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PHOTOENOLISATION OF CONJUGATED ESTERS: SYNTHESIS OF A SAN JOSE SCALE PHEROMONE BY PARTIALLY REGIO-CONTROLLED PHOTOCHEMICAL DECONJUGATION[1].

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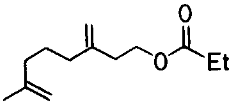
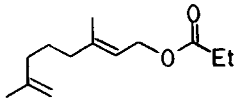
ABSTRACT: The photochemical deconjugation reaction of an α,β-unsaturated ester is applied to the synthesis of one of the components of the San Jose scale pheromone, compound 1. The use of a weak organic base as a means of control of the regiochemistry of the deconjugation reaction was demonstrated.

The San Jose scale, *Quadraspidiotus pernicious*, is a serious economic pest in North American orchards[2,3]. The female San Jose scale produces a mixture of three pheromones, possessing structures 1, 2, and 3, which serve to attract the male of the species. Syntheses of the pheromones 2 and 3 by reduction and esterification of the geometrical isomers of the conjugated ester 4 have been reported[3], and the isomer 1 has also been prepared[3].



1



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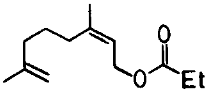

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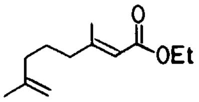
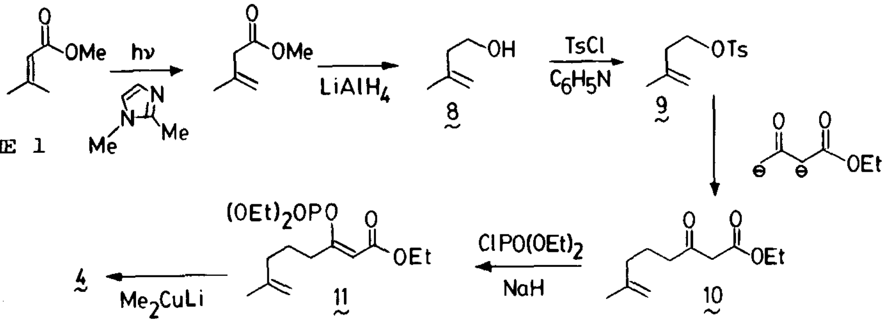


4

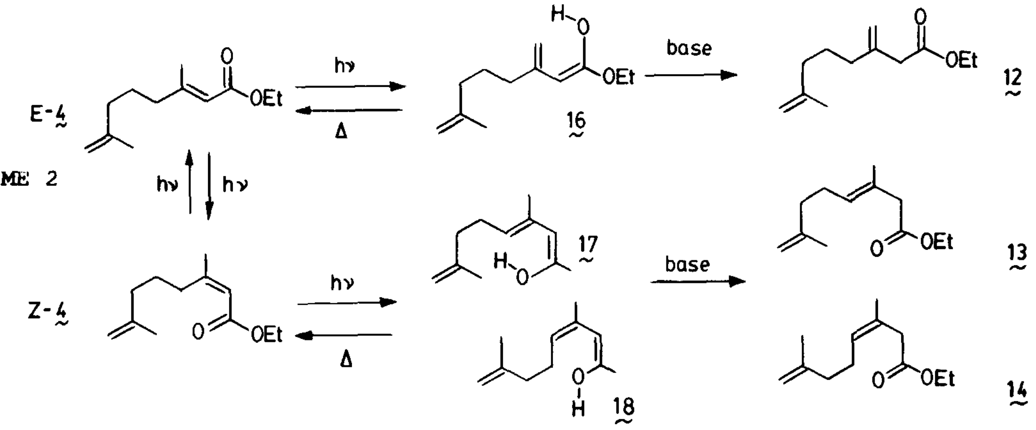
Another procedure which would appear feasible for the synthesis of pheromone 1 is deprotonation of the conjugated ester 4 by strong base followed by kinetic reprotonation of the dienolate to yield the deconjugated isomer, which could then be converted to 1 by reduction and esterification. This procedure would require that the deprotonation of 4 be regioselective so that the methyl group and not the methylene group is deprotonated. Techniques have recently been developed which might allow this[4], but they require that the geometrical isomers of 4 be available separately. An alternative to such a base catalysed route is the photochemical conversion of α,β-unsaturated esters to their β,γ-unsaturated isomers[5,6]. This reaction proceeds via photoenolisation, and recent work[5] has suggested that some control over the regiochemistry of the photochemical deconjugation reaction can be achieved by interception of the intermediate dienol by a weak organic base added to the reaction mixture. These observations prompted us to examine the photochemical deconjugation of ester **4** as a key step in a route for the synthesis of the pheromone **1**.

