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Radical-Induced Fragmentations of Ketoepoxides

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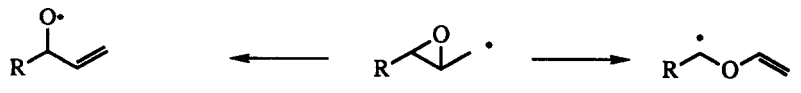
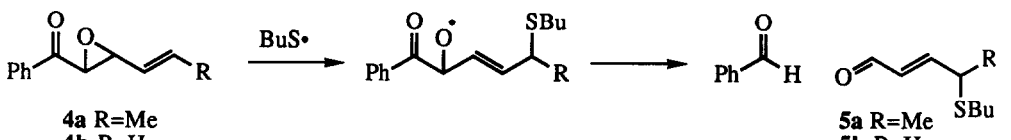
Abstract The cleavage of α-ketoepoxycarbinyl radicals has been investigated for six substrates using two methods of radical formation Products resulting from carbon-oxygen bond cleavage were observed in each case, but vinyl ethers derived from epoxide carbon-carbon cleavage were isolated in one case

The regiochemistry of cleavage of epoxycarbinyl radicals **1** is intriguing[1] Initial studies showed that simple alkyl-substituted cases underwent C-O bond cleavage to **2**, although the product of C-C bond cleavage would be expected on the basis of bond dissociation energies[2]



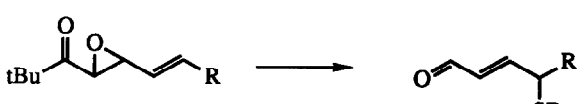
2 **1** **3**

We[3] and others[4] have shown that C-C bond cleavage resulting in **3** can occur for aryl- and vinyl-substituted epoxides Whether the resulting alkoxyalkyl radicals form as a result of kinetic or thermodynamic factors has not yet been definitively established A recent study has shown epoxide C-C bond cleavage occurs in some aryl-substituted epoxides regardless of stereoelectronic factors[5] and yet other epoxides[6] seem to show regioselectivity determined by such factors Accordingly, the nature of the products may depend on the kinetics of reversal of C-O and C-C cleavages, the size of the stereoelectronic effects and the rates of quenching of intermediate carbon- and oxygen-centred radicals



4a R=Me
4b R=H

5a R=Me
5b R=H



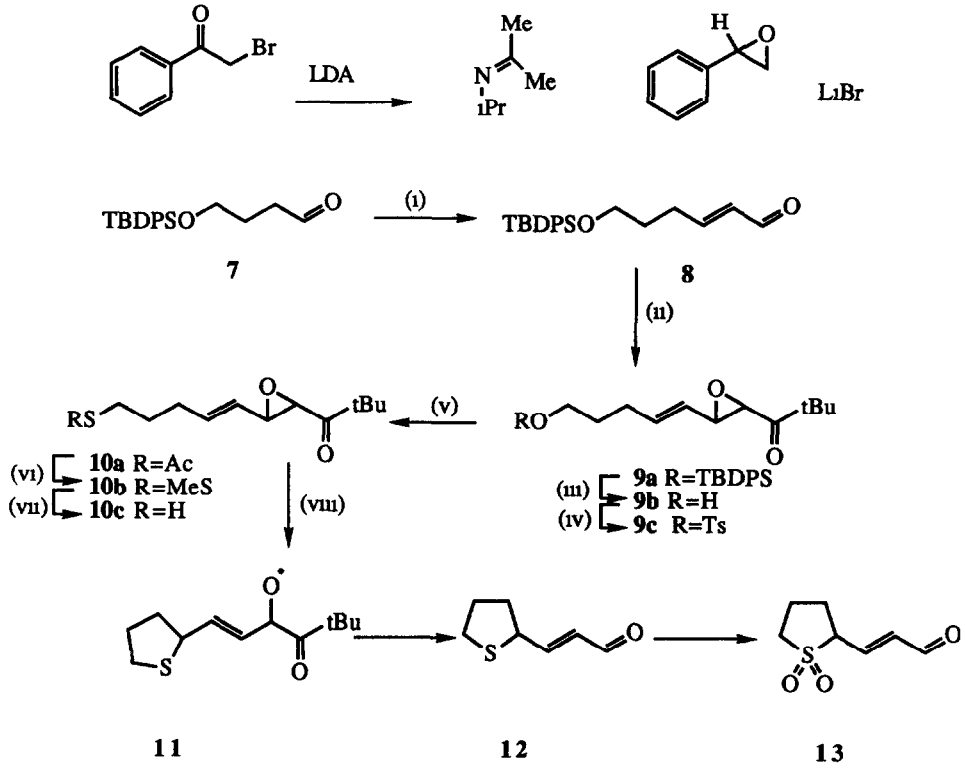
6a R=Me
6b R=H

5a R=Me
5b R=H

Because these reactions are now proving to be of substantial synthetic interest[7], we sought to determine

the effect of other groups adjacent to the epoxide in influencing the regiochemistry of fragmentation In this paper, we report on the effect of an adjacent carbonyl group[8] A carbonyl group stabilises an adjacent radical rather less than a vinyl group[9], and so whatever stabilising factors apply in the C-C bond cleavages described above would be expected to be less important here

Two types of activation have been used in the generation of the relevant radicals addition of thiyl radicals to a vinyl epoxide and reaction of tributyltin radicals with α-bromoepoxides Simple vinyl epoxides **4** and **6** were synthesised by Darzens reaction of α-bromopinacolone or α-haloacetophenones with acrolein or crotonaldehyde It was observed that α-haloacetophenones were much less successful than α-bromopinacolone in this regard This was because of the conversion of the former to styrene oxide, presumably with lithium diisopropylamide acting as a reductant[10]



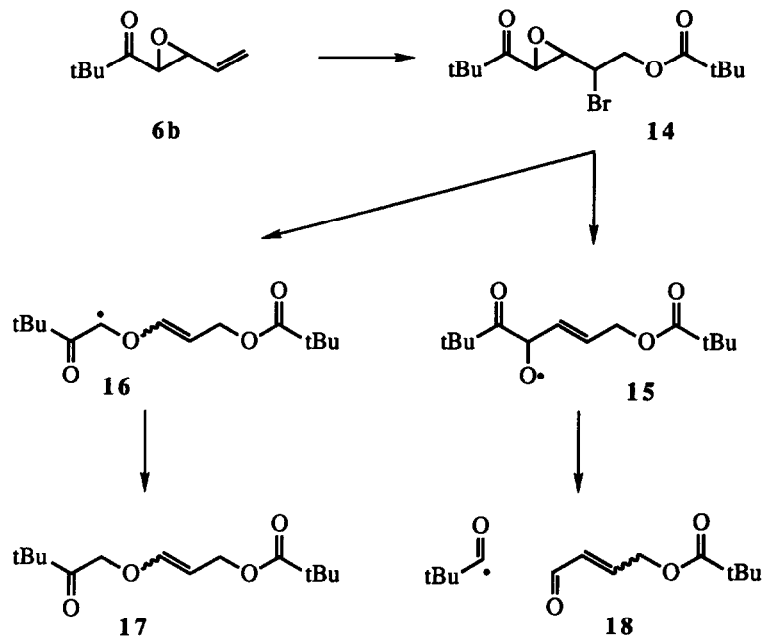
(i) $Ph_3PCHCHO$, $CHCl_3$, 41h, (ii) [LDA, 1-bromopinacolone] -78°C-> r t ,24h, (iii) TBAF, THF, 1 7h, (iv) $BnEt_3NCl$, TsCl, NaOH, CH_2Cl_2, (v) KSAc, acetone, 2 5h, (vi) piperidine, DMAP, Me_2S_2, 25°C, 12days, (vii) nBu_3P, THF, H_2O, (viii) AIBN, THF, Δ, 2h

