Tandem Michael–Claisen Condensation of Cyclohexenone with Methyl 3-(Phenylthio)-4-(methoxycarbonyl)but-2-enoate

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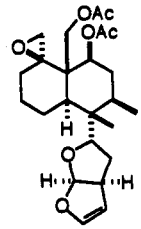
Introduction

Previously in our laboratory[1] we reported a 4C + 2C annelation reaction based on the tandem Michael–Claisen condensation of 3-(phenylthio)-1-(trimethylsiloxy)-1-methoxy-1,3-butadiene 1 with a number of α,β-unsaturated ketones, such as 2-cyclohexen-1-one (Scheme I). Compound 1 was readily available from vinyl sulfide 2.[2] This methodology was applied to the preparation of the 9-methyldecalin system,[1] the hydrindane system,[3] and the synthesis of two sesquiterpenes, aristolone and fukinone.[4] We have recently detailed the angular hydroxymethylation of decalins such as 3.[5]

A number of diterpenoid natural products (e.g. clerodin (–4)) have the decalin structure with functional substit-



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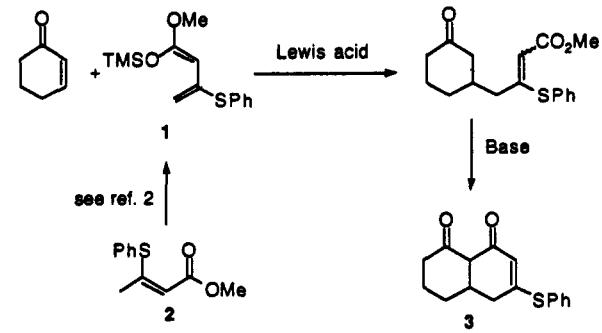
uents at the C-4, in addition to the C-1 and C-8 positions. Since the tandem Michael–Claisen condensation methodology provides a facile entry into decalin structures with functionality at C-1 and C-8, we are interested in extending the methodology to include functionality at C-4 as well. We have thus examined the reaction of cyclohexenone with methyl 3-(phenylthio)-4-(methoxycarbonyl)but-2-enoate (5) and its silyl ether derivative for the preparation of decalin 6.

Results and Discussion

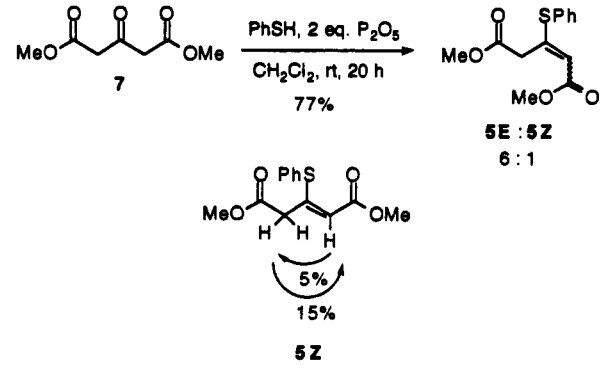
Vinyl sulfide 5 was prepared from dimethyl 1,3-acetonedicarboxylate (7) using the procedure by Trost.[6] Thus 7 was reacted with thiophenol in the presence of phosphorus pentoxide to give vinyl sulfide 5 as a 6:1 mixture of isomers in 77% yield (Scheme II). The stereochemistry of the major isomer formed was established as *E* (5E). The minor isomer 5Z showed NOE enhancement between the methylene protons and the vinyl proton, whereas the major isomer exhibited no NOE enhancement.

Several attempts were made to prepare the TMS enol silyl ether 8 from vinyl sulfide 5, but at best a 1:1 mixture

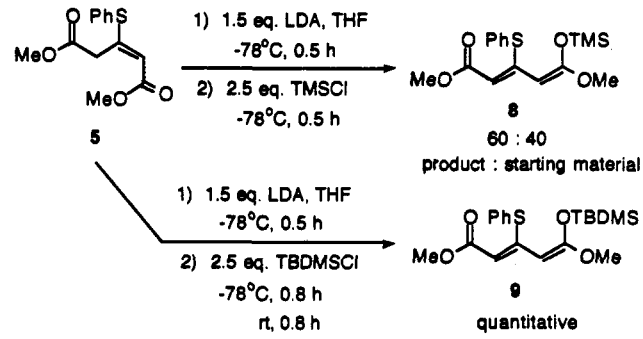
Scheme I



Scheme II

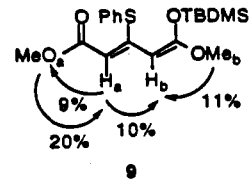


Scheme III



of product and starting material was obtained. However, the respective TBDMS siloxy diene 9 could be prepared in quantitative yield by quenching the anion with TBDMS-Cl and leaving the reaction for an additional 0.8 h at room temperature before the removal of the THF solvent (Scheme III). It seems that compound 8 is extremely sensitive to hydrolysis, whereas compound 9 can be stored in the fridge for 3 weeks without appreciable hydrolysis taking place.

