An Approach to Cytochalasan Synthesis: Macrolide Formation by an Intramolecular Diels-Alder Reaction. *X*-Ray Structure of Methyl (1*RS*, 2*SR*, 5*RS*, 6*RS*)-2,5-Dimethyl-1-hydroxy-6-[(1*RS*)-1-hydroxy-2-phenylethyl]cyclohex-3-ene-1-carboxylate

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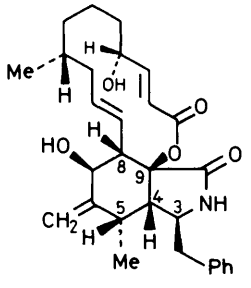
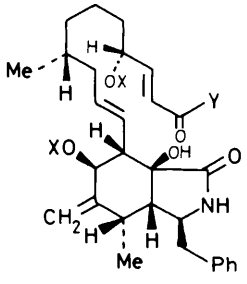
When heated in toluene under reflux, under high dilution conditions, *trans,trans*-hexadeca-12,14-dienoyloxymaleic anhydride (4) cyclized *via* an intramolecular Diels-Alder reaction to give the macrocyclic lactone (5) in 27% yield together with 5% of a regioisomer (23). (1*RS*, 2*SR*, 5*RS*, 6*RS*)-2,5-Dimethyl-1-octanoyloxycyclohex-3-ene-1,6-dicarboxylic acid anhydride (11) was converted into methyl (1*RS*, 2*SR*, 5*RS*, 6*RS*)-2,5-dimethyl-1-octanoyloxy-6-benzylcarbonylcyclohex-3-ene-1-carboxylate (33), but selective reduction of this ketone was unsuccessful. The structure of one of the reduction products, methyl (1*RS*, 2*SR*, 5*RS*, 6*RS*)-2,5-dimethyl-1-hydroxy-6-[(1*RS*)-1-hydroxy-2-phenylethyl]cyclohex-3-ene-1-carboxylate (35) was confirmed by an *X*-ray structure determination.

The cytochalasans, *e.g.* cytochalasin B (1), are an important group of fungal metabolites which exhibit unique effects on mammalian cells, and are widely used as research tools in cell biology.[1] Several approaches to the isoindolone unit of the cytochalasans have been reported which use Diels-Alder reactions to establish the correct relative stereochemistry at C(4), C(5), C(8), and C(9), and in some cases at C(3) (cytochalasan numbering), since this stereochemistry follows from the '*endo*' rule.[2] However the macrolide ring has been more elusive,[3] the one successful preparation reported to date involving closure of the hydroxy-thioester (2), obtained by degradation of natural cytochalasin B, to give the corresponding macrolide in 36% yield.[4] The bis-tetrahydropyranyl ether (3) has been prepared by total synthesis,[5] and the conversion of this into the macrolide precursor (2) is known.[4] Other approaches to cytochalasans involving fragmentation reactions have been described.

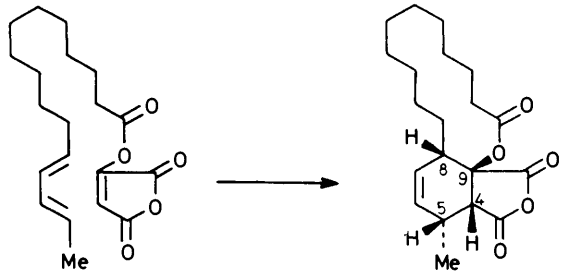
We were interested in developing an alternative approach to the cytochalasans which avoids the difficult macrolactonization of a tertiary alcohol. It was decided to see whether the formation of the macrocycle could be achieved *via* an intramolecular Diels-Alder reaction which should, by analogy with the work mentioned above, also establish the correct stereochemistry at C(4), C(5), C(8), and C(9). Since macrocycle formation *via* an intramolecular Diels-Alder reaction has scarcely been studied, it was decided to examine the cyclization of the long-chain diene anhydride (4); formation of the lactone (5) would constitute a model for a cytochalasan synthesis. We now report details of the preparation and cyclization of the diene-anhydride (4),[6] together with preliminary studies concerning the introduction of the pyrrolidinone ring.



(1)



(2) X = Ac, Y = SPh
(3) X = THP, Y = OH



(4) (5)

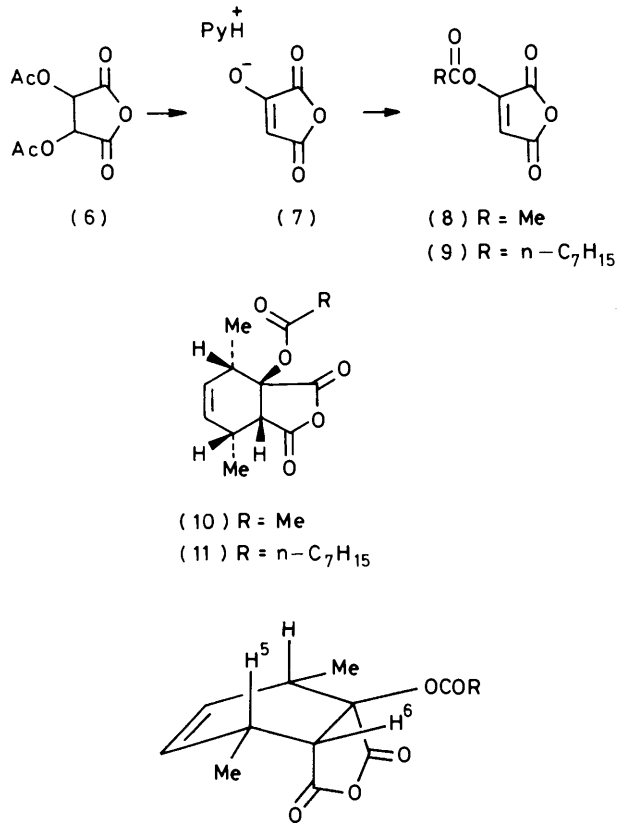
Results and Discussion

We first studied the preparation and Diels-Alder reactivity of simple acyloxymaleic anhydrides as models for the projected cyclization of the diene-anhydride (4).

Diels-Alder Reactions of Simple Acyloxymaleic Anhydrides.—Acetoxymaleic anhydride (8) available from diacetyltartaric anhydride (6) *via* the unstable pyridinium salt of hydroxymaleic anhydride (7)[7] is known to undergo a Diels–Alder reaction with cyclopentadiene.[8] We first examined the reaction between acetoxymaleic anhydride and *trans,trans*-hexa-2,4-diene.[9]

It was found that when heated to 115 °C for 12 h in toluene, acetoxymaleic anhydride (8) and *trans,trans*-hexa-2,4-diene reacted to give the Diels-Alder adduct (10), isolated in 57% yield by crystallization of the crude product mixture. No minor *exo*-isomer of the adduct was isolated, although the ^{1}H n.m.r. spectrum of the crude adduct mixture did indicate that a very small amount, less than 5%, may have been present. Similarly n-octanoyloxymaleic anhydride (9), also available (82%) from the pyridinium salt of hydroxymaleic anhydride (7),[7] gave the Diels-Alder adduct (11) with *trans,trans*-hexa-2,4-diene. The adduct (11) was an oil; it was purified either by careful distillation in high vacuum, or by column chromatography.

Structures were assigned to adducts (10) and (11) on the basis of spectroscopic data. The stereochemistry shown was initially assigned on the basis of the '*endo*' rule, the ^{1}H n.m.r. spectra of the adducts being consistent with the boat conformation shown in Figure 1. Both vinylic protons show small vicinal and moderate allylic coupling, and the H(5)–H(6) coupling is 5 Hz. Similar couplings were observed for the macrocyclic adducts (5) and (23). The stereochemistry of the



(6) (7) (8) R = Me (9) R = n-C_7H_{15}

(10) R = Me (11) R = n-C_7H_{15}

Figure 1

adduct (11) was eventually confirmed by an *X*-ray structural study on the alcohol (35) (see below).

