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# CYTOCHALASAN SYNTHESIS SYNTHESIS OF (17S,18S)-17,18-DIHYDROXY-10-(PROP-2-YL)-14-METHYL-[11]CYTOCHALASA-6(7),13Z,19E-TRIENE-1,21-DIONE, AN ISOMER OF ASPOCHALASIN C

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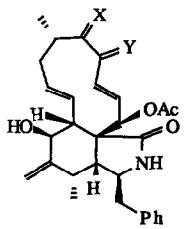
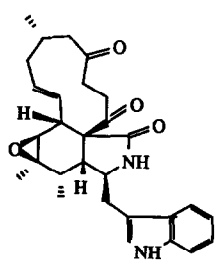
Abstract On heating a dilute solution of a 2 1 mixture of the (8'E)- and (8'Z)-3-(1-oxotrienyl)-$\Delta^3$-pyrrolin-2-ones (36), Diels Alder cyclization occurred The minor (8'Z)-pyrrolinone cyclized stereoselectively to give the endo adduct (39) which has the aspochalasan stereochemistry around the hydrogenated isoindolone nucleus However the major (8'E)-pyrrolinone gave a mixture of endo and exo isomers (41) and (43) in which the undesired exo adduct (43) was the major component Adduct (39) was converted into dihydroxyenone (48), the (13,14)-Z-isomer of aspochalasin C(4)

The cytochalasans, e.g. cytochalasin D (1), comprise a group of fungal metabolites of some interest because of their biological activity [1] Recently a synthetic approach to these compounds was developed which uses a stereoselective intramolecular Diels Alder reaction to form the large-ring and hydrogenated isoindolone fragments simultaneously [2] Using this strategy total syntheses of cytochalasins H (2) and G (3) have been completed [3,4]



(1) X = O, Y = ß-Me, -OH
(2) X = $H_2$, Y = ß-OH, -Me



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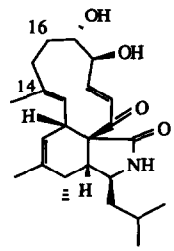
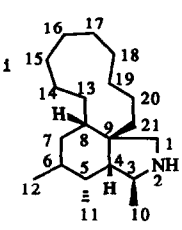


(4)

A small group of natural products related to the cytochalasans but differing from them in having a methyl substitutent attached to C(14) and no methyl substitutent at C(16), are the aspochalasans, e.g aspochalasin C (4) [5] The aspochalasans also differ from the cytochalasans in that they are derived biosynthetically from leucine which gives rise to a prop-2-yl substituent at C(10).[6,7] Because of the usefulness of the intramolecular Diels Alder

A special nomenclature has been developed for the cytochalasans and will be used in this paper.[6] Formula i shows the parent [11]cytochalasan nucleus and the numbering system used Unnatural stereochemistry and extra substituents are named in the usual way, e.g aspochalasin A, ii, is 14-methyl-10-(prop-2-yl)-[11]-cytochalasa-6(7),13E,19E-triene-1,17,18,21-tetra-one



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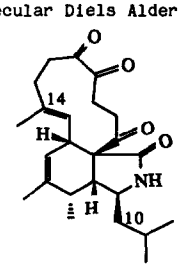
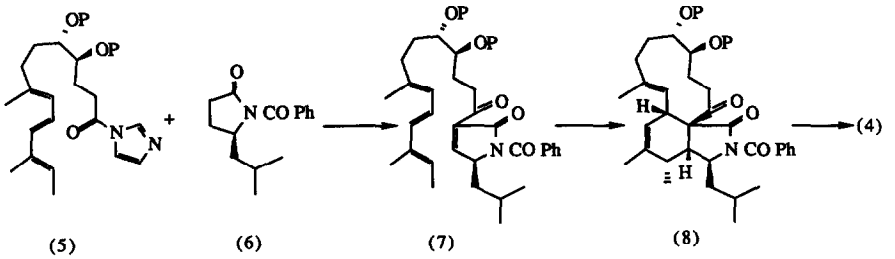


ii

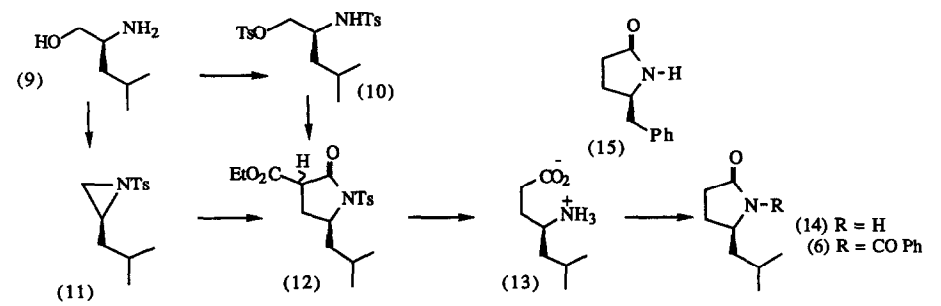
reaction for the synthesis of cytochalasans, it was of interest to examine the suitability of this approach for aspochalasan synthesis

To synthesize aspochalasin C(4), it was proposed to condense a suitably functionalized long-chain trienoyl imidazolide (5) with the L-leucine derived (5R)-5-(2-methylpropyl)-pyrrolidinone (6) Pyrrolidinone oxidation would then provide the 3-(1-oxotrienyl)-$\Delta^3$-pyrrolin-2-one (7), which, by analogy with earlier work,[2-4] was expected to undergo a stereoselective intramolecular Diels Alder cyclization giving adduct (8), a promising intermediate for aspochalasin C synthesis.



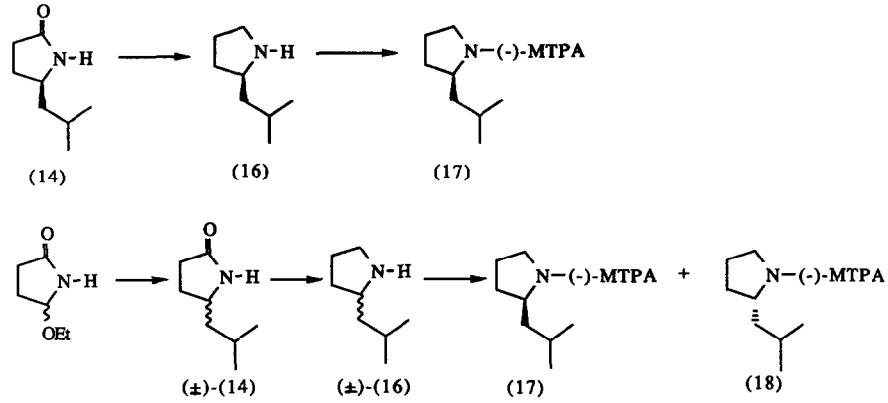

(5) (6) (7) (8)

Synthesis of the (5R)-1-Benzoyl-5-(2-methylpropyl)pyrrolidinone (6) The synthesis of pyrrolidinone (6) from L-leucine was based upon the literature synthesis of the corresponding 5-phenylmethylpyrrolidinone (15) from phenylalanine [7,8] Thus lithium aluminium hydride reduction of L-leucine methyl ester gave the amino-alcohol (9) which was converted into its bis-toluene-p-sulphonate (10). This was heated under reflux in tetrahydrofuran with an excess of potassium t-butoxide and diethyl malonate, which gave the 3-ethoxycarbonylpyrrolidinone (12) as a mixture of epimers at C(3). This mixture could also be obtained by treatment of the N-toluene-p-sulphonylaziridine (11) with potassium t-butoxide - diethyl malonate. Hydrolysis, decarboxylation, and removal of the toluene-p-sulphonyl group, were achieved by heating in 47% hydrogen bromide, and the amino-acid (13) so formed cyclized by heating in solution in damp dioxan for several hours to provide pyrrolidinone (14) Benzoylation then gave the N-benzoyl-5-(2-methylpropyl)-pyrrolidinone (6)



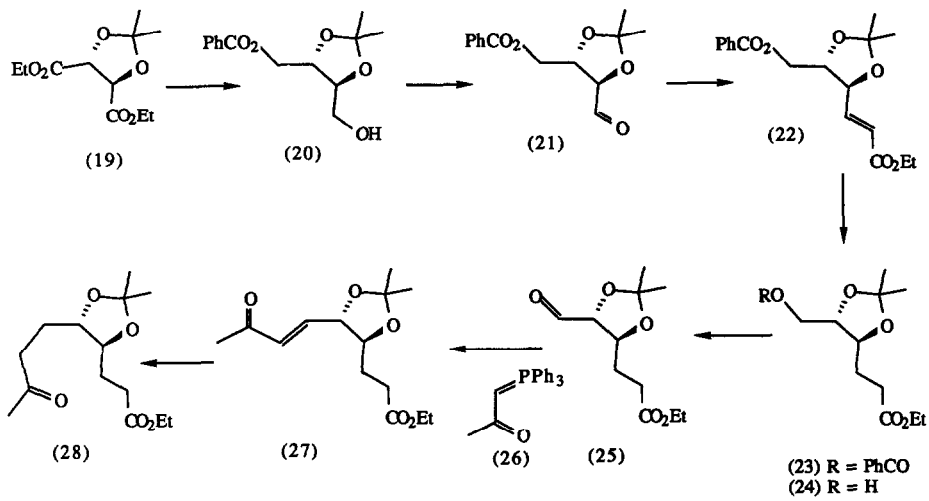

(9) (10) (15) (11) (12) (13)

