Synthesis of The Natural Enantiomers of Irones from (+)-Citronellal

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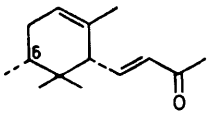
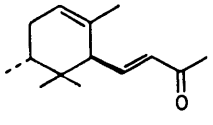
Some irone isomers with the natural chirality have been synthesised from (+)-citronellal (7). (+)-Methyl citronellate (21) obtained from compound (7) was methylated stepwise to give methyl 2,2,3,7-tetramethyloct-6-enoate (23). After hydrolysis of the ester (23), the resulting acid was converted into the corresponding acyl chloride, which was then cyclised by means of tin(IV) chloride to give 2,2,3-trimethyl-6-(1-chloro-1-methylethyl)cyclohexanone (24). The cyclohexanone (24) was dehydrochlorinated, reduced, acetylated, and then ozonised to give 2-acetoxy-3,3,4-trimethylcyclohexanone (27). The Wittig reaction of the ketone (27) with methoxymethylenetriphenylphosphorane followed by hydrolysis and elimination of acetic acid provided 3,3,4-trimethylcyclohexene-1-carbaldehyde (28). The vinyl ether of an allylic alcohol obtained by reduction of the aldehyde (28) was thermolysed to give the key intermediate, 1-(2,2,3-trimethyl-6-methylenecyclohexyl)acetaldehyde (13), stereoselectively. Elongation of the side-chain in (13) afforded (+)-*trans*-γ-irone (32a) as the major product. Treatment of the irone (32a) with phosphoric acid yielded (−)-*trans*-α-irone (2).

IRONES are the major fragrant constituents of orris oil, which is used in the preparation of perfumes of high quality, and four isomers, (+)-*cis*-α- (1), (−)-*trans*-α- (2), (+)-β- (3), and (+)-*cis*-γ-irone (4), have been isolated from the natural source. In 1971, approximately 80 years after the discovery of irones, Rautenstrauch and



(1)



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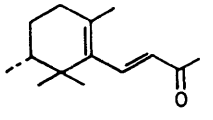

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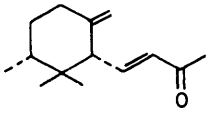
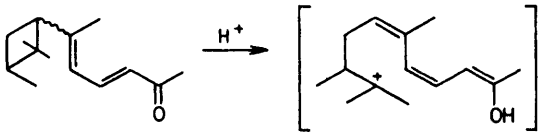


(4)

Ohloff [1] established their absolute stereochemistry by a chemical correlation with (−)-camphor, showing that all the isomers had the 6*R*-configuration. On the other hand, most of the previous syntheses of irones involved polyene cyclisation culminating in the racemic compounds.[2] Of these, Eschinazi synthesised irones (6) by acidic ring-opening of the cyclobutane derivative (5) obtained from α-pinene followed by cyclisation.[3] Unfortunately, he reported no optical rotations of the irone isomers separated, although a low value recorded for a mixture of the irones [3a] allows us to surmise that considerable racemisation occurred during the acid treatment.

In this paper we describe the synthesis of some irone isomers [(1)—(3)] and (32a)] having the natural chirality starting from the readily available, inexpensive (+)-citronellal (7) (80% enantiomeric excess) [4] of citronella oil *via* a route in which the *R*-configuration of the C-3 methyl in compound (7) was preserved throughout the synthesis.

At the outset of this research, two routes (*a*) and (*b*) outlined below, were envisaged. In route (*a*) it appeared that the ene reaction or acid-catalysed cyclisation of the aldehyde (8) would be ideally suited for obtaining the desired stereochemistry and functionality of the irones (10). In this route, extension of the side-chain in the starting material (7) followed by geminal dimethylation at C-2 and selective oxidation of the isopropylidene group of the dimethylation product leading to compound (8), is required.



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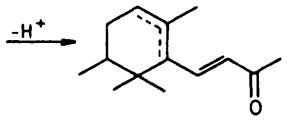
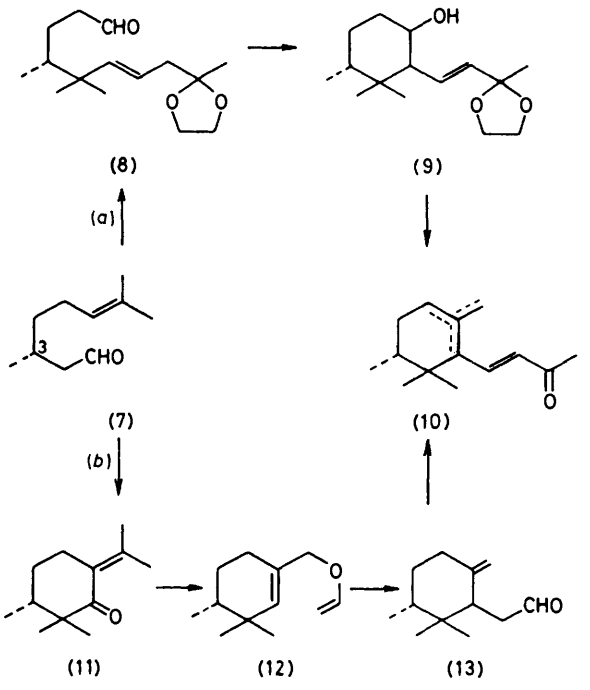


(6)

In contrast, route (*b*) commenced with the cyclisation of the dimethylated citronellal (or its equivalent) to the cyclohexanone (11), and we considered that the Claisen rearrangement of the vinyl ether (12), obtainable from the ketone (11), would offer an efficient synthesis of irones (10), particularly γ-irones. As seen, an important feature is that no racemisation is presumable in either of the routes.

