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Metalation of 1,3-Dithiolanes. Mercaptan Synthesis and Carbonyl Transposition

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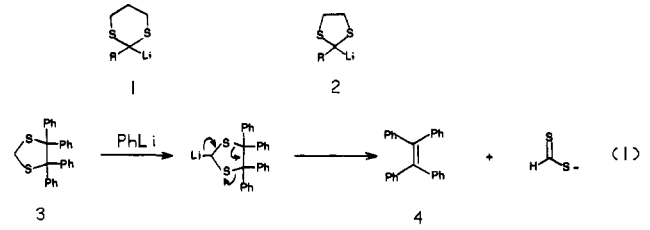
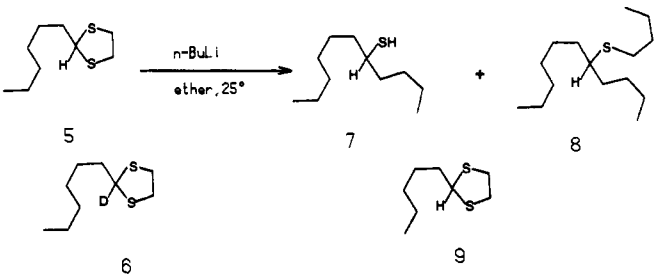
Abstract: The reaction of 1,3-dithiolanes with *n*-butyllithium results in fragmentation to the corresponding thiocarbonyl compound followed by further reaction with *n*-butyllithium. All four types of thiocarbonyl reactions are observed: reduction, S-addition, C-addition, double addition. Synthetic applications of this reaction for the synthesis of secondary mercaptans and 1,2-carbonyl transposition (**23** → **24a–c**) are described.

Umpolung[1] of carbonyl reactivity via 1,3-dithiane anions such as **1** has had substantial impact on synthetic organic chemistry. In contrast, anion **2** has been reported[2,3] to undergo facile elimination to form ethylene. This hypothesis was apparently based on the work of Schönberg[4] (eq 1), who showed



(1)

that compound **3** was cleaved with phenyllithium to tetraphenylethylene (**4**). Our results indicate that *the fragmentation shown in eq 1 is not the major mode of 1,3-dithiolane/n-butyllithium reaction.* When **5** was treated with 1 equiv of *n*-butyllithium in ether at −20 °C followed by D_2O (conditions under which the corresponding 1,3-dithiane is deuterated), no **6** could be detected by GC/MS. Excess (4 molar equiv) *n*-butyllithium in ether at 25 °C reacted with **5** to yield a product mixture (bp ~120 °C at 0.3 Torr, 91% yield) consisting of 73% **7** and 19% **8**. Thus 2-lithio-1,3-dithiolane is not formed under these conditions. The results of a number of reactions of **5** and **9** are summarized in Table I. There appears to be a solvent dependence, since **5** does not lead to significant cleavage in THF at 0 °C, conditions under which 2-lithio-1,3-dithiolane has been reported[6,7] to be stable.



Our mechanistic rationale[9] for the cleavage process is shown in Scheme I. All products obtained from this and subsequent

Scheme I

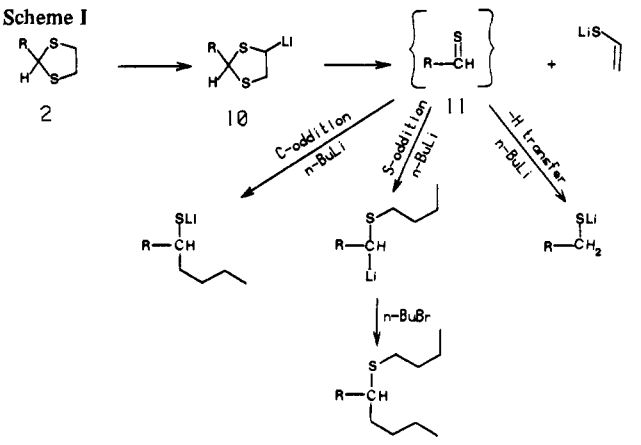


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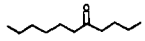
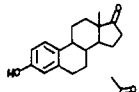
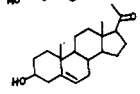
Table I. Cleavage of Thioacetals with *n*-Butyllithium

 compd	*n*-BuLi, mol	temp, °C/time, min	solvent	RCH_2SH, %	RCH(SH)-*n*-Bu, %	RCH_2S-*n*-Bu, %	 %	RCH(S-*n*-Bu)-*n*-Bu, %
5	1.0	−20/30	ether	0.3	7	2	86	2
5	1.0	0/30	ether	1	17	4	74	2
5	1.0	0/30	THF	1	2	4	92	
5	4.0	25/240	ether	3	73	4		19
9	4.0	25/240	ether	2	67	7		22

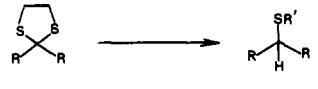
Table II. Synthesis of Mercaptans from Thioketals

Entry	Ketone (Thioketal, 12)	% Thiol (13a)	% Methyl Sulfide[a] (13b)
1.		90	84
2.		79	99
3.		81[b]	90
4.		93	--
5.		90[c]	95[c]
6.		78[b]	98
7.		36[d]	--
8.		93[e]	--
9.		65[e]	--

[a] By quenching with CH_3I. [b] Simple distillation could not cleanly separate thiol from *n*-octane (present in commercially available *n*-BuLi). Yields include thiol in fractions containing *n*-octane. Yields of pure, octane-free fractions were 30–40% lower than those listed in table. [c] Axial/equatorial ratio 40:60. [d] By extraction in base (purity 85–93%). [e] A mixture of isomers by capillary VPC (SE-52).

reactions can be explained by involving initial cleavage to thiocarbonyl[13] compound **11** followed by reaction with excess alkyllithium.[14,15] The cleavage reaction appears to be general and we now describe two synthetic applications of this process.

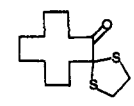
Mercaptan Synthesis. Thioketals of saturated ketones **12** were cleaved under these conditions (2–4 equiv of *n*-BuLi, ether, 25 °C) to give secondary mercaptans **13a** (the result of



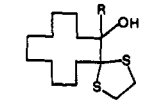
12 → 13a R′=H; 13b R′=CH_3

reduction[16] of the thiocarbonyl with *n*-butyllithium) in good yields (Table II). Sulfides **13b** could be obtained by quenching the reaction mixture with methyl iodide. Only traces of the products which arise from other pathways in Scheme I were detected. The thioketal of acetophenone (entry 7) cleaved to a more complex mixture from which the product mercaptan could be obtained by base extraction. The synthesis of secondary mercaptans of the type in Table II is not easy,[17] this route being the method of choice in many cases. Obviously, compatibility with strong metalating conditions is a limitation of this method.