The optical purity of the pyrrolidinone (14) was checked by lithium aluminium hydride reduction to the corresponding pyrrolidine (16) which was N-acylated using (-)-Mosher's acid chloride, and the N-acylated pyrrolidine (17) so obtained compared with the mixture of derivatives prepared from the racemic pyrrolidinone. Thus reduction of succinimide using sodium borohydride in ethanol gave 5-ethoxypyrrolidin-2-one which was converted into the racemic 5-(2-methylpropyl)-pyrrolidinone (14) by treatment with 2-methylpropylmagnesium bromide [9] Reduction and acylation using (-)-Mosher's acid chloride, then gave the two diastereoisomeric derivatives (17) and (18) which could be separated, and which were clearly distinguishable by $^1$H n m r. None of the (2S)-pyrrolidine Mosher's derivative (18) could be detected in the crude mixture obtained from the (5R)-pyrrolidinone (14) indicating that the optical purity of (17) corresponded to an enantiomeric excess of at least 95%




MTPA = α-methoxy-α-trifluoromethylphenylacetyl-

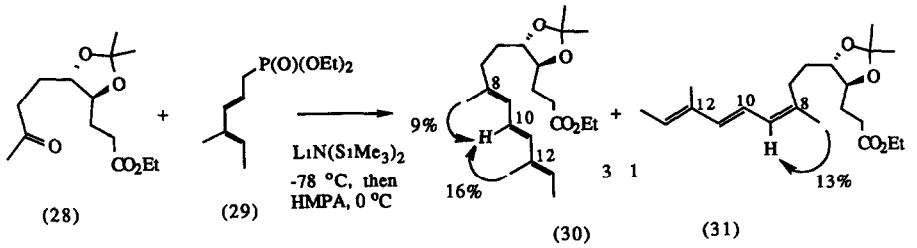
Synthesis of the Long-chain Trienoyl Imidazolide. Following published procedures,[10,11] L-(+)-diethyl tartrate (19) was converted into the hydroxybenzoate (20) which was oxidized and the aldehyde (21) so obtained condensed with triethylphosphonoacetate to provide the unsaturated ester (22) (60%) Hydrogenation and treatment with sodium ethoxide in ethanol then gave the saturated alcohol (24), which was oxidized to aldehyde (25) using oxalyl chloride - dimethyl sulphoxide, and the aldehyde condensed with the keto-ylid (26) to give the unsaturated keto-ester (27) A second hydrogenation then gave the key keto-ester (28).




The next stage of the synthesis of the trienoyl imidazolide involved the introduction of the sensitive conjugated triene unit To achieve this the condensation of ketone (28) with the dienyl phosphonate (29) was investigated This dienyl phosphonate, as its lithium salt, had been used during the syntheses of cytochalasans (2) and (3),[3,4] and conditions for its stereoselective condensation with aldehydes to provide (E,E,E)-trienes in good yield had been developed.[2] However in the present case, the presence of the 14-methyl substitutent in aspochalasin C(4) required the condensation of the dienyl phosphonate be carried out using a methyl ketone, and so lower stereoselectivity was expected

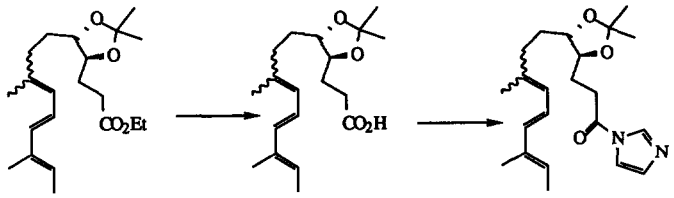
In the event, the conditions[2] that had proved useful for condensing dienylphosphonate (29) with aldehydes were found to be less useful for its condensation with ketones. Thus addition of the lithium salt of the dienyl phosphonate (29) to the methyl ketone (28) at -78°C, followed by warming to 0°C with addition of hexamethylphosphoric triamide to promote

the fragmentation step, gave only modest yields, 10 - 25%, of trienes (30) and (31), ratio ca 3 1. However the use of the potassium salt of the dienyl phosphonate, formed using potassium hexamethyldisilazide as base, gave significantly better results, with yields of the trienes or up to 90%. The mixture of trienes so obtained, after flash chromatography over base washed silica, was again estimated to contain the (8E)- and (8Z-)-isomers (30) and (31) in a ratio of 3 1, together with a minor component accounting for about 10% of the mixture. This minor component was not identified, but may correspond to one of the (12Z)-isomers



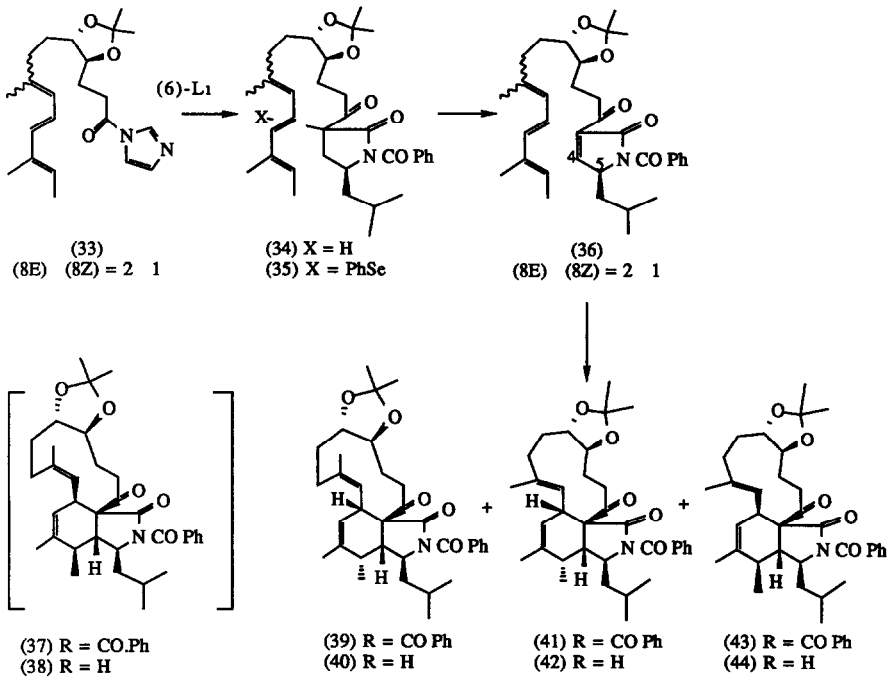

The conjugated trienes (30) and (31) were very sensitive to acid, and no attempt was made to separate them However n.O.e difference studies, at 500 MHz on a mixture of the corresponding methyl esters in benzene-$d_6$, showed that the major isomer was the desired (8E)-isomer (30) since irradiation of the 8-methyl group caused a 9% enhancement of H(10) and had no effect on H(9), whereas for the minor isomer (31), irradiation of the 8-methyl group had no effect on H(10) but caused a 13% enhancement of H(9). For the major isomer (30) irradiation of the 12-methyl group also enhanced H(10) (16%). This selective but not exclusive formation of the (E,E,E)-triene had been expected by analogy with the corresponding aldehyde condensations

The mixture of trienyl esters (30) and (31) was hydrolysed, and the acid (32) so obtained treated with carbonyl 1,1'-diimidazole to give the trienoyl imidazolide (33) as a mixture of (8E)- and (8Z)-isomers, ratio ca 2 1, respectively.




Diels Alder Reaction and Aspochalasan Synthesis. A solution of the acyl imidazolide (33) was added to the lithium salt of the pyrrolidinone (6), generated using lithium hexamethyldisilazide as base, to provide the 3-(1-oxotrienyl)pyrrolidinone (34) as a mixture of epimers at C(3). These could not be separated from the excess of unchanged pyrrolidinone (6), however treatment of this mixture with just enough base to deprotonate the more acidic 3-(1-oxotrienyl)pyrrolidinone, followed by addition of benzeneselenenyl chloride, gave the 3-phenylselenopyrrolidinone (35) which was separated from the unchanged pyrrolidinone (6) by flash chromatography on base washed silica. Oxidative elimination of the phenylseleno-substituent was then carried out under the conditions developed previously[2] using m-chloroperoxybenzoic acid and excess hydrogen peroxide, first at -50°C followed by brief warming to 0°C This gave a solution which $^1$H n m.r showed to contain the sensitive pyrrolin-2-one (36), $\delta_H$ 5.16 (1 H, m, 5-H) and 8 12 (1 H, narrow m, 4-H). Because of the known tendency of 3-(1-oxotrienyl)-$\Delta^3$-pyrrolinones to polymerize on isolation, no attempt was made to isolate pyrrolinone (36) [2-4] Instead, after brief drying, the pyrrolinone solution was diluted with

toluene and heated at 85°C for several hours. Under these conditions Diels Alder cyclization occurred and a mixture of three Diels Alder products was isolated [combined yield ca 30% based on selenide (35)].




The two major adducts could be isolated pure by repeated chromatography of the mixture of Diels Alder products and were identified as the (13Z)-endo-isomer (39) and the (13E)-exo-isomer (43). However it was more convenient to remove the N-benzoyl substituent by treatment with sodium hydroxide in methanol. This gave a mixture of the corresponding NH compounds which were separated by flash chromatography and identified as the (13Z)-endo-, the (13E)-endo-, and the (13E)-exo-isomers (40), (42), and (44), ratio 3 1 2, respectively. None of the (13Z)-exo-adduct (37) or its debenzoylated product (38) was isolated

Structures were assigned to the Diels Alder adducts (39) and (43), and to the corresponding NH-compounds (40), (42), and (44), on the basis of extensive $^1$H n.m r. studies Figure 1 shows selected n.O.e data for the two major Diels Alder adducts (39) and (43) together with further data acquired for the three NH-products (40), (42), and (44)

In particular the stereochemistry around the isoindolone nucleus for the major adduct (39) was established by the strong n.O e enhancement (17%) of H(3) and absence of any n.O e. enhancement of H(4) on irradiation of Me(11), and by the enhancements of H(8) (9%) and H(4) (7%) on irradiation of H(5). For the major NH-compound (40) this stereochemistry was confirmed by the 5% enhancement of H(3) observed on irradiation of Me(12) However of particular interest for these compounds were the n O e effects observed across their 13,14-double-bonds Thus for the Diels Alder adduct (39) irradiation of H(13) caused an n.O e. enhancement of the 14-methyl group of 1.6% consistent with the 13,14-double-bond having the Z-geometry [cf the 1.4% enhancement of Me(12) on irradiation of H(7)] This was confirmed for the major NH-compound (40) when irradiation of the 14-methyl substituent caused a 9% n.O e. enhancement of H(13).

