dioxane–water have been found to yield ca. 10–12% of trans hydration and 85–90% cis hydration products.[6e] The reaction of **2** in 5 mM $GMPH^-$ in 10% dioxane–water at pH 6.32 yielded ca. 83% of **12** (trans hydration) and 17% of **13** (cis hydration). This ratio is similar to that reported[6e] for H_3O^+-catalyzed hydrolysis of **2** (81–86% trans hydration in water and 92–93% in 10% dioxane–water) but quite different from the product ratio for spontaneous reaction of **2** (ca. 45:55 trans/cis hydration).

Additional evidence consistent with the proposed mechanisms for reaction of **1** and **2** with $GMPH^-$ is provided by the solvent effect on their rates of reaction (Figure 2 for **1**). For instance, the rate-limiting step in the hydrolysis of **1** catalyzed by $GMPH^-$ is presumably the protonation of **1** by $GMPH^-$ to yield the carbocation **6** and GMP^{2-} (**5**). This reaction involves the generation of charge, and therefore its rate would be expected to decrease as the polarity of the solvent decreases. From Figure 2, it can be seen that the rates for reaction of **1** in $GMPH^-$ solutions fall off markedly (ca. 46-fold) as the polarity of the solvent is decreased in going from 5% dioxane–water to 25% dioxane–water. By comparison, the apparent bimolecular rate constant (k_{H^+}) for **1** is decreased by only about 30% as the solvent is changed from water to 25% dioxane–water.[6e,15] A summary of the rate constants for the $GMPH^-$ reactions of **1** and **2** as a function of solvent is provided in Table II. Benzo[*a*]pyrene tetrahydroepoxide **3** is even more reactive with $GMPH^-$ than either **1** or **2** (Table II). Therefore the relative reactivities of **1–3** toward $GMPH^-$ (**3** > **2** > **1**) parallel their order of reactivities toward hydronium ion catalyzed hydrolysis.[6e]

The rates of inorganic phosphate ($H_2PO_4^-$) catalyzed hydrolysis of **1** and **2** were also determined in 5% and 10% dioxane–water solutions, and the data are summarized in Table II. It has been postulated that $H_2PO_4^-$ acts as a general acid in the hydrolysis of **1** and **2** in a mechanism similar to that outlined in Scheme I for reaction of **1** with $GMPH^-$.[7] The values of $k_{H_2PO_4^-}$ are also found to be lower in 10% dioxane–water, consistent with the fact that $H_2PO_4^-$ is of the same charge type as $GMPH^-$. Noteworthy, however, is the observation that $GMPH^-$ is ca. 60–80 times more effective than $H_2PO_4^-$ in catalyzing the hydrolysis of **1** and **2**, even though the pK_a of $GMPH^-$ is very similar to that of $H_2PO_4^-$.[10,16]

In summary, 5′-GMP acts as a general acid in the hydrolysis of **1** and **2** at pH ~7 and not as a nucleophilic reagent. Ionization state **4** ($GMPH^-$) is the reactive species, and it is much more effective as a general acid than one would predict, based on its pK_a value. The enhanced effectiveness of $GMPH^-$ as a general acid compared to $H_2PO_4^-$ might possibly be due to an association complex between $GMPH^-$ and **1** or **2**. If such association complexes exist, then it would be feasible to design reagents capable of forming more favorable complexes with **1** and **2** and acting as even more efficient catalysts in the hydrolyses of **1** and **2**. Such reagents might block the mutagenic and carcinogenic actions of **1** and **2** by acting as highly efficient scavengers that detoxify **1** and **2** by promoting their hydrolyses to inactivate tetraols.

The foregoing results also suggest that site-selective alkylation of nucleic acids and proteins by epoxide metabolites may not be determined strictly by the relative basicities of the nucleic acid or protein bases but may also depend on the nearness of groups capable of acting as general acid catalysts.

Acknowledgment. This investigation was supported by Public Health Service Grant No. CA-26086 from the National Cancer Institute (D.L.W.).

Registry No. 1, 58917-91-2; **2**, 58917-67-2; **3**, 64608-56-6; **8**, 62697-17-0; **9**, 62697-13-6; **10**, 62697-19-2; **11**, 62697-16-9; 5′-GMP, 85-32-5; guanosine, 118-60-3.

