The Addition of Thiols to Phosphonodithioformates: Reactivity of Phosphorylated Dithioacetal Disulfides

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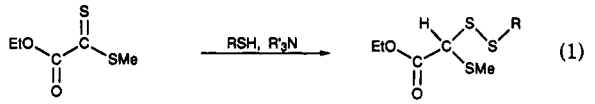
A high-yielding, thiophilic attack of thiolate ions onto phosphonodithioformates 1 led to the formation of the novel phosphorylated dithioacetal disulfides 2. Their lithiated carbanions could be both alkylated, giving access to [tris(alkylthio)methyl]phosphonates 5 via a [1,2]-Steven's type rearrangement of an intermediate sulfonium ylide D and used in Wittig-Horner reactions to give the ketene dithioacetal disulfides 7, which in turn could be cleaved by thiolate anions to the dithioesters 6. This second sequence represents a new synthesis of dithioesters starting from aldehydes with a one-carbon homologation.

The reaction between a nucleophile and the thiocarbonyl group of a dithioester is known to follow one of three possible pathways: either an attack at the carbon atom (carbophilic addition),[1] an attack at the sulfur atom (thiophilic addition),[2] or with strongly basic nucleophiles, such as organolithium reagents, deprotonation at the α-carbon (enethiolization).[3]

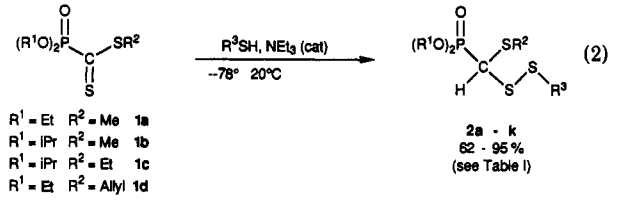
Phosphonodithioformates 1 are nonenethiolizable dithioesters functionalized by a phosphonic ester group.[4] Our choice to study the reactivity of these compounds was not arbitrary, as studies have shown that the presence of an electron-withdrawing substituent adjacent to the C=S bond of a dithioester favors thiophilic addition.[5] For example, trifluoromethanethiol has been shown to add thiophilically to hexafluorodithioacetate.[6] Moreover, conjugation between thiocarbonyl groups and an α-carbonyl function enhances the electrophilicity of the thiocarbonyl sulfur atom to the extent that thiophilic additions are observed even with nucleophiles such as thiols (eq 1) and allylic Grignard reagents which would otherwise react carbophilically.[5,7]



(1)

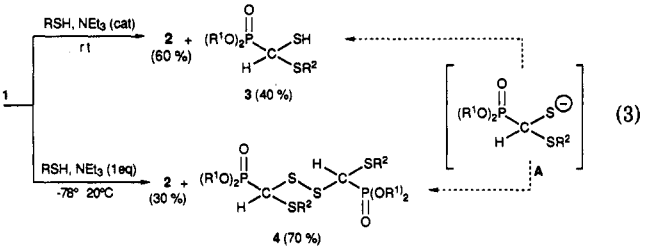
Following our previous work related to the addition of nucleophilic reagents (organometallics and trialkylphosphites) to phosphonodithioformates,[8,9] we report here our results concerning the addition of thiols to these functionalized dithioesters and the reactivity of the resulting phosphorylated dithioacetal disulfides.

Reaction of Phosphonodithioformates with Thiols. When the phosphonodithioformates **1a-d** were treated with alkyl-, aryl-, or benzylmercaptans, in the presence of a catalytic quantity of base (NEt_3) and at low temperature, the phosphorylated dithioacetal disulfides **2a-k**, resulting from a thiophilic attack, were obtained in good yields. The respective yields and ^1H and ^{31}P NMR characteristics of the products **2a-k** are assembled in Table I.



(2)

It was found that the products obtained were very much dependent on the conditions employed. If the addition was carried out at room temperature, the hemidithioacetal **3** was also obtained and the presence of 1 equiv of triethylamine led to the formation of (2,3-dithiabutylene)-diphosphonates **4** as the principal product. The possible formation of such alternative products shows that cleavage of the S-S bond can easily occur in the basic reaction medium leading to the thiolate anion A (eq 3), precursor of compounds **3** and **4**. Compound **3** results from the protonation of A, and the formation of **4** can result either by an attack of A on the S-S bond of the dithioacetal disulfide **2** or by a thiophilic addition of A to the starting dithioester **4**.



(3)

Equilibria between disulfides and thiolates have already been well documented,[10-12] with the relative stability of the disulfide bond of compound **4** probably originating from steric hindrance. This inherent steric stability of a disulfide bond will hereafter be employed in the successful synthesis of the ketene dithioacetal disulfides **7**.

Reactivity of the Phosphorylated Dithioacetal Disulfides. The use of carbanions stabilized by a phosphoryl group for the formation of carbon-carbon double bonds is well documented in the literature, and these preparations are known as the Wittig-Horner-Wadsworth-Emmons (W-H-W-E) reaction.[13-15] As such, eventual application

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Table I. ^1H and ^{31}P NMR Characteristics and Yields of Phosphorylated Dithioacetal Disulfides 2a–k

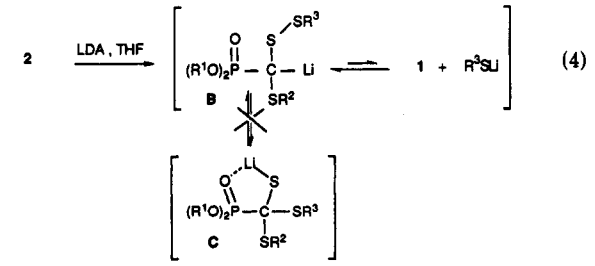
compd	R^1	R^2	R^3	yield (%)	^1H (CCl_4) δ PCH/J_{HP}	^{31}P ($CDCl_3$) δ P
2a	iPr	Me	tBu	95	3.57/17	16.11
2b	iPr	Me	$nC_{12}H_{25}$	92	3.80/16	16.16
2c	iPr	Me	nPr	90	3.60/16	16.22
2d	iPr	Me	Me	89	3.68/16	15.96
2e	iPr	Me	Ph	80	3.80[a]/17	16.02
2f	iPr	Me	Bz	62	3.50/17	18.10
2g	iPr	Et	Et	90	3.73/17	16.56
2h	Et	Me	Me	87	3.87/17	17.87
2i	iPr	Me	Et	90	3.73/16	16.16
2j	iPr	Et	Me	88	3.90/16	16.57
2k	Et	Allyl	tBu	69	3.77/16	18.62

[a] $CDCl_3$.

of these novel phosphorylated dithioacetal disulfides 2 in synthetic methodology was dependent on finding a suitable deprotonation method which did not cleave the disulfide bond.

