

A STEREOSELECTIVE SYNTHESIS OF A PROPOSED CODLING MOTH SEX PHEROMONE

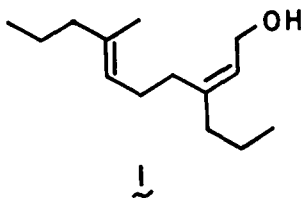
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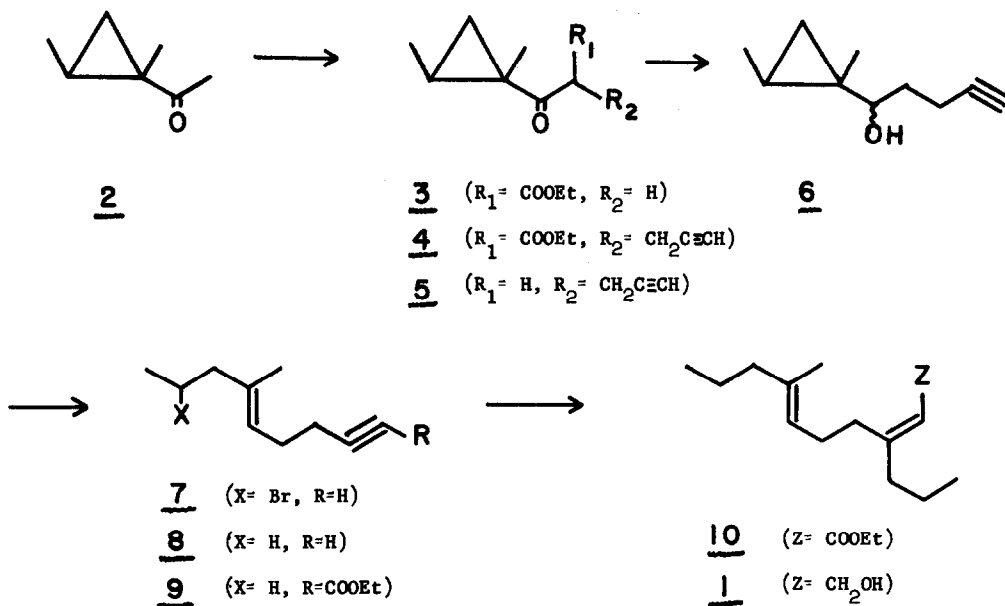
McDonough and coworkers have recently isolated¹ from the Codling Moth, Laspeyresia pomonella (L.), a compound believed to be (2Z,6E)-7-methyl-3-propyl-2,6-decadien-1-ol (1) and have reported evidence suggesting that it is a component of the sex pheromone. A mixture of isomers obtained by a non-stereoselective synthesis was originally believed² to be as active as the natural material in preliminary field tests. While the gross structure of the natural product was established through its identity with one of the synthetic isomers, the stereochemical assignment was made on the basis of glpc data and the position of the C-7 methyl proton resonance.



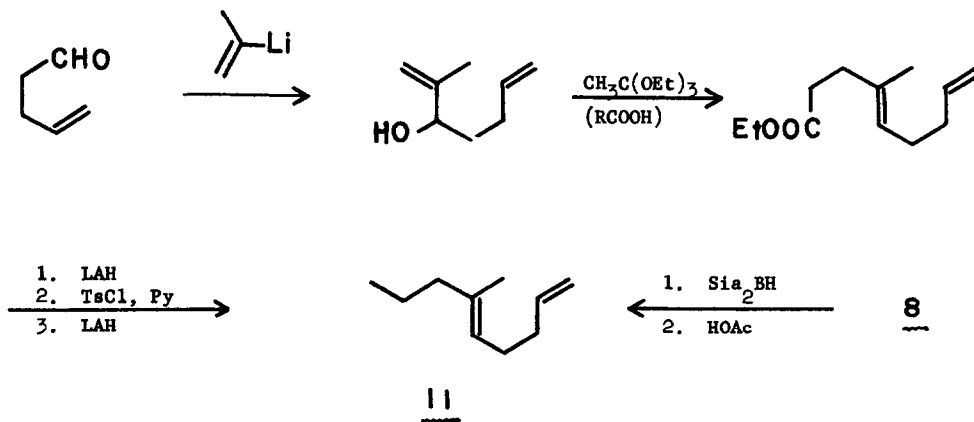
We wish to report a stereoselective synthesis of the proposed pheromone (1) (Scheme 1) which has been shown to be different from the natural material indicating that the suggested structure of the natural material is incorrect with regard to stereochemical detail.

