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

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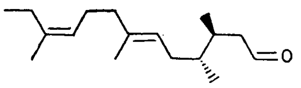
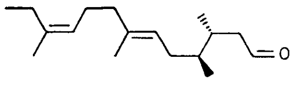
Summary Racemic (3*R*,4*S*/3*S*,4*R*)-faranal, has been synthesised by a convergent, stereospecific route from (1*E*,5*Z*)-1-iodo-2,6-dimethylocta-1,5-diene in good overall yield; this synthesis employed the addition of alkylcopper complexes to terminal acetylenes to generate the two trisubstituted double bonds, and a Diels–Alder reaction to establish the relative configuration of the C-3,C-4 methyl groups.

The Pharaoh's ant, *Monomorium pharaonis*, is now well established as a major pest in hospitals, bakeries, and food stores in the United Kingdom.[1] It is a particularly serious pest in hospitals since it has been shown to carry a number of disease vectors, and has been frequently found in sterile dressing packs, and in the wounds of post operative patients.[1] The most active component of the trail pheromone of *M. pharaonis*, given the name faranal, has recently been shown to be (6*E*,10*Z*)-3,4,7,11-tetramethyltrideca-6,10-dienal,[2] and its absolute configuration has been demonstrated to be (3*S*,4*R*)-(**1a**).[3] Although the naturally occurring isomer is the most biologically active, a mixture of (3*S*,4*R*)- and (3*R*,4*S*)-faranal has been shown to possess considerable activity.[3]



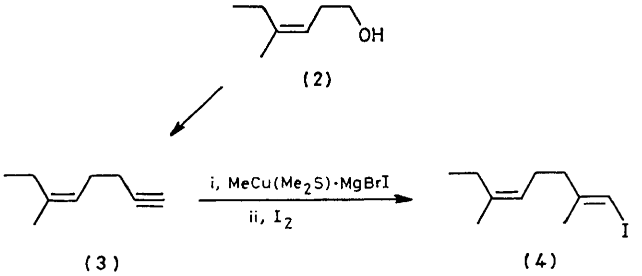
(1a)

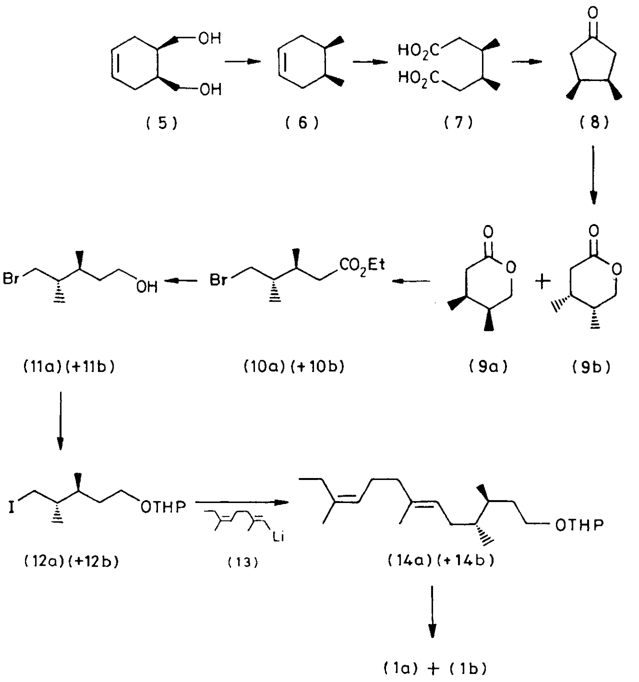


(1b)

We now report a convergent, highly stereospecific synthesis of racemic (3*S*,4*R*/3*R*,4*S*)-faranal in which the stereospecific formation of a trisubstituted double bond and a substituted vinyl iodide is controlled by the addition of alkylcopper complexes to terminal acetylenic intermediates, and the relative configuration of the methyl groups at C-3 and C-4 is established by the use of *cis*-4,5-dimethylcyclohexene as an important intermediate.

