$	25	24 h	100	0	0
5	$MeCeCl_2$	25	24 h	100	0	0
6	Ph_2CuLi	−78	20 min[d]	0	82	0
7	Me_2CuLi[e]	−78	20 min	0	10	79
8	Me_2CuLi	0	30 min[f]	*j*	*j*	*j*
9	$Me_2Cu(CN)Li$[g]	−78	20 min[d]	0	13	74
10	$n\text{-}Bu_4NCu(CN)_2MeLi$[e,h]	−78	20 min	52	5	18
11	MMBCuMeLi[e,i]	−78	20 min	0	21	66
12	$(MMB)_2CuLi$[e,i]	25	24 h	100	0	0
13	$(vinyl)_2CuLi$[e]	0	1 h	100	0	0
14	$(allyl)_2CuLi$[e]	−78	20 min	0	0	80
15	$(n\text{-}Bu)_2CuLi$[e]	−78	20 min	0	0	80
16	MeCu[e]	−78	20 min	0	9	45
17	MeCu	−78	1 h	78	3	7
18	MMBCu[e,i]	25	24 h	100	0	0
19	$CuBr\text{–}Me_2S$	25	24 h[d]	100	0	0
20	CuI	25	24 h	100	0	0

[a] THF solution unless otherwise indicated. [b] Inseparable by chromatography. [c] A 63% yield of ketone **35** was also isolated. [d] 1:1 Me_2S/THF. [e] 5 equiv. [f] Ether. [g] See ref 36. [h] See ref 37. [i] MMB = 2-methyoxy-2-methyl-1-butyne ligand. [j] Complex mixture.

with lithium dimethylcuprate. The product ratio was similar to entry 7 of Table VIII; the deoxygenated material contained none of the methoxymethyl ether (Scheme XIV). This clearly indicated that the silicon-bridging mechanism of Scheme XIV was not the likely reaction pathway.

Conclusions

A variety of cyclooctenyl phenyl sulfones were prepared and treated with organometallic reagents. In most cases, these substrates underwent conjugate addition with organolithium reagents. γ-Alkoxy vinyl sulfones showed some diastereoselectivity (directed addition), but steric factors competed successfully with larger nucleophiles. These directed additions were more sluggish than their unsubstituted counterparts, presumably due to steric shielding of the π-faces of the vinyl sulfone. Epoxy vinyl sulfones were the only substrates studied which reacted in a satisfactory manner with Grignard reagents.

Flattening the cyclooctane ring by installation of an additional carbon–carbon double bond or an epoxide accelerated the reactions, again presumably due to removal of steric shielding of the vinyl sulfone. Cuprates generally did not react with γ-substituted cyclooctenyl sulfones[42] but added to or reduced epoxy vinyl sulfones. An electron-transfer mechanism for this reduction was implicated.

Experimental Section

General Procedures. All reactions were performed under a positive pressure of nitrogen or argon in flame-dried flasks equipped with rubber septa for the introduction of reagents via syringe. Analytical TLC was performed on silica gel 60 F-254 plates. THF and ether were purified by distillation from benzophenone–sodium ketyl under nitrogen in a standing still. All recrystallization, chromatographic and workup solvents were also distilled. Proton NMR spectra were recorded on Perkin-Elmer R-32 (90 MHz), Varian XL-200 (200 MHz and variable temperature), and Nicolet NT 470 (470 MHz) instruments. Proton chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as an internal reference (0.0 ppm). Carbon NMR spectra were also recorded on the Varian XL-200 instrument (50 MHz). Carbon chemical shifts are reported in ppm relative to the center line of the $CDCl_3$ triplet (77.0 ppm) and are denoted as "e" (none or two protons) or "o" (one or three protons), as determined from the APT pulse sequence.[43] All NMR spectra were recorded in $CDCl_3$ as solvent unless otherwise noted. Infrared spectra were recorded on a Perkin-Elmer 1420 or 710B spectrophotometer as $CHCl_3$ solutions (unless otherwise noted) and are reported in micrometers. The mass spectra were obtained on a Finnigan 4000 mass spectrometer or a CEC-21-110-B high-resolution mass spectrometer using electron impact and chemical ionization, with the molecular ion designated as M. Melting points were ascertained on a Fisher-Johns hot stage apparatus. Kugelrohr distillations were performed on a Buchi GKR-50 unit. Melting and boiling points are uncorrected.

***trans*-2-Chloro-1-(phenylsulfonyl)cyclooctane (6).**[11] To a slurry of *N*-chlorosuccinimide (3.55 g, 26.6 mmol) in CH_2Cl_2 (25 mL) was added 5 drops of thiophenol. When the mixture had turned orange (ca. 2 min), the flask was immersed in an ice bath and the remainder of the thiophenol (total: 2.60 mL, 25.3 mmol) added dropwise over a 2 min. The cooling bath was then removed and the mixture allowed to stir at room temperature for 30 min. The reaction was then cooled to −78 °C and transferred via cannula into a solution of cyclooctene (3.65 mL, 28.0 mmol) in CH_2Cl_2 (50 mL) at −78 °C at a rate so as to maintain the reaction at or below −50 °C. The orange PhSCl color was discharged as quickly as it was added; the resultant clear solution was then warmed to ambient temperature for 1 h. The solvent was evaporated on a rotary evaporator *without heating*.[44] To the residue was added CH_2Cl_2 (60 mL) and the mixture filtered. The filtrate was washed with water (25 mL), dried (Na_2SO_4), and evaporated to a volume of ca. 20 mL.

The crude chloro sulfide was then added dropwise over 10 min (at a rate to maintain a temperature of 20 °C) to a slurry of mCPBA (11.0 g, 80% peracid, 51.0 mmol) in CH_2Cl_2 (100 mL). After the ice bath was removed, the mixture was stirred at room temperature for a period of 24 h. At this time, the slurry was filtered and the filtrate cautiously treated with saturated Na_2SO_3 (10 mL) to neutralize the remaining peracid. The organic layer was separated and washed with saturated Na_2SO_3 (50 mL), 10% Na_2CO_3 (2 × 100 mL), and water (100 mL). Drying (Na_2SO_4) and evaporation of the solvent afforded 6.2 g of white solid, which

(41) The attempted preparation of **38** under the usual conditions (MOMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2) resulted only in destruction of the starting material. Facile protection was achieved upon treatment of **28** with MOMCl and $AgNO_3$ in DMF. Further studies of this methodology will be the subject of a future publication.

(42) For an example of an α′-amino vinyl sulfone which failed to react under conditions in which the present vinyl sulfone did react, see: Hutchinson, D. K.; Hardinger, S. A.; Fuchs, P. L. *Tetrahedron Lett.* **1986**, *27*, 1425.

(43) Patt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535.

