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Synthesis of Putative Δ^6-, Δ^{12}- and Δ^{15}-Desaturase Inhibitors

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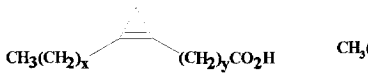
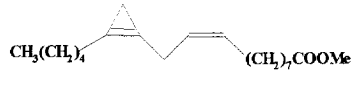
Abstract: Cyclopropene fatty acid esters (5) and (6) and (7) have been synthesised as potential structure-based inhibitors of Δ^6-, Δ^{12}- and Δ^{15}-desaturases

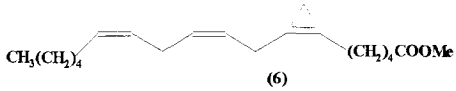
The naturally occurring cyclopropene fatty acid (CPFA) sterculic acid **(1)** is a potent inhibitor of Δ^9-desaturase which converts stearic acid into oleic acid.[1] This has been of considerable interest in view of the physiological effects of diets containing sterculic acid,[2] in its effects in luteal cell function in sheep[3] and in the apparent importance of the balance of stearic and oleic acids in cancer.[4] The detailed mechanism by which the inhibition occurs is still not clear; however, the close similarity in overall structure between sterculic and oleic acids, and in particular the stereochemical arrangement about the 1,2-disubstituted cyclopropene and the Z-alkene, coupled to the high strain of the small ring seem likely to be significant factors. It is also known that **(2)** inhibits a Δ^5-desaturase in mycolic acid biosynthesis,[5] and that **(3)** inhibits a Δ^{11}-desaturase involved in the biosynthesis of the sex pheromone of the cricket.[6] Moreover, compound **(4)** has been reported to inhibit Δ^{12}-desaturation in a yeast, leading to the production of linoleic acid from oleic acid.[7#]



(1) x = 7, y = 7 (3) x = 1, y = 10
(2) x = 17, y = 3 (4) x = 4, y = 10



(5)



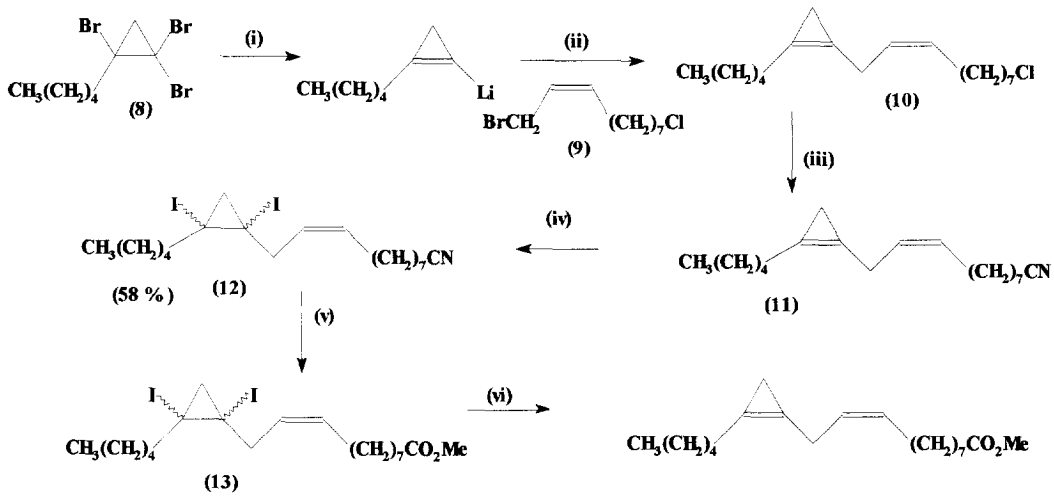
(6)

(7)

Given, however, that the normal substrate for Δ^{12}-desaturase is oleic acid and not stearic acid, it would be expected that a better inhibitor would be **(5)**.[8] In the same way, it may be postulated that **(6)** and **(7)** would be structure based inhibitors of Δ^6- and Δ^{15}-desaturases respectively. In view of the key importance of these enzymes in a variety of systems - for example, Δ^6-desaturase has been reported to be abnormal in all cancers and of key importance in ageing,[9] and evening primrose oil, containing high levels of essential Δ^6-unsaturated fatty acids, has been claimed to show beneficial effects in a large number of medical conditions[10] - we now report the synthesis of **(5)** - **(7)**, the first examples of CPFA esters containing additional alkene functionality.

The Δ^{12}-inhibitor **(5)** was synthesised from 2-bromohept-1-ene by dibromocyclopropanation to give the tribromide **(8)** followed by reaction with 2.1 mol.equiv. of butyl lithium at -78 °C and coupling of the derived 1-lithiocyclopropene[11]

with the allylic bromide (**9**). The derived chloride (**10**) was converted into the corresponding cyanide, protected as the di-iodide (**12**)[12] and then hydrolysed under acidic conditions to give the ester (**13**). Deiodination using butyl lithium at low temperature then gave the desired cyclopropene (**5**) (Scheme 1).

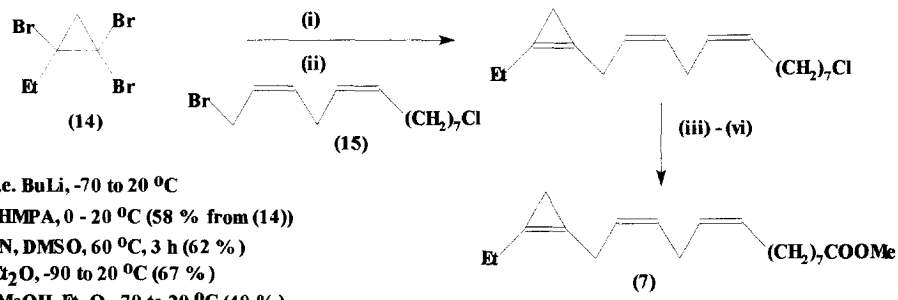


(i) 2.1 mol.eq. BuLi, -70 to 20 °C (ii) (9), HMPA, 0 - 20 °C, 57 % from (8) (iii) NaCN, DMSO, 60 °C, 3 h, 65 % (iv) I_2, Et_2O, -90 to 20 °C, 58 % (v) HCl, MeOH, Et_2O, -70 to 20 °C, 60 % (vi) 1.1 m.e. n-BuLi, -90 °C, then H_2O, -70 °C, 91 %