Addition of the dimethyl sulphide–cuprous bromide complex of ethylmagnesium bromide (0·17 mol) to propyne (0·17 mol) by the method of Helquist,[4] gave a vinylcopper complex, which reacted with ethylene oxide over 36 h to give the (*Z*)-homoallylic alcohol (**2**) in 73% yield [14·2 g, b.p. 75 °C/20 mmHg;[5] no evidence of contamination by (*E*)-isomer was apparent by capillary g.l.c. of the trimethylsilyl ether].† This alcohol has previously been prepared by a multistep procedure from 2-cyclopropylbut-3-yn-2-ol.[5] Conversion of the alcohol (**2**) into its toluene-*p*-sulphonyl ester, and subsequent reaction of this ester with the ethylenediamine complex of lithium acetylide in dimethyl sulphoxide for 3 h at 25 °C gave the terminal acetylene (**3**) in 70% yield (b.p. 52 °C, 20 mmHg). In agreement with the findings of others,[6] we experienced difficulty in performing the addition of the dimethyl sulphide–cuprous bromide complex of methylmagnesium iodide to the unactivated terminal acetylene (**3**) under the conditions specified in ref. 4, observing essentially no reaction using the time and temperature recommended. By allowing the reaction mixture to warm up to room temperature for 15 min, however, before stirring for 24 h at −15 °C, we were able to observe the formation of an alkenylcopper complex, which on subsequent quenching with iodine[7] gave (1*E*,5*Z*)-1-iodo-2,6-dimethylocta-1,5-diene (**4**) in 66% yield (b.p. 80 °C, 0·01 mmHg).





Scheme. THP = tetrahydropyranyl.

The *cis*-diol (**5**) was prepared from reaction of buta-1,3-diene and maleic anhydride by a literature procedure,[8] in 83% yield (b.p. 135 °C, 1·0 mmHg).[8] Conversion of this

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† For a full discussion of the very high stereoselectivity of this reaction see ref. 4.

diol (**5**) into a dimethanesulphonate, and subsequent reduction of this ester with 8 equiv. of a 1 : 1 mixture of sodium hydride and lithium aluminium hydride in diethyl ether, gave *cis*-4,5-dimethylcyclohexene (**6**) in 95% yield (b.p. 123—124 °C).[9] Previous published procedures for the reduction of (**5**) to (**6**) *via* either the dimethanesulphonate, or ditoluene-*p*-sulphonate gave (**6**) in only 25—50% yield.[9] Ozonolysis of (**6**) in CH_2Cl_2 at -78 °C followed by oxidation of the product with Jones reagent gave the diacid (**7**) in 80% yield (m.p. 128 °C).[10] Following the literature conditions, (**7**) was pyrolysed in the presence of barium hydroxide to give *cis*-3,4-dimethylcyclopentanone (**8**) in 78% yield (b.p. 62—80 °C, 15 mmHg),[11] which was oxidised with *m*-chloroperbenzoic acid in methylene chloride to give a 50/50 mixture of the enantiomeric lactones (**9a**) and (**9b**) in 87% yield (b.p. 80—84 °C, 0·6 mmHg).[11] For brevity only the products derived from (**9a**) are depicted in the remainder of the Scheme. Treatment of this mixture of lactones with anhydrous hydrogen bromide in ethanol gave bromoesters (**10a**) and (**10b**) in 64% yield (b.p. 70—72 °C, 0·14 mmHg)[11] which were reduced with lithium aluminium hydride in diethyl ether to the bromoalcohols (**11a**) + (**11b**) in 80% yield (b.p. 76 °C, 0·02 mmHg). Reaction of this mixture of bromoalcohols with dihydropyran, followed by halogen exchange using sodium iodide in acetone gave the iodotetrahydropyranyl ethers (**12a**) + (**12b**) in 70% yield.

Treatment of vinyl iodide (**4**) with 2 equiv. of t-butyllithium in diethyl ether at -90 °C for 1 h gave a vinyllithium derivative (**13**),[12] which was successfully alkylated with the mixture of iodides (**12a**) + (**12b**) in diethyl ether/tetrahydrofuran (1 : 3),[13] to give the protected alcohols (**14a**) + (**14b**) in 60% yield (after purification on silica gel). These alcohols were deprotected using toluene-*p*-sulphonic acid in methanol (80% yield), and oxidation wlth pyridinium chlorochromate on alumina gave racemic (3*R*,4*S*/3*S*,4*R*)-faranal (**1a** + **1b**) in 84% yield. The i.r., m.s., and 400 MHz ^{1}H n.m.r. spectra of this material are identical with the published data.[11]

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