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Chemistry of Fruit Flies

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I. Introduction

The family Tephritidae (true fruit flies) contains about 4000 species organized in 500 genera and is thus one of the largest families of Diptera (true flies).[1,2] The chief reason for the widespread study of Tephritid fruit flies is related to their economic importance, as a significant number are extremely destructive pests of many forms of horticulture in the tropical and temperate world and costly monitoring and control programs are necessary to counter this scourge. Tropical Tephritidae are relatively long-lived, have a high capacity for dispersal, and are usually polyphagous with an ever-expanding host range, which exacerbates the problem of control. For example, the oriental fruit fly *Bactrocera dorsalis* (Hendel) is considered to damage in excess of 50 fruit species in Taiwan,[3] and *B. tryoni* (Frogatt) (Queensland fruit fly) has been recorded from more than 100 host plants in Queensland, but probably affects many more.[4] Temperate species, e.g. *Rhagoletis* spp., have a much reduced capacity for dispersal and are monophagous or oligophagous and differ from most of their tropical counterparts in employing oviposition-deterring pheromones (ODPs) to achieve economy in egg distribution.[5]

The classification of the Tephritidae is complex and even unsettled and the excellent monographs by Drew[2] and White and Elson-Harris[1] should be consulted for recent discussions of this subject. Most pestiferous flies belong to the subfamilies Dacinae and Trypetinae. Within the former subfamily, the tribe Dacini contains the important old-world genera *Bactrocera* and *Dacus*, and the tribe Ceratitini contains the important pest, Mediterranean fruit fly, *Ceratitis capitata* (Wiedemann). Within the subfamily Trypetinae are some 230 or so genera, placed into seven named tribes. In this subfamily are located the pest genera *Dirioxa, Anastrepha, Toxotrypana*, and *Rhagoletis*. Very few members of

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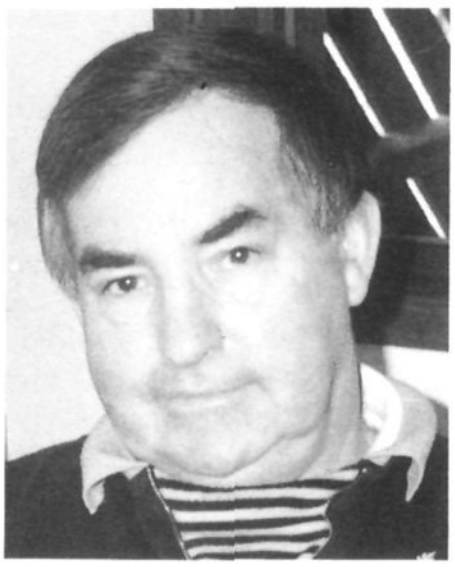


Professor Bill Kitching completed his Ph.D. (1964), B.Econ. (1974), and D.Sc. (1979) degrees at the University of Queensland. Following the award of the Ph.D. degree he was a Fulbright Scholar in the United States, working at the University of Cincinnati (R. E. Dessy) and then at the University of California at Los Angeles (1965–1966) with the late Professor S. Winstein. He returned to a lectureship at the University of Queensland in 1966 and was promoted to Reader (1974) and then full Professor. He has held visiting appointments at The Ohio State University, the University of North Carolina at Chapel Hill, Imperial College of Science in London, Universite Bordeaux, and Corpus Christi College (Visiting Fellow), University of Cambridge. Professor Kitching is a former Rennie Medallist of the Royal Australian Chemical Institute and is the author of over 180 research publications, reviews, and invited chapters in the areas of organometallic and physical organic chemistry, organic synthesis, and natural product chemistry.

the third subfamily, Tephritinae, are of pest status, but some such as *Urophora* are beneficial species for the biological control of noxious weeds.[1]

In recent years more attention has been given to the possible use of pheromone-based attractants in fruit fly control. Male tephritids store the pheromone in a reservoir and secrete it from a sac, both organs being located in the lower abdominal (rectal) area and appearing in the male (e.g. *B. tryoni,* Queensland fruit fly)[6] two days after the pupal−adult apolysis. As the flies mature, droplets of material form. In only one species, *B. oleae* (Gmelin) (olive fruit fly) does the female release the sac pheromone,[7] whereas male generated pheromones have been identified in several tephritid fruit flies. The release of the pheromone is generally accompanied by courting behavior, and females may respond to other stimuli.

The use of synthetic sex pheromones and other intraspecific chemical communicants is established in Lepidopteran species (where the females secrete and release the chemical blend) but use of Dipteran pheromones for control or monitoring is not common, despite its obvious potential. This is related to the fact that Lepidopteran chemistry has received close scrutiny, whereas much detailed work is required with Dipteran species.

The purpose of this review is to consolidate the available information concerning chemical studies of fruit flies and to indicate cases for which this data may be of value in behavior modification or taxonomic clarification. The studies described pertain to the rectal gland secretions of male flies (excepting the olive fly) or to aeration/trapping experiments of released volatile components. Descriptions of techniques for gland excision, combined gas chromatography−mass spectrometry etc., and other experimental details are located in the original referenced literature, or in monographs. Species distribution and host ranges described are generally obtained from the texts by Drew[2] and White and Elson-Harris[1] or private communication with these authors. The discussion that follows commences with the Dacinae subfamily followed by information on members of the Trypetinae and Tephritinae subfamilies.

II. Subfamily Dacinae

A. Genus *Bactrocera*

Bactrocera is a genus of about 440 species located predominantly from tropical southern Asia through Australia to parts of the South Pacific, with very few species in Africa and only *B. oleae* in southern Europe. Prior to the reclassification by Drew,[2] most authors placed all *Bactrocera* species within the genus *Dacus*. Pheromonal information has been reported for some 24 *Bactrocera* species of both pest and nonpest status (see text) and chemical comparisons have provided interesting chemotaxonomic insight in some cases. The biological activity of reported components has only been examined in the important pest species *B. oleae*, *B. cucurbitae*, and *B. tryoni*. This review covers these species on a roughly regional basis, commencing with the Mediterranean *B. oleae* (and species of similar pheromonal composition), followed by species from Southeast Asia and lastly those from Australia and the South Pacific.

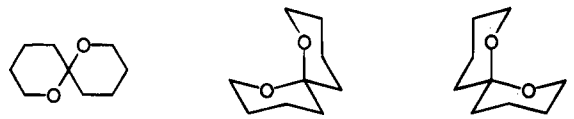
1. Bactrocera oleae (Olive Fruit Fly)

a. Identification of Bactrocera oleae Pheromone. *Bactrocera oleae* (Gmelin), the olive fruit fly, is a very serious pest of olives in Southern Europe and North Africa, particularly in Spain, Italy, Greece, and Israel, where olive growing is a major agricultural pursuit. The larvae bore into and feed on olive fruit and are strictly monophagous. Crop losses as high as 30% annually may be experienced, and of course

much higher in the absence of controls, which are based on insecticidal application. The sustained use of wide-spectrum insectides in air-bait and cover sprays has clear ecological consequences, and accordingly studies which demonstrated the existence of a sex pheromone in this species focused attention on its possible use in monitoring and control. A number of reports discuss the control of olive fly by sex pheromone-based methods,[7-9] and these should be consulted for further information.

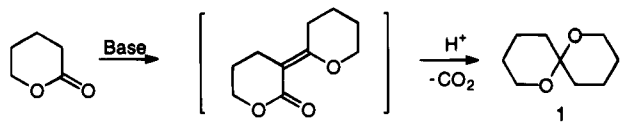
Studies and observations by Economopoulos[10] and Schultz[11] led to the idea that pheromone-mediated attractancy occurred in the olive fly and some other species, and laboratory and field tests confirmed that female flies released a volatile mixture which acted as a male attractant.[12] This capacity of the female to secrete and release the pheromone is unique among Tephritid fruit flies, as this is normally the task of the male.

Three groups conducted studies independently on the chemical nature of the female sex pheromone, although the first report was due to Baker and Francke and their groups.[13] The major female-specific component in the gland secretion, with apparent M = 156 ($C_9H_{16}O_2$) and a typical spiroacetal fragmentation pattern, was shown to be 1,7-dioxaspiro[5.5]undecane (**1**), a simple example of the class of spiroacetals which are found extensively in a wide range of biologically active molecules. Amounts of 300 ng/insect were found.[13] Note that **1** is chiral (C_2 symmetry) and can exist in the enantiomeric forms, (*R*)-**1** and (*S*)-1.



Racemic **1** was synthesised[13] by the method of Erdman,[14] which involves the base-catalysed condensation of δ-valerolactone as shown in Scheme 1. This

Scheme 1

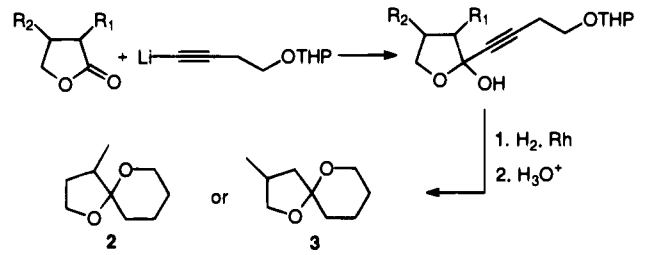


material was used in field experiments in Granada, and sticky "delta" traps, incorporating the spiroacetal, attracted very predominantly male olive flies.[13]

In 1980, Mazomenos and Haniotakis[15] reported that the pheromone of females, obtained from a "total condensation cold trap", consisted of four components, whereas only two of these were present in the rectal gland secretion. The biological activity of all four compounds and combinations thereof was determined, with the most abundant component in the mixture (~56%) showing the highest activity, although combination of all compounds significantly increased activity. The major component in both samples was **1**, in amounts ranging from 64 to 128 ng/fly, with the three minor components being α-pinene, *n*-nonanal, and ethyl dodecanoate.[16] The attraction of male olive flies to synthetic pheromone components, under laboratory and field conditions was also examined, and spiroacetal **1** was confirmed as being more attractive than any of the remaining three components.[17]

Italian workers also reported studies of the volatile compounds emitted by female olive flies, as well as those present in the rectal gland. In the former report[18] (*E*)-6-nonen-1-ol and *p*-cymene from the condensed material were described as exhibiting attractive and aphrodisiac effects in both laboratory and field experiments. Subsequently, Gariboldi reported[19] on the compounds present in the rectal glands of 6-day-old virgin females and identified 17 compounds, 16 of which were esters of fatty acids. The most volatile component was considered to be a spiroacetal on the basis of its mass spectrum,[20] and three structures were considered, viz. **1**, **2**, and **3**, with **1** being synthesized as in Scheme 1, and **2** and **3** by the addition of 1-alkynyllithium reagents to a suitable lactone, following the report of Phillips[21] (Scheme 2). Careful gas chromatography confirmed

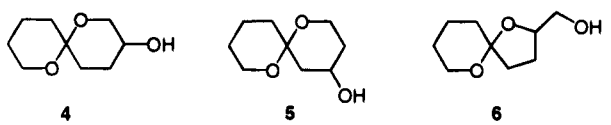
Scheme 2



the identify of the major volatile compound (other than esters) as **1**, whereas examination of the rectal glands of male olive flies revealed the presence of C_{10}–C_{18} aliphatic hydrocarbons only.

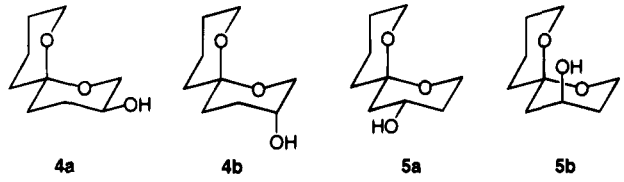
Some uncertainty surrounds Gariboldi's assertion[18] that (*E*)-6-nonen-1-ol and *p*-cymene are female produced with "attractive and aphrodisiac effects". Rossi and co-workers[22] have discussed the biological activity of various nonenols with (*Z*)-6-nonen-1-ol being most efficacious. However, Baker[13] detected no field activity for (*Z*)-6-nonen-1-ol, and Mazomenos[7] commented that his research group was not able to isolate (*E*)-6-nonen-1-ol or *p*-cymene from female *B. oleae* volatiles nor were they able to detect activity with synthetic components.

Subsequent studies by Baker and his group identified hydroxy derivatives of spiroacetal **1** at low levels (*ca.* 10 ng/individual) in the rectal gland of female olive flies.[23,24] On the basis of mass spectral analysis, these components were identified as **4** and **5**, the 1,7-dioxaspiro[5.5]undecan-3- and -4-ols. Under certain GC conditions, **4** may rearrange to 1,6-dioxaspiro[4.5]decan-2-ylmethanol (**6**). Synthesis of



the four alcohols **4a,b** and **5a,b** enabled Baker and Herbert[24] to deduce that the natural diastereomers were the equatorial isomers **4a** and **5a**. At that

stage, there was no information on the absolute stereochemistry of **4a** and **5a** and how it might relate to 1.



Hydroxy-substituted spiroacetals have been detected in a number of other fruit fly species and are discussed elsewhere in this review. Absolute stereochemistries have been determined in some instances. [See for example the report by Perkins *et al.*[25] on hydroxyspiroacetals from *B. cucumis* (French).]

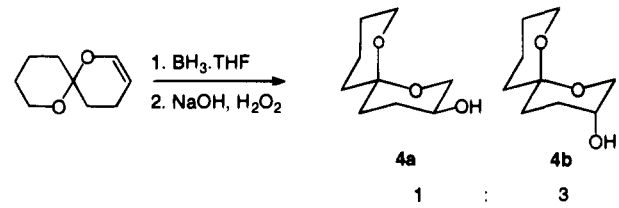
With respect to olive flies, a comment on ovipositional deterrents is relevant. Girolami and co-workers[26] reported that deterrent substances are present in the juice released from oviposition wounds, with the important compounds being present in theoil fraction. Acetophenone, benzaldehyde, and *o*-diphenols were suggested as possessing deterrent activity.[26,27] Another study examined the attractive/repellent features of the headspace volatiles from olives of varying degrees of ripeness and crushed olives. Toluene and ethylbenzene proved attractive, whereas (*Z*)-2-hexenal, emitted by crushed olives, was decidedly repellent, as was hexanal.[28]

b. Synthesis of 1,7-Dioxaspiro[5.5]undecane (1) and the 1,7-Dioxaspiro[5.5]undecan-3- and -4-ols (4 and 5), in Racemic and Enantiomeric Forms. Identification of **1** as the major pheromone of the olive fly, and isomers of **4** and **5** as accompanying low-level components (of unestablished biological significance) together with the characterization of an expanding variety of other biologically active molecules incorporating the spiroacetal substructure, stimulated much interest in the development of methods for construction of the spiroacetal unit. The efficiency of many of these new methods was tested by synthesizing relatively simple spiroacetals, of the types reported from various insect species. The general approaches to 1,7-dioxaspiro[5.5]undecanes were reviewed relatively recently[29,30] and here important methods for the synthesis of **1**, **4**, and **5**, in both racemic and enantiomeric modifications will be discussed, before consideration of the chirality of the natural pheromone and accompanying hydroxy derivatives, and biological responses to the enantiomers of **1**.

Some methods for the synthesis of **1** have been presented in the context of the pheromone identification and Baker[13] utilized the method of Erdman[14] (see Scheme 1) to confirm the identity of natural **1**. Utilizing a method of no general utility, Mićović demonstrated that **1** (3.3%) was one of many products formed by treating 1,9-nonanediol with $Pb(OAc)_4$ in hot benzene.[31]

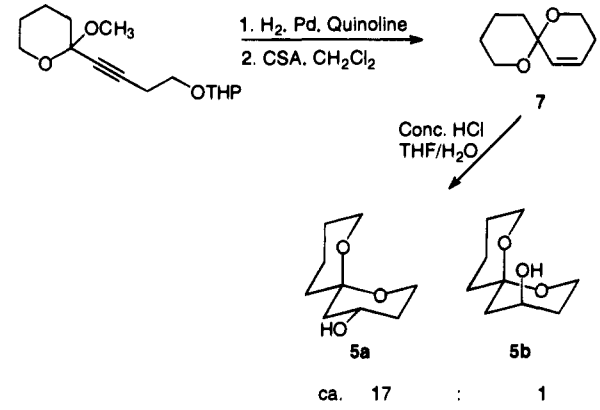
Full details of the synthesis of the alcohols **4** and **5** were also reported by Baker and Herbert.[24] For the former alcohol, hydroboration–oxidation of 1,7-dioxaspiro[5.5]undec-2-ene (acquired using the method of Ireland[32]) provided diastereomers **4a** and **4b** in a ratio of 1:3, and these could be separated and derivatized to the dinitrobenzoate ester (Scheme 3).

Scheme 3



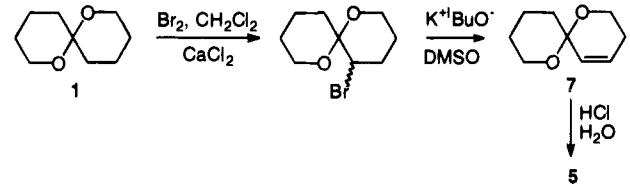
The regioisomeric alcohol **5** resulted from partial reduction of the alkyne shown in Scheme 4 (and obtained by the method of Delongchamps[33]), followed by acid-induced cyclization to the unsaturated spiroacetal **7**, treatment of which with concentrated HCl in $THF-H_2O$ provided diastereomers **5a** and **5b** (Scheme 4).

Scheme 4



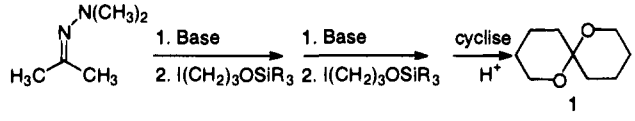
A very direct route to the unsaturated spiroacetal in Scheme 4 has recently been reported, and a "one-pot" conversion of **1** to diastereomers of **5** developed,[34] as shown in Scheme 5.

Scheme 5



Enders[35] has developed a general procedure for the diastereo- and enantioselective synthesis of spiroacetals (and other systems) based on deprotonation and alkylation of appropriate hydrazones. This methodology has been used to acquire **1** and various other spiroacetals (Scheme 6) and remains as one of

Scheme 6

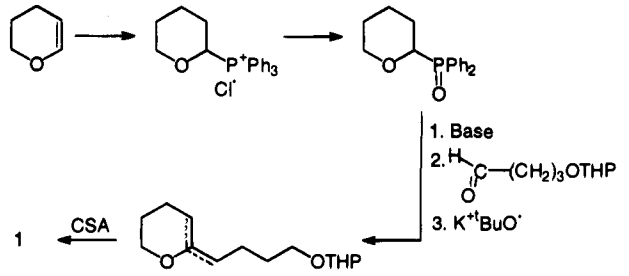


the more attractive general procedures for spiroacetal synthesis.

In a major advance in this area, Ley and co-workers[36] developed procedures for generating

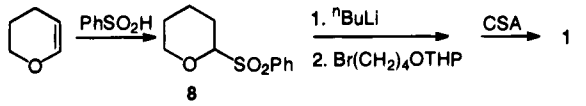
carbon–carbon bonds at the 2-position of cyclic ethers e.g. tetrahydrofuran and tetrahydropyran, such derivatives being found in a wide variety of natural products. The methodology hinges on the placement of anion-stabilizing groups at the 2-position (mainly by addition reactions to the enol ethers themselves) so that deprotonation and alkylation can occur efficiently. Wittig and Horner–Wittig coupling reactions were developed,[36] and the sequence is illustrated (Scheme 7) for the synthesis of **1**.

Scheme 7



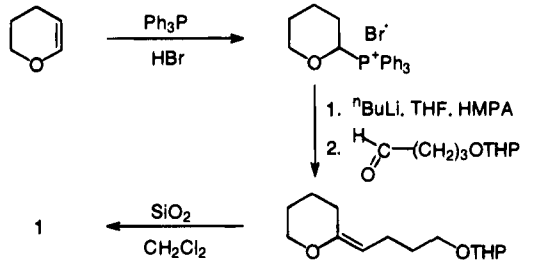
Ley[37] also demonstrated that 2-(phenylsulfonyl)-tetrahydropyran (**8**) was a useful spiroacetal precursor, and olive fly compound **1** was again easily acquired as shown in Scheme 8.

Scheme 8



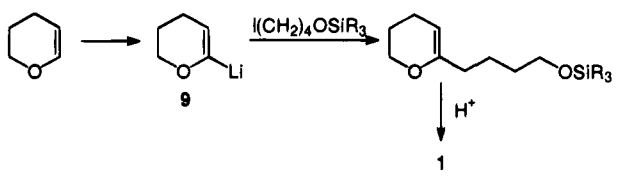
The synthetic utility of enol ethers and their derivatives in this area was also examined by French workers,[38] and use of the phosphonium bromide derived from dihydropyran led efficiently to **1** (Scheme 9).

Scheme 9



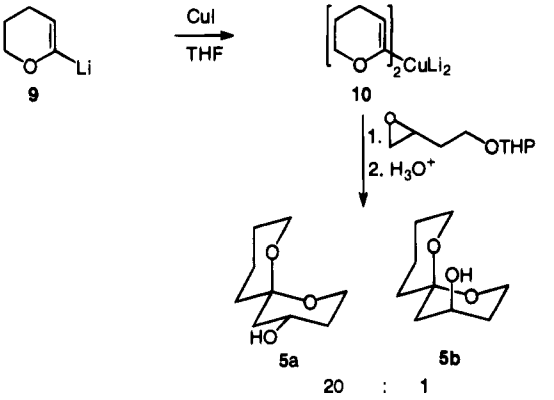
Deprotonation of 3,4-dihydro-2*H*-pyran is well documented[39] and reaction of the lithio derivative[40] **9** with the appropriate protected hydroxy iodide, followed by acid-induced cyclization furnishes **1** (Scheme 10).

Scheme 10



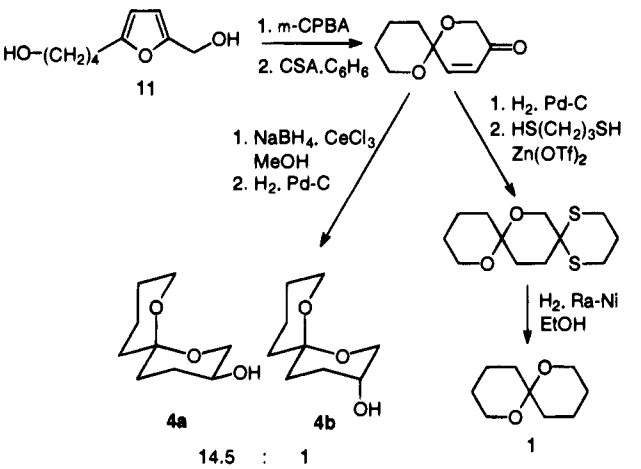
The cuprate **10** derived from 6-lithio-3,4-dihydro-2*H*-pyran (**9**) by treatment with CuI in THF has been employed in a straightforward synthesis of 1,7-dioxaspiro[5.5]undecan-4-ol (**5**), by Kocienski.[41] The efficiency of the oxirane ring opening by this cuprate is noteworthy (Scheme 11).

Scheme 11



General access to the 1,7-dioxaspiro[5.5]undecane class of spiroacetals has been reported by DeShong, in which oxidation of an appropriate furfurol e.g. **11** to provide a pyranone, is the key step.[42] The sequence leading to spiroacetal **1** and hydroxy derivatives **4a** and **4b** is shown in Scheme 12.

Scheme 12

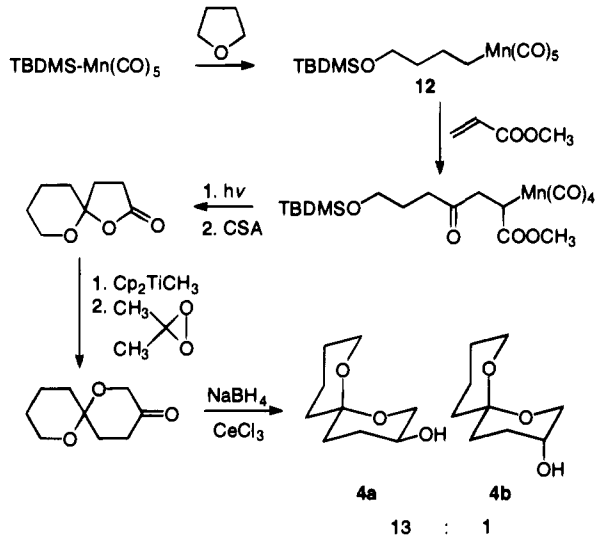


DeShong[43] has utilized a silylmanganese pentacarbonyl reagent (**12**), to generate a key spirolactone which can be elaborated to both the [4.5] and [5.5] families of spiroacetals. In this way, hydroxyspiroacetals **4a** and **4b** were obtained as a diastereomeric mixture. The key elements of this unusual route are shown in Scheme 13, but the generality of the method and utility in more complex cases await demonstration.

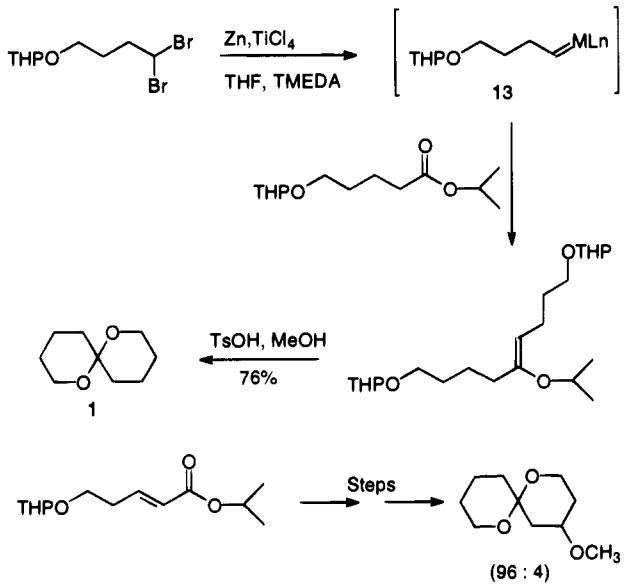
In a somewhat related vein, Kociénski[44] has reported that metal–carbene complexes **13** prepared from alkoxy-substituted 1,1-dibromoalkanes react with alkoxy-substituted esters to provide enol ethers which undergo spiroacetalization in acidic methanol. A variety of spiroacetals was described, including **1** and the methyl ether of **5** (Scheme 14).

Carbenoid insertion, with a cyclopropylidene (**14**), is the basis of a novel route to **1**, but the regiochemistry of insertion favors the [4.5] rather than the [5.5] spiro system and overall it is difficult to envisage

Scheme 13

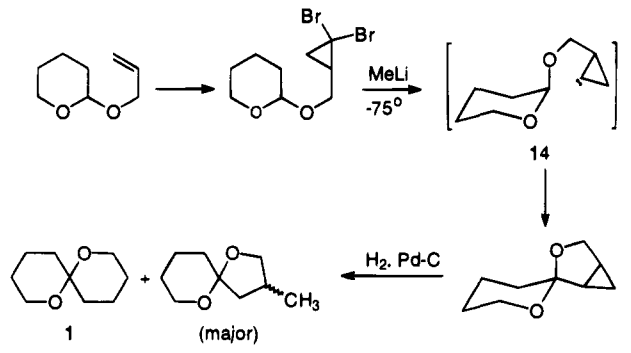


Scheme 14



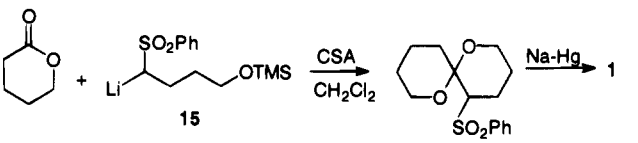
any generality for this approach in spiroacetal synthesis[45] (Scheme 15).