The stereochemistry of 9 could not be determined unambiguously. NOE enhancement was observed between MeO_a and H_a, H_b and MeO_b, and H_a and H_b as indicated below. Thus, the stereochemistry of the enol silyl ether 9 was tentatively assigned as *Z,Z*.



The conjugate addition of siloxy diene 9 onto 2-cyclohexen-1-one under Lewis acid-catalyzed conditions pro-

(1) Chan, T. H.; Prasad, C. V. C. *J. Org. Chem.* **1987**, *52*, 110.
(2) Chan, T. H.; Prasad, C. V. C. *J. Org. Chem.* **1986**, *51*, 3012.
(3) Prasad, C. V. C.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 3242.
(4) Prasad, C. V. C.; Chan, T. H. *J. Org. Chem.* **1987**, *52*, 120.
(5) Chan, T. H.; Schwerdtfeger, A. E. *J. Org. Chem.* **1991**, *56*, 3294.
(6) Trost, B. M.; Lavoie, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075.

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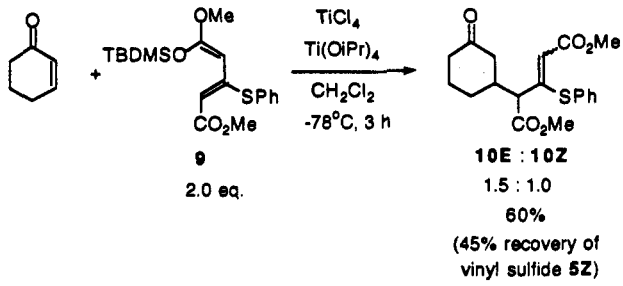
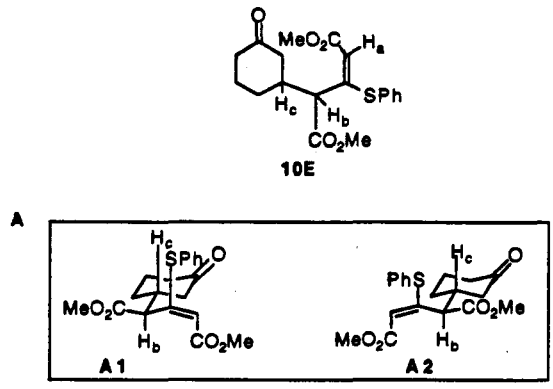
Scheme IV



Scheme V



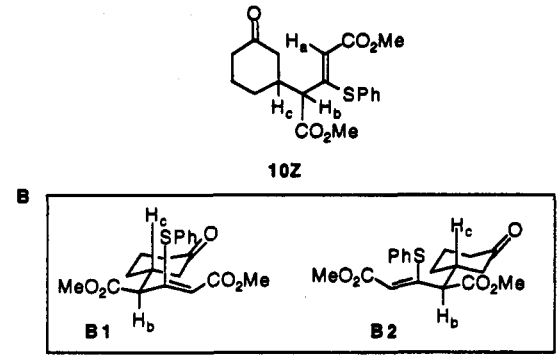
vided the *E*- and *Z*-Michael adducts **10E** and **10Z** in a 1.5 to 1.0 ratio in 60% yield along with 45% recovered vinyl sulfide **5Z**, due to the hydrolysis of **9** which was used in excess (Scheme IV). The two Michael adducts **10E** and **10Z** could be separated readily by column chromatography.