(15) The relatively small solvent effect on k_{H^+} is reasonable since the rate-limiting step for this reaction does not involve the generation of charge but rather a dispersal of charge.

(16) From titration curves, the apparent pK_a values of 5′-$GMPH^-$ (**4**) in 5%, 10%, and 25% dioxane–water solutions (v/v, μ = 0.1 ($NaClO_4$)) were determined to be 6.42, 6.50, and 6.86, respectively.

Tin-Assisted Sulfuration: A Highly Potent New Method for the Conversion of Carbonyl Units into Their Corresponding Thiocarbonyl Analogues[1a,b]

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Contribution from the Department of Chemistry, Université de Montréal, Montréal, Québec, Canada H3C 3V1. *Received October 21, 1981*

Abstract: Treating bis(tricyclohexyltin) sulfide with boron trichloride in the presence of a carbonyl-containing compound converts the carbonyl unit into its corresponding thiocarbonyl analogue in high yield. Using this technique, several examples of thioaldehydes, thioketones, thiolactones, and thiolactams were prepared. This potent new sulfurating method is efficient even with highly hindered ketones such as di-*tert*-butyl ketone (65% isolated yield di-*tert*-butyl thioketone) hitherto inert to direct sulfuration. Other group 4 organometallic sulfides such as bis(trimethylsilyl) sulfide, bis(tri-*n*-butyltin) sulfide, and bis(triphenyltin) sulfide can be used in this new sulfurating process with equal effect.

Thiocarbonyl-containing compounds have gained prominence because of their rich photochemistry.[2] However, their recent application to the synthesis of complex natural products[3] as key intermediates, which allow for difficult synthetic transformations[3b,4] under mild reaction conditions,[3c,5] has accentuated interest in this

(1) (a) For the previous paper in the series of "Reagents for Organic Synthesis", see: Steliou, K.; Szczygielska-Nowosielska, A.; Favre, A.; Poupart, M.-A.; Hanessian, S. *J. Am. Chem. Soc.* **1980**, *102*, 7578. (b) Presented in part at the 180th National Meeting of the American Chemical Society, Las Vegas, NV, Aug 1980; "Abstracts of Papers", American Chemical Society, Washington D.C., 1980, No. ORGN 299. (c) Holder of a CIDA fellowship administrated by le Ministère de l'Education du Gouvernement du Québec.

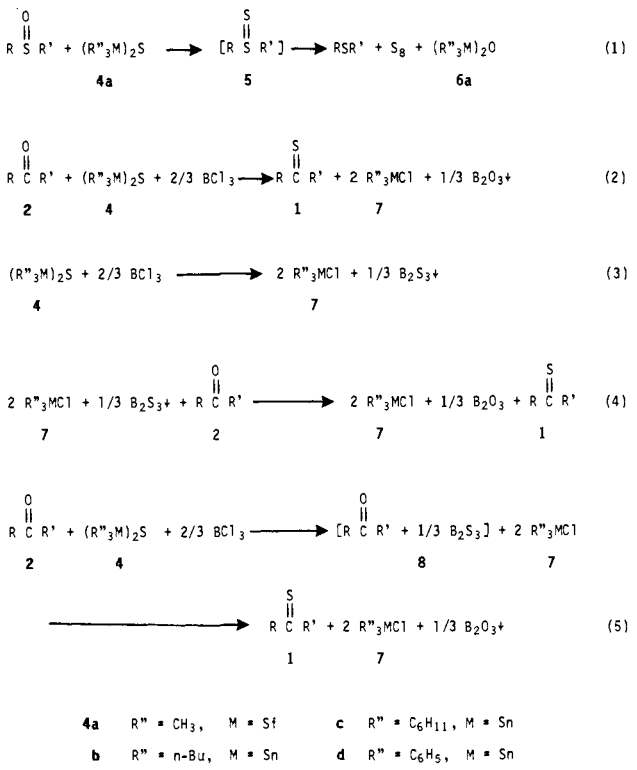
(2) de Mayo, P.; Sydnes, L. K.; Wenska, G. *J. Org. Chem.* **1980**, *45*, 1549, and references cited therein.

(3) (a) Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710. (b) Ireland, R. E.; Brown, F. R., Jr. *J. Org. Chem.* **1980**, *45*, 1868. (c) Tamaru, Y.; Harada, T.; Yoshida, Z.-I. *J. Am. Chem. Soc.* **1980**, *102*, 2392, and references cited therein.

