Cytochalasan Synthesis: Total Synthesis of the Naturally Occurring [13]Cytochalasan Proxiphomin

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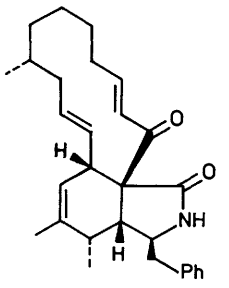
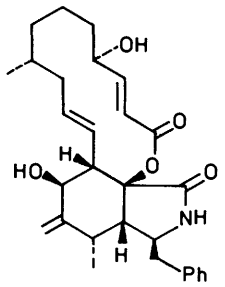
Proxiphomin (**1**), a naturally occurring [13]cytochalasan, has been synthesized by a route which uses an intramolecular Diels–Alder reaction of the long chain 3-(1-oxotrienyl)pyrrol-2(5*H*)-one (**18**) to form the 13-membered ring. This cyclization gave a mixture of *endo* and *exo* isomers (**19**) and (**21**), the *endo* isomer (**19**) being carried through to proxiphomin. Although the *endo–exo* selectivity was small, (**19**) : (**21**) = 52:48, the Diels–Alder cyclization was useful in that no epimerization had occurred at C-5. Cyclization of a mixture of Diels–Alder precursors (**18**) and (**33**) prepared from racemic pyrrolidinone (**32**) gave all four cyclized products (**19**), (**21**), (**34**), and (**36**) which were 1-debenzoylated, separated, and characterized.

Synthesis of the cytochalasans, a group of biologically active fungal metabolites,[1] provides a considerable challenge to synthetic organic chemistry because of the presence of the large ring together with the highly substituted, hydrogenated, isoindolone nucleus. In the previous paper in this series,[2] a synthetic approach to these compounds was introduced which uses an intramolecular Diels–Alder reaction of a long chain 3-(1-oxotrienyl)pyrrol-2(5*H*)-one to assemble the cytochalasan skeleton. We now describe the application of this approach to the synthesis of proxiphomin (**1**),[3] a naturally occurring cytochalasan which is believed to be a biosynthetic precursor of cytochalasin B (**2**) and the other macrolide cytochalasans.[4,5]



(**1**)



(**2**)

Results and Discussion

Total Synthesis of Proxiphomin (**1**).—(3*R*)-(+)-Citronellol (**3**), prepared from (*R*)-(+)-pulegone,[6] was chosen as the starting material for the introduction of the chiral centre at C-16. Hydroxy protection and ozonolysis with a dimethyl sulphide work-up gave the protected hydroxy aldehyde (**5**), which was condensed with the phosphorane formed from the phosphonium salt (**6**) (Scheme 1).[7] This gave the alkene (**7**), which was deprotected and hydrogenated to provide (8*R*)-ethyl 10-hydroxy-8-methyldecanoate (**9**), as a colourless liquid, b.p. 170—180 °C (0.1 mmHg).

Formation of the conjugated triene system required for the Diels–Alder cyclization was next achieved using chemistry developed during our preliminary studies.[2] Thus Swern oxidation of the alcohol (**9**) gave aldehyde (**10**), which was condensed with the lithium salt of diethyl 4-methylhexa-2,4-dienylphosphonate (**11**),[8] using hexamethylphosphoric triamide to promote the elimination step, to give the acid-sensitive (*E,E,E*)-triene (**12**). The *trans*-geometry of the newly introduced double bond of this triene was not confirmed at this stage, but was supported by precedent,[2,8] and by the structures of the 1-debenzoylated Diels–Alder products (**20**) and (**22**); no other isomer was evident in the high-field ^{1}H n.m.r. spectrum of the triene.

Ester hydrolysis and treatment of the corresponding acid with 1,1′-carbonyldi-imidazole then gave the imidazolyl hexadecatrienone (**14**). This was condensed with (5*R*)-1-benzoyl-5-benzylpyrrolidinone (**15**),[9] using lithium hexamethyldisilazide as base to avoid competing imide carbonyl addition, to give the 3-(1-oxotrienyl) pyrrolidin-2-one (**16**) as a mixture of epimers at C-3. Regioselective phenylselenation using benzeneselenenyl chloride–lithium hexamethyldisilazide, and oxidative elimination of the phenylselenenyl group with one molar equivalent of *m*-chloroperoxybenzoic acid (MCPBA) in the presence of an excess of hydrogen peroxide at −50 to 0 °C, generated the unstable 3-(1-oxotrienyl)pyrrol-2(5*H*)-one (**18**). No attempt was made to isolate the pyrrolone (**18**) because of the known propensity of these systems to polymerize,[2] but it was detected in solution by ^{1}H n.m.r. However, dilution of the pyrrolone solution using toluene, and heating at 100 °C, effected the crucial cyclization, and gave a mixture of Diels–Alder adducts which were identified as the *exo* and *endo* isomers (**19**) and (**21**), ratio (**19**):(**21**) = 52:48, combined isolated yield 52%.

The Diels–Alder adducts could not be separated, but debenzoylation using potassium hydroxide in methanol–benzene gave the corresponding NH compounds (**20**) and (**22**) which were separated by short column chromatography. The less polar diastereoisomer was identified as that required for proxiphomin synthesis by spectroscopic methods. In particular n.O.e. data provided information about the stereochemistry around the isoindolone fragment, *e.g.* irradiation of the 11-methyl doublet enhanced the peaks due to 3-H (6.8%) and the overlapping peaks due to 4- and 5-H (13.6%), and irradiation of the 8-H multiplet enhanced the overlapping peaks assigned to 4- and 5-H (5%). The more polar diastereoisomer was identified as the *exo* adduct (**22**) also on the basis of spectroscopic data. In this case irradiation of the 11-methyl doublet enhanced the peaks due to 4-H (11%) and 5-H, but had no significant effect on 3-H, and irradiation of the 8-H multiplet enhanced the vinylic proton peaks and 22-H (2.8%) but had no effect on 4- or 5-H. These n.O.e. results for the *exo* adduct (**22**) were supported by analogous studies carried out on the pure 1-benzoyl compound (**21**) prepared by benzoylation of the NH compound (**22**), and are summarized in the Figure.