COSY ^{1}H NMR and ^{13}C NMR spectra showed that **10E** was a single diastereomer. The ^{1}H COSY NMR indicates that the doublet (J = 0.8 Hz) at 5.2 ppm (H_a) is coupled to the double doublet at 5.4 ppm (H_b). This proton is markedly deshielded, presumably as a result of the influence of the α,β-unsaturated ester moiety. The double doublet (J = 0.8 Hz and J = 10.4 Hz) at 5.4 ppm (H_b) is coupled to the multiplet at 2.5 ppm (H_c). The assignment of H_b at 5.4 ppm was confirmed by a HETCOR experiment which indicated that the methoxy carbon of the saturated ester, at 52.4 ppm in the ^{13}C NMR, couples both to its own methoxy protons, at 3.59 ppm in the ^{1}H NMR, as well as to proton H_b, at 5.4 ppm in the ^{1}H NMR. The large H–H coupling constant of H_b (J = 10.4 Hz) with H_c suggests that there is a *trans* relationship between protons H_b and H_c. The ^{13}C NMR shows only one signal for each carbon. Thus, the *E* isomer in solution exists as mainly one rotamer, i.e. one of the two diastereomers shown in box A (Scheme V). Recrystallization of **10E** gave a crystalline solid which permitted us to distinguish between these two possibilities by carrying out an X-ray diffraction study on the crystalline compound. X-ray structure determination clearly indicated that **10E** is diastereomer **A1**.[7]

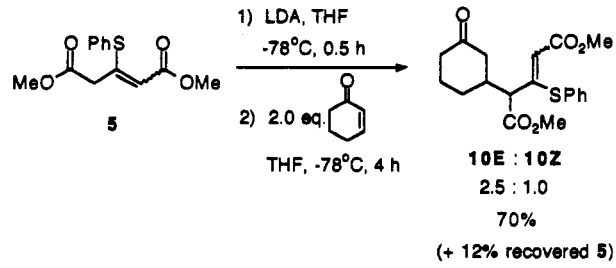
For the *Z* isomer **10Z**, its ^{1}H COSY NMR spectrum indicates that the two doublets (H_a) at 6.06 and 6.10 ppm (J = 0.8 Hz each) are coupled to the double doublet at 3.03 ppm (H_b). In the *Z* isomer, proton H_b is not as severely affected by the α,β-unsaturated ester as in the *E* isomer. The double doublet (J = 0.8 Hz and J = 10.0 Hz) at 3.03

(7) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ UK.

Scheme VI



Scheme VII



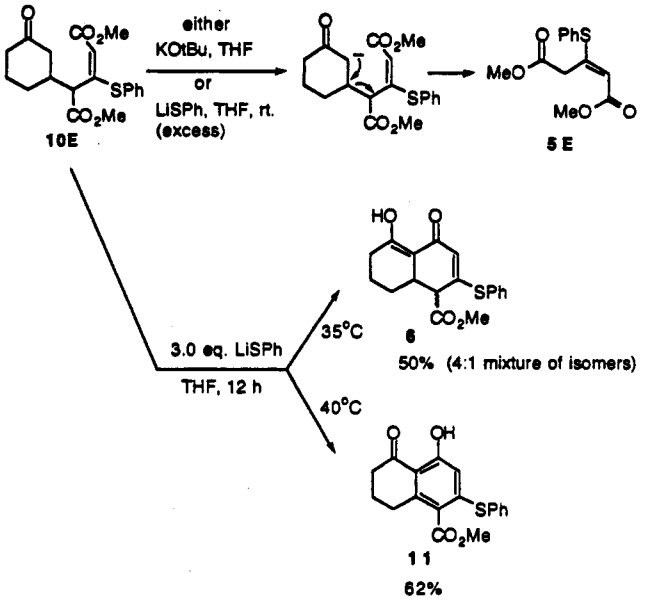
ppm (H_b) is coupled to the multiplet at 2.0 ppm (H_c). The large coupling constant (J = 10.0 Hz) of H_b with H_c suggests that H_b and H_c are oriented *trans* to each other. In the ^{1}H NMR the signals for H_a and the two OMe moieties are doubled in a 1:1 ratio. The ^{13}C NMR shows a doubling of each carbon signal. Thus the *Z* isomer **10Z** is in fact a 1:1 ratio of two diastereomers, i.e. the two diastereomers shown in Scheme VI, **B1** and **B2**.

The Michael adducts **10E** and **10Z** can also be prepared in 70% yield directly from vinyl sulfide **5** by treatment of the latter with LDA, followed by quenching of the resulting anion with 2-cyclohexen-1-one (Scheme VII). In this case the ratio of isomers *E*/*Z* is 2.5:1.0 with the *E* isomer crystallizing out directly from the crude reaction product mixture, thus facilitating purification.

