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A Total Synthesis of (±)-Zoapatanol and Demethyl-ORF13811

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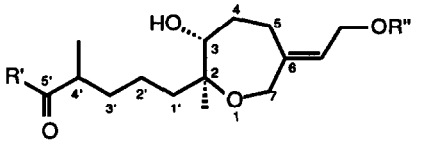
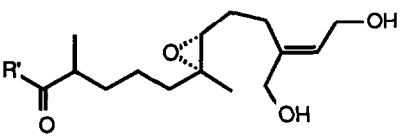
Abstract: Total syntheses of the spasmogenic diterpenoid zoapatanol and a demethyl analogue of the potent antigestational agent ORF 13811 are reported. A Ni^0-catalysed coupling of MeMgBr with a dihydrofuran, and a carbo- or hydro-magnesiation of an acetylene were used to construct the tri-substituted alkenes in the key intermediates with high stereoselectivity.

Tea prepared from the leaves of zoapatle (*Montanoa tomentosa*) has long been used in Mexico to induce menses and labour, and to terminate early pregnancy[1]. The oxepane diterpenes zoapatanol (1) and montanol (2) were isolated from the tea[2] and the former shown to be biologically active. More recently tomexathin[3] (3), tomentol[4] (4), tomentanol[5] (5), and the probable biosynthetic precursors of these diterpenes - (6), (7), & (8)[6] - have been isolated.

Zoapatanol will terminate pregnancy in guinea pigs and has[7] a significant spasmogenic effect on isolated cat coronary artery and guinea pig ileum, being somewhat less active than the prostaglandin endoperoxide (PGH_2) analogues 9,11-methano-epoxy-PGH_2 and 9,11-epoxy-methano-PGH_2. Notably pinane-thromboxane-A_2, a PGH_2 antagonist, blocks the latter effect, but only reduces that due to zoapatanol by 30% suggesting a different binding site. Unlike prostaglandins, zoapatanol has no effect on rabbit uterus or human platelets. This suggests that anti-fertility agents based on zoapatanol may avoid the unpleasant side effects associated with the use of prostaglandins $F_{2\alpha}$ and E_2 to terminate pregnancy and accounts for the great interest in them.

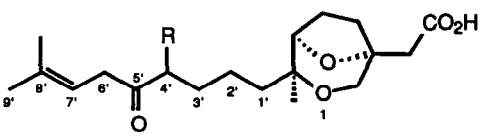
A structure - activity study[8] on zoapatanol derivatives demonstrated a marked increase in potency on oxidative cyclisation to give 3,8-dioxabicyclo[3.2.1]octanes and lead to the selection of ORF13811 (9) for extensive[9] investigation. It has been suggested[8] that *in vivo* transformations of the monocyclic oxepane to the bicyclic system, an easy transformation *in vitro*, is a prerequisite for biological activity.





(1) R' = $CH_2CHC(Me)_2$, R" = H.
(2) R' = $CHC(Me)CH(Me)_2$, R" = H.
(3) R' = $CHCHC(OH)(Me)_2$, R" = Ac.
(4) R' = $CHC(CH_2)CH(Me)_2$, R" = H.
(5) R' = $CH_2CH(Me)C(Me)CH_2$, R" = H.

(6) R' = $CH_2CHC(Me)_2$,
(7) R' = $CHCHC(OH)(Me)_2$
(8) R' = $CH_2C(CH_2)C(OH)(Me)_2$



(9) R = Me
(10) R = H

Some doubt has been raised[10] as to whether zoapatanol itself is the active component of zoapatle tea on the basis of its poor extraction into water and thermal instability. ORF13811 (9) is[9] an effective antifertility agent after oral administration in a range of rodents (ED_{50} 6-10 mg/kg), dogs (ED_{50} 10-30 mg/kg), and baboons (ED_{50} 40-60 mg/kg).

Several total syntheses of (±)-zoapatanol have appeared,[11-14] those of Nicolaou and co-workers[11] (16 steps, 12% overall yield) and Cookson and co-workers[12] (17 steps, 5% overall yield) being the most efficient. There has also been synthetic interest in the bicyclic analogues. For example, ORF13811 has been synthesised by two groups[15,16] in around 3% overall yield. We now report full details of an efficient stereocontrolled synthesis of (±)-zoapatanol[17] (1) and the demethyl analogue (10) of ORF13811[18]. In common with other syntheses we did not attempt the diastereocontrolled introduction of the remote C-4' methyl group since its stereochemistry, or indeed stereochemical integrity, in natural zoapatanol has not been established. In order to work with homogeneous compounds we omitted this methyl group in our synthesis of the ORF13811 analogue (10), and designed our synthesis of (±)-zoapatanol to introduce this chiral centre at a late stage.

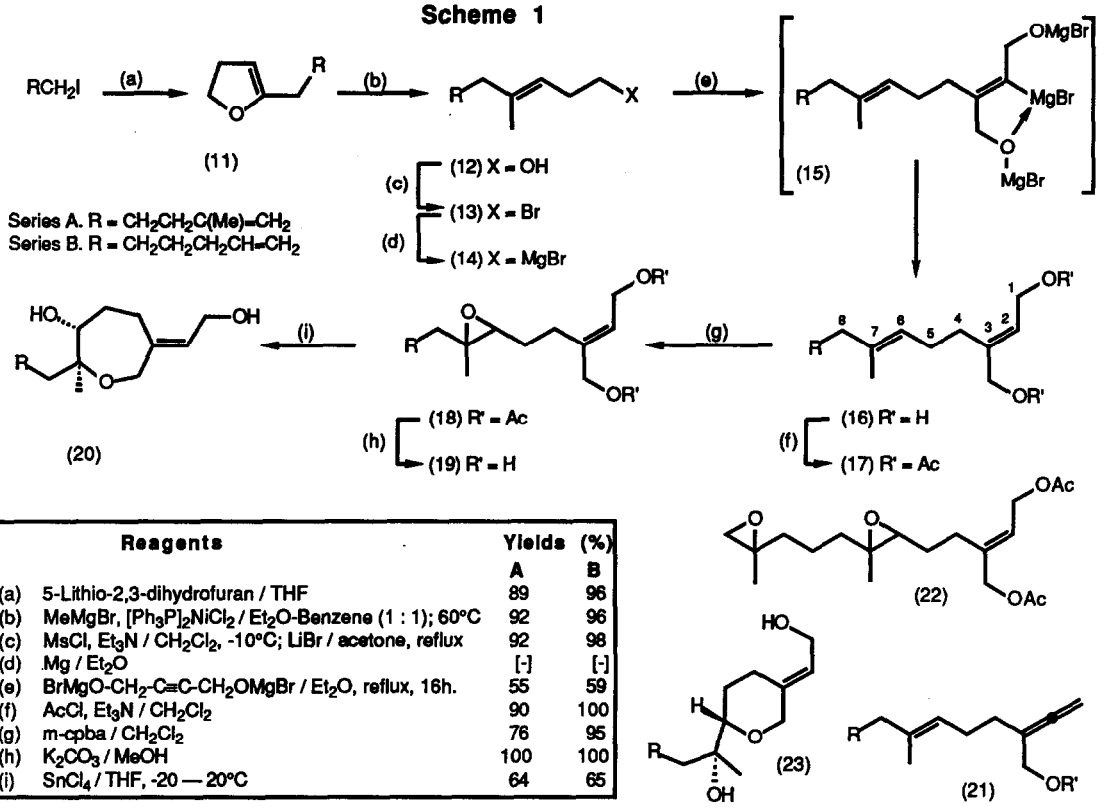
Our synthetic strategy was based on the biomimetic[6] cyclisation of the epoxy-diols (19A) and (19B) to afford the oxepane ring systems (20A) and (20B) with the correct relative stereochemistry, which could then be elaborated to (±)-zoapatanol (1) and demethyl-ORF11381 (10) respectively. Since the stereochemistry of the epoxide is derived from the precursor alkene the first stage in the synthesis was the stereoselective construction of the key diols (16A) and (16B). This was accomplished in 41 and 53% yields from 1-iodo-4-methyl-4-pentene and 1-iodo-5-hexene respectively, by a route incorporating two highly stereoselective tri-substituted alkene syntheses (Scheme 1).

The C-6—C-7 double bond was introduced *via* a Ni°-catalysed coupling[19] of MeMgBr with the 2-alkyl-dihydrofurans by the method of Wenkert and co-workers[20]. Two important modifications to the original method were developed to aid work on a large (0.2 Mol) scale: the reactions were run in a mixture of benzene and ether; and the amount of catalyst was reduced from 10 to 2 mol%. The Wenkert reaction is slower in coordinating solvents and previously the ether from the Grignard reagent was removed *in vacuo* before the addition of the enol ether. However dihydrofurans are highly reactive substrates and the presence of ether did not reduce the rate noticeably. With a model compound, 2-pentyl-4,5-dihydrofuran, the reaction was run successfully in pure ether with only 0.5 mol% catalyst. The dihydrofurans (11) were obtained in high yield by the reaction of 2-lithiodihydrofuran with the appropriate alkyl iodide and reacted with MeMgBr in the presence of $(PPh_3)_2NiCl_2$ to afford the alcohols (12). Both steps could be carried out on a large scale and overall yields were up to 94%. The products were greater than 99.5% isomerically pure by capillary g.c. provided that care was taken with the work-up[19].

The C-2—C-3 double bond in the diols (16) was constructed with >95% stereoselectivity by the unusual carbomagnesiation[21] of butyne-1,4-diol with the Grignard reagents (14) derived from the alcohols (12) by standard methods. Careful optimisation of the reaction conditions was necessary before a consistent yield of 55-60% was obtained. Initially considerable amounts of the Wurtz coupled dimer were produced during formation of the Grignard reagent limiting the overall yield. This problem was overcome by using a high purity magnesium powder which had been cleaned before use with hydrochloric acid, and by the co-addition of ethylene dibromide with the required bromide. Another problem was that the addition step had to be carried out in ether since in THF the intermediate carbomagnesiated compounds (15) undergo 1,2-elimination to afford the allenes (21). This was unfortunate since the dimagnesium salt of butyne-1,4-diol was best prepared by the addition of MeMgBr to a solution of the diol in THF. The problem was overcome by exchanging solvents during the reaction by repeated washing of the flocculent precipitate of $BrMgOCH_2C{\equiv}CCH_2OMgBr$ with ether by settling and decantation. With these conditions the main by-products were the allene (21) (5%) and protonated Grignard reagent (30%). It should be noted that when an excess of the Grignard reagent can be used this reaction occurs in better than 80% yield. The ease and high *trans*-stereoselectivity of this addition probably reflects internal coordination of the alkenylmagnesium bromide intermediates (15).