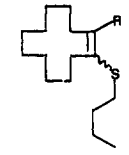
Carbonyl Transposition. This new 1,3-dithiolane cleavage reaction offers a unique approach to 1,2-carbonyl transposition.[19] When α-ketodithiolane **14**[20c] is treated with 4 molar equiv of *n*-butyllithium, **16c** is formed cleanly as the only nonpolar product in 38% yield.[25] Alcohols **15a** and **15b** give



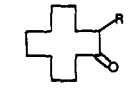
14



15a R=H
15b R=CH_3
15c R=$(CH_2)_3CH_3$

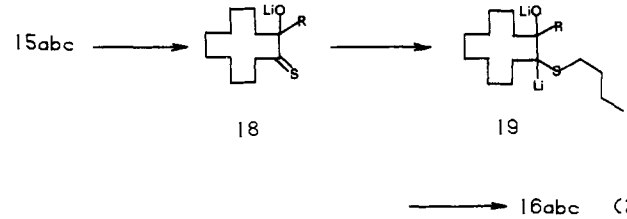


16a R=H
16b R=CH_3
16c R=$(CH_2)_3CH_3$

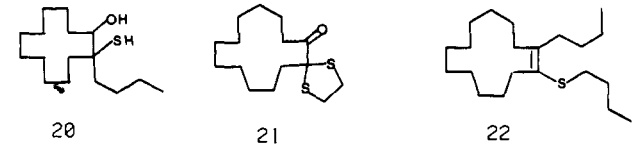


17a R=H
17b R=CH_3
17c R=$(CH_2)_3CH_3$

16a (30%) and **16b** (65%), respectively. The origin of these products follows closely the mechanistic scheme outlined above. Fragmentation (eq 2) of **15a–c** to thiocarbonyl com-



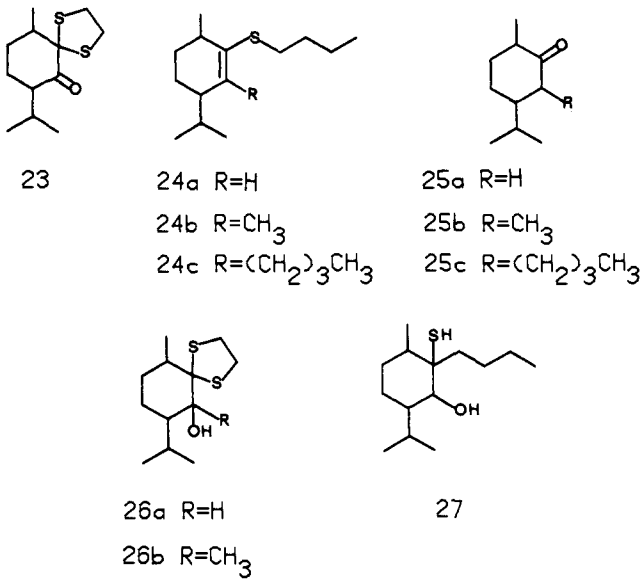
15abc → 18 → 19 → 16abc (2)



20 21 22

pound **18** followed by S-addition should give anion **19**, which would be expected[21] to eliminate the elements of lithium oxide. In support of this scheme, the lower yielding reaction of **15a** → **16a** also gave **20** (23%), the result of competing C-addition due to the less hindered environment of the thiocarbonyl carbon (when R = H). Hydrolysis of vinyl sulfides[22] **16a–c** gave the corresponding ketones **17a–c** in good yield. The homologous system **21** also gave vinyl sulfide **22** in 55% yield.[20c,25]

When the α-ketodithiolane **23** (derived from menthone)[20b] was treated with excess *n*-butyllithium, vinyl sulfide **24c** was formed in 63% yield. Hydrolysis gave the 1,2-transposed ketone

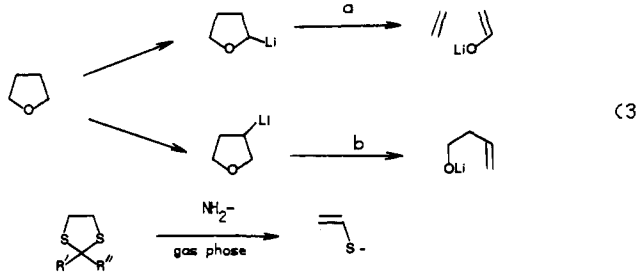


23 24a R=H 24b R=CH_3 24c R=$(CH_2)_3CH_3$ 25a R=H 25b R=CH_3 25c R=$(CH_2)_3CH_3$

26a R=H 26b R=CH_3 27

25c. Methyllithium adds to **23** in high yield, giving alcohol **26b** which can be transformed into **24b** (52% overall) under the cleavage conditions. Hydrolysis of **24b** of course yields **25b.** When **23** was reduced to the secondary alcohol **26a,** however, the *n*-butyllithium cleavage yields **27** as the major product (41%) with only 14% of the vinyl sulfide **24a** formed.

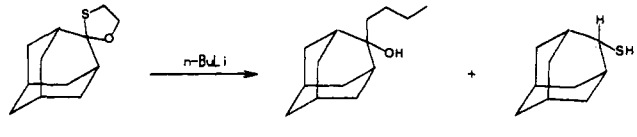
Mechanistic Considerations. Cleavages of cyclic ethers such as THF have been known for some time and have been reviewed.[9b] In general α-attack and cleavage is most favorable, that is, fragmentation via Woodward-Hoffman allowed [$_\pi 4_s + {}_\pi 2_s$] cycloreversion (eq 3a) rather than E2-type elimination (eq 3b).



(3)

28a R′=R″=H 28b R′=CH_3, R″=H 28c R′=R″=CH_3 29

We have shown that **28a–c** cleave with strong base in the gas phase (ICR spectrometer) yielding thioacetaldehyde anion **29** as the major product.[23] 1,3-Dithiane, however, forms the expected M − 1 ion in the gas phase and 2,2-dideuterio-1,3-dithiane forms the expected M − 2 ion. We have also examined the cleavage of oxathioketal **30** under our conditions (3 equiv of *n*-BuLi, ether, 25 °C). Cleavage occurred via "metalation" next to sulfur, rather than oxygen, subsequently yielding alcohol **31.** Less than 1% **32** was detected.



30 31 32

In summary, the cleavage of dithiolane thioacetals with *n*-butyllithium is a general method for the production of thiocarbonyl compounds in situ. Subsequent reactions with the excess *n*-butyllithium present depend on the substrate giving predominantly C-addition in unhindered cases (aldehyde precursors), reduction for unsubstituted ketones, or S-addition in α-alkoxide substituted examples. This methodology provides an excellent route to secondary mercaptans and a reasonable process for 1,2-carbonyl transposition via α-ketodithiolanes.

Experimental Section

All reactions were carried out under a nitrogen or argon atmosphere. Melting points were obtained on a Thomas capillary melting point apparatus and are uncorrected. Boiling points are uncorrected.

Infrared (IR) spectra were obtained using a Perkin-Elmer Infracord Model 137 spectrometer. Proton nuclear magnetic resonance (NMR) spectra were obtained using a Varian T-60A and/or a Varian HR-220 spectrometer. All chemical shifts were measured relative to an internal standard, tetramethylsilane (Me_4Si). Elemental combustion analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Mass spectral analyses were obtained on a Hewlett-Packard 5992-A GC/MS, or at the NIH Mass Spectral Center at Michigan State University, East Lansing, Mich.

Analytical TLC analyses were determined using J. T. Baker Baker-flex (silica gel 1B-F) sheets. Preparative TLC separations were performed using Analtech precoated plates (silica gel GF, 2000 μm). Short-column chromatography was performed using EM Laboratories, Inc., silica gel G (Type 60) containing a $CaSO_4$ binder. Vapor phase (VPC) analyses were performed on a Varian Model 3700 gas chromatograph with FID (5 ft × $\frac{1}{8}$ in. 5% OV-101 on Chromosorb G); capillary VPC analyses employed a 25 m × 0.28 mm SE-52 glass column. Preparative gas chromatography was performed on a Varian Aerograph Model 920 on a 20% OV101 on Chromosorb W column (5 ft × $\frac{1}{4}$ in.).

All chemicals used were commercial samples unless reference is given to their purification or preparation. THF and ether were distilled from $LiAlH_4$.

