

STEREOSELECTIVE TOTAL SYNTHESIS OF SOME INSECT PHEROMONES: (±)-SERRICORNINE AND (±)-INVICTOLIDE

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An efficient (12 steps, 12% overall yield) and stereoselective total synthesis of (±)-serricornine (1) the sex pheromone of the cigarette beetle (Lasioderma serricornine F) is described. The preparation of intermediate 5, which encompasses the proper relative configuration of three contiguous chiral centers of (±)-invictolide, (3), is discussed.

Key words: total synthesis – (±)-serricornine – (±)-invictolide – pheromones

Pheromones have established themselves as a valuable tool in integrated pest management and brought about a fruitful collaboration between chemists and biologists. Many pheromones can have stereoisomeric forms and the insects biosynthesize and utilize as such only one enantiomer or a specific ratio of enantiomers. Synthetic organic chemists have responded to the challenge of stereoselective synthesis of insect pheromones with the invention of new reactions and the reinvestigation of some old ones.

The sex pheromone produced by the female cigarette beetle (*Lasioderma serricorne* F), the major pest for cured tobacco leaves and also found in spices, cereals and seeds, was detected in 1970 (Burkholder, 1970), isolated in 1979 (Chuman et al., 1979a, b; Ono et al., 1980) and its absolute configuration definitively established by Mori as (4*S*, 6*S*, 7*S*)-4, 6-dimethyl-7-hydroxy-3-nonanone (1) (Mori et al., 1982a, b). Since both the racemic and the optically pure forms were shown to elicit pheromone activity in male cigarette beetles (Chuman et al., 1979b, 1985; Ono et al., 1980) several stereoselective synthetic approaches have been reported (Chuman et al., 1979a; Mori et al., 1982b; Bartlett et al., 1984; Mori & Watanabe, 1985; Takeda et al., 1985; Kobayashi et al., 1986; Katsuki & Yamaguchi, 1987).

The fire ant *Solenopsis invicta* Buren, a native species of South America, produces a mixture of three lactones which was established

