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A BIOMIMETIC SYNTHESIS OF CHRYSANTHEMOL†

D. BABIN, J. D. FOURNERON, L. M. HARWOOD and M. JULIA*

Laboratoire de Chimie de l'Ecole Normale Supérieure, associé au CNRS, No. 32, 24, rue Lhomond, 75231 Paris, Cedex 05, France

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Abstract - The factors governing the competition between 1,2- and 1,3-eliminations have been studied and the results obtained have been applied to a biomimetic synthesis of chrysanthemol

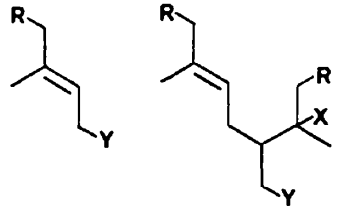
In the biosynthesis of squalene[1] two molecules of farnesyl pyrophosphate **1** are first condensed to form presqualene alcohol pyrophosphate **3a** which is then reduced, with ring opening and rearrangement, to squalene **4**. The two steps raise a number of very interesting chemical questions and challenges. This paper is concerned with the first one, namely the factors governing the formation of the cyclopropane ring.

Stereochemical investigations of the *in vivo* coupling of two molecules of **1** have shown that one primary pyrophosphate group remains intact whereas the other farnesyl component the C atom of which appears in the 3-membered ring, loses the pro(S) hydrogen.[2]

Several hypotheses have been brought forward to account for the ring closing reaction. In one of these[3] electrophilic attack on one moiety by the other would take place on C_2 with an unknown but nucleophilic X group neutralisating the positive charge which accumulates on C_3. This would be followed by base promoted 1,3-elimination of HX in the intermediate **2a**.

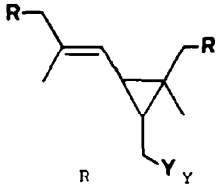
In another related hypothesis,[4] where the X group is thought to be a pyrophosphate residue, isomerisation of the double bond in the intermediate **2a** would lead to a homoallylic pyrophosphate **5**. Participation of the new double bond and proton removal would lead to cyclopropane formation[3] in a chemically precedented manner.

2,3-Sigmatropic rearrangements of difarnesyl sulphonium salts have been considered[5] and the cyclopropanation of normal olefins by sulphonium methylides associated with copper salts has also been shown to be possible.[6] The homologue of presqualene alcohol in the monoterpene series is the irregular terpene chrysanthemol **3h**. In their "unified approach" to the biogenesis of irregular monoterpenes Epstein and Poulter[7] suggest that condensation of two C5 units leads to a precursor **2b** which may either give the lavandulyl skeleton by 1,2-elimination or cyclise by a 1,3-elimination to lead to the chrysanthemyl structure. Earlier work in our laboratories[8] has established a C5 + C5 biomimetic approach to the diol analogue **2c** of the proposed precursor **2b** of which the potassium bisulphate catalysed 1,2-elimination leads directly to lavandulol **6**. At this stage it was thus decided to undertake an investigation into the possibility of cyclopropane ring formation by 1,3-elimination in the manner suggested above.

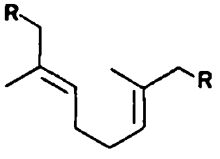


	R	Y	X
2a	geranyl	OPP	unknown nucleophile
2b	H	OPP	
2c	H	OH	OH
2d	H	OH	SPh

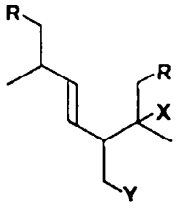
1 geranyl OPP



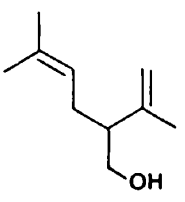
	R	Y
3a	geranyl	OPP
3b	H	OH
3c	H	3,5-dinitrobenzoate



4 R geranyl



5 R geranyl X,Y OPP



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†Dedicated to the memory of Professor Robert B. Woodward

The strain of the 3-membered ring would of course have to be paid for in the desired cyclisation but it can be estimated to be of the order of 27 Kcal/mole;[9] not so much more than the strain in a double bond which is about 22 Kcal/mole.[9] One factor expected to favour the 1,3-elimination is the more acidic character of the proton on C_1 to be removed due to its allylic position. This of course would come into operation particularly if and when a large negative charge is accumulating on this carbon atom in the transition state.

It is recognised that groups, normally considered to be "poor" leaving groups, part when in opposition to a preformed β-carbanionic centre (E_1cb elimination).[10] Could then a leaving group be found that would not eliminate in the 1,2-manner but would, with the help of the allylic activation 1,3-eliminate?

Considerable information about departing abilities of such leaving groups has been produced by Stirling[10] and his group who measured the rates of 1,2-elimination of a large number of substrates where removal of the β-proton was facilitated by electron withdrawing groups. Stirling[10] has been able to calculate "ranks" for these leaving groups. For example ammonium ions do not undergo rapid base promoted elimination in simple substrates. However trimethylamine becomes an outstanding leaving group when situated β to an activating group, (e.g. sulphonyl or phenyl). This is thus an example of a highly "ranked" leaving group using Stirling's terminology.