Reactions of 5 and 9 with *n*-Butyllithium (Table I). To a solution of 1.3–1.6 mmol of thioacetal **5** or **9** in 8 mL of dry ether was added a 1–4 equiv hexane solution of *n*-butyllithium (Table I) by syringe at the temperature indicated. The mixture was stirred for the time indicated, then quenched with 1 mL of water. The reaction mixture was diluted with water and extracted several times with ether. The combined ether extracts were washed with water and saturated sodium chloride solution and then dried over anhydrous magnesium sulfate. Removal of the solvent left a light pink oil which was analyzed by GC and GC/MS as indiated in Table I. Authentic samples of all products were available for direct comparison by GC/MS. No incorporation of deuterium (**6**) in recovered starting material was observed by NMR or MS when the reaction was quenched with D_2O.

5-(*S*-*n*-Butylmercapto)undecane. To a solution of 0.27 g (0.0014 mol) of 5-mercaptoundecane in 10 mL of dry ether was added 0.71 mL (0.0017 mol) of *n*-butyllithium solution by syringe at −40 °C under argon. After the addition, the reaction mixture was stirred at −40 °C for 15 min and then 0.5 mL of HMPA was added followed by 1.5 mL (0.014 mol) of 1-bromobutane. The reaction mixture was then allowed to warm to room temperature and stirred for an additional 30 min. After quenching with water and extraction several times with ether, the combined ether extracts were washed with water, dilute KOH solution, and NaCl solution and dried over anhydrous magnesium sulfate. Removal of solvent gave 0.33 g (95.2%) of yellow oil: NMR ($CDCl_3$) δ 0.8–2.03 (m, 30 H) and 2.33–2.6 (m, 2 H). Exact mass: calcd for $C_{15}H_{32}S$, 244.222 05; found, 244.222 47.

***n*-Butyl Heptyl Sulfide.** To a solution of 0.66 g (0.005 mol) of *n*-heptanethiol in 10 mL of dry ether was added 2.3 mL (0.0055 mol) of *n*-butyllithium in hexane through syringe. After the addition, the reaction mixture was stirred for 10 min and then 1.0 mL of HMPA was added. The reaction mixture was cooled to −20 °C and 2.7 mL (0.025 mol) of 1-bromobutane was added. The mixture was then warmed to room temperature while stirring for 15 min, quenched with water, and extracted several times with ether. The combined ether extracts were washed with water, dilute KOH solution, 1 N HCl solution, and salt solution and dried over anhydrous magnesium sulfate. Removal of solvent followed by distillation (Kugelrohr, bp 100–120 °C (1 mm)) gave 0.8 g (85%) of colorless oil: NMR ($CDCl_3$) δ 0.8–2.06 (m, 20 H) and 2.36–2.63 (m, 4 H). Exact mass: calcd for $C_{11}H_{24}S$, 188.1597; found, 188.1598.

Reaction of 30 with *n*-Butyllithium. In the same manner as de-

scribed above, 0.38 g (0.0018 mol) of **30** in ether and 3.05 mL (0.0073 mol) of *n*-butyllithium in hexane at 25 °C for 18 h gave 0.58 g of semisolid. Purification by short-column chromatography (50 g of silica gel) using hexane and 5% ether as eluent gave (0.02%) adamantanethiol **31** and compound **32** (78.4%), respectively.

General Procedure for the Synthesis of Ethylene Thioketals (See Table II). To a solution of the ketone in benzene were added 1 equiv of 1,2-ethanedithiol and a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was azeotropically distilled until the theoretical amount of water was collected and then poured into water. The organic layer was separated, dried ($MgSO_4$ or Na_2SO_4), and concentrated. Liquids were distilled under reduced pressure in a Kugelrohr apparatus.

Thioketal of Cyclododecanone (Entry 1). From 46.5 g (0.26 mmol) of cyclododecanone was recovered 66 g (>99%) of a white solid: mp 84–86 °C; IR ($CHCl_3$) 3.42, 6.82, 6.94 μ; NMR (CCl_4) δ 1.34 (s, 18 H), 1.93 (crude t, 4 H), 3.18 (s, 4 H); mass spectrum *m/e* (rel intensity) 258 (M^+, 35), 230 (18), 197 (28), 131 (100), 55 (21), 41 (27). Exact mass: calcd for $C_{14}H_{26}S_2$, 258.147 58; found, 258.146 48.

Thioketal of 2-Adamantanone (Entry 2). From 16 g (0.11 mmol) of 2-adamantanone was recovered 23 g (92%) of colorless crystals after recrystallization (absolute ethanol): mp 55–55.5 °C; IR (CCl_4) 3.40, 6.90, 7.86, 9.11, 9.62 (weak), 10.40 μ; NMR (CCl_4) δ 1.53–2.47 (broad m, 14 H), 3.23 (s, 4 H); mass spectrum *m/e* (rel intensity) 226 (M^+, 67), 198 (100), 166 (14), 165 (15), 133 (34), 105 (16), 91 (32). Exact mass: calcd for $C_{12}H_{18}S_2$; 226.084 99; found, 226.084 94.

Thioketal of 4-Heptanone (Entry 3). From 5 g (44 mmol) of 4-heptanone was recovered 8.15 g (98%) of a light yellow oil: IR (neat) 3.36, 6.85, 7.25, 7.85, 8.78, 10.25 (weak), 11.70, 13.00 μ; NMR (CCl_4) δ 0.77–1.10 (m, 6 H), 1.17–2.07 (m, 8 H), 3.20 (s, 4 H); mass spectrum *m/e* (rel intensity) 190 (M^+, 26), 147 (100), 105 (31), 87 (23), 61 (20), 59 (25), 55 (24), 45 (30), 41 (40). Exact mass: calcd for $C_9H_{18}S_2$, 190.084 99; found, 190.083 15.

Thioketal of 5-Undecanone (Entry 4). From 1.72 g (10 mmol) of 5-undecanone after bulb-to-bulb distillation (bp ~150–160 °C (0.3 mm)) was recovered 2.1 g (85%) of a clear liquid: IR (neat) 3.36, 6.90, 7.30 (weak), 8.89 (weak) μ; NMR ($CDCl_3$) δ 0.90–2.10 (m, 22 H), 3.26 (s, 4 H); mass spectrum *m/e* (rel intensity) 246 (M^+, 11), 211 (15), 189 (100), 161 (78), 105 (21), 85 (20), 71 (25), 69 (26), 57 (41), 55 (38), 43 (60). Exact mass: calcd for $C_{13}H_{26}S_2$, 246.147 58; found, 246.147 08.

Thioketal of 4-*tert*-Butylcyclohexanone (Entry 5). From 2 g (13 mmol) of 4-*tert*-butylcyclohexanone was recovered 2.9 g (98%) of a white solid: mp 59.5–61.5 °C; IR (CCl_4) 3.42, 6.76, 6.94, 7.02, 7.19 (weak), 7.33, 7.81, 8.47, 9.80 μ; NMR (CCl_4) δ 0.87 (s, 9 H), 1.17–2.33 (broad m, 9 H), 3.23 (s, 4 H); mass spectrum *m/e* (rel intensity) 230 (M^+, 30), 202 (5), 170 (7), 131 (100), 79 (11), 57 (29), 41 (21), 29 (8). Exact mass: calcd for $C_{12}H_{22}S_2$, 230.116 29; found, 230.116 25.

Thioketal of Cyclohexanone[26] (Entry 6). From 4.9 g (50 mmol) of cyclohexanone was recovered 8.5 g (98%) of a yellow oil: IR (neat) 3.43, 6.94, 7.87, 9.90, 13.19 μ; NMR ($CDCl_3$) δ 1.45–2.15 (m, 10 H), 3.16 (s, 4 H).