(4) (a) Baxter, S. L.; Bradshaw, J. S. *J. Org. Chem.* **1981**, *46*, 831. (b) Guziec, F. S., Jr. Murphy, C. J. *Ibid.* **1980**, *45*, 2890. (c) Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, *21*, 4061.

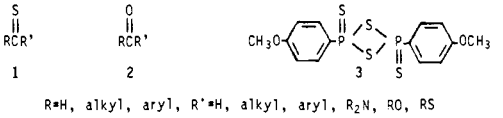
0002-7863/82/1504-3104$01.25/0

Scheme I



versatile functionality to the forefront of synthetic organic chemistry. Our interest in the construction of sulfur-bridged polycyclic disulfides as model compounds for a group of natural products whose family includes the antibiotics[6] gliotoxin, sporidesmin, verticillin, aronotin, chetamin, and other sulfur-bridged biologically active molecules[7] requires that we have access to a highly efficient procedure for the conversion of carbonyl units into their corresponding thiocarbonyl analogues under strictly neutral and mild reaction conditions. Herein we report the results of our effort in the development of a group 4 metal-assisted, new sulfurating process.

A vast array of methods[8] which range from pyrolysis to photochemical techniques are described in the literature for the formation of **1**. Synthetically, the most useful are those that directly convert the more readily available **2** into **1**. Of these methods, none appears to be of general applicability, and yields tend to vary drastically depending upon the substrate used. Although 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (**3**) has been known for some time,[9a] its application



R=H, alkyl, aryl, R'=H, alkyl, aryl, R_2N, RO, RS

as a sulfurating agent is recent.[4a,c,9b,c] Remarkably, it is the most effective sulfurating reagent to be reported to date, and yields, particularly with simple substrates, are generally excellent.[9b]

Table I

2	4	time, h	1, % yield[a,b]
trimethylacetaldehyde	a	5	65[c,d]
benzaldehyde	c	1	85[c,d]
p-anisaldehyde	c	1	95[c,e]
p-nitrobenzaldehyde	c	1	83[c,e]
benzophenone	a, c	2	90[f]
4,4'-bis(dimethylamino)benzophenone	c	3	93[d]
di-*tert*-butyl ketone	a[h]	48	65[i]
2-adamantanone	c	2	72[j]
d,l-camphor	a-d	2.5	95[i]
l-fenchone	a-d	48	90[i]
coumarin	c, d	7	94[k]
pentcyclo[6.2.1.$0^{2,7}$.$0^{5,9}$]undecane-3,6-dione	c	2	84
N-phenyl-3-methyl-4-phenyl 2-azetidinone	c	2	90[l]
ϵ-caprolactam	c	3	92[m]

[a] Yields are isolated. [b] Melting points compare favorably with literature values. [c] Isolated as the trimer. [d] Jerumanis, S.; Lalancette, J. M. *Can. J. Chem.* 1964, *42*, 1928. [e] Kamel, A.; Quereshi, A. A. Pak. *J. Sci. Res.* 1963, *15*; cf. *Chem. Abstr.* 1964, *60*, 8034a. [f] Viola, H.; Scheithauer, S.; Mayer, R. *Chem. Ber.* 1968, *101*, 3517. [g] Reference 14. [h] No solvent was used. [i] Reference 16e. [j] Greidanus, J. W.; Schwalm, W. J. *Can. J. Chem.* 1969, *47*, 3715. [k] Imaeda, H.; Hirabayashi, T.; Itoh, K.; Ishi, Y. *Organomet. Chem. Syn.* 1970, *1*, 115. [l] Reference 10b. [m] Scheibye, S.; Pederson, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* 1978, *87*, 229.