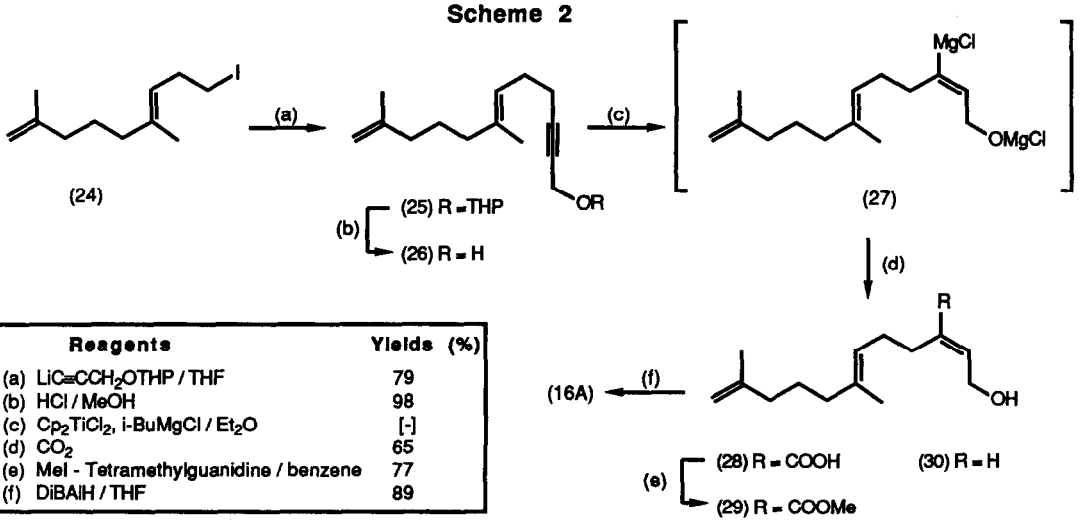
In an attempt to circumvent the problems mentioned above we investigated an alternative route to the diol (16A) in which the key step was a titanium-catalysed hydromagnesiation[22] of the alkyne (26) (Scheme 2). Thus the alcohol (12A) was converted to the iodide (24) which was displaced with the lithium salt of THP-protected propargyl alcohol to afford the acetylene (25) - a reaction which failed under many other conditions due to elimination of the homoallylic iodide to afford a butadiene. Deprotection and hydromagnesiation gave the magnesiated intermediate (27). The stereoselectivity of the reaction was confirmed by a water quench to give the *cis*-alkene (30) (the coupling between the alkene protons was 10.7 Hz) with better than 99% selectivity by capillary g.c. Quenching with carbon dioxide followed by esterification and reduction gave the required diol with high selectivity, but only 44% overall yield from (26). Quenching with formaldehyde gave (16A) directly but the yields were only slightly improved and separation of by-products was more difficult. The easy

Scheme 1



Reagents		Yields (%) A	B
(a)	5-Lithio-2,3-dihydrofuran / THF	89	96
(b)	MeMgBr, $[Ph_3P]_2NiCl_2$ / Et_2O-Benzene (1 : 1); 60°C	92	96
(c)	MsCl, Et_3N / CH_2Cl_2, -10°C; LiBr / acetone, reflux	92	98
(d)	Mg / Et_2O	[-]	[-]
(e)	$BrMgO-CH_2-C\equiv C-CH_2OMgBr$ / Et_2O, reflux, 16h.	55	59
(f)	AcCl, Et_3N / CH_2Cl_2	90	100
(g)	m-cpba / CH_2Cl_2	76	95
(h)	K_2CO_3 / MeOH	100	100
(i)	$SnCl_4$ / THF, -20 — 20°C	64	65

Scheme 2



Reagents	Yields (%)
(a) $LiC\equiv CCH_2OTHP$ / THF	79
(b) HCl / MeOH	98
(c) Cp_2TiCl_2, i-BuMgCl / Et_2O	[-]
(d) CO_2	65
(e) MeI - Tetramethylguanidine / benzene	77
(f) DiBAlH / THF	89

esterification of the acid (28) using tetramethylguanidine and MeI by the procedure of Wlostowski and Jaworski[23] is notable as an alternative to the use of diazomethane when acidic conditions must be avoided.

With the diols (16A) and (16B) in hand we turned to their conversion into the oxepane ring system *via* the epoxydiols (19).

Epoxidation of the C-6—C-7 double bond could only be achieved after protection of the hydroxyl functions as the acetates, which

were then easily removed by methanolysis. Epoxidation of (17A) was not totally chemoselective, the terminal disubstituted alkene competing with the required site. Typically the diepoxide (22) (15%) and recovered starting material (9%) were isolated as well as the required epoxide (18A) (75%) when 1 equivalent of mcpba was used.

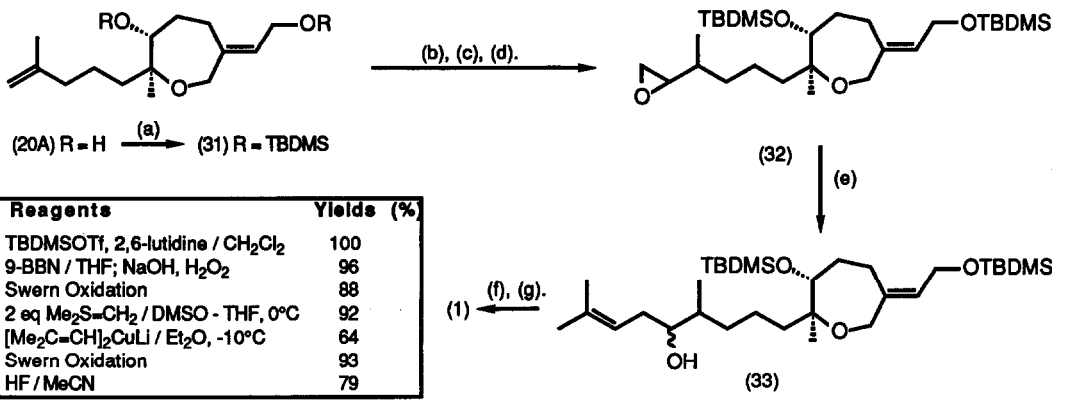
Cyclisation of the epoxydiols occurred on treatment with $SnCl_4$ in THF at -20 to 20°C in moderate yield to afford the required oxepanes (20A) and (20B) as white crystalline solids m.p. 71.5-72.5 and 38.5-39.5°C respectively. The choice of catalyst was crucial to the success of this cyclisation[24], $SnCl_4$ being exceptional in forming the oxepane product selectively rather than pyran (23).

This completed the synthesis of the key oxepane ring system in good overall yield from simple starting materials by methods readily amenable to large scale work.

Synthesis of (±)-zoapatanol.

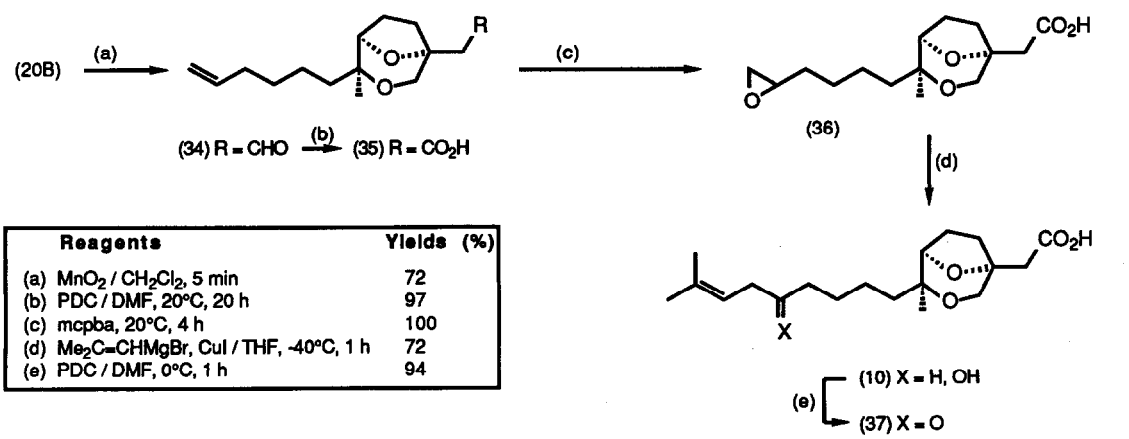
Conversion of the oxepane (20A) to zoapatanol (Scheme 3) commenced with protection of the hydroxyl functions as their *tert*-butyldimethylsilyl ethers, followed by selective hydroboration of the terminal double bond. Swern oxidation and reaction of the so-formed aldehyde with dimethylsulphonium methylide gave the epoxide (32). Nucleophilic cleavage of the epoxide was best achieved with the homocuprate derived from 2,2-dimethylvinyl-lithium and CuI to afford the alcohol (33) together with 30% of the alkene derived from reductive deoxygenation of the epoxide. Swern oxidation of the secondary alcohol and removal of the protecting groups with HF in acetonitrile gave (±)-zoapatanol as a 1 : 1 mixture of diastereoisomers due to the uncontrolled stereochemistry of the side chain methyl group. The carbon-13 n.m.r. of this material was consistent with that reported[25] for natural zoapatanol, and the 360 MHz proton n.m.r. was identical with that of synthetic (±)-zoapatanol prepared by Cookson and Liverton[12].

Scheme 3



Reagents	Yields (%)
(a) TBDMSOTf, 2,6-lutidine / CH_2Cl_2	100
(b) 9-BBN / THF; NaOH, H_2O_2	96
(c) Swern Oxidation	88
(d) 2 eq $Me_2S{=}CH_2$ / DMSO - THF, 0°C	92
(e) $[Me_2C{=}CH]_2CuLi$ / Et_2O, -10°C	64
(f) Swern Oxidation	93
(g) HF / MeCN	79

Scheme 4



Reagents	Yields (%)
(a) MnO_2 / CH_2Cl_2, 5 min	72
(b) PDC / DMF, 20°C, 20 h	97
(c) mcpba, 20°C, 4 h	100
(d) $Me_2C{=}CHMgBr$, CuI / THF, -40°C, 1 h	72
(e) PDC / DMF, 0°C, 1 h	94

Synthesis of demethyl-ORF13811 (Scheme 4).

Manganese dioxide oxidation of the oxepane (20B) gave the bicyclic aldehyde (34) *via* an intramolecular Michael addition. Further oxidation with pyridinium dichromate in DMF afforded the acid (35); epoxidation with mcpba then gave the epoxide (36). Nucleophilic opening with dimethylvinylmagnesium bromide catalysed by CuI afforded demethyl-ORF13811 (10) in 50% overall yield from (20B). This, like ORF13811, is a 1:1 mixture of diastereomers due to the C(5') hydroxyl group. One isomer could be obtained pure by fractional recrystallisation, the other was isolated in around 90% purity from the mother liquors. Oxidation of the mixture gave the ketone (37), the 4'-methyl analogue of which has been obtained from zoapatanol by $Pt / O_2 / NaHCO_3$ oxidation.

In conclusion we have developed stereocontrolled routes to (±)-zoapatanol (15 steps, 6.6% overall yield) and demethyl-ORF13811 (13 steps, 16.5% overall yield) which can be run on a large scale, and which have involved the development of two stereocontrolled trisubstituted alkene syntheses.

EXPERIMENTAL

^1H N.m.r. (270 or 360 MHz) and ^{13}C n.m.r. (68 or 90 MHz) were carried out on JEOL GX270 or Bruker EM-360 machines. Unless otherwise indicated they are for $CDCl_3$ solutions with tetramethylsilane as internal standard run at 360 MHz (proton) and 90 MHz (carbon). Signal multiplicities are described by : s (singlet), d, (doublet), t (triplet), q (quartet), and m (multiplet). For ^{13}C spectra they refer to attached protons only and were determined by DEPT techniques. A * by the multiplicity indicates that the signal was observed as a pair of lines, $\Delta\delta<0.1$ ppm due to the presence of diastereomers.

Infra red spectra were recorded on a Perkin-Elmer 298 spectrometer and are for neat samples between NaCl plates unless a solvent is specified when they are for solutions. C-H stretch absorptions are not reported.

Mass spectra were recorded on a Kratos MS-30 spectrometer by electron impact at 20 eV, unless otherwise indicated.

THF and diethyl ether (ether) were dried by distillation from sodium / benzophenone. Pyridine was distilled from and stored over KOH. Triethylamine, dichloromethane, and light petroleum (b.p. 40 - 60 °C) were distilled from calcium hydride. 1-Iodo-5-hexene was prepared from 5-pentene-1-ol by mesylation and displacement of the mesylate with sodium iodide. 5-Iodo-2-methylpent-1-ene was prepared from 2-methylpropenol *via* a Claisen rearangement (triethyl orthoacetate, H^+, Δ), reduction of the so formed ethyl 4-methylpent-4-enoate to the alcohol ($LiAlH_4$) and conversion to the iodide as above. 1-Bromo-2-methyl-prop-1-ene was prepared from 3-methyl-but-2-enoic acid by addition of bromine followed by base induced decarboxylative elimination of bromide.

Synthesis of the triene-diols (16A) and (16B).