Thioketal of Acetophenone (Entry 7). From 12 g (98 mmol) of acetophenone was recovered 19 g (99%) of a clear liquid: IR (neat) 3.28, 3.44, 6.28, 6.71, 6.99, 7.30, 7.86, 13.00, 14.35 μ; NMR ($CDCl_3$) δ 2.06 (s, 3 H), 3.28 (s, 4 H), 7.05–7.71 (m 5 H); mass spectrum *m/e* (rel intensity) 196 (M^+, 39), 181 (70), 167 (69), 136 (27), 121 (100), 103 (45), 77 (36), 59 (23).

Thioketal of Estrone (Entry 8). From 2 g (3.7 mmol) of estrone was recovered 2.27 g (99%) of a white solid: mp 141–143 °C; IR (KBr pellet) 2.91 (strong), 3.40, 6.20, 6.31, 6.70, 6.90, 7.80, 8.02, 10.91, 11.50, 12.22, 12.71 μ; NMR ($CDCl_3$) δ 0.93 (s, 3 H), 1.14–2.59 (m, 13 H), 2.64–2.82 (m, 2 H), 3.05–3.27 (m, 4 H), 4.91 (broad s, 1 H), 6.43–6.59 (m, 3 H), 7.02–7.18 (m, 2 H); mass spectrum *m/e* (rel intensity) 346 (M^+, 32), 318 (37), 285 (7), 253 (31), 226 (56), 213 (59), 131 (100), 69 (40). Anal. Calcd for $C_{20}H_{26}OS_2$: C, 69.32; H, 7.56; S, 18.50. Found: C, 69.06; H, 7.55; S, 18.53.

Thioketal of Pregnenolone (Entry 9). From 1 g (3.2 mmol) of pregnenolone was recovered 1.1 g (89%) of a white powder (wide melting range)[24] after recrystallization (acetone): IR ($CHCl_3$) 2.90, 3.40, 6.25 (weak), 6.95, 7.29 μ; NMR ($CDCl_3$) δ 0.80 (s, 3 H), 1.00 (s, 3 H), 1.86 (s, 3 H), 0.75–2.43 (broad m, 21 H, overlapping with s at 0.80, 1.00, and 1.86 ppm), 3.09–3.41 (m, 4 H), 3.55 (m, 1 H), 5.32 (m, 1 H); mass spectrum *m/e* (rel intensity) 392 (M^+, 14), 145 (11), 131 (12), 121 (59), 119 (100), 107 (12), 105 (15), 91 (23), 81 (16), 79 (17), 67 (14), 61 (16), 59 (23), 55 (19), 44 (21). Exact mass: calcd for $C_{23}H_{36}OS_2$, 392.220 76; found, 392.219 82.

General Procedure for the Synthesis of Mercaptans (13a) from Ethylene Thioketals (Table II). To a solution of ethylene thioketal was added 3–4 equiv of *n*-butyllithium at room temperature, or at 0 °C, and then the mixture was allowed to warm to room temperature. The reaction mixture was stirred overnight (the reaction was usually complete within about 6 h) and then carefully quenched with H_2O. The mixture was poured into water and shaken, and the organic layer was separated, dried ($MgSO_4$ or Na_2SO_4), and concentrated.

Cyclododecyl Mercaptan. From 25.8 g (0.1 mol) of the thioketal of cyclododecanone (entry 1) after distillation (103–108 °C (1 mm)) was recovered 17.9 g (90%) of a liquid with a slight pinkish tinge: IR (neat) 3.40, 3.70 (weak), 6.82, 6.94, 7.46 (weak), 8.03 (weak), 14.00 μ; NMR (CCl_4) δ 1.14–1.18 (d, 1 H, J = 6 Hz), 1.32 (broad s, 20 H), 1.64–1.82 (m, 2 H), 2.73–2.91 (m, 1 H); mass spectrum *m/e* (rel intensity) 200 (M^+, 11), 173 (30), 166 (49), 96 (54), 82 (61), 69 (51), 67 (48), 60 (62), 55 (100), 41 (86). Exact mass: calcd for $C_{12}H_{24}S$, 200.159 88; found, 200.159 71. Anal. Calcd for $C_{12}H_{24}S$: C, 71.93; H, 12.07; S, 16.00. Found: C, 71.71; H, 11.94; S, 16.08.

2-Adamantanethiol.[27] From 22.6 g (0.1 mol) of the thioketal of 2-adamantanone (entry 2) after recrystallization (ethanol) was recovered 13.2 g (79%) of a white solid: mp 139–142 °C; IR (CCl_4) 3.42, 3.75 (weak), 6.84, 6.92, 6.97, 7.41, 7.78, 9.21, 10.42 μ; NMR (CCl_4) δ 1.41 (d, 1 H, J = 6 Hz), 1.47 (broad s, 1 H), 1.53 (broad s, 1 H), 1.72 (broad s, 2 H), 1.79 (broad, 8 H), 2.15 (broad s, 1 H), 2.20 (broad, 1 H), 3.30 (broad d, 1 H, J = 7 Hz); mass spectrum *m/e* (rel intensity) 168 (M^+, 41), 135 (100), 93 (38), 91 (33), 79 (52), 77 (26), 67 (41), 41 (40). Exact mass: calcd for $C_{10}H_{16}S$, 168.097 27; found, 168.097 21. Anal. Calcd for $C_{10}H_{16}S$: C, 71.37; H, 9.58; S, 19.05. Found: C, 71.02; H, 9.64; S, 18.93.

4-Heptyl Mercaptan. From 3.954 g (20.81 mmol) of the thioketal of 4-heptanone (entry 3) after distillation was recovered a clear liquid in two fractions. Fraction 1 (750 mg, bp 130–140 °C) was shown by VPC analysis (OV101, 80 °C) to contain 15% octane, 85% product, and fraction 2, 1.6 g (58%) of a clear liquid, bp 143–147 °C (VPC analysis showed only product) had IR (neat) 3.39, 6.88, 7.30, 7.90, 8.35, 13.10, 13.40 μ; NMR (CCl_4) δ 0.67–1.75 (characteristic m, 15 H), 2.70 (broad, 1 H); mass spectrum *m/e* (rel intensity) 132 (M^+, 48), 98 (17), 89 (30), 70 (29), 69 (30), 57 (100), 56 (62), 55 (100), 47 (49), 43 (49), 41 (83), 29 (43), 27 (55). Exact mass: calcd for $C_7H_{16}S$, 132.097 27; found, 132.097 46.

5-Mercaptoundecane. From 1.23 g (5 mmol) of the thioketal of 5-undecanone (entry 4) after distillation (~110–120 °C, 0.3 mm) was recovered 880 mg (93%) of a pale yellow oil: IR (neat) 3.45, 6.85, 7.25, 13.75 μ (weak); NMR ($CDCl_3$) δ 0.66–1.73 (m, 23 H), 2.73 (broad s, 1 H); mass spectrum *m/e* (rel intensity) 188 (M^+, 9), 154 (7), 111 (8), 97 (20), 85 (20), 84 (16), 83 (17), 71 (31), 70 (36), 69 (68), 61 (10), 60 (20), 57 (82), 56 (55), 55 (100). Exact mass: calcd for $C_{11}H_{24}S$, 188.159 88; found, 188.159 77.

