

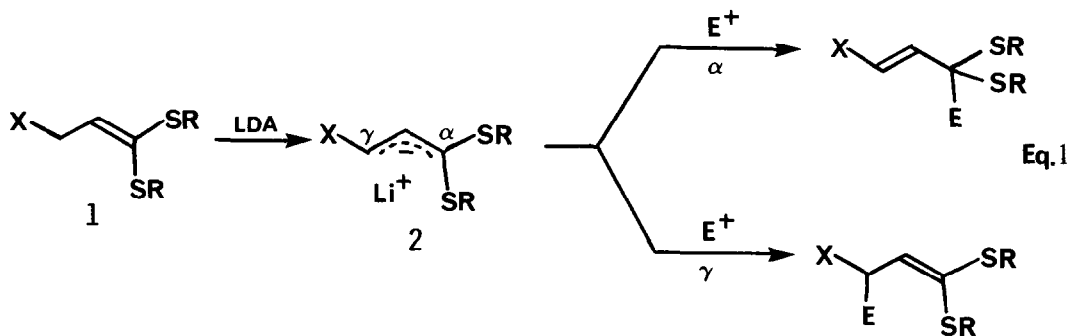
γ -SUBSTITUTED KETENE THIOACETALS AS β -LITHIOACRYLATE EQUIVALENTS.
THE SYNTHESIS OF (\pm)-ELDANOLIDE

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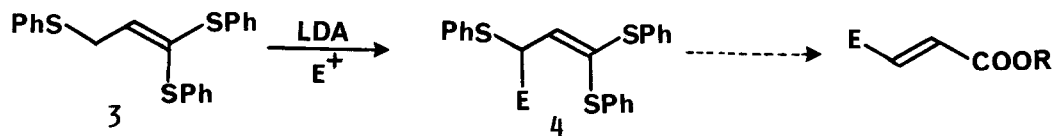
Summary: Lithiation of 1,1-bis(phenylthio)-3-phenylthio-1-propene **3** and reaction with a range of electrophiles gave exclusively the γ -substituted product **4**. This reagent has been used in a short synthesis of the pheromone, (\pm)-eldanolide.

The ready availability of ketene thioacetals has reinforced the role of these compounds as useful synthetic intermediates.¹ A particularly important aspect of their chemistry that has been widely exploited involves lithiation of **1** and reaction of the resulting anion **2** with various electrophiles.



The synthetic value of this process is controlled by the regioselectivity (α vs γ) of electrophilic attack at this ambident anion. In general alkylation (with RX, Me₃SiCl, also D₂O) takes place at the 'harder' α -site while aldehydes and ketones react predominantly at the 'softer' γ -site. (Eq. 1)² However this regioselectivity is sensitive to a number of factors one of which is the nature of the substituent (X) at the γ -position of **1**.³



We now report that incorporation of a γ -phenylthio group into **1** (R=R'=Ph, X=SPh i.e. **3**) directs both 'hard' and 'soft' electrophiles to the γ -site exclusively. In addition, hydrolysis of the ketene thioacetal moiety and elimination of thiophenol from these adducts (i.e. **4**) allows 1,1-bis(phenylthio)-3-phenylthio-1-propene **3** to be regarded as a versatile β -lithioacrylate equivalent.⁴



Preparation of **3** was carried out in two steps, in 83% overall yield, from α -bromoacrolein. Addition of thiophenol (3eq. PhSH/BF₃·Et₂O/CH₂Cl₂) to α -bromoacrolein followed by elimination of HBr (DBU/CH₂Cl₂) gave **3** as a pale yellow oil which crystallised at -15°C.⁵ Lithiation of **3** was carried out using LDA/THF at -78°C. The resultant solution was warmed to -40°C and maintained at this temperature for 30 minutes. The anion solution was then recooled to -78°C and treated with the appropriate electrophile. The reaction mixture was generally allowed to warm to room temperature before addition of aqueous NH₄Cl. When cyclopentanone and cyclohexanone were involved, however, best results were obtained by quenching the reaction mixture at -78°C.