In order to complete the preparation of **6**, Michael adduct **10E** was then treated with potassium *tert*-butoxide in THF in an attempt to effect cyclization. However, instead of cyclization, a retro-Michael reaction occurred, resulting in the recovery of vinyl sulfide **5E** (Scheme VIII). Reducing the reaction temperature to −78 °C and varying the reaction time did not result in any improvement.

However, when 3 equiv of lithium thiophenoxide was used as the base and the mixture was gently warmed at 35 °C, the desired product **6** was obtained in 50% yield as a 4:1 mixture of isomers. In the ^{1}H NMR spectra of the two isomers there appears a sharp singlet downfield of 14.90 ppm, indicating that both isomers exist predominantly in their enol forms. A slight increase in reaction temperature (40 °C) led to the production of an aromatic compound **11**, possibly arising from the oxidation of compound **6** by a small quantity of air. The ^{1}H NMR of this compound features a sharp singlet at 12.83 ppm, due to the phenolic proton, and vinyl (singlet at 6.26 ppm) and methoxy (singlet at 3.94 ppm) protons which are markedly deshielded. The signals of the remaining protons include two triplets (centered at 2.92 and 2.64 ppm) and a quintet (centered at 2.06 ppm), all three signals being clearly defined as a result of the rigidity of the structure. Finally, the ^{13}C NMR signal at 204.1 ppm confirms the presence

Scheme VIII



of the saturated ketone. Reducing the reaction temperature (25 °C) resulted in the production of a mixture of the desired product **6** (35%) and the vinyl sulfide **5E** (20%). Thus it seems that careful monitoring of the reaction temperature and the amount of lithium thiophenoxide reagent used are critical to the success of this cyclization.

Experimental Section

Melting points (mp), determined on a Gallenkamp block, and boiling points (bp) are uncorrected. The ^1H NMR spectral data are reported in parts per million (ppm) relative to the $CHCl_3$ reference line. The mass spectra were recorded on a Du Pont 21-492B mass spectrometer operating at an ionization potential of 70 eV and are reported as m/z (relative intensity %). All high resolution mass spectra were recorded on a ZAB 2F HS instrument using ammonia chemical ionization. Column chromatography was performed on Merck silica gel 60 (230–400 mesh). All glassware was predried in an oven at approximately 200 °C before use.

Methyl 3-(Phenylthio)-4-(methoxycarbonyl)but-2-enoate (5). Dimethyl 1,3-acetonedicarboxylate (4.50 mL, 0.031 mol) and thiophenol (3.14 mL, 0.031 mol) were combined in 50 mL of CH_2Cl_2 at room temperature under argon together with P_2O_5 (8.75 g, 0.062 mol). The yellow reaction mixture was stirred for 22 h. The then orange slurry was poured into a separatory funnel along with 25 mL of CH_2Cl_2 rinsings. The organic layer was carefully washed with 10% NaOH and brine. The combined organic extracts were then dried ($MgSO_4$) and filtered, and the solvent was removed. Vacuum distillation (138–142 °C/0.15 mm) provided a pale yellow viscous oil (6.27 g, 77%), the vinyl sulfide **5**, as a mixture of the *E* and *Z* isomers in a 6:1 ratio, separable by chromatography:

5E: ^1H NMR ($CDCl_3$) δ 7.23–7.57 (m, 5H), 5.41 (s, 1H), 3.81 (s, 2H), 3.69 (s, 3H), 3.54 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.5, 165.3, 155.2, 135.5, 130.2, 129.9, 129.0, 113.4, 52.2, 51.1, 38.3; MS 267 (11, M + H$^+$), 266 (73, M$^+$), 235 (49), 206 (33), 203 (25), 192 (40), 161 (18), 149 (21), 147 (100), 125 (57), 110 (60), 69 (24), 67 (25), 59 (29), 39 (25), 28 (26); exact mass calcd for $C_{13}H_{14}O_4S$ (M$^+$) 266.061, found 266.061.