We first explored route (*a*), because it seemed to be a shorter course than route (*b*). Introduction of two methyl groups at C-2 in citronellal (7) was performed by stepwise methylation of the cyclohexylimine (14) (Scheme 1). Employing the usual procedure, the first methylation afforded the monomethylated product (15) quantitatively, and the crude product was successively methylated in the presence of hexamethylphosphoramide to give the dimethylated product (16) in good

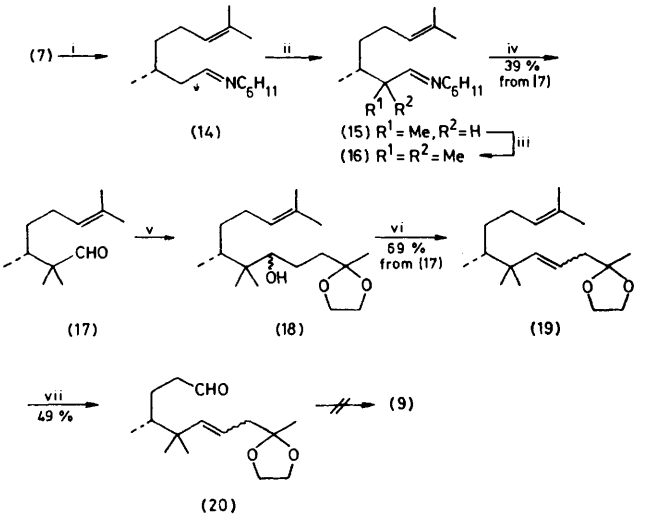
yield. The imine (16) was readily hydrolysed by chromatographic treatment on silica gel to yield the unstable aldehyde (17). Introduction of a substituent equivalent to an oxobutyl-group into compound (17) was achieved by reaction with the Grignard reagent of 2-methyl-2-(2-bromoethyl)-1,3-dioxolan.[5] The alcohol (18), obtained as a diastereoisomeric mixture, was converted,



via the corresponding methanesulphonates, into the olefin (19), which consisted of the *E*- and *Z*-isomers in an approximate ratio of 1 : 1 (g.l.c.). To derive the unsaturated aldehyde (20), the olefin mixture (19) was selectively epoxidised with *m*-chloroperbenzoic acid (*m*-CPBA) under controlled conditions, and the resulting mono-epoxide was then oxidised with periodic acid. Spectral data supported the proposed structure for compound (20) and demonstrated that the aldehyde was inevitably a mixture of geometrical isomers.

Having obtained the olefinic aldehyde (20), its ene reaction was then examined. However, contrary to expectations, the reaction in the vapour phase at temperatures of 250—300 °C and also the liquid-phase reaction at a variety of temperatures (210—370 °C), always resulted in the formation of complex mixtures. As an alternative, the zinc bromide-catalysed cyclisation[6] of (20) was investigated, but the results were disappointing because of the formation of intractable mixtures.

After the fruitless outcome of route (*a*), we turned our attention to route (*b*). (+)-Methyl citronellate,[4,7] obtained from compound (7) by Jones oxidation followed by esterification, was submitted to stepwise methylation to afford the dimethylated ester (23) *via* the monomethylated ester (22) (Scheme 2). Alkaline hydrolysis of the ester (23) with an excess of potassium hydroxide solution produced the corresponding acid quantitatively. The acid obtained was converted into an acyl chloride, which was then treated with tin(IV) chloride[8] in dichloromethane to give the cyclic chloroketone (24) as an epimeric

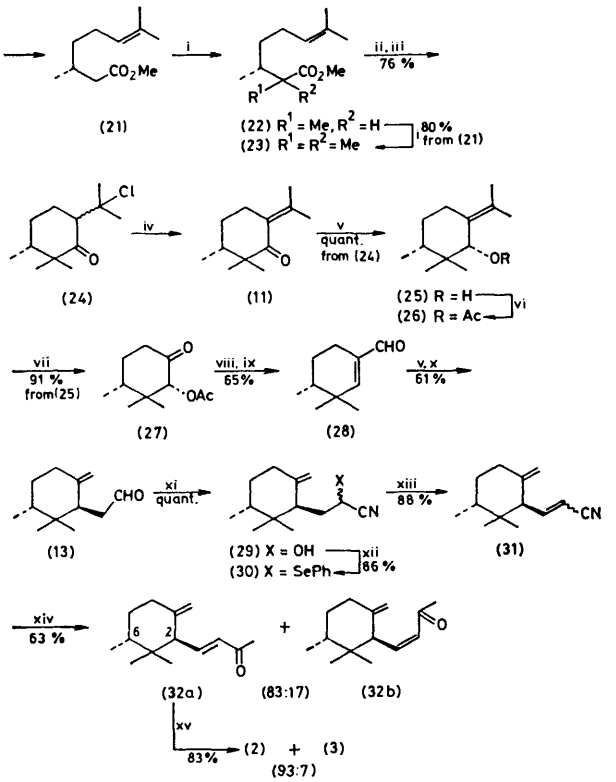


SCHEME 1 *Reagents:* i, $C_6H_{11}NH_2$, Na_2CO_3, Et_2O; ii, LDA, MeI, THF; iii, LDA, MeI, HMPA, THF; iv, silica gel; v, MeC-$(OCH_2)_2$·$(CH_2)_2$MgBr, THF; vi, MsCl, C_5H_5N then Li_2CO_3, DMA; vii, *m*-CPBA (1 equiv.), CH_2Cl_2 then H_5IO_6, THF

mixture with respect to the chloroisopropyl group (^{1}H n.m.r.). Dehydrochlorination of compound (24) provided the homogeneous enone (11). The reduction of the enone (11) with lithium aluminium hydride proceeded stereoselectively and the stereochemistry of the resulting hydroxy-group was, on the basis of a presumed attack at the less hindered face of the hydride, assigned as (25). The acetate (26) was ozonised to afford the crystalline keto-acetate (27). In order to extend the keto-group of compound (27) by a one-carbon unit, we examined the Wittig reaction of the ketone (27) with methoxymethylenetriphenylphosphorane under a variety of reaction conditions. Conventional conditions (n-butyl-lithium in tetrahydrofuran, sodium hydride in dimethyl sulphoxide *etc.*) resulted in poor yields of the desired product, while a good and reproducible yield was obtained from the reaction in toluene containing a crown ether. The product was hydrolysed with acid to give a β-acetoxy-aldehyde, which was then treated with neutral alumina to provide the unsaturated aldehyde (28), resulting from the elimination of acetic acid, in good overall yield from the ketone (27).

