Synthesis of Substituted *cis*-Decalins as Potential Insect Antifeedants

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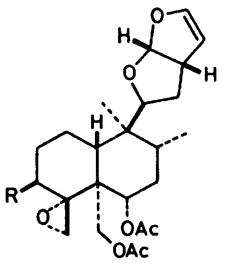
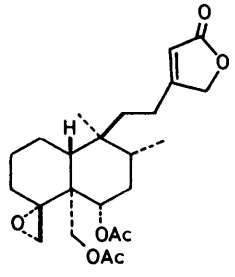
2β-Acetoxy-1α-acetoxymethyl-5,5-dimethyl-1α,6α,10*O*α-bicyclo[4.4.0]decane-10-spiro-2'-oxiran (4) has been prepared from 4,4-dimethylcyclohex-2-enone in eight steps, one of which involves a useful Lewis acid-catalysed cyclisation of an acetylenic β-oxo-ester (7). The structure of (4) was determined by *X*-ray crystallography. At a concentration of 1 000 p.p.m. compound (4) showed a 72% inhibition of feeding by *Locusta migratoria*.

OVER the past few years, there has been considerable interest in highly oxygenated diterpenes which show insect antifeedant activity. Typical examples of this series are clerodin (1),[1] *epi*-caryoptin (2),[1] and ajugarin I (3).[2]

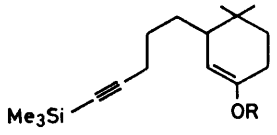
While certain structural features are known to be important for biological activity,[3] there is still a real need to prepare other derivatives in order to probe this



(1) R = H
(2) R = OAc



(3)



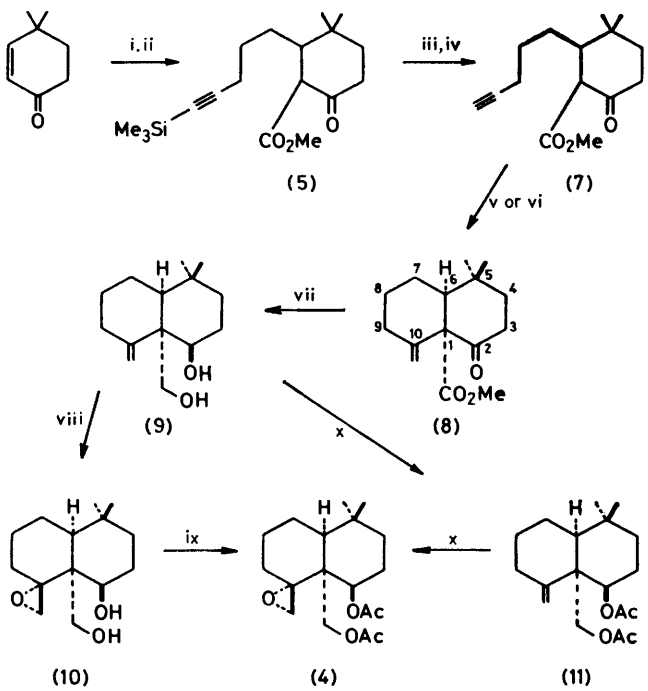
(6) a; R = CO_2Me
b; R = $SiMe_3$

activity in greater detail. Here we describe a synthesis of a *cis*-fused decalin system which has sufficient flexibility to prepare a number of potentially useful insect antifeedants.[4]

Our synthetic route to the model *cis*-decalin epoxydiacetate (4) is shown in Scheme 1. Copper(I)-catalysed conjugate addition of 5-trimethylsilylpent-4-ynylmagnesium iodide, in ether, to 4,4-dimethylcyclohex-2-enone and quenching of the resultant enolate with freshly distilled methyl chloroformate [5] afforded the adduct (5) in 60% yield. If the corresponding magnesium chloride Grignard reagent, or other cuprates, were used to effect the conjugate addition, in tetrahydrofuran as the solvent, quenching by the chloroformate occurred exclusively on oxygen to produce (6a). Alternatively, the enolate could be trapped as the trimethylsilyl ether (6b). However, regeneration of the regiospecific enolate from (6b) and subsequent reaction on carbon with methyl chloroformate was not possible.

