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The Synthesis of d_6-α-Farnesene

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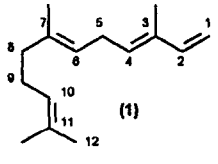
Summary

d_6-α-Farnesene (3,7-dimethyl-11-$^2H_3$-methyl-12,12,12-$^2H_3$-dodeca-1,3E ,6E,10-tetraene) has been synthesised by two routes. Thermolysis of 2-geranyl-3-methylsulpholene (5) yielded unlabelled α-farnesene (93%) which was epoxidized at Δ10 in 31% yield. Oxidative cleavage of the epoxide (42%) and Wittig elaboration of the resultant trienal with d_6-isopropyl triphenylphosphorane gave d_6-α-farnesene (73%). Alternatively, selective epoxidation of (5) gave the terminal 6',7' mono-epoxide in 74% yield. Oxidative cleavage (73%) and Wittig elaboration of the resultant aldehyde yielded deuterated 2-geranyl-3-methylsulpholene (46%). Thermal elimination of sulphur dioxide afforded the title compound in 91% yield.

Key Words: *α-farnesene, synthesis, deuterium labelling, sulpholene.*

Introduction.

The sesquiterpene α-farnesene (1) (3,7,11-trimethyldodec-1,3E,6E,10-tetraene) is an important aroma compound that occurs naturally in the skin of apples[1] and other fruit[2,3]. In addition, (1) has been identified as an attractant and oviposition stimulant to the codling moth (*Laspeyresia pomonella*)[4] and is also implicated as the causal agent of superficial scald, an economically important storage disorder of apples[5] and pears[6].



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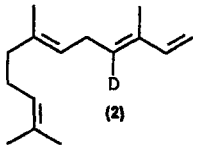

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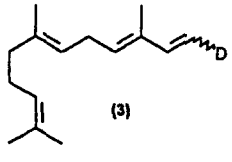

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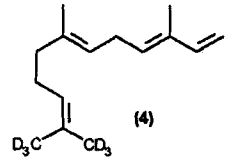

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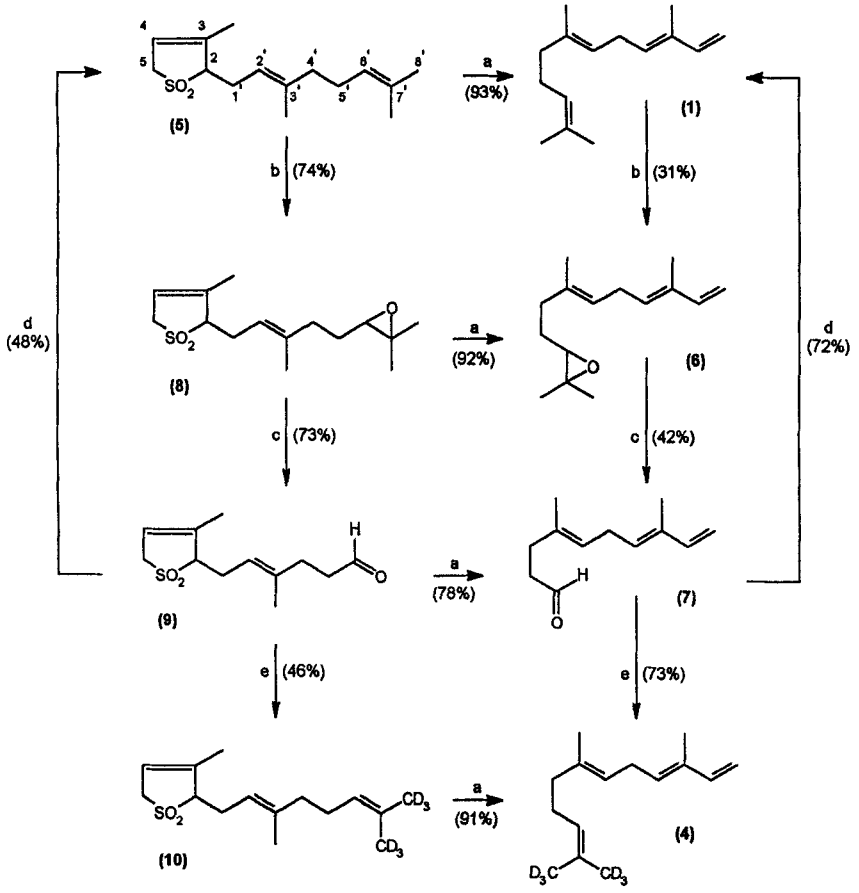
Several syntheses of unlabelled α-farnesene (**1**) have appeared in the literature[7,8,9,10] and we have recently reported the preparation of the mono-deuterium labelled analogues (**2**) and (**3**)[11]. As part of a continuing study into the induction of superficial scald of apples, a sample of α-farnesene bearing a higher proportion of deuterium was required. Here we report the synthesis of d6-α-farnesene (**4**) (3,7-dimethyl-11-$^2H_3$-methyl-12,12,12-$^2H_3$-dodeca-1,3E ,6E,10-tetraene).