On treatment with *n*-butanethiol and AIBN in benzene, fragmentations of **4** and **6** to the α,β-unsaturated aldehydes **5** occurred This indicates that epoxide C-O bond cleavage has occurred, with the resulting α-alkoxycarbonyl radical undergoing the expected rapid fragmentation[11] No pivalaldehyde was

observed in the reactions of **6**, indicating that facile[12] decarbonylation had occurred No products derived from epoxide C-C bond cleavage were observed. However, benzaldehyde was detected in the decomposition of the aryl epoxides These reactions are not very efficient, but it is surprising that the α,β-unsaturated aldehydes can be isolated in a reaction in which butanethiol is one of the reagents.

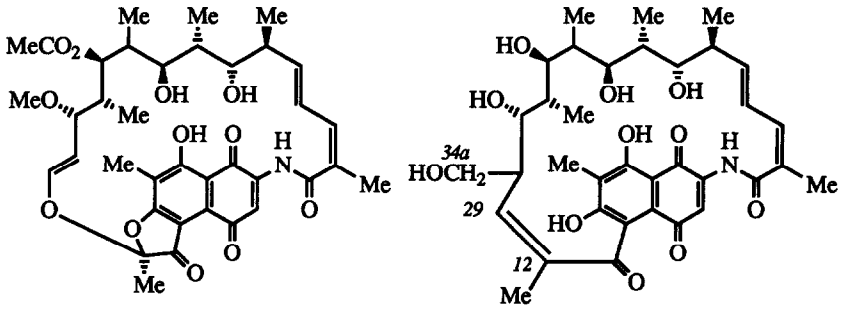
In an attempt to get a more efficient reaction, an intramolecular addition of a thiyl radical to a vinyl epoxide was designed using substrate **10c** This compound was synthesised by the route shown On heating with AIBN, the thiyl radical addition did indeed take place, but the volatility of the product **12** made isolation a real problem However, by oxidising the tetrahydrothiophene *in situ* with "Oxone", the corresponding sulfone **13** was isolated and characterised Once again, we could not detect any products resulting from cleavage of the epoxide C-C bond

To approach the fragmentations using different chemistry, the bromopivalate **14** was prepared from the alkene **6b** using N-bromosuccinimide and potassium pivalate It was possible to isolate one of the diastereoisomers in a pure state following chromatography, although the stereochemistry was not determined Treatment of this compound with tributyltin hydride and AIBN led to isolation of the the vinyl ether **17** as a mixture of (*E*) and (*Z*) isomers as well as the α,β-unsaturated aldehyde **18**

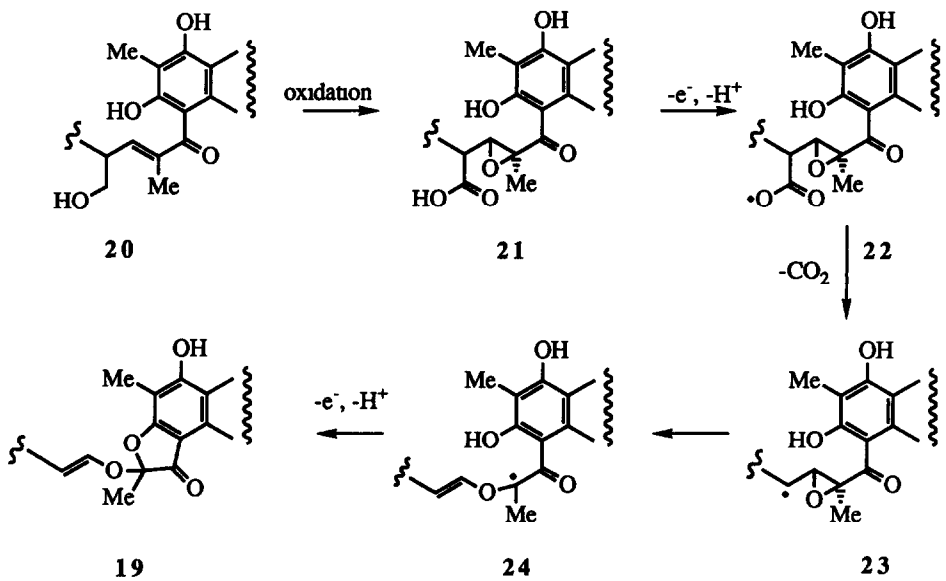


The C-C bond cleavage leading to (**17**) is particularly interesting It is possible that just such a reaction occurs in Nature in the biosynthesis of the important antibiotic rifamycin S (**19**)[13] from its precursor rifamycin W (**20**)[14] In this transformation loss of C-34a occurs, although it is not known at what oxidation level this happens Compounds related to (**20**) at both the aldehyde and carboxylic acid level of oxidation have been isolated from such biosynthetic incubations The converting brew thus features a range of oxidative enzymes Oxidation of the C*29*-C*12* alkene to an epoxide and oxidation of the C*34a* carboxylate to its carboxyl radical would then trigger loss of carbon dioxide to form (**21**) and epoxide C-C bond cleavage to give radical (**22**).

Proton loss and electron loss then complete the conversion Whether this is the mechanism by which rifamycin S is produced will require detailed biosynthetic investigations.



19 **20**



20 **21** **22** **23** **24** **19**

In summary, the cleavage of six ketoepoxycarbinyl radicals has been explored Evidence of epoxide C-O bond cleavage was observed in each case, and for one substrate products of C-C bond cleavage were also observed. These observations agree with previous findings that the extent of carbon-carbon bond cleavages in epoxides correlate with the stabilisation of the resltng carbon radical. Aryl and vinyl epoxides undergo predominant or exclusive C-C cleavage, alkyl epoxides show exclusive C-O cleavage, ketoepoxides lie in between these two extremes.

Experimental Section.

