***n*-Butyl 4-cyclohexenecarboxylate (13b)** was isolated by column chromatography (silica gel, 1:10 AcOEt–hexane): IR (film) 2930, 1710, 1165 cm^{-1}; NMR (CCl_4) δ 0.96 (t, J = 4.5 Hz, 3 H), 1.15–2.70 (m, 1 H), 4.03 (t, J = 4 Hz, 2 H), 5.63 (s, 2 H). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.18; H, 9.92.

***n*-Butyl 3,7-dimethyl-6-octenoate (14b)** was isolated by column chromatography (silica gel, 1:10 AcOEt–hexane): IR (film) 2960, 2930, 1735, 1190, 1155 cm^{-1}; NMR (CCl_4) δ 0.97 (br t, J = 4 Hz, 6 H), 1.10–1.40 (m, 1 H), 1.60 (s, 3 H), 1.67 (s, 3 H), 4.00 (t, J = 4 Hz, 2 H), 5.06 (t, J = 4.5 Hz, 1 H). Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.14; H, 11.71.

***n*-Hexyl 3,7-dimethyl-6-octenoate (14c)** was isolated by column chromatography (silica gel, 1:10 AcOEt–hexane): IR (film) 2920, 1730, 1190, 1160 cm^{-1}; NMR (CCl_4) δ 0.92 (br t, J = 4.5 Hz, 6 H), 1.10–2.30 (m, 15 H), 1.60 (s, 3 H), 1.67 (s, 3 H), 4.00 (t, J = 4 Hz, 2 H), 5.06 (t, J = 4.5 Hz, 1 H). Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 75.19; H, 11.73.

***n*-Butyl 3,7-dimethyl-6,7-epoxyoctanoate (15b)** was isolated by column chromatography (silica gel, 1:3 AcOEt–hexane): IR (film) 2955, 2870, 1730, 1165 cm^{-1}; NMR (CCl_4) δ 0.83–1.10 (m, 6 H), 1.23 (s, 3 H), 1.26 (s, 3 H), 1.30–1.73 (m, 8 H), 1.80–2.33 (m, 3 H), 2.40–2.63 (m, 1 H), 4.03 (t, J = 4 Hz, 2 H). Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 68.95; H, 11.09.

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Registry No. **5**, 124-13-0; **5a**, 111-11-5; **6**, 112-31-2; **6a**, 110-42-9; **7**, 2043-61-0; **7a**, 4630-82-4; **7b**, 6553-81-7; **8**, 6654-36-0; **8a**, 627-93-0; **9**, 104-53-0; **9a**, 103-25-3; **9b**, 20627-49-0; **10**, 93-53-8; **10a**, 31508-44-8; **11**, 111-71-7; **11b**, 5454-28-4; **12**, 100-52-7; **12b**, 136-60-7; **13**, 100-50-5; **13b**, 37981-14-9; **14**, 106-23-0; **14b**, 98652-74-5; **14c**, 98652-75-6; **15**, 25825-48-3; **15b**, 98652-76-7; KI, 7681-11-0; KBr, 7758-02-3.

Group 14 Metal Assisted Carbon–Sulfur Bond Formation[1]

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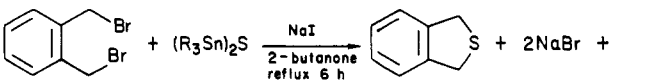
Protein-bound macrocyclic thiolactones, owing to their diverse and important biochemical properties,[2a] are a special class of the macrolide family of compounds that is currently under intensive investigation.[2] In contrast to the many new macrolide-forming methods that have recently been developed,[1] very few procedures for the preparation of macrocyclic thiolactones are reported in the chemical literature.[3] In conjunction with our ongoing studies directed toward the synthesis of synthetic and naturally occurring sulfur-bridged cyclic systems,[1,4] we require efficient methodology for the facile construction of large- and medium-sized thiacycloalkanes. We herein describe a group 14[11] metal assisted method for carbon–sulfur bond formation that is applicable to the synthesis of cyclic organosulfides and macrocyclic thiolactones.