(44) This system is prone to retro-sulfenylation: Schmid, G. H.; Fitzgerald, P. H. *J. Am. Chem. Soc.* **1971**, *93*, 2547.

was recrystallized from CCl_4/hexane to afford white needles, 5.50 g, 19.1 mmol, 76% yield: mp 89–90 °C; IR 7.67, 8.89 (sulfone); ^{1}H NMR 7.93 (d, of d, 2 H, ortho Ar), 7.65 (m, 1 H, para Ar), 7.57 (m, 2 H, meta Ar), 4.55 (m, 1 H, $PhSO_2CH$), 3.45 (m, 1 H, $ClCH$), 2.54–1.88 (m, 12 H, CH_2); ^{13}C NMR 138.92 (e), 133.72 (o), 129.04 (o), 128.90 (o), 74.43 (o), 57.77 (o), 31.85 (e), 28.92 (e), 25.46 (e), 25.12 (e), 24.04 (e), 23.50 (e).

1-(Phenylsulfonyl)-*cis*-cyclooctene (7). A solution of chloro sulfone **6** (4.78 g, 16.7 mmol), DBU (2.60 mL, 17.4 mmol), and CH_2Cl_2 (50 mL) was heated at reflux for 22 h. The mixture was then washed with 5% HCl (25 mL), saturated $NaHCO_3$ (25 mL), and saturated NaCl (25 mL). After the mixture was dried (Na_2SO_4), the solvent was evaporated to afford 4.05 g (16.2 mmol, 93% yield) of pure **7** as an oil, which solidified on standing. Recrystallization from CCl_4/hexane afforded white crystals: mp 75.5–76.5 °C; IR 7.69, 8.66 (sulfone); ^{1}H NMR 7.90 (d, 2 H, ortho Ar), 7.60 (t, 1 H, para Ar), 7.55 (d of d, 1 H, meta Ar), 7.12 (t, 1 H, vinyl), 2.37 (br s, 2 H, α'-CH_2), 2.32 (d of d of d, 2 H, γ-CH_2), 1.70–0.80 (m, 8 H, CH_2); ^{13}C NMR 141.71 (e), 141.10 (o), 139.83 (e), 132.96 (o), 128.93 (o), 128.01 (o), 28.95 (e), 28.11 (e), 26.41 (e), 25.74 (e), 25.46 (e), 24.93 (e); exact mass calcd for $C_{14}H_{18}O_2S$ 250.1027, found 250.1570 (M). Anal. Calcd: C, 67.16; H, 7.25; S, 12.81. Found: C, 66.93; H, 7.32; S, 13.00.

General Procedure for the Reaction of Vinyl Sulfones with Organolithium or Grignard Reagents. To a solution of the vinyl sulfone in the appropriate solvent (ca. 0.1 M) at −78 °C was added the organometallic reagent slowly via syringe. The mixture was warmed as needed. When complete, the reaction was again cooled to −78 °C, saturated NH_4Cl added, and the mixture allowed to warm to room temperature. The crude product was isolated by dilution with CH_2Cl_2, washing with 5% HCl, saturated $NaHCO_3$, and saturated NaCl, and then drying (Na_2SO_4). Evaporation of the solvent afforded the crude adduct, which was analyzed by ^{1}H NMR to determine the ratio of products. Flash chromatography on silica gel with ethyl acetate/hexane mixtures provided the pure adducts. Yields and diastereomeric product ratios are shown in tables in the text. Spectral data for the adducts are detailed below.

***cis*- and *trans*-2-Methyl-1-(phenylsulfonyl)cyclooctane (8, R = CH_3).** To a slurry of CuI (Alfa Ultrapure, 423.1 mg, 2.22 mmol) in THF (5.0 mL) at −10 °C (ice–acetone bath) was added MeLi (2.90 mL of a 1.54 M solution in ether, 4.47 mmol) dropwise, followed by warming to 0 °C for 15 min. The bright yellow MeCu which had initially precipitated dissolved during this time to afford a colorless, slightly hazy solution. This cuprate was then cooled to −78 °C, a solution of **7** (110.0 mg, 0.439 mmol) in THF (2.0 mL) was added slowly, and the mixture was warmed to 0 °C for 1 h. The reaction was then cooled to −78 °C, saturated NH_4Cl (1 mL) added slowly, and the mixture warmed to room temperature. After dilution with 1:1 concentrated NH_4OH/saturated NH_4Cl (20 mL), the organics were extracted with CH_2Cl_2 (3 × 20 mL) and washed with 1:1 concentrated NH_4OH/saturated NH_4Cl (2 × 10 mL) and water (10 mL). Drying (Na_2SO_4) and evaporation afforded 170 mg of the crude adduct as an oil, which was analyzed and purified as above: IR 7.75, 8.93 (sulfone); ^{1}H NMR 7.90 (d of d, 2 H, ortho Ar), 7.64 (t, 1 H, para Ar), 7.55 (d of d, 2 H, meta Ar), 3.35 (m, 1 H, α-sulfone, J = 2.9 Hz, cis isomer), 2.90 (d of d, 1 H, α-sulfone, J = 9.3 Hz, trans isomer), 2.48 (m, 1 H, CH_3CH, cis isomer), 2.32 (m, 1 H, CH_3CH, trans isomer), 2.00–1.20 (m, 12 H, CH_2), 1.23 (d, 3 H, CH_3, trans isomer), 1.12 (d, 3 H, CH_3, cis isomer).

***cis*- and *trans*-2-Phenyl-1-(phenylsulfonyl)cyclooctane (8, R = Ph).** To a solution of CuBr–Me_2S[45] (457.7 mg, 2.23 mmol) in 1:1 Me_2S/THF (8.0 mL) at −10 °C was added PhLi (2.0 mL of a 2.20 M solution in 70:30 cyclohexane/ether, 4.40 mmol) dropwise, followed by warming to 0 °C for 15 min. To the resultant colorless solution was added a solution of **7** (108.5 mg, 0.433 mmol) in THF (2.0 mL) and the mixture heated at reflux for 24 h. The reaction was then worked up, analyzed, and purified in a manner similar to the lithium dimethylcuprate reaction described above: IR 7.75, 8.77 (sulfone); ^{1}H NMR 7.65–7.15 (m, 10 H, Ar), 3.75 (m, 1 H, α-sulfone, cis isomer), 3.40 (m, 1 H, α-sulfone, trans isomer), 2.10–1.20 (m, 13 H, benzyl and CH_2). Coupling constants could not be ascertained due to overlapping signals; diastereomers assigned by comparison of 8 (R = CH_3).

Spectral data for *cis*- and *trans*-2-*n*-butyl-1-(phenylsulfonyl)cyclooctane (8, R = *n*-Bu): IR 7.75, 8.93 (sulfone); ^{1}H NMR 7.90 (d of d, 2 H, ortho Ar), 7.65 (t, 1 H, para Ar), 7.55 (d of d, 2 H, meta Ar), 3.34 (m, 1 H, α-sulfone, J = 0 Hz, cis isomer), 2.83 (m, 1 H, α-sulfone, J = 7.7 Hz, *trans* isomer), 2.33 (br d, 1 H, *n*-BuC*H*, cis isomer), 2.20 (m, 1 H, *n*-buCH, *trans* isomer), 2.00–1.00 (m, 18 H, CH_2), 0.89 (d, 3 H, CH_3).

