Cytochalasan Synthesis: Macrocycle Synthesis Using Intramolecular Diels–Alder Reactions. *X*-Ray Crystal Structure of 10-Phenyl[11]cytochalasa-6(7),13^{t}-diene-1,21-dione

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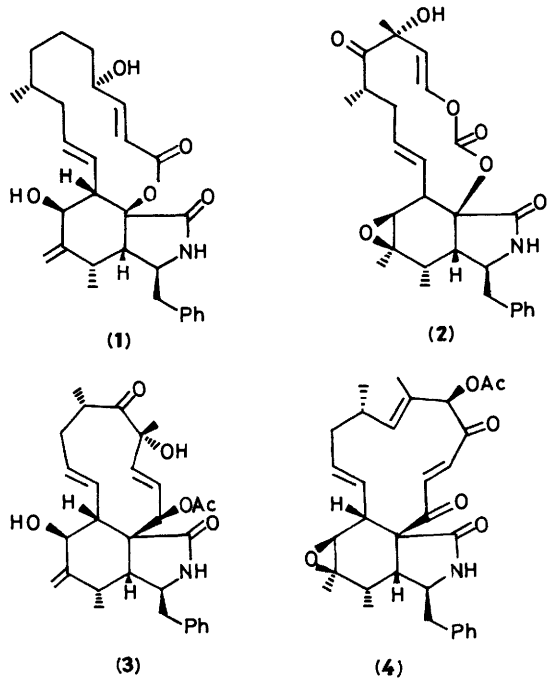
An approach to the total synthesis of cytochalasans has been developed which makes use of an intramolecular Diels–Alder reaction to close the large ring simultaneously forming the hydrogenated isoindolone unit with the desired stereochemistry. Conjugated trienes were found to be more efficient than dienes as the diene components for these reactions. Thus the long chain 3-(1-oxotrienyl)pyrrol-2(5*H*)-one (**36**) gave a useful yield of the [11]cytochalasan (**37**) when heated in toluene at 100 °C. The structure of 10-phenyl[11]cytochalasa-6(7),13^{t}-diene-1,21-dione (**38**) was established by *X*-ray crystallography.

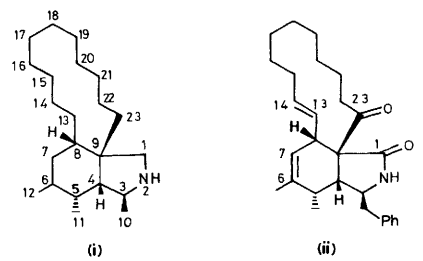
The cytochalasans together with the chaetoglobosins and aspochalasans constitute a group of biologically active fungal metabolites which have attracted considerable attention in recent years.[1] Structurally they are characterized by the presence of a hydrogenated isoindolone unit fused to a macrocyclic ring. The macrocyclic ring can either be a lactone, as in cytochalasan B (**1**),[1] a carbonate, as in cytochalasan E (**2**),[2] or more frequently, a carbocycle, as in cytochalasins D (**3**)[1] and K (**4**).[3] The biosynthesis of the cytochalasans has been carefully examined, and the origins of the carbon atoms thoroughly established.[4] Phenylalanine has been shown to be incorporated into many cytochalasans including (**1**)—(**4**), and provides the N-2–C-4 fragment including the benzyl substituent.[5] Other amino acids can be incorporated into cytochalasans; cytochalasin G (**5**), for example, is derived from tryptophan,[6] and the aspochalasans, *e.g.* aspochalasin C(**6**), are derived from leucine.[7]

The total synthesis of cytochalasans has attracted considerable attention. Stork first synthesized cytochalasin B (**1**) using an intermolecular Diels–Alder reaction to set up the stereochemistry around the isoindolone nucleus.[8] A macrocyclic analogue of cytochalasin B was then synthesized using an intramolecular Diels–Alder reaction,[9] and this approach was used by Stork in his second synthesis of the macrolide cytochalasans.[10] Both inter- and intra-molecular Diels–Alder reactions have been used to assemble the reduced isoindolone fragment of carbocyclic cytochalasans,[11] and elegant ring expansion[12] and fragmentation[13] procedures developed to synthesize the eleven-membered ring of the [11]cytochalasans.‡,[14] We now report the stereoselective synthesis of [11]- and [13]-cytochalasans using intramolecular Diels–Alder reactions.[15]

Studies on *inter*molecular Diels–Alder reactions have shown that 1-acylated pyrrol-2(5*H*)-ones are useful dienophiles with their reactivity depending upon the nature of the 3-substituent,[11,16] higher temperatures being required for Diels–Alder reactions of 1-acyl-3-alkylpyrrol-2(5*H*)-ones than for their 3-acyl counterparts. Good diastereoface selectivity is observed in additions to 5-substituted pyrrol-2(5*H*)-ones, the dienes preferring to approach the less hindered face of the pyrrolone ring away from the larger substituent at C-5. This preference, together with the usually observed *endo-exo* selectivity, *i.e.* addition *endo* to the pyrrolone ring, induces the stereochemistry



‡ The prefixes [11] and [13] refer to the size of the large ring. A special nomenclature has been devised for the cytochalasans (see ref. 14), and will be used in this series of papers. Formula (**i**) shows the structure, stereochemistry, and numbering of the [13]cytochalasan nucleus. Additional structural features are indicated by conventional prefixes and suffixes, *e.g.* compound (ii) is 10-phenyl[13]cytochalasa-6(7),13^{t}-diene-1,23-dione. The configurations of the chiral carbons in the isoindolone nucleus are only defined if they differ from those in the natural series. Some of the Diels–Alder products in this paper lack the 12-methyl group. For consistency they will be described as 12-normethylcytochalasans.



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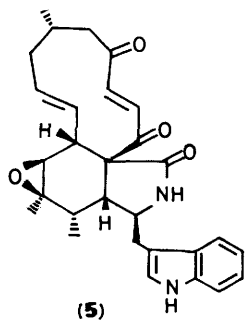

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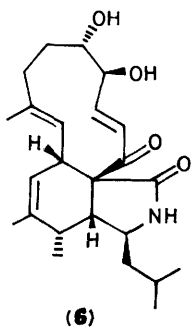

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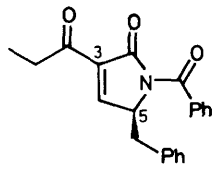

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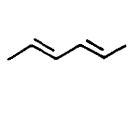
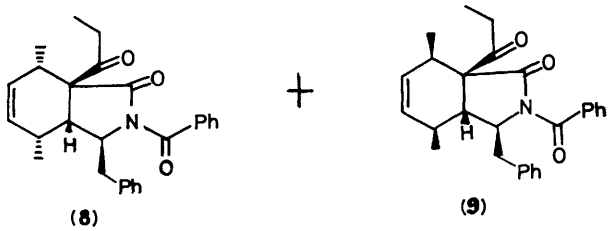




(8) (85 : 15) (9)

required for cytochalasan synthesis, *e.g.* adduct (**8**) is the major product from the Diels–Alder reaction between 1-benzoyl-5-benzyl-3-(1-oxopropyl)pyrrol-2(5*H*)-one (**7**) and (2*E*,4*E*)-hexa-2,4-diene.[16]

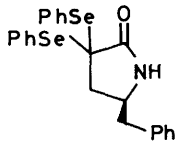
Results and Discussion

*Intramolecular Diels–Alder Reactions of Long Chain Diene Pyrrol-*2(5H)*-ones.*—The viability of the *intra*molecular Diels–Alder approach to carbocyclic cytochalasans was first investigated using long chain 3-dienylpyrrol-2(5*H*)-ones, preliminary studies being carried out using the 3-alkadienyl pyrrolones (**13**)—(**15**) prepared in three steps from 5-benzyl-3,3-bis(phenylseleno)pyrrolidin-2-one (**10**). Thus treatment of the bis-selenide (**10**)[16] with two equivalents of butyl-lithium and the tetradecadienyl iodide (**16**) gave the 3-alkyl-3-phenylselenopyrrolidin-2-one (**11**) (66%) which was 1-acylated and oxidized to give the 3-tetradecadienylpyrrol-2(5*H*)-one (**13**) after selenoxide elimination (Scheme 1). However, attempted Diels–Alder cyclizations of (**13**) using dilute solutions in *tolu*ene, at temperatures known to be effective for the analogous *inter*molecular reactions, 170—190 °C,[16] were unsuccessful, no identifiable products being isolated even after prolonged reaction times of up to 40 h. The analogous 1-benzoyl and homologous 3-hexadecadienylpyrrol-2(5*H*)-ones (**14**) and (**15**) also failed to provide any Diels–Alder product under these conditions.

Next the intramolecular Diels–Alder cyclizations of 3-(1-oxodienyl)pyrrol-2(5*H*)-ones were investigated, the substrate for this study being prepared from the 1-silylated pyrrolidinone (**27**) following procedures developed during our intermolecular Diels–Alder work.[16] Thus, treatment of the 1-silylated pyrrolidinone (**27**) with lithium di-isopropylamide (LDA) and the imidazolylhexadecadienone (**17**) gave the 3-acyl pyrrolidinone (**18**) as a mixture of epimers at C-3. This was phenylselenated using LDA–benzeneselenenyl chloride, and the 1-silyl group replaced by a benzoyl group by treatment with benzoyl chloride in anhydrous benzene,[16,17] to give the 1,3-diacyl pyrrolidinone (**20**) (66%), together with a small amount of the corresponding NH pyrrolidinone (**21**) (15—20%) (Scheme 2). Oxidative elimination of the phenylselenenyl group was then achieved using an excess of hydrogen peroxide, to give the 3-(1-oxohexadecadienyl)pyrrol-2(5*H*)-one (**22**) which was found to be relatively unstable and so was used without purification.