The literature contains scattered examples of the 1,3- vs 1,2-competition we are considering. More than forty years ago Ingold and Rogers[11] obtained by decomposition of 3,3-dicarbethoxy-4-phenyl-butyl trimethyl ammonium hydroxide, a compound which was recognised twenty years later by Weinstock[12] and Rogers[13] to be a cyclopropane derivative formed by displacement of the trimethylamine leaving group by an α-carbethoxy carbanion. A similar carbanion has been used in the displacement of sulphinate anion in a chrysanthemic acid synthesis.[14] Activation by a phenyl group has been shown to favour 1,3-over 1,2-elimination with some leaving groups such as trimethylamine and fluoride ion,[15] or sulphenate ion[16] and allylic activation has led to cyclopropane formation with an epoxide oxygen as the leaving group.[17]

RESULTS

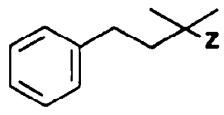
We carried out model experiments with the readily available 2-methyl-4-phenylbut-2-yl derivatives **7a-k** having different leaving groups Z, with the view of applying the knowledge gained to the synthesis of chrysanthemol. The results of this study using various systems of base are summarised in Table 1.

Unexpectedly the dimethyl sulphonium **7b** and the alkyldimethylammonium **7c** salts (highly "ranked" leaving groups[10]) gave none of the desired cyclopropane but only olefins **9**, **10**, despite the fact the Bumgardner,[15] had previously observed smooth formation of phenylcyclopropane with the corresponding primary ammonium salt. This difference is probably due to the fact that in our case the leaving group is attached to a tertiary rather than a primary C atom.

The toluenesulphinate ester **7d** underwent only attack on sulphur to yield the original alcohol. The phenyl sulphoxide **7e** did give a small amount of phenyl dimethyl cyclopropane **8** but the olefins **9** and **10** were the major products.

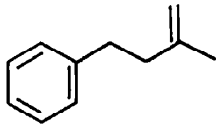
The phenylsulphone **7f** gave a larger proportion of cyclopropane to olefins but a fair amount of butylbenzene was formed when n-butyllithium/TMEDA was used.[18] Other bases did not cause elimination.

Sulphides gave varied and interesting results. The methyl sulphide **7g** gave smoothly a mixture of the isomeric olefins without any cyclopropane as did the benzyl sulphide **7h**. With **7g** D_2O quenching immediately after base treatment led to deuteration on the S Me. In contrast the lauryl sulphide **7i** proved to be resistant to elimination. This has some precedent in view of the α, β-elimination of short chain sulphides and the resistance of long chain sulphides reported by Biellmann.[19] The t-butyl sulphide **7j** did not undergo appreciable elimination ($< 2\%$) when treated with n-BuLi/TMEDA but gave the cyclopropane **8** (50% conversion, quantitative yield) with KOtBu/n-BuLi



Z

7a -NH-COMe
7b $-\overset{+}{S}Me_2$
7c $-\overset{+}{N}Me_2Et$
7d -O-SO-Tol.
7e -SO-Ph
7f $-SO_2-Ph$
7g -S-Me
7h $-S-CH_2-Ph$
7i $-S-C_{12}H_{25}$
7j -S-tBu
7k -S-Ph



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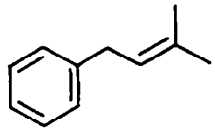

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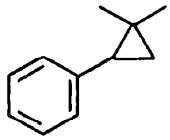

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Table 1.

Z	Conditions	yield % Recov.	yield % elim.	Ph (10) %	Ph (9) %	Ph (8) %
SMe_2	A	0	35	13	87	0
	B	0	38	7	83	0
	C	0	94	7	83	0
	D	0	25	20	80	0
$^+NMe_2Et$	C	68	24	10	90	0
	D	0	91	5	95	0
SOPh	A,B	98				
	C	51	15	27	73	0
	D	0	66	26	67	7
SO_2-Ph	A,B	90-100				
	D	0	4		33	66
S-Me	D	28	63	32	68	
S-CH_2-Ph	D	0	80	20	80	
$SC_{12}H_{25}$	D	100				
S-tBu	D	83	2			99
	E	50	50			99
	F	50	48			99
S-Ph	A,B,C	95				
	D	8	87	0	0	99
	E	70	30	0	0	99
	F	0	90	0	0	99
	G	65	35	86	14	

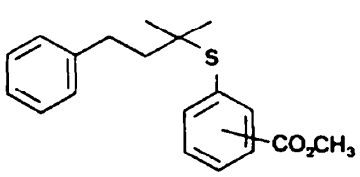
A : LDA, ether, 3h, -78° ; B : LDA, ether, HMPA, 3h, -78° ; C : $NaNH_2$, NH_3 liq., 3h ; D : nBuLi, TMEDA, hexane, 24h, 19° ; E : tBuOK, DMSO, 60h, 19° ; F : nBuLi, tBuOK, pentane, 48h, 19° ; G : $LiNEt_2$, ether, HMPA, 20h, 19°.

and $LiNEt_2$/HMPA. The phenyl sulphide **7k** gave the best results (yield and purity) for cyclopropane formation in the model series. With LDA/HMPA total conversion of starting material was observed whereas with n-BuLi/TMEDA reaction was never complete.

Information about the cyclisation of the phenyl sulphide **7k** using n-BuLi/TMEDA was obtained by quenching the mixture with carbon dioxide and esterification of the acids obtained; showing that metalation is very rapid (~ 5 min) on the aromatic ring of the phenylthio moiety (78 % *ortho* **11**, 12.5 % *meta* and *para* **11** to the S atom) with 9 % metalation in the benzylic position giving **12**. Quenching after 10 hr at room temperature indicated metalation almost totally *meta* and *para* to the sulphur in the recovered starting material. Apparently the *ortho* metalated product may undergo ring closure whereas the *meta* and *para* isomers are inert.