Although carbon–sulfur bond formation enjoys many well-established synthetic avenues,[5] negotiating sulfur into a medium-sized cyclic hydrocarbon skeleton, on the other hand, is limited to but a few useful routes.[6] To help reduce unwanted polymerization, these methods rely on the use of techniques of high dilution and special functional group activation. Since the mercaptide ion is one of the more powerful nucleophiles known, an S_N2-type displacement reaction is usually invoked to attach sulfur onto a carbon atom.[5,6]

In previous work relating to thiocarbonyl synthesis,[4b] we demonstrated the utility of group 14 metal sulfides as effective transporters of the sulfur atom. These readily available reagents can also be used, in a simple way, to efficiently form carbon–sulfur bonds. Thus, when benzylic bromides are treated with alkyl-/aryltin sulfides in refluxing 2-butanone with stoichiometric amounts of sodium iodide (eq 1), a quantitative yield of the benzylic sulfide



1 2(100%)

$$2R_3SnI \quad (1)$$

R = cyclohexyl, phenyl

is readily obtained. Unfortunately however, alkyl bromides, even under considerably more vigorous (refluxing mesitylene) reaction conditions, are completely resistant to this exchange and sulfuration of these substrates requires an alternate approach.

We have found that addition of 2 equiv of MeLi to an anhydrous THF solution of hexamethyldisilathiane (HMDST)[7] at room temperature, followed by refluxing for 2 h, produces a clear solution of "Li_2S" and Me_4Si (eq 2).

$$Me_3SiSSiMe_3 + 2MeLi \xrightarrow[25\ °C]{THF} \text{"}Li_2S\text{"} + 2Me_4Si \quad (2)$$

If left to stand for a few hours, the reaction mixture becomes turbid and after 24 h a high yield of Li_2S is precipitated. The chemical and physical properties of this precipitated form of Li_2S are entirely consistent with those recorded in the literature for this compound.[5c] In sharp contrast however, and in accordance to similar observations by Gladysz,[5c] the soluble form of the Li_2S thus produced, was found to be considerably more reactive than the precipitated form with the extent of chemical reactivity dependent on the "age" of its formation. For example, addition of dibromide 1 to a freshly prepared solution of Li_2S with continued refluxing for an additional 6 h affords 1,3-dihydroisothianaphthene (2) in greater than *95% yield*; whereas the precipitated form of Li_2S results (after 24 h

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0022-3263/85/1950-4969$01.50/0

Table I

$(Me_3Si)_2S + 2MeLi + Br(CH_2)_nBr \xrightarrow[\text{reflux 6 h}]{\text{THF}} (CH_2)_nS + 2Me_4Si + 2LiBr$

$Br(CH_2)_nBr$ n	$(CH_2)_nS$ monomer (dimer)	lit.[6f]
6	61 (18)	78
7	34 (22)	48
8	22	28
9	15	22
10	20 (20)	25
12	31 (18)	55

Table II

$Br(CH_2)_nC(=O)Cl \xrightarrow[LiEt_3BH]{HMDST/THF} (CH_2)_n\overset{O}{\overset{\|}{C}}S + 2Me_3SiH$

$Br(CH_2)_nC(=O)Cl$ n	$(CH_2)_n\overset{O}{\overset{\|}{C}}S$ HMDST, $LiEt_3BH$	S_8, $LiEt_3BH$
5	73	
7	0 (50)	0 (30)
10	19 (21)	9
11	47 (16)	25
15	64	

in refluxing THF) in only 40% formation of **2**. Furthermore, the Li_2S[8a] prepared from HMDST, in our hands, consistently gave higher yields than that prepared by the Gladysz route.[5c]

This time-dependent diminishing reactivity of the in situ formed Li_2S is probably related to a changing of the structural nature of Li_2S with respect to time ("aging" effect).[8b] Since lithium cations are known to participate strongly in chelation,[9] the freshly prepared solution of Li_2S must have a higher concentration of the initially formed, nonassociated (and therefore more soluble and thus more reactive) monomeric form of Li_2S. With time, as this converts into the more stable aggregated material, it precipitates with a concomitant loss in chemical reactivity.