An initial attempt with *n*-butyllithium at −78 °C followed by reprotonation gave an unidentified mixture of oligomeric products. When LDA was used, however, the starting dithioacetal disulfide 2 and/or the coupled compound 4 were isolated after the reaction, the ratios of which were dependent on the pH of the medium during the reprotonation step. When methanol acidified with hydrogen chloride gas was used the starting disulfide was regenerated quantitatively. However, when aqueous THF was used the coupled disulfide 4 was obtained (95%) with only a little of the starting disulfide 2 (5%).

To further elucidate the reaction sequence, we followed the deprotonation of compound **2d** by ^{31}P NMR (δ P = 15.96). The addition of LDA at −78 °C led to the clean appearance of two peaks. A major peak at δ 24.05 (>95%) and a minor peak at δ −4.24 (<5%). Considering that acidic reprotonation of the lithiated species gave the disulfide 2 and not a hemidithioacetal 3, we concluded that the lithiated species was a stabilized carbanionic intermediate B (eq 4) formed via deprotonation and not the thiolate ion A formed via S–S cleavage. The minor peak at δ −4.24 corresponded to the phosphonodithioformate **1a** formed via a β-elimination of lithium methanethiolate. The absence of other signals and the dependence on the pH for the formation of the coupled disulfide 4 strongly suggested that the latter was formed during the reprotonation step.



(4)

The proposed β-elimination, that is to say the formation of the equilibrium shown in eq 4, was confirmed by a simple crossover experiment. Equimolar quantities of dithioacetal disulfides **2d** and **2g** (Table I) were mixed together and treated with LDA. β-Elimination from **2d** gives the *S*-methyl dithioester **1b** and a methylthiolate ion and that from **2g** gives the *S*-ethyl dithioester **1c** and an ethylthiolate ion. Addition of these alkylthiolate ions onto the two dithioesters **1c** and **1b** with scrambling led to the formation of four carbanions. Acidic reprotonation, after 8 h, then gave a mixture of four dithioacetal disulfides **2d**, **2g**, **2i**, **2j** in identical yields. **2i** and **2j** were independently prepared by the base-catalyzed addition of methanethiol and ethanethiol to **1b** and **1c**, respectively, making possible the identification and ratio determination (^{31}P NMR) of the four dithioacetal disulfides in the reaction mixture.

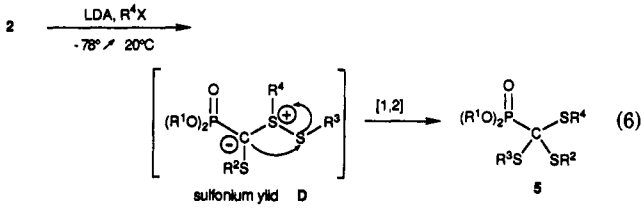
Table II. ^{31}P and ^{13}C NMR Characteristics and Yields of [Tris(alkylthio)methyl]phosphonates 5a–f

compd	R^1	R^2	R^3	R^4	yield (%)	NMR ^{31}P ($CDCl_3$) δ P	NMR ^{13}C ($CDCl_3$) δ PC/J_{CP}
5a	Et	Me	Me	Me	73	17.30	62.06/163.0
5b	iPr	Me	Me	Me	72	15.71	63.21/162.4
5c	iPr	Me	Me	Et	64	15.21	63.55/163.5
5d	iPr	Me	tBu	Me	68	14.68	64.50/165.2
5e	iPr	Et	Et	Me	67	14.99	63.88/163.0
5f	iPr	Me	Me	Cr[a]	66	15.97	62.70/163.7

[a] Cr = crotyl.

(5)

Alkylation of Lithiated Dithioacetal Disulfides. Having ascertained that selective deprotonation was possible, we then investigated the reactivity of the carbanions formed. The lithiated carbanions were generated from the starting disulfides 2 and then treated with alkyl or crotyl halides. After workup and isolation, the major products obtained were the [tris(alkylthio)methyl]phosphonates **5** (eq 6) and no C-alkylation products were detected. The respective yields and ^{31}P and ^{13}C NMR characteristics of compounds **5a–f** are given in Table II.



(6)

The possibility that the carbanion B existed in equilibrium with a thiolate ion C (eq 4), whereby protonation was occurring at the harder carbon atom but with alkylation occurring preferentially at the softer sulfur atom, was ruled out, for when the disulfide **2i** ($R^2 \neq R^3$) was treated with LDA and subsequently reprotonated, none of the potential R^2 and R^3 scrambling was observed. Therefore, the formation of [tris(alkylthio)methyl]phosphonate **5** is most probably due to an initial alkylation on the α-disulfide sulfur atom to form a sulfonium ylide D[16–19] which spontaneously undergoes a Steven's type [1,2] sigmatropic shift.[20]

A second crossover experiment (alkylating with methyl iodide after deprotonation) from the 50/50 mixture of dithioacetal disulfides **2d** and **2g** led to a mixture of the [tris(alkylthio)methyl]phosphonates **5b**, **5c**, and **5e** in the

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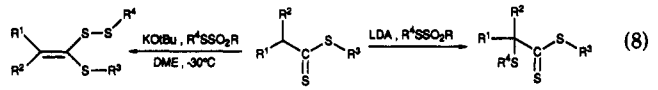
respective proportions 36/27/37 (eq 7). The formation

$$\underset{50\ :\ 50}{\mathbf{2d} + \mathbf{2g}} \xrightarrow[\text{MeI}]{\text{LDA, -78 °C, 15min}} \underset{36\ :\ 27\ :\ 37}{\mathbf{5b} + \mathbf{5c} + \mathbf{5e}} \qquad (7)$$

of the scrambled product **5c** (unexpected from an intramolecular transposition) can again be explained by the β-elimination (already above mentioned with carbanion B) leading here to a partial scrambling during the deprotonation step. The Steven's transposition is usually considered as an intramolecular rearrangement which can proceed via ion or radical pair inside a solvent cage.[20,21] In the present case, the hypothetical intermolecular rearrangement which would have given compounds **5b**, **5c** and **5e** in the ratio 25/50/25, can be ruled out.

With reference to compound **5f** (R^4 = crotyl), note that crotylation did not proceed via an S_N2' mechanism with inversion of the crotyl chain. Furthermore, no product resulting from the potentially competitive [2,3] sigmatropic rearrangement of the intermediate *S*-allylic sulfonium ylide D was observed.