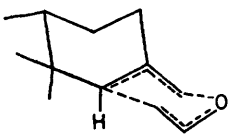
To examine the proposed Claisen rearrangement, the aldehyde (28) was reduced with lithium aluminium hydride and the resulting allylic alcohol was converted into the vinyl ether (12). Thermolysis of compound (12) in a sealed tube proceeded smoothly to give the aldehyde (13) as the sole product. The highly selective formation of compound (13) in the rearrangement can be better rationalised by the preferred transition state (12a) to the alternative, more congested transition state (12b). The

trans-stereochemistry shown by the formula (13) was thus tentatively assigned to this aldehyde, and this surmise was eventually proven by securing *trans*-γ-irone (32a).



SCHEME 2 *Reagents:* i, LDA, MeI, THF; ii, KOH, EtOH; iii, $(COCl)_2$, PhH then $SnCl_4$, CH_2Cl_2; iv, Li_2CO_3, DMA; v, LAH, Et_2O; vi, Ac_2O, C_5H_5N; vii, O_3; viii, Ph_3P=CHOMe, PhMe, 18-crown-6; ix, $HClO_4$ then Al_2O_3; x, EtOCH=CH_2, Hg(AcO)$_2$ then heat; xi, KCN, HOAc, EtOH; xii, MsCl, C_5H_5N then PhSeNa, EtOH; xiii, H_2O_2, C_5H_5N, CH_2Cl_2; xiv, MeLi, Et_2O; xv, H_3PO_4

The remaining task was the introduction of a substituent which could eventually be transformed into the oxobutyl-group present in irones. Since the reaction of the aldehyde (13) and lithiated 2-methyl-1,3-dithian failed to give compound (33), compound (13) was treated with hydrogen cyanide to give the cyanohydrin (29) as a diastereoisomeric mixture. Although an attempt to obtain the unsaturated nitrile (31) by base treatment of the methanesulphonate of compound (29) led to the formation of a complex mixture, the selenenylated nitrile (30) was obtained in high yield from the methanesulphonate on treatment with benzeneselenolate. Oxidation of compound (30) with hydrogen peroxide gave the unsaturated nitrile (31), the g.l.c. and ^{1}H n.m.r. properties of which indicated that it was a mixture of *E*- and *Z*-isomers (82 : 18), the former predominating (δ 5.29, *J* 16 Hz). The mixture was then treated with methyl-lithium to afford a mixture of ketones, from which highly fragrant (+)-*trans*-γ-irone (32a) * and its *Z*-isomer (32b) were isolated by chromatography. The former irone gave i.r. and ^{1}H n.m.r. spectra resembling those of natural (+)-*cis*-γ-irone (4).[1] However, the spectra were not superimposable and our compound showed a much higher optical rotation value ($[\alpha]_D$ +57°) than that of the natural compound [1] ($[\alpha]_D$ +2°). To determine the structure of the irone (32a) unambiguously, isomerisation of it to the known irone isomers was attempted. Thus, treatment of (32a) with 85% phosphoric acid gave, in high yield, a mixture of (+)-*trans*-α-irone (2) and (+)-β-irone (3) in a ratio of 93 : 7 (g.l.c.).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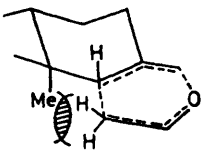
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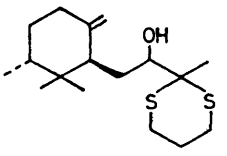
(33)

The former product was identified spectroscopically (i.r., ^{1}H n.m.r., and mass spectrometry), and the latter by g.l.c.–mass spectrometry. It is worthy of note that no *cis*-α-irone (1) was found in the isomerisation product of compound (32a). A similar observation was made by Rautenstrauch and Ohloff,[1] who observed no formation of *trans*-α-irone (2) from *cis*-γ-irone on treatment with acid. These facts obviously demonstrated that these α- and β-irones were kinetic products of γ-irones in the acid isomerisation.

Since the isomerisation of *trans*-α-irone (2) with base to *cis*-α- and β-irones (3) had been reported,[1] the synthesis of irones (1), (2), (3), and (32a) was thus complete.

EXPERIMENTAL

I.r. spectra were obtained, unless otherwise stated, as liquid films with a JASCO A-3 spectrophotometer. ^{1}H N.m.r. spectra were recorded with a JEOL C-60HL (60 MHz) or a JEOL PS-100 (100 MHz) spectrometer; throughout † indicates that δ values are at 100 MHz. Mass spectra were determined with a Shimazu LKB-9000 (low resolution) or JEOL JMS-OlSG-2 (high resolution) mass spectrometer and optical rotations with a JASCO DIP-4S spectropolarimeter. G.l.c. analyses were performed with a JEOL 750 gas chromatograph (10% SE30 or OV17, 2 m). Solvent systems for development of the major reaction products in a moderate R_F range (0.3—0.7) are described for preparative thin-layer chromatography (t.l.c.) on silica gel. Throughout, ether refers to diethyl ether.

2,2,3R,7-Tetramethyloct-6-enal (17). — Cyclohexylamine (3.44 ml, 39 mmol) was added dropwise to a stirred mixture of freshly distilled citronellal (7) [4.63 g, 30 mmol, $[\alpha]_D^{25}$ +12.0° (neat)[4]], anhydrous sodium carbonate (5.57 g, 52.5

* For an alternative synthesis of (±)-γ-irone, see ref. 9.

mmol), and dry ether (20 ml) at room temperature under argon. After being stirred for 17 h, the mixture was filtered and the filtrate was evaporated. The residue was distilled to give the cyclohexylimine (14) (6.73 g, 88%), b.p. 112—115 °C/0.8 mmHg; $\nu_{max.}$ 1 670 cm^{-1} (imine); $\delta(CCl_4)$ 0.93 (3 H, d, *J* 6 Hz, CH*Me*), 1.57 and 1.65 (2 × 3H, each br s, $=CMe_2$), 5.0 (1 H, t, *J* 6 Hz, C=CH), and 7.85 (1 H, t, *J* 5 Hz, N=CH).