Scheme 1

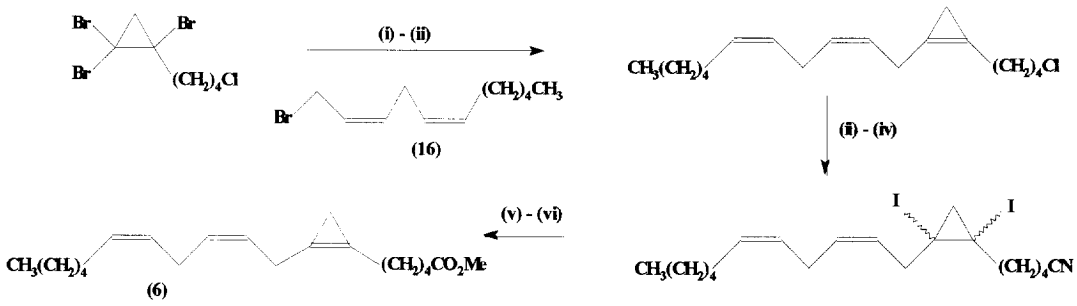
The bromide (9) was prepared from the coupling of propargyl alcohol and 1-chloro-7-bromoheptane in the presence of base to give 10-chlorodec-2-yn-1-ol (72 %), followed by hydrogenation in ethanol using nickel boride and hydrogen to give the 13-chloro-Z-alken-1-ol (93 %) and then bromination using diphos and bromine (95 %).[13]

The putative Δ^{15}-inhibitor (7) was prepared from the tribromide (14) and allylic bromide (15), using reaction conditions which were the same as those in Scheme 1. The allylic bromide (15) was prepared from 1-bromo-10-chlorodec-2-yne by coupling with propargyl alcohol in the presence of lithium in liquid ammonia to give 13-chlorotrideca-2,5-diyn-1-ol (73 %) followed by cis-hydrogenation of the alkynes in ethanol using nickel boride and hydrogen to give the corresponding Z,Z-2,5-dien-1-ol (92 %), and then bromination as above (90 %).



(i) 2.1 m.e. BuLi, -70 to 20 °C
(ii) (15), HMPA, 0 - 20 °C (58 % from (14))
(iii) NaCN, DMSO, 60 °C, 3 h (62 %)
(iv) I_2, Et_2O, -90 to 20 °C (67 %)
(v) HCl, MeOH, Et_2O, -70 to 20 °C (40 %)
(vi) 1.05 m.e. BuLi, -90 °C, then H_2O, -70 °C (95 %)

The putative Δ^6-inhibitor (**6**) was obtained by a sequence involving coupling of 1-lithio-2-(4-chlorobutyl)cyclopropene to the allylic bromide (**16**), which was prepared from 1-bromodec-2-yne by a method similar to that for (15): [14##]



(i) 2.1 mol equiv. BuLi, -78 to 20 °C (ii) (16), HMPA, 0 - 20 °C (65 % from tribromide) (iii) NaCN, DMSO, 60 °C, 3 h (63 %) (iv) Iodine, ether, -90 to 20 °C (70 %) (v) HCl, MeOH, Et_2O, -70 to 20 °C (63 %) (vi) 1.1 m.e. BuLi, -90 °C, then H_2O, -70 °C (92 %)

The effects of these compounds, (**5**), (**6**) and (**7**), in inhibiting the target desaturase enzymes are currently being examined. In a separate assay, compound (**5**) showed no effect on pea-seed lipoxygnase activity using sodium linoleate as substrate; however, in an assay using phosphatidyl choline as substrate, [15] activity was stimulated by a factor of 5 - 20; [16] the origin of this effect, which is also shown by tocopherol, [15] is as yet not clear.

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Experimental Section

Reagents were obtained from commercial suppliers and used without further purification unless stated. Diethyl ether (ether) and tetrahydrofuran were distilled over sodium wire. Dichloromethane was distilled over calcium hydride. Petrol was either of boiling point 40 - 60 °C or 60 - 80 °C and was distilled. Reactions requiring anhydrous conditions were performed using oven dried glassware (250 °C) that was cooled under dry nitrogen and were conducted under a positive atmosphere of the gas. Organic solutions were dried over anhydrous magnesium sulphate, and, unless stated, were evaporated at 14 mmHg. Yields quoted are for the purified compounds unless stated. New compounds were homogeneous by tlc or by glc. Glc was conducted using a Perkin-Elmer Model F17 F.I.D. on a capillary column (30 m x 0.32 mm id Phase, DB5) using nitrogen as carrier gas. Tlc was performed using Aldrich silica gel 60 plates (F254). Compounds were visualised under an ultraviolet source or by exposure to iodine vapour. Column chromatography was conducted with Merck 7736 silica gel under medium pressure. Infrared spectra were obtained as liquid films on a Perkin-Elmer 1600 FTIR spectrometer. Low resolution mass spectra were obtained on a Finnigan Mat 1020 spectrometer. Mass measurements refer to ^{79}Br isotope unless stated and were obtained either from the Swansea Mass Spectrometry Service or using a Finnigan 8400 spectrometer. Microanalyses were performed with a Carlo-Erba Model 1106

CHN analyser. Unless stated, nmr spectra were recorded on a Bruker AC250 at 250 MHz for ^{1}H and 62.5 MHz for ^{13}C and in the latter case were either broad-band or gated decoupled.

Preparation of 6-chlorohex-1-yne.

Lithium acetylide ethylene diamine complex (10 g, 0.109 mole) was added slowly to liquid ammonia (100 ml). 1-Bromo-4-chlorobutane (18.6 g, 0.109 mole) was added dropwise over 30 m. The mixture was stirred at 10-15 °C for 3 h then at room temperature until all the liquid ammonia has evaporated, and then quenched by adding water (150 ml). The product was extracted into ether (3 x 150 ml) and the ether layer washed with 10% hydrochloric acid (150 ml) and water (150 ml), dried and evaporated carefully at 0 °C to give 6-chlorohex-1-yne as a yellow oil (17.6 g, 75%),[17] which showed δ_H: 3.56 (2 H, t, J 6.5 Hz), 2.17 - 2.27 (2 H, m), 1.96 (1 H, t, J 2.7 Hz), 1.81 - 1.89 (2 H, m), 1.51 - 1.75 (2 H, m); δ_C: 83.7, 68.9, 44.5, 31.4, 25.6, 17.9; υ_{max}: 3298, 2952, 2868, 2117; m/z: 116/114 (M^+), 115/113 (M^+-H), 101/99 (M^+-CH_3).

Preparation of 2-bromo-6-chlorohex-1-ene.