Wittig-Horner-Wadsworth-Emmons Reaction of Lithiated Dithioacetal Disulfides. The preparation of vinyl disulfides by the alkylthiolation of enethiolates in liquid ammonia using thiosulfonates or thiocyanates was described by Brandsma et al.[22] The same sort of reaction starting from the enethiolates of dithioesters, however, may follow one of two different reaction pathways depending on the experimental conditions employed (eq 8). When

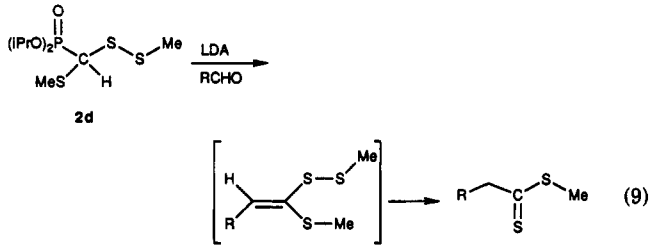


(8)

the enethiolate, generated in 1,2-dimethoxyethane with potassium *tert*-butoxide, was added to a slight excess of thiosulfonate, the corresponding ketenedithioacetal disulfide was obtained.[23]

If, however, the addition was inversed, a slight excess of *tert*-butoxide or more basic lithium amides were used, the only product obtained results from an alkylthiolation of the α-carbon. It has been shown in this last case that a ketenedithioacetal disulfide was initially formed but that cleavage of the disulfide bond occurred even in the presence of catalytic quantities of base with alkylthiolation of the α-carbon leading to the observed products.[23]

When we treated the α-phosphorylated dithioacetal disulfide **2d** with LDA at -78 °C followed by 1 equiv of aldehyde and then rapidly (20 min) warmed the mixture to room temperature before stirring for a further 4 h, we isolated, after purification, the dithioesters **6** (eq 9) in



(9)

6

a) R = C_6H_5- : 81% b) R = 4-CH_3-C_6H_4- : 82%
c) R = 4-CH_3O-C_6H_4- : 80% d) R=$(CH_3)_2CH$- : 18%.

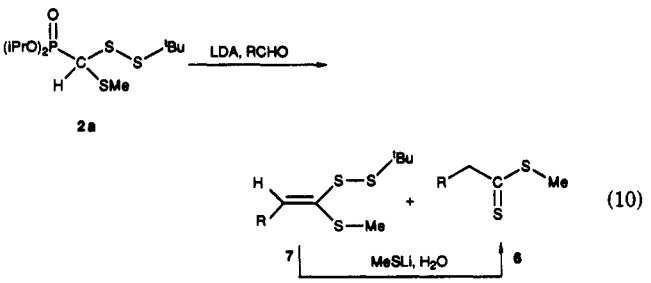
modest yields. Their formation may be interpreted by a W-H-W-E reaction leading to a ketene dithioacetal disulfide intermediate, which in the basic reaction medium undergoes S-S cleavage followed by protonation during workup. We did not, however, observe the formation of any α-methylthio dithioesters.[23]

The yields of the dithioesters were markedly improved (80% with nonenolizable aldehydes) when an excess of the dithioacetal disulfide **2d** was used, being maximized when 2.2 equiv were used. We concluded from this that the lithiated carbanion B not only participated in the W-H-W-E reaction but also in the cleaving of the disulfide bond. The thioalkylation of a stabilized carbanion such as B is probably not a very quick reaction. It is, therefore, plausible to envisage the breaking of the S-S bond by a methylthiolate ion, present in the mixture due to the partial β-elimination mentioned previously, to form methyl disulfide instead of the α-methylthio dithioesters described by Brandsma.

Having investigated the possibilities of this option as a novel synthesis of dithioesters and in order to confirm the mechanism of this reaction, we redirected our efforts to the initial objective of preparing the presumed intermediate ketene dithioacetal disulfides and in particular to protecting the disulfide bond with a bulkier substituent.

Thus, we carried out the reaction using molar equivalents to [(*tert*-butyldithio)(methylthio)methyl]-phosphonate (**2a**) and benzaldehyde, and without altering any other of the experimental conditions we isolated the ketene dithioacetal disulfide **7a** in 82% yield after publication. The ^1H and ^{13}C NMR spectra show the presence of a single isomer (probably the sterically favored *E*-isomer) which can be slowly isomerized in refluxing xylene (140 °C) to a mixture of the two isomers.

When we repeated the reaction with 2 equiv of dithioacetal per 1 equiv of benzaldehyde, a mixture of the ketene dithioacetal disulfide **7a** and the dithioester **6a** were obtained. This shows that the excess of the lithiated carbanion B leads to a partial cleavage of the disulfide bond. The combined yields of these two products is quantitative with respect to the starting aldehyde. This reaction was also carried out with tolualdehyde and isobutyraldehyde. In these two cases we observed, even with equimolar amounts of **2a** and aldehyde, the formation of noticeable amounts of the dithioesters along with the ketene dithioacetal disulfides. The subsequent conversion of these ketene dithioacetal disulfides to the corresponding dithioesters could be readily achieved by treating them with lithium methylthiolate followed by hydrolysis. This is in accordance with a probable intervention of the methylthiolate anion in the partial or complete cleavage of the S-S bond which occurs during these W-H-W-E reactions.



(10)

In Table III are listed the results obtained from the different stoichiometric mixtures of the disulfides **2a** and **2d** with the various aldehydes. For comparison purposes, the overall yields of dithioesters (after lithium methylthiolate conversion when appropriate) are given in the last column.

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Table III. Reactions of Lithiated 2a and 2d with Aldehydes

method[a]	aldehyde RCHO	dithioester no./yield (%)	disulfide no./yield (%)	overall yield (%) of dithioesters 6a–d
A	C_6H_5–	6a/81	7a/0	81
A	$CH_3C_6H_4$–	6b/82	7b/0	82
A	$CH_3OC_6H_4$–	6c/80	–/0	80
A	$(CH_3)_2CH$–	6d/18	7d/0	18
B	C_6H_5–	6a/0	7a/82	58
B	$CH_3C_6H_4$–	6b/24	7b/44	54
B	$(CH_3)_2CH$–	6d/6	7d/23	23
C	C_6H_5–	6a/29	7a/70	78
C	$(CH_3)_2CH$–	6d/30	7d/43	62

[a] A = 2 equiv of 2d; B = 1 equiv of 2a; C = 2 equiv of 2a.

Conclusion

The base-catalyzed, thiophilic addition of thiols to phosphonodithioformates 1 leads to the formation of the novel phosphorylated dithioacetal disulfides 2 in high yields. These compounds may be deprotonated by LDA, and the carbanions B so formed may be subsequently (a) alkylated to give [tris(alkylthio)methyl]phosphonates 5, via a [1,2] sigmatropic rearrangement of an intermediate sulfonium ylide D and (b) condensed onto aldehydes to give either ketene dithioacetal disulfides 7 or dithioesters 6. As dithioesters can be easily transformed into dithioacetals by thiophilic addition of Grignard reagents,[24] this second reaction is the synthetic equivalent of a one-carbon homologation with respect to the starting aldehyde. Moreover, to our knowledge it is the first example of synthetic use of a carbanion α to a disulfide function.

