Carbene Anion Formation from a Dithioacetal Anion Bearing an Allylic Oxyanion Substituent at the 2 Position. Divergent Behavior of the Dianion in Ether and THF

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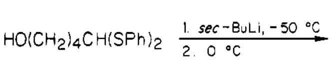
The recently proposed principle that diphenyl dithioacetal anions decompose to carbenes when present in a molecule possessing a second anionic site has been applied to a dithioacetal anion possessing an oxyanion at the 2 position. When the alcohol **3**, arising from 1,2-addition of tris(phenylthio)methyllithium to crotonaldehyde, is treated with 2 molar equiv of *sec*-butyllithium at −50 °C, the dianion **4** is produced by deprotonation and sulfur–lithium exchange. When this dianion is warmed to 0 °C in THF, the carbene anion that is generated undergoes the expected 1,2-H transfer to yield *trans*-1-(phenylthio)pent-3-en-2-one (**5**). The main product (**7**) of decomposition of the same dianion in ether solution arises by loss of the Li_2O and 1,4-addition of *sec*-butyllithium to the resulting conjugated ketene dithioacetal (**10**).

Recent work from this laboratory has provided a number of examples of a new principle whereby the conjugate base of a diphenyl dithioacetal exhibits carbene or carbenoid behavior when it exists in a molecule with a second negative charge; in most cases the reactions of the carbene or carbenoid carbon atom are dictated by the nature of the second anionic site and its juxtaposition with respect to the dithioacetal anion.[1-4] Examples have been provided in which this second negative charge residues mainly on carbon,[1,3] oxygen,[1-4] and nitrogen.[4] Equations 1–3 illustrate three examples in which this charge residues on oxygen.



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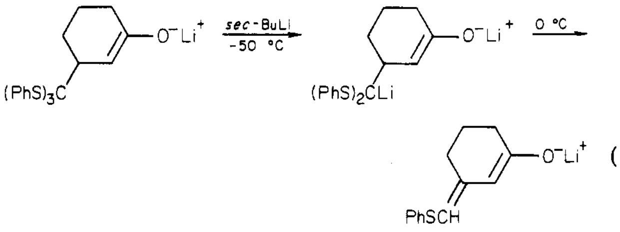

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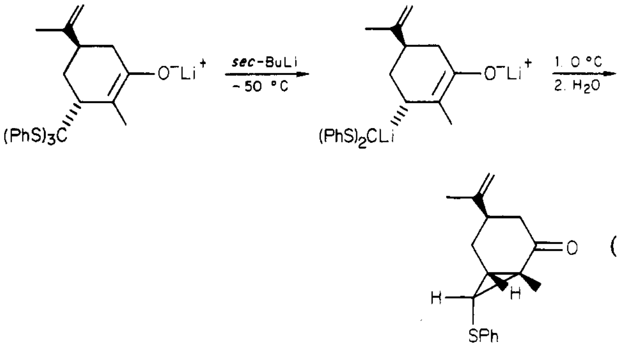

(3)

In the first two examples,[1,2] the carbenoid carbon atom inserts into weakened CH bonds adjacent to a negatively charged atom. In the last example, it attacks the π orbital of the enolate system.[2]

The present work is concerned with the chemical behavior of **4** in which both negatively charged atoms are attached to the same allylic carbon atom. It will be seen that the expected carbene type chemistry is manifested when the decomposition of **4** is allowed to proceed in tetrahydrofuran (THF) solution but that the main reaction in ether solution is quite different.

Results

Tris(phenylthio)methyllithium (**2**) adds in a 1,2-fashion to crotonaldehyde (**1**) in ether solution to yield the alcohol **3** in 98% yield based on consumed tris(phenylthio)methane, the precursor of the organolithium reagent;[5,6] 20% of tris(phenylthio)methane is recovered, presumably formed by enolization. In THF, the 1,2- and 1,4-addition products are produced in about equal quantities.[7]

Treatment of **3** with 2.2 molar equiv of *sec*-butyllithium at −50 °C for 6 h in THF effects clean sulfur–lithium exchange[2] to produce the dianion **4**; aqueous workup provides *sec*-butyl phenyl sulfide and the conjugate acid of **4**, *trans*-1,1-bis(phenylthio)pent-3-en-2-ol, both in 83% yield. When **3** is treated with 2.2 equiv of *sec*-butyllithium in THF at −78 °C, the solution is warmed to 0 °C at which temperature it is maintained for 5 h, methyl iodide is added in order to trap and inactivate the released thiophenoxide ion, and the reaction is quenched with water, *trans*-1-(phenylthio)pent-3-en-2-one (**5**) is produced in 60% yield along with 57% of thioanisole and 96% of *sec*-butyl phenyl sulfide. If methyl iodide is not added prior to workup, the 1,4-adduct (**6**) of thiophenol and **5** is a major product.