Dry hydrogen bromide was bubbled into a stirred solution of tetraethylammonium bromide (45.6 g, 0.217 mole) in dichloromethane (300 ml) with cooling in ice, until one equivalent had been absorbed. The solution was allowed to reach room temperature and 6-chlorohex-1-yne (23 g, 0.197 mole) was added. After 1 h at 25 °C the mixture was refluxed for 2 h, cooled and poured into ether (200 ml). The precipitated salts were filtered off on a bed of silica; the filter cake was washed with ether and the solvent was evaporated carefully from the combined ether layers to give 2-bromo-6-chloro-hex-1-ene (31.2 g, 80 %), which showed δ_H: 5.59 (1 H, m), 5.42 (1 H, d, J 1.6 Hz), 3.56 (2 H, t, J 6.3 Hz), 2.46 (2 H, t, J 6.4 Hz), 1.62-1.87 (4 H, complex m); δ_C: 134.5, 117.7, 45.3, 41.3, 31.9, 25.8; υ_{max}: 1629, 746 cm^{-1}; m/e: 196/194/192 (M^+), 170/168/166 (M^+-C_2H_4), 117/115 (M^+-Br).

2-Bromohept-1-ene.

The reaction of hept-1-yne with HBr as above gave *2-bromohept-1-ene* (85 %),[18] b.p. 34 °C and 0.3 mm/Hg (Found: C, 46.42; H, 7.50. $C_7H_{13}Br$ requires C, 46.48; H, 7.4), δ_H: 5.63 (1 H, m), 5.41 (1 H, d, J 1.5 Hz), 2.4 (2 H, t J 7.5 Hz), 1.56 (2 H, m), 1.2-1.4 (4 H, m), 0.91 (3 H, t, J 6.7 Hz); δ_C: 134.8, 116.2, 41.4, 30.7, 27.6, 22.4, 14.6; υ_{max}: 1629, 883 cm^{-1}.

Preparation of 1,1,2-tribromo-2-alkylcyclopropanes

(i) **1,1,2-tribromo-2-(4-chlorobutylcyclopropane):** Sodium hydroxide (60 g) in water (60 ml) was added in portions to a rapidly stirred mixture of 2-bromo-6-chlorohex-1-ene (30 g, 0.1518 mole), bromoform (57.58 g, 0.227 mole) and cetrimide (3 g) in dichloromethane (100 ml). The mixture was stirred vigorously overnight at room temperature. When G.L.C. showed no starting material, the reaction was diluted with brine and the product was extracted into dichloromethane (4 x 200 ml). The combined organic layers were evaporated to give a thick brown oil.

Petroleum/ether (200ml) was added to precipitate the cetrimide. The solid was filtered off, the solvent was removed at 14 mm/Hg and bromoform at 0.1 mm/Hg, leaving a pale yellow oil, which purified by distillation at 0.1 mm/Hg and 100 °C to give 1,1,2-tribromo-2-(4-chlorobutylcyclopropane) (44.3 g, 79 %) (Found M^+: 365.8024. $C_7H_{10}Br_3Cl$ requires: 365.8021) which showed δ_H: 3.53 (2 H, t, J 6.2 Hz), 1.99 (1 H, d, J 9.0 Hz), 1.86 (1 H, d, J 9.3 Hz), 1.85 (6 H, m); δ_C: 45.2, 44.6, 40.9, 38.0, 32.8, 31.8, 25.2; υ_{max}: 2992, 884, 814, 740 cm^{-1}.

(ii) **1,1,2-Tribromo-2-pentylcyclopropane (8)** was prepared in the same way from 2-bromohept-1-ene (87 %) b.p.70 °C at 0.1 mmHg (Found: C, 27.92; H, 3.88. $C_8H_{13}Br_3$ requires C, 27.76, H 3.79 %) and showed δ_H: 2.1-1.99 (2 H, m), 1.95 (1 H, d, J 9.2 Hz), 1.83 (1 H, d, J 9.2 Hz), 1.7 (2 H, m), 1.34 (4 H, m), 0.92 (3 H, t, J 6.8 Hz); δ_C: 46, 41.7, 38.1, 33.4, 31.1, 27.4, 22.5, 14.0; υ_{max}: 2954, 2859, 1465, 691 cm^{-1}.

(iii) **1,1,2-Tribromo-2-ethylcyclopropane (14)** was prepared in the same way from 2-bromobut-1-ene (55%) and showed δ_H: 2.2-1.92 (2 H, m), 1.93 (1 H, d, J 9.2 Hz), 1.79 (1 H, d, J 9.2 Hz), 1.21 (3 H, t, J 7.2 Hz); δ_C: 47.0, 37.9, 35.4, 33, 12; υ_{max}: 1019, 690 cm^{-1}; m/e: 306/304/302/300 (M^+), 227/225/223 (M^+-Br).

Coupling of propargyl alcohol to haloalkanes

(a) **Preparation of Oct-2-yn-1-ol:**[19] Liquid ammonia (1000 ml) was decanted into a 2-litre 2-necked flask under a liquid nitrogen -methylated spirit condenser protected by a soda lime guard tube. Lithium wire (0.2 g) was added in portions to obtain a dark blue colour. Ferric nitrate (0.2 g) was added and the solution was stirred mechanically for 5 m. Lithium wire (5.44 g, 0.78 mole) was added in 2 cm portions over a period of 40 m. Stirring was continued for a further 30 m, then a solution of propargyl alcohol (20 g, 0.356 mole) in ether (20 ml) was added dropwise over 20 m. After a further 30 m, a solution of 1-bromopentane (48.5 g, 0.32 mole) in ether (20 ml) was added dropwise. Stirring was continued for 3 h with the condenser attached; this was then removed and the ammonia was allowed to evaporate overnight leaving a black gum. The product was carefully acidified to pH 1 with dil. sulphuric acid (10 %, 300 ml) yielding a pale yellow solution which was extracted with ether (3 x 300 ml). The ether extracts were washed with a sat.aq. sodium bicarbonate (200 ml), dried and evaporated to yield a pale yellow oil. Purification by chromatography on silica eluting with 3:2 petroleum/ether gave oct-2-yn-1-ol[19] as a colourless liquid (35 g, 78 %), which showed δ_H: 4.26 (2 H, t, J 2.2 Hz), 2.22 (2 H, tt, J 7, 2.2 Hz), 1.72 (1 H, br.s), 1.46-1.57 (2 H, m), 1.31-1.42 (4 H, m), 0.9 (3 H, t, J 7.0 Hz); δ_C: 86.7, 78.2, 51.3, 31.1, 28.3, 22.2, 18.7, 14.0; υ_{max}: 3312, 2225, 1011 cm^{-1}.