A variety of electrophiles were examined (see Table) and in all cases the γ -regioisomer **4** was the only product isolated.⁶

This regiochemical assignment is based primarily on NMR (¹H and ¹³C) and, for entries (viii), (ix) and (x), this assignment was confirmed by conversion of the product to the corresponding α,β -unsaturated lactone (**5**, **6** and **7** respectively) using the conditions described below.⁷

TABLE	Entry	Electrophile	Yield of 4 (%)
	(i)	MeI	82 ^a
	(ii)	PhCH ₂ Br	87 ^b
	(iii)	Br-CH=CH ₂	82
	(iv)	 Br	42
	(v)	Me ₃ SiCl	95
	(vi)	D ₂ O	88
	(vii)	PhCHO	70 ^c
	(viii)		72
	(ix)	cyclopentanone	70 ^d
	(x)	cyclohexanone	93

a. Use of (MeO)₂SO₂ gave **4** (E=Me) in 81% yield.

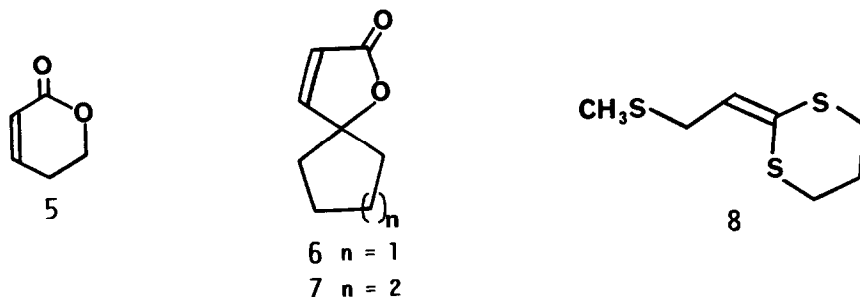
b. Alkylation in the presence of HMPA still gave the γ -regioisomer as the sole product.

c. Obtained as a 3:2 mixture of diastereoisomers.

d. Unlike cyclohexanone, cyclopentanone has been shown to react preferentially at the α -site.²

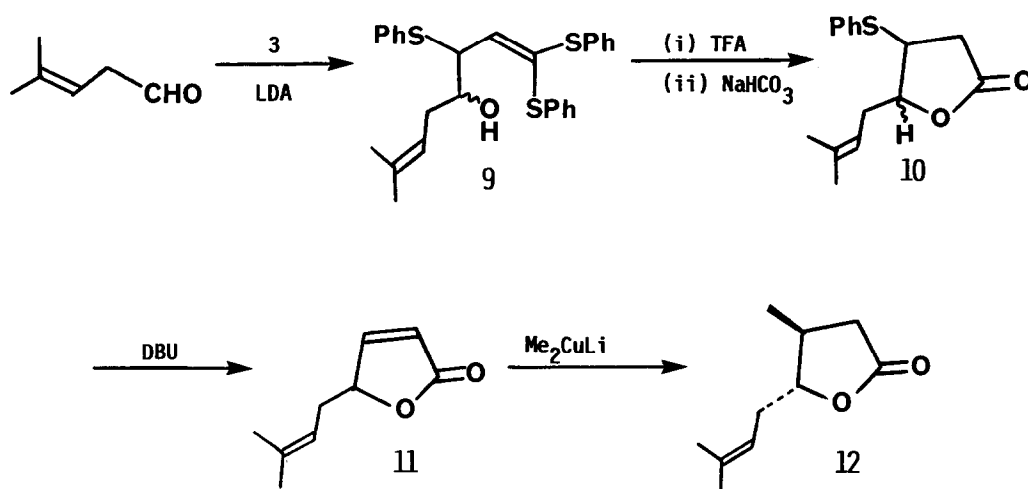
Entries (v) and (vi) are of particular interest. Even in systems that show a preference for γ alkylation (e.g. 1 R/R'=(CH₂)₃, X=Ph) these two electrophiles (Me₃SiCl and D₂O) still react

exclusively at the α -position.³ Benzylation of **3** is also significant (entry (ii)). Studies on a closely related system **8** by Corey and Kozikowski have shown that, in this case, the α -benzylated regioisomer was formed.⁸ Clearly further investigation is necessary to more accurately define the factors influencing α vs γ selectivity in carbanions of this type.



