The Synthesis of 4-^{2}H-α-Farnesene and 1-^{2}H-α-Farnesene.

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Summary

α-Farnesene deuterated at C1 or C4 was synthesised by regiospecific deuteration of 2-geranyl-3-methylsulpholene (2). Treatment of (2) with butyl lithium in dimethylpropenylurea (DMPU) mediated THF resulted in deprotonation at C2. Quenching with D_2O/CH_3CO_2D gave a mixture of deuterated sulpholenes (43-68%), predominantly 2-^{2}H-2-geranyl-3-methylsulpholene (5), together with bond migrated product (25-49%). Thermal elimination of sulphur dioxide gave 4-^{2}H-α-farnesene (6)(85%) but with low deuterium incorporation (60%) and poor regiospecificity. Treatment of (2) with butyl lithium in TMEDA mediated THF resulted in deprotonation at C5 with minimal bond migration (1%). Quenching with D_2O/CH_3CO_2D yielded 5-^{2}H-2-geranyl-3-methylsulpholene (18)(75%) which on thermolysis gave 1-^{2}H-α-farnesene (19)(86%) with high regiospecificity and improved deuteration (85%). Some mechanistic aspects of the alkylation of 3-methylsulpholenes are discussed.

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

Introduction.

The sesquiterpene α-farnesene (3,7,11-trimethyldodec-1,3E,6E,10-tetraene) is an important primary aroma component which occurs naturally in the skin of apples[1] and several other fruit[2,3]. α-Farnesene has also been identified as an attractant and oviposition stimulant to the codling moth (*Laspeyresia pomonella*)[4] and is implicated as the causal agent of superficial scald, an economically important storage disorder of apples[5] and pears[6]. As part of a study of the induction of superficial scald in apples, we required isotopically labelled α-farnesene.

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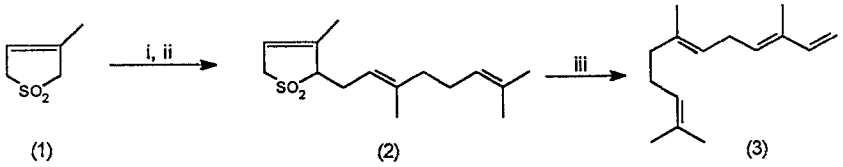
Several syntheses of α-farnesene have been reported in the literature[7,8,9]. One effective strategy (Scheme 1)[10] involved the regiospecific alkylation of 3-methylsulpholene (1) with geranyl bromide to give 2-geranyl-3-methylsulpholene (2) as a masked α-farnesene equivalent. Thermal elimination of sulphur dioxide at 240°C in the injection port of a gas chromatograph then furnished α-farnesene (3). We considered this synthesis readily adaptable to the incorporation of a deuterium label as deprotonation of (2) and quenching the resulting carbanion with D_2O, would yield a sulpholene adduct (5) deuterated at the 2-position (Scheme 2). Thermolysis would then yield preparative quantities of 4-^{2}H-α-farnesene (6) bearing deuterium at C4.

Scheme 1. **Synthetic route to α-farnesene.**

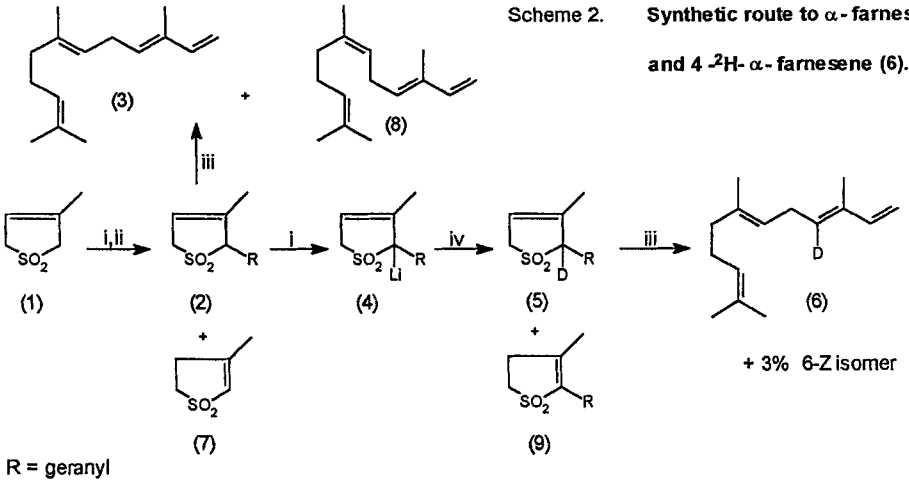


i, LiN(SiMe$_3$)$_2$ / THF ii, Geranyl Bromide iii, Thermolysis, GC (240°C)

Alkylation of 3-methylsulpholene (1) has been achieved using a variety of bases and solvent systems[10] but ring opening to yield butadienyl sulphones is often a major side reaction[11]. Ring opening can be minimised by the use of butyl lithium in hexamethylphosphoramide (HMPA) mediated THF at -105°C[12]. However, in view of the carcinogenicity of HMPA[13], substitution with the less toxic dimethylpropenylurea (DMPU)[14] was made.