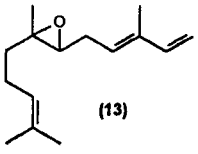
(a) Xylene reflux, 5 min.; (b) mCPBA, CH_2Cl_2, rt.; (c) H_5IO_6, THF, rt.;

(d) $(CH_3)_2CHPPh_3I$ (**11**), BuLi, THF, -78°C; (e) $(CD_3)_2CDPPh_3I$ (**12**), BuLi, THF, -78°C.

Results and Discussion

Thermolysis of 2-geranyl-3-methylsulpholene (**5**)[10,11,12] in refluxing, degassed xylene gave α-farnesene (**1**) in 93% yield. Epoxidation of (**1**) with *meta*-chloroperbenzoic acid (*m*CPBA) gave a complex mixture from which the 10,11-monoepoxide (**6**) was isolated as the major product in 31% yield. The 6,7-monoepoxide (**13**) (11%), the 3,4-monoepoxide (**14**) (2%), the 6,7;10,11-diepoxide

(**15**) (1%) and unreacted starting material (**1**) (18%), were also isolated. No additional selectivity was achieved by varying the temperature or duration of the epoxidation reaction and even in the presence of excess reagent unreacted α-farnesene was recovered.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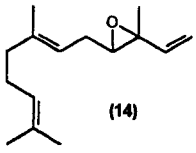
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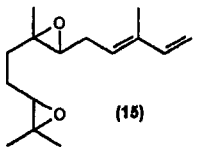
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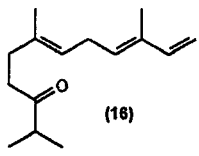
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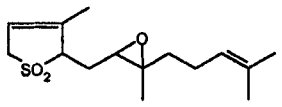
Periodic acid cleavage of epoxide (**6**) was rapid at room temperature and gave the trienal (**7**) in 42% yield. Rearrangement of (**6**) competed with epoxide cleavage and the isopropyl ketone (**16**) was also isolated in 6.5% yield.

Wittig elaboration of (**7**) with isopropyl triphenylphosphorane was carried out as a preliminary to olefination with the corresponding deutero-ylid and gave (**1**) in 72% as the sole reaction product with a 4% recovery of unreacted starting material. Repetition with d_6-isopropyl triphenylphosphorane gave (**4**) in 73%, again as the sole reaction product with unreacted starting material recovered in 4.7%. The ^{1}H nmr of (**4**) saw the loss of two methyl resonances observed at 1.67ppm and 1.59ppm in the spectrum of unlabelled α-farnesene (**1**), while ^{13}C nmr showed the corresponding loss of two high field resonances at 17.6ppm (C-11Me) and 25.6ppm (C-12). GCMS gave a molecular ion of *m/z*=210 with consistent shifts of the fragmentation ions relative to the unlabelled material.

Epoxidation of (**5**) with *m*CPBA in dichloromethane gave the 6',7'-monoepoxide (**8**) in 74% yield. The 2',3'-monoepoxide (**17**) and the diepoxide (**18**) were also isolated in 3% and 9% respectively together with an 11.3% recovery of unreacted starting material. Alternatively reaction of (**5**) with *N*-bromosuccinimide (NBS), followed by base treatment of the crude bromohydrin yielded the monoepoxide (**8**) in comparable yield (70.5%) over the two steps. Epoxides (**17**) and (**18**) were also isolated but no starting material was detected. Ring epoxidation was not observed with either *m*CPBA or NBS.

Periodic acid cleavage of epoxide (**8**) at room temperature gave the aldehyde (**9**) in 73% yield after flash chromatography. Rearrangement of (**8**)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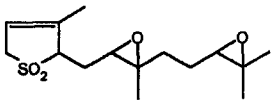
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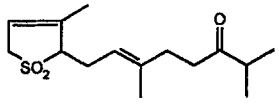
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competed with the epoxide cleavage and the isopropyl ketone (**19**) was isolated in 18% yield.

Wittig elaboration of (**9**), with isopropyl triphenylphosphorane was carried out as a preliminary to olefination with the corresponding deutero-ylid and gave the sulpholene (**5**) in 48% yield with a 17% recovery of unreacted starting material. Repetition with d_6-isopropyl triphenylphosphorane gave (**10**) in 46% yield again with a significant recovery (19%) of unreacted starting material. Comparison between the ^1H nmr spectra of (**5**)[11] and (**10**) showed the loss of two high field methyl signals at δ 1.63 and 1.57, while the ^{13}C nmr showed the loss of 2 carbon resonances at δ 25.3 and 17.3 assigned as C8' and C7'-Me respectively. The moderate yields of (**5**) and (**10**) and the recovery of unreacted starting material were consistent with sulpholene deprotonation and aldehyde enolization competing as side reactions.

