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A TOTAL SYNTHESIS OF (±)-FARANAL, THE TRUE TRAIL PHEROMONE OF PHARAOH'S ANT, MONOMORIUM PHARAONIS

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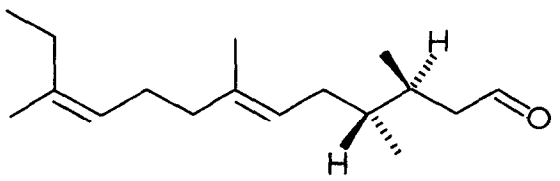
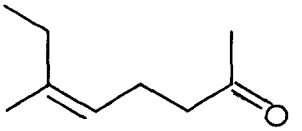
Summary: A relatively brief total synthesis of (±)-Faranal [3SR,4RS), (6E,10Z)-3,4,7,11-tetramethyl-6,10-tridecadien-1-al] (1) is reported.

The true trail pheromone of Pharaoh's ant, Monomorium pharaonis was first isolated in 1977 and shown to be (6E,10Z)-3,4,7,11-tetramethyl-6,10-tridecadien 1-al.[1] The two chiral centres in the pheromone, given the trivial name of faranal, were originally[1] thought to be (3S,4S) or (3R,4R), but further examination of the ozonolysis products of the pheromone established the (3S,4R) or (3R,4S) geometry at these centres.[2] Subsequently, a rather small scale bio-organic synthesis revealed that natural (+)-faranal has the (3S,4R) stereochemistry shown in formula (1)[3]; this was further confirmed by a more conventional if lengthy total synthesis.[4] Herein, we wish to report our total synthesis of (3RS,4SR)-faranal (1); a similar racemic mixture has been reported to possess significant biological activity.

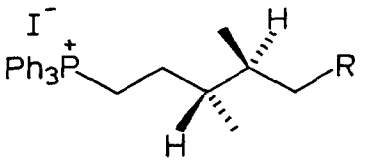
Our plan was to construct the central double bond of faranal using a Wittig condensation for which we required the ketone (2) and a suitable phosphonium salt (3), in which the terminal substituent, R, could be readily converted into the aldehyde function present in (1). The ketone (2) was obtained in a "one-pot" reaction, based on the approach of Helquist et al.,[6] by the addition of [EtMgBr.CuBr.Me_2S] to propyne to give an intermediate vinyl cuprate species which was converted into an ate complex by the addition of 1-lithio-1-hexyne. The resulting intermediate was condensed with methyl vinyl ketone to give the desired product (2) in ca. 30% isolated yield. Although the yield was rather low, this was compensated for by the stereochemical purity of the product, which was ≥ 98% as judged by ^{1}H n.m.r. and GLC analysis. We then examined a number of model Wittig reactions using commercially available 6-methylhept-5-en-2-one as the ketone component and a range of appropriate phosphonium salts (4) - (8).[7] Under a variety of conditions, salts (4) - (7) failed to give useful yields of the desired olefinic products. However, condensation between the model ketone and the ylid salt derived from (8) using two equivalents of NaH in DMSO gave a ca.70%



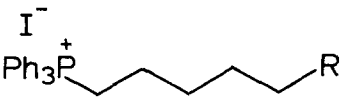
(1)



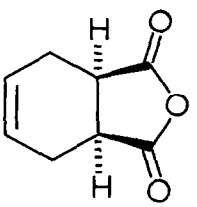
(2)



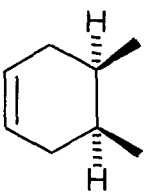
(3)



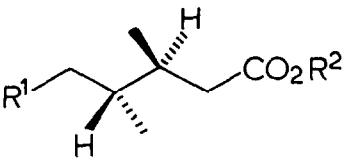
(4) R=CH_2OH
(5) R=CH_2OThP
(6) R=CH_2OMEM
(7) R= 
(8) R=CO_2H



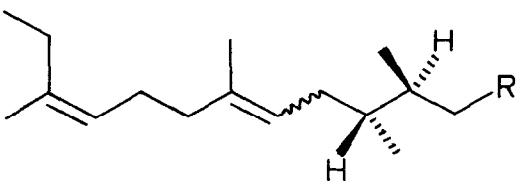
(9)