2-(4-*Methyl*-4-*pentenyl*)-4, 5-*dihydrofuran* (11A)

To 4, 5-dihydrofuran (6.54 g, 93.4 mmol) in THF (50 ml) was added ^{t}BuLi (47.0 ml of a 1.8M solution in pentane, 80.0 mmol) dropwise over 1h, maintaining the temperature around -40°C. The reaction mixture was allowed to warm to -5°C over 1h, cooled to -20°C and 5-iodo-2-methylpent-1-ene (14.0 g, 66.7 mmol) added over 10 min. The reaction mixture was allowed to warm slowly to r.t. (16h) before cooling to 0°C and pouring into NH_4Claq (100 ml) and ether (100 ml). The organic phase was separated, diluted with ether (100 ml), and washed with brine (100 ml), before drying rapidly ($MgSO_4$), removal of the solvent and rapid Kugelrhor distillation (150°C, 1 mmHg) to afford the *title dihydrofuran* (9.23 g, 91%) as a colourless oil IR: 1660s, 1640m, 1450m, 1380m, 1250w, 1180m, 1170m, 1010s, 940s, 890s, 720m. PMR: (CCl_4) 4.64 (2H, d, J 7 Hz), 4.45 (1H, s), 4.22 (2H, t, J 8 Hz), 2.55 (2H, t with fine splitting, J 8 Hz), 2.00 (4H, m), 1.69 (3H, s), 1.59 (2H, qn, J 8 Hz) CMR: 158.9 (s), 144.5 (s), 110.4 (t), 93.0 (d), 69.2 (t), 37.2 (t), 30.0 (t), 27.4 (t), 24.5 (t), 22.2 (q).

2-(5-*Hexenyl*)-4,5-*dihydrofuran (11B)*

Prepared as above in 96% yield as a colourless oil. IR:1670, 1470, 1255, 1180, 1165, 1050, 930 cm^{-1}. PMR: 5.814 (1H, ddt, J 17.1, 10.3, 6.7 Hz), 5.008 (1H, dq, J 17.1, 1.8 Hz), 4.947 (1H, d+fs, J 10.3 Hz), 4.577 (1H, bs s), 4.304 (2H, t, J 9.4 Hz), 2.597 (2H, tq, J 9.2, 2.0 Hz), 2.0-2.1 (4H, m), 1.3-1.6 (4H, m).

(3E)-4,8-*Dimethynona*-3,8-*dien*-1-*ol* (12A)

To $(PPh_3)_2NiCl_2$ (0.783 g, 1.2 mmol) in dry benzene (50 ml) under argon at room temperature was added dropwise MeMgBr (0.9 ml of a 3M solution in ether, 2.64 mmol). After stirring for 15 min MeMgBr (44.0 ml, 132 mmol) and then 2-(4-methyl-4-pentenyl)-4,5-dihydrofuran (11A) (9.0 g, 59.9 mmol) in benzene (5 ml) were added and the mixture refluxed for 3h. After cooling to 0°C the green reaction mixture was quenched by pouring as a slow stream into vigorously stirred saturated aqueous NH_4Cl solution (200 ml) at -10°C. The stirring was continued for 15 min (until the mixture was white) before the organic layer was separated and the aqueous phase extracted with ether (3 x 110 ml). The combined organic layers were dried ($MgSO_4$), the solvent removed, and the residue chromatographed on silica gel (ether:light petroleum 1:4-1:2 as elutant) to remove biphenyl impurity. Capillary gas chromotography (CP wax, 140°C) showed 1 peak with a retention time of 8.7 min. Kugelrhor distillation (150°C, 1 mmHg) gave the *title alcohol* (12A) (8.82 g, 90%) as a colourless oil. Found: $M^{+\cdot}$ 168.1498; $C_{11}H_{20}O$ requires 168.1509. IR: 3320br s, 1655m, 1450m, 1360m, 1055s, 890s cm^{-1}. PMR: 5.15 (1H, t with fine splitting, J 7.1, 1.3 Hz), 4.68 (2H, d with fine splitting, J 11.4, 1.1 Hz), 3.59 (2H, t, J 6.8 Hz), 2.42 (1H, s, O*H*), 2.28 (2H, q, J 7.1 Hz), 1.99 (4H, q, J 7.8 Hz), 1.71 (3H, s), 1.63 (3H, s), 1.58-1.50 (2H, m). CMR: 145.8 (s), 138.3 (s), 120.1 (d), 109.9 (t), 62.5 (t), 39.4 (t), 37.5 (t), 31.6 (t), 26.0 (t), 22.3 (q), 16.1 (t). m/z: 153 (1%), 150 (2), 135 (5), 112 (17), 109 (21), 95 (23), 81 (100), 68 (38), 67 (46), 55 (41), 41 (60).

(3E)-4-*Methyl-deca*-3,9-*dien*-1-*ol (12B)*.

Prepared as above as a colourless oil b.p. 200°C / 14 mmHg (Kugelrohr) in 96% yield, > 98% pure by g.c. (150°C, OV101 on chromosorb). (Found for 1-naphthylcarbamate: C, 78.11; H, 8.07; N, 4.16. $C_{22}H_{27}NO_2$ requires C, 78.3; H, 8.06; N, 4.15%). IR: 3340br s, 1635w, 1435, 1045, 905 cm^{-1}. PMR: 5.805 (1H, ddt, J 17, 10.3, 6.7 Hz), 5.127 (1H, br t, J 8 Hz), 4.995 (1H, dq, J 17, 1.8 Hz), 4.933 (1H, br d, J 10.3 Hz), 3.630 (2H, t, J 7 Hz), 2.65 (1H, br s, OH), 2.286 (2H, q, J 6.8 Hz), 2.10 (4H, m), 1.630 (3H, s), 1.4-1.5 (4H, m). CMR: 139.09 (d), 138.57 (s), 119.99 (d), 114.41 (t), 62.51 (t), 39.74 (t), 33.79 (t), 31.67 (t), 28.70 (t), 27.52 (t), 16.18 (q).

(3E)-1-*Bromo*-4,8-*dimethyl-nona*-3,8-*diene* (13A)

To alcohol (12A) (7.1 g, 42.3 mmol) and triethylamine (8.2 ml, 59.2 mmol) in dry dichloromethane (110 ml) was added dropwise *via* syringe mesyl chloride (3.94 ml, 50.8 mmol) maintaining the temperature between -10°C and -5°C. After 0.5 h the reaction mixture was poured into $NaHCO_3$aq (170 ml), the phases separated and the aqueous phase extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), and the solvent removed. Lithium bromide (14.7 g, 169 mmol) dissolved in dry acetone (300 ml) was added and the mixture stirred under reflux (2 h). The bulk of the acetone was removed by rotatory evaporation, the residue taken up in water (170 ml), and the product extracted into light petroleum (4 x 85 ml). The combined organic phases were washed with 2M HClaq (85 ml), $NaHCO_3$aq (85 ml), and brine (2 x 85 ml), before drying ($MgSO_4$). After removal of the solvent the residue was chromatographed on silica (light petroleum as elutant) to give the *title bromide* (9.0 g, 92%) as a

colourless oil. IR: 1655m, 1450m, 1270m, 890m cm^{-1}. PMR: 5.14 (1H, t with fine splitting, J 7.1, 1.3 Hz), 4.69 (2H, d with fine splitting, J 11.1, 1.2 Hz), 3.34 (2H, t, J 6.1 Hz), 2.57 (2H, q, J 7.1 Hz), 2.02-1.96 (4H, m), 1.71(3H, s), 1.62 (3H, s), 1.58-1.51 (2H, m). CMR: 145.8 (s), 138.6 (s), 121.2 (d), 110.0 (t), 39.3 (t), 37.5 (t), 32.7 (t), 31.9 (t), 26.0 (t), 22.4 (q), 16.3 (q). m/z: 230/232 (M^+, 0.1%), 217/215 (0.6), 203/201 (0.3), 189/187 (0.8), 176/174 (21), 109 (10), 95 (100), 81 (43), 68 (53), 55 (39), 41 (58).

(3E)-1-*Bromo-4-methyl-deca-3,9-diene (13B)*

Method as above but replacing chromatography with Kugelrohr distillation (130°C / 1 mmHg) gave the title bromide 98% as a colourless oil (pure by g.l.c. on 6% OV101 / chromosorb at 150°C). IR: 1640, 1440br, 1270, 913 cm^{-1}. PMR (60 MHz): 5.82 (1H, ddt, J, 17, 9.5, 5.5 Hz), 4.8-5.3 (3H, m), 3.32 (2H, t, J 6.6 Hz), 2.55 (2H, q, J 7 Hz), 2.0 (4H, m), 1.61 (3H, s), 1.4 (4H, m).

(2E, 6E)-3-*Hydoxymethyl-7,11-dimethyl-dodeca-2,6,11-trien-1-ol* (16A)

To vigorously stirred butyne-1, 4-diol (3.18 g, 36.7 mmol) in THF (95 ml) was added MeMgBr (25.8 ml of a 3M solution in ether, 77.4 mmol) dropwise *via* syringe, maintaining the temperature between 18 and 22°C. Stirring was continued for 1h and then ether (200 ml) added, the precipitate allowed to settle, and the supernatant solvent (175 ml) removed. By the same procedure the precipitate was washed with more ether (2 x 175 ml) before adding ether (30 ml).

To magnesium powder (2.58 g, 106 mmol, activated by washing with 0.3M HCl, water, ethanol, ether, and drying overnight at 0.5 mmHg) in ether (65 ml) at 20°C was added dropwise over 1h a mixture of (3E)-1-bromo-4, 8-dimethyl-nona -3, 8-diene (13A) (7.75 g, 33.6 mmol) and 1,2-dibromoethane (5.62 g, 29.9 mmol) in ether (20 ml). The mixture was stirred at 30°C for 1h and the Grignard reagent so formed transferred *via* cannula into the butyne-1, 4-diol salt formed above. The reaction mixture was refluxed for 20h, then poured into NH_4Claq (175 ml). The phases were separated and the aqueous phase extracted with ether (3 x 140 ml). The combined organic layers were washed with brine (30 ml), dried ($MgSO_4$), and the solvent removed. The residue was chromatographed on silica (ethyl acetate:light petroleum 3:2 as elutant) to give the *title diol* (16A) as a pale yellow oil (3.36 g, 55%). Kugelrohr distillation (190°C, 0.01 mmHg) gave a colourless viscous oil. (Found: C, 75.1; H, 10.9. $C_{15}H_{26}O_2$ Requires: C, 75.6; H, 11.0%). IR: 3420br s, 1655m, 1450m, 1010s, 890m cm^{-1}. PMR: 5.63 (1H, t, J 6.8 Hz), 5.10 (1H, t, J 6.7 Hz), 4.68 (2H, d, J 11.6 Hz), 4.17 (2H, d, J 6.8 Hz), 4.03 (2H, s), 3.85 (1H, br s, *OH*), 3.67 (1H, br s, *OH*), 2.15-2.02 (4H, m), 2.01-1.91 (4H, m), 1.71 (3H, s), 1.58 (3H, s), 1.55-1.47 (2H, m). CMR: 145.9 (s), 142.1 (s), 136.1 (s), 124.6 (d), 123.6 (d), 109.9 (t), 66.0 (t), 58.7 (t), 39.3 (t), 37.5 (t), 28.4 (t), 27.2 (t), 26.0 (t), 22.3 (q), 15.9 (q). m/z: 137 (M^+-$CH_2C(CH_2OH)$=$CHCH_2OH$), 135 (6), 133 (80), 121 (7), 112 (7), 110 (5), 109 (41), 95 (40), 81 (100), 67 (21), 55 (31), 41 (25).