As well as facilitating assignment of structures to these products, the n.O.e. data also provided information about their

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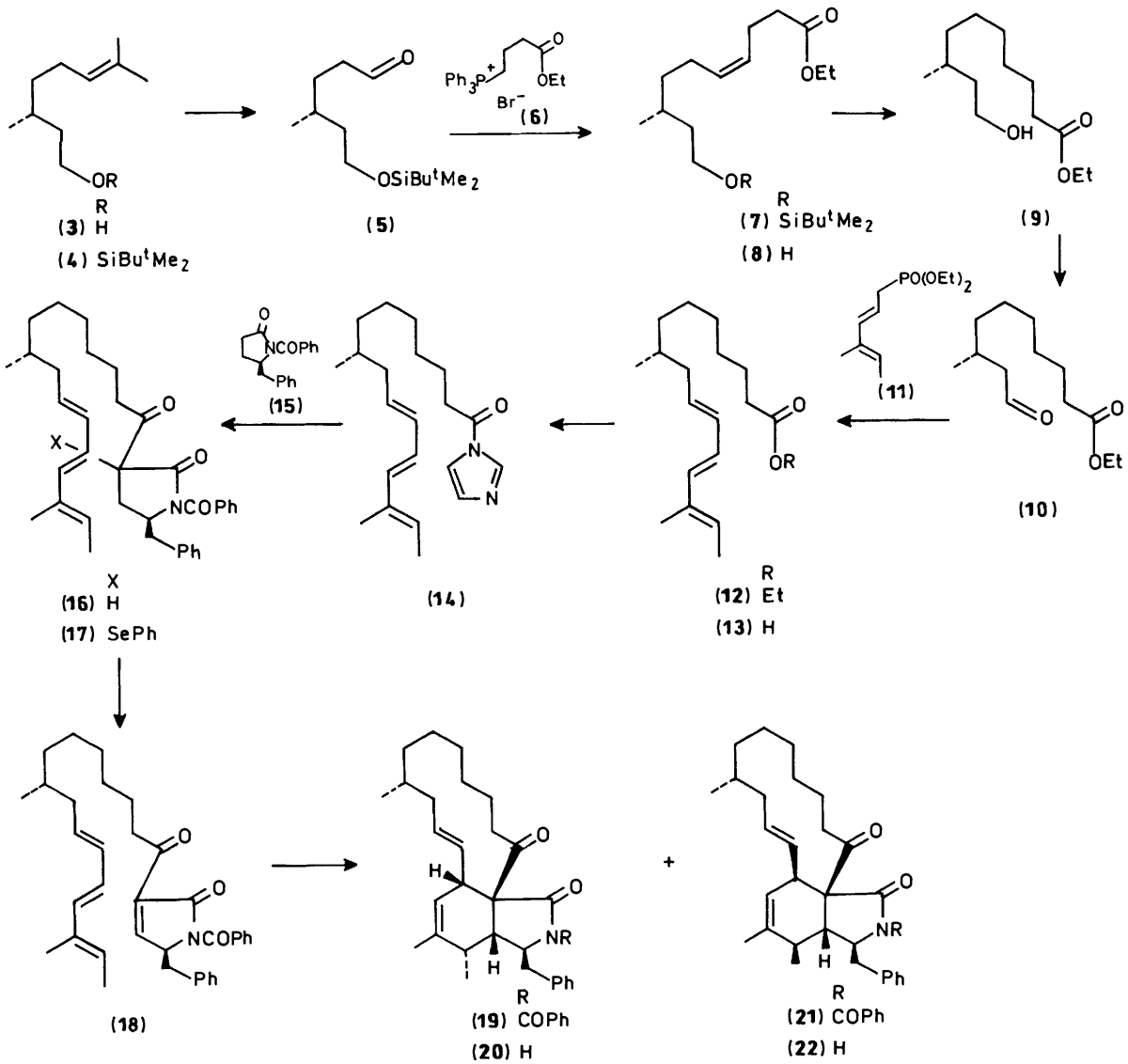


Scheme 1.

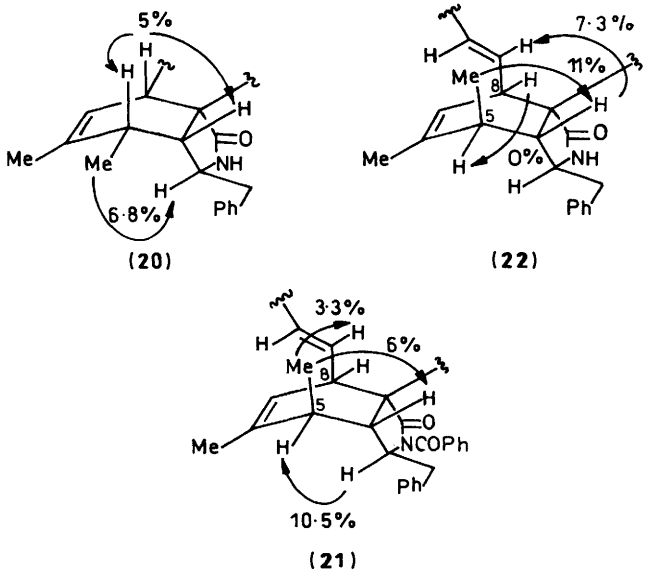
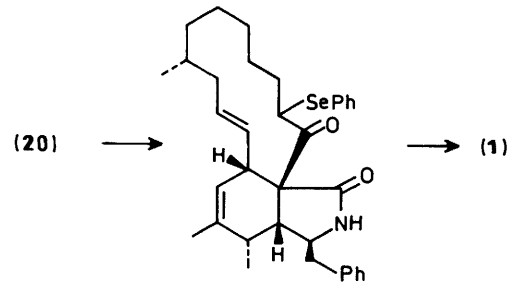


Figure. Selected n.O.e. data for compounds (**20**), (**22**), and (**21**)

conformations. Of interest here is the n.O.e. enhancement of the multiplet due to 13-H on irradiation of 4-H and 11-Me for the *exo*-isomer (**22**) and its 1-benzoyl derivative (**21**); this supports the conformation shown in the Figure for these compounds in which the alkyl groups at C-5 and -8 have adopted axial positions.

Having assigned structures to the two debenzoylated Diels–Alder products (**20**) and (**22**), the less polar isomer (**20**) was converted into proxiphomin. Phenylselenation at C-22 using lithium di-isopropylamide–benzeneselenenyl chloride, and oxidative elimination with hydrogen peroxide in pyridine, gave proxiphomin which had physical and spectroscopic properties identical (within experimental error) with those reported for the natural material.[3] This work completed the first synthesis of proxiphomin.

The Diels–Alder cyclization of the 3-(1-oxotrienyl)pyrrol-2(5*H*)-one (**18**) was effective in that it provided macrocyclic products in useful yields which enabled the proxiphomin synthesis to be completed; however its *endo-exo* selectivity was disappointing. This contrasts with the stereoselective formation of the [11]- and [13]-cytochalasans (**25**) and (**27**) by intramolecular Diels–Alder cyclization of the 3-(1-oxotetradecatrienyl)- and 3-(1-oxohexadecadienyl)-pyrrol-2(5*H*)-ones (**24**) and



(23)

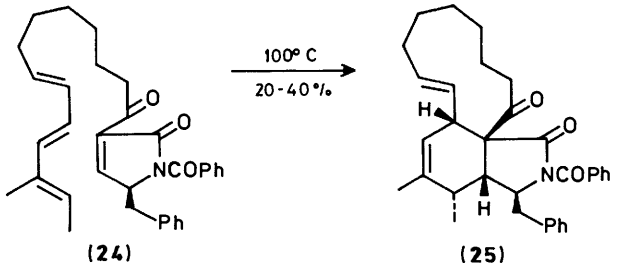
(**26**), respectively.[2] The origin of these variable stereoselectivities was not investigated, but it does appear that although the formation of [11]cytochalasans by cyclization of 3-(1-oxotrienyl) pyrrolones is stereoselective, the analogous formation of [13]cytochalasans is not. Preliminary investigations into cyclization of the 16-normethylhexadecatrienyl system (**29**) also gave rise to the formation of the *endo* and *exo* isomers (**30**) and (**31**) in an approximately 1:1 ratio.