Spectral data for *cis*-2-*tert*-butyl-1-(phenylsulfonyl)cyclooctane (8, R = *t*-Bu): IR 7.72, 8.77 (sulfone); ^{1}H NMR 7.84 (d of d, 2 H, ortho Ar), 7.67 (t, 1 H, para Ar), 7.49 (d of d, 2 H, meta Ar), 3.37 (d of d, 1 H α-sulfone), 2.10–1.30 (m, 12 H, CH_2), 0.78 (s, 9 H, *t*-Bu); ^{13}C NMR 139.58 (e), 133.19 (o), 128.97 (o), 128.56 (o), 65.97 (o), 44.49 (o), 35.29 (e), 28.33 (e, two coincident resonances), 28.09 (o), 26.74 (e), 22.08 (e), 21.76 (e), 20.73 (e). Only the cis isomer was detected by 470-MHz ^{1}H NMR.

***trans*-3-(Phenylthio)-4-hydroxy-*cis*-cyclooctene (9).** To a mechanically stirred mixture of 1,3-cyclooctadiene (38.1 g, 0.352 mol), anhydrous Na_2CO_3 (150 g, 1.42 mol), and CH_2Cl_2 (500 mL) at 0 °C was added CH_3CO_3H (63 mL of a 37% solution in HOAc, 0.342 mol, which had been pretreated with 1.50 g anhydrous NaOAc to remove H_2SO_4) dropwise over 35 min. The mixture was then stirred at room temperature for 18 h, at which time moist KI/starch paper indicated that all the peracid had been consumed. After filtration, the filtrate was concentrated and distilled (bp 178–179 °C) to afford the monoepoxide as a clear oil, 33.59 g, 0.270 mol, 72% yield.[16]

A solution of the monoepoxide (15.62 g, 0.126 mol), thiophenol (39.0 mL, 0.138 mol), triethylamine (19.3 mL, 0.138 mol), and DMF (140 mL) was heated at 50 °C for 12 h. The resultant dark solution was then diluted with water (450 mL), and the organics were extracted into hexane (3 × 200 mL), washed with 10% NaOH (200 mL), 5% HCl (200 mL), and saturated NaCl (200 mL), and dried (Na_2SO_4). Evaporation of the solvent yielded 31 g of crude product, which was distilled [bp 130–132 °C (0.4 mm)] to afford pure sulfide alcohol **9**, 26.24 g, 0.112 mol, 89% yield: IR (neat) 2.94 (OH); ^{1}H NMR 7.60–7.20 (m, 5 H, Ar), 5.55–5.90 (m, 2 H, vinyl), 3.95 (d of d, 1 H, α-phenylthio), 3.63 (br d of d, 1 H, carbinol), 2.40–2.00 (m, 2 H, allylic CH_2), 2.00–1.00 (m, 6 H, CH_2); ^{13}C NMR 131.95 (e), 131.58 (o), 131.40 (o), 130.94 (o), 128.79 (o), 127.13 (o), 72.67 (o), 53.56 (o), 32.40 (e), 28.82 (e), 27.33 (e), 21.51 (e).

***trans*-3-(Phenylsulfonyl)-4-hydroxy-*cis*-cyclooctene.** To a mechanically stirred solution of sulfide alcohol **9** (240.7 g, 1.03 mol) in CH_2Cl_2 (2.4 L) at 0 °C was added CH_3CO_3H (415 mL of a 35% solution in HOAc, 2.16 mol, which had been pretreated with 10.0 g of anhydrous NaOAc to remove H_2SO_4) over 60 min at a rate to maintain the reaction temperature below 20 °C. After an additional 60 min at room temperature, the mixture was again cooled to 0 °C, and the residual peracid was destroyed by cautious addition of saturated Na_2SO_3 (200 mL). The layers were separated and the organics washed with 5% HCl (1 L), saturated $NaHCO_3$ (1 L), and saturated NaCl (1 L) and dried (Na_2SO_4). Evaporation of the solvent afforded 273 g of a white solid, which was recrystallized from benzene/hexane to afford a total of 204.2 g of white crystals (three crops), 0.767 mol, 74% yield, mp 89–90 °C: IR 2.89 (OH), 5.89 (olefin), 7.17, 8.93 (sulfone); ^{1}H NMR 7.90 (d, 2 H, ortho Ar), 7.66 (t, 1 H, para Ar), 7.56 (d of d, 2 H, meta Ar), 5.94 (d of t, 1 H, $PhSO_2CHCH$=), 5.53 (d of t, 1 H, CH_2CH=CH), 4.48 (d of d of d, 1 H, α-sulfone), 4.16 (t, 1 H, carbinol), 2.10–1.19 (m, 8 H, CH_2); ^{13}C NMR 137.95 (e), 137.54 (o), 133.84 (o), 128.97 (o), 128.31 (o), 121.58 (o), 70.24 (o), 68.14 (o), 32.76 (e), 28.47 (e), 28.00 (e), 21.99 (e).

3-(Phenylsulfonyl)-1,3-cyclooctadiene (10). To a solution of the sulfone alcohol (100.0 g, 0.375 mol) and methanesulfonyl chloride (34.9 mL, 0.451 mol) in THF (500 mL) at 0 °C was added triethylamine (130 mL, 0.933 mol) dropwise over 25 min at a rate to maintain the reaction temperature below 20 °C. After an additional 10 min at 0 °C, DBU (167 mL, 1.12 mol) was added dropwise over 20 min, and stirring was continued for 14 h at room temperature. The reaction was then diluted with 5% HCl (500 mL), and the organics were extracted with CH_2Cl_2 (3 × 250 mL), washed with saturated $NaHCO_3$ (500 mL) and saturated NaCl (500 mL), and dried (Na_2SO_4). Evaporation of the solvent gave 101.3 g of a yellow solid, which was recrystallized from CCl_4/

(45) Thies, A. B.; Townsend, C. A. *Synth. Commun.* **1981**, *11*, 157.

hexane to afford pure **10** as white crystals, 83.7 g, 0.337 mol, 90% yield: mp 90–91 °C; IR 7.66, 8.70 (sulfone); ^{1}H NMR 7.95 (d, of d, 1 H, ortho Ar), 7.68 (t, 1 H, para Ar), 7.60 (d of d, 2 H, meta Ar), 7.15 (t, 1 H, $PhSO_2C$=C*H*), 6.08 (m, 2 H, $PhSO_2CC$*H*=C*H*), 2.00–1.20 (m, 6 H, CH_2); ^{13}C NMR 140.43 (o), 139.80 (e), 139.32 (e), 138.16 (o), 132.87 (o), 128.77 (o), 127.79 (o), 119.11 (o), 28.16 (e), 27.47 (e), 22.07 (e), 21.90 (e); exact mass calcd for $C_{14}H_{16}O_2S$ 248.0871, found 248.0861 (M). Anal. Calcd: C, 67.71; H, 6.49; S, 12.91. Found: C, 67.81; H, 6.59; S, 12.64.

