

1,5-Dienes from Allylic Alcohols and Carbonyl Compounds by Successive Claisen Rearrangement, Wittig Reaction, and Cope Rearrangement: an Attempted Synthesis of 'Propylure'

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3,3-Dialkylallyl alcohols and aldehyde dimethyl acetals condense with Claisen rearrangement to form substituted pent-4-enals. The hexa-1,5-dienes made from these aldehydes by the Wittig reaction then rearrange in the opposite direction according to Cope. While this scheme worked very well with *n*-heptanal dimethyl acetal and 3-methylbut-2-en-1-ol, yielding 2-methyldodeca-2,6-diene, it was less successful when applied to an attempted synthesis of 'propylure' [(5*E*)-10-propyltrideca-5,9-dienyl acetate].

THE high potency and great specificity of pheromones make their use a promising method for the control of insect pests.¹ 'Propylure' [(5*E*)-10-propyltrideca-5,9-dienyl acetate] (4), is considered to be the sexual pheromone of the female pink bollworm moth *Pectinophora gossypiella* Saunders, a pest which causes great damage to cotton crops.

The compound was first isolated and characterised by Jones *et al.*² and synthesised in 0.2% overall yield. A non-stereospecific synthesis by Eiter *et al.*³ produced a product which exhibited no physiological activity, and it was later shown⁴ that the presence of 15% of the *cis*-isomer inhibited all activity. More recent syntheses⁵⁻⁷ have been more successful, although these procedures are all either lengthy or non-stereospecific.

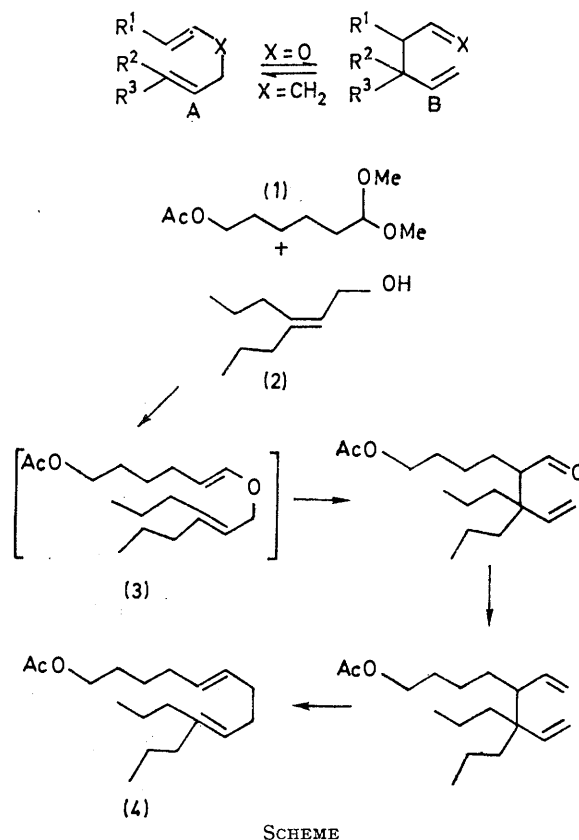
A simple and stereospecific synthesis of propylure was envisaged (Scheme) utilising a Claisen rearrangement of a suitable vinyl ether (3), with the stability of the resulting aldehyde group providing the driving force for the rearrangement. Conversion of this aldehyde into an olefin would then permit a Cope rearrangement to the desired product, with the greater thermodynamic stability of the multiply-substituted double bonds now causing the straight-chain product to be the more stable: *i.e.* the equilibrium $A \rightleftharpoons B$ was expected to lie on the right when $X = O$ but on the left when $X = CH_2$, as shown in the Scheme.

In order to test the feasibility of this scheme, a model reaction, between isoprenyl alcohol (6) and the acetal of *n*-heptanal (5), was first undertaken. The condensation and subsequent Claisen rearrangement proceeded smoothly in boiling mesitylene at 170° when catalysed by *o*-nitrobenzoic acid.⁸ The product, 3,3-dimethyl-2-*n*-pentylpent-4-enal (7), characterised by n.m.r. and mass spectrometry, was obtained in good yield.