However, one encouraging aspect of the cyclization of the 3-(1-oxotrienyl) pyrrol-2(5*H*)-one (**18**) was that no epimerization of the pyrrol-2(5*H*)-one had occurred at C-5.[10] Since this result could have implications for planning syntheses of more complex cytochalasans, this aspect of the cyclization of (**18**) was investigated in more detail.

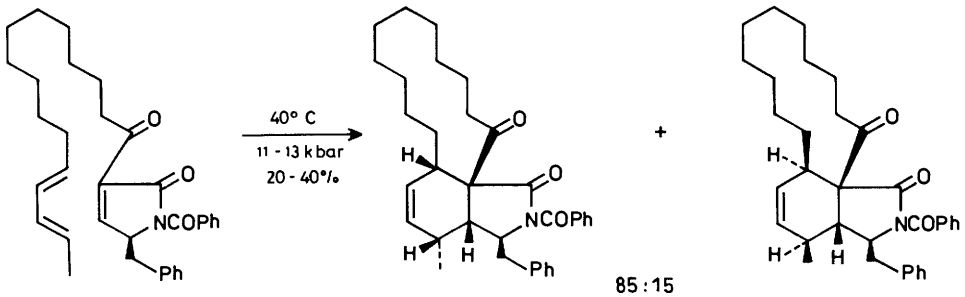
Table. Optical rotations of [13]cytochalasans (°)

Compound	$[\alpha]_D^{20}$
(**20**)	−86.2
(**35**)	+86.1
(**22**)	−179.4
(**37**)	+162

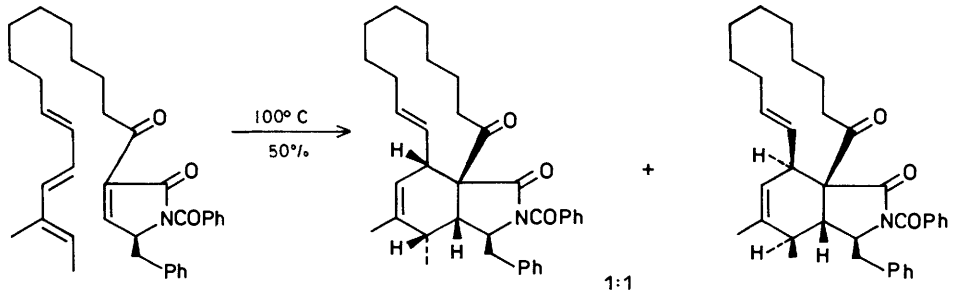
Diels–Alder Cyclization of Long Chain 3-(1-*Oxotrienyl*) *Pyrrol*-2(5H)-*ones Derived from Racemic Pyrrolidinone* (**32**).—The racemic pyrrolidin-2-one (**32**) was acylated using the imidazolyl hexadecatrienone (**14**) to provide a mixture of diastereoisomeric 3-(1-oxotrienyl)pyrrol-2(5*H*)-ones (**18**) and (**33**) after phenylselenation–oxidative elimination (Scheme 2). Cyclization of this mixture as before gave a mixture of four Diels–Alder products which were separated after 1-debenzoylation by a combination of short column chromatography and preparative t.l.c. Two of the products were identified as the *endo* and *exo* isomers (**20**) and (**22**) isolated previously, but the other two products were new, and were identified as adducts (**35**) and (**37**). Interestingly the four isomers (**20**), (**22**), (**35**), and (**37**), could be grouped into two pairs since (**35**) is the enantiomer of the C-16 epimer of (**20**), and (**37**) is similarly related to (**22**). This relationship is reflected in their optical rotations as shown in the Table.



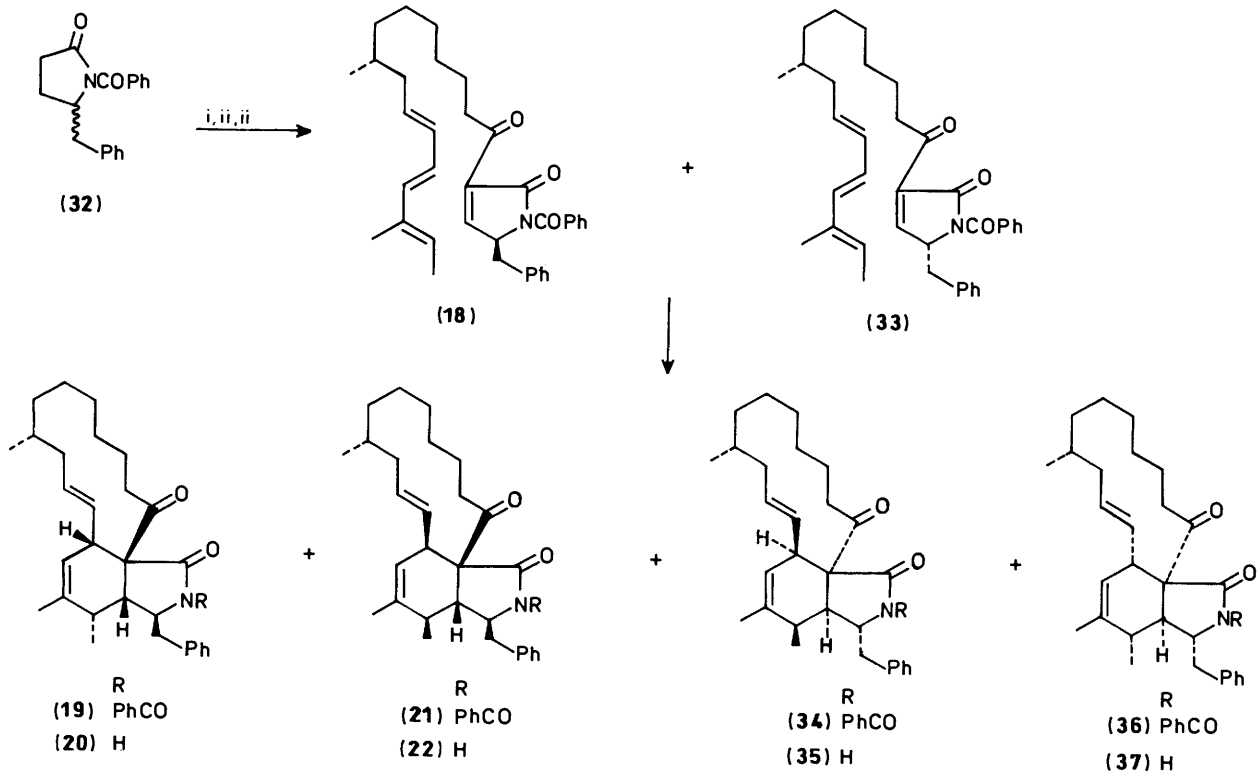
(24) (25)



(26) (27) (28)



(29) (30) (31)



Scheme 2. *Reagents:* i, base, (**14**); ii, base, PhSeCl; iii, MCPBA,H_2O_2

Finally the Diels–Alder reaction of the 3-(1-oxotrienyl)pyrrol-2(5*H*)-one (**18**) was repeated and the crude product mixture after 1-debenzoylation examined for the presence of adducts (**35**) and (**37**). However, only trace quantities (1—2%) of these products were found showing that no significant amount of epimerization of the pyrrol-2(5*H*)-one (**18**) had taken place at C-5 during the Diels–Alder cyclization. Moreover, both the pyrrolidin-2-one (**15**) and imidazolyl trienone (**14**) must have been synthesized without significant racemization.