4-*tert*-Butylcyclohexyl Mercaptan. From 500 mg (2.17 mmol) of the thioketal of 4-*tert*-butylcyclohexanone (entry 6) after distillation (bp ~80 °C (0.5 mm)) was recovered 335 mg (90%) of a clear oil (a mixture of axial and equatorial isomers): IR (neat) 3.41, 6.76, 6.82, 6.90, 7.19, 7.33 μ; NMR (CCl_4) δ 1.73 (d, 9 H, J = 6 Hz), 1.07–2.09 (m, 6 H), 2.55 (m, 3/5 H), 3.39 (m, 2/5 H); mass spectrum *m/e* (rel intensity) 172 (M^+, 40), 138 (19), 123 (17), 115 (22), 95 (11), 81 (62), 67 (31), 57 (100), 41 (42). Exact mass: calcd for $C_{10}H_{20}S$, 172.128 57; found, 172.128 65.

Cyclohexyl Mercaptan. From 5.2 g (30 mmol) of the thioketal of cyclohexanone (entry 6) after distillation was recovered 2.55 g (73%) of cyclohexyl mercaptan identical with an authentic sample (Aldrich Chemical Co.).

α-Methylbenzyl Mercaptan.[28] The crude reaction mixture was washed with water and the aqueous layer was separated, acidified with concentrated HCl solution, and extracted with ether. From 3.92 g (20 mmol) of the thioketal of acetophenone (entry 7) after distillation (bp 70–75 °C (0.5 mm)) was recovered 500 mg (36%) of a colorless oil: NMR ($CDCl_3$) δ 1.65 (d, 3 H, J = 7 Hz), 1.95 (d, 1 H, J = 5 Hz), 2.53 (qd, J = 7, 5 Hz), 7.1–7.4 (m, 5 H).

Estrone-17-thiol.[29] From 346 mg (1 mmol) of the 17-thioketal of estrone (entry 8) after preparative TLC on silica gel (10% ethyl acetate/benzene) was recovered 267 mg (93%) of an air-sensitive yellow solid: mp 170–175 °C (capillary VPC analysis, SE-52, 100–250 °C, indicates a mixture of 17α- and 17β-thiol isomers); IR (KBr pellet) 2.95 (broad), 3.45, 6.20, 6.39, 6.71, 6.98, 7.50, 7.85, 8.29, 8.75, 11.0,

11.60, 12.90 μ; NMR ($CDCl_3$) δ 1.68–2.95 (characteristic m, 20 H), 4.61 (broad s, 1 H), 6.73–6.84 (m, 2 H), 7.11 (s, 1 H); mass spectrum *m/e* (rel intensity) 288 (M^+, 20), 213 (32), 160 (43), 159 (38), 158 (19), 157 (37), 133 (44), 131 (30), 115 (31), 107 (38) 91 (43), 79 (43), 77 (48), 55 (55), 53 (38), 41 (100). Exact mass: calcd for $C_{18}H_{24}OS$, 288.154 81; found, 288.154.

Pregnenolone-20-thiol. From 250 mg (0.64 mmol) of the 20-thioketal of pregnenolone (entry 9) after preparative TLC on silica gel ($CHCl_3$) was recovered 140 mg (65%) of a light pink solid (wide melting range, capillary VPC analysis, SE-52, 100–250 °C, indicated a mixture of at least two isomers): IR ($CHCl_3$) 2.90, 3.48, 6.25 (weak), 6.95, 7.35 μ; NMR (CCl_4) δ 0.59–2.90 (characteristic m, 32 H), 3.32 (m, 1 H), 5.23 (m, 1 H); mass spectrum *m/e* (rel intensity) 334 (M^+, 55), 319 (13), 316 (23), 301 (26), 300 (20), 283 (16), 271 (23), 267 (25), 249 (21), 159 (19), 133 (23), 121 (21), 119 (24), 107 (40), 105 (42), 91 (54), 79 (54), 67 (43), 57 (52), 55 (92), 43 (76), 41 (100). Exact mass: calcd for $C_{21}H_{30}OS$, 334.233 05; found, 334.233.

General Procedure for Synthesis of Methyl Sulfides (13b) from Ethylene Thioketals (Table II). The identical procedure used in the mercaptan synthesis (**13a**) was employed, except that after overnight stirring the reaction mixture was cooled to −78 °C and HMPA (dried by distillation from calcium hydride) was added such that a 5% HMPA solution was obtained, followed by a large excess of methyl iodide. The reaction mixture was allowed to warm to room temperature followed by the workup procedure described earlier.

Cyclododecyl Methyl Sulfide. From 1 g (3.88 mol) of the thioketal of cyclododecanone (entry 1) after short-column chromatography (hexane) was recovered 700 mg (84%) of a clear oil: IR (neat) 3.40, 6.83, 6.94, 7.43 (weak), 8.03 (weak), 13.89 μ; NMR (CCl_4) δ 1.33 (broad s, 22 H), 1.99 (s, 3 H), 2.57 (broad m, 1 H); mass spectrum *m/e* (rel intensity) 214 (M^+, 33), 199 (67), 166 (37), 97 (27), 96 (47), 95 (26), 83 (42), 82 (34), 69 (40), 68 (32), 67 (48), 55 (88), 41 (100). Exact mass: calcd for $C_{13}H_{26}S$, 214.175 52; found, 214.175 60.

2-Adamantyl Methyl Sulfide. From 1 g (4.42 mmol) of the thioketal of 2-adamantanone (entry 2) after distillation (90 °C (0.5 mm)) was recovered 795 mg (99%) of a clear liquid: IR (neat) 3.45, 6.82, 6.92, 7.41, 7.78, 8.20, 9.17, 10.42 μ; NMR (CCl_4) δ 1.45 (broad s, 1 H), 1.51 (broad s, 1 H), 1.68–1.98 (m, 10 H), 2.02 (s, 3 H), 2.11 (broad s, 1 H), 2.17 (broad s, 1 H), 2.85 (s, 1 H); mass spectrum *m/e* (rel intensity) 182 (M^+, 81), 135 (100), 107 (16), 93 (25), 79 (40), 67 (38), 41 (24). Exact mass: calcd for $C_{11}H_{18}S$, 182.112 93; found, 182.112 95.

4-Heptyl Methyl Sulfide. From 2 g (10.5 mmol) of the thioketal of 4-heptanone (entry 3) after distillation (~40 °C (5 mm)) was recovered 1.38 g (90%) of a clear liquid: IR (neat) 3.39, 6.85, 7.30, 8.05, 8.41, 10.50 μ; NMR (CCl_4) δ 0.91 (m, 6 H), 1.44 (m, 8 H), 1.94 (s, 3 H), 2.39 (broad, 1 H); mass spectrum *m/e* (rel intensity) 146 (M^+, 51), 103 (71), 61 (100), 57 (68), 41 (69), 27 (44). Exact mass: calcd for $C_8H_{18}S$, 146.112 92; found, 146.112 96.

(4-*tert*-Butyl)cyclohexyl Methyl Sulfide. From 500 mg (2.17 mmol) of the thioketal of 4-*tert*-butylcyclohexanone (entry 5) after distillation (100 °C (0.5 mm)) was recovered 383 mg (95%) of a clear liquid (capillary VPC analysis, OV101, programmed from 100 to 150 °C showed this to be a 40:60 mixture of axial:equatorial isomers): IR (neat) mixture of isomers 3.41, 6.80, 6.85, 6.94, 7.22, 7.35 μ; NMR (CCl_4) axial isomer (separated by preparative VPC, OV101, 140 °C) δ 0.94 (s, 9 H), 1.20–1.91 (m, 9 H), 1.96 (s, 3 H), 2.91 (m, 1 H); equatorial isomer δ 0.92 (s, 9 H), 0.95–1.27 (m, 6 H), 1.80 (m, 2 H), 1.98 (s, 3 H), 2.05 (broad, 1 H), 2.34 (tt, 1 H, J = 12, 4 Hz); mass spectrum *m/e* (rel intensity) (axial isomer) 186 (M^+, 68), 171 (4), 138 (32), 123 (22), 110 (19), 95 (16), 81 (100), 67 (30), 57 (83), 41 (39); (equatorial isomer) 186 (M^+, 83), 171 (11), 138 (35), 129 (49) 123 (35), 110 (10), 95 (48), 81 (100), 67 (28), 57 (80), 41 (51). Exact mass: calcd for $C_{11}H_{22}S$, 186.144 23; found, 186.144 29.