When the allylic alcohol **3** is treated with 2.2 equiv of *sec*-butyllithium at −78 °C in ether, rather than THF, and the solution is warmed to −50 °C, the dianion **4** is again produced, as indicated by an experiment in which the solution was quenched with water. When the ethereal solution of **4** is allowed to remain at 0 °C for 5 h, only a relatively minor amount of enone **5** is formed; 9% of **5** is isolated along with 9% of its thiophenol addition product (**6**) when the reaction mixture is quenched with water (eq 4). The main product, formed in 30% yield, is *trans*-1,1-

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[1] Cohen T.; Ritter, R. H.; Ouellette, D. *J. Am. Chem. Soc.* **1982**, *104*, 7142.

[2] Cohen, T.; Yu, L.-C. *J. Am. Chem. Soc.* **1983**, *105*, 2811.

[3] Cohen, T.; Ritter, R. H., Unpublished results.

[4] Cohen, T.; Ritter, R. H.; Yu, L.-C. "Abstracts of Papers", 186th National Meeting of the American Chemical Society, Washington, DC, August 28–September 3, 1983; American Chemical Society: Washington DC, 1983; ORGN 159.

[5] The absolute yield of **3** is 78%.

[6] Other examples of the addition of this organolithium compound to aldehydes: Seebach, D. *Chem. Ber.* **1972**, *105*, 487. Scholz, D. *Synth. Commun.* **1982**, 12, 527.

[7] (a) For a discussion of competitive 1,2- and 1,4-addition of sulfur-stabilized anions to enals and enones and extensive references, see: Wartski, L.; El Bouz, M. *Tetrahedron* **1982**, *38*, 3285. (b) Tris(phenylthio)methyllithium has a strong tendency to undergo conjugate addition to enones in THF solution; see ref 2 and citations therein.

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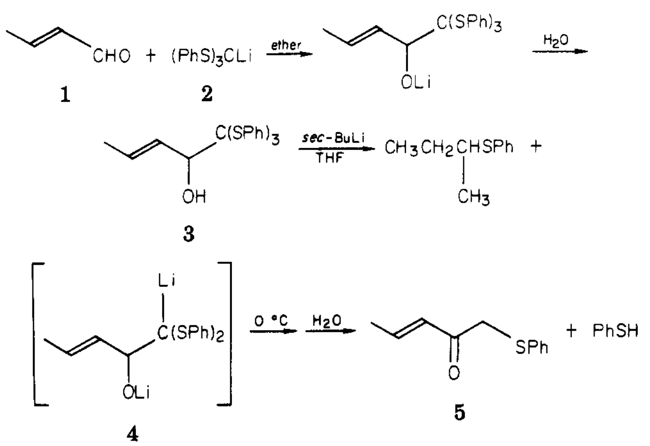
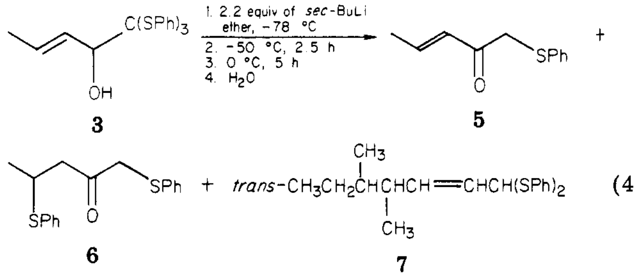


bis(phenylthio)-4,5-dimethyl-2-heptene (7) as a nearly equimolar mixture of two diastereomers (eq 4).