Experimental Section

General Procedures. All commercial reagents employed were checked for purity before use and purified if necessary. All solvents were dried and freshly distilled before use according to described procedures.

Preparative medium-pressure liquid chromatography was carried out on a Jobin-Yvon Modulprep apparatus using Merck 60 (4–5 μm) silica gel packed with the appropriate solvent at 10 bars of pressure. The samples were injected at a pressure of 1–2 bars and subsequently eluted at 10 bars. Flash liquid chromatography was carried out on Merck 60 (63–200 μm) silica gel.

The ^1H NMR spectra were recorded at either 60 or 200 MHz. The chemical shifts (δ) are referenced against an internal TMS standard, and the coupling constants (J) are given in hertz. The ^{13}C and ^{31}P NMR spectra were both recorded at 20.15 and 32.44 MHz, respectively, with the chemical shifts referenced against the deuterated solvent and external H_3PO_4, respectively.

The mass spectra were recorded by electron impact at 70 eV. The chemical ionization mass spectra were carried out using ammonia.

Phosphonodithioformates (1). The starting dark red liquid dithioesters were prepared according to the method described by Grisley.[4]

Methyl (Diethoxyphosphinyl)methanedithioate (1a). 70% yield.

Methyl (Diisopropoxyphosphinyl)methanedithioate (1b). 80% yield.

Ethyl (Diisopropoxyphosphinyl)methanedithioate (1c). 50% yield. ^1H (CCl_4): 1.30 and 1.39 (2d, 12 H, J_{HH} = 7, $[(CH_3)_2CHO]_2P(O)$), 1.40 (t, 3 H, J = 7, SCH_2CH_3), 3.31 (q, 2 H, J = 7, SCH_2CH_3), 4.78 (dsept, 2 H, $J_{HH} \approx J_{HP} \approx 7$, $[(CH_3)_2CHO]_2P(O)$). ^{31}P ($CDCl_3$): –4.25. ^{13}C ($CDCl_3$): 11.49, 23.60, and 24.02 (2d, J_{CP} = 4.6), 29.90 (d, J = 2.9), 73.50 (d, J = 6.4), 231.03 (d, J = 176.5, C=S). MS m/z: 270 ($M^{\bullet+}$, 100), 229 (93), 228 (31), 227 (24), 187 (46), 123 (34), 105 (41), 77 (22), 45 (20), 43 (54).

Allyl (Diethoxyphosphinyl)methanedithioate (1d). 30% yield. ^1H (CCl_4): 1.33 (t, 6 H, J = 7, $(CH_3CH_2O)_2P(O)$), 3.90 (m, 2 H, $SCH_2CH{=}CH_2$), 4.17 (dq, 4 H, $J_{HH} \approx J_{HP} \approx 7$, $(CH_3CH_2O)_2P(O)$), 5.39–5.50 (m, 3 H, $CH_2CH{=}CH_2$). ^{31}P ($CDCl_3$): –2.71. ^{13}C ($CDCl_3$): 16.26 (d, J = 5.9), 38.33 (d, J = 2.4), 64.63 (d, J = 6.8), 120.59, 129.38, 228.50 (d, J = 174.9; C=S). MS m/z: 254 ($M^{\bullet+}$, 12), 182 (11), 165 (13), 138 (12), 65 (18), 41 (100), 29 (96).

Phosphorylated Dithioacetal Disulfides 2. A solution of phosphono dithioester 1 (2 mmol) in THF (20 mL) is placed in a 50-mL two-necked round-bottomed flask fitted with a thermometer and magnetic stirring bar under an inert atmosphere (N_2). At –78 °C, thiol (2.2 mmol) is added, followed by triethylamine (15 μL). The mixture is stirred at this temperature until total decolorization of the dithioester is achieved. The solvent is removed on a rotary evaporator and the crude product purified by silica gel flash chromatography[25] (petrol–ether (3:1)). In some cases, slight formation of the starting dithioester (β-elimination) occurs during the purification.

If the reaction is carried out at rt then the thiol 3 is obtained in 40% yield, and if the reaction is carried out using 1 equiv or more of amine then the coupled disulfides 4 are obtained in ca. 70% yields. All products (2a–2k, 3, and 4a–4c) are colorless oils.

Diisopropyl [(*tert*-Butyldithio)(methylthio)methyl]phosphonate (2a). 95% yield. ^1H (CCl_4): 1.35 (d, 12 H, J = 7, $[(CH_3)_2CHO]_2P(O)$), 1.40 (s, 9 H, $(CH_3)_3CS$), 2.31 (s, 3 H, SCH_3), 3.57 (d, 1 H, J = 17, PCH), 4.77 (dsept, 2 H, $J_{HH} \approx J_{HP} \approx 7$, $[(CH_3)_2CHO]_2P(O)$). ^{31}P ($CDCl_3$): 16.11. ^{13}C ($CDCl_3$): 14.83 (d, J = 3.6), 23.80 and 24.21 (2d, J = 5.9), 30.00, 48.33, 54.70 (d, J = 149.0, PCH), 72.07 and 72.26 (d, J = 7.2). MS m/z: 346 ($M^{\bullet+}$, 23), 225 (9), 183 (100), 141 (45), 57 (40). Sulfur analysis: calcd 27.75, found 27.73.

Diisopropyl [(*n*-Dodecyldithio)(methylthio)methyl]phosphonate (2b). 92% yield. ^1H (CCl_4): 0.87 (t, 3 H, J = 7, $SC_{11}H_{22}CH_3$), 1.30 (m, 20 H, $SCH_2C_{10}H_{20}CH_3$), 1.38 (d, 12 H, J = 7, $[(CH_3)_2CHO]_2P(O)$), 2.30 (s, 3 H, SCH_3), 2.70 (t, 2 H, J = 7, $SCH_2C_{11}H_{23}$), 3.80 (d, 1 H, J = 16, PCH), 4.80 (dsept, 2 H, $[(CH_3)_2CHO]_2P(O)$). ^{31}P ($CDCl_3$): 16.11. ^{13}C ($CDCl_3$): 14.05, 15.29 (d, J = 4.4), 23.97 and 24.16 (2d, J = 6.8), 22.66, 24.34, 28.51, 28.95, 29.24, 29.35, 29.52, 29.59, 29.63 and 31.93, 39.60 (d, J = 1.3), 54.98 (d, J = 149.3, PCH), 72.19 and 72.41 (d, J = 7.3). MS m/z: 458 ($M^{\bullet+}$, 1), 225 (49), 183 (100), 143 (32), 141 (22), 69 (37), 59 (40), 57 (38), 55 (52). Sulfur analysis: calcd 20.96, found 21.28.