Scheme 15



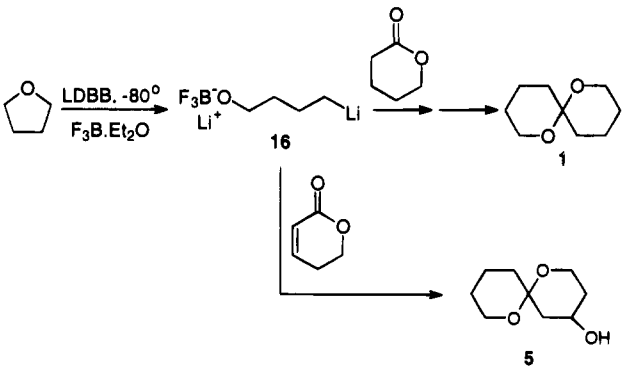
The addition of organometallic reagents to lactones features prominently in approaches to spiroacetals, and examples have been shown in Schemes 2 and 4. The use of α-sulfonylcarbanions (e.g. **15**) has found significant application and may be a very useful general procedure. In particular, Brimble[46] reported acquisition of **1**, along with other spiroacetals by this method (Scheme 16).

Scheme 16



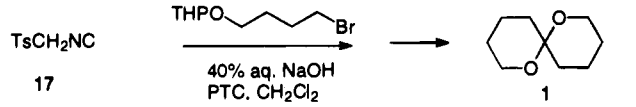
Cohen[47] has reported that Lewis acid-promoted cleavage of THF with lithium 4,4′-di-*tert*-butylbiphenylide (LDBB) proceeds well at −80 °C to yield 4-lithiobutoxide (**16**) (Scheme 17) which adds to lactones to provide spiroacetals **1** and **5**.

Scheme 17



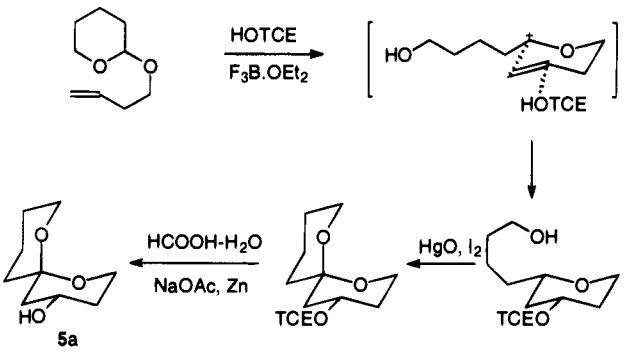
Tosylmethyl isocyanide (TosMIC) (**17**) has also been utilized in spiroacetal synthesis, including the olive fly component **1**[48] (Scheme 18).

Scheme 18



A fundamentally different approach to the synthesis of 1,7-dioxaspiro[5.5]undecan-4-ol (**5a**) was reported by Kay and Williams[49] and uses a novel cation–alkene cyclization, with final spirocyclization being effected via the hypoiodite, as shown in Scheme 19.

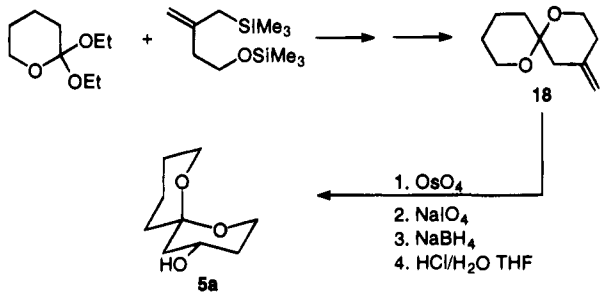
Scheme 19



This approach was applied by the same group[50] to a total synthesis of the avian toxin (±)-talaromycin B.

A further approach to racemic **5** was reported by Markó and co-workers,[51] utilizing a variant of the Sakurai reaction and using ortholactones as substrates, as shown in Scheme 20. The initially formed *exo*-methylene compound **18** when subjected to 1,2-

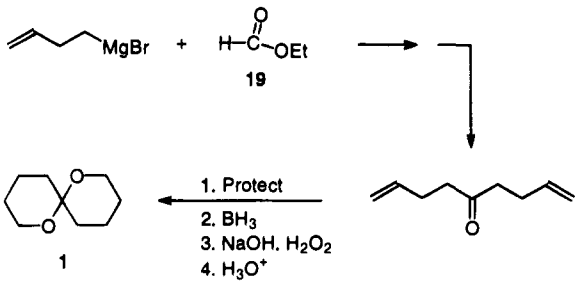
Scheme 20



dihydroxylation, periodate cleavage, reduction, and epimerization provided the *equatorial* alcohol **5a**, predominantly (19:1).

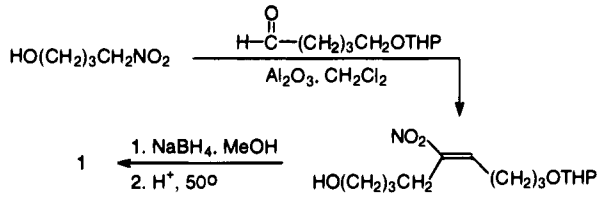
A straightforward procedure for the synthesis of **1**, and which has the capacity to permit deuterium incorporation at several stages, has been developed by Hungerford[52] and uses ethyl formate (**19**) to provide the one-carbon spirocenter (Scheme 21).

Scheme 21



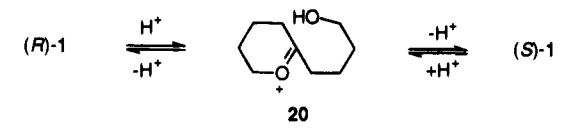
Functionalized nitroalkanes have been utilized in spiroacetal synthesis[53] and **1** has been obtained by employing the appropriate hydroxy-substituted conjugated nitroalkene,[54] as shown in Scheme 22.

Scheme 22



The efficacy of pheromone-based controls is known in a number of cases to be a function of chirality, double-bond configuration and stereochemical features generally, and therefore provision of enantiomers of **1** for behavioral studies was important. Similar considerations apply to the 3- and 4-hydroxy derivatives although the status of these minor components in the lifecycle of the olive fly is not established. It is important to note that enantiomers of **1** could be anticipated to racemize in the presence of a sufficiently strong acid that could promote formation of an achiral monocyclic oxonium ion (**20**) followed by reclosure to the spiroacetal (Scheme 23).

Scheme 23

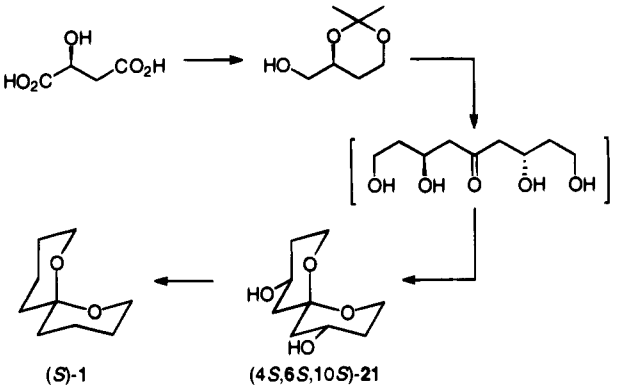


It eventuates, however, that provided reasonable precautions are taken, enantiomers of **1** are relatively optically stable.

There are several reports describing the synthesis of enantiomers of **1**, **4**, and **5**, and Mori and his group have made notable contributions, which were described in a number of preliminary[55,56] and then full reports.[57,58]

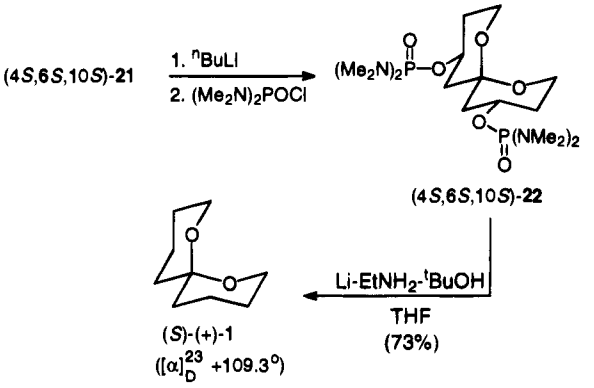
Mori's approach to the enantiomers of **1** was based on the temporary attachment of groups to the tetrahydropyranyl rings to control the stereochemistry of the spiro center, but with no racemization during the removal of such groups. The hydroxy group was chosen to perform this task and thus (4*S*,6*S*,10*S*)-4,10-dihydroxy-1,7-dioxaspiro[5.5]-undecane (**21**), and its antipode were key targets.[57] The synthetic plan utilized (*S*)-(−)-malic acid as a source compound, as shown in Scheme 24.

Scheme 24



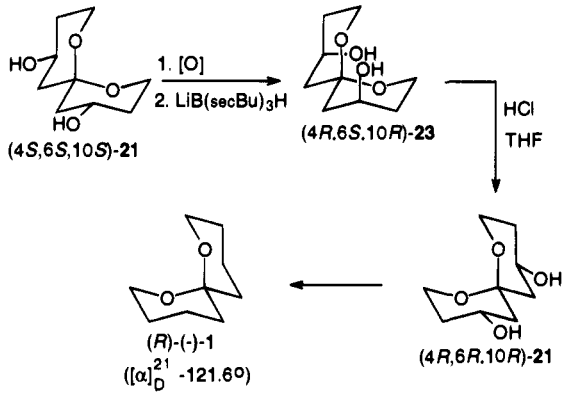
Although diol **21** was available in a straightforward way, its dideoxygenation was very difficult and many standard procedures were unsuccessful.[57] Eventually, deoxygenation was achieved by reduction of the *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate (**22**), acquired from **21** by a metal−ethylamine reduction (Scheme 25).

Scheme 25



The synthesis of (*R*)-(−)-**1** was based on the formation of the crystalline *diaxial* diol **23** that resulted from reduction (LiB(*sec*-Bu)$_3$H) of the diketone, as shown in Scheme 26. A key step was the facile acid-catalyzed conversion of **23** to the more stable (4*R*,6*R*,10*R*)-diol **21** by epimerization at the spirocenter. Formation of the phosphorodiamidate and reduction furnished (*R*)-(−)-**1**.

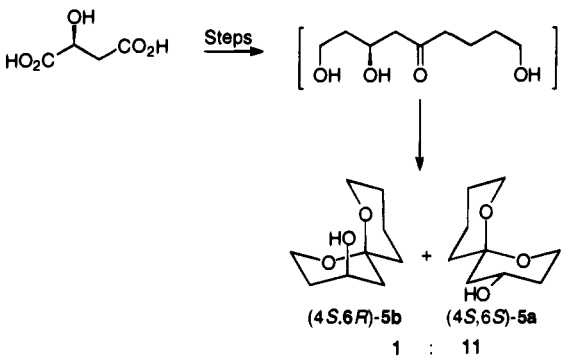
Scheme 26



The optical purities of the (*R*) and (*S*) enantiomers of **1** were determined by complexation gas chromatography (Prof. Dr. V. Schurig) to be 73% and 100% respectively, although there was thought to be some postpreparative racemization prior to this analysis in one case. The overall yield of (*R*)-(−)-**1** was 2.2% from (*S*)-(−)-malic acid in 15 steps.

Subsequently Mori reported[58] in detail the syntheses of the enantiomers of **1**, the 3-hydroxy compound **4**, and the 4-hydroxy compound **5**. These latter routes were more efficient, and instead of employing a "keto−tetrol" approach (see Scheme 24), a "keto−triol" intermediate was utilized, which is equivalent to a monohydroxy derivative of **1**. Malic acid, in the (*S*)-(−) form was again chosen as the source material, and the route to (4*S*,6*S*)-1,7-dioxaspiro[5.5]undecan-4-ol (**5a**) is summarized in Scheme 27.

Scheme 27

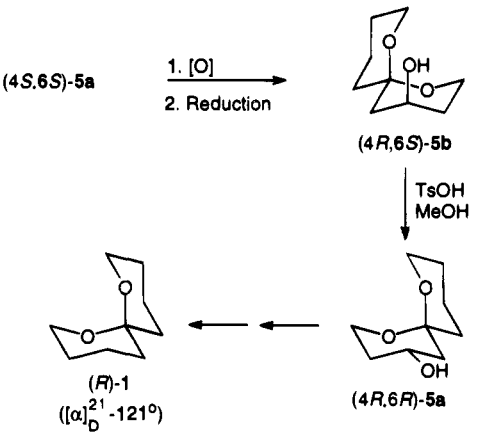


Separated (4*S*,6*S*)-**5a** was transformed, through reduction of its phosphorodiamidate, to (*S*)-(+)-**1** ([α]$^{21}_{D}$ +119°, 92% ee), as described in Scheme 25. Conversion of (4*S*,6*S*)-**5a** to its antipode was achieved by oxidation to the ketone and hindered borane reduction (see Scheme 26). Epimerization then provided (4*R*,6*R*)-**5a**, which on deoxygenation yielded (*R*)-(−)-**1** of >99.5% ee. This chemistry is summarized in Scheme 28.

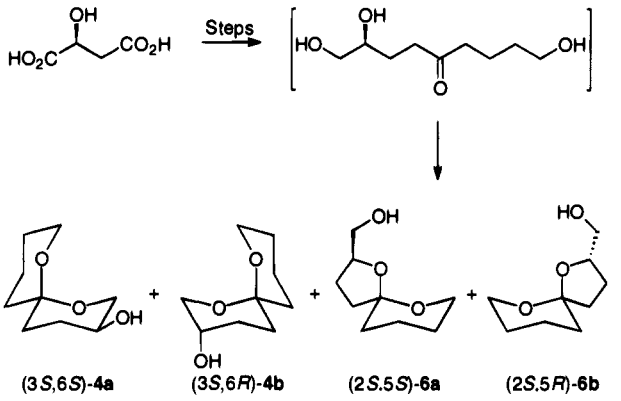
(*S*)-Malic acid was then used[58] to obtain the enantiomers of the 3-hydroxy compounds, (3*S*,6*S*)-**4a** and (3*S*,6*R*)-**4b**. This work was complicated by the production of isomers of the [4.5]spiro system, as shown in Scheme 29, necessitating extensive separations and characterisations.

The synthesis of (3*R*,6*R*)-**4a** was required and Mitsunobu inversion of (3*S*,6*R*)-**4b**, followed by

Scheme 28

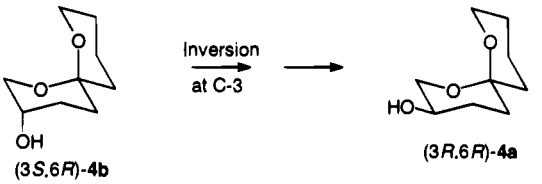


Scheme 29



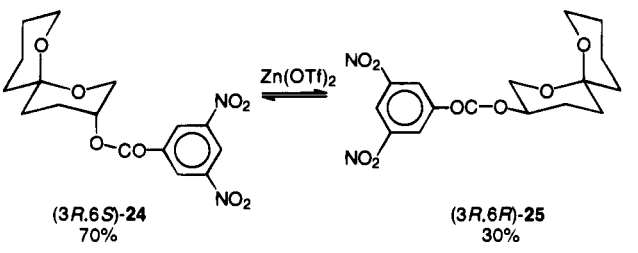
dinitrobenzoate hydrolysis, provided the target (3*R*,6*R*)-**4a** (Scheme 30).

Scheme 30



A remarkable feature of some equilibration studies was that the (3*R*,6S) *axial* dinitrobenzoate **24** was more stable than the (3*R*,6*R*) isomer **25** which has an *equatorial* grouping (Scheme 31). Structural

Scheme 31

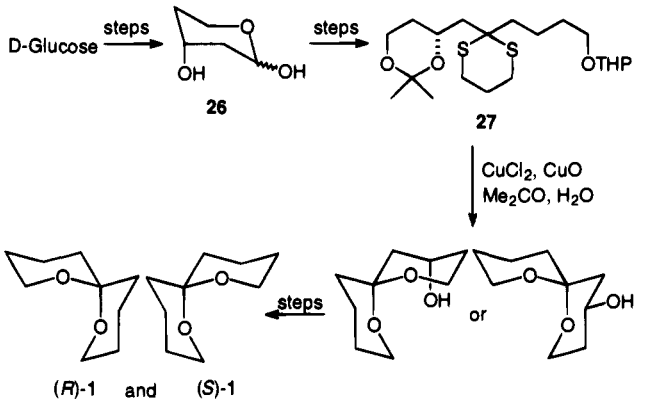


studies (X-ray) shed no light on this situation. The answer probably is related to the *vic-anti* nature of C−O bonds in the *equatorial* isomer.

Further syntheses of (*R*)- and (*S*)-1,7-dioxaspiro-[5.5]undecane were reported by Redlich and Francke[59] and also by Iwata.[60] In the former work, D-glucose

was transformed into 2,4-dideoxy-D-*glycero*-pentapyranose (**26**) which was dithioacetalized and protected and converted to an all-protected version of a "keto–triol" **27**. Although conducted independently of the work of Mori, an installed hydroxy group once again serves to control the absolute stereochemistry at the spirocenter. Deprotection and cyclization to hydroxy derivatives was followed by separation and deoxygenation, via the tosylate, elimination on Al_2O_3 and hydrogenation in the presence of Et_3N to afford the (*R*)- and (*S*)-**1** of greater than 95% ee. These procedures are summarized in Scheme 32.

Scheme 32



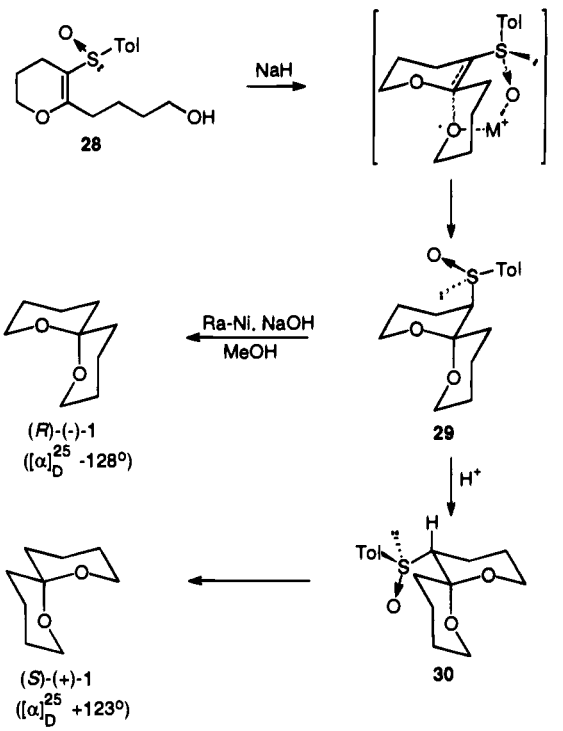
The approach of Iwata is fundamentally different in that the "chiral pool" is not employed, but relies instead on asymmetric induction in an intramolecular Michael addition to a chiral vinyl sulfoxide unit. Treatment of key intermediate **28**[60] with NaH (5 equiv) led to kinetically controlled spiroacetal **29** with an *axially* disposed sulfinyl group. Treatment of this isomer with acid leads to diastereomer **30**. Removal of the chiral source (desulfurization) then provided separately (*R*)-**1** and (*S*)-**1** (Scheme 33). This approach to spiroacetals has been discussed in detail by Iwata and his co-workers.[61,62]

D-Fructose has also been elaborated into olive fly components, mainly by Cubero and his co-workers. In the first report[63] (*R*)-1,7-dioxaspiro[5.5]undecane ((*R*)-**1**) was acquired in high ee. Reaction of the ylide from [3-(benzyloxy)propyl]triphenylphosphonium bromide with the D-fructose derivative **31**, followed by reduction and spiroacetalisation afforded (3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-1,7-dioxaspiro[5.5]-undecane (**32**) which was deoxygenated etc. to provide (*R*)-(−)-**1** (Scheme 34).

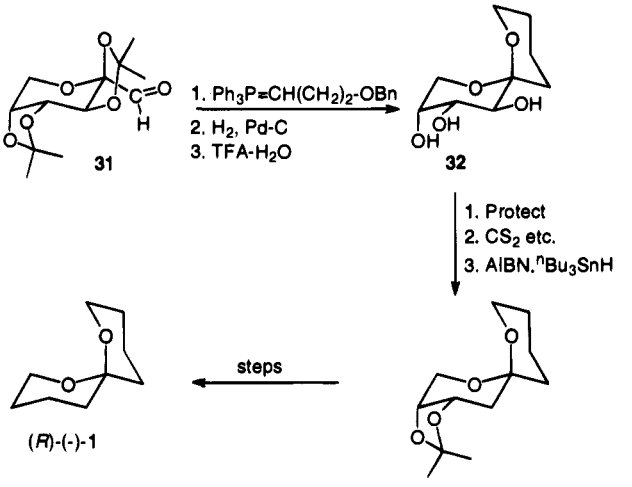
In a derivative way, Cubero[64] utilized one of the intermediates of Scheme 34 viz. (3*R*,4*S*,6*R*)-3,4-dihydroxy-1,7-dioxaspiro[5.5]undecane (**33**) for conversion to certain enantiomers of the 3- and 4-hydroxy compounds, **4** and **5** respectively. Selective hydroxyl group manipulation and deoxygenation were required to afford each of the 3- or 4-hydroxy derivatives, as shown in Scheme 35.

The easy conversion of D-mannitol to (*R*)-isopropylideneglyceraldehyde has served as the basis for two additional enantioselective syntheses of the 3-hydroxy systems **4**. Bestmann[65] employed the ketenylidenetriphenylphosphorane **34** as starting material to generate a new phosphorane which was

Scheme 33



Scheme 34

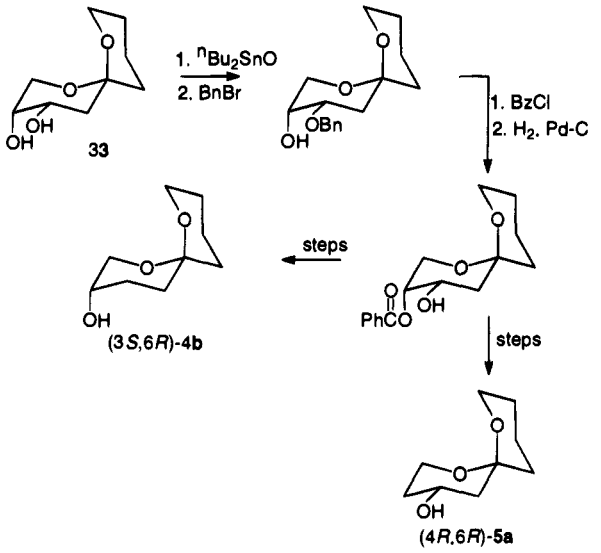


then linked to the (*R*)-aldehyde, as shown in Scheme 36. Double-bond reduction, followed by deprotection and concomitant cyclization, yielded a mixture of isomers, which were separated and characterized.

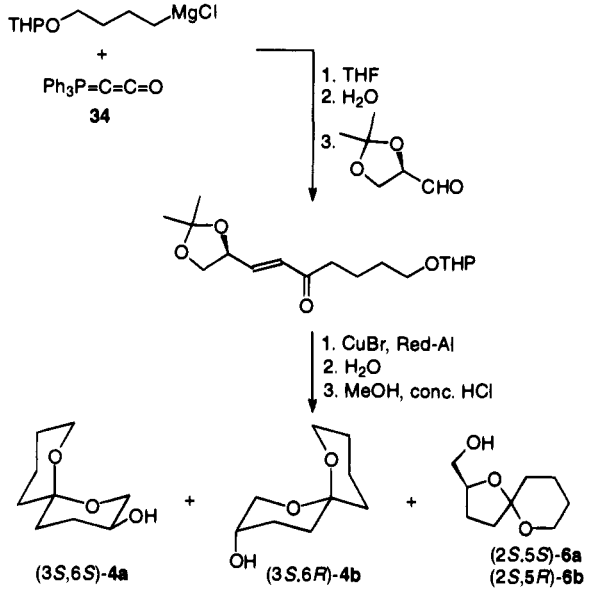
In an alternative approach, Fletcher, Jacobs, and Kitching[66] utilized the chiral iodide **35** available from the (*R*)-isopropylideneglyceraldehyde to alkylate the anion of acetone *N*,*N*-dimethylhydrazone as a key step in the overall sequence shown in Scheme 37. These alcohols were employed in the determination of the absolute configurations of the natural hydroxyspiroacetals of certain fruit fly species.

c. Absolute Stereochemistry of Spiroacetals Present in the Female Olive Fly. The availability of both the (*R*) and (*S*) enantiomers of **1**, their optical stability under nonacidic conditions and their separation by "chiral" gas chromatography enabled some biological testing, and determination of the enantiomeric composition of the released **1**. In an important paper, Haniotakis, Francke, Mori, Redlich, and Schurig[67]

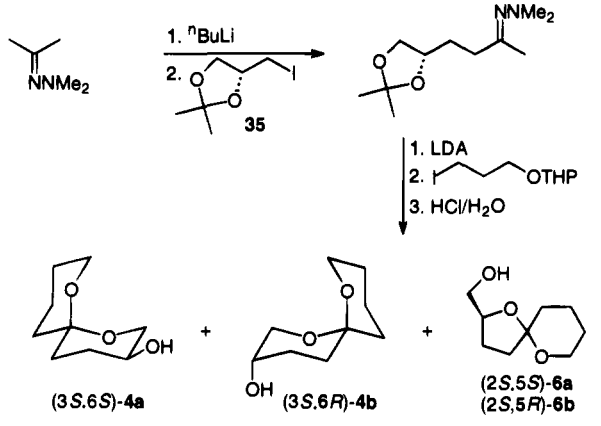
Scheme 35



Scheme 36



Scheme 37



established that **1** as secreted and released by the female olive fly was a racemate, and furthermore males responded only to the (*R*)-(−) enantiomer in the laboratory and in the field, and this response coincided with the mating period. However, females responded only to the (*S*)-(+) isomer in the laboratory, but not in the field. There were indications that this enantiomer functioned as a short-range arrestant in the day and as an aphrodisiac in the mating process, but careful work is required to support further these conjectures.

With respect to the 1,7-dioxaspiro[5.5]undecan-3- and -4-ols present in female olive fly secretion, Baker[23,24] reported that the *equatorial* alcohols **4a** and **5a** were the natural diastereomers. With the availability of the enantiomers of these alcohols, and the development of cyclodextrin-based gas chromatography phases for enantiomer separations, determination of the absolute stereochemistry of these alcohols was feasible. The alcohols **4**−**6** (and parent spiroacetal 1) were nicely separated into enantiomers on a 50 m β-cyclodextrin column,[66] and it was established that, from the gland secretion, **1** was racemic as previously determined.[67] In fact, **1** is racemic in all fruit flies in which it has been identified viz. *B. oleae, B. cacuminata* (Hering), and *B. distincta* (Malloch).[66] Furthermore, for the olive fly extract, enantiomeric excesses for the 3- and 4-ols did not exceed 20% i.e. *equatorial* 4-ol **5a** is predominantly (4*S*,6*S*) and *equatorial* 3-ol **4a** is predominantly (3*R*,6*R*). The previously unreported *axial* 3-ol **4b** was also detected and is predominantly (3*R*,6*S*). For further discussion of these stereochemistries and how they compare with the alcohols in *B. cacuminata* and *B. distincta*, the original report[66] should be consulted.