Spectral data for *cis*- and *trans*-4-methyl-3-(phenylsulfonyl)-*cis*-cyclooctene (11c and 11t, R = CH_3): IR 7.69, 8.76 (sulfone), ^{1}H NMR 7.82 and 7.79 (d, 2 H, ortho Ar), 7.54 (t, 1 H, para Ar), 7.46 (d of d, 2 H, meta Ar), 6.00–5.30 (m, 2 H, vinyl), 4.01 (d of d, 1 H, α-sulfone, J = 3.6 Hz, cis isomer), 3.89 (t, 1 H, α-sulfone, J = 10.6 Hz, trans isomer), 2.61 (m, 1 H, CH_3C*H*, cis isomer), 2.29 (m, 1 H, CH_3CH, trans isomer), 2.10–1.05 (m, 8 H, CH_2), 1.37 (d, 3 H, CH_3, trans isomer), 1.08 (d, 3 H, CH_3, cis isomer).

Spectral data for *cis*- and *trans*-4-phenyl-3-(phenylsulfonyl)-*cis*-cyclooctene (11c and 11t, R = Ph): IR 7.59, 8.61 (sulfone); ^{1}H NMR 7.64 (d, 2 H, ortho Ar), 7.55–7.10 (m, 8 H, Ar), 6.14 (d of d, 1 H, $PhSO_2CHCH$=C*H*, cis isomer), 6.05 (d of d, 1 H, $PhSO_2CHCH$=C*H*, trans isomer), 5.83 (t, 1 H, $PhSO_2CHCH$=CH, trans isomer), 5.77 (t, 1 H, $PhSO_2CHCH$=CH, cis isomer), 4.76 (d of d, 1 H, α-sulfone, trans isomer: coupling constant determination obscured by apparent long-range coupling), 4.48 (d of d, 1 H, α-sulfone, J = 4.8 Hz, cis isomer), 3.73 (m, 1 H, benzyl, cis isomer), 3.41 (m, 1 H, benzyl, trans isomer), 2.60–1.25 (m, 8 H, CH_2).

3-(Phenylthio)-*cis*-cyclooctene.[18] A mixture of cyclooctene (22.6 mL, 0.174 mol), *N*-bromosuccinimide (30.8 g, 0.173 mol), benzoyl peroxide (130 mg, 5.4 mmol), and CCl_4 (100 mL) was heated at reflux for 1 h. After cooling to room temperature, the reaction was filtered and the filtrate washed with 5% $NaHCO_3$ (100 mL) and water (2 × 100 mL) and dried (Na_2SO_4). Distillation through a 15-cm Vigreux column provided a mixture of CCl_4 and 3-bromo-*cis*-1-cyclooctene [bp 72 °C (4 mm)], which was employed directly in the next step.

To a slurry of NaH (oil-free, 5.0 g, 0.208 mol) in THF (300 mL) was added thiophenol (20.5 mL, 0.200 mol) dropwise (vigorous and exothermic reaction!) with ice–water bath cooling as necessary. The allylic bromide prepared above was then added dropwise over 13 min and the resultant mixture stirred for 24 h at room temperature. The reaction was diluted with 10% Na_2CO_3 (200 mL), and the organics were extracted into hexane (3 × 100 mL), washed with 5% HCl (100 mL) and saturated NaCl (100 mL), and dried (Na_2SO_4). Evaporation of the solvent and Kugelrohr distillation of the residue [bp 102–103 °C (0.02 mm)] afforded pure allylic sulfide as a colorless oil, 19.55 g, 89.5 mmol, 51% yield from cyclooctene: ^{1}H NMR 7.33 (d of d, 2 H, ortho Ar), 7.25 (d of d, 2 H, meta Ar), 7.16 (d of d, 1 H, para Ar), 5.73 (d of d, 1 H, $PhSCHC$*H*=), 5.48 (t of d, 1 H, CH_2C*H*=CH), 4.18 (m, 1 H, α-thio ether), 2.30–1.30 (m, 10 H, CH_2); ^{13}C NMR 136.31 (e), 133.14 (o), 130.65 (o), 129.89 (o), 128.64 (o), 125.92 (o), 43.56 (o), 35.68 (e), 29.33 (e), 26.76 (e), 26.46 (e), 25.74 (e); exact mass calcd for $C_{14}H_{18}S$ 218.1129, found 218.1115 (M).

***cis*-3-(Phenylsulfonyl)-*cis*-cyclooctene Oxide (12).** To a solution of the allylic sulfide (18.38 g, 84.2 mmole) in CH_2Cl_2 (200 mL) at 5 °C was added mCPBA (71.9 g, 80% peracid, 0.333 mol) in small portions at a rate to maintain the reaction temperature below 25 °C. After the mixture was stirred an additional 10 min at 0 °C, the cooling bath was removed and the mixture stirred at room temperature for 72 h. The slurry was then filtered, the filtrate cooled to 0 °C, and residual peracid destroyed by cautious treatment with saturated Na_2SO_3 (100 mL), followed by addition of 10% Na_2CO_3 (200 mL) and stirring for an additional 15 min. The organics were washed with 5% HCl (100 mL) and saturated NaCl (100 mL) and dried (Na_2SO_4). Evaporation of the solvent gave 23.3 g of crude material, which was recrystallized from methanol/hexane to afford pure epoxy sulfone **12** as large needles, 19.30 g, 72.5 mmole, 86% yield: mp 107–107.5 °C; IR 7.63, 8.66 (sulfone); ^{1}H NMR (methanol-d_4) 7.85 (d, 2 H, ortho Ar), 7.63 (t, 1 H, para Ar), 7.54 (d of d, 2 H, meta Ar), 3.06 (t of d, 1 H, α-sulfone, J = 4.4 Hz), 2.96 (d of d, 1 H, $PhSO_2CHC$*H*O), 2.84 (d of t, 1 H, OC*H*CH_2), 2.05 (m, 2 H, CH_2CHO), 1.75–1.30 (m, 8 H, CH_2); ^{13}C NMR 138.44 (e), 133.63 (o), 128.83 (o), 128.75 (o), 64.56 (o), 54.21 (o), 52.84 (o), 26.77 (e), 26.18 (e), 25.05 (e), 24.70 (e), 24.40 (e).

3-Hydroxy-1-(phenylsulfonyl)-*cis*-cyclooctene (13). To a solution of the epoxy sulfone (18.80 g, 70.6 mmol) in THF (100 mL) was added NaH (5.70 g of a 60% suspension in mineral oil, 0.143 mol) in portions over 5 min. The resultant slurry was stirred for 22 h at room temperature and then cautiously quenched with 5% HCl (100 mL). The organics were extracted into CH_2Cl_2 (3 × 100 mL), washed with saturated $NaHCO_3$ (100 mL) and saturated NaCl (100 mL), and dried (Na_2SO_4). Evaporation of the solvent and recrystallization of the residue from $CHCl_3/CCl_4$ afforded pure **13** as small prisms, 14.7 g, 55.2 mmol, 78% yield: mp 72–73 °C; IR 2.90 (OH), 7.66, 8.66 (sulfone); ^{1}H NMR 7.92 (d of d, 2 H, ortho Ar), 7.61 (t, 1 H, para Ar), 7.55 (d of d, 2 H, meta Ar), 7.03 (d, 1 H, vinyl), 4.48 (m, 1 H, carbinol), 2.65–1.10 (m, 10 H, CH_2); ^{13}C NMR 144.90 (o), 139.42 (e), 139.03 (e), 133.26 (o), 129.05 (o), 128.03 (o), 69.31 (o), 38.03 (e), 28.83 (e), 25.39 (e, two conincident resonances), 23.30 (e); exact mass calcd for $C_{14}H_{18}O_3S$ 266.0976, found 266.0968 (M). Satisfactory combustion analysis could not be obtained.