(b) **10-Chlorodec-2-yn-1-ol**,[20] prepared as above using 1-bromo-7-chloroheptane (72%) showed δ_H: 4.22 (2 H, t, J 2.1 Hz), 3.51 (2 H, t, J 6.7 Hz), 2.2 (2 H, tt, J 6.9, 2.2 Hz), 2.05 (1 H, brs), 1.68-1.77 (2 H, m), 1.26-1.51 (8 H, m); δ_C: 86.2, 78.3, 51, 45, 32.5, 28.5, 28.3, 28.2, 26.6, 18.6; m/e: 188/186 (M^+), 187/185 (M^+-H), 171/169 (M^+-OH), 157/155 (M^+-CH_2OH); υ_{max}: 3357, 2225, 650 cm^{-1}.

Oct-2-yn-1-bromide

Bromine (15.87 g, 0.1 mole) in dry dichloromethane (50 ml) was added dropwise to a stirred solution of 1,2-bis(diphenylphosphino)ethane (19.76 g, 0.0496 mole)[18] in dry dichloromethane (150 ml) at 0 °C, under nitrogen. Oct-2-yn-1-ol (10 g, 0.0793 mole) in dichloromethane (40 ml) was added. The mixture was allowed to warm to room temperature and stirred for 2 hr. When t.l.c. showed no starting material, ether (300 ml) was added and precipitated salts were removed by filtration through a pad of silica and washed with 2:1 petrol/ether. The filtrate was evaporated to give a pale yellow oil. Chromatography on silica, eluting with petroleum gave oct-2-yn-1-bromide[19] as a colourless oil (14 g, 93 %), which showed δ_H: 3.89 (2 H, t, J 2.3 Hz), 2.2 (2 H, tt, J 2.3, 6.9 Hz), 1.5 (2 H, m), 1.32 (4 H, m), 0.86 (3 H, t, J 7.07 Hz); δ_C: 88.28, 75.2, 30.9, 28, 22.1, 18.9, 15.7, 13.9; υ_{max}: 2225 cm^{-1}.

1-Bromo-10-chlorodec-Z-2-ene

1-Bromo-10-chlorodec-Z-2-ene (**9**) was prepared as above from 10-chlorodec-2-en-1-ol (95 %) and showed δ_H: 5.65 (2 H, m), 3.93 (2 H, t, J 2.3 Hz), 3.54 (2 H, t, J 6.7 Hz), 2.24 (2 H, dt, J 2.25, 6.8 Hz), 1.78 (2 H, pent, J 6.6 Hz), 1.58-1.28 (8 H, m); δ_C: 88.11, 75.4, 45.1, 32.5, 28.6, 28.3, 28.2, 26.7, 18.9, 15.8; υ_{max}: 2230 cm^{-1}; m/z 171/173 (M^+ - Br).

Undeca-2,5-diyn-1-ol

Magnesium turnings (3.2 g, 0.1336 mole) were stirred in tetrahydrofuran (40 ml) with ethyl bromide (15.92 g, 0.146 mole) in tetrahydrofuran (30 ml); propargyl alcohol (3.74 g, 0.067 mole) in tetrahydrofuran (25 ml) at ~5 °C was added followed by cuprous chloride (150 mg) and 1-bromooct-2-yne (7.9 g, 0.0417 mole) in tetrahydrofuran (40 ml) as described.[19] The crude product was columned on silica eluting with petroleum/ether (5:2) to give undeca-2,5-diyn-1-ol,[21] as a yellowish liquid (5.34 g, 78 %), which showed δ_H: 4.23 (2 H, t, J 2.13 Hz), 3.15 (2 H, pent, J 2.3 Hz), 2.1 (2 H, dt, J 2.4, 6.9 Hz), 1.9 (1 H, brs), 1.45 (2 H, m), 1.3 (4 H, m), 0.83 (3 H, t, J 6.9 Hz); δ_C: 81.2, 80.8, 78.3, 73.2, 51.2, 31, 28.3, 22.16, 18.6, 13.9, 9.8; υ_{max}: 3395, 2208 cm^{-1}.

Coupling of 1-bromo-10-chlorodec-2-yne with propargyl alcohol

This was carried out using the method above[19] to give *13-chlorotrideca-2,5-diyn-1-ol* (73 %), δ_H: 4.25 (2 H, t, J 2.1 Hz), 3.53 (2 H, t, 6.7 Hz), 3.18 (2 H, pen, J 2.1 Hz), 2.14 (2 H, dt, J 2.2, 6.83 Hz), 2.1 (1 H, br.s), 1.76 (2 H, pent, J 6.7 Hz), 1.54-1.3 (8 H, m); δ_C: 81, 80.7, 78.3, 73.4, 51.2, 45.1, 32.5, 28.6, 28.4, 28.3, 26.7, 18.6, 9.8; υ_{max}: 3332, 2360, 2258 cm^{-1}.

Preparation of Undeca-2(Z),5(Z)-dien-1-ol

Sodium borohydride (0.203 g, 5.3 mmole) in ethanol (15 ml) was added to a vigorously stirred solution of nickel acetate tetrahydrate (1.335 g, 5.36 mmole) in absolute ethanol (80 ml) under hydrogen. After 30 m, ethylene diamine (0.895 ml, 13.4 mmole) was added followed by undec-2,5-diyn-1-ol (4.4 g, 26.8 mmole) in ethanol (30 ml). Stirring was continued until one equivalent of hydrogen had been absorbed, when no more was absorbed. The

product was diluted with ether and filtered through a pad of silica. The precipitate was washed with ether and this was then evaporated. The residue was diluted with dichloromethane (150 ml), washed with water (2 x 100 ml) and dried; evaporation gave undeca-2(Z),5(Z)-dien-1-ol[21] as a pale yellow oil (4.2 g, 94 %), which was used without purification, and showed δ_H: 5.67-5.23 (4 H, m), 4.2 (2 H, d, J 6.2 Hz), 2.8 (2 H, br.t, J 6.5 Hz), 2.0 (2 H, m), 1.72 (2 H, p, J 6.7 Hz), 1.45 (1 H, b.s), 1.3 (4 H, m), 0.85 (3 H, t, J 6.64 Hz); δ_C: 131.2, 130.9, 128.5, 126.9, 58.5, 31.5, 29.2, 27.2, 25.8, 14.1; υ_{max}: 3331, 1657 cm^{-1}.