Diisopropyl [(Methylthio)(*n*-propyldithio)methyl]phosphonate (2c). 90% yield. ^1H (CCl_4): 1.00 (t, 3 H, J = 7, $CH_2CH_2CH_3$), 1.35 (d, 12 H, J = 7, $[(CH_3)_2CHO]_2P(O)$), 1.67 (tq ≈ sext, 2 H, $J \approx J \approx 7$; $CH_2CH_2CH_3$), 2.27 (s, 3 H, SCH_3), 2.83 (t, 2 H, J = 7; $CH_2CH_2CH_3$), 3.60 (d, 1 H, J = 16; PCH), 4.67 (dsept, 2 H, $[(CH_3)_2CHO]_2P(O)$). ^{31}P ($CDCl_3$): 16.22. ^{13}C ($CDCl_3$): 12.99, 15.24 (d, J = 5.0), 22.42, 23.65 and 24.40 (2d, J = 4.1), 41.42 (d, J = 1.4), 54.91 (d, J = 149.4, PCH), 71.90 and 72.48 (2d, J = 7.2). MS m/z: 332 ($M^{\bullet+}$, 3), 225 (46), 183 (100), 143 (35), 141 (64), 123 (16), 59 (25), 47 (18), 45 (37). Sulfur analysis: calcd 28.93, found 28.55.

Diisopropyl [(Methyldithio)(methylthio)methyl]phosphonate (2d). 89% yield. ^1H (CCl_4): 1.32 (d, 12 H, J = 7, $[(CH_3)_2CHO]_2P(O)$), 2.27 (s, 3 H, SCH_3), 2.37 (s, 3 H, $SSCH_3$), 3.68 (d, 1 H, J = 16, PCH), 4.70 (dsept, 2 H, $[(CH_3)_2CHO]_2P(O)$). ^{31}P ($CDCl_3$): 15.96. ^{13}C ($CDCl_3$): 15.33 (d, J = 4.6), 23.94, 23.90 and 24.21 (2d, J = 4.1), 54.63 (d, J = 149.9 PCH), 72.18 and 72.44 (2d, J = 7.2). MS m/z: 304 ($M^{\bullet+}$, 10), 225 (52), 183 (80), 143 (56), 141 (100), 127 (18), 123 (34), 91 (21), 77 (36). Sulfur analysis: calcd 31.60, found 31.81.

Diisopropyl [(Methylthio)(phenyldithio)methyl]phosphonate (2e). 80% yield. ^1H ($CDCl_3$): 1.35 (d, 12 H, J = 7, $[(CH_3)_2CHO]_2P(O)$), 2.16 (s, 3 H, SCH_3), 3.80 (d, 1 H, J = 17, PCH), 4.80 (dsept, 2 H, $[(CH_3)_2CHO]_2P(O)$), 7.20–7.70 (m, 5 H, $H_{arom.}$). ^{31}P ($CDCl_3$): 16.02. ^{13}C ($CDCl_3$): 15.18 (d, J = 4.3), 23.94, 23.88 and 24.20 (2d, J = 4.5), 53.82 (d, J = 149.4, PCH), 72.39 and 72.74 (2d, J = 6.5), 127.59, 129.04, 129.16, and 137.02 (4s, $C_{arom.}$).

Diisopropyl [(Benzyldithio)(methylthio)methyl]phosphonate (2f). 62% yield. ^1H (CCl_4): 1.32 (d, 12 H, J =

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7, [(CH_3)$_2$CHO]$_2$P(O)), 2.23 (s, 3 H, SCH_3), 3.50 (d, 1 H, J = 17, PCH), 4.13 (s, 2 H, C$H_2C_6H_5$), 4.73 (dsept, 2 H, [(CH_3)$_2$CHO]$_2$P(O)), 7.30 (m, 5 H, H_{arom}). ^{31}P (CDCl$_3$): 18.10.

Diisopropyl [(Ethyldithio)(ethylthio)methyl]phosphonate (2g). 90% yield. ^{1}H (CCl$_4$): 1.27 (t, 3 H, J = 7, SCH$_2$CH_3), 1.30 (t, 3 H, J = 7, SSCH$_2$CH_3), 1.35 (d, 12 H, J = 7, [(CH_3)$_2$CHO]$_2$P(O)), 2.83 (q, 2 H, J = 7, SCH_2CH$_3$), 2.97 (q, 2 H, J = 7, SSCH_2CH$_3$), 3.73 (d, 1 H, J = 17, PCH), 4.77 (dsept, 2 H, [(CH_3)$_2$CHO]$_2$P(O)). ^{31}P (CDCl$_3$): 16.56.

Diethyl [(Methyldithio)(methylthio)methyl]phosphonate (2h). 87% yield. ^{1}H (CCl$_4$): 1.33 (t, 6 H, J = 7, (CH_3CH_2O)$_2$P(O)), 2.30 (s, 3 H, SCH_3), 2.57 (s, 3 H, SSCH_3), 3.87 (d, 1 H, J = 17, PCH), 4.14 (dq, 4 H, $J_{HH} \approx J_{HP} \approx 7$, ($CH_3CH_2$O)$_2$P(O)). ^{31}P (CDCl$_3$): 17.87.

Diisopropyl [(Ethyldithio)(methylthio)methyl]phosphonate (2i). 90% yield. ^{1}H (CCl$_4$): 1.32 (t, 3 H, J = 7, SCH$_2$CH_3), 1.35 (d, 12 H, J = 7, [(CH_3)$_2$CHO]$_2$P(O)), 2.30 (s, 3 H, SCH_3), 2.83 (q, 2 H, J = 7, SCH_2CH$_3$), 3.73 (d, 1 H, J = 16, PCH), 4.73 (dsept, 2 H, [(CH_3)$_2$CHO]$_2$P(O)). ^{31}P (CDCl$_3$): 16.16. ^{13}C (CDCl$_3$): 14.32, 15.30 (d, J = 4.5), 23.87 (d, J = 6.1), 33.18, 54.99 (d, J = 149.6, PCH), 72.11 and 72.41 (2d, J = 6.1).