Unfortunately, **3** is extremely sensitive to moisture and very difficult to prepare and handle in pure form.[9a] This in itself is usually not a hindrance since the reagent is generally used in large excess. However, the accompanying impurities and the resulting oxygenated analogues of **3**[9a] lead to an acidic reaction mixture which for some substrates causes side products to predominate.[10]

Hexamethyldisilthiane[11a] (**4a**) smoothly converts sulfoxides into sulfides, reportedly[11b] through the intermediacy of thiosulfoxide **5** (Scheme I, eq 1). The driving force for this reaction is the net formation of the Si–O bond[11b] in **6a**. We reasoned that an analogous reaction with carbonyl-containing compounds might also be a favorable process, affording thiocarbonyls under mild and neutral reaction conditions. Although for some carbonyls (aldehydes), low yields of the corresponding thiocarbonyls are reported with reagent **4a**,[12] the yields are considerably enhanced if the reaction is carried out in the presence of a Lewis acid. We found that a stoichiometric amount of boron trichloride consistently gave the best results (Scheme I, eq 2).

Sulfuration by this in situ formation of boron trisulfide[13] in the presence of the carbonyl-containing compound (eq 2) is considerably more rapid and usually quantitative, even for substrates that are reported to be inert to sulfuration by B_2S_3[14] or reagent **3** (see Table I).

(5) (a) Tamaru, Y.; Harada, T.; Nishi, S.-I.; Mizutani, M.; Hioki, T.; Yoshida, Z.-I. *J. Am. Chem. Soc.* **1980**, *102*, 7806. (b) Belsin, P.; Lagain, D.; Vialle, J. *J. Org. Chem.* **1980**, *45*, 2517, and references cited therein. (c) Laycock, D. E.; Alper, H. *Ibid.* **1981**, *46*, 289.

(6) Taylor, A. In "Microbial Toxins"; Kadis, S., Ciegler, A., Ajl, S. J., Eds.; Academic Press: New York, 1971; Vol. VII, Chapter 10, p 337.

(7) Nicolaou, K. C.; Gasic, G. P.; Barnette, W. E. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 293.

(8) (a) Klages, C.-P.; Voss, J. *Chem. Ber.* **1980**, *113*, 2255, and references cited therein. (b) Nader, R. G.; Kaloustian, M. K. *Tetrahedron Lett.* **1979**, 1477, and references cited therein.

(9) (a) Lecher, H. Z.; Greenwood, R. A.; Whitehouse, K. C.; Chao, T. H. *J. Am. Chem. Soc.* **1956**, *78*, 5018. (b) Shabana, R.; Rasmussen, J. B.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1981**, *90*, 75, and references cited therein. (c) Walter, W.; Proll, T. *Synthesis* **1979**, 941.

(10) (a) Shabana, R.; Rasmussen, J. B.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1981**, *90*, 103. (b) Shabana, R.; Scheibye, S.; Clausen, K.; Olesen, S. O.; Lawesson, S.-O. *Nouv. J. Chim.* **1980**, *4*, 47. (c) Pedersen, B. S.; Lawesson, S.-O. *Tetrahedron* **1979**, *35*, 2433. (d) Scheibye, S.; Kristensen, J.; Lawesson, S.-O. *Ibid.* **1979**, *35*, 1339.

(11) (a) Harpp, D. N.; Steliou, K. *Synthesis* **1978**, 721. (b) Soysa, H. S. D.; Weber, W. P. *Tetrahedron Lett.* **1978**, 235. Beachler, R. D.; Daley, S. K. *Ibid.* **1978**, 101. Beachler, R. D.; Daley, S. K.; Daley, B., McGlynn, K. *Ibid.* **1978**, 105.

(12) During the course of this study, the preparation of thioaldehydes in modest yields using hexamethyldisilthiane as the sulfurating agent was published. See: Lebedev, E. P.; Mizhiritskii, M. D.; Baburina, V. A.; Zaripov, Sh. I. *Zh. Obshch. Khim.* **1978**, *49*, 1084.

(13) (a) Abel, E. W.; Armitage, D. A.; Bush, R. P. *J. Chem. Soc.* **1964**, 5584. (b) Abel, E. W.; Armitage, D. A.; Bush, R. P. *Ibid.* **1965**, 3045. (c) Abel, E. W.; Brady, D. B.; Crosse, B. C. *J. Organometl. Chem.* **1966**, *5*, 260. (d) Abel, E. W.; Armitage, D. A. *Adv. Organometl. Chem.* **1967**, *5*, 1.

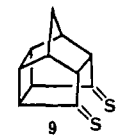
(14) Dean, F. M.; Goodchild, J.; Hill, A. W. *J. Chem. Soc. C* **1969**, 2192.