3-[(*tert*-Butyldimethylsilyl)oxy]-1-(phenylsulfonyl)-*cis*-cyclooctene (14). A solution of **13** (1.3673 g, 5.13 mmol), *tert*-butylchlorodimethylsilane (938.6 mg, 6.23 mmol), triethylamine (0.80 mL, 5.74 mmol), 4-(dimethylamino)pyridine[20] (30.1 mg, 0.246 mmol), and DMF (20 mL) was stirred at room temperature for 15 h. The reaction was then diluted with 5% HCl (150 mL). The organics were extracted into hexane (3 × 50 mL), washed with saturated $NaHCO_3$ (50 mL) and water (4 × 50 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue on silica gel with CH_2Cl_2 afforded an oil, which solidified on standing. Recrystallization from hexane afforded plates, 1.9430 g, 5.10 mmol, 99% yield: mp 42–43 °C; IR 7.60, 8.62 (sulfone); ^{1}H NMR 7.92 (d of d, 2 H, ortho Ar), 7.61 (t, 1 H, para Ar), 7.55 (d of d, 2 H, meta Ar), 6.93 (d, 1 H, vinyl), 4.55 (m, 1 H, carbinol), 2.60–1.20 (m, 10 H, CH_2), 0.83 (s, 9 H, *t*-Bu), 0.10 (s, 6 H, CH_3); ^{13}C NMR 145.46 (o), 139.52 (e), 139.12 (e), 133.18 (o), 129.02 (o), 128.11 (o), 70.25 (o), 38.85 (e), 29.06 (e), 25.72 (o), 25.61 (e, two coincident resonances), 23.31 (e), 18.05 (e), −4.74 (o), −4.87 (o); exact mass calcd for $C_{20}H_{32}O_3SSi$ 380.1841, found 380.1833 (M).

Spectral data for *cis,cis*-3-hydroxy-2-methyl-1-(phenylsulfonyl)cyclooctane (15cc, R = CH_3): IR 2.90 (OH), 7.63, 8.66 (sulfone), ^{1}H NMR 7.87 (d of d, 2 H, ortho Ar), 7.61 (t, 1 H, para Ar), 7.55 (d of d, 2 H, meta Ar), 3.65 (t, 1 H, carbinol, J = 6.7 Hz), 3.51 (d of d of d, 1 H, α-sulfone), 2.45 (d of d, 1 H, CH_3C*H*, J = 6.7 Hz), 1.90–1.15 (m, 10 H, CH_2), 1.13 (d, 3 H, CH_3); ^{13}C NMR 138.45 (e), 133.48 (o), 129.17 (o), 128.63 (o), 75.25 (o), 62.28 (o), 37.72 (o), 32.47 (e), 26.28 (e), 24.96 (e), 23.49 (e), 22.57 (e), 13.26 (o). Only the cis isomer was detected by 470-MHz ^{1}H NMR.

Spectral data for *cis,cis*- and *cis,trans*-3-hydroxy-2-phenyl-1-(phenylsulfonyl)cyclooctane (15cc and 15ct, R = Ph): IR 2.88 (OH), 7.69, 8.66 (sulfone); ^{1}H NMR could not be assigned due to ambiguous coupling patterns (see text).

***cis*-3,4-Epoxy-2-(phenylsulfonyl)-*cis*-cyclooctene (17).** A mixture of **10** (12.05 g, 48.5 mmol), mCPBA (10.85 g, 80% peracid, 50.3 mmol), 3,3′-thiobis(5-*tert*-butyl-*m*-cresol)[28] (295.8 mg, 0.895 mmol), and CCl_4 (200 mL) was heated at reflux for 6 h. The reaction was then cooled with an ice bath and filtered. The cold filtrate was cautiously treated with saturated Na_2SO_3 (20 mL) to destroy any residual peracid and then stirred 15 min with 10% Na_2CO_3 (100 mL). The organic layer was washed with 5% HCl (50 mL) and saturated NaCl (50 mL) and dried (Na_2SO_4). Evaporation of the solvent and recrystallization of the residue from CCl_4 afforded pure epoxy vinyl sulfone **17**, 9.71 g, 36.7 mmol, 76% yield: mp 102–103.5 °C; IR 6.13 (olefin), 7.69, 8.77 (sulfone); ^{1}H NMR 8.08 (d of d, 2 H, ortho Ar), 7.70 (t, 1 H, para Ar), 7.65 (d of d, 2 H, meta Ar), 7.36 (t, 1 H, vinyl), 3.72 (d, 1 H, OC*H*CSO_2Ph), 3.14 (d of t, 1 H, CH_2CHO), 2.45 (q, allylic CH_2), 2.15–0.90 (m, 6 H, CH_2); ^{13}C NMR 144.73 (o), 140.57 (e), 136.99 (e), 132.90 (o), 128.57 (o), 127.93 (o), 56.66 (o), 50.40 (o), 28.59 (e), 26.50 (e), 24.23 (e), 23.68 (e); exact mass calcd for $C_{14}H_{16}O_3S$ 265.0898, found 265.0896 (M + H).

5-Hydroxy-3-(phenylsulfonyl)-1,3-cyclooctadiene (18). A solution of **17** (9.00 g, 34.0 mmol), triethylamine (9.5 mL, 68.2 mmol), and CH_3CN (250 mL) was heated at reflux for 2 h, then diluted with 5% HCl (125 mL), and washed with saturated NaCl

(125 mL). The organics were extracted into $CHCl_3$ (3 × 100 mL), washed with saturated $NaHCO_3$ (200 mL) and saturated NaCl (200 mL), and dried (Na_2SO_4). Evaporation of the solvent and recrystallization of the residue from methanol afforded pure **18** as large prisms, 7.75 g, 29.3 mmol, 86% yield; mp 111–112.5 °C; IR 2.92 (OH), 5.92 (olefin), 7.69, 8.77 (sulfone); ^1H NMR 7.84 (d, 2 H, ortho Ar), 7.59 (d of d, 1 H, para Ar), 7.50 (d of d, 2 H, meta Ar), 6.87 (d, 1 H, $PhSO_2C{=}CH$), 6.07 (d, 1 H, $PhSO_2CCH{=}$), 5.95 (m, 1 H, $CH_2CH{=}$), 4.24 (m, 1 H, carbinol), 2.15–1.20 (m, 6 H, CH_2); ^{13}C NMR 145.21 (o), 139.68 (o), 139.14 (e), 135.92 (e), 133.47 (o), 129.28 (o), 127.42 (o), 118.21 (o), 68.83 (o), 32.73 (e), 27.65 (e), 20.39 (e); exact mass calcd for $C_{14}H_{16}O_3S$ 26.5.0898, found 265.0907 (M + H). Anal. Calcd: C, 63.91; H, 6.10; S, 12.13. Found: C, 63.55; H, 6.24; S, 11.70.

