Stereoselective Total Synthesis of Racemic (3*S*,4*R*/3*R*,4*S*)- and a Diastereoisomeric Mixture of (6*E*,10*Z*)-3,4,7,11-Tetramethyltrideca-6,10-dienal (Faranal); The Trail Pheromone of the Pharaoh's Ant

Raymond Baker,* David C. Billington, and Neelakanthie Ekanayake
Department of Chemistry, The University, Southampton SO9 5NH

Racemic (3*S*,4*R*/3*R*,4*S*)-faranal [(1a) + (1b)] has been synthesised by a convergent, stereospecific route which employed the addition of alkylcopper complexes to terminal acetylenes, to generate two trisubstituted double bonds, and a Diels–Alder reaction to establish the relative stereochemistry of the C-3, C-4 methyl groups. A diastereoisomeric mixture of faranals, enriched in the (3*S*,4*S*/3*R*,4*R*)-enantiomeric pair [(1c) + (1d)], has been synthesised by a somewhat shorter route *via* an intermediate diester, obtained from electrochemical dimerisation of ethyl crotonate.

The Pharaoh's ant, *Monomorium pharaonis*, originally a tropical insect, is now a major pest in the U.K. and Western Europe.[1] Particular problems arise when hospitals are affected, as the ants have been shown to carry a number of disease vectors,[2] and the use of insecticides in hospital environments poses special problems. The most active component of the trail pheromone of the Pharaoh's ant has been shown to be (6*E*,10*Z*)-3,4,7,11-tetramethyltrideca-6,10-dienal (faranal)[3] and a recent bio-organic synthesis of the four enantiomers of faranal identified the most likely absolute configuration of the natural compound as (3*S*,4*R*) (1a).[4] All four optical isomers of faranal have been shown to be biologically active.[4] Interestingly, a racemic mixture of (3*R*,4*S*)- and (3*S*,4*R*)-faranal has approximately one tenth the biological activity of the pure natural product,[5] and a 50 : 50 mixture of the '4*R*' faranals (3*R*,4*R* + 3*S*,4*R*) has an activity close to that of the natural product.[4] These results have been interpreted as indicating that the 4*R* configuration is important for biological activity.

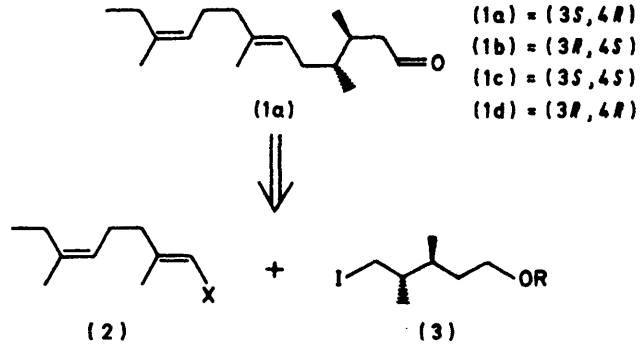
Three previous syntheses of faranal have appeared, none of which were successful in generating the two trisubstituted double bonds of faranal stereoselectively.[5–7] We have synthesised faranal *via* a convergent route in which the stereochemistry of the two trisubstituted double bonds is completely controlled by the addition of alkylcopper complexes to terminal alkynes.[8]

Two samples differing in isomeric composition have been obtained. A racemic mixture of (3*S*,4*R*/3*R*,4*S*)-faranal [(1a) + (1b)] has been prepared using *meso*-4,5-dimethylcyclohexene as an important intermediate, and a mixture of diastereoisomeric faranals enriched in the (3*S*,4*S*/3*R*,4*R*) [(1c) + (1d)] enantiomeric pair has been prepared *via* an intermediate generated from the electrochemical dimerisation of ethyl crotonate. A preliminary communication on part of this work has been published.[9]

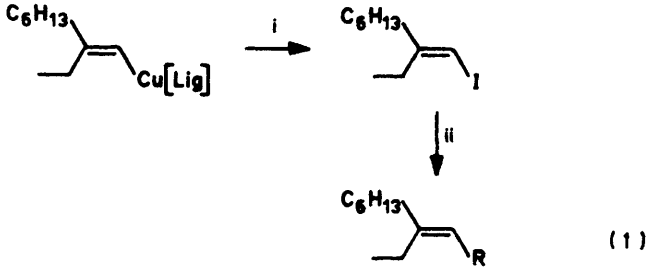
Results and Discussion

Retrosynthetic analysis (Scheme 1) suggested the formation of the 5,6-bond at a late stage, thus allowing a convergent approach. The most direct route, involving the coupling of an alkenylcopper complex (2; X = Cu) [obtained from the addition of a methylcopper complex to the corresponding acetylene [8]] with the iodide (3), was examined using model compounds, but gave at best only low yields of the desired products (*i.e.* <40%).

The stereospecific conversion of alkenylcopper complexes into vinyl iodides [10] and the stereospecific reaction between vinyl iodides and Grignard reagents in the presence of copper



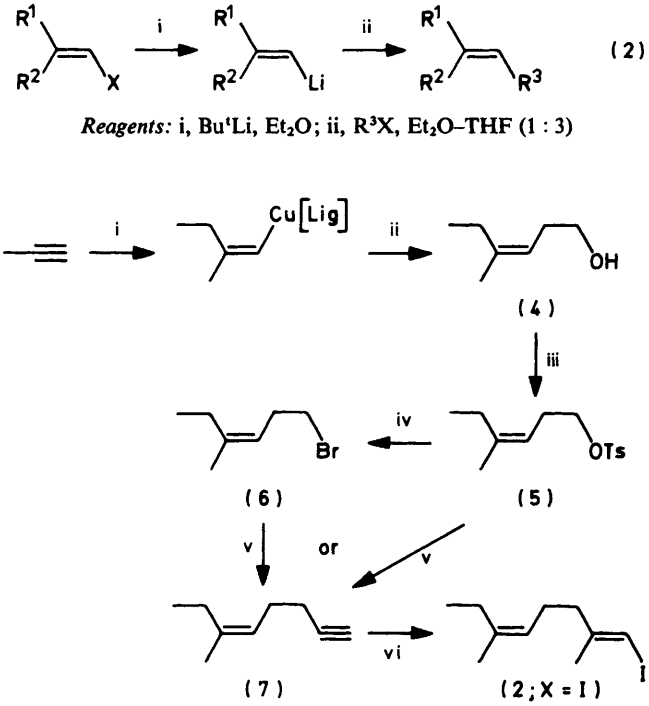
Scheme 1.