(2E, 6E)-3-*Hydroxymethyl-trideca-2,6,12-trien-1-ol (16B)*

The title diol was prepared as above (58%) as a viscous, colourless oil. IR: 3340br s, 1640, 1450br, 1130, 1010br, & 915 cm^{-1}. PMR: 5.81 (1H, ddt, J 17.2, 10.2, 6.6 Hz), 5.69 (1H, t, J 6.8 Hz), 5.10 (1H, t, J 6.9 Hz), 5.00 (1H, dq, J 16.8, 1.7 Hz), 4.94 (1H, d, J 9.8 Hz), 4.21 (2H, d, J 6.9 Hz), 4.09 (2H, s), 2.0-2.2 (6H, m), 1.97 (2H, t, J 7.0 Hz), 1.58 (3H, s), 1.3-1.45 (4H, m). CMR: 141.9 (s), 139.0 (d), 136.1 (s), 124.4 (d), 123.4 (d), 114.2 (t), 65.8 (t), 58.6 (t), 39.5 (t), 33.6 (t), 28.6 (t), 28.4 (t), 27.4 (t), 27.2 (t),15.9 (q). m/z 207.176 (M^+-CH_2OH, $C_{14}H_{23}O$ requires 207.175, 0.2%), 189 (0.2), 147 (0.3), 109 (11.8), 95 (21.4), 81 (41.4), 69 (27), 55 (100), 41 (79). This was analysed as its di-p-phenylbenzoyl derivative m.p. 62-63°C (from hexane-ether) (Found: C, 82.1; H, 7.1. $C_{41}H_{42}O_4$ requires C, 82.2; H, 7.1%)

Also isolated were the the following:

(6E)-3-*Hydroxymethyl-7-methyl-trideca-1,2,6,12-tetraene (21B)*.(0.86 g, 7.5%), IR: 3340br s, 1960, 1640 cm^{-1}. PMR: 5.79 (1H, ddt, J 17.1, 10.2, 6.6 Hz), 5.13 (1H, t, J 6.5 Hz), 4.98 (1H, dq, J 16.8, 1.6 Hz), 4.92 (1H, d, J 9.7 Hz), 4.83 (2H, quintet, J 3.0 Hz), 4.03 (2H, t, J 2.9 Hz), 2.40 (1H, br s, OH), 2.14 (2H, q, J 7.3 Hz), 2.0-2.05 (4H, m), 1.97 (2H, t, J 7.3 Hz), 1.58 (3H, s), 1.35-1.40 (4H, m). CMR: 204.9 (s), 139.0 (d), 135.7 (s), 123.8 (d), 114.2 (t), 104.3 (s), 77.8 (t), 63.0 (t), 39.5 (t), 33.6 (t), 29.1 (t), 28.5 (t), 27.4 (t), 26.2 (t),15.9 (q). m/z: 220 (M^+, 0.3%), 212 (0.5), 205 (0.5), 191 (6.5), 151 (8.3), 149 (5.8), 138 (21), 109 (34), 107 (20), 105 (19), 95 (63), 81 (100), 55 (92), 41 (73).

(3E)-4-*Methyl-deca-3,9-diene*.(2.46 g, 31%), IR: 1640, 1450br, 995, 913 cm^{-1}. PMR: 5.8 (1H, ddt, J 17, 9, 6 Hz), 4.8-5.2 (3H, m), 1.8-2.2 (6H, m), 1.56 (3H, s), 1.4 (4H, m), 0.92 (3H, t, J 7 Hz). CMR: 139.1 (d), 134.4 (s), 126.5 (d), 114.2 (t), 39.6 (t), 33.8 (t), 28.7 (t), 27.6 (t), 21.2 (t), 15.7 (q), 14.4 (q).

Alternative preparation of (16A) *via* hydromagnesiation.

(3E)-1-*Iodo-4,8-dimethyl-nona-3,8-diene* (24)

To alcohol (12A) (3.36 g, 20 mmol) and triethylamine (3.89 ml, 28 mmol) in dry dichloromethane (50 ml) was added dropwise *via* syringe mesyl chloride (1.86 ml, 24 mmol) maintaining the temperature below -10°C. After 10 min the reaction mixture was poured into water (50 ml) and dichloromethane (50 ml), the phases separated and the organic layer washed with water (50 ml), dried ($MgSO_4$), and the solvent removed. Sodium iodide (12.0 g, 80 mmol) dissolved in dry acetone (150 ml) was added and the mixture stirred under reflux (2h), before cooling to 20°C and pouring into 50% brine (150 ml), sodium thiosulphate (10 ml), and light petroleum (150 ml).The phases were separated and the aqueous phase washed with light petroleum (100 ml). The combined organic phases were dried ($MgSO_4$), the solvent removed and the residue chromatographed on silica (light petroleum as elutant) to give the *title iodide* (5.16 g, 93%) as a colourless oil. IR: 1655m, 1450s, 1380m, 1255s, 1170s, 895s cm^{-1}. PMR: (270 MHz) 5.11 (1H, t, J 7.3 Hz), 4.70 (2H, d, J 6.0 Hz), 3.12 (2H, t, J 7.3 Hz), 2.59 (2H, q, J 7.3 Hz), 2.02-1.96 (4H, m), 1.72 (3H, s), 1.62 (3H, s), 1.62-1.49 (2H, m). CMR: 146.0 (s), 138.2 (s), 123.2 (d), 110.0 (t), 39.3 (t), 37.4 (t), 32.5 (t), 25.8 (t), 22.6 (q), 16.4 (q), 16.3 (q).

(6E)-O-*Tetrahydropyranyl-7,11-dimethyl-dodeca-6,11-dien-2-yne-1-ol* (25).

To vigorously stirred O-tetrahydropyranyl propargyl alcohol (1.61 g, 11.5 mmol) in THF (40 ml) at 0°C was added Bu^nLi (2.5M in hexanes, 4.5 ml, 11.3 mmol) dropwise *via* syringe. After 20 min. (3E)-1-iodo-4,8-dimethyl-nona-3,8-diene (2.78 g, 10.0 mmol) in THF (10 ml) was added and the solution stirred under reflux (20h). A further 11 mmol of the lithium salt of O-tetrahydropyranyl propargyl alcohol was then added *via* cannula and refluxing continued for 5h. After cooling to 0°C water (1 ml) was added, and the mixture poured into brine (30 ml) and ether (50 ml).The phases were separated and the aqueous phase extracted with ether (2 x 20 ml). The combined organic layers were dried ($MgSO_4$), the solvent removed and the residue chromatographed on silica (ether:light petroleum 1:50 as elutant) to give a mixture of the title compound and the propargyl starting material. This was subjected to rotary evaporation (90°C, 0.01 mmHg, 20 min) and the residue Kugelrohr distilled (140°C, 0.01 mmHg) to give the *title alkyne* (2.29 g, 79%) as a colourless oil. IR: 1655m, 1450s cm^{-1}. PMR: 5.15 (1H, m), 4.80 (1H, m), 4.67 (2H, d, J 7.0 Hz), 4.27 and 4.18 (2H, ABq, J 15.1 Hz), 3.82 (1H, m), 3.51 (1H, m), 2.21 (8H, br s), 1.96 (4H, m), 1.90 (3H, s), 1.59 (3H, s), 1.51 (2H, m). CMR: 146.0 (s), 136.6 (s), 123.0 (d), 109.9 (t), 96.7 (d), 86.5 (s), 54.7 (t), 39.3 (t), 37.5 (t), 30.5 (t), 27.4 (t), 26.0 (t), 25.6 (t), 22.4 (q), 19.4 (t), 19.2 (t), 16.1 (q).

(6E)-7,11-*Dimethyl-dodeca-6,11-dien-2-yne-1-ol* (26).

To O-tetrahydropyranyl-7,11-Dimethyl-dodeca-6,11-dien-1-ol (0.040 g, 0.17 mmol) in methanol (5 ml) was added hydrochloric acid (2M, 1 drop) and the solution stirred for 2.5 h at 20°C. Triethylamine (1 ml) was added, and the solvent removed.The residue was dissolved in ethyl acetate (10 ml), washed with 50% brine (5 ml), dried ($MgSO_4$) and the solvent removed. The residue was chromatographed on silica (ethyl acetate:light petroleum 1:20 as elutant), and then Kugelrohr distilled (140°C, 0.01 mmHg) to give the *title alcohol* (0.028 g, 98%) as a colourless oil. IR: 3360br s, 1655m, 1460m, 1360m, 1140m, 1020s, 895s cm^{-1}. PMR (270 MHz): 5.17 (1H, m), 4.84 (2H, d, J 10.0Hz), 4.22 (2H, br s), 2.22 (4H, br s), 1.98 (4H, m), 1.85 (1H, br s, *OH*), 1.66 (3H, s), 1.61 (3h, s), 1.60-1.43 (2H, m). CMR 146.0 (s), 136.6 (s), 122.8 (d), 109.8 (t), 86.2 (s), 78.5 (s), 51.2 (t), 39.2 (t), 37.3 (t), 27.3 (t), 25.8 (t), 22.4 (q), 19.3 (t), 16.0 (q).

(2E, 5E)-6,10-*Dimethyl-2-(2'-hydroxyethylidene)-undeca-5,10-dienoic acid (28)*.

To *iso*-butyl magnesium chloride (14.0 ml of a 2.2M solution in ether, 29.7 mmol) and ether (10 ml) at 0°C was added titanocene dichloride (0.012 g, 0.05 mmol) and vigorous stirring continued for 15 min. 7, 11-Dimethyl-dodeca-6,11-dien-2-yn-1-ol (26) (0.100 g, 0.48 mmol) in ether (1.0 ml) was

then added and the solution stirred at 20°C for 4h. The bulk of the ether was removed *in vacuo*, and THF (50 ml) added. The solution was stirred under an atmosphere of cabon dioxide for 16h, before NH_4Claq (30 ml) and 1M HCl were added. The phases were separated and the aqueous phase extracted with ether (7 x 50 ml). The combined organic layers were dried ($MgSO_4$), the solvent removed, and the residue chromatographed (ethyl acetate:light petroleum 2:5 to 3:5 as elutant) to give the *title acid* as an orange oil (2.13 g, 65%). IR 3400br s, 1700s, 1655m, 1460s, 1280m, 1020m, 890m cm^{-1}. PMR: 7.7-6.4 (2H, br s), 6.96 (1H, t, J 6.1 Hz), 5.12 (1H, t, J 6.8 Hz), 4.68 (2H, d, J 11.0 Hz), 4.36 (2H, d, J 6.1 Hz), 2.31 (2H, m), 2.12 (2H, q, J 7.4 Hz), 1.98-1.93 (4H, m), 1.71 (3H, s), 1.58 (3H, s), 1.58-1.47 (2H, m). CMR: 172.5 (s), 146.0 (s), 142.8 (d), 136.8 (s), 132.5 (s), 123.1 (d), 109.9 (t), 59.6 (t), 39.3 (t), 37.5 (t), 27.4 (t), 26.0 (t,), 22.5 (q), 16.0 (q).

Methyl (2E, 5E)-6,10-*dimethyl*-2-(2'-*hydroxyethylidene*)-*undeca*-5,10-*dienoate (29)*

To acid (28) (1.433 g, 5.66 mmol) dissolved in benzene (10 ml) was added N, N'-tetramethylguanidine (0.78 ml, 6.23 mmol) and the solution stirred for 0.5 h at 20°C. MeI (0.42 ml, 6.79 mmol) was then added and stirring continued for 2 h. The mixture was filtered, the filtrate evaporated to dryness, and the residue chromatographed on silica gel (ether:light petroleum 1:9 to 1:4 as elutant) to give the *title ester* (1.16 g, 77%) as a colourless oil. IR: 3440br s, 1725vs, 1650m, 1440s, 1270s, 1170m, 1120m, 1025m, 890m, 750w cm^{-1}. PMR (270 MHz): 6.82 (1H, t, J 6.2 Hz), 5.10 (1H, t, J 7.2 Hz), 4.67 (2H, d, J 8.5 Hz), 4.32 (2H, d, J 6.2 Hz), 3.75(3H, s), 2.32 (2H, t, J 7.2 Hz), 2.10 (2H, m), 1.95-1.93 (5H, m), 1.70 (3H, s), 1.56 (3H, s), 1.50 (2H, m). CMR (68 MHz): 169.8 (s), 146.1 (s), 140.7 (d), 136.7 (s), 132.9 (s), 123.1 (d), 109.9 (t), 59.6 (t), 52.0 (q), 39.4 (t), 37.5 (t), 27.5(2 x t), 26.0 (t), 22.6 (q), 16.6 (q). m/z: (NH_3 C.I.): 284 ([M+NH_4]$^+$, 43%), 267 (100), 249 (21), 235 (17), 189 (22), 109 (11), 81 (14), 58 (27).

