Usefully Functionalized Products from Conjugate Addition of Sulfur-Stabilized Anions to α-Enones[1]

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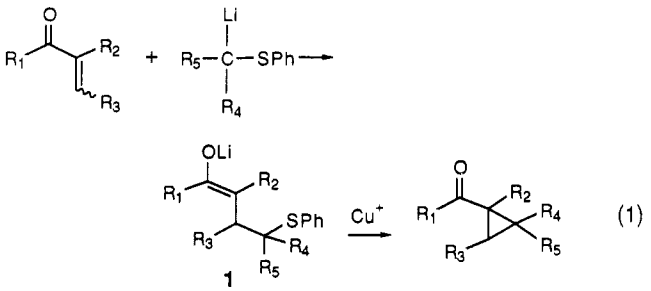
Received August 19, 1988

The addition to α,β-unsaturated ketones of a variety of organolithiums stabilized by at least two phenylthio groups provides mainly the 1,4-addition products at low temperatures in the absence of complexing agents such as HMPA. The products thus generated provide usefully functionalized synthetic intermediates.

An earlier report from this laboratory demonstrated a novel preparation of highly functionalized cyclopropyl ketones from α-enones and sulfur-stabilized organolithiums.[2] The conjugate addition products obtained were treated in situ with the benzene complex of cuprous trifluoromethanesulfonate (triflate) to provide the corresponding cyclopropanes in very good overall yields in a one-pot sequence (eq 1). We have also reported a remarkable temperature effect[3] upon the regioselectivity of nucleophilic addition to α-enones; namely, *low temperatures favor kinetic 1,4-addition over 1,2-addition.*



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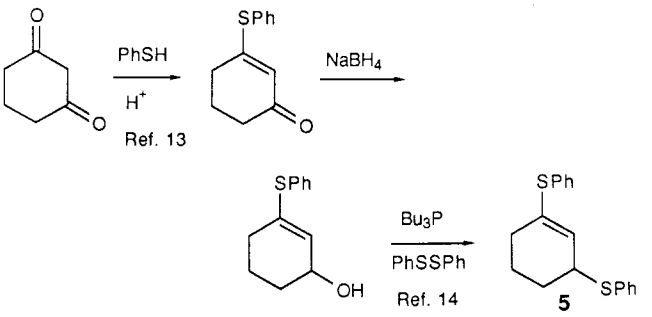
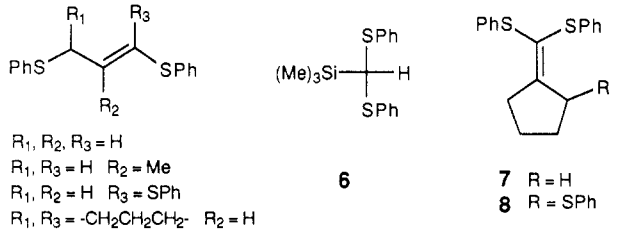
We now report the preparation of a number of products resulting from conjugate addition to enones of anions that are stabilized by at least two phenylthio groups. These products include, but are not restricted to, those obtained by quenching the intermediate enolates **1** from the previous cyclopropanation study.[2] Many such anions are readily available, and the products of conjugate addition (Chart I) are of richly varied functionality. The versatile phenylthio substituents should allow considerable further elaboration.

The preparation of the 1,3-bis(phenylthio)alkenes **2**, **3**, and **5** has been described previously.[4] The open-chain compounds **2** and **3** are prepared by a two-step procedure from commercially available allyl and methallyl phenyl sulfides, respectively. The cyclic analogue **5** was previously[4] prepared by treatment of cyclohex-2-en-1-one with boron thiophenoxide, but, in order to avoid a tedious chromatographic separation from a minor contaminant, we have devised an alternative route (Scheme I). Compound **4** was prepared by acid-catalyzed reaction of α-bromoacrolein with thiophenol followed by base-induced elimination of HBr as described by Dziadulewicz and Gallagher,[5] but it would presumably be available as well by the reaction of ethyl acrylate with aluminum thiophenoxide.[6] Bis(phenylthio)(trimethylsilyl)methane (**6**) was prepared[7] by silylating the anion of commercially available bis(phenylthio)methane. The ketene thioacetal **7** was prepared from cyclopentanecarboxylic acid and $Al(SPh)_3$ according to the method of Cohen, Gapinski, and Hutchins.[6] In turn, **8** was prepared[6] by deprotonation of **7** with *n*-BuLi and sulfenylation of the anion with *S*-phenyl (phenylthio)sulfinate.[8]

Scheme I





2 $R_1, R_2, R_3 = H$
3 $R_1, R_3 = H$ $R_2 = Me$
4 $R_1, R_2 = H$ $R_3 = SPh$
5 $R_1, R_3 = -CH_2CH_2CH_2-$ $R_2 = H$

6

7 R = H
8 R = SPh

The earliest indication that highly stabilized sulfur-substituted organolithium compounds would add in a conjugate fashion to α-enones was the work of Manas and Smith[9] who reported such regioichemistry with tris(phenylthio)methyllithium. Ziegler[10] reported similar behavior for the lithio derivatives of ethylidene- and isopropylidenedithiane. Less stabilized sulfur-substituted organolithium compounds generally exhibit mainly 1,2-addition except in the case of cuprates[11] or in the presence of hexamethylphosphoric triamide.[12]

(1) Taken from the Ph.D. Thesis of Michael R. Myers, University of Pittsburgh, 1987.
(2) Cohen, T.; Myers, M. R. *J. Org. Chem.* **1988**, *53*, 457.
(3) Cohen, T.; Abraham, W.; Myers, M. R. *J. Am. Chem. Soc.* **1987**, *109*, 7923.
(4) Cohen, T.; Bennett, D. A.; Mura, A. J., Jr. *J. Org. Chem.* **1976**, *41*, 2506.
(5) Dziadulewicz, E.; Gallagher, T. *Tetrahedron Lett.* **1985**, *26*, 4547.
(6) Cohen, T.; Gapinski, R. E.; Hutchins, R. R. *J. Org. Chem.* **1979**, *44*, 3599.
(7) Seebach, D.; Kolb, M.; Gröbel, B. *Chem. Ber.* **1973**, *106*, 2277.
(8) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.
(9) Manas, A. R. B.; Smith, R. A. J. *J. Chem. Soc., Chem. Commun.* **1975**, 216. Smith, R. A. J.; Lal, A. R. *Aust. J. Chem.* **1979**, *32*, 353.
(10) Ziegler, F. E.; Tam, C. C. *Tetrahedron Lett.* **1979**, 4717.
(11) Mukaiyama, T.; Narasaka, K.; Furusato, M. *J. Am. Chem. Soc.* **1972**, *94*, 8641.
(12) Review through 1979: Kreif, A. *Tetrahedron* **1980**, *36*, 2531. For a discussion of more recent results in such competitions, see ref 1 and 3.
(13) Danishefsky, S.; Harayama, T.; Singh, R. K. *J. Am. Chem. Soc.* **1979**, *101*, 7008.
(14) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409. Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Ibid.* **1970**, 1901.