Results and Discussion

Alkylation of 3-methylsulpholene (1) with geranyl bromide in the presence of DMPU gave 2-geranyl-3-methylsulpholene (2) in a 60% yield after chromatography (Scheme 2) and demonstrated that DMPU was a suitable replacement for HMPA. The bond migrated product, 3-methyl-2-sulpholene (7)(3%) was also isolated from the reaction mixture. Thermolysis of (2) under nitrogen in refluxing, degassed xylene[15] gave α-farnesene (3) in high yield, (85%-95%) and purity. The ^{1}H NMR, GC and GC/MS data were consistent with data obtained for α-farnesene isolated from natural sources[16]. The presence of a small quantity of the 6Z-isomer of α-farnesene (8)(3% by GC), was attributed to contamination of the geranyl bromide with a small quantity of the Z isomer (neryl bromide).



Scheme 2. **Synthetic route to α-farnesene (3) and 4-²H-α-farnesene (6).**

i, BuLi / DMPU / THF −105°C ii, geranyl bromide iii, xylene reflux iv, D_2O or D_2O / CH_3CO_2D / THF.

Quenching of the carbanion (4) with D_2O (10.0 equivs.) gave a 41% yield of deuterated sulpholene (5) identical with (2) by tlc. The non-deuterated, bond migrated product (9) was also isolated (23%). Thermolysis of (5) in refluxing xylene gave 4-²H-α-Farnesene (6)(85%) which also contained 3% of the deuterated 6Z isomer as an impurity detectable by GC. The ^1H NMR data was consistent with partial deuteration at C4, i.e. structure (6). The broad triplet of the doubly allylic methylene protons at C5 (2.81 ppm) collapsed to a broad multiplet and the C4 methine triplet (5.45 ppm) had diminished in intensity indicating incorporation had occurred to approximately 50%. ^{13}C NMR was consistent with these observations with the signal at 131.8 ppm. (C4) greatly diminished. GC/MS analysis of this material gave the molecular cluster 206 (0.82%), 205 (3.78%) and 204 (3.23%) consistant with a 48.4 mole% contrbution from undeuterated material, 47.6 mole% monodeuteration and 4.0 mole% dideuteration indicating that deuteration of (2) under these conditions was poorly controlled and not regiospecific. This low deuterium incorporation was considered to result from a rapid equilibration of (4), quench products and lithium deutroxide, giving rise to additional deuteration and bond migration. Such base catalysed exchange has been observed in the 'perdeuteration' of sulpholene.[11,17]

In an attempt to improve yields and deuterium incorporation several modifications to the reaction conditions were investigated. A solution of CH_3CO_2D/D_2O in THF proved to be both an effective quenching agent and buffer, preventing unwanted secondary deprotonation whilst being fully soluble in the low temperature reaction medium (a problem encountered with both neat D_2O and

CH_3CO_2D). However sulpholene (5) prepared via this modified deuteration procedure still showed poor regiospecificity with reduced deuterium incorporation albeit in increased yield (43.4%). Further modification was made by varying the concentration of DMPU and testing other co-solvents. (Table 1.)

Table 1. Variation of yields and deuterium content of sulpholenes with equivalents of co-solvent.

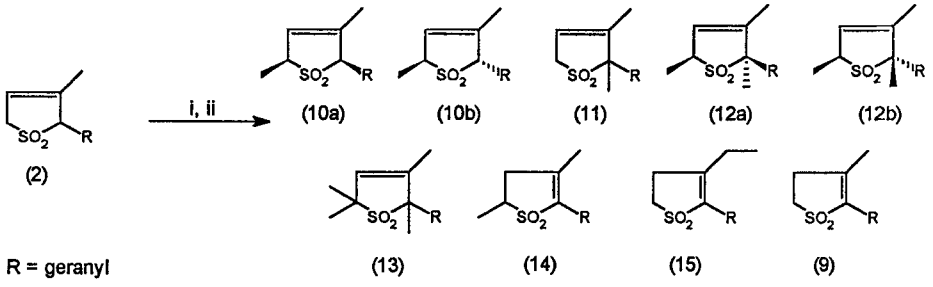
Experiment.	Equivalents/ co-solvent.	% recovered non bond migrated prod.	% recovered bond migrated prod.	% mass balance.	Composition of recovered non bond migrated product, mole%		
					H	D	D_2
1	2.2 DMPU[a]	40.9	23.1	64.0	48.4	47.6	4.0
2	2.2 DMPU	43.4	49.2	92.7	52.9	38.3	8.8
3	4.0 DMPU	62.8	32.6	95.4	46.1	46.8	7.1
4	8.0 DMPU	68.2	25.5	93.7	31.2	60.1	8.7
5	8.0 HMPA	43.4	53.4	96.8	41.3	52.0	6.7
6	8.0 TMEDA	75.1	1.0	76.0	11.6	85.0	3.4