A solution of compound (14) (4.59 g, 19.5 mmol) in dry tetrahydrofuran (THF) (30 ml) was added dropwise to a stirred solution of lithium di-isopropylamide (LDA), prepared from di-isopropylamine (23.4 mmol) and n-butyl-lithium (23.4 mmol) in THF (30 ml), at −60 °C under argon. The mixture was gradually warmed to 0 °C during 2 h and then cooled to −78 °C. Methyl iodide (2.19 ml, 35 mmol) was added and the mixture was stirred for an additional 2 h at the same temperature. After dilution with water, the product was extracted with ether, and the extract was washed with water and brine, and dried. Evaporation of the solvent gave the monomethylated compound (15) (4.86 g) as an oil, which was used in the next step without purification.

A solution of the crude compound (15) (4.86 g) in THF (30 ml) was added dropwise to a solution of LDA, prepared on the same scale as described above, at −50 °C, and then hexamethylphosphoramide (4.24 ml) was added. After being warmed, the mixture was stirred at 3—5 °C overnight and methyl iodide (2.2 ml, 35 mmol) was added. After being stirred for 1 h at 0 °C, water was added and the product was extracted with ether. The extract was washed with water and brine, and dried. The residue was distilled to afford the dimethylated imine (16) (3.50 g, 68%) as an oil, b.p. 120—130 °C (bath temp.)/0.6 mmHg; $\delta(CCl_4)$ 0.83 (3 H, d, *J* 6 Hz, CH*Me*), 0.97 (6 H, s, CMe_2), 1.58 and 1.67 (2 × 3 H, each br s, $=CMe_2$), 5.0 (1 H, t, *J* 7 Hz, C=CH), and 7.42 (s, 1 H, N=CH).

The dimethylated imine (16) (112 mg) was placed on a silica-gel t.l.c. plate at room temperature for 20 min and the plate was eluted with hexane–ether (10 : 1) to give the aldehyde (17) [50 mg, 39% from (7)], $\nu_{max.}$ 2 690 and 1 720 (formyl), and 1 660 cm^{-1} (olefin); $\delta(CCl_4)$ 0.87 (3 H, d, *J* 7 Hz, CH*Me*), 0.93 (6 H, s, CMe_2), 1.58 and 1.67 (2 × 3 H, each br s, $=CMe_2$), 5.0 (1 H, t, *J* 6 Hz, =CH), and 9.28 (1 H, s, CHO).

The aldehyde (17) was not stable enough for the preparation of a sample for microanalysis.

E- *and* Z-6,6,7R,11-*Tetramethyldodeca*-4,10-*dien*-2-*one Ethylene Acetals* (19).—2-(2-Bromoethyl)-2-methyl-1,3-dioxolan [5] (439 mg, 2.25 mmol) was slowly added to a stirred mixture of magnesium turnings (164 mg, 6.75 g-atom), 1,2-dibromoethane (15 μl), and THF (0.8 ml) at room temperature under argon. When the reaction started, the mixture was diluted with THF (3 ml). After completion of the addition of the reagent, the aldehyde (17) (273 mg, 1.5 mmol) in THF (1 ml) was added and the mixture was stirred for an additional 1.5 h at room temperature. Cold aqueous ammonium chloride was added to the mixture at 0 °C, and the product was extracted with ether. Work-up afforded an oil, which was purified by t.l.c. [light petroleum–ether (2 : 1) as solvent] to give the alcohol (18) (426 mg, 95%), $\nu_{max.}$ 3 450 cm^{-1} (hydroxy).

A solution of the alcohol (18) (1.67 g, 5.67 mmol) and methanesulphonyl chloride (1.38 ml, 17.5 mmol) in pyridine (15 ml) was stirred at room temperature overnight and then poured into ice–water. The product was extracted with ether, and the extract was washed with 10% aqueous copper sulphate, water, and brine. Work-up gave a crude methanesulphonate (1.75 g), which was dissolved in dry dimethylacetamide (40 ml). Lithium carbonate (4.40 g, 59.5 mmol) was added to the solution and the mixture was stirred at 130 °C for 3 h. After filtration through a Celite pad with ether, the filtrate was extracted with ether. The residue obtained from the extract gave, on distillation, the olefin (19) [1.10 g, 67% from the aldehyde (17)] as an oil, b.p. 130 °C (bath temp.)/0.5 mmHg; $\nu_{max.}$ 1 640 (olefin), 1 060 (acetal) cm^{-1}; $\delta(CCl_4)$ 0.8 (3 H, d, *J* 5 Hz, CH*Me*), 0.9 (6 H, br s, CMe_2), 1.18 (3 H, s, OCMeO), 1.53 and 1.62 (2 × 3 H, each br s, $=CMe_2$), 3.77 [4 H, s, $O(CH_2)_2O$], and 4.67—5.3 (3 H, m, =CH) (Found: C, 77.0; H, 11.5. $C_{18}H_{32}O_2$ requires C, 77.1; H, 11.5%).

G.l.c. analysis of compound (19) showed two peaks in a ratio of approximately 1 : 1.

E- *and* Z-4R,5,5-*Trimethyl*-9-*oxodec*-6-*enal* 9-*Ethylene Acetals* (20).—*m*-CPBA (702 mg, 3.25 mmol) was added to a solution of the olefin (19) (828 mg, 2.96 mmol) in dichloromethane (30 ml) at 0 °C, and the mixture was stirred for 1 h at the same temperature. After dilution with ether, the mixture was washed with aqueous sodium hydrogencarbonate, water, and brine, and dried. The residue obtained on evaporation was purified by t.l.c. [benzene–ether (3 : 1) as solvent] to give an oily mono-epoxide (701 mg, 80%), $\nu_{max.}$ 1 640 (olefin), 1 260 (oxiran) cm^{-1}; δ† (CCl_4) 0.8—1.1 (9 H in total, complex methyl signals), 1.20—1.24 (9 H in total, each s, methyls on the oxiran ring and OCMeO), 2.44 (1 H, t, *J* 6 Hz, H on the oxiran ring), 3.80 and 3.81 [4 H in total, each s, $O(CH_2)_2O$], 4.67 (1 H, =CH), and 5.27 (1 H, m, =CH).