Deprotection of the acetylene using standard methods,[6] *i.e.* KF in aqueous dimethylformamide (DMF), led to complications in the form of unwanted aldol condensations.[7] However, using $AgNO_3$–KCN,[8] the reaction proceeded smoothly to give the acetylenic β-oxoester (7) in 89% yield. The structures of both (5) and (7) are consistent with their spectroscopic properties.

Cyclisation of (7) to (8) was first achieved using high temperatures (>260 °C) typical of Conia's work [9] on



SCHEME 1 Reagents: i, $Me_3Si{\cdot}C{\equiv}C{\cdot}(CH_2)_2{\cdot}CH_2MgI$–CuI–$Et_2O$ at −23 °C; ii, MeO·COCl; iii, $AgNO_3$; iv, KCN; v, ZnI_2, toluene, heat; vi, $SnCl_4$, CH_2Cl_2; vii, $LiAlH_4$; viii, $VO(acac)_2$, Bu^tO_2H; ix, Ac_2O, py, 4-(*NN*-dimethylamino)pyridine; x, *m*-CPBA

related systems. While these reactions went well, we felt that lower temperatures would be beneficial, particularly so if more highly functionalised substrates were to be used as starting materials. Consequently, it was found that the addition of catalytic quantities of Lewis acids allowed the cyclisation to proceed under much milder conditions. Hence (7) in the presence of ZnI_2 in

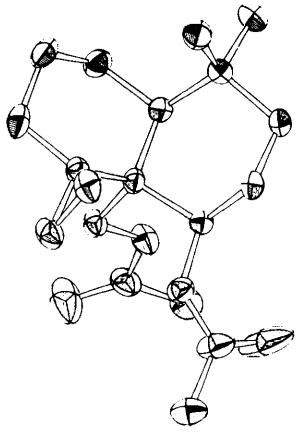
boiling toluene or at room temperature with $SnCl_4$ in methylene chloride gave an essentially quantitative yield of (8). Recently, White [10] and Weiler [11] have noted similar cyclisations of β-oxoesters to alkenes in the presence of $SnCl_4$.

The (1α,6α-) *cis*-ring junction of the decalin (8) was expected on mechanistic grounds and was later confirmed by an *X*-ray structure determination of a subsequent derivative. The ^1H n.m.r. spectrum of (8) showed structurally significant absorptions at δ 1.06 and 1.13 corresponding to the methyl groups with the methoxy-resonance at 3.7 and the methylene signals at 4.3 and 4.79.

Reduction of (8) with lithium aluminium hydride afforded a single crystalline diol (9) in 89% yield; the reduction stereochemistry was again assigned as a consequence of later results.

Epoxidation of (9) under Henbest's [12] conditions using *m*-chloroperbenzoic acid (*m*-CPBA) afforded the epoxide (10). However, owing to its sensitivity to both acid and base it proved difficult to isolate. In contrast, epoxidation with $VO(acac)_2$–Bu^tO_2H [13] was much cleaner and allowed the epoxydiol (10) to be isolated in 83% yield.

Treatment of (10) with acetic anhydride–pyridine in the presence of a small amount of 4-(*NN*-dimethylamino)-pyridine, gave the diacetate (4) in high yield. The same diacetate (4) could also be obtained, in 85% yield, from (9) by diacetylation to give (11) followed by epoxidation with *m*-CPBA.

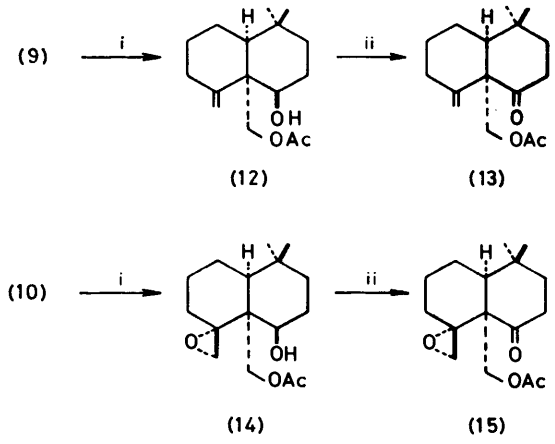


While the ^1H n.m.r. spectrum of (4) was consistent with the structure shown, final unambiguous assignment could only be made after *X*-ray crystallographic determination (see Figure).*

Various other *cis*-decalins (12)—(15) were prepared from (9) and (10) by conventional methods (Scheme 2). Attempted epoxidation of either (12) or (13) with *m*-CPBA to produce (14) and (15) led to complex reaction mixtures. Ways to epimerise the equatorial secondary acetate function in (4) to the axial isomer were not successful, although we did not expect that the product would have high biological activity.