Melting points were measured on a Kofler hot stage apparatus unless otherwise indicated Microanalyses were determined using a Perkin-Elmer 240B elemental analyser. Ultraviolet spectra were recorded on a Philips PU 8720 spectrometer Infrared spectra were recorded on a Perkin-Elmer 1720-X FTIR spectrometer ^{1}H nmr (^{13}C nmr) spectra were recorded at 80MHz on a Bruker WP80SY, at 90MHz (22 5MHz) on a Jeol FX90Q, at 250MHz on a Bruker WM250, at 270MHz (67 5MHz) on a Jeol EX270 and at 400MHz (100MHz) on a Bruker AM400 spectrometer For both ^{1}H and ^{13}C nmr, the solvent used was deuteriochloroform, and with any solvent the internal reference was tetramethylsilane at 0 00ppm, unless otherwise indicated Mass spectra were recorded on VG Micromass 70E and AEI MS902 spectrometers, or (for Accurate FAB spectra) at the SERC mass spectrometry unit in Swansea

Column chromatography was performed using Sorbsil C60 silica gel (May and Baker) unless otherwise indicated. Also used was Fluka Kieselgel HF254 silica (for preparative TLC) and Brockmann Grade I neutral alumina (BDH) 40-60° petrol, pentane, dichloromethane, ethyl acetate and toluene were distilled before use

For reactions, solvents were dried and/or distilled before use where necessary Tetrahydrofuran was freshly distilled from sodium-benzophenone Benzene and ether were dried over sodium wire Acetonitrile was distilled from phosphoric oxide onto 3Å molecular sieves and potassium carbonate Methanol was distilled from magnesium and iodine onto 3Å sieves Dichloromethane and chloroform were distilled onto 3Å sieves

2,3-Epoxy-1-phenyl-4-hexen-1-one (**4a**)

A solution of lithium diisopropylamide (90 0mmole) in THF (40ml), was cooled to -78°C Phenacyl bromide (5 97g, 30 0mmole) in THF (5ml) was added dropwise and stirred for a period of 30mins A solution of crotonaldehyde (2 55g, 30 0mmole) in dry THF was added rapidly and the resulting mixture was allowed to gradually warm up to room temperature The contents of the flask were stirred for a further twelve hours The reaction was quenched by the addition of water (2ml) Removal of the solvent under reduced pressure yielded a viscous yellow oil This was dissolved in ethyl acetate (110ml), washed with water (2 x 50ml), and saturated brine (50ml) The organic phase was dried over sodium sulphate, filtered and evaporated to leave a pungent yellow oil which was purified by column chromatography (hexane/chloroform) giving the desired *epoxide* (**4a**) as a white crystalline solid (0 67g, 8 5%) (m p 88°C (from hexane/chloroform)) (Found C, 74 09, H, 6 22 $C_{12}H_{12}O_2$ requires C, 74 56, H, 6 43%), ν_{max} (KBr) 3070, 1685 and 900cm^{-1}, δ_H (250MHz, $CDCl_3$, Me_4Si), 1.77 (3H, dd, *J* 1 45 and 6 45, CH_3), 3 50 (1H, dd, *J* 1 99 and 7 98, -CHO), 4 17 (1H, d, *J* 1 99, CHO), 5 15-5 48 (1H, qdd, *J* 1 55, 7 98 and 15 4, =C*H*CHO), 5 84-6 28 (1H, qd, *J* 6 45 and 15 4, =CHMe), 7 34-7 71 (3H, m, Ar-H), 7 93-8 09 (2H, m, Ar-H), δ_C (62 5MHz, $CDCl_3$, Me_4Si) 17 69, 58 79, 60 58, 126 81, 128 22, 128 81 ,133 86, 134 26, 135 49, 193 94, *m/z* 188 (M^+, 5%), 159 (8), 105 (100) (Found M^+, 188 0832, $C_{12}H_{12}O_2$ requires *M*, 188 0837) The major product of this reaction was identified as styrene oxide by comparison with an authentic sample

2,2-Dimethyl-4,5-epoxy-6-octen-3-one (**6a**)

Lithium diisopropylamide (50 0mmole)was cooled to -78°C 1-Bromo-3,3-dimethylbutan-2-one (9 84g 50 0mmole) in dry THF (10ml) was added gradually, *via* syringe, over 10 min The resulting solution was stirred for 20mins at -78°C to ensure complete deprotonation of the pinacolone derivative A solution of crotonaldehyde (3 6g, 50 0mmol) in THF (5ml) was added rapidly The contents of the flask were allowed to warm to room temperature and stirring was continued for a further four hours The reaction was quenched with water (10ml), and the excess solvent was removed by rotary evaporation The viscous residue was dissolved in diethyl ether (200ml) and sequentially washed with water (2 x 75ml), and saturated brine

(50ml) The aqueous washings were extracted with ethyl acetate (50ml) The combined organic extracts were dried over anhydrous sodium sulphate, filtered and evaporated to dryness The amber liquid was purified by column chromatography (silica HF_{254} 98 2 hexane/diethyl ether) to afford a pale yellow oil which solidified on scratching Recrystallisation from hexane yielded the desired *keto-epoxide* (**6a**) as a colourless solid (3 68g, 46 2%) m p 42°C (from hexane). (Found C, 71 4; H, 9.7 $C_{10}H_{16}O_2$ requires C, 71 4, H, 9 6%), ν_{max} (KBr), 2975, 1713, and 895cm^{-1}, δ_H (80MHz, $CDCl_3$, Me_4Si), 1.21 (9H, s, Bu^t), 1 77 (3H, dd, *J* 1 5 and 6 5, CH_3), 3 25 (1H, dd, *J* 1 9 and 7 9, CHO), 3 79 (1H, d, *J* 1 9, CHO), 5 20 (1H, qdd, *J* 1 5, 7 9 and 15 4, =CHCO), 5.80-6 24 (1H, qd, *J* 6 5 and 15 4, =CH), δ_C (20MHz, $CDCl_3$) 17 23, 25 13, 42 84, 56 15, 58 75, 126 73, 132.73, 207 99, *m/z* 168 (M^+, 7 6%), 84 (20), 57 (100). (Found· M^+, 168 1167, $C_{10}H_{16}O_2$ requires *M*, 168 1150).

2,2-Dimethyl-4,5-epoxy-6-hepten-3-one (**6b**)

Lithium diisopropylamide (50 0mmole) was cooled to -78°C while under a nitrogen atmosphere 1-Bromo-3,3-dimethylbutan-2-one (9 84g, 50 0mmole) in dry THF (10ml) was added gradually. The resulting solution was stirred at -78°C for 10 mins A solution of acrolein (2 80g, 50.0mmole) in dry THF (5ml) was added rapidly to the stirred solution of lithium enolate The resulting mixture was then allowed to warm to room temperature and was stirred for four hours prior to quenching with water (10ml). The residue remaining after evaporation was taken up into diethyl ether (100ml), washed with saturated brine and separated The organic phase was dried over magnesium sulphate, filtered and evaporated to dryness Purification was effected by column chromatography (silica HF_{254}, 95 5 hexane/diethyl-ether) to yield the *trans-epoxide* (**6b**) as a pale yellow oil (2 97g, 39%) (Found C, 69 3, H, 9 35 $C_9H_{14}O_2$ requires C, 70 0, H, 9 15%); ν_{max} 3098, 1710 and 740cm^{-1}, δ_H (90MHz, $CDCl_3$, Me_4Si), 1 19 (9H, s, Bu^t), 3 30 (1H, m, CHO), 3 75 (1H, d, *J* 1 9, CHO), 5 36 (1H, m, =CH), 5.54-5 66 (2H, m, $=CH_2$), δ_C (22 5MHz, $CDCl_3$) 25.94, 43.82, 56 93, 59 53, 121 28, 124.02, 206 12, *m/z* 154 (M^+, 9%), 139 (7), 57 (100). (Found M^+, 154 0986, $C_9H_{14}O_2$ requires *M* 154.0994)