5Z: ^1H NMR ($CDCl_3$) δ 7.29–7.52 (m, 5H), 5.89 (s, 1H), 3.71 (s, 3H), 3.48 (s, 3H), 3.11 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 169.1, 166.2, 153.5, 136.5, 130.0, 129.9, 129.8, 114.6, 52.2, 51.4, 42.1; MS 267 (12, M + H$^+$), 266 (77, M$^+$), 235 (51), 206 (34), 203 (26), 192 (42), 161 (18), 147 (100), 125 (58), 110 (61), 69 (19), 59 (27), 39 (21); exact mass calcd for $C_{13}H_{14}O_4S$ (M$^+$) 266.061, found 266.062.

Mixture of **5E** and **5Z**: IR (film) 2952, 1742, 1706, 1613, 1599, 1432, 1347, 1321, 1202, 1165 cm^{-1}.

1-(Trimethylsiloxy)-1-methoxy-3-(phenylthio)-4-(methoxycarbonyl)but-1,3-dienoate (8). To a solution of dry diisopropylamine (0.63 mL, 4.50 mmol) in 7.5 mL of THF at 0 °C under argon was added 2.5 M *n*BuLi (2.25 mL, 5.62 mmol). After stirring for 30 min at 0 °C, the pale yellow solution was cooled to −78 °C and chlorotrimethylsilane (0.95 mL, 7.48 mmol) was added, followed immediately by a solution of vinyl sulfide **5** (0.80 g, 3.01 mmol) in 5.0 mL of THF. The orange solution was stirred at −78 °C for another 30 min and then allowed to warm to room temperature. The solvent was removed. Under argon the orange residue was washed with dry hexane and filtered. The hexane was removed, providing an orange oil consisting of a 60:40 mixture of product and starting material. ^1H NMR ($CDCl_3$) showed signals corresponding to the product **8** (cf. data given in the procedure below): δ 7.20–7.65 (m), 6.58 (s), 4.75 (s), 3.78 (s), 3.56 (s), 0.26 (s); and the starting material **5** (cf. data given in procedure above) δ 7.20–7.65 (m), 5.49 (s), 3.86 (s), 3.75 (s), 3.61 (s).

1-(*tert*-Butyldimethylsiloxy)-1-methoxy-3-(phenylthio)-4-(methoxycarbonyl)-but-1,3-dienoate (9). To a solution of dry diisopropylamine (3.60 mL, 0.026 mol) in 50 mL of THF at 0 °C under argon was added 2.5 M *n*BuLi (10.0 mL, 0.025 mol). The pale yellow solution was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of vinyl sulfide **5** (4.64 g, 0.017 mol) in 25 mL of THF was added. After another 30 min at −78 °C, *tert*-butyldimethylsilyl chloride (7.18 g, 0.048 mol) was added and stirring was continued for another 45 min. The orange solution was then slowly warmed to room temperature while stirring for another 45 min. The solvent was removed under reduced pressure. Under argon the red residue was washed with dry hexane and filtered. The hexane was removed providing the product **9** in quantitative yield as a viscous red oil: ^1H NMR ($CDCl_3$) δ 7.31–7.57 (m, 5H), 6.55 (s, 1H), 4.67 (s, 1H), 3.76 (s, 3H), 3.53 (s, 3H), 1.00 (s, 9H), 0.28 (s, 6H); IR (film) 2952, 1691, 1611, 1442, 1254, 1232, 1165, 1068, 840 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 166.9, 162.0, 158.9, 136.2, 135.5, 129.9, 128.7, 102.3, 55.9, 50.4, 38.4, 26.5, 25.9, 18.3.

Methyl 3-(Phenylthio)-4-(3-oxocyclohexyl)-4-(methoxycarbonyl)but-2-enoate (10). To a mixture of titanium tetrachloride (0.080 mL, 0.73 mmol) and titanium isopropoxide (0.17 mL, 0.58 mmol) in 5 mL CH_2Cl_2 at −78 °C under argon was added a solution of 2-cyclohexen-1-one (0.07 mL, 0.72 mmol) in 2 mL of CH_2Cl_2. The pale yellow mixture was stirred for 30 min at which time a solution of enol silyl ether **9** (0.605 g, 1.59 mmol) in 3 mL of CH_2Cl_2 was added. After stirring for 3 h at −78 °C the red solution was diluted with ether and carefully quenched with 10 mL of saturated $NaHCO_3$ solution. The aqueous layer was extracted with ether, the combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent was removed. Column chromatography (1:4 EtOAc/hexane) of the crude material provided the white crystal *E*-Michael adduct **10E** (0.097 g, 37%) and *Z*-Michael adduct **10Z** (0.060 g, 23%) along with some recovered vinyl sulfide **5Z** (0.191 g, 45%). The *E* isomer was recrystallized from a 3:2:2 solution of ether/methylene chloride/hexane.