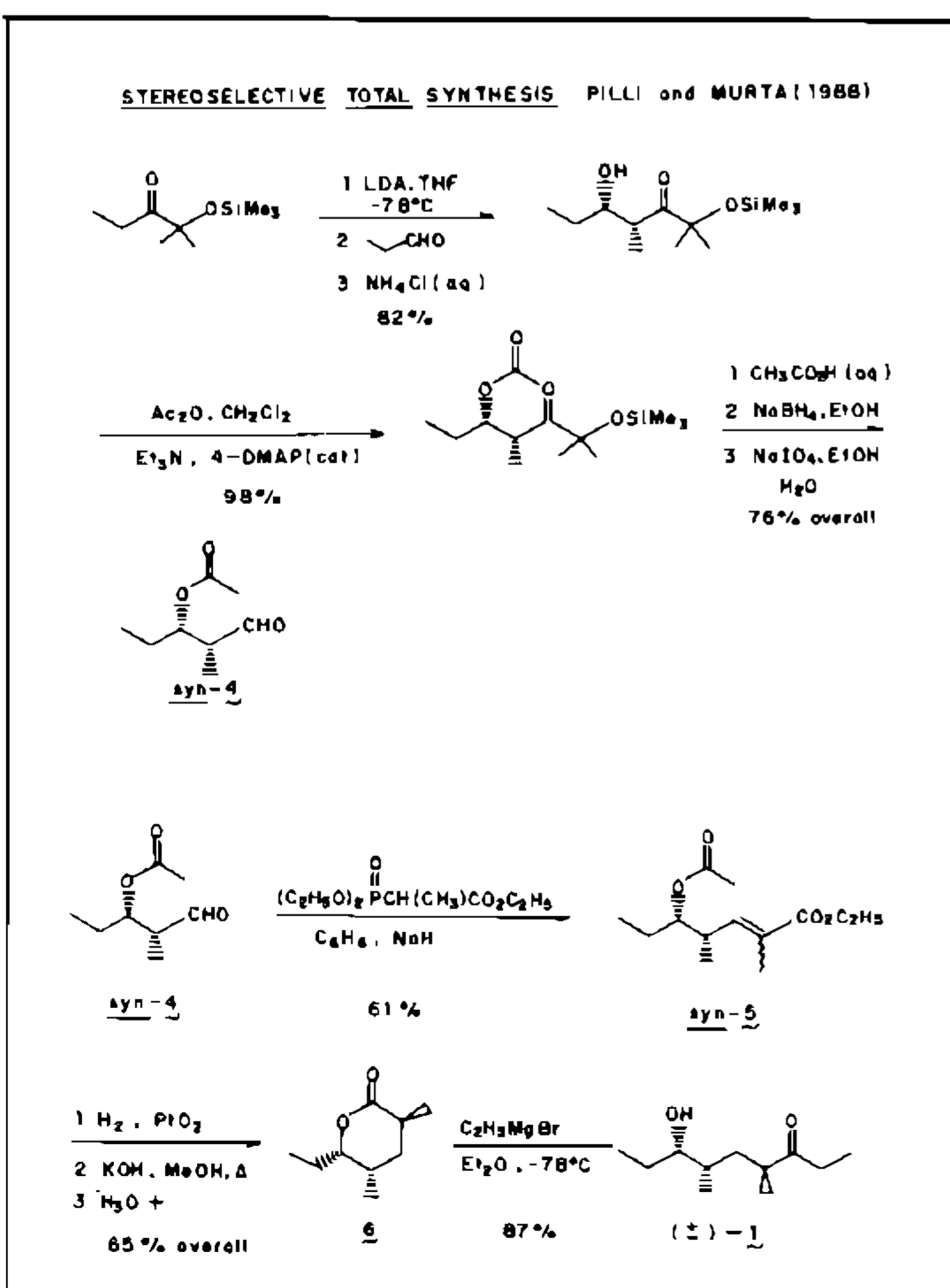
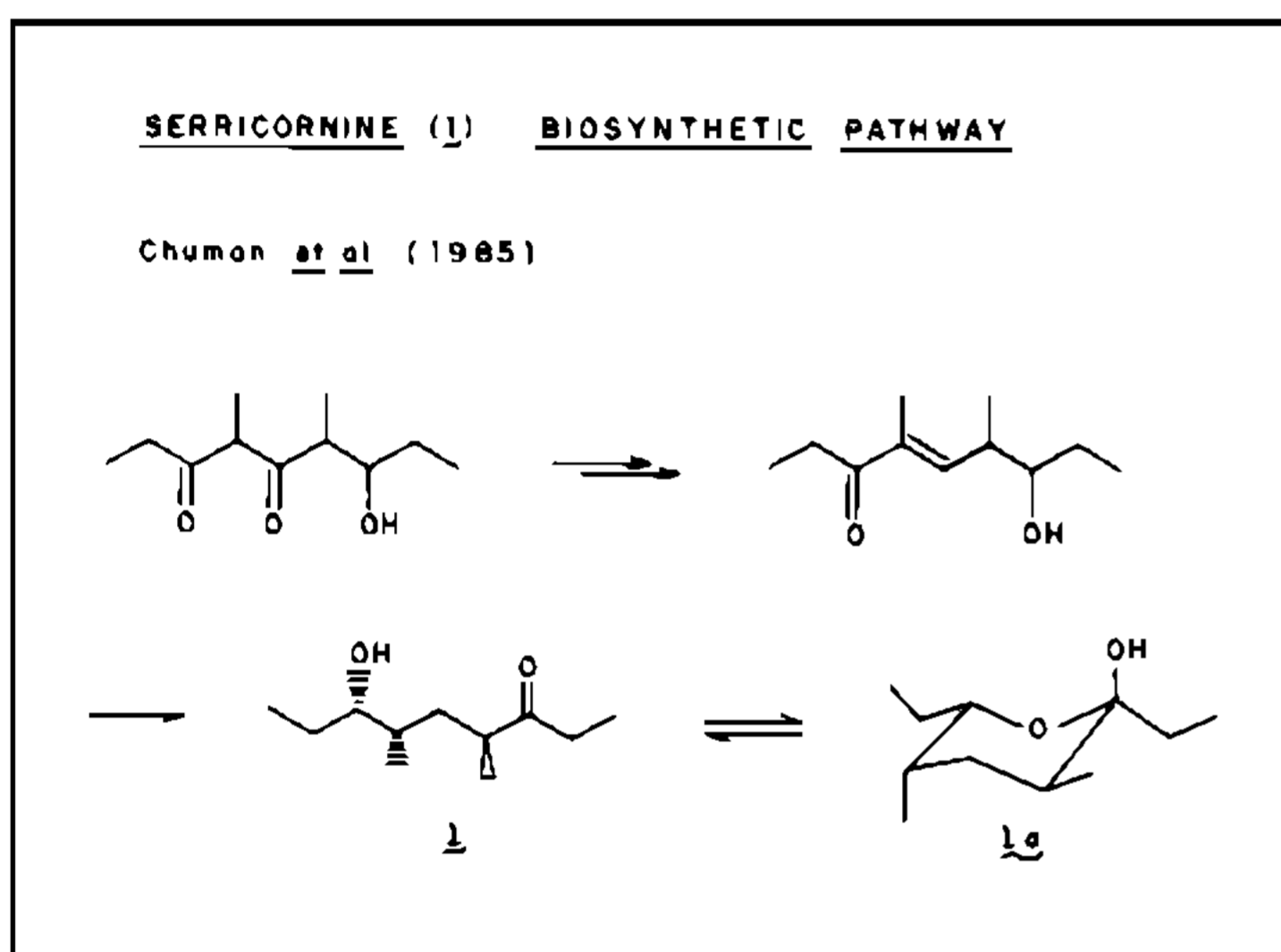
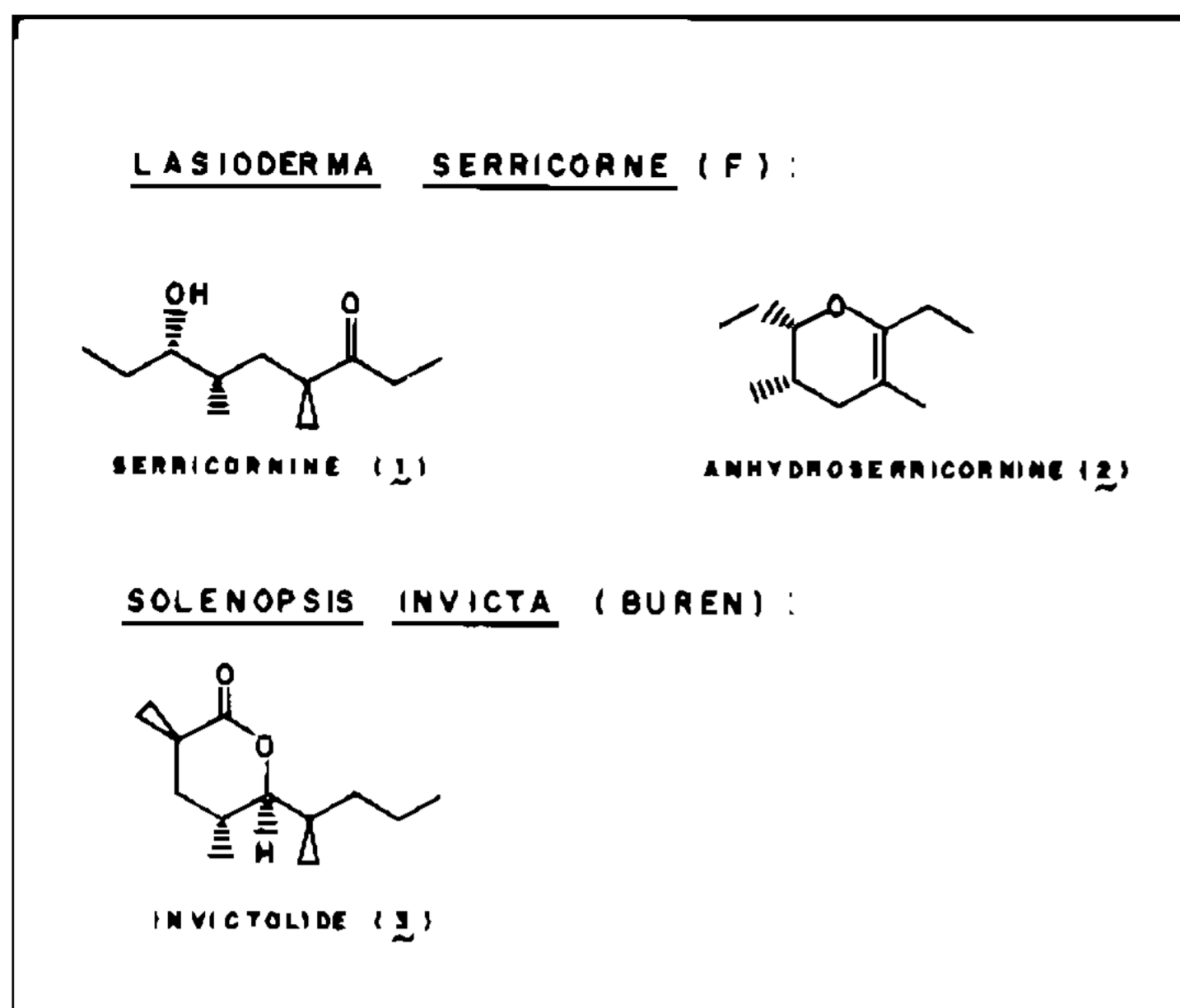
to act as the queen recognition pheromone. Invictolide (3) is one component of this mixture (Rocca et al., 1983) and its stereochemistry was demonstrated by synthesis and spectroscopic analysis (Hoye et al., 1984; Schreiber & Wang, 1985; Yamamoto et al., 1985; Ziegler et al., 1986; Mori & Nakazono, 1986; Ziegler et al., 1988). Up to 1986, no determination had been made as to whether invictolide was a single enantiomer or a racemic mixture. Ziegler's total synthesis of (+)-invictolide made its bioassay possible and it turned out to be biologically inactive. In the same year, Mori reported the total synthesis of (–)-invictolide and inactive (+)-invictolide in 17 steps from propargyl alcohol, in 0.7% and 0.2% overall yield, respectively.

