Stereochemical Aspects of Pheromonal Communications: Diversity is the Key Word

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The relationships between stereochemistry and bioactivity of pheromones are not simple but complicated, and a naturally occurring pheromone is not always the most bioactive stereoisomer. Pheromones are not necessarily stereochemically pure, and they are sometimes a mixture of stereoisomers. In 1973 when I started my pheromone synthesis, almost nothing was known about stereochemistry of pheromones. The reason was that conventional methods for determining their absolute configuration, such as degradation to a known chiral molecule or X-ray analysis, could not be useful in the case of pheromones, because they were usually oils secured in extremely minute amounts.

My synthesis of (*S*)-(+)-trogodermal in 1973 resulted in the assignment of the *R*-configuration to the naturally occurring (–)-trogodermal, the pheromone of *Trogoderma* grain beetles. Since then enantioselective synthesis of a pheromone has become the standard method for the determination of its absolute configuration (Mori 2007).

My 1974 synthesis of the enantiomers of *exo*-brevicomin was soon followed by the synthesis of the enantiomers of frontalin in 1975. Their pheromone activity was examined against the western pine beetle by David Wood, who found that only (1*R*,5*S*,7*R*)-(+)-brevicomin and (1*S*,5*R*)-(–)-frontalin were bioactive. This was the beginning of a long and still continuing journey to clarify the significance of chirality in chemical communication.

Diversity is the Hallmark of the Stereochemistry-Bioactivity Relationships Among Pheromones Conventional wisdom since the days of Louis Pasteur demands that only the pure enantiomers are bioactive. Indeed in the cases of the bark beetle pheromone components *exo*-brevicomin and frontalin, only (1*R*,5*S*,7*R*)- and (1*S*,5*R*)- isomers are bioactive, respectively, although they possess a 6,8-dioxabicyclo[3.2.1]octane framework of opposite absolute configuration. However, further synthetic works on chiral pheromones were followed by bioassays that reveal the diverse stereochemistry-bioactivity relationships among pheromones (Mori 2007, 2010, 2011).

Gypsy moth employs (7*R*,8*S*)-(+)-disparlure as its pheromone. Its opposite (7*S*,8*R*)-(–)-enantiomer inhibits the action of (+)-isomer. Accordingly, (7*R*,8*S*)-(+)-disparlure is manufactured, and employed for the population monitoring of the moth. In the case of sulcatol, the pheromone of an ambrosia beetle, both the enantiomers are necessary for bioactivity, and the natural pheromone is a mixture of (*R*)-(–)- and (*S*)-(+)-isomers in a ratio of 35:65. Olean, the olive fruit fly pheromone, is a 1:1 mixture of (*R*)-(–)- and (*S*)-(+)-isomers, the former activating the males and the latter females. The

bioactive stereoisomer of the cigarette beetle pheromone is (4*S*,6*S*,7*S*)-serricornin, and its (4*S*,6*S*,7*R*)-diastereoisomer inhibits the pheromone action. In the case of the tsetse fly *Glossina pallidipes*, *meso*- isomer is the bioactive stereoisomer. The female German cockroach employs the (3*S*,11*S*)-(+)- form as her pheromone, although it is the least active one among its four stereoisomers. Male *Drosophila melanogaster* fruit fly employs a far less potent (3*R*,11*Z*,19*Z*)-(–)-CH503 form as his anti-aphrodisiac pheromones. Its unnatural (*S*)-isomers are much more bioactive.

Pheromones are Not Always Enantiomerically Pure As described above, the naturally occurring pheromone of *Gnathotrichus sulcatus* is (*S*)-(+)-sulcatol of only 30 % ee, and that of *Bactrocera oleae* is racemic (0 % ee) olean.

Our recent study in 2011 showed that the naturally occurring pheromone of *Tribolium castaneum* (tribolure) is a mixture of all the four stereoisomers of tribolure. Recent advances in synthetic and analytical methodologies have enabled us to clarify the subtle biomolecular heterogeneity, which has been observed among many other natural products besides pheromones (Mori 2011).

In summary, my own studies, together with others including Milt Silverstein, Shingo Marumo, and Jim Tumlinson, have firmly established the importance of chirality in pheromone perception, and the following three conclusions should be remembered. (1) Chirality of biomolecules is very important for the expression of their bioactivity. (2) Natural products are not always enantiomerically pure. Sometimes only such “impure” biomolecules can express bioactivity. (3) The existing dogma only one enantiomer is bioactive must be modified (Mori 2010).

We should take advantage of any remarkable advance in science so as to listen to the sound of a soft breath in mother nature.

And, after the earth- shock a fire, but Lord was not in the fire. And after a fire, the sound of a soft breath. And Elijah, hearing it, went out... (1 Kings 19:12–13)

References

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