* We thank Professor D. Rogers and Dr. M. A. A. F. de C. T. Carrondo for this result.

When compound (4) was tested for antifeedant activity against *Spodoptera littoralis* and *Heliothis virescens* on *Gosypium hirsatum* δ-pine (cotton leaves) no significant activity was observed. However, when tested against *Locusta migratoria* at 1 000 p.p.m. on GF/A discs containing 5% sucrose, a 72% inhibition of feeding was



SCHEME 2 i, Ac_2O–py; ii, CrO_3·2py

observed. In contrast, the oxoepoxydecalin (15) showed less than half the activity of (4) in a similar screen. This reduced activity for similarly substituted oxo-derivatives also appears to be fairly general for many other related polyoxygenated diterpenes.[14]

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. ^1H N.m.r. spectra were obtained for solutions in $CDCl_3$ (Me_4Si as internal standard). Thin-layer and preparative-layer chromatography were carried out on silica gel (Merck GF_{254} Type 60) and column chromatography on Merck Kieselgel 60 H. Light petroleum refers to the fraction b.p. 40—60 °C. Solutions were dried over magnesium sulphate and solvents by standard techniques.

Preparation of Compound (5).—To a mixture of 4,4-dimethylcyclohexenone (6.25 g, 50 mmol) and CuCN (0.5 g) in diethyl ether (400 ml) at −23 °C, under argon, was added a solution of 5-trimethylsilylpent-4-ynylmagnesium iodide [from the iodide (20 g, 75 mmol) and magnesium (3.5 g, 145 mg-atom)] in diethyl ether (100 ml) during 4 h. Methyl chloroformate (8 ml, 100 mmol) was added and stirring continued for 1 h at −23 °C and 0.5 h at room temperature. 2M-Hydrochloric acid (100 ml) was then added and the organic phase separated and dried. The solvent was removed and the residue chromatographed (light petroleum then 5% diethyl ether–light petroleum) to give *2-methoxycarbonyl-4,4-dimethyl-3-(5-trimethylsilylpent-4-ynyl)cyclohexanone* (5) (9.66 g, 60%); δ 0.13 (9 H, s), 0.93 (3 H, s), 1.02 (3 H, s), 1.2—2.3 (11 H, m), and 3.74 (3 H, s); $\nu_{max.}$ 2 000, 2 140, 1 755, 1 715, 1 660, 1 615, 1 440, 1 280, 1 250, 1 225, 1 205, and 845 cm^{-1} (Found: C, 67.1; H, 9.65. $C_{18}H_{30}O_3Si$ requires C, 67.05; H, 9.4%).

Preparation of Compound (6a).—To a mixture of 4,4-dimethylcyclohex-2-enone (1 g, 8 mmol) and CuCN (0.1 g) in tetrahydrofuran (50 ml) at −23 °C, under argon, was added 5-trimethylsilylpent-4-ynylmagnesium chloride [from

the chloride (3 g, 17 mmol) and magnesium (0.5 g, 21 mg-atom) at reflux] in tetrahydrofuran (50 ml) during 0.5 h. After 1 h methyl chloroformate (0.95 ml, 12 mmol) was added in a single portion and stirring continued for 1 h at −23 °C and 0.5 h at room temperature. 2M-Hydrochloric acid (100 ml) was added and the mixture extracted with diethyl ether (2 × 100 ml). After drying, the solvent was removed to afford 1-*methoxycarbonyloxy*-4,14-*dimethyl*-3-(5-*trimethylsilylpent*-4-*ynyl*)-*cyclohex*-1-*ene* (6a) as an oil which was unstable to chromatography; δ 0.12 (9 H, s), 0.84 (3 H, s), 0.98 (3 H, s), 1.4—2.3 (11 H, m), 3.71 (3 H, s), and 5.29 (1 H, br s); $\nu_{max.}$ 2 930, 2 150, 1 760, 1 250, and 850 cm^{-1} (Found: M^+, 322.1968. $C_{18}H_{30}O_2Si$ requires 322.1964).