The second major Diels Alder adduct was identified as an exo-isomer because of the n O.e. enhancements of H(4) (8%) and H(13) (6%) on irradiation of Me(11), and the lack of any n.O.e. enhancement of H(5) and the n O.e. enhancement of H(13) (3%) on irradiation of H(4).* However this adduct was shown to possess the (E)-geometry across the 13,14-double-bond since irradiation of the 14-methyl-substitutent of the corresponding NH-compound had only a small effect (2%) on H(13) [cf. the 11% enhancement of H(7) on irradiation of Me(12)], and a larger effect (11%) on H(8). The second Diels Alder adduct was therefore identified as shown in formula (43).

The structures assigned to adducts (39) and (43), and their NH-derivatives (40) and (44), were supported by their H(7)-H(8) coupling constants Thus for (39) and (40) the dihedral angle between the C(7)-H and C(8)-H bonds is approximately 90° and results in very small H(7)-H(8) coupling as was observed (1 - 2 Hz). In contrast the H(7)-H(8) coupling for compounds (43) and (44) is significantly larger (ca. 7 Hz) consistent with the smaller C(7)-H to C(8)-H dihedral angles This effect has been observed before for related Diels Alder adducts and would appear to be a good guide to endo - exo stereochemistry

Finally the minor NH-compound was shown to be an endo-isomer because of the small H(7)-H(8) coupling, and by the n O e. enhancement of H(3) on irradiation of Me(11) and Me(12), 13 and 2%, respectively. Its structure was therefore identified as that shown in formula (42), and the (E)-geometry across the 13,14-double-bond was confirmed by irradiation of the 14-methyl group which had little effect on H(13) but a significant effect on H(8) (10%) [cf. the results obtained for (44)]

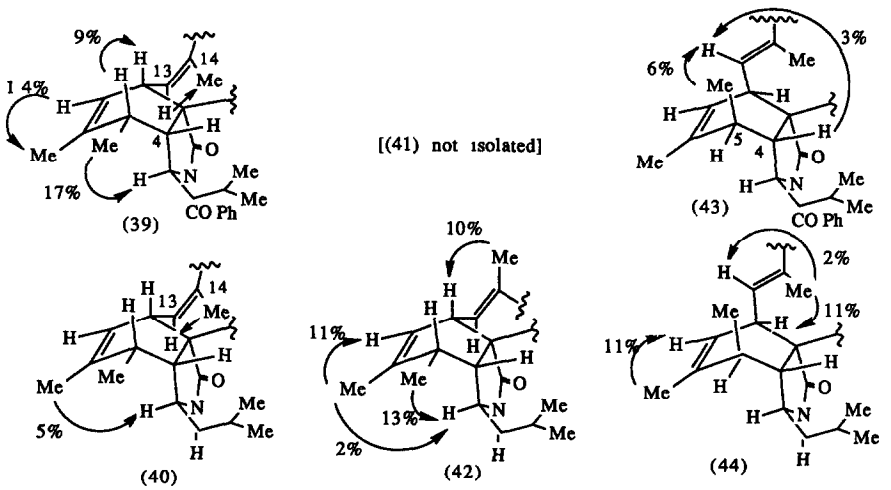
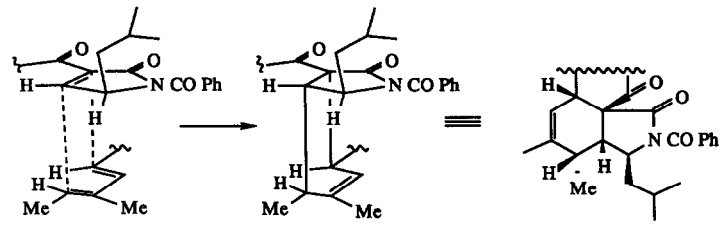



Figure 1

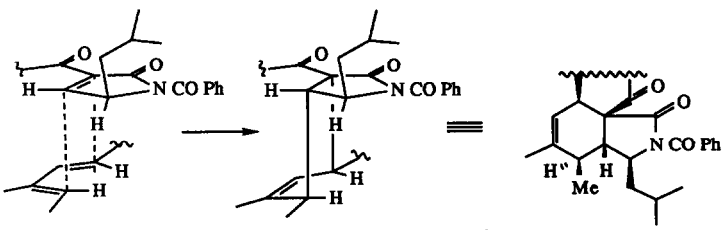
The distribution of adducts from the Diels Alder reaction was unexpected. Firstly although a 2 1 mixture of (8'E)- to (8'Z)-3-(1-oxotrienyl)pyrrolinones (36) had been cyclized, the ratio of 13,14-(E)- to 13,14-(Z)-adducts, i e [(41) + (43)] (39), was 1 1. Secondly although the cyclization of the (8'Z)-3-(1-oxotrienyl)pyrrolinone (36) was stereoselective and gave only the endo-adduct (39), the cyclization of the (8'E)-isomer had not been stereoselective and indeed had given more of the unwanted exo-isomer (43) with the ratio (43) (41) being approximately 2 1 It thus transpired that the major Diels Alder adduct (39) had been derived from the minor trienylpyrrolinone starting material, and that the endo-isomer (41) required for an aspochalasan synthesis was the minor component of the mixture

* The n O e. effects observed between H(13) and Me(11) and H(4) have been observed before for exo-Diels Alder adducts structurally related to (43), and have been interpreted in terms of the conformation shown in Figure 1

All three Diels Alder products had been formed by addition of the triene onto the less hindered face of the pyrrolinone away from the 2-methylpropyl substitutuent at C(5). For the formation of the endo-adducts (39) and (41), this addition had taken place with the triene endo to the pyrrolinone ring, whereas for the exo-adduct (43), the triene must have been endo to the ketone substituent as shown in Figure 2.




Triene endo to pyrrolinone (39), (41)



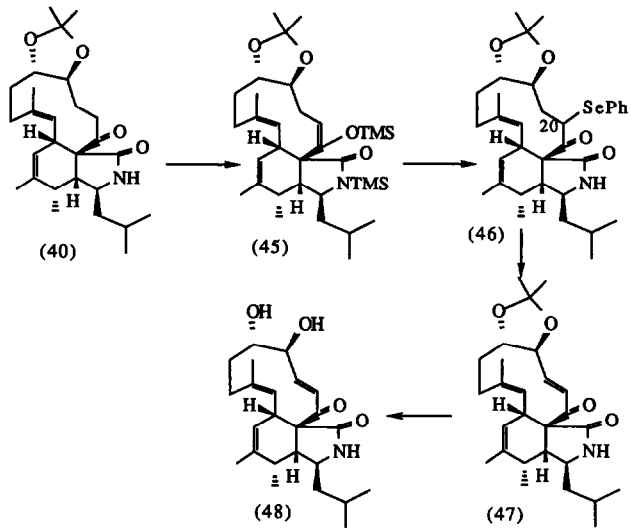

Triene endo to ketone (43)

Figure 2

In previous studies of the formation of [11]cytochalasans via intramolecular Diels Alder reactions of long-chain 3-(1-oxotrienyl)pyrrolinones, the endo-exo selectivity observed was strongly in favour of the desired endo-isomers as found here for the (8'Z)-3-(1-oxotrienyl)-pyrrolinone (36) [2-4] However the formation of [13]cytochalasans shows only low endo-exo selectivity,[12] and so it appears that the factors controlling the stereoselectivity may be rather finely balanced. In the present case it may be that the additional methyl substituent attached to C(8) of the trienylpyrrolinone discourages cyclization endo to the pyrrolinone ring for the (8'E)-isomer but not for the (8'Z)-isomer, but the precise steric origins of this are not clear The formation of the increased percentage of (Z)-adducts may reflect more efficient cyclization of the (8'Z)-trienylpyrrolinone (36), or it may be a consequence of triene equilibration before cyclization Preliminary investigations carried out to check the possibility of triene equilibration were inconclusive.

Finally the major Diels Alder adduct (39) was taken through to the dihydroxy-enone (48), the 13,14-(Z)-isomer of aspochalasin C(4) [5] Thus treatment of the major NH-product (40) with lithium diisopropylamide and trimethylsilyl chloride gave the enol ether (45) which reacted with benzeneselenenyl chloride to give selenide (46) as a single diastereoisomer, although the configuration at C(20) was not formally established Oxidative elimination of the phenylselenyl group then was achieved using hydrogen peroxide - pyridine, and the acetal protecting group removed by acid hydrolysis in aqueous methanol, to provide isoaspochalasin C (48) as a colourless oil Although the spectroscopic data obtained for this product resembled those of aspochalasin C (4), there were significant differences in their $^1$H n m r spectra and by t l c.* The corresponding diacetates were also distinctly different.