Preparation and Cyclization of trans,trans-*Hexadeca*-12,14-*dienoyloxymaleic Anhydride* (4).—*trans,trans*-Hexadeca-12,14-dien-1-ol (12) was best prepared by coupling hexa-2,4-dienyl acetate (15) with the Grignard reagent (14) derived from 10-bromodecyl tetrahydropyranyl ether at −78 °C in the presence of Li_2CuCl_4.[10,11] Hydrolysis of the crude product gave the desired alcohol (12) isolated in 40% yield by recrystallization. An alternative route to the alcohol (12) which was briefly examined involved coupling a mixture of *trans,trans*- and *trans,cis*-7-bromohepta-2,4-dienes (18), ratio 12:5, available from but-2-enyl(cyclopropyl)methanol (17) and 48% HBr, with the Grignard reagent (19) derived from 9-bromononyl tetrahydropyranyl ether in the presence of Li_2CuCl_4.[12] In this case a mixture of the *trans,trans*- and *cis,trans*-hexadeca-12,14-dien-1-ols (12) and (13) was obtained after hydrolysis, from which the *trans,trans*-isomer (12) was isolated in 26% yield. Attempted couplings between hexa-2,4-dienyl bromide (16) and the Grignard reagent (14) were unsuccessful in our hands.[13]

trans,trans-Hexadeca-12,14-dien-1-ol (12) was oxidized to the aldehyde (20) using pyridinium chlorochromate,[14] and the aldehyde (20) oxidized to the acid (21) using alkaline silver nitrate in aqueous ethanol.[15] The acid (21) was converted into its acid chloride (22) using thionyl chloride in toluene buffered with anhydrous sodium carbonate, and the acid chloride (22) treated with an excess of the pyridinium salt of hydroxymaleic anhydride (7)[7] to give *trans,trans*-hexadeca-12,14-dienoyloxymaleic anhydride (4) (50—80% after recrystallization).

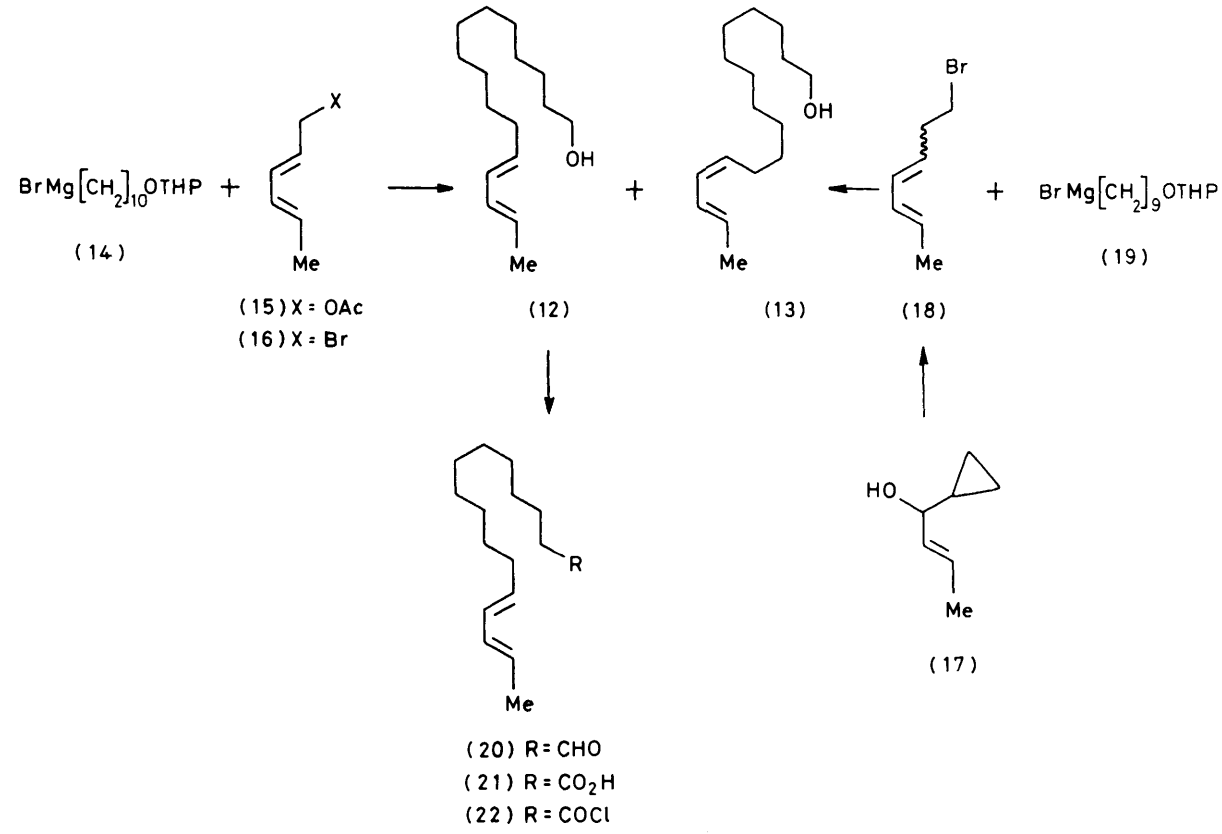
Having prepared the Diels-Alder precursor, the critical cyclization step could be examined.[16] It was found that heating a solution of the long-chain diene-anhydride (4) in anhydrous toluene under high dilution conditions (*ca.* 100 mg per 100 ml) for 90 h gave a mixture of two products separated by short-column chromatography, and identified as the desired adduct (5) (27% after recrystallization) and a regioisomer (23) (5%). Lower yields were obtained when the reaction was attempted at higher temperatures for shorter periods of time. The major side-product isolated was the acid (21). This may have been formed by adventitious hydrolysis of the enol ester moiety of the diene-anhydride (4) under the high-dilution conditions.[17]

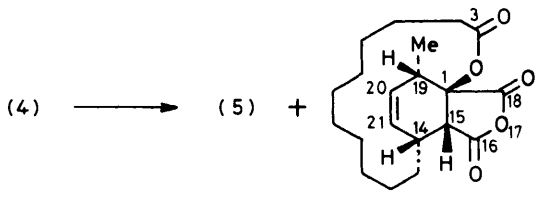
The structure assigned to the major adduct was established by spectroscopic methods and confirmed by an *X*-ray diffraction study.[18] The minor adduct was shown to be a regioisomer by selective spin-decoupling of the allylic protons; one allylic proton, H(14), was shown to be coupled to the bridgehead proton H(15), the other, H(19), to the exocyclic methyl group. The stereochemistry shown is consistent with the '*endo*' rule and with the ^1H n.m.r. coupling constants of the vinylic and bridgehead protons as discussed above for adducts (10) and (11).

Aspects of the Chemistry of Diels-Alder Adduct (11).—Having isolated the adduct (5) as the major product of the intramolecular Diels-Alder reaction of the long-chain diene anhydride (4), it was decided to examine methods of converting the anhydride group into the lactam system present in cytochalasans. Because of the ready availability of the simple ester-anhydrides (10) and (11), it was decided to preface this work by a study of the chemistry of the octanoyloxymaleic anhydride adduct (11).

Reduction of the anhydride (11) with sodium borohydride gave a mixture of the lactones (24) and (25), in which isomer (24), formed by reduction of the more hindered anhydride carbonyl, predominated, the ratio (24):(25) being approximately 2:1. In addition some side-chain elimination was observed, cyclohexadiene-lactone (26) also being isolated. The selective reduction of the (apparently) more hindered carbonyl of *cis*-fused cyclohexane-1,2-dicarboxylic acid anhydrides is well known, although in our case the influence of the side chain was difficult to predict.[19,20] Preliminary studies of reactions between the anhydride (11) and Grignard reagents gave rise to complex mixtures of products and these were not examined further.[21] Attempted selective hydrolysis of the anhydride (11) was complicated by side-chain cleavage; under basic conditions the cyclohexadiene diacid (27) was obtained on acidification, under acidic conditions the hydroxycyclohexene diacid (28) was formed. However it was found that treatment of the anhydride (11) with slightly acidic methanol under reflux gave the ester-acid (29), which could be purified by column chromatography, but which was more conveniently esterified by diazomethane to give the bis-methyl ester (30), isolated after chromatography in a 75% yield based on anhydride (11). Treatment of the bis-methyl ester (30) with trimethylsilyl iodide gave a different ester-acid from that obtained by methanolysis of the anhydride. This new ester-acid was identified as (31), being formed by selective cleavage of the more accessible methyl ester moiety.