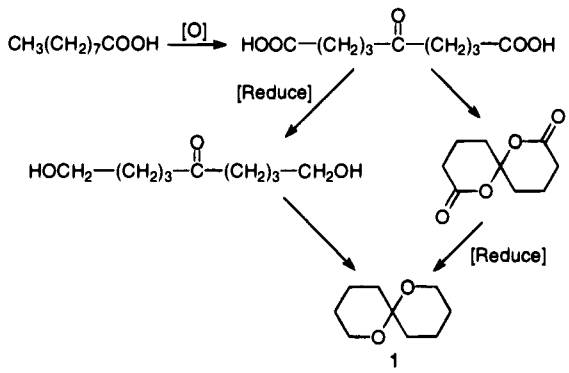
In this context, Haniotakis[68] has reported that the nonnatural compound 1,5,7-trioxaspiro[5.5]undecane displays high biological activity for the olive fly, and in laboratory tests its activity was comparable to that of the naturally occurring **1**. Other analogues of **1** have been reported.[69]

d. Biosynthesis of Sex Pheromones in the Female Olive Fly. Although the characterization and evaluation of insect pheromones continues at a rapid rate, there has not been a commensurate understanding of pheromone biosynthesis and other aspects relating to reception and deactivation, etc. Valuable discussions of some features of pheromone biosynthesis were recently published,[70,71] and Prestwich has demonstrated the use of tritium-labeled pheromones in studies of transformations and degradations.[72]

With respect to the biosynthesis of 1,7-dioxaspiro-[5.5]undecane (**1**), the first studies were conducted by Mazomenos and reported as a thesis.[73] Subsequently, some of this work was described[74] and then included in a general discussion[7] of the biology and pheromone of the olive fly. In what was probably the first report of a biosynthetic study of pheromones in tephritids, Pomonis and Mazomenos[74] reported that female olive flies incorporated dietary administered ^{14}C-labeled malonate, succinate, glutamate, and propionate into the major pheromone, 1,7-dioxaspiro[5.5]undecane (**1**), whereas acetate was not significantly incorporated. Excised female glands, when incubated at pH 7 (phosphate buffer) with labeled malonate, incorporated the label into spiroacetal **1**, but did not incorporate glutamate. The low level of acetate incorporation may be associated with its diversion to other anabolic processes. The isolation of 5-oxononandioate (and indeed spiroacetal **1**)

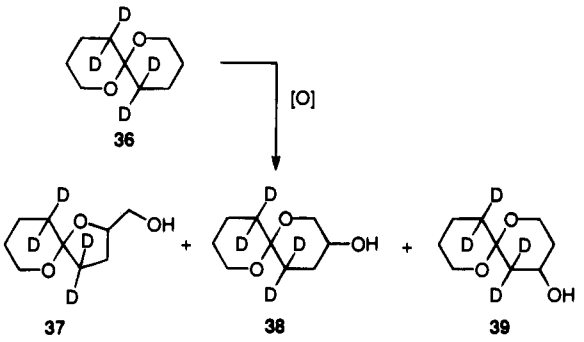
from wild males[75] led to the suggestion that biosynthesis proceeds by the fatty acid synthetase system, employing activated propionate in a "starter" role. Subsequently it was demonstrated that wild males incorporated labeled malonate and propionate into both **1** and the 5-oxononanedioate, with the latter being transformed by excised female glands into **1**.[76] A scheme accounting for the formation of **1** was then proposed[7] and is shown in Scheme 38.

Scheme 38



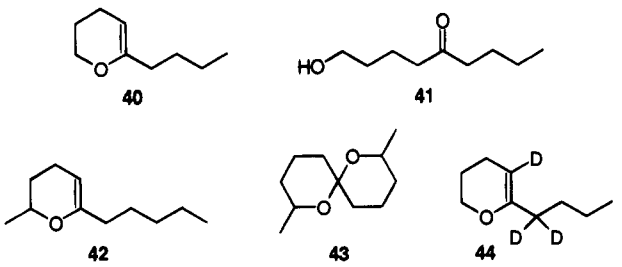
Other studies of the biogenesis of spiroacetals in the female olive fly have also been conducted by Haniotakis and Kitching[52] and the first aspect examined concerned the origin of the hydroxy derivatives **4** and **5** which consistently accompany **1**. Dietary administration of predominantly [$^2H_4$] **1** (**36**) to female flies was carried out, and GC-MS analyses of methanol or pentane extracts of excised rectal glands led to the identification of the labeled hydroxy derivatives **37**–**39**. Comparison with a control group showed that **36** was very efficiently oxidized to **37**–**39** (Scheme 39). The enantiomeric composition of the

Scheme 39



hydroxy derivatives from the trial group closely matched that derived from the control group. This correspondence supported the view that spiroacetals **4** and **5** arise from intact **1** by direct hydroxylation or an equivalent series of events.

The same group[52] turned to the origin of **1** and selected 6-*n*-butyl-3,4-dihydro-2*H*-pyran (**40**) as a somewhat advanced potential precursor. Although **40** has not been identified in the olive fly, it does cooccur with **1** in *B. cacuminata*, in which keto alcohol **41** (which is related to **40** by cyclization–dehydration) also occurs. 2-Methyl-6-*n*-pentyl-3,4-dihydro-2*H*-pyran (**42**) accompanies isomers of 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**43**) in *B. halfordiae* (Tryon), so that a similar nexus applies.



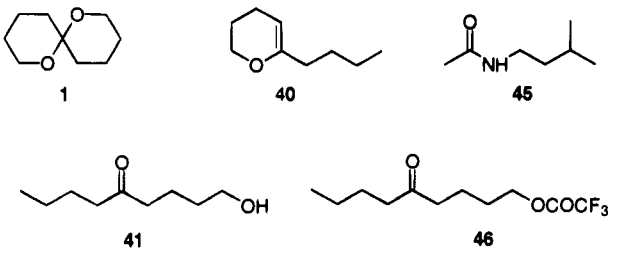
A [$^2H_3$]-labeled derivative of **40** viz. **44** was made available to female olive flies, and GC-MS examinations established that spiroacetal **1** from excised rectal glands was significantly ^2H-enriched, as were the accompanying hydroxy derivatives, **4** and **5**. These experiments confirm that dihydropyran **40** serves well as an *in vivo* precursor of **1** by formal methyl oxidation, and the same is probably true for **42** with respect to **43** except that now formal methylene oxidation is required. The efficient conversion of **40** to **1** is not necessarily in conflict with the general ideas in Scheme 38, as hydrated **40** i.e. **41** is a midchain oxidized form of 1-nonanol. Clearly there are further points to be clarified, especially how the presumed (Scheme 38) nonanoic acid is constructed and centrally oxidized and terminally reduced. In this connection, nonanal has been identified[15,16] as a minor female rectal gland component. Further labeling studies in progress should shed light on these and related matters, and whether higher unsaturated acids (e.g. C_{18}) are involved.

2. *Bactrocera cacuminata* and *Bactrocera distincta*

Although *Bactrocera cacuminata* (Hering) is an "Australian" member of the *B. dorsalis* complex of fruit flies which is discussed in detail later, the chemistry of *B. cacuminata* and *B. distincta* (Malloch) is so similar to that of *B. oleae* that it is presented at this stage. (We have previously[66,77] described this species incorrectly as *B. cacuminatus*; the correct name is *B. cacuminata*.[2]) *B. cacuminata* is a medium-sized species that is distributed along much of the eastern Australian coastline from Cape York to East Gippsland in Victoria. It is of low pest status (tomatoes and capsicums in Queensland) and is of interest in that it appears to have a single host, the wild tobacco plant (*Solanum mauritianum*) which flourishes in fringing rainforest vegetation. *B. distincta* is a potential pest of breadfruit and star-apple and is found in the South Pacific areas of American and Western Samoa, Fiji, and Tonga.

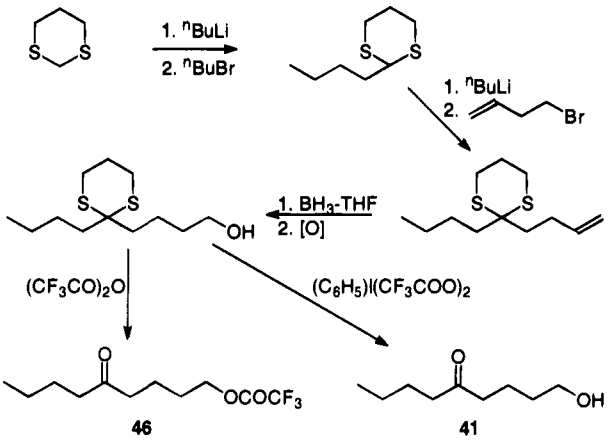
B. oleae females and *B. cacuminata* and *B. distincta* males secrete spiroacetal **1** as their major volatile component, and **1** is racemic in all three species.[66]

In the case of *B. cacuminata*, the level of **1** is about 90% of the volatiles, and estimated at 8 μg/individual.[77] A minor earlier eluting component (~1%) was shown to be 6-*n*-butyl-3,4-dihydro-2*H*-pyran (**40**), and a later eluting compound (1.5%) was *N*-3-methylbutylacetamide (**45**), which is present in other species (for example, *B. tryoni*) discussed later. Two significant, more slowly eluting components were of interest, with the first (~2%) being keto alcohol **41**, which was also characterized as its

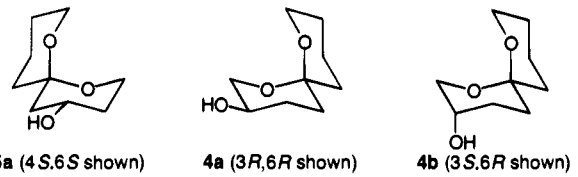


trifluoroacetate **46**. Compounds **41** and **46** were synthesized as shown in Scheme 40.

Scheme 40



A slightly slower eluting very minor compound (~0.5%) with an apparent $M^+ = 172$ ($C_9H_{16}O_3$) was shown to be the 4-hydroxy derivative **5**, solely as the *equatorial* epimer **5a**. Chiral gas chromatographic analysis of the trifluoroacetates showed that **5** as present in *B. cacuminata* was the (4*S*,6*S*) stereoisomer (80% ee) as shown. In this report,[77] it was pointed out that only the 4-hydroxy system **5** was detected, whereas in earlier preliminary examinations, GC-MS data indicated the presence of other hydroxy derivatives of 1. This inconsistency led to a very thorough examination[66] that demonstrated that both 3- and 4-hydroxy derivatives (**4** and **5**) were present as low level components in both *B. cacuminata* and *B. oleae* (see above). In *B. cacuminata*, the equatorial alcohols **4a** and **5a** were predominantly (3*R*,6*R*) (ee indeterminable) and (4*S*,6*S*) (75% ee) and the axial alcohol **4b** predominantly (3*S*,6*R*) (>80% ee). In the previously unexamined species *B. distincta*, the major component, spiroacetal **1** was accompanied by a trace amount of alcohol **5a** which was shown to be (4*S*,6*S*) (95% ee). Sample limitations prevented the positive identification of smaller components thought to be alcohols **4a** and **4b**. The discussion of the possible biosynthetic routes in the case of *B. oleae* components may apply also to *B. cacuminata* and *B. distincta*.



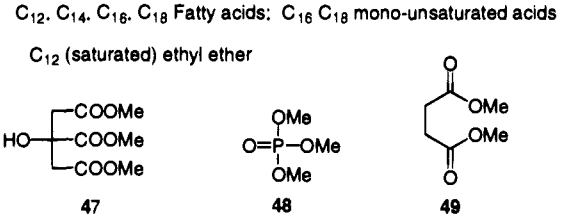
5a (4*S*,6*S* shown) **4a** (3*R*,6*R* shown) **4b** (3*S*,6*R* shown)

3. Bactrocera dorsalis Species Complex

The Oriental fruit fly, *Bactrocera dorsalis*, is part of a species complex, and in 1969, Hardy[78] attempted to resolve the considerable confusion surrounding the taxonomy of this complex. Application of modern technology has enabled Drew and Hancock[79] to further unravel the complexities of the *dorsalis* complex in Asia. The complex contains at least 52species[79] which have a taxonomic resemblance to *B. dorsalis*, and many are major pests of cultivated hosts. Members of the complex extend throughout Asia and the Oceanian region and into Australia, but the differentiation of close species has been dependent on techniques such as electron microscopy and tissue enzyme analysis as well as morphological and biological data. Within the complex, species have occasionally been incorrectly identified, and distribution and host records have been wrongly attributed. One approach to the determination of species limits has been based on male rectal gland pheromone analysis, and this study has been published[80] and more completely discussed in a thesis.[81]

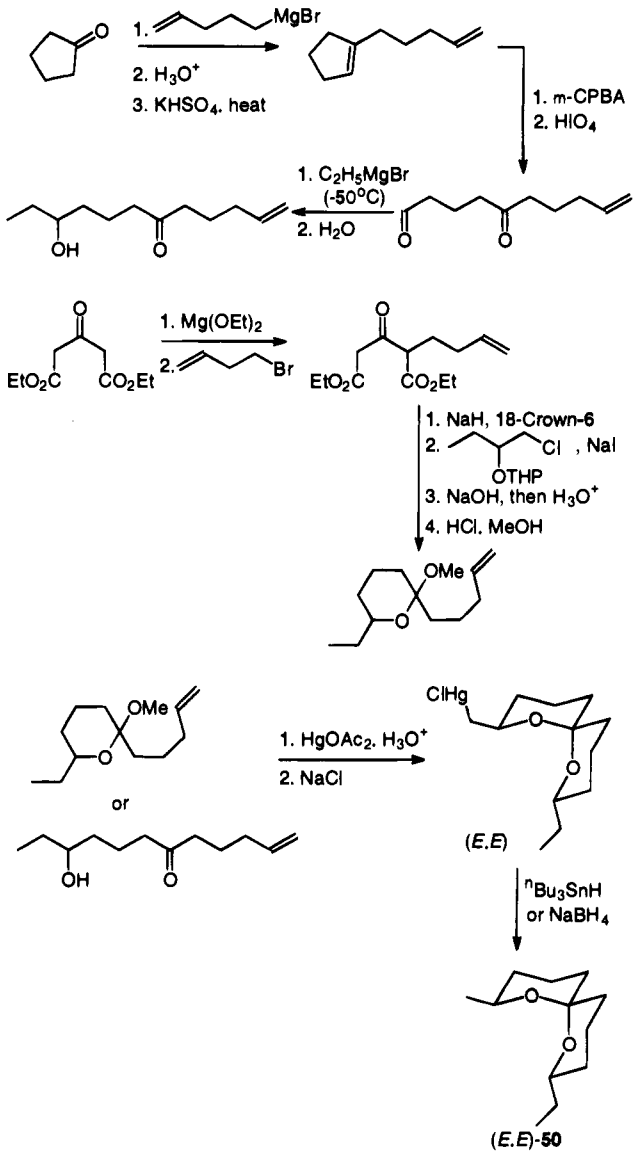
B. dorsalis (Hendel), a member of the complex, is restricted in habitat from India to Southern China, Taiwan, and Hawaii.[79] Consequently *B. dorsalis* is not as widespread as previously reported.[4] *B. occipitalis* (Bezzi) was originally described from the Philippines, and later regarded as being widespread over Southeast Asia including Malaysia. It is now known to be confined to the Philippines and Borneo.[79] Three sibling pest species, previously confused with *B. occipitalis* or *B. dorsalis*, occur in Southeast Asia: *B. carambolae* Drew and Hancock (previously called Mal A), *B. papayae* Drew and Hancock (previously called Mal B), and *B. philippinensis* Drew and Hancock (previously called Phil B). Chemical examination[80] of the volatile components of the glandular secretions of some members of this complex have been carried out to support the taxonomic revisions[79] and to extend the pheromone profile of these economically important Tephritids.

Our GC-MS examination[80] of an acetone extract of rectal glands of sexually mature male *B. dorsalis* obtained from the USDA culture at Honolulu, indicated that the major components were long-chain fatty acids, with one as the ethyl ester. A noticeable feature was that the glands, as a general rule, were sparingly filled with secretion, unlike many other *Bactrocera* species. Treatment of the extract with diazomethane resulted in the detection of the trimethyl ester of citric acid (**47**) (major), the trimethyl-ester of phosphoric acid (**48**), dimethyl succinate (**49**), and the methyl esters of the fatty acids shown.



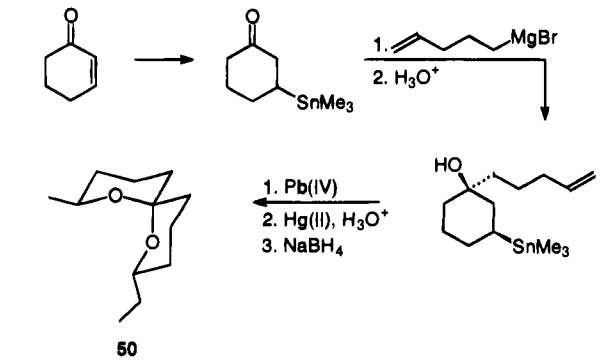
The more volatile minor components were of some interest, with one showing an apparent M = 198 (5%), loss of 29 (C_2H_5) and 15 (CH_3) amu, and intense ions at m/z 112 and 115, indicating a 2,8-dialkyl-1,7-dioxaspiro[5.5]undecane. That this represents an example of the unusual class of even-carbon-

Scheme 41

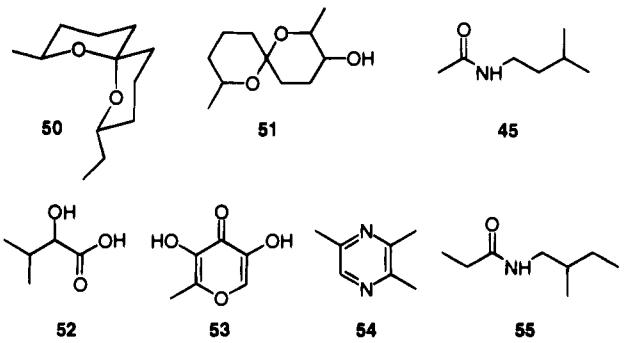


numbered insect-derived spiroacetals was confirmed by synthesis as outlined in Scheme 41. The natural compound was predominantly the (*E*,*E*) diastereomer **50**. Spiroacetal **50** has also been synthesized in other ways, one of which is shown in Scheme 42.[82]

Scheme 42

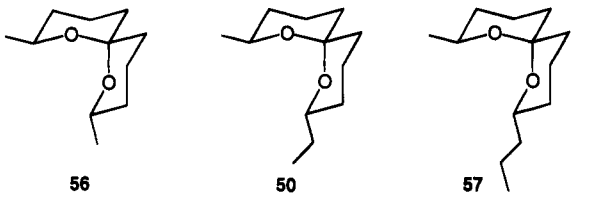


A low level of 3-hydroxy-2,8-dimethyl-1,7-dioxaspiro-[5.5]undecane (**51**) was also observed and confirmed by mass spectral comparisons with an authentic sample, the synthesis of which is described later. Other minor components were amide **45**, hydroxy acid **52**, pyranone **53**, and pyrazine **54**. It should be emphasized that the fatty acids were the very dominant glandular components with the C_{16} saturated acid being present to the extent of 5 μg/fly.



Male *B. dorsalis* emit a smokelike substance at dusk which corresponds to the mating period, and Ohinata[83] reported that *ca.* 90% of the smoke collected on Millipore filters was (tri)sodium phosphate in agreement with our identification[80] of the phosphate ester (from the acid). Other components were *N*-(2-methylbutyl)propanamide (**55**) and heptacosane.

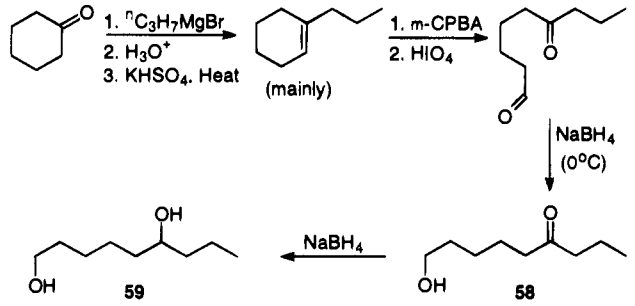
Baker and Bacon[84] have reported studies of the volatile secretions of sexually mature female *B. dorsalis*, by passing filtered air through a chamber containing live females and absorption on activated charcoal. The major component was concluded to be amide **45**, *N*-(3-methylbutyl)acetamide, a very minor component in male rectal gland secretion as noted above, and different from the amide **55** (*N*-(2-methylbutyl)propamide) identified in the "smoke" by Ohinata.[83] Three spiroacetals were identified with the major one being (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro-[5.5]undecane (**56**), probably the (*E*,*E*) diastereomer of the 2-ethyl-8-methyl system (**50**), and the 2-*n*-propyl-8-methyl-1,7-dioxaspiro[5.5]undecane (**57**). An homologous series of ethyl esters of the C_{12}, C_{14}, and C_{16} saturated fatty acids, as well as of the C_{16} unsaturated fatty acid, was identified also. No chirality determinations of the dimethyl and 2-ethyl-8-methyl spiroacetals shown have been conducted for *B. dorsalis*, but it would be surprising if their absolute configurations did not correspond with those determined for other *Bactrocera* species (see later).



B. carambolae occurs across Malaysia, Thailand, Indonesia, and Singapore.[79] The chemistry of this species was studied firstly by Fletcher and some aspects were mentioned in a brief report.[85] These specimens were collected in the field in Malaysia and were, at the time, wrongly described as *B. occipitalis*. Drew[79] now regards this species as distinct from *B. occipitalis*. At this stage, we have been unable to acquire authentic specimens of *B. occipitalis* for

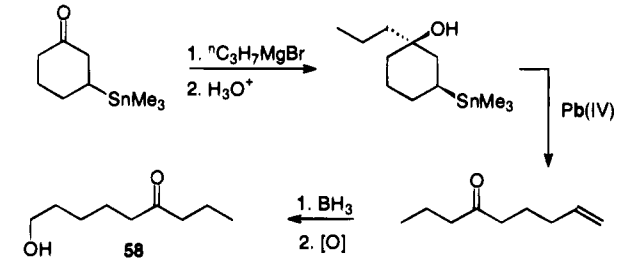
examination. A more recent study by Perkins[80] has confirmed the earlier results of Fletcher[85] on *B. carambolae* specimens (then called Mal A), except that suspected methyl eugenol metabolites were not detected. Analysis of an acetone extract of excised glands showed the presence of one major (~70%; 5 μg/fly) and several minor components. The major component, with apparent M = 158, was thought to be 6-oxo-1-nonanol (**58**) on the basis of the fragmentation pattern. A minor (~4%) more slowly eluting compound was considered to be 1,6-nonanediol (**59**) on the basis of chromatography and mass spectra. The keto alcohol **58** and diol **59** were synthesised as shown in Scheme 43 and were identical with the

Scheme 43

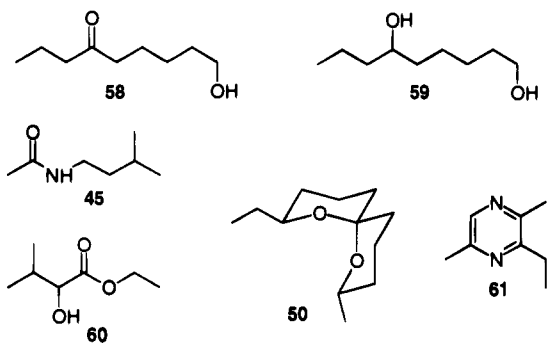


glandular components. Keto alcohol **58** has also been synthesized by O'Shea,[82] using a Pb(IV) triggered fragmentation of a γ-hydroxystannane as a key step (Scheme 44).

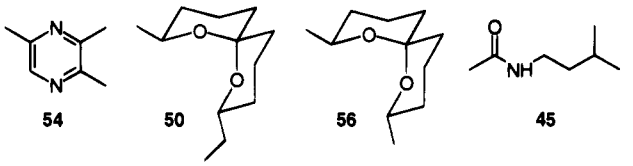
Scheme 44



The chirality of the 1,6-nonanediol (**59**) has not been established. Other minor compounds present were the amide, *N*-(3-methylbutyl)acetamide (**45**) (6%), the ester, ethyl 3-methyl-2-hydroxybutanoate (**60**), the even carbon number spiroacetal **50**, and the pyrazine **61**.



B. papayae also occurs across Malaysia, Thailand, Indonesia, and Singapore, but has a glandular content vastly different from *B. carambolae*. In *B. papayae* (then called Mal B) the major glandular components (acetone extract) were the C_{16}, C_{18}, and C_{20} saturated and unsaturated fatty acids, along with some high molecular weight hydrocarbons.[80] In the volatile region, low levels of pyrazine **54**, spiroacetals **50** and **56**, and amide **45** were present. *B. papayae* is taxonomically very close to *B. dorsalis*, and both have low levels of volatile glandular components. Fatty acids dominate in each species, but there were differences including the absence of the C_{12} ethyl ester and the appearance of the dimethyl spiroacetal **56** in *B. papayae*.



Examination of *B. philippinensis* (then called Phil B) showed a similarity to *B. dorsalis* with low levels of volatile components, and with fatty acids dominating.[80] The results differed from that for *B. papayae* in that large amounts of the ethyl esters of C_{12}, C_{14} saturated, and C_{16} saturated and unsaturated acids were present. Small amounts of the methyl, ethyl spiroacetal **50**, amide **45**, and trimethylpyrazine **54** were observed, but *not* the dimethyl spiroacetal **56**.

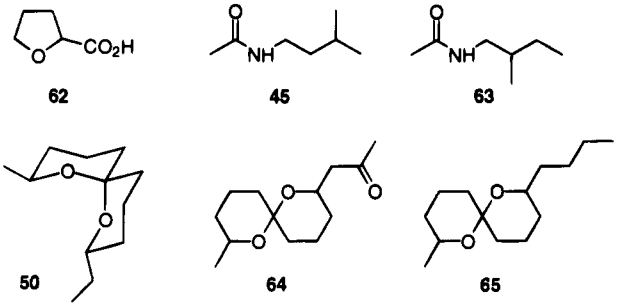
The above results indicate that two very closely related members of the complex (*B. carambolae* and *B. papayae*) exist as distinct species with similar distribution. Indeed, they are difficult to differentiate by normal morphological examination, but show pronounced differences in the chemistry of their rectal gland secretions. *B. carambolae* has a glandular chemistry that is very unlike that of any other species examined, whereas *B. papayae*, *B. philippinensis*, and *B. dorsalis* have similar glandular components, but minor consistent differences were found between *B. papayae* and *B. philippinensis* and authentic *B. dorsalis*. The aforementioned study of a small number of members of the *dorsalis* complex illustrates that the nature of the rectal glandular components may be a powerful taxonomic criterion, and studies of other members of this significant pest complex may be worthwhile.

4. Other Southeast Asian Bactrocera species

Taxonomic and biological studies within the *B. dorsalis* complex by Drew and Hancock[79] have encouraged chemical studies as an integral part of the overall investigation of other fruit flies in Southeast Asia. Certain fruit flies cause substantial losses of fruit and vegetable crops which constitute an important part of the Oriental diet. Some species in this category are now discussed.