Cyclohexyl Methyl Sulfide. From 870 mg (5.12 mmol) of the thioketal of cyclohexanone (entry 6) was recovered 640 mg (98%) of a yellow oil: IR (neat) 3.38, 6.85, 7.40 (weak), 7.85, 8.25, 9.91, 10.39, 11.22 μ; NMR ($CDCl_3$) δ 0.85–2.10 (m, 12 H), 2.07 (s, 3 H), 2.53 (broad s, 1 H); mass spectrum *m/e* (rel intensity) 130 (M^+, 18), 97 (11), 87 (11), 83 (52), 82 (68), 81 (24), 69 (17), 67 (83), 57 (20), 55 (100). Exact mass: calcd for $C_7H_{14}S$, 130.081 62; found, 130.081 61.

1,4-Dithiaspiro[4.11]hexadecan-6-ol (15a). From 405 mg (1.49 mmol) of 1,4-dithiaspiro[4.11]hexadecan-6-one (**14**) after $LiAlH_4$ reduction in ether and recrystallization from aqueous ethanol was recovered 360 mg (88%) of colorless needles, mp 110–112 °C.[20c]

***n*-Butyllithium Reaction of 14.** To a solution of 100 mg (0.37 mmol) of 1,4-dithiaspiro[4.11]hexadecan-6-one (**14**) in 5 mL of ether at 0 °C was added 0.60 mL (1.47 mmol, 2.45 M in *n*-hexane) of *n*-butyllithium. After warming to room temperature the reaction mixture was stirred for 5 h, then poured into 10 mL of water overlaid with 10 mL of ether. The organic layer was separated, dried (Na_2SO_4), and concentrated. Preparative TLC on silica gel (5% ether/pentane) yielded 44 mg (38%) of a pale yellow oil (**16c**): IR (neat) 3.45, 6.85, 7.27, 8.20, 13.89 μ; NMR (CCl_4) δ 0.89 (m, 6 H), 1.34 (broad, 24 H), 2.09 (t, 2 H, J = 6 Hz), 2.14–2.32 (m, 4 H), 2.41 (crude t, 2 H, J = 6 Hz); mass spectrum *m/e* (rel intensity) 310 (M^+, 50), 267 (9), 253 (78), 109 (20), 95 (36), 81 (47), 67 (47), 55 (68), 41 (100). Exact mass: calcd for $C_{20}H_{38}S$, 310.269 44; found, 310.269 29.

***n*-Butyllithium Reaction of 15a.** To a solution of 306 mg (1.13 mmol) of 1,4-dithiaspiro[4.11]hexadecan-6-ol (**15a**) in 10 mL of ether at 0 °C was added 1.65 mL (3.96 mmol, 2.4 M in *n*-hexane) of *n*-butyllithium. After warming to room temperature the reaction mixture was stirred for 3 h and poured into 20 mL of water overlaid with 10 mL of ether. The organic layer was separated, dried (Na_2SO_4), and concentrated. Preparative TLC on silica gel (5% ether/pentane) gave a band at lower R_f, 72 mg (23%) of a pale yellow oil (**20**), which upon cooling solidified to a white solid [mp 84–87 °C; IR (neat) 2.92, 3.45, 6.90, 9.52, 13.70 μ; NMR (CCl_4) δ 0.93 (crude t, 3 H), 1.09 (s, 1 H), 1.14–1.86 (broad, 27 H), 3.36–3.50 (m, 1 H); mass spectrum *m/e* (rel intensity) 272 (M^+, 15), 254 (10), 238 (27), 215 (9), 195 (17), 182 (22), 98 (35), 97 (29), 95 (30), 83 (37), 81 (37), 69 (47), 67 (41), 55 (100). Exact mass: calcd for $C_{16}H_{32}OS$, 272.217 38; found, 272.217 22] and 85 mg (30%) of a yellow oil after isolation of the band at higher R_f, **16a** (VPC analysis, 200 °C, OV101, showed this to be a 50:50 mixture of two isomers). Preparative TLC of **16a** (pentane) gave two UV-active bands. The band at higher R_f gave a clear oil (VPC analysis showed this to be the isomer at shorter retention time): IR (neat) 3.42, 6.17 (weak), 6.85 μ; NMR (CCl_4) δ 0.89 (t, 3 H, J = 6.5 Hz), 1.14–1.55 (broad, 20 H), 2.20 (m, 4 H), 2.48 (t, 2 H, J = 7.5 Hz), 5.70 (t, 1 H, J = 8 Hz); mass spectrum *m/e* (rel intensity) 254 (M^+, 67), 197 (92), 165 (33), 109 (64), 95 (54), 83 (99), 67 (58), 55 (71), 41 (100). Exact mass: calcd for $C_{16}H_{30}S$, 254.206 82; found, 254.206 71. The band at lower R_f value gave a clear oil (VPC analysis showed this to be the isomer at longer retention time). IR and mass spectrum: identical with those of previously described isomer; NMR (CCl_4) δ 0.91 (t, 3 H, J = 7 Hz), 2.16–2.61 (broad, 20 H), 2.09 (q, 2 H, J = 7 Hz), 2.50 (t, 2 H, J = 7 Hz), 5.18 (t, 1 H, J = 7.5 Hz). Exact mass: found for $C_{16}H_{30}S$, 254.206 73.

Preparation of Compound 15b. To a solution of 198 mg (0.73 mmol) of 1,4-dithiaspiro[4.11]hexadecan-6-one (**14**) in 15 mL of ether at 0 °C was added 0.5 mL of *n*-butyllithium (0.80 mmol, 1.6 M). The reaction mixture was warmed to room temperature and stirred for 1 h. The solution was quenched with 1 mL of H_2O and poured into 15 mL of water overlaid with 15 mL of ether. The organic layer was separated, dried (Na_2SO_4), and concentrated. Preparative TLC on silica gel (10% ether/pentane) yielded 136 mg (65%) of a light yellow oil (**15b**): IR (neat) 2.87, 3.44, 6.90, 7.30, 7.81, 9.00 μ; NMR (CCl_4) δ 1.36 (broad s, 21 H), 1.95 (m, 2 H), 2.18 (s, 1 H), 3.16 (s, 4 H); mass spectrum *m/e* (rel intensity) 288 (M^+, 41), 245 (10), 229 (17), 227 (13), 131 (8), 105 (100), 71 (12), 61 (10), 55 (14), 43 (49). Exact mass: calcd for $C_{15}H_{28}OS_2$, 288.158 14; found, 288.158 20. A 38-mg (19%) quantity of the starting ketone **14** was obtained.[20c,25]

***n*-Butyllithium Reaction of 15b.** To a solution of 136 mg (0.47 mmol) of **15b** in 10 mL of ether at 0 °C was added 0.70 mL (1.72 mmol, 2.45 M in *n*-hexane) of *n*-butyllithium. After warming to room temperature the reaction mixture was stirred for 3.5 h and poured into 15 mL of H_2O overlaid with 10 mL of ether. The organic layer was separated, dried (Na_2SO_4), and concentrated. Preparative TLC on silica gel (pentane) yielded 79 mg (63%) of a light yellow oil: IR (neat) 3.42, 6.23 (weak), 6.85, 7.30, 13.89 μ; NMR (CCl_4) δ 0.89 (crude t, 3 H), 1.14–1.64 (broad, 20 H), 1.86 (s, 3 H), 2.09 (t, 2 H, J = 7 Hz), 2.20 (t, 2 H, J = 7 Hz), 2.41 (t, 2 H, J = 7 Hz); mass spectrum *m/e* (rel intensity) 268 (M^+, 100), 211 (93), 144 (33), 123 (28), 109 (38), 97 (73), 81 (63), 67 (45), 55 (75), 41 (74). Exact mass: calcd for $C_{17}H_{32}S$, 268.222 47; found 268.222 44.