Structures were assigned to products (29)—(31) on the basis of their spectroscopic data. Methanolysis of *cis*-fused cyclohexane-1,2-dicarboxylic acid anhydrides is known to occur at the less hindered carbonyl in contrast to hydride reduction.[8,19] The product from the reaction between the dimethyl ester (30) and trimethylsilyl iodide was clearly different from the acid-ester (29), and was assumed to be a regioisomer rather than a stereoisomer (formed by epimerization at C-6), because of the exclusive formation of one product in this reaction. These





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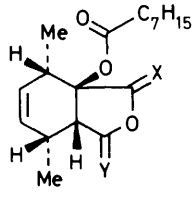
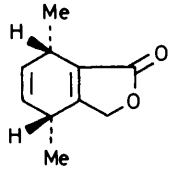


(24) X = H_2, Y = O
(25) X = O, Y = H_2



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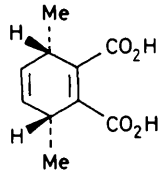

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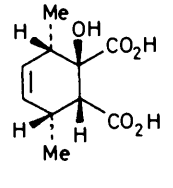


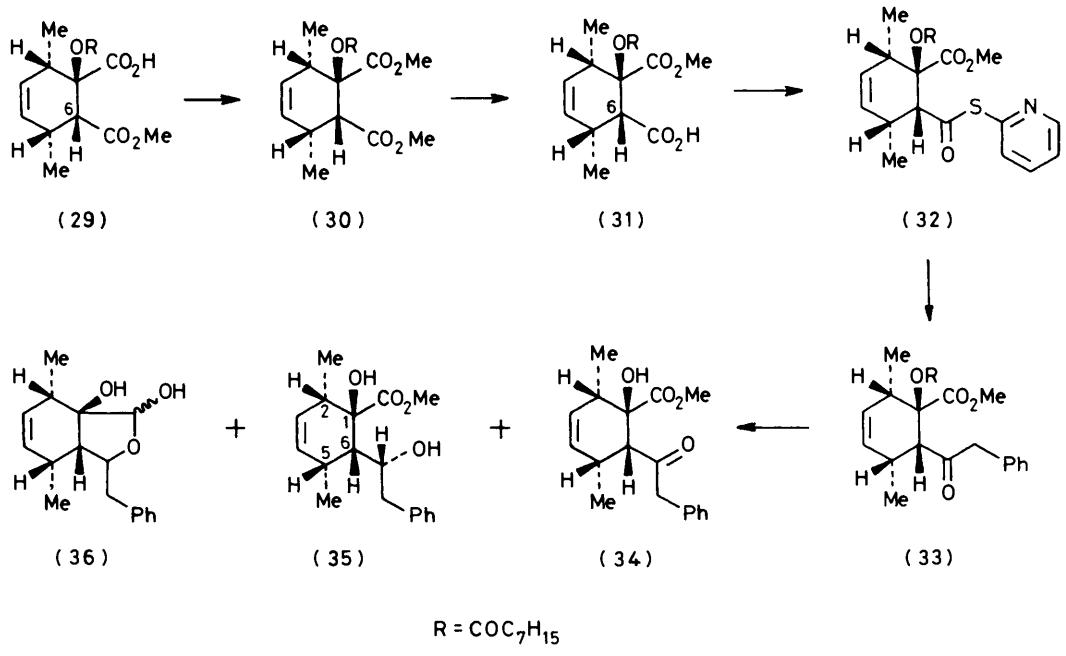
(28)

structures were confirmed by the *X*-ray structure determination of alcohol (35) (see below).

The acid ester (31) was converted into the *S*-pyridyl thioester (32) using 2,2′-dipyridyl disulphide and triphenylphosphine (73—84%),[22] and treatment of this thioester with benzylmagnesium bromide gave the ketone (33).[23] This procedure was found to be more convenient than that using lithium dibenzyl cuprate on the corresponding acid chloride.[24]

However, attempts to reduce the ketone carbonyl of the ester-ketone (33) selectively were unsuccessful. Treatment with di-isobutylaluminium hydride gave a complex mixture of products, all of which had been reduced at the side-chain. In particular the hydroxy-ketone (34) and the diol (35) were characterized, together with a more polar product tentatively identified as a mixture of the lactols (36), and a considerable amount of polar base-line material. Sodium borohydride did not reduce the ketone (33), simple ester hydrolysis being observed on prolonged treatment with sodium borohydride in aqueous tetrahydrofuran. Use of lithium aluminium hydride gave a complex mixture of products, from which the diol (35) was the only characterizable compound. Preliminary studies using sodium cyanoborohydride and ammonium acetate were unsuccessful: unchanged starting material was recovered. Attempts to convert the ketone (33) into its *O*-methyl oxime were not successful.

Structures were assigned to the hydroxy-ketone (34) and the diol-ester (35) on the basis of spectroscopic data; the coupling between 6-H and the C*H*OH proton in the ^{1}H n.m.r. spectrum of the diol (35) confirmed the assigned regiochemistry. The stereochemistry of the alcohol (35) was established by an *X*-ray diffraction study. Figure 2 shows a computer drawn projection of the molecule which clearly establishes the configuration at each of the chiral centres including the exocyclic position. This *X*-ray structure confirms several of the stereochemical assignments made above. Firstly, since epimerization at C(1), C(2), or C(5) is unlikely to have occurred, the *endo*-configuration assigned to the Diels-Alder adduct (11) is now established. Secondly, no overall epimerization has occurred at C-6 during the conversion of the anhydride



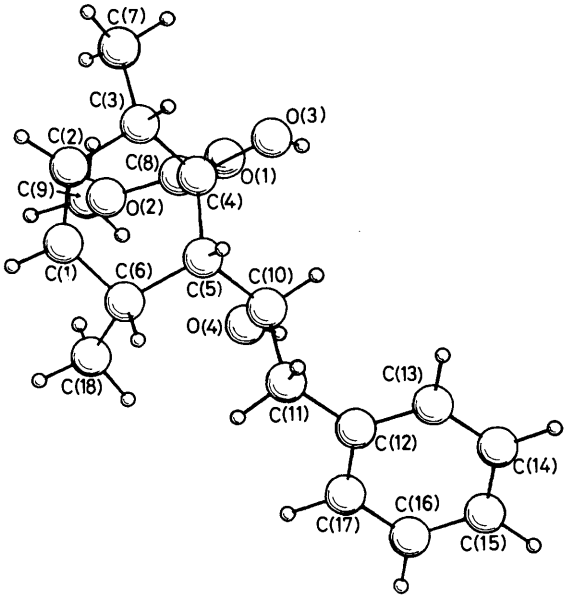


Figure 2. Ball and stick picture of diol (35) showing the crystallographic numbering scheme used. Drawn using SNOOPI (E. K. Davies, SNOOPI User Guide, Chemical Crystallography Laboratory, University of Oxford, Oxford, 1982)

(11) into the diol (35). On the assumption that two adventitious epimerizations at C-6 would have been detected, *e.g.* by the formation of mixtures, the configurations of the intermediates in this reaction sequence are confirmed. Since the half-esters (29) and (31) are not stereoisomers, they must be regioisomers; their identification followed from conversion of the isomer (31) into the diol (35).

The difficulty in selectively reducing the ketone (33) was disappointing but not unexpected, since the ketone carbonyl is shielded by neighbouring substituents. The configuration of the diol (35) at the exocyclic position is not that required at C-3 of a cytochalasan, and so the direct reductive amination of the ketone (33) was not pursued.

Summary and Conclusions.—The present work shows that the diene-anhydride (4) does undergo an intramolecular Diels-Alder reaction to give the macrolide (5). This reaction may have some application to cytochalasan synthesis, but model studies based on the ester-anhydride (11) show that the conversion of such anhydrides into pyrrolidinones analogous to cytochalasans is not straightforward, being hampered by ester cleavage and insufficient differences in reactivity between the different functional groups present. A more convergent route to cytochalasans using an intramolecular Diels-Alder reaction to form the macrolide ring would incorporate a lactam dieneophile into the long-chain Diels-Alder precursor. This would minimize the number of steps required after the critical cyclization step, so making the synthesis more efficient overall, but may be limited by the unreactivity of pyrrolinones as dieneophiles. Work along these lines, and an extension of the project to include the 'carbocyclic' cytochalasans such as cytochalasin D, is in progress.

The *X*-ray structure determined for the diol (35) shows the cyclohexene ring in a half-chair conformation in which C-4 and C-5 (crystallographic numbering, see Figure 2) deviate in opposite directions from the best plane through the four other ring carbon atoms. The methyl carbon, C-18, occupies a 'pseudo axial' position being displaced further (1.215 Å) from this plane than the 'pseudo equatorial' methyl carbon, C-7 (0.786 Å). The rather long ring bond between C-5 and C-6 [1.554 (3) Å], and the asymmetry in the exocyclic bond angles at C-6, 118.9(2)° and 109.5(2)°, show an attempt to reduce the steric strain between the C-18 methyl group and the C-5 side-chain. The carbon atoms C-10 and C-18 are 3.10 Å apart which is well within the sum of the Van der Waals radii for two methyl groups (4.0 Å). The molecule displays no other exceptional features, the rather short ring olefin bond having been observed in other cyclohexene derivatives bearing no substituents on these carbons.

Experimental

I.r. spectra were measured on Perkin-Elmer 257 and 297 spectrophotometers, and ^1H n.m.r. spectra on a Bruker HFX-90 spectrometer (90 MHz), on a Perkin-Elmer R34

spectrometer (220 MHz), and on a Bruker WH-300 spectrometer (300 MHz). M.p.s were determined on a Kofler hot-stage apparatus, and are uncorrected. Mass spectra were measured on AEI MS 30 and VG-micromass ZAB-IF spectrometers.

T.l.c. was carried out using Merck $60F_{254}$ silica gel precoated plates, and short column chromatography was used for preparative purposes using Hopkin and Williams silica gel for t.l.c. (MFC without binder).