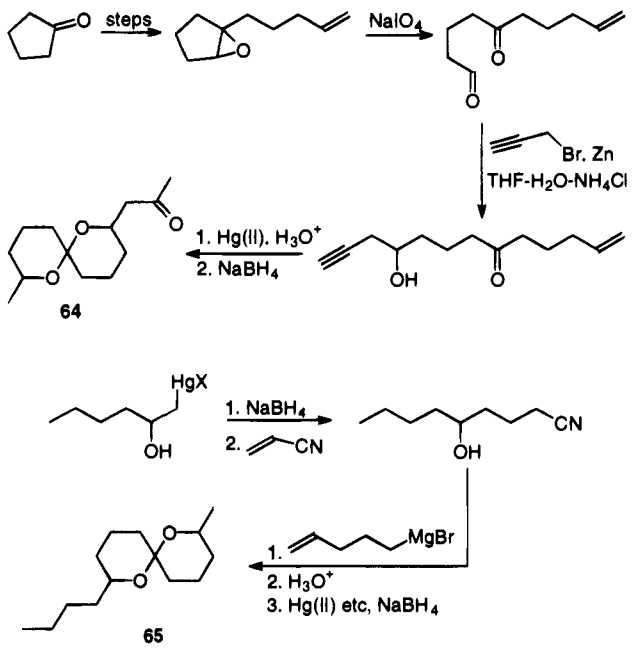
a. Bactrocera latifrons. *Bactrocera latifrons* (Hendel) is a serious pest throughout Southeast Asia from Vietnam to Hawaii and shows some resemblance to both *B. dorsalis* and *B. musae* (Tryon) (banana fly). This species may have been introduced into Hawaii during the Vietnam war. Our examinations[86] of the male rectal gland secretion were conducted on specimens obtained from a USDA culture in

Honolulu, and some aspects were reported in a preliminary communication.[85] Analyses conducted on three different samples showed considerable variation in the proportions of components. The most volatile component identified was tetrahydrofuran-2-carboxylic acid (**62**), a synthetic sample of which was obtained by oxidation of the corresponding alcohol. The mass spectrum (M = 116, with prominent ions at m/z 71, M − CO_2H) and chromatographic behavior were identical, and both natural and synthetic material provided the same methyl ester. As far as we are aware, **62** has not been reported previously from an insect. Amides **45** and **63** were also present. A number of other nitrogen-containing components were detected, and at least three of these were considered to be *N*-alkylpyrrolidines but this situation remains to be clarified.[86]



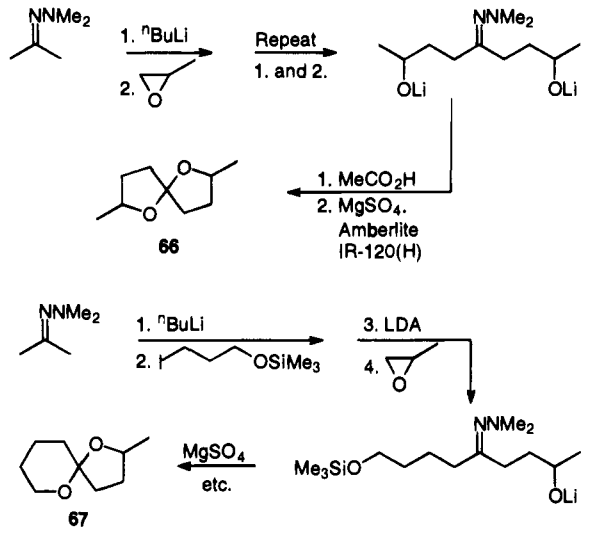
Several spiroacetals were also found at a low level, and one with M = 198 and prominent loss of C_2H_5 and CH_3 was confirmed as the (*E*,*E*) diastereomer **50**, by comparisons with an authentic sample as before. Another minor component had an apparent M = 226 with loss of 57 amu (C_4H_9 or C_3H_5O) (m/z 169) and other ions at m/z 115, 112, 97 characteristic of a 2,8-dialkyl-1,7-dioxaspiro[5.5]undecane. Structures **64** and **65** were considered and both were synthesized as shown in Scheme 45.[82,87,88] Comparisons demonstrated that 2-*n*-butyl-8-methyl-1,7-dioxaspiro[5.5]-undecane (**65**) was the natural product. Less volatile components in the secretion were long-chain fatty acids and among them, 9-hexadecenoic, hexadecanoic, *x*-octadecenoic, and octadecanoic acids were identified. The same acids, in different proportions, have been identified in other species and discussed in this report.

Scheme 45



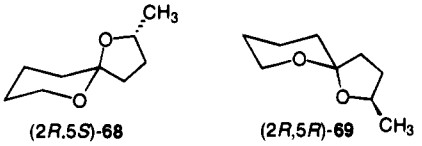
b. Bactrocera umbrosa. *Bactrocera umbrosa* (Fabricius) commonly infests jack-fruit and other *Artocarpus* spp. and is widely distributed throughout Malaysia, Indonesia, Thailand, and southwest Pacific areas. (This species was incorrectly referred to as *B. umbrosus* in the report by Perkins.[89]) The major components of the acetone extract of the male rectal gland were isomeric (26 and 18%, M = 156), with prominent loss of 15 amu (CH_3) and characteristic spiroacetal fragmentations.[89] The spiroacetal systems **66** and **67** were considered and both were synthesized by sequential epoxide alkylation of acetone *N*,*N*-dimethylhydrazone (Scheme 46).

Scheme 46



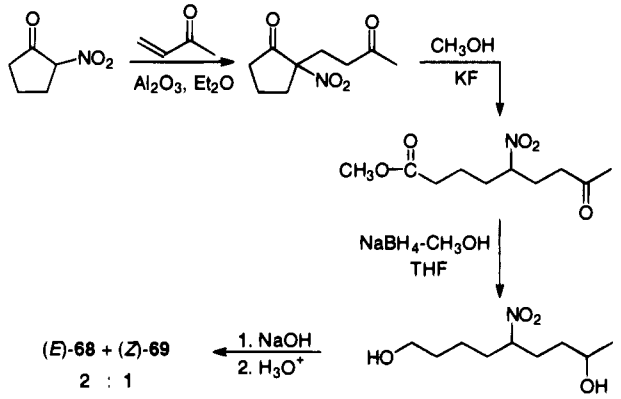
Comparisons of natural and synthetic material demonstrated 2-methyl-1,6-dioxaspiro[4.5]decane (**67**) to be the natural product, and to our knowledge, no isomer of 2,7-dimethyl-1,6-dioxaspiro[4.4]nonane (**66**) has been shown to occur naturally. Spiroacetal system **67** has also been identified in workers of the common wasp, *Paravespula vulgaris*.[90] Chiral gas chromatography of the racemate of **67** and of the natural product, using a camphoratonickel(II) chelate as a stationary phase, showed the latter to consist mainly of one enantiomer of each of the (*E*) and (*Z*) diastereomers of spiroacetal **67**. Use of (*S*)-(−)-propylene oxide in the above synthesis provided the (2*S*) enantiomers of the (*E*) and (*Z*) diastereomers, and again chiral gas chromatography established that the natural spiroacetals were predominantly (85% ee) the (2*R*,5*S*)-(*E*) and (2*R*,5*R*)-(*Z*) stereoisomers **68** and **69**. These are epimeric at the spiro center.

The (*E*)- and (*Z*)-2-methyl-1,6-dioxaspiro[4.5]decanes (**68** and **69**) have been acquired as racemates using nitroalkane chemistry, with a crucial step being chemoselective reduction of the ketone and ester groups, without modifying the nitro group.[91] This



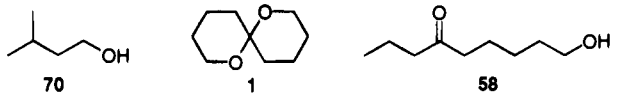
was achieved by the addition of methanol to a refluxing THF solution of the nitro keto ester and sodium borohydride, as shown in Scheme 47. An

Scheme 47



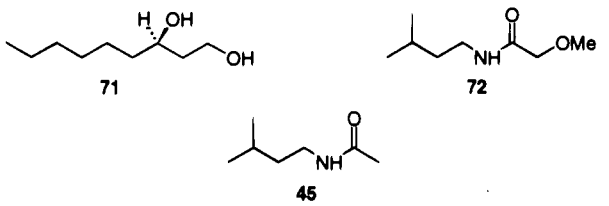
improved two-phase Nef reaction was conducted to provide a 2:1 mixture of the (*E*) and (*Z*) isomers.

3-Methylbutanol (**70**, 10%) and 1,7-dioxaspiro-[5.5]-undecane (1, 14%) were also present in the *B. umbrosa* extract, along with 6-oxononan-1-ol (**58**), with the latter being the major component of *B. carambolae*, a member of the *dorsalis* fly complex. The chirality of the 1,7-dioxaspiro[5.5]undecane was not established, but results from female *B. oleae, B. cacuminata*, and *B. distincta* would suggest it to be racemic.[66]

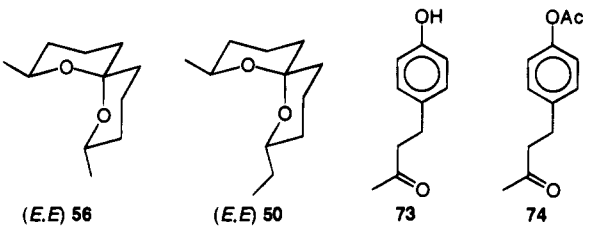


c. Bactrocera tau. Bactrocera tau (Walker) has a wide distribution over Southeast Asia and has been reported from Malaysia, Indonesia, Philippines, Thailand, and India. This species is a severe pest of cucurbits but it is not an aggressive species like the melon fly, *B. cucurbitae* (Coquillett) (see later). The rectal gland secretion of *B. tau* collected in Malaysia consisted largely of one component (80%) exhibiting prominent ions at *m/z* 113 and 75 in the mass spectrum.[89] This component was shown to be nonane-1,3-diol by comparison with an authentic sample and was further shown to be the (*R*)-(−) enantiomer (**71**) (>99% ee) by chiral gas chromatography. (For synthesis and chirality determination of the nonane-1,3-diols, see the discussion under *B. cucumis*.) Two other minor components were identified as the unusual methoxymethylamide **72** (10%) (also a component of *B. cucurbitae*) and the simple amide **45** (~2%) (also found in *B. cucurbitae* and *B. tryoni*). A number of low-level components (~1% each) could not be identified.

d. Bactrocera nigrotialis. Bactrocera nigrotibialis (Perkins) is located throughout Thailand, Malaysia, and Laos. The extract (acetone) of the male anal



gland contained[89] largely (85%) (*E,E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**56**) along with a low level (~3%) of the homologue, (*E,E*)-2−ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane (**50**), already noted as a minor component in several other species, e.g. *B. dorsalis* and *B. latifrons*. The 4-phenylbutanone derivative **73** was also detected and is structurally related to the synthetic attractant Cue-Lure (**74**) used in the trapping of this species. Consequently it is probably a metabolite of **74** (see Lure Metabolites section). The absolute stereochemistry of the two

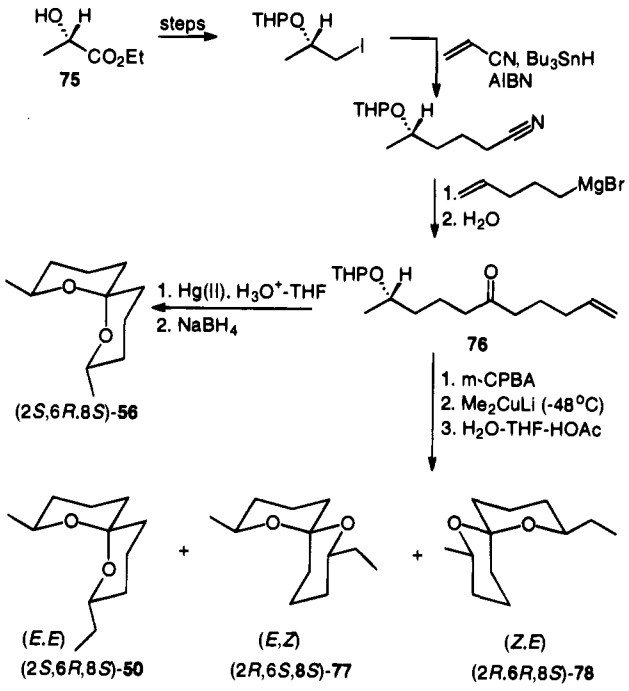


spiroacetals was investigated, and that of the 2,8-dimethyl system **56** was shown to be (2*S*,6*R*,8*S*) by comparison of chiral gas chromatographic data obtained in the case of *B. cucumis* (French) (see later). The level of the even-carbon-numbered spiroacetal **50** (~3%) was higher in *B. nigrotibialis* than in other species, and determination of its absolute stereochemistry was undertaken. This required synthesis of enantiomers of this system, and the route developed[92] actually provided enantiomers of the 2,8-dimethyl system (**56**) as well as of the 2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane system (**50**) (Scheme 48).

Ethyl (*S*)-(+)-lactate (**75**) was used as starting material and a derived protected iodide was engaged in a free radical addition to acrylonitrile.[92] The resulting protected hydroxy nitrile, on reaction with pent-4-enylmagnesium bromide, afforded (*S*)-2-(tetrahydropyran-2-yloxy)undec-10-en-6-one (**76**) which was converted to either spiroacetal system as shown in Scheme 48. Oxymercuration of this hydroxyenone **76**, under reversible conditions, followed by reductive demercuration, provided essentially pure (2*S*,6*R*,8*S*)-2,8-dimethyl-1,7-dioxaspiro[5.5]-undecane (**56**). Epoxidation of the enone **76**, followed by dimethylcuprate opening, led to a mixture of the (*E,E*) and two possible (*E,Z*) diastereomers of the 2-ethyl-8-methyl spirosystem, with the former being the (2*S*,6*R*,8*S*) isomer **50**. Separation of the (*E,E*) **50** from the two (*E,Z*) isomers **77** and **78** was achieved by preparative gas chromatography. GC analysis of these samples and of the rectal glandular secretion of male *B. nigrotibialis*, using a cyclodextrin phase, demonstrated that the (2*S*,6*R*,8*S*) isomers of both spiroacetal systems were the natural products, with no detectable level of the antipodes.

All determinations of the chirality of (*E,E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane from insect

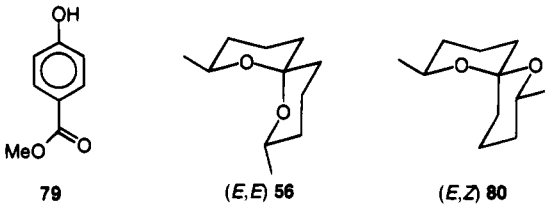
Scheme 48



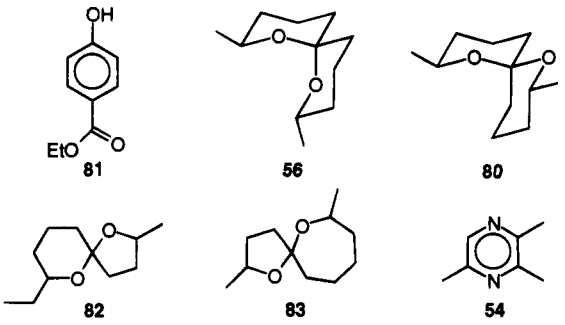
sources have provided a uniform result, viz. (2*S*,6*R*,8*S*)-**56** of very high ee. Although generalization may be difficult, it is probable that the (2*S*,6*R*,8*S*) configuration will also characterize the 2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane from insect sources and it would be of some interest to establish the situation for 2-butyl-8-methyl-1,7-dioxaspiro[5.5]undecane found in *B. latifrons,* but the level of this component is very low. The above results confirm high specificity in the biosynthetic pathways employed, as the lack of any (*E*,*Z*) diastereomers implies complete hydroxylation specificity in formation of the notional keto diol precursor.

e. Bactrocera albistrigata. Bactrocera albistrigata (de Meijere) is of minor pest status and is distributed throughout Thailand, Indonesia, and Malaysia. (This species was incorrectly referred to as *B. albistrigatus* in the paper by Perkins.[89]) The acetone gland extract[89] was rich in methyl 4-hydroxybenzoate (**79**) identified by mass spectral comparisons with an authentic sample and discussed later. The (*E*,*E*)- and (*E*,*Z*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecanes (**56** and **80**), of undetermined chirality, were also present and occurred in a *EE*:*EZ* ratio of 30:70, whereas in other cases studied, the (*E*,*E*) diastereomer predominates, usually by a substantial amount. This requires (on the assumption that a keto diol is involved biosynthetically) hydroxylation to occur predominantly with opposite chiralities at C_2 and C_8 along the undecane chain. This is opposite to the *B. nigrotibialis* case above, in which no (*E*,*Z*) was detectable, requiring hydroxylation to occur at C_2 and C_8 with the same chirality.

f. Undescribed Bactrocera (Zeugodacus) species. As part of this study of fruit fly chemistry,[89] we also examined an undescribed, large *Bactrocera (Zeugodacus)* species collected in Malaysia, and the major component (66%) of the acetone extract was identified as ethyl 4-hydroxybenzoate (**81**), the mass spectral behavior of which is discussed later. The

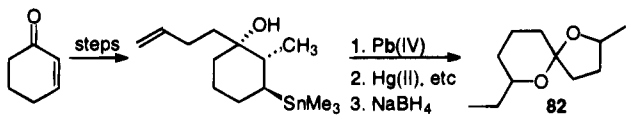


pentane extract contained the spiroacetals, (*E*,*E*)- and (*E*,*Z*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecanes [**56** (25%) and **80** (1%)], respectively.



Another component (~8%) exhibited apparent M = 184 and ions at *m*/*z* 169 (M − CH_3) and 155 (M − C_2H_5), along with typical spiroacetal fragmentations. This compound was suspected to be a diastereomer of 7-ethyl-2-methyl-1,6-dioxaspiro[4.5]-decane (**82**), and this was confirmed by mass spectral comparisons with a sample synthesized as shown in Scheme 49.

Scheme 49

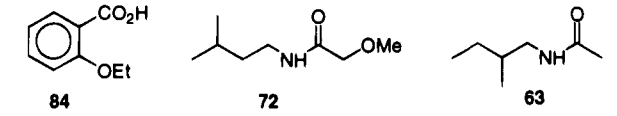


A very minor component (~1%) also exhibited a spiroacetal-like fragmentation, although it lacked a molecular ion. However, this feature, and unusually intense ions at *m*/*z* 140 and 111 indicated spiroacetal **83**, 2,7-dimethyl-1,6-dioxaspiro[4.6]undecane, and its mass spectrum corresponded very closely with published spectra.[93,94] This appears to be the only example of the [4.6]undecane system in a Dipteran species, although isomers of **83** have been identified in *Andrena haemorrhoa.*[93] Pyrazine **54** and fatty acids (C_{16}, C_{18}) completed the profile of this interesting species.

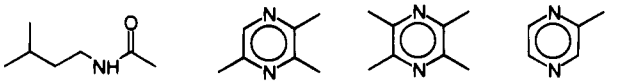
g. Bactrocera cucurbitae. Bactrocera cucurbitae (Coquillett) (melon fly) is one of the most active and destructive fruit fly pests and infests more than 80 plant species, most of which are Cucurbitaceae. Distribution ranges from East Africa to India, Southeast Asia, the South Pacific as well as Hawaii, but this species does not occur in Australia. There is strong evidence that female melon flies do not employ oviposition deterrents to foster egg economy, based on observations with a native host fruit in Okinawa,[95] so this approach to control seems inapplicable.

Several chemical studies of melon fly popuations have been published, and another reported in a thesis. Baker, Herbert, and Lomer[96] studied the

rectal gland secretions of sexually mature male flies, employing a solid sampling technique utilizing GC-MS methods. The major component (4 μg/individual) was concluded to be 2-ethoxybenzoic acid (**84**), with other components being the amides **45**, **72**, and **63**, and several pyrazines **54**, **85**, **86**. Ethyl esters of a number of fatty acids were also present. In a wind tunnel bioassay, both live males and excised male rectal glands elicited strong responses from female *B. cucurbitae*.[96] Amide **45** was reported to elicit activation and increased flight activity of female *B. cucurbitae*, but the exact role of other components was not defined.



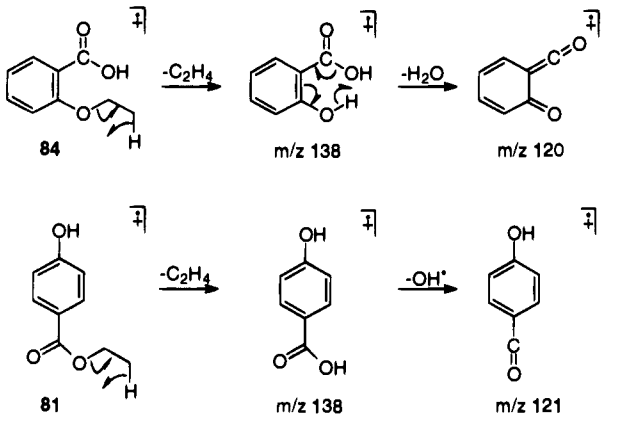
84 **72** **63**



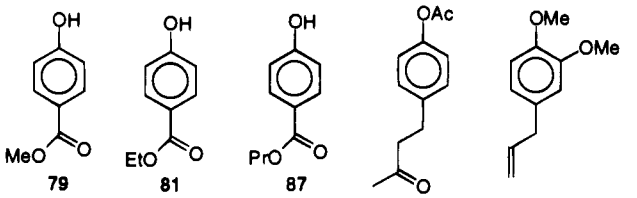
45 **54** **85** **86**

Most of these components were confirmed in a thesis by Lewis,[97] who studied wild male melon flies collected in the Philippines, but amide **63** and the monomethylpyrazine **86** were not detected. However, a new minor component was tentatively concluded to be propyl 4-hydroxybenzoate (**87**) and this raised the question whether the major component was possibly ethyl 4-hydroxybenzoate (**81**) and not ethoxybenzoic acid (**84**). In a very careful study, Perkins[89] showed that the major component was indeed the 4-hydroxybenzoate (**81**) and this was based on mass spectral fragmentation behavior and GC behavior. Authentic 2-ethoxybenzoic acid (**84**) and ethyl 4-hydroxybenzoate (**81**) display very different mass spectra, with the former showing a base peak at m/z 120, corresponding to $C_7H_4O_2$, which can arise by a double hydrogen transfer characteristic of *ortho*-substituted systems. On the other hand, the ethyl 4-hydroxybenzoate (**81**) shows a base peak at m/z 121, corresponding to $C_7H_5O_2$, and lacks an ion at m/z 120. These features are shown in Scheme 50.

Scheme 50



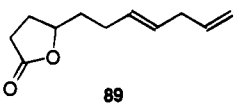
An independent but virtually simultaneous study of *B. cucurbitae* rectal gland volatiles by Nishida[98] confirmed these findings. From the ethanolic extract of macerated whole insects, Nishida was able to separate six components observed in rectal gland volatiles. From mass spectral and ^{1}H NMR evidence these compounds were determined to be amides **45** and **72**, 1,3-nonanediol (**71**) (undetermined chirality), and the methyl, ethyl and propyl esters **79**, **81**, and **87**. None of the other reports[96,97,89] mentioned the diol **71**.



79 **81** **87** **74** **88**

It is worth noting that esters of 4-hydroxybenzoic acid have been identified in other species e.g. methyl 4-hydroxybenzoate (**79**) in *B. albistrigata*, and the ethyl ester **81** in the undescribed species discussed above. Simple alkyl 4-hydroxybenzoates show some structural similarity to the attractant Cue-Lure (**74**). Interestingly, males of one of the major cucurbit infesting flies in Southern Africa, *Dacus vertebratus* Bezzi (taxonomically distinct from *B. cucurbitae*) are attracted to methyl 4-hydroxybenzoate (**79**) (known as Vert-Lure) but not to Cue-Lure (**74**) or methyl eugenol (**88**). Propyl 4-hydroxybenzoate (**87**) also attracts *D. vertebratus*.[99]

Studies of volatiles emitted by melon flies have also been conducted. Prior to mating, male melon flies emit a "smoke" like substance from erectile ampoules on their rectum.[83,100] Analyses by Ohinata[83] indicated this "smoke" contained large quantities of trisodium phosphate, some hydrocarbons, and the unusual lactone **89**. Amides were not detected in the



89

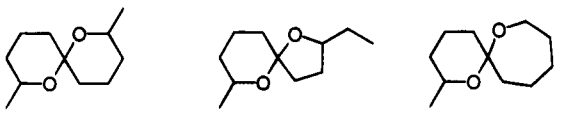
smoke, whereas the volatile secretion from female melon flies was reported to contain the amide **45**, with minor amounts of the (*E*,*E*)- and (*E*,*Z*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**56** and **80**). Other fruit fly species that mate at dusk and develop a cloudy atmosphere are *B. dorsalis* and *B. tryoni* (discussed later) and careful analyses of the components of these aerosols could provide the key to the use of male pheromones. A very useful discussion of the mating behavior and some aspects of pheromone production have been presented by Kuba.[101]

5. Bactrocera Species from Australia and Oceanian Regions

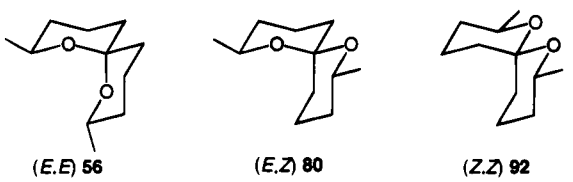
Although the actual geographical distribution of certain species is not known with great precision, especially in the Northern Australian, Papua New Guinea, and Southeast Asian regions, it is convenient to now discuss, studies of those species that are established in Australia and in the islands to the east and northeast of the Eastern Australian coast.

Australia is relatively rich in tephritid fruit fly species, with 80 or so species indigenous to the continent. Because of the constant risk of introduction of exotic species from other parts of the Pacific region, regular quarantine monitoring and detection must be undertaken. The males of most tephritids in the South Pacific region are strongly attracted to either Cue-Lure (**74**) or methyl eugenol (**88**) (so-called parapheromones), but a third group of flies is attracted to neither, and hence population variations and penetration of previously uninfested areas is much more difficult to detect. Chief among this group of flies are *B. cucumis* (French) (cucumber fly), *B. latifrons*, *B. halfordiae* (Tryon), *B. jarvisi* (Tryon), and *B. decipiens* (Drew). *B. decipiens* is a serious pest of cucurbits and is thought to be confined to New Britain, but has the potential to be a very damaging pest if introduced into Australia. Specimens of this insect have not been available for analysis. The cucumber fly (*B. cucumis*) is taxonomically close to *B. decipiens*, and is a major pest in Queensland, of cucurbits, tomatoes, and papayas. Our early attention was directed to this group of flies, particularly *B. cucumis* and the closely related although less economically important *B. halfordiae*. Studies have also been conducted on *B. latifrons* (also a pest in Southeast Asia as discussed above) and *B. jarvisi*.

a. Bactrocera cucumis. GC–MS examination of extracts of male *Bactrocera cucumis* (French) rectal glands showed the presence of one major component (~60%) and a number of minor components.[85,102] Consideration of the mass spectra confirmed that spiroacetals were predominant. Three systems were represented with *ca.* 70% being isomers of 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**43**) and only low levels of 1,6-dioxaspiro[4.5]decanes (**90**) and 1,7-dioxaspiro[5.6]dodecanes (**91**). Certain hydroxy derivatives were also present, with one being significant at ~15%.

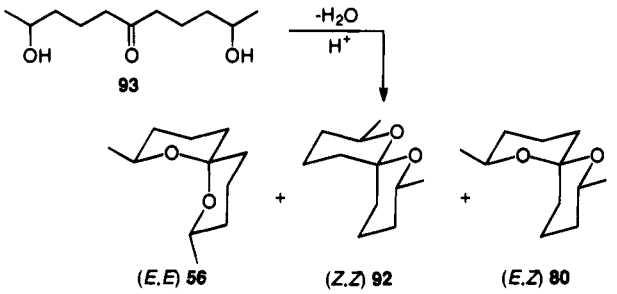


The major spiroacetal was shown by mass spectral and chromatographic comparisons to be (*E,E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**56**) (M = 184, *m/z* 169, and intense ions at *m/z* 115, 112 (100%)). Two later eluting compounds had very similar mass spectral patterns (M = 184), except that *m/z* 115 was the base peak. GC comparisons of the known and characterized (^{1}H, ^{13}C NMR) (*E,Z*) diastereomer confirmed the presence of this isomer (5%) and it was concluded, somewhat tentatively, that the (*Z,Z*) diastereomer (**92**) was also present, in larger amount (8%) than the (*E,Z*) isomer (**80**).



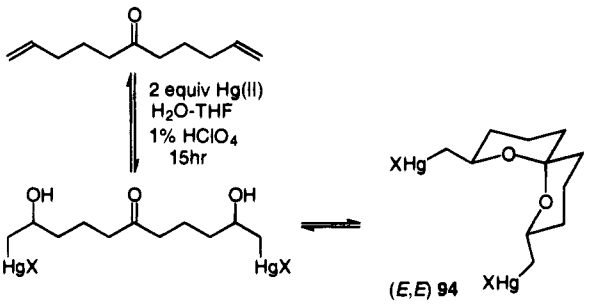
The (*Z,Z*) diastereomer **92** is of much interest as it lacks anomeric stabilization and is considered to be *ca.* 4.8 kcal/mol higher in energy than the (*E,E*) diastereomer **56**. It was therefore of major importance to provide convincing evidence for the natural occurrence of this previously uncharacterized(*Z,Z*) diastereomer. Tactical acquisition of this isomer is difficult in that under sufficiently acidic conditions, equilibration with the (*E,E*) isomer would be highly favored, being regulated by the anomeric effect. Reversible dehydrative spiroacetalization of a notional racemic keto diol (**93**) can, in principle, provide the three isomers (*E,E*), (*Z,Z*), and (*E,Z*) with the former two representing 50% of the total, but (*E,E*) would dominate to the virtual exclusion of the (*Z,Z*), in the presence of sufficiently strong acid (Scheme 51).