[a] Quench carried out with D_2O (10.0 equivs.)

Higher recoveries of sulpholene (5) and increased mole% contribution from monodeuterated species were obtained with increased concentrations of co-solvent. However the continued appearance of bond migrated product (9) and dideuteration lead us to suspect that even in the absence of LiOD, proton/deuteron exchange between sulpholene products and as yet unquenched anionic species was still occurring during the quench procedure. This was supported when a methyl iodide quench (4.0 equivs.), gave a complex mixture of di, tri, and bond migrated methylation products (9)-(15) (Scheme 3). HMPA showed no advantage over DMPU as a co-solvent in deuteration sequence.

Treatment of (2) with butyl lithium in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA)[18] and quenching with methyl iodide yielded only two methylation products, the diasteriometric 5-methylsulpholenes (10a) and (10b), in a combined yield of 82% with no evidence of bond migration (Scheme 4). Sulpholenes (10a) and (10b) were separated by repeated preparative centrifugal chromatography and thermolysed to give dienes (17a) and (17b) respectively. By a comparison of the chemical shifts and couple constants[19] of the C3 methine protons in (17) it was possible to established the stereochemistry of diene (17a) as 2E (δ 6.47,

Scheme 3. **Methylation of 2-geranyl-3-methylsulpolene. (2)**

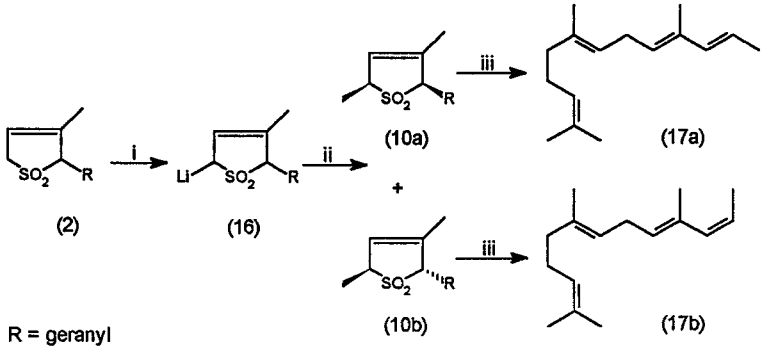


i, BuLi / DMPU / THF -105 °C ii, CH_3I

J=16.6 Hz) and of diene (17b) as 2Z (δ 6.07, J=15.8 Hz). Based on the symmetry rules governing the cheleotropic elimination of sulphur dioxide from 2,5-disubstituted sulpholenes[15,20], the stereochemistry of (10a) and (10b) was assigned as cis and trans respectively.

Using this methodology, sulpholene (2) was treated with butyl lithium in TMEDA mediated THF at -105°C and the lithiated intermediate (16) was quenched with a solution of D_2O/CH_3CO_2D in THF (Scheme 5). Sulpholene (18) was recovered in 75% yield with 1% of bond migrated material. MS analysis of (18) indicated 85 mole% monodeutration. Thermolysis in refluxing xylene yielded 1-²H-α-farnesene (26) in 86% yield. The ^1H nmr indicated the product was consistent with a 1:1 mixture of cis and trans 1-²H-α-farnesene comprising ≈80% of the mixture. The characteristic doublet of doublets associated with the C2 methine proton of α-farnesene (≈20%) was overlaid with two additional doublets at 6.34 ppm. (J=15.8 Hz) and 6.32 ppm. (J=8.4 Hz) assigned as the 2E and 2Z isomers of 1-²H-α-farnesene (19) respectively.