(2E, 6E)-3-*Hydoxymethyl*-7,11-*dimethyl*-*dodeca*-2,6,11-*trien*-1-*ol* (16A)

To ester (29) (0.923 g, 3.47 mmol) in THF (30 ml) at -75°C was added diisobutylaluminium hydride (11.8 ml of a 1M solution in hexanes) dropwise *via* syringe. The solution was allowed to warm slowly to 20°C over 2h, and then NH_4Claq (15 ml) added.The mixture was stirred until all the aluminium salts had precipitated, the phases separated, and the aqueous phase extracted with ether (4 x 20 ml). 2M HCl was added to the aqueous phase until all the aluminium salts had dissolved, followed by extracting with ether (3 x 20 ml). The combined organic layers were dried ($MgSO_4$), the solvent removed, and the residue chromatographed on silica gel (ethyl acetate:light petroleum 1:1 to 7:3 as elutant) and then Kugelrohr distilled (190°C, 0.01 mmHg) to give the *title diol* (0.723 g, 89%) as a colourless viscous oil with identical physical properties to those reported above.

Conversion of Diols (16A) and (16B) to Oxepanes (20A) and (20B)

(6E)(2SR, 3RS)-2-(4-Methyl-4-penten-1-yl)-6-(2-hydroxyethylidene)-2-methyl-oxepan-3-ol (20A).

(2E, 6E)-1-*Acetoxy*-3-*acetoxymethyl*-7,11-*dimethyl*-*dodeca*-2,6,11-*triene* (17A)

To diol (16A) (4.45 g, 18.6 mmol) and triethylamine (8.27 ml, 59.5 mmol) in dry dichloromethane was added acetyl chloride (3.58 ml, 50.3 mmol) dropwise *via* syringe, maintaining the temperature between -10 and -5°C. Stirring was continued for 15 min before pouring the reaction mixture into $NaHCO_3$aq (90 ml). The organic phase was separated, washed with brine (30 ml), dried ($MgSO_4$), the solvent removed and ethyl acetate (40 ml) added. The mixture was filtered and the residue from rotatory evaporation chromatographed on silica (ethyl acetate:light petroleum 1:19 as elutant) to give the *title diacetate* (17A) (5.44 g, 90%) as a colourless oil. Found: C, 70.7; H, 9.1. $C_{19}H_3O_4$ Requires C, 70.8; H, 9.4%. IR: 1750vs, 1655w, 1450m, 1370s, 1235vs, 1030s, 890m cm $^{-1}$. PMR: 5.64 (1H, t, J 6.9 Hz), 5.12 (1H, t, J 6.9 Hz), 4.69 (2H, d, J 10.5 Hz), 4.64 (2H, d, J 6.9 Hz), 4.55 (2H, s), 2.06-2.20 (4H, m), 2.09 (3H, s), 2.06 (3H, s), 2.00-1.93 (4H, br t, J 7.7 Hz), 1.71 (3H, s), 1.60 (3H, s), 1.57-1.47 (2H, br qn). CMR: 171.0 (2 x s), 145.82 (s), 139.7 (s), 136.4 (s), 123.1 (d), 122.5 (d), 109.9 (t), 67.1 (t), 60.5 (t), 39.3 (t), 37.5 (t), 28.8 (t), 26.9 (t), 26.0 (t), 22.3 (q), 20.8 (q), 15.9(q). m/z: 202 (M-2AcOH, 4%), 187 (9), 159 (8), 146 (18), 131 (27), 119 (23), 109 (32), 93 (37), 81 (100), 69 (23), 55 (39), 43 (67).

(2E)-1-*Acetoxy*-3-*acetoxymethyl*-6,7-*epoxy*-7,11-*dimethyl*-*dodeca*-2,11-*diene* (18A)

To diacetate (17A) (6.96 g, 21.6 mmol) in dry dichloromethane (115 ml) at -10°C was added mcpba (85% pure, 4.81 g, 23.7 mmol) and the mixture stirred for 1h at -10°C. The precipitate was removed by filtration and the filtrate washed with sodium sulphite solution (30 ml), $NaHCO_3$aq (60 ml), brine (50 ml), followed by drying ($MgSO_4$). The solvent was removed and the residue chromatographed on silica (ethyl acetate:light petroleum 1:9-1:1 as elutant), to give the *title epoxide* (5.53 g, 76%) as a pale yellow oil. IR: 1750vs, 1650w, 1450m, 1380s, 1235vs, 1030s cm^{-1}. PMR: 5.6 (1H, t, J 7.0 Hz), 4.69 & 4.66 (4H, overlapping doublets, J 13 and 7 Hz respectively), 4.57 (2H, s), 2.72 (1H, dd, J 7.1, 5.4 Hz), 2.39-2.22 (2H, m), 2.09 (3H, s), 2.05 (s, 3H), 2.01 (2H, br t, J 7.1 Hz), 1.71 (3H, s), 1.70-1.40 (6H, m), 1.26 (3H, s). CMR: 170.33 (s) 170.13 (s), 145.2 (s), 138.9 (s), 123.2 (d) 110.1 (t), 66.9 (t), 62.3 (d), 60.6 (s), 60.1 (t), 38.1 (t), 37.6 (t), 27.7 (t), 25.5 (t), 23.0 (t), 22.1 (q), 20.6 (q), 16.5 (q).

Also isolated were the diepoxide (22) (1.1 g, 15%) and starting material (17A) (0.62 g, 9%). (2E)-1-*Acetoxy*-3-*acetoxymethyl*-6,7-11,12-*diepoxy*-7,11-*dimethyl*-*dodeca*-2-*ene* (22).IR: 1750vs, 1450m, 1370s, 1235vs, 1030s cm $^{-1}$. PMR: 5.68 (1H, t, J 6.9 Hz), 4.66 (2H, d, J 6.9 Hz), 4.56 (2H, s), 2.74-2.69 (1H, ddd, J 7.2, 5.4, 2.8 Hz), 2.61 (1H, t, J 4 Hz), 2.57 (1H, dd, J 4.9, 1.7 Hz), 2.2-2.4 (2H, m), 2.09 (3H, s), 2.06 (3H, s), 1.75-1.42 (8H, m), 1.31 (3H, s), 1.26 (3H, d, J 2.0 Hz). CMR: 170.3 (s), 170.2 (s), 138.9 (s), 123.3 (d), 66.9 (t), 62.3 (d), 60.5 (s), 60.1 (t), 56.4 (s) 53.6 (t), 53.5 (t), 38.4 (t), 38.3 (t), 36.6 (t), 36.5 (t), 27.6 (t), 25.5 (t), 20.84 (q), 20.77 (q) 20.58 (t), 20.55 (t), 16.5 (q).

(2E)-1-*Hydroxy*-3-*hydroxymethyl*-6,7-*epoxy*-7,11-*dimethyl*-*dodeca*-2,11-*diene* (19A)

To epoxydiacetate (18A) (5.35 g, 15.8 mmol) in methanol (85 ml) at -5°C was added potassium carbonate (4.46 g, 32.4 mmol). After 40 min the solid was filtered off and the residue from rotatory evaporation of the filtrate partitioned between water (25 ml) and ether (65 ml). The aqueous layer was extracted with dichloromethane (5 x 60 ml), the combined extracts dried ($MgSO_4$) and the solvent removed to give crude epoxydiol (19A) (4.02 g, 100%).

This material could be chromatographed on silica (ethyl acetate as elutant) to afford a colourless oil. IR: 3390br s, 3420br s, 1655m, 1450m, 1380m, 1010br m, 890m cm^{-1}. PMR: 5.69 (1H, t, J 6.8 Hz), 4.69 (2H, d, J 16.2 Hz), 4.18 (2H, d, J 6.8 Hz), 4.04 (2H, s), 3.87 (1H, br s), 3.77 (1H, br s), 2.74 (1H, dd, J 7.8, 4.7 Hz), 2.18-2.35 (2H, m), 2.00 (2H, t, J 7.1 Hz) 1.70 (3H, s), 1.62-1.37 (6H, m), 1.26 (3H, s). CMR: 145.3 (s) 141.1 (s), 125.6 (d), 110.2 (t), 66.0 (t), 63.3 (d), 61.5 (s), 58.4 (t), 38.2 (t), 37.7 (t), 27.7 (t), 25.1 (t), 23.1 (t), 22.2 (q), 16.6 (q), 22.2 (q).

Tin tetrachloride (1.90 ml, 16.3 mmol) was added dropwise *via* syringe to THF (200 ml) at -20°C with vigorous stirring. The mixture was warmed to 0°C and epoxy-diol (19A) (3.95 g, 15.5 mmol) in THF (20 ml) added dropwise over 40 min. The reaction mixture was warmed to 20°C, stirred for 0.5h, and poured into $NaHCO_3$aq (100 ml). The phases were separated and the aqueous phase extracted with ether (3 x 100 ml). The combined organic layers were dried ($MgSO_4$), the solvent removed and the residue chromatographed on silica (ethyl acetate:light petroleum 4:1 as elutant) to give a yellow oil which solidified on standing at 4°C. Recrystallisation afforded the *title oxepane* as white crystals (2.5 g, 64%) m.p. 71.5-72.5°C. Found : C, 70.7; H, 10.3. $C_{15}H_{26}O_3$ Requires C, 70.8; H, 10.3%. IR (CCl_4): 3390br, 1655w, 1450m, 1380m, 1120s, 1070s, 1030m, 895m cm^{-1}. PMR: 5.40 (1H, t, J 6.5 Hz), 4.69 (2H, d, J 10.1 Hz), 4.18-4.07 (2H, m), 4.09 (2H, s), 3.53 (1H, dd, J 8.2, 3.1 Hz), 3.00 (1H, br s), 2.85 (1H, br s), 2.48 (1H, ddd, J 15, 7.6, 3.6 Hz), 2.22-2.12 (1H, m), 2.33-1.97 (2H, m), 1.87-1.71 (2H, m), 1.71(3H, s), 1.60-1.40 (4H, m), 1.15 (3H, s) CMR: 145.7 (s), 143.0 (s), 123.6 (d), 110.0 (t), 80.1 (s), 76.6 (d), 69.0 (t), 58.5 (t) 38.3 (t), 37.9 (t), 31.4 (t), 23.7 (t), 22.3 (q), 21.3 (t), 18.3 (q). m/z: 154 (4%), 136 (9), 121 (16), 109 (74), 95 (38), 81 (51), 68 (100), 55 (61), 43 (67).

(6E)(2SR, 3RS)-2-(5-Hexenyl)-6-(2-hydroxyethylidene)- 2-methyl-oxepan-3-ol (20B)

Prepared in a way similar to above with the following intermediates (all colourless oils) and yields, those of (18B), and (19B) referring to crude material used in the next step.

(2E, 6E)-1-*Acetoxy*-3-*acetoxymethyl*-*trideca*-2,6,12-*triene (17B)* (94%)

IR: 1740, 1225 cm^{-1}. PMR: 5.80 (1H, ddt, J 17, 10, 7 Hz), 5.62 (1H, t, J 7 Hz), 5.10 (1H, t, J 6 Hz), 4.99 (1H, d, J 17 Hz), 4.93 (1H, d, J 10 Hz), 4.64 (2H, d, J 7 Hz), 4.54 (2H, s), 2.00-2.20 (8H, m), 2.08 (3H, s), 2.06 (3H, s), 1.97 (2H, t, J 7 Hz), 1.58 (3H, s),1.37 (4H, m). CMR: 170.6 (s), 170.3 (s), 139.6 (s), 138.9 (d), 136.5 (s), 123.0 (d), 122.5 (d), 114.2 (t), 67.1 (t), 60.5 (t), 39.5 (t), 33.6 (t), 28.7 (t), 28.6 (t), 27.4 (t), 26.9 (t), 20.8 (2 x q), 15.9 (q).