* We thank Dr H H Peter and Dr K Scheibli and Ciba-Geigy Ltd , Basle, Switzerland, for a sample of authentic aspochalasan C diacetate




## EXPERIMENTAL

I.r. spectra were measured on Perkin Elmer 297 and 1710 FT spectrophotometers, and $^1$H n.m r spectra were recorded on a Bruker WH 300 spectrometer (300 MHz) in chloroform-$d_1$, unless otherwise stated. Mass spectra were recorded on VG Micromass 16F, 30F, and ZAB 1F spectrometers using either electron impact (EI) or chemical ionization (CI) modes. Melting points were determined on a Kofler Block apparatus, and are uncorrected

Flash chromatography was carried out using Merck silica gel 60 Base washed silica was prepared by washing flash silica with saturated aqueous $KHCO_3$, and then with distilled water until neutral, followed by drying at 170°C for 3 days

All solvents were dried and distilled before use Ether refers to diethyl ether throughout, and light petroleum to the fraction boiling between 40 and 60°C. Lithium diisopropylamide (LDA) was prepared from equimolar amounts of n-butyl-lithium in hexane and diisopropylamine in tetrahydrofuran (THF) under an atmosphere of nitrogen at 0°C, lithium hexamethyldisilazide being similarly obtained from hexamethyldisilazane

(2S)-4-Methyl-2-toluene-p-sulphonylamidopentyl Toluene-p-sulphonate (10) - Toluene-p-sulphonyl chloride (1 16 g, 6 1 mmol) was added to a solution of the amino-alcohol (9) (0.18 g, 1.5 mmol) in pyridine (5 ml), and the mixture stirred at room temperature for 24 h before being poured into cold water (2 ml) The mixture was extracted with ethyl acetate, and the combined organic layers washed with dilute aqueous HCl (3 ml), aqueous $CuSO_4$ (3 ml), water (3 ml), saturated aqueous $NaHCO_3$ (3 ml), and brine (3 ml). After drying ($MgSO_4$), concentration under reduced pressure and flash chromatography of the residue using ether-light petroleum (1 5) as eluant gave (2S)-4-methyl-2-toluene-p-sulphonylamidopentyl toluene-p-sulphonate (10) (0 47 g, 72 %), as a white solid, m p. 101 - 102°C (Found C, 56.55, H, 6.4, N, 3.30 $C_{20}H_{27}NO_5S_2$ requires C, 56.45, H, 6.40, N, 3.3 %), $[\alpha]_D^{\circ}$ -68 4° (c 0 87 in benzene), $\nu_{max}$ ($CHCl_3$) 3 380, 3 030, 1 600, 1 190, 1 178, 1 162, 1 092, and 984 cm$^{-1}$, $\delta_H$ 0 59 and 0 76 (each 3 H, d, J 6.5 Hz, $CH_3$), 1.25 (2 H, m, $CH_2$), 1 40 (1 H, m, $CHMe_2$), 2.41 and 2.45 (each 3 H, s, aromatic-$CH_3$), 3.42 (1 H, m, CHN), 3.83 (1 H, dd, J 10, 4.5 Hz, OHCH), 3 93 (1 H, dd, J 10, 3 5 Hz, OHCH), 4 81 (1 H, d, J 8 5 Hz, NH), and 7 2 - 7 7 (8 H, m, aromatic H), m/z (CI) 443 ($M^+$ + 18, 100 %) and 254 ($M^+$ - 171, 92 %).

(3RS,5S)-3-Ethoxycarbonyl-5-(2-methylpropyl)-1-toluene-p-sulphonylpyrrolidin-2-one (12).- Diethyl malonate (0.51 ml, 3 3 mmol) was added to a solution of potassium t-butoxide (0 37 g, 3 3 mmol) in THF (20 ml), and the mixture heated under reflux under an atmosphere of nitrogen for 40 min After cooling, the bis-toluene-p-sulphonate (10) (0 47 g, 1 1 mmol) in THF (20 ml) was added dropwise, and the mixture heated under reflux for 4 h before being cooled Water (5 ml) and aqueous HCl (3 M) were added to adjust the pH to 6, and the mixture extracted with ether The combined organic layers were washed with brine (5 ml), dried ($MgSO_4$), and concentratred under reduced pressure Flash chromatography of the residue using ethyl acetate-light petroleum (1 8) as eluant gave (3RS,5S)-3-ethoxycarbonyl-5-(2-methylpropyl)-1-toluene-p-sulphonylpyrrolidin-2-one (12) (0 26 g, 66 %) as a white solid, a mixture of epimers at C(3), m p 74-78°C, $\nu_{max}$ 1 725 br, 1 600, 1 368, 1 170, and 1 088 cm$^{-1}$, $\delta_H$ 0.98 (6 H, overlapping d, J 6 5 Hz, 2 x $CH_3$), 1 22 and 1 24 (each 1.5 H, t, J 7 Hz, $OCH_2CH_3$ of each isomer), 1 35 - 2 65 (5 H, complex m), 2 43 (3 H, s, aromatic $CH_3$), 3 41 (0 5 H, dd, J 10 5, 5 Hz, 3-H), 3 56 (0 5 H, dd, J 11 5, 8 5 Hz, 3-H), 4 15 and 4 18 (each 1 H, q, J 7 Hz, $CH_2CH_3$ of each isomer), 4 3 - 4 5 (1 H, m, 5-H), 7 31 (2 H, d, J 8 Hz, aromatic H), and 7 92 (2 H, m, aromatic H), m/z (CI) 368 ($M^+$ + 1, 100 %)

via (2S)-2-(2-Methylpropyl)-1-toluene-p-sulphonylaziridine (11) Toluene-p-sulphonyl chloride (6.5 g, 34 mmol), 4-dimethylaminopyridine (0.1 g, 0.8 mmol), and triethylamine (3.4 g, 34 mmol), were added to a solution of the amino-alcohol (9) (1 0 g, 8.5 mmol) in dichloromethane (35 ml) at 0°C, and the mixture stirred for 15 h Water was added, and the organic phase separated, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography using ether-light petroleum as eluant gave (2S-2-(2-methylpropyl)-1-toluene-p-sulphonylaziridine (11) (1.5 g, 71 %) as a colourless oil, $\delta_H$ 0 86 and 0.87 (each 3 H, d, J 6 5 Hz, $CH_3$), 1 32 (2 H, m, $CH_2$), 1.61 (1 H, m, $CHMe_2$), 2 01 (1 H, d, J 4 5 Hz, HCHN), 2 44 (3 H, s, aromatic $CH_3$), 2 61 (1 H, d, J 7 Hz, HCHN), 2.77 (1 H, m, 2-H), and 7.32 and 7 81 (each 2 H, d, J 10 Hz, aromatic H), m/z (CI) 254 ($M^+$ + 1, 100 %) Treatment of the aziridine (11) with potassium t-butoxide and diethyl malonate as above gave the pyrrolidin-2-one (12) (70 - 75 %)

(5R)-5-(2-Methylpropyl)pyrrolidin-2-one (14).- A mixture of the 1-toluene-p-sulphonylpyrrolidinone (12) (1.45 g, 3 9 mmol) and 47 % aqueous HBr (8 4 ml, 72 mmol) was heated under reflux for 16 h. After cooling, water (10 ml) was added, and the mixture washed with ether. The aqueous phase was then concentrated under reduced pressure, and the resiude chromatographed on Amberlite IR 120 $H^+$ resin eluting with water and then with 1 1 880 $NH_3$ water to provide (4R)-4-amino-6-methylheptanoic acid (13) (0 56 g, 90 %) as a white solid, $\nu_{max}$ ($CHCl_3$) 2 500 - 3 600, 1 670, and 1 600 $cm^{-1}$, $\delta_H$ (methanol-$d_4$) 0.95 and 0 96 (each 3 H, d, J 6.5 Hz, $CH_3$), 1 46 (2 H, t, J 7 Hz, 5-$CH_2$), 1 66 - 1.85 (3 H, m, 3-$CH_2$ and 6-H), 2 35 - 2 42 (2 H, m, 2-$CH_2$), and 3 23 (1 H, m, 4-H).

The 4-amino-6-methylheptanoic acid (13) (0.17 g, 1.1 mmol) and dioxan (5 ml) were heated under reflux for 16 h Concentration under reduced pressure and flash chromatography using ethyl acetate-light petroleum (1 2) as eluant gave (5R)-5-(2-methylpropyl)pyrrolidin-2-one (14) (0 1 g, 67 %) as a white solid, m.p 72 - 74°C, $[\alpha]_D^{\mathring{A}}$° -13.4° (c 0.87 in $CHCl_3$), $\nu_{max}$ ($CHCl_3$) 3 440, and 1 690 $cm^{-1}$, $\delta_H$ 0 87 and 0 89 (each 3 H, d, J 6.5 Hz, $CH_3$), 1.23 and 1.43 (each 1 H, m, 4-H), 1 62 (2 H, m, 1'-$CH_2$), 2 19 (1 H, m, 2'-H), 2.28 (2 H, m, 3-$CH_2$), 3 67 (1 H, m, 5-H), and 7 48 (1 H, br s, NH), m/z (EI) 141 ($M^+$, 91 %).