Experimental

For general experimental details, see the previous paper in this series.[2] (*R*)-(+)-Citronellol was prepared from (*R*)-(+)-pulegone according to Plesek,[6] and had $[\alpha]_D^{20}$ + 4.57° (*c* 1.005 in $CHCl_3$) [lit.,[11] + 5.45° (neat)]. (3-Ethoxycarbonylpropyl)triphenylphosphonium bromide (**6**) was prepared from ethyl 4-bromobutanoate, and had m.p. 172—174 °C (from ether–methanol) (lit.,[7] 177 °C). Potassium hexamethyldisilazide was prepared under argon by adding an equimolar amount of hexamethyldisilazane to hexane washed potassium hydride suspended in THF, and stirring for 20 min at room temperature and for 1 h at 40 °C.

(8R,4Z)-*Ethyl* 10-(*Dimethyl-t-butylsiloxy*)-8-*methyldec*-4-*enoate* (**7**).—Dry ozone was bubbled through a solution of (*R*)-(+)-citronellol dimethyl-t-butylsilyl ether (**4**)[12] (15 g, 55.5 mmol) in methanol (100 ml) at −78 °C until a blue colour was observed. Oxygen was then bubbled through for 5 min until the solution became colourless. Dimethyl sulphide (15 ml) was added, and the mixture stirred at −78 °C for 2 h, and at room temperature for 12 h before being concentrated under reduced pressure. The mixture was diluted with water (100 ml) and extracted with ether to provide (4R)-4-*methyl*-6-*dimethyl-t-butylsiloxyhexanal* (**5**) (13.2 g, 95%) as a colourless liquid after distillation, b.p. 76—78 °C (0.2 mmHg); $[\alpha]_D^{20}$ −1.37° (*c* 1.68 in $CHCl_3$); $\nu_{max.}$(film) 1 730, 1 250, 1 093, 835, and 774 cm^{-1}; δ_H 0.05 (6 H, s, $SiMe_2$), 0.91 (12 H, s and overlapping d, $SiCMe_3$ and 4-Me), 1.25—1.75 (5 H, complex m, 2 × CH_2 and C*H*Me), 2.35 (2 H, m, CH_2CHO), 3.65 (2 H, m, OCH_2), and 9.62 (1 H, t, *J* 2 Hz, CHO); *m*/*z* (c.i.) 245 (M^+ + 1, 100%).

Pre-cooled potassium hexamethyldisilazide (36 mmol) in THF (25 ml) was added to the phosphonium salt (**6**) (14.95 g, 36 mmol) in THF (100 ml) at −78 °C under argon to form a bright red solution which was stirred for 10 min before the slow addition of aldehyde (**5**) (8.0 g, 32.8 mmol) in THF (20 ml). The mixture was stirred at −78 °C for 2 h, and then at room temperature for 1 h. Ethanol (20 ml) was cautiously added, and the mixture poured into brine, and extracted into ether. After drying ($MgSO_4$), and concentration under reduced pressure, the residual oil was triturated with hexane, filtered, and the filtrate concentrated and distilled to give the *title compound* (**7**) (8.35 g, 74%), a colourless liquid, b.p. 114—116 °C (0.1 mmHg) (Found: C, 66.35; H, 10.8. $C_{19}H_{38}O_3Si$ requires C, 66.6; H, 11.2%); $[\alpha]_D^{20}$ −1.03° (*c* 0.974 in $CHCl_3$); $\nu_{max.}$(film) 1 740, 1 250, 1 160, 1 090, 830, and 777 cm^{-1}; δ_H 0.08 (6 H, s, $SiMe_2$), 0.91 (12 H, m, $SiCMe_3$ and 8-Me), 1.25 (3 H, t, *J* 7 Hz, OCH_2Me), 1.0—1.6 (5 H, m, CH_2CHCH_2) 2.05 (2 H, m, CH_2), 2.37 (4 H, m, 2 × CH_2), 3.63 (2 H, m, OCH_2), 4.15 (2 H, q, *J* 7 Hz, OCH_2Me), and 5.38 (2 H, m, vinylic H); *m*/*z* (c.i.) 343 (M^+, 100%).

(8R,4Z)-*Ethyl* 10-*Hydroxy*-8-*methyldec*-4-*enoate* (**8**).—Tetrabutylammonium fluoride in THF (32 ml, 1M solution) was added to silyl ether (**7**) (10 g, 29 mmol) in THF (100 ml), and the mixture stirred at room temperature for 3 h before being poured into water. Ether extraction and flash chromatography using ether–light petroleum (1 : 1) as eluant gave the *title compound* (**8**) (6.9 g, 96%) as a colourless oil (Found: C, 68.25, H, 10.4. $C_{13}H_{24}O_3$ requires C, 68.4; H, 10.5%); $[\alpha]_D^{20}$ +3.8° (*c* 1.20 in

$CHCl_3$); $\nu_{max.}$(film) 3 600—3 200, 1 735, and 1 370 cm^{-1}; δ_H(60 MHz) 1.1—2.5 (18 H, complex m), 3.73 (2 H, t, *J* 7 Hz, CH_2O), 4.20 (2 H, q, *J* 7 Hz, OCH_2Me), and 5.45 (2 H, m, vinylic H); *m/z* (c.i.) 229 ($M^+ + 1$, 80%) and 175 ($M^+ - 53$, 100%).

(8R)-*Ethyl* 10-*Hydroxy*-8-*methyldecanoate* (**9**).—A solution of ethyl 10-hydroxy-8-methyldec-4-enoate (**8**) (4.5 g, 19.7 mmol) in ethanol (40 ml) was added to 10% Pd–C (0.5 g) in ethanol (40 ml) and the mixture stirred under an atmosphere of hydrogen for 2 h at room temperature. The mixture was filtered through Celite and concentrated under reduced pressure to give an oil which was distilled using a Kugelrohr to give the *title compound* (**9**) (4.05 g, 90%), a colourless oil, b.p. 170—180 °C (0.1 mmHg); $[\alpha]_D^{20}$ +3.6° (*c* 1.00 $CHCl_3$); $\nu_{max.}$(film) 3 600—3 100, 1 735, and 1 170 cm^{-1}; δ_H 0.92 (3 H, d, *J* 7 Hz, 8-Me), 1.16 (3 H, t, *J* 7 Hz, CH_2Me), 1.25—1.66 (14 H, complex m), 2.18 (2 H, t, *J* 7.5 Hz, CH_2CO), 3.66 (2 H, m, CH_2OH), and 4.15 (2 H, q, *J* 7 Hz, OCH_2Me); *m/z* (c.i.) 231 ($M^+ + 1$, 80%) and 175 ($M^+ - 55$, 100%).