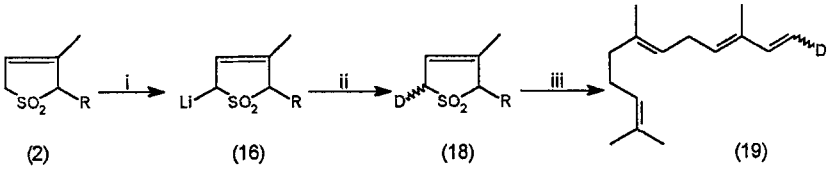
Scheme 4. **Regiospecific C5 alkylation of 2-geranyl-3-methylsulpholene (2).**



i, BuLi / TMEDA / THF -105 °C ii, CH_3I iii, xylene reflux

^{13}C NMR demonstrated the collapse of the signal at 110.4 ppm. to an overlaid 1:1:1 triplet at 110.2 ppm. GC-MS indicated 85 mole% monodeuteration, 3.4 mole% dideuteration and the remainder as unlabelled material. (Table 1.)

Scheme 5. **Synthesis of 1-^{2}H-α-farnesene (19).**



R = geranyl

i, BuLi / TMEDA / THF -105°C. ii, CH_3CO_2D / D_2O / THF iii, xylene reflux

Using the reactions described, deuterated α-farnesene can be synthesised from 3-methylsulpholene (1) with incorporation of deuterium at either C1 or C4. Appropriate choice of the co-solvent used during generation of the sulpholene anion permits sequential alkylation and deuteration of 3-methylsulpholene at the 2 and then the 5 positions. This intriguing aspect of 3-methylsulpholene metalation will be reported more fully elsewhere.

Experimental.

Melting points were determined with a Kyowa Hot Stage Apparatus and are uncorrected. NMR spectra were recorded on a Bruker WP80SY (80 MHz.) spectrometer in $CDCl_3$. NMR data is reported in parts per million (δ) and referenced to residual $CHCl_3$ at δ7.24 for ^1H spectra and δ77.0 for ^{13}C. Mass spectra were obtained with a VG70-250S spectrometer at 70eV. 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 2 psi He head pressure and directly coupled to the VG70 mass spectrometer. 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 nitrogen. Ether is diethyl ether (BDH analar). Room temperature (RT) 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 100°C. Preparative chromatography was carried out using either Mallinckrodt SilicaR CC-7, column; or Merck GF-254 type 60 (Merck Art. 7730), preparative centrifugal chromatography on silica gel rotors (Chromatotron, U.S. patent no. 4139458).

2-3',7'-dimethylocta-2'E,6'-dienyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (2),and3-methyl-4,5-dihydrothiophene-1,1-dioxide (7).

To a stirred solution of 3-methyl-2,5-dihydrothiophene-1,1-dioxide. (3) (0.8057g, 6.09mmol) in THF (25.0 ml) and DMPU (1.62ml, 13.4mmol, 2.2 equivs.) at -105°C [ethanol/liquid N_2] under dry N_2 was

added BuLi (6.09mmol in hexane) dropwise over 10 mins. Freshly distilled geranyl bromide (1.32g, 6.09mmol) was added in one portion and the mixture allowed to warm to RT over 30 mins. THF was removed under reduced pressure and the DMPU slurry was stirred for 30 mins with ether (50.0 ml). Solid material was filtered off and solvent removed under reduced pressure. DMPU was removed by elution through silica gel (ether/hexane 1:1) to give the crude 2-alkylated sulpholene (2) as a viscous yellow oil. This material was subjected to preparative centrifugal chromatography (hexane/ether 1:1) to afford (2) as a clear viscous oil(0.98g, 60%); R_f 0.30 (ether/hexane 1:1); ^{1}H NMR δ 5.64(m, 1H), 5.20(bm, 2H), 3.62(m, 2H), 3.47(bt, J=6.5 Hz, 1H), 2.53(bt, J=6.5 Hz, 2H), 1.99(m, 4H), 1.82(m, 3H), 1.63(bs, 6H), 1.57(bs, 3H); ^{13}C NMR 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; MS (m/z, rel.int.) 205(0.57), 204(M^+-SO_2, 3.46), 123(38.3), 119(39.3), 107(42.5), 93(100), 69(41.3).

A second component was eluted with ether and recrystallised from methanol to afford (7) as white plates (0.0242g, 3.0%); mp 70.0-71.0°C; R_f 0.3 (ether); ^{1}H NMR δ 6.28(m, 1H), 3.25(m, 2H), 2.75(m, 2H), 1.93(s, 3H); ^{13}C NMR δ 151.2, 126.2, 49.5, 30.6, 18.5.

α-Farnesene (3,7,11-trimethyldodeca-1,3E,6E,10-tetraene) (3).