The enhanced chemical reactivity of the in situ formed Li_2S is further demonstrated in the synthesis of medium-sized thiacycloalkanes. For example, with this method, α,ω-dibromoalkanes are readily converted, under normal dilution (10–30 mM) concentrations, into their corresponding cyclic organosulfides in yields comparable (see Table I) to those obtained through the use of more elaborate techniques of high dilution.[6f] Similarly treated, ω-bromo carboxylic acid chlorides afford the corresponding macrocyclic thiolactones. Some representative examples are given in Table II. As expected, under more dilute conditions, the monomer yield can be considerably improved. For example, when 12-bromododecanoyl chloride is treated with HMDST and $LiEt_3BH$ in 1–3 mM concentrations, an 86% yield of the corresponding monomeric thiolactone is achieved compared to 47% with normal (3–30 mM) concentrations.

Thus, this methodology provides a simple, versatile, and general route to the construction of large- and medium-sized thiacycloalkanes and macrocyclic thiolactones.

Experimental Section

All reactions were carried out under anhydrous conditions and under an atmosphere of argon. Reagents were obtained from commercial sources and used directly. Proton nuclear magnetic resonance spectra were recorded on a Bruker Model WH-90 90-MHz instrument and ^{13}C on a Bruker Model WH-80 instrument. All chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Significant ^1H NMR data are tabulated in following order: chemical shift (number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant(s) in hertz). Infrared spectra were recorded on a Perkin-Elmer 710B grating spectrophotometer, calibrated with the 1602 band of a polystyrene film. Mass spectra were obtained with Micromass-1212 (chemical ionization (CI); low resolution) and Kratos MS-902 (electron impact; high resolution) mass spectrometers. Analytical and preparative thin-layer chromatography (TLC) were carried out with E. Merck F-254 silica gel plates.

Preparation of 1,3-Dihydroisothianaphthene (2) with Bis(triphenyltin) Sulfide. A mixture of α,α'-dibromo-*o*-xylene (1 mmol; 264 mg), bis(triphenyltin) sulfide (1 mmol; 731 mg), and NaI (2 mmol; 300 mg) was stirred in refluxing 2-butanone (50 mL) for 6 h. The solvent was then removed under vacuo and the residue transferred to a separatory funnel with 50 mL of ether. The ether layer was washed with H_2O (3 × 5 mL), dried ($MgSO_4$), and then concentrated under reduced pressure. Chromatography (silica gel) of the resulting residue using hexanes as the eluent afforded 132 mg (97 %) of 1,3-dihydroisothianaphthene as a colorless oil:[5c] ^1H NMR ($CDCl_3$) δ 7.2 (4 H, s), 4.2 (4 H, s); IR (film) 2925 (s), 1260 (s) 1100 (s), 1030 (s), 750 (s) cm^{-1}.

Preparation of 2 with Precipitated Li_2S. A solution of HMDST[7b] (1 mmol; 208 μL) and MeLi (2 equiv) in anhydrous THF (10 mL) was refluxed for 2 h and then left to stand for 24 h, causing a light yellow solid to precipitate out. A THF (1 mL) solution of α,α'-dibromo-*o*-xylene (1 mmol; 264 mg) was then added and the mixture refluxed for an additional 24 h. Workup as above afforded 54 mg (40 %) of 1,3-dihydroisothianaphthene identical in all respects with the material obtained by the above procedure.