Homolytic cleavage of 2,3-epoxy-1-phenyl-4-hexen-1-one (**4a**)

Degassed benzene (15ml), butane thiol (0 42g, 4 2mmole) and the epoxide (**4a**) (0 11g, 0 58mmole) were mixed under nitrogen The stirred mixture was refluxed with periodic addition of small aliquots (*ca* 0 1ml) of AIBN (10mgs) in benzene (2ml). The reflux was continued for eighteen hours after which time the solvent was removed under reduced pressure The remaining oil was taken up into diethyl ether (20ml) and washed with 1M NaOH (10ml) and water (20ml) The ethereal phase was dried over magnesium sulphate, filtered and evaporated NMR of the crude material indicated the presence of two aldehydic products Preparative tlc (dichloromethane) afforded both aldehydes The first, identified as *4-butylthio-2-pentenal* (**5a**) a colourless oil, was characterised, as also was its *2,4-dinitrophenylhydrazone* derivative

4-butylthio-2-pentenal (**5a**) (20 4mgs, 22 3%), ν_{max} 2960, 2825, 1691, 1630 and 1450cm^{-1}, δ_H (90MHz, $CDCl_3$, Me_4Si), 0 89 (3H, t, *J* 6 1, $S(CH_2)_3CH_3$), 1 17-1 72 (7H, m, $SCH_2(CH_2)_2CH_3$ and $CHCH_3$), 2 41 (2H, m, SCH_2R), 3 53 (1H, m, 4-H), 6 00 (1H, dd, *J* 7 6 and 15 5, =CH), 6 73 (1H, dd, *J* 7 8 and 15, =CHCH), 9 56 (1H, d, *J* 7 6, CHO), δ_C (22 5MHz, $CDCl_3$), 13 50, 19 29, 21 89, 30 45, 31 43, 40 97, 130 40, 157 54, 193 25, *m/z* 172 (M^+, 22%), 115 (39), 82 (100). (Found M^+, 172 0917, $C_9H_{16}OS$ requires *M*, 172 0922) Dinitrophenylhydrazone derivative (m p 212°C dec (from EtOH)), ν_{max} (KBr) 3095, 2930, 1610, and 1332cm^{-1}; δ_H (400MHz $CDCl_3$, Me_4Si), 0 91 (3H, t, *J* 7 3, $S(CH_2)_3CH_3$), 1 36-1 52 (5H, m, $S(CH_2)_2CH_2CH_3$) and CH_3), 1 55-1 60 (2H, m, $SCH_2CH_2CH_2CH_3$), 2 43-2 49 (2H, m, SCH_2R), 3 50 (1H, dq, *J* 7 1 and 8 4, $CHCH_3$), 6 11 (1H, dd, *J* 8 7 and 15 5, =CH), 6 29 (1H, dd, *J* 8 7 and 9 1, MeCHCH), 7 80 (1H, d, *J* 9 1, CHN), 7 93 (1H, d, *J* 9 6, ArH aromatic), 8 29 (1H, dd, *J* 2 6 and 9 6, ArH), 9 12 (1H, d, *J* 2 6Hz, ArH), 11 14 (1H, brs, NH), δ_C (62 5MHz, $CDCl_3$) 13 72,

19 97, 22 06, 30 54, 31 56, 41.87, 116 63, 124 48, 125 06, 129 99, 138 17, 144 66, 146 02, 149 07, *m/z* 352 (M^+, 23%), 263 (100) (Found M^+, 352 1187, $C_{15}H_{20}N_4O_4S$ requires *M*, 352 1205) The remaining product was identified as benzaldehyde and was characterised as its 2,4-dinitrophenylhydrazone derivative (4 3mgs, 2 1%) (m p 235°C (from EtOH) (Lit ,[13] 237°C, δ_H (90MHz, $CDCl_3$, Me_4Si), 7 35-7 53 (3H, m, 2,4,6-H), 7 86-7 89 (2H, m, ArH), 8 26 (1H, d, *J* 9 5, ArH), 8 43 (1H, dd, *J* 2 5 and 9 5Hz, ArH), 8 64 (1H, s, HC=N-), 9 01 (1H, d, *J* 2 5, ArH), 11 51 (1H, brs, NH), *m/z* 286 (M^+, 100%), 165 (22), 107 (76), 77 (69). (Found M^+, 286 0652, $C_{13}H_{10}N_4O_4$ requires *M*, 286 0702)

Homolytic cleavage of 2,2-dimethyl-4,5-epoxy-6-octen-3-one (**6a**)

Butane thiol (0 84g, 9.4mmole) and epoxide (**6a**) (0 5g, 2 6mmole) were dissolved in dry benzene (25ml) Small amounts of the radical initiator AIBN (30 0mgs) in benzene (3ml) were added at periodic intervals over the twelve hour reflux The dark oil remaining after removal of the solvent under reduced pressure was dissolved in diethyl ether (40ml) and washed with 1M NaOH (15ml) and then water (20ml) The separated ethereal phase was dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure Preparative tlc (silica / dichloromethane) afforded 4-butylthio-2-pentenal (**5a**) (22 7mgs, 24 7%) Spectroscopic data were identical to those obtained for the same product derived from homolytic fission of keto-epoxide (**4a**) No other product was isolated

Homolytic cleavage of 2,2-dimethyl-4,5-epoxy-6-hepten-3-one (**6b**)