Almost quantitative conversion of the aldehyde (7) into the diene (8) was achieved using the modified Wittig reaction of Corey,⁹ and heating the diene (8) in dimethyl

sulphoxide at 190° effected quantitative conversion into the desired propylure analogue (9).

With the efficacy of the reaction sequence thus established, preparation of suitable starting materials † for the production of propylure was undertaken. The



† The alternative but apparently less convenient version of this sequence would have started with a 7-oxygenated hept-2-en-1-ol and 2-*n*-propylpentanal [equivalent to interchanging the enol-ether O and CH₂ in the intermediate (3)] leading to the same diene after Wittig reaction.

¹ D. A. Evans and C. L. Green, *Chem. Soc. Rev.*, 1973, **2**, 75.

² W. A. Jones, M. Jacobson, and D. F. Martin, *Science*, 1966, **152**, 1516.

³ K. Eiter, E. Truscheit, and M. Boness, *Annalen*, 1967, **709**, 29.

⁴ M. Jacobson, *Science*, 1969, **163**, 190.

requisite allylic alcohol, 3-propylhex-2-en-1-ol (2), was initially produced by a Reformatsky reaction with ethyl bromoacetate on heptan-4-one followed by dehydration, and reduction of the ester to the alcohol.² This dehydration, however, was rather difficult. Use of toluene-*p*-

⁵ M. Stoll and I. Flament, *Helv. Chim. Acta*, 1969, **52**, 1996; G. Pattenden, *J. Chem. Soc. (C)*, 1968, 2385.

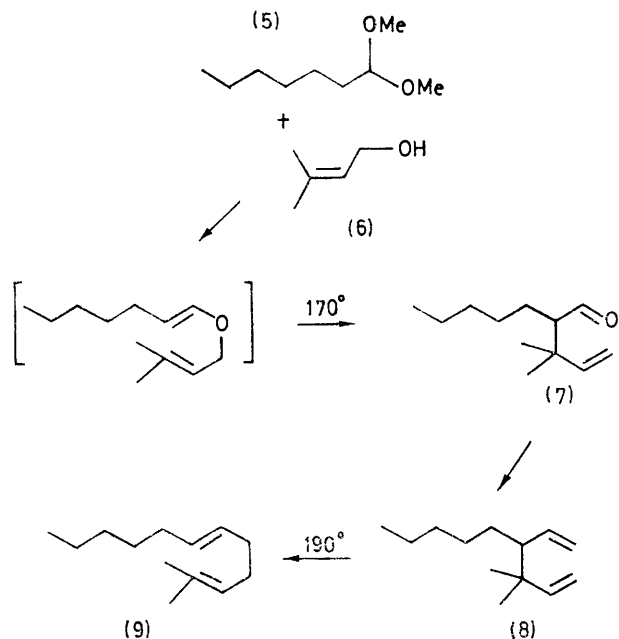
⁶ J. C. Stowell, *J. Org. Chem.*, 1970, **35**, 244.

⁷ A. I. Meyers and E. W. Collington, *Tetrahedron*, 1971, **27**, 5979.

⁸ Cf. R. C. Cookson and N. R. Rogers, *J.C.S. Chem. Comm.*, 1972, 248.

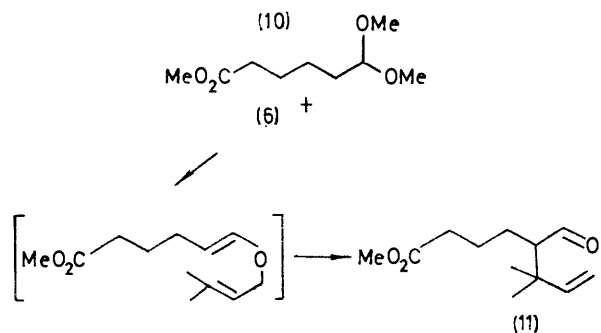
⁹ E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1962, **84**, 866.

sulphonic acid, phosphoryl chloride, and thionyl chloride, all resulted in a mixture of the isomeric ethyl 3-propylhex-2-enoate and ethyl 3-propylhex-3-enoate, which were



not readily separable. The use of dicyclohexylcarbodiimide with copper(II) ion catalyst¹⁰ afforded exclusively the desired 2-ene, but on a large scale this reaction was very slow. Accordingly, ethyl 3-propylhex-2-enoate was made directly by a modified Wittig reaction using triethyl phosphonoacetate,¹¹ and reduction of the ester with lithium aluminium hydride gave the desired allylic alcohol (2).