Preparation of 2 with Soluble Li_2S. To a refluxing (2 h) THF (10 mL) solution of HMDST[7b] (1 mmol; 208 μL) and MeLi (2 equiv) was added a THF (1 mL) solution of α,α'-dibromo-*o*-xylene (1 mmol; 264 mg). After an additional 6 h of refluxing the reaction mixture was worked up as above to give 130 mg (95 %) of **2** identical in all respects with the material obtained by the above procedures.

Preparation of the Thiacycloalkanes Listed in Table I. General Procedure: Preparation of Thiacyclotridecane. To a refluxing (2 h) anhydrous THF (140 mL) solution of HMDST[7b] (1 mmol; 208 μL) and MeLi (2 equiv) was added dropwise a THF (10 mL) solution of 1,12-dibromododecane (1 mmol; 330 mg). After an additional 6 h of refluxing, the reaction mixture was flash evaporated and the residue taken up in benzene (25 mL), filtered to remove inorganic material, and then concentrated in vacuo. Chromatography of the resulting oily residue on silica gel using hexanes/benzene (9:1) as the eluent gave three mobile components identified as a monomer, a dimer, and a trimer. Monomer[6f] (31%): ^1H NMR ($CDCl_3$) δ 2.54 (4 H, t, J = 7 Hz), 1.39–1.62 (20 H, m); MS, calcd for $C_{12}H_{24}S$ m/z 200.1598, found m/z 200.1608. Dimer (18%): ^1H NMR ($CDCl_3$) δ 2.51 (4 H, t, J = 8 Hz) 1.30–1.57 (20 H, m); MS, calcd for $C_{24}H_{48}S_2$ m/z 400.3195, found m/z 400.3173. Trimer (8%): ^1H NMR ($CDCl_3$) δ 2.51 (4 H, t, J = 8 Hz) 1.28–1.58 (20 H, m); MS, calcd for $C_{36}H_{72}S_3$ m/z 600.4793, found m/z 600.4799.

Preparation of the Thiolactones Listed in Table II. General Procedure: Preparation of Thiododecanolide. All the bromo acid chlorides used in this study were prepared according to the procedure described by Lee.[10] To a refluxed (2

(8) (a) The Gladysz procedure[5c] for the preparation of Li_2S is based on a degradative process of elemental sulfur (S_8) and therefore more likely produces an aggregated form of Li_2S as compared to our approach which uses HMDST, a reagent that essentially delivers a masked form of atomic sulfur. (b) We observed a similar "aging" effect with the preparation of B_2S_3.[4b]

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h) anhydrous THF (140 mL) solution of HMDST[7b] (1 mmol; 208 μL) and $LiEt_3BH$ (2 equiv) was added (at 25 °C) dropwise a THF (10 mL) solution of 12-bromododecanoyl chloride (1 mmol; 330 mg). The reaction mixture was then refluxed for 6 h and flash evaporated and the residue taken up in benzene (25 mL), filtered to remove inorganic material, and then concentrated in vacuo. Chromatography of the resulting oily residue on silica gel using hexanes/benzene (1:1) as the eluent gave three mobile components identified as a monomer, a dimer, and a trimer. Monomer (47%): ^1H NMR ($CDCl_3$) δ 2.96 (2 H, t, J = 5 Hz), 2.53 (2 H, t, J = 5 Hz), 1.29–1.77 (18 H, m); IR ($CHCl_3$) 1680 cm^{-1} (C=O); MS, calcd for $C_{12}H_{22}OS$ m/z 214.1389, found m/z 214.1393. Dimer (16%): ^1H NMR ($CDCl_3$) δ 2.89 (2 H, t, J = 7 Hz), 2.54 (2 H, t, J = 6 Hz), 1.26–1.55 (18 H, m); MS, calcd for $C_{24}H_{44}O_2S_2$ m/z 428.2778, found m/z 428.2753. Trimer (9%): ^1H NMR ($CDCl_3$) δ 2.87 (2 H, t, J = 7 Hz), 2.54 (6 H, t, J = 7 Hz), 1.26–1.58 (18 H, m); MS, calcd for $C_{36}H_{72}O_3S_3$ m/z 642.4167, found m/z 642.4119. Carrying out the same reaction using 1.4 L (instead of 140 mL) of solvent gave an 86% isolated yield of the monomer and only trace quantities of the dimer and trimer.