Preparation of Compound (6b).—To a mixture of 4,4-dimethylcyclohex-2-enone (0.5 g, 4 mmol) and CuCN (0.05 g) in tetrahydrofuran (25 ml) at −23 °C, under argon, was added 5-trimethylsilylpent-4-ynylmagnesium chloride [from the chloride (1.5 g, 8.5 mmol) and magnesium (0.25 g, 10.5 mg-atom) at reflux] in tetrahydrofuran (20 ml) during 0.5 h. After 0.5 h, trimethylsilyl chloride (2.5 ml) was added and the mixture allowed to warm to room temperature. After removal of the solvent, the resulting oil was triturated with light petroleum. Removal of solvent gave crude 4,4-*dimethyl*-1-*trimethylsilyloxy*-3-(5-*trimethylsilylpent*-4-*ynyl*)-*cyclohex*-1-*ene* (6b) (3 g) which was unstable to chromatography; δ 0.13 (9 H, s), 0.16 (9 H, s), 0.80 (3 H, s), 0.95 (3 H, s), 1.2—2.3 (11 H, m), and 4.77 (1 H, br s); $\nu_{max.}$ 2 800, 2 165, 1 670, 1 250, and 1 050 cm^{-1} (Found: $M^{+\cdot}$, 336.2296. $C_{19}H_{36}OSi_2$ requires M, 336.2305).

Preparation of Compound (7).—To a solution of silver nitrate (8 g) in ethanol–water [150 ml (3 : 1)] was added 2-methoxycarbonyl-4,4-dimethyl-3-(5-trimethylsilylpent-4-ynyl)cyclohexan-1-one (5) (8.5 g, 26 mmol) in ethanol (120 ml) over 0.75 h, with vigorous stirring. After 0.5 h, potassium cyanide (20 g) was added in ethanol–water [180 ml (1 : 1)]. The mixture was stirred for 3 h, poured into water (500 ml), and extracted with CH_2Cl_2 (2 × 200 ml). The solvent was removed, water (250 ml) added, and the organic components extracted with CH_2Cl_2 (2 × 150 ml). After drying and removal of solvent, the residue was subjected to chromatography (5% diethyl ether–light petroleum) to afford 2-*methoxycarbonyl*-4,4-*dimethyl*-3-*pent*-4-*ynylcyclohexan*-1-*one* (7) (4.56 g, 60%); δ 0.9 (3 H, s), 0.99 (3 H, s), 1.2—2.3 (12 H, m), and 3.70 (3 H, s); $\nu_{max.}$ 2 900, 1 750, 1 710, 1 650, 1 615, 1 440, 1 280, 1 225, and 1 205 cm^{-1} (Found: C, 71.87; H, 9.14. $C_{15}H_{22}O_3$ requires C, 71.95; H, 8.86%).

Preparation of Compound (8).—(a) The ketone (7) (4.35 g, 17.5 mmol) was boiled in toluene (60 ml) with zinc iodide (200 mg) until the reaction was complete, as shown by t.l.c. analysis (*ca.* 5 h). The mixture was filtered and the solvent removed under reduced pressure to afford 1β-*methoxycarbonyl*-5,5-*dimethyl*-10-*methylene*-1α,6α-*bicyclo*[4.4.0]-*decan*-2-*one* (8) (4.35 g, 100%); δ 1.06 (3 H, s), 1.13 (3 H, s), 1.25—2.8 (11 H, m), 3.70 (3 H, s), 4.30 (1 H, s), and 4.79 (1 H, s); $\nu_{max.}$ 2 900, 1 720 br, 1 635, and 1 230 cm^{-1} (Found: C, 72.0; H, 9.05. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%.)

(b) The ketone (7) (100 mg, 0.4 mmol) was stirred at room temperature with tin tetrachloride (0.8 ml of a 0.5M solution in CH_2Cl_2) in CH_2Cl_2 (8 ml) for 2.5 h. The mixture was washed with saturated aqueous sodium hydrogen carbonate solution, and the organic phase separated, and dried. Removal of solvent gave the ketone (8) (95 mg, 95%) identical with the above sample.