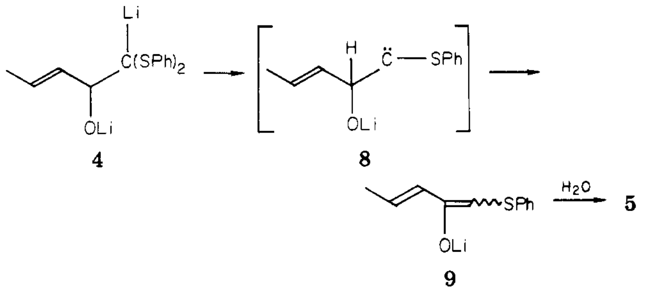


(4)

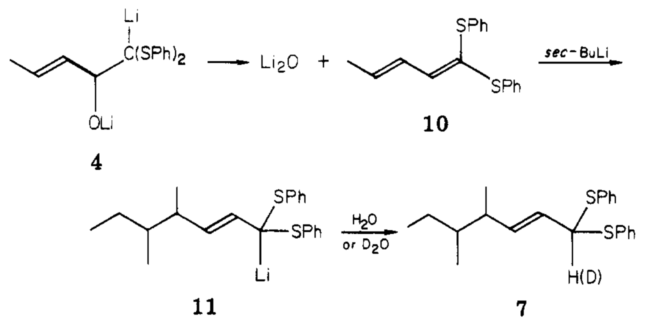
The mass spectrum of 7 at 15 eV consists of a very weak parent peak at *m/e* 342.1465 (calcd for $C_{21}H_{26}S_2$, 342.1476) and a base peak at *m/e* 233.1352 (calcd for $C_{15}H_{21}S$, 233.1364) for M − PhS, an expected fragmentation for the diphenyl dithioacetal of an enal. The ^{1}H NMR spectra in $CDCl_3$ and C_6D_6 of 7 and the 1-deuterio derivative, obtained by quenching the reaction mixture with D_2O, are completely consistent with the assigned structures (see Experimental Section). When the same experiment is repeated except that only 1 mol equiv of alkyllithium is used, only starting 3 is recovered.

Discussion

In THF solution, the dianion 4 apparently behaves in a manner analogous to that of other anions of diphenyl dithioacetals which are incorporated into molecules bearing a second negatively charged atom.[1-4] In the case of 4, the two negative charges are closer together than in the other examples that we have studied. It has been pointed out[1] that lithio derivatives of diphenyl dithioacetals are fairly stable at 0 °C and that the decomposition that does occur results in an extensive array of products which do not include the obvious ones expected from the intermediacy of a carbene. In the case of 4, the alkoxide grouping must induce the dithioacetal anion to either behave as a carbenoid or to actually lose lithium thiophenoxide to produce the carbene 8. The carbenoid carbon atom inserts into the weak and electron-rich CH bond shown to produce the enolate (9) of 5.



Scheme I



Compounds $RCH(OH)CH(SPh)_2$ produced by the addition of bis(phenylthio)methyllithium to aldehydes have been found to yield ketones analogous to 5 upon treatment with methyllithium[8] and we have interpreted these results by the types of transformations indicated above.[1,2] However, it was reported that under the same conditions no reaction was observed with the adduct of bis(phenylthio)methyllithium and cinnamaldehyde.[8] From the results reported here, it seems very likely that this was due to an inability to deprotonate the dithioacetal group of the adduct. The dianion, if produced, would be analogous to 4 and would certainly be expected to behave in a similar fashion.

The procedure described here constitutes a two-flask method for converting an enal to a potentially useful dienolate ion or a vinyl phenylthiomethyl ketone. In THF solution, the behavior of 4 is precisely predictable on the basis of the newly enunciated principle of carbene anion formation from precursor dithioacetal anions bearing a second negatively charged species and the overwhelming control of the reactivity of the carbenic site by the anionic moiety.[1,9]

In ether, however, the main reaction course for 4 is apparently the loss of Li_2O to yield the conjugated ketene dithioacetal 10. Such compounds are known[10] to undergo 1,4-addition of organolithium reagents in the manner shown in Scheme I for the additon of *sec*-butyllithium. Quenching of the adduct 11 with water or D_2O produces 7 or its 1-deuterio analogue, respectively, as expected.[10]

An excellent precedent is available for the loss of Li_2O from a dianion somewhat analogous to 4.[11] Such reactions are not common and in the present case a key factor must

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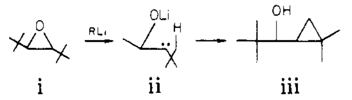
[8] Kuwajima, I.; Kurata, Y. *Chem. Lett.* **1972**, 291.