SCHEME 1



The ester **4** was prepared as shown in scheme 1 by a route based upon a procedure described by Weiler and co-workers[3]. The alcohol **8** was formed in quantitative yield by lithium aluminium hydride reduction of methyl 3-methyl-3-butenoate, which was obtained by photochemical deconjugation of methyl 3-methyl-2-butenoate[5]. The tosyl derivative[7] of **8** (compound **9**) was then added to the dianion of ethyl acetoacetate to yield[3,9] the β-keto ester **10**. This was converted[11] to the the enol phosphate **11**, which upon treatment with dimethyl copper lithium gave the conjugated ester **4** as a mixture of the E and Z geometrical isomers (E:Z ratio 95:5) in 38% yield based upon **10**, after spinning band distillation[10, 12].

SCHEME 2



The E-ester **4** was irradiated[13] under four sets of conditions. Direct irradiation in diethyl ether in the presence of 1,2-dimethylimidazole resulted in rapid E-Z isomerisation followed by the formation of three products, the deconjugated isomers **12**, **13** and **14** in the ratio 2.7:1.8:1.0 and in a combined yield of 83% at 100% conversion[14] (see scheme 2). Reduction of the reaction mixture with lithium aluminium hydride followed by treatment of the alcohols obtained with propionyl chloride in the presence of pyridine gave the corresponding esters with pheromone **1** as the major component. Irradiation of the ester **4** in ether for the same period of time and under the same conditions, except that the base was not added, produced a mixture of E-**4** and

Z-**4** containing less than 10% of the deconjugated isomers **13** and **14**. When pentane was used as solvent, and no base was added, irradiation of **4** for the same period of time resulted in 40% conversion to a mixture of **13** and **14** in the ratio 1.0:1.4. In neither of these irradiations in the absence of added base was any detectable amount of the deconjugated isomer **12** formed. Finally, irradiation of **4** in benzene under conditions such that the benzene absorbed all of the light (i.e. so that the ester was sensitised directly into its triplet excited state) resulted in E-Z isomerisation only and no conversion to the deconjugated products. Extended irradiation eventually resulted in the formation of a mixture of products some of which are assigned to intramolecular cyclo-adducts on the basis of G.C.-mass spectrometry and chemical precedent[15].

The results are consistent with the previously proposed mechanism for the photochemical enolisation and deconjugation of esters[5]. Thus irradiation of **4** results in rapid E-Z isomerisation from both the singlet and triplet excited states, and slower photoenolisation of the E and Z isomers from their singlet excited states to give the dienols **16**, **17** and **18**. In the absence of added base the dienol **16** efficiently reverts to the conjugated ester by a thermal 1,5-sigmatropic hydrogen shift; this process is made more efficient by the side chain which helps maintain the dienol in the cisoid conformation necessary for the 1,5-hydrogen shift. However, when base is added to the reaction mixture, this dienol is intercepted and equilibrated with its dienolate, which is kinetically reprotonated to give the deconjugated ester. In the case of the dienols **17** and **18** the same arguments apply, except that the side chain now inhibits the adoption of the cisoid conformation of the dienol. necessary for reversion to the conjugated ester **4**. This lengthens the dienol lifetime to the point that the solvent (acting as a Lewis base) or impurities in the solvent[5] can catalyse conversion of the dienol to the deconjugated ester via the dienolate anion. The increased proportion of the E deconjugated ester **13** (relative to its Z-isomer **14**) formed in the reaction in the presence of base supports this, since the dienol **17** (the precursor of **13**) can revert to **4** by a 1,5-hydrogen shift more readily than can dienol **18**.

The results described illustrate how the mild reaction conditions of ester photochemical deconjugation can be synthetically useful and define the limitations of the procedure for control of the stereochemistry and regiochemistry of the reaction.