To establish the optical purity of the 5-(2-methylpropyl)pyrrolidin-2-one (14), a sample (0 16 g, 1 1 mmol) in THF (2 ml) was added to a suspension of lithium aluminium hydride (87 mg, 2 2 mmol) in THF (2 ml), and the mixture heated under reflux under an atmosphere of nitrogen for 16 h Water was added, and the mixture extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure, to provide the 2-(2-methylpropyl)pyrrolidine (16) (0 14 g) as a colourless oil, $\delta_H$ 0 9 (6 H, d, J 6.54 Hz, 2 x $CH_3$), 1 20 (1 H, m, 2'-H), 1.25 - 1 38 (2 H, m, 1'-$CH_2$), 1 59 - 1 91 (5 H, complex m, 2 x $CH_2$ + NH), 2 80 (1 H, m, 2-H), and 2 99 (2 H, m, 5-$CH_2$).
(-)-α-Methoxy-α-trifluoromethylphenylacetyl chloride (150 mg, 0 6 mmol) was added to a solution of the pyrrolidine (16) (70 mg, 0.55 mmol) in $CCl_4$ (5 drops) and pyridine (5 drops), and the mixture stirred for 16 h Water was added, and the mixture extracted with ethyl acetate. After drying the combined organic extracts ($MgSO_4$), concentration under reduced pressure, and flash chromatography using ether-light petroleum (1 2) as eluant gave (2R)-2-(2-methylpropyl)-1-[(2S)-α-methoxy-α-trifluoromethylphenylacetyl]-pyrrolidine (17) (81 mg, 43 %) as a white solid, m p 163 - 165°C, $\nu_{max}$ ($CHCl_3$) 1 645 $cm^{-1}$, $\delta_H$ 0 96 and 1.03 (each 3 H, d, J 6 Hz, $CH_3$), 1 55 - 1 72 (5 H, complex m, 2 x $CH_2$ + $CHMe_2$), 1 88 (2 H, m, $CH_2$), 2 42 and 3.40 (each 1 H, m, 5-H), 3 66 (3 H, s, $OCH_3$), 4 29 (1 H, m, 2-H), and 7.36 - 7 56 (5 H, m, aromatic H), m/z (CI) 344 ($M^+$ + 1, 100 %)

(5RS)-5-(2-Methylpropyl)pyrrolidin-2-one [(±)-(14)] - A solution of 2-methylpropylmagnesium bromide in THF (0 65 M, 28.6 ml, 19 mmol) was added to 5-ethoxypyrrolidin-2-one (2.0 g, 16 mmol) in THF (15 ml) over 30 min with heating under reflux, under an atmosphere of nitrogen, and the heating was continued for 2 h The mixture was cooled, and saturated aqueous $NH_4Cl$ (5 ml) added Ether extraction, drying ($MgSO_4$), and concentration under reduced pressure, gave (5RS)-5-(2-methylpropyl)pyrrolidin-2-one [(±)-(14)] (1 83 g, 81 %), m p. 54 -57°C spectroscopically indistinguishable from the optically active material prepared earlier

Reduction to the (±)-2-(2-methylpropyl)pyrrolidine [(±)-(16)] using lithium aluminium hydride and acylation of the racemic pyrrolidine using (-)-α-methoxy-α-trifluoromethylphenylacetylchloride was carried out as described above for the optically active series Separation of the (2R)- and (2S)-diastereoisomers (17) and (18) was achieved by repeated flash chromatography using ether-light petroleum (1 2) as eluant to give (2S)-2-(2-methylpropyl)-1-[(2S)-α-methoxy-α-trifluoromethylphenylacetyl]pyrrolidine (18) as the less polar derivative, a white solid, m p. 126 - 128°C, $\nu_{max.}$ ($CHCl_3$) 1 650 $cm^{-1}$, $\delta_H$ 0 95 and 1 03 (each 3 H, d, J 6 Hz, $CH_3$), 1.1 - 1 9 (7 H, complex m, 3 x $CH_2$ + $CHMe_2$), 2.82 and 3 19 (each 1 H, m, 5-H), 3.69 (3 H, s, $OCH_3$), 4.32 (1 H, m, 2-H)and 7 34 - 7 58 (5 H, m, aromatic H), m/z (CI) 344 ($M^+$ + 1, 100 %), followed by the (2R)-diastereoisomer (17) identical with the sample prepared earlier.
(5R)-1-Benzoyl-5-(2-methylpropyl)pyrrolidin-2-one (6).- A solution of the 5-(2-methylpropyl)pyrrolidin-2-one (14) (50 mg, 0.35 mmol) in THF (1 ml) was added to a suspension of sodium hydride (20 mg of a 50 % dispersion in mineral oil, 0 43 mmol) in THF (2 ml), and the mixture stirred for 30 min. Benzoyl chloride (49 mg, 0 39 mmol) in THF (1 ml) was added, and the reaction stirred for 35 min before being quenched by the addition of water The mixture was extracted with ethyl acetate, and the combined organic extracts dried ($MgSO_4$), and concentrated under reduced pressure Flash chromatography using ether-light petroleum (2 3) as eluant gave (5R)-1-benzoyl-5-(2-methylpropyl)pyrrolidin-2-one (6) (48 mg, 57 %) as a white solid, m p. 81-83°C (Found C, 73 5, H, 7 95. $C_{15}H_{19}NO_2$ requires C, 73 45, H, 7 8 %), $[\alpha]_D^{\mathring{A}}$° + 207° (c 2 06 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3 025, 3 010, 1 740, 1 675,

1 305, 1 290, and 1 235 $cm^{-1}$, $\delta_H$ 0.98 and 1 01 (each 3 H, d, J 6.5 Hz, $CH_3$), 1 43 (1 H, m, 1'-H), 1.71 (1 H, m, 2'-H), 1.85 (2 H, m, 4-H and 1'-H), 2.28 (1 H, m, 4-H), 2.50 and 2.67 (each 1 H, m, 3-H), 4.55 (1 H, m, 5-H), and 7.38 - 7 63 (5 H, m, aromatic H), m/z (CI) 246 ($M^+$ + 1, 100 %)

Ethyl (4S,5S,2E)-6-Benzoyloxy-4,5-isopropylidenedioxyhex-2-enoate (22) - Triethylphosphonoacetate (3.39 g, 15.1 mmol) was added to a suspension of sodium hydride (0.73 g, 50 % dispersion in mineral oil, 15.2 mmol) in dimethoxyethane (20 ml), under an atmosphere of nitrogen, and the mixture stirred for 1 h at 0°C. A solution of the aldehyde (21)[11] (3.4 g, 12.8 mmol) in dimethoxyethane (8 ml) was added at 0°C, and the reaction mixture stirred for 50 min. before being warmed to 30°C. Water was added, and the mixture extracted with ether. After drying ($MgSO_4$), the combined organic extracts were concentrated under reduced pressure. Flash chromatography using ether-light petroleum (1 3) as eluant gave ethyl (4S,5S,2E)-6-benzyloxy-4,5-isopropylidenedioxyhex-2-enoate (22) (2.69, 60%) as a colourless oil, $[\alpha]_D^{20}$ -25.3° (c 1 15 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 1 720, 1 600, and 1 380 $cm^{-1}$, $\delta_H$ 1.29 (3 H, t, J 7 Hz, $CH_2CH_3$), 1.48 (2 H, s, 2 x $CH_3$), 4 13 (1 H, dt, J 8, 5 Hz, 5-H), 4.20 (2 H, q, J 7 Hz, $CH_2CH_3$), 4.49 and 4 54 (each 1 H, dd, J 12, 5 Hz, 6-H), 4.51 (1 H, m, 4-H), 6.16 (1 H, dd, J 16, 1 Hz, 2-H), 6.93 (1 H, dd, J 16, 6 Hz, 3-H), 7.44 (2 H, m, aromatic H), 7.57 (1 H, m, aromatic H), and 8 05 (2 H, m, aromatic H), m/z (CI) 352 ($M^+$ + 18, 52%) and 277 ($M^+$ - 57, 100%).

Ethyl (4S,5S)-6-Hydroxy-4,5-isopropylidenedioxyhexanoate (24).- A solution of the hex-2-enoate (22) (4.6 g, 14 mmol) in ethanol (50 ml) was added to a suspension of Pd/C (0.72 g, 10% Pd) in ethanol (100 ml), and the mixture stirred at room temperature under an atmosphere of hydrogen until no further uptake of hydrogen took place (2 5 h). The catalyst was filtered off, and the filtrate concentrated under reduced pressure Flash chromatography of the residue using ether-light petroleum (1 10) as eluant, gave the 6-benzoyloxyhexanoate (23) (3.7 g, 79%) as a colourless oil, $\delta_H$ 1 23 (3 H, t, J 7 Hz, $CH_2CH_3$), 1.41 and 1.43 (each 3 H, s, $CH_3$), 1.90 and 2 10 (each 1 H, m, 3-H), 2 47 - 2 56 (2 H, m, 2-$CH_2$), 3.98 (2 H, m, 4-H and 5-H), 4.13 (2 H, q, J 7 Hz, $CH_2CH_3$), 4.41 (1 H, dd, J 12, 5 Hz, 6-H), 4 49 (1 H, dd, J 12, 4 Hz, 6-H), 7.45 (2 H, m, aromatic H), 7.58 (1 H, m, aromatic H), and 8.1 (2 H, m, aromatic H).

Sodium (0 75 g, 32 mmol) was added to anhydrous ethanol (40 ml) followed by a sample of the benzoate (23) (5.5 g, 16 mmol), prepared as described above, in ethanol (20 ml). After 15 min saturated aqueous $NH_4Cl$ was added to the yellow solution, and the mixture concentrated under reduced pressure. Water and ether were added, and the organic phase separated, dried ($MgSO_4$), and concentrated under reduced pressure Flash chromatography of the residue using ether-light petroleum (1 3) as eluant gave ethyl (4S,5S)-6-hydroxy-4,5-isopropylidenedioxyhexanoate (24) (3.5 g, 91%), as a colourless oil, $\nu_{max}$ ($CHCl_3$) 3 580, 1 730, and 1 375 $cm^{-1}$, $\delta_H$ 1.25 (3 H, t, J 7 Hz, $CH_2CH_3$), 1.39 and 1.40 (each 3 H, s, $CH_3$), 1 79 - 1.97 (2 H, m, 3-$CH_2$), 2.15 (1 H, br.s, OH), 2.40 - 2.53 (2 H, m, 2-$CH_2$), 3 63 (1 H, m, 6-H), 3.77 (2 H, m, 4-H and 6-H), 3.90 (1 H, dt, J 8, 4 Hz, 5-H), and 4.13 (2 H, q, J 7 Hz, $CH_2CH_3$), m/z (EI) 217 ($M^+$ - 15, 60%).

Ethyl (4S,5S,6E)-4,5-Isopropylidenedioxy-8-oxonon-6-enoate (27).- Dimethyl sulphoxide (3.1 ml, 44 mmol) in dichloromethane (10 ml) was added to oxalyl chloride (1.9ml, 22 mol) in dichloromethane (30 ml) at -78°C under an atmosphere of argon. After 15 min, the 6-hydroxyhexanoate (24) (4 5 g, 19 mmol) in dichloromethane (15 ml) was added, followed after 30 min by triethylamine (6 7 ml, 48 mmol). The reaction mixture was warmed to room temperature, and saturated aqueous $NH_4Cl$ was added. Ether was added, and the organic phase separated, dried ($MgSO_4$), and concentrated under reduced pressure to leave the aldehyde (25) (4.4 g), $\delta_H$ (60 MHz) 9.4 (1 H, d, J 2 Hz, CHO).