Control studies of the n-BuLi/TMEDA system on t-butyl phenyl sulphide **13** followed by carbonation and methylation indicated 95 % *ortho* **14** and 5 % *meta* and *para* metalation.

Under these conditions the t-butyl **13** and t-amyl **15** sulphides do not undergo elimination whereas phenyl



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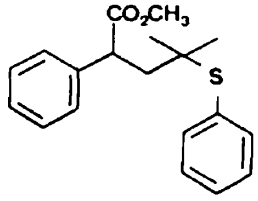

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(2-methyl-1-phenyl) prop-2-yl sulphide **16** (which possesses an activated methylene group β- to the phenylthio group undergoes facile 1,2-elimination to give olefins **17** and **18** (ratio 84:16).

The corresponding chrysanthemyl precursor **2d** was next synthesised. Attempts to convert the tertiary OH of the readily available diol **2c**[8] into the required leaving group met with difficulties when protonation of the double bond with participation of one of the O atoms was observed. This unwanted participation of the double bond in the diol **2c** was used to put it out of the way in a reversible manner. Bromination of lavandulol† **6** with NBS in wet ether led to the bromotetrahydropyranyl ethers *cis* and *trans* **19** to which the perchloric acid catalyzed addition of thiophenol could be carried out efficiently, giving **20**. Reductive elimination then regenerated the double bond and the primary alcohol to give 5-methyl-2(1'-methyl-1'-phenylthioethyl)hept-4-en-1-ol **2d**.

When **2d** was treated with BuLi/TMEDA in hexane about 50% of the starting material disappeared in 24 hr at room temperature and two new compounds were formed which were easily isolated in 15% yield by chromatography on silica. They were identical with *cis* and *trans* chrysanthemyl alcohol **3b** (20:80) by gc on a capillary column, ^{1}H NMR, ^{13}C NMR and gc-mass. Less than 2% lavandulol **6** was detected in this product. The main component (*trans*) of the mixture was isolated by HPLC separation of the crystalline 3,5-dinitrobenzoates **3c** (*trans*-3,5-dinitrobenzoate, mp 105.5 alone or mixed with an authentic sample).

It is remarkable that the reaction stops at 50% conversion. Quenching with D_2O shows that the "starting material" is metalated in the aromatic ring *ortho* to the sulphur. This carbanion thus appears to be inert, unlike the observations in the model series. With LDA in ether/HMPA at room temperature most of the starting material disappeared but the yield of chrysanthemol was only 20% accompanied by 15% lavandulol.

DISCUSSION

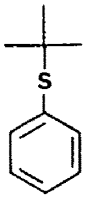
The investigations by carbonation into the mode of elimination of the phenyl sulphide **7k** on treatment with n-BuLi/TMEDA allow us to conclude that the major pathway proceeds by a rapid irreversible metalation of the aromatic nucleus of the phenylthio moiety mainly *ortho* to the sulphur. This carbanion *ortho* **21** is able to abstract a benzyl proton and the new species **22** then gives rise to the cyclopropane.

This abstraction/cyclopropanation is most likely to be non-concerted due to the possibility of trapping the benzylic anion **22** by carbonation during the early stages of the reaction. The intramolecular character of this process is shown by the stability of the *meta* and *para* anions **21** under the reaction conditions.

When a base is used in which the conjugate acid remains in the system, all of the anionic species exist in equilibrium and thus the irreversible cyclopropanation step displaces the equilibria to give total conversion of **7k**.

The stability of the t-butyl **13** and t-amyl **15** sulphides in comparison with the 1,3- and 1,2-elimination of substrates **7k** and **16** respectively indicates that a certain degree of acidification of the proton to be removed is necessary.

In the thiothers **7g** and **7h** where the carbanion is generated α- to the sulphur 1,2-elimination is observed. This most likely also explains the 1,2-elimination observed in the sulphonium **7b** and ammonium **7c** salts where ylid formation is possible. The importance of an initial carbanion either α- or β- to the S atom, as a preliminary to expulsion of the leaving group when using n-BuLi/TMEDA is underlined by the observation that the t-butyl sulphide **7j** does not undergo elimination (<2%) when similarly treated. Broaddus[20] has indeed shown that metalation of alkyl benzenes with n-BuLi/TMEDA is disfavoured at the benzylic position. In contrast, use of a base which allows equilibration of the carbanionic species (e.g.



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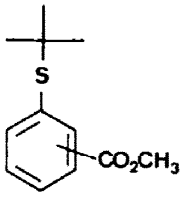

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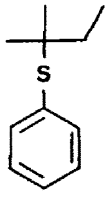

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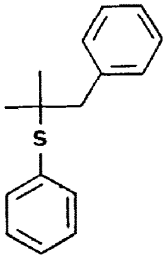

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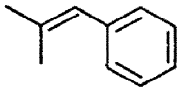

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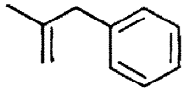

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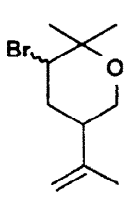
†We thank Rhone Poulenc SA for a generous gift of lavandulol



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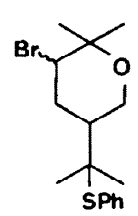

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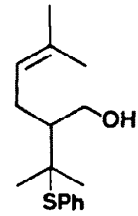
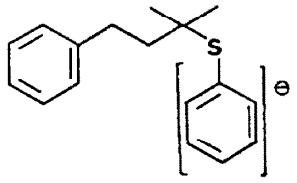


2d



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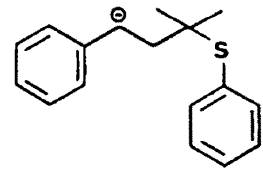

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tBuOK/n-BuLi[21] or LDA/HMPA[17]) gives rise to a 50% conversion of **7j** to the cyclopropane **8**.