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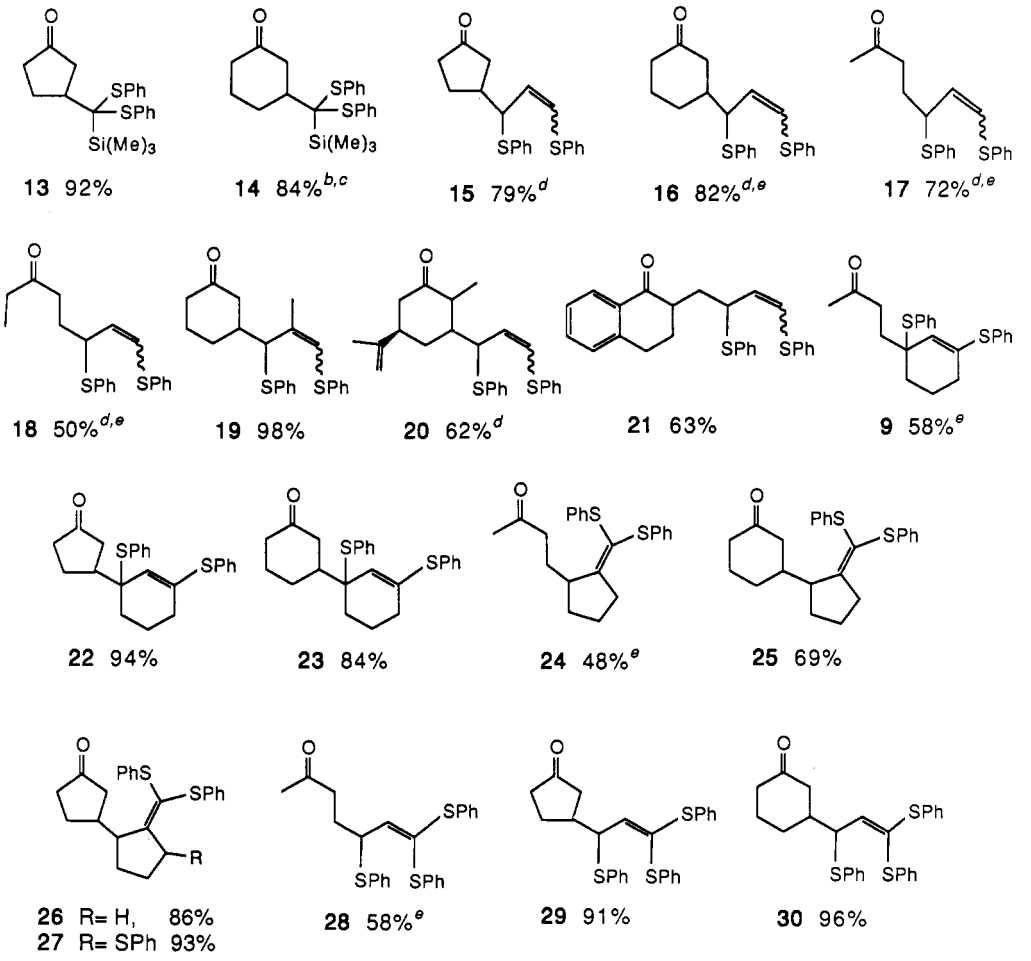
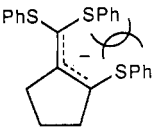
Chart I. Conjugate Addition Products of Enones and Sulfur-Stabilized Anions[a]



[a] All yields are based on isolated products. Mixtures of diastereomers were obtained for compounds capable of diastereomerism. [b] Previously prepared in substantially lower yield by conjugate addition at ambient temperature.[25] [c] Addition of the corresponding cuprate[26a] provided a nearly quantitative yield (see the Experimental Section). [d] Additions performed at −100 °C. [e] Mixture of 1,2- and 1,4-products obtained.[3]

Although treatment of lithio derivatives of compounds **2–8** with alkyl halides has been reported,[4-8,15] the present study is the first of their addition to α,β-unsaturated ketones.[16] Several examples of successful additions to a variety of α-enones are illustrated in the table. It should be noted that the addition of the lithium salts of **2–8** to the unsubstituted α,β-unsaturated ketones methyl and ethyl vinyl ketone provides mixtures of 1,4- and 1,2-addition products although the former greatly predominate at low reaction temperatures (−78 °C or less).[3] In the case of cyclic α–enones only conjugate addition products were isolated except for **2**, which gave small amounts of 1,2-addition products even at low temperatures.

In most cases, the structures of the conjugate adducts are readily predictable from those of the reactants. However, the conjugate bases of the ketene thioacetals **4** and **7** are bidentate, and it is found that only the carbon atom bearing the least number of phenylthio substituents becomes attached to the β-position of the enone. An analogous result was reported by Ziegler[10] in the case of the alkylthio analogues. At first glance, the result of the deprotonation of **8** may appear surprising. Although a phenylthio substituent usually greatly facilitates proton removal from the carbon atom to which the sulfur atom is attached, of the two types of allylic protons of **8**, only one that is *not* on a carbon atom attached to a phenylthio group is removed. In this case, removal of the tertiary proton would lead to the highly congested carbanion **8A**; in such an intermediate, the bis(phenylthio)methylene substituent probably would be forced out of the plane of the ring, thus decreasing allylic stabilization.



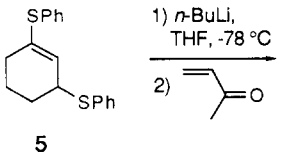
8A

We[4] and others[15] have demonstrated that hydrolysis of the alkylation products of **2** and the methylthio[15] analogues generate α,β-unsaturated aldehydes. Thus, **2** and similarly substituted reagents such as **3**, **4**,[5] and **5** exhibit "umpolung"[17] behavior. For example, treatment of **5** with *n*-butyllithium in THF at −78 °C followed by treatment with methyl vinyl ketone provides a readily separable mixture of the 1,4- and 1,2-addition products in 58% and 3% yields, respectively (eq 2). Mercuric ion mediated hydrolysis[15] of the conjugate addition product **9** provides the unsaturated diketone **10** in 88% yield; the anion of **5**

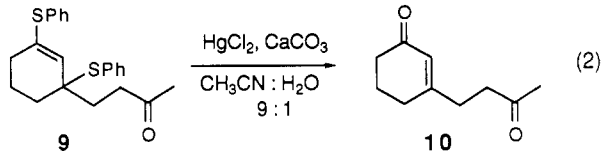
(15) The methylthio analogues of **2** and **3** have been alkylated and the alkylation products hydrolyzed. Corey, E. J.; Noyori, R. *Tetrahedron Lett.* **1970**, 311. Corey, E. J.; Erickson, B. W.; Noyori, R. *J. Am. Chem. Soc.* **1971**, *93*, 1724.