Light petroleum refers to that boiling in the range 60—80 °C unless otherwise stated. All solvents were dried and distilled before use. Ether refers to diethyl ether throughout.

Octanoyloxymaleic Anhydride (9).—Freshly prepared pyridinium 2,5-dihydro-2,5-dioxofuran-3-olate (7) (36.8 g) [7] was suspended in anhydrous ether (200 ml) at 0 °C under nitrogen, and a solution of octanoyl chloride (24.7 g) in ether (100 ml) added during 45 min. The mixture was stirred for 0.5 h at 0 °C, and for 1.5 h at 20 °C. The residue was filtered off, washed with boiling ether, and the ether extracts combined and concentrated under reduced pressure to leave a red solid, which was recrystallised from light petroleum to give *octanoyloxymaleic anhydride* (9) (30.3 g), m.p. 42—43 °C; $\nu_{max.}$ (Nujol) 3 140, 1 850, 1 785, 1 635, 1 235, 1 180, 1 115, 1 090, and 860 cm^{-1}; δ($CDCl_3$) 0.7—2.0 [13 H, m, $(CH_2)_5CH_3$], 2.67 (2 H, t, *J* 7 Hz, CH_2CO), and 6.79 (1 H, s, vinylic H); *m/z* 127 ($M^+ - C_4HO_4$) (Found: C, 60.4; H, 6.9. $C_{12}H_{16}O_5$ requires C, 60.0; H, 6.7%).

(1RS, 2SR, 5RS, 6RS)-1-*Acetoxy*-2,5-*dimethylcyclohex*-3-*ene*-1,6-*dicarboxylic Acid Anhydride* (10).—Acetoxymaleic anhydride (8) (1.97 g) [25] and *trans,trans*-hexa-2,4-diene (1.0 g) were dissolved in anhydrous oxygen-free toluene (30 ml), hydroquinone (0.1 g) was added, and the solution heated in a sealed tube at 115 °C for 12 h. The solution was then filtered, concentrated under reduced pressure, and the residue recrystallised from light petroleum to give (1RS, 2SR, 5RS, 6RS)-1-*acetoxy*-2,5-*dimethylcyclohex*-3-*ene*-1,6-*dicarboxylic acid anhydride* (10) (1.64 g), m.p. 105.5—106.5 °C; $\nu_{max.}$ (Nujol) 3 135, 1 850, 1 780, 1 745, 1 630, 1 240, 1 210, 1 160, 1 030, 1 010, 960, 900, 770, and 720 cm^{-1}; δ($CDCl_3$) 1.38 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.49 (3 H, d, *J* 7.3 Hz, $CHCH_3$), 2.17 (3 H, s, $COCH_3$), 2.27—2.93 (2 H, m, CH–CH=CH–CH), 3.3 (1 H, d, *J* 5 Hz, 6-H), and 5.61 and 5.88 (each 1 H, dt, *J* 9.1, 2.6 Hz, vinylic H); *m/z* 239 ($M^+ + 1$) (Found: C, 60.2; H, 5.9. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%).

(1RS, 2SR, 5RS, 6RS)-2,5-*Dimethyl*-1-*octanoyloxycyclohex*-3-*ene*-1,6-*dicarboxylic Acid Anhydride* (11).—Octanoyloxymaleic anhydride (9) (26.4 g) and *trans,trans*-hexa-2,4-diene (9.0 g) were dissolved in dry, oxygen-free toluene (250 ml), hydroquinone (0.2 g) was added, and the solution heated in an autoclave at 115 °C for 12 h. Filtration and concentration under reduced pressure gave a red oil, which was distilled using a Kugelrohr to give (1RS, 2SR, 5RS, 6RS)-2,5-*dimethyl*-1-*octanoyloxycyclohex*-3-*ene*-1,6-*dicarboxylic acid anhydride* (11) as a colourless liquid, b.p. 220 °C at 0.1 mmHg; $\nu_{max.}$ (film) 3 040, 1 860, 1 780, 1 735, 1 155, 1 015, and 965 cm^{-1}; δ($CDCl_3$) 0.9 (3 H, m, CH_2CH_3), 1.32 [8 H, m, $(CH_2)_4$], 1.39 and 1.50 (each 3 H, d, *J* 7 Hz, 2 × $CHCH_3$), 1.65 (2 H, m, CH_2), 2.42 (2 H, m, CH_2CO), 2.67 (2 H, m, allylic H), 3.26 (1 H, d, *J* 5.0 Hz, 6-H), and 5.62 and 5.88 (each 1 H, dt, *J* 9, 2.5 Hz, vinylic H); *m/z* 322 (M^+) (Found: C, 67.4; H, 8.2. $C_{18}H_{26}O_5$ requires C, 67.1; H, 8.1%).

trans,trans-*Hexadeca*-12,14-*dien*-1-*ol* (12).—*From hexa*-2,4-*dienyl acetate* (15). 10-Bromodecan-1-ol (20 g) [26] and dihydropyran (14.4 g) were dissolved in anhydrous ether, toluene-*p*-sulphonic acid (0.1 g) was added, and the mixture stirred at 20 °C for 17 h. Anhydrous potassium carbonate (0.2 g) was added, and the mixture stirred for a further 0.25 h; it was then filtered and concentrated under reduced pressure to give 10-bromodecyl tetrahydropyranyl ether (27.4 g). This was dissolved in anhydrous tetrahydrofuran (80 ml) and slowly added to magnesium turnings (2.2 g) in tetrahydrofuran (5 ml) under nitrogen with warming to maintain reflux. After the addition the mixture was heated under reflux for a further 1.5 h, and cooled to −70 °C. Lithium tetrachlorocuprate (17.0 ml of a 0.1M-solution in tetrahydrofuran [27]) was added, followed by hexa-2,4-dienyl acetate (15) (11.8 g) in tetrahydrofuran (50 ml). The solution was allowed to warm to 20 °C and was then stirred for 17 h after which it was poured into water. The mixture was concentrated under reduced pressure to remove most of the tetrahydrofuran after which it was acidified to pH 3 (dilute HCl), and extracted with ether (4 × 300 ml). The combined extracts were washed with 2% aqueous NaOH (250 ml), water (2 × 200 ml), and brine (200 ml), and then dried ($MgSO_4$) and concentrated to give a yellow oil (28.8 g). This was dissolved in methanol (250 ml) containing toluene-*p*-sulphonic acid (0.1 g), and the solution heated under reflux for 1 h. Solid K_2CO_3 (0.1 g) was added, the mixture stirred for 0.5 h, concentrated under reduced pressure, dissolved in water, and the product extracted into ether. After drying ($MgSO_4$), concentration of the ether extracts gave a yellow oil (24.5 g). Crystallization of this from ethyl acetate–light petroleum gave eicosane-1,20-diol (2.83 g), m.p. 101—103 °C (lit.,[28] 102—105 °C); *m/z* 315 ($M^+ + 1$). Further crystallization of the mother liquor (19.4 g) from ether–light petroleum (b.p. 30—40 °C) gave trans,trans-*hexadeca*-12,14-*dien*-1-*ol* (12) (6.5 g), m.p. 48—49 °C (lit.,[11] 45 °C); $\nu_{max.}$ (Nujol) 3 350, 3 015, 1 070, 985, and 720 cm^{-1}; δ($CDCl_3$) 1.0—2.2 [21 H, m, $(CH_2)_{10}$ + OH], 1.71 (3 H, d, *J* 6.2 Hz, CH_3), 3.58 (2 H, m, CH_2OH), and 5.2—6.1 (4 H, m, vinylic H); *m/z* 238 (M^+) (Found: C, 80.55; H, 12.7. $C_{16}H_{30}O$ requires C, 80.6; H, 12.68%). Column chromatography of the mother liquor, eluted with ethyl acetate–light petroleum, gave more *trans,trans*-hexadeca-12,14-dien-1-ol (12) (1.0 g); n-decanol (2.49), an oil, *m/z* 157 ($M^+ + 1$); and eicosane-1,20-diol (1.2 g), together with a small amount of hexa-2,4-dienyl alcohol (0.47 g).