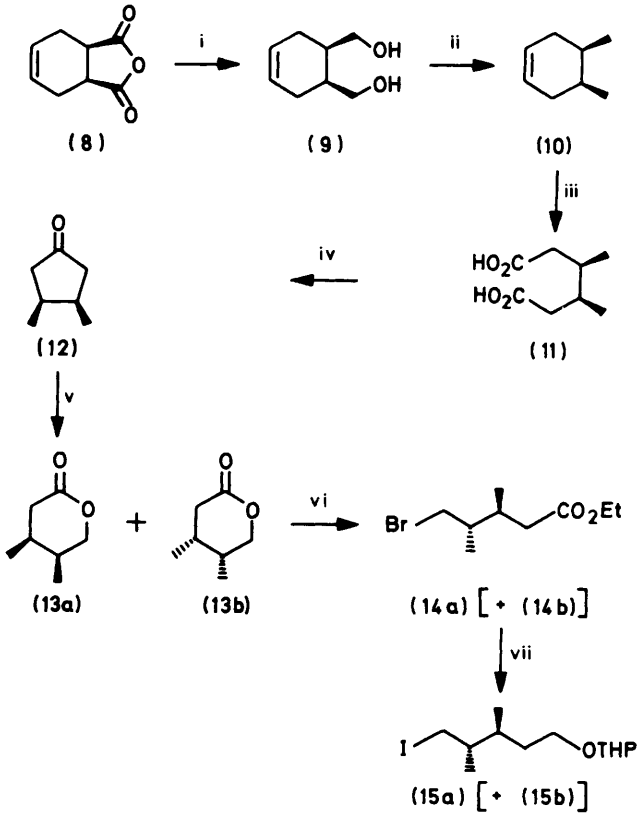
Reagents: i, I_2; ii, RMgX–Li_2CuCl_4

salts to give trisubstituted olefins [equation (1)][11] has been reported. An examination of this method using models of the building blocks (2) and (3) showed that, although low molecular weight Grignard reagents gave good yields,[11] those of higher molecular weight gave little or no yield of the desired olefins {*e.g.* in equation (1), R = C_2H_5, 77%; $(CH_3)_2CHCH_2$, 73%; C_7H_{15}, 23%; $C_8H_{16}OTHP$, 0%; and $C_7H_{14}OTHP$ [compound (3; R = THP)], 0%} (THP = tetrahydropyran-2-yl). These results probably reflect the insolubility of the higher molecular weight Grignard reagents at the low temperatures required to avoid decomposition of the intermediate organocopper complexes which are presumably involved in this reaction.

Alkyl-lithiums react rapidly with vinyl halides at low temperatures to give vinyl-lithiums and one equivalent of alkyl halide [equation (2)].[12] Normant *et al.*[12] have observed that, in diethyl ether, reaction between the vinyl-lithium and alkyl halide is sufficiently slow (50% reaction in 24 h at 20 °C) that the vinyl-lithium may also react with other electrophiles, for



Scheme 2. *Reagents:* i, $EtCu[Me_2S]MgBr_2$, Et_2O, Me_2S; ii, (a) 1-lithiopent-1-yne, HMPA (b) CH_2CH_2O; iii, toluene-*p*-sulphonyl chloride–pyridine; iv, LiBr, acetone; v, Li[EDTA]C≡CH, DMSO; vi, (a) $MeCu[Me_2S]\cdot MgBrI$ (b) I_2



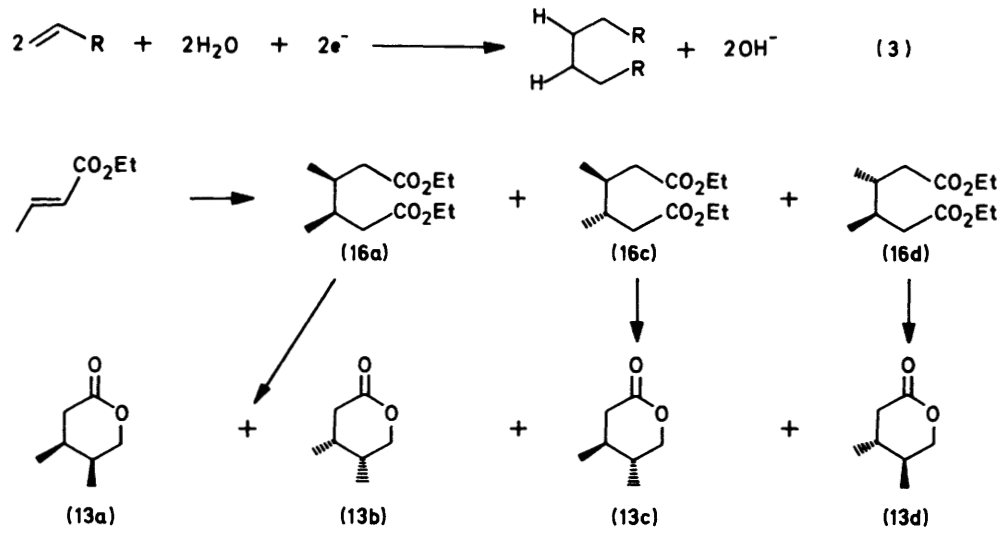
Scheme 3. *Reagents:* i, LAH, THF; ii, (a) $MeSO_2Cl$–pyridine (b) $LiAlH_4$–NaH (1 : 1), $(Et)_2O$; iii, (a) O_3, CH_2Cl_2, −78 °C (b) Jones reagent; iv, $Ba(OH)_2$, heat; v, *m*-CPBA, CH_2Cl_2; vi, HBr–EtOH; vii, (a) $LiAlH_4$, $(Et)_2O$ (b) DHP, $(Et)_2O$ (c) NaI, acetone

example, carbonyl compounds. In contrast, in THF (tetrahydrofuran), the reaction between the vinyl-lithium and the alkyl halide produced rapidly gives a trisubstituted olefin in *ca.* 3 h at −50 °C.[12] Seebach and Neumann [13,14] have shown that treatment of a vinyl bromide with two equivalents of t-butyl-lithium in the Trapp solvent system at −120 °C leads to a vinyl-lithium derivative free of alkyl halide. This is due to the mutual destruction of t-butyl-lithium and t-butyl iodide under these conditions. It was also demonstrated that these vinyl-lithiums could then react with a range of electrophiles, including alkyl halides, to give trisubstituted olefins stereospecifically.[14] Combining these procedures we found that the vinyl-lithium derivative of (2; X = I) could be generated using 2 equiv. of t-butyl-lithium in diethyl ether and was successfully alkylated with compound (3) in 3 : 1 THF–diethyl ether to give the desired trisubstituted olefin.

Synthesis of (1E,5Z)-1-*Iodo*-2,6-*dimethylocta*-1,5-*diene* (2; X = I).—Addition of the dimethyl sulphide–copper(I) bromide complex of ethylmagnesium bromide to propyne, by the method of Helquist and his co-workers,[8] gave a vinylcopper complex (Scheme 2). This was converted into an 'ate' complex by the addition of 1-lithiopent-1-yne, and reaction with ethylene oxide gave the (*Z*)-homoallylic alcohol (4) in 74% yield. This alcohol has previously been prepared by a multistep procedure from 2-cyclopropylbut-3-yn-2-ol.[15] Helquist and his co-workers,[8] have demonstrated that these addition reactions proceed with >99.9% stereoselection. In order to verify the stereochemical purity of the alcohol (4) it was converted into its TMS (trimethylsilyl) ether, and examination of this ether by capillary g.l.c. showed no evidence of contamination by the (*E*)-isomer. Treatment of the alcohol (4) with toluene-*p*-sulphonyl chloride in pyridine gave the toluene-*p*-sulphonate (5) (92%) which was converted into the bromide (6) by treatment with lithium bromide in acetone (82%). Reaction of either the toluene-*p*-sulphonate (5) or the bromide (6) with the ethylenediamine complex of lithium acetylide in dimethyl sulphoxide (DMSO) gave (*Z*)-6-methyloct-5-en-1-yne (7) in 70% yield.