Diels–Alder reactions of the 3-(1-oxodienyl)pyrrol-2(5*H*)-one (**22**) were first carried out by heating dilute solutions in toluene at 120 °C for 15—20 h, but were found to be low yielding and capricious. More effective were reactions under high pressure conditions. Thus a dilute solution of 3-(1-oxodienyl)pyrrol-2(5*H*)-one (**22**) in dichloromethane at 40 °C, under a pressure of 11—13 kbar for *ca.* 15 h, gave mixtures of the *endo* and *exo* Diels–Alder adducts (**23**) and (**25**) in yields of up to 30%, the ratio (**23**):(**25**) = 85:15, being similar to that observed in the thermal reactions.

The Diels–Alder adducts (**23**) and (**25**) could not be separated. However, removal of the 1-benzoyl group using potassium hydroxide in methanol–benzene gave the corresponding NH compounds (**24**) and (**26**) which were separated by short column chromatography. The structures of these depro-



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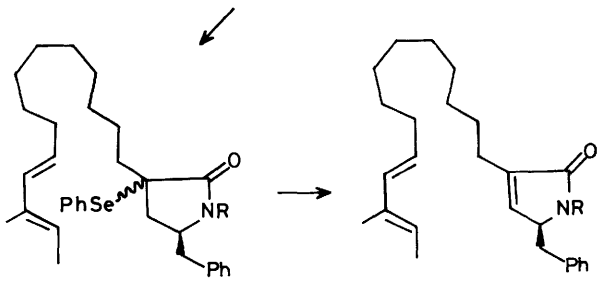
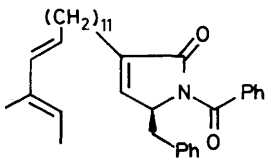


R
(11) H
(12) Ac

R
(13) Ac
(14) COPh

Scheme 1.



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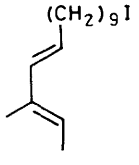

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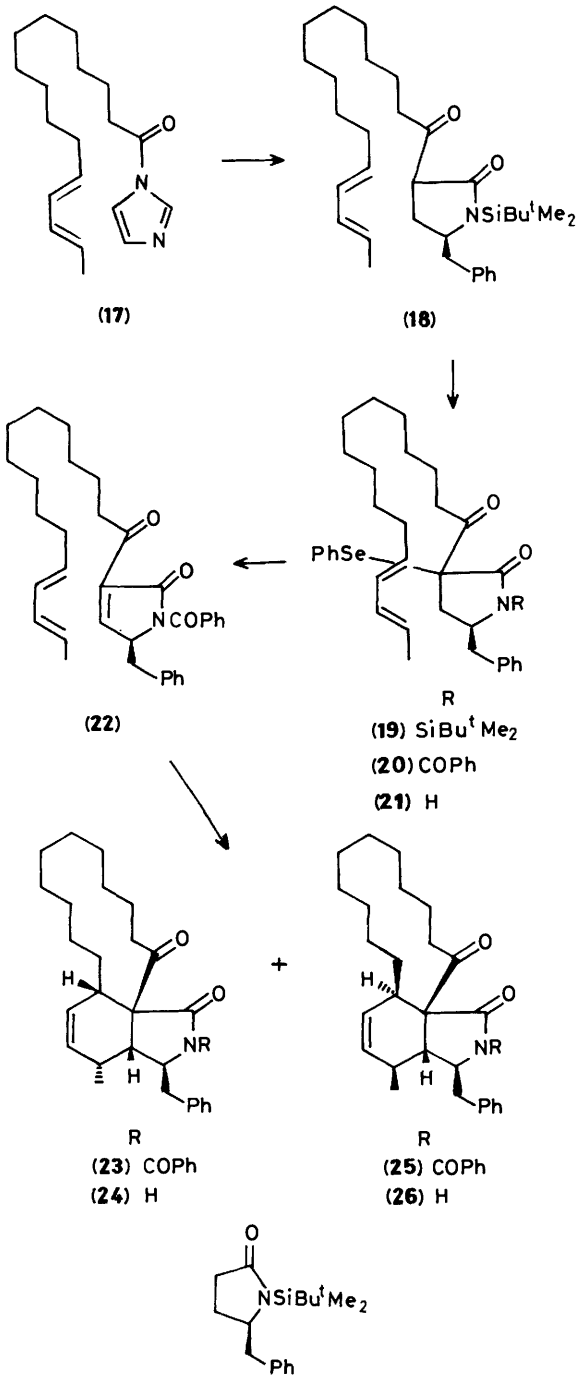


Scheme 2.

tected adducts were established as shown in formulae (**24**) and (**26**) by spectroscopic methods. In particular n.O.e. studies established the isoindolone stereochemistry since irradiation of 3-H caused a small but significant enhancement (1.1%) of the vinylic proton 6-H for the major adduct, and a 7% enhancement of 5-H for the minor adduct. These results are consistent with the conformations* shown in Figure 1, and with analogous intermolecular Diels–Alder reactions.

* The conformation shown for the 1-debenzoylated adduct (**26**) was unexpected, but is consistent with the n.O.e. data obtained for related adducts (see the following paper).

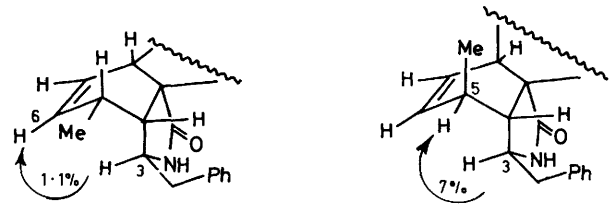
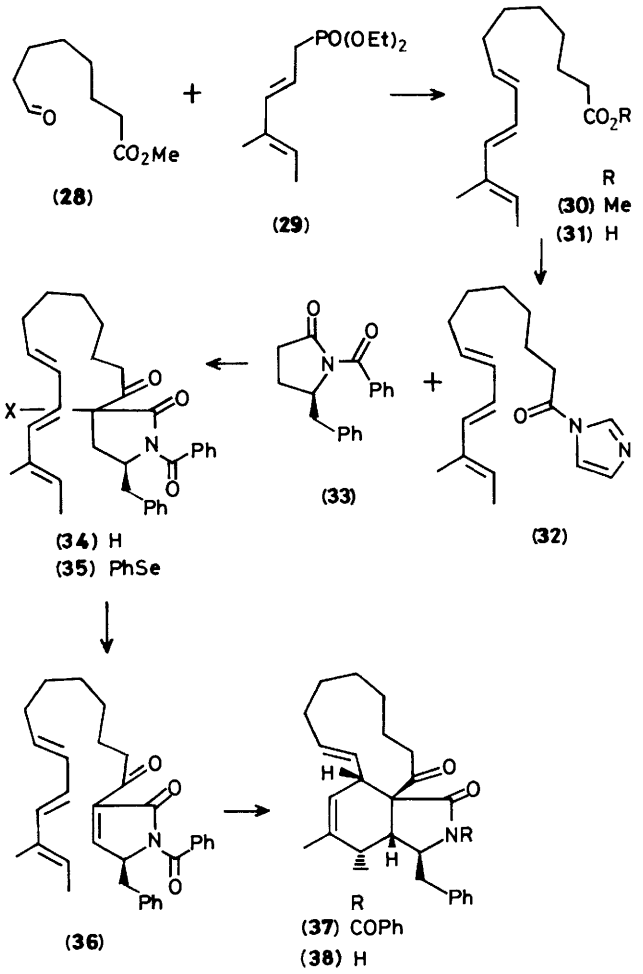


Figure 1. Conformations and selected n.O.e. data for adducts (**24**) and (**26**)

Therefore it would appear that the long chain 1-acyl-3-(1-oxodienyl)pyrrol-2(5*H*)-ones will undergo intramolecular Diels–Alder reactions, but only in modest yield. It was felt that one reason for these low yields could be the instability of the 1,3-diacylpyrrol-2(5*H*)-one system which, in the *inter*molecular Diels–Alder reactions, was being trapped by the high concentration of excess of diene, but which in the *intra*molecular reaction was undergoing decomposition at a rate competitive with cyclization. It was decided to see whether the yields of cyclized products could be improved by increasing the Diels–Alder reactivity of the diene component of these reactions. Since conjugated trienes are more reactive than dienes in Diels–Alder reactions, and since all naturally occurring cytochalasans have a double bond at C-13–C-14, it was decided to investigate the synthesis and intramolecular Diels–Alder chemistry of long chain 1-acyl-3-(1-oxotrienyl)pyrrol-2(5*H*)-ones.

Intramolecular Diels–Alder Reactions of Long Chain 3-(1-Oxotrienyl)Pyrrol-2-(5H)-ones.—Conditions for several crucial reactions had to be developed before a synthesis of long chain 3-(1-oxotrienyl)pyrrol-2(5*H*)-ones could be achieved. Firstly a method had to be found for the stereoselective synthesis of (*E,E,E*)-trienes since preliminary investigations showed iodine catalysed triene equilibration to be inefficient because of polymerization. Secondly a procedure had to be developed for the direct acylation of 1-benzoylpyrrolidin-2-ones at C-3, since the acid sensitivity of long chain conjugated trienes precluded the 1-silyl to 1-benzoyl exchange used in the synthesis of the 3-(1-oxodienyl)pyrrol-2(5*H*)-one (**22**). Finally a method had to be found for the oxidation of 3-phenylselenopyrrolidinones into pyrrol-2(5*H*)-ones which was compatible with a sensitive conjugated triene unit.