(16) An exception is the addition of the lithium salt of **5** to chalcone.[4]

(17) Gröbel, B. T.; Seebach, D. *Synthesis* **1977**, 357.



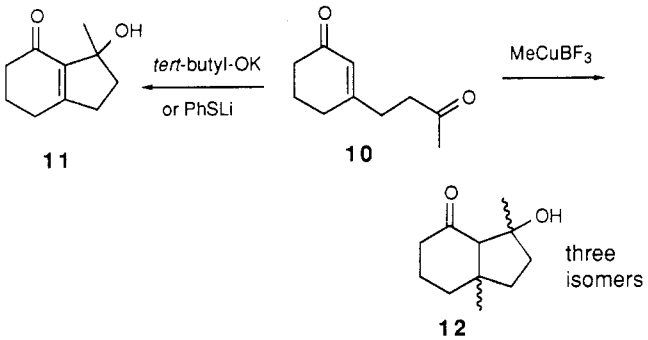
5



9 10 (2)

is thus the synthetic equivalent of the "beta anion" of cyclohexenone. Similar hydrolyses to ketoenones and ketoenals of **15–23** would be expected.

Such hydrolysis products are obviously of potential synthetic value. In preliminary experiments **10** was shown to cyclize to the 5-membered annulation product **11**, albeit in poor (21%) yield upon treatment with either potassium *tert*-butoxide of lithium thiophenoxide. In the latter case, the reaction presumably proceeds by initial conjugate addition followed by aldol addition and loss of lithium thiophenoxide.[18] Finally, treatment of **10** with methylcopper–boron trifluoride complex[19] provides a 58% yield of the dimethylindanone aldol **12**. Similar transformations of diketones analogous to **10** have been reported.[20]



11 10 12

In contrast to the ease of hydrolysis of 1,3-bis(phenylthio)alkenes in the presence of various acids, tetrasubstituted ketene thioacetals have been reported to be inert to hydrolysis.[21] It is thus not surprising that attempts to hydrolyze the conjugate addition products of **7** and various α-enones under a variety of conditions have met with failure. For example, treatment of **26** with $HgCl_2$, 6 N HCl, and CF_3CO_2H in refluxing methanol resulted in recovery of the starting material along with some unidentified byproducts. Nevertheless, it is likely that the ketone-protected versions of this type of adduct could be further elaborated by taking advantage of the acidity of the allylic protons and/or of the ability of ketene thioacetals to undergo reductive lithiation to sulfur-stabilized vinyl anions.[22] We hoped that a thiophenyl group at the allylic position as in **27** would assist hydrolysis by allowing removal of the allylic thiophenoxide to produce a highly stabilized carbocation, which, by reacting with water at the thioacetal carbon atom, could result in further carbon–sulfur bond cleavage. However, attempted hydrolysis of **27** using mercury salts under a variety of conditions resulted mainly in elimination products and those resulting from trapping of the intermediate carbocation by water at the sulfur-free allylic terminus.

Perliminary experiments have shown that the intermediate enolate produced in the addition of **4** to cyclohexenone may be susceptible to capture with electrophiles such as allyl bromide;[23] similar enolates have been captured by more elaborate electrophiles.[24] This type of highly regioselective conjugate addition should provide a valuable augmentation to the repertoire of synthetic chemistry.

Experimental Section

Flash chromatography[27] and radial chromatography (Harrison Model 7924 Chromatotron) were used for purification of products. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 247 grating infrared spectrophotometer, calibrated with a polystyrene film. ^1H NMR spectra were recorded on a Bruker WH-300 spectrometer with TMS as an internal standard. Data are reported as follows: chemical shift, multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant, integration, and assignment. Low-resolution mass spectra were recorded on a LKB-9000 combined gas chromatograph–mass spectrometer. Exact mass spectra were obtained on a CH-5 double-focusing Varian Mat mass spectrometer. Reactions requiring an inert atmosphere were performed under argon.

3-(Phenylthio)-2-cyclohexenone was prepared according to the method of Danishefsky.[13] Its spectral characteristics were as reported.[28]

3-(Phenylthio)-2-cyclohexenol. A mixture of 3-(phenylthio)-2-cyclohexenone (36.5 mg, 0.178 mmol) and $NaBH_4$ (6.7 mg, 0.18 mmol) in absolute ethanol (1 mL) was heated at reflux for 15 min. Analytical TLC indicated complete reduction. Water (2 mL) was added, and the mixture was heated at reflux for 5 min, cooled, and extracted with pentane (4 × 15 mL). The organic layer was washed with brine and dried ($MgSO_4$). The oil, obtained in quantitative yield, was chromatographically and spectroscopically pure (R_f 0.42 in 30% EtOAc/hexanes, brown spot with *p*-anisaldehyde slowly turning to purple-red): IR (neat) 3385 (br), 3059 (m), 2936 (s), 1628 (m), 1582 (m), 1476 (m), 1439 (m), 1333 (m), 1159 (m), 1024 (m); ^1H NMR δ 7.1–7.5 (m, 5 H, aromatic H), 5.72 (m, 1 H, vinyl H), 4.25 (br m, 1 H), 1.5–2.2 (m, 6 H); high-resolution mass spectrum calcd for $C_{12}H_{14}OS$ 206.0765, obsd 206.0766.