[9] The behavior of 8 or its precursor carbenoid and the analogous intermediates presumably produced from anions similar to 4 in the work of Kuwajima[8] contrasts sharply with that of the apparently similar intermediate carbene, which was indicated for the sake of simplicity as ii by Crandall and produced by the deprotonation of *trans*-di-*tert*-butylethylene oxide (i) by *tert*-butyllithium in hydrocarbon solvent. This species underwent little if any insertion into the adjacent CH bond but instead produced mainly the cyclopropanes (iii) arising by insertion into the CH bond of the adjacent *tert*-butyl group. The latter behavior is readily rationalized by the assumption, implied in the paper, that the species undergoing the insertion is not the oversimplification ii but some species in which the CO bond is not completely severed. In such a species, the developing vacant orbital on the carbenoid carbon atom would be essentially orthogonal to the adjacent CH bond and thus incapable of inserting into it. Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4526.



[10] Seebach, D.; Kolb, M.; Gröbel, B.-T. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 69.

[11] Barluenga, J.; Flórez, J.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1153. See also: Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4527.

be the allylic character of the CO bond which weakens it to the extent that cleavage can occur. Another crucial factor is evidently the lower degree of solvation of lithium ions in ether as compared to THF; as a consequence the LiO bond must be stronger in ether than in THF thereby allowing the Li_2O to behave as a group with a minimal negative charge on oxygen.

Experimental Section

All reactions were performed under argon. Flash chromatography[12] was performed with 40–63 μm silica gel 60 (E. Merck). Preparative reversed-phase medium-pressure liquid chromatography (MPLC) was performed at 30 psi with a Merck LiChroprep RP-8 (40–63 μm) column (240 mm × 10 mm ID). Proton NMR spectra were determined in $CDCl_3$ (unless otherwise stated) on a Bruker WH-300 spectrometer using Me_4Si as an internal standard. Low-resolution mass spectra were recorded on an LKB-9000 mass spectrometer and high-resolution mass spectra on a CH-5 double-focussing Varian Mat mass spectrometer.

***trans*-1,1,1-Tris(phenylthio)pent-3-en-2-ol (3).** To a solution of 1.97 g (5.79 mmol) of tris(phenylthio)methane[13] in 40 mL of anhydrous ether was added by hypodermic syringe to *n*-butyllithium (5.50 mL of a 1.17 M solution in hexane, 6.44 mmol) at −78 °C. In order to remove the resulting colorless precipitate of the lithio salt (2) from the surface of the flask and to maintain it as a suspension, a horseshoe magnet was used to induce the magnetic stirring bar to continually scrape the inside of the flask while the contents were being vigorously stirred. The addition at −78 °C of 0.47 mL (5.8 mmol) of crotonaldehyde (1), freshly distilled from calcium sulfate, caused the formation of a white cloudy suspension which was stirred for 5 h before being quenched with 5 mL of water. The mixture was partitioned between ether and water. The aqueous layer was extracted with 3 portions of ether and the combined organic phase was washed with water and brine, dried ($MgSO_4$), and concentrated to give 2.53 g of crude product which was subjected to flash chromatography (elution with a solution of 250 mL of ethyl acetate and 1250 mL of hexanes). Tris(phenylthio)methane (0.39 g, 20%) was eluted first followed by 1.84 g (78%) of the spectroscopically pure title compound (**3**, R_f 0.38). Recrystallization from hexanes gave white crystals: mp 69–70 °C; ^{1}H NMR δ 1.67 (dd, J = 6.47, 0,81 Hz, 3 H, CH_3), 2.76 (d, J = 4.24 Hz, 1 H, OH), 4.19 (dd, J = 6.87, 4.24 Hz, $C\mathit{H}OH$), 5.68 (dqd, J = 15.26, 6.26, 0.81 Hz, 1 H, $CH_3C\mathit{H}{=}$), 5.86 (ddq, J = 15.26, 6.87, 1.42 Hz, 1 H, (${=}C\mathit{H}CH(OH)$)), 7.29–7.40 (m, 9 H, aromatic), 7.67–7.70 (m, 6 H, aromatic); IR (KBr) 3500 (OH), 1661 (C=C) cm^{-1}; MS (15 eV), *m/e* 392 (M − H_2O, 1.4%), 339 ($(PhS)_3C^+$, 29%), 301 (M − PhS, 100%); exact mass calcd for $C_{17}H_{17}OS_2$ (M − SPh), 301.0721; found, 301.0719; calcd for $C_{19}H_{15}S_3$ ($(PhS)_3C^+$), 339.0336; found, 339.0335.