After considerable experimentation into triene synthesis, the use of the lithium salt of the dienylphosphonate (**29**), in the presence of hexamethylphosphoric triamide to promote the fragmentation step, as originally reported by Stork,[10] was found to be the most effective. Thus treatment of the dienylphosphonate (**29**) with butyl-lithium at −78 °C, with warming to −30 °C to effect complete deprotonation, gave an orange–red solution of lithiated phosphonate. To this solution recooled to −78 °C, was added aldehyde (**28**) which quenched most of the colour leaving a pale yellow mixture. Hexamethylphosphoric triamide was then added, and after stirring at room temperature for several hours, the desired triene ester (**30**) was isolated, and was purified by flash chromatography on base washed silica (isolated yields *ca.* 50—70%) (Scheme 3). This procedure was found to be at least 90% stereoselective since only the (*E,E,E*)-isomer was evident in the high-field ^{1}H n.m.r. spectrum of the product. The *E*-stereochemistry of the newly formed double bond was not confirmed at this stage, but was supported by precedent, and by the structure of the Diels–Alder product (**37**). Other procedures that were investigated for this phosphonate coupling, *e.g.* the use of sodium and potassium bases, different solvents *etc.*, were either less efficient or gave mixtures of isomers.[18] For the crucial C-3 pyrrolidinone acylation step, the triene ester was hydrolysed, and the free acid (**31**) treated with



Scheme 3.

1,1′-carbonyldi-imidazole to provide the acyl imidazolide (**32**). Early studies of the direct acylation of 1-benzoylpyrrolidinones had used LDA as base, and had been complicated by competing addition to the imide carbonyl group.[16] However, it was now found that the use of lithium hexamethyldisilazide as base, at −78 °C, gave clean enolate anion formation from 1-acyl pyrrolidinones, and that these enolates could be acylated efficiently by long chain imidazolyl derivatives. Thus, acylation of the 1-benzoyl pyrrolidinone (**33**)[16] with the imidazolyl trienone (**32**) gave the 1,3-diacyl pyrrolidinone (**34**) as a mixture of epimers at C-3, in good yield.

Conversion into the pyrrol-2(5*H*)-one (**36**) was then carried out by phenylselenation using lithium hexamethyldisilazide–benzeneselenenyl chloride, followed by oxidative elimination using *m*-chloroperoxybenzoic acid–hydrogen peroxide, first at −50 °C, and then at 0 °C, which effected selective oxidation of the phenylselenenyl moiety. The pyrrol-2(5*H*)-one (**36**) could not be isolated, all attempts to remove solvent simply leading to the formation of polymer; however, it could be detected in solution by ^{1}H n.m.r. with the proton at C-4 being distinctive as a narrow multiplet at δ 7.97. To effect the Diels–Alder reaction, the solutions of the 3-(1-oxotrienyl)pyrrol-2(5*H*)-one (**36**) were dried, diluted with toluene, and heated for several hours at *ca.* 100—110 °C. From these reactions the Diels–Alder product (**37**) was isolated in synthetically useful yields (40—50%).

Formation of the [11]cytochalasan (**37**) was stereoselective in that only a single adduct identified as the desired isomer was isolated after flash chromatography. Minor products, <5%, were detected in crude product mixtures, but were not isolated or identified. The structure of the major Diels–Alder adduct was initially assigned on the basis of spectroscopic studies, and was confirmed by *X*-ray crystallography for the 1-debenzoylated adduct which clearly established the stereochemistry as shown in formula (**38**). (One ^{1}H n.m.r. feature which has been found a useful guide to the stereochemistry of these adducts is the 7-H—8-H coupling constant which is small, 1—2 Hz, for isoindolones with the natural configuration at C-8, but which is distinctly larger, *ca.* 7 Hz, for isoindolones with the unnatural configuration at C-8.)

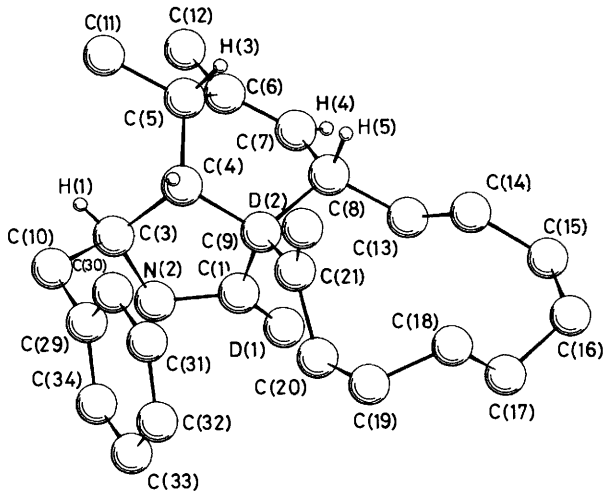


Figure 2. Ball and stick representation of the 10-phenyl[11]cytochalasa-6(7),13′-diene-1,21-dione (**38**) showing the crystallographic numbering scheme

Summary and Conclusions

This work shows that the effectiveness of large ring formation using an intramolecular Diels–Alder reaction is markedly influenced by the reactivity of the diene and dienophile components. The improvement in cyclization yields obtained using the conjugated triene (**36**) was reflected in similarly good cyclization yields in the [13]cytochalasan series,[19] and may be due to the greater cycloaddition reactivity of trienes as suggested above, but mechanistic aspects of this hypothesis were not explored. However, the successful cyclization of the 1-benzoyl-3-(1-oxotrienyl)pyrrol-2(5*H*)-one (**36**) demonstrates the viability of this approach to carbocyclic cytochalasans. The cyclised product (**37**) has been formed by a process in which the triene has approached the less hindered face of the dienophile *endo* to the pyrrolone ring so establishing the desired relative stereochemistry for cytochalasan synthesis at all five chiral centres (see Figure 3). The application of this chemistry to cytochalasan synthesis is reported in the following papers.

Experimental

I.r. spectra were measured on Perkin-Elmer 257 and 297 spectrophotometers, and ^{1}H n.m.r. spectra were recorded on a Bruker WH 300 spectrometer (300 MHz) in $CDCl_3$, unless otherwise stated. Mass spectra were recorded on Varian MAT CH7, and VG-Micromass 16F and ZAB-16F spectrometers using either electron impact (e.i.) or chemical ionization (c.i.) modes. Characteristic groups of peaks were obtained for compounds containing selenium; the peaks corresponding to ^{80}Se are given below. M.p.s were determined on a Buchi 510 apparatus and are uncorrected, and optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Short column and flash chromatography were carried out on

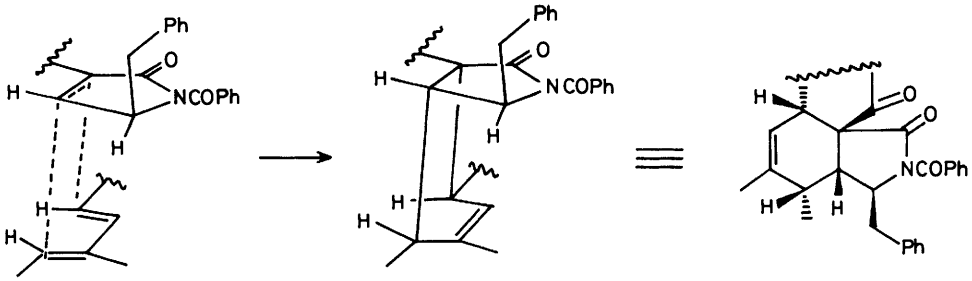


Figure 3. *Endo* transition state for formation of Diels–Alder adduct (**37**)

Merck Kieselgel 60H and Merck silica gel 60, respectively. 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 di-isopropylamide (LDA) was prepared from equimolar amounts of butyl-lithium in hexane and di-isopropylamine in THF under nitrogen at 0 °C, lithium hexamethyldisilazide being similarly obtained from hexamethyldisilazane.

(2E,4E)-14-*Iodo*-3-*methyltetradeca*-2,4-*diene* (**16**).—Pyridine (75 μl) was added to a suspension of triphenyl phosphite-methiodide (0.48 g) in anhydrous CH_2Cl_2 (0.3 ml) at 0 °C followed by (10*E*,12*E*)-12-methyltetradeca-10,12-dien-1-ol[9,18] (200 mg) in CH_2Cl_2 (0.2 ml), and the mixture stirred at 0 °C for 3 h. CH_2Cl_2 and water were added, and the organic phase washed with dilute aqueous HCl, water, dilute aqueous NaOH, and brine. Concentration under reduced pressure, and flash chromatography using ether–light petroleum as eluant gave the *title compound* (**16**) (143 mg, 48%) as an oil (Found: M^+, 334.1162. $C_{15}H_{27}I$ requires M^+, 334.1159); $\nu_{max.}$(film) 1 630, 1 180, 1 025, 965, 915, 790, and 735 cm^{-1}; δ_H 1.34 (12 H, complex m, 6 × CH_2), 1.72 (6 H, m, 2 × Me), 1.83 (2 H, m, CH_2), 2.10 (2 H, m, 6-CH_2), 3.20 (2 H, t, *J* 7.6 Hz, 14-CH_2), 5.45 (1 H, m, 2-H), 5.55 (1 H, dt, *J* 15, 7.6 Hz, 5-H), and 6.07 (1 H, d, *J* 15 Hz, 4-H); *m/z* (e.i.) 334 (M^+, 19%).