1,3-Bis(phenylthio)cyclohexene (5). A solution of diphenyl disulfide (3.00 equiv, 43.5 mmol, 9.48 g) and tri-*n*-butylphosphine (4.0 equiv, 58 mmol, 12.3 g of 95% pure material from a freshly opened container) in benzene (200 mL) was stirred for 3 h at ambient temperature. A solution of 3-(phenylthio)-2-cyclohexenol (2.99 g, 14.5 mmol) in benzene (10 mL) was added, and the mixture was allowed to stir overnight. The solution resulting from addition of Et_2O was washed twice with 5% NaOH and once with brine and dried ($MgSO_4$). The solvent was removed in vacuo, and the crude mixture was subjected to column chromatography (silica, 2% EtOAc/hexanes) to remove tri-*n*-butylphosphine oxide. The product, obtained as a colorless oil in quantitative yield, displayed spectral characteristics identical with those reported.[26b]

1-[Bis(phenylthio)methylidene]cyclopentane (7). The method of Cohen, Gapinski, and Hutchins[6,29] was used. A mixture of trimethylaluminum (20 mL, 0.040 mol, 2.0 M solution in toluene, from a freshly opened bottle) and thiophenol (13.2 g, 0.120

(18) Cohen, T.; Kosarych, Z.; Suzuki, K.; Yu, L.-C. *J. Org. Chem.* **1985**, *50*, 2965.
(19) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119.
(20) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.
(21) (a) Okuyama, T.; Inaoka, T.; Fueno, T. *J. Org. Chem.* **1986**, *51*, 4988. Okuyama, T.; Fueno, T. *J. Org. Chem.* **1987**, *52*, 1405. Okuyama, T.; Kawao, S.; Fujiwara, W.; Fueno, T. *J. Org. Chem.* **1984**, *49*, 89. (b) A suitably placed hydroxyl function may accelerate the hydrolysis. Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5829. Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 5221.
(22) Cohen, T.; Weisenfeld, R. B. *J. Org. Chem.* **1979**, *44*, 3601.
(23) Determined by 300-MHz ^1H NMR and low-resolution MS of an inseparable mixture of isomers of the dialkylated and monoalkylated products.
(24) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831.
(25) Ager, D. J.; East, M. B. *J. Org. Chem.* **1986**, *51*, 3983.
(26) (a) Mura, A. J., Jr., Ph.D. Thesis, University of Pittsburgh, 1976, p 162. (b) *Ibid.* p 188.
(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(28) Bakuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1981**, *46*, 235.
(29) Gapinski, R. E., Ph.D. Thesis, University of Pittsburgh, 1979, p 150.

mol) in 200 mL of xylene (freshly distilled from CaH_2) was mechanically stirred and heated at reflux overnight (19 h). A white solid precipitate was broken up by addition of 100 mL of xylene and vigorous mechanical stirring. To the cooled mixture was added cyclopentanecarboxylic acid (1.82 g, 0.016 mol). The mixture was heated at reflux overnight, and the reaction was cautiously quenched with 10% NaOH solution. Ether was added to the mixture, and the organic layer was washed with 10% NaOH; drying ($MgSO_4$) and evaporation of the solvents provided a slightly impure oil. The compound was purified by column chromatography over silica (hexanes), which provided 4.03 g of a white crystalline material (mp 37 °C) in 84% overall yield: IR (neat) 3058 (m), 2957 (s), 2867 (m), 1941 (w), 1582 (s), 1478 (s), 1439 (s), 1422 (m); ^1H NMR δ 7.1–7.3 (m, 10 H), 2.6–2.7 (m, 4 H, allylic hydrogens), 1.7–1.9 (m, 4 H, alkyl); high-resolution mass spectrum calcd for $C_{18}H_{18}S_2$ 298.0850, obsd 298.0850.

1-[Bis(phenylthio)methylidene]-2-(phenylthio)cyclopentane (8). The yellow solution resulting from adding 3.85 mmol of *n*-butyllithium to [bis(phenylthio)methylidene]cyclopentane (7, 1.09 g, 3.66 mmol) in 60 mL of THF at −78 °C was stirred for 30 min. To this solution was added *S*-phenyl benzenethiosulfonate[8] (963 mg, 3.85 mmol) dissolved in 2 mL of THF, resulting in an immediate disappearence of color. The reaction was worked up in Et_2O and 5% NaOH. The solvents were removed in vacuo, and the resulting oil was subjected to flash chromatography (2% EtOAc, R_f 0.30, green spot with *p*-anisaldehyde) to yield 1.41 g of the title compound (95%): IR (neat) 3057 (w), 2963 (w), 1946 (w), 1582 (m), 1478 (m), 1439 (m); ^1H NMR δ 7.0–7.5 (m, 15 H, aromatic H), 4.75 (br s, 1 H, H α to SPh), 2.7–2.8 (m, 1 H, allylic H), 2.5–2.7 (m, 1 H, allylic H), 1.8–2.3 (m, 4 H); high-resolution mass spectrum calcd for $C_{18}H_{17}S_2$ (loss of SPh) 297.0772, obsd 297.0772. CIMS gave the expected parent ion at *m/e* 407 (parent + H^+) at 5% of the base peak; a parent ion (*m/e* 406) was not observed in the normal EIMS.

General Procedure for Conjugate Addition: 3-[Bis(phenylthio)(trimethylsilyl)methyl]cyclohexanone (14). Cyclohexenone (148 mg, 1.54 mmol) was added dropwise to a solution of the anion, which had been prepared by adding *sec*-butyllithium (1.35 mL, 1.20 M, 1.62 mmol) to a solution of bis(phenylthio)-(trimethylsilyl)methane (486 mg, 1.54 mmol) in 15 mL of THF at −78 °C and stirring for 1 h to ensure complete anion formation. After the mixture had been stirred for 0.5 h, the reaction was quenched with 15 mL of saturated NH_4Cl solution. The mixture was taken up in 50 mL of ether and washed with 2 × 25 mL of saturated NH_4Cl and dried over $MgSO_4$. Chromatotron chromatography (10% EtOAc/hexanes, R_f 0.20) provided 516 mg of the desired product (84% overall yield). Use of the corresponding cuprate (applied only in this case) gave a nearly quantitative yield; the anion from 1.94 mmol of the substrate was treated with cuprous iodide (185 mg, 0.97 mmol) at −78 °C, the solution was stirred for 1 h, and cyclohexenone (0.97 mmol) was added dropwise to the solution, which was then stirred at −78 °C for an additional 2 h. Standard workup and column chromatography gave 390 mg of the product: IR (neat) 3060 (m), 2940 (s), 1700 (s), 1540 (m), 1510 (m), 1480 (m), 1460 (m); ^1H NMR (tetramethylsilane was not used as a reference since accurate integration was not possible in its presence; therefore, the values are reported using the trimethylsilyl peak as 0.0) δ 7.55–7.70 (m, 4 H, ortho H of SPh), 7.2–7.4 (m, 6 H, aromatic H), 1.3–3.0 (m, 9 H), 0.0 (s, 9 H, TMS); low-resolution mass spectrum 291 (M^+ − SPh), 182 (M^+ − 2SPh); high-resolution mass spectrum calcd for $C_{16}H_{23}OSSi$ 291.1239, obsd 291.1239.

3-[Bis(phenylthio)(trimethylsilyl)methyl]cyclopentanone (13). Flash chromatography (10% EtOAc/hexanes, R_f 0.33) of the crude oil provided the title compound in 92% isolated yield: IR (neat) 3061 (m), 2961 (m), 2901 (m), 1744 (s), 1582 (m), 1472 (m), 1439 (m), 1404 (m), 1331 (m); ^1H NMR δ 7.1–7.8 (m, 10 H), 2.0–3.0 (m, 7 H), 0.05 (s, 9 H); high-resolution mass spectrum calcd for $C_{21}H_{26}OSiS_2$ 386.1194, obsd 386.1193.

