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TOTAL SYNTHESIS OF VERTICILLENE. A BIOMIMETIC APPROACH TO THE TAXANE FAMILY OF ALKALOIDS‡

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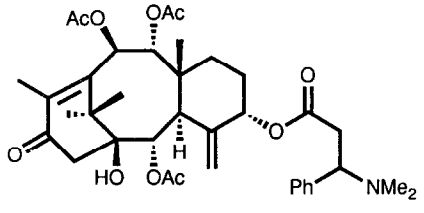
Summary: Intramolecular reductive coupling of the bis-aldehyde (10) in the presence of Ti(O), followed by 1,4-reduction of the resulting tetraene (9) using sodium in ammonia, provides a facile synthesis of E,E-verticillene (8), the putative biogenetic precursor of the taxane family of alkaloids *e.g.* (1) and (2). Treatment of either verticillene (8), verticillene 7,8-epoxide (21), verticillol 7,8-epoxide (27) or anhydroverticillol 7,8-epoxide (29) with Lewis acids fails to produce the corresponding taxane carbon framework, *viz* (3), and instead only products *e.g.* (23), (24) and (31) resulting from rearrangements of the epoxide rings in the substrates are obtained.

Taxane is the generic name applied to the group of alkaloids, e.g. taxinin (1) and taxol (2), first isolated from the common yew, Taxus baccata.[1] The alkaloids show structures based on the novel diterpenoid tricyclo[10.3.1.$0^{4,6}$]pentadecene carbon framework (3). A number of taxanes have been shown to exhibit potent anti-tumor and anti-leukemic activities,[2] and these properties in combination with their relatively complex structures have made the molecules an interesting and challenging group of compounds for total synthesis.[3] The bicyclo [9.3.1.]pentadecadienol (4), known as verticillol, is a constituent of the wood of the conifer Sciadopitys verticillata (Taxodiaceae).[4] The hydrocarbon (8) corresponding to (4), and designated



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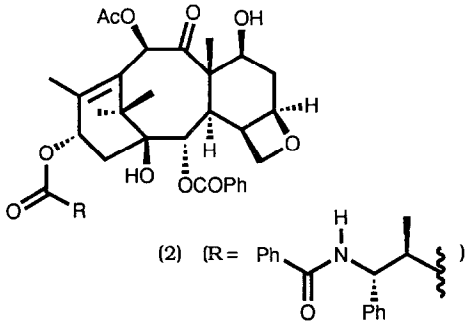

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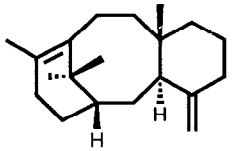

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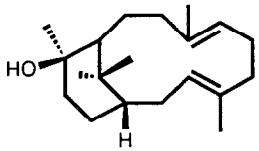

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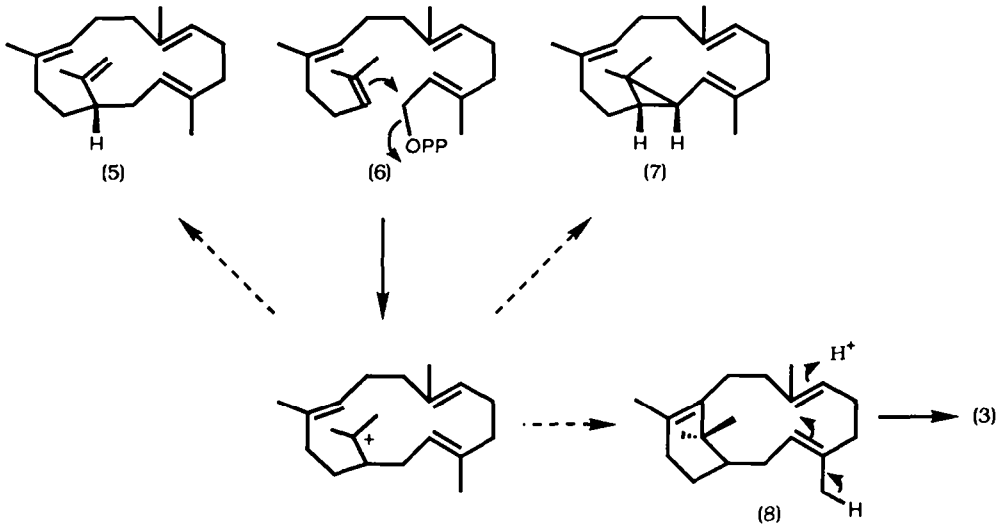
‡ Dedicated to Professor W. D. Ollis on the occasion of his 65th birthday

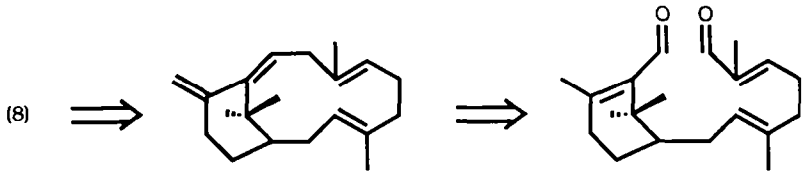
verticillene, is the putative biogenetic precursor of the taxanes. Verticillene (8) has its origins in geranyl geranyl pyrophosphate (6), and correlates with both cembrene (5),[5] also a constituent of conifer wood, and with casbene (7)[6] produced by seedlings of Ricinus communis (Euphorbiaceae). It is probable that the taxane ring system (3) is derived in Nature *via* transannular cyclisation across the twelve-membered ring of verticillene (8), produced by macrocyclisation of geranyl geranyl pyrophosphate as outlined in Scheme 1. Although a number of syntheses of cembrene and casbene have now been described,[7] the synthesis of the novel bicyclo[9.3.1] pentadecadiene verticillene (8)[8] has not hitherto been accomplished. In this paper we describe a total synthesis of E,E-verticillene (8) and summarise our attempts to effect transannular electrophilic cyclisation of (8) and its derivatives to the taxane ring system (3).[9]



Scheme 1

Our synthesis of E,E-verticillene (8) features intramolecular reductive coupling of the bis-aldehyde (10) in the presence of Ti(O), with concomitant 1,5-hydrogen sigmatropic rearrangement, to elaborate the twelve-membered ring, followed by 1,4-reduction of the 1,3-diene unit in the resulting tetraene (9) using sodium in liquid ammonia (Scheme 2). Thus, alkylation of the enolate derived from 3-isobutoxycyclohex-2-enone (11)[10] with E-3,7-dimethylocta-2, 6-dienyl bromide first gave the 4-substituted 1,3-dione enol ether (12), which, after addition of methyllithium followed by hydrolysis with dilute acid provided the disubstituted cyclohexenone (13). The cyclohexenone (13) was next added to a solution of lithium dimethylcuprate, and the resulting enolate was quenched at -78°C with chlorotrimethylsilane to give the corresponding silyl enol ether (14).[11]

When the silyl enol ether (14) and trimethyl orthoformate were added concurrently over two minutes to titanium tetrachloride in dichloromethane, separation and chromatography led to the cis-ketoacetal (15) in 58% yield. Addition of methylmagnesium iodide to the ketoacetal (15) then provided the tertiary alcohol (16), which

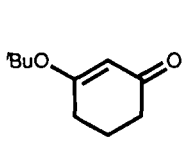


(9) (10)

Scheme 2

upon dehydration in the presence of phosphorus oxychloride-pyridine, gave rise to a mixture of positional isomers of the unsaturated aldehyde (17). Equilibration of the mixture of isomers in the presence of methanolic potassium hydroxide[12] then provided the pure aldehyde (17). Oxidation of the trienal (17), using catalytic selenium dioxide in the presence of t-butyl hydroperoxide[13] was regioselective, and gave the E-allylic alcohol (18) which on oxidation with manganese dioxide provided the key intermediate bis-aldehyde (10).