In agreement with the findings of others [16] we encountered considerable difficulty in the addition of the dimethyl sulphide–copper(I) bromide complex of methylmagnesium iodide to the terminal acetylene (7) under the conditions described by Helquist and his co-workers [8] (accurate temperature control at −23 °C), observing essentially no reaction. Attempts to prepare the iodide (2; X = I) by the addition of the alkylcopper complex described by Theis and Townsend,[16] and by Vermeer and his co-workers,[17] to the alkyne (7) did not result in any improvement. After a series of trial experiments, however, this reaction showed that an initial increase of temperature was required. Thus by allowing the reaction mixture to warm to room temperature for 15 min before incubation at −15 °C, a good yield of alkenylcopper complex could be obtained. Finally, quenching this complex with iodine at low temperature [10] gave (1*E*,5Z)-1-iodo-2,6-dimethylocta-1,5-diene (2; X = I) in 49% yield.

Synthesis of Racemic (2S,3S/2R,3R)-1-*Iodo*-2,3-*dimethyl*-5-(*tetrahydropyran*-2-*yloxy*)*pentane* [(15a) + (15b)].—Diels–Alder reaction between butadiene and maleic anhydride gave the adduct (8) in 80% yield. Reduction of this adduct with $LiAlH_4$ (LAH) gave the *meso*-diol (9) in 83% yield (Scheme 3). Previous literature procedures for the reduction of either the



Scheme 4. Ratio *meso*-diester (16a) to racemic diester [(16c) + (16d)] 33 : 67 by ^{13}C n.m.r. spectroscopy. Ratio [(13a) + (13b)] to [(13c) + (13d)] 25 : 75 by g.l.c.

dimesylate * or ditosylate * of (9) to give *meso*-4,5-dimethylcyclohexene (10) were reported to give very low yields,[18] and these results were verified by our own experiments. The procedure of Walborsky *et al.*,[19] however, which has been successful in the reduction of a *trans*-dimesylate of (9), when applied to the *cis*-dimesylate of (9) gave the hydrocarbon (10) in 99% yield. Ozonolysis of compound (10) in CH_2Cl_2 at −78 °C, followed by treatment of the product with Jones reagent, gave *meso*-3,4-dimethylhexanedioic acid (11) in 80% yield. Pyrolysis of the diacid (11) in the presence of barium hydroxide [5] gave *meso*-3,4-dimethylcyclopentanone (12), in 80% yield, which was oxidised to a 50 : 50 mixture of the enantiomeric *cis*-4,5-dimethyltetrahydro-2-pyrones (13a) and (13b) with *m*-chloroperbenzoic acid in CH_2Cl_2 (81% yield).[5] Treatment of the mixture of lactones [(13a) + (13b)] with HBr in dry ethanol resulted in the formation of the racemic bromo ester ethyl (3*S*,4*S*/3*R*,4*R*)-5-bromo-3,4-dimethylpentanoate [(14a) + (14b)] in 69% yield. Reduction of the racemic mixture of bromo esters with LAH gave a racemic mixture of alcohols (70% yield). After protection by reaction with dihydropyran, and halogen exchange using sodium iodide in acetone, racemic (2*S*,3*S*/2*R*,3*R*)-1-iodo-2,3-dimethyl-5-(tetrahydropyran-2-yloxy)pentane [(15a) + (15b)] was obtained in *ca.* 70% yield.

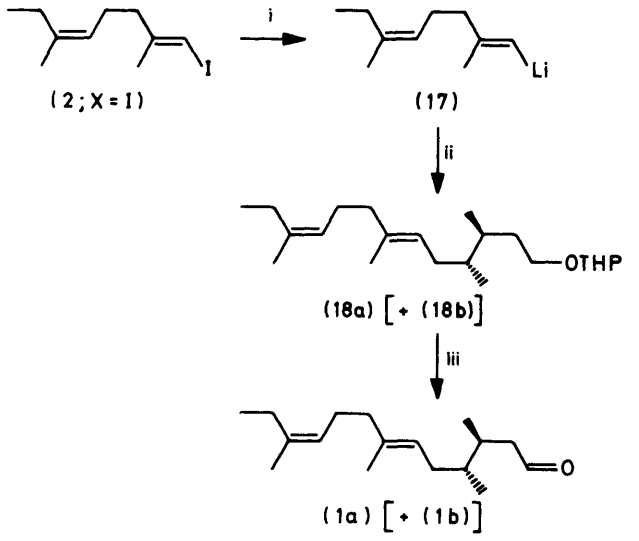
Synthesis of a Diastereoisomeric Mixture of 1-*Iodo*-2,3-*dimethyl*-5-(*tetrahydropyran*-2-*yloxy*)*pentanes* (15a—d).—Activated olefins can be dimerised electrochemically [equation (3), R = electron-withdrawing group] [20] and the electrochemical dimerisation of ethyl crotonate was examined as a possible route to diethyl 3,4-dimethylhexanedioate (16). Using the conditions described by Baizer,[21] generation of compound (16) was attained in 60% yield. The electrochemical dimerisation of ethyl crotonate can give rise to three isomeric diesters, the *meso*-compound (16a), and the (*S*,*S*) (16c) and (*R*,*R*) (16d) isomers. The racemic component [(16c) + (16d)] and the *meso*-component (16a) proved inseparable by capillary g.l.c. The ^{13}C n.m.r. spectrum of the product confirmed that a mixture of diastereoisomers was formed. The resonances were assigned by comparison with the spectrum of an authentic sample of the *meso*-component (16a). By recording spectra using a delayed-pulse technique,[22] the requirements for direct comparison of line intensities were fulfilled,[23] and a value for the composition of the mixture was obtained. This method indicated that the mixture contained 33% *meso*-diester (16a) and 67% racemic diester [(16c) + (16d)]. Hydrolysis of this mixture of diesters to a mixture of diacids (10% NaOH solution; 98% yield), followed by pyrolysis to a mixture of 3,4-disubstituted cyclopentanones (92% yield) and oxidation of this mixture of cyclopentanones to a mixture of lactones by the methods described earlier gave the lactones (13a—d) in 84% yield (Scheme 4). The diastereoisomeric pairs were separable by g.l.c. (5% Carbowax 20M on Diatomite C AAW DMCS, 3mm × 3m; 152 °C) and this analysis showed that the mixture consisted of 25% [(13a) + (13b)] derived from the *meso*-diester (16a) and 75% [(13c] + (13d)] derived from the racemic diester [(16c) + (16d)].