The other starting material, 6,6-dimethoxyhexyl acetate (1), requires oxygenation at each end of the carbon chain, but with the functional groups in two different oxidation states, and we used methyl 6,6-dimethoxyhexanoate (10), readily prepared by the action of lead tetra-acetate on adipoin.¹² The reduction of the



methyl ester and acetylation of the resulting alcohol could then be performed as final steps.

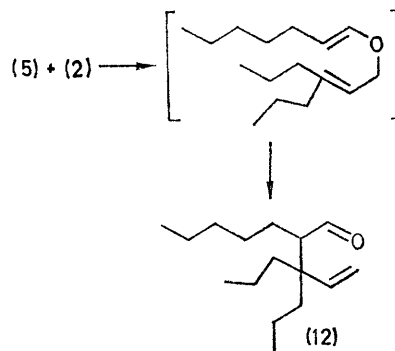
Using these starting materials, two trial reactions

¹⁰ C. Alexandre and F. Rouessac, *Compt. rend. (C)*, 1972, **274**, 1585.

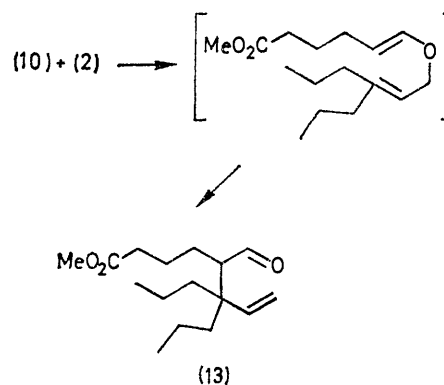
¹¹ W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1733.

were performed. To check the stability of the acetal ester (10), it was treated with isoprenyl alcohol (6) under the conditions employed in the model reaction, and the isolation of the expected product, methyl 5-formyl-6,6-dimethyloct-7-enoate (11), indicated that the condensation and Claisen rearrangement had occurred.

Then, to check the stability of the allylic alcohol (2), this compound was similarly treated with 1,1-dimethoxyheptane (5), and again the expected aldehydic product (12) was obtained in fair yield.



Reaction of the allylic alcohol (2) and the acetal ester (10) in boiling mesitylene at 170°C in the presence of *o*-nitrobenzoic acid did not, however, lead to satisfactory yields of the desired propylure precursor (13). A small



amount of this product was evidenced by g.l.c.-mass spectrometry, but the bulk of the product was methyl 5-formylpentanoate, presumably arising from hydrolysis of the acetal (10) by dehydration of the alcohol (2), as the reaction was performed under anhydrous conditions.

At this juncture, doubt was thrown upon the identity of the pheromone of the pink bollworm moth,¹³ and hence it was not considered worthwhile to proceed with the synthesis of propylure. However, we report this work as an example of the synthetic potential of successive Claisen and Cope rearrangements connected by a Wittig reaction, at least in simple cases such as (5) + (6) → (9).

¹² C. D. Hurd and W. H. Saunders, *J. Amer. Chem. Soc.*, 1952, **74**, 5324.

¹³ J. C. Keller, L. W. Sheets, N. Green, and M. Jacobson, *J. Econ. Entomol.*, 1969, **62**, 1520.

EXPERIMENTAL

¹H N.m.r. spectra were obtained at 60 MHz on a Perkin-Elmer R-12 spectrometer, and g.l.c. analyses were performed on a Pye-Unicam Series 104 chromatograph using a 5 ft column containing 5% Carbowax 20M. I.r. spectra were determined on a Unicam SP 200 instrument, and mass spectra on an A.E.I. MS12 spectrometer with an ionising beam of 70 eV. The phrase 'worked up as usual' refers to washing the extracts with water, then brine, drying the extracts over anhydrous sodium sulphate, and evaporation of the solvent at 20 mmHg and 35°. Petroleum used had b.p. 40–60°.