Scheme 51



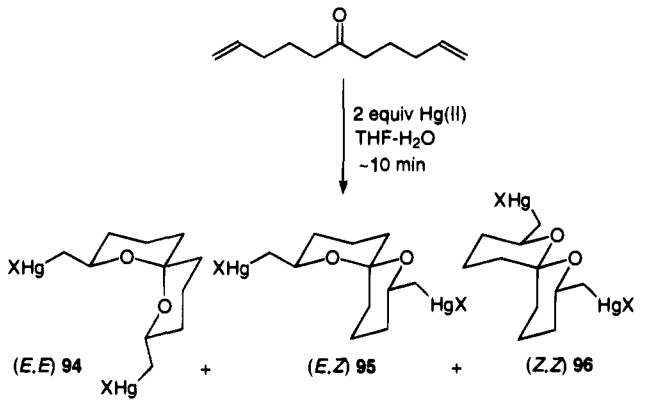
Consequently an approach to the (*Z,Z*) isomer **92** should avoid equilibrating conditions and perhaps incorporate features stabilising intermediates on the way to the (*Z,Z*) isomer. This presumably is a factor *in vivo* (in the cucumber fly) where the (*Z,Z*):(*E,E*) ratio is much greater than its equilibrium value. A procedure based on double oxymercuration of 1,10-undecadien-6-one was developed,[87] and differing conditions were investigated.[102] When 1% $HClO_4$ was present in the THF–H_2O medium, and reaction times were long (~15 h), (*E,E*) mercurial **94** of >90% diastereomeric purity could be obtained directly from the reaction mixture. This is a result of the reversibility of both spiroacetalization and oxymercuration under these conditions (Scheme 52).

Scheme 52



However, significant quantities of the (*E,Z*) mercurial **95** could be produced (~40%) when added acid was omitted, and reaction times were minimized (<10 min) (Scheme 53). Under these conditions, a third diastereomer, presumed to be the (*Z,Z*) (**96**) was observed, on the basis of ^{13}C NMR signals in the spirocarbon region. Reductive demercuration of this

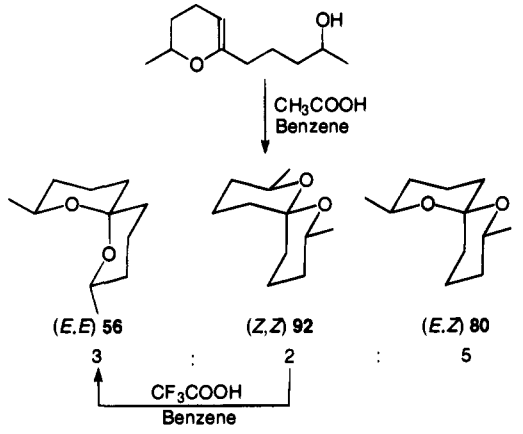
Scheme 53



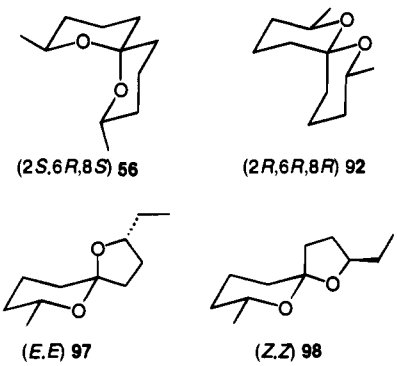
mixture provided the (*E*,*E*) (48%), (*E*,*Z*) (40%), and the slowest eluting isomer (~3%) (capillary GC OV101) concluded to be (*Z*,*Z*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**92**). Further variations in conditions may lead to improvements in the level of the (*Z*,*Z*) form.

Very careful preparative gas chromatography of this mixture resulted in isolation of the known (*E*,*E*) and (*E*,*Z*) isomers (each of >90% diastereomeric purity) and the presumed (*Z*,*Z*), in ~85% isomeric purity. That the isomer, concluded to be the (*Z*,*Z*) **92**, possessed a 2-fold axis was confirmed by its six-line ^{13}C NMR spectrum, and certain features in the 400 MHz ^{1}H NMR spectrum. Full details of this spectroscopic characterization are presented elsewhere.[102] Exposure of (*Z*,*Z*)-**92** to aqueous acid resulted in isomerisation to the (*E*,*E*) diastereomer **56**, as expected. Confirmation of the identity of this (*Z*,*Z*) diastereomer was recently provided by Pothier, Goldstein, and Deslongchamps,[103] who examined the cyclization of hydroxyenol ethers into spiroacetals, under both kinetic (CH_3COOH in benzene) and thermodynamic conditions (CF_3COOH in benzene) (Scheme 54).

Scheme 54

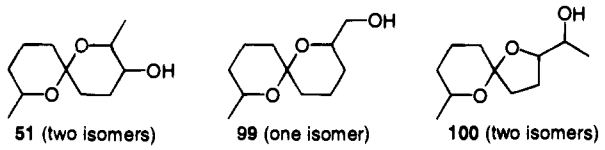


With the (*E*,*E*)-, (*E*,*Z*)-, and (*Z*,*Z*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecanes (**56**, **80**, and **92**), available, combined GC-MS examinations confirmed that these diastereomers were present in the *B. cucumis* secretion to the extents of 60%, 5%, and 8% respectively.[102] This result may point to the possible role of metal ion coordination within spiroacetal precursors and consequential stereochemical direction. Examination of the mixture by chiral gas chromatography established that the (*E*,*Z*) diastereomer **80** was racemic, and the (*E*,*E*)-**56** was highly enantiomerically pure, possessing the (2*S*,6*R*,8*S*) configuration,[102] as previously described for *B. nigrotibialis*. By similar means, the (*Z*,*Z*)-**92** has recently been shown to be enantiomerically pure, possessing the (2*R*,6*R*,8*R*) configuration.[104]



Minor dialkyl-substituted spiroacetals were also present in *B. cucumis*, and included the (*E*,*E*)- and (*Z*,*Z*)-2-ethyl-8-methyl-1,6-dioxaspiro[4.5]decanes (**97** and **98**). Previously the (*E*,*E*) and (*E*,*Z*) diastereomers had been identified in other insects.[105] A full listing of the minor spiroacetals has been presented elsewhere.[102]

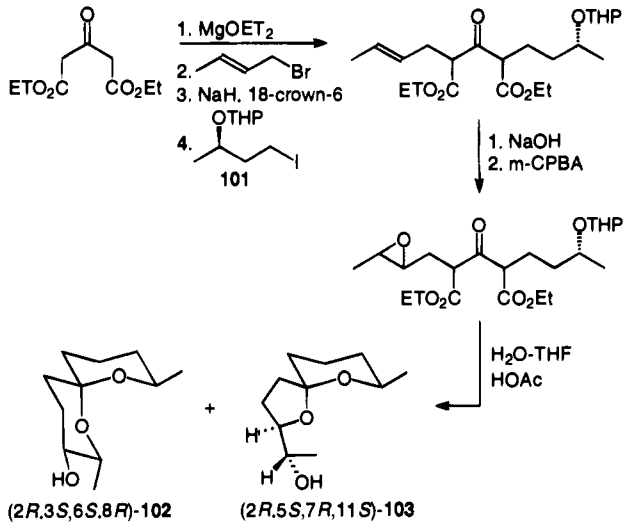
Of considerable interest was the suspected presence of hydroxy derivatives of the 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane system, with one in significant amount (15%). This parallels the cooccurrence of 1,7-dioxaspiro[5.5]undecane and certain hydroxy derivatives thereof in both *B. oleae* and *B. cacuminata*, for example. Compared with the parent system, the mass spectra exhibited ions consistent with the presence of an additional oxygen atom, and the hydroxy derivatives **51**, **99**, and **100** were considered likely. Identification of the hydroxy derivatives followed from comparisons with synthesized samples acquired as discussed in detail elsewhere (see later), and the *E*,*E*,*E* diastereomer of the 3-hydroxy derivative **51** was confirmed as the major hydroxy derivative in the natural secretion. A second minor isomer of **51** and one isomer of the hydroxymethyl system **99**, and two of the spiro[5.4]-decane system **100**, were also confirmed as present.



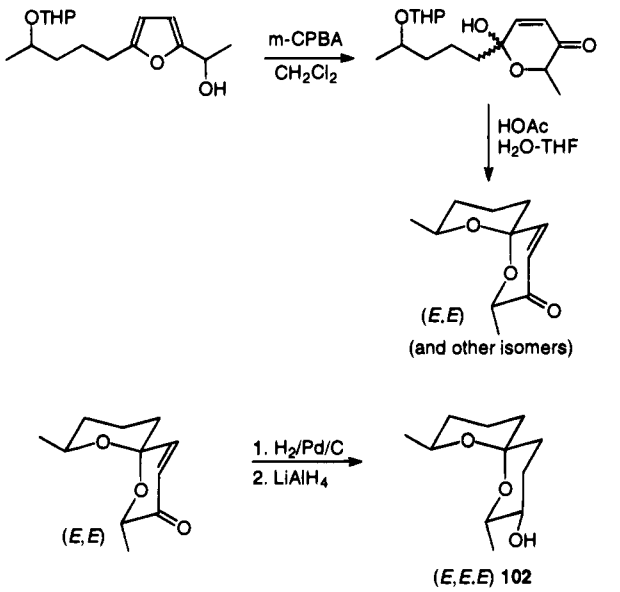
For the determination of the absolute configuration of the (*E*,*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-3-ol present in *B. cucumis*, it was necessary to acquire one enantiomer (or at least an enantiomerically enriched sample) of this system.[25] The route employed utilizing chiral iodide **101** is shown in Scheme 55.

The two alcohols (2*R*,3*S*,6*S*,8*R*)-**102** and (2*R*,5*S*,7*R*,-11*S*)-**103** were separated by preparative GC, and the [5.5] isomer **102** was spectroscopically identical with the racemate obtained as shown in Scheme 56. The

Scheme 55



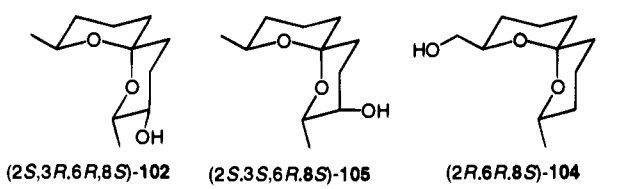
Scheme 56



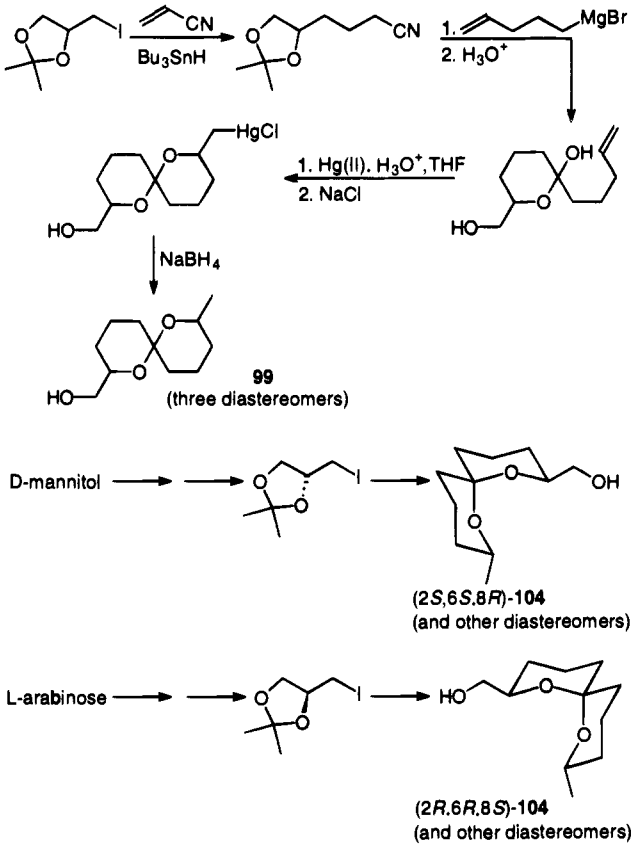
trifluoroacetate of the optically active alcohol **102** showed a single enantiomer on the Lipodex A column.

With respect to (8-methyl-1,7-dioxaspiro[5.5]-undecan-2-yl)methanol (**99**) this was obtained in racemic and both enantiomeric forms by using the appropriate glycerol acetonide as shown in Scheme 57. This procedure produces (*E,E*) diastereomer **104** as the major product with smaller amounts of the (*E,Z*) and (*Z,E*) diastereomers.[25]

Comparisons established that the major hydroxyspiroacetal present in the extract was the (*E,E*)-*equatorial* alcohol **102** but with a minor amount of the *axial* alcohol, **105**, and the trace amount of (8-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)methanol (**104**) was also the (*E,E*) as shown. Furthermore, with the availability of the enantiomerically enriched samples



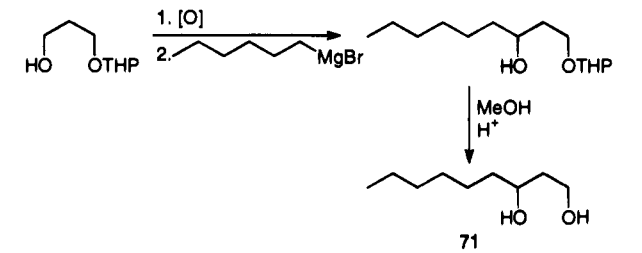
Scheme 57



of these alcohols, chiral GC analyses, mainly of the derived trifluoroacetates, demonstrated the absolute configurations shown. Thus, the hydroxyl derivatives possess the same ring chirality as the dominant (*E,E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**56**) itself and are probably derived from it by hydroxylation.

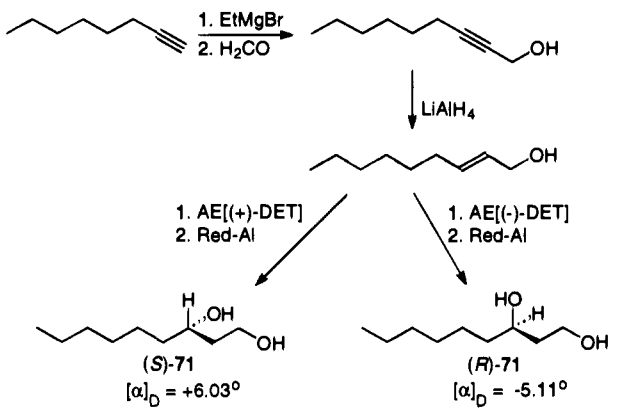
Another significant component in the male *B. cucumis* extract exhibited highest *m/z* 113 (30%) and 75 (100%), and chemical ionization techniques identified ions at 159 (M − 1) and 142 (M − H_2O), providing M = 160. This component was suspected to be 1,3-nonanediol (**71**) and confirmed as such when comparisons were made with an authentic sample obtained as described in Scheme 58.

Scheme 58

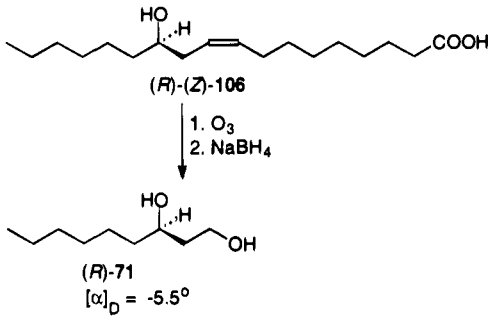


The question of the chirality of this diol was next addressed, and enantioselective syntheses of both (*S*)-(+)- and (*R*)-(−)-1,3-nonanediols, using Sharpless asymmetric epoxidation, were performed as outlined in Scheme 59. The above stereochemistries were authenticated by ozonolysis and reduction of (*R,Z*)-(+)-12-hydroxy-9-octadecenoic acid (**106**) (riconoleic acid) of established absolute configuration (Scheme

Scheme 59



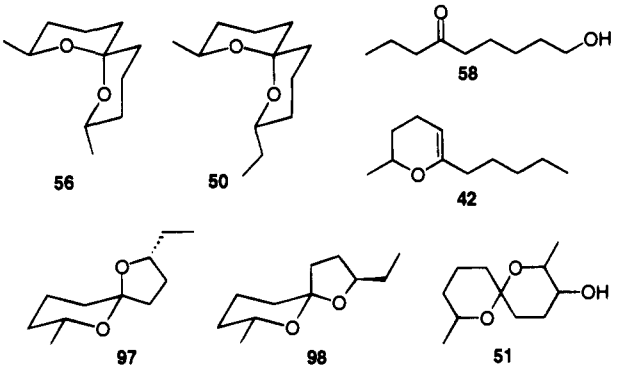
Scheme 60



60). Treatment of the glandular secretion extract of male *B. cucumis* with phosgene (to form the cyclic carbonate of the diol), followed by chiral GC analyses using the carbonates of the (*R*)-(−)- and (*S*)-(+)-nonanediols as standards, showed the presence of the (*R*)-(−) enantiomer of **71** only.

b. Bactrocera halfordiae. *Bactrocera halfordiae* (Tryon) is of low pest status and restricted to Southeast Queensland and New South Wales, but is of interest as it does not respond to any male lures. The major volatile component (~70%) in male *B. halfordiae* rectal glands was (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**56**) as observed for *B. cucumis*, but this component was not accompanied by the (*E*,*Z*) or (*Z*,*Z*) diastereomers.[102] The chirality of **56** was not determined in this case, but it almost certainly possesses the (2*S*,6*R*,8*S*) configuration. The absence of the (*E*,*Z*) isomer indicates enantiospecific hydroxylation (in the same chiral sense) in formation of the assumed keto diol precursor. A somewhat minor component (~6%) with M = 198 was confirmed as (*E*,*E*)-2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane (**50**) such component being present in other species e.g. *B. latifrons* and alluded to above.

The keto alcohol, 6-oxo-1-nonanol (**58**) was also present to a significant extent (10%), whereas it is the major component (~65%) in *B. carambolae*, and these are the first reports of **58** as an insect component. A minor component with apparent M = 168 ($C_{11}H_{20}O$) and prominent *m*/*z* 125 and 112 (100%) ($C_7H_{12}O$) was suspected to be a dihydropyran, and was shown to be 2-methyl-6-*n*-pentyl-3,4-dihydro-2*H*-pyran (**42**) by mass spectral comparisons with an authentic sample. One side-chain oxygenation of **42** could lead to the spiroacetal **56**. A further minor component was either **97** or **98**,[102] and not



(*E*,*Z*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane as previously suggested.[85]

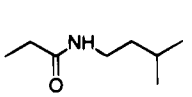
c. Bactrocera jarvisi. The important pest species *Bactrocera jarvisi* (Tryon) is distributed in Northern and Eastern Australia from Torres Strait to Sydney and infests deciduous fruits, mangoes, persimmons, and guavas. This fly is taxonomically distinct from other Australian species and does not respond to the male lures in use and is thus awkward from a management viewpoint. The volatile profile[106] from male *B. jarvisi* glands consists of a large number (>50) of components, all at a fairly low level. Considerable inconsistency was noted with repeated extractions and the possibility of outside contamination from the environment, food source, etc. is high at these levels. Compounds consistently present were C_{12}, C_{14}, C_{16} ethyl esters, various terpenoid components including linalool, a number of methyl and ethyl substituted pyrazines, spiroacetals **56**, **50**, and **51**, and various saturated and unsaturated long-chain acids and alcohols. Volatiles collected from female *B. jarvisi* presented a relatively clean profile with C_{12} ethyl ester and spiroacetal **56** as major components and C_{14} ethyl ester and spiroacetal **50** at significant levels. Examinations of male *B. jarvisi* volatiles were inconclusive.

d. Bactrocera tryoni and Bactrocera neohumeralis. The major pest species in Australia are *Bactrocera tryoni* (Frogatt) (Queensland fruit fly) and *Bactrocera neohumeralis* (Hardy), and both species breed in a wide variety of mature and commercial fruits in eastern Australia. *B. tryoni* has in excess of 200 host plants. In northern coastal Australia, both species occur sympatrically, but only *B. tryoni* is found south of Queensland, as far as northern Victoria. In the wild, the two species seem to be reproductively isolated but produce fertile hybrids in the laboratory.[107] *B. tryoni* mate at dusk at a low level of light intensity, whereas *B. neohumeralis* utilize the midday period with its higher light intensity. These species are the most destructive of all pests to horticulture in Australia, and strict controls regarding transportation and marketing of fruit are enforced to counter their menace.

Fletcher[6] reported that males of *B. tryoni* produce a pheromone (released at the time of stridulation) that is secreted in a gland complex, consisting, in mature males, of a secretory sac and reservoir. The pheromone (released through the anus by muscular contraction) causes responses in sexually receptive females when the glandular extracts are placed on filter paper. Congregation and ovipositor probing

occur and response is maximized at dusk. Sexually excited males of both *B. tryoni* and *B. neohumeralis* emit an oily secretion with a sweet pungent heavy odor, from the glandular complex described above. The examination of the reservoir contents by Bellas and Fletcher[108] was the first chemical examination of a *Bactrocera* species. The purpose was 2-fold: (a) to establish whether any significant differences occurred between the two species which could act as a deterrent to interspecies mating and (b) whether the glandular components might be useful in control measures.

Bellas and Fletcher[108] identified a series of six amides from the glandular secretion of cultured male *B. tryoni*, and these were identified as **107** (major), **45**, **108**, **55**, **63**, and **109** (in decreasing order of abundance). A similar set of amides was found in *B. neohumeralis* and were present in both cultured and wild male flies, ruling out the possibility of dietary artifacts. The amides were thought to be biosynthesized from leucine (**110**) and isoleucine (**111**).



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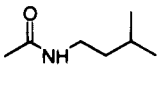

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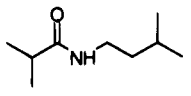

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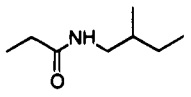

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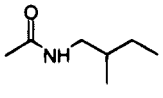

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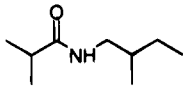

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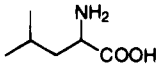

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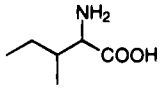

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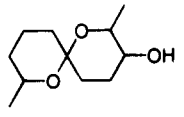
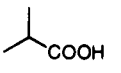


51

A subsequent study of *B. tryoni* male glands by Lewis[97] confirmed the findings of Bellas and Fletcher,[108] with proportions of the six amides being similar to those previously reported. The structures were confirmed by synthesis and spectral comparisons. A very minor component was shown to be 3-hydroxy-2,8-dimethyl-1,7-dioxaspiro[5.5]-undecane (**51**).

Behavioral studies indicated that the "glandular blend" of amides may function as a short-range stimulant, but not as a long-range attractant.[108] The extremely strong smell of *B. tryoni* males is dissimilar to that of the amides. In an attempt to identify further components Krohn *et al.*[109] have further investigated the glandular components and also examined volatiles released by *B. tryoni* males and females. Volatiles from female *B. tryoni* contained amides **107** and **45**, dimethylspiroacetal **56**, and C_{12} and C_{14} ethyl esters as significant components (in varying proportions). Spiroacetals **50** and **57** were identified among the many minor components. *B. tryoni* male volatiles contained amides **107**, **45**, **108**, and **55** in comparable proportion to the glandular composition, and the free acids **112** and **113**. On careful examination, methanolic extracts of *B. tryoni* male glands were found to contain the volatile acids **112** and **113** as well as the amide mix reported by other authors. When reared separately from females, *B. tryoni* male glands contain no trace of the hydroxy spiroacetal **51** reported by Lewis[97] and this component may be a metabolism product of the spiroacetal **56** produced by female *B. tryoni*.



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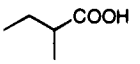


113

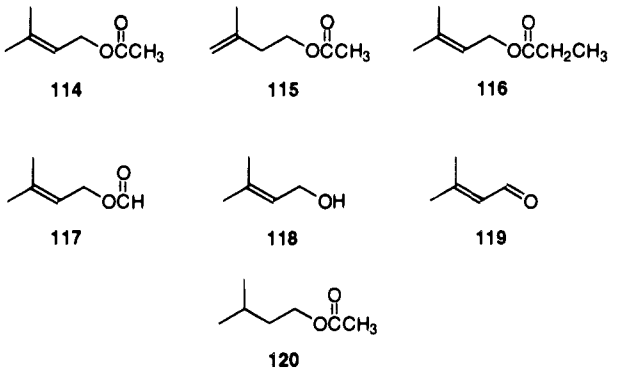
Amides **55**, **63**, and **109** and acid **113** are chiral and the absolute configurations of the natural components are of interest. Racemic acid **113** was resolved as the methyl ester on Lipodex E and the *B. tryoni* glandular component was shown to have the (*S*) configuration.[110] The chirality of amides **55**, **63**, and **109** is currently being determined.[110] The (*S*) configuration present in acid **113** is consistent with biosynthesis from L-isoleucine (**111**) which has the (*S*) configuration at C3,[111] and it is presumed that amides **55**, **63**, and **109** will have the same configuration. The biological activity of components other than amides[108] has not been determined.

e. Bactrocera aquilonis. *Bactrocera aquilonis* (May) is closely related to *B. tryoni* and is located mainly in the Northern Territory and western Australia. Laboratory studies[4] have revealed that the two species hybridize readily, producing fertile offspring, but geographical barriers may lead to reproductive isolation in the wild. Lewis[97] reported that the glandular components of wild adult male *B. aquilonis* (from Northern Territory) contained a similar amide mixture to *B. tryoni*, except that very minor amide **109** was unable to be detected and the proportion of the major amide **107** relative to the other amides **45**, **108**, **55**, and **63** was significantly greater in *B. aquilonis*. These minor differences in rectal gland composition between the closely related *B. tryoni*, *B. neohumeralis*, and *B. aquilonis* do not provide a secure basis for taxonomic differentiation.

f. Bactrocera visenda. *Bactrocera visenda* (Hardy) is a medium-sized species that is not of pest status and is taxonomically different from all other species in mainland Australia. It does resemble *Bactrocera mesonotochra*,[2] a species localized in Morobe province in Papua New Guinea. In view of this taxonomic isolation, it appeared that the chemistry of the male rectal gland secretion would be of interest, as other studies have shown that glandular contents can provide significant taxonomic information. *B. visenda* is widespread in southern coastal areas of Papua New Guinea, northeastern coastal areas of Queensland, and the Torres Strait Islands and infests only certain rainforest hosts such as "mangosteen" (*Garcinia warrenii*).

The glandular secretion was characterized[112] by one dominant volatile component (>90% of volatiles), four minor components (1–2% each) and a number of trace components. The major component was identified as 3-methyl-2-butenyl acetate (**114**) by comparisons with a synthetic sample. In a similar way, the minor components were identified as 3-methyl-3-butenyl acetate (**115**), 3-methyl-2-butenyl-

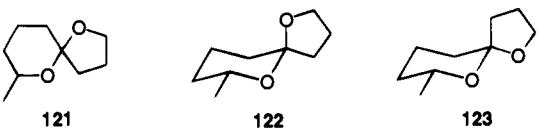
propionate (**116**), 3-methyl-2-butenyl formate (**117**), and 3-methyl-2-buten-1-ol (**118**). Very minor components were demonstrated to be 3-methyl-2-butenal (**119**) and 3-methylbutyl acetate (**120**).



