

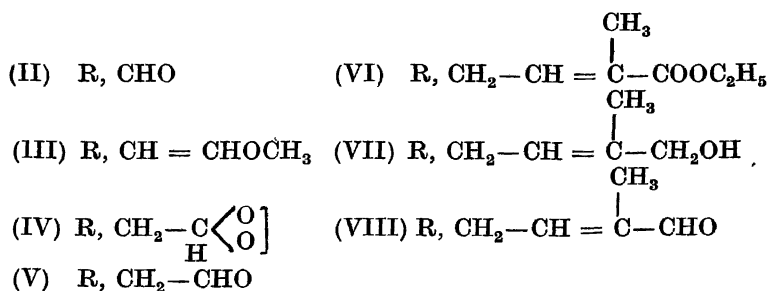
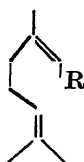
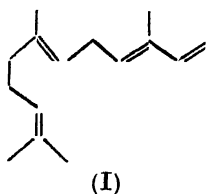
Terpenoids LIX—A Synthesis of α -Farnesene

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A synthesis of α -farnesene, starting from citral through the application of Wittig and modified Wittig reactions, is described.

An acyclic sesquiterpene hydrocarbon α -farnesene has been isolated¹ from the natural coating of "Grammy Smith" apples and also from *Duffours gland secretion in Ant Aphoenogaster* (F. Sm)². Prior to isolation its presence was detected in various other essential³ oils. On the basis of spectral data and chemical reactions, α -farnesene has been assigned constitution (I).

The present investigations record a synthesis of the structure (I) assigned to α -farnesene. The synthesis is patterned after the synthesis of α -ocimene⁴ as both the compounds are having the same diene systems as a part of their structures and the scheme proceeds as follows.



The methoxy methylene derivative (III) was obtained from citral (II) by Wittig reaction with methoxymethylene triphenylphosphorane⁵ followed by chromatography over alumina

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with *n*-hexane as the eluent. The compound (III) was ketalised with ethylene glycol according to the conditions laid down by Corey *et al*⁶. The ketal (IV) was treated with aqueous acetone and *p*-toluene sulphonic acid at room temperature⁷ to give aldehyde (V) after repeated fractionations under vacuum. The possibility of migrating β - γ trisubstituted double bond into conjugation with aldehyde was eliminated by using mild reaction conditions. This was also supported through spectral data. I.R. spectrum showed characteristic peak at 1715 cm^{-1} (sat. aldehyde) in place of 1680 cm^{-1} (as in citral for conj. aldehyde)⁸. U.V. spectrum did not show any absorption corresponding to α , β -unsaturated aldehyde. This aldehyde (V) was converted into ethyl 2, 6, 10 trimethyl-2,5,9-undecatrien-1-oate (VI) through its modified Wittig reaction⁹ with ethyl α -diethyl phosphonopropionate in dimethyl ether of diethylene glycol and sodium hydride. It was chromatographed over alumina with petroleum ether benzene (88 : 12) as the eluent. Lithium aluminium hydride reduction (VI) at low temperature furnished the corresponding allylic carbinol (VII) which was smoothly oxidised¹⁰, to 2,6,10-trimethyl,2,5,9-undecatrien-1-al with active MnO_2 . This was purified by chromatography over alumina with petroleum ether-benzene (95 : 5) as the eluent. Wittig reaction¹¹ with methylene triphenylphosphorane on α , β -unsaturated aldehyde (VIII) gave the hydrocarbon (I). I.R. and U.V. spectral data were in good agreement with those reported for natural α -farnesene.

EXPERIMENTAL

3,7-Dimethyl-1-methoxymethylene-2,6-ocadiene (III): To the phosphorane, prepared from sodium hydride (3.6 g.) in dimethylsulphoxide (36 ml.) and methoxymethylene triphenyl phosphonium chloride (27 g.) in dimethylsulphoxide (72 ml.) in the usual manner, was added citral (II, 6 g.) in tetrahydrofuran (15 ml.) with efficient stirring and cooling. The reaction mixture was kept stirring overnight. Thereafter it was decomposed by pouring into cold water (60 ml.) and the organic layer was taken up in petroleum ether and washed with cold water (3×40 ml.). After drying and solvent removal, the residue was chromatographed over alumina (80 g.) with *n*-hexane followed by distillation under vacuum to give the methoxymethylene derivative (III, 5.9 g.) in 74% yield, b.p. 115–118°/7–8 mm. $\eta_D^{20} = 1.4912$ (Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}$; C, 79.44; H, 11.18. Found : C, 79.48; H, 11.63). I.R. spectrum showed prominent bands at 2900, 1650, 1440, 1400, 1350, 1210, 1120, 1065, 960, 855, 820 and 770 cm^{-1} .

4,8-Dimethyl-1,1-ethylenedioxy-3,7-nonadiene (IV): A mixture of (III, 5.5 g.), ethylene glycol (3.2 g.), anhydrous benzene (125 ml.) and *p*-toluene sulphonic acid (250 mg.) was refluxed at 130° under a Dean and Stark continuous water separator for 6 hrs. The reaction mixture was neutralised with sodium bicarbonate and worked up in the usual manner when

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ketal (IV, 5.0 g.) was obtained in 77% yield, b.p. 125–128°/7–8 mm. $\eta_D^{20} = 1.4933$. I.R. spectrum had prominent band at 2900, 1450, 1385, 1260, 1140, 1090, 1030, 960, 898, 820, 800 and 740 cm^{-1} .