5-[(*tert*-Butyldimethylsilyl)oxy]-3-(phenylsulfonyl)-1,3-cyclooctadiene (20). A solution of **18** (7.75 g, 29.3 mmol), *tert*-butylchlorodimethylsilane (5.00 g, 33.2 mmol), triethylamine (5.1 mL, 36.6 mmol), 4-(dimethylamino)pyridine[20] (179.4 mg, 1.47 mmol), and DMF (100 mL) was stirred at room temperature for 5 h and then diluted with 5% HCl (300 mL). The organics were extracted into hexane (3 × 100 mL), washed with saturated $NaHCO_3$ (100 mL) and water (4 × 100 mL), and dried (Na_2SO_4). Evaporation of the solvent afforded pure **20**, 9.45 g, 25.0 mmol, 85% yield: mp 103.5 °C (recrystallized from hexane or methanol/water); IR 7.69, 8.73 (sulfone); ^1H NMR 7.83 (d of d, 2 H, ortho Ar), 7.58 (t, 1 H, para Ar.) 7.50 (d of d, 2 H, meta Ar), 6.81 (d, 1 H, $PhSO_2C{=}CH$), 6.04 (d, 1 H, $PhSO_2CCH{=}$), 5.95 (m, 1 H, $CH_2CH{=}$), 4.17 (m, 1 H, carbinol), 2.20–1.15 (m, 6 H, CH_2), 0.87 (s, 9 H, *t*-Bu), 0.10 (s, 6 H, CH_3); ^{13}C NMR 144.69 (o), 139.59 (o), 136.84 (e), 136.83 (e), 133.06 (o), 128.83 (o), 127.89 (o), 118.76 (o), 71.13 (o), 33.99 (e), 28.19 (e), 25.71 (o), 20.70 (e), 18.02 (e), −4.66 (o), −4.96 (o); exact mass calcd for $C_{20}H_{30}O_3SSi$ 378.1685, found 378.1672 (M).

Spectral data for *cis*,*cis*-5-hydroxy-4-methyl-3-(phenylsulfonyl)-*cis*-1-cyclooctene (21cc, R = CH_3): IR 2.88 (OH), 7.63, 8.70 (sulfone); ^1H NMR 7.85 (d, 2 H, ortho Ar), 7.60 (t, 1 H, para Ar), 7.52 (d of d, 2 H, meta Ar), 5.85 (m, 2 H, vinyl), 4.30 (d of d, 1 H, α-sulfone, J = 2.3 Hz), 3.58 (t of d, 1 H, carbinol, J = 1.5 Hz), 2.63 (t of d, 1 H, CH_3CH, J = 1.5 and 2.3 Hz), 1.95–1.35 (m, 6 H, CH_2), 1.22 (d, 3 H, CH_3); ^{13}C NMR 139.28 (e), 135.70 (o), 133.33 (o), 128.87 (o), 128.05 (o), 121.83 (o), 75.27 (o), 62.47 (o), 40.79 (o), 31.00 (e), 26.56 (e), 25.44 (e), 12.69 (o).

Spectral data for *trans*,*cis*- and *trans*,*trans*-5-hydroxy-4-phenyl-3-(phenylsulfonyl)-*cis*-cyclooctene (21tc and 21tt, R = Ph): IR 2.84 (OH), 7.63, 8.70 (sulfone); ^1H NMR 7.60–7.20 (m, 10 H, Ar), 6.15–6.00 (m, 2 H, vinyl), 4.54 (d of d, 1 H, α-sulfone, J = 4.6 Hz, tt isomer), 4.49 (d of d, 1 H, α-sulfone, J = 8.0 Hz, tc isomer), 3.94 (t, 1 H, carbinol, J = 0 Hz, tc isomer), 3.76 (d of d, 1 H, benzyl, J = 8.0 and 10.0 Hz, tc isomer), 3.66 (t, 1 H, carbinol, J = OHz, tc isomer), 3.52 (d of d, 1 H, benzyl, J = 4.6 and 0 Hz, tt isomer), 2.50–1.40 (m, 6 H, CH_2).

Spectral data for *cis*,*cis*-, *trans*,*cis*-, and *trans*,*trans*-5-[(*tert*-butyldimethylsilyl)oxy]-4-methyl-3-(phenylsulfonyl)-*cis*-1-cyclooctene (22cc, 22tc, and 22tt, R = CH_3): IR 7.66, 8.70 (sulfone); ^1H NMR, the complexity of the 470-MHz ^1H NMR of this mixture prevents assignment.

Spectral data for *cis*,*cis*- and *trans*,*cis*-5-[(*tert*-butyldimethylsilyl)oxy]-4-phenyl-3-(phenylsulfonyl)-*cis*-1-cyclooctene (22cc and 22tc, R = Ph): IR 7.66, 8.70 (sulfone); ^1H NMR 7.67–7.20 (m, 10 H, Ar), 6.15–5.85 (m, 2 H, vinyl), 4.73 (d of d, 1 H, α-sulfone, J = 3.0 Hz, cc isomer), 4.59 (d of d, 1 H, α-sulfone, J = 3.0 Hz, cc isomer), 3.90 (m, 1 H, carbinol, both isomers), 3.63 (d of d, 1 H, benzyl, J = 7.8 and 3.0 Hz, tc isomer), 3.48 (d of d, 1 H, benzyl, J = 12.0 and 3.0 Hz, cc isomer), 2.30–1.40 (m, 6 H, CH_2), 0.87 (s, 9 H, *t*-Bu, cc isomer), 0.73 (s, 9 H, *t*-Bu, tc isomer), 0.05 (s, 3 H, CH_3, cc isomer), −0.08 (s, 3 H, CH_3, tc isomer).

Spectral data for 4-hydroxy-3-methyl-2-(phenylsulfonyl)-*cis*-1-cyclooctene (26) and 4-hydroxy-1-methyl-2-(phenylsulfonyl)-*cis*-2-cyclooctene (27, R = CH_3): IR 2.88 (OH), 7.66, 8.70 (sulfone); ^1H NMR 8.10–7.60 (m, 5 H, Ar), 7.30 (t, 1 H, vinyl, **26**), 7.07 (d, 1 H, vinyl, **27**), 5.05 (br m, 1 H, carbinol, **27**), 3.97 (m, 1 H, carbinol, **26**), 3.05–1.15 (m, 9 H, CH_2 and CH_3CH), 1.05 (d, 3 H, CH_3).

Spectral data for 4-hydroxy-1-phenyl-2-(phenylsulfonyl)-*cis*-2-cyclooctene (27, R = Ph): IR 2.87 (OH), 7.69, 8.73 (sulfone); ^1H NMR 7.70–6.99 (m, 10 H, Ar), 7.16 (d, 1 H, vinyl), 4.76 (br s, 1 H, carbinol), 4.07 (br s, 1 H, benzyl), 2.18–1.40 (m, 8 H, CH_2).