From trans,trans-7-*bromohepta*-2,4-*diene* (18). The Grignard reagent (19) from 9-bromononyl tetrahydropyranyl ether (8.9 g) [29] and magnesium turnings (0.73 g) prepared in tetrahydrofuran (110 ml) as described above, was cooled to −70 °C, and added to a solution of 7-bromohepta-2,4-dienes (18) (4.8 g) in tetrahydrofuran, at −70 °C, under nitrogen. Lithium tetrachlorocuprate (0.4 ml; 0.1M in THF) was added, and the reaction mixture stirred for 3 h at 0 °C, and for 17 h at 20 °C. Work-up and hydrolysis, as described above, gave a yellow oil, which was crystallized from light petroleum to give *trans,trans*-hexadeca-12,14-dien-1-ol (12) (1.8 g), identical with a sample prepared as described above. Chromatography of the mother liquor (2.9 g), eluted with ethyl acetate–light petroleum, gave a mixture of *trans,trans*, and *cis,trans*-hexadeca-12,14-dien-1-ols (12) and (13) (0.9 g); $\nu_{max.}$ (film) 987 (*trans,trans*), 982 (*cis,trans*), and 950 cm^{-1} (*cis,trans*); two peaks on g.l.c. (210 °C, 15% Carbowax 20M on Chromosorb W, 80—100 mesh), relative retention times 26.2 : 27.4, ratio 1 : 1, the faster peak being coincident with the authentic *trans,trans*-isomer (12).

trans,trans-*Hexadeca*-12,14-*dienal* (20).—*trans,trans*-Hexadeca-12,14-dien-1-ol (12) (9.55 g) in dichloromethane (60 ml) was added to pyridinium chlorochromate (12.9 g) [14] suspended in dry dichloromethane (90 ml). After being stirred for 3 h at 20 °C, the mixture was diluted with ether (350 ml), and

decanted from the solid which was washed with more ether (2 × 100 ml). The combined ether extracts were washed with 2% aqueous NaOH (2 × 250 ml), 5% aqueous HCl (250 ml), saturated $NaHCO_3$ (150 ml), and water (150 ml), before being dried ($MgSO_4$) and concentrated under reduced pressure to give trans,trans-*hexadeca*-12,14-*dienal* (20) (7.4 g) as a pale brown viscous oil, $\nu_{max.}$ (film) 3 020, 2 820, 1 725, and 990 cm^{-1}; δ($CDCl_3$) 0.7—2.2 [21 H, m, $(CH_2)_9 + CH_3$], 2.2—2.6 (2 H, m, CH_2CHO), 4.9—6.2 (4 H, m, vinylic H), and 9.76 (1 H, m, CH=O); *m/z* 236 (M^+) (Found: M^+ 236.2144. $C_{16}H_{28}O$ requires *M* 236.2140).

trans,trans-*Hexadeca*-12,14-*dienoic Acid* (21).—*trans,trans*-Hexadeca-12,14-dienal (20) (2.5 g) in ethanol (200 ml) was added to silver nitrate (2.25 g) in water (25 ml) to give a homogeneous solution. Sodium hydroxide (1.69 g) in water (80 ml) was added, with stirring, over a period of 0.5 h. After further stirring for 3 h, the mixture was filtered, washed with ether (3 × 50 ml), acidified with dilute HCl, and extracted with ether (5 × 75 ml). The combined extracts were dried ($MgSO_4$) and concentrated to leave a yellow solid which recrystallised from light petroleum (b.p. 30—40 °C), to give trans,trans-*hexadeca*-12,14-*dienoic acid* (21) (1.68 g), m.p. 63—64.5 °C; $\nu_{max.}$ (Nujol) 3 010, 1 710, 980, and 720 cm^{-1}; δ($CDCl_3$) 1.0—2.5 [23 H, m, $(CH_2)_{10} + CH_3$], 5.2—6.3 (4 H, m, vinylic H), and 10.7br (1 H, s, exch. D_2O, OH); *m/z* 252 (M^+) (Found: M^+ 252.2086. $C_{16}H_{28}O_2$ requires *M* 252.2089).

trans,trans-*Hexadeca*-12,14-*dienoyloxymaleic Anhydride* (4).—*trans,trans*-Hexadeca-12,14-dienoic acid (21) (3.9 g) was dissolved in toluene (100 ml), anhydrous Na_2CO_3 (2.1 g), and thionyl chloride (5.5 g) added, and the mixture stirred for 2 h at 40 °C and at 20 °C for 17 h. Filtration and concentration under reduced pressure gave the *acid chloride* (22) (4.2 g) as a light brown oil, used without further purification; $\nu_{max.}$ (film) 3 020, 1 795, and 990 cm^{-1}; δ($CDCl_3$) 1.0—2.5 [21 H, m, $(CH_2)_9 + CH_3$], 2.82 (2 H, m, CH_2CO), and 5.1—6.2 (4 H, m, vinylic H). This acid chloride (22) (4.2 g) in ether (75 ml) was added slowly to a suspension of freshly prepared pyridinium salt (7) (3.86 g)[7] in ether (100 ml) at 0 °C under nitrogen, and the mixture stirred for 0.5 h at 0 °C, and for 1.5 h at 20 °C. The supernatant liquid was then decanted off from the semi-solid residues, which were washed with boiling ether (3 × 50 ml). The ether extracts were combined and concentrated to give an oil (5.25 g), which crystallized from light petroleum (b.p. 30—40 °C), to afford trans,trans-*hexadeca*-12,14-*dienoyloxymaleic anhydride* (4) (3.23 g), m.p. 63—64.5 °C; $\nu_{max.}$ (Nujol) 3 140, 3 020, 1 855, 1 780, 1 635, 1 180, 1 085, 987, and 907 cm^{-1}; δ($CDCl_3$) 1.0—1.5 [14 H, m, $(CH_2)_7$], 1.72 (3 H, d, *J* 6.2 Hz, CH_3), 1.9—2.5 (4 H, m, 2 × CH_2), 2.67 (2 H, t, *J* 7.2 Hz, CH_2), 5.2—6.2 (4 H, m, vinylic H), and 6.83 (1 H, s, =C*H*–CO); *m/z* 348 (M^+) (Found: M^+ 348.1941. $C_{20}H_{28}O_5$ requires *M* 348.1937).

Cyclization of the Diene-anhydride (4).—Toluene (350 ml) was dried and deoxygenated by distilling it twice from P_2O_5 under nitrogen. *trans,trans*-Hexadeca-12,14-dienoyloxymaleic anhydride (4) (0.4 g) was added, and the solution heated under reflux under a nitrogen atmosphere for 90 h. Removal of the solvent under reduced pressure gave an oil (0.41 g) which was chromatographed on silica (20 g), with ethyl acetate–light petroleum (1 : 19) as eluant. The first eluted product was identified as (1RS, 14RS, 15RS, 19SR)-2,17-*dioxa*-19-*methyltricyclo*[12.4.3.$0^{1,15}$]*heneicosa*-21-*ene*-3,16,18-*trione* (23) (20 mg), m.p. 107—109 °C; $\nu_{max.}$ (Nujol) 1 855, 1 780, 1 740, 1 240, 1 220, 1 055, 1 000, 960, and 720 cm^{-1}; δ($CDCl_3$) 1.2—1.9 [20 H, m, $CHCH_3 + (CH_2)_8 +$ HC*H*], 2.2—2.8 (5 H, m, *HC*–CH=CH–C*H* + CH_2CO + HC*H*), 3.47 (1 H, d, *J* 4 Hz, H-15), and 5.61 and 5.87 (each 1 H, dt, 9, 2.5 Hz, vinylic H); *m/z* 348 (M^+) (Found: C, 68.65; H, 8.05. $C_{20}H_{28}O_5$ requires C, 68.95; H, 8.05%). The second eluted product was (1RS, 14SR, 17RS, 18RS)-2,20-*dioxa*-17-*methyltricyclo*[16.3.$0^{1,14}0^{1,18}$]*heneicosa*-15-*ene*-3,19,21-*trione* (5) (108 mg), m.p. 117—118.5 °C; $\nu_{max.}$ (Nujol) 1 855, 1 785, 1 740, 1 225, 1 140, 1 035, 1 000, 990, 910, and 720 cm^{-1}; δ($CDCl_3$) 1.2—1.9 [17 H, m, $(CH_2)_8$ + *H*CH], 1.49 (3 H, d, *J* 7 Hz, $CHCH_3$), 2.19 (1 H, m, HCH), 2.45 (2 H, t, *J* 7 Hz, CH_2CO), 2.52 and 2.70 (each 1 H, m, allylic H), 3.32 (1 H, d, *J* 4.9 Hz, 18-H), and 5.62 and 5.84 (each 1 H, dt, *J* 9, 2.5 Hz, vinylic H); *m/z* 348 (M^+) (Found: C, 68.65; H, 8.0%). Finally *trans,trans*-hexadeca-12,14-dienoic acid (21) (0.125 g) was eluted.