Addition of a solution of the bis-aldehyde (10) in dimethoxyethane *via* a syringe pump over 20 hours to a slurry of titanium trichloride and Zn-Cu couple in dimethoxyethane[14] led to a mixture of three hydrocarbon



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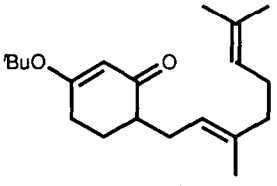

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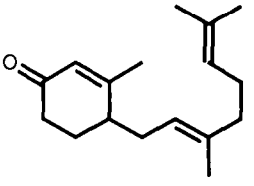

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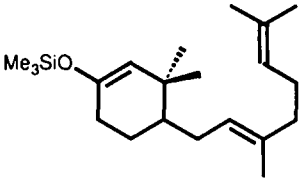

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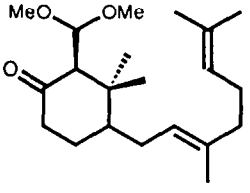

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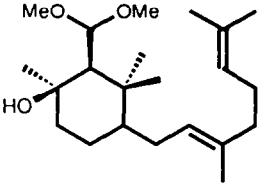

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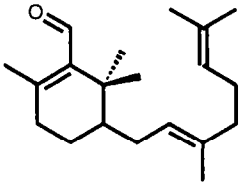

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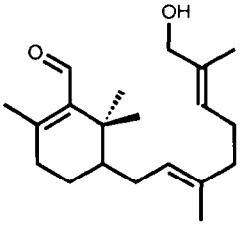

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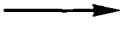
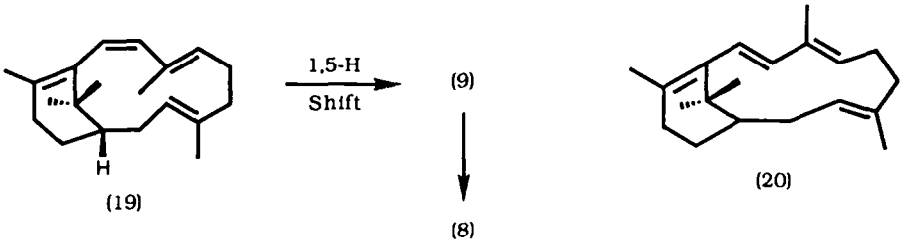


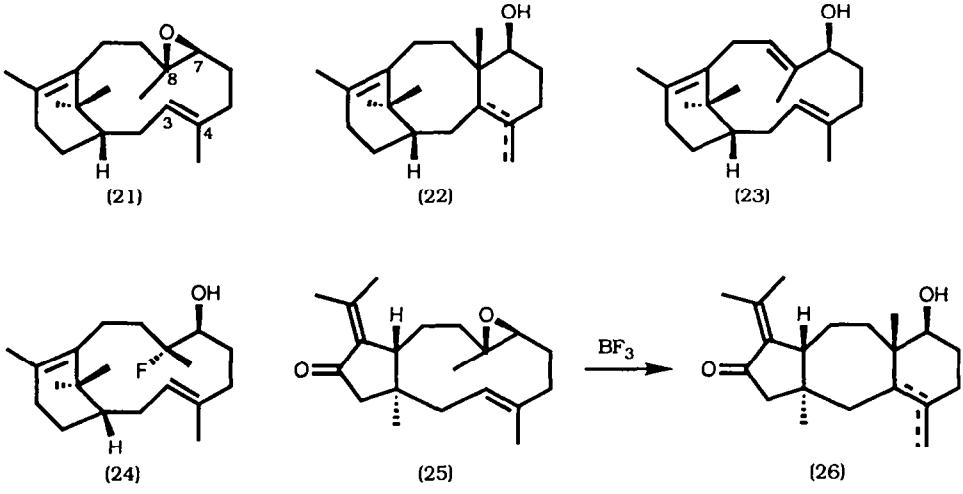
(10)

products in a combined yield of 40%. The mixture was separated by chromatography on silica gel impregnated with silver nitrate. The major product (~24%) showed spectroscopic data consistent with the bicyclic tetraene (9) which we presume arises *via* 1,5-hydrogen sigmatropic rearrangement of the initial coupled product (19). We assume that the driving force for the sigmatropic rearrangement in (19) is provided by migration of the bridgehead double bond from the six-ring to the twelve-ring in the bicycle. The structure and stereochemistry of one of the minor products (~7%) resulting from intramolecular reductive coupling of (10) was established as (19) by X-ray crystallography (see Figure 1), whereas the other minor product (~6%) was assigned as the geometrical isomer (20) of (19) from comparative spectroscopic data together with specific n.m.r. decoupling experiments.[15]



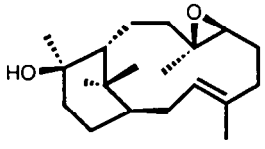
The synthesis of E,E-verticillene (8) was then completed by treating the 1,3-diene (9) with sodium in liquid ammonia for 30 minutes followed by quenching with ammonium chloride.[16] This procedure gave the verticillene (8) as a colourless oil, whose structure and stereochemistry were established by correlation of its spectroscopic data with those of natural verticillol (4).[4]

Having secured a viable synthesis of E,E-verticillene (8) we were now in a position to evaluate its *in vitro* (biomimetic) transannular cyclisation to the taxane ring system (3). We first investigated the transannular cyclisation of (8), using boron trifluoride under varying conditions.[17] To our surprise however we found no evidence for the formation of cyclisation products under all conditions investigated, and instead the verticillene underwent extensive decomposition. Suspecting that this might be due to preferential complexation between



BF_3-etherate and the more nucleophilic bridgehead double bond in (8), rather than the 7,8-double bond, we next decided to prepare the corresponding 7,8-epoxide (21) of verticillene and investigate its transannular cyclisation. Thus, treatment of verticillene (8) with meta-chloroperbenzoic acid (MCPBA) in dichloromethane in the presence of disodium hydrogen phosphate led to a mixture of 3,4- and 7,8-monoepoxides, which were separated by chromatography. The 7,8-epoxide (21) showed spectroscopic data which were closely similar to those of verticillol 7,8-epoxide (27) which we synthesised independently from natural verticillol (4) and whose structure and stereochemistry were rigidly established by X-ray crystallography.

Treatment of the verticillene 7,8-epoxide (21) with BF_3-etherate under conditions used previously by Look and Fenical[18] to effect transannulation of the 11-ring epoxide (25) to (26), gave none of the hoped-for tricyclic alcohol (22). Instead the corresponding allylic alcohol (23) was isolated as the major product (52%) together with the fluorohydrin (24; 35%). These observations led us to suspect that the initial epoxide (21) had the alternative α-configuration at the epoxide, with epoxidation occurring from the 'inside' face of the macrocycle (8). Transannulation in a crown conformation and through a chair-like transition state would then be much less favoured, and possibly account for the formation of the allylic alcohol (23), rather than (22). An X-ray structure determination of the alcohol (23) however fully established the pseudo-equatorial orientation of the hydroxyl group(see Figure 2), thereby confirming that the original epoxide (21) was produced from attack of peracid on the outside β-face of the twelve-membered ring in (8).



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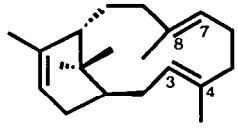

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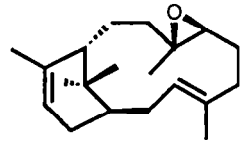

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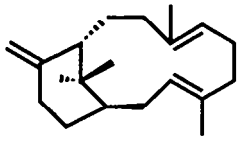

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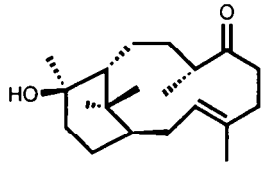

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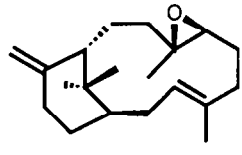

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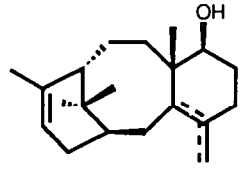
(29) → 

(33)

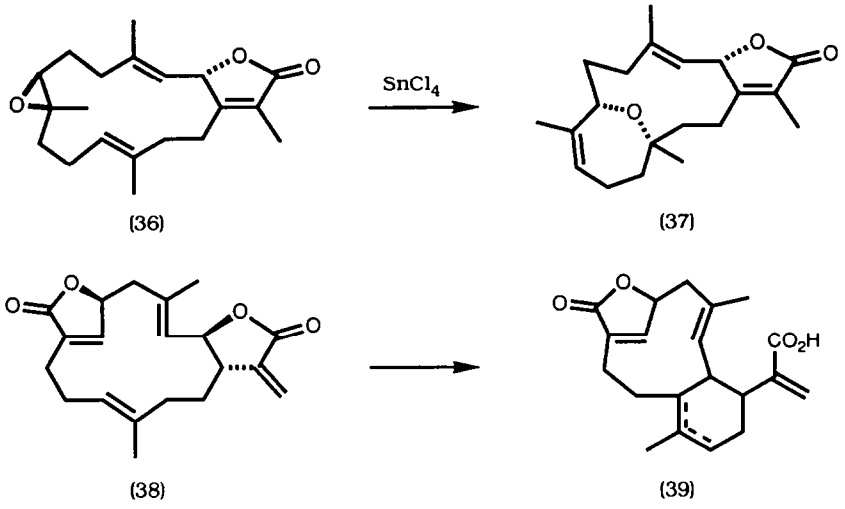
With the failure of verticillene (8) and its 7,8-epoxide (21) to undergo transannular cyclisation to the taxane ring system (3), we next decided to examine transannulation of the epoxides (27) and (29) derived from natural verticillol (4). Treatment of verticillol with MCPBA, in a similar manner to that described earlier for (8), followed by chromatography gave the 7,8-epoxide (27; 47%) as colourless crystals, together with the corresponding 3,4-epoxide, m.p. 139-140°C and the known bis-epoxide.[4] The structure and stereochemistry of verticillol 7,8-epoxide (27) were established rigorously by X-ray crystallography (see Figure 3). Dehydration of verticillol (4) produced a mixture of endo- and exo- anhydroverticillols which could be separated by chromatography. The endo-isomer (28) then gave rise to a mixture of the corresponding 3,4- and 7,8-monoepoxides, from which the 7,8-epoxide (29) could be separated by chromatography. We were unable however to resolve the mixture of 3,4- and 7,8- monoepoxides resulting from epoxidation of the exo-anhydroverticillol (30). Interestingly, in neither case were we able to detect products resulting from concurrent epoxidation of the six-ring double bonds in the anhydroverticillols (28) and (30).