A mixture of the above epoxide (701 mg, 2.37 mmol), periodic acid (540 mg, 2.37 mmol), and THF (30 ml) was stirred at 0 °C for 1 h, and then poured into water. The product was extracted with ether, and the extract was washed with aqueous sodium hydrogencarbonate, water, and brine. Work-up gave an oil, which was purified by t.l.c. [benzene–ether (5 : 1) as solvent] to afford the aldehyde (20) as an oil [368 mg, 49% from (19)], $\nu_{max.}$ 2 720 and 1 720 (formyl), 1 640 (olefin), 1 060 (acetal) cm^{-1}; δ† (CCl_4) 0.8—1.04 (9 H in total, complex methyl signals), 1.2 (3 H, s, OCMeO), 3.78 [4 H, s, $O(CH_2)_2O$], 4.7 (1 H, m, =CH), 5.3 (1 H, m, =CH), and 9.62 (1 H, br s, CHO).

This oil gave no satisfactory microanalytical data.

Attempted Cyclisation of the Aldehyde (20).—(*a*) *Thermolysis in the vapour phase.* The aldehyde (20) (69 mg), dissolved in ether, was slowly fed into a Pyrex tube packed with glass helices, which was maintained at 250—300 °C in a furnace, in a slow stream of nitrogen, and the pyrolysate (51 mg) was trapped in a cold receiver. T.l.c. showed that the pyrolysate was a complex mixture.

(*b*) *Thermolysis in liquid phase.* The aldehyde (20) (59 mg), sealed in a glass tube, was heated at 210—250 °C (350—370 °C in another run) for 1 h. The product was a complex mixture (t.l.c.).

(*c*) *Zinc bromide cyclisation.* A mixture of (20) (45 mg), zinc bromide (37 mg), and dichloromethane (2 ml) was stirred at room temperature. Since the reaction was slow, the mixture was heated at *ca.* 60 °C for 3 h. An oil, obtained on work-up, was a complex mixture (t.l.c.).

Methyl Citronellate (21).—Citronellal was oxidised with a slight excess of Jones reagent in acetone at 0 °C and the acidic product was esterified with methanol–sulphuric acid or diazomethane to give the ester (21) (59—67% overall

yield), b.p. 71—73 °C/1 mmHg; $\nu_{max.}$ 1 740 cm^{-1} (ester); δ† ($CDCl_3$) 0.96 (3 H, d, *J* 7 Hz, CH*Me*), 1.60 and 1.70 (2 × 3 H, each s, $=CMe_2$), 3.66 (3 H, s, OMe), and 5.10 (1 H, t, *J* 7 Hz, =CH) (Found: C, 71.6; H, 11.2. $C_{11}H_{20}O_2$ requires C, 71.7; H, 10.9%).

Methyl 2,2,3R,7-*Tetramethyloct*-6-*enoate* (23).—A solution of the ester (21) (14.49 g, 78.7 mmol) in THF (60 ml) was added to a stirred solution of LDA, prepared from di-isopropylamine (16.5 ml, 118 mmol) and n-butyl-lithium (94.4 mmol) in THF (100 ml), at −60 °C under argon and stirred for an additional 1 h, while the temperature was allowed to rise to −40 °C. Methyl iodide (9.8 ml, 157 mmol) was added dropwise to the solution at −60 °C, and the mixture was further stirred for 1 h at −40 °C. After quenching with water, the product was extracted with ether. Work-up of the extract followed by distillation gave the monomethylated ester (22) (13.46 g), b.p. 68—70 °C/1 mmHg.

To a solution of LDA prepared from di-isopropylamine (5.9 ml, 42 mmol) and n-butyl-lithium (33.6 mmol) in THF (40 ml) was added, dropwise, the ester (22) (5.54 g, 28.0 mmol) in THF (30 ml) at −50 °C under nitrogen with stirring. The mixture was further stirred for 2 h while it was gradually warmed to 0 °C. The mixture was cooled to −60 °C, methyl iodide (4 ml, 64 mmol) was added to it, and stirring was continued for 1 h. Water was added and the product was extracted with ether. The extract was worked up and the residue was chromatographed on a silica-gel column to afford, on elution with hexane–ether (20 : 1), the dimethylated ester (23) [5.54 g, 80% from compound (21)], b.p. 85—88 °C/2 mmHg; $[\alpha]_D^{25}$ +27.0° (*c* 0.41 in dichloromethane); $\nu_{max.}$ 1 740 cm^{-1} (ester); δ† ($CDCl_3$) 0.85 (3 H, d, *J* 7 Hz, CH*Me*), 1.08 (6 H, s, CMe_2), 1.60 and 1.70 (2 × 3 H, each s, $=CMe_2$), 3.64 (3 H, s, OMe), and 5.08 (1 H, t. *J* 8 Hz, =CH) (Found: C, 73.3; H, 11.2. $C_{13}H_{24}O_2$ requires C, 73.5; H, 11.4%).

Diastereoisomeric Mixture of 2,2,3R-*Trimethyl*-6-(1-*chloro*-1-*methyl*)*ethylcyclohexanone* (24).—A solution of (23) (5.36 g, 25.3 mmol), potassium hydroxide (14.2 g, 253 mmol) dissolved in a minimum quantity of water, and ethanol (120 ml) was refluxed for 3 days under argon. Ether was added to the residue obtained on evaporation, and the mixture was extracted with water. The aqueous layer was acidified with dilute hydrochloric acid and the acidic product was extracted with ether. Work-up gave an oily acid (4.98 g), $\nu_{max.}$ *ca.* 2 400 and 1 700 cm^{-1} (carboxyl); δ (CCl_4) 0.91 (3 H, d, *J* 7 Hz, CH*Me*), 1.10 (6 H, s, CMe_2), 1.59 and 1.69 (2 × 3 H, each s, $=CMe_2$), 5.05 (1 H, t, *J* 6 Hz, =CH), 11.8—12.2 (1 H, br signal, CO_2H).