3-[1,3-Bis(phenylthio)prop-1-en-3-yl]cyclohexanone (16). The orange-red solution resulting from the addition of *n*-butyllithium (0.27 mL, 1.41 M, 0.38 mmol) to a solution of 1,3-bis-(phenylthio)propene (95.4 mg, 0.37 mmol, mixture of cis and trans isomers) in dry THF (10 mL) at −100 °C was stirred for 30 min, and neat cyclohexenone (35.5 mg, 36 μL, 0.37 mmol) was added over 5 min. Standard workup followed by flash chromatography of the resulting oil (10% EtOAc/hexanes) gave 107 mg of a mixture of stereoisomers in 82% yield: IR (CCl_4), 2920 (w), 1705 (s), 1570 (w), 1475 (m), 1425 (m); ^1H NMR δ 6.95–7.50 (m, 10 H, aromatic H), 5.65–5.95 (m, 2 H, olefin C*H*=C*H* mixture of cis and trans), 3.55–3.65 (m, 1 H, H α to SPh), 1.50–2.65 (m, 9 H); high-resolution mass spectrum calcd for $C_{21}H_{22}OS_2$ 354.1112, obsd 354.1113. The ratio of 1,4- to 1,2-products obtained varied with the temperature as described previously.[3]

3-[1,3-Bis(phenylthio)propen-3-yl]cyclopentanone (15). Flash chromatography (12% EtOAc/hexanes, R_f 0.21, 0.30) of the crude oil provided a 79% yield of the product as a mixture of isomers (74:26, trans:cis, by HPLC). The spectral properties of the fast moving cis isomer are as follows: IR (neat) 3051 (m), 2961 (w), 1738 (s), 1582 (m), 1480 (m), 1437 (m), 1402 (m), 1275 (m), 1026 (m); ^1H NMR δ 7.1–7.5 (m, 10 H, aromatic H), 6.25 (dd, 1 H, diastereomeric mixture of cis isomers, olefinic H α to SPh, J = 9.25 and J = 9.25), 5.72 (m, 1 H, vinyl H β to SPh), 4.28 (m, 1 H, H α to SPh), 1.7–2.7 (m, 7 H); high-resolution mass spectrum calcd for $C_{20}H_{20}OS_2$ 340.0956, obsd 340.0954. The spectral properties of the slow moving trans isomer are as follows: IR (neat) 3057 (m), 2965 (m), 1744 (s), 1582 (m), 1480 (m), 1439 (m), 1402 (m), 1275 (m), 1024 (m); ^1H NMR δ 6.9–7.5 (m, 10 H, aromatic H), 5.9 (d, 1 H, olefinic H α to SPh, J = 14.8 Hz), 5.65–5.80 (m, 1 H, olefinic H, mixture of diastereomers), 3.6–3.7 (m, 1 H, H α to SPh), 1.7–2.7 (m, 7 H); high-resolution mass spectrum calcd for $C_{20}H_{20}OS_2$ 340.0956, obsd 340.0954.

1,3-Bis(phenylthio)hept-1-en-6-one (17). Flash chromatography (5% EtOAc/hexanes) of the crude oil provided the conjugate addition product as a mixture of isomers in 72% yield: IR (neat) 1708 (s), 1592 (m), 1492 (m), 1441 (m); ^1H NMR δ 7.0–7.1 (m, 10 H, aromatic H), 5.5–6.3 (m, 2 H, cis and trans isomers, J = 9.1 and 15 respectively, C*H*=C*H*SPh), 3.6 and 4.3 (m, 1 H C*H*SPh, mixture of diastereomers), 2.1 (s, 3 H, Me), 1.8–2.7 (m, 4 H, methylene); high-resolution mass spectrum calcd for $C_{19}H_{20}OS_2$ 327.0877, obsd 327.0877.

1,3-Bis(phenylthio)oct-1-en-6-one (18). Flash chromatography of the crude residue provided the product in 50% yield: IR (neat) 3057 (m), 2974 (m), 2936 (m), 1713 (s), 1653 (m), 1582 (m), 1480 (m); ^1H NMR δ 7.0–7.5 (m, 10 H, aromatic H), 5.6–6.3 (m, 2 H, cis and trans C*H*=C*H*SPh), 3.7 and 4.25 (2 m, 1 H, C*H*SPh, mix of geometric isomers), 0.8–2.7 (m, 9 H); high-resolution mass spectrum calcd for $C_{20}H_{22}OS_2$ 342.1112, obsd 342.1111.

3-[3-[2-Methyl-1,3-bis(phenylthio)propenyl]]cyclohexanone (19). With 2-methyl-1,3-bis(phenylthio)propene (3) and cyclohexenone as starting materials, an oil was obtained and subjected to flash chromatography (15% EtOAc/hexanes) to provide a 98% yield of the desired product: IR (neat) 3058 (m), 2944 (m), 2868 (m), 1715 (s), 1582 (m), 1480 (m), 1439 (m), 1377 (m), 1312 (m) 1227 (m), 1024 (m); ^1H NMR trans isomers δ 6.8–7.5 (m, 10 H, aromatic H), 5.7 (s, 1 H, vinyl H), 3.57 (2 d, 1 H, mixture of diastereomers, H α to SPh), 2.9 (dt, 0.7 H, tertiary H β to SPh), 2.0–2.6 (m, 5.3 H) 1.87 and 1.84 (two s, 3 H combined, CH_3), 1.2–1.8 (m, 3 H); high-resolution mass spectrum calcd for $C_{22}H_{24}OS_2$ 368.1268, obsd 368.1268; ^1H NMR cis isomers δ 6.9–7.5 (m, 10 H, aromatic H), 5.98 and 5.96 (2 s, 1 H combined, J = 1 Hz, vinyl H), 4.5 (dd, 1 H, mixture of diastereomers, H α to SPh), 3.02 and 2.56 (dt, 1 H combined, tertiary H β to SPh), 1.2–2.5 (m, 11 H, methyl resonances at 1.90 and 1.87 show J = 1 Hz); high-resolution mass spectrum calcd for $C_{22}H_{24}OS_2$ 368.1268, obsd 368.1268.