Reactions between verticillol 7,8-epoxide (27) and BF_3-etherate, and between (27) and trimethylsilyl triflate, under a range of reaction conditions resulted in the formation of largely the ketone (31) accompanied by small amounts of the products (29) and (32) resulting from straightforward dehydration of (27). In a similar manner, treatment of the endo- anhydroverticillol epoxide (29) with BF_3- etherate led only to decomposition, and none of the hoped-for taxol (33) could be detected amongst the products.

(34)

(35)

The failure of either of the verticillenes (8), (21), (27) and (29) to undergo transannular electrophilic cyclisation, *in vitro*, to the corresponding taxane ring systems is both interesting and perplexing. Transannular cyclisations involving 1,5-diene systems set within 8-, 9-, 10- and 11-membered carbocyclic rings have been studied with particular vigour over recent years.[17] Furthermore, these fundamental studies have led to a number of novel 'biogenetically inspired' syntheses of a large range of complex ring-fused natural products of both biosynthetic significance and biological importance. Indeed, our own laboratory has highlighted the value of such electrophilic transannulations in the biomimetic syntheses of the triquinanes capnellene (34)[19] and pentalenene (35).[20] Although transannular electrophilic cyclisations involving large rings (*i.e.* >11-membered) have not been studied in any great detail, the available information does suggest that these reactions occur only with difficulty. Thus, the cembranoid diterpene sarcophine (36) produces only the oxepine derivative (37) on transannulation in acid. Interestingly however, when the 14-membered



(36) (37)

(38) (39)

diterpene ovatodiolide (38) is treated with methanolic hydrochloric acid or with p-toluenesulphonic acid it produces the tricycle (39) in acceptable yield.[21] Although our present observations do not disprove the involvement of verticillenes in the biosynthetic sequence leading to the taxane ring system (3) from geranyl geranyl pyrophosphate (GGPP) (Scheme 1), they do lead us to suspect that this is a much more subtle sequence than we had hitherto imagined. This sequence may involve an alternative reaction pathway or alternative reactive intermediates[22] for example, or it could involve the same overall pathway using different geometrical/positional isomers of GGPP for its purpose. More work is now needed in order to unravel these subtleties.

EXPERIMENTAL

General Details. - Melting points were determined with a Kofler hot stage apparatus. Infrared spectra were recorded on a Perkin-Elmer 710B instrument as liquid films on sodium chloride discs or as chloroform solutions. Proton n.m.r. spectra were either recorded at 90MHz on a Perkin-Elmer R32 or at 250MHz on a Brucker WM 250 PFT instrument; the samples were dilute solutions in deuteriochloroform, unless otherwise stated. Chemical shifts are quoted relative to internal tetramethlysilane and the line separations (J) are expressed in Hertz. Signals were singlets unless specified otherwise when the following abbreviations are used; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; b, broad. Carbon n.m.r. spectra were determined as dilute solutions in deuteriochloroform on a Brucker WM 250 PFT instrument. The chemical shifts are recorded relative to internal tetramethylsilane in a broad band decoupled mode and the multiplicities are taken from the off resonance spectrum. Molecular weights were determined from mass spectra measured with a VG MM 7070F or an AEI M5-902 instrument. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser. Dry nitrogen was used to provide an inert atmosphere and all organic solvents were dried over magnesium sulphate, unless stated otherwise. Analytical t.l.c. plates (Merck Kieselgel $60F_{254}$ on glass or aluminium sheets) were visualized with acidic 2,4-dinitrophenylhydrazine, basic potassium permanganate or methanolic sulphuric acid. Routinely, dry solvents were stored over freshly

activated 4A molecular sieves. Ether, benzene and toluene were dried over sodium wire. Chlorotrimethylsilane, boron trifluoride etherate, triethylamine, diisopropylamine, 1,2-dimethoxyethane, hexamethylphosphoramide, pyridine and ethanol were distilled from the respective magnesium alkoxide. Alkyl lithiums were used as standard solutions obtained from Aldrich.

Reverse phase HPLC was carried out using a Waters Associates 6000A instrument (R401 refractive index detector) and a 7.8mm I.D. x 300mm long m-bondapak C18 column; the solvent system used was 85:15 methanol:water.

6-(3,7-Dimethylocta-2E,6-dienyl)-3-(2-methylpropyloxy)-2-cyclohexen-1-one (12). - A solution of n-butyl lithium (1.7M) in hexane was added to a stirred solution of diisopropylamine (25.2ml) in dry tetrahydrofuran (150ml) at -25°C for 10 min, and then cooled to -78°C. A solution of 3-isobutoxy-2-cyclo-hexenonenone[10] (26.8g) in dry tetrahydrofuran (50ml) was introduced during 50min. The resulting solution was stirred at -78°C for 1h, and then E-3,7-dimethylocta-2,6-dienyl bromide[23] (38.37g) was added over 10 min. After stirring overnight while warming to room temperature the dark coloured solution was quenched with aqueous ammonium chloride solution. The aqueous phase was extracted with ether (3 x 75ml), and the combined organic layers were then washed successively with water (100ml) and saturated saline (100ml). Evaporation of the dried organic layers left a brown oil (52.3g), δ_H 0.98 (d, J 7Hz, 2 x CH_3), 1.62 (2 x CH_3), 1.68 (CH_3), 1.80-2.70 (m, 12H), 3.63 (d, J 7Hz, OCH_2), 4.97-5.30 (m, 2 x :CH), 5.36 (:CH), p.p.m., which was used immediately in the next reaction without further purification.

4-(3,7-Dimethylocta-2E,6-dienyl)-3-methyl-2-cyclohexen-1-one (13). - A solution of methyllithium (1.4M) in ether (125ml) was added dropwise over 1h to a stirred solution of the crude 2-cyclohexenone[12] (52.3g) in dry tetrahydrofuran (250ml) at -40°C under nitrogen. The solution was allowed to warm to room temperature and then stirred for 3h. After cooling to -5°C, dilute hydrochloric acid (2N; 300ml) was added cautiously, and the resulting two phase yellow solution was then stirred rapidly at room temperature for 15h. The aqueous phase was extracted with ether (3 x 50ml) and the combined organic layers were then washed successively with water (100ml) and saturated saline (100ml). Evaporation of the dried organic layers left a brown oil. Distillation gave the cyclohexenone (30g, 76%) as a red liquid, b.p. 145-6° at 0.1mm Hg; ν_{max} (film) 1675 cm^{-1}; λ_{max} (ethanol) 239nm; δ_H 1.64 (2 x CH_3), 1.70 (CH_3), 1.90-2.80 (m, 11H), 2.0 (CH_3), 4.97-5.30 (m, 2 x :CH), 5.90 (br, :CH); m/z 246.1982; $C_{17}H_{26}O$ requires M 246.1983.

3,3-Dimethyl-4-(3,7-dimethylocta-2E,6-dienyl)-1-trimethylsilyloxy-1-cyclohexene (14). - A solution of methyllithium (1.4M) in ether (63ml) was added dropwise over 0.5h to a stirred suspension of cuprous iodide (8.4g) in dry ether (80ml) under nitrogen at -5°C. A solution of the 2-cyclohexenone (13) (9.84g) in ether (20ml) was added dropwise over 0.3h, and the resulting yellow slurry was then stirred at <0°C for 2h. The mixture was cooled to -78°C and chlorotrimethylsilane (22ml) was then introduced followed by triethylamine (22ml). The dark coloured mixture was stirred overnight while warming to room temperature and then poured onto ice. After filtration through kieselguhr, the aqueous phase was extracted with ether (3 x 40ml) and the combined organic layers were then dried and evaporated. The crude enol ether was disssolved in dimethylsulphoxide (50ml) and the solution was then extracted with hexane (4 x 15ml). The combined organic

layers were washed with saturated saline (3 x 15ml) then dried and evaporated to leave the enol ether (11.8g, 88%) as a very pale yellow liquid. A small portion of the enol ether was distilled to give a pure sample as a colourless liquid, b.p. 114-115°C at 0.5mm Hg; ν_{max} (film) 1632cm^{-1}; δ_H 0.23 (Me_3Si) 0.91 (CH_3), 1.08 (CH_3), 1.69 (br, 2 x CH_3), 1.75 (CH_3), 1.30-2.40 (m, 11H), 4.72 (br, :CH), 5.05-5.37 (M, 2 X :CH); m/z 334.2678; $C_{21}H_{38}SiO$ requires M 334.2692).