The thermolysis of (**10**) in refluxing, degassed xylene gave d_6-α-farnesene (**4**) in a 91% yield. ^1H nmr, ^{13}C nmr, GC and GCMS data were identical to that obtained for d_6-α-farnesene prepared by the olefination of trienal (**7**).

As an alternative means of preparation, thermolysis of the sulpholene (**8**) in refluxing xylene gave the triene monoepoxide (**6**) in high yield (92%). Similarly trienal (**7**) was obtained by the thermolysis of (**9**) in 78% yield.

Conclusion

d_6-α-Farnesene (**4**) (3,7-Dimethyl-11-$^2H_3$-methyl-12,12,12-$^2H_3$-dodeca-1,3E,6E,10-tetraene) has been prepared by two parallel routes from the common starting material 2-geranyl-3-methylsulpholene (**5**).

Unmasking the conjugated diene as the first synthetic step and subsequent manipulation of the 10,11 double bond was both poorly selective and inefficient (9%). Alternatively manipulation of the terminal double bond of sulpholene (**5**), and exposure of the conjugated diene as a final step, (**10**)→(**4**) proved doubly advantageous. The overall yield was improved (23%) and (**10**) could be stored as a stable, convenient source of d_6-α-farnesene, readily transformed when required. A higher overall yield of 31% could be achieved by the conversion of (**9**) to the trienal (**7**) and its subsequent olefination, however the convenience of storing (**10**) as a stable precursor to d_6-α-farnesene outweighed this improved efficiency.

Experimental.

NMR spectra were recorded on a Bruker WP80SY (80 MHz.) spectrometer unless stated or a Bruker AMX300 (300MHz) in either $CDCl_3$ or CD_3OD. NMR data is reported in parts per million (δ)

and is referenced to $CHCl_3$ at δ7.24 or CH_3OH at δ3.50 for ^1H spectra and δ77.0 or δ49.3 for ^{13}C. Mass spectra were obtained with a VG70-250S spectrometer (VG instruments, Manchester, UK) at 70eV. FAB mass spectra were obtained using a matrix of *m*-nitrobenzyl alcohol where 1μg of sample in 1μl of methanol was placed on the probe with approximately 3 μl of matrix. Ionisation was achieved using a cesium ion gun operating at a potential of 20 KeV. GC-MS was carried out using an HP 5890 Series II gas chromatograph fitted with a 30m x 0.25mm ID DB1 column, 0.25μ film thickness. Temperature programmed for 5min @ 40°C, 5°C/min, 20min @ 280°C, with 2psi He head pressure and directly coupled to the VG70 mass spectrometer. GC was carried out using an HP 5830A gas chromatograph fitted with a 30m x 0.25mm ID SE30 Alltech Econo Cap™ column, 0.25μ film thickness. Temperature programmed for 5min @ 40°C, 10°C/min, 5min @ 280°C, with 10psi N_2 head pressure. Retention times (rt) in minutes.

All reagents [Aldrich Chemical Company, unless stated] were used without further purification unless stated. THF was freshly distilled from sodium/benzophenone blue under dry N_2. Dichloromethane (CH_2Cl_2) [BDH analar] was freshly distilled from P_2O_5 under dry N_2. Ether was diethyl ether [BDH analar]. Room temperature is 18-23°C.

Tlc was performed on foil backed silica gel plates (0.2mm), (Merck Art. 5554), and developed by lightly spraying with vanillin (1.0g) in conc. H_2SO_4 (50ml) and heating to 150°C. Preparative chromatography was carried out using either Mallinckrodt SilicaR CC-7, flash column; or Merck GF-254 type 60 (Merck Art. 7730), preparative centrifugal chromatography on silica gel rotors (Chromatotron, U.S. patent no. 4139458).

3,7,11-Trimethyldodeca-1,3E,6E,10-tetraene (1) [α-farnesene], by thermolysis.

A solution of (5) (0.1497g, 0.56mmol) in dry degassed xylene (5ml) was refluxed under dry N_2 for 5 mins. The solvent was removed under reduced pressure and the crude product purified by flash chromatography (pentane) to afford α-farnesene (1) (0.1059g, 93%) as a clear mobile oil; R_f 0.80 (pentane); ^1H NMR ($CDCl_3$) δ 6.37(dd, J=17.4Hz, J=10.6Hz, 1H), 5.45(bt, J=7.3Hz, 1H), 5.21-4.85(bm, 4H), 2.82(bt, J=7.2Hz, 2H), 2.00(bs, 4H), 1.76(bs, 3H), 1.67(bs, 3H), 1.62(bs, 3H), 1.59(bs, 3H); ^{13}C NMR ($CDCl_3$) δ 141.5, 135.8, 133.7, 131.8, 131.3, 124.3, 122.1, 110.4, 39.6, 27.2, 26.7, 25.6, 17.6, 16.1, 11.6; GC rt 23.26; MS (m/z, rel.int.) 204(M^+, 4.38), 123(37.7), 119(34.6), 107(34.1), 93(100.0), 79(29.8), 69(56.5), 55(43.4), 41(46.6).