(5S,10′E,12′E)-1-*Acetyl*-5-*benzyl*-3-(12′-*methyltetradeca*-10′,12′-*dienyl*)*pyrrol*-2(5H)-*one* (**13**).—Butyl-lithium (1.15 ml of a 1.65M solution in hexane, 1.9 mmol) was added during 5 min to a solution of the bis(phenylseleno)pyrrolidinone (**10**)[16] (456 mg, 0.94 mmol) in THF (5 ml) under an atmosphere of N_2 at 0 °C, and the solution stirred for 1 h. 14-Iodo-3-methyltetradeca-2,4-diene (**16**) (360 mg, 1.08 mmol) in THF (1.5 ml) was added, and the solution stirred at 0 °C for 3 h before being quenched by the addition of water. Ether extraction and flash chromatography using ether–light petroleum (3:1) as eluant gave butyl phenyl selenide (200 mg, 100%), recovered iodide (**16**) (74 mg, 20%), and (5S,10′*E*,12′E)-5-*benzyl*-3-(12′-*methyltetradeca*-10′,12′-*dienyl*)*phenylselenopyrrolidin*-2-*one* (**11**) (334 mg, 66%), as a colourless oil, an inseparable mixture of epimers at C-3, ratio *ca.* 4:1; $\nu_{max.}$(CCl_4) 3 435, 3 065, 3 035, 1 714, 1 698, and 690 cm^{-1}; δ_H 1.20—1.86 (16 H, m, 8 × CH_2), 1.67—1.75 (6 H, m, 12′- and 14′-Me), 2.05—2.17 (3.2 H, m, 9′-CH_2 and 4-H), 2.23 (0.8 H, dd, *J* 8, 13 Hz, HC*H*Ph), 2.47 (0.8 H, dd, *J* 5, 13 Hz, *H*CHPh), 2.42—2.55 (0.8 H, m, 4-H), 2.61 (0.2 H, dd, *J* 8, 13 Hz, *H*CHPh), 2.79 (0.2 H, dd, *J* 5, 13 Hz, HC*H*Ph), 3.52 (0.2 H, m, 5-H), 3.67 (0.8 H, m, 5-H), 5.45 (1 H, q, *J* 7 Hz, 13′-H), 5.55 (1 H, dt, *J* 15, 7.5 Hz, 10′-H), 5.81 (1 H, br s, NH), 6.06 (1 H, d, *J* 16 Hz, 11′-H), and 6.99—7.79 (10 H, m, ArH); *m/z* (c.i.) 538 (M^+ + 1, 15%), 444 (M^+ − 93, 70%), and 288 (100%).

Butyl-lithium (0.31 ml of a 1.65M solution in hexane, 0.53 mmol) was added to pyrrolidinone (**11**) (284 mg, 0.53 mmol) in THF (3.5 ml) under an atmosphere of N_2 at 0 °C followed, after 10 min, by acetyl chloride (210 μl, 2.95 mmol) in THF (5 ml). The mixture was stirred for 45 min, concentrated under reduced pressure, and the residue diluted with ether. Filtration through Celite and flash chromatography gave (5S,10′E,12′E)-1-*acetyl*-5-*benzyl*-3-(12-*methyltetradeca*-10′,12′-*dienyl*)-3-*phenylselenopyrrolidin*-2-*one* (**12**) (261 mg, 85%), a colourless oil, a mixture of epimers at C-3, ratio *ca.* 4:1; $\nu_{max.}$(CCl_4) 3 065, 3 035, 1 732, 1 704, 1 375, 1 350, 1 273, and 692 cm^{-1}; δ_H 1.3—1.59 (16 H, m, 8 × CH_2), 1.65—1.81 (6 H, m, 12′- and 14′-Me), 1.95—2.39 (4 H, m, 2 × CH_2), 2.59 (3 H, s, Ac), 2.92 (1 H, t, *J* 12.5 Hz, HC*H*Ph), 3.39—3.63 (0.2 H, m, HC*H*Ph), 3.56 (0.8 H, dd, *J* 3, 13 Hz, *H*CHPh), 4.10 (0.2 H, m, 5-H), 4.47 (0.8 H, m, 5-H), 5.46 (1 H, br q, *J* 7 Hz, 13′-H), 5.56 (1 H, dt, *J* 15, 7 Hz, 10′-H), 6.07 (1 H, d, *J* 16 Hz, 11′-H), and 7.08—7.73 (10 H, m, ArH); *m/z* (c.i.) 580 (M^+ + 1, 32%) and 91 (100%).

50% Aqueous hydrogen peroxide (0.7 ml, 12.11 mmol) in water (9.3 ml) was added dropwise to a solution of the selenide (**12**) (200 mg, 0.35 mmol) in dichloromethane (2 ml) containing pyridine (65 μl, 0.8 mmol) at 0 °C. After being stirred vigorously for 1 h, the mixture was allowed to warm to 25 °C, and was poured into 10% aqueous $NaHCO_3$–dichloromethane (1:3). Stirring was continued for 15 min, and the organic layer separated, washed with brine, and dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography using ether–light petroleum as eluant gave the *title compound* (**13**) (84 mg, 54%), as an oil (Found: M^+, 421.2979. $C_{28}H_{39}NO_2$ requires *M*, 421.2981); $\nu_{max.}$(CCl_4) 3 040, 1 729, 1 699, 1 379, 1 358, 1 292, and 702 cm^{-1}; δ_H 1.18—1.47 (14 H, m, 7 × CH_2), 1.67—1.81 (6 H, m, 12′- and 14′-Me), 2.08 (2 H, m, 9′-CH_2), 2.17 (2 H, m, 1′-CH_2), 2.58 (3 H, s, Ac), 2.84 (1 H, dd, *J* 8.5, 13.5 Hz, HC*H*Ph), 3.49 (1 H, dd, *J* 3, 13 Hz, *H*CHPh), 4.82 (1 H, m, 5-H), 5.45 (1 H, br q, *J* 7 Hz, 13′-H), 5.55 (1 H, dt, *J* 15, 7 Hz, 10′-H), 6.05 (1 H, d, *J* 16 Hz, 11′-H), 6.67 (1 H, d, *J* 2 Hz, 4-H), and 7.07—7.35 (5 H, m, ArH); *m/z* (e.i.) 421 (M^+, 5% and 91 (100%).

Similar procedures were used to prepare (5S,10′E,12′E)-1-*benzoyl*-5-*benzyl*-3-(12′-*methyltetradeca*-10′,12′-*dienyl*)*pyrrol*-2(5H)-*one* (**14**) (103 mg, 59%), an oil, $[\alpha]_D^{20}$ +272.6° (*c* 0.5 in $CHCl_3$); $\nu_{max.}$(CCl_4) 3 040, 1 740, 1 677, 1 349, 1 309, and 1 218 cm^{-1}; δ_H 1.25—1.49 (14 H, m, 7 × CH_2), 1.65—1.79 (6 H, m, 12′- and 14′-Me), 2.05—2.16 (4 H, m, 2 × CH_2), 3.08 (1 H, dd, *J* 8, 13.3 Hz, HC*H*Ph), 3.38 (1 H, dd, *J*, 3.3, 13.3 Hz, *H*CHPh), 5.16 (1 H, m, 5-H), 5.45 (1 H, br q, *J* 6.6 Hz, 13′-H), 5.55 (1 H, dt, *J* 15.5, 7.1 Hz, 10′-H), 6.01 (1 H, d, *J* 15.5 Hz, 11′-H), 6.87 (1 H, br s, 4-H), and 7.14—7.56 (10 H, m, ArH); *m/z* (c.i.) 484 (M^+ + 1, 63%) and 390 (100%): and (5S,12′E,14′E)-1-*benzoyl*-5-*benzyl*-3-(14-*methylhexadeca*-12′,14′-*dienyl*)*pyrrol*-2(5H)-*one* (**15**) (38 mg, 50%), an oil, $[\alpha]_D^{20}$ +238.5° (*c* 0.34 in CCl_4); $\nu_{max.}$(CCl_4) 3 070, 3 040, 1 740, 1 678, 1 350, 1 309, 1 222, and 1 170 cm^{-1}; δ_H 1.20—1.50 (18 H, m, 9 × CH_2), 1.66—1.80 (6 H, m, 14′- and 16′-Me), 2.04—2.20 (4 H, m, 2 × CH_2), 3.07 (1 H, dd, *J* 8, 13.3 Hz, HC*H*Ph), 3.38 (1 H, dd, *J* 3.4, 13.4 Hz, *H*CHPh), 5.15 (1 H, m, 5-H), 5.44 (1 H, br q, *J* 7.5 Hz, 15′-H), 5.54 (1 H, dt, *J* 15, 7 Hz, 12′-

H), 6.05 (1 H, d, *J* 15.5 Hz, 13′-H), 6.86 (1 H, d, *J* 1.9 Hz, 4-H), and 7.12—7.58 (10 H, m, ArH); *m/z* (c.i.) 512 ($M^+ + 1$, 72%), 418 ($M^+ - 93$, 70%), and 105 (100%).