(8R)-*Ethyl* 9-*Formyl*-8-*methylnonanoate* (**10**).—Dimethyl sulphoxide (3.8 ml, 55 mmol) in dichloromethane (30 ml) was added to oxalyl chloride (2.6 ml, 29 mmol) in dichloromethane (30 ml) at −60 °C under argon, and the mixture stirred for 5 min. The alcohol (**9**) (6.3 g, 27.4 mmol) in dichloromethane (40 ml) was then added slowly, and the mixture stirred at −60 °C for a further 15 min. Triethylamine (19 ml, 137 mmol) was added, the mixture stirred for 30 min, warmed to room temperature, and poured into brine (100 ml). Extraction into ether, and concentration under reduced pressure gave an oil which was distilled using a Kugelrohr to give the *title compound* (**10**) (5.4 g, 89%), a colourless liquid, b.p. 125—130 °C (0.1 mmHg); $[\alpha]_D^{20}$ +6.46° (*c* 0.48 in $CHCl_3$); $\nu_{max.}$(film) 2 860, 1 730, and 1 180 cm^{-1}; δ_H 0.95 (3 H, d, *J* 7.5 Hz, 8-Me), 1.16 (3 H, t, *J* 7 Hz, OCH_2Me), 1.1—1.4 (8 H, complex m), 1.6 (2 H, m, 3-CH_2), 2.05 (1 H, m, 8-H), 2.15—2.45 (4 H, m, 2- and 9-CH_2), 4.14 (2 H, q, *J* 7 Hz, OCH_2Me), and 9.76 (1 H, t, *J* 1.5 Hz, CHO); *m/z* (c.i.) 246 ($M^+ + 18$, 100%) and 229 ($M^+ + 1$, 55%).

(8R,10E,12E,14E)-*Ethyl* 8,14-*Dimethylhexadeca*-10,12,14-*trienoate* (**12**).—A solution of butyl-lithium in hexane (1.6M; 16.7 ml, 26.7 mmol) was added to a solution of the dienylphosphonate (**11**)[8] (6.2 g, 26.7 mmol) in THF (50 ml) at −78 °C under argon, and the mixture stirred for 1 h. A pre-cooled solution of the aldehyde (**10**) (5.54 g, 24.3 mmol) in THF (25 ml) was added slowly *via* a cannula, and the mixture stirred for 1 h. Hexamethylphosphoric triamide (6.5 ml, 36.5 mmol) was added, and the mixture warmed to room temperature, and stirred for 3 h before being poured into saturated aqueous NH_4Cl (100 ml). Ether extraction and flash chromatography using base washed silica with ether–light petroleum (1:14) as eluant gave the *title compound* (**12**) (5.46 g, 73%), a colourless oil (Found: M^+, 306.2577. $C_{20}H_{34}O_2$ requires *M*, 306.2559); $[\alpha]_D^{20}$ −7.54° (*c* 0.61 in $CHCl_3$); $\nu_{max.}$(film) 3 020, 1 735, 1 630, 1 380, 1 180, 1 035, and 987 cm^{-1}; δ_H 0.85 (3 H, d, *J* 7.5 Hz, 8-Me), 1.26 (3 H, t, *J* 7 Hz, CH_2Me), 1.23—1.36 (9 H, complex m), 1.6 (2 H, m, CH_2), 1.75 (6 H, m, 2 × Me), 1.85—2.15 (2 H, m, 9-CH_2), 2.30 (2 H, t, *J* 7 Hz, 2-CH_2), 4.05 (2 H, q, *J* 7 Hz, OCH_2Me), 5.54 (1 H, q, *J* 6 Hz, 15-H), 5.65 (1 H, dt, *J* 15, 7 Hz, 10-H), and 6.0—6.2 (3 H, m, vinylic H); *m/z* (c.i.) 306 (M^+, 90%).

(8R,10E,12E,14E)-8,14-*Dimethylhexadeca*-10,12,14-*trienoic Acid* (**13**).—The triene ester (**12**) (5.46 g, 17.8 mmol) in ethanol (20 ml) was added dropwise to a solution of NaOH (3 g, 71.2 mmol) in ethanol–water (44 ml; 10:1), the mixture stirred for 3 h at room temperature, and poured into water (60 ml). A solution of tartaric acid (26.7 g, 178 mmol) in water (40 ml) was added to adjust the pH to 5, and ether extraction gave, after concentration under reduced pressure, the *title compound* (**13**) (4.62 g, 93%), a white solid, m.p. 34—36 °C (Found: M^+, 278.2246. $C_{18}H_{30}O_2$ requires *M*, 278.2245); $[\alpha]_D^{20}$ −6.4° (*c* 0.5 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 300—2 800, 1 710, and 990 cm^{-1}; δ_H 0.86 (3 H, d, *J* 7.5 Hz, 8-Me), 1.05—1.65 (9 H, complex m), 1.65 (2 H, m, 3-CH_2), 1.73 (6 H, m, 2 × Me), 1.85—2.15 (2 H, m, 9-CH_2), 2.36 (2 H, t, *J* 7 Hz, 2-CH_2), 5.55 (1 H, q, *J* 7 Hz, 15-H), 5.65 (1 H, dt, *J* 15, 7 Hz, 10-H), and 6.0—6.2 (3 H, m, vinylic H); *m/z* (c.i.) 278 (M^+, 100%).

(8R,10E,12E,14E)-(1-*Imidazol*-1-*yl*)-8,14-*dimethylhexadeca*-10,12,14-*trien*-1-*one* (**14**).—A solution of the triene acid (**13**) (4.62 g, 16.6 mmol) in THF (20 ml) was added to a stirred suspension of 1,1′-carbonyldi-imidazole (3.6 g, 21.6 mmol) in THF (40 ml) under argon, and the mixture stirred for 12 h at room temperature. The mixture was diluted with ether (200 ml), washed with ice-cold water (200 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave a white crystalline solid identified as the *title compound* (**14**) (4.92 g, 90%), m.p. 47—48 °C (from ether–pentane) (Found: C, 76.6; H, 9.7; N, 8.65. $C_{21}H_{32}N_2O$ requires C, 76.8; H, 9.8; N, 8.55%); $[\alpha]_D^{20}$ −5.75° (*c* 1.096 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 730, 1 355, and 985 cm^{-1}; δ_H 0.88 (3 H, d, *J* 7.5 Hz, 8-Me), 1.05—1.55 (9 H, complex m), 1.7—1.85 (8 H, m, 2 × Me and CH_2), 1.85—2.15 (2 H, m, 9-CH_2), 2.85 (2 H, t, *J* 7 Hz, 2-CH_2), 5.55 (1 H, q, 15-H), 5.65 (1 H, dt, *J* 15, 7.5 Hz, 10-H), 6.0—6.2 (3 H, m, vinylic H), 7.12 (1 H, narrow m, 4′-H), 7.48 (1 H, narrow m, 5′-H), and 8.16 (1 H, s, 2′-H); *m/z* (e.i.) 328 (M^+, 2%) and 278 ($M^+ - 50$, 5%).