13-Chloro-Z,Z-trideca-2,5-dien-1-ol

Hydrogenation of 13-chlorotrideca-2,5-diyne-1-ol with nickel acetate and sodium borohydride as above gave *13-chloro-Z,Z-trideca-2,5-dien-1-ol* (92 %) which showed δ_H: 5.6-5.3 (4 H, m), 4.2 (2 H, d, J 6.1 Hz), 3.53 (2 H, t, J 6.7 Hz), 2.82 (2 H, br,t, J 6.65 Hz), 2.03 (2 H, m), 1.77 (2 H, pent, J 6.7 Hz), 1.65 (1 H, br, s), 1.3 (6 H, m); δ_C: 131, 130.6, 128.5, 127, 58.4, 45.1, 32.5, 29.4, 29, 28.7, 27.1, 26.8, 25.8; υ_{max}: 3336, 1651, 1460.

10-Chlorodec-Z-2-en-1-ol

Hydrogenation of 10-chlorodec-2-yn-1-ol as above gave *10-chlorodec-Z-2-en-1-ol* (93 %), δ_H:5.46-5.67 (2 H, m), 4.18 (2 H, d, J 5.8 Hz), 3.51 (2 H, t, J 6.6 Hz), 2.03-2.12 (2 H, m), 1.7-1.78 (2 H, m), 1.52 (1 H, br,s), 1.26-1.49 (8 H, m); δ_C: 133.1, 128.4, 58.6, 45.1, 32.6, 29.4, 29.0, 28.7, 27.3, 26.8; υ_{max}: 3346, 2937, 1658, 645 cm^{-1}.

Preparation of 1-bromoundeca-2(Z),5(Z)-diene

Bromine (7.14 g, 0.046 mole) in dry dichloromethane (30 ml) was added dropwise at 0 - 5 °C under nitrogen to 1,2-bis(diphenylphosphino)ethane (8.9 g, 0.022 mole) in dry dichloromethane (130 ml). Undec-2(Z),5(Z)-dien-1-ol (6 g, 0.357 mole) in dry dichloromethane (20 ml) was added dropwise and the reaction stirred at room temperature for 5 h. Ether (100 ml) was added followed by petroleum (200 ml) to precipitate the undesired by-products. The mixture was filtered through a pad of silica on a sinter and washed twice with 1:2 ether/ petroleum (300 ml). The combined washings were dried, filtered and evaporated. The crude product was quickly columned on silica eluting with petroleum/ether (10:1) to give 1-bromo-undeca-2(Z),5(Z)-diene[21] (**16**) (7.4 g, 90 %), which showed δ_H: 5.77-5.25 (4 H, m), 3.95 (2 H, d, J 8.2 Hz), 2.86 (2 H, br.t, J 7.12 Hz), 2.0 (2 H, m), 1.3 (6 H, br.s), 0.86 (3 H, t, J 6.6 Hz); δ_C: 134, 131.5, 125.9, 125.3, 31.5, 29.2, 27.2, 27.1, 26.3, 22.5, 14.1; υ_{max}: 3009, 2920, 1643, 1455, 1203, 730 cm^{-1}.

Bromination of 13-chlorotrideca-2(Z),5(Z)-dien-1-ol

Bromination of 13-chlorotrideca-2(Z),5(Z)-dien-1-ol using the method above gave 1-bromo-13-chlorotrideca-2(Z),5(Z)-diene (**15**) (90 %) which showed δ_H: 5.7-5.25 (4 H, m), 4.0 (2 H, d, J 8.25 Hz), 3.5 (2 H, t, J 6.7 Hz), 2.8

(2 H, t, J 6.9 Hz), 2.03 (2 H, br,m), 1.77 (2 H, m), 1.3 (8 H, m); δ_C: 133.97, 131.3, 126.1, 125.3, 45.1, 32.5, 29.3, 29.0, 28.7, 27.16, 27.0, 26.78, 25.3; υ_{max}: 1719, 1461, 1078, 737 cm^{-1}.

Preparation of 1-(4-chlorobutyl)-2-(undeca-2Z,5Z-dienyl)cyclopropene

n-Butyllithium (21.93 ml, 28.5 mmole) was added dropwise with stirring to 1,1,2-tribromo-2-(4-chlorobutyl)-cyclopropane (4.9 g, 13.2 mmole) in dry ether (30 ml) under nitrogen at -78 °C. The mixture was allowed to reach room temperature, stirred for 0.5 h, and then cooled to 0 °C and hexamethylphosphoramide (4.84 g, 27 mmole) was added dropwise followed by 1-bromo-undeca-2Z,5Z-diene (2.7 g, 11.9 mmole). The mixture was stirred overnight at room temperature and then cooled to 0 °C and water (30 ml) was added; the product was extracted with ether (2 x 100 ml) and the combined organic layers washed with water (2 x 20 ml), dried and evaporated to give a yellow liquid. This was flash distilled at very high vacuum to give 1-chloro-4-(2-butylcycloprop-1-enyl)butane as the distillate. The residue was chromatographed on silica eluting with petroleum to give *1-(4-chlorobutyl)-2-(undeca-2Z,5Z-dienyl)cyclopropene* (2.42 g, 65 %) (Found M^++H 281.2036. $C_{18}H_{29}Cl$ +H requires: 281.2036) which showed δ_H: 5.56-5.2 (4 H, m), 3.52 (2 H, t, J 6 Hz), 3.15 (2 H, br, d, J 6.14 Hz), 2.8 (2 H, br, t, J 6.2 Hz), 2.41 (2 H, br, t, J 6.93 Hz), 2.0 (2 H, m), 1.75 (4 H, complex m), 1.3 (6 H, br.s), 0.86 (3 H, t, J 6.8 Hz), 0.82 (2 H, s); (600 HMz)[##] included: 5.52 (1H, tdt, J 1.28, 10.47, 7.05 Hz), 5.45 (1 H, tdt, J 1.28, 10.68, 7.05 Hz), 5.39 (1 H, tdt, J 1.50, 10.68, 7.05 Hz), 5.325 (1 H, tdt, J 1.5, 10.68, 7.05 Hz); δ_C: 130.6, 129.6, 127.3, 125.1, 109.3, 108.7, 44.8, 32.2, 31.5, 29.3, 27.2, 25.6, 25.1, 24.7, 24.6, 22.5, 14.0, 7.7; υ_{max}: 1733, 1461, 728, 648 cm^{-1}.