A solution of this aldehyde (4.4 g) and the ylid (26) (6.7 g, 21 mmol) in benzene (20 ml) was heated under reflux for 16 h. After cooling the solvent was removed under reduced pressure Flash chromatography of the residue using ether-light petroleum (1 5) as eluant gave ethyl (4S,5S,6E)-4,5-isopropylidenedioxy-8-oxonon-6-enoate (27) (3 7 g, 72%) as an oil (Found $M^+$ 270 1465. $C_{14}H_{22}O_5$ requires M 270.1467), $\nu_{max.}$ ($CHCl_3$ 1 730, 1 600, and 1 380 $cm^{-1}$, $\delta_H$ 1.24 (3 H, t, J 7 Hz, $CH_2CH_3$), 1 40 and 1.42 (each 3 H, s, $CH_3$), 1 86 and 1 98 (each 1 H, m, 3-H), 2.28 (3 H, s, 9-$CH_3$), 2.41 - 2.51 (2 H, m, 2-$CH_2$), 3 77 (1 H, dt, J 4, 8 Hz, 4-H), 4.12 (2 H, q, J 7 Hz, $CH_2CH_3$), 4 17 (1 H, m, 5-H), 6 63 (1 H, dd, J 16, 1 Hz, 7-H), and 6 6 (1 H, dd, J 16, 6 Hz, 6-H), m/z (EI) 269 ($M^+$ - 1, 15%).

Ethyl (4S,5S)-4,5-Isopropylidenedioxy-8-oxononanoate (28).- A solution of the unsaturated ketoester (27) (4.1 g, 15 mmol) in ethyl acetate (100 ml) containing 10% Pd/C (0.81 g) was stirred under an atmosphere of hydrogen until the uptake of hydrogen ceased. The catalyst was filtered off, and the filtrate concentrated under reduced pressure Flash chromatography of the residue using ether-light petroleum (1 3) as eluant gave ethyl (4S,5S)-4,5-isopropylidenedioxy-8-oxononanoate (3 7 g, 88%), as an oil, distilled before use, b p 150°C (3 mm) (Found C, 61.6, H, 9 15 $C_{14}H_{24}O_5$ requires C, 61 75, H, 8 9%), $[\alpha]_D^{20}$ -38.5° (c 2 43 in $CHCl_3$), $\nu_{max.}$ (film) 1 720, 1 370, 1 240, 1 160, and 1 075 $cm^{-1}$, $\delta_H$ 1 26 (3 H, t, J 7 Hz, $CH_2CH_3$), 1.36 (6 H, s, 2 x $CH_3$), 1 64 -2 00 (4 H, m, 2 x $CH_2$), 2 17 (3 H, s, 9-$CH_3$), 2 40 - 2 58 (2 H, m, $CH_2$), 2 60 - 2 73 (2 H, m, $CH_2$), 3 63 (2 H, m, 4-H and 5-H), and 4 14 (2H, q, J 7 Hz, $CH_2CH_3$), m/z (CI) 273 ($M^+$ + 1, 23 %) and 215 ($M^+$ - 57, 100%).

Ethyl (4S,5S,8EZ,10E,12E)-8,12-Dimethyl-4,5-isopropylidenedioxytetradeca-8,10,12-trienoate (30)/(31).- Hexamethyldisilazane (0.57 ml, 2.7 mmol) was added to a suspension of potassium

hydride (0.31 g of a 35% dispersion in mineral oil, 2.7 mmol) in THF (12 ml), and the mixture stirred at 40°C for 45 min under an atmosphere of argon After cooling to -78°C, a solution of the phosphonate (29) (0.67 g, 2.9 mmol) in THF (6 ml) was added, and the mixture stirred for 1 h to give an orange solution. A solution of the ketone (28) (0.57 g, 2.1 mmol) in THF (12 ml), pre-cooled to -78°C, was added, and the reaction stirred for 3 h. Hexamethylphosphoric triamide (0.52 ml, 3.0 mmol) was added, and the solution warmed to room temperature and stirred for 3 h. Ethanol (1 ml) was added, and the mixture partioned between water and ether. The ethereal extracts were combined, dried ($Na_2SO_4$), and concentrated under reduced pressure. Flash chromatography of the residue on base washed silica using ether-light petroleum (1 8) as eluant gave ethyl (4S,5S,8EZ,10E,12E)-8,12-dimethyl-4,5-isopropylidenedioxytetradeca-8,10,12-trienoate (30)/(31) (0.68 g, 92%), (8E 8Z) = 2-4 1, $\nu_{max.}$ ($CHCl_3$) 1 725, 1 625, 1 600, 1 380, 1 150, 1070, and 960 $cm^{-1}$, $\delta_H$ 1.27 (3 H, t, J 7 Hz, $CH_2CH_3$), 1.30 (6 H, s, 2 x $CH_3$), 1.75 (3 H, d, J 6 Hz, 14-$CH_3$), 1.78 and 1.80 (each 3 H, s, vinylic $CH_3$), 1.60 - 2.05 (4 H, complex m, 2 x $CH_2$), 2.12 - 2 57 (4 H, complex m, 2 x $CH_2$), 3.65 (2 H, m, 4-H and 5-H), 4.16 (2 H, q, J 7 Hz, $CH_2CH_3$), 5.56 (1 H, q, J 6 Hz, 13-H), 5.93 (1 H, d, J 10 Hz, 9-H), 6 15 [0 25 H, d, J 15 Hz, 11-H (8Z-isomer)], 6.18 [0 75 H, d, J 15 Hz, 11-H (8E-isomer)], and 6.35 (1 H, dd, J 15, 10 Hz, 10-H), m/z (CI) 350 ($M^+$, 20%) and 293 ($M^+$ - 57, 100%).

(4S,5S,8EZ,10E,12E)-8,12-Dimethyl-4,5-isopropylidenedioxytetradeca-8,10,12-trienoyl Imidazolide (33).- A solution of sodium hydroxide (0.31 g, 7 8 mmol) in water (3 ml) was added to the ester (30)/(31) (0 68 g, 1.9 mmol) in ethanol (6 ml), and the mixture stirred for 1 5 h at room temperature Tartaric acid (2 9 g, 19 mmol) in ice-cold water (3 ml) was then added, the mixture extracted with ether, and the ethereal extracts combined, dried ($Na_2SO_4$), and concentrated under reduced pressure to leave the acid (32) (0.61 g, 97%), $\nu_{max.}$ ($CDCl_3$) 3 160, 1 715, 1 640, and 1 385 $cm^{-1}$, $\delta_H$ 1 37 and 1.39 (each 3 H, s, $CH_3$), 1.75 (3 H, d, J 7 Hz, 14-$CH_3$), 1.78 and 1 80 (each 3 H, s, vinylic $CH_3$), 1.5 - 2.05 (4 H, m, 2 x $CH_2$), 2.1 -2.42 (2 H, m, 7-$CH_2$), 2 53 (2 H, m, 2-$CH_2$), 3 64 (2 H, m, 4-H and 5-H), 5.55 (1 H, q, J 7 Hz, 13-H), 5.91 (1H, d, J 10 Hz, 9-H), 6.16 [0.25 H, d, J 15 Hz, 9-H (8Z-isomer)], 6 18 [0 75 H, d, J 15 Hz, 9-H (8E-isomer)], and 6.32 (1 H, dd, J 10, 15 Hz, 11-H), m/z (CI) 322 ($M^+$, 19%) and 265 ($M^+$ -57, 100%)

The acid (32) was dried by dissolving in benzene and concentrating under reduced pressure. To a solution of the acid (32) (0 45 g, 1.4 mmol) in THF (2 ml) was added carbonyl 1,1'-diimidazole (0.46 g, 2 8 mmol) in THF (5 ml), and the mixture stirred for 18 h at room temperature under an atmosphere of nitrogen. Ether was added, and the mixture washed with ice-cold water, dried ($Na_2SO_4$) and concentrated under reduced pressure to leave (4S,5S,8EZ,10E,12E)-8,12-dimethyl-4,5-isopropylidenedioxytetradeca-8,10,12-trienoylimidazolide (33) (0 49 g, 92%) as an oil, $\nu_{max.}$ (benzene) 1 745, 1 640, 1 230, 1 120, 1 035, 967, and 918 $cm^{-1}$, $\delta_H$ 1 39 and 1 41 (each 3 H, s, $CH_3$), 1.77 (3 H, d, J 7 Hz, 14-$CH_3$), 1.81 and 1.84 (each 3 H, s, vinylic $CH_3$), 1 5 - 1.95 (2 H, m, 6-$CH_2$), 2.10 - 2.48 (4 H, complex m, 3-$CH_2$ and 7-$CH_2$), 2 97 - 3 20 (2 H, m, 2-$CH_2$), 3.69 (2 H, m, 4-H and 5-H), 5 55 (1 H, q, J 7 Hz, 13-H), 5.94 (1 H, d, J 12 Hz, 9-H), 6.16 [0.25 H, d, J 15 Hz, 11-H (8Z-isomer)], 6.18 [0.75 H, d, J 15 Hz, 11-H (8E-isomer)], 7.12 (1 H, d, J 1 Hz, 5'-H), 7 51 (1 H, d, J 1 Hz, 4'-H), and 8.21 (1 H, s, 2'-H)