Preparation of Compound 23. A solution of 3.10 g (17 mmol) of α-hydroxymethylenementhone,[30] 6.13 g (15.3 mmol) of ethylene dithiotosylate,[20b] and 4.41 g (45 mmol) of anhydrous potassium acetate in 70 mL of anhydrous methanol was refluxed for 10 h. The reaction mixture was cooled to room temperature and concentrated and the residue dissolved in 50 mL of H_2O overlaid with 50 mL of ether.

The ether layer was separated, dried (Na_2SO_4), and concentrated. Short-column chromatography in two portions on 70 g of silica gel (5% ether/pentane) afforded 1.693 g (45%) of a white solid, mp 80–85 °C (**23**): IR (CCl_4) 3.40, 5.88, 6.90, 7.06, 7.28, 7.35, 7.90, 9.26 μ; NMR (CCl_4) δ 0.89 (m, 6 H), 1.04 (d, 2 H, J = 8 Hz), 1.25 (d, 1 H, J = 6 Hz), 1.55–1.91 (m, 3 H), 2.02–2.27 (m, 2 H), 2.58 (m, 1 H), 2.77 (m, 1 H), 3.09–3.20 (m, 4 H); mass spectrum *m/e* (rel intensity) 244 (M^+, 31), 216 (24), 188 (48), 173 (12), 155 (11), 145 (100), 132 (13), 131 (17), 105 (25), 85 (13), 82 (33), 71 (13), 69 (28), 55 (28). Exact mass: calcd for $C_{12}H_{20}OS_2$, 244.095 54; found, 244.095 69.

Preparation of Compound 26a. From 900 mg (3.69 mmol) of **23** after $LiAlH_4$ reduction in ether was recovered 875 mg (96%) of a light yellow oil (**26a**): IR (neat) 2.80, 3.40, 6.90, 7.25, 7.87, 8.10, 8.61, 9.50, 12.18, 13.70 μ; NMR (CCl_4) δ 0.78 (d, 1 H, J = 6 Hz), 0.85–0.91 (m, 6 H), 1.14 (d, 1 H, J = 6 Hz), 1.25 (d, 2 H, J = 7 Hz), 1.32–1.89 (m, 5 H), 2.23 (m, 1 H), 2.34 (m, 1 H), 3.07–3.23 (m, 4 H), 3.65 (broad s, 1 H); mass spectrum *m/e* (rel intensity) 246 (M^+, 39), 145 (67), 105 (100), 81 (18), 61 (30), 55 (25), 43 (36), 41 (56). Exact mass: calcd for $C_{12}H_{22}OS_2$, 246.111 19; found, 246.111 16.

Preparation of Compound 24c. To a solution of 337 mg (1.38 mmol) of **23** in 10 mL of ether was added 2.3 mL (5.52 mmol, 2.4 M in *n*-hexane) of *n*-butyllithium at room temperature. After stirring for 5 h, the reaction mixture was quenched with 1 mL of H_2O and poured into 20 mL of water overlaid with 10 mL of ether. The organic layer was separated, dried ($MgSO_4$), and concentrated. Preparative TLC on silica gel (pentane) afforded 243 mg (62%) of a clear liquid (**24c**): IR (neat) 3.41, 6.89, 7.30 μ; NMR (CCl_4) δ 0.66 (crude d, 3 H, J = 6 Hz), 0.89–0.96 (m, 9 H), 1.08 (crude d, 3 H, J = 6 Hz), 2.15–2.59 (m, 12 H), 2.87–3.83 (broad m, 7 H); mass spectrum *m/e* (rel intensity) 282 (M^+, 16), 239 (100), 149 (15), 93 (58), 57 (62), 41 (33), 29 (26). Exact mass: calcd for $C_{18}H_{34}S$, 282.238 13; found, 282.237 85.

Reaction of 26a with *n*-Butyllithium. To a solution of 827 mg (3.36 mmol) of **26a** in 20 mL of ether was added 4.9 mL (11.8 mmol, 2.4 M in *n*-hexane) of *n*-butyllithium at room temperature. After stirring for 10 h, the reaction mixture was quenched with 1 mL of H_2O and poured into 30 mL of water overlaid with 10 mL of ether. The organic layer was separated, dried (Na_2SO_4), and concentrated. Short-column chromatography of 40 g of silica gel (5% ether/pentane) yielded 108 mg (14%) of a clear oil (**24a**) [IR (neat) 3.40, 6.20 (weak), 6.86, 7.30 μ; NMR (CCl_4) δ 0.82–0.95 (m, 9 H), 1.07 (t, 3 H, J = 6 Hz), 1.18–1.70 (m, 9 H), 1.86–2.05 (m, 1 H), 2.07–2.25 (m, 1 H), 2.39–2.64 (m, 2 H), 5.30 (m, 1 H); mass spectrum *m/e* (rel intensity) 226 (M^+, 8), 183 (55), 93 (100), 77 (13), 57 (29), 41 (26). Exact mass: calcd for $C_{14}H_{26}S$, 226.175 52; found, 226.175 60] and 335 mg (41%) of a pale yellow oil (**27**) [IR (neat) 2.80, 3.40, 6.86, 7.25, 9.59 μ; NMR (CCl_4) δ 0.76–1.00 (m, 10 H), 1.05–2.00 ppm (m, 17 H), 3.09–3.40 (m, 1 H); mass spectrum *m/e* (rel intensity) 244 (M^+, 23), 226 (12), 211 (10), 193 (42), 187 (11), 183 (12), 81 (31), 69 (56), 57 (33), 55 (61), 43 (53), 41 (100). Exact mass: calcd for $C_{14}H_{28}OS$, 244.186 08; found, 244.186 00].

Preparation of Compound 24b. To a solution of 203 mg (0.83 mmol) of **23** in 10 mL of ether was added 0.55 mL (1 mmol, 1.84 M in ether) of methyllithium at room temperature. The reaction mixture was stirred for 30 min (GC/MS analysis of an aliquot quenched with H_2O showed **26b** to be the major product present). Then 0.90 mL (2.1 mmol, 2.4 M in *n*-hexane) of *n*-butyllithium was added. After stirring for 3 h, the reaction mixture was quenched with 1 mL of H_2O and poured into 20 mL of water overlaid with 20 mL of ether. The organic layer was separated, dried (Na_2SO_4), and concentrated. Preparative TLC on silica gel (pentane) afforded 103 mg (52%) of a light yellow oil (**24b**): IR (neat) 3.40, 6.90, 7.30, 10.20 μ; NMR (CCl_4) δ 0.65 (d, 3 H, J = 6 Hz), 0.80–0.97 (m, 6 H), 1.09 (d, 3 H, J = 7 Hz), 1.27–1.64 (m, 8 H), 1.84 (s, 3 H), 1.95–2.61 (m, 5 H); mass spectrum *m/e* (rel intensity) 240 (M^+, 11), 197 (61), 107 (100), 91 (15), 43 (14), 41 (31). Exact mass: calcd for $C_{15}H_{28}S$, 240.191 18; found, 240.191 12.