5-Isopropenyl-2-methyl-3-[1,3-bis(phenylthio)propen-3-yl]cyclohexanone (20). Flash chromatography (7% EtOAc/hexanes) of the crude residue gave two separate fractions (each containing a mixture of isomers) with identical IR spectra and similar NMR spectra, all consistent with the conjugate addition product: IR (CCl_4), 2970 (m), 2922 (m), 1715 (s), 1645 (m), 1583 (m), 1479 (m), 1439 (m), 1090 (m); ^1H NMR δ 6.9–7.5 (m, 10 H, aromatic H), 5.5–6.3 (m, 2 H, C*H*=C*H*SPh), 4.7–5.0 (m, 2 H, isopropenyl =C*H*$_2$), 1.0–4.2 (m, 14 H, several overlapping methyl signals indicating several isomers); high-resolution mass spectrum calcd for $C_{19}H_{23}OS$ (M^+ − SPh) 299.1469, obsd 299.1468.

2-[1,3-Bis(phenylthio)but-1-en-4-yl]-3,4-dihydro-1(2*H*)-naphthalenone (21). With 2-methylene-1-tetralone[30] as starting material, prepared by the method of Kellog,[31] an oil was obtained,

(30) Muhlstadt, V. M.; Gensrich, H. J. *J. Prakt. Chem.* **1966**, *34*, 139.

which was subjected to flash chromatography (7% EtOAc/petroleum ether, R_f 0.38 in 10% EtOAc/hexanes) to give a mixture of isomers in 63% yield: IR (neat) 3057 (m), 2926 (m), 1682 (s), 1601 (m), 1584 (m), 1478 (m), 1454 (m); ^{1}H NMR δ 6.9–8.1 (m, 14 H, aromatic H), 5.6–6.3 (m, 2 H, olefinic CH, mixture of cis and trans isomers), 4.0–4.6 (m, 1 H, PhSC*H*), 1.6–2.1 (m, 7 H); high-resolution mass spectrum calcd for $C_{20}H_{19}OS$ (M^+ – SPh) 307.1163, obsd 307.1160.

3-(3-Oxobutan-1-yl)-1,3-bis(phenylthio)cyclohexene (9). Chromatotron chromatography (CH_2CL_2, R_f 0.60, red spot with *p*-anisaldehyde) of the crude residue resulted in isolation of the product as a viscous oil in 58.5% yield: IR (neat) 3058 (m), 2936 (m), 1717 (s), 1582 (m), 1474 (m), 1439 (m), 1358 (m), 1267 (m), 1163 (m), 1024 (m); ^{1}H NMR δ 7.2–7.5 (m, 10 H, aromatic H), 5.5 (s, 1 H, vinyl H), 2.65 (m, 2 H, CH_2 α to C=O), 2.15 (s, 3 H, Me) 1.5–2.1 (m, 8 H, alkyl H); high-resolution mass spectrum calcd for $C_{16}H_{18}OS$ (M^+ – HSPh) 258.1078, obsd 258.1079. The 1,2-addition product was isolated in ca. 3% yield as a mixture of diastereomers: IR (neat) 3470 (br), 3059 (m), 2936 (m), 2865 (m), 1622 (w), 1582 (m), 1474 (m), 1439 (m), 1410 (m), 1373 (m), 1337 (m), 1265 (m), 1157 (m), 1024 (m); ^{1}H NMR δ 6.9–7.5 (m, 10 H, aromatic H), 6.1 and 5.9 (2 dd, 1 H, upfield portion of AMX pattern), 5.52 and 5.58 (2 s, 1 H, vinyl H from cyclohexene), 5.1–5.4 (m, 2 H, terminal methylene hydrogens, mixture of isomers), 2.85 and 2.90 (s, 1 H, OH), 1.6–2.2 (m, 6 H), 1.27 and 1.38 (2 s, 3 H, CH_3 two isomers); high-resolution mass spectrum calcd for $C_{16}H_{19}OS$ (M^+ – SPh) 259.1157, obsd 259.1158.

3-[3-[1,3-Bis(phenylthio)cyclohexenyl]]cyclohexanone (23). Chromatotron chromatography (25% EtOAc/hexanes) of the crude oil provided 76.5 mg of the product (84% yield): IR (neat) 3059 (w), 2941 (m), 2867 (m), 1713 (s), 1582 (m), 1476 (m), 1439 (m), 1024 (m); ^{1}H NMR δ 7.1–7.5 (m, 10 H), 5.48 and 5.38 (2 s, 1 H combined, mixture of diastereomers, olefinic H), 1.4–3.0 (m, 15 H); high-resolution mass spectrum calcd for $C_{18}H_{20}OS$ (M^+ – HSPh) 284.1235, obsd 284.1236.

3-[3-[1,3-Bis(phenylthio)cyclohexenyl]]cyclopentanone (22). Flash chromatography (12% EtOAc/hexanes, R_f 0.30, purple-red spot with *p*-anisaldehyde turns green on standing) of the crude oil provided the product in 94% yield: IR (neat) 3056 (m), 2938 (m), 1740 (s), 1620 (m), 1582 (m), 1474 (m), 1439 (m), 1402 (m), 1265 (m), 1242 (m), 1161 (m), 1024 (m); ^{1}H NMR δ 7.0–7.5 (m, 10 H, aromatic H), 5.47 and 5.44 (2 s, 1 H combined, mixture of diastereomers, vinyl H), 1.4–2.5 (m, 13 H); high-resolution mass spectrum calcd for $C_{17}H_{18}OS$ (M^+ – PhSH) 270.1078, obsd 270.1078.

3-[1-[Bis(phenylthio)methylidene]cyclopentan-2-yl]-cyclopentanone (26). The yellow mixture from the addition of *sec*-butyllithium (0.82 mL, 1.1 M, 0.90 mmol) to a solution of **7** (256 mg, 0.860 mmol) in THF (5 mL) at 0 °C was stirred for 30 min and cooled to –78 °C. Dropwise addition of 2-cyclopentenone (70.5 mg, 0.860 mmol) resulted in a colorless solution, which was stirred for an additional 30 min before the reaction was quenched with saturated NH_4Cl. Column chromatography of the dried organic extracts with CH_2Cl_2 (R_f 0.36, brown spot with *p*-anisaldehyde) provided 282 mg of the title compound (86%) as a colorless oil: IR (neat) 3058 (m), 2959 (m), 1740 (s), 1582 (m), 1478 (s), 1439 (m); ^{1}H NMR δ 7.05–7.35 (m, 10 H), 1.5–3.3 (m, 14 H); high-resolution mass spectrum calcd for $C_{23}H_{24}OS_2$, 380.1269, obsd 380.1269.