2-(1,1-Dimethoxymethyl)-3,3-dimethyl-4-(3,7-dimethylocta-2E, 6-dienyl)-1-cyclohexanone (15). - A solution of trimethyl orthoformate (2.32g) in dry dichloromethane (5ml) and a solution of the trimethylsilyl enol ether (14) (6.62g) in dry dichloromethane (5ml) were added concurently over 1-2min to a stirred solution of titanium tetrachloride (2.35ml) in dry dichloromethane (85ml) under nitrogen at -78°C. The yellow/orange slurry was stirred at -78°C for 3h, and then quenched with saturated aqueous sodium hydrogen carbonate (50ml) at this temperature. After warming to room temperature and filtration through kieselguhr the aqueous phase was extracted with dichloromethane (3 x 20ml). Evaporation of the dried organic layers left a yellow oil which was purified by chromatography on silica Woelm using hexane-ethyl acetate (9:1) as eluant to give the ketoacetal (3.8g, 58%) as a colourless oil, ν_{max} (film) 1705 cm^{-1}; δ_H 0.83 (CH_3), 1.08 (CH_3), 1.62 (br, 2 x CH_3), 1.70 (br, CH_3),1.30-2.70 (m, 12H), 3.35 (OCH_3), 3.37 (OCH_3), 4.79 (d, J 7Hz, CH (OCH_3)$_2$), 5.00-5.32 (m, 2 x :CH); m/z 336.2667 $C_{21}H_{36}O_3$ requires M 336.2664.

2-(1,1-Dimethoxymethyl)-4-4-(3,7-3,7-dimethylocta-2E,6-dienyl)-1,3, 3-trimethyl-1-cyclohexanol (16). - A solution of the ketoacetal (15) (7.34g) in ether (25ml) was added dropwise over 0.5h to a stirred solution of methyl magnesium iodide (2ml) in ether (65ml) under nitrogen. The resulting cloudy solution was stirred overnight at room temperature, and then quenched with aqueous ammonium chloride solution. The aqueous phase was extracted with ether (3 x 20ml) and the combined organic layers were then washed with water (20ml) followed by saturated saline solution. Evaporation of the dried organic layers left the alcohol (7.6g, 98%) as a colourless liquid, ν_{max} (film) 3530cm^{-1}; δ_H 1.02 (CH_3), 1.22 (CH_3), 1.35 (CH_3), 1.63 (br, 2 x CH_3), 1.70 (br, CH_3), 1.50-2.30 (m, 12H), 3.42 (OCH_3), 3.54 (OCH_3), 3.98 (br, OH), 4.52 (CH(OCH_3)$_2$), 5.00-5.28 (m, 2 x :CH); δ_c 134.7, 130.9, 124.8(d), 124.4(d), 109.9(d), 72.2, 56.8(q), 55.9(q), 50.9(d), 46.6(d), 39.9(t), 35.8(t), 35.5, 32.0(q), 29.5(q), 26.7(t), 26.2(q), 25.7(q), 25.5(t), 20.3(t). 17.6(q), 16.1(q); m/z 320.2712; $C_{22}H_{40}O_3$-CH_3OH requires M 320.2715.

2,6,6-Trimethyl-5-(3,7-dimethylocta-2E,6-dienyl)-1-cyclohexene-1-carboxaldehyde (17). - Phosphorus oxychloride (13.5ml) was added during 20min to a stirred ice-cooled solution of the alcohol (16) (2.0g) in dry pyridine (60ml) under nitrogen. The ice cooling was removed, and the solution was then warmed to 65°C and stirred for 90 min. After cooling to room temperature the solution was added cautiously and dropwise to a cooled (0-5°C) solution of saturated aqueous sodium hydrogen carbonate (300ml). The aqueous phase was extracted with ether (3 x 50ml) and the combined organic layers were then washed successively with saturated aqueous copper sulphate solution (3 x 50ml), water (50ml) and saturated saline solution (50ml). Evaporation of the dried organic layers left a yellow oil (1.77g). The oil was dissolved in tetrahydrofuran (30ml) and diluted with saturated saline solution (150ml) and then extracted with ether (3 x 50ml). The combined organic layers were washed with water (30ml) and saturated saline solution (30ml). Evaporation of the dried organic layers left a golden liquid (1.55g). The liquid was dissolved in methanolic potassium hydroxide (0.6g in 40ml) and the solution was then stirred under nitrogen at room temperature for 90min.[12] The solution was diluted

with saturated saline solution (250ml) and then extracted with ether (3 x 50ml). The combined organic layers were washed with water (30ml) and saturated saline solution (30ml). Evaporation of the dried organic layers left the crude aldehyde (1.53g, 93.5%) as a brown oil. A small sample of the crude aldehyde was purified by chromatography on silica Woelm using hexane-ethyl acetate (19:1) as eluant, to give the pure α, β-unsaturated aldehyde as a colourless oil, ν_{max} (film) 1675 cm^{-1}; λ_{max} (ethanol) 247.2nm; δ_H 1.11 (CH_3), 1.29 (CH_3), 1.63 (2 x CH_3), 1.70 (CH_3), 1.6-2.4 (m, 11H), 2.1 (CH_3), 5.0-5.30 (m, 2 x :CH), 10.19 (CHO); δ_c 192.4(d), 155.0, 141.0, 135.8, 131.1, 124.5(d), 124.2(d), 46.6(d), 39.9(t), 36.4, 35.1(t), 27.8(t), 26.7(t), 26.2(q), 25.7(q), 22.6(t), 21.2(q), 19.4(q), 17.7(q), 16.1(q); m/z 288.2458; $C_{20}H_{32}O$ requires M 288.2453.

3-(3,7-Dimethyl-8-hydroxy-2E,6E-octadienyl)-2,2,6-trimethyl-1-cyclohexene-1-carboxaldehyde (18). - A solution of t-butylhydroperoxide (0.47g) and selenium dioxide (0.035g) in dichloromethane (1.25ml) was added to a stirred solution of the crude aldehyde (17) (0.5g) in dichloromethane (5ml). The mixture was stirred at room temperature for 3h and then evaporated to dryness. The residue was purified by chromatography on silica Woelm using hexane-ethyl acetate as eluant (19:1) to give recovered starting material (0.12g, 24%) and the allylic alcohol (0.11g, 21%), ν_{max} 1670 and 3400cm^{-1}; λ_{max} (ethanol) 248.4nm; δ_H 1.10 (CH_3), 1.28 (CH_3), 1.62 (CH_3), 1.68 (CH_3), 2.10 (CH_3), 1.50-2.70 (m, 12H), 4.00 (-CH_2OH), 5.04-5.30 (m, :CH), 5.32-5.55 (m, :CH), 10.20 (CHO); δ_c 192.7(d), 155.5, 140.9, 135.6, 134.9, 125.7(d), 124.3(d), 68.7(t), 46.5(d), 39.5(t), 36.4, 35.1(t), 27.7(t), 26.3(t), 26.1(q), 22.5(t), 21.2(q), 19.4(q), 16.1(q), 13.6(q); m/z 304.2398; $C_{20}H_{32}O_2$ requires M 304.2402.

3-(3,7-Dimethyl-8-oxo-2E,6E-octadienyl)-2,2,6-trimethyl-1-cyclohexene-1-carboxaldehyde (10), - Active manganese dioxide (1.0g) was added to a stirred solution of the allylic alcohol (18) (0.105g) in dichloromethane (10ml). The brown slurry was stirred at room temperature for 45min then filtered and evaporated to leave the dialdehyde (0.093g, 90%) as a pale yellow oil; ν_{max} (film) 1680cm^{-1}; λ_{max} (ethanol) 234.2nm; δ_H 1.12 (CH_3), 1.30 (CH_3), 1.67 (CH_3), 1.70 (CH_3), 2.13 (CH_3), 1.50-2.70 (m, 11H), 5.10-5.40 (m, :CH), 6.43-6.68 (m, :CH), 9.50 (CHO), 10.25 (CHO); δ_c 195.0(d), 192.6(d), 155.3(d),154.3, 140.9, 139.5, 134.4, 125.5(d), 46.5(d), 38.2(t), 36.4, 35.1(t), 27.8(t), 27.4(t), 26.1(q), 22.6(t), 21.1(q), 19.4(q), 16.0(q), 9.2(q); m/z 302.2242; $C_{20}H_{30}O_2$ requires M 302.2246.