The low yield of chrysanthemol from the thioether **2d** and the fact that recovered **2d** is totally deuterated on the aromatic ring forces the conclusion that in this case the previously discussed transmetalation is not operative and that the chrysanthemol is formed by direct removal of the allylic proton by base; the reaction stopping when the phenylthio group becomes itself metalated (and therefore no longer a leaving group). Attempting to improve the yield of chrysanthemol by using LDA/HMPA resulted in total disappearance of starting material coupled with the formation of important quantities of lavandulol.

CONCLUSION

It has thus proved possible to carry out in the laboratory a reaction similar to the scheme first proposed ten years ago by Rilling and Poulter for the biosynthesis of presqualene alcohol. Obviously several problems require investigation. If this is the real biosynthetic route, how does the living cell carry out the cyclisation step and how is the stereochemistry controlled? This problem might be related to the one previously mentioned concerning the direction of elimination of HX in the head to tail adduct in the prenyl transferase reaction, and it is hoped that further work on this approach will contribute to the understanding of the *in vivo* processes.

EXPERIMENTAL

IR spectra were recorded with a Perkin–Elmer 599 spectrometer as the neat liquid, in chloroform sol or as a nujol mull as stated. Mass spectra were recorded using either a Varian Mat C.H.7 spectrometer or a Ribermag R. 10 10 G.C./Mass coupled with a 25 m × 0.30 mm SE 52 capillary column. ^{1}H NMR spectra were obtained using a Bruker WH 80 operating at 80 MHz, a Varian EM 390 at 90 MHz and a Cameca 250 at 250 MHz. Chemical shifts (δ) were measured relative to TMS as internal standard. Routine gc analyses were performed using columns charged with 5% SE 30, 5% Carbowax and 15% DC 550 on Chromosorb WHMDS. Capillary gc analyses were carried out using Carbowax 600M, 30 m × 0.30 mm. Mps were taken using a Buchi m p apparatus and are uncorrected. Microanalyses were carried out by the staff of the Service Central de Microanalyses, I.C.S.N., 91190 Gif-sur-Yvette. All solvents were distilled before use. The phrase "usual work up" refers to sequential washing of the reaction mixture with 5% HCl aq and 5% $NaHCO_3$ aq, drying over $MgSO_4$, filtration and removal of the solvent at reduced pressure.

2-Methyl-4-phenylbutan-2-ol. The alcohol was prepared by the reported procedure.[22] Distillation at reduced pressure gave a colourless oil (73%) b.p.t. = 92–96 /2 torr ^{1}H NMR. 80 MHz($CDCl_3$): 1.45(s, 6H); 1.83(m, 2H); 2.75(m, 2H); 7.30(s, 5H).

2-Acetamido-2-methyl-4-phenylbutane **7a**. Conc. H_2SO_4 (10 cm^3) was added dropwise to a soln of 2-methyl-4-phenylbutan-2-ol (5.00 g, 30.5 mmole) in MeCN (40 ml) cooled to 0°. After agitation for 30 min, the mixture was poured into 8 N NaOH (25 ml) and extracted with ether (2 × 25 ml). Normal work up afforded crystalline **7a** (6.50 g, 95%) mp (ether) = 61° (Lit[23] 57°). IR (nujol): 3400, 1645 cm^{-1}, ^{1}H NMR. 80 MHz ($CDCl_3$): 1.35 (s, 6H); 1.87 (s, 3H); 2.02 (m, 2H); 2.58 (m, 2H); 5.58 (s, 1H); 7.10 (s, 5H).

Dimethyl ethyl (2-methyl-4-phenyl)but-2-yl ammonium iodide **7c**. The acetamide **7a** (4.00 g, 20 mmole) in dry ether (30 ml) was stirred with $LiAlH_4$ (0.75 g). The amine thus obtained was quaternised by reaction with MeI (8.50 g, 60 mmole) in MeOH (20 ml) at room temp for 12 hr. The ammonium salt **7c** was precipitated by addition of ether (4.86 g, 70%) mp (ether) = 171.0° (Found: C, 51.78; H, 7.29; N, 4.04; Calc.: C, 51.88; H, 7.55; N, 4.03%) MS. *m/e* = 146(M$^+$ − EtMe$_2$N, HI), 131, 91. ^{1}H NMR. 80 MHz ($CDCl_3$): 1.51(t, J = 7.5 Hz, 3H); 1.64 (s, 6H); 2.13 (m, 2H); 2.76 (m, 2H); 3.10 (s, 6H); 3.60 (q, J = 7.5 Hz, 2H); 7.23 (s, 5H).

Dimethyl (2-methyl-4-phenyl) but-2-yl sulphonium perchlorate **7b**. The title compound was obtained following the lit method[24] by addition of excess dimethyl sulphide to **7** (6.66 g, 40 mmole) in trifluoroacetic acid/CH_2Cl_2 followed by exchange with perchloric acid/MeOH. Recrystallisation gave colourless needles (5.70 g, 46%) mp (MeOH) = 128.5–129.5° (dec). (Found: C, 50.33; H, 6.77; Cl 11.60; S, 10.33; Calc.: C, 50.56; H, 6.85; Cl, 11.48; S, 10.38%). IR (nujol): 1180–900 cm^{-1}; MS *m/e*: 146(M$^+$ − Me$_2$S, $HClO_4$); 131; 91; ^{1}H NMR. 90 MHz ($(CD_3)_2CO$): 1.70 (s, 6H); 2.15–2.35 (m, 2H); 2.70–3.00 (m, 2H); 3.05 (s, 6H); 7.20–7.40 (m, 5H).