To dry degassed benzene (20ml) were added n-butanethiol (0 84g, 8 4mmole) and the epoxide (**6b**) (0 75g, 4 86mmole) The stirred mixture was refluxed under a nitrogen atmosphere with the periodic addition of small aliquots (*ca* 0 25ml) of a solution of AIBN (20mgs) in dry benzene (2ml) The resulting solution was heated under reflux for a period of ten hours After evaporation, the residue was purified by colum chromatography (85 15 hexane/diethyl ether) Purification afforded *3-butylthio-2-butenal* (**5b**) which was isolated and characterised as its *2,4-dinitrophenyl hydrazone* derivative · 3 butylthio-2-butenal (**5b**) was isolated as a colourless pungent oil (89mgs, 12%), ν_{max} 2954 , 1682 and 1377cm^{-1}, δ_H (90MHz, $CDCl_3$, Me_4Si), 1 19 (3H, t, *J* 7 0, $S(CH_2)_3CH_3$), 1 25-1 79 (4H, m, $SCH_2(CH_2)_2R$), 2 48 (2H, t, *J* 7 0, SCH_2R), 3 36 (2H, d, *J* 7 2, SCH_2CH=), 6 17 (1H, dd, *J* 7 6 and 14 4, =CH), 6 79 (1H, td, *J* 7 2 and 14 4, CH_2CH=), 9 67 (1H, d, *J* 7 6, CHO), δ_C (22 5MHz, $CDCl_3$) 13 61, 31 06, 31 32, 33 11, 65 77, 133 33, 152 29 and 193 03 The dinitrophenylhydrazone derivative was isolated as an orange-red solid, (m p 122°C), δ_H (80MHz, $CDCl_3$, Me_4Si), 1 19 (3H, t, *J* 7 0, $S(CH_2)_3CH_3$), 1 23-1 83 (4H, m, $SCH_2(CH_2)_2CH_3$), 2 45 (2H, t, *J* 7 1, SCH_2R), 3 38 (2H, d, *J* 7 2, SCH_2CH=), 6 20-6 37 (2H, m,CH=CH), 7 75 (1H, d, *J* 7 3, *CH*N), 7 92 (1H, d, *J* 9 6, ArH), 8 33 (1H, dd, *J* 2 6 and 9.6, ArH), 9 18 (1H, d, *J* 2 6, ArH), 9 65 (1H, br s, NH), δ_C (22 5MHz, $CDCl_3$), 13 69, 21 97, 30 99, 31 40, 33 88, 116 68,123 43, 127 83, 129 43, 129 98, 138 30, 140 04, 144 68 and 148 82, *m/z* 338 (M^+, 39%), 249 (55), 231 (47), 67 (100) (Found M^+, 338 1040, $C_{14}H_{18}N_4O_4S$ requires *M*, 338 1049)

4-t-butyldiphenylsilyloxybutan-1-ol [15]

To a solution of dry distilled butane-1,4-diol (62 8g, 700mmol, 10eq) and imidazole (9 6g, 140mmol, 2eq) in dry dimethylformamide (140ml) under nitrogen was added a solution of t-butyldiphenylsilyl chloride (19 24g, 70mmol) in dimethylformamide (70ml) over 70 min After 17 h, the solution was poured onto water (500ml) and extracted with dichloromethane (2x500ml) The combined organic layers were extracted with water, dried ($MgSO_4$), evaporated to dryness and chromatographed (CH_2Cl_2, R_F 0 19) giving

4-t-butyldiphenylsilyloxybutan-1-ol as a colourless syrup (16 36g, 49 8mmol, 71 1%) (Found· C, 73 42, H, 8 86% $C_{20}H_{28}O_2Si$ requires C, 73 12, H, 8 59%), ν_{max} (film) 3350, 3110, 3061 and 702 cm^{-1}, δ_H (250MHz) 1 05 (9H, s, ^tBu), 1 67 (4H, m, CH_2CH_2), 2 02 (1H, s, OH), 3 67 (2H, t, *J* 6.1Hz,

HOCH_2), 3 70 (2H, t, *J* 5 8Hz, ROCH_2), 7 41 (6H, m, ArH) and 7 67 (4H, m, ArH); δ_C (22 5MHz) 19 12, 26 87, 29 15, 29 42 , 62.30, 63 93, 127 58, 129 53, 135.49 and 133 81; *m/z* (CI) 329 (MH^+, 22%), 311 (36), 271 (56), 251 (47), 239 (62), 229 (54), 199 (100), 193 (70), 167 (73) and 73 (48)

4-t-butyldiphenylsilyloxybutanal (7)

A solution of oxalyl chloride (4 8ml, 54 6mmol, 1.1eq) in dry dichloromethane (125ml) under nitrogen was cooled to -63°C and dry dimethyl sulphoxide (7.75ml, 109 2mmol, 2.2eq) in dichloromethane (25ml) added After 5 min, a solution of 4-t-butyldiphenylsilyloxybutan-1-ol (16 31g, 49 65mmol) in dichloromethane (50ml) was added over 10 min After 50min. at -63°C, dry diisopropylethylamine (43 24ml, 248 3mmol, 5eq) was added, stirred for 5 min and allowed to warm to room temperature The solution was poured onto water (150ml), the organic layer dried ($MgSO_4$), evaporated to dryness and chromatographed [40-60° petrol / dichloromethane (6 1, 2 1 and 1 1)] giving

4-t-butyldiphenylsilyloxybutanal (**7**) as a colourless oil (13 53g, 41 45mmol, 83 5%) (Found MH^+, 327 1678 $C_{20}H_{27}O_2Si$ requires *MH*, 327.1780), ν_{max} (film) 3071, 3050, 2720, 1727, 1590, 1473 and 703 cm^{-1}, δ_H (250MHz) 1 04 (9H, s, ^tBu), 1 89 (2H, tt, *J* 7, 7 CH_2CH$_2$), 2 55 (2H, td, *J* 7 and 1 7, CH$_2$CH_2), 3 69 (2H, t, *J* 6 0, ROCH_2), 7 41 (6H, m, ArH), 7 65 (4H, m, ArH) and 9 79 (1H, t, *J* 1 6Hz, HCO), δ_C (22 5MHz) 19 33, 25 46, 27 08, 40 79, 63 16, 127 84, 129 85, 135 65, 133 86 and 202 01, *m/z* (CI) 327 (MH^+, 1%), 269 (100), 249 (4 9), 251 (4), 199 (87), 139 (44), 77 (10), 71 (36) and 57 (8)

E-6-t-butyldiphenylsilyloxyhex-2-enal (8)

A solution of 4-t-butyldiphenylsilyloxybutanal (**7**) (3 27g, 10mmol) and formylmethylenetriphenylphosphorane (3 35g, 11mmol, 1.1eq) in dry chloroform (125ml) under nitrogen was heated under reflux for 41 h The solution was evaporated to dryness and the residue extracted with cold (-20°C) ether (6x20ml) The extract was filtered to remove phosphorane and phosphine oxide, evaporated to dryness and chromatographed using 40-60° petrol / ether (15 1 and 9 1 giving

E-*6-t-butyldiphenylsilyloxyhex-2-enal* (**8**) as a yellow syrup (2 194g, 6 22mmol, 62 2%) (Found C, 74 93, H, 8 20% $C_{22}H_{28}O_2Si$ requires C, 74 95, H, 8 00%), λ_{max} (MeCN)/nm 219sh (ε 25 000), 259 (870) and 264 5 (820), ν_{max} (film) 3071, 3050, 2738, 1693, 1638, 1590, 1473 and 703 cm^{-1}, δ_H (250MHz) 1 06 (9H, s, ^tBu), 1 75 (2H, tt, *J* 7, CH$_2$), 2 45 (2H, ddd, *J* 7, 7 and 1 5, =CHCH_2), 3 70 (2H, t, *J* 6 1, OCH_2), 6 10 (1H, ddt, *J* 15 7, 7 9 and 1 5, HCO C*H*), 6 82 (1H, dt, *J* 15 6, 6 8, CHCH$_2$), 7 39 (6H, m, ArH), 7 65 (4H, m, ArH) and 9 46 (1H, d, *J* 7 8, HCO), δ_C (22 5MHz) 19 33, 27 08, 29 30, 30 93, 63 00, 127 84, 129.85, 133 26, 135 65, 157 97 and 193.56 , *m/z* (CI) 353 (MH^+, 8%), 335 (3), 295 (62), 275 (84), 199 (21), 155 (26), 125 (46), 97 (100), 77 (8) and 57 (5)