A solution of (2) (0.0363g, 0.13mmol) in dry degassed xylene was refluxed under dry nitrogen for 15 mins. The solvent was removed under reduced pressure and the crude product purified by preparative centrifugal chromatography (pentane) to afford α-farnesene (3) as a clear mobile oil (0.0278g, 83.0%); R_f 0.80 (pentane); ^{1}H NMR δ 6.37(dd, J=17.4 Hz, J=10.6 Hz, 1H), 5.45(bt, J=7.3 Hz, 1H), 5.21-4.85(bm, 4H), 2.82(bt, J=7.2 Hz, 2H), 2.00(bs, 4H), 1.76(bs, 3H), 1.67(bs, 3H), 1.62(bs, 3H), 1.59(bs, 3H); ^{13}C NMR 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; MS (m/z, rel.int.) 205(1.0), 204(M^+, 4.38), 123(37.7), 119(34.6), 107(34.1), 93(100), 79(29.8), 69(56.5), 55(43.4), 41(46.6); GC rt 26.7.

2-^{2}H-2-3',7'-dimethylocta-2'E,6'-dienyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (5) and (9), DMPU procedure, D_2O quench.

To a stirred solution of (2) (0.0435g, 0.162mmol) in THF (5.0 ml) and DMPU (0.043ml, 0.356mmol, 2.2 equivs.) at -105°C [ethanol/liquid N_2] under dry N_2 was added BuLi (0.162mmol in hexane) dropwise over 10 mins. D_2O (0.032g, 1.62mmol, 10.0 equivs) was added in one portion and the mixture was stirred for 5 mins in the cooling bath before ammonium chloride solution (1ml, 10%) was added. The reaction mixture was allowed to warm to RT, diluted with water (20ml) and extracted with ether (3x20ml). The combined ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Preparative centrifugal chromatography afforded (5) as a clear, viscous oil(0.0173g, 40.9%); R_f 0.30 (ether/hexane 1:1); ^{1}H NMR δ 5.64(m, 1H), 5.12(bm, 2H), 3.61(m, 2H), 3.49(bt, J=6.9 Hz, 0.5H)[≈50% deuteration at C2], 2.52(bm, 2H), 1.99(m, 4H), 1.81(m, 3H), 1.63(bs, 6H), 1.55(bs, 3H); ^{13}C NMR δ 138.9, 138.7 131.4, 123.9, 118.3, 117.1, 67.3(t), 66.9, 55.6, 39.6, 26.3, 26.3, 25.5, 18.1, 17.6, 16.2; MS (m/z, rel.int.) 206(1.07), 205(M^+-SO_2, 4.86), 204(4.20), 69(100).

A second component (9) was eluted as a colourless oil which slowly solidified on storage at -18°C.; (0.0101g, 23.1%) R_f 0.1 (ether/hexane 1:1); ^{1}H NMR δ 5.13(m, 2H), 3.16(m, 4H), 2.67(m, 2H), 2.07(m, 4H), 1.86(s, 3H), 1.68(s, 3H), 1.66(s, 3H), 1.58(s, 3H); ^{13}C NMR δ 141.6, 137.7, 136.4, 131.4, 124.1, 118.8, 47.5, 39.5, 29.2, 26.5, 25.6, 21.5, 17.6, 16.4, 16.1; MS (m/z, rel.int.) 269(1.4), 268(M^+, 5.7), 225(26.5), 137(52.9), 123(100), 69(93.6).

2-^{2}H-2-3',7'-dimethylocta-2'E,6'-dienyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (5), DMPU procedure, D_2O/CH_3CO_2D/THF quench.

Procedure identical to that outlined above but with quenching of the anionic intermediate (4) carried out with a molar solution of D_2O and CH_3CO_2D in anhydrous THF (10.0 equivs.). The crude product was subjected to preparative centrifugal chromatography to afforded (5) as a clear, viscous oil(43.4%); R_f 0.30 (ether/hexane 1:1); ^{1}H NMR ($CDCl_3$) δ 5.63(m, 1H), 5.10(bm, 2H), 3.59(m, 2H), 3.45(bt, 0.45H), [≈55% deuteration at C2], 2.51(m, 2H), 2.00(m, 4H), 1.82(m, 3H), 1.63(s, 6H), 1.57(s, 3H); ^{13}C NMR δ 138.9, 138.7 131.4, 123.9, 118.3, 117.1, 67.3(t), 66.9, 55.6, 39.6, 26.3, 26.3, 25.5, 18.1, 17.6, 16.2; MS (m/z, rel.int.) 271(0.18), 270(0.45), 269(M^+, 1.12), 268(0.96), 205(2.78), 204(5.71), 203(4.33), 123(48.5), 93(70.7), 69(100).