(2E)-*1-Acetoxy-3-acetoxymethyl-6,7-epoxy-7-methyl-2,12-tridecadiene (18B)* (100%) IR: 1745, 1640w, 1230, 1030 cm^{-1}. PMR: 5.68 (1H, ddt, J 10, 17, 7 Hz), 5.56 (1H, t, J 7 Hz), 4.88 (1H, d, J 17 Hz), 4.83 (1H, d, J 10 Hz), 4.55 (2H, d, J 7 Hz), 4.45 (2H, s), 2.58 (1H, t, J 6 Hz), 2.19 (2H, m), 1.9-2.0 (2H, m), 1.97 (3H, s), 1.94 (3H, s), 1.4-1.6 (4H, m), 1.29 (4H, m), 1.13 (3H, s). CMR: 170.3 (s), 170.1 (s), 138.8 (s), 138.4 (d), 123.1 (d), 114.3 (t), 66.8 (t), 62.3 (d), 60.6 (s), 60.0 (t), 38.3 (t), 33.4 (t), 28.8 (t), 27.6 (t), 25.3 (t), 24.4 (t), 20.6 (2 x q), 16.4 (q).

(2E)-1-*Hydroxy-3-hydroxymethyl-6,7-epoxy-7-methyl-2,12-tridecadiene (19B)* (100%). IR: 3460br, 1640w, 1460, 1000, 910 cm^{-1}. PMR: 5.79 (1H, ddt, J 10, 17, 7 Hz), 5.70 (1H, t, J 7Hz), 4.99 (1H, d, J 17 Hz), 4.94 (1H, d, J 10 Hz), 4.18 (2H, d, J 7 Hz), 4.05 (2H, s), 2.72 (1H, dd, J 5, 8 Hz), 2.28 (2H, m), 2.05 (2H, m), 1.73 (1H, m), 1.58 (2H, m), 1.39 (5H, m), 1.24 (3H, s). CMR: 141.2 (s), 138.6 (d), 125.6 (d), 114.6 (t), 66.1 (t), 63.3 (d), 61.6 (s), 58.5 (t), 38.5 (t), 33.6 (t), 28.9 (t), 27.7 (t), 25.1 (t), 24.6 (t), 16.6 (q).

The *title oxepane (20B)* (65%) was obtained as white crystals m.p. 38.5-39.5°C (from hexane-ether) (Found: C, 70.7; H, 10.4. $C_{15}H_{26}O_3$ requires C, 70.8; H, 10.3%). IR: 3370br, 1640w, 1440 cm^{-1}. PMR: 5.80 (1H, ddt, J 17, 10, 7 Hz), 5.41 (1H, t, J 7 Hz), 5.00 (1H, d, J 17 Hz), 4.94 (1H, d, J 10 Hz), 4.05-4.15 (4H, m), 3.52 (1H, d, J 8 Hz), 3.27 (1H, br s, OH), 3.02 (1H, br s, OH), 2.48 (1H, ddd, J 3, 8, 15 Hz), 2.17 (1H, ddd, J 3, 9, 15 Hz), 2.03-2.10 (2H, m), 1.70-1.85 (2H, m), 1.50-1.63 (2H, m), 1.2-1.45 (4H, m), 1.14 (3H, s). CMR: 142.9 (s), 138.9 (d), 123.6 (d), 114.4 (t), 80.2 (s), 76.6 (d), 69.0 (t), 58.4 (t), 38.2 (t), 33.7 (t), 31.4 (t), 29.6 (t), 23.7 (t), 22.7 (t), 18.3 (q). m/z: 171 (0.8%), 153 (2.8), 127 (8.7), 110 (46), 95 (16), 82 (46), 81 (32), 68 (100), 43 (100).

Conversion of Oxepane (20A) into (±)-Zoapatanol

(6E)(2SR, 3RS)-3-*Dimethyl-t-butyl-silyloxy-6-(2-dimethyl-t-butyl-silyloxyethylidene)-2-(4-methyl-4-penten-1-yl)-2-methyloxepane* (31)

Dimethyl-t-butylsilyltrifluoromethanesulphonate (2.08 ml, 9.06 mmol) was added dropwise to a stirred solution of the diol (20A) (1.00 g, 3.94 mmol) and 2, 6-dimethylpyridine (1.43 ml, 12.3 mmol) in dry dichloromethane (35 ml) at -20°C under nitrogen. After 20 min the mixture was poured into $NaHCO_3$ (90 ml), the phases separated and the aqueous phase extracted with dichloromethane (3 x 20 ml). The combined organic phases were washed with cold 0.3M HCl (20 ml), brine (20 ml), and then dried ($MgSO_4$). The solvent was removed and the residue chromatographed on silica (ethyl acetate:light petroleum 1:25 as elutant) to give the *protected diol (31)* (1.92 g, 100%) as a colourless oil. Found: M^+ 482.3576, $C_{27}H_{54}O_3Si_2$ requires 482.3611. IR: 1655w, 1475m, 1260s, 1080br s, 840s, 780s cm^{-1}. PMR: 5.35 (1H, t, J 6.2 Hz), 4.69 (2H, d, J 5.7 Hz), 4.21 (2H, d, J 6.2 Hz), 4.13 and 4.04 (2H, ABq, J 14.2 Hz), 3.55 (1H, dd, J 9.9, 3.4 Hz), 2.47 (1h, ddd, J 14, 7.6, 2.0 Hz), 2.10 (1h, ddd, J 12, 2, 2 Hz), 1.96-2.04 (2H, m), 1.83-1.62 (2H, m), 1.71 (3H, s), 1.62-1.25 (4H, m), 1.11 (3H, s), 0.91 (9H, s,), 0.89 (9H, s), 0.07-0.05 (12H, m). CMR: 146.0 (s), 141.5 (s), 124.0 (d), 110.1 (t), 80.4 (s), 78.3 (d), 69.0 (t), 59.7 (t), 40.0 (t), 38.5 (t), 32.0 (t), 26.12 (q), 26.01 (q), 24.3 (t), 22.4 (q), 21.3 (t), 18.4 (s), 18.1 (s), -3.87 (q), -4.8 (q*, Δδ 0.25), -4.96 (q), -4.98 (q). m/z: 482 (M^+, 0.4%), 467 (0.1), 425 (4), 350 (9), 299 (50), 293 (15), 224 (37), 211 (14), 201 (11), 189 (26), 167 (70), 147 (100), 109 (9.1), 93 (71.0), 75 (7.5).

(6E)(2SR, 3RS)-3-*Dimethyl-t-butyl-silyloxy-6-(2-dimethyl-t-butyl-silyloxyethylidene)-2-(5-hydroxy-4-methylpentyl)-2-methyloxepane (38)*

To a solution of the protected diol (31) (0.900 g, 1.87 mmol) in THF (10 ml) at room temperature was added a solution of 9-borabicyclononane (0.250 g, 2.06 mmol) in THF (10 ml) dropwise *via* syringe over 15 min. The reaction mixture was stirred (2.5 h), cooled to 10°C, and 3M NaOHaq (0.72 ml of 3M aqueous solution, 2.15 mmol) added followed by H_2O_2 (0.72 ml of 30 wt% solution, 7.05 mmol), keeping the temperature between 25°C and 30°C. The reaction mixture was stirred vigorously for 30 min at 20°C, and then ether (30 ml) and water (10 ml) added. The phases were separated and the aqueous phase extracted with ether (2 x 10 ml), and the combined organic phases washed with brine (20 ml) and then dried ($MgSO_4$). After removal of the solvent the residue was chromatographed on silica gel (ethyl acetate:light petroleum 1:9-1:4 as elutant) to give the *title alcohol* (0.900 g, 96%) as a colourless oil. IR: 3400br s, 1460m, 1250m, 1100br s, 840s, 670m cm^{-1}. PMR: 5.33 (1H, t, J 6.2 Hz), 4.12 and 4.01 (2H, ABq, J 14.1 Hz), 3.53 (1H, ddd, J 9.6, 3.2, 1.4 Hz), 3.47 (1H, q, J 5.8 Hz) and 3.38 (1H, ddd, J 10.4, 6.4, 2.9 Hz), 2.43 (1H, ddd, J 14.6, 7.6, 2.1 Hz) and 2.07 (1H, br t, J 11.8 Hz), 1.87-1.70 (2H, m), 1.70-1.55 (2H, m), 1.55-1.43 (2H, m), 1.43-1.28 (4H, m), 1.09 (3H, s), 0.92 (3H, m), 0.88 (9H, s), 0.86 (9H, s), 0.04 (12H, m). CMR 141.5 (s), 124.0 (d), 80.5 (s), 78.3 (d), 69.0 (t), 68.45 (t*, Δδ 0.16), 59.7 (t), 40.67 (t*), 36.09 (d*), 34.07 (t*), 31.98 (t*), 26.11 (q,), 26.02 (q), 24.3 (t), 20.66 (t*), 18.6 (s), 18.2 (s), 16.81 (q*), 16.71 (q), -3.9 (q), -4.8 (q*, Δδ 0.25).

(6E)(2SR,3RS)-3-*Dimethyl-t-butyl-silyloxy-6-(2-dimethyl-t-butyl-silyloxyethylidene)-2-(4-methyl-5-oxo-pentyl)-2-methyloxepane. (39).*

To a stirred solution of oxalyl chloride (0.072 g, 0.56 mmol) in dichloromethane (1 ml) at -80°C was added DMSO (0.092 g, 1.18 mmol) in dichloromethane (0.5 ml) dropwise *via* syringe over 10 min. After 20 min the alcohol (38) (0.242 g, 0.49 mmol) in dichloromethane (1 ml) was added *via* syringe over 10 min, and 30 min later triethylamine (0.34 ml, 2.45 mmol) was added. The reaction mixture was allowed to warm to -20°C (1 h) and then quenched by pouring into 0.3M HClaq (10 ml). The phases were separated and the aqueous phase extracted with dichloromethane (2 x 15 ml).The combined organic layers were washed with $NaHCO_3$ (10 ml), brine (10 ml), dried ($MgSO_4$), and the solvent removed. The residue was chromatographed on silica (ethyl acetate:light petroleum 1:19 as elutant) to give the *title aldehyde* (39) (0.212 g, 88%) as a colourless oil. IR: 1735m, 1470m, 1260s, 1095br s, 840s, 780s cm^{-1}. PMR: 9.62 (1H, dd, J 4.0, 1.8 Hz), 5.34 (1H, t, J 6.2 Hz), 4.20 (2H, d, J 6.2 Hz), 4.12 and 4.02 (2H, ABq, J 14.3 Hz), 3.52 (1H, dd, J 9.9, 3.4 Hz), 2.43 (1H, m), 2.07 (1H, m), 2.40-2.24 (1H, m), 1.77 (1H, tt, J 10.7, 3.2 Hz), 1.75-1.20 (7H, m), 1.26 (3H, s), 1.09 (3H, s), 0.87 (18H, m), 0.05 (12H, m). CMR: 204.8 (d), 141.5 (s), 124.0 (d), 80.3 (s), 78.3 (d), 69.1 (t), 59.7 (t), 46.6 (d), 40.525 (t*), 32.1 (t), 31.41 (t*, Δδ 0.12), 26.10 (q), 25.99 (q), 24.3 (t), 20.7 (t), 18.45 (s), 18.10 (s), 16.470 (q*), 13.5 (q*, Δδ 0.15), -3.9 (q), -4.71 (q*, Δδ 0.25). m/z 441 (M^+-Bu^t, 1.3%), 366 (0.9), 309 (1), 299 (2), 224 (2), 211 (3), 199 (3), 189 (3), 171 (2), 167 (13), 147 (20), 109 (3), 93 (100), 75 (17).