(5R,8′R,10′E,12′E,14′E)-1-*Benzoyl*-5-*benzyl*-3-(8′,14′-*dimethyl*-1′-*oxohexadeca*-10′,12′,14′-*trienyl*)*pyrrolidin*-2-*one* (**16**).—(5R)-1-Benzoyl-5-benzylpyrrolidin-2-one (**15**)[9] (6.3 g, 22.8 mmol) in THF (40 ml) was cooled to −78 °C and added to lithium hexamethyldisilazide (22.8 mmol) in THF–hexane at −78 °C under argon *via* a cannula. The mixture was stirred for 1 h and then added to a solution of the imidazolylhexadecatrienone (**14**) (3.73 g, 11.4 mmol) in THF (60 ml) at −78 °C under argon. After 8 h stirring, saturated aqueous NH_4Cl (20 ml) was added, and the mixture warmed to room temperature, and poured into more aqueous NH_4Cl. Ether extraction and flash chromatography over base washed silica using ether–light petroleum (1:4) as eluant gave the *title compound* (**16**) (3.8 g, 61%), as an oil, a mixture of epimers at C-3 (Found: M^+, 539.3403. $C_{36}H_{45}NO_3$ requires *M*, 539.3399); $[\alpha]_D^{20}$ + 65.4° (*c* 1.11 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 730, 1 700, 1 670, 1 280, 1 215, and 985 cm^{-1}; δ_H 0.85 (3 H, overlapping d, 8′-Me), 1.05—1.60 (11 H, complex m), 1.73 (6 H, m, 14′- and 16′-Me), 1.8—3.75 (9 H, complex m), 4.62 (0.3 H, m, 5-H), 4.75 (0.7 H, m, 5-H), 5.66—6.22 (5 H, m, vinylic H), and 7.22—7.66 (10 H, m, ArH); *m/z* (c.i.) 540 ($M^+ + 1$, 100%).

(5S,8′R,10′E,12′E,14′E)-1-*Benzoyl*-5-*benzyl*-3-(8′,14′-*dimethyl*-1′-*oxohexadeca*-10′,12′,14′-*trienyl*)-3-*phenylselenopyrrolidin*-2-*one* (**17**).—The (1-oxohexadecatrienyl)pyrrolidinone (**16**) (3.79 g, 7.05 mmol) in THF (25 ml) was cooled to −78 °C under argon, and added *via* a cannula to a solution of lithium hexamethyldisilazide (10.57 mmol) in THF–hexane (16 ml) at −78 °C under argon. After stirring for 1 h, a pre-cooled solution of benzeneselenenyl chloride (2.02 g, 10.57 mmol) in THF (20 ml) was added, and the mixture stirred for 2 h at −78 °C before being quenched by saturated aqueous NH_4Cl (20 ml). The mixture was then allowed to warm to room temperature, and was poured into more saturated aqueous NH_4Cl (100 ml). Ether extraction and flash chromatography over base washed silica using ether–light petroleum (1:8) as eluant gave the *title compound* (**17**) (3.6 g, 75%), as an oil, a mixture of C-3 epimers (Found: M^+, 695.4704. $C_{42}H_{49}NO_3{}^{80}Se$ requires *M*, 695.4701); $[\alpha]_D^{20}$ +94.5° (*c* 2.04 in $CHCl_3$);

$\nu_{max.}$($CHCl_3$) 3 060, 3 020, 1 725, 1 690, 1 600, 1 280, 990, and 910 cm^{-1}; δ_H 0.92 (3 H, d, *J* 7 Hz, 8′-Me), 1.0—1.70 (11 H, complex m) 1.76 (6 H, m, 14′- and 16′-Me) 1.85—2.15 (3 H, complex m), 2.46—3.35 (5 H, complex m), 4.56 (1 H, m, 5-H); 5.5—5.8 (2 H, m, vinylic H), 6.00—6.30 (3 H, m, vinylic H), and 7.05—7.66 (15 H, m, ArH); *m/z* (c.i.) 696 (M^+ + 1, 3%) and 540 (M^+ − 155, 100%).

Generation and Diels–Alder Cyclization of (5S,8′R,10′E,12′E,-14′E)-1-*Benzoyl*-5-*benzyl*-3-(8′,14′-*dimethyl*-1′-*oxohexadeca*-10′,12′,14′-*trienyl*)*pyrrol*-2(5H)-*one* (**18**).—*m*-Chloroperoxybenzoic acid (300 mg, 1.73 mmol) in $CDCl_3$ (10 ml) was added to the selenide (**17**) (1 g, 1.44 mmol) in $CDCl_3$ (60 ml) at −50 °C followed immediately by 30% H_2O_2 (1 ml) in water (3 ml). After 15 min, the mixture was warmed to 0 °C, and stirred for a further 15 min before being washed with ice-cold aqueous $NaHCO_3$ (2 × 50 ml), brine (50 ml), and water (50 ml). After drying (Na_2SO_4), a small sample was examined by ^1H n.m.r. which showed the presence of the pyrrol-2(5*H*)-one (**18**); δ_H 0.92 (3 H, d, *J* 7 Hz, 8′-Me), 1.00—1.75 (11 H, complex m), 1.92 (6 H, m, 14′- and 16′-Me), 1.85—2.15 (2 H, m, 9′-CH_2), 2.78 (2 H, t, *J* 7.5 Hz, 2′-CH_2), 3.17 (1 H, dd, *J* 8, 14 Hz, HC*H*Ph), 3.48 (1 H, dd, *J* 3, 14 Hz, *H*CHPh), 5.33 (1 H, m, 5-H), 5.55—6.20 (5 H, m, vinylic H), 7.15—7.64 (10 H, complex m, ArH), and 7.96 (1 H, d, *J* 1 Hz, 4-H). The remainder of the pyrrol-2(5*H*)-one solution was diluted with anhydrous toluene (1 l), and heated at 100 °C for 5 h under argon. After cooling, the mixture was concentrated under reduced pressure and the residue purified by flash chromatography using ether–light petroleum (1:10) as eluant to provide a mixture of the Diels–Alder adducts (**19**) and (**21**) (338 mg, 52%) as an amorphous, white powder; $\nu_{max.}$($CHCl_3$) 3 030, 1 760, 1 700, 1 620, 1 560, and 1 300 cm^{-1}; *m/z* (c.i.) 538 (M^+ + 1, 100%).