(5S,4'S,5'S,8'EZ,10'E,12'E)-N-Benzoyl-3-(8,12-dimethyl-4,5-isopropylidenedioxy-1-oxotetradeca-8,10,12-trienyl)-5-(2-methylpropyl)-3-phenylselenopyrrolidin-2-one (35).- A solution of the pyrrolidinone (6) (0.78 g, 3.2 mmol) in THF (5 ml) was added to lithium hexamethyldisilazide (3.2 mmol) in THF-hexane (12 ml) at -78°C under an atmosphere of argon, and the mixture stirred for 30 min before being transferred vis a cannula to a solution of the imidazolide (33) (0.59 g, 1.6 mmol) in THF (10 ml) at -78°C, also under an atmosphere of argon. After stirring for 8 h saturated aqueous $NH_4Cl$ was added, and the reaction mixture warmed to room temperature and extracted with ether. After drying and concentrating under reduced pressure, flash chromatography of the residue on base washed silica using ether-light petroleum (1 10) as eluant gave a mixture of the unchanged pyrrolidinone (6) and the 3-(1-oxotrienyl)-pyrrolidinone (34) as a mixture of epimers at C(3) (0 85 g), $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 675 $cm^{-1}$, $\delta_H$ 3.77 and 3.92 (each 0.5 H, m, 3-H) This pyrrolidinone [estimated by $^1H$ n.m r to contain 0 51 g of (34), 0 92 mmol] in THF (12 ml), pre-cooled to -78°C, was added to a solution of lithium hexamethyldisilazide (0.95 mmol) in THF-hexane (13 ml) at -78°C under argon After stirring for 1 h, a solution of benzeneselenenyl chloride (0.23 g, 1.2 mmol) in THF (10 ml) was added, and the mixture stirred for a further 3 h before being quenched by the addition of saturated aqueous $NH_4Cl$. Ether extraction and flash chromatography of the extract using ether-light petroleum (1 4) as eluant gave (5S,4'S,5'S,8'EZ,10'E,12'E)-N-benzoyl-3-(8,12-dimethyl-4,5-isopropylidenedioxy-1-oxotetradeca-8,10,12-trienyl)-5-(2-methylpropyl)-3-phenylselenopyrrolidin-2-one (35) (0.52 g, 80%) as a pale yellow oil, $\delta_H$ 0 89 and 0 92 (each 3 H, d, J 7 Hz, $CH_3$), 1.35 (6 H, s, 2 x $CH_3$), 1.50 -1.95 (9 H, complex m), 1 78 (3 H, d, J 7 Hz, 14'-$CH_3$), 1 83 and 1 85 (each 3 H, s, vinylic $CH_3$), 2.1 - 2.4 (4 H, m, 2 x $CH_2$), 3.68 (2 H, m, 4'-H and 5'-H), 4 38 (1 H, m, 5-H), 5.55 (1 H, m, 13-H), 5 92 (1 H, d, J 10 Hz, 9-H), 6 16 [0.3 H, d, J 15 Hz, 11-H (8Z-isomer)], 6 18 [0.7 H, d, J 15 Hz, 11-H (8E-isomer)], 6.38 (1 H, m, 10-H), and 7 3 - 7 7 (10 H, m, aromatic H).

Generation and Diels Alder Cyclization of (5S,4'S,5'S,8'EZ,10'E,12'E)-N-Benzoyl-3-(8,12-dimethyl-4,5-isopropylidenedioxy-1-oxotetradeca-8,10,12-trienyl)-5-(2-methylpropyl)-$\Delta^3$-pyrrolin-2-one (36).- Hydrogen peroxide (0.84 ml of a 30% aqueous solution, 7.4 mmol) and water (2.5 ml) were added to a solution of the selenide (35) (0.5 g, 0.71 mmol) in chloroform (110 ml) at -50°C, followed by m-chloroperoxybenzoic acid (0.18 g, 0.84 mmol) in chloroform (15 ml) After 30 min, the reaction was warmed to 0°C, and stirred for 15 min The mixture

was then washed with aqueous $Na_2CO_3$, distilled water, and dried ($Na_2SO_4$). A sample was removed for $^1H$ n m.r which showed the presence of the pyrrolin-2-one (36), $\delta_H$ 5 16 (1 H, m, 5-H) and 8.12 (1 H, d, J 2 Hz, 4-H). The remainder of the pyrrolinone solution was added to hot nitrogen purged toluene (500 ml), and the mixture heated under an atmosphere of nitrogen for 5 h at 90°C After cooling, concentration under reduced pressure gave a residue which on flash chromatography using ether-light petroleum (1 5) as eluant gave a mixture of the three Diels Alder adducts (39), (41), and (43) (133 mg, 34 %), ratio 3 1 2, respectively. Repeated flash chromatography using ether-light petroleum (1 8) as eluant gave samples of (17S,18S)-2-benzoyl-17,18-isopropylidenedioxy-14-methyl-10-prop-2'-yl-[11]cytochalasa-6(7),13$^Z$ diene-1,21-dione (39), $\nu_{max}$ ($CHCl_3$) 1 736, 1 713, 1 685, 1 602, 1 584, 1 382, 1 371, 1 288, 1 232 and 910 $cm^{-1}$, $\delta_H$ 0.91 and 0 99 (each 3 H, d, J 6 Hz, $CHMe_2$), 1 34 (3 H, d, J 7 Hz, 11-$CH_3$), 1 38 and 1.41 (each 3 H, s, $=CMe_2$), 1 5 - 1 9 (6 H, complex m), 1.75 (3 H, br s, 14-$CH_3$), 1.80 (3 H, br.s, 12-$CH_3$), 2 21 - 2.37 (4 H, complex m), 2 66 (1 H, m, 5-H), 2.96 (1 H, dd, J 7, 1 Hz, 4-H), 3 22 (1 H, m, 8-H), 3.29 (1 H, m, 20-H), 3.62 and 4.01 (each 1 H, m, 17-H and 18-H), 4.25 (1 H, m, 3-H), 5.38 (1 H, br s, 7-H), 5 96 (1 H, d, J 11 Hz, 13-H), and 7.4 -7.56 (5 H, m, aromatic H), m/z (CI) 548 ($M^+$ + 1, 100%), together with (5R,8R,17S,18S)-2-benzoyl-17,18-isopropylidenedioxy-14-methyl-10-prop-2'-yl-[11]cytochalasa-6(7),13$^E$-diene-1,21-dione (43), $\delta_H$ 0.98 and 1.05 (each 3 H, d, J 7 Hz, $CHMe_2$) 1.29 (3 H, d, J 7 Hz, 11-$CH_3$), 1.37 and 1 42 (each 3 H, s, = $CMe_2$), 1 5 - 2.1 (8 H, complex m), 1 67 (3 H, br s, 14-$CH_3$), 1.68 (3 H, s, 12-$CH_3$), 2 10 - 2.38 (3 H, complex m), 2 76 (1 H, m), 2 90 (1 H, d, J 5.5 Hz, 4-H), 3.44 (1 H, d, J 11 Hz, -CHO), 3.76 (1 H, dd, J 11, 6 Hz, 8-H), 3.81 (1 H, d, J 10 Hz, -CHO), 4.22 (1 H, dd, J 11, 4 5 Hz, 3-H), 4.71 (1 H, d, J 11 Hz, 13-H), 5.22 (1 H, d, J 6 Hz, 7-H), and 7.37 - 7 53 (5 H, m aromatic H), m/z (EI) 547 ($M^+$, 9%)

Debenzoylation of Diels Alder Adducts.- A solution of sodium hydroxide (203 mg, 5.08 mmol) in methanol (7 ml) containing water (0 23 ml) was added at room temperature to a solution of Diels Alder adducts (140 mg, 0.25 mmol) in methanol (7 ml), and the resulting solution stirred for 2 h The reaction mixture was poured into water (10 ml) and extracted with ethyl acetate (3 x 15 ml) After washing with brine (10 ml), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure Flash chromatography of the residue using ether-light petroleum (1 1) as eluant gave three products together with some mixed fractions (17 mg) (total yield 85 mg, 75%). The least polar product was identified as (17S,18S)-17,18-isopropylidenedioxy-14-methyl-10-prop-2'-yl-[11]cytochalasa-6(7),13$^Z$-diene-1,21-dione (40) (35 mg, 30%) (Found C, 73 25, H, 8.75, N, 2 8. $C_{27}H_{41}NO_4$ requires C, 73 10, H, 9 3, N, 3.1%), $\nu_{max}$ ($CHCl_3$) 3 430, 1 740, 1 700, 1 611, and 1 513 $cm^{-1}$, $\delta_H$ 0 90 (6 H, d, J 6.5 Hz, $CHMe_2$), 1 22 (3 H, d, J 7 Hz, 11-$CH_3$), 1.24 (2 H, m), 1 37 and 1.4 (each 3 H, s, $CH_3$), 1.52 (1 H, m, $CHMe_2$), 1 6 - 1 9 (4 H, m), 1 76 (3 H, d, J 1 Hz, 14-$CH_3$), 1 79 (3 H, s, 12-$CH_3$), 2 23 (1 H, m, 20-H), 2 34 (2 H, m), 2 56 (1 H, m, 5-H), 2 72 (1 H, t, J 4 5 Hz, 4-H), 3.05 (2 H, m, 3-H and 8-H), 3 55 (1 H, m, 20-H), 3 62 and 3.91 (each 1 H, m, 17-H and 18-H), 5 34 (1 H, br.s, 7-H), 5 83 (1 H, br s, NH), and 6 05 (1 H, dd, J 11, 1 Hz, 13-H), m/z (CI) 444 ($M^+$ + 1, 75%) and 386 ($M^+$ -57, 100%). The next product was identified as (17S,18S)-17,18-isopropylidenedioxy-14-methyl-10-prop-2'-yl-[11]cytochalasa-6(7),13$^E$-diene-1,21-dione (42) (11 mg, 10%), $\delta_H$ 0 89 and 0 90 (each 3 H, d, J 6.5 Hz, $CHMe_2$), 1.18 (2 H, m), 1 20 (3 H, d, J 7 Hz, 11-$CH_3$), 1 43 and 1 47 (each 3 H, s, $CH_3$), 1 54 (1 H, m, $CHMe_2$), 1 59 (3 H, d, J 1 Hz, 14-$CH_3$), 1 76 (3 H, br.s, 12-$CH_3$), 1 8 - 1 85 (3 H, m), 2 11 (2 H, m), 2.24 and 2 36 (each 1 H, m), 2 45 (1 H, dd, J 6, 2 Hz, 4-H), 2 65 (1 H, m, 5-H), 3 20 (1 H, m, 3-H), 3 34 (1 H, m, 8-H), 3.36 (1 H, ddd, J 17, 9, 1 5 Hz, 20-H), 3 63 and 4.18 (each 1 H, m, 17-H and 18-H), 5 48 (1 H, br s, 7-H), 5.83 (1H, br.s, NH), and 6.32 (1H, dd, J 7, 1 Hz, 13-H) The most polar product was identified as (5R,8R,17S,18S)-17,18-isopropylidenedioxy-14-methyl-10-prop-2'-yl-[11]cytochalasa-6(7),13$^E$-diene-1,21-dione (44) (22 mg, 20%), $\delta_H$ 0.94 (6 H, 2d, J 6 5 Hz, $CHMe_2$), 1 1 - 1 4 (2 H, m), 1 22 (3 H, d, J 7 Hz, 11-$CH_3$), 1 36 and 1 40 (each 3 H, s, $CH_3$), 1 60 (3 H, m), 1.69 and 1 76 (each 3 H, s, 12-$CH_3$ and 14-$CH_3$), 1.9, 2.11, and 2 41 (each 2 H, m), 2.8 (1 H, m, 20-H), 2.90 (1 H, m, 4-H), 3.11 (1 H, m, 3-H), 3 45 (1 H, m, 18-H), 3.79 (1 H, m, 17-H), 3.83 (1 H, m, 8-H), 4 71 (1 H, d, J 10 Hz, 13-H), 5.29 (1 H, d, J 6.5 Hz, 7-H), and 5 73 (1 H, br s, NH)

