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SYNTHESIS OF THE THREE ISOMERIC COMPONENTS OF SAN JOSE SCALE PHEROMONE

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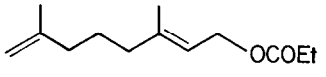
Abstract: The three isomeric components of the San Jose scale pheromone have been synthesized stereospecifically from a common intermediate β-keto ester.

The San Jose scale, Quadraspidiotus pernicious, is a serious world-wide insect pest which attacks fruit, shade, and ornamental trees. It is particularly harmful to deciduous fruit trees, and for this reason it is a serious economic pest in North American orchards. Three active components, 1-3, have been isolated from the pheromone mixture of female scales (1). All three components were found to be almost equally attractive to male scales (1). In this paper, we report a stereospecific synthesis of each of the isomers of the pheromone from a common precursor.



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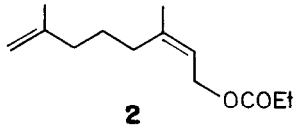

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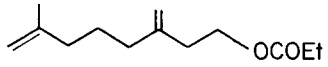

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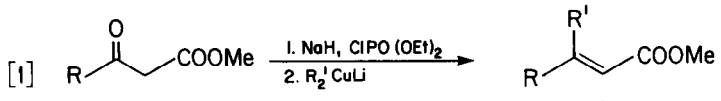
Recently, we have developed a stereoselective method to convert a β-keto ester into the alkene 4, as shown in equation 1 (2). We now report methods to convert this same β-keto ester into the alkene 5 and the 1,1-disubstituted alkene 6.



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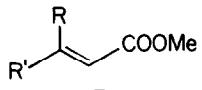

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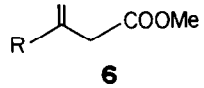
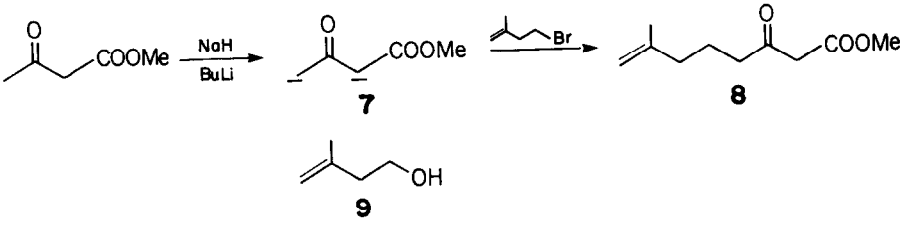
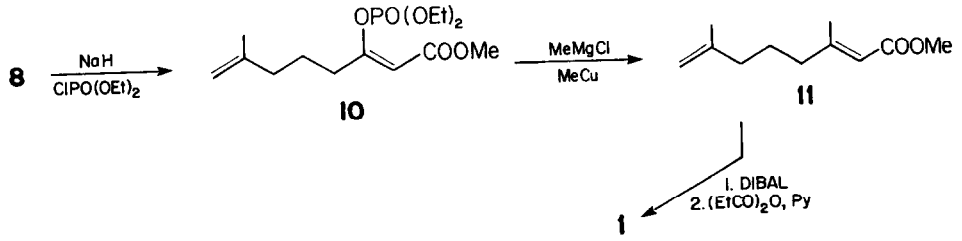


6

Several years ago we reported a facile procedure to generate the dianion of β-keto esters. The dianion was then alkylated at the γ-position with a range of halides (3). Earlier we had alkylated the dianion 7 with 1-bromo-3-methyl-3-butene to give 8 in reasonable yield (4). Unfortunately this halide is not readily available but it must be prepared from the corresponding alcohol. Since the benzenesulfonate of the alcohol 9 is easily prepared, we decided to investigate the reaction of dianion 7 with the sulfonate of 9. Fortunately this alkylation proceeded in 60-65% yield in THF at 0°. We have found that other tosylates, mesylates, and triflates react with dianion 7 to give the alkylated products as well (5). This should extend the utility of these dianion alkylations.