General Procedure for Titanium(IV) Chloride Hydrolysis of Vinyl Sulfides 16a–c and 24a–c. To a solution of the vinyl sulfide in acetic acid was added excess titanium(IV) chloride. The yellow solution was stirred for 30 min; then several drops of water were added. The reaction mixture was stirred for 4 h and poured into chloroform overlaid with water and the organic layer was separated, washed with saturated sodium bicarbonate and sodium chloride solutions, dried ($MgSO_4$), and concentrated.

Hydrolysis of 16a. From 90 mg (0.35 mmol) of **16a** (a mixture of isomers) was recovered 58 mg (91%) of cyclododecanone **17a.**

Hydrolysis of 16b. From 65 mg (0.24 mmol) of **16b** was recovered 45 mg (96%) of a light yellow oil (**17b**): IR (neat) 3.40, 5.85, 6.81, 7.30 μ; NMR (CCl_4) δ 1.02 (d, 3 H, J = 6 Hz), 1.33 (broad, 14 H), 1.47–1.90 (m, 4 H), 2.07–2.87 (m, 3 H); mass spectrum *m/e* (rel intensity) 196 (M^+, 11), 167 (4), 139 (9), 112 (8), 111 (8), 98 (22), 83 (22), 72 (37), 69 (33), (81), 43 (53), 41 (100). Exact mass: calcd for $C_{13}H_{24}O$, 196.182 71; found, 196.182 60.

Hydrolysis of 16c. From 27 mg (0.09 mmol) of **16c** was recovered 19 mg (92%) of a yellow oil (**17c**): IR (neat) 3.41, 5.85, 6.81, 7.35 μ; NMR (CCl_4) δ 0.87 (crude t, 3 H, J = 7 Hz), 1.27 (broad, 19 H), 1.41–1.70 (m, 6 H), 2.21–2.55 (m, 2 H); mass spectrum *m/e* (rel intensity) 238 (M^+, 9), 182 (18), 98 (29), 83 (24), 69 (35), 55 (90), 43 (61), 41 (100). Exact mass: calcd for $C_{16}H_{30}O$, 238.229 64; found, 238.229 58.

Hydrolysis of 24a. From 27 mg (0.12 mmol) of **24a** was recovered 17 mg (92%) of carvomenthone **25a.**

Hydrolysis of 24b. From 50 mg (0.21 mmol) of **24b** was recovered 33 mg (94%) of a yellow oil (**25b**): IR (neat) 3.41, 5.86, 6.90, 7.30 μ; NMR (CCl_4) δ 0.60–0.82 (m, 10 H), 0.86–2.10 (broad m, 10 H); mass spectrum *m/e* (rel intensity) 168 (M^+, 13), 125 (34), 110 (36), 97 (23), 83 (20), 69 (32), 55 (100), 41 (43). Exact mass: calcd for $C_{11}H_{20}O$, 168.151 40; found, 168.151 46.

Hydrolysis of 24c. From 135 mg (0.48 mmol) of **24c** was recovered 95 mg (94%) of a dark yellow oil (**25c**): IR (neat) 3.40, 5.85, 6.84, 7.30 μ; NMR (CCl_4) δ 0.78–0.96 (m, 12 H), 1.00–2.50 (broad m, 14 H); mass spectrum *m/e* (rel intensity) 210 (M^+, 1), 167 (3), 154 (6), 111 (100), 69 (19), 55 (36), 43 (37), 41 (37). Exact mass: calcd for $C_{14}H_{26}O$, 210.198 41; found, 210.198 42.

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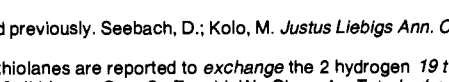

i ii

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Palladium-Assisted Cyclization–Insertion Reactions. Synthesis of Functionalized Heterocycles

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Abstract: *o*-Allylbenzoic acids and N-substituted *o*-allylanilines undergo facile palladium-assisted cyclization/carbonylation to produce dihydroisocoumarin acetic acid esters and dihydroindolacetic acid esters in high yield. With *o*-allylanilines lacking β hydrogens in the cyclized intermediate σ-alkylpalladium(II) complex, conjugated enones such as methyl vinyl ketone and methyl acrylate insert, giving highly functionalized indolines. Intramolecular insertions of this type lead to tricyclic compounds of the pyrroloindole or pyridinoindole type.

Introduction

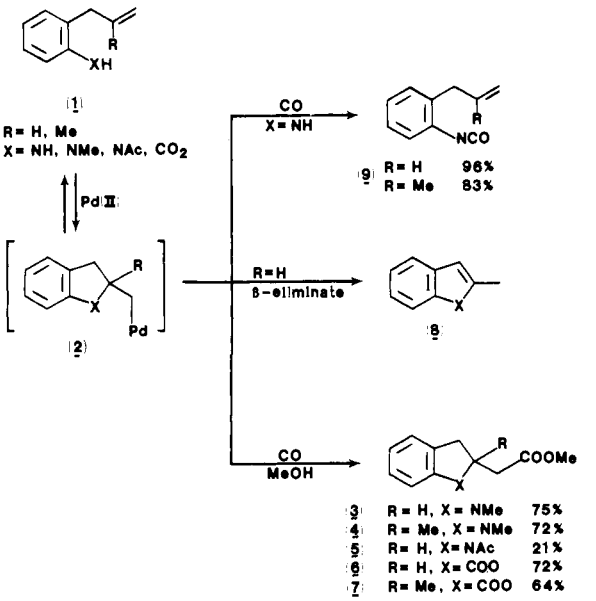
A typical reaction of σ-alkylpalladium(II) complexes is insertion of unsaturated molecules into the metal–carbon σ bond. Carbon monoxide inserts most readily, usually under mild conditions. Thus, σ-alkylpalladium(II) complexes arising from oxidative addition of organic halides to palladium(0) complexes,[1-6] from transmetalation reactions,[7] and from nucleophilic attack of methoxide,[8-11] amines,[12,13] and carbanions[14] on both chelating and simple olefin–palladium(II) complexes, react with CO to produce acylated organic products. Olefins, including conjugated enones, simple olefins, and enamides, also insert into σ-alkylpalladium(II) complexes. However, more severe experimental conditions are usually required, limiting this reaction to stable σ-alkyl complexes and/or those lacking β hydrogens.[1,15-20] A number of heterocyclic compounds were prepared by the insertion of conjugated enones into stable σ-alkylpalladium(II) complexes.[21-23] Similar chemistry was used in an elegant approach to the prostaglandins.[24]

We have recently reported the synthesis of indoles[25] and isocoumarins[26] by a palladium-assisted cyclization reaction. Herein we report insertion reactions of the unstable σ-alkylpalladium(II) complexes intermediate in these heterocyclization reactions.

Results and Discussion

Carbon Monoxide Insertion. The palladium-assisted cyclization of *o*-allylanilines and -benzoic acids to indoles and isocoumarins, respectively, is thought to proceed through σ-alkylpalladium(II) intermediates. While lacking sufficient stability to allow isolation, these complexes had sufficient lifetime to undergo CO insertion reactions (Scheme I). Several requirements must be met to accomplish the desired cyclization–carbonylation sequence, a process involving three distinct palladium-mediated reactions. First, the reaction must be carried out under conditions which will allow cyclization to occur, to produce the σ-alkylpalladium complex (**2**) required for subsequent insertion. Second, CO must insert under conditions sufficiently mild to preclude competitive β-hydride elimination reactions in systems having β hydrogens. Finally, carbonylation of the nucleophilic center itself, prior to cyclization, must be avoided.

Scheme I



With unsubstituted allylanilines, direct carbonylation of the

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