E-1-t-butyldiphenylsilyloxy-6,7-epoxy-9,9-dimethyldec-4-ene-8-one (9a)

To a solution of dry diisopropylamine (1 08ml, 7 69mmol, 1 2eq) in dry tetrahydrofuran (5ml) under nitrogen, cooled to -78°C, was added a solution of n-butyllithium in hexanes (1 4M, 5 04ml, 7 05mmol, 1 1eq) dropwise over 8 min After 10 min stirring, a solution of 1-bromopinacolone (0 947ml, 7 05mmol, 1 1eq) in tetrahydrofuran (5ml) was added dropwise over 5 min After 30 min stirring, a dry solution of *E*-6-t-butyldiphenylsilyloxyhex-2-enal (**8**) (2 253g, 6 39mmol) in tetrahydrofuran (10ml) was added rapidly, the solution allowed to warm to room temperature and stirred for 24 h The mixture was evaporated to dryness, dissolved in ether (50ml), extracted with water (2x75ml), dried ($MgSO_4$), evaporated and chromatographed [40-60° petrol / ether (20 1)] giving the *cis* and *trans* isomers about the epoxide (**9a**) Trans isomer

E-*1-t-butyldiphenylsilyloxy-6,7*-trans-*epoxy-9,9-dimethyldec-4-ene-8-one* (**9a**) as a colourless oil

(1 92g, 4 26mmol, 66 7%) [R_F 0 51, 4 1 petrol / ether] (Found MH^+, 451 267 $C_{28}H_{39}O_3Si$ requires *MH*, 451 267), ν_{max} (film) 3071, 3050, 1716, 1669, 1590, 1475 and 706 cm^{-1}, δ_H (250MHz) 1 05 (9H, s, ^tBu), 1 21 (9H, s, ^tBu), 1.66 (2H, tt, *J* 7, 7, CH_2), 2.20 (2H, tdd, *J* 7, 7 and 1.2, $CHCH_2$), 3 28 (1H, dd, *J* 8 2 and 1.9, CHO), 3 66 (2H, t, *J* 6.2, $ROCH_2$), 3 74 (1H, d, *J* 1 9, CHO), 5.20 (1H, ddt, *J* 15 5, 8 2 and 1 4, =CH), 5 98 (1H, dt, *J* 15 5 and 7, $=CHCH_2$), 7 41 (6H, m, ArH) and 7 66 (4H, m, ArH), δ_C (22 5 MHz) 19 23, 25 73, 26.92, 28 60, 31 58, 43 45, 56 88, 59 32, 63.00, 126 01, 127 64, 129 59, 133 97, 135 49, 138 14 and 208 46, *m/z* (CI) 451 (MH^+, 5%), 433 (5), 393 (26), 373 (27), 199 (5), 195 (14), 85 (26) and 57 (100); and cis isomer

E-*1-t-butyldiphenylsilyloxy-6,7*-cis-*epoxy-9,9-dimethyldec-4-ene-8-one* (**9a**) as a yellow oil (0 2092g, 0 464mmol, 7 3%) [R_F 0 33, 4 1 petrol / ether] ν_{max} (film) 3071, 3049, 1715, 1590, 1474 and 704 cm^{-1}, δ_H (250MHz) 1.04 (9H, s, ^tBu), 1 18 (9H, s, ^tBu), 1 61 (2H, tt, *J* 7, CH_2), 2 16 (2H, dt, *J* 7, 7 $=CHCH_2$), 3 63 (1H, dd, *J* 8 9 and 5, CHO), 3 64 (2H, t, *J* 7, OCH_2), 4.10 (1H, d, *J* 5 0, CHO), 5 13 (1H, ddt, *J* 15 6, 8 8 and 1 4, =CH), 6 03 (1H, dt, *J* 15 6 and 6.9,$=CHCH_2$), 7 40 (6H, m, ArH) and 7 65 (4H, m, ArH), δ_C (22 5MHz) 19 12, 25 84, 26 87, 28 71, 31 75, 43 34, 57 05, 58 29, 63 06, 122 92, 127 58, 129 53, 133 87, 135 44, 139 61 and 208 0, *m/z* (CI) 393 (M^+-^tBu, 20%), 373 (3), 199 (43), 195 (14), 85 (19) and 57 (100)

*E-1-hydroxy-6,7-trans-epoxy-9,9-dimethyldec-4-ene-8-one (**9b**)*

To a solution of *E*-1-t-butyldiphenylsilyloxy-6,7-*trans*-epoxy-9,9-dimethyldec-4-ene-8-one (**9a**, trans) (8 20g, 18 19mmol) in dry tetrahydrofuran (100ml) was added a solution of tetra-n-butylammonium fluoride (1M, 36 4ml, 36 4mmol, 2eq) in tetrahydrofuran After 1 7 h, the brown solution was evaporated to dryness, taken up in dichloromethane (200ml), extracted with water (2x150ml), dried ($MgSO_4$) and evaporated to dryness Due to decomposition on silica and alumina, the alcohol was used crude in the following tosylation step

*E-1-tosyloxy-6,7-trans-epoxy-9,9-dimethyldec-4-ene-8-one (**9c**)*

To a solution of crude *E*-1-hydroxy-6,7-*trans*-epoxy-9,9-dimethyldec-4-ene-8-one (**9a**) (18 19mmol) and benzyltriethylammonium chloride (0 2072g, 0 910mmol, 5mole%) in dichloromethane (50ml) was added sodium hydroxide solution (40%, 50ml) and the mixture mechanically stirred A solution of toluenesulfonyl chloride (10 40g, 54 6mmol, 3eq) in dichloromethane (25ml) was added over 10 min, the mixture mechanically stirred for 21 5 h, and poured onto dichloromethane (150ml) and water (400ml) The aqueous layer was extracted with dichloromethane (2x100ml) and the combined organic layers extracted with water (2x100ml), dried ($MgSO_4$), evaporated to dryness and chromatographed using 40-60° petrol / ether (6 1 and 2 1) giving