Preparation of Compound (9).—A solution of the ketone (8) (4.1 g, 16.4 mmol) in diethyl ether (50 ml) was added dropwise to a suspension of lithium aluminium hydride (1.5 g) in diethyl ether (50 ml) at room temperature. After 3 h water (7 ml) was added cautiously until evolution of hydrogen ceased, and this was followed by solid sodium sulphate (25 g). The mixture was filtered and the solid washed several times with ether. Removal of solvent gave 1β-*hydroxymethyl*-5,5-*dimethyl*-10-*methylene*-1α,6α-*bicyclo*-[4.4.0]*decan*-2α-*ol* (9) (3.27 g, 89%), m.p. 132—133 °C (from cyclohexane); δ 0.88 (3 H, s), 1.05 (3 H, s), 1.25—2.2 (11 H, m), 3.25 (1 H, d, J 11 Hz), 3.50 (1 H, d), 3.81 (2 H, br s), 4.19 (1 H, d, J 11 Hz), 5.0 (1 H, s), and 5.45 (1 H, d); $\nu_{max.}$ 3 400, 2 950, 1 635, 1 440, and 1 090 cm^{-1} (Found: C, 75.1; H, 10.85. $C_{14}H_{24}O_2$ requires C, 74.94; H, 10.79%).

Preparation of Compound (4).—To a solution of the alcohol (9) (0.83 g, 3.7 mmol) and $VO(acac)_2$ (50 mg) in benzene (4 ml) was added t-butyl hydroperoxide (0.6 g, 90%) in benzene (5 ml). After 17 h, the solvent was removed and pyridine (15 ml), acetic anhydride (5 ml), and 4-(*NN*-dimethylamino)pyridine (50 mg) were added. Excess of reagents were removed under reduced pressure after 7 h, and the residue was chromatographed on Florisil (5% light petroleum–CH_2Cl_2) to afford 2β-*acetoxy*-1α-*acetoxymethyl*-5,5-*dimethyl*-1α,6α,10Oα-*bicyclo*[4.4.0]*decane*-10-*spiro*-2′-*oxiran* (4) (0.945 g, 79%), m.p. 64 °C (from light petroleum); δ 1.04 (3 H, s), 1.05 (3 H, s), 1.24—1.80 (11 H, m), 1.97 (3 H, s), 2.02 (3 H, s), 2.33 (1 H, d, J 4 Hz), 3.05 (1 H, d, J 4 Hz), 3.82 (1 H, d, J 12 Hz), 4.18 (1 H, d, J 12 Hz), and 4.76 (1 H, t); $\nu_{max.}$ 2 900, 1 745, 1 240, and 1 045 cm^{-1} (Found: C, 66.7; H, 8.65. $C_{18}H_{28}O_5$ requires C, 66.62; H, 8.70%).

Preparation of Compound (11).—A mixture of the alcohol (9) (120 mg, 0.54 mmol), pyridine (1 ml), acetic anhydride (0.5 ml), and 4-(*NN*-dimethylamino)pyridine (5 mg) was stirred at room temperature for 1.5 h. Excess of reagents was removed under reduced pressure and the residue was purified by p.l.c. [ether–light petroleum (1 : 1)] to afford 2β-*acetoxy*-1α-*acetoxymethyl*-5,5-*dimethyl*-10-*methylene*-1α,6α-*bicyclo*-[4.4.0]*decane* (11) (152 mg, 96%), m.p. 56—67 °C; δ 0.97 (3 H, s), 1.08 (3 H, s), 1.35—2.20 (11 H, m), 2.0 (3 H, s), 2.02 (3 H, s), 3.98 (1 H, d, J 12 Hz), 4.34 (1 H, d, J 12 Hz), 4.70 (1 H, d), 5.02 (1 H, br s), and 5.28 (1 H, s); $\nu_{max.}$ 2 950, 1 750, 1 640, 1 240, and 1 050 cm^{-1} (Found: C, 70.1; H, 9.28. $C_{18}H_{28}O_4$ requires C, 70.08; H, 9.16%).

Alternative Preparation of Compound (4).—A mixture of compound (11) (185 mg, 0.6 mmol) and *m*-chloroperbenzoic acid (130 mg, 85%) were stirred overnight in CH_2Cl_2 (10 ml). The organic phase was washed successively with sodium metabisulphite solution, sodium hydrogen carbonate solution, and water. After drying, the solvent was removed to afford the spiro-compound (4) (173 mg, 89%) identical to the previous sample.