Oxalyl chloride (17 ml, 195 mmol) was added to a solution of the above acid (12.88 g, 6.51 mmol) in dry benzene (250 ml) at room temperature, and the mixture was stirred at the same temperature for 1.5 h and then refluxed for 3 h. The resulting mixture was evaporated, and the residue was dissolved in dry dichloromethane (250 ml) and cooled to −65 °C. Tin(IV) chloride (7.5 ml, 6.51 mmol) in dichloromethane (15 ml) was added dropwise to the above solution under argon. After the mixture had been stirred for an additional 3 h at −65 to −50 °C, a saturated solution of sodium hydrogencarbonate was added at −50 °C; the mixture was then warmed to 0 °C, and filtered through a Celite pad. The filtrate was extracted with ether and the product obtained was chromatographed on a Florisil column (hexane as solvent) to give the ketone (24) as an oil (10.76 g, 76%), b.p. 70 °C (bath temp.)/5 mmHg; $\nu_{max.}$ 1 710 cm^{-1} (ketone); δ† (CCl_4) 0.84—1.04 (9 H in total, complex methyl signals), 1.64 and 1.71 (2 × 3 H, each s, $CClMe_2$), and 2.92 and 3.04 (1 H in total, each m, *J* 5 and 12 Hz, O=CCH). (Found: C, 66.4; H, 9.7; Cl, 16.3. $C_{12}H_{21}ClO$ requires C, 66.5; H, 9.8; Cl, 16.4%).

6-*Isopropylidene*-2,2,3R-*trimethylcyclohexanone* (11).—A mixture of the ketone (24) (2.50 g, 11.5 mmol), lithium carbonate (8.50 g, 115 mmol), and dry dimethylacetamide (DMA) (100 ml) was stirred at 100 °C for 6 h, and then filtered. An ethereal solution of the filtrate was washed with water, and the aqueous layer was extracted with ether. Work-up of the combined organic layers gave the crude ketone (11) (2.06 g) as an oil. A pure sample of compound (11) was obtained by t.l.c. [hexane–ether (10 : 1) as solvent], $\nu_{max.}$ 1 690 and 1 630 cm^{-1} (conjugated enone); δ(CCl_4) 0.8—1.2 (9 H in total, complex methyl signals), and 1.73 (6 H, br s, $=CMe_2$) (Found: M^+, 180.1543. $C_{12}H_{20}O$ requires *M*, 180.1513).

6-*Isopropylidene*-2,2,3R-*trimethyl*-1S-*cyclohexanol* (25).—To a solution of the crude ketone (11) (2.06 g, 11.4 mmol) in dry ether (100 ml) was added lithium aluminium hydride (433 mg, 11.4 mmol) at 0 °C, and the mixture was stirred at the same temperature for 30 min. After decomposition of the excess of reagent with wet ether followed by water, the mixture was filtered through a Celite pad, and the filtrate was dried and evaporated to give an oil. Distillation of the oil, b.p. 80 °C (bath temp.)/5 mmHg, afforded the alcohol (25) (2.13 g, quantitative yield from the ketone (24), $\nu_{max.}$ 3 500 cm^{-1} (OH); δ† (CCl_4) 0.83 and 1.01 (2 × 3 H, each s, CMe_2), 1.13 (3 H, d, *J* 6 Hz, CH*Me*), 1.70 and 1.73 (3 H, each s, $=CMe_2$), and 4.10 (1 H, s, OCH). (Found: C, 78.9; H, 12.4. $C_{12}H_{22}O$ requires C, 79.1; H, 12.2%).

2S-*Acetoxy*-3,3,4R-*trimethylcyclohexanone* (27).—A mixture of the alcohol (25) (2.13 g, 11.4 mmol), acetic anhydride (8.8 mmol), and pyridine (22 ml) was stirred at 70 °C for 8 h. After ice–water had been added, the mixture was vigorously stirred for 2 h at 0 °C ,and then extracted with ether. The extract was washed with 10% aqueous copper sulphate, water, and brine, and worked up. The product was distilled, b.p. 70 °C (bath temp.)/5 mmHg, to give the ester (26) (2.53 g), $\nu_{max.}$ 1 740 cm^{-1} (acetate); δ† (CCl_4) 0.92 (6 H, s, CMe_2), 1.12 (3 H, d, *J* 7 Hz, CH*Me*), 1.71 and 1.78 (2 × 3 H, each s, $=CMe_2$), 1.98 (3 H, s, O=CMe), and 5.38 (1 H, s, AcOC*H*) (Found: C, 74.6; H, 10.6. $C_{14}H_{24}O_2$ requires C, 75.0; H, 10.8%).

Ozone was passed through a solution of compound (26) (2.53 g, 11.4 mmol) in dichloromethane (100 ml) at −78 °C and the ozonised solution was agitated with water (20 ml) at 60 °C for 1 h. The product obtained on work-up was chromatographed on a silica-gel column [hexane–ether (2 : 1) as solvent] to give the keto-ester (27) [2.12 g, 91% from (25)] as crystals, m.p. 70—71 °C (from hexane); $[\alpha]_D^{25}$ +41.0° (*c* 0.4 in dichloromethane); $\nu_{max.}$ (CCl_4) 1 760 (acetate) and 1 740 cm^{-1} (ketone); δ(CCl_4) 0.73 and 1.03 (2 × 3 H, each s, CMe_2), 0.98 (3 H, d, *J* 7 Hz, CH*Me*), 2.08 (3 H, s, O=CMe), and 4.75 (1 H, s, AcOC*H*) (Found: M^+, 198.1229. $C_{11}H_{18}O_3$ requires *M*, 198.1254).