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7. The tosylate **9** was prepared by the method of Bartlett et al[8] and had ^1H-nmr ($CDCl_3$, δ) 7.79, 7.55 (AA'BB',4H), 4.79, 4.67 (two brd s,2H), 4.12 (t,2H), 2.45 (s,3H), 2.35 (t,2H), 1.65 (s,3H): M^+ 240.0815; calc. 240.0820
8. P.A. Bartlett, C.K. Marlow, P.J. Connolly, K.M. Banks, D.W.H. Chiu, P.S. Dahlberg, A.M. Haberman, J.S. Kim, K.J. Klassen, R.W. Lee, R.T. Lum, E.W. Mebane, J.A. Ng, J.C. Ong, N. Sagheb, B. Smith, and P. Yu, **J. Chem. Ed.** 1984, **61**, 816.
9. The alkylation of the dianion was performed using the method of Weiler and co-workers[3,10]. The yield of the desired keto ester present in the crude product was determined as 57% by nmr, and the yield of pure **10** was 15% after spinning band distillation (88-92°/1.0 mm). ^1H-nmr ($CDCl_3$, δ) 4.73, 4.48 (two brd s,2H), 4.19 (q,2H), 3.43 (s,2H), 2.54 (t,2H), 2.17 (t,2H), 1.71 (s,3H), 1.28 (t,3H). M^+ 198.1253; calc. 198.1256.
10. F.W. Sum, and L. Weiler, **Can. J. Chem.** 1979, 57, 1431; M. Alderdice, F.W. Sum, L. Weiler, **Org. Syn.**, 62, 14.
11. The enol phosphate was prepared by reaction of **10** with NaH followed by addition of diethyl chlorophosphate[10]; after rapid aqueous work-up **11** was used directly for the preparation of **4**. **11** had ^1H-nmr ($CDCl_3$, δ) 5.38 (brd s,1H), 4.69, 4.74 (two brd s,2H), 4.27 (q,4H), 4.15 (q,2H), 2.43 (t,2H), 2.07 (t,2H), 1.74 (m,2H), 1.72, (s,3H), 1.37 (t,6H), 1.27 (t,3H). M^+ 334.1545; calc. 334.1545.
12. The E-ester **4** had ^1H-nmr ($CDCl_3$, δ) 5.69 (s,1H), 4.72, 4.68 (two brd s,2H), 4.14 (q,2H), 2.16 (s,3H), 2.14 (t,2H), 2.01 (t,2H), 1.71 (s,3H), 1.62 (m,2H), 1.23 (t,3H). M^+ 196.1466; calc. 196.1463.
13. The irradiations were performed at room temperature using light of wavelength 254 nm emitted from a low pressure mercury lamp immersed in the reaction solution. The solutions were approximately 0.05 M in ester 4 and 0.01 M in base when present; 10.0 mL samples of each solution were irradiated for 3 hours.
14. For **12** ^1H-nmr ($CDCl_3$, δ) 4.92 (brd d,2H), 4.72, 4.70 (two brd s,2H), 4.10 (q,2H), 2.95 (s,2H), 2.0-2.2 (m,4H), 1.78 (brd s,3H), 1.70 (m,2H), 1.22 (t,3H). For **13** ^1H-nmr ($CDCl_3$, δ) 5.27 (tq,2H), 4.69 (brd s,2H), 4.11 (q,2H), 2.95 (s,2H), 1.78 (brd s,6H), 2.0-2.2 (m,4H), 1.22 (t,3H). For **14** ^1H-nmr ($CDCl_3$, δ) 5.33 (brd t,1H), 4.69 (brd s,2H), 4.12 (q,2H), 3.01 (s,2H), 2.0-2.2 (m,4H), 1.78 (brd s,6H), 1.23 (t,3H). For Z-**4** ^1H-nmr ($CDCl_3$, δ) 5.66 (brd s,1H), 4.70 (brd s,2H), 4.11 (q,2H), 2.61 (t,2H), 2.06 (t,2H), 1.84 (s,3H), 1.72 (s,3H), 1.59-1.66 (m,2H), 1.23 (t,3H).
15. A.C. Weedon, "Enone Photochemical Cycloaddition in Synthesis" in "Synthetic Organic Photochemistry", ed. W.M. Horspool, Plenum, 1984, pp 61-143.

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