4,8,12,15,15-Pentamethylbicyclo[9.3.1.]pentadeca-3E,7E,9E,11-tetraene (19). - 12-Methylene-4,8,15,15-tetramethyl-bicyclo[9.3.1]pentadeca-3E,7E,10Z-triene (9) and -4,8,12,15,15-Pentamethylbicyclo[9.3.1.]-pentadeca-3E,7E,9Z, 11-tetraene (20). - A slurry of titanium trichloride (1.20g) and zinc-copper couple (1.20g) in dry 1,2-dimethoxyethane (60ml) was stirred under reflux in an atmosphere of argon for 1h. A solution of the dialdehyde (10) (0.214g) in dry 1,2-dimethoxyethane (20ml) was added during 22h using a syringe pump, and the mixture was then stirred under reflux for 3h. The dark grey-green mixture was cooled and filtered through kieselguhr. The filtrate was washed with water (2 x 20ml) then dried and evaporated to leave the crude mixture of cyclised products as a colourless oil. Purification by chromatography on Silica Woelm impregnated with silver nitrate ($AgNO_3$:silica; 1:4) using gradient elution conditions (hexane: ethyl acetate; 19:1 → 100% ethyl acetate) gave in order of elution: (i) the bicyclo [9.3.1]pentadecane (20), (15mg, 7.8%) as a colourless oil; δ_H 0.87 (CH_3), 1.05 (CH_3, 1.47 (m, CH_3), 1.62 (2 x CH_3), 1.45-2.85 (m, 11H), 5.05-5.45 (m, 2 x :CH), 5.85 (br, 2 x :CH); δ_c136.6, 134.7(d), 132.0, 131.4, 128.2(d), 126.7, 126.7(d),

126.6(d), 42.9(d), 39.8(t), 36.2, 33.8(t), 31.9(q), 30.1(t), 26.2(t), 25.4(t), 24.2(q), 21.6(q), 16.5(q), 14.4(q); m/z 270.2329; $C_{20}H_{30}$ requires M 270.2348. (ii) the bicyclo[9.3.1]pentadecane (9), 45mg, 23.5%) as a colourless oil; δ_H 1.06 (CH_3), 1.18 (CH_3), 1.57 (br, CH_3), 1.73 (br, CH_3), 1.55-2.56 (m,12H), 3.46 (t, J 12Hz, CH), 4.64 (m, C:CHH), 5.02 (m, C:CHH), 4.90-5.00 (m, :CH), 5.23-5.33 (m, :CH), 5.37 (dd, J 12 and 4Hz, :CH-CH_2); δ_c 146.7, 145.6, 135.1, 132.3, 126.7(d), 126.1(d), 120.2(d), 111.4(t), 46.6(d), 40.7, 40.2(t), 38.3(t), 34.2(t), 32.3(t), 30.5(q), 29.4(t), 25.9(q), 23.3(t), 17.3(q), 15.5(q); m/z 270.2362; $C_{20}H_{30}$ requires M 270.2348. (iii) the bicyclo[9.3.1]pentadecane (19) (15mg, 7.8%) as a white solid; δ_H 0.87 (CH_3), 1.10 (CH_3), 1.56 (br, 2 x CH_3), 1.60 (br, CH_3), 1.40-2.60 (m, 11H), 4.86-5.15 (m, :CH), 5.50-5.75 (m, :CH), 6.08 (br, 2 x :CH); δ_c 143.8, 134.9, 134.2, 133.1(d), 131.8(d), 130.6(d), 128.3(d), 126.3, 52.0(d), 39.5(t), 37.4, 29.2(t), 28.7(t), 27.7(q), 26.5(t), 26.2(t), 22.6(q), 21.6(q), 16.4(q), 15.3(q); m/z 270.2367; $C_{20}H_{30}$ requires M 270.2348.

4,8,12,15,15-Pentamethylbicyclo[9.3.1]pentadeca-3E,7E,11-triene (8). - Sodium metal (10mg) was added to a solution of the bicycle (9) (30mg) in freshly distilled ammonia (20ml) and ether (2ml). The mixture was heated under reflux for 30min and then quenched by addition of solid ammonium chloride until the blue colour disappeared. The ammonia was allowed to evaporate and the residue was then diluted with water. The aqueous solution was extracted with ether (3 x 15ml) and the combined organic layers were then washed with water (10ml). Evaporation of the dried organic layers, followed by chromatography on Silica Woelm impregnated with silver nitrate ($AgNO_3$:silica; 1:3) using hexane-ethyl acetate (17:3) as eluant gave the triene (23.7mg, 78.4%) as a colourless oil, δ_H 0.87 (CH_3), 0.97 (CH_3), 1.55 (m, 2 x CH_3), 1.7 (CH_3),1.50-2.90 (m, 15H), 4.65-4.87 (m, :CH), 5.10-5.35 (m, :CH); δ_c 136.1, 132.8, 131.5, 128.6(d), 126.8(d), 126.3, 42.9(d), 40.2(t), 38.5(t), 37.0, 34.2(t), 32.9(q), 31.5(t), 27.5(t), 26.1 (t), 26.0(t), 24.6(q), 21.7(q), 16.6(q), 15.4(q), m/z 272.2501; $C_{20}H_{32}$ requires M 272.2502 [and recovered starting material (2.6mg, 8.7%)].

Epoxidation of Verticillene (8). - Disodium hydrogen phosphate (13.7mg) was added to a stirred solution of verticillene (21mg) in dichloromethane (2ml). m-Chloroperbenzoic acid (14.7mg) was added and the mixture was then stirred at room temperature for 1h. The solvent was evaporated and the residue was then dissolved in ether (25ml). The organic phase was washed with 10% aqueous sodium sulphite (2 x 10ml) and then saturated aqueous sodium hydrogen carbonate (10ml). Evaporation of the dried organic layer followed by chromatography on silica Woelm using petroleum ether (b.p. 40-60°C)-ethyl acetate (19:1) as eluant gave, in order of elution: (i) recovered starting material (2.8mg, 13.3%), and (ii) a mixture of two monoepoxides (17.5mg, 78.8%). The monoepoxides were separated by reverse phase HPLC, using methanol-water (17:3) as eluant to give in order of elution: (i) verticillene-3,4-epoxide (9.3mg, 42%); as a colourless oil, δ_H 0.93 (CH_3), 1.02 (CH_3), 1.21 (CH_3), 1.62 (CH_3), 1.68 (CH_3), 1.50-2.50 (m, 15H), 3.10 (dd, J 8 and 1Hz, epoxide H), 4.70-4.97 (m, :CH); δ_c 136.2, 133.8, 128.3(d), 127.4, 62.0, 61.2(d), 41.8(d), 40.2(t), 38.4(t), 37.0, 34.2(t), 32.6(q), 30.8(t), 26.6(t), 26.5(t), 25.6(q), 24.1(t), 21.4(q), 17.2(q), 16.2(q); m/z 288.2456; $C2_{20}H_{32}O$ requires M 288.2452; and (ii) verticillene-7,8-epoxide (21) (4.6mg, 21%) as a colourless oil, δ_H 0.2 (CH_3), 1.10 (CH_3), 1.29 (CH_3), 1.60 (m, CH_3), 1.63 (CH_3), 1.50-2.50 (m, 15H), 2.6 (dd, J 9 and 2Hz, epoxide H), 5.28-5.53 (m, :CH); δ_c 135.5, 132.2, 127.5, 125.8(d), 66.3(d), 61.9, 43.4(d), 39.2(t), 37.9(t), 37.3, 33.8(t), 32.8(q), 31,7(t), 27.0(t), 26.2(q), 25.5(t), 24.0(t), 22.2(q), 16.8(q), 15.5(q); m/z 288.2447; $C_{20}H_{32}O$ requires M 288.2452.

Attempted Transannular Cyclisation of Verticillene-7,8-epoxide (21). - Freshly distilled boron trifuloride etherate (7.5µl) was added to a stirred solution of verticillene-7,8-epoxide (16mg) in ether (3ml) at 0-5°C under argon. The solution was stirred at 0-5° and two further aliquots (6ml) of boron trifluoride etherate were added at 20min and 135min. After a total reaction time of 4.5h the mixture was quenched by the addition of 2-3 drops of deionised water. The organic phase was washed with saturated aqueous sodium hydrogen carbonate solution (2 x 5ml), then dried and evaporated. Gradient elution chromatography on silica Woelm using petroleum ether (b.p. 40-60°C) - ethyl acetate (19:1 → 9:1) as eluant gave, in order of elution: (i) recovered starting material (8.5mg, 53.1%); (ii) the fluorohydrin (24) (3mg, 17.5%) as a white solid; δ_H 1.05 (CH_3),1.09 (CH_3),1.22 (d, J 23.5Hz, CH_3CF),1.61(CH_3), 1.64 (CH_3),1.30-2.25 (m,13H), 2.50-2.83 (m,2H), 3.98-4.06 (dd, J 8.3 and 2.8Hz, -CHOH), 5.20-5.30 (m, :CH). m/z 308.2521; $C_{20}H_{33}OF$ requires M 308.2515, and (iii) the allylic alcohol (23) (4mg, 25%) as colourless needles, m.p. 174-176.5°C (ethyl acetate); δ_H 0.99 (CH_3), 1.01 (CH_3), 1.51 (m, CH_3), 1.58 (m, CH_3, 1.69 (CH_3), 1.45-2.80 (m, 13H), 3.95-4.04 (m, -CHOH), 4.88-5.00 (m, :CH), 5.30-5.40 (m, :CH); δ_c 135.4, 132.0, 131.8, 126.3(d), 126.2, 125.9(d), 82.0(d), 42.3(d), 37.6(t), 33.7(t), 32.7(q), 30.0(t), 29.7, 29.6(t), 26.1(t), 25.8(q), 20.5(q), 14.6(q), 10.6(q), m/z 288.24252; $C_{20}H_{32}O$ requires M 288.2453.