Thiohexanolide. Monomer (73%): ^1H NMR ($CDCl_3$) δ 2.78–3.03 (4 H, m), 1.73–2.11 (6 H, m); IR ($CHCl_3$) 1660 cm^{-1} (C=O); MS, calcd for $C_6H_{10}OS$ m/z 130.0451, found m/z 130.0453.

Thiooctanolide. Dimer (30%): ^1H NMR ($CDCl_3$) δ 2.91 (2 H, t, J = 7 Hz), 2.54 (2 H, t, J = 7 Hz), 1.32–1.62 (12 H, m); IR ($CHCl_3$) 1675 cm^{-1} (C=O); MS, calcd for $C_{16}H_{28}O_2S_2$ m/z 316.1529, found m/z 316.1554.

Thioundecanolide. Monomer (19%): ^1H NMR ($CDCl_3$) δ 3.01 (2 H, t, J = 6 Hz), 2.54 (2 H, t, J = 6 Hz), 1.30–1.89 (16 H, m); IR ($CHCl_3$) 1670 cm^{-1} (C=O); MS, calcd for $C_{11}H_{20}OS$ m/z 200.1234, found m/z 200.1263. Dimer (20%): ^1H NMR ($CDCl_3$) δ 2.91 (2 H, t, J = 7 Hz), 2.55 (2 H, t, J = 7 Hz), 1.28–1.85 (16 H, m). Trimer (12%): ^1H NMR ($CDCl_3$) δ 2.91 (2 H, t, J = 7 Hz) 2.54 (2 H, t, J = 7 Hz), 1.28–1.86 (16 H, m).

Thiohexadecanolide. Monomer (64%): ^1H NMR ($CDCl_3$) δ 2.94 (2 H, t, J = 5 Hz), 2.56 (2 H, t, J = 7 Hz), 1.30–1.58 (26 H, m); IR ($CHCl_3$) 1670 cm^{-1} (C=O); MS, calcd for $C_{16}H_{30}OS$ m/z 270.2016, found m/z 270.2020.

Preparation of the Thiolactones Listed in Table II by the Gladysz Route.[5c] General Procedure: Preparation of Thiododecanolide. To a suspension of elemental sulfur (1 mmol; 32 mg) in anhydrous THF (140 mL) was added $LiEt_3BH$ (2 equiv). After the mixture was stirred for 15 min, a THF (10 mL) solution of 12-bromododecanoyl chloride was added dropwise. The reaction mixture was then refluxed for 6 h and worked up as above to give 53 mg (25%) of monomeric thiododecanolide identical in all respects with the material obtained by the above procedure.