(12E,14E)-*1-(Imidazol-1-yl)hexadeca-12,14-dien-1-one* (**17**).—A solution of (12*E*,14*E*)-hexadeca-12,14-dienoic acid[9] (206 mg, 0.82 mmol) in THF (1.5 ml) was added to a suspension of 1,1′-carbonyldi-imidazole (136 mg, 0.84 mmol) in THF (1.5 ml) under N_2. The mixture was stirred for 1 h before being concentrated under reduced pressure, and quenched by the addition of ice-cold water and ether. Separation and concentration of the ether extract gave the *title compound* (**17**) (199 mg, 81%), an amorphous solid, m.p. 77—78 °C (from ether–light petroleum) (Found: C, 75.3; H, 10.2; N, 9.0. $C_{19}H_{20}N_2O$ requires C, 75.45; H, 10.0; N, 9.3%); $\nu_{max.}(CCl_4)$ 3 025, 1 747, 1 473, 1 388, 1 228, 985, and 650 cm^{-1}; δ_H 1.24—1.7 (14 H, m, 7 × CH_2), 1.73 (3 H, d, *J* 6.7 Hz, CH*Me*), 1.81 (2 H, m, 3-CH_2), 2.05 (2 H, dt, *J* 6.8, 7 Hz, 11-CH_2), 2.86 (2 H, t, *J* 7.4 Hz, 2-CH_2), 5.51—5.63 and 5.95—6.08 (each 2 H, m, vinylic H), 7.11 (1 H, d, *J* 1 Hz, 4′-H), 7.50 (1 H, d, *J* 1 Hz, 5′-H), and 8.17 (1 H, s, 2′-H); *m/z* (e.i.) 302 (M^+, 2%) and 69 (100%).

(5R,12′E,14′E)-5-*Benzyl*-1-(*dimethyl-t-butylsilyl*)-3-(1′-*oxohexadeca*-12′,14′-*dienyl*)*pyrrolidin*-2-*one* (**18**).—A solution of 5-benzyl-1-(dimethyl-t-butylsilyl)pyrrolidin-2-one[16] (**25**) (131 mg, 0.452 mmol) in THF (1.5 ml) was added to a solution of LDA (0.93 mmol) in THF (1.5 ml) at −75 °C under N_2. After 50 min, (12*E*,14*E*)-1-(imidazol-1-yl)hexadeca-12,14-dien-1-one (**17**) (140 mg, 0.463 mmol) in THF (1.5 ml) was added, and the reaction mixture allowed to warm gradually to 0 °C (1.5 h) before being poured into acidic NH_4Cl solution. Ether extraction and flash chromatography using ether–light petroleum as eluant (1:4), gave the *title compound* (**18**) (132 mg 56%), as an oil, a 1:1 mixture of epimers at C-3 (Found: M^+, 523.3857. $C_{33}H_{53}NO_2Si$ requires *M*, 523.3845); $\nu_{max.}(CCl_4)$ 3 020, 1 720, 1 682, 1 373, 1 230, and 1 087 cm^{-1}; δ_H 0.33, 0.39, 0.42, and 0.45 (each 1.5 H, s, SiMe), 0.97 and 1.00 (each 4.5 H, s, $SiCMe_3$), 1.22–1.62 (16 H, m, 8 × CH_2), 1.73 (3 H, d, *J* 6.3 Hz, CH*Me*), 1.82–1.98 (1 H, m, HC*H*), 2.04 (2 H, br q, *J* 7 Hz, CH_2), 2.42—2.68 (3 H, m, 3 × *H*CH), 2.88—3.08 (2 H, m, 2 × HC*H*), 3.49 (0.5 H, dd, *J* 8, 11.1 Hz, 3-H), 3.55 (0.5 H, dd, *J* 3.5, 11 Hz, 3-H), 3.75 and 3.84 (each 0.5 H, m, 5-H), 5.51—5.63 and 5.95—6.08 (each 2 H, m, vinylic H), and 7.26—7.40 (5 H, m, ArH); *m/z* (e.i.) 523 (M^+, 22%) and 466 (100%); together with (12*E*, 14*E*)-hexadeca-12,14-dienoic acid (33 mg).

(5S,12′E,14′E)-1-*Benzoyl*-5-*benzyl*-3-(1′-*oxohexadeca*-12′,-14′-*dienyl*)-3-*phenylselenopyrrolidin*-2-*one* (**20**).—The acylated pyrrolidinone (**18**) (656 mg, 1.25 mmol) in THF (4 ml) was added to LDA (1.5 mmol) in THF (3 ml) under N_2 at −75 °C. After 1 h, benzeneselenenyl chloride (346 mg, 1.81 mmol) in THF was added and the resulting mixture allowed to warm to 0 °C (1 h) before being poured into saturated aqueous NH_4Cl. Ether extraction and flash chromatography using ether–light petroleum (1:20) as eluant gave (12′E,14′E)-5-*benzyl*-1-(*dimethyl-t-butylsily*)-3-(1-*oxohexadeca*-12,14-*dienyl*)-3-*phenylselenopyrrolidin*-2-*one* (**19**) (600 mg, 71%), as an oil, a mixture of epimers at C-3, ratio *ca.* 3:1; $\nu_{max.}(CH_2Cl_2)$ 1 673, 1 378, 1 352, 1 238, 1 098, 993, and 844 cm^{-1}; δ_H 0.42 and 0.45 (each 3 H, s, SiMe), 1.05 (6.75 H, s, $SiCMe_3$ of major isomer), 1.06 (2.25 H, s, $SiCMe_3$ of minor isomer), 1.25—1.70 (16 H, m, 8 × CH_2), 1.76 (3 H, d, *J* 7 Hz, CH*Me*), 2.0—2.4 (4 H, m), 2.6—3.0 (3 H, m), 3.08—3.40 (1 H, m, HC*H*), 3.65 (0.75 H, m, 5-H), 3.77 (0.25 H, m, 5-H), 5.6 and 6.02 (each 2 H, m, vinylic H), and 6.96—7.54 (10 H, m, ArH); *m/z* (c.i.) 680 ($M^+ + 1$, 6%) and 524 (100%).

Benzoyl chloride (1.2 ml of an 0.91M solution in benzene) was added to a solution of the 1-silylpyrrolidinone (**19**) (623 mg, 0.918 mmol) in benzene (3.8 ml) under an atmosphere of N_2, and the resulting solution was heated at 80 °C for 12 h. Concentration under reduced pressure, and flash chromatography using ether–light petroleum (1:7) as eluant gave the *title compound* (**20**) (403 mg, 60%), as an oil, a mixture of epimers at C-3, ratio 3:1; $\nu_{max.}(CH_2Cl_2)$ 1 730, 1 689, 1 603, 1 348, 1 270, 1 222, 994, and 655 cm^{-1}; δ_H 1.20—1.68 (16 H, m, 8 × CH_2), 1.74 (3 H, d, *J* 7 Hz, CH*Me*), 1.96—2.13 (3 H, m, CH_2 + *H*CH), 2.50 (0.75 H, dd, *J* 7, 15 Hz, HC*H*), 2.60—3.30 (4.25 H, m), 4.55 (1 H, m, 5-H), 5.56 and 6.05 (each 2 H, m, vinylic H), and 7.05—7.67 (15 H, m, ArH); *m/z* (c.i.) 670 ($M^+ + 1$, 1%) and 105 (100%).

A second product isolated from this reaction was identified as the 1-deprotected pyrrolidinone, (5S,12′E,14′E)-5-*benzyl*-3-(1-*oxohexadeca*-12′,14′-*dienyl*)-3-*phenylselenopyrrolidin*-2-*one* (**21**) (93 mg, 18%), an oil, a mixture of eipimers at C-3; $\nu_{max.}(CCl_4)$ 3 430, 3 200, 1 714, 1 699, and 909 cm^{-1}; δ_H 1.23—1.72 (16 H, m, CH_2), 1.76 (3 H, d, *J* 7 Hz, CH*Me*), 1.94—2.23 (3 H, m, CH_2 + HC*H*), 2.47 (1 H, dd, *J* 15, 7.5 Hz, 4-H), 2.62 (1 H, dd, *J* 9.5, 13 Hz, HC*H*Ph), 2.74—3.07 (2 H, m, 2 × HC*H*), 3.13—3.32 (1 H, m, HC*H*), 3.67—3.82 (1 H, m, 5-H), 5.55 and 6.05 (each 2 H, m, vinylic H), and 7.07—7.59 (10 H, m, ArH); *m/z* (c.i.) 566 ($M^+ + 1$, 9%) and 410 (100%).

Preparation and Diels–Alder Cyclization of (5S,12′E,14′E)-1-*Benzoyl*-5-*benzyl*-3-(1′-*oxohexadeca*-12′,14′-*dienyl*)*pyrrol*-2(5H)-*one* (**22**).—A solution of 3% hydrogen peroxide in water (1 ml, 13 equiv.) was added dropwise to a vigorously stirred solution of the phenylselenopyrrolidinone (**21**) (51 mg, 0.074 mmol) in dichloromethane (1 ml). After 0.5 h, the mixture was poured into ice-cold 10% aqueous $NaHCO_3$, and extracted quickly into cold dichloromethane. After drying ($MgSO_4$), concentration under reduced pressure gave the *title compound* (**22**) (36 mg, 92%), an unstable yellow oil which polymerized with time; $\nu_{max.}(CH_2Cl_2)$ 3 020, 1 740, 1 679, 1 621, 1 300, 994, 910, 843, and 664 cm^{-1}; δ_H 1.20—1.60 (16 H, m, 8 × CH_2), 1.76 (3 H, d, *J* 7 Hz, CH*Me*), 2.05 (2 H, m, 11′-CH_2), 2.79 (2 H, t, *J* 7 Hz, 2′-CH_2), 3.17 (1 H, dd, *J* 8, 12.5 Hz, HC*H*Ph), 3.47 (1 H, dd, *J* 3, 13 Hz, HC*H*Ph), 5.34 (1 H, m, 5-H), 5.50—5.65 and 5.96—6.12 (each 2 H, m, vinylic H), 7.12—7.65 (10 H, m, ArH), and 7.97 (1 H, d, *J* 2 Hz, 4-H). This material was used immediately without purification.

Thermal Diels–Alder cyclization of dienyl pyrrolone (**22**). A solution of the dienyl pyrrolone (**22**) in degassed toluene (*ca.* 2mM) was sealed under argon in a flame-dried Carius tube and heated at 120 °C for 15—22 h. Concentration under reduced pressure and flash chromatography using ether–light petroleum as eluant (1:5) gave adducts (**23**) and (**25**) as an oil (5—10%, *ca.* 85:15 mixture).