Epoxidation of Verticillol (4). - Disodium hydrogen phosphate (66.7mg) was added to a stirred solution of verticillol (101.7mg) in dichloromethane (5ml). m-Chloroperbenzoic acid (66.7mg) was added and the solution was stirred for 80min. The solvent was evaporated, and the residue was then dissolved in ether (25ml). The organic phase was washed successively with 10% aqueous sodium sulphite (2 x 10ml) and saturated aqueous sodium hydrogen carbonate (10ml). Evaporation of the dried organic layer followed by chromatography on silica Woelm using petroleum ether (b.p. 40-60°C) - ethyl acetate (4:1) as eluant gave, in order of elution: (i) recovered starting material (7.8mg, 7.7%); (ii) verticillol-3,4-epoxide (24.5mg, 23%) as a white solid, m.p. 139-140°C (ethyl acetate); δ_H 0.77 (CH_3), 0.85 (CH_3), 1.26 (CH_3), 1.31 (CH_3), 1.62 (br, CH_3), 1.20-2.50 (m, 16H), 3.47 (dd, J 7 and 4Hz, epoxide H), 4.97-5.26 (m, :CH); δ_c 133.9, 129.6(d), 75.4, 64.3(d), 63.4, 46.1(d), 43.0(d), 41.2(t), 40.5(t), 40.4(t), 36.9, 34.9(t). 29.0(q), 28.2(t), 25.6(q), 24.6(q), 24.4(t), 21.8(t), 16.4(q), 15.8(q); m/z 306.2541 $C_{20}H_{34}O_2$ requires M 306.2557; (iii) verticillol-7,8-epoxide (27) (49.9mg, 47%) as a white solid, m.p. 146-149°C (ethyl acetate); δ_H 0.81 (CH_3), 0.97 (CH_3), 1.27 (CH_3), 1.28 (CH_3), 1.64 (m, CH_3), 1.40-2.85 (m, 16H), 2.98 (dd, J 9 and 1.5Hz, epoxide H), 5.81-6.10 (m, :CH); δ_c 133.1, 128.0(d), 75.4, 66.3(d), 62.1, 45.3(d), 44.0(d), 41.4(t), 39.9(t), 38.8(t), 37.4, 33.6(t), 29.4(q), 28.1(t), 26.3(t), 24.9(q), 21.1(t), 16.6(q), 15.2(q), m/z 306.2561; $C_{20}H_{34}O_2$ requires M 306.2557; (iv) verticillol diepoxide (14.8mg, 13.1%) as a white solid, m.p. 160-1°C (ethyl acetate - petroleum ether) (lit[4] 159-160°C), δ_H 0.87 (CH_3), 0.98 (CH_3), 1.32 (br, 3 x CH_3), 1.2-2.45 (m, 16H), 2.99 (m, epoxide H), 3.53 (m, epoxide H); δ_c 75.0, 65.5(d), 64.6(d), 63.2, 61.7, 46.7(d), 42.6(d), 41.4(t), 39.1(t), 37.9(t), 36.9, 34.3(t), 30.6(q), 27.6(t), 25.4(q), 24.5(q), 24.1(t), 21.3(t), 16.9(q), 15.9(q); m/z 322.2506; $C_{20}H_{34}O_3$ requires M 322.2506.

Attempted Trannsanular Cyclisation of Verticillol-7,8-epoxide (27). - Freshly distilled boron trifluoride etherate (25µl) was added to a stirred solution of verticillol-7,8-epoxide (30.7mg) in dry ether (5ml) at 0°C under nitrogen. The solution was stirred for 6h and then quenched by the addition of 2-3 drops of water. The

organic phase was washed with saturated aqueous sodium hydrogen carbonate (2 x 5ml), then dried and evaporated to leave a white solid (32.8mg). Gradient elution chromatography on Silica Woelm using petroleum ether (b.p. 40-60°C) -ethyl acetate (19:1 → 3:1) as eluant gave, in order of elution: (i) a 1:1 mixture of endo-anhydroverticillol-7,8-epoxide (29) and exo-anhydroverticillol-7,8-epoxide (32), (2.1mg, 7.3%); (ii) the ketone (31) (13.2mg, 43%) as a white solid, m.p. 130-133°C (ethyl acetate); ν_{max} (chloroform solution) 1670, 3450 cm^{-1}; δ_H 0.84 (2 x CH_3), 1.03 (CH_3), 1.12 (d, J 7Hz, -$CHCH_3$), 1.65 (m, CH_3), 1.20-3.10 (m, 17H), 3.40-3.70 (br, OH), 5.60-5.95 (m, :CH); δ_C 219.7, 131.9, 128.2(d), 72.9, 50.9(d), 47.5(d), 42.9(d), 40.8(t), 38.4, 35.3(t), 34.3(t), 33.8(t), 32.1(t), 28.6(t), 27.7(q), 24.9(q), 24.1(t), 22.5(q), 18.8(q), 16.3(q), m/z 306.2545; $C_{20}H_{34}O_2$ requires M 306.2557; and (iii) recovered starting material (12.1mg, 39.4%).

4,8,12,15,15-Pentamethylbicyclo[9.3.1]pentadeca-3E,7E,12Z-triene (28) and 12-Methylene-4,8,15,15-tetramethylbicyclo[9.3.1]pentadeca-3E,7E-diene (30). - Phosphorus oxychloride (0.75ml) was added during 1-2 min to a stirred and cooled (ice/water) solution of verticillol (0.3g) in dry pyridine (10ml) under nitrogen. The yellow solution was stirred at 0°C for 65h and then it was diluted with cold water (ca. 50ml). The aqueous phase was extracted with ether (4 x 10ml) and the combined organic layers were then washed with saturated aqeuous copper sulphate solution (2 x 15ml) and water (15ml). Evaporation of the dried organic layer left a yellow waxy solid which was purified by gradient elution chromatography on Silica Woelm impregnated with silver nitrate (silica:$AGNO_3$; 3:1) using hexane-ethyl acetate (49:1 → 3:1) as eluant to give, in order of elution; (i) endo-anhydroverticillol (28) (141.8mg, 50.4%) as a pale yellow unstable waxy solid, δ_H 0.77 (CH_3), 0.83 (CH_3), 1.52 (m, CH_3), 1.60 (m, CH_3), 1.79 (m, CH_3), 1.20-2.90 (m, 14H), 4.70-5.00 (m, :CH), 5.20-5.53 (m, 2 x :CH); δ_C 135.9, 132.8, 132.6, 130.0(d), 124.8(d), 121.7(d), 42.6(d), 41.0(t), 39.7(t), 38.1(d), 35.8, 34.2(t), 30.8(t), 27.2(q), 26.8(t), 23.7(q), 23.0(q), 21.5(t), 15.7(q), 15.2(q); m/z 272.2495; $C_{20}H_{32}$ requires M 272.2502, and (ii) exo-anhydroverticillol (30) (114.4mg, 40.6%) as a pale yellow unstable waxy solid[4], δ_H 0.75 (CH_3), 0.87 (CH_3), 1.58 (m, 2 x CH_3), 1.10-3.05 (m, 16H), 4.57 (m, C:CHH), 4.85 (m, C:CHH), 4.62-4.90 (m, :CH), 5.50-5.80 (m, :CH); δ_C 149.4, 133.8, 132.8, 128.4(d), 127.4(d), 105.3(t), 45.0(d), 42.7(d), 41.4(t), 37.8(t), 37.7, 36.1(t), 33.6(t), 30.4(t), 27.3(q), 26.4(t), 24.5(q), 19.5(t), 15.6(q); m/z 272.2498; $C_{20}H_{32}$ requires M 272.2502.

Epoxidation of exo-Anhydroverticillol (30). - Disodium hydrogen phosphate (53mg) was added to a stirred solution of exo-anhydroverticillol (70mg) in dichloromethane (10ml). m-Chloroperbenzoic acid (53mg) was added and the solution was stirred for 75min. The solution was washed successively with 10% aqueous sodium hydrogen carbonate (10ml) and saturated saline solution (10ml). Evaporation of the dried organic layer left a waxy solid (98mg) which was purified by gradient elution chromatography on Silica Woelm using hexane-ethyl acetate (49:1 → 9:1) as eluant to give, in order of elution: (i) recovered starting material (7.5mg, 10.7%); (ii) a mixture of exo-anhydroverticillol-3,4-epoxide and exo-anhydroverticillol-7,8-epoxide (32) (40mg, 57.1%), and (iii) exo-anhydroverticillol-3,4,7,8-diepoxide (19mg, 24.0%), as a white solid, m.p. 156.5-157.5°C (ethyl acetate) (lit[4] 160°C); δ_H 0.81 (CH_3), 1.03 (CH_3), 1.35 (2 x CH_3), 1.17-2.60 (m, 17H), 3.43 (dd, J 9 and 3Hz, epoxide H), 4.62 (bs, C:CHH), 5.00 (bs, C:CHH); δ_C 146.9, 108.2(t), 65.6(d), 64.5(d), 62.8, 61.8, 44.9(d), 43.8(d), 37.8, 37.0(t), 36.3(t), 36.2(t), 33.4(t), 28.7(t), 27.9(q), 24.3(t), 23.2(q), 20.0(t), 16.8(q), 16.2(q); m/z 304.2421; $C_{20}H_{32}O_2$ requires M 304.2401. The two monoepoxides could not be separated but exhibited the following spectral data: (i) major isomer (32) (7.8-epoxide), δ_H 0.75

(CH_3), 1.02 (CH_3), 1.27 (CH_3), 1.66 (m, CH_3), 1.20-3.00 (m, 17H), 4.52 (m, C:CHH), 4.90 (m, C:CHH), 5.75-6.00 (m, :CH); δ_C 148.4, 132.7, 127.6(d), 106.5(t), 65.5(d), 62.0, 45.1(d), 44.0(d), 38.6(t), 38.3, 36.8(t), 36.0(t), 33.3(t), 30.0(t), 27.6(q), 26.1(t), 23.5(q), 19.9(t), 16.7(q), 15.9(q); (ii) minor isomer (3,4-epoxide), δ_H 0.8 (CH_3) 0.88 (CH_3), 1.27 (CH_3), 1.66 (m, CH_3), 1.20-3.0 (m, 16H), 3.32 (dd, J 8 and 4Hz, epoxide H), 4.52 (m, C:CHH), 4.90 (m, C:CHH), 4.70-4.97 (m, :CH); δ_C 148.0, 134.3, 127.6(d), 106.7(t), 65.3(d), 63.5, 44.5(d), 43.5(d), 40.0(t), 37.4, 36.9(t), 36.3(t), 33.8(t), 29.1(t), 27.8(q), 24.5(t), 24.0(q), 20.3(t), 16.1(q), 15.1(q); The mixture showed m/z 288.2449; $C_{20}H_{32}O$ requires M 288.2452.