Diisopropyl [(Ethylthio)(methyldithio)methyl]phosphonate (2j). 88% yield. ^{1}H (CCl$_4$): 1.32 (d, 12 H, J = 7, [(CH_3)$_2$CHO]$_2$P(O)), 1.40 (t, 3 H, J = 7, SCH$_2$CH_3), 2.57 (s, 3 H, SCH_3), 2.83 (q, 2 H, J = 7, SCH_2CH$_3$), 3.90 (d, 1 H, J = 16, PCH), 4.83 (dsept, 2 H, [(CH_3)$_2$CHO]$_2$P(O)). ^{31}P (CDCl$_3$): 16.57.

Diethyl [(Allylthio)(*tert*-butyldithio)methyl]phosphonate (2k). 69% yield. ^{1}H (CCl$_4$): 1.33 (t, 6 H, J = 7, (CH_3CH_2O)$_2$P(O)), 1.37 (s, 9 H, SC(CH_3)$_3$), 3.50 (d, 2 H, SCH_2), 3.77 (d, 1 H, J = 16, PCH), 4.17 (dq, 2 H, $J_{HH} \approx J_{HP} \approx 7$, ($CH_3CH_2$O)$_2$P(O)), 4.93–6.20 (m, 3 H, CH$_2$CH=CH_2). ^{31}P (CDCl$_3$): 18.62. ^{13}C (CDCl$_3$): 16.36 and 16.65 (2d, J = 4.9), 30.14, 35.45 (d, J = 3.7), 48.41, 51.03 (d, J = 149.9, PCH), 63.72 and 63.81 (2d, J = 7.0), 118.71, 133.1. MS m/z: 344 (M$^{\bullet+}$, 7), 225 (3), 223 (100), 151 (22), 137 (13).

Diisopropyl [Mercapto(methylthio)methyl]phosphonate (3). 40% yield. ^{1}H (CCl$_4$): 1.32 (d, 12 H, J = 7, [(CH_3)$_2$CHO]$_2$P(O)), 2.30 (s, 3 H, SCH_3), 2.40 (dd ≈ t, 1 H, $J \approx J \approx 9$, SH), 3.68 (dd, 1 H, J = 16, 9, PC(SH)H), 4.70 (dsept, 2 H, [(CH_3)$_2$CHO]$_2$P(O)). ^{31}P (CDCl$_3$): 17.90. ^{13}C (CDCl$_3$): 15.00 (d, J = 4.2), 23.69 and 24.34 (2d, J = 4.7), 38.82 (d, J = 156.9, PCH), 72.60 and 72.66 (2d, J = 7.3). MS m/z: 258 (M$^{\bullet+}$, 20), 211 (22), 174 (45), 169 (25), 141 (21), 128 (99), 127 (100), 123 (24), 47 (33), 45 (83).

Tetraisopropyl [1,4-Bis(methylthio)-2,3-dithiabutylene]diphosphonate (4a). 70% yield (2 diastereoisomers A and B ≈ 1:1). ^{1}H (CCl$_4$): A 1.28 (d, 24 H, J = 7, [(CH_3)$_2$CHO]$_2$P(O) × 2), 2.23 (s, 6 H, SCH_3), 4.40 (d, 2 H, J = 15, PCH), 4.70 (dsept, 4 H, [(CH_3)$_2$CHO]$_2$P(O) × 2); B 1.28, 2.25, 4.42 (J = 13), and 4.70. ^{31}P (CDCl$_3$): A 15.55; B 15.71. MS m/z: 514 (M$^{\bullet+}$, 100), 467 (15), 257 (16), 229 (15), 215 (23), 183 (41), 141 (30), 127 (29), 123 (23), 91 (20).

Tetraethyl [1,4-Bis(methylthio)-2,3-dithiabutylene]diphosphonate (4b). 69% yield (2 diastereoisomers A and B ≈ 1:1). ^{1}H (CDCl$_3$): A 1.38 (t, 12 H, J = 7, (CH_3CH_2O)$_2$P(O) × 2), 2.37 (s, 6 H, SCH_3), 4.22 (dq, 8 H, $J \approx J \approx 7$) 4.40 (d, 2 H, J = 14, PCH × 2); B 1.32, 2.33, 4.18, and 4.42. ^{31}P (CDCl$_3$): A 18.21; B 18.34. ^{13}C (CDCl$_3$): A 15.63, 16.46 (d, J = 5.8), 53.31 (d, J = 149.8, PCH × 2), 63.63 and 64.02 (2d, J = 7.8); B 15.35, 16.46, 53.18 (J = 149.9), 63.63 and 64.02. MS m/z: 458 (M$^{\bullet+}$, 100), 229 (20), 197 (23), 141 (36), 109 (10), 91 (14), 81 (9), 61 (50). Sulfur analysis: calcd 27.95, found 27.76.

Tetraisopropyl [1,4-Bis(ethylthio)-2,3-dithiabutylene]diphosphonate (4c). 72% yield (2 diastereoisomers A and B ≈ 1:1). ^{1}H (CCl$_4$): A, 1.30 (t, 6 H, J = 7, SCH$_2$CH_3), 1.37 (d, 24 H, J = 7, [(CH_3)$_2$CHO]$_2$P(O) × 2), 2.82 (q, 4 H, J = 7, SCH_2CH$_3$), 4.52 (d, 2 H, J = 14, PCH), 4.83 (dsept, 4 H, [(CH_3)$_2$CHO]$_2$P(O) × 2); B, 1.32, 1.37, 2.80, 4.45 (J = 14), and 4.83. ^{31}P (CDCl$_3$): A 17.03; B 16.73. MS m/z: 542 (M$^{\bullet+}$, 100), 271 (27), 239 (15), 212 (9), 210 (31), 197 (18), 155 (16), 153 (16). Sulfur analysis: calcd 23.62, found 23.60.

[Tris(alkylthio)methyl]phosphonates 5. In a 100-mL, two-necked round-bottomed flask, fitted with a thermometer and magnetic stirrer and under a nitrogen atmosphere is generated a solution of LDA (2.2 mmol) in THF (20 mL) from diisopropylamine (2.3 mmol) and *n*-butyllithium (2.2 mmol) at −20 °C. The resulting solution is cooled to −78 °C, and the phosphono dithioacetal disulfides **2a**, **2d**, **2g**, or **2h** (2 mmol) are added dropwise. The formation of a lithiated carbanion is evidenced by an orange coloration of the solution. After 15 min and at the same temperature, methyl, ethyl, or crotyl halide (2.2 mmol) is added and the mixture left to warm slowly overnight.

After evaporation of the solvent, the reaction mixture is poured onto saturated NH_4Cl solution overlaid with ether. The combined organic phases are then washed with brine before being dried (Na_2SO_4). The pure product is obtained as a yellow oil after silica gel chromatography (ether–petrol (1:3)).