(6E)(2SR,3RS)-3-*Dimethyl-t-butyl-silyloxy-6-(2-dimethyl-t-butyl-silyloxyethylidene)-2-(4-methyl-5,6-epoxy-hexyl)-2-methyloxepane* (32)

Sodium hydride (0.131 g, 60% dispersion in oil, 3.28 mmol) was washed with light petroleum (3 x 3 ml), and the last traces of solvent removed in a stream of argon. DMSO (5.0 ml) was added and the mixture heated with stirring at 60°C (15 min), and at 75°C (2 min). The dark green solution was cooled to 20°C. To an aliquot of the above solution (1.80 ml) was added THF and the solution cooled to -5°C. Trimethylsulphonium iodide (0.253 g, 1.24 mmol) in DMSO (1.20 ml) was added over 2 min maintaining the temperature between -5°C and 0°C. After stirring for a futher 5 min the aldehyde (39) (0.294 g, 0.59 mmol) in THF (2 ml) was added over 2 min. The reaction mixture was stirred at 0°C for 2h, then at 20°C for 2h. NH_4Claq (10 ml) was added, the phases separated and the aqueous phase extracted with ether (4 x 15 ml).The combined organic layers were washed with brine (15 ml), dried ($MgSO_4$), the solvent removed, and the residue chromatographed on silica gel (ethyl acetate:light petroleum 1:9 as elutant) to give the *title epoxide* (32) (0.278 g, 92%) as a colourless oil. (Found: M^+ 512.3727. $C_{28}H_{56}O_4Si_2$ requires 512.3717). IR (CCl_4): 1470m, 1260s, 1100br s, 840s, 780s cm^{-1}. PMR: 5.32 (1H, t, J 6.2 Hz), 4.19 (2H, d, J 6.2 Hz), 4.11 and 4.01 (2H, ABq, J 14.3 Hz), 3.51 (1H, dd, J 9.8, 3.4 Hz), 2.75-2.72 (0.5H, m) and 2.52-2.49 (0.5H, m), 2.72-2.63 (1H, m), 2.49-2.38 (1H m), 2.49-2.38 (1H, m), 2.13-2.02 (1H, br t, J 12Hz), 1.83-1.71 (1H, m), 1.71-1.55 (1H, m), 1.55-1.18 (7H, m), 1.09 (3H, s), 1.01 (1.5H, dd, J 6.1, 3.2 Hz) and 0.90 (1.5H, 4 lines), 0.45 (12H, m). CMR: 141.48 (s*), 123.99 (d*), 80.41 (s*), 78.22 (d*), 69.03 (t), 59.69 (t), 57 (d*), 46.89 (t*, Δδ 0.11), 45.57 (t*, Δδ 0.19), 40.65 (t*), 36.4 (d*, Δδ 0.11), 36.16 (d*, Δδ 0.14), 35.24 (t*, Δδ 0.16), 34.37 (t*, Δδ 0.25), 31.94 (t*), 26.09 (q), 25.98 (q), 24.24 (t), 20.72 (t*), 20.56 (t*), 18.44 (s), 18.08 (s), [17.25, 17.00, 16.75, 16.65, 16.62, 16.57, 15.78, 15.54 (q from 2 methyl groups in 4 diastereoisomers

due to uncontrolled stereochemistry at C-4' and 5' relative to each other and the oxepane ring)].-3.85 (q), -4.85 (q*, Δδ 0.25)

(6E)(2SR,3RS)-3-*Dimethyl-t-butyl-silyloxy-6-(2-t-butyldimethylsiloxy-ethylidene)-2-(5-hydroxy-4,8-dimethyl-non-7-enyl)-2-methyloxepane (33)*

To CuI (0.047 g, 0.25 mmol) in ether at -20°C was added 1,1-dimethylvinyl lithium (3.02 ml of a 0.19 M solution in ether, 0.57 mmol) dropwise over 2 min to give a pale yellow solution. Stirring was continued for 15 min before the epoxide (32) (0.042 g, 0.082 mmol) in ether (1.5 ml) was added. The reaction mixture was warmed to -5°C and after stirring for a further 3 h NH_4Claq (5 ml) added rapidly. The phases were separated and the aqueous phase extracted with ether (3 x 10 ml), the combined organic layers washed with brine (10 ml), followed by drying ($MgSO_4$) and removal of the solvent. Chromatography on silica (ether:light petroleum 1:4 as elutant) afforded the *title alcohol* (0.030 g, 64%) as a colourless oil. Found: M^+-C_4H_8, 511.3654. $C_{28}H_{56}O_4Si_2$ requires 511.3638. IR: 3480br m, 1470m, 1260s, 1100br s, 840s, 780s cm^{-1}. PMR: 5.34 (1H, t, J 5.8 Hz), 5.18 (1H, dt, J 6.8, 1.3 Hz), 4.21 (2H, d, J 6.2 Hz), 4.13 and 4.03 (2H, ABq, J 14.2 Hz), 3.55 (1H, ddd, J 9.7, 3.0, 1.4 Hz), 3.52-3.48 (0.5H, 5 lines) and 3.47-3.38 (0.5H, m), 2.46 (1H, ddd, J 14.7, 7.8, 2.4 Hz), 2.25-2.05 (3H, m), 1.74 (3H, s), 1.65 (3H, s), 1.10 (3H, s) 1.83-1.05 (9H, m), 0.90 (21H, m), 0.05 (12H, s). CMR (68 MHz): 141.4 (s), 135.6 (s*), 123.9 (d*), 120.8 (d*, Δδ 0.11), 80.4 (d), 78.0 (s*), 75.3 (t*, 2 pairs (Δδ 0.2) of signals separated by 0.6 ppm due to C-5'), 69.0 (t), 59.6 (t), 40.5 (t,), 37.9 (t*), 33.5 (t*), 33.3 (t*, 2 pairs of t seperated by 1.4 ppm), 31.8 (t*), 26.0 (q), 25.9 (q), 24.1 (t), 20.9 (t*), 18.4 (s*), 18.0 (q*), 16.6 (q*), 15.4 (q*), 13.9 (q*), -4.0 (q), -4.9 (q*). Complexity of signals due to uncontrolled stereochemistry at C-4 and 5 in the side chain relative to each other and the oxepane ring. m/z 511 (M-C_4H_8, 1%), 367 (7), 299 (14), 224 (14), 167 (25), 147 (33), 93 (100), 73 (50).

(6E)(2SR,3RS)-3-*t-Butyldimethylsiloxy-(2-t-butyldimethylsiloxy-ethylidene)-2-(4, 8-dimethyl-5-oxo-non-7-enyl)-2-methyloxepane (40).*

To an aliquot (0.5 ml) of a solution of oxalyl chloride (0.1 ml) in dichloromethane (10 ml) at -75°C was added an aliquot (0.4 ml) of a solution of DMSO (0.2 ml) in dichloromethane (10 ml), dropwise *via* syringe. Stirring was continued for 10 min, and then the alcohol (33) (0.027 g, 0.048 mmol) in dichloromethane (0.5 ml) added dropwise over 5 min. After stirring for a further 35 min triethylamine (0.024 ml, 0.171 mmol) was added and the mixture allowed to warm to -20°C over 2h. NH_4Claq (5 ml) and ether (5 ml) was added, the phases separated and the aqueous phase extracted with ether (3 x 5 ml). The combined organic layers were washed with water (5 ml), dried ($MgSO_4$), and the solvent removed. Chromatography on silica gel (ether:light petroleum 1:9 as elutant) gave the *title ketone* (0.025 g, 93%) as a colourless oil. Found: M^+, 566.4134. $C_{32}H_{62}O_4Si_2$ Requires 566.4186. IR: 1710s, 1460m, 1250s, 1080s, 830s, 770s, 730s cm^{-1}. PMR (270 MHz): 5.36-5.25 (2H, m), 4.19 (2H, d, J 6 Hz), 4.10 and 4.01 (2H, ABq, J 14.4 Hz), 3.50 (1H, dd, J 9.5, 3.2, 1.0 Hz), 3.13 (2H, dd, J 7.1, 0.7 Hz), 2.57 (1H, sextet, J 6.3 Hz), 2.44 (1H, ddd, J 15.4, 7.6, 5.6 Hz), 2.07 (1H, br t, J 12 Hz), 1.1-1.8 (8H, m), 1.74 (3H, s), 1.62 (3H, s), 1.07 (3H, s), 1.06 (3H, dd, J 4.9, 1.5 Hz), 0.89 (9H, s), 0.87 (9H, s), 0.05 (12H, m). CMR (68 MHz): 213.3 (s*), 141.4 (s), 135.5 (s), 124.0 (d), 116.3 (d), 80.5 (s), 78.1 (t*), 69.1 (t), 59.7 (t), 46.0 (d), 41.2 (2x d), 40.6 (t), 33.7 (t), 34.0, 31.9 (t), 26.1 (t), 25.9 (t), 24.2 (t), 21.1 (t*), 18.5 (s*), 18.2 (q), 18.1 (q), 16.6 (q), 16.4 (q), -3.9 (q), -4.85 (q* Δδ 0.25). m/z 566 (M^+, 1%), 551 (1), 509 (19), 434 (8), 365 (17), 299 (20), 224 (16), 211, (15), 167 (27), 147 (39), 93 (100), 73 (56).

(±)-*Zoapatanol.*

A solution of ketone (40) (0.097 g, 0.17 mmol) in acetonitrile (3.8 ml) and 40% hydroflouric acid (1.3 ml) was stirred at room temperature for 1h. The mixture was poured into $NaHCO_3$ (25 ml) and extracted into ether (4 x 20 ml). The combined extracts were washed with brine (20 ml), dried ($MgSO_4$), and the solvent removed. Chromatography on silica gel (ether as elutant) afforded the *title diol* (0.045 g, 78%) as a colourless oil. Found: M^+ 338.2441. $C_{20}H_{34}O_4$ Requires 338.2457. IR: 3400bs, 1710s, 1440m, 1030s cm^{-1}. PMR (270 MHz): 5.43 (1H, t, J 6.8 Hz, =C*H*CH_2OH), 5.26 (1H, t with fine splitting, J 7.1, 1.5Hz, Me_2C=C*H*), 4.20 (2H, d, J 6.8 Hz, CH_2OH), 4.12 (2H, br s, CH_2O), 3.52 (1H, br dd, J 8, 3Hz, C*H*OH), 3.12 (2H, br d, J 7.1Hz, CH_2CO), 2.56 (1H, sextet, J 6.6 Hz, C*H*CO), 2.45 (1H, m, *H*CHC=), 2.3-2.1 (3H, m, HC*H*C= + 2 x O*H*), 1.73 (3H, d, J 1.5 Hz, *Me*C=), 1.88-1.69 (2H, m, CH_2CHOH), 1.68-1.46 (4H, m, CH_2CHC=O+CH_2C-O), 1.60 (3H, br s, *Me*C=), 1.38-1.20 (2H, m, CH_2CH_2CHC-O), 1.12 and 1.11 (1.5H each, *Me*C-O), 1.07 and 1.04 (1.5H each, *Me*CHC-O). CMR (68 MHz), 213.7 (s, C=O), 143.2 (s*, Δδ 0.04, CH_2C=), 135.6 (s, Me_2C=), 123.5 (d*, Δδ 0.02, =*C*HCH$_2$OH), 116.1 (d, Me_2C=*C*H), 80.0 (s, *C*-O), 76.5 (d*, Δδ 0.2, *C*HOH), 69.3 (t*, Δδ 0.01, *C*H$_2$O), 58.7 (t, *C*H$_2$OH), 45.9 (t*, Δδ 0.01, *C*HC=O), 41.0 (t*, Δδ 0.14, *C*H$_2$C=O), 38.3 (t*, Δδ 0.12, *C*H$_2$CHC=O), 33.6 (t, *C*H$_2$C-O), 31.7 (t, *C*H$_2$CHOH), 25.9 (q, *Me*C-O), 23.6 (t*, Δδ 0.07, *C*H$_2$C=), 21.1 (t*, Δδ 0.05, *C*H$_2$CH$_2$C-O), 18.6 (q, *Me*C-O), 18.2 (q*, Δδ 0.04, *Me*C=), 16.8 (q, *Me*CHC-O). m/z 338 (M^+, 1%), 320 (M-H_2O, 8), 267 (11), 251 (M-C_5H_9-H_2O, 26), 211 (McLafferty rearangement, 74), 171 (M-side chain, 14), 141 (80), 113 (100), 81 (35), 68 (31).

