CHM 811C
Seminar 15

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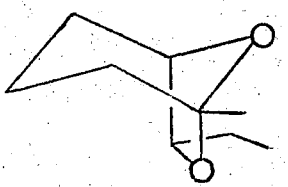
BREVICOMIN: STRUCTURE AND SYNTHESIS OF A NOVEL NATURAL PRODUCT

Brevicomin (1) is the trivial name proposed by Silverstein for exo-7-ethyl-5-methyl-6, 8-dioxabicyclo [3.2.1] octane. He isolated and identified the compound from the frass of the female Dendroctonus brevicomis, a western pine beetle.[1]



(1)

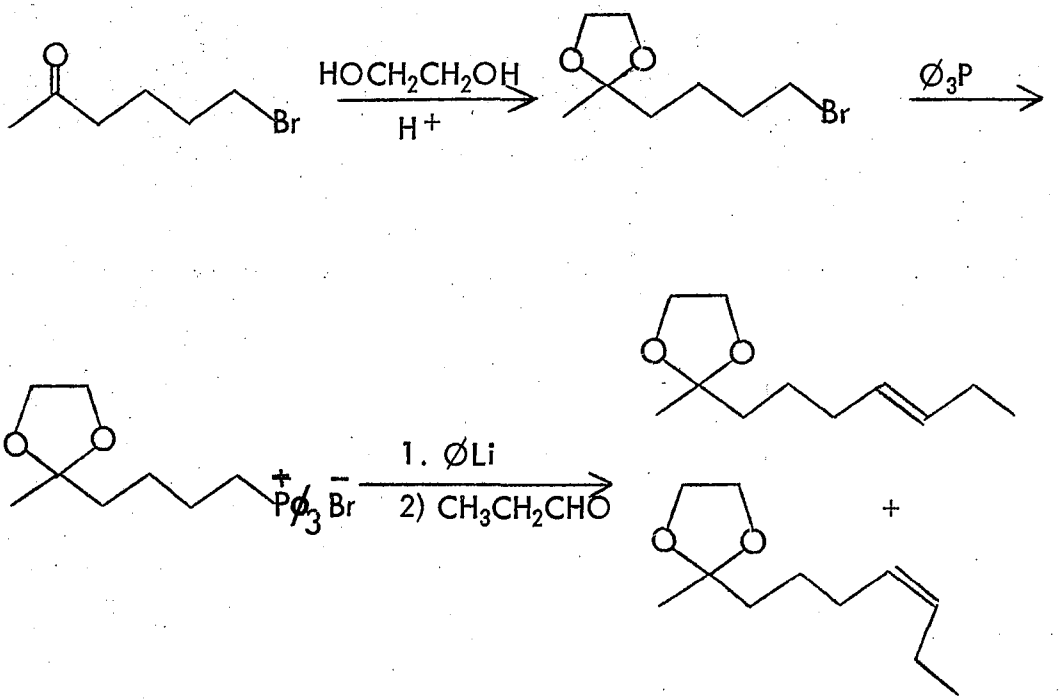
Brevicomin is included in a class of compounds called pheromones which were initially defined by Karlson and Lüscher (1959) as "substances which are secreted to the outside by an individual and received by a second individual of the same species in which they release a specific reaction, for example, a definite behavior or developmental process."[2]

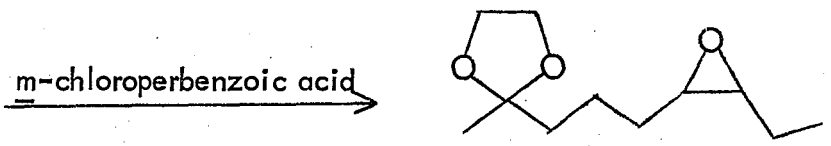
This specific pheromone is a sex attractant found in the female beetle which initiates the mass attack by both sexes that usually kills the tree. Brevicomin is active without any additional components, but is synergized with myrcene which is present in the host tree, the ponderosa pine.[3]

There are many ways brevicomin could be used for pest management by suppressing or surveying the beetle population.[4] These uses are extremely attractive considering the environmental harm and development cost of pesticides. In developing pheromones for pest control, one avoids the tedious work involved in discovering