The use of **3** as a β -lithioacrylate equivalent is exemplified here by a short synthesis of (\pm)-eldanolide **11**, the wing gland pheromone of *Eldana saccharina* (wlk).⁹ Treatment of the lithio derivative of **3** with 4-methyl-3-pentenal¹⁰ gave alcohol **9** (85%) as a mixture of diastereoisomers. Lactonisation of **9** (TFA/ CH_2Cl_2 followed by $\text{NaHCO}_3/\text{H}_2\text{O}/\text{MeOH}$) and subsequent elimination of thiophenol from lactone **10** (DBU/ CH_2Cl_2) gave butenolide **11** (60% yield from **9**). This compound has been previously reported and was converted to (\pm)-eldanolide **12** (Me_2CuLi , 60%) as described by Kunesch *et al.*^{9d} (see Scheme).

SCHEME



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REFERENCES

1. M. Kolb, 'The Chemistry of Ketenes, Allenes and related compounds' S. Patia (Ed), Wiley (1980) p.670. B.T. Gröbel and D. Seebach, *Synthesis*, **1977**, 357.
2. A.P. Kozikowski and Y-Y. Chen, *J. Org. Chem.*, **45**, 2236, (1980) and references cited therein. See also F.E. Ziegler, J-M. Fang and C.C. Tam, *J. Am. Chem. Soc.*, **104**, 7174, (1982).
3. W.S. Murphy and S. Wattanasin, *J.C.S. Perkin I*, **1980**, 2678 and ref. 2.
4. a. D. Caine and A. Frobese, *Tetrahedron Letters*, **1978**, 883, 5167.
b. S. De Lomaert, B. Lesur, and L. Ghosez, *Tetrahedron Letters*, **1982**, 4251.
c. H.J. Gais, *Angew Chem. Int. Ed. Eng.*, **23**, 143, (1984).
d. K. Tanata, H. Yakita, H. Yoda, A. Kaji, *Chem. Lett.*, **1984**, 1359.
5. **4**: ^1H NMR $\delta(\text{CDCl}_3)$ 7.3-6.7(15H,m), 6.06(1H,t,J=7.5Hz), 3.76(2H,d,J=7.5Hz).
Although this material decomposed on attempted distillation it was easily purified by filtration through silica gel.
6. Satisfactory i.r., n.m.r. (^1H and ^{13}C) and high resolution mass spectral data were obtained for all new compounds. In general adducts **4**, which were all obtained as colourless or pale yellow oils, decomposed on attempted distillation. Purification was readily effected by chromatography over silica gel and all yields quoted are of purified products.
7. Spectral data (i.r. and n.m.r.) for spirolactones **6** and **7** were consistent with the assigned structures. See P. Canonne, D. Bélanger and G. Lemay, *J. Org. Chem.*, **47**, 3953, (1982).
8. E.J. Corey and A.P. Kozikowski, *Tetrahedron Letters*, **1975**, 925.
9. a. T. Uematsu, T. Uemura and K. Mori, *Agric. Biol. Chem.*, **47**, 597, (1983).
b. Y. Yokoyama and M. Yunokihara, *Chem. Lett.*, **1983**, 1245.
c. T.K. Chakraborty and S. Chandrasekaran, *Tetrahedron Letters*, **1984**, 2891.
d. J.P. Vigneron, R. Méric, M. Larchevêque, A. Debal, J.Y. Lallemand, G. Kunesch, P. Zagatti and M. Gallois, *Tetrahedron*, **40**, 3521, (1984).
e. K. Suzuki, T. Ohkuma and G. Tsuchihashi, *Tetrahedron Letters*, **1985**, 861.
f. Recently another synthesis of (+)-eldanolide has been completed (Dr. S.M. Roberts, private communication).
10. M. Julia and G. Le Thuillier, *Bull. Soc. Chim. Fr.*, **1966**, 717.

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