Reduction of (1RS, 2SR, 5RS, 6RS)-2,5-*Dimethyl*-1-*octanoyloxycyclohex*-3-*ene*-1,6-*dicarboxylic Acid Anhydride* (11).—A solution of the anhydride (11) (0.5 g) in tetrahydrofuran (5 ml) was added to a suspension of sodium borohydride (75 mg) in tetrahydrofuran (5 ml) at −30 °C, and the mixture allowed to warm to room temperature before being stirred for 5 h. Aqueous HCl (8.0 ml; 0.1N) was added, and the tetrahydrofuran removed under reduced pressure. Dilution with water, and ether extraction gave a pale yellow oil (0.49 g) which was chromatographed on silica (30 g), with ethyl acetate–light petroleum (1 : 9) as eluant. The first fraction eluted was identified as a mixture of the *lactones* (24) and (25) (130 mg; ratio 4 : 9) an oil; $\nu_{max.}$ (film) 2 920, 2 850, 1 780, 1 730, 1 450, 1 365, 1 150, and 1 045 cm^{-1}; δ($CDCl_3$) 0.87 (3 H, m, CH_2CH_3), 1.08 (3 H, d, *J* 7 Hz, $CHCH_3$) 1.2—1.8 [13 H, m, $(CH_2)_5 + CHCH_3$], 2.2—3.2 (5 H, m, CH_2CO + allylic H + 6-H), 3.79 [1 H, dd, *J* 9, 6 Hz, *H*CHO of isomer (25)], 4.02 and 4.22 [each 1 H, d, *J* 10 Hz, CH_2O of isomer (24)], 4.28 [1 H, t, *J* 9 Hz, *H*CHO of isomer (25)], and 5.4—5.9 (2 H, m, vinylic H) (Found: C, 70.2; H, 9.5. $C_{18}H_{28}O_4$ requires C, 70.13; H, 9.19%). The second fraction eluted was (2RS, 5SR)-2,5-*dimethyl*-8-*oxabicyclo*[4.3.0]*nona*-1(6),3-*dien*-7-*one* (26) (100 mg) as a colourless oil; $\nu_{max.}$ (film) 1 745, 1 680, 1 630, 1 440, 1 340, 1 235, 1 048, 1 005, and 760 cm^{-1}; δ($CDCl_3$) 1.27 (6 H, d, *J* 6.5 Hz, 2 × $CHCH_3$), 3.1 (2 H, m, *HC*–CH=CH–C*H*), 4.8 (2 H, m, CH_2O), and 6.0 (2 H, m, vinylic H).

Hydrolysis of (1RS, 2SR, 5RS, 6RS)-2,5-*Dimethyl*-1-*octanoyloxycyclohex*-3-*ene*-1,6-*dicarboxylic Acid Anhydride* (11).—*With* KOH. The anhydride (11) (1.0 g) was added to aqueous KOH (50 ml; 1N), and the mixture heated under reflux until a clear solution was obtained (1 h). Acidification and ether extraction gave, after recrystallisation from ethyl acetate–light petroleum, *cis*-3,6-dimethylcyclohexa-1,4-diene-1,2-dicarboxylic acid (27) (0.35 g), m.p. 111—113 °C (lit.,[30] 115 °C); *m/z* 196 (M^+); δ($CDCl_3$) 1.28 (6 H, d, *J* 7 Hz, 2 × $CHCH_3$), 3.3 (2 H, m, *HC*–CH=CH–C*H*), 5.8 (2 H, m, vinylic H), and 9.78 (2 H, s, exch. D_2O, OH).

With HCl. Anhydride (11) (0.5 g) in aqueous HCl (11 ml, 45%), dioxan (40 ml), and water (9 ml), was heated under reflux for 5 h. Ether extraction and crystallisation from ether–light petroleum gave (1RS, 2SR, 5RS, 6RS)-1-*hydroxy*-2,5-*dimethylcyclohex*-3-*ene*-1,6-*dicarboxylic acid* (28) (90 mg), m.p. 200—203 °C (decomp.); $\nu_{max.}$ (Nujol) 3 500—2 200br (OH), 3 420, 3 220, 1 750, 1 705, 1 200, 1 100, 1 060, 785, 760, 750, 705, and 625 cm^{-1}; δ[$(CD_3)_2CO$] 1.0 and 1.15 (each 3 H, d, *J* 7.35 Hz, $CHCH_3$), 2.2 (1 H, m, 5-H), 2.46 (1 H, m, 2-H), 3.16 (1 H, d, *J* 8.2 Hz, 6-H), 5.39 (1 H, dt, *J* 10, 1.9 Hz, vinylic H), and 5.62 (1 H, dt, *J* 10, 2.45 Hz, vinylic H); *m/z* 214 (M^+) and 196 ($M^+ - H_2O$) (Found: C, 56.0; H, 6.7. $C_{10}H_{14}O_5$ requires C, 56.07; H, 6.54%).

(1RS, 2SR, 5RS, 6RS)-2,5-*Dimethyl*-1-*octanoyloxy*-6-*methoxycarbonylcyclohex*-3-*ene*-1-*carboxylic Acid* (29).—The anhydride (11) (2.0 g) was dissolved in methanol (20 ml) containing 35% aqueous HCl (0.3 ml), and the mixture was heated under reflux for 17 h. The solution was cooled, diluted with ether, washed with brine to constant pH, dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow oil (2.2 g). A portion (0.5 g) was chromatographed on silica (25 g), with ether–light petroleum (b.p. 30—40 °C)–acetic acid, (1 : 1 : 0.01) as eluant, to give (1RS, 2SR, 5RS, 6RS)-2,5-*dimethyl*-1-*octanoyloxy*-6-*methoxycarbonylcyclohex*-3-*ene*-1-*carboxylic acid* (29) (0.34 g) as a colourless oil, $\nu_{max.}$ (film) 3 180br, 3 015, 1 740, 1 380, 1 165, 1 105, 1 045, 980, 720, and 645 cm^{-1}; δ($CDCl_3$) 0.86 (3 H, m, CH_2CH_3), 0.98 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.23 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.26 [8 H, m, $(CH_2)_4$], 1.59 (2 H, m, CH_2), 2.33 (2 H, m, CH_2CO), 1.45 and 1.55 (each 1 H, m, $CHCH_3$), 3.58 (1 H, d, *J* 6 Hz, $CHCO_2Me$), 3.62 (3 H, s, CO_2CH_3), 5.44 and 5.68 (each 1 H, m, vinylic H), and 8.2br (1 H, s, OH); *m/z* 354 (M^+) (Found: C, 64.55; H, 8.6. $C_{19}H_{30}O_6$ requires C, 64.41; H, 8.47%).

Dimethyl (1RS, 2SR, 5RS, 6RS)-2,5-*Dimethyl*-1-*octanoyloxycyclohex*-3-*ene*-1,6-*dicarboxylate* (30).—The acid-ester (29) (2.2 g) in ether was esterified using an excess of diazomethane. Column chromatography gave the *bis-methyl ester* (30) (1.73 g), as an oil; $\nu_{max.}$ (film) 3 015, 1 785, 1 740, 1 275, 1 255, 1 190, 1 160, 1 105, 1 050, and 960 cm^{-1}; δ($CDCl_3$) 0.84 (3 H, m, CH_2CH_3), 0.97 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.13 (3 H, d, *J* 7.3 Hz, $CHCH_3$), 1.24 [8 H, m, $(CH_2)_4$], 1.57 (2 H, m, CH_2), 2.26 (2 H, m, CH_2CO), 2.44 and 2.48 (each 1 H, overlapping m, 2 × $CHCH_3$), 3.54 (1 H, d, *J* 5 Hz, $CHCO_2Me$), 3.65 and 3.69 (each 3 H, s, CO_2CH_3) and 5.41 and 5.63 (each 1 H, m, vinylic H); *m/z* 368 (M^+) (Found: M^+ 368.2200. $C_{20}H_{32}O_6$ requires *M* 368.2198).

(1RS, 2RS, 5SR, 6RS)-2,5-*Dimethyl*-6-*octanoyloxy*-6-*methoxycarbonylcyclohex*-3-*ene*-1-*carboxylic Acid* (31).—Trimethylsilyl iodide (3.6 g) in carbon tetrachloride (30 ml) was added to dimethyl ester (30) (3.33 g) under nitrogen in the dark. The solution was heated at 60 °C for 20 h and poured into ether (200 ml). The ethereal solution was washed with 2% aqueous sodium thiosulphate (2 × 25 ml), brine (2 × 25 ml), and then dried ($MgSO_4$) and concentrated under reduced pressure to give an oil (3.3 g). This was chromatographed on silica, with ether–light petroleum (b.p. 30—40 °C)–acetic acid (3 : 7 : 0.05) as eluant to give (1RS, 2RS, 5SR, 6RS)-2,5-(*dimethyl*-6-*octanoyloxy*-6-*methoxycarbonylcyclohex*-3-*ene*-1-*carboxylic acid* (31) (61%) as an oil, $\nu_{max.}$ (film) 3 400—1 500br OH), 3 020, 1 750, 1 730, 1 710, 1 230, 1 095, 725, and 705 cm^{-1}; δ($CDCl_3$) 0.88 (3 H, m, CH_2CH_3), 1.12 and 1.14 (each 3 H, d, *J* 7 Hz, $CHCH_3$) 1.31 [8 H, m, $(CH_2)_4$], 1.63 (2 H, m, CH_2), 2.32 (2 H, m, CH_2), 2.44 (2 H, m, 2 × $CHCH_3$), 3.58 (1 H, d, *J* 6 Hz, $CHCO_2H$), 3.76 (3 H, s, CO_2CH_3), and 5.45 and 5.65 (each 1 H, m, vinylic H); *m/z* 354 (M^+) (Found: C, 64.36; H, 8.8. $C_{19}H_{30}O_6$ requires C, 66.41; H, 8.47%).