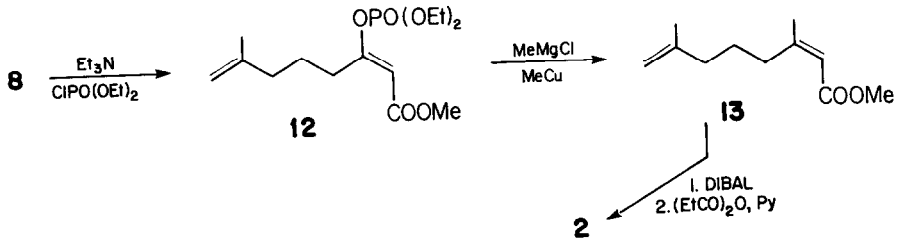


The β-keto ester 8 was treated with sodium hydride in THF and diethyl chlorophosphate to give the Z-enol phosphate 10 in 90-95% yield (>99% Z). This was treated with dimethyllithium cuprate (2) to give the E-alkene 11. The ratio of E:Z isomers in the crude reaction mixture was 5:1. Subsequently we found that higher stereoselectivities were obtained using copper catalyzed Grignard reagents in the conjugate addition (6), and that the stereoselectivity also depended on the counterion i.e. Cl>Br>I (7). Using the Grignard reagent from methyl chloride and methyl copper as catalyst, alkene 11 was obtained in 69% yield of purified product and the ratio of E:Z alkenes in this product was 98:2. The ester 11 was cleanly reduced and propionated to give the San Jose scale pheromone isomer 1 which had spectral properties identical to those reported for this isomer (1).

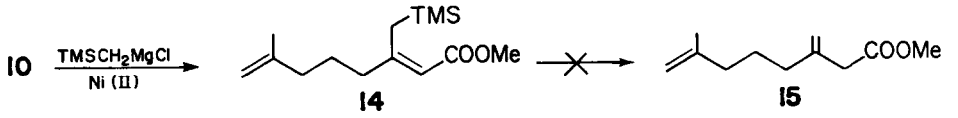


The E-enol phosphate 12 was prepared by treating the β-keto ester 8 with triethyl amine in HMPA and diethyl chlorophosphate to give 12 in >90% yield (8). Presumably, under these conditions, the E-enolate is formed (9) and it is trapped by the phosphorylating agent to give 12. The coupling of this enol phosphate with methylmagnesium chloride in the

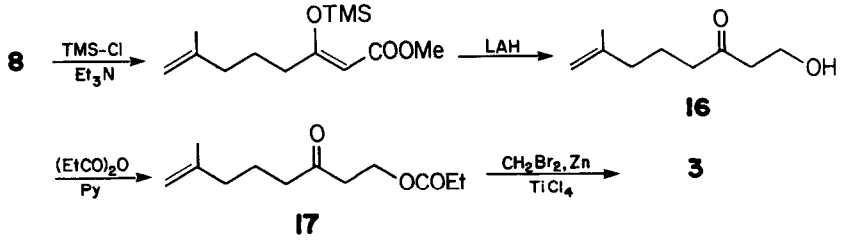
presence of methyl copper gave the Z-alkene 13 in 68% yield. The ratio of E:Z alkenes in this reaction was 2:98. The ester 13 was reduced and acylated to give isomer 2 of the San Jose scale pheromone. Again, the spectral properties of our synthetic material were identical to those reported for 2 (1).



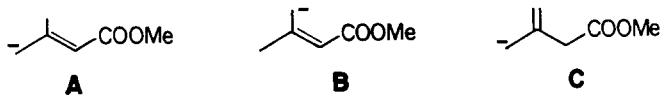
The synthesis of the third isomer proved more troublesome than initially expected. The allylsilane 14 was prepared by coupling the enol phosphate 10 with trimethylsilylmethylmagnesium chloride (10). Treatment of this allylsilane with acids or Lewis acids gave



mainly cyclized products (10) rather than simple protonation of the allylsilane to give 15. This problem was circumvented by using an olefination reaction to introduce the terminal methylene group. The β-keto ester 8 was converted into the corresponding trimethylsilyl enol ether and reduced to give the crude hydroxy ketone 16 in 65% yield. This product was acylated to give the propionate 17 in 90% yield after purification. The keto group of 17 was converted into the methylene using the titanium tetrachloride -dibromomethane - zinc reagent (11) in ca. 50% yield. This gave the alkene 3 with spectral properties identical to those reported for the third isomeric component of the San Jose scale pheromone (1).



In this synthesis we demonstrate a method to stereoselectively introduce the units A-C in a molecule via the β-keto ester dianion alkylation. This should prove useful in the synthesis of other acyclic natural products.



A number of procedures have been developed for the stereoselective synthesis of alkenes, but only a very limited number of these are also stereospecific, i.e. allow for generation of either the E- or Z-alkene. To date all of these stereospecific routes have involved controlled addition of an organometallic reagent to an acetylene (12). The method reported here is comparable in stereospecificity to the best acetylenic addition routes, and should complement these methods when the β-keto ester unit is more readily introduced into the target molecule than an alkyne. In addition this new route provides access to the 1,1-disubstituted alkenes, eg. C, which are not available via the alkene intermediates (13).

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