***m*CPBA epoxidation of 3,7,11-trimethyldodeca-1,3E,6E,10-tetraene (α-farnesene) (1). 10,11-Epoxy-3,7,11-trimethyldodeca-1,3E,6E-triene (6), 6,7-Epoxy-3,7,11-trimethyldodeca-1,3E,10-triene (13), 3,4-Epoxy-3,7,11-trimethyldodeca-1,6E,10-triene (14) and 3,4;10,11-diepoxy-3,7,11-trimethyldodeca-1,3E-diene (15).**

*m*CPBA [50-60%, Pfaltz & Bauer Inc.] (0.4798g, 2.78mmol) was added to a stirred solution of α-farnesene (1) (0.1894g, 0.93mmol) in CH_2Cl_2 (20ml) at room temperature under an atmosphere of dry N_2. The reaction mixture was stirred overnight whereupon anhydrous potassium fluoride (0.3231g, 5.56mmol) was added and the slurry stirred for 10 mins. prior to filtration through a glass sinter under reduced pressure. The filtrate was washed, K_2CO_3 5% aq. (25ml), water (25ml), brine (25ml), then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a viscous oil, (0.1935g). Tlc showed the presence of 5 components including starting material (1). R_f

0.68(1), 0.37, 0.24, 0.17, 0.08 (30-40 petrol ether/ether 20:1). Flash chromatography (as tlc solvent) gave 5 homogeneous fractions.

(1) (0.0333g, 17.6%) [recovered starting material]; R_f 0.68 (30-40 petrol ether/ether 20:1).

(6) (0.0633g, 31%); R_f 0.37 (30-40 petrol ether/ether 20:1); ^{1}H NMR ($CDCl_3$) δ 6.35(dd, 17.4Hz, 10.6Hz, 1H), 5.43(bt, J=7.3Hz, 1H), 5.26-4.84(m, 3H), 2.82(bt, J=7.2Hz, 2H), 2.67(t, J=6.0, 1H), 2.21-2.03(m, 2H), 1.73(bs, 3H), 1.73-1.56(m, 2H), 1.64(bs, 3H), 1.27(s, 3H), 1.23(s, 3H); ^{13}C NMR ($CDCl_3$) δ 141.5, 134.9, 133.9, 131.4, 122.8, 110.6, 64.1, 58.2, 36.3, 27.4, 27.3, 24.8, 18.7, 16.1, 11.6; GC rt 24.47; MS (m/z, rel. int.) 220(M^+, 1.4), 187(2.1), 159(3.9), 147(5.0), 134(55.7), 119(100), 105(38.6), 93(97.1), 80(86.4), 55(51.4), 41(70.7).

(13) (0.0225g, 11%). (14) (0.0041g, 2%). (15) (0.0020g, 1%).

Spectroscopic and mass spectral data for epoxides (13), (14) and (15) was consistent with reported values[12].

4,8-Dimethyldeca-4E,7E,9-trienal (7) and 2,6,10-Trimethyldodeca-6E,9E,11-trien-3-one (16).

Periodic acid (0.1422g, 0.624mmol) was added to a stirred solution of epoxide (6) (0.1375g, 0.624mmol) in THF (20 ml) at room temperature under an atmosphere of dry N_2. The heavy white precipitate was stirred vigorously for 2 mins. and the slurry poured into water (25ml). The THF was removed under reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (3x25ml). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a yellow oil, (0.1445g). Tlc showed 2 components, R_f 0.64, 0.54 (30-40 petrol ether/ether 1:1). Flash chromatography (30-40 petrol ether/ether 20:1) gave two compounds.

(7) (0.0464g, 42%) colourless oil; R_f 0.54 (30-40 petrol ether/ether 1:1); ^{1}H NMR ($CDCl_3$) δ 9.72(t, J=1.7Hz, 1H), 6.33(dd, J=17.4Hz, J=10.6, 1H), 5.40(bt, J=7.3Hz, 1H), 5.24-4.83(m, 3H), 2.80(bt, J=7.2Hz, 2H), 2.58-2.22(m, 4H), 1.72(s, 3H), 1.63(s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.1, 141.4, 134.1, 133.8, 131.0, 123.3, 110.7, 42.1, 31.8, 27.2, 16.1, 11.6; GC rt 22.08; MS (m/z, rel. int.) 220(M^+, 2.9), 163(3.9), 145(16.1), 134(31.4), 119(84.3), 105(30.7), 93(100), 85(28.6), 79(61.4), 67(29.6), 55(41.1), 41(62.1).