Hydrolysis of Diels–Alder Adducts.—A solution of KOH (1.5 g, 8 mmol) in water (3 ml) was added to a solution of the Diels–Alder adducts (**19**) and (**21**) (1.1 g, 2.05 mmol) in benzene–methanol (3:1; 40 ml) with cooling at 0 °C, and the mixture stirred for 3 h before being poured into aqueous $NaHCO_3$ (50 ml), and extracted into ether. After drying ($MgSO_4$), the solvent was removed under reduced pressure, and the residue chromatographed using short column chromatography with dichloromethane–methanol (99:1) as eluant. The first fraction off the column was identified as (16R)-16-*methyl*-10-*phenyl*[13]*cytochalasa*-6(7),13′-*diene*-1,23-*dione* (**20**) (354 mg, 40%), a white amorphous solid (Found: M^+, 433.2981. $C_{29}H_{39}NO_2$ requires *M*, 433.2988); $[\alpha]_D^{20}$ −86.2° (*c* 0.45 in $CHCl_3$); $\nu_{max.}$(CCl_4) 3 430, 3 200, 3 090, 3 060, 3 030, 1 690, 1 620, 1 590, 1 550, 1 250, and 1 220 cm^{-1}; δ_H 0.88 and 1.20 (each 3 H, d, *J* 7.5 Hz, CH*Me*), 1.00—1.60 (12 H, complex m), 1.75 (3 H, s, 12-Me), 1.93 (1 H, m, 22-H), 2.06 (1 H, m, 15-H), 2.47—2.62 (3 H, m, HC*H*Ph, 4-, and 5-H), 2.87 (1 H, dd, *J* 4, 15 Hz, *H*CHPh), 3.04 (1 H, m, 22-H), 3.17—3.30 (2 H, m, 3- and 8-H), 5.33 (1 H, m, 14-H), 5.47 (1 H, narrow m, 7-H), 5.61 (1 H, s, NH), 6.00 (1 H, ddd, *J* 15, 10, 2 Hz, 13-H), and 7.13—7.30 (5 H, m, ArH). After a mixed fraction (83 mg, 9%), the second fraction was obtained and was identified as (5R,8R,16R)-16-*methyl*-10-*phenyl*[13]*cytochalasa*-6(7),13′-*diene*-1,23-*dione* (**22**) (281 mg, 32%), a white amorphous solid (Found: M^+, 433.2983. $C_{29}H_{39}NO_2$ requires *M*, 433.2988); $[\alpha]_D^{20}$ −179.4° (*c* 0.655 in $CHCl_3$); δ_H 0.87 and 1.00 (each 3 H, d, *J* 7.5 Hz, CH*Me*), 1.15—1.60 (11 H, complex m), 1.70 (3 H, s, 12-Me), 1.80—2.00 (2 H, m), 2.07 (1 H, m), 2.45—2.64 (2 H, m), 2.80 (1 H, dd, *J* 14, 5 Hz, HC*H*Ph), 2.88 (1 H, t, *J* 4 Hz, 4-H), 2.94 (1 H, m, 22-H), 3.25 (1 H, m, 3-H), 3.51 (1 H, m, 8-H), 5.25 (1 H, dd, *J* 15, 10 Hz, 13-H), 5.42 (1 H, d, *J* 6 Hz, 7-H), 5.59 (1 H, s, NH), 5.64 (1 H, m, 14-H), and 7.06—7.30 (5 H, m, ArH).

(5R,8R,16R)-2-*Benzoyl*-16-*methyl*-10-*phenyl*[13]*cytochalasa*-6(7),13′-*diene*-1,23-*dione* (**21**).—A solution of lithium hexamethyldisilazide (0.25 mmol) in THF–hexane was added to (5*R*,8*R*,16*R*)-16-methyl-10-phenyl[13]cytochalasa-6(7),13′-diene-1,23-dione (**22**) (90 mg, 0.208 mmol) in THF (4 ml) at 0 °C under argon, and the mixture stirred for 1 h. Benzoyl chloride (30 μl, 0.25 mmol) was added, and the mixture stirred for 3 h before being quenched by the addition of saturated NH_4Cl (10 ml) and extracted into ether. After drying ($MgSO_4$), concentration under reduced pressure, and flash chromatography using ether–light petroleum (1:10) as eluant gave the *title compound* (**21**) (85 mg, 72%) as a white powder (Found: C, 80.3; H, 6.6; N, 2.7. $C_{36}H_{43}NO_3$ requires C, 80.4; H, 6.3; N, 2.6%); $[\alpha]_D^{20}$ −38.1° (*c* 0.76 in $CHCl_3$); ν_{max} ($CHCl_3$) 3 030, 1 760, 1 700, 1 620, 1 560, and 1 300 cm^{-1}; δ_H 0.75 and 0.92 (each 3 H, d, *J* 7.5 Hz, CH*Me*), 1.00—1.83 (13 H, complex m), 1.62 (3 H, br s, 12-Me), 2.08 (1 H, ddd, *J* 15, 10, 6 Hz, 15-H), 2.33—2.52 (2 H, m, HC*H*Ph and 22-*H*CH), 2.77 (1 H, dd, *J* 7.5, 2 Hz, 4-H), 2.82 (1 H, m, 22-H*H*), 3.20 (1 H, dd, *J* 13, 4 Hz, HC*H*Ph), 3.43 (1 H, m, 8-H), 4.33 (1 H, dd, *J* 10, 5 Hz, 3-H), 5.20 (1 H, dd, *J* 15, 8 Hz, 13-H), 5.43 (1 H, br d, *J* 6 Hz, 7-H), 5.66 (1 H, m, 14-H), and 7.25—8.20 (10 H, m, ArH); *m/z* (c.i.) 538 (M^+ + 1, 100%).

(16R)-16-*Methyl*-10-*phenyl*-22-*phenylseleno*[13]*cytochalasa*-6(7),13′-*diene*-1,23-*dione* (**23**).—A pre-cooled solution of LDA (0.92 mmol) in THF–hexane (1.9 ml) was added to a solution of the [13]cytochalasadiene (**20**) (100 mg, 0.23 mmol) in THF (4 ml) at −78 °C under argon. After stirring for 1 h, a solution of benzeneselenenyl chloride (177 mg, 0.92 mmol) in THF (3 ml) was added, and the mixture stirred for 2 h at −78 °C before being quenched with saturated aqueous NH_4Cl. Ether extraction and flash chromatography using ether–light petroleum (1:1) as eluant gave the *title compound* (**23**) (84 mg, 62%) as an oil (Found: M^+, 589.6131. $C_{35}H_{43}NO_2{}^{80}Se$ requires *M*, 589.6128); $[\alpha]_D^{20}$ −109° (*c* 0.85 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 690, 1 670, 1 600, 980, and 910 cm^{-1}; δ_H 0.85 and 1.18 (each 3 H, d, *J* 7.5 Hz, CH*Me*), 1.20—1.73 (12 H, complex m), 1.75 (3 H, s, 12-Me), 2.08 (1 H, m, 15-H), 2.70—2.86 (4 H, complex m, CH_2Ph, 4- and 5-H), 3.23 (1 H, m, 3-H), 3.33 (1 H, m, 8-H), 4.50 (1 H, t, *J* 7.5 Hz, 22-H), 5.33 (1 H, m, 7-H), 5.40 (1 H, dt, *J* 15, 7 Hz, 14-H), 5.48 (1 H, s, NH), 6.30 (1 H, ddd, *J* 15, 10, 2.5 Hz, 13-H), and 7.13—7.55 (10 H, m, ArH); *m/z* (c.i.) 589 (M^+, 10%) and 434 (M^+ − 155, 100%).