1,1-Dimethoxyheptane (5).—n-Heptanal (45 g) in methanol (220 ml) and trimethyl orthoformate (126 ml) containing toluene-*p*-sulphonic acid (10 mg) were stirred together at 0° for 2 h, then at 20° for a further 20 h. The mixture was diluted with petroleum (500 ml), then washed with sodium hydrogen carbonate solution, potassium dihydrogen phosphate solution, and then worked up as usual to give a clear liquid. Distillation afforded 1,1-dimethoxyheptane (5) (40 g), b.p. 68–70° at 20 mmHg, τ 5.75 (1H, t, *J* 5 Hz, acetal proton) and 6.8 (6H, s, 2 × OMe).

3-Methylbut-2-en-1-ol (6).—3-Methylbut-2-en-1-ol (6) had b.p. 52–54° at 20 mmHg, τ 4.70 (1H, t, *J* 6 Hz, vinyl proton), 5.95 (1H, s, OH), 6.10 (2H, d, *J* 6 Hz, allylic protons), and 8.30 and 8.40 (both s, 3H, methyl groups).

3,3-Dimethyl-2-n-pentylpent-4-enal (7).—3-Methylbut-2-en-1-ol (6) (2.58 g, 30 mmol), 1,1-dimethoxyheptane (5) (4.8 g, 30 mmol), and *o*-nitrobenzoic acid (1.7 g, 10 mmol) in mesitylene (25 ml) were heated under a stream of dry nitrogen to distil off methanol produced in the reaction. After 1 h the temperature of the boiling solution had stabilised at 170°, and the mixture was cooled, diluted with ether, washed with sodium hydrogen carbonate solution, and then worked up as usual. Distillation gave the pentenal (7) (3.0 g), b.p. 110–115° at 20 mmHg, τ 0.4 (1H, d, *J* 4 Hz, CHO), 4.2 (1H, m), and 5.1 (2H, m, vinyl protons), ν_{\max} 1710 cm⁻¹, *m/e* 182 (*M*⁺, 3%) (C₁₂H₂₀O), 167 (25), 122 (35), 97 (95), 70 (100), 55 (95), and 41 (90) [Found (after redistillation, b.p. 101° at 15 mmHg): C, 78.9; H, 12.2. C₁₂H₂₂O requires C, 79.1; H, 12.2%].

3,3-Dimethyl-4-n-pentylhexa-1,5-diene (8).—Sodium hydride (1.2 g; 50% dispersion in oil) was washed with petroleum several times, then dried under vacuum. Dry nitrogen was introduced, dimethyl sulphoxide (30 ml) added, and the mixture stirred and heated at 75–80° for 45 min. After cooling, a solution of methyltriphenylphosphonium bromide (8.9 g, 25 mmol) in dimethyl sulphoxide (25 ml) was added, and the reaction was stirred at 20° for 15 min. The pentenal (7) (4.5 g, 25 mmol) in dimethyl sulphoxide (10 ml) was added, and the reaction stirred at 20° for 16 h, when it was poured into water, and extracted with petroleum. The extracts were washed with water, dried (Na₂SO₄), and then filtered through a column of activated alumina (10 g). Evaporation yielded the hexadiene (8) (4.5 g), τ 4.2 (2H, m) and 5.1 (4H, m, vinyl protons) (identical with the pattern displayed by the starting material) and no signal for an aldehydic proton, i.r. spectrum showed no carbonyl absorption, *m/e* 180 (*M*⁺, 20%) (C₁₃H₂₄), 137 (55), 69 (70), and 41 (100) [Found (after redistillation, b.p. 80° at 15 mmHg): C, 86.5; H, 13.3. C₁₃H₂₄ requires C, 86.6; H, 13.4%].