Epoxidation of endo-Anhydroverticillol (28). - Disodium hydrogen phosphate (53mg) was added to a stirred solution of endo-anhydroverticillol (68.9mg) in dichloromethane (10ml). m-Chloroperbenzoic acid (52.4mg) was added and the solution was stirred for 75 min. The solution was washed successively with 10% aqueous sodium sulphite (2 x 10ml), saturated aqueous sodium hydrogen carbonate (10ml), and saturated saline solution (10ml). Evaporation of the dried organic layer left a waxy solid (70.9mg) which was initially purified by chromatography on Silica Woelm using hexane-ethyl acetate (19:1) as eluant to give, in order of elution: (i) recovered starting material (4.5mg, (6.5%); (ii) a mixture of endo-anhydroverticillol-3,4-epoxide and endo-anhydroverticillol-7,8-epoxide (29) (45.5mg, 61.9%), and (iii) endo-anhydroverticillol-3,4,7,8-diepoxide (21.5mg, 27.6%) as a white solid, m.p. 136.5-139.5°C (methanol); δ_H 0.85 (CH_3), 1.06 (CH_3), 1.32 (CH_3), 1.37 (CH_3), 1.78 (m, CH_3), 1.20-3.20 (m, 16H), 5.50-5.75 (m, :CH); δ_C 134.8, 124.5(d), 66.2(d), 62.7(d), 62.0, 61.5, 41.8(d), 39.9(d), 38.4(t), 36.5(t), 36.2, 33.3(t), 30.0(t), 28.0(q), 24.2(t), 23.8(q), 23.1(t), 22.7(q), 16.6(q), 16.4(q); m/z 304.2387; ($C_{20}H_{32}O_2$ requires M, 304.2400 (this product was contaminated with several minor impurities). The mixture of mono-epoxides was separated by reverse phase HPLC using methanol-water (17:3) as eluant to give in order of elution: (i) endo-anhydroverticillol-7,8-epoxide (29) (16.2mg, 22%) as an unstable waxy solid; δ_H 0.82 (CH_3), 0.85 (CH_3), 1.27 (CH_3), 1.61 (m, CH_3), 1.61 (m, CH_3), 1.80 (CH3), 1.20-2.70 (m, 14H), 2.95 (dd, J 9 and 2Hz, epoxide H), 4.80-5.05 (m, :CH), 5.40-5.60 (m, :CH); δ_C 135.6, 133.0, 130.1(d), 122.6(d), 62.6, 62.5(d), 42.6(d), 40.1(t), 38.7(t), 38.5(d), 35.4, 33.7(t), 30.0(t), 27.8(q), 24.4(t), 23.2(q), 23.1(q), 22.7(t), 16.7(q), 16.1(q); m/z 288.2457; $C_{20}H_{32}O$ requires M 288.2452; and (ii) endo-anhydroverticillol-3,4-epoxide (20.6mg, 28%) as an unstable waxy solid; δ_H 0.75 (CH_3), 1.00 (CH_3), 1.25 (CH_3), 1.64 (m, CH_3), 1.76 (m, CH_3), 1.38-2.90 (m, 14H), 2.65 (dd, J 10 and 2Hz, epoxide H), 5.40-5.67 (m, 2 x :CH); δ_C 135.0, 132.8, 124.8(d), 123.4(d), 66.6(d), 62.1, 42.7(d), 39.4(d), 39.1(t), 37.8(t), 36.6, 33.8(t), 30.6(t), 27.4(q), 26.5(t), 23.5(q), 22.9(t), 22.9(q), 16.3(q), 15.0(q); m/z 288.2452; $C_{20}H_{32}O$ requires M 288.2452.

Crystallographic Analysis of the Pentadecatetraene (19), the Allylic Alcohol (23) and Verticillol-7,8-epoxide (27).

Crystal data of (19) $C_{20}H_{20}$, M = 270.44, Triclinic, a = 8.705(4), b = 9.392(2), c = 12.810(2) Å, α = 93.47(2), β = 100.84(3), γ = 122.95(3)°, U = 846.15 $Å^3$, z = 2, Dc = 1.06g cm^{-3}, F(000) = 500, Space group $\bar{P}1$, Cu-k_α radiation λ = 1.54178 Å, μ (Cu-k_α) = 4.4 cm^{-1}, Crystal size 0.6 x 0.35 x 0.03mm, θmax = 66°. 2946 reflections, 1568 observed, Final R 4.02%, R_W 4.53%

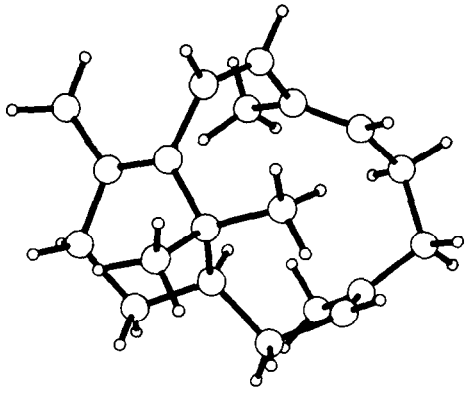


Figure 1. Crystal structure of the pentadecatetraene (19)

Crystal data of (23). $C_{20}H_{32}O_1$, M = 288.46, Monoclinic, a = 25.308(3), b = 16.308(2), c = 8.945(1) Å, β = 109.66(1)°, U = 3476.84 $Å^3$, z = 8, Dc = 1.10g cm^3, F(000) = 1280, Space group C2/c, Cu-k_α radiation λ = 1.54178 Å, μ (Cu-k_α) = 5.0 cm^{-1}, Crystal size 0.6 x 0.2 x 0.12 mm, θmax = 76°, 3622 reflections, 1939 observed, Final R 4.48%, R_W 4.89%.

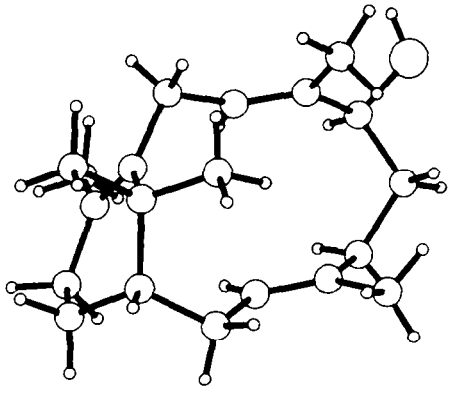


Figure 2. Crystal structure of the allylic alcohol (23)

Crystal data of (27). $C_{20}H_{32}O_2$, M = 306.47, Monoclinic, a = 8.468(1), b = 9.591(1), c = 11.423(1) Å, β = 94.77(1)°, U = 924.56 $Å^3$, z = 2, Dc = 1.10g cm^{-3}, F(000) = 340, Space group $P2_1$, Cu-k_α radiation λ = 1.54178 Å, μ(Cu-k_α)= 5.3cm^{-1}, Crystal size 0.75 x 0.6 x 0.1mm, θmax = 76°, 2043 reflections, 1632 observed, Final R 3.45%, R_W4.27%.

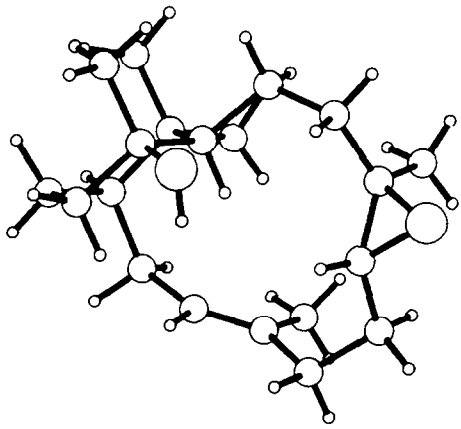


Figure 3. Crystal structure of the verticillol-7,8-epoxide (27)

In each case crystals were mounted on an Enraf-Nonius CAD4 diffractometer and 25 reflections were used to dermine accurate lattice parameters. Intensity data were collected over the ranges above, those with $I > 3\,\sigma(I)$ were considered observed and used in the subsequent refinement. The data were corrected for Lorentz and polarisation factors but no absorption corrections were made. Crystallographic calculations were performed using the CRYSTALS system of programs. The structures were solved by direct methods using the MULTAN program. Least squares refinement including anisotropic thermal parameters for non-hydrogen atoms and isotropic refinement of hydrogen atoms located in a difference Fourier synthesis terminated at the R values indicated above. Final difference maps showed no features in excess of 0.2 $eÅ^{-3}$.