A similar reaction performed in THF instead of ether for 2 h yielded 22% of recovered tris(phenylthio)methane and a mixture the ^{1}H NMR spectrum of which provided strong evidence that it contained about 32% yields of **3** and of the 1,4-adduct, 4,4,4-tris(phenylthio)-3-methylbutanal. In addition to the peaks present in the spectrum of **3**, there were peaks at δ 1.27 (d, J = 6.67 Hz, 3 H, CH_3), 2.32 (ddd, J = 15.26, 6.87, 2.43 Hz, 1 H, CH_2CO), 2.80 (m, 1 H, $CH_3C\mathit{H}$), 3.18 (d, J = 15.26 Hz, 1 H, CH_2CO), 7.29–7.40 (m, 9 H, aromatic), 7.67–7.70 (m, 6 H, aromatic), 9.32 (d, J = 2.43 Hz, 1 H, CHO).

Treatment of 3 with *sec*-Butyllithium. A. In THF. To a solution of 0.144 g (0.35 mmol) of **3** in 10 mL of THF was added 0.68 mL (0.78 mmol) of a 1.14 M solution of *sec*-butyllithium in hexane at −78 °C and stirring was continued for 0.5 h. The yellow solution was then stirred at 0 °C for 5 h during which time the solution turned red. Methyl iodide (0.024 mL, 0.39 mmol) was added and the yellow solution was stirred for 0.5 h, cooled to −23 °C, and quenched with 2 mL of water. The mixture was worked up as in the above experiment to provide 0.162 g of crude product. Since the yield of *sec*-butyl phenyl sulfide in nearly quantitative (see below), the yield of *trans*-1-(phenylthio)pent-3-en-2-one (**5**) could be determined at this point to be 60% by comparing the integrated intensity of the ^{1}H NMR peaks for the protons on the sulfur-bearing carbon atoms of **5** and this thioether. Flash chromatography (elution with a solution of 38 mL of ethyl acetate and 212 mL of hexanes) provided 0.056 g (96%) of *sec*-butyl phenyl sulfide, 0.025 g (57%) of thioanisole, and 0.021 g (32%) of *trans*-1-(phenylthio)pent-3-en-2-one (**5**), which is somewhat unstable to the chromatographic conditions. The thioanisole exhibited identical TLC and ^{1}H NMR properties with those of an authentic sample.

***sec*-Butyl phenyl sulfide**: ^{1}H NMR δ 1.00 (t, J = 7.28 Hz, 3 H, $C\mathit{H}_3CH_2$), 1.27 (d, J = 6.67 Hz, 3 H, $C\mathit{H}_3CHS$), 1.46–1.71 (m, 2 H, CH_2), 3.10–3.21 (m, J = 6.67 Hz, 1 H, CHS), 7.17–7.30 (m, 3 H, aromatic), 7.37–7.41 (m, 2 H, aromatic); MS (15 eV), *m/e* 166 (M, 69%), 137 (M − Et, 10%), 110 ($PhSH^+$, 100%); exact mass calcd for $C_{10}H_{14}S$, 166.0816; found, 166.0819.

5: ^{1}H NMR δ 1.90 (dd, J = 6.87, 1.62 Hz, 3 H, CH_3), 3.77 (s, 2 H, $C\mathit{H}_2SPh$), 6.35 (dt, J = 15.56, 1.62 Hz, 1 H, ${=}CHCO$), 6.92 (dq, J = 15.56, 6.87 Hz, 1 H, $CH_3C\mathit{H}$), 7.19–7.37 (m, 5 H, aromatic); IR (neat) 1683 (CO), 1663 (C=C) cm^{-1}; MS (15 eV), *m/e* 192 (M, 63%), 69 (M − CH_2SPh, 100%); exact mass calcd for $C_{11}H_{12}OS_2$, 192.0609; found, 192.0608.

In a similar experiment, except that the solution was stirred at −50 °C instead of 0 °C for 5 h, 83% of *sec*-butyl phenyl sulfide was produced along with 83% of 1,1-bis(phenylthio)pent-3-en-2-ol, the conjugate acid of **4**: ^{1}H NMR δ 1.72 (d, J = 5.66 Hz, 3 H, CH_3), 2.78 (d, J = 5.46 Hz, 1 H, OH) 4.31 (m, 1 H, $C\mathit{H}OH$), 4.48 (d, J = 4.45 Hz, $C\mathit{H}(SPh)_2$), 5.76 (m, 2 H, olefinic), 7.24–7.32 (m, 6 H, aromatic), 7.41–7.45 (m, 4 H, aromatic): IR (neat) 3425 (OH), 1661 (C=C) cm^{-1}; MS (15 eV), *m/e* 302 (M, 6%) 231 ($(PhS)_2CH^+$, 100%) 193 (M − PhS, 14%); exact mass calcd for $C_{17}H_{18}OS_2$, 302.0799; found, 302.0792.