The above mixture of lactones (13a—d) was converted into a mixture of 1-iodo-2,3-dimethyl-5-(tetrahydropyran-2-yloxy)-pentanes (15a—d) by the methods described above for the racemic mixture of the lactones (13a) and (13b).

Synthesis of Faranals.—Treatment of (1*E*,5*Z*)-1-iodo-2,6 dimethylocta-1,5-diene (2; X = I) with two equivalents of t-butyl-lithium in diethyl ether at −85 °C gave, quantitatively, a vinyl-lithium derivative (17) (Scheme 5). Reaction of this derivative with the racemic mixture of iodides [(15a) + (15b] overnight in a mixture of THF and diethyl ether (3 : 1) gave, after chromatography, a 60% yield of the protected alcohols (18a) and (18b). This mixture was deprotected (toluene-*p*-sulphonic acid–MeOH) in 93% yield and the product alcohol was oxidised (PCC–alumina) † to racemic (3*S*,4*R*/3*R*,4*S*)-faranal [(1a) + (1b)] in 84% yield. The above procedure was repeated using the mixture of iodides (15a—d) and a mixture of faranals (1a—d), consisting of 25% (3*S*,4*R*/3*R*,4*S*)-faranal [(1a) + (1b)] and 75% (3*S*,4*S*/3*R*,4*R*)-faranal [(1c) + (1d)], was obtained. The spectroscopic properties (n.m.r., i.r., m.s.) of the racemic sample were identical with those reported elsewhere,[5] and the spectroscopic properties of the mixture of faranals were very similar to those of the racemic mixture. No evidence of contamination by unwanted double-bond isomers

* Mesylate = methanesulphonate. Tosylate = toluene-*p*-sulphonate.

† PCC = Pyridinium chlorochromate.



Scheme 5. *Reagents and conditions:* i, t-butyl-lithium, $(Et)_2O$, −78 °C, 30 min; ii, (a) [(15a) + (15b)], 18 h, −78 °C ⟶ 0 °C (b) THF (3 vols); iii, (a) toluene-*p*-sulphonic acid, MeOH (b) PCC, alumina

(*i.e.* 6*E*,10*E*; 6*Z*,10*E*; or 6*Z*,10*Z*) was apparent in the 400-MHz ^{1}H n.m.r. spectra of the samples (*cf.* reference 5 where evidence of contamination by unwanted geometric isomers was obtained by high-field ^{1}H n.m.r. spectroscopy *after* purification by preparative g.l.c.). Both samples of faranal prepared were shown to have substantial biological activity and the detailed results will be published elsewhere.

Experimental

^{1}H N.m.r. spectra were recorded on a Perkin-Elmer R12 spectrometer at 60 MHz, at 100 MHz on an XL100 machine, and at 400 MHz on a Brücker WH/400 spectrometer. All δ-values refer to samples in $CDCl_3$ unless otherwise stated, with tetramethylsilane as an internal standard. ^{13}C N.m.r. spectra were recorded on a Varian Associates XL100 spectrometer. I.r. spectra were obtained on a Perkin-Elmer 157G spectrometer for liquid films unless otherwise stated. Mass spectra were recorded on a Kratos MS30 spectrometer equipped with a DS 505 data system, operating at 70 eV; ammonia gas was used under c.i. (chemical ionisation) conditions. Gas-liquid chromatography was carried out using a Pye Unicam GCD chromatograph, with nitrogen as carrier gas at a flow rate of 20 ml min^{-1}. Analytical t.l.c. was performed on pre-coated silica plates (Merck, type 25 UV_{254}), and using appropriate diethyl ether–light petroleum (b.p. 40—60 °C) mixtures as eluants. Flash chromatography refers to the method of Still *et al.*,[24] and was performed using MN Kieselgel 60 (230—400 mesh). Kugelrohr distillation refers to short-path distillation using a Büchi Kugelrohr (bulb-to-bulb) system and boiling points quoted are oven temperatures. Solutions of alkylmagnesium halides were standardised by titration according to the method of Watson and Eastham.[25] All commercially available solvents were purified by standard procedures before use. Solvents for moisture-sensitive reactions were dried by distillation from calcium hydride–LAH under nitrogen. Substrates for moisture-sensitive reactions were dried by the addition of calcium hydride. Solvent evaporation under reduced pressure refers to use of a Büchi rotary film evaporator operating at 15 mmHg and a bath temperature of 25 °C. Organic solutions were dried with anhydrous magnesium sulphate.

(Z)-4-*Methylhex*-3-*en*-1-*ol*[8,15] (4).—Dry dimethyl sulphide (230 ml) was added to a suspension of dimethyl sulphide–copper(I) bromide[26] (34.7 g, 0.17 mol) in dry diethyl ether (207 ml) under nitrogen. The colourless solution which resulted was stirred and cooled to −45 °C and a solution of ethylmagnesium bromide (106 ml of a 1.6M solution,[25] 0.17 mol) was added during 5 min. The orange suspension was stirred under nitrogen at −45 °C for 2 h and then propyne (9.6 ml, 0.17 mol) was added. The solution was warmed to −25 °C and stirred for 3 h.

A solution of n-butyl-lithium in hexane (106 ml of a 1.6M solution, 0.17 mol) was added to a stirred solution containing dry pent-1-yne (17 ml, 0.17 mol) and hexamethylphosphoric triamide (HMPA) (29 ml) in dry diethyl ether (212 ml) at −78 °C, under nitrogen, and the resulting solution was stirred at −70 °C for 30 min. The solution containing the alkenyl organocopper complex was cooled to −60 °C, and the solution containing the lithiopentyne (0.17 mol) in diethyl ether–HMPA was added during 5 min. The mixture was stirred for 1 h at −60 °C, dry ethylene oxide (8.4 ml, 0.17 mol) was added, and the resulting solution was stirred for 36 h at −35 °C. Saturated aqueous ammonium chloride (50 ml of a saturated solution adjusted to pH 8 with aqueous ammonia) was added, and the mixture was stirred vigorously in the presence of air for 1.5 h. The organic phase was decanted, and the aqueous phase was extracted with diethyl ether (3 × 100 ml). The combined extracts were washed with saturated aqueous sodium chloride (3 × 50 ml), dried, and the solvents were removed under reduced pressure. The resulting oil was dissolved in diethyl ether (500 ml) and the solution was washed with saturated aqueous sodium chloride (3 × 50 ml) and passed through a short column of silica gel to remove residual HMPA. Purification of the residue by flash chromatography (CH_2Cl_2 as eluant) gave (*Z*)-4-methylhex-3-en-1-ol (4) (14.2 g, 74%) as an oil, b.p. 75 °C/20 mmHg (lit.,[15] 64—65 °C/10 mmHg). Conversion of this alcohol into its TMS ether and g.l.c. analysis (capillary column, SE30 SCOT, 0.5 mm × 50 m; 100—250 °C/8 °C min^{-1}) showed no contamination by the (*E*)-isomer.

