CHAPTER III

Synthesis of Insect Pheromones
Introduction

The interdisciplinary investigations of insect kingdom by biologists and chemists have established the importance and complexity of chemosensory communication amongst the insects. Many facets of insect behavior have shown to be regulated by chemical stimulation. The current outcry over indiscriminate use of insecticides has provided much of the motivation for this work since the species-specificity and high potency of many naturally occurring chemosensory substances hold great promise for manipulation and control of insect population.

Natural insect attractants fall broadly into two categories: a) secretions of insect origin, which produce responses for mating and aggregation within a single species: the term "Pheromone" applies to this type of intra-species attractant; b) volatile constituents of plant or animal hosts utilized by insects in searching for food and egg-laying sites.

The term "Pheromone" coined by Karlson and Lusher\textsuperscript{1} is derived form the Greek pherin, means transfer, and harmon, means excite. Pheromones are defined as substances that are secreted to the outside by an insect and received by the opposite sex of the same species in which they release a specific reaction, for example, a definite behavior or a developmental process. Pheromones are classified into distinct types by Wilson\textsuperscript{2} according to the response they elicit. The chemical stimuli that trigger an intermediate and reversible change in the behavior of the recipient are called releasers, whereas those including delayed, lasting responses are referred to as primers.

A variety of chemicals have been identified by screening as attractive to one sex, but until these compounds have been isolated and identified from the opposite sex, they are called as sex attractants or Para-pheromones. In some species, particularly among beetles, the pheromones may attract both sexes and therefore serve more than one function and they are called as aggregation pheromones.

The potential economic and environmental importance of biological pest control is currently undergoing experimental evaluation and several groups have reported the successful use of natural insect attractants. Insect attractants have been used to reduce pest population by employing attractant-baited traps. Sex pheromone attractants have also been used in the 'confusion technique' whereby normal mating behavior is disrupted by permeating the atmosphere with synthetic sex attractants.
These methods of pest control have considerable advantages over the use of conventional insecticides. The relatively small amounts of synthetic attractants required, minimizes the possibility of environmental pollution and the species specificity of many natural attractants reduces the risk of destroying beneficial insects such as predators, parasites and pollinators resistant to natural attractants is very unlikely. The most general application of insect attractants probably lies in integrated control measures as population survey tools to probe the degree of infestation. Limited applications of chemical pesticides would then suffice in area of intolerable infestation and the need for blanket spraying programmes throughout the season, with its attendant hazards would be obviated. The synthetic approach has been very important in pheromone research.

Many staphylinid beetles possess exocrine glands, yet the secretion of only two species have been identified, the principle components being monoterpenes. A more complex molecule has been found in the blood of a staphylind. The pygidial secretions of two species of staphylinds of the genus Bledius contain 6-Hexadecalactones 1 & 2, 1-undecene 3, bezoquinone 4, neral 5 (terpenes) and geranial 6 (Fig. 1).

Pygidial glands of Bledius mandibularis and Bledius spectabilis from the Atlantic coasts of the United States and Europe, respectively, were excised and immersed in methylene chloride and the resulting extract analyzed by combined GC-MS revealed the same five components in both species.
6-Hexadecalactones, the first lactones from insect sources has a fruity odour and have been isolated from various fruits and butterfat. Few other lactones have been reported from exocrine secretions of animals, functioning as queen pheromones in hornets and sex related recognition pheromones in male black-tailed deer.

5-Hexadecanolide, 1 and 2, a pheromone isolated from the mandibular glands of the oriental hornet Vespa orientalis in 1969, has been proposed as a pheromone playing the role of a queen substance.

6-Acetoxyl-5-hexadecanolide, 7, is the major component of the apical droplets that form on the eggs of the mosquito Culex pipiens fatigans. The substance acts as an oviposition pheromone attracting gravid females of the same and same related mosquito species inducing them to oviposit in the same spot where the original eggs are found. These behaviours can be used to lure the mosquito away from populated areas to a place where they can be readily trapped.

Tanikolide, 8, is a new brine-shrimp toxic and anti-fungal metabolite has been isolated from the marine cyanobacteria (blue-green alga) Lyngbya majuscule Gomont collected from Tanikeli Island, Madagascar (Fig. 2).

![Chemical structures](image-url)
comprise structural moieties frequently present in insect pheromones. Intrigued by the important biological activities of 5-(S)-Hexadecanolide and 6-Acetoxy-5-hexadecanolide, a number of synthetic procedures have been reported both in racemic and optically active form. In continuation with our studies on the synthesis of naturally occurring lactones, we became interested in the total synthesis of 5-(S)-Hexadecanolide 1 and 6-Acetoxy-5-hexadecanolide 7.
This section of the thesis deals with previous synthetic approaches for 5S-hexadecanolide.

**Previous synthetic approaches:**

5-(S)-hexadecanolide was prepared by various research groups, which are described here.

Masanori Utaka et al\(^t\)\(^1\) synthesized various \(\delta\)-lactones from 5-oxoalkanoic acid (Scheme 1) employing Baker’s yeast. 5S-hexadecanolide was prepared by asymmetric reduction of corresponding 5-oxoalkanoic acid with fermenting bakers yeast (*Saccharomyces cerevisiae*) that resulted in corresponding alcohol that upon acid catalyzed lactonization resulted in desired product 5S-hexadecanolide 1.

\[
\begin{align*}
\text{C}_{11}H_{21} & \quad \text{baker's yeast} \quad \text{C}_{11}H_{21} \\
\text{CO}_2H & \quad \text{OH} \quad \text{CO}_2H \quad \text{H}^+ \\
\end{align*}
\]

**Scheme 1**

Yoshinobu Naoshima et al\(^t\)\(^2\) reported the synthesis of 1, starting from alkylation of 11 with ethyl-3-bromo propionate and followed by decarboxylative hydrolysis with aqueous sodium hydroxide to give a keto acid 12. The keto acid 12 was reduced to optically pure alcohol by baker’s yeast immobilized in carrageenan and subsequently corresponding alcohol was lactonized to get 5S-hexadecanolide 1 (Scheme 2).

\[
\begin{align*}
\text{Et}_2\text{OC} & \quad \text{C}_{11}H_{21} \\
\text{CO}_2Et & \quad \text{Et}_2\text{OC} \quad \text{C}_{11}H_{21} \quad \text{baker's yeast} \\
\text{OH} & \quad \text{H}^+ \\
\text{HO}_2\text{C} & \quad \text{C}_{10}H_{21} \\
\text{O} & \quad \text{O} \quad \text{C}_{11}H_{21} \\
\end{align*}
\]

**Scheme 2**

Shui-Tein Chen et al\(^t\)\(^3\) reported the synthesis of 1 by involving Grignard addition. Grignard reagent of 1-bromoundecane was added to 5-benzyl-1-pentanal 15 and afforded \(O\)-benzyl alcohol 16. The hydroxyl group 16 was acetylated by