B. In Ether. To a solution of 0,84 g (2.05 mmol) of **3** in 120 mL of ether was added *sec*-butyllithium (4.0 mL of 1.14 M solution, 4.6 mmol) at −78 °C. The yellow solution was stirred at −78 °C for 0.5 h, at −50 °C for 2.5 h and at 0 °C for 5 h before being quenched with 5 mL of water. Workup as above produced 0.86 g of crude product. Flash chromatography (elution first with a solution of 54 mL of ethyl acetate and 1146 mL of hexanes to remove the nonketonic products and then with 175 mL of ethyl acetate and 825 mL of hexanes to remove the ketones) provided, in addition to *sec*-butyl phenyl sulfide, 36 mg (9%) of *trans*-1-(phenylthio)pent-3-en-2-one (**5**), 55 mg (9%) of 1,4-bis(phenylthio)pentan-2-one(**6**), and 212 mg (30%) of *trans*-1,1-bis(phenylthio)-4,5-dimethyl-2-heptene (**7**) as a mixture of two diastereomers. The latter mixture was contaminated with traces of *sec*-butyl phenyl sulfide and another impurity. It could be further purified by reversed-phase MPLC (elution with 10% water in methanol).

6: ^{1}H NMR δ 1.23 (d, J = 6.67 Hz, 3 H, CH_3), 2.76 (dd, J = 17.18, 8.29 Hz, 1 H, $CHC\mathit{H}_2CO$), 2.89 (dd J = 17.18, 5.46 Hz, 1 H, $CHC\mathit{H}_2CO$), 3.63 (s) and 3.64 (s) (total 2 H, $C\mathit{H}_2SPh$), 3.67 (m, 1 H, $C\mathit{H}SPh$), 7.11–7.46 (m, 10 H, aromatic); IR (neat) 1702 (CO); MS (15 eV), *m/e* 302 (M, 36%), 193 (M − PhS, 100%); exact mass calcd for $C_{17}H_{18}OS_2$, 302.0799; found, 302.0792.

7: ^{1}H NMR ($CDCl_3$) δ 0.59 (d, J = 6.87 Hz) and 0.62 (d, J = 6.67 Hz) (total 3 H, CH_3C-5), 0.76 (d, J = 6.87 Hz, 3 H, H_3C-7), 0.80 (d, J = 6.87 Hz, 3 H, CH_3C-4), ~0.8–1.2 (m, 3 H, HC-5 and H_2C-6), 1.91–2.06 (m, 1 H, HC-4), 4.91 (m, 1 H, HC-1), 5.36 (m, 2 H, olefinic), 7.16–7.33 (m, 6 H aromatic), 7.42–7.48 (m, 4 H, aromatic). Irradiation at δ 2.0 caused the peak at δ 0.80 to collapse to a singlet. Irradiation at δ 1.1 caused the peaks at δ 0.59 and 0.62 to become singlets. The product from a similar reaction quenched with D_2O exhibited no peak at δ 4.91. The olefinic region of the spectrum was greatly simplified when the solvent was C_6D_6: δ 0.57 (d, J = 6.87 Hz) and 0.59 (d, J = 6.87 Hz) (total 3 H, CH_3C-5), 0.69 (d, J = 6.87 Hz, 1 H, H_3C-7), 0.74 (d, J = 6.87 Hz, 1 H, CH_3C-4), ~0.8–1.2 (m, 3 H, HC-5 and H_2C-6), 1.77–1.93 (m, 1 H, HC-4), 4.96 (d, J = 8.69 Hz, 1 H, HC-1), 5.29 (dd, J = 15.16, 8.08 Hz, 1 H, HC-3), 5.49 (dd, J = 15.16, 8.69 Hz, 1 H, HC-2), 6.94-6.98 (m, 6 H, aromatic), 7.02–7.47 (m, 4 H, aromatic). When the peak at δ 1.8 was irradiated, that at δ 5.29 became a broad doublet, J = 15.16 hz. In the spectrum of the 1-deuterio analogue in C_6D_6, the peak at δ 4.96 was absent and that at δ 5.49 became a doublet, J = 15.16 Hz; IR (neat) 1660 cm^{-1} (C=C); MS (15 eV), *m/e* 342 (M, 1%), 233 (M − PhS, 100%); exact mass calcd for $C_{21}H_{26}S_2$, 342.1476; found 342.1465; calcd for $C_{15}H_{21}S$ (M − PhS),

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[12] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[13] Seebach, D.; Geiss, K.-H.; Beck, A. K.; Graf. B.; Daum, H. *Chem. Ber.* **1972**, *105*, 3280.