(16) (0.0090g, 6.5%) colourless oil; R_f 0.64 (30-40 petrol ether/ether 1:1); ^{1}H NMR ($CDCl_3$) δ 6.35(dd, J=17.4Hz, J=10.7Hz, 1H), 5.41(bt, J=7.3Hz, 1H), 5.22-4.84(m, 3H), 2.80(bt, J=7.2Hz, 2H), 2.67-2.25(m, 5H), 1.73(bs, 3H), 1.63(s, 3H), 1.07(d, J=6.7Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 214.2, 141.5, 134.7, 134.0, 131.3, 122.6, 110.6, 40.9, 39.0, 33.5, 27.2, 18.2, 16.2, 11.6; GC rt 24.94; MS (m/z, rel. int.) 220(M^+, 3.6), 177(2.5), 159(3.0), 134(67.9), 119(100), 105(13.6), 93(23.2), 81(19.3), 71(20.0), 55(16.4), 43(56.4).

Isopropyl triphenylphosphonium iodide (11).

2-Iodopropane [Riedel-de Haen] (1.94g, 11.4mmol) and triphenylphosphine (3.0g, 11.4mmol) were heated together at 138°C for 3hrs in a thick, glass walled tube sealed with a Rotaflo™ teflon stopcock. On cooling the crystalline mass was transferred to a small flask and recrystallized from hot ethyl acetate/ethanol (2:1) (30ml) to give 2.35g of the phosphonium salt as a white crystalline solid. The mother liquor was concentrated and yielded a further 1.0g of (11) (3.35g, 67.8%); ^{1}H NMR (CD_3OD) δ 8.08-7.60(m, 15H), 4.20(dm, J=11.0Hz, 1H), 1.37(dd, J=18.6Hz, J=7.0Hz, 6H);

^{13}C NMR (CD_3OD) δ 136.2(d, J=2.7Hz), 135.1(d, J=9.2Hz), 131.6(d, J=12.2Hz), 119.0(d, J=83.2Hz), 22.8(d, J=48.4Hz), 16.8(d, 2.0Hz); FAB MS (m/z) 305(M^+-Iodine).

$^2H_7$-Isopropyl triphenylphosphonium iodide (12).

Prepared by the method described for the unlabelled salt (11) using d_7-2-iodopropane (98 atom% D) (2.03g, 11.4mmol) and triphenylphosphine (3.0g, 11.4mmol). Recrystallization from hot ethyl acetate/ethanol (2:1) (30ml) gave 2.76g of the phosphonium salt as a white crystalline solid. The mother liquor was concentrated and yielded a further 1.1g of (12) (3.86g, 75.6%); ^1H NMR (CD_3OD) δ 8.05-7.63(m, 15H); ^{13}C NMR (CD_3OD) δ 136.5(d, J=2.3Hz), 135.4(d, J=9.0Hz), 131.9(d, J=12.3Hz), 119.3(d, J=83.1Hz); FAB MS (m/z) 312(M^+-Iodine).

3,7,11-Trimethyldodeca-1,3E,6E,10-tetraene (1) [α-farnesene], Wittig reaction.

A suspension of isopropyl triphenylphosphonium iodide (11) (0.0885g, 0.20mmol) in THF (2ml) was stirred at room temperature while *n*-butyl lithium [1.88M in pentane] (0.114ml, 0.215mmol) was added over 5 mins. The dark red ylid solution was transferred by syringe (plus THF washings (2x0.5ml)) to a pre-cooled solution of aldehyde (7) (0.0365g, 0.20mmol) in THF (3ml). The reaction mixture was stirred at -78°C for a further 15mins. then quenched with 10% ammonium chloride sol. (5ml). The THF was removed under reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (3x20ml). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a viscous oil. Flash chromatography (pentane then 30-40 petrol ether/ether 1:1) gave (1) (0.0302g, 72.2%) as a mobile, colourless oil; R_f 0.80 (pentane). (7) (0.0015g, 4%) [unreacted starting material] was also isolated.

3,7-dimethyl-11-$^2H_3$-methyl-12,12,12-$^2H_3$-dodeca-1,3E,6E,10-tetraene (4) [d_6-α-Farnesene], Wittig reaction.