Reaction of 1,1,2-tribromo-2-pentylcyclopropane with 1-bromo-10-chlorodec-2Z-ene

This gave *1-chloro-10-(2-pentylcycloprop-1-enyl)dec-8Z-ene* (**10**) (57 %) (Found M^+-H: 281.204. $C_{18}H_{30}Cl$ requires: 281.2036), which showed δ_H: 5.46-5.54 (2 H, complex, m), 3.53 (2 H, t, J 6.7 Hz), 3.12 (2 H, d, J 5.4 Hz), 2.38 (2 H, br.t, J 7.2 Hz), 2.03-2.08 (2 H, m), 1.71-1.79 (2 H, m), 1.48-1.57 (2 H, m), 1.27-1.42 (12 H, br.m), 0.89 (3 H, t, J 6.8 Hz), 0.82 (2 H, s); δ_C: 131.2, 125.2, 110.5, 108.3, 45.2, 36.2, 31.6, 29.4, 29.1, 28.8, 27.2, 26.9, 25.9, 24.6, 22.5, 20.3, 14.1, 7.7; υ_{max}: 1872, 1463, 1010, 654 cm^{-1}.

Reaction of 1,1,2-tribromo-2-ethylcyclopropane with 1-bromo-13-chlorotrideca-2(Z)-5(Z)-diene.

This gave *1-chloro-13(2-ethylcycloprop-1-enyl)-trideca-8(Z),11(Z)-diene* (58 %) (Found M^++H: 281.2036. $C_{18}H_{29}Cl$+H requires: 281.2036) which showed δ_H: 5.6-5.3 (4 H, m), 3.5 (2 H, t, J 6.7 Hz), 3.14 (2 H, br, d, J 6.62Hz), 2.8 (2 H, t, J 6.22 Hz), 2.37 (2 H, br.q, J 7.3 Hz), 2.01 (2 H, br.m), 1.73 (2 H, pent, J 6.7 Hz), 1.38-1.29 (8 H, br.m), 1.1 (3 H, t, J 7.4 Hz), 0.8 (2 H, s); δ_C: 130.3, 129.3, 127.6, 125.5, 111.3, 107.6, 45, 32.6, 29.5, 29.1, 28.7, 27.3, 27.2, 26.8, 25.7, 19.6, 12.1, 7.7; υ_{max}: 2929, 2856, 1680, 1458, 1010 cm^{-1}.

Preparation of Nitriles from Haloalkenes

(i) 4-(2-(undeca-2Z,5Z-dienyl)-cycloprop-1-enyl)pentanonitrile: Sodium cyanide (0.47 g, 0.0096 mole) was added to a stirred solution of 1-(4-chlorobutyl)-2-(undeca-2Z,5Z-dienyl)cyclopropene (0.9 g, 0.0032 mole) in dimethylsulphoxide (5 ml). The mixture was heated to 60 °C for 3 h. When T.L.C. showed no starting material was left, water (3 ml) was added to the cooled solution and the product extracted into ether (3 x 10 ml). The combined organic layers were washed with sat.aq. ammonium chloride, dried and evaporated to give a crude product. Short column chromatography on silica eluting with 5:1 petroleum/ether gave *4-(2-(undeca-2Z,5Z-dienyl)-cycloprop-1-enyl)pentanonitrile* (0.55 g, 63 %) (Found $M^+ + H$: 272.2378. $C_{19}H_{29}N + H$ requires: 272.2378), which showed δ_H: 5.6-5.3 (4 H, m), 3.19 (2 H, br.d, J 5.63 Hz), 2.83 (2 H, t, J 6.24 Hz), 2.4 (2 H, m), 2.37 (2 H, m), 2.0 (2 H, m), 1.65 (4 H, m), 1.25 (6 H, br.m), 0.9 (3 H, t, J 6.6 Hz), 0.8 (2 H, s); δ_C: 130.6, 129.7, 127.2, 125.0, 119.6, 109, 108.5, 31.5, 29.3, 27.2, 26.4, 25.6, 24.9, 24.6, 22.6, 16.9, 14.1, 7.75; υ_{max}: 2246, 1871, 1659, 1011 cm^{-1}.

(ii) **11-(2-pentylcycloprop-1-enyl)undec-9(Z)-enonitrile:** This was prepared as above from the corresponding chloride (65 %) (Found M^+: 273.2456. $C_{19}H_{31}N$ requires: 273.2457) and showed δ_H: 5.4-5.54 (2 H, m), 3.12 (2 H, d, J 5.6 Hz), 2.22-2.4 (6 H, m including at δ 2.32, t, J 7.1 Hz), 2.02-2.07 (4 H, m), 1.26-1.71 (12 H, br.m), 0.89 (3 H, t, J 6.8 Hz), 0.8 (2 H, s); δ_C: 138.6, 129.6, 126.2, 110.2, 107.6, 31.5, 28.2, 27.0, 26.3, 25.8, 24.8, 24.5, 23.4, 22.7, 22.3, 17.0, 14.1, 7.8; υ_{max}: 2246, 1879, 1714, 1461, 1010 cm^{-1}.

(iii) **14-(2-ethylcycloprop-1-enyl)-tetradeca-9-(Z),12(Z)-dienonitrile:** This was prepared as above from the corresponding chloride (62 %) (Found $M^+ + H^+$ 272.2378. $C_{19}H_{29}N + H$ requires: 281.2036) and showed δ_H: 5.2-5.65 (4 H, m), 3.18 (2 H, br,dd, J 1.24, 6.6 Hz), 2.81 (2 H, br,t, J 6.2 Hz), 2.41 (2 H, t, J 1.7, 7.4 Hz), 2.32 (2 H, t, J 6.9 Hz), 2.06 (2 H, m), 1.65 (2 H, m), 1.5-1.3 (8 H, br.m), 1.13 (3 H, t, J 7.4 Hz), 0.84 (2 H, s); δ_C: 130.2, 129.3, 127.6, 127.2, 119.8, 111.3, 107.6, 29.4, 28.9, 28.6, 28.6, 27.1, 25.6, 25.3, 24.5, 19.5, 17.1, 12.1, 7.7; υ_{max}: 2246, 1871, 1678, 1654 cm^{-1}.