The potent sulfurating ability of this in situ preparation of B_2S_3 (eq 2) must thus be a consequence of the structural nature of the boron trisulfide produced. For example, treatment of organometallic sulfides **4** with BCl_3 in the absence of carbonyl-containing compounds (eq 3) affords almost immediately a polymeric glassy white precipitate of B_2S_3.[13a,15] Addition of carbonyls to this mixture (eq 4), depending upon the "age" of the precipitate, effects sulfuration to the extent reported in the literature for B_2S_3.[14] We find that addition of benzophenone to a freshly prepared precipitate of B_2S_3 (eq 4) effects sulfuration to approximately 50% (VPC), whereas, addition to a 48 h-old precipitate results in only trace sulfuration. On the other hand, preparation of B_2S_3 in the presence of benzophenone (eq 2) results in a homogeneous reaction mixture with quantitative sulfuration occurring within 2 h using refluxing toluene as the solvent. The color of most of the thiones prepared using this technique becomes evident even as the BCl_3 is added to the reaction mixture. As sulfuration approaches completion, the B_2O_3 that is produced begins to precipitate out of solution as a white polymer.

What is evident from these experimental results is that the organometallic sulfide (**4**) acts only as a transporter of sulfur to the reaction medium. Thus, little difference is noted in the yields of sulfuration from interchanging sulfides **4a** to **4d** in eq 2. However, the extreme moisture sensitivity of silyl reagent **4a** and the difficulty of preparing it or reagent **4b**[13d] in pure form make these reagents less desirable than **4c**[16a] or **4d**[13d] which are crystalline, easily prepared,[16a] and completely stable to moisture hydrolysis. In addition, reagent **4c** and its chloride **7c**[16b] are nonvolatile and insoluble in polar solvents, allowing for easier product isolation. For a variety of reasons bis(tricyclohexyltin) sulfide (**4c**) is the reagent of choice for this new sulfurating process.[16c]

We rationalize that the potent sulfurating ability of this in situ preparation of B_2S_3 must in large part be due to its solubility in the reaction medium. Its solubility in turn is probably related to the formation of a stablized carbonyl-coordinated, low-molecular-weight form of B_2S_3 (**8**, eq 5, Scheme I). In the absence of carbonyl containing compounds, B_2S_3 rapidly precipitates out of solution as a high-molecular-weight polymer.[13a] This effect is similarly observed if the carbonyl is severely sterically hindered by α,α' substituents (di-*tert*-butyl ketone), whereas, otherwise, a homogeneous reaction mixture is obtained. The organometallic chloride **7** does not play a central role in the sulfurating process.[16f]

Thus, using this technique, aldehydes, ketones, lactones, and lactams (including β-lactams hitherto sulfurated in very low yield ($\simeq$4%) by B_2S_3[17]) can be readily converted into their corresponding thioanalogues in high yield (see Table I). The method is also convenient for the reduction of sulfoxides to sulfides[11b] (i.e., diphenyl sulfoxide to diphenyl sulfide). More importantly, this new procedure for sulfuration has allowed us entry into an exciting new class of compounds such as the pentacyclic caged dithione **9**. Although this particular dithione is stable in solution (bright



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orange), it is extremely labile and not amicable to isolation without considerable polymerization and decomposition. It is anticipated however, that structural modifications (α,α' substituents) will lead to stable isolable derivatives. Replacing bis(tricyclohexyltin) sulfide (**4c**) by its corresponding selenide, **10**,[18a] in these reactions results in selenation.[18b]

$[(C_6H_{11})_3Sn]_2Se$

10

Acknowledgment. We thank Research Corporation, the Natural Sciences and Engineering Research Council of Canada, le Ministère de l'Education du Gouvernement du Québec, and the Upjohn Company for financial assistance. We especially thank Dr. Melvin H. Gitlitz of M&T Chemicals for the very generous gift of tricyclohexyltin hydroxide, and Professor Denis Gravel for his fruitful discussions.