E-*1-tosyloxy-6,7*-trans-*epoxy-9,9-dimethyldec-4-ene-8-one* (**9c**) as a colourless oil (6 06g, 16 55mmol, 91 0% over 2 steps) (Found C, 62 29, H, 7 24%, $C_{19}H_{26}O_5S$ requires C, 62 27, H, 7 15%,) (Found M^+, 366 1470 $C_{19}H_{26}O_5S$ requires *M* 366 1501), ν_{max} (film) 1714, 1669, 1599, 1478, 665 and 556 cm^{-1}, δ_H (80MHz) 1 22 (9H, s, ^tBu), 1 75 (2H, tt, *J* 7, CH_2), 2 16 (2H, br dt, *J* 7, 7 $CHCH_2$), 2 45 (3H, s, Me of OTs), 3 26 (1H, dd, *J* 7 7 and 2 0, CHO), 3 72 (1H, d, *J* 2 0,CHO), 4 03 (2H, t, *J* 6 0, CH_2), 5 20 (1H, ddt, *J* 15 6, 7 7 and 1 3, =CH), 5 90 (1H, dt, *J* 15 6, 6 5, $=CHCH_2$), 7 35 (2H, d, *J* 8 5, ArH) and 7 78 (2H, d, *J* 8 4, ArH), δ_C (22 5MHz) 21 51, 25 68, 27 85, 27 95, 43 39, 56 73, 58.94, 69 51, 127 20, 127 74, 129 91, 136 09, 133 27, 144 81 and 208 52, *m/z* (EI) 366 (M^+, 1 5%), 353 (11), 281 (10) and 57 (100)

*E-1-acetylthio-6,7-trans-epoxy-9,9-dimethyldec-4-ene-8-one (**10a**)*

Potassium thioacetate (2 159g, 18 91mmol, 1 15eq) was added to a solution of *E*-1-tosyloxy-6,7-*trans*-epoxy-9,9-dimethyldec-4-ene-8-one (**9c**) (6 02g, 16 44mmol) in acetone (65ml) under nitrogen and the mixture brought to reflux, giving an immediate precipitate of potassium tosylate. After 2 5 h, the reaction was cooled in ice, filtered, and the residue washed with ice-cold acetone The filtrate was evaporated to dryness, dissolved in ether (50ml), washed with water (4x60ml), dried ($MgSO_4$), evaporated and chromatographed [40-60° petrol / ethyl acetate (7 1 [R_F 0.25])] giving

E-*1-acetylthio-6,7*-trans-*epoxy-9,9-dimethyldec-4-ene-8-one* (**10a**) as a slightly yellow oil (2 76g, 10 21mmol, 62.1%). (Found. C, 61 82, H, 8.43%. $C_{14}H_{22}O_3S$ requires C, 62.19, H, 8.18%); ν_{max} (film) 1714, 1693, 1479, 893 and 627 cm^{-1}, δ_H (250MHz) 1.23 (9H, s, ^tBu), 1 69 (2H, tt, *J* 7, 7, CH_2), 2 18 (2H, tdd, *J* 7, 7 and 1 4, =CHCH_2), 2 34 (3H, s, Me of AcS), 2 87 (2H, t, *J* 7 3, SCH_2), 3 31 (1H, dd, *J* 8 2 and 1 8, CHO), 3 78 (1H, d, *J* 1 9, CHO), 5 25 (1H, ddt, *J* 15 5, 8 1 and 1 4, =CH) and 5 98 (1H, dt, *J* 15 5 and 7, =C*H*CH_2), δ_C (22 5MHz) 25 68, 28 22, 28.66, 30 45, 31 15, 43 39, 56 77, 59 00, 126 93, 136 74, 194 70 and 208 19, *m/z* (EI) 226 (10%), 171 (6), 141 (40), 57 (100) and 43 (68)

*E-6,7-trans-epoxy-8-oxo-9,9-dimethyldec-4-en-1-yl methyl disulphide (**10b**)*

A solution of *E*-1-acetylthio-6,7-*trans*-epoxy-9,9-dimethyldec-4-ene-8-one (**10a**) (1 4034g, 5 190mmol), piperidine (1 4050g, 16 5mmol, 3eq) and 4-dimethylaminopyridine (67.2mg, 0 55mmol, 10mole%) in hexane (200ml) and dimethyl disulphide (15ml) under nitrogen was stirred at 25°C for 12 days The solution was diluted with ether (50ml), extracted with sulphuric acid (0 1M , 2x100ml), then water (100ml), dried ($MgSO_4$) and evaporated to dryness Though unstable to TLC, rapid chromatography using 40-60° petrol / ether (7 1 [R_F 0 20]) successfully gave

E-*6,7*-trans-*epoxy-8-oxo-9,9-dimethyldec-4-en-1-yl methyl disulphide* (**10b**) as a colourless oil (1 01g, 3 68mmol, 71%) (Found C, 56 95, H, 8 33%, $C_{13}H_{22}O_2S_2$ requires C, 56 90, H, 8 08%)(Found M^+ 274 1074 $C_{13}H_{22}O_2S_2$ requires *M*, 274 1061), λ_{max} (MeCN)/nm 208sh (ε 14 000), ν_{max} (film) 1714, 1668 and 892 cm^{-1}, δ_H (250MHz) 1 23 (9H, s, ^tBu), 1 82 (2H, tt, *J* 7, 7, CH_2), 2.23 (2H, tdd, *J* 7, 7 and 1 4 , =CHCH_2), 2 41 (3H, s, SMe), 2 70 (2H, t, *J* 7 2, SCH_2), 3 31 (1H, dd, *J* 8 2 and 1 9, CHO), 3 78 (1H, d, *J* 2 0, CHO), 5 26 (1H, ddt, *J* 15.5, 8 4 and 1 4, =CH) and 6 00 (1H, dt, *J* 15 5 and 7, =C*H*CH_2), δ_C (22 5MHz) 23 13, 25 62, 28 01, 30 77, 37 22, 43.29, 56 67, 59 00, 126 71, 137 01 and 208 14, *m/z* (EI) 274 (M^+, 6%), 227 (17), 189 (48), 141 (64) and 57 (100)

*E-6,7-trans-epoxy-8-oxo-9,9-dimethyldec-4-en-1-yl thiol (**10c**)*

To an ice-cooled solution of *E*-6,7-*trans*-epoxy-8-oxo-9,9-dimethyldec-4-en-1-yl methyl disulphide (**10b**) (0 3876g, 1 41mmol) in tetrahydrofuran (40ml) and deionized water (10ml) under nitrogen was added tri-n-butylphosphine (0 37ml, 1 48mmol, 1 05eq) After 1 h, the tetrahydrofuran was removed *in vacuo* and the aqueous residue extracted with dichloromethane (3x10ml) The combined organic layers were extracted with water (10ml), dried ($MgSO_4$) and evaporated to dryness The product was unstable to column chromatography and thus was used crude in the following radical cyclisation