S-(2-*Pyridyl*) (1RS, 2RS, 5SR, 6RS)-2,5-*Dimethyl*-6-*octanoyloxy*-6-*methoxycarbonylcyclohex*-3-*ene*-1-*thiocarboxylate* (32).—The acid-ester (31) (1.0 g), triphenylphosphine (1.1 g), and 2,2′-dipyridyl disulphide (0.9 g) were dissolved in anhydrous oxygen-free toluene (30 ml), and the solution was stirred at room temperature under nitrogen for 17 h. The toluene was removed under reduced pressure and the residue dissolved in ether (60 ml); the solution was then washed with 1% aqueous Na_2CO_3 (3 × 75 ml) and brine (75 ml) and finally dried ($MgSO_4$) and concentrated to give a residue which was dissolved in light petroleum, filtered, and concentrated to leave an oil (1.72 g). This was chromatographed to give S-(2-*pyridyl*) (1RS, 2RS, 5SR, 6RS)-2,5-*dimethyl*-6-*octanoyloxy*-6-*methoxycarbonylcyclohex*-3-*ene*-1-*thiocarboxylate* (32) (0.75 g), m.p. 82.5—83.5 °C; $\nu_{max.}$ (Nujol) 3 020, 1 750, 1 735, 1 710, 1 570, 1 560, 1 275, 1 165, 1 100, 1 020, and 760 cm^{-1}; δ($CDCl_3$) 0.93 (3 H, m, CH_2CH_3), 1.09 and 1.28 (each 3 H, d, *J* 7 Hz, $CHCH_3$), 1.32 [8 H, m, $(CH_2)_4$], 1.65 (2 H, m, CH_2), 2.37 (2 H, m, CH_2), 2.60 (2 H, m, 2 × $CHCH_3$), 3.80 (3 H, s, CO_2CH_3), 3.89 (1 H, d, *J* 5 Hz, $CHCO.Spy$), 5.47 and 5.67 (each 1 H, m, vinylic H), 7.29 (1 H, m, aromatic H), 7.74 (2 H, m aromatic H), and 8.63 (1 H, m, aromatic H); *m/z* 447 (M^+) (Found: M^+ 447.2046. $C_{24}H_{33}O_5NS$ requires *M* 447.2039).

Methyl (1RS, 2SR, 5RS, 6RS)-2,5-*Dimethyl*-1-*octanoyloxy*-6-*benzylcarbonylcyclohex*-3-*ene*-1-*carboxylate* (33).—Benzylmagnesium chloride (0.9 ml; 0.47M) in ether was added to the thioester (32) (160 mg) in ether (3 ml) under nitrogen, and the solution heated under reflux for 0.5 h. T.l.c. showed the presence of unchanged thioester, so more benzylmagnesium chloride (0.2 ml) was added, and the solution heated under reflux for a further 0.25 h. Aqueous HCl (2.2 ml; 0.24M) was added, followed by more ether (10 ml) and saturated NH_4Cl (10 ml). Separation followed by ether extraction gave ether extracts which were washed with 1% Na_2CO_3 (3 × 10 ml) and water (10 ml) and then dried ($MgSO_4$) and concentrated to give an oil which was chromatographed on silica, with ethyl acetate–light petroleum as eluant to afford *methyl* (1RS, 2SR, 5RS, 6RS)-2,5-*dimethyl*-1-*octanoyloxy*-6-*benzylcarbonylcyclohex*-3-*ene*-1-*carboxylate* (33) (115 mg) as an oil, $\nu_{max.}$ (film) 3 080, 3 060, 3 020, 1 745, 1 725, 1 275, 1 100, and 705 cm^{-1}; δ($CDCl_3$) 0.92 (3 H, m, CH_2CH_3), 0.98 and 1.00 (each 3 H, d, *J* 7 Hz, $CHCH_3$), 1.32 [8 H, m, $(CH_2)_4$], 1.65 (2 H, m, CH_2), 2.36 (2 H, m, CH_2), 2.49 (2 H, m, 2 × $CHCH_3$), 3.76 (3 H, s, CO_2CH_3), 3.78 and 4.28 (each 1 H, d, *J* 20 Hz, CH_2Ph), 3.92 (1 H, d, *J* 4.5 Hz, $CHCOCH_2Ph$), 5.41 and 5.64 (each 1 H, m, vinylic H), and 7.28 (5 H, m, aromatic H); *m/z* 337 ($M^+ - C_7H_7$) (Found: $M^+ - C_7H_7$ 337.2010. $C_{19}H_{29}O_5$ requires *M* 337.2014).

Reduction of the Ketone (33).—DIBAL (6 ml of 1M solution in toluene) was added slowly to the keto-ester (33) (300 mg) in toluene (3 ml) at −72 °C under N_2, and the mixture allowed to warm to 20 °C. After 17 h, methanol (6 ml) and aqueous HCl (6 ml, 0.3 M) were added, and the mixture filtered and extracted with ether (4 × 50 ml); the combined extracts were dried ($MgSO_4$) and concentrated to give an oil (279 mg), shown to be a complex mixture of products by t.l.c. Chromatography gave side-chain residues (28 mg), followed by *methyl* (1RS, 2SR, 5RS, 6RS)-2,5-*dimethyl*-1-*hydroxy*-6-*benzylcarbonylcyclohex*-3-*ene*-1-*carboxylate* (34) (10 mg) as an oil; $\nu_{max.}$ (CCl_4) 3 600, 3 500, 3 070, 3 020, 1 755, 1 730, and 1 235 cm^{-1}; δ($CDCl_3$) 0.92 and 0.98 (each 3 H, d, *J* 7 Hz, $CHCH_3$), 2.41 and 2.91 (each 1 H, m, $CHCH_3$), 3.53 (1 H, d, *J* 8 Hz, $CHCOCH_2Ph$), 3.76 and 3.81 (each 1 H, d, *J* 20 Hz, CH_2Ph), 3.77 (3 H, s, CO_2CH_3), 3.97 (1 H, s, *OH*), 5.38 and 5.63 (each 1 H, m, vinylic H), and 7.3 (5 H, m, aromatic H); *m/z* 303 ($M^+ \times 1$). After a mixed fraction, the next product eluted was identified as *methyl* (1RS, 2SR, 5RS, 6RS)-2,5-*dimethyl*-1-*hydroxy*-6-[(1RS)-1-*hydroxy*-2-*phenylethyl*]*cyclohex*-3-*ene*-*carboxylate* (35) (30 mg), m.p. 112 °C; $\nu_{max.}$ (CCl_4) 3 620, 3 500, 3 020, 1 740, and 1 240 cm^{-1}; δ($CDCl_3$) 0.95 and 1.33 (each 3 H, d, *J* 7 Hz, $CHCH_3$), 1.55 (1 H, broad s, OH), 2.22 (1 H, dd, *J* 9, 3 Hz, $CHCHOH$), 2.47 (1 H, m, $CHCH_3$), 2.77 (1 H, dd, *J* 15, 4 Hz, $HCHPh$), 2.84 (1 H, m, $CHCH_3$) 2.97 (1 H, dd, *J* 15, 12 Hz, $HCHPh$), 3.72 (3 H, s, CO_2CH_3), 4.08 (1 H, s, OH), 4.62 (1 H, m, *CH*OH), 5.38 and 5.65 (each 1 H, m, vinylic H), and 7.26 (5 H, m, aromatic H); *m/z* 305 ($M^+ + 1$) (Found: C, 70.8; H, 7.75. $C_{18}H_{24}O_4$

Table 1. Bond lengths for (35) in Å with e.s.d.s in parentheses

O(1)–C(8)	1.200(3)
O(2)–C(8)	1.320(3)
O(2)–C(9)	1.446(3)
O(3)–C(4)	1.428(3)
O(4)–C(10)	1.420(3)
C(1)–C(2)	1.311(4)
C(1)–C(6)	1.497(4)
C(2)–C(3)	1.495(4)
C(3)–C(4)	1.542(3)
C(3)–C(7)	1.532(4)
C(4)–C(5)	1.546(3)
C(4)–C(8)	1.523(3)
C(5)–C(6)	1.554(3)
C(5)–C(10)	1.530(3)
C(6)–C(18)	1.532(4)
C(10)–C(11)	1.524(3)
C(11)–C(12)	1.504(3)
C(12)–C(13)	1.385(3)
C(12)–C(17)	1.369(4)
C(13)–C(14)	1.379(4)
C(14)–C(15)	1.364(5)
C(15)–C(16)	1.355(5)
C(16)–C(17)	1.381(4)