2-Methyl-dodeca-2,6-diene (9).—The hexadiene (8) (0.5 g) in dimethyl sulphoxide (10 ml) was heated under reflux at

190° under nitrogen for 18 h. After cooling, the mixture was poured into water, extracted with petroleum, and the extracts were dried (Na₂SO₄) and filtered through a small column of activated alumina (5 g). Evaporation afforded 2-methyl-dodeca-2,6-diene (9) (0.5 g), τ 4.65br (2H) and 4.90br (1H) (olefinic protons), 7.98br (6H, allylic protons), 8.33 (3H, s) and 8.41 (3H, s) (allylic methyl groups), 8.70br (6H, aliphatic protons), and 9.12br (3H, s, methyl group), *m/e* 180 (*M*⁺, 15%) (C₁₃H₂₄), 165 (3), 150 (3), 137 (10), 109 (15), 96 (15), 69 (90), and 41 (100) [Found (after redistillation, b.p. 82° at 15 mmHg): C, 86.3; H, 13.2. C₁₃H₂₄ requires C, 86.6; H, 13.4%].

Ethyl 3-Hydroxy-3-propylhexanoate.—Zinc wool (20 g, 0.3 mol) was dried at 100° under nitrogen, cooled, and a solution (10 ml) of ethyl bromoacetate (42 g, 0.25 mol) and heptan-4-one (30 g, 0.27 mol) in benzene (40 ml) and ether (10 ml) was run in. After reaction had started, the remainder of the solution was run in at a rate sufficient to keep the mixture boiling and the liquid was stirred and heated under reflux for a further 1 h after addition was complete. After cooling, the mixture was poured into sulphuric acid (0.5M; 100 ml), extracted with ether, and the extracts were worked up as usual to yield ethyl 3-hydroxy-3-propylhexanoate (50 g), τ 5.9 (2H, q, CH₂CH₃), 6.7 (1H, s, OH), 7.6 (2H, s, CH₂CO₂Et), and 8.5–9.1 (m, aliphatic protons including CH₂CH₃ triplet).

Ethyl 3-Propylhex-2-enoate.—(a) Ethyl 3-hydroxy-3-propylhexanoate (0.9 g) and dicyclohexylcarbodi-imide (1.38 g) with copper(II) chloride (10 mg) were heated at 100° for 18 h. After cooling, ether (30 ml) was added and the precipitate filtered off. Evaporation gave a yellow oil, purified by chromatography in petroleum on a silica gel (10 g) column. Elution with ether-petroleum (2:23) gave ethyl 3-propylhex-2-enoate (0.6 g), τ 4.4 (1H, s, olefinic proton) and 5.95 (2H, q, CH₂CH₃).

On a larger scale (50 g) this reaction did not go to completion even after 70 h, and some decomposition was evident. It was found preferable to leave the reaction at 20° for 2–3 weeks.

(b) Sodium hydride (50% dispersion in oil; 2.4 g) was stirred in dry benzene (100 ml) under nitrogen, and triethyl phosphonoacetate (11.2 g) was added dropwise, then stirred until evolution of hydrogen ceased (*ca.* 1 h). Heptan-4-one (5.7 g) was added slowly so as to keep the reaction temperature below 30°, then the solution was stirred at 60° for 18 h, poured into water, extracted with ether, and worked up as usual to yield ethyl 3-propylhex-2-enoate identical with that prepared in (a) (Found: C, 71.9; H, 10.9. Calc. for C₁₁H₂₀O₂: C, 71.7; H, 10.9%).

3-Propylhex-2-en-1-ol (2).—Ethyl 3-propylhex-2-enoate (5 g) in ether (25 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (2 g) in ether (25 ml), then heated under reflux for 1 h. After cooling, excess of reagent was decomposed by careful addition of water, then sodium potassium tartrate solution was added, and the ether layer was worked up as usual to yield 3-propylhex-2-en-1-ol (2) (3.2 g), b.p. 96–99° at 15 mmHg, τ 4.7 (1H, t, *J* 6 Hz, olefinic proton), 6.0 (2H, d, *J* 6 Hz, -CH₂O-), and 6.45 (1H, s, OH), *m/e* 142 (*M*⁺, 15%) (C₉H₁₈O), 124 (20), 109 (10), 99 (70), 81 (50), and 57 (100) (Found: C, 75.9; H, 12.5. Calc. for C₉H₁₈O: C, 76.0; H, 12.8%).