(Z)-1-*Bromo*-4-*methylhex*-3-*ene*[15] (6).—The bromo compound was prepared by the method of Mori *et al.*,[15] *via* the tosylate (5), in 75% overall yield, b.p. 65—70 °C (Kugelrohr)/15 mmHg (lit.,[15] 80—82 °C/35 mmHg).

(Z)-6-*Methyloct*-5-*en*-1-*yne* (7).—The bromide (6) (2.92 g, 15 mmol) was added to a stirred suspension of the ethylenediamine complex of lithium acetylide (2.03 g, 22 mmol) in dry DMSO (9 ml) at 10 °C under nitrogen. The suspension was stirred for 30 min at 10 °C, then for 3 h at 25 °C, and was then cooled in ice. Hydrochloric acid (4 ml of a 5M solution) was added, followed by water (15 ml), and the mixture was extracted with pentane (5 × 30 ml). The combined extracts were washed with water (10 ml), dried, and the solvent was removed at atmospheric pressure using an efficient fractionating column. The residual oil was distilled (Kugelrohr) to give (*Z*)-6-methyloct-5-en-1-yne as a liquid (1.28 g, 70%), b.p. 55—60 °C/15 mmHg, δ 1.0 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.2 (3 H, s, MeC=C), 2.1 (7 H, m), and 5.1 (1 H, t, *J* 7.5 Hz, C=CH); *m/z* 122 (M^+, 4%), 107 (5), 83 (48), and 55 (100) (Found: M^+, 122.1070. C_9H_{14} requires *M*, 122.1214). Use of the tosylate (5) in place of the bromide (6) gave a similar yield of the alkyne (7).

(1E,5Z)-1-*Iodo*-2,6-*dimethylocta*-1,5-*diene* (2; X = I).—A solution of methylmagnesium iodide (9.2 ml of a 1.6M solution, 14.7 mmol) was added to a stirred suspension of dimethyl sulphide–copper(I) bromide (3.02 g, 14.7 mmol) in dry diethyl

ether (19 ml) and dry dimethyl sulphide (19 ml) at −45 °C under nitrogen. The orange suspension was stirred at −45 °C for 2.5 h and then the alkyne (7) (1.8 g, 14.7 mmol) was added. The suspension was warmed to room temperature for 15 min and then stirred under nitrogen at −15 °C. The reaction was monitored by g.l.c. (OV101; 100—300 °C at 8 °C min^{-1}) and after 54 h the mixture was cooled to −50 °C and powdered, nitrogen-purged iodine (3.7 g, 14.7 mmol) was added. The dark brown solution was warmed to −30 °C and when it became colourless, trimethyl phosphite (1.5 ml) was added. The solution was stirred for 2 min, hydrochloric acid was added (35 ml of a 5M solution, 175 mmol) and, after being stirred for 10 min, the solution was poured into diethyl ether (25 ml). The organic phase was separated, washed in turn with hydrochloric acid (5 ml; 5M), water (2 × 5 ml), and saturated aqueous sodium hydrogencarbonate (5 ml), dried, and the solvents removed under reduced pressure. The residual oil was filtered and distilled (Kugelrohr) to give starting material (0.7 g, 38% recovery) and (1*E*,5*Z*)-1-iodo-2,6-dimethylocta-1,5-diene (2; X = I) (1.03 g, 49%), b.p. 85—90 °C/0.2 mmHg; pure by g.l.c. (OV101; 100—300 °C at 16 °C min^{-1}); δ 0.99 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.69 (3 H, s, *Me*CR=CRH), 1.85 (3 H, s, *Me*CR=CHI), 2.1 (6 H, br m, 3 × CH_2), 5.1 (1 H, m, MeCR=CR*H*), and 5.9 (1 H, m, MeCR=C*H*I); *m/z* * 137 (M^+ − I, 87%), 83 (76), and 55 (100).

meso-4,5-*Bis*(*hydroxymethyl*)*cyclohexene* (9).—The above compound was prepared from *cis*-1,2,3,6-tetrahydrophthalic anhydride (8) [27] by the method of Walborsky *et al.*[19] in 83% yield, b.p. 137 °C/1 mmHg (lit.,[28] 130—137 °C/1.0—1.5 mmHg).

meso-4,5-*Dimethylcyclohexene* (10).—This was prepared *via* the dimesylate of the diol (9) using the reduction conditions described by Walborsky *et al.*[19] The dimesylate, m.p. 79—82 °C (lit.,[18] 82—83 °C), was prepared in 94% yield and was reduced with LAH–NaH in boiling diethyl ether to give the hydrocarbon (10) in 99% yield; b.p. 123 °C (lit.,[18] 123—124 °C).

meso-3,4-*Dimethylhexanedioic Acid* (11).—A mixture of ozone in oxygen (*ca.* 2% O_3) was bubbled through a solution of the cyclohexene (10) (10 g, 90 mmol) in dichloromethane (600 ml) at −78 °C until a permanent blue colour resulted. The solution was then freed of ozone by bubbling nitrogen, warmed to 0 °C, and treated with excess of Jones reagent.[29] After being kept at 25 °C for 15 h, the organic phase was separated and the aqueous phase was saturated with sodium chloride and was then extracted with diethyl ether (2 × 50 ml). The combined organic phases were dried and the solvent removed under reduced pressure to provide an oily residue. This residue was taken up in 1% aqueous sodium hydroxide (100 ml) and the aqueous solution was washed with diethyl ether (2 × 50 ml), acidified, and the free acid extracted with diethyl ether (5 × 100 ml). The organic solution was dried and the solvent removed under reduced pressure to give *meso*-3,4-dimethylhexanedioic acid (11) (12.6 g, 80%), m.p. 125—129 °C (lit.,[30] 128—131 °C).

meso-3,4-*Dimethylcyclopentanone* (12).—This was prepared by the method described by Thorpe and Kon [31] for the racemic compound. Thus, pyrolysis of the diacid (11) in the presence of barium hydroxide gave the ketone (12) in 80% yield, b.p. 60—80 °C/15 mmHg (lit.,[32] 62—80 °C/15 mmHg).

cis-4,5-*Dimethyltetrahydro*-2-*pyrone* [(13a)—(13b)].—*m*-Chloroperbenzoic acid (32 g, 185 mmol) was added to a stirred solution of the cyclopentanone (12) (8.15 g, 72 mmol) in dichloromethane (100 ml) and the suspension was stirred for 6 h. A 1 : 1 mixture of water and dichloromethane was added (100 ml) and, after being stirred for 10 min, the phases were separated The organic phase was washed in turn with 1% aqueous sodium thiosulphite (50 ml) and saturated aqueous sodium hydrogencarbonate (50 ml) until the organic phase was clear (six times each). The organic phase was dried and the solvent removed under reduced pressure to give a pale yellow oil which was distilled to give *cis*-4,5-dimethyltetrahydro-2-pyrone [(13a) + (13b)] as a liquid (7.5 g, 81%), b.p. 80—84 °C/0.8 mmHg (lit.,[5] 73—76 °C/0.55 mmHg).