General technique for the preparation of thioethers **7g, 7h, 7i, 7j, 7k, 13, 15, 16**. The title compounds were obtained following the general technique of Cain *et al.*[25]

Methyl (2-methyl-4-phenyl) but-2-yl sulphide **7g**. bp = 97–102°/1.3 torr. 92%. (Found: C, 74.39; H, 9.33; S, 16.23; Calc.: C, 74.17; H, 9.34; S, 16.50%) IR (film): 3050,

3020, 1725, 1600, 760, 710 cm^{-1}; MS. *m/e*: 194 (M^+) 146, 131, 91; ^{1}H NMR. 250 MHz ($CDCl_3$): 1.32 (s, 6H); 1.72 1.84 (m, 2H); 2.04(s, 3H); 2.66 2.78 (m, 2H); 7.14–7.36 (m, 5H).

Benzyl (2-methyl-4-phenyl) but-2-yl sulphide **7h**. bp = 147 °/1.0 torr 75% (Found: C, 79.73; H, 7.97; S, 11,85; Calc.: C, 79.94; H, 8.20; S, 11.86%) IR (film): 3010, 1595, 1490, 1450, 760, 710 cm^{-1}; MS. *m/e*: 270(M^+), 145, 130, 105, 91, 90; ^{1}H NMR. 250 MHz ($CDCl_3$): 1.36 (s, 6H); 1.74 1.86 (m, 2H); 2.65–2.80 (m, 2H); 3.72 (s, 2H); 7.05 7.50 (m, 10H).

Dodecyl (2-methyl-4-phenyl) but-2-yl sulphide **7i**. 23% (isolated by chromatography) (Found: C, 79.68; H, 11.42, S, 8.77; Calc.: C, 79.31; H, 11.49; S, 9.19%) IR (film): 3020, 1725, 1600, 760, 710 cm^{-1}; MS *m/e*: 348, 146, 131; ^{1}H NMR. 80 MHz ($CDCl_3$): 0.88 (t, J = 7.5 Hz, 3H); 1.24 1.60 (m, 20H); 1.77 (m, 2H); 2.56 (m, 4H); 7.20 (m, 5H).

t-Butyl (2-methyl-4-phenyl) but-2-yl sulphide **7j**. bp = 97–102 °/1.5 torr. 66% (Found: C, 75.49; H, 10.22; S, 13.38; Calc.: C, 76.21, H, 10.23; S, 13.56%) IR (film): 3050, 3010, 1720, 1595, 1360, 755, 710 cm^{-1}; MS *m/e*: 180 (M^+-tBu) 146, 131, 91; ^{1}H NMR. 80 MHz ($CDCl_3$): 1.35 (s, 15H); 1.56 1.92 (m, 2H); 2.47 2.77 (m, 2H); 6.80 (s, 5H).

Phenyl (2-methyl-4-phenyl) but-2-yl sulphide **7k**. B.p.t. = 135–140 °/1.0 torr. 97% (Found: C, 79.72; H, 7.88; S, 12.54; Calc.: C, 79.63; H, 7.86; S, 12.50%). IR (film): 3050, 3020, 1725, 760, 705 cm^{-1}; MS *m/e*: 256 (M^+), 146, 131, 110, 91; ^{1}H NMR. 90 MHz ($CDCl_3$): 1.30 (s, 6H); 1.60 1.90 (m, 2H); 2.65 2.95 (m, 2H), 7.00–7.30 (m, 8H); 7.35 7.55 (m, 2H).

t-Butyl phenyl sulphide **13**. B.p.t. = 73 °/5.0 torr (lit[26] = 73 °/5.0 torr). 84%; ^{1}H NMR 90 MHz ($CDCl_3$): 1.25 (s, 9H); 7.00–7.30 (m, 3H); 7.35 7.60 (m, 2H).

Phenyl (2-methyl) but-2-yl sulphide **15**. This was prepared similarly from 2-methylbut-2-ene (2.10 g, 30 mmole) and excess thiophenol (5.0 ml). (3.32 g, 80%) b.p.t. = 80 81 °/1.0 torr. (Found: C, 73.36; H, 8.68; S, 17.77; Calc. C, 73.27; H, 8.94; S, 17.78%). IR (film): 3030, 1450, 1360, 1330, 760, 710 cm^{-1}; MS *m/e* = 180 (M^+), 110, 100, 71; ^{1}H NMR 250 MHz ($CDCl_3$) 1.00 (t, J = 7.5 Hz, 3H); 1.20 (s, 6H), 1.50 (q, J = 7.5 Hz, 2H); 7.32 (m, 3H); 7.52 (m, 2H).

Phenyl (2-methyl-1-phenyl) prop-2-yl sulphide **16**. mp (pet. ether) = 59.5–60.0 °, 90% (Found: C, 79.03; H, 7.57; S, 13.05; Calc.: C, 79.23; H, 7.49; S, 13, 23%) IR (nujol): 3020, 3005, 1600, 1120, 760, 750, 715, 705 cm^{-1}; MS *m/e*: 242 (M^+), 151, 110, 109, 91; ^{1}H NMR 80 MHz ($CDCl_3$) 1.20 (s, 6H); 2.90 (s, 2H); 7.00–7.75 (m, 10).