Prepared by the method described for (1), from aldehyde (7) (0.0365g, 0.20mmol) and $^2H_7$-isopropyl triphenylphosphonium iodide (12) (0.0899g, 0.20mmol). Flash chromatography (pentane then 30-40 petrol ether/ether 1:1) gave (4) (0.0316g, 73.3%) as a mobile, colourless oil; R_f 0.80 (pentane); ^1H NMR 300MHz ($CDCl_3$) δ 6.37(dd, J=17.4Hz, J=10.7Hz, 1H), 5.46(t, J=7.3Hz, 1H), 5.12(m, 3H), 4.91(d, J=10.7Hz, 1H), 2.84(t, J=7.2Hz, 2H), 2.05(m, 4H), 1.76(s, 3H), 1.64(s, 3H); ^{13}C NMR 300MHz ($CDCl_3$) δ 141.6, 135.8, 133.8, 131.8, 131.3(weak), 124.3, 122.1, 110.5, 39.7, 27.2, 26.7, 16.1, 11.7; GC rt 23.17; MS (m/z, rel. int.) 211(M+1, 0.6), 210(M+, 3.3), 161(3.6), 135(6.4), 129(19.6), 119(26.1), 107(37.9), 93(100.0), 75(40.0), 55(48.2), 41(27.1). (7) (0.0017g, 4.7%) [unreacted starting material] was also isolated.

***m*CPBA epoxidation of 2-3',7'-dimethylocta-2'E,6'-dienyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (5).**

2-3',7'-Dimethyl-6',7'-epoxyocta-2'E-enyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (8), 2-3',7'-dimethyl-2',3'-epoxyocta-6-enyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (17) and 2-3',7'-dimethyl-2',3',6',7'-diepoxyoctyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (18).

*m*CPBA [50-60%, Pfaltz & Bauer Inc.] (1.53g, 8.88mmol) was added to a stirred solution of 2-3',7'-dimethylocta-2'E,6'-dienyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (5) (0.5958g, 2.22mmol) in

CH_2Cl_2 (50 ml) at room temperature under an atmosphere of dry N_2. After 3hrs, anhydrous potassium fluoride (1.03g, 17.8mmol) was added and the slurry stirred for 10 mins. prior to filtration through a glass sinter under reduced pressure. The filtrate was washed with K_2CO_3 5% aq. (50ml), water (50ml), brine (50ml) then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a viscous oil, (0.6660g). Tlc showed the presence of 4 components including starting material (**5**). R_f 0.57(**5**), 0.41, 0.27, 0.09 (CH_2Cl_2/ether 20:1). Flash chromatography (30-40 petrol ether/ether 2:1) gave 4 homogeneous fractions.
(**5**) (0.0675g, 11.3%), [recovered starting material]; R_f 0.57 (CH_2Cl_2/ether 20:1).
(**8**) (0.4655g, 73.7%), colourless oil; R_f 0.27 (CH_2Cl_2/ether 20:1); ^1H NMR ($CDCl_3$) δ 5.65(m, 1H), 5.26(tt, J=7.1Hz, J=1.3Hz, 1H), 3.62(m, 2H), 3.48(bt, J=6.6Hz, 1H), 2.67(t, J=6.0Hz, 1H), 2.54(bt, J=6.6Hz, 2H), 2.14(m, 2H), 1.81(m, 3H), 1.73-1.52(m, 2H), 1.72(bs, 3H), 1.27(s, 3H), 1.23(s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.6, 138.1, 119.0, 117.2, 67.3, 63.8, 58.2, 55.7, 36.4, 27.3, 26.3, 24.8, 18.7, 18.2, 16.2; GC rt 24.48; MS (m/z, rel. int.) 220(M^+-SO_2, 3.9), 202(1.8), 187(3.2), 159(5.0), 147(5.0), 134(48.9), 119(100), 105(30.7), 93(76.4), 85(35.0), 80(72.5), 69(19.3), 55(37.1), 41(63.2).
(**17**) (0.0206g, 3.3%), colourless oil; R_f 0.41 (CH_2Cl_2/ether 20:1); ^1H NMR ($CDCl_3$) δ 5.68(m, 1H), 5.55(bm, 1H), 3.61(m, 3H), 2.94(m, 1H), 2.52(m, 2H), 2.23-2.01(m, 2H), 1.84(m, 3H), 1.75-1.50(m, 2H), 1.66(s, 3H), 1.58(s, 3H), 1.27(s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.6, 133.5, 123.5, 117.3, 67.2, 65.0, 62.3, 55.9, 38.7, 26.6, 26.3, 25.6, 18.2, 17.8, 17.6; MS (m/z, rel. int.) 220(M^+-SO_2, 2.5), 139(17.1), 123(6.1), 111(10.7), 95(2.9), 81(11.4), 69(100), 55(15.3), 41(42.1).
(**18**) (0.0552g, 8.7%), colourless oil; R_f 0.09 (CH_2Cl_2/ether 20:1); ^1H NMR ($CDCl_3$) δ 5.67(m, 1H), 3.67(m, 3H), 2.95(m, 1H), 2.65(m, 1H), 2.22-1.93(m, 2H), 1.83(m, 3H), 1.63(m, 4H), 1.28(s, 3H), 1.26(s, 3H), 1.22(s, 3H); ^{13}C NMR ($CDCl_3$) δ (138.2, 137.9), 117.4, 65.2, 63.7, 61.4, (60.3, 60.0), 58.2, (56.0, 55.5), (35.4, 35.3, 35.1), 27.6, 27.1, (24.7, 24.5), 18.6, 17.8, 16.7, 16.7; GC rt 24.71; MS (m/z, rel. int.) 236(M^+-SO_2, 1.1), 155(100), 137(19.3), 111(19.3), 95(13.2), 81(15.4), 71(41.0), 55(15.7), 43(55.7).