1,2-Epoxy-5-hydroxy-3-(phenylsulfonyl)-3-cyclooctene (28) and 4-Hydroxy-2-(phenylsulfonyl)-9-oxabicyclo[4.2.1]-1-nonene (31). A solution of **30** (1.6655 g, 4.22 mmol) in HF/CH_3CN (7.0 mL of a 1.45 M solution, prepared by dilution of 5.0 mL of 48% aqueous HF with 95 mL of CH_3CN; 9.15 mmole) was stirred for 8 h in a Teflon vial at room temperature. After dilution with CH_2Cl_2 (20 mL), neutralization with solid K_2CO_3, and filtration, the filtrate was evaporated. The residue was then recrystallized from $CHCl_3$/hexane, to afford **28** as small white prisms, 949.6 mg, 3.39 mmol, 80% yield: mp 149.5–151 °C; IR 2.91 (OH), 7.63, 8.70 (sulfone); ^1H NMR 7.80 (d, 2 H, ortho ar), 7.62 (t, 1 H, para Ar), 7.54 (d of d, 2 H, meta Ar), 6.81 (d, 1 H, vinyl), 4.38 (m, 1 H, carbinol), 3.65 (d, 1 H, $PhSO_2CCHO$), 3.02 (m, 1 H, CH_2CHO), 1.85–1.20 (m, 6 H, CH_2); ^{13}C NMR (Me_2SO-d_6) 149.30 (o), 140.29 (e), 134.20 (e), 133.49 (o), 129.13 (o), 127.79 (o), 67.93 (o), 56.50 (o), 50.78 (o), 36.48 (e), 26.98 (e), 19.41 (e); exact mass calcd for $C_{14}H_{16}O_4S$ 280.0769, found 280.0771 (M). Satisfactory combustion analysis could not be obtained.

Evaporation of the mother liquor afforded pure **31**, 193.9 mg, 0.692 mmol, 16% yield: mp 147.5–149 °C (recrystallized from CCl_4/hexane); IR 2.89 (OH), 7.69, 8.70 (sulfone); ^1H NMR 7.93 (d, 1 H, ortho Ar), 7.62 (t, 1 H, para Ar), 7.54 (t, 2 H, meta Ar), 7.07 (d, 1 H, vinyl), 4.65 (d of d, 1 H, $PhSO_2CCHO$), 4.50 (t, 1 H, $CHCHO$), 4.08 (t, 1 H, carbinol), 2.11–1.45 (m, 6 H, CH_2); ^{13}C NMR 142.33 (o), 141.42 (e), 139.63 (e), 133.60 (o), 129.22 (o), 127.77 (o), 69.79 (o), 68.14 (o), 63.16 (o), 26.64 (e), 23.89 (e), 14.81 (e).

5-[(*tert*-Butyldimethylsilyl)oxy]-1,2-epoxy-3-(phenylsulfonyl)-3-cyclooctene (30). A mixture of **20** (199.9 mg, 0.528 mmol), Na_2CO_3 (272.0 mg, 2.57 mmol), CF_3CO_3H (0.27 mL of a 2.52 M solution in CH_2Cl_2, 0.680 mmol), and CH_2Cl_2 (10 mL) was stirred at room temperature for 1 h. The reaction was then cooled to 0 °C, and cautiously quenched with saturated Na_2SO_3 (5 mL). The organics were washed with 5% HCl (10 mL), saturated $NaHCO_3$ (10 mL), saturated NaCl (10 mL) and dried (K_2CO_3). Evaporation of the solvent and radial chromatography of the residue with CH_2Cl_2 afforded pure **30**, 148.0 mg, 0.375 mmol, 71% yield: mp 98–98.5 °C; IR 7.63, 8.66 (sulfone); ^1H NMR 7.95 (d of d, 2 H, ortho Ar), 7.55 (br d, 1 H, para Ar), 7.50 (d of d, 2 H, meta Ar), 6.92 (d, 1 H, vinyl), 4.50 (br t, 1 H, carbinol), 3.68 (d, 1 H, $OHCCSO_2Ph$), 3.05 (m, 1 H, CH_2CHO), 2.05–1.05 (m, 6 H, CH_2), 0.87 (s, 9 H, *t*-Bu), 0.05 (s, 6 H, CH_3); ^{13}C NMR 148.57 (o), 140.95 (e), 135.64 (e), 133.94 (o), 129.47 (o), 128.96 (o), 70.76 (o), 57.66 (o), 51.65 (o), 38.00 (e), 28.08 (e), 26.31 (o), 20.07 (e), 18.67 (e), −4.03 (o), −4.26 (o); exact mass calcd. for $C_{20}H_{30}O_4SSi$ 395.1712, found 395.1711 (M).

Continued elution with a CH_2Cl_2/ether gradient afforded **31**, 30.6 mg, 0.109 mmol, 21% yield, identical (TLC, ^1H NMR) with material prepared above.

Spectral data for 1,5-dihydroxy-4-methyl-3-(phenylsulfonyl)-*cis*-2-cyclooctene (32, R = CH_3): IR 2.90 (OH), 7.74, 8.73 (sulfone); ^1H NMR (Me_2SO-d_6) 7.84 (d of d, 2 H, ortho Ar), 7.70 (m, 3 H, meta and para Ar), 6.76 (d, 1 H, vinyl), 5.34 (d, 1 H, allylic carbinol), 4.76 (d, 1 H, homoallylic carbinol), 2.50 (m, 1 H, CH_3CH), 1.90–1.20 (m, 6 H, CH_2), 1.05 (d, 3 H, CH_3).

Spectral data for 1,5-dihydroxy-4-phenyl-3-(phenylsulfonyl)-*cis*-2-cyclooctene (32, R = Ph): IR 7.66, 8.73 (sulfone); ^1H NMR 7.67–6.90 (m, 11 H, Ar and vinyl), 4.68 (m, 1 H, allylic carbinol), 4.20 (m, 1 H, homoallylic carbinol), 4.00 (d, 1 H, benzyl), 2.62–1.40 (m, 6 H, CH_2).

Spectral data for 1-[(*tert*-butyldimethylsilyl)oxy]-5-hydroxy-4-methyl-3-(phenylsulfonyl)-*cis*-2-cyclooctene (33) and 1-[(*tert*-butyldimethylsilyl)oxy]-5-hydroxy-2-methyl-3-(phenylsulfonyl)-*cis*-3-cyclooctene (34, R = CH_3): IR 2.92 (OH), 7.69, 8.77 (sulfone); ^1H NMR, NMR analysis of the inseparable mixture indicated the presence of three compounds, presumably **33**, *cis*-**34**, and *trans*-**34**. The plethora of overlapping signals made any assignment highly speculative.