Methyl 6,6-Dimethoxyhexanoate (10).—6,6-Dimethoxyhexanoate¹² (10) had b.p. 126–128° at 15 mmHg, τ 5.7 (1H, t, *J* 5 Hz, acetal proton), 6.4 (3H, s, CO₂Me), 6.8 (6H, s, 2 × MeO), 7.7 (2H, m, CH₂CO₂Me), and 8.6br (6H, aliphatic

protons), m/e 190 (M^+ , 5%) ($C_9H_{18}O_4$), 159 (85), 143 (10), 127 (85), and 75 (100).

Propylure Trial Reactions.—(a) *Methyl 5-formyl-6,6-dimethyloct-7-enoate* (11). 3-Methylbut-2-en-1-ol (6) (1.29 g), methyl 6,6-dimethoxyhexanoate (10) (2.85 g), and *o*-nitrobenzoic acid (0.85 g) in mesitylene (25 ml) were heated under a stream of dry nitrogen to distil off methanol produced by the reaction. After 1 h the temperature of the boiling solution had stabilised at 170°, and the reaction was cooled, diluted with ether, washed with sodium hydrogen carbonate solution and then worked up as usual. Distillation gave *methyl 5-formyl-6,6-dimethyloct-7-enoate* (11), (1.4 g), b.p. 150—160° at 20 mmHg, τ 0.4 (1H, d, J 4 Hz, CHO), 4.2 (1H, m) and 5.1 (2H, m) (vinyl protons) [*cf.* compound (7)], and 6.6 (3H, s, CO_2Me), m/e 212 (M^+ , 3%) ($C_{15}H_{20}O_3$), 197 (15), 180 (10), 165 (20), 143 (25), and 69 (100) (Found: C, 67.5; H, 9.3. $C_{15}H_{20}O_3$ requires C, 67.9; H, 9.5%).

(b) *2-n-Pentyl-3,3-di-n-propylpent-4-enal* (12).—3-Propylhex-2-en-1-ol (2) (1.42 g), 1,1-dimethoxyheptane (5) (1.60 g), and *o*-nitrobenzoic acid (0.6 g) in mesitylene (25 ml) were heated together and worked up as in (a). Distillation of the product afforded the pentenal (12) (1.0 g), b.p. 120—140° at 20 mmHg, τ 0.45 (1H, d, J 4 Hz, CHO), and 4.2 (1H, m) and 5.1 (2H, m) (vinyl protons) [*cf.* compound (7)], m/e 238 (M^+ , 10%) ($C_{16}H_{30}O$), 195 (15), 153 (18), and 55 (100).

Attempted Formation of Methyl 5-Formyl-6,6-di-n-propyl-oct-7-enoate (13).—3-Propylhex-2-en-1-ol (2) (0.67 g), methyl 6,6-dimethoxyheptanoate (10) (0.95 g), and *o*-nitrobenzoic acid (0.4 g) in mesitylene (15 ml) were heated together and worked up as in the formation of (11) above. Distillation of the product afforded methyl 5-formylpentanoate (0.5 g), b.p. 120—130° at 20 mmHg, τ 0.35 (1H, t, J 3 Hz, CHO) and 6.4 (3H, s, CO_2Me). [This identification was confirmed by regeneration of the starting acetal on treatment with methyl orthoformate (2 ml) in methanol (10 ml) containing toluene-*p*-sulphonic acid (10 mg).] Further distillation gave a fraction, b.p. 130—180° at 20 mmHg (0.2 g), τ 0.3—0.4br (<0.1H), 3.0—5.3, (~6H, m), and 6.4 (3H, s), m/e 268 (M^+ , 2%) ($C_{18}H_{28}O_3$), 144 (20), and 55 (100).

Heating the latter compound, in mesitylene at 170° for 1 h, in dimethylsulphoxide at 190° for 4 h, and in triglyme at 216° for 3 h, all returned unchanged material.

Similar reactions using other catalysts [mercury(II) acetate (0.5 g)—sodium acetate (0.5 g), 2,4-dinitrophenol (0.5 g), and *o*-chlorobenzoic acid (0.5 g)] were also unsuccessful and returned largely unchanged materials.

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