(16R)-16-*Methyl*-10-*phenyl*[13]*cytochalasa*-6(7),13′,21′-*triene*-1,23-*dione* (*Proxiphomin*) (**1**).—Pyridine (1 ml) and 30% H_2O_2 (0.4 ml) in water (1.2 ml) were added to the selenide (**23**) (84 mg, 0.14 mmol) in CH_2Cl_2 (5 ml), and the mixture stirred for 2 h at room temperature before being diluted with ether (30 ml), and washed with ice-cold 3M aqueous HCl (30 ml) and aqueous $NaHCO_3$ (30 ml). After drying ($MgSO_4$), the solvent was removed under reduced pressure, and the residue flash chromatographed using ether–light petroleum (1:1) as eluant to give the *title compound* (**1**) (43 mg, 65%) as an amorphous solid (Found: M^+, 431.2831. $C_{29}H_{27}NO_2$ requires *M*, 431.2824); $[\alpha]_D^{20}$ −136° (*c* 0.765 in $CHCl_3$) [lit.,[3] $[\alpha]_D^{20}$ −140° (*c* 0.156 in $CHCl_3$)]; $\nu_{max.}$($CHCl_3$) 3 440, 3 200, 3 040, 1 700, 1 620, and 1 300 cm^{-1}; δ_H 0.88 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.0 (1 H, m), 1.20 (3 H, d, *J* 7.5 Hz, CH*Me*), 1.10—1.70 (6 H, complex m), 1.75 (3 H, s, 12-Me), 1.85 and 2.06 (each 1 H, m, 15-H), 2.20 and 2.3 (each 1 H, m, 20-H), 2.43—2.55 (2 H, m, HC*H*Ph and 5-H), 2.66 (1 H, m, 8-H), 2.83 (1 H, dd, *J* 14.5 Hz, *H*CHPh), 3.15—3.29 (2 H, m, 3- and 4-H), 5.23 (1 H, ddd, *J* 15, 10, 3 Hz, 14-H), 5.43 (1 H, narrow m, 7-H), 5.45 (1 H, s, NH), 6.28 (1 H, ddd, *J* 15, 10, 2 Hz, 13-H), 6.82 (1 H, ddd, *J* 15, 10, 5 Hz, 21-H), and 7.10—7.32 (6 H, m, 22-H and ArH); *m/z* (c.i.) 432 (M^+ + 1, 100%).

(16R)-16-*Methyl*-10-*phenyl*[13]*cytochalsa*-6(7),13′-*diene*-1,23-*diones* (**35**) *and* (**37**).—Using the procedures outlined above racemic 1-benzoyl-5-benzylpyrrolidin-2-one (**32**)[10] was con-

densed with (8*R*,10*E*,12*E*,14*E*)-1-imidazol-1-yl-8,14-dimethylhexadeca-10,12,14-trien-1-one (**14**), and the product phenylselenated and oxidized to provide a mixture of the pyrrol-2(5*H*)-ones (**18**) and (**33**) which were detected in solution by ^{1}H n.m.r. Dilution of the pyrrol-2(5*H*)-one solution using toluene, and heating for several hours at 100 °C gave a crude mixture of adducts (**19**), (**21**), (**34**), and (**36**). Hydrolysis of this mixture of adducts (338 mg, 0.63 mmol) using 50% aqueous KOH (1 ml) in benzene–methanol (3:1; 20 ml) gave a yellow oil which was separated into four fractions by short column chromatography using CH_2Cl_2–methanol (99:1) as eluant. The least polar fraction was then separated into two components by multiple elution preparative t.l.c., the faster component being identified as (16*R*)-16-methyl-10-phenyl[13]cytochalasa-6(7),13'-diene-1,23-dione (**20**) (29 mg, 11%), and the slower component being identified as (3R,4S,5S,8S,9R,16R)-16-*methyl*-10-*phenyl*[13]-*cytochalasa*-6(7),13'-*diene*-1,23-*dione* (**37**) (32 mg, 12%) (Found: M^+, 433.2984. $C_{29}H_{39}NO_2$ requires *M*, 433.2987); $[\alpha]_D^{20}$ +162° (*c* 0.24 in $CHCl_3$); $\delta_H(C_6D_6)$ 0.78 (6 H, overlapping d, 2 × CH*Me*), 0.8—1.7 (10 H, complex m), 1.88 (1 H, m), 2.02 (2 H, m), 2.15 (1 H, m), 2.37 (2 H, m, HC*H*Ph and 5-H), 2.53 (1 H, dd, *J* 15, 8.5 Hz, HC*H*Ph), 2.87 (1 H, m, 3-H), 2.93—3.05 (2 H, m, 22-H), 3.15 (1 H, t, *J* 2.5 Hz, 4-H), 4.86 (1 H, m, 8-H), 5.13—5.42 (3 H, m, vinylic H), 5.87 (1 H, s, NH), and 7.10—7.33 (5 H, m, ArH); *m/z* (e.i.) 433 (M^+, 33%), 405 (M^+ − 28, 40%), and 342 (M^+ − 91, 80%). The second fraction off the column was identified as (5*R*,8*R*,16*R*)-16-methyl-10-phenyl[13]cytochalsa-6(7),13'-diene-1,23-dione (**22**) (38 mg, 14%), the third fraction comprised unidentified polymer (42 mg), and the most polar fraction was identified as (3R,4S,5R,8R,9R,16R)-16-*methyl*-10-*phenyl*[13]*cytochalasa*-6(7),13'-*diene*-1,23-*dione* (**35**) (36 mg, 13%) (Found: M^+, 433.2983. $C_{29}H_{39}NO_2$ requires *M*, 433.2987); $[\alpha]_D^{20}$ +86.1° (*c* 0.57 in $CHCl_3$); δ_H 0.88 and 1.22 (each 3 H, d, *J* 7.5 Hz, CH*Me*), 1.13—1.82 (13 H, m), 1.75 (3 H, narrow m, 12-Me), 2.11 (1 H, m, 22-H), 2.48 (1 H, dd, *J* 15, 8 Hz, HC*H*Ph), 2.53 (1 H, d, *J* 5.2 Hz, 4-H), 2.58 (1 H, m, 5-H), 2.87 (1 H, dd, *J* 15, 5 Hz, *H*CHPh), 3.05 (1 H, dt, *J* 12.4, 5 Hz, 22-H), 3.12 (1 H, m, 8-H), 3.27 (1 H, m, 3-H), 5.45 (1 H, narrow m, 7-H), 5.57 (1 H, ddd, *J* 15, 10, 5 Hz, 14-H), 5.66 (1 H, s, NH), 6.04 (1 H, dd, *J* 15, 10 Hz, 13-H), and 7.10—7.30 (5 H, m, ArH); *m/z* (e.i.) 433 (M^+, 20%), 405 (M^+ − 28, 83%), and 342 (M^+ − 91, 20%).

Acknowledgements

We thank the S.E.R.C. and the Wellcome Research Laboratories for support to (J. W. F. W.) under the CASE Scheme. We also thank Professor C. Tamm for copies of spectra of proxiphomin isolated from natural sources, and Dr. J. P. Watts for separating the normethyl[13]cytochalasans (**30**) and (**31**). We are also grateful to Dr. A. E. Derome and Mrs. E. McGuinness for n.m.r. spectra, and Dr. R. T. Aplin for mass spectra.

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Received 15*th June* 1988; *Paper* 8/02405G