The resulting structures and conformations of all three molecules are shown in Figures 1-3. In verticillol 7,8-epoxide (27) the cyclohexane ring adopts an ideal chair conformation with ring C(2) and methyl axial and ring C(10) and alcohol equatorial. In the allylic alchohol (23) the cyclohexene ring is in the half-chair conformation with ring C(2) again axial. However, in the pentadecatetraene (19) the cyclohexene ring is in the less stable half-boat conformation, presumably due to the different stereochemistry at C(1) where the ring C(2) is now equatorial. The more flexible 12-membered rings are in broadly similar conformations in (23) and (27) after allowance is made for the different constaints in the 7,8,9 region caused by double bond and epoxide ring formation. However this ring is in a very different conformation in (19). Although this structure contains three alternating double bonds these are totally unconjugated and the major cause of the different conformation appears to be the change in configuration at the C(1) centre. Despite these differences in conformation the bond lengths and bond angles in all three structures are remarkably similar, showing the same distortions to close the large ring, with the most extreme example the enlargement of the bond angle at C(3).

Structures (23) and (27) both show intermolecular hydrogen bonding. In (23), with only one oxygen atom, there are two hydrogen bonds to two different symmetry related molecuoles of identical length, with the hydrogen atom disordered 50-50 between the two possible sites. In (27) the alcoholic hydrogen forms an intermolecular hydrogen bond to a symmetry related epoxide oxygen.

The refined fractional atomic coordinates, bond lengths, bond angles, torsion angles, deviations from the

mean ring planes, thermal parameters and observed and calculated structure factors are all listed in a Supplementary Publication (See Notice to Authors, Tetrahedron, **1984**, 40(2), ii.).

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REFERENCES

1. See: R.W.Miller, *J. Nat. Prod.*, **1980**, *43*, 425; B.Lythgoe, *The Alkaloids*, Ed. R.H.F.Manske, Acad. Press, N.Y., **1968**, Vol X, p 597, and references cited therein.
2. e.g. M.C.Wani, H.L.Taylor, M.E.Wall, P.Coggon and A.T.McPhail, *J. Am. Chem. Soc.*, **1971**, *93*, 2325; see also citations in ref 3.
3. For complete bibliography see: J.D.Winkler and J.P.Hey, *J. Am. Chem. Soc.*, **1986**, *108*, 6425; A.S.Kende, S.Johnson, P.Sanfilippo, J.C.Hodges and L.N.Jungheim, *J. Am. Chem. Soc.*, **1986**, *1 108*, 3513; C.S.Swindell and S.F.Britcher, *J. Org. Chem.*, **1986**, *51*, 793; G.A.Kraus, P.J.Thomas and Y-S Hon, *J. Chem. Soc., Chem. Commun.*, **1987**, 1849; L.Pettersson, T.Frejd and G.Magnusson, *Tetrahedron Lett.*, **1987**, *28*, 2753; C.S.Swindell and B.P.Patel, *Tetrahedron Lett.*, **1987**, *28*, 5275; P.A.Wender and M.S.Snapper, *Tetrahedron Lett.*, **1987**, *28*, 2221; R.A.Holton, R.R.Juo, H.B.Kim, A.D.Williams, S.Harusawa, R.E.Lowenthal and S.Yogai, *J. Am. Chem. Soc.*, **1988**, *110*, 6558; C.S.Swindell and B.P.Patel, *J.Org. Chem.*, **1990**, *55*, 3.
4. B.Karlsson, A-M.Pilotti, A-C.Söderholm, T.Norin, S.Sundin and M.Sumimoto, *Tetrahedron*, **1978**, *34*, 2349.
5. D.F.Wiemer, J.Meinwald, G.D.Prestwich and I.Miura, *J. Org. Chem.*, **1979**, *44*, 3950; T.Kato, M. Suzuki and T.Kobayashi and B.P.Moore, *ibid*, **1980**, *45*, 1126.
6. D.R.Robinson and C.A.West, *Biochem.*, **1970**, *9*, 70.
7. See for example: W.G.Dauben, G.H.Beasley, M.D.Broadhurst, B.Muller, D.J.Peppard, P.Pesnelle and C.Suter, *J. Am. Chem. Soc.*, **1974**, *96*, 4724; L.Crombie, G.Kneen, G.Pattenden and D.Whybrow, *J. Chem. Soc., Perkin Trans I*, **1980**, 1711.
8. Preliminary communication: C.B.Jackson and G.Pattenden, *Tetrahedron Lett.*, **1985**, *26*, 3393; for a synthesis of a geometrical isomer of an anhydroverticillol see: T.Kumagai, F.Ise, T.Uyehara and T.Kato, *Chemistry Lett.*, **1981**, 25.
9. Preliminary communication: M.J.Begley, C.B.Jackson and G.Pattenden, *Tetrahedron Lett.*, **1985**, *26*, 3397.
10. G.Stork and R.L.Danheiser, *J. Org. Chem.*, **1973**, *38*, 1775.
11. J.K.Rasmussen, *Synthesis*, **1977**, 91, and references cited therein; J.W.Patterson Jr. and J.H.Fried, *J. Org. Chem.*, **1974**, *39*, 2506; T.Mukaiyama and M.Hayashi, *Chem. Lett.*, **1974**, 15; T.Mukaiyama,

K.Saigo and O.Takazawa, *ibid.*, **1976**, 1033.

12. J.B.Heather, R.S.D.Mittal and C.J.Sih, *J. Am. Chem. Soc.*, **1976**, *98*, 3661.
13. M.A.Umbreit and K.B.Sharpless, *J. Am. Chem. Soc.*, **1977**, *99*, 5526 and references cited therein.
14. J.E.McMurry and K.L.Kees, *J. Org. Chem.*, **1977**, *42*, 2655; J.E.McMurry, M.P.Fleming, K.L.Kees and L.R.Krepski, *ibid.*, **1978**, *43*, 3255; J.E.McMurry, Acc. Chem. Res., **1983**, *16*, 405.
15. C.B.Jackson, PhD Thesis, University of Nottingham, 1985.
16. See: A.J.Birch, *Quarterly Rev.*, **1950**, *4*, 69; G.W.Watt, *Chemical Rev.*, **1950**, *46*, 317.
17. For a recent review of electrophilic transannular cyclisations see: D.A.Harrowven and G.Pattenden, *Comprehensive Organic Synthesis*, Vol.3, Pergamon **1990**.
18. S.A.Look and W.Fenical, *J. Org. Chem.*, **1982**, *47*, 4129.
19. a) A.M.Birch and G.Pattenden, *Tetrahedron Lett.*, **1982**, 23, 991; b) A.M.Birch and G.Pattenden, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1913.
20. a) G.Pattenden and S.J.Teague, *Tetrahedron Lett.*, **1984**, 25, 3021; b) G.Pattenden and S.J.Teague, *Tetrahedron*, **1987**, *43*, 5637.
21. a) P.S.Manchand and J.F.Blount, *J. Org. Chem.*, **1977**, *42*, 3824; b) R.Toubiana, M.-J.Toubiana, A.T.McPhail, R.W.Miller and K.Tori, *J. Chem. Soc., Perkin Trans. II*, **1976**, 1881.
22. For examples *via* radical intermediates see: a) R.Dowbenko, *J. Org. Chem.* **1964**, *29*, 946; b) T.W.Sam and J.K.Sutherland, *J. Chem. Soc., Chem. Commun.*, **1971**, 970; c) P.Y.Johnson and M.A.Priest, *J. Am. Chem. Soc.*, **1974**, *96*, 5618; d) P.Y.Johnson and M.A.Priest, *Tetrahedron Lett.*, **1975**, 3133; e) M.E.Kuehne and R.E.Damon, *J. Org. Chem.* **1977**, *42*, 1825; f) E.Malamidou-Xenikaki and N.Alexandrou, *Tetrahedron Lett.*, **1982**, *23*, 3957; g) J.D.Winkler and V.Sridar, *J. Am. Chem. Soc.*, **1986**, *108*, 1708; h) Y.Tobe, T.Iseki, K.Kakiuchi and Y.Odaira, *Tetrahedron Lett.*, **1984**, *25*, 3895; i) T.Sato, K.Nishiyama, A.Morita and Y.Iitaka, *Bull. Chem. Soc. Jpn.*, **1985**, *58*, 2366; j) A.J.Bloodworth, D.Crich and T.Melvin, *J. Chem. Soc., Chem. Comun.*, **1987**, 786; k) F.MacCorquodale and J.C.Walton, *J. Chem. Soc., Chem. Commun.*, **1987**, 1456.