Registry No. 4a, 3385-94-2; **4b**, 4808-30-4; **4c**, 13121-76-1; **4d**, 77-80-5; 2,2-dimethylpropanethial trimer, 81193-97-7; benzenecarbothioaldehyde trimer, 81193-98-8; *p*-methoxybenzenecarbothioaldehyde trimer, 81193-99-9; *p*-nitrobenzenecarbothioaldehyde trimer, 81194-01-6; diphenylmethanethione, 1450-31-3; bis[*p*-dimethylaminophenyl]-methanethione, 1226-46-6; bis-*tert*-butylmethanethione, 54396-69-9; 2-adamantanethione, 23695-65-0; *dl*-thiocamphor, 54713-16-5; *l*-thiofenchone, 53402-11-2; thiocoumarin, 3986-98-9; pentacyclo-[6.2.1.$0^{2,7}$.$0^{5,9}$]undecane-3,6-thione, 81194-02-7; 2-azetidinethione, 74632-70-5; 8-thiocaprolactam, 7203-96-5; trimethylacetaldehyde, 630-19-3; benzaldehyde, 100-52-7; *p*-anisaldehyde, 123-11-5; *p*-nitrobenzaldehyde, 555-16-8; benzophenone, 119-61-9; 4,4'-bis(dimethylamino)-benzophenone, 90-94-8; di-*tert*-butyl ketone, 815-24-7; 2-adamantanone, 700-58-3; *dl*-camphor, 21368-68-3; *l*-fenchone, 7787-20-4; coumarin, 91-64-5; pentacyclo[6.2.1.$0^{2,7}$.$0^{5,9}$]undecane-3,6-dione, 81194-03-8; *N*-phenyl-3-methyl-4-phenyl-2-azetidinone, 7468-12-4; ϵ-caprolactam, 105-60-2; BCl_3, 10294-34-5.

(15) (a) Diercks, H.; Krebs, B. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 313. (b) Krebs, B.; Hurter, H.-U. *Ibid.* **1980**, *19*, 481.

(16) (a) Prepared in quantitative yield by treating tricyclohexyltin chloride[16b] with $Na_2S{\cdot}9H_2O$ in refluxing ethanol (95%) for 2 h. Recrystallized from CH_2Cl_2/MeOH, mp 132 °C; ^{13}C NMR ($CDCl_3$) δ (Me_4Si) 32.73, 32.08, 29.30, and 27.01. (b) Krause, E.; Pohland, R. *Ber.* **1924**, *57*, 532. (c) To a mechanically stirred dry toluene (15 mL) solution of sulfide **4c** (1.1 mmol, 843 mg) and *d,l*-camphor (1 mmol, 152 mg) kept under an atmosphere of nitrogen was injected 0.84 mL (0.67 mmol) of a 0.8 M toluene[16d] solution of BCl_3. The reaction solution was then refluxed for 2.5 h. Infrared and VPC analysis showed complete consumption of the ketone after 2 h. The reaction mixture was allowed to reach ambient temperature and the solvent stripped by flash evaporation. The residue was sublimed (50 °C (16 mm Hg)) to provide *d,l*-thiocamphor (160 mg, 95% yield) as bright orange crystals, mp 143–145 °C (lit.[16e] 145–146 °C). The pot residue was recrystallized from CH_2Cl_2/MeOH, to afford 384 mg (95% yield) of tricyclohexyltin chloride, mp 127 °C (lit.[16b] 127 °C). (d) A methylene chloride solution can be purchased from Aldrich. (e) Barton, D. H. R.; Guziec, F. S., Jr.; Shahak, I. *J. Chem. Soc., Perkin Trans 1* **1974**, 1794. (f) With some substrates sulfuration would not go to completion using organometallic sulfide **4d**. This is probably due to the Lewis acidity of the resulting triphenyltin chloride.[14]

(17) Wojtkouski, P. W.; Dolfini, J. E.; Kocy, O.; Cimarusti, C. M. *J. Am. Chem. Soc.* **1975**, *97*, 5628.

(18) (a) Prepared in quantitative yield by treating tricyclohexyltin chloride with Na_2Se in refluxing anhydrous THF for 2 h. Recrystallized from CH_2Cl_2/MeOH, mp 130–132 °C; ^{13}C NMR ($CDCl_3$) δ (Me_4Si) 32.39, 32.01, 28.99, and 26.33. (b) In this way, selenofenchone[18c] (90% yield) was prepared directly from its corresponding ketone. (c) Back, T. G.; Barton, D. H. R.; Britten-Kelley, M. R.; Guziec, F. S., Jr.; *J. Chem. Soc. Perkin Trans 1* **1976**, 2079.