None of these compounds has been identified previously from a *Bactrocera* species, and this supports the view that *B. visenda* is taxonomically distant from other *Bactrocera* species identified from the Australian mainland. This collection of compounds adds to the types utilized by Dipteran species and emphasizes their biosynthetic capability. However, some of these compounds are known as components of the aroma of certain fruits,[113,114] and α,β-unsaturated aldehyde **119** is a constituent of commercial proteinaceous baits for fruit flies.[115]

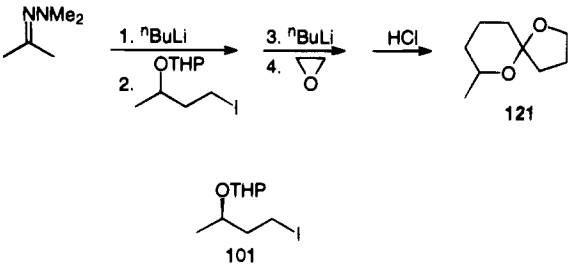
With respect to insect derivation, certain of the compounds, including **114**, have been identified as minor or trace headspace components from the odor of calling male Mediterranean fruit flies (*Ceratitis capitata*).[116] Other components of the *B. visenda* secretion have been identified from the European hornet[117] and the alarm pheromone of honey-bee workers.[118,119] Interestingly, aza analogues of the minor component, 3-methylbutyl acetate are known from the alarm pheromone of the wasp, *Vespula squamosa*,[120] and also from *B. cucurbitae, B. tryoni, B. neohumeralis*, and *B. aquilonis*. The biosynthetic routes to the short-chain compounds in insects are unclear, but those with branched structures may be derived from isoprenoid units or amino acids.[70,121,122]

g. Bactrocera xanthodes. Studies have also been conducted[123] of a number of species located predominantly in the southwest Pacific region, and spiroacetals are very prominent components of several of the rectal glandular secretions. *Bactrocera xanthodes* (Broun) is distributed throughout Fiji, Western Samoa, Tonga, the Cook Islands, and Vanuatu, and has been bred from a variety of hosts including pineapple, citrus, guava, tomatoes, and watermelon. This species has the potential to become a major pest and already causes substantial losses in areas of subsistence horticulture in the southwest Pacific locations mentioned. Extracts from young mature flies contained two relatively volatile components (*ca.* 20:1) each with apparent M = 156, *m/z* 141 (M − CH_3) and fragmentations indicative of spiroacetal structures, and specifically, isomers of 7-methyl-1,6-dioxaspiro[4.5]undecane (**121**), with the anomerically stabilized (*E*)-isomer **122** predominating over the (*Z*) isomer **123**.



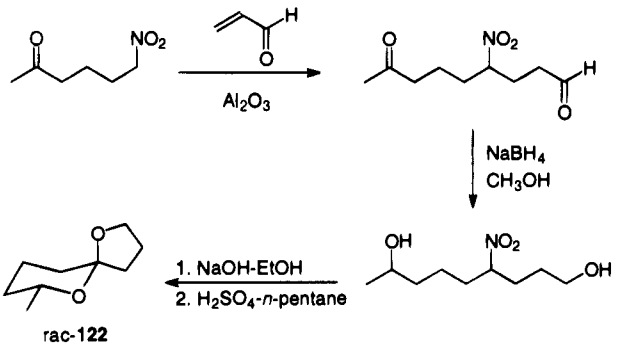
These structures were confirmed by comparisons with synthesized samples, obtained by sequential alkylations of anions generated from acetone *N,N*-dimethylhydrazone with 3-(tetrahydropyranyloxy)-1-iodobutane and ethylene oxide, followed by hydrolysis, deprotection, and cyclization (Scheme 61).

Scheme 61



Use of enantiomeric iodide **101**, provided (5*R*,7*R*)-**122** (ee 98%, $[\alpha]^{22}_D$ +84° (pentane)), but chiral gas chromatographic analyses showed the natural component to be (5*S*,7*S*)-**122** with an ee of 95%. As far as we are aware, isomers of this system have not been detected in other fruit fly species, but (5*S*,7*S*)-**122** has been identified in various species of bark beetles,[110] in common wasps[110] and pine tip beetles.[124] An alternative synthesis of the (*E*) isomer **122** as a racemate has been reported[91] and is based on the conjugate addition of a primary nitroalkane to acrolein, as shown in Scheme 62.

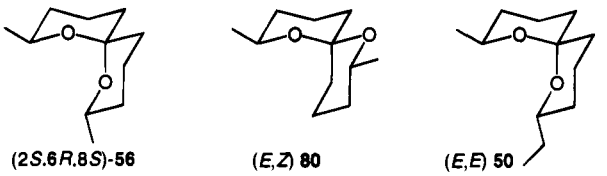
Scheme 62



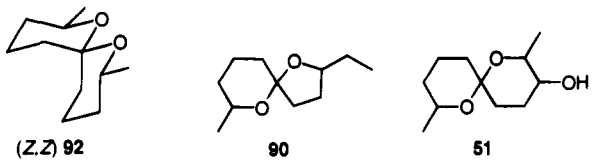
Components of lower volatility than the spiroacetals were detected in the extracts of young, mature *B. xanthodes*. Acetates of saturated and unsaturated C_{16}, C_{18} and C_{20} fatty alcohols were present, and those are listed elsewhere.[123] Long-chain hydrocarbons were present and consisted of two major components (3:1), with many minor components. The more abundant component was considered to be an unsaturated C-29 hydrocarbon, with the C_9 double bond confirmed by addition of dimethyl disulfide and GC−MS analysis. Mass spectral evidence showed the smaller component to be a mixture of 11-, 13-, and 15-methylnonacosane. There was also considerable variation in the relative amounts of certain of

the components, and this appeared to be related to the age of the flies.

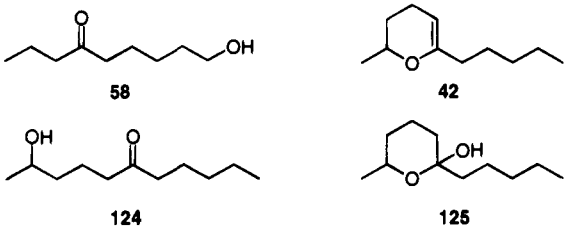
h. Bactrocera kirki. *Bactrocera kirki* (Froggatt) is a medium-sized species that also is distributed widely in the South Pacific islands of Western and American Samoa, Tonga, and Tahiti and has been bred from mango, peach, guava, and capsicum. It is a destructive pest of commercial and small-scale horticulture. A single major component was detected[123] in the glandular extract of male *B. kirki*, and this was shown to be (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane of (2*S*,6*R*,8*S*) configuration **56**, (ee >95%) by GC–MS comparisons, and chiral gas chromatography. This absolute stereochemistry is that found for *B. cucumis* and *B. nigrotibialis*. Minor components were shown to be (*E*,*Z*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**80**) and (*E*,*E*)-2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane (**50**) of undetermined chirality, but likely to be (2*S*,6*R*,8*S*), as shown for *B. nigrotibialis*. In view of the pest status of this species, a lure based on (*E*,*E*)-**56** may be feasible.



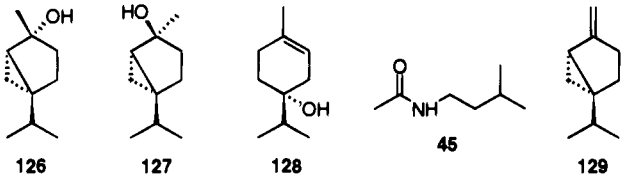
i. Bactrocera kraussi. *Bactrocera kraussi* (Hardy) is a medium-sized species in the *fragraea* complex of flies and is located in the coastal regions of far northeastern Queensland and Cape York. This non-pest species is closely related to *B. halfordiae* (Tryon) and infests only rainforest fruit. The rectal gland secretion was rich[123] in spiroacetals, with (2*S*,6*R*,8*S*)-(*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (~40%) (**56**) being the major component. Four of the less abundant compounds in *B. kraussi* were spiroacetals, with the even-carbon-numbered (*E*,*E*)-2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane (**50**), and another isomer of the 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane being significant. This latter isomer exhibited a mass spectrum similar to that of the authentic (*E*,*Z*) and (*Z*,*Z*) isomers, but with a retention time longer than that of the authentic (*E*,*Z*) isomer **80**. This is considered to be the (*Z*,*Z*) diastereomer **92** found previously in *B. cucumis*.[102] Two other minor spiroacetals were also identified and are considered to be either (*E*,*E*)- or (*E*,*Z*)-2-ethyl-7-methyl-1,6-dioxaspiro-[4.5]decane (**90**) and an isomer of 3-hydroxy-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**51**).



Three components that could be biosynthetically related to spiroacetals were also observed. 9-Hydroxynonan-4-one (**58**), 2-methyl-6-*n*-pentyl-3,4-dihydro-2*H*-pyran (**42**), and its open chain, hydrated form, 2-hydroxyundecan-6-one (**124**) were tentatively identified. Synthesis of the latter compound **124** was carried out by alkylation of acetone *N*,*N*-dimethylhydrazone, as discussed above. Thus alkylation with *n*-butyl bromide, and 3-(tetrahydropyranyloxy)-1-iodobutane led to the hydroxy ketone **124** and its hemiketal **125** (ca. 5:1), and dehydration of the latter under preparative gas chromatographic conditions, provided the dihydropyran **42**. Use of enantiomeric secondary iodide (*R*)-**101** provided the (*R*)-configured dihydropyran (ee 97%), and further chiral GC analyses showed the natural dihydropyran **42** to be (*S*)-configured, and because of the structural relationship between this dihydropyran and keto alcohol **124**, the latter is also assigned the (*S*) configuration. The related spiroacetal i.e. 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**56**) also has the (*S*) configuration. Dihydropyran **42** occurs also in *B. halfordiae*, and probably has (*S*) configuration here as well. Some other very minor components, including amides were characterized at very low levels. Examination of the volatile emissions from male *B. kraussi* was also conducted, and the (*E*,*E*) spiroacetal **56** was the major constituent. Overall, there is a close similarity between the contents of the glandular secretions of *B. halfordiae* and *B. kraussi*.



j. Bactrocera passiflorae and B. facialis. Two other species from the Pacific Islands were also examined. *Bactrocera passiflorae* (Froggatt) has been recorded from Fiji and Tonga and is known to infest citrus, passion fruit, and mango, whereas *Bactrocera facialis* (Coquillett) infests citrus, peach, mango, and capsicum and has the potential to become a major pest. The major component in *B. facialis* was *cis*-thujan-4-ol (**126**), with three minor components being the terpenes **127** and **128** and amide **45**.



B. passiflorae gland extracts contained **126** as the major component, with other significant components being **127**, **128**, and amide **45**. Three pyrazines were also detected. Chiral resolution on a 6-methyl-2,3-dipentyl-γ-cyclodextrin gas chromatography column showed that *cis*-thujan-4-ol (**126**) present in *B. facialis* and *B. passiflorae* was the (+)-(1*R*,4*R*) isomer in both cases.[110] These two flies are unrelated, and the terpenes observed are believed to be diet related, as pawpaw pulp (the laboratory diet base) contains sabinene (**129**) along with other terpenes.[125] Gland extracts from *B. passiflorae* bred from field-collected rose-apple (*Syzygium jambos*) contained fewer vola-

tiles with the major component being terpinen-4-ol (**128**) (a reported component of *S. jambos* volatiles[126]).

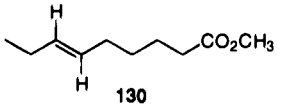
B. Genus *Ceratitis*

Ceratitis is another genus of the Dacinae subfamily and contains about 65 species found in tropical and southern Africa. One species, *C. capitata* (Wiedmann) has spread to almost all tropical and warm temperate areas and is probably the most serious pest species in the entire Tephritidae family.[1]

1. *Ceratitis capitata (Mediterranean Fruit Fly or Medfly)*

Ceratitis capitata (Wiemann), Mediterranean fruit fly, is a most active and destructive pest of citrus and other deciduous and tropical fruits and has a wide distribution range encompassing northern Africa, Southern Europe, the Middle East, South Western Australia, Hawaii, and Central and South America. Periodic outbreaks occur in Florida and Texas, and the rich California fruit industry must remain constantly vigilant.

Feron[127,128] first reported that mature male *C. capitata* release a volatile substance from erectile anal ampoules that induces sexual excitement in virgin females. The first chemical study of this volatile secretion was reported in 1973 by Jacobson and his USDA associates[129] who isolated pure components from the condensate obtained by passing air over 20000 caged male flies. Compounds identified by spectroscopic means and syntheses were methyl (*E*)-6-nonenoate (**130**) and (*E*)-6-nonen-1-ol (**131**). Both **130** and **131** were reportedly highly attractive to caged laboratory female flies, but their attractiveness was much reduced in field cage trials when compared with crude male condensate.[129,130] (Ester **130** did exhibit a useful level of attractiveness to male *C. capitata*.[131]) However, comparable activity was noted when **130** and **131** were mixed with the (inactive) acidic fraction of the condensate, which consisted of *ca.* 10 fatty acids ranging from C_6 to C_{18}.[129,130] In a subsequent study, Jacobson and Ohinata[132] identified (−)-β-fenchol (**132**) as a minor component with alcohols **130** and **131** in *C. capitata* male volatiles trapped on Porapak Q. (−)-β-Fenchol (**132**) was reported to be biologically inactive.[132]



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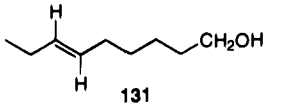

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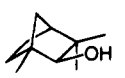
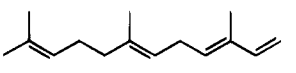


132

These findings of Jacobson[129,132] cannot be reconciled with more recent studies[133-136,110,116] which have failed to identify methyl (*E*)-6-nonenoate (**130**), (*E*)-6−nonen-1-ol (**131**), or (−)-β-fenchol (**132**) in *C. capitata* volatiles. Jacobson's results[129,132] are probably incorrect and attributable to the limited analytical methodology available at the time.

In 1985 Baker, Herbert and Grant[133] collected the volatile emission from *ca.* 40 male *C. capitata* on both Porapak Q and activated charcoal. These authors also examined the anal gland secretion by solid-sample gas chromatography−mass spectrometry (SS GC−MS). The major component (*ca.* 200 ng/insect) was identified as (*E*,*E*)-α-farnesene (**133**) with significant levels of ethyl (*E*)-oct-3-enoate (**134**) and geranyl acetate (**135**). A low, but difficult to establish, level of the unstable cyclic imine, 1-pyrroline (**136**), was also determined by mass spectrometry and derivatization. An aqueous solution of imine **136** was found in olfactometer tests to be highly attractive to virgin female flies and was regarded by Baker *et al.*[133] as the key component involved in sexual attraction of virgin females. Other components were concluded to be (*E*)-hex-2-enoic acid (**137**), dihydro-3-methylfuran-2(3*H*)-one (**138**), 2-ethyl-3,5-dimethylpyrazine (**139**), linalool (**140**), and ethyl acetate (**141**). None of these nine compounds **133**−**141** was detected in aeration products from female *C. capitata*.



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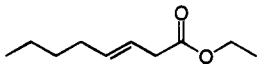

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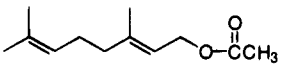

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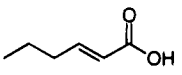

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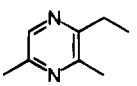

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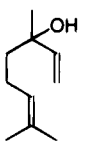

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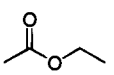

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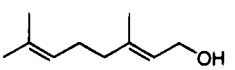


142

De Voss[134] identified (*E*,*E*)-α-farnesene (**133**) as the major component along with C_{16}, Δ^9C_{16}, C_{18}, and Δ^9C_{18} fatty acids in an acetone extract of excised male *C. capitata* anal glands (GC−MS). (Pure **133** could be easily obtained from hexane washings of the skin of Granny Smith apples.[137]) Francke[110] has also undertaken some examination of *C. capitata* and identified α-farnesene (major) (**133**), geranyl acetate (**135**) and geraniol (**142**) along with a very minor compound which *could* be (*E*)-6-nonen-1-ol (**131**), as male-specific compounds. Non-sex-specific compounds included heptadecane, various methyl ketones and a range of ethyl esters of fatty acids. Under both examination conditions[134,110] the very volatile imine **136** would have escaped detection.

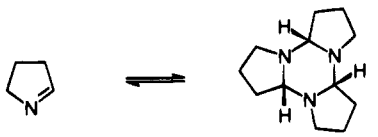
Jang *et al.*[116] identified 56 compounds from the odor of "calling" *C. capitata* males by headspace trapping on Tenax followed by thermal desorption and GC−MS analysis. The five major components were ethyl acetate (**141**), 1-pyrroline (**136**), ethyl (*E*)-3-octenoate (**134**), geranyl acetate (**135**), and (*E*,*E*)-α-farnesene (**133**). This study by Jang *et al.*[116] identified 8 of the 9 components **133**−**141** reported by Baker *et al.*[133] [with the exception of (*E*)-2-hexenoic acid (**137**)]. Quantitative discrepancies in relative concentrations

of the major components were attributed[116] to differences in methodology. Jang tested 54 of the compounds identified from male headspace trapping on both male and female *C. capitata* using the electroantennogram (EAG) technique and found no apparent correlation between relative abundance and EAG potency. However, Jang himself noted[116] that his work did not include EAG dosage/response studies and was thus inconclusive, as compounds reported as having high EAG responses may have high threshold values for detection and may elicit lower responses at more biologically relevant doses. A behavioral bioassay showed that a blend of the five major components **133**, **134**, **135**, **136**, and **141** with one of the intermediate components linalool (**140**) elicited comparable degrees of attraction to that of the natural pheromone with similar behavioral responses.[116]

Heath *et al.*[135] subsequently collected volatiles from virgin male and female *C. capitata* on charcoal and Porapak Q traps. Solvent elution followed by GC–MS analysis determined the presence of three major male specific components, geranyl acetate (**135**), ethyl (*E*)-3-octenoate (**134**) and (*E*,*E*)-α-farnesene (**133**). These are three of the five major components reported by Jang *et al.*[116] (1-Pyrroline (**136**) and ethyl acetate (**141**) would have been obscured by solvent.) A synthetic blend of **133**, **134**, and **135** was formulated to release the compounds in a ratio similar to that emitted by wild male *C. capitata*, and attractiveness of the blend to female *C. capitata* was demonstrated in the field.[135]

Baker, Heath, and Millar[138] have undertaken a detailed stability study of 1-pyrroline (**136**) to determine mechanisms for a controlled release of volatiles and new test methods for analysis. These authors established that 1-pyrroline (**136**) exists as both monomer and trimer in solution with the trimer **143** being thermodynamically more stable (Scheme 63). In the neat form **136** is stable and exists purely

Scheme 63



136 **143**

in the trimeric form. Contrastingly in the vapor phase only the monomer was found (infrared analysis). Thus it was proposed that imine **136** could be formulated for release in field trials as neat material in capillary tubes similar to that described by Heath.[135]

The most recent report of pheromonal emissions from male *C. capitata* by Flath *et al*[136] studied the effect of fly age and time of day. A total of 32 components were identified by Tenax trapping followed by either thermal or solvent desorption. The five major components were ethyl acetate (**141**), 1-pyrroline (**136**), ethyl (*E*)-oct-3-enoate (**134**), geranyl acetate (**135**), and (*E*,*E*)-α-farnesene (**133**) in agreement with previous results reported by some of the authors.[116] (*E*)-2-Hexenoic acid (**137**) (previously reported by Baker[133]) was also a major component but difficult to quantify due to instability in thermal transfer lines.

III. Subfamily Trypetinae

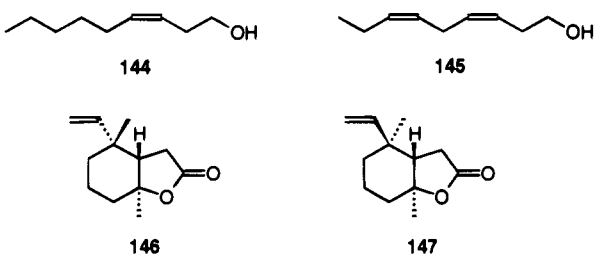
A. Genus *Anastrepha*

The genus *Anastrepha* contains about 180 species of tropical and subtropical flies, the majority of which utilize wild or less economically important hosts and have not been extensively studied. The role of pheromones in the mating system of *Anastrepha* fruit flies has been summarized by Nation,[139] and this text contains many references to behavioral and biological studies. Chemical information has been reported only for the Caribbean, *A. suspensa* (Loew), and Mexican, *A. ludens* (Loew) fruit flies.

1. *Anastrepha suspensa* (Caribbean Fruit Fly)

The Caribbean fruit fly (*Anastrepha suspensa* (Loew)) is a major pest of citrus and tropical fruits and nuts in the Caribbean and southern Florida. Nation[140,141] demonstrated that males produce a pheromone that is attractive to females and which serves as an aggregation pheromone, suggesting its usefulness as a field tool for population monitoring. Subsequently, Nation[142] reported that a blend of four biologically active components could be isolated from whole male *A. suspensa*, as well as from holding cage washings, and that two alcohols and two lactone esters were present, with the latter compounds dominating. Each compound was attractive to female flies with the combination of all four being most attractive.

Nation[143] identified the alcohols as (*Z*)-3-nonen-1-ol (**144**) and (*Z*,*Z*)-3,6-nonadien-1-ol (**145**), and synthetic samples were separately biologically active with 10-day-old flies. Subsequently, Battiste and Nation[144] separated all four components in high purity by silver nitrate–silicic acid chromatography. The structures of the optically active γ-lactones called anastrephin (**146**) and epianastrephin (**147**) respectively, were assigned on the basis of spectro-



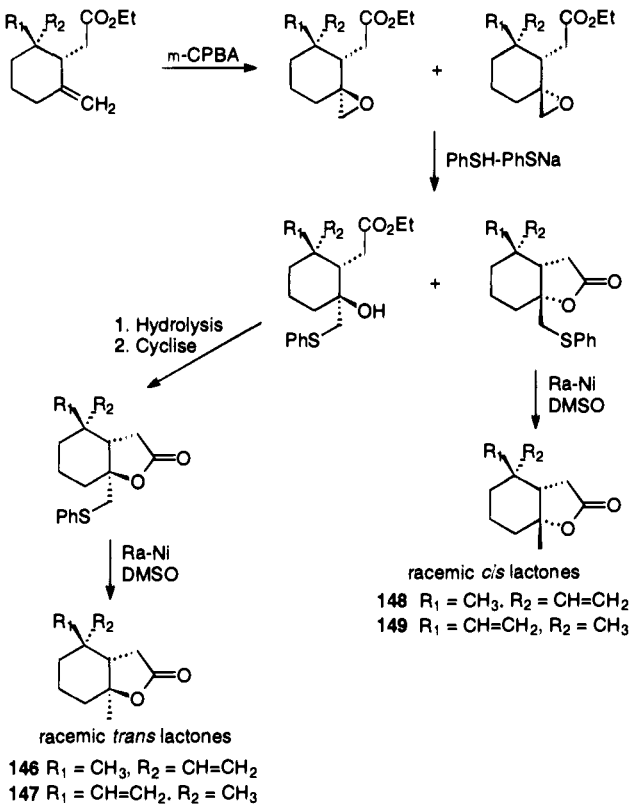
144 **145**

146 **147**

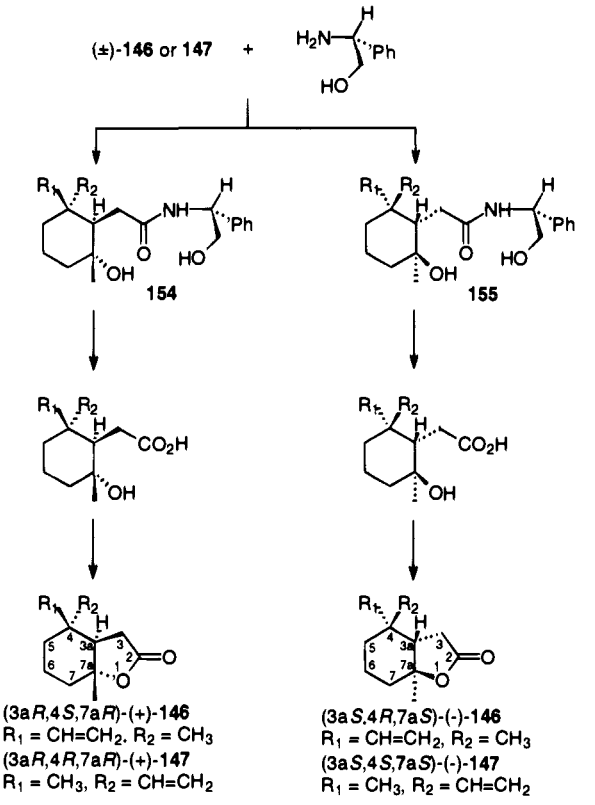
scopic data and synthesis,[145] not only of **146** and **147**, but also the corresponding *cis*-fused lactones **148** and **149**. A straightforward, but stereochemically limited approach based on sodium benzenethiolate ring opening of γ,δ-spiroepoxy esters was employed (Scheme 64). The major products of the oxirane ring opening with PhSH/PhSNa are the *cis*-lactone and *trans*-hydroxy ester which are readily separated by normal chromatographic procedures.

The final desulfurization step of the above synthesis adventitiously served to confirm the relative

Scheme 64

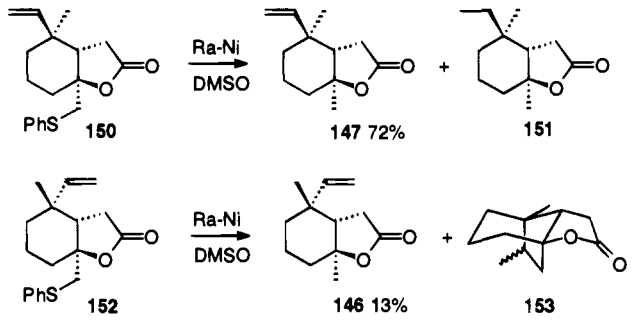


Scheme 66



stereochemistry of the quaternary center carrying the vinyl group. Raney-Nickel desulfurization of the *trans*-thiolactone **150** afforded (±)-epianastrephin (**147**) (72%) along with minor amounts of the reduced lactone **151**. Similar desulfurization of *trans*-thiolactone **152** however provided (±)-anastrephin (**146**) as a minor product (13%) with the isomeric saturated lactone **153** (formed by radical cyclization onto the proximate axial vinyl group of **152**) (Scheme 65).

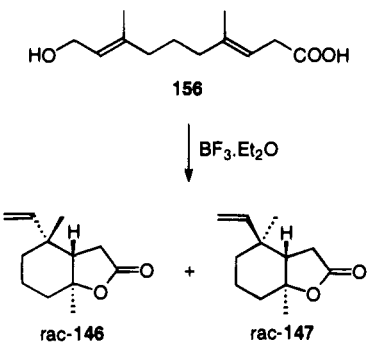
Scheme 65



Battiste and co-workers[146] reported procedures for assigning absolute configurations to the enantiomers of **146** and **147**, having established[144] that the natural lactones were enantiomeric mixtures 55 ± 3(−)/45 ± 3 (+), with **146** and **147** as drawn probably representing the absolute configuration of the major (−) enantiomer. This assignment was confirmed[146] by the resolution of racemic lactones by chromatographic separation of the diastereomeric hydroxyamides **154** and **155** formed from the reaction of the lactones with (*R*)-(−)-α-phenylglycinol. Hydrolysis and lactonization of the hydroxy acids afforded enantiomeric **146** and **147** in high optical purity (Scheme 66). Absolute configurations were assigned using a combination of NMR and optical and chemical methods. Thus the predominant (−) enantiomer of anastrephin has the (3a*S*,4*R*,7a*S*) configuration as depicted **146**, and the (−) enantiomer of epianastrephin has the (3a*S*,4*S*,-7a*S*) configuration as depicted **147**.