Preparation of Compound (12).—A mixture of (9) (0.5 g, 2.2 mmol), pyridine (5 ml), and acetic anhydride (2.5 ml) were stirred for 1 h at room temperature. The excess of reagents was removed under reduced pressure and the residue subjected to p.l.c. (25% light petroleum–ether) to afford 1α-acetoxymethyl-2β-hydroxy-5,5-dimethyl-10-methylene-1α,6α-bicyclo[4.4.0]decane (12) (0.56 mg, 94%), m.p. 68—70 °C (from light petroleum); δ 0.93 (3 H, s), 1.00 (3 H, s), 1.2—2.2 (11 H, m), 2.01 (3 H, s), 2.87 (1 H, br s), 3.48 (1 H, dd, J 11 Hz, 4 Hz), 4.00 (1 H, d, J 11 Hz), 4.35 (1 H, d, J 11 Hz), 4.94 (1 H, br s), and 5.45 (1 H, br s); $\nu_{max.}$ 3 500, 2 930, 1 740, 1 635, 1 240, and 735 cm^{-1}.

Preparation of Compound (13).—A solution of compound

(12) (0.134 g, 0.5 mmol) in CH_2Cl_2 (10 ml) was stirred overnight with Collins [15] reagent (1.3 g). The mixture was diluted with ether (50 ml) and filtered through a pad of Celite. The solvent was removed and the residue subjected to p.l.c. [ether–light petroleum (1 : 1)] to afford 1α-*acetoxymethyl*-5,5-*dimethyl*-10-*methylene*-1α,6α-*bicyclo*[4.4.0]*decan*-2-*one* (13) (0.125 g, 95%); δ 1.05 (3 H, s), 1.20 (3 H, s), 1.6—1.26 (9 H, m), 1.98 (3 H, s), 2.2–2.5 (2H, m), 4.08 (1 H, d, *J* 10 Hz), 4.53 (1 H, d, *J* 10 Hz), 4.43 (1 H, s), and 4.87 (1 H, s); $\nu_{max.}$ 2 920, 1 750, 1 720, 1 230, and 1 040 cm^{-1} (Found: C, 72.45; H, 9.3. $C_{16}H_{24}O_3$ requires C, 72.67; H, 9.16%).

Preparation of Compound (14).—The epoxydiol (10) was prepared from the alcohol (9) (225 mg, 1 mmol) as previously described. The solvent was removed and replaced by pyridine (3 ml) and acetic anhydride (1 ml). The mixture was stirred for 0.5 h and the excess of reagents removed under reduced pressure. The residue was chromatographed on Florisil (CH_2Cl_2) to afford 1α-*acetoxymethyl*-2β-*hydroxy*-5,5-*dimethyl*-1α,6α,10Oα-*bicyclo*[4.4.0]*decane*-10-*spiro*-2′-*oxiran* (14) (130 mg, 46%), m.p. 96—98 °C; δ 0.97 (3 H, s), 1.05 (3 H, s), 1.2—1.8 (11 H, m), 2.07 (3 H, s), 2.57 (1 H, d), 3.4—3.6 (3 H, m), and 4.41 (2 H, d); $\nu_{max.}$ 3 450, 2 940, 1 750, 1 235, and 1 080 cm^{-1} (Found: C, 67.85; H, 9.25. $C_{16}H_{26}O_4$ requires C, 68.05; H, 9.28%).

Preparation of Compound (15).—Compound (14) (130 mg, 0.46 mmol) was stirred overnight with Collins reagent [15] (1.3 g) in CH_2Cl_2 (10 ml). Ether (50 ml) was added and the mixture filtered through a pad of Celite. Purification on Florisil (eluting with CH_2Cl_2) gave 1α-*acetoxymethyl*-5,5-*dimethyl*-2-*oxo*-1α,6α,10Oα-*bicyclo*[4.4.0]*decane*-10-*spiro*-2′-*oxiran* (15) (85 mg, 66%), m.p. 101—103 °C (from cyclohexane); δ 1.20 (6 H, s), 1.50—1.35 (9 H, m), 1.97 (3 H, s), 2.25—2.6 (4 H, m), 4.08 (1 H, d, *J* 11 Hz), and 4.62 (1 H, d, *J* 11 Hz); $\nu_{max.}$ 2 930, 1 750, 1 715, 1 240, and 1 045 cm^{-1} (Found: C, 68.65; H, 8.8. $C_{16}H_{24}O_4$ requires C, 68.53; H, 8.63%).

We thank the S.R.C. for a research studentship (to W. P. J.) and I.C.I. Plant Protection, Jealotts Hill, for additional financial support.

[0/1737 *Received*, 11*th November*, 1980]

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