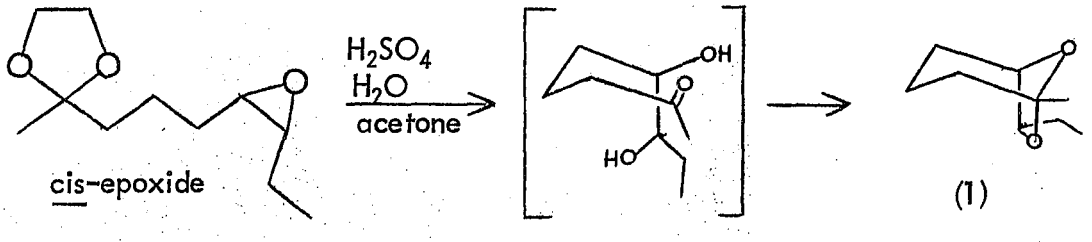
and refining the chemical structure of an active pesticide, since the active ingredients and optimum concentrations are defined by the insect in question.[5]

The frass of unmated female beetles was the source of material for structural determination. Pure brevicomin was obtained by extracting 1.6 kg of frass with benzene and chromatographing the resulting concentrate to obtain approximately 2 mg of the pure active compound. High resolution mass spectrometry determined the molecular weight to be 156.11572, and the calculated value for $C_9H_{16}O_2$ is 156.11502. The IR precluded the presence of carbonyl or alcohol groups, and the UV showed no absorption above 200 nm. The compound did not react when exposed to lithium aluminum hydride, while catalytic hydrogenolsis yielded n-nonane. The NMR showed peaks at 3.98 ppm (1 proton, triplet, J=6.2 hz), 1.1-1.9 (8 protons), 1.30 (3 protons, triplet), and 0.87 ppm (3 protons, triplet). The above evidence indicated that the compound might be exo-brevicomin since the protons attached to carbons 1 and 7 are at right angles to each other and thus effectively decoupled. Finally, the exo-isomer (1) was synthesized by the following procedure to assure the proposed identity.





cis- and trans-epoxides
separated by glc

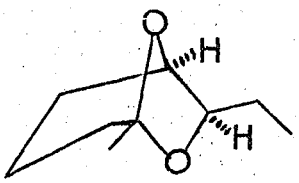


cis-epoxide

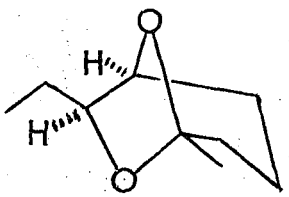
(1)

The various spectra of the synthetic product were identical to those of the natural product. The other isomer, obtained by acidic treatment of the trans-epoxide, proved to be endo-brevicomin, an inactive compound isolated from the frass.[1]

Silverstein reported in his original paper that a 0.05% hexane solution of the exo-isomer gave no optical rotation between 350 and 250 nm. Later Mori synthesized (2) from (2S:3S)-tartaric acid and (3) from (2R:3R)-tartaric acid.



(2)