Phenyl (2-methyl-4-phenyl) but-2-yl sulphoxide **7e**. A soln of $NaIO_4$ (2.25 g, 10.5 mmole) in water (20 ml) was added to a stirred soln of **7k** (2.56 g, 10 mmoles) in acetone (25 ml) at 0°. After 3 hr the mixture was allowed to warm to room temp and stirred for 12 hr. Extraction with CH_2Cl_2 (2 × 25 ml) followed by normal work up gave a yellow oil which after silica chromatography afforded starting material (1.19 g) and **7e** (1.06 g, 73% accounting for recovered **7k**) mp (pentane) = 73–74°. (Found: C, 74.96; H, 7.40; S, 11.89; Calc.: C, 74.84; H, 7.19; S, 11.77%) IR ($CHCl_3$): 1590, 1125, 1085, 1035, 710, 680 cm^{-1}; MS *m/e*: 272 (M^+), 256, 147, 126, 91; ^{1}H NMR 90 MHz ($CDCl_3$): 1.20 (s, 6H); 1.60–2.15 (m, 2H); 2.60 2.95 (m, 2H) 7.10–7.40 (m, 5H), 7.45 7.75 (m, 5H).

Phenyl (2-methyl-4-phenyl) but-2-yl sulphone **7f**. The sulphide **7k** (1.25 g, 4.90 mmole) was added to a stirred mixture of AcOH (15 ml) and H_2O_2 (75 ml). After 24 hr the white ppt was filtered and the solid dried and crystallised from pentane/ether (1.40 g, quantitative) m.p.t. = 98.5 99.0°. (Found: C, 70.80; H, 6.99; S, 11.12; Calc.: C, 70.53; H, 6.77; S, 11.14%) IR (nujol) 1390, 1135, 1075, 735, 705 cm^{-1}; MS *m/e*: 288 (M^+), 147, 131, 105, 91; ^{1}H NMR 90 MHz ($CDCl_3$): 1.40 (s, 6H); 2.00 (m, 2H); 1.70 (m, 2H); 7.10 7.45 (m, 5H); 7.55 7.75 (m, 3H), 7.95 (dd, J = 8.0 Hz, J' = 2.0 Hz, 2H).

2-Methyl-4-phenylbut-2-yl toluenesulphinate **7d**. Toluenesulphinyl chloride[27] (1.91 g, 10 mmole) was added to a soln of the alcohol (1.64 g, 10 mmole) and pyridine (0.87 g) in dry ether (20 ml) at 0°. After stirring for 3 hr the unstable **7d** was obtained by filtration through silica, washing the residue with ether. Removal of solvent at reduced pressure gave the product, pure by NMR, as a colourless gum. (2.81 g, 90%) IR (film): 1590, 1140 cm^{-1}; MS *m/e*: 210 (M^+-$PhCH_2$) 146, 131, 105, 91; ^{1}H NMR 90 MHz ($CDCl_3$): 1.55 (s, 6H); 1.85–2.15 (m, 2H); 2.35 (s, 3H); 2.60 2.85 (m, 2H); 7.03 7.35 (m, 7H); 7.55 (d, J = 8.0 Hz, 2H)

Investigations into the action of various systems of bases on model substrates

All investigations were carried out using 1 mmole of substrate. The reaction conditions followed were those cited in the literature for the various reagents:
A, lithium diisopropylamide/ether;[17] B, lithium diisopropylamide/HMPA/ether;[17] C, Sodamide liq. NH_3;[15] D, n-BuLi/TMEDA/hexane;[19] E, KOtBu/DMSO;[19] F, KOtBu/nBuLi/pentane;[20] G, lithium diethylamide/HMPA ether.[17] In the early studies the olefins **9**, **10**, the cyclopropane **8** and the olefins **17**, **18** were isolated and their spectral properties shown to be in complete agreement with their proposed structures and with the data given in the lit (**8**[28], **9**, **10**;[29] **17**, **18**;[30]). In subsequent work identity was proven by comparison on a 15% DC 550 (silicone) column, 3 m long, at 170° with these samples. Yields were determined by comparison with a known quantity of tridecane added as an internal standard and were repeatable to ± 3% the values quoted in table 1 being averaged results. The response factor of the cyclopropane **8**: olefins (9): (10): tridecane was found to be 0.95: 0.95: 1.00. Unreacted starting material was recovered by silica chromatography of the reaction mixture in the case of **7k** whereas thioethers **7g** and **7j** were determined by gc under the same conditions as above, their response factors being 0.48 and 0.20 respectively compared with the tridecane standard.

1,1-Dimethyl-2-phenylcyclopropane—Illustrative preparative procedures.

(i) *System D.* n-BuLi (12.00 cm^3, 1.6 M soln. in hexane, 18 mmole) was added dropwise to a soln of **7k** (3.09 g, 12 mmole) in TMEDA (2.70 ml) at room temp with vigorous stirring under N_2. The deep red-brown soln was stirred for 12 hr and then quenched by addition of water (20 ml). Extraction with ether (2 × 20 ml) and usual work up gave a green oil from which the pure **8** was obtained by bulb to bulb distillation (1.07 g, 61%, bath temp = 100–110 °/15 torr. Lit[28] b.p.t. = 30 °/0.3 torr). The residue was purified by silica chromatography (ether) to give starting material (0.84 g, 27%).