Diethyl [Tris(methylthio)methyl]phosphonate (5a). 73% yield. ^{1}H (CDCl$_3$): 1.37 (t, 6 H, J = 7, (CH_3CH_2O)$_2$P(O)), 2.30 (s, 9 H, SCH_3 × 3), 4.30 (dq, 4 H, $J_{HH} \approx J_{HP} \approx 7$, ($CH_3CH_2$O)$_2$P(O)). ^{31}P (CDCl$_3$): 17.30. ^{13}C (CDCl$_3$): 13.87 (d, J = 1.4), 16.48 (d, J = 5.4), 52.06 (d, J = 162.6, PC), 64.42 (d, J = 7.4). MS (CI with NH_3) m/z: 291 (M$^{\bullet+}$, 2), 245 (11), 244 (10), 243 (100), 187 (3), 153 (3), 91 (4). Sulfur analysis: calcd 33.10, found 32.83.

Diisopropyl [Tris(methylthio)methyl]phosphonate (5b). 72% yield. ^{1}H (CDCl$_3$): 1.38 (d, 12 H, J = 7, [(CH_3CH_2O)]$_2$P(O)), 2.27 (s, 9 H, SCH_3 × 3), 4.83 (dsept, 2 H, $J_{HH} \approx J_{HP} \approx 7$, [($CH_3$)$_2CH$O]$_2$P(O)). ^{31}P (CDCl$_3$): 15.71. ^{13}C (CDCl$_3$): 13.91 (d, J = 1.2), 23.66 and 24.38 (2d, J = 4.4), 62.30 (d, J = 163.5, PC), 72.96 (d, J = 7.5). MS m/z: 318 (M$^{\bullet+}$, 1), 271 (94), 187 (100), 121 (18), 107 (52), 91 (68), 61 (15), 47 (34). Sulfur analysis: calcd 30.19, found 29.79.

Diisopropyl [Bis(methylthio)(ethylthio)methyl]phosphonate (5c). 64% yield. ^{1}H (CCl$_4$): 1.23 (t, 3 H, J = 7, SCH$_2$CH_3), 1.35 (d, 12 H, J = 7, [(CH_3)$_2$CHO]$_2$P(O)), 2.23 (s, 6 H, SCH_3 × 2), 2.83 (q, 2 H, J = 7, SCH_2CH$_3$), 4.77 (dsept, 2 H, [(CH_3)$_2$CHO]$_2$P(O)). ^{31}P (C_6D_6): 15.21. ^{13}C (C_6D_6): 13.81, 14.17 (d, J = 1.3), 23.75 and 24.46 (2d, J = 4.6), 25.45 (d, J = 1.5), 63.55 (d, J = 163.6, PC), 72.74 (d, J = 7.4). MS m/z: 332 (M$^{\bullet+}$, 1), 285 (48), 271 (34), 243 (93), 229 (95), 187 (100), 167 (42), 91 (43), 47 (33). Sulfur analysis: calcd 28.92, found 28.85.

Diisopropyl [(*tert*-Butylthio)bis(methylthio)methyl]phosphonate (5d). 70% yield. ^{1}H (CDCl$_3$): 1.38 and 1.42 (2d, 12 H, J = 7 [(CH_3)$_2$CHO]$_2$P(O)), 1.57 (s, 9 H, SC(CH_3)$_2$), 2.37 (s, 6 H, SCH_3 × 2), 4.90 (dsept, 2 H, [(CH_3)$_2$CHO[$_2$P(O)). ^{31}P (CDCl$_3$): 14.68. ^{13}C (CDCl$_3$): 15.25, 23.71, and 24.12 (2d, J = 5.9), 32.43, 52.07 (d, J = 3.9), 64.5 (d, J = 165.2, PC), 73.13 (d, J = 8.0). MS m/z: 360 (M$^{\bullet+}$, 1), 313 (17), 271 (100), 215 (20), 173 (72), 139 (16), 91 (93), 57 (77).

Diisopropyl [Bis(ethylthio)(methylthio)methyl]phosphonate (5e). 67% yield. ^{1}H (CCl$_4$): 1.23 (t, 6 H, J = 7, SCH$_2$CH_3 × 2), 1.35 (d, 12 H, J = 7, [(CH_3)$_2$CHO]$_2$P(O)), 2.27 (s, 3 H, SCH_3), 2.87 (q, 4 H, J = 7, SCH_2CH$_3$ × 2), 4.77 (dsept, 2 H, [(CH_3)$_2$CHO]$_2$P(O)). ^{31}P (C_6D_6): 14.99. ^{13}C (C_6D_6): 13.87, 14.20 (d, J = 1.5), 23.78 and 24.50 (2d, J = 4.6), 25.47 (d, J = 1.5), 63.60 (d, J = 163.6, PC), 72.73 (d, J = 7.8). MS m/z: 346 (M$^{\bullet+}$, 1), 299 (90), 285 (100), 243 (62), 215 (57), 181 (21), 105 (31), 91 (64). Sulfur analysis: calcd 27.75, found 27.55.

Diisopropyl [(Crotylthio)bis(methylthio)methyl]phosphonate (5f). 66% yield. ^{1}H (CDCl$_3$): 1.38 and 1.42 (2d, 12 H, J = 7, [(CH_3)$_2$CHO]$_2$P(O)), 1.70 (d, 3 H, J = 5, CH_3CH=CH), 2.30 (s, 6 H, SCH_3 × 2), 3.53 (d, 2 H, J = 5, SCH_2CH=CH), 4.87 (dsept, 2 H, [(CH_3)$_2$CHO]$_2$P(O)), 5.40–5.83 (m, 2 H, SCH$_2$CH=CHCH$_2$). ^{31}P (CDCl$_3$): 15.97. ^{13}C (CDCl$_3$): 14.20 (d, J = 1.1), 17.78, 23.75, and 24.42 (2d, J = 4.5), 33.80 (d, J = 1.2), 62.70 (d, J = 163.7, PC), 73.23 (d, J = 8.0), 125.45, 129.82. MS m/z: 358 (M$^{\bullet+}$, 1), 311 (75), 271 (68), 257 (37), 215 (32), 187 (54), 173 (85), 91 (100).

Dithioesters 6 and Ketene Dithioacetal Disulfides 7. In a 100-mL, two-necked round-bottomed flask, fitted with a thermometer and magnetic stirrer and under a nitrogen atmosphere is generated a solution of LDA (4.4 mmol) in THF (30 mL) from diisopropylamine (4.6 mmol) and *n*-butyllithium (4.4 mmol) at −20 °C. The resulting solution is cooled to −78 °C and the phosphono dithioacetal disulfide **2d** or **2a** (4 mmol) is added dropwise. The formation of a lithiated carbanion is evidenced by an orange coloration of the solution. At the same temperature, the aldehyde (2 mmol) is added, after which the flask is immediately removed from the dry ice bath and left to stir overnight.