RESULTS AND DISCUSSION

(±)-Serricornine – During the isolation of serricornine (1) by Chuman et al. (3.1 mg of serricornine acetate from 26000 beetles!) a minor component was isolated and later on identified as its dehydration product. Anhydro-serricornine (2) was claimed to be significantly more active than 1 by Levinson et al (1981).

By the time we started our studies this controversy was unresolved and the only stereoselective total synthesis of (±)-serricornine (1) required 13 steps with 5% overall yield. The proposal by Chuman et al. that (±)-1 and (±)-2 might be formed from a C-11 poliketide derived from four propionate units led us to propose a biomimetic route to (±)-1 and (±)-2 which features an stereoselective aldol condensation to control the relative configuration of two chiral centers.

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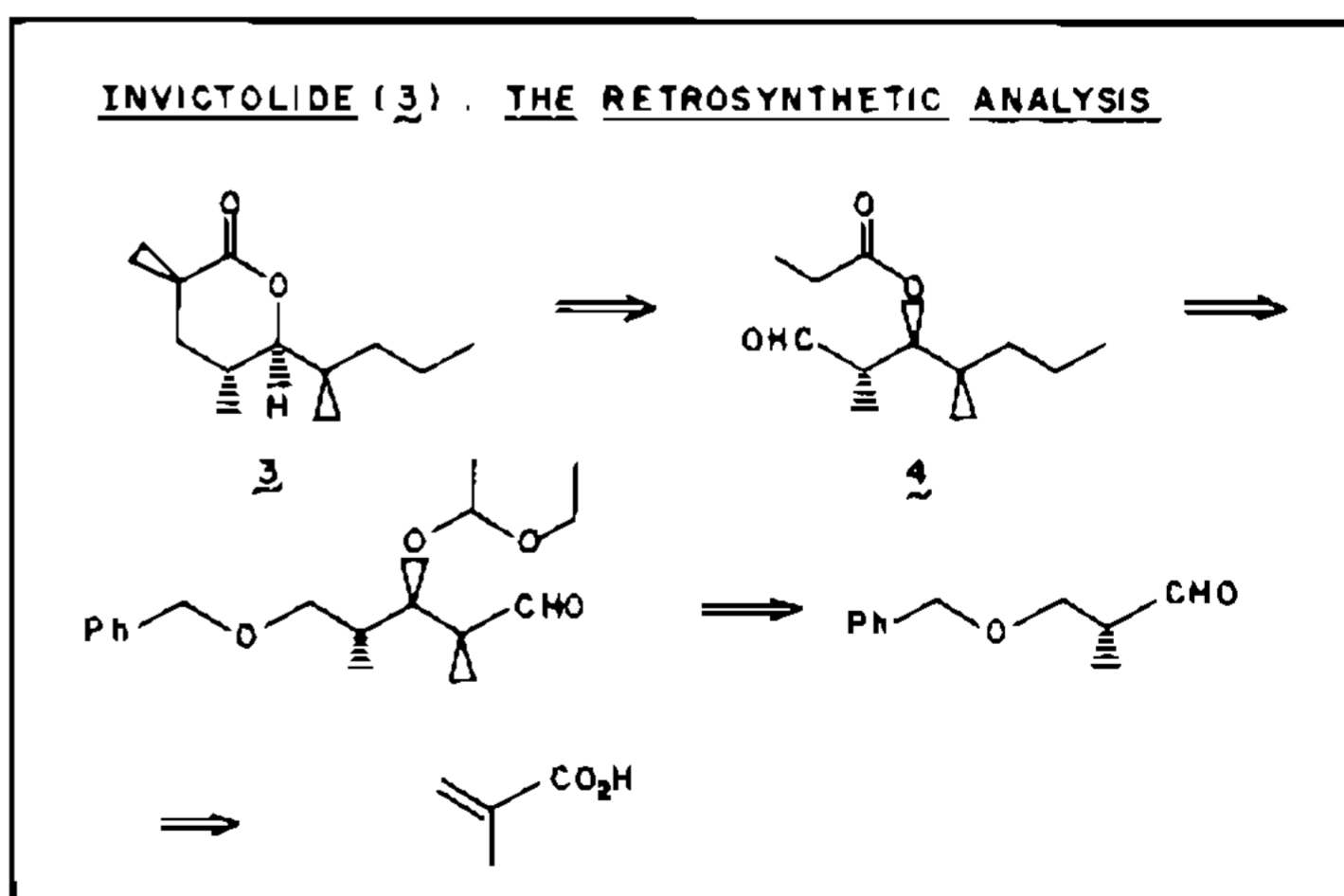


Our synthetic approach proved to be very efficient yielding (±)-serricornine in 12% overall yield (Pilli & Murta, 1988) as a mixture of the acyclic and hemiketal forms. Acetylation of the synthetic material provided the acetyl derivative as a single diastereoisomer by capillary gas chromatography and identical by $^1\text{H-NMR}$ spectroscopy, mass spectrometry and infrared spectroscopy to the acetate derived from natural serricornine.