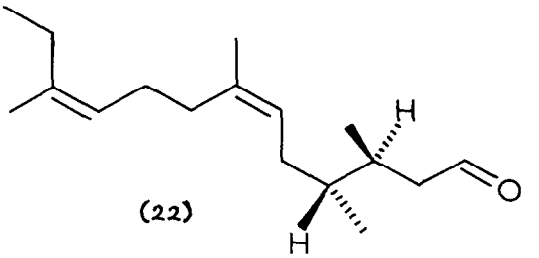
(10)



(11) R^1=CO_2H; R^2=H,
(12) R^1=CO_2H; R^2=Et
(13) R^1=CH_2OH; R^2=Et
(14) R^1=CH_2OTs; R^2=Et
(15) R^1=CH_2I; R^2=Et
(16) R^1=CH_2I; R^2=H
(17) R^1=$CH_2\overset{+}{P}Ph_3I^-$; R^2=H



(18) R=CO_2H
(19) R=CO_2Me
(20) R=CH_2OH
(21) R=CHO



(22)

yield of the required products. Therefore, for the preparation of (±)-faranal (1), we required the phosphonium salt (17).

Reduction of the commercially available cis-anhydride (9) with $LiALH_4$ in THF gave the corresponding cis-bis-hydroxymethylcyclohexene[8] which was mesylated[8] and reduced using $LiALH_4$ in THF to give cis-1,2-dimethyl-4-cyclohexene (10) (68%; b.p. 120-121°). Oxidative cleavage[9] of (10) using potassium permanganate in a two-phase system of water and benzene with tetra-n-butylammonium hydrogensulphate as transfer catalyst led to the meso-diacid (11) (65%; m.p. 134.5 - 135.5° (Lit.[10] m.p. 133 - 134°)). ^{13}C n.m.r. showed the diacid (11) to be stereochemically pure; in $(CD_3)_2CO$ it displayed resonances at 16.9, 35.2, 38.3, and 174.5 ppm.[11] The diacid was partially esterified[12] ($EtOH-H_2O-H_2SO_4$) to give the half-ester (12)[13] (90%; b.p. 119 - 120° at 0.02 mm Hg) and then reduced using BH_3-THF[14] to the hydroxy-ester (13) (92%); b.p. 108 - 110° at 0.2 mm Hg). (13) was converted into the tosylate (14) using TsCl in pyridine and thence into the iodide (15), b.p. 98° at 0.5 mm Hg, using NaI in acetone, in 86% overall yield. Careful saponification using cold, ethanolic potassium hydroxide gave the iodo-acid (16) (82%) which was transformed into the required phosphonium salt (17), m.p. 218 - 219°, in 90% yield using triphenylphosphine in benzene under reflux.

The Wittig condensation between ketone (2) and the salt (17) proceeded as expected, using 2 eq. NaH in DMSO, to give the desired acid (18) in 70% yield as a mixture of the (6E)- and (6Z)-isomers. These were reduced to the alcohols (20) (80%) with $LiAlH_4$-THF or, in slightly higher yield, by prior conversion to the methyl esters (19) (CH_2N_2) followed by reduction using $LiAlH_4$ in ether. GLC analysis[15] of the esters showed an isomer ratio of (6Z)-(19): (6E)-(19) of 54:46. Finally, the alcohols (20) were oxidised to the aldehydes (21) in 70% yield using pyridinium chlorochromate;[16] these were separated by preparative-scale GLC[15] to give (±)-faranal (1), which exhibited ^1H n.m.r. infra-red, and mass spectral data indistinguishable from those recorded for the natural product.[1] The (6Z,10Z) isomer (22) (eluted first) was readily distinguished from (1) by ^1H n.m.r. spectroscopy, both in the overall appearance of the spectrum, and particularly by the occurrence of two, separate, broad triplets at δ 5.13 and 5.20 for the two olefinic protons (in faranal, these occur as overlapping triplets at δ 5.16 and 5.19) and of the 7-methyl resonance at δ 1.68. (δ 1.56 in faranal).

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