To a refluxing solution of azobisisobutyronitrile (0 1806g, 1 1mmol, 1eq) in dry tetrahydrofuran (33ml) under nitrogen were added separately azobisisobutyronitrile (0 1806g, 1 1mmol, 1eq) in tetrahydrofuran (8ml) and crude *E*-6,7-*trans*-epoxy-8-oxo-9,9-dimethyldec-4-en-1-yl thiol (**10c**) (0 5113g, 1 1mmol) in tetrahydrofuran (8ml) dropwise over 1 hour (syringe pump) After a further 1 hour at reflux, the solution was allowed to cool overnight To reduce the volatility of the tetrahydrothiophene product, the solution was cooled to 0°C and a solution of "Oxone" (2 029g, 3 3mmol, 3eq) in deionized water (11ml) was

added rapidly After 3 hrs at 0°C and 3 hrs at 25°C, the tetrahydrofuran was removed *in vacuo* , the aqueous slurry diluted with water (20ml) and extracted with dichloromethane (3x20ml) The combined organic layers were extracted with water (15ml), dried ($MgSO_4$), evaporated to dryness and chromatographed using dichloromethane, dichloromethane / ethyl acetate (20 1 and 4:1) and ethyl acetate giving unreacted azobis-isobutyronitrile (0.3025g, 1.84mmol), and

2-(3-oxo-1-propenyl)-tetrahydrothiophene 1,1-dioxide (**13**) purified by preparative TLC [1 2 petrol / ethyl acetate] as a white solid (4 1mg, 0 024mmol, 2 1% from the disulphide (**10b**), m p 176-179°C (dec) (Found MH^+, 175 0432 $C_7H_{11}O_3S$ requires *M*, 175 0429), λ_{max} (MeCN)/nm 214sh (ε 1 400) and 273sh (290), ν_{max} (film) 2851, 2749, 1691, 1642, 1303, 1120 and 978 cm^{-1}, δ_H (250MHz) 2 2-2 6 (4H, m, CH_2CH_2), 3 12 (1H, m, SCH_2), 3 28 (1H, m, SCH_2), 3 86 (1H, m, SCH), 6 33 (1H, ddd, *J* 15 7, 7 4 and 0.9, =C*H*CHO), 6.75 (1H, dd, *J* 15.8 and 8 3, =CH) and 9 62 (1H, d, *J* 7.4, CHO), δ_C (100MHz) 20 45, 29 27, 51 32, 63 56, 136 97, 144 85 and 192 08, *m/z* (EI) 175 (MH^+, 17%), 173 (4), 146 (4), 109 (12) and 81 (25).

Formation of potassium pivalate Trimethylacetic acid (20 4g, 0 2mole) in ethanol (40ml) was added slowly to an ethanolic solution of potassium hydroxide (7 80g, 0 19mole) in ethanol (100ml) The resulting solution was stirred for 30 mins before removal of the solvent under reduced pressure The white solid was washed with diethyl ether (50ml) and dried *in vacuo* over potassium hydroxide

6-Bromo-2,2-dimethyl-4,5-epoxy-7-(trimethylacetoxy)-3-heptanone (**14**)

Trimethylacetic acid (10 0g, 98mmole), N-bromosuccinimide (19 0g, 107mmole), potassium pivalate (22 7g, 0 2mole), and epoxide (**6b**) (3 31g, 21 5mmole) were added to a flask shielded from light in aluminium foil and then heated at 50°C, allowing the solid contents of the flask to become molten. The resulting solution was stirred at 50°C for thirty six hours The contents of the flask were poured onto diethyl ether (300ml) held in a separating funnel The ethereal phase was cautiously treated with saturated sodium hydrogen carbonate solution (5 x 200ml) until no further gas evolution was evident The separated orgnaic phase was sequentially washed with water (100ml) and saturated brine (100ml), dried over sodium sulphate, filtered and then evaporated to low volume Purification of the material was achieved with two successive chromatography columns (6 1 hexane/diethyl ether) This afforded pure one of the diastereoisomers of the desired *epoxide* (**14**), as a colourless crystalline solid, (0 146g, 2 1%) (m p., 56°C), ν_{max} 2991, 1729 and 1710cm^{-1}, δ_H (250MHz, $CDCl_3$, Me_4Si), 1 24 (18H, 2 x s, Bu^t x 2), 3 32 (1H, dd, *J* 1 9 and 6 1 , epoxide CHO), 3 95 (1H, d, *J* 1 9, epoxide CHO), 4 11 (1H, m, BrCH), 4 29-4.95 (2H, m, OCH_2), δ_C (22 5MHz, $CDCl_3$), 25 79, 28 27, 39 01, 43 94, 47 86, 55 59, 59 27, 64 26, 177 75, 207 44, *m/z* 251 011 (M^+ -82, 11%), 249 (12), 153 (18), 97 (16), 85 (33), 57 (100)

Homolytic fission of 6-bromo-2,2-dimethyl-4,5-epoxy-7-(trimethylacetoxy)-3-heptanone (**14**).

Epoxide (**14**) (0 10g, 0 3mmol) was dissolved in degassed benzene (20ml) A solution of AIBN (15mgs) and tributyltin hydride (86 4mgs, 0 3mmole) in dry benzene (5ml) was added in small aliquots (*ca* 0 25ml), *via* syringe, to the refluxing solution over a period of five hours Reflux was continued for a further twelve hours before removal of the solvent under reduced pressure Purification by column chromatography (dichloromethane) and HPLC (solvent 3 1 hexane/diethyl ether) afforded enal **18** (15mg, 19%) δ_H (400MHz, $CDCl_3$, Me_4Si), 1 25 (9H, Bu^t), 4 85 (2H, br d, *J* 4, OCH_2), 6 3 (1H, dd, *J* 16, 7 5 =CH), 6 85 (1H, dt, *J* 16, 4, =CH), 9 76 (1H, d, *J* 7 5, CHO), δ_C (20MHz, $CDCl_3$), 11 1, 46 3, 115 9, 27 19, 133 9, 176 7, 200 0

and pure *vinyl ether* (**17**), as a mixture of the *cis* and *trans* isomers (23 3mgs, 29 6%), ν_{max} 2980, 1728, 1659cm^{-1}, δ_H (400MHz, $CDCl_3$, Me_4Si), 1 19 (18H, 2 x s, Bu^t x 2), 4 47 (2H, dd, *J* 0 79 and 7, *trans*

OCH_2CH), 4 59 (2H, s, *trans* OCH_2CO), 4 62-4 73 (5H, m, *cis* =CH and 2 x OCH_2), 4.94-4.99 (1H, td, *J* 7 and 12 6, *trans* =$CHCH_2$), 5.95-5 98 (1H, dd, *J* 1 0 and 5 2 *cis* OCH=), 6 55-6.60 (1H, br. d, *J* 12 6, *trans* OCH=), δ_C (100MHz, $CDCl_3$), 26 14, 26 24, 27.15, 27 19, 27 33, 38 66, 42 90, 43 10, 58 11, 62 07, 69 55, 72 16, 99 43, 102 25, 148 07, 151 19, 178 54, 178.58, 208 85 and 210.19, *m/z* 256 (M^+, 0 4%), 171 (24), 99 (18), 85 (60), 57 (100) (Found· M^+, 256 1689, $C_{14}H_{24}O_4$ requires *M*, 256 1674)

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