NBS/Base epoxidation of 2-3',7'-dimethylocta-2'E,6'-dienyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (5).

2-3',7'-dimethyl-6',7'-epoxyocta-2'E-enyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (8), 2-3',7'-dimethyl-2',3'-epoxyocta-6-enyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (17) and 2-3',7'-dimethyl-2',3',6',7'-diepoxyoctyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (18).

To a solution of (**5**) (0.1762, 0.656mmol) in THF (12ml) at 0°C was added enough water (4ml) to give a cloudy mixture. The reaction was shielded from light and NBS (0.1285g, 0.72mmol) was added in one portion. The mixture was stirred for 1hr then quenched with cyclohexene (0.1ml, 1.0mmol). THF was removed under reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (3x20ml). The extract was washed with brine (20ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude mixture of bromohydrins as a yellow oil that was used directly in the next step. To a solution of the crude bromohydrin mixture (0.2486g) in methanol (10ml) was added dry K_2CO_3 (0.2405g, 1.3mmol). After stirring at room temperature for 1hr. the methanol was removed under reduced pressure and replaced with ether (20ml). The organic phase was washed with water (20ml) and brine (20ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude mixture of epoxides (0.1677g) as a pale yellow oil. Tlc indicated the

presence of 3 components, with no starting material present. R_f 0.41, 0.27, 0.09 (CH_2Cl_2/ether 20:1). Flash chromatography (30-40 petrol ether/ether 2:1) afforded 3 homogeneous fractions. (8) (0.1316g, 70.5%). (17) (0.0019g, 1%). (18) (0.0197g, 10.3%).

2-3'-Methyl-6'-oxohexa-2'E-enyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (9) and 2-3',7'-dimethyl-6'-oxoocta-2'E-enyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (19).
Periodic acid (0.1495g, 0.656mmol) was added to a stirred solution of epoxide (8) (0.1865g, 0.656mmol) in THF (20 ml) at room temperature under an atmosphere of dry N_2. The heavy white precipitate was stirred vigorously for 2 mins. and the slurry poured into water (25ml). The THF was removed under reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (3x25ml). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a clear oil, (0.1770g). Tlc analysis showed 2 components , R_f 0.25, 0.12 (30-40 petrol ether/ether 1:1). Flash chromatography (tlc solvent) gave two compounds. (9) (0.1163g, 73%), colourless oil; R_f 0.12 (30-40 petrol ether/ether 1:1); ^{1}H NMR ($CDCl_3$) δ 9.69(t, J=1.5Hz, 1H), 5.63(m, 1H), 5.20(bt, J=7.0Hz, 1H), 3.63-3.46(m, 3H), 2.58-2.22(m, 6H), 1.78(bs, 3H), 1.63(s, 3H); ^{13}C NMR ($CDCl_3$) δ 201.4, 138.3, 137.0, 119.3, 117.3, 67.1, 55.7, 41.8, 31.7, 26.1, 18.0, 16.3; GC rt 21.80; MS (m/z, rel. int.) 176(M^+-SO_2, 2.9), 163(3.9), 145(16.1), 134(31.4), 119(84.3), 105(30.7), 93(100), 85(28.6), 79(61.4), 67(29.6), 55(41.1), 41(62.1).
(19) (0.0334g, 18%), colourless oil; R_f 0.25 (30-40 petrol ether/ether 1:1); ^{1}H NMR ($CDCl_3$) δ 5.63(m, 1H), 5.18(bt, J=7.1Hz, 1H), 3.55(m, 2H), 3.44(bt, J=5.8Hz, 1H), 2.72-2.13(m, 7H), 1.80(m, 3H), 1.61(s, 3H), 1.03(d, J=6.9Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 213.7, 138.5, 137.9, 118.7, 117.3, 67.2, 55.7, 40.8, 38.6, 33.3, 26.2, 18.2, 18.2, 16.4; GC rt 24.71; MS (m/z, rel. int.) 220(M^+-SO_2, 3.6), 177(2.5), 159(3.0), 134(67.9), 119(100), 105(13.6), 93(23.2), 81(19.3), 71(20.0), 55(16.4), 43(56.4).