4,8-Dimethyl-1,3-nonadiene-1-al (V): The ketal (IV, 4.6 g.) was dissolved in aqueous acetone (121.5 ml.) (prepared by dissolving 108 ml. of acetone in 13.5 ml. of water). To this was added *p*-toluene sulphonic acid (1.35 g.) and was allowed to stand at room temperature for 4 hrs. The contents were diluted with saturated sodium chloride solution (100 ml.) and the product taken up in ether. It was dried and the solvent was expelled followed by repeated fractionations under vacuum (thrice) to give saturated aldehyde (V, 1.2 g.) in 50% yield, b.p. 114–115°/9–10 mm. $\eta_D^{20} = 1.4771$ (Calcd. for $\text{C}_{11}\text{H}_{18}\text{O}$, C, 79.46; H, 10.92. Found: C, 79.67; H, 10.45). I.R. spectrum had prominent bands at 2940, 2700, 1715, 1630, 1450, 1375, 1245, 1130, 1100, 1060, 1030, 970, 930, 900, 865, 820 and 790 cm^{-1} . U.V. spectrum did not show any absorption in the α , β -unsaturated carbonyl region.

Ethyl 2,6,10-trimethyl-2,5,9-undecatrien-1-oate (VI): To the slurry of sodium hydride (0.98 g.) in diglyme (100 ml.) was added ethyl α -diethylphosphonopropionate (5 g.) dropwise below 20°. To the resultant clear solution was added aldehyde (V, 2.5 g.) slowly below 20°. After addition, the solution was further stirred for an hour. The product was extracted with ether (3x60 ml.) after decomposing with cold water. The ethereal layer was dried. After removal of solvent, the residue was chromatographed over alumina with petroleum ether-benzene (88 : 12) as the eluent followed by vacuum distillation to secure the unsaturated ester (VI, 2.8 g.) in 77% yield, b.p. 139–140°/5–6 mm. $\eta_D^{20} = 1.4750$ (Calcd. for $\text{C}_{16}\text{H}_{26}\text{O}_2$, C, 76.75; H, 10.47. Found: C, 76.99; H, 10.10). I.R. spectrum had prominent peaks at 2950, 1730, 1650, 1450, 1380, 1310, 1300, 1280, 1270, 1260, 1185, 1170, 1100, 1060, 1020, 980, 910, 865, 810 and 700 cm^{-1} .

2,6,10-Trimethyl-2,5,9-undecatrien-1-ol (VII): To a suspension of lithium aluminium hydride (0.8 g.) in dry ether (30 ml.) was added slowly with stirring the unsaturated ester (VI, 2.5 g.) in ether (25 ml.) at 0°. After the addition the mixture was stirred for 2 hrs. at room temperature. Thereafter the contents were decomposed with a solution of sodium potassium tartrate 10%, 100 ml. The product was extracted with ether, washed with brine and dried. Solvent was removed and the residue on distillation under vacuum gave carbinol (VII, 1.5 g.) in 75% yield, b.p. 108–110°/4 mm. $\eta_D^{24} = 1.4910$ (Calcd. for $\text{C}_{14}\text{H}_{24}\text{O}$, C, 80.71; H, 11.61. Found: C, 80.89; H, 10.90). I.R. spectrum did not show any absorption in the carbonyl region but had prominent bands at 3400, 2950, 1645, 1460, 1390, 1250, 1130, 1045, 970, 920, 890, 860 and 820 cm^{-1} .

2,6,10-Trimethyl-2,5,9-undecatrien-1-al (VIII): The allylic alcohol (VII, 2.0 g.) was added to a suspension of manganese dioxide (30 g.) in 350 ml. of petroleum ether. The reaction mixture was stirred vigorously for 8 hrs. The solid was then separated from the reaction mixture by filtration and the residue was washed with petroleum ether (6x33 ml.). The combined solvent was concentrated and the residue was chromatographed over neutral alumina (50 g.) with petroleum ether-benzene (95 : 5) as the eluent followed by fractionation under vacuum to furnish α , β -unsaturated aldehyde (VIII, 1.56 g.) in 78% yield, b.b. 104–106°/4–5 mm. $\eta_D^{24.5} = 1.4709$. I.R. spectrum showed no absorption in –OH region but had

main peaks at 3045, 2925, 2700, 1680, 1635, 1450, 1360, 1245, 1135, 1020, 995, 960, 898, 860, 845 and 815 cm^{-1} .

2,6,10-Trimethyl-2,6,9,11-dodecatetraene (I): To the phosphorane, prepared from sodium hydride (0.11 g.) in dimethylsulphoxide (1.1 ml.) and methyltriphenylphosphonium iodide (1.0 g.) in dimethyl sulphoxide (2.2 ml.) was added aldehyde (VIII, 0.5 g.) with stirring and cooling. The stirring was prolonged for 3 hrs. at 40°. The reaction mixture was cooled and decomposed with ice-cold water and worked up in the usual way to give the crude compound I. This was chromatographed over neutral alumina (26 g.). When on elution with petroleum ether the desired hydrocarbon was obtained which was further purified by distillation under vacuum to have (I, 0.35 g.) in 70% yield, b.p. 98–102°/4 mm., $\eta_D^{25} = 1.4790$ (Calcd. for $\text{C}_{15}\text{H}_{24}$. C, 88.16; H, 11.84. Found: C, 89.49; H, 12.32). I.R. spectrum had comparable peaks with those reported for neutral α -farnesene at 3100, 2900, 1645, 1600, 1450, 1360, 1285, 1130, 1105, 1075, 1035, 990, 890, and 825 cm^{-1} . U.V. spectrum had $\lambda_{\text{max}}^{\text{ethanol}} = 234 \text{ m}\mu$ ($\epsilon \sim 30,000$).

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