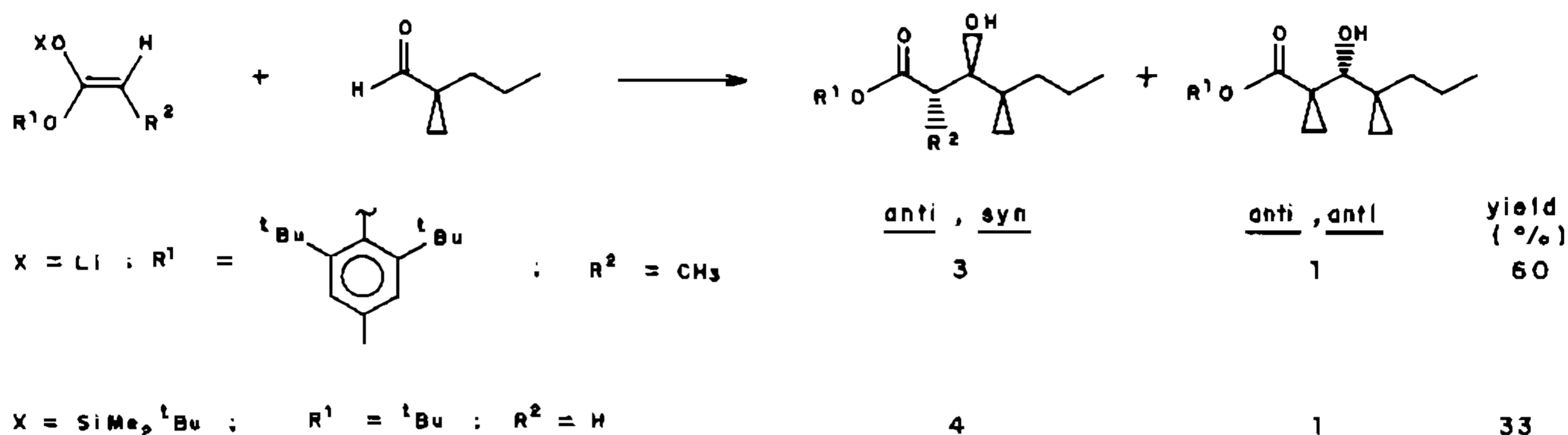
To our delight racemic serricornine attracted dozens of beetles from the fields surrounding our campus which were classified as *Lasioderma serricornne* F. Moreover, when beetles confined in a Petri dish were exposed to a capillary impregnated with our synthetic serricornine the responses observed included leg extension antennal elevation, rapid locomotion to the pheromone source and attempted mating as described by Coffelt & Burkholder (1972).

By the time we prepared (±)-serricornine (1), Chuman et al., had already published a definite study about the pheromone activity of anhydroserricornine showing that it did not play an important role in the occurrence of sex pheromone activity. In any event, (±)-anhydroserricornine (2) could be prepared by refluxing (±)-1 in benzene with catalytic p-toluenesulfonic acid.

(±)-Invictolide – Since at the onset of our studies it was not established whether invictolide was a single enantiomer or a racemic mixture, we decided to approach it through a route which would enable us to prepare both enantiomers as well.



Our first attempt was to prepare stereoselectively the intermediate 4 through aldol addition to α -methylwaleraldehyde which is available in both enantiomeric forms using Ender's methodology (Enders & Eichenauer, 1979).