High pressure Diels–Alder cyclization of dienyl pyrrolone (**22**). A solution of the dienyl pyrrolone (**22**) in dichloromethane (16 ml, *ca.* 2—6mM) was placed in a Teflon vessel, which was then immersed in hydraulic fluid, maintained at 40 °C, and subjected to 11—13 kbar pressure. After 18—24 h the pressure was released, and the solvent removed under reduced pressure. Flash chromatography as above, followed by filtration (MeOH elution) through a Sephadex LH-20 column (30 × 2.5 cm) to remove traces of hydraulic fluid, gave a mixture of 2-*benzoyl*-10-*phenyl*-12-*normethyl*[13]*cytochalas*-6(7)-*ene*-1,23-*dione* (**23**) and its (5*S*,8*R*)-diastereoisomer (**25**), ratio 85:15 (*ca.* 10 mg, 16—35%); $\nu_{max.}(CH_2Cl_2)$ 1 735, 1 700, 1 678, 1 600, 1 370, 1 270, 1 218, and 655 cm^{-1}; δ_H(major isomer) 1.00—1.61 (18 H, m, 9 × CH_2), 1.17 (3 H, d, *J* 7.3 Hz, CH*Me*), 1.83 (1 H, m, 22-H), 2.24 (1 H, m, 8-H), 2.51 (1 H, m, 5-H), 2.84 (2 H, m, 4-H and HC*H*Ph), 3.08 (1 H, m, 22-H), 3.19 (1 H, dd, *J* 6.4, 13.5 Hz, *H*CHPh), 4.35 (1 H, m, 3-H), 5.71 (1 H, dt, *J* 8.8, 3.2 Hz, vinylic H), 5.80 (1 H, dt, *J* 8.9, 2.8 Hz, vinylic H), and 7.08—7.62 (10 H, m, ArH); *m/z* (c.i.) 512 ($M^+ + 1$, 100%).

50% Aqueous KOH (0.4 ml) was added slowly to a solution of Diels–Alder adducts (**23**) and (**25**) (22 mg, 0.043 mmol) in

methanol–benzene (2:1) (1.2 ml) with vigorous stirring. After 1 h, the reaction was poured into 3M aqueous HCl (5 ml), and the product extracted with ether to give an oil after concentration under reduced pressure. Short column chromatography using ether–light petroleum, gradient elution, gave firstly 10-*phenyl*-12-*normethyl*[13]*cytochalas*-6(7)-*ene*-1,23-*dione* (**24**) (13 mg, 74%) as an oil, $[\alpha]_D^{20}$ −74.0° (*c* 0.53 in $CHCl_3$); $\nu_{max.}(CH_2Cl_2)$ 3 410, 3 200, 1 695, 1 302, 909, and 665 cm^{-1}; δ_H 1.10—1.83 (18 H, m, 9 × CH_2), 1.22 (3 H, d, *J* 6.9 Hz CH*Me*), 1.92 (1 H, t, *J* 12 Hz, 22-H), 2.28 (1 H, br d, *J* 10.8 Hz, 8-H), 2.46 (1 H, dd, *J* 7.9, 13.6 Hz, *H*CHPh), 2.54 (1 H, m, 5-H), 2.58 (1 H, t, *J* 4.2 Hz, 4-H), 2.87 (1 H, dd, *J* 3.8, 13.6 Hz, HC*H*Ph), 3.37 (1 H, m, 3-H), 3.45 (1 H, ddd, *J* 2.3, 11.7, 19.5 Hz, 22-H), 5.71 (2 H, m, vinylic H), 5.85 (1 H, br s, NH), and 7.09—7.32 (5 H, m, ArH); *m/z* (c.i.) 408 (M^+ + 1, 100%), 379 (M^+ − 28, 60%), and 316 (M^+ − 91, 90%); followed by (5S,8R)-10-*phenyl*-12-*normethyl*[13]*cytochalas*-6(7)-*ene*-1,23-*dione* (**26**) (1.6 mg, 9%), an oil (Found: M^+, 407.2823. $C_{27}H_{37}NO_2$ requires *M*, 407.2824); $\nu_{max.}(CH_2Cl_2)$ 1 714 cm^{-1}; δ_H 0.99 (3 H, d, *J* 7.1 Hz, CH*Me*), 1.21—1.77 (17 H, m, 8 × CH_2 and 21-H), 1.97 (2 H, m, 21- and 5-H), 2.35 (1 H, m, 22-H), 2.52 (2 H, m, *H*CHPh and 4-H), 2.65 (1 H, m, 8-H), 2.67 (1 H, dd, *J* 6.6, 13.3 Hz, HC*H*Ph), 3.17 (1 H, ddd, *J* 3.6, 10.2, 19.5 Hz, 22-H), 3.36 (1 H, m, 3-H), 5.69 (2 H, m, 6-H and NH), 5.85 (1 H, ddd, *J* 2.1, 4.5, 9.9 Hz, 7-H), and 7.15—7.37 (5 H, m, ArH); *m/z* (e.i.) 407 (M^+, 5%) and 57 (100%).

(8E,10E,12E)-*Methyl* 12-*Methyltetradeca*-8,10,12-*trienoate* (**30**).—Butyl-lithium (20.66 ml of a 1.5M solution in hexane, 31 mmol) was added dropwise to a stirred solution of phosphonate (**29**)[10] (7.4 g, 31 mmol) in THF (25 ml) at −60 °C under an atmosphere of N_2. The mixture was stirred at −30 °C for 2 h, and then added to a stirred solution of methyl 7-formylheptanoate (**28**) (5.0 g, 29 mmol) in THF (30 ml) at −70 °C also under N_2. After 1.5 h the mixture was allowed to warm to room temperature and hexamethylphosphoric triamide (8 ml, 46.5 mmol) was added. The stirring was continued for 3 h before the mixture was diluted with ether (150 ml), and washed with brine (2 × 70 ml) and water (50 ml). After drying (Na_2SO_4) the ethereal phase was concentrated under reduced pressure, and flash chromatographed on base washed silica using ether–light petroleum (1:10) as eluant to give the *title compound* (**30**) (4.5 g, 60%) as a colourless oil (Found: M^+, 250.1933. $C_{16}H_{26}O_2$ requires *M*, 250.1933); $\nu_{max.}(CHCl_3)$ 3 020, 1 730, 990, and 910 cm^{-1}; δ_H 1.25—1.45 (6 H, m, 3 × CH_2), 1.6 (2 H, m, 3-CH_2), 1.68—1.8 (6 H, m, 2 × Me), 2.09 (2 H, m, 7-CH_2), 2.32 (2 H, t, *J* 7 Hz, 2-CH_2), 3.68 (3 H, s, OMe), 5.55 (1 H, br q, *J* 7 Hz, 13-H), 5.67 (1 H, m, 8-H), and 6.0—6.2 (3 H, m, vinylic H); *m/z* (c.i.) 251 (M^+ + 1, 100%).

8E,10E,12E)-1-*Imidazol*-1-*yl*-12-*methyltetradeca*-8,10,12-*trien*-1-*one* (**32**).—A solution of the methyl ester (**30**) (440 mg, 1.76 mmol) and NaOH (0.28 g, 7 mmol) in aqueous ethanol (EtOH–water = 7:1, 8 ml) was stirred at room temperature for 3 h. Tartaric acid (1.32 g, 8.8 mmol) was then added, and the solution diluted with water, and extracted with ether. After drying (Na_2SO_4), concentration under reduced pressure gave an off-white solid identified as (8E,10E,12E)-12-*methyltetradeca*-8,10,12-*trienoic acid* (**31**) (410 mg, 99%) (Found: M^+, 236.1777. $C_{15}H_{24}O_2$ requires *M*, 236.1776); $\nu_{max.}(CCl_4)$ 3 400—2 500, 1 712, and 990 cm^{-1}; δ_H 1.25—1.45 (6 H, m, 3 × CH_2), 1.55—1.68 (2 H, m, 3-CH_2), 1.74 (6 H, m, 2 × Me), 2.09 (2 H, m, 7-CH_2), 2.35 (2 H, t, *J* 7 Hz, 2-CH_2), 5.55 (1 H, br q, *J* 7 Hz, 13-H), 5.67 (1 H, dt, *J* 14, 7 Hz, 8-H), and 6.0—6.2 (3 H, m, vinylic H).

Without purification the acid (**31**) (380 mg, 1.65 mmol) in THF (5 ml) was added to a stirred suspension of 1,1′-carbonyldiimidazole (270 mg, 1.7 mmol) in THF (5 ml) under an atmosphere of N_2 at room temperature, and the mixture stirred for 20 h. Dilution with ether, washing with ice-cold water, and drying (Na_2SO_4) gave, after concentration under reduced pressure, an off-white solid identified as the *title compound* (**32**) (390 mg, 85%); $\nu_{max.}(CCl_4)$ 1 740, 1 060, and 990 cm^{-1}; δ_H 1.2—1.5 (6 H, m, 2 × CH_2), 1.6—1.85 (8 H, m, 2 × Me and 3-CH_2), 2.05 (2 H, m, 7-CH_2), 2.79 (2 H, t, *J* 7 Hz, 2-CH_2), 5.55 (1 H, br q, *J* 7 Hz, 13-H), 5.7 (1 H, dt, *J* 14, 7 Hz, 8-H), 6.0—6.2 (3 H, m, vinylic H), 7.25 (1 H, narrow m, 4′-H), 7.41 (1 H, narrow m, 5′-H), and 8.1 (1 H, s, 2′-H); *m/z* (e.i.) 286 (M^+, 7%) and 236 (M^+ − 50, 12%).