4-[1-[Bis(phenylthio)methylidene]cyclopentan-2-yl]-2-butanone (24). Column chromatography (CH_2Cl_2) of the crude oil provided the product as a colorless oil in 48% yield: IR (neat) 3057 (m), 2955 (m), 1715 (s), 1582 (m), 1478 (m); ^{1}H NMR δ 7.05–7.40 (m, 10 H, aromatic H), 2.55–3.05 (m, 3 H, allylic H), 2.49 (t, 2 H, CH_2 α to C=O), 2.11 (s, 3 H, Me), 1.60–2.50 (m, 6 H); high-resolution mass spectrum calcd for $C_{22}H_{24}OS_2$ 368.1269, obsd 368.1268. A small amount of a compound that showed spectral characteristics typical of a 1,2-addition product was isolated (3% yield).

3-[1-[Bis(phenylthio)methylidene]cyclopentan-2-yl]-cyclohexanone (25). Column chromatography (CH_2Cl_2) of the crude oil provided the product as a colorless oil in 69% yield: IR (neat) 1705 (s); ^{1}H NMR δ 7.05–7.30 (m, 10 H, aromatic H), 1.4–3.2 (m, 16 H, alkyl H); high-resolution mass spectrum calcd for $C_{24}H_{26}OS_2$ 394.1425, obsd 394.1426.

3-[1-[Bis(phenylthio)methylidene]-5-(phenylthio)cyclopentan-2-yl]cyclopentanone (27). The light yellow solution resulting from adding *n*-butyllithium (0.30 mL, 1.35 M, 0.41 mmol) to **8** (156 mg, 0.384 mmol) in THF (10 mL) at –78 °C was stirred for 30 min, and then cyclopentenone (32 μL, 31.5 mg, 0.384 mmol) was added, resulting in an immediate decolorization. MPLC of the crude residue (11% EtOAc/hexanes, R_f 0.25) provided 174 mg of a partially separated mixture of diastereomers (93% yield): IR (neat) 3058 (m), 2959 (m), 1740 (s), 1582 (m), 1478 (m), 1439 (m), 1402 (m); ^{1}H NMR δ 7.0–7.6 (m, 15 H, aromatic H), 4.8 (m, 1 H, H α to SPh), 3.25 (m, 1 H), 3.15 (m, 1 H), 1.5–2.7 (m, 10 H). When the four diastereomers were separated (HPLC), the two major products (trans substituted on the cyclopentane ring) gave doublets near δ 4.8, whereas the two minor diastereomers (cis substituted on the cyclopentane ring) give a doublet of doublets with a long-distance "*W*" coupling constant of 3 Hz with the allylic proton. High-resolution mass spectrum calcd for $C_{23}H_{23}OS_2$ (loss of SPh) 379.1190, obsd 379.1190. CI mass spectroscopy with NH_4^+ gave a parent ion at *m/e* 489 (parent + H^+) at 2.5% of the base peak at *m/e* 379; the parent ion was not observed in the normal EIMS.

1,1,3-Tris(phenylthio)hept-1-en-6-one (28). Chromatotron separation of the crude oil gave 7.3 mg (2.6%) of the 1,2-addition product (as ascertained by ^{1}H NMR) and 157 mg (58%) of the 1,4 product, which demonstrated the following spectral characteristics: IR (neat) 1705 (s); ^{1}H NMR δ 6.9–7.5 (m, 15 H, aromatic), 5.97 (d, 1 H, J = 10.2), 4.47 (m, 1 H, H α to SPh), 2.6 (m, 2 H), 1.8–2.2 (m, 2 H), 2.1 (s, CH_3); high-resolution mass spectrum calcd for $C_{19}H_{19}OS_2$ (M^+ – SPh) 327.0877, obsd 327.0877.

3-[3-[1,1,3-Tris(phenylthio)propenyl]]cyclopentanone (29). Column chromatography (CH_2CL_2) provided the desired compound in 91% yield: IR (neat) 3058 (m), 2969 (m), 1744 (s), 1582 (m), 1478 (m), 1439 (m), 1402 (m), 1157 (m), 1024 (m); ^{1}H NMR δ 6.8–7.6 (m, 15 H), 6.0–6.1 (dd, 1 H combined, mixture of diastereomers), 4.5–4.6 (m, 1 H), 2.0–2.7 (m, 6 H), 1.8–2.0 (m, 1 H); high-resolution mass spectrum calcd for $C_{26}H_{24}OS_3$ 448.0989, obsd 448.0990.

3-[3-[1,1,3-Tris(phenylthio)propenyl]]cyclohexanone (30). Flash chromatography (CH_2Cl_2, R_f 0.38) provided the product as a mixture of diastereomers in 95.6% yield: IR (neat) 3058 (m), 2940 (m), 2867 (m), 1713 (s), 1582 (m), 1476 (m), 1439 (m), 1265 (m), 1225 (m), 1157 (m), 1024 (m); ^{1}H NMR δ 6.8–7.5 (m, 15 H, aromatic H), 6.05 (2 d, 1 H, mixture of diastereomers), 4.43 (m, 1 H, H α to SPh), 1.4–2.8 (m, ca. 9 H); high-resolution mass spectrum calcd for $C_{27}H_{26}OS_3$ 462.1146, obsd 462.1146.

3-(3-Oxobutan-1-yl)-2-cyclohexenone (10). A mixture of the adduct **9** (2.03 g, 5.52 mmol), 3 equiv of $HgCl_2$ (4.49 g, 16.5 mmol), and 3 equiv of $CaCO_3$ (1.65 g, 16.5 mmol) in 40 mL of acetonitrile and 5 mL of water was heated at reflux for 5 h, cooled, and filtered through a pad of florisil/celite with Et_2O as an eluent. The ether phase was dried (Na_2SO_4) and concentrated in vacuo. The resultant oil was immediately subjected to flash chromatography (50% EtOAc/hexanes, R_f 0.3, red spot with *p*-anisaldehyde). The product was isolated as a colorless oil in 88% yield (805 mg). An analytical sample was obtained by a performing a second chromatography to remove trace amounts of mercury salts to obtain 785 mg of a pure sample in 85% overall yield: IR (neat) 2944 (m), 1717 (s), 1667 (s), 1626 (m), 1418 (m), 1368 (m); ^{1}H NMR δ 5.81 (s, 1 H, vinyl H), 2.67 (t, 2 H, CH_2CH_2COMe), 2.49 (t, 2 H, CH_2CH_2COMe) 2.3–2.4 (m, 4 H, ring CH_2CH_2), 2.19 (s, 3 H, Me), 1.95–2.05 (m, 2 H, CH_2 α to ring carbonyl); high-resolution mass spectrum calcd for $C_{10}H_{14}O_2$ 166.0994, obsd 166.0993.