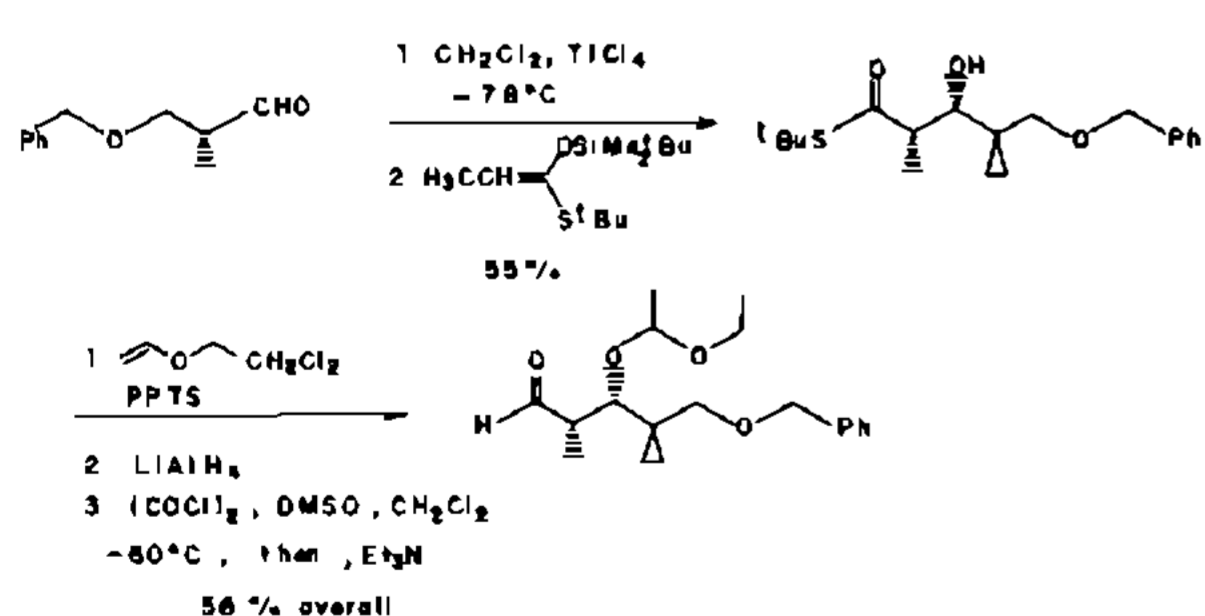
A DRAWBACK: POOR DIASTERO SELECTION WITH α -METHYLVALERALDEHYDE

The poor diastereoselection observed with (\pm)- α -methylvaleraldehyde and several nucleophiles led us to explore an indirect route to intermediate 4 which would benefit from the high diastereoselection observed in additions of some nucleophiles to 2-benzyloxy-1-methyl propionaldehyde (Gennari et al., 1986). The steps towards intermediate 4 are depicted in 3 and provides us with a straightforward route to the advanced intermediate 5 which features three chiral centers present in 3 with the proper relative configuration. Moreover the availability of (*R*)-methyl 3-hydroxy-2-methyl propionate renders this approach suitable for the preparation of bioactive (–)-invictolide (2).

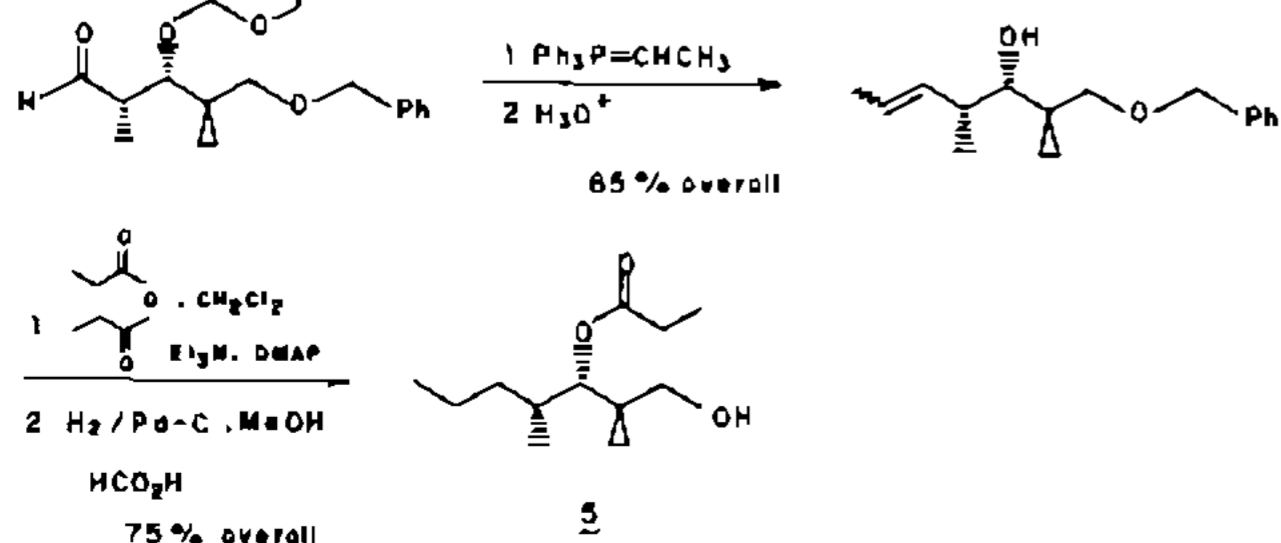
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THE PROPER RELATIVE CONFIGURATION



EXTENDING THE FRAMEWORK



- of optically active insect pheromones, (2*R*, 5*S*)-2-methyl-5-hexanolide, (3*S*, 11*S*)-3,11-dimethyl-2-nonacosanone and serricornin. *Tetrahedron Letters*, 651-654.
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