(8′E,10′E,12′E)-1-*Benzoyl*-5-*benzyl*-3-(12′-*methyl*-1′-*oxotetradeca*-8′,10′,12′-*trienyl*)-3-*phenylselenopyrrolidin*-2-*one* (**35**).—A solution of the 1-benzoyl-5-benzylpyrrolidinone (**33**)[16] (1.56 g, 5.6 mmol) in THF (15 ml) was added to a solution of lithium hexamethyldisilazide (5.6 mmol) in THF–hexane (30 ml) at −78 °C under N_2. After 35 min this solution was transferred using a cannula to a solution of the imidazolyl trienone (**32**) (800 mg, 2.8 mmol) in THF under N_2, and the mixture stirred at −78 °C for 8 h. Saturated aqueous NH_4Cl was added, and the mixture allowed to warm to room temperature. Ether extraction and flash chromatography using base washed silica gave (8′E,10′E,12′E)-1-*benzoyl*-5-*benzyl*-3-(12′-*methyl*-1′-*oxotetradeca*-8′,10′,12′-*trienyl*)*pyrrolidin*-2-*one* (**34**) (0.98 g, 71%) as an oil, a mixture of epimers at C-3, ratio *ca.* 3:2; $\nu_{max.}$(film) 3 020, 1 735, 1 705, 1 680 1 280, 1 220, 990, and 700 cm^{-1}; δ_H 1.15—1.65 (8 H, m, 4 × CH_2), 1.75 (6 H, m, 2 × Me), 1.9—2.2 (3 H, complex m, 7′-CH_2 and 4-H*H*), 2.25—3.0 (4.6 H, complex m, 2′-CH_2, 4-H*H*, and *H*CHPh), 3.25 (0.4 H, dd, *J* 4, 14 Hz, HC*H*Ph), 3.42 (0.6 H, m, 3-H), 3.7 (0.4 H, dd, *J* 6, 7 Hz, 3-H), 4.58 (0.4 H, m, 5-H), 4.75 (0.6 H, m, 5-H), 5.45—5.75 (2 H, m, vinylic H), 6.0—6.2 (3 H, m, vinylic H), and 7.15—7.7 (10 H, m, ArH); *m/z* (c.i.) 498 (M^+ + 1, 100%).

The 3-(1-oxotetradecatrienyl)pyrrolidinone (**34**) (0.98 g, 1.97 mmol) in THF (5 ml) was cooled to −78 °C and added to lithium hexamethyldisilazide (1.97 mmol) in THF–hexane (11 ml) at −70 °C under N_2. After 1 h a solution of benzeneselenenyl chloride (4.52 g, 2.36 mmol) in THF was added, and the mixture stirred at −70 °C for 2 h. Aqueous NH_4Cl (2 ml) was added, and the mixture allowed to warm to room temperature. Ether extraction and flash chromatography on base washed silica using ether–light petroleum (1:5) as eluant gave (8′E,10′E,12′E)-1-*benzoyl*-5-*benzyl*-3-(12′-*methyl*-1′-*oxotetradeca*-8′,10′,12′-*trienyl*)-3-*phenylselenopyrrolidin*-2-*one* (**35**) (1.06 g, 82%) as an oil; $\nu_{max.}$(film) 3 020, 1 720, 1 680, 1 280, 1 220, 980, 740, and 690 cm^{-1}; δ_H 1.2—1.7 (8 H, complex m, 4 × CH_2), 1.75 (6 H, m, 2 × Me), 1.95—2.15 (3 H, 7′-CH_2 and 4-H*H*), 2.45—3.4 (5 H, complex m, 2′-CH_2, CH_2Ph, and 4-H*H*), 4.58 (1 H, m, 5-H), 5.55 (1 H, m, 13′-H), 5.68 (1 H, m, 8′-H), 6.0—6.25 (3 H, m, vinylic H), and 7.0—7.7 (15 H, m, ArH); *m/z* (c.i.) 652 (M^+ − 1, 2%), 600 (M^+ − 53, 8%), and 497 (M^+ − 156, 100%).

Generation and Diels–Alder Cyclization of (5S,8′E,10′E,12′E)-1-*Benzoyl*-5-*benzyl*-3-(12′-*methyl*-1′-*oxotetradeca*-8′,10′,12′-*trienyl*)*pyrrol*-2(5H)-*one* (**36**).—A solution of 30% H_2O_2 (0.5 ml) in H_2O (1.5 ml) was added to the 3-phenylselenopyrrolidinone (**35**) (500 mg, 0.76 mmol) in $CDCl_3$ (20 ml) at −50 °C followed immediately by a solution of *m*-chloroperoxybenzoic acid (157 mg, 0.91 mmol) in $CDCl_3$. The mixture was stirred at −50 °C for 15 min, and warmed to 0 °C for 5 min before being washed with ice-cold aqueous $NaHCO_3$ (2 × 15 ml), brine (10 ml), and water (10 ml). After drying (Na_2SO_4) a sample of the solution was examined by ^1H n.m.r. which showed the presence of the title compound (**36**); δ_H 5.31 (1 H, m, 5-H) and 7.97 (1 H, narrow m, 4-H). The remainder of the solution was diluted with argon purged toluene (500 ml) and heated under reflux under a N_2 atmosphere for 12 h. The mixture was then cooled, concentrated under reduced pressure, and the

Table 1. Fractional atomic co-ordinates (× 10) with e.s.d.s in the least significant figures in parentheses

Atom	*x/a*	*y/b*	*z/c*
C(1)	2 835(2)	1 584(2)	4 278(2)
N(2)	2 437(2)	481(2)	4 418(2)
C(3)	1 979(3)	−210(2)	3 210(2)
C(4)	1 993(2)	620(2)	2 157(2)
C(5)	2 954(3)	250(2)	1 631(2)
C(6)	4 360(2)	563(2)	2 596(2)
C(7)	4 558(2)	1 643(2)	3 023(2)
C(8)	3 401(2)	2 436(2)	2 571(2)
C(9)	2 317(2)	1 812(2)	2 807(2)
C(10)	616(3)	−763(3)	2 800(3)
C(11)	2 748(3)	−986(3)	1 147(3)
C(12)	5 449(3)	−307(3)	3 014(3)
C(13)	3 725(2)	3 619(2)	3 164(2)
C(14)	3 329(3)	4 576(2)	2 476(3)
C(15)	3 602(4)	5 755(2)	3 079(4)
C(16)	2 388(4)	6 452(3)	2 825(4)
C(17)	1 425(4)	5 856(3)	3 192(4)
C(18)	335(3)	5 199(3)	2 042(3)
C(19)	−241(3)	4 218(3)	2 498(3)
C(20)	729(3)	3 242(2)	3 134(3)
C(21)	1 101(2)	2 612(2)	2 216(2)
C(22)	2 759(3)	−69(2)	5 620(3)
C(23)	2 980(3)	627(3)	6 799(3)
C(24)	2 270(3)	1 602(3)	6 713(3)
C(25)	2 513(5)	2 212(4)	7 853(4)
C(26)	3 463(5)	1 826(5)	9 068(4)
C(27)	4 145(4)	852(5)	9 158(3)
C(28)	3 907(3)	221(4)	8 026(3)
C(29)	−468(3)	67(3)	2 555(3)
C(30)	−1 287(3)	490(4)	1 287(3)
C(31)	−2 254(3)	1 284(5)	1 069(4)
C(32)	−2 444(4)	1 687(4)	2 090(5)
C(33)	−1 660(4)	1 278(5)	3 349(4)
C(34)	−696(3)	477(3)	3 567(3)
O(1)	3 499(2)	2 210(2)	5 174(2)
O(2)	502(2)	2 700(2)	1 026(2)
O(3)	2 808(3)	−1 108(2)	5 667(2)

Table 2. Bond lengths with e.s.d.s in parentheses

C(1)–N(2)	1.402(3)	C(16)–C(17)	1.527(5)
C(1)–C(9)	1.525(3)	C(17)–C(18)	1.532(5)
C(1)–O(1)	1.198(3)	C(18)–C(19)	1.534(5)
N(2)–C(3)	1.469(3)	C(19)–C(20)	1.521(4)
N(2)–C(22)	1.404(3)	C(20)–C(21)	1.503(4)
C(3)–C(4)	1.555(3)	C(21)–O(2)	1.208(3)
C(3)–C(10)	1.551(4)	C(22)–C(23)	1.494(4)
C(4)–C(5)	1.550(3)	C(22)–O(3)	1.216(4)
C(4)–C(9)	1.542(3)	C(23)–C(24)	1.379(5)
C(5)–C(6)	1.514(3)	C(23)–C(28)	1.389(4)
C(5)–C(11)	1.525(4)	C(24)–C(25)	1.397(5)
C(6)–C(7)	1.334(4)	C(25)–C(26)	1.381(7)
C(6)–C(12)	1.505(4)	C(26)–C(27)	1.359(8)
C(7)–C(8)	1.500(3)	C(27)–C(28)	1.403(6)
C(8)–C(9)	1.575(3)	C(29)–C(30)	1.397(4)
C(8)–C(13)	1.507(3)	C(29)–C(34)	1.391(5)
C(9)–C(21)	1.549(3)	C(30)–C(31)	1.379(6)
C(10)–C(29)	1.499(5)	C(31)–C(32)	1.372(6)
C(13)–C(14)	1.321(4)	C(32)–C(33)	1.378(7)
C(14)–C(15)	1.507(4)	C(33)–C(34)	1.381(6)
C(15)–C(16)	1.522(5)		