(17S,18S)-17,18-Isopropylidenedioxy-14-methyl-20-phenylseleno-10-prop-2'-yl-[11]cytochalasa-6(7),13$^Z$-diene-1,21-dione (46) - A solution of the major debenzoylated Diels Alder adduct (40) (39 mg, 87 µmol) in THF (2 ml), pre-cooled to -78°C, was added to lithium isopropylamide (0.85 mmol) in THF-hexane (2 6 ml) at -78°C under an atmosphere of argon, and the mixture stirred for 1 h Trimethylsilyl chloride (164 µl, 1 3 mmol) was added, and the stirring continued for 2 h before being quenched by the addition of anhydrous $NH_4Cl$ The mixture was concentrated under reduced pressure and the residue triturated with hexane (3 x 10 ml) The combined hexane washings were concentrated under reduced pressure to leave a white solid identified as the enol-ether (45), $\delta_H$ 0 93 and 0 97 (each 3 H, d, J 6 Hz, $CHMe_2$), 1.24 (3 H, d, J 7 Hz, 11-$CH_3$), 1.40 and 1 43 (each 3 H, s, 2 x $CH_3$), 1 75 and 1 80 (each 3 H, br s, 12-$CH_3$ and 14-$CH_3$), 3 05 (2 H, m, 3-H and 8-H), 3 70 (1 H, d, J 11 Hz, 17-H), 4 04 (1 H, d, J 11 Hz, 18-H), 5.32 (2 H, m, 7-H and 20-H), and 5.64 (1 H, d, J 10 Hz, 13-H)

This enol-ether (45) was dissolved in THF (1 ml) at 0°C, and a solution of benzeneselenenyl chloride (43 mg, 0.22 mmol) in THF (0 5 ml) added After being stirred for 3 h at 0°C under an atmosphere of argon, ether and saturated aqueous $NH_4Cl$ were added The organic phase was separated, dried ($MgSO_4$), and concentrated under reduced pressure Flash chromatography of the residue using ether-light petroleum (1 1) as eluant gave (17S,18S)-17,18-isopropylidenedioxy-14-methyl-20-phenylseleno-10-prop-2'-yl-[11]cytochalasa-6(7),13$^Z$-diene-1,21-dione (46) (30 7 mg, 60%) (Found $M^+$ 599 2514 $C_{33}H_{44}NO_4{}^{80}Se$ requires M 599.2514), $\nu_{max}$ ($CHCl_3$) 3 429, 1 687, 1 382, 1 371, and 1 240 $cm^{-1}$, $\delta_H$ 0 93 and 0 95

(each 3 H, overlapping d, J 6 Hz, 2 x $CH_3$), 1 2 (3 H, d, J 7 Hz, 11-$CH_3$), 1 2 and 1.32 (each 3 H, s, $CH_3$), 1.2 - 2.0 (7 H, complex m), 1.78 (6H, br s, 12-$CH_3$ and 14-$CH_3$), 2.06 and 2 21 (each 1 H, m), 2.66 (1 H, m, 5-H), 2 81 (1 H, t, J 4 5 Hz, 4-H), 3 07 (2 H, m, 3-H and 8-H), 3 76 (2 H, m, 17-H and 18-H), 4.87 (1 H, dd, J 12,2 Hz, 20-H), 5 30 (1 H, br s, 7-H), 6.00 (1 H, d, J 7 Hz, 13-H), 6.02 (1 H, br.s, NH), and 7.29 - 7 46 (5 H, m, aromatic H), m/z (EI) 599 ($M^+$, 21%).

(17S,18S)-17,18-Isopropylidenedioxy-14-methyl-10-prop-2'-yl-[11]cytochalasa-6(7),13Z,19E-triene-1,21-dione (47).- Hydrogen peroxide (0.2 ml of a 30% aqueous solution, 1 7 mmol) and water (0.2 ml) were added to a solution of the selenide (46) (31 mg, 51 µmol) in pyridine (0 1 ml) and dichloromethane (0 15 ml), and the mixture stirred at room temperature for 18 h Ether was then added, and the organic phase separated, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue using ether-light petroleum (1 1) as eluant gave (17S,18S)-17,18-isopropylidenedioxy-14-methyl-10-prop-2'-yl-[11]cytochalasa-6(7), 13Z,19E-triene-1,21-dione (47) (13 mg, 58%), as a white solid, m p 170°C (decomp) (Found $M^+$ 441.2877. $C_{27}H_{39}NO_4$ requires M 441 2879), $\nu_{max.}$ ($CHCl_3$) 3 428, 1 693, 1 646, 1 376, and 1 064 $cm^{-1}$, $\delta_H$ 0 92 and 0 93 (each 3 H, overlapping d, J 6 5 Hz, $CHCH_3$), 1 21 (3 H, d, J 7.5 Hz, 11-$CH_3$), 1 42 (6 H, s, 2 x $CH_3$), 1 74 and 1 89 (each 3 H, s, 12-$CH_3$ and 14-$CH_3$), 1 35 - 1.6 (4 H, m), 1 7 - 2 3 (4 H, m), 2 65 (1 H, m, 8-H), 3.05 (1 H, m, 3-H), 3 30 (1 H, dd, J 6 5, 3 5 Hz, 4-H), 3 68 (1 H, dt, J 2 5, 8.5 Hz, 17-H), 4 07 (1 H, t, J 8.5 Hz, 18-H), 5.25 (1 H, br s, 7-H), 5.56 (1 H, d, J 12 Hz, 13-H), 5.56 (1 H, s, NH), 6 33 (1 H, dd, J 16, 9 Hz, 19-H), and 7 44 (1 H, d, J 16 Hz, 20-H), m/z (CI) 442 ($M^+$ + 1, 64%) and 384 ($M^+$ - 57, 100%)

(17S,18S)-17,18-Dihydroxy-14-methyl-10-prop-2'-yl-[11]cytochalasa-6(7),13Z,19E-triene-1,21-dione (isoaspochalasin C) (48) - Aqueous methanolic HCl (0 5 ml of 2% HCl in 5 1 methanol-water) was added to the enone (47) (6 mg, 13.5 µmol), and the mixture stirred for 1 h at room temperature. Ether and water were then added, and the ether extracts combined, dried ($MgSO_4$), and concentrated under reduced pressure Flash chromatography of the residue using ether as eluant gave (17S,18S)-17,18-dihydroxy-14-methyl-10-prop-2'-yl-[11]cytochalasa-6(7), 13Z,19E-triene-1,21-dione (isoaspochalasin C) (48) (5 mg, 90%) as an oil, $\nu_{max.}$ ($CHCl_3$) 3 500 -3 600, 3 430, 1 740, and 1 689 $cm^{-1}$, $\delta_H$ 0 91 and 0 93 (each 3 H, d, J 5 5 Hz, $CHCH_3$), 1 21 (3 H, d, J 7.5 Hz, 11-$CH_3$), 1.73 and 1.76 (each 3 H, br s, 12-$CH_3$ and 14-$CH_3$), 1 2 - 1.8 (4 H, m), 1 9 - 2.25 (3 H, m), 2.40 (1 H, m, 5-H), 2.56 (2 H, br.s, OH), 2.82 (1 H, m, 8-H), 3 14 (2 H, m, 3-H and 4-H), 3.49 (1 H, m, 17-H), 4 02 (1 H, t, J 9 Hz, 18-H), 5.13 (1 H, d, J 11 Hz, 13-H), 5.20 (1 H, br s, 7-H), 5 53 (1 H, br s, NH), 6 47 (1 H, dd, J 16 5, 7 5 Hz, 19-H), and 7 32 (1 H, d, J 16.5 Hz, 20-H), m/z (EI) 401 ($M^+$, 12%).

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