Spectral data for 1-[(*tert*-butyldimethylsilyl)oxy]-5-hydroxy-4-phenyl-3-(phenylsulfonyl)-*cis*-2-cyclooctene (33) and 1-[(*tert*-butyldimethylsilyl)oxy]-5-hydroxy-2-phenyl-3-(phenylsulfonyl)-*cis*-3-cyclooctene (34, R = Ph): IR 2.87 (OH), 7.69, 8.73 (sulfone); ^1H NMR 7.75–7.00 (m, 11 H, Ar and vinyl), 5.00 (m, 1 H, allylic carbinol), 3.95 (m, 1 H, homoallylic

carbinol), 3.05 (m, 1 H, benzyl), 2.25–1.65 (m, 6 H, CH_2), 0.90 and 0.75 (s, 9 H, *t*-Bu), 0.10 (s, 6 H, CH_3).

1-[(*tert*-Butyldimethylsilyl)oxy]-3-(phenylsulfonyl)-5-oxa-*cis*-3-cyclooctene 35. To a vigorously stirred suspension of FeI_2 (Alfa, 401.0 mg, 1.29 mmol) in THF (6.1 mL) at −20 °C was added MeLi (2.30 mL of a 1.69 M solution in ether, 3.89 mmol) slowly. After the mixture was stirred for 15 min, the black ferrate reagent was cooled to −78 °C, a solution of **30** (102.9 mg, 0.261 mmole) in THF (2.0 mL) was added dropwise, and stirring was continued for 20 min. At this time, saturated NH_4Cl (1 mL) was added, and the mixture allowed to warm to room temperature. The organics were extracted into CH_2Cl_2 (3 × 10 mL); washed with saturated $NaHCO_3$ (10 mL) and saturated NaCl (10 mL) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue on silica gel with 30% ethyl acetate/hexane afforded enone **35** as an oil, 65.0 mg, 0.165 mmol, 63% yield: IR 5.84 (C=O), 7.63, 9.00 (sulfone); ^1H NMR 7.98 (d of d, 2 H, ortho Ar), 7.75 (t, 1 H, para Ar), 7.70 (d of d, 2 H, meta Ar), 7.22 (d, 1 H, vinyl), 4.52 (m, 1 H, carbinol), 3.35 (d of d, 2 H, O=CCH_2C=, J = 18.0 Hz), 2.32 (m, 1 H, CH_2CH_2C=O), 1.85 (m, 4 H, CH_2), 0.87 (s, 9 H, *t*-Bu), 0.05 (s, 6 H, CH_3); ^{13}C NMR: 207.48 (e), 145.11 (o), 138.30 (e), 135.09 (e), 133.75 (o), 129.40 (o), 128.26 (o), 69.36 (o), 41.47 (e), 40.63 (e), 35.64 (e), 25.67 (o), 21.41 (e), 18.09 (e), −4.93 (o), −5.05 (o).

Continued elution afforded **18**, 8.5 mg, 0.0321 mmol, 12% yield, identical (TLC, ^1H NMR) with material prepared previously.

***cis*-1,2-Epoxy-5-(methoxymethoxy)-3-(phenylsulfonyl)-3-cyclooctene (38).** To a solution of **28** (92.0 mg, 0.325 mmol), $AgNO_3$ (282.6 mg, 1.66 mmol), and DMF (1.0 mL) was added MOMCl (0.25 mL, 3.29 mmol) dropwise. A white precipitate, presumably AgCl, formed immediately. After 2 h, the mixture was diluted with ether (20 mL) and filtered and the filtrate washed with water (3 × 10 mL) and dried. Evaporation of the solvent and flash chromatography of the residue on silica gel employing a 10–40% ethyl acetate/hexane gradient elution afforded pure **38** as a glass, 105.0 mg, 0.324 mmol, 99% yield: IR 7.63, 8.73 (sulfone); ^1H NMR 8.12 (d of d, 2 H, ortho Ar), 7.73 (t, 1 H, para Ar), 7.70 (d of d, 1 H, meta Ar), 7.14 (d, 1 H, vinyl), 4.72 (s, 2 H, OCH_2O), 4.60 (m, 1 H, allylic carbinol), 3.73 (d, 1 H, $PhSO_2CCHO$), 3.42 (s, 3 H, CH_3), 3.15 (m, 1 H, CH_2CHO), 2.18 −1.10 (m, 6 H, CH_2); ^{13}C NMR 145.76 (o) 140.17 (e), 137.02 (e), 133.41 (o), 128.91 (o), 128.43 (o), 95.18 (e), 73.54 (o), 57.07 (o), 55.70 (o), 51.18 (o), 34.26 (e), 27.55 (e), 19.33 (e).

Reaction of 38 with Lithium Dimethylcuprate. The procedure for the reaction of **7** with Me_2CuLi was employed using **38** (33.4 mg, 0.103 mmol) in THF (2.3 mL) at −78 °C for 10 min, to afford 25.5 mg of a mixture of **18** and **39** in a ratio of 9:1 (470-MHz ^1H NMR integration).

The regiochemistry of the addition was determined by oxidation of the crude adduct with PCC in CH_2Cl_2, followed by 470-MHz ^1H NMR analysis. That the minor vinyl sulfone signal remained as a doublet showed the addition had occurred to the epoxide (to afford **40**), not to the vinyl sulfone.

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Preparation of 2-Substituted Podophyllotoxin Derivatives

Margaret B. Glinski, James C. Freed, and Tony Durst*

Ottawa-Carleton Chemistry Institute, Department of Chemistry, University of Ottawa, Ottawa, Canada K1N 9B4

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A series of 2-substituted podophyllotoxin derivatives, including 2-methyl-, 2-chloro-, 2-hydroxy-, and 2-bromopodophyllotoxin, were prepared, in order to determine whether nonenolizable podophyllotoxins had enhanced in vivo activity against P388 and L1210 tumor cells. Significant activity against P388 (T/C 156, 40 mg/kg) was observed for 2-chloropodophyllotoxin; under similar conditions, podophyllotoxin was toxic. The corresponding 2-picro isomers were formed as byproducts in the above reactions and were, when tested, inactive against tumors at similar concentrations. An attempt to prepare 2-fluoropodophyllotoxin by reacting podophyllotoxin 4-*O*-THP enolate with $FClO_3$ resulted in a violent explosion, causing serious injury. Extreme caution should be taken when reacting enolates with $FClO_3$.

A number of years ago, Gensler and co-workers[1,2] attempted the preparation of nonenolizable podophyllotoxins of the type **1**. (The numbering for podophyllotoxin is that used in ref 7.) The impetus for this work was the earlier observation that podophyllotoxin (**2**) rapidly isomerized to the biologically inactive picropodophyllotoxin (**3**)[3] when exposed to mild base[4] and the suggestion[5] that podophyllotoxin might be inactivated via such an isomerization. However, in 1980 it was shown that the in vitro deactivation of the clinically used anticancer drug Etoposide (**4**) does not occur via epimerization to the cis-fused lactone but via ring opening to the hydroxy acid **5**.[6]

In addition to the initial attempts by Gensler et al.[1] that produced the undesired cis-fused γ-lactone **6**, several other reports have appeared that describe the preparation of derivatives in which the trans-fused lactone of both podophyllotoxin[2] and Etoposide[7] had been replaced by trans-fused furan, thiolane, thiolanyl sulfone, or cyclo-

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