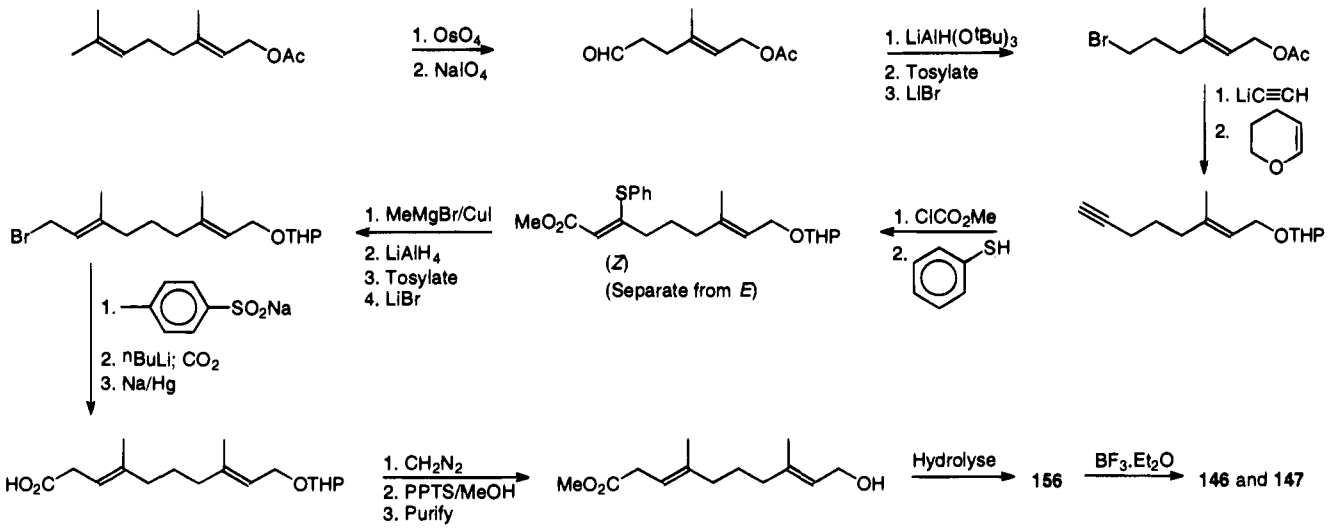
An efficient cyclization procedure for the synthesis of (±)-anastrephin (**146**) and (±)-epianastrephin (**147**) was reported by Saito and co-workers[147] who cyclized 10-hydroxy-4,8-dimethyldeca-(3*E*,8*E*)-3,8-dienoic acid (**156**) with borontrifluoride etherate (Scheme 67).

Scheme 67



Subsequently, Mori[148] reported syntheses of (±)-anastrephin (**146**) and (±)-epianastrephin (**147**) utilizing the same cyclization of **156**. This work described a new, more efficient synthesis of geometrically pure **156** from the acetate of geraniol (Scheme 68), and the efficient resolution of (±)-**146** and (±)-**147** employing (*S*)-(+)-prolinol as the resolving agent.[148] Lactone enantiomers were recrystallized to 100% ee (^{1}H NMR in the presence of the chiral shift reagent (*R*)-(−)-1-(9-anthryl)-2,2,2-

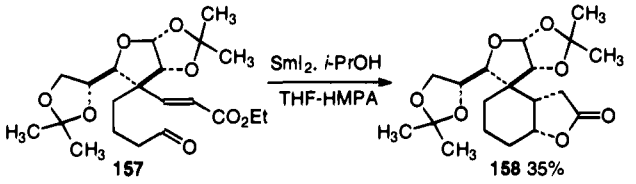
Scheme 68



trifluoroethanol) and absolute configurations were assigned from CD spectra using the sector lactone rule. The final stereochemical conclusions of Battiste[146] and Mori[148] were harmonious.

Tadano *et al.*[149] have very recently reported an enantiospecific route to the (−) enantiomers of **146** and **147**—a route that does not necessitate an optical resolution process. A key step in the synthesis was the samarium diiodide (SmI_2)-mediated intramolecular reductive coupling of α,β-unsaturated ester **157** (derived from D-glucose) to provide a diastereomeric mixture of hexahydrobenzofuran-2(3*H*)-ones, in which *cis*-fused product **158** was obtained as the major isomer (Scheme 69). The tetrahydrofuran part

Scheme 69

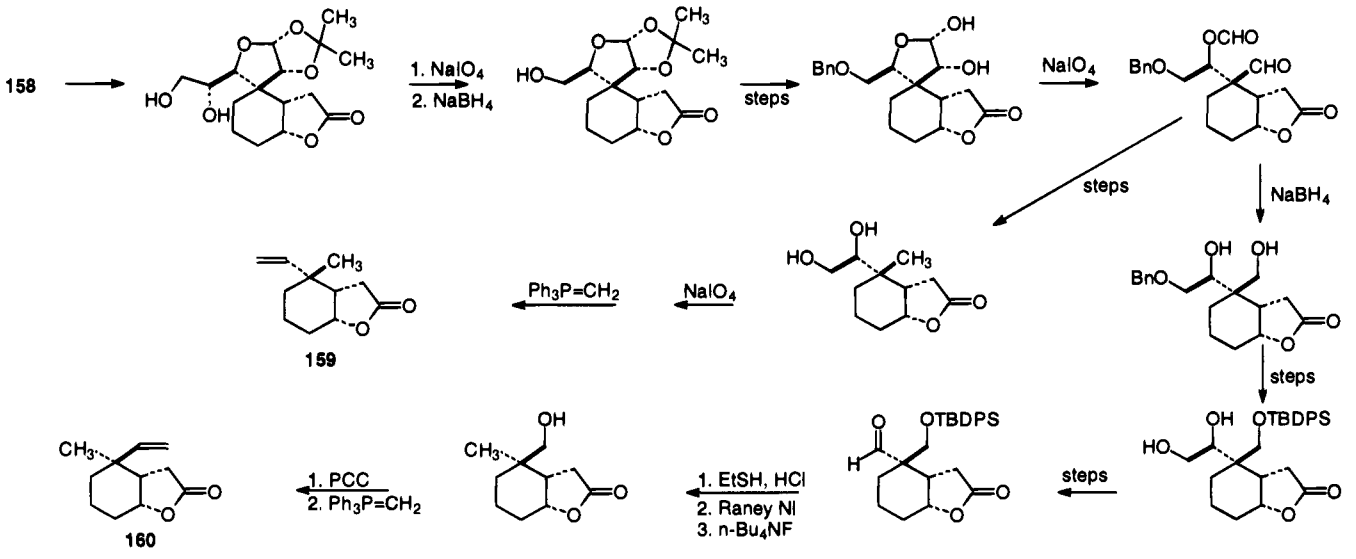


of **158** was then functionalized as shown in Scheme 70 to give vinyl derivative **159** or by a different route, the epimeric vinyl derivative **160**. The final part of the synthesis of (−)-anastrephin (**146**) was the introduction of a methyl group into C-7a of **159** as outlined in Scheme 71. (−)-Epianastrephin (**147**) was prepared from **160** by a similar route. The melting point, $[\alpha]_D$, and ^1H and ^{13}C NMR of **146** and **147** synthesized by this method[149] were identical with those previously reported.[148]

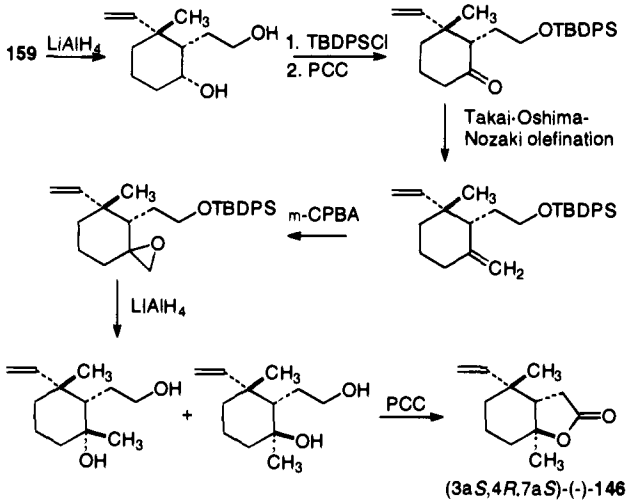
Electroantennogram (EAG) data from *A. suspensa* showed responses to the anastrephins in the order (−)-**147** ≫ (+)-**146** and (−)-**146** > (+)-**146**.[150] A synthetic mixture containing **144**, **145**, (−)-**146**, (+)-**146**, (−)-**147**, and (+)-**147** did not, however, significantly attract flies in a field trial.[139] (Insufficient quantities of components prevented examination of release rates and release ratios of the components.) This failure in the field led to a reexamination and the discovery of additional components in the *A. suspensa* pheromonal blend.

In 1988, Tumlinson, Battiste, Nation, and co-workers[151] conducted examinations of volatiles emitted by "calling" *A. suspensa* males and characterized as a major component a novel macrolide,

Scheme 70

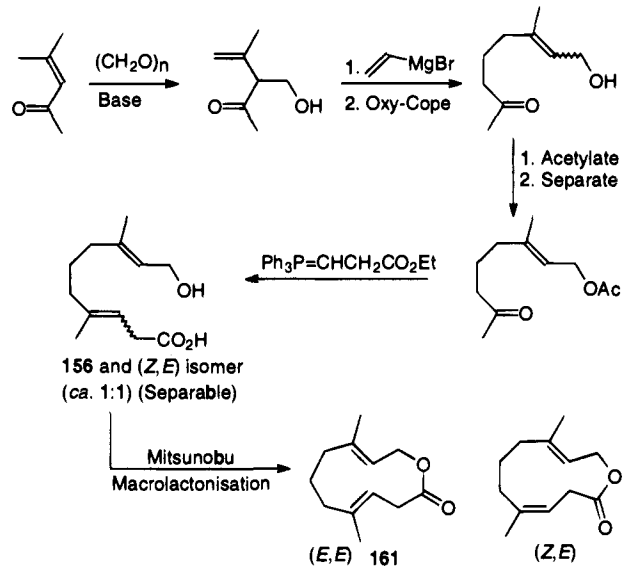


Scheme 71



(*E*,*E*)-4,8-dimethyl-3,8-decadien-10-olide (**161**) (called "suspensolide") by spectroscopic methods. The assigned structure was confirmed by synthesis in six steps from mesityl oxide,[152] a route that lacked control over double-bond geometry, but did permit aquisition of the (*Z*,*E*) suspensolide, in addition to the natural (*E*,*E*) macrolide **161** (Scheme 72).

Scheme 72



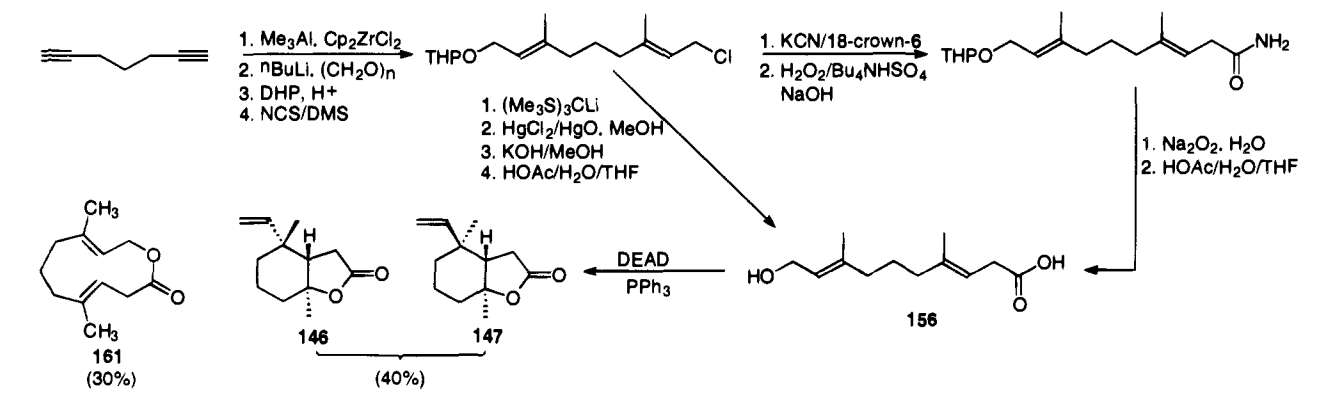
Mori[148] descibed a synthesis of suspensolide (**161**) utilizing the same Mitsunobu macrolactonization of hydroxy acid **156**. This work employed geraniol as a starting material and achieved greater control over olefin geometry. (Mori's preparation of **156** is shown in Scheme 68 as part of his synthesis of **146** and **147**).

Very recently, a more efficient and novel 10-step synthesis (overall yield 10%) of suspensolide (*E*,*E*-4,8-dimethyl-3,8-decadien-10-olide) (**161**) was reported by Vecchio and Oehlschlager.[153] The presence of two *E*-trisubstituted double bonds in the nearly symmetrical structure **161** suggested that double carboalumination of a diyne followed by alanate generation and quenching with formaldehyde would develop the essential part of the carbon skeleton. The resulting diol was monoprotected (as a tetrahydropyran-2-yl ether) and one carbon elongation of the free hydroxymethyl group was achieved by chloride formation and subsequent reaction with either cyanide or a thioorthoester anion and hydrolysis. This sequence led to (*E*,*E*)-10-hydroxy-4,8-dimethyl-3,8-decadienoic acid (**156**) as shown in Scheme 73. Hydroxy acid **156** was macrolactonized as before under Mitsunobu conditions to provide suspensolide (**161**) (30%), together with the anastrephins **146** and **147**, presumably resulting from acid-catalyzed cyclization of **161**.

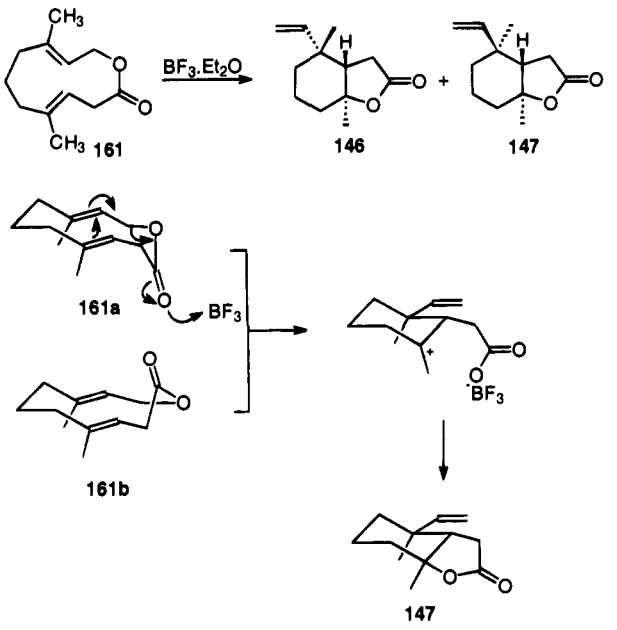
A stereoselective acid-catalyzed rearrangement of (*E*,*E*)-suspenolide (**161**) to anastrephin (**146**) and epianastrephin (**147**) in a 1:2.3 ratio has recently been reported by Battiste, Strekowski, Coxon, *et al.*[154] (Scheme 74). This ratio is consistent with molecular modeling and NMR studies of suspensolide (**161**) by the same workers[155] which showed the predominance of conformers **161a** and **161b** with the C4 and C8 methyl groups in a *syn* relationship. Formation of the major lactone **147** can occur with stereochemical integrity at C8 from these *syn* conformers, while a similar rearrangement of the minor *anti* conformers would give the minor lactone **146**.[154]

Battiste and co-workers[156] have reported a more detailed examination of the volatiles emitted by Caribbean fruit flies, *A. suspensa*. This analysis has shown three sesquiterpene hydrocarbons: α-farnesene (**133**), β-bisabolene (**162**) and α-*trans*-bergamotene (**163**) and the monoterpene (*Z*)-β-ocimene

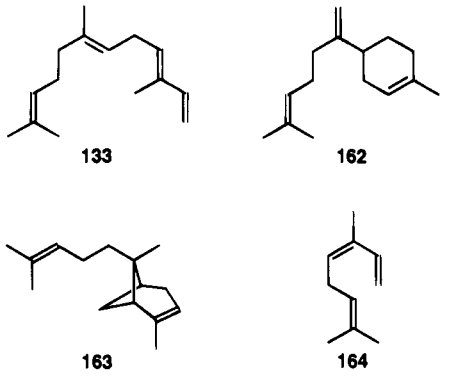
Scheme 73



Scheme 74



(**164**) in addition to the previously reported C9 alcohols **144** and **145** and lactones **146**, **147**, and **161**.



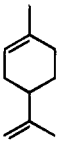
A recent review by Heath *et al.*[157] of attractants for monitoring Caribbean fruit flies contained a detailed overview of food, visual, acoustical, and pheromone attractants. These authors concluded that further isolation of pheromonal components was of little value if detailed behavioral bioassays were not developed. Subsequent to such bioassays, pheromone-based trapping systems would require a formulation "to release the chemicals at a rate and ratio used in nature".[157] Such mimicry of nature over an extended period of time presents considerable difficulty when dealing with complex pheromonal blends as detailed above for *A. suspensa*.

Mention has been made of the use of oviposition-deterring pheromones in certain insect genera to mediate regularity in egg distribution among available hosts.[5] Observations by Prokopy[158] of female Caribbean fruit fly indicate the employment of an oviposition-deterring pheromone, with egg-laying females dragging their ovipositors on the fruit surface after egg laying. The chemical nature of this pheromone is not established but it is water soluble and stable and may bear some resemblance to that employed by the cherry fly (*Rhagoletis cerasi*) (see relevant section) in the same subfamily. The pheromone was collected and when sprayed (water solution) on uninfested fruit, largely deterred boring attempts (for at least six days) by other females.[158]

2. Anastrepha ludens (Mexican Fruit Fly)

Mexican fruit fly (*Anastrepha ludens* (Loew)) is responsible for substantial losses to citrus and other crops in Mexico and may engage in seasonal migration into citrus areas in the southwestern United States. In the mid-1970s, Aguirre[159] and Steer[160] both suggested that male flies attracted females with a sexual lure, and Gaxiola[161] isolated four components from male *A. ludens*. He identified two unsaturated alcohols **144** and **145** and two cyclohexyl-based lactones. Subsequently in a detailed structural study, Stokes and co-workers[162] determined by extensive spectroscopic and X-ray analyses that (*Z*)-3-nonen-1-ol (**144**), (*Z*,*Z*)-3,6-nonadien-1-ol (**145**), anastrephin (**146**), and epianastrephin (**147**) corresponded to the male *A. ludens* components. Compounds **144**, **145**, and (−)-**147** have been shown to elicit behavioral responses from female *A. ludens* in laboratory bioassays.[163,164] Single enantiomers of lactones **146** and **147** elicit EAG responses from female flies in the order (−)-**147** ≫ (+)-**147** and (−)-**146** > (+)-**146**.[165] The enantiomeric composition of anastrephin (**146**) and epianastrephin (**147**) produced by *A. ludens* males has not been reported.

The study of *A. ludens* (Mexican fruit fly) pheromones by Stokes *et al.*[162] proceeded independently from those of Battiste and Nation,[144] who, as described previously, identified the same components in *A. suspensa* (Caribbean fruit fly). In addition to alcohols **144** and **145** and lactones **146** and **147**, Battiste and co-workers[156] have now identified the macrolide suspensolide (**161**) (previously known only from *A. suspensa*) in volatiles from *A. ludens* males. These volatiles also contained the sesquiterpenes: α-farnesene (**133**), β-bisabolene (**162**), and α-*trans*-bergamotine (**163**) (similarly detected in *A. suspensa* volatiles although in different proportion) and also the monoterpene limonene (**165**) (not seen in *A. suspensa*).



165

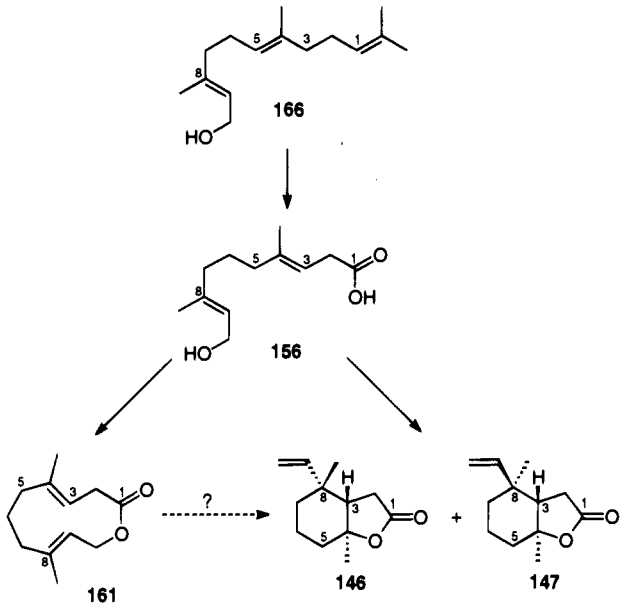
Thus males of both *Anastrepha* species synthesize and release the same volatile components with the exception of the two monoterpenes, limonene (*A. ludens*) and β-ocimene (*A. suspensa*).[156] In laboratory bioassays,[143] extracts of male *A. suspensa* attracted female *A. ludens* and extracts of male *A. ludens* attracted female *A. suspensa*. These species are not known to be sympatric and thus the chemical similarity is intriguing, suggesting a close evolutionary relationship.[156]

3. Biosynthesis of Anastrepha Volatiles

A biosynthetic connection between suspensolide (**161**) and the anastrephins **146** and **147** has been

suggested by various authors.[151,155,156,166] A thus far unsubstantiated biosynthetic route from farnesol (**166**) to suspensolide (**161**) and the anastrephins **146** and **147** via the hydroxy acid **156** has been proposed by Battiste and co-workers[156] (Scheme 75). Nation[166]

Scheme 75

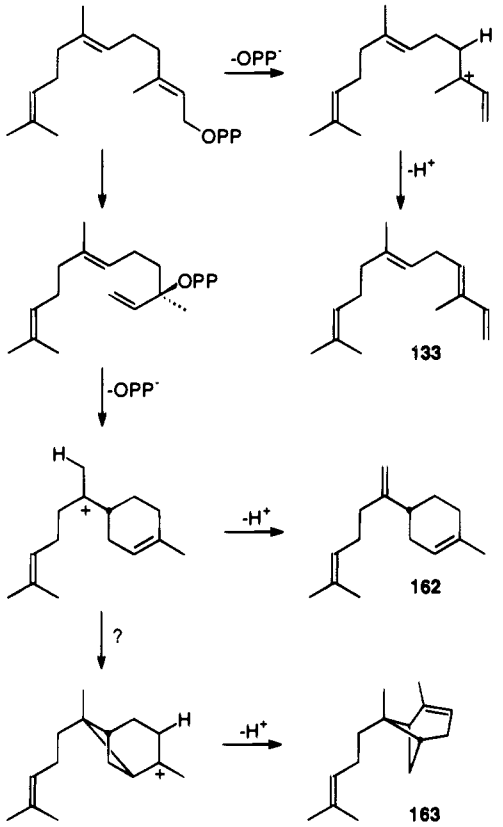


has reported that in *A. suspensa*, suspensolide (**161**) (with the sesquiterpene) is located primarily in the salivary glands and epidermal cells, while the anastrephins **146** and **147** (and nonenols) are concentrated in the hindgut. Thus it was presumed[156] that at least two enzymes would be involved in the cyclizations of **156**. These authors[156] also considered the possibility of "in vitro" conversion of suspensolide (**161**) to the anastrephins. In the laboratory, the facile acid-catalyzed rearrangement of **161** produces **147** and **146** in a 1:2.3 ratio,[155] while the acid-catalyzed cyclizations of hydroxy acid **156** gives **147** and **146** in a 1:1 ratio.[147] Neither ratio replicates the natural ratio of 1:4.5 to 1:4.7 reported by Nation[166] for *A. suspensa* volatiles, and detailed labeling experiments will need to be undertaken to verify the pathways shown in Scheme 75.

To this end, careful ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy has been conducted[167] on anastrephin (**146**), epianastrephin (**147**), and the related suspensolide (**161**). Full proton and carbon assignments have been reported and the relative stereochemistries demonstrated by nuclear Overhauser difference spectroscopy. This information will facilitate the location of ^{13}C or ^{2}H labels incorporated into the lactones from suitably isotopically enriched dietary sources. Some exploration of the conformational profile of the 11-membered ring lactone suspensolide (**161**) was undertaken by low-temperature NMR experiments,[167] and at 220 K, the majority of signals for two conformations[155] were identified.

Battiste[156] also depicted a possible biosynthetic route from farnesyl pyrophosphate or nerolidyl pyrophosphate to the three sesquiterpenes: α-farnesene (**133**), β-bisabolene (**162**), and α-*trans*-bergamotene (**163**) found in *A. suspensa* and *A. ludens* (Scheme 76).

Scheme 76



B. Genus *Dirioxa*

Dirioxa is a genus of four species found in Australia and Vietnam. Pheromonal information is not generally known for this genus with the exception of behavioral information relating to *Dirioxa pornia*.

1. *Dirioxa pornia (Island Fruit Fly)*

Dirioxa pornia (Walker) is widespread in eastern Australia but it is not a pest as it usually attacks only damaged fruit. Pritchard[168] has studied the mating behavior of this fly. In the late afternoon, the male assumes a position with abdomen raised and the pleural regions of abdominal segments 3, 4, and 5 distended. The wings execute slow movements and an unpleasant odor is produced and is easily detectable by the human nose up to 50 cm from the fly. This odor activates downwind females who quiver their abdomens and walk toward the inflated male. The male then appears to cease pheromone production and produces a small mound of foam on which the female is induced to feed, prior to copulation attempts. The chemical nature of the volatile pheromone and foam have not been reported.

C. Genus *Rhagoletis*

The genus *Rhagoletis* includes about 65 known species located in the Americas, Europe, and temperate Asia. Sex pheromones have been recognized in only two *Rhagoletis* species, *R. pomonella*, and *R. cerasi* and two types of pheromonal activity have been demonstrated, i.e. male-produced female sex attrac-

tant and female-produced male arrestant and probable sexual stimulant.[169] However, nothing is yet known about the chemical composition of these sex pheromones.

A more interesting and more intensely studied aspect of *Rhagoletis* behavior is the use of oviposition-deterring pheromones (ODPs) which represent a signal to alighting conspecific egg-laying females that the fruit already contains an egg. This results in economy in egg distribution. Evidence exists for the utilization of ODPs by about 11 *Rhagoletis* species, two *Anastrepha* species, and in *Ceratitis capitata* but not apparently in the generally polyphagous Dacinae species.[5] The potential use of ODPs in fruit fly management strategies has been reviewed by Boller.[170]

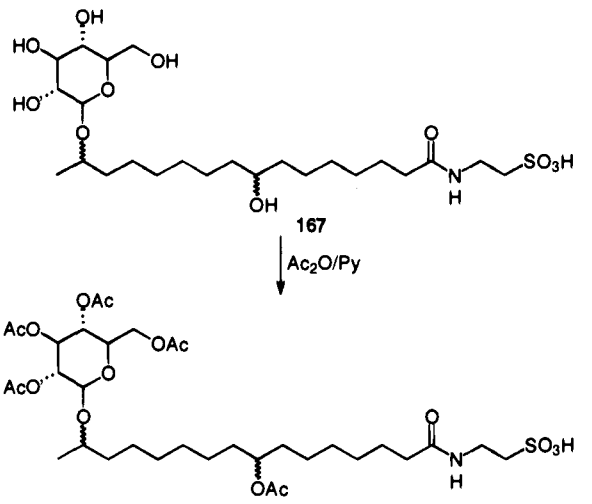
Definitive information in the structure of the ODP from only one species, *R. cerasi* has been reported.[171]

1. Oviposition-Deterring Pheromone of Rhagoletis cerasi

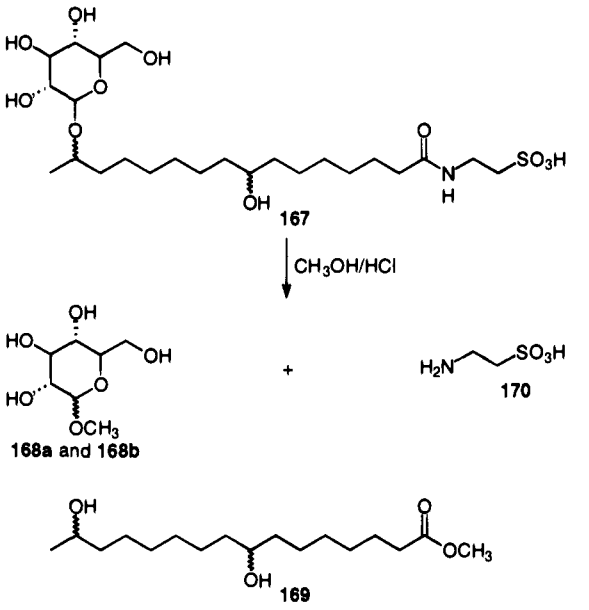
The European cherry fruit fly (*Rhagoletis cerasi* (Linnaeus)) lays one egg into a half-ripe cherry,[172] but double or triple ovipositions were noted to be much less than the statistical levels,[173,174] and it was hypothesized that the egg-laying female marks the fruit with a deterrent secretion. It was further speculated that the observed dragging of the ovipositor over the fruit surface after oviposition was connected with the postulated marking procedure.[175] Katsoyannos[176,177] noted that markings on artificial sites were water soluble and when such solutions were applied to cherries in the field, infestation levels were greatly reduced. Oviposition-deterring pheromone (ODP) was isolated by Hurter and coworkers[171] from the methanol extract of female cherry fly feces. A series of cellulose and reverse-phase TLC and HPLC separations provided a very polar material whose biological activity was evaluated by behavior and electrophysiological recordings from tarsal contact chemoreceptors. FAB mass spectral analysis of the purified ODP **167** enabled the identification of $[M + H]^+$, m/z 558 and a series of cluster ions $[M + Na]^+$, $[M + NH_4]^+$, $[M + K]^+$, etc. An elemental composition of $C_{24}H_{47}O_{11}NS$ was deduced by accurate mass measurements under high-resolution conditions. Pronounced losses of a 162 D neutral particle in FAB MS–MS of the $[M + H]^+$ and $[M + Na]^+$ ions indicated the presence of a hexose subunit which was further supported by the FAB MS–MS spectra of the peracetylation product (Scheme 77).