2-3',7'-dimethylocta-2'E,6'-dienyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (5).
A suspension of isopropyl triphenylphosphonium iodide (11) (0.1928g, 0.446mmol) in THF (5ml) was stirred at room temperature while *n*-butyl lithium [1.88M in pentane] (0.24ml, 0.446mmol) was added over 5 mins. The dark red ylid solution was transferred by syringe (plus THF washings (2x1ml)) to a pre-cooled solution of aldehyde (9) (0.1081g, 0.446mmol) in THF (5ml). The reaction mixture was stirred at -78°C for a further 15mins., then quenched with 10% ammonium chloride sol. (10ml). The THF was removed under reduced pressure and the aqueous residue extracted with CH_2Cl_2 (3x20ml). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a viscous, opaque oil (0.2584g). Flash chromatography (30-40 petrol ether/ether 1:1) gave (5) (0.0516g, 48.4%) as a colourless oil; R_f 0.32 (30-40 petrol ether/ether 1:1); ^{1}H NMR ($CDCl_3$) δ 5.64(m, 1H), 5.20(bm, 2H), 3.62(m, 2H), 3.47(bt, J=6.5Hz, 1H), 2.53(bt, J=6.5Hz, 2H), 1.99(m, 4H), 1.82(m, 3H), 1.63(bs, 6H), 1.57(bs, 3H); ^{13}C NMR ($CDCl_3$) δ 138.4, 138.4, 131.0, 123.7, 118.2, 116.9, 67.0, 55.4, 39.4, 26.1, 26.1, 25.3, 17.9, 17.3, 15.9; GC rt 23.26; MS (m/z, rel. int.) 205(0.6), 204(M^+-SO_2, 3.5), 123(38.3), 119(39.3), 107(42.5), 93(100.0), 69(41.3). (9) (0.0185g, 17.1%) [recovered starting material] was also isolated.

2-3'-methyl-7'-$^2H_3$-methyl-8',8',8'-$^2H_3$-octa-2'E,6'-dienyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (10).
A suspension of $^2H_7$-isopropyl triphenylphosphonium iodide (12) (0.4186g, 0.952mmol) in THF

(8ml) was stirred at room temperature while *n*-butyl lithium [1.88M in pentane] (0.51ml, 0.952mmol) was added over 5 mins. The dark red ylid solution was transferred by syringe (plus THF washings (2x1ml)) to a pre-cooled solution of aldehyde (**9**) (0.2309g, 0.952mmol) in THF (10ml). The reaction mixture was stirred at -78°C for a further 15mins., then quenched with 10% ammonium chloride sol. (20ml). The THF was removed under reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (3x25ml). The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a pale yellow oil (0.5457g). Flash chromatography (30-40 petrol ether/ether 1:1) gave (**10**) (0.1198g, 45.8%) as a colourless oil; R_f 0.31 (30-40 petrol ether/ether 1:1); ^{1}H NMR 300MHz ($CDCl_3$) δ 5.67(m, 1H), 5.22(t, J=6.7Hz, 1H), 5.07(t, J=6.6Hz, 1H), 3.66(m, 2H), 3.50(t, J=6.2Hz, 1H), 2.57(m, 2H), 2.06(m, 4H), 1.85(m, 3H), 1.66(s, 3H); ^{13}C NMR 300MHz ($CDCl_3$) δ 139.1, 138.9, 131.4(weak), 124.1, 118.3, 117.2, 67.4, 55.7, 39.7, 26.5, 26.4, 18.3, 16.3; GC rt 23.17; MS (m/z, rel. int.), 211(M+1, 0.6), 210(M^+-SO_2, 3.3), 161(3.6), 135(6.4), 129(19.6), 119(26.1), 107(37.9), 93(100.0), 75(40.0), 55(48.2), 41(27.1). (**9**) (0.0430g, 18.6%) [unreacted starting material] was also isolated.

3,7-Dimethyl-11-$^2H_3$-methyl-12,12,12-$^2H_3$-dodeca-1,3E,6E,10-tetraene (4) [d_6-α-Farnesene], by thermolysis.

Prepared by the method described for (**1**), from (**10**) (0.0344g, 0.125mmol) to afford d_6-α-farnesene (**4**) (0.0240g, 91%) as a clear mobile oil.

10,11-Epoxy-3,7,11-trimethyldodeca-1,3E,6E-triene (6), by thermolysis.

A solution of (**8**) (0.0278g, 0.1mmol) in dry degassed xylene (1ml) was refluxed under dry N_2 for 5 mins. The solvent was removed under reduced pressure and the crude product purified by flash chromatography (30-40 petrol ether/ether 20:1) to afford (**6**) (0.0198g, 92%) as a clear oil.

4,8-Dimethyldeca-4E,7E,9-trienal (7), by thermolysis.

A solution of (**9**) (0.0820g, 0.34mmol) in dry degassed xylene (3ml) was refluxed under dry N_2 for 5 mins. The solvent was removed under reduced pressure and the crude product purified by flash chromatography (30-40 petrol ether/ether 20:1) to afford (**7**) (0.0470g, 78.3%) as a clear oil.

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