(ii) *System F.* A soln of **7k** (946 mg, 3.7 mmole) in dry ether (5 ml) was added dropwise to a previously prepared soln of $LiNEt_2$ (10 mmole) in dry ether (5 ml) and HMPA (5 ml) stirred at 0°. After addition the dark mixture was stirred for 4 hr at room temp and quenched with water (20 ml). Extraction with ether and usual work up gave an oil which afforded the pure **8** by bulb to bulb distillation (485 mg, 90%). No starting material was recovered.

Action of n-butyllithium/TMEDA on t-butylphenylsulphide **13**

This was carried out, as previously described, on **13** (1.66 g, 10 mmole) to give, after quenching with solid CO_2 and extraction of the acids thus formed, the crude product as a white solid (1.53 g, 73%). A portion was esterified with diazomethane to give a mixture of 3 isomeric methyl (t-butylthio)benzoates **14** (gc/MS) in 95: 4:1 ratio. Repeated recrystallisation of the remaining acid product (pentane) gave colourless needles (m.p. 82 83°. Lit[31] for *ortho* isomer 80–81°) which on methylation gave only the major product of the previously obtained mixture of isomeric esters **14** (*ortho* metalation: *para* + *meta* metalation = 19:1) MS *m/e*: methyl *ortho* (t-butylthio)benzoate, *ortho* **14**; 224 (M^+), 168 (M^+-C_4H_8), 136, ($PhCO_2Me^+$), 57 ($C_4H_9^+$) *meta,para* (t-butylthio)benzoate (fragmentations identical), 224 (M^+), 168 (M^+-C_4H_8), 137 (M^+-C_4H_9S), 57 ($C_4H_9^+$).

Action of n-butyllithium/TMEDA on thioether **7k**

(a) *Carbonation after 5 min.* The thioether **7k** (1.02 g, 4 mmole) in TMEDA (1.5 ml) was treated with n-BuLi

(4.0 ml, 1.6 M soln in hexane). 5 min after addition the mixture was poured onto dry ice. Addition of 5% NaOH (25 ml) followed by extraction with ether (2 × 20 ml) gave, after usual work up recovered starting material (0.63 g). Acidification of the alkaline aqueous soln followed by extraction with ether (2 × 20 ml) gave, after drying and removal of solvent, a brown syrup. Methylation with diazomethane gave a mixture (98 mg) of 4 isomeric esters (gc/MS) present as 9%, 78%, 11% and 1.5% (in order of elution) of the ester mixture. Examination of the fragmentations of each product in the mass spectrum allowed the tentative assignment of structure **12** to the first *ortho* **11** to the second (major) and *meta/para* **11** to the last two products. MS *m/e*: **12**; 314 (M^+), 205 (M^+-PhS), 145(M^+-PhSH, HCO_2Me) 92 *ortho* **11**; 314 (M^+) 168 (M^+-PhC_6H_6), 146 (M^+-$MeO_2C(C_6H_4)SH$), 136 ($PhCO_2Me$) 92. *meta para* **11** 314, 168, 146, 131, 92.

(b) *Carbonation after 10 hr.* In the same manner as before a mixture of 3 isomeric esters was obtained corresponding to *ortho, meta* and *para* **11** (7% *ortho*, 93% *meta* + *para*).

Cis- and trans-3-bromo-2,2-dimethyl-5-isopropenyltetrahydropyran isomers **19**

N-bromosuccinimide (19.0 g, 100 mmole) was added over 15 min to a soln of **6** (15.4 g, 100 mmole) in moist ether (200 ml). After 1 hr the mixture was filtered to give, after usual work up, an oil (23 g) which was distilled at reduced pressure to afford a mixture of isomers *cis*- and *trans*-**19** (22.0 g, 94%, b.p. = 66–68° 1 torr). Capillary GC indicated 2 products (40:60) which could be separated by chromatography on silica (pentane:ether 8:2). The minor, less polar product 19 was assigned the *cis*-structure on the basis of its NMR spectrum. All other spectral properties were identical. (Found: C, 51.96; H, 7.25. $C_9H_{13}OBr$ requires: C, 51.52; H, 7.35; O, 6.86; Br, 34.27%). IR (film): 3070, 1635, 1450, 1135, 750, 700 cm^{-1}; MS *m/e*: 234, 232 (M^+) 219, 217, 206, 204, 126, 68; ^{1}H NMR 250 MHz ($CDCl_3$): *Cis*-**19**: 1.40 (s, 6 H); 1.72 (s, 3 H), 2.10 (q, H_2), 2.26 (dtd, H_3); 2.40 (tt, H_4ax.); 3.50 (t, H_6); 3.74 (ddd, H_6); 4.00 (dd, H_1); 4.72 (s, 1 H); 4.80 (s, 1 H). Coupling constants, $J_{H_nH_m}$:- 1–2 12.5 Hz, 1–3 4.0 Hz; 2–3 12.5 Hz; 2–4 12.5 Hz; 3–4 4.0 OHz; 3–5 2.0 Hz 4–6 12.5 Hz; 4–5 4.0 Hz; 5–6 12.5 Hz. *Trans*-**19**: 1.70 (s, 3 H); 1.74 (s, 3 H); 1.76 (s, 3 H); 1.86 (dt, Hz); 2.96 (16 line multiplet, H_4 eq); 3.00 (dt, H_3); 3.70 (dd, H_6); 3.9 (dd, H_1); 4.02 (t, H_5); 4.76 (s, 1 H); 4.80 (s, 1 H); Coupling constants, $J_{H_nH_m}$:- 1–2 10.0 Hz; 1–3 6.0 Hz; 2–3 12.0 Hz; 3–4 6.0 Hz; 4–5 8.0 Hz; 4–6 10.0 Hz; 5–6 10.0 Hz.