10E (mp 162–163 °C): ^1H NMR ($CDCl_3$) δ 7.46 (s, 5H), 5.39 (dd, J = 0.8 Hz and J = 10.4 Hz, 1H), 5.23 (d, J = 0.8 Hz, 1H), 3.78 (s, 3H), 3.59 (s, 3H), 1.38–2.77 (m, 9H); IR ($CHCl_3$) 2952, 1739, 1733, 1701, 1598, 1436, 1204, 1181 cm^{-1}; MS: 362 (100, M$^+$), 331 (26), 266 (44), 221 (71), 206 (44), 193 (82), 161 (38), 147 (48), 125 (38), 110 (94), 109 (57), 105 (22), 97 (53), 91 (22), 77 (26), 69 (61), 65 (30), 59 (38), 55 (48), 41 (66), 39 (20); exact mass calcd for $C_{19}H_{22}O_5S$ (M$^+$) 362.118, found 362.123; ^{13}C NMR ($CDCl_3$) δ 210.4, 170.9, 165.3, 159.2, 135.8, 130.2, 130.0, 127.9, 113.5, 52.4, 51.0, 43.9, 41.1, 38.9, 30.1, 24.5.

10Z (mp 96–98 °C): ^1H NMR ($CDCl_3$) δ 7.40–7.60 (m, 5H), 6.06 and 6.10 (two d in a 1:1 ratio, J = 0.8 Hz each, together 1H), 3.74 and 3.75 (two s in a 1:1 ratio, together 3H), 3.65 and 3.67 (two s in a 1:1 ratio, together 3H), 3.03 (dd, J = 0.8 Hz and J = 10 Hz, 1H), 0.88–2.50 (m, 9H); IR ($CHCl_3$) 2952, 1739, 1711, 1690, 1587, 1434, 1223, 1204, 1189, 1158 cm^{-1}; MS 362 (100, M$^+$), 266 (50), 221 (71), 206 (50), 193 (84), 161 (38), 147 (55), 129 (36), 125 (38), 110 (80), 109 (57), 97 (51), 77 (23), 69 (62), 65 (36), 59 (35), 55 (48), 41 (64); exact mass calcd for $C_{19}H_{22}O_5S$ (M$^+$) 362.118, found 362.119; ^{13}C NMR ($CDCl_3$) δ 209.5, 170.7, 166.1, 155.4, 136.3, 130.0, 129.5, 113.0, 53.2, 52.3, 44.9, 42.0, 40.1, 28.7, 24.4. All the

signals in the ^{13}C NMR are doubled, indicating the presence of two rotamers as a mixture.

Alternative Procedure. To a solution of dry diisopropylamine (0.30 mL, 2.14 mmol) in 10 mL of THF at 0 °C under argon was added 2.5 M *n*BuLi (0.90 mL, 2.25 mmol). The pale yellow solution was stirred for 20 min at 0 °C and then cooled to −78 °C. A solution of the vinyl sulfide **5** (0.542 g, 2.03 mmol) in 2 mL of THF was added and stirring was continued at −78 °C for another 20 min. Then a solution of 2-cyclohexen-1-one (0.35 mL, 3.62 mmol) in 2 mL of THF was added. After stirring for 4 h at −78 °C, the orange mixture was diluted with ether and quenched with dilute NH_4Cl solution. The aqueous layer was extracted with ether, the combined ether extracts were dried ($MgSO_4$) and filtered, and the solvent was removed. Column chromatography (1:4 EtOAc/hexane) of the crude material provided the *E*-Michael adduct **10E** (0.303 g, 49%) and *Z*-Michael adduct **10Z** (0.117 g, 19%) in a 2.6:1.0 ratio along with recovered vinyl sulfide **5Z** (0.066 g, 12%). See above for spectral data.