233.1364; found, 233.1352. In a similar experiment, except that the solution was stirred at −50° C for 6 h before being quenched with water, 62% (69% based on consumed starting material) of 1,1-bis(phenylthio)pent-3-en-2-ol, 10% of recovered starting alcohol, and 8% of 7 were produced.

Acknowledgment. We thank the National Science Foundation for general support of this work (CHE 8210245) and for providing the funds for purchase of the 300-MHz Bruker NMR instrument used in this study (CHE 7905185). We also thank Dr. Alvin Marcus for recording the mass spectra.

Registry No. 1, 4170-30-3; 2, 14572-78-2; 3, 88130-66-9; 4, 88130-67-0; 4 (conjugate acid), 88130-75-0; 5, 88130-68-1; 6, 88130-69-2; (*E*)-(R^*,R^*)-7, 88130-71-6; (*E*)-(R^*,S^*)-7, 88130-70-5; (*E*)-(R^*,R^*)-7-*1-d*, 88130-77-2; (*E*)-(R^*,S^*)-7-*1-d*, 88130-76-1; 8, 88130-72-7; 10, 88130-73-8; *sec*-BuLi, 598-30-1; *sec*-BusPh, 14905-79-4; 4,4,4-tris(phenylthio)-3-methylbutanal, 88130-74-9; thioanisole, 100-68-5.

Ring Expansion of Ketones to 1,2-Keto Thioketals. Control of Bond Migration[1]

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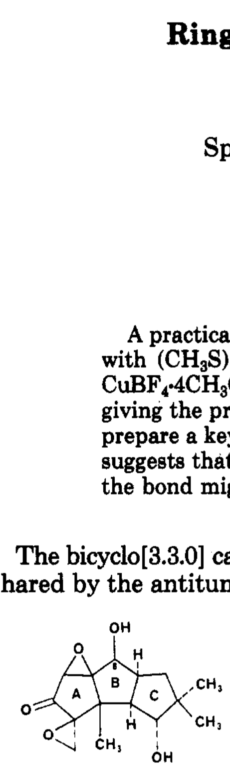
A practical two-step procedure for the title transformation has been developed. Treatment of cyclic ketones with $(CH_3S)_3CLi$ gave adducts 6 and 13–17, which underwent ring expansion at 75 °C in the presence of $CuBF_4{\cdot}4CH_3CN$ to the keto thioketals 7 and 18–21. In the cases examined the reaction was highly regioselective, giving the product resulting from migration of the more substituted carbon. The procedure has been used to prepare a key bicyclic intermediate (33) for a total synthesis of (±)-coriolin (1). An alternative synthesis of 33 suggests that where there is steric crowding in the vicinity of the tris(methylthio)methyl group of the adduct, the bond migration is controlled by the location of the obtruding group.



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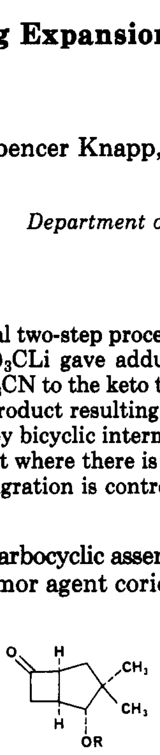

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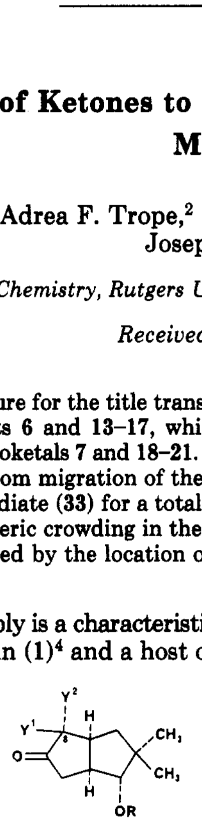
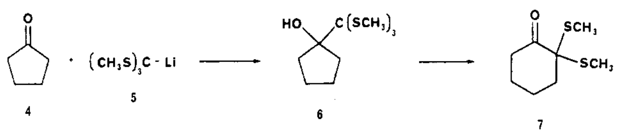