Table 3. Bond angles with e.s.d.s in parentheses

C(9)–C(1)–N(2)	108.0(2)	C(15)–C(14)–C(13)	124.3(3)
O(1)–C(1)–N(2)	125.1(2)	C(16)–C(15)–C(14)	115.3(3)
O(1)–C(1)–C(9)	126.9(2)	C(17)–C(16)–C(15)	115.1(3)
C(3)–N(2)–C(1)	112.9(2)	C(18)–C(17)–C(16)	113.4(3)
C(22)–N(2)–C(1)	125.7(2)	C(19)–C(18)–C(17)	113.0(3)
C(22)–N(2)–C(3)	119.0(2)	C(20)–C(19)–C(18)	112.8(2)
C(4)–C(3)–N(2)	105.0(2)	C(21)–C(20)–C(19)	114.8(2)
C(10)–C(3)–N(2)	112.2(2)	C(20)–C(21)–C(9)	119.1(2)
C(10)–C(3)–C(4)	113.8(2)	O(2)–C(21)–C(9)	117.6(2)
C(5)–C(4)–C(3)	113.5(2)	O(2)–C(21)–C(20)	123.4(2)
C(9)–C(4)–C(3)	106.1(2)	C(23)–C(22)N(2)	119.5(2)
C(9)–C(4)–C(5)	112.7(2)	O(3)–C(22)N(2)	119.1(3)
C(6)–C(5)–C(4)	111.2(2)	O(3)–C(22)–C(23)	121.3(3)
C(11)–C(5)–C(4)	112.9(2)	C(24)–C(23)–C(22)	122.9(2)
C(11)–C(5)–C(6)	115.1(2)	C(28)–C(23)–C(22)	116.9(3)
C(7)–C(6)–C(5)	115.8(2)	C(28)–C(23)–C(24)	120.1(3)
C(12)–C(6)–C(5)	120.8(2)	C(25)–C(24)–C(23)	120.3(3)
C(12)–C(6)–C(7)	123.4(2)	C(26)–C(25)–C(24)	119.5(4)
C(8)–C(7)–C(6)	119.2(2)	C(27)–C(26)–C(25)	120.3(4)
C(9)–C(8)–C(7)	107.5(2)	C(28)–C(27)–C(26)	121.1(4)
C(13)–C(8)–C(7)	114.9(2)	C(27)–C(28)–C(23)	118.6(4)
C(13)–C(8)–C(9)	113.2(2)	C(30)–C(29)–C(10)	121.2(3)
C(4)–C(9)–C(1)	104.8(2)	C(34)–C(29)–C(10)	122.3(3)
C(8)–C(9)–C(1)	110.0(2)	C(34)–C(29)–C(30)	116.5(3)
C(8)–C(9)–C(4)	111.5(2)	C(31)–C(30)–C(29)	121.2(3)
C(21)–C(9)–C(1)	113.1(2)	C(32)–C(31)–C(30)	121.0(4)
C(21)–C(9)–C(4)	111.8(2)	C(33)–C(32)–C(31)	119.1(4)
C(21)–C(9)–C(8)	105.7(2)	C(34)–C(33)–C(32)	119.9(4)
C(29)–C(10)–C(3)	114.9(2)	C(33)–C(34)–C(29)	122.2(3)
C(14)–C(13)–C(8)	124.5(2)		

residue flash chromatographed using ether–light petroleum (1:4) as eluant to provide 2-*benzoyl*-10-*phenyl*[11]*cytochalasa*-6(7), 13^1-*diene*-1,21-*dione* (**37**) (150 mg, 40%) as a white crystalline solid, m.p. 139—140 °C (from ether–light petroleum) (Found: C, 80.2; H, 7.65; N, 2.70. $C_{33}H_{37}NO_3$ requires C, 80.0; H, 7.5; N, 2.8%) (Found: M^+, 495.2765. $C_{33}H_{37}NO_3$ requires M, 495.2773); $[\alpha]_D^{20}$ +39.1° (*c* 0.53 in $CHCl_3$) $\nu_{max.}(CHCl_3)$ 3 020, 1 732, 1 702, 1 674, 1 290, 1 117, and 984 cm^{-1}; δ_H 0.85—1.15 (4 H, m, 2 × CH_2), 1.04 (3 H, d, *J* 7 Hz, 11-Me), 1.21 (1 H, m, HC*H*), 1.4 (2 H, m, CH_2), 1.59 (1 H, m, *H*CH), 1.78 (3 H, br s, 12-Me), 1.82—2.0 (2 H, m, CH_2), 2.22 (1 H, m, HC*H*), 2.51 (1 H, m, 5-H), 2.76—2.9 (2 H, m, 10-*H*CH and 8-H), 3.01—3.1 (2 H, m, 10-H*H* and 4-H), 3.45 (1 H, m, 20-H), 4.35 (1 H, m, 3-H), 5.28 (1 H, m, 14-H), 5.47 (1 H, br s, 7-H), 6.1 (1 H, m, 13-H), and 7.05—7.6 (10 H, m, ArH); *m/z* (e.i.) 495 (M^+, 10%), 477 (M^+ − 18, 20%), and 404 (M^+ − 91, 24%).

10-*Phenyl*[11]*cytochalasa*-6(7),13^1-*diene*-1,21-*dione* (**38**).—50% Aqueous KOH (0.8 ml) was added to a solution of the 2-benzoyl [11]cytochalasadienedione (**37**) (400 mg, 0.8 mmol) in methanol–benzene (2:1, 21 ml) with cooling and stirring. After 2 h the reaction mixture was poured into cold 3M aqueous HCl (30 ml). Ether extraction and concentration under reduced pressure gave a residue which was purified by flash chromatography using ether–light petroleum (1:1) as eluant to give the *title compound* (**38**) (250 mg, 79%), as a white crystalline solid, m.p. 98—100 °C (Found: M^+, 391.2510. $C_{26}H_{33}NO_2$ requires M, 391.2511); $[\alpha]_D^{20}$ −68.7° (*c* 0.49 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 420, 3 030, 3 010, and 1 698 cm^{-1}; δ_H 0.7—2.0 (10 H, complex m, 5 × CH_2), 1.04 (3 H, d, *J* 7 Hz, 11-Me), 1.63 (3 H, narrow m, 12-Me), 2.15 (1 H, m, HC*H*), 2.3—2.5 (2 H, m, 10-*H*H and 5-H), 2.6—2.8 (3 H, m, 10-H*H*, 8-, and 4-H), 3.2 (1 H, m, 3-H), 3.67 (1 H, m, 20-H), 5.17 (1 H, m, 14-H), 5.35 (1 H, br s, 7-H), 5.75 (1 H, br s, NH), 6.15 (1 H, m, 13-H), and 7.00—7.35 (5 H, m, ArH); *m/z* (e.i.) 391 (M^+, 30%), 373 (M^+ − 18, 60%), 363 (M^+ − 28, 50%), and 300 (M^+ − 91, 100%).

Crystal Data for 10-*Phenyl*[11]*cytochalasa*-6(7),13[1]-*diene*-1,21-*dione* (**38**).—$3_{33}H_{37}NO_3$, M = 495.6. Monoclinic, a = 11.510(5), b = 11.691(3), c = 11.468(3) Å, β = 118.12(3)°, U = 1 361.0 Å^3, space group $P2$, Z = 2, D_C = 1.209 g cm^{-3}, μ(Mo-K_α) = 0.824 cm^{-1}, crystal size 0.95 × 0.55 × 0.45 mm. Refined cell parameters were obtained from the setting angles of 25 reflections on an Enraf-Nonius CAD4 F diffractometer. 4 665 Reflections were measured in the range $0 < \theta < 27.5°$ with graphite monochromated Mo-K_α radiation (λ = 0.710 69 Å), using the $\omega/2\theta$ scan technique and a 4 mm square aperture. The scan angle was calculated from $\omega = 1.20 + 0.35 \tan\theta$, with the scan speeds varying between 1.3 and 5.5 deg min^{-1} depending upon the intensity of the reflection. The data were corrected for Lorentz and polarization but not for absorption effects, equivalent reflections were merged to give 3 275 unique reflections R_m = 0.033 of which 2 830 were considered to be observed $I > 3\sigma(I)$.

The solution of the structure proved difficult; various attempts using direct methods gave no success. Finally using YZARC[20] a fragment was found which consisted of a six-membered ring fused to a five-membered ring. This was input for two cycles of Karle recycling[21] at which point the E map revealed all the non hydrogen atoms. The direct methods package used was MITHRIL.[22]

Refinement proceeded initially with isotropic followed by anisotropic temperature factors. The polar space group required that the sum of the shifts along the y-axis be restrained to zero. All bar one of the hydrogen atoms were found in different Fourier maps, but it was decided to geometrically place the hydrogen atoms with their temperature factors being set at 1.2 × U_{eq} of the atom to which the hydrogen was bonded and refined them with a riding model. Refinement was by full-matrix least-squares to R = 0.049 R_w = 0.063 [final (shift/e.s.d.) < 0.3]. Weights were calculated from a 3 term Chebychev series with coefficients 2004.1, 2696.3, and 709.6.[23] Computations were carried out on an in house VAX 11/750 computer using the CRYSTALS set of programs.[24]

Table 1 gives the fractional atomic co-ordinates. Tables 2 and 3 give the bond lengths and angles. Isotropic and anisotropic thermal parameters are available on request from the Cambridge Crystallographic Data Centre.*

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* See Instructions for Authors (1989), para. 5.6.3., *J. Chem. Soc., Perkin Trans. 1*, 1989, Issue 1.

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