3-(Phenylthio)-4-(methoxycarbonyl)-4a,5,6,8a-tetrahydronaphthalene-1,8(4*H*,7*H*)-dione (6) and 1-Hydroxy-3-(phenylthio)-4-(methoxycarbonyl)-5,6-dihydronaphthalene-8(7*H*)-one (11). To a solution of thiophenol (0.12 mL, 1.17 mmol) in 10 mL of THF at 0 °C under argon was added 2.5 M *n*BuLi (0.50 mL, 1.25 mmol). After stirring for 20 min a solution of the *E*-Michael adduct **10E** (0.144 g, 0.40 mmol) in 5 mL of THF was added. The reaction mixture was stirred at 35 °C for 12 h, at which time ether was added and the reaction was quenched with 10% sodium hydroxide. The organic layer was washed with 10% sodium hydroxide, followed by water. The combined aqueous layer was then extracted with ether. The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent was removed. Column chromatography (1:4 EtOAc/hexane) of the crude material provided a thick yellow oil **6** (0.070 g, 50%) as a 4:1 mixture of two isomers.

When the reaction was carried out in the same way except that the mixture was stirred at 40 °C for 12 h, then an aromatic product **11** is obtained in 62% yield.

Major isomer of **6**: ^1H NMR ($CDCl_3$) δ 14.96 (s, 1H), 7.41–7.54 (m, 5H), 5.60 (d, J = 1.8 Hz, 1H), 3.71 (d, J = 1.8 Hz, 3H), 3.33 (dd, J = 1.8 Hz and 6 Hz, 1H), 3.11–3.20 (m, 1H), 2.26–2.40 (m, 2H), 1.84–2.03 (m, 2H), 1.18–1.73 (m, 2H); IR ($CHCl_3$) 2948, 1731, 1629, 1616, 1582, 1442, 1331, 1245, 1165, 754 cm^{-1}; MS 330 (100, M^+), 328 (25), 295 (37), 271 (77), 270 (39), 221 (51), 189 (30), 123 (54), 86 (30), 84 (48), 55 (33); exact mass calcd for $C_{18}H_{18}O_4S$ (M^+) 330.093, found 330.093; ^{13}C NMR ($CDCl_3$) δ 187.1, 177.0, 169.4, 157.6, 135.3, 130.3, 130.0, 127.7, 121.8, 113.3, 103.6, 52.4, 50.5, 36.2, 29.6, 26.8, 20.8.

Minor isomer of **6**: ^1H NMR ($CDCl_3$) δ 15.28 (s, 1H), 7.39–7.56 (m, 5H), 5.55 (d, J = 2 Hz, 1H), 3.86 (s, 3H), 3.40 (dd, J = 2 Hz and 13 Hz, 1H), 3.15 (dt, J = 4.8 Hz and 12.8 Hz, 1H), 2.33–2.43 (m, 2H), 1.82–1.98 (m, 2H), 1.25–1.70 (m, 2H); IR same as above; MS 330 (15, M^+), 271 (54), 270 (44), 221 (85), 206 (50), 204 (39), 147 (34), 110 (40), 109 (45), 97 (25), 86 (67), 84 (88), 77 (42), 69 (67), 65 (43), 59 (64), 55 (85), 41 (47), 39 (54), 28 (100); exact mass calcd for $C_{18}H_{18}O_4S$ (M^+) 330.093, found 330.100; ^{13}C NMR ($CDCl_3$) δ 185.0, 179.4, 171.9, 158.9, 135.7, 130.5, 130.1, 129.7, 120.8, 104.3, 53.9, 52.4, 36.7, 30.2, 28.0, 20.5.

Aromatic compound **11**: ^1H NMR ($CDCl_3$) δ 12.83 (s, 1H), 7.40–7.60 (m, 5H), 6.26 (s, 1H), 3.94 (s, 3H), 2.92 (t, J = 6 Hz, 2H), 2.64 (t, J = 6 Hz, 2H), 2.06 (quintet, J = 6 Hz, 2H); IR ($CHCl_3$) 2948, 1717, 1630, 1582, 1437, 1359, 1260, 1187 cm^{-1}; MS 328 (68, M^+), 295 (100), 267 (19), 28 (12); exact mass calcd for $C_{18}H_{16}O_4S$ (M^+) 328.077, found 328.077; ^{13}C NMR ($CDCl_3$) δ 204.1, 167.8, 163.7, 148.6, 144.1, 135.2, 130.5, 129.9, 129.7, 122.2, 114.1, 52.3, 38.4, 27.8, 22.4.

Acknowledgment. Financial support from NSERC and FCAR is gratefully acknowledged. We thank Dr. Rosi Hynes for the determination of the X-ray structure of Michael adduct **10E**.

Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra for compounds **5**, **6**, and **9–11** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.