Conversion of the oxepane (20B) into demethyl-ORF-13811 (10)

(1RS,4SR,5RS)-4-*(5-Hexenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-ethanal (18).*

To oxepane (20B) (2.00 g, 7.9 mmol) in dichloromethane (200 ml) was added MnO_2 (27 g) at room temperature. After 5 min the MnO_2 was removed by filtration through a pad of silica and washed with ether (1 l). The combined filtrate was concentrated & chromatographed on silica (ether : light petroleum, 1:1) to afford the *title aldehyde* (34) (1.42 g, 72%) as a colourless oil (Found: M^+ 252.175, $C_{15}H_{24}O_3$ requires M^+ 252.173). IR: 1730, 1640w, 1070 cm^{-1}. PMR: 9.81 (1H, t, J 2.5 Hz), 5.79 (1H, ddt, J 17, 10, 7 Hz), 4.99 (1H, d, J 17 Hz), 4.93 (1H, d, J 10 Hz), 3.86 (1H, d, J 7 Hz), 3.73 (1H, d, J 11 Hz), 3.34 (1H, dd, J 11, 1 Hz), 2.62 (2H, m), 2.03-2.20 (4H, m), 1.85 (1H, m), 1.67 (1H, m), 1.2-1.45 (6H, m), 1.33 (3H, s). CMR: 199.7 (d), 138.6 (d), 114.5 (t), 81.1 (d), 79.3 (s), 75.2 (s), 69.7 (t), 48.3 (t), 38.6 (t), 33.5 (t), 31.9 (t), 29.5 (t), 25.0 (t), 22.5 (t), 18.2 (q). m/z 252 (M+, 0.1%), 234 (0.2), 209 (0.4), 197 (0.7), 169 (10), 141 (12), 127 (29), 113 (10), 109 (22), 83 (33), 81 (34), 69 (58), 55 (34), 43 (100), 41 (42).

(1RS,4SR,5RS)-4-*(5-Hexenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-ethanoic Acid (35).*

To aldehyde (34) (1.02 g, 4.04 mmol) in DMF (20 ml) was added pyridinium dichromate (4.2 g, 12 mmol) at room temperature. After stirring for 20 h the reaction mixture was poured into water (50 ml) and the products extracted into ether (4 x 100 ml). The combined organic phases were washed with brine (30 ml), dried ($MgSO_4$), solvent removed, and the residue chromatographed (0.25% acetic acid in ether as elutant) to afford the *title acid* (35) (1.05 g, 97%) as white crystals m.p. 34-37°C (from light petroleum) (Found: C, 67.1; H, 9.1%; M^+ 268.165. $C_{15}H_{24}O_4$ requires C, 67.1; H, 9.0%, M^+ 268.167). IR: 3100br, 1740, 1715, 1640w cm^{-1}. PMR: 10.6 (1H, br s, CO_2H), 5.78 (1H, ddt, J 10, 17, 7 Hz), 4.99 (1H, d, J 17 Hz), 4.94 (1H, d, J 7 Hz), 3.89 (1H, d, J 7 Hz), 3.79 (1H, d, J 11 Hz), 3.49 (1H, d, J 11 Hz), 2.64 (2H, ABq, J 15 Hz), 2.05-2.2 (4H, m), 1.80 (2H, m), 1.2-1.45 (6H, m), 1.33 (3H, s). CMR: 174.2 (s), 138.7 (d), 114.5 (t), 81.4 (d), 79.3 (s), 75.6 (s), 69.5 (t), 40.2 (t), 38.5 (t), 33.5 (t), 31.5 (t), 29.5 (t), 25.0 (t), 22.6 (t), 18.3 (q). m/z 269 (1.3%), 268 (M^+, 2.7), 213 (3.2), 208 (1.7), 185 (16), 143 (20), 129 (9), 127 (12), 109 (12), 97 (11), 96 (14), 68 (26), 55 (30), 43 (100), 41 (52).

(1RS,4SR,5RS)-4-*(5,6-Epoxyhexyl)-4-methyl-3,8-dioxabicyclo [3.2.1]octane-1-ethanoic Acid (36)*

Alkene (35) (0.34 g, 1.3 mmol) was dissolved in dichloromethane (8 ml) and mcpba (0.4 g, 80% pure) added. After 4 h at room temperature the volatiles were removed and the residue chromatographed on silica (0.5% AcOH in ether : light petroleum 1:1) to afford the *title epoxide* (25) (0.36 g, 99%) as a viscous oil. IR:. 3150br, 1730, 1200, 1055, 825 cm^{-1}. PMR: 10.2 (1H, br s, CO_2H), 3.89 (1H, d, J 7 Hz), 3.79 (1H, d, J 11 Hz), 3.49 (1H, d, J 11 Hz), 2.77 (1H, m), 2.93 (1H, m), 2.63 (2H, ABq, J 15 Hz), 2.49 (1H, dd, J 3, 5 Hz), 2.1 (2H, m), 1.8 (2H, m), 1.25-1.6 (8H, m), 1.33 (3H, s). CMR: 173.5 (s), 81.4 (d), 79.3 (s), 75.3 (s), 69.5 (t), 52.3 (d), 46.9 (t*), 40.1 (t), 40.1 (t), 38.5 (t), 32.1 (t*), 31.4 (t), 26.5 (t*), 24.9 (t), 22.8 (t*), 18.2 (q).

(1RS,4SR,5RS)-4-*(8-Methyl-5-hydroxy-7-nonenyl)-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-ethanoic Acid (10) (Demethyl-ORF13811).*

A solution of 1-bromomagnesio-2-methyl-1-propene was prepared from the bromide and excess magnesium in THF. The magnesium bromide was

allowed to crystallise out at 0°C and the supernatent solution transferred to another flask. The concentration of the Grignard reagent was estimated by total base titration of an aliquot. After cooling to -70°C and allowing more magnesium bromide to crystallise out 11 ml (10 mmol) of this solution was added to copper (I) iodide (0.5 g) in THF (20 ml) at -70°C. The mixture was allowed to warm to -40°C before the epoxide (36) (0.73 g, 2.6 mmol) in THF (10 ml) was added over 20 min. After stirring for a further 1 h at this temperature the reaction was quenched by pouring into NH_4Claq (100 ml) and the products extracted into ether (5 x 100 ml). The residue from the dried ($MgSO_4$) solution was subjected to careful chromatography (1% acetic acid in 1 : 1 ether : light petroleum to ether) to afford the *title compound* (10) (0.63 g, 72%) as white crystals. Recrystallisation from ether-light petroleum gave a single diastereoisomer m.p. 87-89°C. Concentration of the residues gave white crystals m.p. 44-63°C shown to be >90% the other diastereoisomer at C-5' by ^{13}C n.m.r. (Found: C, 67.0; H, 9.45%; M^+ 340.227. $C_{19}H_{32}O_5$ requires: C, 67.0; H, 9.45%; M^+ 340.225). IR: 3400br, 1735, 1090, 1060, 825 cm^{-1}. PMR: 6.6 (2H, br s, CO_2H + OH), 5.15 (1H, t, J 7 Hz), 3.88 (1H, d, J 7 Hz), 3.78 (1H, d, J 11 Hz), 3.60 (1H, pentet, J 6 Hz), 3.50 (1H, d, J 11 Hz), 2.62 (2H, ABq, J 15 Hz), 2.15 (4H, m), 1.7-1.9 (2H, m), 1.73 (3H, s), 1.63 (3H, s), 1.2-1.5 (8H, m), 1.32 (3H, s). CMR: 173.3 (s), 134.8 (s), 120.1 (d), 81.5 (d), 79.4 (s), 75.5 (s), 71.9 (d), 69.6 (t), 40.2 (t), 38.7 (t), 36.5 (t), 36.2 (t*), 31.5 (t), 26.4 (t*), 25.8 (q), 25.0 (t), 23.2 (t), 18.3 (q), 17.9 (q). m/z 341 (M^++1, 0.1%), 340 (0.02), 322 (2.6), 271 (43), 253 (10), 185 (8), 163 (8), 143 (11), 129 (23), 111 (43), 97 (20), 95 (28), 83 (25), 81 (30), 70 (65), 69 (50), 55 (54), 43 (100), 41 (58).

(1RS, 4SR, 5RS)-4-*(8-Methyl-5-oxo-7-nonenyl)*-4-*methyl*-3,8-*dioxabicyclo[3.2.1]octane*-1-*ethanoic Acid (37).*

To alcohol (10) (88 mg, 0.26 mmol) in DMF (4 ml) and dichloromethane (4 ml) was added pyridinium dichromate (0.45 g) in one portion at 0°C. After stirring at this temperature for 1h the reaction mixture was poured into water (30 ml) and the product extracted into ether (3 x 40 ml). The combined organic extracts were washed with brine (2 x 10 ml), solvent removed and the residue chromatographed on silica (ether : light petroleum : acetic acid :: 25 : 75 : 1) to afford the *title ketone* (82 mg, 94%) as a colourless oil (Found: M^+ 338.2078. $C_{19}H_{30}O_5$ requires M^+ 338.2093). IR: 3100br, 1740, 1720, 1380, 1210, 1100, 1060, 830, 740 cm^{-1}. PMR: 9.2 (1H, br s, CO_2H), 5.25 (1H, t, J 7 Hz), 3.05 (1H, d, J 11 Hz), 2.58 (2H, ABq, J 12 Hz), 2.39 (2H, t, J 7 Hz), 2.09 (2H, m), 1.7-1.8 (2H, m), 1.71 (3H, s), 1.59 (3H, s), 1.52 (2H, m), 1.28 (3H, s), 1.15 - 1.40 (4H, m). CMR: 209.49 (s), 173.86 (s), 136.0 (s), 116.07 (d), 81.48 (d), 79.33 (s), 75.33 (s), 69.54 (t), 42.73 (t), 41.93 (t), 40.13 (t), 38.46 (t), 31.49 (t), 25.68 (q), 25.02 (t), 24.40 (t), 22.77 (t), 18.23 (q), 18.02 (q). m/z: 338 (M^+, 20%), 269 (46), 251 (15), 226 (7), 205 (9), 161 (7), 157 (10), 143 (13), 139 (25), 127 (33), 111 (27), 109 (34), 97 (29), 91 (25), 81 (100), 69 (57), 43 (84).

This was analysed as the corresponding amide, white crystals, m.p. 68-69°C (from ether) (Found: C, 67.6; H, 9.4; N, 4.1%; M^+ 337.2224. $C_{19}H_{31}NO_4$ requires C, 67.6; H, 9.3; N, 4.1%; M^+ 337.2253). IR: 3510, 3380, 2960, 1715, 1680, 1593, 1370, 1050, 911 cm^{-1}. PMR: 6.61 (1H, br s, NH), 5.34 (1H, br s, NH), 5.29 (1H, t, J 7 Hz), 3.89 (1H, d, J 7 Hz), 3.78 (1H, d, J 11 Hz), 3.28 (1H, d, J 11 Hz), 3.10 (2H, d, J 7 Hz), 2.57 & 2.42 (2H, ABq, J 15 Hz), 2.44 (2H, t, J 7 Hz), 2.18 (1H, ddd, J 11, 10, 4 Hz), 2.03 (1H, ddd, J 12, 10, 5 Hz), 1.7 (1H, m), 1.76 (3H, s), 1.86 (1H, m), 1.63 (3H, s), 1.57 (2H, m), 1.31 (3H, s), 1.2-1.5 (4H, m). m/z: 337 (M^+, 10%), 320 (12), 268 (22), 250 (5), 205 (7), 197 (13), 156 (8), 142 (35), 113 (50), 97 (29), 81 (64), 69 (57), 55 (47), 43 (100).

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