3-Hydroxy-3-methyl-2,3,4,5,6,7-hexahydro-1*H*-inden-4-one (11). A solution of **10** (35 mg, 0.21 mmol) and KOtBu (24 mg, 0.21 mmol) in *tert*-butyl alcohol (2 mL) was stirred at ambient temperature overnight (14 h). The product had an R_f value identical with that of the starting material but gave a yellow spot with *p*-anisaldehyde spray without the TLC plate being heating. The product was isolated by chromatography (50% EtOAc/hexanes, R_f 0.28, UV active) of the crude organic extracts (7.3 mg obtained, 21% yield): ^{1}H NMR δ 3.3 (s, br, 1 H, OH), 2.5–2.6 (m, 6 H), 1.9–2.1 (m, 4 H), 1.49 (s, 3 H, Me). The reaction could be performed in MeOH with KOH or NaOH, but these reactions

(31) Kellog, R. M.; Kruizinga, W. H. *J. Am. Chem. Soc.* **1981**, *103*, 5183. The method used was a modification of that of Gras, J. L. *Tetrahedron Lett.* **1978**, 2111.

always resulted in poorer yields with starting matrial being recovered, even after stirring for several days, as an inseparable mixture with the product. Alternatively, the title compound could be prepared in 21% yield by the treatment of **10** with 1 equiv of PhSLi in THF at 0 °C.

3,7a-Dimethyl-3-hydroxy-2,3,3a,4,5,6,7,7a-octahydro-1*H*-inden-4-one (12). A mixture of methyllithium (3.15 mmol, 2.25 mL) and cuprous iodide (3.00 mmol, 570 mg) in Et_2O (10 mL) was stirred for 20 min at −40 °C and cooled to −78 °C. Boron trifluoride etherate (425 mg, 3.00 mmol) was added to the solution, and the resulting mixture was stirred for 5 min before the enedione **10** (1.00 mmol, 166 mg, in 2 mL of Et_2O) was added. The yellow-tan heterogeneous mixture was warmed to ambient temperature before being quenched with saturated NH_4Cl. Ether was added, and the organic layer was washed with saturated NH_4Cl and dried ($MgSO_4$). Analytical TLC indicated that the starting material had been completely consumed, and two new spots were observed (R_f 0.10 and 0.28, 20% EtOAc/hexanes, non-UV active, green spots with *p*-anisaldehyde spray). Flash chromatography of the crude mixture provided the product as a mixture of three isomers (58% yield). The slow moving isomer had the following spectral characteristics: IR (neat) 3411 (br, s), 2949 (s), 2870 (m), 1694 (s), 1462 (m), 1418 (m), 1375 (m), 1296 (m), 1233 (m), 1148 (m), 1117 (m); ^1H NMR δ 1.50–2.65 (m, 12 H), 1.21 (s, 3 H, Me), 1.17 (s, 3 H, Me); high-resolution mass spectrum calcd for $C_{11}H_{18}O_2$ 182.1307, obsd 182.1308. The fast moving isomers had the following spectral characteristics: IR (neat) 3414 (br, s), 2949 (s), 2868 (m), 1684 (s), 1456 (m); ^1H NMR δ 2.25–2.45 (m, 1 H), 1.2–2.6 (m, 11 H), 1.43 and 1.35 (2 s, 3 H combined, Me α to OH), 1.10 and 1.04 (2 s, 3 H combined, Me); high-resolution mass spectrum calcd for $C_{11}H_{18}O_2$ 182.1307, obsd 182.1308.

Acknowledgment. We thank the National Institutes of Health for financial support and Dr. Alvin Marcus for recording the mass spectra.

Arenesulfonate Derivatives of Homochiral Glycidol: Versatile Chiral Building Blocks for Organic Synthesis

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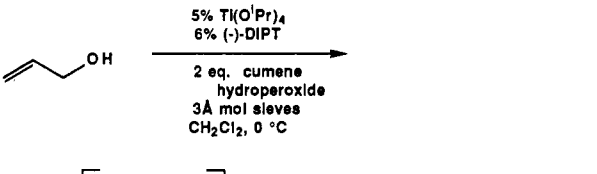
Received September 15, 1988

The preparation of a series of crystalline arenesulfonate derivatives of enantiomerically enriched glycidol is described. The enhancement of optical purity by recrystallization was particularly successful for two of these derivatives, glycidyl tosylate and glycidyl 3-nitrobenzenesulfonate, which were obtained in 97% ee and 99% ee, respectively. Very high regioselectivity was observed in the reactions of these compounds with a variety of nucleophiles, including aryl oxides, Et_2AlCN, organometallic reagents, and BH_3–$NaBH_4$. The application of this methodology to the synthesis of homochiral β-adrenergic blocking agents and homochiral terminal epoxides is discussed.

Homochiral glycidol (1) and related C_3-synthons have found widespread application as chiral building blocks for asymmetric synthesis.[1] Although D-mannitol has traditionally served as the ultimate precursor for many of these compounds, glycidol of high optical purity may now be more conveniently prepared by the catalytic asymmetric epoxidation of allyl alcohol.[2] However, this parent allylic alcohol is epoxidized with somewhat lower (i.e. ~90% ee) enantioselectivity than the ≥95% ee realized for most substituted allylic alcohols. This fact, in addition to special problems associated with the isolation and purification of the unstable and water-soluble product, prompted us to investigate the preparation of crystalline derivatives of glycidol, which would potentially enable the enhancement of optical purity by recrystallization. Work with two such compounds, glycidyl tosylate and glycidyl *p*-nitrobenzoate, has appeared elsewhere.[3] Here we report, in full, an investigation of the preparation and reactions of arenesulfonate derivatives of glycidol.

Preparation. Glycidyl arenesulfonates were initially prepared by treatment of glycidol with a sulfonyl chloride and triethylamine in toluene or methylene chloride at −10 °C, according to the literature procedure.[4] All derivatives were prepared in both racemic and enantiomerically enriched forms, the requisite optically active glycidol being prepared by catalytic asymmetric epoxidation of allyl alcohol.[2] Later, nonracemic glycidyl arenesulfonates were prepared more conveniently by in situ derivatization of enantiomerically enriched glycidol (eq 1),[2] a procedure that is particularly advantageous for the preparation of large quantities of a single derivative.[5]



Physical data for the glycidyl arenesulfonates that were prepared are presented in Table I. The data provided for

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(3) (a) Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 3710. (b) Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Org. Chem.* **1987**, *52*, 667.

(4) (a) Nakabayashi, N.; Masuhara, E.; Iwakura, Y. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 413. (b) Chautemps, P.; Pierre, J.-L.; Arnaud, P. *C. R. Seances Acad. Sci., Ser. 3* **1968**, *266*, 622.

(5) (*R*)- and (*S*)-Glycidol of ≥88% ee have recently become commercially available (ARCO, Aldrich Chemical Co.), rendering the in situ derivatization procedure less advantageous.

0022-3263/89/1954-1295$01.50/0