The hexose unit was identified as glucose by acidic methanolysis of **167** (Scheme 78), with GC–MS analysis of the silylated cleavage products. Two components in the gas chromatogram were identified as the 2,3,4,6-tetrakis(trimethylsilyl)ethers of the α- and β-anomeric methyl 1-*O*-glucopyranosides (**168a** and **168b**). ^1H NMR evidence showed a β-glucosidic linkage was present in ODP **167**. GC–MS analysis of the silylated methanolysis products also enabled the determination of a further structural unit. EI–MS of a third component showed pronounced α-cleavage consistent with the bis(trimethylsilyl) derivative of methyl 8,15-dihydroxypalmitate (**169**) (with unknown stereochemistry at the two chiral centers). From elemental composition, taurine (**170**) was proposed as the remaining structural moiety with support from FAB MS–MS and ^1H NMR evidence. Taurine (**170**) was subsequently identified as one of the reaction products from the methanolysis of **167** by TLC in two chromatographic systems.

Scheme 77



Scheme 78



The natural ODP was thus determined to be *N*-[15-[(β-D-glucopyranosyl)oxy]-8-hydroxypalmitoyl]-taurine (**167**) and may be viewed as carrying a lipophilic core flanked on either side by hydrophilic ensembles. The β-aminosulfonic acid residue (taurine) accounts for the ready water solubility, salt formation, and possibly the necessary surface activity to function as an ODP. Taurine is known to be a constituent of a range of invertebrate and vertebrate tissues, and in some cases is thought to discharge an important neurophysiological function.[171] Although not yet established, it is possible that ODPs of other species are structurally similar and the revelation of structure **167** at least provides an opportunity for synthesis of simpler analogues that may incorporate the essential features and properties of **167**.

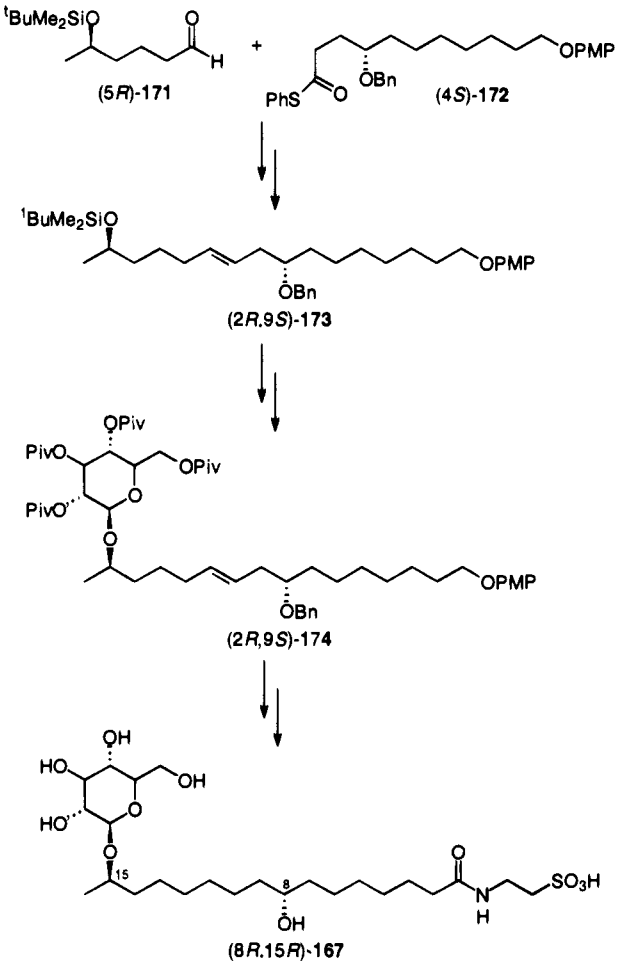
Mueller, Domon, and Richter[178] have also used ODP **167** as a test case to determine the potential of tandem mass spectrometry (MS–MS) as a stand-

alone technique in structure elucidation. ODP **167** was subjected to MS–MS analysis under a variety of conditions with and without preceding chemical degradation (acidic methanolysis or trideuterioacetylation) and the reported results may be useful in structure determinations of similar ODPs.

2. Synthesis of the Oviposition-Deterring Pheromone

With chiral centers at C_8 and C_{15}, **167** may exist as one (or several) of four possible stereoisomers which would presumably differ in their behavioral effect. Ernst and Wagner[179] synthesized the four possible stereoisomers of **167** by condensing for example, the building block (5*R*)-**171** with the boron enolate of (4*S*)-**172** to provide (2*R*,9*S*)-**173** (Scheme 79). Glycosylation with tetra-O-pivaloylgluco-

Scheme 79

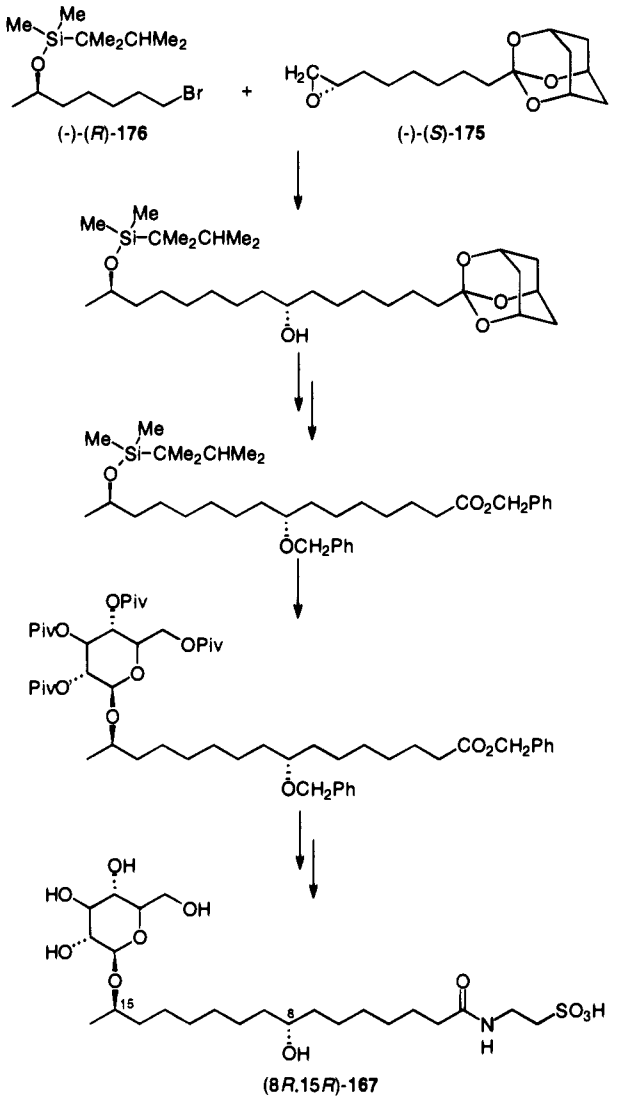


pyranosyl fluoride provided (2*R*,9S)-**174**. Oxidation to the carboxylic acid followed by taurine amide formation and deprotection provided (8*R*,15*R*)-**167**. The other three stereoisomers of **167** were acquired in analogous fashion.

The (8*R*,15*R*) and (8*S*,15*R*) isomers of **167** exhibited the same chemical shifts for H-C_{15} and CH_3-C_{15} as the natural product, hence the latter has the (15*R*) configuration.[179] Biological evaluation of the synthesized isomers of **167** demonstrated that the (8*R*,15*R*) and (8*S*,15*R*) isomers were biologically active,[180] and further ^1H and ^{13}C NMR studies showed both epimers to be present in the natural pheromone (communication Ernst to Kuchler *et al.*[181]).

A further synthesis of (−)-(8*R*,15*R*)-**167** and a mixture of the two compounds (−)-(8*R* and 8*S*,15*R*)-**167** from (−)-(*S*) and (±) epoxide **175** was reported by Kuchler *et al.*[181] The scheme to provide (−)-(8*R*,-15*R*)-**167** from Grignard coupling of (−)-(*R*) bromide **176** and (−)-(*S*) epoxide **175** is shown in Scheme 80.

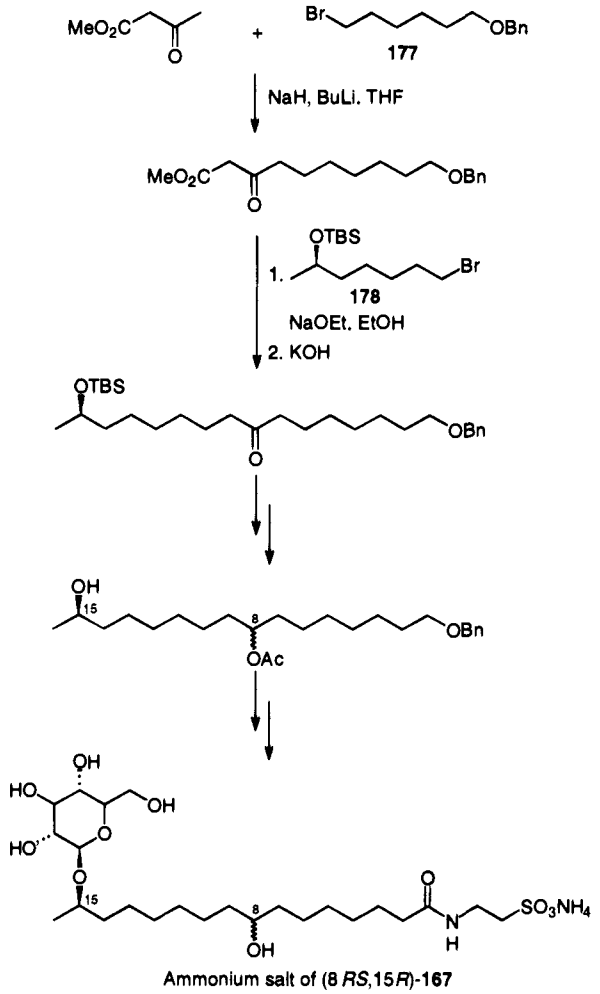
Scheme 80



Mori[182] has recently reported a synthesis of the ammonium salt of (8*RS*,15*R*)-**167** in which the hexadecanetriol unit is constructed from four cheap building blocks. Methyl acetoacetate was alkylated, as shown in Scheme 81, firstly with bromide **177** (derived from 1,6-hexanediol) and then with bromide **178** (derived from ethyl (*R*)-3-hydroxybutanoate and propargyl alcohol). Alkaline hydrolysis, decarboxylation, and reduction, etc. gave the desired hexadecanetriol unit which was then coupled with the sugar moiety and taurine.

The synthetic pheromones (8*R*,15*R*)- and (8*RS*,-15*R*)-**167** have been trialed under seminatural conditions[183] and are highly effective at eliciting behavioral responses similar to those for the natural ODP with the (8*RS*,15*R*) mixture being the most effective. Aluya and Boller[184] report that the (8*RS*,-

Scheme 81



Ammonium salt of (8 *RS*,15*R*)-**167**

15*R*) mixture reduced fruit infestation by approximately 90% under field conditions. The synthetic ODP in its desmethyl form has been submitted to the Swiss registration authority and received a preliminary permit for large-scale field tests in 1994.[185]

D. Genus *Toxotrypana*

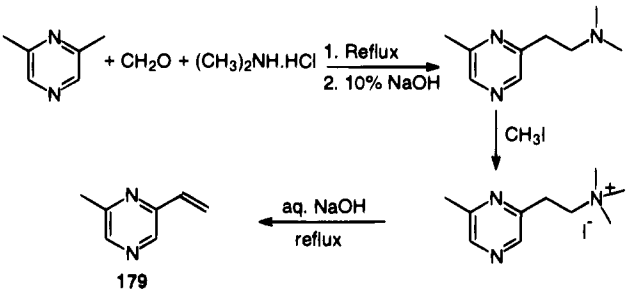
Toxotrypana is a genus of seven largely South American species. Only one of these, *T. curvicauda*, is a major economic pest.

1. *Toxotrypana curvicauda (Papaya Fruit Fly)*

The papaya fruit fly [*Toxotrypana curvicauda* (Gerstaeker)] is the major insect pest of papaya in the Caribbean, South Florida, and Central America. The papaya fruit fly is unusual in that unlike most tropical tephritids which are polyphagous, it appears to select a single host.[1] This fruit fly is not attracted to any of the usual lures[186] or protein baits[187] so that levels of infestation and expansion are difficult to assess or monitor. Thus a species specific pheromonal attractant is of considerable interest.

Landolt[188] reported studies which suggested the existence of a male generated pheromone which elicited excitatory behavior in conspecific females. Subsequently, Chuman, Landolt, Heath, and Tumlinson[189] trapped and purified the volatiles from "calling" male *T. curvicauda* and essentially one component, not emitted by females, was present. This situation is ideal for subsequent testing but somewhat unusual as most Tephritid secretions are multicomponent in nature with minor components probably playing a crucial role. This single component was shown to be 2-methyl-6-vinylpyrazine (**179**) by spectroscopic evidence and synthesis (Scheme 82).

Scheme 82



Behavioral studies[189] with synthetic material in an arena bioassay confirmed that **179** acted as a genuine sex pheromone, being attractive to sexually mature virgin females at a substantial distance and responses were comparable to those observed for natural material from males. Wind tunnel bioassays[190] have demonstrated that **179** is attractive to both unmated and mated mature females. Mated females are thought to use the male sex pheromone (released by males puffing on host fruit in the field) to locate host fruit for oviposition. These wind tunnel bioassays[190] and field trials[191] have shown that papaya fruit fly females respond best to a combination of pheromone and visual cues. Field tests[191] also demonstrated a significant male response to pyrazine (**179**) which was hypothesized to have a secondary aggregation function.

IV. Subfamily Tephritinae

A. Genus *Urophora*

The genus *Urophora* includes almost 100 species of gall-forming tephritids occurring in Europe, temperate Asia, Africa, and the Americas.[1] Several species of this genus are currently being used or considered for use as biocontrol agents of noxious weeds, especially thistles. These insects can reduce the reproductive capacity of their host plant by concentrating nutrients and energy in the gall induced by larvae.[192]

1. *Urophora cardui and Urophora stylata*

Urophora cardui (Linnaeus) is a native of cooler areas of Europe and Asia where it attacks creeping or Canadian thistle (*Cirsium arvense*).[1] Consequently, *U. cardui* has been released in Canada, but has failed to be an effective means of thistle control.

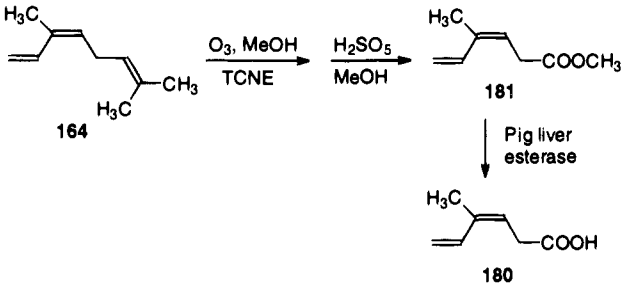
Urophora stylata (Fabricius) occurs throughout Europe and temperate Asia where it attacks thistle (*Cirsium* and *Carduus* spp.).[1] In British Columbia the introduction of *U. stylata* has substantially reduced seed production by bull thistle (*Cirsium vulgare*).

Harris[193] reported that males of a number of *Urophora* species including *U. cardui* and *U. stylata* emit a strong odor which he supposed might be an arresting pheromone. Frenzel *et al.*[192] have examined the volatile contents of the rectal ampulla from both *U. cardui* and *U. stylata* males, and in both species a single identical volatile component was detected.

GC–MS analysis followed by synthesis determined the component to be 4-methyl-3(*Z*),5-hexadienoic acid (**180**).

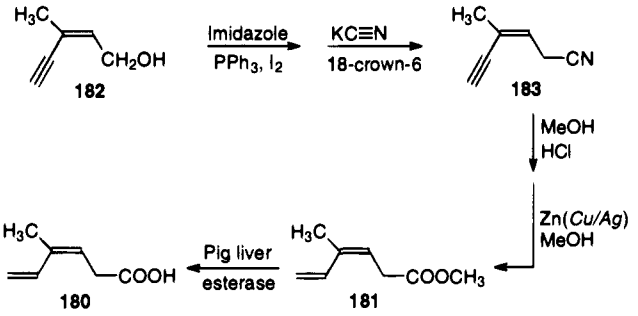
Frenzel[192] synthesized acid **180** by two different routes. The first involved the selective ozonolysis of (*Z*)-ocimene (**164**) and tetracyanoethylene reduction of the ozonides, followed by immediate oxidation to give the more stable methyl ester **181** (*ca.* 80% (*Z*) isomer) as shown in Scheme 83. Pig liver esterase

Scheme 83



hydrolysis gave the free acid **180** without rearrangement of the double bonds. In a second more stereoselective synthesis (Scheme 84), the iodide

Scheme 84

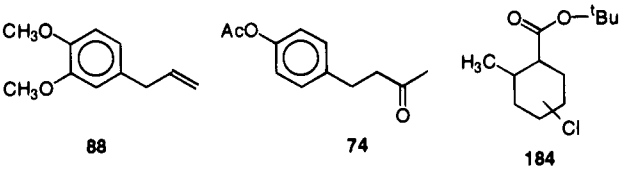


from *cis*-3-methyl-2-penten-4-yn-1-ol (**182**) was treated with cyanide under phase transfer conditions. Methanolysis of the resulting nitrile (**183**), followed by reduction of the triple bond with activated zinc, gave the pure *cis* ester **181** from which free acid **180** was obtained as before.

Laboratory bioassays performed by Frenzel *et al.*[192] did not support the arrestant hypothesis of Harris.[193] Signaling between sexual partners of *U. cardui* and *U. stylata* is considered unlikely, and Frenzel *et al.*[192] have proposed that isolated acid **180** may have an intraspecies defensive function.

V. Metabolism of Male Lures

Males of most *Bactrocera* species can be attracted to and feed vigorously on either methyl eugenol (**88**) or Cue-Lure (**74**), but generally not both.[194] Some researchers regard these lures as pseudopheromones while others argue that they are really behavior-modifying plant chemicals or kairomones.[195] Trimedlure (**184**) is a synthetic attractant for males of *Ceratitis capitata* and many other *Ceratitis* species.[1] The history and biological relevance of these lures has been adequately summarized by Cunningham,[195] and the present review will deal only with the metabolism of lures ingested by male flies and the analysis of lure metabolites in pheromonal glands.

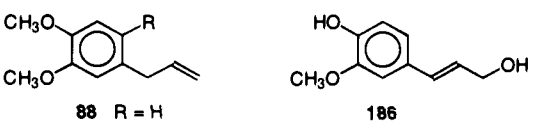


The occurrence of food constituents and their metabolites in the pheromonal gland of *Bactrocera* flies has been documented: the amides of *B. tryoni* are believed to be derived from dietary leucine and isoleucine,[108] and the glandular terpene composition of *B. passiflorae* could be altered by changing the food source from paw-paw to rose-apple.[123] It is thus not surprising that ingested male lures could be similarly metabolized and stored. The biological significance of these metabolites however opens a whole new arena in the debate over the role of male lures.

A. Methyl Eugenol Metabolites

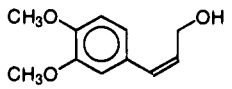
Methyl eugenol (**88**) attracts males of many *Bactrocera* species and some *Ceratitis* species,[1] and is widely distributed in various plants such as *Cassia fistula*,[196] *Zieria smithii*,[197] *Ocimum sanctum*,[198] and *Spathiphyllum cannaefolium*.[199]

Nishida *et al.*[200] have reported that two phenylpropanoid compounds, 2-allyl-4,5-dimethoxyphenol (**185**) and coniferyl alcohol (**186**) accumulate in rectal glands of *B. dorsalis* males fed with methyl eugenol (**88**). Phenol **185** was detected in volatile emissions at dusk (coinciding with the fly courtship period) and attracted males as strongly as **88**, whereas alcohol **186** was inactive. Nishida isolated compounds **185** and **186** from the body tissue of wild *B. dorsalis* males collected at various sites in West Malaysia. Compound **185** was identified from mass spectral and ^{1}H NMR and ^{13}C NMR evidence, while compound **186** was identified by spectral comparisons with an authentic sample. These compounds were absent from laboratory-reared *B. dorsalis* males fed on a honey–yeast diet. Nishida[200,201] has suggested that as well as a male attractant, the metabolites may function as an allomone, as an extract of methyl eugenol-fed male *B. dorsalis* deterred feeding of the Japanese tree sparrow. Phenol **185** was a more potent deterrent than methyl eugenol (**88**), while **186** was inactive.[200]

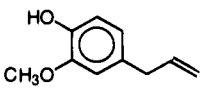


In a subsequent paper, Nishida[202] reported that male *B. dorsalis* rectal glands dissected within 1–3

days after feeding with methyl eugenol (**88**) often contained *cis*-3,4-dimethoxycinnamyl alcohol (**187**) as well as compounds **185** and **186**. Compound **187** was identified from its mass spectra and was prepared by a photochemical isomerization of its *trans* isomer. Nishida[202] was uncertain whether **187** played any biological role.



187

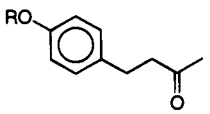


188

Fletcher[86] examined rectal glands of wild male *B. dorsalis* trapped with methyl eugenol (**88**) and allowed to feed on the lure. Compounds **185** and **186** were present as major components (mass spectral comparisons with literature[202]) with a smaller amount of methyl eugenol (**88**). Compound **187** was not observed. Further analysis of laboratory-reared flies not exposed to methyl eugenol did not show these components.[80] Similarly, rectal gland analysis[86] of the related species *B. carambolae* (previously called Mal A[80] and originally confused with *B. occipitalis*[85]) caught with methyl eugenol (**88**) and allowed to feed on the lure, showed three phenylpropanoid components along with other components reported[80] in wild flies not allowed to feed on **88**. The major phenylpropanoid was coniferyl alcohol (**186**), with a smaller amount of phenol **185** and a minor amount of a third component with apparent M^+ of 162 and major ions at *m/z* 147, 130, 119, 102, and 91. This component was presumed to be eugenol (**188**) (or an isomer thereof). Methyl eugenol metabolites (unidentified) have also been reported[203] in the pheromone secretion of *B. opiliae* (Drew and Hardy) males within 24 h of methyl eugenol ingestion.

B. Cue-Lure Metabolites

Cue-Lure (**74**) attracts males of many *Bactrocera* and *Dacus* species.[1] It is not known to occur in nature, but its deacetyl derivative **73** (known as Wilson's lure or "raspberry ketone") has been reported from various plants.[204-209]



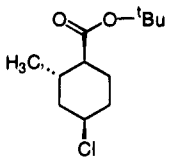
73 R = H
74 R = Ac

Nishida[98] reported that laboratory-reared *B. cucurbitae* males fed once with Cue-Lure (**74**) accumulated the deacetyl compound **73** in the rectal gland within 24 h. Subsequently Nishida[209] reported the occurrence of **73** in the orchid *Dendrobium superbum*. Male *B. cucurbitae* compulsively licked the flower surface and sequestered the compound in their rectal gland. Furthermore, Nishida[209] reported that males fed either **74** or **73** were attractive to unfed males but that neither the rectal volatile mixture nor **73** induced any apparent behavioral response from females.

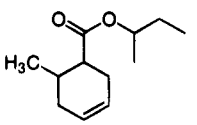
Fletcher[86] found that rectal glands from wild male *B. melanota* (Coquillett) (from Cook Islands) that had fed on Cue-Lure (**74**), contained the deacetyl compound **73** as the sole dominant component.

C. Trimedlure

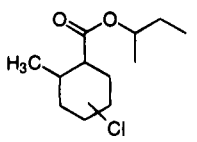
The synthetic male lure trimedlure (**184**) has been used for more than 25 years as an attractant for monitoring *Ceratitis capitata* (Mediterranean fruit fly). Commercial trimedlure (**184**) is a mixture of eight stereoisomers of which (1*S*,2*S*,4*R*)-**189** is the most biologically active.[210] Trimedlure (**184**) is known to be relatively unpalatable[4] and there are no literature reports on the insect metabolism of **184** or its less biologically active analogues siglure (**190**) or medlure (**191**).



189



190



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D. Biological Role of Male Metabolites

The role of lure metabolites sequestered in the pheromonal sac is an area of increasing interest. Shelly and Dewire[211] have recently reported that in laboratory experiments male *B. dorsalis* (Hendel) that fed on methyl eugenol mated more frequently than control males. Compared with control males, treated males displayed higher levels of wing fanning and attracted more female flies. This mating advantage was long lasting (35 days from a single feeding). These authors attributed the increased mating to the production of methyl eugenol metabolites as discussed above. Contrastingly, Nishida[209] reported that the Cue-Lure metabolite **73** did *not* induce any apparent behavioral responses in female *B. cucurbitae*.

Future research in this area should aim to establish the abundance of these lure metabolites in wild flies. Pheromonal analysis should ideally be performed on males which have matured in the field and had the opportunity to find, ingest, and metabolize chemicals naturally present in the wild. Comparison of such wild specimens with laboratory-reared flies may bring to light the metabolism and sequestering of other chemicals as was the case with the *B. passiflorae* terpenes.[123]

VI. Overview

Fruit flies are very serious pests of horticulture in many tropical and subtropical areas, and the usual methods of control are based on blanket insecticide spraying, or a combination of attractants such as protein "baits" or male lures with insecticide. On general environmental grounds the former method is increasing unacceptable. Protein hydrolysate baits or male lures (which are not insect natural products) are of moderate efficiency for many species, but are almost completely ineffective for some important species. Consequently, the observation that males of most fruit fly species secrete and release a mixture that appears to play a role in communication with conspecific females, generated hope that species-

specific environmentally friendly controls might result from detailed chemical studies of such secretions and released volatiles. In addition, control of *female* populations promises the most effective approach to the fruit fly problem, with pheromone-based methods having considerable potential.

The present review summarizes what is known in the area of fruit fly chemistry and provides the essential knowledge for development and biological assaying of species-specific female attractants. The considerable chemical diversity in the fruit fly secretions and volatile emissions demonstrates that more varied biosynthetic routes are available to these Dipteran species than appear to operate in Lepidopteran species where females of numerous species utilize blends of fairly similar compounds to attract conspecific males. Systematic examinations of additional fruit fly species, which may not be serious commercial pests, are required to define the chemical horizons of these insects and permit detailed studies of biosynthetic and pheromone pathways crucial to the lifecycles of these insects. Careful chemical studies have already contributed to taxonomic clarifications in the *B. dorsalis* complex, and this feature will undoubtably be of increasing importance in other fruit fly complexes as well.

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