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Registry No. **2**, 2471-92-3; HMDST, 3385-94-2; $Br(CH_2)_6Br$, 629-03-8; $Br(CH_2)_7Br$, 4549-31-9; $Br(CH_2)_8Br$, 4549-32-0; $Br(CH_2)_9Br$, 4549-33-1; $Br(CH_2)_{10}Br$, 4101-68-2; $Br(CH_2)_{12}Br$, 3344-70-5; $CH_2(CH_2)_5S(CH_2)_6S$, 295-32-9; $CH_2(CH_2)_6S(CH_2)_7S$, 295-80-7; $CH_2(CH_2)_{11}S(CH_2)_{12}S$, 98268-21-4; $Br(CH_2)_5COCl$, 22809-37-6; $Br(CH_2)_7COCl$, 73674-09-6; $Br(CH_2)_{10}COCl$, 15949-84-5; $Br(CH_2)_{11}COCl$, 61658-00-2; $Br(CH_2)_{15}COCl$, 73782-15-7; $CH_2(CH_2)_4COS$, 17689-16-6; $CH_2(CH_2)_6COS(CH_2)_7COS$, 98268-22-5; $CH_2(CH_2)_9COS$, 98268-23-6; $CH_2(CH_2)_9COS(CH_2)_{10}COS$, 98268-24-7; $CH_2(CH_2)_{10}COS$, 98268-25-8; $CH_2(CH_2)_{10}COS(CH_2)_{11}COS$, 98268-26-9; $CH_2(CH_2)_{14}COS$, 98268-27-0; Li_2S, 12136-58-2; MeLi, 917-54-4; $CH_2(CH_2)_{11}S(CH_2)_{12}S(CH_2)_{12}S$, 98303-54-9; $LiEt_3BH$, 89556-21-8; $CH_2(CH_2)_{10}COS(CH_2)_{11}COS(CH_2)_{11}COS$, 98268-28-1; $CH_2(CH_2)_9COS(CH_2)_{10}COS(CH_2)_{10}COS$, 98268-29-2; thiepane, 4753-80-4; thiocane, 6572-99-2; thionane, 6007-54-1; thiecane, 6048-83-5; thiacycloundecane, 408-32-2; 1,12-dithiacyclodocosane, 296-90-2; thiacyclotridecane, 295-05-6; α,α′-dibromo-o-xylene, 91-13-4; bis(triphenyltin) sulfide, 77-80-5.

(11) In this paper the periodic group notation is in accord with recent actions by IUPAC and ACS nomenclature committees. A and B notation is eliminated because of wide confusion. Groups IA and IIA become groups 1 and 2. The d-transition elements comprise groups 3 through 12, and the p-block elements comprise groups 13 through 18. (Note that the former Roman number designation is preserved in the last digit of the new numbering: e.g., III → 3 and 13.)

Synthesis of Aldehydes and Ketones from Nitro Paraffins[1]

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In connection with recent studies in this laboratory on the total synthesis of epimeric bicyclo[2.1.0]pentane derivatives **1a** and **1b** as potential thromboxane (TXA_2) inhibitors, and as synthetic precursors to prostaglandin endoperoxide PGH_2 (Scheme I), aldehyde **3a** figured prominently in our synthetic scheme.[3]

Several attempts to prepare this aldehyde by meticulously following the published procedure[4] for the ethyl carbamate analogue **3b** (Scheme II), in our hands, ended in complete and frustrating failure for both derivatives. With these examples, the Nef procedure's success is inhibited by the extreme lability of potassium salt derivatives **5**.[4] Since nitro paraffins are readily available[5] and since the Nef[6a] reaction presents one of the more attractive ways of converting nitro functionalities into carbonyl units,[6] we have developed, and describe herein, experimental modifications to this reaction that overcome the need to isolate labile intermediates such as **5**.

Ever since Nef[6a] first reported that primary and secondary nitro paraffins could upon treatment with mineral acids be respectively transformed into aldehydes and ketones, several variations of this reaction have appeared in the chemical literature.[6b-f] However, even recent experimental improvements as the most promising one of Kornblum,[6b] based on earlier work,[6c] failed to give appreciable yields for such functionally endowed structures such as our **3**. We have found that treatment of primary or secondary nitro paraffins with methanolic potassium hydroxide, in methanol at 0 °C, produces a stable, soluble form of the corresponding potassium salt. Oxidation, in situ, into its corresponding carbonyl derivative is then readily achieved and in high yield (see Table I) by addition

(1) Reagents for Organic Synthesis. 5. For the previous paper in this series, see: Steliou, K., Salama, P.; Corriveau, J. *J. Org. Chem.*, in press.

(2) Holder of a Merck (Canada) Predoctoral Fellowship.

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