Ethyl (3S,4S/3R,4R)-5-*Bromo*-3,4-*dimethylpentanoate* ([14a) + (14b)].—Hydrogen bromide was bubbled through a solution of the lactones (13a) + (13b) (7.5 g, 59 mmol) in dry ethanol (200 ml) until the exothermic reaction had ceased. The solution was concentrated under reduced pressure to a brown oil which was dissolved in diethyl ether (150 ml) and the solution was washed with water (2 × 20 ml), dried, and evaporated under reduced pressure. Distillation of the residue gave ethyl (3*S*,4*S*/3*R*,4*R*)-5-bromo-3,4-dimethylpentanoate [(14a) + (14b)] as a liquid (9.67 g, 69%), b.p. 76 °C/0.02 mmHg (lit.,[5] 87—90 °C/1 mmHg).

(2S,3S/2R,3R)-1-*Iodo*-2,3-*dimethyl*-5-(*tetrahydropyran*-2-*yloxy*)*pentane* [(15a) + (15b)].—A solution of the bromo ester [(14a) + (14b)] (12.1 g, 51 mmol) in dry diethyl ether (50 ml) was added dropwise to a stirred suspension of LAH (5.1 g, 137 mmol) in dry diethyl ether (50 ml) at 0 °C. The suspension was stirred at 0 °C for 15 h, treated with saturated aqueous ammonium chloride (10 ml), stirred for 1 h, and treated with anhydrous sodium sulphate (20 g, 0.14 mol). After being stirred for a further 5 h, the mixture was extracted with diethyl ether (3 × 100 ml) and the combined extracts were washed with saturated brine (2 × 10 ml), dried, and concentrated under reduced pressure to give a pale oil. Distillation (Kugelrohr) gave the desired alcohol as a liquid † (6.9 g, 70%), b.p. 76 °C/0.02 mmHg; $\nu_{max.}$ 3 500br and 2 900s cm^{-1}; δ 0.9 (6 H, m, 2 × Me), 1.8 (4 H, m, CH_2 + 2 × CH), 3.3 (2 H, d, *J* 8 Hz, CH_2Br), 4.6 (2 H, t, *J* 8 Hz, CH_2OH), and 5.1 (1 H, s); *m/z* 195 (0.01%), 193 (0.02), 177 (0.06), 175 (0.04), 97 (42), and 55 (100).

A solution of the above bromo alcohol (5 g, 25 mmol), dihydropyran (2.5 g, 29 mmol), and toluene-*p*-sulphonic acid (5 mg) in dry diethyl ether (250 ml) was stirred at 25 °C for 22 h. Water (5 ml) was then added and the organic phase was washed in turn with 2% aqueous sodium hydrogencarbonate (25 ml) and saturated brine (25 ml), dried, and evaporated under reduced pressure to give the bromo tetrahydropyranyl ether. G.l.c. (5% OV101 on Chromosorb W-HP, 3 mm × 3 m; 100—300 °C at 16 °C min^{-1}) indicated the presence of *ca.* 5% of a low-boiling impurity which was removed by distillation (Kugelrohr) to leave the bromo-tetrahydropyranyl ether † as an oil (6.2 g, 87%), b.p. 80—90 °C/0.01 mmHg, $\nu_{max.}$ 2 900s cm^{-1}; δ 0.95 (6 H, m, 2 × Me), 1.6 (10 H, m), 3.48 (2 H, m, CH_2Br), 3.8 (4 H, m, 2 × CH_2O), and 4.6 (1 H, m, OCHO); *m/z* 280 and 278 (M^+, 0.4%), 179 (6), 177 (6), 101 (7), 97 (28), and 85 (100).

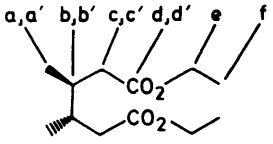
A solution of the bromo tetrahydropyranyl ether (0.5 g, 1.7 mmol), and sodium iodide (3 g, 20 mmol) in dry AnalaR acetone (15 ml) was stirred at 25 °C for 15 h under nitrogen. Water (10 ml) was then added, the reaction mixture was extracted

* M^+ for this compound was not obtainable under low eV or chemical ionisation conditions.

† The bromo alcohol and the corresponding tetrahydropyranyl ether were found to be unstable and hence we recommend their use soon after purification. M^+ for the bromo alcohol could not be obtained even under c.i. conditions.

with diethyl ether (50 ml), and the extract was dried and concentrated under reduced pressure to give (2*S*,3*S*/2*R*,3*R*)-1-iodo-2,3-dimethyl-5-(tetrahydropyran-2-yloxy)pentane [(15a) + (15b)] as a pale oil (0.6 g, 79%), $\nu_{max.}$ 2 900s and 1 640m cm^{-1}; δ (100 MHz) 0.9 (6 H, m, 2 × Me), 1.6 (10 H, m), 3.2 (2 H, m, CH_2I), 3.4 (2 H, m, CH_2O), 3.8 (2 H, m, CH_2O), and 4.6 (1 H, m, OCHO); *m/z* 325 ($M^+ - 1$, 0.5%), 225 (4), 199 (1.5), 85 (100), and 55 (28) (Found: $M + NH_4^+$, 344.0661. $C_{12}H_{23}IO_2 + NH_4^+$ requires *m/z*, 344.1040). This compound decomposed on attempted distillation.

Diethyl 3,4-*Dimethylhexanedioate* (16a, c, d) *by Electrochemical Dimerisation of Ethyl Crotonate*.—Following the method outlined by Baizer,[21] ethyl crotonate (114 g, 0.99 mol) was electrolysed using a two-compartment cell. The catholyte consisted of DMF (dimethylformamide) (132 g), methyltriethylammonium toluene-*p*-sulphonate (104 g of a 76% aqueous solution), and *p*-nitroso-*N*,*N*-dimethylaniline (10 mg). The anolyte consisted of a solution of methyltriethylammonium toluene-*p*-sulphonate (50 ml of a 38% aqueous solution). A platinum anode and a mercury cathode were employed, and the pH of the catholyte was maintained at 7—8 by the addition of acetic acid, whilst a constant current of 2.90 A was passed through the cell (current density 0.054 A cm^{-2}). After 9.1 h the electrolyte was concentrated under reduced pressure and diluted with water (200 ml). The aqueous solution was extracted with diethyl ether (2 × 100 ml), dried, and evaporated under reduced pressure to give an oil which, on fractional distillation, gave diethyl 3,4-dimethylhexanedioate (16a, c, d) as a liquid (68 g, 60%), b.p. 80—110 °C/2 mmHg (lit.,[33] 103 °C/1.55 mmHg). ^{13}C N.m.r. spectroscopy using a 3-s pulse delay [22] gave the following signals with intensity comparisons in parentheses: δ_C $C^{a,a'}$ 14.30, 16.63 (213 : 82), $C^{b,b'}$ 34.20, 34.68 (153 : 65), $C^{c,c'}$ 39.62, 38.44 (180 : 75), $C^{d,d'}$ 173.09, 173.22 (60 : 29), C^e 60.27 (193), and C^f 14.89 p.p.m. (238).