Cis and trans-2,2-Dimethyl-3-bromo-5-(1'-methyl-1'-phenylthioethyl)tetrahydropyran **20**

$HClO_4$ (70%, 0.3 ml) was added to a vigorously stirred soln of the bromoethers *cis*- and *trans*-**19** (7.00 g, 30 mmole) in thiophenol (15 ml) at 20°. After 5 min the mixture was poured into 5 N NaOH (100 ml) and extracted with ether (2 × 50 ml). After usual work up an orange oil (9.50 g) was obtained which after silica chromatography afforded the isomer mixture **20** as a colourless oil (7.60 g, 74%). The isomers could be separated by HPLC on silica. (Found: C, 56.24; H, 6.71; Br, 23.55; S, 9.37; Calc.: C, 55.98; H, 6.75; Br, 23.27; S, 9.34%). IR (film): 3050, 1450, 1360, 1085, 760, 705 cm^{-1}; MS *m/e*: 342, 344 (M^+), 264, 151, 137, 123, 110, 69; ^{1}H NMR 250 MHz ($CDCl_3$) less polar isomer: 1.20 (s, 6 H), 1.36 (s, 3 H); 1.37 (s, 3 H), 1.87 (dt, 1 H); 2.09 (q, 1 H); 2.44 (m, 1 H); 3.65 (t, 1 H), 3.95 (m, 2 H); 7.28–7.38 (m, 3 H); 7.46–7.58 (m, 2 H). More polar isomer: 1.20 (s, 3H); 1.26 (s, 3 H); 1.72 (s, 3 H); 1.78 (s, 3 H); 1.90 (dd, 1 H); 2.06 (td, 1H); 2.52 (tt, 1H); 3.80 (dd, 1H); 3.91 (t, 1 H); 4.00 (t, 1 H); 7.28–7.38 (m, 3 H); 7.46–7.58 (m, 2 H).

5-*Methyl-2(1'-methyl-1'-phenylthioethyl)hept-4-en-1-ol*) **2d**. The mixture of isomers **20** (3.43 g, 10 mmole) was added dropwise to a previously prepared soln of isopropyl magnesium bromide (30 mmole) in ether (20 ml) and the mixture stirred at room temp for 12 hr. Usual work up followed by chromatography on silica gave the product **2d** (0.75 g, 30%) as a colourless oil. (Found: C, 72.99; H, 8.99; S, 11.70; Calc.: C, 72.68; H, 9.15; S, 12.12%). IR (film): 3650–3100, 3050, 1435, 1380, 760, 705 cm^{-1}; MS *m/e*: 264(M^+), 155, 154, 123, 110, 109, 69; ^{1}H NMR 250 MHz ($CDCl_3$): 1.26 (s, 3H); 1.30 (s, 3H); 1.64 (s, 3H); 1.70 (s, 3H); 2.12 (m, 1 H); 2.20–2.30 (m, 2 H); 2.40–2.50 (m, removable with D_2O, 1 H); 3.72 (dd, J = 11.5 Hz, J' = 4.5 Hz, 1 H); 3.84 (dd, J = 11.5 Hz, J' = 4.5 Hz, 1 H); 5.16 (t, J = 7.0 Hz, 1 H); 7.26–7.40 (m, 3 H); 7.48–7.58 (2 H).

Conversion of **2d** *to chrysanthemol* **3b**

Alcohol **2d** (264 mg, 1 mmole) in TMEDA (0.4 ml) was treated with n-BuLi (3.5 ml, 1.6 M in hexane) and the red soln stirred at room temp for 24 hr. Quenching with water (5 ml), extraction with ether (2 × 10 ml) and work up in the usual manner gave an oil which on silica chromatography afforded starting material **2d** (132 mg, 50%) and chrysanthemol **3b** (23 mg, 15%). Investigation of other fractions in the separation indicated the presence of some lavandulol formed in less than 1% yield. Capillary GC of the chrysanthemol thus obtained indicated 2 peaks (20:80) which possessed the same retention times as authentic *cis*- and *trans*-chrysanthemols respectively. The mixture of 3,5-dinitrobenzoates **3c** obtained from the product was separated by HPLC on a silica column (25 × 1.25 cm) eluting with cyclohexane:ethyl acetate (95:5). The major component was thus obtained with a purity of 97% as yellow needles (m.p. 105.5°, Lit[32] 108–9°, undepressed on admixture with authentic *trans*-3,5-dinitrobenzoate obtained in the same manner from the mixture of authentic *cis*- and *trans*-chrysanthemols). The minor component was obtained 90% pure and did not crystallise.

3,5-*Dinitrobenzoate of* trans-*chrysanthemol*. trans-**3c**. ^{1}H NMR 250 MHz ($CDCl_3$): 1.06 (m, 1 H); 1.10 (s, 3 H); 1.21 (s, 3 H); 1.30 (m, 1 H); 1.70 (s, 3 H), 1.72 (s, 3 H); 4.40 (dd, J = 12.0 Hz, J' = 8.5 Hz, 1 H), 4.62 (dd, J = 12.0 Hz, J' = 8.5 Hz, 1 H); 4.90 (d, J = 8.0 Hz, 1 H); 9.14–9.20 (m, 2 H) 9.20–9.26 (m, 1 H).

3,5-Dinitrobenzoate of *cis*-chrysanthemol, *cis*-**3c** Identical to that of the *trans*-**3c** except for the methylene protons which appear at δ4.42 (d, J = 3.0 Hz, 1 H) and 4.62 (d, J = 3.0 Hz, 1H).

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