3,3,4R-*Trimethylcyclohexene*-1-*carbaldehyde* (28).—n-Butyl-lithium (15 mmol) was added to a stirred mixture of methoxymethyltriphenylphosphonium chloride (6.86 g, 20 mmol) and dry toluene (40 ml) at room temperature under argon, and the mixture was further stirred for an additional 2 h at the same temperature. A solution of the keto-ester (27) (2.00 g, 1.01 mmol) in toluene (20 ml) was added dropwise to the above solution at room temperature and then 18-crown-6 (1.06 g, 4.02 mmol) was added. After being

stirred overnight, the mixture was diluted with ether and washed with water. The organic layer was evaporated to give an oil, which was dissolved in ether (40 ml). Hydrogen peroxide (30%; 10 drops) was then added at 0 °C and the mixture was stirred at room temperature for 30 min. After filtration through a neutral alumina column, the filtrate was concentrated and the residue was dissolved in ether (40 ml) containing perchloric acid (5 ml). After being stirred for 40 min at room temperature, the mixture was poured into cold water. The product was extracted with ether, and the extract was washed with aqueous sodium hydrogencarbonate, water, and brine. The residue obtained on evaporation was passed through a neutral alumina column [pentane–ether (2 : 1) as solvent]. The eluate was evaporated and the residue was purified by t.l.c. [hexane–ether (7 : 1) as solvent] to afford the aldehyde (28) as an oil (990 mg, 65%), $\nu_{max.}$ 2 710 and 1 690 (formyl), and 1 645 cm^{-1} (olefin); δ† (CCl_4) 0.94 (3 H, d, *J* 8 Hz, CH*Me*), 0.94 and 1.11 (2 × 3 H, each s, CMe_2), 6.30 (1 H, br s, =CH), and 9.41 (1 H, s, CHO). 2,4-Dinitrophenylhydrazone derivative, m.p. 155—157 °C (Found: C, 57.9; H, 6.1; N, 16.9. $C_{16}H_{20}N_4O_4$ requires C, 57.8; H, 6.1; N, 16.9%).

1R-(2,2,3R-*Trimethyl*-6-*methylenecyclohexyl*)*acetaldehyde* (13).—Lithium aluminium hydride (247 mg, 6.51 mmol) was added to a stirred solution of the aldehyde (28) (990 mg, 6.51 mmol) in dry ether (50 ml) at 0 °C. After being stirred for 30 min at 0 °C, the reaction was quenched by the addition of wet ether and then water. Work-up of the mixture gave an oil (986 mg). A mixture of the oil, ethyl vinyl ether (60 ml), and mercury(II) acetate (250 mg) was refluxed for 3 d and then poured into aqueous sodium hydrogencarbonate. Extraction with ether and work-up of the extract gave an oil (1.408 g), which was then heated in a sealed tube at 180—185 °C for 3 h. The product was purified by t.l.c. [hexane–ether (15 : 1) as solvent] to afford the aldehyde (13) (714 mg, 61%). An analytical sample was obtained by distillation, b.p. 90 °C (bath temp.)/6 mmHg; $[\alpha]_D^{25}$ +62.4° (*c* 0.42 in dichloromethane); $\nu_{max.}$ 3 070, 1 650, and 893 (*exo*-CH_2), 2 720 and 1 725 cm^{-1} (formyl); δ† (CCl_4) 0.89 and 0.95 (6 H in total, each s, CMe_2), 4.85 and 4.92 (1 H, each br s, $=CH_2$), and 9.97 (1 H, t, *J* 2 Hz, CHO) (Found: C, 80.1; H, 11.4. $C_{12}H_{20}O$ requires C, 79.9; H, 11.2%).

Diastereoisomeric Mixture of 3-[1R-(2,2,3R-*Trimethyl*-6-*methylenecyclohexyl*]-2-*hydroxypropionitrile* (29).—Acetic acid (6.5 ml) and potassium cyanide (4.33 g, 66.6 mmol) were added to a solution of the aldehyde (13) (600 mg, 3.33 mmol) in ethanol (20 ml) at 0 °C, and the mixture was stirred at 0 °C for 1 h and then at room temperature for an additional 2 h. After dilution with water, the product was extracted with ether, and the extract was washed with water, aqueous sodium hydrogencarbonate, and water. Work-up gave the nearly pure cyanohydrin (29) (728 mg), as analytical sample of which was obtained by evaporative distillation, b.p. 85 °C (bath temp.)/0.8 mmHg. T.l.c. showed the product to be diastereoisomeric mixture (roughly 1 : 1), $\nu_{max.}$ 3 450 (OH), 3 080, 1 650, and 900 (*exo*-CH_2), 2 260 (CN) cm^{-1}; δ(CCl_4) 0.8—1.1 (9 H in total, complex methyl signals), 3.4—3.8 (1 H, m, OH), 4.0—4.5 (1 H, m, OCHCN), and 4.7—5.0 (2 H, m, $=CH_2$) (Found: C, 75.7; H, 9.9; N, 7.1. $C_{13}H_{21}NO$ requires C, 75.3; H, 10.2; N, 6.8%).