Carboethoxylation³ of cis-1,2-dimethylcyclopropyl methyl ketone (2)⁴ with diethyl formate and sodium hydride gave keto-ester 3 in 78% yield⁵ (bp 108-9°, 4 mm). Treatment of the sodium salt prepared from 3 and sodium hydride with propargyl bromide in THF gave the acetylenic keto-ester 4 which was converted without purification into ketone 5 (bp 105°, 17 mm) by treatment with barium hydroxide followed by acidification. The overall yield of 5 from 3 was 45%. Reduction of 5 with lithium aluminum hydride gave alcohol 6 in nearly quantitative

Scheme 1



Scheme 2



yield. Treatment of the crude alcohol with zinc bromide in hydrobromic acid³ gave the homoallylic bromide 7 contaminated by approximately 7% of the undesired Z isomer. While spectral analysis⁶ and previous experience³ with this type of rearrangement suggested that the trisubstituted double bond of 7 possessed the E configuration, this point ⁷ was confirmed by an alternate synthesis of a later derivative (vide infra). Dehalogenation of the base sensitive homoallylic bromide was achieved using lithium in THF with excess diethyl malonate as a proton source. In this way en-yne 8 (bp 109-110°, 100 mm) was obtained in 62% overall yield from 6. The stereochemistry of the trisubstituted double bond was further established by partial reduction of 8 to diene 11 which was identical to the diene produced by the sequence shown in Scheme 2 using the Johnson orthoester Claisen reaction⁸ known to give the trans trisubstituted double bond.

Treatment of 8 with butyllithium in THF followed by ethyl chloroformate gave the acetylenic ester 9 (bulb-to-bulb distillation, T_{bath} 150°, 2 mm) in 75% yield. Stereoselective conjugate addition of di-n-propylcopper lithium to 9 gave diene-ester 10 in 40-60% yield after purification by preparative tlc and bulb-to-bulb distillation (T_{bath} 170°, 2 mm). The stereochemistry of the newly introduced double bond follows from the known cis addition of alkyl cuprate derivatives to conjugated acetylenic esters⁹. Reduction of diene-ester 10 with aluminum hydride in THF (0°) gave the proposed pheromone 1 which was purified by preparative tlc followed by bulb-to-bulb distillation (T_{bath} 160°, 2 mm).

The spectral properties of 1 closely resembled those reported for the natural product except for the position of the C-7 methyl proton resonance at 1.58 ppm in contrast to a value of 1.66 ppm found for the natural product. Indeed, glpc comparisons¹⁰ showed synthetic 1 to be different from the natural material. The differences in the positions of the C-7 methyl resonances indicate that the pheromone actually possesses the 6Z configuration. The reported glpc elution order data further suggests¹⁰ that the stereochemistry of the C-2 double bond has also been misassigned and that the likely structure of the natural material is (2E,6Z)-7-methyl-3-propyl-2,6-decadien-1-ol. Proof of the structure must await further synthetic efforts.

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REFERENCES

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2. Dr. McDonough has informed us in a private communication that more recent results reveal that the synthetic mixture has no field activity and that the activity shown by the natural material may be due to an unidentified impurity.
3. S. F. Brady, M. A. Ilton and W. S. Johnson, J. Amer. Chem. Soc., 90, 2882 (1968).
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5. The ir, nmr and mass spectra were in agreement with the assigned structures of all compounds reported. Satisfactory elemental analyses were obtained for all purified intermediates.
6. In addition to the 1.65 ppm C-7 methyl resonance of the E isomer, the C-7 methyl peak of the small amount of Z isomer present could be seen at 1.76 ppm. This is in keeping with the general observation that the allylic methyl resonance of trisubstituted olefins having an E configuration occurs at a slightly higher position than in the Z isomer (see J. W. K. Burrell, R. F. Garwood, L. M. Jackman, E. Oskay and B. C. L. Weedon, J. Chem. Soc. (C), 2144 (1966)).
7. The presence of a second methyl group on the cyclopropyl ring of 6 places certain restrictions on the cyclopropylcarbinyl rearrangement which make the stereochemical outcome less clear than in the previously studied systems.³ The mechanism and stereochemistry of such systems will be discussed elsewhere.
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10. We thank Dr. McDonough for making the gas chromatographic comparisons of synthetic 1 with both the natural material and his synthetic mixture of isomers. Synthetic 1 corresponds to the third eluting isomer of the synthetic mixture of isomers while the natural product elutes second.