Table 2. Bond angles for (35) in ° with e.s.d.s in parentheses

C(8)–O(2)–C(9)	115.0(2)
C(2)–C(1)–C(6)	125.4(2)
C(1)–C(2)–C(3)	125.1(2)
C(2)–C(3)–C(4)	113.2(2)
C(2)–C(3)–C(7)	112.3(2)
C(4)–C(3)–C(7)	113.2(2)
O(3)–C(4)–C(3)	104.8(2)
O(3)–C(4)–C(5)	108.4(2)
O(3)–C(4)–C(8)	106.0(2)
C(3)–C(4)–C(5)	110.1(2)
C(3)–C(4)–C(8)	112.0(2)
C(5)–C(4)–C(8)	114.9(2)
C(4)–C(5)–C(6)	116.9(2)
C(4)–C(5)–C(10)	111.5(2)
C(6)–C(5)–C(10)	115.1(2)
C(1)–C(6)–C(5)	110.3(2)
C(1)–C(6)–C(18)	109.5(2)
C(5)–C(6)–C(18)	118.9(2)
O(1)–C(8)–O(2)	123.0(2)
O(1)–C(8)–O(4)	123.8(2)
O(2)–C(8)–C(4)	113.1(2)
O(4)–C(10)–C(5)	110.4(2)
O(4)–C(10)–C(11)	112.4(2)
C(5)–C(10)–C(11)	112.9(2)
C(10)–C(11)–C(12)	113.6(2)
C(11)–C(12)–C(13)	120.7(2)
C(11)–C(12)–C(17)	121.5(2)
C(13)–C(12)–C(17)	117.7(2)
C(12)–C(13)–C(14)	121.1(3)
C(13)–C(14)–C(15)	119.9(3)
C(14)–C(15)–C(16)	119.8(3)
C(15)–C(16)–C(17)	120.6(3)
C(12)–C(17)–C(16)	121.0(3)

requires C, 71.05; H, 7.89%). The third product eluted was tentatively identified as a mixture of *lactols* (36) (26 mg), m.p. 116 °C; $\nu_{max.}$ ($CHCl_3$) 3 600, 3 500, 3 010, 1 175, and 1 135 cm^{-1}; δ($CDCl_3$) 1.12 and 1.14 (each 3 H, d, *J* 7 Hz, CHC*H*$_3$), 2.14 (1 H, m, C*H*CHO), 2.32 and 2.26 (each 1 H, m, C*H*CH$_3$), 2.84 (1 H, dd, *J* 18, 10 Hz, *H*CHPh), 3.05 (1 H, dd, *J* 18, 4 Hz, HC*H*Ph), 3.58 (1 H, d, *J* 9 Hz, exch. D_2O, OH), 3.71 (1 H, m, C*H*O), 4.78 (1 H, d, *J* 9 Hz, C*H*OH), 5.57 and 5.69 (each 1 H, m, vinylic H), and 7.27 (5 H, m, aromatic H); *m/z* 274 (M^+) (Found: C, 74.35; H, 8.0. $C_{17}H_{22}O_3$ requires C, 74.45; H, 8.03%). Finally a complex mixture of slowly moving products was eluted (38 mg).

Table 3. Fractional atomic co-ordinates for (35)

U_{iso} for non-hydrogen atoms is calculated as the cube root of the product of the principal axes of the ellipse of vibration

Atom	*x/a*	*y/b*	*z/c*
O(1)	1.007 2(1)	0.232 0(2)	0.180 7(1)
O(2)	0.954 24(9)	0.308 1(2)	0.038 2(1)
O(3)	0.868 1(1)	0.182 8(2)	0.098 5(1)
O(4)	0.942 50(9)	0.525 6(2)	0.145 0(1)
C(1)	0.761 4(2)	0.371 3(4)	−0.164 2(2)
C(2)	0.771 2(2)	0.235 3(4)	−0.152 0(2)
C(3)	0.811 6(1)	0.158 5(3)	−0.059 2(2)
C(4)	0.863 6(1)	0.253 9(2)	0.034 1(2)
C(5)	0.821 1(1)	0.395 8(2)	0.003 4(1)
C(6)	0.791 0(1)	0.473 9(3)	−0.086 7(2)
C(7)	0.856 2(2)	0.028 1(3)	−0.039 2(2)
C(8)	0.949 6(1)	0.264 5(2)	0.093 5(2)
C(9)	1.034 9(2)	0.320 3(5)	0.091 8(3)
C(10)	0.866 5(1)	0.486 7(2)	0.095 8(1)
C(11)	0.817 9(1)	0.612 4(3)	0.071 1(2)
C(12)	0.857 7(1)	0.693 4(2)	0.162 8(2)
C(13)	0.854 4(2)	0.646 6(3)	0.222 3(2)
C(14)	0.889 8(2)	0.721 4(4)	0.305 7(2)
C(15)	0.929 2(2)	0.843 1(4)	0.330 9(2)
C(16)	0.933 0(2)	0.890 3(3)	0.273 5(2)
C(17)	0.897 5(2)	0.816 0(3)	0.189 8(2)
C(18)	0.846 4(2)	0.580 2(3)	−0.065 0(2)
H(3)	0.9241	0.2019	0.1722
H(4)	0.9816	0.5431	0.2063
H(11)	0.7317	0.4109	−0.2316
H(21)	0.7506	0.1803	−0.2100
H(31)	0.7671	0.1208	−0.0745
H(51)	0.7683	0.3732	−0.0267
H(61)	0.7459	0.5358	−0.1135
H(71)	0.8828	−0.0227	0.0232
H(72)	0.8999	0.0562	−0.0283
H(73)	0.8191	−0.0385	−0.0979
H(91)	1.0347	0.3538	0.0460
H(92)	1.0625	0.2260	0.1200
H(93)	1.0675	0.3876	0.1499
H(101)	0.8803	0.4271	0.1477
H(111)	0.8093	0.6761	0.0247
H(112)	0.7637	0.5788	0.0333
H(131)	0.8244	0.5549	0.2035
H(141)	0.8888	0.6835	0.3508
H(151)	0.9534	0.8993	0.3916
H(161)	0.9641	0.9806	0.2945
H(171)	0.9006	0.8534	0.1465
H(181)	0.8200	0.6224	−0.1297
H(182)	0.8969	0.5296	−0.0314
H(183)	0.8630	0.6559	−0.0192

Crystal Data for Diol (35).—$C_{18}H_{24}O_4$, M_r = 304.4, monoclinic, *C*2/*c*, *Z* = 8, *a* = 26.302 (5), *b* = 9.559 (1), *c* = 20.885 (5) Å, β = 140.67 (1)°, *U* = 3327.6 Å^3, D_c = 1.52 g cm^{-3}, μ(Mo-K_α) = 1.14 cm^{-1}, final *R*-value = 0.053.

X-Ray Crystal Structure Determination for (35).—A small uniform piece of (35), cut from a large crystal grown by slow evaporation of an ether solution, was mounted on a glass fibre and transferred on to a computer-controlled Enraf Nonius CAD4-F four-circle diffractometer. A triclinic cell was calculated from the setting angles of 25 strong reflections found by the SEARCH routine, and this was transformed to a C-centred monoclinic lattice on the basis of the Niggli values. Diffraction intensities were measured by *w*/2θ scans out to

$2\theta = 50°$ which gave 2 682 unique records after the application of Lorentz and polarisation corrections, the rejection of systematic absences, and the merging of equivalent reflections. All non-hydrogen atoms were located with MULTAN 80 [31] and refined with isotropic temperature factors by full-matrix least squares using the 2 129 reflections with $I \geqslant 3\sigma(I)$. The refinement was continued by blocked-matrix least-squares using anisotropic temperature factors. The hydroxy hydrogen atoms were deliberately located from a difference Fourier synthesis but the remaining hydrogens were placed geometrically and all were assigned an overall isotropic temperature factor which refined to 0.069 (positional parameters were not refined). A weight for each reflection in the final rounds of refinement was calculated from the Chebyshev series $w = [1\,858.2\ t_0(X) + 2\,505.8\ t_1(X) + 874.7\ t_2(X)]^{-1}$ where $^7X = F_0/F_{max.}$.[32] The structure converged at a final R value of 0.053. All calculations were performed with the CRYSTALS [33] package on the Chemical Crystallography Laboratory VAX 11/750 computer. Bond lengths, bond angles, and fractional co-ordinates for compound (35) are listed in Tables 1—3. Tables of temperature factors and structure factors are available in Supplementary Publication No. 23535 (20 pp.).*

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* For details of the Supplementary publications scheme, see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1983, Issue 1.

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