Diastereoisomeric Mixture of 3-[1R-(2,2,3R-*Trimethyl*-6-*methylenecyclohexyl*)]-2-*phenylselenopropionitrile* (30).—Methanesulphonyl chloride (1.14 g, 10 mmol) was added to a solution of the above crude cyanohydrin (29) (728 mg, *ca.* 3.52 mmol) in pyridine (15 ml) at 0 °C, and the mixture was stirred for 5 h at the same temperature under argon. After dilution with water, the product was extracted with ether, and the extract was washed with 10% aqueous copper sulphate, water, and brine. Evaporation left an oil (981 mg). To a solution of sodium benzeneselenolate, prepared from diphenyl diselenide (780 mg, 2.5 mmol) by reduction with sodium borohydride (189 mg, 5 mmol) in ethanol (12 ml),[10] was added a solution of the above methanesulphonate in ethanol (8 ml) at 0 °C, and the mixture was stirred at room temperature for 2 h. The mixture was diluted with water and extracted with ether. Work-up gave an oil, which was purified by t.l.c. [hexane–ether (15 : 1) as solvent] to give a diastereoisomeric mixture of the phenylselenide (30) [995 mg, 86% from the aldehyde (13)], $\nu_{max.}$ 3 070, 1 645, and 900 (*exo*-CH_2) and 2 230 cm^{-1} (CN); δ† (CCl_4) 0.82 (6 H, s, CMe_2), 0.84 (3 H, d, *J* 8 Hz, CH*Me*), 3.24—3.44 (1 H, m, SeCHCN), 4.80 (2 H, br s, $=CH_2$), and 7.2—7.8 (5 H, m, phenyl) (Found: M^+, 347.1110. $C_{19}H_{25}NSe$ requires *M*, 347.1150).

E- *and* Z-*Isomers of* 3-[1R-(2,2,3R-*Trimethyl*-6-*methylenecyclohexyl*)]*acrylonitrile* (31).—Aqueous hydrogen peroxide (15%, 610 μl, *ca.* 2.7 mmol) was added to a solution of the phenylselenide (30) (94 mg, 0.27 mmol) and pyridine (50 μl) in dichloromethane (1 ml) at room temperature. The mixture was stirred for 2 h and then diluted with ether. The solution was washed with 10% aqueous copper sulphate, water, and brine. Work-up gave an oil, which was purified by t.l.c. [hexane–ether (15 : 1) as solvent] to afford the acrylonitrile (31) as an oil (45 mg, 88%). G.l.c. showed the product to be a mixture of *E*- and *Z*-isomers (82 : 18). An analytical sample was obtained by distillation, b.p. 90 °C (bath temp.)/3 mmHg: $\nu_{max.}$ 3 080, 1 650, and 900 (*exo*-CH_2), 2 230 and 1 625 (conjugated nitrile), and 970 cm^{-1} (*trans*-olefin); δ† (CCl_4) 0.81 and 0.94 (2 × 3 H, each s, CMe_2), 0.88 (3 H, d, *J* 7 Hz, CH*Me*), 2.61 (1 H, d, *J* 9 Hz, =CCHC=), 4.66 and 4.78 (1 H, each br s, $=CH_2$), 5.29 (1 H, d, *J* 16 Hz, CH=C*H*CN), and 5.60 (1 H, dd, *J* 16 and 9, C*H*=CHCN) (Found: C, 82.5; H, 10.2; N, 7.3. $C_{13}H_{19}N$ requires C, 82.5; H, 10.1; N, 7.4%).

(+)-2R,6R-trans-γ-*Irone* (32a) *and Its* (−)-*Z-Isomer* (32b).—An ethereal solution of methyl lithium (*ca.* 6.7 mmol) was added to a stirred solution of the acrylonitrile (31) (490 mg, 2.59 mmol) in ether (20 ml) at −55 °C, and the temperature was then allowed to rise gradually to 0 °C during 3 h. The reaction was quenched with aqueous ammonium chloride at 0 °C, and the organic layer was worked up. The oil obtained was purified by t.l.c. [hexane–ether (10 : 1) as solvent] to yield the irones (32a) (275 mg, 52%) and (32b) (59 mg, 11%). For the irone (32a), $[\alpha]_D^{25}$ +57.0° (*c* 0.33 in dichloromethane); $\nu_{max.}$ 3 070, 1 650, and 895 (*exo*-CH_2), 1 680 and 1 620 (conjugated enone), and 990 cm^{-1} (*trans*-olefin); δ† ($CDCl_3$) 0.83 and 0.91 (2 × 3 H, each s, CMe_2), 0.87 (3 H, d, *J* 8 Hz, CH*Me*), 2.25 (3 H, s, O=CMe), 2.66 (1 H, d, *J* 9 Hz, =CCHC=), 4.69 and 4.78 (1 H, each br s, $=CH_2$), 6.12 (1 H, d, *J* 16 Hz, CH=C*H*C=O), and 7.10 (1 H, dd, *J* 16 and 9 Hz, C*H*=CHC=O) (Found: M^+, 206.1632. $C_{14}H_{22}O$ requires *M*, 206.1669).

For the irone (32b), $[\alpha]_D^{25}$ −42.0° (*c* 0.40 in dichloromethane); $\nu_{max.}$ 3 080, 1 645, and 890 (*exo*-CH_2), and 1 690 and 1 610 cm^{-1} (conjugated enone); δ† ($CDCl_3$) 0.88 and 0.93 (2 × 3 H, each s, CMe_2), 0.97 (3 H, d, *J* 7 Hz, CH*Me*), 2.31 (3 H, s, O=CMe), 4.84 (2 H, br s, $=CH_2$), and 6.1—6.6 (2 H, m, C*H*=C*H*C=O) (Found: M^+, 206.1686. $C_{14}H_{22}O$ requires *M*, 206.1669).

(−)-2R,6R-trans-α-*Irone* (2) *and* (+)-6R-β-*Irone* (3).—A solution of the irone (32a) (70 mg) in 85% phosphoric acid (1.8 ml) was stirred at room temperature for 6 h. After dilution with water, the product was extracted with ether and washed with aqueous sodium hydrogencarbonate, water, and brine. Work-up afforded an oil, which was purified by t.l.c. [hexane–ether (10 : 1) as solvent] to give a mixture (58 mg, 83%) of the irones (2) and (3) in a ratio of 93 : 7 (g.l.c.). Further purification by t.l.c. gave the pure irone (2), $[\alpha]_D^{25}$ −318° * (*c* 0.33 in dichloromethane). The i.r. and ^{1}H n.m.r. spectra were identical with those of natural *trans*-α-irone.[1] Identification of β-irone (3) was performed by comparison of the mass spectra [1] of the above irone mixture (g.l.c.–mass spectrometry).

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* 76% Enantiomeric excess (lit.,[1] $[\alpha]_D^{20}$ −420°).

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