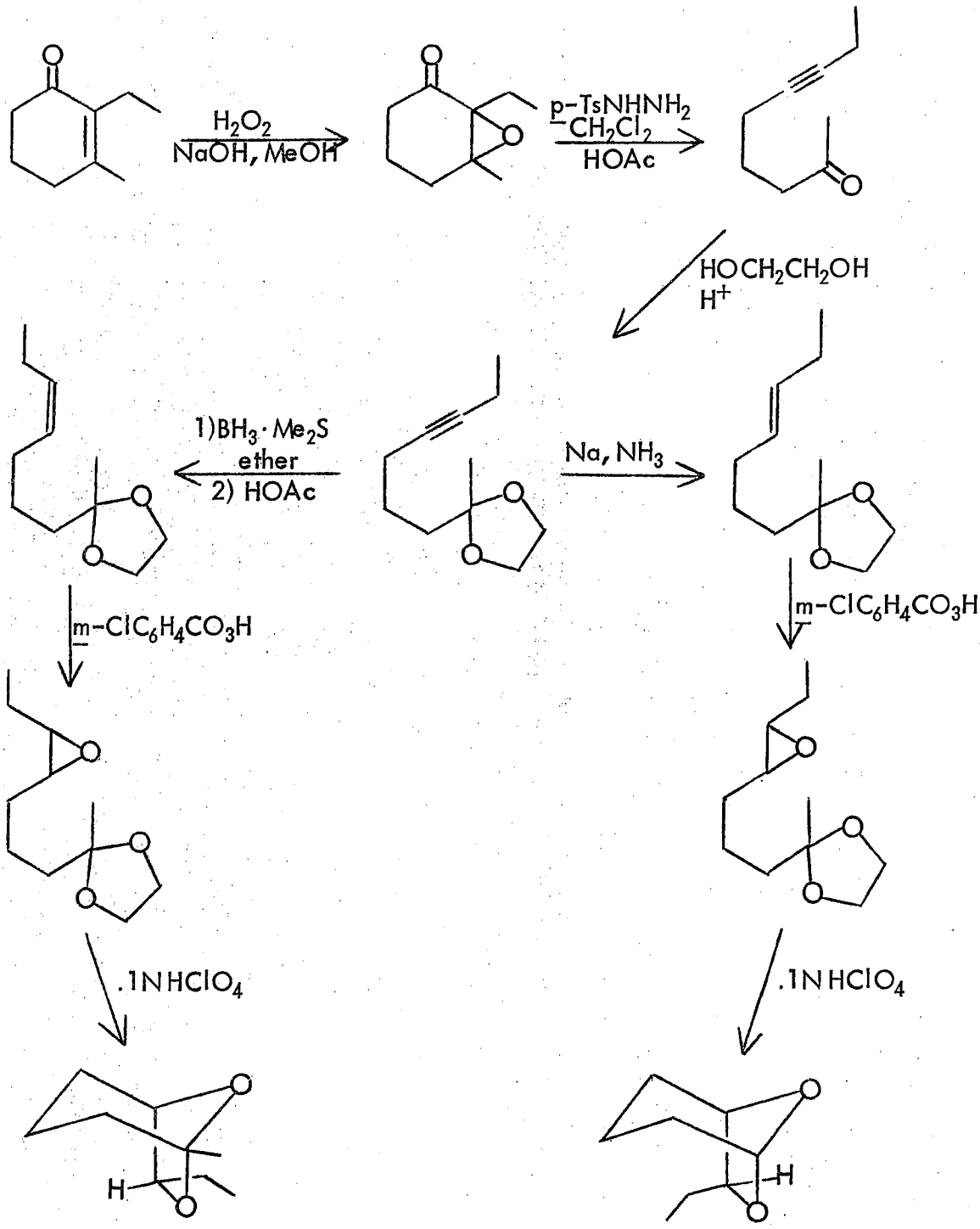
(3)

(2) (1R:7R) was dextrorotatory and (3) (1S:7S) was levorotatory.[6] Biological studies with the enantiomers demonstrated that (2) was more active than (3) in eliciting response in the pine beetle.[7]

For a synthesis to be of practical use for the production of sex attractant, it must have a good yield, low cost, and most importantly have stereoselectivity. There are many syntheses of brevicomin in the literature, but the majority are either

low in yield, non-stereospecific, or involve complicated and time consuming purification by preparative glc. The synthesis shown in Scheme I is highly attractive since all nine carbons of the brevicomin skeleton are present in the starting material.[8] The yields for the synthesis are excellent, purification processes are at a minimum, and the appropriate path gives exo-brevicomin with less than 1% of endo-isomer present.

Even though many pheromones such as brevicomin have been successful in field test,[4] they are still not being intensively researched or developed by industry. The reason they are not attractive industrially is that their high developmental and registration cost do not permit an adequate return on investment.[9] Also, since they are natural products, the proprietary position of the product is not as definite as that of a novel synthetic compound, thus leading to a highly competitive market. Therefore, for the immediate future, pheromones will be used only in survey work, or in timing of pesticide applications.[10]


H_2O_2
NaOH, MeOH
p-TsNHNH$_2$
CH_2Cl_2
HOAc
$HOCH_2CH_2OH$
H^+
1)$BH_3 \cdot Me_2S$
ether
2) HOAc
Na, NH_3
m-$ClC_6H_4CO_3H$
m-$ClC_6H_4CO_3H$
.1N $HClO_4$
.1N $HClO_4$
H
H

(1)

SCHEME I

References

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2. M. C. Birch, in "Frontiers of Biology", Vol. 32, North Holland Publishing Company, London, 1974, p. 1.
3. W. D. Bedard, P. E. Tilden, Science, 164, 1284 (1969).
4. W. D. Bedard, D. L. Wood in "Frontiers of Biology", Vol. 32, M. C. Birch, Ed., North Holland Publishing Company, London, 1974, p. 441.
5. J. B. Siddall, C. M. Olsen in "Pest Management with Insect Sex Attractants", M. Beroza, Ed., American Chemical Society, Washington, D.C., 1976, p. 89.
6. K. Mori, Tetrahedron, 30, 4223 (1974).
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8. P. J. Kociensti, R. W. Ostrow, J. Org. Chem., 41, 398 (1976).
9. See Ref. 4, p. 445.
10. W. G. Phillips, "Pest Management with Insect Sex Attractants", M. Beroza, Ed., American Chemical Society, Washington, D.C., 1976, pp. 135-144.