Preparation of Di-iodocyclopropanes

(i) 4-(1,2-diiodo-2-(undeca-2Z,5Z-dienyl)cycloprop-1-yl)pentanonitrile: Iodine (0.45 g, 0.0017 mole) in dry diethyl ether (50 ml) was added dropwise to a stirred solution of 4-(2-(undeca-2Z,5Z-dienyl)-cycloprop-1-enyl)pentanonitrile (0.4 g, 0.00147 mole) in dry ether (40 ml) at -90 °C. The mixture was allowed to reach room temperature for 1 h. When T.L.C. showed no starting material, the reaction was quenched with sat.aq. sodium thiosulphate (15 ml) to remove any excess of iodine and the aqueous layer extracted with ether (2 x 30 ml). The combined ether layers were washed with water (2 x 10 ml), dried and evaporated to give *4-(1,2-diiodo-2-(undeca-2Z,5Z-dienyl)cyclo prop-1-yl)pentanonitrile* as a brown oil which was further purified by treatment with petroleum and filtered to give an oil (0.54 g, 70 %) which showed two spots by T.L.C. very close together (Found $M^+ + NH_4^+$: 543.0733. $C_{19}H_{29}NI_2 + NH_4^+$ requires: 543.0733) which showed δ_H: 5.4-5.6 (2 H, m), 5.35-5.2 (2 H, m), 3.02 (ca. 0.8 H, dd, J 6.3, 15.6 Hz), 2.75 (ca. 3.2 H, m), 2.35 (ca. 3.2 H, m), 1.95 (ca. 3.2 H, m), 1.5-1.8 (8 H, m), 1.25 (3.2 H, m), 1.12 (0.2 H, d, J 8 Hz), 0.97 (0.2 H, d, J 8 Hz), 0.85 (3 H, t, J 6.6 Hz); δ_C: 130.9, 130.8, 127.46, 127, 126.9, 119.6, 49.7,

48.5, 39.8, 38.4, 35.3, 35.1, 31.5, 30.8, 29.3, 29.1, 27.3, 26.4, 26.2, 24.8, 26.7, 22.6, 22.1, 21.7, 17.4, 14.1 (for two isomers); υ_{max}: 2245, 1457, 1425, 722 cm^{-1}.

(ii) **14-(2-ethyl-1,2-diiodocycloprop-1-yl)tetradeca-9(Z),12(Z)-dienonitrile**: Addition of iodine to 14-(2-ethyl-cycloprop-1-enyl)tetradeca-9(Z),12(Z)-dienonitrile as above gave the di-iodide (67 %) which showed δ_H: 5.5-5.7 (2 H, m), 5.3-5.4 (2 H, m), 3.05 (0.7 H, dd, J 5.8, 16 Hz), 2.75 (3.3 H, br.m), 2.3 (2 H, t, J 7.0 Hz), 2.18-2.02 (3 H, m), 1.88-1.74 (6 H, m), 1.68-1.57 (2 H, m), 1.4-0.93 (1 H, m, including t, J 6.9, at δ 1.12 and d, J 7.97 Hz at δ 0.95); δ_C: 130.4, 130.36, 127.9, 127.3, 127.2, 127.1, 119.8, 48.74, 44.28, 38.13, 35.1, 34.9, 34.2, 29.4, 28.9, 28.6, 27.2, 26.4, 26.1, 25.3, 22.34, 20.3, 17.13; υ_{max}: 2245, 1457, 1425, 722 cm^{-1}.

(iii) **11-(2-pentyl-1,2-diiodocycloprop-1-yl)undec-9(Z)-enonitrile:** Addition of iodine to 11-(2-pentylcyclo-prop-1-enyl)undec-9(Z)-enonitrile as above gave the di-iodide (**12**) (58 %) (Found $(M + NH_4)^+$: 545.089). $C_{19}H_{35}N_2I_2$ requires: 545.0890) which showed δ_H: 5.52-5.61 (2 H, m), 3.02-3.10 (0.8 H, br.dd, J 6.5, 15.9 Hz), 2.72-2.82 (1.2 H, m), 2.35 (2 H, t, J 7.0 Hz), 2.05-2.09 (3 H, m), 1.6 - 1.9 (6 H, m), 1.1 - 1.5 (12 H, br.m, including d (J 8 Hz) at 1.15), 0.9 - 1.02 (4 H, m, including d (J 8 Hz) at δ 0.99); δ_C: 132.2, 127.6, 127.2, 50.8, 48.8, 40.7, 38.3, 35.4, 35.1, 31.3, 31.0, 29.5, 29.2, 29.0, 28.6, 27.9, 27.7, 25.4, 23.7, 22.7, 22.6, 20.3, 17.1, 14.1; υ_{max}: 1679, 1425, 1377, 1043, 724 cm^{-1}.

Hydrolysis of di-iodocyclopropanenitriles

(i) Gaseous hydrogen chloride was bubbled through an ice-cooled solution of dry methanol (2 ml) and dry diethyl ether (4 ml) for 5 m. The solution was cooled to -70 °C and 14-(2-ethyl-1,2-diiodocycloprop-1-yl)-tetradeca-9(Z),12(Z)-dienonitrile (0.5 g, 0.9 mmole) in dry ether (3 ml) was added dropwise. The stirred mixture was allowed to warm slowly to reach room temperature. After 12 h, it was cooled to -50 °C and sat.aq. sodium bicarbonate (2 ml) was added. The mixture was warmed to room temperature, neutralised to pH ~7 and extracted with ether (3 x 10 ml); the combined ether layers were dried and evaporated to give a brown oil. Chromatography, eluting with petroleum/ether (5:1), gave one isomer of *methyl 14-(2-ethyl-1,2-diiodocycloprop-1-yl)tetradeca-9(Z),12(Z)-dienoate* (0.21 g, 40 %) (Found $(M + NH_4)^+$: 576.084. $C_{20}H_{32}NI_2 + NH_4^+$ requires: 576.084) which showed δ_H 5.6 (2 H, m), 5.4 (2 H, m), 3.68 (3 H, s), 3.08 (1 H, dd, J 10, 15.7 Hz), 2.8 (3 H, complex m), 2.3 (3 H, t, J 7.4 Hz), 2.15 (1 H, dd, J ca. 14, 7 Hz), 2.05 (2 H, m), 1.85 (1 H, d, J 14, 7 Hz), 1.6 (2 H, br.s), 1.25 (9 H, br.s), 1.17 (3 H, t, J 7.0 Hz). A second fraction contained this together with a minor isomer (0.179, 32 %); δ_C: 174.3, 130.5, 127.2, 51.4, 48.7, 44.3, 34.9, 34.0, 29.5, 29.1, 27.3, 27.2, 26.4, 25.3, 24.9, 22.3, 20.3, 14.2; υ_{max}: 1739, 1434, 1196, 1169 cm^{-1}.

(ii) *Methyl 11-(1,2-diiodo-2-pentylcycloprop-1-yl)undec-9(Z)-enoate* (**13**) was prepared as above from 11-(2-pentyl-1,2-diiodocycloprop-1-yl)undec-9(Z)-enonitrile (59.5%) (Found $M^+ + NH_4^+$: 578.09990. $C_{20}H_{34}O_2I_2 + NH_4^+$ requires: 578.0992) (δ_H: 5.49-5.68 (2 H, m), 3.67 (3 H, s), 3.00-3.1 (0.8 H, dd, J 7.0, 15.5 Hz), 2.7-2.81 (1.2 H, m), 2.31 (2 H, t, J 7.5 Hz), 1.96-2.17 (3 H, m), 1.56-1.85 (4 H, m), 1.26-1.43 (12 H, br.m), 1.14 (0.5 H, d, J 7.9 Hz), 0.98 (0.5 H, d, J 8.0 Hz), 0.83-0.95 (5 H, m); δ_C: 174.3, 132.4, 132.3, 127.5, 127.0, 51.4, 50.6, 48.7, 40.8, 38.3,

35.4, 35.1, 34.1, 31.3, 31.0, 29.5, 29.3, 28.0, 27.8, 24.9, 23.7, 22.6, 22.5, 20.3, 14.1, 14.0; υ_{max}: 1651, 1435, 1362, 1197, 1171 cm^{-1}).