The solvent is removed on the rotary evaporator and the crude mixture extracted from a saturated solution of ammonium chloride overlaid with ether. The organic phase is then washed with brine

before being dried over sodium sulphate. The products are obtained as yellow oils by silica gel flash chromatography (eluent = pentane).

Methyl 2-Phenylethanedithioate (6a).

Methyl 4'-Methyl-2-phenylethanedithioate (6b).

Methyl 4'-Methoxy-2-phenylethanedithioate (6c).

Methyl 3-Methyl-butanedithioate (6d).

1-[2-(*tert*-Butyldithio)-2-(methylthio)ethenyl]benzene (7a). 82% yield. ^{1}H (CCl_4): 1.27 (s, 9 H, $SC(CH_3)_3$), 2.20 (s, 3 H, SCH_3), 7.00–7.63 (m, 5 H, H_{arom}), 7.47 (s, 1 H, $Ph(H)C{=}C$). ^{13}C ($CDCl_3$): 17.78, 30.07, 49.69, 127.34, 128.13, 128.9, 135.50, 135.91, 130.26. MS *m/z*: 270 ($M^{\bullet+}$, 24), (46), 181 (27), 149 (60), 134 (100), 121 (13), 91 (68), 57 (52). Sulfur analysis: calcd 35.56, found 35.76.

1-[2'-(*tert*-Butyldithio)-2'-(methylthio)ethenyl)-4-methylbenzene (7b).[26] 44% yield. ^{1}H (CCl_4): 1.40 (s, 9 H, $SC(CH_3)_3$), 2.33 (s, 3 H, SCH_3), 2.50 (s, 3 H, $C_6H_4CH_3$), 7.13 (s, 1 H, $C_6H_4(H)C{=}$), 7.28 (AB system, 4 H, d_A = 7.08, d_B = 7.48, J = 8, H_{arom}). ^{13}C ($CDCl_3$): 17.72, 21.20, 30.07, 49.57, 128.91, 129.16, 134.34, 137.20, 133.17, 130.59.

(26) Compounds **7b** and **7d** were characterized by NMR from the crude mixtures before complete conversion to the dithioesters **6** by treatment with lithium methylthiolate.

1-(*tert*-Butyldithio)-1-(methylthio)-3-methylbutene (7d).[26] 43% yield. ^{1}H (CCl_4): 0.98 (d, 6 H, J = 7, $(CH_3)_2CHC(H){=}$), 1.33 (s, 9 H, $SC(CH_3)_3$), 2.13 (s, 3 H, SCH_3), 2.73–3.33 (m, 1 H, $(CH_3)_2CHC(H){=}$), 6.10 (d, 1 H, J = 9, $(CH_3)_2CHC(H){=}$). ^{13}C ($CDCl_3$): 17.76, 22.42, 30.08, 49.59, 60.92, 130.9, 142.0.

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Registry No. **1a**, 55921-51-2; **1b**, 92659-86-4; **1c**, 141982-83-4; **1d**, 141982-84-5; **2a**, 141982-85-6; **2b**, 141982-86-7; **2c**, 141982-87-8; **2d**, 141982-88-9; **2e**, 141982-89-0; **2f**, 141982-90-3; **2g**, 141982-91-4; **2h**, 141982-92-5; **2i**, 141982-93-6; **2j**, 141982-94-7; **2k**, 141982-95-8; **3**, 141982-96-9; (*R**,*R**)-**4a**, 141982-97-0; (*R**,*S**)-**4a**, 141982-98-1; (*R**,*R**)-**4b**, 141982-99-2; (*R**,*S**)-**4b**, 141983-00-8; (*R**,*R**)-**4c**, 141983-01-9; (*R**,*S**)-**4c**, 141983-02-0; **5a**, 141983-03-1; **5b**, 141983-04-2; **5c**, 141983-05-3; **5d**, 141983-06-4; **5e**, 141983-07-5; **5f**, 141983-08-6; **6a**, 2168-85-6; **6b**, 68542-17-6; **6c**, 76579-50-5; **6d**, 66312-45-6; (*E*)-**7a**, 141983-09-7; (*Z*)-**7a**, 141983-10-0; **7b**, 141983-11-1; $(CH_3)_2C{=}CH(SMe)SSBu\text{-}t$, 142003-29-0; $(i\text{-}PrO)_2P(O)C(SMe(SSMe^-)\cdot Li^+$, 141983-12-2; $(CH_3)_2CHO$, 78-84-2; *t*-BuSH, 75-66-1; $CH_3(CH_2)_{11}SH$, 112-55-0; PrSH, 107-03-9; MeSH, 74-93-1; PhSH, 108-98-5; $Ph(CH_2)_2SH$, 4410-99-5; EtSH, 75-08-1; PhCHO, 100-52-7; $4\text{-}MeC_6H_4CHO$, 104-87-0; $4\text{-}MeOC_6H_4CHO$, 123-11-5.

Synthetic Studies on Furanoheliangolides. Stereocontrolled Construction of the Oxygen-Bridged Tricyclic Framework

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The heavily functionalized 6,9-epoxycyclodeca[*b*]furan-11-ones **34** and **37** have been prepared in 13 steps from 4-methyl-2-[(phenylmethoxy)methyl]furan. The key elements of the scheme include a high-pressure Diels–Alder cycloaddition to 1-cyanovinyl acetate, highly regioselective hydroboration, controlled stepwise oxidation to give keto aldehyde **20**, and thermal oxy-Cope rearrangement of both **32** and **36b**. The prior introduction of a phenylthio substituent provides for the accommodation of different levels of unsaturation at a more advanced stage of furanoheliangolide construction. While the present strategy is developed around a racemic model, the potential for adoption of enantioselective features is immediate. The overall stereocontrolled sequence provides a general and flexible entry into oxygen-bridged frameworks closely related to substructures occurring in many furan-type germacranolides.

Many sesquiterpenes characterized by the presence in their framework of a 6,9-epoxycyclodeca[*b*]furan structural array have been identified[2] since zexbrevin (**1**), the first member of this class to be isolated, was reported in 1970.[3] This large family of tricyclic α-methylene lactones features an enormous range of stereochemical variation and pattern of oxygenation as reflected in goyazensolide (**2**),[4] isocentratherin (**3**),[4a,5] tagitinin B (**4**),[6] and tirotundin (**5**).[6a,b,7] Additional cyclization to the ester side chain as found in eremantholide C (**6**)[4b,c,8] further enriches the variations

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(2) For a survey of this area of natural products, see: Brown, D. S.; Paquette, L. A. *Heterocycles* **1992**, *34*, 807.

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