Diethyl meso-3,4-*Dimethylhexanedioate* (16a).—A solution of the *meso*-diacid (11) (0.1 g, 0.57 mmol) and concentrated sulphuric acid (1 drop) in dry ethanol (1 ml) was boiled under reflux for 6 h. Diethyl ether (50 ml) was then added and the solution was washed in turn with saturated aqueous sodium hydrogencarbonate (5 ml) and saturated brine (5 ml) and dried. Concentration under reduced pressure gave the *meso*-diester (16a) (0.12 g, 92%) as a liquid, b.p. 80—100 °C/2 mmHg (Kugelrohr); δ_C 16.63 (C^a), 34.68 (C^b), 38.45 (C^c), 173.28 (C^d), 60.32 (C^e), and 14.26 p.p.m. (C^f).

4,5-*Dimethyltetrahydro*-2-*pyrone* (13a, b, c, d).—A solution of the mixture of diesters (16a, c, d) (35 g, 0.152 mol) in 10% aqueous sodium hydroxide (400 ml) was boiled under reflux for 1 h, cooled to room temperature, and extracted with diethyl ether (100 ml). The aqueous phase was acidified (5M sulphuric acid), saturated with sodium chloride, and extracted with diethyl ether (5 × 200 ml). The combined organic phases were dried and evaporated under reduced pressure and the residue was recrystallised from diethyl ether to give the mixture of diacids (11) as a solid (26 g, 98%), m.p. 104 °C (lit.,[34] 104—105 °C).

Following the procedure outlined above for the *meso*-diacid (11), this mixture of diacids was converted *via* the 3,4-dimethylcyclopentanones (92%), b.p. 56—80 °C/15 mmHg into a mixture of 4,5-dimethyltetrahydro-2-pyrones (13a—d) (84%), b.p. 70—72 °C at 0.4 mmHg. G.l.c. analysis and comparison with authentic racemic lactone [(13a) + (13b)] (see above) (5% Carbowax 20M on Diatomite C AAW DMCS, 3 mm × 3 m; 152 °C) showed the ratio of the diastereoisomers present to be 25 : 75 [(13a) + (13b)] : [(13c) + (13d)]. As (13a) and (13b) were derived from the *meso*-diester (16a), and (13c) and (13d) from the racemic diester [16c) + (16d)], this accurate analysis confirms the approximate analysis of the mixture of diesters obtained by the comparison of ^{13}C n.m.r. line intensities outlined previously.

1-*Iodo*-2,3-*dimethyl*-5-(*tetrahydropyran*-2-*yloxy*)*pentane* (15a—d).—Following the procedure outlined above for the racemic materials, the mixture of lactones (13a—d) was converted into a mixture of the corresponding iodo tetrahydropyranyl ethers (80%) *via* the bromo esters (71%), b.p. 70—72 °C/0.01 mmHg; bromo alcohols (70%), b.p. 75—76 °C/0.02 mmHg; and bromo tetrahydropyranyl ethers (53%).

(10R,11S/10S,11R)-(3Z,7E)-3,7,10,11-*Tetramethyl*-13-(*tetrahydropyran*-2-*yloxy*)*trideca*-3,7-*diene* [(18a) + (18b)].—t-Butyl-lithium (1.35 ml of a 1.6M solution in pentane, 2.04 mmol) was added under argon to a stirred solution of the vinyl iodide (2; X = I) (0.26 g, 1.02 mmol) in dry diethyl ether (10 ml) at −85 °C. The solution was stirred at −85 °C for 1 h whence g.l.c. analysis showed complete conversion into the lithio compound (17) had occurred (5% OV101 on Chromosorb W-HP, 3 mm × 3 m; 100—300 °C at 16 °C min^{-1}). The iodo tetrahydropyranyl ether [(15a) + (15b)] (0.585 g, 1.8 mmol) was added, followed by dry THF (30 ml), and the reaction mixture was stirred and allowed to warm to 0 °C during 18 h.* Saturated aqueous ammonium chloride was added (20 ml), the phases were separated, and the aqueous phase was extracted with diethyl ether (2 × 20 ml). The combined organic phases were dried and the solvents were removed under reduced pressure to give a pale oil which on purification by flash chromatography [diethyl ether–light petroleum (b.p. 40—60 °C) (8 : 92 v/v) as eluant], gave (10*R*,11*S*/10*S*,11*R*)-(3*Z*,7*E*)-3,7,10,11-tetramethyl-13-(tetrahydropyran-2-yloxy)trideca-3,7-diene [(18a) + (18b)] as an oil (0.41 g, 60%), δ (100 MHz) 0.84 (6 H, m, 2 × Me), 0.96 (3 H, t, *J* 8 Hz, *Me*CH_2), 1.6 (3 H, s, 7-Me), 1.69 (3 H, s, 3-Me), 2.01 (8 H, m, 4 × allylic CH_2), 3.5 (2 H, m, CH_2O), 3.8 (2 H, m, CH_2O), 4.6 (1 H, m, OCHO), 4.62 (10 H, m), and 5.1 (2 H, m, 4- and 8-H); *m/z* 337 (0.1), 336 (0.2), 137 (4.4), 123 (3.2), 109 (43), 95 (14.3), and 85 (100).

(3R,4S/3S,4R)-(6E,10Z)-3,4,7,11-*Tetramethyltrideca*-6,10-*dien*-1-*ol*.[5]—A solution of the tetrahydropyranyl ether [(18a) + (18b)] (0.1 g, 0.29 mmol) and toluene-*p*-sulphonic acid (1 mg) in dry methanol (20 ml) was heated to 50 °C for 1.5 h. The solvent was removed under reduced pressure, the residue was taken up in diethyl ether (20 ml), and the solution was washed with saturated aqueous sodium hydrogencarbonate (1 ml). The solution was dried and the solvent was removed under reduced pressure to give the known [5] (3*R*,4*S*/3*S*,4*R*)-(6*E*,10*Z*)-3,4,7,11-tetramethyltrideca-6,10-dien-1-ol [(18a) + (18b)] as a pale oil (68 mg, 93%), $\nu_{max.}$ (5% solution in $CHCl_3$) 3 400s and 2 900m cm^{-1}; δ 0.85 (9 H, m, 3 × Me), 1.5 (3 H, s, allylic Me), 1.52 (5 H, m), 1.59 (3 H, s, allylic Me), 1.90 (8 H, m, 4 × allylic CH_2), 3.60 (2 H, t, *J* 8 Hz, CH_2O), and 5.01 (2 H, m, 6- and 10-H).

* The success of this alkylation depends entirely on the use of absolutely dry reagents and solvents, and flame-dried glassware.