4-^{2}H-α-farnesene (3,7,11-trimethyl-4-^{2}H-dodeca-1,3E,6E,10-tetraene) (6)

Thermolysis of (5), [prepared from D_2O quench of (2)] under standard conditions (as above), (0.0873g, 0.32mmol) afforded (6) as a clear mobile oil (0.0566g, 85.3%); R_f 0.80 (pentane); ^{1}H NMR δ 6.36(dd, J=17.5, J=10.5, 1H), 5.45(bt, J=7.5, 0.5H), [≈50% deuteration at C4], 5.21-4.82(bm, 4H), 2.81(m, 2H), 2.00(m, 4H), 1.74(bs, 3H), 1.67(bs, 3H), 1.62(bs, 3H), 1.58(bs, 3H); ^{13}C NMR δ 141.5, 135.8, 133.7, 131.8(weak), 131.3, 124.3, 122.1, 110.4, 39.6, 27.2, 26.7, 25.6, 17.6, 16.1, 11.6; MS (m/z, rel.int.) 206(0.82), 205(M^+, 3.78), 204(3.23), 123(52.4), 119(33.9), 107(50.1), 93(100), 81(43.0), 69(85.7), 55(61.2), 41(87.5); Deuteration (mole %) ^{1}H 48.4, ^{2}H 47.6, $^2H_2$ 4.0; GC rt 26.7.

Methylation of 2-3',7'-dimethylocta-2'E,6'-dienyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (2), DMPU procedure.

To a stirred solution of (2), (0.0749g, 0.28mmol) in THF (2.0 ml) and DMPU (0.27ml, 2.23mmol, 8.0 equivs.) at -105°C [ethanol/liquid N_2] under dry N_2 was added BuLi (0.29mmol, 1.05 equivs. in hexane) dropwise over 10 mins. Methyl iodide (0.158g, 1.11mmol, 4.0 equivs) was added in one portion and the mixture was stirred for 5 mins in the cooling bath before ammonium chloride solution (5.0ml, 10%) was added. The reaction mixture was allowed to warm to RT, diluted with water (20ml) and extracted with ether (3x20ml). The combined ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, (0.1870g). Tlc analysis showed 9 components were present including starting material. R_f 0.55, 0.50, 0.45, 0.40, 0.34, 0.30(2), 0.19, 0.15, 0.10(9) (ether/hexane 1:1). Repeated preparative centrifugal chromatography afforded 9 homogeneous fractions:

(13) colourless oil; R_f 0.55; ^{1}H NMR δ 5.49(d, J=1.5 Hz, 1H), 5.23(bm, 2H), 2.49(d, J=7.5 Hz, 2H), 1.98(m, 4H), 1.73(d, J=1.5 Hz, 3H), 1.66(s, 3H), 1.62(s, 3H), 1.59(s, 3H), 1.41(s, 3H), 1.39(s, 3H), 1.37(s, 3H); MS (m/z, rel.int.) 311(3.1), 310(M^+, 12.5), 246(M^+-SO_2, 9.4), 245(35.9), 69(100).

(12) [undefined stereoisomer], colourless oil; R_f 0.50; ^{1}H NMR δ 5.50(m, 1H), 5.18(bm, 2H), 3.64(m, 1H), 2.51(bd, J=7.8 Hz, 2H), 2.04(m, 4H), 1.75(m, 3H), 1.66(s, 3H), 1.62(s, 3H), 1.60(s, 3H), 1.37(d, J=7.0 Hz, 3H), 1.35(s, 3H); MS (m/z, rel.int.)) 232(M^+-SO_2, 2.8), 147(33.6), 121(100), 107(35.7), 69(42.9).

(10a) and (12) [undefined stereoisomer], colourless oil; R_f 0.45 (10a); ^{1}H NMR δ 5.51(m, 1H), 5.14(bm, 2H), 3.46(m, 2H), 2.55(bt, J=6.9 Hz, 2H), 2.03(m, 4H), 1.78(m, 3H), 1.65(s, 6H), 1.59(s, 3H), 1.37(d, J=7.1 Hz, 3H); MS (m/z, rel.int.) 219(5.0), 218(M^+-SO_2, 25.0), 149(100), 107(78.6), 69(58.6).

(12); ^{1}H NMR δ 5.51(m, 1H), 5.14(bm, 2H), 3.67(m, 1H), 2.47(bd, J=7.4 Hz, 2H), 2.04(m, 4H), 1.75(m, 3H), 1.66(s, 3H), 1.62(s, 3H), 1.60(s, 3H), 1.37(d, J=7.0 Hz, 3H), 1.35(s, 3H); MS (m/z, rel.int.)