3

The bicyclo[3.3.0] carbocyclic assembly is a characteristic shared by the antitumor agent coriolin (1)[4] and a host of other sesquiterpenes.[5] A number of laboratories have recently produced methods for the construction of this ring system,[6] and a variety of total syntheses have appeared.[7,8] Our own efforts at a total synthesis of 1 were founded on the belief that a ring-expansion method could be developed for the transformation 2 → 3, wherein the unit CY^1Y^2 is inserted next to the carbonyl carbon in regioselective fashion.[9,10] Ideally Y^1 and Y^2 would be groups that block enolate formation at C-8 (coriolin numbering) and are removeable or convertible to the C-8 hydroxyl of 1. In the preliminary report[11] we reported the ring expansion of 2 to 3 where R = $COCH_3$ and $Y^1 = Y^2 = SCH_3$ or SPh. In this paper we present our optimized conditions for ring expansion of simple ketones and describe the efficient synthesis of 3 ($R = CH_2OCH_2CH_2SiMe_3$, $Y^1 = Y^2 = SCH_3$). We have also examined, in parallel synthetic sequences, the relative importance of electronic and steric influences on bond migration during the ring-expansion reaction.

Results

Model Studies. Treatment of cyclopentanone (4) with 1.5 equiv of tris(methylthio)methyllithium[12] (5) in tetrahydrofuran solution at −78 °C gave the adduct 6, which was isolated in 83% yield after chromatography or 78% yield after bulb-to-bulb vacuum distillation at 110 °C. IR and TLC analyses indicated that the only other product



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(1) This paper is dedicated to the memory of Paul D. Michna (1957–1982).

(2) Johnson and Johnson Industrial Fellow, 1982.

(3) (a) Henry Rutgers Undergraduate Scholar, 1980–1981. (b) Henry Rutgers Undergraduate Scholar, 1979–1980.

(4) (a) Takeuchi, T.; Iinuma, H.; Iwanaga, J.; Takahashi, T.; Takita, T.; Umezawa, H. *J. Antibiot.* **1969**, *22*, 215. (b) Takahashi, S.; Naganawa, H.; Iinuma, H.; Takita, T.; Maeda, K.; Umezawa, H. *Tetrahedron Lett.* **1971**, 1955. (c) Nakamura, H.; Takita, T.; Umezawa, H.; Kunishima, M.; Nakayama, Y.; Iitaka, Y. *J. Antibiot.* **1974** *27*, 301.

(5) For a recent compilation of references, see: Greene, A. E.; Luche, M.-J.; Depres, J.-P. *J. Am. Chem. Soc.* **1983**, *105*, 2435.

(6) For leading references, see: Schuda, P. F.; Ammon, H. L.; Heimann, M. R.; Bhattacharjee, S. *J. Org. Chem.* **1982**, *47*, 3434.

(7) Coriolin syntheses: (a) Tatsuta, K.; Akimoto, K.; Kinoshita, M. *J. Antibiot.* **1980**, *33*, 100; *Tetrahedron* **1981**, *37*, 4365. (b) Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3460. (c) Iseki, K.; Yamazaki, M.; Shibasaki, M.; Ikegami, S. *Tetrahedron* **1981**, *37*, 4411. (d) Trost, B. M.; Curran, D. P., *J. Am. Chem. Soc.* **1981**, *103*, 7380. (e) Mehta, G.; Reddy, A. V.; Murthy, A. N.; Reddy, D. S. *J. Chem. Soc., Chem. Commun.* **1982**, 540. (f) Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477.

(8) For leading references to syntheses of related sesquiterpenes, see: *Tetrahedron* **1981**, *37* and ref 5.

(9) Gutsche, C. D.; Redmore, D. "Carbocyclic Ring Expansion Reactions", Academic Press: New York, 1968.

(10) (a) Cohen, T.; Kuhn, D.; Falck, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 4749. (b) Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42*, 459. (c) Yamashita, M.; Onozuka, J.; Tsuchihashi, G.; Ogura, K. *Tetrahedron Lett.* **1983**, *24*, 79. (d) Taguchi, H.; Yamamoto, H.; Nozaki, H. *Ibid.* **1976**, 2617. (e) Smith, R. A. J.; Keng, G. S. *Ibid.* **1978**, 675 (footnote 10).

(11) Knapp, S.; Trope, A. F.; Ornaf, R. M. *Tetrahedron Lett.* **1980**, *21*, 4301.

(12) Seebach, D. *Angew, Chem., Int. Ed. Engl.* **1967**, *6*, 442, 443.

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