(3R,4S/3S,4R)-(6E,10Z)-3,4,7,11-*Tetramethyltrideca*-6,10-*dienal; Racemic Faranal*[5] [(1a) + (1b)].—Pyridinium chlorochromate on neutral alumina[35] (0.6 g, 0.6 mmol PCC) was added to a stirred solution of the alcohol [(18a) + (18b)] (67 mg, 0.27 mmol) in dichloromethane (10 ml) and the mixture was stirred under nitrogen for 15 h. Diethyl ether (3 ml) was added and the mixture was filtered through a short column of silica gel to give a solution which, on concentration under reduced pressure, gave pure (3*R*,4*S*/3*S*,4*R*)-(6*E*,10*Z*)-3,4,7,11-tetramethyltrideca-6,10-dienal [(1a) + (1b)] as an oil (56 mg, 84%), homogeneous by g.l.c. (on Chromosorb W-HP, 3 mm × 3 m); $\nu_{max.}$ 2 700m and 1 720s; δ (400 MHz; [$^2H_6$]benzene) 0.69 (3 H, d, *J* 7 Hz, Me), 0.72 (3 H, d, *J* 7 Hz, Me), 0.94 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.52 (4 H, m), 1.55 (3 H, s, 7-Me), 1.69 (3 H, s, 11-Me), 2.0 (8 H, m, 4 × allylic CH_2), 5.15 (1 H, m, C=CH), 5.19 (1 H, m, C=CH), and 9.39 (1 H, dd, *J* 1.5 and 2.5 Hz, CHO); *m/z* (probe) 250 (M^+, 1.4%), 249 (1.5), 137 (10), 123 (16), 95 (19), 85 (100), 55 (52), and 41 (27) (Found: M^+, 250.2454. $C_{17}H_{30}O$ requires *M*, 250.2298). No evidence of contamination by unwanted double-bond isomers was apparent from the 400-MHz ^1H n.m.r. spectrum (*cf.* ref. 5).

(6E,10Z)-3,4,7,11-*Tetramethyltrideca*-6,10-*dienal; Faranal* (1a—d).—Following the procedure described above for the racemic sample, the mixture of iodo tetrahydropyranyl ethers (15a—d) was converted into a mixture of faranals (1a—d). Based on the isomeric composition of the lactones (13a—d) (obtained by g.l.c. analysis as described above), the composition of this mixture of isomeric faranals was 25% (3*R*,4*S* + 3*S*,4*R*)-faranal and 75% (3*R*,4*R* + 3*S*,4*S*)-faranal.

Acknowledgements

We thank the S.E.R.C. for financial support and Drs. B. T. Golding and O. W. Howarth of the University of Warwick for 400-MHz ^1H n.m.r. spectra.

References

1 A. Krzeminska, B. Stycznska, H. Mankowska, and B. Sereda, *Rocz. Panstw. Zakl. Hig.*, 1979, **30**, 623 (*Chem. Abstr.*, 1980, **93**, 2176f).
2 S. H. Beatson, *Lancet*, 1972, 425.
3 F. J. Ritter, I. E. M. Brüggemann-Rotgans, P. E. J. Verwiel, C. J. Persoons, and E. Talman, *Tetrahedron Lett.*, 1977, 2617.
4 M. Kobayashi, T. Koyama, K. Ogura, S. Seto, F. J. Ritter, and I. E. M. Brüggemann-Rotgans, *J. Am. Chem. Soc.*, 1980, **102**, 6602.
5 K. Mori and H. Ueda, *Tetrahedron Lett.*, 1981, **22**, 461.
6 F. J. Ritter, U.S.P. 4 200 590/1980 (*Chem. Abstr.*, 1980, **93**, 132078m).
7 D. W. Knight and B. Ojhara, *Tetrahedron Lett.*, 1981, **22**, 5101.
8 A. Marfat, P. R. McGuirk, and P. Helquist, *J. Org. Chem.*, 1979, **44**, 3888.
9 R. Baker, D. C. Billington, and N. Ekanayake, *J. Chem. Soc., Chem. Commun.*, 1981, 1234.
10 J. F. Normant, G. Cahiez, C. Chuit, and J. Villieras, *J. Organomet. Chem.*, 1974, **77**, 269.
11 A. Commercon, J. F. Normant, and J. Villieras, *J. Organomet. Chem.*, 1977, **128**, 1.
12 J. F. Normant, G. Cahiez, and D. Bernard, *Synthesis*, 1976, 245.
13 D. Seebach and H. Neumann, *Chem. Ber.*, 1974, **107**, 847.
14 H. Neumann and D. Seebach, *Tetrahedron Lett.*, 1976, 4839.
15 K. Mori, M. Ohki, A. Sato, and M. Matsui, *Tetrahedron*, 1972, **28**, 3739.
16 A. B. Theis and C. A. Townsend, *Synth. Commun.*, 1981, **11**, 157.
17 H. Westmijze, J. Meijer, H. J. T. Bos, and P. Vermeer, *Recl. Trav. Chim. Pays-Bas*, 1976, **95**, 299, 304.
18 J. F. Bussert, K. W. Greenlee, J. M. Derfer, and C. F. Boord, *J. Am. Chem. Soc.*, 1956, **78**, 6076; B. Rickborn and S.-Y. Lwo, *J. Org. Chem.*, 1965, **30**, 2212; H. Peters, R. A. Archer, and H. S. Mosher, *ibid.*, 1967, **32**, 1382.
19 H. M. Walborsky, L. Barsh, and J. C. Davis, *Tetrahedron*, 1963, **19**, 2333.
20 F. Beck, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 760.
21 M. M. Baizer, *Tetrahedron Lett.*, 1963, 973.
22 J. B. Stothers, 'Carbon-13 NMR Spectroscopy,' Academic Press, New York, 1972.
23 G. G. Levy and G. L. Nelson, 'Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley-Interscience, New York, 1972.
24 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
25 S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, 1967, **9**, 165.
26 H. O. House, C.-Y. Chu, J. M. Wilkins, and M. J. Umen, *J. Org. Chem.*, 1975, **40**, 1460.
27 A. C. Cope and E. C. Herrick, *J. Am. Chem. Soc.*, 1950, **72**, 983.
28 W. J. Bailey and J. Rosenberg, *J. Am. Chem. Soc.*, 1955, **77**, 73.
29 L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' John Wiley, New York, 1967, vol. 1, p. 723.
30 P. Ganis, E. Martuscelli, and G. Avitabile, *Ric. Sci.*, 1968, **38**, 689.
31 J. F. Thorpe and G. A. R. Kon, *Org. Synth.*, (1961), Coll. Vol. 1, 192.
32 W. C. M. C. Kokke and F. A. Varkevisser, *J. Org. Chem.*, 1974, **39**, 1535.
33 M. R. Ort and M. M. Baizer, *J. Org. Chem.*, 1966, **31**, 1646.
34 M. L. Bouguerra and J. Wiemann, *C.R. Acad. Sci., Ser. C*, 1966, **263**, 782 (*Chem. Abstr.*, 1967, **66**, 3423c).
35 Y. S. Cheng, W. L. Liu, and S. Hsiachen, *Synthesis*, 1980, 223.

Received 18*th October* 1982; *Paper* 2/1773