233(2.9), 232(M^+-SO_2, 10.7), 147(15.7), 121(100), 107(61.4), 69(77.8).

(**10b**) colourless oil; R_f 0.40; ^{1}H NMR δ 5.59(m, 1H), 5.16(bm, 2H), 3.58(m, 2H), 2.51(bt, J=7.3 Hz, 2H), 2.03(m, 4H), 1.80(m, 3H), 1.65(s, 6H), 1.59(s, 3H), 1.34(d, J=7.1 Hz, 3H); MS (m/z, rel.int.) 219(2.1), 218(M^+-SO_2, 7.1), 149(12.9), 107(100), 69(80.7).

(**11**) colourless oil; R_f 0.34; ^{1}H NMR δ 5.65(m, 1H), 5.16(bm, 2H), 3.57(m, 2H), 2.49(bd, J=7.6 Hz, 2H), 2.04(m, 4H), 1.77(q, J=2.0 Hz, 3H), 1.66(s, 3H), 1.63(s, 3H), 1.59(s, 3H), 1.36(s, 3H); MS (m/z, rel.int.) 219(1.4), 218(M^+-SO_2, 5.7), 133(29.3), 107(100), 69(52.9).

(**2**) colourless oil; R_f 0.30.

(**14**) colourless oil; R_f 0.0.19; ^{1}H NMR δ 5.10(m, 2H), 3.15(m, 3H), 2.71(bd, J=7.9 Hz, 2H), 2.00(m, 4H), 1.87(s, 3H), 1.68(s, 3H), 1.66(s, 3H), 1.58(s, 3H), 1.38(d, J=6.8 Hz, 3H); MS (m/z, rel.int.) 283(2.1), 282(M^+, 6.1), 239(30.7), 137(60.4), 123(86.4), 69(79.3), 41(100).

(**15**) colourless oil; R_f 0.15; ^{1}H NMR δ 5.10(m, 2H), 3.13(m, 4H), 2.73(m, 2H), 2.25(q, J=7.6 Hz, 2H), 2.02(m, 4H), 1.68(s, 3H), 1.66(s, 3H), 1.58(s, 3H), 1.06(t, J=7.7 Hz, 3H); MS (m/z, rel.int.) 283(2.1), 282(M^+, 6.8), 239(30.7), 151(45.7), 123(86.9), 69(82.1), 41(100).

(**9**) colourless oil which slowly solidified on storage at -18°C.; R_f 0.1; Data as above.

Methylation of 2-3',7'-dimethylocta-2'E,6'-dienyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (2), TMEDA procedure.

To a stirred solution of (**2**), (0.0675g, 0.25mmol) in THF (2.0 ml) and TMEDA (0.30ml, 2.01mmol, 8.0 equivs.) at -105°C [ethanol/liquid N_2] under dry N_2 was added BuLi (0.26mmol, 1.05 equivs. in hexane) dropwise over 10 mins. Methyl iodide (0.143g, 1.01mmol, 4.0 equivs) was added in one portion and the mixture was stirred for 5 mins in the cooling bath before ammonium chloride solution (5.0ml, 10%) was added. The reaction mixture was allowed to warm to RT, diluted with water (20ml) and extracted with ether (3x20ml). The combined ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, (0.1260g). Tlc analysis of the crude product indicated 3 components were present. R_f 0.45(**10a**), 0.40(**10b**), 0.10(**9**) (ether/hexane 1:1), which were separated by repeated preparative centrifugal chromatography.

4,8,12,-trimethyltrideca-2E,4E,7E,11-tetraene (17a).

Thermolysis of (**10a**) (0.0195g, 0.069mmol) under standard conditions, afforded (**17a**) as a clear mobile oil (0.0128g, 84.8%); R_f 0.58 (pentane); ^{1}H NMR δ 6.47(d, J=16.6 Hz, 1H), 5.73(m, 1H), 5.30-4.96(bm, 3H), 2.83(bt, J=6.9 Hz, 2H), 2.00(m, 4H), 1.77(m, 6H), 1.66(s, 3H), 1.63(s, 3H), 1.59(s, 3H); MS (m/z, rel.int.) 218(M^+, 10.9), 203(2.5), 149(10.0), 133(41.4), 121(20.7), 107(100), 93(57.1), 69(70.7).

4,8,12,-trimethyltrideca-2Z,4E,7E,11-tetraene (17b).