(iii) *Methyl 5-(1,2-diiodo-2-(undeca-2Z,5Z-dienyl)cycloprop-1-yl)pentanoate* was prepared as above (63 %) (Found $M^+ + NH_4^+$: 576.084. $C_{20}H_{32}O_2I_2 + NH_4^+$ requires: 576.084) and showed δ_H: 5.45-5.65 (2 H, m), 5.28-5.45 (2 H, m), 3.68 & 3.67 (2 x s, total 3 H, ratio ca. 3:1), 3.06 (0.8 H, dd, J 6.9, 16.97 Hz), 2.7 - 2.9 (m, ca. 3.2 H, including br.d, J 5.7 Hz), 2.37 (3 H, br.t, J 7.4 Hz), 2.25 - 2.00 (3 H, m), 1.55-1.9 (6 H, br.m), 1.4 - 0.97 (6 H, m, including 2 x d, J 8.1 Hz, at δ 1.14 and 0.99 each ca. 0.2 H), 0.85 (3 H, distorted t, J 6.6 Hz); δ_C: 173.9, 130.7, 127.7, 127.1, 51.5, 50.2, 48.7, 40.4, 38.3, 35.3, 35.1, 34.0, 33.9, 31.5, 30.9, 29.4, 29.3, 27.3, 26.4, 26.2, 24.33, 24.08, 22.7, 22.6, 22.2, 14.1.

Methyl cyclopropenylalkenoates

(i) **Methyl 14-(2-ethylcycloprop-1-enyl)tetradeca-9(Z),12(Z)-dienoate:** n-Butyl lithium (0.96 ml, 1.05 mmole) was added dropwise with stirring to methyl 14-(2-ethyl-1,2-diiodocycloprop-1-yl)tetradeca-9(Z),12(Z)-dienoate (0.56 g, 1.003 mmol) in dry ether (5 ml) at -90 °C. The temperature was allowed to reach -70 °C and water (1 ml) was added dropwise. The product was extracted with ether (2 x 10 ml) and the combined organic layers washed with water (1 x 5 ml), dried and the solvent was removed at 14 and then 0.4 mm Hg to give methyl 14-(2-ethylcycloprop-1-enyl)tetradeca-9(Z),12(Z)-dienoate (7) (0.3 g, 95 %), which showed δ_H: 5.54-5.25 (4 H, m), 3.6 (3 H, s), 3.13 (2 H, br.d, J 7 Hz), 2.78 (2 H, br.t, J 6.3 Hz), 2.35 (2 H, br.t, J 7.5 Hz), 2.27 (2 H, t, J 7.4 Hz), 2.00 (2 H, br.m), 1.5 (4 H, br.m), 1.48-1.2 (6 H, m), 0.87 (3 H, t, J 7.3 Hz), 0.8 (2 H, s); δ_C: 174.3, 130.3, 129.3, 127.5, 125.5, 111.3, 107.6, 51.4, 38.95, 34.0, 29.6, 27.1, 25.6, 24.9, 24.6, 23.8, 23.3, 14.1, 12.0, 7.7; υ_{max}: 1740, 1643 cm^{-1}.

(ii) Methyl 11-(2-pentylcycloprop-1-enyl)undec-9(Z)-enoate, prepared as above from methyl 11-(1,2-diiodo-2-pentylcycloprop-1-yl)undec-9(Z)-enoate (91%), showed δ_H: 5.4-5.55 (2 H, m), 3.66 (3 H, s), 3.11 (2 H, d, J 5.4 Hz), 2.37 (2 H, br.t, J 7.2 Hz), 2.29 (2 H, t, J 7.5 Hz), 2.01-2.06 (2 H, m), 1.48-1.63 (4 H, m), 1.13-1.40 (12 H, br. m), 0.88 (3 H, t, J 6.8 Hz), 0.8 (2 H, s); δ_C: 174.3, 131.7, 125.1, 109.9, 107.9, 51.4, 34.1, 31.6, 29.5, 29.1, 29.0, 27.2, 25.9, 24.9, 24.6, 22.5, 14.0, 7.7; υ_{max}: 1875, 1741, 1642, 1170, 1011 cm^{-1}, m/e: (M^+) 306, (M^+-CH_3) 291, (M^+-OMe) 275.

(iii) Methyl 5-(2-(undeca-2(Z),5(Z)-dienyl)cycloprop-1-enyl)pentanoate prepared as above from methyl-5-(1,2-diiodo-2(Z)-5(Z)-undec-2-enylcyclopropyl)pentonoate (92 %) showed δ_H: 5.58-5.2 (4H, m), 3.6 (3H, s), 3.18 (2H, br, d, J 6.2 Hz), 2.81 (2H, t, J 5.66 Hz), 2.4 (2H, tt, J 1.6, 7 Hz), 2.3 (2H, t, J 7.3 Hz), 2.04 (2H, br.q, J 6.6 Hz), 1.6 (4H, m), 1.3 (6H, br.m), 0.88 (3H, t, J 6.5 Hz), 0.83 (2H, s); δ_C: 174, 130.5, 129.5, 127.4, 125.2, 109.5, 108.4, 51.4, 39.0, 33.8, 31.5, 29.3, 27.2, 26.9, 25.7, 25.5, 24.6, 22.5, 14.0, 7.7; υ_{max}: 1745, 1640 cm^{-1}.

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Analogues of the pheromones of three insect species in which a Z-alkene has been replaced by a 1,2-disubstituted cyclopropene block the effect of the pheromone on insect behaviour at the same dose as that at which the pheromone is active (Al Dulayymi, J.R.; Baird, M.S.; Nyman , S.; Port, G.J. *Tetrahedron*, 1996, **38**, 12509).

The stereochemistry of the alkenes in, eg., the chloride precursor of (6), was established by analysis of the

coupling constants in 600 MHz proton n.m.r. spectra; thanks are due to the EPSRC service in Edinburgh for obtaining these spectra.

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