Thermolysis of (**10b**) (0.0062g, 0.022mmol) under standard conditions, afforded (**17b**) as a clear mobile oil (0.0034g, 70.9%); R_f 0.58 (pentane); ^{1}H NMR δ 6.07(d, J=15.8 Hz, 1H), 5.60(m, 1H), 5.35-5.06(bm, 3H), 2.81(bt, J=6.9 Hz, 2H), 1.99(m, 4H), 1.75(m, 6H), 1.68(s, 3H), 1.63(s, 3H), 1.60(s, 3H); MS (m/z, rel.int.) 219(2.5), 218(M^+, 9.6), 203(5.0), 149(9.9), 133(52.5), 121(22.9), 107(100), 93(55.7), 69(55.0).

5-^{2}H-2-3',7'-dimethylocta-2'E,6'-dienyl-3-methyl-2,5-dihydrothiophene-1,1-dioxide (18), TMEDA procedure, D_2O/CH_3CO_2D/THF quench.

To a stirred solution of (2) (0.1067g, 0.398mmol) in THF (10.0 ml) and TMEDA (0.48ml, 3.20mmol, 8.0 equivs.) at -105°C [ethanol/liquid N_2] under dry N_2 was added BuLi (0.417mmol, 1.05 equivs. in hexane) dropwise over 10 mins. A molar solution of D_2O and CH_3CO_2D in anhydrous THF (4.0ml, 10.0 equivs.) was added in one portion and the mixture was stirred for 5 mins in the cooling bath before ammonium chloride solution (1ml, 10%) was added. The reaction mixture was allowed to warm to RT, diluted with water (20ml) and extracted with ether (3x20ml). The combined ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Preparative centrifugal chromatography afforded (18) as a clear, viscous oil(0.0804g, 75.1%); R_f 0.30 (ether/hexane 1:1); ^{1}H NMR δ 5.62(m, 1H), 5.09(bm, 2H), 3.57(m, 1H), 3.45(bt, J=7.0 Hz, 1H) 2.51(bt, J=6.7, 2H), 2.00(m, 4H), 1.80(m, 3H), 1.61(bs, 6H), 1.55(bs, 3H); ^{13}C NMR δ 138.8, 138.7 131.3, 123.9, 118.2, 117.0, 67.2, 55.6, 55.2(t), 39.5, 26.3, 26.3, 25.5, 18.1, 17.5, 16.1; MS (m/z, rel.int.) 206(1.07), 205(M^+-SO_2, 4.86), 204(4.20), 69(100).

1-^{2}H-α-farnesene (3,7,11-trimethyl-1-^{2}H-dodeca-1,3E,6E,10-tetraene) (19).

Thermolysis of (18) (0.0665g, 0.246mmol) under standard conditions afforded (19) as a clear mobile oil (0.0435g, 85.8%); R_f 0.80 (pentane); ^{1}H NMR δ 6.36(dd, J=17.5, J=10.5, 0.2H), [≈80% deuteration], 6.34(d, J=15.8 Hz, 0.4H), 6.32(d, J=8.4 Hz, 0.4H), 5.44(bt, J=7.3, 1H), 5.19-4.82(bm, 3H), 2.82(t, J=7.2 Hz, 2H), 1.99(bs, 4H), 1.74(bs, 3H), 1.66(bs, 3H), 1.62(bs, 3H), 1.59(bs, 3H); ^{13}C NMR δ 141.5, 135.8, 133.8, 131.8, 131.3, 124.3, 122.1, 110.4 (weak), 110.2(t), 39.7, 27.3, 26.8, 25.6, 17.6, 16.1, 11.6; MS (m/z, rel.int.) 206(0.68), 205(M^+, 4.04), 204(0.95), 123(52.9), 120(40.4), 107(42.9), 94(100), 80(43.9), 69(84.3), 55(42.1), 41(68.6); Deuteration (mole %) 1H 11.6, ^{2}H 85.0, $^2H_2$ 3.4; GC rt 26.7.

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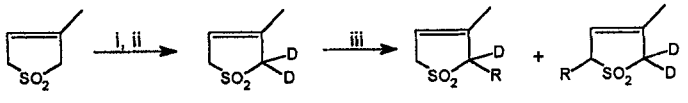
17 The 'perdeuteration' of sulpholene under basic conditions (ref. 11) suggested an alternative strategy, whereby deuterium exchange at the 2- and 5- position of 3-methylsulpholene (1) would yield 2,2,5,5-$^2H_4$-3-methylsulpholene. However, under exchange conditions, only low yields of 2,2-$^2H_2$-3-methylsulpholene (20)(<20%) were produced with no evidence of 'perdeuteration' observed. Alkylation of (20) gave an inseparable mixture of the 2- and 5-alkylated products (21) and (22), hence this route was abandoned



(1) (20) (21) (22)

i, BuLi / DMPU / THF ii, D_2O iii, Geranly bromide

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